Where Biology and Traditional Polymers Meet: The Potential of Associating Sequence-Defined Polymers for Materials Science

Audra J. DeStefano, Rachel A. Segalman, and Emily C. Davidson*

ABSTRACT: Polymers with precisely defined monomeric sequences present an exquisite tool for controlling material properties by harnessing both the robustness of synthetic polymers and the ability to tailor the inter- and intramolecular interactions so crucial to many biological materials. While polymer scientists traditionally synthesized and studied the physics of long molecules best described by their statistical nature, many biological polymers derive their highly tailored functions from precisely controlled sequences. Therefore, significant effort has been applied toward developing new methods of synthesizing, characterizing, and understanding the physics of non-natural sequence-defined polymers. This perspective considers the synergistic advantages that can be achieved via tailoring both precise sequence control and attributes of traditional polymers in a single system. Here, we focus on the potential of sequence-defined polymers in highly associating systems, with a focus on the unique properties, such as enhanced proton conductivity, that can be achieved by incorporating sequence. In particular, we examine these materials as model systems for studying previously unresolvable questions in polymer physics including the role of chain shape near interfaces and how to tailor compatibilization between dissimilar polymer blocks. Finally, we discuss the critical challenges—such as scalability and characterization—that must be overcome for sequence-defined polymers to attain their potential and achieve ubiquity.

KEYWORDS: sequence-defined polymer, copolymer, polypeptoid, self-assembly, dispersity, patterning, morphology

1. INTRODUCTION

The development of synthetic sequence-defined polymers represents the achievement of a long-standing "grand challenge" in polymer science.1 The inspiration for pursuing sequence control as a means of attaining unique material properties is largely derived from nature. Many biological systems precisely control the arrangement of monomers within polymer chains into specific orders, or sequences, to achieve diverse functions such as information storage,2 signaling and circuitry,3 templating of biomineralization,4 and hierarchical assembly5 that facilitate binding, transport, and material properties. Synthetic techniques capable of directly producing polypeptides,6 RNA, and DNA have been developed7 but lack the chemical diversity and stability of synthetic polymers. At the other end of the spectrum, traditional synthetic polymers feature distributions of molecular weight and, where multiple monomers are included, the monomers are arranged into statistical or blocky regions that vary from chain to chain. Sequence-defined polymers bridge both classes of polymers by precisely ordering diverse chemical functionalities with non-natural backbones and side chains (Figure 1). To date, these diverse chemistries have spanned from biomimetic polypeptoids for protein-mimetic folding and function in solution5,9 to sequences with the goal of achieving synthetic materials capable of information storage.10,11 Control over precise monomer sequence confers significant tools to tune monomer–monomer associations over multiple length scales, while also allowing the integration of elements of chemical functionality.

Notably, while biological systems leverage sequence-defined materials to excellent effects, many critical biological materials are not fully defined by sequence, such as polysaccharides. For example, seaweeds are largely composed of alginites, polysaccharides of mannuronate (M) and guluronate (G) residues. These residues are organized into blocks which are themselves primarily M, primarily G, or an alternating sequence of the two.12 The block composition varies between species and tissue of the young vs old seaweed, with accompanying differences in mechanical properties—an
example of nature controlling properties via principles quite familiar to synthetic polymer science! Even in proteins, a precise sequence does not fully articulate the 3D arrangement of monomers; many proteins are now well-understood to lack a precisely defined structure or are composed of a mixture of well controlled and disordered regions. Ultimately, polymer science will need to make similar decisions regarding the use of synthetic sequence-defined polymers: for what applications is defined monomer sequence truly transformative, and worth the additional challenge in synthesis and purification, and for what
applications are chains with statistically incorporated monomers more appropriate?

The fields of polymer physics, foldamers, and protein engineering have largely advanced independently; sequence-defined polymers bridge these fields. While numerous perspectives have been written about the potential for sequence-defined materials in single chain assemblies for protein-mimetic catalytic and binding function,14–17 here we focus on the implications for multichain assemblies and bulk materials. By necessity we must still consider the single chain as it plays a role—importantly, an assembly pathway-dependent role—in the properties of the final structure, but the role of each chain must be viewed in concert with those surrounding it. Unique material architectures and properties can be accessed by encoding intra- and intermolecular interactions in polymer sequence. We anticipate that advancing our fundamental understanding of how sequence impacts self-interactions in polymer sequence. We anticipate that advancing can be accessed by encoding intra- and intermolecular

2. DEFINING AND QUANTIFYING PERFECTION

In studies of associating polymer chains, it is important to consider the properties of not just an individual chain, but of collections of chains; indeed, this has formed the basis of many traditional studies in polymer science. While assembly of a single chain in solution concerns only the interactions of that chain with its solvent and itself, in bulk and concentrated polymer systems, interactions of many polymer chains with each other must be considered. Traditional synthetic polymer samples contain many chains, with properties including molecular weight, amount and distribution of each monomer, and spatial conformation varying from chain to chain. These differences in overall composition and/or sequence influence associating and bulk material properties18 and, therefore, are crucial to contextualizing material systems containing sequence-defined polymers.

