The Virus Bioresistor: Wiring Virus Particles for the Direct, Label-Free Detection of Target Proteins

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Supporting Information

ABSTRACT: The virus bioresistor (VBR) is a chemiresistor that directly transfers information from virus particles to an electrical circuit. Specifically, the VBR enables the label-free detection of a target protein that is recognized and bound by filamentous M13 virus particles, each with dimensions of 6 nm (w) × 1 μm (l), entrained in an ultrathin (~250 nm) composite virus–polymer resistor. Signal produced by the specific binding of virus to target molecules is monitored using the electrical impedance of the VBR: The VBR presents a complex impedance that is modeled by an equivalent circuit containing just three circuit elements: a solution resistance (Rsolv), a channel resistance (RVBR), and an interfacial capacitance (CVBR). The value of RVBR, measured across 5 orders of magnitude in frequency, is increased by the specific recognition and binding of a target protein to the virus particles in the resistor, producing a signal ΔRVBR. The VBR concept is demonstrated using a model system in which human serum albumin (HSA, 66 kDa) is detected in a phosphate buffer solution. The VBR cleanly discriminates between a change in the electrical resistance of the buffer, measured by Rsolv, and selective binding of HSA to virus particles, measured by RVBR. The ΔRVBR induced by HSA binding is as high as 200 Ω, contributing to low sensor-to-sensor coefficients-of-variation (<15%) across the entire calibration curve for HSA from 7.5 nM to 900 nM. The response time for the VBR is 3−30 s.

KEYWORDS: Bacteriophage, chemiresistor, biosensor, impedance, human serum albumin

Investigating the electrical properties of microscopic biological entities such as organelles, bacteria, eukaryotic cells, and viruses is both interesting from a fundamental science perspective, as well as challenging because they are electrically insulating. How does one “wire” such structures to an external circuit?1−3 Elegant solutions to this problem have been demonstrated involving interfaces to single cells, bacteria, etc., involving single nanostructures or ensembles of nanostructures (nanowires, nanotubes, nanosheets, etc.). For example, electrical signals from single cells have been measured using graphene field-effect transistors and nanowire-embedded n-p junctions.3,4 The “wiring” of bacteria to electrode surfaces has been accomplished using outer sphere redox mediators.6−8

A new approach, the virus bioresistor (or VBR), provides the means for incorporating virus particles into an electrical circuit (Figure 1). The key to the VBR is an electronically conductive channel composed of poly(3,4-ethylenedioxythiophene) or PEDOT into which M13 virus particles are embedded (Figure 1a). Individual M13 virus particles are filamentous with dimensions of 6 nm (w) × 1.0 μm (l). The recognition and binding of target molecules to thousands of M13 virus particles embedded in this polymeric channel is signaled by an electrical impedance signature, that can be measured by an external circuit (Figure 1b,c). The impedance response of the VBR is modeled by a simple equivalent circuit containing just three circuit elements: a solution resistance (Rsolv), a channel resistance (RVBR), and an interfacial capacitance (CVBR) (Table 1). Information on target binding is contained in the Rbr, which can be measured either at a single frequency or from the best fit of the Nyquist plot across 40 or 50 discrete frequencies using this equivalent circuit.

We demonstrate the VBR concept using a model system in which human serum albumin (HSA, 66 kDa) is detected in a phosphate buffer solution. The VBRs described here have a baseline dc resistance of 200−250 Ω, which is the same in air or in an aqueous buffer solution, and are capable of producing large signals (ΔRVBR ≈ 250 Ω, or ΔRVBR/Rsolv ≈ 100%) for the detection of HSA in phosphate buffer solutions across the entire HSA binding curve ranging from [HSA] = 7.5 nM to 900 nM. In spite of the fact that the electrical signal generated by...
VBRs derives purely from ensembles of biological entities, extremely high sensor-to-sensor reproducibility of this signal is attainable for the response of VBR biosensors culminating in a coefficient-of-variation of the measured [HSA] for 20 sensors less than 15% across the entire HSA binding curve. The VBR achieves these metrics using a two-terminal, monolithic device architecture that is simple, robust, manufacturable, and inexpensive. No reagents and no sandwich amplification of the impedance signal are required, and no redox species are added to the test solution. Collectively, these data demonstrate the feasibility of adapting the VBR concept to rapid, inexpensive urine and blood-based assays at the point-of-care.

