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Towards mimicking biological function with responsive surface-grafted polymer brushes

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ABSTRACT

Responsive or smart polymer brushes undergo pronounced changes in their surface properties and conformation in response to changes in their environment, including variation in temperature, solution pH or ionic strength, and presence of light. Because the brush stimulus response resembles the ability of natural systems to react to environmental changes, responsive polymer brushes have been incorporated into a number of soft biomimetic structures. Nonetheless, the ability to design soft matter systems that recreate the complexity of life remains limited. Here, we survey the use of responsive surface-grafted polymer brushes to mimic biological function. We summarize various ways in which surface-grafted brushes respond to stimuli. Next, we highlight examples of biomimetic engineering that mimic specific biological structures, including molecular motors, ion channels, leukocytes, and leaves. Finally, we discuss recent studies that design brushes to generate lifelike behavior and interrogate their response under the non-equilibrium, spatiotemporally heterogeneous conditions in living systems. Specifically, we focus on hysteresis in the brush response, as one example of nonlinear response; slow diffusion, used by biological systems to maintain chemical gradients; self-oscillation, as an example of auto-amplification of stimuli; and patterned responsiveness, as an example of compartmentalization. This focus emphasizes the emerging need to rationally design the response of brushes for use as soft components in dynamic, life-inspired systems.

1. Introduction

Designing materials that adapt their structure and function in response to spatially and temporally varying signals constitutes a grand challenge in materials science. Such materials offer new opportunities in sensing and detection [1], in controlled release of drugs and therapeutics [2], and in soft robotics [3], among other areas. Strategies to rationally design the material response continue to be inspired by the properties of living matter. In particular, many biological materials are *soft*: they are readily deformed by thermal fluctuations and by small stresses and strains. Thus modest energy inputs are able to generate often dramatic changes in the structure, conformation, or properties of soft materials.

Polymer brushes, consisting of polymer molecules covalently anchored by one end to a substrate, are an increasingly important and versatile component of the toolbox for tailoring the surfaces of adaptive soft materials. At low grafting densities (areal density of grafted chains), the chain conformation of a solvated brush is close to that expected for a bulk solution polymer; at high grafting densities, however, the chains interact laterally and become stretched and extended in the direction normal to the surface (Fig. 1a and b), due to the competition between the polymer elasticity and the repulsion from neighboring monomers (theory reviewed in [4,5]). Importantly, a grafted brush of thickness of only a few nanometers can impart striking differences to surface properties. In nature, for example, thin polyelectrolyte glycoprotein brushes modulate the surface wettability of cartilage in joints, and polymeric periciliary brushes lubricate the surfaces of lung tissue [6].

To generate an adaptive surface requires the use of polymers whose properties alter in response to changes in local environmental conditions. Stimulus-responsive brushes, which undergo changes in physicochemical properties under application of a stimulus, have been widely used to generate a remarkable diversity of adaptive surfaces [7]. Here, we focus on the use of responsive brushes on planar substrates (as opposed to curved nanoparticles, micelles, or molecular brushes). We first highlight examples of responsive brushes used to generate switchable surfaces that mimic biological structures. Reproducing the adaptive complexity of biological systems, however, requires moving beyond a simple binary response. Living systems operate out-of-equilibrium, maintain chemical gradients that drive biochemical reactions through compartmentalization, and exhibit nonlinear responses that can be amplified by feedback or autonomously self-sustain. We summarize recent studies that probe hysteresis, diffusion, self-oscillation, and patterning in responsive polymer brushes, and highlight opportunities to extend the fundamental understanding of these responses to advance the design of ever more biomimetic structures.

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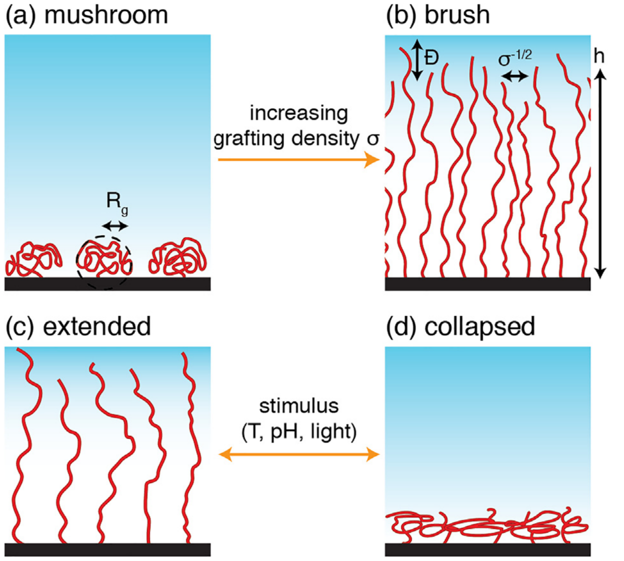

Fig. 1. (a) and (b) Schematic illustration of the conformation of a solvated neutral brush as a function of increasing grafting densityσ: (a) mushroom (radius of gyration R_g); (b) brush (height h, dispersity Đ). (c) and (d) Schematic illustration of one change in polymer conformation, a transition from extended to collapsed, upon response to a stimulus (e.g., pH-responsive polyelectrolytes or thermoresponsive polymers).

2. Responsive surface-grafted polymer brushes

Polymer brushes are a convenient platform for the development of responsive surfaces, in which the polymer conformation and surface properties undergo drastic changes in response to an external stimulus [7–9]. Polymer brushes are typically prepared through either adsorption of pre-formed polymers to a substrate (i.e. grafting-to method) or attachment of a polymerization initiator to the substrate, from which polymer chains are grown (grafting-from method), using a variety of surface-initiated polymerization methods, such as surface-initiated atom transfer radical polymerization (SI-ATRP), surface reversible addition–fragmentation chain transfer polymerization (S-RAFT), and surface-initiated nitroxide-mediated polymerization (SI-NMP) [10]. A variety of chemistries enabling responsive behavior can be incorporated into the polymer brush: pH-responsive polyelectrolytes, thermoresponsive polymers, including zwitterionic polymers, light-responsive polymers, among others.

Polyelectrolyte brushes respond to variations in pH by transitioning from a neutral state, in which the polymer chains are collapsed and relatively hydrophobic, to a charged state, in which the polymer chains are extended and relatively hydrophilic; this transition occurs with increasing pH for polyacid brushes and with decreasing pH for polybasic brushes [11,12]. Polyelectrolyte brushes are very sensitive to not only the solution pH, but also the ionic strength [13,14]. Thermoresponsive brushes undergo a transition from collapsed to swollen with variations in temperature. Depending on the choice of thermoresponsive polymer, the brush may exhibit a lower critical solution temperature (LCST) or upper critical solution temperature (UCST) [15], below or above which, respectively, the brush is miscible with the solvent. Light-responsive brushes undergo chemical changes, such as isomerization, and resulting surface property changes, in response to variations in the wavelength of light [16]. Finally, polymers undergo conformational changes in response to changes in solvent quality, whose extent depends on the specific combination of polymer nad solvent [6]. In all cases, the brush surface properties and response to the presence of the external stimulus (Fig. 1c and d) depend not only on the polymer composition and nature of the stimulus, but also on the polymer molecular weight and grafting density. In responsive brushes, the brush surface properties and polymer conformation can often be switched repeatedly between disparate states through cycling of the external stimulus (Fig. 2) [17–20]. Brushes that incorporate more than one kind of polymer – a block polymer brush of two or more dissimilar polymers chemically grafted together, or a mixed brush of two or more types of polymers grafted to a substrate – can exhibit cooperative changes in conformation.

The changes in polymer conformation in response to an applied stimulus can lead to pronounced changes in the brush properties. As one example, the wet thickness of a poly(acrylic acid) (PAA) brush in one study changed threefold (~13 nm to ~35 nm) as the pH was changed from 3 to 8 [13], and in another study by up to 30% (~16 nm to ~22 nm) as the ionic strength was increased [14]. The response time of the brushes, the time scale for equilibration of the polymer conformation in response to the applied stimulus, can vary significantly between experimental systems. Response times can vary significantly—e.g. from tens of seconds to tens of minutes for PAA brushes exposed to changes in solution pH [21–23]. Kinetically frozen brushes (whether pH-responsive, thermoresponsive, or otherwise) can exhibit exceedingly long response times of minutes to hours. The response time is related to the dynamics of polymer conformational changes, affected by polymer composition, molecular weight and brush grafting density [24,25], and can depend on other factors such as the time to equilibrate the solvent or charge (in the case of polyelectrolytes) through the brush.

