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Journal of Physics: Materials

TOPICAL REVIEW

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Keywords: thin films, membranes, surface modification, vapor deposition, soft biomaterials

OPEN ACCESS

RECEIVED
19 December 2022

REVISED
28 June 2023

ACCEPTED FOR PUBLICATION
10 July 2023

PUBLISHED
8 August 2023

Abstract

Soft biomaterials are a crucial component in several application fields. They are used, for example, in biomedical implants, biosensors, drug delivery systems as well as in tissue engineering. In parallel to extensive ongoing efforts to synthesize new materials, the development of means to tailor the materials' surface properties and thus their interaction with the environment is an important field of research. This has led to the emergence of several surface modification techniques that enable the exploitation of biomaterials in a broader range of technologies. In particular, the use of functional thin films can enable a plethora of biomedical applications by combining advantageous bulk properties of the substrate (e.g. flexibility, lightweight, structural strength) with tailored surface properties of the thin film (e.g. enhancing/prevention of cell proliferation, controlled drug release). For some biomedical applications, thin films can also be the main functional components, e.g. in biosensors. The present review focuses on recent developments in the applications of soft biomaterials based on thin films deposited from the vapor phase. In the field of soft biomaterials, the possibility of depositing from the vapor phase—without the need for any solvents—offers the unprecedented benefit that no toxic leachables are included in the biomaterial. Further, due to the complete lack of solvents and chemicals overall being used in small quantities only, depositing thin films from the vapor phase can be a more sustainable choice than other techniques that are commonly used.

1. Introduction

A biomaterial is a substance designed to interact with biological systems such as living tissues or organs, and is intended to improve, replace, or augment their function. Biomaterials can be synthetic or naturally occurring, and they are used in various medical devices, implants, drug delivery systems, tissue engineering, and regenerative medicine. Soft matter, which includes liquids, colloids, polymers, foams, gels and liquid crystals, has gained attention due to the similarity of its properties with those of biological systems [1, 2]. In the year of 1991, Pierre-Gilles de Gennes, frequently referred to as the 'founding father of soft matter', received the Nobel Prize in physics for studying order phenomena within liquid crystals and polymers [3].

Among others, Pierre-Gilles de Gennes dedicated himself to the topic of polymer gels [4, 5]. Polymer gels are physically or chemically crosslinked polymer-networks with an entrapped solvent, resulting in a macroscopic viscoelastic solid-like appearance, while on the molecular length scale, a liquid-like behavior is present. If the dispersion solvent is water, such gels are called hydrogels. Hydrogels are typical examples of soft biomaterials and have pervaded our daily lives through their use in various applications, such as contact lenses, disposable diapers, and cosmetic or wound gels.

Soft biomaterials have proven their potential for versatile biomedical purposes such as drug delivery systems [6, 7], scaffolds for tissue engineering [8], biosensors and actuators, to name a few. Polymer thin

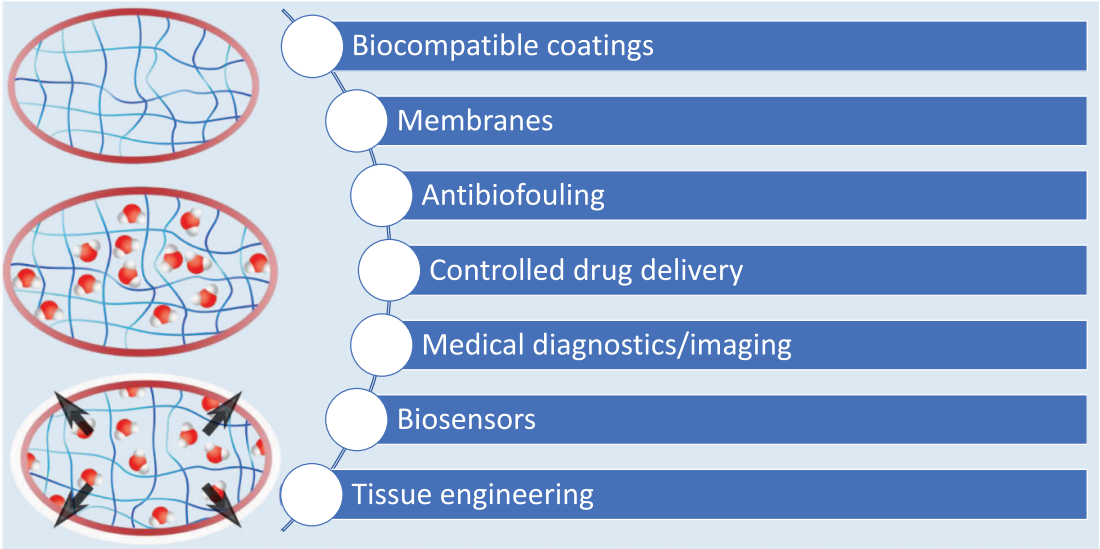

Figure 1. Image showing the application fields discussed within the review paper. On the left, a schematic of a crosslinked hydrogel is depicted as a typical example of a soft biomaterial. It swells when water molecules penetrate into the voids of the network matrix and shrinks when they diffuse out.

films, in particular, can be a versatile tool to modify the interaction of the biomaterial with the environment whilst leaving the bulk characteristics of substrate materials intact. In this way, they can alter the material properties with minimal intrusion due to their small thickness. For example, a thin film may enhance the biocompatibility of the material surface. Responsive polymer thin films can be used to create sensors on inert substrates or to design controlled drug delivery systems. Freestanding polymer thin films, e.g. membranes or scaffolds, can also be applied for drug adsorption and controlled release. Further, thin films are often more sustainable and environmentally friendly, since lower amounts of chemicals are involved in their fabrication. In some cases, they can even be recycled and reused, for example by peeling them off one substrate and applying them to another.

The formation of thin films of soft biomaterials often relies on solution-based methods [9]. Drawbacks of these techniques include the non-conformality of coatings caused by surface tension, the inapplicability to some substrates that could degrade when in contact with certain solvents, and the entrapment of toxic solvents within the polymer. Especially with biological applications in mind, the polymers must be entirely free of noxious inclusions that might get released during usage. Vacuum-based techniques, in particular chemical vapor deposition (CVD) methods, are able to forego some of these issues. CVD methods allow the synthesis of conformal, organic and hybrid thin films via a completely dry, direct deposition process. Working at low pressures, chemicals in typical CVD processes adsorb out of the gas-phase directly onto the substrate, and react with radical species or precursors activated by temperature [10], plasma [11], UV-radiation or lasers [12]. Some disadvantages of CVD methods are the costly vacuum setup, the limits in choice of chemicals due to their required vaporization characteristics, and the slow growth of films. Nevertheless, CVD techniques allow for a wide array of possible combinations of different substrates with homogeneous thin coatings of various chemical compositions.

This review aims to summarize the progress made over the past five years in the field of applications of soft biomaterials that are based on organic and hybrid thin films deposited from the vapor phase. The first part provides an overview of the methods most commonly used to deposit soft thin films, as well as a short dive into patterning techniques. Though the latter are not necessarily linked to vapor depositions, the synergy between creating patterns and coating them with a uniform and conformal film, as obtainable by vapor deposition processes, seems promising for the field of soft biomaterials. The review will continue with a section on two common kinds of soft materials frequently used in bio-applications: hydrogels and patternable polymers. Finally, the applications, including drug delivery systems, tissue engineering, biosensors and protective coatings, with self-healing, antifouling, or antimicrobial properties, will be discussed. Figure 1 shows a summary of the main application fields covered within this review.

2. Methods

This chapter provides an overview of the most frequently applied vapor-based techniques for the fabrication of soft organic and hybrid thin films. Further, the chapter briefly discusses some patterning methods for soft

biomaterials. One of the most prominent advantages of vapor depositions, especially in the field of medical and biotechnological applications, is the complete absence of solvents from the process. Solvents are a common reason for impurities, since it is impossible in practice to remove a solvent completely. The use of additional post-purification processes can lead to degradation or structural alteration of the coating and the substrate, making ultra-high purity materials very hard to obtain. The absence of solvents in vapor deposition allows for the creation of materials free of components that are hazardous to human health.

2.1. Synthesis of soft thin films from the vapor phase

Traditional thin film deposition technologies can be divided into physical vapor deposition (PVD) and CVD. PVD methods are based on the transport of material from the source to the gas phase, and eventually to the solid thin film form without (substantial) chemical reactions. Classical examples are evaporation, sputtering and molecular beam epitaxy. These methods are mostly used for the deposition of inorganic thin films, which do not fall into the category of soft materials and will therefore not be discussed further in this review. CVD processes are characterized by chemical reactions in the vapor phase, making the final material that is deposited in the form of a thin film different from the source material. Typical examples of CVD processes used to deposit soft biomaterials are discussed within the following paragraphs.

2.1.1. Initiated chemical vapor deposition (iCVD)

iCVD is well-known for being a versatile and novel technique that enables the formation of nanometric polymeric coatings from a wide variety of monomers. It has been employed in various fields, such as optics, electronics, separation technologies, the textile industry, medicine, and biotechnology. Compared to other vapor-based techniques for polymers, such as temperature-, plasma- or photo-induced methods, in iCVD, an initiator molecule activated by a hot filament acts as the promoter of a free radical chain polymerization reaction. This unique characteristic of iCVD allows the deposition of polymer thin films on various substrates, such as pharmaceutics, paper or ionic liquids, which would otherwise degenerate in harsher process environments [13, 14]. The chemical composition of the polymers retains that of the original monomers, since the monomers are not fragmented at the low operating temperatures of iCVD.

For the process, monomers and initiators which can be vaporized at reasonably low temperatures are needed. In addition, the monomers used for iCVD need to have at least one unsaturated bond, reactive for radical reactions (e.g. a C=C double bond), while the initiator needs to include a labile bond, which can be easily cleaved at low energy input (e.g. O–O in peroxides). The vapors of the monomer and the initiator are delivered to the substrate inside a vacuum chamber kept below 1 Torr (see figure 2(a)). The initiator is activated by the elevated temperature of hot wires ($T = 200$ °C–400 °C), which are usually positioned above the substrate. Changing the temperature of the hot wires allows to generate different kinds of radicals, which will in turn influence the growth rates of the polymer chains on the substrate [15]. It has been demonstrated that the polymerization takes place on the substrate surface where the monomer molecules adsorb. When an initiator radical hits a monomer molecule, it reacts by forming a secondary radical and initiating the polymerization, which then propagates to other monomer molecules. This continues until termination occurs due to the reaction between two radicals, i.e. between a growing chain and an initiator radical or between two growing chains. The adsorption process depends upon the temperature of the substrate, which is typically below 50 °C [16, 17]. An important variable to consider during the iCVD process is the monomer saturation ratio at the substrate temperature, since by controlling this ratio, it is possible to adjust the concentration of monomer at the surface [18]. The rate of the deposition has been determined to be of second order with respect to the monomer concentration, similar to the polymerization in the liquid state [16]. This demonstrates that solely the classical steps of a chain-growth polymerization occur during the process, without any unwanted side-reactions and/or fragmentations. More details on the polymerization mechanism can be found in [16].

2.1.2. Plasma enhanced chemical vapor deposition (PECVD)

In PECVD, the polymerization reaction is activated by a plasma that causes the precursor molecules to break into neutrals and ions and deposit on the substrate surface [19]. A schematic of the process is shown in figure 2(b). Organic and inorganic thin films can be deposited via PECVD. However, contrary to iCVD, organic coatings do not preserve the structure of the orginal monomer as the monomers are fragmented in the plasma and can undergo several reaction pathways in the gas phase or on the surface.

The plasma in PECVD is defined by several parameters, such as the power density, the gas type, flowrate, pressure and the employed plasma power, which, together with the geometry of the reactor, influence the properties of the coating. Low-energy plasmas are typically generated using radio frequencies, whereas high energy plasmas are generated by inductively coupled and electron cyclotron resonance plasmas [20].