The fabrication of a VBR involves the preparation of two gold electrical contacts on a glass substrate by photolithography (Figure 2). On top of these contacts, a two-layer VBR channel (15 mm (l) × 20 mm (w)) is prepared consisting of a spin-cast PEDOT−PSS semiconductor bottom layer (200–300 nm in thickness) and an electrodeposited virus-PEDOT composite top layer containing thousands of engineered M13 virus particles\textsuperscript{9}−\textsuperscript{11} (90–100 nm in thickness). This virus-PEDOT electrodeposition process involves the application of two oxidizing voltammetric scans to an aqueous solution containing 8 nM M13 virus particles in 12.5 mM LiClO\textsubscript{4} and 2.5 mM EDOT (Figure 3a).

If the PEDOT−PSS/PEDOT-virus layer that electrically connects the two metal electrodes is severed, forcing current traveling between these two electrodes into the solution phase, we recently demonstrated that the resulting device still functions as a biosensor.\textsuperscript{20} However, the VBR has three attributes not found in this device: (1) an impedance signal that is amplified by a factor of 20 (200 Ω here versus 12 Ω in our prior work.)\textsuperscript{20} The result is a limit-of-detection of 7.5 nM in the VBR versus 100 nM in the earlier device;\textsuperscript{20} (2) the ability to decouple this signal from the salt concentration of the solution (vide infra); and (3) a dramatically faster response time of ∼5 s here versus 8−10 min.\textsuperscript{20}

Table 1. Equivalent Circuits and Equations Representing the Electrical Response of a VBR Biosensor

<table>
<thead>
<tr>
<th>Eq. Circuit</th>
<th>Circuit Diagram</th>
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<tbody>
<tr>
<td>Z_{eq} =</td>
<td>[ \frac{R_{VBR} R_{soln} (R_{VBR} + R_{soln})}{(R_{VBR} + R_{soln})^2 + \frac{1}{2} \omega^2 C_{eq}} ]</td>
</tr>
<tr>
<td>Z_{eq}</td>
<td>[ \frac{R_{VBR}^2}{(R_{VBR} + R_{soln})^2 + \frac{1}{2} \omega^2 C_{eq}} ]</td>
</tr>
<tr>
<td>Z_{eq}’</td>
<td>[ \frac{R_{VBR} Q_{VBR} \omega (Q_{VBR} + R_{soln}) \cos \frac{\omega t}{2} + R_{VBR} Q_{VBR} \omega^2 \sin \frac{\omega t}{2}}{Q_{VBR} Q_{VBR} (Q_{VBR} + R_{VBR}) (R_{soln} + R_{VBR}) Q_{VBR} \omega \frac{\omega t}{2} + 1} ]</td>
</tr>
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\textsuperscript{#}Capacitive equivalent circuit. \textsuperscript{#}Equivalent circuit with constant phase elements (CPEs).

VBRs derives purely from ensembles of biological entities, extremely high sensor-to-sensor reproducibility of this signal is attainable for the response of VBR biosensors culminating in a coefficient-of-variation of the measured [HSA] for 20 sensors less than 15% across the entire HSA binding curve. The VBR achieves these metrics using a two-terminal, monolithic device architecture that is simple, robust, manufacturable, and inexpensive. No reagents and no sandwich amplification of the impedance signal are required, and no redox species are added to the test solution. Collectively, these data demonstrate the feasibility of adapting the VBR concept to rapid, inexpensive urine and blood-based assays at the point-of-care.

