Structure and reactivity of water at biomaterial surfaces

Erwin A. Vogler*
Becton Dickinson Research Center, 21 Davids Drive, Research Triangle Park, NC 27709-2016, USA

Abstract

Molecular self association in liquids is a physical process that can dominate cohesion (interfacial tension) and miscibility. In water, self association is a powerful organizational force leading to a three-dimensional hydrogen-bonded network (water structure). Localized perturbations in the chemical potential of water as by, for example, contact with a solid surface, induces compensating changes in water structure that can be sensed tens of nanometers from the point of origin using the surface force apparatus (SFA) and ancillary techniques. These instruments reveal attractive or repulsive forces between opposing surfaces immersed in water, over and above that anticipated by continuum theory (DLVO), that are attributed to a variable density (partial molar volume) of a more-or-less ordered water structure, depending on the water wettability (surface energy) of the water-contacting surfaces. Water structure at surfaces is thus found to be a manifestation of hydrophobicity and, while mechanistic/theoretical interpretation of experimental results remain the subject of some debate in the literature, convergence of experimental observations permit, for the first time, quantitative definition of the relative terms 'hydrophobic' and 'hydrophilic'. In particular, long-range attractive forces are detected only between surfaces exhibiting a water contact angle $\theta > 65^\circ$ (herein defined as hydrophobic surfaces with pure water adhesion tension $\gamma^d = \gamma^w \cos \theta < 30$ dyn/cm where $\gamma^w$ is water interfacial tension = 72.8 dyn/cm). Repulsive forces are detected between surfaces exhibiting $\theta < 65^\circ$ (hydrophilic surfaces, $\gamma^d > 30$ dyn/cm). These findings suggest at least two distinct kinds of water structure and reactivity: a relatively less-dense water region against hydrophobic surfaces with an open hydrogen-bonded network and a relatively more-dense water region against hydrophilic surfaces with a collapsed hydrogen-bonded network. Importantly, membrane and SFA studies reveal a discrimination between biologically-important ions that preferentially solubilizes divalent ions in 'more-dense water regions relative to less-dense water regions in

*E-mail: vogler@bd.com EAV30PSU.EDU

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which monovalent ions are enriched. Thus, the compelling conclusion to be drawn from the collective scientific evidence gleaned from over a century of experimental and theoretical investigation is that solvent properties of water within the interphase separating a solid surface from bulk water solution vary with contacting surface chemistry. This interphase can extend tens of nanometers from a water contacting surface due to a propagation of differences in self association between vicinal water and bulk-phase water. Physicochemical properties of interfacial water profoundly influence the biological response to materials in a surprisingly straightforward manner when key measures of biological activity sensitive to interfacial phenomena are scaled against water adhesion tension \( \sigma \) of contacting surfaces. As examples, hydrophobic surfaces \( (\sigma < 30 \text{ dyn/cm}) \) support adsorption of various surfactants and proteins from water because expulsion of solute from solution into the interphase between bulk solid and solution phases is energetically favorable. Adsorption to hydrophobic surfaces is driven by the reduction of interfacial energetics concomitant with replacement of water molecules at the surface by adsorbed solute (surface dehydration). Hydrophilic surfaces \( (\sigma > 30 \text{ dyn/cm}) \) do not support adsorption because this mechanism is energetically unfavorable. Protein-adsorbing hydrophobic surfaces are inefficient contact activators of the blood coagulation cascade whereas protein-repellent hydrophobic surfaces are efficient activators of blood coagulation. Mammalian cell attachment is a process distinct from protein adsorption that occurs efficiently to hydrophilic surfaces but inefficiently to hydrophobic surfaces. Thus, the hydrophobic/hydrophilic contrast in the biological response to materials, often disputed in biomaterials science, is very clear when viewed from the perspective of water structure and reactivity at surfaces. The key measure of water structure and activity important to biomaterial scientists is \( \sigma \) rather than parameters such as Zisman's critical surface tension \( \gamma_c \) or 'surface free energy' \( \gamma_f \) that are shown not to correlate sensibly with either \( \sigma \) or results from the surface force apparatus. © 1998 Elsevier Science B.V.

**Keywords:** Water structure; Biomaterials; Biological response; Surface energy; Hydrophobic; Hydrophilic; Surface forces

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1. Introduction

Biomaterials are non-viable materials used in medical devices intended to interact with biological systems [1]. In the broadest sense, biomaterials embrace any material designed to supplement, store, or otherwise come into intimate contact with living biological cells or biological fluids [2]. The key words here are intended and designed. Prospective design or 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. The keywords here are specific biomedical task. Biocompatibility must be articulated within the context of an end-use application and has measurable dimensions only within this context [3].

Quantitative connections between material chemistry and the biological response to materials form the essential rule base required for the prediction of biocompatibility for diverse biomedical applications. This rule base, this set of structure-reactivity relationships, is the ultima Thule of biomaterials research.

Surface and colloid science has played an important role in biomaterials research for more than two decades. It was recognized early on that the forces governing protein adsorption and cellular adhesion must be in some way related to the forces that mediate or control surfactant and colloid stability [4]. However, the path forward has not been at all straight due to a number of complicating factors that include: the complexity of biology at interfaces; the cross-disciplinary nature of biomaterials science and the misapplication of the standard tools of biological and physical sciences that cross-disciplinary work invites; dogmatization of paradigms of spent utility; poorly-constructed syllogisms; failure to embrace a rigorous reductionist strategy; and a rather disorganized approach to very broad suite of in vitro and in vivo problems with vastly different degrees of complexity.

Then there are a few important outstanding issues in surface and colloid science that, if finally solved and articulated in a manner consumable by biomedical
researchers not schooled in the rigors of chemical physics, might greatly influence positive outcomes to the classical problems of biomaterials science. In so doing, surface and colloid science can have favorable impact on worldwide health care because biomaterials are the essential building blocks of all medical devices, including the ubiquitous disposable specimen collection devices and syringes used by the billions in modern clinical practice [5]. Notable among these outstanding issues are the structure and reactivity of water at surfaces, the nature of ‘hydrophobic’ and ‘hydration’ forces and the mediating role these forces have on solute (including ionic) adsorption and cell adhesion from water to surfaces [6].

Recently, say over the last 5 years or so, there has been a convergence of experimental and theoretical understanding of the structure and reactivity of water at surfaces arising from different points of view and literature sources. Although a considerable amount of debate remains in the mechanistic details, it is not too early to seek guidance from this new understanding to help resolve some of the aforementioned problems in biomaterials. It is the objective of this review article to capture some of this knowledge and interpret it within the context of biomaterials surface science.

The starting point will be the physical phenomenon of self association that is especially important in water, the universal biological solvent system. After a brief examination of the history of scientific investigation into water structure at surfaces, recent results from the surface force apparatus and ancillary techniques will be reviewed, from which it will be evident that there is different water structure associated with ‘hydrophobic’ and ‘hydrophilic’ surfaces. Quantitative definition of the relative terms hydrophobic and hydrophilic will be found from the surface force work. Utility of water contact angle as expressed in terms of water adhesion tension \( \tau^0 = \gamma^0 \cos \theta \) (where \( \gamma^0 \) is water interfacial tension = 72.8 dyn/cm) will likewise become evident and, by comparison, parameters computed from various theories, such as ‘surface free energy’ \( \gamma_s \) and Zisman’s critical surface energy \( \gamma_c \) will be shown to have limited predictive utility. Finally, specific examples selected from the biomaterials literature will be correlated with water structure and reactivity at surfaces. These examples will be drawn from a broad spectrum of in vitro experimental observations including protein adsorption, contact activation of the blood plasma coagulation cascade and the attachment of mammalian and microbial cells to surfaces; all toward illustrating the controlling effect of water on biology at surfaces.

2. Molecular self association

Self association of molecules in the liquid state results from so-called polar interactions between molecules. Fowkes identified these interactions as Lewis acid–base interactions (including hydrogen bonding, hereafter termed ‘Lewis sites’) in his seminal article on the subject of interfacial interactions between self-associated polar liquids published shortly before his death in 1990 [7], although Dolezalek first introduced the concept of molecular association in 1908 [8] and
connections between molecular association and Lewis acid–base theory can be found in the literature as early as 1920 [9] shortly after G.N. Lewis articulated his theory of atomic bonding in 1916 (see reference [10] for an excellent review of acid–base interactions with surfaces). But it was Fowkes and coworkers who clearly identified molecular association as the driving force behind surface and interfacial tensions and the governing factor that controls solubility, heats of mixing, heats of adsorption and chemical shifts observed in infrared and NMR spectra [11–13]. Clearly, molecular association has rudimentary importance in surface and colloid science and, by extension, great importance in biomaterials surface science.

Molecular association is chemically specific to the acid–base interactions involved between molecules in solution or between solution-phase molecules and a surface. There must be both a Lewis acid and base present for polar interactions to influence interfacial phenomena. An example cited in Fowkes’ article is that of a tertiary amine, one of the strongest of organic bases. Since tertiary amines have no acidic sites, self-association between these molecules does not occur and surface tension of these liquids is consequently controlled by van der Waals (dispersion force) interactions alone. On the other hand, tertiary amines can interact strongly with acidic sites on surfaces.¹

Chemical specificity of molecular association is the undoing of popular theories aimed at computing (from contact angles) a ‘surface free energy’ γ for solid surfaces that propose an interfacial combining rule for acid–base interactions based on root-mean-square analogs to the combining rule used for dispersion forces operating across interfaces invented by Fowkes [14]. These simple combining rules fail to properly account for the chemical specificity (heats of reaction) in acid–base interactions. Surface free energy (also termed surface tension component) and equation-of-state (EoS) theories are under attack on experimental [15,16] and rigorous theoretical grounds as well [10,17–25], to the point of being dubbed ‘disposable theories’ [17]. For the biomaterials practitioner, all of the mania over interpreting contact angles is nothing more than a divestiture as it has been pointed out that wetting parameters, such as γ and γ, are not, in any event, biomedically relevant [4]. It will be shown in Section 2.1.4 that surface energy and interfacial component theories do not correlate with the structure and reactivity of water as resolved by the surface force apparatus nor do limits on these surface energy parameters agree sensibly with measured water contact angles. Failure of these earlier wetting has prompted a call for improved methods for predicting interfacial properties [16] and some new theoretical developments that specifically include molecular association effects have come forward [26].

2.1. Self association in water and structure of the aqueous interface

Self association in water is especially important because water can form a

¹Fowkes distinguished between self-associated and non-self-associated states based miscibility in squalane rather than water. Self-associated substances may be either soluble or insoluble in water.
more-or-less ordered three-dimensional (3D) hydrogen-bonded network. This special property of water, which is quite unlike most other self-associating molecules that can form only bimolecular associations, has been recognized since the early 1900s [9,27] and has been under continuous investigation ever since [28–32].

The importance of this propensity to form a 3D network is that localized perturbations in water chemical potential can induce compensating changes in solvent properties that can propagate through the network considerable distances from the point of origin of the perturbation. Small changes in chemical potential can thus promote considerable changes in water properties, as has been elegantly demonstrated in studies of lipid bilayers [33]. Evidence for this self-associated structure (water structure) is derived from a wide variety of experimental observations that have been the source of a continued debate in the history of science that can be traced back nearly two centuries. The following subsection capsulizes this history for the interested reader.

Section 2.1.2 relates water self association to the hydrophobic effect, surface hydrophobicity and hydrophobic forces. Section 2.1.2.1 and Section 2.1.2.2 extend discussion of these relationships with somewhat more physical–chemical detail. It is concluded that self association is a primary driver of each of these physical phenomenon. Experimental results selected from the recent colloid literature will be summarized and discussed within the context of self association in Section 2.1.2.3 and Section 2.1.2.4; one involving measurement of surface forces and the other equilibrium thickness of condensate water films on quartz by measured ellipsometry. These latter two studies frame a picture of water structure and reactivity at surfaces that will be correlated with the biological response to materials in Section 3.

2.1.1. A brief history of water structure and reactivity at surfaces

Fig. 1 capsulizes, in time-line form, the history of the structured-water concept as it applies to forces across interfaces. The intent of Fig. 1 is to provide a sense of the scientific activity in the area but is by no means comprehensive; readers with historical interest are directed to Franks for more detail [34]. Entries to Fig. 1 were more-or-less arbitrarily selected for the purposes of this review from an enormous volume of work that, as noted by Ninham [35,36], ultimately originates in the force-at-a-distance concept that has been a subject of discussion by founding principals, such as Newton, Poisson and Clerk Maxwell. These eminent scientists were concerned with the veracity of continuum theories proposing that the propagating medium between interacting objects is uniform and non-active.

Thinking of water as a continuum medium implicitly or explicitly pervades modern thinking too, not only by surface and colloid scientists, but also biomaterial scientists. In the biomaterials literature, one frequently finds, almost universally in fact, that the aqueous phase with dissolved proteins is regarded as a simple, neutral carrier of biology that does not interact with surfaces [3,4]. This is clearly an extreme, unwarranted simplification of biology at surfaces that runs afoul of the most basic laboratory observation that the biological response to water-wettable surfaces is quite different to the biological response to poorly-water-wettable
surfaces. For example, as will be discussed further in Section 3, blood coagulates (clots) rapidly in contact with clean, water-wettable glass tubes whereas the clotting process is quite slow in poorly-water-wettable plastic tubes [37]. Clearly behavior of water at these surfaces cannot be summarily dismissed as it is this very behavior that, in an as-yet poorly defined way, defines the surface property ‘hydrophobic’ or ‘hydrophilic’. Quoting Ninham [36], ‘We tend to regard an intervening medium as an annoying complication and by a process of sympathetic magic, sweep the whole mess into an effective vacuum or uniform continuum wherein, in truth, sits all of the interesting physics’.

