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# Size Distribution in Self-Assembly Matters

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## IN BRIEF

(Co)polymer size distribution: how narrow is narrow enough when it comes to self-assembling these large molecules? How does a broad distribution affect the resulting morphologies? Can we predict the self-assembly of a multicomponent copolymer? Does sequence matter? These questions are becoming relevant as modern synthetic tools allow preparation of copolymers with predetermined sizes, size distributions, and compositions.

## INTRODUCTION

Lack of precision and homogeneity in chemistry is taught at undergraduate levels as an indication of improper synthesis and purification and is frowned upon (and rightfully so). Polymer chemistry, however, that has become a powerhouse of syntheses for new and functional materials, almost never achieves the purity and precision that one sees in *e.g.* drug syntheses (to the dismay of those undergraduates). Some of the most powerful synthetic protocols in large-scale polymer preparation yield chains with "narrow dispersities", while increasing the number of components to prepare copolymers adds to the complexity of the chain distribution, now also in terms of composition. Efforts to prepare perfectly uniform sized and sequence-defined copolymers has been at the epicenter of many research efforts, mainly aiming at mimicking the properties of their naturally-occurring counterparts (*e.g.* proteins) in carrying information, directed self-assembly, catalysis, etc.[1] There has been a lot of speculation throughout the years regarding the significance of dispersity of polymers in terms of molecular weight distribution and heterogeneity. This Catalyst article aims at capturing the essence of recent research efforts on the subject and setting the challenge for future works in the field.

Often misused as a single qualitative measure, polymer dispersity (*i.e.* $M_w/M_n$, often referred to as "polydispersity index, PDI", but denoted per IUPAC regulations as molecular weight distribution or dispersity, $Đ_M$)[2] describes the variation of the sizes of the individual polymer chains within a sample and is often considered a measure of inconsistency of the size of polymer chains in a mixture and an indicator of (lack of) control during the polymerization process. Inherent limitations in the control (or even elimination) of dispersity in polymer synthesis are well-described in a recent review.[3] It is noted that, while herein we focus on the dispersity in terms of molecular weight distribution and compositional drift, other forms of dispersities are imaginable, such as stereochemical, or architectural, *e.g.* through cyclization, back-biting, or chain-transfer, all of which can dramatically alter the effective volume of the polymer and thus its self-assembling properties of the copolymer.

When it comes to the self-assembly of block copolymers, a wealth of literature can be found that addresses the formation of highly ordered structures, either in solution or in bulk, as a function of the macromolecular characteristics of the copolymer. Extrapolating from the

Flory-Huggins equation regarding polymer miscibility, it is generally accepted that the chain length (referred to as $N$) and the (im)miscibility of the respective blocks (namely the $\chi$ parameter) in a medium, which can be a selective solvent, or the counterpart block of the copolymer, dictate the phase behavior of the copolymer as a function of the volume fractions of the respective components. It is often suggested in the literature that disparity in the chain length will vary the $N$ thus drastically broadening the $\chi N$ compound that effectively describes the boundaries of each phase. Similarly, deviation of the sequence of the copolymer building blocks, for example through a gradient transition of the two blocks around the junction, affects the $\chi$ parameter by effectively diluting the (otherwise) immiscible blocks with a compatibilizing component. While these factors point towards the need of precise compositions and uniform sizes in order to achieve highly ordered and well-defined self-assembled structures, recent reports have shown that this may not be the case, and the hitherto perceived drawback of dispersity in polymer systems may be in the future a desired characteristic for optimal self-assembled structures.

The polymer science community is now well-equipped with a wealth of techniques that enable researchers to harness the composition, molecular weight, and size distribution of synthetic copolymers. Nonetheless, high precision does not always correlate to optimal properties, especially with regards to applications that call for polymers with high molecular weight distributions owing to their improved processability. Furthermore, many reports in the literature describe the self-assembly of disperse copolymers into well-defined ordered structures. This leaves a lingering question: how monodisperse should a polymer be to result in predictable self-assemblies?

