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The Design and Manufacture of Biomedical Surfaces

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Abstract

Surfaces are the primary place of contact between a biomaterial and its host organism. Typically, prostheses have to fulfil demanding structural and mechanical requirements, yet the material best for those functions may be bio-incompatible. Surface treatment or coating provides a means to overcome that problem, which means both integration within the host physiology and stabilization with respect to corrosion and wear. The adsorption of biomacromolecules is pivotal for biocompatibility. The impossibility of keeping proteins away from most implants means that very careful consideration has to be given to this aspect, and both prevention (for bloodstream implants) and promotion (for bone replacement and repair) occur with equal importance. This paper also considers the metrology of relevant physical and chemical aspects of surfaces.

Keywords

Biomedical, Surface, Metrology

1. INTRODUCTION

The increasing trend to incorporate artificial devices into the human body has sharply focused attention onto the compatibility of the materials from which such devices are made with human physiology. Given that it is widely predicted that more and more functions will be taken over by artificial devices, not only for repairing damaged function but also for enhancing function, the need to solve the problem of how to design and manufacture such materials to make them maximally compatible with living tissue (including biofluids such as blood) has become a major priority of the medical device industry.

The dictionary definition of 'biocompatible' is 'tolerant of life'. A more useful definition for the materials scientist is 'responding appropriately to a given physiological situation'. For an implant designed to remain for a long time in the body, this may not be adequate: the material should be *adapted* to its environment, i.e. able to cope with the full variety of conditions prevailing during its lifetime, or that of its host.

In nearly every case, it is the surface of the artificial object that constitutes its interface with the living tissue. This fact determines the emphasis of this paper. Mechanical and other bulk properties are only considered insofar as they have some bearing on surface properties.

1.1 Areas of application

Long-term implants are defined as objects in contact with living tissue more-or-less permanently. In reality, that might only mean several years, after which a fresh operation to replace the implant is necessary. These repeated interventions are, however, extremely problematical, especially in the case of elderly patients, for whom each successive intervention becomes more and more life-threatening. Therefore, it is a major current challenge in biomaterials to develop implants that are truly permanent. Examples of this kind of application are bone and joint replacements, dental prostheses, implanted sensors (e.g. for blood glucose), stents, heart pacemakers and heart valves.

Two of the gravest problems associated with long-term implants are bacterial colonization and wear. In the former, prostheses become and remain infected by bacteria. For reasons that are currently not well understood, such infections are extremely persistent, the bacteria becoming resistant to all usable antibiotics. In relatively benign cases, deleterious effects may be confined to local inflammation, but in more severe cases, systemic effects may arise. Usually the infection can only be halted by removing the prosthesis.

Wear of artificial joints releases particles into the body. The nature of the surface of the particles determines what adsorbs onto them, and how. Certain surfaces are known to promote the denaturation of adsorbed proteins, with the result that they become recognized by the immune system as foreign bodies, and an immune reaction of greater or lesser severity is initiated, often leading to problematic inflammation and even cancer [124]. Since the particles typically become distributed throughout the body, the inflammation is likely to be systemic. The emergence of deliberately fabricated nanoparticles as therapeutic agents has focused attention onto their potential toxicity [154], especially when penetrating into the lung and the brain, and the potentially deleterious effects of the nanoparticles produced adventitiously from the wear of prostheses have probably been underestimated.

Medium-term implants are defined as objects in contact with living tissue for a limited duration. Examples are: tissue scaffolds, e.g. for skin replacement and reconstruction, some of which are made from deliberately biodegradable materials; and drug delivery particles circulating in the bloodstream with the aim of targeting specific tissues, e.g. tumours. Such implants are attractive candidates for being given bioactive surface coatings. At present, this means coatings that either slowly release a hormone or other bioactive substance into their immediate environment over an extended interval (obviously the storage capacity of an implant is finite), or a coating endowed with specific recognition elements (e.g. short oligopeptide sequences) that steer the primary bioresponse to the implant immediately following its insertion into the body. A more advanced form of bioactivity, not yet realized in practice, would imply that the coating steers the metabolism of the bio-environment in which it is in contact in order to make it produce what is

necessary to optimize biocompatibility. If nanotechnology succeeds in packing sufficient function into a minute volume, even a miniature factory to make any required drug from available raw matrials becomes conceivable.

Short-term implants are defined as objects only very briefly in contact with living tissue. This category includes needles, scalpels and other surgical tools.

A useful way of classifying the surfaces of long- and medium-term implants is to distinguish those that should ideally completely resist the adsorption of biomacromolecules (mostly proteins, which constitute the bulk of biomass) from those that are destined to become assimilated as completely as possible with the living tissue, for which the first step is the adsorption of proteins [92]. The first class covers all implants placed in the bloodstream, or in the mouth, or in the presence of some other biofluid (e.g. the contents of the stomach). The second class has the opposite characteristic: in order to promote assimilation with the living tissue it must absorb one or more layers of proteins. This also applies if the surface must fulfil a lubricating rôle in its contact with the living matter—in this case too protein, or glycoprotein, adsorption is a prerequisite.

Hence, it is clear that the understanding of adsorption is a key feature in the design of biomedical surfaces. We may anticipate that a profound understanding of the underlying principles will enable both haemocompatible and tissue-compatible surfaces, i.e. both adsorption-resistant and adsorption-promoting, to be designed and fabricated. This knowledge should also permit surfaces to have the attribute of resisting bacterial infection, which is a general requirement of prosthetic implants: bacterial colonization is also typically initiated by biomacromolecule adsorption. It needs to be emphasized that the protein adsorption events that generally precede the entire subsequent history of the implant largely obliterate whatever special arrangement of atoms, in either a physical or a chemical sense, exist in the fabricated implant when it is freshly inserted into the body.

Only for surfaces destined for extremely short contact (i.e. of the order of seconds) with living tissue does the issue of adsorption become unimportant, because there is not time for adsorption processes to take place. The main requirement for such surfaces is simply an extremely low coefficient of friction.

1.2 The nature of the bio-environment

The milieu of a biomedical implant is very different from that of other, more familiar engineering environments. With their typically warm (37 °C), aqueous and salty nature, the milieux encountered by biomedical materials can be aggressive and give rise to both corrosion- and wear-related problems. From this viewpoint, the most important characteristics of the milieu are chloride content, dissolved oxygen level and pH. Apart from that, the bio-environment is a very complex medium containing dozens of small molecules, some of which may be ions, and hundreds of different kinds of biopolymers, mainly proteins. Water is invariably the dominant chemical species, but the actual nature of the water, in particular its hydrogen bonding pattern, will depend significantly on the other species present, either dissolved or as surfaces [13]. Interfacial water in particular is likely to be very different from the bulk [210] [111]. Cells are present either as a confluent mass, as in the case of tissue, which may be soft (e.g. skin, tendon, pericardium, cornea) or hard (e.g. bone, dentine, cuticle), or as isolated bodies circulating in the aqueous biofluids, such as the blood. As living objects, the cells are more or less active, modulating their environment according to the stimuli they receive. One of the most important of these modifications is the coating of an artificial implant with a layer of proteins [92].

1.3 Attributes of materials

The great barrier to the rational design of biomedical surfaces is that while the desired functional attributes are clear enough (e.g. absence of protein adsorption for an implant in the bloodstream, or promotion of cell adhesion for an implant in contact with tissue), the physical and chemical attributes with which the surface should be endowed in order for it to achieve those functional attributes still remain largely mysterious. Hence the work of the designer has to be heavily based on past experience, i.e. empirical knowledge, rather than rational design. Given the current explosion of the variety of available materials, especially composites, this limitation strongly hampers progress in the field. A major priority is therefore to make a significant advance in understanding the bio/non-bio interface.

The main physical attribute is surface roughness. At the lowest level of sophistication, there is the root mean square roughness or interface width:

$$R^2_{\mathrm{q}} = \sum_{i}^{N} (h_i - \langle h \rangle)^2 / N \qquad (1)$$

where h_i is the ith of N small contiguous areas into which the surface is divided, and $\langle h \rangle$ the mean height [115]. More sophisticated measures quantify texture [167], or spatial correlations in the topographical undulations. The power spectral density of surface features encapsulates information about the lateral distribution of asperity:

$$S(f_X, f_Y) = \lim \frac{1}{L^2} \left(\int_0^{L} \int_0^{L} h(x,y) e^{-i2\pi(f_X x + f_Y y)} dx dy \right)^2 \qquad (2)$$

where the f are the spatial frequencies in the (x,y) plane of the two dimensional surface profile $h(x,y)$ defined for a square of side L. It may be noted that the metrology of surfaces (Section 4) is well ahead of biocompatibility testing.

Systematic data on the influence of roughness—at all relevant length scales—on the responses evoked in the biological milieu is lacking. Since interfacial energy is strongly curvature-dependent, the distribution of curvatures, another roughness parameter, is likely to be very important, but again there is a dearth of data. The rule of thumb is that implants destined for the bloodstream should be as smooth as possible, in order to discourage protein adsorption, and implants incorporated into tissue should be rather rough, to facilitate cell anchorage. Now that it is technically possible to machine metal and other surfaces to a roughness of the order of 1 nm, it is very important to know whether the cost of such ultraprecision machining is justified through superior performance.

The chemical behaviour of the surface is determined by its atomic and molecular composition. The main goal of the surface chemist dealing with biomedical materials is to determine the interfacial free energy. This energy, to good approximation, can be considered to be the linear sum of the Lifshitz-van der Waals, electrostatic, and Lewis acid/base interactions. Labelling the biomedical surface with subscript 1, the liquid medium bathing it with subscript 2, and the particle (e.g. a protein) potentially able to adsorb on the surface with subscript 3, one can write [123] [13]

$$\Delta G_{123} = \Delta G_{22} + \Delta G_{13} - \Delta G_{12} - \Delta G_{23} \qquad (3)$$

i.e. the interfacial energy is the sum of the cohesive

energy of the liquid and the direct energy of interaction between the surface and the particle in the absence of liquid, minus the solvation energies of surface (adsorbent) and particle (adsorbate). In aqueous systems, the main manifestation of the Lewis acid/base interaction, (also known as the electron donor-acceptor interaction) is hydrogen bonding. This is likely to dominate the ubiquitous but weak van der Waals interaction. Many metal oxides become hydroxylated in the presence of water, and these -OH groups can be protonated or deprotonated depending on the pH of the bulk [13], whereupon the oxide surface acquires an electrostatic charge, but in salty biofluids this charge is very strongly screened and typically becomes insignificantly small. Roughly speaking, 80 to 90% of the interfacial energy of a protein contacting a metal oxide in the presence of blood is due to Lewis acid/base interaction, around 5% is due to the Lifshitz-van der Waals interaction, and around 5% due to the electrostatic interaction [145]. Hence in what follows the main focus will be on the Lewis acid-base interaction (i.e. hydrogen bonding in aqueous milieux).

The last two terms of the right-hand side of equation 3 refer to the hydrophobicity (or hydrophilicity) of the materials 1 and 3. If $\Delta G_{12} > 0$, material 1 is hydrophobic; if $\Delta G_{12} < 0$, material 1 is hydrophilic. The biomedical surface engineer can control the parameters ΔG_{13} and ΔG_{12}; what he has no control over is the very large and negative ΔG_{22} of water. In the absence of any other interactions, Equation (3) shows that particle 3 will therefore adhere to surface 1 because of the very strong cohesive energy of water. So-called 'hydrophobic' substances will stick to each other because of the absence of sufficient hydration energy, ΔG_{12} or ΔG_{23}, to counter ΔG_{22}.

For proteins (and living cells), the above considerations are only a first, or even zeroth, approximation, because of the significant chemical heterogeneity of protein surfaces [14]. Proteins are made up of folded amino acid chains, and the amino acid side chains (residues) may be polar or apolar, and among the polar residues there are those of hydrogen bond-donating (i.e. electron accepting) and hydrogen bond-accepting (i.e. electron donating) character. Another complication is that the folded conformation of the protein can be easily disrupted if the protein comes into contact with a foreign surface [34]. This is the phenomenon of denaturation. Furthermore, the stickiness of a protein is not determined purely by the electron-donating or electron-accepting character of the residues, but also by the presence of apolar residues in the vicinity of the backbone hydrogen bonds [35,36]. There is a complex interplay of intramolecular and intermolecular (i.e. protein-surface) bonding that needs to be considered when attempting to predict the fate of a protein arriving in the vicinity of a biomedical surface. These issues will be considered in more detail in Section 2.

The individual terms of Equation (3) can be calculated from contact angle data. In the absence of electrostatic charges, each term has three components, the Lifshitz-van der Waals potential, the electron donating potential (dativită) and the electron accepting potential (recettivită). Hence the contact angles of three different liquids (typically water, an apolar liquid such as bromonaphthalene, and a third liquid such as formamide whose dativită and recettivită are different from those of water), with the material under investigation must be measured, and the three corresponding Young-Dupré equations solved simultaneously to yield the three component potentials of the material [123] [13]. Fairly extensive tabulations for a wide range of solids, including metal oxides, organic polymers, and proteins are already available [123], which provide an important resource for initial design considerations regarding biomedical surfaces.

1.4 Selection of materials

Implants and prostheses are manufactured from a wide variety of materials, including metals, polymers, ceramics and their composites [191]. Synthetic biomedical materials can be grouped into (with examples):

- Polymeric: Ultra High Molecular Weight Polyethylene (UHMWPE), polymethylmethacry-late (PMMA), polyethyletherketone (PEEK), silicone, polyurethane (PU), polytetrafluoro-ethylene (PTFE)
- Metallic: stainless steel (offers good corrosion resistance, formability, and reasonable fatigue resistance), cobalt-based alloy (Co-Cr-Mo, offering good corrosion- and wear-resistance), titanium (a durable and biocompatible metal, commonly used in heart valves, pacemakers, artificial hips and joints, dental implants and surgical equipment), titanium alloy (Ti-Al-V, usually given a TiN coating to overcome the problem of the cytotoxicity of vanadium), nitinol (a superelastic nickel-titanium alloy that is biocompatible, corrosion resistant, and cytocompatible; its shape-memory and elasticity make it a popular choice among manufacturers of implantable devices; vascular stents made from it can be bent to facilitate their insertion into the body with an endoscope and then returned to the prescribed shape by heating to a certain temperature), tantalum (offering biocompatibility, durability, and corrosion resistance), gold, platinum
- Ceramic: alumina (Al_2O_3), zirconia (ZrO_2), carbon, hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], tricalcium phosphate [$Ca_3(PO_4)_2$], bioglass [$Na_2O(CaO)(P_2O_3)(SiO_2)$], calcium aluminate [$Ca(Al_2O_4)$]
- Composite: carbon fibre (CF)/PEEK, CF/UHMWPE, CF/PMMA, zirconia/silica/BIS-GMA

These materials have traditionally been selected based on their bulk characteristics—properties necessary to ensure mechanical integrity and shape manufacturability. However, the surface properties may not always be particularly biocompatible, and therefore a useful design strategy is to use surface engineering, which aims to enhance corrosion and wear resistance, antibacterial characteristics and tissue compatibility (including suppressing any adverse immune response).

For acceptable corrosion resistance it is important that metallic systems form thin protective passive oxide films that act as a barrier separating the metal from its environment, unless the metal is extremely inert, such as gold, which has been important for dental prostheses. The metals and alloys often used for biomedical applications, such as 316L stainless steel, titanium, Ti-6Al-4V, Co-Cr-Mo and Ni-Ti, do form passive surface oxide films within the human body environment, which provide some measure of corrosion resistance. Even so, corrosion is a common problem, occurring as a global phenomenon or localized in the form of pitting, crevice corrosion, galvanic corrosion or stress corrosion cracking. The Pourbaix diagram [164] is a useful guide to corrosion. Mechanical loading can result in corrosion fatigue and accelerated wear processes such as fretting. Passive oxide films may be disrupted, accelerating localized corrosion, and resulting in a strong synergy between chemical and mechanical processes. As noted by Blackwood et al. [9], the Pourbaix diagram predicts that stainless steels are

likely to undergo corrosion in many biomedical environments. However, titanium should remain passive in almost all aqueous solutions, a major advantage that accounts for its popularity.

2. FUNDAMENTALS OF BIOMACROMOLECULAR ADSORPTION

As already stated, it is an essential feature of the behaviour of artificial materials inserted into the human body that within a very short interval they will become covered by proteins and other biopolymers, obliterating the careful two and three-dimensional structuring that may have been applied to the surface during fabrication. The blood in particular contains thousands of different proteins, but model experiments in which exogenous proteins are rigorously excluded have shown that cells brought into contact with an artificial surface promptly synthesize and excrete their own proteins [92]. Protein adsorption cannot therefore be evaded. The ultimate goal of the biomedical surface engineer is to design the surfaces in such a way that control over these adsorption processes is retained. This is however a very difficult challenge, which is far from being solved.

A protein can be considered as a minute nanoparticle with its own surface, although due account must be taken of its high curvature. As a first approximation, the surface tension formalism characterizing bulk materials sketched out in Section 1.3 can be used [145]. This allows one to estimate what is formally the equilibrium energy of interaction between a protein and the surface in the presence of a liquid bathing both of them. In nearly every case investigated, however, the equilibrium situation is of less relevance than the kinetics of the adsorption process. It was one of the earliest definite results in the field that protein adsorption/desorption shows very marked hysteresis, to the extent that the adsorption often appears to be irreversible, at least on laboratory time scales [137] [146]. Another important result is that adsorption from a complex mixture of proteins shows a complicated succession of adsorption events, such that the composition of the adsorbed protein layer is constantly evolving. This phenomenon is known as the Vroman effect, after its first observer [203]. Subsequent, more quantitative studies have shown that the course of the succession of adsorption events depends on parameters such as the wall shear rate of the flow [82]. One implication of this result is that a stent made from a material optimized for use in a blood vessel of a certain diameter might turn out to be quite unsuitable in a different vessel with faster or slower blood flow.

