Surface Modification of Porous Anodic Alumina for Medical and Biological Applications

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Introduction

Membranes are one of the key elements of medical, biological, chemical and environmental industries [1]. In the last decades, the emergence of nanotechnology has led to the fabrication of high-performance nanoporous membranes with well-defined properties and pores sizes. Nanoporous membranes have been used for numerous medical and biological applications [2], including biosensors [3, 4], protein separation and DNA sequencing [5, 6], cell growth [7, 8], tissue engineering [8] and drug delivery [9]. The potential applications of membranes are strongly determined and influenced by the physical and chemical properties of a membrane material. The other important parameters of effective membranes are pores size, uniformity, porosity, thickness, aspect ratio, surface chemistry and morphology [10]. Membranes used in biological and medical environments should also have very good biocompatibility as well as excellent physical and chemical stability. Solid state membranes made of inorganic materials, such as oxides (Al, Si, Ti, Nb, Zr, W, Ta oxides), are well-known for their mechanical stability and robustness. They can be prepared by different methods to achieve nanopores with well-engineered pore size, shape and aspect ratio. Anodization is one of the methods which is most commonly used for their production because it is a simple and scalable method that offers a unique control over the membrane pore shape, size, thickness and chemical composition.

Nanoporous anodic aluminum oxide (AAO) membranes have been the center of the attention since 1995 [11], due to their fast, facile and cheap fabrication. AAO can be easily fabricated by simple anodization of aluminum in an acidic electrolyte. Different anodization regimes can be applied in the fabrication process, leading to different pore diameters in the range of 10-450 nm [12, 13]. The two-step anodization of aluminum gives rise to a well-ordered closed pack hexagonal porous oxide structure, with vertical pores that have almost the same pore sizes and pore distances. All these properties have made AAO a very popular materials platform for different membrane applications, such as separation, filtration, catalysis and chemical reactors [14, 15]. However, the use of AAO in biomedical applications has been limited owing to its low chemical stability in acidic or basic conditions [16]. Biocompatibility of AAO has also not been well established yet [17, 18]. For this reason researchers have been trying to modify and improve the surface of AAO by different biocompatible materials [19-23]. The advantage of this surface modification approach is that it largely preserves the nanoporous structure of AAO templates, while opening up a range of new possibilities to improve its chemical, physical and biological properties. Depending on the purpose and the applications, different types of fabrication methods and materials can be used to modify the surface of AAO structures.

In this chapter, we review a range of different surface modification methods and materials that have been applied to AAO membranes over the past years. In particular we focus on the surface modifications that are suitable for biomedical applications and discuss their advantages and disadvantages. We summarize different available surface modifications techniques, including chemical immobilization (grafting) [24], sol-gel [25], thermal evaporation [26], atomic layer deposition [27] and chemical vapor deposition [28]. The use of these techniques for the fabrication of surface modified AAO membranes using different types of materials is discussed. We describe how these techniques can modify the surface of AAO templates to improve its surface properties, such as surface charge, surface chemistry, porosity, hydrophobicity, selectivity, surface activity, permeability, protein and cell adhesion. Under the surface modification methods, we also review different types of materials used for surface modifications, including metals, silica, polymers, diamond and diamond-like carbon. We present an overview of how surface modified AAO membranes have been used for drug separation, microbe detection, protein adsorption, purification and sensing [19, 29-32]. Finally, we discuss possible future directions and challenges of surface modified membranes.
Fabrication and Properties of Uncoated Anodic Alumina

Anodic porous alumina (AAO) membranes have been intensively studied by many different groups all over the world [11, 33-39]. AAO is a relatively robust porous ceramic material which has a great potential in drug delivery [40], bio-sensing [31, 32, 41], bio-patterning [7, 29], bio-separation [6, 42], catalysis [10] and many other applications [14, 33]. AAO is obtained by electrochemical etching of aluminum in an acidic electrolyte. Figure 18.1.a shows a simple setup for anodization of aluminum. A piece of aluminum foil is set in front of another electrode (e.g. graphite or platinum) in an electrolyte solution, and an electric field is applied over the two electrodes. The acidic electrolyte contains both positive (H$^+$) and negative (e.g. X-O$^-$ & X-O$^{2-}$) ions and they accelerate as a result of the applied electric field. Positive hydrogen ions travel to the cathode and turn to hydrogen gas by receiving an electron. Negative ions, on the other hand, move toward the anode (aluminum), giving rise to the following chemical process:

\[
\begin{align*}
(1) & \quad 2\text{Al}^{3+} + 3\text{O}^{2-} \rightarrow \text{Al}_2\text{O}_3, \\
(2) & \quad \text{Al}_2\text{O}_3 + 6\text{H}^+ \rightarrow 2\text{Al}^{3+} (\text{aq}) + 3\text{H}_2\text{O}.
\end{align*}
\]

Reaction (1) & (2) leads to the formation and dissolution of aluminum oxide, respectively. The anodization conditions are crucial because they determine the rate of the formation and dissolution of the oxide layer. Higher formation rates lead to the growth of the oxide layer. This process is called anodization. Whereas higher dissolution rates produce a polished surface of the metal and therefore this process is called electropolish. In anodization process, the formed oxide layer is usually porous as a result of the penetration of the ions into the formed oxide layer [43].