Sometimes the importance of water structure and reactivity is explicitly acknowledged by biomaterial scientists [38]; but then these same scientists promote use of surface energy parameters, such as Zisman’s critical surface energy $\gamma_c$ [39] for biomaterials applications [40], even though $\gamma_c$ is determined with a series of (organic) liquids that only sometimes includes water and therefore cannot effectively measure water structure and reactivity at biomaterial surfaces. We will return to this and related points in Section 2.1.4.

Moving forward on the time line of Fig. 1, the 1910 Faraday Society symposium was dedicated to the structure of water [41]. By 1927 a review on the structure of water appeared in Chemical Reviews [27], referring to work by luminaries, such as Lowry, Nernst, Raoult, Röntgen and Langmuir. In this same time frame, Langmuir was developing concepts that dealt with a 3D interphase separating a solid surface...
from bulk solution by collapsing it into a 2D interface dominated by short-range effects associated with molecular interactions and packing along the interface, choosing to ignore long-range force-over-distance, especially electrostatic contributions [36,42]. This concept will be discussed in more detail relative to the approach of Gibbs in Section 2.1.3.

Later, in the middle 1930s before World War II, Derjaguin and coworkers in the Russian schools of surface science developed the disjoining pressure concept that attempted to explicitly account for structural (and other) effects of the medium (water) in surface and colloid interactions [43–54]. It is interesting that DLVO theory, perhaps first formalized in Verwey and Overbeek’s seminal work ‘Theory of Stability of Lyophobic Colloids’ [55], did not include disjoining pressure and stands as the consummate continuum theory that does not speak to structural aspects of the medium separating two objects. However, DLVO theory establishes the magnitude of interacting forces between objects in a continuum medium. It is the forces measured over-and-above that anticipated by DLVO that provides very strong evidence for the structural effects in water [55] that disjoining pressure attempts to accommodate. The disjoining pressure concept serves as a basis for some of the modern theories of wetting [56,57].

Many imaginative experimental schemes to measure the disjoining pressure and water structure ensued development of the disjoining pressure idea, especially with respect to thermal anomalies in surface effects [58], and the rate of literature contributions on the subject takes on a noticeable up-turn in this era.

Interest in water structure was not isolated to the surface and colloid science arena. As briefly reviewed by Wiggins (see citations in [59,60]), claims of ordered or structured cytoplasmic water appeared as early as 1956 to account for preferential accumulation of ions within cells. It is of interest to compare and contrast scientific points of view between physical and biological scientists in this regard, especially with respect to ion distribution in structured water, because divalent ions, such as calcium and magnesium that have potent allosteric effects on enzyme function. These aspects will be discussed in more detail in Section 2.1.2.5.

Another major review on the subject of water structure entitled ‘The Depth of the Surface Zone of a Liquid’ appeared in 1949 [61], after which the volume of scientific investigation into water structure and reactivity again increases considerably, culminating in the infamous polywater incident, probably precipitated by Anisimova et al. [62]. Water polymerization was not a new concept to Anisimova, having an appearance in 1920-vintage chemical literature [27], but the isolation of a water polymer grown from bulk water in fine capillaries certainly was. Polywater, finally traced to silica impurities, was a startling discovery that found its way into the popular press in a manner not unlike the contemporary cold-fusion episode.

Following the polywater incident there is a noticeable down-turn in the literature on the subject of water structure, undoubtedly due to the unpopularity of the subject within the surface and colloid science community. Now and again, however, polywater receives some attention in contemporary literature [63], usually aimed at a better understanding of the origin of the fracas. Franks’ comprehensive treatise
on water [64] effectively captured the state of affairs in water research up to late 1970.

Some aspects of modern work on water structure as it applies to understanding the biological response to material surfaces is discussed in the following sections.

2.1.2. The hydrophobic effect, surface hydrophobicity and hydrophobic forces

Mixed in to the work on water structure and reactivity outlined in Fig. 1 are subjects related to the solvent properties of water; the hydrophobic effect, surface hydrophobicity and hydrophobic forces. The hydrophobic effect refers to the sparing solubility of non-polar solutes (hydrocarbons) in water, originally and erroneously attributed to strong self-association of hydrocarbon molecules (the like-likes-like rule) [65,66]. The hydrophobic effect is now properly understood as a phenomenon dominated by the strong self association of water molecules that excludes association with, and solubilization of, non-polar solutes [65,67–69]. In Hildebrand's words '...there is no hydrophobia between water and alkanes; there only is not enough hydrophilia to pry apart the hydrogen bonds of water so that the alkanes can go into solution without assistance from attached polar groups' [70].

By contrast, surface hydrophobicity (water non-wettability) seems less well understood, especially in biomaterials science, even though self association dominates water wettability too [7]. In my opinion, this lack of clarity is generally due to the complicating factors in biomaterials mentioned in the introduction of this writing, more specifically associated with the confusion introduced by surface energy parameters mentioned in Section 2.1 and directly attributable to widespread application of relative terms, such as 'hydrophobic' or 'hydrophilic' with no widely-accepted reference standard.

In the same sense that the hydrophobic effect is predominately due to self association of water molecules, so too is surface hydrophobicity predominately due to the state of water self association in contact with a non-polar surface. Taking liberties with the previously-quoted statement of Hildebrand, there is no hydrophobia between water and hydrocarbon surfaces; there only is not enough hydrophilia to pry apart the hydrogen bonds of water (disrupt water self association) so that water can wet the surface without assistance from attached 'polar groups' (Lewis sites).

Water structure at surfaces is a manifestation of surface hydrophobicity. Or looked at from another perspective, hydrophobicity is a manifestation of water structure at surfaces. Apparently then, analytical measures of hydrophobicity must come from techniques that directly probe water structure rather than those that simply respond to water structure, such as contact angle and wettability (tensiometry). Measurement of surface forces is one such approach to quantifying hydrophobicity, as will be disclosed in Section 2.1.2.3. As background for surface force work, the phenomenon of surface hydrophobicity and the relationship to water self association will first be discussed from a qualitative thermodynamic perspective (Section 2.1.2.1) and then extended through a more rigorous theory of wetting (Section 2.1.2.2).
2.1.2.1. *Chemical potential of water near polyelectrolytes and surfaces.* Wiggins has argued that the osmolarity of water in a compartment near a dissolved polyelectrolyte is necessarily greater than that of a compartment of water distant from the polyelectrolyte because the distribution of counter ions is not uniform throughout the bulk solution, but rather localized around each polyelectrolyte molecule [60]. Indeed, it is osmotic pressure in balance with electrostatics that forms the counter charge ‘atmosphere’ around polyelectrolytes in solution [71].

At constant temperature, pressure and mole fraction of components, the only degree-of-freedom available to equilibrate chemical potential of water between compartments in such a system of solvated polyelectrolytes is adjustment of water partial molar volume or, equivalently, water density. Thus, this line of reasoning conjures up the notion of contiguous regions of varying water density. Near the polyelectrolyte, where the osmolarity is high and water activity low, chemical potential of water is increased by collapsing the hydrogen bonded network in a manner that decreases partial molar volume (increases water density). Conversely, chemical potential of water in a compartment of water distant from the polyelectrolyte is decreased by expanding the hydrogen-bond network in a manner that increases partial molar volume (decreases water density).

The same logic applies to surfaces as well. Water near a non-polar surface is at high interfacial energy and equilibrates chemical potential with bulk water by increasing partial molar volume. Presumably, water accomplishes this by forming a more complete 3D-network of self-associated molecules near the surface than occurs in bulk water as illustrated in Fig. 2. Wiggins refers to this water as ‘stretched’ water and its occurrence at non-polar interfaces has been confirmed by vibrational sum frequency generation (VSFG) spectroscopy [72]. Thus, self association of water is promoted at purely non-polar surfaces where surface–water interactions are dominated by dispersive (van der Waals) forces, yielding an extended or open water structure at lower density than bulk water. Interestingly, such a water structure requires that the hydrogen-bond network of water directly adjacent to a non-polar surface is interrupted, yielding ‘dangling hydrogen bonds’. These dangling hydrogen bonds have been theoretically predicted [73] and recently spectroscopically resolved from hydrogen bonds in bulk water [32,74,75]. Conversely, the hydrogen-bond network of water near a surface bearing Lewis sites that can compete with self association is collapsed, increasing chemical potential in a manner that accommodates decreased interfacial energy (Fig. 2). Based on these arguments, one might expect that the degree of self association scales in proportion to the surface density of Lewis sites on a water-contacting surface and that local density of water scales with water wettability. In fact, this expectation is a prediction of modern wetting theory that incorporates disjoining pressure, as discussed below, and a rationalization of the origin of hydrophobic forces described in subsequent subsections.

2.1.2.2. *Theory of wetting.* Churaev has recently reviewed the state of modern wetting theory toward prediction of contact angles on solid surfaces [56]. Structural force contributions are explicitly included through the disjoining pressure concept
Fig. 2. Two dimensional projection of water at or near (A) water-wettable (hydrophilic) and (B) poorly-water-wettable (hydrophobic) surfaces illustrating the hypothetical state of self association (water structure; extensively adapted from [60]). Note that interactive Lewis sites on the hydrophilic surface (indicated by the lattice site array) competes with water self association leading to a more dense (relative to bulk water) region near the surface. By contrast, water at the hydrophobic surface bearing no competing Lewis sites forms a region less dense than bulk water.

[47,49,54,76–78]. Disjoining pressure essentially measures the change in total chemical potential of water in the adsorbed state as a function of thickness [79] and can therefore be related to the qualitative thermodynamic arguments discussed in Section 2.1.2.1.

In brief summary, Churaev attributes high contact angles (poor water wettability) on hydrocarbon surfaces to water structuring and finds that water structure at modestly-wettable surfaces within the approximate range of contact angles $40^\circ > \theta > 15^\circ$ ($7 > \tau^\circ > 56$ dyn/cm) is not too different from bulk-water structure. Water structure is greatest (relative to bulk water) at poorly-water-wettable surfaces and disappears as water contact angles decrease below approx. $40^\circ$ ($\tau^\circ = 56$ dyn/cm). Said another way, increased surface density of Lewis sites on a surface erodes water structure by competing with self association. At still more wettable surfaces
with $\theta < 15^\circ$, Churav predicts a water structure associated with 'hydrophilic structural forces', possibly related to the repulsive forces observed between opposing wettable surfaces brought into close proximity in water using the surface force apparatus (see Section 2.1.2.3).

The experimental example cited in Churav's review is that of a methylated quartz. It is observed that water contact angles on these surfaces gradually increase with modest methyl-group surface coverage, after which contact angles increase to approx. $\theta_{\text{adv}} = 88^\circ$ ($\tau^0 = 25$ dyn/cm) at 72% coverage [80].\(^2\) These contact angle results are illustrated in Fig. 3A and translated into water adhesion tension in Fig. 3B. Churav notes that contact angles on methylated quartz change even though the total dispersion and electrostatic force contributions to wetting remain essentially unchanged due to surface methylation. In other terms, even though changes in DLVO-type interactions (continuum theory) due to silanization are insignificant, contact angles increase significantly due to water structuring at poorly-wettable surfaces.

It is interesting that $\tau^0$ scales linearly with surface methylation over a wide dynamic range of water wettability, as has been observed with surface oxidation of polystyrene [4]. We will return to Fig. 3 in Section 2.1.4.

2.1.2.3. Surface forces. One of the surprising observations arising from the surface force apparatus is that of long-range (< 100 nm) attraction between opposing hydrophobic surfaces immersed in water, over-and-above that anticipated by DLVO. These so-called 'hydrophobic forces' are observed to decay exponentially in separation distance $h$ with a characteristic decay length $D_o$ having the form $\exp(-h/D_o)$. On occasion, surface force data are fit with the sum of two exponential decays\(^3\) [$\exp(-h/D_1) + \exp(-h/D_2)$], where $D_1$ is the characteristic decay length of short-range forces (typically less than 1 nm) and $D_2$ is the characteristic decay length of longer-range forces (typically not greater than 40 nm). However interpreted, the origin of hydrophobic forces has been a mystery since the initial observations were made by Israelachvili and Adams [84,85]. Recent theoretical progress traces the origin of these forces to localized changes in water structure [86,87], specifically water density, in general agreement with expectations based on the qualitative thermodynamic arguments discussed in Section 2.1.2.1.

The left-hand ordinate of Fig. 4 collects one set of experimental observations of surface forces measured by Yoon et al. using a modified atomic force microscope (AFM) [88]. In these elegant experiments, a silane-treated glass sphere with a water contact angle\(^4\) $\theta = 109^\circ$ glued to the AFM tip was brought into close contact.

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\(^2\)Similar observations have been made using surfaces with controlled chemical heterogeneity [81,82] prepared for the analysis of contact angle hysteresis, but the sensitivity of advancing contact angles to relatively low surface density of hydrocarbon monolayers was not interpreted in terms of water structure in these reports.

\(^3\)A practice apparently introduced by Christenson et al. [30]. Power laws have also been suggested [83].

\(^4\)Data were reported as 'equilibrium' contact angles and not identified as either advancing or receding.
Fig. 3. (A) Water contact angles $\theta$ on partially methylated quartz surfaces increase with surface coverage of trimethyl silane (TMS) groups. (B) Water adhesion tension $\tau^*$ decreases linearly with TMS surface coverage.

(in pure water$^5$) with a silica plate made more-or-less water wettable by silanization. Either attractive (hydrophobic) or repulsive (hydration) forces, over-and-above that anticipated by DLVO, were measured depending on the water wettability of the silica plate. Data abstracted from Yoon’s work is collected in Table 1 wherein the wettability of the silica plate reported by Yoon et al. as $\theta$ values have been converted to water adhesion tensions $\tau^* = \gamma^* \cos \theta$ using $\gamma^* = 72.8$ dyn/cm for pure water.