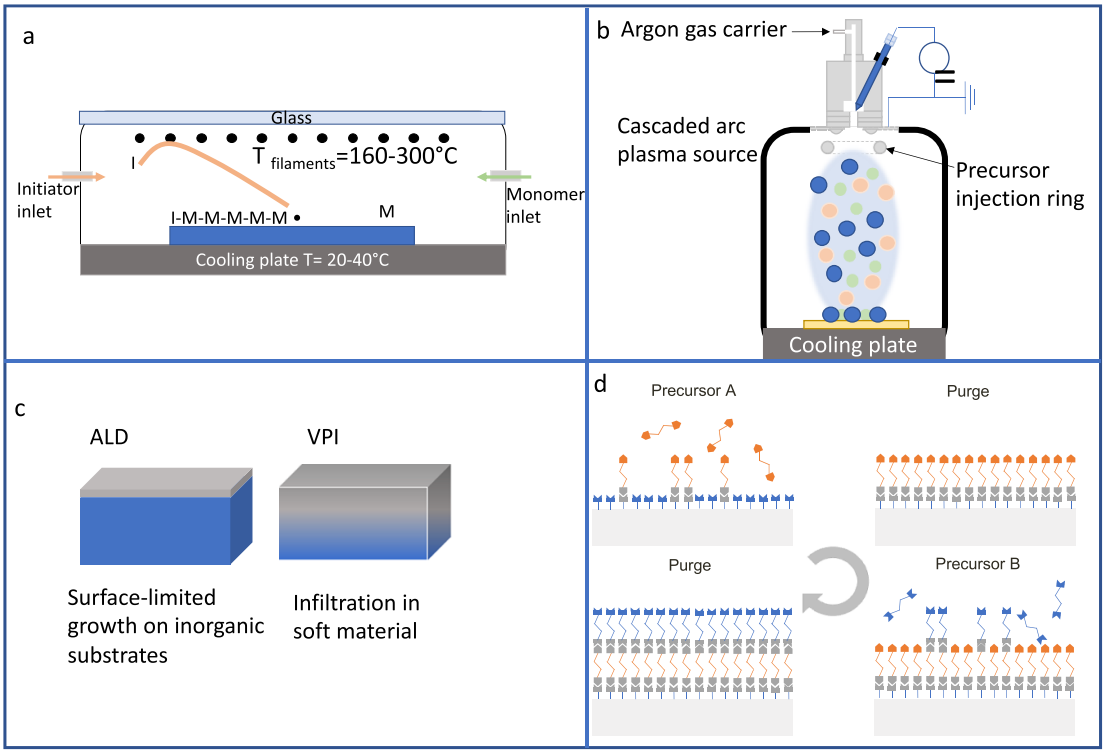

Figure 2. (a) Schematic of an iCVD setup and the polymerization mechanism. I indicates the initiator and M the monomer molecules. (b) Schematic of a PECVD setup. The blue, orange and green circles represent the electrons, ions and neutrals typical of the plasma phase. (c) Difference between an ALD and a VPI process. (d) Schematic of an ideal MLD cycle.

To start a PECVD process, a vacuum chamber is first fed with the reactive gases and vapors. When the plasma generator is turned on, electrons start travelling from one electrode to the other, colliding with gas molecules and establishing the plasma phase. Electrons in a plasma possess high kinetic energies, which they transfer to the gas molecules via electronic collisions, causing ionizations and decompositions. For fragmentation reactions and excitation processes to take place in a plasma, the energy transferred via electronic collisions to the molecules must be higher than the activation energy required for that specific reaction or excitation process. For example, electronic collisions with ions can induce charge exchange reactions that cause the formation of charged species from neutral molecules, which then form radicals via dissociative recombination with low energy electrons. More details on the deposition mechanism can be found in [19]. In terms of precursors, PECVD offers much higher versatility than iCVD. In fact, any substance that can be vaporized could be polymerized or reacted in a plasma, whilst in iCVD, at least one unsaturated bond is needed.

The plasma bulk in total is neutral. When it meets a solid surface, a boundary region is created. If the surface is at a floating potential within the boundary region, the net current is zero and the space charge will increase to balance the flow of ions and electrons. This leads to ion bombardment on every surface exposed to plasma. Ions hitting on the substrate surface generate active sites via surface atom displacement, which act as anchors for film growth. The fragmentation of the monomer in the plasma phase is recognized as the limiting step, rather than the mass transport to the substrate. Due to the low heat generation inside the plasma, PECVD is compatible with thermosensitive substrates such as polymers, and can create thin films at low pressures and under conditions where growth could usually only happen at higher temperatures. Furthermore, the high energy of the electrons in a plasma enables the polymerization of species in which all bonds are saturated and therefore quite inert to other techniques such as iCVD. This makes PECVD highly versatile, which is why the method is often used for the fabrication of soft biomaterials [21].

2.1.3. Atomic layer deposition (ALD) and vapor phase infiltration (VPI)

Even though ALD and VPI are techniques applied to deposit inorganic, rather than polymeric, materials, they can be used for the surface modification of soft materials or for their transformation to hybrid inorganic-organic materials, where, in both cases, the soft nature of the material is retained. ALD is a cyclic process that relies on temporarily separated and self-limiting surface reactions between reactive vapor-phase precursors and surface functional groups. Due to the self-limiting nature of the reactions, i.e., the reaction

stops once the surface is saturated with adsorbed precursor molecules, thin films can ideally be grown monolayer by monolayer, which enables precise control over their thickness. A typical ALD cycle consists of four steps: (I) dosing of precursor A, (II) purge, (III) dosing of precursor B, (IV) purge. In the case of metal oxide thin films, precursor A is usually a metal-containing molecule and precursor B, often referred to as co-reactant, is either water vapor or oxygen plasma. During step I and III, the precursors react with the functional groups on the surface. The purge steps in between the precursor doses are essential to remove any unreacted precursor molecules and reaction by-products to retain the self-limiting nature of ALD, and distinguish the technique from other CVD methods where both co-reactants are present in the chamber at the same time, resulting in a continuous film growth. The portfolio of materials that can be deposited via ALD encompasses many inorganic materials, i.e. metals, metal oxides and nitrides in both their crystalline and amorphous phase. More details on the growth mechanism can be found in ref [22]. Since the process is already inherently slow due to its 'layer-by-layer' growth mechanism, the precursors need to have functional groups that quickly react with the functional groups on the surface.

While ALD produces dense, highly uniform and conformal thin films on inorganic substrates, soft polymeric materials prove porous to most of the commonly used ALD precursors, ultimately resulting in sub-surface diffusion and growth and a loss of ALD's surface saturation characteristics [23]. Several research groups recognized the potential of this non-ideal ALD behavior for the hybridization of polymeric materials with inorganic infiltrates. The underlying mechanism can be described as a solution-diffusion of the precursor into the polymer matrix, followed by either physical entrapment of the precursor or its reaction with functional polymer groups, resulting in a hybrid material with strongly modified properties. To maximize the infiltration, long precursor exposure times are used (up to several hours compared to typically less than a second for ALD), sometimes in combination with multi-pulsing schemes, i.e. each precursor is delivered in several consecutive pulses before switching to the respective co-reactant (see figure 2(c)).

Such infiltration schemes can be encountered in literature under several different names, e.g. sequential infiltration synthesis, multiple pulsed infiltration or sequential vapor infiltration, but have been unified under the term 'vapor phase infiltration (VPI)' by Leng and Losego, who published a comprehensive review paper on this subject in 2017 [24].

Despite having evolved from ALD and sharing several process characteristics with the technique, the kinetics of VPI are fundamentally different from ALD. VPI is commonly used to produce hybrid organic-inorganic materials. By infiltrating a soft material with inorganic species, its properties can be dramatically altered in a top-down fashion, e.g. several studies demonstrated that VPI of a metal oxide can strongly enhance the mechanical strength of synthetic as well as biopolymers [25, 26].

2.1.4. Molecular layer deposition (MLD)

Another thin film technique that is closely related to ALD is MLD. While ALD is a powerful tool to deposit inorganic materials, MLD uses the same cyclic process with different precursors for the deposition of organic thin films via condensation polymerization reactions. Instead of monolayers of atoms, MLD processes assemble molecular fragments in a layer-by-layer fashion.

MLD of purely organic films dates back to the 1990s, when the research group of Sotoyama first reported the deposition of polyimide through layer-by-layer growth [27]. Since then, a variety of polymers have been deposited by MLD. Most commonly, homo-bifunctional monomers are used as precursors (e.g. pyromellitic dianhydride and 4,4′-diaminodiphenyl ether to obtain polyimide). However, the use of other precursors, such as homo-trifunctional, hetero-bifunctional or ring-opening molecules, have been reported as well. In order to be compatible with MLD, precursors need to have a sufficiently high vapor pressure (ideally $>$ 100 mTorr), good temperature stability and a high reactivity to their coupled co-reactant. A schematic of a typical MLD process using homo-bifunctional monomers as precursors can be found in figure 2(d). For a comprehensive list of MLD processes and materials, the authors would like to refer the reader to the review paper by Meng [28].

By combining organic precursors from MLD with inorganic precursors from ALD, hybrid films can be deposited. In many cases, these hybrid processes are included in the definition of MLD, but since MLD would strictly speaking only encompass processes that result in the deposition of purely organic films, the term ALD/MLD seems more appropriate. The most important class of hybrid MLD/ALD materials are metal alkoxides, commonly referred to as 'cones' due to their structural similarity to silicone. They are deposited by coupling a metalorganic precursor typically used for ALD of metal oxides with, for example, a diol. Prominent examples are alucone (e.g. using trimethylaluminum and ethylene glycol) [29–31], zincone [31, 32] or titanicone [31, 33].

By using more than two precursors (e.g. one metal containing and two organic ones in a three-step ABC reaction cycle), thin film mixtures, superstructures and nanolaminates can be deposited with exact control

over their composition. MLD/ALD also opens up possibilities to produce many other promising hybrid materials, e.g. metal-organic frameworks [34].

2.2. Patterning methods

The possibility to pattern soft materials is extremely important for applications in the bio-realm. For example, hydrophobic-hydrophilic patterns have proven effective for enhancing cell attachment and growth [35]. In addition, patterning methods can be combined easily with vapor deposition to enhance thin film properties. Though not the focus of this paper, it is for this reason that this section briefly reviews the most frequently used patterning techniques that can be applied to the field of soft bio thin films. The polymeric materials that can be patterned or used for patterning will be discussed in more detail in chapter 3.

2.2.1. Direct laser writing (DLW) (two-photon polymerization (2PP))

2PP is a DLW technique based on two-photon absorption processes that locally initiate a radical chain polymerization reaction of a photoresist material. During two-photon-absorption, a molecule is excited from the ground state to a higher lying energy state by absorbing two photons of the same or different frequencies simultaneously [36]. The difference in energy between the two states is equal to the sum of the energies of the two photons [37]. The process strength depends on the square of the light intensity and is therefore a second order and non-linear optical process.

To achieve a patterned surface, a substrate coated with a photoresist, which usually comprises the monomers and a photoinitiator, is exposed to a laser beam. The photoresist is transparent to the wavelength of the laser. The laser beam then locally excites a highly confined sub-micrometer volume within the photoresist. To generate high resolutions, a pulsed fiber laser is used to deposit photons in femtosecond pulses on the sample [36]. Two-photon absorption can be restricted to such a small voxel size because the threshold for two-photon absorption to occur scales with the square of the intensity. The focal spot of the laser is then moved to other specific sites of the photoresist via a laser lithography system. The molecules within the photoresist absorb two photons simultaneously, therefore, the effective wavelength at the focal side is equal to the half of the wavelength of the laser beam. Upon absorption, the photosensitive molecules, also known as photoinitiators and photosensitizers, produce reactive species which drive the chain polymerization process between neighboring monomers. The unexposed part can then be removed through dissolution in a suitable solvent.

2PP allows to polymerize a photoresist with high precision and resolution. This printing technique allows to fabricate 3D structures with sub-100 nm resolution. No photomask is needed for the patterning. It is, however, a slow process and can only be realized with special, as well as expensive, equipment [37]. Furthermore, the resolution limit highly depends on the photoinitiator, the composition of monomer/polymer in the photoresist, and the laser system itself. As a result, material selection is a key element to achieve a proper resolution.

2.2.2. Nanoimprint lithography (NIL)

In NIL, patterning is achieved by applying pressure against a resist with a mold exhibiting the desired 3D pattern [38]. The resin typically consists of softened thermoplastic polymers or liquid polymer precursors. For example, PMMA, a thermoplastic material frequently used for NIL, is heated above its glass transition temperature and pressed against the mold. After the polymer is cooled down below its glass transition temperature, the mold is removed and a negative imprint is left behind, according to the surface pattern of the mold [39]. This specific process is also known as thermal NIL. Instead of thermoplastic films, polymer precursors can also be used in this technique. Such precursors are UV-photocured in order to achieve the desired pattern, a method referred to as UV-NIL.

The feature size, and therefore the resolution of the patterning, depends on the surface pattern of the mold. Such molds can be produced either by direct patterning of rigid materials, such as silicon or quartz, via electron-beam- or ion-beam-lithography, or via indirect patterning by double replication of hard masters, using heat-softened materials [40].

NIL is a popular technique to achieve patterns in the sub-10 nm range at low costs with a high throughput rate [41]. Furthermore, two very special benefits of NIL are the ability to pattern complex 3D structures and large areas [42]. One problem that is frequently encountered with this method is that the mold needs special treatment to remove residuals from the films after use, consequently reducing their lifetime and, therefore, limiting the productivity [43]. Further, additional techniques such as EBL are required to generate suitable molds in the first place. Other drawbacks are the difficulties in the overlay alignment and defect control that this method comes with [42].

