Orthogonal Surface-Grafted Polymer Gradients: A Versatile Combinatorial Platform

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ABSTRACT: Orthogonal polymer brush gradients are assemblies of surface-anchored macromolecules, in which two material properties of the grafted chains (e.g., grafting density, molecular weight) vary independently in orthogonal directions. Here, we describe the formation and applications of two such orthogonal assemblies, involving: (1) molecular weight and grafting density (MW/\(r\)) gradients of a given polymer and (2) molecular weight gradients (MW1/MW2), of two different polymers. Each point on orthogonal gradient substrate represents a unique combination of the two surface properties being varied, thus facilitating systematic investigation of a phenomenon that depends on the two said properties. We illustrate this point by employing orthogonal structures to study systematically: (1) formation of polymer brush-nanoparticle composite assemblies, (2) protein adsorption and cell adhesion, and (3) chain conformations in tethered diblock copolymers exposed to selective solvents. ©2005 Wiley Periodicals, Inc. J Polym Sci Part B: Polym Phys 43: 3384–3394, 2005
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INTRODUCTION

Combinatorial materials research and high throughput experimentation (HTE) methods received a great deal of academic as well as industrial attention in recent years because of their ability to explore systematically a multi-parameter phenomenon and enhance data acquisition speed and efficiency.1–4 While the primary beneficiary of the application of HTE methods has been the pharmaceutical industry inundated with a large number of potential drug candidates that need to be screened effectively,5 the successful implementation of HTE techniques in pharmaceutical research has triggered the growth of combinatorial approaches in materials science also. Specifically, materials such as catalysts,6 electronic and luminescent materials,7 ceramics, and polymers8,9 have witnessed intense research efforts devoted toward identifying better formulations by optimizing a number of system variables. Bulk polymeric systems and thin polymer coatings, which are used in a number of industrially relevant applications, were rigorously subjected to HTE to comprehensively map out the structure–property relationship.4,8–11 In this regard, recent efforts in combinatorial materials research carried out at the National Institute of Standards and Technology9,12 and the Dutch Polymer Insti-
One major class of thin polymer films that has not yet been fully explored by the aforementioned studies pertains to systems involving surface-anchored polymers. Grafted polymer films are vital components in many important applications such as prevention of biofouling, surface modification and patterning, creation of responsive surfaces, improving stability of colloidal dispersion, enhancing adhesion and wettability, etc. The performance of grafted polymers in these applications is decided primarily by their molecular weight (MW), grafting density ($\sigma = \text{number of polymer chains per unit area of grafted surface}$), and composition.

In light of the importance of surface-bound polymeric systems, we developed multivariate grafted polymer substrates with the overarching goal of utilizing these combinatorial substrates for understanding the behavior of anchored polymers and their interaction with foreign materials. To this end, we created substrates having gradients in MW, $\sigma$, and composition of grafted polymers, using surface-initiated controlled radical polymerization. A gradient in $\sigma$ so formed was employed to study mushroom-to-brush crossover in surface-anchored polyacrylamide (PAAm). Similar gradients in $\sigma$ of grafted poly(acrylic acid) facilitated detailed study of the response of end-anchored polyelectrolyte to ionic solutions. Gradient in MW of anchored PAAm was utilized as templates for assembling gold nanoparticles. Number density of particles attached to PAAm brush was altered by varying MW of PAAm chain. In another study, spatial distribution of dispersed nanoparticles was controlled through the use of polymer assembly having gradient in $\sigma$. In these experiments, gradient geometry allowed methodical exploration of the effect of polymer MW or $\sigma$, while keeping the other parameters constant.

