Soft Matter

Cite this: *Soft Matter*, 2012, **8**, 31

www.rsc.org/softmatter

REVIEW

Design of conformal, substrate-independent surface modification for controlled protein adsorption by chemical vapor deposition (CVD)

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Received 14th July 2011, Accepted 7th September 2011
DOI: 10.1039/c1sm06334k

Biofouling is a crucial consideration in a variety of applications including biosensors, biomedical implants and devices, food packaging, and industrial and marine equipment. On the other hand, the controlled adsorption of proteins is desired in certain fields such as bioassays and tissue engineering. As such, significant progress has been made in fabricating surface chemistries that are able to resist or regulate protein adsorption through the manipulation of the protein–water–surface interactions. However, a conformal, substrate-independent surface modification method is required in order to extend such chemistries to a wider range of applications including delicate substrates, nanostructured surfaces, and polymer nanotubes. Here, we review the chemical vapor deposition (CVD) of coatings to control protein adsorption. These CVD coatings can be classified into four categories: hydrophilic coatings or hydrogels, which resist protein adsorption through surface hydration; fluorinated coatings, which have especially been studied in the context of fouling release in marine environments; amphiphilic coatings involving a unique antifouling mechanism; and switchable or stimuli-responsive coatings. Many of the techniques in each group are compatible with the synthesis of surface or free-standing nanostructures, and can be easily integrated into the existing fabrication infrastructure.

Introduction

Controlling protein adsorption on surfaces has been a significant challenge due to its crucial role in many applications including biosensors, medical implants, surgical equipment and protective apparel in hospitals, water purification systems, and marine and industrial equipment.[1] Innovative techniques have been developed to fabricate surfaces that strongly resist protein adsorption and cell adhesion, termed "inert" surfaces, as well as nanostructures that combine large surface areas with the antifouling

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nature of the surface chemistry to enhance the sensitivity of bioassays and biosensors.[2–11]

With the rapidly growing number of antifouling surface chemistries come the challenges of applying such functionalities to a much wider range of substrates and fabricating more sophisticated surface structures with these materials. Self-assembled monolayers (SAMs), used to systematically study the properties of surfaces with fouling resistance, can only be applied to gold substrates with limited coating thickness.[4] Brush structures can be formed by surface-initiated grafting, or grafting-to methods,[12] but not all substrates possess or could possess (through pretreatment) the functional groups required by these methods. Atmospheric pressure (AP) plasma-induced graft polymerization is a relatively new surface modification scheme for the antifouling purpose.[13,14] However, the application is mostly on reverse osmosis (RO) and nanofiltration (NF) membranes. Self-assembly to form fouling resistant brushes relies strongly on the base materials, as well as on the processing scheme.[15] Conformality describes the degree to which coating thickness is maintained over the topography of non-planar substrates. The non-conformal nature of various solution phase methods (*e.g.*, spin-coating) renders it very difficult to fabricate surface nanostructures or free-standing nanotubes. Hence, one of the most important aspects in controlling protein adsorption is the development of substrate-independent and conformal surface modification methods that extend the above-mentioned methods to a wider range of applications.

This review focuses on conformal, customizable, functional coatings that have the potential to control fouling in a substrate-independent manner and are able to be conveniently fabricated as or integrated into nano-scale structures. Chemical vapor deposition (CVD) is suitable for this purpose due to its solvent-free nature and low processing temperature (Table 1). CVD methods are particularly valuable for insoluble and infusible films, including fluoropolymers and controllably crosslinked networks.[16] This can be viewed as a new direction in protein adsorption control, as a platform that can translate the mechanism and knowledge from surface modifications in the liquid phase to heterogeneous processes for many real, applied cases. This review will be complementary to the excellent reviews on solution phase synthesis methods for protein adsorption control.[1,17–19]

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Overview of CVD processing

The majority of reports describing the CVD surface modification for controlling fouling and protein adsorption employ CVD of poly(*p*-xylylenes) (or parylene), plasma enhanced CVD (PECVD), or initiated CVD (iCVD)/photoinitiated CVD (piCVD). Therefore these three methods will be the main focus of the following discussion.

During the synthesis of poly(*p*-xylylenes) and derivatives, substituted [2.2]paracyclophane dimer vapor is thermally cracked and the resultant monomer subsequently self-initiates the polymerization on a cool substrate.[16,20,21] Poly(*p*-xylylenes) and derivatives have long been prized for enabling conformal coating of high-aspect-ratio structures, and a combination of topological and chemical patterning has been extensively used for selectively immobilizing biomolecules onto functionalized poly(*p*-xylylenes). However, the use of functionalized poly(*p*-xylylenes) in many cases requires the custom synthesis of substituted [2.2]paracyclophanes, which is costly and difficult to scale-up and commercialize. In addition, the coating of complex substrates with feature sizes on the submicrometre scale is challenging for the CVD of poly(*p*-xylylenes) (Fig. 1).[19,21–23]

In PECVD, the radical species are created by vapor phase plasma excitation, together with a wide range of chemical species that react and deposit on the surface.[24] The degree to which organic functionality is preserved often improves by decreasing the plasma power through strategies such as pulsing the plasma excitation[16] or performing the deposition downstream of the active plasma region.[16,24] Often, PECVD processes use monomers which are commercially available and scale-up of PECVD processes has been demonstrated and commercialized.[25,26]

To achieve better functionality retention, the formation of the plasma can be avoided with the initiating radical species generated using an alternative method. For this purpose, an initiating species can be introduced through the gas phase along with the monomers. The initiator can be selectively decomposed to free radicals through gas-phase heating (iCVD) or by photons (piCVD).[27] By avoiding the need for nonselective plasma excitation, high-rate deposition of true linear free-radical polymer chains can be achieved by iCVD and piCVD with essentially 100% functionality retention. Monomers used for iCVD and piCVD are widely commercially available. Large scale iCVD reactors and ability to operate iCVD in semi-continuous roll-to-roll processing mode have been demonstrated.[28,29]

Table 1 Comparison of CVD-based polymer coatings with other techniques

Method	SAMs	Grafting-to	Grafting-from	Spin coating	CVD
Solvent-free	×	×	×	×	√
Long-term stability	×	√	√	√	√
Conformality	High	High	High	Low	High
nm to μm scale thickness control	×	×	×	×	√
Substrate independent	×	×	×	√	√
Full functional retention	√	√	√	√	√
Synthesis speed	Slow	Slow	Slow	Fast	Fast
Scalable	×	×	×	√	√
Single step process	×	×	×	×	√

