Subsecond-Resolved Molecular Measurements in the Living Body Using Chronoamperometrically Interrogated Aptamer-Based Sensors

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Supporting Information

ABSTRACT: Electrochemical, aptamer-based (E-AB) sensors support the continuous, real-time measurement of specific small molecules directly in situ in the living body over the course of many hours. They achieve this by employing binding-induced conformational changes to alter electron transfer from a redox-reporter-modified, electrode-attached aptamer. Previously we have used voltammetry (cyclic, alternating current, and square wave) to monitor this binding-induced change in transfer kinetics indirectly. Here, however, we demonstrate the potential advantages of employing chronoamperometry to measure the change in kinetics directly. In this approach target concentration is reported via changes in the lifetime of the exponential current decay seen when the sensor is subjected to a potential step. Because the lifetime of this decay is independent of its amplitude (e.g., insensitive to variations in the number of aptamer probes on the electrode), chronoamperometrically interrogated E-AB sensors are calibration-free and resistant to drift. Chronoamperometric measurements can also be performed in a few hundred milliseconds, improving the previous few-second time resolution of E-AB sensing by an order of magnitude. To illustrate the potential value of the approach we demonstrate here the calibration-free measurement of the drug tobramycin in situ in the living body with 300 ms time resolution and unprecedented, few-percent precision in the determination of its pharmacokinetic phases.

KEYWORDS: aptamer, chronoamperometry, in vivo, E-AB, electrochemical sensors, precision medicine

Electrochemical, aptamer-based (E-AB) sensors provide a modular approach to the continuous, real-time measurement of specific molecular targets irrespective of their chemical reactivity. The platform, which consists of an aptamer "probe" modified with a redox-active "reporter" and attached to an interrogating electrode (Figure 1A), signals via a binding-induced conformational change that alters electron transfer from the reporter, leading in turn to an easily measurable electrochemical output (Figure 1B). Because their signaling mechanism mimics the conformation-linked signal transduction employed by naturally occurring receptors in the body, E-AB sensors are particularly insensitive to nonspecific binding and easily support continuous, multihour measurements directly in flowing, undiluted blood serum. While E-AB sensors often exhibit significant drift when challenged in undiluted whole blood, we have recently shown that, when combined with protective membranes, improved surface passivation chemistries and/or active drift correction algorithms, E-AB sensors support the continuous, multihour measurement of specific molecules in whole blood both in vitro and in situ in the living body.

E-AB signaling is driven by binding-induced changes in the electron transfer kinetics of the aptamer-bound redox reporter. Previously we have used cyclic, alternating current, or square wave voltammetry to monitor this change in transfer kinetics indirectly by converting it into a change in peak current. The most commonly employed of these methods, square wave voltammetry (SWV), achieves this conversion by subjecting the sensor to a series of potential pulses and sampling the resultant faradaic currents after a delay defined by the square wave frequency. The magnitude of the observed current is thus dependent on the electron transfer rate (which defines how much the current has decayed by the time it is measured), which, in turn, depends quantitatively on the fraction of aptamers that are bound to target and thus on the concentration of the target. Specifically, when an E-AB sensor is interrogated by SWV the resultant peak current monotonically rises or falls (depending on the square-wave frequency) with rising target concentration (Figure 1B,C). The relative magnitude of this binding-induced change (i.e., the sensor’s signal gain) is dependent on the aptamer employed in the
sensor and can be maximized by optimizing the square wave frequency and amplitude.\textsuperscript{13}

Although SWV has proven a particularly convenient and reliable means of converting binding-induced changes in electron transfer kinetics into an easily measurable output, the approach is not without limitations. First, the absolute peak currents (as measured in amperes) produced by SWV are dependent not only on the presence or absence of target but also on the number of redox-reporter-modified aptamers on the sensor’s surface, which can fluctuate significantly from device-to-device due to variations in fabrication (Figure 1C). We have historically addressed this problem by calibrating each device in a reference sample of known (typically zero) target concentration prior to use, which, while effective (Figure 1D), increases complexity. Second, while SWV-interrogated E-AB sensors are selective enough to deploy directly in undiluted blood serum,\textsuperscript{6} they drift significantly when deployed in whole blood,\textsuperscript{2,7} a problem that, as noted above, we have previously overcome using a variety of drift correction and drift-avoidance approaches.\textsuperscript{2,7,9,14} Finally, because of the time required to scan the necessary several hundred millivolt potential window of SWV, its time-resolution is limited to several seconds. Here, in contrast, we show that, by replacing voltammetry, which measures changes in electron transfer rates indirectly, with chronoamperometry, which measures them directly, we can overcome these limitations to achieve the calibration-free, subsecond-resolved, drift-resistant measurement of specific molecules in situ in the living body.