It is interesting that $D_o$ decays linearly with $\tau^*$ over a range $40 < \tau^* < 30$ dyn/cm as $D_o = (-0.544 \pm 0.027)\tau^* + 18.12 \pm 0.41$ ($R^2 = 98.74\%$). Somewhere

$^5$It is important that no ions were added to the water phase; see Section 2.1.2.5.
Table 1
Characteristic decay length from surface force measurements [88]

<table>
<thead>
<tr>
<th>Plate $\theta$ (°)</th>
<th>$D_o$ (nm)</th>
<th>$\tau^o$ (dyn/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>72.8</td>
</tr>
<tr>
<td>75</td>
<td>9</td>
<td>18.8</td>
</tr>
<tr>
<td>83</td>
<td>12</td>
<td>8.87</td>
</tr>
<tr>
<td>92</td>
<td>20</td>
<td>-2.54</td>
</tr>
<tr>
<td>97</td>
<td>22</td>
<td>-8.87</td>
</tr>
<tr>
<td>100</td>
<td>25</td>
<td>-12.64</td>
</tr>
<tr>
<td>105</td>
<td>28</td>
<td>-18.84</td>
</tr>
<tr>
<td>109</td>
<td>32</td>
<td>-23.70</td>
</tr>
</tbody>
</table>

Fig. 4. Left-hand axis: monotonic decrease in the characteristic decay length of surface forces $D_o$ with water adhesion tension $\tau^o$ observed using an atomic force microscope (AFM) as a surface force apparatus ([88], see text for discussion). Note that extrapolation of the linear trend through attractive hydrophobic forces crosses $D_o = 0$ very close to the limit of detectable hydrophobic forces suggested by Berg et al. [89] noted as the 'Berg limit'. Right-hand axis: exponential-like increase in condensate film thickness formed from saturated water vapor on quartz surfaces with increasing $\tau^o$ [79].

Within the range $20 < \tau^o < 40$ dyn/cm attractive (hydrophobic) forces become repulsive (hydration) forces. Extrapolation of the linear trend to $D_o = 0$ suggests that hydrophobic forces are not supported on surfaces more wettable than $\tau^o = 33.7$ dyn/cm ($\theta = 62.4^\circ$), in close agreement with the $65^\circ$ limit estimated by Berg et al. [89] (see 'Berg limit' annotations in Fig. 4). This general trend seems evident in historical surface force measurements taken as a whole, as illustrated in Fig. 5 and summarized in Table 2, although a good deal of caution must be applied in
### Table 2
Characteristic decay lengths from literature disclosing surface wettability

<table>
<thead>
<tr>
<th>Surface type</th>
<th>(D_x) (nm)</th>
<th>Force</th>
<th>(\theta_{adv}) (°)</th>
<th>(\theta_{rec}) (°)</th>
<th>(\rho) (dyn/cm)</th>
<th>Reference</th>
</tr>
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<tr>
<td>Hydrophobic quartz</td>
<td>12</td>
<td>A</td>
<td>100</td>
<td>—</td>
<td>-12.6</td>
<td>[53]</td>
</tr>
<tr>
<td>PFG</td>
<td>16</td>
<td>A</td>
<td>113</td>
<td>60</td>
<td>-28.4</td>
<td>[91]</td>
</tr>
<tr>
<td>DDOA</td>
<td>13</td>
<td>A</td>
<td>93</td>
<td>60</td>
<td>-3.8</td>
<td>[92]</td>
</tr>
<tr>
<td>DDOA</td>
<td>5.5</td>
<td>A</td>
<td>94</td>
<td>70</td>
<td>-5.1</td>
<td>[93]</td>
</tr>
<tr>
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<td>12.2 ± 1</td>
<td>A</td>
<td>100</td>
<td>80</td>
<td>-12.6</td>
<td>[54]</td>
</tr>
<tr>
<td>Mica</td>
<td>1 ± 0.2</td>
<td>R</td>
<td>3.2</td>
<td>-</td>
<td>72.7</td>
<td>[95]</td>
</tr>
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<td>R</td>
<td>3.2</td>
<td>-</td>
<td>72.7</td>
<td>[96]</td>
</tr>
<tr>
<td>LB amphiphile (up stroke)</td>
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<td>A</td>
<td>94</td>
<td>-</td>
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<td>[97]</td>
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<td>1.57</td>
<td>R</td>
<td>0</td>
<td>0</td>
<td>72.8</td>
<td>[98]</td>
</tr>
<tr>
<td>DHDDA</td>
<td>1.4</td>
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<td>95</td>
<td>-</td>
<td>-6.3</td>
<td>[99]</td>
</tr>
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<td>96</td>
<td>66</td>
<td>-7.6</td>
<td>[100]</td>
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<td>82</td>
<td>69</td>
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<td>A</td>
<td>96</td>
<td>75</td>
<td>-7.6</td>
<td>[103]</td>
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<tr>
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<td>16</td>
<td>A</td>
<td>113</td>
<td>60</td>
<td>-28.4</td>
<td>[104]</td>
</tr>
<tr>
<td>DDOA</td>
<td>13</td>
<td>A</td>
<td>93</td>
<td>50</td>
<td>-3.8</td>
<td>[105]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>32</td>
<td>A</td>
<td>109</td>
<td>-</td>
<td>-23.7</td>
<td>[106]</td>
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<td>Glass–silica</td>
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<td>A</td>
<td>100</td>
<td>-</td>
<td>-12.6</td>
<td>[107]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>10</td>
<td>A</td>
<td>92</td>
<td>-</td>
<td>-2.5</td>
<td>[108]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>2</td>
<td>R</td>
<td>81</td>
<td>-</td>
<td>11.4</td>
<td>[109]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>0.4</td>
<td>R</td>
<td>0</td>
<td>-</td>
<td>72.8</td>
<td>[110]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>21.7</td>
<td>A</td>
<td>116</td>
<td>-</td>
<td>-31.9</td>
<td>[111]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>18.8</td>
<td>A</td>
<td>115</td>
<td>-</td>
<td>-30.8</td>
<td>[112]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>16.6</td>
<td>A</td>
<td>105</td>
<td>-</td>
<td>-18.8</td>
<td>[113]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>20.5</td>
<td>A</td>
<td>95</td>
<td>-</td>
<td>-6.3</td>
<td>[114]</td>
</tr>
<tr>
<td>Glass–silica</td>
<td>16.4</td>
<td>A</td>
<td>88</td>
<td>-</td>
<td>2.5</td>
<td>[115]</td>
</tr>
<tr>
<td>DDOA</td>
<td>4.5</td>
<td>A</td>
<td>94</td>
<td>-</td>
<td>-5.1</td>
<td>[116]</td>
</tr>
<tr>
<td>FSL2</td>
<td>19</td>
<td>A</td>
<td>110</td>
<td>90</td>
<td>-24.9</td>
<td>[117]</td>
</tr>
<tr>
<td>Silanized glass</td>
<td>5.6</td>
<td>A</td>
<td>98</td>
<td>80</td>
<td>-10.1</td>
<td>[118]</td>
</tr>
</tbody>
</table>

Decay lengths \(D_x\) are either \(D_1\) from single exponential fit or \(D_2\) from summed exponential fit to data corresponding to attractive (A) or repulsive (R) forces with estimated error listed where provided in original citation.

PFG, perfluoroglutamate; DDOA, dimethyldioctadecyl ammonium bromide; DHDDA, dihexadecyl(dimethylammonium acetate; FSL2, fluorinated silane; HADMOA, \(\omega\)-(hydroxyalkyl)dimethyloctadecyl ammonium bromide.

comparison of results from so many investigators over two decades of intermolecular force research.

An interpretation of the above results within the context of the preceding Section 2.1.2.1 and Section 2.1.2.2 is that water captured between the poorly-water-wettable glass sphere and silanized silica plate (both at \(\theta = 109^\circ\)) forms a 'stretched' (in the words of Wiggins) or open self-associated 3D network that propagates an attractive force between these surfaces in the manner described by
Fig. 5. Collage of characteristic decay lengths $D_o$ collected from intermolecular force literature spanning more than 15 years that disclose water contact angles of opposing surfaces (here converted to water adhesion tension $\tau^\circ$, see Table 2 for further details). Note that the generalized data trend suggested by the shaded region is in qualitative agreement with that illustrated in Fig. 4 wherein attractive hydrophobic forces were observed only between surfaces with $\tau^\circ < 20$ dyn/cm. ‘Berg limit’ annotations are reproduced from Fig. 4.

Yaminsky et al. [86,87]. Reduction of water chemical potential in response to increased interfacial energetics is the driving force for increased molar volume (decreased density) as water attempts to equilibrate with surrounding bulk water. Water-interactive Lewis sites on the silica plate (decreased degree of silanization with corresponding increased water wettability $\tau^\circ$) competes with self association in a manner that degrades the open 3D structure, increases water density within the interphase between opposing surfaces and decreases hydrophobic attractive forces. This trend progresses linearly with $\tau^\circ$ until water structure within the interphase is not different from that within the surrounding bulk water, which occurs at or near the ‘Berg limit’ $\tau^\circ = 30$ dyn/cm. These experimental results are in qualitative agreement with Churaev’s theoretical predictions discussed in Section 2.1.2.2.7 Further interpreted in terms of Fig. 3, it is apparent that the self association of water that drives hydrophobic forces between surfaces immersed in

---

6Yaminsky and Ninham propose density fluctuations that propagate forces between opposing surfaces through ‘subcritical’ cavity formation. Other explanations of the hydrophobic force suggest a hydrodynamic propagation of forces between opposing surfaces through oscillating pressure fields (see [90] for discussion).

7Quantitative comparison of experiment with theory must account for the wetting asymmetry between the glass sphere and silica plate, possibly using the combining rules derived by Yoon et al. [88].
water is not defeated until approximately half of the surface is occupied by Lewis sites, as gauged from the approx. 50% methyl-group surface coverage occurring at the Berg limit. Thus, surface force measurements indicate that water in contact with surfaces structures itself to assure uniformity in chemical potential. This structuring increases with decreasing water wettability of the contacting surface, even though changes in the total dispersion and electrostatic force contribution to wetting are quite modest within the range $-40 < \tau^0 < 30 \text{ dyn/cm}$, as in the methylated quartz example cited by Churaev (see Section 2.1.2.2).

It is concluded that surface hydrophobicity is dominated by the state of water self association. Results from surface force investigations permit quantitative definition of the relative terms 'hydrophobic' and 'hydrophilic'. Hydrophobic surfaces are those that support hydrophobic forces and are less water wettable than the Berg limit ($\tau^0 < 30 \text{ dyn/cm}, \theta > 65^\circ$) whereas hydrophilic surfaces do not support hydrophobic forces and are more wettable than the Berg limit ($\tau^0 > 30 \text{ dyn/cm}, \theta < 65^\circ$).

2.1.2.4. Condensate films. The right-hand ordinate of Fig. 4 compares results of the work of Pashley and Kitchener [79] to the previously-discussed work of Yoon et al. In these carefully-performed studies, equilibrium thickness of 'condensate' water films grown from vapor onto crystalline quartz plates was determined by ellipsometry. Quartz surface wettability was controlled using rigorous cleaning, heat dehydroxylation and methylation. Data abstracted from the article of Pashley and Kitchener are collected in Table 3 wherein reported contact angles are converted to $\tau^0$ assuming $\gamma^0 = 72.8 \text{ dyn/cm}$. It is evident from Fig. 4 and Table 3 that very thick ($\leq 150 \text{ nm}$) water films are supported on fully-wettable quartz surfaces ($\tau^0 \rightarrow 72.8 \text{ dyn/cm}$). Water film thickness sharply decreases as surface water-wettability decreases ($18 < \tau^0 < 70 \text{ dyn/cm}$).

Condensate films are occasionally discounted as microdroplets, but this possibility has been eliminated by Pashley et al. Also, formation of thick condensate water films have been confirmed by other investigators [104], finding that the Kelvin equation correctly predicts the equilibrium vapor pressure of water confined in a wedge between fused silica surfaces, provided that condensate film thicknesses of the order reported by Pashley are taken into account. Thick water films cannot be silicic acid gels (as in the polywater caper) because there is no chemical or

<table>
<thead>
<tr>
<th>$\theta_{adv}$ (°)</th>
<th>$\tau^0$ (dyn/cm)</th>
<th>Condensate film thickness (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>72.8</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>68.4</td>
<td>11.0</td>
</tr>
<tr>
<td>40</td>
<td>55.8</td>
<td>7.0</td>
</tr>
<tr>
<td>75</td>
<td>18.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>
spectroscopic evidence that hydrated silicon oxides are much thicker than 1–2 nm [105–109]. Thus, Pashley and Kitchner provide seemingly incontrovertible evidence for multilayer water adsorption, corroborating work of others on the same subject extending back as far as 1887 (see citations in McHafie and Lenher [110]).

Water molecules in direct contact with fully-water-wettable quartz surfaces are adsorbed with an adhesion tension \( \tau^* = \gamma^0(\cos \theta^0) = 72.8 \text{ dyn/cm} \). Israelachvili points out that this bound water layer has little to do with water–water (self association) interactions at wettable surfaces but rather is completely dominated by surface–water (Lewis site) interactions [71]. It is this water–surface interaction that deprives bound-water molecules from a nearest-neighbor hydrogen-bonded association. Somehow both binding energy propagates into subsequent layers, supporting up to 150-nm thick, free-standing condensate films comprised of something of the order of 600 water molecules.\(^8\)

The mechanism of propagation favored by Pashley and Kitchner is long-range double-layer repulsion, although this mechanism was not interpreted in terms of water structure or state-of-association. Perhaps the condensate film is comprised of water-molecule-layers with alternating oriented dipoles like that described by Israelachvili [71,111] in which water molecules stack in an asymmetric or ‘staggered’ arrangement, with the surface-bound layer in a hydrogen-atom-down configuration (for a Lewis base surface, net dipole pointed up) and subsequent layers alternating dipole direction. Note that this hypothetical arrangement defeats water self association throughout the condensate film in a manner that would not permit propagation of hydrophobic forces through the formation of low-density, stretched water mentioned in the previous Section 2.1.2.3. This kind of water is consistent with the low-viscosity, high-density water formed by collapsing the hydrogen-bonded network as a means of increasing chemical potential in response to formation of a low-energy interface. This collapsed network is furthermore consistent with slip planes of water associated with oscillations in repulsive surface forces observed when water-wettable surfaces immersed in water are brought into close (< 2 nm) proximity [56,71,111–116].\(^9\)

It is interesting, in comparison to the surface force data discussed in the preceding section, that surfaces below the Berg limit supporting hydrophobic attraction (as measured by \( D_a \) on the left-hand axis) do not support condensate water films (as determined by ellipsometry on the right-hand axis).\(^10\) By contrast, thick condensate water films can be obtained on surfaces more wettable that Berg limit that support repulsive hydration forces. In this sense there is a convergence of experimental observations collected in Fig. 4 that speaks to at least two types of water structure and reactivity at surfaces.

