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Translational bioadhesion research: embracing biology without tokenism

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Bioadhesion has attracted a sizable research community of scientists and engineers that is striving increasingly for translational outcomes in anti-fouling and bioinspired adhesion initiatives. As bioadhesion is highly context-dependent, attempts to trivialize or gloss over the fundamental physical, chemical and biological sciences involved will compromise the relevance and durability of translation.

This article is part of the theme issue 'Transdisciplinary approaches to the study of adhesion and adhesives in biological systems'.

Driven by renewed initiatives to remediate biofouling on the one hand, and by biomimetics of natural adhesive strategies on the other, bioadhesion research has made great strides during the last 20 years. The antifouling focus has maintained that a fundamental understanding of surface attachment by sessile organisms will ultimately provide insights leading to the design of attachment-resistant surfaces [1]. Biomimetic adhesion, by contrast, is defined as the abstraction and implementation of good adhesive design from biology [2]. It too depends on diligent characterization prior to practical translation. Both emphases have the potential for profound economic impacts [3,4].

Interdisciplinary collaboration, particularly between biologists and engineers, played and continues to play an important role in enabling progress in both the biofouling and biomimetics faces of bioadhesion. In the most successful collaborations, biologists provide expertise about ecology, life history, biochemistry and behaviour, whereas the engineers bring materials and surface science, spectroscopy, electronics, measurement and systems analysis. It seems straightforward, but balancing these skills in an investigation to make useful and enduring discoveries can be challenging. An exemplary case of imbalance was a classic and elegant study inspired by mussel adhesion in 2006 [5]. Mussel adhesion involves interfacial proteins, e.g. mfp-3 and mfp-5 [6] in which tyrosines have been modified to 3, 4-dihydroxyphenyl-L-alanine (Dopa) residues reaching levels of nearly 30 mol%. Using conditions of reduced complexity, the team of engineers set out to assess the Dopa contribution to adhesion onto various surfaces by attaching a single residue of Dopa to a polyethylene glycol-passivated cantilever tip in an atomic force microscope (AFM).

The adhesion of a tethered Dopa to titania surfaces at pH 7.5 failed at a force half that of a covalent bond yet was completely reversible and approximately 10-fold greater than the tyrosine controls. When Dopa was oxidized to Dopa-quinone, adhesion to titania was reduced greater than 80%, yet over an amine-rich surface, an irreversible covalent bond was formed between the amine and quinone. The team concluded that Dopa-mediated mussel adhesion to minerals and metal oxides was strong and reversible, yet also versatile enough for covalent bonding to polymer surfaces following Dopa oxidation. The results were exciting and highly influential (cited over 1300 times) and launched hundreds of studies into the synthesis and adhesion of catechol-functionalized polymers. Although the results have been independently confirmed [7], tethering Dopa to an AFM tip has not proven applicable to adhesion on minerals or metal oxide surfaces by mussels nor even by synthetic polymers functionalized with catechols [8,9]. For example, Dopa-containing proteins and polymers exhibited much lower adhesion to titania at or above

pH 6 than in the single Dopa experiment presumably because of facile Dopa oxidation to Dopaquinone under actual field or testing conditions [8,10–12]. The engineering study lacked insight about the true ‘context’ of Dopa, meaning those conditions relevant to the synthesis, storage, deposition and maintenance of Dopa-functionalized proteins or polymers *in situ*.