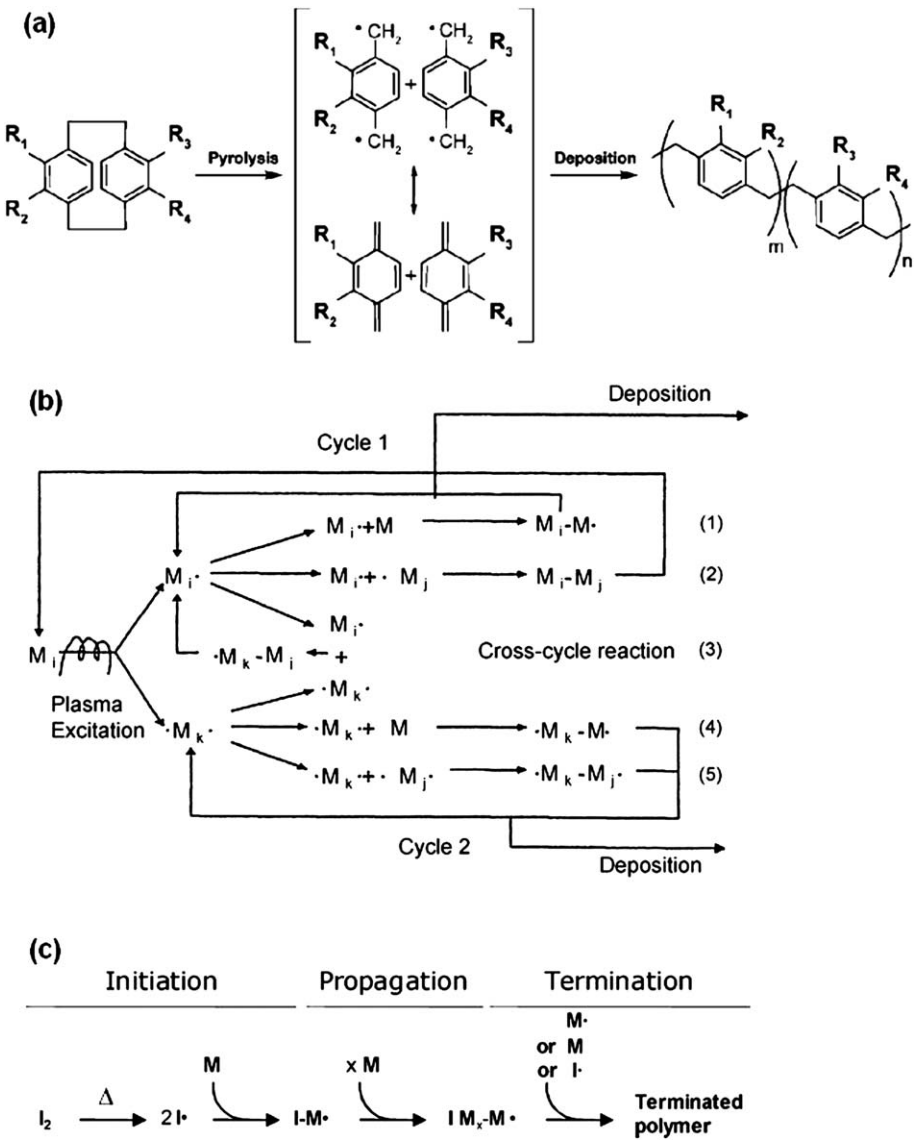

Fig. 1 Mechanisms of CVD techniques.[21,27] (a) CVD polymerization of substituted [2.2]paracyclophanes to prepare functionalized poly(*p*-xylylenes). (b) The supplied energy creates radical species from the monomer in PECVD, and the polymerization proceeds through various radical species. (c) The thermal energy dissociates the initiator into radicals and the chemistry of iCVD resembles standard solution-phase polymerizations with a free-radical mechanism. Reproduced with permission from (a) ref. 21, (b) and (c) ref. 27. (a) Copyright 2011 American Chemical Society.

CVD conformal coatings for protein adsorption control

Surface chemistry and protein adsorption

It has been suggested that inert surfaces share the following molecular-level characteristics: (i) they are hydrophilic, (ii) they contain hydrogen bond acceptor groups but not hydrogen bond donor groups, and (iii) their net charge is neutral.[3,6] This set of properties was identified by screening SAMs with approximately 60 different surface chemistries.[3,4] Among these surfaces, the ones containing derivatives of oligo(sarcosine), *N*-acetylpiperazine, and permethylated sorbitol groups showed protein resistance close to polyethylene oxide (PEO)-modified surfaces, often considered to be the gold standard in protein resistance. Conformational flexibility is also a characteristic of many of these groups, but it is not essential.[30] These characteristics have also been observed in other antifouling chemistries. Inert surfaces were obtained with monolayers of chimeric peptoids—oligomers of peptide structures made of non-natural amino-acids.[7,8] The ultra-low fouling zwitterionic coatings synthesized *via* SAMs,[1] atom transfer radical polymerization (ATRP)[18] and vapor phase method[31] exhibited the same traits.

These general characteristics describe many but not all inert surfaces. It has been reported that SAMs terminating in mannose groups (a hydrogen bond donor) resist the protein adsorption as well as cell attachment to a degree comparable to the SAMs containing oligo(ethylene oxide).[9] Other studies focus on alternative mechanisms of controlling protein adsorption, which include highly hydrophobic surfaces, amphiphilic surfaces and poly(*N*-isopropylacrylamide)-based-stimuli-responsive surfaces. Fluorinated surfaces have been studied for the release of biofilms on ship hulls by shear,[19,32,33] and recent data report the use of fluorinated surfaces that are more easily cleaned.[34] Compositional heterogeneities on the length scale of the foulant of interest may discourage thermodynamically favorable interactions between the foulant and the surface, which in turn would limit adsorption events.[22,32,35] Thermo- and pH-responsive polymers that switch in hydrophilicity and the degree of swelling have also been used to impart a biofouling-release property to surfaces. Biofoulants can be released upon changing the temperature of the underlying material that has been coated with responsive polymers, leaving the surface clean.[1,36] Among various antifouling chemistries, we will primarily focus on the traditional antifouling material—hydrophilic coatings, the recently developed amphiphilic coatings and stimuli-responsive coatings. Although the fluorinated surfaces have not shown protein-adsorption resistance, there will be a short section on this topic to demonstrate the capability of CVD to obtain conformal fluorinated films with defined composition. This allows for the fabrication of amphiphilic copolymers with CVD.

Hydrophilic coatings

Hydrophilic surfaces tend to foul less because the enthalpic driving force for the adsorption of the protein at the interface is lower. This is why modification of the surfaces to deposit a thin hydrophilic layer has been a common method to limit non-specific protein adsorption. Due to their good antifouling performance and extraordinary biocompatibility, thin hydrophilic polymer coatings (*e.g.*, poly(2-hydroxyethyl methacrylate) (pHEMA) and polyvinylpyrrolidone (PVP)) have been of great interest for applications including biomedical implants,[37] tissue engineering,[38] drug delivery[39] and biosensor fabrication.[40] By applying hydrophilic thin films by CVD, protein-adsorption and wetting behavior of virtually any substrate can be changed without affecting the bulk properties.

Hydrophilic surface nanostructures (*e.g.*, hydrogel nanotubes) with large surface area to volume ratios are desired for tissue engineering, drug release, cell culture and fundamental studies on protein adsorption mechanisms, and can be fabricated conveniently and economically *via* conformal CVD methods.[38,41] In this section, we will review the development of CVD hydrophilic coatings/nanostructures and their applications in antifouling and surface protein adsorption tuning.