Extending definitions derived in the preceding sections, hydrophobic surfaces are

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\(^8\)Assuming a nominal water-molecule diameter of 0.25 nm.

\(^9\)Slip planes are noted between hydrophobic surfaces as well [116].

\(^10\)More detailed interpretation of Fig. 4 in terms of water structure and reactivity must account for the fact that water is captured between two objects in close proximity in the surface force experiments whereas the condensate films are freely formed against nearly saturated water vapor.
those that support hydrophobic forces but not formation of condensate water films. Hydrophobic surfaces are less water wettable than the Berg limit (\(\tau^0 < 30\ \text{dyn/cm, } \theta > 65^\circ\)). Hydrophilic surfaces do not support hydrophobic forces but support formation of condensate water films and are more wettable than the Berg limit (\(\tau^0 > 30\ \text{dyn/cm, } \theta < 65^\circ\)).

The subject of repulsive 'hydration' forces between wettable surfaces cannot be passed by without mention of the debate in the literature regarding structured water-of-hydration that arose in the early 1990s [117]. This interlude is warranted here not only because it is a thread in the fabric of scientific history but also because the controversy seems to have prompted very valuable investigation into the state of hydration of ions at surfaces, as will be discussed in the following Section 2.1.2.5. Hydration water structure has been advocated as an explanation of osmotic stress measurements between lipid bilayers, DNA helices and linear polysaccharides [33,118–123]. Others insist there is no evidence for a special water structure responsible for repulsive hydration forces [71,124,125], preferring instead a mechanism related to osmotic forces between molecular chains protruding from opposing molecularly-rough surfaces (such as lipid bilayers) or the state of hydration of adsorbed ions on opposing molecularly-smooth surfaces (such as sheets of mica).

2.1.2.5. Ion solvation. The Hofmeister or lyotropic series that orders strength of ionic binding to surfaces and polyelectrolytes as a function of molecular size is related to the solvation of ions in water. In turn, ionic solvation has long been associated with structuring of water around ions in a manner that has been classified as 'structure promoting' or 'structure breaking'. Structure-promoting ions are those that impose more local order in surrounding water (presumably more self associated) than occurs distant from the ion whereas structure-breaking ions increase local disorder and mobility of adjacent water molecules (see, for example, Wiggins [59] and citations therein). Detailed explanation of the liquid-phase physics underlying the lyotropic series has remained a mystery ever since the relationships between anion type and precipitation of proteins were observed by Hofmeister in 1888 [126]. However, recent theoretical advances by Ninham and Yaminsky that specifically couple double-layer and van der Waals forces, as opposed to employing the simple additivity assumption of classical theory, seem to naturally predict consequences of the lyotropic series [127].

The lyotropic series manifests itself in repulsive surface forces measured against opposing water-wettable mica surfaces, as has been reviewed by Israeličvili

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\(^{11}\)The terminology 'hydrophobic structure' and 'hydrophilic structure' has also been applied (see, for example, Lyklema [69]).

\(^{12}\)On the other hand, attractive hydrophobic forces are not observed to be strongly influenced by electrolyte composition (at least within \(h < 10\ \text{nm}, [59,128]\), which is taken as evidence that hydrophobic forces do not have an electrostatic origin [92,116,129]. The weak effect of electrolytes on the hydrophobic force may be related to the connections between double-layer and van der Waals forces described by Ninham and Yaminsky [127].
[116,130]. Briefly summarizing, it is found that whenever proton H\(^+\) or oxonium ions H\(_2\)O\(^+\) (Lewis acids) saturate Lewis base sites on mica surfaces brought into close proximity in water, measured surface forces are exactly those predicted by DLVO, with no additional force contribution over a full range of separations up to and including contact. In the presence of 1:1 or 2:1 chloride electrolytes, however, repulsive forces are measured above critical concentrations characteristic of the cation type that follow the order of ionic hydration (the lyotropic series; Cs\(^+\) < K\(^+\) < Na\(^+\) < Li\(^+\) < Ca\(^{2+}\) ≈ Mg\(^{2+}\)). This effect is rationalized on the basis that repulsive forces occur between partially-dehydrated, surface-adsorbed ions on opposing water-wettable surfaces.\(^\text{13}\) The more strongly-hydrated ions (Li\(^+\), Ca\(^{2+}\), Mg\(^{2+}\)) adsorb to ionic surfaces less readily than poorly-hydrated ions (Cs\(^+\), K\(^+\), Na\(^+\)) and require higher concentration to effectively displace protons on surface sites. The 1:1 electrolytes promote repulsive hydration forces and prevent adhesive contact between surfaces. On the other hand, Ca\(^{2+}\) and Mg\(^{2+}\) are so highly hydrated that these ions are always displaced and permit adhesive contact between opposing surfaces.

It seems reasonable to expect that ion adsorption to hydrophilic surfaces from a mixture of aqueous 1:1 and 2:1 electrolytes will discriminate against Ca\(^{2+}\) and Mg\(^{2+}\) because these ions are highly solubilized relative to 1:1 electrolytes that are consequently more readily adsorbed.\(^\text{14}\) Said in other terms, Ca\(^{2+}\) and Mg\(^{2+}\) are preferentially solubilized in water against hydrophilic surfaces, possibly because of the ready-availability of free hydrogen bonds in the collapsed hydrogen-bond network that putatively occurs in water against hydrophilic surfaces. A lemma to this proposition is that monovalent cations are better solubilized in the more self-associated water that occurs against hydrophobic surfaces.

Wiggins and coworkers provide compelling evidence for such a selective partitioning of ions between regions of water at different densities (degrees of self association). These studies were based on membrane studies that rediscover the lyotropic series through a route completely different than surface force investigations [59,60,132–135]. In Wiggins' work, enzyme function was used as a reporter of local environment in hydrated membranes which was, in turn, interpreted in terms of local water structure.

Thus, from two points of view and literature sources, it seems evident that local solvent properties of water vary with the wettability of the contacting surface and produce gradients in ion chemistry within the interphase separating bulk solid and bulk solution phases. These interfacial gradients can have dramatic biological consequences, especially for the 2:1 cations that exhibit potent allosteric effects in enzyme function. Activation of the blood plasma coagulation cascade by water-wettable surfaces is one possible example of this effect that will be discussed in Section 3.2.

\(^{13}\)Some details of this rationalization are disputed in recent studies of repulsive forces in Al\(_2\)O\(_3\) slurries at high ionic strengths [131].

\(^{14}\)Anion type will profoundly influence the distribution of cations as well. The following discussion is focused on the relatively simplified system of a single anion type (chloride).
2.1.3. Structure of the aqueous biological interface

There seems to be two, unequally-populated schools of thought on the structure of biological interfaces within the biomaterials community and perhaps to a lesser extent in the general surface science community as well. One school is based on a paradigm that essentially regards the interface as a stagnant, 2D region in which solute molecules are irreversibly adsorbed to a solid surface by occupying lattice sites energetically favorable to adsorption. I will refer to this as a ‘Langmuirian’ paradigm because it emphasizes the short-range effects associated with molecular interactions and packing along an interfacial plane briefly mentioned in Section 2.1.1 in the context of the scientific history of water structure (see also the brief historical introduction in [42] for more discussion). Solvent is all but ignored in the Langmuirian paradigm along with structural effects.

The other school of thought in interfacial structure prefers a 3D interphase paradigm in which the region separating two bulk phases (e.g. solid and liquid) is comprised of continuously-changing component concentrations (activities) that can include adsorbate reversibly or irreversibly bound to the surface and a zone of solute enrichment near to, but not bound to the surface. I will refer to this to a ‘Gibbsian’ paradigm in deference to the interface construction introduced by J.W. Gibbs.15 Solvent is explicitly included in the Gibbsian paradigm.

The utility of any paradigm is that it provides an ordered means of thinking of complex subjects. Paradigms or models are frequently subtle in that the user may not be explicitly aware of the various assumptions and constructions of the paradigm. The paradigm is useful so long as it bears some relationship to the physical system under consideration. If, on the other hand, the paradigm is a poor representation of the physical system, or accurate only under an extreme set of boundary conditions, then this thought construct may be more than misleading; it can actually be quite destructive because of a human predilection to convert comfortable paradigms into dogma that is typically supplemented with a tendency to discriminate against alternative ideas.

Given all of the preceding discussion regarding changes in self association of water at surfaces, the Langmuirian paradigm seems grossly oversimplified and does not in any way account for variation in the solvent properties of water local to surfaces with differing water wettability. In my opinion, the Langmuirian paradigm has fallen into the destructive category, at least in biomaterials science where water is the universal solvent, because water is all but ignored (see Section 2.1.1); ‘dry-state’ chemistry as resolved in a surface spectrometer frequently regarded as

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15 It will be recalled that Gibbs regarded an interphase as a zone bounded by two parallel planes drawn somehow within opposing bulk phases between which all ‘excess’ deviations from bulk component activity, either positive or negative, are collected. Through the application of the Gibbs–Duhem equation, a boundary located somewhere within the interphase is determined at which all excess values are compared. This boundary is the Gibbs’ interface and associated excess quantities are expressed in per unit area of interface (e.g. pmol/cm²; see any good text on surface and colloid science [69,136]). Guggenheim is generally credited with the use of an interphase as a thermodynamic model of a surface region [137].
primary driver of biology at surfaces (not interfaces) [3,4]; and interfacial chemistry interpreted as a stable biofilm (see, for example citations in [138]) that can be frozen, dried, or otherwise randomly perturbed without dramatic structural consequences that renders the biofilm of limited relevance to the real circumstance.

The Langmuirian paradigm does not account for the fact that interfacial chemistry is created through physico-chemical interaction of the various interactive components, especially including water, and this interfacial chemistry does not exist if these components are separated or altered. A more accurate view of biomaterial interfaces recognizes that the primary biological response to a surface is formation of an interphase [139] that has dynamic structure associated with hydration, formation of water structure driven by self association and possibly solute (especially protein) adsorption in the circumstance of favorable interfacial energetics [140]. The Gibbsian paradigm readily embraces complexities of an aqueous interface [4].

2.1.3.1. The protein problem. A specific and important problem introduced into the biomaterials literature associated with widespread use of a Langmuirian paradigm is the confusion surrounding protein adsorption. Nearly a century of research has been invested into protein adsorption, probably beginning with observation of the adsorption of horse-blood serum proteins onto inorganic powders by Landsteiner and Uhlz in 1905 (see the brief historical review in [140,141]). This investment has been made because adsorbed protein, or lack thereof, has been widely thought to effectively mediate the biological response to materials.

The literature on protein adsorption is very controversial. Nearly every imaginable claim and counter claim can be found in print by reputable investigators. Some find a relationship between the affinity of protein for a surface and surface energy, others find no relationship whatsoever; here one finds evidence for only monolayer adsorption consistent with a Langmuir (or some modification thereof) isotherm, there others report multilayer adsorption; one investigator reports irreversibly-bound protein, another demonstrates adsorption reversibility (see, as examples, citations in [142]). Thus, for every yin there is seems an equally-compelling yang. Indeed, even the coarsest categorization of biomaterials into ‘fully-water-wettable’ and ‘not-fully-water-wettable’ fails to bring the protein adsorption picture into focus [143].

Some of this controversy in the protein adsorption literature can be traced to implicit or explicit use of a Langmuirian paradigm which leads investigators to use rinse-and-measure protocols\(^\text{16}\) that would be regarded as wholesale invasive under the Gibbsian paradigm. These protocols destroy the interphase region, essentially measuring only irreversibly-bound protein [146] and are thus rife with potential

\(^{16}\text{Certain radiometric, ellipsometric and surface spectroscopic protocols are typical examples wherein a surface is immersed in protein solution to permit adsorption for some time, rinsed to remove bulk solution and subsequently subjected to analysis for surface-bound adsorbate in the form of radioactively counts, thickness measurements, or characteristic peak intensity, respectively (see, as examples, [144–147]).}\)
artifacts that seriously compromise biomedical relevance of the work. Certainly these results introduce considerable confusion when compared to protein adsorption measurements obtained using non-invasive methods that measure both surface-bound protein and protein occupying the entire interphase region. Such techniques include ATR-IR [148,149], in situ ellipsometry [145,150], neutron reflectometry (NR, [106,151–153]), scanning-angle reflectometry [154,155], solution-depletion measurements [156–159], surface force measurements [145,160–163] and tensiometry [4,164–166] (the citations given here are arbitrarily selected from a burgeoning literature source).