In 1995, Masuda and Fokuda reported the formation of the ordered porous structure of AAO by controlling the anodization process using selected acid solutions, applied voltages and temperatures [11]. The formed structure was a close packed array of uniform cylindrical pores arranged in a hexagonal form (Figure 18.1.b). Their method is known as “two-step anodization”, and is schematically described in Figure 18.1.c. In the first step of anodization, random pores nucleate at different positions of the aluminum surface, but as they grow more towards the inside of the material, they become more regular in a self-organized manner. The formed oxide is chemically removed at the end of the first step, leaving the ordered pattern on the aluminum surface. By anodizing the patterned aluminum in the second step (with the same anodization conditions as the first step), an ordered porous oxide structure is formed as shown in Figure 18.1.b. Finally, the aluminum substrate can be removed to form a free-standing AAO membrane. There have been reported different chemical and electrochemical methods to detach the oxide layer from the aluminum substrate to achieve a free standing AAO membrane [44, 45].
The thickness of the formed oxide layer depends on the anodization time, and it can range from 100 nm up to few hundred microns [33, 34]. The growth rate is usually very low (≈1-2 μm h⁻¹), but by using different anodization conditions in a so called “hard anodization” it can be as high as 70 μm h⁻¹ [35]. The size and the distance of the pores can also be precisely controlled by using anodization parameters such as applied voltage, temperature, electrolyte type and concentration [34, 39]. Pore size can be tuned from 10 to 650 nm, and the porosity can reach up to 50% [12, 13]. Although the resulting pore size strongly depends on the applied voltage it can also be tuned by the type of electrolyte and widened by post chemical etching [45]. Figure 18.2. shows a graph of commonly used electrolytes and a range of voltages to achieve different interpore distances. Fabrication of different pore shapes of AAO has also been reported by pre-texturing the aluminum surface with triangle or square shaped holes before the anodization process [36]. This pre-texturing allows even a change in the arrangement of the pores in AAO. For more details on the anodization process and how to obtain controllably different pore structures in AAO membranes we refer readers to recent reviews [34, 46].
Various interesting AAO nanoarchitectures can be obtained with anodization when cleverly engineered. For example Li et al. [47] reported the fabrication of Y-branched carbon nanotubes inside the branched pores of AAO. A fast formation of three-dimensional pore structures with variable pore sizes inside the channels has been reported by Mayamai et al. [38]. Zhao et al. [37] fabricated different pores in the shape of nanocontainers. Anodic alumina tubular membranes have also received a lot of interests and there is a great potential to use them for drug delivery or as filters [48, 49]. These examples show that the control over the nanostructure shape and size in the anodization process is quiet unique. Nanopores in AAO membranes can be made in an array of uniform, cylindrical, straight and various other pore shapes. Additionally, this fabrication process is cheap, straight forward and very consistent and therefore it is suitable for large scale production [34].

As a result of the anodization process, the surface chemistry of AAO is complicated. The AAO material in addition to aluminum oxide contains also some other anion contaminations from the anodization process, which diffused from the electrolyte into the formed oxide during the fabrication process [45]. For this reason, the surface of AAO contains a combination of different atomic and molecular bonding such as oxides, hydroxides, carboxyl and etc. [45]. It is very important to note that anodic aluminum oxide is very different from pure aluminum oxide (e.g. sapphire) in terms of the atomic structure, chemistry and chemical stability. AAO is amorphous and dissolves in most of acidic or basic conditions [16]. Consequently, the biocompatibility of AAO varies in the literature [17, 18]. All these drawbacks strictly limit the direct application of AAO in different biomedical applications. However, these limitations can be overcome by modifying the surface and surface chemistry of AAO by different materials and coatings. These coatings can be made of other materials with better bioresistivity and biocompatibility than AAO. Additionally, the surface of AAO can also be functionalized with different organic and inorganic molecules to be used for other advanced applications that would not be possible with uncoated AAO. In the next section we review different methods and materials for surface modification and functionalization of AAO for various biomedical applications.

**Surface Modification Methods**

As mentioned in the previous section, despite of the great aspects of AAO, its surface chemistry is not suitable for biomedical applications. The best approach to make the structure more biocompatible and chemically stable is to modify the surface with other materials. This approach provides an attractive and versatile strategy for fabrication of nanoporous AAO-based materials with different and improved physical and chemical properties. Both organic and inorganic materials can be used for the surface modification and functionalization of AAO. Over the last years, the surface of AAO have been coated with different materials, such as polymers [20, 24, 40, 50-52], proteins [53, 54], DNAs [29], metals [26], oxides [19, 25, 55-58], diamond [59, 60] and diamond-like carbon [26, 59, 61]. Figure 18.3. shows a schematic illustration of an ideal surface modification of AAO, where all the surface of nanoporous AAO is uniformly and homogenously coated with a more resistive, robust and biocompatible material, while maintaining the original nanoporous structure. The most common methods to fabricate these coatings are as follows: physical evaporation [26], grafting [52], sol-gel [19, 25], (electro-)chemical deposition, chemical vapor deposition (CVD) [28, 59, 61], plasma deposition [22], and atomic layer deposition [27, 57]. Each of these methods has got its advantages and disadvantages. In the following text, we describe these methods in more detail, overview different materials that they can produce and discuss how they are suitable for surface modification of nanoporous AAO and biomedical applications.
**Grafting methods**

Grafting is a technique to covalently immobilize a molecule (usually polymer) to a surface. The process happens by immersing a membrane into a grafting solution. A grafting solution usually contains polymer chains, a linking molecule and a catalyst. The linking molecule is attached at the end of the polymer and covalently bonds to the surface of a membrane in the presence of the catalyst. Temperature, polymer type and concentration are effective parameters in this method [20]. Popat et al. [20] have applied this grafting method by attaching poly(ethylene glycol) (PEG) to the surface of AAO. The reaction is shown in Figure 18.4. A PEG-OSiCl₃ couple forms by reacting PEG with silicon tetrachloride in the presence of triethylamine as a catalyst. Then the PEG-OSiCl₃ reacts with the -OH groups on the surface of the membrane, by forming a covalent bonding network of Si-O-Si bonds on the surface interface, resulting in a PEG-immobilized on the alumina surface. The thickness of the PEG layer on AAO was ~2.5 nm and it covered both the pore walls and the top surface of the membrane [20]. PEG coatings have been used in this study for their good biocompatibility and low protein fouling. As a result the PEG-modified membranes have shown 70% less protein adsorption compared to the non-modified membranes [20].

**FIGURE 18.3**
Schematic illustration of an ideal surface modification of an AAO membrane, where the entire inner and outer surface is coated by a more resistive, robust and compatible material, while maintaining the original structure of nanoporous AAO

**FIGURE 18.4**
Reaction mechanism of PEG immobilization on alumina surfaces using a covalent grafting technique. (Adapted with permission from [20]. Copyright (2004) American Chemical Society.)
In another study, a grafting method has been used to cover the top surface of AAO by hyperbranched poly(acrylic acid) (PAA) without filling the pores (Figure 18.5) [52]. This approach is suitable for encapsulation of the pores and might find its application in drug delivery. First a 5 nm thick gold layer was evaporated on the top surface of AAO membrane, as a grafting layer. A monolayer mixed anhydrides were formed on the gold layer which then had been used as an attachment point for the grafting of a PAA layer. The advantage of this process is that the molecular grafting can be repeated several times resulting in a hyperbranched PAA film. Although a hyperbranched 6-layer PAA film covered the whole top surface of AAO, it did not block the inside of 20 nm pores of the AAO template as schematically shown in Figure 18.5. PAA is a biocompatible material which is suitable for biological studies. Moreover it can be further modified to show fluorescent and/or hydrophobic characteristics [62].

