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Toward artificial Life-supporting Macromolecules

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Abstract. Terrestrial Life is based on polymers. In all known living organisms, DNA stores genetic information, mutates, self-replicates and catalyzes the synthesis of messenger molecules. Although the function of nucleic acids is well-understood, the development of artificial macromolecular mimics remains very limited. Laboratory-synthesized nucleic acids still support Life and some nucleic acids analogues exhibit biological functions. Yet, after hundred years of polymer science, no other type of Life-supporting macromolecule (*i.e.* non-nucleic acids) has ever been reported. In this context, the aim of the present viewpoint is to discuss important challenges that shall be addressed by polymer chemists to achieve artificial Life. Similarly to DNA, an artificial Life-supporting macromolecule shall store information, transfer information and mutate. Many tools, such as sequence-defined polymer synthesis, polymer modification, supramolecular polymer chemistry and dynamic chemistry, are already available to chemists to attain these properties. However, the design of artificial Life-supporting macromolecules is hindered by two main factors. First, the chemical search space is enormous and it is hard to predict promising structures, even with the help of combinatorial and chemoinformatic tools. Secondly, rational design is probably a limited approach to achieve macromolecules that shall be involved in non-equilibrium metabolic systems. Hence, a synergic combination of classical polymer chemistry with the more recent field of systems chemistry is probably the key toward the emergence of artificial Life-supporting macromolecules.

This viewpoint is written in the context of the centennial anniversary of the first article written by Hermann Staudinger about polymerization.¹ All along his career, Staudinger has pointed out the similarities between man-made and biological macromolecules. In particular, in the last pages of his 1953 Nobel lecture,² he discussed the transition from inanimate to living matter and the fact that living organisms and heredity are operated by macromolecules. Earlier that year,³ the structure of DNA was first revealed by Watson and Crick. More than sixty years later, the fact that Life is operated by polymers and the so-called central dogma of molecular biology⁴ involving DNA, RNA and proteins have become textbook knowledge. In particular, it is well understood that DNA is an informational polymer, which stores genetic information using controlled monomer sequences, as well as a molecular replicator, which has the ability to transfer its sequence information to macromolecules of similar (replication) or different (transcription) nature. It also undergoes mutations (*i.e.* random monomer alterations), which enable Darwinian evolution to proceed.

Yet, despite significant progress in polymer chemistry and molecular biology during the past decades, it is still not possible to create synthetic polymers that can support Life in the same way DNA does. Still, very important milestones have been reached with chemically-synthesized nucleic acids. For instance, it has been evidenced that fragments or even whole genomes can be prepared in a laboratory and still operate Life when included in a host organism.^{5,6} It has also been reported that nucleic acids containing non-natural backbones^{7,8} (so-called xeno nucleic acids) or expanded genetic alphabets^{9,10} still exhibit operational biological functions. Nevertheless, in those examples, natural molecular design (*i.e.* nucleic acids) is used, either as such or in a slightly-modified form. In this context, a crucial question shall be asked to polymer chemists: are nucleic acids the only type of macromolecule that can efficiently support Life in the Universe? In other words, is it possible to support Life using chemically-different (*i.e.* non-nucleic acids) informational polymers? In recent years, significant progress has been made on the synthesis of

sequence-controlled polymers;¹¹ including some advances for the design of abiotic informational polymers.¹²⁻¹⁴ Yet, as mentioned above, artificial Life was never achieved using man-made polymers. In a recent Essay,¹⁵ I have discussed the historical, philosophical and scientific aspects of polymer-based artificial Life, and the reader is referred to this earlier text for broader information on the topic. The present viewpoint is specifically addressed to synthetic polymer chemists and discusses specific challenges that shall be overcome to achieve artificial Life-supporting macromolecules.