The microscopic explanation of adsorption/desorption hysteresis is that the complicated system of intramolecular hydrogen bonds that maintains the protein in its folded conformation is only marginally stable [118]. If some of the intramolecular contacts can be replaced by protein-surface contacts (Figure 1), then there may be no, or little, change in enthalpy, but substituting an extended adsorbed conformation for the compact folded conformation results in a considerable gain of entropy [34]. Numerous studies have evinced this surface-induced denaturation [118] [186].

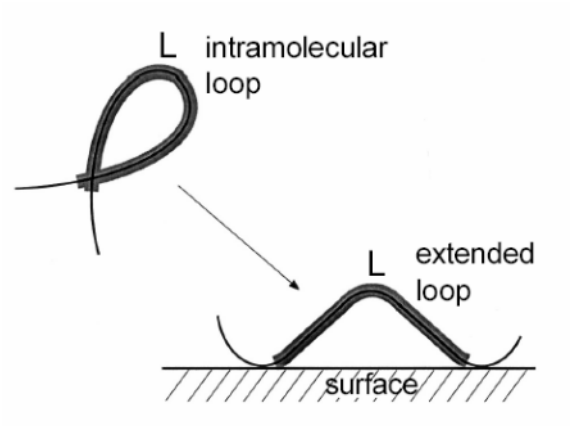


Figure 1: Surface-induced denaturation of a protein [34].

When a soluble protein approaches a surface, in most cases it will experience a repulsive force. Most proteins have an excess of dativită [123] (otherwise they would already aggregate in the cell or in the bloodstream; in the normal healthy organism such aggregation is a pathological state typically caused by mutation, as in sickle cell anaemia [186]. Many commonly encountered biomedical surfaces such as titania (but not zirconia) have a similar excess of dativită [123]. This gives rise to relatively long range 'hydration repulsion' (Figure 2). Nevertheless, once a protein has surmounted the repulsive barrier (and on average this may be only after several hundred attempts) it will fall into a potential well that will rapidly deepen due to the unfolding process illustrated in Figure 1.

Once this surface-induced denaturation has taken place, not only is it extremely difficult to then remove the protein, but the protein itself may have drastically changed its characteristics. Since it is no longer the native protein, it may be recognized as foreign by the immune system of the host, and a succession of inflammatory responses may be initiated. Furthermore, other normally innocuously soluble proteins may now adhere to the denatured protein,

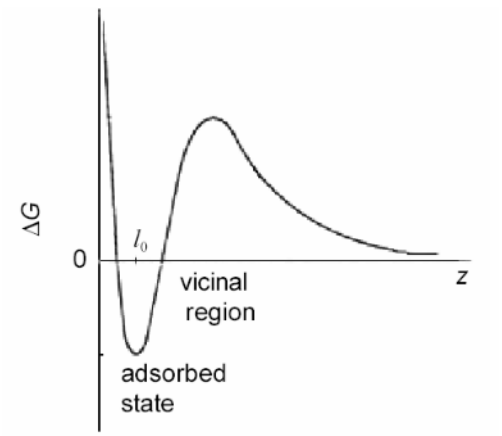


Figure 2: Sketch of the interfacial potential Δ*G* between the protein and the biomedical surfaces as a function of their separation distance *z* [146]. The range of *z* on the horizontal axis is typically 20–30nm; the vicinal region is of molecular dimensions (a few nm) (not drawn to a uniform scale) and the equilibrium separation distance ℓ_0 is ~0.15 nm [123].

even if they themselves are able to resist adsorption to the implant.

The first step in understanding these events, and therefore in being able to control them, is to quantitatively measure them. Modern techniques of high resolution molecular microscopy ([148]; see also Section 4.2) are able to yield high-quality data with excellent time resolution, suitable for subjecting to careful kinetic analysis. From this, not only the interfacial potential, but also the dimensions of a protein, the symmetry of its arrangement at the surface, and the kinetics of its internal rearrangement processes may be determined [140] [142] [146].

The long-term goal of work in this field is to be able to predict the behaviour of a protein at any interface in the presence of any chosen biological medium from its structure or better still, from its amino acid sequence. We are still a considerable way from this goal. Detailed studies have shown that drastic changes in adsorption behaviour can take place due to minute changes in the amino acid sequence, which may have minimal, even negligible, structural consequences for the protein itself [139]. Not surprisingly, in view of these difficulties, modelling and numerical simulations of the adsorption process are also being brought to bear and have already been useful in revealing some of the hitherto unsuspected subtleties in the process (e.g. [96]).

2.1 Lubricating surfaces

Lubricants in biological and biomedical surfaces consist of one or more layers that exist between two surfaces able to undergo relative movement. Lubricants are required to prevent excessive friction and wear. High friction coefficients usually lead to increased energy losses in the biomedical system and ultimately to wear, in which parts of the surfaces are removed and in which the removed debris may in turn form particulates, which lead to further wear as well as an adverse immune response.

Lubrication of biomedical surfaces can conveniently be divided into several régimes, whose natures are dependant on the ratios of thickness of the lubricating film, h, to a measure of the roughness of the surfaces, R. In fluid film lubrication the h/R ratio is high and a fluid film completely separates the two surfaces, which only come into contact when starved of lubricant. On the other hand, in boundary lubrication, where the h/R ratio is low, physically and chemically absorbed films on the surfaces control the friction, which may be several orders of magnitude greater than in fluid film lubrication. Between the two régimes lies a third régime: mixed lubrication that is, as the name suggests, a mixture of fluid film and boundary mechanisms.

It follows from the above that biological systems should display good lubrication behaviour when fluid film thicknesses can be consistently maintained, when film thickness is high and when surface roughnesses are low.

A classic biomedical example of such an approach in practice is that of the hip replacement joint. In this artificial joint, the lower surface roughness that is often achievable with ceramic surfaces leads to improved lubrication behaviour, (albeit still within the mixed lubrication régime), in comparison with more conventional metal-based joints [75]. Articular cartilage however, which comprises the surfaces of natural synovial fluid joints in the human body, functions well although its roughness is 2–5 μm, three orders of magnitude greater than that of man-made ceramic surfaces.

This apparent contradiction can be resolved by taking into account the deformation of biological surfaces under load to reduce surface roughness. This is the phenomenon of elasto-hydrodynamic lubrication (EHL), and is a feature of biological surfaces, because of their relatively low stiffness [42]. Because of this, in ‘soft’ EHL systems the elastic deformation of the surface under load is typically several orders of magnitude greater than the film thickness [74]. Cartilage displays a phenomenon known as microelastohydrodynamic lubrication (mEHL) , where the projecting tips of the cartilage significantly deform during loading. This allows the lubrication of the cartilage to be adequate at the synovial fluid film thicknesses in a human joint [26]. Such complex natural phenomena suggest how human biological systems can provide analogues for the development of future biomedical lubricated systems.

One of the most recent developments in the field is the introduction of monocrystalline sapphire prostheses [99] [100]. Pioneered in the Ukraine, the application of this material to hip endoprostheses has many advantages, not least that of reducing wear.

Wet lubrication phenomena within the human body are ubiquitous. Approximately 60% of the body is composed of water, with some 40% of body weight being intracellular fluid (much of which is structured by the vicinity of interfaces or the presence of the sort of macromolecules [210] [111]) and 20% extracellular fluid. The human body produces a wide variety of aqueous biological fluids that lubricate biological and biomedical surfaces. Typical environments are likely to contain transient loadings, non-Newtonian lubricants, low film thicknesses, film thicknesses that vary both spatially and with time, permeable tribological surfaces and non-linear elastic surfaces [71].

An important practical example of the importance of lubrication is that of processes in the eye. Natural ocular lubrication comprises two tribological surfaces, the cornea and the eyelid, with tear fluid providing the intervening lubricant layer. However the tear film is actually quite complex [121], consisting of lipid, aqueous and mucin layers [127]. The component forms the superficial layer of the tear film. The aqueous component contains electrolytes, oligopeptides, proteins and glycoproteins. The mucins themselves are glycoproteins expressed by the epithelial tissues of mucous surfaces. Into this environment the man-made contact lens is then introduced. The modern ‘soft’ contact lens is formed of a hydrogel, i.e. a material that ensures adequate oxygen supply to the cornea but that has mechanical properties sensitive to humidity, water content and contact pressure. For a significant number of potential users, soft contact lenses result in excessive eye irritation, which may arise due to high friction. Lack of sufficient lubricant may even damage the ocular surface. An increase in its roughness of perhaps an order of magnitude leads to the higher friction coefficient, boundary lubrication then becoming the dominant lubrication mechanism [64]. Ways to increase the fluid layer thickness on the lens have been studied, with such additives as hydroxypropyl methylcellulose (HPMC) appearing to be effective [192]. Laboratory studies suggest that in a normally lubricated ocular environment the dominant friction mechanisms involve viscoelastic dissipation within the lens and surface shear stress, rather than hydrodynamics [153].

Another important lubricated environment is that of microscale blood vessels, in which the oxygen exchange phenomena occur. The diameter of an undeformed red blood cell may be larger than that of the microvessel (note that whole blood, unlike plasma, is a non-Newtonian shear-thinning fluid at normal red cell concentrations). As

with articulated joints, EHL-based lubrication phenomena are essential for understanding the successful natural lubrication of blood flow. EHL in microcapillaries is aided by the presence of the glycocalyx, a polysaccharide matrix excreted by endothelial cells lining the blood vessels [168]. In EHL the glycocalyx appears to act as a deformable porous layer [205]. Incidentally, mimicking the combination of cytoskeleton and glycocalyx of real cell membranes shows promise for the production of more robust bioanalytical sensor platforms [19].

3. THE MANUFACTURE OF BIOMEDICAL SURFACES

This section deals with manufacturing routes to control surface topography. Certain biomedical devices that need very specific manufacturing processes have come to prominence in the last decade, e.g. stents, hypodermic needles and microneedle arrays, joint prostheses and catheters. Each pose specific manufacturing challenges as discussed below.

Stents (Figure 3) are used to support weakened arterial walls and thus prevent them from collapsing, or to open up cardiovascular channels that have become coated with residues such as plaque. Recent advances in NiTi shape memory alloy stent manufacture include: the ability to machine stents that are continually being reduced in size, e.g. from 7F (diameter 2.3 mm) in the 1990s down to 2F (diameter 0.64 mm) in 2004 (currently tubes 0.5 to 15 mm in diameter (but normally 1.5 to 3.0 mm) are the predominant starting materials, as opposed to the foils of a decade ago); the enhancement of X-ray visibility by adding tantalum rivets and sleeves (implying that the tantalum must be polished at the same time as the NiTi); the ability to reduce the roughness of the surface finish, now recognized as important for non-interference with laminar blood flow, and less risk of tissue damage during insertion into the cardiovascular system.

NiTi stent manufacturing sequences include laser cutting, honing of inner surfaces, thermal treatments, honing of outer surfaces, and electropolishing that can achieve roughnesses of 50–80 nm, compared with 90–230 nm by mechanical (abrasive) methods [177]. Liquid honing of Nitinol stents employs abrasive slurries to remove scale and heat-affected zones. The process is controlled by weight loss measurements. Auger electron spectroscopy (AES) has revealed that the top 3 nm has a titanium- and oxygen-rich composition, i.e. depleted in nickel.

Stainless steel stents are not activated by a temperature-induced phase change (unlike those made from NiTi), but are expanded by a pressurized balloon. To avoid bursting

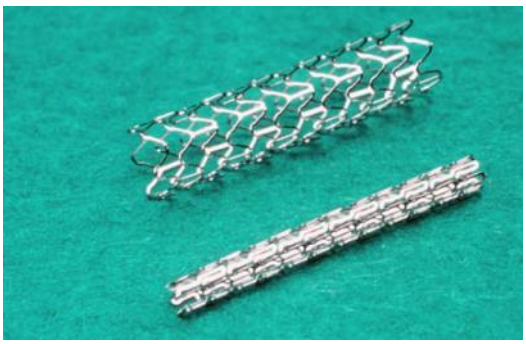


Figure 3: Examples of modern stainless steel stents designed for insertion into human blood vessels of different sizes (Charité – Universitätsmedizin Berlin).

the balloon by perforation, surfaces must be burr-free and smooth, i.e. with a surface roughness of Rq < 100 nm [110]. It is therefore important to produce smooth surfaces. As a precursor to polishing, stents are descaled by acid etching (pickling) followed by electrolytic cleaning [152]. Another point to be borne in mind is that nickel, a constituent of stainless steels, is toxic. To seal the nickel within the body of the implant, chemical passivation processes can be used to increase the Cr/Fe surface ratio, and impart corrosion resistance by thickening the protective chromium oxide surface film.

Needles: the traditional way of delivering drugs transdermally is via a hypodermic syringe, with an estimated 3.5×10^{10} produced worldwide annually from hollow stainless steel using laser cutting and electropolishing. There is great interest in developing more effective methods of painless transdermal drug delivery via microneedles. Alternative painless mechanical methods include shape-memory alloy stretching of the skin, while non-mechanical methods include electrophoresis and phonophoresis [17]. Currently, microneedle arrays are still overcoming acceptance challenges however. A considerable variety of materials and processes are under consideration for mass production of microneedles: solid stainless steel and laser cutting and electropolishing (e.g. [45]), solid silicon and anisotropic etching, solid and tapered biodegradable polymers, solid titanium and PCM, hollow silicon and photolithography, hollow PMMA and LIGA, hand-drawn hollow glass, and hollow nickel and PEF.

Joint prostheses enable the ageing population to achieve a higher quality of life by ensuring maintenance of mobility. Nevertheless, hip and shoulder joints gradually wear and produce painful medical conditions that can typically only be rectified by replacement of the ball and socket joint with an artificial joint [73] [99]. An orthopaedic implant, or artificial joint, consists of the same basic parts as a healthy joint. Total hip arthroplasty is a widely performed surgical procedure (total shoulder arthroplasty is less commonly performed). It involves replacing the damaged parts of the hip (femur and pelvis) with artificial parts. The hip prosthesis can be made of metals, ceramics and plastics, and consists of a cup, a ball and a stem. Commonly used materials include polyethylene, stainless steel, and titanium. The friction behaviour of the femoral head-acetabular cup pair is crucial in determining the acceptability of the artificial replacement. Sapphire is a very promising new material able to reduce wear and prolong the lifetime of the endoprosthetic system [99] [100].

Catheters: urinary incontinence is only recently receiving attention from engineers to determine whether better ways can be found to relieve the suffering caused to both young and old by this distressing medical condition (it has been estimated that some 400 million urinary catheters are used worldwide each year). Unfortunately, catheters (usually made of silicone or latex) are notorious for becoming encrusted and blocked due to chemical reactions initiated by the bacterium *Proteus mirabilis* reacting with urea to form ammonium hydroxide, thereby raising pH and causing the precipitation of insoluble by-products such as struvite (magnesium ammonium phosphate) and hydroxyapatite [24] [179]. In the case of long-term catheterization (> 28 days) virtually all patients develop painful urinary tract infections [179]. Keeping catheter surfaces free of deposits is therefore of fundamental importance in incontinence treatments, and current research is focused on improved catheter coatings and the use of antibiotics such as Triclosan to impregnate

silicone and prevent bacterial colonization (by *P. mirabilis*) of the catheter.

3.1 Surface generation

This subsection deals with the modification of the texture (morphology and chemistry) of surfaces other than by coating (dealt with in Section 3.3). Surfaces in biomedical engineering have been considered as a subset of surfaces in precision engineering, microengineering and nanotechnology [21]. Each biomedical surface is designed to be application-specific. For instance, in designing a hypodermic needle surface for transdermal drug delivery, the needle consists of a cannula and a pointed tip made up of a series of bevels. The sharp point is typically obtained by grinding the cannula into three bevels. Redesigning the needle and grinding five bevels to reduce the penetration force required to pierce the skin has been successfully carried out, resulting in reduced pain for the patient [199], greatly increasing acceptance of this mode of drug delivery. To reduce the pain level even further electropolishing is used to produce a very fine and smooth cutting edge.

3.1.1 Machining

Ultraprecision and micro-machining of metals, ceramics and polymers is carried out to produce ultrasmooth surfaces and rough surfaces with controlled texture.

Precision grinding, diamond turning and micromilling are important for generating structured surfaces in many biomedical applications. In particular, ultraprecision grinding, diamond turning and micromachining are finding ever wider application, either for the direct fabrication of surface features or as a means of manufacturing tooling for replication and moulding processes. Overviews of micromachining processes and the generation of structured and textured surfaces have been provided in several recent CIRP keynote papers [25] [31] [105]. The number of biomedical applications that use ultraprecision micromachining technology is increasing rapidly for several reasons. Firstly, there is a requirement for miniaturization of surgical equipment and devices following developments in less invasive surgery. The ability to achieve smooth surfaces and well-defined edges is critical for applications such as tissue removal tools operated through an endoscope. Secondly, prosthetic surfaces need to be tailored to optimize properties and performance, such as adhesion, wear resistance and interface stability. Surface characteristics are also particularly important for microfluidic devices used for (bio)chemical analysis or as smart sensors and other monitoring systems. Applications for such systems include blood analysis, cell sorting and characterization, glucose monitoring systems, genetic analysis and general lab-on-a-chip functions. Key to achieving the appropriate characteristics and performance from a moulded microfluidic device is the level of precision with which surfaces and features are generated on the mould insert by a micromachining process. There is also a demand for microsized prosthetic devices, which now rely on recent advances in manufacturing technology and materials for their production. Figure 4 illustrates a sensor housing for a hearing aid application. Each part weighs only 0.0022 g and is manufactured from polyoxymethylene (also known as POM or acetal) using a microinjection moulding process, a key part of which is the design and manufacture of the microinjection moulding tooling for which dimensional control and surface finish are critical.