\section*{RESULTS AND DISCUSSION}

Unlike SWV, which converts changes in electron transfer rates into a change in peak current, thus \textit{indirectly} reporting on transfer kinetics, chronoamperometry measures electron transfer kinetics \textit{directly}.\textsuperscript{15−17} It does so by determining the lifetimes of current transients generated in response to a stepping of the electrode’s potential to values where the redox reporter will either be fully oxidized or fully reduced (see Figure SI-1). For example, when we subject an E-AB sensor responsive to the aminoglycoside antibiotics to a sufficiently negative potential the resultant current decay traces are multiexponential (Figure 2). Specifically, in the absence of their target they exhibit a rapid exponential phase with a lifetime of \(100 \pm 30 \mu s\) (throughout this manuscript, errors represent the standard errors derived from 5 independently fabricated electrodes) and a slower phase with lifetime of \(6.5 \pm 0.5 \text{ ms}\). We attributed the more rapid phase to charging of the double layer formed on the electrode surface at this potential bias (i.e., the migration of aqueous ions, which occurs over time-scales of microseconds\textsuperscript{15}) which remains insensitive to changes in target concentration (Figure SI-2). The slower phase, in contrast, corresponds to the faradaic reduction of the methylene blue reporter to leuco-methylene blue. Upon the addition of saturating target the second phase becomes more rapid with a lifetime of \(1.20 \pm 0.01 \text{ ms}\). This \(\sim 5\)-fold decrease in lifetime reflects a population of target-bound aptamers that transfers electrons more rapidly than the target-free aptamer.

If the binding of the sensor’s aptamer obeys a two-state model\textsuperscript{19,20} the relative amplitudes of the two faradaic exponential phases (which reflect the populations of bound
and unbound aptamers) would change monotonically with target concentration. This assumes, however, that the two exponential phases can be accurately extracted from the data. Because their lifetimes are quite similar, however, it is difficult to extract the relevant amplitudes with sufficient precision. We overcome this limitation by approximating the current decay lifetime using a monoexponential fit (Figure 3A). Empirically we find that the lifetime of this “best fit” monoexponential is monotonically related to the concentration of the target, providing a means of determining target concentration (Figure 3B).

The monotonic relationship between the chronoamperometric lifetime of an E-AB sensor and the concentration of its target provides a calibration-free approach to performing E-AB measurements. That is, unlike absolute SWV peak currents, which depend on the total number of aptamers on the sensor, the lifetime of chronoamperometric decays depend only on the relative populations of the bound and unbound aptamer. Thus, once established for a given type of sensor, the lifetime–concentration relationship can be used to determine target concentrations without the need to calibrate each individual sensor. To illustrate this we established the lifetime–concentration relationship for aminoglycoside-detecting E-AB sensors when being used for the detection of tobramycin in vitro in flowing whole blood. Specifically, we performed a nonlinear regression of lifetime versus concentration to a Langmuir isotherm (red line in Figure 3B) and solved it for concentration. We then fabricated a batch of five new E-AB sensors (i.e., sensors not in our initial training set), challenged them with tobramycin in vitro in whole blood, and used the previously determined Langmuir isotherm to convert the observed chronoamperometric lifetimes into estimated concentrations (Figure 3C). Doing this we successfully determined concentrations of the drug with precision and accuracy of better than 10% over the range from 1 μM to 1 mM.

In addition to being calibration-free, chronoamperometrically interrogated E-AB sensors are also relatively resistant to drift. Again, while SWV-interrogated E-AB sensors are selective enough to perform well in undiluted blood serum,7,8 they often exhibit severe baseline drift when deployed directly in flowing whole blood (black circles in Figure 4A). We have previously corrected this using square wave voltammetry approaches that involve differential measurements taken at multiple frequencies drifting in concert (red circles in Figure 4A). Chronoamperometric lifetime measurements, in contrast, are inherently resistant to such drift; as noted above, while the total amplitude of the current transient drifts significantly, the lifetime of its exponential decay is independent of its amplitude and thus is largely drift-free (Figure 4B).