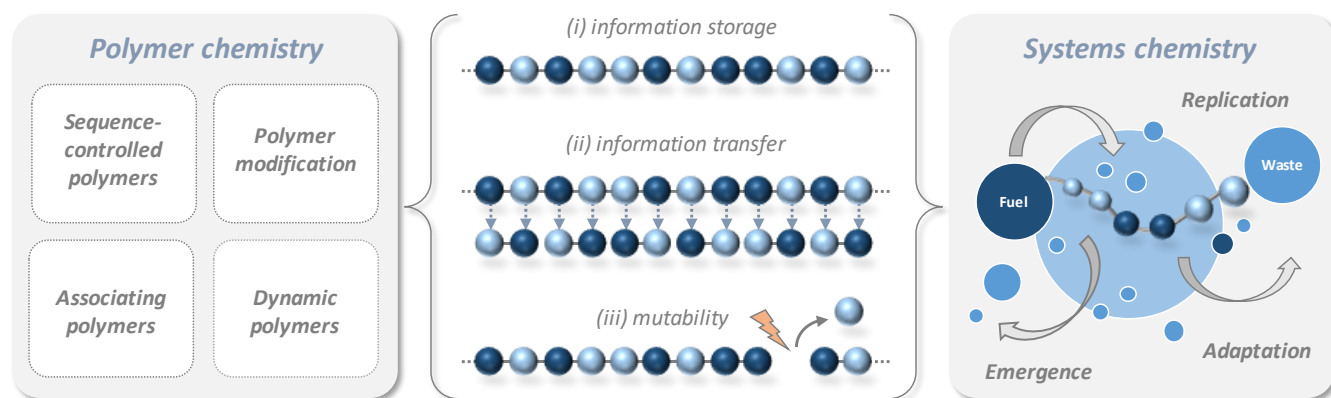


Figure 1. Required properties and available chemical tools for achieving artificial Life-supporting macromolecules. As shown in the middle panel, in order to support Life, a synthetic macromolecule shall at least combine the three following properties: (i) information storage, (ii) information transfer and (iii) mutability. Although some of these properties can be attained by rational design using the polymer chemistry tools listed in the left panel, Life can only occur in non-equilibrium thermodynamic conditions as schematized on the right panel. Thus, artificial Life-supporting macromolecules will probably result from a synergic combination of polymer chemistry and systems chemistry.

What has already been achieved? Although there is no universally-admitted definition of Life,¹⁶⁻¹⁹ living matter can be described - at least from a chemist's point of view - as an individual entity that can exchange matter and energy with its environment, grow, reproduce, react to environmental variations, adapt and evolve. Hence, in order to support Life, a synthetic macromolecule shall exhibit at least the following properties: information storage, information transfer and mutability (Figure 1).¹⁵ Macromolecular storage, which is the possibility to store information using controlled monomer sequences, has now

been widely demonstrated in synthetic copolymers.^{13,20} A few years back,¹¹ that property was restricted to nucleic acids. However, during the last five years, significant research has been dedicated to the synthesis of non-natural information-containing macromolecules,^{12,14,21} including so-called digital polymers that show promise in data storage,²²⁻²⁴ cryptography,²⁵ traceability and anti-counterfeiting²⁶ applications. Such macromolecules are, in most cases, prepared by multistep growth approaches,²⁷ in which coded monomer sequences are constructed step-by-step. Among recent progress, it has been shown that these syntheses can be greatly simplified by the use of protecting-group-free strategies,²⁸ the selection of fast coupling reactions,²² as well as the development of engineering protocols, which facilitate purification.²⁹ In addition, macromolecular storage density can be increased by the use of expanded monomer alphabets,^{13,23,30} which exceed the number of monomers found in nucleic acids. Hence, the synthesis of small-and medium-size abiotic informational polymers has almost become routine laboratory practice. The automated synthesis of relatively long chains is also possible,³¹ even if the maximum chain-length attainable by chemical synthesis is still rather small in comparison with biological sizes.¹⁵

