Discussion on "Aperiodic Copolymers"

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ABSTRACT: In a recent Viewpoint (*ACS Macro Lett.* **2014**, 3, 1020), J.-F. Lutz brought to the community's attention the need for more informative nomenclature, especially with respect to macromolecules with prescribed but not repeating sequences of monomers. Lutz proposes the use of the term "aperiodic" for this situation. In this Viewpoint, we comment on the need for such nomenclature, and offer some alternatives for consideration.

Accessing sequence specificity in synthetic polymers, with the same level of sequence control as peptides or nucleic acids, has been a "Holy Grail" for polymer scientists since the early days of the field. While this has yet to be achieved in high molecular weight synthetic polymers, there have been some significant developments in polymer chemistry that have sparked a growing interest and a resurgence in these synthetic targets. With the advent of access to these complex polymer structures, issues of terminology naturally arise. In an interesting Viewpoint[1] published late last year in *ACS Macro Letters*, Jean-François Lutz proposed new terminology to address a specific class of sequence-controlled polymers. He proposed the term *aperiodic copolymers* to describe a subset of sequence-controlled polymers that do not exhibit periodic, *i.e.*, repeating sequences. Figure 1 shows where such terminology would fit among terms that are commonly used by the polymer community.[2] "Periodic copolymer" is an IUPAC term that is defined as "a copolymer consisting of macromolecules comprising more than two species of monomeric units in regular sequence."[3] Consequently, Lutz proposed that "aperiodic copolymers are copolymers in which monomer sequence distribution is not regular but follows the same arrangement in all chains." The "*follows the same arrangement in all chains*" part of the definition is an important one as it differentiates the class of polymers with the same aperiodic message "in all chains" from random or statistical copolymers. This also highlights opportunities with these materials for information storage/transfer, akin to what is achieved with DNA. Lutz also notes that there is some flexibility here with his proposed definition to allow sequence deviations to be tolerated, using the analogy to a copolymer containing 90% alternating dyads that is still generally considered to be an alternating copolymer (or at least to have alternating tendency).

Lutz goes on to give examples (Figure 2) of Aperiodic Copolymers. These include multiblock copolymers whose block sequence is aperiodic, multisite copolymers with different repeat units that are aperiodically distributed along a homopolymer backbone, and sequence-defined copolymers without regular repeating sequences (akin to what is seen in most proteins and DNA).

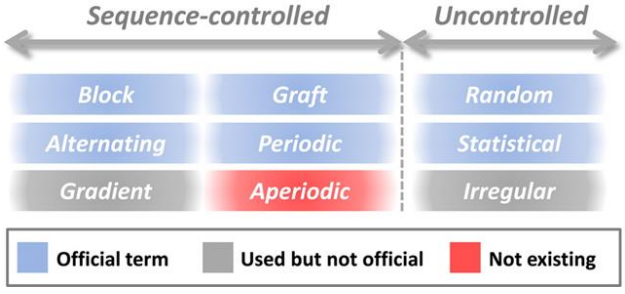

Figure 1. Schematic (taken from the Lutz Viewpoint[1]) showing the relationship of selected official (blue) and unofficial (gray) to the new proposed terminology (red) that can be used to classify synthetic copolymers.

