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Surface behaviour of biomaterials: The *theta surface* for biocompatibility

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Abstract "Biomaterials" are non-living substances selected to have predictable interactions with contacting biological phases, in applications ranging from medical/dental implants to food processing to control of biofouling in the sea. More than 30 years of empirical observations of the surface behaviours of various materials in biological settings, when correlated with the contact-angle-determined Critical Surface Tensions (CST) for these same materials, support the definition of the "theta surface". The "theta surface" is that characteristic expression of outermost atomic features least retentive of depositing proteins, and identified by the bioengineering criterion of having measured CST between 20 and 30 mN/m. Biomaterials applications requiring strong bioadhesion must avoid this range, while those requiring easy release of accumulating biomass should have "theta surface" qualities. Selection of blood-compatible materials is a main example. It is forecast that future biomaterials will be safely and effectively translated directly to clinical use, without requiring animal testing, based on laboratory data for CST, protein denaturation, and cell spreading alone.

1 Introduction

Future biomaterials designers need not struggle to emulate Nature's specific biochemical mechanisms, but rather can use engineering applications of fundamental physical principles to address issues of affordability, longevity, safety and function of fabricated materials that must interface successfully over long periods with biological substances. Surface scientists can now better understand, predict, and control generic bioadhesive interactions between biological and synthetic substances using stochastic physical phenomena that can be measured and manipulated based on global empirical criteria of wetting and spreading.

Respecting "A Forecast of the Future for Biomaterials" as the theme for the Professor Larry L. Hench Retirement Symposium, this contribution predicts that development of new biomaterials will benefit from a robust "general field" theory that supports bioengineering solutions to continuing needs for biocompatibility and control of biofouling. The material surface structures that will perform best in these applications will be simple, homogeneous monolayer expressions from corrosion-resistant substrata of different textures chosen for abhesive versus adhesive outcomes.

There will be no need to know the names or identities of specific biological substances that will be encountered, since all biological systems share the same fundamental chemistry and pattern of events.

As a first contribution to this theoretical foundation, introduced here is the concept and engineering definition of the *theta surface* for biocompatibility of materials, emphasizing biological systems best served by *minimizing* their interfacial interactions with contacting materials. This concept will be familiar to bio-macromolecule analysts and structural biologists, as it derives from that of "theta solvents" for macromolecules—that is, suspending liquid phases that allow large, complicated molecules such as proteins to retain their thermodynamically most-stable conformations, resisting "denaturation" in 3-dimensional suspensions.

The *theta surface* is that controlled atomic force expression from solid surfaces, placed into aqueous biological media, that will least denature glycoproteinaceous macromolecules encountering those surfaces.

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It is the adsorbed configurations, and strengths of binding/retention of biomass to contacting materials under water, that determine resistance to shear-induced re-entrainment of that matter into the biological stream. So, maintenance at the interface of near-solution-state conformations of the first arriving macromolecules is the most effective approach to thromboresistant materials for long-term contact with flowing blood, and to fabrication of "easy-release" coatings for exposure to any other biological system, from seawater to dairy products, and from water purification units to sewage flow lines, as well.

Universal features of all such systems are the presence of water, and of glycoproteinaceous macromolecules or their refractory remnants (surface-active humic substances in the sea, for example) as the dominant "conditioning film"-forming, water-displacement agents entropically favored as the new interfacial occupants.

The *theta surface* condition in all tested cases, from blood to tissue to saliva, tear, and oceanographic biofluids, is defined by display of empirical, measurable Critical Surface Tensions (as surrogates for otherwise inaccessible ideal surface free energy values) in the range of 22–24 mN/m, close to the van der Waals, dispersive-force contributions to the composite surface energy of water. Composite surface energy is the sum of the theoretically separate dispersive force contributions and polar force contributions to a material's surface tension, 22 mN/m and 50 mN/m being the conventionally accepted values, respectively, for water. Critical Surface Tension is a graphically extrapolated characteristic for any solid or semi-solid (hydrogel, or tissue) material defined as that value of liquid/vapor surface tension required for any substance to be at equilibrium with that solid at a contact angle of just zero degrees, the border between spreading and non-spreading behaviour. Biomaterials brought to this surface state before, or soon after their exposure to biological systems always demonstrate the minimal strengths of retention for all of any system's biomass coming into contact with their *theta surfaces*. It is thermodynamically less costly for water to re-enter the interfacial zones.

