

# 100th Anniversary of Macromolecular Science Viewpoint: Opportunities in the Physics of Sequence-Defined Polymers

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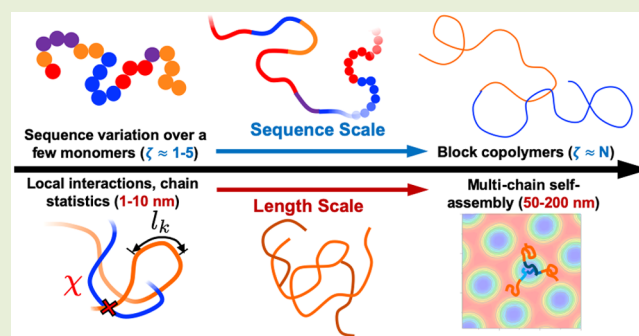
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**ABSTRACT:** Polymer science has been driven by ever-increasing molecular complexity, as polymer synthesis expands an already-vast palette of chemical and architectural parameter space. Copolymers represent a key example, where simple homopolymers have given rise to random, alternating, gradient, and block copolymers. Polymer physics has provided the insight needed to explore this monomer sequence parameter space. The future of polymer science, however, must contend with further increases in monomer precision, as this class of macromolecules moves ever closer to the sequence-monodisperse polymers that are the workhorses of biology. The advent of sequence-defined polymers gives rise to opportunities for material design, with increasing levels of chemical information being incorporated into long-chain molecules; however, this also raises questions that polymer physics must address. What properties uniquely emerge from sequence-definition? Is this circumstance-dependent? How do we define and think about sequence dispersity? How do we think about a hierarchy of sequence effects? Are more sophisticated characterization methods, as well as theoretical and computational tools, needed to understand this class of macromolecules? The answers to these questions touch on many difficult scientific challenges, setting the stage for a rich future for sequence-defined polymers in polymer physics.



Polymers are sequence-defined when the precise pattern of monomers is the same for all of a set or subset of molecules,<sup>1,2</sup> going beyond sequence-controlled polymers with merely statistical monomer patterns.<sup>3</sup> Truly sequence-defined polymers remain an elusive goal for polymer chemists; sequence-definition implies a level of synthetic control<sup>4</sup> only achievable in a few cases outside the realm of biology and, even then, with limitations on chain length or the amount of material.<sup>4–7</sup> However, motivated by the ubiquity and importance of sequence-defined macromolecules in biological systems, the goal of sequence-definition is being increasingly realized,<sup>4–13</sup> and the boundaries of polymer chemistry are being pushed ever further from the simple copolymers that have dominated polymer science for the past 100 years. We still have alternating, random, blocky, and gradient copolymers;<sup>14,15</sup> however, it is realistic now to imagine synthetic polymers that must be described by the specific sequence of monomer units rather than a few statistical parameters (i.e., monomer fraction, reactivity ratios, block length, etc.).

The focus of this Viewpoint is to highlight the immense challenges in translating synthetic advances in sequence control into new materials, though we refer the reader elsewhere for details on the synthetic techniques.<sup>4–6,8–13</sup> Realized applications of sequence-defined polymers have focused on, for example, information storage,<sup>16</sup> relying on the ordering of monomers as covalently dictated by the chemist, or as tunable

biomaterials<sup>17</sup> specifically designed to penetrate cells,<sup>18</sup> interact with receptors,<sup>19</sup> or undergo programmed degradation.<sup>20</sup> These ideas stem from innumerable examples of sequence-defined biomacromolecules that assemble into complicated and hierarchical structures.<sup>6</sup> It is these secondary and higher-order structures and their behavior in the presence of other similarly complicated biomacromolecules that are driven by physical phenomena that lead to biological function. These examples from the biological world hint at the potential for using polymer sequence as a tool for the molecular engineering of soft materials. However, the disparity in the types of synthetic materials that can be designed today, as compared to the elegance of biology, highlights the urgent need for polymer physics to begin to bridge the gap between chemical information and soft material properties.

Polymer physics has a role to play in addressing this grand challenge; this community has the tools to ask and address many questions about sequence-defined polymers. How do we

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understand, measure, and develop theories to predict their properties? Also, what do we ultimately want to do with sequence-defined polymers?