The drift-resistance of chronoamperometrically interrogated E-AB sensors is sufficient to support continuous, real-time measurements directly in situ in the bloodstreams of live animals. To demonstrate this we fabricated aminoglycoside-binding E-AB sensors on 75-μm-diameter gold wires (Figure 5A), encased them in 22-gauge catheters for structural support, and deployed them directly in the jugular veins of live rats (Figure 5B). We then used these to determine the plasma pharmacokinetics of the antibiotic tobramycin following an

**Figure 2.** Chronoamperometry. When using chronoamperometry to interrogate aminoglycoside-binding E-AB sensors in flowing whole blood in vitro, the observed current decay is well described as the sum of two exponential phases, as revealed in this log–log plot. From left to right, first we observe the decay of charging current, visible here (colored red) at about 100 μs. In the absence of target we then observe a slower exponential decay of faradaic current. In the presence of target (here tobramycin), this slower process becomes more rapid, suggesting the presence of a new population of redox-reporter-modified aptamers differing in their electron transfer kinetics. The illustrated transients were recorded by stepping the potential from −0.1 V to −0.3 V (all potentials reported versus Ag/AgCl) and sampling the resultant current every 10 μs (dots). The solid lines are multiexponential fits of the experimental data.

**Figure 3.** Calibration-free E-AB sensing. (A) Chronoamperometry produces decaying current transients with lifetimes that decrease with increasing target concentration. The solid lines represent monoexponential fits of the two current transients. (B) The resultant lifetimes vary monotonically and quantitatively with target concentration. The difference in dissociation constants between buffer and whole blood may arise from partitioning of the drug between blood cells and plasma. The differences in lifetimes are likely due to changes in electrolyte composition and viscosity that affect electron transfer from methylene blue. (C) Using this approach to estimate the concentration of tobramycin in flowing whole blood we achieve accurate and precise measurements over a broad range of concentrations without the need to calibrate individual sensors. Here we have employed 5 independently prepared sensors, all of which produce concentration estimates (calculated from response curve in panel B) within 10% of the actual (spiked) concentration of tobramycin over the range from 1 μM to 1 mM when challenged in undiluted whole blood. In panels B and C the colored points represent the average of 5 electrodes and the error bars (which are so small as to be difficult to see in panel B) represent their standard deviation.

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intravenous administration of 30 mg/kg by performing continuous chronoamperometric measurements for a total of 2 h (Figure 3C). We achieved continuous measurements by pulsing the potential of the E-AB sensors serially between −0.1 V and −0.3 V, holding each pulse with a duration of only 100 ms. Then, we performed nonlinear regression analysis of the current transients generated at −0.3 V to extract current decay lifetimes in real time. The lifetimes of these decays are independent of the number of aptamers remaining on the sensor, rendering them quite resistant to drift.

Figure 4. Drift-free E-AB sensing using chronoamperometry. (A) When E-AB sensors are challenged in vitro in flowing whole blood (here lacking target) the peak currents recorded from SWV drift significantly over the course of a few hours (black circles). We have traditionally corrected this by implementing kinetic differential measurements (KDM), which report on the difference in signaling observed at multiple square-wave frequencies; for example, here we show experimental peak currents from voltammograms recorded for an aminoglycoside-detecting sensor at 30 and 240 Hz that respond different to target but drift in concert; thus, by subtracting signals recorded at these two frequencies in real time we obtain KDM drift-corrected measurements. (B) The amplitude of a chronoamperometric current decay, which likewise depends on the number of aptamer molecules on the sensor, also drifts quite significantly. In contrast, however, the lifetimes of these decays are independent of the number of aptamers remaining on the sensor, rendering them quite resistant to drift.

