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Perspective

Engineering Materials Layer-by-Layer: Challenges and Opportunities in Multilayer Assembly

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DOI 10.1002/aic.12769

Keywords: layer-by-layer, electrostatic assembly, polyelectrolyte multilayer, polyelectrolyte complex, self assembly, thin film, multilayer assembly, review

Introduction

The introduction of alternating layer-by-layer (LbL) adsorption, approximately 20 years ago,[1–3] has led to a new way of looking at and appreciating the power of electrostatic assembly. In the LbL process, different charged species—polymeric, colloidal, nano- and microscale—are deposited on a substrate in sequences of alternating charge or other complementary interactions such as hydrogen bonding (Figure 1). This approach enables the fine control desired for tunable design of functional materials, as well as a broad diversity of components that can be readily incorporated into these nanoscale thin films with ease. The area has grown at an unusually rapid pace since its inception, introducing a wealth of new fundamental science and a broad range of engineering applications. Of particular interest to the chemical engineer have been applications in reactive and passive membranes, drug delivery systems, and electrochemical and sensing devices. These applications generally require controlled transport— of ions, electrons, organic molecules, water—as well as the ability to tune the assembly and disassembly of the films, and manipulate properties with a high level of control. Key to all of the aforementioned is the ability to control film composition across thickness.

To advance this technology from the realm of exciting demonstrations to real-world applications, one must be able to engineer layer-by-layer assemblies with the same ease with which one engineers other bulk materials systems. There are several chemical engineering challenges in the area of layer-by-layer assembly that, when mastered, can lead to the generation of complex thin film architectures and morphologies. Furthermore, the viability of these engineered materials will rest on whether they can be reproduced on the commercial length scale, using a range of simple and accessible processing operations. In this perspective, some of the key engineering opportunities, as well as the challenges, in electrostatic assembly are presented. Both passive and responsive, or ‘‘smart'' materials systems, based on multilayer assembly will be used as examples of how the LbL approach to building materials nanolayer by nanolayer can yield promising systems for drug delivery, energy, reactive membrane and electrochemical applications. Finally, new means of generating or processing multilayer thin films using rapid assembly methods are opening up possibilities for commercialization, and new territories for exploration, as the key driving forces for final morphology of these films—i.e., kinetics vs. thermodynamics—are manipulated to gain new control over thin film composition, morphology and function.

LbL films as nanoscale blends

One of the most important advantages of layer-by-layer assembly is the ability to bring together polymers, small molecules and inorganic materials systems in a singular thin film without the constraints that are usually associated with the formation of polymer blends and composites. Because the adsorbed layers of a polyelectrolyte multilayer thin film are highly interpenetrated, chain segments from a polymer adsorbed in any given layer will typically exist in the 3 or 4 layers above and below the point of adsorption.[4] Such a high degree of integration of the components in multilayer films allows the use of LbL assembly as a means of creating nanoscale blends. The thermodynamic driving forces that govern the formation of mixtures work against homogeneous polymer blends, which have a much lower entropic driving force for mixing. Polymers are usually able to dissolve small molecules in blend matrices at low-percent loadings (1–5%), and the blending of one polymer with another is typically very difficult even at very low-molar fractions. With layer-by-layer,

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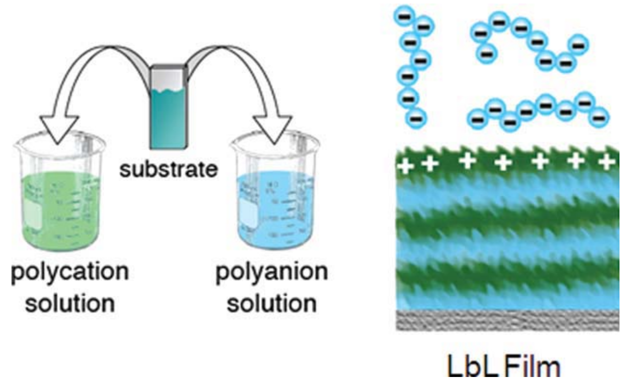

Figure 1. Schematic illustrating the construction of LbL films from the alternating adsorption of positively and negatively charged species from water solutions on a substrate.

polymeric species of interest can be designed to exhibit charged groups that enable incorporation into multilayers. Polymer backbones that would normally be fairly difficult to combine together to form a homogeneous blend system can, thus, be alternately adsorbed through the corresponding strong electrostatic interactions, forming multivalent ionic complexes that stabilize the thin film. Furthermore, the use of electrostatic assembly allows a tuning of the relative composition of the thin film in a manner that is not accessible with traditional blends through the manipulation of the ionic strength and the pH of the polyelectrolyte solutions. This flexibility is not feasible with traditional blends that are dictated solely by a narrow window of compositions that are thermodynamically stable. The resulting multilayer consists of a polymer network of both polymer types, and properties that indicate a true molecular level blend.

This ability to use layer-by-layer assembly as a means of generating unique blend materials systems offers significant advantages in the design of materials systems that regulate transport of ionic, electronic, and molecular species across a polyelectrolyte multilayer membrane. A number of examples have shown that LbL can be used to generate thin-film membranes that can exhibit selective gas transport[5–10] or act as a means of rejecting salt ions in water filtration[11–15] and ion exchange[16,17] applications. Multilayer films present excellent opportunities to combine polymers that exhibit desired diffusivity and solubility characteristics for given applications. For example, the author and her collaborators have taken advantage of this capability to address limitations in methanol fuel-cell proton exchange membranes.[18] Methanol fuel cells require that the proton exchange membrane facilitates rapid transport of protons, while preventing the cross-over of liquid methanol fuel into the membrane and to the opposite electrode. Fuel crossover not only represents lost efficiency due to loss of fuel, but also leads to the fouling of the cathode catalyst. The commonly used membrane is a sulfonated perflouroether ionomer composed of Nafion®, which is highly effective in hydrogen fuel cells, but is fairly permeable to liquid methanol, because the methanol molecules readily diffuse through sulfonated pores within the Nafion matrix. Poly-*p*-phenylene oxide has excellent mechanical and thermal stability and a very low permeability to liquid methanol. By creating highly sulfonated ($> 80\%$) poly-*p*-phenylene oxide (sPPO), one can generate a fully water-soluble polymer, that would not be of use as a homopolymer in a membrane, because of its tendency to swell or dissolve in the aqueous environment of a fuel cell membrane. However, when layered with a polycation, such as polydiallyl dimethylammonium chloride (PDAC), sPPO can be used to generate a polyion complex blend that is stable in water, and has low-methanol permeability, but high-ionic conductivity. The ionic strength of the polyion solutions changes the degree of shielding of the polymer backbone as it is adsorbed, thus, leading to a means of (a) tuning the effective ionic crosslink density of the film, and (b) changing the relative amounts of sPPO and PDAC adsorbed by adding salt only to the sPPO bath.[19] These simple changes in ionic strength lead to nearly two-orders of magnitude increases in ionic conductivity. It was found that just a few bilayers deposited on a nafion membrane (Figure 2a) led to increases in methanol fuel-cell performance of up to 50%.[18]

Similar principles apply to the use of LbL techniques to generate novel composite structures with compositions or morphologies that would be difficult to achieve through direct mixing or blending of traditional polymers to form composites. These include the incorporation of catalytic micro- and nanoparticles for electrodes,[20–24] sensors and reactive membranes,[25–31] the introduction of redox-active inorganic species for electrochromic,[32–36] photorefractive and light-emitting applications,[37–40] and the use of a broad range of carbon nanomaterials.[41–45] Of particular interest is the impact of nanomaterials on the mechanical strength of organic polymer films. Layer-by-layer offers the unique advantage that it uses a charged nanomaterial that is fully dispersed in water and is self-stabilizing. This property, in turn, ensures that the nano-objects that are adsorbed into multilayer films are not aggregates or clusters, as is typical with dispersions from organic solvents, but individual materials with highly accessible surface area—making it possible to exhibit percolative properties, such as mechanical enhancement or conductivity increases at low amounts of the nanomaterial. Such property enhancements have been demonstrated with the incorporation of nanotubes into polyelectrolyte multilayer composites leading to materials with remarkable gains in mechanical strength and toughness.[41] Similar enhancements have been observed with the incorporation of two-dimensional (2-D) nanomaterials, such as graphene oxide and silicate clays, in LbL multilayer thin films. For example, clays, which are negatively, charged nanomaterials, 1–3 nm, and submicron to micron-scale sheet-like structure, have net negative charge and can be directly incorporated into multilayer films. The resulting highly stratified and organized structures (Figure 2b) have been compared to the naturally occurring “nacre” of oyster shell.[46] The resulting thin films can provide very interesting mechanical and barrier properties, and exhibit anisotropic thin film properties, such as conductivity and gas permeation.[9,47]

The aforementioned examples involve multilayers for which at least one component is a polyion, yielding organic–inorganic hybrid materials. It is also possible to use LbL to