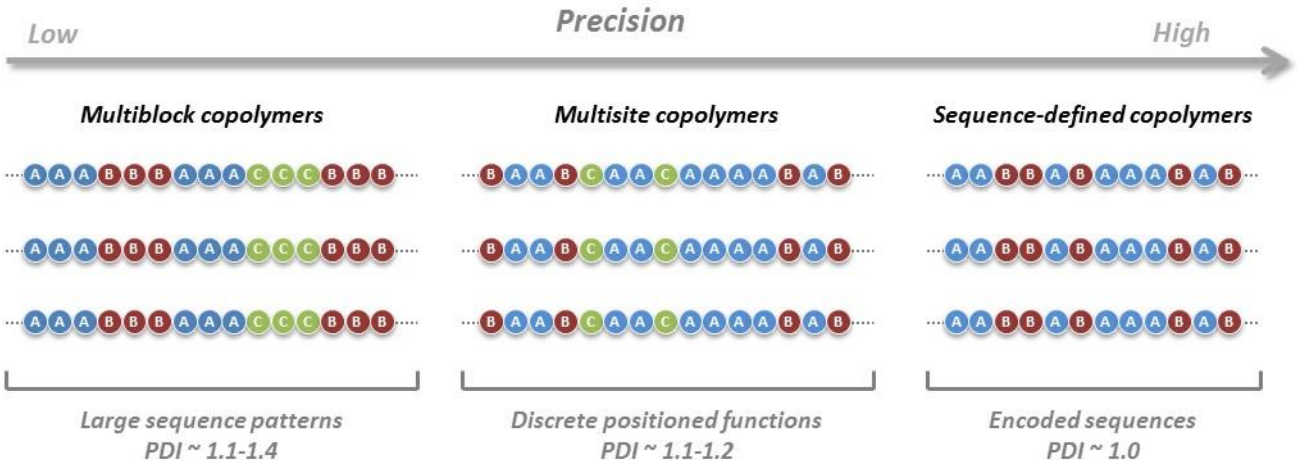

Figure 2. Schematic representation, proposed by Lutz,[1] of different types of aperiodic copolymers: multiblock copolymers (left), multisite copolymers obtained using time-controlled monomer additions (middle), and monodisperse sequence-defined copolymers (right).

Scientific terminology can be a sensitive topic, and intrigued by this Viewpoint, the Editors thought it would be interesting to elicit comments from the members of the community on the proposed use of the term *aperiodic copolymers*.[4] The following distills and summarizes the comments received from the coauthors of this Viewpoint. Two broad conclusions emerge from the individual comments received. First, there was general agreement that current terminology is not adequate to describe the kinds of macromolecular structures that are synthetically accessible, and that Lutz has done the community a service by bringing up such an important point. Second, however, there was near unanimity that "aperiodic" is not the ideal term to describe the structures that Lutz considers. This is due to the fact that the term "aperiodic" is really stressing what the target polymer structure is *not*, rather than what it *is*. To many, "aperiodic" carries a strong implication of "irregular" or even "random", which is the opposite of what the term wishes to convey in this context. While, "aperiodic" does not require the notion of randomness, it is nevertheless associated with it in everyday use by many, which was confirmed by a questioning of a (non-representative) series of colleagues, PhD students and post-doctoral fellows.

As such, the term aperiodic copolymer was viewed as being too broad to describe the sort of copolymers that Lutz wishes to define. Nonetheless Lutz is correct in pointing out that a population of information-containing copolymers (such as the interesting and synthetically challenging structures shown on the right hand side of Figure 2) should differ from a population of statistical copolymers, even though the individual copolymers of both populations have sequences without apparent regularity. Such a differentiation can have important implications, for example, in DNA replication.

In seeking suitable nomenclature, some generally desirable principles emerge. These include: (i) name things by what they are (or strive to be), rather than what they are not; (ii) aim for simplicity and minimal ambiguity; (iii) favor shorter terms when the meaning is clear from the context, but allow for increased specificity when needed; (iv) for synthetic polymers, with their inherent probability of heterogeneity within a population, tolerate modest deviations from the ideal. Accordingly, it seems to us that the terms "sequence-specific" or "sequence-defined" would cover the intention of "aperiodic". From a synthetic perspective, controlling sequence is the critical question and is a separate issue from periodicity—whether the resulting polymer structure is aperiodic, periodic, gradient, *etc.*, is secondary. As such the descriptor "sequenced" might be more versatile, especially if the level at which the sequencing occurred could be specified: "monomer-sequenced", "block-sequenced", (and perhaps "functional group or functionality-sequenced," though there may well be a better term to be found for this concept).