2.2.3. Photolithography

In photolithography, patterns are achieved by exposing certain areas of a monomer-, oligomer- or polymer-coated surface to photoirradiation [38]. Area-selectivity can be achieved by applying a photomask to the photoresist. The irradiation triggers photopolymerization, photo-crosslinking, functionalization or decomposition reactions, or induces a phase separation in the exposed areas. After irradiation, the unexposed or exposed area, depending on the used photoresist, can be removed by dissolution in a suitable solvent.

Since photolithography is an optical process, the resolution of the patterning is limited by the Rayleigh-Abbe diffraction limit. To achieve even smaller resolutions, advanced setups using small wavelength light sources, e.g. extreme UV or x-rays, and different photoresists have been designed [44]. The most common techniques to obtain resolutions below the Rayleigh-Abbe diffraction limit with photolithography include optical proximity correction, introduction of an artificial phase shift, immersion, and double exposure and double patterning [45]. If all influential parameters, such as the setup, the wavelength, the photoresist etc. are optimized, resolutions down to 9 nm can be achieved. However, such high resolutions come with higher costs, which is why larger patterns with resolutions around 50 nm are more economical to produce with the method of optical photolithography [44].

For these feature sizes, photolithography is a cost-effective, high-throughput technique that is suitable for large-area surface patterning with good alignment, controlled topography and a broad range of manufacturable features [38]. However, there are still difficulties in patterning functional polymers without influencing their characteristics. It is, for instance, not possible to apply photolithographic processes to bioactive materials which are sensitive to UV-irradiation, or to the photoinitiators and solvents used in the developing process.

2.2.4. Electron-beam lithography (EBL)

EBL is another direct writing method that can be applied to thin films of electron-sensitive resists. A pattern is achieved by precisely moving an electron beam via electronic lenses over the surface. The electron beam locally polymerizes or decomposes the resin.

EBL is a method with a minimum resolution of less than 10 nm, high accuracy and low defect density [44]. Unlike photolithography, EBL does not require the use of a photomask. However, the method comes with long processing times and high costs, making it unsuitable for large-area surface patterning [39]. To improve the throughput rate, concepts of multi electron-beam direct write systems (>10 000 beams) have been introduced. To avoid interferences from scattered electrons and secondary electrons, the system must be equipped with proper shielding.

3. Materials

Depending on the specific application case, a wide range of different organic and hybrid materials are used. Due to their responsiveness to multiple stimuli such as temperature and humidity, hydrogels are a class of materials of particular interest for various applications based on soft biomaterials. Though hydrogels are not the only type of soft biomaterial, they make up a large proportion of them. For this reason, the following chapter of this review is dedicated to discuss the fundamental characteristics of hydrogels, and presents an overview of the different stimuli that hydrogels can be designed to respond to. As mentioned earlier, the use of patterning methods on polymers has become a relevant field of research over the past years as well. Therefore, the second part of this chapter briefly discusses the materials frequently mentioned in the context of patterning methods such as DLW and lithography.

3.1. Hydrogel thin films as soft biomaterials

Hydrogels are polymers that can take up significant amounts of water from the environment into their structure, resulting in an expansion in size (i.e. swelling). Their ability to take up water stems from functional groups such as $–NH_2$, –COOH, $–CONH_2$, –CONH–, as well as the capillary effect and osmotic pressure [46].

To ensure mechanical integrity during swelling, the individual macromolecular chains need to be crosslinked. A distinction is made between physical and chemical crosslinking. Examples for physical crosslinks are hydrogen bonds, ionic complexes and entangled macromolecular chains. Such crosslinks are strongly dependent on the chemical structure of the used polymer and the polymerization process itself. In chemical crosslinking, the individual macromolecular chains are connected via covalent bonds. Such crosslinks can, for example, be achieved by copolymerizing a monomer that can link two separate macromolecular chains with the monomer exhibiting the desired functionalities. The resulting polymer can be viewed as a crosslinked network of macromolecular chains (i.e. polymer-mesh or -network). The crosslinks limit the extent of (elastic) deformation that the polymer can undergo. Further, the hydrogel exhibits a certain degree of solubility, originating from the hydrophilic units within its macromolecular

chains. Both these properties of solubility and the limit of deformation result in the distinct mesh size of the polymer network, which in turn influences the maximum amount of water the hydrogel is able to take up in equilibrium [47]. Thus, the swelling behavior of hydrogels depends on the chemical nature of the polymer and the degree of crosslinking.

The development of the entire field of hydrogel materials was first initiated in 1960 by Wichterle & Lím, who reported on the polymerization of poly(2-hydroxy- ethyl methacrylate) (pHEMA) as a water swollen, elastic and clear gel [48]. Over the years, numerous chemical structures of polymers were found to exhibit similar functionalities. Their biocompatibility, together with other favorable characteristics, have lead to hydrogels being deemed as promising for their usage in treating or replacing biological tissues and organs or, more generally, for all kinds of applications that interact with biological systems [49]. They are, for example, a material of choice for producing scaffolds for tissue engineering [37]. Hydrogels can be divided in two main categories: (1) synthetic hydrogels and (2) natural polymers and proteins. The most versatile and commonly used synthetic hydrogel is polyethylene glycol (PEG), which has the advantage of being a low-cost material [37]. To date, hydrogels are used to provide an aqueous/wet matrix or environment in many biological settings. The described properties enable their application in contact lenses, wound care coverings, in setups for the controlled release of drugs, as matrices for cell encapsulation, etc. [46, 49]. A subclass of polymers that is particularly interesting and promising for broadening the range of possible applications in this context is referred to as smart hydrogels.

3.1.1. Smart hydrogels

Hydrogels exhibiting elements that actively change upon exposure to an external stimulus are named stimuli-responsive or smart hydrogels. Such materials can be utilized, inter alia, in the field of soft robotics, where sophisticated interfaces between robots and humans need to be developed. Furthermore, their inherently responsive behavior makes them interesting for sensing and actuating applications in general. Nature itself has already evolved stunning smart hydrogels within living tissue. Nearly every cell within the body contains an extracellular matrix comprised of collagen protein fibers which embed water and further exhibit responsive behaviors, such as an elastic response to strain in cartilages. The understanding of matter found in nature, its structures and properties plays an important part in the design process of new materials with advanced functionalities [50, 51].

Next to materials of macroscopic physical dimensions, thin films are being applied in ‘smart’ setups for miniaturization and optimization purposes. In diffusion-driven processes, especially those where kinetic aspects are relevant, the size of the structures involved plays a critical role.

Besides yielding an aqueous matrix for certain applications, a further asset of stimuli-responsive hydrogel materials is their ability to respond to the environment by changing some of their properties, the most obvious of which are their physical dimensions. This behavior can be directly utilized to apply hydrogels as the active material in sensor and actuator setups. Smart hydrogels exhibit a change in their swelling when exposed to a certain stimulus, such as humidity, pressure, light, pH, electromagnetic fields or temperature.

In the following sections, temperature-, pH- and light-responsive hydrogels shall be discussed briefly. In fact, materials that are able to respond to an external stimulus, such as temperature [52, 53], pressure [54], electric or magnetic fields [55, 56], light [57] or a chemical compound [58], are already the essential basis for many applications, including sensors, actuators or active coatings, among others.

3.1.1.1. pH-responsive hydrogels

The polymer-chain of a pH-responsive hydrogel is characterized by weak acid (or base) functional groups. With a changing pH value, such polymers exhibit a phase transition at the material’s dissociation constant pKa.

If the functional groups are acids, then the acidic groups are fully protonated and oriented towards each other below pKa. This results in a collapsed and shrunken hydrogel. Above pKa, the acid group releases a proton, resulting in ionized side chains within the polymer which repel each other, creating open voids in the hydrogel where water molecules can be incorporated. On the other hand, when the functional groups are bases, the groups will be protonated, hence swollen, at pH below pKa , while the groups deprotonate back at pH above pKa resulting in a collapsed state.

3.1.1.2. Temperature-responsive hydrogels

Temperature is the most studied of all possible stimuli of responsive hydrogels [59, 60]. The swelling of temperature-responsive hydrogels in the temperature domain exhibits a phase transition at a critical temperature. If the system changes to a phase separated, i.e. a shrunken or collapsed state, when exposed to heating, the critical temperature is called lower critical solution temperature (LCST), while if the hydrogel

changes from a shrunken to a swollen state with increasing temperature, the critical temperature is called upper critical solution temperature (UCST).

The best explored temperature-responsive hydrogels are polymers containing N-isopropylacrylamide (NIPAAm) [61]. When immersed in water, the polymer contracts upon heating and swells upon cooling in a fully reversible fashion. With a typical LCST of around 32 °C in water, these polymers sparked particular interest in the field of biomedicine.

3.1.1.3. Light-responsive hydrogels

Light-responsive hydrogels are polymers containing light-responsive groups (e.g. azobenzene, diazocine, spiropyran) in their structure [62]. These could be functional groups that undergo either isomerization or crosslinking upon light stimulation. The light-induced response can be reversible (like in the case of isomerization) or irreversible, and may induce changes in the wettability of the polymer, in its viscosity, or in its shape. The advantage of using light as a stimulus to trigger a response is that it can be easily focused so that only a small area of the polymer is stimulated. Light-responsive hydrogels are interesting for a variety of applications, including shape-memory systems [63], molecular machines [64] and drug delivery systems [65, 66].

A novel approach controlling hydrogel swelling by light was reported by Coclite´s group [67]. The light-responsive hydrogel was produced by post-functionalizing a copolymer of 2-hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) with azobenzene, a photoswitchable molecule that undergoes a reversible photoisomerization upon illumination with UV or blue light. To achieve the functionalization, first, a thin layer of pentafluorophenyl acrylate was deposited on the copolymer followed by a substitution of the pentafluorophenyl groups with azobenzene. It could be shown that the photoisomerization influences the polarity of the hydrogel which, as a consequence, changes its affinity to water and its degree of swelling.

In subsequent years, Faupel´s group optimized two main elements in the concept of light-responsive hydrogels [68]. The first was to integrate the post-functionalization with the photoresponsive compound into the overall vapor deposition process. This was achieved through a sublimation unit coupled directly to the reactor and using a carrier gas to transport the photoresponsive compounds into the reaction chamber. The second consisted of changing the photoresponsive compound of the light-responsive hydrogel from azobenzene to diazocine [69]. Similar to azobenzene, diazocine experiences a reversible photoisomerization, but in contrast to azobenzene, the stable state of diazocine corresponds to a compact structure and the wavelength needed to trigger the photoisomerization is within the visible spectrum. This alleviates the risk of damaging pharmaceutical compounds or living cells during light irradiation, making the diazocine system an attractive candidate for drug release applications.

3.2. Patternable polymers

This section aims at giving an overview of the materials used for patterning soft biomaterials with the methods discussed previously in section 2.2.

A material intended to be structured with DLW must contain a mixture of monomers and oligomers transparent at the two-photon absorption wavelength ($\lambda/2$). Further, the resist is required to contain a photoinitiator, which absorbs the laser beam and provides the reactive species to start a polymerization process. [37] The photoinitiator must be transparent at the laser wavelength and have a high two-photon cross section, a high radical quantum yield, and not to mention have the ability to generate highly active radical species [37].

Besides the need to meet all these criteria, there is an increased interest in biocompatible materials for DLW. Dyes such as Bengal Rose, Eosin, Nile Red, biomolecules such as flavin mononucleotide, but also novel, synthetic photoinitiators are often used [37].

Acrylate photopolymers were one of the first materials to be used in 2PP. Such materials are low-cost, easily available, transparent in the visible and near infrared range, chemically and mechanically stable after polymerization, and they further allow rapid polymerization with low shrinkage. In the context of bio-applications, acrylate photopolymers have been used mostly for cell migration, as stated by Selimis *et al* [37]. Photosensitive hybrid materials are frequently used as well, examples being silicate-only based photopolymers like ORMOCER® and its different formulations, which can be applied as scaffolds for biomolecular immobilization and cell growth applications [37].

Patterning via NIL is compatible with a variety of biomaterials [70]. As specified by Guo [71], Poly(methyl methacrylate) (PMMA) has been a widely popular thermoplastic polymer used for NIL despite its requirements for high operating temperature (∼200 °C) and pressure (∼2000 psi). Polystyrene (PS), polycarbonate and poly(vinyl alcohol) are also frequently used for patterning with thermal NIL [38].

