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Mediated electrochemistry for redox-based biological targeting: entangling sensing and actuation for maximizing information transfer☆

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Biology and electronics are both expert at receiving, analyzing, and responding to information, yet they use entirely different information processing paradigms. Biology processes information using networks that are intrinsically molecular while electronics process information through circuits that control the flow of electrons. There is great interest in coupling the molecular logic of biology with the electronic logic of technology, and we suggest that redox (reduction-oxidation) is a uniquely suited modality for interfacing biology with electronics. Specifically, redox is a native biological modality and is accessible to electronics through electrodes. We summarize recent advances in mediated electrochemistry to direct information transfer into biological systems intentionally altering function, exposing it for more advanced interpretation, which can dramatically expand the biotechnological toolbox.

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Introduction

Biology and electronics have powerful and complementary information processing capabilities. Biology is adept at receiving and transmitting information that is coded in molecular structure while electronics generally receives and transmits information that is coded in electromagnetic radiation. The fusion of biological-electronic information processing could have transformative impacts, such as the development of molecular biodevices that enable direct communication with biology [1•,2•]. However, a key challenge to realizing this vision is the interfacing of biology and electronics. We contend that the biology's native redox modality (i.e. the exchange of electrons between chemical species) can uniquely serve as the interface between biology and electrodes. Here, we describe the interfacing of biology to electrodes through redox and summarize recent studies in which biological systems were engineered to respond to electrode-imposed cues in order to control responses that range from molecular assembly to gene expression (i.e. electrogenetics). In turn, the same redox-enabled bioelectronics can enable assessment. Overall, the entanglement of sensing and actuation enables far more advanced interpretation and understanding.

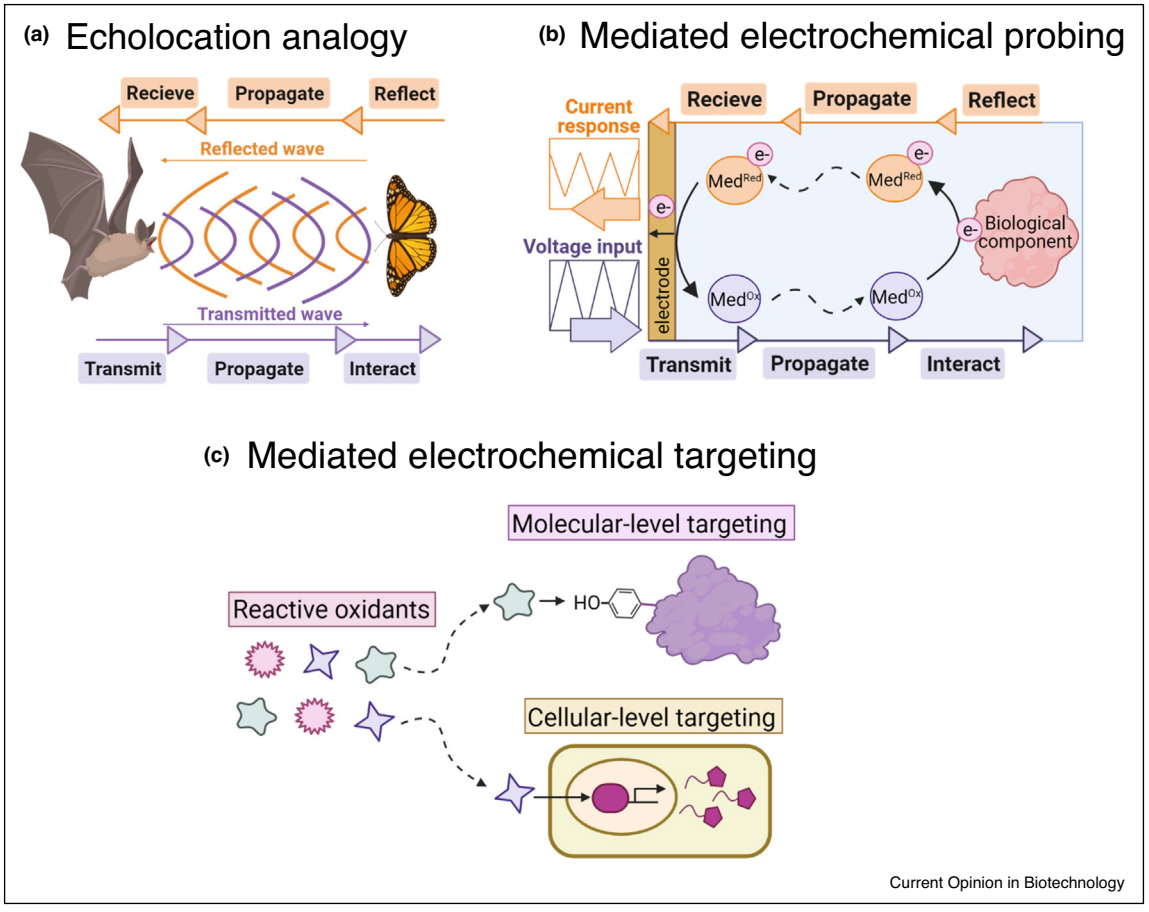
Mediated electrochemistry to access the redox modality