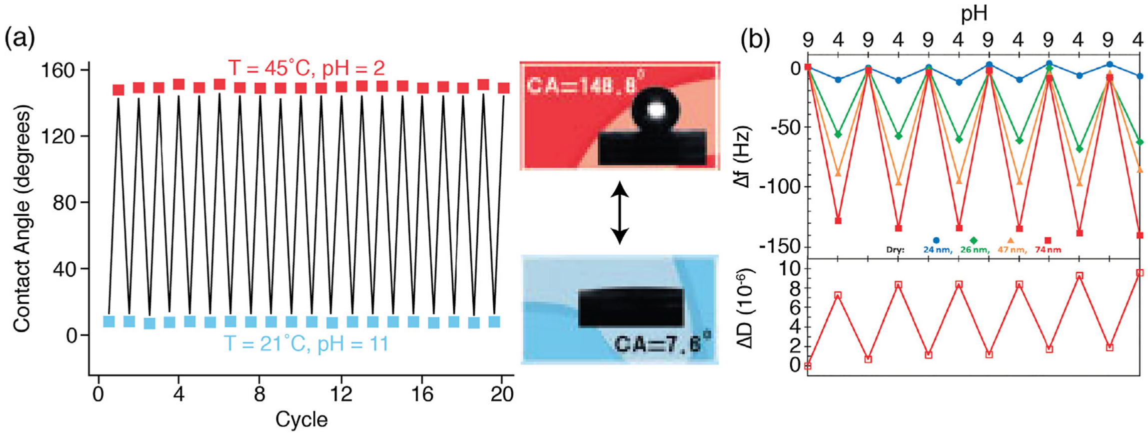

Fig. 2. Responsive brushes have the ability to repeatedly cycle between distinct states, with differing surface properties and polymer conformations. (a) Dual responsive poly(*N*-isopropyl acrylamide-*co*-acrylic acid) brushes were cycled between high contact angle (CA) and low CA states under varying temperature and pH. Reproduced and adapted with permission from Ref. [18]. (b) Polybasic poly[(2-diethylamino)ethyl methacrylate)] brushes exhibited cyclic changes in their degree of swelling (examined through QCM-D, via changes in frequency Δf and dissipation ΔD) under varying pH. Reproduced and adapted with permission from Ref. [19].

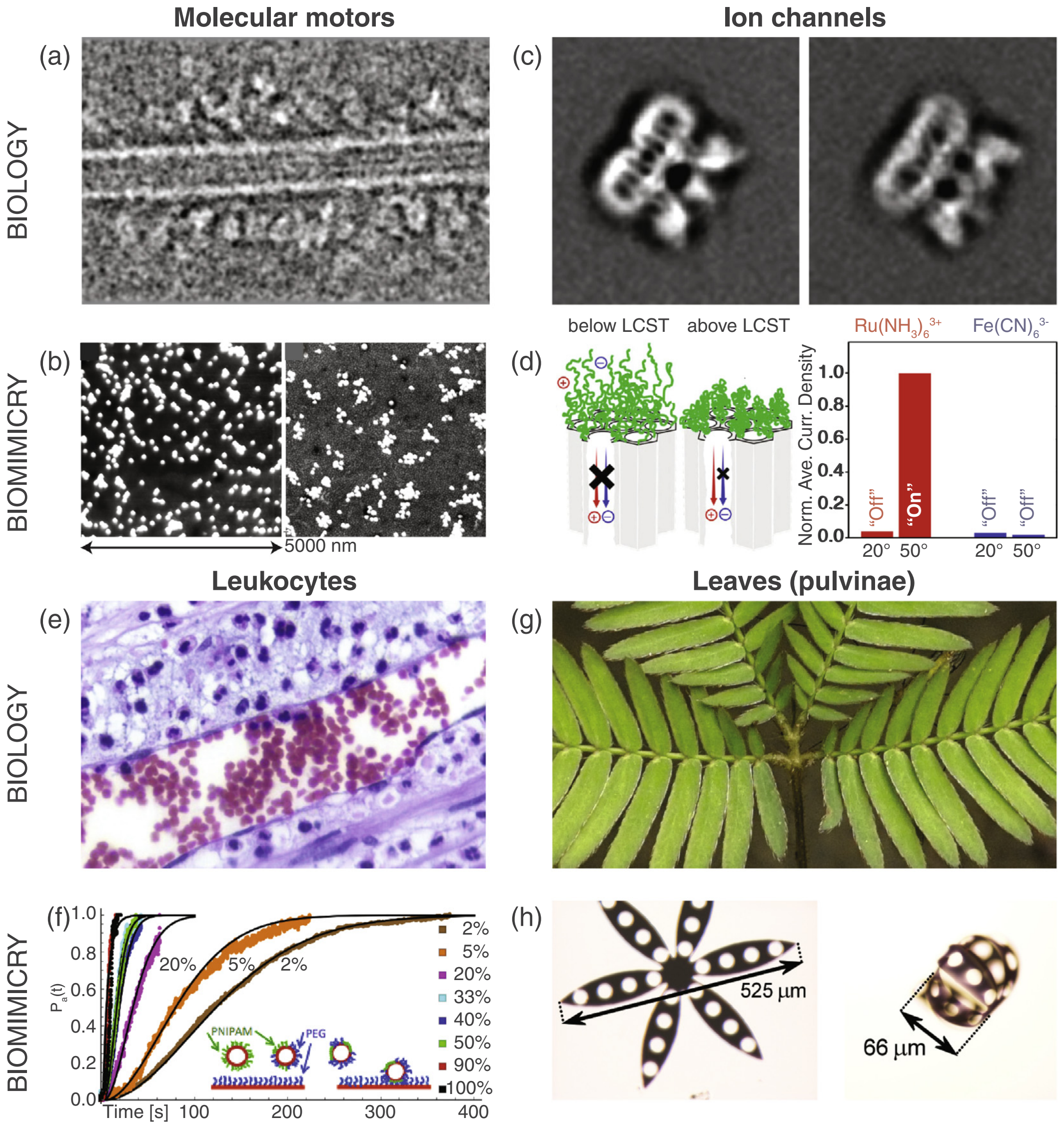

Fig. 3. Examples of (a, c, e, g) biological and (b, d, f, h) biomimetic structures incorporating responsive polymer brushes. (a) Cryo-electron micrograph of *Dictyostelium discoideum* dynein dimers moving along microtubules, reproduced under a CC BY 3.0 license from Ref. [26]. (b) Responsive polymer brushes used as artificial muscles to move particles. Reproduced with permission from Ref. [27]. (c) Cryo-electron micrographs of the TRPV1 ion channel. Reproduced with permission from Ref. [28]. (d) Mesopores functionalized with thermoresponsive poly(N-isopropylacrylamide) (PNIPAAm) brushes, used to selectively control cation transport. Reproduced with permission from Ref. [29]. (e) Rolling adhesion of neutrophils during inflammation. Histological micrograph from the Department of Pathology, Calicut Medical College, and reproduced under a CC BY-SA 4.0 license [https://creativecommons.org/licenses/by-sa/4.0/], via Wikipedia Commons. (f) Probability of capture $P_a(t)$ of PNIPAAm-brush nanoparticles as a function of time, for various surface coverages. Reproduced with permission from Ref. [54], G. Boniello, C. Tribet, E. Marie, V. Croquette, and D. Zanchi, *Phys. Rev. E* 97, 012609 (2018). (g) Pulvinus of a *Mimosa pudica* leaf. Image from Vengolis and reproduced under a CC BY-SA 4.0 license [https://creativecommons.org/licenses/by-sa/4.0/], via Wikimedia Commons. (h) Biomimetic responsive poly(glycidyl methacrylate) brushes incorporated into quasi-2-D bilayer structures that fold through anisotropic shape-change. Reproduced with permission from Ref. [30].