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Figure 2. VBR biosensor fabrication. (a) Two pairs of gold-electrodes from which two VBRs are prepared. The gold electrodes have a width of 2 mm, and their separation of 1.5 mm defines the channel length of these devices. The two pairs of gold electrodes are separated by 0.5 mm. (b) A layer of PEDOT:PSS is spin-coated onto the gold-electrode device and baked for 1 h at 90 °C. (c) A 2 mm × 2 mm PMMA cell is attached defining the area of the bioaffinity layer. (d) A virus-PEDOT top layer is electropolymerized on top of the PEDOT−PSS bottom layer by using ∼100 μL of plating solution and applying two oxidizing voltammetric scans. (e) The virus-PEDOT plating solution is removed, and the cell is rinsed. Electrodes are used to enable impedance measurements at each of the two VBR sensors. One background impedance measurement is acquired in buffer and a second in a solution containing added HSA. The calculated ΔR_{VBR} is used to determine the HSA concentration in this sample with reference to a calibration curve.
Solution of 2.5 mM EDOT and 12.5 mM LiClO₄ show a SEMs of pure PEDOT three-dimensional rendering of these the same data shown in (e,f). If this layer is produced to contain virus particles, a slightly rougher surface is seen with an RMS roughness of 10 nm; however, a distinct topography reveals the presence of fiber-like structures that can be attributed to PEDOT-covered virus strands protruding from the PEDOT surface (Figure 3f,h). After the virus-PEDOT top layer is electrodeposited, the bioaffinity layer is complete, and the VBR is ready to use.

We elected to monitor VBRs using an ac impedance measurement, rather than applying a simpler dc resistance measurement, because prior work on conductive polymer based chemiresistors have shown conclusively that dramatically lower noise can be accessed using ac detection, even at frequencies as low as 5 Hz. Analytical equations for the real and imaginary components of the complex impedance, $Z_{re}$ and $Z_{im}$ (Table 1), are used to fit experimental impedance data to extract the values of the three circuit elements: $R_{col}$, $R_{VBR}$ and $C_{VBR}$. A version of the equivalent circuit in which a constant phase element (CPE) is substituted for each capacitor is used for this purpose. This elaboration provides better agreement between the calculated and the experimental impedance data, resulting in improved precision for the measurement of $R_{VBR}$ (Table 1). The impedance of a CPE, $Z_{CPE}$, and the capacitive impedance, $Z_C$, are defined by these equations:

$$Z_C = \frac{1}{i\omega C} \quad Z_{CPE} = \frac{1}{i\omega Q^n}$$

where $\omega$ is the angular frequency (radians s$^{-1}$), $i = \sqrt{-1}$, $Q^n$ is the CPE capacitance (F) where $n$ has a value of 1.0 if the CPE is purely capacitive. $n$ is used as a fitting parameter in this study and has a value of 1.0 $< n < 1.2$.

The VBR produces a distinctive impedance response consisting of a semicircular Nyquist plot ($Z_{im}$ versus $Z_{re}$ as a function of frequency) (Figure 4a–c). This response resembles the Randles equivalent circuit that is commonly seen for electrochemical biosensors operating in the presence of an added redox species, such as Fe(CN)$_6^{3-/4-}$. The semicircular Nyquist plot for electrochemical biosensors derives from electron transfer to and from the redox species present in the solution. When a redox species is not added, no semicircle is observed. The VBR produces a semicircular Nyquist plot without added redox species. Instead, the VBR channel presents a parallel resistance, dominated by electron conduction through the polymer composite VBR, and capacitance, produced by the non-Faradaic charging and discharging of the electrical double layer at the surface of the VBR. The semicircular Nyquist plots aids in the precision with which $R_{VBR}$ can be measured, just as it does in electrochemical biosensors that use the diameter of this semicircle, the so-called charge transfer resistance, to transduce target binding.

VBR biosensors are able to distinguish between changes in the electrical resistance of the test solution, caused by variations in the salt concentration, for example, and the concentration of target molecules present in this solution. Information on the electrical conductivity of the solution is contained in $R_{soln}$ whereas the concentration of target protein is encoded by $R_{VBR}$.

