Molecular processes in an electrochemical clozapine sensor

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Selectivity presents a crucial challenge in direct electrochemical sensing. One example is schizophrenia treatment monitoring of the redox-active antipsychotic clozapine. To accurately assess efficacy, differentiation from its metabolite norclozapine—similar in structure and redox potential—is critical. Here, the authors leverage biomaterials integration to study, and effect changes in, diffusion and electron transfer kinetics of these compounds. Specifically, the authors employ a catechol-modified chitosan film, which the authors have previously presented as the first electrochemical detection mechanism capable of quantifying clozapine directly in clinical serum. A key finding in our present work is differing dynamics between clozapine and norclozapine once the authors interface the electrodes with chitosan-based biomaterial films. These additional dimensions of redox information can thus enable selective sensing of largely analogous small molecules.

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I. INTRODUCTION

Clozapine is a highly effective antipsychotic medication for treating schizophrenia, providing symptom relief even to patients unresponsive to first- or other second-line medication.\textsuperscript{1,2} It is also one of the few antipsychotics with a well-established effective range of blood plasma levels, namely, 1–3 \textmu M.\textsuperscript{3} Below this range, the drug is unlikely to provide relief, while above, toxicity side effects such as seizures become much more likely. Therapeutic drug monitoring for accurate clozapine dosage control has been shown to improve outcomes and decrease the risk of toxicity.\textsuperscript{4}

Moreover, such monitoring addresses the widespread challenge of nonadherence to medication regimens, which is found to be one of the more frequent reasons for relapse, rehospitalization and higher treatment costs.\textsuperscript{5} Current procedures, however, require invasive blood draws and testing at centralized laboratories, implying a significant burden for patients as well as treatment teams in terms of time, effort, and cost.\textsuperscript{6}

Electrochemical detection of clozapine represents an appealing avenue toward point-of-care treatment monitoring to reduce this burden due to the relative ease of miniaturization of this transduction approach and the lack of specific biorecognition elements (antibodies, aptamers, etc.) for the small molecule.\textsuperscript{7} Initially reported by Kauffmann \textit{et al}., clozapine has a standard reduction potential of $E^\circ \sim +0.95$ V (versus standard hydrogen electrode), undergoing a partially reversible two-electron, one-proton reaction.\textsuperscript{8} A number of researchers have since presented approaches to leverage this

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redox activity to detect clozapine in clinical serum samples.\textsuperscript{9–12} We have ourselves presented the first instance of electrochemical detection of clozapine directly in human serum without the need for sample dilution or pretreatment.\textsuperscript{13} This relies on the chitosan–catechol redox cycling system. Therein, electrodeposited chitosan—a versatile biodegradable hydrogel-forming polysaccharide\textsuperscript{14}—serves as a matrix to immobilize electroactive catechol near the electrode via electrografting.\textsuperscript{15} Small redox species diffuse through the film for oxidation at the electrode; the catechol in close proximity enables subsequent reduction of the analyte, establishing a signal-amplifying redox cycle.

In the present study, we investigate the underlying electrochemical processes in our system—diffusion and electron transfer kinetics—and their interplay with the biomaterial films. These factors can help in understanding and potentially enhancing selectivity of the system—a major challenge in any direct electrochemical detection approach. In particular, we focus on clozapine as compared to its major metabolite norclozapine, which is structurally similar and known to have weak therapeutic activity as well, though possibly only in combination with clozapine itself, and is typically reported alongside clozapine levels in traditional clinical analysis.\textsuperscript{17} With these compounds, as well as the standard redox mediator 1,1'-ferrocenedimethanol (Fc) as a control, we study the limiting molecular processes for a range of timescales and how they are affected by chitosan and chitosan–catechol electrode modifications. The study expands and builds upon our previous work, which has focused on sensing figures of merit,\textsuperscript{13} stability and charge/discharge properties of the chitosan–catechol films,\textsuperscript{18} and sensor miniaturization.\textsuperscript{19} Here, our goal is to systematically study and gain a deeper understanding of the interplay between the chitosan matrix, catechol grafting, and clozapine detection. These insights will shed light onto how biomaterial films can confer differentiation abilities between clozapine and norclozapine that is critical for successful treatment monitoring. The strategy of employing diffusion and kinetics information to understand and enhance selectivity—a central challenge for direct redox-based detection of small molecules in complex matrices—is also more broadly applicable and can serve to advance translation of this facile transduction mechanism to the point of care.

