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Biopolymer-Based Coatings: Promising Strategies to Improve the Biocompatibility and Functionality of Materials Used in Biomedical Engineering

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It was a physicist, Wolfgang Pauli, who recognized a century ago that "God made the bulk; the surface was invented by the devil." And indeed, adjusting the surface properties of materials has kept engineers and chemists busy since—and it still does. In the context of biomedical engineering, the key challenge is ensuring the functionality of an artificial object, which is inserted into the human body—an environment that passively and actively rejects foreign materials. Here, recent advances in this area while focusing on those approaches that employ surface coating strategies with biopolymers are summarized.

1. Introduction

In the past decades, with the increasing number of senior citizens in our society and the high level of activity people across all age groups have become used to in their private lives, the demand for biomedical devices, which can reside in the human body for extended time periods, has considerably increased. Examples of devices that aim at facilitating an active lifestyle of people include implants and materials that improve or replace the function of natural tissues and organs.[1] In this context, the development of anti-biofouling surfaces or surfaces, which release pharmaceuticals, has become crucial for extending the residence time of artificial materials in the human body.[2] At the same time, developing economical and reliable medical diagnostics as well as methodologies and devices for environmental monitoring to estimate pathological alterations utilizing biochemical pathways has gained attention; to a certain extent—improvements in those areas are due to innovations in biosensor development.[3]

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Owing to the large field of materials science, a plethora of novel materials with a broad range of interesting properties has become available for applications in biomedical engineering. Here, the bulk properties of a material are, of course, critical as they not only determine its mechanical and biological stability but also contribute to its biocompatibility (especially if the material releases components into the environment, e.g., when it is partially degraded by the human body). However, for the latter, the surface properties of a material are even more relevant, as it is the surface of an object that gets directly in contact with the human body. Yet, it is rare for a material to possess both, optimal bulk properties and surface characteristics suitable for biomedical applications, at the same time.

The most typical issues related to insufficient compatibility of material surfaces can be summarized in four categories: First, a material may be incompatible in terms of its mechanical or topographical properties; if a material surface is too stiff or too rough, it can cause tissue damage when coming into contact with the human body (**Figure 1**a).[4] Second, any artificial material brought into the body environment is at risk of being subjected to biofouling, and this process often leads to infections and entails device failure (Figure 1b).[5] Finally, a direct reaction of the immune system to the implant material can cause various problems: those can either be due to the immune system actively fighting the foreign material (Figure 1c),[6] or the body may induce a permanent separation of the artificial material from the tissue environment by fibrous encapsulation (Figure 1d).[7]

To alleviate or even eliminate the issues mentioned above, different types of surface modifications have been developed. Examples include plasma etching,[8] ion-implantation,[9] laser beam treatment,[10] and coating.[11] Among those options, the coating of either natural and synthetic materials with a biocompatible and functional layer appears to be the most promising and economic strategy:[12] typically, with this approach, the important bulk characteristics of a material are maintained very well while its surface properties can be adjusted such that the material now interacts with tissues, cells or macromolecules in a desired and controlled fashion.

Polymers, and in particular biopolymers, have emerged as very promising and versatile candidates to generate such coatings for biomedical applications. Different from their synthetic counterparts, biopolymers—also known as polymeric biomolecules—are mostly generated by animals,

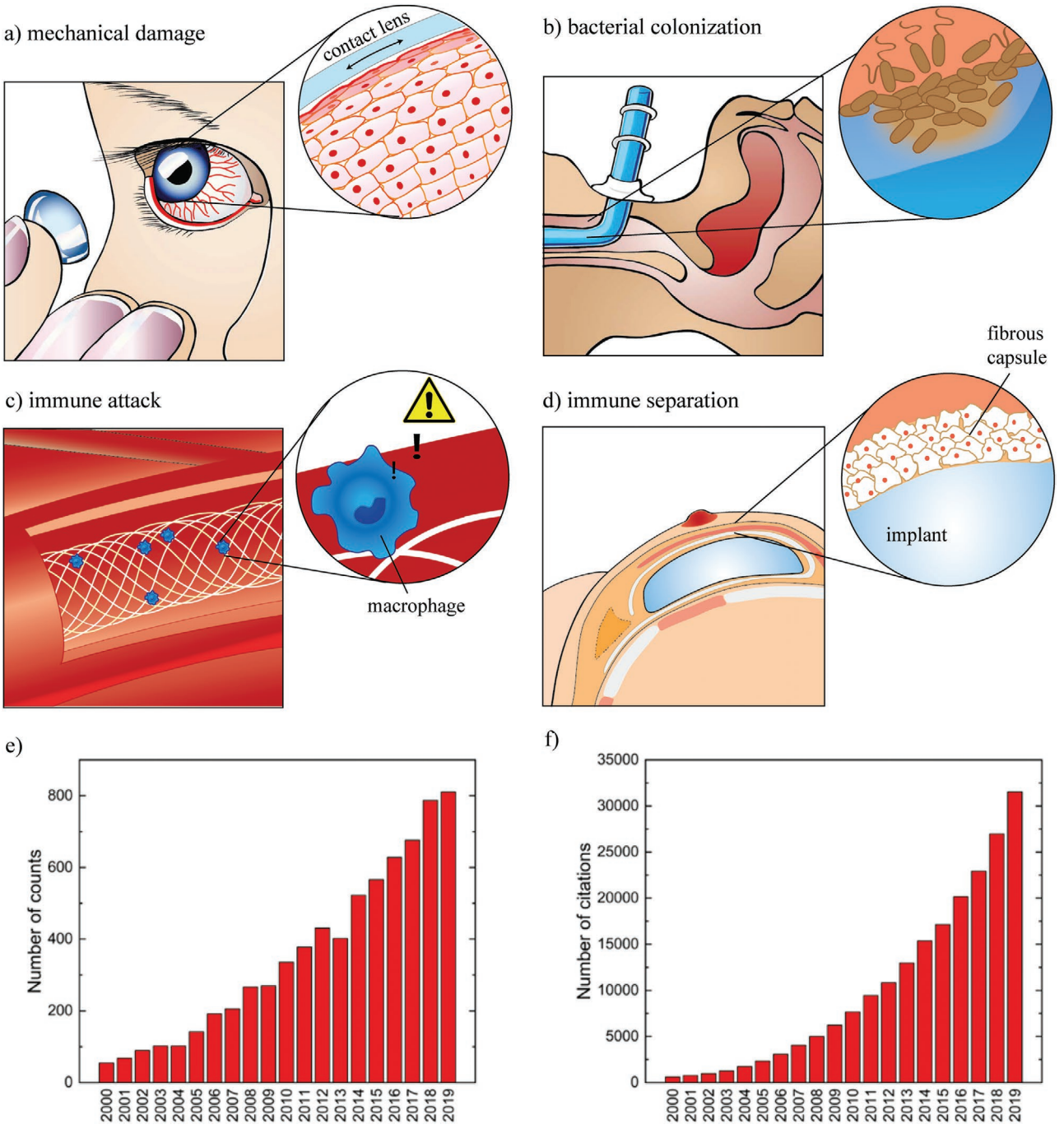


Figure 1. The most typical issues related to insufficient compatibility of material surfaces: a) First, a material may be incompatible in terms of its mechanical or topographical properties; if a material surface is too stiff or too rough, it can cause tissue damage when coming into contact with the human body. b) Second, any artificial material brought into the body environment is at risk of being subjected to biofouling, and this process often leads to infections and entails device failure. c) Finally, a direct reaction of the immune system to the implant material can cause various problems: those can either be due to the immune system actively fighting the foreign material, or d) the body may induce a permanent separation of the artificial material from the tissue environment by fibrous encapsulation. The published papers were searched on Web of Science Core Collection, using topic (TS) as (BIOPOLYMER* or BIO-POLYMER*) and (COAT* or FILM*), on 27 January 2020. e) The number of counts and f) the number of citations in the last 20 years (from 2000 to 2019) are presented.

plants, bacteria, and fungi. Due to their biological origin, biopolymers exhibit excellent biocompatibility, good availability and many other beneficial properties. Accordingly, research in the field of biopolymer coatings has gained speed during the last decade. A simple search in the Web of Science Core Collection on January 27, 2020, using the phrases (BIOPOLYMER* or BIO-POLYMER*) and (COAT* or FILM*) as topics yield a graph that nicely visualizes this

trend (Figure 1e). In addition, as presented in Figure 1f, the number of citations in this field increases even more strongly, indicating the high relevance and attractiveness of this field which keeps drawing the attention of many scientists from different disciplines.

