PERSPECTIVE

The challenges of controlling polymer synthesis at the molecular and macromolecular level

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Modern applications of polymers demand further elaboration of molecular-level structures as well as control of various macro-level features. There have been significant advances towards applying the science of synthetic organic chemistry to this end with ever-developing precision. Polymers present a singularly unique challenge and opportunity because their synthesis is an inherently divergent process and therefore yields statistical materials. Furthermore, it is a challenge to simultaneously control chemical features of polymers on both the micro and macro level, as one does not inform the other in a straightforward way. In this Perspective article, we highlight developments and opportunities in the broad aspects of synthesising polymers in a controlled fashion, particularly through radical chemistry.

Introduction

Chemical synthesis is key to the construction of well-defined matter at the molecular level. Polymers are no exception, with continuous developments in chemical synthesis sparking a paradigm shift. Polymers are no longer seen as random, ill-defined plastics or rubbers. Rather, they are increasingly being regarded, similarly to how we regard proteins or polynucleotides, as macromolecules with a definition at the molecular level.

Thinking of polymers in this way can, however, be somewhat contradictory. On one hand, the principles of organic synthesis underlying the microstructure of discrete small molecules also hold true for polymers.[1] On the other hand, the processes used to obtain said molecular level structure are fundamentally statistical, translating to a fundamentally statistical product. Chemical synthesis is the way one would assimilate these two ideas.

Here, microstructure is defined by both the composition of repeating units and by how they are assembled and/or distributed in a single macromolecule, demarcated by chain ends (*e.g.,* end groups). These are known to be highly accessible within a polymer. As such, end groups can impart uniquely important structural properties, but also serve as substrates for post-polymerisation reactions.[2]

From the end groups, we can topologically rearrange monomeric units within a macromolecule, yielding hundreds of different compositions from these isomers. Given the profound effect of isomerism in small molecules, most of these compositions may have distinct physical, chemical and biological properties.[3,4]

Within a single linear polymer, we can even conceive of isomerism from the sequence combinations of monomer units, with prochiral monomers creating even more sequence possibilities (*e.g.,* tacticity). This distribution of heterogeneous functionality within polymer chains can affect its ensemble properties and even allow for discrete single-chain properties to be realised (such as in folding).[5,6]

From these considerations, it quickly becomes apparent that from simple syntheses all manner of variables concerning the exact microstructure and broader statistical properties of polymeric products emerge. Control of these translates to emergent properties at the macroscopic level, be it in self-assembly or interactions in increasingly complex systems (most notably, biological systems).[7] Crucially, being able to obtain such specificity in polymer synthesis can broaden the systems that polymers can be applied in.[8]

The field of self-assembly and its applications have seen the greatest development corresponding with advances in controlled polymer synthesis. Various industrially relevant substances have shown to be compatabilised in an increasingly specific manner for specific applications.[9] As a more advanced extension of this, analogous to how molecules are often compartmentalised and transported in native biological systems, solution-assembled polymeric nanoparticles such as capsules, micelles, polymersomes, coacervates and polymer-drug complexes have been developed.[10–15] These have been shown to deliver various cargoes ranging from small molecules to proteins.[16–19] Bulk self-assembly of controlled polymers has also been applied in photonics, where polymeric segments of differing in refractive index are regularly arranged.[20,21] Self-assembled materials can be fabricated into thin films with

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various pore sizes and chemistries.[22,23] Finally, the specificity of which organic matter can be arranged at various length scales has garnered interest in translating this toward nanostructured inorganic matter by way of soft templating.[24,25]

There are also developments in applications which rely more and more on the specific microstructure of polymeric materials. The ever-expanding scope of functionality which can be introduced at the molecular level in a polymer synthesis can further allow classifications of materials into "sensors", "actuators" and "networks". This can endow such materials with crude forms of "intelligence".[26,27]

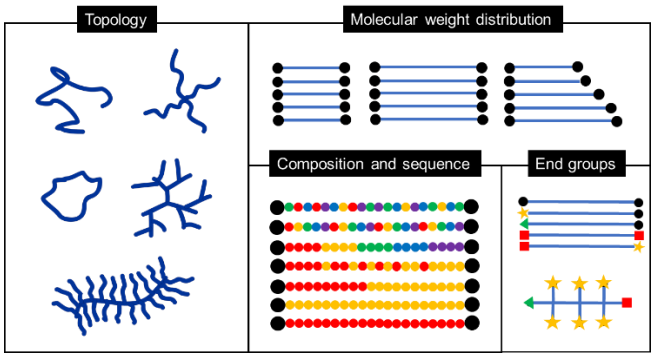

Figure 1. Overview of various polymer characteristics accessible *via* controlled synthesis.

In this Perspectives, we aim to reiterate a few fundamental concepts, and offer our outlooks relevant to each aspect in controlled polymer synthesis: we define these to be molecular weight distribution, end groups chemistry, architecture, backbone composition and sequence/tacticity. Moreover, we discuss recent developments concerning specifically radical-driven methodologies. There have been many excellent, in-depth reviews concerning ever-developing methodologies regarding either these parameters individually or in combination.[1,27–32] We argue that the pursuit of absolute control over a polymer synthesis is somewhat limited given the various size-regimes where this control can be exerted, but also (and more importantly) given the fundamentally statistical nature of polymerisations and polymers. This Perspective will, therefore, emphasise the interplay between the parameters concerning controlled polymer synthesis, as well as their exclusivity, presenting their own unique scientific challenges.

1. Chain length and molecular weight distribution

Living Polymerisation

One of the most important steps towards developing the science of controlled polymer synthesis has coincided with the development of living polymerisation.[33–36]

This involves stringent conditions at every stage of the process – initiation, propagation and termination.[37] Initiation occurs prior to any subsequent reactions, and therefore uniformly, by a specific entity. The chain propagation then occurs in an environment without side-reactions or impurities. Finally, termination (technically not existing in a true living polymerisation) occurs only at the desired chain length by a pre-determined 'quencher'.[38]

Immediately, this has implications on the molecular weight distribution control of polymers. Firstly, the molecular weight is dependent on only the stoichiometry of the monomer relative to the initiator, and the conversion of monomer. Secondly, molecular weight at an incomplete conversion is easy to predict because the polymerisation is a pseudo first-order process. Finally, the molecular weight of the polymers is roughly Poisson distributed and so the distribution spread is inversely proportional to the average molecular weight.[39]

The classical means to achieve this level of control has been *via* anionic polymerisation.[34] In hindsight, a carbanion is an ideal propagating species for a pure living addition polymerisation of common vinyl/acrylic polymers. This is because the propagating anion at the end of the polymer is the most stable intermediate on an electron deficient polyethylene derived chain (its conjugate acid providing the most acidic proton). As such, in an environment without and exogenous quencher or impurities, termination events are very unlikely.