In contrast to thermal NIL, UV-NIL enables the use of liquid precursors at lower temperatures. Most UV-curable liquid resists are based on the free radical polymerization of acrylic and methacrylic monomers. These materials are favored due to their high reactivity but pose the disadvantage of being highly sensitive to oxygen inhibition. Guo and his group [71] developed a UV-curable epoxysilicone material based on cationic crosslinking of cycloaliphatic epoxies, which is, in contrast to the free radical polymerization of acrylate monomers, not prone to oxygen inhibition, and therefore, less defects can be expected.

Photolithography is another versatile method applied in biomedical applications, for instance in tissue engineering or biosensors. It has been used to pattern biomaterials such as proteins, cells and extracellular matrices. In the case of biosensors, micropatterning of hydrogels via photolithography has been employed. For example, some studies displayed the application of Poly(ethylene glycol) (PEG) hydrogels as biotin-streptavidin biosensors by a combination of surface graft polymerization and photolithography [72]. Multifunctional hydrogel microparticles have also been generated by photolithography and used in bioassays. Negative photoresist-like polymer systems were created in which crosslinkable PEG-triacrylates served as photosensitive units and long-chain polyvinylpyrrolidone (PVP) served as the supporting scaffold [70].

In the case of cell patterning, typically used materials include synthetic hydrogels (e.g. PEG or poly-N-isopropylacrylamide), biological hydrogels like chitosan, and biohybride hydrogels, such as PEG-based hydrogels modified with peptide Arg-Gly-Asp (RGD) [38].

4. Applications of soft biomaterials

The following chapter provides an overview of the wide range of applications of soft biomaterials from thin films, structured according to application case. For each case, applications resulting from the different vapor-based techniques will be discussed. While iCVD, PECVD and MLD produce purely organic, soft materials, ALD/MLD and ALD/VPI processes deal with hybrid or inorganic structures whose inclusion in this review requires an explanation. ALD of thin inorganic films on soft biomaterials, for example, can be a powerful tool to achieve surface functionalization, modifying properties such as wettability, bioactivity, bacterial or fungal adhesion, or cell attachment for applications in tissue engineering or medical implants. Several metal oxides that can be easily deposited by ALD (e.g. TiO_2 or Al_2O_3) exhibit excellent biocompatibility, antimicrobial activity and non-toxicity [73, 74], making them attractive candidates for biomedical applications. Since the softness of the polymer substrate is retained when using very thin films, applications based on the surface functionalization of soft biomaterials by ALD are also included in this review. The same reasoning can be applied to VPI and ALD/MLD processes where the resulting hybrid materials can be classified as soft. In addition, it should be noted that in the case of soft substrates, there is no clear dividing line between ALD and VPI, as already briefly mentioned in section 2.1. Due to the polymers' porous nature, a VPI component is always present, though its extent strongly depends on the reactivity of the polymer to the used precursor gases as well as on the process conditions (such as exposure times). In many published works on ALD, the possible presence of infiltration in addition to surface growth has not been discussed or quantified.

4.1. Biocompatible coatings

For materials to be used in biological systems for therapeutic or diagnostic medical applications, biocompatibility is a fundamental requirement. Depending on the specific application cases, further material properties such as bioactivity, good cell adhesion, antibacterial or antifungal characteristics, or corrosion-resistance may be desired. Since all these properties are surface-related, an efficient and versatile tool to tune them is the application of biocompatible coatings to achieve a functionalization of the surface. For example, changing the surface wettability, surface charge or available surface functional groups can have a strong influence on cell adhesion and growth [75, 76]. Vapor-based deposition techniques are perfectly suited for the task due to the wide range of materials that can be deposited, their outstanding conformality and uniformity, and due to the precise thickness control of the coatings. For some techniques, such as VPI, ALD and MLD, the chemisorptive nature of the surface reactions additionally provide a strong adhesion of the coatings to most substrates [77].

4.1.1. iCVD

Silicon-based hybrid polymer thin films, such as polysiloxanes and polysilazanes, are frequently discussed as applied biomaterials, owing to their insolubility, chemical inertness, and non-toxicity, amongst others. They can be readily synthesized by iCVD and their use as biocompatible coatings, e.g. for drug delivery, has already been demonstrated [78]. Other recent biocompatible coatings produced by iCVD were based on pyrrolidone, which, to give an example, was grafted on the surface of catheters [79]. This enhanced the biocompatibility of

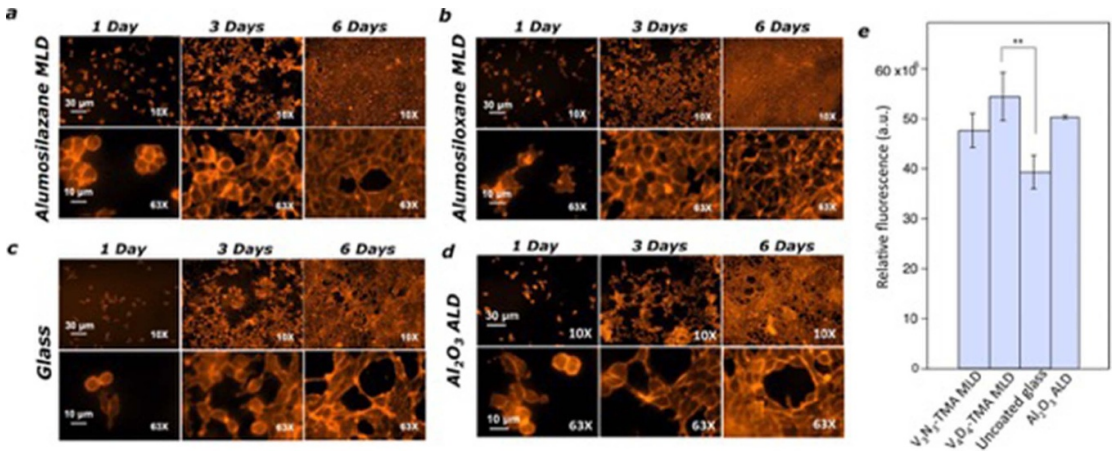

Figure 3. Biocompatibility evaluation showing confocal microscopy images of Human Embryonic Kidney293T (HEK293T) cells, cultured for 1–6 d on (a) MLD SiAlCNH, (b) MLD SiAlCOH, (c) uncoated glass coverslips (control group), and (d) ALD Al_2O_3. The cells were stained with CellMask Orange plasma. (e) Fluorescence intensity calculated from confocal images of HEK293T cell proliferation after 6 d of culturing. Reprinted with permission from [81]. Copyright (2018) American Chemical Society.

the material during a 4 week *in-vivo* test. Another example of a bio-based polymer film obtained by iCVD was provided by Graur *et al* [80], who deposited Poly(tulipalin A) with advanced material properties, such as a high glass transition temperature, high thermal stability, optical transparency, and solvent resistance.

4.1.2. ALD/MLD/VPI

The synthesis of silicon-based polymer thin films by MLD has also been investigated, for example for silicon oxycarbide (Si_2O_4C), which has been demonstrated to be stable to air, water, ethanol, hydrochloric acid, and sodium hydroxide, suggesting stability to an even wider range of acids, bases and solvents [81]. In 2020, the group of Mato Knez introduced a 'ring-opening' reaction mechanism to MLD, demonstrated this mechanism for the synthesis of Si-based polymers and studied their biocompatibility [77, 82–84]. In this fashion, alumosilazane (SiAlCNH) [84] and alumosiloxane (SiAlCOH) films [83] have been deposited. The biocompatibility of the alumosiloxane and alumosilazane thin films was tested via the proliferation of human embryonic kidney (HEK293) cells, which proved significantly higher on the MLD thin films than on the reference glass substrates after six days of culturing, forming a uniform and coherent biofilm (figure 3). A higher concentration of cells was found on the alumosiloxane films, which was attributed to the higher surface hydrophobicity, as wettability affects the adhesion of different types of cells to the surface differently [84]. The findings suggest that the hydrophobicity and therefore the cell attachment could be tunable by varying the organosilicon block length using different siloxane or silazane monomers.

Silicon-based polymers are not the only material class synthesized by the ALD/MLD method that show promise as biocompatible coatings. One study reports photoactivated MLD of an all-carbon backboned fluoropolymer, an interesting candidate for a hydrophobic biomaterial, by polymerizing an iodine-containing fluorocarbon monomer and a diene monomer in a step-growth sequence under UV irradiation [85]. Another class of compounds deposited by ALD/MLD with high potential for bioactive coatings are the so-called 'titaminates', a combination of titanium with linkers of amino acids. For the deposition, titanium tetra-isopropoxide (TTIP) was combined with glycine, L-aspartic acid, L-lysine, L-aspartic acid, L-arginine, tymine, uracil, or adenine [75, 76, 86]. Glycine, L-aspartic acid and L-arginine are part of the tripeptide 'RGD', which has been shown to promote the attachment of numerous cell types to a variety of materials. Titanium-containing coatings have also been recognized to support bone forming cells due to protein absorption [76]. The bioactivity of the titaminate films was investigated by growth of epithelial cells (rat goblet cells), and a significantly increased proliferation compared to uncoated glass coverslips was found after four days. Cell viability was high (>85%) for all substrates [76, 86].

ALD/VPI methods can also be used to functionalize the surface of biomaterials for their use in prosthetics or implants. VPI of TiO_2 into polylactic acid (PLA), a biocompatible plastic prone to degradation, was shown to enhance its tensile strength and its chemical stability [87]. Its biocompatibility and nontoxicity have been tested both *in vivo* and *in vitro*. VPI-modified bioinert poly-trivinyltrisiloxane (pV_3D_3) has also been proposed as a candidate for biocompatible coatings for prosthetic devices and implantable materials that provides better wear resistance and durability compared to its pristine

counterpart. It could be shown that upon ZnO infiltration, the elastic modulus and hardness were increased by 10.2% and 67.0%, respectively [88].

4.1.3. PECVD

PECVD has also been employed as a method to enhance the resistance of biomaterials to degradation [89]. It has been demonstrated that PECVD of biocompatible diamond-like carbon (DLC) on metal surfaces reduces corrosion, making such coatings suitable for metal implants [90, 91]. Because of the often poor adhesion of DLC coatings on metals, Figueroa *et al* [92] presented the use of polymerized organosilane films deposited by PECVD from a hexamethyldisilane (HMDS) precursor as a promising alternative. For deposition temperatures above 250 °C, the organosilane films, exhibiting a similar degree of hardness to DLC, have been shown to adhere well to a 360L steel substrate.

Another approach to improve the corrosion resistance of stainless steel was demonstrated by Ting *et al* [93], who deposited a 140 nm thick coating of plasma-polymerized hexamethyldisilazane (ppHMDSZ) by PECVD. Tests in a simulated bodily fluid (Hank's solution) showed that the coating can reduce corrosion currents by 90%. This was attributed to the fact that the ppHMDSZ layer blocks charge transfer between the steel surface and the electrolyte environment.

PECVD has been used to improve cell adhesion to different biomaterial surfaces, too. It has been shown that coatings functionalized with amine or amide groups enhance the interaction of cells with the polymer materials due to electrostatic forces and covalent bonding [94]. For example, Yu *et al* [95] used PECVD to modify the surface of carbon fiber-reinforced polyetheretherketone (PEEK) by amino groups, thus achieving improved cell adhesion, proliferation and osteogenic differentiation. Similarly, Barletta *et al* [96] demonstrated the fabrication of biocompatible amine/amide-rich coatings with a high concentration of NH groups (up to 8 at.%) on PE in a single plasma step. In contrast to the previous example, the coating exhibited low cell adhesion and proliferation. Another demonstration of enhanced cell colonization was provided by Sardella et al who coated polycaprolactone scaffolds with crosslinked poly(ethylene oxide) (PEO)-like domains distributed in gradients along the scaffold depth [97].

4.2. Membranes

Membranes serve an important role in a wide range of biomedical applications, from enantioselective membranes that allow the isolation of molecules with a specific chirality, e.g. for pharmaceutical production, to antibacterial membranes used for wound dressings.

4.2.1. ALD/MLD/VPI

Up to date, most of the approaches to fabricate enantioselective functional films involve the use of chiral templates or a surface functionalization of the substrate by self-assembled monolayers of chiral molecules. Recently, however, it has been demonstrated that well-defined enantioselective thin films can be deposited directly via ALD/MLD, with the chiral properties originating from the precursor [98]. In a first attempt, trimethylaluminum (TMA) and either the amino acid L-cysteine (LCys) or L-alanine (LAla) were used as precursors (see figure 4). Even though ideal MLD growth could not be achieved and the deposition self-terminated after ∼16 nm, the resulting films showed enantioselective properties. When dipped into aqueous solutions of either D- or L-enantiomers of phenyl-alanine (Phe) for 72 h, circular dichroism spectroscopy revealed a reproducible preference of L-Phe to adsorb onto the LCys-films (about 17%) and a preference of about 15% for the adsorption of the D-Phe enantiomer onto LAla films [99].