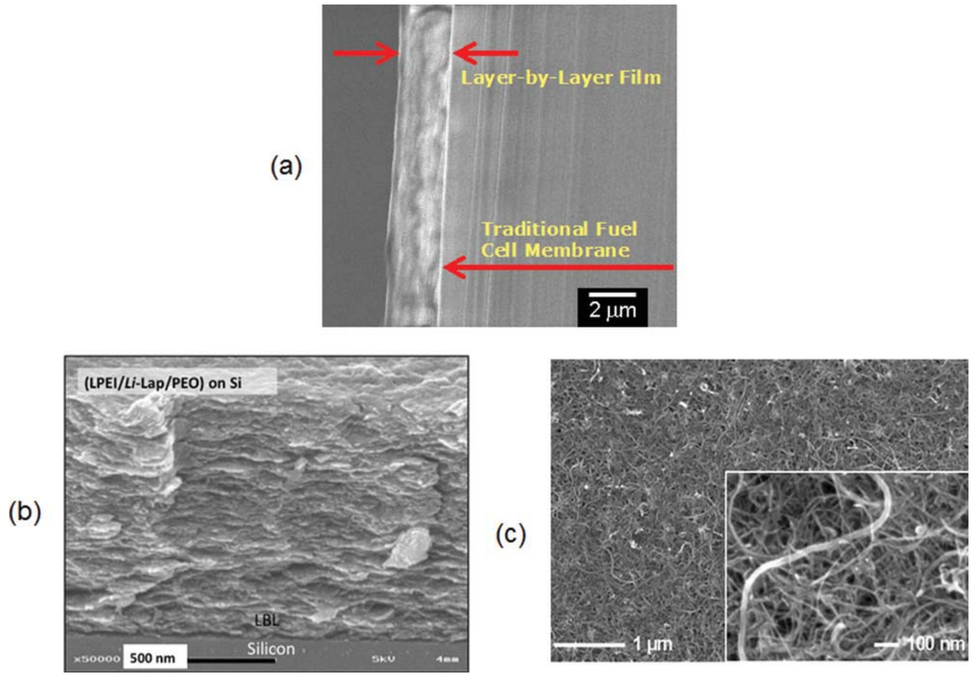

Figure 2. LbL nanostructures can create highly interpenetrated networks that yield molecular scale blends and hybrid composite structures with great uniformity.

(a) Cross-sectional SEM micrograph of an LbL thin film of a highly sulfonated aromatic polyanion with a polycation deposited on a traditional sulfonated perfluoroether Nafion® fuel-cell membrane (full thickness of 90 microns) that can regulate ion and methanol transport; film shown is thicker than those used for fuel cell operation (which were < 100 nm) to enable visualization of the LbL/nafion interface, (b) alternating hydrogen bonding polymer (poly(ethylene oxide)) with negatively charged laponite clays and a simple polycation yields layered nanosilicate LbL films with anisotropic conductivity and transport properties, and (c) the formation of all-carbon nanotube LbL fims yields isolated carbon nanotubes in porous high-surface area networks. Sources: (a) Argun et al[18], and (b) Lutkenhaus et al.[47] (c) Lee et al.[48]

generate thin films that consist solely of nanomaterials systems. In these cases, films with interesting nanoporous morphologies are often obtained, determined by the irregular shape of the associated nanomaterials systems and the nature of their packing. For example, alternating deposition of positively and negatively charged carbon nanotubes to form a cohesive thin film with an extraordinary density of nanotube as well as a large amount of available surface area made accessible by the open network of the CNTs (see Figure 2c) has been demonstrated.[48] These films consist of well isolated nanotubes rather than the bundled aggregates of tubes typically observed in cast films or other processed versions of CNT films. After heat treatment, the carbon nanotube film is mechanically stabilized, the nanotube surface becomes available for lithium ion insertion via the residual carboxylated and other functional groups on the outer graphitic surfaces of the nanotube, and the nanotube inner walls act as electron conducting channels. The LbL nanolayered CNT films were shown to act as the positive electrode for lithium ion batteries; the electrodes exhibit unusually high power as well as high-energy density by combining the redox characteristics of a traditional lithium ion battery with the rapid charge/discharge properties of a capacitor.[49] Other examples of hybrid multilayer films in the literature include the combination of inorganic and organic nanomaterials to create optical coatings, biosensors, catalytic and electrochemical electrodes.[50–53]

The body of experimental evidence has been growing at a significant pace and the conclusion is clear: LbL films provide an excellent technological platform for achieving (a) uniform blending of materials, with uniformity extending to very small scales, e.g., 100 nm to 1 μm, and (b) desired nanostructured morphologies of composite or hybrid materials systems.

From Stratified to Fully Mixed Multilayer Systems—Role of Diffusion and Kinetically Locked Structures

One of the most attractive aspects of electrostatic assembly is the technological ability it provides to control materials structure on the length scale of a few nanometers. Thus, if one desires two elements of complementary functions to be integrated over regions of fairly well-defined thicknesses, multilayer assembly enables the insertion of materials components at given points along the thickness of the film. As was discussed in the previous section, the highly interpenetrating nature of polymer chains provides molecular level connectivity between chain segments that can occur over

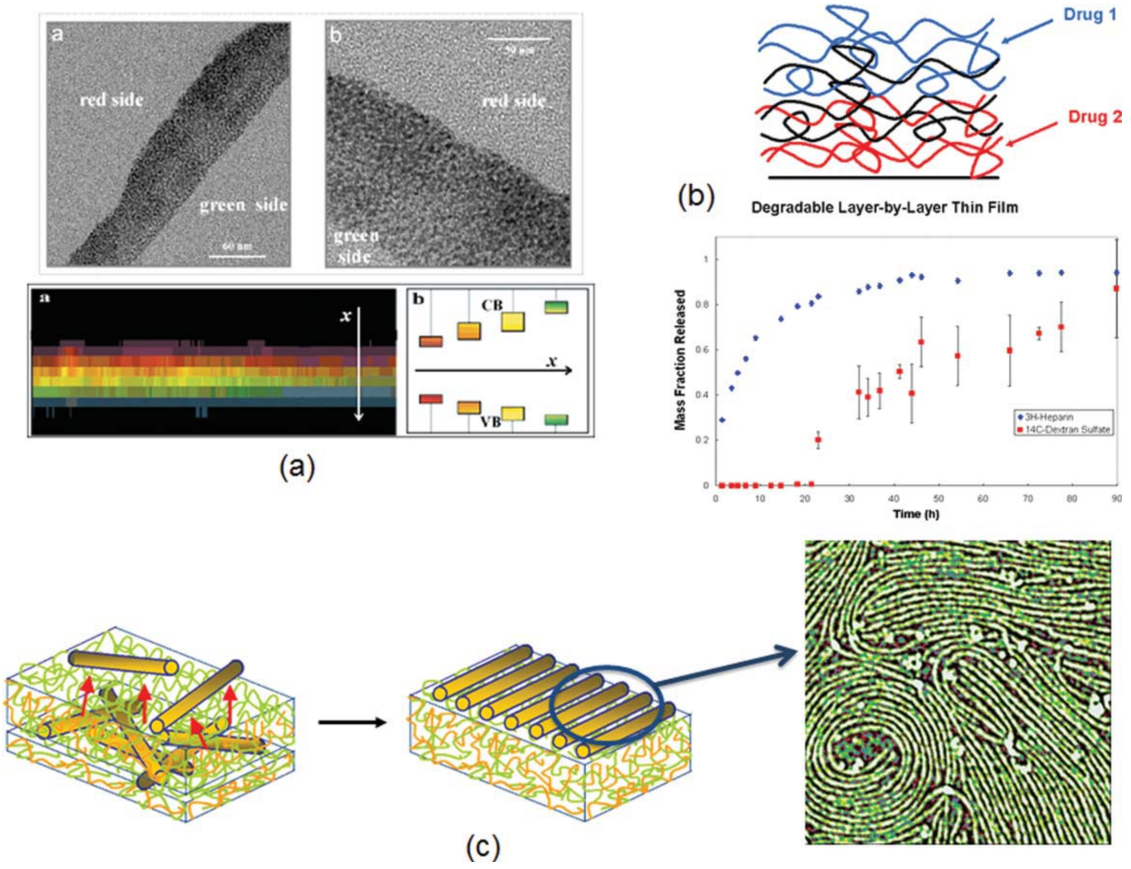

Figure 3. The ability to introduce nanometer-scale systems can lead to desired control of structure, depending on whether films grow in a linear fashion without mixing, or with interdiffusion and mixing during assembly.

