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Perspective

Redefining polymer science via multi-stimulus responsiveness

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SUMMARY

Driven by synthetic advances combined with the ability of processing and characterization methods, multi-stimulus responsive (MSR) polymers offer technological opportunities with significant societal impacts. The purpose of this perspective is not to itemize every possible MSR polymer system but instead to highlight recent advances along with current and future trends that redefined modern polymer science. In the context of spatiotemporal and energetic requirements, this perspective explores multi-stimulus responses driven by compositional, structural, and hierarchical macromolecular arrangements, where multi-stimulus may be achieved by combining mechano-responsiveness, pH changes, electromagnetic radiation, magnetic/electric fields, redox reactions, humidity and temperature changes, solvents and gases, or biologically triggered responses. Multi-stimulus responses may be orthogonal, competitive, or synergistic and governed by the redefined principles in developing polymers with signaling and communications, encoding phenotypic properties with precisely defined sequences, programmable assembly/disassembly, and recognition attributes, and MSR materials will pave the next generations of ingenious technological advances with living-like attributes.

INTRODUCTION

Although the interest in stimuli-responsive polymers has evolved over several years, the last two decades witnessed tremendous progress in developing this class of materials.[1–4] Initially driven by the desire to create bio-sensitive nanomaterials capable of drug delivery to living organisms, the field expanded to unprecedented dimensions. Although initially the primary focus has been devoted to polymers with only one responsive moiety, the last decade brought considerable advances in the development of "stealth-smart-polymers" with embedded multi-stimulus responsiveness (MSR).[5,6] Owing to the significant progress in controlled and/or statistical polymerization techniques that enabled the creation of well-defined copolymer topologies and polymer network architectures, MSR functional polymers remain the focal point of many often nature-inspired studies. Furthermore, recent advances frequently focus on MSR in commodity polymers providing technologically affordable and sustainable opportunities for meeting societal needs.

Defined as the ability of materials to respond to a combination of two or more stimuli, including but not limited to mechanical forces, temperature, pressure, pH, ionic strength, concentration gradients, electric and magnetic fields, electromagnetic radiation, or biological environments, MSR may be reversible or irreversible. Responses of polymers can present themselves as volumetric or non-volumetric events, which may involve conformational changes, alterations of the radius of

THE BIGGER PICTURE

Challenges and opportunities:

- Multi-stimulus responsive (MSR) polymers will pave the next generations of ingenious technological advances with signaling and communications, encoding phenotypic properties, programmed assembly/disassembly, and recognition functions.
- New opportunities in rapid developments of microfabrication involving additive manufacturing (AM) and artificial intelligence (AI) will enable emerging demands for device-level MSR polymers and their applications.
- High strength and stiffness commodity MSR polymers capable of responding without intervention under ambient conditions and capable of self-healing are particularly technologically attractive.
- The grand challenge will be leveraging advances in the biological sciences and redefined MSR polymer research that will lead to a new field of materials with metabolic functions.

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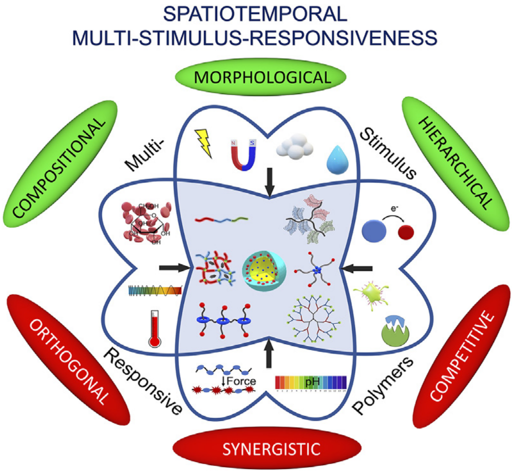

Figure 1. Spatiotemporal requirements for MSR: spatial requirements are typically achieved by compositional, morphological, or hierarchical features

Temporal MSR may involve orthogonal, synergetic, or competitive events.

gyration, solubility changes, degrees of aggregation, reversible or irreversible bond cleavage, inter-chain interactions, inter-diffusion, radiation/emission, and other processes. In general, multi-responsiveness is typically manifested by chemical or/and physical spatiotemporal transformations often associated with energy conversions from one type to another. Stimuli can be physical, chemical, biological, or a combination of the above. One of the most intriguing phenomena is the ability of materials to repair mechanical damage resulting in visually observable autonomous macroscopic remending.[7] Although developing MSR polymers is as exciting as a highly demanding task, it often requires multi-disciplinary physicochemical approaches that are not trivial to execute experimentally or theoretically predicted. If successful, though, new scientific principles will parallel the development of new dynamic materials, redefining traditional polymer science and engineering static structure-property relationships.

The objective of this perspective is not to list all polymeric systems and reactions that exhibit every possible stimuli-responsive feature. The aim is to highlight recent advances by exploring existing and future opportunities, scientific challenges, and potential technologies that have yet to be exploited or have the potential for further advancements. In the context of spatiotemporal requirements, directionality, and time dependence, multi-stimulus-responsive processes may be orthogonal, competitive, or synergistic. At the same time, spatial responses are typically predisposed by compositional, structural, and hierarchical features at various scale lengths (Figure 1), resulting in isotropic or anisotropic properties.