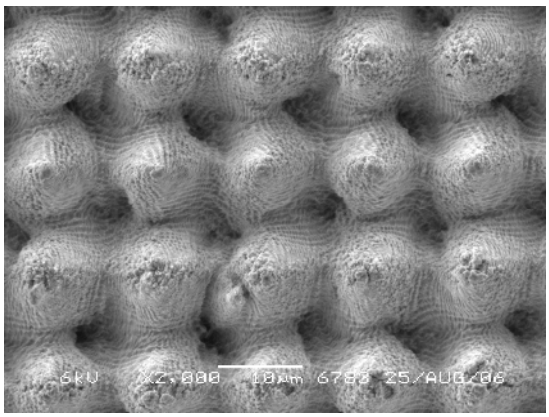
3.1.2 Laser micromachining

The industrial manufacture of Nitinol stents employs laser micromachining, typically nanosecond diode-pumped solid state Nd-YAG lasers for Nitinol [165] [182]. AISI 316LVM stainless steel stents are also laser-cut, predominantly in the far east [152]. Infrared laser cutting of arrays of microneedles bent at right angles to a 75 µm thick flat stainless steel sheet, producing needles 500–750 µm long, resulted in only 5–10% of the pain sensation produced by a 26 gauge hypodermic needle [45].

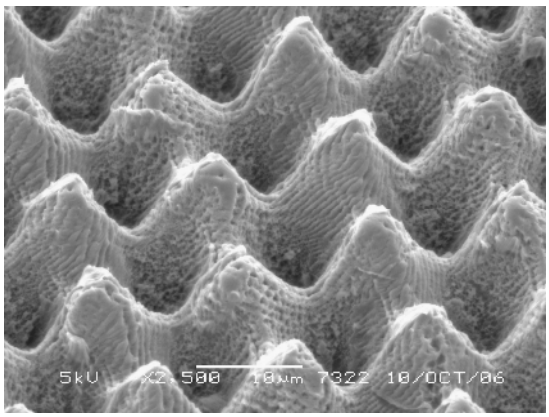
Figure 4: Micro cochlear implants, compared with the head of a safety match (courtesy of Battenfeld).

Laser interference surface texturing: the leaves of the lotus plant (*Nelumbo nucifera*) are roughened with a specific microstructure, which in turn is covered with tiny wax crystals. The microstructure enhances the hydrophobicity of the wax. In consequence, lotus leaves contaminated by dirt are easily cleaned by rainwater: the water droplets are unable to wet the surface, and any dirt on the leaf sticks to the droplets and is carried away as they roll off the leaf. To mimic this structure, injection moulds have been post-machined by femtosecond pulsed lasers [54]. Roughness on two scales was found to be necessary: a pattern of cone structures with feature sizes in the 10 µm régime, and a submicrometre superimposed structure was needed. This two-scale roughness was found by serendipity: during the first experiments with the femtosecond pulsed laser, the emergence of periodic ripple structures and more chaotic rough structures in the submicrometre régime were found. Their occurrence was then intensively studied whilst varying the machining parameters [54]. The ripple pattern was found to be a general phenomenon occurring with all kinds of materials after illumination with several pulses. The ripple spacing was usually between 600–700 nm, just shorter than the wavelength of the femtosecond pulsed laser (800 nm). Highly regular patterns can be machined using homogenized intensities. After irradiation with further pulses, the ripple pattern is degraded by trenches occurring perpendicular to the ripple patterns. By applying even more pulses, highly chaotic structures emerge. The point of transition between the two self-structuring régimes as well as the morphology of the emerging rough structures are dependant on the laser machining parameters, including repetition rate (10–300 kHz). The injection moulds are then used to fabricate replicas from polypropylene, a cheap polymer that already has quite hydrophobic properties. By imposing a designed microstructure on it, ultrahydrophobicity can be achieved, comparable to that of the lotus leaf (Figure 5). Contact angles in water of up to 165° have been measured, hence the surfaces are non-wetting and water droplets are very mobile. In summary, the properties of a lotus leaf have been mimicked successfully.

Other applications for such surfaces are manifold: control of (microfluidic) flows, friction control in lubrication, control



(a)



(b)

Figure 5: SEM images of: (a) Laser interference surface texturing on a steel mould surface; and (b) the mould replicated in polypropylene (courtesy of Groenendijk and Meijer).

of drop formation in emulsification, wetting control of scaffolds for tissue engineering, and wherever the behaviour of liquid and solid phases in contact have the potential for improvement by control of the wetting properties.

Laser sintering can be used to prepare glass-ceramic materials for potential use as a bone replacement material [51]. This additive rapid prototyping technology is attractive as it should be able to produce parts customized relatively cheaply to individual patient requirements.

3.1.3 Electrochemical machining and electroplating

This subsection deals with processes involving the passage of Faradaic currents, including electropolishing.

Electrochemical machining (ECM) has been used, for instance, in the production of textured surfaces on hip prosthesis stems in stainless steel.

Electrolytic photoetching is a hybrid process employing ECM and photochemical machining techniques to dissolve metal through apertures defined by photoresist stencils [2]. It has been used to fabricate planar stents from flat NiTi foils. A thick titanium oxide layer on the foil surface gives the material its corrosion resistance and prevents leaching of potentially toxic nickel into the body [79].

Electropolishing is used as a final treatment for finishing stents after liquid honing [4] [8] [37]). The technique is also used for reducing surface roughness on needles [45].

Electroplating has been used in many of the processes for manufacturing microneedles and microneedle moulds

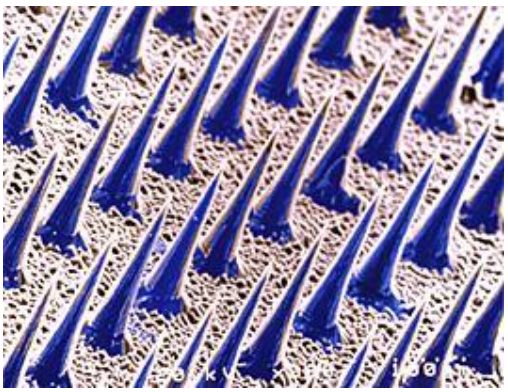


Figure 6: Painless injection needles produced at Georgia Institute of Technology, USA.

[102]. Typically, hollow nickel-iron microneedles in a 20 x 20 array are 80 µm at their bases, taper to 10 µm at the tips and are 150 µm in height with 3 µm wall thickness and 150 µm centre-to-centre spacing. The needle bores are conical too. These needles are strong enough to be repeatedly inserted into and removed from the human epidermis [106].

3.1.4 Photolithography and etching

Photolithography and chemical etching have been used to produce painless injection needles (Figure 6) by anisotropic etching techniques that follow atomically-flat, slow-etching crystal planes.

Deep reactive ion etching (DRIE) is used in the first stage of micro-needle bore production from silicon. The process relies on multiple etch-and-passivate processes for the production of high aspect ratio (10:1) features.

Photochemical machining (PCM) has been used to etch complex structures into polyimide (Kapton) sheets to fabricate intra-ocular haptics (holders for replacement eye lenses) [3]. Polyimide is especially attractive for this application: its flexibility is comparable to polypropylene and PMMA and it has greater tensile strength and superior shape memory. Since polyimide is safe for implanting, additional medical applications are likely to emerge, exploiting its shape-retention spring properties.

3.1.5 Embossing and injection moulding

Hot embossing (HE) is a replication technique that uses thermoplastic polymer thin foils as the starting material. The process is divided into the following major steps:

1. The thermoplastic polymer sheet is inserted into the moulding machine (occasionally it is preheated);
2. A tool insert is preheated to a temperature just above the glass transition temperature (T_g) of the polymer material and then is pressed into the polymer film. The process is typically carried out under vacuum to allow the cavities' evacuation and to prolong the lifetime of the tool insert, which would otherwise quickly degrade because of oxidation at high temperatures;
3. The tool is cooled, still under pressure, at a temperature below the polymer T_g and then released from the substrate, which now contains the desired features. This processing step is the most critical because replication errors can be introduced during cooling due to the different thermal expansion coefficients of tool and substrate. Hence the cooling cycle should be as short as possible. Other replication errors can occur during the mould insert release, in particular when high aspect ratio features are embossed. In this case an automated mould

release is typically needed to avoid distortion, especially if high accuracy is required.

Injection moulding (IM) is an established technology for the production of macroscopic components from thermoplastic material. The thermoplastic is fed in the form of granules into the so-called plasticating unit and then injected at high pressure into a mould having the inverse of the desired shape. The molten polymer freezes into the mould, becoming a solid part, and is then released from the mould by opening its end and ejecting the plastic part with a set of pins. The whole process is normally very fast with production cycles of a few seconds.

In microinjection moulding, the mould cavities contain features in the micrometre range. They need to be completely filled by the polymer melt; in many cases this requires the process to be adapted to take into account the air entrapped in the small features and for the very fast cooling of the injected melt in small, cold mould features. In order to ensure proper cavity filling, high injection speeds and pressures are required. Removal of the air entrapped in the cavities is normally carried out by evacuating the mould with an external pump prior to injection.

Fast cooling of the polymer melt in the mould typically causes the polymer to prematurely freeze within the very small cavities, resulting in the cavity being only partially filled. The Variotherm process was developed to avoid this problem [104] [163] [130] [131]. In this process, the mould is heated to allow the polymer to flow within the mould without freezing along the walls. Depending on the aspect ratio of the features, the mould temperature can be as high as the no-flow temperature of the polymer material. When the polymer has filled the microfeatures in the mould, the mould itself needs to be cooled to allow solidification and defect-free demoulding of the plastic part. The Variotherm process allows fabrication of parts with features in the micrometre range and with high aspect ratios. However, the time required to heat and subsequently cool down the mould significantly slows down the process (cycle times of a few minutes).

Applications of microinjection moulding for the production of microfluidic devices include the fabrication of channels with specific surface characteristics for clinical diagnostics, of e.g. blood group, diabetes, pregnancy, malaria and HIV. In the future, microreactors for individualized drug synthesis will be another important application. Others include the manufacture of solid and hollow metal, silicon, plastic and glass microneedles that range in size from one millimetre to one thousandth of a millimetre, by etching microneedle masters from silicon, then using the masters to fabricate micromoulds for metal and polymer needles [102]. In order to produce an exact inverse copy of a mould by injection moulding or hot embossing the replication must be perfectly repeatable throughout the lifetime of the mould. The fidelity of polymer replication processes has been studied and documented in detail by Theilade [193]. Biocompatible surfaces have been made by drilling a mould with many microholes, which are then used to create a surface with many fibrils, reportedly stable in contact with blood [41] [132].

3.2 Surface engineering

The processes dealt with in this subsection are defined as those that are separately applied to an object subsequent to its basic fabrication, but excluding coatings, which are dealt with in Sections 3.3 and 3.4

The interactions that occur at the surfaces of biomedical materials are critical to their performance, and it is therefore essential that surfaces are tailored to achieve optimum structure and composition in order to control both adsorption (especially of biomacromolecules) and degradation processes. A range of surface treatment and coating processes is available for enhancing the performance of biomedical materials.

Surface engineering can be considered in terms of surface treatment (modification of a surface by changing its composition or microstructure or both) or surface coating (the addition of a distinct layer of material to the original surface). The surface engineered system can therefore be considered as a composite system, consisting of a near surface region of a modified coating, which is optimized for the working environment, and the substrate or bulk material, which is often selected based on mechanical and physical characteristics and manufacturability. A key feature of such a composite system is that it will exhibit a performance superior to the coating or substrate alone.

For biomedical applications such as implants and prostheses, the majority of coatings and surface treatments are applied to enhance corrosion or wear resistance, or to help with hard tissue compatibility by promoting bone growth. Although many coating types and deposition processes have been researched for biomedical applications, the majority of them fall into the following categories: plasma modification; surface modification by ion implantation; surface oxide modification by anodizing; thin film ceramic coatings by physical vapour deposition (PVD) or chemical vapour deposition (CVD); thicker ceramic coatings by plasma spraying; self-assembled polymer coatings; and bioactive coatings. The first three are dealt with in this subsection, the next three in Section 3.3, and the last one in Section 3.4.

Plasma modification of polymeric materials such as polyamide (PA-6), poly(vinyl chloride) (PVC), poly(ethylene terephthalate) (PET), PET containing titanium dioxide (PET + TiO_2), poly(methyl methacrylate) (PMMA) and poly(tetrafluoroethylene) (PTFE) has been used to enhance their wettability—this is the first step in the immobilization of selected biological macromolecules such as heparin [27]. For example, after a 10 s dielectric barrier discharge in helium, the interfacial tension between blood and PET and PET + TiO_2 is considerably reduced [196] [195]. The coating of PTFE vascular prostheses and polystyrene with diamond-like carbon (DLC) films from energized acetylene plasma beams, followed by treatment with an ammonia plasma, improved haemocompatibility of the surfaces (178).

Ion implantation is a surface modification process in which positively charged high-energy ions, typically 10–200 keV, are implanted into the near-surface region of a substrate. The ions arrive at the target surface with kinetic energies 4–5 orders of magnitude higher than the binding energy of the host solid, and essentially form an alloy in the near-surface region. Commonly used ions are nitrogen and boron. To form the beam, an appropriate gas is fed into an ion source, in which electrons emitted from a hot filament ionize the gas to form plasma. An electrostatic field accelerates of the positive ions to high energies under high vacuum (pressures below 10^{-5} torr). The ions penetrate the target surface, typically down to 0.1 µm. Products of an ion implantation process typically include nitrides, borides or carbides.

Ion implantation offers numerous advantages for treating component surfaces. The primary benefit is the ability to selectively modify the surface without detrimentally affecting bulk properties, largely because the process is carried out at low substrate temperatures. The process is

also extremely controllable and reproducible and can be tailored to modify different surfaces in desired ways. Although it is a line-of-sight process, specialized fixturing can be used to uniformly treat complex geometries.

Many surface properties can be improved with ion implantation, including hardness and wear resistance, resistance to chemical attack, and diminished coefficients of friction. Examples of components treated with ion implantation are Ti and Co-Cr orthopaedic prostheses, which are made harder and more wear resistant with the process, and silicone rubber catheters, which are made less tacky and more hydrophilic, improving insertion ability and biological compatibility. There is evidence that ion implantation improves the lifetime of prostheses such as hip joints and knee components [173].

Changing the local chemistry at the surface of the prosthesis may also be beneficial. Bone integration of titanium and Ti-6Al-4V dental implants was improved by C^+ and CO^+ ion implantation; XPS indicated that better bone integration was due to Ti-O-C covalent bonds at the bone-implant interface, stronger and more stable than the ionic bonds typically formed between TiO_2 and bone [98].

The treatment of polymers has also been shown to be beneficial, e.g. improvement in the antithrombogenecity of silicone rubber [184], and better control of cell adhesion on polymer surfaces [185]. Iwaki has reported the production of hybrid vascular grafts of PTFE tubes by Ne^+ bombardment of the inner wall, plasma protein coating of the inner wall, and finally He^+ ion bombardment before being implanted in a carotid artery [69].

Ion implantation is now routinely undertaken to improve the tribological properties of ultra-high-molecular-weight polyethylene (UHMWPE) used for example in hip and knee implants (UHMWPE wear debris can initiate tissue inflammation, bone loss (osteolysis) and implant loosening). Nitrogen ion implantation into both the polymer and the Co-Cr-Mo alloy metal parts of prostheses has been shown to be beneficial [122]. Testing using a knee wear simulator for up to 5 million cycles, equivalent to three years of implant life, achieved a fivefold reduction in wear rate.

Anodizing: a thin layer of TiO_2, typically 2–5 nm thick, naturally forms on titanium in oxidizing environments, generating a passive layer that provides excellent corrosion resistance. This oxide layer can be modified by anodizing treatments to increase its thickness and alter its morphology to enhance surface biocompatibility for orthopaedic implants [23]. Typically the anodizing process consists of alkaline cleaning, acid activation and electrolytic anodizing to produce an oxide that may be between 20 and 1000 nm thick, with the thicker films exhibiting porous outer regions. The acid pretreatment removes surface contaminants and the general appearance of the anodic film gives a good indication of the homogeneity of an implant surface [23]. An example is shown in Figure 7—these porous surfaces exhibited better histomorphometrical parameters (bone-implant contact and quality of newly formed bone) and osteoconductivity was more pronounced around the implants (cf. work on bone response to pore-free oxides [85]).

A further feature of anodic oxide films formed on titanium is that their colour may be controlled as a function of oxide thickness and minor compositional changes. This has been used to provide colour-coded implant systems, making the logistics of their supply and manipulation in the operating theatre easier.

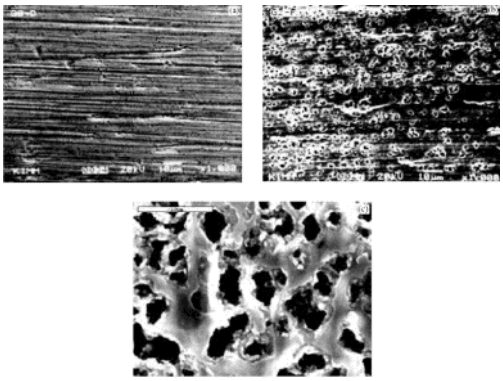


Figure 7: Pure titanium screw-shaped implants anodized in acetic acid to generate a range of oxide film thicknesses; SEM images show two different types of surface morphology: (upper left) a non-porous barrier in the control implant; and (upper right) a porous barrier in the test implant; the lower image, at a tenfold higher magnification than the upper two, shows the honeycomb-like structure of the porous implant (the width of the lower image is 33 μm) [183].

