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Review article

Electrochemistry for bio-device molecular communication: The potential to characterize, analyze and actuate biological systems

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ABSTRACT

Molecular communication offers an exciting vision for extending the advances of communication technology to the chemical modalities of biology. Realizing this vision is often impeded by the technical difficulties in creating devices capable of sending and/or receiving information that is coded in a specific chemical structure. Here we suggest that reduction–oxidation (redox) reactions offer interesting opportunities for molecular communication. Redox has features of an electrical modality as redox reactions are essentially a flow of electrons, but redox also has features of molecular modalities as the electrons are not "bare" but must be carried by molecular species. Electrochemistry provides the tools to measure redox based information. Consistent with an electrical modality, electrochemical measurements are simple, rapid and sensitive, while the data is in a convenient format for signal analysis. Importantly, redox also has features of a global modality that is not specific to individual chemical structures but can be accessed at a systems-level by electrochemical measurements. In fact, emerging research suggests biology uses redox as a global signaling modality. We describe an approach to access redox information through interactive electrochemical probing that is analogous to sonar. Tailored electrical inputs are coupled with diffusible redox mediators (electron shuttles) to access redox information in a local environment and generate complex but interpretable electrical output signatures. We use results from recent experimental demonstrations to illustrate the opportunity for redox to bridge bio-device communication.

Contents

1. Introduction

An exciting vision for molecular communication is to extend the remarkable advances of information technology to the molecular

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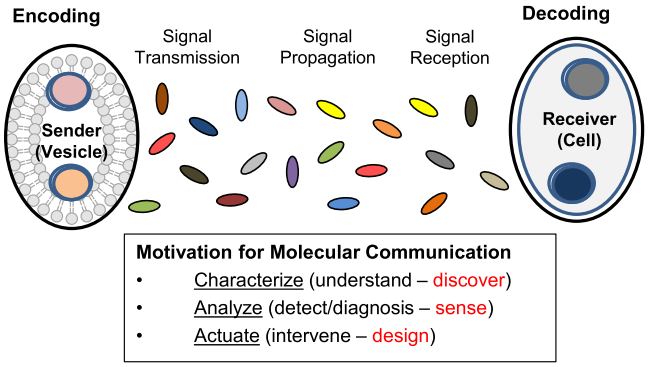

Fig. 1. Schematic vision for bio-device molecular communication.

modalities of biology [1–13]. This vision is illustrated in Fig. 1 which shows a molecular communication device (e.g., a vesicle) that is capable of exchanging information with biology. The motivations for creating such devices are: to observe biology to discover how it functions (i.e., to characterize); to detect information of homeostasis or pathology (i.e., to analyze); and to intervene in biological processes (i.e., to actuate). One challenge to realizing this vision is that the molecular signals in biology are generally believed to be highly specific—an enzyme generates a signal with a specific chemical structure and this signal is recognized by a receptor with high molecular specificity. This specificity suggests that a near infinite number of molecular signals could be simultaneously propagating through a single medium (e.g., blood) while the assembly of the necessary device components (enzymes and receptors) to transmit and receive any individual signal poses a substantial technical challenge. Thus there remains a wide chasm between the exciting conceptual vision of Fig. 1 and the capabilities to fabricate the necessary "hardware" to create devices that enable us to communicate with biology.

While the vision in Fig. 1 to build devices that can communicate with and actuate biology through individual molecular modalities is a great long term goal, it is a difficult starting point for experimentalists. The obvious question is whether molecular-specificity is an essential feature of all biological communication or if biology uses alternative global modalities that can be more easily accessed at a systems level using relatively simple hardware. The obvious example of such a global modality is the electrical modality associated with the ionic potentials and currents that are integral to neural and neuromuscular communication. Fig. 2(a) illustrates that early neurobiologists used electrode measurements to characterize the action potentials that underpin this ion-based electrical communication in biology [14]. Fig. 2(b) shows that electrocardiograms (EKGs) use a set of electrodes to access these electrical activities to provide a robust signature pattern that allows analysis of a complex biological system (the cardiovascular system). Fig. 2(c) shows that defibrillators can impose electrical signals that are devoid of molecular specificity to actuate biology: these electrical signals can intervene to reprogram pathological trajectories.

In Section 2 of this tutorial, we suggest that biology uses a second electrical modality based on reduction and oxidation (redox) reactions and this modality also has features that are somewhat global. In Section 3, we argue that electrochemistry provides a bridge between the electrical modality convenient for information processing and the molecular modality that is integral to bio-based communication. In Section 4, we provide two illustrative examples from our recent work. In the first example, we use electrochemistry to detect the synthesis of a small redox-active bacterial signaling molecule that is associated with virulence. In the second example, we enlist synthetic biology for the recognition and transduction of a molecular signal into a convenient electrochemically detectable signal. In both examples, hydrogel thin film technologies were used to prepare electrode coatings with appropriate information processing capabilities. In the final section, we provide a perspective of the opportunities and challenges for applying electrochemistry as a tool for molecular communication.

2. Redox in biological molecular communication

As mentioned in Fig. 2, biology is well-known for using a global electrical modality associated with ionic currents to perform communication functions. We contend that redox is another global modality, which has features of both electrical and molecular modalities. In contrast to the currents and potentials associated with ion transport across lipid membranes, redox is essentially a flow of electrons. Since free electrons do not generally exist in water, it seems counter-intuitive that an electron-based electrical modality could operate in the aqueous environments that are characteristic of life. However, the currents "flowing" through this electron-based redox modality are not associated with the movement of "bare" electrons, but rather the individual electrons must be transferred via chemical species through reduction–oxidation (redox) reactions. Often these redox reactions involve chemical species that are stable in two states (oxidized and reduced states) and these chemical electron carriers are referred to as redox couples. From a biological standpoint, electron transfer through stable redox-couples is essential for energy harvesting through respiration and photosynthesis. For instance, in the respiratory chain, individual or pairs of electrons are transferred from a biological reducing agent (e.g., NADH) through series of stable redox species (e.g., cytochrome c and ubiquinone) and ultimately to O_2 to generate water. Redox reactions are also essential in biosynthesis. For instance, diffusible reductants (e.g., NAD(P)H) generated during catabolism (e.g., glycolysis) are used to supply the electrons necessary to synthesize more-reduced products (lipids) from more-oxidized substrates (glucose).

2.1. Biology uses redox signals for communication

In addition to using redox reactions for energy harvesting and biosynthesis, there is emerging evidence that biology uses redox as a modality for communication [15]. Biological mechanisms are known for the partial reduction of O_2 to yield reactive oxygen species (ROS) [16] such as H_2O_2 that can diffuse across cell membranes and propagate through the intercellular space to different locations. Such a redox signal can be "received" by cells at a destination through mechanisms that do not appear to conform to the conventional lock-and-key receptor–ligand model. In particular, protein receptors may have cysteine residues that can undergo redox reactions with H_2O_2 that serve to switch the cysteine thiol (-SH) into a disulfide crosslink (-S-S-) that alters protein conformation and activities [17–21]. These sulfur switches are not molecularly specific, but rather are atomically specific, and it has been proposed that such sulfur switches provide a means for redox signals to be recognized and transduced generically through multiple biological regulatory pathways to enable information to be processed and responses to be coordinated at a more global level [15,21–26].

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