Combining Top-Down and Bottom-Up with Photodegradable Layer-by-Layer Films

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ABSTRACT: Layer-by-layer (LbL) self-assembly of polymer coatings is a bottom-up fabrication technique with broad applicability across a wide range of materials and applications that require control over interfacial properties. While most LbL coatings are chemically uniform in directions both tangent and perpendicular to their substrate, control over the properties of surface coatings as a function of space can enhance their function. To contribute to this rapidly advancing field, our group has focused on the top-down, spatiotemporal control possible with photochemically-reactive LbL coatings, harnessed through charge-shifting polyelectrolytes enabled by photocleavable ester pendants. Photolysis of the photocleavable esters degrades LbL films containing these polyelectrolytes. The chemical structures of the photocleavable groups dictate the wavelengths responsible for disrupting these coatings, ranging from ultraviolet to near-infrared in our work. In addition, spatially segregating reactive groups into "compartments" within LbL films has enabled us to fabricate reactive free-standing polymer films and multi-height photopatterned coatings. Overall, by combining bottom-up and top-down approaches, photoreactive LbL films enable precise control over the interfacial properties of polymer and composite coatings.

Introduction

Polymer coatings are a critical class of materials that define interactions at the interface between substrates they coat and their environments. Such coatings can encourage dispersion or solubility, serve as barriers to prevent mixing, and protect otherwise sensitive materials from unwanted decomposition or fouling. The chemical structures of polymers present limitless opportunities for creative design—precise control over monomer structure, sequence, molecular weight and dispersion, and polymer topology allow fine-tuning of physical and chemical properties in polymeric materials. Incorporation of stimuli-responsive functionality into polymer coatings can imbue dynamic or on-demand changes of their critical interfacial properties in response to their environment.[1] These kinds of responsive or "smart" coatings have found use in a range of applications for which their interfaces are key to their function, such as membranes or drug delivery platforms. Deposition methods that allow for precise structural control, such as layer-by-layer (LbL) self-assembly, present opportunity for innovation at the material interface.

Briefly, LbL deposition involves alternatively exposing a substrate to two solutions containing different materials. Attractive interactions between the two materials cause each to adsorb onto the substrate during deposition.[2] Between each deposition step is one or more rinsing or washing steps to remove weakly adsorbed material. Each deposit-rinse-deposit-rinse cycle produces one so-called "bilayer". The properties of these films are dictated by deposition conditions, including the total number of bilayers deposited, polymer concentration, pH, and ionic strength. This bottom-up fabrication technique offers numerous advantages that have continuously expanded its popularity (Figure 1).

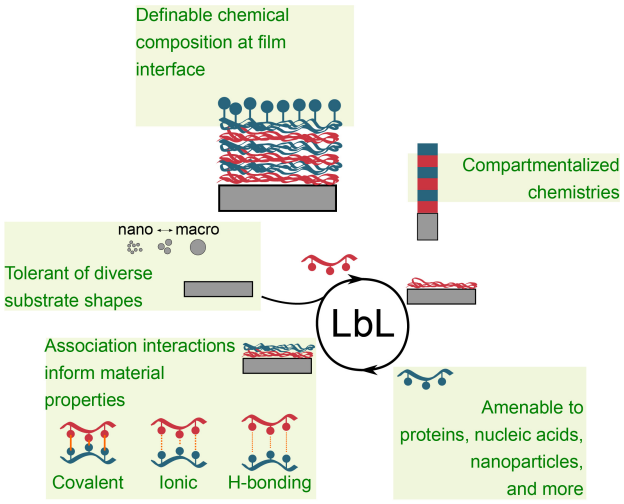

Figure 1. Some of the advantages of the LbL coating process.

All-Aqueous Processing: Most LbL deposition schemes use only aqueous solutions to deposit and rinse coatings, reducing the need for toxic solvents and expanding the eligible classes of materials beyond lipophilic synthetic polymers.

Diverse Material Tolerance: Although synthetic polyelectrolytes are the most common and best understood components of LbL films, many types of natural polymers, including polysaccharides,[3-5] proteins,[6,7] and nucleic acids[8,9] can be integrated into LbL films. Inclusion of such biopolymers are crucial for biological interfaces,[10] as they enable functions such as biomolecule delivery[11] and programmable interactions with biological species, including cells.[12,13] Incorporation of inorganic materials and metal complexes has yielded composite films with unique properties.[14-16] In addition, various types of inorganic or polymeric nanoparticles can also be integrated into the bilayers used in LbL coatings.

Substrate Compatibility: For coating small objects, especially microscopic or nanoscopic materials, traditional coating methodologies such as spray coating, spin coating, or doctor blade coating are difficult or impossible to implement. LbL processes can coat diverse substrates such as microparticles or nanoparticles, hydrophobic and flame-retardant textiles,[17,18] microneedles,[19,20]

cells,[21] or gas bubbles.[22] Further, selectively degradable inorganic or polymeric particle substrates can yield hollow LbL containers for the encapsulation and release of therapeutic cargo.[23,24]

Coating Methodologies: Although the immersion method for LbL coating is popular and easily amenable to most substrates, it can be time-consuming and laborious. Therefore, numerous other methods have emerged to improve the deposition speed and properties of LbL coatings,[25] which include spray-coating,[26] spin-coating,[27,28] microfluidics, and electrochemical deposition.

Nanoscale Control of Film Construction: The sequential deposition of layers raises the possibility that chemistries can be segregated within strata of films, the final thicknesses of which can be as thin as tens to hundreds of nanometers. Nanostructured combinations of materials can yield precisely engineered coated particles that perform multiple important functions in various applications.[29] The degree of stratification depends on the extent to which individual polymer chains interpenetrate during assembly. Low degrees of interpenetration, often associated with strong synthetic polyelectrolytes, affords glassy thin films, while complete mixing throughout the entirety of the film thickness often occurs with fluid-like films comprising weak or strongly hydrated polyelectrolytes. Although structural order is lost, films with greater interpenetration often experience rapid increases in film thickness as a function of the number of coating steps.

Beyond these advantages as a coating technology, LbL is also applicable to a broad swath of chemical design space. Excellent review articles describe the panoply of materials and interactions for which LbL has been demonstrated.[2,30] The early approach of alternatively depositing polycations such polyallylamine hydrochloride (PAH) and polyanions such as polystyrene sulfonate (PSS) into polyelectrolyte multilayer (PEM) films remains popular, and is the focus of our group's work in this paper. Hydrogen bonding between acidic polymers such as poly(acrylic acid) (PAA) and hydrogen bond accepting polymers such as polyvinyl pyridine (P4VP) is also a

popular and versatile approach for building LbL films.[31,32] Subsequent research has led to other classes of non-covalent interactions for LbL, such as protein-ligand interactions, metal-ligand chelation, and supramolecular host-guest complexes. Finally, there are numerous examples of LbL films built using covalent bonding between polymer chains, as opposed to only non-covalent interactions.[33,34]

Stimuli-Responsive LbL Films

The versatility of LbL from both chemistry and material science perspectives has fostered new responsive coatings and surfaces with far-reaching implications. Numerous applications of functional and responsive LbL materials have emerged, including membranes for chemoselective separations, optoelectronic devices, tunable interfaces for cell growth and tissue engineering, self-healing materials, and antimicrobial and biofilm-resistant treatments.[35] Beyond this host of target applications, drug delivery platforms are among the most popular target application of these materials. Degradation of films is defined by the chemistry in the film, allowing for either on-demand burst-release or long-term sustained release of cargo from LbL-enforced confinement.[36] For example, as poly(anionic) nucleic acids integrate into LbL films readily, on-demand degradation of such biomaterials can release DNA or RNA for gene therapy.[8] In addition, small molecule therapeutics can be trapped within films and released into the environment upon degradation of the LbL interface.[37] Practical applications in drug delivery generally require chemical control over the nature of the environment/film interface, such that a specific stimulus or environmental condition degrades the material integrity of the once-stable LbL film and releases encapsulated cargo. Long-term stability in physiological conditions is important for such films, as targeted payload release requires film dissolution exclusively at the point of stimulus application.