3.3 Surface coating technologies

This subsection deals with the deposition of material on bulk objects in order to modify their surfaces. Topics covered include physical vapour deposition, chemical vapour deposition and thermal spraying technology. Attention will be paid to the control of deposit microstructure and coating composition via deposition parameters. Both thick and thin coatings are covered, as well as sensory and smart (i.e. with both sensor and actuator properties) coatings.

A wide range of surface engineering processes is available; the selection of a particular one depends on many factors, including the substrate material, component design and geometry, cost and, obviously, the end application. Two aspects of the surface engineering process that are often highlighted are coating thickness and process temperature. The depths of surface treatment and thicknesses of coatings can vary over several orders of magnitude from less than 100 nm for ion implantation to several mm for thermal spraying and weld overlays (Figure 8). The importance of coating deposition temperature depends on the substrate material. The temperatures commonly encountered for surface engineering processes range from ambient up to the melting point of many substrate materials (Figure 9). High processing temperatures may adversely affect substrate properties but may be necessary to achieve the required coating stoichiometry and structure. This may be the limiting factor when selecting a coating and the corresponding deposition process.

Physical vapour deposition (PVD) processes include evaporation and sputtering. As with CVD (see below), there are benefits to using plasma-assisted deposition (PAPVD), in which the substrate is subjected to a flux of high energy ions both before and during deposition [155]. The coating characteristics are a function of composition, microstructure and the deposition conditions. Simultaneous evaporation or sputtering from source materials of varied composition enables functionally graded or nano-laminated coatings to be produced. Temperature and pressure influence the nucleation and growth processes occurring, enabling control over coating microstructure and surface topography.

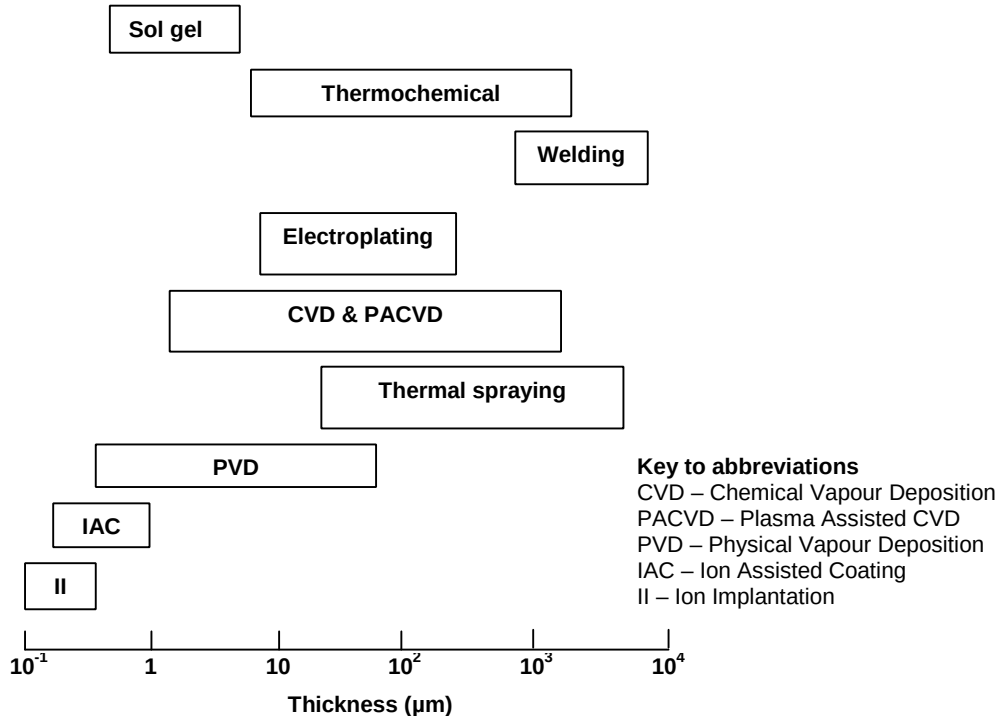


Figure 8: Typical thickness ranges for various coating and surface treatments [155].

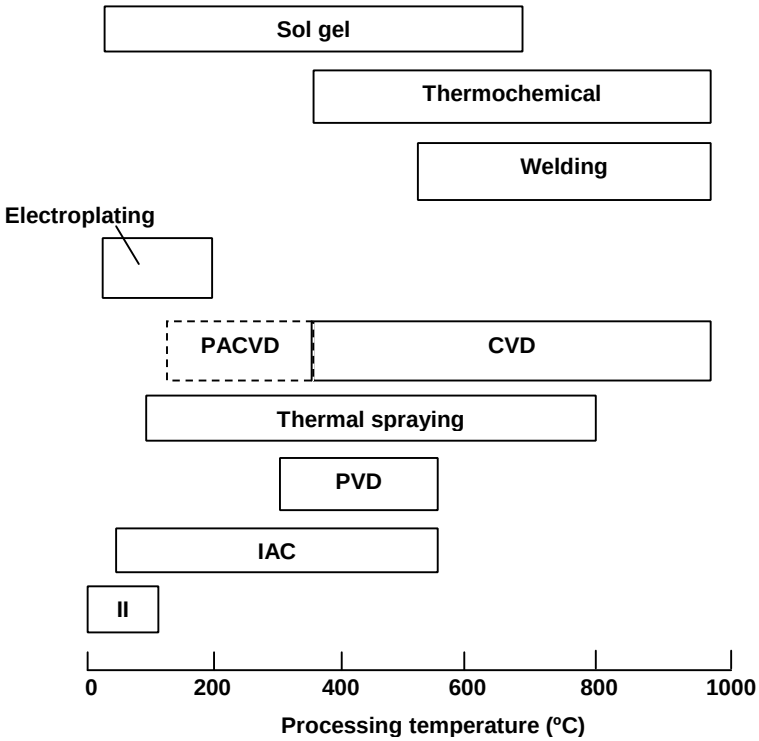


Figure 9: Typical processing temperatures for various coating and surface treatments [155].

PVD and PAPVD coatings have been applied to a range of biomedical applications. Much of the interest is in corrosion and wear resistance and the majority of work reported in the literature has concentrated on thin hard coatings. For example, (Ti6Al4V)N thin films deposited onto silicon or steel by reactive magnetron sputtering exhibited excellent mechanical properties and corrosion resistance in prosthetics [68].

Bioimplants such as hip joints and bone plates are prone to undergo fretting fatigue failures during service within the body. Thin hard coatings have been shown to improve fretting fatigue resistance because of superior tribological properties compared with uncoated alloys. PVD TiN, for example, has been shown to perform well on titanium alloys used in hip joints [198].

Diamond-like carbon (DLC) coatings produced by PAPVD have been studied by Brizuela et al. [12]. Magnetron sputtering was used to deposit titanium-alloyed DLC onto Co-Cr-Mo substrates by using titanium targets in a mixture of argon and acetylene. The acetylene flow rate was varied to generate a graded coating that was titanium-rich at the substrate and DLC at the surface. The coatings exhibited excellent mechanical properties and adhesion, low friction and exceptional wear resistance. They also passed all biocompatibility tests for implants based on ISO 10993. Cell attachment on DLC coatings on PMMA has been investigated by Li and Gu [91]; higher levels of ion bombardment promoted a higher fraction of sp^3 bonding, resulting in greater hydrophobicity. Cell attachment studies showed low macrophage attachment on DLC, which provided conditions for normal growth of fibroblasts. The number of neutral granulocytes and platelets adhering to DLC was also shown to be low, indicating that the coatings were highly biocompatible.

The antimicrobial properties of implant surfaces are critical in preventing biofilm formation and deep infection of endoprostheses [32], and surface coatings can play a major rôle in modifying surface characteristics. For example, titanium/silver coatings about 2 μm thick deposited by combined titanium evaporation and silver sputtering, containing 9 wt% silver, which is slowly released into the aqueous environment, have antimicrobial activity, and at the same time the necessary load-bearing capability and wear resistance needed for applications such as prostheses [32].

Chemical vapour deposition (CVD) and related deposition processes can typically produce coatings in the thickness range 1–100 μm (Figure 8). For the coating of biomedical components such coatings tend to be thin (1–10 μm) and based on ceramics that will provide enhanced wear and corrosion resistance. There are many variants of CVD [129] [155]. Essentially, a workpiece is heated in a reactor into which a mix of reactive gases is introduced. Near to or on the workpiece surface a chemical reaction takes place to form a solid reaction product, which deposits as a coating. The chemical reactions may require high deposition temperatures, possibly resulting in problems with the thermal stability of the workpiece material.

In recent years there has been considerable effort aimed at reducing the temperature of CVD processes. Rather than thermal reactions only, plasma-assisted (or plasma-enhanced) deposition (PACVD or PECVD) has proved to be very successful. Plasma-assisted reactions can occur at lower temperatures and the application of ion bombardment to the surface before and during coating deposition can influence both the adhesion and the structure of the deposit.

There is considerable current interest in the use of diamond and diamond-like coatings for biomedical applications, e.g. of DLC produced by PACVD as anti-infection coatings on implant surfaces. Medical implants have also been coated with diamond-like carbon (DLC) to increase wear resistance, reduce friction and provide corrosion protection. Because the DLC is deposited by PACVD, deposition temperatures are low, which means that organic polymers, as well as metals and ceramics, can be coated.

Coatings may contain a diamond phase, a graphite phase and other allotropic forms of carbon. Crystal size is typically in the nanometre range and provides a coating with excellent mechanical properties, a high strength passive film and good wear resistance. Biocompatibility can be determined by *in vivo* testing according to ASTM 98186 standards over a period of one year. Histopathological investigations show that implants coated with DLC have excellent biotolerance. The coatings also effectively protect against corrosion and metal-induced toxicity.

DLC coatings have also been applied to the NiTi shape-memory alloys used for implants and orthodontic wires in order to improve biocompatibility [128]. Patients may be sensitive to this alloy due to a nickel allergy, but the PACVD DLC coating acts as an effective barrier that is inert with respect to the local body environment.

The benefits of the low temperature deposition afforded by plasma-assisted CVD have been demonstrated [108]. Thin films of amorphous hydrogenated carbon (αC:H) coatings on polystyrene are applied using a methane-hydrogen gas mix, and are not toxic to living cells, appear to increase cell attachment and afford normal cell growth rates [108]. However, due to the low deposition temperature, the position of the substrate in the plasma was critical to ensure good coating adhesion. More recent work [161] has resulted in hydrogen-free amorphous diamond coatings with the potential to enhance the wear resistance of total hip prostheses. The amorphous diamond films were biologically inert and highly adherent. Simulator testing of conventional total hip prostheses with either the ball or both surfaces coated demonstrated that there was no detectable wear even after 15 million test cycles, equivalent to 15 years of clinical use [161].

DLC coatings have also been applied to metal stent surfaces in order to reduce thrombogenecity [51]. A key requirement for the coating is uniform and complete coverage to ensure that the release of nickel ions is minimized; small defects will result in crevice corrosion and localized dissolution of the metal substrate. DLC coatings have been shown to be effective in preventing nickel dissolution from 316L stainless steel stents [52]. A further advantage of DLC coating is the ability to generate ultrasmooth surfaces, which are, as already discussed, critical for components such as stents. Recent studies have suggested mechanisms for the rapid smoothing that can occur even when a rough substrate is used, because of erosion of hills into neighbouring hollows [114].

Vapour phase deposition is also appropriate for the manufacture of highly porous structures. An example is ‘trabecular metal’, a highly porous biomaterial that is being developed for various orthopaedic applications. It has an appearance similar to cancellous (trabecular) bone, having an open porous structure and a finely textured surface (Figure 10). The material is manufactured by pyrolysis of polyurethane foam to form a low density reticulated vitreous carbon skeleton that is then coated with tantalum by CVD or chemical vapour infiltration. The resulting material has up to 80% porosity and pore sizes typically between 400 and 600 μm. The interconnected pores promote greater bone ingrowth and the textured tantalum surface is highly osteophilic, promoting rapid bone growth.

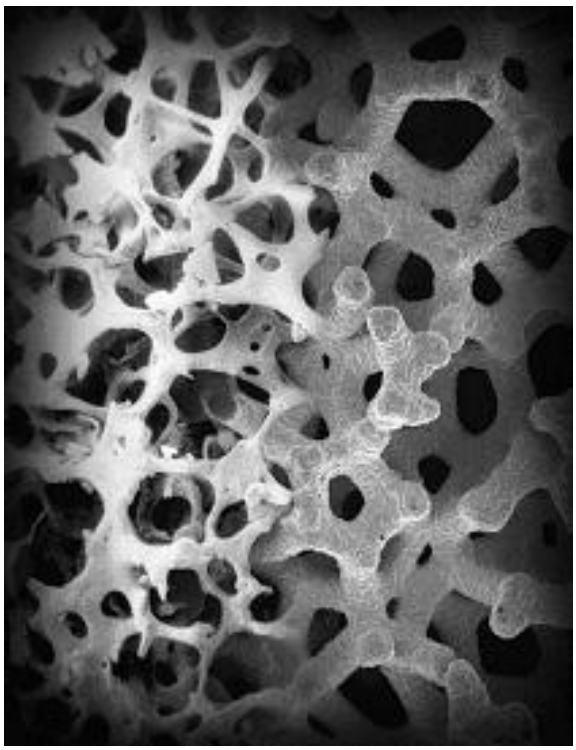


Figure 10: The structure of trabecular metal (courtesy of Zimmer). See text for details.

Ceramic coatings by plasma spraying: plasma spraying belongs to the family of thick overlay coatings produced by heating a material in a hot gaseous medium and accelerating it at high velocity onto a substrate surface (thermal spraying). In plasma spraying a DC electric arc is used to generate a stream of high temperature plasma, which acts as the spraying heat source. The coating material is normally in powder form and is supplied to the plasma in an inert gas stream where it is heated and accelerated towards the workpiece. The high temperature and high thermal energy of the plasma jet mean that materials with high melting points can be deposited.

Hydroxyapatite (HAp), $Ca_{10}(PO_4)_6(OH)_2$, is a commonly used biomaterial for prostheses encompassing orthopaedic, maxillofacial and dental applications. HAp is chemically similar to the mineral component of bone. It is applied to metallic implants of titanium alloys and stainless steels, most usually by plasma spraying, in order to promote bone ingrowth. Key issues are the adhesion of the coating to the metallic substrate and the control of coating composition and microstructure during deposition and when in service.

HAp is thermodynamically unstable at the high temperatures used in plasma spraying and this promotes the formation of CaO, which reacts with water and has a high solubility in body fluids. High deposition processes are also responsible for the formation of amorphous phases that reduce the coating-metal interfacial strength. Therefore recent developments have concentrated on improving coating stability and adhesion. A controlled atmosphere plasma spraying (CAPS) system was found to be useful for controlling the degree of melting of the HAp powder, enabling coatings of tailored microstructure to be produced [56]. Yttria-stabilized zirconia incorporated into HAp results in composite coatings containing more unmelted particles and greater porosity [16]. The ZrO_2 reacts with CaO to form $CaZrO_3$ and bond strength increases. Microstructural control has also been achieved by thermal treatment of the coating after deposition. A post-heat treatment promotes the complete crystallization of the amorphous calcium phosphate and this results in much improved adhesion [43].

A recent study [117] addressed the poor bond strength between HAp and the metal substrate by considering the mismatch in physical and chemical properties between the ceramic coating and metal. The large difference in thermal expansion coefficient and rapid cooling of the plasma sprayed droplets resulted in residual stress in the coating that may compromise adhesion. A computerized closed-loop powder feed system was used to plasma spray a functionally graded coating by altering the ratio of HAp, Ti, Al_2O_3, and ZrO_2 during the deposition. A typical microstructure coating is shown in Figure 11. It consists of a mixture of hydroxyapatite, alumina-bioglass (Al_2O_3áP_2O_5) and zirconia. The composition changes continually so that the modulus increases to that of the titanium alloy substrate as the interface is approached. The outer layer is 30–50 µm of porous hydroxyapatite. It was shown that coating performance and long term stability were much improved through a reduction in tensile residual stress (from 67 to 16 MPa) and an increase in adhesive strength (from 19 to 53 MPa).

Self-assembled polymer coatings have the potential to be applied at low cost to surfaces of arbitrary shape to yield great chemical sophistication and variety. Once the polymer has been synthesized, in principle it can be applied simply by dipping the object to be modified in a solution of the polymer. A useful approach to polymer architecture is to create block copolymers, in which one block is made from a polymer that interacts strongly with the material of the object to be coated, and the other block has the required interactions with the environment.

One of the most common applications of this principle is the use of poly(ethylene glycol) (PEG), i.e. poly(ethylene oxide) (PEO), as an agent to inhibit the adsorption of proteins. PEG (PEO) is the most hydrophilic substance known to man [123], which accounts for its remarkable ability to repel (hydrophilic) proteins, due to the very strong Lewis acid/base repulsive interaction. A popular architecture is a block copolymer of PEG and poly(propylene glycol) (PPG), i.e. poly(propylene oxide), typically the triblock PEG-PPG-PEG. These materials are produced commercially on a considerable scale by BASF under the name of Pluronics. The rather hydrophobic PPG section adsorbs strongly onto surfaces that would otherwise interact with, and probably denature, proteins, leaving the hydrophilic sections in the aqueous environment of the surface. There are endless variations

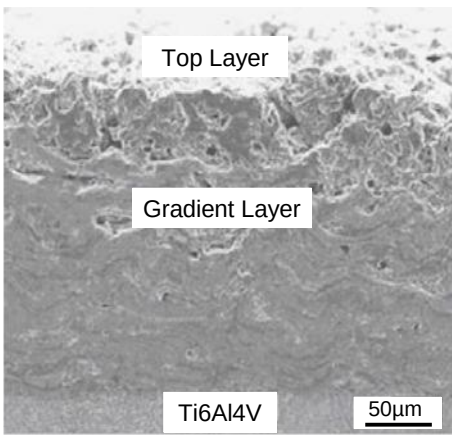


Figure 11: Section through a plasma sprayed bioactive gradient coating [117].

