On the biomedical relevance of surface spectroscopy

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Abstract

Practical utility of surface spectroscopy in biomaterials is viewed from an abstract analytical science perspective in which the desired target information is compared to that obtained through spectroscopic probes. Through a five step reasoning process it is concluded that much of the information obtained by surface spectroscopy is not directly relevant to biomaterial end-use properties. A context is proposed to make more effective use of the indirect, but still very useful, analytical information derived from surface spectroscopy in biomaterials research.

Keywords: Biocompatibility; Biomaterials; Interface; Spectroscopy; Surface

1. Introduction

Little tangible progress has been made toward quantitative understanding of the relationships connecting surface and interfacial chemistry with the biological response to materials despite more than two decades of intense research that has applied ever-increasingly-sophisticated surface spectroscopic methods [1–4]. Very few, if any, basic concepts have emerged with wide predictive power that are based solely on spectroscopic measurements, even though biomaterials research of the last 5 to 10 years has widely applied techniques such as ESCA and SSIMS [5]. Given that the rules of biocompatibility are not readily apparent from spectroscopy, biomaterial surface scientists are obliged to view the field from an abstract analytical- or information-science perspective, and ask “why?” This paper seeks answers to this basic question. Considerations are rooted in the author’s research in biomaterials which, at this writing, spans nearly fifteen years of applying surface science to practical industrial problems associated with polymeric biomaterials in various biomedical device applications (see Ref. [6] and citations therein). Also, experience gained through participation in consortiums dedicated to understanding biology at interfaces is drawn upon, together with more focused interactions with leading academics in the field.

A five-step reasoning process will be applied. Firstly, biocompatibility will be defined from a practical operational point of view. Secondly, the nature of biomaterial surfaces and interfaces will be considered with the goal of identifying the surface region important in the determination of biocompatibility. This will be the zone where the analytical information to be extracted is contained. The type and relevance of surface analytical information derived from surface spectroscopies will be generally considered in light of this target information in the third part. The fourth step is a crucial one in
which a dispassionate comparison of conclusions drawn from the second and third reasoning steps will reveal that much of what is learned from surface spectroscopy, particularly spectroscopies of the high-vacuum variety, is not directly relevant to biomaterial end-use properties. With this in mind, the original proposition of this paper articulated in the introductory paragraph will be examined further. The fifth and final part of the reasoning process will concentrate on the analytical information content derived from surface spectroscopy that is indirectly related to biocompatibility but still very useful in biomaterials surface science. A context that may make more effective use of this surface spectroscopic information in biomaterials research will be proposed, both toward solution of practical biomaterial problems and in search of the elusive fundamentals of biocompatibility.

2. Discussion

2.1. Step 1: Biocompatibility defined

2.1.1. Biomaterials by design

A consensus definition of biomaterials [7] is “a non-viable material used in a medical device intended to interact with biological systems” or, more elegantly stated [8], “any material designed to supplement, store, or otherwise come into intimate contact with living biological cells or biological fluids.” Keywords here are intended and designed. Prospective design or appropriate selection of a material, as opposed to a random search through all possibilities, should be a predictive outcome of biomaterials research. Biocompatibility is a relative term that measures success of the design or selection process for a specific biomedical task. Thus, the precise meaning of material biocompatibility must be articulated within the context of an end-use application and has measurable dimensions only within this context. Biocompatibility is the successful result of translating biomedical properties into materials properties. Stated in the terminology of the consensus definition [7], biocompatibility is “the ability of a material to perform with an appropriate host response in a specific application.”

2.1.2. Biocompatibility is not a material property

Biocompatible is frequency stated to be an absolute property of a material without reference to a specific biomaterials application. This is correct usage only in the most abstract or universal sense of the word. After all, use of a relative term with no measurable dimension or standard of comparison has little scientific utility. No one material can possess properties that permit universal biomedical application and hence achieve pan-biocompatibility. This is because different applications require different, often mutually exclusive, properties for successful end use. Otherwise, the field might be referred to in the singular form, biomaterial science, as opposed to the plural form, biomaterials science.