In a follow-up publication, Zn/Cysteine thin films were grown via ALD/MLD on various substrates, this time for both the L- and D-enantiomers. This ALD/MLD process was not affected by self-limiting behavior and in enantioselectivity tests, both types of films exhibited a preferential uptake of the L-Phe enantiomers, which was about 8% for the Zn/L-Cys surface and about 13% for the Zn/D-Cys thin film [98].

An MLD process was also used to synthesize translocation membranes, structures with nanometer-sized pores that enable the characterization of biomolecules, such as proteins and DNA, by measuring the change of ionic current as molecules translocate through the membrane. Kim *et al* [100] fabricated a thin (<10 nm) polyurea membrane using MLD

and investigated the translocation of DNA and the protein MDM2 through a 4–10 nm sized nanopore drilled into the membrane with a focused electron beam. Polyurea was chosen due to its high mechanical stability, chemical resistance, and thermal stability. Investigating the translocation of DNA and MDM2 protein through the highly negatively charged polyurea nanopores, the capture frequency of negatively charged DNA was found to be low, whereas that of positively charged MDM2 was much higher. Although the detected flicker noise (1/f noise) of 60 pA at 100 mV could not be improved, the membranes still had a sufficiently low noise level to detect biomolecules at 100 kHz signal bandwidths, proving the feasibility of the MLD-approach for the synthesis of translocation membranes.

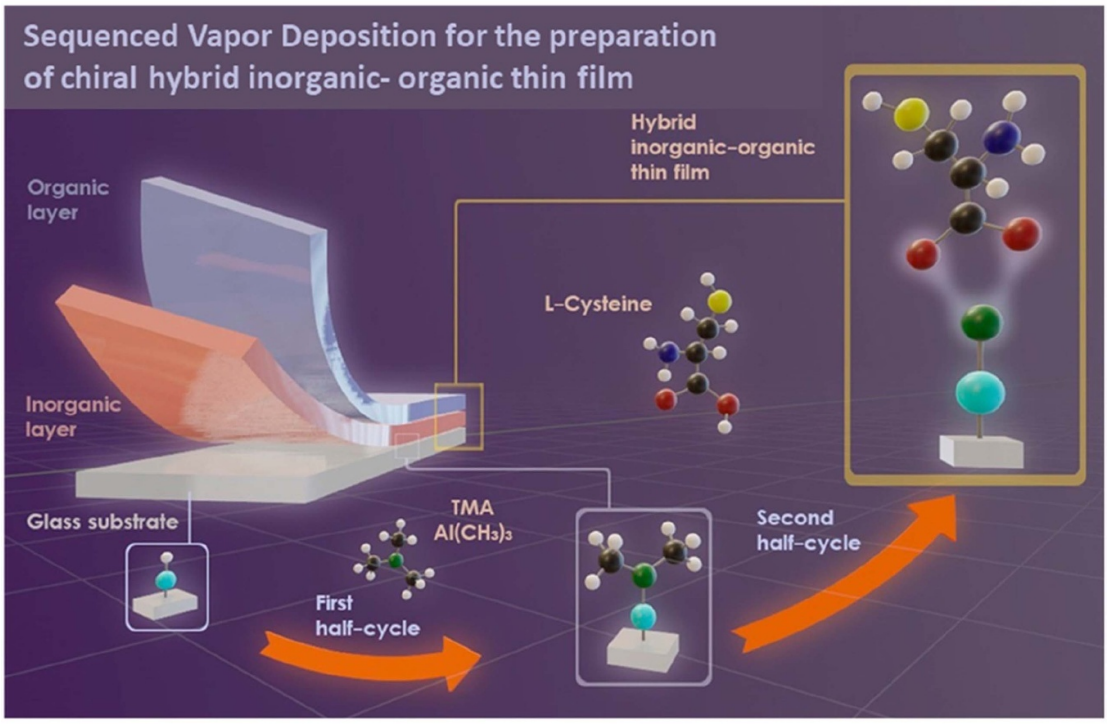

Figure 4. Schematic representing the process of depositing chiral thin films by MLD/ALD. Reprinted with permission from [99]. Copyright (2019) American Chemical Society.

4.2.2. iCVD

While ALD/MLD was used to grow free-standing membranes, iCVD was demonstrated as a promising means to functionalize existing polymeric membranes for specific application cases [101]. Wang *et al* [102], for example, reduced blood clotting of polylactide (PLA) membranes by coating them with 50 nm of crosslinked poly (methacrylic acid-ethylene glycol diacrylate), P(MAA-EGDA), with their envisioned application being in hemodialysis therapy. The P(MAA-EGDA)-altered membranes showed enhanced anti-clotting properties, inhibiting the adhesion of platelets and thus, avoiding blood coagulation.

Another use case of iCVD was found by An *et al* [103], who developed a Janus membrane, a membrane whose two sides possess different properties. It was developed by first coating a polyester fabric with hydrophobic poly (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate) (PHFDMA) via iCVD, followed by a chemical treatment of the bottom side of the membrane to render it hydrophilic and the subsequent functionalization by a gelatin methacrylate hydrogel with embedded recombinant human vascular endothelial growth factor, which has been shown to promote skin regeneration. The group could demonstrate the antibacterial properties of PHFDMA *in vitro* using *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*), and improved wound healing could be shown *in vivo* using mice.

4.3. Antibiofouling

Biofouling means the unwanted accumulation of microorganisms, bacteria, plants or algae on the surface of a solid and poses huge challenges to a variety of objects, from medical equipment and implants to textiles used in health care industry to reverse osmosis (RO) membranes used in wastewater treatment or the pharmaceutical industry. Bacterial presence, in particular, can lead to severe and dangerous infections. The sterilization of medical instruments and biomaterials has always been a latent concern since the presence of bacteria on a surface poses a high risk when it comes to medical instrumentation. Bacteria are well-known for rapid proliferation and biofilm formation, the latter of which is extremely hard to remove once formed. Intense research efforts are therefore devoted to developing anti-fouling and antibacterial surfaces, and vapor-based thin film technology has proven to be an effective tool for this purpose.

4.3.1. PECVD

PECVD is one of the techniques that have been successfully used to prepare anti-fouling surfaces [104, 105]. Kim *et al* [106], for example, applied PECVD for the fabrication of non-fouling amine-functionalized PEG thin films from a single PEG-diamine precursor and demonstrated that the surface functional group density is adjustable with the plasma power. The fabricated films could not only efficiently immobilize biomolecules

(demonstrated by immobilization of metalloproteinase-7 (MMP-7) enzyme) but also prevent non-specific adsorption. PEG-containing coatings with cell repulsive properties were also deposited by aerosol-assisted plasma depositions through dielectric barrier discharges, a novel method developed by Treglia *et al* [107].

Since fluoride has previously proven good antibacterial properties [108], Chen *et al* [109] used PECVD to deposit fluorine- and oxygen-rich coatings on high purity titanium. They could indeed demonstrate that the fluorine-coated titanium could effectively kill *S. aureus* and had satisfactory antibacterial properties. Bacterial adhesion can also be influenced by modifying the roughness and increasing the hydrophobicity of a surface. As explained by Morozow *et al* [110], bacteria are less likely to stick to a surface if its roughness has features of relief below the size of bacteria and hence minimizes the contact area between the bacteria and the surface. Morozow *et al* subjected an elastic polyurethane surface to PECVD treatment involving the plasma-chemical decomposition of acetylene in a wide electron beam of low-energy argon plasma and obtained inhomogeneous, carbon-containing nanolayers. Exploring and finding the ideal duration of the PECVD treatment of the layers, Morozow *et al* not only demonstrated that the mechanical properties of the layers improved, but their biomedical properties as well. They showed enhanced adsorption of the protein albumin and higher resistance to *E. coli* bacteria.

Reverse osmosis is a water purification process that uses a partially permeable membrane to separate ions, unwanted molecules and larger particles from drinking water. It can remove many types of dissolved and suspended chemical species as well as biological ones (principally bacteria) from water and is used in both industrial processes and the production of drinking water. Ng *et al* [111] presented a concept for a polyamide (PA) layer that incorporates titanate nanotubes (NTs) as nanofillers to form a thin-film composite RO membrane. In this innovative approach, PECVD was used to coat the titanate NTs with hexafluorobutyl acrylate (HFBA) or hydroxyethyl methacrylate (HEMA), both of which were found to enhance the membrane's water permeability by >25% and >40%, respectively, without affecting its salt rejection. Rejection of boron from the membranes embedded with HFBA- and HEMA-modified titanate NTs were recorded at 75.56% and 70.73%, respectively. Additionally, the modified membranes exhibited higher antifouling performance with >94% water flux regeneration due to their improved surface hydrophilicity. Further concepts of membrane surface modification using PECVD have been reported [112, 113].

Despite their great antibiofouling properties, titania NTs have a hydrophilic nature, making it difficult for them to be homogeneously dispersed in organic solvents for interfacial polymerization to create a RO membrane. Khoo *et al* [114] used rotating-bed PECVD to deposit methyl methacrylate on the surface of titania NTs to enhance their dispersion properties in organic solvents. The group showed that the PECVD-improved dispersion of such nanofillers in a polyamide layer of a thin film nanocomposite (TFN) RO membrane not only led to an improved membrane water flux, it further enhanced the fouling resistance. Using PECVD, the membrane flux recovery rate for the TFN was 85.77%,while it was 57.94% for the control membrane without PECVD functionalization.

Khoo *et al* [115] used 15 s and 60 s PECVD treatments with two different hydrophilic precursors, one an aniline monomer, the other oxygen, to enhance the fouling resistance and desalination performance of a commercial thin film composite extra-low energy RO membrane. Due to the polar functional groups on the surface, a 15 s plasma treated oxygen-modified membrane performed better than the polyaniline (PANI)-modified membrane, as well as the unmodified membrane. Oxygen plasma etching might lead to a smaller membrane resistance due to a lower polyamide densification. The oxygen-modified membrane was found to have a higher permeability to pure water compared to the PANI-modified membrane. Compared to the water contact angle of 88° of the unmodified membrane, the 15 s plasma-treated oxygen-modified membrane exhibited higher hydrophilicity with a contact angle of 79°. The oxygen-modified membrane showed a rejection of NaCl and Na_2SO_4 that was 4.2% and 2.6% higher, respectively, than the unmodified membrane. The fouling resistance of the oxygen-modified membrane was tested using a 1000 ppm sodium alginate solution, and it exhibited a flux recovery rate of 96%, higher than that of the unmodified membrane which only achieved 76.5%.

4.3.2. iCVD

Antifouling surfaces have been successfully produced via iCVD as well. In the work presented by Jeong's group, an array of materials, including glass, latex, polyethylene, and paper, were functionalized with antimicrobial properties. This was accomplished by immobilizing antimicrobial peptides using a film of 2,4,6,8-tetravinyl-2,4,6,8-tetra-methyl cyclotetrasiloxane deposited via iCVD. Through this approach, antimicrobial activity of >96% was obtained in a solvent-free process, highlighting its potential for the application on medical ware [116].

Another antibacterial and antifouling surface was presented in the work by Su *et al* [117], who designed a polymer out of layers with varying properties, the bottom layer consisting of a homopolymer of dimethyl amino methyl styrene, an effective bactericidal, and the top layer composed of a copolymer of dimethyl

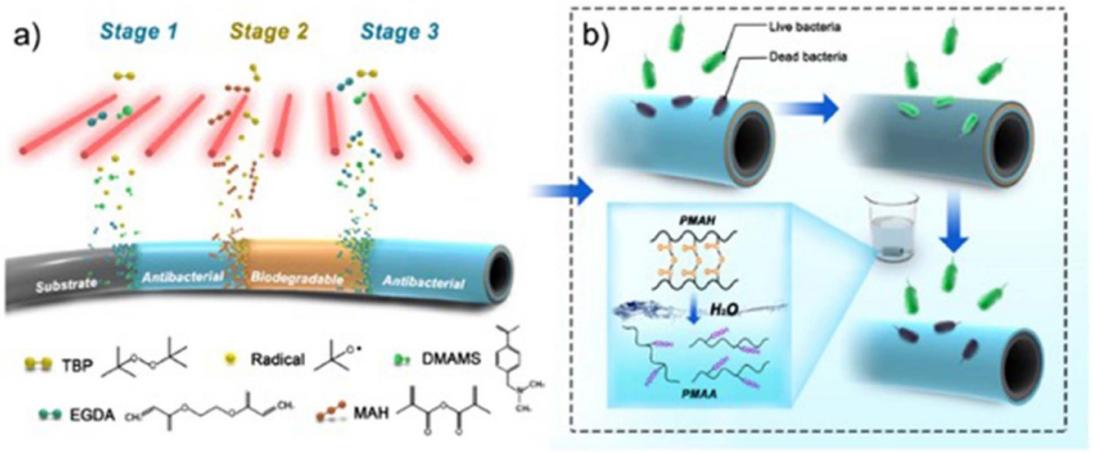

Figure 5. (a) Schematic representation of the construction of a self-regenerating antibacterial coating. (b) Schematic representation of the mechanism: after the first layer has lost its functionality, the biodegradable layer is removed by hydrolysis together with the top layer, and a new antibacterial layer is exposed. Reprinted with permission from [120]. Copyright (2021) American Chemical Society.

amino methylstyrene and hydrophilic vinyl pyrrolidone, the latter being an effective antifouling agent. Through a graded approach, both antimicrobial and antifouling properties were obtained, along with enhanced biocompatibility.

