Mimicking Biology's Sulfur Switching Mechanism for Redox Signal Reception

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ABSTRACT

Bridging communication between biology and electronics is critically dependent on the modality. There have been remarkable successes in bio-device communication through the electrical modality associated with the flow of ions across cellular membranes because this modality is integral to communication in biology (e.g., in neuromuscular systems) and this modality is readily accessible to convenient electrode measurements. There has been considerably less success in establishing bio-device communication through molecularly-specific biological modalities because of the intrinsic measurement challenges. We are focused on a third modality associated with reduction and oxidation (redox) reactions. From a biological perspective, this redox modality is integral to immune responses and wound healing, and even appears to inter-connect biological systems (e.g., the gut-brain axis) and biological kingdoms (e.g., the gut microbiome and epithelium). From a technological perspective, this redox modality has global electrical features that are accessible to convenient electrode measurements. Further, this redox modality has molecular features that offer some level of selectivity to redox-based bio-device communication. Here, we focus on a single mechanism integral to biological redox-based signal processing - the oxidative switching of thiols to disulfides. Biology uses this sulfur switching for the redox-responsive expression of genes associated with stress responses. Using model polymers, we show that electrochemical inputs can be used to induce redox-based sulfur switching.

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Experimental results demonstrate that variations in the “strength” (i.e., voltage) of the redox input signal can lead to qualitatively and quantitatively different responses in polymer assembly. Potentially, these observations recapitulate the redox-responsive sulfur switching that alters the permeability of mucous membranes.

KEYWORDS

Bioelectronics, Redox biology, Disulfide bond, Electrochemistry

1 Introduction

Biology can be considered to be a network of interconnected communicating sub-systems. From this perspective, common technology goals are to acquire information to understand a biological system (e.g., to diagnose) or to participate in communication to alter a biological system (e.g., for treatment). A key question is what modality can access this communication?

2 Bio-relevant Communication Modalities

The most successful example of technological access to biological information probably involves the electrical modality associated with the flow of ions across cellular membranes. This modality enabled neurobiologists to observe the communication of nerve cells decades before the biotechnology revolution. It also enables clinicians to make EKG measurements that enable characterization of the complex cardiovascular system. In addition to observing biology, this ionic electrical modality also enables interventions (e.g., pacemakers) to re-program pathological trajectories. The remarkable success of this ionic electrical modality for enabling access to biology is limited by the fact that not all biological systems use this electrical modality for communication.

Alternatively, biology is known to communicate through molecularly specific modalities (e.g., the endocrine system uses hormones). Typically, molecular modalities involve cell-surface receptors that recognize an extracellular molecular signal (e.g., a

ligand) with “lock-and-key” specificity. Ligand binding often results in intracellular signal transduction cascades that ultimately can alter biological responses (e.g., induce gene expression). Accessing such molecularly-specific biological information often requires complex instrumentation (e.g., mass spectrometry) while participating in this communication (e.g., to alter a pathological trajectory) often involves specific therapeutics. Therefore, communicating with biology through such molecular modalities is challenging: highly trained personnel are required and drug development is a long and costly process.

We are focused on a third modality involving redox reactions. Biology extensively uses this redox modality for energy harvesting and immune defense (e.g., inflammation). Importantly, this redox modality has both electrical and molecular features. The electrical features reflect the fact that electrons are “flowing” through these redox-reactions, while the molecular features reflect the fact that electrons must be “carried” by molecular species.

3 Mediator Probing for Access to Redox

Our approach to access redox information and participate in redox communication is analogous to sonar as illustrated in **Figure 1a**. [1] Specifically, we use the electrode as a transmitter and/or receiver that interconverts electrical and redox inputs/outputs (**Figure 1b**). We purposely add molecular redox mediators (e.g., electron shuttles) to our samples and diffusion of these mediators serve as the transmission of the redox signals. These mediators can be thought of as redox switches that can exist in either oxidized or reduced states, and redox interactions with chemical components in the sample serves to switch their redox state.

Importantly, redox interactions between mediators and the chemical/biological components in a sample are constrained by thermodynamics: electrons tend to “flow” from chemicals with more-reducing redox potentials (E^0 's that are more-negative) to chemicals with more-oxidizing redox potentials (E^0 's that are more-positive). This thermodynamic constraint provides some intrinsic selectivity to redox probing.

4 Mimicking Sulfur Switching

One of the best-studied redox signaling molecules in biology is hydrogen peroxide (H_2O_2) [2] and a common H_2O_2 -recognition mechanism involves the oxidative conversion of the cysteine residues of proteins into disulfides (**Figure 1c**) [3]. Because this reaction involves the switching of the sulfur (S) atoms between reduced and oxidized states, this mechanism is often referred to as S-switching. One such S-switching mechanism is the H_2O_2 -based bacterial stress response involving the OxyRS regulon [4]. Also, it has been proposed that S-switching is involved in redox-control of the permeability of mucous membranes in the gut and lungs [5].

As illustrated in **Figure 1d**, we are mimicking the S-switching mechanisms using redox mediators as our diffusible molecular signal (analogous to H_2O_2) that induces the oxidative conversion of thiols to disulfides. As illustrated, information is coded and

transmitted at the electrode by oxidation of the mediator. Diffusion of the mediator into the solution serves to propagate the signal, and the oxidation of thiols into disulfides serves as signal reception and decoding. This concept is illustrated by the oxidative crosslinking of a thiol-containing polymer into a disulfide crosslinked polymeric network (as demonstrated by the inset photograph). Importantly, these mediated oxidation reactions are sufficiently mild that they can be performed in the presence of living cell populations. Thus, this oxidative disulfide crosslinking mechanism mimics the mechanisms used by biology to generate crosslinked mucous membranes and allows populations of viable cells to be entrapped within the hydrogel membrane.

Figure 1: (a) Sonar analogy; (b) electrochemical interactive probing of a chemical environment; (c) an important mechanism in biological redox signaling is sulfur-switching; (d) mediated electrochemical sulfur-switching.

5 Conclusions

We are developing the experimental toolkit for redox-based molecular communication. Emerging biological research illustrates the importance of redox as a signaling modality while the electrical features of this modality provides relatively simple access through electrochemistry. Here we describe how the use of mediators can mimic an important mechanism (S-switching) for the recognition and reception of redox signals.

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