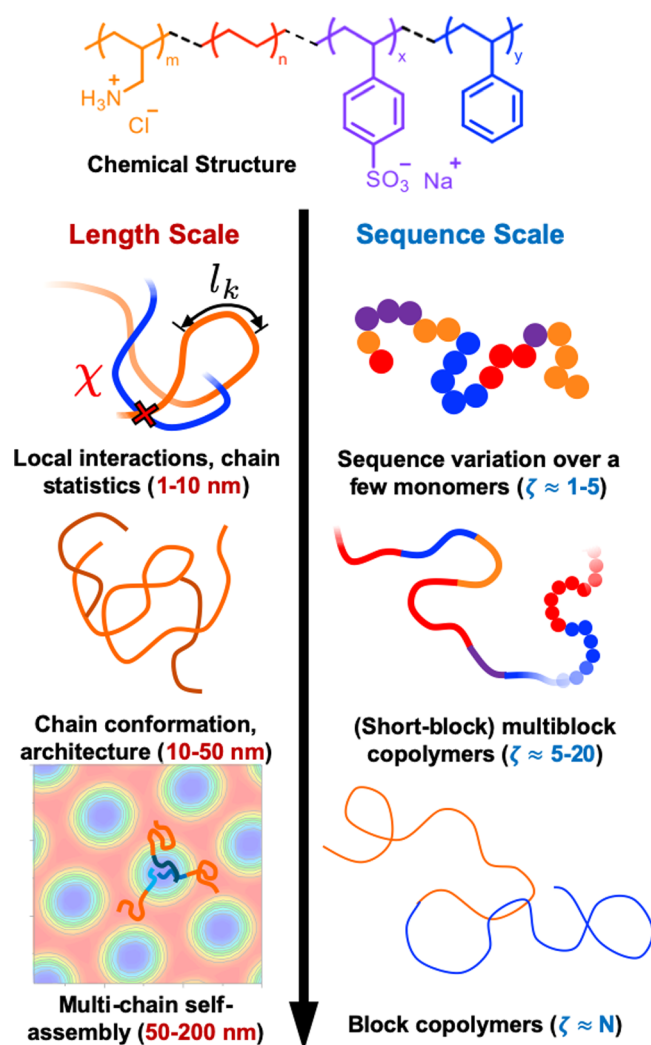
### Sequence-defined polymers: Beyond biomacromolecules.

In asking these questions, it is important to clarify distinctions and similarities between fields in close proximity. Biophysics, especially, shares an interest in sequence-defined polymers via information storage and folded structures in DNA,<sup>21,22</sup> RNA,<sup>23,24</sup> and proteins.<sup>25–27</sup> Protein folding, in particular, has shared a historic lineage with polymer physics, but has tended to focus on different types of systems.<sup>25</sup> We suggest an arbitrary but useful distinction: protein folding is primarily concerned with specific biological systems and a small number of well-defined, folded, low-energy states.<sup>25–28</sup> In contrast, work in sequence-defined polymers is (i) interested in an expanded palette of nonbiological monomers, (ii) consists of polymer chains that sample a broad continuum of molecular conformations, and (iii) seeks to establish design rules for building materials instead of affecting biophysical processes. This distinction is intended to be fluid and not mutually exclusive (e.g., in the case of intrinsically disordered proteins, IDPs);<sup>29,30</sup> however, it remains a useful reminder that viewing sequence-defined polymers through a polymer physics lens provides new perspectives, even as we look to this neighboring discipline for tools and inspiration.

**Sequence versus spatial length scales.** The central paradigm of soft matter physics is the importance of length scales and energy scales in determining physical properties.<sup>15,31</sup> Equilibrium structure in soft materials arises from the coupling between these two characteristics, often leading to the formation of a hierarchy of length scales due to the competition between important molecular interactions. For example, the self-assembled structure of melt block copolymers<sup>32,33</sup> is dictated by the length scales set by the chain contour and the energy scales determined by the immiscible blocks, with subtle competitions among these length and energy scales resulting in a wide array of observed morphologies.<sup>32,34–36</sup>