3. Biomimicry using polymer brushes

Responsive polymer brushes are tunable, synthetic systems in which changes in surface properties, including chemical changes and variations in polymer conformation, are triggered by varying the environmental conditions. This stimulus response mimics the changes in structure and function that biological materials undergo. Hence polymer brushes have been widely used as responsive or reconfigurable components in biomimetic structures. We summarize in this section a variety of designs incorporating polymer brushes that reproduce, replicate, or are otherwise inspired by biological functionality.

3.1. Artificial muscles: actuated motion

Molecular motors provided one early inspiration for biomimicry, designed using the switchable polymer brush response. Macromolecular complexes within cells are able to do mechanical work through the use of chemically stored energy. As two examples, myosin motors along actin filaments generate contractile muscle motion, and dynein and kinesin motors transport cargo along microtubules (Fig. 3a) through hydrolysis of adenosine triphosphate. In each case, a conformational change in the motor, driven by the utilization of chemical energy, drives its directional translation.

Conformational changes in polymer brushes can be exploited to move adherent nanoparticles. Multicomponent polymer brushes phase-separate upon exposure to solvent, modulating not only the topography of the surface but also its chemical potential and surface energy. These considerations indicate that the thermodynamics of the brush surface can be altered via solvent-driven conformation changes. Rühe and collaborators, however, harnessed the *dynamics* of the brush conformational change to perform mechanical work, by sequentially exposing brushes to solvents of different quality to generate net displacement of particles on the brush surface [31]. Specifically, poly(methyl methacrylate-*b*-glycidyl methacrylate) (PMMA–*b*-PGMA) diblock copolymer brushes that were briefly (~1 s) exposed to liquid toluene, a poor solvent for the PGMA block, underwent microphase separation, leading to topographic features of height ~10 nm and lateral separation ~50 nm. Short exposures to liquid chloroform, a good solvent for both polymers, restored a flat topography.

Silica particles of diameter 50 nm placed on the brushes were able to dynamically reconfigure upon repeated exposure to chloroform and to toluene. Particles on the brush surface rearranged over multiple switching cycles (Fig. 3b), forming compact islands or linear strings depending on the lengths of the two blocks [27]. Lack of change of particle structure on homopolymer brushes cyclically exposed to solvents confirmed that the motion was not due to thermal diffusion. The interactions of particles with the substrate (van der Waals forces, of order $F_{\mathrm{vdw,s}} \sim 5$ nN, and adhesion forces, of order $F_{\mathrm{adh},s} \sim 30$ nN) and with other particles ($F_{\mathrm{vdw,p}} \sim 2$ nN, $F_{\mathrm{adh,p}} \sim 15$ nN) were comparable in magnitude [32], indicating that the particles were able to rearrange laterally even in the presence of strong forces with the substrate. The lateral motion induced by polymer conformational changes was best suited for simultaneous movement of large numbers of particles [27]. These lateral motions were further controlled by imposing steep local gradients [33] in brush density and height.

Other groups have also used responsive brushes to move nanoscale objects. Purely vertical motion was obtained for particles that were chemically bound to brushes, as demonstrated for cadmium selenide nanoparticles on polystyrene-*b*-poly(methyl methacrylate) brushes [34]. Finally, other kinds of stimulus response can be used to control motion of microscale objects. Conformational changes in thermoresponsive poly(N-isopropylacrylamide) (PNIPAAm), which undergoes a transition from swollen to collapsed as the temperature is raised above its LCST of 32 °C, were used to control the motility of microtubules [35]. Together, these experiments show that conformational changes in brushes can be used to actuate nanoparticle motion, in analogy to molecular motors; the speeds at which objects are propelled by the conformational changes in polymer brushes, however, are limited by the stimulus response and are lower than those attainable by molecular motors (~0.2–60 μm s^{-1}, for myosin moving on actin). In addition, molecular motors are optimized for high speed (e.g. myosin, which acting cooperatively can generate large displacement of actin) or processivity (kinesin, which can move long distances along microtubules without dissociating) – these features have not been reproduced in brushes.

3.2. *Artificial ion channels: controlling ion transport*

A second example of biomimicry utilizing the responsive properties of polymer brushes is the development of artificial ion channels. Ion channels are pore-forming proteins that transport ions through cell membranes, down an electrochemical gradient, at rates that can exceed 10^6 ions s^{-1} (Fig. 3c). Biological ion channels are selective for ions of a given size and charge; moreover, ion transport depends sensitively on environmental conditions, as conformational changes within the protein can gate ion transport by opening or closing the pore. The selectivity, speed, and gating properties of biological ion channels, attractive for applications from sensing to separations to electronics, has inspired biomimetic analogues that reproduce these desirable features.

As one example, rectified ion transport in solid-state conical nanopores arises from a synergy between an entropic driving force, due to the channel asymmetry, and the electrostatic force due to charges on the nanopore surface [36]. To control the surface charge and hence the extent of rectification (departure of the current-voltage relationship from linear ohmic behavior), Azzaroni and collaborators grew zwitterionic poly(methacryloyl-l-lysine) brushes inside polyimide conical nanopores using a surface-initiated free radical polymerization [37]. The extent of charge on the polymer brushes was manipulated via the solution pH, allowing the degree of rectification to be sensitively tuned. At pH 2, poly(methacryloyl-l-lysine) bore positively-charged amine groups ($-\mathrm{NH_3}^+$) and the high degree of surface charge led to strong rectification. When the pH was increased to near the isoelectric point of the polymer (pI ≈ 4.7), the degree of rectification dropped dramatically. Further increasing the pH, so that the polymer bore negatively-charged carboxylic acid groups ($-\mathrm{COO}^-$), reversed the permselectivity and once again increased the degree of rectification. Thus smart polymer brushes were used to control both the selectivity and degree of rectification in an artificial ion channel.

The choice of polymer dictates the transport properties of artificial ion channels. Surface polymerization of polyprotic poly(2-(methacryloyloxy)ethyl phosphate), which exhibits two distinct $\mathrm{p}K_\mathrm{a}$ values, generated artificial nanopores with a tunable degree of rectification over a broad pH range [38]. This device was inspired by the pH-gated ion channel M2 from influenza A, in which ion transport is modulated through the degree of protonation of specific residues within the pore, and illustrates the importance of electrostatics in natural systems for modulating ion transport [38]. Spatially-controlled polymerization of poly(acrylic acid) (PAA), a weak polyelectrolyte, within one-half of an asymmetric hourglass-shaped nanochannel enabled pH-tunable gating [39]. At low pH, where PAA is fully protonated, ionic transport through the nanochannel was greatly reduced by the relative hydrophobicity of the channel walls. Functionalization of a cylindrical nanopore with poly(2-vinylpyridine) (P2VP), a pH-responsive polymer, also enabled pH-dependent gating [40]. Increasing the solution pH above its $\mathrm{p}K_\mathrm{a} \approx 5.25$, for which the pyridine moieties in P2VP are fully deprotonated, halted ionic transport through the channel. This example illustrates that surface wettability also plays a key role in controlling ion transport: a strongly hydrophobic surface hinders the mobility of the electrolyte layer near the wall that controls ionic transport [40].