II. EXPERIMENT

We employ three-electrode electrochemical cells controlled by a VSP-300 potentiostat (Bio-logic, Claix, France). The cells consist of a 1.5 ml volume sample reservoir with immersed platinum wire counter, Ag/AgCl (1 M KCl electrolyte) reference, and 2 mm gold disk working electrodes (all from CH Instruments, Austin, TX). The latter are polished before each use with alumina powder according to the manufacturer’s specifications for consistency. Potentials are denoted versus the aforementioned reference electrode from this point onward.

All chemicals were purchased from Sigma-Aldrich (St. Louis, MO), and solutions prepared with deionized (DI) water (R > 17 Ω cm). Test solutions are generally based on 0.1 M pH 7 phosphate buffer (PB), with 25 μM hexammineruthenium (Ru) added as a reducing mediator for experiments with the chitosan–catechol redox cycling system. We utilize every prepared electrode surface or film twice—first a baseline measurement (PB, plus Ru where needed), followed by one in solution also containing 250 μM of the analyte—clozapine, norclozapine, or Fc.

For electrode modification, we prepare a 1% w/w solution of chitosan by adding flakes to DI water under constant stirring overnight, with the pH gradually adjusted to 5.5 by titrating 1 M hydrochloric acid. The solution is then filtered successively through a mesh filter and a porous glass filter to remove any undissolved chitosan. Chitosan electrodeposition is achieved by applying a constant cathodic current of 6 A/m\textsuperscript{2} for 45 s, followed by immersing the electrode in PB. Catechol is prepared as a 5 mM solution in DI water. It is electrografted onto chitosan films at a constant anodic potential of +0.6 V over 180 s, followed by rinsing in DI water. The compound chitosan–catechol films are further electrochemically cleaned and initialized by cyclic voltammetry in a solution of 25 μM Ru and 25 μM Fc.

We employ cyclic voltammetry for our measurements, operated between −0.4 and +0.8 V (+0.6 V for Fc) at scan rates of ν = 0.001, 0.01, 0.04, 0.14, 0.5, 1.2, 2.5, 4.5, 7, and 10 V/s. For each scan rate and electrode surface, the background-subtracted current is calculated from the two measurements performed. We analyze the resulting data in terms of peak current $I_p$ and corresponding potential $E_p$ using ORIGINPRO (OriginLab, Northampton, MA). The software is also employed to calculate goodness of fit or correlation in terms of $R^2$ or root mean standard error (RMSE), as well as analysis of variance, reported in terms of $p$-values (significance level 0.05).

III. THEORY

A. Governing cyclic voltammetry equations

It is worth here to consider the governing equations for the two parameters $I_p$ and $E_p$ in traditional electrochemical systems, i.e., with bare, unmodified electrodes. The Randles–Sevck equation describes the peak current as\textsuperscript{20}

$$I_p = 0.4463 A C F n \sqrt{\frac{F n \nu D}{R T}}. \quad (1)$$

Therein, $A$ is the electrode surface area, $C$ the concentration of the analyte, $D$ its diffusion coefficient, $n$ the number of electrons per reaction, $T$ the solution temperature, $F$ the Faraday constant, and $R$ the universal gas constant. The corresponding potential for this (here, oxidative) current peak is given by the Nernst equation at equilibrium\textsuperscript{20}.
$$E_p = E^\circ + \frac{29.58 \text{ mV}}{n}. \quad (2)$$

To simplify notation, we define $E^\circ$ as the redox potential at neutral pH and versus a Ag/AgCl (1 M KCl electrolyte) reference electrode, as opposed to the standard reduction potential $E^\circ$ at pH 0 versus standard hydrogen electrode. Both equations assume an ideal, diffusion-limited, fully reversible redox couple, assumptions that do not apply to the quasireversible clozapine or norclozapine.8,16 However, the equations can still serve as first-order approximations, and deviations can give insight into underlying processes.