Hydrophilic thin film coatings. Hydrophilic thin film coatings can act as hydrogels as well as biocompatible anti-fouling coatings.[16,42] The density of proteins adsorbed onto hydrogel thin films (*e.g.*, PHEMA) is on the order of one hundred ng cm^{-2} before any washing steps are carried out to remove reversibly adsorbed foulants. The surface density of irreversibly adsorbed proteins on CVD hydrogels is generally on the order of tens of ng cm^{-2} (ref. 22 and 43) or below 10 ng cm^{-2} (ref. 44) (depending on the surface chemistries) as measured after prolonged washing of the hydrogel films at the end of a protein adsorption experiment (Table 2). CVD offers one-step processing of crosslinked hydrogel thin films with excellent thickness control and they are not limited to growth on flat substrates or on particular substrate materials. The use of solvents such as *N*,*N*-dimethylformamide is avoided, so there is no potential for the undesirable retention of solvents or solvent-induced degradation or swelling in the CVD films. For medical applications, all-dry processing eliminates the detrimental effects of the release of solvent entrained in the coatings.

Crosslinking is usually introduced into PHEMA films to control the gel properties, even though linear PHEMA chains do not completely dissolve in water.[16] PECVD methods have long been used to form crosslinked PHEMA hydrogels.[43,45–47] The crosslinking is due to the high-energy plasma excitation, and the crosslink density depends on the power applied to the system. However, the high-energy excitation causes a variety of side reactions that affect the functionality of the monomer and therefore compromise the antifouling performance of the gel. For example, PHEMA was deposited on non-woven poly (butyleneterephtalate) filter materials using a discharge power ranging from 40–100 W.[45] The adsorption of proteins onto the plasma-coated filters increased with the higher discharge power. The adsorption of fibrinogen onto the film deposited using 100 W discharge power was about 50% more than that of the film deposited using 40 W discharge power. The surface composition deviated from solution-phase synthesized PHEMA due to the loss of hydroxyl groups resulting from side reactions during the PECVD process.[45] Similarly, it has been reported that PECVD at low substrate temperature could reduce the fragmentation of the HEMA monomer and obtain lower irreversible protein adsorption density on the PHEMA thin film than that obtained under high substrate temperature.[43] The protein adsorption onto the

Table 2 Comparison of reported surface protein density of different antifouling chemistries

Chemistries	Total protein adsorption	Irreversible protein adsorption
Bare gold surface[a] (ref. 118)	~270 ng cm^{-2}	~240 ng cm^{-2}
Hydrogel thin film coating[22,43,44]	~250 ng cm^{-2}	~25 ng cm^{-2} or ~2 ng cm^{-2}
Hydrogel nano-structures[b] ref. 11	0.17–0.31 mg cm^{-2}	n.a.
Zwitterionic thin film coating[a] (ref. 18 and 119)	~10 ng cm^{-2}	<0.3 ng cm^{-2}
Amphiphilic coating[22,23]	~10 ng cm^{-2}	~1 ng cm^{-2}
Switchable surface[103,120]	Protein adsorption above LCST ~150 ng cm^{-2}	Protein adsorption below LCST ~10 ng cm^{-2}

[a] The values were calculated from figures in the corresponding references. [b] The unit of protein adsorption for hydrogel nano-structures is mg cm^{-2}, which is equivalent to 10^6 ng cm^{-2}.

PHEMA plasma-deposited at low temperature (HEMA-PDLT) was comparable to that of the hydrogels synthesized by solution methods. It has also been demonstrated that pulsed[46] and initiated[47] PECVD methods can successfully deposit thin films of PHEMA with approximately 80% retention of the surface hydroxyl groups.[46] Due to the inherent crosslinking and some functional loss in the film, a maximum swelling ratio of approximately 12% was achieved using an initiated PECVD technique, compared to 55% reported for conventional polymerization techniques for bulk HEMA.[47] Two factors most likely contribute to the lower swelling observed for the PECVD films. One is the difference in chemical structure, as the PECVD has a higher density of crosslinking sites and a lower density of hydroxyl (–OH) functional groups. Secondly, in contrast to bulk materials which display three-dimensional swelling, thin films swell primarily along the axis perpendicular to the growth surface as a result of the constraints imposed by their physical attachment to an underlying substrate.[48]

Thin films of PHEMA have also been deposited using iCVD[49–51] and piCVD.[52,53] 100% retention of the hydroxyl functionality was achieved at deposition rates greater than 100 nm min^{-1}. The gel properties can be systematically controlled through the metered addition of crosslinkers (*e.g.*, ethylene glycol diacrylate (EGDA)) during the deposition. Microparticles were conformally coated with piCVD PHEMA thin films (Fig. 2).[52] No aggregation of the microparticles was observed, a result which is difficult to achieve for solution-based coating methods. The protein fouling on the piCVD PHEMA coated biosensors was reduced by nearly 8-fold over bare silicon. The exposure to plasma excitation and potential plasma degradation was avoided in the piCVD process and thus sensor's response time was not changed upon deposition. The rapid synthesis (~1.5 μm min^{-1}) of ultrahigh molecular weight PHEMA films has been reported.[51] The adsorption of bovine serum albumin (BSA) to the modified surface was reduced to one-third of that of Si wafer according to the standard bicinchoninic acid (BCA) assay. Significant physical entanglements resulting from the ultrahigh molecular weight (~8.2 × 10^5 g mol^{-1} for the viscosity average molecular weight) kept the PHEMA films insoluble. Good mechanical properties were obtained without the addition of crosslinkers, retaining the high hydrophilicity of PHEMA homopolymer.

PVP hydrogels are also of interest in the scope of antifouling coatings because of their hydrophilic and biocompatible nature.[54] As with PHEMA, PVP has been studied extensively *via* PECVD.[55–58] PVP synthesized from RF plasma polymerization was demonstrated to be non-cytotoxic and biocompatible.[55] Solution phase polymerization was used prior to the plasma CVD to form an adhesive layer for better long-term stability. Better control of the chemistry and less undesirable crosslinking can be obtained using low duty cycle pulsed PECVD.[56,57] The greater retention of the hydrophilic functionality was evidenced by the low contact angle of ~10° for advancing and 1° for receding sessile drops.[56] As an alternative to PECVD, the exterior of the scleral lenses was modified with PVP *via* grafting CVD (gCVD) with UV-induced initiator benzophenone and this avoided the usage of organic solvents during the grafting step.[59] The hydrophilicity imparted by gCVD remained throughout 120 day saline soak-testing period. The gCVD modification reduced the contact angle of the surface from 92.38° ± 2.18° to 39.58° ± 2.68°, which is desired for both antifouling purposes and the hydration of the lenses. UV-induced vapor phase polymerization has also been used to deposit films with up to 1600 μg cm^{-2} grafting coverage (depending on the grafting time and the monomer) and reduce the static contact angle to ~25°.[60] However, UV-induced crosslinking might occur during these processes, as indicated by the insolubility of the film and the comparatively high contact angle for PVP. The undesirable crosslinking induced by plasma or UV can be prevented in iCVD PVP films. Linear chains were crosslinked with the addition of a crosslinker monomer such as EGDA. The contact angle of the iCVD chemically crosslinked PVP was ~11°.[61]