(and patents pending or granted) on this theme. For example, for enhancing protein repulsion from titania, which is weakly negatively charged under physiological conditions, instead of PPG a polycation such as polyallylamine or polylysine will bind more strongly to the metal oxide.

One disadvantage of this approach is that any sudden change in the environment (e.g. lowering the pH) might lead to complete removal of the protective coating, with potentially disastrous consequences in a medical situation. Furthermore, the adsorbed polymer system is actually quite complex and still a very active field of theoretical investigation, and experimental results are by no means fully understood. At present, therefore, this technology has only found very limited applications in medicine. There is more promise in applications such as the prevention of biofouling on boats, for which somewhat different criteria apply, although the general principle is the same [212] [204].

3.4 Bioactive coatings

The concept here is in effect to transform biomedical implants into pharmaceuticals, such that they actively intervene in the physiology of the host organism [67]. The kinds of activities that are of interest are the prevention of blood coagulation, the encouragement of endothelial cell attachment, the prevention of excessive smooth muscle cell proliferation, etc. These activities go beyond what might be considered to be the basic functions of implants, e.g. joint replacement and keeping a blood vessel open, but the effectiveness of a purely passive implant is likely to be rapidly vitiated by undesirable physiological responses. In other words, there is no such thing as a truly passive implant; its mere presence will trigger extraordinary, and usually undesirable, physiological activity around it, and the purpose of bioactive coatings is to steer that extraordinary activity back to ordinary activity, and in some cases to promote extraordinary but beneficial activity. The antimicrobial silver ion-releasing coatings mentioned in Section 3.3 are a successful realization of the concept; silver is also used to dope polymeric materials used for catheters.

The two main ways in which bioactivity is achievable are (1) coating with fragments of biomacromolecules (polypeptides or polysaccharides), and (2) incorporating a reservoir of small molecules (drugs, hormones, growth factors etc.) within the implant, most typically as a thick porous coating, from which the small molecules are slowly released during the lifetime of the implant. (1) is very useful for promoting the adhesion of cells to an implant. A synthetic material such as polyethylene will, in an uncoated state, first of all be coated by biopolymers adsorbing from the bloodstream or secreted by cells in its vicinity. At present, we lack sufficient knowledge to effectively control this process; therefore the deliberate coating of the implant with biomacromolecular fragments known to elicit a specific response is a very practical way for achieving some degree of control over the organism's response to the presence of the implant.

Some of the most extensively researched adhesion-promoting coatings are based on the tripeptide motif arginine-glycine-aspartic acid (RGD), which is a fragment of the ubiquitous adhesion protein fibronectin. RGD is a receptor for a particular integrin present on the surface of endothelial cells. It is much more effective to coat the implant with the RGD fragment than with the whole protein, firstly because the receptor density can be much higher (and the possible problem of the denaturation of the immobilized entire protein is avoided), and secondly because the coating is then highly specific for endothelial cells: fibronectin contains many other fragments acting as receptors for other kind of cells.

Coatings that can slowly release or generate *in situ* bioactive substances are very promising as biocompatibilizing agents. For example, the simple molecule nitric oxide, NO, is a well-known inhibitor of platelet adhesion and activation. It is therefore a candidate for incorporation into the surface of a stent, for example. Endothelial cells are estimated to release about a million molecules of NO per second [40], which would therefore be the quantitative target for the drug-releasing material. Possible approaches include blending a small-molecule NO-donor into a polymer, covalently binding the NO-donor to polymer side chains, and covalently binding the donor to the polymer backbone.

Bioactivity also includes the ultimate in implant assimilation—the implant that is totally degraded and metabolized or excreted by its host after it has fulfilled its function. The most promising approaches to this goal are materials that do not simply decompose in a predetermined fashion, but which react according to signals (e.g. secreted enzymes) emitted by the cells surrounding them [67].

4. METROLOGY OF BIOMEDICAL SURFACES

This section deals with the chemical, physical and mechanical characterization of surface form and finish. In the production of conventional engineering components, dimensional metrology is a vital element in the process to ensure that the specifications for size, shape and surface texture have been achieved. In particular, with the dual trends of miniaturization and increased component functionality, the accurate measurement of surface texture plays an increasingly important rôle in the creation of new and innovative products. Such measurement of surface topography provides valuable data optimizing functional characteristics such as wear resistance [66], reflectivity, wetting [70] [176], unimpeded fluid flow [119], and lubricant retention. The task of surface metrology in the field of characterizing biomedical materials is, however, arguably more demanding, since the physical and chemical environments are more complex than in the realm of conventional materials. One of the prime foci of biomaterial development is to understand what affects a surface's ability to be biocompatible (i.e. to be non-toxic, non-immunogenic and non-inflammatory) [197] [171], and for this we need a multi-facetted approach to surface measurement.

In order to explore the factors affecting biocompatibility, it is often necessary to understand the surface chemistry and its variation over the surfaces of interest. To make the metrologist's life harder, surfaces for biomedical applications are modified as described in the preceding section, i.e. by coating, implantation or texturing, to achieve added functionality, hence the measurement techniques have to be ever more discriminating. The dimensional range of scale of such surface texture and topography measurements is from water molecules to small proteins (nanometric) to cells (micrometric), with the critical parameters being size, shape distribution of features (which can be discrete—holes or peaks—or continuous, such as ridges and furrows), and whether random or periodic. A multiscale approach to measuring some surfaces may be useful [175]. This need makes the range of measurement techniques available rather small, and in many cases measurement techniques have to be used that are significantly compromised by the experimental environment.

Optimizing the performance of devices and materials for biomedical applications is often critically dependent on characterizing their surfaces, not only as a way of controlling the production process, but also determining various qualities associated with the surfaces as they are formed, or modified, and the way such surfaces age with time. Generally, the sort of specialized materials used in medical applications, such as polymers, advanced alloys and ceramics, coupled with their complex shapes, such as those occurring in tissue scaffolds, stents and substitute bone, makes characterizing their surfaces a considerable challenge. There are strong trends towards making 'three-dimensional' surfaces (i.e. by introducing, and deliberately controlling, relief) to confer the functionality required for biomedical applications. Thus, any measurement problem has to be specified very carefully and the measurement requirements and environmental restrictions considered in very fine detail before a measurement strategy can be said to be the optimum approach to achieving the desired result. Ideally, several measurements of different quantities might have to be made at the same time, and this has led to the development of a number of multifunctional instruments [46] [94] [172].

Biomedical surfaces are, therefore, arguably amongst the most demanding which a metrologist might attempt to characterize. An encouraging trend is the setting up of standards, typically by national measurement institutes, so that the results of measurements can be referred to them, providing all users of the results with an enhanced level of confidence in them. The range of applications is exceptionally wide, from implanted joints to the implanted biocapsules being developed to implement the latest sophisticated drug delivery mechanisms, all of which drive the metrologist to acquire an extensive range of tools for his or her measurement armoury, because of the widely varying technical requirements. In the following, the topic has been divided into physical characterization, mainly texture, and chemical characterization; biological (medical) characterization means essentially performance in practice, at least at present, and is therefore a matter for the medical practitioner rather than the metrologist.

4.1 Surface texture measurement

Definitions, parameters and techniques. The majority of definitions, instruments and methods associated with surface texture measurement have their roots in the field of conventional engineering where the materials are generally metallic and have simple departures from ideal, regular shapes. Descriptions of the myriad of parameters that can be used to describe relatively simple surfaces, for which a two-dimensional pattern (2D) can provide a realistic representation, can be found in many books and reviews [174] [209] [20] [194]. Very often, however, a two-dimensional (2D) representation of a surface is insufficient to quantify directional surface features; three-dimensional parameters are discussed in a number of reference works [181] [189] [180]. These parameters are the language by which measurements can be compared on a like-with-like basis. In some biomedical applications they will have special relevance, for example where the wear characteristics of different hip joints, or dental implants, need to be compared.

Given the exceptionally wide ranges of materials, feature sizes and surface textures, choosing the most appropriate measuring instrument and measurement technique is by no means straightforward. Describing measurement space graphically with the characteristic wavelength of the instrument and the surface to be measured along an axis (see for example [190]), is a useful first step. The main point to note is that most contacting measurement techniques have natural limitations dictated by, for example, the dimensions of the stylus, that restrict the resolution or operating speed or both. A useful distinction is between contacting and non-contacting methods.

4.1.1 Contact methods

Conventional methods. The characteristics, advantages, shortcomings and fields of application of contacting instruments have been described and reviewed extensively (e.g. [174] [209]), although the application of such instruments to biomedical applications [28] [169]), especially those involving soft surfaces, is relatively restricted.

Contacting instruments with a large dynamic range, i.e. where the resolution of vertical height measurements enables the texture information to be extracted directly from the data, are useful when assessing the performance of, for example, hip joints [11] and dental implants. Contacting techniques are especially advantageous where very steep-sided features need to be evaluated; see refs [206] and [59] for the variety of probes that can be used.

The emergence of structured surfaces is a key development in the field of biomedical applications, see ref. [31] at the 'engineering' scale and refs [1] [38] for other applications at the nanoscale. However, it should be remembered that besides modifying the surface topography of a surface, many other types of modifications can be achieved by implantation, coating etc. [78], about which a contact technique may give little clue.

*Nano-indentation hardness: a*lthough mechanical characterization of the surfaces and thin biomaterials at the nanoscale is not yet well developed, there are however already some applications where this will be useful [29] [22] [101] [18].

4.1.2 Scanning probe microscopes

This family includes scanning tunnelling microscopy, (STM) (tunnelling current contrast) and atomic force microscopy (AFM) (interatomic force contrast) [213]. In practice, AFM [201] [60] [10] [72] has the advantage over more traditional methods such as scanning electron microscopy (SEM) that surfaces can be measured in the presence of hydration or even liquid water *in vivo*, and there is no need for staining as in the optical microscopies, or even worse, the high vacuum and conductive films needed for SEM studies [61]. Wright and Armstrong [211] have recently reviewed the extensive use of variants of the AFM principle for characterizing microbial surfaces. Moreover, with the AFM it is possible to examine very fragile surfaces like those associated with soft contact lenses [53] and to some extent observe events such as hydrolytic degradation in real time [86], or probe individual biomolecules [62] [166]. Furthermore, AFM can be used not only for imaging, but also to yield data on the viscoelasticity and other physical properties of biomolecular layers on biomedical surfaces [116].

4.1.3 Non-contact methods

With many of the scanning probe microscopies, it is a moot point whether they are really contacting. On the one hand they are conceptually simply scaled-down versions of the profilometers, which are considered to be contact methods. On the other hand, the scanning tip cannot come closer to the sample than the ''minimum contact distance'' determined by the Born repulsion. Two varieties of scanning microscopy that definitely would not be considered as contact methods are SEM (based on electron contrast) and scanning near-field acoustic microscopy (SNAM) [47] [48].

4.1.4 Non-contacting methods: optical techniques

Light interacting with surfaces has been used extensively for measurement for many years. The main advantage is that the surface under test is seldom physically damaged, or chemically changed. Hocken et al. [63] have reviewed optical techniques for surface measurement and have discussed their strengths and shortcomings as well as their fields of application, and many references are given. Optical profilers are analogous to the mechanical stylus instruments but use focused beams to detect the location of the surface. Many different types of optical microscopy have been successfully used to measure surface texture, most recently confocal microscopy [207], and scanning near field optical microscopy (SNOM) is another recent development [58]. In general, the results obtained from optical methods differ from those obtained from contact methods, and may indeed not be directly comparable. Therefore the advantages of speed of operation and lack of surface damage have to be balanced against results that are often difficult to interpret and compare with more conventional methods. This is especially true for biological surfaces and environments. Nevertheless, optical imaging techniques are well suited for monitoring changes to surface roughness, see refs [159], [83] and [158].

4.1.5 Light scattering techniques

Microscopy is based on images, which penetrate powerfully into the human psyche, although they may not be easy to interpret quantitatively, and their scientific value is often diminished because insufficient images are examined to determine whether those selected for detailed examination are truly representative. The alternative approach is directed towards statistical, non-imaging methods based on light scattering. Conventional techniques include specular reflexion, total integrated scattering, and angle-resolved scattering. Speckle techniques include speckle contrast, speckle pattern illumination, and angular- or wavelength-dependent speckle correlation. Powerful laser diodes and LEDs, and fast CMOS and CCD cameras, have moved these techniques into the domain of real time surface roughness measurement [90] [87] [89] [125] [44] [202]. The diameter of the zone over which the measurement is integrated typically ranges from 0.5–10 mm, and roughnesses from 1 nm to 10 µm are accessible. Many investigations of the statistics of speckle patterns produced by coherent illumination have been undertaken [120].

The speckle pattern illumination method [87], based on doubly scattered coherent light, is suitable for measuring the roughness of specularly reflecting surfaces with roughness ranging from 1 to about 125 nm, i.e. hip replacements, stents and eye lens implants. Experimentally, the surface is illuminated with a (monochromatic) fully developed speckle pattern, whose phase distribution is modulated by the rough surface.

Polychromatic speckle autocorrelation involves illuminating the surface with a collimated, partially coherent (i.e. polychromatic) light beam, either discrete (produced by a combination of laser diodes) or continuous (produced by superbright LEDs for example). The method is suitable for diffusely scattering surfaces with a root mean square roughness of less than a quarter of a wavelength, i.e. about 150 nm (e.g. the stem of a hip replacement) [90] [89]. The resulting scattered light intensity distribution shows a roughness-dependent speckle elongation (Figure 12). An efficient procedure to obtain a numerical parameter starts from the ratio of the mean speckle diameter D_x (estimated using a local 2D autocorrelation function) in the horizontal direction to the mean speckle diameter D_y in the vertical direction, calculated for different segments of each speckle pattern [126] [88] [187] [188].

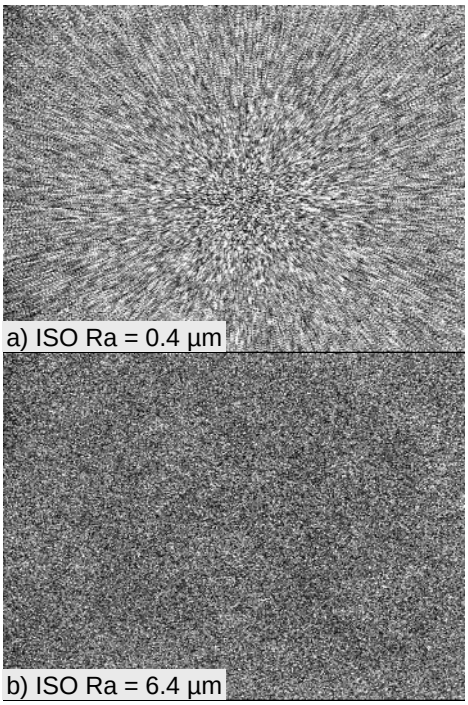


Figure 12: Polychromatic speckle patterns for (a) *Ra* = 0.4 µm with clearly elongated speckles; and (b) *Ra* = 6.4 µm, with completely decorrelated speckles.

4.1.6 Photothermal near surface zone analysis

Using longer wavelengths (infrared) radiation, this technique is especially useful to evaluate near-surface zones of a workpiece, using the basic photothermal principle of heating up a specimen by letting it absorb radiation energy (usually from a pulsed or intensity-modulated laser) and observing the local temperature changes (heat propagation, i.e. a temperature wave) [157]. Thermal inhomogeneities within the detection depth of a few µm to mm reflect or scatter portions of the thermal wave, modifying the amplitude and phase of the temperature oscillation at the surface, which is detected by infrared sensors [49]. Typical applications are the determination of coating thicknesses [6] and the detection of coating defects such as poor adhesion [93] [50] [134], and the measurement of porosities and hardening depths [133] [81] e.g. of artificial hip joints.

4.1.7 Choice of approach

Confronted with a myriad of measurement techniques it will always be difficult for the metrologist to optimize the instrument or instruments to be used. The literature is very rich in describing different experimental setups but often the approaches taken are dictated by available equipment and expertise. The reader is strongly encouraged to identify the quantity to be measured, choosing a direct measurement technique rather than having to infer the magnitude of the parameter from a series of supplementary measurements, consider the range over which measurements are needed, the accuracy required, the data acquisition rates and so on, and specify the environmental conditions under which measurements ought to be made. Whilst it is usually helpful to review the measurement techniques used by others, it is often the case that new methods become

available, or existing systems can be adapted to specialized requirements. Whatever approach is finally chosen it is vital that a traceable route is established, which may include the use of reference materials, transfer standards and/or periodically referring the measurements to equipment with higher, and certified, accuracy. Kohles et al. [80] have presented an interesting comparison of different roughness techniques, showing many differences in accuracy and precision.

4.2 Chemical surface analysis

In the same way as there are a host of optical and non-optical methods for analysing the physical attributes of a surface, there is an equally wide-ranging collection of spectroscopic and other analytical techniques that enable information to be derived about the chemical condition of the surface; specific methods for particular investigations tend to be determined by a combination of applicability, instrument cost and complexity, and user experience. Often different techniques are combined to gain additional insight into the characteristics of the surface under test.

Techniques that can be used in the presence of moisture/water—highly relevant for biomedical surfaces—include Raman spectroscopy, but many of the techniques, such as ion spectroscopy and electron spectroscopy, require that the specimen under test be under vacuum conditions.