A further equation of interest pertaining to the current and potential described above is the thickness of the diffusion or depletion layer $\delta$, describing the distance over which most molecules have to diffuse to reach the electrode. Under the given assumptions and limitations, this can be calculated as:

$$\delta = 1.3133 \sqrt{\frac{RT}{FDn\nu}}. \quad (3)$$

### B. Diffusion coefficient estimation

While literature values for the diffusion coefficient $D$ are available for Fc,22 this is not the case for clozapine and norclozapine. Thus, we derive diffusion approximations from a modified version of the Stokes–Einstein equation23

$$D = \frac{k_BT}{6\pi\mu} \frac{4\pi}{3V_{vdW}}. \quad (4)$$

Therein, $k_B$ is the Boltzmann constant and $\mu$ the viscosity of the medium. The equation is typically expressed as a function of the molecular radius. However, as becomes obvious from the molecular structures shown in Fig. 1(a), both clozapine and norclozapine are distinctly nonspherical. Therefore, we instead rely on the van der Waals volume $V_{vdW}$—determined from molecular dynamics simulations24—to derive the expected diffusion coefficients given alongside the experimental results in Table I.

### C. Molecular charge

Although the structures of clozapine and norclozapine are highly analogous, one important difference between them is their effective molecular charge. This is illustrated in Fig. 1(b) as a function of the solution pH as predicted by molecular dynamics calculations.24 The absent methyl group on the norclozapine molecule increases the pKa value associated with the relevant nitrogen atom [starred in the structural representations of Fig. 1(a)] from 7.35 to 8.83. This results in a shift of the transition from +1 to neutral net charge toward a higher pH for norclozapine compared to clozapine, in turn yielding a pronounced difference in charge state at neutral or physiological pH. This factor is shown to have large relevance for the experiments in this study with regard to electrostatic interactions.

### IV. RESULTS AND DISCUSSION

As laid out in the introduction, we seek to understand the molecular and electrochemical processes at play for clozapine and norclozapine, and how they are affected by the presence of the chitosan-catechol-based redox cycling system. As a control to validate the general approach, we utilize the well-described fully reversible redox mediator Fc ($E^\circ = 0.23$ V), known to be suitable for redox cycling.15 We compare this with clozapine for three conditions: bare gold electrodes to establish a baseline, chitosan–catechol, and chitosan only to differentiate matrix effects from those of the full redox cycling system. Additionally, we compare clozapine to its metabolite norclozapine—structurally similar and

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**Table 1.** Expected and experimental diffusion behavior of the three analytes. The Stokes–Einstein calculations and experimental measurements are described in the text.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Literature</th>
<th>Theory [Eq. (4)]</th>
<th>Experiments [Eq. (1)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fc</td>
<td>7.5 (Ref. 22)</td>
<td>7.6</td>
<td>8.2 ± 0.2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>—</td>
<td>5.3</td>
<td>8.5 ± 0.5</td>
</tr>
<tr>
<td>Norclozapine</td>
<td>—</td>
<td>5.4</td>
<td>11 ± 1</td>
</tr>
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</table>
also known to be redox-active\textsuperscript{16}—under the same conditions to investigate selectivity. The approach and the dominant processes are illustrated schematically in Fig. 2.

In Fig. 3(a), we first show background-subtracted cyclic voltammetry data for all three analytes in our study at an exemplary scan rate of $\nu = 10$ mV/s from a bare gold electrode. These measurements highlight the ideal, reversible nature of clozapine and norclozapine signals. In Fig. 3(b), we further plot data for clozapine at a range of scan rates from $\nu = 1$ to 500 mV/s with a bare electrode, as well as for electrodes modified with chitosan or the redox cycling system at an exemplary scan rate of $\nu = 500$ mV/s. This graph illustrates the parameter space we explore with each analyte, and the in some cases drastic resulting changes that can be observed in peak potentials and currents. Considering the governing electrochemical equations in Sec. III, it becomes clear that such cyclic voltammetry data can yield insights into the underlying molecular processes. In the simplest model of an electrochemical reaction, as shown in Fig. 2, these are twofold: diffusion of the species to the electrode surface, inferred from the peak current; and the electron transfer at the electrode, where the kinetics determine the peak potential. Accordingly, our Results and Discussion are divided into two subsections discussing these aspects of clozapine’s electrochemical behavior and its interactions with the biomaterial interfaces of the redox cycling system.