Numerous classes of stimuli have been applied to degradable LbL films. Examples of these stimuli beyond the photo-responsive LbL films on which this article focuses include:

Hydrolytically unstable films: Several categories of these materials exist, such as those that contain polyesters whose backbones hydrolyze in water,[38,39] and those with hydrolytically cleavable ester side chains that cause "charge-shifting" of polyelectrolytes.[40-42] The rate of hydrolysis and erosion of such films is tunable based on polymers used in the films as well as external factors such as pH and ionic strength, allowing for controlled release of cargo to occur over a range of durations.

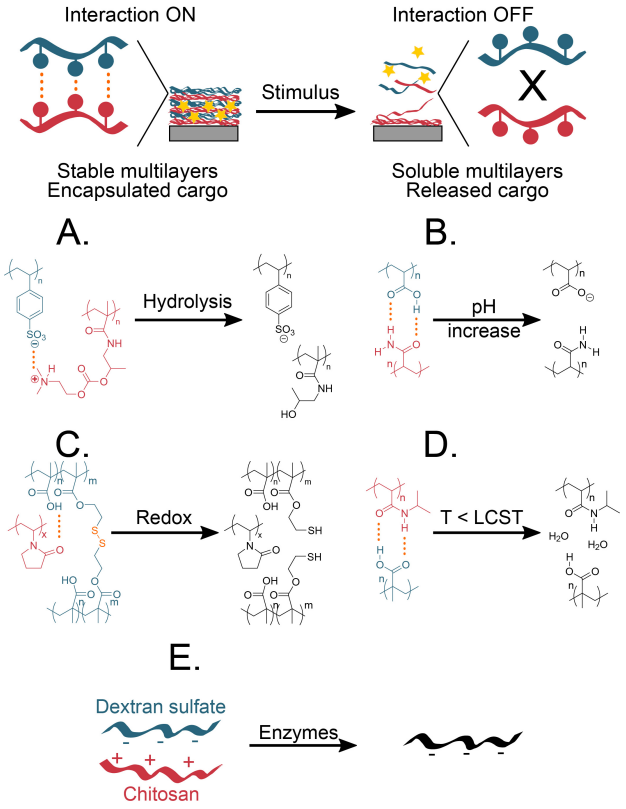

Figure 2. Examples of on-demand degradation of stimuli-responsive LbL films.

pH-responsive films:[43-46] Beyond the influence of pH on hydrolysis rate, the protonation state of weak polyelectrolytes can influence the coating/microenvironment interface for LbL films assembled by either ion pairing or hydrogen bonding.

Redox-responsive films: Changing the oxidation state of specific moieties can disrupt LbL films. An effective option for this mode of action in LbL films is chemical reduction of disulfide bonds with reducing agents such as glutathione.[47-50] In addition, electrochemical redox processes can change the interaction strength between polymer layers in LbL films, as was realized upon oxidation of Prussian Blue-containing LbL films.[51]

Thermally-responsive films: Polymers such as poly(*N*-isopropylacrylamide) with critical solution temperatures have been incorporated into LbL films.[52,53] These materials respond to changes in temperature, undergoing reversible thermal transitions that impact bulk and/or surface properties. Films that transition at or near physiological temperature are especially interesting for biological applications.

Chemically-responsive films: Other chemical stimuli, such as sugars, chelating agents or enzymes degrade polymers or disrupt inter-chain interactions to degrade or swell the LbL interface.[54-56]

Photoresponsive LbL Films

From the perspective of stimuli-responsive polymers, light offers a unique set of advantages, especially when photons are considered as reagents for executing chemical reactions. 1. Light can travel long distances and penetrate many barriers that are impervious to chemicals. 2. Readily available tools such as photomasks, lasers, or LEDs can control the spatiotemporal distribution of light-where it goes and when it goes there. 3. In the parlance of more traditional chemical reactions, real-time control over the precise energy (wavelength of light) and stoichiometry (intensity of light) of photons added to a sample is straightforward. 4. The wave nature of light brings two

additional methods for controlling how light interacts with samples, both of which have implications in photoresponsive thin films: the interference and diffraction of light waves enables spatial patterning of light at surfaces, and polarized light can orient the transition dipoles of photochromic molecules such as azobenzenes.[57,58]

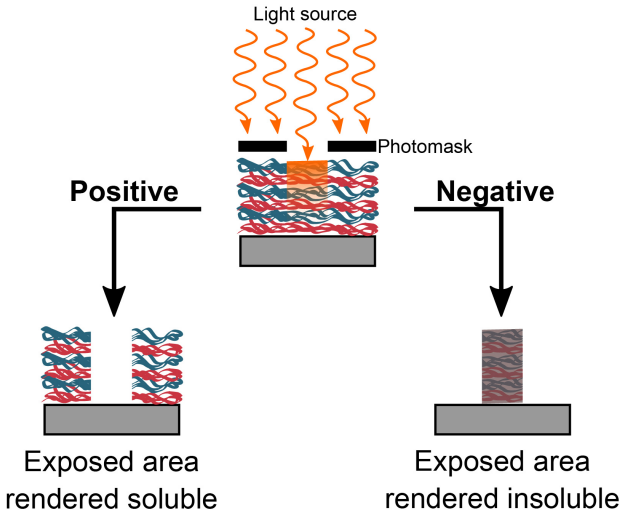

Figure 3. Schematic of positive-tone and negative-tone photolithography using LbL films.

The interface of polymer coatings and photochemistry has had enormous technological implications in using specific photochemical reactions to transfer images to polymer films with high fidelity. Although photographic film has declined markedly in popularity with the growth of digital photography, color film remains an impressive combination of photochemistry and polymer science. In addition, photolithography is a critical step for fabricating integrated circuits, and can be categorized depending on whether the irradiated material is selectively rendered insoluble (negative-tone lithography) or soluble (positive-tone lithography) in a developer. This general concept of disrupting and/or dissolving polymeric materials using photochemical reactions extends, for example, to hydrogels for targeted release of therapeutics.[59] As part of an interdisciplinary worldwide effort to enhance the impact of photoresponsive polymer materials, our group has interest in combining the top-down fabrication technique of photo-patterning with

the bottom-up deposition approach of layer-by-layer self-assembly. As presented throughout this article, photodegradable LbL films present a toolbox for controlling matter and interfaces on the micro- and nano-scale, offering potential in, for example, innovative tissue engineering platforms capable of controllable cellular adhesion, migration, and differentiation.[60-62]

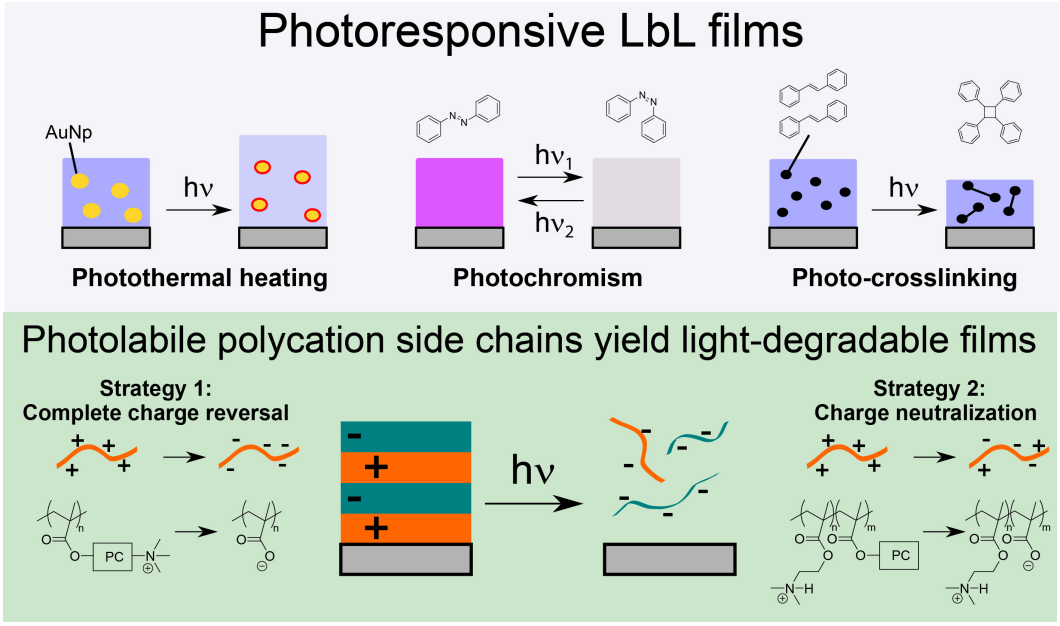

Figure 4. Summary of approaches for designing photo-responsive LbL films from other groups (*top*) and from our group (*bottom*).