Laboratory testing for *theta surface* qualities of biomaterials requires contact angle measurements with a large variety of diagnostic liquids having different sizes, shapes, polarities, and hydrogen bonding capabilities. Water, glycerol, thiodiglycol, and formamide are most useful for determining polar-polar and hydrogen bonding interactions, while methylene iodide, bromonaphthalene, and methylnaphthalene are best for the dispersive and pi-bonding interactions of aliphatic and ring structures, with the normal alkanes in descending order from hexadecane through pentane best utilized for the purely dispersive interactions. Measurement of reliable contact angles for most of these diagnostic liquids on fully hydrated/solvated biomaterials is usually straightforward, followed by accepting only the equilibrium advancing contact angle values for use in the graphical extrapolation of Critical Surface Tension. Receding and non-equilibrium contact angle values, although interesting and relevant to many practical biomaterials challenges such as lenses in the blinking eye, do not accurately reflect the initial material surface qualities that correlate with subsequent bioadhesion. Surprisingly, most effective atomic group exposures for *theta surface* results are intrinsically hydrophobic, closely-packed methyl, CH3, terminals or repeating CH2CF2 runs in polyvinylidene fluoride (PVDF). Repeating CH2's of polyethylene or CF2's of polytetrafluoroethylene are both less favorable with higher interfacial energy excesses to sustain bioadhesion. The reason is that the dispersive-force-dominated Critical Surface Tensions of 31 mN/m and 18 mN/m for polyethylene and polytetrafluoroethylene, respectively, are outside of the zone where the thermodynamic interfacial free energy function minimizes at the 22 mN/m dispersive-force-value for water, best matched by the values of 22 mN/m and 24 mN/m for closely packed methylated materials and PVDF, respectively. This is also the reason why fully hydrated polyethylene oxide (polyethylene glycol) materials fail to resist biofouling in practical situations for periods longer than a week or so, as their bound water is always displaced by multiple side chains of macromolecular proteins exposed to the intrinsically higher Critical Surface Tensions of the highly oxygenated surfaces and better retained there than single water molecules. Some synthetic hydrogel materials are among the most fouling-retentive substances ever tested after long-term contact with biological systems, while natural tissue hydrogel surfaces are effective foul-release materials indefinitely.

2 Surface chemistry/energy infuences on bioadhesion, adsorption and retention

The next section provides a brief recapitulation of the path of identification of an *empirically* sound and theoretically reasonable approach to prediction and beneficial control of biological responses to nonphysiologic materials by modulation of the surface energetics of the components interacting under water. It is axiomatic that actual interactions of materials in biological settings require that water be displaced from the interface—so measurements of aqueous contact angles are useful mainly to estimate how long it will take before the important biopolymer-to-material contacts will occur. Water contact angle data, alone, are *not* sufficient to determine or correlate bioadhesive strengths developed when—inevitably—interfacial dehydration does take place.

As an example, note that hydrophilic soft contact lenses—some with more than 70% initial water content—do always become severely soiled by proteinaceous matter from the tear fluids of the eyes. As another instance, note that there

are no hydrophilic or hydrogel paints or coatings that resist, for more than a few weeks, biofouling by organisms in the sea!