## In bulk

When it comes to the self-assembly of block copolymers in bulk, theoretical studies have shown that dispersity of one of the blocks skews the phase diagram. While the interfacial energy is not dispersity-dependent, the domain spacing of the resulting structure is. This can be ascribed to the fact that dispersity reduces the stretching energy of polymer chains. Furthermore, the stability of the interface is compromised due to the presence of lower molecular weight blocks. As a consequence, the phase diagram is shifted towards the disperse polymer block and the order-disorder transitions shift to higher $\chi N$ values. Indeed, it has been since experimentally shown that disperse blocks are influenced by the lower molecular weight chains and appear to occupy smaller volumes which effectively induces curvature of the interface towards the disperse domain. While a handful of such reports can be found in the literature (the reader is encouraged to refer to the aforementioned reviews for more details), there might just be more to dispersity than just deviation from the average molecular weight.

One easy way to introduce compositional and size distribution is through blending otherwise uniform copolymers. With variations of this approach described in the literature, the overarching conclusion is that greater variation results in larger phase domains (ultimately macrophase separation), an effect that can be conveniently exploited to tune the domain spacing of periodic structures. Nonetheless, it is impossible to extrapolate the phase behavior of *any* copolymer blend from the existing literature and this is one of the main challenges of disperse copolymers self-assembly.

So far, dispersity was assessed a one-dimensional interpretation of the polymer size distribution, but Fors and co-workers' reports focus on depicting the molecular weight distribution with regards to its skewness (Figure 1). By determining the domain spacings of block copolymers consisting of a poly(styrene) and a poly(methyl methacrylate) block, whereby the dispersity of the former was varied both in absolute value, but also with respect to the shape of the molecular weight distribution,[4] otherwise identical block copolymers were shown to self-assemble into lamellae with significantly different domain spacings depending on the skewness of the molecular weight distribution. This difference was ascribed to the copolymers being dominatingly high or low molecular weight chains, respectively, thus pointing to the fact that dispersity alone is not a sufficient measure to characterize the macromolecular properties of copolymers as it does not mirror the skewness of the distribution which can ultimately dictate the self-assembly characteristics in bulk. It is noted that the overall dispersity of the studied copolymers was below 1.3, thus, by measures of controlled radical polymerizations, the polymers have narrow molecular weight distributions.
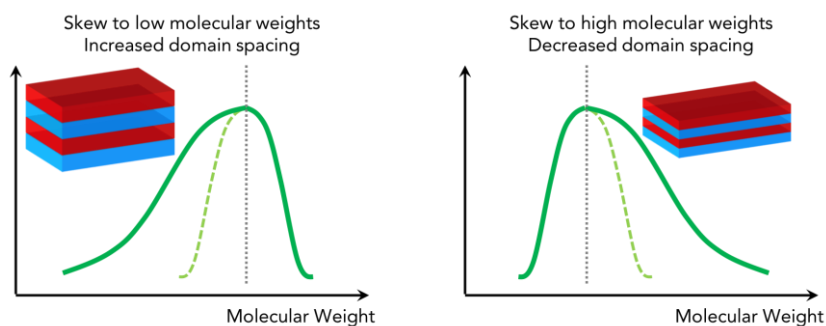
**Figure 1. Skewness matters**

As reported by Fors and co-workers, polymers with similar dispersity and molecular weight self-assemble into lamellae with different domain spacings. Skewness to high molecular weights resulted in smaller domain spacings that their counterparts with skewness to low molecular weights.