The good practice guide to choose the most appropriate analytical technique would be voluminous, but detailed reviews of surface analysis techniques useful for evaluating the applicability of different approaches are available [150] [112] [77] [200] [109] [7] [15] [97] [5] [113] [208] [136] [151] [103] [76]. Some of the most appropriate techniques for biomaterials are discussed below.

X-ray photoelectron spectroscopy (XPS) involves the absorption of X-rays by the surface under test leading to the ejection of photoelectrons, which provide a way of determining what elements on the sample gave rise to their production [107].

Neutron reflexion [95] [39] is useful for making *in situ* measurements of protein structures at the solid/solution interface. The main disadvantage of this technique is the expensive infrastructure required, starting with a sufficiently powerful source of neutrons.

A large family of optical techniques uses evanescent waves generated at the the interface between two dielectrics, e.g. solid/liquid or solid/gas. In order of historical development, they are reflectometry, ellipsometry, surface plasmon resonance (SPR), and optical waveguide lightmode spectroscopy (OWLS) [141]. Each of them has advantages and disadvantages. Reflectometry and ellipsometry are the most versatile in terms of the surfaces with which they can be used, there being essentially no restriction on opacity. Reflectometry has the advantage that the interpretation of the results involves a straightforward application of Fresnel's equations, but it is slow and the achievable precision is low. Ellipsometry can be used in both reflexion and transmission mode, and has higher precision, but there is no closed-form solution of the governing equations, and therefore in order to extract surface parameters of interest a tedious fitting procedure has to be applied, with no guarantee of a unique result at the end. Furthermore, it is notoriously poor for the determination of the thickness and refractive index of surface layers, which are often of great interest in biocompatibility studies; its main use is to determine the total amount of adsorbed material. Surface plasmon resonance spectroscopy is restricted to investigating noble metal surfaces, for which it is more sensitive than ellipsometry. Nevertheless, since surface plasmons only exist in the p-polarization, the amount of information that can be extracted from the measurements is limited.

The most recent technique is optical waveguide lightmode spectroscopy (OWLS), in which the surface under investigation is made part of an optical waveguide, and the actual measured parameters are the propagation constants of the lightmodes guided therein. The technique is at least an order of magnitude more sensitive than SPR, both s- and p-polarizations can be measured, and there is a straightforward relation between the measured parameters and the opto-geometrical parameters of the surface, which can therefore be determined with high precision and reliability [143] [149]. The technique is extremely valuable for studying the adsorption of proteins and nanoparticles at surfaces [135], for which it has been extensively used (e.g. [55] [170]). Another strength of the technique is its versatility, since the optical waveguides can be made out of any high refractive index transparent dielectric material, or coated with a thin (~ 10 nm) film of the material whose biocompatibility is under investigation. The investigation of opaque materials such as steel may be problematical: in this case a nanoparticle monolayer of the metal, or its oxide, can be assembled on the waveguide surface in order to approximate the opaque bulk [144]. Various approaches have been adopted for measuring the lightmode spectrum: the two main ones are via grating coupling, and interferometry in one form or another [149]. The use of OWLS for measuring the behaviour of living cells at biomedical surfaces has also been reported [138] [33]. In all these applications, it is the very high sensitivity, excellent time resolution and multiplicity of measurable outputs interpretable as real physico-chemical parameters of the system that give it an unchallenged advantage for the quantitative investigation of biocompatibility. Of particular value in far-reaching and fundamental studies is the possibility of reliably extracting the thermodynamic and kinetic parameters characterizing protein adsorption, discussed in Section 2.

The final class of techniques to be discussed in this section are those based on the accumulation of material on a vibrating object, whose resonant frequency diminishes as mass is built up [136]. The quartz crystal microbalance (QCM) is well established in vacuum chambers for monitoring physical vapour deposition processes, but the data are much more difficult to interpret when used with viscoelastic biodeposits in the presence of water, although careful scrutiny of the dissipation seems to be a promising approach towards extracting less ambiguous and more interpretable results from the data [156]. Surface acoustic wave (SAW) devices are a variant of this technique, and the vibrating cantilever [84] is a typical MEMS realization that could form the basis of high throughput, massively parallel devices useful for combinatorial optimization of biomaterials. Although the output from such devices does not have the straightforward interpretation of the output from an OWLS experiment, large-scale screening might not require that level of detail and reliability. An interesting parallel study of QCM, ellipsometry and OWLS [65] suggested that QCM might be useful for determining features important in biocompatibility, such as the degree of hydration of an adsorbed protein layer.

5. INFORMATIONAL ASPECTS OF BIOMEDICAL SURFACES

The surface of a cell—and this applies as much to the tissue cells in contact with a prosthetic implant as to the

blood lymphocytes transiently in contact with a stent—is constantly relaying information about its chemical, physical and mechanical environment back to its ‘‘command centre’’—the protein expression machinery mainly localized in the cell nucleus [147]. Within the limitations of the likely modification of any artificial surface by its biological environment, this information channel opens up the possibility of designing smart materials that can direct the work of the cell in secreting desirable macromolecules. The design concept involves ensuring that some appropriate molecule, or molecular motif, embedded in the biomedical surface interacts with a receptor on the surface of the cell, triggering internal changes that eventually lead to the activation of transcription of a protein, or the inhibition of transcription. That protein, in turn, could well be secreted at the surface of the cell, providing a kind of feedback. Given the complexity of the inflammatory response (e.g. [57]), there are numerous points of possible intervention, both morphological and chemical, available to the biomaterials designer [162]. In fact, this aspect of biomaterials design has only just begun to be seriously investigated; knowledge is still highly fragmentary at present, and it has not proven easy to even establish the main attributes of foreign particles present within the body responsible for inducing an inflammatory response [124].

As pointed out in Section 1.3, few correlations between surface attributes and physiological response have been established. There has been an attempt to determine whether fibrous encapsulation of implanted polymer fibres depends on their diameter [160], and an attempt to establish the effect of surface roughness on the expression of certain cellular adhesion molecules in endothelial cells, with admittedly very ambiguous results [110]. An investigation of bacterial adhesion on model implant surfaces established that roughening at the nm to μm scale tended to diminish the adhesion [30], a potentially useful result since implant assimilation is improved by such roughening. This area of the field is probably the one currently most in need of extensive, systematic investigations.

6. SUMMARY

This paper deals with the surfaces of objects destined to be introduced into the human body. Many of these objects have to fulfil demanding structural or mechanical requirements, which typically impose strong constraints on the material and design of the object. Nevertheless, the surface is the primary zone of contact between the object and its host organism. The environments in which these objects find themselves are often hostile from the materials engineering viewpoint—warm, corrosive and full of dissolved proteins. The environment is, moreover, highly active; the introduced object is sensed as a foreign intrusion and the natural reaction of the host organism is to eliminate or destroy it. Biomedical surface engineering endeavours to deflect that reaction by creating biocompatible surfaces that, depending on the purpose of the object, evoke no adverse reaction or are fully assimilated within the host. This paper reviews the nature of the bio-environment, and the essential features of protein adsorption, which is almost inevitably the first event to occur after an object has been introduced into the human body. The relationship between the morphology and chemistry of the surface and the biological response it evokes is reviewed. Aspects of the manufacture of biomedical objects with a bearing on their surfaces are considered. In favourable cases, the object can be manufactured directly with the appropriate surface finish; in other cases bio-incompatible materials whose use is necessitated by the structural or other requirements of the object’s function must be made biocompatible by surface engineering or surface coating. The metrology of biomedical surfaces, essential for optimizing surface finish and for quality control, is considered in some detail. Finally the object-host relationship is briefly considered in terms of information exchange.

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8. GLOSSARY

Cyto- : living cell-

Endothelial cells : highly specialized cells that line the endothelium, polygonal in shape and joined together by tight junctions, which allow for variable permeability to specific macromolecules that are transported across the endothelial layer. These cells line the vascular system. They act as a barrier between the bloodstream and target cells that hormones must pass through in order to reach their receptors and exert their biological action.

F : French catheter scale (commonly used in the medical field to measure the circumference of cylindrical medical instruments and defined as $F = \pi d$ where d = outer diameter of the cylinder).

Glycoprotein : a protein to which oligosaccharides are attached.

Haemo- : blood-

Immune response : a physiological response in humans and higher animals to defend the body against the introduction of foreign material.

Mucin : a ubiquitous animal glycoprotein

Oligopeptide ; a short (typically up to about 25) sequence of amino acids polymerized via peptide bonds

Plaque: a semi-hard accumulation of substances from fluids that bathe an area (e.g. dental plaque, cholesterol plaque in arteries).

Thrombogenecity : propensity to promote thrombus formation.

9. REFERENCES

[1] Ademovic, Z. and Kingshott, P., 2005, Micro- and nanoscale surface patterning techniques for localising biomolecules and cells: the essence of nanobiotechnology, in: Surfaces and Interfaces for Biomaterials, ed. P. Vadgama, Abington: Woodhead Publishing, pp.150–180.

[2] Allen D.M., 1987, Methanol-sulphuric acid; a versatile non-aqueous etchant for use in electrolytic photoetching of difficult-to-etch materials,

Proceedings of the Symposium on Electrochemical Technology in Electronics, L.T. Romankiw and T. Osaka (eds), The Electrochemical Society Proceedings Series, Pennington, New Jersey, PV 88–23, 685.

[3] Allen, D.M., 2004, Photochemical machining: from 'manufacturing's best kept secret' to a $6 billion per annum, rapid manufacturing process, Annals CIRP, 53/2, 559–572.

[4] Aslanidis D., Roebben G., Bruninx J. and Van Moorleghem W., 2001, Electropolishing for medical devices: relatively new, fascinatingly diverse, Proc. International Conference on Shape Memory and Superelastic Technologies and Shape Memory Materials, Kunming, China, 2–6 September, *qua* Materials Science Forum, 394–395, 169–172.

[5] Belu, A.M, Graham, D.J. and Castner, D.G., 2003, Time-of-flight secondary ion mass spectrometry: techniques and applications for the characterisation of biomaterial surfaces, Biomaterials, 24, 3635–3653.

[6] Bennett, C.A. and Patty, R.R., 1982, Thermal wave interferometry: a potential application of the photoacoustic effect. Appl. Optics, 21, 49–54

[7] Berger, S., Mondon, M., Stadler, H. and Ziegler, Ch., 2004, Nanoanalysis of biomaterials, in: Encylopedia of Nanoscience and Nanotechnology, vol. 6, H.S. Nalwa, ed., American Scientific Publishers, pp. 1–22.

[8] Bhuyan, A., Gregory, B., Lei, H., Yee, S.Y. and Gianchandani, Y.B., 2005, Pulse and DC electropolishing of stainless steel for stents and other devices, Proc. IEEE Sensors Conference, 30 October–3 November, Irvine, California, pp. 314–317.

[9] Blackwood, D.J., Seah, K.H.W., Teoh, S.H., 2004, Corrosion of metallic implants, in: Engineering Materials for Biomedical Applications, S.H. Teoh, ed., Singapore: World Scientific, ch. 3, pp. 1–50

[10] Bottomley, L.A., 1998, Scanning probe microscopy, Anal. Chem., 70, 425R–475R.

[11] Bowsher, J.G. and Sheldon, J.C., 2001, A hip simulator study of the influence of patient activity level on the wear of crosslinked polyethylene under smooth and roughened femoral conditions, Wear, 250, 167–179.

[12] Brizuela, M., Garcia-Luis, A., Viviente, L., Braceras, I., Onate, J.I., 2002, Tribological study of lubricious DLC biocompatible coatings', J. Mater. Sci.: Materials in Medicine, 13, 1129–1133.

[13] Cacace, M.G., Landau, E.M. and Ramsden, J.J., 1997, The Hofmeister series: salt and solvent effects on interfacial phenomena, Q. Rev. Biophys., 30, 241–278.

[14] Calonder, C., Talbot, J. and Ramsden, J.J., 2001, Mapping the electron donor/acceptor potentials on protein surfaces, J. Phys. Chem. B, 105, 725–729.

[15] Castner, D.G. and Ratner, B.D., 2002, Biomedical surface science: foundations to frontiers, Surface Science, 500, 28–60.

[16] Chang, E., Chang, W.J., Wang, C. and Yang, C.Y., 1997, Plasma spraying of zirconia reinforced hydroxyapatite composite coatings on titanium: Part 1 Phase, microstructure and bonding strength, J. Mater. Sci.: Materials in Medicine, 8, 193–200.

[17] Chowdhury, D.F. and Allen, D.M., 2007, Enhancement of transdermal drug delivery using MEMS technologies, Proc. 7th Euspen International Conference, 20–24 May, Bremen, vol. 1, pp. 49–52.

[18] Clifford, C. and Seah, M.P., 2006, Modelling of nanomechanical nanoindentation measurements using an AFM or nanoindenter for compliant layers on stiffer substrates, Nanotechnology, 17, 5283–5292.

[19] Daniel, S., Albertorio, F. and Cremer, P. S., 2006, Making lipid membranes rough, tough, and ready to hit the road, MRS Bulletin, 31, 536–540.

[20] De Chiffre, L., Lonardo, P., Trumphold, H., Lucca, D.A., Goch, G., Brown, C.A., Raja, J. and Hansen, H.N., 2000, Quantitative characterisation of surface texture, Annals CIRP, 49/2, 635–652.

[21] De Chiffre, L., Kunzmann, H., Peggs G.N. and Lucca, D.A., 2003, Surfaces in precision engineering, microengineering and nanotechnology, Annals CIRP, 52/2, 561–577.

[22] Dickinson, M.E. and Mann, A.B., 2005, Nanoscale characterization of salivary pellicle, Materials Research Society Proceedings, vol. 841, paper R2.3/Y2.3.

[23] Disegi, J.A., 1997, Anodizing treatments for titanium implants, Proc. 16th Southern Biomedical Engineering Conference, 4–6 April, Biloxi, Mississippi, pp. 129–132.

[24] Donlan, R.M., 2001, Biofilms and device-associated infections, Emerging Infectious Diseases, 7, 277–281.

[25] Dornfeld, D., Min, S., Takeuchi, Y., 2006, Recent Advances in Mechanical Microengineering, Annals CIRP, 55/2, 745–768.

[26] Dowson, D. and Jin, Z.-M., 1986, Micro-elastohydrodynamic lubrication of synovial joints, Engng in Medicine, 15, 63–65.

[27] Dumitrascu, N., Topala I. and Popa, G., 2005, Dielectric barrier discharge technique in improving the wettability and adhesion properties of polymer surfaces, IEEE Trans. Plasma Sci., 33, 1710–1714.

[28] Durakbasa, M.N., Osanna, P.H., Afjehi-Sadat, A., Samarawickrama, D. and Kresk, A., 2005, Application of sophisticated production metrology and nanometrology for quality control in bio-engineering, Measurement Sci. Rev., 5, 1–10.

[29] Ebenstein, M.E., Kou, A., Rodrigo, J.J., Hari Reddi, A., Ries, M. and Pruit, L., 2004, A nanoindentation technique for functional evaluation of cartilage repair tissue, J. Mater. Res., 19, 273–281.

[30] Emerson, R.J., Bergstrom, T.S., Liu, Y., Soto, E.R., Brown, C.A., McGimpsey, W.G. and Camesano, T.A., 2006, Microscale Correlation between Surface Chemistry, Texture, and the Adhesive Strength of *Staphylococcus epidermidis*, Langmuir, 22, 11311–11321.

[31] Evans, C.J. and Bryan, J.B., 1999, 'Structured', 'Textured', or 'Engineered' surfaces, Annals CIRP, 48/2, 541–556.

[32] Ewald, A., Gluckermann, S.K., Thull R. and Gbureck, U., 2006, Antimicrobial titanium/silver PVD coatings on titanium, Biomedical Engineering Online, 5:22, available at http://www.biomedical-engineering-online.com/contents/5/1/22

[33] Fang, Y., 2006, Label-free cell-based assays with optical biosensors in drug discovery. Assay Drug. Dev. Technol. 4, 583–595.

[34] Fernández, A. and Ramsden, J.J., 2001, On adsorption-induced denaturation of folded proteins, J. Biol. Phys. Chem., 1, 81–84.

[35] Fernández, A. and R. Scott, R., 2003, Dehydron: a structurally encoded signal for protein interaction, Biophys. J., 85, 1914–1928.

[36] Fernández, A., Kardos, J., Scott, L.R., Goto, Y. and Berry, R.S. 2003, Structural defects and the diagnosis of amyloidogenic propensity, Proc. Natl Acad. Sci. USA, 100, 6445–6451.

[37] Fitz, M.J., Tarapata, C.J. and Wang, J., 2002, Electro-polishing fixture and electrolyte solution for polishing stents and method, US Patent 6,375,826.

[38] Flemming, R.G., Murphy, C.J., Abrams, G.A., Goodman, S.L. and Nearley, P.F., 1999, Effects of synthetic micro and nano structured surfaces on cell behaviour, Biomaterials, 20, 573–588.

[39] Fragneto-Cusani, G., 2001, Neutron reflectivity at the solid/liquid interface: examples of applications in biophysics, J. Phys. Cond. Matter, 13, 4973–4989.

[40] Frost, M.C., Reynolds, M.M. and Meyerhoff, M.E., 2005, Polymers incorporating nitric oxide releasing/generating substances for improved biocompatibility of blood-contacting medical devices, Biomaterials, 26, 1685–1693.

[41] Fujisawa, N., Poole-Warren, L.A., Woodard, J.C., Bertram, C.D. and Schindhelm, K., 1999, A novel textured surface for blood contact, Biomaterials, 20, 955–962.

[42] Furey, M.J. and Burkhardt, B.M., 1997, Biotribology: friction, wear, and lubrication of natural synovial joints, Lubrication Sci., 9, 255–271.