The functionalization of a surface to achieve antifouling properties has been investigated not solely with the intention to avoid the interaction with undesired microorganisms. In the work published by Hanak *et al* [118], ventricular catheters were functionalized with poly(2-hydroxyethyl methacrylate) (pHEMA) to avoid the adhesion of proteins which promotes the subsequent adhesion of specific cells. Although the functionalization of catheters to avoid infections was previously reported and even commercialized, Hanak *et al* demonstrated a new strategy using iCVD to conformally coat the catheters. Previous attempts using traditional wet-chemistry approaches failed to conformally coat the three-dimensional structures of catheters, exhibiting de-wetting defects and a lack of thickness control during fabrication. A conformal coating of pHEMA was successfully achieved across the entire structure, highlighting the advantages of iCVD over traditional solvent-based methods.

More research leveraging the advantages of iCVD was shared by Choi *et al* [119], who united selective antibacterial and cell-growth promoting characteristics in one structure. Substrates of polyethylene terephthalate (PET), polydimethylsiloxane (PDMS) and titanium were functionalized with an antimicrobial coating formed by a crosslinked ionic copolymer film consisting of vinyl benzyl chloride and 2-(dimethylamino)ethyl methacrylate. The antimicrobial properties originate from the ionic quaternary ammonium chloride moieties in the copolymer. The coating was tested with different bacterial microorganisms, and a complete annihilation of the bacteria, as well as enhanced growth promotion of cells could be shown. Though antibacterial coatings have demonstrated a high efficiency in killing bacteria and therefore avoiding biofilm formation, the bacterial cells usually remain on the surface even after being killed off, eventually leading to a deterioration in the functionality of the coating. For this reason, antimicrobial coatings are not feasible for usage over long time periods.

An appealing approach to overcome this issue was presented by Su *et al* [120]. As an alternative for the 'one-time' functionality of antibacterial coatings, a self-regenerating antibacterial coating was developed, once again using the method of iCVD, and tested on urinary catheters. The work introduces a stacked structure as shown in figure 5 with one layer consisting of a coating with poly(dimethyl amino methyl styrene) as an antimicrobial agent, and another layer with poly(methacrylic anhydride) as the biodegradable component. As the exterior antibacterial coating loses its effectivity, the biodegradable layer beneath can be degraded through the process of hydrolysis, delaminating the exterior layer and exposing the fresh antibacterial coating of the bottom. With this concept, antibacterial surfaces can be employed for longer terms in various medical devices.

4.3.3. ALD/MLD/VPI

The functionalization of biomaterial surfaces by ALD has been reported by two studies. Shahmohammadi *et al* [121] deposited mixed TiO_2/ZrO_2 on poly (methyl methacrylate) (PMMA) and demonstrated an improved wettability (by 30%), reduced bacterial and fungal adhesion, as well as decreased biofilm

formation on the functionalized PMMA. The second study, by Puvvada *et al* [122], investigated the functionalization of cotton fabric by ZnO thin films to achieve antibacterial textiles for the health care industry. They found that for 50–100 ALD cycles (corresponding to a film thickness between 10 and 20 nm), ZnO has a cytotoxic effect to *E. coli* bacteria in an aqueous solution. For thinner ZnO films (below 10 nm), however, bacterial growth was enhanced. This was attributed to the amount of Zn^{2+} ions dissolving from the ZnO films. At a low concentration, Zn^{2+} acts as a nutrient for bacterial growth, while it becomes cytotoxic towards *E. coli* at higher loadings. In pseudo-dry conditions, bacterial growth was initially enhanced for all ZnO thicknesses, presumably due to suppressed ZnO dissolution, but upon prolonged exposure of up to 1 d, an ALD treated fabric (100 cycles) showed significantly fewer colony-forming units than an untreated fabric.

4.4. Controlled drug delivery

Smart drug delivery systems enabling a controlled release of bioactive substances come with numerous advantages, among others they achieve optimal use of the drug, mitigate unwanted side effects due to a localized release, maintain drug levels within a desired range and reduce the number of necessary administrations [123]. Controlled drug release is made possible by the use of smart polymers, i.e., polymeric structures that respond to external stimuli and can thus trigger the release of bioactive substances embedded in or enclosed by the polymer. The most prominent example are hydrogels that swell or collapse in response to different stimuli such as contact with water, temperature, pH value, etc. Another approach is to tailor the dissolution rate of encapsulating polymeric coatings by tuning their properties, e.g. their thickness, crosslinking density or hydrophobicity. Solventless vapor-based techniques are ideally suited for drug encapsulation due to the absence of undesired drug-solvent interactions and their excellent conformality which allow for drug powders or small particles being coated.

4.4.1. iCVD

iCVD has been frequently used to fabricate responsive hydrogels for drug release applications due to the wide range of biocompatible monomers applicable to the technique. A detailed analysis of the factors influencing the drug release of thermo-responsive hydrogel encapsulants, performed in Coclite's group, showed that both the swelling state, as well as the polymer-drug interaction play a role in determining the release rate [18]. Different drugs were encapsulated by a hydrogel layer deposited from N-isopropylacrylamide (NIPAAm) crosslinked with di(ethyleneglycol) divinyl ether (DEGDVE). At low pH, all drugs were released faster if the hydrogel was in its collapsed state, i.e. above the low critical solution temperature (LCST), while at pH 7, for one of the drugs, the release rate was higher below the LCST with the polymer in its swollen state. This was attributed to differences in bond formation between polymer and drug. In a different study performed by the same group, a broad-spectrum antibiotic was encapsulated with a film of methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) using the degree of crosslinking, determined by the amount of EGDMA in the copolymer, as a means to control drug release [124]. It could be shown that a higher degree of crosslinking restricts hydrogel swelling and slows down the release of the active compound. Furthermore, it could be demonstrated that the iCVD process does not affect the antimicrobial properties of the active compound. In another study, the retarded release of aspirin was demonstrated by depositing a polymer thin film directly on the powder by iCVD (figure 6(a)). During the deposition, the powder was placed on a speaker, which made the powder vibrate with the song 'Thunderstuck' of AC-DC. The vibration allowed to deposit a coating with improved thickness uniformity around the powder, thus enhancing the retarded release of aspirin in water compared to aspirin powder coated in static conditions [125].

Sayin *et al* [126] demonstrated that the release of the chemotherapeutic agent Rose Bengal loaded into polyvinyl alcohol nanofibers can be drastically altered by a thin layer of poly (4-vinylpyridine-co-ethylene glycol dimethacrylate), or p(4VP-co-EGDMA) for short, deposited via iCVD. While the release of Rose Bengal from the uncoated fibers did not depend on the pH and was completed within 2 h, release from the coated fibers was shown to be both retarded and pH-dependent. After 3 h, only 50% of the loaded Rose Bengal was released at a pH of 4, while 100% was released at a pH of 9. It could further be demonstrated that the coated fibers loaded with Rose Bengal show enhanced cell apoptosis and decreased cell proliferation, verifying the therapeutic efficiency against tumor cells.

In another study done by the same group, a Janus membrane was fabricated from a porous anodic aluminum oxide template coated via iCVD on one side with poly (methylacrylic acid-co-ethylene glycol dimethacrylate), p(MAA-co-EGDMA), and on the other side with poly (4-vinylpyridine-co-ethylene glycol dimethacrylate), p(4VP-co-EGDMA) (figure 6(b)) [127]. It was shown that the membrane can act as an on-off gate for switchable controlled release due to the different pH responsiveness of the two materials on the opposite sides. Exposed to pH 3, the p(MAA-co-EGDMA) structure is in its shrunken state and the pores are open, while at pH 9, in the swollen state, the pores are closed. The other side of the Janus membrane shows the opposite behavior: p(4VP-co-EGDMA) is in its swollen state and acts as a barrier at pH 3, while at

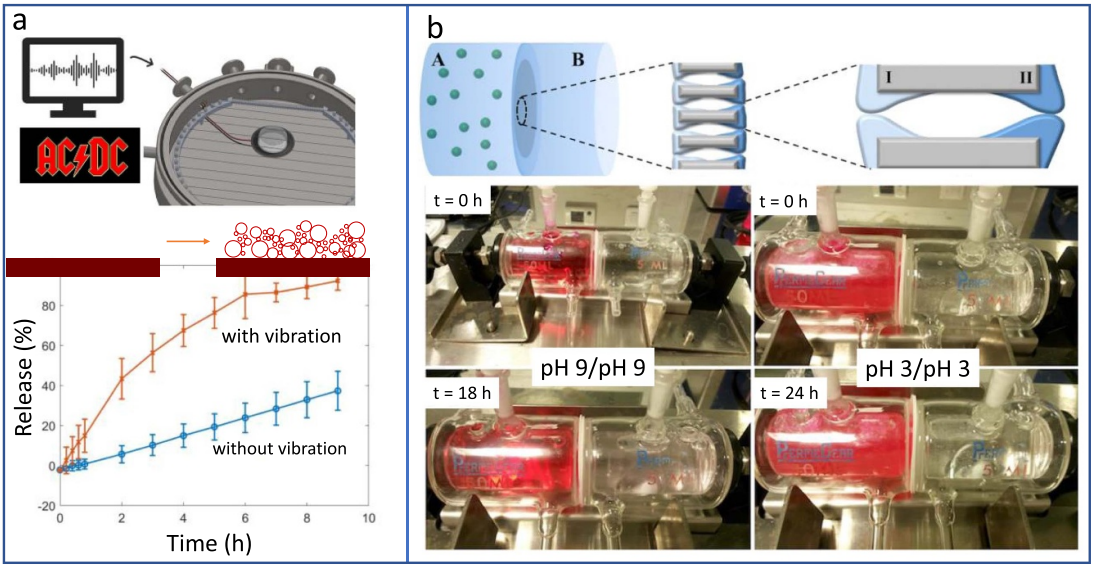

Figure 6. (a) During an iCVD process, Aspirin powder was vibrated by speakers inserted in the deposition chamber to improve the coating thickness uniformity. The release profiles of aspirin in water are reported in the lower figure for the aspirin coated with vibration and the aspirin coated without vibration. Reproduced from [125]. CC BY 4.0. (b) Schematic of the Janus membrane composed of an AAO template with non-conformal coatings of p(MAA-co-EGDMA) on side I and p(4VP-co-EGDMA) on side II. The membrane is placed in a diffusion cell with a protein on the feed side (A) and PBS on the permeate side (B). The bottom figures show diffusion experiments using the Rose Bengal dye as permeant for visualization. On the left, both cells were kept at pH 9. In this case, diffusion of the dye was observed after 18 h. In the image on the right, both cells were kept at pH 3. In this case, after 24 h no permeation of the dye to the permeate side was observed. Reprinted from [127], Copyright (2019), with permission from Elsevier.

pH 9, the pores are open. Diffusion experiments with a protein, bovine serum albumin, demonstrated a pH switchable opening and closing of the gate with the ability to actively trap proteins inside the Janus membrane and release them on the opposite side. These membranes can therefore be used as drug delivery carriers due to their ability to control the release of biomolecules.

Moving away from hydrogels to drug release by controlling the dissolution of the encapsulating polymer coating, Shi *et al* [130] designed a pH-responsive system by depositing a thin capping layer of poly(methacrylic anhydride) (PMAH) by iCVD on microporous PLA membranes loaded with rifampicin. They could show a strong dependence of the degradation behavior of the PMAH coating on the pH value which in turn defined the release rate of rifampicin.

4.4.2. PECVD

In addition to iCVD, PECVD has been used to deposit various hydrogel films, such as thermo-responsive poly(N-isopropylacrylamide) (PNIPAAm) [128] or copolymers from N-vinylcaprolactam (NVCL) and ethylene glycol dimethacrylate (EGDMA) [113, 129], that could be employed for similar biomedical applications.

A recent example of drug delivery from coating deposited by PECVD was provided by the group of Favia [137]. They developed a synthetic routine in which drug molecules are sprayed in the glow of an atmospheric pressure plasma deposition, resulting in nanocapsules containing the drug in a one-step process. Different molecules were embedded in the same polyethylene-like plasma-deposited matrix: vancomycin, gentamicin and lysozyme. Release tests demonstrated the effectiveness of the drug molecules upon exposure to the plasma deposition [138].