Electrochemistry is a broad field that encompasses a large number of applications and concerns the flow of electrons at the electrode surface. A subset of the field is mediated electrochemistry, where redox mediators are used to shuttle electrons from the electrode surface into solution in a manner analogous to biology's use of diffusible oxidants (e.g. O_2) and reductants (e.g. NADPH) to shuttle electrons within and between cells.

Our approach for using mediated electrochemical probing is approximately analogous to how bats use echolocation to hunt for prey. As depicted in Figure 1a, bats echolocate by transmitting a finely tuned signal (i.e. a high-frequency sound wave) to probe their local environment. This signal propagates through air and is perturbed by interactions with objects to generate a response signal (i.e. the echo) that is detected by the bat's ears and transduced into an electrical signal that is decoded in the brain. The bat's survival depends on its ability to convert these real-time measurements of the activities in a local environment into actionable information.

☆ Given his role as Guest Editor, William E. Bentley had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Julian N. Rosenberg.

Figure 1



Redox probing and targeting. **(a)** Analogy to echolocation. **(b)** Mediated electrochemical probing to access redox-based biological information. **(c)** Mediated electrochemistry for redox-based actuation of biology. Reactive oxidants target molecules and cells, modifying function.

Similar to echolocation, mediated electrochemical probing uses a tunable electrode-generated transmission that probes a local environment for redox-based information. As illustrated in Figure 1b, these transmissions are redox-active mediators (i.e. electron shuttles) that are either exogenously added or natively present. Information is then coded into these transmissions using the electrode to set the mediators' redox state. These diffusible mediators propagate into the local environment where they undergo redox-based electron-transfer interactions with a biological component that switches the mediator's redox state. The changes in the mediator's redox state then serve as the response signal (analogous to the echo). The response signal is sensitively detected by the electrode and transduced into an electronic format that can be decoded using advanced information processing methods. Thus, mediated electrochemical probing offers a sensitive real-time measurement that provides information of redox characteristics and activities in a local environment. This echolocation analogy emphasizes the use of mediated electrochemical probing for sensing, and various studies have shown the detection of information that ranges from intracellular redox activities [3–8], to cell viability [9], and metabolic activity [10], as well as new insight on biological materials [11–13] and to extracellular measures of oxidative stress [14–17].