SPATIAL CONSIDERATIONS

For an isolated macromolecule, the energy input required to generate one form of response will be substantially different from responses anticipated for macromolecular chains bundled up into one entity. Two often cited examples of the effect of the environment are photochromic responses[8,9] and physicochemical interactions near interfacial regions.[10] Although photochromic responses in bulk polymers primarily involve nonlinear switching between two isomeric states, surface and interfacial responses, which may also involve photochromic responses, require energy input to mobilize the responsiveness is a function of the distance from surface/interfacial regions. Although intuitively, further away from the surface, higher flexibility and lower energy input are anticipated,[2,11] greater brush density may necessitate higher intakes due to chain packing. Practical examples of this behavior are switchable

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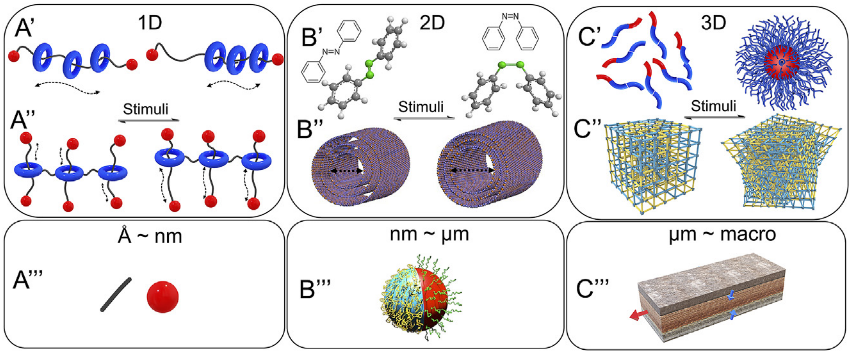

Figure 2. Selected examples of multi-dimensional responsiveness

(A) (A′ and A″) One-directional response at Å-to-nm scale lengths: rotaxanes can slide or rotate (A′) back and forth from one side of a polymer backbone to another along a polymer backbone; if the rings are chemically connected (A″), they may move in an orchestrated manner.

(B) (B′ and B″) Two-directional *trans-cis* isomerization in azo compounds resulting in dimensional rearrangements and color changes (B′) and dimensional nanotube diameter/wall thickness changes in one direction (B′).

(C) (C′ and C″) Three-directional rearrangements of block copolymers lead to an assembly into polymeric micelle-like spherical aggregates (C′) and multi-dimensional and multi-directional mechanical twists of solid polymer networks leading to chiral reconfigurability and geometrical restructuring (C″). Examples of typical dimensional responsiveness in 1D at Å-nm (A‴), 2D at nm-to-μm (B‴), and 3D at μm-to-macro (C‴) length scales.

surface wettabilities or surface hardness changes. Reduction in the glass transition temperature (T_g)[12] and the increase of the free volume near-surface interfacial regions relative to bulk will also play a vital role[13] in stimuli responsiveness.

Considering spatial restrictions due to limited access of "free" volume, for solid-state materials thermoplastic and reprocessable thermosets, energetic requirements may be affected by the glass (T_g), stimuli-responsive (T_{SR}),[14] or crystallization temperatures (T_c).[15] Furthermore, topological and morphological copolymer features may exhibit directional anisotropy. Responsiveness may occur in many directions and dimensions that may or may not be linearly independent. While directionality of responsiveness identifies the propagation direction, dimensionality is characteristic of newly occupied space. For example, stimuli responsiveness may occur along a polymer backbone and can be one-, two-, three-, or multi-directional events. As shown in Figure 2A′, rotaxanes facilitating the movement of the macrocycle can rotate or slide back and forth along the axis from one side of a polymer backbone to another. One can envision that when macrocycles are side-by-side covalently linked, they may collectively move back and forth along neighboring parallel macromolecular threads in a coordinated fashion. This process will require the availability of larger space and higher energy inputs (Figure 2A″). For MSR involving non-volumetric input/responses, such as electric/magnetic, electromagnetic, and nuclear radiation, spatial requirements may not be as critical because absorption or emission of energy typically leads to non-radiative or radiation-emitting deexcitations events. However, volumetric changes may be substantial in photorefractive polymers that involve photogeneration of charge carriers, charge transport, or electro-optic effects, ultimately impacting temporal responses. If energy conversions occur from one type to another, spatiotemporal responses may range from Å to microns and from picoseconds to longer times.

Two-directional classical responsiveness for azo-type (–N=N–) compounds feature *trans-cis* isomerization resulting from the exposure to UV light at 320–350 nm and reversibility upon 400–450 nm irradiation (Figure 2B′). This photoisomerization process decreases the distance between the most outer aromatic carbon atoms from *trans* (~9.0 Å) to *cis* (~5.5 Å) confirmations.[16] Although the *trans* isomer is practically flat, its *cis*-counterpart takes angular geometry, thus responsiveness is 1D at least in two directions. In a solid state, these molecular entities may also serve as the signaling component to remotely report the events during physical network rearrangements,[17] a wall thickness controller and sensor in nanotubes (Figure 2B″),[18] or stimuli-responsive moieties in the Janus nanoparticles.[19] Although the Å-level changes occur at a single molecular level, spatiotemporal requirements for an array of AZO macromonomers may range from nm-to-μm and psec-to-min or longer.

Three-directional responses may occur across all dimensions in all length scales (Figure 2C′). Depending on the size of individual elements and the type of responses, stringent spatial considerations are necessary for designing MSR polymers that are expected to restructure molecular architectures reversibly or irreversibly. Block copolymers may assemble into micelle-like spherical aggregates (Figure 2C′), but mechanical twists may lead to three-directional chiral reconfigurability (Figure 2C″), resulting in anisotropic mechanical properties. Regardless of the length scale, physically, chemically, or biologically induced rearrangements at Å-to-nm (Figure 2A‴), nm-to-μm (Figure 2B‴), or μm-to-macro (Figure 2C‴) will involve orchestrated and synchronized spatiotemporal responses in multi-directions. Multi-dimensional responsiveness may occur if light absorption causes simultaneous thermal excitations, volume changes, or energy-emitting events. These, in turn, may cause pH or temperature changes associated with physical conformational changes in multi-directions. Choosing compositional and/or structural elements to achieve MSR at various scale lengths and dimensions will require rational designs. Although chemical and physical responses are typically associated with intrinsic materials' properties, quantities such as mass or volume being an extrinsic property will also impact spatiotemporal responsiveness dictated by compositional, morphological, and hierarchical features.