Here we present brief summaries of some chemical approaches other groups have used to render LbL films photodegradable or otherwise photoreactive. For a more comprehensive treatment we point readers to a 2014 review by Mano and coworkers.[63]

Photothermal heating using plasmonic nanoparticles. Metallic nanostructures, such as those comprising gold and silver, can efficiently convert visible or near-infrared (NIR) light into heat through the non-radiative decay of plasmons. This localized heating can disrupt numerous types of polymeric encapsulants,[64] including LbL films, which degrades the film/environment interface and releases encapsulated guests.[65-69]

Photochromism: Reversible photochemical reactions such as the color-changing of photochromic moieties have also proven useful in LbL constructs. Negatively-charged polyoxometalates are readily integrated into polyelectrolyte multilayer films prepared by LbL, and can yield photochemical reactivity or photoinduced disruption of these composite coatings.[70-72] Alternatively, the binding of *trans*-azobenzene groups with supramolecular hosts such as cyclodextrins or curcurbitrils weakens dramatically upon photochromic isomerization to *cis* isomers, while also altering the interface between LbL film and environment.[73-75]

Photochemical crosslinking: Aside from pairs of reactive copolymers such as azlactone-based materials, the vast majority of LbL films are assembled using non-covalent interactions between polymer chains. Among the covalent bonding strategies[33,76] to strengthen mechanical properties, tune permeability, and direct behavior of cells on surfaces, a variety of photo-crosslinking chemistries have been incorporated into LbL films. Examples of these include benzophenone groups for C-H abstraction and radical coupling,[77-79] azide or diazo photolysis followed by inter-chain coupling of the resulting intermediates,[80-82] and addition reactions of vinyl pendants.[83,84]

Polyelectrolytes with Charge-Shifting Photocleavable Esters

In contrast to these photochemical bond-forming and isomerization reactions, our group has focused on integrating photocleavable groups and linkers into LbL films with the objective of rendering them photochemically degradable. Photolabile "caging" groups undergo photochemical "un-click" reactions, for which light of appropriate wavelengths selectively cleaves a particular bond.[85-88] With original and ongoing utility as protecting groups for organic synthesis, photolabile groups have become increasingly important in a range of disciplines for which on-demand, specific bond cleavage is useful: "caged" biomolecules are useful photo-activated tools in chemical biology

and biochemistry studies,[88] while materials applications benefit from photoinduced tuning of the structure and resulting properties of polymers and their assemblies.[89,90] As Klan and coworkers described in their comprehensive review article, a wide range of photoremovable chromophores have been identified and understood.[85] A variety of functional groups can be unmasked upon photolysis of these groups, such as carbamates revealing amines, ethers and carbonates revealing alcohols, or esters revealing carboxylic acids (Figure 5). Recent research continues both in extending the spectral coverage of photoremovable capabilities to lower photon energies through new reactive chromophores,[91,92] as well as further extending the capabilities of known photoremovable groups through creative integration strategies. The incorporation of multiple chromophores in LbL films has made sequential responses possible, with films demonstrating wavelength selectivity.

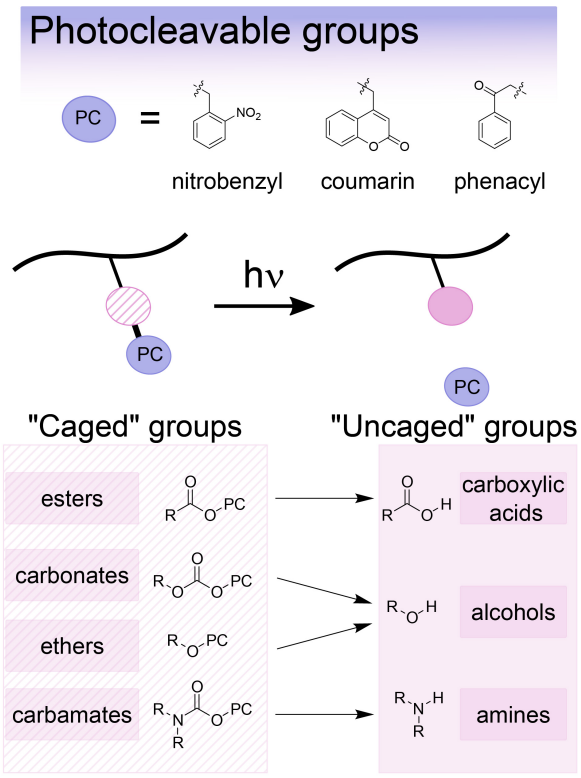

Figure 5. Examples of photocleavable groups and functional groups that they "cage".

We have focused on utilizing photochemical control over polyelectrolyte charge to disrupt multilayer films. The films we report demonstrate stability in mild aqueous base before light exposure, exhibiting minimal dissolution by changes in film absorbance ranging from 0-10%. Photolysis of photoremovable esters reveals carboxylic acids, which introduces negative charge in polymers when deprotonated at basic or neutral pH. Therefore, incorporation of photoremovable esters into polycationic materials allows "charge-shifting" reactions, where light exposes negative charges in previously positively charged polymers. Two outcomes of these reactions combine to render these LbL films soluble upon photolysis: 1. Introducing additional negative charge into the LbL film, specifically on the polycation, decreases attractive interchain ion pairing interactions between polyelectrolytes, and 2. The polymeric photoproducts are more hydrophilic after cleavage of the lipophilic photoremovable groups, increasing their solubility in water and decreasing hydrophobic interactions in the films. Below, we report recent developments of this technology from our group's published results.

Our initial design for a photoreactive polycation, which uses the *o*-nitrobenzyl (ONB) ester photoremovable group to yield a carboxylic acid bound to the polymer backbone, was inspired by the work of Lewis, Moore, and co-workers: in 2005 they demonstrated light-induced change of colloidal stability by cleaving ammonium groups from siloxane-modified surfaces using ONB ester linkers.[93] Our design, shown in Figure 6, undergoes a complete polycation-to-polyanion conversion.[94] We chose ONB photocleavable groups because they are readily prepared as bi-functional linkers, and the Norrish Type II-like ONB photolysis proceeds in nearly any environment, as opposed to some other photocleavable groups that require the presence of water. We designed this initial example **P1** to be prepared by ring-opening metathesis polymerization

(ROMP), due to its excellent functional group compatibility, straightforward implementation, and control over molecular weight.[95,96]