Informative quantification of forms of variation and dispersity in a sample requires polymer scientists to move beyond standard measurements of dispersity (Figure 2a). The classic measure of variation between polymer chains in a sample is the molecular weight distribution via the ratio of the number-average \( M_n \) and weight-average \( M_w \) molecular weights, defining a dispersity index, \( D \). This value gives only general information about the shape of the distribution (in other words, a bimodal vs a broad single modal distribution could in principle have identical \( D \), but very different impacts on assembly and other properties).19–21 As samples with more complexity are synthesized—for example, random copolymers and block copolymers—materials begin to also be characterized by an average volume fraction and composition profile defined by the monomers available and biasing of the polymerization statistics.22 Underneath this is the realization that individual chains are composed of a distribution of these available monomers. For example, for a given volume fraction \( f_A \) of monomer in a sample, individual chains will vary regarding their individual volume fraction of \( A \); \( f_A \) simply represents a population average.23 This form of dispersity is referred to as compositional dispersity. Likewise, the sequence of monomers along a polymer chain can vary. Even in a population of chains where the monomers are randomly distributed from end-to-end, individual chains will deviate to greater or lesser extents from even spacing (indeed, a single chain cannot be evenly distributed due to the discrete nature of monomers!).25 Separately examining the impacts of compositional and sequence dispersity on behavior and assembly is nearly impossible in traditional polymer systems, but may be achieved leveraging controlled combinations of sequence-defined polymers.

While a population of “perfect” sequence-defined polymers lack all of the aforementioned forms of dispersity (perfectly defined in molecular weight, composition, and sequence, similar to a protein or small molecule level of purity), the statistical nature of polymer chains will still cause significant variability in adopted chain shape. In traditional polymer systems, monomer identity controls the polymer persistence length and resulting radius of gyration (polymer size). In polymer systems that exhibit self-assembly in the bulk, changes in polymer chain conformation, particularly near interfaces, have significant impacts on self-assembly.24,25 For example, block copolymers exhibit significant changes in assembly in response to changes in local persistence length and nematic interactions.26–28 Further, even elements such as side chain chirality can drive significant changes in polymer conformation, such as from a coil to a helical moiety.29,30 The extreme of sequence-biased chain shape is found in polymer chains such as proteins assembled into well-defined conformations; the “foldamer” community works to build synthetic mimics of these materials.31 Even in well-defined protein structures, significant conformational fluctuations and flexibility persist (and are important for function) and much of the utility in leveraging sequence ultimately is derived from the ability to selectively bias local polymer chain conformation.32,33 Notably, changes in chain conformation are often intricately linked to materials with significant stimuli-response. For example, micelles can be engineered to transition from helix to coil chain conformations useful for drug release,31,32 poly(N-isopropylacrylamide) demonstrates temperature responsive chain collapse/expansion,33 and liquid crystalline polymers demonstrate stimuli-responsive changes in chain anisotropy.34 Highly controlled incorporation of stimuli-responsive elements in sequence-defined materials is expected to enable the localization and degree of stimuli-responsive changes in material response, with implications for broader material properties. There are biological inspirations for this: protein domains that, depending on their local environment, sample different sets of conformational states (only some of which are “active”) are capable of serving as feedback control elements.35,36 As we develop sequence-defined polymers for targeted material properties, it will be critical to develop more precise descriptors for the relationship between sequence and accessible chain conformation.

Given the intrinsic challenges in scalable production of synthetic sequence-defined polymers, it is important to take a moment to ask the question: how can we best use sequence to control matter? When and how can we leverage it—and do we always have to do so in a way that is biomimetic, or are there broader ways to control the role of sequence? Key behaviors in polymer systems derive from a combination of precision and the statistical nature of polymer chains and distributions. Different “kinds” of interactions are likely to be more sensitive to sequence than others—small numbers of precisely placed
“specific” interactions (such as charged species) have been shown to demonstrate outsized influence relative to “non-specific” interactions. In addition, important questions can be asked about the extent to which assembled systems are sensitive to small levels of impurities. As discussed in the next section, methods for synthesizing sequence-defined polymers remain imperfect. Modern synthetic techniques easily make material that is, for example, only 40% “pure”, but with the remaining 60% mostly only differing by one to two monomers from the target sequence, as visualized in Figure 2b. Compared to a polymer generated by previously state-of-the-art anionic synthesis, this material is remarkably well-defined, yet laborious purification methods and tremendous reductions in yield are commonplace to achieve a rigorously “pure” sample. We propose that many bulk assemblies of these sequence-defined materials are tolerant of low levels of impurity and that researchers must evaluate their purification needs based on each system and the interactions at play. Further, considering the role of a proposed “monomer length scale” will, in concert with computational efforts, play a significant role in predicting systems for which precise sequence control will be more or less influential.