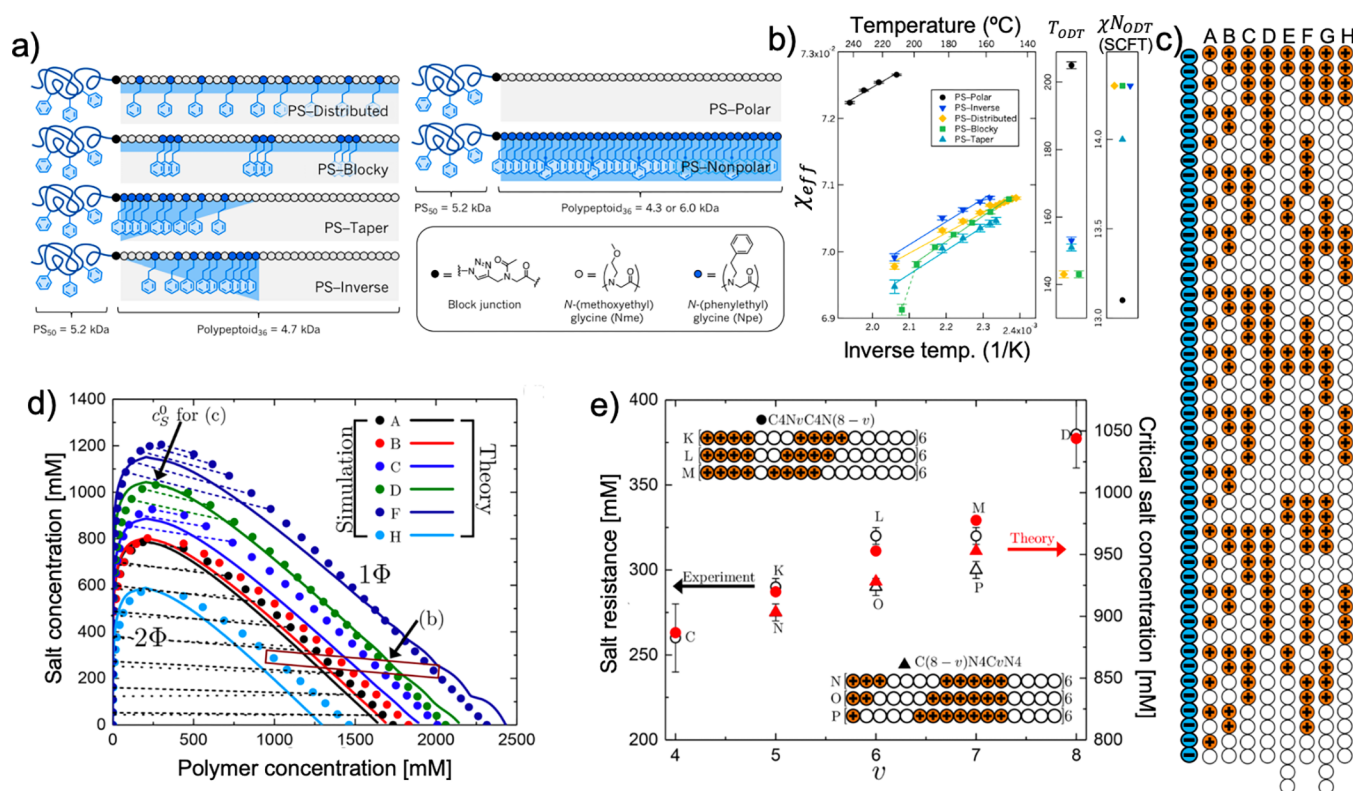
In Figure 1 we illustrate a spectrum of spatial length scales typically important for polymer systems: (i) atomistic structure is foundational to the chemical features and interactions in polymer systems; however, these are often coarse-grained to (ii) chain parameters ( $\chi$  parameters<sup>37–43</sup> and Kuhn length<sup>44–46</sup>) that describe an otherwise featureless polymer chain.<sup>15</sup> (iii) Local chain conformations and architectural features give rise to overall chain dimensions,<sup>47,48</sup> and via (iv) interchain interactions, lead to self-assembled morphologies such as block copolymers.<sup>33,49,50</sup> Much of polymer physics revolves around understanding and manipulating these length scales, with a particular focus on universal properties at (or larger than) the chain conformational length scales.<sup>31</sup> This stems from a desire to understand a wide range of different polymer chemistries with a minimal set of parameters rather than needing to consider the specific chemistries involved in any polymer chain.

This approach of polymer physics, centering on this hierarchy of length scales, has been remarkably successful; yet, the physics of sequence-defined polymers suggests the presence of another, related hierarchy that, in this Viewpoint, we call the sequence-scale  $\zeta$ . We consider the sequence scale of a sequence-defined polymer to be a characteristic number of monomers along the contour over which the variation of monomer types occurs, in the spirit of blockiness parameters used in the copolymer literature.<sup>51</sup> We suggest  $\zeta$  as an illustrative concept rather than a rigorously defined quantity; for example, an alternating copolymer would have a sequence scale  $\zeta \sim O(1)$ , while for a



**Figure 1.** Length vs sequence scales. In traditional polymer physics, chemical structure gives rise to a hierarchy of increasingly large length scale effects; first, the persistence length  $l_k$  and local interactions  $\chi$  that parametrize chemical structure, affect the overall chain conformation and architecture. Self-assembled structure can therefore arise from multiple, interacting chains. With sequence precision, we suggest a concomitant hierarchy of sequence scales related to the number of monomers involved in the variation of monomer identity. This ranges from variation only over a few monomers (small  $\zeta$ ) to full block copolymers (large  $\zeta$ ).

diblock copolymer,  $\zeta \sim O(N)$  (where  $N$  is the degree of polymerization). The nascent field of sequence-defined polymer physics is just beginning to reckon with the  $\zeta$  hierarchy, which we also illustrate in Figure 1, with a direct comparison to the length-scale hierarchy. At the level of atomistic resolution  $\zeta \sim 1$ , the identity and structure of a given monomer are jointly defined. With increasing  $\zeta \approx 1-5$ , the sequence scale is on the order of a few monomers and couples, for example, to the Kuhn segment orientation. Larger values of  $\zeta \approx 5-20$  begin to exhibit behaviors associated with “multiblock” copolymers, affecting the local chain conformation or chain–chain interactions. Finally,  $\zeta \sim N$  represents the block copolymer limit, where sequence variations drive self-assembly into microphase-separated structures.



