ACS APPLIED MATERIALS & INTERFACES

www.acsami.org

Perspective

Biomimetic Redox Capacitor To Control the Flow of Electrons

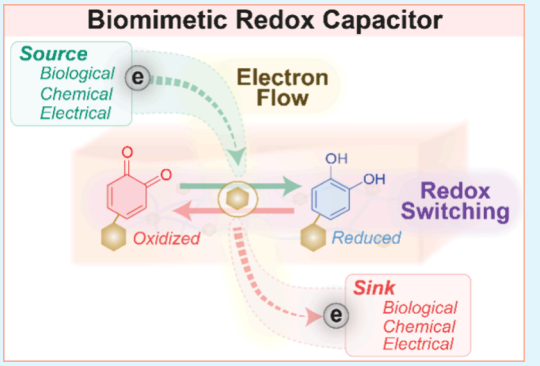
Eunkyoung Kim,* Zhiling Zhao, Si Wu, Jinyang Li, William E. Bentley, and Gregory F. Payne*

Cite This: *ACS Appl. Mater. Interfaces* 2024, 16, 61495−61502

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In biological systems, electrons, energy, and information "flow" through the redox modality, and we ask, does biology have redox capacitor capabilities for storing electrons? We describe emerging evidence indicating that biological phenolic/catecholic materials possess such redox capacitor properties. We further describe results that show biomimetic catecholic materials are reversibly redox-active with redox potentials in the midphysiological range and can repeatedly accept electrons (from various reductants), store electrons, and donate electrons (to various oxidants). Importantly, catechol-containing films that are assembled onto electrode surfaces can enhance the flow of electrons, energy, and information. Further, catechol-containing films can serve as redox-based interactive materials capable of actuating biological responses by turning on gene expression from redox-responsive genetic circuits. Looking forward, we envision that the emerging capabilities for measuring dynamic redox processes and reversible redox states will provide new insights into redox biology and will also catalyze new technological opportunities for information processing and energy harvesting.



KEYWORDS: *biomimetic, redox, capacitor, catechol, energy, information*

CONTROLLING ELECTRON FLOW IN TECHNOLOGY AND BIOLOGY

Our technological world relies on devices that control the flow of electrons to process information (e.g., computers) and deliver energy (e.g., batteries). Electron flow is also important in biology as summarized by Albert Szent-Györgyi's famous quote that "life is nothing but an electron looking for a place to rest". But, these "restless" electrons are not soluble in water and must "flow" through reduction−oxidation (redox) reactions. Probably the most familiar redox reaction pathway is the respiratory electron transport chain (Figure 1a) in which electron flow is coupled to an asymmetric transport of H^+ ions across a membrane to generate an electrochemical gradient. This separation of ionic charge across the membrane provides a means to store energy (i.e., an ionic capacitor) which can be used to synthesize ATP (the cell's energy currency). More broadly, Figure 1b illustrates that cellular metabolism involves the flow of electrons with the intracellular reducing equivalents (e.g., NAD(P)H) shuttling electrons for biosynthesis or for export to terminal electron acceptors (e.g., oxygen (O_2), nitrate (NO_3^-), and sulfate (SO_4^{2-})). In the absence of a terminal electron acceptor, cells need alternative mechanisms to export electrons, and this can lead to the export of partially reduced metabolites (e.g., ethanol, lactate, or CH_4). One final example of electron flow involves the transfer electrons to O_2 to generate reactive oxygen species (ROS) which are commonly used in immune responses (i.e., to defend against pathogen attack). Figure 1c shows that these ROS can drive extracellular electron flow through a redox reaction network (i.e., a redox interactome) that can lead to oxidative stresses and pathogen killing. At lower concentrations, these ROS (e.g., H_2O_2) can perform redox signaling functions.[1,2]

Capacitors that store electrons are integral to controlling the flow of electrons in technology, and these include the capacitor elements in the integrated circuits of electronic devices and the double-layer and redox capacitors in advanced energy systems. While Figure 1 illustrates that biology has pathways for electron-flow, we pose the question: does biology have materials and mechanisms to store electrons?

Biological Redox Capacitors: Three Examples. Before answering the above question, it is useful to consider three additional, background questions. First, what is the charge carrier when a current is flowing? The answer to this question is not always so obvious. Sometimes a current describes the flow of electrons (e.g., the "sea" of electrons in conducting metals that flow in response to an applied voltage), other times ions are flowing (e.g., the H^+ transport that is coupled to ATP synthesis), and still other times the flow of electrons and ions is coupled in complex ways (e.g., the flow of electrons and counterions in a battery). Second, what is the charge carrier in "bioelectricity"? Recent work emphasizes that biology actually

Received: August 13, 2024
Revised: October 16, 2024
Accepted: October 21, 2024
Published: October 31, 2024

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

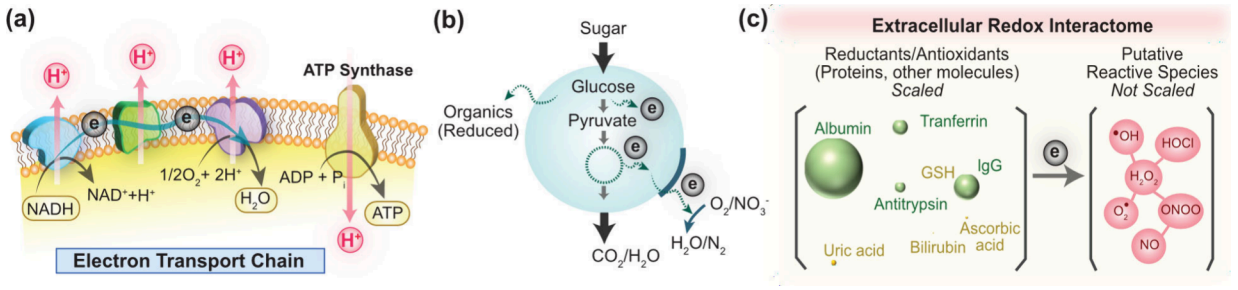


Figure 1. Flow of electrons in (a) the respiratory electron transport chain, (b) cellular metabolism, and (c) the extracellular redox "interactome" in our bodies.