While pH-responsive polymers offer the ability to directly mimic the mechanisms controlling ionic transport in natural ion channels, other kinds of stimuli-responsive polymers replicate other biological responses. The transient receptor potential channels in the surface membranes of sensory neurons, for example, permit the passage of cations only under very specific thermal conditions. Temperature-responsive polymers allow these properties to be reproduced in synthetic channels. Polymerization of PNIPAAm brushes on the surface of a conical nanopore generated a thermally-controlled molecular gate [41]. Collapse of PNIPAAm brushes above the LCST increased the effective cross-sectional area of the nanopore and hence its conductance [41]. Because PNIPAAm is uncharged, transport through the thermally-controlled molecular gate was linear and ohmic, without rectification. Attachment of thiolated PNIPAAm to a gold-coated nanopore surface, however, enabled thermally-controlled rectification, due to the anions adsorbed to the bare gold around the brushes [42]. Finally, functionalization of nanopores with dual-stimulus-responsive polymer brushes, such as the copolymer poly(N-isopropylacrylamide-*co*-acrylic acid) [43] or the homopolymer poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) [44], enabled separate control over conductivity (via the temperature response) and rectification (via the pH-response). The ability to generate nanopores that respond to multiple stimuli represents a first step towards mimicking the complexity of biological ion channels, aimed at practical applications in biosensing [45]. Additional structural complexity can be obtained by grafting polymer brushes to the surface of mesoporous thin films to generate ion-selective mesochannels (Fig. 3d) [29,46,47].

To date, polymer-brush grafted channels have been able to reproduce several properties of biological ion channels, including ligand

[47], pH [48], and temperature [29] gating as well as multi-property gating [49]. The minimum pore diameter of brush-bearing artificial ion channels (~1 nm, using mesoporous thin films), however, is still approximately an order of magnitude larger than that of biological ion channels (~1 Å).

3.3. Artificial cell surfaces: modeling cell and particle capture

The surfaces of living cells are often "brushy," bearing heterogeneous macromolecular structures. Gut epithelial cells, as one example, feature microvilli, thin protrusions that form a thin "brush layer" with high surface area and are embedded with digestive enzymes for carbohydrates. Interactions of particles with the brushy layer control the uptake of nutrients into the body and play a key role in signaling the presence of pathogens to the immune system.

Kalasin and Santore developed a model system to explore the effects of hydrogen bonding, thought to be important for particle uptake in the gut as well for the rolling adhesion used by leukocytes to initially adhere to the inner surface of blood vessels (Fig. 3e) [50]. Silica particles were flowed over surfaces grafted with short (molecular weights of 2 and 5 k mol^{-1}) poly(ethylene glycol) (PEG) brushes. Short-range hydrogen bonds between the silica and PEG slowed particle capture, so that particles transported in flow gradually rolled before permanently arresting. Particles captured by long-range electrostatic interactions, however, did not gradually slow but instead rapidly arrested. This result demonstrated that hydrogen bonds between polymer brushes and particles can play an important role in particle capture. On a substrate bearing isolated polyelectrolyte PDMAEMA coils, whether particles rolled or arrested depended on the particle size, PDMAEMA density, and Debye length, set by the solution ionic strength [51]. This result suggested that a nanoscopic contact area determined the likelihood of capture, subsequently exploited to capture mammalian cell through non-specific interactions [52].

The use of responsive polymers enables capture to be tuned via environmental conditions, as expected in dynamic, nonequilibrium biological systems. To demonstrate that brush interactions could be tuned to modulate particle capture, Zanchi and collaborators functionalized silica nanoparticles with thermoresponsive polymer brushes via adsorption of a poly(l-lysine) (PLL) backbone bearing PNIPAAm grafts [53]. The density of the thermoresponsive moieties was controlled by co-adsorption of a non-responsive poly(l-lysine-graft-ethylene glycol) comb polymer. Raising the temperature above the LCST collapsed the PNIPAAm chains, driving aggregation of the functionalized nanoparticles on a flat brush-coated substrate. Brush-coated nanoparticles also exhibited rolling adhesion prior to irreversible arrest, with the duration of rolling adhesion tunable via the fraction of discrete sticky patches on the particle surface (Fig. 3f) [54]. The slow capture of a heterogeneously-functionalized particle was reminiscent of the slow capture of a rolling leukocyte, signaling the importance of heterogeneous surfaces in this biological process. This scenario, however, represents a highly idealized version of leukocyte adhesion. The existing experiments modulate polymer brush-mediated interactions with a surface to drive a transition to immobilized particles. Leukocytes, however, undergo this transition in response to chemical cues that vary in space and in time, and in the presence of fluid shear (i.e., blood flow). Furthermore, the speed of rolling depends non-monotonically on the shear rate, consistent with a stress-enhanced adhesion. Such features have not been generated using biomimetic brushes.

3.4. Artificial leaves: responsive shape

The ability of responsive polymer brushes to selectively uptake or exclude water suggests them as components in structures that reproduce the hydration-induced changes observed in plants. Leaves, tendrils, and flowers respond to changes in environmental humidity through variation in turgor pressure. Anisotropic loss of turgor pressure (e.g., on one side of a vascular tissue) causes the plant structure to bend or fold.

The pulvinus, as one example, is an enlarged joint at the base of a leaf, consisting of a core of vascular tissue within a sheath of thin-walled parenchyma cells. This structure enables the rapid folding of *Mimosa pudica*, the sensitive plant, in response to a mechanical stimulus (Fig. 3g). Huck and collaborators incorporated polymer brushes into artificial folding structures whose folding mechanism was inspired by that of the pulvinus [30]. Poly(glycidyl methacrylate) (PGMA) or poly (methacryloxyethyl trimethylammonium chloride) (PMETAC) brushes were grown via ATRP on thin gold sheets to generate a quasi-2D bilayer. Each brush underwent a conformational change in response to an environmental stimulus: Au-PGMA bilayers irreversibly folded when the PGMA brushes were immersed in methanol (Fig. 3h) [30], and Au-PMETAC bilayers folded on a time scale of ~5 min when the PMETAC brushes were immersed in a concentrated salt solution [55]. The extent of folding, quantified by the radius of curvature, was determined by the interplay between the brush free energy and the elastic free energy of deformation of the gold substrate [55]. Because responsive polymer brushes are geometrically constrained only at the point of tether to the surface, they can undergo large changes in extension ratio to offer large changes in properties. Although not extensively characterized, the dynamics of these objects are likely controlled by the transport of solvent in and out of the responsive polymer brush, suggesting that the response may be able to be tuned to generate hysteresis in these and other bilayer biomimetic structures [56].

The Au-brush bilayers [30,55] respond to chemical stimuli. Brush-bearing biomimetic structures responding to a light or mechanical stimulus (as *M. pudica* does) have not yet been reported, although polymers with these stimulus responses are known. Further, the time scale on which *M. pudica* leaves fold, ~1 s, is much faster than typical response times reported for polymer brushes.

4. Advances in brush response: towards designing brushes for life-inspired systems

The examples in Section 3 involve responsive brushes that were incorporated into an engineered system designed to mimic a specific biological structure. These structures represent "top-down" engineering, in which components are integrated into a design, and are representative of how engineers often design a system for a particular task or goal. In particular, molecular engineering of polymer brushes has focused on synthesizing responsive chemistries for specific applications [7–9], and on controlling their spatial localization and organization to achieve a desired response.

Nature, however, designs differently – especially at the nanoscale. Critically, natural systems are dynamic, featuring self-organization in both time and in space, in contrast to spatially-organized engineered systems. This remarkable self-organization, as surveyed recently in a perspective by Grzybowski and Huck [57], occurs in crowded yet compartmentalized environments whose function is to maintain the chemical gradients that drive biological activity. Thus understanding how to control the spacetime response of nanotechnological components is essential for designing the next generation of biomimetic systems.