Beyond macromolecular information storage, examples of intermolecular information transfer in abiotic molecules are much more scarce. Although several examples of non-natural self-replicators have been reported,³² most of them deal with non-informational low molecular weight molecules.³³ Very recently, Hunter and colleagues have reported the transfer of a trimer information sequence into a complementary copy using a covalent template.³⁴ A related strategy using dynamic diimine duplexes was also described by Prywes and coworkers; however only for the transfer of a single bit of information.³⁵ The translation of a nucleic acids sequence into an abiotic informational strand was also described by Liu and coworkers.³⁶ There is also almost no example of targeted mutations in synthetic copolymers, despite an abundant literature on polymer modification.³⁷ Yet, our group has reported very recently the sequence-directed photo-mutation of synthetic informational polymers.³⁸

Open challenges for polymer chemists. To attain polymer-based artificial Life (if attainable at all), major challenges lie ahead for polymer chemists. First, research on sequence-controlled polymers is far from being finished. For instance, methods allowing preparation of long non-natural informational chains (*i.e.* above 100 monomers) would be an important breakthrough in the field. In addition, the reduction of synthesis times and the simplification (eventually the avoidance) of complex multi-step procedures remain important problems to solve. Still, the main challenges are elsewhere. For instance, intermolecular information transfer has never been demonstrated with “real” polymers, *i.e.* with synthetic structures containing at least 10-20 monomer units. In fact, the transition from low molecular weight models containing a few bits of information to real informational macromolecules is far from being trivial. Important progress still has to be done regarding the supramolecular association of complementary polymer strands as well as on templated polymerizations. For instance, there are still very few examples of sequence-specific hybridization of non-natural strands,³⁹⁻⁴² and most of them deal with relatively short oligomers. Similarly, non-enzymatic self-replication has only been reported with natural oligomers^{43,44} or with very small non-natural models (*vide supra*).³² Overall, the supramolecular association and polymerization of functional monomers on polymeric templates remain poorly-controlled, despite numerous attempts and studies.^{45,46} Although template polymerizations may be useful to replicate some molecular parameters such as average chain-length or narrow polydispersity,^{47,48} it is not possible at present to transfer accurately (*i.e.* without defects) a non-natural information sequence from parent to daughter-strand. Hence, sequence-specific hybridization and intermolecular information transfer remain important challenges in synthetic macromolecular chemistry. A crucial aspect of this problem is chirality and stereoregularity. Homochirality is essential in terrestrial molecular biology and is known to influence molecular informational content,⁴⁹ macromolecular folding⁵⁰ and self-replication.⁵¹ While the preparation of stereoregular polymers remain a highly stimulating area of polymer science,⁵² it is probably easier to first study information transfer using polymers with achiral backbones, in which informational side-groups are attached to symmetric carbons⁵³

or nitrogen atoms (*e.g.* as in peptide nucleic acids,⁵⁴ peptoids⁵⁵ and other unnatural polymers^{34,56}). Such studies could help to assess if homochirality is also a mandatory requirement for artificial Life. If the implementation of mutations in synthetic informational polymers seems easier from a polymer chemistry point of view, this aspect has barely been studied, as underlined in the previous section. Thus, research shall be conducted in order to design functional repeat units that can be deleted or altered by simple chemical or physical triggers.

The limits of rational design. As discussed in the previous section, synthetic polymer design is mandatory to achieve artificial Life-supporting macromolecules. Yet, it is highly unlikely that artificial Life will be reached by pure rational design. There are two main reasons for that. The first one is that the chemical search space (*i.e.* number of possible reactions, building blocks and macromolecular parameters) is extremely wide, not to say infinite. Taking into account that the number of possible sequences in a 100-mer protein (which is only a single type of polymer) exceeds the number of atoms in the observable Universe,⁵⁷ the situation will be even worse considering more types of monomers and polymers. Even with the help of chemoinformatics, including recent tools such as machine learning and deep learning, it is unlikely that an optimal Life-supporting macromolecule can be entirely predicted. The second limiting aspect is the fact that the largest majority of polymer structures that are synthesized by traditional polymer chemistry are stable molecules than can be isolated, stored and characterized. In contrast to that, living systems are not at thermodynamic equilibrium.⁵⁸ In order to support Life, a macromolecular replicator has to be involved in an out-of-equilibrium metabolic network. Similarly, artificial Life shall rely on dissipative systems, in which a Life-supporting macromolecule shall be in constant interaction with nutrients, waste and eventually other components. Many of these aspects are covered by the emerging domain of systems chemistry,⁵⁹ even though very few works have been done so far in this area with synthetic mac-