As examples in support of the above, surface-treated polystyrene is a very successful substitute for glass in the culture of animal cells in vitro. In fact, proprietary pretreatment of tissue-culture plastics is undoubtedly the highest volume commercial example of a prospectively-designed surface chemistry (at least in part) for a specific biomaterials application [6,9]. Tissue-culture-grade polystyrene is therefore biocompatible for most cell culture operations. However, few would suggest surface-treated polystyrene for an in vivo blood-contact application because the same surface chemistry that leads to good cell adhesion and proliferation would trigger blood clotting and complement cascades [10,11], to say nothing of inappropriate brittle physical properties. For this application tissue-culture-grade polystyrene could not be considered to be biocompatible. Polyurethanes are softer, more compliant materials that have enjoyed successful use as short-term (<7 days) in-dwelling peripheral catheters. Thus, certain polyurethane formulations exhibit adequate biocompatibility (hemocompatibility) for this important nosocomial application. However, long term implant patency can be compromised by enzymatic digestion of urethane linkages and hydrolytic reactions that degrade physical properties [12]. In this sense, polyurethane is not biocompatible. An unambiguous definition of biocompatible has eluded biomaterials scientists [13,14] partly because the definitional attachment to success in end use has been overlooked.
2.1.3. Biocompatibility as a code word

Use of the term biocompatible herein without a specified end use as in, for examples, the phrases "rules of biocompatibility" or "determination of biocompatibility" is meant as a sort of code word, globally embracing those leading properties that make the biomaterial successful in an as-yet unspecified biomedical application. Understanding and predicting those properties in the design of biomaterials is the underlying scientific task at hand. Delineation of the role that surface spectroscopy can play in elucidating surface properties leading to biocompatibility is the subject of this paper.

2.2. Step 2: The nature of biomaterial surfaces and interfaces

2.2.1. Surfaces and interfaces

There is a subtle distinction between the terms surface and interface, related more to common parlance than to strict scientific definition, that has colored or confused fundamental thinking in biomaterials surface science. The term surface is usually reserved for the boundary region between a material and vacuum [6,15]. Surface analysis has become strongly associated with high-vacuum surface spectroscopies that have been developed over the last decades since the introduction of the electron spectrometer. Consequently, surface chemistry usually refers to the chemical composition of the surface layers against a vacuum as determined by use of one of these spectroscopic methods. Scientific usage of the term interface has historical roots in Gibbsian surface thermodynamics and has special meaning when so applied (see, for examples Refs. [6,15–18]). For practical biomaterial applications in which only the hydrated state is important, it is convenient to restrict use of this term to aqueous systems such as liquid–vapor (lv), liquid–liquid (ll), or solid–liquid (sl) interfaces. Of course, in the application of arbitrary definitions there will be exceptions that must be dealt with on an individual basis. But experience suggests that this level of systematization is well suited to biomaterials and can help organize fundamental issues associated with surface and interfacial chemistry.

2.2.2. Chemistry and physics at the interface

Confusion results when the terms surface and interface are used interchangeably. Surface and interfacial chemistry are not the same and do not probe the same physical phenomena. Fig. 1 is a diagrammatic representation of a polymeric bio–material interface at high magnification that is useful in further addressing this point. Broadly speaking, there are two main types of physicochemical interactions between a biomaterial surface and the biological environment across a solid–liquid interface. Interactions of the chemical type involve direct transfer or sharing of electrons in the formation of ionic or covalent bonds, or more readily reversible exchanges such as hydrogen bonding or divalent ion bridging. So called "hydrophobic forces" also termed van der Waals' or dispersion forces, emanate from the upper 1 nm of a material surface and propagate into the fluid phase. These physical forces arise from the coupling of momentary dipoles associated with rapid fluctuations in the electron density within the molecular orbitals of matter located in the interphase region (see, for examples, Refs. [16–18]). The biological milieu represented in Fig. 1 consists of a number of interactive components. The aqueous phase is a high-ionic-strength saline solution with both monovalent and multivalent ions containing dissolved proteins together with suspended cells or tissue. Exactly how physics, chemistry, and biology conspire in the complex panoply of interfacial events depicted in Fig. 1 that determine biocompatibility is not known with clarity at this time. However, for present purposes, we can address the extent to which surface spectroscopy can contribute relevant information leading to a better understanding of biocompatibility without this detailed knowledge.