Towards this end, living nanotechnologies exhibit several key features not significantly considered in the design and characterization of responsive brushes to date. First, biological systems operate under out-of-equilibrium conditions, which may feature hysteresis or other nonlinear responses. Second, biological systems are crowded and/or compartmentalized, slowing diffusive processes and preventing homogenization of chemical signals. Third, biological systems incorporate feedback loops to generate nonlinear responses, enabling auto-amplification or auto-inhibition of an external stimulus [57]. Here, we summarize studies that explore these features in responsive polymer brushes, representing a first step towards understanding brush response

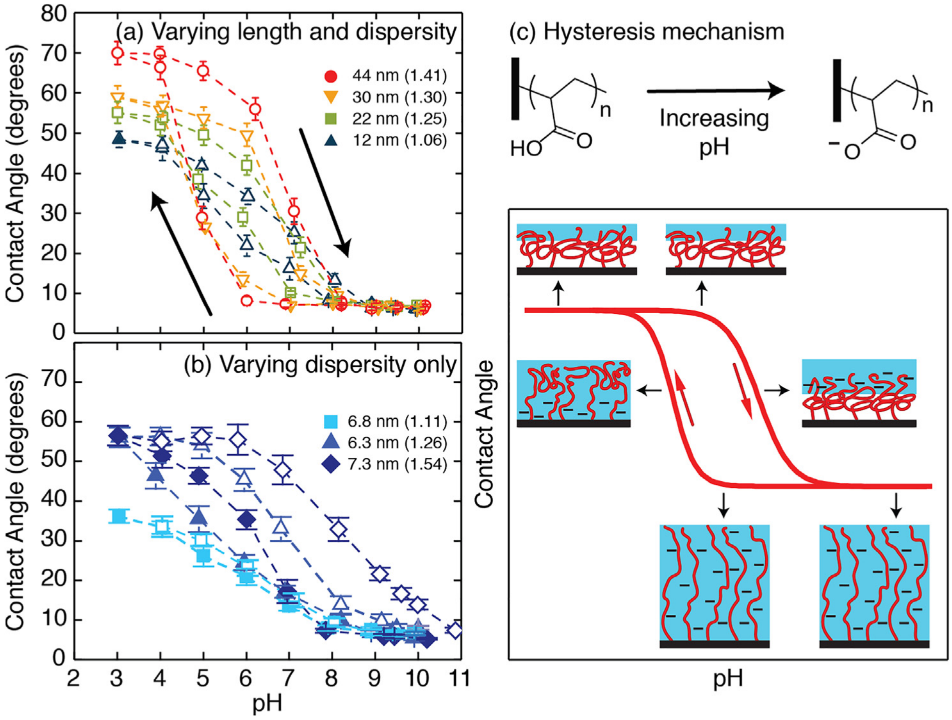

Fig. 4. pH-dependent static water contact angle for two series of densely grafted poly(acrylic acid) (PAA) brushes. In the first series (a), both brush length and brush dispersity were varied whereas in the second series (b) dispersity alone was varied. Error bars represent the standard deviation from at least five measurements obtained from the same substrate. Brushes in both series exhibited hysteretic memory, in which the contact angle was dependent on the direction of pH change. (c) Illustration of the proposed mechanism for changes in brush conformation and charge distribution as a function of pH, in which conformational changes in the brushes, enabled by the high dispersity in the molecular weight distribution, were the origin of this behavior. At high pH, the brush was negatively charged, extended, and solvated. After decreasing the pH to the collapsed state, water was expelled from the brush. Upon subsequent increase in pH, the phase separated brush structure hindered ion and water transport through the brush, leading to memory behavior. Adapted with permission from Ref. [59].

under the out-of-equilibrium conditions increasingly in demand for biomimetic nanotechnological systems.

4.1. Hysteretic brush response

Living systems operate dynamically in non-equilibrium conditions, responding to various chemical or other external inputs driving their actions. Polymer brushes also have the capability of demonstrating nonequilibrium and nonlinear responses to external stimuli. Hysteresis (i.e. a memory effect) is one class of nonlinear response, in which the response magnitude depends on the stimulus direction of change. Hysteretic memory has been observed in the pH-response of densely grafted polyelectrolyte brushes. PAA brushes are protonated and collapsed at low pH and become charged and extended at high pH. The water contact angle of PAA brushes, a measure of the surface wettability and also degree of brush ionization, depended on the direction of pH change, observed in PAA brushes prepared through grafting-to techniques [58] as well as in densely-grafted brushes prepared through SI-ATRP (grafting density $\sigma \sim 0.38$ chains nm^{-2}) (Fig. 4a) [59]. When observed directly through infrared spectroscopy, the degree of ionization also showed hysteretic memory and therefore depended on the direction of pH change [58]. Polybasic brushes, which transition from collapsed to extended upon decreasing pH, showed related memory effects. The pH-dependent hydrated thickness and swelling ratio of poly[(2-diethylamino)ethyl methacrylate)] brushes, prepared through SI-ATRP, exhibited hysteretic memory within the first pH cycle, which subsequently disappeared [19,60]. It was proposed that hysteretic memory in these polybasic brushes arose from the formation of a hydrophobic skin upon deprotonation of the brush periphery, which prevented transport of solvent and ions through the brush [19,60].

Polymer properties that affect transport within the brush affect hysteretic memory, as shown for the example of polymer dispersity, related to the breadth of the polymer molecular weight distribution. Densely grafted polyacid PAA brushes composed of low-dispersity polymers did not exhibit a water contact angle that was dependent on the direction of pH change, whereas increasing the brush dispersity generated this behavior (Fig. 4b) [59]. This hysteretic memory was proposed to originate from the exclusion of water from the PAA brush at low pH, hindering transport of ions and water through the brush as the pH was subsequently increased, with these effects driven by pH-induced conformational changes in high dispersity brushes (Fig. 4c) [59]. These experimental observations on polyelectrolyte brushes are in line with theoretical studies demonstrating the internal phase separation of collapsed polyelectrolyte brushes in poor solvents and the related hysteretic memory in grafting density-induced changes in brush properties [61].

Polyelectrolyte brushes also exhibit nonlinear responses to varying salt concentration. Polymethacryloyl ethylene phosphate brushes grown from a cantilever exhibited hysteretic memory in the salt-driven response of the cantilever bending [62]. Other non-monotonic, non-uniform responses were also reported. The thickness of a densely-grafted PAA brush ($\sigma = 0.25$–0.4 chains nm^{-2}), for example, first increased and then decreased as the concentration of monovalent salt in solution was increased [63]. Non-monotonic changes in thickness were also observed for a poly(methacrylic acid) (PMAA) brush ($0.01\ \mu\mathrm{mol\ m}^{-2}$), but the type of the response depended on the valency of the metal ion and its location in the periodic table, leading to primarily ionic, hydration, or bridging interactions [64]. Whether these stimuli lead to hysteretic interactions has, to our knowledge, not yet been explored.

Thermoresponsive polymer brushes exhibit temperature-induced hysteretic memory behavior in their properties. PNIPAAm brushes with a diverse range of grafting densities (0.08–0.33 chains nm^{-2}) exhibited hysteretic memory in their conformation and swelling behavior [65–67], which was lessened by the presence of salts (Fig. 5a) [68]. This hysteretic memory occurred only above a critical molecular weight (Fig. 5b) [69], and has been attributed to two mechanisms: the presence of hydrogen bonding interactions [70] or chain entanglements [69] in the collapsed state, which delay the transition from collapsed to swollen states. Polymethacrylates or polyacrylates with poly(ethylene oxide) side-chains also exhibit LCST behavior; unlike PNIPAAm, however, they did not typically show hysteretic memory in their conformational changes in solution [15]. Interestingly, molecular brushes composed of these polymers showed hysteretic memory in their conformational changes upon heating and cooling, which was dependent on their side-chain composition [71].