[43] Gaona, M., Fernandez, J. and Guilemany, J.M., 2006, The influence of thermal treatment on hydroxyapatite coatings obtained by HVOF, International Thermal Spray Conference, 15–17 May, Seattle, Washington.

[44] Giglio, M., Musazzi, S., Perini, U., 1979, Surface roughness measurements by means of speckle wavelength decorrelation, Optics Communications, 28, 166–170.

[45] Gill, H.S. et al., 2006, Effect of microneedle design on pain in human subjects, American Institute of Chemical Engineers Conference, 16 November, San Francisco, California.

[46] Gitis, N., Daugela, A., Sikder, A., Vinogradov, M. and A. Meyman, A., 2004, In-situ quantitative integrated tribo-spm nano-micrometrology, Proc. TRIB2004, ASME/STLE International Joint Tribology Conference, 24–27 October, Long Beach, California, pp. 1–3.

[47] Goch, G. and Lehmann, P., 1999, Contactless topography and microhardness measurements using scanning near-field acoustic microscopy (SNAM). Proc. 1st Conf. European Society of Precision Engineering (Euspen), Bremen, vol. 2, pp. 479–482.

[48] Goch, G. and Volk, R., 1994, Contactless surface measurement with a new acoustic sensor. Annals CIRP 43/1, 487–490.

[49] Goch, G. Schmitz, B. Geerkens, J. Karpuschewski, B. Reigl, M. Sprongl, P. and Ritter, R., 1999, Review of non-destructive measuring methods for the assessment of surface integrity: a survey of new measuring methods for coatings, layered structures and processed surfaces. Precision Engng, 23, 9–33.

[50] Goch, G., Prekel, H., Patzelt, S., Ströbel, G., Lucca, D.A., Stock, H.-R. and Mehner, A., 2004, Non-destructive and non-contact determination of layer thickness and thermal properties of PVD and sol-gel layers by photothermal methods, Annals CIRP, 53/1, 471–474.

[51] Goodridge, R.D., Dalgarno, K.W., 2006, Indirect selective laser sintering of an apatite-mullite glass-ceramic for potential use in bone replacement applications, Proc. IMechE, 220, Part H, J. Engng in Medicine, 57–68.

[52] Grewe, P.H., Muller, K.M., Deneke, T., Harrer, E., Germing, A., Mugge, A. and Lemke, B., 2002, Stents: material, surface texture and design, in theory and practice, Minimally Invasive Therapy Allied Technol., 11, 157–163.

[53] Grobe, G.L., Valint, P.L. and Ammon, D.M., 1996, Surface chemical structure for soft contact lenses as a function of polymer processing, J. Biomed. Mater., 32, 45–54.

[54] Groenendijk, M. and Meijer, J., 2006, Microstructuring using femtosecond pulsed laser ablation, J. Laser Applications, 18, 227–235.

[55] Guemouri, L., Ogier, J. and Ramsden, J.J., 1998, Optical properties of protein monolayers during assembly, J. Chem. Phys., 109, 3265–3268.

[56] Guipont, V., Espanol, M., Borit, F., Llorca-Isern, N., Jeandin, M., Khor, K.A., P Cheang, P., 2002, High-pressure plasma spraying of hydroxyapatite powders, Mater. Sci. Engng, A 325, 9–18.

[57] Hakim, R.M. and Himmelfarb, J., 1996, Biocompatibility—principles, in: Replacement of Renal Function by Dialysis (C. Jacobs, C.M. Kjellstrand, K.M. Koch and J.F. Winchester, eds, 4th edn, Dordrecht: Kluwer.

[58] Heinzelmann, H., 1999, Scanning near-field optical microscopy, 3rd International Workshop on Molecular Recognition at Surfaces, 25–25 November, Basel.

[59] Hidaka, K., 2006, Study of a small-sized ultrasonic probe, Annals CIRP, 55/1, 567–570.

[60] Hilal, N., Bowen, W.R., Alkhatib, L. and Ogunbiyi, O., 2006, A review of atomic force microscopy applied to cell interactions with membranes, Chem. Engng Res. Design, 84, 282–292.

[61] Hillman, P., 1991, The Case for New Paradigms in Cell Biology and in Neurobiology. Lewiston: Edwin Mellen Press.

[62] Hinterdorfer, P., Baumgartner, W., Gruber, H.J., Schilcher, K. and Schindler, H., 1996, Detection of localization of individual antibody-antigen recognition events by atomic force microscopy, Proc. Natl Acad. Sci. USA, 93, 3477–3481.

[63] Hocken, R.J., Chakraborty, N. and Brown, C., 2005, Optical metrology of surfaces, Annals CIRP, 54/2, 705–719.

[64] Holly, F.J. and Holly, T.F., 1994, Advances in ocular tribology, Adv. Experimental Medicine Biol., 350, 275–283.

[65] Höök, F., Vörös, J., Rodahl, M., Kurrat, R., Böni, P., Ramsden, J.J., Textor, M., Spencer, N.D., Tengvall, P. Gold, J. and Kasemo, B., 2002, A comparative study of protein adsorption on titanium oxide surfaces using in situ ellipsometry, optical waveguide lightmode spectroscopy, and quartz crystal microbalance/dissipation, Colloids Surf. B 24, 155–170.

[66] Howell, J.R., Blunt, L.A., Lee, A.J.C., Hooper, R.M., Gie, G.A., Timperley, A.J. and Ling, R.S.M., 2000, An investigation of the fretting wear seen on explanted hip replacement femoral stems, J. Bone Surgery, B 82, 52–53.

[67] Hubbell, J.A., 1999, Bioactive biomaterials, Current Opinion Biotech. 10, 123–129.

[68] Hubler, R., 1999, Hardness and corrosion protection enhancement behaviour of surgical implant surfaces treated with ceramic thin films, Surf. Coatings technol., 116–119, 1111–1115

[69] Iwaki, M., 1999, Progress in ion implantation technology for metal surface treatments and other related topics, Proc. International Conference on Ion Implantation Technology, vol. 2, pp. 824–826.

[70] Iwasaki, Y. and Nakabayashi, N., 2005, Interaction between biomaterials and cell tissues, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 389–413.

[71] Jacobson, A. 2003, Biotribology: the tribology of living tissues, Tribol. Lubrication Technol., 59, 32–38.

[72] Jena, B.P., Geibel, J. and Schneider, S.W. (eds), 1999, papers in Microscopy Res. Technique, 44 (special issue (5), 'Use of atomic force microscopy and optical tweezers in biology').

[73] Jiang, X.Q. and Blunt, L., 2001, Morphological assessment of *in vivo* wear of orthopaedic implants using multiscalar wavelets, Wear, 250, 217–221.

[74] Jin, Z.M. and Dowson, D., 2005, Elastohydrodynamic lubrication in biological systems, Proc. Inst. Mech. Engineers, Part J: J. Engng Tribol., 219, 367–380.

[75] Jin, Z.M., Stone, M., Ingham, E. and Fisher, J., 2006, Biotribology, Current Orthopaedics, 20, 32–40.

[76] Johansson, B., 2006, ToF-SIMS imaging of lipids in cell membranes, Surf. Interface Anal., 38, 1401–1412.

[77] Kannan, R.Y. Salacinski, H.J., Vara, D.S., Odlyha, M. and Seifalian, A.M., 2006, Review paper: principles and applications of surface analytical techniques at the vascular interface, J. Biomater. Appl., 21, 5–32.

[78] Kasemo, B. and Gold, J., 1999, Implant surfaces and interface processes, Adv. Dental Res., 13, 8–20.

[79] Kohl, M., Skrobanek, K.D., Goh, C.M. and Allen, D.M., 1996, Mechanical characterisation of shape memory micromaterials, SPIE Proceedings, vol. 2880, Microlithography and Metrology in Micromachining II, pp. 108–118.

[80] Kohles, S., Clark, M. B., Brown, C.A., and Kenealy, J., 2004, Direct assessment of profilometric roughness variability from typical implant surface types, Intl J. Oral Maxillofacial Implants, 19, 510–515.

[81] Kruse, D., Prekel, H., and Goch, G., 2006, Automated photothermal detection of burning and hardening depth, Proc. 9th International Conference on Infrared Sensors and Systems, Nuremberg, pp. 341–346.

[82] Kurrat, R., Wälivaara, B., Marti, A., Textor, M., Tengvall, P., Ramsden, J.J. and Spencer, N.D., 1998, Plasma protein adsorption on titanium. Colloids Surf. B, 11, 187–201.

[83] Landis, F.A., Cicerone, M.T., Cooper, J.A., Washburn, N.R. and Junkers, J.P., 2004, Macro to nano, Proc. IEEE International Symposium on Biomedical Imaging, April 15–18, vol. 2, pp. 1533–1536.

[84] Lang, H.P., Baller, M.K., Berger, R., Gerber, Ch., Gimzewski, J.K., Battiston, F.M., Fornaro, P., Ramseyer, J.P., Meyer, E. and Güntherodt, H.J., 1999, An artificial nose based on a micromechanical cantilever array, Anal. Chim. Acta 393, 59–65.

[85] Larsson, C., Emanuelsson, L., Thomsen, P., Ericson, L.E., Aronsson, B.O., Rodahl, M., Kasemo, B. and Lausmaa, J., 1997, Bone response to surface modified titanium implants: studies on the tissue response after 1 year to machined and electropolished implants with different oxide thicknesses, J. Mater. Sci.: Materials in Medicine, 8, 721–729.

[86] Leadley, S.R., Shakesheff, K.M., Davies, M.C., Heller, J. Franson, N.M., Paul, A.J. Brown, A.M. and Watts, J.F. 1998, The use of SIMS, XPS, and in situ AFM to probe the acid catalysed hydrolysis of poly(orthoesters), Biomaterials, 19, 1353–1360.

[87] Lehmann, P., 1999, Surface roughness measurement based on the intensity correlation function of scattered light under speckle-pattern illumination, Appl. Optics, 38, 1144–1152.

[88] Lehmann, P., 2002, Aspect ratio of elongated polychromatic far-field speckles of continuous and discrete spectral distribution with respect to surface roughness characterization, Appl. Optics, 41, 2008–2014.

[89] Lehmann, P., Goch, G., 2000, Comparison of conventional light scattering and speckle techniques concerning an in-process characterization of engineered surfaces, Annals CIRP, 49/1, 419–422.

[90] Lehmann, P., Patzelt, S., Schöne, A., 1997, Surface roughness measurement by means of polychromatic speckle elongation, Appl. Optics, 36, 2188–2197.

[91] Li, D.J. and Gu, H.Q., 2002, Cell attachment on diamond-like carbon coating', Bull. Mater. Sci., 25, 7–13.

[92] Li, S.-Y., Ramsden, J.J., Prenosil, J.E. and Heinzle, E., 1994, Measurement of adhesion and spreading kinetics of baby hamster kidney and hybridoma cells using an integrated optical method. Biotechnol. Prog. 10, 520–524.

[93] Liu, H.; Wang, L.; Goch, G., 2002, Simulation photothermischer Signale von Randzonen mit eindimensionalen Profilen thermischer Parameter. Tagungsband XVI. Messtechnisches Symposium der Hochschullehrer für Messtechnik e. V., Kassel, pp. 75–88.

[94] Liu, X. and Gao, F., 2004, A novel multi-function tribological probe microscope for mapping surface properties, Measurement Sci. Technol., 15, 91–102.

[95] Lu, J.R., 2005, Neutron reflection, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 299–321.

[96] Luthi, P.O., Ramsden, J.J. and Chopard, B., 1997, The role of diffusion in irreversible deposition. Phys. Rev. E 55, 3111–3115.

[97] Lyman, D., 2002, Characterisation of biomaterials, in: Integrated Biomaterials Science, R. Barbucci, ed., Kluwer Academic/Plenum Publishers, pp. 325–336.

[98] de Maeztu, M.A., Alava, J.I., Gay-Escoda, C., 2003, Ion implantation: surface treatment for improving the bone integration of titanium and Ti6Al4V dental implants, Clin. Oral Impl. Res., 14, 57–62.

[99] Mamalis, A.G., Ramsden, J.J., Grabchenko, A.I., Lytvynov, L.A., Filipenko, V.A. and Lavrynenko, S.N., 2006, A novel concept for the manufacture of individual sapphire-metallic hip joint endoprostheses, J. Biol. Phys. Chem., 6, 113–117.

[100] Mamalis, A.G., Lytvynov, L.A., Filipenko, V.A., Lavrynenko, S.N., Ramsden, J.J. and Soukakos, P.N. 2007, Perfection of contemporary hip joint endoprostheses by using a sapphire–sapphire friction pair, J. Biol. Phys. Chem., 7, 3–5.

[101] Mann, A.B., 2005, Nanoindentation, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 225–247.

[102] Martano, W., 2005, Microinjection into skin using microneedles, PhD thesis, Georgia Institute of Technology, USA.

[103] Mathieu, J.H., Cheolot, Y., Ruiz-Taylor, L. and D. Leonard, D., 2003, Engineering and the characterisation of polymer surfaces for biomedical applications, Adv. Polymer Sci., 162, 1–34.

[104] Maus, S.M. and Galic, G., 1994, Precision surface-replicating thermoplastic injection molding method and apparatus, using a heating phase and a cooling phase in each molding cycle, US Patent 5,376,317.

[105] Mazusawa, T., 2000, State of the art of micromachining, Annals CIRP, 49/2, 473–488

[106] McAllister, D.V., Allen, M.G. and Prausnitz, M.R., 2000, Microfabricated microneedles for gene and drug delivery, A. Rev. Biomedical Engng, 2, 289–313.

[107] McArthur, S.L., 2006, Applications of XPS in bioengineering, Surf. Interface Anal., 38, 1380–1385.

[108] McColl, I.R., Grant, D.M., Green, S.M., Wood, J.V., Parker, T.L., Parker, K., Goruppa, A.A., Braithwaite, N.St J., 1993, Low temperature plasma-assisted chemical vapour deposition of amorphous carbon films for biomedical-polymeric substrates, Diamond Related Materials, 3, 83–87.

[109] McGuire, G.E., Ray, M.A., Simko, S.J., Perkins, F.K., Brandow, S.L., Dobisz, E.A., Nemanich, R.J., Chourasia, A.R. and Chopra, D.R., 1993, Surface characterisation, Anal. Chem., 65, 311R–333R.

[110] McLucas, E., Moran, M.T., Rochev Y., Carroll, W.M. and Smith, T.J., 2006, An investigation into the effect of surface roughness of stainless steel on human umbilical vein endothelial cell gene expression, Endothelium, 13, 35–41.

[111] Mentré, P., 2004, Interfacial water: a modulator of biological activity, J. Biol. Phys. Chem., 4, 115–123.

[112] Merrett, K., Cornelius, R.M., McClung, W.G., Unsworth, L.D. and Sheardown, H., 2002, Surface analysis methods for characterizing polymeric biomaterials, J. Biomater. Sci., Polymer Edn, 13, 593–621.

[113] Michel, R. and Castner, D.G., 2006, Advances in time-of-flight secondary ion mass spectrometry analysis of protein films, Surf. Interface Anal., 38, 1386–1392.

[114] Moseler, M., Gumbsch, P., Casiraghi, C., Ferrari, A. and Robertson, J., 2005, The ultrasmoothness of diamond-like carbon surfaces, Science, 39, 1545–1548.

[115] Narayan, P., Hancock, B., Hamel, R., Bergstrom, T.S. and Brown, C.A., 2006, Using fractal analysis to differentiate the surface topography of various pharmaceutical excipient compacts, Mater. Sci. Engng A: Structural Mater.: Properties, Microstruct. Processing, 430, 79–89.

[116] Nemes, Cs., Rozlosnik, N. and Ramsden, J.J., 1999, Direct measurement of the viscoelasticity of adsorbed protein layers using atomic force microscopy. Phys. Rev. E 60, 1166–1169.

[117] Ning, C.Y., Y J Wang, Y.J., Lu, W.W., Qiu, Q.X., Lam, R.W.M., Chen, X.F., Chiu, K.Y., Ye, J.D., Wu, G., Wu, Z.H. and Chow, S.P., 2006, Nano-structural bioactive gradient coating fabricated by computer controlled plasma-spraying technology, J. Mater. Sci: Materials in Medicine, 17, 875–884.

[118] Norde, W. and Lyklema, J., 1991, Why proteins prefer interfaces, J. Biomater. Sci. Polymer Edn 2, 183–202.

[119] van Oeveren, W., 2005, Blood flow dynamics and surface interactions, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 414–446.

[120] Ogilvy, J. A., 1991, Theory of Wave Scattering from Random Rough Surfaces, Bristol: Hilger.

[121] Ohashi, Y., Dogru, M. and Tsubota, K., 2006, Laboratory findings in tear fluid analysis, Clin. Chim. Acta, 369, 17–28.

[122] Onate, J.I., Comin, M., Braceras, I., Garcia, A., Viviente, J.L., Brizuela, M., Garagorri, N., Peris, J.L., Alava, J.I., 2001, Wear reduction effect on ultra-high-molecular-weight polyethylene by application of hard coatings and ion implantation on cobalt chromium alloy, as measured in a knee wear simulation machine, Surf. Coatings Technol., 142–144, 1056–1062.

[123] van Oss, C.J., 1996, Forces Interfaciales en Milieux Aqueux, Paris: Masson.

[124] van Oss, C.J., Naim, J.O., Costanzo, P.M., Giese, R.F., Wu, W and Sorling, A.F., 1999, Impact of different asbestos species and other mineral particles on pulmonary pathogenesis, Clays Clay Minerals, 47, 697–707.

[125] Patzelt, S., Goch, G., 2004, Scattered light techniques for surface characterization of optical components, XI. Internationales Oberflächenkolloquium, Chemnitz, Aachen: Shaker Verlag, 1:214–223.