### A. Diffusion

In the Randles–Sevcik Eq. (1), the measured peak current $I_p$ is related to the diffusion coefficient $D$. The latter can thus be extracted from cyclic voltammetry measurements, more accurately so when conducted at various scan rates $\nu$ (an experimental parameter in the equation). While the relation is derived for reversible redox couples, it can also serve as a first-order approximation for quasi-reversible ones. We determine the experimental diffusion coefficients listed in Table I accordingly by conducting cyclic voltammetry with scan rates from $\nu = 1$ mV/s to 10 V/s on bare electrodes, and fitting the resulting peak currents $I_p$ with the Randles–Sevcik Eq. (1) ($R^2 > 0.99$ for all analytes). The obtained values are presented alongside the expected ones from literature (where available) and theoretical calculations per Eq. (4).

For the control mediator Fc, the experimental result agrees reasonably well with the expected values, considering that the exact value can be sensitive to the buffer utilized. For both clozapine and norclozapine, however, we observe a much more significant twofold difference between theory and experiments. Since the diffusion calculation per Eq. (4) is quite accurate for Fc with respect to the literature value, the approximations contained therein are insufficient to explain such a large discrepancy. One aspect is likely to be the nonideal redox nature of both clozapine and norclozapine, which renders the Randles–Sevcik equation itself only an approximation, even though this would generally be expected to lead to an underestimation of $D$.\textsuperscript{20} Thus, we theorize that electrophoretic effects may also play a role, where negative charge on the electrode at low potentials during the voltammetry cycle may attract the (at neutral pH) predominately positively charged clozapine and norclozapine.\textsuperscript{24} Such electrophoretic effects have also been observed in previous studies.\textsuperscript{18}

Next, we consider the presence of a chitosan film on the electrode surface. The film is expected to restrict diffusion of all species due to its network of pores the molecules need to traverse toward the electrode. For this case, calculating the effective diffusion coefficient $D$ from the Randles–Sevcik Eq. (1) at each scan rate becomes insightful. Figure 4(a) reveals two distinct regimes for all species, indicated with line segments for visual guidance. At low scan rates, coefficients approach those observed with a bare electrode (shaded gray area). At high scan rates, effective diffusion coefficients drop—1.9-fold for Fc, a more drastic 17 × for clozapine and 31 × for norclozapine—before saturating. This behavior is explained by the limited (tens of micrometers) thickness of the chitosan films. At low scan rates, the depletion layer $\delta$
[cf. Eq. (3)] will extend significantly beyond the thin film (>100 μm), therefore leading to dominance of bulk diffusion in solution as with a bare electrode. At high scan rates, the depletion layer will be fully contained within the chitosan film, which restricts diffusion compared to free solution as expected.

The smaller Fc is significantly less restricted compared to both other species. However, the orders-of-magnitude difference, especially in light of the reversed trend on bare electrodes (i.e., clozapine and norclozapine both showing slightly higher experimental $D$ than Fc), also points to clozapine-specific interactions with the chitosan. A likely candidate is electrostatic interactions of the largely positively charged clozapine with the similarly positively charged chitosan matrix. One aspect not necessarily expected $ab initio$ is the consistently twofold lower effective diffusion coefficient of norclozapine compared to clozapine—both molecules are practically the same size and were observed to have largely similar diffusion behavior on bare electrodes (cf. calculated diffusion coefficients in Table I). The trend is in line, however, with the charge repulsion hypothesis, since norclozapine is even more positively charged (+1.0) compared to clozapine (+0.7) at neutral pH as seen in Fig. 1(b), and would thus be more strongly restricted within the chitosan matrix. These chitosan-based differentiation capabilities are remarkable, considering the identical electrochemical characteristics of both species with bare electrodes.

With the chitosan–catechol system, diffusion determination is not as straightforward. Due to redox cycling, underlying assumptions of the Randles–Sevcik Eq. (1) break down,
with multiple diffusion lengths and rates (in bulk solution, within the film, and between the electrode and the catechol) and redox reactions (at the electrode and with the catechol) becoming relevant. Thus, apparent diffusion coefficients calculated based on the equation will mostly reflect signal amplification in the system. Indeed, Fig. 4(b) shows all species with almost consistently higher apparent $D$ compared to their chitosan-only values (indicated by a line for clozapine), indicating the expected signal amplification. While the signal for Fc is amplified two times above its bare electrode values (shaded gray regime) for all scan rates, clozapine and norclozapine show this behavior only at the lowest scan rates investigated. Critically, clozapine amplification by a factor of up to 5 (compared to bare electrode) is shown to be higher than for norclozapine (threelfold), further emphasizing emergent species differentiation due to electrode biomaterial modifications. The reasons for this can in part be attributed to the differing diffusion behavior observed in chitosan, as well as to the differing electron transfer kinetics considered in Sec. IV B. At high scan rates, the observed $D$ for clozapine again saturates at the same value as when there is only chitosan on the electrode. In this regime, the electron transfer kinetics are too slow to allow for redox cycling, thus again reflecting true diffusion inside the film, which is apparently not significantly altered by the presence of catechol in the film.