Further, mediated electrochemistry is being extended from sensing to actuation [18]. In this case, Figure 1c shows how redox input signals can be imposed to 'target' biological interactions that induce changes in structure and function. In terms of a biological analogy, such redox-mediated actuation mimics biology's use of reactive oxidants (including reactive oxygen species; ROS) for the targeted post-translational modification of proteins. Importantly, advances in redox biology are revealing a broader range of biological redox targets and this knowledge is being translated into an expanding redox-based biotechnological toolbox. Next, we highlight recent advances in mediated electrochemistry for molecular-level and cellular-level redox-targeting.

Mediated electrochemistry for molecular-level redox targeting

As noted above, our use of mediated electrochemistry is analogous to biology's use of reactive oxidants (e.g. ROS) when used for targeting. Initially, ROS were recognized as important molecules for the immune system's targeting of pathogens [19,20], but more recently there has been a growing appreciation of the broader roles of reactive oxidants. We now realize that biology uses redox as a communication modality, with ROS serving as redox signaling molecules that transfer information and actuate responses through electron transfer reactions [21–23]. Further, the oxidation of amino acid residues by ROS provides mechanisms for post-translational modification that can adjust a protein's functional attributes [24–28]. Importantly, emerging research in redox biology is revealing a surprising level of chemical selectivity in the reactions of reactive oxidants which further supports their roles in targeting [29,30•].

Analogous to biology's use of reactive oxidants, mediated electrochemistry allows the controlled generation of oxidants for the selective targeting of amino acid residues for protein post-translational modification. For instance, Figure 2a depicts three redox mediators that can each be oxidized at an electrode but have differing abilities to oxidize (i.e. target) amino acid residues [31]. In some cases, the differing reactivities of the mediators can be simply explained in terms of their thermodynamic redox potential. The mediator with the least oxidative redox potential, ferrocene dimethanol (Fc), can oxidize Cys to generate a disulfide, but Fc cannot oxidize the amino acids Lys or Tyr. In contrast, acetosyringone (AS) and K_3IrCl_6 (Ir) have more oxidative redox potentials and these mediators can oxidize all three amino acids [31]. This example demonstrates that redox mediators can be selected to have different oxidative targeting abilities analogous to biology's use of different ROS to target different amino acid residues.