Zwitterionic materials have been widely studied for their protein resistance properties and some are comparable to the best known materials for resisting protein adsorption (Table 2).[6,18] The strong electrostatic hydration of the zwitterionic surface has been proposed to be the reason behind the ultralow fouling property, which might render it enthalpically unfavorable for the protein adsorption.[18,62] Zwitterionic coatings can be synthesized onto glass or gold surfaces *via* SAMs,[6,18] ATRP,[18] solution polymerization and solvent evaporation.[63,64] However, these methods generally involve harsh process conditions and/or require specific surface functionalities which limit their range of application. Poly(sulfobetaine) (pSB)-based zwitterionic coatings have been synthesized using iCVD and grafted onto reverse osmosis (RO) membranes through a vapor phase reaction.[31] While the organic solvents can damage the RO membrane during the coating step,[65] the iCVD method avoids this damage. The

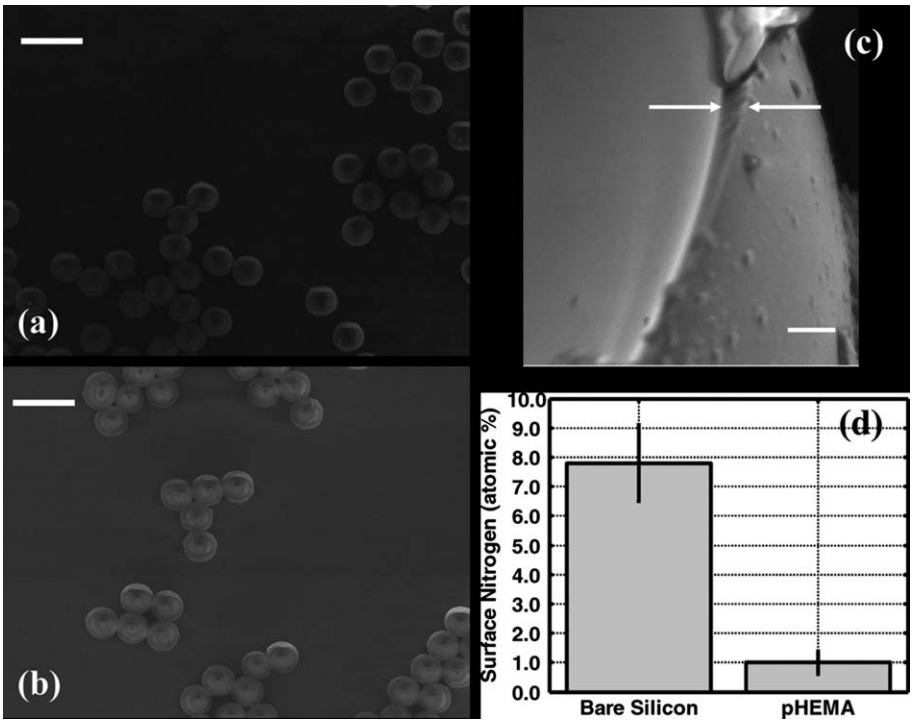

Fig. 2 (a) Uncoated silica microspheres and (b) silica microspheres coated with piCVD PHEMA (the scale bars represent 10 μm for both (a) and (b)). (c) SEM cross-section of a silica microsphere coated with piCVD PHEMA (the scale bar represents 2 μm and the arrow indicates the polymer layer) and (d) protein adsorption on the bare silicon wafer and piCVD PHEMA coated surfaces after incubation in a 1 wt% protein solution for three hours at 37 °C. The as-prepared surfaces contain no nitrogen, so any nitrogen signal after incubation must be due to the presence of adsorbed protein.[52] Reproduced with permission from ref 52. Copyright 2008 American Chemical Society.

antifouling property of the as-fabricated zwitterionic coating was tested with static bacterial adhesion and the coated RO membrane exhibited no adhesion of *E. coli* at the end of the test.

Hydrophilic surface patterning, polymer nanotubes and nanoparticles. Surface or free-standing nanostructures have been used to tune the adsorption of proteins. As compared to bulk materials, nanostructured materials usually have a larger surface to volume ratio and unique topologies, making them important for surface engineering applications. For example, larger surface area can enhance the sensitivity and detection limit of biosensors. Tissue engineering may require the attachment of certain cells in specific locations to create organized structures with the lowest possible fouling probability, which can be achieved by topologic patterning of non-fouling materials. Patterning techniques are also very useful in understanding the influence of the protein–material interface on the behavior of proteins. Vapor phase polymerization processes avoid the difficulties resulting from surface tension and non-wetting effects, and usually accomplish polymer synthesis and surface patterning in a single step.[10,11,41,66–70] This offers great promise for a simple and economical way to control the surface protein adsorption.

Materials patterning through nonconventional lithography can reduce the cost of patterning fine structures when compared to traditional nanofabrication techniques[16] and will be the focus of this section. A common approach to generate surface nanostructures with CVD is to pattern a blanket film of the vapor-deposited polymer by selectively localizing target molecules onto the reactive films using an elastomeric stamp,[71,72] hard mask,[21] or other spatially selective transfer process. A combination of topological and chemical patterning has been extensively used for selectively immobilizing biomolecules onto vapor-deposited patterns from functionalized poly(*p*-xylylene) films.[21,73,74]

An example of such patterning using PECVD demonstrates the creation of 2-D poly(acrylic acid) (PAA) domes with a diameter around 500 nm by top-down patterning. PAA was deposited with PECVD; the colloidal lithography technique was combined with oxygen plasma etching to fabricate the surface nanostructure. The carboxylic functionalities of the PAA film present between the colloidal masks were exposed to the O_2 plasma and showed a strong loss of the functionalities. Therefore BSA molecules are selectively bound to the functional plateau of the PAA domes.[70] Similar dome structures have been patterned with PAA/PEG.[66] However, subtractive processing is often incompatible with functional-group retention. The use of high-energy plasma etching or corrosive solvents can destroy the delicate reactive moieties in the CVD films. The lack of etch selectivity between organic CVD layers and organic resists can exacerbate these issues.