Figure 5. Chronoamperometry enables the determination of in vivo pharmacokinetics with unprecedented subsecond temporal resolution. (A) Being only 75 μm in diameter, our E-AB sensors are small enough to be emplaced in the veins of live rats. (B) We encase them in a 22-gauge catheter for structural support, and place them inside the external jugular vein at a depth of 2 cm. Then, we implant an infusion line in the opposite side to carry out drug infusions. (C) We perform real-time nonlinear regression analysis of the current transients generated by chronoamperometry to extract their lifetimes and convert them to target concentration in real time. The red trace is the rolling average of 30 points (10 s). (D) At 300 ms per time point the time resolution of this approach is sufficient to monitor not only the injection of the drug but also the subsequent few tens of seconds “mixing with blood” phase associated with the drug homogenizing within the circulatory system. This panel corresponds to the zoomed area marked in green dashes from panel C. (E) This unprecedented time resolution allows us to, for example, measure the few-minute distribution phase of the drug with more than 1000 experimental points, producing in turn ultrahigh precision estimates of the associated pharmacokinetic parameters. The concentration data collected 30 min after the drug administration illustrates the excellent in vivo drift-resistance of chronoamperometrically interrogated E-AB sensors.
(limited by data acquisition and computation time) our chronoamperometric measurements resolve not only the duration of the drug infusion but also the time it takes for the drug to “mix” within the blood and reach homogeneity in the bloodstream after the end of the infusion (Figure 5D).

The subsecond time resolution of chronoamperometrically interrogated E-AB sensors allows us to measure drug pharmacokinetics with unprecedented precision. To show this we have determined the distribution, α, and elimination, β, lifetimes of tobramycin by fitting our in vivo data to a two-compartment pharmacokinetic model (Figure 5E). The 300 ms time resolution of chronoamperometrically interrogated E-AB sensors supports the determination of the distribution phase of the drug, α = 3.74 ± 0.04 min, with more than 1000 measurement points and a calculated standard error from the fit of ∼1%. This contrasts sharply with state-of-the-art chromatographic or radioimmunochemical methods which, because of its short lifetime, cannot be determined at all (other than in our prior work, we are not aware of it ever having been reported).

Similarly, we determined the elimination phase of the drug β = 69 ± 2 min with 14,000 measurement points, bringing down the standard error of our fit to only 3%, with much of this small deviation likely arising due to metabolic fluctuations in the animal over the course of the experiment (i.e., β fluctuates with kidney function and is thus not truly a constant). While the value of β we so derive is in agreement with previously reported values, the precision we achieve is an order of magnitude improved over SWV-based in vivo E-AB measurements and a far larger improvement over earlier measurements determined using blood draws and ex vivo analysis.

We have employed chronoamperometric interrogation of E-AB sensors to achieve the calibration-free, subsecond-resolved measurement of a specific small molecule directly in vivo. When coupled with the modularity of aptamers, the unprecedented temporal resolution of this approach suggests that it could improve our understanding of rapidly fluctuating physiological events, such as neurotransmitter release. The ability to perform the calibration-free measurement of specific molecules in the body in real-time could also improve our understanding of drug uptake, hormone release, and the movement of drugs and metabolites within body. And when coupled to feedback control systems, it could even enhance the efficiency and accuracy with which drugs are dosed.

E-AB sensors are not the only class of biosensors that relies on binding-induced changes in electron transfer kinetics for the detection of analytes. Other examples include sensors that measure changes in electron transfer from solution-phase redox reporters, electron transfer changes due to binding-induced displacement of ligands changes in the reporter’s reorganizational energy, or sterically induced changes in the efficiency with which a scaffold-attached redox reporter approaches an underlying electrode surface. From this perspective, we postulate that the ability of chronoamperometry to measure electron transfer kinetics directly may also prove of value in the interrogation of these other platforms.

**METHODS**

Sulfuric acid, tris(hydroxymethyl)aminomethane (Tris), sodium hydrogen phosphate, sodium chloride, ethylenediaminetetraacetic acid (EDTA), potassium chloride, and potassium dihydrogen phosphate were obtained from Fisher Scientific (Waltham, MA). 6-Mercapto-1-hexanol and tris(2-carboxyethyl)phosphine (TCEP) were obtained from Sigma-Aldrich (St. Louis, MO). Tobramycin sulfate (USP grade) was obtained from Gold BioTechnology, Inc. (St. Louis, MO). Tobramycin reference standards were obtained from The United States Pharmacopeial Convention (Rockville, MD). All reagents were used as received. A 1X stock solution of phosphate buffered saline (PBS) was prepared containing: 10 mM sodium hydrogen phosphate, 2.7 mM potassium chloride, 137 mM sodium chloride, and 1.76 mM potassium phosphate. A 1X stock solution of Tris-EDTA buffer was prepared containing: 10 mM Tris-HCl (pH 8.0) and 1 mM EDTA.