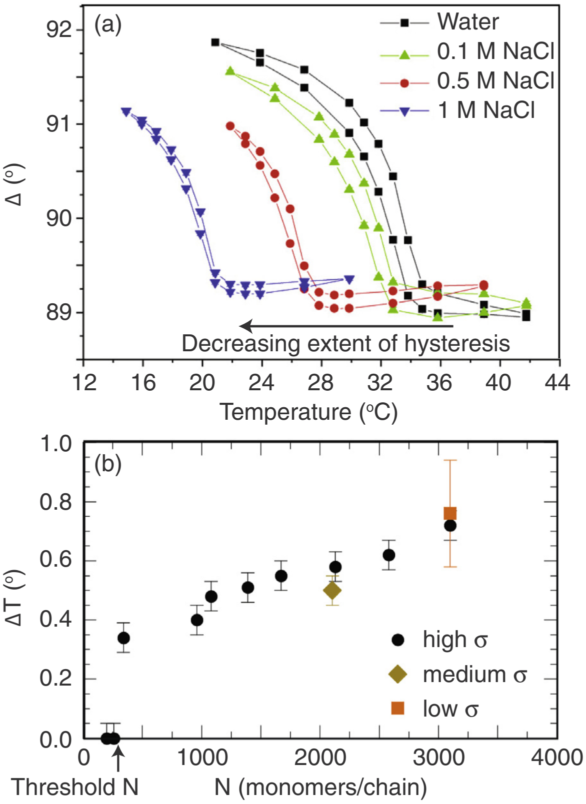

Fig. 5. (a) Relative phase shift (Δ, measured using ellipsometry) as a function of temperature for swollen PNIPAAm brushes. Brushes exposed to water exhibited hysteretic memory in their swelling behavior and this effect was reduced for brushes exposed to salt solutions. Adapted with permission from Ref. [68], M. Koenig, K.B. Rodenhausen, S. Rauch, E. Bittrich, K.-J. Eichhorn, M. Schubert, M. Stamm, and P. Uhlmann, *Langmuir* 34, 2448–2454 (2018). Copyright 2018 American Chemical Society. (b) Temperature shift (ΔT) required to overlap heating and cooling curves for PNIPAAm at low, medium, and high grafting density (σ), as a function of number of monomer repeat units per chain (N). Above a threshold value of N, hysteretic memory was observed (ΔT > 0). Adapted with permission from Ref. [69], S. Varma, L. Bureau, and D. Débarre, *Langmuir* 32, 3152–3163 (2016). Copyright 2016 American Chemical Society.

These studies highlight the ability of polymer brushes to generate nonlinear responses and begin to identify the mechanistic origins of such responses. Many open questions still remain, however, on how to precisely control such behaviors in the dynamic, non-equilibrium settings encountered in nature.

4.2. Slow diffusion through brushes

Control over diffusion is essential for maintaining the strong spatiotemporal gradients that drive biological reactions within living cells. Densely-grafted polymer brushes provide one route to locally and anisotropically modulate diffusion: diffusion laterally through the brush and normally into the brush may have strikingly different functional dependences.

Within a polymer brush, the grafting density and molecular interactions within the polymer and with the solvent dominate ion and molecular transport. Inside anionic polyelectrolyte poly(styrene sulfonate) (PSS) brushes, cationic rhodamine 6G was used as a model of counterion transport. Coulombic forces between this molecular probe and the anionic brush slowed diffusion by a factor of 10^4 compared to free diffusion, as measured via fluorescence correlation spectroscopy (FCS); strong confinement within the brush led to anisotropic, oriented transport of the molecule [72]. The pH response of a poly[(2-dimethylamine) ethyl methacrylate)] (PDMAEMA) brush was harnessed to tune its chemistry from neutral to cationic. Transport of cationic (rhodamine 6G) and anionic (AlexaFluor 555) probes within PDMAEMA brushes varied with brush charge: the anionic probe sequestered within the brush under the low-pH conditions for which the brush was positively charged, and exhibited extremely slow diffusion (Fig. 6a) [73]. This strong slowing of the anionic probe was attributed to interactions between the anionic probe and cationic traps within the brush, or to local geometric heterogeneities within the brush. Transport of the redox couple $[Fe(Cn)_6]^{3-/4-}$ through collapsed poly[2-(methacryloyloxy)ethyl]trimethylammonium chloride (PMETAC) brushes in the presence of different salts, assessed through cyclic voltammetry and impedance spectroscopy, depended on whether brush collapse was driven by electrostatic screening or ion-pairing, which altered the water content [74].

Molecular probes with varying interaction with thermoresponsive PNIPAAm (non-interacting Alexa 647, weakly interacting Alexa 488, and strongly interacting rhodamine 6G) were used to distinguish the effects of interactions on probe transport within PNIPAAm brushes using FCS [75]. Interactions between the tracers and polymers precluded a universal scaling of diffusion behavior, signaling the importance of local processes such as chain dynamics and/or local domains of network collapse on tracer transport [75]. Strong diffusive slowing was also reported for transport of $[Fe(Cn)_6]^{3-/4-}$, assessed using electrochemical methods, through thin (5–10 nm) pNIPAAm brushes as the grafting density was increased or as the brush collapsed upon a temperature increase [76].

FCS [72,73,77] and electrochemical methods [74,76] provide information on the average diffusivity of probes. By contrast, single-molecule methods can provide insight into the heterogeneity of molecular or probe transport. These methods follow individual molecules with high spatial resolution and generate trajectories that subsequently can be analyzed using a variety of statistical approaches, and are useful for separating slow and fast modes of diffusion when the diffusivities are separated by at least an order of magnitude [78]. Such methods were applied to understand how collapse of a thermoresponsive PNIPAAm brush affected spatial and temporal heterogeneities within the brush. Rhodamine 6G probes in the collapsed brush (above the LCST) were confined to smaller areas and were more likely to undergo large hops between confined regions than those in the extended brush (below the LCST) (Fig. 6b) [79]. These experiments revealed that conformational changes in the brush also altered the spatial heterogeneity within.

Diffusion of probes and macromolecules on the brush surface can exhibit different features than diffusion through the brush. Interactions between diffusing macromolecules and the brush surface control surface diffusion. Fluorescently-labeled PEG molecules (of molecular weight 10 kDa) diffusing on the surface of a densely-grafted PEG brush, studied through single-molecule tracking, exhibited faster short-time diffusion coefficients as the brush density was increased, reflecting the increasing homogeneity of the brush surface [80]. Triggering the brush response can change, in situ, the interactions between diffusing species and the brush surface and thereby modulate diffusion. Increasing the temperature of a thermoresponsive PNIPAAm surface, such that the brush surface became more hydrophobic, slowed the average surface diffusion of molecular rhodamine 6G and rhodamine 123, determined through FCS [81]. Finally, changes in brush structure in response to an external stimulus can but do not necessarily alter probe diffusion near the brush periphery. Measurements of diffusion of two ionic probes, sulforhodamine B and rhodamine 6G, on the surface of brushes of opposite charge—poly([2-(methylacryloyloxyl)ethyl] trimethylammonium chloride) (PMETAC) and PSS, respectively—revealed that diffusive slowing occurred at salt concentrations that were three orders of magnitude lower than those required to observe full brush collapse; this result was attributed both to the non-uniform collapse of the segments near the brush surface and to an increase in the ability of oppositely-charged probes to penetrate the brush as the osmotic pressure was increased [82]. These and similar studies highlight the ongoing challenge

