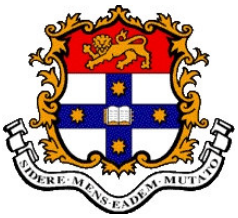

COMPUTATIONAL METHODS FOR THE ANALYSIS OF HIV DRUG RESISTANCE DYNAMICS

A thesis submitted in fulfillment of the requirements for the degree of

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In

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ALI AL MAZARI

CERTIFICATION BY THE SUPERVISORS

We certify that the thesis entitled: “Computational Methods for the Analysis of HIV Drug Resistance Dynamics” submitted by Ali Al Mazari, for the Degree of Doctor of Philosophy, Biomedical Informatics Sciences, is ready for examination.

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DECLARATION

I, the author of the thesis, declare that none of the material in this thesis has been previously submitted by me or any other candidate for any degree to this or any other university.

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ETHICS REVIEW COMMITTEE APPROVAL

Ethics approval from the Sydney South West Area Health Service Ethics Review Committee (SSWAHS ERC X05–0205) was obtained for this project.

ABSTRACT

Despite the extensive quantitative and qualitative knowledge about therapeutic regimens and the molecular biology of HIV/AIDS, the eradication of HIV infection cannot be achieved with available antiretroviral regimens. HIV drug resistance remains the most challenging factor in the application of approved antiretroviral agents. Previous investigations and existing HIV/AIDS models and algorithms have not enabled the development of long-lasting and preventive drug agents. Therefore, the analysis of the dynamics of drug resistance and the development of sophisticated HIV/AIDS analytical algorithms and models are critical for the development of new, potent antiviral agents, and for the greater understanding of the evolutionary behaviours of HIV.

This study presents novel computational methods for the analysis of drug-resistance dynamics, including: viral sequences, phenotypic resistance, immunological and virological responses and key clinical data, from HIV-infected patients at Royal Prince Alfred Hospital in Sydney. The lability of immunological and virological responses is analysed in the context of the evolution of antiretroviral drug-resistance mutations. A novel Bayesian algorithm is developed for the detection and classification of neutral and adaptive mutational patterns associated with HIV drug resistance. To simplify and provide insights into the multifactorial interactions between viral populations, immune-system cells, drug resistance and treatment parameters, a Bayesian graphical model of drug-resistance dynamics is developed; the model supports the exploration of the interdependent associations among these dynamics.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

3TC	Lamivudine
AA	Amino acid
ABC	Abacavir sulfate
AD	Adherence
ADRA	Antiviral drug resistance analysis
AE	AIDS event
AIDS	Acquired immune deficiency syndrome
ANRS	French national agency for AIDS research
APV	Amprenavir
ARV	Antiretroviral
ATV	Atazanavir sulfate
AZT or ZDV	Zidovudine or Azidothymidine
BMI	biomedical informatics
BNs	Bayesian belief networks
CA	Capsid
CART	Combination antiretroviral therapy
CDC	Centres for disease control and prevention
CI	Confidence interval
CM	Codon of mutations
CMP	Category of mutational pattern
CPT	Conditional probability table
CREST	Can resistance enhance selection of therapy
d4T	Stavudine
ddC	Zalcitabine or Dideoxycytidine
ddI	didanosine or dideoxyinosine
DI	Death incidence
DLV	Delavirdine
DNA	Deoxyribonucleic acid
EFV	Efavirenz

EM	Expectation maximisation
EoR	Evolution of resistance
FDA	Food and Drug Administration
FIs	Fusion inhibitors
FPV	Fosamprenavir Calcium
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIVdb	Stanford university's HIV database
IDV	Indinavir
IN	Integrase
JPD	Joint probability distribution
LOESS	LOcally wEighted Scatter-plot Smoothing
MA	matrix
MDR	Multi-drug resistance
mRNA	messenger RNA
NA	Nucleotide acid
NC	Nuclecapsid
NE	Neutral evolution
NFV	Nelfinavir mesylate
NIH	National Institutes of Health
NIR	Non-responding immunological response
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRL	National Serology Reference Laboratory
NRTI	Nucleotide reverse transcriptase inhibitor
NS	Negative selection
NVP	Nevirapine
NVR	Non-responding virological response
NWT	non-wild-type
OI	Opportunistic infection
PCR	Polymerase chain reaction
PI	Protease inhibitor
PIR	Positive immunological response

PMCC	Pearson product moment correlation coefficient
Pol	Polymerase
PR	Protease
PS	Positive selection
PTA	Phenotypic assays
PVR	Positive virological response
RCG	Resistance collaborative group
RE	Resistance emergence
RFLP	Restriction fragment-length polymorphism
RNA	Ribonucleic acid
RPAH	Royal Prince Alfred Hospital
RT	Reverse transcriptase
RT-PCR	Reverse transcriptase-polymerase chain reaction
RTV	Ritonavir
SARS	Severe acute respiratory syndrome
SPSS	Statistical Package for the Social Sciences
SQV	Saquinavir mesylate
STI	Structured treatment interruption
T-20	Enfuvirtide
TA	Toxicity of CART
TAMs	Thymidine analogue mutations
TDF	Tenofovir disoproxil fumarate
TMC114	Darunavir
TPV	Tipranavir
UNAIDS	United Nations Programme on HIV/AIDS
vDNA	viral DNA
VL	Viral load
WHO	World Health Organisation
WT	wild-type

PUBLICATIONS FROM THESIS

1. A. A. Mazari, A. Y. Zomaya, M. Charleston, H. Salem, A. Maher, and R. J. Garsia, "Immunological and virological responses correlated with evolution of resistancein patients treated with antiretroviral agents. Abstract No: 95," presented at 18th Annual Conference of the Australasian Society for HIV Medicine, Melbourne, VIC, Australia, 2006.

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3. A. A. Mazari, A. Y. Zomaya, M. Charleston, and R. J. Garsia, "A Novel Algorithm for Adaptive and Neutral Evolutionary Patterns Associated with HIV Drug Resistance," The fifth ACS/IEEE International Conference on Computer Systems and Applications (AICCSA-07), [Accepted], Amman, Jordan, 2007.

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