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Information processing through a bio-based redox capacitor: Signatures for redox-cycling

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ABSTRACT

Redox-cycling compounds can significantly impact biological systems and can be responsible for activities that range from pathogen virulence and contaminant toxicities, to therapeutic drug mechanisms. Current methods to identify redox-cycling activities rely on the generation of reactive oxygen species (ROS), and employ enzymatic or chemical methods to detect ROS. Here, we couple the speed and sensitivity of electrochemistry with the molecular-electronic properties of a bio-based redox-capacitor to generate signatures of redox-cycling. The redox capacitor film is electrochemically-fabricated at the electrode surface and is composed of a polysaccharide hydrogel with grafted catechol moieties. This capacitor film is redox-active but non-conducting and can engage diffusible compounds in either oxidative or reductive redox-cycling. Using standard electrochemical mediators ferrocene dimethanol (Fc) and $Ru(NH_3)_6Cl_3$ (Ru^{3+}) as model redox-cyclers, we observed signal amplifications and rectifications that serve as signatures of redox-cycling. Three bio-relevant compounds were then probed for these signatures: (i) ascorbate, a redox-active compound that does not redox-cycle; (ii) pyocyanin, a virulence factor well-known for its reductive redox-cycling; and (iii) acetaminophen, an analgesic that oxidatively redox-cycles but also undergoes conjugation reactions. These studies demonstrate that the redox-capacitor can enlist the capabilities of electrochemistry to generate rapid and sensitive signatures of biologically-relevant chemical activities (i.e., redox-cycling).

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1. Introduction

Electrodes provide a simple, sensitive, and rapid means to acquire information. One common goal is to acquire information of an individual chemical species. In this case, the challenge is selectivity and several approaches can be used to improve the selectivity of an electrochemical measurement. For instance, selectivity can be improved by tailoring the electrical inputs (e.g., by pulse voltammetry) or by modifying the electrode to "filter out" unwanted information (e.g., by using molecular recognition elements or selectively-permeable membranes).

An alternative goal is to characterize states, functions or activities using measurements from multiple electrodes. The challenge in this case is to process the information to recognize characteristic patterns. For instance, electrocardiograms provide a pattern of electrode measurements that characterize the functioning of a complex organ (i.e., the beating heart). Also, the artificial/electronic nose may provide information from a "breath print" that can be correlated with pathologies [1–4].

We are investigating a hybrid approach using a hydrogel redox-capacitor film to manipulate electron exchange and thereby "process" information acquired by the electrode. Specifically, we focus on biologically-relevant redox-cycling activities. Probably the most familiar redox-cycling couples in biology are $NAD(P)^+$/NAD(P)H which are essential for energy-harvesting and biosynthesis. Yet, redox-cycling may be much more prevalent because many biology systems (e.g., the lungs and intestinal tract) [5] are characterized by steep gradients in redox potential that provides the necessary context (i.e., the thermodynamic driving forces) for redox-cycling. For instance, the opportunistic pathogen *Pseudomonas aeruginosa* produces a redox-active virulence factor pyocyanin that can accept electrons from host cells (thus disrupting their redox homeostasis) and then donate these electrons to O_2 to generate reactive oxygen species (ROS) [6–8]. Another example is acetaminophen where its ability to interrupt the redox-cycling of hemeproteins (e.g., cyclooxygenase; COX) is believed to confer therapeutic benefit [9,10] while its oxidation by liver cytochrome enzymes is believed to be responsible for its sometimes lethal side effects [11,12].

Redox-cycling assays have been developed using enzymatic [13] or chemiluminescence [14–16] methodologies. Such redox-cycling assays can be used for detection/diagnosis [14] or employed in drug screening programs either to eliminate false-positives [17–20] or to discover promising leads (e.g., for anticancer drugs) [21]. Electrochemistry

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should be particularly well-suited for detecting redox-cycling activities and in fact redox-cycling is a common electrochemical amplification method [22,23]. The challenge is to generate and interpret electrochemical signals capable of discerning redox-cycling from other redox-activities. Here, we probed redox-cycling activities; (i) using an electrode modified with a redox-capacitor film, (ii) coupling film-charging and film-discharging reactions, (iii) imposing varying chemical and electrical inputs, and (iv) analyzing outputs to generate characteristic signature patterns.