(a) TEM micrographs and confocal fluorescence image of "nanorainbows" reported by Kotov et al. with sequential introduction of series of layers with differently sized quantum dots (CdTe NPs made of 10 bilayers each of "green", "yellow", "orange", and "red" NPs), (b) cartoon schematic llustrating the layering of two different model drugs separated by a thin "barrier" layer that prevents interdiffusion, and data illustrating the achievement of sequential release of the two drugs from an LbL film, and (c) demonstration of how the interlayer diffusion phenomenon can lead to interdiffusion and exchange of polyions, thus, enabling the mobilization and entropic ordering of kinetically trapped phage onto the surface of an LbL thin film. Sources: (a) Mamedov et al[54], (b) Wood et al.[60] and (c) Yoo et al.[61]

several layers, thus, enabling molecular level blending. However, over larger length-scales of 10 or more bilayer pairs, one can generate relatively discrete regions of homogeneous composition by generating ''blocks'' of multilayers with differing compositions. The ability to generate these well-defined compositional variations across film thickness is dependent on the idea that the adsorbing species primarily adsorb to the top surface regions of the growing film, where it remains kinetically ''locked'', resulting in overcompensation and charge reversal. Upon rinsing, any nonadsorbed material at the interface is removed, and the film construction continues with a single ''monolayer'' adsorption step with the oppositely charged polymer. This linear growth behavior is the most commonly observed kind of multilayer film buildup, and it can lead to the development of structures with exquisite levels of control in film composition. Examples include the precision placement of charged quantum dots into nanometer-scale layers, with variation of QD size to achieve films with a gradient of electron transfer across the film thickness and a gradation of luminescent color to form ''rainbow'' structures (Figure 3a).[54] The ability to place a nano-object within any desired plane of the multilayer is also illustrated in the formation of optical coatings for which polyelectrolytes that bind metal cations are assembled in certain regions in alternation with nonmetal binding polyions to create antireflective surfaces and complex optical diffractors.[55]

However, not all polyelectrolytes adsorb in this linear fashion. In some cases, the polyelectrolyte or multivalent species is readily solubilized within the water-swollen multilayer film. Rather than merely adsorbing onto the top surface due to strong electrostatic attractions, the polymer chains are free and mobile enough to absorb into the bulk of the growing film and remain sequestered within the film interior as excess polymer. When the film is then immersed in the rinse and subsequent polyion baths, it diffuses back toward the top surface and ultimately complexes with oppositely charged polymer from the second adsorption step. With each subsequent step, the film thickness increment gets larger, leading to films with exponentially growing thickness.[56] The thickness per bilayer pair can exceed 100 nm, reaching 200–400 nm in some cases. Polymer chains in these interdiffusing LbL films get redistributed with each step of the alternating adsorption cycle. Consequently, attempts to generate isolated thin film structures by using blocks with different composition are often thwarted by the absorption of polymer within the film.[57,58] This phenomenon can be problematic in the construction of complex functional devices in which different groups of layers act as separate device components, or as isolated reactive, electro-optical, or permselective components in complex LbL films.[59]

The technological ability to obtain and control stratified layers through LbL systems is of particular significance for the controlled release of drugs from surfaces. Multilayer assemblies offer the unique advantage of introducing a range of different types of drugs into the multilayer thin film. If one can generate films in which release is based predominately on surface erosion, it should be possible to incorporate different drug components at different layers in an LbL film. This film would then erode to release the drugs in the inverse sequence of their construction, as shown in the schematic of Figure 3b. For example, one might wish to have an anti-infective agent eluted from the coating of a biomedical implant initially, followed by biologic wound healing agents. Such a system would be formed by adsorption of a series of LbL layers containing first the wound healing agents, followed by multilayers incorporating an antibiotic, for example; however, the sequential release of drugs can be thwarted by the interdiffusion and mixing that is common to many biomacromolecules and small charged molecules during LbL assembly. One means of addressing this problem of intermixing is the introduction of ‘‘barrier layers’’ between different sets of LbL film layers (components); in building LbL films with multiple components, such separating barrier layers would not allow the interdiffusion of one drug component into the underlying multilayer film containing the other component during film assembly. This concept was demonstrated by constructing a multilayer barrier system that was heated to enable the formation of amide bonds between a polyacid and polyamine, thus enabling the introduction of two LbL drug release systems in tandem, for which the top layers could controllably be released first, followed by release of the bottom drug-containing layers after a 24 h pause.[60] A similar approach has also worked for the generation of all-LbL electronic devices, such as electrochromic devices, for which the active components need to be separated. Although this method can work well for certain systems, there are many others for which even a crosslinked layer is not sufficient to prevent interdiffusion, or in which the amidation process can lead to deactivation of an encapsulated drug or degradation of an active component. In such cases, structured LbL films can be difficult to generate. Engineering challenges in this area include, among others, the introduction of more effective barriers or separators that can be implemented with the water-based LbL approach. Solutions may include judicious exploitation of the nanomaterials such as silicate clays and graphene, implementation of orthogonal crosslinking chemistries at mild conditions, or finding a means of directly modulating the interdiffusion behavior of the materials.

While the issue of interdiffusion in certain layer-by-layer systems is clearly a critical problem requiring drastic intervention, for other systems the increase in mobility of chains during the interdiffusion process can actually be a true asset and a differentiating advantage. For example, material components that would be kinetically pinned into less ordered, and possibly less efficient or desirable arrangements, are able to interdiffuse freely within these films during the adsorption step. The added mobility enables events that would otherwise be hindered by the presence of long-range electrostatic attractions. Thus, while the film is growing, interdiffusion leads materials in and out of the film and polymer chains or/and nanoscale objects take on their more entropically favorable configurations. The net result of these processes is the increasing stratification of the materials at the top or bottom regions of the film, which could produce the desired geometric structures. This was the case with the ordered distribution of M13 phage, incorporated into multilayers of linear polyethyleneimine (LPEI), a linear weak polycation, and polyacrylic acid (PAA).[61] Specifically, the interdiffusion of LPEI into adjacent layers of the matrix, following adsorption of negatively charged viruses, led to a reassembly of the viruses in highly ordered liquid-crystalline-like packings (Figure 3c) on the top surface of the multilayer film—a configuration that is very difficult to achieve with electrostatic adsorption on a traditional 2-D substrate. The dense, high-surface area monolayer of viruses has been used as the basis of a battery cathode that can exhibit significantly higher capacitance in comparison with conventional battery electrode systems for lithium batteries.[62]

Several researchers have examined the nature of interdiffusion and how to manipulate or control it.[63–69] It has been observed that interdiffusion and exchange take place under conditions when the polyion of interest exhibits low charge density and a high degree of mobility during the adsorption process.[70] The rate of exchange increases as degree of ionization decreases, indicating that polyions with high-charge density are too ‘‘sticky’’ to undergo large-scale interdiffusion, thus, decreasing both the rate and penetration depth of the interdiffusion processes. Molecular weight has a significant effect on polyion interdiffusion as well. At higher molecular sizes, the rate of interdiffusion and/or exchange is much slower than the time scale of the adsorption step, consistent with models of reptation diffusion behavior for macromolecules in a polymer medium.[71] These questions present interesting opportunities for the chemical engineer to model these systems as a function of macromolecular size and shape, and predict interdiffusion behavior. This capability could lead to improved design and control of materials compositions and geometric structures in LbL systems. Understanding the mechanism and driving factors under which interdiffusion occurs and minimizing its effects, as well as finding ways to generate—and control— artificial barriers between film compartments are areas of great opportunity in this field.

Rapid LbL Approaches—Means to New Structure and Commercial Translation

One of the key challenges for the translation of multilayer assembly to industrial applications is the ability to generate these thin film systems at sufficiently high throughput and low cost. For many applications, including, for example, simple surface modification to manipulate wetting behavior or introduction of key functional groups to a surface, only two or three bilayers are needed to achieve the desired effect. In such cases, simple adaptations of the traditional dipping process may be sufficient to create a viable product. In traditional dipped solution adsorption (dip-LbL), typical adsorption times range from 5 to 30 min, depending on the species to be adsorbed, its concentration in solution, and its charge density, leading to typical cycle times, for a single bilayer pair, of 45 min. In addition to short time for assembly, additional manufacturing constraints for the commercialization of dip-LbL include, film uniformity and potential out-diffusion of components during film assembly over long time periods.

Many important commercial opportunities, based on the use of multilayer thin films, involve the formation of much thicker films that can be generated rapidly. Such applications include the generation of battery electrodes, photovoltaics, and reactive electrode systems, solid state electrolytes, responsive thin films, and drug release systems generated using LbL assembly techniques. Therefore, it is quite a critical that engineers examine ways in which the alternating assembly process can be accommodated on a larger scale and with greater flexibility for application to a broad range of substrates and surfaces.

In the past 10–15 years, several alternative modes of building multilayer films, promising to offer high-speed processing, have been suggested and demonstrated. In spin-assisted LbL,[72] dilute aqueous polymer solutions are spin-coated onto a charged substrate, followed by a rinse spin-coat cycle that removes the polyions that have not been electrostatically (truly) adsorbed. The spin-assisted LbL method has been used to generate highly controlled and uniform LbL films on flat planar substrates such as silicon, glass, and indium-tin oxide (ITO) electrodes. Researchers have discovered that spin-LbL yields thin films that exhibit slightly less interpenetration between layers, and some degree of lateral chain orientation and stratification.[72] Nanoparticle/polyion composite films, generated with spin-LbL, can exhibit remarkable biaxial strength and toughness,[73] and it has been demonstrated that even at low-nanoparticle content, such films can act as photoacoustic membranes, sensors, and functional thin films even at very low-overall thicknesses of several nanometers. Spin-LbL is a very promising process for controlling the fabrication of multilayer assemblies on solid planar surfaces, but cannot be used to coat 3-D, porous, or otherwise complex substrates, such as biomedical devices, porous electrodes, etc. It is also not amenable to scale-up for coating very large surfaces, such as a window, a dielectric mirror, or as a component in a display.