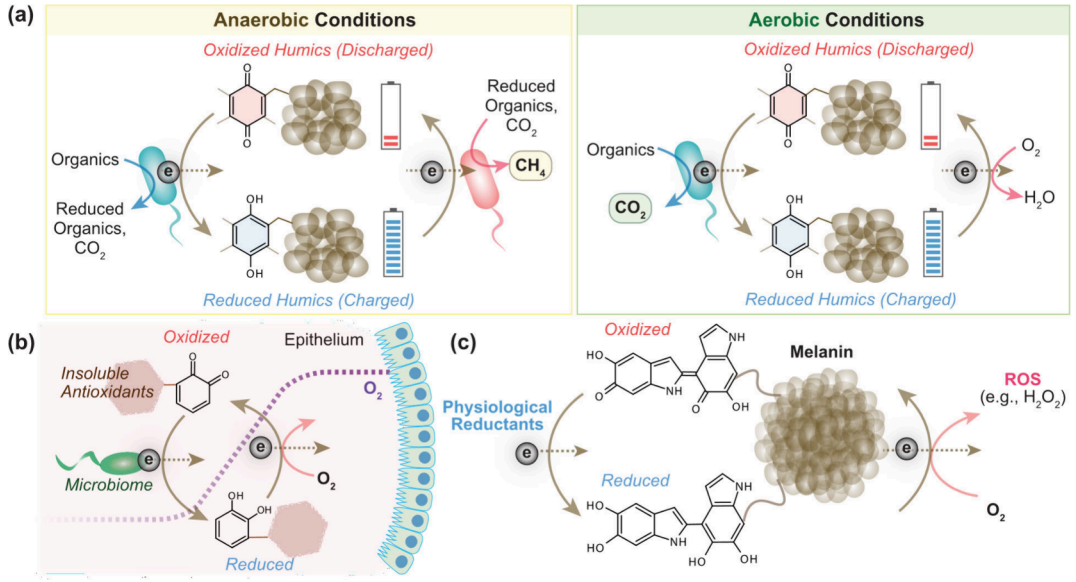


Figure 2. Biology's phenolic redox-capacitors that can accept, store, and donate electrons. (a) Humics in soil have been referred to as "geobatteries" and "bio-geobatteries". (b) Insoluble dietary antioxidants can accept and donate electrons in response to local redox context. (c) Melanins can "catalyze" the transfer of electrons from reductants to O_2 to generate reactive oxygen species (ROS).

has two electrical modalities: one involves the flow of ions and the other involves the flow of electrons.[3] Biology's ionic electrical modality is integral to signaling in the nervous and neuromuscular systems (e.g., through action potentials), while biology's electron-based (i.e., redox) modality is especially important for shuttling electrons outside the cell.[4] Third, how are insoluble electrons exported from a cell? Sometimes, extracellular electron transport (EET) involves "indirect mechanisms" involving diffusible terminal electron acceptors (e.g., O_2 or NO_3^-) or reversible electron shuttles (i.e., mediators), and other times, EET appears to involve "direct" mechanisms in which electrons flow through specialized appendages (e.g., pili) that have conducting properties.[5]

Example. No. 1. Bio-geobatteries. Possibly the best known and largest scale examples of biologically relevant redox capacitors are "geobatteries" or "bio-geobatteries"[6,7] in aquatic and soil systems. Figure 2a illustrates that microbial activity in these environments is highly dependent on redox context, with CH_4-generation being favored in the absence of O_2 (or alternative terminal electron acceptors) and CO_2-generation being favored in the presence of O_2. These systems also have phenol-based humic substances that serve as redox capacitors (termed geobatteries) that can accept, store, and donate electrons. Importantly, these geobatteries respond to localized hydrological contexts by accepting electrons under reducing conditions (e.g., water inundation) and donating electrons when the O_2 can permeate into the soil (e.g., when water recedes). These geobatteries can also interact with the microorganisms serving to buffer redox contexts, and this can be important since the CH_4 emissions from such systems are a potent source of greenhouse gas. Importantly, a key to understanding the redox properties of humic-based geobatteries was the development of in vitro-mediated electrochemical measurement methods in which diffusible mediators were used to shuttle electrons between an electrode and the humics.[8]

Example. No. 2. Insoluble Dietary Antioxidants. While, it is well-recognized that humics perform important electron-storage and buffering functions in ecosystems, other phenolics possess similar redox activities, but their functional importance is not as well understood. One example are redox-active plant phenolics that become the most abundant antioxidants in our diet.[9] Mediated electrochemical studies with insoluble dietary antioxidants showed that they are reversibly redox-active and can accept, store, and donate electrons with the direction of electron-exchange (donate vs accept) controlled by the localized redox context.[10] The gut can be an especially complex redox context as illustrated in Figure 2b which shows that the gut's epithelium can supply O_2 but its rapid consumption yields steep gradients with oxidizing

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

and reducing conditions separated by small distances (sub-millimeter).[11] As suggested in Figure 2b, this complex redox context may control the redox state-switching of the dietary phenolics, which can further impact the localized context: oxidation may release stored electrons (and protons), while reduction may absorb electrons (and protons). Potentially, these dietary phenolics maybe act as buffers both for redox and pH. Recent studies also suggest that dietary antioxidants may modulate the redox context in the gut in ways that extend beyond the gut and into the central nervous system (i.e., to modulate activities along the gut−brain axis).[12]