A cross-sectional SEM image of a VBR biosensor film shows a virus-PEDOT top layer with a thickness of $\sim$92 nm on top of a $\sim$ 245 nm PEDOT:PSS bottom layer (Figure 3b). Plan-view SEMs of pure PEDOT films prepared in an aqueous plating solution of 2.5 mM EDOT and 12.5 mM LiClO₄ show a smooth, homogeneous surface (Figure 3c). Virus-PEDOT films prepared from the same plating solution with the addition of 8 nM virus show dark, filamentous structures within the virus-PEDOT top layer (Figure 3d). These filaments are M13 bacteriophage, which have typical dimensions of 6 nm (diameter) $\times$ 1.0 $\mu$m (length). Atomic force microscopy (AFM) images show that in the absence of virus particles, the virus-PEDOT top layer is smooth with an RMS surface roughness of 5 nm (Figure 3e,g). If this layer is produced to contain virus particles, a slightly rougher surface is seen with an RMS roughness of 10 nm; however, a distinct topography reveals the presence of fiber-like structures that can be attributed to PEDOT-covered virus strands protruding from the PEDOT surface (Figure 3f,h).
Virtually no cross-talk occurs between these two circuit elements. For example, Nyquist plots (Z$_{im}$ versus Z$_{re}$ as a function of frequency) for a VBR in three concentrations of PBS buffer (1× PBS, 2.5× PBS, and 5× PBS) show the same ΔR$_{VBR}$ = R$_{VBR,HSA} - R_{VBR,buffer}$ signal for 75 nM HSA (Figure 4e) independent of the salt concentration ([NaCl]) over the range of 134 to 670 mM. Notably, R$_{soln}$ decreases dramatically with increasing salt concentration (Figure 4d).

The complementary experiment is to vary [HSA] in a 1× PBS buffer solution (Figure 4f). Here, Nyquist plots are shown for five buffer solutions containing [HSA] = 0, 70, 220, 370, and 750 nM. In this case, a quasi-linear increase in ΔR$_{VBR}$ with [HSA] is measured (Figure 4h), and R$_{soln}$ remains constant (Figure 4g). This property of VBRs, the ability to parse changes in impedance due to the solution resistance and target binding, provides an enormous advantage in terms of the application of this biosensor technology to body fluids where salt concentrations are unknown and uncontrolled.

VBR performance was evaluated for the detection of HSA using 20 VBRs in order to assess sensor-to-sensor reproducibility and coefficient-of-variance (CoV) to determine their practicality for single use biosensors. Two methods for analyzing VBR impedance data are also assessed here. The first method was previously used for non-Faradaic impedance biosensors where the signal-to-noise guided the selection of a single frequency at which either ΔZ$_{im}$ or ΔZ$_{re}$ was calculated by, for example, Z$_{re,HSA} - Z_{re,20}$. Using this approach, the sensing signal at 5 Hz was selected. The second method exploits a range of impedance data across 40–50 discrete frequencies and employs a fit to the equations of Table 1 to determine ΔR$_{VBR}$. Method 1 will afford more rapid analysis because impedance data at a single frequency is required. Method 2 requires longer analysis times; however, the approach has the potential to provide for higher precision and reduced noise for an assay, but can this advantage be demonstrated? To answer this question, the two methods were compared for three independent VBR biosensors (N = 3) at each HSA concentration from 7.5 to 750 nM to evaluate sensor-to-sensor reproducibility. In addition, two sensors (N = 2) were tested at 900 nM [HSA].
The performance of Methods 1 and 2 are summarized in the plots of Figure 5a and b, respectively. The main conclusion is that there is little difference in the performance of these two methods in terms of sensitivity, precision, and noise. Both \( \Delta Z_{re,5\,\text{Hz}} \) (Method 1) and \( \Delta R_{VBR} \) (Method 2) track increases in the HSA concentration from 7.5 to 900 nM HSA, saturating at close to 900 nM. These two calibration plots are both fitted with the Hill equation, which is frequently used to model biosensor response:21

\[
\Delta Z_{re} = \Delta Z_{re,0} - \Delta Z_{re,lim} \cdot \frac{(C_{\text{HSA}})^h}{(C_{\text{HSA}})^h + K_h^{h^*}}
\]