![Figure 18.5](image)

**FIGURE 18.5**
PAA grafting to the top surface of an AAO membrane: a) idealized formation and b) schematics of the mechanism. (Adapted with permission from [52]. Copyright (2000) American Chemical Society.)

Generally polymer grafting is one of the easiest and cheapest methods to attach polymers to the surface, but there are some problematic issues associated with it [63]. First of all the surface chemistry of AAO is usually not homogenous because it contains different hydroxyl, oxide and carboxyl groups on the surface [33, 43]. This might result in incomplete coverage of the grafted molecules on the surface. This can be overcome by using other techniques, such as an hydrogen peroxide treatment [64], which can maximize the -OH bonding groups on the surface of AAO. Secondly, polymers are usually suffering from some drawbacks such as short life time, inhomogeneous structure, limited chemical and biological stability and functionality [65]. Therefore these coatings on AAO will be applicable only for applications which require a short term usage in biomedical environments.

**Sol-gel methods**

Generally, the term “sol-gel” denotes the formation of a solid material remained after hydrolysis of the adsorbed molecules and subsequent evaporation of the solvent part of the precursor. Sol-gel is a widely used technique to synthesize silicon and titanium oxide structures, and there have appeared different alternatives of this process in the literature [3, 19, 25, 42, 56]. One of the main disadvantages of the sol-gel methods is that they are limited to a certain type of materials and they contain traces of the used precursors, which hinders their wider usage.
Figure 18.6 shows an example of a sol-gel process, where the inside of the pores of an AAO membrane is coated with a silica film [56]. It uses SiCl₄ that adsorbs on the surface of AAO, which is then hydrolyzed to SiO₂. CCl₄ is used to wash the solvent after each cycle. The chemical composition of the resulting surface coating is (SiO₂)ₓ(SiOH)ₙ [56]. The advantage of this process is that the thickness of the formed layer can be varied by the number of the cycles, where an each cycle adds approximately a 1 nm layer on the surface [56]. In another sol-gel approach, TIP (titanium isopropoxide) or TEOS (tetraethoxysilane) has been used to synthesize TiO₂ and SiO₂ on AAO, respectively [25]. TiO₂ and SiO₂ layers have been formed by a quick immersion of the membrane into a TIP or TEOS solution, respectively.

![Diagram of sol-gel process](image)

**FIGURE 18.6**
An example of a sol-gel process inside the channels of AAO producing free-standing SiO₂ nanotubes by subsequent etching of an AAO membrane. (Adapted with permission from ref [56].)

Sol-gel approach can also be used for reducing the pore size of nanoporous AAO membranes, which might be useful for applications that require pore size < 10 nm. Figure 18.7. shows a formation of well-ordered silica-surfactant nanocomposite channels inside the nanopores of AAO, which has been demonstrated by Yamaguchi et al. [42]. The formed surfactant channels in the nanopores have a parallel arrangement to the channels of AAO with a very narrow pore size diameter of the order of 3.4 nm. This has been achieved by passing the precursor solution through AAO membranes with 25 nm and 47 nm pore sizes [42]. The precursor contained a mixture of TEOS and cetyltrimethylammonium (CTAB). The exact concentration of each precursor in this mixture has shown to play a crucial role on the size of the formed surfactant nanochannels [42]. These nanoscopic AAO-based nanocomposite channels show a great potential for size-exclusive separation of molecules.
FIGURE 18.7
TEM images of an alumina membrane with nanoporous silica–surfactant nanocomposites inside the columnar alumina pores: a) low-magnification top view, b) higher magnification top view, and c) side view. Scale bars correspond to 100 nm (a) and 50 nm (b,c). (Reprinted by permission from Nature Publication, ref [42], copyright (2004))

Atomic Layer Deposition

Atomic layer deposition (ALD) is conformal deposition using sequential, self-limiting surface reactions on the sample surface [27]. In this process, one or more chemical interaction(s) take place on a surface, giving rise to deposition of a thin film, usually a monolayer. ALD is commonly used for deposition of a whole range of oxides (Al₂O₃, HfO₂, HfSiO, La₂O₃, SiO₂, STO, Ta₂O₅, TiO₂, ZnO), nitrides (AlN, HfN, SiNx, TaN, TiN) and metals (Au, Cu, Pt, Ru, W). This method has been successfully applied to deposit oxides in AAO, such as aluminum oxide [28], zinc oxide [55], and titanium and silicon oxides [57]. ALD is a well-controlled method that can be used to reduce the pore size of AAO membranes below 10 nm, as demonstrated by Velleman et al. [23]. In this study, a SiO₂ layer has been deposited on AAO with 20, 100 and 200 nm pore sizes using ALD to reduce the pore size to 1-2 nm. The growth rate of SiO₂ on AAO was estimated to be about 2.5-3 nm/cycle (at 250°C) when using tri(tert-butoxy) silanol and trimethylaluminum (TMA) as precursors and nitrogen to purge the reactor at the end of each cycle. Although ALD is considered as a conformal coating technique, the deposition of the added layer can be different on the surface than inside the nanopores of AAO. Figure 18.8. shows a SEM image of a SiO₂ coated AAO by ALD [23]. Due to the space confinement in the nanometer-sized pores, the deposition inside the pores has a lower rate, and even it can be totally different, than on the top surface. Even though it is not possible to see any changes in the pore size from the profile of AAO in Figure 18.8 the size of the pores is shrunken at the top surface due to the formation of multilayers. The thickness of the deposited layer in ALD decreases as a function of depth from the surface towards the channels inside the material [23]. In a short cycle, the precursors do not have enough time to fill the pores and they are purged by the gas before they completely cover the surface of the pores. This is the reason why ALD methods need to be carefully optimized to achieve conformal deposition inside of confined nanospaces. By adjusting different ALD conditions, it has been possible to fabricate nanotubes and nanowires inside AAO’s channels using ALD (Figure 18.9) [66]. This method employed a combination of a delayed reaction that happened after one (or more) cycle and a partial purge of the chamber, which was used to let some time for the residues to reach and saturate the bottom of the pore walls.
FIGURE 18.8
SEM images of AAO membranes with 200 nm pore size after 20 cycles of ALD deposition of silica. (Adapted from ref [23], Copyright (2009), with permission from Elsevier.)