Since 2006, several clues about the Dopa context in mussel adhesion have emerged. To begin with, the mussel foot deposits Dopa proteins under conditions of low pH [10,13], low ionic strength [10], and strongly reducing redox [10,14]. Applying these conditions to AFM or surface forces apparatus (SFA) tests achieved adhesion energies of greater than 15 mJ m^{-2} for mfp-5 on mica [11,15], exceeding even the high-mark of the biotin-streptavidin interaction [16]. However, such conditions are unsustainable in seawater (pH 8.2, ionic strength 0.7 M and a redox potential of +0.8 V relative to the standard hydrogen electrode [17]), thus reigniting concerns about how a mussel maintains adhesion in the field after the foot has withdrawn. The thermodynamics are worth examining (figure 1): combining the redox potential for Dopa oxidation [18] and oxygen reduction at pH 8 predicts a very favourable oxidation, i.e. $\Delta E_o = +0.58 \text{ V}$, with a ΔG of -20 kJ mole^{-1} (figure 1, triangles 1 and 3). Because mfp adhesion to mineral surfaces is diminished in proportion to increasing Dopaquinone content, mussels must have the resources to prevent or counteract this oxidative damage. Yu *et al.* [10] first proposed that mussels protect their adhesives with antioxidants, which is also a widespread practice in industry [19]. However, this too is a short-lived strategy because the redox potential of a good antioxidant is by definition lower than that of the group it is designed to protect. For example, thiols in mfp-6 are effective at reducing Dopaquinone back to Dopa at pH 8 and actually do restore Dopa-mediated adhesion in the SFA after oxidative damage has occurred (figure 1, triangles 1 and 2), but only briefly at best because thiols are even more readily oxidized by O_2 than Dopa, i.e. $\Delta E_o = +1.0 \text{ V}$, which translates to a ΔG of -58 kJ mole^{-1} (figure 1, triangles 1 and 3). Again, turning to nature, we discover that although the pH and ionic strength of mussel adhesive plaques equilibrate with seawater, reducing redox conditions do not and even persist for months [20]. How mussels maintain a reducing reservoir in plaques surrounded by the oxidative environment of seawater thus becomes the foremost new focus of collaborative research.

Given the thermodynamics of Dopa open to the environment, successful redox management in the plaque is likely tied to kinetic traps that contrive, often by confinement, to insulate redox from bulk conditions without disabling targeted and controlled redox exchange [21]. Coacervation and liquid–liquid phase separations by mfps [22–26] are increasingly being implicated as kinetic trap arenas in plaques. Our research is indicating that adhesive proteins with Dopa

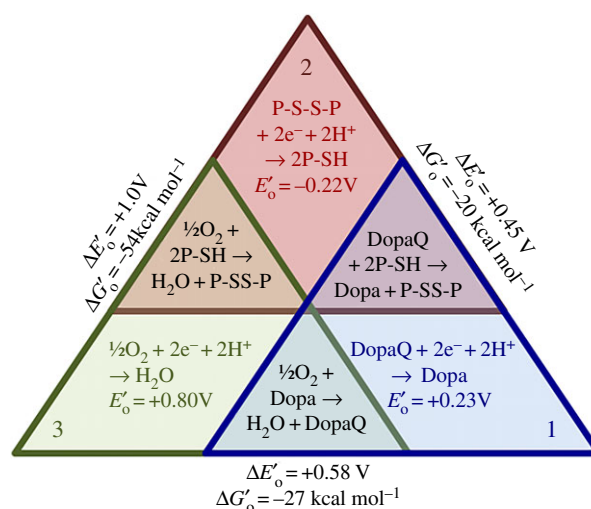


Figure 1. Redox in mussel adhesive plaques is governed by three half-reactions denoted by coloured triangles: 1 (blue), the reduction of Dopaquinone (DopaQ); 2 (red), disulfide reduction; and 3 (green), oxygen (O_2) reduction with redox potentials at pH 8, 20°C , 1 atm and relative to the standard hydrogen electrode. The half-reactions couple in a pairwise manner for three redox exchanges (overlaps) with $\Delta E'_o$ and $\Delta G'_o$ as indicated. (Online version in colour.)

and thiols segregate to different phase-separated compartments some (adhesive proteins, for example) of which are exposed to, whereas others (antioxidant proteins) are insulated from, the ambient environment—the latter serving as electron reservoirs for the former. Characterizing and measuring electronic exchanges between these compartments *in situ* and *in vitro* will require inspired collaborations that embrace biology as much as engineering.

A significant lesson emerging from research on mussel adhesion that is widely applicable to other organisms is that there is no substitute for penetrating biological exploration at many length and time scales [27,28]. Indeed, this exploration is as essential for good translation as it is for discovery. As reviewers and funding agencies place more and more emphasis on translation for its own sake we should stand together to insist that a retreat from the biology is counter-productive and may even be a misuse of taxpayer money. Translations driven by superficial impressions or fantasies about biology will not stand the test of time because they have missed the point.

Data accessibility. This article has no additional data.

Competing interests. I declare I have no competing interests.

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