**Figure 2.** Physical effects from subtle sequence variation. (a) The inclusion of nonpolar monomers into a diblock copolymer can be performed in a sequence-defined fashion using solid-phase peptoid synthesis.<sup>83</sup> (b) The  $\chi_{\text{eff}}$  can be determined by scattering via fits to the scattering function predicted by RPA,<sup>49</sup> but this is inconsistent with the experimentally measured  $T_{\text{ODT}}$ .<sup>83</sup> Both are also inconsistent with self-consistent field theory (SCFT) predictions for the  $\chi_{\text{NODT}}$ , suggesting physical phenomena due to subtle sequence effects. Reprinted with permission from ref 83. Copyright 2019 American Chemical Society. (c) Sequence effects have also been studied via the copolymerization of positively charged and neutral amino acids in peptide synthesis,<sup>84</sup> in the context of complex coacervation with a homopolyanion.<sup>85,86</sup> (d) Select sequences in (c) exhibit significantly different phase diagrams, predicted consistently from theory and simulation, sensitive to both the fraction of charged monomers and average block length.<sup>85</sup> (e) Even small monomer-level variations in sequence at the same charge monomer fraction and average block length exhibit changes in the experimental salt resistance (Perry) and the theoretical critical salt concentration (Sing).<sup>85</sup> Reprinted with permission from ref 85. Copyright 2019 American Chemical Society.

The juxtaposition of sequence-scale and length-scale hierarchies underscores the major questions of sequence-defined polymers for the polymer physics communities:

- (1) To what extent does sequence “matter” for material properties? At the onset, we should determine if the added challenge of synthesizing sequence-defined polymers is worth the benefits for unique material design.
- (2) How does the sequence scale relate to length scale? Of particular concern is how sequence information at small  $\zeta$  could give rise to effects at large length scales. Are there fundamental limits associated with how sequence can govern structure and vice versa? Relatedly, how do we effectively measure experimentally, and predict with computation and theory, effects that span multiple length and sequence scales?
- (3) How do we consider a vast sequence parameter space? We need strategies to explore the nearly infinite number of possible sequences efficiently. This challenge is further compounded by the need to consider sequence dispersity.

In essence, these are familiar problems when restricted to simply the “length scale” challenges in polymer systems; yet, they will require additional techniques and physical principles that can account for true along-the-backbone sequence effects.

**Does sequence matter?** The exploration of sequence space has, for the most part, been approached from its limiting cases;

variations on block copolymers (the large- $\zeta$  limit) and alternating or random copolymers (the small- $\zeta$  limit) have long been considered in the pursuit of new material properties. For the former, gradient and tapered copolymers represent sequence definition at the large- $\zeta$  limit,<sup>52–62</sup> and are synthesized by statistical copolymerization of two or more monomers at a proportion that varies at a defined extent over a defined portion of the chain.<sup>58,63</sup> These perturbations from standard block copolymers have been extensively studied as a way to modify phase diagram boundaries in a controlled fashion, as the large- $\zeta$  sequence resolution becomes commensurate with the associated microphase-separated length scales.<sup>54,56,59,64</sup> At the small- $\zeta$  limit, the study of random copolymers has explored how random sequences may lead to the emergence of microphase-separated structures or affect polymer miscibility.<sup>51,65–82</sup> This is a traditional way of imbuing a polymer material with the advantageous properties of two monomer chemistries.<sup>37</sup> Theory often relates these local sequence effects to effective interaction parameters or other local physical parameters.<sup>73–76</sup>

These examples underscore a major challenge, however, to determining the importance of sequence; namely, statistical variations of standard copolymer types lead to perturbative differences in material properties at commensurate length scales (i.e., modified phase diagrams<sup>56,59,64</sup> and effective  $\chi$ -parameters<sup>73–76</sup>). It remains unclear when the precision of sequence-



defined polymers provides access to unique or emergent properties or physical ideas. The salient question that must be addressed is the following: *can the properties of a sequence-defined polymer be retained by substituting a statistical copolymer?* For example, the unique properties of tapered polymers emerge from the definition of a region of tapering and the rate of change in the copolymer composition.<sup>55,58,60,63</sup> In this sense, sequence definition is only relevant at large  $\zeta$  and, correspondingly, connected to standard descriptors (e.g., blockiness and average monomer fraction) that polymer physics is well-equipped to characterize and predict.

To contrast, we highlight two recent cases where low- $\zeta$  features lead to nontrivial physical properties: block copolymers with sequence-defined blocks and sequence-defined polyelectrolytes. Patterson et al.<sup>83</sup> used solid-phase peptoid synthesis to examine the effect of a sequence-defined block on the order-disorder transition (ODT) in block copolymer self-assembly. Polymers with different monomer sequences exhibited qualitatively different behaviors than predicted from standard field theory methods, including the effective  $\chi$ -parameter determined from the random phase approximation (RPA).<sup>49,83</sup> This represents a breakdown in established polymer physics tools due to the presence of a defined chemical sequence (shown in Figure 2a,b). This establishes a key tension of sequence-defined systems, in that large- $\zeta$  effects (i.e., block copolymer microphase separation) are influenced in nontrivial ways by small- $\zeta$  features. This type of competition is also at play in some charged systems, such as in electrostatically driven phase separation (a phenomena known as complex coacervation)<sup>87,88</sup> studied by Perry and Sing.<sup>85,86,89</sup> In this situation, even subtle changes in monomer sequence, studied in sequence-defined polypeptides, can lead to significant changes in polymer phase behavior. A variety of polycation sequences (Figure 2c) were mixed with polyanions; simulation and theory consistently predict salt and polyelectrolyte concentrations where phase-separation occurs (Figure 2d, 2 $\Phi$ ) for these sequences. Experiments measured the phase boundary via turbidity, matching the salt concentration where miscibility occurs with theory predictions (Figure 2e); significant differences were observed even for sequences with similar values for common variables such as blockiness and monomer composition.<sup>85</sup>