Indeed, there are already some excellent reviews and progress reports on surface coatings of medical implants, and this previous work covers different aspects of this subject.[13] We here focus on biopolymer-based films, summarize the most popular macromolecules used for such coatings and give an overview of different physical and chemical techniques that are suitable for their generation. Finally, we highlight several examples from the areas of implants/biomedical devices, tissue engineering, drug delivery and biosensing to present recent developments where biopolymer coatings have been employed to improve the functionality and/or biocompatibility of artificial materials.

2. Biopolymers

Biopolymers—with their multiple functions and beneficial properties such as good biocompatibility, nontoxicity, and bioresorbability—have been one of the hottest research topics during the last decade. To harness their properties for biomedical applications, i.e., to be able to coat them onto artificial materials via physical or chemical deposition methods, a detailed knowledge about their (chemical) structure is a key requirement.[14] Biopolymers typically comprise a backbone which consists of repeating units of saccharides, amino acids, or nucleotides. In addition, some biopolymers carry functional groups on this backbone or on side chains. However, the biochemical properties of the backbone dictate, which of the following three main groups a biopolymer is assigned to:[15] polysaccharides, polypeptides, and polynucleotides (**Table 1**). Generally, biopolymers are prepared in (aqueous) solutions for the coating process. Both, the solubility of biopolymers and the viscosity of the created solutions depend on the molecular weight of the biopolymer: According to the Mark–Houwink equation, a high MW leads to solutions with higher viscosity but decreases the solubility of the biopolymer.[16]

2.1. Polysaccharides

In the natural world, more than 90% of the carbohydrate mass exists in form of polysaccharides,[17] and they serve as a source of energy, support cell division, and growth and maintain a normal metabolism. Polysaccharides are formed by monosaccharide units through glycosidic linkages and are the most abundant class of biological molecules. They can be commercially derived from a variety of sources, including animals, renewable plants, and bacterial fermentation. Several polysaccharides are already used in the context of biomedical coatings, and examples include chitosan, heparin, cellulose, alginate, pectin, and dextran.

Chitosan, the *N*-deacetylated derivative of chitin, is obtained industrially from shrimp shells, crab and fungal mycelia. The average molecular weight range of chitosan is 4–300 kDa,[18] which is why chitosan is typically divided into three groups: low (LMWC), medium (MMWC), and high molecular weight chitosan (HMWC). As, in chitosan, the pK_a value of the amino group is ≈6.5, chitosan is polycationic at acidic conditions. Thus, it can be dissolved in aqueous acidic solutions but is insoluble in water at neutral pH and in organic solvents.[19]

Heparin is a glycosaminoglycan with an average molecular weight of 5–35 kDa,[20] which can be extracted from bovine and ovine lungs, respectively, or from porcine intestinal mucosa. Different from chitosan, heparin molecules are highly soluble in both, water and organic solvents, and their sulfate groups are deprotonated under physiological conditions, which renders heparin polyanionic and helps attract positively charged counter ions.[21] Thus, commercial heparin products are usually available in the form of salts, e.g., heparin sodium or heparin calcium.

Another polysaccharide that is widely used in biomedical applications is hyaluronic acid (HA, also referred to as hyaluronan), a linear, polyanionic (but nonsulfated) glycosaminoglycan with an average molecular weight of 4–8000 kDa.[22] HA is well water-soluble and can be obtained from, e.g., bovine vitreous and rooster combs.[23] However, since animal-based HA is expensive and—to some extent—always contaminated by protein impurities, commercial HA is typically produced from microbial organisms (e.g., *Streptococcus equi* or *Streptococcus zooepidemicus*).

Compared to the rather expensive polysaccharides derived from animal sources, cheaper polysaccharides can be found in and purified from plants. For instance, cellulose—the most abundant polysaccharide in nature—can be obtained from wood, cotton, hemp and many other plant-based materials. Owing to the absence of any side chains, cellulose can form a rigid structure by chain-packing with strong inter- and intramolecular hydrogen bonding. As a consequence, cellulose is difficult to dissolve, i.e., it is insoluble in water and most organic solvents. However, there are some types of cellulose that can be dissolved in dilute aqueous NaOH solutions at low temperature since, under those conditions, the hydrogen bonds are weakened.[24] Moreover, there are modified cellulose variants such as carboxymethylcellulose where this problem is (at least at alkaline pH) alleviated by the introduction of charged carboxyl groups.

Different from cellulose, the polyanionic macromolecule alginate (MW range: 30–400 kDa) is typically well soluble in water (but not in organic solvents) and thus often used for bio-coating applications. Alginate is commercially derived from algae via alkaline extraction and available in form of salts. Importantly, the solubility of alginate depends on the cationic counterion, e.g., sodium alginate is water-soluble whereas calcium alginate is not.

Finally, in addition to the animal and plant sources, polysaccharides can be also obtained from microorganisms such as yeast and bacteria. One example of such a microbial-produced polysaccharide that is widely used for coating applications is dextran. Depending on the species of the bacterium used for dextran production, the structure and organization of the dextran main chain can vary.[25] Dextrans are soluble in both, organic solvents and water (except for large dextrans with MW in the range of 5–40 MDa). Three particular types of dextrans, i.e., Dextran 40, 70, and 75, (typically referred to as clinical dextrans; they have slightly different molecular weights as indicated by the numbers in their name) are already used in biomedical applications.[26] Moreover, there are several modification approaches of dextrans available which convey

Table 1. Biopolymers mainly used as coatings for biomedical applications. For each biopolymer, the average molecular weight (MW) and key applications are listed.

Biopolymers		Molecular weight [MW]	Source	Lubrication and antiwear formation	Anti-biofouling	Cellular adhesion promotion	Drug delivery	Biosensing	Refs.
Polysaccharides	Chitosan	20–300 kDa	Animal (shrimp shells, crab) microorganism (fungal mycelia)	✓	✓	✓	✓	✓	[94c,100,138,149,159]
	Heparin	5–35 kDa	Animal (pig, cow, sheep)		✓	✓	✓	✓	[107,118b,169]
	HA	4–8000 kDa	Animal (cow, chicken) microorganism (yeast)	✓	✓	✓	✓	✓	[94c,96c,133,151,170]
	Cellulose	0.1–44 kDa	Plant (wood, cotton, hemp) microorganism (bacteria)	✓		✓	✓	✓	[171]
	Alginate	30–400 kDa	Plant (algae)		✓	✓	✓	✓	[114,172]
	Pectin	50–150 kDa	Plant (apple, berries, citrus)	✓		✓	✓	✓	[121,173]
	Dextran	3–2000 kDa	Microorganism (bacteria)	✓	✓	✓	✓	✓	[114,174]
Polypeptides	Collagen	300 kDa	Animal (pig, cow)	✓	✓	✓		✓	[175]
	Fibronectin	220 kDa	Animal (blood plasma)			✓		✓	[122,176]
	Gelatin	15–250 kDa	Animal (pig, cow, chicken, fish)			✓	✓	✓	[124,177]
	PLL	20–300 kDa	Microorganism (bacteria)	✓	✓	✓	✓	✓	[86,120,150,178]
	Antibodies	25–150 kDa	Microorganism (bacteria, yeast, eukaryotic cells)					✓	[153]
	Enzymes	10–2000 kDa	Microorganism (bacteria, yeast, fungi)		✓			✓	[179]
	Mucin	0.5–50 MDa	Animal (pig, cow, snail, eel) microorganism (eukaryotic cells)	✓	✓	✓			[96a,109b]
	Lubricin	230–280 kDa	Animal (cow) microorganism (eukaryotic cells)	✓	✓				[94b,110]
Polynucleotides	DNA	0.08–20 MDa	Animal (various), plant (various), microorganism (various), synthesis				✓	✓	[180]
	RNA	0.46–6.3 MDa					✓	✓	[181]
Others	PDA	11.2 kDa	Animal (mussel)	✓	✓	✓	✓	✓	[95a,b,126,182]
	PLA	60–300 kDa	Plant (corn, tapoca, sugarcane)		✓		✓		[115,148b]

either cationic, anionic, or (partially) hydrophobic properties to the otherwise uncharged polysaccharide.[27]

2.2. Polypeptides

Polypeptides are long, linear chains comprising 20 or more different amino acids. These amino acids are connected by so-called peptide bonds, which give this family of biopolymers its name. When the molecular weight of a (natural or synthetic) polypeptide exceeds a certain threshold (this limit is not well-defined, but often a value of ≈10 kDa is used), it is referred to as a protein. The largest known protein species can actually reach molecular weights up to a few MDa. Proteins are naturally synthesized in cells, and also most proteins for industrial applications (e.g., biopharmaceuticals) are today produced

recombinantly using bacterial or eukaryotic cell cultures. Some short oligopeptide chains can, however, also be synthesized chemically, which allows for incorporating non-natural amino acids with functional groups or fluorescent dyes into the biopolymer.