Carbanions are, however, typically incompatible with more complex systems, or even more complex monomers.[40,41] An increasingly sophisticated understanding of synthetic chemistry has allowed for the realisation of essentially living polymerisation but in a more practical sense; without the stringent requirements of "an environment without side-reactions or impurities".[37]

To that end, other developments in synthetic chemistry have translated to other pseudo living polymerisation mechanisms. For example, cations can undergo a living addition polymerisation analogous to anions.[42] While there are numerous functionalities which are compatible with cationic polymerisation, cations have more potential termination reaction by way of cation rearrangement. Further examples polymerisation methodologies which display living characteristics are coordination driven polymerisation, ring-opening metathesis polymerisation (ROMP) or anionic/cationic ring opening polymerisation (AROP/CROP) and Lewis acid/base immortal polymerisation.[43–47]

A chain growth polymerisation can also propagate by way of a radical species. Being that they are uncharged, exist in a unique S= ±½ spin state, and react based on bond dissociation energy rather than dipole moment, these serve as an interesting means for chemoselective polymerisation. However, one cannot rule out other competitive termination reactions, such as intramolecular hydrogen atom abstraction (leading to branching or backbiting), intermolecular hydrogen atom abstraction, disproportionation and chain-chain coupling.[48] Additional reversible termination reactions are therefore implemented in radical polymerisation to offer methodologies with similar characteristics to living polymerisation, such as reversible addition-fragmentation degenerative chain transfer (RAFT) polymerisation, atom

transfer radical polymerisation (ATRP) and nitroxide mediated polymerisation (NMP). These are classed under the broad umbrella of reversible activation-deactivation polymerisation (RDRP).[49–51]

RAFT utilises chain transfer through a thiocarbonylthio compound which, when added in stoichiometric amounts, occurs frequently enough to maximise the lifetime of propagating radicals. Since chain transfer here is a degenerative process in equilibrium, the kinetics of this process is key to molecular weight control, quantified by the chain transfer constant C_{tr}.[52] At the main equilibrium, this can be altered through the stability of the chain transfer intermediate which varies by the "Z-group" substituent on the thiocarbonylthio species.[53] Through the massive scope of thiocarbonylthio derivatives explored over the past couple of decades, RAFT generally exhibits the widest scope of ethylene derivatives which can be polymerised within some range of uniformity.[54–58] ATRP is different in that propagating radicals are actively capped and released in a $Br^{\bullet}/Br^{-}$ redox couple, driven typically by a redox couple, traditionally, Cu^{I}/Cu^{II}. Both redox processes occur in equilibrium and thus the key descriptor of an ATRP governing the molecular weight control is the equilibrium constant, termed K_{ATRP}, which can be tuned by a number of factors.[59–61] NMP also involves an equilibrium of activated and deactivated species but involves homolytic cleavage. Molecular weight control would therefore be much alike ATRP *i.e.*, determined by the positioning of the homolysis equilibrium.[51,62,63]

These examples of RDRP do not comprehensively exhibit all the hallmarks of a pure living polymerisation but allow for a controlled molecular weight with uniformity to an acceptable degree.[64] While there are numerous other examples of RDRP, the most part of this Perspective will be concerned with RAFT and ATRP in this space. In the context of controlled polymer synthesis, these are the most well-studied reactions.

As mentioned earlier, a richer understanding of synthetic chemistry allows for a more practicable application of the various tenants of living polymerisation. This, by default has implication of the more practicable realisation of various facets of controlled polymer synthesis discussed in this Perspective. There has also been a massive development in methodologies driven by a variety of stimuli *e.g.,* photochemical, electrochemical, as well as thermal, which afford a new suite of parameters to tune towards molecular weight control. There have already been a number of reviews and perspectives outlining such development in great detail.[65–69]

The rapid development of means to control the statistical outcome of polymerisations has in some cases translated to a quantitative precision. This has opened the door to automation and computationally-driven optimisation of the simple process of homopolymerisation.[70–72] (**Figure 2**)

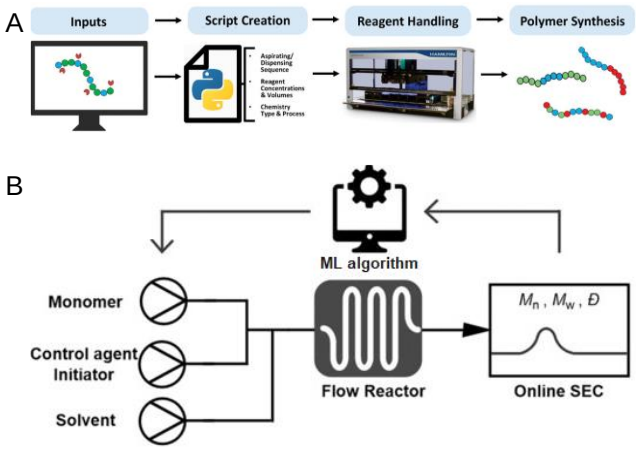

Figure 2. Automated molecular weight control in (A) batch and (B) a self-optimising flow setting, adapted with permission from Rubens *et al.*[73,74] Copyright 2019 American Chemical Society and 2019 Wiley VCH, respectively.

Even in ideal (even automated) circumstances, complete molecular weight purity in a polymerisation is incredibly rare.[75] In state-of-the-art step-by-step syntheses of completely defined macromolecules (*i.e.*, sequential solid-phase synthesis), monomer truncations are often still observed. As with sequential solid-phase synthesis, fractionation has a key role to play in achieving complete molecular weight control in polymerisations.[76–78] For certain applications, the uniformity of polymer chains is crucial. This is particularly evident in processes relying on polymer crystallinity (which is, often, dependent on the homogeneity of species involved). Examples of this would be bulk separation into crystalline phases or crystallisation-driven self-assembly (CDSA) in solution.[79–81]

Higher order statistical control

Molecular weight distribution control from various methodologies discussed has, yet only been concerned with chain length uniformity. Polymerisations are fundamentally a statistical process, and therefore, total chain length uniformity remains elusive. It is rare that a polymerisation mixture can yield an appreciable quantity of macromolecules with perfectly uniform chain length, even with an idealised living polymerisation.[75,82]

In non-trivial cases, the molecular weight distribution can be described in various ways. Generally, a distribution is described by its horizontal position, spread, skew and tailedness (**Figure 3**).[83–85] Currently, these are accounted for in polymer science by various (weighted) averages and their quotients. Apart from the more common (weighted) averages such as M_n and M_w (along with $Đ$), higher-order weighted averages, such as M_z, can be quantified and used to calculate higher-order distribution descriptors such as skewness or kurtosis.[86]

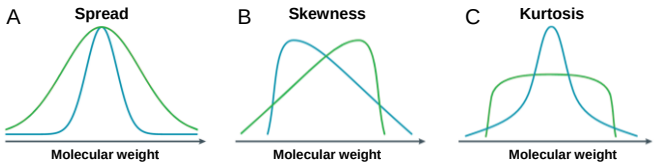

Figure 3. The fundamental shape characteristics of molecular weight distributions at their relative extremes.