FIGURE 18.9
Schematic of an ALD process to create titania nanotube arrays on a substrate. 1) Nanoporous-alumina template on a substrate created by anodization of an Al film, 2) TiO$_2$ deposited onto the surface of the template by ALD. 3) Top layer of TiO$_2$ on alumina removed by gentle mechanical polish. 4) Alumina template chemically etched away to reveal array of titania nanotubes on the substrate. (Adapted with permission from ref [66].)
Overall the advantage of ALD methods lies in excellent conformal coverage of the surface, in a self-limiting manner. These methods have a high control over the thickness of the grown layers and therefore are very suitable for deposition of different inorganic materials in AAO. Additionally, ALD can be combined with plasma to deposit nanostructures even at lower temperatures than in the usual ALD [27]. Current limitations of ALD, however, include a typically small size of the chamber, slow and expensive procedure, and a limited choice of the deposited elements.

Plasma modification and Chemical Vapor Deposition Methods

Plasma modifications and chemical vapor deposition (CVD) methods are becoming increasingly popular due to several advantages compared to other conventional surface modification and deposition techniques. CVD is a method for depositing solid materials onto a substrate as a result of chemical reactions between precursors and a substrate. The precursor needs first to become reactive by using a source of energy, such as heat or plasma. Then the reactive high energy precursor molecules can chemically react with the substrate, giving rise to the formation of a new layer on the surface. Plasma can be used to assist the CVD process by accelerating the process due to the higher activity of ions compared to neutral molecules. The detailed CVD process of the deposition is quite complicated and out of the scope of this chapter. To get a more advanced understanding of CVD using plasma and its applications, interested readers are encouraged to read a recent review on versatile nanofabrication using reactive plasmas [67].

Thermal (hot filament) CVD and plasma-enhanced CVD (PECVD) methods are currently the most popular CVD techniques used for deposition of different materials [67]. PECVD has the additional advantage in comparison to thermally driven CVD because it offers extended capability for changing the deposited structure morphology and surface properties by using different plasmas [68-75]. CVD methods are relatively cheap, energy efficient and capable of producing conformal coatings on different substrates. For all these reasons, CVD has been widely used for a broad range of biological and medical purposes [9, 22]. One of the most promising ways is to use plasmas at room temperatures [70] and atmospheric pressures [72], as recently developed by Ostrikov’s group. CVD is an especially useful method for deposition of different carbon materials, such as diamond [68], diamond-like carbon (DLC) [61], graphene [71], carbon nanotubes and nanofibers [73]. Carbon-based materials possess a wide range of physical and chemical properties which are suitable for biomedical applications [74]. In particular, the biocompatibility of sp3-bonded carbon materials - such as DLC and ultra nanocrystalline nanodiamond (UNC-D) - is well established and it has been already successfully used in many commercial bionic devices, such as bionic eye [75].

PECVD deposition of polymer based materials on AAO have been recently demonstrated by Losic et al. [22]. In this work, a plasma polymerization of n-heptylamine plasma polymer (HAPP) was employed to functionalize and reduce the pore size of AAO membranes. A 13.56 MHz RF generator was used to polymerize HAPP on AAO using a very low power (40W) and high pressure (0.2 Torr) for a very short time (20 s - 200 s). Longer deposition times have caused further polymer growth but blocked the pores as schematically shown in Figure 18.10. The advantage of HAPP coatings on AAO is that their surface can be subsequently functionalized with amino groups to attach other chemical functionalities, which offers a broad range of possibilities to use these coatings in various separation and drug delivery applications [23].
CVD methods have also been used for template growth of nanostructures in AAO nanopores [37, 69]. Carbon nanotube-AAO composites [76] and free-standing carbon nanotube arrays [77] have been obtained using CVD growth of carbon nanotubes inside of porous anodic alumina templates. These composite materials have shown improved mechanical and electrical properties, which make them useful for sensing, catalysis and battery applications. Deposition of diamond-like carbon (DLC) on AAO has also been recently demonstrated [59, 61]. Karan et al. [61] has fabricated subnanometer-sized nanopores in 10-40 nm thick free-standing DLC coatings on AAO membranes by plasma polymerization of organic compounds. These highly cross-linked networks of sp³ carbons have demonstrated ultrafast permeation of organic solvents through the membranes. In our recent study, the whole surface of AAO has been coated with a homogeneous ultrathin DLC using chemical vapor deposition [59]. A very thin layer of DLC (~2 nm) was grown homogenously all over the internal and external surface of AAO in a self-limiting manner. The advantage of this CVD process is that it covers the whole surface of the membrane (Figure 18.11.a,b) in a very short time (~5 min). Membranes with variable pore sizes (10-200 nm) have been produced using this method. DLC is a very strong, robust and biocompatible material which has been shown very suitable for different biomedical applications. Ultra-nanocrystalline diamond (UNCD) films can also be grown on the top surface of AAO using CVD [78]. For this purpose, however, the membrane needs to be first pre-seeded with detonation nanodiamond before putting the membranes in a CVD diamond chamber. The seeding process is done in an ultrasonic condition where the membrane is merged in a solution containing nanodiamond nanoparticles. The nanodiamonds stick to the surface and act as the nucleation sites in the CVD diamond growth [68]. Figure 18.11.c shows a nanocrystalline diamond-coated AAO membrane. The size and the thickness of the nanocrystalline diamond layer depend on the time of the deposition. By controlling the deposition time nanometer pore size is achievable. Another advantage of the diamond coatings - in addition to their biocompatibility and chemical resistivity - is that they can be functionalized with different chemical functional groups to be used for further applications [74].
Other Deposition Methods

In addition to the techniques discussed so far, there are also other techniques that have been used for modifying nanoporous AAO structures in the literature. These methods include electron beam evaporation [26], laser pulse deposition [26], and electrochemical and electroless deposition methods [79]. Thermal, electron-beam and other evaporation methods are commonly used for deposition of thin films made of almost any material. However, evaporation in vacuum usually leads to deposition of a material only on the top surface of porous AAO structures similarly to Figure 18.10, and as demonstrated in references [26, 41, 80]. Laser pulse deposition is also a directional deposition method that can effectively coat only the top surface of nanoporous AAO, for example by DLC layer [26]. On the other hand, electrochemical and electroless deposition methods offer the possibility to coat the whole surface of AAO with different materials, such as metals [79]. Electrochemically grown gold nanotubes and nanowires inside the channels of AAO have been recently reported [79]. These materials hold a great promise for bioseparation applications. Additionally it is important to note that the coatings on AAO membranes should be very well bonded to the AAO substrate for biomedical applications in order to possess a good stability in different chemical and biological solutions. Therefore methods using physical bonding between the coated material and AAO, such as evaporation, do not always produce highly stable layers. Therefore it is better to use methods that utilize chemical bonding [52].