Successful application of one-property gradient in providing insight into the complex behavior of anchored polymers prompted us to construct the second generation of combinatorial grafted polymer substrate, wherein effect of two independent system parameters can be simultaneously studied. For example, one can vary MW along one direction of the substrate and $\sigma$ along the other direction, thus generating a (MW, $\sigma$) matrix on the substrate. We call such substrates orthogonal gradients wherein two material properties vary continuously along two mutually perpendicular substrate directions (see Fig. 1). Since these two properties are changing continuously, every possible combination of the two properties can be probed systematically by using such a set-up. Working with orthogonal gradient substrates not only saves time and resources, but it also minimizes the systematic errors associated with carrying out a large set of individual experiments. Additionally, concurrent variation of the two properties facilitates investigation of their cooperative effect on a given phenomenon. In this article, we describe the formation of two different orthogonal gradient motifs, involving: (1) molecular weight and grafting density (MW/$\sigma$) gradients of a given polymer, and (2) molecular weight gradients (MW1/MW2) of two different polymers. In addition, we demonstrate how these orthogonal structures can be utilized to probe systematically: (1) protein adsorption and cell adhesion, and (2) chain conformations of diblock copolymers exposed to selective solvents.

**Figure 1.** Schematic illustrating the concept of an orthogonal gradient. Orthogonal gradients are formed by combining two individual linear gradients, which propagate in two mutually orthogonal directions. Examples of material properties inherent to surface-bound polymeric systems that can be gradually varied involve (but are not limited to): molecular weight, grafting density, charge, composition, and so forth. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
MOLECULAR WEIGHT/GRAFTING DENSITY (MW/σ) ORTHOGONAL GRADIENT

MW and σ determine the conformation of polymer chains on the substrate, which, in turn, governs the effectiveness of polymer coating for a given application. Thus, it is desirable to be able to systematically manipulate the chain conformation by controlling MW and σ of the chains. Fabrication of surface-grafted orthogonal gradient entails two steps: (1) formation of concentration gradient of initiator molecules and (2) growth of surface-anchored chains with a MW gradient in a direction perpendicular to that of the initiator concentration gradient. Figure 2 depicts the procedure used to construct MW/σ orthogonal gradient of surface-anchored polymers. First a molecular gradient of the polymerization initiator is formed on a solid substrate by vapor deposition of \( n \)-octyltrichlorosilane followed by solution backfilling with \( [11-(2\text{-bromo-2-methylpropionyloxy}) \text{undecyl} ] \) trichlorosilane (BMPUS), which acts as an initiator for the atom transfer radical polymerization (ATRP). The substrate is then placed into a polymerization chamber with the BMPUS gradient positioned horizontally. The polymerization mixture is generated using the draining method, as described in Ref. 15. In Figure 3, we plot the dry thickness of poly(dimethyl aminoethyl methacrylate) (PDMAEMA) in an orthogonal gradient grafted on a flat silica substrate. The data in Figure 3 demonstrate that for a given σ, the polymer thickness increases upon increasing the MW of PDMAEMA (i.e. moving along the Y-direction). Concurrently, fixing the MW and increasing the σ (i.e. moving along the X-direction) also causes an increase in the film thickness. To study the ability of the MW/σ polymer brush gradients to influence
the assembly of nanoparticles (citrate-stabilized gold particles with diameter $\approx 17$ nm) on grafted polymer surfaces, the PDMAEMA orthogonal gradient substrate was simply immersed in gold nanoparticle sol having pH 6.5. At this pH, the electrostatic interaction between the positively charged DMAEMA groups and the citrate groups adsorbed on the surface of the gold particles cause the nanoparticles to bind to the underlying brush (see Fig. 4). Color of the glass slide in Figure 4 changes gradually from light pink (region of low MW and low $\sigma$) to dark violet blue (region of high MW and high $\sigma$) as one moves along the directions of increasing MW and $\sigma$. This color change of gold coating is due to the well-known interparticle plasmon coupling, which occurs upon crowding of the particles. It is clear that increase in either MW or $\sigma$ results in increased loading of particles on the brush. In Figure 4(b), we plot visible light absorbance spectra collected along $\sigma$ (path A) and MW (path B) gradients. Increase in the intensity of the plasmon absorbance peak in the direction of increasing MW or $\sigma$ are due to the increasing number of particles attached to the polymer chains. The concomitant redshift of the plasmon peak position suggests intensified interparticle plasmon coupling associated with increase in nanoparticle density on the surface. Upon altering $\sigma$, the color variation is more pronounced for low MW (shorter) chains relative to longer chains, suggesting that the number of particles bound to the brush depends on the number of favorable sites that particles have access to. Our experimental results concerning the effect of increasing MW and $\sigma$ on particle attachment match very well with theoretical predictions.

