Mean-Field Analysis of Basal Ganglia and Thalamocortical Dynamics

A thesis submitted for the degree of Doctor of Philosophy

by

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Declaration of originality

I affirm that this thesis is my own work and contains no material that has been previously submitted for a degree or diploma at any institute of tertiary education. Information based on the published or unpublished work of others has been duly acknowledged in the text.

Sacha van Albada
Included papers and attribution

Chapters 2–3 and 5–6 are based on the following papers:

Chapter 2  Transformation of arbitrary distributions to the normal distribution with application to EEG test-retest reliability
van Albada, S.J., Robinson, P.A.
I was primarily responsible for this work, with an overall contribution of about 70%.

Chapter 3  Variability of model-free and model-based quantitative measures of EEG
van Albada, S.J., Rennie, C.J., Robinson, P.A.
I was primarily responsible for this work, with an overall contribution of about 90%.

Chapter 5  Mean-field modeling of the basal ganglia-thalamocortical system. I. Firing rates in healthy and parkinsonian states
van Albada, S.J., Robinson, P.A.
I was primarily responsible for this work, with an overall contribution of about 90%.

Chapter 6  Mean-field modeling of the basal ganglia-thalamocortical system. II. Dynamics of parkinsonian oscillations
van Albada, S.J., Gray, R.T., Drysdale, P.M., Robinson, P.A.
I was primarily responsible for this work, with an overall contribution of about 90%.
Dedicated to my grandparents: Régine Schouten-Jansen, whose gentle heart warmed all around her, Elsa van Albada-van Dien, who will continue to be an inspiration, Bruno van Albada, prevented by a parkinsonian syndrome from learning of my existence, and Wil Schouten, whom I always hoped to make proud.
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Summary

When modeling a system as complex as the brain, considerable simplifications are inevitable. The nature of these simplifications depends on the available experimental evidence, and the desired form of model predictions. A focus on the former often inspires models of networks of individual neurons, since properties of single cells are more easily measured than those of entire populations. However, if the goal is to describe the processes responsible for the electroencephalogram (EEG), such models can become unmanageable due to the large numbers of neurons involved. Mean-field models in which assemblies of neurons are represented by their average properties allow activity underlying the EEG to be captured in a tractable manner.

The starting point of the results presented here is a recent physiologically-based mean-field model of the corticothalamic system, which includes populations of excitatory and inhibitory cortical neurons, and an excitatory population representing the thalamic relay nuclei, reciprocally connected with the cortex and the inhibitory thalamic reticular nucleus. The average firing rates of these populations depend nonlinearly on their membrane potentials, which are determined by afferent inputs after axonal propagation and dendritic and synaptic delays. It has been found that neuronal activity spreads in an approximately wavelike fashion across the cortex, which is modeled as a two-dimensional surface. On the basis of the literature, the EEG signal is assumed to be roughly proportional to the activity of cortical excitatory neurons, allowing physiological parameters to be extracted by inverse modeling of empirical EEG spectra.

One objective of the present work is to characterize the statistical distributions of fitted model parameters in the healthy population. Variability of model parameters within and between individuals is assessed over time scales of minutes to more than a year, and compared with the variability of classical quantitative EEG (qEEG) parameters. These parameters are generally not normally distributed, and transformations toward the normal distribution are often used to facilitate statistical analysis. However, no single optimal transformation exists to render data distributions approximately normal. A uniformly applicable solution that not only yields data following the normal distribution as closely as possible, but also increases test-retest reliability, is described in Chapter 2. Specialized versions of this transformation have been known for
some time in the statistical literature, but it has not previously found its way to the empirical sciences.

Chapter 3 contains the study of intra-individual and inter-individual variability in model parameters, also providing a comparison of test-retest reliability with that of commonly used EEG spectral measures such as band powers and the frequency of the alpha peak. It is found that the combined model parameters provide a reliable characterization of an individual’s EEG spectrum, where some parameters are more informative than others. Classical quantitative EEG measures are found to be somewhat more reproducible than model parameters. However, the latter have the advantage of providing direct connections with the underlying physiology. In addition, model parameters are complementary to classical measures in that they capture more information about spectral structure. Another conclusion from this work was that a few minutes of alert eyes-closed EEG already contain most of the individual variability likely to occur in this state on the scale of years.

In Chapter 4, age trends in model parameters are investigated for a large sample of healthy subjects aged 6–86 years. Sex differences in parameter distributions and trends are considered in three age ranges, and related to the relevant literature. We also look at changes in inter-individual variance across age, and find that subjects are in many respects maximally different around adolescence. This study forms the basis for prospective comparisons with age trends in evoked response potentials (ERPs) and alpha peak morphology, besides providing a standard for the assessment of clinical data. It is the first study to report physiologically-based parameters for such a large sample of EEG data.

The second main thrust of this work is toward incorporating the thalamocortical system and the basal ganglia in a unified framework. The basal ganglia are a group of gray matter structures reciprocally connected with the thalamus and cortex, both significantly influencing, and influenced by, their activity. Abnormalities in the basal ganglia are associated with various disorders, including schizophrenia, Huntington’s disease, and Parkinson’s disease. A model of the basal ganglia-thalamocortical system is presented in Chapter 5, and used to investigate changes in average firing rates often measured in parkinsonian patients and animal models of Parkinson’s disease. Modeling results support the hypothesis that two pathways through the basal ganglia (the so-called direct and indirect pathways) are differentially affected by the dopamine depletion that is the hallmark of Parkinson’s disease. However, alterations in other components of the system are also suggested by matching model predictions to experimental data.

The dynamics of the model are explored in detail in Chapter 6. Electrophysiological aspects of Parkinson’s disease include frequency reduction of the
alpha peak, increased relative power at lower frequencies, and abnormal synchronized fluctuations in firing rates. It is shown that the same parameter variations that reproduce realistic changes in mean firing rates can also account for EEG frequency reduction by increasing the strength of the indirect pathway, which exerts an inhibitory effect on the cortex. Furthermore, even more strongly connected subcircuits in the indirect pathway can sustain limit cycle oscillations around 5 Hz, in accord with oscillations at this frequency often observed in tremulous patients. Additionally, oscillations around 20 Hz that are normally present in corticothalamic circuits can spread to the basal ganglia when both corticothalamic and indirect circuits have large gains. The model also accounts for changes in the responsiveness of the components of the basal ganglia-thalamocortical system, and increased synchronization upon dopamine depletion, which plausibly reflect the loss of specificity of neuronal signaling pathways in the parkinsonian basal ganglia. Thus, a parsimonious explanation is provided for many electrophysiological correlates of Parkinson’s disease using a single set of parameter changes with respect to the healthy state.

Overall, we conclude that mean-field models of brain electrophysiology possess a versatility that allows them to be usefully applied in a variety of scenarios. Such models allow information about underlying physiology to be extracted from the experimental EEG, complementing traditional measures that may be more statistically robust but do not provide a direct link with physiology. Furthermore, there is ample opportunity for future developments, extending the basic model to encompass different neuronal systems, connections, and mechanisms. The basal ganglia are an important addition, not only leading to unified explanations for many hitherto disparate phenomena, but also contributing to the validation of this form of modeling.
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Chapter 1
Overview

“The seat of the soul and the control of voluntary movement — in fact, of nervous functions in general — are to be sought in the heart. The brain is an organ of minor importance, perhaps necessary to cool the blood.”

Aristotle, cited by Nussbaum (1978)

People have sought to understand the workings of the brain certainly since the beginning of recorded history. The ancient Egyptians believed thoughts, intentions, and emotions to originate from the heart, and deemed the brain of insufficient importance to preserve it during the mumification process. Nevertheless, an Egyptian physician from ancient times was the first to document various types of brain injuries and their preferred treatments (Breasted, 1930). The brain has alternatively been viewed as an organ to cool the heart, a distribution center for a vital substance called ‘psychic pneuma’, or a collection of convolutions each representing a distinct personality trait (Bennett, 1999; Crivellato and Ribatti, 2007; Simpson, 2005).

The advent of techniques that allowed individual neurons to be imaged revolutionized the view of the brain. It became clear that nervous tissue is composed of a vast network of cells encapsulated in membranes but communicating through the exchange of chemicals at synapses (Ramón y Cajal, 1911). The brain turned out to be exceedingly complex, comprising about $10^{11}$ neurons connected via $10^{15}$ synapses. Electrical signals traveling along neuronal processes called axons trigger the release of neurotransmitters, which changes the potential across the membrane of the receiving neuron. If enough signals reach the dendrites and cell body of a neuron in a short time window, it will in turn generate an action potential, both transforming and propagating the signal (Bear et al., 2001; Kandel et al., 1995).

The highly complex dynamics of the brain can be described on many different levels, in terms of cellular and molecular biology, the computational
properties of neuronal networks, or the partially synchronized activity of aggregates of neurons. Depending on the relevant spatial and temporal scales, and the presence or absence of functional interpretations, various approaches have been implemented for characterizing brain dynamics. Comparatively abstract neural network models can be used to understand some of the computational operations performed by the brain and the formation of particular spatiotemporal patterns (Ermentrout, 1998; McCulloch and Pitts, 1943; Hebb, 1949; Hopfield, 1982). Models that more closely mirror the underlying physiology can clarify the firing properties of individual neurons or oscillations in realistic neuronal assemblies (Deco et al., 2008; Hodgkin and Huxley, 1952; Izhikevich and Edelman, 2008; Markram, 2006).

The partially synchronized oscillations of many aligned cortical neurons are responsible for the voltage fluctuations on the scalp that are measured with the electroencephalogram (EEG) (Nunez, 1995; Ray, 1990). The neuronal substrates underlying the EEG can be described using mean-field models, which have a coarse spatial, but relatively fine temporal, scale (Jirsa and Haken, 1996; Rennie et al., 1999; Robinson et al., 1998b; Steyn-Ross et al., 1999; Wright and Liley, 1996). Fitting model predictions to data allows parameters to be extracted that give information about the physiology of the brain (Robinson et al., 2004).

This thesis explores a way of modeling interactions of neuronal assemblies in terms of their large-scale properties. The first three chapters consider distributions of model parameters in the healthy population, and variations in these parameters on different temporal scales. A key component of the thesis investigates the influence of the basal ganglia, a part of the brain involved in movement preparation and execution, on brain rhythms in health and disease. Slow changes in brain activity, whether due to normal diurnal or seasonal variation, aging, or a disease process, are the common thread linking the chapters. The body of the thesis consists of five chapters that have either appeared in print (Chapters 2 and 3), are being prepared for submission (Chapter 4), or are in press (Chapters 5 and 6). Each chapter commences with an introduction that allows it to be read as a self-contained unit, so the relevant material is only outlined in this overview chapter.

The following sections provide some background information on large-scale brain anatomy and physiology, mechanisms responsible for the EEG, recording and analysis techniques, and individual differences and age trends in EEG spectra. In addition, existing brain models are reviewed, which serve as a stepping stone for the introduction of our model of the basal ganglia-thalamocortical system.
1.1 Large-scale organization of the brain

“The brain immediately confronts us with its great complexity. The human brain weighs only three to four pounds [1.4–1.8 kg] but contains about 100 billion neurons. Although that extraordinary number is of the same order of magnitude as the number of stars in the Milky Way, it cannot account for the complexity of the brain. The liver probably contains 100 million cells, but 1000 livers do not add up to a rich inner life.”

Gerald Fischbach (1992)

Following the lines of embryonic development, the brain is divided into three major compartments: the rhombencephalon or hindbrain, the mesencephalon or midbrain, and the prosencephalon or forebrain (Bear et al., 2001; Kandel et al., 1995). The cerebellum is a control center situated in the hindbrain with diverse functions including motor learning and execution, coordination, and the integration of sensory perceptions. The midbrain and the medulla and pons in the hindbrain together constitute the brainstem, which maintains respiratory and cardiac function, the sleep cycle, arousal, and is an important relay center for motor and sensory information. The diencephalon is the part of the forebrain that comprises the thalamus, hypothalamus, and subthalamus, along with some nearby structures. The thalamus consists of two ovoid structures just above and on either side of the brainstem, which relay and process all sensory input to the cortex, except smell. High-level cognitive functions such as memory, planning, language, and perceptual awareness are regulated by the cerebral cortex, the major constituent of the telencephalon in the forebrain. The telencephalon also contains the bulk of the basal ganglia, a group of interconnected nuclei occupied with reinforcement learning, movement facilitation and modulation, and certain emotional functions. Based on both anatomical location and functional characteristics, the hemispheres of the brain are divided into frontal, temporal, parietal, and occipital lobes. A fiber bundle called the corpus callosum links the left and right hemispheres (Bear et al., 2001; Kandel et al., 1995).

The cerebral cortex is an approximately 2 to 5 mm thick sheet with a convoluted structure, forming alternating crests (gyri) and troughs (sulci). This allows a surface area of around 2600 cm² when flattened to be compressed into a smaller superficial area of about 1600 cm² (Henery and Mayhew, 1989; Mountcastle, 1998). The outer layers of the cerebrum consist of so-called gray matter, which is actually pink in the living brain, made up of neuronal cell bodies and unmyelinated processes. Below the gray matter lies the white matter, which derives its color from the fatty myelin sheaths surrounding axons. The cerebral cortex is further organized into layers, a continuum of overlapping columns, and larger functional areas, which were first investigated in detail by Brodmann (1909), based on their histology.
Apart from a few areas, including the olfactory and hippocampal cortices, the cerebral cortex has six layers and is referred to as the neocortex (Bear et al., 2001; Kandel et al., 1995). The outermost Layer I, also referred to as the molecular layer, contains many dendritic arborizations and axonal terminations, but is devoid of neurons except for a scattering of interneurons (Douglas and Martin, 2004). Layers II and III are the main source of short intracortical and interhemispheric corticocortical (or association) fibers. Layer IV receives both prominent thalamocortical and intrahemispheric corticocortical inputs. The neurons in Layers V and VI are the main efferents to the thalamus and other subcortical structures (Douglas and Martin, 2004). Despite their great functional significance, fibers connecting the cortex and thalamus are responsible for only a small percentage of all cortical connections (Nunez and Srinivasan, 2006).

Intrinsic axon collaterals establish extensive connections within 200–800 μm of cortical surface, forming overlapping cortical columns (also called hypercolumns or macrocolumns), which span all layers (Calvin, 1995). These columns are conceptually defined to describe what is in reality a continuum of neuronal connections (Buzsáki, 2006). Each macrocolumn consists of 50–100 minicolumns typically containing about 80–120 neurons each, which share receptive fields and are thought to be the basic units of cortical organization (Mountcastle, 1998). By inhibiting neighboring regions, interneurons enhance the specificity of minicolumns (Buxhoeveden et al., 2000).

In the human brain, glial cells, including astrocytes, oligodendrocytes, and microglia, are about ten times as numerous as neurons. These non-neuronal cells fulfill such diverse functions as providing nutrition, producing myelin, mediating inflammatory reactions, and maintaining brain vascular tone. Recently, these cells have also been shown to modulate synaptic transmission and neuronal excitability, and play a role in synapse formation and adult neurogenesis. Moreover, astrocytes participate in direct signal transmission to both neurons and other astrocytes through a process referred to as ‘gliotransmission’. The corresponding gliotransmitters are released upon increases in calcium concentration that may arise spontaneously or in response to neurotransmitters (Haydon, 2001; Volterra and Medolesi, 2005).

Cortical neurons are classified according to their shape, targets, and use of either glutamate or gamma-aminobutyric acid (GABA) as a neurotransmitter. About 80% of cortical neurons are glutamatergic spiny pyramidal cells, which are long-range and have an excitatory effect on their targets. Apart from spiny stellate cells, all other types of cortical neurons, including small and large basket cells, chandelier cells, Martinotti cells, and double-bouquet cells, are GABAergic and inhibitory. These short-range neurons make up about 20% of neocortical neurons, and project only intracortically. Cortical neurons establish
on average 4000–8000 synaptic contacts, of which the fractions of excitatory and inhibitory ones are approximately proportional to the corresponding neuron counts (Beaulieu and Colonnier, 1985; Braitenberg and Schüz, 1998).

1.2 Origins and applications of the EEG

“Aristotle maintained that women have fewer teeth than men; although he was twice married, it never occurred to him to verify this statement by examining his wives’ mouths.”

Bertrand Russell (1952)

Over the years, a number of techniques have been developed for imaging the living brain, which are sensitive to different aspects of brain organization and activity. In computed or computer-assisted tomography (CT/CAT), an image of the gray and white matter is reconstructed from X-ray scans acquired at various angles (Bear et al., 2001; Kandel et al., 1995). More detailed images are obtained using magnetic resonance imaging (MRI), which makes use of the electromagnetic signals emitted by hydrogen atoms exposed to strong magnetic fields. Functional magnetic resonance imaging (fMRI) is an extension of this technique that measures changes in cerebral blood flow based on the relative amounts of oxygenated and deoxygenated hemoglobin. Positron emission tomography (PET) gives information about regional glucose metabolism through the introduction of 2-deoxyglucose into the bloodstream. The accumulation of a phosphate-bound form of this molecule can be visualized using a radioactive source of positrons, which causes photons to be emitted upon the interaction between positrons and electrons (Bear et al., 2001; Kandel et al., 1995). Changes in cerebral blood flow and metabolism can often be related to changes in neural activity, although the relationship is not straightforward, and the two types of processes generally occur on different time scales (Moore and Cao, 2008). Magnetoencephalography (MEG) is a method for detecting the magnetic fields of the brain resulting mainly from intracellular currents tangential to the head surface (Lopes da Silva and van Rotterdam, 1982). It has the advantage that magnetic fields pass through the skull and scalp without significant distortion (Buzsáki, 2006). The electrocorticogram (ECoG) is a recording of electrical activity made directly on the cortical surface, for instance to pinpoint epileptic foci during brain surgery. The amplitude of voltage fluctuations is an order of magnitude larger on the cortical surface than on the scalp. Due to the absence of volume conduction through cerebrospinal fluid, skull, and scalp, the ECoG is sensitive to activity at smaller spatial and temporal scales than the EEG (Buzsáki, 2006; Niedermeyer, 1982c; Nunez and Srinivasan, 2006). Yet different information is provided by invasive local field potential (LFP) recordings,
which make use of extracellular microelectrodes to pick up synaptic and non-
synaptic activity of neurons within a range of a few mm (Bédard et al., 2004; 
Buzsáki, 2006). The recording of single units proceeds in a similar manner, but 
with the electrode tip close enough to a neuron to measure its spiking activity 
(Hubel, 1957; Magnin et al., 2000). In Chapters 5 and 6 we use evidence ob-
tained using a range of imaging methods to infer electrophysiological changes in 
Parkinson’s disease. However, this thesis focuses primarily on the EEG, which 
measures the voltage fluctuations on the scalp resulting from the components 
of extracellular currents that are orthogonal to the head surface.

Human brain waves were first reported by Berger (1929), and shown by 
Adrian and Matthews (1934) to be strongest in the occipital region. These 
waves, referred to by Berger as the Elektrenkephalogramm, are recorded from 
electrodes placed on the scalp. EEG signals have been shown to provide a win-
dow on various cognitive processes, including sensory perception, attention, 
and memory (Klimesch, 1999; Low, 1982). Furthermore, inspection of EEG 
time series can be used to characterize sleep stages, to monitor the depth of 
anesthesia or coma, to identify seizures and epileptic foci, or to detect other 
medical conditions including brain tumors, strokes, severe head injury, infec-
tious diseases, drug overdoses, metabolic disorders, and brain death (Nunez 
and Srinivasan, 2006; Spehlmann, 1981). However, diagnoses based on the 
EEG are often relatively nonspecific, requiring verification from independent 
clinical tests. The origins of EEG activity are still relatively poorly understood, 
although significant progress has been made in the decades since its discovery.

1.2.1 Source of EEG activity

“Swiftly the head-mass becomes an enchanted loom where millions of flashing 
shuttles weave a dissolving pattern though never an abiding one; a shifting 
harmony of subpatterns.”

Charles Sherrington (1940)

EEG signals were initially thought to arise due to the summation of action 
potentials in cortical neurons. However, it was later recognized that action 
potentials do not cause significant voltage differences between distant ends of 
cortical neurons, since they are associated with current flowing almost simultane-
ously across all parts of the membrane (Humphrey, 1968). This confirmed 
the hypothesis that longer-lasting postsynaptic potentials were responsible for 
the relatively large voltage fluctuations of the EEG (about 10–100 μV on the 
scalp) (Clare and Bishop, 1955; Eccles, 1951; Purpura, 1956).

All types of cortical neurons contribute to the EEG, but deep-lying pyrami-
dal neurons are implicated in particular because of their long apical dendrites, 
which often extend all the way up to Layers I and II (Goldensohn, 1979), and
their large degree of alignment perpendicular to the cortical surface. Apical dendrites of deep pyramidal neurons establish many excitatory contacts with intra- and interhemispheric corticocortical fibers (Nieuwenhuys, 1994), whereas inhibitory basket cells synapse less profusely onto the cell bodies of pyramidal neurons (Goldensohn, 1979). Both excitation in superficial layers and inhibition in deep-lying layers cause extracellular currents that translate into surface-negative waves, as illustrated in Fig. 1.1. At rest, the inside of the pyramidal cell is negatively charged with respect to the extracellular medium. Excitatory impulses depolarize the membrane by causing positively charged sodium ions to flow into the cell, whereas inhibitory inputs result in hyperpolarization of the membrane due to the influx of chloride ions and/or efflux of potassium ions (Spehlmann, 1981). In either case, the extracellular medium near the base of the cell becomes positively charged with respect to that at the apex, causing current to flow towards the cortical surface. The superficial layers thus act as a current sink, yielding a negative deflection in scalp potential (Goldensohn, 1979; Lopes da Silva and van Rotterdam, 1982).

Despite the similarities, excitation at apical dendrites is thought to provide a contribution to the EEG about an order of magnitude larger than inhibition at basal dendrites or the cell body, for a number of reasons. For one, inhibition at the cell body or basal dendrites causes a large portion of the passive inward currents, which neutralize the active outward currents, to flow directly through the cell-body membrane. Thus, the net outward currents are relatively small, resulting in small inward currents into the dendrites near the surface, and a weak dipole between the synaptic site and these dendrites (Mitzdorf, 1985). Furthermore, the parallel arrangement of apical dendrites supports dipoles with strong additive effects, whereas basal dendrites are more radially (i.e., more isotropically) distributed, causing their dipole moments to largely cancel out (Lopes da Silva and van Rotterdam, 1982; Towe, 1966). Also, inhibitory synaptic actions are not as layer-specific as excitatory synaptic actions, and are therefore summed in a more diffuse manner (Mitzdorf, 1985).

Since pyramidal neurons in cortical gyri are relatively close to the surface, and aligned in the perpendicular direction, whereas neurons in sulci are more distant from the surface and oriented obliquely or parallel to the surface, the EEG mainly reflects gyral sources. Scalp potentials that are measurable without averaging (of the order of 10–50 μV) require synchronous activity to be distributed over roughly 6 cm² of cortical gyri, or about 70 million neurons (Ebersole, 1997). The scalp EEG has a relatively coarse spatial resolution on the order of centimeters due mainly to volume conduction between sources and sensors, a single electrode picking up the combined signal of roughly 100 million to 1 billion neurons. On the other hand, its temporal resolution is high, lying in the millisecond range (Nunez and Srinivasan, 2006).
Figure 1.1: Diagram of pyramidal neurons receiving either excitatory input at apical dendrites or inhibitory input at basal dendrites. Both cause extracellular currents to flow toward superficial layers, creating a negative deflection in scalp potential. Reproduced from Goldensohn (1979).

1.2.2 Recording and analysis methods

“...we have normality, I repeat we have normality. (...) Anything you still can’t cope with is therefore your own problem.”


EEG waves are always recorded with respect to a reference, which may be an electrode at a different site on the scalp or on the earlobe(s), the average of all scalp electrodes, or a weighted average of surrounding electrodes. A common choice of electrode placements follows the International 10–20 system, in which adjacent channels are either 10% or 20% of the total front-to-back or left-to-right distance apart. The EEG recordings used in our studies were acquired at 26 electrodes of an extended 10–20 system, which are depicted schematically in Fig. 1.2.

When recording the EEG, filters are applied to remove components above the Nyquist frequency, which would otherwise lead to aliasing. The signal is amplified, digitized at a specified sampling rate, and visually inspected to remove portions contaminated by eye movements or other artifacts. Time series
can be converted to spectra consisting of the squared amplitude of fluctuations at each frequency. Spectra are generally divided into several frequency bands thought to represent distinct processes (Klimesch, 1999). Principal component or factor analysis reveals that activity in at least some of these bands varies independently, although recording and statistical methodology can strongly affect band limits (Kubicki et al., 1979; Mecklinger et al., 1992). Although some activity is always present in all frequency bands, and power generally decreases with frequency, peaks in specific bands of the human EEG are associated with distinct cognitive or clinical states, development stages, or levels of arousal. The following is a rough classification of the origins of increased activity in specific frequency ranges, keeping in mind that activity is never confined to any single band (Niedermeyer, 1982a,b):

- **Delta (0–4 Hz):** High-amplitude waves seen in adults during deep sleep, and normally in babies. Delta waves also occur in certain pathological cases, for instance due to brain lesions.

- **Theta (4–8 Hz):** Normally seen in young children, but also during drowsiness or arousal in older children and adults, and in certain pathologies.
- **Alpha (8–13 Hz):** So named by Berger (1929), alpha waves are most prominent during the eyes-closed resting state, especially in posterior regions. Activity that follows this pattern occurs at a lower frequency in children. When associated with the sensorimotor cortex, activity in the alpha band is often termed the *mu rhythm*.

- **Beta (13–30 Hz):** Bilaterally and frontally distributed waves, generally of low amplitude. Waves with multiple and varying frequencies are associated with active thinking, concentration, and anxiety. Pathologies and drug effects may cause rhythmic beta activity with a dominant set of frequencies.

- **Gamma (30–100 Hz):** Associated with alert wakefulness, gamma activity is thought to accompany binding of distributed aspects of a sensory percept. Since the cerebrospinal fluid, skull, and scalp act as a low-pass filter, gamma rhythms associated with high wavenumbers (i.e., periods per unit length) can only be recorded reliably with MEG or ECoG.

A set of mathematical, statistical, and visualization methods jointly referred to as quantitative EEG (qEEG) is commonly used to compare patterns of EEG activity between subjects, electrodes, and states (Duffy et al., 1994; Nuwer, 1988). Absolute band powers are computed by integrating spectra over the relevant frequency ranges, and relative band powers are the absolute values divided by the total spectral power. Standard measures also include the frequency of the peak in the alpha band, and mean frequencies calculated for instance by weighting with the power at each frequency (Chotas et al., 1979). A less conventional measure, used in Chapters 2 and 3, is the so-called spectral entropy, which quantifies the ‘peakiness’ of the EEG spectrum. More elaborate methods include significance probability mapping, coherence and cross-correlation analyses, automated event detection, source analysis, and topographic EEG mapping (Lopes da Silva, 1982; Nuwer, 1988; Nuwer et al., 2005). In our studies, we consider only band powers, total power, alpha peak frequencies, and spectral entropy, and restrict our analysis to the Cz electrode, which is relatively unsusceptible to muscle artifacts (Saunders, 1979).

The means of qEEG measures can be compared between different (groups of) individuals, electrodes, or states using the Student’s t-test, a nonparametric version such as the Mann-Whitney U test, or analysis of variance (ANOVA) for multiple comparisons (Conover, 1971; Howell, 2008). Since parametric statistical tests, which yield accurate results only for normally distributed variables, are generally more powerful than their nonparametric counterparts, transformations are often used to render non-normal data approximately normal. Thus, absolute band powers are often converted into their logarithms, and the closely related logit transformation is applied to relative band powers (Gasser et al., 2005).
However, finding an appropriate transformation is not always straightforward, especially if variables do not follow well-known distributions. In Chapter 2 we describe an exact transformation that normalizes distributions regardless of their shape, and specify some circumstances in which this transformation is useful. As one application, we find that the transformation improves the test-retest reliability of non-normal variables, which is relevant to the study of intra- and inter-individual differences in EEG spectra in Chapter 3.

1.2.3 Reproducibility of EEG parameters

“I have (...) tried to inquire into the nature and justification of the physicalist’s skepticism toward the value of neurological research. In so doing, I have discovered that this skepticism should really be distinguished into two basic kinds, one of which I shall call principled skepticism and the other boggled skepticism.”

Patricia Churchland (1980)

The EEG is not a static picture of brain activity. Spectral profiles change dynamically on time scales from fractions of minutes to many years. Drug effects, hormonal cycles, ultradian, circadian, and seasonal variations, and aging can all affect the EEG in different ways. These changes are interesting in their own right, because they provide information about the underlying brain activity. In addition, it is essential to know the normal amount of variation to be able to make valid inferences from statistical tests, for instance to classify a subject as belonging to a healthy or a clinical group.

In Chapter 3 we assess the normal amount of variation in spectral parameters obtained from 193 recordings of 32 male subjects selected from the Brain Resource International Database (BRID) (Gordon et al., 2005), spread out over six weeks to approximately a year. Classical measures evaluated are band powers, total power, the frequency of the alpha peak, and spectral entropy. Physiological parameters obtained by fitting spectra to our mean-field model of the corticothalamic system are effective delays or rates associated with dendritic and synaptic integration and axonal propagation, gain parameters describing the effective connectivity between populations, and a scaling factor relating the firing rate of cortical pyramidal neurons to the scalp potential.

Besides estimating the variability in parameters in the healthy population, trial-to-trial correlations are computed, which depend on the relative amounts of variation within and between individuals. If these correlations are high, the relevant parameters allow individuals to be reliably distinguished. Although classical qEEG measures are found to be on average somewhat more reproducible than model parameters, both types of measures can reliably characterize a subject’s EEG spectrum. The comparison between classical qEEG
measures and model parameters suggests that some of the variability in the latter is due to the imperfect representation of corticothalamic dynamics by the model, and the sensitivity of model parameters to noise. Therefore, reproducibility may be improved with successive refinements of the model and fitting routine. However, model parameters already have the advantage that they relate EEG spectra to underlying physiology, whereas classical measures are purely phenomenological. Moreover, the information contained in model parameters is complementary to that in band powers and alpha peak frequency, since the model describes spectral shape within bands that is not captured by qEEG measures.

Another aspect of EEG dynamics considered in Chapter 3 is the time scale necessary to capture most of the variability in spectral parameters. To estimate this time scale, spectra are computed over 30 s epochs, and the variability of parameters is computed for intervals ranging from 30 s to many weeks. Characteristic time scales are calculated under the assumption that the level of intertrial variability tends exponentially to an asymptote for large intervals, which is supported by the data and the literature. Although more tests at more evenly spaced intervals are needed to increase the reliability of the estimates, our data suggest that 95% of the variability in EEG spectra corresponding to the alert eyes-closed state can be captured in recordings of one to a few minutes. This is an important result, since alertness varies on the scale of minutes (Jung et al., 1997), and drowsiness could therefore affect the interpretation of recordings longer than a few minutes.

1.2.4 Changes in model parameters across age

“Old age puts more wrinkles in our minds than on our faces.”

Michel de Montaigne (1585–88)

The study of brain aging is among the most prolific areas of neuroscience. We are naturally fascinated by the aging process, which affects everyone, and better understanding of which has the potential to improve the quality of life.

Chapter 4 looks at changes with age in model parameters derived from the EEG spectra of 1503 healthy individuals aged between 6 and 86 years. The data were again provided by the Brain Resource International Database (BRID) (Gordon et al., 2005). Sex differences in average values and age trends are investigated, since male and female brains are known to have distinctive properties (Coffey et al., 1998; Cosgrove et al., 2007; de Bellis et al., 2001; Pakkenberg and Gundersen, 1997).

Parameter distributions are compared with those in Chapter 3, and with those reported previously by Rowe et al. (2004a). We find that the values for males aged 18–28 years are consistent with those in the reproducibility study,
but that significant differences exist versus Rowe et al. (2004a), presumably due to changes in the fitting algorithm. We argue that the new version of the fitting routine represents an improvement, since it reduces bias introduced by arbitrary parameter initialization. The robustness of fits is further addressed to check (i) to what extent parameters are biased by noise, (ii) how the bias in different parameters is interrelated, and (iii) how much of the variability in parameters can be attributed to fitting uncertainty. This information facilitates the next steps in the analysis.

Several parameters differ significantly between males and females, including corticothalamic axonal loop delays and various gains. These same parameters are found to vary together across age, in parallel with decreases in power normalization in both males and females. Nonlinear fits of parameters versus age indicate that the slopes of many trendlines change considerably around 14 and 20 years of age. Therefore, median-based linear trendlines are fitted in each of the ranges 6–14, 14–20, and ≥ 20 years. The relationships between model parameters and classical qEEG parameters are also examined.

Interestingly, the variance in most model parameters peaks around adolescence. We explain this as follows. There is some spread in the age at which children enter the adolescent stage, and the rates of brain maturation during adolescence. Children with early/rapid maturational changes initially diverge from those with late/slow changes. However, when the former reach the adult stage, the latter start to catch up, causing model parameters to reconverge.

Overall, we find that parameters develop most rapidly in childhood, in agreement with findings on EEG changes in the literature (Niedermeyer, 1982d). The extent of changes in old age depends on the prevalence of disease in the sample under study (Duffy et al., 1984, 1993; Evans and Starr, 1994). Although a restrictive set of criteria was applied to select only healthy participants, it is possible that some abnormalities went unnoticed, leading to more rapid changes during senescence than would have occurred in a healthier sample. On the other hand, it is imaginable that the oldest subjects in the sample, having already survived for longer, were in fact healthier than those who were slightly younger. We present our findings with these qualifications in mind.

The results in Chapter 4 provide a standard for future comparisons with EEGs of clinical groups, cognitive, behavioral, and genetic data, and recordings obtained at other electrode sites. Prospective studies will take advantage of progress in the automatic characterization of single and multiple alpha peaks (Chiang et al., 2008), and physiologically-based modeling of evoked response potentials (ERPs) (Kerr et al., 2008). This will enable the analysis of interrelationships between parameters derived from EEG spectra, measures of alpha peak morphology, and physiologically-based ERP parameters. Chapter 4 is a work in progress, and its results are being prepared for publication.
1.3 Models of brain electrical activity

“Essentially, all models are wrong, but some are useful.”

George Box and Norman Draper (1987)

Historically, EEG analysis has often been based on phenomenological correlations between band powers and cognitive or behavioral measures. This has mainly been due to poor understanding of the mechanisms underlying the EEG, preventing such measures from being directly related to physiological processes. Modeling brain activity from the scale of single neurons to large neuronal assemblies can provide insight in the processes responsible for the EEG.

The mean-field model that has been used to investigate intra- and inter-individual differences (Chapter 3) and age trends (Chapter 4) in brain parameters related to the EEG was developed by Robinson et al. (1997, 1998a, 2001b, 2003a), Rennie (2001), and coworkers. The addition of the basal ganglia (Chapters 5 and 6) is aimed not only at gaining new insights into processes underlying the EEG, but also at explaining the results of invasive measurements of neuronal activity in parkinsonian patients and animals with symptoms resembling Parkinson’s disease (to which we shall refer below as parkinsonian animals, although no precise equivalent of the human syndrome exists). A mean-field approach is appropriate also for the latter purpose, since it permits the description of many electrophysiological correlates of Parkinson’s disease, including steady-state firing rates, rhythmic modulations in average rates, and phase relationships between oscillatory activity in different nuclei.

1.3.1 A short overview of brain models

“...the only complete description of a system is the system itself.”

Walter Freeman (1975)

Before discussing mean-field models, and more specifically our model of the basal ganglia-thalamocortical system, we give a brief account of existing models of brain electrical activity. The formulation by Hodgkin and Huxley (1952) of equations for the ionic currents underlying action potentials provided the starting point for a proliferation of conductance-based models of single neurons. Conductance-based models are predicated on the analogy between neuronal membranes and electrical circuits, in which the membrane acts as a capacitor and ion channels are represented by conductances that are often voltage-dependent. The Hodgkin-Huxley model includes sodium and potassium currents plus a leak current, but other currents can be added to describe a wide
range of neuronal types (Connor and Stevens, 1971; Morris and Lecar, 1981; Prinz et al., 2003; Terman et al., 2002).

Models of the Hodgkin-Huxley type are biologically realistic and their parameters can be precisely measured. Nevertheless, for reasons of simplicity it is sometimes convenient to study more mathematically abstract models. Such models can help to determine conditions necessary for particular behaviors to arise, such as spontaneous or rebound bursting, spike rate adaptation, or after-hyperpolarization following trains of spikes (Dayan and Abbott, 2001; Koch, 1999). Many simplifications of the Hodgkin-Huxley model and related models have been presented (FitzHugh, 1961; Nagumo et al., 1962; Rinzel, 1985; Rose and Hindmarsh, 1989). Some methods employed to reduce the complexity of conductance-based models are to eliminate the dynamics of “fast” variables that quickly reach an equilibrium value, or to combine variables that evolve on similar time scales (Kepler et al., 1992). Alternatively, the fast dynamics of action potential generation can be simplified by assuming a spike occurs whenever the potential reaches a specified threshold, and instantly resetting the potential to its resting value (Dayan and Abbott, 2001; Koch, 1999). Variations of such integrate-and-fire models are also possible (Destexhe, 1997; Ermentrout, 1998).

At the next level of complexity, single neurons can be combined into neural networks typically comprising tens to thousands of neurons. Neural network models possess varying degrees of physiological realism, ranging from close representations of biological systems to highly abstract or simplified models, and may be spatially structured or unstructured (Ermentrout, 1998). Neural network models can be analyzed either without reference to the information embodied by their dynamics, or using an information-theoretic approach, in which computational properties are ascribed to network elements. This approach goes back to the proposition by McCulloch and Pitts (1943) that the neuronal integration of synaptic inputs can be viewed as a binary operation with an all-or-none result: either the neuron fires an action potential or it does not. Abstract models in particular often focus on gaining a better understanding of neural computations using highly idealized neurons, since they are formulated with an eye on mathematical tractability. Hopfield nets are sets of interconnected binary threshold nodes with a form of associative memory, allowing activation states to be retrieved by local minimization of an energy function given an input that resembles the stored state (Hopfield, 1982). Neuronal plasticity can be encoded by dynamically updating connection weights in response to specific stimulation or activity patterns. This allows a network to retain a memory of past activity and adapt its responses accordingly, a process that has been termed Hebbian learning (Dayan and Abbott, 2001; Hebb, 1949).

Recent ambitious projects in neural network modeling include that by Izhikevich and Edelman (2008) to simulate the activity of one million neurons of 22
different types in the thalamocortical system, and the Blue Brain Project, which aims to model the activity of a macrocolumn of rat neocortex in great detail (Markram, 2006). These simulations are only feasible with the computational power of large supercomputers.

Another way to capture large-scale brain dynamics is to average the properties of neuronal assemblies over small distance scales and describe their effective interactions using a mean-field model (Coombes, 2005; Deco et al., 2008). This approach is aimed at characterizing those aspects of brain activity that are widely distributed and reflect global function, rather than being “hard-wired” in specific neuronal networks (Ingber, 1982). The regions of choice should be sufficiently large for their average properties not to be dominated by statistical fluctuations, but small enough to be approximated as uniform (Freeman, 1975). Mean-field modeling is well-suited to describing the activity underlying the scalp EEG because of the low spatial resolution of this recording modality.

1.3.2 Mean-field models of brain activity

“...it is highly improbable that emergent properties are properties that cannot be explained by low-level properties (...), or that they are in some sense irreducible, causally sui generis, or as philosophers are wont to say, ‘nomologically autonomous,’ meaning, roughly, ‘not part of the rest of science’.”

Patricia Churchland and Terrence Sejnowski (1992)

Mean-field models are approximations to more general ensemble density models, obtained by ignoring interactions between modes of higher order than the average activity (Deco et al., 2008). Pioneering work in mean-field brain modeling includes that by Beurle (1956) and Griffith (1963a, 1965), which focused on populations of excitatory neurons. The stabilizing influence of inhibitory interactions was recognized by Griffith (1963b). Subsequently, Wilson and Cowan (1972) used two coupled nonlinear integrodifferential equations to describe fractions of cells firing action potentials per unit time in interacting excitatory and inhibitory neural populations. To facilitate analysis, this model was temporally coarse-grained and spatial variations were excluded, leading to a lumped-parameter description. In contrast, Wilson and Cowan (1973) considered neurons distributed in homogeneous sheets with an exponential fall-off of connection densities. Based on studies of the olfactory bulb and cortex of cats and rabbits, Freeman (1972) described static nonlinearities in the input-output relationships of neural masses. In the regime where both voltage-to-spike conversion at axon hillocks and spike-to-voltage conversion at dendrites and synapses could be approximated as linear, he derived gains quantifying the number of outgoing pulses per incoming pulse. Furthermore, he introduced
transfer functions to describe sequences of excitatory and inhibitory projections, sometimes forming closed loops. Freeman (1975) elaborated the model of the olfactory bulb and cortex in great detail, consecutively lumping neuronal populations, each described by a second-order ordinary differential equation with a static nonlinearity. To analyze the resulting complex model, he proceeded by piecewise linear approximation. Lopes da Silva et al. (1974) presented a simple neuronal network model containing excitatory and inhibitory thalamic neurons, and reduced this to a neural mass model without spatial characteristics.

Nunez (1974b) added the idea that an exponential range distribution of cortical fibers with finite conduction velocities led to waves of activity spreading from active patches of cortex, which satisfy dispersion relations. This feature was inspired by the experimental observation of such waves of activity in the cortex (Burns, 1951; Nunez, 1974a), as confirmed by more recent studies (Chervin et al., 1988; Golomb and Amitai, 1997; Lopes da Silva and Storm van Leeuwen, 1978; Prechtl et al., 1997; Rubino et al., 2006; Schiff et al., 2007; Wu et al., 1999; Xu et al., 2007). In later work, Nunez (1989, 1995) focused on so-called ‘global modes’, standing waves that arise when the cortex is treated as a closed surface, dendritic and synaptic delays are negligible compared to maximal axonal delays, and waves are assumed to be weakly damped. This contrasts with the work of Rennie et al. (1999), Rennie (2001), and Robinson et al. (1997, 1998a, 2001b, 2002, 2003a), in which it is found that dendritic and synaptic delays and the damping rate of cortical waves are sufficiently large for boundary conditions to play a minor role in determining their frequency content (Robinson et al., 2001a). The existence of cortical waves is now widely accepted, and modifications of traveling-wave solutions for inhomogeneous synaptic weight distributions or inputs have been described for instance by Bressloff (2001); Bressloff et al. (2003).

Wright and Liley (1995, 1996) introduced such features as random connectivity of cortical neurons, Gaussian distributions of firing thresholds, and the assumption that the local field potential of a volume of cortical tissue is proportional to the activity density of excitatory neurons. Another prominent model is that developed by Jirsa and Haken (1996, 1997), who recast a simplified version of the Wilson-Cowan equations in differential form and analyzed the resulting behavior for a one-dimensional strip of cortex with periodic boundary conditions. Frank et al. (1999, 2000) presented adaptations of the Jirsa-Haken model, including stochastic terms and synaptic dynamics. The main innovations afforded by the work of Robinson, Rennie, and coworkers were the differential formulation of all components of the model, including synaptodendritic dynamics, restriction to physiologically realistic parameters, and the inclusion of corticothalamic dynamical interactions.

17
The importance of focused and diffuse thalamic inputs for the generation of cortical waves was recognized early on (Morison and Dempsey, 1942). The thalamic reticular nucleus, a thin layer of GABAergic cells covering the thalamus, is also critical to the generation of rhythmic EEG activity. Andersen and Andersson (1968) surmised that intrathalamic interactions were responsible for both spindle oscillations appearing in the anesthetized condition, and for alpha waves, which lie in a similar frequency range. However, spindle waves and alpha waves differ in the concomitant activity of the thalamic reticular nucleus, which powerfully inhibits the relay nuclei during sleep or anesthesia, but is relatively quiescent during normal wakefulness. Spindle waves are thus thought to originate from strong recurrent excitation and inhibition between the relay and reticular nuclei, whereas a different explanation is required for alpha waves. A prominent hypothesis is that alpha rhythms arise at least partly within the cortex, due either to intrinsically rhythmic (‘pacemaker’) cells, to network interactions (David and Friston, 2003; Liley et al., 1999, 2002; van Rotterdam et al., 1982), or to a combination of these possibilities (Karameh et al., 2006). Without discounting the importance of intrinsically rhythmic cells and intracortical interactions, analysis of our model has shown that corticothalamic population interactions can produce alpha resonances (Robinson et al., 2001b, 2003a). This hypothesis goes back to Bishop (1936), who was the first to suggest that corticothalamic reverberations lay at the heart of rhythmic oscillations recorded on the cortical surface or scalp, although he later restricted his attention to intrinsically rhythmic cells. Corticothalamic reverberations were also recorded directly by Chang (1950) upon stimulation of cat, monkey, or rabbit cortex. These recordings showed that repetitive discharges following the primary response always appeared in the same cortical area that was stimulated, indicating the importance of topographically focused projections from the specific thalamic relay nuclei. On the other hand, nonspecific thalamic projections may synchronize activity across large areas of the cortex (Jones, 2001).

Notable studies of corticothalamic dynamics were undertaken by Lumer et al. (1997a,b), who described a large-scale model of integrate-and-fire units organized into cortical layers interacting with thalamic relay and reticular units. In this model, local cortical circuits supported 20–60 Hz synchronous oscillations that were strengthened by corticothalamic loops. Steriade and Deschênes (1984), Steriade et al. (1990, 1998), Steriade (2006), McCormick (1992); McCormick and Bal (1997), Buzsáki (1991, 2004, 2006), Destexhe and Sejnowski (2001, 2003), Llinás et al. (2005), and Llinás and Steriade (2006) have focused attention on the interplay between cortical and thalamic structures in producing rhythms at various frequencies during sleep and waking. These works have emphasized that both intrinsic cellular properties and network interactions are
crucial to the generation of brain rhythms, where synchronization is accomplished by the latter.

The model used here shares many properties with preceding models. Our equations follow those given by Robinson, Rennie, and coworkers, with certain restrictions, leading to the following set of features:

- separate populations of long-range excitatory and short-range inhibitory cortical neurons with reciprocal and intrinsic connections,
- finite axonal delays,
- uniform axonal propagation speed within the cortex,
- linear summation of synaptic inputs,
- a second-order linear differential equation describing the rise and decay of the cell-body potential, with different rise and decay times,
- sigmoidal voltage-to-spike rate conversion,
- spatial homogeneity and isotropy in the cortex, so that the spatial connectivity distribution depends only on the distance between neurons,
- interactions between cortex and subcortical structures.

In addition, a damped-wave equation is given for propagation of activity along the cortical surface; however, we only consider homogeneous solutions. Furthermore, volume conduction effects are taken into account in the fits to empirical EEG spectra used in Chapters 2–4. Features that are not part of the version of the model we shall use, but have been discussed elsewhere, include multiple excitatory cortical populations with different characteristic axonal ranges (Nunez, 1989; Rennie et al., 2002; Robinson, 2005), local feedback representing for instance neuromodulator actions or relative refractoriness (Rennie et al., 1999), explicit treatment of slow neuromodulator dynamics (Clearwater et al., 2007, 2008), spatial inhomogeneities (O'Connor and Robinson, 2004, 2005), the saturation of the cell-body potential for high levels of synaptic inputs (Freeman, 1972; Rennie et al., 2000), continuously distributed axonal delays (Freeman, 1975; Nunez, 1974a, 1995; Roberts and Robinson, 2008), the laminar (David et al., 2005) and convoluted structure of the cortex, and a detailed analysis of contributions of current sources and sinks to the total potential field (Freeman, 1975; Nunez and Srinivasan, 2006).

The properties of a number of representative models are summarized in Table 1.1. This summary is by no means exhaustive, and makes no reference to the level of detail achieved in modeling properties such as modal effects or volume conduction. Refractoriness is implicit in models with maximum firing rates, including the present model, although explicit and self-consistent treatment of refractoriness causes these maximum rates to be time-dependent (Wilson and Cowan, 1973). The modeling studies of Robinson, Rennie, and
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Table 1.1: Summary of macroscopic brain models. ● Feature included in the work or combination of works cited. * Feature approximated or ignored in the detailed analysis in the given references. △ Freeman (1975) discussed the saturation of cell-body potentials for high levels of input, but used linear summation as an approximation. □ Wilson and Cowan (1973) presented a particularly thorough treatment of refractoriness, which in most studies was approximated by imposing maximum firing rates. References for the next-to-last column are given in the text.
coworkers are grouped into two columns, one indicating the restricted version used in this thesis, and the other describing the characteristics captured in the combined body of work.

1.3.3 Model of the basal ganglia-thalamocortical system

“The love of complexity without reductionism makes art. The love of complexity with reductionism makes science.”


The basal ganglia are not a part of the brain often mentioned in relation to the EEG. Nevertheless, these nuclei influence cortical rhythms via GABAergic projections to the thalamus (Bolam et al., 2000; Haber and Gdowski, 2004; Ilinsky et al., 1993; Parent, 1990), and dopaminergic projections directly to the cortex (Gaspar et al., 1992; Williams and Goldman-Rakic, 1993). Another reason for including these nuclei in a basic large-scale model of the brain is that they are of key importance to a number of common neurological disorders, such as Parkinson’s disease, Huntington’s disease, and schizophrenia (Bergman and Deuschl, 2002; Gray et al., 1991; Rolls et al., 2008; Swerdlow and Koob, 1987; Walker, 2007). Furthermore, the basal ganglia are involved in reinforcement learning and mediate addictive behaviors (Schultz, 1998; Wise, 1996). The role of the basal ganglia in each of these conditions is not well understood, although many models have been formulated and considerable advances have been made in this respect. Our starting point for the study of the basal ganglia-thalamocortical system is the model formulated by Robinson, Rennie, and coworkers, and we focus on changes engendered by the dopamine loss characteristic of Parkinson’s disease (Bernheimer et al., 1973; Ehringer and Hornykiewicz, 1960).

Background

“If the human brain were so simple that we could understand it, we would be so simple that we couldn’t.”

Emerson Pugh, quoted by George Pugh (1977)

The core of the basal ganglia is formed by the striatum, substantia nigra, pallidum, and subthalamic nucleus (STN) (Bolam et al., 2000; Haber and Gdowski, 2004; Yelnik, 2002). Some definitions add to this the centromedian-parafascicular complex (Percheron et al., 1991) or the pedunculopontine nucleus (Mena-Segovia et al., 2004). The term ‘ganglia’ is more usually reserved for elements of the peripheral nervous system, but the historical name persists in the present context. The basal ganglia are depicted along with a number of related brain structures in Fig. 1.3.
The substantia nigra contains both the *pars reticulata* (SNr) and the *pars compacta* (SNC), which releases the neuromodulator dopamine at nigrostriatal terminals. This affects striatal neurons both presynaptically, by changing the amount of glutamate released at corticostriatal terminals, and postsynaptically by modulating intrinsic cellular properties (Cepeda et al., 1998; Kiyatkin and Rebec, 1996; Levine et al., 1996; Hu and White, 1997; Hsu et al., 1995; Umemiya and Raymond, 1997). In addition, so-called mesocortical dopaminergic projections target frontal cortical areas, where dopamine exerts a predominantly inhibitory effect (Gao and Goldman-Rakic, 2003; Gulledge and Jaffe, 2001; Sesack and Bunney, 1989; Williams and Goldman-Rakic, 1993; Zhou and Hablitz, 1999). The nigrostriatal and mesocortical pathways are the main substrates of dopaminergic activity, although practically all components of the basal ganglia receive some dopaminergic input (Bernheimer et al., 1973; Lavoie et al., 1989;
In Parkinson’s disease, neurons are selectively lost from the SNc and adjacent dopamine-producing structures, due either to known genetic or environmental factors, or unknown causes (idiopathic Parkinson’s disease). This triggers a cascade of chemical and physiological changes that ultimately results in outward signs such as difficulty initiating movements (akinesia), slowness of movement (bradykinesia), an approximately 5 Hz tremor of the limbs evinced in the resting state, and muscular rigidity (Berardelli et al., 2001; Bergman and Deuschl, 2002; Deuschl et al., 2000; Elble, 2002; Lang and Lozano, 1998; Parkinson, 1817).

Albin et al. (1989) proposed that the antikinetic effects of dopamine loss result from the differential modulation of corticostriatal connection strengths to two populations of striatal projection neurons. Of these, one population expresses mainly the D1 class of dopamine receptor, and the other mainly the D2 class of receptor. D1 neurons send inhibitory projections to the globus pallidus internal segment (GPi) and SNr (the output nuclei, which have similar connection patterns and are modeled as a single structure), whereas D2 neurons inhibit the globus pallidus external segment (GPe). The GPe inhibits the STN, which in turn excites the output nuclei. Alexander and Crutcher (1990) termed the first pathway the direct pathway, and that passing through the STN the indirect pathway. These pathways are illustrated in Fig. 1.4. A so-called hyperdirect pathway involving a corticosubthalamic projection was later added to the basic schema of basal ganglia organization (Nambu et al., 2000). Furthermore, there is a direct GPe-GPi/SNr projection, the STN projects back to the GPe, the thalamic relay nuclei form a re-entrant circuit by innervating the striatum, and powerful local inhibition exists in both the striatum and the GPe (Bolam et al., 2000; Gonzalo et al., 2002; Hazrati et al., 1990; Kita, 1994; Koós and Tepper, 1999; Ogura and Kita, 2000; Parent and Hazrati, 1995b; Sadikot et al., 1992; Shink and Smith, 1995).

By increasing cortical activation of D2 neurons and decreasing cortical activation of D1 neurons, dopamine loss would reduce inhibition of the output nuclei by D1 neurons, and increase their excitation by the STN. Hyperactivity of the output nuclei would lead to antikinetic symptoms through excessive inhibition of the thalamic relay nuclei, suppressing cortical activation. The direct/indirect loop hypothesis would also explain the increased firing rates of the GPe and STN, and the decreased rate of GPe neurons often observed in parkinsonian patients and animals (Bergman et al., 1994; Filion and Tremblay, 1991; Heimer et al., 2002). In Chapter 5 we refine this hypothesis and quantify the resulting predictions using a mean-field model.

Tremor has been suggested to arise via similar mechanisms as akinesia/bradykinesia, since thalamic relay neurons can fire bursts of spikes in response to
Figure 1.4: Model diagram of the basal ganglia-thalamocortical system, where the following abbreviations are used: ACh = acetylcholine; GABA = gamma-aminobutyric acid; SNc, SNr = substantia nigra pars compacta and pars reticulata; VTA = ventral tegmental area; D1, D2 = striatal neurons mainly expressing either the D1 or D2 type of dopamine receptor; GPI, GPe = globus pallidus internal and external segments; STN = subthalamic nucleus. Gray arrows indicate the direct, indirect, and hyperdirect pathways.

hyperpolarization (Hurtado et al., 1999; Llinás, 1984; Paré et al., 1990; Sarnthein and Jeanmonod, 2007). These rebound bursts sometimes occur rhythmically at a rate comparable to that of tremor. Rhythmic activation of premotor and motor areas of the cortex by thalamic neurons could cause limb muscles to contract at the same rate. However, the pattern of interspike intervals in thalamic bursts in parkinsonism differs from that expected from rebound bursts (Lenz et al., 1993; Zirh et al., 1998), potentially indicating that thalamic bursts result from oscillations already present upstream from the output nuclei. Indeed, rhythmic modulations of spike rates have been observed in all elements of the basal ganglia-thalamocortical system (Bergman et al., 1994; Dejean et al., 2008; Filion and Tremblay, 1991; Lenz et al., 1994; Timmermann et al., 2003). Thus, alternative hypotheses have been put forward, placing the origin of oscillations either in the loop formed by STN and GPe, in corticothalamic loops, or in re-entrant circuits through cortex, basal ganglia, and thalamus (Deuschl et al., 2000; Leblois et al., 2006; Humphries et al., 2006; Terman et al., 2002; Wichmann and DeLong, 2003). Despite the general consensus that central oscillations, rather than loops involving sensory feedback, are responsible for parkinsonian tremor, even the latter are still not completely discounted by some researchers (Rivlin-Etzion et al., 2008). Recent evidence indicates that central
oscillations drive tremor, although a bidirectional coupling exists between motor cortex and peripheral systems (Smirnov et al., 2008).

