Bioadhesion—a phenomenon with multiple dimensions

Per-Olof J. Glantz, Thomas Arnebrant, Tommy Nylander and Robert E. Baier

Department of Prosthetic Dentistry, Malmö University, Malmö, Sweden; Swedish Institute for Surface Chemistry, Stockholm, Sweden; Department of Physical Chemistry 1, Lund University, Lund, Sweden; Department of Oral Diagnostic Sciences, New York State University at Buffalo, Buffalo, NY, USA

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This paper reviews some relevant citations regarding the non-specific forces that must be considered in oral bioadhesive events. These range from forces related to restorative dentistry to those related to prevention and molecular biology. Types of interactions discussed are: 1. Van der Waal's forces; 2. electrostatic double-layer forces; 3. solvent-dependent interactions; 4. hydrogen bonding; 5. hydrophobic interactions; 6. hydration forces; 7. steric forces; and 8. covalent bonds. Examples are given of the various types of interaction that occur at different surface separation ($\leq$400 Å) between adsorbed films of a pure salivary protein fraction (PRP1). □ *Long-range interactions; non-specific interactions; oral adhesion*

Per-Olof Glantz, Malmö högskola, Hjälmaregatan 1, SE-205 06 Malmö, Sweden. Tel. + 46 40 6657100, fax. + 46 40 6657305, e-mail. Per-Olof.Glantz@mah.se

There is probably no more successful reconstructive profession than that of restorative dentistry. In replacement, capping, crowning, varnishing, sealing, bonding, and otherwise mating of living and non-living materials in the oral cavity, dentists attain functional adhesive joints that can resist extremes of temperature, force, and reactive chemistry for useful periods of enormous benefit to those who seek their services. This is all done through a practical, clinical knowledge of and respect for the basic principles of adhesion science, with virtually no claims made for "specificity" of interaction over the entire range from cavity varnishes through 4th-generation dentin-bonding composites.

Dentistry has not yet come as far in preventive and therapeutic tasks that engage challenges of microbial colonization, plaque build-up, and molecular biology. In dental research and development approaches to these problems, the most frequent path is to discover and overcome the so-called "specific" forces of biological interaction presumed to be responsible for the patient's ills. Even if there is frequently a need to address the underlying physical/chemical bases of all adhesive phenomena, this is seldom explicitly reported in published manuscripts.

With a broader baseline concept, dental research reports would also be better appreciated by researchers in other disciplines, who note, for example, that:

- "specific" charge–charge interactions in saline fluids (like saliva) cannot occur until the potentially adhesive partners are within a few nanometers of one another
- "summed" non-specific forces prompt such interactions at distances 10-fold greater
- adsorbed macromolecules are present on virtually every interacting partner in the form of a complex biological fluid (like saliva) masking potential lock-and-key sites from one another until contact is made, and
- surface "reconstruction" takes place after contact of potentially mating partners and not at-a-distance in anticipation of a coming collision that may never take place.

With this background in mind, and as a service to authors and readers of *Acta Odontologica Scandinavica*, we therefore provide a brief review and list of some relevant citations regarding the universal non-specific forces that must be considered in all studies of bioadhesion, from restorative materials to bioadhesive events of all types.

Types of interaction

Initially, it is essential to recognize that the total forces between any types of surface increase with the interacting areas. It is also essential to note that the strength and range of interaction between single molecules in solution are in many cases orders of magnitude less than between macroscopic surfaces made up of similar molecules. This generally means that long-range forces between macroscopic surfaces can be averaged over the molecular structures as the distances are larger than the dimensions of the involved molecules. In biological systems, for particles such as single or aggregated cells, this means that the range over which they may interact increases with the particle diameter. Apart from the curvature, factors such as the topography of the macroscopic surfaces can have a major impact.

In biological systems it must be recognized that, owing to the amphiphilicity of many biological macromolecules, orientation effects can often occur at interfaces. These are crucially important and have in fact been reported to be so dramatic as to change overall long-range interactions from

being purely repulsive to their becoming attractive (1). For proteins, conformational changes may also occur in addition to pure orientational effects, and some so-called "specific" protein-ligand (e.g. antigen-antibody) interactions have been demonstrated to have strong orientation/conformation dependence (2–5).

Before directing our attention to the various individual types of interaction between atoms, ions, and molecules, it should also be recognized that for any type of charged surface, such as biosurfaces, it is common to distinguish between pure electrostatic repulsive forces, which oppose adhesion, and attractive forces, which, if the surfaces come close enough, will strive to bring the interacting bodies together. This balanced relationship between repulsive and attractive interactions is expressed in the so-called DLVO theory, named after the scientists behind it (6, 7)

Van der Waal's (dispersion) forces

The attractive forces included in the DLVO theory are normally termed van der Waal's forces. These are of quantum mechanical origin and may be further divided into the following three components (8, 9): (i) The so-called dispersion (London) forces. These originate out of the electronic motions in paired molecules and give rise to attractive interactions. (ii) The electrostatic interaction between permanent dipoles (Keesom type forces). (iii) The interactions between permanent and induced dipoles (Debye type forces).

