Biomaterials 32 (2011) 6670–6675

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The Goldilocks Surface☆

Erwin A. Vogler

Departments of Materials Science and Engineering and Bioengineering, The Pennsylvania State University, University Park, PA 16802, USA

ARTICLE INFO

Article history:
Received 24 March 2011
Accepted 24 May 2011
Available online 17 June 2011

Keywords:
Biological response
Biocompatible
Surface energy
Water wetting
Hydrophilic
Hydrophobic

ABSTRACT

A minimum in the biological response to materials that is observed to occur within a narrow surface energy range is related to the properties of water at these biology-contacting surfaces. Wetting energetics are calculated using a published theory from which it is further estimated that water molecules bind to these special surfaces through a single hydrogen bond, leaving three other hydrogen bonds to interact with proximal water molecules. It is concluded that, at this Goldilocks Surface, the local chemical environment of surface-bound water is nearly identical to that experienced in bulk water; neither deprived of hydrogen bond opportunities, as it is in contact with a more hydrophobic surface, nor excessively hydrogen bonded to a more hydrophilic surface. A minimum in the biological response occurs because water vicinal (near) to the Goldilocks Surface is not chemically different than bulk water. A more precise definition of the relative terms hydrophobic and hydrophilic for use in biomaterials becomes evident from calculations: >1.3 kJ/mole-of-surface-sites is expended in wetting a hydrophilic surface whereas <1.3 kJ/mole-of-surface-sites is expended in wetting hydrophobic surfaces; hydrophilic surfaces wet with >1 hydrogen bond per water molecule whereas hydrophobic surfaces wet with <1 hydrogen bond per water molecule.

1. Introduction

Robert Southey is credited with the modern version of the children's story *Goldilocks and the Three Bears* in which the little blond-haired girl Goldilocks unlawfully enters the bears' domicile and samples porridge left on a table to cool while the three bears were out on morning walk. Goldilocks found that one bowl of porridge was too hot, a second too cold, and the third just right to her felonious taste test. Henceforth, the adjective "Goldilocks" has been applied in popular and scientific literature in reference to anything that has a particularly balanced set of properties as in, for examples; the Goldilocks Principle that describes the perfect planetary conditions for life to arise, a Goldilocks Planet to which this principle refers, the Goldilocks Enigma that seeks a meta-physical reason why Earth happens to be a Goldilocks Planet, or the workings of a Goldilocks Economy for the planet.

Biomaterials generally seeks materials that meet different medical-device application needs and thereby exhibit the end-use criteria referred to as "biocompatible" [1–5]. No one material can satisfy very different performance requirements of diverse medical devices. A biomaterial that might be regarded as "too hot" (hydrophilic for example) for certain applications, such as blood contact [6], can be "just right" in a different application; adhesion of mammalian cells to cultureware surfaces for example [7–9]. Consequently, there is no single "Goldilocks Biomaterial" to be discovered. But if our core understanding of biocompatibility is correct [1], there should be a Goldilocks Principle appropriate to biomaterials that describes how to make a perfect biomaterial for a particular medical application. To suspect otherwise is to give up all hope of rational biomaterials engineering; a loss of faith few in the biomaterials community are willing to condone, even though this putative Goldilocks Principle has not been forthcoming from more than five decades of focused research.

Our core understanding of biocompatibility is built on the basic tenet that proteins adsorbed to biomaterial surfaces from solution catalyze, mediate, or moderate the biological response to materials in a manner that ultimately dictates biocompatibility. It is thus apparent that a full-and-quantitative understanding of how proteins arrive at, and adsorb to, biomaterial surfaces from complex biological milieu is essential to prospective biomaterials design for advanced medical devices. If the number and kind of proteins adsorbed to a surface are not clearly known, then evidence-based biochemical mechanisms of the biological response to materials cannot be responsibly proposed. And if mechanisms of the biological response to materials remain obscure, then structure-property relationships cannot be formulated, leaving biomaterials

---

☆ A Contribution from the Hematology at Biomaterial Interfaces Research Group.
E-mail address: EAV3@PSU.EDU.

0142-9612/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biomaterials.2011.05.066

development dependent on design-directed or trial-and-error approaches [10,11]. Thus, the entirety of biomaterials surface science seems critically dependent on a thorough understanding of protein adsorption.

Experimental evidence gathered in my laboratories over the last three decades strongly suggests that water controls energetics of protein adsorption and that the adsorption process has more to do with solvent properties than solute [7,9,12–23]. Combined with the above-stated theory of biocompatibility, it logically follows that water ultimately controls the biological response to materials, albeit through the convoluted agency of protein activity at hydrated surfaces. Indeed, it is observed that different biological responses to materials ranging from blood plasma coagulation [6] to mammalian cell adhesion [7] to zymogen activation [24–26] correlate with the structure and reactivity of water inferred from diverse studies of water properties drawn from the condensed-phase physics literature [15,16] (note that refs. [6,7] and [15,16] are review articles summarizing and comparing work from a broad literature). All taken together, these experimental facts and correlations argue that, if a Goldilocks Principle exists for biomaterials, then it is reasonable to seek it in the way water reacts with different material surfaces.