Several natural and synthetic polypeptides are already in use as coatings for materials, and examples include collagen, fibronectin, gelatin, antimicrobial peptides, poly-L-lysine (PLL), antibodies and some enzymes. Most synthetic polypeptides can be engineered to be soluble in water, as this property can be controlled by avoiding amino acids with hydrophobic side chains in the peptide sequence. For naturally occurring polypeptides, however, this property is dictated by the genetic sequence that codes for the polypeptide sequence. Indeed, there are many examples where a polypeptide sequence contains areas with very different properties, including charged and uncharged areas as well as hydrophobic sequences.

A special type of polypeptides with a complex biochemical structure and, thus, locally very different physical properties are glycoproteins, i.e., proteins that contain oligosaccharide groups (glycans) bound to the side-chains of the polypeptide backbone. Those glycan motifs participate in controlling protein folding and cell signaling, and improve the stability of the macromolecule.[28] A prominent example of this particular class of polypeptides is mucin, the main functional component of mucus. Mucins are high molecular weight glycoproteins (0.5–20 MDa) that are secreted by many organisms as a protective lining of epithelial surfaces. Here, mucins act as a chemical and biological barrier toward pathogens, dust particles, and toxins and provide lubrication and hydration. Due to their broad range of biomedically interesting properties,[29] mucins have been applied as coatings onto different substrates in vitro and in vivo. The charge state of mucin is (like that of most other polypeptides) strongly dependent on pH—at least in its nonglycosylated, terminal areas. Interestingly, those termini also contain a relatively high number of hydrophobic amino acids. Together, this allows mucins to spontaneously adsorb to a broad variety of materials. Mucins can be purified from different animal tissues, the most common sources are porcine stomachs and bovine submaxillary glands.[30] Moreover, also other mucinous glycoproteins have been explored as coatings for biomedical applications. For instance, lubricin (also known as proteoglycan 4/PRG4), is a mucin-related glycoprotein that can either be isolated from the synovial fluid of bovine joints[31] or produced recombinantly.[32] Similar to mucin, the glycosylated regions of lubricin render it well soluble in water, and also lubricin comprises nonglycosylated, rather hydrophobic termini, which allow lubricin to adsorb onto hydrophobic surfaces.[33] Furthermore, these termini are thought to allow lubricin to interact with cartilage proteins and polysaccharides thus improving its lubricity.[34]

2.3. Polynucleotides

Polynucleotides are linear, unbranched biopolymers built from "nucleotides" as monomeric units. Since every nucleotide combines a nucleoside unit (comprising a sugar and one organic base) and a phosphate group, polynucleotides are strongly polyanionic. Polynucleotides such as DNA or RNA occur naturally in all living organisms, where they fulfill a set of important biological functions. Synthetic polynucleotides can be created as well, yet with limited chain length. Especially in pharmacological research, the use of synthetically produced polynucleotides has gained increased interest in the last decade, where custom-made DNA and RNA sequences opened new ways for gene-based cancer therapies.[35] In addition, various functional structures have been created via sequence-specific pairing interactions of polynucleotide strands, and such polynucleotide sequences have been utilized to coat artificial objects, e.g., colloids. With such a DNA coating, the colloids can then bind (either directly or mediated by single-stranded oligonucleotide linkers) to other particles or surfaces which, in turn, are coated with complementary single-stranded DNA sequences. Indeed, with this approach, many interesting biomedical applications were demonstrated; examples include ultra-sensitive biomarkers, molecular detectors, and efficient drug- or gene-delivery carriers.[36]

2.4. Artificial Biopolymers

In addition to polysaccharides, polypeptides, and polynucleotides mentioned above, there are also some man-made "artificial biopolymers," which comprise biological molecules as subunits but do not naturally occur as polymers. Similar to natural biopolymers, also those artificial biopolymers exhibit good functionality, biocompatibility and thus they are also used in biomedical applications.[37] Two famous examples from this class that are applied as coatings are poly(dopamine) (PDA) and poly(lactic acid) (PLA).

PDA is a dopamine-derived, synthetic eumelanin polymer and was already described to be used as a coating in the year 2007.[38] Since dopamine can be obtained from a variety of sources (i.e., both from animal eumelanins and plant melanins) it is commercially available in large quantities in the form of a hydrochloride salt (dopamine hydrochloride). From this commercial dopamine, PDA can be synthesized by adding an oxidizing agent (potassium chlorate, ammonium persulfate, or sodium periodate) at basic (pH 8.5), neutral (pH 7), or acidic (pH 4) conditions.[39] Generally, PDA is a black solid and insoluble in water, but it can be rendered water-soluble via Kumada-coupling or other chemical treatments.[40] Although the chemical properties and molecular structure of PDA are yet to be fully understood and depend on the specific conditions chosen for polymerization, PDA coatings are already used in biomedical applications. One reason for the popularity of PDA is its ability to spontaneously adsorb to a broad range of surfaces and to provide the coated material with an excellent biocompatibility.[38]

PLA is a thermoplastic, high-strength aliphatic polyester with a high molecular weight (60–300 kDa). It is insoluble in water and alcohol but can be dissolved in a range of organic solvents such as acetonitrile, chloroform, and dioxane. Owing to its nontoxic properties, it has been employed to form biocompatible or bioabsorbable coatings on biomedical devices. In comparison to other biopolymers, PLA has a better thermal processibility[41] but generates coatings with relatively high contact angles of

≈80°, which leads to low cell affinity. Since PLA does not contain any reactive side-chain groups, it is chemically quite inert; several strategies, have been proposed to introduce reactive groups into the polymer to control and improve its toughness, degradation rate and hydrophobicity so that it becomes better suitable for biomedical applications.[42]

3. Coating Methods

Biopolymer-based coatings can be prepared via different physical or chemical techniques. When physical coating approaches are used, the biopolymer is deposited directly onto the substrate via a technical process, e.g., spin coating, dip coating, electrospinning, vapor transport, etc. In contrast, chemical coating strategies make use of chemical reactions between the biopolymer and the substrate, and they typically require (sometimes complex) chemical pretreatments of either the biopolymer or the substrate surface. Which of the different possible coating approaches is chosen for a specific application, thus depends on several factors, including the chemical properties of the substrate, the desired coating thickness and properties, as well as economic considerations.

3.1. Substrates for Coating

When selecting an artificial substrate for use in or on the human body, the biocompatibility of the material is an important factor. Yet, only a limited number of materials that are generally considered to possess good biocompatibility can be used for biomedical applications. In those cases, where the biocompatibility of the substrate is not a problem, scientists and engineers can concentrate on coatings that provide other functionalities than biocompatibility. Still, so-called "medical grade" products exist for most material classes, including metals and metal alloys, ceramics, and polymers. Traditionally, stainless steel, titanium alloys, zirconia, alumina, polyethylene (PE), polyetheretherketone (PEEK), and polydimethylsiloxane (PDMS) show decent biocompatibility and are thus used frequently; nevertheless, the surface properties of those materials sill require improvement which can be achieved by the application of a coating (**Table 2**).

3.1.1. Metals and Metal Alloys

Metals and especially metal alloys are used for all those application areas in medical technology, where mechanical strength is required and heavy loads have to be carried, e.g., as hip or knee implants, dental implants, or stents. Furthermore, metal-based materials are also employed, when a conductivity of the engineered device is required, e.g., in biosensors. Of course, the most frequently employed metal alloys are medical-grade stainless steels (SAE 316L) and cobalt chromium alloys. Both groups exhibit a very high mechanical strength, high corrosion and wear resistance, and they are comparably easy to process.[43]

The second most frequently used group of metal substrates are based on titanium. Their best-known representative is the titanium–aluminum–vanadium alloy Ti6Al4V, but also nickel–titanium alloys (nitinol) are very common. Compared to stainless steel, titanium-based materials show a better biocompatibility as the spontaneous formation of titanium oxide ceramic on titanium surfaces shields the underlying bulk material from corrosive attack induced by body fluids.[44] Furthermore, titanium alloys exhibit a very good integration into and high bonding strength toward bone tissue.[43b]

Also other metals, such as gold, platinum, or silver can be found in many medical devices. Gold, for instance, is used both, in its pure state and as part of alloys; here, typical examples include dental fillings and implants, reconstructive surgeries of the middle ear, pacemakers, but also microchip applications in vivo.[45] Platinum possesses a very good biocompatibility, is inert and resistant against corrosion. In combination with its electrical conductivity, these properties make

Table 2. Biopolymer-based coatings were mainly deposited onto the following substrates for biomedical applications. For each substrate, the elastic modulus, hardness, deposition type, and application are listed.