The aminoglycoside-binding aptamer sequence employed in this work was obtained from previous reports.2,3 We purchased the relevant methylene-blue-and-thiol-modified DNA sequence from Biosearch Technologies:

\[
\begin{align*}
\text{S}^- \cdot \text{HO}^-(\text{CH}_3)_2 & \cdot \text{S}^- \cdot (\text{CH}_3)_2 \cdot \text{PO}_4^+ \\
\text{GGGACCTGGTTAGTTAAGTGCTCC} & \cdot \text{CH}_2
\end{align*}
\]

\[
\begin{align*}
\text{CCH}_2\text{OH} & \cdot (\text{CH}_3)_2 \cdot \text{NH} \cdot \text{CO} \cdot (\text{CH}_3)_2 \cdot \text{Methylene Blue} \cdot 3' \\
\end{align*}
\]

The S’ end was modified with a thiol on a 6-carbon linker and the 3’ end was modified with a carboxy-modified methylene blue attached to the DNA via the formation of an amide bond to a primary amine on a 7-carbon linker. The modified DNA was purified through dual HPLC by the supplier and used as received. Upon receipt, each construct was dissolved to 100 μM in 1X Tris-EDTA buffer and frozen at −20 °C in individual 2 μL aliquots until use.

Catheters (22G) and 1 mL syringes were purchased from Becton Dickinson (Franklin Lakes, NJ). Insulated pure gold, platinum, and silver wires (75 μm diameter, 64 μm insulation thickness) were purchased from A-M Systems (SEQUIM, WA). Heat-shrink polytetrafluoroethylene insulation (PTFE, HS Sub-Lite-Wall, 0.02, 0.005, 0.003 ± 0.001 in, black-opaque, Lot #17747112–3) to insulate wires was purchased from ZEUS (Branchburg Township, CA). Custom-made, open-ended, mesh-covered three channel connector cables to fabricate in vivo probes were purchased from PlasticsOne (Roanoke, VA).

E-AB sensors were fabricated as follows: segments of pure gold (12 cm in length), platinum (11.5 cm), and silver (11 cm) wire were cut to make sensors. The insulators at both ends of these wires, about 2 cm, was removed using a surgical blade to allow electrical contact. These were then soldered each to one of the three ends of a connector cable using 60% tin/40% lead rosin-core solder (0.8 mm diameter) and then attached together by applying heat to shrinkable tubing around the body of the wires, except for a small window of about 5 mm at the edge of each wire. The wires were attached in a layered fashion, with the gold wire being insulated alone first, then both gold and platinum wires together, and finally all three wires together. The purpose of this three-layer-thick insulation was to give mechanical strength to the body of the malleable probe. To prevent electrical shorts between wires, different lengths were used for each wire as described above.

The sensor window (i.e., the region devoid of insulation) of in vivo probes was purchased from PlasticsOne (Roanoke, VA).

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For the SWV measurements, the sensors were interrogated from 0.0 V to −0.5 V versus Ag/AgCl, using 50 mV amplitude, potential step sizes of 1–5 mV, and frequencies varying from 10 to 500 Hz. The file
corresponding to each voltammogram were recorded in serial order using macros in CH Instruments software. All SWV measurements were performed using a three-electrode setup and with a CH Instruments electrochemical workstation (Austin, TX, Model 660D) using commercial Ag/AgCl reference electrodes filled with saturated KCl solution and platinum counter electrodes. For chronoamperometry, the potential of the sensors was serially stepped from −0.1 V to −0.3 V, each step for a duration of 100 ms. Current sampling was carried out every 10 μs for in vitro measurements, and every 100 μs for in vivo measurements (to reduce the number of experimental points and speed data acquisition). All chronoamperometric measurements were performed using the three-electrode E-AB sensor described above and recorded with a GAMRY Reference 600+ Potentiostat/Galvanostat/ZRA (Warminster, PA). Post-experiment data processing was carried out in Igor Pro v 7 software. Images were assembled using Adobe Creative Cloud Illustrator using EPS files exported from Igor Pro.