Both 3–7 Hz and 7–30 Hz oscillations are commonly observed in parkinsonian patients and animals (Bergman et al., 1994; Dejean et al., 2008; Filion and Tremblay, 1991; Levy et al., 2001; Magnin et al., 2000; Timmermann et al., 2003). These may either arise in a single circuit, or in two or more different ones, especially considering that the low- and high-frequency oscillations are generally not harmonically related. In Chapter 6 we explore the possibility that approximately 5 Hz oscillations arise in the indirect circuit, while rhythms around 20 Hz arise in corticothalamic loops and spread to the basal ganglia when the indirect pathway becomes strong. We also consider several other electrophysiological correlates of Parkinson’s disease.

Development

“Theorizing at this stage is like skating on thin ice — keep moving, or drown.”

Donald Hebb (1949)

The basic corticothalamic model is introduced in Chapter 3. This includes inhibitory and excitatory cortical populations, excitatory thalamic relay neurons, and inhibitory reticular thalamic neurons. The relevant equations are taken from the work of Robinson, Rennie, and coworkers, as summarized for instance in Robinson et al. (2004). Inputs from different populations are summed linearly, then low-pass filtered by the synapses and the dendritic tree, and a sigmoid function relates the average cell-body potential of each population to the instantaneous firing rate. Finally, a damped-wave equation describes the spreading of activity across the cortex. The scalp EEG is approximated as being proportional to the firing rate of cortical pyramidal neurons after volume conduction through the cerebrospinal fluid, skull, and scalp.

Adding the basal ganglia to this basic model was complicated by the wide range of functional connections linking the components of the basal ganglia-thalamocortical system, of which the relative influences are difficult to ascertain. We ultimately settled on the connections depicted in Fig. 1.4, of which in particular the direct GPe-GPi/SNr projection, the thalamostriatal projection, and the local inhibitory circuits in striatum and GPe are not often included in quantitative models. The basic equations governing the dynamics of these components and connections are the same as those for the corticothalamic system. Parameters were chosen to match as closely as possible empirical findings on delays, connection strengths, threshold potentials, and maximum and average firing rates, as discussed in detail in Chapter 5.

Ways to model dopamine depletion were again determined using information from many sources. A number of studies suggest that dopamine loss re-
duces the signal-to-noise ratio in striatal neurons, causing them to fire less selectively in response to inputs (Nicola et al., 2004; O’Donnell, 2003). It has been proposed that this simultaneously decreases corticostriatal connection strengths and the firing thresholds of striatal neurons (Leblois et al., 2006). This contrasts with the direct/indirect loop hypothesis, according to which dopamine loss increases the corticostriatal connection strength to D2 neurons, while decreasing that to D1 neurons. Besides changes at the striatal level, an elevated concentration of the opioid peptide enkephalin in the GPe may reduce lateral inhibition in this nucleus (Betarbet and Greenamyre, 2004; Maneuf et al., 1994; Stanford and Cooper, 1999), while reduced levels of dynorphin may lower the GPe threshold potential (Ogura and Kita, 2000). Elevated levels of extracellular potassium in the STN appear to decrease the effective firing threshold of this nucleus (Strauss et al., 2008). The effects of reduced dopaminergic innervation of the cortex can be approximated by decreasing cortical connection strengths, and in particular inhibition (Gao and Goldman-Rakic, 2003; Gulledge and Jaffe, 2001; Sesack and Bunney, 1989; Thurley et al., 2008; Zhou and Hablitz, 1999). Finally, reduced dopaminergic innervation of the GPe by nigral afferents may increase the inhibitory influence of the striatum over the GPe (Floran et al., 1997; Querejeta et al., 2001).

In Chapter 5 we investigate the effects of the above ways of modeling dopamine depletion on firing rates in the basal ganglia-thalamocortical system by deriving and solving fixed-point equations, which give the average firing rates of each component for a constant brainstem input. In Chapter 6 we consider the dynamic effects of the same parameter changes for small and large perturbations about the equilibrium firing rates. In the linear approximation we derive a transfer function relating the brainstem input to the cortical excitatory firing rate field, and investigate the effects of changes in cortical gains on the strengths and latencies of maximal transient voltage perturbations. In addition, we study limit cycle oscillations that appear for parameters outside the linearly stable region. In the nonlinear regime we consider the effects of the given parameter changes on the amplitude of firing rate fluctuations in the various populations. The influence of dopamine loss on EEG or local field potential spectra is studied for each population. The model predictions are compared with empirical findings, allowing us to infer realistic parameter changes, and possible mechanisms, underlying the electrophysiological correlates of Parkinson’s disease.
Outcomes

“Most oscillations in the brain are not driven by an independent pacemaker but emerge from nonoscillatory constituents.”

György Buzsáki (2006)

One use of the model is to distinguish between the changes in average firing rates that result from simultaneous decreases in corticostriatal connection strengths and striatal firing thresholds, and parameter changes based on the direct/indirect loop hypothesis. The analysis in Chapter 5 suggests that the latter scenario is most compatible with experimental data, since it yields increased rates of the STN and the output nuclei and a reduced GPe rate, whereas the former has little effect on firing rates. However, strengthening the indirect pathway and weakening the direct pathway leads to suppression of cortical and thalamic activity, whereas studies in parkinsonian animals suggest that the cortical rate is unchanged (Dejean et al., 2008; Goldberg et al., 2002). Model results indicate that this may be partly explained by mesocortical dopamine loss, reduced lateral inhibition in the GPe, and a lower GPe firing threshold. These and other parameter changes also help to account for the relatively large increase in STN rate, and the relatively small decrease in GPe rate apparent from a cross-section of experimental studies (Bergman et al., 1994; Boraud et al., 1998; Goldberg et al., 2002; Hollerman and Grace, 1992; Hutchison et al., 1994, 1998).

The dynamical changes implied by the direct/indirect loop hypothesis are also compatible with empirical findings. In Chapter 6 we show that strengthening the indirect pathway and weakening the direct pathway decreases $|G_{ex} + G_{el}|$, which leads to slower and less pronounced changes in the cell-body potentials of cortical neurons. Reduced intracortical inhibition due to mesocortical dopamine loss also contributes to this effect. Based on electrophysiological recordings in parkinsonian patients and monkeys (Doudet et al., 1990; Kleine et al., 2001), we posit a relationship between decreased cortical gains and antikinetic symptoms. In addition, the direct/indirect loop hypothesis predicts altered responses to transient cortical stimuli that accord with experiments, including enhanced responsiveness of the STN and the output nuclei. Furthermore, a greater cortico-D2 connection strength amplifies firing rate fluctuations throughout the basal ganglia, indicating enhanced synchronization between neurons. Although it is unclear to what extent increased synchronization is limited to oscillatory activity (Levy et al., 2002), this appears to match findings reported in the literature (Goldberg et al., 2004; Hammond et al., 2007; Morris et al., 2005).

Perhaps the most interesting part of this work concerns limit cycle oscillations in basal ganglia-thalamocortical circuits. The origins of parkinsonian oscillations have been under keen investigation since the classic account by
James Parkinson (1817). As mentioned above, many possible explanations have been offered, but the evidence for any particular one is inconclusive to date. Oscillations in the right frequency ranges can be predicted in any feedback loop if the parameters are appropriately tuned. To distinguish between hypotheses, it is therefore necessary to achieve a parsimonious description of multiple phenomena in a single model. Terman et al. (2002) found that the STN-GPe network can support 4–6 Hz oscillations and Leblois et al. (2006) found that oscillations near 11 Hz may be sustained by the hyperdirect loop in Parkinson’s disease. We find that, although increasing the cortico-D2 strength and decreasing the cortico-D1 strength slightly raises the gains of the STN-GPe and hyperdirect loops, the main effect is on the indirect pathway, which is therefore more likely to develop oscillatory activity in our model. Depending on the gain of the loop between cortex and thalamic relay nuclei, a strong indirect pathway can lead to oscillations around 5 Hz or around 20 Hz, closely matching the frequencies of parkinsonian rhythms. The slower rhythm arises when the indirect pathway is many times stronger than the corticothalamic loop, although corticothalamic coupling needs to be relatively strong to permit limit cycle oscillations. The faster rhythm arises already for a smaller ratio between indirect and corticothalamic loop gains, where the latter is relatively large. This rhythm appears as a pathological extension of the normal beta rhythm, spreading from corticothalamic components to the basal ganglia due to strong cortico-D2 coupling. This underlines the importance of including interactions with the thalamocortical system in models of basal ganglia activity. The indirect loop is a likely substrate of parkinsonian oscillations not only because experimental results suggest that dopamine loss increases cortico-D2 and decreases cortico-D1 coupling, and because differential modulation of the direct and indirect pathways leads to realistic changes in firing rates, neuronal responses, and synchronization. Measured phase relationships between the cortex and basal ganglia also support an origin in this loop, and contradict the hypothesis that implicates the hyperdirect loop (Walters et al., 2007; Zold et al., 2007a). The very large gain values necessary to induce limit cycle oscillations in our model imply that such oscillations only arise in small subcircuits, which explains the limited number of cells with rhythmically modulated firing rates usually found (Lemstra et al., 1999; Levy et al., 2001; Wichmann and Soares, 2006). It should be noted that local inhibition in many structures may help to constrain oscillations to subcircuits (Buzsáki, 2006), and spatial modeling of such inhibition could clarify this phenomenon by introducing inhomogeneities in effective gain values.

Another important modeling result is that increased inhibition of the cortex via the indirect pathway lowers the frequency of the alpha peak in the cortical spectrum, increases the relative power in the delta and theta bands, and
decreases relative alpha power. All these findings accord with experimental observations (Bosboom et al., 2006; Neufeld et al., 1994; Sinanović et al., 2005; Soikkeli et al., 1991; Stoffers et al., 2007). Total EEG power appears to be increased in parkinsonian patients (Moazami-Goudarzi et al., 2008; Tanaka et al., 2000), but increased activation may be limited to cortical areas not functionally related to the basal ganglia, or periods when the striatum is not significantly activated (Monchi et al., 2004, 2007). However, the literature suggests that even in such periods or areas, total EEG power is not substantially reduced. In Chapter 6 we describe parameter changes that help limit the decrease in total EEG power engendered by stronger cortico-D2 coupling.

The main strength of our work is that a large number of electrophysiological phenomena are explained using a single, restricted, set of parameter changes around physiologically-based values. Thus, the model achieves a parsimonious description of multiple related phenomena, yielding a range of mutually reinforcing results. As such it is a promising starting point for further theoretical exploration of the basal ganglia-thalamocortical system. Ultimately it is hoped that improved understanding of the mechanisms underlying electrophysiological changes in Parkinson’s disease, and of the correlations between neuronal activity and parkinsonian symptoms, will eventually inspire refined treatment methods. Detailed models incorporating the effects of various neurotransmitter and neuromodulator systems, and intrinsic neuronal dynamics, might yield useful quantitative predictions on the effects of drug administration, therapeutic lesions, or deep brain stimulation. In addition, the analysis of such models may be extended to cover disorders including Huntington’s disease, addictive behaviors, and schizophrenia (Rolls et al., 2008).
Chapter 2

Transformation of arbitrary distributions to the normal distribution with application to EEG test-retest reliability

Many variables in the social, physical, and biosciences, including neuroscience, are non-normally distributed. To improve the statistical properties of such data, or to allow parametric testing, logarithmic or logit transformations are often used. Box-Cox transformations or ad hoc methods are sometimes used for parameters for which no transformation is known to approximate normality. However, these methods do not always give good agreement with the Gaussian. A transformation is discussed that maps probability distributions as closely as possible to the normal distribution, with exact agreement for continuous distributions. To illustrate, the transformation is applied to a theoretical distribution, and to quantitative electroencephalographic (qEEG) measures from repeat recordings of 32 subjects which are highly non-normal. Agreement with the Gaussian was better than using logarithmic, logit, or Box-Cox transformations. Since normal data have previously been shown to have better test-retest reliability than non-normal data under fairly general circumstances, the implications of our transformation for the test-retest reliability of parameters were investigated. Reliability was shown to improve with the transformation, where the improvement was comparable to that using Box-Cox. An advantage of the general transformation is that it does not require laborious optimization over a range of parameters or a case-specific choice of form.
2.1 Introduction

The purpose of this paper is to bring to the attention of neuroscientists a general-purpose method of transforming non-normal distributions to the Gaussian. Remarkably, although the method is quite simple and its subcomponents are even mentioned in some textbooks, it is not known in the relevant applied scientific literature, while enormous effort is devoted to finding ad hoc or approximate solutions. Some of the advantages of the method described here lie in its ease of application (an identical recipe can be followed for any data), the rendering of the data into a familiar form, and the convenience of interpretation this affords.

Although non-normally distributed quantitative electroencephalographic (qEEG) parameters are used as a test case here, there are many examples of neuroscientific variables that follow skewed or kurtotic distributions. Among them are hippocampal and ventricular volumes (Lloyd et al., 2004), age of onset of clinical conditions [see, e.g., Bellivier et al. (2003)], fitted parameters for a model of changes in neurotransmitter concentrations (Napper et al., 2001), questionnaire responses, and many more. Further application of the method is found in the study of test-retest reliability, since Dunlap et al. (1994) showed that skew and kurtosis reduce test-retest correlations, and potentially in the transformation of non-normally distributed variables in data mining (Ultsch, 2000).

The existing literature reveals a wide interest in normalizing transformations. These are relevant in many disciplines of engineering and the social, physical, and biosciences, but qEEG is used as an example here. In studies of qEEG, it is common to apply the logarithmic transformation to improve the normality properties for absolute power, and to apply the logit transformation (log\([x/(1-x)]\)) for relative power (John et al., 1980), where log represents the natural logarithm, and \(x\) is a dimensionless version of the quantity being transformed. Gasser et al. (1982) investigated the transformations \(\log(x), \log(x+1), \sqrt{x}, \sqrt[3]{x}, 1/\sqrt{x}\) for absolute power, and \(\arcsin \sqrt{x}\) and \(\log[x/(1-x)]\) for relative power. They found \(\log(x)\) to be the best transformation for the absolute power except in the delta band, where \(\sqrt{x}\) may be appropriate, and confirmed the superiority of \(\log[x/(1-x)]\) over other transformations for relative power. Oken and Chiappa (1988) investigated the reduction in skewness resulting from square root and logarithmic transformations of EEG power measures and the logit transformation for relative powers. They anticipated a decrease in the coefficient of variation (standard deviation divided by the mean) of spectral measures on transformation to normality, similar to the results of Dunlap et al. (1994).

The statistical literature describes a range of more systematic methods for transforming distributions toward the Gaussian. Notably, Box and Cox (1964)
considered a family of transformations that result to a good approximation in data with normally distributed, homoskedastic (constant variance) errors, and a simple relation to the predictor variables. These transformations depend either on a single parameter $\lambda$, or on two parameters $\lambda = (\lambda_1, \lambda_2)$, and take the form

\[
y^{(\lambda)} = \begin{cases} 
y^{\lambda-1} \frac{\lambda}{y} & (\lambda \neq 0), \\
\log y & (\lambda = 0), 
\end{cases}
\] (2.1)

for $y > 0$, or

\[
y^{(\lambda)} = \begin{cases} 
\frac{(y + \lambda_2)^{\lambda_1} - 1}{\lambda_1 \log (y + \lambda_2)} & (\lambda_1 \neq 0), \\
\log (y + \lambda_2) & (\lambda_1 = 0), 
\end{cases}
\] (2.2)

for $y > -\lambda_2$. The parameters can be estimated using either classical maximum likelihood or Bayesian methods, under the assumptions that for each value of the predictor variables, $y^{(\lambda)}$ is normally distributed with constant variance, and that the observations can be described by a linear model. This leads to values for $\lambda_1$ and $\lambda_2$ which minimize the residual sum of squares in the linear regression of

\[
\frac{(y + \lambda_2)^{\lambda_1} - 1}{\lambda_1 \log (y + \lambda_2)}^{\lambda_1-1},
\] (2.3)

where $gm$ is the geometric mean, and $\lambda_2$ may be taken to be zero. From the confidence interval(s) for the parameter(s) one can pick a value that facilitates interpretation of the transformed variable. While the Box-Cox transformation is aimed at obtaining normally distributed errors relative to a linear regression line, the method has been adapted to find transformations that result to a good approximation in normality of the sample as a whole. The method remains approximate, since only a limited class of transformations is considered.

Other examples from a vast literature on normality transformations include Draper (1952), who discussed three families of transformations and methods for finding the relevant coefficients, and Chen and Tung (2003), who described several variants of a third-order polynomial transformation. Each method has its drawbacks: determining the coefficients is cumbersome, the transformations are often only one-to-one in certain regimes, and even then achieve only approximate normality. The wide interest in normalizing transformations is also evidenced by the highly cited paper of Gasser et al. (1982). To spare researchers and practitioners the effort of applying complicated transformations that can be different in form for each new type of data, and only render distributions approximately normal, we discuss here the simple general solution.

In Sec. 2.2 a transformation is discussed that brings distributions as close as possible to the Gaussian, and takes a reasonably simple form. Sec. 2.3 illustrates the use of the transformation on an empirical set of non-normal EEG spectral measures. The implications of the transformation for the test-retest reliability of the quantities is discussed.
2.2 Methods

In Sec. 2.2.1 the form of the transformation is derived. Sec. 2.2.2 deals with its application to empirical distributions, which are not continuously defined. Sec. 2.2.3 gives a short description of the data set and the statistical methods used to test normality and test-retest reliability.

2.2.1 The transformation

The transformation consists of two parts, both of which are founded on the fundamental law of probabilities, which states that the infinitesimal area under a probability density function (PDF) is invariant under one-to-one transformations \( x \mapsto y(x) \); i.e.,

\[
|p_y(y)dy| = |p_x(x)dx|.
\]  

(2.4)

Here \( p_y \) and \( p_x \) are probability densities, and \( dx \) and \( dy \) are infinitesimal increments. Equation (2.4) suggests a way to transform a continuous variable into a variable that is uniformly distributed, as follows. Substituting the PDF for the uniform distribution, \( p_x(x) = 1 \), we have

\[
p_y(y) = \left| \frac{dx}{dy} \right|.
\]  

(2.5)

The solution of (2.5) is \( x = \pm P_y(y) \), where \( P_y(y) \) is the indefinite integral of \( p_y(y) \). In other words, \( p[P_y(y)] = p_x(\pm x) = 1 \), showing that the cumulative distribution function (CDF) of a continuous variable is itself uniformly distributed on the interval (0,1). This fact was noted by Lévy (1937) and Rosenblatt (1952), and is now a textbook result.

All we now need to do is find a transformation from a uniform deviate on (0,1) to a normally distributed quantity. If we denote the standard normal PDF by \( \phi(y) \), we have to solve \( dx/dy = \phi(y) \). As before, we can integrate to obtain \( x = \Phi(y) \), or, since the CDF is always monotonically increasing and hence invertible, \( y = \Phi^{-1}(x) \). The inverse CDF of the standard normal distribution is

\[
\Phi^{-1}(x) = \sqrt{2} \text{erf}^{-1}(2x - 1).
\]  

(2.6)

where \( \text{erf} \) represents the error function. The variable \( y = \Phi^{-1}(x) \) will follow the normal distribution if \( x \) is itself uniformly distributed. But we saw above that a uniform distribution can be obtained from any variable by taking the CDF. Therefore, if we start from a variable \( v \) following a continuous PDF, the transformed variable

\[
y(v) = \sqrt{2} \text{erf}^{-1}[2P_x(v) - 1]
\]  

(2.7)
has a normal distribution with mean $\mu = 0$ and variance $\sigma^2 = 1$. The mean and standard deviation can be adjusted by multiplying by the desired standard deviation and adding a constant, which results in

$$y(v) = \mu + \sigma \sqrt{2} \operatorname{erf}^{-1}[2P_v(v) - 1].$$  \hfill (2.8)

The transformation (2.8) is order-preserving.

Not surprisingly, a thorough literature search reveals that the transformation (2.8) has been known among statisticians for some time, and is for instance mentioned in Liu and Der Kiureghian (1986). However, its use appears to have been almost entirely restricted to the technical statistics literature, and it is essentially unknown to applied workers who could benefit most from the method.

The function (2.6) proves to be the inverse of the first of a set of functions proposed by Rosenblatt (1952) to map the multivariate normal distribution onto the multidimensional uniform distribution. For instance, in the two-dimensional case, letting $\Phi(z) = (2\pi)^{-1/2} \int^z_{-\infty} e^{-t^2/2} dt$, the transformations of normally distributed variables $y_1, y_2$ with means $\mu_1, \mu_2$, variances $\sigma_1^2, \sigma_2^2$ and correlation coefficient $\rho$, to uniform deviates $x_1, x_2$ on $(0, 1) \times (0, 1)$ are (Rosenblatt, 1952)

$$x_1 = P(y_1) = \Phi \left( \frac{y_1 - \mu_1}{\sigma_1} \right), \quad (2.9)$$

$$x_2 = P(y_2 | y_1) = \Phi \left( \frac{y_2 - \mu_2 + \frac{\rho \sigma_1}{\sigma_2} (y_1 - \mu_1)}{\sigma_2 \sqrt{1 - \rho^2}} \right). \quad (2.10)$$

The inverse of (2.9) and (2.10) is given by

$$y_1 = \sigma_1 \Phi^{-1}(x_1) + \mu_1, \quad (2.11)$$

$$y_2 = \sigma_2 \sqrt{1 - \rho^2} \Phi^{-1}(x_2) + \mu_2 - \frac{\rho \sigma_1}{\sigma_2} (y_1 - \mu_1). \quad (2.12)$$

In particular, when the quantities $y_1$ and $y_2$ are uncorrelated, (2.11) factorizes into two separate realizations of the transformation (2.8). However, note that in general $y_1$ and $y_2$ will not have the given correlation or even be normal unless $x_1$ and $x_2$ obey (2.9) and (2.10).

If the CDF can be determined analytically, applying the transformation (2.7) is straightforward. As an example to show how well this works, we consider the two-parameter Weibull distribution, and choose parameters for which the distribution deviates strongly from normality, with nonzero mean and skew, and excess kurtosis. The density and distribution functions are given by

$$p(x) = ab^{-a}x^{a-1}e^{-(x/b)^a}, \quad (2.13)$$

$$P(x) = 1 - e^{-(x/b)^a}, \quad (2.14)$$
defined on \( x \in [0, \infty) \). The transformation to the standard normal distribution is

\[
y(x) = \sqrt{2} \text{erf}^{-1} \left[ 1 - 2e^{-(x/b)^a} \right].
\]  

(2.15)

The skewed and leptokurtic distribution (2.13) with shape parameter \( a = 9 \) and scale parameter \( b = 3 \) is shown in Fig. 2.1, along with the standard normal distribution obtained after the transformation (2.15).

![Figure 2.1: The Weibull PDF with shape parameter \( a = 9 \) and scale parameter \( b = 1 \) (solid) and the standard normal PDF after transformation (dashed).](image)

One case of interest is the lognormal distribution, for which the transformation reduces to taking the logarithm, which is already widely used in practice.

### 2.2.2 Use on empirical distributions

In Sec. 2.3.1 we apply the transformation (2.7) to empirical distributions rather than to continuously defined analytic distributions. When working with empirical distributions, we compute the empirical distribution function (EDF) instead of an analytic CDF. For brevity only continuous variables are considered here. The standard definition of the EDF is

\[
F_N(x) = \frac{1}{N} \sum_{i=1}^{N} I(x_i \leq x),
\]  

(2.16)

where \( N \) is the number of observations in the sample, and \( I \) is an indicator function having a value of 1 if the argument is true, and 0 otherwise. In other words, (2.16) gives the fraction of observations smaller than or equal to \( x \). However, we do not want to map the largest observation to the value 1, nor the smallest to 0, since the extremes of an underlying continuous distribution
are never sampled in an empirical study. Therefore we subtract $1/(2N)$ from the normalized rank numbers computed in (2.16), obtaining an EDF that runs from $1/(2N)$ for the smallest observation, in steps of $1/N$, to $1 - 1/(2N)$ for the largest observation.

The set of values representing the EDF is uniformly distributed. We then apply the transformation (2.6) to obtain a distribution that is symmetric and as close as possible to the Gaussian. This can be done using any mathematics package that provides the inverse error function (e.g., Matlab). A code that implements the transformation can be accessed at http://www.physics.usyd.edu.au/complex-systems/public_repository/normal.m.

### 2.2.3 EEG example

As an empirical example, in Sec. 2.3.1 we apply the transformation (2.7) to a number of qEEG measures obtained from repeat Cz-electrode recordings of 32 subjects. We stress that these data constitute an illustrative example, and use of the method is not restricted to EEG measures.

The recordings were done at Westmead Hospital in Sydney and at Queen Elizabeth Hospital in Adelaide in the context of a reproducibility study of the EEG. All subjects were healthy males with an age at the first session in the range of 18 to 27 years (mean = 22.3, sd = 2.7). Eyes-closed resting scalp EEG was recorded with a NuAmps amplifier (Neuroscan) at 26 electrode sites according to an extended International 10–20 system. The sampling rate was 500 Hz and a linked-ears reference was used. Data were low-pass filtered at 40 dB per decade above 100 Hz after correcting off-line for eye movements. Power spectra were computed from 2 minutes of EEG by multiplying sequential 2.048 s epochs by a Welch window and performing a Fast Fourier Transform with 0.49 Hz resolution. The intervals between recordings ranged from 1 week to several months. Measures include powers in five frequency bands (delta, theta, alpha, beta, gamma), total power, relative band powers (defined as the power in a single band divided by the total power), and spectral entropy. Band power limits for the study were as follows: delta (0.2–3.7 Hz), theta (3.7–8.1 Hz), alpha (8.1–12.9 Hz), beta (12.9–30.5 Hz), and gamma (30.5–49.6 Hz).

The Anderson-Darling (AD) test for normality [see for instance Thode (2002)] is used to determine the degree of correspondence with the normal distribution before and after transformation. A $p$-value < 0.05 for this test would mean that the null hypothesis of normality is rejected at the 95% level. The results are also compared with the logarithmic transformation for band powers and total power, the logit ($\log(x/(1 - x))$) transformation for relative powers, and the Box-Cox transformation for all spectral measures. The latter was implemented by maximizing the $p$-value of the AD-test over a range of values for $\lambda_1$ and $\lambda_2$. 


The test-retest reliabilities of the spectral measures, quantified by Pearson correlations, were determined over the first six weeks of recording without transformation and after applying the various transformations. A paired-samples t-test was used to compare the average correlation before and after transformation to normality. Finally, the reliabilities were compared with those computed using nonparametric Spearman correlations.

2.3 Results

To illustrate the use of the transformation, we apply it to the empirical distributions of a number of qEEG measures in Sec. 2.3.1 and show that it achieves optimal agreement with the normal distribution. Sec. 2.3.2 contains a further illustrative application to a study of qEEG test-retest reliability.

2.3.1 Empirical example: EEG spectral data

Histograms of the five sets of band powers are presented in the left column of Fig. 2.2. All distributions are greatly skewed to the right. Taking the logarithm brings the distributions closer to normal, but some skew remains in the delta band, while skew is overcorrected in the alpha band (middle column of Fig. 2.2).

Significance values for the Anderson-Darling (AD) test for normality of band power data from this study, before and after taking the logarithm, are listed in Table 2.1. It is seen that, although taking the logarithm improves the normality of the data, agreement with the normal distribution is still poor especially for the alpha and delta bands. Results of the AD-test are also listed for total power, spectral entropy, and relative band powers before and after a logit transformation. Relative band powers are defined as the corresponding band power divided by the total power and indicated by ‘rel’. None of the untransformed relative band powers, and only three of the relative band powers transformed with the logit transformation, pass the normality test at the 0.05 significance level. No result is listed for spectral entropy, since it does not have a commonly used normalizing transformation.

Better results are obtained using the Box-Cox transformation, although relative alpha power still does not pass the normality test at the 0.05 significance level. The parameters $\lambda_1$ and $\lambda_2$ used in the transformations are listed in Table 2.2. For band powers and total power, the optimal values for $\lambda_1$ are all close to zero, confirming that the logarithmic transformation can improve the normality of these measures. However, better agreement with the normal distribution is reached when adding a constant ($\lambda_2$) before taking the logarithm. Judging
Figure 2.2: Histograms for band powers (indicated by P) corresponding to 193 eyes-closed EEGs of 32 healthy subjects recorded at the Cz electrode in a longitudinal study, giving the number of observations in each bin. Untransformed quantities are plotted in the left column, log-transformed data in the middle column, and data transformed with (2.7) in the right column. The symbol y represents the transformation function.
<table>
<thead>
<tr>
<th>Quantity</th>
<th>p-value</th>
<th>Quantity</th>
<th>p-value</th>
<th>Quantity</th>
<th>p-value</th>
<th>Quantity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>delta power</td>
<td>&lt; 2.2e-16</td>
<td>log delta</td>
<td>0.0039</td>
<td>deltaBC</td>
<td>0.99</td>
<td>deltaT</td>
<td>1</td>
</tr>
<tr>
<td>theta power</td>
<td>&lt; 2.2e-16</td>
<td>log theta</td>
<td>0.19</td>
<td>thetaBC</td>
<td>0.25</td>
<td>thetaT</td>
<td>1</td>
</tr>
<tr>
<td>alpha power</td>
<td>6.6e-09</td>
<td>log alpha</td>
<td>0.00061</td>
<td>alphaBC</td>
<td>0.056</td>
<td>alphaT</td>
<td>1</td>
</tr>
<tr>
<td>beta power</td>
<td>1.2e-15</td>
<td>log beta</td>
<td>0.34</td>
<td>betaBC</td>
<td>0.61</td>
<td>betaT</td>
<td>1</td>
</tr>
<tr>
<td>gamma power</td>
<td>&lt; 2.2e-16</td>
<td>log gamma</td>
<td>0.20</td>
<td>gammaBC</td>
<td>0.53</td>
<td>gammaT</td>
<td>1</td>
</tr>
<tr>
<td>total power</td>
<td>1.0e-10</td>
<td>log total</td>
<td>0.12</td>
<td>totalBC</td>
<td>0.26</td>
<td>totalT</td>
<td>1</td>
</tr>
<tr>
<td>entropy</td>
<td>3.6e-08</td>
<td></td>
<td></td>
<td>entropyBC</td>
<td>0.082</td>
<td>entropyT</td>
<td>1</td>
</tr>
<tr>
<td>rel delta</td>
<td>0.083</td>
<td>logit rel delta</td>
<td>0.34</td>
<td>rel deltaBC</td>
<td>0.71</td>
<td>rel deltaT</td>
<td>1</td>
</tr>
<tr>
<td>rel theta</td>
<td>1.5e-08</td>
<td>logit rel theta</td>
<td>0.69</td>
<td>rel thetaBC</td>
<td>0.95</td>
<td>rel thetaT</td>
<td>1</td>
</tr>
<tr>
<td>rel alpha</td>
<td>0.0030</td>
<td>logit rel alpha</td>
<td>0.0016</td>
<td>rel alphaBC</td>
<td>0.0080</td>
<td>rel alphaT</td>
<td>1</td>
</tr>
<tr>
<td>rel beta</td>
<td>2.4e-06</td>
<td>logit rel beta</td>
<td>0.31</td>
<td>rel betaBC</td>
<td>0.34</td>
<td>rel betaT</td>
<td>1</td>
</tr>
<tr>
<td>rel gamma</td>
<td>&lt; 2.2e-16</td>
<td>logit rel gamma</td>
<td>0.0024</td>
<td>rel gammaBC</td>
<td>0.37</td>
<td>rel gammaT</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2.1: Significance values for the Anderson-Darling test for normality applied to qEEG measures derived from 193 eyes-closed EEGs of 32 healthy subjects recorded at the Cz electrode in a longitudinal study. Absolute and relative band powers are tested before and after applying the commonly used transformations toward normality (logarithmic for absolute band powers; logit (log[x/(1 – x)]) for relative band powers). The second column is left blank for spectral entropy, for which no widely used transformation toward the normal distribution is known. All quantities are also tested after the Box-Cox transformation (2.2), indicated by a subscript BC, and after the transformation (2.7), indicated by a subscript T. The latter is seen to yield optimal agreement with the normal distribution.
from Table 2.1, Box-Cox performed slightly better than the logit transformation, and much better for relative gamma power.

In terms of normality, the transformation (2.7) does better than all other transformations; with this method, both the Kolmogorov-Smirnov (KS) test (see for instance Conover, 1971) and the AD-test for normality yield a $p$-value of 1 for all spectral measures.

The histograms resulting after applying (2.7) to band powers are plotted in the right column of Fig. 2.2. Note that, although all sets of band powers have the same distribution after transformation, differences between individuals are preserved because they are located in different parts of the distributions.

### 2.3.2 Test-retest reliability

One application of the methods outlined above is to test-retest reliability, which has been shown to improve with the normality of data when the original variables are highly skewed (Dunlap et al., 1994). Table 2.3 lists the average Pearson correlation coefficients for band powers, total power, and spectral entropy over the first six weeks of testing, with and without the relevant transformations. For comparison, Spearman rank correlations are also given.

It can be seen from Table 2.3 that transforming to normality improves test-retest reliability. Combining the results of Table 2.1 and Table 2.3 shows that the increase in correlation is not due only to the normality of the distributions, since log delta, log alpha, logit rel alpha, and logit rel gamma are significantly non-normal, but their test-retest reliabilities are comparable to those obtained after our transformation. A paired-samples t-test was used to compare the original correlations for all spectral measures investigated with those obtained using (2.7). This yielded $p = 0.013$, and the average correlation was increased from 0.59 to 0.64. The improvement tended to be most pronounced when the original variables were highly non-normal (e.g., delta and gamma power, and

<table>
<thead>
<tr>
<th>Quantity</th>
<th>$\lambda_1$</th>
<th>$\lambda_2$</th>
<th>Quantity</th>
<th>$\lambda_1$</th>
<th>$\lambda_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>delta power</td>
<td>0.0</td>
<td>-42.2</td>
<td>rel delta</td>
<td>0.55</td>
<td>-0.1</td>
</tr>
<tr>
<td>theta power</td>
<td>-0.35</td>
<td>18.3</td>
<td>rel theta</td>
<td>-0.25</td>
<td>0.1</td>
</tr>
<tr>
<td>alpha power</td>
<td>0.35</td>
<td>-10.2</td>
<td>rel alpha</td>
<td>0.75</td>
<td>0.0</td>
</tr>
<tr>
<td>beta power</td>
<td>-0.15</td>
<td>-0.6</td>
<td>rel beta</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>gamma power</td>
<td>0.0</td>
<td>-0.9</td>
<td>rel gamma</td>
<td>-0.29</td>
<td>0.0</td>
</tr>
<tr>
<td>total power</td>
<td>0.35</td>
<td>-100.0</td>
<td>entropy</td>
<td>2.75</td>
<td>-0.30</td>
</tr>
</tbody>
</table>

Table 2.2: Coefficients for the Box-Cox transformations (2.2) leading to optimal agreement with the normal distribution.
<table>
<thead>
<tr>
<th>Quantity</th>
<th>r (original)</th>
<th>r (log/logit)</th>
<th>r (Box-Cox)</th>
<th>r (normal)</th>
<th>( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>delta power</td>
<td>0.36</td>
<td>0.47</td>
<td>0.51</td>
<td>0.51</td>
<td>0.45</td>
</tr>
<tr>
<td>theta power</td>
<td>0.83</td>
<td>0.87</td>
<td>0.87</td>
<td>0.85</td>
<td>0.83</td>
</tr>
<tr>
<td>alpha power</td>
<td>0.85</td>
<td>0.88</td>
<td>0.88</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>beta power</td>
<td>0.73</td>
<td>0.78</td>
<td>0.79</td>
<td>0.78</td>
<td>0.77</td>
</tr>
<tr>
<td>gamma power</td>
<td>0.45</td>
<td>0.53</td>
<td>0.54</td>
<td>0.55</td>
<td>0.50</td>
</tr>
<tr>
<td>total power</td>
<td>0.61</td>
<td>0.72</td>
<td>0.71</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>entropy</td>
<td>0.29</td>
<td></td>
<td>0.35</td>
<td>0.38</td>
<td>0.36</td>
</tr>
<tr>
<td>rel delta</td>
<td>0.55</td>
<td>0.56</td>
<td>0.57</td>
<td>0.58</td>
<td>0.50</td>
</tr>
<tr>
<td>rel theta</td>
<td>0.79</td>
<td>0.78</td>
<td>0.78</td>
<td>0.77</td>
<td>0.75</td>
</tr>
<tr>
<td>rel alpha</td>
<td>0.61</td>
<td>0.63</td>
<td>0.62</td>
<td>0.60</td>
<td>0.53</td>
</tr>
<tr>
<td>rel beta</td>
<td>0.58</td>
<td>0.57</td>
<td>0.57</td>
<td>0.54</td>
<td>0.54</td>
</tr>
<tr>
<td>rel gamma</td>
<td>0.42</td>
<td>0.51</td>
<td>0.53</td>
<td>0.51</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Table 2.3: Average correlation coefficients for qEEG measures over six sets of eyes-closed EEGs recorded at weekly intervals at the Cz electrode. The second column gives Pearson correlations for the original, untransformed quantities, the third column refers to quantities transformed according to commonly used transformations (log for absolute power and logit for relative power), the fourth column to quantities transformed using the Box-Cox method, and the fifth column to quantities transformed according to \((2.7)\). The last column lists Spearman rank correlations. The third column is left blank for spectral entropy, which does not have a widely used normalizing transformation.

Relative gamma power). Spearman correlations were slightly lower on average than Pearson correlations after transformation to the Gaussian (reduced from 0.64 to 0.61, \( p = 0.0025 \)). After optimization, results for the Box-Cox transformation were very similar to those obtained using \((2.7)\) \( p = 0.25 \).

### 2.4 Discussion

We have derived a transformation of any given probability density as nearly as possible to the normal distribution. Results collectively equivalent to this transformation have been known in the technical statistics literature, but have made little or no impact in engineering or the behavioral, social, environmental, medical, physical or biological sciences, despite wide use of ad hoc transformations to achieve a similar outcome.

The transformation appears to be particularly useful for quantities for which no transformation is as yet known to improve agreement with the Gaussian, and for quantities that deviate strongly from normality. It provides a systematic
way of achieving normality, unlike the miscellany of ad hoc methods hitherto employed. It leads to better agreement with the Gaussian than any other method, including the Box-Cox (1964) transformation. Another advantage of the transformation is that the resulting distribution is symmetric, so that the mean coincides with the mode and the median, and there is a straightforward relation between quantiles and the standard deviation. This aspect, as well as the familiarity of the standard Gaussian form, is especially useful to facilitate comparing and interpreting differences between measured values. In addition, the method can be used to obtain distributions of any form, by taking the cumulative distribution function of the data, leading to a uniform distribution, and then applying the inverse CDF of the desired distribution.

In an illustrative example, the transformation was shown to improve the average test-retest reliability of qEEG parameters as measured by Pearson correlations, which confirms the findings of Dunlap et al. (1994). Pearson correlations after our transformation were slightly higher on average than nonparametric Spearman rank correlations. Test-retest reliability using our transformation was also comparable to that obtained using the logarithm for absolute power measures, and the logit transformation for relative band powers, but the advantage of the transformation described here is that it can also be applied to quantities for which no transformation is known to approximate normality. The test-retest reliability of quantities transformed with the Box-Cox method was comparable to that obtained with our transformation. However, the advantage of our method over the Box-Cox method is that it is much easier to implement, and does not involve laborious optimization of parameter values.

We stress that the transformation can be applied not only to EEG data, but to any non-normal data in neuroscience or other disciplines. There are many instances of such variables, and although the central limit theorem ensures that the average of many measurements of the same quantity will be approximately normally distributed, this argument does not hold in the study of test-retest reliability, which concerns separate measurements. Moreover, the distribution of values for different subjects does not necessarily tend to normal even if we compute averages of many different measurements for each subject. This is because measurements on different subjects constitute estimates of different quantities, whereas the central limit theorem governs the distribution of estimates of the same quantity.

As is the case for any transformation, applications should be chosen with care, since transforming to the Gaussian is not a panacea for problems arising from non-normality even if normality is an assumption of the relevant statistical test.

First, as always with empirical studies, one must minimize the presence of illegitimate observations by appropriate study design and careful collection of
data. Moreover, most tests make additional assumptions besides normality, such as independence and identical distribution of the observations, constancy of error variance, and/or a simple (linear) relation to predictor variables. If other assumptions besides normality are important one may look for compromise transformations that give weight to these properties.

For small sample sizes, the transformation may differ significantly from that in a repeat study, since the underlying distribution is incompletely represented in a small sample. This may complicate the comparison of results between studies. One solution is to use a single transformation based on the combined data sets, which is likely to render each partial distribution only approximately normal.

The power and specificity of a test for the comparison of means do not depend directly on normality of the samples after transformation. Rather, a suitable transformation should selectively increase the test statistic when the null hypothesis is false, and/or decrease it otherwise. Instead of using a normalizing transformation (which can help in some cases), one could apply bootstrapping techniques [see, e.g., Davison and Hinkley (1997)], or estimate improved confidence intervals for the t-test based on the first three moments of the empirical distributions (Zhou and Dinh, 2005). However, these are much more complex undertakings.

Thus, while it is not a cure for all ills, the transformation described here has possible applications in a wide range of statistical problems where a distribution of normal (or any other particular) form is desirable.
Chapter 3

Variability of model-free and model-based quantitative measures of EEG

Variable contributions of state and trait to the electroencephalographic (EEG) signal affect the stability over time of EEG measures, quite apart from other experimental uncertainties. The extent of intra-individual and inter-individual variability is an important factor in determining the statistical, and hence possibly clinical, significance of observed differences in the EEG. This study investigates the changes in classical quantitative EEG (qEEG) measures, as well as of parameters obtained by fitting frequency spectra to an existing continuum model of brain electrical activity. These parameters may have extra variability due to model selection and fitting. Besides estimating levels of intra-individual and inter-individual variability, we determine approximate time scales for change in qEEG measures and model parameters. This provides an estimate of the recording length needed to capture a given percentage of the total intra-individual variability. Also, if more precise time scales can be obtained in future, these may aid the characterization of physiological processes underlying various EEG measures. Heterogeneity of the subject group was constrained by testing only healthy males in a narrow age range (mean = 22.3 years, sd = 2.7). Resting eyes-closed EEGs of 32 subjects were recorded at weekly intervals over an approximately six-week period. Of these 32 subjects, 13 subjects had follow-up recordings spanning up to a year. QEEG measures, computed from Cz spectra, were powers in five frequency bands, alpha peak frequency, and spectral entropy. Of these, theta, alpha, and beta band powers were most reproducible. Of nine model parameters obtained by fitting model predictions to experiment, the most reproducible ones quantified the total power and the time delay between cortex and thalamus. About 95% of the maximum change in spectral parameters was reached within minutes of record-
ing time, implying that repeat recordings are not necessary to capture the bulk of the variability in EEG spectra likely to occur in the resting eyes-closed state on the scale of a year.

3.1 Introduction

The electroencephalogram (EEG) provides a noninvasive picture of brain electrical activity with a high temporal resolution of the order of milliseconds. As a clinical tool, it has been used successfully in a wide range of contexts, including characterizing sleep disorders, charting the effects of focal abnormalities and epilepsy, and as an aid in the diagnosis of dementia (Niedermeyer and Lopes da Silva, 1982). Applications to other disorders, such as attention-deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), and depression, have also been investigated.

Measures of EEG are influenced by state and trait contributions, and by factors such as instrumental noise and muscle artifact. Parameters obtained by fitting experimental frequency spectra to predictions from physiology-based models of EEG generation are also affected by the choice of model and fitting procedure, which may or may not provide an optimal and unique solution to the inverse problem. The relative contributions of state, trait, and noise determine the stability of the relevant parameters, which can be quantified by the amount of intra-individual variability. It is essential to know the normal amount of intra-individual variability when determining whether an observed difference between two measurements of the same individual is statistically significant. This in turn may help to estimate the clinical significance of the difference.

As a vast amount of neuroscientific data is becoming available in standardized databases [see, e.g., Gordon et al. (2005)], candidate markers have emerged for many psychiatric disorders. The specificity of such markers is important in the context of increasingly personalized medicine. Standardization of selection criteria and acquisition methods allows reliable extrapolation of reproducibility and stability findings to individuals within the same database.

Reproducibility, as defined here, depends on the relative amounts of intra-individual and inter-individual variability. Parameters for which the ratio of intra-individual variation to group variation is small distinguish better between individuals than parameters for which this ratio is large. Reproducible parameters are likely to be less affected by noise than others, although they may also have a relatively large variable component due to trait as opposed to state. To estimate the relative contributions of state, trait, and noise, it is therefore necessary to quantify both intra-individual and inter-individual variability. This information is complementary to independent measures, such as
correlations with direct physiological measurements, which are not the topic of the current paper. The physiological interpretation of the particular model parameters used here was investigated in detail in Robinson et al. (2004) and related works, including testing for consistency with independent estimates.

Previous work by a number of authors has investigated the variability of the EEG. A sample of these studies reveals a great diversity in focus, study design, and analysis. Results are greatly dependent on whether the variability is compared to the mean, to the variation in the population (as with correlation coefficients), or is taken as a raw quantity. Oken and Chiappa (1988) measured the degree of short-term variability in eyes-closed EEG spectra of adults aged 17–75 years, and found median frequency and peak power frequency to be more stable than absolute or relative band powers (band power divided by total power), where the frequency bands were delta (1.5–4 Hz), theta (4.25–8 Hz), alpha (8.25–13 Hz), beta_1 (13.25–20 Hz), beta_2 (20.25–32 Hz), and total (1.5–20 Hz). Hawkes and Prescott (1973) studied the influence of visual tasks on intra-individual EEG variability, which did not appear to have a significant effect. For 27 subjects (16 males, 11 females) in the age range 19–59 years, they found EEG variability to be independent of both age and sex. Matoušek and Petersén (1973) determined coefficients of variation for differences between individuals and within individuals in recordings of children and adolescents aged 1–21 years. Intra-individual variability was found to be highest in the alpha bands (7.5–12.5 Hz) and lowest in the beta_1 band (12.5–17.5 Hz). Like Hawkes and Prescott, Matoušek and Petersén found EEG intra-individual variability to be largely independent of age, while inter-individual variability was smaller in younger subjects. Gasser et al. (1985) and Salinsky et al. (1991) compared within-test to between-test reliability of broad-band spectral parameters using rank correlations. Both studies revealed within-session reliability to be higher than between-session reliability in all bands and at various sites. According to Gasser et al., reproducibility of spectral parameters varied across frequency bands, but not so much across electrodes, while Salinksy et al. found reliability to be generally lower at the T3 and T4 sites. Fein et al. (1983) computed intraclass correlations (Winer, 1971) for absolute and relative band powers in the eyes-open and the eyes-closed conditions; both showed good reliability, which was comparable for absolute and relative power measures. A more thorough overview of the existing literature is given in the Discussion.

Aging is one possible cause of changes in the EEG. Various studies have shown the high-frequency content of the background EEG to increase with age in healthy subjects (Duffy et al., 1984; John et al., 1980; Matoušek and Petersén, 1973) with a concurrent decrease in low-frequency activity (Duffy et al., 1984). Disease or brain damage, on the other hand, tends to shift the alpha peak to lower frequencies (John, 1977). Overall EEG amplitude has been
observed to be inversely related to age (Matousek et al., 1967). To control the
effect of age as a confounding factor, we restrict our study to a limited age range
of 18–28 years. The EEG is expected to show little systematic development in
this age range, due to the slowing down of changes in brain electrical activity
in late adolescence to early adulthood (Matousek and Petersén, 1973).

On shorter time scales, changes in brain electrical activity may occur due
to external stimuli, drowsiness, or changes in attention or processing. All this
occurs in an interplay with local or global changes in blood flow and neuro-
transmitter levels. In addition, various factors contribute to uncertainty in the
data, most notably muscle activity, head movement, imperfect calibration, and
loss of data due to digitization. We can classify these sources of changes in the
EEG into controlled (i.e., fixed or manipulated) variables, such as sex, age, or
attention; and uncontrolled (i.e., unmeasured or random) variables, including
instrumental noise and head shape. Of course, variables that are controlled in
one study may be sources of noise in another study.

<table>
<thead>
<tr>
<th>Sources of Variability</th>
<th>Controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static</strong></td>
<td>Sex</td>
<td>Genotype</td>
</tr>
<tr>
<td><strong>Slow (years)</strong></td>
<td>Montage</td>
<td></td>
</tr>
<tr>
<td><strong>Slow - Medium (months)</strong></td>
<td>Age</td>
<td>Chronic anxiety</td>
</tr>
<tr>
<td><strong>Medium (days)</strong></td>
<td>Menstrual cycle</td>
<td>Seasonal changes, Chronic anxiety</td>
</tr>
<tr>
<td><strong>Medium - Fast (hours)</strong></td>
<td>Diurnal rhythm</td>
<td>Ultradian rhythms, Calibration drift</td>
</tr>
<tr>
<td><strong>Fast (minutes)</strong></td>
<td>Caffeine intake</td>
<td>Arousal</td>
</tr>
<tr>
<td><strong>Very fast (seconds)</strong></td>
<td>Attention</td>
<td>Instrumental noise, Muscle artifact</td>
</tr>
<tr>
<td></td>
<td>of primary cortex</td>
<td>Brain microstates</td>
</tr>
</tbody>
</table>

Table 3.1: Controlled (fixed or manipulated) and uncontrolled (random)
 sources of variability in the EEG on various time scales, and including fac-
tors contributing to intra-individual as well as inter-individual variation. A
variable that is controlled in one study may be uncontrolled in another; for in-
stance, while seasonal changes may be easily controlled in a short-term study,
they were uncontrolled in the present study, which ran over approximately a
year. The classification shown here corresponds to the present study.

An overview of controlled and uncontrolled factors associated with changes
in the EEG on various rough time scales is presented in Table 3.1. Of these,
some contribute to within-subject variability (e.g., attention and brain mi-
crostates), others to between-subject variability (e.g., genotype and sex). Most factors contribute to both types of variability. The significance of the time scales of the various uncontrolled sources of variability is that they affect the amount of variability in a recording. For example, a brief recording will have uncertainty due only to instrumental noise, muscle artifact, and multiple microstates, while a recording (or set of recordings) covering a longer span of time will have additional sources of variance. Of course the advantage of longer recordings is usually that the greater volume of data allows for more precise statistical estimation. Balancing these factors is part of experimental design, but this is rarely done quantitatively.

The aim of the current study is to investigate the variability of spectra both in the ‘classical’ way [qEEG; for an early review see Duffy et al. (1994)] and with reference to a recent physiology-based quantitative model of EEG generation. We reiterate that we focus on stability and reproducibility and that the physiological interpretation and consistency of the model parameters, which were investigated in detail for instance by Robinson et al. (2004); Rowe et al. (2004b), is not at issue in this study.

The comparison between the reproducibility of qEEG measures and that of model parameters provides a valuable testing ground for the utility of the model. There is no reason to assume that model parameters have a larger component of state as opposed to trait than qEEG measures, especially if we compare model parameters and qEEG measures that have a straightforward relation (we will see below that our model has a parameter which is directly related to alpha peak frequency, and one that reflects the total spectral power). Therefore, if the model is a complete and accurate description of the processes responsible for EEG generation, and if the model parameters can be uniquely fitted without being greatly affected by noise in the spectra, we expect reproducibility of model parameters to be comparable to that of qEEG measures.

Besides estimating overall levels of variability of qEEG measures and model parameters, we consider variability as a function of the time interval between recordings. This allows us to compute approximate characteristic time scales for variability in the various spectral measures, which may be related to underlying processes in future work, using in particular the relationship between the model parameters and brain physiology suggested by our model of EEG generation.

Elaborating on previous work by a number of researchers (Freeman, 1975; Jirsa and Haken, 1996; Lopes da Silva et al., 1974; Nunez, 1974a, 1995; Steriade et al., 1990; Wilson and Cowan, 1973; Wright and Liley, 1996) the model provides a large-scale continuum representation of corticothalamic dynamics by averaging neural properties over a few tenths of a millimeter. Biophysical properties included in the model are rise and decay rates of the potential at the soma, synaptic strengths, nonlinear responses to cell-body potential, axonal ranges
and transmission speeds, connectivities between excitatory and inhibitory neural populations in cortex and thalamus, and volume conductivity through the cerebrospinal fluid, skull, and scalp. The model, its steady states, parameter dependences, effects of feedback, and behavior in many regimes have been described and investigated in detail by Robinson et al. (1997, 1998a, 2001b, 2002, 2003a,b, 2004, 2005), Rennie et al. (1999), and Rowe et al. (2004a). A brief overview is given in Sec. 3.2.3.

3.2 Methods

The study design was longitudinal, following all subjects over a period of about six weeks at approximately one-week inter-test intervals, and some subjects another three or four times over the course of a year. This was done to compare intra-individual variability over time with the inter-individual variation in the population. Consistent time and age trends were expected to be minimal due to the limited age range and duration of the study, and variability to consist mainly of fluctuations around some mean value for each subject.

3.2.1 Subjects

All 32 subjects were healthy males with an age at the first session in the range of 18 to 27 years (mean = 22.3, sd = 2.7) selected from the Brain Resource International Database (BRID) (Gordon et al., 2005). To control sources of variation in the sample, a number of criteria precluded participation in the study: brain injury, a personal or family history of mental illness, psychological, psychiatric, neurological, or genetic disorders, a personal history of heavy drug or alcohol use, a personal history of cancer or a serious medical condition related to thyroid or heart, a blood-borne illness, or a serious impediment to vision, hearing, or hand movement. In addition, participants in the present study were right-handed, non-smokers, had a mass of 65–95 kg, had no previous exposure to stimulant medication, had not been taking any prescribed medications on a regular basis in the months prior to study entry (except antibiotics, which were completed at least two weeks before the start of the study), and tested negative for illicit drug use at the outset. Participants were also asked to refrain from caffeine consumption for at least three hours before testing, and to forego alcohol for at least 24 hours prior to testing.

3.2.2 EEG recording and quantification

All subjects underwent six consecutive weeks of testing, of which 13 subjects were retested after intervals of three to four months over the course of approx-
imately a year. Allowing for drop-outs, this gave us 208 recordings at intervals of 1–71 weeks. Half of the subjects were tested at Westmead Hospital in Sydney, the other half at Queen Elizabeth Hospital in Adelaide. To limit the effect of diurnal variations, the EEG was recorded at the same hour of day every session, chosen to be between 9 and 10 am for subjects to be awake and non-drowsy. Eyes-closed resting scalp EEG was recorded with a NuAmps amplifier (Neuroscan) at 26 electrode sites according to an extended International 10–20 system at a sampling rate of 500 Hz with average of mastoids as reference. Only the Cz electrode was used in the present analysis, since it is the least affected by muscle artifact. Subjects were seated in a sound and light attenuated room at a constant temperature of 24°C. Skin resistance was less than 5 kΩ. The electro-oculogram was recorded at four channels to correct offline for vertical and horizontal eye movements according to the method of Gratton et al. (1983). Corrected data were low-pass filtered at 40 dB per decade above 100 Hz. Power spectra for the Cz electrode were computed from two minutes of EEG by multiplying sequential 2.048 s epochs by a Welch window and performing a Fast Fourier Transform with 0.49 Hz resolution.