Example. No. 3. Melanins. Melanin is a biological pigment of ill-defined structure and poorly characterized properties that is ubiquitous in nature and throughout our bodies (e.g., in our skin, hair, eyes, and brain).[13,14] Decades ago, melanin was reported to have semiconducting properties, and there has been considerable research trying to resolve whether measurable currents are due to the flow of ions or electrons.[15] Also, a couple decades ago, it was proposed that the melanin synthesized during an insect's immune response might be redox-active and, as illustrated in Figure 2c, might accept electrons from physiological reductants (e.g., ascorbate) and transfer them to O_2 to locally generate reactive oxygen species (ROS) at a wound site.[16] In vitro evidence for this hypothesis was provided by mediated electrochemical studies that showed that melanins from various sources are reversibly redox-active with redox potential's in the midphysiological range and can accept electrons from various reductants and donate these electrons to various oxidants (including O_2).[17,18] These redox properties may be important medically, as in vitro studies showed that melanin can undergo redox-cycling with environmental toxins[19] and drugs[20] and can display context-dependent pro- or antioxidant properties.[21]

While various biological molecules (e.g., enzymes[22]) are redox-active, phenols/quinones are among nature's most abundant redox-active organics,[23] and only recently has it been recognized that they possess redox capacitor properties (i.e., to repeatedly accept, store, and donate electrons). We suggest that understanding these redox-capacitor properties may help unravel the unique and often opposing biological functions of natural phenolic/catecholic materials. For instance, melanins have been reported to have pro- and antioxidant properties and photoprotective and photosensitizing properties, and melanins synthesized by some pathogens have been proposed to promote virulence while those synthesized by some hosts have been proposed to perform immune defense functions.[24] Importantly, detecting such redox activities generally relies on the development of new experimental tools based on mediated electrochemistry. In the following, we describe studies in which catechol-based biomimetic redox capacitors are being studied for technological applications.

APPLICATIONS OF BIOMIMETIC REDOX CAPACITOR FILMS

Bioelectronic Materials for Information Processing. There is growing interest in using redox as a modality to bridge communication between biology and electronics.[25] Specifically, the redox modality is native to biology and is also accessible to electronics through electrochemistry.[26] The redox properties of phenolic/catecholic materials appear to offer important capabilities for the emerging field of redox-based bioelectronics.

Biology uses redox-active *p*-(hydro)quinones in the respiratory and photosynthetic electron transport chains and uses catechols and their *o*-quinones as building blocks in familiar biological materials. Catechol's oxidation product, the *o*-quinone, is a reactive electrophile that can undergo various nonenzymatic reactions: biology uses such reactions to cross-link the mussel glue protein, synthesize melanin, and harden the insect cuticle. As shown in Figure 3a, we electrochemically

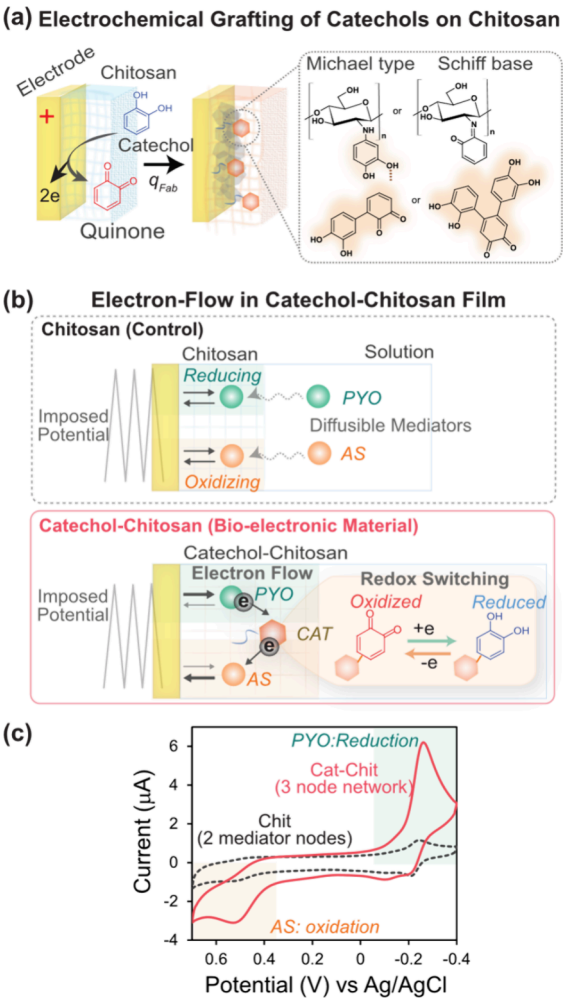


Figure 3. Catechol-based redox capacitor film assembled on an electrode surface can control the mediated flow of electrons. (a) Electrochemical grafting of catechols on chitosan film. (b) Redox interaction graphs for two diffusible biological mediators (PYO and AS) that bracket the redox potential of the grafted catechol moieties. (c) Cyclic voltammetry (CV) results demonstrate that PYO-CAT-AS form a redox reaction network that serves to amplify, rectify, and gate electron flow. Reproduced from ref 27 with permission from American Chemical Society, Copyright 2013.

(i.e., anodically) oxidize catechols to initiate grafting of their *o*-quinones onto films of the aminopolysaccharide chitosan to create catechol-modified chitosan films for bioelectronic applications.[3] Importantly, the catechol−chitosan films have been observed to be nonconducting but redox-active: electrons cannot flow through these films in response to an imposed potential, but the films can accept electrons from diffusible reductants, store the electrons, and donate electrons to diffusible oxidants.

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

One important feature of this catechol−chitosan film is that electron flow through this film can be networked: electrons flow through a redox reaction network, as illustrated in Figure 3b. A chitosan film (without catechol) serves as a redox-inactive control that is permeable and allows the free diffusion of both the bacterial metabolite pyocyanin (PYO) and the plant phenolic acetosyringone (AS). Both PYO and AS are reversibly redox-active, and when an oscillating electrode potential is imposed, they can be repeatedly oxidized and reduced. The results for this control chitosan film are displayed in the cyclic voltammetry (CV) in Figure 3c. When we graft catechol (CAT) moieties to the film, we essentially add a third "node" to create a network: the CAT node cannot directly exchange electrons with the electrode (because it is physically separated from the electrode), but CAT can accept electrons from PYO and donate electrons to AS. As illustrated by the interaction graph in Figure 3b, this three-node system forms a redox-reaction network: electrons flow into the network through the PYO node, transiently accumulate in the CAT node, and then flow out of the network through the AS node. As illustrated by the CV in Figure 3c, the electrical response to the imposed oscillating input potential is dramatically different (compared to that of the control chitosan film).