Composition-driven responsiveness

Composition-dependent MSR can be achieved by the chemical construction or modifications of a polymer backbone and/or side groups or processing. Although incorporating specific multi-stimuli-responsive chemistries is one approach, physical considerations may involve stress concentration reductions during processing to optimize local stiffness, toughness, or flexibility or embedding the monomer sequence gradients along a copolymer backbone. To illustrate the richness of opportunities in the chemistries and physics of MSR, Figure 3 summarizes the *galaxies* of chemical and physical approaches that may guide existing and lead to new developments of MSR polymers. Starting from the left and climbing up, chemical, physical, and biological stimuli include mechanophores,[20,21] pH and temperature,[22] electromagnetic radiation,[19] redox reactions,[23,24] H_2O,[25] gases,[26,27] magnetic and/or electric fields,[28] glucose,[29,30] and enzymes[31] at the top. Although each stimulus category can be executed by choosing selected reactions or reactants, among the most popular combinations are temperature/pH and electric-magnetic fields/electromagnetic radiation. The richness of physicochemical *galaxies* offers various possibilities for embedding MSR components into polymers or polymer networks, and the reader is directed to several review articles for details.[32,33] Ideally, future MSR physicochemical responsiveness embedded into polymers should employ responsive elements capable of performing nonlinear optimizations to continually respond to chemical and/or physical environmental changes in which the magnitude

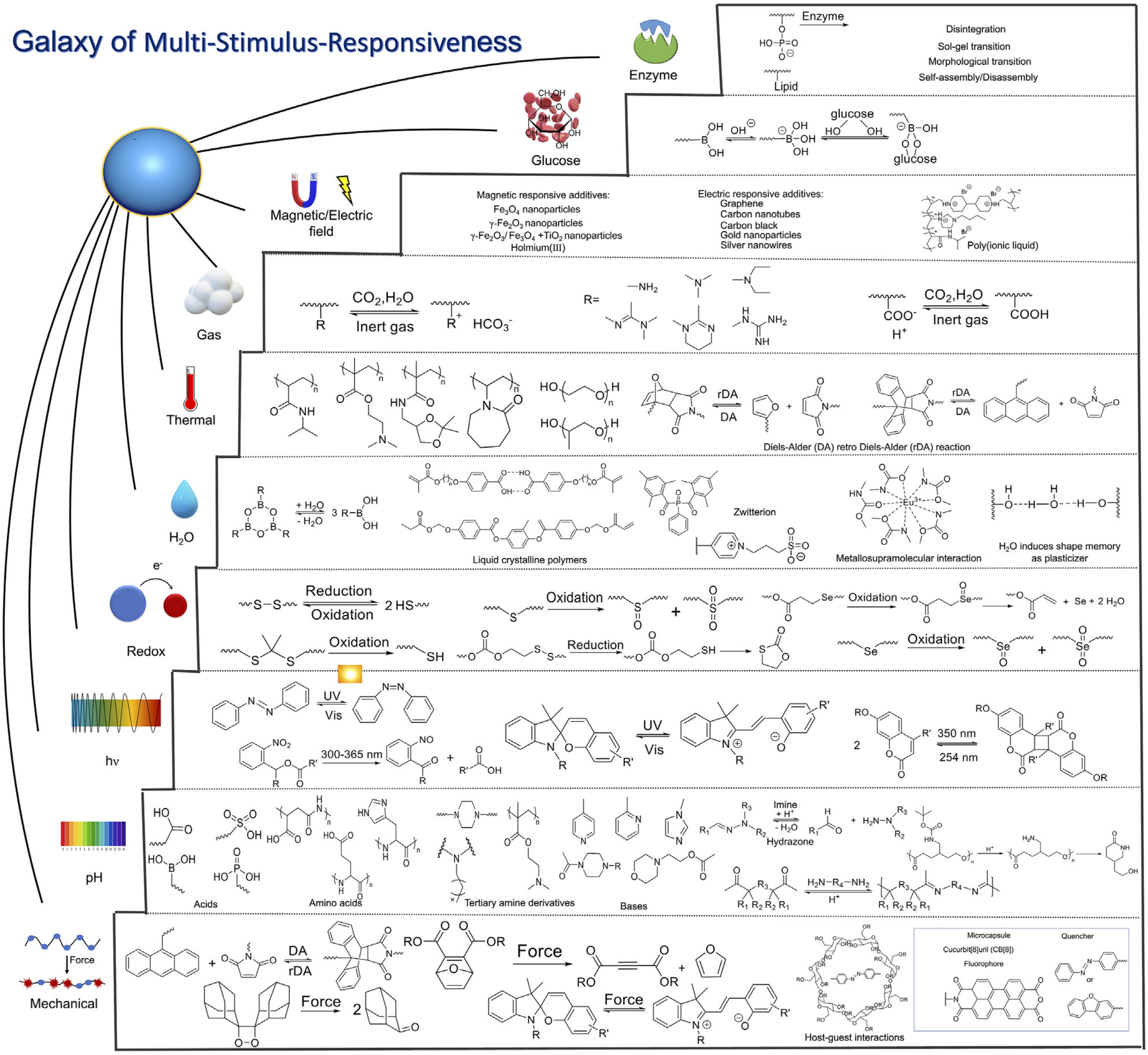

Figure 3. Galaxy of responsive chemical and physical MSR utilized in polymers: mechanical forces (mechanophores), pH changes, electromagnetic radiation, redox reactions, humidity and temperature changes, gases, magnetic/electric fields, glucose, and enzyme-triggered reactions

Chemical reactions, monomers, nanoparticles, and bioactive elements combined into MSR moieties[32] can be incorporated into commodity acrylic, siloxane, epoxy, urethane, ester, and carbonate-based polymers to enable the development of new technologies.[34]

of spatial responses will depend upon compositional, structural, or hierarchical polymer attributes.