The best fit to the Hill equation for the \( \Delta Z_{re} \) calibration plot results in \( \Delta Z_{re,lim} = 250 \pm 40 \, \Omega, \Delta Z_{re,0} = 16 \pm 5 \, \Omega, K_h = 480 \pm 120 \, \text{nM}, h = 1.6 \pm 0.3, \) and \( R^2 = 0.97. \) Fit the Hill equation for the \( \Delta R_{channel} \) calibration plot results in \( \Delta R_{VBR,lim} = 250 \pm 30 \, \Omega, \Delta R_{VBR,0} = 20 \pm 5 \, \Omega, K_h = 410 \pm 60 \, \text{nM}, h = 1.9 \pm 0.4, \) and \( R^2 = 0.98. \) These data provide no justification for the use of multiple analysis frequencies (Method 2) as compared with a single, S/N-selected, analysis frequency (Method 1). Apparent \( K_h \) values are identical within experimental error. Values of \( h, \) which indexes the degree of cooperativity in target binding to virus particles, are also identical and equal to 1.6, which indicates significant cooperativity for phage binding to HSA in this system.

The origin of the VBR impedance signal is of interest and remains the subject of investigation. Either of two signal transduction mechanisms could reasonably account for our observations: First, the PEDOT–PSS can function as a p-type organic semiconductor field effect transistor (FET). In this case, an increase in \( \Delta R_{VBR} \) with [HSA] is accounted for by the binding of a positively charged target molecule to the VBR, leading to depletion of majority carriers and an increase in impedance. However, HSA has an isoelectric point, pI = 5.3, and our PBS buffer has pH = 8.0, so the HSA in these experiments is expected to have an overall negative charge, not a positive charge, at this pH. The binding of HSA to the PEDOT VBR should therefore cause the accumulation of majority carriers, reducing its electrical impedance, which is contrary to our experimental observations. As demonstrated in Figure 4e, the signal amplitude observed for HSA is unaffected by increases in the salt concentration of the test solution from 1× PBS to 5× PBS. This observation suggests that an electric field effect is not involved in the signal transduction process since the Debye length in these buffer solutions is both very small (2–8 Å) and variable.

A second, previously observed mechanism involves the disruption of long-range ordering in the PEDOT–PSS polymer chains. For example, bulky intercalators such as tosylate anions can cause an increase in electrical resistance, or “secondary dopants”, including diethylene glycol, oleylene glycol, and dimethyl sulfoxide, that lubricate the motion of polymer chains thereby promoting a higher degree of long-range

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ordering and a lower electrical resistance. HSA is readily classified as falling into the first category of bulky, structure disrupter. This description qualitatively explains the increase in resistance seen for VBRs upon exposure to HSA reported here. Furthermore, this model is consistent with the observed impedance signal for HSA measured at VBRs remaining unrelated to the salt concentration of the test solution. More work needs to be done with other analytes and solutions to cement our understanding of the VBR signal transduction mechanism.

In addition to sensitivity and reproducibility, selectivity and speed are the two other attributes important for biosensors. The selectivity of VBR biosensors was examined with two control conditions: (1) a VBR virus-PEDOT film containing HSA-binding virus measured for binding to 750 nM BSA protein, which is closely matched to HSA in terms of both size (both 66.5 kDa) and amino acid sequence (76% homologous), and (2) a VBR virus-PEDOT film containing the negative control STOP4 virus, which has no displayed peptide ligands, in the presence of 750 nM HSA protein. The sensing observe a rapid (3 s) response function for a biosensor and demonstrates the potential utility of VBRs for point-of-care applications.

The VBR simplifies the problem of electrically communicating with virus particles and, importantly, extracting valuable information in this process. Communication takes the form of signals the degree to which virus-displayed peptides have recognized and bound a particular target protein, leading to a precise and highly reproducible measurement of the concentration of this target molecule. The VBR is able to bypass a ubiquitous noise source in electrical or electrochemical biosensing: the variable electrical impedance of the solution itself.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.nanolett.8b00723.

Detailed description of experimental methods including VBR fabrication, impedance measurements, AFM and SEM analysis, and virus receptor selection (PDF)

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### Author Contributions

* A.B. and A.F.O. contributed equally to this work.

### Notes

The authors declare the following competing financial interest(s): The biosensor described here has been licensed to PhageTech, a company co-founded by Drs. Penner and Weiss. PhageTech is developing products related to the research described here. The terms of this arrangement have been reviewed and approved by the University of California, Irvine in accordance with its conflict of interest policies.

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