Polymers coated substrates are used to prevent protein adsorption and thus minimize subsequent

Figure 3. Dry thickness of poly(dimethyl aminoethyl methacrylate) (PDMAEMA) on orthogonal PDMAEMA gradient grafted on a silica substrate. Thickness was measured in a grid of $5 \times 5$ mm$^2$ on the substrate. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 4. (a) Photograph of a glass slide showing gold nanoparticles bound to an orthogonal gradient of surface grafted PDMAEMA. The color variation along the direction of molecular weight (MW) as well as grafting density ($\sigma$) gradients indicates different gold particle uptake along each gradient. (b) Visible light absorbance spectra taken along (left) red circles (constant molecular MW, $\sigma$ gradient—path A) and (right) green squares (constant $\sigma$, gradient MW—path B). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
biofouling. 30,31 Polymer chains chemically grafted to the surface 30–36 have been predicted and shown to be more efficient at preventing protein adsorption than physisorbed polymers. Theoretical models revealed the roles of different molecular features of the grafted polymer in controlling protein adsorption. 37–39 Polymer MW and $\sigma$ have been predicted to be two important parameters regulating protein adsorption on a grafted polymer surface. 30,31,39,40 While there is no consensus on the relative importance of MW and $\sigma$ in imparting protein resistance to a grafted polymer surface, 30,41,42 it has been demonstrated experimentally that protein adsorption systematically decreases upon increasing either MW and/or $\sigma$ of anchored chains. 30,33,36,43 Herein, we utilize our novel polymer gradient substrates to manipulate protein adsorption and consequently tailor the adhesion of cells.

Recently, we have employed the MW/$\sigma$ polymer brush gradient for measuring the absorption of model proteins on surfaces. 44 Substrates comprising orthogonal assemblies of poly(2-hydroxy ethyl methacrylate) (PHEMA) were prepared using the aforementioned method. The adsorption experiments were conducted by immersing the PHEMA-coated silica substrates in protein solutions for 24 h. Subsequent to this step, the specimens were

**Figure 5.** (a) (left) Dry thickness of poly(2-hydroxyethyl methacrylate) (PHEMA) brush in an orthogonal gradient as a function of the PHEMA grafting density and molecular weight. The scale represents the thickness of dry polymer (in nm). (right) Adsorbed amount of fluorescently labeled lysozyme (Lys) as a function of the position on the orthogonal PHEMA gradient. The scale represents the fluorescence intensity (in a.u.). (b) (left) Dry thickness of PHEMA brush in an orthogonal gradient as a function of the PHEMA grafting density and molecular weight. The scale represents the thickness of dry polymer (in nm). (right) Adsorbed amount of fibronectin (FN) as a function of the position on the orthogonal PHEMA gradient. The scale represents the thickness (in nm). The protein dimensions are: Lys (3 x 3 x 4.5 nm$^3$) and FN (60 x 2.5 x 2.5 nm$^3$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
removed from protein solution, washed with phosphate buffered saline (PBS) solution and water and then blow-dried with nitrogen. The adsorbed amount of protein was assessed by either fluorescent microscopy (when the protein was tagged with a fluorescence dye) or by ellipsometry, which evaluated the dry thickness of protein layer. In Figure 5, we present the results of the adsorption of (a) lysozyme (Lys) and (b) fibronectin (FN) on PHEMA substrates. The left part of Figure 5 depicts the dry thickness ($h$) profile of PHEMA on the substrate (darker color indicates thicker polymer layer). It should be noted that while the variation of MW is linear along the MW axis, $\sigma$ varies in a nonlinear fashion along $\sigma$ axis. $\sigma$ has diffusion-like profile as variation in $\sigma$ was achieved through vapor deposition process. The right part of the figure depicts the amount of adsorbed protein (darker color indicates more adsorbed protein). As elucidated from fluorescence microscopy (for Lys) and ellipsometry (for FN) measurements, the amount of protein on the surface decreased with increasing MW and/or $\sigma$ of PHEMA on the surface. Upon increasing MW and $\sigma$, PHEMA surface coverage increases, as coverage is given by $M\sigma = h\rho N_A$, where $M$ is the molecular weight, $\rho$ is polymer density, and $N_A$ is Avogadro’s number. Hence the data suggest that the amount of protein adsorbed depends on the local concentration of the HEMA groups on the surface. This observation is in accord with the calculations of Szleifer and coworkers who predicted that protein adsorption decreases as surface coverage of protein-resistant polymer increases.