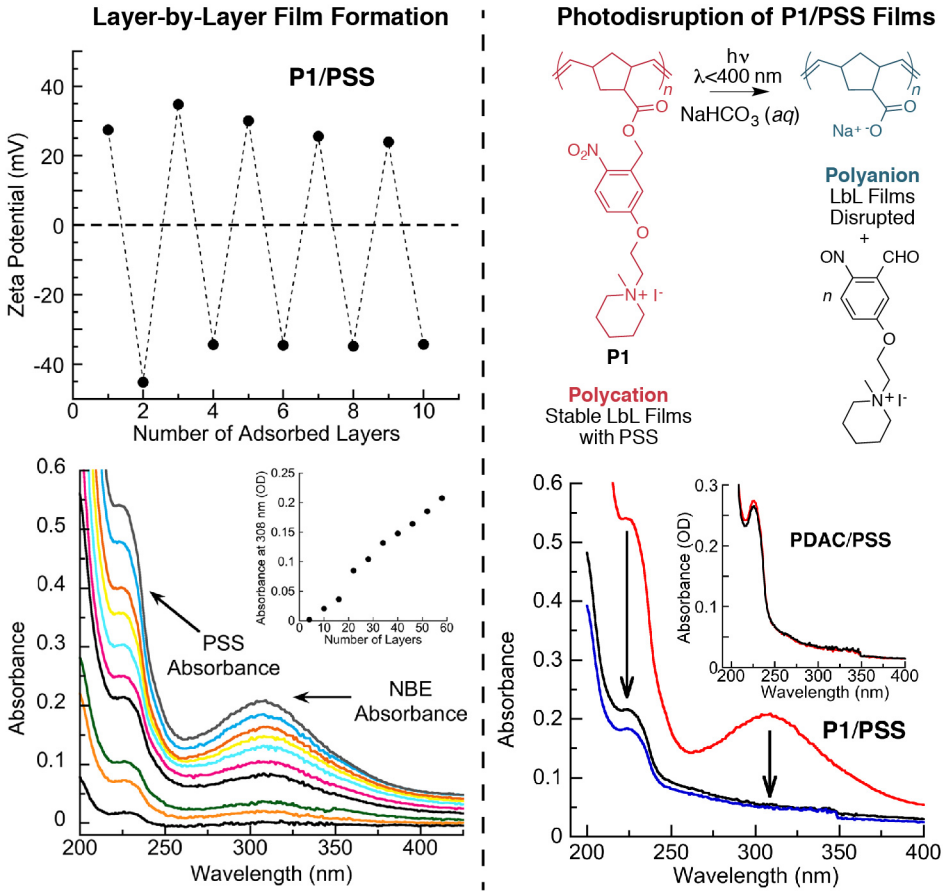

Figure 6. Layer-by-layer assembly of ONB-based charge-shifting polycation **P1**, and UV-induced disruption of **P1**/PSS LbL films. Reproduced with permission from Ref. 86. Copyright 2012 John Wiley and Sons.

UV light disrupted polyelectrolyte multilayer films comprising **P1** and PSS (Figure 6). Cleavage of the ONB esters from **P1** resulted in a positive to negative charge reversal, decreasing the association with the anionic PSS.[94] In preparing LbL films, the hydrophobic **P1** required DMF to be the solvent for deposition of the polycation. Nevertheless, thicknesses of the films grew linearly as a function of the number of deposition steps (~ 3 nm/bilayer), and UV/vis spectrophotometry

indicated that both the arylsulfonate and ONB functional groups were incorporated into the films on planar quartz glass substrates. Irradiation of 10-bilayer **P1**/PSS films for 30 minutes using a 200 W Hg/Xe lamp equipped with a 295 nm long-pass filter resulted in ONB photolysis as judged by diminution of the ONB absorbance at 310 nm. Subsequent rinsing of these irradiated films in sodium bicarbonate aqueous solutions removed 80-90% of the film from the substrate (judged by decrease in absorbance of the PSS at 220 nm), while unirradiated **P1**/PSS films showed no more than a 10% decrease at 220 nm upon rinsing. Two forms of evidence support the claim that ONB photolysis reaction was responsible for this photochemical solubilization: i) Analogous control films lacking the ONB chromophore, but using the commercially available strong polycation poly(diallyldimethylammonium chloride) (PDAC) and PSS decreased in absorbance at 220 nm upon exposure by only 10% to identical irradiation and rinsing, and ii) The zeta potential of **P1**/PSS-coated polystyrene microparticles was negative upon irradiation, regardless of whether the outer layer was **P1** or PSS, consistent with ONB ester photolysis to the carboxylate in basic solution.

Although **P1** did indeed yield photolabile LbL films, and this overall charge-shifting design has yielded photolabile polyelectrolyte complexes,[97,98] the structure of **P1** presented several challenges: i) Even with extended irradiation, some residual material always remained, ii) the use of DMF for deposition counteracts the typical advantage of all-aqueous film processing, iii) the multi-step monomer synthesis precluded large scale synthesis of the polymer, and iv) requiring the photocleavable group to serve as a linker between a cationic group and the polymer backbone, although straightforward for ONB groups, is more difficult to integrate into other photocleavable chemistries. To ameliorate these issues, we adopted a simpler photoresponsive polymer design, which **P2** exemplifies (Figure 7, top). This polycation utilizes two monomers, a photoinert cationic

monomer to provide positive charge to the polymer, and a monomer with masked carboxylates which counteracts the positive charge when photocleaved. Upon complete photolysis, **P2**, which comprises a ~1:1 mixture of the inert and commercially available dimethylaminoethyl methacrylate (DMAEMA) and *o*-nitrobenzyl methacrylate (ONBMA), forms an approximately charge-neutral polyampholyte. The methacrylic main chain is much less hydrophobic than the ROMP polymer, and monofunctional photocleavable methacrylate monomers of a variety of photocleavable groups are also readily prepared.

Despite the uncertainty that polycation charge neutralization (as opposed to charge reversal) would actually disrupt the LbL coatings, the results surpassed our own expectations.[99] Statistical copolymer **P2**, prepared by simple free-radical polymerization, was soluble in water when the amine side chains were protonated and formed optically transparent LbL films that grew linearly as a function of bilayer number when alternatively deposited with PSS (~ 2 nm/bilayer). UV irradiation ($\lambda > 295$ nm) changed the UV/vis spectra of these films consistent with ONB photolysis and fully dissolved the films in sodium bicarbonate solution or pH 7.4 phosphate buffer (Figure 7, middle). Unirradiated films, or irradiated films containing a different polymer comprising a 3:1 molar ratio of DMAEMA and ONBMA, did not dissolve, highlighting the importance of sufficient photolysis to induce water solubility of the coatings.

Given the known relationship between the radical stabilization energy of the benzylic radical after γ-hydrogen atom abstraction and ONB photolysis quantum yield,[100] we prepared a similar analog to **P2** on which each ONB group has a methyl substituent on the benzylic position of the ONB group, **P3**.[101] Our group has also used this strategy for enhancing the ONB photolysis quantum yield (by ~5x) in photodegradable ROMP crosslinkers and conjugated polymers with photocleavable solubilizing alkyl chains.[102,103] Consistent with this trend, **P3**/PSS films dissolved

fully in water upon irradiation ~3-4 times faster than otherwise identical **P2**/PSS films (Figure 7, bottom).

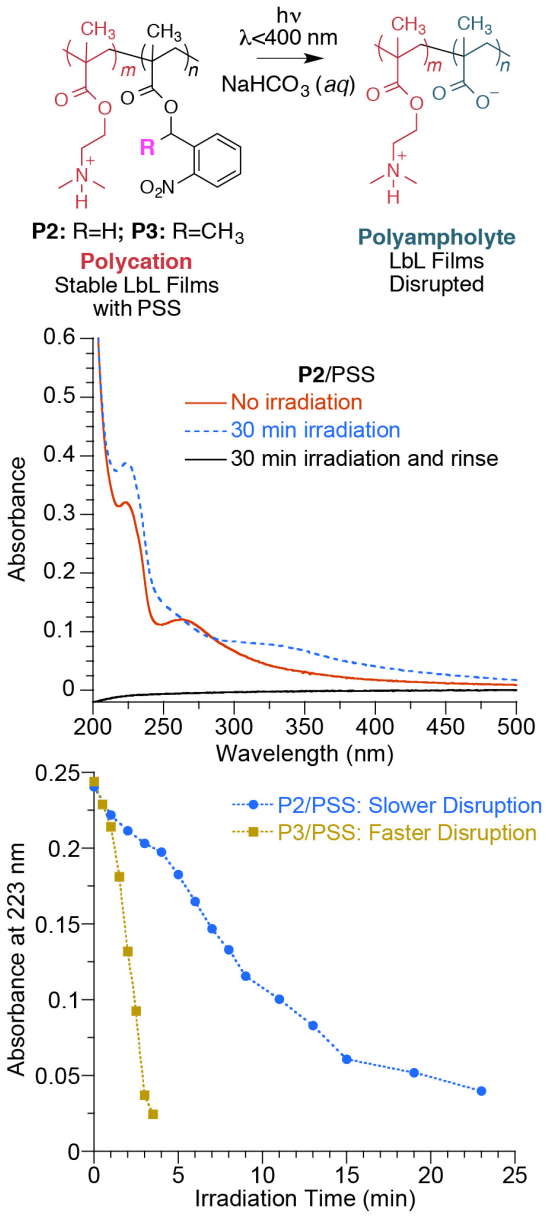

Figure 7. *Top:* Design of 1:1 statistical DMAEMA-ONBMA copolymers **P2** and **P3**, which yield a polyampholytes upon ONB photolysis. A comonomer ratio (m : n) of approximately (0.5 : 0.5) was utilized in **P2** and **P3**. *Middle:* UV-induced disruption of **P2**/PSS LbL film, *Bottom:* LbL films

containing the α-methyl ONB-derivative **P3** respond to UV light faster than analogous films containing **P2**. Reproduced with permission from Ref. 93. Copyright 2015 John Wiley and Sons.