Misting or spraying alternating polyelectrolyte solutions onto a substrate (e.g., misted layer of polycation, misted rinse, misted layer of polyanion) leads to linear build up of simple polyelectrolyte thin films, which are similar in structure and properties to those produced by dip-LbL, as studies have demonstrated.[74–76] The author and her collaborators recently developed the first automated version of the spray-LbL system[77] that enables fabrication and an extensive examination of LbL films' structure and properties, and allows coverage of a broad range of substrates and surfaces (Figure 4). Furthermore, by introducing a pressure drop across the misting nozzles and the membrane, they introduced new vacuum-assisted spray-LbL methods which facilitated the coating of porous membranes with a controlled pressure drop across the membrane. These enhanced capabilities of spray-LbL have expanded significantly the range of multilayer systems that can be fabricated. Cycle times for the generation of LbL films using spray-LbL are of the order of tens of seconds, rather the 30–45 min cycles, as mentioned earlier for the conventional systems. This 50- to 100-fold decrease in assembly times makes feasible the industrial fabrication of a large range of commercial thick multilayered films. The reduced cycle times, combined with the ability to adapt the nozzle spray structure, change the number of nozzles, and control the arrangement of the substrate yield a versatile and highly efficient system for manufacturing thin multilayered film coatings. Ultimately, the use of roll-to-roll manufacture, implementation of sophisticated rapid spray technologies, and use of existing manufacturing infrastructure for spray-coating applications, will make the generation of these films highly accessible to industry. It is anticipated that spray-LbL will be one of the primary means by which this approach will lead to commercial technologies.

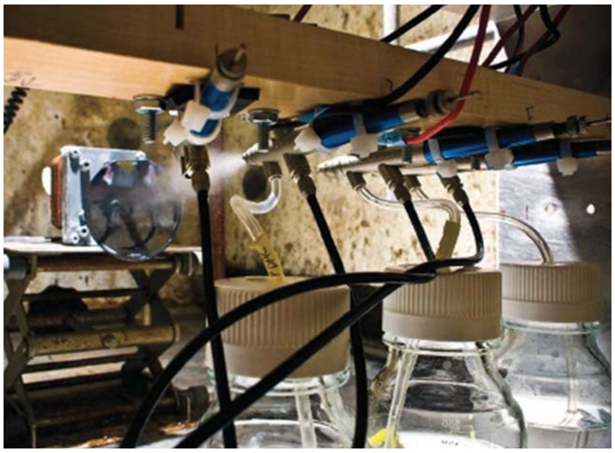

Figure 4. Photograph of simple automated spray-LbL laboratory setup illustrating the coating of a silicon wafer.

Spray nozzles administer independent streams of both positively and negatively charged species, as well as a rinse stream used between each adsorption step.

Source: Photograph from *Technology Review* "Fuel Cell Power-Up" 2008, MIT Press, Cambridge, MA.

The LbL assembly process is driven by kinetics, based on the electrostatic and other secondary attractions/repulsions between the various molecules or/and nanoparticles. Therefore, the means of generating these interactions can have a profound effect on the morphology, structure and final properties of the multilayered films. For this reason, the enhanced

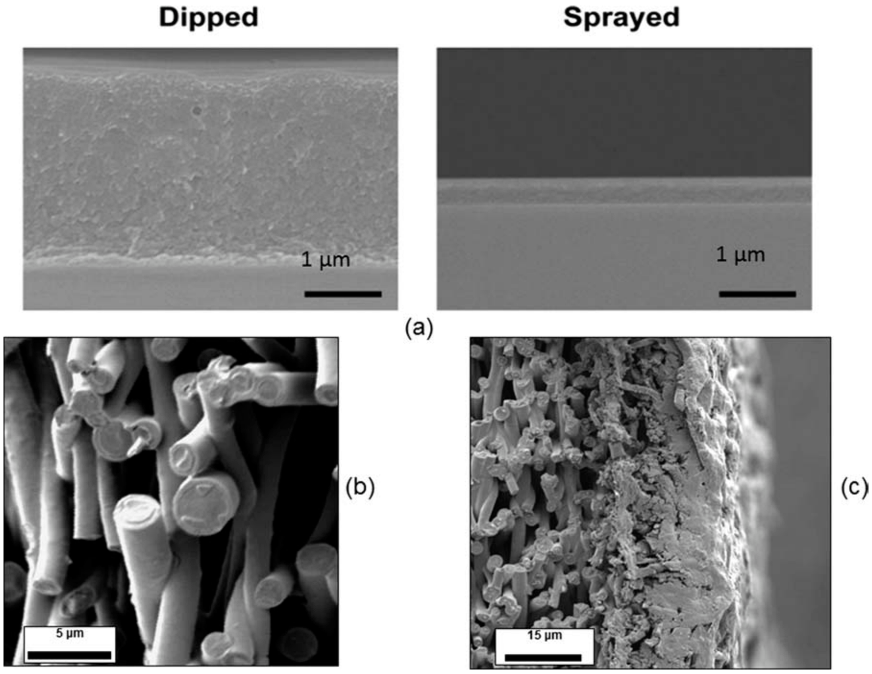

Figure 5. (a) Vancomycin containing LbL thin films undergo differing amounts of small molecule drug interdiffusion during assembly, leading to much thicker films for the same number of layers when assembled using traditional dip-LbL vs. spray-LbL processes—higher drug loadings were observed in the thinner films, (b) nanometer-scale LbL coatings can be deposited with uniformity across a several hundred micron thick electrospun polymer fiber mat, by controlling the rate of flow of spray-LbL droplets through the membrane, and (c) composite membranes can be formed on an electrospun mat, by eliminating pressure drop across the membrane during film assembly, to yield a condensed thin film that spans across the pores on the surface of the membrane and provides a protective barrier layer.

Sources: (a) Shukla et al[78], (b) and (c) Krogman et al.[77]

control, gained with the use of spray-LbL, has led to interesting and unique materials thin film structures, which were not possible to generate, using either traditional polymer film methods or dip-LbL techniques, alone. In general, the spray-LbL films do exhibit many of the film growth and final materials behavior, expected from typical linearly growing polyelectrolyte multilayers. However, for exponentially growing films in which molecular interdiffusion plays a significant role, if the time scale of interdiffusion is comparable to the spray cycle, one can get quite different modes of film growth and film morphologies from the same LbL polyelectrolyte pair. A dramatic example of this phenomenon was observed in the construction of polyelectrolyte drug release films, containing the weakly charged vancomycin molecule.[78] These films are constructed through the alternation of vancomycin (which has a singular positive charge) with negatively charged dextran sulfate and the hydrolytically degradable cationic poly (b-aminoester), Poly1, to generate tetralayers of alternating charge. The weakly charged vancomycin molecule interdiffuses within the film during dip-LbL assembly, leading to unusually thick layers that contain moderate loadings of Vancomycin. The vancomycin is believed to undergo additional secondary interactions with the polysaccharide dextran sulfate that further stabilize the film. When the completed film is released at 37°C in a phospate buffer solution, it exhibits prolonged release of vancomycin over a few days. On the other hand, when the same film is constructed using spray-LbL, with the same number of bilayer pairs, the film exhibits linear growth behavior with interdiffusion greatly suppressed. Typical film thicknesses are up to 9 to 10 times smaller than those of dip-LbL films, as shown in Figure 5a, and the associated loading of vancomycin is much higher; larger than 20% w/w of the film's weight. For this system, the length of the spray-LbL cycle was smaller than the time constant of the kinetics of interdiffusion. Thus, on exposure to the spray cycle, containing the oppositely charged species, the film structure has already been effectively ''locked'' into a specific geometric structure and unable to rearrange or enable mobility for interdiffusion events to take place.

Surprisingly, interdiffusion does eventually take place in the spray-LbL films at much higher film thicknesses. It appears that once a critical film thickness is achieved, there is an effective depot that provides sufficient time for interpenetration of the misted layer into the film before the oppositely charged species can complex and effectively arrests the interdiffusion. At these higher film bilayer thicknesses, one can maintain much higher loadings of vancomycin because there is much less opportunity for its out-diffusion during film assembly. In addition, the secondary interactions, that appear to regulate the rate of drug release, are strengthened and lead to an increase of the period of drug release from a few hours, with the thin spray-LbL films, to several days for films constructed with twice the number of tetralayers that exhibited interdiffusion behavior. Thus, the kinetic time scale achieved with spray-LbL can lead to advantages over the control of interdiffusion, exchange, and rearrangement processes that take place in these films with dip-LbL. This control ultimately leads to the ability to design materials systems with enhanced compositions and controlled film stability.

The ability to manipulate the assembly process and kinetically trap species within the film can be advantageous for reactive membranes and catalysis applications. For example, the author and her collaborators were able to demonstrate the loading of excess metal cations in poly(acrylic acid) (PAA) containing LbL thin films, using spray-LbL.[79] The spray LbL process allowed the incorporation of PAA that was precomplexed with metal ions in alternation with a polycations. Exposure to dip-LbL systems with similar loadings of metal ions led to the ultimate loss of these metal ion species, due to alternating exposure to dilute polyion and rinse solutions. However, the rapid spray-LbL process enabled entrapment of these ionic species within the film. The ions were retained after final film assembly, and could be reversibly complexed with other species as a mechanism for sensing, or converted into metal nanoparticles via reduction.