Sequence, after all, is not the only factor at play in polymer function—other properties intrinsic to polymer chains should also be leveraged. Across soft materials, we have many examples where defects and dispersity are essential to achieving certain desired behaviors. Topological defects in nanofiltration membranes contribute to membrane durability by connecting domains with different orientations. Similarly, polydisperse midblocks within triblock copolymers, for example, have been shown to stabilize assembled microphase structures because mixtures of long and short chains can fill the space more efficiently, thus reducing enthalpic penalties from copolymer chain stretching. As we develop sequence-defined polymers, we should not fear certain forms of dispersity because they are critical to how polymers derive their unique properties. In some ways, sequence-defined polymers are not only a means to drive toward perfection but also an opportunity to achieve precise control over imperfection. Thus, as we design synthetic materials that approach “perfection”, we can also use these as an opportunity to design tailored degrees of imperfection. Characterizing and quantifying of these multiple forms of molecular dispersity will be critical to communicating and benchmarking this research going forward.

3. CURRENT SYNTHETIC APPROACHES AND FUTURE CHALLENGES

Early synthetic polymerization approaches proceeded via mechanisms that resulted in poorly controlled materials (homopolymers and random copolymers), but methods attaining increasing levels of control over polymer sequence and molecular weight have evolved (biased copolymers, block copolymers). Biased copolymers leverage differences in reaction kinetics or controlled monomer addition to influence the arrangement of monomers, while block copolymers allow complete reaction of one monomer type before adding the next. Modern methods that enable true sequence control generally fall into one of two categories (Figure 3). The first consists of methods with precise control over sequence and composition but without molecular weight control (periodic polymers). These methods are generally based on repeats of precise monomers enabled via step growth or ring opening polymerization of precise, oligomeric monomers, enabling scalable synthesis. The second includes iterative methods that lead to both precise sequence and molecular weight control. Generally, it is the latter that are referred to as “sequence-defined”. Here, scalable synthesis remains generally out of reach.
3.1. Precise Macromonomer Methods

Several industrially scalable routes for synthesizing polymers with periodic sequence control from precise macromonomers are illustrated in Figure 3. Acyclic diene metathesis polymerization (ADMET) relies on step growth polymerization of symmetric α,ω-diene monomers to regularly incorporate chemical functionalities along a polyethylene chain.53,54 Both chain ends are identical, so ADMET forms precise sequences only when monomers are symmetrical. This means that nonsymmetric monomers or polymers combining multiple monomers with different chemical functionality will not yield precise sequences. Other precise macromonomer addition methods address this limitation to some degree. Here, macromonomers containing a uniform sequence of chemical functionalities are polymerized together, resulting in repeating blocks of a specific sequence. Polymerization schemes include click chemistry of bifunctional macromonomers55 and regioselective ring opening metathesis (ROMP) of cyclic monomers.56,57 Of these methods, ROMP generally provides the best molecular weight control, but all three methods enable less molecular weight control and sequence complexity than iterative methods. Multicomponent reactions offer another route to sequence control and, when performed iteratively, can also achieve molecular weight control.58

3.2. Iterative Growth Approaches

Methods for the synthesis of synthetic sequence-defined materials with uniform molecular weight generally rely on either iterative exponential (IEG) or iterative sequential (ISG) growth methods. Generally, both IEG and ISG achieve a single coupling at a time via some form of orthogonal chemistry. We note that, for these methods, particularly in solution, coupling efficiency decreases with increasing polymer length. In the IEG approach, a sequence may be composed by first synthesizing the component dimers, from them the component tetramers, and so forth, until a final coupling forms the entire desired chain, as shown in Figure 3.57,58 Notably, stepwise product purification is required for these materials (Figure 4a). The doubling of molecular weight with each step enhances the efficiency and ease of separation, but even in-line purification via flow synthesis does not eliminate the requirement.59 Further, IEG methods require orthogonal “activation” chemistries on the end groups: that can be achieved either via high efficiency protection–deprotection chemistries60 or, elegantly, via orthogonal light-based chemistries.61 While IEG achieves some distinct advantages over ISG methods, both approaches remain limited to only certain polymer backbones, and are challenged by the efficiency of individual steps, limiting the overall molecular weight.

In contrast to IEG, ISG adds a single monomer at a time. Many ISG methods are performed on solid-phase supports, allowing high reagent concentrations to push each individual step to high yield and enabling stepwise addition by retaining the growing polymer chain on the solid support while a solvent flush removes the excess reagent (Figure 4b).62 This strategy is best known for synthesis of biological and bioinspired materials such as polypeptides (via protecting groups) and polypeptides (via a sub-monomer strategy), but is also applicable to other highly efficient chemistries, such as thiolactone-based approaches.63 Drawbacks of solid-phase synthesis include that it requires large amounts of support beads relative to polymer grown and tremendous quantities of excess reagent and solvent. Further, materials synthesized via solid-phase ISG methods typically require further purification postsynthesis, with yields of the desired sequence scaling with molecular weight. If each synthetic step proceeds with 99% efficiency, a 10-mer will result in 90% of the desired product, while a 100-mer will result in only 37% of the desired product! This means that only reactions with extraordinarily high yields are useful in iterative growth strategies, thus limiting possible backbones. Rigorous chromatographic methods of purification.
consume additional solvent and restrict the attainable quantities of product. Solution-phase ISG methods suffer from similar drawbacks. While they do not consume the same degree of support beads and solvent during earlier synthetic steps, they often do so in return for a reduced yield, and require similar purification during the final steps in order to achieve a near-perfect sequence-defined material for additional studies and application. Ultimately, the need for significant purification—even when using some of the most efficient known chemistries for couplings—remains a substantial hurdle in the scale-up of materials synthesized via either iterative method.