Applications of Different Surface-Modified AAO Materials

Template

AAO has been used widely as a template for the growth of a broad range of nanostructures and nanomaterials, including nanodots, nanotubes, nanowires, nanocones and nanocontainers [37, 73, 79, 81, 82]. Nanostructured AAO templates have a great potential to be used in different biological and medical applications due to their easy and cheap way of fabrication [2, 8, 15, 63, 83, 84]. Formation of a highly ordered array of biological molecules can improve the performance of different functional devices [8, 29, 30]. The high surface to volume ratio of AAO templates can also be utilized to produce
high density and three-dimensional (3D) arrays of enzymes, proteins and DNAs. In this section we present a few examples how AAO templates have been used in different biomedical experiments and applications.

AAO is a very suitable template for immobilization of the biological molecules, due to the adjustable pore size and interpore distance. Matsumoto et al. [29] have studied the fabrication of flow-through type 3D DNA arrays inside the channels of AAO. This is an engineered type of sensor to optically detect target DNAs which flow through the channels of a membrane and hybridize with the immobilized probe DNA array. This sensor takes the advantage of high density DNAs arrays. Figure 18.12.a shows the immobilization of probe DNAs on the pore walls of AAO [29]. By passing a complementary fluorescent DNA through the membrane, some of the DNAs hybridized and captured with immobilized DNAs. Other non-complementary DNAs would pass through the membrane without any hybridization. Later on, it is possible to detect the hybridized DNA under a fluorescence microscope, due to the fluorescent emission of the target DNAs. Figure 18.12.b shows fluorescent microscopy images of the DNA-array inside AAO, where the emitted light from DNAs is guided by the AAO channels. Different pore sizes can be used for this aim. However, the used interpore distance should be at least half of the wavelength of the fluorescent light due to the diffraction limit. In this example the wavelength of the emitted fluorescent light (Cy3 dye) was 562 nm, and a good optical resolution of the DNA array was achieved by a membrane with 400 nm interpore distance [29].

Another example of a template use of AAO is the fabrication of bio-imprinted polymers shown that biomolecules attach to a bio-imprinted polymer selectively [30]. As made bio-imprinted polymers can be used as a sensor or as carrier for drug delivery. Ince et al. [30] have demonstrated fabrication of Immunoglobulin G (IgG)-imprinted nanotube polymers using AAO templates. The resulted nanotubes showed a great selectivity to post protein bonding. Briefly the fabrication technique includes the immobilization of IgG inside the channels of AAO, and subsequent growth of polymer nanotubes; resulting in the formation of IgG-imprinted polymeric nanotubes. The nanotubes then can be released by washing away the AAO membrane with 1 M HCl for 24h. Freed nanotubes were soaked in 1 M HCl for another 24 hours followed by several washes with DI water. The imprinted nanotubes can be further loaded with some drugs for drug delivery purposes. The advantage of AAO templates is that they can be easily fabricated in different pore sizes, so that the dimensions of the filled nanotubes can be varied. In this way it has been possible to control the release and diffusion parameters of the targeted biomolecules [30]. As made patterned nanotubes were tested for selectivity in fluorescent BSA, IgG and Lysozyme solutions and shown dominantly higher adsorbed amount of IgG than the non-imprinted nanotubes.
In addition to the above shown template applications, AAO have been used as a template for cell cultures [17]. AAO with its large surface area and nanoporous structure is a suitable material for orthopedic implants which allows the formation of bone inside the nanochannels [85]. Porous materials are widely used for implants due to their ability to mimic the nanoporous dimensions and structure of the bone components, whilst hosting specific genes or drugs within the pores for therapeutic treatments [83, 85]. Swan et al. [7] have reported the growth of the osteoblast cells (bone forming cells) inside the channels of AAO with normal phenotype and morphology. However, more studies are needed for optimization of the cell growth inside the channels. Although the membrane preparation and functionalization methods often use strong acidic/alkali solutions this might not be a problem for further biomedical applications. The biocompatibility of the resulting membrane will be mainly determined by the final surface treatment and impermeability of the top protecting surface coating on AAO membranes. So far there have not been observed any strong effects of these treatments on the biological activity of the membranes. However a more work should be undertaken in this direction as well as proper testing of the biocompatibility of the surface modified membranes and suitability of the used chemical methods and materials.

**Separation**

Nanoporous structures and especially AAO can be used for different kind of molecular separation and filtration applications. Uniform and narrow pore size of the whole-through AAO membrane is playing a crucial role in most of these applications. Selectivity and flux rate are one of the most important factors in the membrane separation applications. Separation of biomolecules has been the subject of long research [5, 6, 19, 22, 79] and many studies have dealt with this important topic. Nanoporous membranes with uniform, aligned and straight pores with a high chemical and mechanical stability offer one of the most suitable methods for separation of biomolecules [2, 6, 79]. There are two main mechanisms of biofiltrations which are based on (1) size limitation and (2) chemical affiliation. In the first mechanism, molecules which are smaller than the pore size of the membrane can pass through, while the bigger molecules are blocked [22, 42]. The second mechanism is related to the bonding of the molecules with the membrane, which would let transfer faster the selected molecules with lower (or higher) chemical affinity through the membrane than the other types of the molecules [5, 19]. Here we give an example of each of these two mechanisms. Transport of nitrogen, water and ovalbumin molecules through AAO and functionalized AAO has been investigated by Lee et al. [24]. In this study, poly(ethyleneimine) (PEI) was first physically attached to the surface of AAO, and then poly(ethylene glycol) (PEG) were grafted by PEI-AAO samples. The PEG modified membranes have shown a reduction in the transportation rate of different molecules, due to the reduction of the membrane permeability. Because PEG has a neutral chemical structure with a hydrophilic character and its brush-like chains sterically exclude other macromolecules, it has a repulsive behavior to proteins. In another protein adsorption test (FITC-BSA), PEG modified samples have shown 20% less bonding to proteins than unmodified AAO [24]. In these experiments it is important to perform a protein concentration test of the membranes at low concentrations (< 1 mg ml⁻¹) to make sure that the adsorption is caused just by the surface interactions and not due to trapping of the proteins inside the pores. The transport behavior of fluids in a nanometer size membrane has been experimentally and theoretically well studied [19, 24, 86]. In an experimental study by Lee et al. [24], it has been shown that the pore size of AAO membranes can effectively change the transport rates of fluids such as nitrogen and water. As mentioned in the previous section, pore size of an AAO membrane can be reduced to molecular size by using different methods, and then molecules bigger than the pore size will
be excluded from transport. As it has been shown in the study of Lee et al. [24], a PEI-PEG coating have been able to reduce the size of the pores until the transport of a small molecules such as ovalbumin was totally excluded.