Molecular weight distribution might just be the tip of the iceberg. While a large body of literature covers various aspects of block copolymers with respect to their chemical composition, molecular weight, dispersity, thermal properties, *etc*. it is often noted that the complexity of a multicomponent system that can self-assemble, drastically increases with increasing the number of components, while new morphologies may also arise. A phase diagram for a triblock copolymer, for example, is not only dependent on the relative volume fractions of the components, but also the order in which these are present along the chain. Current efforts are aimed at understanding the effect of sequence of building blocks on the self-assembly properties of the constituting copolymer. Perhaps the most interesting such work is that of Cheng and co-workers that prepared "giant" monomers to prepare oligomeric sequences that were shown to self-assemble.[5] They effectively introduced an "alphabet" consisting of the various "letters" (*i.e.* building blocks) and demonstrated that by changing the order of the building blocks, not only they formed different "words" (*i.e.* oligomers) on a molecular level, but also the way the "words" assembled vastly changed pointing to a meaningful relation between sequence and self-assembly in bulk. Nonetheless, the effect of dispersity could be lost in the fact that the building blocks are so large. In some cases, the obtained structures were ascribed to the relative volume fractions of the components as different sequences were found to result in the same structures, inasmuch as the mole ratios were the same.

While compositional drift is hard to define, especially for larger polymer chains, molecular dynamic simulations to investigate the self-assembly properties of tapered copolymers, *i.e.* polymers whose composition gradually changes along the chain within a given region point to a predictable behavior.[6] Unsurprisingly, copolymers with a completely statistical monomer sequence exhibit different self-assembly properties to copolymers with sharp block definitions. Furthermore, copolymers with less defined sequences result in assemblies with smaller domains, an observation that is in line with the findings of similar studies on copolymers with molecular weight dispersities (as opposed to composition). To that extent, the effect of monomer sequence on the polymer properties and self-assembly structural characteristics can be simplified by studying a diblock, a tapered and an inverse tapered copolymer.[7] The latter exhibits dramatically different thermal properties and interfacial roughness compared to the diblock copolymer, however, the domain spacing is, surprisingly, comparable.

## In Solution

The effect of dispersity of block copolymers in their ability to self-assemble in selective solvents was investigated in the seminal work of Eisenberg and co-workers.[8] Assessing a set of copolymers of which the dispersity of one block was varied (*i.e.* from *ca.* 1.00 up to *ca.* 2.00), they reported an effect on the size of the self-assembled structures obtained: increasing the dispersity of the hydrophilic block was shown to result in larger vesicles formations, which was attributed to the arrangement of the different sized chains in a fashion that favors increased curvatures, thus smaller particles. Furthermore, a morphological differentiation was also reported for various block dispersities, which was ascribed to mixtures of chain lengths being able to accommodate more chains to aggregate. Similar to the findings of disperse block copolymer self-assembling in bulk, the

core chain stretching dominates the total free energy of the aggregate and thus a morphological change occurs.

A different study of the effect of dispersity on the self-assembly of polymers in solution involved poly(sodium acrylate-*b*-styrene) block copolymers of varying dispersities as stabilizers in the emulsion polymerization of styrene.[9] With increasing dispersity, the aggregation number of the assemblies increased accompanied by an increase of the surface tension. Interestingly, the critical micellization concentration of the copolymer and the size distribution of the particles was consistent over the range of dispersities studied.

Another systematic approach involved studying the ability of narrow dispersity amphiphilic block copolymers to self-assemble in water, compared to disperse copolymers of similar compositions.[10] Interestingly, both types of copolymers resulted in similar sized well-defined aggerates, with the size and aggregation number being dependent only on relative compositions and degree of polymerization. While these findings may stray from earlier conclusions, we note that the copolymers in this study would exhibit low glass transition temperatures, thus their ability to "shuffle" and re-arrange is more favorable. Indeed, this observation points to the fact that when discussing the self-assembly of copolymers in bulk or in solution, there is a wide range of parameters that drastically affect the resulting morphology and its characteristics. It is noted that, to our knowledge, there are limited examples of block copolymers whereby all blocks have high dispersities; indeed, most reports focus on a narrow distribution block connected with a disperse one.