These statistical descriptors depend necessarily on the reaction itself. Distribution of the product polymer can, in theory, be varied through control of reaction parameters. In the context of living chain-growth polymerisation, these would be varied through termination, propagation, and initiation. With tweaking the molecular weight distribution outcome of a living-type chain-growth polymerisation, a key consideration to keep in mind is whether other areas of controlled polymer synthesis (to be discussed later) are compromised or not.

RDRP offers a simple means of altering the termination, and the propagation, to control higher order molecular weight descriptors. This is because the inherent processes of RDRP methodologies involve some sort of rapid, reversible termination.

In ATRP particularly, the equilibrium underlying the propagation allows a clear quantitative means of tuning the dispersity (Equation 3).[87] In practice, this can be achieved by changing the relative amount of $CuBr_2$ in solution by either prior exogenous addition or by irradiation intensity in the case of photoATRP.[88]

$$Đ \approx 1 + \frac{1}{DP} + \left(\frac{[RBr]_0 k_p}{k_{deact}[CuBr_2]}\right)\left(\frac{2}{q} - 1\right) \quad (3)$$

In other RDRP methodologies, this is not as straightforward in a quantitative sense. In RAFT, it can be somewhat intuitive experimentally, because the chain transfer constant for a given polymerisation can be tuned by altering the thiocarbonylthio "Z-group" substituent, which indirectly tunes the dispersity of the polymer.[89,90] Alternatively, an irreversible termination of a pseudo/living polymerisation through the addition of exogenous quenchers can be used. In ATRP, the propagating species can be irreversibly quenched *via* nucleophilic substitution.[91] Similarly, adding a monomer that does not undergo homopolymerisation, as a retardant, can also influence the distrubution.[92]

The propagation itself can be altered *in situ*, for example, *via* continuous flow chemistry. The residence time of individual molecules during a polymerisation, be it in flow or in batch, is a critical determinant of the molecular weight. In flow chemistry, the residence time can be varied throughout the reaction mixture. For example, polymerisations demonstrated different residence time distributions depending on flow regime (laminar or plug flow) which translated to different molecular weight distributions.[93] In addition, the tube diameter was found to influence the molecular weight distribution of the product polymer.[93] When a temporal stimulus, (such as light) was incorporated in flow polymerisations, additional means to alter propagation *in situ* could be realised.[94]

Initiation can be altered during polymerisation. This is generally quite innocuous for controlled polymers synthesis given that this is a fleeting stage of living polymerisation. Performing the polymerisation under continuous flow or semi-batch allows for the rate of initiation to be tuned by the rate of initiator addition.[86,95–97]

Circumventing the need for optimising synthesis parameters, polymer blends tailor molecular weight distributions by superimposing a basis set of distributions.[98–100] A challenge in this space is minimising the size of basis distribution sets required to make specific distributions.

The molecular weight distribution of polymers has a profound effect on emergent, larger scale features, most specifically in self-assembly.[101–105] In biological self-assembly, heterogeneity of fatty acid chain length is known to promote vesicular membrane stability, replicability and permeability at high dilutions.[106,107] In industrial settings, plasticisers are a well-known means of artificially altering the molecular weight distribution to improve the processability commodity polymers.[108,109]

Throughout these examples, it is particularly fascinating that uniformity in the (macro)molecular scale does not always translate to uniformity on the bulk scale. In the past, this has often been a key assumption underpinning polymer self-assembly. This certainly complicates (and enrichens) the study of assembly of matter at various length scales.

Outlook on molecular weight distribution control

As methodologies to more complex molecular weight distributions are developed, so must the characterisation thereof. While relatively intuitive, the current suite of descriptors discussed are not ideal to describe increasingly complex distributions. There has been a further push to use standard deviation to quantify spread rather than dispersity. This is because it is more akin to what is used by the majority of the scientific community, and has a rather straightforward additive property (while dispersity does not), allowing for more seamless quantification of the molecular weight distribution of various architectures.[110] Dispersity was originally used to describe the Poisson-type distributions obtained in an ideal living polymerisation in which the spread scales inversely with degree of polymerisation.[39,111] With the advent of various polymerisation methodologies, the need for descriptors deriving from more complete ways model the molecular weight distribution becomes apparent. Ideally, these descriptors ought to have some sort of connection to kinetic factors which give rise to skewness or kurtosis.

All considerations of molecular weight distribution descriptors must come with the understanding that the distributions are typically generated with their own internal error arising from using SEC to generate them. These errors arise from three distinctly different sources, band broadening, baselining and non-universal calibration.[112] Band broadening arises because an injected sample will inevitably diffuse upon

elution through an SEC system,[113] thus generating a distribution with a greater spread and skewness than that of the true molecular weight distribution.

There are means to theoretically correct for this *via* deconvolution.[113,114] Picking the region from SEC data to use to calculate the molecular weight distribution can also be fraught with error. Massive deviations in the apparent spread of the molecular weight distribution can result from picking the baseline differently, be it algorithmically or through selection.[115,116] Even if band broadening and baselining is corrected, SEC fundamentally yields a relative molecular weight distribution, which is often not reflective of polymers of increasing complexity.[116–118]

There are however promising efforts towards using diffusion NMR to alleviate the issues of calibration in SEC.[119,120] While this is good for measuring molecular weight, it is still yet to be developed for higher-order moments and the distribution as a whole. The dispersity can also be measured from diffusion NMR where an isolated signal for end groups is currently required, in the case of polydisperse samples.[121]

Assuming quantitative distribution measures are well-established, another challenge associated with higher order distribution control will be that of automation. This is analogous to how automation is increasingly involved in molecular weight control mentioned earlier. However, another layer of complexity is introduced when polymer blends are used to create custom distributions. This simply concerns the minimum number of different polymer samples required to such distribution. Machine learning techniques are going to be invaluable in this space.