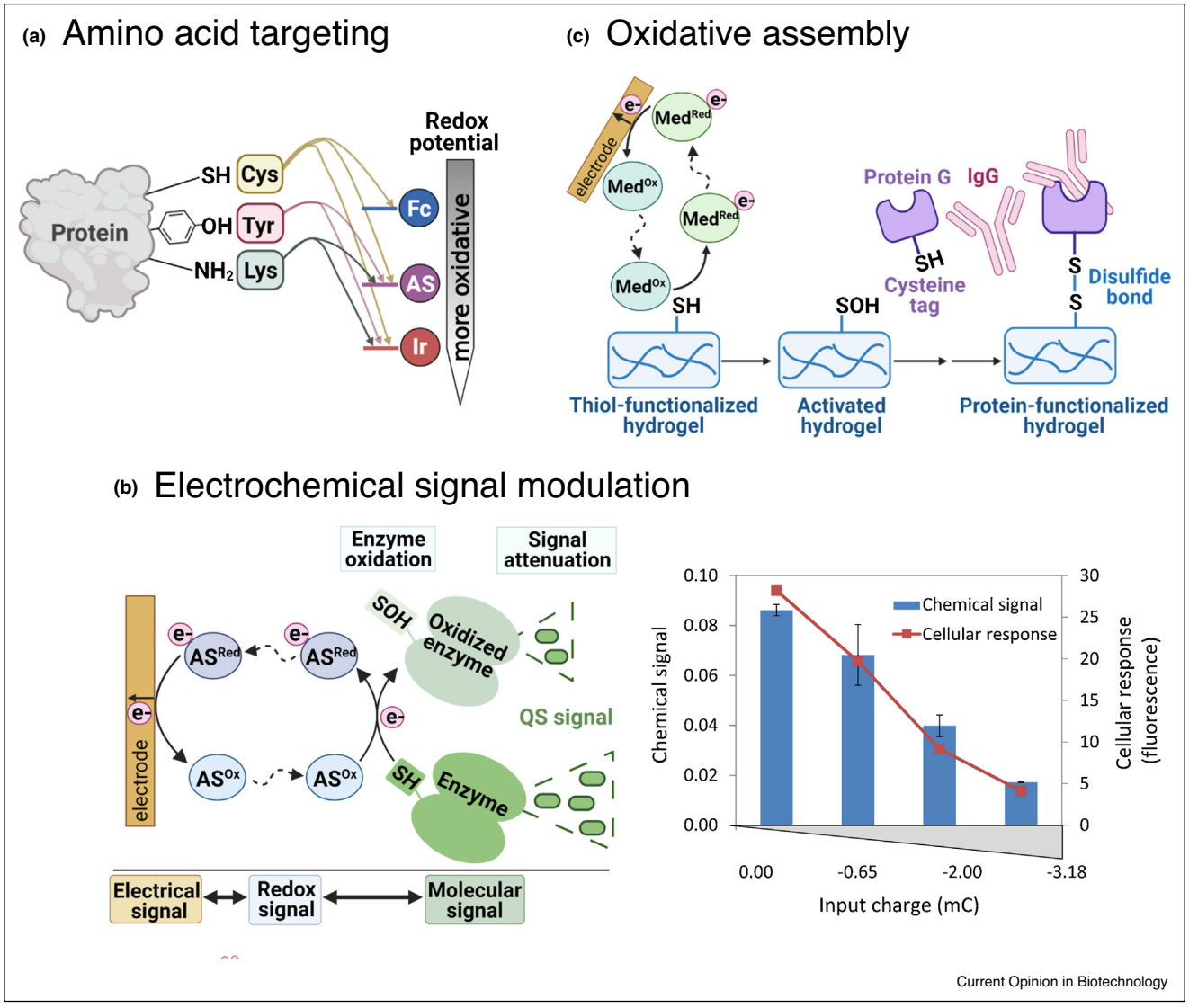
In biology, oxidative post translational modifications can alter a protein's structure and function. The most familiar example is probably the oxidation of cysteine thiols to disulfides (sometimes referred to as sulfur switching) with the resulting change in protein structure sometimes being integral to intracellular signal transduction pathways that regulate biological response [32••]. For example, oxidation of the cysteine-rich protein, Keap1, leads to activation of the transcription factor, Nrf2, which acts as a master regulator of the antioxidant responses [33,34]. Similarly, redox mediators can be used as reactive oxidants to alter a protein's activity. Such mediated electrochemical actuation is illustrated in Figure 2b which shows the AS-targeting of solvent-accessible sulfhydryl groups to attenuate enzymatic activity [35]. In this example, a multi-domain fusion protein was engineered by fusing the enzymes (LuxS and Pfs) from a two-step biosynthetic pathway for the bacterial quorum sensing (QS) signaling molecule, autoinducer-2 (AI-2) [36]. Both enzymes have labile Cys residues that upon oxidation leads to an attenuation in the generation of the AI-2 quorum signal [35]. This attenuation of AI-2 signal generation attenuates an AI-2-inducible biological response in a surrounding bacterial population (e.g. in this example expression of a fluorescent protein). The plot in Figure 2b shows that an increase in electrical input (i.e. the number of electrons transferred during AS-mediated oxidation) results in a systematic attenuation of both the AI-2 signal generated and the response of the bacterial population. This study illustrates how mediators and electrical inputs can controllably attenuate the generation of a biochemical signaling molecule to modulate biological function.