## Applications and Implications

The implications of dispersity and inhomogeneity for potential applications of copolymers vary. DNA molecules are characterized by uniform and precise compositions which dictate subsequent functions (e.g. protein synthesis) and as much as one misplaced building block can imbalance a whole organism (such as in the case of sickle cell disease), thus pointing towards the importance of precise macromolecular sequences. On the other hand, the functions of enzymes are often mimicked by self-assembled block-type copolymers (i.e. with some dispersity) that bear a catalytic moiety: the core of the assembly affords the confinement and hydrophobicity that is often considered key in enzymatic catalysis, albeit lacking in efficiency and substrate selectivity. In this case, the function is achieved despite the disperse nature of the macromolecule. Drug delivery is another potential application for well-defined self-assembled copolymers. The complexity of such systems makes it difficult to gauge the effect of dispersity, however, considering the scenario where a moiety present on the polymer chains (e.g. a binding ligand) is responsible for the affinity of the assembly to a target (e.g. to a cancer cell), inconsistency in the location and amount of the moiety amongst chains would drastically vary the affinity across the assembled nanostructures, and consequently the drug dosage delivery.

In the absence of solvent, the effect of phase separation is aimed equally delicate functions. Considering, for example, the optical properties of a self-assembled structure, diversity of the domain size (which we discussed earlier is related to size and composition homogeneity) results in a drop of the wavelength-specific reflectance and thus loss of the structural coloration. As such structures are employed in light manipulating applications, e.g. reflecting coatings, lenses, and "smart" colorants, some of which are commercially available, the effect of dispersity is imminent and of broad significance.

The use of synthetic sequence-defined polymers for information storage has emerged as a potential application and its feasibility has been demonstrated. While dispersity and inhomogeneity amongst the macromolecules will surely compromise the information readout, it is not impossible to imagine the importance of the median composition which could be correctly interpreted through appropriate statistical analysis. Is it more favorable to ensure uniformity and definition at the expense of strenuous syntheses, or optimize the analytical methods that can account for inhomogeneities? Once the applicability of sequence-controlled polymers gains momentum, such questions will surely be answered.

## Conclusions

Here, we note some advances in the field that investigate the effect of dispersity and the importance of the sequence of the building blocks on the self-assembly of these copolymers and we draw different conclusions when comparing self-assembly in bulk and in solution. In bulk, dispersity as a one-dimensional value largely affects the volume fraction of the

respective building blocks and thus alters the phase diagram of the copolymer. Moreover, the shape of the polymer size distribution further influences the dimensions of the periodic structure. With regards to the building block sequence, it is apparent that there is still a lot of ground to cover in order to generalize and understand the governing principles, as the χ parameter may not be adequately precise to predict the self-assembly behavior of multi-component and/or sequence-defined copolymers.

The morphology of polymer self-assemblies in solution appears to be less sensitive to greater dispersities. With the size of the assembled structures being reported largely consistent, the only occasion where a change in the morphology was observed occurred for dispersities ranging from 1.0 to 2.0, a much greater variation than that of the studies in bulk. One could assume that in solution, the solvent and its miscibility with the copolymer components dominates and compensates for variations in the molecular weight of the copolymer, at least within a reasonable margin. With the relatively recent development of sequence-controlled polymers, a systematic investigation of the effect of variations in the composition of a copolymer with respect to the characteristics of its self-assembly in solution is yet to be reported.

With the development of techniques that allow great precision in the synthesis of polymers of defined molecular weight and composition, it is exciting to see how this new generation of materials will alter the field of self-assembly and the consequent properties and applications. This short article points to existing literature on the topic but also suggests some future challenges, such as the investigation of the self-assembly of diblock copolymers with varying the dispersity of both blocks (in bulk and in solution), experimentally decoupling size and composition dispersity in the self-assembly of copolymers and particularly with respect to the precision required (sequence-controlled *vs.* sequence-defined), systematically showing the ability of disperse copolymers to "shuffle" into ordered structures with respect to their mobility (glass transition, plasticization effects, etc.), and evaluating the directed self-assembly of disperse copolymers in solution.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## REFERENCES AND NOTES