To study the behavior of chronoamperometric current decays, to measure aptamer affinity, and to correlate signal gain to target concentration, sensors were interrogated by either square wave voltammetry or chronoamperometry first in flowing PBS and next in flowing heparinized bovine blood with increasing concentrations of the corresponding target. These experiments were carried out in a closed flow system intended to mimic the type of blood transport found in veins. Blood flow was achieved using a magnetic gear pump (Benchtop Analog Drive, 0.261 mL/rev) from Cole Parmer (Vernon Hills, IL), setting flow rates to 1−10 mL/min as measured by a flow meter. To construct the binding curves (titrations of aptamer with target), stock solutions of tobramycin were prepared fresh prior to measurements in PBS buffer or blood, respectively. The sensor challenge to demonstrate calibration-free behavior was performed by challenging a fresh batch of aminoglycoside-binding E-AB sensors against stock solutions made from a tobramycin reference standard.

In vivo measurements were performed in male and female Sprague−Dawley rats (4−5 months old) purchased from Charles River Laboratories (Santa Cruz, CA), weighing between 300 and 500 g. All animals were pair-housed in a standard light cycle room (08:00 on, 20:00 off) and allowed ad libitum access to food and water. For in vivo measurements rats were anesthesia-induced with 5% isoflurane gas for the duration of the experiment. While anesthetized, an infusion line was inserted into the left jugular vein of the rats and E-AB sensors were inserted into the opposite, right vein. Briefly, the area above each jugular vein was shaved and cleaned with betadine and 70% ethanol. A small incision was made above the veins, and each vein was isolated. A small hole was cut into each vein with spring-loaded microscissors, and either a silastic catheter was inserted for infusions or the E-AB sensor was placed for measurements. Before the recording of measurements started, 30 units of heparin were infused into the rat. Then both the E-AB sensor and the infusion line were tied into place with silk suture. All in vivo measurements were performed using a three-electrode setup in which the reference electrode was a silver wire coated with a heparin were infused into the rat. Then both the E-AB sensor and the infusion line were tied into place with silk suture. In vivo measurements rats were anesthesia-induced with 5% isoflurane in a Plexiglas anesthesia chamber. The rats were then maintained on 2% isoflurane gas for the duration of the experiment. While anesthetized, an infusion line was inserted into the left jugular vein of the rats and E-AB sensors were inserted into the opposite, right vein. Briefly, the area above each jugular vein was shaved and cleaned with betadine and 70% ethanol. A small incision was made above the veins, and each vein was isolated. A small hole was cut into each vein with spring-loaded microscissors, and either a silastic catheter was inserted for infusions or the E-AB sensor was placed for measurements. Before the recording of measurements started, 30 units of heparin were infused into the rat. Then both the E-AB sensor and the infusion line were tied into place with silk suture. All in vivo measurements were performed using a three-electrode setup in which the reference electrode was a silver wire coated with a silver chloride film as described above, and the counter electrode was a platinum wire. A 20 min sensor baseline was established before performing the drug infusion. For drug infusions, a stock solution of tobramycin was prepared at 100 mM in sterilized PBS buffer. This solution was then employed to inject a dose of 30 mg/kg as calculated from the animal’s weight, injected at a rate of 0.25 mL/min. Recordings were taken for up to 3 h, with sampling rates of one point every 300 ms. The real-time plotting and analysis of chronoamperometric data were carried out with the help of Matlab scripts coded in-house.

To obtain pharmacokinetic profiles from our real-time data we performed nonlinear regression analysis using a two-compartment model to fit intravenous injections. The equation employed in the regressions was the following:

\[ C_P = e^{-t/\alpha} + Be^{-t/\beta} \]

where \( C_P \) is the measured plasma concentration, \( A \) and \( B \) are contributions of each pharmacokinetic compartment to the maximum concentration \( A + B = C_{\text{max}} \), \( \alpha \) is the first-order time constant of drug distribution and \( \beta \) the drug’s elimination time constant. During the regression analysis, all variables were floating such that the best fit was determined by minimizing the squared errors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssensors.7b00787.

Two additional figures: (1) schematic representation of stepped-potential program employed in the chronoamperometric interrogation of E-AB sensors, and (2) graph demonstrating that the lifetime of the first exponential phase seen in current decays of aminoglycoside-binding E-AB sensors is independent of concentration (PDF)

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Notes

The authors declare no competing financial interest.

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