The following qEEG measures were computed from spectra: (i) band powers: delta (0.2–3.7 Hz), theta (3.7–8.1 Hz), alpha (8.1–12.9 Hz), beta (12.9–30.5 Hz), and gamma (30.5–49.6 Hz). These frequency limits were chosen as the midpoints between frequencies at which the power spectral density was computed (each 0.49 Hz); (ii) total power: the sum of the five band powers; (iii) alpha peak frequency, defined to be that frequency at which the power was maximal; and (iv) spectral entropy (Shannon, 1948a, b), defined as

$$H(p_1, p_2, \ldots, p_N) = -\frac{1}{\ln N} \sum_{i=1}^{N} p_i \ln p_i,$$  \hspace{1cm} (3.1)

where $i$ is a frequency index, $N$ the total number of frequency bins, and $p_i$ is the spectral density, normalized by dividing by the total power. The combination of the natural base for the logarithm and the prefactor $1/\ln N$ is chosen so that the entropy obeys $H(1/N, \ldots, 1/N) = 1$, which provides a normalization for the case of equiprobable frequencies (i.e., a flat spectrum).

The spectral entropy is a measure of the structure of the spectrum. It is greater when power is distributed evenly over a large range of frequencies than when power is concentrated mainly in a few peaks. This corresponds with the intuitive meaning of entropy as a measure of the number of active degrees of freedom in a system, since a lower spectral entropy implies a more limited range of frequencies at which the energy of the system resides. The power is thus interpreted as a probability that the energy of the system is concentrated at a certain frequency. Normalization ensures that the entropy depends only on the shape of the spectrum, and not on the total power. It
should be noted that the frequencies at which the peaks occur do not matter. Hence, spectral entropy does not say anything about the relative amounts of fast and slow activity. The entropy changes with the degree of activation of the brain, being generally lower with increased drowsiness, but the relationship is not completely straightforward (Jantti et al., 2004). Inouye et al. (1991) noted an increase in spectral entropy mainly in the left hemisphere relative to the resting condition when subjects performed mental arithmetic.

3.2.3 Theoretical model

The components described by our physiology-based mean-field model of EEG generation are excitatory and inhibitory neurons in the cerebral cortex, excitatory specific relay neurons in the thalamus, and the neurons of the thalamic reticular nucleus, which have an inhibitory effect on their targets. In addition, the model allows for input $\phi_n$ to the thalamus from underlying neural structures, which in the present study was set to have a constant modulus and a random phase in the Fourier domain, corresponding to spatiotemporal white noise. The connections between components are as shown in Fig. 3.1, where $\phi_a$ ($a = e, i, n, r, s$) symbolizes the relevant firing rate field. Long-range corticothalamic connections are excitatory in nature, while inhibitory feedback occurs internally within the cortex and thalamus. Gains are represented in Fig. 3.1 by pairs of letters, the first of which refers to the receiving neural population, while the second refers to the type of incoming neurons.

The first equation of the model relates the mean firing rate $Q_a(r, t)$ of each population of neurons to the cell-body potential $V_a(r, t)$ relative to resting:

$$Q_a(r, t) = S[V_a(r, t)],$$

(3.2)

with $a = e, i, r, s$. Here, $r$ parameterizes the cortex, which is approximated as two-dimensional owing to its relative thinness. The function $S[V_a(r, t)]$ has a sigmoidal shape that results from averaging over a large number of step functions representing different threshold responses. It increases smoothly from 0 to the maximum attainable firing rate $Q_{\text{max}}$ (~250 Hz) as $V_a$ runs from $-\infty$ to $\infty$, and takes the specific form

$$S(V_a) = \frac{Q_{\text{max}}}{1 + \exp[-(V_a - \theta)/\sigma']}$$

(3.3)

where $\theta$ is the mean threshold potential, and $\sigma'\pi/\sqrt{3}$ is the standard deviation of the distribution of firing thresholds in the neural population.

The cell-body potentials $V_a$ are made up of contributions from all afferent neurons, whose inputs drive synaptic changes that result in signals that propagate down the dendritic tree. The effect of a given incoming firing rate field $\phi_b$
Figure 3.1: Schematic representation of the model components and their interconnections: $e =$ cortical excitatory, $i =$ cortical inhibitory, $s =$ specific relay, $r =$ thalamic reticular. Input from underlying structures is represented by $\phi_n$. 

The cell-body potential of target neurons of type $a$ depends on the number of synapses from afferent axons onto dendrites of the target population ($N_{ab}$), as well as the typical change in cell-body potential per unit input ($s_{ab}$). The dendritic tree and synapses act in effect as a low-pass filter that attenuates high-frequency activity due to differential delays for signals traveling through them. We use an analytic form for the synaptodendritic filter function which has been found to conform closely to experimental observations (Freeman, 1991; Rennie et al., 1999). This leads to (Robinson et al., 1997, 2004)

$$D_a(t)V_a(r, t) = \sum_b N_{ab}s_{ab}\phi_b(r, t - \tau_{ab}),$$

$$D_a(t) = \frac{1}{\alpha \beta} \frac{d^2}{dt^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta}\right) \frac{d}{dt} + 1.$$  

Here, $\tau_{ab}$ represents any discrete time delay for signals to travel from neurons of type $b$ to neurons of type $a$. As an approximation, the discrete time delays for signals traveling between neural populations are taken to be zero locally within the cortex and thalamus. The only nonzero $\tau_{ab}$ are therefore $\tau_{es} = \tau_{se} = \tau_{re} = t_0/2$, with $t_0$ the time necessary to complete a full loop through cortex and thalamus. The inverse rise and decay times for the potential at the soma due to dendritic propagation and temporal smoothing are represented by $\beta$ and $\alpha$, respectively. In practice, we set $\alpha = \beta/4$ in rough agreement
with experiment (Rowe et al., 2004a), to reduce the number of independent parameters and hence the robustness of those that are independently fitted. The product $N_{ab} s_{ab}$ times the derivative of the sigmoid (3.3) at the steady-state value of the potential, $V_a^{(0)}$, results in a set of gains,

$$G_{ab} = \rho_a N_{ab} s_{ab},$$  \hspace{1cm} (3.6)

$$\rho_a = \left. \frac{dQ_a(r,t)}{dV_a(r,t)} \right|_{V_a^{(0)}},$$  \hspace{1cm} (3.7)

which characterize the connection strengths between neural populations.

The final aspect of the model is axonal propagation that spreads electrical activity within the cortex, and can be approximated by a damped-wave equation with source $Q_a(r,t)$ (Robinson et al., 1997, 2004),

$$\frac{1}{\gamma_a^2} \left[ \frac{\partial^2}{\partial t^2} + 2\gamma_a \frac{\partial}{\partial t} + \gamma_a^2 - v_a^2 \nabla^2 \right] \phi_a(r,t) = Q_a(r,t).$$  \hspace{1cm} (3.8)

Here, $\nabla^2$ is the Laplace operator, representing a second-order spatial derivative. The damping rate $\gamma_a = v_a/r_a$ is the ratio of the average axonal transmission speed $v_a \approx 10$ m/s and characteristic axonal range $r_a$. In the local inhibition approximation (Robinson et al., 1998a), all inhibitory axons are taken to be short enough to justify setting $\gamma_i = \gamma_r = \infty$. Furthermore, local excitatory connections within the thalamus are assumed short enough to set $\gamma_s = \infty$, so that the corresponding equations simply become

$$\phi_{i,r,s}(r,t) = Q_{i,r,s}(r,t).$$

From now on, we will refer to $\gamma_e$ as $\gamma$, the only spatial damping rate retained. We assume the EEG signal to be proportional to the cortical excitatory firing rate field $\phi_e$, since macroscopic cortical potentials are thought to arise from the activity of many long-range excitatory cortical neurons firing in synchrony. The calculation of the spectral power from $\phi_e$ is quite mathematically involved; for details see the Appendix. The effect of volume conduction on the resulting scalp potential is incorporated in Eq. (3.11) via a spatial smoothing function. For our present purposes, it suffices to give a brief description of the model parameters that are determined by fitting theoretically predicted spectra to experimental spectra.

In all, we fit eight physiological parameters representing aspects of brain function that are central to the generation of the EEG, in addition to an attenuating factor $p_0$, which represents filtering of the signal through cerebrospinal fluid, skull, and scalp [see Eq. (3.16)]. The time delay for signals to complete one full loop between cortex and thalamus via long-range excitatory connections is given by $t_0$. The quantities $\gamma$ and $\alpha$ are inverse time constants; $\gamma$ representing the average damping rate due to spreading cortical activity, and $\alpha$ the decay rate of the potential at the soma. The remaining five parameters are dimensionless gains; $G_{ee}$ representing the average connection strength
between excitatory neurons in the cerebral cortex, \( G_{ei} \) the average connection strength between short-range inhibitory cortical neurons and their excitatory target neurons, \( G_{ese} = G_{es}G_{se} \) the gain for the direct loop from the cortex to the specific relay nuclei of the thalamus and back to the cortex, \( G_{esre} = G_{es}G_{sr}G_{re} \) the gain for the same loop but passing through the reticular thalamic nucleus, and finally \( G_{srs} = G_{sr}G_{rs} \), the gain for the intrathalamic loop from specific relay nuclei through the reticular thalamic nucleus, and back to the relay nuclei. These are the only independent gains in our model. The gains depend on \( \theta \) and \( \sigma' \) [cf. Eqs (3.3) and (3.6)], but these are not determined separately. Approximate nominal values of the independently fitted model parameters are given in Table 3.2. The given parameter ranges are physiologically realistic, in agreement with independent estimates (Robinson et al., 2004).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_0 )</td>
<td>Delay time for the corticothalamic loop</td>
<td>( 0.06 ) – ( 0.13 ) s</td>
</tr>
<tr>
<td>( p_0 )</td>
<td>Logarithm of an overall multiplicative factor for the power</td>
<td>No limits*</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>Damping rate of action potentials in the axon</td>
<td>( 40 ) – ( 280 ) s(^{-1})</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>Inverse decay time of the cell-body potential</td>
<td>( 10 ) – ( 200 ) s(^{-1})</td>
</tr>
<tr>
<td>( G_{ee} )</td>
<td>Gain for interconnections between excitatory cortical neurons</td>
<td>( 0 ) – ( 20 )</td>
</tr>
<tr>
<td>( G_{ei} )</td>
<td>Gain for inhibitory cortical neurons synapsing on excitatory cortical neurons</td>
<td>( -35 ) – ( 1 )</td>
</tr>
<tr>
<td>( G_{ese} )</td>
<td>Product ( G_{es}G_{se} ), i.e., the gain of the direct corticothalamic loop</td>
<td>( 0 ) – ( 20 )</td>
</tr>
<tr>
<td>( G_{esre} )</td>
<td>Product ( G_{es}G_{sr}G_{re} ), i.e., the gain of the loop from cortex through the reticular thalamic nucleus, to the specific relay nuclei, and back to cortex</td>
<td>( -30 ) – ( 2 )</td>
</tr>
<tr>
<td>( G_{srs} )</td>
<td>Product ( G_{sr}G_{rs} ), i.e., the gain of the intrathalamic loop</td>
<td>( -15 ) – ( 0.5 )</td>
</tr>
</tbody>
</table>

Table 3.2: Description of the model parameters with the physiologically realistic ranges (Robinson et al., 2004) over which they were allowed to vary. * Although no limits were imposed on \( p_0 \), it is possible to calculate an approximate range in which \( p_0 \) is expected to fall, as shown in the Appendix.

### 3.2.4 Model fits

Parameter estimates were obtained by fitting the logarithm of the theoretical power spectral density, \( \log(P_{the}) \) to the logarithm of the experimental spectral density.
density, \( \log(P_{\text{exp}}) \). Taking the logarithm ensures that differences in power spectral density are weighted more or less equally at each frequency. Best fits were obtained by minimizing the \( \chi^2 \) error between \( \log(P_{\text{the}}) \) and \( \log(P_{\text{exp}}) \), defined as a sum over all frequencies indexed by \( i \), and weighted using the standard deviation \( \sigma_i \),

\[
\chi^2 = \sum_{i=1}^{N} \frac{[\log(P_{\text{exp},i}) - \log(P_{\text{the},i})]^2}{\sigma_i^2},
\]

(3.9)

using a Levenberg-Marquardt optimization (Press et al., 1992; Rowe et al., 2004a). Limits corresponding to the ranges in Table 3.2 were employed to keep parameters within physiologically realistic ranges. The stopping criterion was that \( \Delta \chi^2 \) be smaller than \( 10^{-5} \) for six successive iterations.

The fitting procedure led to the convergence of model parameters in 194 cases out of 208 (i.e., 93.3%). In the remaining 14 cases, no combination of parameters gave a prediction that was sufficiently close to the experimental spectrum for six successive iterations, even though these spectra were reasonably free of artifact. A single spectrum with \( \chi^2 = 584.1 \) was removed because visual inspection revealed a high level of artifact. This left 193 spectra for further analysis, of which \( \chi^2 \) ranged from 6.6 to 199.5 (mean = 49.3).

Some examples of fits to experimental spectra with varying goodness of fit for both the eyes-open and the eyes-closed state can be found in Rowe et al. (2004a).

### 3.2.5 Statistical analysis

The analysis consisted of four parts:

1. Means and standard deviations of qEEG measures and model parameters over all trials were computed, and distributions were plotted as histograms. Variability was split into components arising from intra-individual and inter-individual differences, by giving standard deviations due to both sources. Within-subject standard deviations were computed by adding the squared deviations from the mean for each person, then dividing by the number of degrees of freedom, which is the number of trials minus the number of subjects (i.e., \( 193 - 32 = 161 \)), and finally taking the square root. Between-subject standard deviations were computed to be the root mean square deviation of subject means from the mean of all observations. The total sum of squared deviations is composed of the within-subject and between-subject sums of squares.

Since skewness can reduce the test-retest reliability for otherwise normal data (Dunlap et al., 1994), all quantities were transformed towards the Gaussian with a method based on a transformation described by Rosenblatt (1952) for the following parts of the analysis (see Chapter 2). This method yields
the best possible agreement with the normal distribution starting from non-
normally distributed quantities, and can thus also be applied to quantities for
which no standard transformation is known to achieve approximate normality.

(2) Elaborating on intra-individual and inter-individual differences given
in Part (1), we calculated ratios of intra-individual to total sample variances,
which are related to the distinguishing power of parameters in the normal
population. The width of a subject’s distribution relative to the population
distribution determines the certainty with which we can conclude whether a
subject is an outlier on a given measure.

(3) We computed average Spearman rank correlation coefficients [see, e.g.,
Becker et al. (1988)] between spectral measures from the first six weeks at one-
week intervals. Trial-to-trial correlations were determined from 31 recordings
in Week 1, 25 in Week 2, 26 in Week 3, 23 in Week 4, 21 in Week 5, and 24
in Week 6. Correlation coefficients provide a direct estimate of the certainty
with which future parameter values can be predicted from measured values,
and also characterize the relative amounts of intra- and inter-individual dif-
fferences. Spearman rather than Pearson correlations were used because the
rank correlation is the same before and after transformation to the normal
distribution.

(4) Finally, we explored the time scales on which the bulk of the intra-
individual variation occurred, using the two widely different scales at our dis-
posal: seconds or minutes within trials, and weeks or months between trials.
This was done by computing average absolute intra-individual differences in
normalized qEEG measures and model parameters for spectra that were a cer-
tain number of weeks apart (Fig. 3.2), and between spectra from the same
trial separated by 30, 60, or 90 s. By normalizing the parameter distributions,
intra-individual variation was expressed as a fraction of the population
variance. An implicit assumption was that the amount of difference between
recordings depended only on the time interval, not on the date of recording
itself.

With each time scale is thus associated an average level of change in spectral
parameters, which is expected to increase with time up to a certain stage, and
then level off when the bulk of intra-individual variation has been sampled.
Such a relation between intra-individual differences and the time interval was
also noted by John et al. (1987) for intervals of one hour to 2.5 years. Different
quantities were expected to change on different time scales, depending on the
neural processes and noise contributions that determine them.

To equate levels of power and noise in spectra used to assess long-term
variability and spectra used to assess short-term variability, all spectra in this
analysis phase were computed from 30 s of EEG. For intervals of a week or
more, spectra were derived from the third 30 s epoch from each trial — the
epoch that was successfully fitted to the model in the highest percentage of cases. The use of such short epochs may result in slightly larger differences between spectra than would be obtained on the basis of longer recordings, although 40 or 60 s epochs were found by some authors to be not significantly more reproducible than 20 s epochs (Gasser et al., 1985; Möcks and Gasser, 1984).

Of 193 two-minute recordings, spectra for the first 30 s were successfully fitted to the model in 182 cases, in 178 cases for the next 30 s, in 188 cases for the penultimate 30 s, and in 181 cases for the final 30 s. The number of differences that could be derived was constrained by the number of subsequent spectra coming from the same trial, being $n = 485$ in number for spectra taken 30 s apart, $n = 328$ for spectra taken 60 s apart, and $n = 163$ for spectra 90 s apart.

All measures were transformed to the standard normal distribution for direct comparison of levels of variability. We then calculated median absolute differences in normalized quantities over the relevant time intervals. The median rather than the mean was used as an appropriate measure of central tendency for the highly skewed distributions of absolute differences.

To characterize the magnitude and to derive time scales for changes in the various quantities, we fitted average differences to curves of the form

$$\Delta(t) = c \left(1 - e^{-t/\tau}\right), \quad (3.10)$$
where $\Delta(t)$ is the median absolute difference between spectral parameters after a time interval $t$, $c$ is the asymptotic value of the median absolute difference, and $\tau$ is a time scale for change in the relevant parameter. In general, $c$ will be well determined from the asymptotic level of trial-to-trial differences, but $\tau$ will not be well determined unless it falls near one or the other end of the range of time scales. Still, the fits (3.10) constrain the possible values of $\tau$, which is useful for estimating the length of EEG trials that are likely to capture a certain percentage of the total intra-individual variability, for the design of longitudinal studies, and for relating EEG variability to underlying factors. Significance values for the goodness of fit to empirical differences were determined by computing the linear correlation between median absolute differences and the function (3.10).

The above measures of variability complement each other, together allowing in principle for: (i) estimation of the width of individuals’ distributions for qEEG measures and model parameters (ii) estimation of the certainty with which we can make predictions about future spectra (correlation coefficients); (iii) estimation of the discriminatory power of spectral measures in the normal population (ratios of intra-individual to population variances); (iv) estimation of the time scale on which changes in brain electrical activity occur, where different scales point to different underlying neural and noise processes (absolute differences as a function of time interval); (v) insight into the physiological sources of intra- and inter-individual variability in EEG (model parameters); and (vi) comparison between intra- and inter-individual variability in qEEG measures and physiologically based parameters.

### 3.3 Results

Presented here are the findings from the four stages of our statistical analysis: distributions of qEEG measures and model parameters, ratios of intra-individual variances to the total sample variances, trial-to-trial correlations, and intra-individual differences versus the time interval. None of the investigated measures showed a significant time trend over the duration of the study when correcting for multiple comparisons.

#### 3.3.1 Distributions

To give an idea of the level of variability in spectra across recordings, spectra for two subjects are plotted in Fig. 3.3. The two sets of spectra appear quite distinctive, especially in the alpha frequency range.

Quantitative analysis of variability in qEEG measures and model parameters shows more clearly the distinctiveness of individual spectra. Table 3.3 lists
means and standard deviations when all data are pooled, along with purely within-subject and between-subject standard deviations.

Frequency histograms for qEEG measures are plotted in Fig. 3.4, while Fig. 3.5 shows the distributions of fitted model parameters for the 193 spectra. It is seen that some parameters appear to reach a lower or upper boundary. For instance, the cortical excitatory gain $G_{ee}$ often has a value close to 0, while the gain for the direct corticothalamic loop, $G_{ese}$, is often close to 20. It was investigated whether this was due to constraints imposed during the fitting process, by fitting the model to eyes-closed Cz spectra of 100 healthy subjects recorded at Brain Resource, Sydney (http://www.brainresource.com) while allowing all gains to vary without bound. This resulted in a distribution of $G_{ee}$ very similar to that observed in the present study with bounds, having many values close to 0 but still none smaller than $-1$. We thus interpret $G_{ee} \geq 0$ as a physiological constraint rather than an artificial one imposed during the fitting routine. Similarly, $G_{ese}$ only exceeded 20 in 10% of cases, and was larger than 30 in only 4% of cases.

### 3.3.2 Ratios of intra-individual to sample variance

Proportions of the total variance accounted for by differences within subjects over time, for both untransformed quantities and quantities transformed toward the standard normal distribution (cf. Sec. 3.2.5), are summarized in Table 3.4. Of transformed qEEG measures, theta, alpha, and beta band power had the
Table 3.3: Means and standard deviations of measures derived from experimental and fitted spectra. The last two columns show the partitioning of the sum of squares into within-subject and between-subject contributions. The numbers of significant figures are chosen such that the standard deviation is reasonably small compared to the last significant digit in the mean (no larger than 25 times 10, 1, 0.1, 0.01, or 0.001, depending on the precision of the mean).

The lowest ratios of intra-individual variance to the total sample variance (17%, 19%, and 25%, respectively). The delta and gamma bands were less reliable with variance ratios of 49% and 53%, respectively, consistent with Gasser et al. (1985). The spectral entropy was the least reproducible of the investigated qEEG measures with variance ratio 62%.

The most distinguishing model parameter was $p_0$, which quantifies the total power, with a ratio of 44%. Least reproducible was the cortical inhibitory gain $G_{ei}$, with a variance ratio of 77%.

The above findings may be visualized using boxplots, one for each subject, juxtaposed with a boxplot for the whole group. This has the advantage of exposing differences between subjects, and shows that some subjects are more variable than others. Boxplots for theta power, spectral entropy, $p_0$, and cortical inhibitory gain $G_{ei}$ are shown in Fig. 3.6. Investigation of all sets of boxplots shows that a high level of variability on one measure does not imply
Figure 3.4: Histograms for qEEG measures, giving the number of occurrences versus the value of the measure for 193 spectra. Units for band powers are $\mu V^2$, the alpha peak frequency is given in Hz, and spectral entropy is dimensionless.

high variability on other measures.

3.3.3 Trial-to-trial correlations

Mean Spearman rank correlations between Week 1 and Week 2, Week 2 and Week 3, etc. are given in Table 3.4. It is seen that traditional qEEG measures generally predicted future values more accurately than fitted model parameters, theta, alpha, and beta power being the most reliable ($\rho = 0.83$, $\rho = 0.87$, and $\rho = 0.77$, respectively). These values are slightly higher than those reported by Gasser et al. (1985) for Cz spectra of children derived from 20 s of EEG taken approximately 10 months apart, but comparable to those they reported for the ‘best’ and ‘worst’ epoch within trials of 120 s. Their bands were defined
Figure 3.5: Histograms for model parameters, giving the number of occurrences versus the parameter value for 193 spectra. Corticothalamic delay parameter $t_0$ is measured in s, axonal and dendritic rates $\gamma$ and $\alpha$ in s$^{-1}$, and the other parameters are dimensionless.

as theta, 3.5–7.5 Hz; alpha$_1$, 7.5–9.5 Hz; alpha$_2$, 9.5–12.5 Hz; beta$_1$, 12.5–17.5 Hz; and beta$_2$, 17.5–25.0 Hz. According to their study, correlations for the 10-month interval were theta, 0.71; alpha$_1$, 0.77; alpha$_2$, 0.76; beta$_1$, 0.58; beta$_2$, 0.71; those within trials were theta, 0.87; alpha$_1$, 0.87; alpha$_2$, 0.86; beta$_1$, 0.88; beta$_2$, 0.85. We found an average rank correlation for the alpha peak frequency of $\rho = 0.67$, somewhat lower than the value of 0.82 reported by Gasser et al. after a 10-month interval. The relatively low correlations for gamma ($\rho = 0.50$) and delta band power ($\rho = 0.45$) suggest either more true variability or a higher level of artifact in these bands than in other bands. The value of $\rho = 0.45$ for the delta band is much lower than that found by Gasser et al. ($\rho = 0.61$ for 10-month intervals, $\rho = 0.71$ within trials), possibly due to the
Figure 3.6: Boxplots for each subject (left frames) and for the whole group (right frames), of (a) theta power, (b) spectral entropy, (c) overall power factor $p_0$, and (d) cortical inhibitory gain $G_{ei}$. The number of measurements per subject varies. Boxes represent the interquartile range, thick horizontal lines the median, and whiskers extend to the most extreme data points at a distance of no more than $1.5 \times$ the interquartile range from the box. Any observations that do not lie within the extent of the error bars are indicated by circles. The height of subjects’ boxplots compared to the height of the group boxplot gives an indication of the proportion of the overall variance that is accounted for by intra-individual differences. Ratios of intra-individual to sample variance were (a) 14%, (b) 68%, (c) 40%, and (d) 87%.
<table>
<thead>
<tr>
<th>Quantity</th>
<th>VR (original)</th>
<th>VR (transformed)</th>
<th>$\rho$</th>
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<tr>
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<td>0.45</td>
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<tr>
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<td>0.14</td>
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<tr>
<td>beta power</td>
<td>0.24</td>
<td>0.25</td>
<td>0.77</td>
</tr>
<tr>
<td>gamma power</td>
<td>0.58</td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td>total power</td>
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<td>0.33</td>
<td>0.70</td>
</tr>
<tr>
<td>alpha peak freq.</td>
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<td>0.37</td>
<td>0.67</td>
</tr>
<tr>
<td>entropy</td>
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<td>0.62</td>
<td>0.36</td>
</tr>
<tr>
<td>$t_0$</td>
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<td>0.52</td>
<td>0.56</td>
</tr>
<tr>
<td>$p_0$</td>
<td>0.40</td>
<td>0.44</td>
<td>0.53</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.80</td>
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</tr>
<tr>
<td>$\alpha$</td>
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<td>Model $G_{ee}$</td>
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<td>0.36</td>
</tr>
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<td>0.77</td>
<td>0.21</td>
</tr>
<tr>
<td>$G_{esc}$</td>
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<tr>
<td>$G_{srs}$</td>
<td>0.44</td>
<td>0.47</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Table 3.4: Ratios of intra-individual to sample variances for qEEG measures and model parameters, next to average Spearman rank correlations ($\rho$) between quantities from Week 1 and quantities from the following five weeks (cf. Sec. 3.3.3). Original quantities are given as well as those transformed to conform to the standard normal distribution (cf. Sec. 3.2.5). Rank correlations are the same for both, since all transformations were monotonically increasing. A low ratio of variances corresponds to a high correlation coefficient.

The fact that we employed a lower frequency limit for this band, yet in both cases delta power was found to be the least reproducible of band powers. The total power had a mean trial-to-trial correlation between that of the band powers ($\rho = 0.70$). The spectral entropy was the least reproducible with a mean rank correlation over the first six weeks of $\rho = 0.36$. This may be compared with the test-retest reliability of $\rho = 0.27$ found by Gasser et al. for a parameter counting the number of peaks in each spectrum. Kondacs and Szabó (1999) found an average trial-to-trial correlation after 25–62 months of 0.59 for the spectral entropy derived at 16 electrodes, but this was for frequencies up to 25 Hz.

Of model parameters, the corticothalamic delay parameter $t_0$ had the highest trial-to-trial correlation, $\rho = 0.56$. The overall power parameter $p_0$ ($\rho = 0.53$) and the gain for the loop passing through the specific relay nuclei and the reticular thalamic nucleus, $G_{esre}$ ($\rho = 0.50$) also showed relatively high
reproducibility. The least reliable was the cortical inhibitory gain, $G_{ei}$, with a low correlation of $\rho = 0.21$.

As can be seen in Table 3.4, especially for qEEG measures, there is a strong correspondence between ratios of intra-individual variance to total variance and correlation coefficients as measures of reproducibility. This is due to the absence of consistent parameter trends in the present study. Consistent time trends across the population would leave correlation coefficients unaltered, but would increase the proportion of the population variance accounted for by intra-individual differences.

### 3.3.4 Intra-individual differences versus time interval

Fits of median absolute trial-to-trial differences in normalized qEEG measures and model parameters to functions of the form (3.10) are shown in Figs. 3.7 and 3.8.

The exponential fit decreased the residual sum of squares for all measures except $\alpha$, $G_{sse}$, and $t_0$, for which the fit did not converge, because within-trial differences were at least as large as between-trial differences. However, for these quantities we were able to estimate $c$ by taking the mean of all between-trial differences. Asymptotic differences, times after which 95% of the variability in spectral parameters was reached, and $p$-values for the goodness of fit to curves of the form (3.10) are listed in Table 3.5. Since the linear correlation between median absolute difference and $c(1 - e^{-t/\tau})$ was not highly significant for most quantities, and since there is a gap in observations between the scales of minutes and weeks, the results should be taken as rough estimates. Nonetheless, Table 3.5 shows that all quantities changed on relatively short time scales of the order of minutes, suggesting that recordings of a few minutes suffice to capture the bulk of the variability in a subject’s EEG.

The high levels of asymptotic differences in delta power, spectral entropy, and the inhibitory cortical gain $G_{ei}$ should be compared with the level of differences expected for a completely random quantity following the standard normal distribution (0.95). Since this means that each subject’s distribution becomes as wide as the population distribution, these quantities cannot be used to distinguish between individuals after intervals of more than a week. On the other hand, the decay rate of the cell-body potential ($\alpha$), the parameter that quantifies the total power ($p_0$), and the gain for the intrathalamic loop ($G_{srs}$), all had asymptotic levels of trial-to-trial differences that were comparable to those of the three most reliable band powers, theta, alpha, and beta. Comparing with Table 3.4, we find that the ratios of intra-individual to sample variance are smaller for theta, alpha, and beta band power than for $\alpha$, $p_0$, and $G_{srs}$. The difference between these two measures of reproducibility arises because the current section considers intra-subject variability as a function of the time
Table 3.5: Values of the median difference in normalized qEEG measures and model parameters after long time intervals, with approximate time scales for change defined as the time after which 95\% of the asymptotic variability has been reached. Significance values in the rightmost column refer to correlations between data points and fits of the form $\Delta(t) = c \left(1 - e^{-t/\tau}\right)$, where $\Delta(t)$ is the median absolute difference between spectral parameters after a time interval $t$, $c$ is the asymptotic value of the median absolute difference, and $\tau$ is a time scale for change in the relevant parameter.
Figure 3.7: Median absolute differences in qEEG measures versus the time interval in seconds, with fits of the form (3.10), for which the parameters $c$ and $\tau$ are given. The shorter the time scale $\tau$, the more quickly a quantity fluctuates. The given estimates are only very approximate, and data points at intervals of $10^2 - 10^3$ s are needed in order to determine time scales more precisely. The number of significant figures for time scales is one fewer than the number shown. The higher the asymptotic difference level, the less predictable a quantity becomes after a period of time. For comparison, the median absolute difference predicted for a random quantity following the standard normal distribution is around 0.95.
Figure 3.8: Median absolute differences in model parameters versus the time interval in seconds, with fits of the form (3.10), for which the parameters \( c \) and \( \tau \) are given. For \( t_0 \), \( \alpha \), and \( G_{se} \) only the asymptotic difference level is given, since within-trial differences were at least as large as between-trial differences. Recordings at intervals of \( 10^2 - 10^3 \) s are needed to determine the time scales for fluctuations in parameters more precisely.

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interval between recordings, and because longer recordings were used for the analysis in Sec. 3.3.2.

We stress that the form of the function chosen for fitting is tentative, and that time scales cannot be determined precisely, since there is a large gap in observations for intervals of 100 s to $10^6$ s. Rather, we provide a bound to the possible time scales for changes in EEG parameters. Therefore, in order to arrive at more precise estimates, it will be necessary to consider recordings on intermediate time scales in future work.

3.4 Discussion

In order to estimate the significance of a difference in the electroencephalogram (EEG) between two recordings of the same individual, or between an individual’s recording and the population, one needs to know the normal amounts of variability within and between individuals.

Many factors influence the reproducibility of EEG spectra, including the choice of sample; the age range, health criteria, and the homogeneity or heterogeneity of the subject group. A heterogeneous sample may have higher test-retest correlations than a homogeneous sample due to larger inter-individual differences (Gasser et al., 1985). This may have reduced the correlations in the present study, where the subject group was purposely chosen to be homogeneous.

Longer recordings reduce the amount of intra-individual variability by averaging out noise, but only up to some point. Gasser et al. (1985) found an average improvement of 0.01 for absolute power and 0.02 for relative power correlations when using 40 or 60 s instead of 20 s epochs. Also according to Salinsky et al. (1991), correlation coefficients for 60 s epochs were slightly higher on average than coefficients based on 20 or 40 s epochs, in agreement with our finding that most, but not all, EEG variation is sampled within 20–40 s. Another reason for using short epochs is the difficulty of obtaining relatively artifact-free data over long time spans.

Factors such as the choice of electrodes and montage are also relevant. Fein et al. (1983) found reliability of measures to be lower for temporal than for central or parietal derivations, especially in high and low-frequency bands. Salinsky et al. (1991) reported a similar result, with the T3 and T4 electrodes being less reliable on average than other electrodes. It has been found that linked ear references lead to lower test-retest correlations than a vertex reference (Fein et al., 1983). However, a vertex reference could not have been used here since the signal at the Cz electrode was considered.

Reproducibility is also intimately linked to the parameters used to quantify the spectra. Low and high-frequency bands have been consistently found to
have higher intra-individual variability than intermediate bands (Fein et al., 1983; Gordon et al., 2005), in agreement with the findings in this study. Because reliability depends on the frequency, it will also depend on the band power limits employed, which differ from study to study. Similar considerations apply to determining the alpha peak frequency, for which different authors use different criteria. Comparisons between relative and absolute band powers have been inconclusive, with some authors reporting a higher reliability for absolute power (Fein et al., 1983), others a higher reliability for relative band powers (John et al., 1980), and yet others reporting very little difference between relative and absolute band powers (Salinsky et al., 1991). Gasser et al. (1985) noted a higher reliability of relative power in the beta band but not in other bands. For the present data set, we found week-to-week correlation coefficients to be lower for relative band powers than for absolute ones, except for the delta band, which showed a slight improvement. This confirms the results of Kondacs and Szabó (1999).

Finally, quantification of the reproducibility itself can be done in many ways, methods in the literature including coefficients of variation, Spearman or Pearson correlations, intraclass correlations (Winer, 1971), and average absolute or relative differences. These may be determined between epochs or trials separated by widely different time intervals, ranging from seconds to years. It is quite difficult to estimate the uncertainty in reproducibility values due to differences in methodology and quantification, except by comparing many different studies. The findings from our study are summarized in the following paragraphs.

In a comparison between model-free and model-based spectral parameters of EEG for healthy males in the age range of 18–28 years, model parameters derived from resting eyes-closed Cz spectra for 2 minutes of EEG had a test-retest reliability that was slightly lower than that of classical qEEG measures. Fitting to a theoretical model has the complication that no model can provide a perfect description of the brain and the measuring process, and hence not all aspects of experimental spectra will be perfectly represented. This may produce intra-individual variances that are slightly higher than would be predicted on purely physiological grounds. On the other hand, fitting to a model may capture those aspects of spectra that are relatively stable within individuals by averaging out noise components. Besides, it circumvents arbitrary band power limits, and captures information on spectral shape within bands. Table 3.4 shows that the first effect played a role in producing ratios of intra-individual to sample variances that were generally higher for model parameters than for qEEG measures.

Both for qEEG measures and model parameters, transformation towards the normal distribution using a broadly applicable new method (see Chapter 2)
decreased ratios of intra-individual to total sample variance when the original distribution was highly skewed, in agreement with the finding that certain skewed data have a lower test-retest reliability than non-skewed data (Dunlap et al., 1994). Spearman correlations and ratios of intra-individual to sample variance yielded very similar results due to the lack of time trends in the present study.

Some parameters quantifying the EEG spectra or model fits to spectra were more reproducible than others. The theta and the alpha band powers were the most reproducible band powers, followed by the beta band, and finally the gamma and delta bands, which tend to be most affected by electromyographic (EMG) and electrooculographic artifact, respectively. The alpha peak frequency also showed relatively good reproducibility, which increased slightly after rejection of cases where no clear alpha peak could be discerned (from $\rho = 0.67$ to $\rho = 0.74$). Spectral entropy had rather poor reproducibility, in line with its dependence on vigilance (a state, rather than a trait, parameter), although artifact in the delta and gamma bands may also play a role. Of the model parameters, the conduction delay between cortex and thalamus $t_0$, and the normalization of the signal $p_0$, had the highest trial-to-trial correlations. We attribute this both to the anatomical factors determining these parameters (distance between cortex and thalamus, amount of myelination of long-range axons, skull thickness), and to the relatively straightforward relation between these parameters and spectra. The corticothalamic delay parameter $t_0$ is directly related to the alpha peak frequency, since, in our model, the alpha peak is caused by a resonance between cortex and thalamus (Robinson et al., 2001b), and $p_0$ is directly related to the total power. The least reproducible model parameter was found to be $G_{ei}$, the inhibitory cortical gain. We hypothesize that this is partly due to the confounding of parameters by the fitting program in some cases, because simultaneously changing some pairs of parameters by complementary amounts leaves the spectrum virtually unchanged. Such cases would allow us to reliably fit only a combination of the parameters, rather than each parameter separately. The extent of this effect will be investigated in future studies.

In general, reproducibility was rather low for effective comparison between individuals or groups, certainly considering that results for the Cz electrode provide a rough upper limit for the reproducibility of spectral parameters at other electrodes due to the relative absence of muscle artifact. However, increasing the sample size can improve the power of group comparisons, while repeat recordings can replace the standard deviation of a subject’s score by the standard error of the mean.

Random variations increased with the time interval due to contributions from the extra sources of variability given in Table 3.1. Based on intra-
individual differences leveling off after intervals of increasing duration, as also reported by John et al. (1987) for intervals of an hour to 2.5 years, we fitted an exponential with a characteristic time scale to median absolute differences in spectral parameters. Because of a large spread in data points, as well as a large gap in observations on time scales between 1.5 minutes and 1 week, we have to be careful in interpreting our findings. For all investigated quantities, the bulk of the changes occurred with high certainty on time scales \( \gtrsim 1 \) min and \( \ll 1 \) week, and most probably on the scale of minutes. It is a characteristic of all physical systems (animate or inanimate) that fast changes arise from fast processes. Therefore, these relatively short time scales suggest that the variation was mainly caused by those factors in Table 3.1 that act on the scale of seconds or minutes: instrumental noise, muscle artifact, brain microstates, arousal, and attention. The latter two factors are especially implicated in fluctuations in the spectral entropy, since they act on the scale of minutes and have been linked to a broadening of the spectrum, corresponding to an increase in spectral entropy.

Our findings thus suggest that the total level of intra-individual variation in the resting (non-drowsy) eyes-closed EEG may be estimated using recordings of only a few minutes. To establish more precisely the time scales for change in different measures, recordings at intervals intermediate between a few minutes and a week will be required in future work, where it would also be desirable to increase the number of spectra at each interval length. Time scales could then be more effectively linked to physiological factors responsible for the EEG, aided by the physiological interpretations suggested by the model. Measures that have an asymptotic level of intra-individual differences that is comparable to that of a completely random quantity cannot be used to distinguish between individuals in the long run. This is the case for delta power, spectral entropy, and the cortical inhibitory gain \( G_{ei} \) in the current version of the model and fitting routine.

The spatial aspects of the model and fitting routine are being adapted to allow for multi-electrode fits, and hence to increase the amount of information that can be extracted from spectra recorded at multiple sites. This will involve modeling volume conduction and neural projection effects across the cortex, thus providing a relation between spectra at different sites. Besides leading to an improved understanding of the physiological processes responsible for the EEG, this is expected to enhance our ability to distinguish between individuals, and between normal and clinical groups, on the basis of model fits to measured cortical electrical activity. We expect that use of the methods outlined above in more extensive studies that encompass larger numbers of recordings at more diverse time scales, will greatly enhance our knowledge and understanding of the extent and sources of variability in the EEG.
Appendix

The power as a function of angular frequency $\omega = 2\pi f$ can be calculated after Fourier transformation of the relevant quantities, as follows (Robinson et al., 2001b),

$$P(\omega) = \iint |\phi_e|^2 \exp[-k^2/k_0^2] d^2k$$

$$= |\phi_n|^2 \frac{G_{es}LP}{1 - G_{ei}L} \iint \frac{\exp[-k^2/k_0^2]}{|k^2r_e^2 + q^2r_e^2|^2} d^2k,$$

$$= \frac{\pi |\phi_n|^2}{r_e^2} \frac{G_{es}LP}{1 - G_{ei}L} \frac{\text{Im}[\exp(q^2/k_0^2)E_1(q^2/k_0^2)]}{\text{Im} q^2r_e^2}.$$  \(3.11\)

Here, the factor $\exp[-k^2/k_0^2]$ is a smoothing function chosen to represent volume conduction through cerebrospinal fluid, skull, and scalp [see Robinson et al. (2001b)]. The exponential integral function, $E_1$, is given by (Abramowitz and Stegun, 1970)

$$E_1(z) = -\gamma - \ln z - \sum_{j=1}^{\infty} \frac{(-z)^j}{jj!}.$$  \(3.12\)

for $|\arg z| < \pi$, where $\gamma = 0.5772\ldots$ is Euler’s constant. The quantity $L$ is the dendritic filter function given by

$$L = (1 - i\omega/\alpha)^{-1}(1 - i\omega/\beta)^{-1},$$  \(3.13\)

with $\alpha$ the decay rate and $\beta$ the rise rate for the potential at the soma. The symbol $P$ represents the contribution of external input to the subcortical firing rate field,

$$\phi_s = P\phi_n + S\phi_e$$

$$P = \frac{LG_{sn}}{1 - L^2G_{srs}} \frac{e^{i\omega t_0/2}},$$

$$S = \frac{LG_{se} + L^2G_{sr}G_{re}}{1 - L^2G_{srs}} e^{i\omega t_0}.$$  \(3.14\)

Using the above expression for $S$, the quantity $q^2r_e^2$ can be written as

$$q^2r_e^2 = \left(1 - \frac{i\omega}{\gamma_e}\right)^2 - \frac{G_{ee}L + G_{es}LS}{1 - G_{ei}L}.$$  \(3.15\)

This notation is used for consistency with previous work.

The model parameter $p_0$ is contained in Eq. (3.11) through

$$P(\omega) = \frac{10^{p_0}}{G_{sn}^2} \left| P \frac{L}{1 - G_{ei}L} \right|^2 \frac{\text{Im}[\exp(q^2/k_0^2)E_1(q^2/k_0^2)]}{\text{Im} q^2r_e^2}.$$  \(3.16\)
where the conversion between theoretical and empirical power is achieved by setting $1 \mu V^2 \text{ Hz}^{-1} \text{ m}^{-2} \equiv 1$. In other words, $p_0$ is the logarithm of the dimensionless version of

$$10^{p_0} = \frac{G^2 \sigma^2 \pi |\phi_n(\omega)|^2 \mu V^2}{r_e^2 \text{ Hz}}, \quad (3.17)$$

with $r_e$ in m. Using Parseval’s theorem,

$$\int_{-\infty}^{\infty} |f(t)|^2 \, dt = \int_{-\infty}^{\infty} |F(\omega)|^2 \, d\omega,$$

where $F(\omega)$ is the Fourier transform of $f(t)$, we can infer that, on average, fluctuations in $|\phi_n(\omega)|^2$ (which is dimensionless) are of the same order as those in $|\phi_n(t)|^2$ (in s$^{-2}$). This allows us to calculate approximate bounds on $p_0$. Assume $|\phi_n(\omega)| \approx 1 - 10$, $G_{es} \approx 0.1 - 2$, and $G_{sh} \approx 0.1 - 2$. Then $p_0$ lies between about $-1.3$ and $5.9$, in agreement with the values in Fig. 3.5.

Continuous wavenumbers $k$ reflect a cortex without boundaries; in the bounded case, the power becomes a sum over a discrete set of wavenumbers. If $L_x$ and $L_y$ are the linear dimensions of a rectangular cortex, the power is

$$P(\omega) = |\phi_n|^2 \left[ \frac{G_{es} L_P}{1 - G_{ei} L_x L_y} \right]^2 \frac{(2\pi)^2}{L_x L_y} \sum_{m,n=-M,-N}^{M,N} \frac{e^{-k_{mn}^2 / k_0^2}}{|k_{mn}^2 r_e^2 + q^2 r_e^2|^2}$$

$$= |\phi_n|^2 \left[ \frac{G_{es} L_P}{1 - G_{ei} L_x L_y} \right]^2 \frac{4\pi^2}{L_x L_y} \left[ \frac{M N}{4} \sum_{m,n=1,1}^{M,N} \frac{e^{-k_{mn}^2 / k_0^2}}{|k_{mn}^2 r_e^2 + q^2 r_e^2|^2} + 2 \sum_{m=1}^{M} \frac{e^{-k_{m0}^2 / k_0^2}}{|k_{m0}^2 r_e^2 + q^2 r_e^2|^2} + 2 \sum_{n=1}^{N} \frac{e^{-k_{0n}^2 / k_0^2}}{|k_{0n}^2 r_e^2 + q^2 r_e^2|^2} + \frac{1}{|q^2 r_e^2|^2} \right], \quad (3.19)$$

where the discrete wavenumbers $k_{mn}$ are given by

$$k_{mn}^2 = (2\pi m/L_x)^2 + (2\pi n/L_y)^2, \quad (3.20)$$

and $p_0$ is the immediate analog to that in the continuous case (3.16). The form (3.19) with (3.20) is the one used in the present study, with $L_x = L_y = 0.5$ m. We used $M = N = 4$, so that fluctuations in the signal are taken into account over a scale of about 3 cm.

On top of the EEG spectrum, we model the EMG component by

$$P_{EMG}(\omega) = A_{EMG} \frac{(\omega/2\pi f_{EMG})^2}{[1 + (\omega/2\pi f_{EMG})^2]^2}, \quad (3.21)$$

such that the EMG component has a maximum proportional to $A_{EMG}$ at about $f_{EMG}$ (taken to be 40 Hz), and tends asymptotically to $\omega^2$ at low frequencies and to $\omega^{-2}$ at high frequencies. The total spectral power density is thus $P(\omega) + P_{EMG}(\omega)$. The quantity $A_{EMG}$ is fitted simultaneously with the other model parameters.
Chapter 4

Electrophysiology of the aging brain probed by inverse modeling of EEG spectra

The objective of this study was to investigate age-associated changes in physiologically-based EEG spectral parameters in the healthy population. Eyes-closed EEG spectra of 1503 healthy subjects aged 6–86 years were fitted to a mean-field model of thalamocortical dynamics. Parameters were synaptodendritic rates, cortical wave decay rates, gains, axonal delays for thalamocortical loops, and power normalizations. Statistical analysis with nonparametric methods yielded nonlinear trends across age, approximated as piecewise linear trends within the ranges 6–14, 14–20, and ≥ 20 years. Sex differences were also considered. Parameters changed most rapidly in childhood. Increases in cortical wave decay rate leveled off around age 20, which also marked the onset of increases in axonal delays after initial decreases. Most gains decreased in absolute value with age, as did power normalization. Axonal delays and gains showed small but significant sex differences. Inter-individual variability in most parameters peaked around adolescence. Trends in axonal delays are consistent with empirical changes in alpha peaks. Changes in power normalization reflect reduced spectral power. Regressive processes, including neuronal loss and synaptic pruning, may account for diminished power and gains. This study illustrates the feasibility of inverse modeling of EEG spectra as a noninvasive method for investigating large-scale corticothalamic dynamics, and provides a standard for future comparisons.
4.1 Introduction

Understanding the structural, chemical, and functional changes that accompany brain aging is one of the major goals of research in neuroscience. Structural changes are particularly rapid during childhood, slow down after adolescence, and appear to accelerate again in late adulthood. Although the morphological, chemical, and functional development of the human brain, as well as changes in the electroencephalogram (EEG), have been tracked extensively (Duffy et al., 1993; Gasser et al., 1988; Hartikainen et al., 1992; Kemper, 1994; Polich, 1997; Rossini et al., 2007; Thompson et al., 2000), knowledge of the specific processes underlying changes in the EEG across age is limited.

Growth and pruning processes affect the volumes of the cortical and subcortical gray matter, cerebral white matter, and the corpus callosum. Cortical gray matter volume increases up to adolescence and decreases thereafter, with regional differences in the age at which peak volume is reached (Giedd et al., 1999), although localized regressive processes occur already during childhood (Caviness et al., 1996). Cranial size increases up to age ~20, with growth continuing a few years longer in males than in females (Dekaban, 1977; Eichorn and Bayley, 1962), and cerebrospinal fluid volume is positively correlated with age (Gur et al., 1991; Sowell et al., 2002). The corpus callosum grows considerably between the ages of 3 and 11 years and more slowly up to 15 years (Thompson et al., 2000). Ongoing myelination increases the white matter content of various cortical and other brain areas throughout childhood (Barnea-Goraly et al., 2005; Perrin et al., 2008; Sowell et al., 2004). The steady decrease in brain volume after adolescence appears to become more severe after about 60–70 years (Haug, 1987; Scahill et al., 2003). Although reductions in brain volume were traditionally attributed to neuronal loss, later studies with improved methodology have largely failed to reveal loss of hippocampal or neocortical neurons with age, and have instead attributed decreased brain volume to shrinkage of neurons (Peters, 2002a; Rapp and Gallagher, 1996; Rasmussen et al., 1996). An exception is Pakkenberg and Gundersen (1997), who reported a loss of about 10% of neurons in the neocortex of both males and females between age 20 and 90. Although some authors have reported white matter volume to be relatively stable compared to gray matter volume (Passe et al., 1997; Sullivan et al., 2004), others have found white matter volume reductions from about age 50 (Ge et al., 2002; Miller et al., 1980). According to a recent study, white matter shows much greater reductions than gray matter between the ages of 46 and 92 (Piguet et al., in press).

Besides the neocortex, areas of the hippocampus, amygdala, hypothalamus, cerebellum, and brainstem lose neurons with age (Kemper, 1994). Small numbers of neuritic plaques and neurofibrillary tangles, characteristic of Alzheimer’s disease, accumulate even in normal aging (Morrison and Hof, 1997; Tomlinson
et al., 1968). Often, advancing age is further accompanied by reductions in cerebral perfusion, oxygen consumption, and glucose utilization (Kuhl et al., 1982; Pantano et al., 1984; Zemcov et al., 1984), although a lack of change in the metabolic rate for glucose was reported for instance by Duara et al. (1983).

There are also important age-related changes in chemical signaling. Cholinergic (Gallagher and Colombo, 1995) and dopaminergic (Suhara et al., 1991; Volkow et al., 2000) systems show notable reductions in activity. Although no decline in serotonin (5-hydroxytryptamine) levels has been observed in studies in rats or humans, the number of serotonin receptors is reduced with age, and the serotonin turnover rate is increased (McEntee and Crook, 1991).

There are sex differences in brain anatomy and chemistry, and in certain aspects of brain development (Coffey et al., 1998; Cosgrove et al., 2007; de Bellis et al., 2001). Female brains have smaller volumes and approximately 16% fewer neocortical neurons at any age than male brains (Caviness et al., 1996; Dekaban and Sadowsky, 1978; Haug, 1987; Pakkenberg and Gundersen, 1997). However, many studies have reported more substantial age-related atrophy or reductions in brain volume in men than in women (Coffey et al., 1998; Cowell et al., 1994; Gur et al., 1991; Tomlinson et al., 1968; Xu et al., 2000), while others have suggested earlier onset or more severe atrophy in women (Hatazawa et al., 1982; Hubbard and Anderson, 1983). Expressed as a percentage of the total volume, women have more gray matter and men have more white matter (Cosgrove et al., 2007).

This study aims to provide a new window on changes in neurophysiology with age using a large-scale model of neuronal activity that incorporates the main structures and connections contributing to the EEG. This approach is based on a mean-field model of corticothalamic dynamics developed over a number of years, primarily by Robinson et al. (1997, 1998a, 2001b, 2003a), and Rennie et al. (1999, 2000, 2002). This model was partly based in turn on work by Nunez (1974a, 1995), Wilson and Cowan (1972, 1973), Wright and Liley (1995), and others. Comparisons of model predictions with data have revealed good agreement with a range of features of EEGs, including evoked response potentials (ERPs) (Kerr et al., 2008), seizure dynamics (Breakspear et al., 2006; Roberts and Robinson, 2008), spectra (Robinson et al., 2001b; Rowe et al., 2004a), coherence and correlations (Robinson, 2003), and changes with arousal (Robinson et al., 2002). Inverse modeling by fitting to spectra yields parameters including corticothalamic axonal delays, synaptodendritic rates, a damping rate for signals in the cortex, a scaling parameter for spectral power, and connection strengths of the cortex, thalamic relay nuclei, and thalamic reticular nucleus. An advantage of our mean-field model is that it provides information on structures as deep as the thalamus without the need for invasive measurements. Moreover, this information is of a different type than would be
obtained by invasive techniques, yielding average properties of large neuronal assemblies and their interconnections, rather than properties of small numbers of individual neurons.

In Sec. 4.2 we describe the subjects and data acquisition, the model, and the methods used for fitting and statistical analysis. Section 4.3 gives parameter values and age trends, also addressing sex differences. The large number of subjects in the study allows for precise estimates and high powers for statistical tests.

4.2 Methods

This section outlines the model and methods used in our analysis. Section 4.2.1 details the composition of the data set and criteria for inclusion. In Sec. 4.2.2 we provide an overview of the theoretical model of EEG generation. Section 4.2.3 summarizes the procedures for fitting model predictions to empirical spectra. Finally, Sec. 4.2.4 describes the statistical techniques used in the analysis of model parameters.

4.2.1 Subjects and EEG recording

A wide range of recordings were obtained from 768 males and 735 females, consisting of both EEG and ERP data. The recordings were carried out by Brain Resource Ltd (www.brainresource.com) and made available through the Brain Resource International Database (BRID) (Gordon et al., 2005). Only the resting eyes-closed EEG data are described here. Other components are to be used for model fits to ERPs (Kerr et al., in preparation), and detailed fits to alpha peaks (Chiang et al., in preparation).

Subjects’ ages were 6.4–86.6 years for males, and 6.1–82.6 years for females. Age distributions are shown in Fig. 4.1. All subjects were healthy, without any known history of brain injury, mental illness, substance abuse, psychological, psychiatric, neurological, or genetic disorders, or other medical conditions that could influence the normality of the EEG [for more details, see Chapter 3].

Recordings were obtained with a NuAmps amplifier (Neuroscan) at 26 electrode sites according to an extended 10–20 International system. The sampling rate was 500 Hz and average of mastoids was used as reference. Only data from the Cz electrode were used for further analysis, being relatively unaffected by muscle artifact (Saunders, 1979). Data were corrected offline for eye movements according to a method based on that of Gratton et al. (1983). Two minutes of relatively artifact-free EEG were low-pass filtered at 40 dB per decade above 100 Hz. The spectrum was calculated at intervals of 0.25 Hz by averaging the spectra of successive 4 s epochs multiplied by a Welch window.
4.2.2 Theoretical model

A schematic diagram of the neuronal populations included in the model, and their interconnections, is given in Fig. 4.2. Within the cortex, the model includes excitatory pyramidal cells, which project both intracortically and to the thalamus, and short-range inhibitory interneurons. The subscripts $e$ and $i$ are used to represent the excitatory and inhibitory cortical populations. The thalamic relay and reticular nuclei are respectively denoted by the subscripts $s$ and $r$. Input from the brainstem to the thalamus is indicated by the subscript $n$.