Substrate	Elastic modulus [*E*, GPa]	Hardness [HV]	Deposition type		Application		Refs.
			Chemical	Physical	In vitro	In vivo	
Titanium and its alloys	105–120	200–350	✓	✓	✓	✓	[182a,183]
Nitinol (NiTi)	15–25	220	✓	✓	✓		[72b,184]
Stainless steel (316L)	210	195	✓	✓	✓	✓	[169a,185]
Gold (Au)	79	188–216	✓	✓	✓		[177a,186]
Aluminum and its alloys	≈70	90–170		✓	✓		[154b]
Magnesium and its alloys	35–120	55–105	✓	✓	✓	✓	[100,187]
Zirconia (ZrO_2)	210	1200	✓		✓		[50]
Alumina (Al_2O_3)	340	1650	✓		✓		[50]
Silica (SiO_2)	75	1100	✓	✓	✓		[95b,174c]
PU	0.01–0.1	25–75 (shore D)	✓	✓	✓	✓	[56,109a,188]
PTFE	0.5	30–70	✓	✓	✓	✓	[189]
PEEK	3–4	144		✓	✓	✓	[190]
PDMS	0.002	45–60 (shore A)	✓	✓	✓	✓	[118d,191]

platinum an ideal electrode material, e.g., for pacemakers, implantable defibrillators, or electrophysiological catheters. More recently, platinum has been used in neuromodulation devices including brain pacemakers and cochlear implants as well as and in coils and catheters for the treatment of brain aneurysms.[46] Finally, silver is well known for its antibacterial properties, and—in a medical context—this particular metal is typically employed in the form of nanoparticles. Yet, there are also examples where silver creates a surface finish or comprises a bulk component in some medical devices such as surgical tools or small bone replacements.[47]

3.1.2. Ceramics

Ceramics are inorganic, nonmetallic solid materials that are composed of either nonmetal or metal compounds with covalent or ionic bonds. The crystallinity of ceramics ranges from highly oriented to semicrystalline, vitrified, or even amorphous. Due to their excellent mechanical properties and corrosion resistance, ceramics have been employed as implant materials in an expanding range of forms and applications of the last 50 years: examples include active oxides applied for tissue engineering and drug delivery systems, bioinert oxides used in tribology-related, load-bearing applications such as dental implants and artificial joints, and recent developments of nonoxide ceramics, magnetic bioceramics, and bioactive glasses.[48]

In detail, active oxides (calcium phosphates) and bioactive glass ceramics (hydroxyapatite and some glassy matrices) with the ability to elicit a specific response at the interface of the material are usually applied as coatings to enhance the fixation of a device or to act as bone graft substitute.[49] However, although these inert oxides (Al_2O_3, ZrO_2, and alumina-stabilized, zirconia-based composites) and nonoxide ceramics (Si_3N_4, SiC, and TiN) demonstrate superior mechanical properties, they sometimes still require biopolymer-based coatings to enhance their bioactivity, and to improve their tissue integration/regeneration abilities.[50]

3.1.3. Synthetic Polymers

Synthetic polymers or—more specifically—thermoplastic and duroplastic materials, are at least of similarly high importance for biomedical applications as their metal-based counterparts. Polyethylene (PE), for example, is the clinical standard as a counter material in total joint replacements and is also used for catheters.[51] Replacements of small joints, i.e., finger joints, are often completely made from polymeric materials, typically from polypropylene (PP), and PP is further used as material for nondegradable sutures. Owing to its excellent transparency, polymethylmethacrylate (PMMA) is used for intraocular lenses; however, it can also be found in tooth fillings and replacements. Artificial tendons/ligaments are frequently manufactured from polyethylene terephthalate (PET),[52] and polyurethane (PU) as well as polyvinylchloride (PVC) are probably the most common components of medical tubings such as endotracheal tubes, catheters or blood bearing tubings.[53] High-performance thermoplastic materials such as polyetheretherketone (PEEK) are, to a certain degree, even used for load-bearing components, e.g., in intervertebral disc replacements[54] or as dental implants.[55]

Polymeric materials offer a set of advantageous properties: Compared to metal-based and ceramic substrates, they are much easier to process and can often be directly casted into the desired shape. Furthermore, there is already a broad spectrum of synthetic polymers that offer different mechanical and physical properties: For instance, the Young's moduli of polymer materials used in medical engineering range from ≈100 MPa (e.g., low-density PE) to a few GPa (e.g., PEEK); some of these polymer materials are rather ductile whereas others are very stiff.[52] Furthermore, the wettability of technical polymers covers the whole possible spectrum, i.e., from (super) hydrophobic to hydrophilic.[56] Also from a chemical point of view, technical polymers are very interesting for biomedical applications, since their composition can be tuned and post-polymerization modifications are possible. Together, this allows for equipping them with specific properties as required for a selected application.

In addition to thermo- and duroplastic polymers, silicone rubbers are a third important class of synthetic polymers. They belong to the group of "polysiloxanes," consist of crosslinked silicone oils, and are typically very ductile materials. The popularity of silicone rubbers in biomedical applications is mostly due to their bioinert character. The stiffness of silicone rubbers can be tuned to a certain degree—depending on their detailed chemical composition and the density of crosslinks. The stiffness is of those silicone materials typically ranges from 2 to 30 MPa, which makes them particularly interesting for all kinds of soft/flexible implants. Examples include small joint replacements or breast implants, and medical tubings. Some silicone materials, e.g., PDMS, are also highly transparent, which allows them to be used as a contact lens material or for endoscopic windows.

Most of the polymers introduced above are very durable in a physiological environment. However, there are also biodegradable polymers which have gained increased interest in the field of biomedical engineering. Typically, most of them are deposited as coatings onto other substrates; however, sometimes biodegradable polymers also serve as support materials for biopolymer-based coatings. For example, polyvinyl alcohol (PVA) hydrogels and polycaprolactone scaffolds are typically coated with biopolymers to improve their lubrication, adhesion, and hemostasis properties.[57]

3.2. Physical Coating Methods

For all the substrates discussed above, creating a biopolymer-based coating by physical methods is, in principle, possible. Yet, the efficiency of such a physical coating process depends on the strength of physical interactions between the biopolymer and the target substrate. Physical deposition approaches can be divided into two groups: dry coating processes (using polymer powders) and wet coating procedures (using polymer solutions). For the biopolymers we discussed above, wet coating methods are much more suitable since most biopolymers are not able to withstand the high temperatures required for a powder coating procedure. The absence of heating steps renders wet coating

processes applicable to almost any substrate, including temperature-sensitive polymer blends or other delicate composites. Electrospinning, dip coating, and spin coating (**Figure 2**) are the most prominent examples of wet coating techniques, and we briefly highlight those three methods in the following section.

Electrospinning (or, as a slight modification of this method, also electrospraying) is a technique that makes use of electrostatic forces to form thin fibers (or particles) from a polymer solution and to deposit them onto a substrate. Typically, an electrospinning setup is composed of at least three parts: a high voltage supplier to generate an electrically charged jet, a capillary tube (e.g., a pipette or needle) with a small diameter to generate fibers with diameters from tens of nanometers to a few micrometers, and a substrate for collecting the fibers.[58] To enable this voltage-driven deposition process, one electrode is attached to the reservoir containing the biopolymer solution and the other one to the substrate.