Morphology-driven responsiveness

Embedding inside existing materials' MSR components is often challenging because it requires either the diffusion of active ingredients to be attached to the reactive site or covalent attachment into open copolymer topologies. In linear polymers (Figure 4A), MSR active entities can be placed in the middle of the inactive backbone or as the end groups. When active pendant side groups decorate a polymer backbone, or the backbone consists of MSR macromolecular segments, responsiveness to external stimuli will vary depending on the environment (for example, solvent

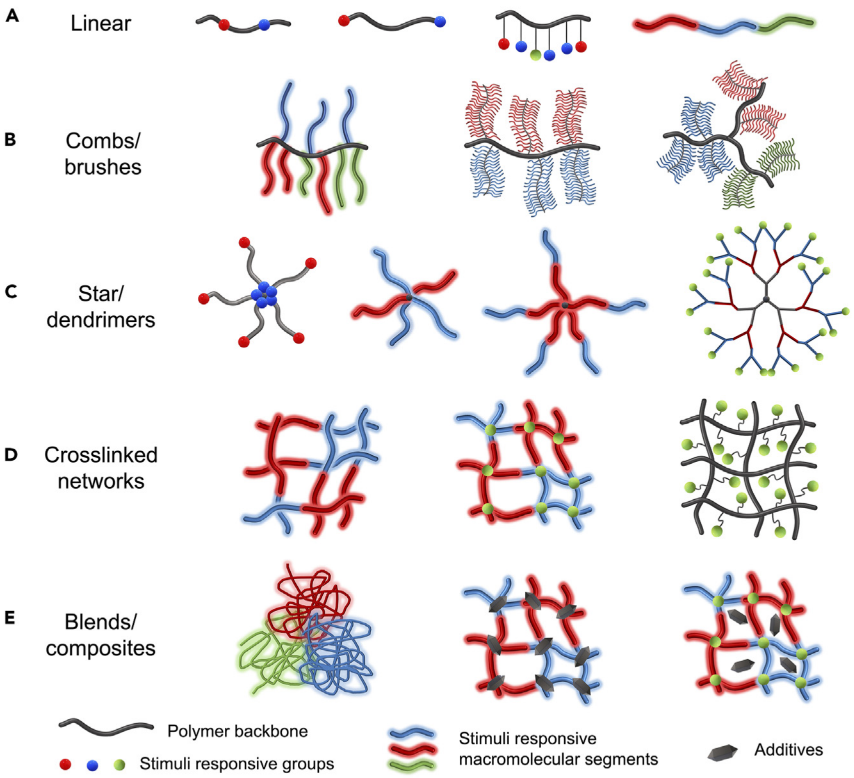

Figure 4. Placements of MSR components in various polymers and their networks

Multi-stimulus-responsive component placements in (A) linear copolymers, (B) combs/brushes, (C) star/dendrimers, (D) crosslinked networks, and (E) blends/composites. Figure legend depicts color-coated active and inactive components.

polarity). More complex architectures forming polymer combs/brushes (Figure 4B) can be advanced into responsive materials by incorporating linear elements with active branches sensitive to multi-stimulus, variable grafting densities, molecular weights, and inter- and/or intra-chain interactions between the backbone and side chains. Being able to stand alone as MSR star/dendrimers can become building blocks of larger 3D constructs (Figure 4C). Multiphase crosslinked networks (Figure 4D), and blends/composites (Figure 4E) may synergistically respond to mechanical, optical, transport, electromagnetic, and/or electrical/magnetic stimuli if each network segments contain hierarchical or orthogonal stimuli responsiveness. One advantage of crosslinked networks and/or blends is that they may also have stimuli responsiveness by doping with inorganic metal or metal oxide nanoparticles, graphene, or other active components. Of particular interest is the dynamic nature of interpenetrating networks enabling the transition into single networks.[35]

Depending upon scale lengths, morphological restructuring architectures (Figure 5A) can exhibit adaptive properties which may impact strength-to-weight ratios, fluid flow paths, surface areas, and other properties. These structural features can be directionally anisotropic. Porous polymer structures and "looser" gel networks are ideal candidates for this restructured intelligence due to space accessibility and highly efficient and energetically favorable adaptability. Creating adaptive architectures facilitating anisotropic flow paths with variable dimensions in various directions leading to anisotropic responses is particularly attractive for biological synthetic interfaces or interphases, which are expected to "communicate" with each other. The

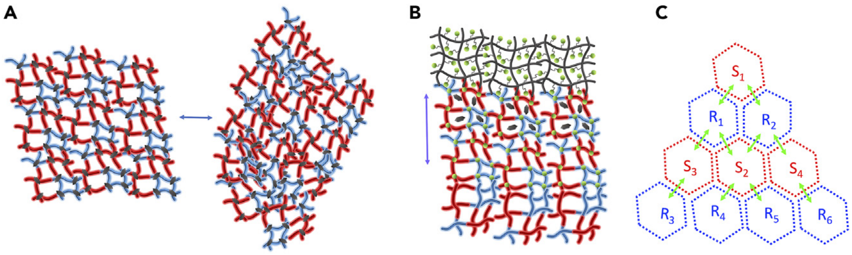

Figure 5. Exampels of hierarchical restructuring of polymer networks

(A) Restructured gels/crosslinked/interpenetrated network morphologies reconfigured to new shapes with anisotropic properties.

(B) Hierarchical MSR polymer gels/crosslinked/interpenetrated networks.