When it comes to multiblock copolymers (Figure 2 left) the complexity of the matter can further be highlighted by an example that Lutz provides on a multiblock **ABCABCABC** polymer (where **A**, **B** and **C** represent different homopolymer segments), which can be considered as a periodic polymer with an $(\mathbf{ABC})_3$ structure. However, this does not say anything about the individual block lengths. Are all blocks of the same chemical composition identical in chain length? If they are not, the degree of periodicity significantly decreases and a more complex description is necessary to precisely describe the polymer. This could be addressed by expanding to "block-sequence-specific" or "block-sequence-defined", and the right side of Figure 2 correspondingly with "monomer-sequence-specific" or "monomer-sequence-defined".

One apparent shortcoming of this proposed terminology is a failure to distinguish between structures with repeating sequences and those without, and this gets to the heart of Lutz's proposed nomenclature. However, it is an interesting question, whether the crucial distinction is really between presence or absence of repetition, or rather whether it is between structures in which the identity of the monomer at every position along the chain is prescribed, or not. We suspect it is the latter dichotomy that is ultimately of more interest. Nevertheless, the proposed nomenclature could be expanded if needed, for example to "aperiodic-monomer-sequence-defined" and "periodic-monomer-sequence-defined". Although bordering on the cumbersome, these terms are unambiguous.

Another possible shortcoming of the above proposed nomenclature is the fact that alternating copolymers, or even homopolymers, could claim to be "monomer-sequence-defined". However, context is everything. No-one would be fooled into believing that an alternating copolymer was some-

how more "sophisticated", because it was given the appellation "sequence-defined". Indeed, **abababababa**...(where **a** and **b** represent different repeat units here) is a sequence, it is just a trivial (and periodic) one. An analogy to number theory might be apt: the fact that 2 and 3 are prime numbers, but of little use in applications where larger prime numbers are important, does not diminish the richness of the general theory of prime numbers.

The proposed nomenclature does not yet provide a unique identifier for the case of multisite polymers illustrated in the middle of Figure 2. Accordingly, possibilities include "intermittent-site-specific", "site controlled" (although, it is worth pointing out here that "site controlled" already has a specific meaning in catalysis and site vs chain-end control is important terminology in catalyzed coordination polymerizations so one has to be careful with the use of this term) or "site-sequenced".

The bottom line is that Lutz is right: IUPAC nomenclature is inapplicable to some complex structures out there and in particular those that show no periodicity. This leaves a situation where researchers working on polymers with a more defined non-periodic sequence than a random copolymer but less precise than a protein have struggled to describe their materials in less than one line. Most publications highlight the potential of their systems by referring to them as "sequence-controlled" polymers, although a truly controlled sequence is hardly ever the case. In other cases, authors of papers describing such polymers have skilfully avoided naming the polymers *per se*, and instead describe the process of their syntheses as "programmed", "sequential", etc. In the case of multiblock copolymers the nomenclature seems to be straightforward, with a Greek-derived descriptor prefix (di, tri, tetra...trideca, etc) followed by the word "block". However, where the degree of polymerization (*DP*) of the respective blocks decreases to only a few repeat units, the resulting polymer will surely lack the properties of a multiblock copolymer (i.e. phase separation, compartmentalization, etc.) and be more similar to a statistical copolymer. The proposed "aperiodic" terminology is interesting but from our very small, unscientific survey, appears not to capture the ideal of a non-periodic sequence-defined synthetic polymer. In this discussion we have suggested alternatives with the realization that exceptions still arise. It may for example, be necessary to find separate definitions for certain classes of polymers discussed herein. One example could be to have different terms for multi-block polymers vs other copolymers. Indeed, Lutz acknowledges that the terminology of block copolymers has evolved in parallel to that of other copolymers wherein the local sequence distribution variations occur at the length scale of a single monomer unit.

In any event, we intend that this discussion along with a set of alternative terms as discussed above, will help to promote dialogue so as to achieve consensus among researchers in the field and even to inspire more in-depth and innovative research in this challenging and exciting segment of polymer science.

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2 For an overview of IUPAC polymer terminology see: *Compendium of Polymer Terminology and Nomenclature, IUPAC Recommendations 2008*; Jones, R.G.; Kahovec, J.; Stepto, R.; Wilks, E.S. Eds.; International Union of Pure and Applied Chemistry, RSC, Cambridge, 2009.

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Graphical Abstract