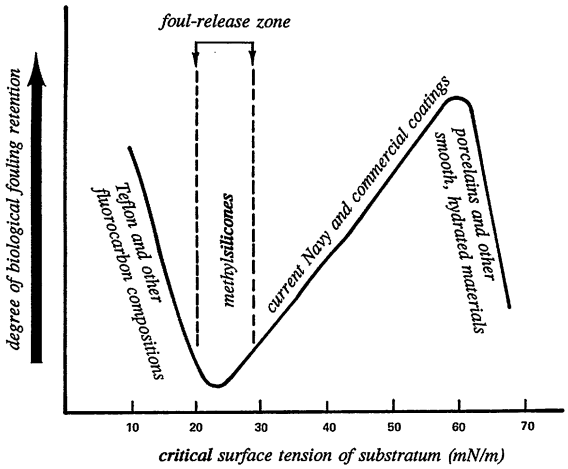
Beyond hydrophilicity, the complete range of wetting, spreading and adhesive interactions important to understanding, predicting and controlling biosurfaces can be easily obtained, however, by extending the measurements of contact angle values to include representative pure liquids for each of the multiple side chains of protein-building amino acids. Relative water wettabilities of materials are certainly not predictive, alone, of the surface energetics of biomaterials. Biocontact experiments that take only minutes to weeks are not adequate, alone, to confirm or refute the predicted long-term bioadhesive outcomes critical to successful medical implants or ship bottom paints, but sufficient clinical data in human patients and actual seawater environments are now available to support direct transfers from laboratory to practice without needing to sacrifice other living species on the way.

3 Experimental and theoretical results supporting the "*theta surface*" concept

3.1 Experimental

Differential adhesion in *all* biological systems is strongly correlated with substratum surface energy [1, 2], transduced to the level of particulate matter—living or dead—via *universally deposited and preferentially retained* proteinaceous "conditioning" films [3]—that produce a *nonlinear* surface energy vs bioadhesion relation minimized at the 20–30 mN/m substratum region of the critical surface tension scale [4]. The most successful correlating curve for these developments, as published to the Marine Technology industries in 1973 [1, 10], is shown as Fig. 1:

Within any given biological system, there is a *dominant identity* of the proteins that deposit and are preferentially retained on *all substrata*, but these compositionally similar protein deposits do have *different* surface-energy-related *conformations, which do also change through time* [5]. Within any given biological system, *specific* particles or cells dominate the "primary" particulate deposits onto the "conditioning" films, but these particles also show surface-energy-related differences in patterns and degrees of spreading, determined after contact with the pre-deposited "conditioning" films and not in the suspension state before surface contact [6]. There is no selectivity in adsorption of macromolecules or bacteria or cells on substrata in biological systems; rather there is selectivity in retention against differential detachment forces as a function of the differing surface energetics associated with the initial concentration- and flux-driven deposition events [7]. Therefore, it is essential that controllable mechanical work, such as shear stress, be present if relative bioadhesive



The curve above shows the demonstrated relationship between critical substratum surface tension and retention strength of attached biofouling organisms. This relationship has been confirmed in numerous natural environments (blood, tissue, bacterial suspensions, saliva, and fresh, brackish, and sea water). Validation of this observation opens the way to the development of nontoxic and nonpolluting means for minimizing fouling in the marine environment.

Fig. 1 A descriptive plot of the generally observed strength of biological adhesion to substrata of different initial critical surface tensions. The minimum is always found in the zone between 20 and 30 mN/m, although at different absolute levels depending upon the specific biological system, the time of contact, and the acting mechanical forces of removal

strengths are to be reliably inferred [8]. Differential "processibility" of the deposited "conditioning" and "primary" layers by shear forces and local biochemical/cellular reactions determines whether the immersed substrata will be retained with their integral "biofilms" or will be "walled off" or dehisced in the classical "foreign-body" reaction [9].

3.2 Theoretical

As the curve in Fig. 1 is meant to illustrate, there is no finding of zero strength of retention of biomass to any underwater substratum, once the intervening layer of water has been displaced. The absolute adhesion strengths do vary with degree of surface polarity, time in contact, type of biology attached, and metabolic activities of the organisms.

Why the universal minimum in biological "stick-to-itiveness" at about 22 mN/m critical surface tension? The critical surface tension for spreading on a liquid substrate is 22 mN/m for interfacial water layers [11].