2. End group chemistry

The "livingness" of a chain-growth polymerisation depends on the integrity of the end group chemistry. Conversely, the control of initiating and terminating species enables controlling the α-end group and the ω-end group of the polymer. Thus, end groups can serve as a key bridge between small-molecule chemistry and macromolecular chemistry.

Complex end group chemistry can be addressed at various stages of a polymer synthesis, that is prior to, during or after (*i.e.* post) polymerisation. Figure 4 highlights successful strategies to establish end group diversity to great effect.

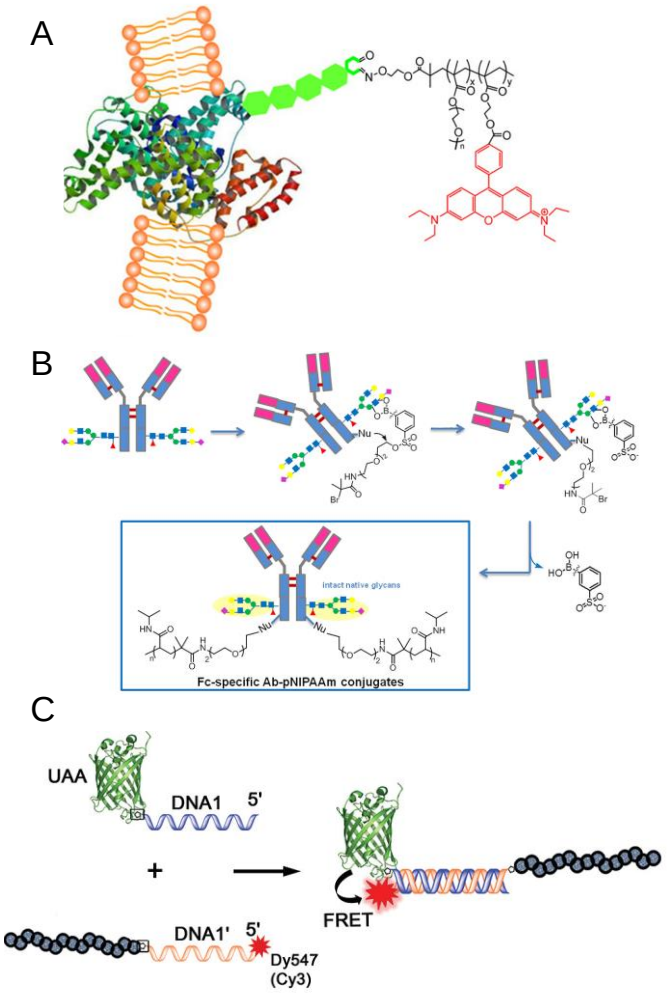

Figure 4. Highlights of biomolecular conjugation through precise control of end group chemistry, including membrane-bound glycoproteins (A), antibodies (B) and nucleotides (C), adapted with permission from Bi *et al.* Copyright 2021 American Chemical Society, Chou *et al.* Copyright 2018 American Chemical Society and Averick *et al.* Copyright 2012 American Chemical Society, respectively.[122–124]

Several initiating species/mediators in living-type polymerisations react chemoselectively to allow incorporating a vast scope of end group functionality. In thermal RAFT polymerisation, the α-end group is often mixed with the initiating species and the "R-group", with variations existing to keep the α-end group specific to the "R-group". Additional scope is added through the ω-end group *via* the thiocarbonylthio derivative (defined by the "Z-group") in RAFT polymerisation.[125,126] The end groups of ATRP are more straightforward. In ATRP, both end groups are contained within one small-molecular alkyl bromide. ATRP can allow for a practically greater variety of α-end group functionality than many living-type polymerisation processes.[127–129] This is due to the stability of alkyl bromides due to the, at times, opposing reactivity of alkyl bromides in a dipolar and a radical reaction. In ROMP, the tuned chemoselectivity of metal-alkylidene

reactivity can also translate into a wide scope of usable end-group chemistry during the polymerisation.

Since living-type polymerisations are terminated by pre-determined species, the reactive species (end group) can be modified during the polymerisation, that is prior to termination. Specifically, this typically involves adding the final monomer unit as a single addition. In RDRP polymerisations, there are examples of monomers which undergo radical addition but their corresponding radical does not continue polymerisation.[130] Depending on the living-type polymerisation, other avenues include varying the exogenous terminating species itself, such as a nucleophile in cationic polymerisation, an electrophile in anionic polymerisation, or a π-donor in ROMP.[131–133]

Deliberately terminated polymers may still be used post-polymerisation modifications. There have been many developments in incorporating functionality onto either end group to generate hetero telechelics. Such post-polymerisation chemistry has mostly been explored in RDRP systems. With the example of RAFT end groups, the thiocarbonylthio functionality is generally available for a variety of chemoselective transformations. These become apparent when considering the thiocarbonylthio as an electrophilic carbon analogous to a carbonyl, a "dieneophile" available for hetero-[4+2] cycloadditions, or as a site for radical chain transfer (**Figure 5A**).[130,134–137] The ω-end group chemistry of ATRP mostly involves the nucleophilicity of the alkyl bromide (**Figure 5B**).[138]

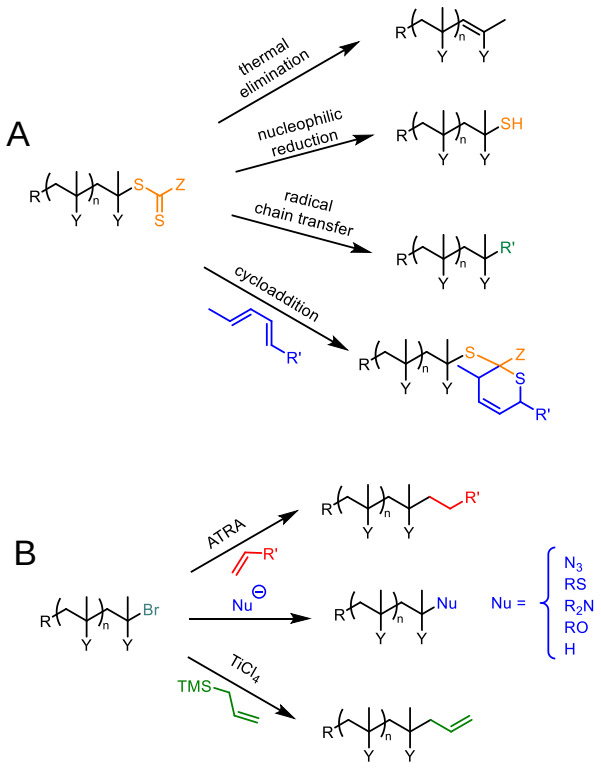

Figure 5. Examples of post-polymerisation end group modifications of (A) RAFT- and (B) ATRP-made polymers.