When an electric field is applied to the end of the capillary tube, a charge is induced on the surface of the liquid. As the intensity of the electric field is increased, the convex surface of the liquid at the tip is elongated and a conical shape known as the Taylor cone is created.[59] By further increasing the electric field, the repulsive forces within the biopolymer solution overcome its surface tension, and a jet erupts. It is important to realize that, although nearly all soluble polymers can be processed by electrospinning, many parameters can affect the spinnability of biopolymers, e.g., the viscosity of the biopolymer solution, its surface tension and conductivity. Especially the latter is important to consider when selecting a biopolymer: for polycationic/-anionic biopolymers, a good conductivity of the solution is automatically guaranteed by the biopolymers themselves; in contrast, when uncharged biopolymers are to be processed, ions need to be added to the solution. Furthermore, also technical parameters of the setup, e.g., the applied flow rate and electric potential as well as the distance between the tip and substrate, influence the outcome.[60] Since fine-tuning of those parameters is necessary to optimize the coating process, this is a drawback of the electrospinning technique. Nevertheless, a main advantage of electrospinning is its versatility, as it allows for fabricating fibers with a broad range of morphological structures on the one hand and for creating different fibers assemblies with a patterned, aligned or random arrangement on the substrate on the other hand.[61]

Another convenient and economical approach to form coatings onto almost any substrate is dip coating. Here, to functionalize a surface, the substrate is immersed into a solution containing the coating polymer and stored in this solution for a while to allow the biopolymer molecules to adsorb onto the substrate. Afterward, the substrate is removed from the solution and the adsorbed, wet film is dried by solvent evaporation. With

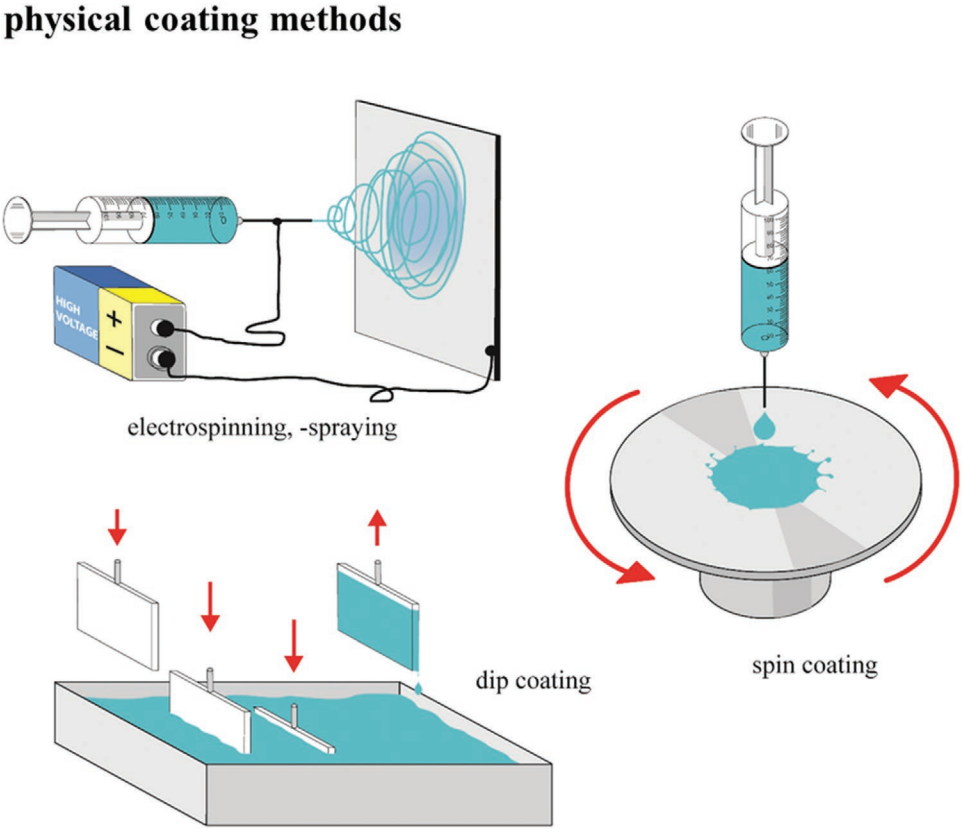


Figure 2. The most frequently used techniques to physically deposit biopolymers onto a substrate include electrospinning, dip coating, and spin coating. Electrospinning makes use of electrostatic forces to form thin from a polymer solution and to deposit them onto a substrate. Dip coating is a method that immerses the substrate into a solution containing the coating polymer to allow the biopolymer molecules to adsorb to the substrate surface. Spin coating is an approach that allows for establishing a homogeneous distribution of biopolymers across the surface of flat substrates via a combination of centrifugal forces and surface tension effects.

this approach, highly uniform coatings are obtained—even on large samples. One item to consider when using dip coating is that the coating thickness is determined by many parameters: the substrate surface, immersion duration (typically in the range of minutes to hours), sample removal speed, number of coating cycles, biopolymer concentration, solution viscosity, and the detailed evaporation conditions of the generated coating are all relevant. This broad set of experimental parameters thus needs to be optimized for each scenario—either empirically or based on theoretical calculations, e.g., according to Landau–Levich theory.[62] Since the polymers attach to the substrate via passive adsorption, the adhesion strength between the coating and the substrate tends to be rather low.[63] Sandblasting of the substrate prior to the dip coating process is a good option to remedy this issue, but the surface roughness of the substrate is increased by this treatment.[64] Other strategies to obtain a better stability of dip coatings include using biopolymers with high unspecific adsorption strengths, e.g., PDA,[38] employing hydrophobic interactions, or electrostatic interactions by selecting a polymer/substrate combination where the two partners have opposite net charges.

Spin coating is another, simple approach for establishing biopolymer-based coatings on flat substrates. Here, the coating process begins with solubilizing and diluting the target biopolymer in a suitable solvent. Then, the biopolymer solution is applied to the center of the substrate; at this step, the substrate can either be static or already set into rotation—albeit at a low angular speed.[65] Afterward, the substrate rotation is rapidly accelerated to a high spin velocity, so that a combination of centrifugal and surface tension effects lead to a homogeneous distribution of the biopolymers across the substrate surface. With this technique, the coating thickness is mainly determined by the spinning speed, the surface tension, and the viscosity of the solution. Although the actual volume of biopolymer solution required for spin coating is (especially compared to dip coating) very low, a considerable amount of material is lost during the spinning process as it is hurled over the edge of the substrate. Different from dip coating, spin coating is difficult to conduct for large substrates since they cannot be rotated at a sufficiently high rate—but this is necessary to obtain a thin and uniform coating.[66] Regarding the stability of the generated coatings, the same considerations as discussed above, i.e., an optimization of the possible binding forces between the chosen substrate and the biopolymer, apply.

The techniques introduced above are routinely used in many labs for the fabrication of biocoatings, at least in such cases where it is not critical to obtain very thin layers. However, for some biomedical devices such as biosensors, ultrathin films (1–100 nm in thickness) are required. Thus, other physical deposition methods, e.g., film formation by Langmuir–Blodgett (LB) troughs,[67] molecular self-assembly,[68] layer-by-layer (LBL) electrostatic deposition[69] and nanopatterning,[70] are sometimes more suitable to prepare very thin (up to monomolecular) layers of biopolymers.

3.3. Chemical Coating Methods

As discussed above, physical coating methods are relatively easy to apply and thus have been employed a lot in the past. However, most of them share a common disadvantage, i.e., the coatings created by them possess only a low stability against mechanical stress, and this can be—dependent on the particular application—an important issue. A good mechanical stability of the coating is of particular importance in such applications, where either the final product is exposed to mechanical forces (this is, e.g., the case for stents, artificial joints, or catheters) or when the liberation of single molecules from the coating layer could create a problem, e.g., if the molecules used for coating can cause side effects in the human body. For those application areas, it is often mandatory to generate highly stable coatings by creating chemical, covalent connections between the biopolymer layer and the substrate.

In general, two different strategies exist to generate such covalently coupled polymer coatings on a substrate: First, the whole molecule can be attached to the surface by creating suitable binding sites, either on the substrate or on the polymer (or on both). This approach is typically referred to as a "grafting to"-method. Vice versa, "grafting from"-approaches rely on the attachment of small initiator molecules to the surface, which are then used to polymerize the macromolecular coating directly on the surface. Thus, this strategy is limited to such coatings, where the macromolecule can be synthesized in situ; as a consequence, for most biopolymers, "grafting to"-methods have to be used when a covalent coating shall be generated. Owing to the broad diversity of biopolymers, there is a multitude of functional groups that can be targeted by chemical coupling efforts. As we cannot provide a complete list of those different chemical coupling strategies here, we rather aim at introducing the reader to three of the most common approaches (**Figure 3**).