The previous example illustrates that MW/$\sigma$ orthogonal gradients are capable of forming protein density gradients on the surface. Recently, we have utilized this feature to adjust the density of cells on surfaces. FN serves as an anchor for the attachment of the osteoblastic cells, in particular, MC3T3-E1, through the amino acid sequence R-G-D (Arg-Gly-Asp) present on the FN molecule. MC3T3-E1 osteoblastic cells were cultured on FN-coated gradient substrate using standard cell culture protocol. For analysis purposes, the cells were stained so as to make the nucleus look blue and the cytoskeleton appear

Figure 6. Contour plots of (a) dry thickness of poly(2-hydroxyethyl methacrylate) (PHEMA) in MW/$\sigma$ orthogonal PHEMA gradient (scale in nm). (b) dry fibronectin (FN) thickness in MW/$\sigma$ orthogonal PHEMA/FN gradient (scale in nm). The scales depicting position on the substrate in parts (a) and (b) are in cm. (Top) Images of MC3T3-E1 cells (nucleus: blue, cytoskeleton/actin: red) cultured on the PHEMA/FN gradient substrates. Images recorded at positions on the sample marked with the numbers in the bottom panel of the figure.
red. In Figure 6, we plot the dry thickness of PHEMA in the MW/\(\sigma\) sample and the corresponding thickness of adsorbed FN. In the upper panel of Figure 6, we present the images of the surface taken at various positions along the diagonal upon incubation of cells. Changes in cell density and morphology are clearly evident. The cell density decreases with increasing PHEMA coverage (decreasing amount of FN) on the surface. Cell morphology also changes as a function of the PHEMA (and hence FN) coverage. Cells attain a polygonal shape on regions of the substrate covered with large amount of FN and they elongate when there is little or no FN present. This behavior likely stems from the fact that on thin PHEMA regions, cells find large amount of FN to interact with, which causes them to spread extensively on the surface. However, on thick PHEMA regions cells cannot experience good traction due to insufficient amount of FN, which causes cells to stretch out to minimize unfavorable contacts with PHEMA surface. The two examples discussed above illustrate how orthogonal MW/\(\sigma\) gradients offer a potent platform that enables systematic exploration and direct visualization of the effects of surface parameters on phenomena of interest, namely nanocomposite formation and cell adhesion.

**“DUAL” MOLECULAR WEIGHT (MW1/MW2) ORTHOGONAL GRADIENT**

Another orthogonal gradient we are going to describe here is made of two mutually perpendicular linear MW gradients. Such a ‘dual’ MW gradient of surface-tethered macromolecules on flat surfaces (MW1/MW2) can be fabricated by following the steps depicted in Figure 7. First, a monolayer of BMPUS, the polymerization initiator, is formed on the specimen and an MW gradient of polymer A is formed by the solution draining method. Taking advantage of the fact that the polymer chains grown by ATRP can be used as macrorinitiators for subsequent polymerization, a second polymer B can be polymerized on top of polymer A. Growing polymer B as an MW gradient, using the solution draining method in the direction perpendicular to the A gradient, results in an array of surface-tethered A–B diblock copolymers with variable lengths of both blocks. Moreover, each spot on the substrate contains copolymer chains that possess a unique combination of the block lengths.