It remains unclear how these situations arise where sequence scales affect dissimilar length scales, and this open question embodies the potential opportunities in this emerging field of sequence-defined polymers. This is, in our opinion, the foundational aspiration; how can we propagate the information engineered in monomer sequences to yield new and interesting material properties?

**Bridging physical length and sequence scales.** Propagating the information in monomer sequences will require the development of new tools in polymer physics, especially in theory/simulation and in experimental characterization, in addition to nurturing effective collaborations with the synthetic chemists working to increase sequence precision. A primary challenge is to probe the disparate length and sequence scales relevant for these investigations.

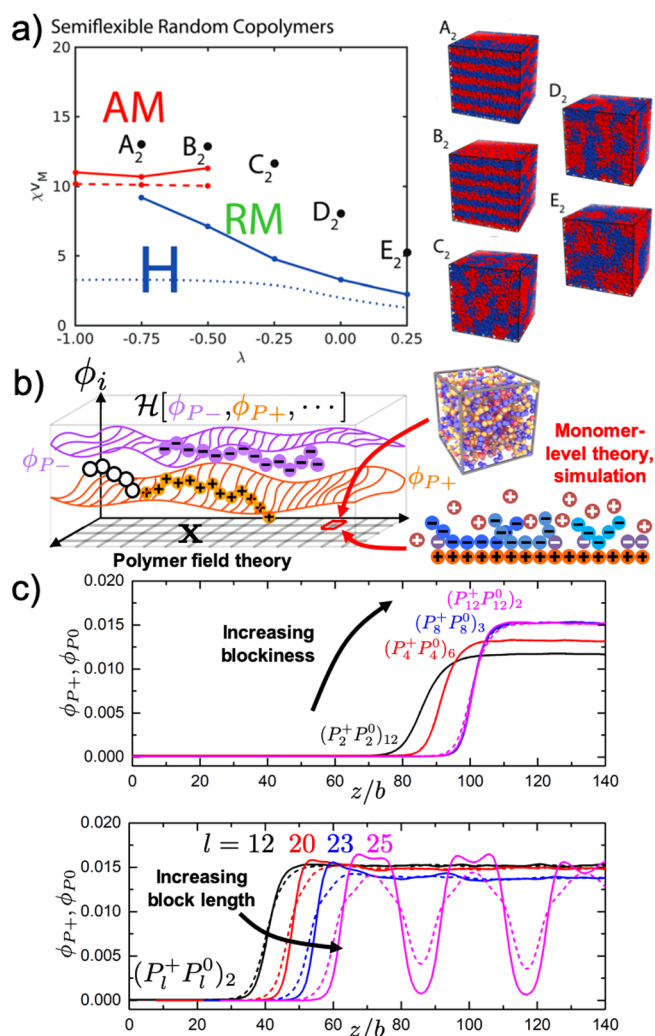
Experimental study of sequence-defined polymers requires, first and foremost, the synthesis of these molecules. While polymer chemists have greatly expanded the palette of sequence-defined systems, we note that experimental polymer physicists will more likely be reliant on commercial techniques such as solid-phase synthesis<sup>90,91</sup> for polypeptides<sup>84,92</sup> and polypeptoids,<sup>93</sup> or other automated approaches that can allow for

combinatoric synthesis.<sup>6,16,94</sup> The advantage of these approaches is that it allows for reliable synthesis of molecules with monomer-level differences, however, it does so at the expense of the length of the polymer molecule and the scale of the synthesis. Alternatively, biosynthesis can lead to polymers that are significantly longer but still sequence-defined;<sup>95,96</sup> however, biological constraints limit the chemistry and regularity of the sequences considered. There may also be promise in recently reported methods for using modular assembly<sup>97</sup> or automation<sup>61,62,94</sup> to realize sequence on larger macromonomer length scales.

Current approaches to characterize these materials remain standard, indirect, and thus require inference of the effect of monomer-level changes on sequence. These include the use of X-ray and neutron scattering, bulk phase separation, and calorimetry. It is worth noting that such methods can be powerful, especially to understand monomer-scale sequence-defined polymers that undergo ordering via crystallization,<sup>105,106</sup> yet all of these methods capture ensemble averages rather than single-chain properties. This is an area where efforts to co-opt biophysical tools represent a promising route to understanding the role of sequence; in particular, fluorescence measurements have begun to play a key role in a number of polymer measurements<sup>107–112</sup> in a way that may be readily utilized for sequence-defined polymers to probe structural position and dynamics and possibly looking at specific monomers. While the promise of single-molecule measurements develops, most methods will rely on the connection between sequence-defined perturbations and observable, averaged properties that must be interpreted through molecular theory and simulation.