Understanding the post-polymerisation chemistry of end groups remains a promising theme of extrapolating and applying knowledge from small-molecular processes. With caution, this methodology can be broadly applied.[1,139]

Various conjugation reactions are further possible due to the chemoselective incorporation of well-defined end groups. This allows for the interfacing of polymers with complex (macro)molecules or surfaces – irrespective of whether chains are grown from a substrate (a divergent approach) or conjugated post-polymerisation (a convergent approach). Biomacromolecular polymer hybrids (as the most notable example of conjugation with complex molecules) allow the specificity of biomacromolecules (such as lipids, nucleotides, proteins/peptides or sugars) to be combined with the stability and predictable self-assembly of polymers.[140] Grafting polymer brushes onto surfaces allows for a modular tuning of its properties such as sorption properties, conductivity, surface structure and surface energy.[141–147]

A natural use of end group variety in polymer synthesis is in conjugation chemistry, where the physical properties of polymers can enhance those of the small-molecule conjugate in the desired application (**Figure 4**).[148] The opposite can also be considered in applications, namely how end groups affect polymers. While end groups generally only form a small component of a polymer, there are occasions where even the bulk, emergent features of polymers can be affected by such small components. The mobility of polymer end units is significantly greater than that of the backbone and thus can be most critical.[2] Silver nanoparticle morphology was found to vary by the end groups of the precursor poly(vinyl pyrrolidone) (M_w = 10-350 kg mol^{-1}) as much as molecular weight and concentration thereof.[149] The effects of end groups have even been captured in molecular dynamics simulations whereby polymer-silica nanocomposite melts varied appreciably in dynamics due to end group differences.[150]

The degradability of polymers also depends on end-group structure. Even though the backbone functionality dictates the thermodynamics of depolymerisation/degradation for a given polymer class, end group chemistry can alter the kinetics. It is this property that allowed for tuning the depolymerisation profile.[151] To this end, progress in the synthesis of degradable polymers to undergo depolymerisation spontaneously or *via* an external trigger (self-immolative polymers) is emerging.[152,153] Similarly, progress towards controlling end group chemistry to offer a lower-temperature degradation has been made.[154–156]

Outlook on end group chemistry

Given the at times dramatic effects that end groups can have on small-to-medium polymers, it may be interesting to consider such polymers akin to copolymers. A library (or a statistical mixture) of homopolymers in the relevant size regime could be simply constructed by alterations of the end group.

Degradable polymers are of increasing importance to which well-defined and well-understood end group chemistry can make great impact. While the main approach towards degradable polymers focusses on the backbone chemistry, end group chemistry may hold the key to kinetics (and overall feasibility) of depolymerisation processes. Investigating this topic further in the context commodity polymers may be valuable as it would allow altering end-of-life degradability, while leaving the overall bulk properties of the polymer untouched.

3. Architecture/Topology

Robust end group chemistry is a key determinant of a successful living polymerisation. Living polymerisation depends largely on the fidelity of the initiator functionality, reflecting in very well-defined end groups. The chain extension therefore depends on the fidelity of the ω-end group. The ability to grow and extend chains of defined molecular weight and end groups serves as the fundamental transformation toward the synthesis of polymer architectures. Complex architectures can often be conceived as a construct of linear polymers with various topologies. These include cyclic polymers, single-chain nanoparticles, stars, molecular polymer bottlebrushes (MPBs) and hyper-branched polymers (**Figure 6**).[157–161]

Intramolecularly cross-linking a linear polymer chain results in coils which are more compacted than their linear counterpart and generally do not entangle with each other as much in bulk. Cross-linking polymers intermolecularly in an ordered fashion in 3D space yields a polymer network. The addition of polymer chains either on a central point or along another polymer chain yields a star or a MPB. Finally, chains can be arranged in a fractal-like manner in a single step, yielding a hyper-branched polymer.

The classic example for the effect of polymer architecture on properties would be low-density and high-density polyethylene (LDPE and HDPE). Altering the topology renders PE suitable for use either as plastic bags or as pipes. In general, polymer architecture is a feature at the interface of local chemical structure and bulk emergent properties. This is somewhat intuitive given that bulk polymer physics depends on the mobility (or lack thereof) of the canonical linear polymer chain. Importantly, various architectures can begin to exhibit emergent, nanoparticular properties as a single macromolecule, prior to any self-assembly. This is most clearly demonstrated in the revisited example of the molecular polymer bottlebrush whereby polymeric sidechains are covalently “assembled” along a single axis, akin to a cylindrical self-assembly. In this way, MPBs have both macromolecular and nanoparticular characteristics which can be tuned for the specific applications.[162,163]

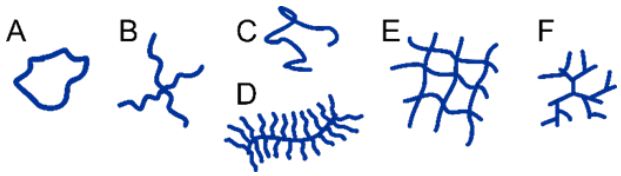

Figure 6. Examples of various distinct architectures yielded upon topologically rearranging the canonical linear architecture (C) into (A) cyclic, (B) star-like, (D) brush-like, (E) network-like and (F) hyperbranched polymers.

The architectural complexity of organic polymers can be imparted onto bulk (in)organic materials, namely in the field of hybrid materials. Architecturally controlled polymers can also find biological application. Although many biological macromolecules are linear in the first instance (especially prior to folding), there are a few exceptions, such as branched proteins (such as the TRAIL protein), oligomeric proteins, antibodies, glycans and some proteoglycans (such as lubricin), where their non-trivial architectural features lend themselves to interesting physiochemical properties such as water retention, lubrication, polyvalency, and specific binding. Chemists have sought to both replicate and interact with them using synthetic macromolecules.[164–166]

Single chain-growth polymerisation reactions can also yield architectural features by transfer processes, be they intramolecular or intermolecular (such as branching or cross-linking). These can be ‘controlled’ towards assembling architectures in one-pot, for example in a free radical polymerisations.[167]

There has also been research concerning how to install reversible bonds in the branching points of various architectures such as molecular polymer brushes or stars.[168–170] This is interesting because it serves as a rare case of discontinuous change in polymer structure at the molecular level.