This paper discusses theoretical and experimental evidence for a Goldilocks Surface that is “just right” from the perspective of bulk water properties. Water adjacent (vicinal) to a Goldilocks Surface is neither deprived of hydrogen bond opportunities, as it is in contact with a hydrophobic surface, nor excessively hydrogen bonded to a hydrophilic surface. In this sense, vicinal water interacts with a Goldilocks Surface in a way that is not different than the interaction with water molecules in bulk solution. A Goldilocks Surface is a water-contacting insoluble phase with water-like hydrogen-bonding properties. As a consequence of this unique chemistry, biological responses mentioned above are observed to “pivot” from low-to-high or high-to-low at the Goldilocks Surface Energy, depending on the specific case under consideration [7,15,16]. A refined definition of hydrophilic and hydrophobic in energetic terms emerges from this analysis.

2. Computational and conceptual methods

Work described herein was built upon wetting theory introduced by C. Extrand [27,28] and expanded upon by linkage with the traditional Dupre’ work function and a lattice model of water (HOH) in a way that permitted calculation of the number of moles of water involved in wetting a mole of surface sites. Table 1 collects theoretical parameter definitions and potential relationships that could be drawn among these parameters. In particular, molar surface area $\overline{A}$, molar HOH area $\overline{H}$, Extrand’s wetting energy function ΔG, the Dupre’ work-of-adhesion W, and the combined term $-(W/\Delta G)\overline{H}$ were used in this work. Outcome of theoretical calculations was compared to different measures of the biological response to material surface energy herein quantified by cosine of the advancing contact angle, $\cos\theta_a$. Three conceptual tools described below were essential to conclusions drawn from the calculations.

2.1. Molar surface area and molar wetting

Extrand developed the concept of “molar surface area” [28] (row 1, Table 1) by envisioning a polymeric surface with smooth area A comprised of a repeat unit with molecular weight M_o. The surface area occupied by a repeat unit A_{site} was approximated as the 2/3 root of site volume $(V_{site})^{2/3}$ which, in turn, was related to M_o and density ρ by $V_{site} = (M_o/\rho N_A)$, where N_A is the Avogadro number. The molar surface area $\overline{A}$ was obtained by multiplication with N_A, yielding $\overline{A} = [(M_o/\rho)^{2/3}N_A^{1/3}]$ with units of cm^2/mole-of-surface-sites. Molar surface area was appropriate for any material that exhibited a discernable repeat unit, such as a polymer or SiO_2 glass for example. Extrand applied this concept in deriving a relationship between the free energy ΔG of wetting a mole of surface sites and the advancing contact angle θ_a of a wetting liquid on that surface, concluding that $\Delta G = (RT/3)\ln[(1-\cos\theta_a)^2 \ \ (2+\cos\theta_a)/4]$ in units of kJ/mole-of-surface-sites (row 3, Table 1) [27]; where RT the product of the gas constant and Kelvin temperature. It is thus evident that ΔG scales directly with temperature which was taken to be 298.15 K in this work. This equation was used to calculate free energy as a function of $\cos\theta_a$ shown on the left-hand ordinate of Fig. 1 and the number of moles of surface sites wetted by 1 mol of water (right-hand ordinate), as discussed further below. ΔG was interpreted as the strength of interaction of the wetting fluid with the surface and was equated with liquid–solid adhesion [27], or (negative of) the work required to remove a wetting fluid from the surface (dehydration energy).

Extrand theory was not specific to a particular wetting fluid and did not explicitly depend on fluid liquid–vapor (lv) interfacial tension γ_{lv} because γ_{lv} is a measure of liquid-molecule cohesion, not intermolecular interactions with the wetted surface (assumingγ_{lv} does not change due to surface wetting) [27]. Furthermore, θ_a was an independent parameter that made no statement about the chemical nature of the surface supporting θ_a. In essence, Extrand’s theory computed the free energy of wetting for any wetting fluid on any surface from θ_a alone. In deriving this thermodynamics, Extrand neglected vapor spreading pressure, which becomes increasingly significant with increasing hydrophilicity, and equated θ_a with an equilibrium angle, but otherwise theory was without additional assumptions. The full range of applicability of Extrand theory was not determined but theory was shown to be in good agreement with experiment for polymeric materials spanning a broad range in water contact angle and wetting-fluid interfacial tensions. Simplifications and approximations utilized by Extrand were not considered to be crucial to the general conclusions of this work, especially in light of the approximate location of the pivot point in the biological response discussed in Section 2.3 (see gray band in Fig. 1). In other words, we

Table 1
Definitions and possible relationships among parameters.

	Row	Parameter	Symbol (units)	Relevant relationships (units)
Material Constants	1	Molar Surface Area	$\overline{A}$ (cm^2/mole surface sites)	
	2	Molar HOH Area	$\overline{H}$ (cm^2/mole HOH)	$\overline{H}/\overline{A}$ (mole-surface-sites/mole HOH)
Functional Relationships	3	Wetting Energy Function	ΔG (kJ/mole surface sites)	$\Delta G/\overline{A}$ (kJ/cm^2)
	4	Wetting Work Function	W (kJ/cm^2)	$W\overline{A}$ (kJ/mole-surface-sites) $W\overline{H}$ (kJ/mole HOH) $W/\Delta G$ (mole-surface-sites/cm^2) $(W/\Delta G)\overline{H}$ (mole-surface-sites/mole HOH)

Notes: ΔG and $(W/\Delta G)\overline{H}$ are the only combination of parameters considered in this work.