One of the most frequently applied groups of coupling strategies employs the crosslinker molecule glutaraldehyde (GA). GA readily reacts with a multitude of functional groups including primary amines, thiol, phenol and imidazole residues,[71] and many of those groups can be found in biopolymers. This broad reactivity renders GA-based coupling a simple and effective tool for the creation of biopolymer coatings. However, to use this strategy, a GA layer needs to be immobilized on the substrate. Such an immobilization of reactive GA is often achieved by generating a primer layer on the substrate first, and for many substrates including different siloxanes, mica or titanium alloys, amine functionalized silane molecules ((3-aminopropyl)triethoxysilane = APTES) have become a popular choice for this purpose.[72] Whereas silanes readily react with hydroxy groups[72a] (and such hydroxy groups can be generated easily on many synthetic polymer materials via oxygen plasma activation,[73] corona discharge,[74] thermal treatment,[75] or solvent oxidization[76]), the primary amine of APTES offers an anchor to which the GA crosslinker can be bound. Then, in a final step, the GA-functionalized surface is incubated with the target biopolymer, which then spontaneously attaches to the GA linker, e.g., via aldol condensation or Michael-type addition.[77]

A second chemical strategy that is well-established in the field of biopolymer coatings is carbodiimide coupling. Although coming with more specific requirements than GA-based coupling reactions, carbodiimide coupling is still applicable for a variety of biopolymers: in this strategy, two of the most abundant functional groups in biopolymer systems are covalently connected, i.e., carboxylic acids residues are coupled to primary

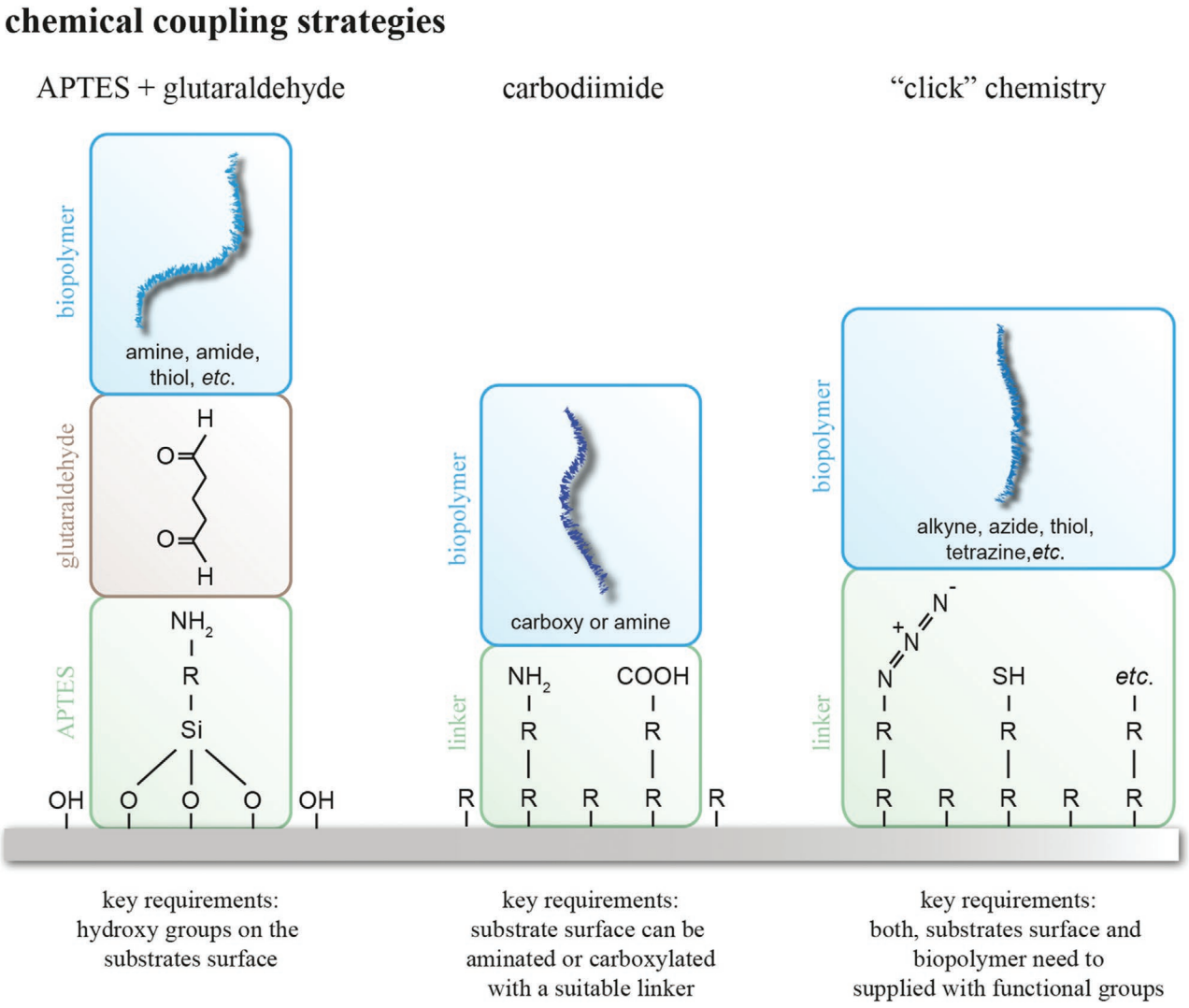


Figure 3. Some of the most frequently used strategies to covalently immobilize biopolymers onto a substrate include linking approaches making use of a combination of APTES and glutaraldehyde, carbodiimide coupling, or "click"-chemistry. Those strategies employ specific linker molecules that later allow for targeting different functional groups on the biopolymers.

amines. To perform this coupling reaction, the carboxylic acid-containing moieties are exposed to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) (or *N*-hydroxysulfosuccinimide = sulfo-NHS), which then form a reactive intermediate. Then, when amine groups are brought into contact with those activated carboxylic acids residues, an amide bond is formed, and an EDC/NHS by-product is released into the solution.[78] Different from GA-based coupling strategies (where the GA crosslinker becomes a spacer molecule between the binding partners), carbodiimide coupling is considered a zero-length crosslinking strategy. Of course, this carbodiimide coupling strategy requires the presence of specific functional groups on the surface of the substrate, i.e., either primary amines or carboxylic acid groups. As for GA-based coupling strategies, silanes (e.g., APTES to generate amine groups) or *N*-[(3-trimethoxysilyl)propyl]-ethylenediamine triacetic acid (TMS-EDTA to obtain carboxyl groups), can be used as a primer layer if the required functional groups are not present on the substrate yet. In addition, there is a plethora of other strategies to aminate[79] or carboxylate[80] the surface of a substrate. It depends on the specific chemistry of the substrate surface, which of those activation strategies is most suitable.

As a third approach to immobilize biopolymers on a surface, we would like to mention "click"-chemistry. "Click" reactions are a group of mechanisms that, per definition, should be modular, facile, highly efficient, and do not generate any (or only uncritical) byproducts.[81] The latter is a key advantage of "click"-chemistry as, in biomedical applications, toxic side-products can often be problematic, e.g., when they compromise the biocompatibility of a product. Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has emerged as one of the most popular methods to employ the principle of "click"-chemistry.[82] Other well-known reactions from the "click"-family include thiol–ene addition reactions[83] and (hetero) Diels–Alder (D–A) reactions.[84] Typically, also these "click" reactions require the deposition of a suitable linker molecule, i.e., a primer, which offers

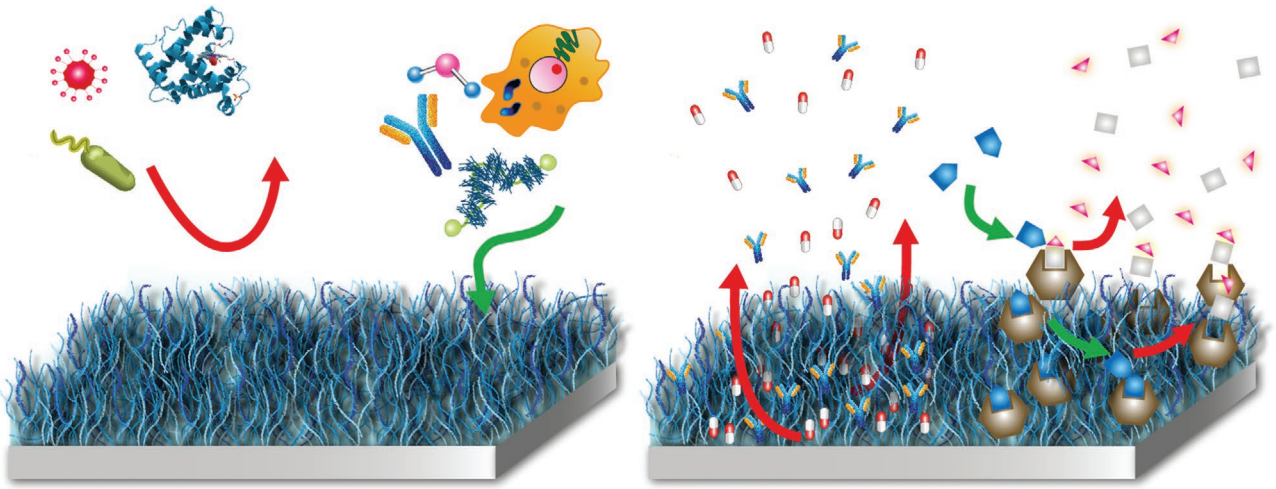
suitable functional groups for the chemical reaction, onto the substrate prior to biopolymer coupling. For this purpose, different precoatings have been proposed in the literature, which enable the conjugation of biomolecules via "click"-chemistry. Examples include self-assembled, azide functionalized monolayers,[85] silanes,[86] or hetero-bifunctional PEG.[87]

4. Coatings for Biomedical Applications

Physiologically, biomacromolecules exist not only in solubilized form, i.e., as components of different body fluids, but they are also present in surface-bound configurations. There, they fulfill crucial functions, e.g., they act as selective barriers for nutrients and pathogens or as mediators for cell signaling.[88] Inspired by this biological role model, surface-immobilized macromolecules are also employed for a variety of biomedical applications. Most of those strategies share a common objective, i.e., they aim at gaining control over molecular and cellular binding to the coated surface. Depending on the particular application, the goal is to either promote or prevent binding events, or to only allow binding for a certain subset of molecules or cells (**Figure 4**). Other applications, however, might require properties of the coating which go beyond the ability to control binding and unbinding. Examples include—but are not limited to—controlling/maintaining the conductivity of the coated object, e.g., for pacemakers[89] or neural electrodes,[90] or its transparency, e.g., for endoscopes.[91] In the following, we will discuss four different categories of functional coatings that either aim at creating lubricious or antifouling surfaces, promote cellular adhesion, act as a drug delivery system or work as a biosensor, and we give examples of applications for which these coatings have and can be used.