Chemistry at the interface is specific to functional groups at the outermost surface layer and spans only atomic bond lengths. These functional groups can be spectroscopically detected, differentiated, and quantified if the spectroscopic technique has sufficient surface sensitivity, as will be discussed in greater detail subsequently. By contrast, material composition within the upper 1 nm of a surface giving rise to hydrophobic forces that can structure water out to about 10 nm into the
Fig. 1. A high-magnification, diagrammatic view of a polymer interface in contact with a generalized biological milieu providing a sense of scale for interfacial phenomena at biomaterial surfaces. Hydrophobic forces emanating from the upper 1 nm of a surface extend about 10 nm into solution. These forces are responsible for adsorption and unfolding of proteins at surfaces that can reveal domains that are ligands or receptors for other biological molecules. Chemical reactions such as ion exchange and hydrogen bonding occur over single-atom distances. A chemical gradient usually exists within the bulk polymer phase and polymeric surfaces can reorganize under hydrating conditions.
interphase [19–23] is not so easily resolvable into individual or group components. Molecules within this surface region interact across an interface in a pairwise manner with molecules comprising matter of the biological fluid phase. Atomic or molecular composition within the upper 1 nm does not measure this force-over-distance contribution to interfacial chemistry, particularly for heterogeneous materials that can significantly vary in composition within the upper 1–100 nm of the surface. Of course, water structure must have a profound effect on biological cells or proteins coming within close proximity of the interfacial region [19].

2.2.3. Surface region of interest

It can be concluded then, with all the aforementioned in mind, that only the upper 1 nm of a surface is important in determination of biocompatibility [6,24]. Underlying substrata are effectively shielded from intimate contact with the biological environment. Practitioners of surface spectroscopy in biomaterials thus face significant challenges of surface sensitivity and resolution. Having identified the surface region relevant to the biomaterials problem, we turn our attention to the third reasoning step in which these challenges will be specifically addressed along with discussion of the biomedical relevance of spectroscopic information.

2.3. Step 3: Surface sensitivity and relevance of spectroscopic information

2.3.1. Surface sensitivity

A universal attribute of surface spectroscopies is surface sensitivity. Surface sensitivity effectively measures the number of molecular layers probed by a particular spectroscopic technique. Any spectroscopic method that derives analytical information from deeper than about 1 nm effectively dilutes the utility of this information for biomaterial problems. This is because only the upper 1 nm has direct contact with the biological environment, as asserted in the preceding discussion of Fig. 1.

There are a number of currently-applied and emerging spectroscopic methods that have the requisite surface sensitivity for biomaterial applications. Although it is not the purpose of this paper to survey extant spectroscopic methods in terms of surface sensitivity, three particular methods can be mentioned as specific examples in point; ESCA, SSIMS, and HREELS. ESCA (electron spectroscopy for chemical analysis) has been the workhorse of biomaterials surface spectroscopy for more than two decades, providing atomic composition (excluding hydrogen) with oxidation state information within the upper 5–10 nm or so of a surface. Thus, ESCA probes something on the order of five to ten fold deeper into a surface than desired in the determination of biomaterial composition as it relates to biocompatibility. Modern instrumentation and ancillary techniques are continuing to push the envelope of ESCA surface sensitivity; however, and biomedical applications of ESCA can be expected to improve in this regard over time. SSIMS (static secondary ion mass spectroscopy) is gaining considerable popularity among biomaterial scientists. Generating mass spectra from the upper 1 nm of a surface, SSIMS probes a region more directly responsible for biocompatibility (see Ref. [25] for a recent review of ESCA and SSIMS applications in biomaterials). HREELS (high resolution electron energy loss spectroscopy) is an evolving technique (see Ref. [26] for a recent review) that provides vibrational spectra from the outermost 0.5 nm, yielding surface sensitivity that rivals or exceeds that of the venerable contact angle and wetting techniques. Clearly, these types of surface spectroscopies must be carefully applied in biomaterial applications, keeping in mind which layer or layers of the material surface interact with the biological environment. Some methods, such as ESCA, yield surface composition that is a composite of a relatively thick surface region having little direct contact with the biological fluid phase. Other methods, such as HREELS, have the potential for being too myopic, probing only the outermost functional groups responsible for specific chemical interactions with the biological environment but not the subadjacent material giving rise to hydrophobic forces. This surface sensitivity aspect of surface spectroscopy not only confounds the usual contemporary problems of spectral deconvolution and interpretation, but also invites difficulties in the inter-comparison of results of different techniques.
2.3.2. Two related relevance issues

The first asks if what the spectrometer "sees" is the same as that confronted by the biological environment. The second is broader and more philosophical in nature, asking if compositional information, even if obtained at sufficient surface sensitivity and resolution under biomedically relevant conditions, is the type of information required in pursuit of the fundamental rules of biocompatibility.