With each neuronal population we associate a pulse rate field, which is a continuum estimate of the average incoming pulse rate for that population. The pulse rate field is denoted $\phi(r, t)$, where $r$ is a spatial coordinate. For a given receiving population, the contributions of all afferent populations are weighted by the relevant connection strengths and summed. Dendritic and synaptic delays are modeled using a second-order differential equation that incorporates characteristic rise and decay rates of the membrane potential. These are denoted by $\alpha$ for the smaller of the two, and $\beta$ for the larger of the two rates, corresponding in practice to the decay and the rise rate, respectively. The equations for dendritic and synaptic summation and integration are (Robinson et al., 2002)

\[ D_{\alpha\beta}(t)V_a(r, t) = \sum_b \nu_{ab}\phi_b(r, t - \tau_{ab}), \]  
\[ D_{\alpha\beta}(t) = \frac{1}{\alpha \beta} \frac{d^2}{dt^2} + \left( \frac{1}{\alpha} + \frac{1}{\beta} \right) \frac{d}{dt} + 1, \]  

where $D_{\alpha\beta}$ is the corresponding differential operator, $V_a$ is the average cell-body potential of population $a$, $\nu_{ab} = N_{ab} s_b$ are connection strengths consisting of the unitary synaptic strength $s_b$ and the number of synapses $N_{ab}$ from neurons.
of type $b$ per type $a$ neuron, and $\tau_{ab}$ is the relevant axonal delay. The axonal delay for a full loop between cortex and thalamus is denoted $t_0$. The total delay necessary to complete a corticothalamic loop depends also on connection strengths, and dendritic and synaptic integration times, and is slightly longer than $t_0$. In our model, the inverse of this total delay determines the location of the alpha peak in the frequency spectrum (Robinson et al., 2002).

The outgoing firing rate field depends on the cell-body potential via a sigmoidal function, which results from the contribution of neurons with different firing thresholds. For computational efficiency, we use the logistic function (Robinson et al., 1997, 1998a, 2001b, 2003a),

$$Q_a(r, t) = S[V_a(r, t)] = \frac{Q_{\text{max}}}{1 + \exp[-(V_a - \theta)/\sigma']}, \tag{4.3}$$

where $Q_{\text{max}}$ is the maximum firing rate, $\theta$ is the average threshold potential, and $\sigma' \pi / \sqrt{3}$ is the standard deviation of firing thresholds (Wright and Liley, 1995). The version of the model used in the present study imposes equal values of $Q_{\text{max}}$, $\theta$, and $\sigma'$ for all components, which may be interpreted as average or effective values.

The cortex is modeled as a two-dimensional sheet owing to its relative thinness. Many experimental studies have shown that localized cortical stimulation leads to waves of neuronal activity spreading across the cortex (Chervin et al., 1988; Nunez, 1974a; Schiff et al., 2007; Xu et al., 2007), a feature included in a number of earlier models (Bresslo, 2001; Bresslo et al., 2003; Jirsa and Haken, 1996, 1997; Nunez, 1995). We use a damped-wave equation for the excitatory pulse rate field (Robinson et al., 1997, 1998a, 2001b, 2003a),

$$\left[\frac{1}{\gamma^2} \frac{\partial^2}{\partial t^2} + \frac{2}{\gamma} \frac{\partial}{\partial t} + 1 - r_e^2 \nabla^2\right] \phi_e(r, t) = Q_e(r, t), \tag{4.4}$$

where isotropy and homogeneity have been assumed, $r_e$ is the characteristic range of pyramidal axons, and $\gamma = v_e/r_e$ is the damping rate of cortical waves, with propagation speed $v_e$ around 3–22 m s$^{-1}$. The typical range of axons in the remaining populations is taken to be short enough to ignore wave propagation effects, allowing us to set $\phi_a(r, t) = Q_a(r, t)$ for $a = i, s, r$, which has been termed the local activity approximation (Robinson et al., 2004). The signals from these populations therefore influence their targets via delayed one-to-one mappings.

Setting the spatial and temporal derivatives in Eqs (4.1) and (4.4) to zero yields an odd number of uniform fixed points $\phi_a^{(0)} = Q_a^{(0)}$, usually one or three (Robinson et al., 2002). For physiological parameters we expect a stable low-firing-rate fixed point, around which small perturbations can be described using
a linear approximation,

\[ Q_a(r, t) = Q_a^{(0)} + \rho_a \left[ V_a(r, t) - V_a^{(0)} \right], \quad (4.5) \]

\[ \rho_a = \frac{dQ_a(r, t)}{dV_a(r, t)} \bigg|_{V_a^{(0)}}, \quad (4.6) \]

\[ = \frac{Q_a^{(0)}}{\sigma'} \left[ 1 - \frac{Q_a^{(0)}}{Q_{max}} \right], \quad (4.7) \]

where \( V_a^{(0)} \) is the steady-state value of the mean membrane potential (Robinson et al., 2004), and \( \rho_a \) is the derivative of the sigmoid at steady state. Henceforth denoting \( V_a - V_a^{(0)} \) simply by \( V_a \), and similarly for \( Q_a \) and \( \phi_a \), Fourier transformation of Eqs (4.1), (4.4), and (4.5) yields (Robinson et al., 2001b)

\[ Q_a(k, \omega) = \rho_a V_a(k, \omega), \quad (4.8) \]

\[ = L(\omega) \sum_b G_{ab} \phi_b(k, \omega) e^{i\omega \tau_{ab}}, \quad (4.9) \]

\[ = \left\{ \begin{array}{ll}
\left[ \left( 1 - \frac{i\omega}{\gamma} \right)^2 + \frac{k^2 r^2}{r^2} \right] \phi_a(k, \omega), \\
\phi_a(k, \omega),
\end{array} \right. \quad (4.10) \]

where the first applies to cortical excitatory neurons, and the second to all other populations. Wavenumbers and angular frequencies are denoted \( k \) and \( \omega \), and \( G_{ab} = \rho_a \nu_{ab} \) are linear gains representing the number of additional pulses out per additional pulse in. In Eq. (4.9),

\[ L(\omega) = \left( 1 - \frac{i\omega}{\alpha} \right)^{-1} \left( 1 - \frac{i\omega}{\beta} \right)^{-1}. \quad (4.11) \]

Equations (4.9) and (4.10) enable a linear transfer function \( \phi_e(k, \omega) / \phi_n(k, \omega) \) to be derived, describing the cortical response to input from underlying structures. For the neuronal connections in Fig. 4.2, the transfer function is (Robinson et al., 2002, 2004)

\[ \frac{\phi_e(k, \omega)}{\phi_n(k, \omega)} = T(k, \omega) = \frac{1}{(k^2 + q^2) r^2} \frac{G_{es}G_{sn} L^2 e^{i\omega t_0 / 2}}{(1 - G_{srs} L^2)(1 - G_{ei} L)}. \quad (4.12) \]

\[ q^2 r^2 = \left( 1 - \frac{i\omega}{\gamma} \right)^2 - \frac{L}{1 - G_{ei} L} \left[ G_{ee} + \frac{(G_{ese} + G_{esre} L^2) e^{i\omega t_0}}{1 - G_{srs} L^2} \right], \quad (4.13) \]

where we have defined \( G_{ese} = G_{es} G_{se} \) for the direct corticothalamic loop, \( G_{esre} = G_{es} G_{sr} G_{re} \) for the indirect corticothalamic loop passing through the reticular nucleus, and \( G_{srs} = G_{sr} G_{rs} \) for the intrathalamic loop between relay nuclei and the reticular nucleus. We see that the cortical signal depends only on these products of gains, which are distributed around loops rather than localized to single populations.
Figure 4.2: Schematic representation of the model components and their interconnections: $e =$ cortical excitatory (pyramidal) neurons, $i =$ cortical inhibitory neurons, $s =$ thalamic (specific and secondary) relay nuclei, $r =$ thalamic reticular nucleus. External input to the thalamus is given by $\phi_n$. Filled arrowheads indicate excitatory connections; open arrowheads inhibitory ones.

4.2.3 Model fitting

The EEG is the result of dendritic and synaptic currents of many cortical neurons firing in partial synchrony (Nunez, 1995; Ray, 1990). Excitatory pyramidal neurons are the largest and most aligned among cortical neuronal types, and are thus expected to dominate the signal (Robinson et al., 2001b). Furthermore, the EEG is thought to depend much more strongly on excitatory synaptic input to apical dendrites of pyramidal cells than on inhibitory input to basal dendrites. This is due to the proximity of basal dendrites to the relatively conductive cell body, causing dipoles only over small distances, the lack of alignment of basal dendrites, and the small degree of layer-specificity of inhibitory synaptic actions (Mitzdorf, 1985; Towe, 1966). We can therefore approximate the dendritic and synaptic currents responsible for EEG fluctuations as being roughly proportional to the pulse rate field $\phi_e$.

The frequency spectrum measured on the scalp is a low-pass filtered version of that on the cortical surface, due to volume conduction attenuating the large-wavenumber content of the signal, and the association of large wavenumbers with high frequencies. Furthermore, the signal measured on the scalp contains a contribution from the muscles. For the purpose of model fitting, input from underlying structures is approximated as spatiotemporal white noise,
represented by a constant modulus and random phase in the Fourier domain, \(|\phi_n(k, \omega)|^2 = |\phi_n|^2\). This is consistent with evidence that EEG activity often has the properties of filtered noise (Lopes da Silva et al., 1974; Stam et al., 1999), and has proven to yield realistic spectra in previous works (Robinson et al., 2001b, 2003a). Although boundary conditions have only small effects on the cortical spectrum (Robinson et al., 2001a), they were found to improve fits in some cases (Rowe et al., 2004a). For a two-dimensional rectangular cortex of size \(L_x \times L_y\), the spectrum can be written as a sum over a discrete set of wavenumbers taking the form (Rennie et al., 2002; Rowe et al., 2004a)

\[
P_{\text{the}}(\omega) = P_{\text{EEG}}(\omega) + P_{\text{EMG}}(\omega),
\]

\[
P_{\text{EEG}}(\omega) = \frac{\pi |\phi_n|^2 G_{es} G_{sn}^2}{r_e^2} \left| \frac{L^2 e^{i\omega t_0/2}}{(1 - G_{srs} L^2)(1 - G_{ei} L)} \right|^2 \mathcal{P},
\]

\[
10^{p_0} \left| \frac{L^2 e^{i\omega t_0/2}}{(1 - G_{srs} L^2)(1 - G_{ei} L)} \right|^2 \mathcal{P},
\]

\[
\mathcal{P} = \frac{4\pi r_e^2}{L_x L_y} \sum_{M,N} e^{-k_{mn}^2 r_e^2 + q^2 r_e^2} \left( \frac{\omega}{\omega_{\text{EMG}}} \right)^2 \left[ 1 + \left( \frac{\omega}{\omega_{\text{EMG}}} \right)^2 \right]^{-1},
\]

\[
P_{\text{EMG}}(\omega) = A_{\text{EMG}} \left( \frac{\omega}{\omega_{\text{EMG}}} \right)^2 \left[ 1 + \left( \frac{\omega}{\omega_{\text{EMG}}} \right)^2 \right]^{-1},
\]

where the theoretical spectrum \(P_{\text{the}}(\omega)\), which is a sum of EEG and electromyographic (EMG) components, is scaled to the empirical spectrum via \(1 \mu V^2\text{Hz}^{-1}m^{-2} \equiv 1\). Furthermore, \(k_0\) is a cut-off wavenumber for filtering by cerebrospinal fluid, skull, and scalp, which is taken into account via \(\exp[-k_{mn}^2 / k_0^2]\), and the discrete wavenumbers are given by

\[
k_{mn} = \left( \frac{2\pi m}{L_x}, \frac{2\pi n}{L_y} \right).
\]

The EMG component has a maximum of \(A_{\text{EMG}}/4\) at \(\omega_{\text{EMG}}\), taken to be \(2\pi \times 40\) Hz. The amplitude \(A_{\text{EMG}}\) is determined along with the other model parameters, but is not further considered here. The parameter \(p_0\) provides a normalization for the spectrum without affecting its shape.

When fitting to empirical spectra, a reduction in the number of independent parameters is achieved by setting \(\alpha = \beta/4\), which agrees roughly with experimental results (Rowe et al., 2004a). The number of fitted parameters is further reduced using the proportionality of the total number of synapses between two populations to the numbers of sending and receiving neurons, which holds approximately in the cortex (Braitenberg and Schütz, 1998; Robinson et al., 2001b; Wright and Liley, 1995). Hence, the number of synapses per cortical neuron
depends only on the afferent population, implying $N_{eb} = N_{ib}$ and $G_{eb} = G_{ib}$ for $b = e, i, s$.

Table 4.1 lists the parameters used to obtain model spectra, some of which were fixed, while others were allowed to vary within the given ranges, which had soft boundaries implemented by imposing a smoothly increasing penalty for smaller or larger values.

<table>
<thead>
<tr>
<th>Par.</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>s$^{-1}$</td>
<td>Decay rate of cell-body potential</td>
<td>10</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>s$^{-1}$</td>
<td>Rise rate of cell-body potential</td>
<td>4$\alpha$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$r_e$</td>
<td>mm</td>
<td>Range of pyramidal axons</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$v_e$</td>
<td>m s$^{-1}$</td>
<td>Propagation speed along pyramidal axons</td>
<td>$\gamma r_e$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>s$^{-1}$</td>
<td>Cortical damping rate</td>
<td>40</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>$t_0$</td>
<td>ms</td>
<td>Corticothalamic axonal latency</td>
<td>60</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>$G_{ee}$</td>
<td>—</td>
<td>Excitatory cortical gain</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>$G_{ei}$</td>
<td>—</td>
<td>Inhibitory cortical gain</td>
<td>$-35$</td>
<td>$1$</td>
<td></td>
</tr>
<tr>
<td>$G_{ese}$</td>
<td>—</td>
<td>Gain for direct corticothalamic loop</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>$G_{esre}$</td>
<td>—</td>
<td>Gain for indirect corticothalamic loop passing through the thalamic reticular nucleus</td>
<td>$-30$</td>
<td>$2$</td>
<td></td>
</tr>
<tr>
<td>$G_{srs}$</td>
<td>—</td>
<td>Gain for intrathalamic loop</td>
<td>$-15$</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>$p_0$</td>
<td>—</td>
<td>Normalization for spectrum</td>
<td>No limits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_0$</td>
<td>m$^{-1}$</td>
<td>Cut-off wavenumber for spatial filtering</td>
<td>37.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$L_x, L_y$</td>
<td>m</td>
<td>Linear dimensions of cortex</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_{EMG}$</td>
<td>$\mu V^2 Hz^{-1}$</td>
<td>Amplitude of EMG component</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>$\omega_{EMG}$</td>
<td>Hz</td>
<td>Peak frequency of EMG component</td>
<td>$2\pi \times 40$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1: Parameters of the corticothalamic model used to fit theoretical predictions to empirical EEG spectra. Some parameters were held fixed, while others were allowed to vary over the given ranges, outside which $\chi^2$ was heavily weighted. * indicates parameters that are investigated in this study.

As described in Rowe et al. (2004a) and Chapter 3, the natural logarithm of the dimensionless version of the spectral power (otherwise measured in $\mu V^2/Hz$) was fitted to the empirical log-transformed spectrum using the Levenberg-Marquardt method (Press et al., 1992), which minimizes the $\chi^2$ error defined by

$$\chi^2 = \sum_{i=1}^{N} \frac{[\log(P_{emp,i}) - \log(P_{the,i})]^2}{\sigma_i^2},$$

(4.20)

where $P_{emp,i}$ is the empirical spectrum, and $\sigma_i$ is the standard deviation of
\[ \log P_{emp} \] for frequency index \( i \). Frequencies up to 50 Hz were taken into account, but the power around 50 Hz was weighted with large \( \sigma \) to downplay the contribution of points contaminated by mains (or grid) power. A Monte Carlo method was used in which different random seeds were used until 30 convergent fits were obtained. The stopping criterion for the fitting routine was \( \Delta \chi^2 < 10^{-5} \) for six successive iterations. Of 1666 subjects’ spectra, 1573 were successfully fitted (94%). The overlap of the set of subjects with successful fits was determined with a set of 1527 subjects having both target and background oddball ERP data at a large number of electrodes, leading to a final set of 1503 subjects. Figure 4.3 gives illustrative examples of fits with different values of \( \chi^2 \). The values of \( \chi^2 \) were larger than those reported in Rowe et al. (2004a) due to a different normalization of weights, but this did not substantially affect the fits obtained.

![Figure 4.3](image)

Figure 4.3: Examples of experimental (solid) and corresponding model spectra (dashed) with varying goodness of fit.

### 4.2.4 Statistical analysis

The statistical analysis was carried out using R Version 2.7.0 (R Development Core Team, 2005). First, the robustness of fits was investigated by refitting empirical spectra with noise added for a large subsample (1375 subjects). Noise
was normally distributed with standard deviation 0.46 times the observed power at each frequency point. Any resulting negative values were replaced with the original power.

Visual inspection of histograms and a Shapiro-Wilk test for normality (Shapiro and Wilk, 1965) revealed that none of the parameters were normally distributed \( p < 1.0e^{-9} \). Therefore, differences between the two sets of fits were assessed using the nonparametric Mann-Whitney test for paired samples, to check for any consistent bias introduced by noise. For each parameter, Spearman correlations were determined between the first and second fits, as a measure of reliability or robustness. In addition, between-fit parameter differences were calculated for each subject, and Spearman correlations between these differences with corresponding \( p \)-values were calculated for each pair of parameters using the R routine `cor.test`. This gave an indication of correlations induced by fitting rather than physiology.

For the original fits, sex differences in model parameters were assessed using the Mann-Whitney test for independent samples. We compared means and distributions of model parameters with those obtained using a previous version of the fitting routine (Rowe et al., 2004a), and those reported in a longitudinal study of healthy males in the age range 18–28 years (Chapter 3). For further comparisons with the literature, we calculated the following quantitative EEG (qEEG) parameters from model spectra using average model parameters over restricted age ranges: absolute and relative powers in the delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–50 Hz) bands, total power, and the frequency corresponding to maximal power in the alpha band.

We determined rank correlations between model parameters and age, and corresponding significance values. Sex differences in correlations between parameters and age were assessed using a bootstrapping method. This method controls the Type I error of finding a significant difference when none exists for nonnormal distributions, and is also robust under heteroskedasticity (which here corresponds to age-dependent variance of model parameters) (Wilcox and Muska, 2002). Bootstrap samples were chosen consisting of 768 age-parameter pairs for males and 735 such pairs for females, using sampling with replacement. This process was repeated 600 times, and the difference in Spearman correlation coefficients was determined for each pair of bootstrap samples, leading to 95% confidence intervals ranging approximately from the 15th to the 585th value. The bootstrapping results were compared with significance levels calculated using Fisher’s \( z \)-transform, which assumes underlying distributions to be normal (Yu and Dunn, 1982). For each Spearman correlation \( \rho \), the \( z \)-transformed value is

\[
\rho' = 0.5 \log \frac{1 + \rho}{1 - \rho},
\]  

(4.21)
where log is the natural logarithm, leading to the test statistic

\[ z = \frac{\rho_1 - \rho_2}{\sqrt{\frac{1}{n_1-3} + \frac{1}{n_2-3}}} \]  

(4.22)

with \( n_1 \) and \( n_2 \) the numbers of subjects in each sample. The quantity (4.22) approximately follows the standard normal distribution under the null hypothesis of equal correlations (Olkin and Finn, 1995).

Regression fits provide information about effect size not contained in correlation coefficients. Weighted locally linear regression was used to assess trends in model parameters with age for the sample as a whole, and for male and female subsamples. This nonparametric method is implemented in R via the function `lowess`. For each point \( x_0 \), a locally linear function is fitted using least squares, where the influence of other points is weighted with the tricube function,

\[
W(x - x_0) = \begin{cases} 
(1 - \left| \frac{x-x_0}{h} \right|^3)^3 & \text{for } \left| \frac{x-x_0}{h} \right| < 1 \\
0 & \text{for } \left| \frac{x-x_0}{h} \right| \geq 1,
\end{cases}
\]  

(4.23)

with \( h \) the half-width of the window centered on \( x_0 \). The function (4.23) falls off with the distance from \( x_0 \), since slopes are expected to be similar only within limited age ranges. The window was taken to enclose 50% of the data for each local regression, providing a good balance between smoothness and flexibility of fits afforded by large and small windows, respectively. For robustness, three iterations were performed with additional weighting of data points according to their residuals with respect to the preceding fit (Cleveland, 1979). These weights were

\[
B(x) = \begin{cases} 
\left[ 1 - \left( \frac{x}{s} \right)^2 \right]^2 & \text{for } \frac{|x|}{s} < 1 \\
0 & \text{for } \frac{|x|}{s} \geq 1,
\end{cases}
\]  

(4.24)

where \( e \) is the residual at \( x \) and \( s \) is the median of all residuals. Multiplying the weights (4.24) by those in (4.23) ensures that fits are relatively insensitive to outliers, and hence to departures from the assumptions of errors with mean zero and constant scale, which underlie the initial least-squares regressions.

Visual inspection of nonlinear parameter trends revealed that the slopes of many trendlines changed considerably around 14 and 20 years. Therefore, besides the nonlinear fits, linear trendlines were fitted for each of the age ranges 6–14 years, 14–20 years, and \( \geq 20 \) years, using a median-based method applicable to nonnormal data. Specifically, we used Siegel’s repeated-medians method (Siegel, 1982), in which the median slope and intercept are determined
for the lines through a given point and each other point, and the medians of these values give the final slope and intercept. This method is implemented in the R function \texttt{mblm}. Confidence intervals for slopes and intercepts were determined using \texttt{confint}. We also checked for significant differences in rank correlation between subsequent age ranges, and between males and females within each range. No correction for multiple comparisons was carried out for any correlations or group comparisons.

Age trends in inter-individual variability were also assessed. To ensure similar uncertainties in data points across age, variances were computed for samples of approximately equal sizes. The total sample was divided into 29 groups of 50 subjects and a final group of 53 subjects, males into 32 groups of 24 subjects, and females into 35 groups of 21 subjects. The variance of each model parameter was plotted against the mean age of each group. Fits were obtained by means of locally linear weighted regression, using 50\% windows and three ’robustifying’ iterations (as above).

### 4.3 Results

The robustness of fitted model parameters is discussed in Sec. 4.3.1. Parameter distributions are given in Sec. 4.3.2 and compared to previously published results. Results on age trends are presented for model parameters in Sec. 4.3.3, and for the variance in these parameters in Sec. 4.3.4.

#### 4.3.1 Robustness of fits

Table 4.2 shows the results of comparing original parameter values with those obtained after adding noise to empirical spectra. Parameter distributions for the first and second fits are shown in Fig. 4.4. Noise had little influence on the mean value of \(G_{ese}\), but introduced a consistent bias in the other parameters. Nevertheless, the high between-fit correlations for \(G_{srs} (\rho = 0.83)\), \(t_0 (\rho = 0.79)\), \(\alpha (\rho = 0.75)\), and \(p_0 (\rho = 0.70)\) show that the bias due to noise was small compared to the total variation, and these parameters were robustly fitted. Furthermore, \(G_{ee}, G_{esre}, \gamma, \) and \(G_{ese}\) were reasonably robust. \(G_{ei}\) was the least robust \((\rho = 0.47)\), so results for this parameter should be interpreted with caution.

Almost all parameter pairs show interactions due to noise. Consequently, age trends of physiological origin in some parameters may cause artificial age trends in other (especially less robust) parameters. Table 4.2 shows that particularly strong correlations exist for between-fit differences in \(p_0 \) and \(G_{ei} (\rho = -0.85)\), \(G_{ese} \) and \(G_{esre} (\rho = -0.76)\), and \(G_{ee} \) and \(G_{ei} (\rho = -0.66)\). This should be kept in mind when interpreting the results in the following sections.
Table 4.2: Robustness of model parameters, assessed by adding noise to empirical spectra and refitting. Units are as in Table 4.1. The second through tenth columns contain rank correlations for between-fit differences in parameters (in upper triangular form), and corresponding significance values (below the diagonal). These correlations obey $\rho(x_1, x_2; y_1, y_2) = \rho(y_1, y_2, x_1, x_2)$ for parameters $x$ and $y$, and fits 1 and 2. New mean values are listed in the penultimate column (cf. Table 4.3 for original mean values), with significance values for the pairwise Mann-Whitney test for differences between the first and second fits. The last column indicates rank correlations between the first and second fits. Significance levels: n.s., not significant; *, 0.05; **, 0.01; ***, 0.001.
4.3.2 Parameter values

Table 4.3 lists parameter means and standard deviations as well as $\chi^2$-values for the entire sample, and for male and female subsamples. The corticothalamic loop gains $G_{ese}$ and $G_{esre}$ were both stronger in males. The intrathalamic loop, represented by the gain $G_{srs}$, was stronger in females. The corticothalamic delay $t_0$ was on average slightly longer in females. No significant differences are found in the intracortical gains $G_{ee}$ and $G_{ei}$, or in the parameters $\alpha$, $\gamma$, and $p_0$. Fits were on average slightly better for females than for males, as indicated by lower values of $\chi^2$.

Dominant alpha frequencies are expected to be approximately inversely proportional to $t_0$ (Robinson et al., 2002). Therefore, we compared values of $t_0$ with alpha peak frequencies determined from empirical Cz spectra. The sex difference in $t_0$ did not translate into a significant sex difference in alpha peak frequencies averaged across age (males, 9.5 Hz; females, 9.4 Hz; $p = 0.30$). Boys up to age 16 did show significantly higher peak frequencies than girls in this age range (boys, 9.6 Hz; girls, 9.3 Hz; $p = 0.0045$), and had significantly lower values of $t_0$ (boys, 77 ms; girls, 81 ms; $p = 1.0e-5$). In contrast, females
aged 16–24 years had higher peak frequencies (females, 9.7 Hz; males, 9.4 Hz; $p = 0.0028$), despite a lack of difference in $t_0$ (females, 78 ms; males, 77 ms; $p = 0.76$). The same pattern of sex differences in alpha peak frequencies was found at occipital sites. We did not find significant sex differences in $t_0$ or Cz alpha peak frequencies in aged individuals, but frontal rhythms occurred at significantly lower frequencies in women than in men above about age 70. These issues are explored further by Chiang et al. (in preparation).

Rowe et al. (2004a) reported distributions of model parameters for eyes-open and eyes-closed spectra of 100 healthy subjects (49 females and 51 males with mean ages 44 and 45 years, respectively) using an earlier version of the fitting routine. Compared to the eyes-closed distributions in that paper, our sample yields larger standard deviations for all parameters except $t_0$ and $\gamma$. The mean values of $\gamma$, $t_0$, $G_{ee}$, and $|G_{srs}|$ are smaller than those in Rowe et al. (2004a), whereas $\alpha$, $|G_{ei}|$, $G_{ese}$, $|G_{esre}|$, and $p_0$ are found to be larger on average. We attribute this to the different fitting algorithms used, since the new algorithm runs through a range of initial values, whereas the version used by Rowe et al. (2004a) initialized parameters at a single set of values. The new fitting algorithm is an improvement over the old one because it reduces bias introduced by the choice of initialization.

In Chapter 3, we reported classic and model-based spectral parameters for 32 healthy males aged 18–28, whose eyes-closed EEGs were obtained in six consecutive weeks, followed for some subjects by intervals of several months. Mean values for males in the range 18–28 years from the present study are compared with those from Chapter 3 in Table 4.3. Overall, differences between the two studies are small, and only $G_{ee}$ and $p_0$ differ substantially.

### 4.3.3 Age trends

Figure 4.5 shows scatter plots and fitted nonlinear age trends, obtained using weighted locally linear regression for the entire sample, and for male and female subsamples. Bootstrap 95% confidence intervals are also indicated. Some trends can be discerned across the entire age range, but many trendlines are approximately piecewise linear, with different slopes in different age ranges. For the sample as a whole, the regression lines for $G_{srs}$ and $t_0$ display bends around age 14, whereas the slopes of the regression lines for $\gamma$ and $p_0$ appear to change around age 20. Linear trends in each of the intervals 6–14, 14–20, and $\geq$ 20 years are indicated in dark gray in Fig. 4.5.

Table 4.4 shows sex differences in age correlations in each range considered. Both nonparametric bootstrapping intervals and $p$-values for the parametric $z$-test are given. These methods yield closely similar results, enabling the use of the $z$-test for further comparisons. The only significant differences between males and females are found for $G_{ee}$ and $t_0$ in the range 14–20 years. The lack
<table>
<thead>
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<th>Parameter</th>
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<th>Females</th>
<th>$p$-value</th>
<th>Mean</th>
<th>MeanA</th>
</tr>
</thead>
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<td>SD</td>
<td>MeanR</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
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<td>75</td>
<td>88</td>
<td>40</td>
<td>87</td>
</tr>
<tr>
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<td>31</td>
<td>140</td>
<td>72</td>
<td>32</td>
<td>72</td>
</tr>
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<td>11</td>
<td>84</td>
<td>78</td>
<td>11</td>
<td>80</td>
</tr>
<tr>
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<td>3.8</td>
<td>4.1</td>
<td>5.8</td>
<td>3.9</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
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<td>3.9</td>
<td>-7.5</td>
<td>-8.0</td>
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<td>-7.9</td>
</tr>
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<td>10.3</td>
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<tr>
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<td>-3.3</td>
<td>-6.3</td>
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<td>-5.2</td>
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<tr>
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<td>0.57</td>
<td>-0.40</td>
</tr>
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<td>2.49</td>
<td>2.92</td>
<td>0.63</td>
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<td>462</td>
<td>2.49</td>
<td>371</td>
<td>461</td>
<td>343</td>
</tr>
</tbody>
</table>

Table 4.3: Means and standard deviations of model parameters and $\chi^2$, for all subjects and for males and females separately. Units are as in Table 4.1. The fourth column gives means for the eyes-closed state from Rowe et al. (2004a) (MeanR). The ninth column lists $p$-values for the Mann-Whitney test comparing males and females. In Chapter 3, we considered healthy males in the age range 18–28 years. Values for males in this age range are compared between the present study and Chapter 3 (MeanA) in the last two columns, and the Mann-Whitney test was used to check for significant differences. Significance levels: *, 0.05; **, 0.01; ***. 0.001.
Figure 4.5: Age trends in model parameters. (a)–(c) Scatter plots of model parameters vs. age (gray dots) with weighted locally linear regression fits (black) and median-based linear fits in each of the ranges 6–14, 14–20, and ≥ 20 years (dark gray). The dashed lines indicate 95% confidence intervals for the nonlinear regression. (a) All subjects; (b) males; (c) females. (d) Weighted locally linear regression fits for males (solid) and females (dashed) plotted over restricted vertical ranges to highlight differences.
of significant differences in the other parameters and age bands does not imply that such differences do not exist; rather that even larger sample sizes would be needed to detect them if they do.

Table 4.5 lists the slopes for each group and each age range, and compares rank correlations in different ranges. The synaptodendritic rate $\alpha$ decreases up to age 20, while the converse holds for the cortical decay rate $\gamma$. In females, the $z$-test for $\alpha$ does not yield a significant result at the 0.05 level, but nonparametric intervals for the slopes indicate a clear difference between 14–20 and $\geq 20$ years. Interestingly, the negative correlation between $t_0$ and age reverses around age 14 in males but not in females, where this only occurs around age 20. For the cortical excitatory gain $G_{ee}$, the only significant linear trend occurs in females in the range 14–20 years, although the nonlinear fit also indicates a decrease in males in this age range (cf. Fig. 4.5). Only the 14–20 year and $\geq 20$ trends in females differ significantly from each other for this parameter. The cortical inhibitory gain $G_{ei}$ decreases in magnitude throughout the entire age range, but less steeply as age progresses. However, trends in $G_{ei}$ show no significant differences between subsequent age bands. The corticothalamic gain $G_{ese}$ diminishes in early childhood and after age 20. In the range 14–20 years, correlations are not found to be significant, but bootstrapping methods indicate a significant linear increase in $G_{ese}$ in females. Nonlinear fits also suggest that trends in $G_{ese}$ reverse around adolescence in females. Changes in trends in $G_{ese}$ are statistically significant for females both at 14 and at 20 years, but not for males, and for the sample as a whole only reach significance for the difference between 14–20 and $\geq 20$ bands. A similar pattern is seen in the indirect corticothalamic gain $G_{esre}$, which decreases in magnitude in early childhood (significant at the 0.05 level according to bootstrapping intervals but not correlations) and after age 20, whereas trends in the range 14–20 years are not significant. The intrathalamic gain $G_{srs}$ increases in absolute value throughout the entire age range, at a gradually diminishing rate. The largest change in slopes for this parameter occurs around age 14 years. The spectral normalization parameter $p_0$ decreases with age, but closer inspection of the data shows that this decrease only occurs systematically from about age 10 years onward. The decrease in $p_0$ appears to decelerate after age 20, although differences between subsequent ranges are not statistically significant. The analysis in Sec. 4.3.1 suggests that uncertainties in fitting provide a negative contribution to the correlation between $G_{ei}$ and $p_0$. Therefore, trends in the fairly robust $p_0$ may be partly responsible for reductions in the less robust $|G_{ei}|$ with age, which may thus not accurately reflect physiological changes.

For interpretation of Table 4.5, we note that the group of subjects aged $\geq 20$ (710 subjects) was larger than either the 6–14 (458 subjects) or 14–20 (335 subjects) bands. This means that differences in correlations between
<table>
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<th>Parameter</th>
<th>$\rho_{all}$</th>
<th>$p$-value</th>
<th>$\rho_m$</th>
<th>$p$-value</th>
<th>$\rho_f$</th>
<th>$p$-value</th>
<th>95% conf. interval</th>
<th>$p$-value</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>$-0.18$</td>
<td>$1.2e^{-4}$</td>
<td>$-0.19$</td>
<td>$0.0017$</td>
<td>$-0.15$</td>
<td>$0.032$</td>
<td>$(-0.21 - 0.14)$</td>
<td>$0.67$</td>
</tr>
<tr>
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<td>$0.20$</td>
<td>$8.4e^{-4}$</td>
<td>$0.17$</td>
<td>$0.018$</td>
<td>$(-0.14 - 0.21)$</td>
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</tr>
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<td>$-0.23$</td>
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<tr>
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<td>$0.74$</td>
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<td>$0.39$</td>
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<td>$0.67$</td>
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<td>$0.065$</td>
<td>$0.29$</td>
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<td>$-0.14$</td>
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<td>$0.074$</td>
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<td></td>
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<td>$0.26$</td>
</tr>
<tr>
<td>$p_0$</td>
<td>$-0.10$</td>
<td>$0.0053$</td>
<td>$-0.16$</td>
<td>$0.0042$</td>
<td>$-0.086$</td>
<td>$0.089$</td>
<td>$(-0.22 - 0.076)$</td>
<td>$0.31$</td>
</tr>
</tbody>
</table>

Table 4.4: Age-parameter correlations. Bootstrap 95% confidence intervals for differences between males and females ($\rho_m - \rho_f$) are given, with two-tailed $p$-values for the z-test. Significance levels: *, 0.05; **, 0.01; ***, 0.001.
Table 4.5: Median-based linear trends. Differences in age-parameter associations over subsequent ranges were assessed with a z-test on Spearman’s ρ. Units as in Table 4.1, with age in years. Significance levels: *, 0.05; **, 0.01; ***, 0.001.
the 14–20 and ≥ 20 bands reached statistical significance more readily than differences between the 6–14 and 14–20 bands. Hence, the larger number of significant changes in slopes at age 20 than at age 14 does not warrant the conclusion that rates of brain development change most rapidly around age 20. In fact, differences in the slopes of α, Gese, and Gesre are greatest between the first two age bands, although correlations change significantly only between the last two bands.

Average theoretical spectra were computed for two sets of age bands using Eqs (4.15)–(4.17). The first consisted of one-year intervals between ages 6 and 20, five-year intervals from 20 to 80, and a single band for age ≥ 80. The second set of bands was < 10, ten-year intervals between 10 and 70, and ≥ 70 years. The corresponding trends in frequency spectra are shown in Fig. 4.6. In agreement with the downward trend in \( p_0 \), the total power, and especially that at low frequencies, decreases with age. The alpha and beta peaks around 10 and 20 Hz become more prominent relative to the power at other frequencies, and relative low-frequency power decreases. The frequency of the alpha peak increases approximately up to 14 years and then decreases slightly into old age. Most of the changes occur in childhood, whereas comparatively little change is observed between about 20 and 70 years.

Table 4.6 illustrates the sensitivity of model spectra to each of the parameters separately in terms of qEEG parameters. Single parameters were changed from their average value for subjects aged < 10 years to their average value for subjects aged > 70 years, and complete sets of average parameters for the youngest and oldest age groups were also considered. These results show to first order (ignoring parameter interactions) which parameters may have contributed to changes such as reductions in absolute power and relative low-frequency power with age. The values of \( t_0 \) were comparable in the youngest and oldest age groups, so this parameter accounts for little of the differences between these groups.

### 4.3.4 Changes in inter-individual differences across age

From Fig. 4.5 it is apparent that the variance in model parameters is not constant across age. Such heteroskedasticity is often a nuisance, since it complicates the regression problem. However, variance trends can themselves be of interest, and complement the information contained in parameter trends. Here we show that changes in variance can be used to infer correlations between parameter values at a given age and the slopes of individual trends in these parameters. We thus consider distributions of initial parameter values \( y_0 \), and slopes \( a \), across the population, and assume \( a \) can depend on \( y_0 \). Intuitively, if the slope of a parameter trend is positively correlated with its initial value, we expect the variance to increase, and if this correlation is negative, we ex-
Figure 4.6: Changes across age in fitted spectra. (a) Spectral power averaged across individuals for frequencies up to 30 Hz. Colors indicate the logarithm of the dimensionless version of spectral power measured in $\mu V^2 \text{Hz}^{-1}$. (b)–(d) Double logarithmic plots of averaged spectra for all subjects, males, and females, respectively. The legends indicate age bands in years.
Table 4.6: Dependence of qEEG parameters on model parameters. The first and last columns represent the spectra obtained using the average model parameters of subjects aged < 10 years and > 70 years, respectively. The remaining column labels indicate which parameter was changed to the average value for subjects aged > 70 years, and the directions of these changes. Band limits were: delta, 0–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta, 12–30 Hz; gamma, 30–50 Hz; total, 0–50 Hz. All values are given to three significant figures.
pect the variance to decrease up to some point and then increase. Note that this differs from determining confidence intervals for the slope in a linear regression: instead of characterizing the average trend for the whole sample, we consider differential rates of development between subjects. Although our data set is cross-sectional, it nevertheless allows some longitudinal information to be extracted.

![Graphs showing age trends in variance](image)

Figure 4.7: Age trends in variance, obtained by locally linear weighted regression. Squares/dashed lines, males; triangles/dotted lines, females. Solid lines indicate trends for all subjects combined.

We can investigate the dependence of the variance on the distribution of individual trends by expressing it in terms of the parameters of these trends.
At any point, the variance in a quantity $y$ is given by

$$
\sigma^2_y = \int_{-\infty}^{\infty} (y - \mu_y)^2 \ p(y) \ dy, \quad (4.25)
$$

where $\mu_y$ is its mean. Approximating the initial age trend as linear, we have

$$
y = y_0 + a(x - x_0), \quad (4.26)
$$

with initial age value $x_0$. Given an age interval $x - x_0$, two of the variables $y_0$, $y$, and $a$ can be chosen independently. Let the corresponding joint probability densities be $p(y_0, y)$, $p(y_0, a)$, and $p(a, y)$. These densities obey

$$
|p(y_0, y) \ dy_0 \ dy| = |p(y_0, a) \ dy_0 \ da| = |p(a, y) \ da \ dy|. \quad (4.27)
$$

Furthermore, we can write $\mu_y$ in terms of the mean values $\mu_{y_0}$ and $\mu_a$,

$$
\mu_y = \int_{-\infty}^{\infty} y \ p(y) \ dy, \quad (4.28)
$$

$$
= \int_{-\infty}^{\infty} [y_0 + a(x - x_0)] \ p(y_0, a) \ dy_0 \ da, \quad (4.29)
$$

$$
= \mu_{y_0} + (x - x_0) \ \mu_a. \quad (4.30)
$$

Thus, the variance (4.25) becomes

$$
\sigma^2(y) = \int_{-\infty}^{\infty} \ [y_0 + a(x - x_0) - \mu_{y_0} - (x - x_0) \ \mu_a]^2 \ p(a, y) \ da \ dy, \quad (4.31)
$$

$$
= \int_{-\infty}^{\infty} (y_0 - \mu_{y_0})^2 \ p(y) \ dy + (x - x_0)^2 \ \int_{-\infty}^{\infty} (a - \mu_a)^2 \ p(a) \ da \quad (4.32)
$$

$$
+ 2(x - x_0) \ \int_{-\infty}^{\infty} (y_0 - \mu_{y_0}) (a - \mu_a) \ dy \ da,
$$

$$
= \sigma^2_{y_0} + (x - x_0)^2 \ \sigma^2_a + 2(x - x_0) \ \rho_{y_0,a} \ \sigma_{y_0} \ \sigma_a, \quad (4.33)
$$

where $\rho_{y_0,a}$ is the correlation between $y_0$ and $a$. Thus, the variance in $y$ initially behaves quadratically, with contributions from the variances in $y_0$ and $a$, and slope

$$
\frac{d \sigma^2_y}{d(x - x_0)} = 2(x - x_0) \ \sigma^2_a + 2\rho_{y_0,a} \ \sigma_{y_0} \ \sigma_a. \quad (4.34)
$$

The minimum variance is obtained for

$$
x - x_0 = -\frac{\rho_{y_0,a} \ \sigma_{y_0}}{\sigma_a}, \quad (4.35)
$$

and equals

$$
\sigma^2_{y,\min} = \sigma^2_{y_0} \ (1 - \rho^2_{y_0,a}). \quad (4.36)
$$
If $\rho_{y_0,a} > 0$, this minimum is located at $x < x_0$, and the variance increases at $x_0$. If $\rho_{y_0,a} < 0$, the minimum is at $x > x_0$, and the variance decreases at $x_0$.

Turning to Fig. 4.7, we see that most parameters display an initial increase in variance, which peaks around adolescence. Combining the information from Fig. 4.7 with age trends described in Sec. 4.3.3, we find that larger (or less negative) values of $\alpha$, $G_{ee}$, $G_{esc}$, $G_{srs}$, $t_0$, and $p_0$ at age 6 are associated with slower reductions in these parameters, while larger initial values of $\gamma$ and less negative initial values of $G_{ei}$ predict more rapid increases ($\rho_{y_0,a} > 0$). On the other hand, the variance in $G_{esre}$ initially decreases, indicating that more negative values of this parameter are associated with rapid increases ($\rho_{y_0,a} < 0$).

The reduction in variance after adolescence indicates an opposite situation to that at age 6, suggesting that individuals who initially developed rapidly then decelerate with respect to those who initially developed more slowly. Presumably this is explained by the slowing down of brain development once parameters reach values within the adult range; thus, on average, individuals with slow or late-onset parameter changes finish developing later than those with fast or early-onset parameter changes.

Since the distribution of slopes changes with $x$, the situation is more complicated than that described by Eqs (4.33)–(4.36). This means that these equations are most useful for obtaining qualitative, rather than precise quantitative, information about the relationships between parameter values and rates of parameter changes with age.

### 4.4 Discussion

This study considered age trends in parameters obtained by model fits to empirical EEG spectra of a large sample (1503 subjects) of healthy males and females aged 6–86 years. Theoretical spectra were generated from a mean-field model of the thalamocortical system, describing interactions between excitatory and inhibitory cortical populations, and thalamic relay and reticular nuclei. Fitting to these spectra provided physiologically meaningful information on the neuronal substrates underlying the EEG. Fitted parameters included an average synaptodendritic decay rate ($\alpha$), a damping rate for cortical propagating waves ($\gamma$), an average axonal delay for a full thalamocortical loop ($t_0$), and an overall power normalization parameter ($p_0$). In addition, gains were obtained for excitatory and inhibitory cortical interactions ($G_{ee}$ and $G_{ei}$, respectively), a direct loop between cortex and relay nuclei ($G_{ese}$), an indirect thalamocortical loop passing through the reticular nucleus ($G_{esre}$), and an intrathalamic loop ($G_{srs}$). Net inhibitory connections or loops were represented by negative gains ($G_{ei}$, $G_{esre}$, and $G_{srs}$), whereas net excitatory interactions had positive gains ($G_{ee}$ and $G_{ese}$). The robustness of fits was assessed by refitting empirical spectra.
with noise added, and comparing old and new parameter values. Nonpara-
metric statistical methods were used to detect trends in parameters across the
entire age span, and in the ranges 6–14, 14–20, and ≥ 20 years, since a number
of slopes changed considerably around 14 and 20 years. Differences in model
parameters between the youngest and oldest age groups were compared with
changes in quantitative EEG (qEEG) measures (absolute and relative power,
and dominant alpha frequency). Aided by the large sample size, many signi-
cificant results were found, which we summarize here and interpret in the light of
the relevant literature.

**General findings**

The most robustly fitted parameter was $G_{srs}$, followed, respectively, by $t_0$,
$\alpha$, $p_0$, $G_{ee}$, $G_{esre}$, $\gamma$, and $G_{ese}$. We found the least robust parameter to be $G_{ei}$,
consistent with the earlier result that this gain varied widely within individuals
in a study of males aged 18–28 years (see Chapter 3).

Between-fit differences in parameters were significantly correlated for a large
number of parameter pairs. This occurs both because different sets of param-
eters can yield identical spectra, and because of the differential dependence of
the goodness of fit on the parameters. The former introduces uncertainty in
fitted parameters even if the spectrum is perfectly known, whereas the latter
introduces additional uncertainty due to the presence of noise. Associations
between parameters due to these effects may cause age trends that are not
physiological in origin, so particularly trends in parameters that are not highly
robust should be interpreted with caution.

Averaged across age, there were significant sex differences in $t_0$, $G_{ese}$, $G_{esre}$,
and $G_{srs}$, which were small compared to changes across the life span in either
sex. Similarly, EEGs depended less on sex than on age in a study of a large
group of healthy children and young adults (Matsuura et al., 1985). Average
values of $\alpha$, $\gamma$, $G_{ee}$, $G_{ei}$, and $p_0$ did not differ significantly between males
and females. Parameters varied together across sex as they did across age:
females and older subjects tended to have larger $t_0$ and $|G_{srs}|$, and smaller
$G_{ese}$ and $|G_{esre}|$ than males and younger subjects. Both common or correlated
underlying physiological processes, and correlations induced by fitting, may
have contributed to this covariation of parameters.

Interestingly, we found a number of significant parameter changes in adoles-
cence, most notably in $\gamma$, despite reports that EEG records show little change
in the range 13–20 years (Niedermeyer, 1982d). These trends highlight the
sensitivity of our model parameters to aspects of EEG spectra that are not
captured by commonly used quantitative methods.
The average decay rate $\alpha$ for cell-body potentials in response to synaptic inputs, and by implication also the rise rate $\beta$ (since $\beta = 4\alpha$ was imposed), decreased significantly from 6–14 years, and continued to decrease until about age 20, after which the trend leveled off. The correlation coefficient for a slight increase in $\alpha$ during adulthood was not significant at the 0.05 significance level. There were no significant sex differences in trends for this parameter.

Smaller values of $\alpha$ enhance the low-pass filter properties of the synapses and dendrites, and correspond to less high-frequency ($\gtrsim 30$ Hz) activity in the EEG (Rowe et al., 2004a). The relative constancy of $\alpha$ for adults in our study suggests that increases in relative high-frequency power with age in adulthood (Dustman et al., 1999) are largely independent of changes in synaptodendritic rates.

Several factors may contribute to the observed trends in $\alpha$. First, a number of studies have found the total length of dendrites in the human cortex to increase in childhood, over longer periods in frontal than in visual areas (Becker et al., 1984; Huttenlocher, 1990), and this process may continue even into old age in some areas (Buell and Coleman, 1979, 1981). Unless dendritic thickness increases proportionally to the square of the length, this is expected to increase the electrotonic length of neurons (Hill et al., 1994), leading to longer effective time constants (Ascoli, 2003). Unfortunately, investigations of dendritic thickness are sparse and rarely quantitative, at best allowing the conclusion that dendritic thickness of pyramidal neurons in certain cortical layers and areas increases slightly at least until age 5 years (Koenderink and Uylings, 1995; Petanjek et al., 2008). A number of studies have reported regression of dendritic trees in adulthood (de Brabander et al., 1998; Esiri, 2007; Jacobs et al., 1997; Uylings and de Brabander, 2002), which may contribute to slight increases in $\alpha$ in this age range.

Alterations in intrinsic membrane properties and numbers of neurotransmitter receptors may also affect $\alpha$. Expanded membrane surface and reduced capacitance have been suggested to contribute to decreases in membrane time constants during maturation (Tennigkeit et al., 1998; Warren and Jones, 1997), in contrast with the trend in $\alpha$ until age 20 found here. The expression of subunits of the NMDA receptor, which mediates slow glutamatergic transmission, reaches a peak in early development, after which it declines at a decreasing rate (Magnusson et al., 2002; Ontl et al., 2004). These changes are also expected to increase $\alpha$. Basic membrane properties of layer 5 pyramidal cells in the monkey prefrontal cortex do not appear to change with aging (Luebke and Chang, 2007), but the input resistance of layer 2/3 pyramidal cells and hippocampal cells was found to be increased in aged relative to young monkeys, possibly
related to decreased numbers of ion channels (Chang et al., 2004; Luebke and Rosene, 2003). Luebke and Rosene (2003) also reported significantly longer decay times of inhibitory postsynaptic currents in hippocampal cells of aged compared to young monkeys. This was tentatively attributed to changes in the subunit composition of GABA_A receptors, as found by Gutierrez et al. (1997) in rat cerebellum and cerebral cortex. These effects would tend to decrease α, and thus do not seem to account for the trends in adults seen in our study. Therefore, these results merit further investigation.

Besides the growth of dendritic trees, another cause of reductions in during childhood may be the positive contribution of fitting to the correlation between G_{srs} and α. Since G_{srs} becomes more negative with age, and this parameter is more robustly fitted than α, smaller estimated synaptodendritic rates may be partly a spurious result of stronger intrathalamic connections.

Cortical damping rate γ

A damped-wave equation for cortical activity was included in the model based on experimental observations of spreading waves of neuronal activity in response to localized stimulation (Chervin et al., 1988; Nunez, 1974a; Schiff et al., 2007; Xu et al., 2007). The parameter γ, representing the average damping rate of such waves, increased in both sexes until about age 20, after which it showed a reduction for which the Spearman correlation was not significant (p = 0.22), but which appeared significant according to a bootstrapping method. Larger values of γ are associated with sharper, larger-amplitude, and slightly higher-frequency peaks in the EEG spectrum (Rowe et al., 2004a). Thus, changes in the damping rate of cortical waves may contribute to the shift of alpha peaks to higher frequencies during childhood (Hughes, 1987; Kooi, 1971; Niedermeyer, 1982d; Somsen et al., 1997), and the narrowing of alpha peaks that was found by Alvarez Amador et al. (1989) at the C3 electrode. Power augmentation due to larger γ was offset by other parameter changes, including reduced p_0 (see below), to yield a net decline in peak amplitudes, in agreement with the literature (Niedermeyer, 1982d).

Since γ is the ratio of the average axonal propagation speed and the typical range of cortical axons, increased γ is associated with faster transmission and/or shorter effective ranges. Ongoing cortical myelination (Perrin et al., 2008; Sowell et al., 2003) may contribute to increases in γ throughout childhood and adolescence by increasing axonal transmission speeds. However, the more rapid growth of white matter in boys than in girls (Perrin et al., 2008) did not translate into greater slopes for γ in our study.

A number of studies have found reductions in white matter volume during aging, especially from the fifth decade onward (Ge et al., 2002; Miller et al.,
1980; Piguet et al., in press). Even in myelin sheaths that continue to grow during aging, defects accumulate, and thick sheaths are prone to splitting (Peters, 2002a,b). A number of studies have related aging and defective myelin with reduced conduction velocities along nerve fibers (Aston-Jones et al., 1985; Felts et al., 1997; Gutiérrez et al., 1995; Morales et al., 1987; Xi et al., 1999). Thus, accumulating myelin defects may be partly responsible for the slight decrease in $\gamma$ in adults in our study.

It should also be considered that correlations of $\gamma$ with $t_0$, $G_{ese}$, $G_{esre}$, and $G_{srs}$ induced by fitting may have contributed to increases in $\gamma$ with age. For instance, $G_{srs}$ decreased with age, and we found that fitting causes a spurious negative association between $G_{srs}$ and $\gamma$. Similar arguments apply to $t_0$, $G_{ese}$, and $G_{esre}$.

Corticothalamic loop delay $t_0$

Averaged across the entire age span, the axonal delay $t_0$ was slightly longer in females than in males. Since the location of the alpha peak in model spectra depends on the inverse of $t_0$, this is expected to correspond to higher alpha peak frequencies in males than in females. Males did consistently show slightly higher peak frequencies across age and sites, except around age 20, when females had higher peak frequencies. Averaged across age, we did not find significant sex differences in alpha peak frequencies at the Cz electrode.

Our results contrast with the finding that alpha peak frequencies are on average slightly higher in females than in males up to age 12–13 (Petersén and Eeg-Olofsson, 1971), as well as averaged over the entire life span (Aurlien et al., 2004). This discrepancy may be partly explained by the fact that neither Petersén and Eeg-Olofsson (1971) nor Aurlien et al. (2004) used spectral analysis, and instead relied on time series (which leads to less precise estimates, particularly since traces are modulated by lower-frequency activity). Furthermore, Aurlien et al. studied 4651 patients with various pathologies (mostly epilepsy), and selected the highest alpha frequency for each subject. All these factors make it difficult to compare their findings with ours.

The decline in $t_0$ observed in males up to age $\sim$14, and in females up to age $\sim$20, reflected accelerated alpha rhythms. This corresponds well with findings reported in the literature, as summarized for instance by Petersén et al. (1975) and Klimesch (1999). An increase in the frequency of the alpha peak from about 5–6 Hz to 10 Hz is observed in children between ages 1 and 15 years (Hughes, 1987; Kooi, 1971; Niedermeyer, 1982d; Somsen et al., 1997), occurring in a number of growth spurts (Epstein, 1980; Hudspeth and Pribram, 1990; Thatcher, 1992). Our data appear to confirm the finding by Petersén and Eeg-Olofsson (1971) that the alpha rhythm increased in frequency faster in girls
than in boys.

We found that $t_0$ increased into old age in both sexes, associated with a gradual reduction in the frequency of the alpha peak. This is consistent with some early studies of aged individuals without organic brain disease (Hughes and Cayaffa, 1977; Obrist, 1954), but was either not found in more tightly controlled samples, or attributed to age-related pathologies (Duffy et al., 1984, 1993; Katz and Horowitz, 1982). However, Klimesch (1999) noted that the absence of a significant trend in alpha peak frequency reported by Duffy et al. (1984) was due to a relative lack of change between 30 and 50 years, whereas this frequency diminished by about 1 Hz between the ages of 60 and 80. We also observe that slight decreases in the frequency of the alpha peak may not have reached statistical significance due to the relatively small sample (63 subjects) used by Duffy et al. (1984). Aurlien et al. (2004) also found dominant alpha frequencies to decrease after age 45, independent of pathology. More detailed analysis of these matters is postponed to future work, in which trends in model parameters will be further compared with empirical spectral and evoked response potential (ERP) data.