Finally, perhaps the most important technological advance that has been enabled by spray-LbL is the ability to manipulate the structure of complex membranes using different LbL processes. By controlling the pressure drop across a high-porosity membrane, such as an electrospun mat, it is possible to generate conformal coatings along the nanopore surfaces that have controlled nanometer level thicknesses,[77] as shown in Figure 5b. This approach can be used to functionalize the interiors of membrane pores, as demonstrated here with a photocatalytic LbL film of alternating titania nanoparticles with PDAC. On the other hand, complete removal of the pressure drop across the membrane leads to pinning of water droplets across the membrane surface. This process supports the bridging of pores as the LbL films begin to build across these water droplets that span multiple pore regions. The net result is the generation of composite membranes as shown in Figure 5c, in which the pores might be functionalized with a reactive materials system, and the top layers of the membrane may serve as a permselective barrier, as in this example of a reactive titania loaded high-surface area interior region combined with a thin, dense selective barrier film. The ability to create such complex membrane structures, in which different LbL film functionalities are introduced with unique and synergistic morphologies, can lead to a range of new applications with alternating assembly as a means of designing functional membranes, coatings and structures. This kind of structure, for example, could readily be adapted to water purification membranes, biomaterial cellular supports and drug delivery platforms.

Outlook

Future directions for the use of alternating LbL assemblies include some key areas of opportunity for which the LbL method provides unique advantages over traditional bulk polymer thin films. In particular, applications for which materials design and control of individual film components are important, will benefit tremendously from the flexibility that LbL provides in combining components. Mild assembly conditions and the ability to manipulate synthetic and natural materials systems also provide inroads to new applications.

Possibly, one of the largest areas of growth and potential opportunity is in the use of LbL systems as biomaterials to generate thin film coatings for biomedical implants, tissue engineering scaffolds and drug delivery systems.[80–82] There are several features of LbL assembly that make it very attractive for these biorelated areas, but the specific feature that offers a strong differentiating advantage is the fact that LbL is a water-based assembly method that enables the direct incorporation of sensitive protein-based drugs such as growth factors, cytokines and small molecules, RNA, DNA and other nucleic acids. In all of these cases, the ability to maintain near 100% activity of this therapeutics is remarkable for any drug delivery system. Traditional degradable polymers usually involve the use of solvent or temperature to generate mixtures with polymers. These harsher conditions usually lead to denaturation or degradation of biological drugs. Furthermore, as mentioned in the section entitled ''LbL Films as Nanoscale Blends``, drug loading capacity is much higher for LbL systems,[83–85] because the resulting thin and uniform coating film is, in effect, constructed from the drug. The conformal nature of LbL films enables the coating of a broad range of surfaces, including porous materials and complex surfaces. For example, multilayer thin films has been used to coat microneedles for transdermal drug delivery,[86,87] as well as stents,[88–90] bandages,[91] and the surfaces of biosensors and detection devices.[92–94] The fact that the LbL assembly is adaptable to the coating of small structures, from nanoparticles to micron-scale features, makes it much more adaptable than traditional, less conformal polymer films. LbL microcapsules[95–97] have been templated on micron- to nanometer-scale objects and used for regulated delivery and release. Such LbL-assembled nanoparticles enable the development of a generic technological platform for the preparation of systemic delivery systems, in which the particles act as delivery or/and sensing vessels in the blood stream. The LbL assembly conditions are so mild that it is actually possible to encapsulate cells in multilayer membranes. A recent exciting development is the ability to attach micron scale LbL thin films to macrophage cell surfaces—the thin film remains attached while the cell is in circulation.[98,99] It has been proposed that these ''cell backpacks'' might be loaded with nutrients or factors that facilitate cellular function or are used to combat other cells targeted by the macrophages.

The assembly of LbL films is driven by electrostatic interactions or hydrogen bonding; a very attractive feature for the design and fabrication of drug delivery systems. These interactions can be designed to undergo disassembly either passively or on demand by manipulating the charge balance within the film. Incorporation of a material that undergoes changes in charge density with a given stimulus can lead to LbL films that can release drugs in response to a small electric field or a change in the localized pH of specific regions in the body.[100–102] These redox active LbL thin films fall apart when the charge is removed at a given potential, leading to film instability and deconstruction until the charge is replaced at the open circuit condition. Hydrogen-bonded LbL films can be assembled with a range of different polymers, enabling the incorporation of highly biocompatible but uncharged polymers such as PEO. Sukhishvili et al.[103,104] have published extensively on these systems. A change in pH for these systems can trigger a corresponding change in charge density, yielding systematic release at a desired pH range, including biological pH or the lowered pH environment of a tumor. Finally, LbL films have been of increasing interest as substrates for cell growth and for surface modifications to enhance cell adhesion or manipulate cellular behavior. It has been shown that the mechanical behavior of these LbL films can dramatically impact cell attachment[105,106] and that these properties can be tuned through the following means: choice of assembly pH to yield stiff, thin films, or thicker, more hydrated thin film surfaces, or the introduction of nanomaterials. The ability to introduce a range of surface functionalities with ease, including binding ligands for cell adhesion and critical growth factors for specific cell interactions and signaling, has made this area one of significant new growth and future potential. Among the critical questions that must be addressed before further progress in this area is realized is the need to design LbL nanomaterials that can withstand systemic delivery through the bloodstream; a requirement that has been difficult to meet due to the inherent charged nature of LbL assemblies. Furthermore, LbL assemblies based on electrostatics or hydrogen bonding can often be destabilized in the presence of serum proteins or salts that compete for or shield these interactions. Recent studies show that careful choice of polyion and assembly conditions can greatly enhance systemic delivery and increase biodistribution of nanomaterials generated using LbL methods.[107,108] Film stability may be enhanced through the manipulation of the number of layers, the introduction of labile crosslinks that can be triggered for release at certain biological conditions, or the use of other nanomaterials that can increase interactions within the film. The issue of cytotoxicity is one that must be also considered carefully by engineers working in this area of biomaterials. Perhaps a greater challenge will be the combination of LbL thin films that can slowly elute drugs, including a range of biological drugs, while enhancing cellular adhesion at surfaces. Often the mechanical stiffness of protein- and nucleic acid-containing multilayers is not optimal for cellular adhesion. A number of approaches can be considered for addressing the need for high loadings of protein while maintaining a cytophilic surface that allows tissue integration on biomedical implant surfaces.

Another exciting area of opportunity for multilayer thin films lies in energy applications. The ability to incorporate a broad range of nanomaterials into these thin films has been demonstrated, including the direct incorporation of single and multiwall carbon nanotubes, graphene, catalytic carbon, noble metal nanoparticles, metal oxides and quantum dots as described in the section entitled ”LbL Films as Nanoscale Blends“. Because the layers generated in the LbL system are thin and highly integrated, electronic and ionic communication between different film components is readily enabled. Energy transfer has been observed between electronic and electro-optical nanoelements in these systems, and the ability to generate fully intercolated structures that combine these elements, or to isolate layers of different components in a controlled fashion, allows us to use LbL fabrication methods as a means of custom-designing devices. Electrochemical and photoelectrochemical devices can be configured through the appropriate layering of nanomaterials. For example, for supercapacitors and battery electrodes, it is necessary to preserve reactive surface area, a requirement that can be achieved by the direct alternation of nanoscale objects such as nanotubes, dots, or particles. In this case, the elimination of a polymeric species provides an inherently porous, high-surface area electrode. The generation of multilayer networks that consist of conductive organic or inorganic nanotubes, nanowires, or other high aspect ratio nanomaterials provide a means of generating a percolative conductive network, upon which additional nanomaterials, such as capacitive or catalytic metal nanoparticles, may be added, following assembly via electrochemical or chemical redox processes. The technological capability to create organic–inorganic hybrid structures, over close to the full range of stoichiometry, is particularly attractive to energy-related technologies such as solar cells, for which the transport of electrons and holes in their excited states can be manipulated by providing nanoscale morphologies that maximize capture of free electrons and decrease recombination of excitons. Economically viable manufacturing of electrodes using the LbL assembly process must resolve scale-up trade-offs of the manufacture process, i.e., rapid incorporation of nanomaterials without losing the inherent advantages of LbL films, e.g., lack of bundling and aggregation of the materials during the film assembly. Spray-LbL may provide some answers in resolving these trades-offs, although the hydrodynamics of the LbL-spray system may need to be adapted for use on irregularly shaped high-aspect ratio nanostructures. Furthermore, significant opportunities in the development of energy devices lie in the ion or proton exchange media required for these devices, including proton exchange membranes and solid state electrolytes for lithium ion and flow batteries and dye-sensitized solar cells. The advantages of LbL include the ability to incorporate a broad range of charged polymers that can present ionic groups that facilitate ion-hopping mechanisms of transport. Chemical and mechanical stability must be addressed in these systems. This issue requires the introduction of a broader range of polyelectrolyte backbones through the functionalization of known high-performance polymer systems with ionic groups. It should be noted although that the adaptation of these systems to battery and other water-free electrolyte applications requires that these films exhibit high-ion conductivity and lithium transference in the dry state. Typical LbL films, studied thus far, are highly plasticized in the presence of water, thus, enabling excellent ionic conductivities in fuel-cell membranes and other aqueous environments. To achieve high-ionic conductivity using LbL, we may need to consider a broader range of low-glass transition polymers that exhibit charge. Polymer backbones of interest include polysiloxanes and polyphosphazenes, for example.

