Intelligent Multi-sensor Arrays for Next Generation Diagnostic Biodevices

Hadar Ben-Yoav
Department of Biomedical Engineering, Ben-Gurion University of the Negev, Beer Sheva, Israel

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Abstract: Redox molecules play an essential role in many biological pathways, including energy metabolism, biosynthesis, and cell respiration. Moreover, a specific spectrum of redox molecules (comprising their type, concentration, and redox state) is involved in the development of diseases, including cancer. Thus, profiling the redox spectrum in the body is highly beneficial for a wide range of biomedical applications, from *in vivo* diagnostics to *in situ* monitoring of cell metabolism. Yet, the fundamental challenge lies within the ability to efficiently extract and analyze physiologically and medically relevant information from redox molecules in biofluids. This paper will discuss the advantageous approach to rapidly and continuously monitor redox molecules in biofluids using electrochemical lab-on-a-chip biodevices. The current approaches will be discussed to selectively measure redox molecules from biofluids without diminishing the rapid and continuous monitoring capabilities of these translational biodevices, i.e., by simultaneously analyzing multiple diagnostic redox biomarkers in a stand-alone operation, without any sample pretreatment or elimination of other interfering molecules. Then, the promising approach of using intelligent multi-sensor arrays will be highlighted for the rapid detection of a spectrum of redox molecules and the current challenges impeding their important utilization for next generation biomedical diagnostic devices.

1 INTRODUCTION

'Redox' molecules—i.e., molecules that transfer electrons through a Reduction-Oxidation reaction—play an essential role in many biological pathways, including energy metabolism, biosynthesis, and cell respiration (Jones and Sies, 2015). Moreover, the specific 'redox landscape' in the body—i.e., the type, concentration, and redox state of various redox molecules—plays an important role in regulation and communication between different physiological pathways (Griffiths, Gao et al., 2017; Sies, 2017), and it is even involved in the development of diseases (Swomley and Butterfield, 2015; Chandrasekaran, Idelchik et al., 2017), including cancer (Yuan, Liu et al., 2015). Importantly, in 2017, the European Cooperation in Science and Technology [COST] Action 'EU-ROS' expressed the significance and need to "providing new insights and tools for better understanding redox biology and medicine and, in the long run, to finding new therapeutic strategies to target dysregulated redox processes in various diseases" (Egea, Fabregat et al., 2017). Thus, profiling the 'redox landscape' in the body is highly beneficial for a wide range of biomedical applications, from *in vivo* diagnostics to *in situ* monitoring of cell metabolism. Yet, the fundamental challenge lies within the ability to efficiently extract and analyze physiologically and medically relevant information from redox molecules in biofluids.

Electrochemical lab-on-a-chip are well suited for the analytical task of measuring redox molecules (Bandodkar and Wang, 2014; Katz, Fernandez et al., 2015; Katz, 2016; Sekretaryova, Eriksson et al., 2016). These translational, cost-effective, and portable miniaturized biodevices enable a rapid and continuous monitoring with superior sensitivity of multiple redox molecules without externally-added labels ['unlabeled'], by directly recording electrochemical reactions happening between the molecules and an electrode, generating a unique electronic signal according to the redox potential of a molecule of interest. Thus, these 'portable laboratories' provide the means in which the sensor continuously measures the *in situ* levels of unlabeled

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redox-active diagnostic markers in the sample (Bandodkar, Jia et al., 2015; Topkaya, Azimzadeh et al., 2016). However, the selectivity of electrochemical lab-on-a-chip towards several diagnostic redox biomarkers dramatically decreases in the presence of multicomponent samples [e.g., biofluids] due to the presence of other redox molecules generating overlapping electrochemical signals, impeding the ability to distinguish between the various unlabeled, redox biomarkers in the sample (Corrie, Coffey et al., 2015; Rocchitta, Spanu et al., 2016).

This paper will focus on current approaches to overcome the key challenge of selectivity in biofluids without diminishing the rapid and continuous monitoring capabilities of electrochemical lab-on-a-chip biodevices, i.e., by simultaneously analyzing multiple diagnostic redox biomarkers from biofluids in a stand-alone operation, without any sample pretreatment or elimination of other interfering molecules. First, the commonly used analytical approaches will be reviewed that enable the selective detection of specific redox biomarkers. Then, the promising approach of using intelligent multi-sensor arrays will be highlighted for the detection of a spectrum of redox molecules and the current challenges impeding unleashing the potential utilization for biomedical diagnostics.