Reductions in $t_0$ early in life may be partly attributed to ongoing white matter development during childhood and adolescence (Barnea-Goraly et al., 2005; Thompson et al., 2000). However, we found no sex difference in the rates of decline in $t_0$ between the ages of 6 and 14 years, in apparent contrast to faster increases in white matter volume in boys than in girls after age 7 (Caviness et al., 1996; de Bellis et al., 2001). Increases in $t_0$ in adulthood may be linked with loss of white matter and accumulating damage to myelin sheaths (Peters, 2002a,b; Piguet et al., in press).

**Gains**

Gain parameters quantify the effective (linear) interactions between populations in our model, and depend on the average numbers of synapses between populations, synaptic strengths, and the excitability of neurons. All gains except that for the loop between thalamic relay and reticular nuclei, $G_{srs}$, had larger average absolute values in males. More negative $G_{srs}$ corresponded to differences in qEEG measures including greater absolute and relative beta power. Thus, the greater beta power in women than in men reported in the literature (Veldhuizen et al., 1993) may be related to stronger interactions between the thalamic relay and reticular nuclei in women.

The absolute values of all gains except $G_{srs}$ diminished with age, although trends in $G_{ee}$ did not reach significance for the sample as a whole. In the range 14–20 years, $G_{ee}$ decreased considerably in females, but stayed almost constant in males. Changes in $G_{ei}$ and $G_{srs}$ occurred fastest in the range 6–14 years,
whereas $G_{ese}$ and $G_{esre}$ changed most rapidly after age 20.

Relative delta and theta power have been found to gradually decrease during childhood (Alvarez Amador et al., 1989). Our results suggest that stronger connections between the thalamic relay and reticular nuclei (quantified by $G_{srs}$) contribute to reductions in relative low-frequency power during development. Weaker intracortical inhibition (quantified by $G_{ei}$) decreases relative theta power, but increases relative delta power, whereas decreases in $G_{ee}, G_{ese},$ and $|G_{esre}|$ have the opposite effect. Therefore, changes in these gains are less likely to result in joint reductions in delta and theta power. We found weaker $G_{ese}$ and $G_{esre}$, and stronger $G_{srs}$ to be associated with increases in relative high-frequency power in adulthood. Such increases in high-frequency power are in agreement with the literature (Koyama et al., 1997).

Reductions in $G_{ee}$ in females aged 14–20 years may have a variety of causes. Extensive pruning of excitatory synapses occurs in primate cortex during adolescence (Gonzalez-Burgos et al., 2008). Particularly the density of NMDA glutamate receptors decreases with age, and reduced cortical glutamate content has been observed in aged animals (Segovia et al., 2001). Although decreased glutamate uptake may compensate partly for the decline in glutamate release, these findings appear to support a reduction in $G_{ee}$. However, these findings do not explain the observed sex differences in trends in $G_{ee}$, so this issue deserves further exploration.

The observed decline in $|G_{ei}|$ during childhood is surprising, since the number of GABAergic synapses increases in this period of life (Heinen et al., 2003), and the brain becomes less vulnerable to epileptic seizures (Camfield et al., 1996). Furthermore, Luebke et al. (2004) found synaptic inhibition in the monkey prefrontal cortex to increase with age. On the other hand, the open times of GABA_A receptors shorten during development, impairing inhibitory synaptic transmission (Bosman et al., 2005). There is some experimental evidence supporting the reduction in inhibitory cortical interactions in adulthood found here. Poe et al. (2001) described an age-related reduction in the numbers of putative inhibitory synapses in layer 2 of rat somatosensory cortex. Furthermore, some studies with transcranial magnetic stimulation have revealed reduced excitability of cortical inhibitory circuits with aging (Hortobágyi et al., 2006; Peinemann et al., 2001). Since $G_{ei}$ was the least robustly fitted parameter, decreases in $p_0$, $G_{ee}, G_{ese},$ and $|G_{esre}|$ may also have caused spurious reductions in $|G_{ei}|$.

Early increases in the strength of interactions between thalamic reticular and relay nuclei, quantified by $|G_{srs}|$, may be related to the growing ability of reticular neurons to sustain bursts of activity (Tennigke et al., 1998; Warren and Jones, 1997). In addition, substantial growth of dendritic arbors occurs during maturation (Warren and Jones, 1997), possibly enabling more synaptic
contacts to be established. However, dendritic growth cannot account for continued increases in $|G_{srs}|$ during adulthood, which is characterized by regressive processes (Abe et al., 2008). Enhanced expression of metabotropic glutamate receptors in the thalamus during aging (Simonyi et al., 2005) may play a role in the observed trends in $G_{srs}$. Loss of synapses may explain the significant reductions in $G_{ese}$ and $|G_{esre}|$ in adults found here. However, in view of the multitude of possible factors involved in determining gain values, it is difficult to assign definite causes to these trends, and further research is required.

*Spectral power normalization $p_0$*

We found that the power normalization parameter $p_0$ was slightly larger on average in females than in males, although this difference was not significant at the 0.05 level ($p = 0.083$). This accords with the finding that the skulls of white males are slightly thicker at the vertex throughout life than those of white females (Adeloye et al., 1975), since thicker skulls cause greater attenuation of the signal. However, no such differences were found in black subjects, and females had thicker skulls than males at parietal and parieto-occipital sites in the third decade and after age 60. Thus, different findings for $p_0$ may be expected at electrode sites other than Cz.

The parameter $p_0$ generally diminished with age, most strongly before age 14 years in females, but mainly from 14 to 20 years in males. The negative trend in $p_0$ agrees with the decrease in EEG amplitude with age reported in the literature (Aurlien et al., 2004; Hartikainen et al., 1992; Matoušek et al., 1967; Polich, 1997). Closer inspection of the data revealed that $p_0$ only decreased systematically from about age 10 onward. This is consistent with reports that EEG amplitude increases until 6–11 years and then diminishes (Hughes, 1987; Petersén and Eeg-Olofsson, 1971; Petersén et al., 1975). Due to the relatively small number of subjects aged $> 80$ years, it was not possible to verify from our data if power increased again in the very old, as reported by Aurlien et al. (2004) for a large number of patients with different pathologies.

Increases in skull thickness in the first two decades of life (Adeloye et al., 1975) may account for substantial decreases in EEG power recorded on the scalp (Eshel et al., 1995). The reduction in brain volume across the life span is also likely to be linked to negative trends in $p_0$. Most studies find that age-related atrophy is more extensive in men than in women (Coffey et al., 1998; Cowell et al., 1994; Gur et al., 1991; Tomlinson et al., 1968; Xu et al., 2000), although the onset may be earlier in women (Hatazawa et al., 1982; Hubbard and Anderson, 1983). Greater changes in peripheral and lateral fissure cerebrospinal fluid volume were also observed in men than in women between 65 and 95 years of age (Coffey et al., 1998). These results accord with the steeper
slope in $p_0$ for males compared to females aged $\geq 20$ in our study, although this difference was not statistically significant.

Variance trends

Inter-individual variances in model parameters were shown to change across age, peaking around adolescence for most parameters. We interpreted this in terms of the correlations between parameter values at age 6 and the rates of changes with age. Since most variances increased in childhood, larger (or less negative) parameter values were generally associated with faster increases or slower reductions in these parameters. This suggests that large values at age 6 were the result of parameter trends initiated already before this age. The opposite applied to $G_{esre}$, for which highly negative values predicted rapid increases. The reversal of variance trends around adolescence indicates that subjects who initially developed rapidly decelerated with respect to subjects with slow initial changes, suggesting that the former were quicker to reach the adult stage.

The data from the current study are partly complemented by our longitudinal study of healthy males aged 18–28 (Chapter 3), which found within-subject differences in the absence of substantial age trends to account for a large percentage of the total variance within and between individuals. The largest age correlations in the present study were around 0.3. Thus, age accounted for $\leq 9\%$ of the inter-individual variance in model parameters. This is expected to complicate the detection of age-related changes in individual subjects. This problem could be circumvented by averaging spectra over more epochs, or obtaining a larger number of recordings at different times.

Limitations and future work

The cross-sectional design is a potential limitation of our study, rendering the results sensitive to any systematic changes in brain size, structure, and physiology in successive generations. Such secular trends have been consistently observed for instance in IQ-type tests, partially invalidating comparisons between scores on the same tests obtained by people from different birth cohorts (Flynn, 1999). If environmental factors such as changes in education or nutrition cause consistent changes in EEG spectra in consecutive birth cohorts, a longitudinal design will be necessary to test the effects of age itself on model parameters.

An identical subject set will be used to compare our results with data on alpha peak morphology (Chiang et al., 2008) and model fits to ERPs (Kerr et al., 2008), eliminating important sources of experimental bias and uncertainty.
In addition, it will be possible to determine links with genetics and measures of general and social cognition using data from the Brain Resource International Database (www.brainresource.com) (Gordon et al., 2005). Great advantages of this standardized database are its size, diversity of recording modalities, and the uniformity of exclusion criteria and experimental conditions. Convergent evidence from different modalities will help to elucidate some of the links between the physiological substrates and functional aspects of brain aging.
Chapter 5

Mean-field modeling of the basal ganglia-thalamocortical system. I. Firing rates in healthy and parkinsonian states

Parkinsonism leads to various electrophysiological changes in the basal ganglia-thalamocortical system (BGTCS), often including elevated discharge rates of the subthalamic nucleus (STN) and the output nuclei, and reduced activity of the globus pallidus external segment (GPe). These rate changes have been explained qualitatively in terms of the direct/indirect pathway model, involving projections of distinct striatal populations to the output nuclei and GPe. Although these populations partly overlap, evidence suggests dopamine depletion differentially affects cortico-striato-pallidal connection strengths to the two pallidal segments. Dopamine loss may also decrease the striatal signal-to-noise ratio, reducing both corticostriatal coupling and striatal firing thresholds. Additionally, nigrostriatal degeneration may cause secondary changes including weakened lateral inhibition in the GPe, and mesocortical dopamine loss may decrease intracortical excitation and especially inhibition. Here a mean-field model of the BGTCS is presented with structure and parameter estimates closely based on physiology and anatomy. Changes in model rates due to the possible effects of dopamine loss listed above are compared with experiment. Our results suggest that a stronger indirect pathway, possibly combined with a weakened direct pathway, is compatible with empirical evidence. However, altered corticostriatal connection strengths are probably not solely responsible for substantially increased STN activity often found. A lower STN firing threshold, weaker intracortical inhibition, and stronger striato-GPe inhibition help explain the relatively large increase in STN rate. Reduced GPe-GPe inhibition and a lower GPe firing threshold can account for the comparatively small
decrease in GPe rate frequently observed. Changes in cortex, GPe, and STN help normalize the cortical rate, also in accord with experiments. The model integrates the basal ganglia into a unified framework along with an existing thalamocortical model that already accounts for a wide range of electrophysiological phenomena. A companion study (Chapter 6) discusses the dynamics and oscillations of this combined system.

5.1 Introduction

The basal ganglia have been studied extensively in connection with a variety of motor and cognitive disorders, including Parkinson’s disease (PD), Huntington’s disease, and schizophrenia (Bar-Gad et al., 2003; Goldman-Rakic and Selemon, 1990; Gray et al., 1991; Graybiel, 1990; Haber and Gdowski, 2004; Swerdlow and Koob, 1987; Walters et al., 2007; Waters et al., 1988). In PD, degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) leads to changes in tonic and phasic neuronal discharges in the components of the basal ganglia-thalamocortical system (BGTC). Many studies have provided detailed descriptions of changes in discharge patterns with parkinsonism, as well as suggestions for the pathways and mechanisms by which these patterns arise (Bar-Gad et al., 2003; Bergman and Deuschl, 2002). An influential proposal is the direct/indirect pathway model of Albin et al. (1989), which postulates distinct pathways through two populations of striatal neurons expressing either the D1 class or D2 class of dopamine receptor. D1-expressing neurons project monosynaptically to the globus pallidus internal segment (GPI) and the substantia nigra pars reticulata (SNr), giving rise to the direct pathway, whereas D2-expressing neurons project polysynaptically to these output nuclei via the globus pallidus external segment (GPe) and the subthalamic nucleus (STN), forming the indirect pathway. By enhancing transmission through D2 cells and reducing transmission through D1 cells, degeneration of nigrostriatal dopaminergic neurons would decrease the GPe firing rate in this model, and increase the rates of STN and the output nuclei. This would amplify the inhibitory effect exerted by the output nuclei on the thalamus, leading to parkinsonian symptoms such as akinesia and tremor. The direct/indirect pathway model was later modified to include the so-called hyperdirect pathway, upon the realization that the STN receives input directly from the cortex, forming another major input station of the basal ganglia (Nambu et al., 2000). The direct, indirect, and hyperdirect pathways are illustrated in Figure 5.1.

Physiologically-based mathematical models allow electrophysiological phenomena to be studied not just qualitatively but also in quantitative terms, thus better clarifying the underlying mechanisms. Most computational studies of the basal ganglia consider networks of neurons. Terman et al. (2002)
presented a model of the network formed by the STN and the GPe, which displayed either <1 Hz or 4–6 Hz oscillations upon dopamine depletion, depending on the network architecture and connection strengths. Rubin and Terman (2004) described a neuronal network model that included also the GPi and the thalamus, and illustrated how high-frequency stimulation of the STN may facilitate signal transmission by the thalamus in parkinsonian patients. Specific aspects of basal ganglia function, such as visual attention (Jackson et al., 1994) and decision threshold tuning (Lo and Wang, 2006) have also been addressed in computational studies. Leblois et al. (2006) presented a neuronal network model that could account for loss of action selection and predicted the appearance of ~7–10 Hz oscillations in the hyperdirect loop after dopamine depletion. In a detailed model building on earlier work (Gurney et al., 2001a,b; Humphries and Gurney, 2001), Humphries et al. (2006) reproduced the enhanced ~1 Hz activity that is observed in the STN and globus pallidus (GP; the rodent homolog of the GPe) of anesthetized rats with nigrostriatal lesions, and gamma-band activity in the healthy state.

The purpose of this chapter is to describe a physiologically plausible mean-field model of the intact BGTCs that can reproduce firing rates characteristic of PD with realistic changes in parameters relative to the non-parkinsonian case. A mean-field model has the advantage over neuronal network models that it can predict large-scale properties of neuronal assemblies and directly assess their dependence on connection strengths between populations. Moreover, mean-field models have comparatively few parameters, and can be implemented for a larger number of populations and connections without leading to an overly complicated set of equations or excessive computational demands. Thus, both numerical and analytical results are more readily obtained. An existing mean-field model has been used successfully to describe thalamocortical oscillations contributing to the electroencephalogram (EEG), yielding predictions of cortical frequency and wavenumber spectra (O’Connor et al., 2002; Robinson et al., 2001b), coherence and correlations (Robinson, 2003), the electrophysiology of epileptic seizures (Breakspear et al., 2006; Robinson et al., 2002), evoked response potentials and steady-state evoked potentials (Kerr et al., 2008; Robinson et al., 2001a), and changes with arousal (Robinson et al., 2005). This study provides a first step towards integrating the thalamocortical system and the basal ganglia in a unified framework.

Our model adds to existing models by estimating the strengths of a large number of connections in the BGTCs, and investigating the dependence of average firing rates on these connection strengths. The influences of various projections not present in the classic direct/indirect pathway model are explored, and possible reasons for the prominent hyperactivity of the STN in parkinsonism are discussed. Estimates of parameters and firing rates are based
on an extensive review of the experimental literature. Changes in firing rates with nigrostriatal dopaminergic denervation are an aspect of the electrophysiology of the BGTCS that remains to be explained quantitatively, and as such are of key scientific interest. Moreover, steady states form an essential basis for the analysis of dynamics and oscillations, which are the subject of a companion study (Chapter 6).

It is almost impossible for a model of a system as complex as the basal ganglia to incorporate all relevant data, especially as new discoveries are regularly being made. Thus we attempt to distill the main findings from the wealth of available data, while providing a framework that allows for more detailed modeling of basal ganglia structure, activity, and function in future.

The physiological background of our model is presented in Sec. 5.2. Section 5.3 details the model equations and the possible effects of dopamine depletion. The model is then used to derive firing rates of the BGTCS in the normal and parkinsonian states in Sec. 5.4. As mentioned above, these results lay the foundation for the analysis of dynamics and oscillations in Chapter 6.

5.2 Physiological background

This section describes the physiological background of the BGTCS on which our model is based, which allows us to compare the predictions of our model with experimental results. Section 5.2.1 details the main connections between the basal ganglia nuclei, its thalamic projection sites, and the cerebral cortex. Section 5.2.2 is devoted to the firing rates of the various components in the healthy state and in PD.

5.2.1 Connectivity of the basal ganglia

The main structures comprising the basal ganglia are the striatum (caudate nucleus, putamen, and ventral striatum), pallidum (internal and external segments and ventral pallidum), substantia nigra (pars compacta, pars reticularis, and pars lateralis), and subthalamic nucleus. They are part of a system of pathways, some of which form closed loops, connecting the basal ganglia with the cerebral cortex and thalamus. Information flow through the basal ganglia has been described as following three parallel, mostly separate, pathways (sensorimotor, association, and limbic), which may be further subdivided into somatotopically organized pathways or pathways concerned with different aspects of motor function and cognition (Alexander et al., 1986; Alexander and Crutcher, 1990). The main connections of the BGTCS are depicted in Fig. 5.1.

The SNc and its medial extension, the ventral tegmental area (VTA), send important dopaminergic projections to the striatum (Gerfen, 1992; Haber et al.,
Figure 5.1: Major connections of the BGTC. External input reaches the thalamus primarily from the brainstem. Filled arrowheads represent excitatory projections, open arrowheads inhibitory ones. Subscripts corresponding to each component are given in parentheses, and gray arrows indicate the direct, indirect, and hyperdirect pathways.

2000; Hanley and Bolam, 1997). Excitatory input from the cortex also reaches the basal ganglia mainly at the striatum; sensorimotor inputs terminate more specifically in the putamen, which also receives some associative input (Perron et al., 1984). The striatum is organized into “patch” and “matrix” compartments, which are distinguished on the basis of biochemical markers and their detailed sources and targets of activity (Gerfen et al., 1987). More than 90% of striatal neurons are medium spiny neurons (Yelnik et al., 1991), which can be classified both according to their compartmental origin and the class of dopamine receptor they primarily express (D1 or D2). These classifications are partly overlapping: both patch and matrix contain D1 and D2 receptors, although relative receptor densities may differ between compartments (Joyce et al., 1988). Neurons with D1-type receptors coexpress the peptides dynorphin and substance P; D2 cells are enriched in enkephalin (Gerfen et al., 1990). According to the classic direct and indirect pathway model (Albin et al., 1989; Alexander and Crutcher, 1990), D1 neurons project primarily to the output nuclei GPi and SNr, whereas D2 neurons project primarily to the GPe. Striatal impulses exert an overall excitatory effect on the thalamus and cortex via the direct pathway from the striatum to the output nuclei, and an inhibitory
effect via the indirect pathway to the output nuclei via the GPe and the STN (cf. Fig. 5.1).

In the direct/indirect pathway model, the SNc would mainly facilitate corticostratial transmission to D1 cells and inhibit transmission to D2 cells, so that dopamine loss would favor the indirect pathway. This simplified view has been called into question by findings that the segregation between D1 and D2 receptors is incomplete (Aizman et al., 2000; Inase et al., 1997; Surmeier et al., 1992, 1996), and that neurons expressing both receptor types project to both pallidal segments (Lévesque and Parent, 2005; Nadjar et al., 2006; Wu et al., 2000). The extent of colocalization of D1 and D2 class receptors reported in the literature ranges from almost none (Hersch et al., 1995; Le Moine and Bloch, 1995), to 20–35% (Inase et al., 1997; Lester et al., 1993; Meador-Woodruff et al., 1991), about half (Surmeier et al., 1996), or nearly all medium spiny neurons (Aizman et al., 2000). Some of these discrepancies may be explained by a lack of sensitivity of in situ hybridization techniques to low levels of mRNA, which are detected after mRNA amplification (Le Moine and Bloch, 1995), suggesting that even in cells where these receptors occur together, one type usually predominates. Therefore we assume that a significant proportion of striatal neurons expresses a large majority of either D1 or D2 class dopamine receptors.

Despite the collateralization of striatofugal axons, many studies have also shown that projections in the direct and indirect pathways can be at least partly distinguished. In a rat model of PD, striatopallidal neurons show increased expression of mRNA encoding D2 receptors and enkephalin, whereas striatonigral neurons show a reduction in mRNA for D1 receptors and substance P (Gerfen et al., 1990). In Huntington’s disease the striatal projection to GPe is more vulnerable than that to GPi (Deng et al., 2004; Reiner et al., 1988; Walker, 2007). In a study of mouse brain slices, Day et al. (2006) found that lack of dopamine causes a profound loss of dendritic spines on striatopallidal neurons but not on striatonigral neurons. Thus, we assume a partial segregation of the projections to the output nuclei and the GPe. However, our model provides an overarching framework in which both possibilities (segregation or overlap) can be incorporated, and differences between these possibilities can be explored.

Besides medium spiny neurons, the striatum contains various types of interneurons, including cholinergic tonically active neurons that make up about 1–5% of the striatum (Aosaki et al., 1995; Kawaguchi et al., 1995; Kimura et al., 1984), and GABAergic inhibitory interneurons that make up only a small percentage of the striatal population but have strong effects (Bolam et al., 2000; Köös and Tepper, 1999). In addition, medium spiny neurons have local axon collaterals through which GABA exerts a depolarizing effect at rest, but a hyperpolarizing effect near spike threshold (Plenz, 2003; Taverna et al., 2004).
Thus, lateral connections between medium spiny neurons will moderate the striatal firing rate with strong cortical inputs.

In primates the SNr and GPi are part of separate circuits, with different target areas and sources of activity (Ilinsky et al., 1993). The SNr receives input mostly from the caudate nucleus, which relays associative information from the prefrontal cortex as well as inputs from the frontal eye fields. It sends GABAergic projections mainly to the magnocellular part of the ventral anterior nucleus (VAmc) of the thalamus and is involved in the control of eye movements (Parent and Hazrati, 1995a). The GPi, on the other hand, receives input mainly from the premotor and primary motor cortices via the putamen, and relays this mainly to the ventrolateral thalamic nucleus (VL) (Haber and Gdowski, 2004). Despite these differences, GPi and SNr are often modeled as a single structure due to their closely related inputs and outputs, as well as similarities in cytology and function (Alexander and Crutcher, 1990; Bar-Gad et al., 2003). Since electrophysiological studies of the remaining basal ganglia nuclei often do not distinguish between associative and sensorimotor territories, it is difficult in practice to differentiate between the inputs to GPi and SNr. We therefore model these nuclei as a single combined structure, although the response to dopaminergic cell loss is more pronounced in the GPi (Mitchell et al., 1986; Wichmann et al., 1999).

Apart from the ventral anterior nucleus (VA) and VL, target sites of the basal ganglia output nuclei have been identified in the centromedian-parafascicular complex (CM-Pf) (Kim et al., 1976; Parent et al., 2001). Neurons in VA, VL, and CM-Pf send axons back mainly to the matrix compartment of the striatum (Carpenter, 1981; Gonzalo et al., 2002; McFarland and Haber, 2000; Parent, 1990; Ragsdale and Graybiel, 1988; Sadikot et al., 1992). Studies suggest that the influence of these projections is excitatory (Haber and Gdowski, 2004; Sadikot et al., 1992).

The GPe sends an important inhibitory projection to the STN, which in turn excites both the GPe and the output nuclei (Hamada and DeLong, 1992; Kita et al., 1983; Parent and Hazrati, 1995a; Shink et al., 1996). However, the pattern of connections between GPe, GPi, and STN is complicated by a direct projection from approximately a third of GPe neurons forming synapses on GPi cell bodies or proximal dendrites (Hazrati et al., 1990; Sato et al., 2000; Shink and Smith, 1995; Smith et al., 1994). These projections derive from axons also branching to STN and sometimes SNr (Sato et al., 2000). Besides its substantial innervation by striatum and STN, the GPe is extensively connected via local axon collaterals, which may exert a strong inhibitory influence since they terminate on cell bodies and proximal dendrites (Kita, 1994; Nambu and Llinás, 1997; Ogura and Kita, 2000).

As discussed in the Introduction, the STN forms an additional input station
of the basal ganglia. The cortico-STN projection originates in the primary motor cortex (M1) and somatosensory and premotor cortices, including the supplementary motor area (SMA) (Afsharpour, 1985; Nambu et al., 1996, 1997, 2000; Parent and Hazrati, 1995a). Because the STN influences the thalamus mainly via direct projections to the GABAergic output nuclei, the overall effect of this pathway on thalamic targets is inhibitory.

Connections within and between the thalamus and cortex complete the basal ganglia-thalamo-cortical system. These connections follow a previous model of brain electrical activity involving only the thalamus and cortex (Rennie et al., 1999; Robinson et al., 1997, 2001b, 2003b, 2005). The thalamic reticular nucleus (TRN) exerts a powerful inhibitory effect over the relay nuclei, from which it receives excitatory input. Both TRN and the relay nuclei are densely innervated by glutamatergic cortical neurons. Within the cortex our model includes excitatory corticocortical and inhibitory local circuit neurons. Finally, sensory stimuli reaching the thalamus mainly from the brainstem are modeled as external input.

5.2.2 Data on firing rates in normal and parkinsonian states

This section provides a summary of the mean firing rates of the basal ganglia nuclei and their thalamic and cortical targets in the normal and parkinsonian states, for comparison with modeling results in Sec. 5.4.

Some studies of firing rates and patterns of basal ganglia are performed during stereotaxic surgery for PD. However, most studies use one of two well-known animal models of parkinsonism. In monkeys, symptoms most closely resembling human parkinsonism are obtained by lesioning nigrostriatal neurons using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (DeLong, 1990). Depending on the species, this can lead to akinesia, bradykinesia, and/or resting tremor at frequencies of 4-8 Hz. Another widely used paradigm is the 6-hydroxydopamine (6-OHDA) rodent model of PD (Ungerstedt, 1968).

The average discharge rate of neurons in the primary motor and somatosensory cortices of monkeys is about 5-20 s^{-1} depending on the level of activity (Wannier et al., 1991). Some studies found the cortical rate to be unchanged with MPTP- or 6-OHDA-induced parkinsonism (Dejean et al., 2008; Goldberg et al., 2002), and parkinsonian symptoms have instead been linked with abnormal temporal organization of motor cortical activity (Brown, 2000; Goldberg et al., 2002; Salenius et al., 2002). On the other hand, fMRI studies in PD patients have found impaired activation of cortical areas normally co-activated with the striatum (Monchi et al., 2004, 2007), and a PET study showed that blood flow in the SMA of PD patients during performance of a motor task is
reduced relative to healthy subjects (Jenkins et al., 1992).

Most striatal medium spiny neurons fire spontaneously at a low rate of 0.5–2 s$^{-1}$ (DeLong et al., 1983; Haber and Gdowski, 2004; Kimura et al., 1996). However, Kiyatkin and Rebec (1999) reported a highly skewed distribution of striatal firing rates in awake rats, with a small fraction of fast-spiking neurons taking the average rate up to $\sim 6$ s$^{-1}$. This matches the rate in monkeys recorded by Goldberg et al. (2002). Several studies in 6-OHDA-lesioned rats have revealed elevated activity in striatal neurons with respect to healthy rats (Chen et al., 2001; Kish et al., 1999; Tseng et al., 2001; Walters et al., 2007), which may be due to a large activity increase in striatopallidal neurons and a smaller activity decrease in striatonigral neurons (Mallet et al., 2006). A relatively high average firing rate of $\sim 10$ s$^{-1}$ was also recorded in the putamen of PD patients (Magnin et al., 2000). On the other hand, one study reported the discharge rate of caudate neurons to be decreased from $\sim 6$ s$^{-1}$ to $\sim 4$ s$^{-1}$ with MPTP lesion (Yoshida, 1991), while another study found no change (Goldberg et al., 2002).

The normal GPi firing rate in primates is in the range 60–90 s$^{-1}$, with an increase of about 10–20 s$^{-1}$ after MPTP treatment in monkeys (Filion and Tremblay, 1991; Heimer et al., 2002; Yoshida, 1991). In line with these results, normalization of dopamine levels by application of the dopamine agonist apomorphine decreases the average firing rate of GPi neurons in PD patients (Merello et al., 1999). On the other hand, some studies found no significant change in average firing rates of GPi (Bergman et al., 1994; Wichmann et al., 1999) or its rodent homolog, the entopeduncular nucleus (EP) (Robledo and Feger, 1991). In one study the mean discharge frequency of GPi neurons in PD patients was only $\sim 59$ s$^{-1}$ (Sterio et al., 1994), and another study (Hutchison et al., 1994) found the average firing rate of GPi neurons in PD patients to be 67 s$^{-1}$ and no different from the average rate reported for normal monkeys. However, the posteroverentral portion of the GPi showed increased activity (mean rate 82 s$^{-1}$). This suggests that dopamine loss increases the firing rate in the sensorimotor portion of the GPi, while other parts are relatively unaffected. Magnin et al. (2000) similarly differentiated between the GPi as a whole, which had a firing rate of 91 s$^{-1}$ in PD patients, and the internal part of the GPi, which discharged at 114 s$^{-1}$.

SNr neurons in normal monkeys discharge at a mean rate comparable to that of GPi neurons (50–70 s$^{-1}$) (DeLong et al., 1983; Schultz, 1986). However, the SNr is less affected by dopamine lesions than other nuclei. For instance, the mean firing rate of SNr neurons in PD patients is $\sim 71$ s$^{-1}$ (Hutchison et al., 1998), very close to that in normal monkeys. In a study by Walters et al. (2007), SNr neurons of 6-OHDA-lesioned rats displayed a nonsignificant decrease in average firing rate 7–10 days post-lesion. MacLeod et al. (1990)
measured a short-term decrease (< 10 days postlesion) in the average firing rate of SNr neurons upon treatment with 6-OHDA, but the firing rate had normalized after a period of > 6 months. On the other hand, Benazzouz et al. (2000) and Burbaud et al. (1995) recorded significantly elevated discharge rates in the SNr of rats several weeks after lesions of the SNc. Alterations in SNr firing rates and patterns reported by Wichmann et al. (1999) were less pronounced than those in the GPi, and no significant change in SNr firing rate was observed.

GPe neurons can be divided into two main categories based on firing characteristics (DeLong, 1971; Filion and Tremblay, 1991; Sterio et al., 1994): about 85% of GPe neurons display high-frequency bursts of activity interspersed with long intervals of silence lasting up to several seconds. These neurons have a mean firing rate of ~55 s\(^{-1}\). The remaining 15% are slowly discharging neurons with occasional bursts and an average rate of ~10 s\(^{-1}\). Conflicting reports exist concerning changes in GPe rate, some studies finding a decrease of about 10–20 s\(^{-1}\) with nigrostriatal lesions (Boraud et al., 1998; Filion and Tremblay, 1991; Heimer et al., 2002; Pan and Walters, 1988), whereas others detected no significant change (Goldberg et al., 2002; Hutchison et al., 1994; Magill et al., 2001; Walters et al., 2007). Average GPe firing rates of 40–60 s\(^{-1}\) have been reported in patients with medication-resistant PD (Hutchison et al., 1994; Magnin et al., 2000; Sterio et al., 1994).

STN cells in monkeys display spontaneous tonic activity, firing at approximately 20–30 s\(^{-1}\), often in pairs or triplets of spikes (DeLong et al., 1985; Georgopoulos et al., 1983). Dopaminergic lesion has been reported to increase this rate by ~7 s\(^{-1}\) (Bergman et al., 1994). In agreement with these findings, STN neurons of PD patients have relatively high discharge rates of 37–43 s\(^{-1}\) (Benazzouz et al., 2002; Hutchison et al., 1998), while Levy et al. (2000) measured a higher median firing rate in STN cells that displayed tremor-related activity (53 s\(^{-1}\)) than in non-tremor-related cells (43 s\(^{-1}\)) of PD patients. Increases of 4–6 s\(^{-1}\) in mean STN discharge rate have been observed in 6-OHDA-treated rats (Kreiss et al., 1997; Walters et al., 2007), although some studies found no change or even a reduction in firing rate up to 4 weeks postlesion (Hollerman and Grace, 1992; Ni et al., 2001a).

Firing in pallidal-receiving areas of the thalamus was found to be 7–8 s\(^{-1}\) in PD patients compared with 18–19 s\(^{-1}\) in patients with essential tremor or pain (Molnar et al., 2005). Since the basal ganglia are not thought to be involved in the pathophysiology of pain or essential tremor, a rate of 18–19 s\(^{-1}\) probably represents normal thalamic activity, suggesting that activity of pallidal-receiving thalamic areas is reduced in PD. A significant decrease in thalamic activity was found in MPTP-treated cats (Schneider and Rothblat, 1996) but not monkeys (Pessiglione et al., 2005). However, metabolic studies in 6-OHDA-treated rats and MPTP-treated monkeys strongly point to hypoactivity of basal
ganglia-receiving areas of the thalamus in parkinsonism (Gnanalingham et al., 1995; Palombo et al., 1988; Rolland et al., 2007).

The TRN has an average firing rate of about 20–30 s\(^{-1}\) in awake cats, which correlates positively with the level of arousal and hence with the activity of the relay nuclei (Steriade et al., 1986). Raeva and Lukashev (1987) measured the activity of TRN neurons during stereotaxic surgery on subjects with dyskinesia, most of whom were parkinsonian. They found three types of cells with different discharge patterns, for which the overall mean firing rate was about 10 s\(^{-1}\). Although information on changes in TRN activity with dopamine loss is limited, this may be taken as indirect evidence that the TRN is hypoactive in PD.

Average firing rates of the components of the BGTCs in the healthy state and changes with parkinsonism are summarized in Table 5.1. We do not report the control rates from many of the studies in rats, because they were performed on animals under general anesthesia, which leads to significantly lower firing rates than the freely moving condition (Benazzouz et al., 2000; Kreiss et al., 1997; Pan and Walters, 1988; Rohlfs et al., 1997). Human control data are not available for most nuclei, since stereotaxic surgery is only performed in clinical cases. Directions of firing rate changes in humans are inferred by comparison with data from monkeys.

5.3 Model formulation and preliminary analysis

In order to arrive at a tractable model of the dynamics governing the system in Fig. 5.1, we use a mean-field formulation, in which neuronal properties are spatially averaged. The dynamics are then governed by a set of equations relating the average firing rates of populations of neurons to changes in cell-body potential, which are in turn triggered by average rates of incoming pulses. This approach is based on earlier work on a model of the electrophysiology of the corticothalamic system (Rennie et al., 1999; Robinson et al., 1997, 2001b, 2003b, 2005). Section 5.3.1 details the basic equations of the model. Parameter values for healthy adults in the alert, eyes-open state are estimated in Sec. 5.3.2, and used to evaluate fixed points in Sec. 5.3.3. In Sec. 5.3.4 we review possible ways of modeling dopamine depletion.

5.3.1 Basic equations

The first component of the model is the description of the average response of populations of neurons to changes in cell-body potential. The mean firing rate \(Q_a(V_a)\) of each population \(a\) is taken to be the maximum attainable firing rate \(Q_a^{\text{max}}\) times the proportion of neurons with a membrane potential \(V_a\) above
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<th>Location</th>
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<td>Relay nuclei</td>
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Table 5.1: Average firing rates of the BGTCs in the healthy state, and changes with respect to this state in PD patients (compared with normal rates in monkeys, humans, or cats, as available), in MPTP-treated monkeys, and in rats treated with 6-OHDA. In the rows for GPi and GPe, changes in firing rates in rats refer to the rodent homologs of these structures, the entopeduncular nucleus (EP) and the globus pallidus (GP). Changes reflect averages; the reaction to loss of dopamine may differ in individual cases. ↑, elevated; —, no change; ↓, reduced. References: a, Goldberg et al. (2002); b, Wannier et al. (1991); c Dejean et al. (2008); d, Jenkins et al. (1992); e Monchi et al. (2004); f Monchi et al. (2007); g, Yoshida (1991); h, Kiyatkin and Rebec (1999); i, Magnin et al. (2000); j Chen et al. (2001); k Kish et al. (1999); l, Tseng et al. (2001); m, Walters et al. (2007); n, DeLong (1971); o, Georgopoulou et al. (1983); p, Kimura et al. (1996); q, Heimer et al. (2002); r, Hutchison et al. (1999); s, Filion and Tremblay (1991); t, Boraud et al. (1998); u, Bergman et al. (1994); v, Wichmann et al. (1999); w, Robledo and Feger (1991); x, DeLong et al. (1983); y, Schultz (1986); z, Hutchison et al. (1998); A, Benazzouz et al. (2000); B, Burbaud et al. (1995); C, MacLeod et al. (1990); D, DeLong et al. (1985); E, Pan and Walters (1988); F, Benazzouz et al. (2002); G, Kreiss et al. (1997); H, Levy et al. (2000); I, Hollerman and Grace (1992); J, Ni et al. (2001); K, Molnar et al. (2005); L, Palombo et al. (1988); M, Gnanalingham et al. (1995); N, Rolland et al. (2007); O, Pessiglione et al. (2005); P, Steriade et al. (1986); Q, Raeva and Lukashev (1987).
the threshold potential $x$. Equivalently, the response of each neuron can be represented by a Heaviside step function $H(V_a - x)$ multiplied by $Q_a^\text{max}$, and the population rate is given by the integral of this response times the distribution $p(x)$ of firing thresholds,

$$Q_a(V_a) = Q_a^\text{max} \int_{-\infty}^{\infty} H(V_a - x)p(x)dx,$$

yielding the cumulative distribution function, which for a Gaussian distribution is the error function. However, the exact distribution of firing thresholds is not known, allowing us to work with the closely similar sigmoidal function

$$Q_a(r, t) \equiv S_a[V_a(t)] = \frac{Q_a^\text{max}}{1 + \exp[-(V_a(t) - \theta_a)/\sigma']},$$

for analytical convenience. Here, $\theta_a$ is the mean threshold potential of the population considered. Fitting (5.2) to the error function we find that $\sigma'$ is $\sqrt{3}/\pi$ times the standard deviation of the Gaussian distribution of firing thresholds (Wright and Liley, 1995). In the absence of detailed information on the standard deviations of firing thresholds in the basal ganglia, we set $\sigma'$ equal for all populations. The function (5.2) increases smoothly from 0 to $Q_a^\text{max}$ as $V_a$ runs from $-\infty$ to $\infty$.

The change in the mean cell-body potential due to afferent activity depends on the mean number of synapses $N_{ab}$ from afferent axons of type $b$ per receiving neuron of type $a$, and the typical time-integrated change $s_{ab}$ in cell-body potential per incoming pulse. Defining $\nu_{ab} = N_{ab} s_{ab}$, the change in the mean cell-body potential of type $a$ neurons is thus modeled as (Robinson et al., 2004)

$$D_{\alpha\beta}(t)V_a(t) = \sum_b \nu_{ab} \phi_b(t - \tau_{ab}),$$

$$D_{\alpha\beta}(t) = \frac{1}{\alpha\beta} \frac{d^2}{dt^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta}\right) \frac{d}{dt} + 1.$$  

Here, $\phi_b(t - \tau_{ab})$ is the incoming pulse rate, $\tau_{ab}$ represents the axonal time delay for signals traveling from type $b$ to type $a$ neurons, and $\alpha$ and $\beta$ are the decay and rise rates of the cell-body potential (we assume $\alpha < \beta$ without loss of generality). The differential operator $D_{\alpha\beta}(t)$ is a physiologically realistic representation of dendritic and synaptic integration of incoming signals (Rennie et al., 2000; Robinson et al., 1997). The synapses and dendrites attenuate high-frequency activity due to differential delays for signals passing through them, forming an effective low-pass filter with cut-off frequency intermediate between $\alpha$ and $\beta$. In general, $\alpha$ and $\beta$ can depend on both the sending and receiving neurons, but in order to restrict the number of parameters we take these to be

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equal for all populations, especially as the values of $\alpha$ and $\beta$ are not relevant to steady states, which are the main focus of the current chapter. Future work may use different rise and decay rates for different populations, as was done for instance by Rennie et al. (2000).

In a number of previous works, neuronal activity was modeled as spreading along the cortex in a wavelike fashion (Bressloff, 2001; Bressloff et al., 2003; Jirsa and Haken, 1996, 1997; Nunez, 1995), based on consistent experimental observations of such waves of activity upon localized cortical stimulation (Burns, 1951; Chervin et al., 1988; Golomb and Amitai, 1997; Lopes da Silva and Storm van Leeuwen, 1978; Nunez, 1974a; Prechtl et al., 1997; Rubino et al., 2006; Schiff et al., 2007; Wu et al., 1999; Xu et al., 2007). Estimates of characteristic axonal ranges and propagation speeds suggest that such waves are significantly damped on the scale of the human cortex (Robinson et al., 2001a, 2004; Wright and Liley, 1995). A damped-wave equation was derived in Robinson et al. (1997) using a range distribution of corticocortical fibers that decayed exponentially at large distances. Ignoring the spatial derivative, which is not relevant in the present context, this equation simplifies to

$$\frac{1}{\gamma_a^2} \left[ \frac{\partial^2}{\partial t^2} + 2\gamma_a \frac{\partial}{\partial t} + \gamma_a^2 \right] \phi_a(t) = Q_a(t),$$

where $\gamma_a = v_a/r_a$ is the damping rate, consisting of the average axonal transmission speed $v_a \simeq 5 - 10$ m s$^{-1}$ and the characteristic axonal range $r_a$. In practice, most types of axons are short enough to justify setting $\gamma_a = \infty$, which has been termed the local activity approximation (Robinson et al., 2004). We therefore take only $\gamma_e$, the damping rate associated with cortical pyramidal cells, to yield significant propagation effects. This turns all wave equations except the cortical one into delayed one-to-one mappings. The temporal dependence in Eq. (5.5) is given for completeness, although we are interested in steady states.

Besides cortical excitatory cells, our model includes eight neuronal populations: cortical inhibitory ($i$), striatal cells projecting to the output nuclei ($d_1$), striatal cells projecting to GPe ($d_2$), GPi/SNr ($p_1$), GPe ($p_2$), STN ($s$), thalamic relay nuclei ($s$), and TRN ($r$). The subscript $s$ for the relay nuclei follows the convention of earlier work, in which it referred only to specific relay nuclei, although here we also consider the diffusely projecting CM-Pf complex. Input from the brainstem to the thalamus is denoted by a subscript $n$. For simplicity, we consider inhibition within the striatum of D1 to itself and D2 to itself, but not between D1 and D2.
5.3.2 Parameter values

Before proceeding to the analysis of fixed points, we here discuss how parameter values were chosen based on known physiology. Among the parameters in our model that can be relatively well measured experimentally are axonal conduction times and maximum firing rates of neuronal populations. The relative strengths of the various connections can be estimated based on experimentally determined densities of projections, types of neurotransmitters, and locations of synapses. Besides, plausible parameters should yield realistic steady-state firing rates both before and after changes that would be expected with loss of dopamine. In this section we constrain parameter values for our model using evidence from a range of studies, leading to the nominal values given in Table 5.2. Note that the results of the present study are independent of axonal or dendritic delays, but these values are listed for completeness and use in Chapter 6.

Conduction delays between neuronal populations can be estimated using antidromic or sometimes orthodromic activation, spike-triggered averaging, or cross-correlation analysis (Nowak and Bullier, 1997). The results of such studies always include axonal propagation times, but may also include dendritic and synaptic delays and neuronal integration times of the sending and/or receiving populations, depending on the method used. It is important to take this into account, since dendritic and synaptic latencies and integration times may be as long or longer than axonal propagation times (Nowak and Bullier, 1997). In addition, care is needed to determine average or characteristic delays rather than the shortest possible ones, since the former are more relevant to ongoing oscillations.

Axonal delays measured using spike timing and correlation in mice, rabbits, cats, and monkeys range from 0.1–5 ms for the thalamocortical projection, and 1–30 ms for the corticothalamic projection, with longer delays expected after scaling these values to human brain size (Roberts and Robinson, 2008). As argued in that paper, ongoing corticothalamic oscillations depend on a weighted average of conduction velocities of many fibers, further increasing the latency with respect to the values found in most experimental studies, which typically select the shortest ones. In accordance with model fits to absence seizure dynamics (Roberts and Robinson, 2008) we split the axonal propagation time for a full loop into a thalamocortical axonal delay of 35 ms and a somewhat longer corticothalamic delay of 50 ms. The hypothesis that the alpha rhythm of the EEG is caused by a resonance in a corticothalamic loop with an axonal delay of ~85 ms has led to excellent agreement with data on a range of electrophysiological phenomena (O’Connor et al., 2002; Robinson et al., 2001b; Robinson, 2003; Breakspear et al., 2006; Kerr et al., 2008).

The corticosubthalamic pathway has been shown in some studies to act
<table>
<thead>
<tr>
<th>Quantity</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
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</tr>
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</tr>
<tr>
<td>$es, is$</td>
<td>$\tau_{es}, \tau_{is}$</td>
<td>35</td>
<td>ms</td>
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<tr>
<td>$d_{1e}, d_{2e}$</td>
<td>$\tau_{d_{1e}}, \tau_{d_{2e}}$</td>
<td>2</td>
<td>ms</td>
<td>Kimura et al. (1996), Nambu et al. (2000)</td>
</tr>
<tr>
<td>$d_{1s}, d_{2s}$</td>
<td>$\tau_{d_{1s}}, \tau_{d_{2s}}$</td>
<td>2</td>
<td>ms</td>
<td>Clugnet et al. (1990)</td>
</tr>
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<td>$p_1d_1$</td>
<td>$\tau_{p_1d_1}$</td>
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<td>ms</td>
<td>Kimura et al. (1996), Nambu et al. (2000)</td>
</tr>
<tr>
<td>$p_1p_2$</td>
<td>$\tau_{p_1p_2}$</td>
<td>1</td>
<td>ms</td>
<td>Kita (2001)</td>
</tr>
<tr>
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<td>$\tau_{p_1\varsigma}$</td>
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<td>ms</td>
<td>Nambu et al. (2000)</td>
</tr>
<tr>
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<td>Kimura et al. (1996), Nambu et al. (2000)</td>
</tr>
<tr>
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<td>Nambu et al. (2000)</td>
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<tr>
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<td>$\tau_{\varsigma e}$</td>
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<td>ms</td>
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<td></td>
<td></td>
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<td>Cortex</td>
<td>$Q_e^{max}, Q_i^{max}$</td>
<td>300</td>
<td>s$^{-1}$</td>
<td>McCormick et al. (1985), Steriade et al. (1998)</td>
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<td>s$^{-1}$</td>
<td>Kiyatkin and Rebec (1999)</td>
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<td>s$^{-1}$</td>
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<td>s$^{-1}$</td>
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<td>s$^{-1}$</td>
<td>Destexhe and Sejnowski (2003)</td>
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<td>mV</td>
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<td>GPe</td>
<td>$\theta_{p2}$</td>
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<td>STN</td>
<td>$\theta_s$</td>
<td>10</td>
<td>mV</td>
<td></td>
</tr>
<tr>
<td>Relay nuclei</td>
<td>$\theta_r$</td>
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<td>mV</td>
<td></td>
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<tr>
<td>TRN</td>
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<td>mV</td>
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<td>Threshold spread</td>
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<td>mV</td>
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<td>$ee, ie$</td>
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<td>mV s</td>
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<td>$\nu_{d1d1}$</td>
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<td>mV s</td>
<td>Bolam et al. (2000), Koós and Tepper (1999)</td>
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<td>$\nu_{d1s}$</td>
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<td>mV s</td>
<td>Groves et al. (1995), Sadikot et al. (1992), Sibidé and Smith (1996)</td>
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<td>$\nu_{d2e}$</td>
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<td>$\nu_{d2d2}$</td>
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<td>mV s</td>
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<td>-0.1</td>
<td>mV s</td>
<td>Kita (2001), Shink and Smith (1995), Strick et al. (1995)</td>
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<td>$p_1 p_2$</td>
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<td>-0.03</td>
<td>mV s</td>
<td>Kita (2001), Shink and Smith (1995), Smith et al. (1994)</td>
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<td>$p_1 s$</td>
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<td>0.3</td>
<td>mV s</td>
<td>Parent and Hazrati (1995), Smith et al. (1990b)</td>
</tr>
<tr>
<td>$p_2 d_2$</td>
<td>$\nu_{p2d2}$</td>
<td>-0.3</td>
<td>mV s</td>
<td>Shink and Smith (1995), Strick et al. (1995)</td>
</tr>
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<td>$p_2 p_2$</td>
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<td>mV s</td>
<td>Kita (1994), Nambu and Llinás (1997), Ogura and Kita (2000)</td>
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<tr>
<td>Quantity</td>
<td>Symbol</td>
<td>Value</td>
<td>Unit</td>
<td>References</td>
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<td>------------------------</td>
<td>--------</td>
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<td>------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
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<td>Corticocortical</td>
<td>$r_e$</td>
<td>80</td>
<td>mm</td>
<td>Nunez, 1995; O’Connor et al. (2002), Robinson (2003)</td>
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<td>Rise rate</td>
<td>$\beta$</td>
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</tr>
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<td>$\nu_{p_2}$</td>
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<td>mV s</td>
<td>Cheruel et al. (1996), Parent and Hazrati (1995), Smith et al. (1990b)</td>
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<td>$\zeta e$</td>
<td>$\nu_{\zeta e}$</td>
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<td>mV s</td>
<td>Afshapour (1985), Nambu et al. (2000), Parent and Hazrati (1995)</td>
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<td>$\zeta p_2$</td>
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<td>mV s</td>
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<td>mV s</td>
<td>Nambu et al. (1988), Uno et al. (1978)</td>
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<tr>
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<td>mV s</td>
<td>Cox et al. (1997), Gentet and Ulrich (2003)</td>
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<tr>
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<td>$\nu_{sn}$</td>
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<td>mV s</td>
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<td>0.03</td>
<td>mV s</td>
<td>Gentet and Ulrich (2003), Steriade et al. (1986)</td>
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</tbody>
</table>

Table 5.2: Parameters used to model the BGTCs in the healthy state, chosen to match known physiology and yield realistic firing rates for all components (cf. Secs. 5.2.2 and 5.4). The last column lists references that form a starting point for estimates of the relevant parameters. Firing thresholds are in realistic ranges, with precise values chosen based on numerical exploration (see text). Populations: $e$, cortical excitatory; $i$, cortical inhibitory; $d_1$, striatal D1 cells; $d_2$, striatal D2 cells; $p_1$, GPi/SNr; $p_2$, GPe; $\zeta$, STN; $s$, thalamic relay nuclei; $r$, TRN.
faster than transmission via the direct or indirect pathways (Bar-Gad et al., 2003). Total cortico-striato-pallidal and cortico-subthalamo-pallidal delays can be inferred from the pattern of GPe responses to cortical activation in healthy monkeys, consisting of an excitation after 8–11 ms, inhibition after 15–19 ms, and a second excitation after 26–32 ms due to disinhibition of the STN (Kita et al., 2004; Nambu et al., 2000; Yoshida et al., 1993). Since we assume synaptic and dendritic integration times of the order of 6–8 ms (time-to-peak) (Destexhe and Sejnowski, 2001; Hestrin et al., 1990), this implies that the cortico-subthalamic and STN-GPe axonal delays are only about 1 ms each. The reciprocal delay from GPe to STN is also $\lesssim 1$ ms (Nambu et al., 2000). A corticostriatal axonal delay of 2 ms and striatopallidal delay of 1 ms lead to onset of GPe excitation after about 8 ms, inhibition after 19 ms, and a second excitation after 28 ms, in accord with the above studies. The latency of postsynaptic responses in EP neurons to GP stimulation is around 3–6 ms in the rat brain slice preparation (Kita, 2001), suggesting an axonal latency of $\lesssim 1$ ms. Anderson and Turner (1991) measured a reduction in the activity of pallidal-receiving thalamic neurons of awake monkeys generally $<4$ ms after stimulation of the GPi, although some cells displayed a longer latency. In anesthetized rats, the average latency of spikes in the striatum evoked by stimulation of the medial geniculate body of the thalamus was $\sim 4$ ms (Clugnet et al., 1990). We can roughly translate this into an axonal delay of $\sim 2$ ms in humans by noting that the value of 4 ms includes striatal integration times, but on the other hand, delays are likely to be slightly longer in humans than in rats (compare for instance the corticosubthalamic axonal plus dendritic and synaptic delay of $\sim 4.5$ ms in rats (Maurice et al., 1998) with the $\sim 6$ ms delay in monkeys (Nambu et al., 2000)). Voloshin and Prokopenko (1978) measured orthodromic and antidromic response latencies of TRN neurons to stimulation of VL in cats. Interpretation of the data is complicated by the possible contribution of polysynaptic pathways, but 2 ms seems to be an adequate approximation to the monosynaptic axonal delay.

A number of studies have provided estimates of the resting membrane potentials, firing thresholds, and maximum firing rates of neurons in the basal ganglia. Most of the data come from studies of rodents, but these provide the closest possible approximation to human values, which are often not readily available. Since the biophysics determining these quantities is likely to be very similar across species, we assume that it is reasonable to use data from rodents.

The maximum firing rate of cortical regular spiking neurons is of order 250 s$^{-1}$ (McCormick et al., 1985), whereas a class of corticothalamic fast rhythmic bursting neurons can fire up to $\sim 400$ s$^{-1}$ in either burst or tonic mode. These populations are not strictly distinct, since neocortical neurons can change their firing properties from regular spiking to fast rhythmic bursting and fast spiking depending on afferent activity (Steriade et al., 1998). The maximum rate of
cortical inhibitory interneurons is of the same order as that of pyramidal neurons \((300–600 \, \text{s}^{-1})\), and we set \(Q_{p}^{\text{max}} = Q_{i}^{\text{max}} = 300 \, \text{s}^{-1}\) for simplicity (cf. Sec. 5.3.3).

A maximum rate of \(\sim 65 \, \text{s}^{-1}\) was recorded for striatal neurons in awake, freely moving rats \((\text{Kiyatkin and Rebec, 1999})\). High-frequency stimulation of the STN can evoke discharges up to about \(200 \, \text{s}^{-1}\) in GPi cells of rhesus monkeys \((\text{Hashimoto et al., 2003})\), while EP neurons were found to fire at rates up to \(300 \, \text{s}^{-1}\) in a rat slice preparation \((\text{Nakanishi et al., 1990})\). We take \(Q_{p1}^{\text{max}} = 250 \, \text{s}^{-1}\) to be an adequate approximation. Of three types of neurons identified in the GP of guinea pigs, the most abundant type had a maximum firing rate close to \(200 \, \text{s}^{-1}\) \((\text{Nambu and Llinás, 1997})\). On the other hand, \text{Cooper and Stanford} \((2000)\) recorded the activity of three types of neuron in the rat GP with a weighted average maximum firing rate of \(\sim 380 \, \text{s}^{-1}\). We assume an intermediate value and let \(Q_{p2}^{\text{max}} = 300 \, \text{s}^{-1}\). STN neurons in rats can fire at rates up to about \(500 \, \text{s}^{-1}\) \((\text{Kita et al., 1983; Nakanishi et al., 1987})\). Finally, low-threshold Ca\(^{2+}\) currents can cause thalamic neurons to fire high-frequency bursts at \(\sim 300 \, \text{s}^{-1}\) \((\text{Destexhe and Sejnowski, 2003})\), while thalamic reticular neurons can fire bursts at up to \(500 \, \text{s}^{-1}\) \((\text{Raeva and Lukashev, 1987})\).