Finally, there are many other applications for which the LbL process is likely to make commercial inroads. Some of the applications require only a few bilayers of application that can be rapidly applied. LbL assembly can be a simple and facile means of providing a highly functional surface, modifying surfaces to achieve superhydrophobic or hydrophilic properties, modifying adhesion, or addressing biofouling on surfaces. For example, microbicidal coatings with

100% killing activity can be introduced on a surface with just three bilayers. Perhaps one of the most promising of these simpler applications is in the use of LbL films to modify membranes. Because only small numbers of layers of an LbL film can introduce significant barriers to a range of small molecules, ions, or biomacromolecules. Chemical engineers provide a unique perspective that is critical for the advance of the field. Although there are already several demonstrations of the utility of these systems, there is a great need for increased efforts to model the fabrication assembly process of these films, and the nature of their degradation or disassembly under certain conditions. Understanding of the interdiffusion and exchange phenomena in LbL assemblies will provide additional opportunities to use these materials systems as platforms to construct a broad range of thin film devices. The understanding of kinetics and transport that impact the construction of these films is much more complex than originally thought, and as one explores broader sets of polymers and nanomaterials, new models will be needed to address film growth and construction, as well as final properties. Ultimately, as demonstrated by the rich behavior of hydrogen-bonded LbL films, increased control of additional secondary interactions can greatly enhance the kinds of systems that can be built using LbL. As the field continues to expand, it is important that engineers begin to tackle a number of the fundamental issues of these LbL systems. There are also several challenges in adapting the means of processing LbL films to achieve rapid assembly and maintain, or possibly increase, the control and flexibility of this approach. These efforts will lead LbL technologies toward ultimate translation in the commercial realm, and to new discoveries in the fields of polymer and materials science.

Acknowledgments

The author acknowledges each of the funding agencies that has funded layer-by-layer work in her research group, with particular thanks to the Division of Materials Research Polymer Program of the National Science Foundation, the National Institutes of Health, including the National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Aging (NIA), and National Institute of Biomedical Imaging and Bioengineering (NIBIB), the U.S. Army funded Institute for Soldier Nanotechnology at MIT, Eni S.P.A. and the MIT Energy Initiative. The author would also like to acknowledge postdoctoral associate Dr. Wei Li for his assistance and design of the cover page for this Perspective.

Literature Cited

1. Decher G, Hong J-D. Buildup of ultrathin multilayer films by a self-assembly process, 1) consecutive adsorption of anionic and cationic bipolar amphiphiles on charged surfaces. *Makromol Chem Macromol Symp.* 1991;46:321–327.
2. Decher G, Hong J-D. Buildup of ultrathin multilayer films by a self-assembly process: ii. consecutive adsorption of anionic and cationic bipolar amphiphiles and polyelectrolytes on charged surfaces. *Ber Bunsenges Ges Phys Chem.* 1991;95(11):1430–1434.
3. Decher G. Fuzzy nanoassemblies: Toward layered polymeric multicomposites. *Science.* 1997;277:1232.
4. Decher G, Lvov Y, Schmitt J. Proof of multilayer structural organization in self-assembled polycation polyanion molecular films. *Thin Solid Films.* 1994; 244(1–2):772–777.
5. van Ackern F, Krasemann L, Tieke B. Ultrathin membranes for gas separation and pervaporation prepared upon electrostatic self-assembly of polyelectrolytes. *Thin Solid Films.* 1998;327:762–766.
6. Bhattacharjee S, Bruening ML. Selective hydrogenation of monosubstituted alkenes by Pd nanoparticles embedded in polyelectrolyte films. *Langmuir.* 2008;24(6): 2916–2920.
7. Bruening ML, Dotzauer DM, Jain P, Ouyang L, Baker GL. Creation of functional membranes using polyelectrolyte multilayers and polymer brushes. *Langmuir.* 2008:24(15);7663–7673.
8. Taylor AD, Michel M, Sekol RC, Kizuka JM, Kotov NA, Thompson LT. Fuel cell membrane electrode assemblies fabricated by layer-by-layer electrostatic self-assembly techniques. *Adv Funct Mater.* 2008; 18(19):3003–3009.
9. Priolo MA, Gamboa D, Holder KM, Grunlan JC. Super gas barrier of transparent polymer-clay multi layer ultrathin films. *Nano Lett.* 2010;10(12):4970–4974.
10. Yang YH, Haile M, Park YT, Malek FA, Grunlan JC. Super gas barrier of all-polymer multilayer thin films. *Macromolecules.* 2011;44(6):1450–1459.
11. Jin WQ, Toutianoush A, Tieke B. Use of polyelectrolyte layer-by-layer assemblies as nanofiltration and reverse osmosis membranes. *Langmuir.* 2003;19(7) 2550–2553.
12. Malaisamy R, Bruening ML. High-flux nanofiltration membranes prepared by adsorption of multilayer polyelectrolyte membranes on polymeric supports. *Langmuir.* 2005;21(23):10587–10592.
13. Li XF, De Feyter S,Chen DJ, Aldea S, Vandezande P, Du Prez F, Vankelecom IFJ. Solvent-resistant nanofiltration membranes based on multilayered polyelectrolyte complexes. *Chem Mater.* 2008;20(12):3876–3883.
14. Ji,YL, An QF, Qian JW, Chen HL, Gao CJ. Nanofiltration membranes prepared by layer-by-layer self-assembly of polyelectrolyte. *Progr Chem.* 2010;22(1): 119–124.
15. Park J, Kim SH, Cho J, Bang J. Desalination membranes from pH-controlled and thermally-crosslinked layer-by-layer assembled multilayers. *J Mater Chem.* 2011;20 (11):2085–2091.
16. Bruening ML, Sullivan DM. Enhancing the ion-transport selectivity of multilayer polyelectrolyte membranes. *Chem Eur J.* 2002;8(17):3833–3837.
17. Liu GQ, Dotzauer DM, Bruening ML. Ion-exchange membranes prepared using layer-by-layer polyelectrolyte deposition. *J Membr Sci.* 2010;354(1–2):198–205.
18. Argun AA, Ashcraft JN, Hammond PT. Highly conductive, methanol resistant polyelectrolyte multilayers. *Adv Mater.* 2008;20 (8),1539–1543.
19. Ashcraft JN, Argun AA, Hammond PT. Structure-property studies of highly conductive layer-by-layer assembled membranes for fuel cell PEM applications. *J Mater Chem.* 2010;20(30):6250–6257.