Outlook on polymer architectures

The primary challenge concerning the synthesis of architecturally unique polymers lies in orthogonal reactions. As polymer architectures become increasingly complex, the chemoselectivity demands of both polymerisation and post-polymerisation reactions become more stringent. Stepwise post-polymerisation methodologies have served as a powerful means of avoiding orthogonality issues towards either installing new end groups for further polymerisations, cross-linking existing chains (effectively closing cycles), or to attach new polymer chains.[171–173] Furthermore, developments in polymerisations driven by a variety of stimuli offer means of chemoselective chain-growth reactions.[174]

Along with synthetic challenges, more consistent characterisation of polymer architectures is required. It remains that standard uses of NMR, SEC and MS (which, in concert, are suitable for homopolymers) are simply inadequate to completely confirm the synthesis and uniformity of the diverse set of architectures discussed herein. Various other characterisation techniques, mostly scattering techniques,

have been incredibly useful in not only providing evidence for specific architectures but also in quantification of macromolecular-scale features.[175,176] A promising advance is also in the combination or extension of the standard characterisation techniques, such as GPC-MS, two-dimensional chromatography systems (*e.g.,* ICCC-GPC) or ion-mobility mass spectrometry (IM-MS).[177–181] These are particularly promising because of their ability to distinguish various architectural outcomes, desired or undesired, allowing "architectural purity" to be, at best, semi-quantitatively determined. While microscopy techniques can provide vivid, apparent visual evidence of architectures, it is generally not an ensemble technique.

4. Chain composition

As alluded to in previous sections, the mechanistic aspects of a polymerisation, and the downstream effects on various aspects of controlled polymer synthesis depend strongly on the chemistry of the corresponding monomer/s (*e.g.,* the corresponding alkene for polyethylene derivatives). Therefore, the converse can also be true, in that for a given backbone composition, there are distinct limitations on the monomer structure. These limitations are largely marked by chemoselectivity and reactivity patterns inherent to the polymerisation. An example of this would be *ansa*-metallocene catalysed polymerisation being mostly suitable for non-polar, inactivated olefins while, on the contrary, radical polymerisation being more suitable for polar, electron-deficient (and some electron-rich) alkenes.[41,182]

An interesting means to expanding the chain composition scope of reactions has recently been to translate analogous processes of one polymerisation into another methodology. The most prominent example of this is in radical ring-opening polymerisation (rROP).[183] The developments around this methodology allow for the introduction of heteroatoms in the polymer backbone during radical polymerisation process. Analogous results can also be achieved in ionic polymerisations.[184]

Another means of expanding chain composition control beyond the scope normally afforded by a single methodology is to combine various others (see Section 1). Through developments in reactions driven by new stimuli, interchanging between different modes of reactivity is now possible.[185] With such combination of methodologies, new backbone compositions become accessible. Examples of this include a combination of radical addition polymerisation with cationic addition polymerisation, and ROMP with cationic addition polymerisation.[186–188] The major limiting factor of these examples is simultaneously maintaining control of the molecular weight distribution while making novel combinations of backbone functionality.

Despite their limitations, developments in the various polymerisation methodologies discussed herein have led to great achievements in composition and architecture of polymers through relatively simple monomeric building blocks.[125,189]

The limits of this are quickly apparent when considering that the backbone functionality obtained from a polymerisation depends strongly on the reactivity of the corresponding monomer. One can easily imagine such scenarios where the corresponding monomer is simply incompatible with any polymerisation methodology. The most famous example is poly(vinyl alcohol), which is synthesised *via* poly(vinyl acetate).[40]

In biological macromolecules, complex functionality is often obtained through a divergent synthesis involving both canonical building blocks and post-synthetic modifications. Analogously, post-polymerisation functionalisation is a means of installing equally rich functionality on synthetic polymers – both as end groups and the backbone.

Research in post-polymerisation backbone modification has garnered interest in the area of commodity polymers to establish an open loop recycling regime.[190] This has mostly centred around exploiting the C-H lability of polymers generally thought of as relatively inert. Even one of the most seemingly inert polymer class in mass production, saturated polyolefins, can be functionalised due to their relatively accessible C-H bond dissociation energy. Indeed, many reports on using either highly reactive single electron (radical) or two electron (carbene/nitrene) species to perform C-H functionalisation on even saturated polyolefins have demonstrated this.[191–193] Commodity polymers with even more labile C-H bonds can also be functionalised.[190,194,195]

The monomer unit scope of polymerisations can be extended post-polymerisation, pseudo-living polymerisations being no exception.[196–198] Clear effects on the self-assembly of controlled polymers from post-polymerisation modifications (particularly of key backbone bonds) have been observed. Through such a radical change in the interaction parameter χ of the backbone, one can drastically reduce the Kuhn length of self-assemblies, correspondingly shrinking the requisite lengths of polymer blocks to achieve self-assembly. Single-digit nanometre feature sizes were obtained through a post-polymerisation full hydrogenation of polystyrene prior to chain extension.[199] The synthesis of controlled architectures generally depends on the orthogonality of various transformations. A combination of polymerisation and post-polymerisation reactions has been used in this space, such as synthesising molecular polymer brushes through successive RDRP steps.[172]

Outlook on backbone composition control *via* post-polymerisation modification

With developments in post-polymerisation methodologies, a key determinant of utility will be whether new monomeric units can be polymerised as is or not. While post-polymerisation reactions can be operationally simple, synthesis of the monomeric unit by small molecule chemistry guarantees a uniform composition. In small-molecule synthesis, incomplete conversion simply translates to diminished product yield, and the starting material can often be removed. In polymer synthesis, incomplete conversion

translates to copolymer composition (of starting and product monomeric unit) of the product, creating whole new library of products; this is without mentioning side-reactions that may occur upon full conversion.[200] The question of differences in reactivity between macromolecules and small-molecules presents itself again.[1,200]

5. Sequence

Even through optimising polymer synthesis around the various parameters discussed so far, one can still obtain a whole library of polymers even in an otherwise uniform sample. For example, in a copolymerisation of two monomers of identical reactivity, with every chain exactly DP=100, one can theoretically sample 2^{100} unique products (assuming monomeric units are ordered by end groups). This is already more than multigram-scale synthesis can possibly sample and features more information entropy than many passwords used today.