In addition to oxidatively modifying proteins to alter structure and function, biology also uses oxidation reactions for hierarchical assembly. Familiar examples of oxidative crosslinking include those that target the: cysteine residues of mucin; lysine residues of collagen [37]; tyrosine residues of the insect's resilin protein [38]; and dopamine residues of the mussel glue protein [39]. In an analogous manner, mediated electrochemistry can be used for oxidative assembly. For instance, Figure 2c shows a thiol-functionalized hydrogel can be oxidatively activated for protein conjugation through accessible sulfhydryl residues. As depicted in Figure 2c, the bacterial protein, protein G, was engineered to have a redox-responsive fusion tag (5 added cysteine residues at its C-terminus) to facilitate its oxidative assembly to the activated hydrogel [31]. This covalently assembled protein G retained its functional activity and was capable of binding IgG antibodies [40] to generate antibody-presenting surfaces. This example demonstrates how mediated electrochemistry and protein engineering can be leveraged to rapidly and simply control covalent bond formation for the hierarchical assembly of functional materials [41].

Mediated electrochemistry for cellular-level redox targeting

In biology, ROS are known to impose oxidative stresses that induce cellular stress-responses (e.g. the Keap1-Nrf2 pathway) [27,42]. Two of the best-known examples are the redox-responsive SoxRS and OxyR regulons in *Escherichia coli* that induce separate antioxidant defense responses. SoxRS has an iron-sulfur cluster that is believed to be targeted by superoxide-related activities and upregulates several genes including superoxide dismutase [43–45], while OxyR has sulfur switching thiols believed to be targeted by H_2O_2 and upregulates H_2O_2 inducible genes such as catalase [26,46,47]. These examples illustrate that biology is equipped with the molecular machinery to recognize imposed redox inputs and transduce these inputs into changes in gene expression. These