Colloidal lithography has also been coupled with iCVD technique to generate a high-resolution grafted HEMA layer with lateral features as small as 25 nm (Fig. 3a). The contact angle of the patterned PHEMA surface was reduced to 15°, resulting from the full retention of hydroxyl groups as well as the nanostructure.[67] Alternatively, transmission electron microscopy (TEM) grids have been used as templates for patterning

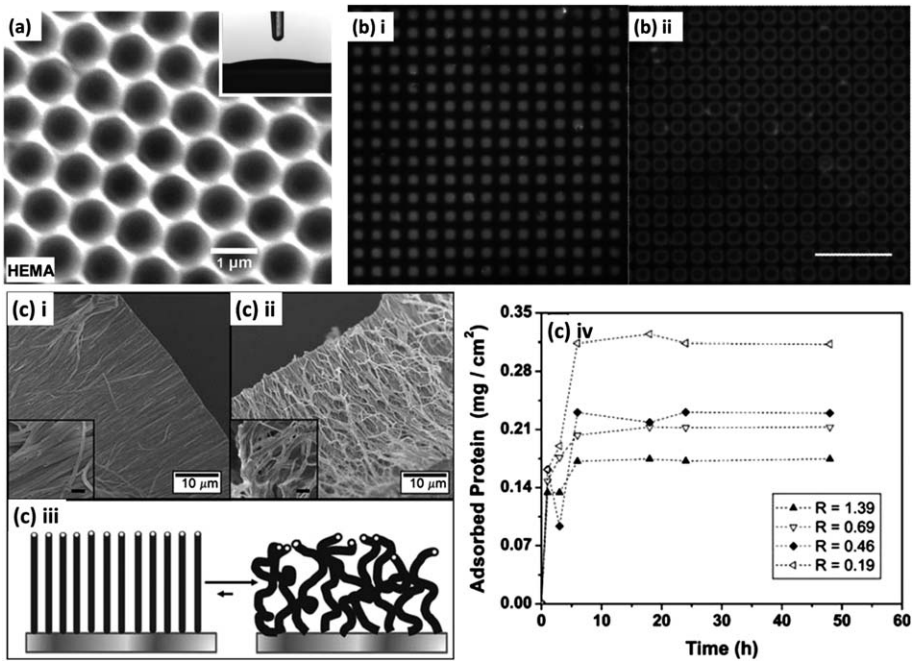

Fig. 3 (a) Colloidal lithographically patterned iCVD PHEMA and the resulting low contact angle with water (inset).[67] (b) Fluorescent images of (i) dry and (ii) swelled hydrogel copolymer poly[maleic anhydride-*co*-dimethyl acrylamide-*co*-di(ethylene glycol) divinyl ether]. The hydrogel was patterned using transmission electron microscope (TEM) grids and subsequently functionalized with cysteamine and linked to CdSe/ZnS nanoparticles (the scale bar represents 50 μm for both (i) and (ii)).[68] (c) Hydrogel nanotube forests fabricated using conformal iCVD PHEMA in the (i) dehydrated and (ii) freeze-dried states. (iii) Schematic of the nanotubes in the dehydrated and swelled states. (iv) The amount of adsorbed protein as a function of time for the hydrogel nanotubes with different crosslinking ratios, *R*.[11] Reproduced with permission from (a) ref. 67, (b) ref. 68 and (c) ref. 11. Copyright 2009 American Chemical Society.

high-fidelity micrometre-scale patterns on hydrogel deposited by iCVD (Fig. 3b).[68]

Highly conformal CVD films can be used to fabricate free-standing nanotube structures.[11,41,69] Conformal coverage over high-aspect-ratio structures is a characteristic that differentiates CVD polymerization from solution methods where the solvent surface tension effects lead to poor step coverage.[27,75] CVD hydrogel nanotubes have been templated by conformally coating the inner pores of anodic aluminium oxide (AAO) membranes with cross-linked hydrogel thin film, followed by etching to remove the AAO template.[11] Compared with their planar film counterparts, the swelling ratio of the CVD hydrogel nanotubes was increased by 4.5 to 6 folds. This was because the template nanotube structures were not physically constrained by the substrate. The protein adsorption to the nanotubes was tunable by adjusting the hydrogel composition (Fig. 3c). These low-fouling hydrogel nanotubes were later applied as an *in vivo* biosensor, termed microworms (Fig. 4a).[10] Lower signal drift otherwise caused by nonspecific protein adsorption and higher biomaterial viability was achieved by the hydrophilic antifouling surface.[51] During the fabrication of the microworms, 50 nm of ultrathin hydrogel layers were deposited onto the AAO templates with an aspect ratio of 300. The excellent conformality of CVD techniques made the unique microworm geometry possible, which was shown to be very important for the *in vivo* retention time of the biosensor (Fig. 4b).[10] The hydrogel nanotube also found its application in the stimuli-responsive burst release of drug molecules (Fig. 4c).[76]

Fluorinated coatings

Self-cleaning coatings have become a major focus in recent years.[1] Superhydrophobic materials composed of fluorocarbon polymers have been extensively studied for marine-fouling release.[19,34,77] Fouling release surfaces can be fabricated with a combination of low surface energy materials and high surface roughness. Therefore, conformal coating methods that are capable of synthesizing fluorinated coatings as well as fabricating nano-patterning or nano-structures are highly desired.

Since the 1970s, the PECVD technique has been widely applied as a unique method to synthesize insoluble fluorocarbon films.[78] However, a variety of bonding environments (including CF_3, CF_2 and CF) exists in a PECVD fluorocarbon film due to the high energy excitation.[79] Limiting the PECVD excitation through pulsing improved the retention of the pendant per-fluoroalkyl chain and decreased surface tension.[80] PECVD from 1*H*,1*H*,2*H*-perfluoro-1-dodecene provided films with a critical surface tension as low as 1.5 mN m^{-1}.[80] The fluorocarbon film with defined composition can be achieved by hot-wire CVD (HWCVD) with the thermally decomposable monomer hexa-fluoropropylene oxide (HFPO).[79,81,82] The addition of initiator into the HWCVD system (representing the iCVD system) greatly enhances the deposition rate as well as enlarges the library of precursors.[83] The iCVD of fluorocarbon films displays conformal coverage without uncontrolled chain cross-linking, undesired dangling bonds, or loss of chemical functionality compared to films grown using plasma excitation.