(C) Pascale triangle: each hexagon represents one event ($S_{1\ldots n}$—stimuli; $R_{1\ldots n}$—response) that may trigger responses of the surroundings ($R_{2\ldots n}$), generating other impulses ($S_{2\ldots n}$).

challenge, though, is to create morphological MSR with precisely controlled pore morphologies that will not collapse upon multi-stimulus events and are still capable of structural reorganizations. Figure 5B depicts interfacial areas or connected interphases composed of different density gradients often observed in gels/crosslinked or interpenetrating networks. If each phase exhibits different responsiveness to the same or other stimuli, interfacial energy gradients between phases may induce shear forces. These molecular changes will result in macroscopic out-of-equilibrium responses obtained by kinetic control and energy dissipations. Just like day-to-night cycles regulate metabolic activities, oscillations of concentration changes across these regions may contribute to hierarchical or orthogonal network responses. Many dynamic unique morphologies[36] ranging from simple guest-host systems to complex self-assembled supramolecular objects,[37] crystalline networks,[38] and monolayers[39] have been used to create intriguing architectures from block copolymer assemblies.[40]

Hierarchical responsiveness

Hierarchical MSR typically combines compositional and morphological gradients in which spatiotemporal properties, auxetic effects in internal structures resulting in uniaxial deformations, or multi-chirality at various length scales and directions can be involved. For example, hierarchical multiphase fibrous morphologies provide strength and elasticity for biological species, facilitating responses to environmental changes.[41] Current studies primarily focus on static approaches to transfer loads and dissipate energy, dynamic multi-cycle MSR, although complicated, needs further understanding and is of particular interest. Just like cells require a continuous energy supply to remain in and out of equilibria, hierarchical approaches in synthetic materials require self-regulatory functions through the feedback mechanisms critical in future materials applications.[42] Using an analogy to Pascal's triangle (Figure 5C), stimulus S_1 (top) may trigger two responses, R_1 and R_2 below, leading to new stimuli S_3, S_4, and S_5. This hierarchical MSR, where neighboring hexagons represent a stimulus (S_1 or $\ldots S_n$)-response (R_1 or $\ldots R_n$) pair, may trigger sequential hierarchical responses. The reversibility of hierarchical MSR with no or minimal energy losses is one of the future challenges in developing polymers with living-like functions.

TEMPORAL CONSIDERATIONS

While single-stimulus programming may already be complicated, MSR increases this complexity exponentially. The most straightforward approach is to incorporate multiple, independent of each other stimuli that also generate separate independent responses. However, the temporal dependence between stimuli-response pairs may complicate the process because each event's simultaneity, successiveness, order, continuity, or duration may exhibit constructive or destructive interference. If Nature is the benchmark of "smart" processes, the products of one reaction may serve as a stimulus and/or signal to the following response pathway(s) or the formation of channeling intermediates while maintaining reactant/product separation. This process will facilitate the rapid destroying toxic products, thus preventing undesired molecular "cross-talks" and signaling. Since responses may interact with each other via either the energy exchange and/or spatial occupancy/proximity, temporal attributes in sequential responses often compete for the same stimuli, or stimuli may trigger other responses. If the events are hierarchically related, the duration of each event, their successiveness, and interactions will contribute to the outcomes.

If two or more chemical or physical stimuli are superimposed, they may exhibit constructive or destructive interference. If stimuli are applied simultaneously, responses may occur simultaneously or sequentially, in-phase and/or out-of-phase, amplified or suppressed, or canceled each other out. If two stimuli lead to two simultaneous responses resulting in exothermic and endothermic reactions generating and requiring the same amount of heat, the net output may be zero. Simultaneous responses may be independent if different energy sources are employed. Responses may occur concurrently or sequentially depending on how fast one stimulus propagates through a polymer system. The delay of responses will be determined by the nature of the physical or chemical properties, their directionality, and the kinetics of spatial propagations.[43] Also, designing MSR polymers responding to electric/magnetic/electromagnetic energies can be challenging because the remote and timely delivery of the energy burst with spatial/temporal precision in a non-controllable manner (duration, energy density, frequency) may lead to undesired irreversible effects resulting in degradation or decomposition. If the latter is avoided, the benefits of selectivity are apparent. Thus, temporal conditions involving orthogonal (A), competitive (B), and synergistic (C) MSR should be considered in designing MSR materials.

Orthogonal responsiveness

Like orthogonal programming language enables independent change in one operation without affecting other functions, orthogonal MSR design will utilize one way to execute the stimulus, exerting no impact on others. Orthogonal MSR schematically illustrated in Figure 6A1 involves the design of independent multi-stimuli $S_1 \ldots S_2 \ldots S_n$ that do not cross-talk and lead to independent, separated responses $R_1 \ldots R_2 \ldots R_n$. These multi-steps can be represented as a Cartesian plot shown in Figure 6A2, where periodic propagating sin, square, and pulse waves represent individual independent S_{1+n} processes that result in parallel non-interacting R_{1+n} responses (R axis). Each response is represented by the propagating waves that do not intervene with each other. Although this concept may often reveal the inherent misconception of judging individual stimuli based solely on their selectivity factor and responsiveness, it may also account for each stimulus-response event's energy inputs and response outputs. The S-R event falling on the diagonal will signify no energy loss during each event.