Note that surface chemistry as defined herein is a "dry-state" chemistry usually (but not exclusively) obtained in a high-vacuum environment that may not, and probably does not, bear any relationship to the hydrated state encountered in biomaterial applications. Some practitioners have attempted to circumvent this problem by performing ESCA on dehydrated (lyophilized) surfaces or even in the frozen state (see Ref. [27] and citations therein). These sorts of approaches attack only one facet of a larger issue which is that surface spectroscopies do not probe the dynamic physicochemical events that transpire at the solid–liquid interface under physiological conditions. The interphase between a solid and biological liquid is not a stagnant region that can be frozen, freeze dried, or replicated in any way. The interfacial chemistry that mediates the biological response to materials is created by the interaction of the various interactive components and does not exist when these components are separated or altered. That is, the biomedical relevance issue associated with treating dry-state surface chemistry as the primary driver of biocompatibility is that the aqueous phase with dissolved proteins is regarded as a simple, neutral carrier of biology that does not interact with surfaces. This sort of interpretation is clearly an unwarranted oversimplification. A more accurate view recognizes that the primary biological response to material surfaces is formation of an interface that has dynamic structure associated with hydration, formation of water structure, and possibly protein adsorption. Subsequent events such as cell/tissue adhesion or the triggering of immune responses are responses to this interfacial chemistry. It has yet to be shown that chemistry within the upper 1–10 nm sensed by most spectroscopic methods is primarily linked to biomaterial interfacial properties through a direct cause and effect; at least no widely predictive theory based on spectroscopic measurements has been proposed.

The second category of biomedical relevance is a philosophical derivative of that just discussed. At issue is the effective use of compositional information in predicting biomaterial properties. A broad generalization that can be drawn regarding compositional information derived from spectroscopy (any kind of spectroscopy not just limited to the surface type) is that this analytical information is useful only in the event that there is some structure–reactivity relationship, some guiding principle or model, that confers functional meaning to this composition. Knowledge of composition with no knowledge of how composition affects or dictates end-use properties has limited utility.

Surface chemistry is quite conspicuous within the broader framework of classical chemistry in that there are few, if any, structure–reactivity relationships available. Compare, as an example in point, classical organic chemistry and surface chemistry. In the former case, provision of a chemical structure is nearly all that is necessary to predict reactivity in an end-use property such as synthetic utility. For the surface chemistry case, even with a priori knowledge of a homogeneous surface with precisely-defined chemical structure, little can be predicted in terms of reactivity, especially with respect to the biological response to materials. As another more rudimentary example in point, consider the circularity in reasoning involved in determination of surface composition through spectroscopy. Let us break into the circle with the point that there are no authentic surface analytical standards with precisely and accurately known composition and structure. This is because there are no absolutely calibrated surface spectrometers that precisely and accurately verify composition and structure without invocation of certain operational assumptions; line width, peak position, peak identification, spectral overlap, to name but a few. This is because there are no absolutely reliable surface analytical standards against which to calibrate instrumental methods. Therefore the circle is closed. Of course, all of the above difficulties are exacerbated by the surface sensitivity issues raised earlier which negatively
influence meaningful intercomparison of spectra from different surface spectroscopies.

2.4. Step 4: Assessing the biomedical relevance of surface spectroscopy

2.4.1. Spectroscopy does not measure biocompatibility

In the preceding sections three broad assertions have been made. Firstly, only the upper 1 nm or so of a surface is involved in the determination of biocompatibility. Secondly, biocompatibility is mediated through two classes of physicochemical interactions; the chemical type involving donation or sharing of electrons over single-atom bond lengths, and the hydrophobic force type that are longer range but less specific in nature. Thirdly, among spectroscopies with surface sensitivity commensurate with the task of determining chemical composition within the upper 1 nm region, there is the issue of biomedical relevance. Either conditions of analysis are very much different than those encountered in the biomaterial application or there is no rule base against which surface composition can be interpreted directly in terms of biocompatibility.