Figure 2

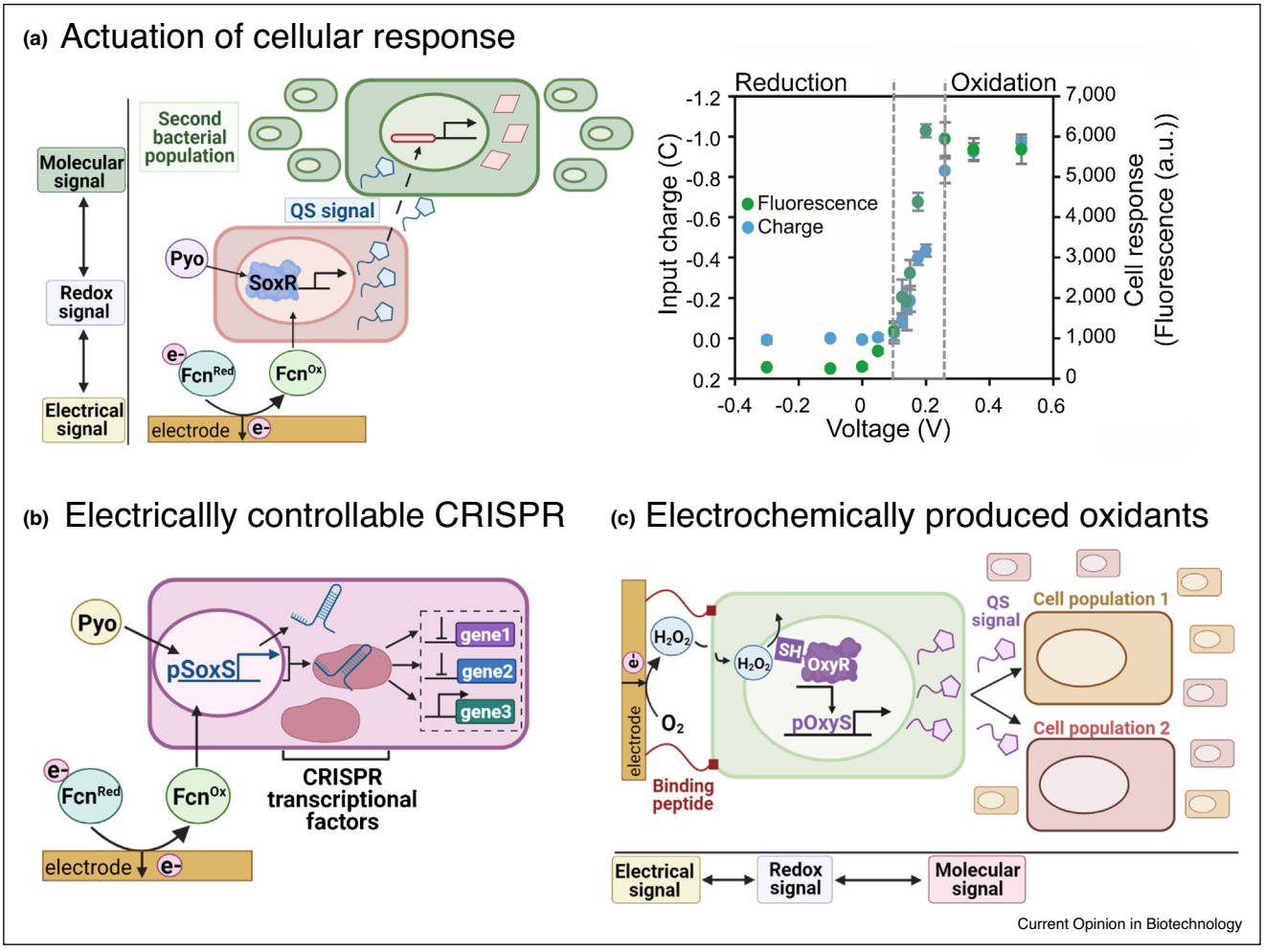


Molecular-level redox targeting. **(a)** Mediators can selectively target a protein's amino acid residues. Selectivity is provided by redox potential, specific mediators, and targeted residues. **(b)** Mediated oxidation of an enzyme's sulfhydryl residues actuates signal response. In this example, the activity of an enzyme complex that synthesizes a quorum sensing (QS) signal is modulated by electrode oxidized mediators. Adapted from [35]. **(c)** Covalent bond formation is electrochemically controlled to generate functional materials. Here, thiolated polyethylene glycol is crosslinked by oxidized mediators and activated to create sulfenic acid groups that subsequently covalently bind to cysteine residues engineered onto the C-terminus of protein G, enabling a platform for sensing IgG.

examples have also motivated efforts to use mediated electrochemistry to impose redox inputs capable to accessing this native redox-based information processing machinery.

Analogous to ROS, mediated electrochemistry can be used to target intracellular redox machinery to regulate signal transduction. As shown in Figure 3a, dual mediators can actuate gene expression from the SoxRS regulon through targeted oxidation of the iron-sulfur clusters of the SoxR protein [48]. One of the mediators, the bacterial metabolite pyocyanin (Pyo), is believed to enter the cell to actuate gene induction by oxidizing SoxR. The second mediator, ferricyanide (Fcn), is electrochemically controlled by the electrode and was used to modulate the level of induction. The plot in Figure 3a shows that as the electrode's voltage was increased to be more oxidative, the electrons transferred for Fcn-oxidation increased thus exposing the cells to a greater redox input (labeled as 'Input Change'). This increased oxidative input resulted in a greater cellular response as measured by the SoxR-inducible expression of a fluorescent protein. The

Figure 3



Cellular-level redox targeting. **(a)** Mediators target intracellular gene expression to modulate cell behavior. On the left, cells (pink) are engineered to synthesize bacterial quorum sensing autoinducer (AI-1) in response to soxR-mediated gene expression that, in turn, is actuated by electrode oxidized pyocyanin and ferricyanide (electrical signal). The synthesized AI-1 signals to a second cell population (green) engineered that, in turn, responds as a collective unit. On the right, soxR-actuated cells generate fluorescent phiLOV marker in response to applied voltage and oxidized Pyo & Fcn. Adapted from [48]. **(b)** eCRISPR is electrochemically controlled to both actuate and silence gene expression from multiple targets in multiplexed manner. **(c)** Electrochemically generated oxidants actuate biological response without added mediators. Here, electrode-generated hydrogen peroxide permeates electrode-assembled bacteria. In turn, they produce quorum sensing signal molecules that convey "information" to cell network (populations 1 and 2) that (i) confer information transfer (population 1) or (ii) generate a model therapeutic (population 2).