Polymers represented by networks with dynamic covalent bonds may undergo multiple deboning-bonding cycles. Particular focus has recently been devoted to utilizing dynamic covalent bonds in self-healing, shape-memory properties, toughness, and ability to transform from one macromolecular architecture to another.[44,45] Typical chemistries involved in the dynamic covalent bond exchange include transesterification and transthioesterfication reactions, nucleophilic substitution, imine

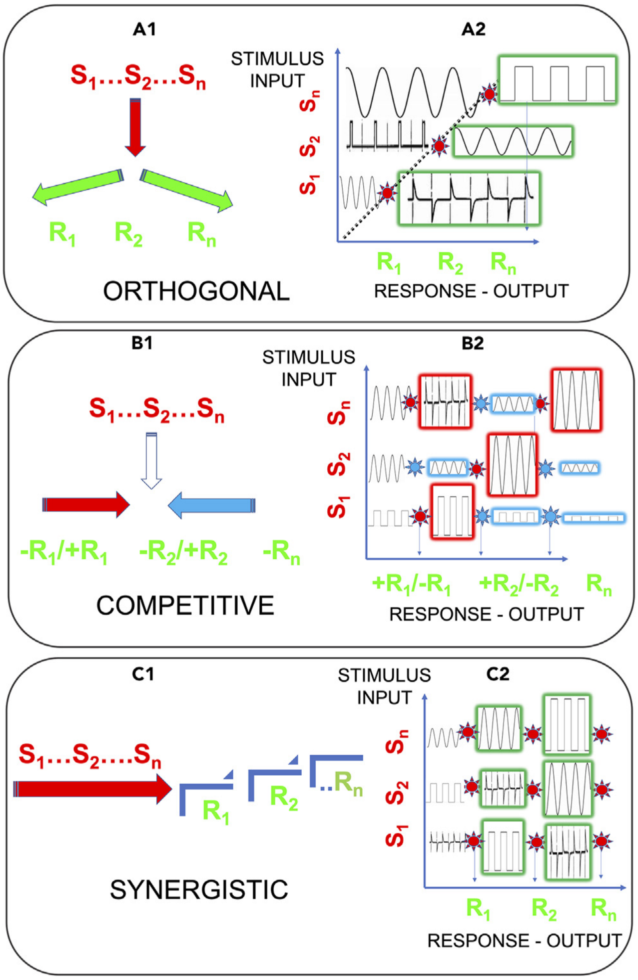

Figure 6. Orthogonal, compatitive, and synergistic responsiveness

(A–C) Vectorial (A1, B1, and C1) and Cartesian (A2, B2, and C2) representation of temporal orthogonal (A), competitive (B), and synergetic (C) multi-stimulus responsiveness. S_1, S_2, and S_n stimuli are represented as periodic functions, and R_1, R_2, and R_n are respective responses.

(A) Orthogonal stimuli-responsiveness results in independent responses.

(B) Competitive stimulus-responsiveness may be amplified (red) or attenuated (blue).

(C) Synergetic stimulus-responsiveness may be amplified (red) in subsequent steps resulting in alteration and/or enhancement of initial responses.

chemistry, Diels-Adler reactions, disulfide exchange, thiol-thioester reactions, or Si–O exchange in siloxanes and silyl ethers (Figure 3). These are typically referred to as covalent adaptive networks (CANs) when incorporated into thermosets. These exchange reactions at elevated temperatures are usually classified into dissociative in which bond cleavage precedes bond reformation, or associative, when bond formation precedes bond dissociation.[46] The orthogonal responsiveness (Figure 7) can be achieved by embedded chemical crosslinker facilitating exchange reactions under pressure at elevated temperatures while independently self-healing under ambient conditions is obtained via van der Waals (vdW) inter-chain interactions.[47] Fluorinated analogs of these materials also exhibit room temperature (RT) self-healing and reprocessability.[48] The design of orthogonal responses typically involves a combination of physical and chemical events, such as shown above or demonstrated by ligands introduced into the oil phase with covalently modified polyoxometalate with β-cyclodextrin (β-CD) through host-guest interactions responsive to multiple

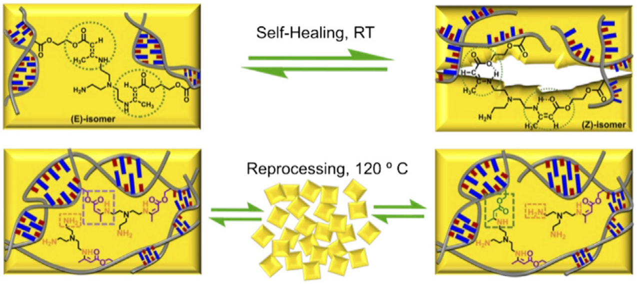

Figure 7. Combining autonomous self-healing and reprocessing in one material offers an extended life span enabling shape configuration changes

This material consists of poly((2-acetoacetoxy)ethyl methacrylate/methyl methacrylate/n-butyl acrylate) (p(AAEMA/MMA/nBA)) copolymer network obtained by copolymerizing (2-acetoacetoxy) ethyl methacrylate (AAEMA), methyl methacrylate (MMA), and n-butyl acrylate (nBA), followed by cross-linking with tristriaminoethyl amine (TREN) to form covalent adaptive networks (CANs). Reproduced with permission from Wang et al.[47] Copyright 2022 American Chemical Society.

stimuli.[49] Ideal orthogonal MSR polymers will inhibit energy cross-talks between the events, although they may occupy the exact space domains and occur during other events.

Competitive responsiveness

It is often difficult to differentiate which portion of electromagnetic radiation directly causes responses and which contributes to local temperature changes, thus potentially resulting in the same net effects. These energetic events can be beneficial in cases where exposure to ultraviolet light causes metal-ligand motifs to be electronically excited, and the absorbed energy is converted into thermal energy to trigger other responses.[50] Competitive stimuli (Figure 6B1) involve multi-sequence (S_1....S_2 ...S_n) that compete for the same responses ($+R_1/-R_1$ ...$+R_2/-R_2$ ...R_n; where "+" and "−" denote constructive and distractive interference, respectively) that may interact constructively (red) or destructively (blue). The Cartesian plot (Figure 6B2) depicts the scenarios where S_1 is enhanced by R_1 (red) but will be attenuated by R_2, followed by further attenuation at R_n. Other possibilities may also occur in which compositional, morphological, or hierarchical responses will involve competitive responsiveness.