Non-invasive techniques can provide direct measurement of interphase thickness. For examples, time-resolved fluorescence of dye-labeled bovine serum albumin (BSA, MW = 66 000 g/mol) adsorbed to silica surfaces clearly resolves a unique interphase region with thickness of the order of 100 nm [167], corroborating earlier (and less quantitative) fluorescence spectroscopy of unlabeled-BSA adsorption to polypeptide particles [168]. Using FTIR, Jeon et al. [169] measured an interphase thickness of 80 nm surrounding a polyurethane-coated internal reflection optical element immersed in a BSA solution (at physiologic concentrations = 4.5 g/100 ml or 682 μM), in close agreement with the 77 nm interphase thickness established for human serum albumin (HSA) at methylated silica determined by NR [151,152].17 NR results reported by Liebman-Vinson et al. [106] reveal an 8-nm thick interphase region between a HSA solution and a modestly water-wettable NH$_2$-terminated self-assembled silane monolayer supported on electronic-grade silicon wafers. No such interphase was resolved at a fully-water-wettable silicon-wafer surface, corroborating the expectation that water-wettable surfaces with strongly-bound water films (see Section 2.1.2.4) do not support protein adsorption (see Section 3.1) and suggesting that interphase thickness varies with water wettability. In situ ellipsometry detects interphase thickness at solid surfaces of the order of 4 nm for HSA on methylated silica at μM concentrations (see citations in Norde [174]) and up to 15 nm at the air–water interface for BSA [150]. Finally, the surface force apparatus has been used to measure forces between opposing mica surfaces immersed in 0.1% thrombin18 [163] and HSA solutions [145], finding a repulsive force onset at separations near 35 nm, suggesting an interphase thickness at a mica surface of 0.5 × 35 = 17.5 nm (see also citations in Leckband and Isaclachvili [175]).

The above-listed studies provide strong evidence for a Gibbsian interphase separating bulk solution and surface phases with thickness that varies with surface water wettability. Interphase protein can apparently be adsorbed in multilayers that are consistent with the interpretation of kinked protein adsorption isotherms frequently noted for proteins (see Norde [174] for further discussion).

Access to interphase thickness provides a means of converting surface concen-

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17These NR results were not corroborated by subsequent investigations that report adsorbed HSA thickness of less than 2 nm [105], seemingly inconsistent with known molecular dimensions [106,170–173] and the citations of this section.

18Thrombin is a proteolytic enzyme of the blood coagulation cascade.
trations (usually reported in units of mass per unit area) into an average interphase concentration. Focusing momentarily on the work reported by Jeon [169], 3.9 μg/cm² of BSA (59 pmol/cm²) in an interphase pool 80-nm thick corresponds to 7.4 mM, which is nearly an 11-fold increase over the 0.68 mM bulk solution concentration used in these studies. Similar interphase enrichments can be calculated from ATR-IR [176–179] and tensiometry studies using 100 nm as a nominal interphase thickness. As an example of the latter, I have reported a surface excess of approx. 100 pmol/cm² for HSA on silanized glass [4]. This corresponds to 10 mM interphase concentration of albumin adsorption, which is consistent with the results above. Interphase concentration for 3 μM HSA solutions against methylated silica examined by ellipsometry are reportedly [145] as high as 17 wt.% (2.6 mM or an 850-fold enrichment over bulk concentration), in general agreement with 6 mM BSA in a 12-nm interphase pool formed at the air–water interface (792-fold enrichment over 7.6 μM bulk concentration [150]).

Clearly, off-hand calculations such as these cannot be regarded as quantitative and more systematic experiments controlling surface, protein type and protein concentrations are called for so that one-for-one comparisons can be made. But evidence based on diverse techniques ranging from spectroscopy to surface force measurements reveals that interphase concentrations can be surprisingly large. A proteinaceous interphase must be a very viscous region.

2.1.4. Surface and interfacial energetics

One of the important inferences to be drawn from Fig. 4 is that water adhesion tension τ° = γ° cos θ scales with water structure as measured by the characteristic decay length D_v, thus recommending itself as the measure of water reactivity appropriate for aqueous phases. This recommendation should be welcome by the biomaterials community since water contact angles are relatively easy and straightforward to measure and do not require a series of contact angle measurements on the same surface with highly purified organic liquids. Importantly, adhesion tension requires no complex theories with hidden assumptions to apply. Unfortunately, τ° has received little emphasis in the biomaterials literature because of the continued and unnecessary fascination with a single, one-number-fits-all-occasions surface energy parameter [4]. Given the demonstrated value of adhesion tension, it is of interest to compare τ° to various surface energy parameters widely used in the biomaterials field. The following analysis of popular approaches to characterizing surface energy of materials is simple enough but, to my knowledge, has not appeared in print elsewhere.

2.1.4.1. Surface energy component theory. Fig. 6 plots the surface energy parameters γ and γ° calculated by Schakenraad et al. [180] from one of the surface energy component theories mentioned in Section 2 against water adhesion tension τ° for a series of polymers with widely varying water wettability (see annotations on Fig. 6). Table 4 collects contact angle data listed by Schakenraad along with computed values of γ and γ°. Contact angles have been converted to τ° = γ° cos θ using γ° = 72.8 dyn/cm in Table 4, which also lists spreading and growth indices.
Table 4
Surface energy of polymer surfaces and cell interactions [180]

<table>
<thead>
<tr>
<th>Surface</th>
<th>$\theta$ (°)</th>
<th>$\gamma$ (dyn/cm)</th>
<th>$\gamma_d$ (dyn/cm)</th>
<th>Spreading index (no serum)</th>
<th>Spreading index (w/serum)</th>
<th>Growth index (no serum)</th>
<th>Growth index (w/serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEP1</td>
<td>105</td>
<td>-18.8</td>
<td>18</td>
<td>17</td>
<td>0.44</td>
<td>0.15</td>
<td>0.26</td>
</tr>
<tr>
<td>FEP2</td>
<td>107</td>
<td>-21.3</td>
<td>19</td>
<td>18</td>
<td>0.41</td>
<td>0.19</td>
<td>0.33</td>
</tr>
<tr>
<td>PTFE</td>
<td>105</td>
<td>-18.8</td>
<td>21</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>0.50</td>
</tr>
<tr>
<td>SIL</td>
<td>100</td>
<td>-12.6</td>
<td>33</td>
<td>32</td>
<td>0.35</td>
<td>0.16</td>
<td>0.31</td>
</tr>
<tr>
<td>PAR</td>
<td>101</td>
<td>-13.9</td>
<td>39</td>
<td>39</td>
<td>0.25</td>
<td>0.15</td>
<td>0.34</td>
</tr>
<tr>
<td>PE</td>
<td>97</td>
<td>-8.9</td>
<td>39</td>
<td>37</td>
<td>0.4</td>
<td>0.15</td>
<td>0.99</td>
</tr>
<tr>
<td>PC</td>
<td>95</td>
<td>-6.3</td>
<td>47</td>
<td>42</td>
<td>0.34</td>
<td>0.55</td>
<td>0.33</td>
</tr>
<tr>
<td>PETU</td>
<td>77</td>
<td>16.4</td>
<td>53</td>
<td>40</td>
<td>0.62</td>
<td>0.15</td>
<td>0.32</td>
</tr>
<tr>
<td>PESU</td>
<td>77</td>
<td>16.4</td>
<td>53</td>
<td>40</td>
<td>0.42</td>
<td>0.24</td>
<td>0.63</td>
</tr>
<tr>
<td>PSU</td>
<td>86</td>
<td>5.1</td>
<td>55</td>
<td>44</td>
<td>0.61</td>
<td>0.3</td>
<td>0.32</td>
</tr>
<tr>
<td>PVF</td>
<td>75</td>
<td>18.8</td>
<td>56</td>
<td>42</td>
<td>0.41</td>
<td>0.2</td>
<td>0.34</td>
</tr>
<tr>
<td>PMMA</td>
<td>71</td>
<td>23.7</td>
<td>60</td>
<td>43</td>
<td>0.75</td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>TC PS</td>
<td>60</td>
<td>36.4</td>
<td>70</td>
<td>43</td>
<td>0.98</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>Glass</td>
<td>26</td>
<td>65.4</td>
<td>116</td>
<td>38</td>
<td>0.94</td>
<td>0.93</td>
<td>1.04</td>
</tr>
</tbody>
</table>

PTFE, polytetrafluoroethylene; SIL, silicone rubber; PAR, paraffin; PE, polyethylene; PC, polycarbonate; PETU, polyetherurethane; PESU, polyurethane; PVF, polyvinylidene fluoride; PMMA, polymethylmethacrylate; TC PS, tissue culture polystyrene.

for human-skin fibroblasts cultured on these materials in vitro (indices estimated from Figs. 2 and 4–5 of Schakenraad [180]). Cell growth parameters will be discussed in Section 3.3.

Focusing first on the general trends in Fig. 6, the total surface energy $\gamma$ increases sensibly with $\tau^o$, reflecting increasing surface density of water-interactive Lewis sites on the various polymeric substratum. It also seems reasonable that the dispersive component $\gamma_d$ dominates $\gamma$ at low water-wettability ($\tau^o < 0$ dyn/cm), presumably due to the exiguousness of Lewis sites on poorly-water-wettable polymers. But this is where the sensibility of Fig. 6 ends.

First, Fig. 6 seems 'shifted' relative to the expectations derived from the surface force apparatus shown in Fig. 4. Contribution of the dispersive component $\gamma_d$ levels off abruptly near $\tau^o = 0$ dyn/cm ($\theta = 90^o$), instead of near the Berg limit at $\tau^o = 30$ dyn/cm, suggesting that polymer surfaces exhibiting $\tau^o > 0$ dyn/cm are already hydrophilic.

Interpreted in terms of the methylated-quartz system presented in Fig. 3, this would imply that surface hydrophobicity is defeated at 72% surface coverage of methyl groups (as estimated from Fig. 3 near $\tau^o = 0$ dyn/cm) instead of the more reasonable 50% methyl-group coverage observed near the Berg limit.

The second disconcerting feature of Fig. 6 is that extrapolation of the $\gamma$ trend through the data range $0 > \tau^o > -22$ dyn/cm leads to the absurd conclusion that $\gamma = 0$ at $\tau^o = -30$ dyn/cm ($\theta = 115^o$); the expectation being that $\gamma = 0$ at $\tau^o = -72.8$ ($\theta = 180^o$). Thus, it is evident that surface tension components, based on erroneous theoretical arguments [17], do not scale with $\tau^o$ nor does $\gamma$ sensibly...
Fig. 6. Surface free energy $\gamma$ and $\gamma^d$ of selected plastics and glass computed from surface energy component theory compared to the water wettability of these surfaces expressed as water adhesion tension $\tau$. 'Berg limit' annotations are reproduced from Fig. 4. Note that extrapolation of the linear trend in $\gamma$ through the range $0 > \tau^o > -22$ dyn/cm leads to the irrational conclusion that $\tau^o = -30.2$ dyn/cm ($\theta = 115^\circ$) when $\gamma = 0$ dyn/cm. See text for more discussion.

correlate with measured surface forces. It must be concluded that previously-reported connections between cell adhesion and growth to $\gamma$ [180] are only fortuitous.

2.1.4.2. Zisman critical surface energy. Zisman noted that a plot of the cosine of the observed contact angle ($\cos \theta$) subtended by a series of organic fluids (and sometimes water) on a test surface against the interfacial tension $\gamma_{lw}$ of these fluids yielded linear trends (Zisman plots) that, when extrapolated to $\cos \theta = 1$ (perfect wetting limit), defined a parameter $\gamma_c$ (critical surface tension) that seemed to sensibly scale with expectations for surface energy [42]. Zisman's critical surface tension parameter has the advantage of any other empirical observation in that there is no complicated underlying theory with dubious assumptions to complicate interpretation, although many subsequent investigators have made the leap-of-faith that $\gamma_c$ and surface free energy are equivalent.

\[19\] In fact, there is no theoretical reason to suppose there is any deep significance to the observation that data on a Zisman plot fall within narrow bands for different test surfaces [181].
Table 5
Critical surface energy and water wettability of polymers and monolayers [182]

<table>
<thead>
<tr>
<th>Surface</th>
<th>Water contact angle $\theta$ ($^\circ$)</th>
<th>$\gamma_c$ (dyn/cm)</th>
<th>$\tau^0$ (dyn/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene (low density)</td>
<td>94</td>
<td>31</td>
<td>-5.1</td>
</tr>
<tr>
<td>Polyethylene (low density)</td>
<td>104</td>
<td>31</td>
<td>-17.6</td>
</tr>
<tr>
<td>Poly(vinyl chloride)</td>
<td>87</td>
<td>39</td>
<td>3.8</td>
</tr>
<tr>
<td>Poly(vinylidene chloride)</td>
<td>80</td>
<td>40</td>
<td>12.6</td>
</tr>
<tr>
<td>Poly(vinyl fluoride)</td>
<td>80</td>
<td>28</td>
<td>12.6</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride)</td>
<td>82</td>
<td>25</td>
<td>10.1</td>
</tr>
<tr>
<td>Poly(trifluoroethylene)</td>
<td>92</td>
<td>22</td>
<td>-2.5</td>
</tr>
<tr>
<td>Poly(tetrafluoroethylene)</td>
<td>108</td>
<td>18.5</td>
<td>-22.5</td>
</tr>
<tr>
<td>Polyethylene terephthalate</td>
<td>81</td>
<td>43</td>
<td>11.4</td>
</tr>
<tr>
<td>Poly(methyl methacrylate)</td>
<td>80</td>
<td>39</td>
<td>12.6</td>
</tr>
<tr>
<td>Nylon-66</td>
<td>70</td>
<td>46</td>
<td>24.9</td>
</tr>
<tr>
<td>Polystyrene</td>
<td>91</td>
<td>43</td>
<td>-1.3</td>
</tr>
<tr>
<td>n-Hexatriacontane</td>
<td>111</td>
<td>21</td>
<td>-26.1</td>
</tr>
<tr>
<td>Paraffin</td>
<td>108</td>
<td>23</td>
<td>-22.5</td>
</tr>
<tr>
<td>Pentaerythritol tetrabutyrate</td>
<td>77</td>
<td>40</td>
<td>16.4</td>
</tr>
<tr>
<td>Pentaerythritol tetranitrate</td>
<td>72</td>
<td>45</td>
<td>22.5</td>
</tr>
<tr>
<td>Fluorinated methacrylic polymer A</td>
<td>120</td>
<td>10.6</td>
<td>-36.4</td>
</tr>
<tr>
<td>Fluorinated methacrylic polymer S</td>
<td>118</td>
<td>11.1</td>
<td>-34.2</td>
</tr>
<tr>
<td>Vinyl chloride acrylonitrile copolymer</td>
<td>81</td>
<td>38.4</td>
<td>11.4</td>
</tr>
<tr>
<td>17-(perfluoroheptyl)-heptadecanoic acid</td>
<td>115</td>
<td>8</td>
<td>-30.8</td>
</tr>
<tr>
<td>17-(perfluoropentyl)-heptadecanoic acid</td>
<td>110</td>
<td>11.4</td>
<td>-24.9</td>
</tr>
<tr>
<td>17-(perfluoropropyl)-heptadecanoic acid</td>
<td>106</td>
<td>16.4</td>
<td>-20.1</td>
</tr>
<tr>
<td>17-(perfluoroethyl)-heptadecanoic acid</td>
<td>105</td>
<td>16</td>
<td>-18.8</td>
</tr>
<tr>
<td>11-(perfluoroacyl)-undecanoyl acid</td>
<td>118</td>
<td>7.8</td>
<td>-34.2</td>
</tr>
<tr>
<td>11-(perfluoroheptyl)-undecanoic acid</td>
<td>115</td>
<td>11.7</td>
<td>-30.8</td>
</tr>
<tr>
<td>11-(perfluorobutyl)-undecanoic acid</td>
<td>108</td>
<td>15.8</td>
<td>-22.5</td>
</tr>
<tr>
<td>11-(perfluoroethyl)-undecanoic acid</td>
<td>105</td>
<td>18.8</td>
<td>-18.8</td>
</tr>
<tr>
<td>$\omega$-Monohydroperfluoroundecanoic acid</td>
<td>97</td>
<td>15</td>
<td>-8.9</td>
</tr>
<tr>
<td>Octadecyamine</td>
<td>101</td>
<td>21.5</td>
<td>-13.9</td>
</tr>
<tr>
<td>Trinitrobutyric acid</td>
<td>73</td>
<td>42</td>
<td>21.3</td>
</tr>
<tr>
<td>Poly(dimethyl siloxane)</td>
<td>101</td>
<td>24</td>
<td>-13.9</td>
</tr>
</tbody>
</table>