**B. Electron transfer**

In the Nernst Eq. (2), the oxidative peak potential $E_p$ is given for ideal redox species at equilibrium as 29.6 mV (or 14.8 mV, for an $n=2$ electron reaction) above the redox potential $E^{\circ}$. Slow (or not fully reversible) redox species will show an increase in peak separation particularly at high scan rates, when the electron transfer rate (rather than diffusion) becomes a limiting factor. The redox kinetics of a given analyte can thus be inferred by tracking $E_p$ relative to $E^{\circ}$. We note that a more traditional approach would consider the separation of the oxidation and reduction peaks; however, the reduction peak is all but eliminated in the redox cycling system, where the catechol serves as an electron donor. The peak is furthermore difficult to determine for the only quasireversible clozapine and norclozapine at high scan rates or in the presence of chitosan, both of which adversely affect peak definition. Thus, we instead determine an experimental redox potential $E^{\circ}$ from the bare electrode experiments, where both peaks can be reliably quantified. With this as a basis, we calculate the ideally expected behavior per the at-equilibrium Nernst equation Eq. (2) for all species in Table II. Fc, with its fully reversible single-electron reaction, should match this prediction closely. Both clozapine and norclozapine feature two-electron redox reactions, and are expected to deviate strongly from the tabulated behavior due to slow and quasireversible kinetics. The experimental values for $E^{\circ}$ also highlight that the two species are practically indistinguishable ($p > 0.05$) based on redox potential alone.

Fc indeed closely follows theoretical expectations on a bare electrode as seen in Fig. 5. Its oxidative peak potential deviates from the expected $E_p = 0.26$ V (dotted line) only at very high scan rates $v > 1$ V/s, highlighting the fast electron transfer kinetics. Both clozapine and norclozapine, conversely, are already noticeably above the expected $E_p \sim 0.385$ V even at a scan rate of 40 mV/s. The peak potential increases drastically with further increasing scan rates, indicating significantly slower reaction kinetics. Interestingly, this trend is highly similar for both species, with a correlation of $R^2 > 0.99$. Combined with the two species’ comparable diffusion coefficients this practically prevents differential determination of the two species with a bare gold electrode.

In the presence of chitosan, as shown in Fig. 6(a), only minimal changes are observed for Fc and clozapine versus their respective bare electrode results. For clozapine, this can be quantified with a correlation of $R^2 > 0.99$, and for Fc with a root mean standard error of RMSE = 3% (since it yields a flat line in both cases, correlation cannot be applied). More interesting is the case of norclozapine, which shows a drastic change toward a nearly constant ($p > 0.05$) oxidation peak potential $0.09 \pm 0.02$ V above its $E^{\circ}$. Similar to its effect on diffusion, chitosan thus appears to confine differentiation capabilities between the two highly similar species to the system. A simple two-process view of the Table II. Experimental redox potential $E^{\circ}$ and theory-derived ideal peak potential $E_p$ of the three analytes. The underlying calculations and measurements are described in the text.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>$E^{\circ}$ (experimental)</th>
<th>$E_p - E^{\circ}$ (ideal)</th>
<th>$E_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fc</td>
<td>0.232 ± 0.003 V</td>
<td>29.6 mV</td>
<td>0.261 V</td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.366 ± 0.015 V</td>
<td>14.8 mV</td>
<td>0.381 V</td>
</tr>
<tr>
<td>Norclozapine</td>
<td>0.376 ± 0.020 V</td>
<td>14.8 mV</td>
<td>0.390 V</td>
</tr>
</tbody>
</table>