Noting that this value also is equal to the dispersive force contribution to the composite surface free energy of water, an independently formulated explanation for the occurrence of a bioadhesion minimum on 20–30 mN/m low energy surfaces is that excess dispersion forces emanate from the solid surface on the high critical-surface-tension side of the minimum while they emanate from the liquid surface on the low critical-surface-tension side [12].

4 Specific application to selecting blood-compatible materials

Before and following the passage of the first implant-related regulations in May, 1976 (Medical Device Amendments) to the Food, Drug and Cosmetics Act, prosthetic and reparative materials and devices were implanted into many thousands of human recipients without formal requirements for materials pre-qualification. Now, benefiting from 30-year clinical-outcome results of this no-longer-possible massive human experimentation, it *is* possible—and probably ethically and legally necessary—to correlate the human, animal-testing, and *in vitro* laboratory testing results to produce reliable selection criteria for new blood-compatible polymers.

Although there still is not consensus, the most accessible compilations of relevant data are those published at the 10-years intervals, 1977 and 1987 [13, 14] from the start of public funding and widespread implantation. Briefly, the problem to be overcome is illustrated in Fig. 2.

Figure 2 illustrates, with the label "layer", how a "conditioning" film of persistently retained—but not first deposited—fibrinogen supports attachment of early arriving blood platelets with differential outcomes depending on the surface properties of the substratum (Epon epoxy) polymer. In the electron micrograph of Fig. 2, the epoxy retains a conformationally distorted layer of predominantly fibrinogen that in turn strongly attaches platelets which have spread, become sticky to their arriving siblings, and evulsed reactive biochemicals that attracted neutrophiles (white cells) and triggered fibrin polymerization that will entrap passing erythrocytes (red blood cells).

The red color of common blood clots is a misleading signal: thrombosis and blood incompatibility are not red-cell-related problems. Thromboresistant, blood-compatible polymers release the attaching biomass at the first-platelet-layer stage, and persist in a deposition-re-entrainment equilibrium in flowing blood from that time forward indefinitely.

5 *In vitro* diagnostic and predictive criteria for thromboresistant polymers

Without killing another animal, it is possible to quickly and relatively inexpensively discover which materials are most likely to be blood-compatible, in the sense that they will be thromboresistant under normal blood flow conditions of the human body or well-engineered extracorporeal circuits. Three *in vitro* criteria must be met: (1) the material's Critical Surface Tension must be between 20 and 30 mN/m, preferably between 22 and 24 mN/m [15]; (2) spontaneous adsorption of pure human fibrinogen to the material's surface, under laminar flow conditions, must produce bound "conditioning" films characteristic of the fibrinogen molecules being present in minimally denatured layers as judged by conformational criteria of ellipsometry and internal reflection infrared spectroscopy [16]; and (3) human platelets settled onto the material's surface from whole human platelet-rich plasma, at 37°C, must remain discoid, unspread and essentially pseudopod-free when inspected at the scanning electron microscopic level [17].

It is not appropriate to substitute platelet number counts for morphological analysis, and extreme care must be taken with the most thromboresistant materials, so that the low adhesive strengths do not lead to platelet loss during specimen preparation. It is not appropriate to study only washed platelets,