Photoinduced Release of Responsive Free-Standing Films

Although LbL films are bound to their substrates for many applications, there are numerous circumstances in which a free-standing film separated from its substrate can be useful. When small particles are coated as substrates but then dissolved selectively, the renaming coating is a capsule that can serve as a delivery vehicle.[23] Macroscopic free-standing LbL films, which have potential utility in tissue engineering and membranes, are typically prepared by either simple separation from a low surface-energy substrate[104,105] or by selective degradation of an inner compartment of a two-compartment film.[106] As the photoreactive LbL films described above have linear growth profiles, indicating only modest interlayer penetration of polymer chains, the possibility of constructing stratified LbL films with spatially segregated compartments, including a photochemically-sacrificial compartment for producing free-standing LbL films arises.

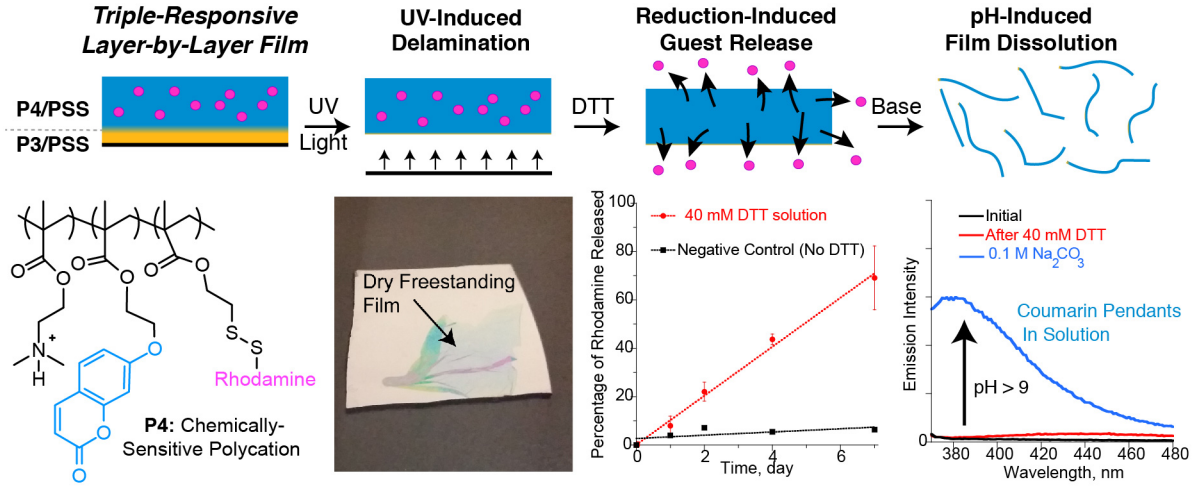

Figure 8. Triple-responsive LbL film that undergoes: i) photoinduced delamination upon irradiation with UV light, ii) release of a chemically bound guest upon chemical disulfide reduction, and iii) dissolution upon deprotonation of the DMAEMA residues at pH > 9. Reproduced with permission from Ref. 93. Copyright 2015 John Wiley and Sons.

Inspired by the work of Hong and coworkers,[107] we prepared triple-responsive, two-compartment LbL films that were capable of releasing free-standing membranes (Figure 8). To prepare the materials, we first deposited a sacrificial, photoreactive inner compartment (at least 16 bilayers of **P3**/PSS), followed by a photochemically inert, but chemically-sensitive outer compartment (**P4**/PSS).[101] The **P4** polycation in the outer compartment comprised 99% DMAEMA, with small quantities of a coumarin methacrylate fluorescent monomer and a rhodamine-functionalized methacrylate bound through a disulfide linkage. The resulting two-compartment films grown on planar quartz substrates (**P3**/PSS)$_{41}$//(**P4**/PSS)$_{140}$ could produce macroscopic free standing films ~200 nm in thickness only when irradiated with UV light (1 hour duration). That is, selective photochemical degradation of the inner compartment released the upper compartment from the substrate. Otherwise identical substrate-bound films that were not irradiated could not delaminate from the quartz, since the upper compartment was still substrate-bound via the intact bottom compartment. The resulting free-standing films were also chemically-sensitive: addition of dithiothreitol (DTT) released rhodamine selectively into solution through reductive cleavage of the disulfide linkage, while increasing the pH higher than 9.3 dissolved the entire **P4**/PSS free standing film through deprotonation of the DMAEMA residues and loss of interchain ion-pairing interactions. These results therefore provide a clear example of the impact that spatial segregation of reactive functionalities in LbL films can have on both bulk and interfacial properties. While chemical structure can directly impart stimuli-responsiveness into films, this work highlights the

fact that consideration of both intra- and inter-polymer interactions, as well as the compartmentalization of chemistries into different areas of the film, can influence how these responses manifest in the overall material.

NIR-Responsive LbL Films

ONB groups are easy to both integrate into a wide variety of materials and functionalize to render them as photocleavable linkers between two different chemical moieties. The confinement of their absorbance to the ultraviolet region of the spectrum, however, limits their utility in some biological applications, especially those that require light to penetrate tissue. The scattering of light in various media, such as polymeric films or biologic tissues, is a major issue for consideration when utilizing photo-activatable groups that depend on delivering considerable photon flux for activation. While ultraviolet light is incompatible with tissues due to its high degree of scattering, absorbance, and damaging effects, longer wavelengths of light can ameliorate these challenges. Tissue is maximally transparent in several near-infrared (NIR) windows, in which scattering and absorbance by biological chromophores and water is minimal.[108] The low energies of these photons, however, limit their utility for executing chemical reactions. Several strategies have emerged that harness NIR photons to break specific bonds in biologically relevant materials.[90] Besides photothermal heating, which has been used in LbL materials extensively (*vide supra*), other strategies use multi-photon processes to reach an electronically excited state of higher energy than the individual photons. Upconverting nanoparticles (UCNPs) form NIR-induced metastable states that subsequently absorb additional photons to reach even higher excited state energies.[109] Transfer of this energy to photocleavable groups such as ONB esters yields NIR-induced bond cleavage,[110] which has been reported to release free-standing LbL films photochemically.[111]

In contrast, our group has focused on integrating photocleavable groups with high inherent two-photon cross-sections into our simply prepared DMAEMA-copolymer platforms. As they exhibit a non-linear dependence of excited state formation on photon flux, multiphoton optical processes require high intensity lasers with femtosecond pulse widths, but offer improved spatial resolution. However, not all efficient chromophores possess high cross-sections for two-photon absorbance. To this point, ONB photocleavable groups generally have unsuitably low two-photon cross-sections.[112] We therefore prepared **P5**, an analogous polycation to **P2** and **P3**, but which contains the 6-bromo-7-hydroxycoumarinylmethyl (Bhc) photocleavable group.[113] In addition to UV-induced photocleavage, the Bhc group offers a two-photon photocleavage cross-section of ~ 1 GM (cm^4s/photon).[114]