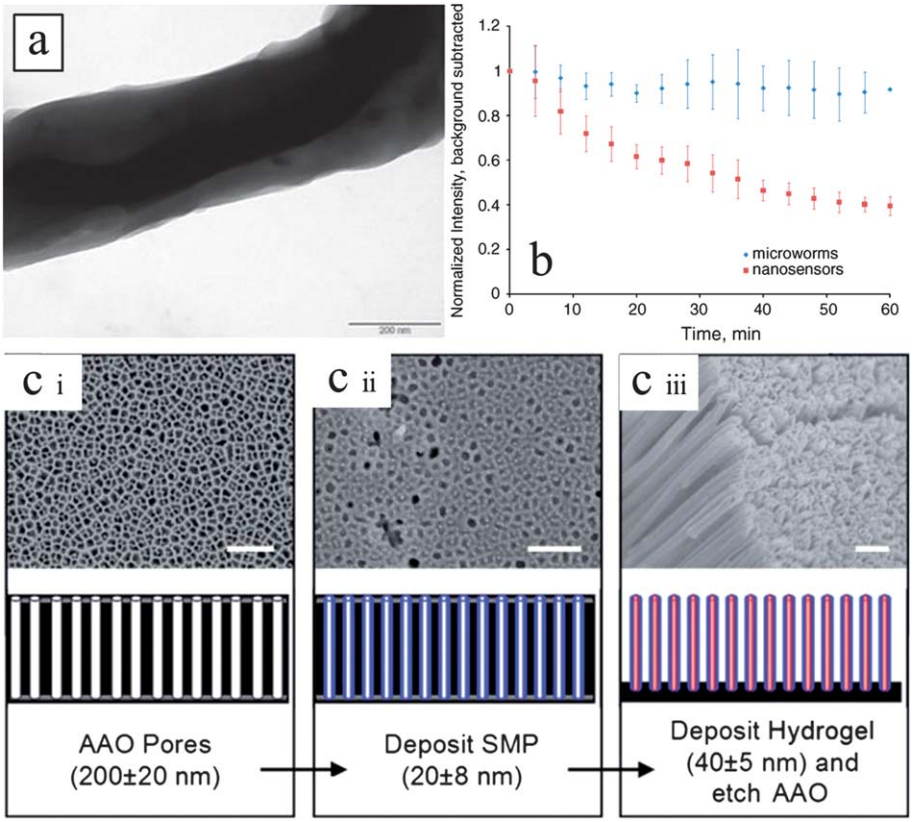

Fig. 4 (a) TEM images of the outer iCVD pHEMA copolymer shell of implantable "microworm" sensors. The inner optode core and the outer hydrogel layer are visible. The hydrogel coating is ultrathin (50 ± 10 nm). (b) Normalized fluorescent intensity of injected spots over time of microworms (blue) and nanosensors (red). Shown is the average with standard deviation for three spots of each type of particle. The decrease in the nanosensor fluorescence intensity is due to the diffusion of the nanosensors away from the injection site. Over a time range of 1 h, no significant diffusion of the microworms is observed.[10] (c) SEM images and schematic of (i) the AAO templates, (ii) coated AAO, and (iii) hydrogel tubes after etching the AAO template. The pores of the AAO templates are 200 nm in diameter and the thickness of AAO is 60 mm. The scale bars on the SEM images are 1 mm.[76] Reproduced with permission from (a), (b) ref. 10 and (c) ref. 76.

Nanostructured fluorocarbon films have been fabricated *via* PECVD with various morphological features.[84] As the distance between the substrate and the plasma glow region increases, the film can be smooth (directly adjacent), nodular (downstream) or "stone rose" (further downstream) (Fig. 5a–c). The combination of the nanostructure and the high fluorine content in the downstream films resulted in self-cleaning superhydrophobicity (advancing contact angle of ~165° with water).[84] A unique nanostructured and porous PTFE coating has been fabricated *via* iCVD (Fig. 5d), where the anisotropic structures are likely to be associated with crystallization of the linear $(CF_2)_n$ chains.[82]

The conformality of the iCVD technique makes it possible to perform surface modifications on various nanostructured surfaces.[67,85] Vertically aligned carbon nanotube forests have been coated with iCVD PTFE, rendering the surface superhydrophobic. Individual nanotubes with high aspect ratios (~40 : 1) were entirely coated with ultrathin (~50 nm) iCVD PTFE and the structure of the forest was preserved (Fig. 6a). Water forms nearly spherical droplets on the iCVD PTFE coated nanotube forest (Fig. 6b).[85] Colloidal lithography coupled with the iCVD technique generated surface patterning (Fig. 6c) and increased the contact angle of poly(1*H*,1*H*,2*H*,2*H*-perfluorodecyl acrylate) (pPFA) by ~40° compared to its flat surface

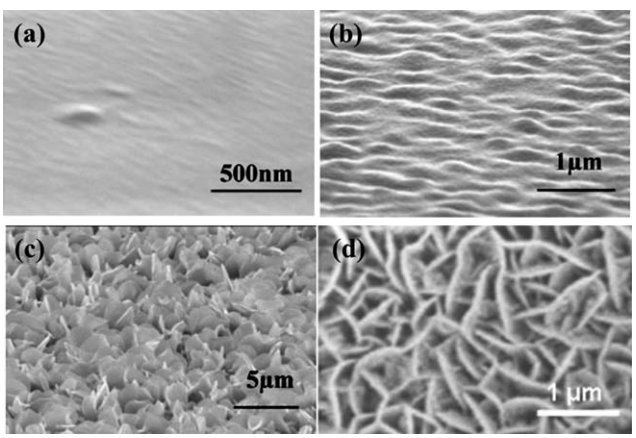

Fig. 5 Nanostructured as-grown CVD polymers (a) Smooth PECVD PTFE-like coatings grown from HFPO by placing the substrate directly adjacent to the plasma glow region; (b) downstream nodular morphology; (c) 'stone rose' morphology of further downstream substrate position;[84] and (d) porous morphology of iCVD PTFE coating grown from HFPO.[82] Reproduced with permission from (a), (b), and (c) ref. 84 and (d) ref. 82.

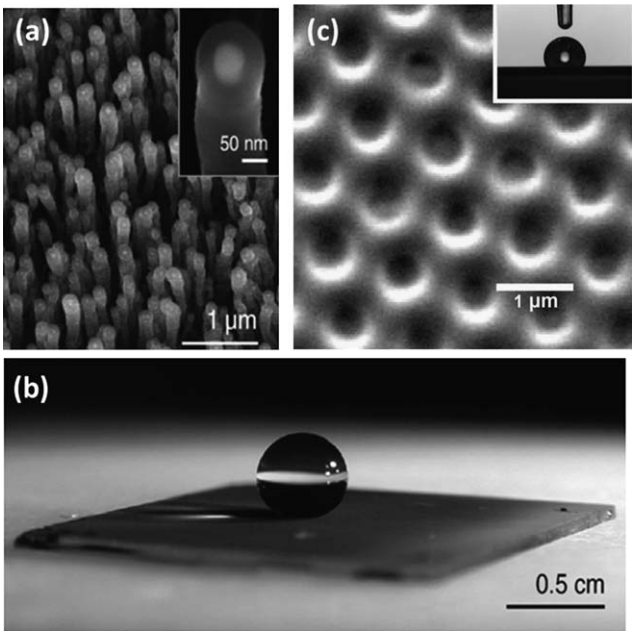

Fig. 6 (a) Vertically aligned carbon nanotubes have been coated with PTFE by HCVD, showing that each individual tube is coated conformally; (b) a spherical water droplet suspended on the PTFE-coated carbon nanotube forest, demonstrating the superhydrophobicity of the surface;[85] and (c) flat substrate coated and patterned with colloidal lithography coupled with the iCVD technique, resulting in high contact angle with water (inset).[67] Reproduced with permission from (a), (b) ref. 85 and (c) ref. 67. Copyright 2003 American Chemical Society. Copyright 2009 American Chemical Society.

counterparts.[67] Capillary pores within a membrane with the aspect ratio of 80 : 1 were conformally coated with iCVD pPFA and the resulting contact angle was ~150°.[86] The same type of conformal fluorocarbon coating was later used to fabricate high-aspect ratio hydrophobic, cylindrical nanopores with the diameter as low as 5 nm. The as-deposited membrane was able to separate solute molecules based on hydrophobicity.[87] Interestingly, a graded copolymer was fabricated using HEMA and pentafluorophenylmethacrylate (PFM) *via* piCVD. This is challenging for solution phase methods because of the lack of a common solvent for those two monomers. The graded copolymer confines the PFM to the near surface region (20 nm), allowing the control of the hydrogel film properties independently of surface reactivity.[53] This capability of CVD methods to copolymerize monomers with drastically different solubilities contributed to the success in amphiphilic coating fabrication, which will be the focus for the next section.