[126] Patzelt, S., Horn, F., Goch, G., 2006, Fast integral optical roughness measurement of specular reflecting surfaces in the nanometer range, XVIII IMEKO World Congress, Metrology for Sustainable Development, Rio de Janeiro.

[127] Paulsen, F., 2006, Cell and molecular biology of human lachrymal gland and nasolachrymal duct mucins. Intl Rev. Cytol., 249, 229–279.

[128] Pelka, A., Ostrowski, G., Niedzielski, P., Johnston, R., Stroz, D., Morawiec, H. and Sysa, A., 2001, Carbon coatings onto shape memory alloys, J. Wide Bandgap Mater., 8, 189–194.

[129] Pierson, H.O., 1999, Handbook of Chemical Vapor Deposition—Principles, Technology and Applications, 2nd Edn, William Andrew Publishing/Noyes.

[130] Piotter, V., Hanemann, T., Ruprecht, R. and Hausselt, J., 1997, Injection molding and related techniques for fabrication of microstructures, Microsystem Technol., 3, 129–133.

[131] Piotter, V., Finnah, G., Örlygsson, G., Ruprecht, R. and Hausselt, J., 2005, Special variants and simulation of micro injection moulding, Injection Moulding Conference, 1–2 March, Copenhagen.

[132] Ponsonnet, L., V.Comte, V., Othmane, A., Lagneau, C., Charbonnier, M., Lissac, M. and Jafrezic, N., 2002, Effect of surface topology and chemistry on adhesion, orientation and growth of fibroblasts on nickel titanium substrates, Mater. Sci. Engng, C, 21, 157–165.

[133] Prekel, H., Ament, C. and Goch, G., 2003, Photothermal characterization of grind-hardened steel, Rev. Scientific Instruments, 74, 670–672.

[134] Prekel, H., Klopfstein, M.J., Giesselbach, M., Patzelt, S., Ghisleni, R., Lucca, D.A., Goch, G. and Stock, H.-R., 2006, Photothermal Investigation of Ti-Cu-N and Ti-Ni-N PVD Films, Annals CIRP, 55/1, 585–588.

[135] Ramsden, J.J., 1993, Review of new experimental methods for investigating random sequential adsorption, J. Statist. Phys. 73, 853–877.

[136] Ramsden, J.J., 1994, Experimental methods for investigating protein adsorption kinetics at surfaces, Q. Rev. Biophys., 27, 41–105.

[137] Ramsden, J.J., 1995, Puzzles and paradoxes in protein adsorption, Chem. Soc. Rev., 24, 73–78.

[138] Ramsden, J.J., Li, S.-Y., Heinzle, E. and Prenosil, J.E., 1995, An optical method for the measurement of number and shape of attached cells in real time, Cytometry 19, 97–102.

[139] Ramsden, J.J., Roush, D.J., Gill, D.S., Kurrat, R.G. and Willson R.C., 1995, Protein adsorption kinetics drastically altered by repositioning a single charge, J. Am. Chem. Soc., 117, 8511–8516.

[140] Ramsden, J.J., 1997, Dynamics of protein adsorption at the solid/liquid interface, Recent Res. Devel. Phys. Chem., 1, 133–142.

[141] Ramsden, J.J., 1997, Optical biosensors, J. Molec. Recog., 10, 109–120.

[142] Ramsden, J.J., 1998, Kinetics of protein adsorption, in: M. Malmsten, ed., Biopolymers at Interfaces, New York: Dekker, ch. 10, pp. 321–361.

[143] Ramsden, J.J., 1998, Biospecific interaction analysis using integrated optics techniques, in: Quantitative Analysis of Biospecific Interactions, P. Lundahl, A. Lundqvist and E. Greijer, eds, Amsterdam: Harwood, pp. 149–162.

[144] Ramsden, J.J. and Máté, M., 1998, Kinetics of monolayer particle deposition, J. Chem. Soc., Faraday Trans., 94, 783–788.

[145] Ramsden, J.J., 1999, On protein-lipid membrane interactions, Colloids Surfaces B 14, 77–81.

[146] Ramsden, J.J., 2002, Adsorption kinetics of proteins, in: Encyclopaedia of Surface and Colloid Science, A. Hubbard, ed., New York: Dekker, pp. 240–261.

[147] Ramsden, J.J., 2004, Bioinformatics: an Introduction, Dordrecht: Kluwer.

[148] Ramsden, J.J., 2006, High resolution molecular microscopy, in: Proteins at Solid-Liquid Interfaces, Ph. Dejardin, ed., Heidelberg: Springer, pp. 23–49.

[149] Ramsden, J.J., 2006, OWLS—a versatile technique for drug discovery, Frontiers Drug Design Discovery 2, 211–223.

[150] Ratner, B.D., Hoffman, A.S., Schoen, F.J. and Lemons, J.E., 2004, Biomaterials Science: an Introduction to Materials in Medicine, Academic Press.

[151] Ratner, B.D., 2004, Characterization of graft polymers for biomedical applications, J. Biomedical Mater. Res., 14, 665–687.

[152] Raval, A., Choubey, A., Engineer, C. and Kothwala, D., 2005, Surface conditioning of 316LVM slotted tube cardiovascular stents, J. Biomater. Applications, 19, 197–213.

[153] Rennie, A. C., Dickrell, P. L. and Sawyer, W. G., 2005, Friction coefficient of soft contact lenses: measurements and modeling, Tribol. Lett., 18, 499–504.

[154] Revell, P.A., 2006, The biological effects of nanoparticles. Nanotechnology Perceptions, 2, 283–298.

[155] Rickerby, D.S. and Matthews, A. (eds), 1991, Advanced Surface Coatings, a Handbook of Surface Engineering, London: Blackie.

[156] Rodahl, M., Höök, F., Krozer, A., Brzezinski, P. and Kasemo, B., 1995, Quartz crystal microbalance setup for frequency and *Q*-factor measurements gaseous and liquid environments, Rev. Scientific Instruments, 66, 3924–3930.

[157] Rosencwaig, A. and Gersho, A. Theory of the photoacoustic effect with solids, 1976, J. Appl. Phys., 47, 64–69.

[158] Rudolph, W. and Kempe, M., 1997, Topical review: trends in biomedical imaging, J. Modern Optics, 44, 1617–1642.

[159] Ruiz Gale, M.F., Landau, M.R., Hogert, E.N. and Gaggioli, N.G., 2004, Changing surfaces—a theoretical and experimental approach, J. Opt. A: Pure Appl. Opt., 6, 187–192.

[160] Sanders, J.E., Styles, C.E. and Hayes, C.L., 2000, Tissue response to single-polymer fibres of varying diameters: evaluation of fibrous encapsulation and macrophage density, J. Biomed. Mater. Res., 52, 231–237.

[161] Santavirta, S., 2003, Compatibility of the totally replaced hip. Reduction of wear by amorphous diamond coating, Acta Orthopaed. Scand. (Suppl. no 310), 74, 1–19.

[162] Santin, M., Mikhalovska, L., Lloyd, A. W., Mikhalovsky, S., Sigfrid, L., Denyer, S.P., Field, S. and Teer, D., 2004, *In vitro* host response assessment of biomaterials for cardiovascular stent manufacture, J. Mater. Sci.: Materials in Medicine, 15, 473–477.

[163] Schaumburg, C., Ehrfeld , W., Schinkothe, W., Walther, T. and Weber, L., 1998, Injection moulding of microstructures with inductive heating, Micro System Technologies Conference, 1–3 December, Potsdam, Germany.

[164] Schenk, R., 2001, The corrosion properties of titanium and titanium alloys, in: Titanium in Medicine: Materials Science, Surface Science, Engineering, Biological Responses, and Medical Applications, D.M. Brunette, P. Tengvall, M. Textor and P. Thomsen, eds, Berlin: Springer, pp. 145–170.

[165] Schluessler, A. and Strobel, M., 2003, Status and trends of Nitinol laser micromachining techniques, International Organization on Shape Memory and Superelastic Technologies (SMST) Conference, 5–8 May, Pacific Grove, California.

[166] Schmidt, Th., P. Hinterdorfer, P. and H. Schindler, H., 1999, Microscopy for recognition of individual biomolecules, Microscopy Res. Technique, 44, 339–346.

[167] Scott, R.S., Ungar, P.S., Bergstrom, T.S., Brown, C.A., Childs, B., Teaford, M.F. and Walker, A., 2006, Dental microwear texture analysis, J. Human Evolution, 51, 339–349.

[168] Secomb, T.W., Hsu, R. and Pries, A.R. 2002, Blood flow and red blood cell deformation in nonuniform capillaries: effects of the endothelial surface layer, Microcirculation, 9, 189–196.

[169] Seitavuopio, P., 2006, The roughness and imaging characterisation of different pharmaceutical materials, PhD Thesis, University of Helsinki.

[170] Shanshiashvili, L.V., Suknidze, N.Ch., Machaidze, G.G., Mikeladze, D.G. and Ramsden, J.J., 2003, Adhesion and clustering of charge isomers of myelin basic protein at phospholipid bilayer membranes, Arch. Biochem. Biophys., 419, 170–177.

[171] Shard, A.G. and Tomlins, P.E., 2006, Biocompatibility and the efficacy of medical implants, Regenerative Medicine, 1, 789–800.

[172] Shaw, J.E., Oreopoulos, J., Wong, D., J.C.Y. Wong, J.C.Y. and Yip, C.M., 2006, Coupling evanescent-wave fluorescence imaging and spectroscopy with scanning probe microscopy: challenges and insights from TIRF-AFM, Surf. Interface Anal., 38, 1459–1471.

[173] Sioshansi, P., 1987, Medical applications of ion beam processes, Nucl. Inst. Meth., B 19/20, 204–208.

[174] Smith, G.T., 2002, Industrial Metrology: Surfaces and Roundness, Heidelberg: Springer.

[175] Soboyejo, W.O., Mercer, C., Allameh, S., Nemetski, B., Marcantonio, N. and J. Ricca, J., 2001, Multi-scale microstructural characterisation of micro-textured Ti-6Al-4V surfaces, Key Engng Mater., 198–199, 203–230.

[176] Spijker, H.T., Graaff, R., Boonstra, P.W., Busscher, H.J. and van Oeveren, W., 2003, On the influence of flow conditions and wettability on blood material interactions, Biomaterials, 24, 4717–4727.

[177] Steegmueller R., Fleckenstein T. and Schuessler, A., 2005, Is electropolishing equal to electropolishing? A comparative study of Nitinol stents., ASM Conference, Session 4B 'Surface Engineering—Cardiovascular', 14–16 November, Boston, Mass.

[178] Steffen, H.J., Schmidt, J. and Gonzalez-Elipe, A., 2000, Biocompatible surfaces by immobilization of heparin on diamond-like carbon films deposited on various substrates, Surf. Interface Anal., 29, 386–391.

[179] Stickler**,** D.J., 1996, Bacterial biofilms and the encrustation of urethral catheters, Biofouling, 94, 293–305.

[180] Stout, K.J., Sullivan, P.J., Dong, W.P., Mainsah, N., Luo, N., Mathia, T. and Zahyouani, H., 1993, The development of methods for the characterisation of roughness in three dimensions, Brussels: Commission of the European Communities.

[181] Stout, K.J. and Blunt, L., 2000, Three Dimensional Surface Topography, 2nd Edn, London: Penton Press.

[182] Strobel, M. and Schuessler, A., 2004, Status and trends in laser micro machining of metallic medical components, The International Organization on Shape Memory and Superelastic Technologies **(**SMST) Conference, 3–7 October, Baden-Baden.

[183] Sul, Y-T., Johansson, C.B., Roser, K.,T Albrektsson, T., 2002, Qualitative and quantitative observations of bone tissue reactions to anodized implants, Biomaterials 23, 1809–1817.

[184] Suzuki, Y., Kusakabe, M., Iwaki, M., Sasabe, H., and Nishisaka, T., 1991, Cell adhesion control by ion implantation into extra-cellular matrix, Nucl. Instr. Meth., B 59–60, 698–704.

[185] Suzuki, Y., Kusakabe, M., Akiba, H., Kusakabe, K. and Iwaki, M., 1994, In vivo evaluation of antithrombogenecity for ion implanted silicone rubber using indium 111 tropolone platelets, Nucl. Instr. Meth., B 91, 588–592.

[186] van Tassel, P.R., Guemouri, L., Ramsden, J.J., Tarjus, G., Viot, P. and Talbot, J., 1998, A particle-level model of irreversible protein adsorption with a postadsorption transition. J. Colloid Interface Sci., 207, 317–323.

[187] Tausendfreund, A., Mader, D., Simon, S., Patzelt, S. and Goch, G., 2006, Simulation of light scattering from surfaces containing spherical and elliptical nanoparticles, Photonics Europe, Strassburg, SPIE Proc., 6195, paper 68.

[188] Tausendfreund, A., Patzelt, S., Mader, D., Simon, S. and Goch, G., 2006, Simulation of light scattering for surfaces with statistically distributed subwavelength cavities, Photonics Europe, Strassburg, SPIE Proc., 6195, paper 56.

[189] Teague, E.C., Scire, F.E., Baker, S.M. and Jensen, S.W., 1982, Three dimensional stylus profilometry, Wear, 83, 1–12.

[190] Teague, E.C., Vorburger, T.V. and Maystre, D., 1981, Light scattered from manufactured surfaces, Annals CIRP, 30/2, 563–570.

[191] Teoh, S.H., 2004, Engineering Materials for Biomedical Applications, Singapore: World Scientific.

[192] Thai, L.C., Tomlinson, A. and Simmons, P.A., 2002, In vitro and in vivo effects of a lubricant in a contact lens solution, Ophthalmic Physiol. Optics, 22, 319–329.

[193] Theilade, U.R.A., 2004, Surface micro topography replication in injection moulding, PhD thesis, Technical University of Denmark.

[194] Tomlins, P.E., Leach, R., Vadgama, P., Mikhalovsky, S. and James, S., 2005, On the topographical characterisation of biomaterial surfaces, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 693–716.

[195] Topala, I.C., 2005, Atmospheric and low pressure plasma: applications in materials science, poster presented at: Marie Curie Summer Schools on Knowledge Based Materials: Single Phase Materials, 8–17 August, Aachen.

[196] Topala, I.C., Dumitrascu, N., Nistor, R., Pohoata, V. and Popa, G., 2004, Haemocompatibility of PA-6 surfaces treated by a barrier dielectric discharge, 15th International Conference on Gas Discharges and their Applications, Toulouse, France, Conf. Proc. vol. II, pp. 1105–1108.

[197] Vadgama, P., Surface biocompatibility, 2005, A. Rep. Prog. Chem., C 101, 14–52.

[198] Vadiraj, A. and M Kamaraj, M., 2006, Fretting fatigue studies of titanium nitride-coated biomedical titanium alloys, J. Mater., Engng Performance, 15, 553–557.

[199] Vedrine, L., Prais, W., Laurent, P.E., Raynal-Olive, C. and Fantino, M., 2003, Improving needle-point sharpness in prefillable syringes, Medical Device Technol., May, pp. 32–33 and 35.

[200] Vickerman J.C., ed., 1997, Surface Analysis—the Principal Techniques, New York: Wiley.

[201] Vorberger, T.V., Dagata, J.A., Wilkening, G. and Lizuka, K., 1997, Industrial uses of STM and AFM, Annals CIRP, 46/2, 587–620.

[202] Vorburger, T.V., Teague, E.C., 1981, Optical techniques for on-line measurement of surface topography, Precision Engng, 3, 61–83.

[203] Vroman, L. and Adams, A.L., 1969, Identification of rapid changes of plasma-solid interfaces, J. Biomed. Mater. Res., 3, 43–67.

[204] Wang, J., Mao, G., Ober, C.K. and Kramer, E.J., 1997, Liquid crystalline, semifluorinated side group block copolymers with stable low energy surfaces: synthesis, liquid crystalline structure, and critical surface tension, Macromolecules, 30, 1906–1914.

[205] Wang, W. and Parker, K. H., 1995, Effect of deformable porous surface layers on the motion of a sphere in a narrow cylindrical tube, J. Fluid Mechanics, 283, 287–305.

[206] Weckenmann, A., Estler, T., Peggs, G., McMurtry, D., 2004, Probing systems in dimensional metrology, Annals CIRP, 53/2, 657–684.

[207] Wennerberg, A., Ohlsson, R., Rosén, B.G. and Andersson, B., 1996, Characterising dimensional topology of engineering and biomedical surfaces by confocal laser scanning and stylus techniques, Med. Engng Phys., 18, 548–556.

[208] Werner, C. and Jacobasch, H.J., 1999, Surface characterisation for polymers for medical devices, Intl J. Artificial Organs, 22, 3, 160–176.

[209] Whitehouse, D.J., 1994, Handbook of Surface Metrology, Bristol and Philadelphia: IoP.

[210] Wiggins, P.M., 2002, Enzyme reactions and two-state water, J. Biol. Phys. Chem., 2, 25–37.

[211] Wright, C.J. and Armstrong, I., 2006, The application of atomic force microscopy to the characterisation of microbial surfaces, Surf. Interface Anal., 38, 1419–1428.

[212] Youngblood, J.P., Andruzzi, L., Ober, C.K., Hexemer, A., Kramer, E.J., Callow, J.A., Finlay, J.A. and Callow, M.E., 2003, Coatings based on side-chain ether-linked poly(ethylene glycol) and fluorocarbon polymers for the control of marine biofouling, Biofouling, 19 (Supplement), 91–98.

[213] Ziegler, C., 2005, Surface microscopies, in: Surfaces and Interfaces for Biomaterials, P. Vadgama, ed., Abington: Woodhead Publishing, pp. 200–224.

The design and manufacture of biomedical surfaces

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