For synthetic sequence-defined materials to become relevant beyond scientifically interesting model systems, their synthesis must become more scalable and accessible. In the short term, increasing adoption of robotic systems will be critical. Currently, robotic systems for sequence-defined polymers are primarily built to handle iterative reactions, particularly for solid-phase synthesis; performing these reactions manually is profoundly tedious for even short sequences. Further, we should not ignore purification while designing these materials; integrated systems are essential going forward. Finally, when processes are performed at the plant scale, recycling steps are engineered into the process to reduce waste. While academic laboratories traditionally do not utilize such recycling steps, the quantity of excess solvent and reagent used in many of the synthetic and purification steps means that automation of recycling where appropriate should be considered for all of these processes at the lab scale, and will in fact be essential to synthesizing these at reasonable scale for bulk laboratory studies. Ultimately, alternative ways to produce sequence-defined polymers that are distinct from those developed by biology should be considered. Whether that is through new coupling chemistries and synthetic techniques or via synthetic engineering approaches such as engineering of ribosomes to handle non-natural monomers,64 significant room for improvement exists—and indeed, improvement must be made before truly scalable synthesis of synthetic sequence-defined polymers will become feasible.

4. CHARACTERIZATION ACROSS TIME AND SPACE

Characterization of sequence-defined polymers—from the molecular to macroscopic assembled structures—presents an additional set of challenges. Again, questions must be raised about how to characterize these materials: what should be measured? Is reporting molecular weight dispersity meaningful for sequence-defined polymers, or should the “purity” of each polymer chain population be prioritized? Is a 100-monomer long material that is only 37% the polymer chain population be prioritized? Is reporting molecular weight dispersity meaningful for sequence-defined polymers, or should the “purity” of each polymer chain population be prioritized? Is a 100-monomer long material that is only 37% the polymer chain population be prioritized? Is a 100-monomer long material that is only 37% the polymer chain population be prioritized? Is a 100-monomer long material that is only 37% the polymer chain population be prioritized?

Potential approaches for achieving detailed sequence-structure insights include borrowing methods from biophysics that allow probes to be installed in specific sites along a polymer chain that can then leverage, for example, nuclear magnetic resonance (NMR)81,82 fluorescence methods,83 or electron paramagnetic resonance (EPR)84,85 to probe distributions of distances in polymer chains (Figure 5a). Of these methods, 2D NMR is unique in that it can determine the structure of small proteins without the use of labels, but extension to longer molecules is made challenging by loss of resolution and increasingly convoluted spectra. Here, automated peak assignment, perdeuteration, and selective labeling enable characterization of larger molecules.82 Single molecule fluorescence resonance energy transfer (smFRET) and double electron—electron resonance (DEER), on the other hand, rely exclusively on interactions between label pairs to extract distances. The necessity of probes, however, may skew results in some instances and should be carefully considered. For
example, smFRET and SAXS experiments routinely draw conflicting conclusions regarding protein response to chemical denaturation, indicating fluorophore interactions promote chain collapse. 86−88 In contrast, DEER utilizes smaller magnetic spin probes, requires fewer assumptions during data processing,88,89 and averages over more molecules, leading to more accurate distance distributions than smFRET. For all of these techniques, sequence-defined polymers offer a straightforward method to install probes anywhere in a sequence, opening doors to molecular-level information difficult to access through more traditional methods. Ideally, however, incorporation of probes could be avoided altogether. Mass spectrometry techniques, for example, do not rely on probes and are beginning to be able to distinguish chains of different conformation.90,91 Ion mobility spectrometry coupled to mass spectrometry (IMS-MS) enables the separation of ionized samples by the time needed to move to the MS detector. In this way, a 3D data set of drift time, m/z, and signal intensity can be constructed that provides insight into chain architecture, such as dispersity in “mikto”-star polymers.91

4.2. Bulk Material Characterization

Measures of chemical sequence and chain conformation are important to understanding the forms of dispersity present in a given batch of polymers, but additional work is necessary to characterize their bulk assembly. Ideally, the identity of each atom and the pathway of every chain would be known, but this level of detail is out of reach for amorphous materials. Tools do, however, exist for moving closer to a thorough spatial understanding of polymer assemblies. Canonical methods for characterizing three-dimensional order include scattering techniques coupled with transmission electron microscopy (TEM) and atomic force microscopy to visualize pattern formation in block copolymer structures. These techniques and others are reviewed extensively elsewhere.92−95 Other emerging techniques include advances in cryo-EM that have enabled atomic-scale resolution of precisely assembled polypeptoids (Figure 5b).96 Additionally, probe-enabled methods such as DEER may have utility for characterizing conformational dispersity at the single chain level within associating materials. Beyond equilibrium morphology, methods of tracking sequence effects on assembly pathways will be critical to the next generation of sequence-defined polymer materials. Here, time-resolved techniques will be of great importance. Time-resolved SAXS,97 high-speed atomic force microscopy,98 and liquid cell TEM99 are just three examples of promising tools in this space.