Bridging length/time scales is not a new paradigm for those in the computational and theoretical research space, where coarse-graining<sup>113</sup> is regularly used to extend beyond the limitations of standard methods. However, this is an existential necessity for the study of sequence-defined polymers; useful tools for predicting and understanding these systems require a reconciliation of both the local, monomer-level sequence behavior and macroscopic or mesoscale observables. In particular, a number of efforts have pushed the bounds of field theoretic techniques; for example, a number of RPA theoretical models have been developed to predict sequence effects, for both specific and random sequences, in coacervation.<sup>114–116</sup> This class of theoretical model has found some success in reproducing trends,<sup>115,117</sup> yet is known to neglect important molecular correlations and often fails in sequence-defined situations. Complex Langevin (i.e., numerical field theory) calculations can address the limitations of RPA,<sup>118</sup> and has also been used to consider sequence-specificity in charged polymer phase behavior.<sup>119–121</sup> However, all of these approaches rely on coarse-grained chain representations (e.g., Gaussian segments) that do not fully resolve the packing and organization of monomer sequences. Related single-chain in mean field (SCMF) simulations have demonstrated the importance of addressing these limitations for copolymers,<sup>122–124</sup> for example, showing that semiflexible random copolymers exhibit nontrivial phase behavior due to how molecular packing and monomer-level structure relate to monomer sequence (Figure 3a).<sup>98,99,125</sup>

There is evidence that detailed models that specifically resolve monomer length-scales are indeed a crucial aspect for studying sequence-defined polymers. Particle-based computational models have demonstrated sequence-specific effects in compatibilization,<sup>126</sup> where highly nonregular sequences decrease the interfacial tension between two species beyond regular blocky or

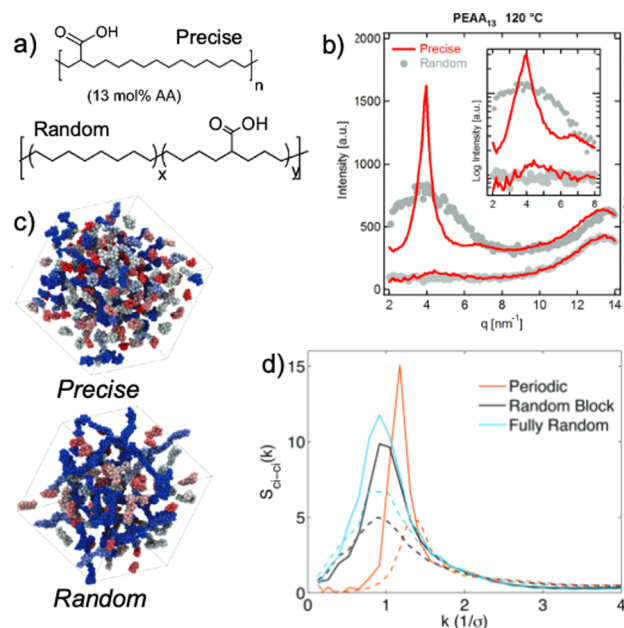


**Figure 3.** Bridging length scales. (a) SCMF calculations by Mao et al. capture how microphase separation emerges from molecular detail in semiflexible random copolymers.<sup>98</sup> Phase behavior is a function of  $\chi$  and a sequence parameter  $\lambda$  ( $\lambda = -1$  is alternating,  $\lambda = 0$  is random,  $\lambda \rightarrow 1$  is increasingly blocky), ranging from homogeneous (H), aligned mesophase separation (AM), and random mesophase separation (RM); these regions change with molecular stiffness.<sup>98,99</sup> Adapted from ref 98. Copyright 2017 Reproduced by permission of The Royal Society of Chemistry. (b) Sing has developed hybrid methods to bridge between local, monomer-level information into polymer field theory and molecular self-assembly.<sup>100–103</sup> The schematic illustrates polymer field theory (left), which maps a multichain system to single chains in a “field” of neighbor densities  $\phi$  with a Hamiltonian  $\mathcal{H}$ ; at each field location  $\mathbf{x}$ , thermodynamic information can be included from simulation or theory (snapshot and schematic shown).<sup>100,104</sup> (c) This method can capture how charge-driven phase separation is affected by the presence of a sequence-defined polycation, upon increasing blockiness while keeping chain length the same, (a local sequence effect, top).<sup>85,86,100</sup> It can also predict the emergence of self-assembled structures, by changing the block length for tetrablock polymers (a nonlocal sequence effect, bottom).<sup>100</sup> Graphs plot species density  $\phi_{P+}$  and  $\phi_{P0}$  (for cationic and neutral monomers respectively) over a spatial dimension  $z/b$ . Reprinted with permission from ref 100. Copyright 2020 AIP Publishing.