With the aforementioned in mind, it can be concluded that surface spectroscopy, at the current stage of development, cannot provide information that is primarily linked to biocompatibility. Interfacial events that transpire upon contacting a biomaterial surface with a biological fluid phase essentially unlink any direct connection between surface chemistry and biocompatibility. These interfacial events include instantaneous hydration, solution partitioning (adsorption), and formation of water structure that profoundly affects secondary biological consequences such as cell/tissue adhesion or the triggering of different biochemical cascades controlling blood clotting or immune responses. Surface spectroscopy either does not probe this dynamic interfacial chemistry or provides chemical information which, at this time, cannot be meaningfully translated in terms of the rules of biocompatibility.

2.4.2. An incomplete interpretive paradigm

Attention is now turned to the original proposition of this paper that little tangible progress has been made toward quantitative understanding of the relationships connecting surface and interfacial chemistry with the biological response to materials. In the author’s opinion, this lack of progress can be traced to an incomplete or erroneous interpretive paradigm. Too often, either implicitly or explicitly, the aqueous phase has been treated as a neutral carrier of biology that does not participate in the determination of biocompatibility, or worse, the aqueous medium has been ignored altogether. In the rush to apply new surface spectroscopic tools to classic biomaterials problems, there has been an attempt to relate surface chemistry directly to the biological response to materials. Biocompatibility is driven by interfacial chemistry, not surface chemistry. Therefore the relationships sought are obscured by an intermediate process, the establishment of interfacial chemistry. An old adage asserts that if the only available tool is a hammer then every problem becomes a nail. Surface spectroscopies have been among the very few available tools that can be generally and routinely applied to biomaterial problems. Perhaps because of this, biomaterial surface science problems have become proverbial nails.

2.4.3. Case in point

Polymer surface chemistry that leads to efficient attachment and proliferation of mammalian cells has received considerable attention from the biomaterials community because tissue adherence is frequently a critical property for biointegration of implants and, as mentioned previously, these materials are of considerable commercial significance in the form of disposable laboratory-ware used in the culture of cells in vitro. It is of interest to focus on this latter application as a case in point because success in end use, that is to say biocompatibility, is rather straightforward to measure through cell attachment and proliferation. Also, there are a number of published studies that have utilized surface spectroscopy and ancillary methods to identify specific surface functional groups that are purported to be primarily responsible for cell adhesion [28–36]. The purpose here is not to critically review these reports but rather to generally consider the veracity of an interpretive paradigm which asserts
that specific surface functionalities can be identified as the primary driver of cell adhesion from aqueous media containing proteins.

Cell biologists describe cell adhesion to a substrate in terms of four separately identifiable stages: protein adsorption, contact, attachment, and spreading. These different phases of adherence are illustrated on a cell attachment-rate curve shown in Fig. 2 which plots percentage of a cell inoculum attached to a substrate (%I = cell number attached/total number of cells x 100) from a sessile fluid phase at various time intervals [37]. The final stage illustrated in Fig. 2 is cell spreading which begins well after initial contact and attachment events, continuing during and after the first hour of attachment (note logarithmic time axis). Cell spreading is quite different from previous steps that lead to a steady-state adhesion plateau (%I$_{max}$ in Fig. 2), involving production of adhesion proteins by cells and formation of adhesion patches or plaques with progressive adherence to substrate (see Ref. [38] and citations therein).

The question at hand is whether specific functional groups identified by surface spectroscopy can possibly be linked to cell adhesion and proliferation in a primary cause-and-effect manner. According to the preceding discussion, no direct relationships can be expected. Let us explore this by working backwards along the attachment curve of Fig. 2 from spreading to adsorption. Note first that cells in long contact with surfaces produce a relatively thick conditioning film or extracellular matrix that separates cell and surface [38]. Clearly, this extracellular matrix obscures cells from the starting chemistry on the as-received surface, and no primary linkage with this surface is thus possible. Attachment and contact steps are not directly influenced by surface chemistry even in the absence of a conditioning film. It is well known from colloid science that close approach of microscopic particles to macroscopic surfaces (frequently termed collectors in the colloid literature) is controlled by the summed electrostatic (repulsive) and van der Waals' forces (attractive) operating across the separating interface. These forces result from the pairwise interactions briefly mentioned in discussion of Step 2 that are not directly probed by surface spectroscopy. Cell attachment through specific ligand--receptor interactions with adsorbed proteins does not directly involve the starting surface chemistry either. However, adhesion directly to the substrate involving displacement of proteins and/or water bound to the surface in the initial adsorption stage shown in Fig. 2 must involve spectroscopically-resolvable surface functional groups. Here again however, the relationship is complex and certainly not direct. As discussed in Step 2, the interfacial chemistry of this adhesion process involves constituents of the fluid phase (water, ions, proteins, and cells). The surface is but one of the interactive partners.