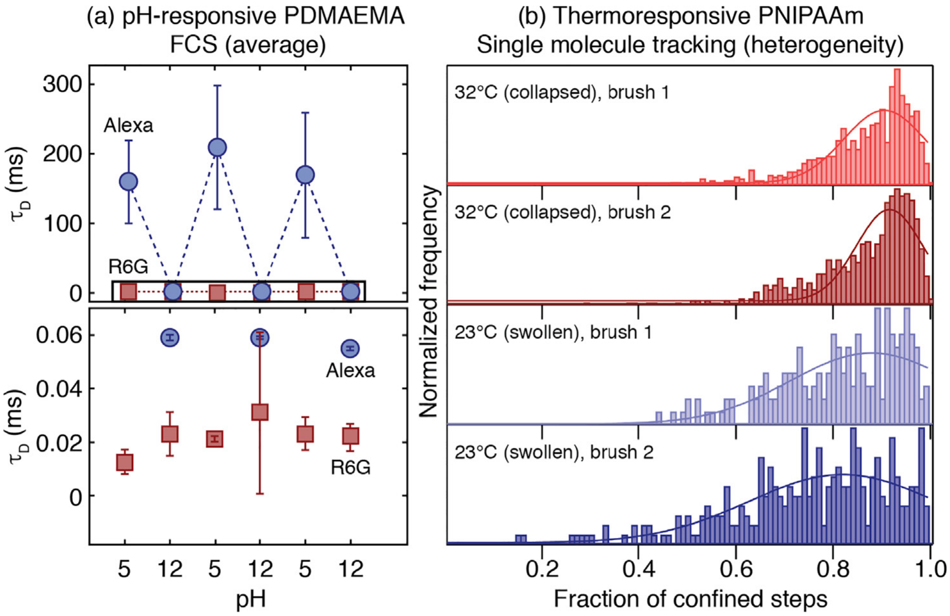

Fig. 6. (a) Probe diffusion within a pH-responsive weak polyelectrolyte, poly(2-(dimethylamino)ethylmethacrylate (PDMAEMA). Top: Diffusion time measured with FCS at different pH values for a cationic Alexa probe (squares) and anionic rhodamine 6G probe (circles) as a function of pH near the surface of a brush of initial thickness 38 nm. The cationic probe has a constant diffusivity, indicating that it does not interact with the brush at either pH. The anionic probe does not interact with the unprotonated brush at pH 12. Bottom: Expanded plot of the black rectangle data. Adapted with permission from Ref. [73], C.R. Daniels, L.J. Tauzin, E. Foster, R.C. Advincula, and C.F. Landes, *J. Phys. Chem. B* 117, 4284–4290 (2012). Copyright 2012 American Chemical Society. (b) Distribution of the fraction of confined steps of a rhodamine 6G probe, determined using single-molecule tracking, in two different poly(N-isopropylacrymide) (PNIPAAm) brushes on glass at 23 °C (dark blue, light blue) and 32 °C (dark red, light red). Solid lines are Gaussian curve fits. The narrower width observed at the higher temperature indicates a higher degree of confinement. Reprinted with permission from Ref. [79], L.C.C. Elliott, M. Barhoum, J.M. Harris, and P.W. Bohn, *Langmuir* 27, 11037–11043 (2011). Copyright 2011 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in distinguishing diffusion near versus diffusion within a polymer brush. This challenge may underlie competing reports that the dynamics of polymer brush chains speed [81,83] or slow [72,84,85] probe diffusion.

When larger objects are transported through polymer brushes, other length scales beyond the grafting density and brush molecular weight become important for macromolecular transport. Polymer brushes are able to act as selective barriers for free chains; for chemically identical chains, the molecular weight of the freely diffusing species determined the selectivity of the brush [86]. Likewise, polymer brushes hindered the diffusion of colloidal particles near a surface distinct from the expected hydrodynamic slowing near a solid wall [87]. Nanoparticles functionalized with chemically similar polymer brushes penetrated deeper into their brush, but their transport was slowed by frictional interactions with the brush [87]. Notably, these studies have been carried out with non-responsive (typically polystyrene) brushes; while brush response is widely used to control the release of proteins and theranostic macromolecules and particles, how (dynamic) changes in brush conformation affect macromolecular or colloidal transport remains incompletely fundamentally understood.

4.3. *Self-oscillation in polymer brushes*

Living organisms have multiple, well-defined mechanisms by which they obtain feedback from their environment, enabling them to adapt and respond to stimuli. Translation of these mechanisms to synthetic nanotechnological systems, and to responsive brushes in particular, remains in the very early stages. Indeed, one of the early perceived advantages of polymer brushes as nanotechnological components was that their ability to change conformation would allow them to act both as sensor and valve, for example to control flow on the microscale [88]. The next step in mimicking a living response is to generate a system that responds autonomously and collectively to environmental changes.

One collective response in a polymer brush, oscillation of the brush thickness, can be attained by coupling the brush response to an externally varying stimulus. As one example, an electrical stimulus applied by placing an electrode close to a pH-responsive PDEAMA brush modified the local solution pH through electrolysis of water, thereby tuning brush swelling and deswelling [89]. When the brush was placed between two electrodes in an electrochemical cell, waves in solution acidity generated continuously-propagating waves in the brush thickness [89]. This response, however, was directly coupled to oscillations in an external stimulus (here, the solution pH).

Towards an autonomous self-oscillating brush system, Yoshida and collaborators coupled a widely-studied oscillating chemical reaction, the Belousov-Zhabotinsky (BZ) reaction, to polymer brushes [90,91]. To prepare a self-oscillating brush, the BZ catalyst Bis(2,2′-bipyridine)(1-(4′-methyl-2,2′-bipyridine-4-carbonyloxy)-2,5-pyrrolidinedione) ruthenium(II)bis(hexafluorophosphate) [abbreviated as $Ru(byp)_3$] was copolymerized with two polymers, thermoresponsive NIPAAm and pH-responsive *N*-(3-aminopropyl) methacrylamide (NAPMAm). Oxidation of the $Ru(byp)_3$ moiety immobilized in the brush, at an appropriate concentration, led to stable oscillations in brush thickness (Fig. 7a) [90]. The characteristic time period of brush oscillations, 20–150 s, was up to an order of magnitude faster than reported in bulk systems due to the small characteristic thickness (30–100 nm) of the brushes (Fig. 7b). Characterization of the period and waveform of the brush oscillation, in comparison to that in free polymer and in microgels, revealed that the immobilized $Ru(byp)_3$ catalyst on the densely grafted chains was less accessible to chemical species participating in the BZ reaction than in the free polymer [91]. Together, these studies demonstrate the initial promise of coupling brush response to generate autonomous motion – as a simplified model of cilia – and highlight the critical role in understanding transport within the brush for design of autonomous brush systems.

4.4. *Patterned responsive brush surfaces*

Compartmentalization in living systems allows the different compartments to perform different functions and communicate with one another. The fabrication of patterned polymer brush surfaces provides a route to compartmentalized structures in synthetic systems [92–94]. Diverse functions can be integrated into patterned surfaces through incorporation of responsive brushes. It is well established that the application of responsive polymers to rough surfaces enhances their response. For example, the switchable wettability of PNIPAAm was greatly enhanced when the polymer was applied to a rough surface [17], and this approach was extended to dual pH-responsive and thermoresponsive poly(*N*-isopropyl acrylamide-*co*-acrylic acid) brushes [18].

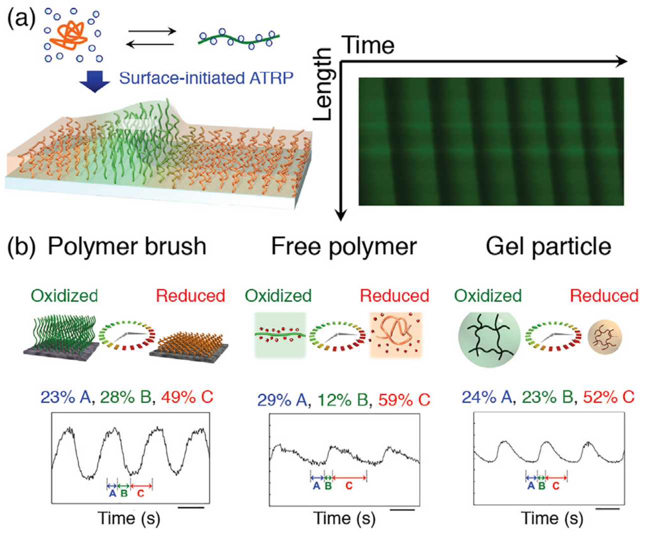

Fig. 7. (a) Left: Schematic illustrating the synthesis of a self-oscillating random copolymer brush (poly(NIPAAm-*r*-NAPMAm-*r*-Ru(bpy)$_3$NAPMAm)) functionalized with a redox-active catalyst, ruthenium tris(2,2′-bipyridine) [Ru(bpy)$_3$], for the Belousov-Zhabotinsky reaction. Right: spatiotemporal pattern of the propagation of chemical waves through the polymer brush, detected through the fluorescence intensity of Ru(bpy)$_3$ in its reduced state. Adapted with permission from Ref. [90], T. Masuda, A.M. Akimoto, K. Nagase, T. Okano, and R. Yoshida, *Chem. Mater.* 27, 7395–7402 (2015). Copyright 2015 American Chemical Society. (b) Top row: Schematic illustration of the conformation of polymer brushes, free polymer, and gel polymers functionalized with Ru(bpy)$_3$. Bottom row: Typical oscillation waveforms for the polymer brush, the free polymer system, and the gel particle system obtained for the B-Z reaction with substrate concentrations of $[HNO_3] = 0.3\,M$, $[NaBrO_3] = 150\,mM$, and $[MA] = 100\,mM$. Adapted with permission from Ref. [91], T. Masuda, A.M. Akimoto, M. Furusawa, R. Tamate, K. Nagase, T. Okano, and R. Yoshida, *Langmuir* 34, 1673–1680 (2018). Copyright 2018 American Chemical Society.