A modified AAO can also be used for separation of two hydrophobic and hydrophilic dyes. As we mentioned in the previous section, ALD is a common method used to coat AAO with SiO₂. The SiO₂-modified AAO can be further modified with perfluorodecyldimethylchlorosilane (PFDS) using other chemistry methods to reduce the pore size to 10 nm [23]. SiO₂-modified AAO is hydrophilic, while whole surface PFDS-SiO₂-modified AAO is highly hydrophobic, showing 12° and 109° contact angles using a water drop measurement [23]. The rate of the diffusion of the two different dye molecules (Rubpy (hydrophobic) and rose bengal (RB) (hydrophilic)) with a size smaller than the pore diameters has been measured by Velleman et al. [23]. This study suggested that the flow rate of the hydrophilic dye can be reduced by a PFDS functionalized membrane, while not changing significantly the flow rate of the hydrophobic dye. The flux (Rubpy:RB) of the modified membrane was two times larger than for the unmodified membranes. The lowest flux has been found for RB in PFDS-modified membranes. The proposed experiment demonstrated the selectivity of the membrane based on their hydrophobic properties, which might be very useful for many applications such as protein separation and purification.

FIGURE 18.13
Schematic illustration of the modification process to fabricate a PFDS-SiO₂-AAO membrane used for separation of hydrophilic and hydrophobic dyes. (Reprinted from ref [23], Copyright (2009), with permission from Elsevier)
Chemical affinity separation by nanofilters can be applied for chiral separation. Chiral separation of drugs is one of the most important issues in pharmaceutical industry [19]. (4-[3-(4-fluorophenyl)-2-hydroxy-1-[1,2,4]triazol-1-yl-propyl]-benzonitrile) is a chiral drug with RS and SR enantiomers [19]. It is desired to selectively separate these two enantiomers. Since they have the same size and same chemical bonding, it is not possible to separate them via size and charge exclusion. The separation of these enantiomeric drugs has been demonstrated in Charles R. Martin’s group [19] using silane modified AAO membranes. Transport of the RS enantiomer measured by a chromatography method has been found twice faster than of SR enantiomer in the silane modified AAO membranes. The principle of this transport difference has been based on the affinity bonding of drug to an immobilized antibody-loaded-silica nanotube [19]. The binding character has been adjusted by addition of dimethyl sulfoxide (DMSO). For the membrane with 35 nm pore diameter, the ratio of RS/SR flux behave been as high as 2.6 at optimal concentration of DMSO [19]. By reducing the pore size to 20 nm the RS/SR flux increases to 4.5 [19]. The stability of these modified AAO membranes confirmed that these flux ratios remained constant even after 1 week.

**Sensing**

AAO materials with specifically modified surfaces show a great promise for sensing of different chemical and biological molecules [4, 31, 41, 64, 80, 87-90]. The main advantage of porous AAO in these sensing applications lies in improved sensitivity of the devices due to a large surface area of AAO in comparison to other materials with flat surfaces. Selectivity is usually provided by different specialized surface coatings on AAO. The sensing principle of AAO-based sensors can be based either on optical or electrical detection mechanism. Electrical sensing usually monitors the change of sensors’ current, resistance, capacitance, impedance and etc. [41, 91]. Optical detection can have different mechanisms, such as fluorescent emission [29, 32], interference [4, 87, 88], surface plasmon excitations [80], surface enhanced Raman spectroscopy (SERS) and optical waveguide coupling. There are also many other integrated methods for biosensing applications, for example AAO grown on quartz crystal microbalance (QCM) can be used for mass adsorption detection. Here we focus on two examples of electrical and optical sensing methods that will demonstrate the benefit of using AAO-based materials in sensing applications. For more information on sensing using AAO we refer interested readers to a recent review [15].

There are many pollutants in the environment that require detection in parts per billion. Achieving such a high sensitivity is often difficult with currently available sensors [32]. Poly chlorobiphenyls (PCBs) are among the toxic organic pollutant which can lead to serious liver damage [32]. To sense these pollutants, Wang et al. [32] has immobilized fluorophore phenyl isothiocyanate (PITC) on AAO membrane (PITC@AAO) to optically detect a presence of PCB. Since it is very hard to covalently bond PITC to AAO, the immobilization took place via simple immersion of the membrane in a PITC-contained solution. The as-made PITC@AAO membrane was used to detect PCBs using a UV-Vis spectrometer. By increasing concentration of PCB from 1 ppb to 6 ppb, the fluorescent intensity of the membrane increased by a factor of 18 (Figure 18.14.a). Furthermore, the selectivity of the membrane to a certain type of PCB (PCB101) among 4 other more PCBs has been tested, and a very good selectivity has been obtained (Figure 18.14.b) [32]. The achieved minimum amount of PCB detected using PITC@AAO membrane has been around 1 ppb [32]. The experiment with the same concentration of the same fluorescent molecules placed on a flat quartz substrate lead to a 25% less intensity than on PITC@AAO [32]. This results show that the high surface area of AAO-based sensors increases the sensitivity. The confinement of the fluorescent molecules inside the channels might have some effects on the enhancement of the fluorescent emission as well. More studies are needed to get a better
understanding of the optical enhancement mechanism in AAO nanochannels. Despite of this the study of Wang et al. has shown the potential of optical detection of pollutants using surface modified AAO sensors which promise high sensitivity and selectivity to the targeted biomolecules.