While the ability to attain a thorough molecular scale understanding of any given polymer will itself be a challenging, but increasingly feasible, task, further development of screening methods will be critical for selecting optimal candidates from wide parameter spaces. Furthermore, as useful sequences are identified for specific applications, scalability becomes a crucial bottleneck. For sequence-defined polymers to fulfill their potential both as model systems and, ultimately, specialized products, automated systems capable of synthesizing, purifying, and characterizing large quantities of material will be essential.

5. CONTROLLING SPATIAL PATTERNING USING MONOMER SEQUENCE AND ASSEMBLY

The explicit sequence of each polymer only tells part of the story in assembled polymer systems. A given monomer remains adjacent to the proceeding and subsequent monomer in its polymer chain; however, as that chain collapses into a single-chain polymer nanoparticle or is surrounded by other chains, the arrangement of monomers becomes much less obvious. Yes, directly adjacent monomers will always be nearest neighbors, but other nearest neighbors may reside in different segments of the polymer or different molecules entirely. Consequently, spatial patterning throughout assemblies is informed but not dictated by individual polymer sequence.

5.1. Biomimetic Single and Multichain Assemblies

Proteins exemplify the impact of polymer sequence on spatial patterning and, thus, function. Polypeptide chains are composed of specific sequences of amino acids that use disulfide bonds and differences in hydrophobicity, hydrogen bonding, and electrostatic interactions to fold into unique structures (Figure 6a).100 These structures vary widely with some being highly ordered and others intrinsically disordered, but all carry out critical biological functions. Protein functionality is largely enabled by areas of heterogeneity on the protein surface, both in chemistry and topology, that are an inherent result of the spatial arrangement of individual polypeptide repeating units.101 For example, spatial variation on the protein Chemotaxis Y influences the behavior of water near its surface.102 These variations in surface water behavior aid in site specific binding and are critical to its function. Furthermore, structural changes in response to external stimuli are also central to the function of many proteins, such as phototropin light switches in which the Jα-helix undocks and unfolds away from the protein.103 Understanding the under-
lying protein sequence responsible for this behavior has enabled use of systematic mutations to enhance the range of photoswitching. While significant progress has been made toward understanding and even predicting protein folding, as discussed in section 6, a thorough understanding of how to use polymer sequence to similarly control interactions and chain conformation, and through them spatial patterning and resulting functionality, in synthetic polymer assemblies is needed.

Amphiphilic copolymers show great promise in mimicking protein folding, as discussed recently, however, most studies of synthetic polymer collapse into single chain nanoparticles or globules have primarily focused on copolymers lacking the precise sequence control upon which proteins rely to achieve their structure. One class of sequence-defined polymers, polypeptoids, are particularly useful for studying sequence effects due to their ease of synthesis, wide range of side chain functionality, lack of backbone hydrogen bonding, and ability to form secondary structures. An example of sequence-controlled single chain collapse is the demonstration that polypeptoid sequences show sequence-dependent globule stability. Notably, these sequences have only two side chain functionalities, in contrast to the 20 amino acids commonly found in proteins (Figure 6b). Here, the placement of hydrophilic monomers in an otherwise hydrophobic chain controls the chain shape. In a good solvent, the chain extends, but in a poor solvent (water) the chain collapses with hydrophilic repeating units guiding which segments of the polymer chain are presented at the surface, thereby controlling surface patterning, globule density, and globule stability. Multichain polypeptoid assemblies elegantly access other protein mimetic structures. A few examples include ribbons, cyclic structures, helices, multihelical bundles, and nanosheets. Of these, nanosheets are particularly interesting because they can be adapted to access a range of secondary structures, such as loops, and serve as scaffolds for further functionalization, as demonstrated with a biologically active streptavidin-binding peptide sequence. Despite progress toward biomimicry, synthetic polymer folding fails to fully emulate the diversity and control over chain shape found in nature. However, given the extensive range of chemical diversity available to synthetic polymers, sequence-defined polymers may ultimately achieve functionalized architectures rivaling, and perhaps diverging from, biological materials.

5.2. Leveraging Sequence in Bulk Assemblies

In more concentrated systems, ion containing polymers demonstrate the power of using sequence control to drive self-assembly of bulk materials. Winey and co-workers synthesized linear polyethylene with regularly spaced acid groups via ADMET to direct self-assembly of linear chains into crystalline structures. While this method lacks control over molecular weight dispersity, in comparison to random acid group placement, precise spacing leads to far more uniform ionic aggregates and, consequently, superior spatial organization and enhanced proton conductivity. The polyethylene backbones can be further aligned with temperature, tensile strain rate, and strain. As shown in Figure 7a, the presence of regular acid groups results in layer formation. Polyethylene is more hydrophobic than the functional groups, so when immersed in water, the linear chains fold at the position of the acid group to reduce the water–polyethylene interface, resulting in sub-nanometer water layers between crystalline regions. These crystalline regions enhance proton conductivity; however, as noted by the authors, material performance could likely be improved by pursuing larger scale alignment. In a subsequent study, temperature and counterion-dependent morphological changes, including bicontinuous gyroid formation, are observed for a similar series of copolymers. This work exemplifies both the influence of carefully placed sequence modifications and the critical need to develop advanced processing techniques to control material structure (here, alignment) and, in doing so, performance.