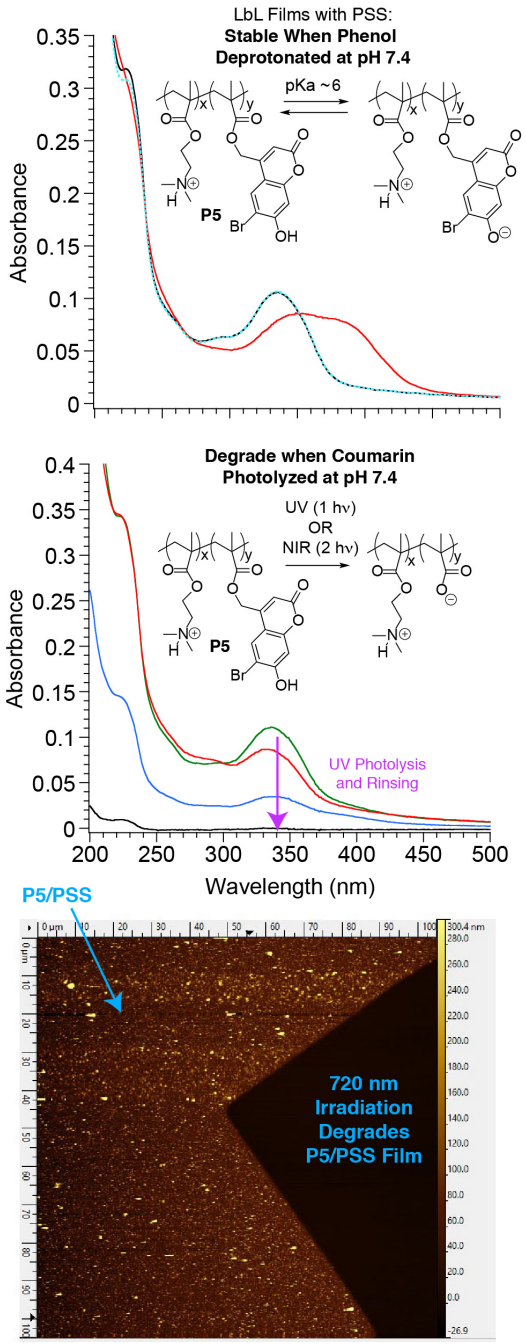

Figure 9. LbL films containing Bhc pendants on **P5** are stable to phenol deprotonation (*top*) but are disrupted by UV (*middle*) and fs-pulsed NIR (bottom) irradiation. A comonomer ratio (x : y) of (0.5 : 0.5) was utilized. Reproduced from *Langmuir* **2017,** *33,* 10877-10885. Copyright 2017 American Chemical Society.

Like **P2** and **P3**, coumarin-containing **P5** formed polyelectrolyte multilayer films with PSS as partner polyanion, and showed clear incorporation of the coumarin chromophore at λ_{max} = 340 nm on planar quartz substrates. UV (λ > 295 nm) irradiation of 8-bilayer **P5**/PSS films followed by rinsing with pH 7.8 phosphate buffer or 0.1 M $NaHCO_3$ dissolved the polymer films. Highlighting the applicability of NIR-responsive photocleavable groups to LbL films, 720 nm light delivered from a femtosecond-pulsed laser also rendered **P5**/PSS films soluble. Atomic force microscopy images (Figure 9) showed dissolution of these (**P5**/PSS)$_{14}$ films (70 nm thick, assembled on borosilicate glass) only in the square areas irradiated. The extent of film removal determined with AFM correlated positively with the applied laser power, with increases in photon flux resulting in larger decreases in film height. Overall, this work improves the reach of photosensitive LbL films to biologically relevant NIR light, and broadens the scope of applicable photocleavable groups in LbL films, which we exploited further in wavelength-selective film disruption (*vide infra*).

As an important negative control experiment, unirradiated films did not dissolve under these basic rinsing conditions, highlighting the importance of photolysis of the coumarin side chains to dissolution. Beyond the typical control, however, this stability of unirradiated **P5**/PSS films to a range of pH values provided important mechanistic information regarding the role of light-induced changes in ion pairing for film dissolution. Based on the literature and our own solution-state titration, the phenol group of the Bhc chromophore has a pKa of ~5.5-6;[115] deprotonation of the phenol increases donor-acceptor character, red-shifting the absorbance spectrum of the resulting phenoxide. This acidochromism persists in LbL films: after initial treatment with 0.1 M HCl, $NaHCO_3$ exposure broadens the UV/vis spectrum of the coumarin chromophore, bathochromically shifting absorbance onset by 50 nm. Subsequent exposure to 0.1 M HCl reproduces exactly the initial spectrum with no loss in extinction, highlighting that the **P5**/PSS film is highly stable to pH

values in this range, even with significant accumulation of negative charge on **P5** (Figure 9). We conclude that simply increasing the anionic character of the polyampholyte is insufficient to disrupt the LbL film, and that increasing the hydrophilicity of these polycations also contributes to photo-induced film instability.

Wavelength-Selective LbL Film Disruption

Beyond selecting wavelengths that penetrate barriers such as tissue, the tunable nature of photon energy offers the prospect of using the wavelength of light to yield chemical selectivity. As described in a 2015 tutorial review by Feringa and coworkers,[116] such photochemical selectivity can be realized by combining multiple photocleavable groups, each of which has a different absorbance and/or reactivity profile at different wavelengths. Materials containing multiple chromophores can be pre-programmed to carry out wavelength-specific functions, where each color of light is responsible for a "job" by triggering photochemical reactions.

Such selectivity can be divided broadly into two categories. *Wavelength orthogonal systems*, introduced here only briefly, allow the different wavelengths of light to be applied in any order and retain a high degree of chemical selectivity. As absorbance spectra of different photocleavable groups tend to overlap at shorter wavelengths in the UV region, this sort of orthogonality is difficult to achieve. However, through precise characterization and understanding of the dependence of quantum yields on excitation wavelength,[117] the group of Barner-Kowollik has demonstrated wavelength-orthogonal photochemistry in numerous material platforms in the last several years.[118-122] Heckel and coworkers also described wavelength-orthogonal two-photon photolyses of photocleavable groups using different colors of NIR light.[123]

The simpler, albeit less elegant, approaches are *wavelength selective systems,* which require a particular sequence of wavelengths to achieve chemoselectivity. This usually occurs by proceeding

from longer wavelengths to shorter wavelengths, taking advantage of some photocleavable groups having absorbance spectra (or more importantly, the product of extinction coefficient and quantum yield of photolysis, $\varepsilon\phi$) that stretch further to the red than others. Therefore, at the longest applied wavelength, only the most red-shifted photocleavable group reacts, as the others do not absorb; attempts to irradiate the mixture with shorter wavelengths of light results in both photocleavable groups reacting, thereby losing selectivity. As an elegant example and inspiration for our efforts, Imperiali and coworkers demonstrated the use of two photocleavable groups to control enzymatic activity—visible light photolyzed only the dialkylaminocoumarinyl methyl (DEACM)-protected enzyme substrate and turned on catalysis, while subsequent irradiation with UV light photolyzed the ONB-protected enzyme inhibitor, turning off catalysis.[124] In the area of materials science, del Campo and coworkers used two different two-photon absorbing nitro-substituted biphenyl-based photocleavable groups to either induce crosslinking or depolymerization of the a polymeric network.[125] Such "multi color uncaging" has also been demonstrated in neuroscience[126] and photo-activated antibiotics.[127]

Our approach to wavelength-selectivity in polymeric materials has been to combine this type of chemo-selectivity unique to photochemistry with layer-by-layer self-assembly, which raises the possibility of segregating these chemistries spatially in the thickness of films. The chemoselectivity of each reaction would therefore be confined to a specific space in the thickness of the film, based upon separating each photocleavable group into a different LbL compartment. Experimental support for combining these top-down (photopatterning) and bottom-up (LbL) fabrication techniques came from our consistent observations that thicknesses of LbL films comprising our DMAEMA-based polycations and PSS show a linear dependence of film thickness on number of bilayers deposited. In contrast to the complete mixing of polymers associated with

"exponential" growth, such linear growth is associated with limited inter-layer mobility of each polymer chain,[128-131] making it possible for the compartments to remain spatially separated by a "fuzzy" interface.

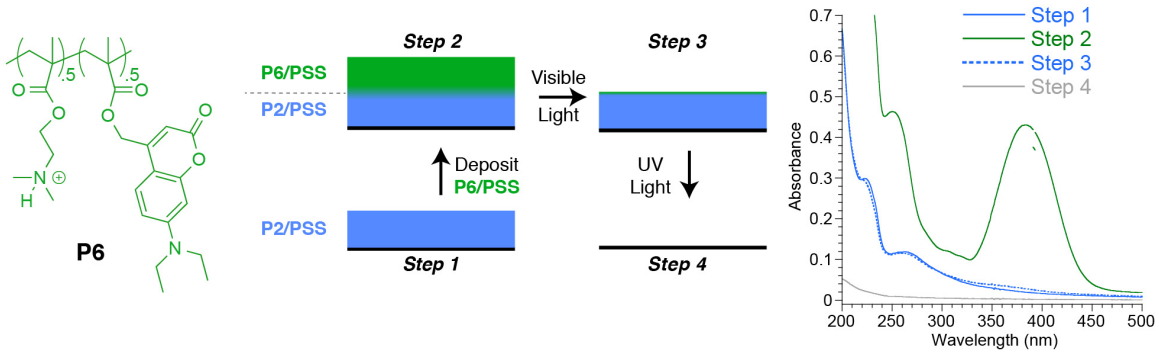

Figure 10. Visible-responsive DEACM-containing polycation **P6**, and its use in a two-compartment LbL film allowing for wavelength-selective removal of individual compartments. Reproduced from *Chem. Mater.* **2014,** *26,* 1450-1456. Copyright 2014 American Chemical Society.