4.1. Biotribology and Antibiofouling

Strongly hydrated macromolecules can supply a thin water film on the surface of a substrate. Such a surface-bound water film can act as a lubricious coating, and binding of water molecules is most efficient for (zwitter)ionic coatings.[92] Ideally, the hydrated macromolecule is attached to the material surface in a brush-like manner: then, both, an optimal coating density and surface separation are achieved.[93] For surfaces exposed to tribological shear forces, the stability of the coating is highly important to guarantee lubricity over extended time periods.



Control over molecular adsorption	Control over cellular adhesion	(Controlled) molecular release	Surface mediated reactions
● Lubricin coating to suppress biofouling	● PDA coating for skin tissue repair	● Degradable chitosan-based coating for drug release from implant surfaces	● Antibody-based coating for virus detection
● Mucin coating to improve the lubricity of contact lenses	● HA coating for bone regeneration	● Stimuli-responsive multilayer coatings to release drugs in presence of bacteria	● Enzyme coated optical fibers as waveguide-based biosensors
● Heparin coatings to prevent the adsorption of blood cells	● Chitosan coating for wound dressing		● Chitosan/tyrosinase coating for phenol detection

Figure 4. The main purpose of most coating strategies applied in biomedical applications is to gain control over the binding of molecules and cells. Such "control" strategies may also include the release of previously bound molecules for drug delivery applications. Moreover, some applications, e.g., biosensors, use surface-bound macromolecules to enable chemical reactions.

Consequently, covalent coating strategies are generally preferred for those applications. However, when the shear forces acting on the coating are comparably low, also physical coating strategies can be sufficient. In the last years, different studies have demonstrated how lubricious coatings can be generated via covalent coupling strategies (see Section 3.3.) by making use of biopolymers such as pectin, lubricin, chitosan, mucin, and PLL.[86,94] Among the noncovalent coating techniques, dopamine mediated immobilization of lubricious polymers has gained increasing interest.[95]

From a developer's point of view, (super)low friction coatings are of great interest for all applications, where a medical implant/device mechanically challenges a (soft/sensitive) biological tissue. Some prominent examples include contact lenses, cartilage and artificial joint prostheses, catheters, intubation tubes, or dental braces. In the field of contact lens development, different biopolymer coatings have already been introduced to improve the lubricity of contact lenses.[94b,96] Here, however, another property of the coating becomes essential, i.e., its transparency. A high coating transparency can sometimes be difficult to achieve; in part, this can be due to the detailed coating chemistry chosen; for instance, whereas lubricin and mucin are structurally very similar biopolymers both of which create lubricious coatings, the transparency of lubricin coatings was reported to be considerably lower than that of mucin coatings.[94b,97] Furthermore, biopolymer coatings generated from chitosan have been shown to improve the tribological characteristics of medical catheters in vitro: with this coating, both, the lubricity and wettability of endovascular catheters were increased.[98] Moreover, also materials for biomedical applications, where high loads need to be carried (such as total hip joint replacements), benefit from a lubricious biopolymer coating[99] since biopolymer-based coatings can improve the wear and corrosion resistance of substrates. Examples include coatings generated from mucin,[86] chitosan,[100] HA,[101] cellulose,[102] and certain proteins.[103] By rendering the coated material more resistant toward the tribological and corrosive challenges they are exposed to in a biologically relevant environment, the residence time of artificial medical devices in the human body can be extended.

Whereas attaching lubricious molecules to a surface is helpful for such biomedical applications, where lubricity, wear and corrosion protection are needed, the uncontrolled adsorption of molecules is almost always undesirable. For many medical implants, e.g., catheters, endotracheal tubes, stents, artificial heart valves or shunts, the deposition of proteins, pathogens or cells on the device surface is a major cause for device-associated infections, and this severely compromises the functionality of the implant.[104] Consequently, preventing these so-called biofouling events is an important concern in the development of medical products.

Whereas antifouling surfaces used in technical settings often employ toxic coatings to suppress the adhesion of living organisms,[105] this is not possible for biomedical implants and devices: here, controlling the wettability of the surface can be a helpful strategy, but also charge effects or specific chemical motifs that hinder binding events contribute to the fouling resistance of a surface.[104b,106] Yet, it is difficult to find one antifouling coating that suits all biomedical applications; instead, it is important to know the detailed biological/biochemical environment in which the fouling events occur—and this can be very different for a stent exposed to blood and for a bone substitution plate implanted into the skull.

Thus, it is not surprising that many different biopolymers have been introduced as components of antifouling coatings. Heparin, for example, is well-known for its anticoagulant properties and reduces the adhesion of certain bacteria to surfaces.[107] Owing to those properties, heparin has been put forward as a coating molecule for materials, which come in direct contact with the hematogenous system.[108] Also, coatings comprising mucin glycoproteins have anti-biofouling properties: they can lower the adhesion efficiency of different bacteria including *S. aureus*, *S. pneumoniae*, and *S. epidermis*.[56,109] Similarly, also coatings employing the mucinous glycoprotein lubricin reduce antibiofouling events by counteracting unspecific protein adsorption[110] and fibroblast adhesion.[111] Other biopolymer coatings which possess antiadhesive properties include those generated from chitosan,[94c,112] phosphorylcholine,[113] dextran[114] and poly (L-lactic) acid.[115] In addition to those anti-adhesive biopolymers, also antimicrobial peptides can overcome biofouling events when immobilized onto a surface via one of the coating strategies discussed above; however, their mode of action is different as they actively eliminate pathogens as soon as they adhere to the surface.[116] Indeed, Yu et al.[117] recently demonstrated in a mouse model that such antimicrobial peptides are a powerful tool to tackle catheter-associated urinary tract infections.

4.2. Promoting Cellular Adhesion

Control over cellular binding is a key goal in all tissue engineering strategies: also here, biomacromolecules have shown to be a promising and versatile tool to achieve a controlled integration of scaffolds and implants into the body environment.[118] Most strategies aim at improving the cell-adhesive characteristics of a material or at actively inducing cell migration, proliferation, and differentiation.[119]

Typical examples of biopolymers employed as coatings for tissue engineering applications include PDA, HA, and chitosan, and their properties have been extensively investigated in recent years. Thus, we will focus on discussing those three examples below. Of course, other biopolymer-based coatings such as PLL,[120] pectin,[121] and fibronectin[122] are used in tissue engineering approaches as well. Moreover, some biopolymer-based hybrid coatings, e.g., HA/chitosan,[123] HA/cationized gelatin,[124] and alginate/chitosan,[125] have been explored regarding tissue engineering applications.