Amphiphilic or hydrophilic–hydrophobic-alternatively patterned coatings

Another novel approach to fouling resistance is based on generating surfaces with compositional heterogeneities on the length scale of the foulant. Such a surface, with alternating hydrophilic and hydrophobic regions, may discourage thermodynamically favorable interactions between the foulant and the surface, and in turn would limit adsorption. These surfaces are usually formed by the self-assembly of amphiphilic macromolecules due to microphase separation.[1,19,88,89]

Most of the work in this field focuses on resistance to the adhesion of microorganisms, where submicron heterogeneities are needed. For example, when hyperbranched fluoropolymers (HBFP) cross-linked with PEO is cast as a thin film, phase segregation creates domains smaller than 1 μm. This structure was found to reduce the irreversible adsorption of zoospores. However, protein adsorption increased with increasing HBFP content, suggesting that the length scale of the compositional heterogeneity was small enough to disrupt microorganisms but too large to sufficiently disrupt protein–surface interactions.[23,90] Comb-like block copolymers with grafted amphiphilic side chains, and patterned hydrophilic/hydrophobic stripes on the microscale also displayed resistance to the adsorption of zoospores and diatoms, but their protein resistance was not examined.[32,35]

While these methods are quite promising, liquid phase casting of these films would have limited conformality, and so would have limited utility on rough or patterned surfaces. CVD-based patterning offers a promising alternative in creating fouling resistant coatings that have alternating hydrophilic and hydrophobic regions of customizable size and shape, as it allows the use of a multitude of patterning techniques.[91–95]

For example, iCVD was used in the preparation of micropatterned surfaces with independently customizable topographic and chemical contrast.[91] In this process, the first component (*e.g.* a hydrophilic polymer such as poly(hydroxyethyl methacrylate), PHEMA) is deposited as a blanket film by iCVD on the surface. Then a mask (A TEM grid that contains 7.5 μm squares with a 12.5 μm pitch) is placed on the film, and the exposed portions of the film are plasma etched. Afterwards, a second film, such as a highly hydrophobic layer of fluorinated poly(perfluorodecyl acrylate) (PPFA), is deposited by iCVD. When the mask is removed, the pattern formed by the mask is displayed, both as chemical contrast, and as a topological contrast that can be customized by controlling the relative thicknesses of the two films. A similar masking approach was used in conjunction with pulsed plasma CVD to form patterned films, though without the same topological control (Fig. 7a).[95] While these systems have not been studied in terms of their fouling resistance performance, the size scale of chemical contrast shows promise for preventing the adhesion of marine organisms.

CVD-based patterning methods have also been extensively studied as a biotechnology tool for selective and localized presentation of functional groups, such as highly hydrophilic poly(ethylene glycol) (PEG) brushes, or ligands for specific attachment of biomolecules. These methods rely on the formation of reactive polymer films by CVD that can be manipulated by patterning methods.[92–94] For example, CVD of [2,2]paracyclophane functionalized with trifluoropropionyl groups has been used to form surfaces that can be patterned by microcontact printing. The unmodified surfaces were reacted with PEG hydrazide.[92] To form patterned surfaces on more complex geometries such as microfluidic channels, microcontact printing is not ideal. For such topologies, CVD of 4-benzoyl[2,2]paracyclophane can yield a photodefinable reactive polymer coating that can be photopatterned.[93,94] This method has been used to form patterns of PEO brushes[93] and hydrogel islands (Fig. 7b).[94]

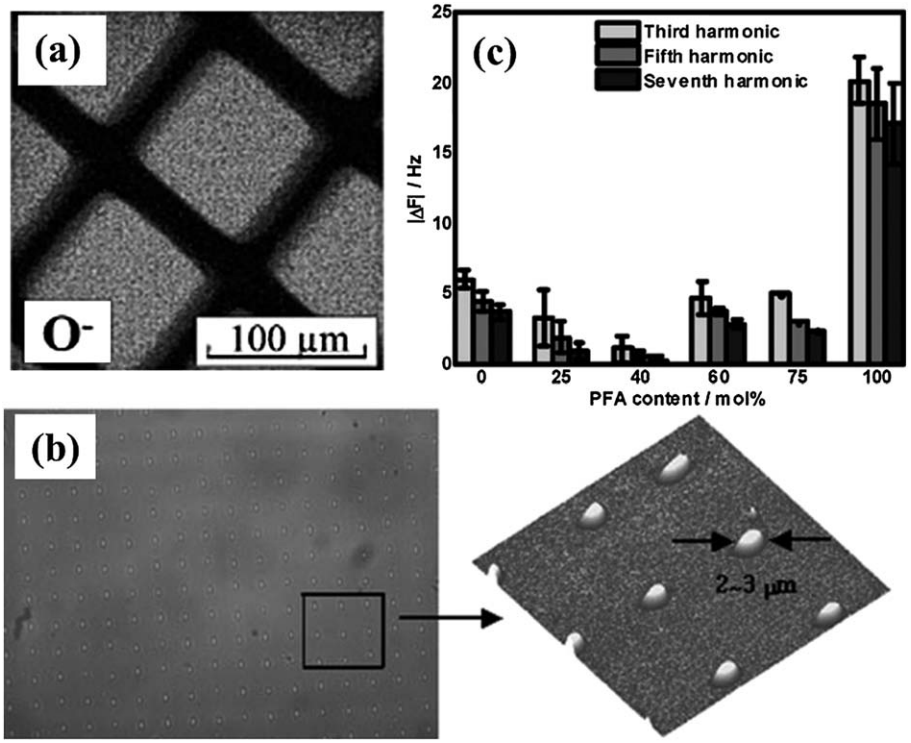

Fig. 7 (a) Patterns of PECVD pHEMA on top of fluorinated coatings generated using TEM grids;[95] (b) optical (left) and AFM (right) images of PEG hydrogel island structures fabricated on top of a reactive coating using 10 μm positive PDMS stamp;[94] (c) protein adsorption to iCVD amphiphilic copolymers *p*(HEMA-*co*-PFA) with various compositions. The copolymer with 40% PFA has less protein adsorption than either of the homopolymers.[22] Reproduced with permission from (a) (b) and (c).

Each of these studies focused on spatial control of protein adsorption, but the methods developed can also extend to forming patterns with hydrophobicity contrast, which can influence the adhesion of microorganisms.