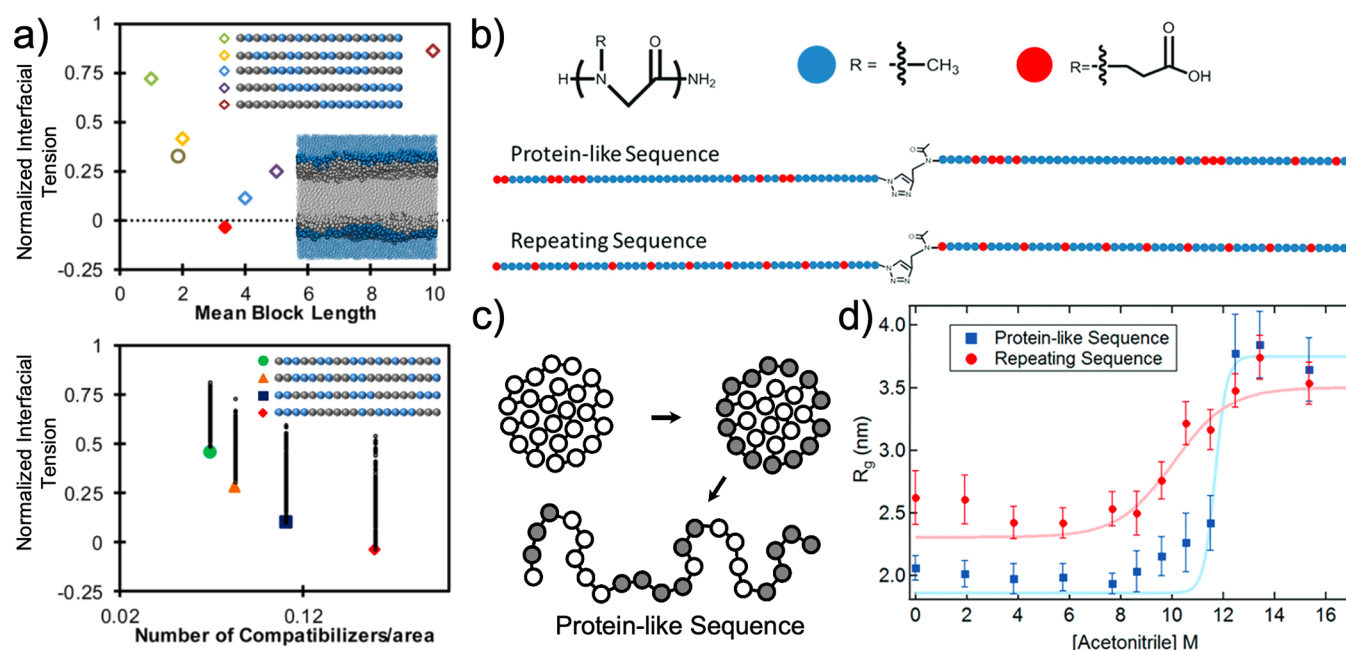
alternating sequences. Polyelectrolyte and polyampholyte complexation is also highly sensitive to sequence,<sup>127,128</sup> which may be crucial to the formation of drug-delivering polyplexes. The authors have used particle-based simulations to study

complex coacervation for a wide range of polyelectrolyte sequences,<sup>85,86</sup> which also inform theories that specifically consider how local correlations arising from charge packing and charged-monomer sequence govern phase behavior (Figure 3b,c).<sup>85,89,100,101</sup> Our view is that the theoretical and computational study of sequence-defined polymers must take advantage of the full suite of computational and theoretical tools, connecting the monomer-level resolution inherent to particle-based methods to larger length-scale methods, such as field theory, that can be used to determine polymer morphology and structure.

In a similar spirit, integration of theory/simulation, characterization, and synthesis is crucial to (i) interpret experimental results based on ensemble averaged quantities and (ii) refine the approximations that must be made to account for disparate length/sequence scales. Indeed, most successful efforts in sequence-defined polymers consist of all three; for example, sequence-precise ionomers synthesized by the Wagener group,<sup>129,130</sup> characterized by the Winey group,<sup>131</sup> and studied via simulation by Frischknecht and Hall,<sup>132–134</sup> have demonstrated the importance of monomer-level spacing on the structural and dynamic properties of ion conducting ionomers (Figure 4). Analogous examples, such as sequence-defined polypeptides or polypeptoids,<sup>135,136</sup> protein environments,<sup>137</sup> synthetic oligomer solution structure,<sup>138</sup> and polyelectrolyte phase behavior<sup>85,86,89,139</sup> highlight the progress that can be made



**Figure 4.** Sequence-defined polymers require close collaboration among polymer science disciplines. Sequence-definition plays a key role in the material properties of precise ionomers. Here, materials synthesized by Wagener (a) were characterized via X-ray scattering by Winey<sup>131</sup> (b) to show how a precise monomer sequence leads to well-defined structural features (i.e., ion clusters). (a) is reprinted with permission from ref 129. Copyright 2007 American Chemical Society. (b) is reprinted with permission from ref 131. Copyright 2010 American Chemical Society. Molecular simulation (c) from Hall and Frischknecht<sup>132–134</sup> provides a glimpse at the distribution of ion clusters to provide context for, and matching with, the averaged ion–ion scattering function  $S_{Cl-Cl}(k)$ . (d). Reprinted with permission from ref 132. Copyright 2012 American Chemical Society.