Fig. 7 plots critical surface energy against $\tau^0$ for a series of polymers and monolayers from data originally compiled by Owens and Wendt in 1969 [182] and re-tabulated here in Table 5 wherein reported angles $\theta$ have been converted to $\tau^0$ assuming $\gamma^0 = 72.8$ dyn/cm. Regression through the data trend of Fig. 7 indicates a modestly-linear relationship $\gamma_c = (0.58 \pm 0.05)\tau^0 + (30.53 \pm 1.09)$ with $R^2 = 80.4\%$. Interestingly, and probably fortuitously, $\gamma_c = 72.8$ dyn/cm at the perfect water-wettability limit ($\tau^0 = 72.8$ dyn/cm, $\theta = 0^\circ$). Extrapolation of the data trend of Fig. 7 to the hypothetical condition that $\gamma_c = 0$ dyn/cm leads to the absurd conclusion that $\tau^0 = -52.6$ dyn/cm ($\theta = 136.3^\circ$); the expectation being that $\tau^0 = -72.8$ dyn/cm ($\theta = 180^\circ$). Thus, although the Zisman plot may be defensible as an empirical tool, it is apparent that $\gamma_c$ does not scale with water-wettability in a sensible manner.

An experimental drawback of the Zisman approach is that a multiplicity of
contact angle readings with various fluids\textsuperscript{29} are required in order to characterize the 'surface energy' of a single surface. Examination of published Zisman plots sometimes reveals considerable non-linearity, particularly near the $\cos \theta = 1$ condition, that compromises an accurate determination of $\gamma_c$ (see, for example, Zisman plots exhibited by Baier and Dutton \cite{40}). That is to say, $\gamma_c$ estimated from contact angles of fluids with higher $\gamma_v$ can be significantly different from that estimated from contact angles of fluids with relatively lower $\gamma_v$. This curvature in Zisman plots is possibly associated with surface solubility of wetting fluids, which also accounts for the significant discrepancy between experimental and theoretically-calculated Zisman plots \cite{81}. These factors exacerbate experimental issues associated with the fact that advocates of critical surface energy seldom report advancing and receding contact angles, preferring instead a metastable contact angle that are probably neither the maximal (advancing) or minimal (receding) angle. The Zisman critical surface energy approach for the characterization of biomaterial surfaces is thus not recommended because it does not apply to aqueous systems.

\textsuperscript{29}Typically selected from water, glycerol, formamide, thioglycol, methylene iodide, 1-bromo-naphthalene, propylene carbonate, 1-methyl-naphthalene, cyclohexyl and n-hexadecane.
Fig. 8. Interfacial tensions $\gamma_{sv}$ and $\gamma_{sl}$ for a hypothetical surface computed from the 'equation of state' compared to water adhesion tension $\tau^o$. 'Berg limit' annotations are reproduced from Fig. 4. Note that linear-like trends in interfacial tensions are exactly equal and opposite. Note that extrapolation of the linear trend in $\gamma_{sv}$ leads to the irrational conclusion that $\tau^o = -57.6$ dyn/cm ($\theta = 142.6^\circ$) when $\gamma_{sv} = 0$ dyn/cm. See text for more discussion.

2.1.4.3. Interfacial tension component (equation-of-state) theory. Fig. 8 plots the interfacial tension components $\gamma_{sv}$ and $\gamma_{sl}$ calculated from Neumann's equation-of-state (Eqs) approach [183] to solving the Young equation $\gamma_{sv} - \gamma_{sl} = \gamma^o \cos \theta = \tau^o$ for the separate interfacial energy components. To avoid any issue with computer programming, data used in construction of Fig. 8 were taken directly from published conversion tables relating contact angles to interfacial tensions [184] for the specific case of a test fluid with $\gamma^o = 72.5$ dyn/cm appropriate to water. As in Fig. 6, some of the general trends in the data are seemingly sensible at first glance; $\gamma_{sl} \rightarrow 0$ dyn/cm as $\tau^o \rightarrow 72.5$ dyn/cm, reflecting increasing water–surface interaction; $\gamma_{sv}$ decreases with decreasing $\tau^o$, reflecting reduced interfacial tension between air (vapor) and low surface energy materials; $\gamma_{sv} = \gamma_{sl}$ at $\tau^o = 0$ dyn/cm ($\theta = 90^\circ$) as required by the Young equation. But this is where the sensibility of Fig. 8 ends.

As with the surface energy components of Fig. 6, interfacial tension components $\gamma_{sv}$ and $\gamma_{sl}$ plotted in Fig. 8 seem 'shifted' relative to the expectations derived from the surface force apparatus. First, $\gamma_{sl}$ decays nearly linearly well past the Berg limit

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21 It is important to note that in this Eqs example all interfacial tensions are entirely hypothetical whereas in the previous Section 2.1.4.1 and Section 2.1.4.2 experimental values were used in construction of surface energy vs. $\tau^o$ plots.
where a considerable change in surface–liquid interaction might otherwise have been anticipated. Second, extrapolation of the linear-like trends in \( \gamma_{lv} \) and \( \gamma_{vl} \) through the range \( 0 > \tau^0 > -20 \text{ dyn/cm} \) leads to \( \gamma_{lv} = -0.5\tau^0 + 28.8 \) and \( \gamma_{vl} = 0.5\tau^0 + 28.8 \). Given that water in the vapor phase is not significantly self-associated as is water in the condensed phase, it is not at all physically obvious why the solid–vapor interaction measured by \( \gamma_{lv} \) should be equal and opposite to the solid–liquid interaction measured by \( \gamma_{vl} \).

Furthermore, one is lead to the absurd conclusions that \( \tau^0 = -57.6 \text{ dyn/cm} \) (\( \theta = 142.6^\circ \)) at \( \gamma_{lv} = 0 \) and \( \gamma_{vl} = 65.2 \text{ dyn/cm} \) at \( \tau^0 = -72.5 \) (\( \theta = 180^\circ \)).\(^\text{22}\) Thus, surface tension components, based on erroneous theoretical arguments [10,19–25], do not scale with \( \tau^0 \) nor do calculated interfacial tensions \( \gamma_{lv} \) and \( \gamma_{vl} \) sensibly correlate with measured surface forces. It goes without saying that conclusions relating the biological response to materials and surface tension components must be fortuitous.

3. The role of water in the biological response to materials

A basic tenet in biomaterials surface science has been that the surface energy of a material drives the biological response to that material. This biological response manifests itself in the form of interfacial phenomena, such as protein adsorption, cell adhesion and the triggering of biological cascades, such as blood coagulation or complement activation. This concept was perhaps first formalized by Baier et al. through the proposal that critical surface energy \( \gamma_c \) (see Section 2.1.4.2) was directly linked to biocompatibility in a rational, predictive manner [2,40,185–190]. Following this lead, at least in a historical sense, other investigators have sought correlations between the biological response to materials and the various surface energy and interfacial tension component theories discussed briefly in Section 2.1.4.

This section will provide evidence that this basic tenet that has guided biomaterials surface science research over the last two decades is incorrect, or at least imprecise, because it does not explicitly describe or include the biophysical role of water. The proposition subscribed to herein is that (i) surface energy controls the structure and reactivity (solvent properties) of water in local contact with a surface and (ii) it is these solvent properties that directly control the biological response to materials, not surface energy per se. The first part of the proposition is not new; water interactions have been long acknowledged as a part of the biological response to materials [38,140]. Part (ii) of the proposition extends part (i) by explicitly including the biophysical role of water and motivates an analytical

\(^{22}\) In pure water with liquid–vapor interfacial tension \( \gamma^0 \), \( \gamma_{lv} \) and \( \gamma_{vl} \) can take on any values that satisfy the Young relationship \( \gamma_{lv} - \gamma_{vl} = \gamma^0 \cos \theta \). At the boundary condition \( \theta = 180^\circ \), \( \gamma_{lv} - \gamma_{vl} = -\gamma^0 \), leading to the conclusion that \( \gamma_{lv} = \gamma^0 \) and \( \gamma_{vl} = 0 \) since interfacial tensions cannot be negative. At the boundary condition \( \theta = 0^\circ \), \( \gamma_{lv} - \gamma_{vl} = \gamma^0 \), leading to the conclusion that \( \gamma_{lv} = \gamma^0 \) and \( \gamma_{vl} = 0 \). At \( \theta = 90^\circ \), \( \gamma_{lv} = \gamma_{vl} = \) an unknown value.
approach that attempts to correlate the biological response to materials with water wettability, herein advocated to be $\tau^o$, rather than surface energy or interfacial tension components that are only distantly related to water wettability through complex, and apparently incorrect, wetting theories (see Section 2.1.4).

The following sections demonstrate a relationship between a diverse set of biological responses and $\tau^o$; adsorption of proteins and surfactants (Section 3.1), activation of the blood plasma coagulation cascade (Section 3.2) and the attachment of biological cells in vitro (Section 3.3). These examples are to be compared to the structure and reactivity of water deduced from surface forces and membrane studies discussed in Section 2. From this comparison it is apparent that the biological response to hydrophobic surfaces ($\tau^o < 30 \text{ dyn/cm}$) is clearly different than to hydrophilic surfaces ($\tau^o > 30 \text{ dyn/cm}$) in a manner that allows a coarse separation of biological responses into hydrophobic and hydrophilic categories. In particular, protein adsorption falls into the hydrophobic category whereas contact activation of the blood coagulation cascade and adhesion of mammalian cells fall into the hydrophilic category.

3.1. Adsorption from water — the adsorption map

Section 2.1.3 compared and contrasted two-dimensional (2D) and three-dimensional (3D) paradigms of interfacial structure, advocating that the 3D interphase model is a more accurate view of the region separating bulk surface and solution phases. Section 2.1.3.1 summarized experimental observations from a diverse set of techniques that support the notion that the proteinaceous interphase against hydrophobic surfaces is a viscous region consisting of protein multilayers possibly tens of nanometers thick resulting from substantial accumulation of protein within the interphase region over-and-above bulk solution concentrations.

Gibbsian surface thermodynamics is uniquely suited to quantifying surfactant and protein adsorption within such an interphase [4,165,166], provided that solution composition is known [164]. Many, if not most, real-world biomaterial problems, however, involve complex biological milieu of unknown chemical composition, such as blood, tissue-culture supernate and diagnostic or bodily fluids. Consequently, surface-thermodynamic concepts are difficult, if not practically impossible, to apply in important biomedical circumstances. A useful tool for these occasions is the ‘adsorption map’ approach [164] which preserves much of the power of thermodynamic approaches but is not in any way restricted to situations in which solution composition needs to be defined. Equally important, the adsorption map is a means of relating adsorption to $\tau^o$ and is therefore directly connected to the structure and reactivity of water at surfaces.

Adsorption map theory has been discussed in detail elsewhere [164] and only a few salient features need to be reiterated here so that the reader can readily interpret adsorption maps and appreciate the revealed relationship between $\tau^o$, protein adsorption and the reactivity of water at surfaces.

An adsorption map is a graphical construction formed by plotting the domain of an adsorption index [$\tau' - \tau^o$] against the range of surface wettability in pure water.
Fig. 9. (A) An adsorption map for EDTA anticoagulated porcine plasma (filled symbols = advancing contact angles, open symbols = receding contact angles). Note that the data trend line (dashed) crosses \([\gamma' - \gamma^o] = 0\) near \(\gamma^o = 37\) dyn/cm where the propensity to activate the coagulation cascade (B) just begins a transition from a relatively flat response to surface energy (as measured by \(\tau^o\)) to an exponential-like increase with surface energy.