1.      Solleder, S.C.; Schneider, R.V.; Wetzel, K.S.; Boukis, A.C.; Meier, M.A.R., (2017). Recent progress in the design of monodisperse, sequence-defined macromolecules. Macromol. Rapid Commun. *38*, 1600711.
2.      Gilbert, R.G.; Hess, M.; Jenkins, A.D.; Jones, R.G.; Kratochvil, P.; Stepto, R.F.T.; Baron, M.; Kitayama, T.; Allegra, G.; Chang, T.; dos Santos, C.; Fradet, A.; Hatada, K.; He, J.; Hellwich, K.H.; Hiorns, R.C.; Hodge, P.; Horie, K.; Jin, J.I.; Kahovec, J.; Kubisa, P.; Meisel, I.; Metanomski, W.V.; Meille, V.; Mita, I.; Moad, G.; Mormann, W.; Ober, C.; Penczek, S.; Rebelo, L.P.; Rinaudo, M.; Schopov, I.; Schubert, M.; Schue, F.; Shibaev, V.P.; Slomkowski, S.; Tabak, D.; Vairon, J.P.; Vert, M.; Vohlidal, J.; Wilks, E.S.; Work, W.J., (2009). Dispersity in polymer science (IUPAC recommendations 2009). Pure Appl. Chem. *81*, 351-353.
3.      Doncom, K.E.B.; Blackman, L.D.; Wright, D.B.; Gibson, M.I.; O'Reilly, R.K., (2017). Dispersity effects in polymer self-assemblies: A matter of hierarchical control. Chem. Soc. Rev. *46*, 4119-4134.
4.      Gentekos, D.T.; Jia, J.; Tirado, E.S.; Barteau, K.P.; Smilgies, D.-M.; DiStasio, R.A.; Fors, B.P., (2018). Exploiting molecular weight distribution shape to tune domain spacing in block copolymer thin films. J. Am. Chem. Soc. *140*, 4639-4648.
5.      Zhang, W.; Lu, X.; Mao, J.; Hsu, C.-H.; Mu, G.; Huang, M.; Guo, Q.; Liu, H.; Wesdemiotis, C.; Li, T.; Zhang, W.-B.; Li, Y.; Cheng, S.Z.D., (2017). Sequence-mandated, distinct assembly of giant molecules. Angew. Chem. Int. Ed. *56*, 15014-15019.
6.      Levine, W.G.; Seo, Y.; Brown, J.R.; Hall, L.M., (2016). Effect of sequence dispersity on morphology of tapered diblock copolymers from molecular dynamics simulations. J. Chem. Phys. *145*, 234907.
7.      Luo, M.; Brown, J.R.; Remy, R.A.; Scott, D.M.; Mackay, M.E.; Hall, L.M.; Epps, T.H., (2016). Determination of interfacial mixing in tapered block polymer thin films: Experimental and theoretical investigations. Macromolecules *49*, 5213-5222.
8.      Terreau, O.; Luo, L.; Eisenberg, A., (2003). Effect of poly(acrylic acid) block length distribution on polystyrene-b-poly(acrylic acid) aggregates in solution. 1. Vesicles. Langmuir *19*, 5601-5607.
9.      George, S.R.; Champagne-Hartley, R.; Deeter, G.A.; Campbell, J.D.; Reck, B.; Urban, D.; Cunningham, M.F., (2017). Amphiphilic block copolymers as stabilizers in emulsion polymerization: Effects of the anchoring block molecular weight dispersity on stabilization performance. Macromolecules *50*, 315-323.
10.     Hirai, Y.; Terashima, T.; Takenaka, M.; Sawamoto, M., (2016). Precision self-assembly of amphiphilic random copolymers into uniform and self-sorting nanocompartments in water. Macromolecules *49*, 5084-5091.