Mechanistically, when the imposed potential is reducing, the PYO can undergo reductive redox-cycling by accepting electrons from the electrode, diffusing into the film, and transferring the electrons to the grafted catechol moieties. As shown in Figure 3c, this reductive redox-cycling amplifies PYO's measured reducing current and attenuates PYO's oxidizing current (i.e., the currents associated with PYO are rectified). PYO's reductive redox-cycling also switches the redox-state of the grafted catechol from its oxidized (e.g., quinone) to its reduced (e.g., catechol) state. In an analogous manner, AS can undergo oxidative redox-cycling, transferring electrons from the grafted catechol moieties to the electrode under oxidative potentials and leading to amplification of AS's oxidative current and attenuation of its reductive currents. AS's oxidative redox-cycling also switches the redox-state of the grafted catechol from its reduced (e.g., catechol) to its oxidized (e.g., quinone) state. Importantly, PYO and AS serve as voltage-gates: reductive currents do not flow until the imposed potential approaches PYO's redox potential (E^0= −0.2 V vs Ag/AgCl), and oxidative currents do not flow until the imposed redox potential approaches AS's redox potential (E^0= +0.5 V). Amplification, rectification, and gating are important signal-features that can be used to extract information from signals.[3]

Also important is that the grafted catechol moieties have redox potentials in the midphysiological range and can accept electrons from a wide range of biological reductants (e.g., NAD(P)H and ascorbate) and donate electrons to a range of biologically relevant oxidants (e.g., O_2). Thus, the catechol moieties can be thought of as "hubs" in a redox reaction network, enabling connections to a broad range of metabolites. The addition of each new metabolite adds a node to the network's interaction graph and can contribute to the redox-state switching of the grafted catechol moieties. The addition of each node also alters the flow of electrons through the catechol film and significantly perturbs the measurable signals (i.e., currents). One goal is to "map" such signal perturbations to reveal information on a local environment's redox context (e.g., to "reconstruct" the redox network).[3,27]

Finally, the catechol moieties can serve as molecular memories that store electrons (and information). This ability to collect electrons can be used to amplify a weak redox signal.[28] Also, because there is a measurable spectral difference between the reduced and oxidized states of the catechol moieties, it is sometimes possible to use simple methods (e.g., cell-phone imaging) to detect the memory state (oxidized vs reduced) for portable biosensing applications.[29]

In summary, redox is a native biological modality that is accessible to electronics via electrochemistry, and we envision that catechol-based biomimetic redox capacitors can serve as the physical interface to bridge redox-based bioelectronic communications. For instance, several studies have shown that the ability of catechol−chitosan films to amplify, rectify, and gate currents allows redox information to be extracted from somewhat complex biological systems.[3,28,30,31]

Biointeractive Materials To Actuate a Biological Response. Over the past decade, there has been increasing recognition that redox is a distinct modality for biological communication, with H_2O_2 emerging as a key redox signaling molecule.[1] At high concentrations, H_2O_2 can serve to kill invading pathogens, but at lower concentrations, H_2O_2 is believed to provide cues that elicit biological responses (e.g., for wound healing).[1,2] Several experimental studies have shown, as hypothesized in Figure 2c,[16] that melanins and other phenolic materials can donate electrons to O_2 to generate ROS (e.g., H_2O_2) and this capability could enable phenolic/catecholic films to interact with biology through the redox modality.

Specifically, Figure 2c hypothesizes that insect melanins can accept electrons from biological reductants and donate them to O_2 to generate H_2O_2 as part of an insect immune response.[16] Recently, a redox-active catechol−chitosan film was investigated as an antimicrobial wound dressing.[32] In vitro studies showed that this film could be reduced by ascorbate and could be oxidized in the presence of O_2 to generate H_2O_2. Animal studies with an infected wound model showed that the catechol−chitosan film could suppress infection and promote wound healing which is consistent with a mechanism of localized ROS (i.e., H_2O_2) generation at the wound site (note: it is difficult to definitively demonstrate molecular mechanisms from in vivo studies).[32]

A more recent study provided definitive evidence that the catechol film (in this case a catechol−PEG film) can act as a biointeractive material.[33] In this study, in vitro experiments indicated that when the film was contacted with an *E. coli* culture, it could accept electrons from an unidentified biological reductant(s) and, upon exposure to O_2, could transfer these electrons to generate H_2O_2. Next, this film was tested by using a synthetic biology *E. coli* construct in which a stress regulon, known to respond to H_2O_2, was engineered to express a fluorescent protein. Figure 4 illustrates that when this synbio construct was contacted with an oxidized film in the presence of O_2, then expression of the fluorescent protein was upregulated while no upregulation was observed for control cultures incubated either without a film or incubated with a film but with the H_2O_2-degrading enzyme catalase.[33]

These studies demonstrate that redox-active materials are not inert but can engage biology in redox-based communication (e.g., by receiving and/or transmitting electrons from reductants to oxidants). Potentially, such redox signaling is ubiquitous in extracellular spaces but has gone unnoticed because conventional measurement methods are not designed

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

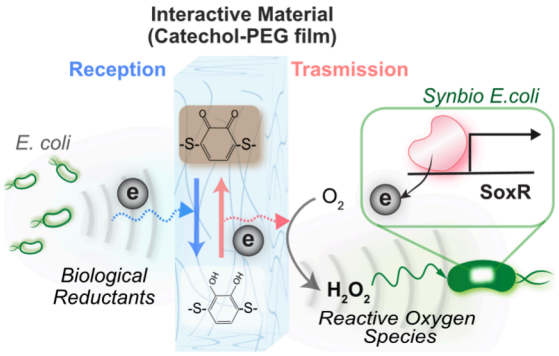


Figure 4. Catechol-based interactive film can "receive" electrons from biological reducing equivalents and "transmit" electrons through H_2O_2. Such redox signaling by an abiotic film has been shown to actuate significant biological responses (e.g., to upregulate gene expression via a redox-responsive promoter).

to detect such redox activities (e.g., omics methods typically do not discern the different redox states of a molecule). Also, such redox-based interactive materials could potentially enable new applications in life sciences.