The threshold values \(\theta_{a}\) are the membrane depolarizations at which the populations fire at half their maximum rate [cf. Eq. \((5.2)\)]. Based on extensive exploration of physiologically realistic ranges, we choose values that give realistic steady-state firing rates for all neuronal populations in our model; these values are listed in Table 5.2. STN and pallidal neurons are taken to have low threshold potentials, while the threshold value is high for the relatively silent striatal neurons. Note that for \(Q \ll Q^{\text{max}}\), a high maximum firing rate and a low threshold \(\theta\) have closely similar effects on the (relatively low) steady-state firing rate, because

\[
\frac{Q^{\text{max}}}{1 + e^{-(V-\theta)/\sigma'}} \approx Q^{\text{max}} e^{(V-\theta)/\sigma'},
\]

which means that adding \(\delta\theta\) to \(\theta\) is equivalent to replacing \(Q^{\text{max}}\) by \(Q^{\text{max}} e^{-\delta\theta/\sigma'}\). Hence, it is possible that the firing thresholds and maximum firing rates are both smaller or both larger than the values used here, leaving the dynamics largely unchanged.

We also choose approximate connection strengths within physiological ranges, finding that the requirement of realistic firing rates restricts connection strengths to relatively narrow subranges. \text{Robinson et al.} \((2004)\) derived values of \(\nu_{es}\) and \(\nu_{se}\) that satisfy both experimental constraints and give realistic firing rates in the purely corticothalamic model. Experiments in rodent neocortex in vitro \((\text{Gil et al., 1999; Thomson, 1997})\) and in vivo \((\text{Bruno and Sakmann, 2006})\) suggest that single thalamocortical and excitatory intracortical stimuli have a time-integrated response of about \(10–20 \mu\text{V s}\). However, \(s_{es}\) should be adjusted

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for reduced probability of transmitter release at thalamocortical synapses upon repeated stimulation (Gil et al., 1999), and the less than additive effect of successive postsynaptic potentials (Bruno and Sakmann, 2006). If we assume the latter adjustment to yield an average unitary response of about 12 μV s, with a release probability of 40% and \( N_{es} = 85 \) (Bruno and Sakmann, 2006), we obtain \( \nu_{es} = 0.4 \) mV s. This value is in agreement with Robinson et al. (2004), although that paper assumed a much smaller unitary response \( s_{es} \) and a correspondingly larger number of synapses per cortical neuron. Studies of cat geniculocortical fibers suggest that the number of synapses of cortical origin per thalamic neuron far exceeds the number of thalamocortical synapses per cortical neuron (Budd, 2004; Peters and Payne, 1993). Corticothalamic fibers display paired-pulse facilitation, but often fail to evoke significant excitatory postsynaptic potentials (EPSPs) (Golshani et al., 2001; Granstedt and Lindström, 2003). Unitary corticothalamic EPSPs have a small amplitude compared to retinogeniculate EPSPs, with a time-integrated response around 12 μV s (Turner and Salt, 1998), similar to that at thalamocortical terminals. This combines with the large number of corticothalamic synapses but high failure rate to yield an approximate synaptic strength \( \nu_{se} = 0.8 \) mV s. We assume \( \nu_{sr} = -0.4 \) mV s, close to the value in Robinson et al. (2004). Although there are fewer inhibitory than excitatory neurons in the cortex, the synaptic strength of the inhibitory projections is larger, such that \( |\nu_{ei}| > |\nu_{ee}| \).

Precise estimates of \( \nu_{re} \) are difficult to obtain from the literature. Although it has been estimated that \(~60\%\) of TRN terminals are of cortical origin (Liu and Jones, 1999), an estimate of the total number of synapses per TRN neuron is not readily available. In mouse brain slices, the unitary postsynaptic reponse of TRN neurons to cortical impulses is 2–3 times greater than that of thalamic relay neurons, and the latter have a high failure rate of transmitter release (\(~68\%)\), suggesting \( s_{se} < s_{re} \). However, paired-pulse facilitation at relay neurons may partly counterbalance this effect (Golshani et al., 2001). More importantly, the relative influences of cortical inputs to relay and TRN neurons depend on the state of alertness (Steriade et al., 1986). During drowsiness or slow-wave sleep, TRN responds to cortical stimuli with bursts of spikes, implying a relatively large \( \nu_{re} \), while TRN neurons are tonically active during attentive wakefulness and REM sleep, implying a lower value of \( \nu_{re} \) (Steriade, 2001). This is corroborated by modeling results, which indicate that the combined influence of the cortico-reticulo-thalamic and direct corticothalamic pathways is inhibitory in sleep states, but excitatory during waking (Robinson et al., 2002). We thus model a state of alert wakefulness in which the direct corticothalamic connection is more important than the cortico-reticulo-thalamic connection, setting \( \nu_{re} = 0.15 \) mV s.

Although a high degree of convergence of corticostriatal inputs is suggested
by the large number of synaptic events per unit time in striatal neurons (Blackwell et al., 2003), the strength of corticostriatal projections is constrained by the relatively low average firing rate of striatal neurons (cf. Sec. 5.2.2). Corticostriatal neurons form about 5000 – 15 000 synapses per striatal cell, but each of these has a weak influence (Wilson, 1995). An immunohistochemical study found that the ipsilateral primary motor cortex innervated D1-expressing cells somewhat more strongly than D2-expressing cells (Hersch et al., 1995). We thus assume a strength per synapse of 0.1 μV s, with 10 000 synapses per striatal D1 cell, and 7000 synapses per D2 cell, which gives \( \nu_{d1e} = 1.0 \text{ mV s} \) and \( \nu_{d2e} = 0.7 \text{ mV s} \).

Steady states are very sensitive to \( \nu_{sp1} \) due to the high firing rate of neurons in the output nuclei. In order for the thalamus not to be overly suppressed by the output nuclei we assume a relatively small connection strength \( \nu_{sp1} = -0.03 \text{ mV s} \). The thalamostriatal projection has been described as “massive” in the squirrel monkey (Sadikot et al., 1992), but this study did not quantify its strength or extent relative to other projections. Studies in rats suggest that it is much less important than the corticostriatal projection (Groves et al., 1995). Sidibé and Smith (1996) found that intralaminar thalamic neurons preferentially innervate striatal neurons that output to GPi rather than GPe, so we let \( \nu_{d1s} = 0.1 \text{ mV s} \) and \( \nu_{d2s} = 0.05 \text{ mV s} \). Evidence to suggest that \( |\nu_{p2d2}| > |\nu_{p1d1}| \) comes from a study in which anterograde transport of a tracer injected into the arm area of the primary motor cortex labeled ten times as many GPe cells as GPi cells (Strick et al., 1995). A somewhat more symmetric distribution of striatal synapses over the two pallidal segments was suggested by Shink and Smith (1995), although the innervation of GPe still appeared stronger than that of GPi. Studies on the reciprocal connections between the GPe and STN suggest that GPe exerts a powerful inhibitory control over the STN (Shink et al., 1996; Smith et al., 1990a), while the STN powerfully excites the GPe (Cheruel et al., 1996; Nambu et al., 2000; Shink et al., 1996). However, model results indicate that the GPe probably has a much weaker effect on the STN rate than vice versa, in view of stability criteria (cf. Chapter 6) and the comparatively high firing rate of the GPe (cf. Secs. 5.2.2 and 5.4). The STN appears to innervate both pallidal segments quite uniformly (Parent and Hazrati, 1995a; Smith et al., 1990b), so we assume equal strengths for these projections. Fewer GPi synapses arise from the GPe than from the striatum, although the GPe may exert a strong effect by forming contacts with the perikarya and proximal dendrites of GPi cells (Shink and Smith, 1995; Smith et al., 1994). Still, we assume the direct pallidopallidal projection to be weaker than other projections, since a high GPe rate would otherwise be incompatible with an even higher GPi rate (cf. Secs. 5.2.2 and 5.4). Finally, given an input \( \phi_n \), the connection strength for projections from brainstem to thalamus, \( \nu_{sn} \), is constrained to a relatively
narrow range since large values lead to unrealistically high cortical, thalamic, and striatal rates.

5.3.3 Fixed points

Stable fixed points of the model equations, obtained assuming a constant input \( \phi_n \), correspond to solutions at which the system settles down unless perturbed. Fixed-point equations are obtained by setting the derivatives in Eqs (5.3)–(5.5) to zero. Denoting fixed-point values by the superscript \((0)\), Eq. (5.5) yields

\[
\phi_a^{(0)} = Q_a^{(0)}, \tag{5.7}
\]

which, when substituted into Eq. (5.3) and using Eq. (5.2), gives

\[
S_a^{-1}(\phi_a^{(0)}) = \sum_b \nu_{ab}\phi_b^{(0)}. \tag{5.8}
\]

Implementing Eq. (5.8) for all nine neuronal populations gives a set of transcendental equations for the fixed-point firing rates \( \phi_a^{(0)} \) that can be solved numerically. These equations are simplified by imposing the random connectivity approximation, in which the number of synapses within the cortex is proportional to the product of the numbers of sending and receiving neurons (Braitenberg and Schüz, 1998; Robinson et al., 2001b; Wright and Liley, 1995). In the connection strengths \( \nu_{ab} = N_{ab}s_{ab} \), the symbol \( N_{ab} \) denotes the number of synapses from neurons of type \( b \) per type \( a \) neuron, which in the random connectivity approximation thus depends only on the afferent population \( b \). If we further assume the unitary synaptic strengths \( s_{ab} \) to be independent of the receiving population, we obtain

\[
\nu_{ee} = \nu_{ie}, \quad \nu_{ei} = \nu_{ii}, \quad \nu_{es} = \nu_{is}. \tag{5.9}
\]

For \( Q_{ee}^{\max} = Q_{ii}^{\max} \) and \( \theta_e = \theta_i \) (cf. Sec. 5.3.2) this implies, in particular, that the fixed-point values of the cortical excitatory and inhibitory firing rate fields are equal, since identical equations are obtained for \( \phi_e^{(0)} \) and \( \phi_i^{(0)} \).

In practice, fixed points can be determined by considering the simultaneous zeros of the five functions

\[
F_1(\phi_e) = \phi_e - S_e[(\nu_{ee} + \nu_{ei})\phi_e + \nu_{es}\phi_s], \tag{5.10}
\]
\[
F_2(\phi_{d1}) = \phi_{d1} - S_{d1}(\nu_{d1e}\phi_e + \nu_{d1i}\phi_i + \nu_{d1s}\phi_s), \tag{5.11}
\]
\[
F_3(\phi_{d2}) = \phi_{d2} - S_{d2}(\nu_{d2e}\phi_e + \nu_{d2i}\phi_i + \nu_{d2s}\phi_s), \tag{5.12}
\]
\[
F_4(\phi_{p2}) = \phi_{p2} - S_{p2}[\nu_{p2d2}\phi_{d2} + \nu_{p2p2}\phi_{p2} + \nu_{p2e}S_e(\nu_{ee}\phi_e + \nu_{ep}\phi_p)], \tag{5.13}
\]
\[
F_5(\phi_s) = \phi_s - S_s(\nu_{se}\phi_e + \nu_{sp1}\phi_{p1} + \nu_{sr}\phi_r + \nu_{sn}\phi_n). \tag{5.14}
\]
First an initial estimate of the thalamic firing rate $\phi_s$ is made. For the given choice of $\phi_s$, the cortical excitatory rate $\phi_e$ is uniquely determined by the zero of $F_1$, as shown in Fig. 5.2(a) using the parameter values in Table 5.2. From this the striatal rates $\phi_{d_1}$ and $\phi_{d_2}$ can be determined using the functions $F_2$ and $F_3$. These are negative at $\phi_{d_1}, \phi_{d_2} = 0$ and positive at the maximum striatal firing rates, crossing zero exactly once since $\nu_{d_1 d_1} < 0$ and $\nu_{d_2 d_2} < 0$ ensure that their derivatives

$$\begin{align*}
\frac{dF_2(\phi_{d_1})}{d\phi_{d_1}} &= 1 - \nu_{d_1 d_1} Q_{d_1}^{\text{max}} \times \\
&\quad \frac{\exp[-(\nu_{d_1 e} \phi_e + \nu_{d_1 d_1} \phi_{d_1} + \nu_{d_1 s} \phi_s - \theta_{d_1})/\sigma']}{\sigma'[1 + \exp[-(\nu_{d_1 e} \phi_e + \nu_{d_1 d_1} \phi_{d_1} + \nu_{d_1 s} \phi_s - \theta_{d_1})/\sigma']]}^2,
\end{align*}$$

$$\begin{align*}
\frac{dF_3(\phi_{d_2})}{d\phi_{d_2}} &= 1 - \nu_{d_2 d_2} Q_{d_2}^{\text{max}} \times \\
&\quad \frac{\exp[-(\nu_{d_2 e} \phi_e + \nu_{d_2 d_2} \phi_{d_2} + \nu_{d_2 s} \phi_s - \theta_{d_2})/\sigma']}{\sigma'[1 + \exp[-(\nu_{d_2 e} \phi_e + \nu_{d_2 d_2} \phi_{d_2} + \nu_{d_2 s} \phi_s - \theta_{d_2})/\sigma']]}^2,
\end{align*}$$

are always positive. The functions $F_2$ and $F_3$ are shown in Figs. 5.2(b) and 5.2(c). The striatal rates increase with both the thalamic rate $\phi_s$ and the cortical rate $\phi_e$. The unique zero of the function $F_4$ determines the GPe rate $\phi_{p_2}$. The value of $\phi_{p_2}$ first decreases, then increases slightly with both $\phi_s$ and $\phi_e$ [Fig. 5.2(d)]. Knowing $\phi_{p_2}$ in turn allows determination of the STN and GPi/SNr rates $\phi_{p_1}$ and finally, the self-consistency relation $F_5 = 0$ must be satisfied for $\phi_s$ to represent a fixed point. The value of $F_5$ is negative at $\phi_s = 0$, and positive at $\phi_s = Q_s^{\text{max}}$, since the last term in (5.14) is always smaller than $Q_s^{\text{max}}$. By continuity of $F_5$, there is always at least one fixed point, and in general an odd number of fixed points. The function $F_5$ plotted in Fig. 5.2(e) shows that there are three fixed points for the parameters in Table 5.2. Since the low-firing-rate fixed point for $\phi_s$ is stable and yields the most realistic firing rates for all populations, we will take this fixed point to represent the physiological situation. It is important to note that we obtain realistic steady states with parameter values that are consistent with experimental findings (cf. Sec. 5.3.2); this is a fundamental test of the physiological realism of the model.

Figs. 5.2(e) and 5.2(f) show that all firing rates increase with the brainstem input $\phi_n$.

### 5.3.4 Modeling dopamine depletion

It is widely recognized that dopamine modulates corticostriatal transmission both presynaptically and postsynaptically (Calabresi et al., 2000). However, observations on these effects are complicated and sometimes paradoxical. For instance, dopamine may facilitate glutamate-induced activity at low concentrations, but be inhibitory at higher concentrations (Hu and White, 1997). Joint
Figure 5.2: Equilibrium firing rates of the BGTCS. (a)–(d) Equilibrium values of $\phi_e$, $\phi_{d_1}$, $\phi_{d_2}$, and $\phi_p$ (zeros of $F_1 - F_4$) for different thalamic rates $\phi_s$. Solid, $\phi_s = 10 \text{ s}^{-1}$; dashed, $\phi_s = 30 \text{ s}^{-1}$; dash-dotted, $\phi_s = 50 \text{ s}^{-1}$; dotted, $\phi_s = 70 \text{ s}^{-1}$. (e) Equilibrium values of $\phi_s$ (zeros of $F_5$) for different external inputs $\phi_n$. Solid, $\phi_n = 5 \text{ s}^{-1}$; dashed, $\phi_n = 10 \text{ s}^{-1}$; dash-dotted, $\phi_n = 20 \text{ s}^{-1}$; dotted, $\phi_n = 30 \text{ s}^{-1}$. (f) Dependence of low-firing-rate fixed points on $\phi_n$. 

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activation of D1 and D2 receptors may have a supra-additive effect on striatal neurons, and upregulation of both receptor types after dopamine depletion may influence corticostriatal transmission (Hu et al., 1990).

Nevertheless, some findings are relatively consistent across studies. Dopamine appears to have a predominantly inhibitory effect via D1 receptors when striatal neurons are in a hyperpolarized state (Nicola and Malenka, 1998), but a facilitatory effect when they are already in an activated state (Hernández-López et al., 1997; Nicola et al., 2000). Such facilitation via D1 activation may primarily affect NMDA receptor-mediated transmission (Cepeda et al., 1998; Levine et al., 1996). In line with these observations, some researchers have suggested that dopamine increases the signal-to-noise ratio (SNR) in the striatum, making medium spiny neurons sensitive only to strong inputs (Nicola et al., 2004; O’Donnell, 2003). This is supported by the finding that dopamine reduces the basal level of striatal activity, but enhances the phasic response to glutamate (Kiyatkin and Rebec, 1996). To model the reduction in SNR following loss of dopamine, Leblois et al. (2006) suggested decreasing the firing thresholds of striatal neurons as well as corticostriatal connection strengths to both D1- and D2-expressing neurons. They assumed both thresholds and connection strengths to depend nearly linearly on the level of dopamine. We use

\[
\begin{align*}
\theta_{d1}^{\text{new}} &= \theta_{d1} - h\chi; \\
\nu_{d1}^{\text{new}} &= \nu_{d1e} - \chi;
\end{align*}
\]

\[
\begin{align*}
\theta_{d2}^{\text{new}} &= \theta_{d2} - h\chi; \\
\nu_{d2}^{\text{new}} &= \nu_{d2e} - \chi;
\end{align*}
\]

(5.17)

(5.18)

where we consider \(h = 5, 10, \text{ and } 15 \text{ s}^{-1}\), and \(\chi\) between 0 and 0.6 mV s. Note that the effective thresholds of D1 and D2 neurons are approximated as equal for simplicity, although their intrinsic properties may differ in practice (Moyer et al., 2007).

In contrast to the above possibility, dopamine loss may also reduce transmission via D1-expressing cells and enhance transmission via D2-expressing cells. In support of this possibility, a number of studies have shown that depression of excitation via glutamatergic, particularly AMPA, receptors follows activation of D2 receptors (Hsu et al., 1995; Levine et al., 1996; Toan and Schultz, 1985; Umemiya and Raymond, 1997). Furthermore, Mallet et al. (2006) found an increase in both the spontaneous activity and responsiveness of striatopallidal neurons after dopamine depletion, whereas striatonigral neurons became less active. Mallet and coworkers suggested that this imbalance may be exacerbated by feedforward inhibition by fast-spiking GABAergic interneurons, which narrow the time window for integration of cortical inputs in striatonigral neurons, and widen the time window in striatopallidal neurons, leading to inappropriate summation of signals in the indirect pathway. This possibility can be modeled by simultaneously increasing the strength of corticostriatal projections giving
rise to the indirect pathway, and decreasing that of projections giving rise to the direct pathway. In the absence of detailed information concerning the relative sizes of the changes in these connection strengths, we decrease $\nu_{d1e}$ and increase $\nu_{d2e}$ by the same factor $\xi$. We also consider the effects of modulating $\nu_{d1e}$ and $\nu_{d2e}$ independently. Of course, the degree of differential modulation of the direct and indirect pathways by dopamine depletion is limited by the extent of segregation of D1 and D2 class receptors, and the separation of striatal projections to GPi/SNr and GPe. Nevertheless, differential modulation may occur with only a partial distinction between the direct and indirect pathways.

Reduced release of dynorphin and enhanced release of enkephalin in the striatum are thought to represent compensatory mechanisms that oppose the effects of chronic dopamine depletion (Augood et al., 1989; Betarbet and Greenamyre, 2004; Engber et al., 1992). For instance, dynorphin appears to inhibit the release of dopamine in the striatum, and oppose the effects of D1-receptor stimulation on striatonigral neurons (Steiner and Gerfen, 1998). Therefore, the loss of dynorphin will enhance the sensitivity of D1-expressing neurons to the remaining dopamine. Dynorphin and enkephalin may also affect striatal input to the GPe as well as intrapallidal inhibition (Ogura and Kita, 2000; Stanford and Cooper, 1999). Enkephalin appears to act presynaptically via opioid receptors to inhibit the release of GABA at both striatopallidal and intrapallidal terminals (Maneuf et al., 1994; Stanford and Cooper, 1999), decreasing the corresponding connection strengths. These effects may be partly opposed by loss of dynorphin from axon collaterals of neurons projecting to both pallidal segments (Ogura and Kita, 2000). Furthermore, the loss of direct dopaminergic afferentation promotes GABA release at striato-GPe terminals through the action of presynaptic D2 receptors (Floran et al., 1997; Querejeta et al., 2001). Assuming that striatopallidal transmission is more affected by dopamine loss than by enkephalin, we model PD with an increase in striato-GPe inhibition. The prevalence of enkephalin over dynorphin in the GPe suggests that the strength of intrapallidal inhibition is reduced. This agrees with the suggestion of Terman et al. (2002) that dopaminergic denervation weakens the lateral connections in the GPe, although they assumed enkephalin and dynorphin to exert concerted rather than opposing effects. Reduced dynorphin levels may also depolarize GPe neurons by blocking membrane potassium conductance (Ogura and Kita, 2000), which we model by lowering the corresponding threshold potential.

Several lines of evidence indicate that STN overactivity is not only caused by reduced GPe firing. For instance, GPe lesions only cause a slight increase in STN rate (Hassani et al., 1996), and blockade of glutamatergic transmission suppresses STN overactivity in rats with haloperidol-induced akinesia (Miwa et al., 1998). Increased enkephalin levels may inhibit GABAergic synaptic
transmission via $\mu$-opioid receptors, which are expressed in high concentration in the human STN (Peckys and Landwehrmeyer, 1999; Raynor et al., 1995), although enkephalin also suppresses excitatory transmission (Shen and Johnson, 2002). Studies in rats have suggested that enhanced excitation by the thalamic parafascicular nucleus (Orieux et al., 2000) and/or the pedunculopontine nucleus (PPN) (Breit et al., 2001, 2006; Orieux et al., 2000) may contribute to STN hyperactivity in parkinsonism. Rats treated with 6-OHDA have elevated levels of extracellular potassium in the STN, possibly due to changes in conductivity and delayed clearance, which increases the activity of this nucleus (Strauss et al., 2008). Furthermore, the extracellular concentration of glutamate is increased (Fujikawa et al., 1996), and that of GABA decreased (Engblom et al., 2003), by higher extracellular levels of potassium. We model the hyperexcitability of STN neurons in PD by reducing their average threshold potential.

The frontal lobe, including the prefrontal cortex, SMA, and M1, receives a significant dopaminergic innervation from the SNc, VTA, and retrorubral area (Gaspar et al., 1992; Williams and Goldman-Rakic, 1993). The predominant influence of dopamine on prefrontal pyramidal cell firing is inhibitory, due to enhanced synaptic inputs from GABAergic interneurons (Gulledge and Jaffe, 2001; Sesack and Bunney, 1989; Zhou and Hablitz, 1999). Gulledge and Jaffe (2001) suggested that this is because of enhanced GABA release by interneurons independent of their spike rate, implying increased synaptic strengths $|\nu_{ei}|$ and $|\nu_{ii}|$. Dopamine also renders interneurons more susceptible to excitatory inputs from pyramidal cells, apparently without affecting their firing threshold or the amplitude of EPSPs (Gao and Goldman-Rakic, 2003). This mechanism has no precise equivalent in our model, but can be approximated by an increased synaptic strength $\nu_{ie}$. Furthermore, changes in intrinsic currents increase the excitability of pyramidal neurons of the rat prefrontal cortex after D1 receptor activation in vitro (Thurley et al., 2008), which may positively affect $\nu_{ee}$. Finally, $\nu_{ee}$ and $\nu_{ie}$ are likely to be affected by the substantial loss of neurons from the pre-supplementary motor area (pre-SMA) in PD patients (MacDonald and Halliday, 2002). This suggests that we can model PD in part by decreasing the synaptic strengths $\nu_{ee}$, $\nu_{ie}$, and especially $|\nu_{ei}|$ and $|\nu_{ii}|$, in accord with the reduced intracortical inhibition observed upon transcranial magnetic stimulation in PD patients off medication (Ridding et al., 1995).

We thus model the effects of nigrostriatal degeneration in the following five ways:

(I) mimicking a decrease in striatal SNR by reducing both firing thresholds and corticostriatal connection strengths according to Eqs (5.17) and (5.18);

(II) increasing $\nu_{dze}$ and decreasing $\nu_{d1e}$ either individually or by the same factor $\xi$, in agreement with the direct/indirect pathway model;
(III) reducing lateral inhibition in the GPe, which mimics enhanced levels of enkephalin;
(IV) attenuating cortical interactions to capture loss of neurons in the pre-SMA and intrinsic cortical dopamine;
(V) a combination of a stronger indirect and weaker direct pathway ($\nu_{d_{1}e} = 0.5$ mV s, $\nu_{d_{2}e} = 1.4$ mV s), reduced intrapallidal inhibition ($\nu_{p_{2}p_{2}} = -0.07$ mV s), weaker intracortical coupling ($\nu_{ee} = \nu_{ie} = 1.4$ mV s, $\nu_{ei} = \nu_{ii} = -1.6$ mV s), lower STN and GPe firing thresholds ($\theta_{p_{2}} = 8$ mV, $\theta_{i} = 9$ mV), and a stronger striato-GPe projection ($\nu_{p_{2}d_{2}} = -0.5$ mV s). We will call the state corresponding to these parameters the ‘full parkinsonian state’.

5.4 Results

We now describe the results of applying the model equations to the system of connections depicted in Fig. 5.1. The steady-state firing rates corresponding to the parameter values in Table 5.2, with a stimulus level of 10 s$^{-1}$, are listed in column $a$ of Table 5.3. All rates are in physiologically realistic ranges for healthy individuals if the average striatal rate is taken to be ($\phi_{d_{1}} + \phi_{d_{2}}$)/2 (cf. Table 5.1). Changes in firing rates are derived when modeling dopamine loss in the five ways listed in Sec. 5.3.4. Model predictions are compared with the empirical findings summarized in Sec. 5.2.2.

*Effects of parameter changes mimicking a reduced signal-to-noise ratio*

Irrespective of the relative sizes of the changes in striatal firing thresholds and corticostriatal connection strengths, a reduction in SNR simulated by increasing $\chi$ [cf. Eqs (5.17) and (5.18)] has little impact on average firing rates (cf. Fig. 5.3). Representative rates are listed for $h = 10$ s$^{-1}$ and $\chi = 0.6$ mV s in Column $b$ of Table 5.3. In the model of Leblois et al. (2006), which lacks an indirect pathway but in which dopamine loss is also modeled by approximating a reduced SNR, resting activity in the GPi also changes little with a lower dopamine level, whereas cortical activity shows a small increase. The model of Leblois et al. (2006) is not directly comparable to ours, since it contains a different set of connections, forming separate streams in the direct path but with diffuse projections from STN to GPi in the hyperdirect pathway. Furthermore, it considers individual neurons with linear response functions above threshold, a different form of the dendritic/synaptic filter function, and identical firing thresholds for different neurons in each given population except the striatal one, whereas the sigmoid function (5.2) results from a distribution of firing thresholds. However, their (deliberately) small change in average activity with a reduced SNR corresponds well with our result.
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Table 5.3: Firing rates of the components of the BGTCs (in s\(^{-1}\)) corresponding to the following cases: (a) healthy state, as represented by the parameters in Table 5.2; (b) reduced-SNR state, obtained from a by setting \(h = 10\) s\(^{-1}\), \(\chi = 0.6\) mV s, which leads to \(\theta_{d_1} = \theta_{d_2} = 13\) mV, \(\nu_{d_1e} = 0.4\) mV s, \(\nu_{d_2e} = 0.1\) mV s; (c) state a with a stronger indirect and weaker direct pathway, \(\nu_{d_1e} = 0.5\) mV s and \(\nu_{d_2e} = 1.4\) mV s; (d) state a with weaker intrapallidal inhibition \(\nu_{p_2p_2} = -0.03\) mV s; (e) state c with \(\nu_{p_2p_2} = 0\) mV s; (f) state a with weaker cortical interactions, \(\nu_{ee} = \nu_{ie} = 1.4\) mV s, \(\nu_{ei} = \nu_{ii} = -1.6\) mV s; (g) state c with \(\nu_{ee} = \nu_{ie} = 1.4\) mV s, \(\nu_{ei} = \nu_{ii} = -1.6\) mV s; (h) full parkinsonian state’ (cf. Sec. 5.3.4); (i) state a with \(\nu_{d_1d_1} = \nu_{d_2d_2} = 0\) mV s; (j) state g with \(\nu_{d_1d_1} = \nu_{d_2d_2} = 0\) mV s; (k) state a with \(\nu_{d_2s} = 0.3\) mV s; (l) state a with \(\nu_{d_2s} = 0.3\) mV s; (m) state a with \(\nu_{p_1p_2} = 0\) mV s; (n) state a with \(\nu_{p_2s} = 0.4\) mV s; (o) state a with \(\nu_{ee} = 0.2\) mV s. Input to the thalamic relay nuclei is 10 s\(^{-1}\) and all rates are given to two significant figures.

**Effects of stronger indirect and weaker direct pathway**

A simultaneous increase in \(\nu_{d_2e}\) and decrease in \(\nu_{d_1e}\) by an identical factor \(\xi\) leads to changes in firing rates that agree well with the average of a cross-section of empirical findings [cf. Fig. 5.4(a) and Table 5.1]: GPe and thalamic rates are reduced, while STN and GPi/SNr rates are elevated. Because the increase in D2 rate is greater than the reduction in D1 rate, the overall striatal rate is slightly increased. Figure 5.4(b) and 5.4(c) show that these changes are effected mainly through the indirect pathway, since a weaker \(\nu_{d_1e}\) decreases \(\phi_{s}, \phi_{d_1}\), and \(\phi_{d_2}\), and barely affects \(\phi_{p_2}\). Doubling the strength of the indirect pathway while reducing that of the direct pathway by the same factor (\(\nu_{d_1e} = 0.5\) mV s and \(\nu_{d_2e} = 1.4\) mV s) leads to the rates in Column c of Table 5.3.

The sizes of these changes are fairly realistic, with a relatively large change in the rate of the output nuclei and smaller changes in cortical, thalamic, and average (over the D1 and D2 populations) striatal rates (cf. Sec. 5.2.2), but
the increase in STN activity is smaller than would be expected on the basis of empirical evidence, while the decrease in GPe activity is quite large. Although our model predicts that GPe lesion increases the rate of the remaining intact GPe neurons (cf. Chapter 6), lesions are nevertheless expected to decrease the total GPe output. Therefore, our finding that a relatively large decrease in GPe output only slightly enhances STN firing accords with the results of GPe lesion reported by Hassani et al. (1996), and confirms the influence of other excitatory mechanisms on the STN rate mentioned in Sec. 5.3.4.

**Effects of weakened intrapallidal inhibition**

Figure 5.5(a) shows the results of weakened lateral inhibition in the GPe. The effects on the pallidal and STN rates are opposite to those expected in PD, in line with the presumed compensatory effects of increased enkephalin levels with chronic dopamine depletion. Figures 5.5(b)–(d) illustrate how a combination of weakened intrapallidal inhibition and a reduced SNR \( h = 10 \text{ s}^{-1} \) in Eq. (5.17) affects the GPi/SNr, GPe, and STN rates, respectively. The corresponding results for a weakened direct and strengthened indirect pathway are shown in Figs. 5.5(e)–(g). The reduction in \( |\nu_{p2p2}| \) causes parkinsonian rates to be reached more slowly with an increase in \( \xi \). Column \( d \) of Table 5.3
Figure 5.4: Changes in firing rates when modeling dopamine loss by an increase in $\nu_{d2e}$ and decrease in $\nu_{d1e}$. (a) Rates when multiplying $\nu_{d2e}$ and dividing $\nu_{d1e}$ by the same factor $\xi$. (b) Rates vs. $\nu_{d1e}$. (c) Rates vs. $\nu_{d2e}$. 
contains the steady-state firing rates for $\nu_{p2p2} = -0.03 \text{ mV s}$, where $\chi = 0 \text{ mV s}$ and $\xi = 1$. The rates for $\nu_{d1e} = 0.5 \text{ mV s}$, $\nu_{d2e} = 1.4 \text{ mV s}$, and $\nu_{p2p2} = -0.03 \text{ mV s}$ are given in Column e.

**Effects of weakened cortical interactions**

Loss of cortico-cortical neurons in the pre-SMA, and depletion of intrinsic cortical dopamine due to degeneration of the mesocortical pathway, are expected to reduce intracortical coupling. The latter especially affects the strength of inhibition. Due to the random connectivity approximation (cf. Sec. 5.3.3), steady-state firing rates depend only on the sum $\nu_{ee} + \nu_{ei}$, rather than on the individual connection strengths. The sensitivity of the firing rates of the various components to this sum is depicted in Fig. 5.6. It is seen that loss of mesocortical dopamine helps to normalize the cortical rate after nigrostriatal damage, and further increases the STN rate. The effect on the GPe rate depends on the relative strengths of the direct and indirect pathways: it remains almost constant with mesocortical dopamine loss if the SNc is intact, but decreases with mesocortical dopamine loss after SNc lesion (modeled with $\nu_{d1e} = 0.5 \text{ mV s}$ and $\nu_{d2e} = 1.4 \text{ mV s}$). The rates for $\nu_{ee} = \nu_{ie} = 1.4 \text{ mV s}$ and $\nu_{ei} = \nu_{ii} = -1.6 \text{ mV s}$ are listed in Column f of Table 5.3, with the corresponding values where also $\nu_{d1e} = 0.5 \text{ mV s}$ and $\nu_{d2e} = 1.4 \text{ mV s}$ in Column g.

**Effects of GPe and STN firing thresholds and the striato-GPe projection**

Besides the above changes, nigrostriatal degeneration may lead to reduced STN and GPe firing thresholds and an increase in $|\nu_{p2d2}|$, as discussed in Sec. 5.3.4. Changes in firing rates with $\theta_{p2}$ and $\theta_{i}$ are shown in Fig. 5.7, where nigrostriatal and mesocortical dopamine depletion and loss of pre-SMA neurons are taken into account via $\nu_{d1e} = 0.5 \text{ mV s}$, $\nu_{d2e} = 1.4 \text{ mV s}$, $\nu_{ee} = \nu_{ie} = 1.4 \text{ mV s}$, and $\nu_{ei} = \nu_{ii} = -1.6 \text{ mV s}$. A reduction in $\theta_{p2}$ normalizes all rates that were altered by SNc lesion, except that of striatal D2 cells. A smaller $\theta_{i}$ has the opposite effect apart from increasing the GPe rate. Together, lower STN and GPe firing thresholds limit the decrease in GPe rate, counterbalance the increase in corticothalamic and striatal rates caused by mesocortical dopamine loss, and help account for a relatively large increase in STN rate.

Figure 5.8 shows the sensitivity of the steady-state firing rates to the remaining connection strengths, with all other parameters held constant at the values in Table 5.2. The shaded regions indicate parameter ranges that yield realistic discharge rates in the healthy state for all neuronal populations (cf. Sec. 5.2.2). It is seen that a stronger striato-GPe projection causes larger increases in STN and GPi/SNr rates, and a larger decrease in GPe rate. The
Figure 5.5: Sensitivity of steady-state firing rates to lateral inhibition in the GPe. (a) Changes in pallidal and STN rates with smaller $|\nu_{p2p_2}|$ are opposite to those in parkinsonism. (b)–(d) From left to right: contour plots of GPi/SNr, GPe, and STN rates as functions of $\nu_{p2p_2}$ and striatal SNR, where $h = 10$ s$^{-1}$ [cf. Eqs (5.17) and (5.18)]. (e)–(g) From left to right: contour plots of GPi/SNr, GPe, and STN rates as functions of $\nu_{p2p_2}$ and the relative strengths of the direct and indirect pathways. Lighter shades correspond to higher rates.
Figure 5.6: Sensitivity of steady-state firing rates to intracortical connection strengths. Rates only depend on the sum $\nu_{ee} + \nu_{ei}$ due to the random connectivity approximation (cf. Sec. 5.3.3). (a) Variations with respect to the healthy state. (b) Variations with respect to the state with $\nu_{d_1e} = 0.5$ mV s, $\nu_{d_2e} = 1.4$ mV s.

Figure 5.7: Sensitivity of steady-state firing rates to STN and GPe firing thresholds, where $\nu_{d_1e} = 0.5$ mV s, $\nu_{d_2e} = 1.4$ mV s, $\nu_{ee} = \nu_{ie} = 1.4$ mV s, and $\nu_{ei} = \nu_{ii} = -1.6$ mV s to mimic nigrostriatal and mesocortical dopamine depletion and loss of pre-SMA neurons. (a) Dependence on $\theta_{p_2}$. (b) Dependence on $\theta_{e}$. 

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change in GPe rate therefore depends on the relative changes in $\nu_{p2d2}$, $\nu_{d1e}$, $\nu_{d2e}$, $\nu_{ee}$, and $\nu_{ei}$ on the one hand, and $\theta_{p2}$ and $\theta_{e}$ on the other, in agreement with the range of experimental findings (Boraud et al., 1998; Filion and Tremblay, 1991; Goldberg et al., 2002; Heimer et al., 2002; Hutchison et al., 1994; Magill et al., 2001; Pan and Walters, 1988; Walters et al., 2007). Equilibrium rates for the full parkinsonian state are given in Column $h$ of Table 5.3.

**Effects of remaining projections**

We now consider the effects of the various projections that are not included in the classic direct/indirect pathway model. Firing rates are not highly sensitive to local striatal inhibition (cf. Fig. 5.8). Removing it altogether ($\nu_{d1d1} = \nu_{d2d2} = 0 \text{ mV s}$) slightly increases all rates except those of the GPe and output nuclei, which are decreased (Table 5.3 Column $i$). The steady-state solutions for $\nu_{d1d1} = \nu_{d2d2} = 0 \text{ mV s}$ in the full parkinsonian state are given in Column $j$ of Table 5.3. Comparison of the difference between Columns $a$ and $h$, and that between Columns $i$ and $j$, reveals that larger $|\nu_{d1d1}|$ and $|\nu_{d2d2}|$ help to attenuate alterations in all rates due to dopamine depletion. Increasing $\nu_{d1s}$ to 0.3 mV s predictably leads to a higher D1 rate, also increasing all other rates except that of the GPi/SNr (Column $k$). Increasing the strength of the thalamo-D2 projection to $\nu_{d2s} = 0.3 \text{ mV s}$ reduces the GPe rate, which in turn leads to a slightly higher STN rate, elevated GPi/SNr activity, and suppression of corticothalamic targets (Column $l$). To assess the influence of the GPe-GPi/SNr projection we let $\nu_{p1p2} = 0 \text{ mV s}$. This reduces all rates except that of the output nuclei (Column $m$). A stronger STN-GPe projection ($\nu_{p2e} = 0.4 \text{ mV s}$) greatly increases the GPe rate, leading to a reduction in the activity of the output nuclei, which increases corticothalamic and striatal rates (Column $n$). By providing a stronger drive to the STN, a larger $\nu_{ce}$ increases the rates of both STN and its target nuclei. As a result, thalamic activity is suppressed, reducing both cortical and striatal rates. Column $o$ of Table 5.3 lists the rates for $\nu_{ce} = 0.2 \text{ mV s}$.

### 5.5 Summary and Discussion

We have formulated a mean-field model of the basal ganglia-thalamocortical system (BGTCS) that yields realistic steady-state firing rates with parameters in physiologically plausible ranges, and takes into account many projections that were excluded from previous models. Estimates of parameter values and firing rates in health and in Parkinson’s disease (PD) were based on an extensive review of the experimental literature. After deriving expressions for the steady states, we have explored the effects of dopamine loss on the average fir-
Figure 5.8: Sensitivity of steady-state firing rates to connection strengths $\nu_{ab}$. Shaded regions indicate parameter ranges that yield realistic firing rates in the healthy state for all neuronal populations. Solid, $\phi_{d_1}$; dashed, $\phi_{d_2}$; dash-dotted, $\phi_{p_1}$; dotted, $\phi_{p_2}$; large dots, $\phi_\varsigma$. 
ing rates of the basal ganglia nuclei, thalamus, and cortex. The influence of a
range of connection strengths on these changes in firing rates was assessed. The
model provides a framework for studying the electrophysiology of the interconnected
basal ganglia, thalamus, and cortex, based on previous work by Rennie et al. (1999); Robinson et al. (1997, 2001b, 2003b, 2005). Furthermore, it lays
the foundation for analysis of dynamics and oscillations in PD, considered in
Chapter 6. Our main results are the following:

(i) A decrease in the strength of cortical projections to striatal D1 neu-
rons and a simultaneous increase in that to striatal D2 neurons, as in the
direct/indirect pathway model (Albin et al., 1989; Alexander and Crutcher,
1990), causes elevated GPi/SNr and STN rates and reduced GPe and thalamic
rates, in agreement with the findings of many experimental studies of animal
models of PD. However, a stronger indirect pathway alone, without modula-
tion of the direct pathway, may be sufficient to approximate empirical results.
Therefore, our results are not predicated on a complete separation between the
direct and indirect pathways. On the other hand, stronger corticostriatal pro-
jections to both D1 and D2 cells, and a simultaneous decrease in striatal firing
thresholds, chosen to mimic a reduction in striatal signal-to-noise ratio, do not
lead to the expected rate changes. This accords with the findings of Leblois
et al. (2006), but in contrast to that study, we conclude from the experimental
literature and our work that dopamine loss often leads to significant changes in
firing rates. Note that our results suggest that a combination of reduced corti-
costriatal connection strengths and striatal firing thresholds of both D1 and D2
populations does not adequately reflect physiological changes upon dopamine
loss, but this does not exclude the possibility that dopamine acts as a contrast
enhancer (Nicola et al., 2004). This role of dopamine may be mediated by
changes in intrinsic properties secondary in importance to changes in synaptic
properties (Moyer et al., 2007).

(ii) Besides changes in corticostriatal coupling, several other connection
strengths and firing thresholds are likely to be altered in PD. Loss of neu-
rons from the pre-supplementary motor area (MacDonald and Halliday, 2002)
is expected to reduce intracortical excitation, and mesocortical dopamine de-
pletion is expected to reduce intracortical excitation and especially inhibition
(Gao and Goldman-Rakic, 2003; Gullledge and Jaffe, 2001; Sesack and Bun-
ney, 1989; Thurley et al., 2008; Zhou and Hablitz, 1999). Enhanced enkephalin
release may result in weakened lateral inhibition in the GPe (Stanford and
Cooper, 1999; Terman et al., 2002), while reduced availability of dynorphin is
expected to lower the GPe firing threshold (Ogura and Kita, 2000). Higher
levels of extracellular potassium after SNc lesion increase the excitability of
the STN (Strauss et al., 2008). In addition, loss of direct dopaminergic innerva-
tion stimulates GABA release at striato-GPe terminals, increasing the
corresponding connection strength (Floran et al., 1997; Querejeta et al., 2001). Modeling results show that reduced intracortical and intrapallidal inhibition and a lower GPe firing threshold help account for the lack of decrease in cortical rate observed in monkeys and rats with nigrostriatal lesions (Dejean et al., 2008; Goldberg et al., 2002).

(iii) Modeling results suggest that changes in corticostriatal coupling strengths are not solely responsible for substantial increases in STN activity observed in animal models of PD (Bergman et al., 1994; Kreiss et al., 1997; Walters et al., 2007). Reduced intracortical inhibition, a stronger striato-GPe projection, and a lower STN firing threshold all contribute to STN hyperactivity. In the first two cases, the increase in STN activity is associated with a further decrease in GPe rate, whereas a lower STN firing threshold increases both rates. Besides increased excitability, it is also possible that altered inputs from the thalamic parafascicular nucleus (Orieux et al., 2000) and/or the PPN (Breit et al., 2001, 2006; Orieux et al., 2000) play a role in STN hyperactivity. The apparent contribution of the PPN to STN hyperactivity found in these studies is paradoxical, because the PPN receives important inhibitory input from the GPi (Yelnik, 2002), which is overactive in PD. Furthermore, PPN lesions have been shown to cause symptoms resembling PD in primates (Aziz et al., 1998; Kojima et al., 1997). The studies of Orieux et al. (2000) and Breit et al. (2001, 2006) were performed in rats, and the results may not generalize to the human situation, since PD is accompanied by significant neuronal loss from the PPN (Pahapill and Lozano, 2000; Zweig et al., 1989), which is not observed in the rat model. The STN also receives a direct dopaminergic projection, which probably contributes to changes in STN activity in PD (Blandini et al., 2000; Brown et al., 1979; Flores et al., 1999; Hassani et al., 1997; Lavoie et al., 1989). An in vivo study in rats suggested that dopamine inhibits STN firing (Campbell et al., 1985), whereas Kreiss et al. (1997) found that dopamine enhanced STN activity in intact animals, but reduced its activity after SNc lesion. However, a predominantly facilitatory effect has been more frequently reported, both in experiments (Loucif et al., 2008; Mintz et al., 1986; Ni et al., 2001b; Zhu et al., 2002), and in a modeling study (Humphries et al., 2006). Therefore it is unlikely that loss of intrinsic dopamine contributes to increased STN firing in PD.

(iv) Our model provides many approximate bounds on connection strengths in the BGTCs, and shows how the strengths of various projections may account for differences in rates between studies. Parameter estimation is an arduous task because the available data do not cover all relevant aspects of the electrophysiology of the basal ganglia, and there are often inconsistencies between studies. However, our main results are sufficiently robust that they hold for a large part of the physiologically realistic range.
When interpreting the above results, a number of qualifications should be taken into account. First, we have necessarily simplified basal ganglia connectivity, ignoring for instance the projections from GPe to striatum and TRN (Gandía et al., 1993; Hazrati and Parent, 1991; Kita et al., 1999), from striatum, STN, and PPN to SNc (Gerfen, 1992; Jiménez-Castellanos and Graybiel, 1989; Lavoie and Parent, 1994), and from thalamus to STN (Gonzalo et al., 2002; Orieux et al., 2000). In addition, the direct dopaminergic innervation from SNc to GPi, GPe, STN, and TRN, which appears to be strongest in GPi (Anaya-Martinez et al., 2006; Jan et al., 2000; Lavoie et al., 1989; Smith et al., 1989), may be incorporated in future studies. Although some of these projections may substantially affect the activity of their targets, their relative influences are difficult to ascertain from the literature. For instance, in addition to its major innervation by the cortex, well-documented reciprocal connections with the thalamic relay nuclei, and inputs from GPe, the TRN receives inputs from diverse brainstem and basal forebrain structures (Cornwall et al., 1990). To keep the model tractable, we have assumed that cortical and thalamic stimuli are the major determinants of TRN activity. Similar arguments hold for the other projections listed above.

Most of our analysis has also been based on the simplifying assumption that each of the basal ganglia nuclei can be treated as a unit in which neurons have common levels of inputs and outputs. However, studies indicate that each nucleus consists of territories with slightly different connectivity patterns. The division of basal ganglia pathways into sensorimotor, associative, and limbic circuits is the most obvious example of this. In addition, parts of the STN have been reported to project specifically to either GPi or GPe (Gonzalo et al., 2002; Parent et al., 1989). Within the GPi, Parent et al. (2001) distinguished between centrally located neurons which terminate in VA, CM-Pf, and PPN, and more peripherally located neurons which innervate the lateral habenula. Moreover, the specific neuronal architectures of the direct and indirect pathways may allow focused excitation of the thalamus via the direct route, and surround inhibition via the indirect route upon cortical stimulation (Haber and Gdowski, 2004). Within the framework provided by our model, the influences of additional projections or more detailed connectivity patterns of the basal ganglia can be assessed with relative ease. The dynamics of the present model is explored in detail in Chapter 6.
Chapter 6

Mean-field modeling of the basal ganglia-thalamocortical system. II. Dynamics of parkinsonian oscillations

Neuronal correlates of Parkinson’s disease include a shift to lower frequencies in the electroencephalogram (EEG) and enhanced synchronized oscillations at 3–7 Hz and 7–30 Hz in the basal ganglia, thalamus, and cortex. This study describes the dynamics of a recent physiologically-based mean-field model of the basal ganglia-thalamocortical system, and shows how it accounts for many key electrophysiological correlates of Parkinson’s disease. Its detailed connectivity comprises partially segregated direct and indirect pathways through two populations of striatal neurons, a hyperdirect pathway involving a corticosubthalamic projection, thalamostriatal feedback, and local inhibition in striatum and external pallidum (GPe). In Chapter 5, realistic steady-state firing rates were obtained for the healthy state, and after dopamine loss modeled by weaker direct and stronger indirect pathways, reduced intrapallidal inhibition, lower firing thresholds of the GPe and subthalamic nucleus (STN), a stronger projection from striatum to GPe, and weaker cortical interactions. Here it is shown that oscillations around 5 Hz and 20 Hz can arise with a strong indirect pathway, which also causes increased synchronization throughout the basal ganglia. Furthermore, increased theta power with progressive nigrostriatal degeneration is correlated with reduced alpha power and peak frequency, in agreement with empirical results. Unlike the hyperdirect pathway, the indirect pathway sustains oscillations with phase relationships that coincide with those found experimentally. Alterations in the responses of basal ganglia to transient stimuli accord with experimental observations. Reduced cortical gains due to both nigrostriatal and mesocortical dopamine loss lead to slower changes in cortical activity and may be related to bradykinesia. Finally, increased EEG power
found in some studies may be partly explained by a lower effective GPe firing
threshold, reduced GPe-GPe inhibition, and/or weaker intracortical connec-
tions in parkinsonian patients. Strict separation of the direct and indirect
pathways is not necessary to obtain these results.

6.1 Introduction

Parkinson (1817) described a syndrome with symptoms including a stooped
posture, shuffling gait (festination), sleep disturbances, and rest tremor. This
disorder, which also leads to slowness of movement (bradykinesia), difficulty ini-
tiating movements (akinesia), and rigidity, was subsequently called Parkinson’s
disease (PD). It is one of the most common movement disorders, affecting 0.5–
3% of those over 65 (Tanner and Goldman, 1996). The pathological hallmark
of PD is the progressive degeneration of dopaminergic neurons in the substan-
tia nigra pars compacta (SNc) and to a lesser extent the ventral tegmental
area (VTA) (Bernheimer et al., 1973; Ehringer and Hornykiewicz, 1960; Hirsch
et al., 1988; Uhl et al., 1985). These nuclei provide dopaminergic input to the
basal ganglia, a group of grey matter structures close to the thalamus concerned
with reinforcement learning and the facilitation and modulation of movement
(Graybiel, 1990; Mink, 1996). The main structures comprising the basal gan-
glia are the striatum, the substantia nigra, the globus pallidus internal (GPi)
and external (GPe) segments, and the subthalamic nucleus (STN). Alterations
in the associative and limbic functions of the basal ganglia are responsible for
some of the cognitive symptoms and mood disturbances seen in PD.

In Chapter 5 we introduced a physiologically realistic mean-field model of
the basal ganglia-thalamocortical system (BGTCS), and assessed changes in
average firing rates caused by loss of nigrostriatal dopamine. We found that
an increase in the strength of cortical transmission to striatal cells expressing
the D2 class of dopamine receptor, with or without a concurrent decrease in
the connection strength to D1-expressing cells, could account for the majority
of changes in firing rates observed in parkinsonism. Reduced lateral inhibition
in the GPe, a lower GPe firing threshold, and reduced intracortical inhibition
helped account for the reported lack of change in cortical rate (Goldberg et al.,
2002). Lower STN and GPe thresholds combined with decreased intrapallidal
inhibition explained the relatively large increase in STN rate and relatively
small decrease in GPe rate observed experimentally (Bergman et al., 1994;
Boraud et al., 1998; Filion and Tremblay, 1991; Goldberg et al., 2002; Heimer
et al., 2002; Hutchison et al., 1994; Kreiss et al., 1997; Pan and Walters, 1988;
Walters et al., 2007). Increases in GPe rate due to changes in GPe and STN
firing thresholds and intrapallidal inhibition were limited by stronger striatal
inhibition of the GPe, which is expected with dopamine loss (Floran et al.,
The purpose of this chapter is to analyze the dynamics of the model presented in Chapter 5 in the healthy and parkinsonian states, and to compare modeling results with experimental findings on electrophysiological changes caused by dopaminergic denervation. Dynamical changes with dopamine loss include altered responses to transient stimuli, a lower frequency of the alpha peak and increased relative low-frequency power in the electroencephalogram (EEG), and synchronized oscillations around 5 Hz and 20 Hz throughout the BGTC. The present work is devoted to modeling these electrophysiological changes, which are described in detail in Sec. 6.2.2. Using parameters that accord well with known physiology, we obtain not only realistic firing rates (see Chapter 5), but also realistic EEG spectra and responses to transient stimuli, oscillations in the theta and beta ranges, and enhanced synchronization in the basal ganglia. In Sec. 6.2 we review the relevant anatomy and electrophysiological changes found experimentally, and place our model in context by describing possible origins of parkinsonian oscillations. Section 6.3 details the model equations and parameter changes in PD, followed by an analysis of changes in neuronal responsiveness in Sec. 6.4. Oscillations and frequency spectra predicted by the model are discussed in Sec. 6.5.

6.2 Physiological background

In Sec. 6.2.1 we summarize the connections of the BGTC included in the model, which were described more fully in Chapter 5. Section 6.2.2 provides an overview of the electrophysiological changes caused by nigrostriatal degeneration. Possible neuronal substrates of parkinsonian oscillations are discussed in Sec. 6.2.3.

6.2.1 Connectivity

The main connections of the BGTC are depicted in Fig. 6.1. Excitatory input from the cortex reaches the basal ganglia mainly at the striatum, of which 90–95% of cells are medium spiny projection neurons (Kemp and Powell, 1971). Medium spiny neurons are classified according to their predominant type of dopamine receptor (D1 or D2). Although a proportion of striatal neurons has both D1 and D2 receptors, a partial segregation appears to exist between these populations (Hersch et al., 1995; Inase et al., 1997; Le Moine and Bloch, 1995; Lester et al., 1993; Meador-Woodruff et al., 1991). A number of studies have suggested that dopaminergic input from the SNc affects D1 and D2-expressing cells differently, primarily increasing the effect of cortical input on D1 cells, and primarily decreasing the sensitivity of D2 cells to cortical input (Gerfen et al., 1997; Querejeta et al., 2001).
Both D1 and D2 striatal neurons exert an inhibitory influence on their projection sites: D1 neurons on the GPi and the substantia nigra pars reticulata (SNr), and D2 neurons on the GPe. SNr and GPi are the main output nuclei of the basal ganglia, sending inhibitory projections primarily to the ventral anterior (VA) and ventrolateral (VL) thalamic nuclei (Parent, 1990; Parent and Hazrati, 1995a), but also to the centromedian-parafascicular complex (CM-Pf) (Kim et al., 1976; Parent et al., 2001). The pathway cortex-D1-GPi/SNr-thalamus, where the loop is completed via excitatory (glutamatergic) projections to the cortex, is termed the direct pathway (Albin et al., 1989; Alexander and Crutcher, 1990). Since D1 inhibits the output nuclei, which in turn inhibit the thalamus, the direct pathway as a whole is excitatory.