electrochemically inducible SoxRS regulon was then engineered (i.e. re-programmed) to produce a QS signaling molecule that subsequently altered the biological response of a second population of cells [48]. This example illustrates how mediated electrochemistry enables controlled access to biology's redox signaling modality to target programmable cellular responses.

Similar to how the SoxRS and OxyR regulons protect against oxidative stress, CRISPR serves as bacteria's protective immune system against viruses [49]. Using synthetic biology approaches, the CRISPR system has been engineered for a multitude of applications including mammalian cell biocomputing [50], information storage [51••], and antibody production. Recently, an electrically controllable CRISPR system (referred to as eCRISPR) was integrated with mediated electrochemistry to enable extensive intracellular control [52]. As depicted in Figure 3b, the eCRISPR genetic system consists of two parts: (i) the redox responsive SoxS-based promotor and, (ii) CRISPR-based transcriptional factors designed to silence the expression of multiple genes associated with the native oxidative stress response. Dual mediators, Pyo and Fcn, were used to actuate the response of the SoxS-based promotor resulting in expression of CRISPR-based transcriptional factors [52]. The dovetailing of

synthetic biology and mediated electrochemistry offers the unique opportunity to program the cell's molecular machinery to be interfaced to electronics through a communication modality (i.e. redox) that is common to both [53–55,56••].

In the examples above, we described how electrochemical inputs could be coupled with redox mediators for the oxidative targeting of intracellular machinery. However, it is also possible to use electrodes to directly generate some of the same reactive oxidants used by biology (e.g. H_2O_2, HOCl) [57]. For instance, as illustrated in Figure 3c, electrochemically generated H_2O_2 (in place of exogenously added mediators) was used to induce the OxyR regulon through oxidative targeting of the cysteine residues of the OxyR protein [58]. The bacterial cells were specifically engineered with (i) a cell surface peptide to allow their uniform assembly onto the electrode surface; and (ii) H_2O_2-responsive gene expression from the OxyR regulon which was re-programmed to produce a QS signal. This synthetic biology construct thus allows electrochemically generated H_2O_2 to locally activate QS signal production to actuate the biological responses from two separate surrounding populations of cells [58]. This example demonstrates how precisely controlled electronic inputs can be transduced into chemical-based molecular outputs by accessing the information processing capabilities of biology.

Perspective

Similar to biology's use of reactive oxidants for selective targeting, mediated electrochemistry provides a simple means to generate redox signals capable of actuating biological responses. We highlighted examples of the use of mediated redox targeting to: modify molecular structure and activities; induce the hierarchical assembly of functional materials; and activate redox-responsive gene expression (e.g. electrogenetics). These examples further illustrate the potential for developing a redox-based biotechnology toolbox for protein engineering and synthetic biology that allows both the re-programming of redox-targetable biological structures and functions for user-defined purposes and for enabling greater insight on biological function. That is, these examples suggest a broader potential for interfacing the molecular logic of biology with the electronic logic of technology to fuse their complementary (and seemingly disparate) information processing capabilities. These can enable far greater understanding than rote use of redox for electrochemical sensing; they enable more in-depth assessment and even control of biological function. Thus, we envision that mediated electrochemistry can act as a unique and transformative bridge between biology and electronics.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Dana Motabar: Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Jinyang Li:** Conceptualization, Writing - original draft, Writing - review & editing, Visualization. **Gregory F Payne:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition. **William E Bentley:** Conceptualization, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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- •• of outstanding interest

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