BIOMIMETIC REDOX CAPACITOR FOR ENERGY MATERIALS

Potentially, catecholic materials could serve as biomimetic redox capacitors for energy applications. Figure 5a shows a schematic of a composite chitosan film that was electrofabricated to contain both graphene and catechol. Graphene confers metallic conductivity, electrocatalytic properties, and double-layer capacitance like a conductive electrode to the film, but graphene confers little redox capacity (electrons can flow through but cannot be stored in graphene). Catechol confers redox activity and redox capacitance. On the basis of functional measurements, Figure 5a illustrates that the catechol–graphene–chitosan (Cat-Gr-Chit) has three operational components: (i) graphene confers conductivity; (ii) conducting catechols are envisioned to be in direct contact with graphene and can directly exchange electrons with graphene, and (iii) nonconducting catechols are envisioned to be physically separated from graphene and can only exchange electrons indirectly through diffusible mediators. Mechanistically, graphene "wires" the conducting catechols to the electode:[34] electrons can flow from the electrode, through graphene, and to the conducting catechol moieties where they switch the catechol's redox-state. Presumably this wiring involves interactions between $\pi-\pi$ electrons of the graphene and the conducting catechols.

There have been growing efforts to characterize the electron transfer mechanisms in electronic materials by coupling spectral measurements of the molecular redox-state with electrochemical measurements of electron-transfer processes.[35−37] We used such operando spectro-electrochemical analysis to provide evidence for the three operational components illustrated in Figure 5a.[34] Figure 5b shows that capacitor films can be assembled onto a transparent gold electrode to allow spectro-electrochemical analysis with the goal of correlating electrical function (i.e., electron flow) to the molecular switching of catechol's redox-state as measured by spectral changes (absorbance at 480 nm; the oxidized quinone moieties have a higher Abs_{480} than the reduced catechol moieties[38]). As suggested in Figure 5b, an oscillating electrode potential (i.e., voltage) was imposed to evoke oscillating electrical currents associated with the sequential flow of electrons into and out of the film, and oscillating spectral signals associated with the sequential switching of the redox state for the grafted catechol moieties. These measurements provided evidence that graphene allows direct electron transfer to the conducting

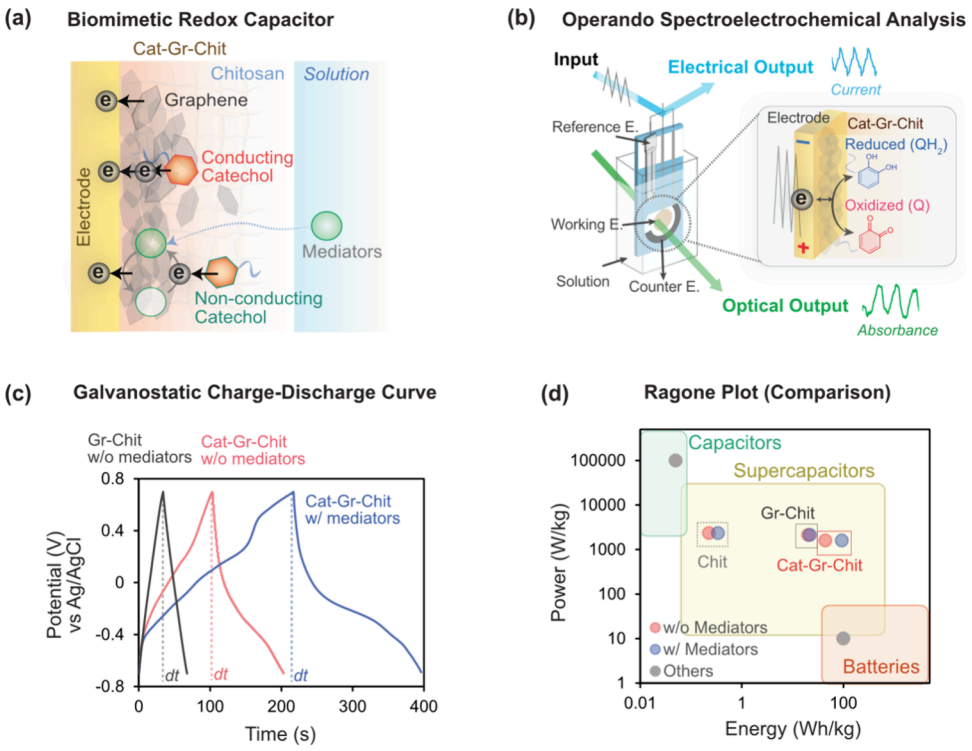


Figure 5. Catechol–graphene–chitosan composite film for energy applications. (a) Measurements suggest that graphene confers conductivity, while one population of catechol is conducting (can directly exchange electrons with graphene) and a second population of catechol is nonconducting (can indirectly exchange electrons through mediators). (b) Operando spectro-electrochemical measurements using oscillating input potentials to evoke oscillating electrical (current), and spectral (absorbance) responses were used to provide mechanistic insights of the capacitor's performance. (c) Performance studies using galvanostatic charge–discharge experiments. (d) Ragone plot summarizes the performance of the films. Reproduced from ref 34 with permission from Wiley, Copyright 2022.