20. Huang M, Bi L, Shen Y, Liu B, Dong S. Nanocomposite multilayer film of preyssler-type polyoxometalates with fine tunable electrocatalytic activities. *J Phys Chem B*. 2004;108(29):9780–9786.
21. Qian L, Gao Q, Song Y, Li Z, Yang X. Layer-by-layer assembled multilayer films of redox polymers for electrocatalytic oxidation fo ascorbic acid. *Sen Actuators B*. 2005;B107(1):303–310.
22. Krogman KC, Zacharia NS, Grillo DM, Hammond PT. Photocatalytic layer-by-layer coatings for degradation of acutely toxic agents. *Chem Mater*. 2008;20(5): 1924–1930.
23. Spricigo R, Dronov R, Rajagopalan KV, Lisdat F, Leimkuhler S, Scheller FW, Wollenberger U. Electrocatalytically functional multilayer assembly of sulfite oxidase and cytochrome c. *Soft Matter*. 2008;4(5): 972–978.
24. Lee JA, Nam Y S, Rutledge GC, Hammond PT. Enhanced photocatalytic activity using layer-by-layer electrospun constructs for water remediation. *Adv Funct Mater*. 2010;20(15):2424–2429.
25. Decher G, Lehr B, Lowack K, Lvov Y, Schmitt J. New nanocomposite films for biosensors - layer-by-layer adsorbed films of polyelectrolytes, proteins or DNA. *Biosens Bioelectron*. 1994;9(9–10):677–684.
26. Li W, Wang Z, Sun C, Xian M, Zhao M. Fabrication of multilayer films containing horseradish peroxidase and polycation bearing Os complex by means of electrostatic layer-by-layer adsorption and its application as a hydrogen peroxide sensor. *Anal Chim Acta*. 2000;418(2):225–232.
27. Ferreira M, Fiorito PA, Oliveria ON. Enzyme-mediated amperometric biosensors prepared with the layer-by-layer (LbL) adsorption technique. *Biosens Bioelectron* 2004;19(12):1611–1615.
28. Guo M, Chen J, Li J, Nie L, Yao S. Carbon nanotubes-based amperometric cholesterol biosensor fabricated through layer-by-layer technique. *Electroanalysis*. 2004;16(23):1992–1998.
29. Crespilho FN, Zucolotto V, Siqueira JRJ, Constantino CJL, Nart FC, Oliveria ON. Immobilization of humic acid in nanostructured layer-by-layer films for sensing applications. *Environ Sci Technol*. 2005;39(14):5385–9.
30. Ram MK, Yavuz O, Lahsangah V, Aldissi M. CO gas sensing from ultrathing, nano-composite conducting polymer film. *Sens Actuators, B*. 2005;106(2):750–757.
31. Kim JH, Heller DA, Jin H, Barone PW, Song C, Zhang J, Trudel LJ, Wogan GN, Tannenbaum SR, Strano MS. The rational design of nitric oxide selectivity in single-walled carbon nanotube near-infrared fluorescence sensors for biological detection. *Nature Chem*. 2009;1(6):473–81.
32. Delongchamp DM, Hammond PT. Layer-by-layer assembly of PEDOT/polyaniline electrochromic devices. *Adv Mater*. 2001;13(19);1455–1459.
33. Liu S, Kurth DG, Mohwald H, Volkmer D. A thin-film electrochromic device based on a polyoxometalate cluster. *Adv Mater*. 2002;14(3):225–228.
34. DeLongchamp DM, Hammond PT. High-contrast electrochromism and controllable dissolution of assembled prussian blue/polymer nanocomposites. *Adv Funct Mater*. 2004;14(3):224–232.
35. Kim E, Jung S. Layer-by-layer assembled electrochromic films for all-solid-state electrochromic devices. *Chem Mater*. 2005;17(25):6381–6387.
36. Xue B, Peng J, Xin Z, Kong Y, Li L, Li B. High-contrast electrochromic multilayer films of molybdenum-doped hexagonal tungsten bronze (Mo0.05-HTB). *J Mater Chem*. 2005;15(45):4793–4798.
37. Onitsuka O, Fou AC, Ferreira M, Hsieh BR, Rubner MF. Enhancement of light emitting diodes based on self-assembled heterostructures of poly(p-phenylene vinylene). *J Appl Phys*. 1996;80(7):4067–4071.
38. Wu A, Yoo D, Lee JK, Rubner MF. Solid-state light-emitting devices based on the tris-chelated ruthenium(II) complex: 3. High efficiency devices via a layer-by-layer molecular-level blending approach. *J Am Chem Soc*. 1999;121(20):4883–4891.
39. Bae WK, Kwak J, Lim J, Lee D, Nam MK, Char K, Lee C, Lee S. Multicolored light-emitting diodes based on all-quantum-dot multilayer films using layer-by-layer assembly method. *Nano Lett*. 2010;10(7):2368–2373.
40. Bendall JS, Paderi M, Ghigliotti F, Pira NL, Lambertini V, Lesnyak V, Gaponik N, Visimberga G, Eychmuller A, Torres CMS, Welland ME, Gieck C, Marchese L. Layer-by-layer all-inorganic quantum-dot-based leds: a simple procedure with robust performance. *Adv Funct Mater*. 2010;20(19):3298–3302.
41. Mamedov AA, Kotov NA, Prato M, Guldi DM, Wicksted JP, Hirsch A. Molecular design of strong single-wall carbon nanotube/polyelectrolyte multilayer composites. *Nat Mater*. 2002;1(3):190–194.
42. Shim BS, Kotov NA. Single-walled carbon nanotube combing during layer-by-layer assembly: From random adsorption to aligned composites. *Langmuir*. 2005;21(21):9381–9385.
43. Zhu Y, Tour JM. Graphene nanoribbon thin films using layer-by-layer assembly. *Nano Lett*. 2010;10(11):4356–4362.
44. Byon HR, Lee SW, Chen S, Hammond PT, Shao-Horn Y. Thin films of carbon nanotubes and chemically reduced graphenes for electrochemical micro-capacitors. *Carbon*. 2011;49(2):457–467.
45. Zhang,B, Cui TH. An ultrasensitive and low-cost graphene sensor based on layer-by-layer nano self-assembly. *Appl Phys Lett*. 2011;98(7).
46. Tang ZY, Kotov NA, Magonov S, Ozturk B. Nanostructured artificial nacre. *Nat Mater*. 2003;2(6): 413–U8.
47. Lutkenhaus JL, Olivetti EA, Verploegen EA, Cord BM, Sadoway DR, Hammond PT Anisotropic structure and transport in self-assembled layered polymer-clay nanocomposites. *Langmuir*. 2007;23(16):8515–8521.
48. Lee SW, Kim BS, Chen S, Shao-Horn Y, Hammond PT. Layer-by-layer assembly of all carbon nanotube ultrathin films for electrochemical applications. *JACS*. 2009;13:671–679.
49. Lee SW, Yabuuchi N, Gallant BM, Chen S, Kim BS, Hammond PT, Shao-Horn Y. High-power lithium

batteries from functionalized carbon-nanotube electrodes. *Nat Nanotechnol*. 2010;5(7):531–537.
50. Ariga K, Ji QM, Hill JP, Vinu A. Coupling of soft technology (layer-by-layer assembly) with hard materials (mesoporous solids) to give hierarchic functional structures. *Soft Mater*. 2009;5(19):3562–3571.
51. Cong HP, Yu SH. Self-assembly of functionalized inorganic-organic hybrids. *Curr Opin Colloid Interface Sci*. 2009;14(2):71–80.
52. Ariga K, Ji QM, Hill JP, Vinu A. Supramolecular Materials from Inorganic Building Blocks. *J Inorg Organomet Polym Mater*. 2010;20(1):1–9.
53. Siqueira JR, Caseli L, Crespilho FN, Zucolotto V, Oliveira ON. Immobilization of biomolecules on nanostructured films for biosensing. *Biosens Bioelectron*. 2010;25(6):1254–1263.
54. Mamedov AA, Belov A, Giersig M, Mamedova NN, Kotov NA. Nanorainbows: Graded semiconductor films from quantum dots. *J Am Chem Soc*. 2001;123(31): 7738–7739.
55. Nolte AJ, Rubner MF, Cohen RE. Creating effective refractive index gradients within polyelectrolyte multilayer films: Molecularly assembled rugate filters. *Langmuir*. 2004;20(8):3304–3310.
56. Porcel C, Lavalle P, Ball V, Decher G, Senger B, Voegel JC, Schaaf P. From exponential to linear growth in polyelectrolyte multilayers. *Langmuir*. 2006;22(9): 4376–4383.
57. Jourdainne L, Arntz Y, Senger B, Debry C, Voegel JC, Schaaf P, Lavalle P. Multiple strata of exponentially growing polyelectrolyte multilayer films. *Macromolecules*. 2007;40(2):316–321.
58. Porcel C, Lavalle P, Decher G, Senger B, Voegel JC, Schaaf P. Influence of the polyelectrolyte molecular weight on exponentially growing multilayer films in the linear regime. *Langmuir*. 2007;23(4):1898–1904.
59. Zacharia NS, DeLongchamp DM, Modestino M, Hammond PT. Controlling diffusion and exchange in layer-by-layer assemblies. *Macromolecules*. 2007;40(5): 1598–1603.
60. Wood KC, Chuang HF, Batten RD, Lynn DM, Hammond PT. Controlling interlayer diffusion to achieve sustained, multiagent delivery from layer-by-layer thin films. *Proc Nat Acad Sci USA*. 2006;103(27):10207–10212.
61. Yoo PJ, Nam KT, Qi JF, Lee SK, Park J, Belcher AM, Hammond PT. Spontaneous assembly of viruses on multilayered polymer surfaces. *Nat Mater*. 2006; 5(3):234–240.
62. Nam KT, Kim DW, Yoo PJ, Chiang CY, Meethong N, Hammond PT, Chiang YM, Belcher AM. Virus-enabled synthesis and assembly of nanowires for lithium ion battery electrodes. *Science*. 2006;312(5775):885–888.
63. Garza JM, Schaaf P, Muller S, Ball V, Stoltz JF, Voegel JC, Lavalle P. Multicompartment films made of alternate polyelectrolyte multilayers of exponential and linear growth. *Langmuir*. 2004;20(17):7298–7302.
64. Zhi ZL, Haynie DT. Direct evidence of controlled structure reorganization in a nanoorganized polypeptide multilayer thin film. *Macromolecules*. 2004;37(23): 8668–8675.
65. Li C, Zhang J, Yang S, Li BL, Li YY, Zhang XZ, Zhuo RX. Controlling the growth behavior of multilayered films via layer-by-layer assembly with multiple interactions. *Phys Chem Chem Phys*. 2009;11(39): 8835–8840.
66. Podsiadlo P, Michel M, Critchley K, Srivastava S, Qin M, Lee JW, Verploegen E, Hart AJ, Qi Y, Kotov NA. Diffusional self-organization in exponential layer-by-layer films with micro- and nanoscale periodicity. *Angew Chem Int Ed*. 2009;48(38):7073–7077.
67. Bieker P, Schonhoff M. Linear and exponential growth regimes of multi layers of weak polyelectrolytes in dependence on pH. *Macromolecules*. 2010;43(11): 5052–5059.
68. Kim YH, Lee YM, Park J, Ko MJ, Park JH, Jung W, Yoo PJ. Spontaneous surface flattening via layer-by-layer assembly of interdiffusing polyelectrolyte multilayers. *Langmuir*. 2010;26(22):17756–17763.
69. Lundin M, Blomberg E, Tilton RD. Polymer dynamics in layer-by-layer assemblies of chitosan and heparin. *Langmuir*. 2010;26(5):3242–3251.
70. Zacharia NS, Modestino M, Hammond PT. Factors influencing the interdiffusion of weak polycations in multilayers. *Macromolecules*. 2007;40(26):9523–9528.
71. Watanabe H. Viscoelasticity and dynamics of entangled polymers. *Progr Polym Sci*. 1999;24(9):1253–1403.
72. Cho J, Char K, Hong JD, Lee KB. Fabrication of highly ordered multilayer films using a spin self-assembly method. *Adv Mater*. 2001;13(14):1076.
73. Jiang CY, Markutsya S, Tsukruk VV. Compliant, robust, and truly nanoscale free-standing multilayer films fabricated using spin-assisted layer-by-layer assembly. *Adv Mater*. 2004;16(2):157.
74. Schlenoff J, Dubas S, Farhat T. Sprayed polyelectrolyte multilayers. *Langmuir* 2000;16(26):9968–9969.
75. Izquierdo A, Ono SS, Voegel J-C, Schaaf P, Decher G. Dipping versus spraying: exploring the deposition conditions for speeding up layer-by-layer assembly. *Langmuir ACS J Surfaces Colloids*. 2005;21(16):7558–7567.
76. Krogman KC, Zacharia NS, Schroeder S, Hammond PT. Automated process for improved uniformity and versatility of layer-by-layer deposition. *Langmuir*. 2007;23 (6):3137–3141.
77. Krogman KC, Lowery JL, Zacharia NS, Rutledge GC, Hammond PT. Spraying asymmetry into functional membranes Layer-by-Layer. *Nat Mater*. 2009;8: 512–518.
78. Shukla A, Avadhany SN, Fang JC, Hammond PT. Tunable vancomycin releasing surfaces for biomedical applications. *Small*. 2010;6(21):2392–2404.
79. Krogman KC, Lyon KF, Hammond PT. Metal ion reactive thin films using spray electrostatic LbL assembly. *J Phys Chem B*. 2008;112(46):14453–14460.
80. Boudou T, Crouzier T, Ren KF, Blin G, Picart C. Multiple functionalities of polyelectrolyte multilayer films: new biomedical applications. *Adv Mater*. 2010; 22(4):441–467.
81. Detzel CJ, Larkin AL, Rajagopalan P. Polyelectrolyte multilayers in tissue engineering. *Tissue Eng Part B*. 2011;17(2):101–113.