Preventing protein adsorption with this approach, however, presents a greater challenge, because these chemical heterogeneities need to be at a scale that is smaller than the size of a protein. The area dimensions of typical protein molecules are in the range of 10–1000 nm^2, but the area that a protein molecule interacts with a surface is calculated to be only 1–2 nm^2 for a variety of proteins.[96] Therefore, the scale of chemical patterning on a surface that takes advantage of this approach for protein resistance needs to be on the order of ~1 nm. This size scale can be achieved through microphase separation of polymers with a random structure,[97,98] but generating such molecules that include sufficient hydrophobicity contrast is difficult by solution methods, due to the difficulty in finding a solvent that will dissolve both components simultaneously.

A random copolymer with a strong contrast between its monomer units formed by iCVD has been reported to mitigate protein adsorption.[22] The casting of similar polymers into thin films by solution methods is difficult and yields rough and uneven coatings,[99] which makes CVD an ideal method to form such films, while the functionality retention characteristic of iCVD is crucial to retain the hydrophobicity contrast. This study reports the formation of random copolymers of hydroxyethyl methacrylate (HEMA), a hydrophilic polymer, and perfluorodecyl acrylate (PFA), a perfluorinated, highly hydrophobic monomer by iCVD.[22] Quartz crystal microbalance (QCM) experiments to quantify protein adsorption showed that films that contain approximately 40% PFA in their structure adsorb less protein than either of the homopolymer films, including the highly hydrophilic PHEMA film (Fig. 7c). This is a demonstration of the use of molecular heterogeneities to prevent protein adsorption, and a starting point for a novel chemical method for fouling prevention.

Switchable coatings

Another approach to modulating protein adsorption involves polymeric surfaces that change their surface energy in response to external stimuli such as temperature, ionic strength and pH.[100] These types of surfaces switch between a highly hydrophilic state, where protein and microbial adhesion is largely prevented, and a hydrophobic state where large quantities of biomolecules adsorb onto the surface. The switch to the hydrophilic state often also involves a large degree of swelling.[101] For most applications, this transition must not cause the denaturation of proteins or cause cell death, which makes extreme changes in pH and ionic strength, and temperature transitions significantly above body temperature, undesirable.

Poly(*N*-isopropylacrylamide) (PNIPAAm) has a lower critical solution temperature (LCST) at approximately 32 °C in water.[102] This means at temperatures below 32 °C, it is in a highly hydrophilic, swollen state. Above this temperature, it transitions into a collapsed form exhibiting isopropyl groups on the surface. This makes it an important candidate for coatings that shift between hydrophilic and hydrophobic properties in response to

temperature. Therefore, PNIPAAm coatings and brushes have been studied extensively in the literature.[1,103]

PNIPAAm films are used for easier cleaning of surfaces and removal of biofilms without using chemicals and other environmentally hazardous methods.[101] In addition to reducing the surface energy driving force for fouling, swelling of the film can serve as a mechanical push for the removal of adsorbed proteins and microorganisms. This results in effective removal of foulants.[101,104]

In addition to fouling release, systems incorporating PNIPAAm layers can be used as protein "traps". For example, to capture proteins within microfluidic channels coated with high-density PNIPAAm brushes, heater lines were incorporated into the device. To trap the proteins, these lines were heated above the LCST of the polymer. To release and collect the proteins, heat was turned off and the cooling resulted in the detachment of proteins. The PNIPAAm brushes in this study were grafted from SAMs with initiating groups in microfluidic channels,[105] PNIPAAm coatings have also been used for the harvesting of tissue constructs without damaging or disturbing the extracellular matrix (ECM). In this application, the tissue scaffolds are coated with PNIPAAm, and cells are grown in the scaffold above the LCST of PNIPAAm. To harvest the cells, the system is cooled below the LCST. The coating becomes hydrophilic and swells, detaching the biofilm.[106,107] Some groups have combined PNIPAAm with other hydrophilic, fouling resistant functionalities such as PEG[108] and zwitterions[109] aiming to enhance this effect.

How the thermoresponsive films are formed can have a significant impact on functionality. Many researchers report the formation of brushes by surface-initiated polymerization methods,[101,104,110] including controlled polymerization techniques such as ATRP.[108] These brushes have good functionality and temperature response, and high conformality can also be achieved. Brush formation, however, requires the presence of specific functional groups on the material surface, so these approaches are strongly dependent on substrate chemistry.

Substrate independent coatings of PNIPAAm and other thermoresponsive polymers are also very promising. PECVD can form such coatings with tunable thickness, and has been applied to the formation of PNIPAAm coatings for thermoresponsive protein resistance.[111,112] The extent and sharpness of the LCST transition, however, is very strongly dependent on the retention of functionality in the polymer. Hence, the various side-reactions that occur in the plasma system hinder the functionality of these coatings, resulting in a wider temperature range through which the transition occurs.[111–113] The reversibility of protein adsorption can also be limited.[113,114]

iCVD can offer an alternative to the formation of such thermoresponsive layers for protein and biofilm removal. PNIPAAm hydrogels, cross-linked with diethylene glycol diethyl ether (DEGDVE), were deposited by iCVD, and the resultant coatings showed a sharp LCST transition as well as good protein removal by a temperature switch.[115] PNIPAAm thin films were also grafted onto patterned PDMS tissue scaffolds, and the temperature response was used to detach the tissue constructs from the templates.[107] Faster response has been achieved by grafting relatively mobile PNIPAAm chains to the base film.[116] This film structure was achieved by depositing a graded copolymer with a NIPAAm-rich surface *via* iCVD. The response time constants around the LCST were significantly smaller in the graded (<143 s) than in the homogeneous films (1000 to 8000 s). In addition to substrate independence and high functionality retention, iCVD offers high synthesis rates (up to 100 nm min^{-1}) and exceptional conformality. This would be an important advantage for commercial application of these coatings for controlling protein adsorption and biofilm formation.

Conclusions

Functional surfaces with a protein adsorption tuning capability are of great interest in fields such as tissue engineering, drug delivery, membranes for water treatment and marine antifouling. This has motivated the development of antifouling surface chemistries. However, application of these materials onto surfaces, particularly in a conformal and substrate-independent manner, presents some unique challenges. As reviewed here, significant progress has been made in the chemical vapor deposition of these chemistries toward a wider variety of substrates and better protein adsorption control. The nanostructures fabricated from antifouling materials by CVD techniques are able to enhance the performance of biosensors and reduce the risk associated with synthetic biomaterial implantations. Due to the unique capability of depositing insoluble and infusible films, CVD techniques also enable the fabrication of novel antifouling chemistries, such as amphiphilic coatings with nm-scale heterogeneities that resist protein adsorption.

Antifouling surfaces based on new functionalities have been the focus of many research groups, but a relatively small number of the many possible applications have been explored. The CVD technique can be viewed as a platform that translates the existing mechanisms and knowledge to a wider spectrum of real applied cases.[16,117]

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