(or buffered saline as appropriate herein) \(\tau^o\) (see Fig. 9A as an example). The adsorption index \([\gamma' - \gamma^o]\) compares the adhesion tension \(\gamma'\) measured with a surfactant or protein mixture (having characteristic interfacial tension \(\gamma'\)) to the adhesion tension \(\gamma^o\) obtained with pure water or saline (having characteristic interfacial tension \(\gamma^o = 72.8\) dyn/cm). The adsorption index is sensitive to adsorption because adsorbed solute causes measurable changes in \(\gamma'\) and, consequently, \([\gamma' - \gamma^o]\).

According to adsorption map theory, \([\gamma' - \gamma^o] > 0\) is characteristic of surfaces that support adsorption whereas surfaces that do not support adsorption are characterized by \([\gamma' - \gamma^o] \leq 0\) dyn/cm. Boundaries of the map are derived from...
surface thermodynamics (the Young equation) and enclose all observable data for a particular protein or surfactant system in what is termed an adsorption triangle (see Fig. 9A for example). Area of an adsorption triangle falling on the map where [τ' − τ₀] > 0 dyn/cm corresponds to surfaces supporting adsorption whereas area of the adsorption triangle falling below [τ' − τ₀] = 0 dyn/cm correspond to solute-repellent surfaces to which water strongly binds. Thus, the adsorption map is a relatively new tool in biomaterials surface science that allows straightforward characterization of the wetting behavior of heterogeneous biological fluids.

Adsorption maps have been prepared for surfactants drawn from non-ionic, anionic, cationic and perflorinated classes as well as for various purified proteins and whole blood serum proteins. In all of these circumstances [τ' − τ₀] data corresponding to advancing and receding contact angle measurements fall along a monotonic trend lines [143,164] within the corresponding adsorption triangle. Consequently, only a few measurements on surfaces with different τ₀ are required to completely characterize the surfactant or protein system. Within this diverse set of test surfactants and proteins, it is generally found that interpolation of the trend line [τ' − τ₀] = 0 dyn/cm occurs between 30 > τ₀ > 15 dyn/cm (average τ₀ = 26.8 ± 6.8 dyn/cm or θ = 68.2° ± 5.7°) in rough correspondence with the Berg limit (see Fig. 4). This observation leads to the hypothesis that surfactant or protein adsorption is driven by the same water structure-reactivity sensed by the surface force apparatus that scales with τ₀ in such a way hydrophobic surfaces (τ₀ < 30 dyn/cm) support adsorption from water whereas hydrophilic surfaces (τ₀ > 30 dyn/cm) do not support adsorption from water. Apparently, water is too strongly bound to hydrophilic surfaces to be displaced by solute through surface dehydration mechanisms. This latter supposition correlates with the formation of strongly-bound condensate water films illustrated in Fig. 4.

As an example that will have utility in the next section discussing the coagulation of blood, the adsorption map for EDTA-anticoagulated porcine blood plasma is shown in Fig. 9A [143], from which it is evident that porcine plasma proteins do not adsorb to surfaces more wettable than τ₀ = 37 dyn/cm corresponding to θₜₐₜ = 59°. Contact angle measurements employed in adsorption mapping of porcine plasma thus positively detect plasma protein adsorption to hydrophobic surfaces but not to hydrophilic surfaces.

3.1.1. Literature corroborating adsorption map results

Only a small percent of the many protein and surfactant adsorption studies reported in the literature disclose results that can be meaningfully compared and contrasted to adsorption mapping, either because 'rinse-and-measure' protocols were applied (see Section 2.1.3) or water contact angles were not reported. However, qualitative corroboration can be found in a few reports free of these vexing limitations and related literature. For example, Wannerberger et al. report

23-This statement is specific to surfactants that adsorb through mechanisms leading to a decreased contact angle and exclude surfactants that adsorb through mechanisms leading to an increased contact angle (dewetting effect).
monotonic decrease of lipase adsorption with increasing substratum water wettability [191], with lipase surface concentration decreasing nearly to zero on surfaces more wettable than approx. \( \tau^o = 35 \) dyn/cm, near the Berg limit. Likewise, protein adsorption onto 'gradient surfaces' [192] typically exhibit sharp inflections in detected surface concentration within the wettability range 25 < \( \tau^o < 35 \) dyn/cm, with more protein detected on hydrophobic surfaces than on hydrophilic surfaces, as is generally claimed in the protein adsorption literature [140,143]. Interestingly, the amino acid constituents of proteins are shown by chromatography to readily adsorb to hydrophobic, silanized silica from water but not to adsorb to hydrophilic silica [193], yielding a region of reduced concentration (relative to bulk) near hydrophilic particle surfaces that may be related to the depletion layers detected by scanning-angle spectroscopy [154]. These studies verify that substitution of surface-bound water molecules on hydrophilic surfaces with solute molecules, an act of surface dehydration, is energetically unfavorable. Likewise, bound water is found to be a controlling factor in the adsorption of fibronectin onto crystal faces bearing know amounts of surface-bound water [194].

Thus it is apparent from these independent reports that significant changes in protein adsorption occurs at surface wettability near the Berg limit as quantitatively demonstrated by adsorption mapping and that both proteins and amino acids exhibit polar adsorption behavior on hydrophobic and hydrophilic surfaces.

3.1.2. Proteins at water wettable surfaces

One of the principal predictions of the adsorption map is that proteins (and some classes of surfactants) do not adsorb to hydrophilic surfaces. Specifically this means that contact angles do not detect changes in solid–liquid (or solid–vapor) interfacial tensions that would otherwise be anticipated upon exchange of surface-bound water molecules with protein molecules through any one of a number of surface dehydration mechanisms. Simply stated, hydrophilic surfaces do not adsorb protein in such a way that the observed surface wettability is changed. Whereas this prediction is corroborated by a few independent investigations mentioned in Section 3.1.1, it is at odds with numerous reports of protein

[24At this juncture it is of interest to comment on the sensitivity of contact angles to surface adsorption. It is a common laboratory observation that water-wettable surfaces are very easily contaminated due to adsorption and that the fully water-wettable condition is a transient state under normal, ambient laboratory conditions. Indeed, rather rigorous cleaning procedures and application of flames or oxygen plasmas are generally required to render a surface completely wettable. Thus, it is the expectation that protein adsorption from aqueous solution to a water-wettable surface, however slight, would yield an observable change in contact angle because surface-bound protein (or any other organic molecule) is poorly water-wettable relative to a highly oxidized glass or polymer surface. As an example, it has been shown that adsorption of cetyl dimethylammonium bromide (ceyl bromide) to water-wettable glass from water can be detected by contact angle goniometry from as little as 1 × 10^{-7} \% w/v solutions [166]. Cetyl bromide adsorption causes contact angles to increase (dewetting or autophobic effect) because the surfactant adsors in a head-down configuration due to charge interactions between the surfactant and surface [195]. This adsorbed conformation extends hydrophobic residues into solution causing the surface become less wettable (see [164] for cetyl bromide autophobic behavior in an adsorption map).
adsorption at ionic and hydrogel surfaces (see citations in [143]). And while the disparity between adsorption map predictions and protein adsorption to hydrogels may be discounted to some degree based on complications introduced by a water-swellable polymer and the related difficulty in discriminating between adsorption and adsorption, observations of protein adsorption on other types of hydrophilic surfaces are not so easily dismissed.

I have suggested that these seemingly orthogonal perspectives on solute adsorption from water onto hydrophilic surfaces can be reconciled if it is assumed that adsorbate is not physicochemically bound to the surface in a manner that alters interfacial tensions but is rather 'associated' with a hydration layer bound to a surface [143]. According to this hypothesis, solute is entrapped in a surface-bound water layer or adsorbed near to but separated from a surface by an aqueous layer. Perhaps this aqueous layer is comprised of water and co-adsorbed electrolytes, as suggested by Norde and Lyklema [109,196] for protein adsorbed to negatively-charged electrolytes and assumed to be of the order of 0.5 nm thick [197–202]. This adsorption model is consistent with solute depletion layers observed between adsorbed protein and silica surfaces using scanning-angle reflectometry [154] and chromatographic analysis of amino acid adsorption [193]. Implicit in this hypothesis is that solid–liquid interfacial tension is entirely dictated by the bound water layer directly in contact with the surface and not significantly affected by the adjacent protein layer. Whereas this concept is qualitatively attractive and consistent with condensate film layers and ion solvation (see Section 2.1.2.4 and Section 2.1.2.5), it has no theoretical basis and deserves more rigorous scrutiny. And this scrutiny is well deserved, at least in the biomaterials field, because the distinction between protein in direct contact with a surface and protein associated or entrapped in a bound hydration layer is likely to be profound. In the former means of adsorption, protein can be concentrated within an interfacial region separating bulk liquid and bulk solid phases in excess of that anticipated from bulk liquid composition in a selective manner (e.g. Vroman effect, see Section 3.1.3), causing surface composition to be quite different from bulk composition. By contrast, a physically-entrapped protein layer seems more likely to reflect bulk liquid composition. Furthermore, this sort of interfacial structure may provoke a change in the interpretation of the activity of enzymes near hydrophilic surfaces, as will be discussed in the context of blood coagulation in Section 3.2.

3.1.3. On the subject of adsorption equilibrium

It is commonly observed that adsorbed proteins and surfactants exhibit continuous changes in packing density associated with molecular conformation and exchange at interfaces that can extend over very long time scales [203,204]. These changes in interfacial chemistry can be detected using many of the techniques mentioned in Section 2.1.3.1. For examples, mass transport and adsorption kinetic effects can be the cause of erratic tensiometric measurements [4] and are related to 'aging' effects observed in pendant drop and balance tensiometry (see, for example, citations in [205,206]). Optical and spectroscopic analyses of protein adsorption kinetics reveal changes over hours [145,154,155,207–209]. And finally, with respect
to molecular exchange at interfaces, the replacement of blood proteins at interfaces has been carefully documented and termed the 'Vroman Effect' (see, for examples and citations, [210–214]). Given these long-term interfacial events involving proteins and surfactants, steady-state or equilibrium conditions may be inaccessible to many measurement techniques. Moreover, access to equilibrium conditions may not even be desirable because the transient state may be more relevant to many biomedical circumstances that are, like all life processes, definitively non-equilibrium processes. This should pose no particular conundrum provided the observer is cognizant that the moving picture is being interpreted frame-by-frame using a model, thermodynamics for instance, derived or constructed from the proposition of equilibrium that is not necessarily applicable to an authentic system operating under constraints that may prevent the timely achievement of equilibrium. Quoting Tanford [66], 'Such constraints, in the form of physical or kinetic barriers, exist whenever the laws of equilibrium thermodynamics are applied and the constraints in living systems are no different from those encountered in simple chemical systems'. With circumspect diligence then, we press on.

3.2. Contact activation of the blood plasma cascade

Fig. 9B shows the exponential-like relationship between $\tau^0$ and the propensity to contact activate the blood plasma coagulation cascade obtained with procoagulant surfaces prepared from oxidized polystyrene film sections and self-assembled monolayers on glass [37]. Comparison to the adsorption map for blood serum in Fig. 9A (see Section 3.1) leads to the conclusion that the hydrophobic surfaces that support protein adsorption from water are inefficient procoagulants whereas protein repellent, hydrophilic surfaces are efficient activators of the blood plasma coagulation cascade. Evidently, enzymes of the blood plasma coagulation cascade exhibit very different activity at hydrophilic surfaces, especially the fully-water-wettable variety, than at hydrophobic surfaces. It is interesting to speculate that the catalytic potential of water-wettable surfaces is in some way related to the special solvent properties of water against these surfaces, especially as related to the distribution of ions described in Section 2.1.2.5. Possibly, the conversion of blood Factor XII to the proteolytic form Factor XIIa that triggers subsequent zymogen–enzyme inter-conversions of intrinsic pathway of blood coagulation does not occur through a formal surface adsorption step, as commonly depicted for contact activation [215–218], but rather through an encounter with an exotic ionic environment in close proximity to water-wettable procoagulant surfaces. This proposition reconciles adsorption map results and biochemical mechanisms as well as possibly explaining why hydrophobic surfaces, known to efficiently adsorb proteins, are not efficient procoagulants.

3.3. Bioadhesion

Adhesion of biological cells, both mammalian and microbial, to surfaces is a complex, multi-step process. Initial bioadhesive steps involve transport of the cells
into the interphase that separates a surface from the suspending medium through mass-transfer processes, such as flow or gravitation (sedimentation). Quite possibly, the interphase encountered by approaching cells is a viscous, proteinaceous region like that described in Section 2.1.3.1 where water solvent properties are quite different from bulk solution. Near the surface, say within a proximity of 2–5 nm, electrostatic and dispersion forces can dictate the rate of attachment of cells to the surface in a manner that can be modeled using DLVO and surface thermodynamics (see discussion in [4,219]).

Attachment is different than adhesion. Adhesion refers to the force necessary to separate adherents and is controlled by short-range forces resulting from the formation of covalent, ionic, hydrogen and charge-transfer bonds. Thus, adhesion occurs only if cellular surfaces (or some extension of the cell surface) ‘touches’ the substratum so that atomic-level contacts can be made. By contrast, attachment can be of the physical kind in which cells are held in an attractive potential well near the substratum, formed through a conspiracy of electrostatic repulsion and dispersion force attraction. Attachment occurs first, then possibly adhesion. Once attached to a substratum, cells can spread and proliferate on this surface. All of these latter stages of bioadhesion are best dealt with as phenomena separate from attachment with different sensitivity to interfacial phenomena. Attachment steps are expected to be primarily driven by interfacial phenomena and will be explored in the subsequent sections.

Mammalian and microbial cells will be examined separately as it may be expected that these organisms have quite different responses to surfaces. Mammalian cells are derived from tissues where materials such as ceramics, metals and polymers are entirely foreign. By contrast, evolutionary forces on naturally-occurring microbes, persevering as individuals or colonies, must have at least partly involved the ability to adhere to both organic and inorganic materials.