Inspired by the DEACM/ONB design of Imperiali, we prepared a 1:1 statistical copolymer of DEACM-functionalized methacrylate and DMAEMA **P6**, which similar to previous polycations, formed PEM films with PSS (Figure 10). As their absorbance spectra extend out to ~ 450 nm, irradiation of ~100 nm thick films of **P6**/PSS using $\lambda > 400$ nm and rinsing with $NaHCO_3$ solution resulted in removal of these films from quartz substrates. Establishing wavelength-selectivity, analogous ONB (**P2**/PSS) films showed no evidence of reaction or dissolution upon exposure to identical conditions. To combine the chemical selectivity of wavelength selective materials and spatial selectivity that LbL uniquely offers, we then prepared a "stacked" film of two compartments comprising: i) an inner compartment was UV-responsive **P2**/PSS, and ii) an outer compartment of visible responsive **P6**/PSS. As visualized by UV/vis spectrophotometry, irradiation with visible light removed only the outer **P6**/PSS compartment (the spectrum after

irradiation was not distinguishable from the initially deposited **P2**/PSS compartment), while subsequent UV irradiation removed the inner **P2**/PSS compartment (Figure 10).

Beyond these two levels of selectivity enabled by DEACM and ONB, it is possible to consider additional levels of photochemical selectivity by choosing additional photocleavable groups with sufficiently different $\varepsilon\phi$ values at more than two wavelengths. With this overall type of objective in mind, Del Campo and coworkers published a comprehensive study in 2011 that identified combinations of photocleavable groups could comprise two, three, or even four levels of wavelength-selective cleavage.[132] Four levels of uncaging function using different photocleavable groups has been realized in other systems, such as the work of Heckel and coworkers in their wavelength-selective deprotection of nucelotides.[133] Differences in efficiencies of photolysis at the same wavelength can also yield pre-programmed, sequential activation of function with light, such as that described by Heckel in their combination of wavelength- and kinetic selectivity,[134] or the coumarin derivatives with carbocation photolysis intermediates of differing stability from Marchán and coworkers.[135]

We therefore extended our photoreactive LbL films to four levels of photochemical selectivity through a combination of photocleavable groups that offer a combination of wavelength-selectivity, and in the case of ONB groups, differences in photolytic efficiency (Figure 11).[136] Our design featured four different photocleavable esters and corresponding DMAEMA-based polymethacrylates: i) **P6** (DEACM) which absorbs wavelengths as high as 450 nm, ii) **P3** (α-Me ONB), which absorbs UV light up until 400 nm, iii) **P2** (ONB), which also absorbs UV light up until 400 nm, but reacts with ~5x lower quantum yield than the methylated derivative **P3** (*vide supra*); and iv) **P7** (methoxyphenacyl), which does not absorb past ~ 330 nm.[85]

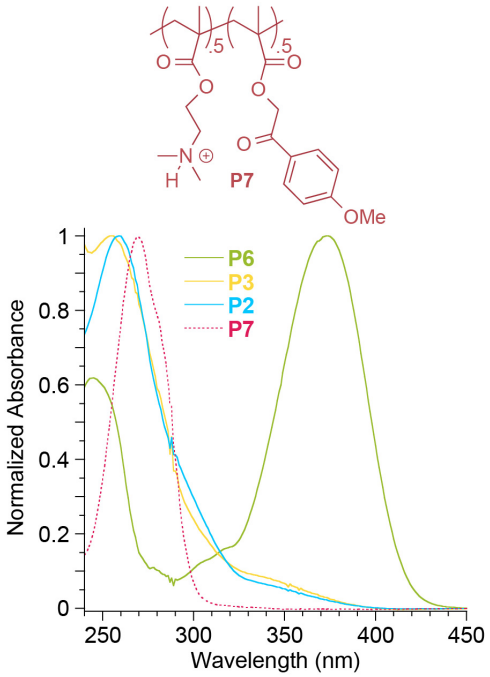

Figure 11. Structure of methoxyphenacyl-containing polycation **P7**, and normalized UV/vis absorbance spectra of the four polymers used for four-level selectivity in photochemical LbL film degradation. Reproduced from *Chem. Mater.* **2017,** *29,* 2951-2960. Copyright 2017 American Chemical Society.

Much like our two-color wavelength-selective materials, these four photocleavable groups were readily distinguished in several types of LbL films. UV/vis spectrophotometry and atomic force microscopy of individual polycation/PSS films, similar to experiments described above, demonstrated the potential for selectivity in these materials. When these four polymers were deposited with PSS as LbL films separately onto silica microparticles, along with one layer of a fluorescent rhodamine-functionalized polycationic guest, each of the four samples of microparticles only released fluorescent cargo when irradiated under the appropriate conditions. i) Only **P6**/PSS released fluorophore during irradiation with λ>400 nm; ii) both **P2**/PSS and **P3**/PSS released fluorophore upon irradiation with 365 nm, but with such different rates that < 20%

fluorophore from **P2**/PSS was released when **P3**/PSS released all fluorophore, demonstrating kinetic selectivity in addition to wavelength-selectivity; iii) **P7**/PSS only released cargo upon irradiation with deeper UV light (λ>280 nm).

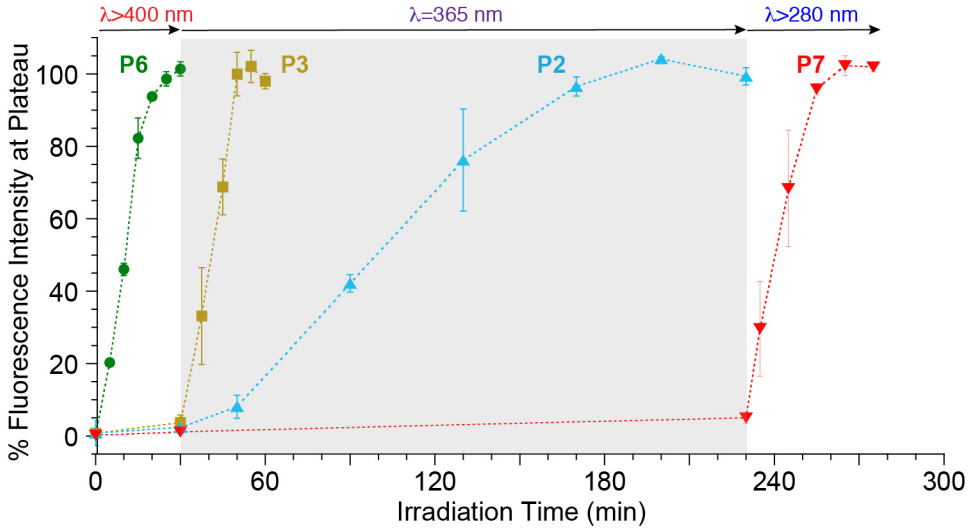

Figure 12. Pre-programmed sequential release of a rhodamine-labeled polymeric guest from LbL-films coated silica microparticles, with a combination of wavelength and kinetic selectivity. Reproduced from *Chem. Mater.* **2017,** *29,* 2951-2960. Copyright 2017 American Chemical Society.

Finally, in a demonstration of the potential for combining top-down photopatterning with bottom-up LbL assembly, we realized multi-level photopatterning using stratified combinations of these polymers combined together on planar quartz glass substrates. Three-level photopatterning of LbL films was readily accomplished through wavelength selectivity by stacking a compartment of **P3**/PSS on top of a compartment of **P7**/PSS—irradiation through a striped photomask at 365 nm photolyzed only the outer **P3**/PSS compartment while irradiating with deeper UV light with the same mask oriented perpendicularly photolyzed through the entirety of the LbL film. Subsequent development of the pattern as previously described yielded the expected three-level

pattern. Incorporating the slower ONB-functionalized **P2**/PSS compartment between the **P3** and **P7** compartments yielded four-level patterning, but required careful control and optimization of the initial irradiation step due to the lack of wavelength-selectivity between **P2** and **P3**. The use of DEACM as an outer layer in these patterning experiments proved difficult, which we have attributed to a combination of the requirement for water to cleave coumarinyl groups, and its high extinction coefficient, which could attenuate photons from reaching further into the film before aqueous development.