FIGURE 18.14
a) UV-vis spectra of the AAO membrane immobilized with (red) and without (black) PITC. b) Fluorescence intensity of PITC@AAO after exposing it to different types of PCBs. (Adapted from Ref. [32] with permission from The Royal Society of Chemistry)

In another example [41], the electrical properties (impedance) of a modified AAO have been measured to detect label-free DNAs based on charge effects (Figure 18.15). For this purpose AAO membrane was first silanized with different proportions of APTS/ETS, and then the two opposite surfaces of the membranes were coated with a thin layer of gold as electrodes. The impedance measurement was done by applying an AC mode over the electrodes. In this case, the impedance of the membrane is given by [41]:

\[ Z_{\text{mem}} = \frac{k_BT}{e^\alpha D \sqrt{\Delta C^1 + 4C_{\text{hel}}^1}} L \]

\( \Delta C \) is a measure of the changes in density of surface charge for a certain pore diameter. \( e, \alpha, D, T, L \) and \( A \) are electron’s charge, porosity, diffusion constant, temperature, channel length and cross section area, respectively. Any changes in the surface charge would have a direct effect on conductance of the nanochannel and the total impedance of the membrane. By comparing this formula to a flat capacitor plate based sensor [41], it is obvious that the impedance change is much larger than in the case of the porous AAO structure. This sensing principle has been utilized by Wang et al. to detect label-free DNAs [41]. In this study, the surface of the modified AAO was positively charged, and since DNA is a highly charged molecule, adsorption of the oppositely charged DNAs by membrane has caused a drop in impedance (Figure 18.18). This sensing mechanism has been suggested as one of the option to detect cystic fibrosis.

In conclusion, we have shown that AAO provide an interesting material platform for different sensing schemes. The main advantage of AAO in these applications lies in its large surface area, porous structure with high density of pores and narrow pore size and distribution. Large surface area of AAO provides a unique platform to capture and sense a very low amount of molecules. Electrical sensing is possible also because anodic alumina is a robust insulator with a relatively high break-down limit. Its adjustable pore size is well suited for optical visualization. High transparency of AAO structure can also be helpful for optical sensing applications and interferometric measurements.
FIGURE 18.15
a) A schematic image of an AAO-based electrical sensor. b) Impedance measurement of the AAO-based membranes as a function of solute concentration, with and without DNA. (Adapted with permission from ref [41]. Copyright (2009) American Chemical Society.)

Drug Delivery

One of the promising applications of nanoporous membranes is controlled drug delivery [8, 14, 40, 50, 65, 83, 85, 91]. In this application, the volume of the nanopores in AAO membranes is utilized for drug storage and subsequent release. An application of a suitable surface modification to AAO membranes is important mainly because it can improve its biocompatibility as well as other important properties for drug capture and release. Biocompatibility of the membranes used in drug delivery is the first condition that should be fulfilled by a device. So far all the illustrated experiments were done in vitro. When it comes to in vivo applications, the stability and biocompatibility of a membrane and its behavior inside a living tissue becomes critically important [18]. Any failure of the device can be dramatic. In vitro tests can be also used for prediction of relative biocompatibility of a material [17, 18]. Cytotoxicity determination is a standard method to test biocompatibility of a material and to get some information about the interaction of the body cells and implanted device [17]. However, in vivo studies give much clearer and reliable information about the body response to the implanted device. This has been illustrated by La Flamme et al. [18], who have investigated the biocompatibility of PEG modified and bare nanoporous AAO membranes both in vitro and in vivo. Although in vitro data showed no toxicity of the samples the in vivo study has shown clear signatures of inflammatory response of the body to the implanted membranes [18]. In the in vivo study, two membranes (PEG-modified and unmodified AAO) were planted in the lower abdominal region of a male Lewis rats for up to 4 weeks. Then membranes and surrounding tissues were removed to observe the fibrous growth and inflammations. There was no fibrous growth in any of the samples after 4 weeks, but there were some moderate inflammations observed after one week in both membranes, with more indications in unmodified membrane (Figure 18.16.). Although it has been argued that this inflammations might be caused by the surgical process, this and other studies clearly suggested that AAO membranes need to be made more bioreisstive and biocompatible [18, 20, 22, 24, 26, 92]. The interaction of AAO membranes with different cell interfaces have been studied in great detail by Brüggemann [17]. Anti-biofouling of a device is very important to resist the adhesion of the proteins of blood or immune system to its surface. PEG coatings on AAO have shown a great improvement in its anti-biofouling characteristics [18]. Other suitable materials for anti-biofouling are diamond [60, 75], diamond-like carbon [26, 60, 93], noble metals and high quality metal oxides such as sapphire [92].
Another important factor in drug delivery is the controlled delivery. Figure 18.17.b shows the release of drug from a normal tablet inside the body, showing a safe profile and a dangerous profile of release [14]. The idealized concentration release is shown in Figure 18.17.b, where the drug releases with almost constant rate after an initial stabilization. Any drug release from nanoporous membranes is required to be in the safe region and therefore it is better to have a release profile similar to the idealized profile. Figure 18.17.a shows a different models of drug release from a nanoporous membrane [14]. Pore size and drug particle size play the most important role in these drug release mechanisms. For a membrane with pores much bigger than drug particles, Fick’s mechanism is found as the dominant mechanism of release profile. As the pore size decreases, the single file diffusion profile dominates because the release profile gets closer to the concentration diffusion profile.

**FIGURE 18.16**
Histological examination of tissue exposed to no material (A) and (D), unmodified capsules (B) and (E), and PEG-modified capsules (C) and (F) after 1 and 4 weeks. Arrows indicate the portion of the tissue that was exposed to the capsule (Adapted with permission from ref [18]. Copyright (2007) American Chemical Society)

**FIGURE 18.17**
a) Release mechanism of drugs from porous structures and b) the therapeutic range of a release profile (top) and the idealized release profile (bottom). (Reprinted from ref [14], Copyright (2012), with permission from Elsevier)
Tubular AAO membranes (Figure 18.18) with different pore sizes have also been used for controlled molecular transport [94]. In this study, fluorescein isothiocyanate (FITC)-dextran molecules with different molecular weight (4 kDa, 20 kDa, 70 kDa and 150 kDa) were encapsulated inside the tube and the diffusion rates were measured. As it is expected the release rate of fluorescein (400 Da) is higher for the bigger pore size (55 nm) [94]. Heavier (bigger) molecules release much slower than lighter (smaller) molecules. It has been observed that even after 24 h there has not been a considerable release of big molecules. This study has clearly shown that the controlled idealized release of the drug from AAO capsules is possible.