Owing to its excellent and unspecific binding abilities (see Section 2.4.), PDA is one of the most frequently used biopolymers enhancing cell adhesion. In fact, Ku et al.[126] suggested that PDA coatings can promote cell adhesion on any type of substrate including PTFE surfaces, which typically repel cells very efficiently. PDA coatings are thought to alter the wettability of substrates, promote the immobilization of adhesive proteins onto the surface and ultimately lead to better cell adhesion.[126–127] Thus, PDA coatings have been successfully deposited onto diverse 3D structures to achieve enhanced bone regeneration,[128]

periodontal tissue regeneration[129] and skin tissue repair.[130] However, not all cells adhere well to such PDA functionalized surfaces. For instance, a PDA coating is reported to enhance the proliferation, viability, and migration of endothelial cells, but reduces the same set of parameters for smooth muscle cells.[131] This cell-specific effect of a PDA coating can be regulated by several parameters including the PDA concentration and temperature level used during the coating process.[131–132]

Another popular biomacromolecule used in tissue engineering research is HA. As an important physiological component of extracellular matrices, it can modulate cell signaling, proliferation, and differentiation. Su et al.[133] prepared decellularized scaffolds coated with HA and concluded that HA increases the adsorption of epidermal growth factors into the scaffolds thus significantly promoting the recovery of wounded skin tissue. However, similar to PDA, it was reported that HA coatings can inhibit fibroblast cell proliferation.[134] Regarding bone tissue engineering applications, Antunes et al.[135] coated poly(L-lactic acid) scaffolds with HA and found that the HA coating can help guide morphogenesis and bone tissue repair. Furthermore, Lebourg et al.[57a] indicated that the detailed microstructure of HA coatings can influence chondrocyte response, and this microstructure can be modulated by employing the electrospinning technique introduced above (see Section 3.2).[136] In addition, the molecular weight of HA is another important parameter that can affect the cellular response: substrates coated with high molecular weight HA show lower levels of cell adhesion and cell-matrix interaction compared to those coated with low molecular weight HA—and this could be due to a rougher and more hydrophilic surface brought about by the former variant.[137] As HA is commercially available in different molecular weights, also this parameter can be controlled in tissue engineering applications.

A third big player in the field of biopolymer coatings for tissue engineering applications is chitosan. Chitosan can be molded into various geometries and triggers only minimal foreign body reactions, and it was shown to be suitable for promoting cell ingrowth and osteoconduction.[138] When applied as a coating on medical-grade titanium substrates, chitosan improves cell adhesion and proliferation, thus demonstrating its great potential for orthopedic and craniofacial/dental implants.[118a,139] As chitosan is degradable by the human body, coatings based on this biopolymer are also employed for wound dressing materials: here, the biopolymer ensures beneficial cellular responses such as keratinocyte migration and wound re-epithelialization.[140] Commercial chitosan is available with different degrees of deacetylation, and this chemical aspect of the macromolecule needs to be taken into consideration regarding the cellular response toward chitosan: For example, although all chitosan variants are nontoxic, cells are unable to adhere to surfaces coated with chitosan that have a low degree of deacetylation.[141] Moreover, Chatelet et al.[142] suggested that the surface morphology of the coated material is a second major parameter that influences cell adhesion.

4.3. Drug Delivery

A third research area, where biopolymer-based coatings have emerged as a powerful tool is the field of drug delivery. Here, stealth coatings,[143] coatings for (cell) specific targeting[144] or coatings as drug depots[145] have applications in nanomedicine, but also macroscopic pharmaceutical objects such as dragées[146] benefit from a coating. Moreover, drug-loaded implant coatings have gained increasing interest; their function is to deal with exogenous pathogens, which enter the surgical site during an implantation operation.[147] This is necessary since, even though anti-biofouling coatings as introduced in Section 4.1. are capable of suppressing many biofouling events taking place directly at the implant/body interface, bacterial infections in the surrounding tissue can still occur.

Although, in clinical practice, the systemic administration of antibiotics after such surgery is still the state-of-the-art, considerable progress has been made in supplying drugs locally via coatings. Here, a precise control over the binding of molecules onto and subsequent release from coated surfaces is the key to success. The most common strategies employing biopolymer coatings for drug delivery systems aim at regulating the duration of the release event by either acting as a diffusion barrier or by temporarily sealing a drug reservoir.[146,148] For example, Gulati et al.[149] developed a drug-loaded, biodegradable coating on titanium implant surfaces that is based on chitosan and polylactic acid. The biopolymer coating serves as a lid for the drug reservoirs; by varying the coating thickness, both, the strength of the coating to act as a diffusion barrier and the degradation time of the coating could be tuned, and this combination allowed for adapting the duration of the drug release event.

However, whereas such strategies are indeed successful in improving the release profile of a drug and altering the release such that it follows zero-order kinetics, they do not offer control over the starting point of the release event. Thus, to allow for an "on-demand" delivery of drugs, other approaches have been proposed in the literature. Recently, Xu et al.[150] presented a drug-loaded PLL-based multilayer coating, which was designed to degrade in the presence of bacteria, thus releasing an antibiotic (and fighting the bacteria) only when needed. Similarly, Cado et al.[151] developed an HA-based surface coating, which releases an antimicrobial peptide targeting both, bacteria and yeast cells; also here, release was only triggered when the pathogens where present, i.e., when the coating was exposed to metabolic products generated by the microbes.

4.4. Biosensing

A fourth area, where coatings with biological macromolecules are important are biological sensors. Here, their function relies on the principle that selected molecules specifically bind to a substrate to become detectable.[152] The required high selectivity is often achieved by immobilizing biomacromolecules such as antibodies onto the substrate surface. One of the latest examples of such an antibody-coated biological sensor is certainly the SARS-CoV-2 test which detects the COVID-19 virus.[153] However, similar mechanisms are also employed in other sensor applications to test for target molecules or determine levels of gene expression.[154] Home pregnancy tests and urinalysis strips are two examples of well-known, commercially available tests from this category.[155]

Yet, biopolymer coatings are not only used to immobilize targets but can also enable chemical reactions with target molecules by embedding reactive molecules. Such chemical reactions can either create a color signal (e.g., by enzymatic conversion of a substrate) or an electrochemical signal (e.g., through oxidizing reactions), and those signals can be further quantified by suitable analytical detection methods.[156] In this context, the typically poor conductivity of most biopolymers can be an issue. Yet, DNA biopolymers have been found to be suitable candidates here as they provide low optical loss and a high electrical conductivity—even compared to inorganic polymer counterparts. Thus, oligonucleotides have been employed as a conductive cladding layer in polymer electrooptic waveguide modulators.[157] Furthermore, chitosan, whose functional groups include amino and hydroxyl groups, can be utilized as an electron donor and is therefore used for sensing applications.[158] Abdullah et al.[159] deposited a chitosan coating containing tyrosinase onto a glass-based biosensor surface; then, they employed this coating to detect phenol via the produced maroon-color adduct. Another example—this time making use of an electrochemical interaction—is the study presented by Geng et al.:[160] here, the researchers developed a biosensor coated with alginic acid with the goal to detect DNA sequences specific for *Escherichia coli*. Since biosensors can be quite expensive, biopolymer coatings are not only used for biomarker detection but also for biosensor regeneration. For instance, enzyme ligation offers the possibility to catalyze reversible bond-forming reactions that enable the molecular regeneration of a biopolymer coated biosensor in situ.[161]

Indeed, biopolymers demonstrate several benefits for biosensing applications. To obtain better electrical conductivity as well as chemical and mechanical resistance, composite coatings comprising a mixture of biopolymers and other functional materials, e.g., iron oxide,[162] carbon nanotube,[163] and silicon,[164] have been proposed.

5. Conclusion and Outlook

In this progress report, we gave an overview of the current state-of-the-art how biopolymer-based coatings are employed to improve the functionality and/or biocompatibility of artificial materials to enhance their suitability for biomedical applications. Yet, although the biopolymer-based coatings studied so far have shown very promising and encouraging results (some of them have indeed already led to improved medical products), the range of biomolecules used so far in coating approaches is still rather limited. Here, exploring more broadly the options nature offers and expanding the range of biopolymers tested as components for coatings will certainly provide new insights and novel opportunities to open the field to further applications. For instance, PDA-based coatings inspired by the adhesion strategy of mussels are only about ten years old, but have nevertheless already demonstrated extremely high versatility and a large number of successful applications.[165]

Of course, the need to generate a stable surface coating limits the use of certain biomolecules—especially if their chemical structure does not offer any good options to covalently couple them to an artificial material. This limitation may, however, soon be remedied by emerging additive manufacturing methods and computer-aided technologies. For example, artificial intelligence and machine learning may help scientists to better plan how to adjust the chemical structure of biopolymers so that they acquire specific functions as needed for a particular application.[166] Moreover, if novel fabrication techniques such as 3D/4D printing are further developed to create complex structures containing biopolymer components, artificial hybrid materials can be printed directly into the shape needed for a biomedical device while installing tailored surface properties (and thus functionalities) during the printing process at the same time.[167] Also here, making use of artificial intelligence contributions may help us choose optimal fabrication parameters, build suitable structural features and thus lead to smarter manufacturing processes and a precise creation of the desired functional performance of coated surfaces.[168] As a result, a new generation of coatings with programmable properties might be within our grasp.

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Conflict of Interest

The authors declare no conflict of interest.

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biomaterials, biomedical application, biopolymers, coating, surface functionalization

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