The non-retarded van der Waal's force is inversely proportional to the square of the distance between two spherical particles, where the proportionality constant is the so-called Hamaker constant. The Hamaker constant, which has the dimension of energy, can be used to describe the strength of the van der Waal's interaction and is dependent on the properties of the involved particles and on the medium where the interaction takes place.

Electrostatic double-layer forces

A charged surface will always be surrounded by a cloud of counter ions (double-layer) which balance the surface charge. When two surfaces with the same charge approach each other, a repulsive force will arise due to the overlap of the double layers. This is the origin of the electrostatic double-layer forces, which can be described by the so-called Poisson-Bolzmann equation. These forces decay exponentially with the surface separation, with a decay length (and hence a range of action) that decreases with increasing ionic strength in the surrounding medium. As pointed out by Ninham & Yaminsky (10), it should be noted that specific dispersion force-induced ion adsorption can sometimes dominate at charged interfaces, thereby making it virtually impossible to distinguish between the contribution of electrostatic and dispersion forces. For simple electrolytes such as sodium chloride solutions the decay length of the double-layer force (the Debye length) is proportional to $1/\sqrt{}$ (salt concentration). In physiological saline, for example, the decay length is approximately 0.8 nm (8 Å).

In more complex biological fluids, however, this simple relation no longer holds, partly because proteins, which generally carry a large net negative charge, contribute significantly to the decay length already at low concentrations (11, 12). Thus, the decay length in saliva is likely to be less than the value of approximately 1.0 nm calculated from its salt composition. Any change in ionic strength will have an impact not only on the adsorption of proteins, but also on microbial adhesion. This has been demonstrated by Larsson & Glantz (13), who studied the adhesion of *Streptococcus sanguis* on hydrophobic and negatively charged hydrophilic surfaces. They found that even at moderate increase in ionic strength bacterial adhesion to negatively charged surfaces was promoted; this was assigned to less repulsion (larger screening of electrostatic repulsive forces) between the surface and the adhering cells.

Solvent-dependent interactions

Since the continuous phase in most biological systems is aqueous, solvent effects involving water are of key importance when discussing interactions between surfaces in biology. Of particular relevance are hydrogen bonds, hydrophobic interactions, and hydration forces (cf. 8, 9).

Hydrogen bonding

Hydrogen bonding is basically an electrostatic interaction that arises when a hydrogen atom bound to an electronegative atom, e.g. nitrogen, oxygen, or fluorine, interacts with another electronegative atom. The force is short range and highly directional. As water molecules form particularly strong hydrogen bonds, such bonds between macromolecules or between macromolecules and surfaces are less important in aqueous solution. However, in a more hydrophobic environment, such as in the interior of a protein, hydrogen bonds become significant and are essential in the formation of protein secondary structure.

Hydrophobic interactions

The so-called hydrophobic effect is another particularly important phenomenon with respect to bioadhesion related to the presence of water. It has been assigned to the tendency of water molecules to form ordered structures in proximity to non-polar (i.e. oily) molecular domains and may give rise to attractive interactions between non-polar residues such as hydrocarbon side chains. Hydrophobic interactions have also been demonstrated to have a major influence on many types of structure formation in biological systems, e.g., folding of proteins and membrane self-

assembly (cf. 8, 9). On the macroscopic level, long-range attractive forces have been observed between hydrophobic surfaces formed by adsorption or deposition of amphiphilic molecules and are believed to be non-equilibrium forces (14, 15). It should be noted that the origin of the long-range attractive forces between hydrophobic surfaces is controversial, but their occurrence has been related to instability of the deposited monolayer (16–19).

Hydration forces

A type of short-range (<1 nm) repulsive interaction, suggested as originating from the binding of water molecules to polar surface sites, has been observed between phospholipids (20) and solid surfaces under certain conditions (21, 22). This so-called hydration force is believed to be particularly important in biological systems, since it prevents contact even in the absence of charge–charge repulsion. The origin of this force is not yet fully understood, but as an alternative to being an effect of water structure, Israelachvili & Wennerström (23) argue that the observed repulsive force is more likely to be dominated by an entropic repulsion.

Steric forces

Repulsive so-called steric interactions or steric forces are considered to be important in biological systems. These do not constitute a special type of interaction but rather appear as the result of the increasing concentration of molecular segments that occurs when surfaces bearing for example bound macromolecules come close to each other.

Covalent bonds

For completeness, the general nature of covalent bonds should also be described. Like metallic bonds, covalent bonds are characterized by the electrons that are shared between the engaged atoms. Covalent bonds operate only over short interatomic distances ($1–2 \times 10^{-1}$ nm); they tend to decrease in strength with increasing bond-length, and are oriented at well-defined angles. Unless chemical reactions take place, based on the formation or breakup of for example disulphide bridges, covalent bonds are unlikely to be important in bioadhesion processes under physiological conditions.