2 ELECTROCHEMICAL LAB-ON-A-CHIP BIODEVICES FOR REDOX BIOMARKERS DETECTION

2.1 Detection of Specific Diagnostic Redox Biomarkers

The signal in electrochemical sensors – namely, the electronic current generated at the surface of the electrode – is determined by three main factors: (a) the properties of the molecules, e.g., their standard redox potentials, molecular weights, particle charges, diffusion rates, and concentrations; (b) the properties of the electrode used, e.g., electrode material type and electrode geometry; and (c) the properties of the redox reaction at the solid–electrolyte interface, e.g., the rate of electron transfer between the molecules and the electrode and the thickness of the electric double layer (Bard and Faulkner, 2001). For samples containing more than one redox molecule [such as biofluids], the resulting electrochemical signal is complex and must undergo digital deconvolution through direct and simple signal processing methods (Jakubowska, 2011; Xia and Behnamian, 2015). Naturally, however, the level of complexity increases as a function of the number of molecules in the solution, making such a separation impractical for solutions with multiple redox molecules – and practically impossible when these molecules have overlapping electrochemical signals.

Another approach to discriminate between molecules in multicomponent mixtures is to use a pre-separation step [e.g., liquid chromatography], which increases the selectivity of the sensor by physically separating the molecule of interest (Huang, Lin et al., 2011; Kutter, 2012; Sikanen, Aura et al., 2012; Chan, Pasikanti et al., 2015; Fekete, Guillarme et al., 2016; Hong, Yang et al., 2016; Songa and Okonkwo, 2016). This solution indeed increases separation efficiency but it is laborious, time-consuming, and increases the number of analytic steps and the overall cost of the discrimination step, thus preventing its effective utilization for *in situ* recording of the numerous molecules continuously generated in the body.

An alternative approach involves modifying the surface of the electrode with a film that recognizes a specific type of molecule in the sample, thus increasing the selectivity of the sensor to the specific electrochemical signal generated by this molecule (Xie, Liu et al., 2015; Bala and Gorski, 2016; Weltin, Kieninger et al., 2016). Both artificial and biological receptors [e.g., enzymes] can be used to produce such highly selective films (Palchetti, 2016; Weltin, Kieninger et al., 2016), and, indeed, these modified electrodes can be integrated into an array of specific sensors [Figure 1] that can analyze the types of the redox molecules at suitable limit-of-detection values [usually between nano- and femto-molars (Bougrini, Florea et al., 2016)]. However, the development of such films is costly and is multiplied by the number of the detected molecules and required electrodes, thereby limiting the multi-molecule detection capabilities of such modified electrodes (Bunyakul and Baeumner, 2015; Zaffino, Galan et al., 2015; Heikenfeld, 2016). Moreover, with the growing evidence that a disease is no more governed by a specific biomarker but profiles of molecules, a single or combination of highly selective measurements may be inadequate as appropriate biomarkers are seldom known for complex diseases.

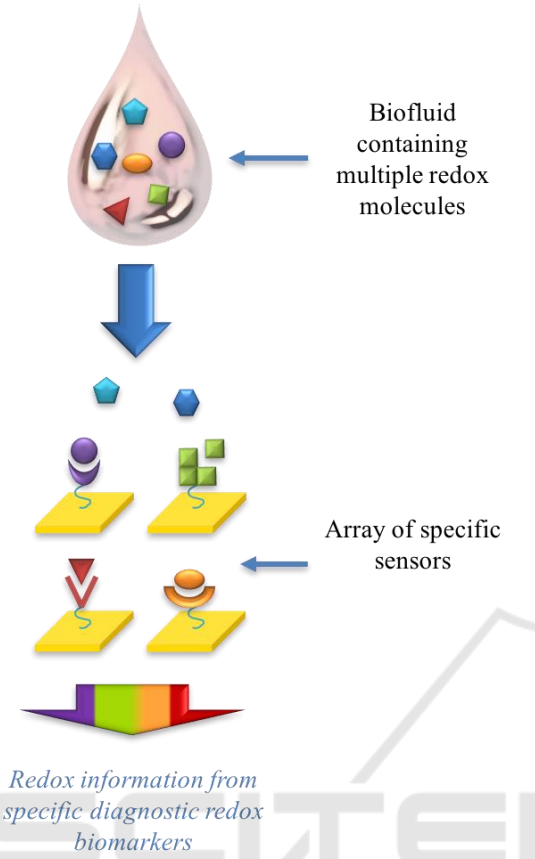

Figure 1: Array of electrodes modified with films that are specific to multiple diagnostic redox biomarkers.

2.2 Detection of a Spectrum of Diagnostic Redox Biomarkers

Recently, a promising trend has emerged based on arrays of partially-selective electrodes that simultaneously cross-react with multiple redox molecules in the mixture [Figure 2]. Such an array of electrodes thus generates a set of complex electrochemical signals that are analyzed using intelligent chemometric algorithms [e.g., pattern recognition algorithms] to facilitate the *in situ* analysis of these molecules (Cipri, Schulz et al., 2016; Kilmartin, 2016; Wadehra and Patil, 2016)).