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

catechols, while the nonconducting catechols can donate/accept electrons through an indirect (i.e., mediator-based) electron transfer mechanism. In both cases, electron transfer to catechol involves its redox-state switching (see Figure S1 of the Supporting Information).

Finally, to test the performance of catechol−graphene−chitosan (Cat-Gr-Chit) films for energy applications, we performed galvanostatic charge−discharge experiments (Figure 5c). The associated Ragone plot in Figure 5d indicates that (i) a Gr-Chit film has higher energy storage capabilities (vs a Chit film) due to graphene's added double-layer capacitance, (ii) a Cat-Gr-Chit film (without mediators) enhances energy storage through a redox capacitance mechanism, and (iii) a mediator-pair can further enhance the energy storage of the Cat-Gr-Chit film through an additional redox capacitance mechanism involving the nonconducting catechols.[34]

CONCLUSION

We started this Perspective by describing recent studies that showed that phenolic/catecholic materials in nature (e.g., soil humics, dietary antioxidants, and melanin) have redox capacitor properties that enable them to accept, store, and donate electrons. We suggest that the recognition of these materials as redox capacitors may help to explain their unique and often context-dependent biological activities (e.g., anti- vs pro-oxidant). We also cited recent translational studies indicating that the redox capacitor properties of catecholic materials can offer unique capabilities to process information in bioelectronics, engage biology in redox communication for applications in medicine (e.g., wound dressings) and biotechnology (e.g., to induce gene expression from stress response regulons), and enhance energy storage.

More broadly, one theme of this Perspective is that both our technological and natural worlds couple the storage/flow of electrons to the storage/flow of energy and information; however, there are fundamental mechanistic differences. Integrated circuits are designed based on knowledge of how electrons flow through circuit elements in response to an imposed voltage. In contrast, our biosphere does not contain a sea of loosely bound electrons that flow in response to an imposed voltage (or electric field). Rather, our biosphere contains insoluble electrons that are transferred from one molecule to another through redox reactions that typically involve individual electrons or electron-pairs (i.e., the number of "flowing" electrons appears as stoichiometric coefficients in half-cell reactions). Because of this mechanistic difference, we believe the flow of electrons in biological and environmental materials is better described by models of redox reactions and reaction networks (vs electrical circuit models). We use such a network modeling approach to characterize our catechol-based biomimetic redox capacitor.[3] Potentially, precisely counting electrons through reaction stoichiometries (vs quantifying electron flow in terms of an electric field) may make it easier to (i) separate (at least conceptually) the relative contributions of electrons and counterions in measured currents and to separate contributions from double-layer and redox capacitance, (ii) "fuse" electrical measurements of current to spectral measurements of redox-state switching, and (iii) optimize the use of redox-active materials and diffusible mediators in energy applications.

A second theme of this Perspective is that redox is a native biological modality, and new measurement methods are expanding our understanding of redox-biology, while this expanding knowledge is providing new biomimetic opportunities. Biology's ionic electrical modality has been studied for centuries and has resulted in familiar applications in sensing (electrocardiogram) and actuation (defibrillation). In contrast, our understanding of the redox modality is still emerging (e.g., the redox code was proposed less than a decade ago[4]). Compared to the ionic electrical modality, the redox modality is slower-acting (often requiring diffusion steps), is especially important in activities outside the cell (e.g., in the biogeosphere), and can actuate biology at both metabolic and gene expression levels. This expanding knowledge is being enabled by new experimental approaches especially involving mediated electrochemical,[8] spectro-electrochemical,[39] and operando[40] methods, as well as advanced methods in redox biology (e.g., synthetic biology).[26]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsami.4c13032.

Figure showing the analysis of catechol−graphene−chitosan composite hydrogel films (PDF)

AUTHOR INFORMATION

Corresponding Authors

Eunkyoung Kim − *Institute for Bioscience and Biotechnology Research and Robert E. Fischell Institute for Biomedical Devices, University of Maryland, College Park, Maryland 20742, United States;* orcid.org/0000-0003-2566-4041; Phone: 1-301-405-8341; Email: ekim@umd.edu

Gregory F. Payne − *Institute for Bioscience and Biotechnology Research and Robert E. Fischell Institute for Biomedical Devices, University of Maryland, College Park, Maryland 20742, United States;* orcid.org/0000-0001-6638-9459; Phone: 1-301-405-8389; Email: gpayne@umd.edu; Fax: 1-301-314-9075

Authors

Zhiling Zhao − *Institute for Bioscience and Biotechnology Research and Robert E. Fischell Institute for Biomedical Devices, University of Maryland, College Park, Maryland 20742, United States;* Present Address: VRB ENERGY Inc., Seventeen Yunshan Rd., Tongzhou, Beijing, China

Si Wu − *College of Resources and Environmental Engineering, Hubei Key Laboratory for Efficient Utilization and Agglomeration of Metallurgic Mineral Resources, Wuhan University of Science and Technology, Wuhan 430081, China;* orcid.org/0000-0001-6325-3951

Jinyang Li − *Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, California 91125, United States*

William E. Bentley − *Institute for Bioscience and Biotechnology Research, Robert E. Fischell Institute for Biomedical Devices, and Fischell Department of Bioengineering, University of Maryland, College Park, Maryland 20742, United States;* orcid.org/0000-0002-4855-7866

Complete contact information is available at: https://pubs.acs.org/10.1021/acsami.4c13032

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (MCB no. 2227598), the Defense Threat Reduction Agency (HDTRA1-19-0021), and the Gordon and Betty Moore Foundation (no. 11395).