Beyond segregation strength and block size, characteristics such as persistence length and conformational asymmetry impact self-assembly and can be tuned using polymer sequence. As one example, the polypeptoid sequence can be leveraged to govern chain shape by controlling side chain chirality to synthesize either helical or disordered chains. Helical polypeptoids are stiffer (longer persistence length) than their nonhelical counterparts while maintaining the same chemical composition, thus isolating the effect of chain stiffness. Helical chains adopt more condensed structures (smaller \( R_g \)); despite this, block copolymers in which the polypeptoid portion is helical self-assemble into hexagonally packed cylinders containing larger polypeptoid domains than their unstructured counterparts. This is likely a result of packing frustrations increased by stiff helical chains. Domain size variations do not extend to lamellar structures, but the thermodynamics of assembly are also impacted by chain shape. Specifically, helical chain geometries lead to decreased numbers of contacts between neighboring chains and larger chain stretching penalties, thus impacting the balance of enthalpic and entropic free energy contributions. These thermodynamic insights can be leveraged to attain more complex geometries, as demonstrated by broadening the double gyroid window using chain shape alone near the polystyrene–polypeptoid interface (Figure 7b). While these effects may be accessed via other approaches, such as well controlled triblock copolymers, sequence control is critical to identifying and refining relevant design rules.

Amphiphilic patterning presents another tactic for tuning bulk material morphology. Polymers with strong segregation strength, such as polystyrene (nonpolar) coupled to a polar polypeptoid, result in sharp interfaces in an effort to reduce
Polypeptoids with identical overall composition adopt blocky and distributed sequences near the block junction because the presence of nearby polar groups suppresses interfacial mixing. The blocky and distributed sequences lead to chain conformations in which the polypeptoid chains prefer to be near the block junction because the nonpolar groups are spread throughout the polypeptoid chain. Tapered and inverse sequences, in contrast, extend away from the interface more because the compatibilizing groups are concentrated near the block junction. These sequence-encoded differences in chain conformation near the interface govern domain spacing and the order−disorder transition temperature when assembled into lamellae.

Taken together, these studies model control of bulk material properties by using sequence to encode local and long-range effects governing self-assembly, but just how sequence specific do polymers need to be to achieve comparable properties? A distribution of chain conformations is unavoidable, even with perfectly uniform sequences, so perhaps more traditional, scalable polymers synthesized to statistically bias monomer placement can attain similar properties with less synthetic effort. Similarly, in cases where patterning in one segment, such as near the block junction, makes a more dramatic impact than in other regions, efforts should be focused on optimizing that portion rather than ensuring broader perfection. Determining allowable levels and regions of dispersity will be an important component of extending observations from fundamental studies to larger scale applications.

5.3. Polymer Processing

Precise sequence control (or lack thereof) is not enough to fully guide assembled morphology. Assembled structures at both single and multichain levels are often pathway dependent, so differences in processing can lead to entirely different structures for the same polymer. While challenging, this added complexity opens up avenues to attain multiple material properties from the same base polymer. In solution assembly, for example, the presence of too much destabilizing solvent has been shown to prevent peptide amphiphiles from self-assembling into β-sheets, instead driving them toward smaller aggregates (Figure 8a). In other cases, entirely different assembly pathways are followed depending on the local environment. This concept is demonstrated in Figure 8b for a relatively small discotic amphiphile that crystallizes by different routes depending on the strength of the pH stimulus. One route proceeds far slower than the other and passes through different intermediate structures, but both eventually reach a crystalline fiber stage. Leveraging and closely understanding the role of processing pathway on structure development can be critical to templating intra- and interchain associations. For example, precisely controlled shear during the processing of liquid crystalline polymer semiconductors induces polymer backbone planarization, eliminating the liquid crystalline phase and leading to improved performance. Intermediate stages of controlled processing pathways are likewise necessary to tune interchain associations needed for polypeptoid nanosheet formation. Detailed studies of polypeptoid nanosheet formation have emphasized that nanosheets form via a monolayer intermediate at either an air−water or oil−water interface. Compression of this interface (achieved via controlled vial rotation) induces collapse of the adsorbed monolayer into the stable bilayer nanosheets. Finally, the

entropic penalties between incompatible segments, but incorporation of nonpolar compatibilizing units into the polypeptoid alters the nature of the interface (Figure 7c). Polypeptoids with identical overall composition adopt sequence-specific differences in chain conformation near the block junction to minimize enthalpic mixing between nonpolar groups and polystyrene. Distributing the nonpolar groups evenly throughout the polypeptoid (blocky and distributed in Figure 7c) softens the interface less than concentrating the polar groups near the interface (inverse and taper) because the presence of nearby polar groups suppresses interfacial mixing. The blocky and distributed sequences lead to chain conformations in which the polypeptoid chains prefer to be near the block junction because the nonpolar groups are spread throughout the polypeptoid chain. Tapered and inverse sequences, in contrast, extend away from the interface more because the compatibilizing groups are concentrated near the block junction. These sequence-encoded differences in chain conformation near the interface govern domain spacing and the order−disorder transition temperature when assembled into lamellae.