The presence of multiple blocks of different functionality leads to an interplay of various interactions/forces, yielding self-assembled structures, either in bulk or solution.[201] One can theoretically imagine narrowing the spatial resolution of these different blocks down to the level of the individual monomer unit. This can cause said interplay of forces to yield a self-assembly of a single molecule, *i.e.* folding. In other words, as the heterogeneous block length scales diminish, the Kuhn length of the subsequent assembly reduces. As with various polymer architectures discussed earlier, the folding of sequence-defined polymers presents another way in which molecular-scale precision leads to defined emergent properties in a single molecule.[202]

There has been progress in utilising the concepts of living polymerisation to yield multiblock polymers at diminishing length scales.[203,204] Through careful reaction design, sequential single unit additions (without further oligomerisation) can be achieved with RDRP, termed SUMI.[205–207] Fascinating differences between single addition methodologies and the pseudo-living polymerisation analogue have been observed,[207–211] including the fact that the monomers are in large excess of the initiator, and that there are distinct possibilities for charge transfer complex formation between different monomers in a copolymerisation.

While sequence control has been discussed here so far from the point of view of living polymerisation (essentially of infinitesimally small blocks), one certainly is not limited to such methodologies to sequentially install monomeric units. The only prerequisite for sequence controlling methodologies is simply that they are high-yielding and robust reactions. In fact, living polymerisation analogues are not often used to assemble sequence-defined macromolecules.[212] The classic examples of this are syntheses not typically associated with polymer chemistry, namely, that of peptides and nucleotides.[213,214]

In order to synthesise polymers with a greater variety of main chain compositions, numerous such high-yielding/robust reactions have been applied in this space. Generally, there are two overall synthetic strategies to construct increasingly large, sequence-defined polymers from such reactions. These are termed iterative sequential growth (ISG) and iterative exponential growth (IEG) (**Figure 7**). While on palindromic sequences are generated in the latter but are synthesised in exponentially fewer steps.[215,216]

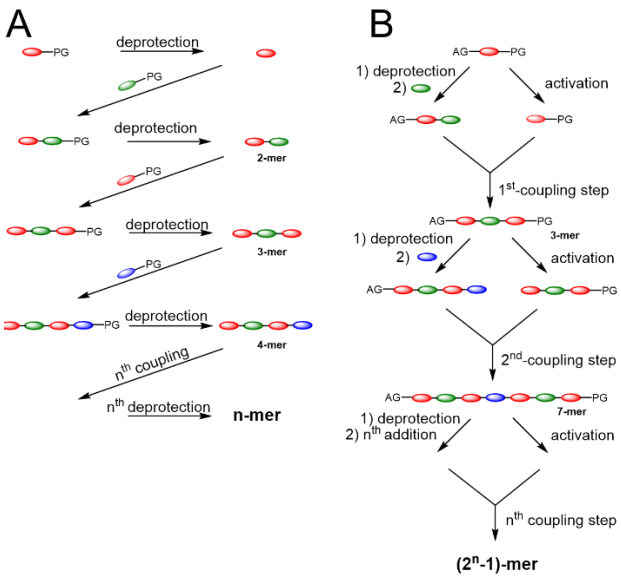

Figure 7. Stepwise methods to achieve sequence-defined, aperiodic polymers by either (A) iterative sequential growth or (B) iterative exponential growth.

Some synthesis strategies toward sequence-defined polymers have also drawn inspiration from biological systems. In general, these approaches use some form of templating by a prior sequence-defined macromolecule, either of the entire backbone or of monomers, to minimise the number of steps to obtain sequence selectivity.[217–219] Even relatively simple polymers can be incredibly information dense. As such, research groups investigated their use as "macromolecular codes" (**Figure 8**).[220–222] In order to characterise the sequences of polymers, making such hypothetical cyphers useable, tandem mass spectrometry (MS/MS) is often critical.[223,224] Because of this, there currently seems to be a trade-off between backbone stability and decipherability of macromolecular codes. The gold standard remains to be proteins and polynucleotides. While these are often feature labile backbones (due to heteroatom density), current synthesis and characterisation techniques still renders these as the ideal macromolecular codes.[225,226]

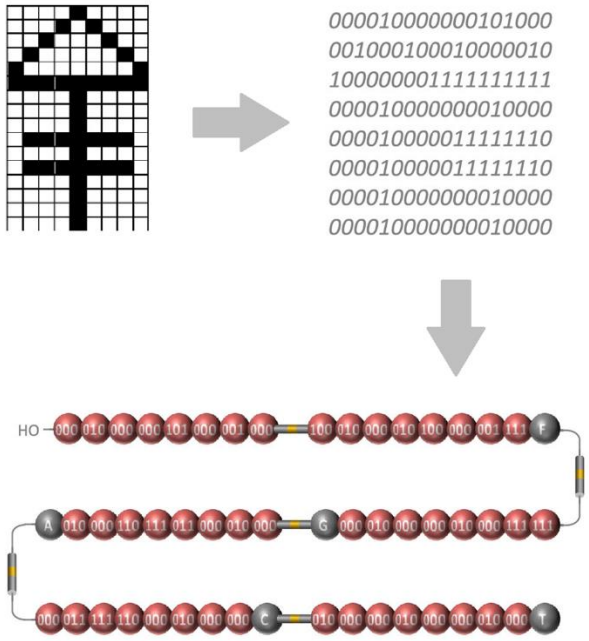

Figure 8. Example application of sequence-defined, aperiodic polymers used as a "macromolecular code", such as an image which is translated into an *n*-base string which can then be made and read from a sequence-defined polymer. Adapted with permission from Laurent *et al.*[220] Copyright 2020 American Chemical Society.

This section has mostly focussed on sequential reactions yielding sequence-defined polymers. However, single copolymerisation reactions can have distinct sequential outcomes in the form of sequence-controlled polymers due to the reactivity ratio (from the Mayo-Lewis equation) of the various monomers. Further studies towards relating this empirical measure to the exact chemistry of the system has been significant in understanding the inherent sequence control of copolymerisations.[227] This can also give researchers clues about single addition reactions.[228] However, the kinetic parameters in the Mayo-Lewis equation assume no penultimate unit effects which are known to be prominent in various systems.[229,230] This is also an example of where developments in polymer chemistry can inform organic chemistry.

Outlook on sequence control

The primary challenge of the synthesis of generic sequence-controlled polymers, particularly those fitting in the subset of aperiodic polymers, is making appreciable quantities of pure material. Most, if not all, methodologies discussed in this section require multiple steps to synthesise the specific polymer which exponentially reduces the possible yield of such polymer. When considering the extent of fractionation required to obtain a pure material and maintaining an efficient process becomes almost untenable. After all, side products that are generated in single additions (such as end group decomposition, undesired double addition *etc*) are also generated in the analogous living polymerisation.