3.3.1. Attachment of mammalian cells to surfaces in vitro

Attachment of mammalian cells to a surface from aqueous suspension typically follows a sigmoidal attachment profile in time, reaching a steady-state plateau that is sensitive to cell-surface compatibility [219]. Adhesive surfaces exhibit significantly higher maximal percentage of cell inoculum attached ($\% I_{max}$) than attachment-resistant surfaces. Fig. 10 plots $\% I_{max}$ obtained for Madin–Darby Canine Kidney (MDCK) cells on a series of glass and polystyrene surfaces with varying water wettability $\tau^\circ$ [220].

As indicated by arbitrary trend lines drawn through the data, $\% I_{max}$ exhibits a sharp transition between $20 < \tau^\circ < 40$ dyn/cm, depending on whether advancing or receding $\tau^\circ$ is examined. Hydrophobic surfaces resist attachment of MDCK cells whereas hydrophilic surfaces promote attachment of cells. It is of interest in the context of these data that the adsorption map for fetal bovine serum proteins (FBS, 10% in Dulbecco's Modified Eagle Medium) used in the culture of these cells indicates that surfaces more wettable than $\tau^\circ = 24.4 \pm 3.7$ dyn/cm (advancing) do not support adsorption of proteins from this heterogeneous biological milieu [164]. According to this point of view, MDCK cells attach to protein-repel-
Fig. 10. Steady-state maximal attachment (as percent of inoculum, %I max) of Madin–Darby Canine Kidney cells (MDCK, epithelioid) to polystyrene and glass surfaces with varying water wettability τ°. Prepared by oxidative gas discharge or silanization [4,164–166]. ‘Berg limit’ annotations are reproduced from Fig. 4.

Silent surfaces (τ° > 30 dyn/cm) but not to surfaces that support protein adsorption (τ° < 30 dyn/cm), in a manner that parallels the propensity of surfaces to contact activate the blood plasma coagulation cascade discussed in Section 3.2.

Similar relationships between cell attachment and τ° can be found in other literature sources as well. Fig. 11 is a collage of data from two literature sources [219,221] collectively providing data on three cell types listed in Table 6 from which it is evident that attachment of MDCK (epithelioid), VERO (African green monkey, fibroblast) and canine endothelial cells exhibit attachment responses to substratum surface energy similar to that shown in Fig. 10. Figs. 12 and 13 plot fibroblast spreading and growth indices obtained for various polymer surfaces listed in Table 4 of Section 2.1.4 taken from the comprehensive studies performed by Schakenradd [222] in the late 1980s relating cell–polymer interactions with γ. These authors purported ‘complex relationships between cell spreading and substratum surface free energy [180] that seem not so complex when related to τ° and are very similar to results represented in Fig. 10.

Apparently, substratum wettability affects latter stages of cell adhesion in a manner similar to attachment. Interestingly, the sigmoidal relationships observed between τ° and cell-spread (with and without serum proteins) and cell-growth indices (without serum proteins) are not observed in instance of cell-growth in the presence of serum proteins (Fig. 13). This is likely due to the strong influence of
Table 6
Attachment of mammalian cells to plastic and glass surfaces [219,221]

<table>
<thead>
<tr>
<th>Substratum</th>
<th>Listed water contact angle (°)</th>
<th>Computed or listed ρ (dyn/cm)</th>
<th>MDCK %I_max</th>
<th>VERO %I_max</th>
<th>Human endothelial %I_max</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCPS</td>
<td>—</td>
<td>57.6</td>
<td>87.6 ± 5.1</td>
<td>38 ± 5.2</td>
<td>—</td>
<td>[219]</td>
</tr>
<tr>
<td>WPP</td>
<td>—</td>
<td>6.8</td>
<td>27.4 ± 4.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BGPS</td>
<td>—</td>
<td>1.9</td>
<td>3.8 ± 1.6</td>
<td>3.8 ± 3.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PE</td>
<td>—</td>
<td>—1.9</td>
<td>6.9 ± 3.0</td>
<td>5.1 ± 1.4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PP</td>
<td>—</td>
<td>—16.9</td>
<td>8.2 ± 2.5</td>
<td>6.3 ± 1.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TCPS</td>
<td>35 ± 3</td>
<td>59.6</td>
<td>—16.0</td>
<td>83 ± 8</td>
<td>—</td>
<td>[221]</td>
</tr>
<tr>
<td>PS</td>
<td>77 ± 2</td>
<td>16.4</td>
<td>—</td>
<td>14 ± 1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TCPET</td>
<td>44 ± 2</td>
<td>52.4</td>
<td>—</td>
<td>86 ± 16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PET</td>
<td>65 ± 2</td>
<td>30.8</td>
<td>—</td>
<td>48 ± 8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PMMA</td>
<td>61 ± 3</td>
<td>35.5</td>
<td>—</td>
<td>42 ± 4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PC</td>
<td>83 ± 3</td>
<td>8.9</td>
<td>—</td>
<td>51 ± 10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FEP</td>
<td>102 ± 2</td>
<td>—15.1</td>
<td>—</td>
<td>9 ± 4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glass</td>
<td>13 ± 3</td>
<td>70.9</td>
<td>—</td>
<td>59 ± 18</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

TC PS, tissue culture grade polystyrene; W PP, wettable ‘petriperm’ culture dish; BG PS, bacteriological grade PS; PE, polyethylene; PP, polypropylene; PET, polyethylene terephthalate; TC PET, tissue culture grade PET; PC, polycarbonate; FEP, fluoroethylene propylene copolymer.

various hormones and factors in serum that profoundly influence cell proliferation that is not observed in the absence of these vital nutrients.

3.3.2. Attachment of microbial cells to surfaces in vitro

Microbial cell attachment is apparently more complex than mammalian cell attachment, as anticipated in Section 3.3, but here too sharp transitions in attachment occur at surface wettability near the Berg limit. Fig. 14 reproduces work of Fletcher and Pringle [223] relating microbial (Aeromonas hydrophilia H22 and Acinobacter sp. H3) attachment from artificial seawater to the wettability of plastic and glass surfaces. Data abstracted from [223] are listed in Table 7. Interestingly, microbial attachment to surfaces increases sharply near the Berg limit (at least for Acinobacter) and does not clearly favor hydrophobic surfaces over hydrophilic surfaces. And unlike the attachment of mammalian cells shown in Figs. 10 and 11 in which cell attachment is negligible on hydrophobic surfaces with τ° < 0 dyn/cm, thousands of microbial cells attach per unit area to these surfaces, suggesting that control of microbial fouling by manipulation surface energy alone may not be possible, especially in light of the prodigious rate at which microbial cells replicate.

Other microbial strains exhibit different attachment patterns on surfaces with varying water wettability. For example strains of Pseudomonas, Arthrobacter and E. Coli [224] and ‘soil bacteria’ [225] are found to exhibit a sigmoidal attachment profile (not shown) on surfaces with varying water contact angle, with more cells attached to hydrophobic surfaces and less on hydrophilic surfaces. Here too,
Fig. 11. Steady-state maximal attachment (as percent of inoculum, %I$_{max}$) of Madin–Darby Canine Kidney (MDCK), VERO African green monkey and human endothelial cells to plastic and glass surfaces listed in Table 6 with varying water wettability $\tau^o$. 'Berg limit' annotations are reproduced from Fig. 4. Compare to Fig. 10.

however, an inflection in attached cell number is noted near the Berg limit ($\theta \approx 65^\circ$). Similarly, Hsieh and Timm [226] find a polar attachment response to hydrophobic and hydrophilic surfaces for Staphylococcus aureus, as shown in Fig. 15 constructed from data compiled in Table 8.

4. Conclusion

Self association of water at surfaces regulates local water solvent properties that in turn mediate the biological response to materials. Water interaction with surface-resident Lewis acid/base sites competes with self association in a manner that scales linearly with wettability as measured by water adhesion tension $\tau^o = \gamma^o \cos \theta$; where $\gamma^o$ = water liquid–vapor interfacial tension (72.8 dyn/cm) and $\theta$ is the water contact angle formed on these surfaces. Self association of water adjacent to a surface can be defeated at a sufficiently high surface density of Lewis-sites. This occurs at $\tau^o = 30$ dyn/cm ($\theta = 65^\circ$) for typical oxidized surfaces reported in the literature.

$\uparrow$ Surface hydrophobicity is a phenomenon driven by water self association in a manner that directly parallels the hydrophobic effect in solution phase. Water

$\uparrow$ Electrophoretic mobility of the attaching microbes was also found to be a strongly-influencing parameter, as is understandable from the framework of DLVO theory.
structure is a manifestation of surface hydrophobicity that can be directly measured using the surface force apparatus. The collective evidence gleaned from more than a decade of intermolecular force research using the surface force apparatus suggests that hydrophobic surfaces exhibit water contact angles greater than 65° ($\tau^o > 30$ dyn/cm) whereas hydrophilic surfaces exhibit water contact angles less than 65° ($\tau^o < 30$ dyn/cm). Water against hydrophilic surfaces forms a
Table 7
Attachment of microbial cells to glass and plastic surfaces [223]

<table>
<thead>
<tr>
<th>Substratum</th>
<th>θ (°)</th>
<th>r (dyn/cm)</th>
<th>Aeromonas hydrophilia (cells × 10^6/cm^2)</th>
<th>Acinetobacter sp. (cells × 10^6/cm^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>0</td>
<td>72.8</td>
<td>0.36</td>
<td>6.8</td>
</tr>
<tr>
<td>TCPET</td>
<td>54</td>
<td>42.8</td>
<td>0.38</td>
<td>13.0</td>
</tr>
<tr>
<td>TCPS</td>
<td>66</td>
<td>29.6</td>
<td>0.44</td>
<td>15.8</td>
</tr>
<tr>
<td>Nylon 66</td>
<td>70</td>
<td>24.9</td>
<td>0.43</td>
<td>26.3</td>
</tr>
<tr>
<td>PMMA</td>
<td>74</td>
<td>20.1</td>
<td>0.60</td>
<td>21.3</td>
</tr>
<tr>
<td>PVDF</td>
<td>76</td>
<td>17.6</td>
<td>0.56</td>
<td>16.0</td>
</tr>
<tr>
<td>PVC</td>
<td>80</td>
<td>12.6</td>
<td>0.89</td>
<td>15.8</td>
</tr>
<tr>
<td>BGPS</td>
<td>90</td>
<td>0.0</td>
<td>0.81</td>
<td>13.8</td>
</tr>
<tr>
<td>PE</td>
<td>95</td>
<td>-6.3</td>
<td>0.31</td>
<td>11.0</td>
</tr>
<tr>
<td>PTFE</td>
<td>110</td>
<td>-24.9</td>
<td>0.37</td>
<td>5.0</td>
</tr>
</tbody>
</table>

TC PET, tissue culture grade polyethylene terephthalate; TC PS, tissue culture grade polystyrene; PMMA, polymethylmethacrylate; PVDF, polyvinylidene fluoride; PVC, polyvinyl chloride; BGPS = bacteriological grade polystyrene; PE, polyethylene; PTFE, polytetrafluoroethylene.

Fig. 14. Microbial cell adhesion to plastic and glass surfaces listed in Table 7 with varying water wettability r°. 'Berg limit' annotations are reproduced from Fig. 4. Compare to mammalian cell adhesion in Figs. 10–13.

Strongly-bound water film that can be displaced only through solute–surface interactions that exceed the adhesive energy of water, which can be as high as the cohesive energy density of water (2γ° = 2 × 72.8 = 145.6 dyn/cm).
Table 8
Attachment of Microbial Cells to Glass and Plastic Surfaces [226]

<table>
<thead>
<tr>
<th>Substratum</th>
<th>$\theta$ (°)</th>
<th>$\tau^0$ (dyn/cm)</th>
<th>Staphylococcus aureus attachment (%/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate</td>
<td>55.2</td>
<td>41.5</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>Nylon 66</td>
<td>63.1</td>
<td>32.9</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>PET</td>
<td>70.2</td>
<td>24.7</td>
<td>0.04 ± 0.004</td>
</tr>
<tr>
<td>PE</td>
<td>92</td>
<td>-2.5</td>
<td>0.21 ± 0.08</td>
</tr>
<tr>
<td>PP</td>
<td>96.9</td>
<td>-8.7</td>
<td>0.16 ± 0.04</td>
</tr>
<tr>
<td>PTFE</td>
<td>108</td>
<td>-22.5</td>
<td>0.21 ± 0.01</td>
</tr>
</tbody>
</table>

PET, polyethyleneterephthalate; PE, polyethylene; PP, polypropylene; PTFE, polytetrafluoroethylene.

![Graph](image)

Fig. 15. Microbial cell adhesion to plastic and glass surfaces listed in Table 8 with varying water wettability $\tau^0$. 'Berg limit' annotations are reproduced from Fig. 4. Compare to Fig. 14 and to mammalian cell adhesion in Figs. 10–13.

Diverse biological responses to materials, such as protein adsorption, contact activation of the blood coagulation cascade and cell adhesion respond to local solvent properties of water against hydrophobic and hydrophilic surfaces. Thus, the hydrophobic/hydrophilic contrast in the biological response to materials, often disputed in biomaterials science, is very clear when viewed from the perspective of water structure and reactivity at surfaces. Biologically-important solutes, such as proteins can adsorb to hydrophobic surfaces ($\tau^0 < 30$ dyn/cm) but not to hy-
drophilic surfaces ($\tau^* > 30$ dyn/cm) because surface dehydration is energetically prohibitive. Literature evidence suggests that proteins can be 'associated' or 'entrapped' within bound-water layers against hydrophilic surfaces in a fashion that does not formally involve surface dehydration. Hydrophilic surfaces support attachment of mammalian cells and efficiently activate the blood plasma coagulation cascade through mechanisms that apparently do not involve surface-adsorbed protein. Selective adsorption of monovalent ions at surfaces and accumulation of divalent ions within the interphase separating bulk solution and a hydrophilic surface may be important drivers of these latter examples of the biological response to surfaces. The key measure of water structure and activity important to biomaterial scientists is $\tau^*$.

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