Inspired by the sensory system of taste in mammals, wherein several taste receptors on the tongue can respond to a large variety of flavor-inducing substances, these intelligent electrochemical sensors enable fast response, low-cost, portability, ease-of-use, and simultaneous detection of a large spectrum of redox molecules in one step without preforming any pretreatment, as data processing stage may offset any matrix or interference effect from the sample itself, drifts or nonlinearity obtained with the sensors (Cetó, Voelcker et al., 2016).

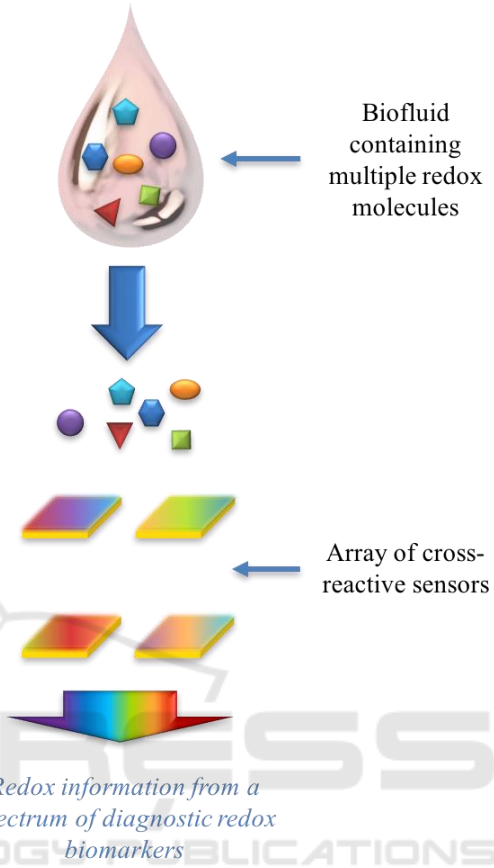

Figure 2: Array of electrodes modified with partially-selective films that cross-react with multiple diagnostic redox biomarkers.

The cross-reactivity is achieved by using electrodes consisting of materials that possess different electron transfer rates, thereby generating slightly diverse electrochemical signals from the analyzed redox mixture. To extract information about the redox molecule of interest [concentration, type, etc.], machine learning algorithms—including multivariate analysis models, such as principal component analysis, artificial neural networks, and others—are used together with training sets of calibration mixtures, thus shifting the complexity of the analysis from the physical domain to the digital processing domain (Górski, Kubiak et al., 2016). However, despite the vast contribution of such 'intelligent sensors' to differentiate between groups of food types or environmental conditions (Wei, Yang et al., 2018), utilizing them for biomedical applications is more challenging, mainly because biofluids contain an abundance of redox molecules,

which generate overlapping electrochemical signals that are hard to distinguish.

To solve this issue and provide an accurate and meaningful profile of the redox molecules in biofluids, previous studies suggested modifying electrodes with films that provide various reactivities between the electrode and the redox molecules based on the films' properties, i.e., their electrocatalytic activity [e.g., noble metals as electrode material or conductive polymers to coat the electrodes (Wei, Yang et al., 2018)] or their biofunctionality [e.g., enzymes immobilized on the electrode (Cetó, Voelcker et al., 2016)]. Indeed, such approaches have enabled, for the first time, profiling a predetermined set of redox molecules—e.g., for identifying the redox state of specific molecules involved in a specific type of cancer [namely, prostate cancer (Pascual, Campos et al., 2016)]. However, despite this marked advancement in the ability to differentiate between groups of specific, disease-oriented 'redox landscapes', this approach is currently lacking the ability to extract redox information from all redox molecules present in a biofluid at a given time, hence limiting the diagnosis to a specific biomedical condition.

3 CONCLUSIONS

This paper highlights the potential contribution of intelligent multi-sensor arrays for the important need to profile the 'redox landscape' in the body. By overcoming the fundamental challenge of selectivity in biofluids, these intelligent sensors will enable the rapid and continuous quantitative analyses of redox information in biofluids. Such an achievement is highly beneficial for a wide range of biomedical applications, from *in vivo* diagnostics to *in situ* monitoring of cell metabolism, and will offer the next generation of diagnostic biodevices that can be used to study and monitor disease initiation and development. Ultimately, integrating these intelligent sensors in electrochemical lab-on-a-chip biodevices will facilitate the development of highly sensitive monitoring tools for the continuous *in vivo* monitoring of various biomedical conditions.

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