Advanced macromolecular engineering

The 21st century opened new avenues for synthesis of macromolecules with precisely controlled architectures and functionality, aiming to mimic biological systems. These polymers have been prepared by various chain-growth reactions using either vinyl or cyclic monomers [1]. Such well-defined (co)polymers are prepared by controlled/living polymerization employing reversible deactivation polymerization (RDP) techniques with the concurrent growth of all polymer chains (fast initiation) and greatly diminished contribution of chain breaking reactions (transfer and termination). Originally, living polymerizations were developed for anionic polymerization of non-polar vinyl monomers such as dienes and styrene and were subsequently extended to ionic ring-opening polymerization, coordination polymerization of both olefins and cycloolefins (ROMP), and eventually to radical polymerization (reversible deactivation radical polymerization, RDRP). Recently various catalysts used at parts per million concentration have been developed to be used in the presence of less expensive reagents, such as alkyl halides in atom transfer radical polymerization (ATRP) [2]. This approach very significantly reduced the cost of commercial synthesis of various (co)polymers and enabled macromolecular engineering (ME). ME can be defined as a process comprising rational design of (co)polymers for specific targeted applications, followed by their precise synthesis and processing procedures.

RDP permits precise control of the primary structure of polymer chains. These chains consist of carbon-carbon backbones formed in polymerization of vinyl monomers. In ring-opening polymerization, one can incorporate various heteroatoms to the backbone. It is also possible to copolymerize vinyl and cyclic comonomers facilitating their subsequent degradation. It is also important to extend the range of monomers from those that are "petroleum-based" to those from renewable resources thereby facilitating better control of polymer degradation and recycling.

Several elements of macromolecular architecture can be controlled in RDP. They include chain topology, chain composition, chain functionality, chain stereostructure and chain uniformity. They can be also combined as illustrated in the *figure 1*. These elements are based on chains with covalent bonds connecting monomeric units. In addition, dynamic non-covalent bonds can also form macromolecular chains with properties strongly affected by the dynamics of chain interactions (dynamers, vitrimers and self-healing materials) [3-6]. Eventually polymer chains can be assembled to secondary or even higher order structures through various weak supramolecular interactions in bulk or in solution as in polymerization-induced self-assembly.

Chain topology elements span from linear chains to cycles and various branching features. They can include long or short chain branching, lose or dense branching but also hyper-branched systems and dendrimers. Branches can be distributed with a tunable density along the chain, typically in graft copolymers, or very densely as in bottlebrush copolymers. Branches can be limited to one focal point as in star polymers which can be formed by an arm-first or core-first approach. The type and degree of branching can tremendously affect mechanical or rheological properties of resulting polymers. For example, bottlebrush copolymers can form photonic materials with regular and tunable periods of > 100 nm. Bottlebrush copolymers can become supersoft and superelastic with moduli lower than those of hydrogels. In contrast to hydrogels, which become hard after water evaporation, bottlebrushes can never dry out since their backbones are diluted by their short unentangled side chains rather than by water [8-9]. By variation of graft density, length of side chains and crosslinking density, it is now possible to prepare elastomeric materials with thermomechanical properties mimicking various biological tissues. It is important to design branching degree, uniformity, or location and correlate these elements with macroscopic properties and then precisely carry out synthesis of such materials.

Another essential parameter is chain composition. Block copolymers and segmented copolymers revolutionized polymer science sixty years ago and have been subject of very intense research both in academia and industry. In the chains of block copolymers, there are abrupt changes in composition on passing from one to another segment. This results in phase separation and formation of various regular nanostructured morphologies. Until recently, only diblock and triblock copolymers have been studied. In the latter case over thirty different morphologies were identified, greatly expanding upon the classical spherical, cylindrical, gyroidal and lamellar structures observed for binary systems. Recent progress in ATRP and RAFT (reversible addition-fragmentation transfer) radical polymerization has permitted synthesis of segmented copolymers with twenty or more blocks. There is a strong interest in controlling sequence in polymer chains, decreasing dimensions from long to short segments and to individual monomeric units. This approach has been expanded from classical periodic sequence such as $(AB)_n$ for alternating copolymers, to $(ABC)_n$, $(ABCD)_n$, and eventually to a programmed sequence that can be recorded and written back or even erased [10]. Such sequence control is inspired by biological systems, such as nucleic acids or proteins, and is indispensable for passing from primary to secondary and eventually to the tertiary structures. Another related objective is to design and prepare gradient copolymers with a smooth change of composition along the polymer chains. Such copolymers may have gradient with a linear, V-like, hyperbolic, exponential, or tapered shape. It is also possible to use gradient control not only in a binary system but also ternary, etc. systems. It is essential to make materials with a particular sequence, including multiblock copolymers and gradient copolymers but also to predict how these copolymers will