romolecules. Thus, the study of non-equilibrium chemical networks involving abiotic informational polymers could be a first step in the direction of polymer-based artificial Life. Furthermore, if a mutable self-replicating artificial macromolecule could be achieved, such non-equilibrium systems would become adaptive.⁶⁰ In other words, they would evolve through generations.

But a crucial question is where to start? Starting from a random mixture of low molecular weight components may lead to the emergence of Life, but, as learned from the development of our planet, it is an extremely long process (on the scale of hundreds of millions to billions of years). Therefore, the process shall be somehow accelerated by Human selection. For example, starting (macro)molecular components could be engineered by polymer chemists and afterwards involved in non-equilibrium systems. Consequently, the combination of conventional polymer design and systems chemistry could be the key towards the development of polymer-based artificial Life. The first fundamental aspect that could be optimized by chemists is the environment, in which such macromolecular systems shall proceed. One feature that is shared by all known living organisms is compartmentalization,⁶¹ which is the fact that a self-replicating chemical machinery is confined in a compartment (*e.g.* a spherical lipid membrane) that keeps it apart from the outside environment; while still allowing selective exchanges between internal and external milieu. Although isolation can be achieved in a variety of colloidal systems,¹⁵ model chemical networks shall probably be first studied in flow reactors allowing chemical input and output. Yet, another important parameter is the choice of the solvent. Even though water is an obvious choice, it would be highly important to assess if artificial Life could be obtained in non-aqueous solvents. For instance, the possibility to find Life in solvents, such as liquid ammonia, formamide and liquid alkanes, has already been discussed.⁵⁷ Last but not least, monomer design could be optimized by Human selection. For instance, the formation of stable backbones (*e.g.* C-C) shall probably be avoided. As learned from Nature – for example, from the natural selection of phosphate linkages in water^{62,63} - heteroatom-containing backbones (*e.g.* including

phosphodiester, ester, amide, imine, carbonate or carbamate linkages) could be more useful for attaining Life-supporting properties since they may enable dynamic rearrangement, degradation and repair. In addition, the chemical composition and stereochemistry of the building-blocks could be predefined by Human reasoning, combinatorial experiments and predictive chemo-informatics modeling. For instance, the development of pseudo-genetic monomer alphabets (*e.g.* type and number of symbols) and monomer-monomer communication (*e.g.* use of specific side-chain associating motifs) could be pre-optimized by *in silico* design and information theory.¹³

Outlook. Nucleic acids, such as DNA and RNA, are probably not the only family of macromolecules that can support Life. This is one possible option that has emerged on Earth through very long period of times under environmental selective pressure. In other words, the formation of these macromolecules has been guided by the history of terrestrial chemical variations (assuming that the primordial soup theory is correct and that Earth was not seeded by extra-terrestrial sources).¹⁵ It could be that this option is, in fact, the only viable one to support Life in the whole Universe. Nevertheless, it is not unreasonable to assume that alternatives could exist.⁵⁷ Other types of Life-supporting macromolecules may already have emerged somewhere else in the Universe; *i.e.* on planets having chemical compositions that differ from the one of Earth. Alternatively, they may be created by intelligent species like our one. Yet, as discussed in this viewpoint, there are still many obstacles to overcome, in terms of polymer chemistry and systems chemistry, before polymer-based artificial Life could be attained. Nonetheless, this is not science fiction. On the contrary, the quest for polymer-based artificial Life appears as an exciting challenge to start the second century of Human polymer science.

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