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importance of processing likewise holds true in bulk polymers. As one example, shear alignment prior to annealing encourages column alignment in cylinder forming block copolymers. Thoroughly understanding these pathways will enable not only attainment of targeted equilibrium structures but also the ability to leverage desirable intermediates through kinetic trapping and multistep processing.

Importantly, synthetic polymers open up processing routes (for example, via temperature and organic solvents) untenable for biological polymers (Figure 8c). Many proteins are easily broken down by proteases and are sensitive to temperature, but synthetic polymers are generally more resilient to these factors. This means that the processing constraints of proteins often do not extend to synthetic polymers, opening up yet another knob to tune in attaining structural control. Another advantage of synthetic polymers is the ability to synthesize larger quantities with relative ease. Substantial effort has been invested into studying sequence-defined polymers in the context of relatively dilute conditions similar to those of interest for many proteins, but relatively little research has probed bulk assembly and the space in between. Are there ways to isolate uniquely useful material properties in this mid ground? Once again, a thorough understanding of kinetic and thermodynamic pathways is essential to developing creative processing techniques inaccessible to many biological polymers.

6. DECIDING WHAT TO MAKE WHEN YOU CAN MAKE ANYTHING

With sequence-specific synthetic methods maturing, the natural question becomes, what should we make? Even for the simple case of a polymer with only 20 total repeating units taken from just two monomers, over one million unique sequences exist to choose from. Longer polymer chains and additional chemical diversity only further increase the possibilities. Increase the length to 80 repeating units and the possibilities surpass Avogadro’s number. Of these essentially limitless options, how does one choose the sequence (and level of perfection) that best accomplishes the desired task? Currently, chemical intuition plays a significant role in selecting polymer sequences. While this approach has yielded powerful results, searching for increasingly intricate sequences based purely on intuition and experience will miss many optimal candidates, in part because optimal sequences are often nonintuitive and in part because a fundamental understanding of many self-assembly driving forces, for example, hydrophobicity, is not fully developed. Armed only with limited predictive capabilities, many fantastic candidates will remain undiscovered in vast sequence design spaces. Such decisions cannot rely on empirical experimental approaches—deliberately selecting polymer sequences will require a predictive understanding of sequence—structure—function relationships not just for single chains, but for assemblies of many polymers.

6.1. Computational Advances and Strategies

Substantial advances have been made in simulating individual sequence-defined polymer chains; however, many of the methods developed for modeling polymer assembly—particularly bulk polymer assembly—are not developed to manage explicit sequence. Modeling is particularly critical for guiding and rationalizing design of these materials; for example, modeling predicted phase behavior regions in block copolymer and polynampholyte self-assembly that was later confirmed via experimental work. As another example, computational work indicates that, counterintuitively, polypeptoid helices are
accurately predict protein structure. Taking inspiration from an incredible example of the power of computational tools to machine-learning methods. AlphaFold, in particular, serves as only now approaching a level of maturity via the integration of decades of work in a highly constrained system from biology. For example, the MARTINI force nonbiological polymers, often by leveraging successful models recent studies have made progress toward coarse-graining AlphaFold, other tools, such RoseTTAFold, are already features, notably methods capturing multichain block copolymer mesostructures is necessary to precisely de scales than are captured with the atomistic approaches accounting for the assembly of relatively short individual chains. In short, methods used to predict assembled structures are not well adapted to include sequence and those with atomic resolution are not easily scale-able.

Likewise, computational modeling of protein folding—despite decades of work in a highly constrained system—is only now approaching a level of maturity via the integration of machine-learning methods. AlphaFold, in particular, serves as an incredible example of the power of computational tools to accurately predict protein structure. Taking inspiration from AlphaFold, other tools, such RoseTTAFold are already emerging to aid in pushing the field forward. These methods rely on large databases of protein data to train predictive algorithms, but the lack of similar databases for synthetic polymers presents challenges in extending these workflows to search for promising sequences. This, together with the challenge of generating massive libraries experimentally, mandates the use of predictive models when training machine learning algorithms in data-scarce regimes. Meenakshisundaram et al. demonstrated such an approach in a study using genetic algorithms coupled with MD simulations to study the impact of monomer sequence in copolymer compatibilizers. This combined workflow predicted highly effective and nonobvious block copolymer sequences. Critically, MD simulations directly modeled each generation of polymers rather than relying on interpolative property predictions that are not robust to capturing outlier materials. Similar approaches coupling simulation and machine learning will be instrumental in identifying uniquely interesting sequenced materials, but they are contingent upon the ability to accurately simulate such materials.