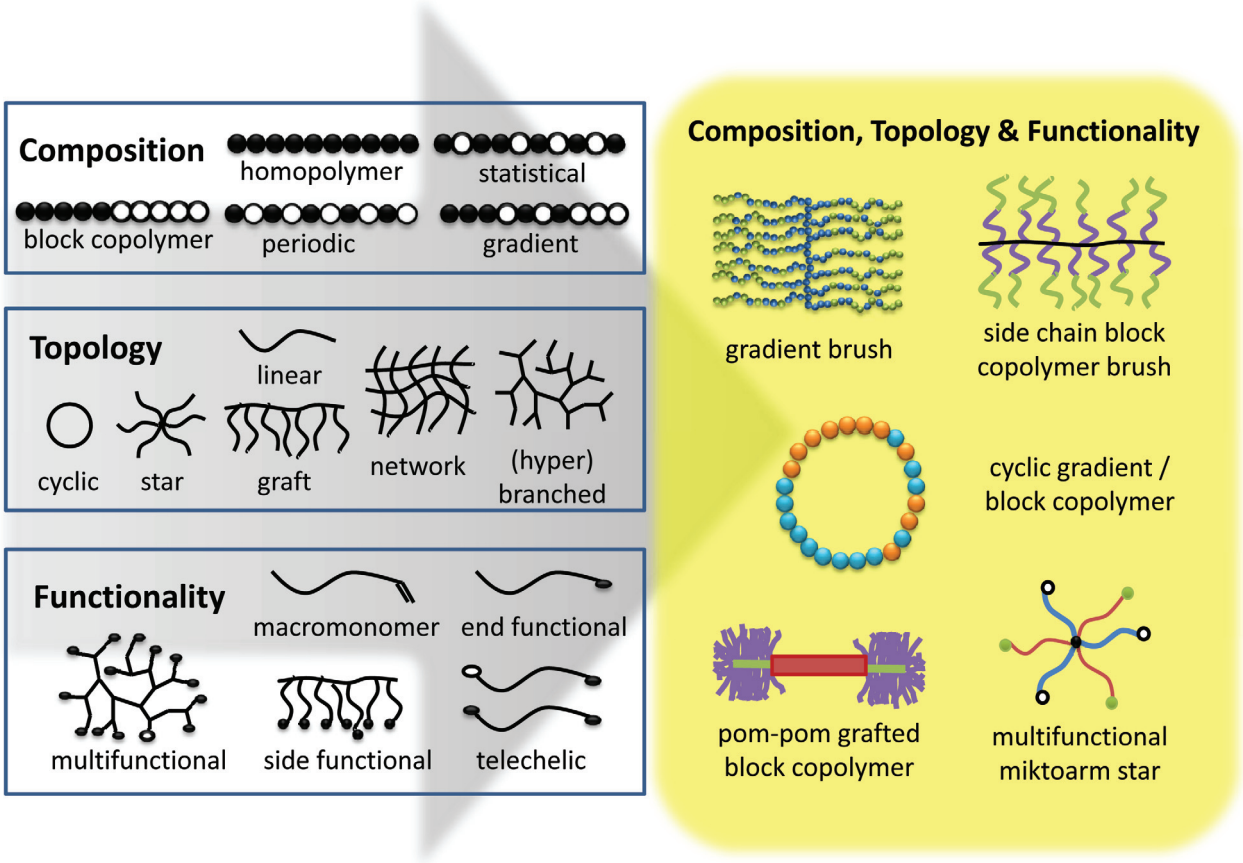

Figure 1 - Individual and combined basic elements of macromolecular architecture. From Matyjaszewski K., *Science*, **2011**, *333*, p. 1104 [7]. Reprinted with permission from AAAS.

assemble to secondary and higher order structures and what kind of properties they will have.

Functional groups can be placed in various parts of macromolecules. They can be located with a pre-determined density along the polymer backbones, at the extreme position of chains, including chain ends in telechelics, chain center, ends of arms in stars and bottlebrushes or in the cores of stars, or chain ends for hyperbranched or dendritic molecules. These groups should carry specific functions that can be used for further reactions, crosslinking or attachments of other moieties whether they are biomolecules, drugs, optoelectronic materials or other species. The site specific functionalities may be not only of one type but also based on several different functionalities. Some functional systems can form self-catalyzed structures that can provide additional control and even facilitate regeneration of formed products by concurrent or consecutive covalent and non-covalent polymerizations [11]. A challenge is to incorporate moieties in a specific position within macromolecules with reactive orthogonal functionalities for further reactions and synergistic effects.

New RDPs, especially proceeding by radical mechanisms, have opened avenues to prepare hybrid materials. They include organic/inorganic hybrids based on nanoparticles, nanotubes and flat surfaces but also bioconjugates formed by the covalent linking of natural products, proteins, nucleic acids, carbohydrates, with synthetic polymers [12]. Proteins with grafted polymer chains can circulate for a longer time in the human body, can survive at low pH, be dispersed in organic solvents and be used as catalysts at higher temperatures or as therapeutics [13-14]. Nucleic acids combined with polymers can self-assemble and pass efficiently through cell membranes and can form various polyplexes. They can be loaded with dyes forming very bright fluorescent probes which can target specific cells after linking with antibodies or aptamers. It is interesting to extend such bioconjugation to larger objects such as living cells or tissue. The challenge is how to design the most efficient materials and how to carry out their precise synthesis. The biohybrids or bioconjugates can be generated at a very basic level by linking proteins and nucleic acids with synthetic polymers in a nonspecific manner. Next step is to position these linkers at a specific location of biomolecule by using biotechnological approaches or by blocking/protection techniques. Eventually, by using macromolecular engineering, the bioconjugates evolve to the next generation of materials with precisely controlled complex architecture such as armored enzymes, exosomes or entirely modified cells [15].

Support from NSF (CHE 1707490) and NIH (R01DE020843) is gratefully acknowledged.

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