4.4.3. ALD/MLD/VPI

Promising concepts for controlled drug release systems based on ALD/MLD processes have also been presented. The group of van Ommen investigated the properties of protein particles [131] and drug powders [132] coated in a fluidized MLD bed reactor. In the case of proteins, UV–vis spectroscopy revealed a rapid decrease of the dissolution rate of the protein particles with increasing number of coating cycles, while the uncoated particles dissolved instantaneously, thus demonstrating tunable controlled-release properties [131].

Modifying the wetting properties of drug powders can improve their bioavailability, for example during the inhalation in pulmonary delivery or by enhancing the dispersion of liquid-based medical products. The tunability of the wettability from highly hydrophilic to superhydrophobic was demonstrated by coating

budesonide—a commercial active pharmaceutical ingredient for respiratory diseases—with inorganic Al_2O_3, TiO_2 and SiO_2 via ALD, as well as with organic poly(ethylene terephthalate) (PET) by MLD and inorganic/organic titanicone by hybrid ALD/MLD [132]. An advantage of using ALD/MLD techniques is the possible minimization of coating material which consequently increases the final drug loading. Water contact angle measurements showed that PET-coated budesonide was hydrophobic, titanicone-coated budesonide mildly hydrophilic, and ALD-coated budesonide highly hydrophilic, the latter due to the presence of metal cations, oxygen anions, and hydroxyl groups on the surface. Additionally, the cytocompatibility of ALD-coated budesonide was assessed by cell viability tests using human epithelial alveolar A549 cells. No toxicity was detected and cell viability remained essentially constant at around 100%.

Another approach using controlled dissolution was reported by Vogel *et al* [133], who showed that coating PVA fiber mats with up to 20 nm of Al_2O_3 slows their dissolution in water, an effect that can be used for the controlled release of small molecules embedded in the fibers. The dissolution of the mat, and with that the release of the molecules, could be tuned from several minutes to multiple weeks, depending on the Al_2O_3 film thickness, rendering the material especially promising for the controlled release of therapeutics in wound healing wraps.

ALD/MLD has also been used to design a photoresponsive drug release system by embedding photoresponsive organic components in an inorganic matrix so that the photostimulated change translates to a structural change in the inorganic host material, thus releasing incorporated molecules. As in the case of the photoresponsive hydrogels discussed above, azobenzene has been used as the photoswitchable component.

So far, ZnO:azobenzene super lattice thin films [134], as well as iron-azobenzene framework thin films, have been synthesized by ALD/MLD [135]. The ZnO:azobenzene films proved photoreactive upon 360 nm irradiation resulting in a decrease in density for the hybrid structures, with the kinetics of the trans-cis photoisomerization slightly depending on the superlattice structure. The reversibility of the photoisomerization reaction was confirmed by a subsequent thermal treatment [134]. For the iron-azobenzene films, the stimuli-induced capture/release of molecules was demonstrated with water, showing reversible absorption/desorption behavior upon repeated humidity-treatment/UV-illumination cycles. The release of the absorbed water molecules was triggered upon 15 min UV irradiation, demonstrating a new approach for e.g. remotely controlled drug delivery [135].

A system enabling electrically controlled drug release was reported by Boehler *et al* [136]. They used an ALD/VPI process to infiltrate ZnO into liquid, gel-like PEG thin films loaded with fluorescein. Upon infiltration, PEG was observed to undergo a phase transition to a solid hybrid material. By applying a bias ($\pm$0.5 V) to a PEDOT layer deposited on top of the hybrid PEG/ZnO structure, the release of the containing fluorescein molecules could be either suppressed or actuated.

4.5. Medical diagnostics and imaging

4.5.1. ALD/MLD/VPI

The MLD/ALD technique has also shown potential for applications in medical diagnostics and imaging, in particular for the fabrication of materials capable of photon upconversion. This mechanism is based on the sequential absorption of two or more long wavelength photons, leading to the emission of a photon with a shorter wavelength. For biomedical applications, the upconversion from near infrared (NIR) to visible or UV light is of special interest, since NIR is within the optical transparency window of biological tissue and NIR-to-vis upconversion would allow improved contrast in fluorescence imaging of deeper-lying tissue (due to the elimination of autofluorescence) [139], as well as deeper penetration in photodynamic therapy for cancer treatment [140].

Molecular metal complexes, e.g. based on lanthanide, could provide direct NIR-to-vis upconversion and offer significantly higher sensitivities than the current state-of-the-art inorganic nanocrystal upconverters.

So far, a few publications have explored the synthesis of lanthanide thin films for upconversion via ALD/MLD: one study by Giedraityte *et al* [139] reported the deposition of (Y,Yb,Er)-pyrazine thin films, which exhibited blue, green, and red upconversion emission with strongly angular-dependent intensities. Upconversion emission could only be obtained within the narrow incident angular range of the laser beam between 20° and 50°, which was attributed to the finite thickness of the thin films. In another study [141], (Yb,Er)-IR-806 upconverting thin films have been synthesized with the so called IR-806 molecule employed as a NIR-absorbing organic ligand. The films exhibited near-infrared to green and red upconversion, but the absorption of IR-806 around 800 nm hampered the excitation of Yb^{3+}/Er^{3+} upconversion at that wavelength.

After the successful synthesis of upconverting lanthanide thin films had been demonstrated, the impact of the backbone of the organic ligand on the luminescence characteristics of lanthanide-organic thin films was explored [142]. For this purpose, the number of aromatic rings in the backbone of the organic ligand in europium-based thin films was varied from one to three. It was found that enlarging the backbone shifts the excitation towards the visible wavelength range but simultaneously decreases the emission intensity. The

reduced emission intensity was explained by the fact that the excitation of the Eu^{3+} ions involves the absorption of photons by the organic ligands and a subsequent energy transfer to the europium, and hence the energy transfer is most efficient with the shortest energy transfer routes, i.e. when the carbon backbone is smallest. Furthermore, the effect of diluting Eu^{3+} with Y^{3+} was examined, resulting in an optimal emission intensity for an Eu^{3+} concentration of 12%. Consequently, the concentration of the luminescent ions must be carefully optimized to obtain the best emission intensity.

4.5.2. iCVD

Deep tissue imaging and sensing was also demonstrated by implanting whispering-gallery mode cavities into live cells [143]. Coating such microcavities with stimuli-responsive polymers by iCVD enabled three-dimensional localization and tracking of individual cells over extended time periods, as well as sensing of their environment, at depths well beyond the light transport length. When a microcavity is coated with a pH-responsive hydrogel, and the pH in the environment changes, the thickness and refractive index of the hydrogel change. This induces a measurable wavelength shift of the whispering-gallery mode.

4.6. Biosensors

Biosensors are sensing devices utilized to monitor chemical or biological entities and processes. They are commonly composed of a biological component combined with a physicochemical detector. Typically, such sensors require multi-step fabrication routines. Due to recent technological advances, miniaturization of such devices is achieved through state-of-the-art nanofabrication techniques, of which vapor deposition processes are of particular relevance [144, 145].

4.6.1. PECVD

Kieninger *et al* [145] presented an example of biosensors utilizing PECVD in the fabrication process, where a sensing cell culture flask (SCCF) equipped with amperometric oxygen and potentiometric pH sensors is used to culture and monitor brain tumor and breast cancer cells, as shown in figure 7(a). Passivation layers are commonly used between metal or semiconductor/liquid interfaces for improved charge transfer. The introduced design utilized PECVD for the deposition of such a passivation layer composed of silicon nitride (800 nm) and silicon oxide (200 nm) on a pH-responsive hydrogel. The influence of the passivation layer on the SCCF performance was not investigated.

PECVD has further been used in the fabrication of conductive polymer thin films, which have been frequently applied in biosensing applications [146]. Kim *et al* [147] employed PECVD to polymerize 3,4-ethylenedioxythiophene (EDOT) and pyrrole, resulting in a PEDOT/PPY copolymer, or p(EDOT-co-PY). It was demonstrated that the plasma power has an influence on the energy bandgap of the copolymer, which increased from 2.62 eV at 10 W to 3.27 eV at 100 W. An opposite trend was observed for the electrical conductivity and the surface roughness, where an increase in the plasma power caused the electrical conductivity to decrease from 2.28×10^{-2} to 1.59×10^{-4} S m^{-1} and the roughness from 1.9 to 0.2 nm for the investigated plasma power range.

Abolpour Moshizi *et al* [149] developed a biomimetic flow sensor inspired by vestibular hair cells. Vertical graphene nanosheets were grown on copper foil using PECVD. PVA solutions were then cast onto the structure and placed in the freezer to obtain a hydrogel layer. Both steady-state and oscillatory flow tests were conducted, showing that the sensor responds to low frequencies (minute frequency of 0.25 Hz in oscillatory test) and flow rates (threshold of detected velocity of a steady state flow in a straight channel is 0.025 mm s^{-1}), as well as to the direction of rotation., In addition to its use as artificial vestibular hair cells, the sensor design shows great potential for many more biomedical applications that require fluid velocity measurements. Due to their high sensitivity to flow, such sensors also pose an attractive opportunity for underwater applications.

4.6.2. iCVD

Glucose-responsive polymers are at the basis of biosensors that monitor the physiological glucose level and/or regulate insulin delivery. Recently, the first example of a vapor-phase deposited glucose-responsive layer was demonstrated by iCVD [150]. This layer was based on a boronic acid compound. It responded to glucose at pH 10 with thickness shrinking. Another interesting biosensor obtained by iCVD was a pH-skin sensor deposited on a temporary tattoo, with possible applications as sweat sensor (see figures 7(b)–(d)) [148]. It was made of screen-printed poly(3,4-ethylenedioxythiophene):polystyrene sulfonate electrodes coated with a pH-responsive hydrogel deposited via iCVD. The tattoo sensor could be easily transferred onto the skin while maintaining full functionality and showing excellent conformability to topographical features of the epidermis.

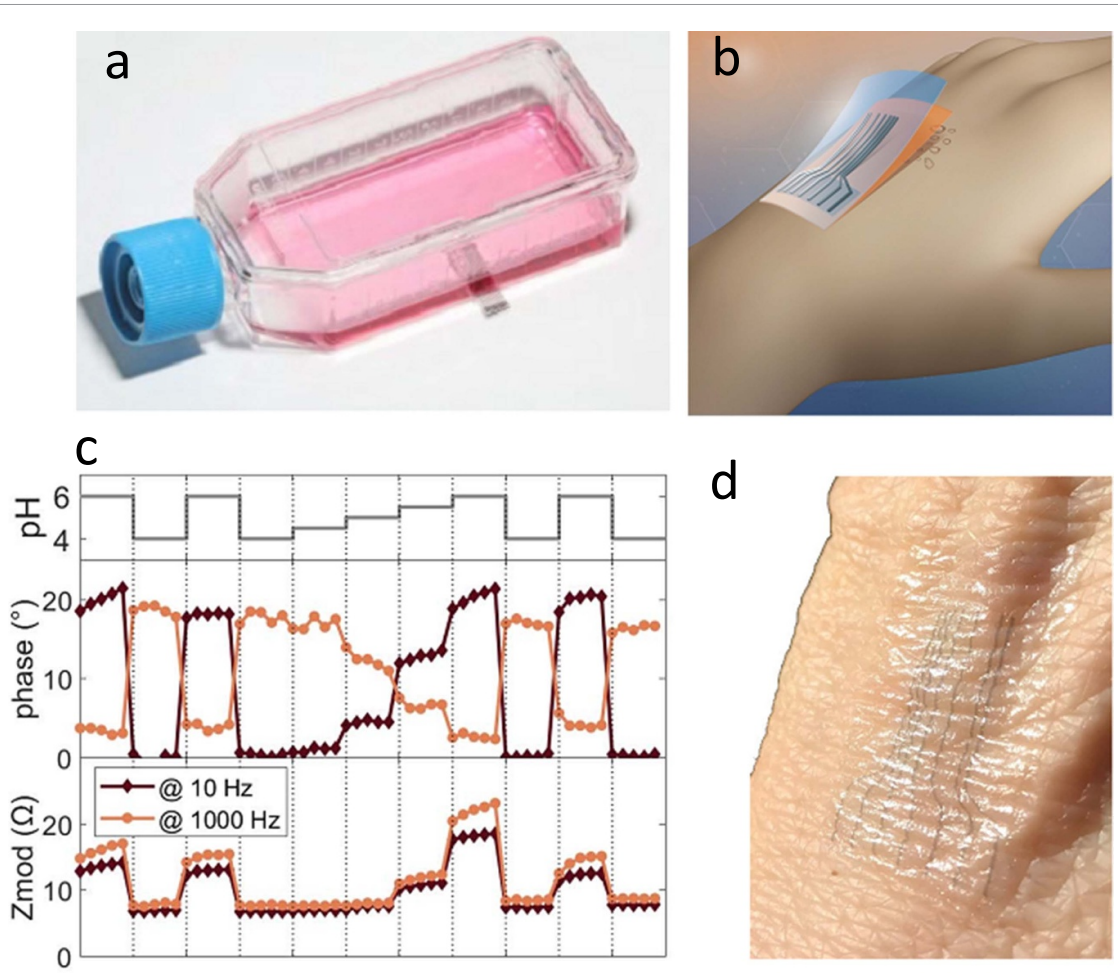

Figure 7. (a) Image of Sensing Cell Culture Flask (SCCF) equipped with amperometric oxygen and potentiometric pH sensors used to monitor and culture brain tumor and breast cancer cells. Reproduced from [145]. CC BY 4.0. (b)–(d) Demonstration of a pH-responsive temporary tattoo ultra-conformable to human skin as shown in the photo in (d). (c) shows the results of the electrochemical impedance spectroscopy, i.e. the phase and the impedance (Zmod) at two frequencies (10 and 1000 Hz) upon pH variations. Reproduced with permission from [148]. © 2021 The Authors. Advanced Materials Technologies published by Wiley-VCH GmbH. CC BY-NC-ND 4.0.