While MD models are capable of explicitly taking sequence into account, they are computationally demanding and limited to relatively small systems. Consequently, simulation of concentrated polymer systems (in contrast to systems containing small numbers of chains) relies on coarse-graining methods in which some degrees of freedom are removed while maintaining the most important physics. Too much coarse graining of MD models of sequence-defined polymers removes the impact of sequence, while too little is too computationally demanding. Efforts to coarse-grain sequence-defined polymers have largely focused on biological polymers, but several recent studies have made progress toward coarse-graining nonbiological polymers, often by leveraging successful models from biology. For example, the MARTINI force field is a general-purpose MD force field commonly used for bio-

molecules that uses a four-to-one mapping that represents, on average, four heavy atoms by a single interaction site, thus accelerating simulations. This model has been extended to synthetic polymers via reparameterization. In particular, the methodology for bottom up reparameterization of polypeptides (a class of synthetic polypeptide mimics) with arbitrary side chains has demonstrated the utility of coarse-graining to accelerate MD simulations.
While coarse-graining enables MD to capture the geometry of multichain structures, characteristics of bulk material systems remain out of reach. Here, connection to the field theories used to understand block copolymer self-assembly may provide a bridge between monomer-level behavior and mesoscale properties.139 Recently, relative entropy coarse-graining was used as a direct connection between the atomistic detail of MD and the assembly level capabilities of field theory (Figure 9b).140 This approach uses small scale MD simulations to replace the phenomenological parameters typically used in field theory with chemically informed parameters. Sherck et al. demonstrated this workflow for poly(ethylene oxide)—extension to sequence-defined polymers could be transformative for understanding sequence effects on self-assembled structures. As methods for connecting monomer level patterning with bulk assembly and spatial patterning are developed, modeling must efficiently explore broad parameter spaces and expand to account for defined polydispersity and controlled assembly pathways, as these are expected to be critical to these materials.

6.2. Challenges of High-Throughput Experimental Characterization

Experimentally, high-throughput synthetic and characterization techniques have long accelerated molecule discovery in the pharmaceutical industry. Similar workflows have been applied to synthetic polymers;141 however, techniques that successfully identify drug candidates are not suitable for studying bulk material properties. For example, combinatorial libraries of thousands of polypeptoid sequences have been synthesized and screened with assays for pharmokinetic activity,142 but the synthetic approaches yield mixtures of hundreds of molecules. Separation of large amounts of individual sequences needed to characterize bulk material properties from such large mixtures is next to impossible. Even given the ability to synthesize libraries with sufficient quantities, high throughput characterization of these materials remains challenging. Probing assembled structures requires characterizing a pure, relatively large (milligrams) sample for each individual sequence, rather than an assay capable of ruling out many molecules. Nevertheless, progress has been made toward characterizing large libraries of materials. For example, protocols developed for measuring globule properties, such as high-throughput small-angle X-ray scattering,143 aid in understanding sequence impacts on globular collapse. As a related example, centrifugation has been leveraged for high-throughput adhesion testing.144 Clearly, screening large libraries of sequence-defined polymers is a challenging undertaking, especially for bulk material properties. Thus, computational insights narrowing the design space are critical to deciding which polymers to pursue experimentally.

Modeling and computation are particularly well-posed, once sufficiently well developed, to answer some of the fundamental questions regarding what scales and kinds of interactions accessible via sequence control—on individual chains and within distributions of chains—are most impactful. Improving the ability to use modeling and computational resources to predict and rationalize the behavior of sequence-defined polymers in the bulk in addition to as individual chains in solution will be critical to focus synthetic and experimental efforts on the most important problems. Ultimately, both machine learning methods, when the appropriate computational resources are provided to achieve robust "training" data sets, as well as selective methods of coarse-graining provide significant insight for identifying optimal polymer sequences.

7. CONCLUSIONS

Drawing on the capabilities of both biological and traditional synthetic polymers, sequence-defined polymers are uniquely positioned to engineer made-to-order materials. Robust and efficient modeling coupled with advanced characterization techniques will be necessary to understand how sequence impacts material properties and, ultimately, predict such effects. These efforts should consider the role of dispersity in highly associated systems and identify the minimal levels of sequence control necessary to drive formation of useful architectures. Realization of the full potential of sequence control, however, will require moving beyond equilibrium self-assembly. Exploring alternative processing routes necessitates mapping out kinetic and thermodynamic assembly pathways and exploring ways to build upon intermediate states. Deliberately designed polymers leveraging both sequence-defined and polydisperse segments coupled with creative processing carry the potential to produce unique hierarchal materials that will transform the capabilities of synthetic polymers and, in doing so, material science.

■ AUTHOR INFORMATION

Corresponding Author
Emily C. Davidson – Department of Chemical and Biological Engineering, Princeton University, Princeton, New Jersey; 08544, United States; orcid.org/0000-0001-5819-9233; Email: edavidson@princeton.edu

Authors
Audra J. DeStefano – Department of Chemical Engineering, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0003-1047-2637
Rachel A. Segelman – Department of Chemical Engineering and Department of Materials, University of California, Santa Barbara, California 93106, United States; orcid.org/0000-0002-4292-5103

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.1c00297

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.A.S. and A.J.D. acknowledge support by the Center for Materials for Water and Energy Systems (M-WET), an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Basic Energy Sciences under Award #DE-SC0019272. A.J.D. also acknowledges support from the U.S. Department of Defense through the National Defense Science & Engineering Graduate (NDSEG) Fellowship Program. E.C.D. acknowledges startup funding from Princeton University and support by the Princeton University Library Open Access Fund.

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