**FIGURE 18.18**
An example of a tubular AAO capsule for drug release from the capsules with pore diameters (Reprinted from ref [95], Copyright (2005), with permission from Elsevier)

Usually the size of the drugs is much smaller than the pore sizes of AAO, which limits the drug release. To improve the release characteristics of drugs from AAO membranes, Losic et al. [50] suggested coating the top surface of the membrane with a plasma polymer after drug loading. Coatings on AAO will decrease the pore size, which will consequently lead to a better release characteristic. This principle has been demonstrated in an innovative integrated method using carriers (polymeric micelles) loaded in the pores of AAO to carry the hydrophobic drugs (Figure 18.19.a) [50]. The top surface of AAO was coated with a plasma polymer to reduce the pore size. Figure 18.19.c shows the release profile of the micelles from the membrane. After the burst release (~ 35%) in first 6 hours, the drug release slowed down for the next couple of days (6-14 days). It can be seen that the profile characteristics is very close to the ideal drug release, which represents the single file diffusion mechanism [14, 50].

Another innovative method is a switchable drug release from AAO membranes which has been demonstrated by Jeon et al. [91]. For this purpose, AAO was first coated with gold and then a layer of polypyrrole was formed on the gold layer by an electropolymerization method.
The principle is based on a special characteristic of polypyrrole, which is able to change its volume in different electrochemical conditions. When the polymer gets oxidized, the hydrated ions expel each other and the chains get shrunken. As a result the pore diameter will increase. On the other hand, when the polymer gets back to the reduced state, chains are expanded and the pore size will decrease (Figure 18.20). This is a reversible process which can be used for on-demand drug release.

**Future of the Modified Membranes**

Currently AAO membranes are among the best potential membranes for biomedical use due to their robustness, uniform and narrow porous structure, and also because of their easy and cheap way of the fabrication. We have shown in the previous sections that there are many research groups around the world who are investigating the potential applications of this great material, while other are trying to modify this material for different desired applications. Surface modification of AAO membranes is used
to improve various properties of the AAO material, opening up new opportunities for other advanced applications, especially for biomedical application that have a big demand for functional membranes. Functional nanoporous membranes can be used in catalysis or as separators and filters which are commonly used in biology and chemistry. A better and more accurate filter is always demanded for pharmaceutical industries or for blood purification applications. Excellent bio filters should separate maximum amount of targeted molecules with a high speed and without any impurities. The separation of the biomolecules by their size is very difficult so the functional membrane should be chemically able to select the targeted molecules to pass. The speed of the permeate is shown to be related to the pore diameter, however some other forces, such as electrostatic or hydrophobic, can be used to fasten the permeation through membranes. More studies on chemical selectivity of the molecules can push the current membranes toward the idealized membrane.

For sensing application, there is a need for a more conformal and uniform membranes that can improve both sensitivity and selectivity of AAO based sensors. Ideally ordered nanoporous structure with a very conformal coating is required for a highly sensitive and reliable membrane. For template applications, again the uniform structure of the pores and more control over the architecture of the pores is needed. If the architecture of the membrane can be controlled in both nanoscale and microscale, there will be many great opportunities for designing implants with specific geometry and functionalization. At the moment the design of the AAO membranes is limited to the flat and tubular membranes, with almost the same pore diameter along the pore length in the membrane. The development of improved anodization or modification techniques promise fabrication of more complex AAO-based membranes with various geometries and desired surface properties and functionalities. For in vivo applications (e.g. drug delivery) the first important and crucial factor is biocompatibility of the used membranes. AAO is not sufficiently biocompatible and chemically stable in the biological conditions [18, 22, 23, 25, 28]. Release of the aluminium ions from the membrane would have some side effects on the long use of uncoated AAO membranes in the body. To prevent infections, the membrane should be coated with a more resistive and biocompatible material. The ideal coating should be homogenous and all over the membrane including inside the pores of the membrane. Any uncoated or agglomerated area might lead to total failure of the device. Engineering of such a coated layer is not easy, especially in the nanopores, but it should be possible with the use of one of the coating methods discussed in section 3. In choosing the best material for the coating the specific function of the device should be considered. However, generally the coated material should lead to an improvement of the chemical and mechanical properties of AAO. Carbon based materials such as diamond and diamond-like carbon are considered among the best candidates for this purpose. Their biocompatibility has been proven and they are very strong materials in terms of physical and chemical properties.

Conclusions

Since the discovery of nanoporous anodic aluminium oxide (AAO), this material has been used for various applications. The main advantage of AAO is that its nanopores are well-ordered, uniform, and organized in a parallel columnar way. Also adjustable and narrow pore size distribution of AAO membranes is very unique. Anodization is a cheap and straightforward method of fabrication of AAO which has made it a very popular membrane and template for different purposes. Despite of all the great advantages, the chemical instability and slight toxicity of these membranes have limited their applications in biomedical devices. In this chapter, we have shown that to take advantages of the unique properties of AAO in biomedical applications, it is important to provide the membranes with
different surface modifications of functionalizations. Very interesting and break-through advances have occurred in this path. We have presented different chemical and physical methods that have been used to modify the surface of AAO in respect to their efficiency, film properties and type of coated materials. Additionally, we have discussed various applications of the coating methods and differently surface modified AAO membranes. Polymer modifications seem very straightforward and cheap, but they are suffering from the polymer drawbacks; such as short-time stability and limited chemical and physical stability. Oxide materials are physically strong and biologically suitable, but usually their fabrication methods require very expensive and slow deposition methods, such as ALD. There have been developed other cheap methods for the deposition of oxide films by using chemical methods such as sol-gel. The other materials such as bioresistive and biocompatible carbon-based materials are very good for biomedical purposes but the current methods are not developed for depositing them on nanoporous AAO nanarchitectures.

The surface modified AAO membranes can be functionalized with different biological molecules for different purposes. Some of the main application of these membranes are: (1) templates for fabrication of the ordered biomolecules or patterned growth of the cells, (2) biosorting and filtering biomolecules by selectively passing the targeted molecules through the membrane, (3) sensing of the targeted molecules, such as DNAs, proteins or even cancer cells and (4) capsules for drug delivery by releasing the previously-loaded drugs. There are many researches active in these areas, who are passing through the cutting-edge technology by introducing new and creative ideas and possibilities.

The future of the biology and medicine will be different from now by developing and designing better and improved membranes, sensors and drug delivery methods. More sensible devices, more accurate measurements, more purified drugs, smarter functions and more targeted delivery of the drugs are some of the possible outcomes of better control to fabricate functional nanoporous membranes. There is lots of work needed to be done to enhance the current limits of the surface modified AAO membranes. More control over the fabrication and modification in nanoscale and microscale is needed. More understanding of the chemical selectivity of the materials and their functionality is needed. Also the modification techniques should be improved for a cheap and reliable method to coat or modify the whole surface of the three-dimensional nanoporous materials.

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