82. Lavalle P, Voegel JC, Vautier D, Senger B, Schaaf P, Ball V. Dynamic aspects of films prepared by a sequential deposition of species: perspectives for smart and responsive materials. *Adv Mater.* 2011;23(10): 1191–1221.
83. Zhang J, Chua LS, Lynn DM. Multilayered thin films that sustain the release of functional DNA under physiological conditions. *Langmuir.* 2004;20(19):8015–8021.
84. Wood KC, Boedicker JQ, Lynn DM, Hammond PT. Tunable drug release from hydrolytically degradable layer-by-layer thin films. *Langmuir.* 2005;21(4): 1603–1609.
85. Smith RC, Leung A, Kim BS, Hammond PT. Hydrophobic effects in the critical destabilization and release dynamics of degradable multilayer films. *Chem Mater.* 2009;21(6):1108–1115.
86. DeMuth PC, Su XF, Samuel RE, Hammond PT, Irvine DJ. Nano-layered microneedles for transcutaneous delivery of polymer nanoparticles and plasmid DNA. *Adv Mater.* 2010;22(43):4851-+.
87. Saurer EM, Flessner RM, Sullivan SP, Prausnitz MR, Lynn DM. Layer-by-layer assembly of DNA- and protein-containing films on microneedles for drug delivery to the skin. *Biomacromolecules.* 2010.
88. Jewell CM, Zhang JT, Fredin NJ, Wolff MR, Hacker TA, Lynn DM. Release of plasmid DNA from intravascular stents coated with ultrathin multilayered polyelectrolyte films. *Biomacromolecules.* 2006;7(9): 2483–2491.
89. Kim TG, Lee H, Jang Y, Park TG. Controlled release of paclitaxel from heparinized metal stent fabricated by layer-by-layer assembly of polylysine and hyaluronic acid-*g*-poly(lactic-co-glycolic acid) micelles encapsulating paclitaxel. *Biomacromolecules* 2009;10(6):1532–1539.
90. Luo LL, Wang GX, Li YL, Yin TY, Jiang T, Ruan CG. Layer-by-layer assembly of chitosan and platelet monoclonal antibody to improve biocompatibility and release character of PLLA coated stent. *J Biomed Mater Res Part A.* 2011;97A(4):423–432.
91. Shukla A, Fleming KE, Chuang HF, Chau TM, Loose CR, Stephanopoulos GN, Hammond PT. Controlling the release of peptide antimicrobial agents from surfaces. *Biomaterials.* 2010;31(8):2348–2357.
92. Chen SH, Yuan R, Chai YQ, Zhang LY, Wang N, Li XL. Amperometric third-generation hydrogen peroxide biosensor based on the immobilization of hemoglobin on multiwall carbon nanotubes and gold colloidal nanoparticles. *Biosens Bioelectron.* 2007;22(7):1268–1274.
93. Huang H, Hu NF, Zeng YH, Zhou G. Electrochemistry and electrocatalysis with heme proteins in chitosan biopolymer films. *Anal Biochem.* 2002;308(1):141–151.
94. Zhao W, Xu JJ, Shi CG, Chen HY. Multilayer membranes via layer-by-layer deposition of organic polymer protected Prussian blue nanoparticles and glucose oxidase for glucose biosensing. *Langmuir.* 2005;21(21): 9630–9634.
95. Shi XY, Caruso F. Release behavior of thin-walled microcapsules composed of polyelectrolyte multilayers. *Langmuir.* 2001;17(6):2036–2042.
96. Ge LQ, Mohwald H, Li JB. Biointerfacing polyelectrolyte microcapsules. *ChemPhysChem.* 2003;4(12): 1351–1355.
97. Zhu HG, Srivastava R, McShane MJ. Spontaneous loading of positively charged macromolecules into alginate-templated polyelectrolyte multilayer microcapsules. *Biomacromolecules.* 2005;6(4):2221–2228.
98. Swiston AJ, Cheng C, Um SH, Irvine DJ, Cohen RE, Rubner MF. Surface functionalization of living cells with multilayer patches. *Nano Lett.* 2008;8(12): 4446–4453.
99. Swiston AJ, Gilbert JB, Irvine DJ, Cohen RE, Rubner MF. Freely suspended cellular "backpacks" lead to cell aggregate self-assembly. *Biomacromolecules.* 2010;11(7):1826–1832.
100. Wood KC, Zacharia NS, Schmidt DJ, Wrightman SN, Andaya BJ, Hammond PT. Electroactive controlled release thin films. *Proc Nat Acad Sci USA.* 2008;105(7):2280–2285.
101. Schmidt DJ, Hammond PT. Electrochemically erasable hydrogen-bonded thin films. *Chemical Commun.* 2010;46(39):7358–7360.
102. Schmidt DJ, Moskowitz JS, Hammond PT. Electrically triggered release of a small molecule drug from a polyelectrolyte multilayer coating. *Chem Mater.* 2010;22 (23):6416–6425.
103. Erel-Unal I, Sukhishvili SA. Hydrogen-bonded hybrid multilayers: film architecture controls release of macromolecules. *Macromolecules.* 2008;41(22):8737–8744.
104. Kharlampieva E, Kozlovskaya V, Sukhishvili SA. Layer-by-layer hydrogen-bonded polymer films: From fundamentals to applications. *Adv Mater.* 2009;21(30): 3053–3065.
105. Thompson MT, Berg MC, Tobias IS, Rubner MF, Van Vliet KJ. Tuning compliance of nanoscale polyelectrolyte multilayers to modulate cell adhesion. *Biomater.* 2005;26(34):6836–6845.
106. Thompson MT, Berg MC, Tobias IS, Lichter JA, Rubner MF, Van Vliet KJ. Biochemical functionalization of polymeric cell substrata can alter mechanical compliance. *Biomacromolecules.* 2006;7(6):1990–1995.
107. Poon Z, Chang D, Zhao XY, Hammond PT. Layer-by-layer nanoparticles with a pH-sheddable layer for in vivo targeting of tumor hypoxia. *ACS Nano.* 2011;5(6): 4284–4292.
108. Poon Z, Lee JB, Morton SW, Hammond PT. Controlling in vivo stability and biodistribution in electrostatically assembled nanoparticles for systemic delivery. *Nano Lett.* 2011;11(5):2096–2103.