There is, therefore, a limit in the molecular weight of sequence-defined polymers that can be accessed through essentially undertaking a total synthesis. Using a single polymerisation reaction to circumvent this problem naturally diminishes the possibility for perfect sequence control. Even with exact knowledge of monomer addition kinetics, the statistics involved with each monomer placement establishes a complementarity between molecular weight control and exact sequence control.[231]

Even with these difficulties resolved, it remains hard to assess the future direction of sequence-defined polymers given the sheer expanse of possibilities. This is with the consideration that in current commonly occurring systems, only a small subset of combinations of a very simple set of canonical monomers yield materials of known use.[232] Furthermore, there is no guarantee that unique sequences will exhibit a unique fold, especially without cross-linking.[223] It is therefore imperative to begin to establish folding rules for the near-endless variety of backbones that may be assembled in a sequence-controlled manner in the future.[233]

The most useful, albeit ambitious, development in sequence-defined polymer synthesis would be to borrow from technologies in chemical biology towards a sort of sequence replicator, or sequence amplification methodology, akin to polymerase chain reaction (PCR). While not directly analogous to PCR, there has indeed been progress in using a templating approach for larger scale sequence-controlled polymers.[218] One development that would make methodologies towards this idea more efficient would be some sort of controlled depolymerisation along with sequence amplification to promote a sequence selection. Borrowing further from the bottom-up synthetic biology field, there is an increasing diversity of macromolecules which are compatible with translation and transcription, key processes in the biosynthesis of sequence-defined polymers.[234,235] Polymers, in general, can prove an interesting contribution in this space due to the possibility of a more hydrolytically stable backbone. This obviously, would come with the penalty that characterising the backbone by MS/MS (which is currently the primary workhorse) may become increasingly difficult.

To this end, another important development in sequence-defined, aperiodic polymer synthesis is in its characterisation. There is a seeming trade-off between sequence readability and backbone stability. Finding other sequence-dependent characterisations (other than tandem mass spectrometry), even *via* indirect means, would prove a major advance in overcoming this trade-off.

6. Tacticity

Even in the homopolymerisation of prochiral monomers, one can still obtain a mixture of macromolecular products, with each product differing by stereochemical sequence, namely, tacticity.

The most important success in tacticity control also sets up its greatest challenge. The *ansa*-metallocene catalysed coordination-addition polymerisation of non-polar monomers serves as the gold standard for stereoselective addition polymerisations. It is deemed as such by important factors such as the *a priori* determination of product tacticity, the extent of stereoselectivity and the scalability of the process.[236–238] The metal catalysts used in this process, however, such as titanocenes and zirconocenes, are highly sensitive to Lewis-basic functional groups, limiting the compositional diversity of the product polymer.[182]

Therefore, the key challenge in stereoselective addition polymerisations has been the tacticity control of polymers with Lewis-basic monomeric units; these comprise most of the monomers in addition polymerisation.[239] The geometry of propagating intermediates of various addition polymerisation mechanisms also demonstrates the challenge underlying tacticity control. The anionic polymerisation of prochiral monomers propagates as a racemate of trigonal pyramidal, chiral carbanions which lends itself to more straightforward means of achieving tacticity control (**Figure 9**).[239,240] However, cationic and radical polymerisations of prochiral monomers propagate as trigonal planar, prochiral species, and therefore contain no inherent stereochemical information until each subsequent monomer addition step.[239]

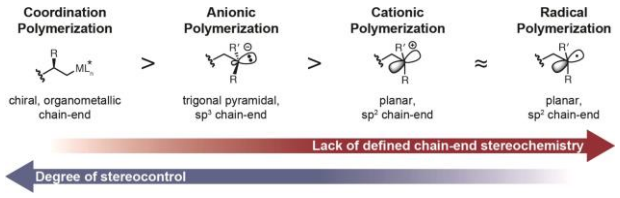

Figure 9. Various propagating functionalities of "living-like" polymerisations arranged in degree of chain-end stereochemical information. Adapted with permission from Teator *et al.*[241] Copyright 2020 American Chemical Society.

A particularly powerful means of generating stereoselectivity, in both small-molecule and polymer synthesis, is the formation of cyclic transition states or intermediates.[239,242,243] It is well known in small-molecule synthesis that these are particularly suited towards driving stereochemical or stereoelectronic differences in the various possible transition states. Developments in stereoselective cationic or radical polymerisation therefore revolve around the aforementioned means (with a pre-determined steric or stereoelectronic bias) often utilising non-covalent interactions with the Lewis basic monomeric units and some exogenous species.[244,245] The challenge in radical polymerisation is, however, that there are limited non-covalent interactions that the propagating species itself can be involved in.[242]

Another use of non-covalent effects to drive the formation of increasingly isotactic (and enantiopure) polymers would be *via* the well-known "sergeants and soldiers" and "majority rules" effects.[246,247]

Concluding Remarks

In summary, there have been incredible developments towards using our ever-expanding knowledge of organic chemistry, particularly radical chemistry, towards the increasingly controlled synthesis of polymers in regard to its various parameters. These developments have been impactful in both pure and applied science, and we anticipate will continue to be a fascinating area of research.

While it may seem that progress in polymer synthesis is therefore simply a matter of refining organic chemistry in this space, polymer chemists are truly in a unique position. The synthesis of polymers sits at an interface between molecular level specificity and statistical properties. In fact, a synthesis between the two ideas is evident given one is an emergent property of the other. It is, therefore, imperative that developments in controlled polymer synthesis do not focus on one side of this interface at the expense of the other.

Indeed, as mentioned earlier, this sets up a contradiction inherent to controlled polymer synthesis. It is important to emphasise that one cannot practically control every aspect of polymer synthesis at every size regime, let alone characterise such materials.[248] It must, therefore, be the application that dictates which aspect is focused on, sometimes at the expense of another. As molecular weight increases, and nanoscale features become more important than molecular-level features, molecular-level structural "defects" (arising from side-reactions on the molecular level) become unavoidable. Furthermore, macro-scale features which are sought after in an application may even be independent of such "defects", namely, if these features exhibit causal emergence.[249]

While synthesis was focused on here, the implementation of new characterisation methods for controlled polymers must keep pace with synthetic developments. The most important strides in this space can be made by techniques which can simultaneously characterise the local chemistry and ensemble properties of polymers. As mentioned previously, there has been great progress towards this end.

Conflicts of interest

There are no conflicts to declare.

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