Striatal output to the GPe is relayed to the SNr and GPi via the STN, where the GPe has an inhibitory influence on the STN, while the effect of the STN on the output nuclei is excitatory. Therefore, the pathway cortex-D2-GPe-STN-GPi/SNr-thalamus as a whole is inhibitory, so that cortical activation results in inactivation of the thalamus. This pathway is referred to as the indirect pathway (Albin et al., 1989; Alexander and Crutcher, 1990). Projections from GPe to STN are reciprocated by excitatory STN-GPe projections. There also exists an important hyperdirect pathway from the cerebral cortex to the STN, particularly from the frontal lobe (Afsharpour, 1985; Hartmann-von Monakow et al., 1978; Nambu et al., 2000; Parent and Hazrati, 1995b). The direct, indirect, and hyperdirect pathways are illustrated in Fig. 6.1(a).

Significant thalamostriatal projections arise from the relay nuclei CM-Pf, VA, and VL (Carpenter, 1981; Gonzalo et al., 2002; Parent, 1990; Sadikot et al., 1990, 1992). Empirical results indicate that the associated neurotransmitter is glutamate (Haber and Gdowski, 2004; Sadikot et al., 1992). The GPe contains a dense network of local axon collaterals (Kita, 1994; Nambu and Llinás, 1997; Ogura and Kita, 2000), and sends a projection to the GPi (Hazrati et al., 1990; Sato et al., 2000; Shink and Smith, 1995; Smith et al., 1994). GABAergic striatal interneurons receiving input from the cortex powerfully inhibit medium spiny neurons, which also provide local axon collaterals (Bolam et al., 2000; Koós and Tepper, 1999; Somogyi et al., 1981; Wilson, 2007). Although striatal axon collaterals appear to exert excitatory effects at hyperpolarized membrane potentials, their influence becomes inhibitory near spike threshold (Plenz, 2003; Taverna et al., 2004). Since the strength of local interactions increases with the firing rate, and in view of the strong inhibitory action of striatal interneurons, we model intrastriatal connections as inhibitory.

Reciprocal connections exist between the relay nuclei and the thalamic retic-
ular nucleus (TRN), both of which receive excitatory (glutamatergic) input from the cerebral cortex. The relay nuclei project back to the cortex, and the cortex contains populations of short-range inhibitory interneurons and long-range excitatory (pyramidal) cells. Sensory input reaches the thalamic relay nuclei from the brainstem via glutamatergic and cholinergic afferents. In contrast, the basal ganglia do not receive significant projections from ascending sensory pathways (Elble, 2002).

Anatomical and physiological studies have shown that connections in the BGTCs form three mostly separate circuits (sensorimotor, association, and limbic), which are further organized into somatotopic regions (Alexander et al., 1986; Alexander and Crutcher, 1990). Since the sensorimotor circuit is most relevant to parkinsonian motor symptoms, in the present work we ignore projections to and from the amygdala, dorsal raphe nucleus, hippocampus, and pedunculopontine nucleus (PPN) of the brainstem, which mostly affect limbic territories. We do not treat the remaining territories separately for two reasons. First, since many empirical studies do not distinguish between sensorimotor, association, and limbic pathways, or between pathways corresponding to different somatotopic regions, sufficient physiological data are not available for each circuit separately. Second, the similarity of the connectivity patterns of all circuits suggests that oscillations may be generated by a common mechanism.

6.2.2 Overview of experimental findings

The wide-ranging effects of nigrostriatal dopamine depletion on the dynamics of the BGTCs include alterations of responses to transient stimuli or during volitional tasks. Regional cerebral bloodflow appears to be diminished in the supplementary motor area (SMA) and the dorsolateral prefrontal cortex, whereas other cortical areas display increased activation during motor tasks (Jenkins et al., 1992; Playford et al., 1992; Sabatini et al., 2000). On the other hand, cortical activation has been shown to be suppressed specifically during tasks with significant involvement of the caudate nucleus, but increased otherwise (Monchi et al., 2007). The increased activation of cortical regions in the absence of striatal involvement may reflect compensation for deficits caused by nigrostriatal dopamine loss (Samuel et al., 1997), or degeneration of direct mesocortical dopaminergic afferents (Mattay et al., 2002). The responsiveness of striatal neurons is expected to change depending on the type of dopamine receptor they primarily express (D1 or D2). Dopamine potentiates the activation of D1-expressing neurons by glutamate unless they are in a hyperpolarized state (Cepeda et al., 1998; Hernández-López et al., 1997; Kiyatkin and Rebec, 1996; Nicola et al., 2000). In contrast, the responsiveness to glutamate is suppressed via D2 receptor activation (Hsu et al., 1995; Levine et al., 1996; Toan and Schultz, 1985; Umemiya and Raymond, 1997). GPi neurons
display more widespread and vigorous responses to passive limb movements in parkinsonian monkeys (Bergman et al., 1994; Filion et al., 1988), especially to extension torque (Wichmann et al., 1994b). Zold et al. (2007b) reported an increase in the number of excitatory responses in the globus pallidus (GP; the rodent homolog of GPe) of rats with moderate nigrostriatal damage, but inhibitory responses increased after more extensive damage. A reduction in pallidal activity upon cortical stimulation was also observed in a rat model of PD (Magill et al., 2001). The STN responds more vigorously to cortical stimulation in parkinsonian rats (Magill et al., 2001). Furthermore, the duration and magnitude of both excitatory and inhibitory responses in the STN of African green monkeys increased after SNc lesion with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), most cells increasing their firing rate (Bergman et al., 1994).

EEG and magnetoencephalographic (MEG) spectra show that relative power in the delta and theta bands (i.e., the proportions of the total power in these frequency bands) is increased in PD patients compared to age-matched controls (Bosboom et al., 2006; Neufeld et al., 1994; Stoffers et al., 2007). In non-demented patients, increased delta and theta power is associated with more severe motor and cognitive symptoms (Bosboom et al., 2006; Neufeld et al., 1994), and may be specific to patients with REM sleep behavior disorder (Gagnon et al., 2004). PD is also accompanied by lower alpha peak frequencies, especially in patients with dementia (Sinanović et al., 2005; Soikkeli et al., 1991); e.g., Soikkeli et al. (1991) reported mean alpha peak frequencies of 9.6 Hz in controls, 8.3 Hz in non-demented PD patients, and 6.8 Hz in demented patients. Some studies also reported that absolute EEG power is increased across the spectrum in PD patients by an amount independent of medication state (Moazami-Goudarzi et al., 2008; Tanaka et al., 2000), although Yaar and Shapiro (1983) found that levodopa increased spectral power in the left occipital lobe over all frequency bands. Increased corticothalamic coherence at \( \sim 7 \) Hz (Sarnthein and Jeanmonod, 2007) is in line with greater EEG power and a lower frequency of the alpha peak. Overall, EEG power appears to decline with advancing dementia, but according to Tanaka et al. (2000) demented patients still had higher delta (1.5–6 Hz), theta (6.5–8 Hz), and beta (13.5–30 Hz) power than controls. On the other hand, Soikkeli et al. (1991) reported higher delta and theta power, but lower beta power in demented patients than in control subjects. EEG frequency reduction in PD may be partly caused by changes in non-dopaminergic neurotransmitter systems (Stoffers et al., 2007). Especially the cholinergic and noradrenergic systems are implicated, since demented PD patients have reduced cortical cholinergic activity due to degeneration of the nucleus basalis of Meynert (Candy et al., 1983; Dubois et al., 1983), as well as more significant noradrenergic deficits than non-demented patients (Cash
et al., 1987). Moreover, loss of cholinergic afferentation from the basal forebrain has been related to EEG frequency reduction with age (Buzsáki et al., 1988; Longo, 1966; Metherate et al., 1992). We propose a mechanism by which nigrostriatal denervation itself also contributes to EEG frequency reduction in PD.

PD is also associated with enhanced oscillations at 3–7 Hz and 7–30 Hz in the BGTCs, which have been observed in humans and in animal models of PD in the GPi and GPe (Filion and Tremblay, 1991; Levy et al., 2002; Nini et al., 1995; Raz et al., 2000), STN (Bergman et al., 1994; Levy et al., 2000; Wang et al., 2005), SNr (Wichmann et al., 1999), palidal and cerebellar-receiving areas of the thalamus (Lamarre and Joffroy, 1979; Lenz et al., 1994; Magnin et al., 2000; Ohye et al., 1974, 1989), striatal medium spiny neurons (Dejean et al., 2008) and tonically active interneurons (Raz et al., 2001), and sensory and motor cortices (Alberts et al., 1969; Cordeau et al., 1960; Lamarre and Joffroy, 1979; Timmermann et al., 2003; Volkman et al., 1996). In the GPi of PD patients, ~5 Hz oscillations were found to be more common than 15–20 Hz oscillations (Levy et al., 2001). A percentage of GPe and GPi neurons in monkeys treated with MPTP displayed 5–8 Hz oscillations for short periods during tremor, and approximately 15 Hz oscillations in both palidal segments in the absence of tremor, which sometimes persisted over longer intervals in the GPi (Filion and Tremblay, 1991). Microelectrode recordings revealed stable 11–30 Hz synchronization and more transient ~5 Hz coherence between pairs of neurons in the STN of PD patients, particularly those with tremor (Levy et al., 2000). The large power of beta oscillations in the STN (Kühn et al., 2005), and the differential modulation of low- and high-frequency activity by dopaminergic medication and during periods of intermittent tremor (Silberstein et al., 2003; Wang et al., 2005), suggest that ~20 Hz oscillations are not generated as a harmonic of the ~5 Hz rhythm.

### 6.2.3 Possible origins of oscillations

Despite the similar frequencies of slow oscillations in the BGTCs and resting tremor, it is unclear whether a direct causal relationship exists between the two, since rhythmically discharging cells have been found in the basal ganglia even without obvious tremor (Bergman et al., 1994; Levy et al., 2001; Ohye et al., 1974; Wichmann et al., 1994a; Williams et al., 2002), as has a lack of coherence even during tremor (Bergman et al., 1994). Furthermore, synchronized beta oscillations are also more prominent in patients with intermittent tremor than in non-tremulous patients, indicating an association between higher-frequency rhythms and tremor (Levy et al., 2000) (although we will see that relatively strong beta resonances can occur in a system that is likely to support theta oscillations, which may well be more directly related to tremor). The fact
that even random electrical (Alberts, 1972) or 10–30 Hz magnetic stimulation (Topka et al., 1999) of the motor cortex can induce 4–7 Hz tremor also shows that basal ganglia oscillations need not directly determine tremor frequency. Finally, the basal ganglia do not appear to initiate movements under normal conditions (Horak and Anderson, 1984; Mink, 1996; Rivlin-Etzion et al., 2006).

Involvement of the cerebellum in the generation of parkinsonian tremor has been suggested since tremor-like oscillations in the cerebellar-receiving ventralis intermedius (Vim) nucleus of the thalamus are stronger and show greater coherence with the EMG than oscillations in basal ganglia targets (Lenz et al., 1988), and Vim has long been a preferred surgical target for PD (Okun and Vitek, 2004). However, all forms of tremor are accompanied by abnormal cerebellar activation, likely due to proprioceptive feedback from the limbs (Deuschl et al., 2001). More telling is the study by Deuschl et al. (1999) on a patient who developed PD 17 years after a stable lesion of the right cerebellar hemisphere. This patient exhibited a bilateral tremor with a frequency of 3.1 Hz on the side of the cerebellar lesion, and 4.3 Hz on the intact side, demonstrating that an intact olivocerebellar circuit is not necessary to produce tremor. The tremor on the lesioned side was a combination of resting, postural, and intention tremors, and was interpreted as rubral or Holmes tremor. The fact that levodopa is effective against Holmes tremor indicates that it is due to a combination of cerebellar and nigrostriatal damage, which is confirmed by PET imaging (Remy et al., 1995; Vélez et al., 2002). The cerebellum may prevent nigrostriatal degeneration from causing tremor during voluntary movement, and may modulate the frequency of resting tremor (Deuschl et al., 1999). The small degree of entrainment and phase resetting of parkinsonian tremor that can be achieved with imposed periodic movements (Rack and Ross, 1986) and mechanical stimulation (Lee and Stein, 1981), respectively, also indicates the limited influence of peripheral factors. Even if the frequency or presence of tremor is not directly determined by oscillations in the BGTC, an important role for the basal ganglia in the production of tremor is therefore evident. Furthermore, a basal ganglia contribution to akinesia, bradykinesia, and rigidity is implied by the fact that pallidal or STN lesions or high-frequency stimulation can ameliorate these symptoms (Gross et al., 1997; Iacono et al., 1995; Limousin et al., 1998; Meissner et al., 2005).

Due to the widespread nature of the oscillatory activity in PD, various parts of the BGTC are implicated as possible sources (Deuschl et al., 2000; Elble, 1996). Several hypotheses have been put forward concerning the origin of parkinsonian oscillations, which can be grouped into the following four — not necessarily mutually exclusive — categories for our purposes.
Figure 6.1: Four possible network origins of parkinsonian tremor, indicated by the shaded areas. Signals are ultimately transmitted to the muscles via the corticospinal tract. Filled arrowheads indicate excitatory projections, and open arrowheads inhibitory ones, with the thickness of the lines representing the strength of connections with respect to the healthy state. Dashed lines indicate the transfer of tremor-related activity. Although some tremor activity may be transferred via the remaining projections, arrows are drawn solid to emphasize that the receiving structures can generate oscillations without rhythmic input. Subscripts used for the various populations are given in parentheses. (a) Thalamic relay nuclei are hyperpolarized by the GPi, causing low-threshold calcium spike bursts. These bursts become synchronized through intrathalamic interactions. Grey arrows indicate the direct, indirect, and hyperdirect pathways. (b) Increased striatal input to GPe and decreased intrapallidal inhibition cause rhythmic oscillations in the GPe-STN system. Rhythmic bursts are seen in the thalamus due to periodic input from the GPi. (c) Resonances arise in the corticothalamic loop or intracortically after hypoactivation of the thalamic relay nuclei. (d) Resonances arise in the cortico-basal ganglia-thalamic circuit as a whole. Combinations of mechanisms are possible; for instance, rhythmic activity generated in the thalamus could be enhanced within the STN-GPe network, or both cortico-basal ganglia-thalamic and STN-GPe circuits could act as sources of rhythmic oscillations.
Hypothesis of thalamic origin

The first scenario, illustrated in Fig. 6.1(a), places the origin in the thalamus (Hurtado et al., 1999; Llinás, 1984; Paré et al., 1990; Sarnthein and Jeanmonod, 2007). The thalamus is implicated since striatal dopamine depletion leads to disinhibition of GPi and SNr, increasing inhibition of the VA and VL thalamic nuclei (Hutchison et al., 1994; Magnin et al., 2000; Pan and Walters, 1988). Hyperpolarization of thalamic relay neurons has been shown to cause low-threshold calcium spike bursts (Deschênes et al., 1982; Jeanmonod et al., 1996; Llinás and Jahnsen, 1982; Llinás and Steriade, 2006), some of which occur rhythmically at an interburst frequency of ~4 Hz in patients with symptoms related to thalamic hypoactivation, including parkinsonian tremor (Jeanmonod et al., 1996; Ohye et al., 1974). Such rebound bursts in response to tonic overinhibition by the GPi and SNr may be synchronized by lateral inhibition within the TRN, and their rhythmicity may be partly determined by network interactions between the TRN and the relay nuclei (Buzsáki, 1991). The thalamic oscillations would mediate their effect on cortical and muscular activity through projections to the prefrontal and premotor cortices (Sarnthein and Jeanmonod, 2007). Rhythmic oscillations may be relayed to the basal ganglia either via the striatum or via the corticosubthalamic projection, and enhanced within the loop formed by STN and GPe (Baufreton et al., 2005), which appear to become more sensitive to rhythmic inputs following loss of striatal and extrastriatal dopamine (Bevan et al., 2006). Finally, GPe and STN could output rhythmic oscillations via projections to GPi and SNr.

Until the recent finding of 5–13 Hz oscillations in medium spiny neurons of unanesthetized rats with nigrostriatal lesions (Dejean et al., 2008), evidence for the involvement of the corticostratial and striatopallidal projections was mostly indirect. The delay in obtaining this experimental evidence is explained by the low firing rate of medium spiny neurons, which prevents autocorrelation functions from showing prominent oscillations. Dejean et al. (2008) overcame this problem by using peri-event histograms, and focused on high-voltage spindles to track rhythmic activity in the unanesthetized condition. An earlier argument put forward for the involvement of striatal projections (Murer et al., 2002) is the relatively long phase delay (20–30 ms) between rhythmic cortical activity at and activity in the STN and GPi of PD patients off medication (Marsden et al., 2001; Williams et al., 2002), which is longer than the corticosubthalamic delay of < 10 ms estimated in a few studies (Ashby et al., 2001; Nambu et al., 2000). Further indirect evidence for striatal transmission of tremor-like rhythms is that the membrane potentials of striatal medium spiny neurons reliably follow ~5 Hz cortical rhythms induced by light anesthesia in animals (Mahon et al., 2001; Wilson, 1993). In addition, Tseng et al. (2001) demon-
strated that slow (~1 Hz) rhythmic cortical inputs induce oscillations at the same frequency in striatal neurons of anesthetized rats with nigrostriatal lesions. Oscillatory activity at ~15 Hz is also observed in the tonically active cholinergic interneurons of the rat striatum (Raz et al., 1996, 2001), although the relationship between these oscillations and the activity of medium spiny neurons is unclear. The cholinergic interneurons may oscillate in response to nigrostriatal afferents, input from the GPe (Sato et al., 2000), or input from CM-Pf (Lapper and Bolam, 1992).

On the other hand, involvement of the corticosubthalamic pathway is implied by the fact that the discharge rate and pattern of GP neurons is not significantly affected by cortical ablation in anesthetized rats, whereas in the STN, this abolishes slow oscillations coherent with the EEG (Magill et al., 2001). The regularization of GP (Ni et al., 2000), SNr (Burbaud et al., 1995; Tseng et al., 2000) and GPi (Wichmann et al., 1994b) activity upon STN lesion has also been put forward as evidence for the contribution of the corticosubthalamic projection, but these findings do not exclude the possibilities that oscillatory activity arises in the STN-GPe network or in cortico-basal ganglial-thalamic loops involving striatopallidal projections.

A possible objection to the hypothesis of a thalamic pacemaker for parkinsonian tremor is the fact that different body parts often tremble at slightly different frequencies, suggesting the absence of the overall synchronizing influence of the TRN (Paré et al., 1990). However, we have seen above that cortical and peripheral factors appear to play a role in determining tremor frequency. Lenz et al. (1993) and Zirh et al. (1998) noted a difference between the pattern of interspike intervals in thalamic bursts in parkinsonism and the gradual lengthening of interspike intervals characteristic of calcium spike-associated bursts. This may indicate that rhythmic GPi inputs to slightly depolarized thalamic neurons, rather than increased tonic GPi activity and consequent low-threshold calcium spike bursts, are responsible for the bursting patterns observed in the thalamus.

Hypothesis of origin in STN-GPe loop

A second hypothesis, illustrated in Fig. 6.1(b), states that changes in tonic input to the STN-GPe system cause these nuclei to produce oscillatory activity, which spreads to the basal ganglia output nuclei, thalamus, and cortex (Deuschl et al., 2000; Terman et al., 2002). It has been shown that STN neurons can switch from a single-spike mode to a burst-firing mode upon hyperpolarization by the GPe (Beurrier et al., 1999; Bevan et al., 2000). Although the GPe generally becomes less active in parkinsonism, excitation by the STN may induce periods of enhanced GPe firing, periodically hyperpolarizing STN neurons and
causing rebound bursts. This mechanism was suggested by Plenz and Kital (1999), who showed that the rat STN-GP network undergoes spontaneous 0.4–1.8 Hz oscillations in the absence of dopamine. Terman et al. (2002) modeled networks of STN and GPe neurons and showed that increased synaptic input from the striatum to the GPe and/or weakened intrapallidal inhibition can lead to slow (< 1 Hz) synchronized oscillations in these nuclei or clustered rhythms at 4–6 Hz, depending on the network architecture and the STN-GPe connection strength. The reduction in lateral inhibition within the GPe would be caused by the enhanced release of enkephalin (Stanford and Cooper, 1999; Steiner and Gerfen, 1998), preventing desynchronization of GPe neurons by intranuclear interactions. Oscillations in the STN-GP circuit have also been replicated in computational models by Gillies et al. (2002); Humphries and Gurney (2001); Humphries et al. (2006).

A requirement of this hypothesis is that the STN-GPe network be able to generate rhythmic activity in the absence of rhythmically modulated input. Both an experimental study (Magill et al., 2001), and a modeling study (Humphries et al., 2006) of rat basal ganglia have shown that small subpopulations of GP and STN neurons can sustain rhythmic oscillations around 1 Hz. However, Magill et al. (2001) reported that most correlated bursting in GPe and SNr was abolished by cortical desynchronization or ablation. A few other studies have also suggested that the isolated STN-GPe network does not generate significant rhythmic bursting activity. First, a study in rats showed that GABA antagonists, mimicking reduced pallidal input to STN, can make bursting patterns more marked, but cannot change an irregular spiking mode into a bursting mode (Urbain et al., 2002). Furthermore, Wilson et al. (2006) showed that rhythmic oscillations were absent in a slice preparation of the isolated pallidosubthalamic network from dopamine-depleted mice. Wilson et al. (2006) pointed out that inputs from striatum and/or cortex may be needed to induce synchronized oscillations in these nuclei in the slice preparation, although these inputs were not necessary in the rat cell culture (Plenz and Kital, 1999). However, the slice preparation of Wilson et al. (2006) may not have left sufficient GP projections intact to significantly inhibit the STN and evoke rebound firing in that nucleus.

Hypothesis of origin in corticothalamic loops

A third possibility, depicted in Fig. 6.1(c), is that rhythmic activity arises from reverberations within the corticothalamic network. If we assume that the frequency of resting tremor is directly determined by central oscillations, the lack of coherence between GPi cells firing near tremor frequencies and the tremor EMG (Lemstra et al., 1999) appears to be evidence for a thalamic or
corticothalamic source of tremor oscillations. Magnin et al. (2000) reported a larger proportion of tremor-locked cells in the GPi than in the thalamus, which provides evidence both for and against this hypothesis. On the one hand, it suggests that oscillations arise upstream from the thalamus; on the other hand, rhythmic oscillations may not be relayed directly from GPi to thalamus. Although Magnin et al. (2000) found no synchronization between individual pallidal-receiving thalamic cells and tremor, it is possible that the average activity of a larger subpopulation was modulated rhythmically in a coherent manner, since even weak correlations between individual cells can lead to strong coherence at the population level (Schneidman et al., 2006).

**Hypothesis of origin in basal ganglia-thalamocortical loops**

Finally, resonances may originate in the BGTCS as a whole, rather than being confined to any particular region (Deuschl et al., 2000; Wichmann and DeLong, 2003) [Fig. 6.1(d)]. This hypothesis implies that the rhythmicity would be determined by the delay for signals to complete a full loop from cortex through the basal ganglia, thalamus, and back to the cortex. Such a mechanism was proposed by Leblois et al. (2006), who described a neuronal network model of interacting direct and hyperdirect pathways, of which the latter sustained oscillations at ~11 Hz when regulation by the direct pathway was suppressed. The objection that GPi and thalamic activity appear to be noncoherent during tremor (Lemstra et al., 1999; Magnin et al., 2000) can be raised against this hypothesis as well as against the hypothesis that oscillations arise in the STN-GPe network. However, as discussed above, lack of coherence of individual cells with the EMG or with other rhythmic cells does not appear to rule out the involvement of these cells in the generation of parkinsonian oscillations.

This chapter investigates which of the above hypotheses is supported by the known anatomy of the BGTCS if the dynamics is governed by mean-field activity.

### 6.3 Dynamical equations

The form of the model developed in Chapter 5 and used here is based on Rennie et al. (1999) and Robinson et al. (1997, 1998b,a, 2002, 2005), work that partly built on models developed by Freeman (1975), Jirsa and Haken (1996), Nunez (1974a, 1995), Wright and Liley (1996), and others. The model incorporates synaptic and dendritic integration effects, nonlinear response functions, axonal conduction delays, and spreading of wave-like activity along the cortical surface. The basic model equations were largely given in Chapter 5, but are summarized
in Sec. 6.3.1 for convenience. Section 6.3.2 contains the equations that govern small perturbations about fixed point. In Sec. 6.3.3 we describe the parameter changes used to model parkinsonism.

6.3.1 Basic equations

The neuronal populations of the model will be indicated by the following subscripts: $e$, cortical excitatory; $i$, cortical inhibitory; $d_1$, striatal D1 cells; $d_2$, striatal D2 cells; $p_1$, Gpi/SNr; $p_2$, GPe; $\varsigma$, STN; $s$, thalamic relay nuclei; and $r$, TRN. We refer to brainstem input using a subscript $n$. The subscript $s$ indicates both specific relay nuclei and the diffusely projecting CM-Pf complex.

The dependence of the mean firing rate $Q_a(r, t)$ of each population of neurons $a$ on the cell-body potential $V_a(r, t)$ relative to resting is modeled by a sigmoidal function taking the form (Robinson et al., 2002)

$$Q_a(r, t) = \frac{Q_{a}^{\text{max}}}{1 + \exp[-(V_a(r, t) - \theta_a)/\sigma_a^\alpha]}.$$ (6.1)

In previous works the cortex was modeled as two-dimensional since it has a large surface area but is comparatively thin, whereas other components were treated as uniform. In the present work we indicate the spatial coordinate $r$ for completeness, although we will only consider spatially uniform solutions. The functional dependence (6.1) results from averaging the response functions of neurons with slightly different firing thresholds. The quantity $Q_{a}^{\text{max}}$ is the maximum firing rate, $\theta_a$ is the mean threshold potential, and $\sigma_a^\alpha$ is the standard deviation of firing thresholds. The latter is taken to be equal for all components, since we lack precise knowledge of the ranges of firing thresholds in different populations.

Changes in the cell-body potential of type $a$ neurons are triggered by pulses that arrive from type $b$ neurons after an axonal delay $\tau_{ab}$, are filtered by the dendritic tree, and summed at the cell body. The effect of an incoming pulse rate $\phi_b(r, t - \tau_{ab})$ on the cell-body potential depends on the connection strengths between the neural populations. These are made up of the mean number of synapses, $N_{ab}$, and the typical time-integrated change in cell-body potential per incoming pulse, $s_{ab}$. Connection strengths are thus given by the products $\nu_{ab} = N_{ab}s_{ab}$. The change in the average cell-body potential of type $a$ neurons due to the summation and temporal integration of incoming signals becomes (Robinson et al., 2004)

$$D_{a\beta}(t)V_a(r, t) = \sum_b \nu_{ab}\phi_b(r, t - \tau_{ab}),$$ (6.2)

$$D_{a\beta}(t) = \frac{1}{\alpha \beta} \frac{d^2}{dt^2} + \left(\frac{1}{\alpha} + \frac{1}{\beta}\right) \frac{d}{dt} + 1.$$ (6.3)
The differential operator $D_{\alpha\beta}(t)$ approximates filtering of signals by the synapses and the dendritic tree (Rennie et al., 2000; Robinson et al., 1997). We assume $\alpha < \beta$ without loss of generality, which in practice means that $\alpha$ is the decay rate and $\beta$ the rise rate of the cell-body potential. The synapses and dendrites reduce the power of signals for angular frequency $\omega \gtrsim \alpha$ and especially for $\omega \gtrsim \beta$. In more complicated models, $\alpha$ and $\beta$ may be taken to depend on both the sending and receiving populations, and the relevant neurotransmitter (Rennie et al., 2000).

The cortical signal depends not only on resonances with underlying structures, but also on corticocortical interactions. Many experiments have revealed propagating waves of neuronal activity upon local cortical stimulation (Chervin et al., 1988; Nunez, 1974a; Schiff et al., 2007; Xu et al., 2007), a feature previously included in a number of modeling studies (Bressloff, 2001; Bressloff et al., 2003; Jirsa and Haken, 1996, 1997; Nunez, 1995). Although Nunez (1995) focused on standing waves obtained when cortical waves are weakly damped, physiological and modeling evidence indicates that considerable damping occurs, and should be taken into account (Robinson et al., 2001a, 2004; Wright and Liley, 1995). We thus model propagation effects along the cortical surface due to long-range excitatory connections via a damped-wave equation with source term $Q_e(r, t)$ (Robinson et al., 1997, 2001a),

\[
\frac{1}{\gamma_e^2} \left[ \frac{\partial^2}{\partial t^2} + 2\gamma_e \frac{\partial}{\partial t} + \gamma_e^2 - v_e^2 \nabla^2 \right] \phi_e(r, t) = Q_e(r, t). \tag{6.4}
\]

The form (6.4) results when the range distribution of corticocortical axons is approximated as isotropic, and exponentially decaying at large distances compared to characteristic range $r_e$ (Robinson et al., 1997). The firing rate field $\phi_e(r, t)$ is damped at a rate $\gamma_e = v_e/r_e$, where $v_e \simeq 5-10$ m s$^{-1}$ is the average propagation rate along pyramidal axons. For the remaining neuronal populations we assume propagation effects to be negligible, since their local interactions are relatively short-range. This leads to a small $r_a$ and large $\gamma_a$, and the simplified equation $\phi_a(t) = Q_a(t)$.

### 6.3.2 Linearized equations

Fixed-point firing rate fields $\phi_a^{(0)}$ for a constant, uniform input $\phi_n$ are found by setting all time and spatial derivatives in Eqs (6.2)–(6.4) to zero (Rennie et al., 1999; Robinson et al., 2005). In the absence of perturbations the system will approach a stable fixed-point solution. Taylor expansion to first order around the fixed-point outgoing firing rates $Q_a^{(0)}$ yields

\[
Q_a(r, t) = Q_a^{(0)} + Q_a^{(1)},
\]

\[
Q_a^{(1)} = \rho_a \left[ V_a(r, t) - V_a^{(0)} \right] = \rho_a V_a^{(1)}, \tag{6.6}
\]
where $V_a^{(0)}$ is the equilibrium potential, and $\rho_a$ is the slope of the sigmoid at the fixed point, given by

$$\rho_a = \left. \frac{dQ_a(r, t)}{dV_a(r, t)} \right|_{V_a^{(0)}},$$

(6.7)

$$= \frac{\phi_a^{(0)}}{\sigma'} \left( 1 - \frac{\phi_a^{(0)}}{Q_a^{\max}} \right).$$

(6.8)

The above quantities lead to a set of gains

$$G_{ab} = \rho_a N_{ab}s_{ab} \equiv \rho_a \nu_{ab},$$

(6.9)

giving the change in firing rate $\phi_a$ per unit change in afferent firing rate $\phi_b$. For products of gains representing loops or sequences of connections we will use the short-hand notation

$$G_{abc} = G_{ab}G_{bc},$$

(6.10)

and similarly for products of more than two gains. This leads to the notations listed in Table 6.1.

<table>
<thead>
<tr>
<th>Number</th>
<th>Loop</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Direct loop</td>
<td>$G_{esp1d1e}$</td>
</tr>
<tr>
<td>2</td>
<td>Indirect loop</td>
<td>$G_{esp1c2d2e}$</td>
</tr>
<tr>
<td>3</td>
<td>Alternative indirect loop with GPe-GPi/SNr projection</td>
<td>$G_{esp1p2d2e}$</td>
</tr>
<tr>
<td>4</td>
<td>Hyperdirect loop</td>
<td>$G_{esp1c3e}$</td>
</tr>
<tr>
<td>5</td>
<td>GPe-STN loop</td>
<td>$G_{p2c3p2}$</td>
</tr>
<tr>
<td>6</td>
<td>Direct thalamocortical loop</td>
<td>$G_{esd4e}$</td>
</tr>
<tr>
<td>7</td>
<td>Indirect thalamocortical loop through TRN</td>
<td>$G_{esre}$</td>
</tr>
<tr>
<td>8</td>
<td>Intrathalamic loop</td>
<td>$G_{srs}$</td>
</tr>
<tr>
<td>9</td>
<td>Basal ganglia-thalamic loop through D1 cells</td>
<td>$G_{d1sp1d1}$</td>
</tr>
<tr>
<td>10</td>
<td>Basal ganglia-thalamic loop through D2 cells</td>
<td>$G_{d2sp1d2}$</td>
</tr>
<tr>
<td>11</td>
<td>Basal ganglia-thalamic loop through D2 with GPe-GPi/SNr projection</td>
<td>$G_{d2sp1p2d2}$</td>
</tr>
</tbody>
</table>

Table 6.1: Gains for the various loops in the model as shown in Fig. 6.1.

The linearized equation (6.6) is solved more easily by passing to Fourier space, transforming from spatial and temporal coordinates $r$ and $t$ to $k$ and $\omega$. If we denote deviations from the fixed-point firing rates by $\phi_a^{(1)}$, substitution of the form of $V_a(k, \omega)$ obtained by Fourier transforming (6.2) yields

$$Q_a^{(1)}(k, \omega) = \rho_a V_a^{(1)}(k, \omega),$$

(6.11)

$$= \left( 1 - \frac{i\omega}{\alpha} \right)^{-1} \left( 1 - \frac{i\omega}{\beta} \right)^{-1} \sum_b G_{ab} \phi_b^{(1)}(k, \omega) e^{i\omega \tau_{ab}}.$$  (6.12)
Also, Fourier transformation of (6.4) yields

\[ Q_a^{(1)}(k, \omega) = \begin{cases} \left[ 1 - \frac{i\omega}{\gamma_e} \right]^2 + \frac{k^2 v_e^2}{\gamma_e^2} \right] \phi_e^{(1)}(k, \omega), \\
\phi_a^{(1)}(k, \omega), \end{cases} \tag{6.13} \]

where the first applies to cortical excitatory neurons, and the second to all other populations. Expanding Eqs (6.12) and (6.13) for each of the components \( a = e, i, d_1, d_2, p_1, p_2, \varsigma, s \), and \( r \) leads to a set of coupled linear equations that can be written in matrix form,

\[
\begin{pmatrix}
D_e \phi_e^{(1)} \\
\phi_{d_1}^{(1)} \\
\phi_{d_2}^{(1)} \\
\phi_{p_1}^{(1)} \\
\phi_{p_2}^{(1)} \\
\phi_s^{(1)} \\
\phi_r^{(1)}
\end{pmatrix}
= L
\begin{pmatrix}
G_{ee} & G_{ei} & 0 & 0 & 0 & 0 & K_{es} & 0 \\
G_{ee} & G_{ei} & 0 & 0 & 0 & 0 & K_{es} & 0 \\
K_{d_1 e} & 0 & G_{d_1 d_1} & 0 & 0 & 0 & K_{d_1 s} & 0 \\
K_{d_2 e} & 0 & G_{d_2 d_2} & 0 & 0 & 0 & K_{d_2 s} & 0 \\
0 & 0 & K_{p_1 d_1} & 0 & 0 & K_{p_1 p_2} & K_{p_1 s} & 0 \\
0 & 0 & K_{p_2 d_2} & 0 & 0 & G_{p_2 p_2} & K_{p_2 s} & 0 \\
K_{c e} & 0 & 0 & 0 & 0 & K_{c p_2} & 0 & 0 \\
K_{s e} & 0 & 0 & 0 & K_{s p_1} & 0 & 0 & K_{s r} \\
K_{r e} & 0 & 0 & 0 & 0 & 0 & K_{r s} & 0
\end{pmatrix}
\begin{pmatrix}
\phi_e^{(1)} \\
\phi_i^{(1)} \\
\phi_{d_1}^{(1)} \\
\phi_{d_2}^{(1)} \\
\phi_{p_1}^{(1)} \\
\phi_{p_2}^{(1)} \\
\phi_s^{(1)} \\
\phi_r^{(1)}
\end{pmatrix}
+ L
\begin{pmatrix}
0 \\
0 \\
0 \\
0 \\
0 \\
0 \\
0 \\
G_{sn} \phi_n^{(1)}
\end{pmatrix} \tag{6.14}
\]

\[
D_e = \left( 1 - \frac{i\omega}{\gamma_e} \right)^2 + \frac{k^2 v_e^2}{\gamma_e^2}, \tag{6.15}
\]

\[
L = \left( 1 - \frac{i\omega}{\alpha} \right)^{-1} \left( 1 - \frac{i\omega}{\beta} \right)^{-1}, \tag{6.16}
\]

\[
K_{ab} = G_{ab} e^{i\omega r_{ab}}. \tag{6.17}
\]

Note that the differential operator \( D_{a\beta} \) associated with synaptodendritic transmission is transformed to \( L \) in the Fourier domain, and differs from the operator \( D_e \) associated with cortical wave propagation. Equation (6.14) allows us to derive a transfer function for input to the thalamus \( \phi_n^{(1)} \) to the cortical excitatory firing rate \( \phi_e^{(1)} \),

\[
\frac{\phi_e^{(1)}(k, \omega)}{\phi_n^{(1)}(k, \omega)} = \frac{1}{k^2 r_e^2 + q^2 r_e^2 (1 - G_{ee} L)(1 - T_{srs}) M} L^2 e^{i\omega r_{es} G_{ee} G_{sn}} + T_{ese} + T_{esre} \frac{G_{ee} L + T_{ese} + T_{esre}}{(1 - T_{srs}) M} + \frac{T_{esp_1 d_1 e}}{(1 - T_{srs})(1 - G_{d_1 d_1} L) M} + \frac{T_{esp_1 p_2 d_2 e}}{(1 - T_{srs})(1 - G_{d_2 d_2} L)(1 - G_{p_2 p_2} L) M} \tag{6.18}
\]

\[
q^2 r_e^2 = \left( 1 - \frac{i\omega}{\gamma_e} \right)^2 - \frac{1}{1 - G_{ee} L} \left[ G_{ee} L + \frac{T_{ese} + T_{esre}}{(1 - T_{srs}) M} + \frac{T_{esp_1 d_1 e}}{(1 - T_{srs})(1 - G_{d_1 d_1} L) M} + \frac{T_{esp_1 p_2 d_2 e}}{(1 - T_{srs})(1 - G_{d_2 d_2} L)(1 - G_{p_2 p_2} L) M} \right], \tag{6.19}
\]
The transfer function is analogous to those customarily derived in control theory for linear systems (Dorf and Bishop, 2001). Each of the $T_{a_1a_2\ldots a_n}$ consists of a product of dendritic and synaptic filter functions $L(\omega)$, gains $G_{ab}$, and phase factor $e^{i\omega \tau_{ab}}$, representing one of the loops of the model: $T_{esre}$ and $T_{esre}$ are the two possible corticothalamic loops, the first from cortex to relay nuclei and back to cortex, and the second passing through the TRN, while $T_{esp_1d_1e}$ represents the classic direct pathway. Activity traveling along the indirect route, $T_{esp_1p_2d_2e}$, the alternative indirect route, $T_{esp_1p_2d_2e}$, and the hyperdirect route, $T_{esp_1c_1e}$, is modulated by the loop between STN and GPe, $T_{p_2sp_2}$. This is expressed in the above equations by division of the relevant circuit strengths $T_{a_1a_2\ldots a_n}$ by $J$, which itself contains a factor to account for intrapallidal connections. The strengths of all pathways passing through the thalamus are modulated by the intrathalamic loop via $T_{srs}$. Pathways through the striatum have a correction factor that accounts for intrastriatal inhibition. Finally, all major pathways are modulated by the loops involving thalamostriatal projections, for which the correction factor is denoted $M$. The transfer function is considerably simplified if the thalamostriatal projection is removed, so that $M = 1$.

The electroencephalographic (EEG) signal is caused by extracellular currents near the dendrites of cortical neurons firing in partial synchrony (Nunez, 1995; Ray, 1990). As in previous works [e.g., Robinson et al. (2001b); Robinson (2003)], we take the cortical potential to be proportional to the excitatory firing rate field $\phi_e$, since pyramidal neurons are the most aligned, most numerous, and largest cells contributing to the cortical signal. Hence, we approximate the EEG spectral power as being proportional to $|\phi_e(k, \omega)|^2$. Parameter values in the healthy state are given in Chapter 5, where their derivation and consistency with physiology are discussed extensively. As in that chapter, we impose the random connectivity approximation (Braitenberg and Schüz, 1998; Robinson et al., 2001b; Wright and Liley, 1995), which leads to $\nu_{eb} = \nu_{ib}$ for $b = e, i, s$.

### 6.3.3 Parameter changes in PD

In Chapter 5 we considered five types of parameter changes for modeling the dopamine depletion that occurs in PD. These parameter changes are:
(I) decreasing both corticostriatal connection strengths and striatal firing thresholds to approximate a reduction in signal-to-noise ratio (SNR) in the striatum (Leblois et al., 2006; Nicola et al., 2004; O’Donnell, 2003), as modeled by

\[
\begin{align*}
\theta_{d1}^{\text{new}} &= \theta_{d1} - h\chi; \\
\nu_{d1e}^{\text{new}} &= \nu_{d1e} - \chi;
\end{align*}
\tag{6.23}
\]

\[
\begin{align*}
\theta_{d2}^{\text{new}} &= \theta_{d2} - h\chi; \\
\nu_{d2e}^{\text{new}} &= \nu_{d2e} - \chi,
\end{align*}
\tag{6.24}
\]

where \(\chi \in [0, 0.6] \text{ mV s}\), and \(h = 5, 10, 15 \text{ s}^{-1}\);

(II) increasing corticostriatal transmission to D2-expressing cells and decreasing transmission to D1-expressing cells, in line with the direct/indirect loop hypothesis (Albin et al., 1989; Alexander and Crutcher, 1990; Mallet et al., 2006);

(III) weakened lateral inhibition in the GPe due to enhanced release of enkephalin (Stanford and Cooper, 1999; Terman et al., 2002);

(IV) weaker intracortical excitation to approximate the effects of neuronal loss from the pre-supplementary motor area (pre-SMA) (MacDonald and Halliday, 2002), and mesocortical dopamine depletion (Gulledge and Jaffe, 2001; Gao and Goldman-Rakic, 2003; Thurley et al., 2008; Zhou and Hablitz, 1999), where the latter also causes a reduction in intracortical inhibition;

(V) a combination of stronger cortico-D2 and weaker cortico-D1 transmission, weaker GPe-GPe inhibition, smaller cortical connection strengths, reduced GPe and STN firing thresholds, and a stronger D2-GPe projection. In particular, we considered the state that is obtained from the normal parameters in Chapter 5 by setting \(\nu_{d1e} = 0.5 \text{ mV s}, \nu_{d2e} = 1.4 \text{ mV s}, \nu_{p2p2} = -0.07 \text{ mV s}, \nu_{ee} = \nu_{ie} = 1.4 \text{ mV s}, \nu_{ei} = \nu_{ii} = -1.6 \text{ mV s}, \nu_{p2d2} = -0.5 \text{ mV s}, \theta_{p2} = 8 \text{ mV}, \text{ and } \theta_{c} = 9 \text{ mV}.

We will refer to this combination of parameters as the ‘full parkinsonian state’.

In this chapter we consider the dynamical implications of dopamine depletion via the parameter changes (I)–(V), including responses to transient and ongoing stimuli, oscillations, and frequency spectra.

### 6.4 Gains and responses to transient and ongoing stimuli

The linear gains (6.9) quantify the effective interactions between populations. In Sec 6.4.1 we consider changes in gains with nigrostriatal denervation, and propose a mechanism by which nigrostriatal and mesocortical dopamine loss can contribute to bradykinesia. Neuronal responses to transient cortical stimuli are derived in Sec. 6.4.2 using the full nonlinear version of the model. In Sec. 6.4.3 neuronal responses for ongoing brainstem inputs to the thalamus are derived.
6.4.1 Changes in gains and a possible contribution to bradykinesia

Linear gains depend on the connection strengths \( \nu_{ab} \) not only directly, but also indirectly via the steady-state firing rates. The gains quantify the dynamic effects of changes in connection strengths. In the following, we discuss changes in gains obtained by manipulating the values of \( \nu_{ab} \) to simulate dopamine loss, and recomputing steady states after each manipulation. The derivative of the sigmoid at each steady state is given by Eqs (6.7) and (6.8), which yields gains via Eqs (6.9) and (6.10). In the absence of thalamic inputs, the rate and amplitude of changes in cortical activity depend mainly on the sum \( G_{ee} + G_{ei} \), which may be relevant to the symptoms of akinesia and bradykinesia, as further discussed below. Therefore, we report the value of this sum in each scenario, besides intracortical gains and the loop gains specified in Table 6.1.

Simultaneous reduction of corticostriatal connection strengths and striatal firing thresholds has relatively little effect on gains, including the sum \( G_{ee} + G_{ei} \) (cf. Fig. 6.2). Especially corticothalamic gains are constant [Fig. 6.2(a)], whereas both the direct and indirect loops become somewhat weaker [Fig. 6.2(b)], and basal ganglia-thalamic gains may become stronger or weaker depending on \( h \) [Fig. 6.2(c); cf. Eq. (6.23)].

Figures 6.3(a) and 6.3(d) show that both increases in \( \nu_{dte} \) and decreases in \( \nu_{dte} \) reduce corticothalamic gains in absolute value. A slight reduction is also seen in \( |G_{ee} + G_{ei}| \). A larger \( \nu_{dte} \) enhances the strength of the indirect pathway while decreasing the strength of the direct pathway [cf. Figs. 6.3(b) and 6.3(e)]. On the other hand, decreasing \( \nu_{dte} \) from its normal value of 1.0 mV s weakens both the direct and indirect pathways. These changes in corticostriatal connection strengths decrease the absolute values of the gains of the STN-GPe loop, \( G_{p2p2} \), and the hyperdirect loop, \( G_{esp1 ce} \).

The enhancement of corticothalamic gains seen in Fig. 6.4(a) supports the view that reduced intrapallidal inhibition acts as a compensatory mechanism. However, Fig. 6.4(b) reveals that all basal ganglia-thalamocortical circuits are strengthened by this change, including the direct, indirect, and hyperdirect loops, as well as the circuit formed by the STN and GPe. Thus, weakened intra-GPe inhibition may help stabilize basal ganglia firing rates, but exacerbate oscillations (cf. Sec. 6.5.1).

As discussed in Chapter 5, a loss of direct dopaminergic inputs to the cortex is expected to reduce \( \nu_{ee}, \nu_{te} \), and especially \( |\nu_{ei}| \) and \( |\nu_{ii}| \). Since intracortical inhibition was taken to be stronger than excitation in the healthy state, this results in more similar strengths of excitation and inhibition, and a consequent decrease in \( |G_{ee} + G_{ei}| \).

Reducing the GPe firing threshold increases the absolute values of corticothalamic gains, including \( |G_{ee} + G_{ei}| \), as well as those of the direct, indirect,
Figure 6.2: Dependence of gains on the striatal SNR, parameterized by $\chi$. Solid lines, $h = 5$ s$^{-1}$; dashed lines, $h = 10$ s$^{-1}$; dash-dotted lines, $h = 15$ s$^{-1}$ [cf. Eqs (6.23) and (6.24)]. Each group of lines starts together at $\chi = 0$ mV s. (a) Corticothalamic gains. The lines of $G_{ee} + G_{ei}$ are indicated by the crosses, and overlap for different values of $h$. (b) Basal ganglia-thalamocortical gains (loops 1–5 in Table 6.1). (c) Basal ganglia-thalamic gains (loops 9–11 in Table 6.1).

and hyperdirect loops, whereas lowering the STN firing threshold has the opposite effect. Reducing either $\theta_1$ or $\theta_p^2$ increases the gain of the STN-GPe loop. The indirect pathway is strengthened by greater $|\nu_{p2d2}|$, which weakens the direct, hyperdirect, and GPe-STN loops. Combining all parameter changes leads to a smaller $|G_{ee} + G_{ei}|$ (0.59 vs. 0.91 in the healthy state), a weaker direct loop ($G_{esp_{1d1e}} = 0.042$ vs. 0.29), and stronger hyperdirect ($G_{esp_{1ce}} = -0.40$ vs. 0.29).
vs. −0.35), STN-GPe ($G_{p2p2} = −1.1$ vs. −0.89), and especially indirect ($G_{esp1p2d2e} = −3.0$ vs. −0.27) loops in the parkinsonian state compared to the healthy state.

Figure 6.3: Dependence of gains on corticostriatal connection strengths. (a) Corticothalamic gains vs. $\nu_{d1e}$, with $G_{ee} + G_{ei}$ indicated by the dashed line. (b) Gains of basal ganglia-thalamocortical loops vs. $\nu_{d1e}$; (c) gains of basal ganglia-thalamic loops vs. $\nu_{d1e}$. (d) Corticothalamic gains vs. $\nu_{d2e}$, with $G_{ee} + G_{ei}$ indicated by the crosses. (e) Gains of basal ganglia-thalamocortical loops vs. $\nu_{d2e}$. (f) Gains of basal ganglia-thalamic loops vs. $\nu_{d2e}$.

We investigate the results of changes in cortical gains by considering only cortical interactions and ignoring the damped-wave equation (6.4), which leads to $\phi_a = Q_a$. Substituting $a = e, i$ in Eqs (6.2) and (6.3), and using the linear approximation $Q_a = V_a^{(0)} + \rho_a V_a^{(1)}$ yields

$$\frac{d^2V_e^{(1)}}{dt^2} = \alpha\beta \left[G_{ee}V_e^{(1)} + G_{ei}V_i^{(1)} - \left(\frac{1}{\alpha} + \frac{1}{\beta}\right)\frac{dV_e^{(1)}}{dt} - V_e^{(1)}\right], \quad (6.25)$$

$$\frac{d^2V_i^{(1)}}{dt^2} = \alpha\beta \left[G_{ee}V_e^{(1)} + G_{ei}V_i^{(1)} - \left(\frac{1}{\alpha} + \frac{1}{\beta}\right)\frac{dV_i^{(1)}}{dt} - V_i^{(1)}\right]. \quad (6.26)$$

Here, we have made use of the random connectivity approximation to obtain
Figure 6.4: Dependence of gains on the strength of lateral inhibition in the GPe. (a) Corticothalamic gains, with $G_{ee} + G_{ei}$ indicated by the crosses. (b) Basal ganglia-thalamocortical gains. (c) Basal ganglia-thalamic gains.

$G_{se} = G_{ee}$ and $G_{ii} = G_{ei}$. The sizes and latencies of the maximums of $V_{e}^{(1)}$ and $V_{i}^{(1)}$ were determined using numerical integration of Eqs (6.25) and (6.26) for three sets of initial conditions, using 200 pairs of values of $G_{ee}$ and $G_{ei}$ uniformly distributed in the intervals $[1,5]$ and $[-9,-5]$. As illustrated in Fig. 6.5, response strength and latency do not depend on $G_{ee}$ or $G_{ei}$ individually, but input responses become slower and less pronounced with decreased $|G_{ee} + G_{ei}|$. The decreased value of $|G_{ee} + G_{ei}|$ due to increased strength of the indirect pathway and/or impaired cortical inhibition after loss of mesocortical dopamine may thus be related to slowness of movement (bradykinesia) or absence of movement (akinesia), since threshold activation levels necessary to initiate movements may be reached more slowly, or not at all. This hypothesis is supported by the observation that MPTP lesion in monkeys causes the activity of motor cortical neurons to build up more slowly and persist longer during voluntary movements (Doudet et al., 1990). Similarly, transcranial magnetic stimulation leads to more gradual modification of motor unit activity in PD patients than in controls (Kleine et al., 2001).

### 6.4.2 Responses to transient stimuli

Figure 6.6 shows the responses in each neural population to a 10 ms square pulse with amplitude 60 s$^{-1}$ applied at the cortex in the healthy condition with parameters as in Chapter 5, and with the five possible results of dopamine loss mentioned in Sec. 6.3.3. To compare these responses to experimental results, we make use of the finding that the average firing rate of motor cortical neurons is increased during movement (Grammont and Riehle, 2003; Thach, 1978).

In the healthy condition, the slight increase in the model rate of the output
nuclei with cortical stimulation is in agreement with experimental findings that the majority of GPi neurons increase their activity before and during movement (Anderson and Horak, 1985; Georgopoulos et al., 1983; Mitchell et al., 1987), presumably because of inhibition of competing motor programs when a target program is activated (Nambu et al., 2002). The latencies and directions of GPe responses seen in the insert to Fig. 6.6(e) closely match those observed upon stimulation of M1, SMA, or S1 in healthy awake monkeys: an early excitation after 8–11 ms, inhibition after 15–19 ms, and a late excitation after 26–32 ms (Kita et al., 2004; Nambu et al., 2000; Yoshida et al., 1993). With the parameters in Chapter 5, onset of GPe excitation by the STN occurs 8 ms after cortical stimulation, inhibition by striatum after 19 ms, and the second excitation by STN after 28 ms. The relative sizes of the peaks and trough depend on the stimulation intensity, longer or faster stimuli leading to a deeper trough. However, excitations are stronger than inhibition for 10 ms inputs up to at least $\phi_n = 60$ s$^{-1}$, in accord with predominantly excitatory responses to movement in healthy monkeys (Anderson and Horak, 1985; Mitchell et al., 1987; Turner and Anderson, 1997). The model and physiological data suggest that this excitation is mediated mainly via the hyperdirect pathway. In reality, movements may elicit stronger GPe excitation in view of the close association of cortico-STN fibers with the pyramidal tract (Giuffrida et al., 1985; Nambu et al., 2002), but we do not distinguish between cortical neurons projecting to striatum or STN in our model. In healthy African green monkeys, Bergman et al. (1994) found that the majority of STN cells increased their firing rates

Figure 6.5: Dependence of cortical response strength and latency on gains. Time derivatives have initial values $dV_e^{(1)}/dt = dV_i^{(1)}/dt = 0$ mV s$^{-1}$ in all cases. (a) Time courses of $V_e^{(1)}$ (solid) and $V_i^{(1)}$ (dashed), with $V_e^{(1)}(0) = -2$ mV and $V_i^{(1)}(0) = -4$ mV, for different values of the intracortical gains. Crosses, $G_{ee} = 3, G_{ei} = -11$; dots, $G_{ee} = 2, G_{ei} = -5$; no markers, $G_{ee} = 1, G_{ei} = -2$. (b) Maximum values of $V_e^{(1)}$ and $V_i^{(1)}$ vs. $G_{ee} + G_{ei}$. (c) Latency of the maximum vs. $G_{ee} + G_{ei}$. 

when torque was applied to the elbow, although cells that decreased their firing rates did so for longer. It is seen in Fig. 6.6(f) that the model STN rate displays a transient increase upon cortical stimulation, in agreement with these results.