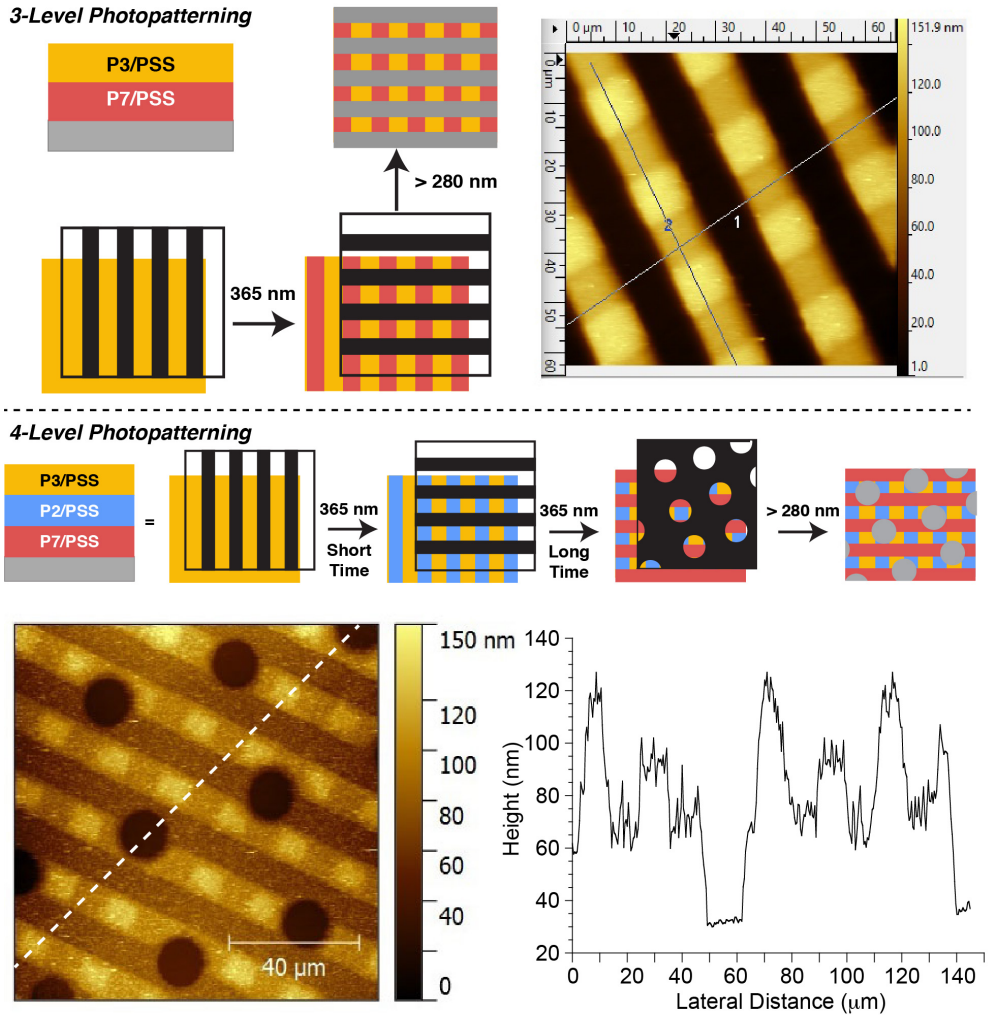

Figure 13. Three-level (*top*) and four-level (*bottom*) photopatterning of compartmentalized photodisruptable LbL films, visualized with atomic force microscopy. Reproduced from *Chem. Mater*. **2017,** *29,* 2951-2960. Copyright 2017 American Chemical Society.

Conclusion

Polymer coatings play an essential role in controlling the interface between substrates and their environment, with the layer-by-layer self-assembly process becoming increasingly important in a range of applications. Altogether, our work over the last several years has enhanced the precise control over LbL polyelectrolyte coatings through the use of photocleavable groups and resulting charge-shifting polymers. Our approach combines simple and easy to prepare photoreactive polymers with convenient, all-aqueous LbL deposition, and extension into near-infrared wavelengths through non-linear absorbance and cleavage. When compartmentalized in these polyelectrolyte multilayer films, reactivity can be restricted to the scale of tens of nanometers in the thicknesses of these films. We have used these stratified materials, the function of which is pre-programmed by the order of polymer deposition, to prepare reactive free-standing films, to release guests in a pre-determined sequence, and for multi-height positive-tone photopatterning of polymer films. Disadvantages of our approach include the requirement for a specific sequence of wavelengths—they are not wavelength-orthogonal—and the slow growth of films with respect to the number of bilayers deposited.

Overall, the unique advantages of photochemical processes in materials, including spatiotemporal control, precise control over wavelength and intensity, polarization, and

interference will yield a continuously expanding impact of photo-responsive materials, and remote-control over the interfacial properties of multilayer polymer coatings. In our opinion, it is these unique advantages of light-responsive materials which showcase their promise moving forward, particularly in the general field of stimuli-responsive materials. This top-down light responsivity, in concert with the bottom-up LbL assembly, affords interfacial material control beyond what either method could provide separately. The enhanced material complexity that this platform presents can be further utilized to realize new functions in polymeric materials. For example, potential future developments include the integration of members of the emerging classes of highly-reactive photocleavable groups with red-shifted absorbance spectra and the preparation of photo-responsive microcapsules or other material platforms for staged delivery of therapeutics.

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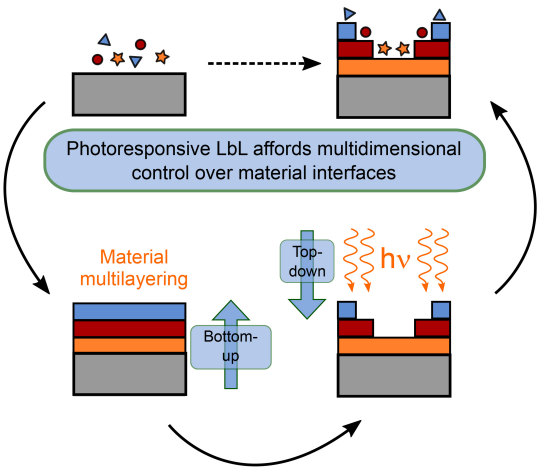
TOC Graphic


Photoresponsive LbL affords multidimensional control over material interfaces
Material multilayering
Top-down
hν
Bottom-up

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Matthew J. Feeney is a Ph.D. student in chemistry at Tufts University, under the supervision of Professor Samuel W. Thomas III. He received a B.A. in Chemistry from Colgate University in 2014, where he worked towards the synthesis of various carbon-linked glycoconjugate mimics under Professor Ernest Nolen. His current work at Tufts is focused on the synthesis of light-responsive polymers for the preparation of layer-by-layer coatings and membranes with reversibly tunable material properties.

Samuel W. Thomas III is Professor of Chemistry and Dean of Academic Affairs in the School of Arts and Sciences at Tufts University, where his research focuses on stimuli-responsive organic materials. He received his B.S. in Chemistry from the University of Rochester in 2000, during which time he worked in the laboratories of Prof. Joshua Goodman (Rochester) and Louis Hegedus (Colorado State). After one year as a research chemist at Eastman Kodak, he earned his Ph.D. in Organic Chemistry in 2006 under the supervision of Prof. Timothy Swager at MIT, where he focused on amplifying fluorescent polymers. He then spent three years as an American Cancer Society Postdoctoral Fellow in the laboratory of Prof. George Whitesides (Harvard University). Since starting at Tufts in 2009, his group's research has been recognized with a DARPA Young Faculty Award, a Thieme Publishers Journal Award, an NSF CAREER Award, and a 3M Non-tenured Faculty Award. His teaching of organic chemistry has also been recognized with a Tufts Teaching with Technology Award.