The energy conversions significantly influence the reversibility and competitiveness of MSR. This has been successfully utilized in developing reversible cross-linking via Diels-Adler (DA) reactions in epoxies, polyacrylates, and polyamides.[51] Retro-DA reactions offer a disconnection between diene and dienophile, but elevated temperatures reconstruct the covalent bonds. Similarly, photochemical [2+2] cycloaddition of a 1,1,1-tris-(cinnamoyl oxy-methyl)ethane (TCE) monomer can be utilized to form cyclobutane structures via the reversibility of cyclobutane-to-C=C bond conversion (Figure 3). One can envision internal or interfacial stresses released during mechanophore chemical transformations that may cause dimensional and shape alterations. The release of stresses may be beneficial in enhancing the efficiency of electromagnetic radiation conversion to electricity or dimensional reconfigurations with encoded anisotropic properties.

Due to the ease of accessibility, gas-responsive polymers have been increasingly attractive, especially to carbon dioxide (CO_2). Transitions from hydrophobic (without CO_2) to hydrophilic (with CO_2) between acid and basic groups upon adding and removing CO_2 facilitate reversible responsiveness. Most CO_2 switchable polymers contain neutral N-containing compounds; for example, amines, amidines, or guanidines, capable of switching to their bicarbonate salts formed upon CO_2 and water exposure. Water often serves as an environmentally friendly stimulus. Water-responsive self-healable epoxy systems containing reversible networks constituted of the B–O bonds enable reversible switching between boroxine and boronic acid.[52] Because phenyl-boronic acids or esters are susceptible to H_2O_2 oxidation,[53] they can be utilized as caging moieties. Aside from H_2O responsiveness, multi-responsiveness to solvents with various polarities has been recognized as competitive means for creating multiple architectures. Due to solvents, temperature, or pH responsiveness, block copolymers can be utilized as templates for lithographic etch resists.[54] Relying on a combination of divalent organic counter ions and solvent mixtures, block copolymers can self-organize from simple to complex architectures, depending upon the solubility of individual blocks of amphiphilic copolymers.

Synergistic responsiveness

The synergy between individual stimuli (S_1…S_2….S_n) that may lead to one or more responses (R_1… R_2 …R_n), or a single stimulus may lead to sequential responses R_1… R_2 …R_n (Figure 6C). The synergetic multi-stimuli responsiveness can be achieved when, for example, the S_1 event triggers the R_1 response that, in turn, will generate another stimulus to trigger R_n, and so on. These synergetic responses are frequently observed when temperature and pH stimuli are employed, but they often exhibit different spatiotemporal dependencies. Temperature/pH responses may co-occur for polymers in a liquid phase, particularly when fast supramolecular assemblies are involved. It is anticipated that temperature responsiveness will occur more quickly for polymeric gels and solids despite the relatively low thermal conductivity due to faster heat propagation compared with the diffusion of acid-base agents. pH-responsive polymers are usually classified into two types, acid- or base-containing monomer units. Weak poly acids, such as poly(acrylic acid) (PAA), accept protons under acidic conditions and release protons in neutral or basic environments.

By contrast, weak polybases such as poly(2-dimethylaminoethyl methacrylate) (pDMAEMA) accept protons in acidic environments resulting in positively charged polymer chains. Physical diffusion of acid/base components is necessary to achieve pH responsiveness throughout a material. The responsiveness kinetics will depend on intrinsic properties (crosslink density, free volume, etc.) and extrinsic properties' physical properties (volume, mass). Thus, energetic requirements for temperature and/or pH responses may differ.

Recent climate changes inspired the development of temperature- and pH-responsive star polymers as nanocarriers for *in vivo* agrochemical delivery. Driven by the hypothesis that heat stresses limit crop productivity, making plants sensitive to other biotic and abiotic stresses, ~30 nm diameter poly(acrylic acid)-block-poly(N-isopropyl acrylamide) (PAA-b-PNIPAm) star polymers with variable block ratios are capable of temperature programmable release of a model antimicrobial agent (crystal violet) at plant-relevant pHs.[55] The uniqueness of this approach is that loaded star polymers can enter plant leaves through cuticular and epidermis penetration, underlining the potential of polymer multi-responsiveness of agricultural produces.

OUTLOOK

Although many advances over the last two decades have been inspired by biology, a hotspot of 21st century science and engineering is the construction of new MSR materials that nature cannot produce. The ultimate challenge is to develop polymer networks with spatiotemporally and energetically favorable properties capable of reversible and robust MSR events. The ideal MSR polymer system ought to continually sense and respond to stimuli over the lifetime to restore original chemical or physical features or be transformed to serve other functions. At the end of the functional cycle, triggered by orthogonal, competitive, or synergistic MSR at various lengths and timescales, convergence will occur, producing new building blocks. Technological sectors that will benefit from MSR are polymeric coatings,[56] fiber-reinforced composites,[57] textiles,[58] biomedicine,[59] and high-performance materials.[60]

Using analogy to proteins, the balance between hydrophilic and hydrophobic interactions in synthetic materials will also be important in developing MSR combined with adaptiveness. Repetitive proteins arranged into microarchitectures in biological systems are particularly attractive motifs that may serve as analogs for future materials. Despite the frequent occurrence of vdW interactions in the presence of polar bonds in biological systems (proteins, lipids, nucleic acids, and polysaccharides), these ubiquitous inter- or inter-chain forces may be a valuable asset in the development of new MSR material using flexible protein motifs in heteropolymers may enable signaling capabilities.[61] Combined with conventional hard materials (silica, silicon, silicon nitride, glass, and quartz) used in lithographic fabrication techniques will open new venues in biosensing and detection with multi-bio-responsiveness. Using flexible protein-based fibers coupled to silica or other inorganic/organic fibers may lead to optical wave-guiding technological platforms that assemble into hierarchical structural sequences.