Fig. 5. Theory-derived (left; cf. Table II) and observed oxidative peak potentials as a function of cyclic voltammetry scan rate for clozapine (blue squares), norclozapine (green circles), and Fc (red crosses) with bare electrodes.
electrochemical reaction (diffusion to the electrode, followed by electron transfer) is insufficient to explain such behavior, as the presence of chitosan on the surface should not change the inherent reaction kinetics between norclozapine and gold, and does not do so for the case of clozapine. A three-process picture, however, is more realistic and can offer additional insight: between diffusing to the electrode and reacting with it, the redox species needs to adsorb to the electrode surface, and subsequently desorb again. We hypothesize that the reaction constant for this adsorption process changes for the case of norclozapine, and actually begins dominating the overall kinetics. We posit that the underlying factor in play here is the strong electrostatic repulsion between norclozapine and chitosan, which would hinder adsorption more strongly than for clozapine, where electron transfer remains the dominant factor.

For the chitosan–catechol redox cycling system, the complexity of the electron transfer system increases to not only include the oxidation at the electrode, but also the reduction facilitated by catechol (separated by a short diffusion path from the electrode) with its separate reaction rate. The electrochemical results in Fig. 6(b) reflect this in a slowdown of apparent electron transfer kinetics across the board, wherein the diffusion between the electrode and the catechol likely becomes a limiting factor with Fc and clozapine (more so for the latter). Norclozapine still exhibits generally constant (p > 0.05) oxidative peak potential (albeit with high variability), now at an even higher $E_p = 0.61 \pm 0.05$ V, likely also reflecting the aforementioned added reaction steps occurring in the system. Importantly, however, this breaks the similarity between clozapine and norclozapine even further than chitosan alone. Indeed, at scan rates $\nu$ below 100 mV/s, the high inherent similarity between both species in diffusion and reaction kinetics is broken for both factors. Thus, the chitosan–catechol film can enable differentiation of clozapine and norclozapine via electrochemical methods, a feat not previously demonstrated using electrochemical detection. This capability applies especially when investigating a range of scan rates, where both species exhibit quite distinctive changes in behavior.

V. SUMMARY AND CONCLUSIONS

In conclusion, our results demonstrate the intricate interplay between biomaterials, bioanalytes, and electrochemistry. With bare gold, both clozapine and norclozapine exhibit practically indistinguishable, slow electron transfer kinetics, in contrast to the Nernstian redox mediator Fc. For diffusion, the species also prove similar, though we observe significant deviations from theory for clozapine and norclozapine that we attribute to electrostatic effects with these positively charged molecules. In the presence of both chitosan and the chitosan–catechol redox cycling system, however, we find that both diffusion and electron transfer behavior are impacted, and importantly that the similarity between clozapine and norclozapine is broken. For diffusion, the effective coefficients $D$ reveal two regimes in chitosan: dominance of bulk solution at the lowest scan rates, and diffusion inside the film becoming limiting at higher scan rates. The sharp difference between Fc and the other larger two can partially be attributed to size-restriction phenomena, but the consistently lower diffusion coefficient for norclozapine points to electrostatic interactions with the positively charged chitosan matrix. This is also apparent in the electron transfer data, where Fc and clozapine remain unaffected, but the behavior of the more positively charged norclozapine possibly points instead toward a surface adsorption-limited process. These trends of broken similarity between clozapine and norclozapine based on electrostatic interactions are reinforced with the redox cycling system. Therein, signal amplification translates into apparent increases in diffusion coefficients for all species, though least so for norclozapine. Only at high scan rates does the apparent $D$ decrease toward the chitosan-
only value as true diffusion asserts dominance. The apparent kinetics are slowed down by the multiple reduction/oxidation reactions enabled by the catechol for all three analytes, increasing the difference in peak potentials between clozapine and norclozapine in the process.

Overall, our work thus reveals intriguing distinguishing characteristics of clozapine from both the largely analogous norclozapine as well as the model Fc. This enables the critical electrochemical differentiation needed between clozapine and its metabolite norclozapine that is required toward eventual point-of-care treatment monitoring. More broadly, our approach can serve as a blueprint to access additional dimensions of information for enhanced selectivity in direct electrochemical sensing through diffusion and kinetics. We envision this being implemented by combining voltammetry data from an array of sensors both bare and with biomaterial modifications, sampled concurrently at a few different scan rates. This variation on the tongue-on-a-chip concept—where an array of cross-reactive yet independent sensors is employed for selective detection—reduces the need for often time-intensive development of new and different electrode coatings by more fully utilizing the information accessible through and contained in electrochemical measurements.

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