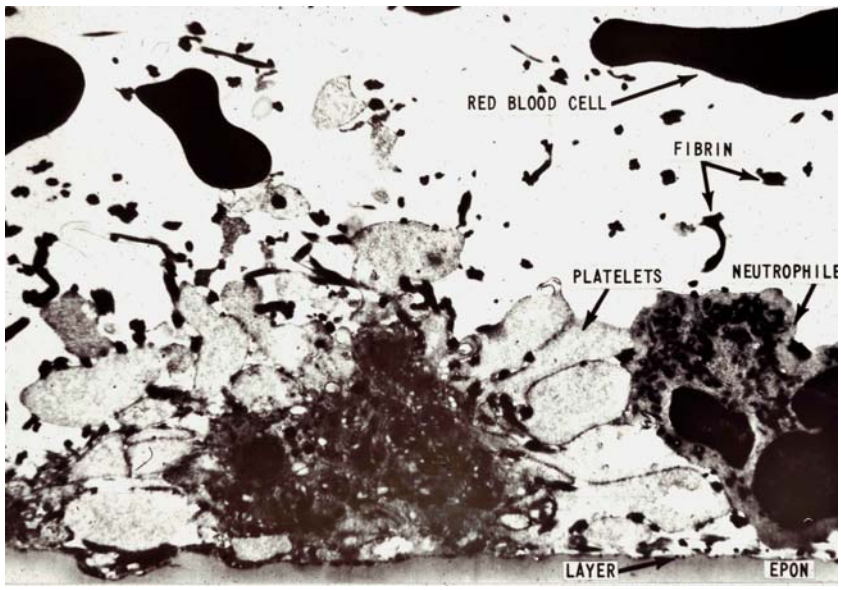


Fig. 2 A transmission electron micrograph of an early thrombus deposit on an epoxy substratum exposed to flowing blood. The individual platelet sizes average 3 micrometers across, with the red cells at 7 micrometers and the neutrophilic white cell at 20 micrometers

isolated from normal plasma, or attempt to correlate results taken at room temperature.

Water contact angle data, alone, are *not* sufficient to determine or correlate polymer properties with blood compatibility. Polytetrafluroethylene, polydimethylsiloxane (PDMS), and polyethylene are all hydrophobic; only the silicone (PDMS) is thromboresistant [18]. Glass tubes and glutaraldehyde-tanned human umbilical cord veins have hydrophilic interiors; only the crosslinked bioprosthetic (Biograft) blood vessels are thromboresistant [19]. Both PDMS and Biografts have Critical Surface Tensions between 20 and 30 mN/m.

6 Conclusion

Safe and effective materials for blood-contact applications can now be reliably selected based on entirely *in vitro* laboratory tests.

This generalizing concept emerges from the outcomes of competing proposed approaches to developing biomaterial "biocompatibility", recognizing that most often the practical goal is either to promote *or* inhibit bioadhesion, and the material(s) involved may be synthetic *or* biological. The main concepts for over thirty years have been control of (a) surface charge, (b) surface texture, and (c) surface energy. Judging each concept by the practical products that have resulted and continue to benefit personal, public and environmental health, there is a good case for surface energy control as the dominant factor in modulating biological responses to synthetic materials.

Safe and effective, *long-term* biological responses to so many different materials are correlated with and controllable by surface energetic factors that it is now appropriate to consider this a "universal" approach to all underwater interactions: witness the blood compatibility of Starr-Edwards heart valves (over 30 years), Dardik Biografts for limb salvage (15 years), pyrolytic carbon heart valves (over 15 million human patients), and the growing successes of the "Hershey heart" as a bridge to cardiac transplantation—*and* at least 9 similarly surface-energy controlled ship bottom paints to resist biofouling now in the commercial marketplace based on the same concepts and polymers as used in artificial heart development.

On the other hand, note the secure biological adhesion routinely obtained to polyethyleneterephthalate vascular grafts and commercially pure titanium dental implants, many millions implanted in people around the globe for more than 2 decades. These utilitarian results have emerged from 3 decades of concurrent inquiry into Nature's own surface properties: natural skin and tissue surfaces, interior walls of living blood vessels, the eye's cornea, red blood cell surfaces, intra-oral mucosa, conjuctival surfaces, temporomandibular discs, cartilage, teeth, porpoise and killer whale integuments, canine heartworms, gorgonian corals and confluent lawns of living bacteria, as noted in the earlier-cited references and a current encyclopedic review [20].

Note that "mixed mode" applications of these concepts produce peril for both persons and products, as in the unwanted scar encapsulation of breast implants rather than the desired tissue integration. For example, without changing the surface energetics, adding surface texture can make tissue integration less secure, and modifications of surface charge, even though they do affect wetting behaviour via dissociable groups in aqueous media, are otherwise without effect in the high-ionic strength environments of biology.

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