4.7. Tissue engineering

Tissue engineering comprises the use of scaffolds, i.e. three-dimensional structures, to promote or guide cell proliferation, growth and differentiation. Often, these scaffolds are coated by thin films to achieve a functionalized surface tailored to the respective application. Due to the often complex 3D microstructures of the scaffolds and their sensitivity to high temperatures, conventional solution-based techniques fail to guarantee a conformal coverage. Paper-based scaffolds are especially attractive because they can fulfil the basic requirements of a conventional scaffold and are highly effective while being low in cost [151].

4.7.1. iCVD

Park *et al* [8] have worked on the biochemical functionalization of different types of paper by iCVD. Due to the absence of organic solvents and the mild operating temperatures in the iCVD process, the cellulose microfibrous structure of the paper was preserved and conformally coated. They concluded that paper-based bioactive scaffolds functionalized with iCVD are a feasible alternative for stem cell cultures.

Another material with promising applications in tissue engineering scaffolds are gelatin nanofibers (GNFs). GNFs are biocompatible and biodegradable protein-based polymers with nanofibrous structures that can be adapted to different biomedical uses. However, their lack in stability and their strong tendency to instantly dissolve in water makes them hard to use. In the work published by Mansurnezhad *et al* [152], electrospun GNFs were coated with poly (ethylene glycol dimethacrylate) (pEGDMA), a biocompatible polymer commonly used in bio-applications, via iCVD. In this case, iCVD has the advantage of operating at low pressures, nearly eliminating the probability for undesired reactions and hence making the inclusion of unreacted monomer species in the final structure highly unlikely. The coating on the nanofibrous structure

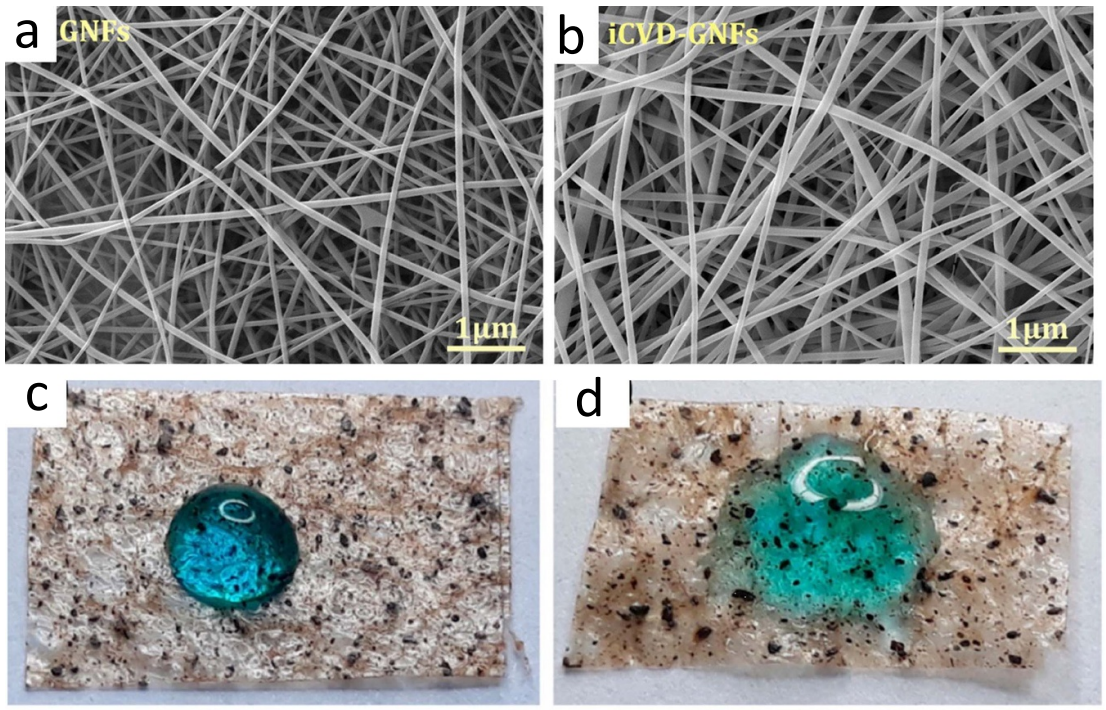

Figure 8. (a) Pristine structure of gelatin nanofibers (GNFs) without coating. (b) GNFs coated with iCVD. The nanofibrous structure was conformally coated with iCVD. Reprinted from [152], Copyright (2020), with permission from Elsevier. (c) and (d) Surface functionalization of a composite patch made of polylactic acid and marine algae. (c) Composite patch without coating exhibiting slightly hydrophobic behavior. (d) Composite patch after p(HEMA-co-EGDMA) coating exhibiting hydrophilic behavior. Reproduced from [154]. CC BY 4.0.

was shown to be highly conformal, enabling water-resistant properties adequate for cell adhesion and proliferation (see figures 8(a) and (b)).

Materials used in bone tissue engineering need to be biocompatible and allow for bone cells to adhere to them, as well as grow and differentiate around them. Titanium implants are often used to replace bones in the human body, whether that be teeth, hip joints, or other, and pose the advantage of being very durable. To enhance the biocompatibility of this material, its surface is usually functionalized with osteoinductive molecules by applying traditional methods that require the use of solvents. However, traces of solvents remaining in the material after functionalization pose the risk of cytotoxicity and can ultimately lead to implant rejection by the body. The use of solvent-free vapor-based deposition techniques resolves this issue. In the work published by Youn *et al* [153], a Titanium surface was functionalized with a coating of glycidyl methacrylate (GMA) deposited via iCVD, which successfully immobilized the osteoinductive rhBMP2 protein. This protein contributes to osteogenic differentiation which allows for a fast recovery of damaged bone tissues.

In the work published by Reichstein *et al* [154], a composite patch made of polylactic acid and marine algae was developed for bone tissue engineering in dentistry and orthopedy. The composite possesses slightly hydrophobic properties which impede cellular interactions, ultimately inhibiting cell adhesion and proliferation. To circumvent this unwanted effect, the wettability properties of the composite were tuned by applying a coating of the copolymer poly (2-hydroxyethyl methacrylate-co-ethylene glycol dimethacrylate) (p(HEMA-co-EGDMA)) via iCVD and creating a highly hydrophilic surface ideal for the cultivation and proliferation of osteoblastic cells (see figures 8(c) and (d)).

4.7.2. ALD/MLD/VPI

Liang *et al* [155] demonstrated that ALD of ultrathin Al_2O_3 and TiO_2 films (∼3–8 nm) on highly porous poly(styrene-divinylbenzene) (PS-DVB) particles leads to enhanced bioactivity. This, in combination with good cell adhesion and growth, is an important property for biomaterials used as scaffolds for guided cell growth in tissue engineering, especially when it comes to bone regeneration. Though the investigated polymer was not tested regarding its biocompatibility, the authors claim that the process can be easily transferred to more suitable porous biocompatible polymers.

In addition to bioactivity, controlled biodegradability is an important property of materials used for guided bone regeneration, where a second surgery to remove the implant is preferably avoided. Choy *et al*

[156] demonstrated that by infiltrating chitin nanofibrous membranes with TiO_2 by VPI, biodegradation can be slowed down (the membranes remained intact for over 12 weeks), and the material's strength and toughness is improved. The infiltrated material exhibited excellent osteointegrative performance and improved immunosuppressive qualities compared to an untreated chitin membrane.

4.7.3. PECVD

The group of Favia developed several approaches to coat scaffolds by PECVD for enhanced cell growth [97] and bone tissue engineering [157]. In particular, for the latter, scaffolds of polycaprolactone were decorated with a magnesium-based coating obtained by sputtering, which formed a hybrid with the underlaying scaffold. The proliferation and adhesion on 3D scaffold surfaces were demonstrated with Saos-2 osteoblast cells showing that deposited magnesium-containing thin films favor osteoblast colonization inside the scaffolds.

5. Conclusion

Soft biomaterials are of increasing importance in the field of biomedicine, (bio)sensing and all other application fields that concern an interaction of matter with a biological environment. Depending on the specific application, high demands are placed on the used materials, constantly driving research efforts in the field of materials design and engineering. Desired properties range from the very fundamental requirement of biocompatibility to advanced characteristics such as antibacterial, antimicrobial or bioactive functionalities, controllable solubility, the inhibition of cell adhesion or biofouling, or even 'smart' properties, such as a responsiveness to various external stimuli. The use of thin films proved a powerful method to meet these requirements while keeping material use and costs at a minimum. In addition, approaches using surface functionalization by thin films allow to stick with bulk structural materials that have already been demonstrated to be well-suited for certain applications, while still being able to exploit the entire portfolio of functional materials developed in the field.

This review aimed to provide an overview of frequently used vapor-based thin film techniques and the organic and hybrid coatings that can be fabricated by them, followed by a detailed discussion of recent biomedical applications of such thin films.

Vapor-based methods are often favored in the fabrication of (soft) biomaterials, as they enable one to overcome some of the drawbacks of traditional solution-based techniques, such as the limited conformality of coatings, their inapplicability to certain substrates, and the undesired entrapment of toxic solvents, plasticizers and other additives in the polymer, an imperative when it comes to biocompatibility. In addition, vapor-based methods achieve coatings along complex material landscapes, such as the inner walls of porous materials, e.g. scaffolds.

We discussed iCVD, a method that allows for the synthesis of functional polymers on various substrates, as well as PECVD, a process operating at low temperatures and pressure, making it particularly suitable for thermosensitive substrates, as is often the case for organic polymers. Another method frequently used to deposit organic thin films is MLD.

Soft biomaterials can also be obtained by depositing a thin inorganic layer on a soft organic substrate. When it comes to the fabrication of inorganic materials, ALD is a method used to grow thin films with high precision, monolayer by monolayer. ALD is especially useful for metals, metal oxides and nitrides, and is further the parent of another method, VPI, which produces hybrid organic-inorganic materials. Since VPI is a rather new technique, the fabrication of hybrid materials for bio-applications from VPI is still in its infancy.

Whilst the previously mentioned methods allow us to achieve uniform coatings on substrates, patterning methods such as DLW and lithography in its various versions can be used to obtain high-precision patterns of polymers on resists and are often cost-effective with a high-throughput rate.

We introduced the concept of hydrogels, crosslinked polymer networks with water entrapped as a dispersion solvent. Such materials have a solid-like appearance on the macroscopic scale but exhibit liquid-like behavior on the molecular length scale. 'Smart' or 'stimuli-responsive' hydrogels can be engineered to change upon exposure to external stimuli such as temperature, pH, light and others, and have become popular in a vast number of applications, especially in the biomedical area where biocompatibility is of the essence.

The relevancy of these techniques and materials was discussed in the context of a wide range of examples, with applications in the preparation of biocompatible coatings, antibiofouling structures, membranes, tissue engineering, controlled drug delivery, biosensors, medical diagnostics and imaging. New materials and refined fabrication processes continuously open up new potential application fields. The field of smart polymers and hydrogels leaves a lot of functionalities and applications to explore.

The complete lack of solvents and the minimal use of chemicals in vapor deposition processes are favorable characteristics to achieve materials that are sustainable by design. Bio-based monomers have already been successfully polymerized using iCVD. Although great progress has been made in materials research, especially when it comes to vapor-based fabrication methods, further steps towards sustainability remain one of the main challenges in the field.

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