■ REFERENCES

(1) Sies, H.; Jones, D. P. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 363−383.
(2) Sies, H.; Belousov, V. V.; Chandel, N. S.; Davies, M. J.; Jones, D. P.; Mann, G. E.; Murphy, M. P.; Yamamoto, M.; Winterbourn, C.; et al. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. *Nat. Rev. Mol. Cell Biol.* **2022**, *23* (7), 499−515.
(3) Zhao, Z. L.; Kim, E.; Motabar, D.; Bentley, W. E.; Payne, G. F. Spectroelectrochemical Network Measurements for Redox Bioelectronics. *Chem. Mater.* **2023**, *35*, 976−990.
(4) Jones, D. P.; Sies, H. The Redox Code. *Antioxidants & Redox Signaling* **2015**, *23* (9), 734−746.
(5) Lovley, D. R. Live wires: direct extracellular electron exchange for bioenergy and the bioremediation of energy-related contamination. *Energy Environ. Sci.* **2011**, *4* (12), 4896−4906.
(6) Peiffer, S.; Kappler, A.; Haderlein, S. B.; Schmidt, C.; Byrne, J. M.; Kleindienst, S.; Vogt, C.; Richnow, H. H.; Obst, M.; Angenent, L. T.; et al. A biogeochemical−hydrological framework for the role of redox-active compounds in aquatic systems. *Nat. Geosci.* **2021**, *14* (5), 264−272.
(7) Cui, S.; Wang, R.; Chen, Q.; Pugliese, L.; Wu, S. Geobatteries in environmental biogeochemistry: Electron transfer and utilization. *Environmental Science and Ecotechnology* **2024**, *22*, 100446.
(8) Aeschbacher, M.; Sander, M.; Schwarzenbach, R. P. Novel Electrochemical Approach to Assess the Redox Properties of Humic Substances. *Environ. Sci. Technol.* **2010**, *44* (1), 87−93.
(9) Di Lorenzo, C.; Colombo, F.; Biella, S.; Stockley, C.; Restani, P. Polyphenols and Human Health: The Role of Bioavailability. *Nutrients* **2021**, *13* (1), 273.
(10) Lee, M. E.; Kim, E.; Liu, Y.; March, J. C.; Bentley, W. E.; Payne, G. F. Rapid and Repeatable Redox Cycling of an Insoluble Dietary Antioxidant: Electrochemical Analysis. *J. Agr Food Chem.* **2014**, *62* (40), 9760−9768.
(11) Espey, M. G. Role of oxygen gradients in shaping redox relationships between the human intestine and its microbiota. *Free Radical Bio Med.* **2013**, *55*, 130−140.
(12) Winiarska-Mieczan, A.; Kwiecień, M.; Jachimowicz-Rogowska, K.; Donaldson, J.; Tomaszewska, E.; Baranowska-Wójcik, E. Anti-Inflammatory, Antioxidant, and Neuroprotective Effects of Polyphenols-Polyphenols as an Element of Diet Therapy in Depressive Disorders. *Int. J. Mol. Sci.* **2023**, *24* (3), 2258.
(13) d'Ischia, M.; Napolitano, A.; Pezzella, A.; Meredith, P.; Buehler, M. Melanin Biopolymers: Tailoring Chemical Complexity for Materials Design. *Angew. Chem., Int. Ed.* **2020**, *59* (28), 11196−11205.
(14) Cao, W.; Zhou, X. H.; McCallum, N. C.; Hu, Z. Y.; Ni, Q. Z.; Kapoor, U.; Heil, C. M.; Cay, K. S.; Zand, T.; Mantanona, A. J.; et al. Unraveling the Structure and Function of Melanin through Synthesis. *J. Am. Chem. Soc.* **2021**, *143* (7), 2622−2637.
(15) Mostert, A. B.; Powell, B. J.; Pratt, F. L.; Hanson, G. R.; Sarna, T.; Gentle, I. R.; Meredith, P. Role of semiconductivity and ion transport in the electrical conduction of melanin. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109* (23), 8943−8947.
(16) Nappi, A. J.; Christensen, B. M. Melanogenesis and associated cytotoxic reactions: Applications to insect innate immunity. *Insect Biochem. Mol. Biol.* **2005**, *35* (5), 443−459.
(17) Kang, M.; Kim, E.; Temocin, Z.; Li, J. Y.; Dadachova, E.; Wang, Z.; Panzella, L.; Napolitano, A.; Bentley, W. E.; Payne, G. F. Reverse Engineering To Characterize Redox Properties: Revealing Melanin's Redox Activity through Mediated Electrochemical Probing. *Chem. Mater.* **2018**, *30* (17), 5814−5826.
(18) Kim, E.; Panzella, L.; Micillo, R.; Bentley, W. E.; Napolitano, A.; Payne, G. F. Reverse Engineering Applied to Red Human Hair Pheomelanin Reveals Redox-Buffering as a Pro-Oxidant Mechanism. *Sci. Rep.* **2015**, *5*, 18447−18447.
(19) Kim, E.; Leverage, W. T.; Liu, Y.; Panzella, L.; Alfieri, M. L.; Napolitano, A.; Bentley, W. E.; Payne, G. F. Paraquat−Melanin Redox-Cycling: Evidence from Electrochemical Reverse Engineering. *ACS Chem. Neurosci* **2016**, *7* (8), 1057−1067.
(20) Temoçin, Z.; Kim, E.; Li, J.; Panzella, L.; Alfieri, M. L.; Napolitano, A.; Kelly, D. L.; Bentley, W. E.; Payne, G. F. The Analgesic Acetaminophen and the Antipsychotic Clozapine Can Each Redox-Cycle with Melanin. *ACS Chem. Neurosci* **2017**, *8* (12), 2766−2777.
(21) Kim, E.; Liu, Y.; Leverage, W. T.; Yin, J.-J.; White, I. M.; Bentley, W. E.; Payne, G. F. Context-Dependent Redox Properties of Natural Phenolic Materials. *Biomacromolecules* **2014**, *15*, 1653−1662.
(22) Sode, K.; Yamazaki, T.; Lee, I.; Hanashi, T.; Tsugawa, W. BioCapacitor: A novel principle for biosensors. *Biosens. Bioelectron.* **2016**, *76*, 20−28.
(23) Uchimiya, M.; Stone, A. T. Reversible redox chemistry of quinones: Impact on biogeochemical cycles. *Chemosphere* **2009**, *77* (4), 451−458.
(24) Kim, E.; Wang, Z.; Phua, J. W.; Bentley, W. E.; Dadachova, E.; Napolitano, A.; Payne, G. F. Enlisting electrochemistry to reveal melanin's redox-related properties. *Mater. Adv.* **2024**, *5* (8), 3082−3093.
(25) Liu, Y.; Kim, E.; Motabar, D.; Zhao, Z.; Kelly, D. L.; Bentley, W. E.; Payne, G. F. Redox-Enabled Bio-Electronics for Information Acquisition and Transmission | IEEE Journals & Magazine | IEEE Xplore. *IEEE Transactions on Molecular, Biological and Multi-Scale Communications* **2023**, *9* (2), 146−166.
(26) Motabar, D.; Li, J.; Payne, G. F.; Bentley, W. E. Mediated electrochemistry for redox-based biological targeting: entangling sensing and actuation for maximizing information transfer. *Curr. Opin. Biotechnol.* **2021**, *71*, 137−144.
(27) Kim, E.; Gordonov, T.; Liu, Y.; Bentley, W. E.; Payne, G. F. Reverse Engineering To Suggest Biologically Relevant Redox Activities of Phenolic Materials. *ACS Chem. Biol.* **2013**, *8* (4), 716−724.
(28) Kim, E.; Gordonov, T.; Bentley, W. E.; Payne, G. F. Amplified and in Situ Detection of Redox-Active Metabolite Using a Biobased Redox Capacitor. *Anal. Chem.* **2013**, *85*, 2102−2108.
(29) Wu, S.; Rzasa, J. R.; Kim, E.; Zhao, Z.; Li, J.; Bentley, W. E.; Payne, N. N.; Shi, X.; Payne, G. F. Catechol Patterned Film Enables the Enzymatic Detection of Glucose with Cell Phone Imaging. *ACS Sustain. Chem. Eng.* **2021**, *9* (44), 14836−14845.
(30) Wu, S.; Kim, E.; Li, J.; Bentley, W. E.; Shi, X.-W.; Payne, G. F. Catechol-Based Capacitor for Redox-Linked Bioelectronics. *ACS Appl. Electron. Mater.* **2019**, *1* (8), 1337−1347.
(31) Liu, Y.; Tsao, C.-Y.; Kim, E.; Tschirhart, T.; Terrell, J. L.; Bentley, W. E.; Payne, G. F. Using a Redox Modality to Connect Synthetic Biology to Electronics: Hydrogel-Based Chemo-Electro Signal Transduction for Molecular Communication. *Adv. Healthcare Mater.* **2017**, *6* (1), 1600908.
(32) Liu, H.; Qu, X.; Kim, E.; Lei, M.; Dai, K.; Tan, X. L.; Xu, M.; Li, J. Y.; Liu, Y. P.; Shi, X. W.; et al. Bio-inspired redox-cycling antimicrobial film for sustained generation of reactive oxygen species. *Biomaterials* **2018**, *162*, 109−122.
(33) Li, J. Y.; Wang, S. P.; Zong, G. H.; Kim, E.; Tsao, C. Y.; VanArsdale, E.; Wang, L. X.; Bentley, W. E.; Payne, G. F. Interactive Materials for Bidirectional Redox-Based Communication. *Adv. Mater.* **2021**, *33* (18), 2007758.
(34) Kim, E.; Argenziano, R.; Zhao, Z.; Chen, C.-y.; Shen, M.; Bentley, W. E.; Napolitano, A.; Payne, G. F. Characterizing Electron Flow through Catechol-Graphene Composite Hydrogels. *Adv. Mater. Interfaces* **2022**, *9* (35), 2202021.