Considering now the parkinsonian scenarios, reducing the SNR has little effect on most responses to a transient stimulus, and cortical and thalamic responses are virtually indistinguishable from normal ones (cf. Fig. 6.6). Striatal inhibition of GPe falls away, resulting in an amplified excitatory response to STN input. Corticothalamic responses are slightly attenuated when modeling dopamine loss with $\nu_{d1e} = 0.5$ mV s and $\nu_{d2e} = 1.4$ mV s, as expected from the smaller gains. These gain changes were inferred from the increased responsiveness of D2 cells and decreased responsiveness of D1 cells to cortical inputs measured experimentally, and are thus in accord with these results (Cepeda et al., 1998; Hernández-López et al., 1997; Hsu et al., 1995; Levine et al., 1996; Kiyatkin and Rebec, 1996; Nicola et al., 2000; Toan and Schultz, 1985; Umemiya and Raymond, 1997). The larger increase in the firing rate of the output nuclei seen in Fig. 6.6(d) is in line with amplified GPi responses to passive limb movements in parkinsonian monkeys (Bergman et al., 1994; Filion et al., 1988; Wichmann et al., 1994b). The inhibitory response in the GPe is greatly amplified in this scenario, as seen in Fig. 6.6(e). This reproduces the effects of extensive nigrostriatal lesions in rats (Magill et al., 2001; Zold et al., 2007b), although facilitated excitation has also been observed (Tremblay et al., 1989). Finally, the more vigorous responses of STN neurons to cortical stimulation in parkinsonian rats, and to elbow flexion and extension in monkeys, corroborates the results in Fig. 6.6(f) (Bergman et al., 1994; Magill et al., 2001). Figures 6.6(a) shows that weakened intrapallidal inhibition ($\nu_{p2p} = -0.03$ mV s) amplifies damped oscillations around the dominant alpha frequency. An even stronger effect on corticothalamic interactions is exerted by smaller cortical gains, causing an amplification of damped oscillations at alpha and beta frequencies throughout the system, as seen in Figs. 6.6(a) and 6.6(g). Damped corticothalamic oscillations are enhanced very slightly by a lower GPe firing threshold, whereas a lower STN threshold and larger $|\nu_{p2d2}|$ have the opposite effect. The full parkinsonian state produces changes in responses similar to those resulting only from stronger indirect and weaker direct pathways, and with a cortical rate that is closer to that in the healthy state, in line with experimental observations.

### 6.4.3 Responses to ongoing stimuli

Figure 6.7 shows pulse rates $\phi_a$ for ongoing stimuli $\phi_n$ in the healthy and two model parkinsonian-type states. In each case the stimulus consisted of Gaussian noise with mean $10$ s$^{-1}$ and standard deviation $2$ s$^{-1}$. Firing rates of each component are plotted over equal intervals along the ordinate to allow compar-
Figure 6.6: Responses of firing rate fields to a square pulse of 10 ms duration and amplitude $60 \text{ s}^{-1}$ applied at the cortex, while the relay nuclei receive a constant brainstem input $\phi_n = 10 \text{ s}^{-1}$. Thin solid lines, healthy state with parameters as in Chapter 5; dotted, ‘reduced-SNR’ state with $\theta_d, = \theta_d, = 13 \text{ mV}$, $\nu_{d,e} = 0.4 \text{ mV s}$, and $\nu_{d,e} = 0.1 \text{ mV s}$; thin dashed lines, state with $\nu_{d,e} = 0.5 \text{ mV s}$, $\nu_{d,e} = 1.4 \text{ mV s}$; dash-dotted, with weaker intrapallidal inhibition, $\nu_{d,e} = -0.03 \text{ mV s}$; thick solid lines, healthy state with $\nu_{c,e} = \nu_{c,e} = 1.4 \text{ mV s}$ and $\nu_{c,e} = \nu_{c,e} = -1.6 \text{ mV s}$ to model cortical dopamine loss; thick dashed lines, full parkinsonian state (cf. Sec. 6.3.3). The inset to (e) shows the triphasic early GPe response.

Comparison of variability across states. Figure 6.7 reveals relatively large fluctuations in pallidal and STN firing rates in modeled parkinsonian states, even in the GPe, where the average firing rate is lower than in the healthy state. These enhanced fluctuations point towards increased synchronization between individual cells in the basal ganglia nuclei. On the other hand, cortical, thalamic, and average striatal signals show reduced variability. The amplitude of fluctuations in the average signal of D1 and D2 cells depends on the relative changes in $\nu_{d,e}$ and $\nu_{d,e}$, and is elevated compared to the healthy state for relatively large increases in $\nu_{d,e}$. Mesocortical dopamine loss and changes secondary to nigrostriatal damage normalize the amplitude of the cortical signal, and further amplify basal ganglia fluctuations, as seen in Fig. 6.7(c). In Sec. 6.5.2 we will relate these observations to changes in frequency spectra.
Figure 6.7: Time series of the cortical ($\phi_c$), striatal ($[\phi_{d+1} + \phi_{d+2}]/2$), GPi/SNr ($\phi_{p+1}$), GPe ($\phi_{p+2}$), STN ($\phi_s$), thalamic relay ($\phi_s$), and TRN ($\phi_r$) firing rate fields (a) in the healthy state, (b) with $\nu_{d+1} = 0.5$ mV s and $\nu_{d+2} = 1.4$ mV s, and (c) in the full parkinsonian state (cf. Sec. 6.3.3). Input to the relay nuclei consisted of Gaussian white noise with mean 10 s$^{-1}$ and standard deviation 2 s$^{-1}$. 

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6.5 Oscillations and spectral changes

In certain regimes the model displays oscillations that may culminate in limit cycles. Section 6.5.1 explores these oscillations, and in particular, we find approximately 5 Hz oscillations in the indirect loop and ~20 Hz oscillations in corticothalamic circuits that may spread to the basal ganglia when the indirect pathway becomes strong. The spectral changes caused by dopamine loss are considered in Sec. 6.5.2. The involvement of the indirect pathway in the generation of parkinsonian symptoms has been questioned (Leblois et al., 2006) because GPe lesion does not lead to the characteristic motor symptoms or oscillations (Soares et al., 2004). In Sec. 6.5.3 we challenge the view that GPe lesion experiments exclude the indirect pathway as a substrate of parkinsonian oscillations.

6.5.1 Limit cycles and the emergence of theta and beta rhythms

The linearized equations given in Sec. 6.3.2 are only valid in a limited regime. Far from a steady state, the system may be attracted to a different fixed point or a limit cycle. Such deviations from steady state entail changes in gains, and we can vary the gains to determine the boundaries of the linearly stable region. A relationship between the frequencies of wave modes and their wavelengths is termed a dispersion relation. The transfer function (6.18) has an associated dispersion relation $k^2 + q^2(\omega) = 0$. For each combination of gain values, the dispersion relation has a specific (usually infinite) set of solutions $\omega(k)$. Of the (complex) solutions $\omega(k)$, the one with the largest imaginary part decays most slowly, since solutions consist of a weighted sum of plane waves $e^{-i\omega(k)t + ikr}$. The boundary of the linearly stable zone occurs where the dispersion relation is satisfied for real $\omega$, because for $\text{Im } \omega > 0$ inputs $\phi^{(1)}_n$ are infinitely amplified at the corresponding frequencies. Previous work has shown that the spatially uniform mode is generally the least stable (Robinson et al., 2001a; Robinson, 2005), leading us to consider this $k = 0$ case. Due to the complexity of our system, instabilities lead to resonances at a range of frequencies depending on the gain being varied.

Perturbations of healthy state

We first consider the types of instabilities that can arise from perturbations around the healthy state, which is the low-firing rate fixed point corresponding to the parameters in Chapter 5. Table 6.2 lists the frequencies of instabilities for changes in gains relative to the healthy state. The gains at which the instabilities first occur are also given. For completeness, limits are listed for
both increases and decreases in gains, partly since the signs of effective interactions are not known with certainty in every case (this applies especially to intrastrital interactions). Some instabilities will not readily occur because of an extremely large threshold value, for instance for $G_{p2d2}$ and $G_{p1c}$. At a 0 Hz instability, the system may shift to a different steady state or go into a limit cycle if one exists.

Many of the instabilities in Table 6.2 are approximately equivalent, because the dispersion relation contains products and ratios of gains. This is clearest for $G_{p2c}$ and $G_{sp2}$, since either raising one or decreasing the other leads to an instability at 46 Hz. A resonant frequency in the gamma band for the STN-GPe loop corresponds with the $\sim$55 Hz oscillation in the model of Humphries et al. (2006), and identifies this loop as a possible substrate for the enhanced gamma oscillations seen in parkinsonian patients on levodopa right before and during voluntary movements (Brown, 2003; Cassidy et al., 2002).

Other gains that occur together in a loop cause instabilities at different frequencies, because they simultaneously modulate at least one other loop. For some of these gains, the loops that sustain the oscillations are relatively easy to determine. For instance, the gain $G_{sr}$ is part of the thalamocortical loop strength $G_{esre}$, whereas $G_{rs}$ is only relevant to the intrathalamic loop, $G_{srs}$. Since $G_{sr}$ and $G_{rs}$ cause instabilities at 3.6 Hz and 30 Hz, respectively, we can conclude that thalamocortical instabilities occur around 3–4 Hz, and intrathalamic rhythms have a frequency of about 30 Hz. In the absence of cortical and corticothalamic feedback and for $\tau_{sr} + \tau_{rs} = 0$, this frequency becomes $f = \sqrt{\alpha\beta}/(2\pi) = 51$ Hz, analogous to spindle instabilities described by Robinson et al. (2002). The 3–4 Hz instability leads to a limit cycle at approximately the same frequency, which often has a spike-wave form and was shown by Robinson et al. (2002) and Breakspear et al. (2006) to have many of the characteristics of petit mal (or absence) seizures.

Other interactions between loops are more difficult to untangle. For example, the gain $G_{d_{dc}}$ is part of the indirect and alternative indirect loops 2 and 3 (cf. Table 6.1 for loop numbering), while $G_{p2d2}$ is part of the same loops and also the basal ganglia-thalamic loops 10 and 11. The basal ganglia-thalamic circuits through D2 support oscillations around 17 Hz for large $G_{d_{ds}}$. The frequency of the instability due to a large negative $G_{p2d2}$ ($\sim$18 Hz) is inversely related to axonal delays in the indirect loop, but also to $\tau_{d_{ds}}$ and $\tau_{se}$. This suggests that the oscillations are sustained by a complex interplay between corticothalamic circuits and the indirect loop, rather than any particular circuit separately. The gain from the output nuclei to the thalamus, $G_{sp1}$, is part of the hyperdirect, direct, classic and alternative indirect (with the GPi-GPI/SNr projection) pathways, as well as loops involving thalamostriatal projections (Loops 1–4 and 9–11). The frequency of the instability for large $G_{sp1}$ is 5.7 Hz, and depends
<table>
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<th>Gain</th>
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<th>Lower threshold</th>
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Table 6.2: Frequencies $f$ of linear instabilities caused by increasing or decreasing individual gains beyond the given threshold values, corresponding to the boundary of the linearly stable region. All other gains are held constant at the values for the healthy state, i.e., the low-firing rate steady state for the parameters given in Chapter 5. The first six gains are varied in pairs, because they are equal in the random connectivity approximation (cf. Sec. 6.3.2). No instabilities occur for reductions in $G_{d1d1}, G_{d2d2}, G_{p2p2}, G_{se}$ and $G_{se}$, or $G_{ei}$ and $G_{ii}$. The second column indicates whether the gain is expected to be excitatory (+) or inhibitory (−) based on physiological considerations. Frequencies of instabilities for which the gain has the expected sign are shaded. All values are given to two significant figures.
inversely on $\tau_{ce}$, $\tau_{ps}$, and $\tau_{es}$, with a weaker dependence on $\tau_{dce}$, $\tau_{psd}$, $\tau_{dse}$, $\tau_{des}$, or $\tau_{psp}$. This indicates that the oscillations are sustained by the hyperdirect pathway. Although the frequency due to strong $G_{ce}$ (6.1 Hz) is close to that of tremor rhythms, we saw in Sec. 6.4.1 that neither a decreased striatal SNR, nor a stronger indirect and weaker direct loop, lead to a large hyperdirect loop gain. This suggests that limit cycle oscillations are unlikely to arise in the hyperdirect loop, as argued further below.

**Perturbations leading to a strong indirect pathway: theta oscillations**

Since electrophysiological evidence and modeling results on firing rates (cf. Chapter 5) suggest that dopamine depletion increases the gain of the indirect pathway, we look at oscillations that appear when the balance is shifted from the direct to the indirect pathway. For parameter values that entail a sufficiently large increase of the indirect loop gain, the system undergoes a Hopf bifurcation, leading to a limit cycle around 5 Hz. In Fig. 6.8(a) we consider $G_{esp_1sp_2d_2} = -49$, which is instantiated by the parameters $\theta_{p_2} = 4$ mV, $\theta_e = 5$ mV, $\nu_{ce} = \nu_{ie} = 1.2$ mV s, $\nu_{ei} = \nu_{ii} = -1.3$ mV s, $\nu_{d_2e} = 1.7$ mV s, $\nu_{p_2d_2} = -0.5$ mV s, $\nu_{p_2p_2} = 0$ mV s, $\nu_{sp_1} = -0.07$ mV s, $\nu_{se} = 0.6$ mV s, and $\phi_n = 30$ s$^{-1}$. Since the indirect loop has a negative overall gain, deviations from the mean activity are inverted after one pass around the loop, so that a single period of the oscillation corresponds to two passes, similar to oscillations in corticothalamic circuits involving the TRN (Robinson et al., 2002). Approximately 5 Hz oscillations only appear when the ratio of the indirect loop and corticothalamic gains is very large, although the latter still need to be sufficiently powerful for the system to support oscillations (here, $G_{ese} = 2.7$). Considering the extreme parameter values and firing rates, such limit cycle behavior is unlikely to occur in the system as a whole, but could appear in subcircuits, which would explain the limited percentage of oscillatory cells generally recorded (Bergman et al., 1994; Lemstra et al., 1999; Levy et al., 2001; Wichmann and Soares, 2006). This scenario is further supported by the finding that oscillatory cells in the striatum, STN, and GPi have substantially higher firing rates than non-oscillatory cells (Dejean et al., 2008; Levy et al., 2000, 2001). Significantly, phase relationships between components comply with those in rats with nigrostriatal lesions (Walters et al., 2007): GPe activity is in antiphase with striatal, STN, cortical, and SNr activity. The fact that the GPe oscillates antiphase to STN implies that it is under inhibitory control of the striatum rather than excitatory control of the STN. A caveat is that the oscillations reported by Walters et al. (2007) occurred around 1 Hz, and may have arisen partly as a result of urethane anesthesia (Humphries et al., 2006; Magill et al., 2000). However, urethane-induced oscillations in GP appear to be in phase with cortical activity in the healthy
state, whereas nigrostriatal lesion produces a subpopulation oscillating in antiphase to cortical slow waves (Zold et al., 2007a).

**Perturbations leading to a strong hyperdirect pathway**

Increasing the gain of the hyperdirect pathway (Loop 4) leads to phase relationships that are not supported by experiments. As an example, Fig. 6.8(b) shows the 6.2 Hz limit cycle corresponding to $G_{esp1c}=−52$, obtained by setting $\theta_{p2} = 4 \text{ mV}$, $\theta_{c} = 20 \text{ mV}$, $\nu_{d2e} = 0.3 \text{ mV s}$, $\nu_{ce} = 0.7 \text{ mV s}$, $\nu_{sp1} = −0.15 \text{ mV s}$, and $\phi_n = 30 \text{ s}^{-1}$. In this case, the GPe oscillates nearly in phase with the striatum, STN, cortex, and SNr, indicating that it is driven by STN input.

**Perturbations leading to a strong indirect pathway: beta oscillations**

As discussed above in relation to increases in $G_{p2d2}$, it is also possible to obtain $\sim 20 \text{ Hz}$ oscillations when the indirect loop is strong, as seen experimentally in PD patients (Brown et al., 2001; Fogelson et al., 2006; Gatev et al., 2006; Levy et al., 2002; Williams et al., 2002). This happens particularly in combination with corticothalamic coupling that is strong in comparison to that leading to 5 Hz oscillations, while the ratio $|G_{esp1c}\nu_{p2d2}|/G_{ese}$ can be somewhat smaller. An example with $G_{esp1c}\nu_{p2d2} = −32$ and $G_{ese} = 7.9$ is presented in Fig. 6.8(c). The corresponding parameters are $\theta_{p2} = 7 \text{ mV}$, $\theta_{c} = 6 \text{ mV}$, $\nu_{ce} = \nu_{ie} = 0.6 \text{ mV s}$, $\nu_{c1} = \nu_{i1} = −0.8 \text{ mV s}$, $\nu_{d1e} = 0.5 \text{ mV s}$, $\nu_{d2e} = 1.4 \text{ mV s}$, $\nu_{p2d2} = −0.4 \text{ mV s}$, $\nu_{p2p2} = 0 \text{ mV s}$, $\nu_{sp1} = −0.04 \text{ mV s}$, and $\phi_n = 20 \text{ s}^{-1}$. The oscillations first appear in the cortex and thalamus, from where they spread to the basal ganglia. Approximately 20 Hz oscillations can also arise in corticothalamic circuits in the healthy state, seen both experimentally (Courtemanche et al., 2003) and in our model. It is possible that either the enhancement of these oscillations in the basal ganglia of PD patients contributes to antikinetic symptoms or tremor, or they may be secondary to other pathological activity rather than a cause of symptoms.

**Perturbations leading to a strong indirect pathway: combined theta and beta**

Our model predicts that if beta oscillations appear in the corticothalamic loop in the absence of nigrostriatal damage, then strong alpha oscillations will also be seen, since beta rhythms arise as a harmonic of the alpha resonance (Robinson et al., 2001b). However, $\sim 20 \text{ Hz}$ and 3–7 Hz oscillations can appear together without $\sim 10 \text{ Hz}$ activity when the alpha resonance is suppressed by nigrostriatal damage. Both $G_{ese}$ and the ratio $|G_{esp1c}\nu_{p2d2}|/G_{ese}$ need to be large for this situation to occur. An example is given in Fig. 6.8(d) for
The strong interaction between the theta and alpha-band roots of the dispersion relation relies on the relatively small distance between these roots, explaining why the indirect loop can suppress alpha, but not beta, activity. This is further discussed in Sec. 6.5.2.

All the above limit cycles have in common that they require relatively strong corticothalamic activation to arise, provided for instance by brainstem input to the thalamus or reduced intracortical inhibition, potentially helping to explain the worsening of tremor during mental stress (Deuschl et al., 2001; Zesiewicz and Hauser, 2001). The direct loop can also contribute to excitation of the cortex and thalamus, so that 5 Hz and 20 Hz oscillations can appear when both the direct and indirect loops are strong. This implies that the direct and indirect loops need not be completely separated for basal ganglia-thalamocortical loops to support theta and beta oscillations.

For a given set of parameters, we can visualize the effects of changes in gains using a surface plot of the region in which the system is linearly stable. Figure 6.9(a) indicates the boundary of the linearly stable region parameterized by the gains of the direct loop, the combined classic and alternative indirect loops (the latter involving the GPe-GPi/SNr projection), and the STN-GPe loop, where the other gains are held constant at the normal values obtained from the parameters in Chapter 5. The top of the bar corresponds to the healthy state. The left-hand boundary corresponds to an approximately 5 Hz instability that arises when the indirect pathway dominates. When \(|G_{p2p2}| \) becomes large, the STN-GPe loop sustains oscillations around 46 Hz. The right-hand boundary indicates that a dominant direct pathway causes the system to become unstable at 0 Hz. Finally, the small region at the front corresponds to an instability at \( \sim 15 \) Hz when both the direct and indirect pathways are strong.

A similar diagram illustrates the dependence of stability and the frequency of theta oscillations on the gains of the hyperdirect, indirect, and corticothalamic loops [Fig. 6.9(b)]. As discussed above, theta instabilities can arise for either strong hyperdirect or indirect pathways. The analogous roles of the hyperdirect and indirect loops are further indicated by the fact that the system remains stable for larger \(|G_{\text{indirect}}| = |G_{\text{esp1p2d2e}} + G_{\text{esp1p2d2e}}| \) (Loops 2 and 3) if \(|G_{\text{esp1c2e}}| \) is relatively small. However, phase relationships, likely changes in corticostriatal connection strengths, and firing rates support the scenario in which \(|G_{\text{indirect}}| \) is large compared to \(|G_{\text{esp1c2e}}| \). Figure 9(b) shows that the system displays an instability at 0 Hz for strong corticothalamic interactions but a weak hyperdirect pathway. The frequency of theta oscillations increases with both
Figure 6.8: Possible limit cycles in the BGTCs. (a) Limit cycle at 5.1 Hz caused by a moderate corticothalamic gain and a much larger indirect loop gain ($G_{esp1,p2,d2,e} = -49, G_{ese} = 2.7$). The GPe oscillates approximately in antiphase with the STN. (b) Limit cycle at 6.2 Hz caused by a strong hyperdirect loop ($G_{esp1,e} = -52$). STN and GPe oscillate approximately in phase. (c) Limit cycle at 20 Hz caused by a large corticothalamic gain and a moderately larger indirect loop gain ($G_{esp1,p2,d2,e} = -32, G_{ese} = 7.9$). Note that the scale differs from (a) and (b). (d) Oscillations arising for a large corticothalamic gain and a much larger indirect loop gain ($G_{esp1,p2,d2,e} = -76, G_{ese} = 8.1$). The strongest resonance occurs at 20 Hz, with a weaker resonance at 3.6 Hz.

$G_{ese}$ and $|G_{esp1,e}|$, ranging from about 4.2 to 7.8 Hz, which closely matches the range of tremor frequencies in parkinsonian patients. The lower frequencies of theta oscillations for smaller $G_{ese}$ (a putative index of arousal) could be related to the slowing of tremor seen with age (Deuschl et al., 1996).
Figure 6.9: Regions of linear stability for the BGTCs. (a) Region parameterized by the gains of the direct and indirect pathways (where $G_{\text{indirect}} = G_{\text{esp1,p2,d2,e}} + G_{\text{esp1,p2,d2,e}}$), and the absolute value of the gain for the STN-GPe loop. The unstable frequencies are indicated for the following situations: dominance of the direct loop (0 Hz), dominance of the indirect loop (~5 Hz), a strong STN-GPe loop (~46 Hz), and both strong direct and indirect loops (~15 Hz). The top of the bar corresponds to the healthy state with parameters as in Chapter 5. (b) Region of linear stability parameterized by the gains of the hyperdirect, corticothalamic, and indirect loops (where $|G_{\text{indirect}}| = |G_{\text{esp1,p2,d2,e}} + G_{\text{esp1,p2,d2,e}}|$). The location of the healthy state, within the stable region, is indicated by ‘H’. Theta instabilities arise for large gains of the indirect or hyperdirect loops, at frequencies that increase with $G_{\text{ese}}$ and $|G_{\text{esp1,ce}}|$. A 0 Hz instability occurs for large $G_{\text{ese}}$ and small $|G_{\text{esp1,ce}}|$. The dashed line indicates that the boundaries in front lie in the $G_{\text{ese}} = 0$ and $G_{\text{esp1,ce}} = 0$ planes. The vertical lines along the right-hand boundary are numerical artifacts.
6.5.2 Changes in spectra with dopamine loss

We now investigate the influence of dopamine loss on frequency spectra. Using the transfer function (6.18) we calculate the linear cortical spectrum up to a proportionality factor via $P(\omega) \propto |\phi_e^{(1)}(\omega)|^2$. The results are shown in Fig. 6.10(a). If parkinsonism is modeled via $\nu_{d_1e} = 0.4$ mV s, $\nu_{d_2e} = 0.1$ mV s, and $\theta_{d_1} = \theta_{d_2} = 13$ mV, parameters that represent a decreased striatal SNR, the cortical spectrum is virtually indistinguishable from that in the healthy state. Modeling dopamine loss with $\nu_{d_1e} = 0.5$ mV s and $\nu_{d_2e} = 1.4$ mV s shifts the frequency of the alpha root from 8.9 Hz to 8.5 Hz, in line with slowed alpha peaks seen in PD patients (Sinanović et al., 2005; Soikkeli et al., 1991). A stronger indirect and weaker direct pathway also reduces overall cortical power and relative power at 7–12 Hz from 20% to 13%, but increases relative power at 3–7 Hz from 9% to 17%. Changes in relative alpha and theta power accord with empirical findings (Bosboom et al., 2006; Neufeld et al., 1994; Stoffers et al., 2007), but absolute power is reduced in contrast to what has been found experimentally (Moazami-Goudarzi et al., 2008; Tanaka et al., 2000). Reduced intrapallidal inhibition and particularly loss of mesocortical dopamine may account for some of the experimentally observed increase in power (cf. Fig. 6.10). It is interesting to note that balancing the relative strengths of excitation and inhibition in the cortex also produces an increase in relative theta and beta power. Thus, our model confirms that lateral disinhibition in the cortex can account for the experimentally observed co-production of low- and high-frequency activity, which has been termed the ‘edge effect’ (Llinás et al., 2005). The full parkinsonian state combines increased relative 3–7 Hz (23% vs. 9%) and decreased relative 7–12 Hz power (15% vs. 20%) with overall power not much lower than in the healthy state (total power $\geq 1$ Hz is 89% of the normal value). Assuming that cortical power is slightly reduced when the striatum is significantly involved, in line with the suppressed excitability of regions normally co-activated with the striatum, or during tasks that specifically require striatal activation (Monchi et al., 2004, 2007), these are realistic spectral changes. In cortical areas not directly linked with the striatum, power may be increased due to diffuse loss of dopaminergic innervation, or due to compensatory mechanisms. Finally, changes in parameters other than corticostriatal coupling strengths further slow the alpha root to 8.2 Hz in the full parkinsonian state.

The dispersion relation for the spatially uniform case is $q^2 = 0$ [cf. Eq. (6.20)]. Its solutions up to 40 Hz are plotted in Figs. 6.10(b) and 6.10(c) for the normal and dopamine-depleted states. Each of the states represents a stable system, since all roots are found in the lower half plane. Increased relative theta power corresponds to a smaller distance between the least stable roots on the imaginary axis, which ‘pulls’ the alpha roots to lower power and
Figure 6.10: Linear cortical spectra and dispersion roots for mean $\phi_\alpha$ of 10 s$^{-1}$. (a) Linear frequency spectra of the cortical signal: thick solid line, healthy state with parameters as in Chapter 5; dotted, ‘reduced-SNR’ state with $\theta_{d_1} = \theta_{d_2} = 13$ mV, $\nu_{d_1e} = 0.4$ mV s, and $\nu_{d_2e} = 0.1$ mV s; thin dashed line, weaker direct and stronger indirect pathway, $\nu_{d_1e} = 0.5$ mV s and $\nu_{d_2e} = 1.4$ mV s; dash-dotted, reduced intrapallidal inhibition, $\nu_{p_2p_2} = -0.03$ mV s; thick solid line, $\nu_{ee} = \nu_{ie} = 1.4$ mV s and $\nu_{ei} = \nu_{ii} = -1.6$ mV s to model loss of pre-SMA neurons and mesocortical dopamine; thick dashed line, full parkinsonian state (cf. Sec. 6.3.3). Note that the spectrum for the reduced-SNR state almost coincides with that in the healthy state. (b) Solutions $f = \omega / (2\pi)$ of the dispersion relation $q^2 = 0$ [cf. Eq. (6.20)]. Proximity to the real axis determines the amplification of the signal at the corresponding frequency. Filled dots, healthy state; open circles, reduced-SNR state; crosses, $\nu_{d_1e} = 0.5$ mV s and $\nu_{d_2e} = 1.4$ mV s; squares, $\nu_{p_2p_2} = -0.03$ mV s. (c) Dispersion roots for the following cases: filled dots, healthy state; crosses, $\nu_{ee} = \nu_{ie} = 1.4$ mV s and $\nu_{ei} = \nu_{ii} = -1.6$ mV s; open circles, full parkinsonian state.
frequency. These root locus diagrams also show that reduced intracortical inhibition and a lower GPe threshold potential enhance gamma-band power around 35 Hz in the STN-GPe network. The frequency of this rhythm goes up as the corresponding roots move closer to the real axis, explaining the higher frequency (∼46 Hz) of limit cycles in the STN-GPe loop.

Figure 6.11: Spectra obtained by numeric integration and averaging the Fourier transforms of 60 successive 2-s epochs. Input consisted of Gaussian white noise with mean 10 s⁻¹ and standard deviation 2 s⁻¹. Thin solid lines, healthy state; dotted, ‘reduced-SNR’ state with θ₁ = θ₂ = 13 mV, ν₁ = 0.4 mV s, and ν₂ = 0.1 mV s; thin dashed lines, state with ν₁ = 0.5 mV s, ν₂ = 1.4 mV s; dash-dotted, with reduced intrapallidal inhibition, ν₁ = −0.03 mV s; thick solid lines, with ν₁ = ν₂ = 1.4 mV s and ν₁ = −1.6 mV s; thick dashed lines, full parkinsonian state (cf. Sec. 6.3.3). (a) φ₁; (b) φ₂; (c) φ₃; (d) φ₄; (e) φ₅; (f) φ₆; (g) φ₇; (h) φ₈.

Spectra obtained by numeric integration of the full nonlinear equations are shown in Fig. 6.11. These were computed by averaging the Fourier transforms of 60 consecutive 2-s epochs for a Gaussian white noise input with mean 10 s⁻¹ and standard deviation 2 s⁻¹. The main results of parameter changes mimicking a reduced striatal SNR are lower-amplitude fluctuations in D1 and D2 cells, and increased relative low-frequency power in the GPe. The parameters ν₁ = 0.5 mV s and ν₂ = 1.4 mV s lead to decreased corticothalamic power, and increased power in all basal ganglia populations except D1. This accords with
the enhanced fluctuations in the responses of the basal ganglia, and reduced fluctuations in thalamocortical responses to ongoing inputs seen in Sec. 6.4.3. Furthermore, these parameter changes amplify relative power at 15–25 Hz in the cortex, D1 neurons, and the STN, in line with increased beta coherence between cortex and STN in PD patients (Brown et al., 2001; Marsden et al., 2001).

Lateral disinhibition of the GPe ($\nu_{p2p2} = -0.03 \text{ mV s}$) enhances fluctuations in all populations, and particularly activity around 20–30 Hz in both pallidal segments and the STN. Weaker cortical interactions ($\nu_{ee} = \nu_{ie} = 1.4 \text{ mV s}$, $\nu_{ei} = \nu_{ii} = -1.6 \text{ mV s}$) cause similar changes, which are more pronounced in all components except the GPe than changes caused by reduced intrapallidal inhibition. Figure 6.11 shows that the full parkinsonian state is accompanied by increased relative 3–7 Hz power throughout the BGTCS compared to the healthy state. Relative power at 15–25 Hz is enhanced in the cortex (5.2% vs. 4.0%), D1 neurons (27% vs. 25%), and the STN (12% vs. 5%), and decreased in the remaining populations, partly due to the increase in theta power. As a fraction of power $\geq 7$ Hz, 15–25 Hz activity is enhanced also in the GPe (38% vs. 36%).

### 6.5.3 The paradox of GPe lesion

Leblois et al. (2006) did not include the indirect pathway in their model partly because of the finding by Soares et al. (2004) that GPe lesion in the monkey does not lead to parkinsonian motor symptoms or altered activity patterns in the GPi. The authors concluded that this invalidates the indirect loop as a candidate for the origin of synchronous oscillations and motor symptoms in PD. We modeled GPe lesion by reducing the absolute values of all gains emanating from the GPe, $\nu_{p1p2}$, $\nu_{p2p2}$, and $\nu_{cp2}$, multiplying each by a factor $\xi$ between 0.1 and 1 with results shown in Fig. 6.12. Although corticothalamic rates are reduced, while pallidal and STN rates are increased by GPe lesion in our model, a reduction in all the gains implies that oscillations are damped rather than enhanced in the indirect, hyperdirect, and STN-GPe loops. However, as we saw in the previous sections, strengthening of the indirect pathway by either increasing $\nu_{de}$ or $\nu_{de}$ can lead to slow oscillations in this loop. Thus, a putative lack of parkinsonian signs following GPe lesion does not preclude the involvement of the indirect pathway in the generation of synchronous oscillations and motor symptoms. In fact, Cheeslet and Delfs (1996) noted that GPe lesion does not necessarily reflect what happens with nigrostriatal degeneration, precisely because it does not reproduce changes elsewhere, such as in STN or GPi. Besides, the negative result of Soares et al. (2004) may be related to a relatively small extent or to the location of the lesions, since Zhang et al. (2006) did report worsened akinetic symptoms after GPe lesions in MPTP-treated rhesus monkeys. This matches the smaller value of $|G_{ee} + G_{ei}|$ with
reduced GPe output in our model (0.6 for $\xi = 0.1$ vs. 0.9 in the healthy state, if impaired cortical inhibition is linked with akinesia (cf. Sec. 6.4.1).

Figure 6.12: Effects of multiplying $\nu_{p1p2}, \nu_{q2},$ and $\nu_{p2p2}$ by a factor $\xi$ to mimic GPe lesion. (a) Corticothalamic gains. (b) Gains involving the basal ganglia. (c) Steady-state firing rates vs. $\xi$.

6.6 Summary and discussion

Using a physiologically-based mean-field model of the basal ganglia-thalamo-cortical system (BGTC), we have reproduced many of the electrophysiological correlates of Parkinson’s disease (PD) with parameter values in the healthy and parkinsonian states estimated from known physiology. The analysis builds on Chapter 5, which examined the effects of nigrostriatal dopamine depletion on firing rates. There we showed that an increase in the cortical connection strength to striatal neurons expressing the D2 class of dopamine receptor, possibly along with a reduced connection strength to D1-expressing striatal neurons, leads to increased rates of the striatum, STN, and output nuclei, and decreased GPe and thalamic rates, in good agreement with many experiments. On the other hand, simultaneous decreases in corticostriatal connection strengths and striatal firing thresholds, chosen to mimic a reduced striatal signal-to-noise ratio, had little effect on rates. We note that these results do not bear directly on the role of dopamine as a contrast enhancer, since these particular parameter changes may not adequately capture a reduced signal-to-noise ratio in the striatum as a whole, and dopamine may enhance differential responses to strong and weak inputs in some striatal neurons but not others. Disinhibition of the cortex due to impaired local dopaminergic innervation helped normalize the cortical firing rate, as seen experimentally. Other changes secondary to nigrostriatal damage, including lower GPe and STN firing thresholds and weaker intrapallidal inhibition, could account for the comparatively large increase in
STN rate and conflicting findings on changes in GPe rate. In the present work
we have investigated the dynamical implications of the above ways of modeling
dopamine depletion. The wide range of phenomena accounted for suggests that
the model provides a physiologically realistic representation of the mean-field
dynamics of the BGTCs. Our main findings are listed below.

Outcomes of model

(i) Reduced availability of cortical dopamine may contribute to bradykine-
sia in PD patients by attenuating intracortical excitation by pyramidal cells,
and especially inhibition by interneurons (Gulledge and Jaffe, 2001; Gao and
Goldman-Rakic, 2003; Thurley et al., 2008), resulting in a smaller difference
between excitatory and inhibitory gains. This causes more gradual changes in
cortical activity, in agreement with slowed motor unit responses to transcranial
magnetic stimulation in PD patients (Kleine et al., 2001), and slowed responses
of motor cortex neurons in monkeys treated with the neurotoxin 1-methyl-4-
phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Doudet et al., 1990). Also, the
silent period after suprathreshold stimulation of the cortex during muscle con-
traction is shortened in parkinsonian patients (Cantello et al., 1991), which
is reversed by dopaminergic medication (Priori et al., 1994). Since the silent
period is considered to be caused by the activation of GABAergic interneurons
(Fuhr et al., 1991), this indicates the importance of impaired cortical inhibition
in bradykinesia. Our model suggests that some of these changes are also ex-
plained by nigrostriatal dopamine loss, which can decrease cortical gains, and
the difference between the strengths of intracortical excitation and inhibition,
due to a shift in balance from the direct to the indirect pathway.

Other explanations for bradykinesia/akinesia have been put forward, such
as overactivity of GPi and/or STN projections to the PPN (Munro-Davies
et al., 1999), which in turn innervates the pontine and medullary reticulospinal
systems (Jackson and Crossman, 1983). In addition, rigidity, muscle weakness,
tremor, slowing of thought, and compensation for loss of movement accuracy
may all contribute to bradykinesia (Berardelli et al., 2001). Thus, other factors
are likely to complement the mechanism proposed here.

(ii) An increase in the cortico-D2 connection strength with or without a
weaker cortico-D1 projection leads to realistic changes in responses to transient
stimuli. More vigorous model responses are observed in the STN and the output
nuclei, in accord with experiments (Bergman et al., 1994; Filion et al., 1988;
Wichmann et al., 1994b). As also observed experimentally (Magill et al., 2001;
Zold et al., 2007b), the inhibitory phase of a triphasic early GPe model response
becomes more pronounced as the indirect loop gains in strength. Changes in
D1 and D2 responsiveness are in line with recorded effects of dopamine on the
sensitivity of striatal medium spiny neurons to cortical inputs: D1 responses are attenuated and D2 responses are amplified with dopamine loss as seen in experiments (Cepeda et al., 1998; Hernández-López et al., 1997; Hsu et al., 1995; Kiyatkin and Rebec, 1996; Levine et al., 1996; Nicola et al., 2000; Toan and Schultz, 1985; Umemiya and Raymond, 1997).

(iii) The indirect basal ganglia pathway can sustain ~5 Hz oscillations if dopamine depletion leads to greater cortical influence on D2-expressing striatal neurons with or without reduced influence on D1-expressing neurons. The fact that modulation of the direct pathway need not be opposite to that of the indirect pathway underlines that a complete separation of D1 and D2 neurons is not required to obtain this result. Limit cycle oscillations around 5 Hz only appear when the indirect loop is very strong compared to thalamocortical interactions, which is unlikely to happen in the system as a whole and confines oscillations to subcircuits. This scenario is supported by the limited proportion of tremor cells recorded in components of the BGTCs in parkinsonian humans and animals (Bergman et al., 1994; Lemstra et al., 1999; Levy et al., 2001; Wichmann and Soares, 2006), and the high firing rate of oscillatory cells compared to non-oscillatory cells (Dejean et al., 2008; Levy et al., 2000, 2001). As explained in the Introduction, central oscillations need not directly determine the frequency of parkinsonian tremor, since cortical and peripheral factors appear to play a modulatory role. However, the frequency of oscillations in the indirect loop predicted by our model is close to the ~4–6 Hz of parkinsonian rest tremor (Deuschl and Lücking, 1989), as well as to measured rhythms in the basal ganglia, cortex, and thalamus (Bergman et al., 1994; Magnin et al., 2000; Raz et al., 2000; Volkmann et al., 1996; Wang et al., 2005; Wichmann et al., 1999). A relatively high level of arousal is required for limit cycle oscillations to appear, possibly helping to explain why tremor is exacerbated by anxiety and stress (Deuschl et al., 2001; Zesiewicz and Hauser, 2001).

(iv) The phase relationships between the basal ganglia components oscillating at ~5 Hz accord with those measured by Walters et al. (2007) for ~1 Hz oscillations in anesthetized rats with dopaminergic lesions. Furthermore, Zold et al. (2007a) reported a population of GP (the rodent homolog of GPe) neurons whose firing rate was modulated in antiphase to cortical slow waves and striatal activation in parkinsonian rats under anesthesia, whereas GP activity was in phase with cortex and striatum in healthy anesthetized rats. This suggests that parkinsonian slow oscillations are relayed via the striatopallidal axis rather than via the hyperdirect pathway through the STN, since the GPe is inhibited by the striatum, but excited by the STN. If these results generalize to PD patients, this is strong evidence for an origin of parkinsonian theta oscillations in the indirect loop. Leblois et al. (2006) proposed that the hyperdirect loop is the main substrate of parkinsonian oscillations based on a neuronal network model.
of the direct and hyperdirect loops. This would imply that GPe activity would be modulated in phase with STN activity, being driven by excitatory input from this nucleus, contrary to experimental observations. Moreover, an origin in the hyperdirect loop was suggested based on the assumption that firing rates are virtually unchanged, which does not appear to be generally applicable (see Chapter 5). In our model, a source of parkinsonian oscillations in the hyperdirect loop is incompatible with increased striatal rates and a decreased GPe rate, often measured in animal models of PD (Boraud et al., 1998; Chen et al., 2001; Filion and Tremblay, 1991; Heimer et al., 2002; Kish et al., 1999; Pan and Walters, 1988; Walters et al., 2007). In contrast, our model predicts both realistic changes in firing rates and oscillations in the indirect loop simultaneously for a stronger cortico-D2 connection. Moreover, striatal involvement in parkinsonian rhythms is strongly implied by the dense dopaminergic innervation of this nucleus, which is expected to powerfully modulate corticostriatal connection strengths.

(v) In the model, oscillations around 20 Hz that are normally largely confined to corticothalamic circuits are enhanced and spread to the basal ganglia (particularly to the STN) when the indirect loop becomes strong due to nigrostrial degeneration, while cortex and thalamic relay nuclei are also relatively tightly coupled. Such enhanced ~20 Hz oscillations have been found in many experimental studies of parkinsonism (Brown et al., 2001; Brown and Williams, 2005; Fogelson et al., 2006; Gatev et al., 2006; Levy et al., 2002; Sharott et al., 2005). Cortical activity has been shown to be phase-advanced with respect to STN activity at <30 Hz, corroborating a corticothalamic origin of beta oscillations (Marsden et al., 2001; Williams et al., 2002). Depending on the relative gains of the corticothalamic and indirect loops, model rhythms at ~20 Hz may be stronger or weaker than ~5 Hz rhythms, and limit cycles may therefore show a combination of these frequencies, also in accord with experiments (Levy et al., 2001).

Enhanced beta oscillations in the basal ganglia may either be a side effect of other pathological changes, or be directly related to parkinsonian symptoms, as suggested by a number of studies. For instance, Silberstein et al. (2003) found a larger percentage of local field potential activity at 11–30 Hz in the pallidum of untreated PD patients compared to treated ones. Moreover, a study in which 20 Hz stimulation of the STN slowed finger-tapping rates supported a relationship between beta oscillations and akinesia/bradykinesia (Chen et al., 2007). A connection between beta oscillations in the basal ganglia and akinetic symptoms is further supported by the fact that the oscillations are attenuated before and during voluntary movement (Kühn et al., 2004), as is 15–30 Hz coherence between motor cortex and muscles (Farmer, 2002). On the other hand, the low-pass filter characteristics of the pallidal-cortex-muscle axis suggest that
beta oscillations may not strongly influence movement (Rivlin-Etzion et al., 2008), and 20 Hz synchronization in the STN was found to correlate with motor improvement after dopamine replacement therapy, rather than with the initial severity of symptoms (Weinberger et al., 2006). Thus, the precise relation between beta oscillations and parkinsonian symptoms remains to be elucidated.

(vi) Our model predicts a resonant frequency in the gamma band (>30 Hz) for the loop formed by STN and GPe, in accord with modeling results of Humphries et al. (2006). Alterations in this network may therefore be responsible for enhanced gamma power in the STN observed in PD patients on levodopa (Fogelson et al., 2005), particularly in relation to movement (Casvidy et al., 2002). More recently, such gamma activity was also recorded in patients after overnight withdrawal from antiparkinsonian medication (Trottenberg et al., 2006). In PD patients, STN activity has been found to lead cortical activity in the gamma band (Williams et al., 2002), supporting our finding of an origin in the STN region.

(vii) Stronger cortico-D2 coupling increases the amplitude of fluctuations in firing rates across the spectrum in D2-expressing striatal neurons, GPe, STN, and the output nuclei, suggesting an increase in synchronization between individual cells. This applies especially to the GPe, where the firing rate is decreased, since increased rates may enhance power without changing the degree of synchronization. However, power at low frequencies is amplified by a factor of up to 40 in the output nuclei, whereas the increase in average rate from 69 s$^{-1}$ to 112 s$^{-1}$ only accounts for an approximate factor of 2.7 if the standard deviation is taken to be proportional to the average rate. STN power is also more amplified than accounted for by its higher average rate in the parkinsonian state. This strongly implies that synchronization is enhanced, in concordance with experimental studies (Goldberg et al., 2004; Hammond et al., 2007; Heimer et al., 2002; Levy et al., 2000; Morris et al., 2005). Levy et al. (2002) proposed that only oscillatory cells are synchronized in parkinsonism, although this study may have failed to detect fluctuations at the population level, and did not compare with healthy subjects. Our results suggest that dopamine loss increases synchronization across the whole spectrum, rather than only in peaks, thus including cells whose activity is not modulated at one of the main resonant frequencies of the system. This result requires further experimental verification.

(viii) Dominance of the indirect pathway increases relative theta power, decreases relative alpha power, and shifts the alpha peak of the electroencephalogram (EEG) to lower frequencies, in agreement with empirical findings (Bosboom et al., 2006; Neufeld et al., 1994; Sinanović et al., 2005; Soikkeli et al., 1991; Stoffers et al., 2007). Changes secondary to nigrostriatal dopamine loss, such as reduced intrapallidal inhibition, a stronger striato-GPe projection due
to enhanced release of GABA, and lower GPe and STN threshold potentials, may also contribute to these spectral changes by further increasing the gain of the indirect loop. More pronounced EEG frequency reduction in demented patients may be partly explained by additional changes in cholinergic and noradrenergic signaling (Buzsáki et al., 1988; Candy et al., 1983; Cash et al., 1987; Dubois et al., 1983; Metherate et al., 1992). Total EEG power is decreased by a stronger indirect pathway in the model, in accord with its inhibitory effect on the thalamus and cortex. However, EEG power has been reported to be increased in PD (Moazami-Goudarzi et al., 2008; Tanaka et al., 2000). Loss of intrinsic cortical dopamine, reduced intrapallidal inhibition, and a lower GPe firing threshold may partly normalize EEG power that is reduced by a dominant indirect pathway. Considering that cortical responses are suppressed in PD in tasks or regions with significant involvement of the striatum (Monchi et al., 2004, 2007), we do not expect these changes to increase EEG power beyond the normal level. Rather, diffuse loss of mesocortical dopamine leading to cortical disinhibition (Mattay et al., 2002), and compensatory changes in areas not directly connected to the basal ganglia (Samuel et al., 1997), may cause the observed EEG amplification, whereas we expect EEG fluctuations in areas strongly connected with the basal ganglia to be diminished.

Wider context and future directions

The above results were obtained using a small number of variations around a single set of parameters representing the healthy state. Thus, the same axonal, dendritic, and synaptic delays that give realistic responses to transient cortical stimuli, a resonant frequency of the STN-GPe loop in the gamma band, and an alpha peak frequency around 9–10 Hz, predict frequencies around 5 Hz and 20 Hz for oscillations in the parkinsonian state. Moreover, the same parameter changes that yield plausible firing rate changes with nigrostriatal damage lead to increased relative theta power, decreased relative alpha power, and a lower alpha peak frequency, all in accord with experiments. This provides firm support for the proposed mechanisms, and strongly suggests that combinations of parameter values required to obtain these results were chosen in physiologically realistic ranges.

The debate on the substrate of parkinsonian oscillations has been fueled by paradoxical results concerning changes in GPi and STN activity and motor behavior following GPe lesion. Soares et al. (2004) observed a lack of parkinsonian symptoms or oscillatory bursting after GPe lesion, prompting Leblois et al. (2006) to reject the indirect pathway as a possible source of parkinsonian oscillations. However, despite the generally decreased firing rate of the GPe in parkinsonism, nigrostriatal and GPe lesions can have notably different effects.
on firing patterns in the BGTCs. This is apparent in our model from the fact that weaker efferent projections from the GPe lower all gains, rendering the system more stable and damping oscillations. Therefore, the supposed lack of parkinsonian symptoms following GPe lesion does not preclude the possibility that tremor rhythms arise in the indirect basal ganglia circuit. In fact, Soares et al. (2004) remarked that the involvement of the GPe is supported by the observation that oscillatory cells in the STN and GPi were slightly less numerous in GPe-lesioned animals than in intact animals. Furthermore, our model predicts that damage to the GPe impairs intracortical inhibition more than excitation, analogous to nigrostriatal damage, which matches the finding by Zhang et al. (2006) that GPe ablation does exacerbate the parkinsonian symptoms of akinesia/bradykinesia in rhesus monkeys previously treated with MPTP.

The different effects of GPe lesion and nigrostriatal lesions that reduce GPe activity exemplify the more general rule that a single structure can contribute to a variety of phenomena, depending on its connections and the parameter values of the system. Single circuits can also support different types of activity, as evidenced for instance by the different frequencies of oscillations in the indirect loop depending on the relative values of corticothalamic and indirect loop gains. This example immediately makes it clear that multiple structures can also contribute to a single effect, underlining the importance of including circuit interactions in models of neural systems rather than focusing only on localized ‘pacemakers’, as has sometimes been done in the past. An aspect of such models that is perhaps less often considered is that certain activity patterns can be sustained by multiple interacting circuits. An example was given in Sec. 6.5.1, where oscillations were derived arising from an interplay between corticothalamic circuits and the indirect loop, rather than in any circuit separately.

It is significant to note that bursting activity is not required to account for increased theta and beta oscillations and EEG slowing. Accordingly, bursting has gradually been deemphasized in the literature as an explanation for parkinsonian oscillations and symptoms, since it appears to be particularly prevalent during dyskinesias (Lee et al., 2001; Silberstein et al., 2003), treatment with the dopamine agonist apomorphine increases aperiodic bursting in STN and GPi (Levy et al., 2001), and bursts around tremor frequency give way to slower rhythmic bursts during voluntary movement (Rodriguez-Oroz et al., 2001). Nevertheless, calcium spike bursts in the relay nuclei may contribute to enhanced thalamocortical theta coherence (Sarnthein and Jeanmonod, 2007), and to overproduction of beta and gamma activity in the cortex via the edge effect (Llinás et al., 2005; Moazami-Goudarzi et al., 2008). Therefore, taking into account thalamic bursting in our model may help explain increases in
EEG power in the theta, beta, and gamma bands. It would also be relevant to include bursting properties of STN (Beurrier et al., 1999; Bevan et al., 2000) and GPe (Nambu and Llinás, 1994) cells, which may modify the amplitude, frequency, and timing of rhythms predicted by our model. We aim to modify our model by including distinctive electrophysiological properties of STN, GPe, and thalamic bursting neurons in future work.

In addition to the interactions included in our model so far, there are projections from the GPe to the TRN (Gandia et al., 1993; Hazrati and Parent, 1991) and to striatal interneurons (Bevan et al., 1998), from the thalamic parafascicular nucleus to the STN (Hassani et al., 1997; Mouroux et al., 1995), and between the PPN and all elements of the BGTCs (Hammond et al., 1983; Jackson and Crossman, 1983; Lavoie and Parent, 1994; Orieux et al., 2000). Studies in rats with nigrostriatal lesions have suggested that excitatory projections from the PPN are partly responsible for STN hyperactivity (Breit et al., 2006), despite the loss of neurons from this region in PD (Zweig et al., 1989), and the induction of akinesia by PPN lesion in otherwise healthy primates (Munro-Davies et al., 1999; Pahapill and Lozano, 2000). Some of these projections may be included in future work. Instead of more detailed modeling, an alternative approach would be to simplify the current model to extract those features essential for explaining phenomena such as changes in firing rates, theta, beta, or gamma rhythms, or trends in EEG spectra. Simplified models could be analyzed more systematically and provide more robust parameter estimates, although these estimates would be less easily related to the underlying complex physiology. Thus, both more detailed and sparser modeling can provide new information complementing the predictions of the current model.
Chapter 7

Concluding remarks

In five chapters we have found our way from a normalizing transformation for arbitrary distributions (Chapter 2), which came forth from a study of the test-retest reliability of physiologically-based spectral parameters of the electroencephalogram (EEG) (Chapter 3), via a study of age trends in fitted EEG parameters (Chapter 4), to an investigation of the basal ganglia-thalamocortical system (Chapters 5 and 6). The common denominator has been a mean-field modeling approach to characterizing brain electrical activity. The variety of topics addressed here is a testament to the versatility of such mean-field models. The present work has strengthened links between model predictions and experiment, and has incorporated mean-field descriptions of the cortex, thalamus, and basal ganglia into a unified framework for the first time. Here we recapitulate some of the main results, place our findings in a wider context, and discuss possible future avenues of research.

A legitimate concern about model fitting is that, given enough free parameters, one could fit just about anything, even the New York skyline. Of course, spatially averaged models already greatly reduce the number of free parameters with respect to lower-level models. Nevertheless, it is reasonable to ask whether EEG spectra contain sufficient information to constrain all the parameters in our model. A subsidiary question is how fitting is affected by noise, which can introduce bias and uncertainty in parameters that are otherwise well constrained. Studies of test-retest reliability (Chapter 3), and robustness to noise (considered in Chapter 4), are therefore central to the validation of model parameters. It is worthwhile to note that there is no clear-cut advantage to either small numbers of tightly constrained parameters, or larger numbers of less well constrained parameters, as long as the uncertainty in the latter is well characterized. In fact, the number of parameters may be constrained either before fitting, by fixing one or more values, or afterwards, for instance by combining highly variable parameters into more robust quantities. The analysis presented in Chapters 3 and 4 is intended to aid interpretation of future results, and may
inspire further refinements of the fitting algorithm.

The main subject of Chapter 4 was the variation across age of fitted EEG spectral parameters in the healthy population. To our knowledge, no other study has considered physiologically-based parameters for such a large sample of EEG data. It was found that significant sex differences exist in average parameter values, as well as rates of parameter changes with age. Overall, changes occurred most rapidly in childhood, and slowed down after adolescence. We also presented age trends in inter-individual variability, which was observed to peak around adolescence. Along with Chapter 3, the study in Chapter 4 has illustrated the feasibility of inverse modeling of EEG spectra as a non-invasive way to obtain large-scale information about the brain, including time constants and connection strengths within and between cortex and thalamus. Furthermore, these studies provide a standard for comparisons with age trends and inter-individual variability in ERPs, the morphology of alpha peaks, EEG recordings obtained at different electrodes, data from clinical groups, and cognitive and behavioral measures.

The model of the basal ganglia-thalamocortical system presented in Chapters 5 and 6 was used to investigate the mechanisms underlying changes in neural activity in Parkinson’s disease, which is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (Bernheimer et al., 1973; Ehringer and Hornykiewicz, 1960). Research on Parkinson’s disease has a long history, and various models have been formulated to elucidate the neuronal substrates of symptoms such as tremor, slowness of movement, and difficulty initiating movements (Gillies et al., 2002; Humphries et al., 2006; Leblois et al., 2006; Rubin and Terman, 2004; Terman et al., 2002). The contribution of the present work is to provide unified explanations for changes in average firing rates, stimulus responses, and EEG spectra, the appearance of approximately 5 Hz and 20 Hz oscillations, and phase relationships between activity in different components of the basal ganglia-thalamocortical system with dopamine depletion. Ultimately the hope is that improved understanding of the mechanisms responsible for parkinsonian symptoms will help fuel developments in treatment methods.

Mean-field models suffer from a number of shortcomings, for instance that the detailed effects of different network architectures are not taken into account, and possibilities for investigating phase relationships between neurons within the same population are highly limited. However, we have seen that many aspects of the neuronal activity in the healthy and parkinsonian basal ganglia can be fruitfully studied using a mean-field approach. To achieve a large-scale description of basal ganglia and thalamocortical dynamics, it has been necessary to synthesize information from a wide range of recording modalities. Increased availability of data on the average activity of neuronal populations

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would facilitate the formulation and verification of mean-field models.

The gap between the mean-field and single-neuron levels of description may be partly bridged in future work by incorporating properties of bursting neurons in the basal ganglia and thalamus. It is further hoped that the present work will help pave the way for research into other disorders involving the basal ganglia, such as Huntington’s disease, schizophrenia, and obsessive compulsive disorder. Modeling the neural activity in the latter two disorders, as well as certain aspects of Huntington’s disease and Parkinson’s disease, will require the present model to be extended with limbic system connections.

This work adds to the accumulating evidence for the value of mean-field models in explaining the activity underlying EEGs and neuronal population dynamics. A potential benefit is that this will improve the accessibility of such models to experimental and clinical neuroscientists, as well as computational neuroscientists using single-neuron and network approaches. A more closely-knit neuroscience community would enable connections between explanations on microscopic, mesoscopic, and macroscopic levels, and between theory and experiment, to be forged more effectively than has hitherto been possible.
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