Thus it is concluded by application of the logic of Steps 1–3 that no direct relationship between cell adhesion and surface chemistry can be anticipated. From formation of the biological interface to the final spreading and proliferation stages, there is a
complex interplay of physics, chemistry, and biology that ultimately determines biocompatibility. Surface spectroscopy can probe only a small piece of the overall process. Correlations that do emerge between surface composition and cell adhesion must be due to some unknown secondary connections, or perhaps only chance. In any event, it should be the responsibility of the purveyor of such information to clearly explain the interrelationships that are being examined and how it is that dry-state surface chemistry drives cell adhesion without involving all other interactive components of the system.

The remaining part of the cell adhesion process shown in Fig. 2 to be discussed is the adsorption step. Here is where important primary relationships between surface chemistry and the interaction with water and proteins may emerge. Thus, more successful use of spectroscopy might be anticipated by compartmentalizing the biological process under study into manageable pieces that can be directly related to surface chemistry effects. This is the kernel of the idea discussed in the next section.

2.5. Step 5: An interpretive framework for surface spectroscopic information applied to biomaterials problems

2.5.1. A hierarchy of causal relations

An alternative formula for understanding biocompatibility is to first understand how surface chemistry controls and determines interfacial chemistry and then, either in series or parallel, understand how interfacial chemistry regulates biocompatibility. This logical hierarchy is diagrammed in Fig. 3 with some direct connections (solid arrows) and other less direct connections (dashed arrows). Dashed arrows are representative of the connections sought in most previous biomaterials research, attempting to directly link composition with the biological response. The solid arrows indicate the logical route proposed herein, leading sequentially from the surface synthetic process through interfacial properties to the goal of understanding the biological response. The intermediate step relating surface chemistry to wetting properties in pure saline unlinks surface composition and complicated events associated with the adsorption of biological solutes such as proteins. This separation is intended to sharpen causal relationships.

According to the plan of Fig. 3, then, the significant surface spectroscopic challenge is to directly correlate composition to water wettability. The objective is to elucidate fundamental structure-reactivity relationships that control the behavior of water at interfaces. This objective complements and converges with emerging understanding of the role of surface functional groups in the wettability
of materials (see, for example, Ref. [39]) and the ability to synthesize well-ordered surfaces using, among other approaches, organosilane and organothiol chemistry. Ideally, analogs of Hammet-type equations that are predictive of reactivity in organic chemistry could be developed for surface chemistry, leading to the quantitative structure-reactivity relationships necessary to interpret surface composition in terms of wettability.

3. Conclusions

The rudimentary problem in biomaterials is translation of the desirable biomedical properties that define biocompatibility for a particular end application into materials properties that lead to correct selection, design, or synthesis of an appropriate material for that biomedical use. This paper has focused on the historical contribution of surface spectroscopy toward the solution of this problem. An analytical-science perspective on the factors that control biocompatibility led to the conclusion that information obtained from modern surface spectroscopies is not directly relevant to biomaterial problems. A major limitation identified was lack of quantitative structure-reactivity relationships that allow effective interpretation of surface composition in terms of biocompatibility. It was concluded that elucidation of these relationships was a fundamental challenge of modern biomaterials surface science toward which surface spectroscopists can play a leading role.

Acknowledgments

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References and notes

[5] Results of these studies are reported in the various journals that directly (e.g. J. Biomed. Mater. Res., Biomaterials, Biomat., Art. Cells, Art. Org.) or indirectly (this journal, Langmuir, J. Colloid Interface Sci., Colloids and Surfaces, etc.) service biomaterials and biomedical device fields.
[24] This conceptual view of a biomaterial interface can be extended to materials supporting a thick biofilm or conditioning layer. In these cases, interfacial chemistry is specific to functional groups at the outermost surface layer of the biofilm and hydrophobic forces emanating from the bulk biofilm and possibly, supporting substratum. For a discussion of biofilm formation see: A.E. Meyer, Dynamics of Conditioning Film Formation on Biomaterials. Doctoral dissertation, Lund University, Department of Prosthetic Dentistry, Malmo, Sweden. 1990 and references cited therein.