The aforementioned procedure has recently been applied to form assemblies of surface-grafted diblock copolymers comprising poly(2-hydroxy ethyl methacrylate) (PHEMA) and poly(methyl methacrylate) (PMMA) blocks.49 In Figure 8, we plot the dry thicknesses of the (1) PHEMA, (2) PMMA blocks, and (3) the total thickness of PHEMA-b-PMMA copolymer. The thickness of each block was determined using ellipsometry after each synthesis step. PHEMA dry thickness increases linearly along the X direction [horizontal direction in Fig. 8(a)] and the PMMA thickness increases linearly in the Y direction [vertical direction in Fig. 8(b)]. Since \(\sigma\) of the chains is approximately constant on the entire specimen,\(^{15}\) the dry thickness of each block, \(h\), is directly proportional to its molecular weight, \(M\) (\(h = \sigma M/\rho N_A\)), where \(\rho\) and \(N_A\) are the density and Avogadro's number, respectively.

![Figure 7](image_url). Schematic illustrating the formation of an MW1/MW2 orthogonal gradient involving variation of molecular weights of two copolymer blocks on a solid substrate. First, a molecular weight gradient of the first block is formed on a solid substrate using the solution draining method. The specimen is then rotated by 90° and a second block is polymerized using the same solution draining method on top of the substrate-bound macrorinitiator. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
As a consequence of increase in the MW of both blocks in two orthogonal directions, the total PHEMA-b-PMMA copolymer thickness varies diagonally across the sample. More information about the various copolymer compositions can be obtained by plotting the dry thicknesses of the PHEMA and PMMA blocks along the various directions indicated by the arrows in Figure 8(c). The horizontally pointing arrows denote copolymers having a constant PMMA length and a linearly increasing PHEMA length. Two cases are highlighted here, copolymers with a short (C140) and long (C141) PMMA block [Fig. 8(d)]. The vertical arrows depict block copolymers with a linearly varying length of the PMMA block and a constant length of the lower PHEMA block. In Figure 8(e), we mark the boundary cases involving a short (Q) and long (Q') PHEMA block. The diagonals in Figure 8(c) mark copolymers that have: (a) approximately constant fraction of both blocks, but an increased total length (I), and (b) those with a constant total length but a linearly varying composition (O) [Fig. 8(f)].

In the following example, we demonstrate the merit of such copolymer assemblies with variable block lengths by exploring the effect of the block lengths on surface morphology after selective solvent treatment. We will validate that these MW1/

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**Figure 8.** Dry thickness profile (in nm) of (a) PHEMA block, (b) PMMA block, and (c) PHEMA-b-PMMA MW1/MW2 orthogonal brush as a function of the position on the substrate. (d–f) PHEMA (red squares) and total copolymer (blue circles) thicknesses along the directions depicted in the total thickness profile shown in part c of this figure. The cartoons on the top illustrate the PHEMA homopolymer (left) and PHEMA-b-PMMA copolymer (right) brushes grafted on a solid substrate. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
MW2 gradient copolymer motifs represent unprecedented combinatorial platform, facilitating systematic and complete characterization of the various copolymer microstructures that arise as a result of the solvent exposure. Several researchers have already reported on utilizing surface-confined copolymer systems in controlling the chain conformations by selectively swelling one of the blocks, while collapsing the other. For instance, Zhao and coworkers demonstrated that selective swelling and collapse of poly(styrene-b-methyl methacrylate) brushes produced variable surface topologies.\(^5_0,5_1\) This simple method of tailoring the substrate roughness has led, in recent years, to some exciting developments in utilizing surface-grafted polymers as potential ‘soft vehicles’ capable of moving nano-sized objects.\(^5_2\)

To fully exploit the power of the copolymer brushes in such applications, one needs to thoroughly explore the effect of the lengths of the two blocks and the composition on the brush response to various stimuli.