2. Redox-capacitor: fabrication and information processing

2.1. Fabrication of bio-based redox-capacitor film

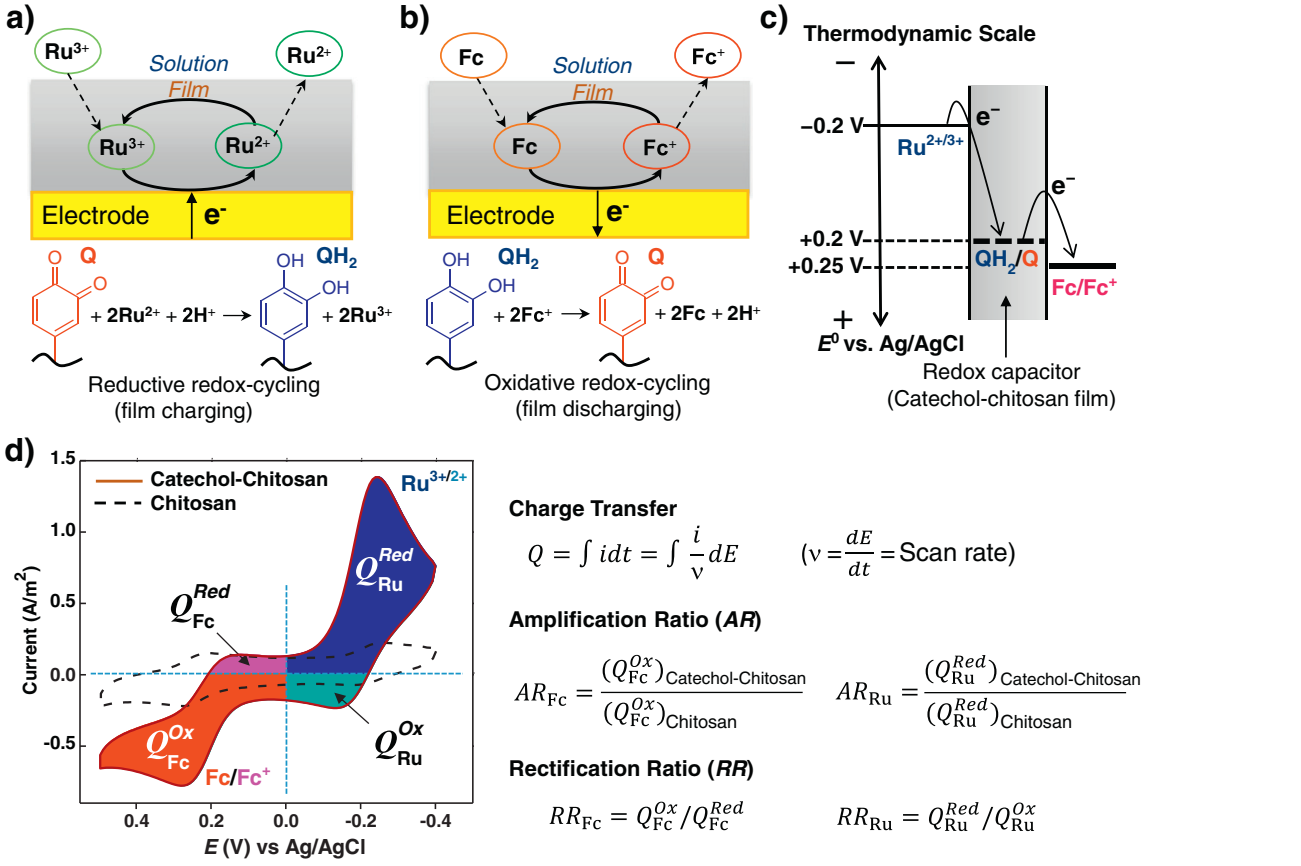
We refer to our film as a redox-capacitor because it can accept, store and donate electrons in a controllable fashion [24]. We use the prefix "bio-based" because the film is prepared from organic components common in biology (e.g., a catechol and a polysaccharide) [25,26] and because it can exchange electrons with biologically-relevant oxidants and reductants [27–30].

Two electrochemical steps are used to fabricate the redox-capacitor film as a coating for the gold electrode. First, a hydrogel film of the aminopolysacccharide chitosan is electrodeposited onto the gold electrode (1% chitosan, pH 5.5, 6 A/m^2, 30 s) [31–33]. Chitosan is pH-responsive and film-forming, and electrodeposits at a cathode by a neutralization mechanism. Once deposited the chitosan film is stable under neutral conditions although it will re-dissolve in mild acid (chitosan's $pK_a \approx 6.3$). Second, the chitosan film is functionalized by grafting catechol moieties. Grafting is achieved by immersing the chitosan-coated electrode in a catechol-containing solution (5.0 mM) and applying an anodic potential to the underlying electrode (0.5 V, 5 min). Catechol diffuses through the chitosan film, is oxidized at the underlying electrode and the oxidized species (e.g., *o*-quinone) grafts to the amine moieties of the chitosan film. After preparation, the catechol-chitosan-coated electrode is sonicated for 3 min, washed extensively with water.

2.2. Redox-capacitor properties of film

Previous studies have shown that the catechol-chitosan films are non-conducting in that they are unable to exchange electrons directly with the underlying electrode [24]. However, the catechol-chitosan films are redox-active and can rapidly and repeatedly exchange electrons with soluble redox-active species (i.e., with mediators). Scheme 1a illustrates reduction (i.e., charging) of the film by a redox-cycling mechanism with the electrochemical mediator $Ru(NH_3)_6Cl_3$ (Ru^{3+}). In this case oxidized mediators (Ru^{3+}) diffuse from the bulk solution through the film and are reduced to Ru^{2+} at the electrode. The reduced Ru^{2+} diffuse from the electrode surface into the film where they undergo redox-cycling thereby transferring electrons to the film to convert Q to QH_2 moieties. Scheme 1b illustrates oxidation (i.e., discharging) of the film through an analogous redox-cycling mechanism in which the reduced 1,1′-ferrocenedimethanol (Fc) mediators diffuse through the film, are oxidized to Fc^+ at the electrode and Fc^+ then diffuse into and accept electrons from the film to convert QH_2 to Q moieties. The plot in Scheme 1c illustrates that electron transfer to/from the film is controlled by thermodynamics.

The Ru^{3+} and Fc mediators provide convenient models of redox-active species that can engage the catechol-chitosan film in separate reductive and oxidative redox-cycling mechanisms. Importantly, these



Scheme 1. Schematics of redox-cycling mechanisms and information processing. (a) Reductive redox-cycling. (b) Oxidative redox-cycling. (c) Thermodynamics of electron transfer. (d) Illustrative CVs comparing catechol-chitosan redox-capacitor film and an unmodified chitosan control film, and the associated analysis.

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