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502

(35) Kim, Y. J.; Wu, W.; Chun, S.-E.; Whitacre, J. F.; Bettinger, C. J. Biologically derived melanin electrodes in aqueous sodium-ion energy storage devices. *Proc. Natl. Acad. Sci. U.S.A* **2013**, *110* (52), 20912−20917.
(36) Song, Z.; Zhang, G.; Deng, X.; Tian, Y.; Xiao, X.; Deng, W.; Hou, H.; Zou, G.; Ji, X. Strongly Coupled Interfacial Engineering Inspired by Robotic Arms Enable High-Performance Sodium-Ion Capacitors. *Adv. Funct. Mater.* **2022**, *32* (38), 2205453.
(37) Deng, X.; Zou, K.; Momen, R.; Cai, P.; Chen, J.; Hou, H.; Zou, G.; Ji, X.; et al. High content anion (S/Se/P) doping assisted by defect engineering with fast charge transfer kinetics for high-performance sodium ion capacitors. *Science Bulletin* **2021**, *66* (18), 1858−1868.
(38) Wu, S.; Kim, E.; Chen, C. Y.; Li, J. Y.; VanArsdale, E.; Grieco, C.; Kohler, B.; Bentley, W. E.; Shi, X. W.; Payne, G. F. Catechol-Based Molecular Memory Film for Redox Linked Bioelectronics. *Adv. Electron. Mater.* **2020**, *6* (10), 2000452.
(39) Garoz-Ruiz, J.; Perales-Rondon, J. V.; Heras, A.; Colina, A. Spectroelectrochemical Sensing: Current Trends and Challenges. *Electroanalysis* **2019**, *31* (7), 1254−1278.
(40) Kim, E.; Chen, C.-y.; Phua, J. W.; Napolitano, A.; Bentley, W. E.; Payne, G. F. Operando Spectroelectrochemical Characterization Shows that the Dynamic Flow of Electrons through Melanin Involves Its Redox-State Switching. *J. Phys. Chem. C* **2023**, *127* (40), 19979−19994.

https://doi.org/10.1021/acsami.4c13032
ACS Appl. Mater. Interfaces 2024, 16, 61495−61502