The fundamental future challenge derived from the differences between synthetic and biological approaches is that the latter is capable of metabolism. Often described as "self-cannibalization" or autophagy,[62] metabolism in materials can be viewed as self-assembly processes leading to the replacement of “outdated” or degradation side reaction products with newer attributes, reversing degradation reactions, or simply eliminating undesirable side reactions. The minute side reactions are not easily controlled and measured, but combining the characteristics of supramolecular networks that practically do not generate site reactions with covalent rebonding and ubiquitous vdW hydrophobic interactions may pave the future of self-growing polymer. Although it is well established that the hydrophobic effect is critical in many diverse phenomena, from the cleaning of laundry to emulsion synthesis or the assembly of proteins into functional complexes, theoretical studies[63] have taught us that this multifaced effect depends on whether hydrophobic molecules are individually isolated or driven to assemble into larger hydrophobic structures in which water molecules may or may not play a role. Theoretical predictions have shown that water molecules can readily participate in four H-bonds with a methane molecule for a single cavity. Still, for larger hydrophobic aggregates, water hydration is significantly diminished.[64] If hydrophobic aggregates are mechanically disturbed due to mechanical damage, water molecules may disrupt vdW interactions and participate in H-bonding, in which the solvation energy will increase with the increase of the cavity.[65]

One may question the ideas of new paths to achieve self-replicating polymers capable of dynamically adapting to environmental changes. The first step in these directions has already been made by creating autocatalytic networks composed of molecules that may store genetic information and self-replicate due to the presence of hereditary structural features that can be transmitted.[66] Within these networks, the simultaneous presence of signaling and reporting groups induced by a combination of stimuli seems a natural extension. Another intriguing aspect of future MSR polymers is using gas components in the air, such as CO_2, H_2O, or O_2, in quantitative amounts to support living functions and metabolically eliminate toxicity. Living systems mediate their functions by complex feedback loops, and polymersome MSR nanoreactors can mimic the compartmentalization of biological systems with life-like properties.[42]

Rapid developments in microfabrication involving additive manufacturing (AM) and artificial intelligence (AI) capable of replicating nature will enable meeting emerging demands of numerous applications and selected fabrication processes,[67,68] particularly recent developments of orthogonal images for steganography.[69] The effects of long-range ordering, including the frequency and form of repetition with spatiotemporal attributes, will require the precision of macromolecular design and assembly. Along these lines, building from the bottom-up strategy will be advantageous when creating MSR molecular "bricks," which can be further connected to larger architectures using top-down approaches. This assembly process will be particularly attractive when energetically weaker but ubiquitous and directional supramolecular interactions are implemented. Since the first synthetic meta-surface was introduced,[70] ongoing race for optical meta-materials continues to obtain tailored nano- and micro-structured materials with modulated negative refractive index, magnetization changes at optical frequencies, or tunable reflectance by impedance matching.

Along the same lines, non-spherical shape-matching objects, such as cubes,[71] clustered spheres,[72] or dimpled particles,[73] have been developed. Still, selecting directional bonding to form larger objects represents significant challenges. One approach is to create shape-induced "lock-and-key" nanomaterials via directional self-assemblies into higher organized structures. In this process, energetic considerations are critical because for nanoparticles to covalently bond, typical energy ranges are 50–200 kcal/mol, whereas ionic and/or dipolar interactions are in the 10–20 and 1–3 kcal/mol range, respectively. Spatiotemporal responsiveness may lead to anisotropic properties if each nanoparticle contains its MSR components. One example is a nanowire that bends along its longitudinal axis upon exposure to stimuli resulting from sectional shrinkage and contraction. By analogy to block copolymers, "blocky" nanowires may bend at various locations depending upon the number and position of stimuli-responsive blocks[74,75] leading to devices with adaptive sensing and externally actuating properties.

New generations of MSR polymers have already impacted fluid properties, including tunable density and viscosity, wettability, and mobility. The fluid-oil and fluid-rock interactions have positively impacted the enhanced oil recovery technologies.[76] Hydrophobically decorated polyelectrolytes with solvent and pH "sensors"[77] are already utilized in water control and hydraulic fracturing processes, or reversible gels that deliver the proppants into hard-to-access locations. Recent advances in ionic liquids (ILs) and poly(ILs) (PILs) are emerging and rapidly growing areas recognized as a new type of functional polyelectrolytes.[78,79] Particularly, ILs copolymerized with multi-stimulus-responsive and/or commodity monomers may offer built-in responsiveness stimulated by electric and/or magnetic fields.[57]

There is significant interest in developing new mechanical properties, which cannot be achieved in conventional strain-softening (ductile) polymers because their moduli decrease gradually with the increasing strain in an irreversible manner. Since self-configurable and self-healing properties are inherently associated with a material's flow during reconfiguration, shape adaptations and recovery modes resulting from the shape-memory effects are fascinating. Taking this concept further, high strength and stiffness commodity materials capable of responding without intervention under ambient conditions and conformational entropic energy during mechanical damage capable of self-healing are particularly technologically relevant.[67] One can envision that when an object at its threshold strain, upon stimuli, rapidly alters properties from a rigid/elastic to a soft/viscoelastic state. During this process, forces imposed on the object will induce non-uniform deformations and strains, enabling rapid softening and shape adaptation, followed by shape recovery to the initial physical state and condition.

In summary, in the last decade, we have witnessed tremendous growth and advances in developing new MSR components that began to redefine the future of polymeric materials. These discoveries created new principles that will govern the design and development of future materials with embedded metabolic functions capable of signaling and communication, encoding phenotypic properties with defined sequences, and programmed assembly/disassembly. The grand challenge of imparting synthetic materials with the adaptability, responsiveness, and sustainability of synthetic "living" polymers will be creating MSR device-level materials through nano-micro-macro scale growth. Using a toolbox of synthetic and fabrication approaches combined with scientific advances, a new generation of life-like functional polymers is in the process of making.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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