An alternative approach is to directly pattern the brush layer, which allows for even greater control over its surface features. Micropatterned thermoresponsive PNIPAAm brushes were created through the use of a PDMS stamp to apply an initiator for surface-initiated polymerization [95]. These patterned responsive brushes acted as motors to move gold nanoparticle aggregates along the brush surface [96] (c.f. Section 3.1). Nanopatterned PNIPAAm brushes have also been synthesized through the use of UV interferometric lithography to selectively photodegrade the surface-immobilized initiator prior to polymerization of the brush [97–100]. These surfaces exhibited temperature-dependent topological changes as well as switchable bioactivity. Regions of the surface containing immobilized bioactive molecules were concealed and exposed upon respective swelling and de-swelling of the brush. Chemical gradients in solution can be established through quiescent diffusion [101] or laminar flow [102] and used to generate patterned brushes at scales as small as 5 μm, as shown for the weak polyelectrolyte PDMAEMA. Self-oscillating brushes (Section 4.3) composed of patterned regions containing a copolymer of PNIPAAm and a catalyst for the BZ reaction, enabled 1D and 2D control over the propagating chemical waves, dependent on the size of the unreactive "gap" regions of the patterned surface [103].

Related approaches have been employed to prepare patterned pH-responsive brush surfaces [11]. Grafting-to methods were employed, along with photolithography, to fabricate micropatterned surfaces containing oppositely charged polymer brush regions of polyacid PAA and polybase P2VP [104]. At low pH, the PAA regions were collapsed whereas the P2VP regions were extended; by contrast, at high pH the PAA regions were extended and P2VP regions collapsed. Thus this patterned brush exhibited inversion of surface wettability of the PAA and P2VP regions induced by pH changes. Photoswitchable polyelectrolyte brushes were fabricated, under masked UV radiation, to contain patterned surface regions containing positive and negative charges, which were then used to form a dual-protein pattern [105]. Patterned surfaces were also prepared containing PAA brush regions, along with regions containing self-assembled monolayers of poly(ethylene glycol) (PEG), using lithography techniques combined with grafting-from syntheses [106]. The differing chemical functionalities were used to immobilize small molecules (in the PAA regions) and prevent nonspecific binding interactions (in the PEG regions). Even the presence of bare silicon regions within a patterned brush can greatly alter the surface properties and thereby modify, as one example, adhesion of cells to patterned PAA brushes [107]. These studies demonstrate the ability to impart differing chemical functionalities and responses to the various regions of a patterned brush surface.

5. Conclusions and outlook

Responsive polymer brushes (Section 2) already show promise as components of biomimetic nanotechnology, featuring in simplified analogues of leaves, molecular motors, and ion channels, among other structures (Section 3). These structures largely exploit a binary (off/on) brush response, without incorporating the full complexity of the brush response explored in recent studies. Nonetheless, the hysteresis, ability to control diffusion, self-oscillation, and enhancements in surface properties due to patterning exhibited by responsive brushes (Section 4) offer attractive features for the design of biomimetic nanotechnological systems.

From a practical standpoint, what properties or features are desired for polymer brushes to be incorporated into such a system?

1. *Tunable nonlinear responses.* Hysteresis in the contact angle, discussed in Section 4.1, represents one example of a nonlinear brush response to external stimuli. Precise control over the extent and location of the nonlinearity, even in this relatively simple response, is still lacking. Whether and how such nonlinearities in the brush response can be harnessed to generate novel function in biomimetic nanotechnological applications is largely unexplored.
2. *Complex feedback loops.* The self-oscillating system discussed in Sections 4.3 and 4.4 represents one example of a feedback loop, to date rarely incorporated into polymer brushes. By contrast, there is an increasing emphasis placed on creating feedback loops in nanotechnological systems. For example, molecular self-assembled monolayers on the surface of nanoparticles generate pH-responsive nanoparticle oscillators that are able to temporally assemble and disassemble [108], and a composite polymer gel loaded with an enzyme and its inhibitor can be used to generate a signaling cascade [109,110]. Coupling a responsive polymer to a self-oscillating system could lead to spontaneous, self-sustaining motion [111]. Finally, feedback loops approaching the complexity of those in natural systems may be obtainable through multi-stimulus response – for example, one that can evolve over time based on the input response.
3. *Spatiotemporal control over brush response.* The ability to precisely locate responsive components on a surface represents the first step towards generating complex function. As one example, exquisite spatiotemporal control over local ionic concentrations in polymer brushes could, when coupled to e.g. enzymes or redox-active moieties, provide new functionality in controlling and maintaining non-equilibrium conditions in reaction/diffusion systems. While the patterning methods discussed in Section 4.4 represent a first step towards achieving the compartmentalization that drives biological function, there remain unmet challenges in generating patterns that are dynamic and that enable communication between different regions. Finally, extending patterning methods to conformally cover 3-D surfaces broadens the capability to create tunable responsive soft surfaces.

(4) *More complex transformations in brush composites.* The polymer brush response is often incorporated into a relatively simple geometry; for example, when changes in brush height are used to selectively expose a pore or channel. Generating composite materials in which the brush response modulates the surface topography offers the potential for new function. Mixed polymer brushes represent one example of a responsive composite that can be applied to selectively control ion permeability [112]. More recently, computational studies in which triggering the polymer response exposes a sensor-bearing nanoparticle [113], a simple model of the cell surface, or a sticky, compliant fiber [114], a simple model of a carnivorous plant, suggest that marrying polymer brushes to other nanostructures has great promise for biomimicry.

There remain important fundamental questions to be addressed to attain these properties in brushes for use in biomimetic systems.

(5) Key to tuning brush properties is an improved understanding of the transport of solvents and ions through the brush. For example, improved understanding of solvent transport is required to control the intra- and intermolecular interactions that underpin changes in surface wettability. Likewise, improved understanding of ionic transport within brushes is required to design brushes that exhibit autonomous behavior and/or respond to external feedback.

(6) In a related issue, how the dynamics of responsive polymer chains affect diffusion of solvents, ions, and (macro)molecules remains incompletely understood. Whether polymer chain dynamics speed or slow probe diffusion depends on the location of the diffusing probe, its size, and its interactions with brushes. Fundamental understanding of how these dynamics affect those of the probe would benefit from the extension of theories that describe the coupling between nanoparticles and polymer dynamics [115], and model hopping in highly confined polymer matrices [116], to brush/probe systems. Likewise, extensions of experiments [117] or simulations [118] that resolve both probe and polymer dynamics in bulk solutions to surface-grafted polymer brushes may generate new insight into coupling mechanisms in this limit. Finally, penetration and transport of larger, macromolecular or colloidal objects remains largely unexplored in the context of responsive brushes, but is an essential step towards mimicking biological pores that allow the transport of proteins or other nanoscale particles.

(7) Finally, a key question from the standpoint of polymer chemistry is how to tune the brush response time across the orders of magnitude observed in biological systems. Certain leaves, for example, can respond to changes in turgor pressure in response to mechanical stimulus on time scales of seconds [119], comparable to response rates currently achieved in polymer brushes; ion channels, however, respond on time scales of order of 0.1–100 ms [120,121], orders of magnitude faster than current brush responses. Variation of brush parameters such as polymer composition, molecular weight, and grafting density may not be convenient methods of manipulating the brush response time, as other important brush properties will also be affected. Mixed or copolymer brushes may offer a route to separately control the response time and other brush properties and functions. Hierarchical systems represent a strategy to incorporate diverse length and time scales within the brush [122]. It remains unknown how to systematically tune the brush response time, using these methods or others, while achieving other desired brush properties. Furthermore, a rapid, almost instantaneous, brush response is likely needed for many applications. A theoretical study by Klushin and collaborators offers one route to achieving response times of less than one second [123], yet further work is needed in this area to bring about rapid responses of brushes to diverse stimuli.

Acknowledgments

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Declarations of interest

None.

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