Discussion

Even in simple systems, interactions between particles or between particles and surfaces are usually determined by several components, as in the classical DLVO-type interactions discussed above. In biological systems, interactions can be more complex, as they often take place in high ionic strength aqueous media and in the presence of macromolecules. Therefore electrostatic contributions may be less important, at least at long range, in favor of force components such as steric forces, hydrophobic interactions, and hydration forces.

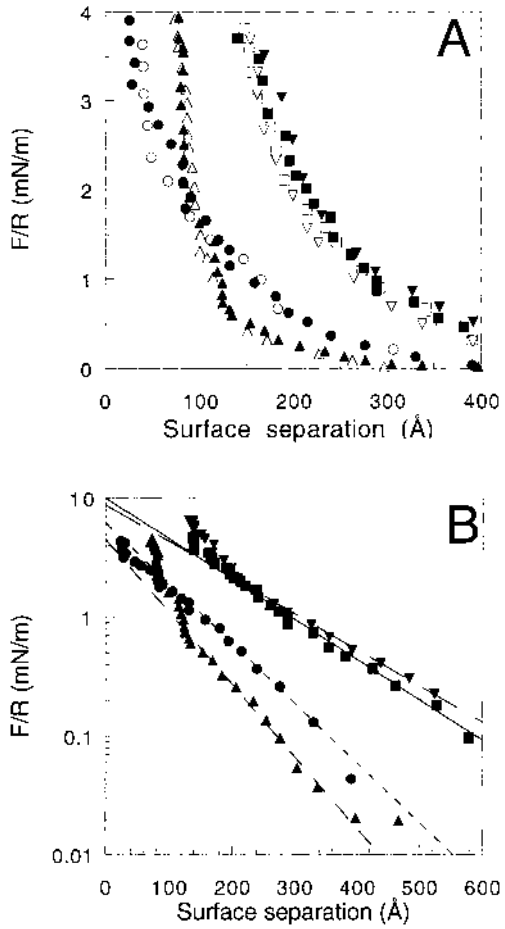

Fig. 1. The normalized force versus distance between mica surfaces 20 h after the addition of 17 mg/ml (1.05 ± 10^{-6} M) PRP in 1 mM NaCl (●), and in 1mM $CaCl_2$ (▲), as well as the curve recorded 20 h after the subsequent addition of 10% saliva to a PRP layer adsorbed from a 1 mM $CaCl_2$ solution (■) and in pure 10% saliva solution (▼). (A) The force curves in linear scale. The force curves recorded on decompression are also inserted and are indicated by the corresponding unfilled symbols. (B) The force curves recorded on compression are shown in logarithmic scale. A linear fit was performed on the long-range part of the force and the resulting lines are inserted. An electrostatic repulsive force is roughly proportional to e^{-kD}, where k^{-1} is the Debye screening length. The obtained slopes of the linear fits correspond to the following values of k^{-1}: 86 Å (- - -) for PRP in NaCl, 72 Å (– – –) for PRP in $CaCl_2$, 129 Å (-) for saliva added after PRP adsorption and 143 Å (— — —) for pure saliva solution.

An example of such interactions is illustrated in Fig. 1A, which shows the distance dependence of the total force acting between mica surfaces bearing adsorbed layers from solutions of a pure salivary protein fraction (Proline Rich Protein 1, PRP 1) (cf. 24) and whole mixed human saliva. The force was measured versus surface separation by means of the so-called interferometric surface force

technique (25–27). Forces are indicated on the Y-axis, and according to common convention attractive ones are indicated as negative and repulsive ones as positive. The X-axis shows the separation of the surfaces in Ångstroms (Å). It is clear that the forces obtained in the cases shown are repulsive and that their ranges of operation are clearly different for the layers adsorbed from pure PRP preparations compared with those obtained in whole saliva.

If plotted on a logarithmic scale (Fig. 1B), the decay length of the measured interaction can be compared with that of the electrostatic double-layer force at the ionic strength prevailing in the experimental conditions. For PRP layers it is evident that the decay length corresponds to what would be expected, except at short separations where a steric contribution sets in. In contrast, the adsorbed layers from the whole secretion show a much longer range interaction than the one expected from electrostatics alone, suggesting a substantial steric contribution. It is interesting that the interaction between the layers adsorbed from whole saliva resembles the one previously reported between layers of adsorbed gastric mucins (28, 29), which points to a strong contribution to the interaction of high molecular weight glycoproteins. Furthermore, the interaction between PRP 1 layers clearly has similarities with the interaction between layers of a milk protein, β-casein, which bears several common structural features with the PRP (1). These results are discussed in detail elsewhere (30, 31).

In conclusion, and bearing in mind the common nature of all adhesive events, interfacial phenomena and forces that are involved in bioadhesion are strongly related to those considered in classical colloid and surface science. In biology, however, particular emphasis has been placed on the contributions from short-range force fields. These fields rarely extend more than a couple of atomic diameters from the generating surface and always act in conjunction with the so-called long-range forces (extending to tenths of nanometers and more) which bring or reject a substrate over large distances to or from an enzyme or a receptor.

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