**Figure 5.** Sequence design. (a) Meenakshisundaram et al. used a genetic algorithm to determine optimal sequences for compatibilization of binary polymer blend interfaces, evaluated via the interfacial tension.<sup>126</sup> The optimal sequence performed distinctly better than regular blocks (open symbols, top), and depended on the compatibilizer concentration (bottom).<sup>126</sup> Reprinted with permission from ref 126. Copyright 2017 American Chemical Society. (b) Irregular sequences were also found to promote polymer collapse compared to repeating sequences in hydrophilic/hydrophobic (HP) model polymers,<sup>142,143,149,150</sup> with sequences determined by decorating the outside of a precollapsed globule (c). Reprinted figure with permission from ref 143. Copyright 1999 American Physical Society. (d) This designed sequence exhibited a sharper collapse transition, a “protein-like” behavior.<sup>150</sup> Reprinted with permission from ref 150. Copyright 2012 American Chemical Society.

when theorists, polymer chemists, and polymer engineers work together.

**Sequence information; Design in a vast parameter space.** Utilizing sequence-defined polymers will require advances in how we consider the vast parameter space of monomer sequence, where the number of permutations for a copolymer of only two monomers is  $O(2^N)$ , yet  $N$  is often large and more monomer types can be considered. Advances in machine learning and other sophisticated data science techniques<sup>140,141</sup> for exploring this space enable the engineering of molecules, complementary with other physics-motivated concepts. Here is another area where borrowing tools from the biophysical protein-folding community will yield new insights, in particular, in the use of machine learning and high throughput experiments to augment the role of fundamental theory, simulation, and materials characterization. Meenakshisundaram et al. provide an example of this sort of study,<sup>126</sup> using genetic algorithms to determine optimal monomer sequences for copolymer compatibilizers; the surprising result being a highly irregular sequence that would likely not have been otherwise predicted (Figure 5a). This combinatorial approach suggests nontrivial physical phenomena are at play, highlighting places in the vast sequence parameter space where more standard theory could focus its efforts to yield explanations.

In addition to combinatorial machine learning techniques, it is possible to leverage “physics-motivated” concepts for sequence design. For example, historical efforts to model or emulate proteins via the collapse<sup>27,142–144</sup> or surface-adsorption<sup>145–148</sup> of hydrophobic/hydrophilic (HP) sequences<sup>149</sup> suggested the design of sequence by tuning monomer sequence as to maximize the stability of a prefolded/adsorbed conformation (Figure 5b,c).<sup>143</sup> This scheme has been realized experimentally,<sup>150</sup> showing that irregular “protein-like” sequences can exhibit

markedly different behaviors during a coil-collapse transition (Figure 5d).

These advances in sequence design face the same challenges that affect the fundamental prediction and characterization of sequence-defined polymers, in that it is unclear how these methods will extend to design across length and sequence scales. The tools of machine learning and physical design schemes must contend with both self-interactions (the focus of, e.g., model polymer collapse) and intermolecular interactions that may form structures analogous to the tertiary and quaternary structures in proteins. The challenge is, thus, once there is a physical basis for bridging  $\zeta$ -scales, to develop strategies to explore an expanded sequence space enriched by the presence of many molecules.

**Sequence precision: How good is good enough?** The further development of the design, characterization, and prediction of sequence-defined polymers must finally contend with a major question at the intersection of fundamental polymer physics and chemistry, and the practical application of sequence-defined polymers to materials; how much precision is necessary to observe changes in properties?<sup>151</sup> This is especially important at the small- $\zeta$  limit, where sequence-dispersity may have a pronounced effect. Yet, in situations where small- $\zeta$  sequence-effects propagate to larger length scales, this becomes a challenging and important question. However, theoretical efforts on random copolymers only hint at the role of this dispersity, and even the language of sequence errors/dispersity is not yet developed; how do we measure, characterize, and predict these type of dispersity effects? We note that, as the physics of sequence-defined polymers gets increasingly specific to the precisely encoded information, in contrast to collective descriptors, it is likely that the types of sequence errors will not be adequately described by single quantitative metrics.



**Conclusion.** The scope of questions related to sequence-defined polymers remain extremely broad, and we think this represents a key area where the next century of polymer science is poised to make significant progress. While enabled by advanced methods and tools, automated synthesis, machine learning algorithms, and computational power, and increasingly sophisticated characterization, the current knowledge of polymer science provides a foundation to study this problem with a unique perspective that complements our neighboring disciplines (e.g., biophysics, colloidal science). However, the ability of the polymer community to take advantage of this opportunity to explore a rich, new world of sequence-defined polymers will be contingent on the development and nurturing of close connections between experimental and theoretical polymer physicists, and those at the forefront of polymer synthesis.

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### Author Contributions

The manuscript was written through contributions of all authors.

### Notes

The authors declare no competing financial interest.

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