We studied the effect of solvent quality by exposing the samples to ethanol, a poor solvent for the PMMA block, and then quickly quenching by immersing the specimens into liquid ethane. The latter procedure ‘freezes’ the polymer conformation, while removing the organic solvent. The sample surface morphology was then probed with tapping mode atomic force microscopy (AFM). In Figure 9, we plot the morphology diagram based on multiple AFM scans collected from several areas on two different PHEMA-b-PMMA orthogonal samples. The results reveal that ethanol does not affect the sample morphology markedly when the PMMA block length is small; the surface stays predominantly flat (F). However, increasing the PMMA block length leads to more distinct variations of the surface topology. First, a transition from flat to micellar (F/M) morphologies is detected. Upon further increase of PMMA block length, the surface micelles (M) become even more pronounced. Additional increase in the PMMA block length leads to a transition of micelles into more continuous nanostructures (M/C). The continuous (C) topology dominates at the highest PMMA length investigated. More experiments are currently underway to quantitatively follow the development of the surface roughness and the topologies of PHEMA-b-PMMA copolymers as a function of various solvents.

Zhulina et al. examined the swelling of surface-tethered copolymers by selective solvents, using self-consistent field calculations and scaling arguments.\(^5_3\) Their calculations revealed that grafted copolymers exposed to a solvent that is a theta solvent for the bottom block and a poor solvent for the top block exhibit several distinct morphologies: flat (I), pure B pinned micelles (PMB), A-legged micelles (MAB), star-like micelles (MA), and a bicontinuous phase (BAB). The type of morphology the copolymer adopts depends on the lengths of the individual blocks. The trends observed in our experiments (see Fig. 9) are in excellent qualitative agreement with those predicted by Zhulina and coworkers.\(^5_3–5_5\)

**CONCLUSIONS AND OUTLOOK**

We have demonstrated the application of orthogonal polymer brush gradients in understanding (1) the formation of polymer-nanoparticle composite (2) adsorption behavior of biological species such as proteins and cells, and (3) morphological transitions of surface-anchored copolymers upon exposure to block-selective solvents. We established that orthogonal gradient surfaces offer facile combinatorial platforms for quick and inexpensive investigation of a multivariate phenomenon. Similar study by traditional methods typically requires preparation of numerous samples, ostensibly under similar experimental conditions. The combinatorial methods in this article obviate such difficulties and enable unambiguous
exploration of the large $\sigma$ and MW space. Since orthogonal gradient substrates permit data collection for several combinations of MW and $\sigma$ in one single experiment, the variability associated with these results is likely to be more consistent on a gradient sample than that associated with performing individual experiments on multiple samples. This is particularly helpful in dealing with systems comprising biological species, where experimental variation can be very large. Additionally, multi-gradient approach allows one to study the cooperative effects originating from the two distinct surface properties. The case studies outlined in this paper have, quite literally, only scratched the surface. There are many more examples of important scientific and technological phenomena that would greatly benefit from utilizing orthogonal gradients. For example, one may think of applying the concepts of independently varying two material properties of surface-anchored polymers to create targets for fast screening of adsorbates, form surface microstructures with tailorable size and composition. Another class of applications involves using orthogonal gradients as directional stimulants. For example, by extending the existing body of work employing molecular gradients for guiding motion of liquid drops on surfaces,\textsuperscript{23,56–61} orthogonal polymer gradients can be devised to probe dynamic phenomena on surfaces, such as liquid or protein separation, cell motility, and so forth. One can also combine the variation in inherent characteristics of grafted polymers with gradients in other physical properties such as temperature or strain to address significant issues in polymer science.\textsuperscript{52–64} Clearly, there is a multitude of possible applications of orthogonal structures, with only a few of them listed here, which will undoubtedly provide a new paradigm for advancing the fundamental understanding of structure–property relationship governing material behavior.

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