Mathematical Models for Sensing Devices Constructed out of Artificial Cell Membranes

Abstract

This paper presents a review of ion channel based biosensors with a focus on the mathematical modeling of the state-of-the-art ion channel switch (ICS) biosensor and the novel cation specific (CS) sensor. The characteristics of the analyte present in the electrolyte, the ionic transport of chemical species, and the bioelectronic interface present in the ICS biosensor and CS sensor are modeled using ordinary and partial differential equations. The methodologies presented are important for modeling similar bioelectronic devices. Biosensors have applications in the fields of medicine, engineering, and biology. The recent emergence of biomimetically engineered nanomachine devices capable of measuring femto-molar concentrations of chemical species and the detection of channelopathies (ion channel disorders) makes them an attractive tool due to their high sensitivity and rapid detection rates. Beyond the continuum models used for the ICS and CS sensors, we present methods by which first-principle approaches such as molecular dynamics combined with stochastic methodologies can be used to obtain macro-level parameters such as conductance and chemical reaction rates.

Keywords

Ion Channel Biosensors • Molecular Dynamics • Stochastic Dynamics • Poisson-Nernst-Planck • Disease Diagnosis and Medicine

1. Introduction

Biological ion channels are protein-based structures that provide pathways for ion transport through cell membranes. These ion channels are present in all biological cells and are responsible for processes such as the propagation of muscle contraction and nerve impulses. Clearly, ion channels play a key role in the electrical signaling of biological organisms. As a result of combined efforts of experimental and computational biophysicists, enormous strides have been made in our understanding of the atomic structure of biological ion channels. At the forefront of nano-engineering, we are witnessing the development of biomimetic sensors that use these remarkable biological systems to detect femto-molar concentrations of molecules and perform disease diagnosis [32, 38].

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Motivated by these results this paper reviews state-of-the-art modeling techniques for ion channel based biosensors and discusses how atomic level simulations utilizing molecular dynamics can be used to estimate the operating characteristics of these biosensors. Two biosensor case studies are considered: the first is the Ion Channel Switch (ICS) biosensor, and the second is the Cation Selective (CS) sensor [11]. These provide interesting examples of engineering at the nano-scale. Both sensors are composed of a synthetic bilayer lipid membrane containing gramicidin A complexes, a common molecule produced by soil bacteria [11]. The ICS biosensor utilizes the characteristics of the gramicidin A (gA) channel, and the CS sensor utilizes the bis-gramicidin A (bis-gA) channel.

Cornell et al. developed the ICS biosensor which is capable of detecting femto-molar concentrations of specific target molecules in complex environments [11]. The detectable target species include proteins, hormones, polypeptides, microorganisms, oligonucleotides, DNA segments, and polymers [32]. The ICS is composed of a synthetic membrane formed from lipids packed with tethered and mobile gA monomers. The stationary gA monomer is tethered to a gold electrode, and the mobile gA monomer is tethered to a biological receptor such as a nucleotide or antibody. These receptors are designed to latch to specific target species. The mechanical setup of the ICS biosensor can be viewed in Fig. 1. When target molecules attach to a receptor, the ion channel (or dimer) breaks and the cation flux drops; this event causes a decrease in the overall conductivity of the biosensor that is detectable by measuring the electrical impedance of the biosensor.

![Fig 1. Diagram of the ion channel switch biosensor. “Flow” indicates the direction of movement of the injected analyte solution. The “Analyte Chamber” contains the electrolyte solution to be tested for the specific analyte of interest. The biomimetic surface is positioned at the bottom of the analyte chamber, and a section of the biomimetic surface is presented illustrating the lipid membrane, the tethered and mobile gramicidin (gA) monomers, the tethered gold electrode, and the tethered antibodies (ab). The dimensions of the lipid membrane $d_{mem} = 4$ nm, the ionic reservoir $d_{res} = 8 - 11$ nm, and the gold electrode $d_{gld} = 200$ nm, are included in reference [74].](image)

Experimental analysis shows that the ICS biosensor can accurately detect the influenza A virus within 10 min; this is in contrast to the lengthy steps involved with the processing and incubation phases of the ELISA assay test [30]. This rapid and accurate detection ability enables physicians to quickly take necessary actions. Despite the complexity of the ICS biosensor, Krishnamurthy et al. have derived mathematical models that accurately predict the response of the biosensor over a wide range of analyte concentrations [31, 54]. The mathematical model that captures the behavior of the ICS biosensor is given by a reaction–diffusion partial differential equation with Neumann and Dirichlet boundary conditions coupled with a set of nonlinear ordinary differential equations. The reaction–diffusion equations are used to compute the transport behavior of the analyte species in the analyte chamber, and the nonlinear ordinary differential equations are used to compute the chemical dynamics present at the biomimetic surface.

Motivated with these results, a state-of-the-art Cation Selective (CS) sensor is currently under development for disease diagnosis by analyzing the release of cations from cells excited by an external potential. This class of sensors is constructed using tethered bis–gramicidin A channels (i.e. a static gramicidin dimer) embedded in a synthetic membrane. The bis–gramicidin A channels only allow the flow of cations from the cell suspension into the ionic reservoir between the the gold electrode and synthetic membrane, as illustrated in Fig. 2. Note that the CS sensor is used for the measurement of the change in cation concentration using fixed gramicidin dimers whereas the ICS biosensor is designed for the detection of specific analyte species.

By measuring the current, $I(t)$, resulting from changes in cation ionic concentration in the ionic reservoir, it is possible to perform disease diagnosis of the cells. A key component to modeling the response of the biosensor is how cations move in the cell suspension. The electro-diffusion of ions in the cell suspension can
be accurately modeled using the Poisson-Nernst-Planck (PNP) system of equations in which the mean-field approximation holds. The PNP theory consists of a set, one for each ionic species, of nonlinear parabolic partial differential equations coupled with an elliptical partial differential equation. The PNP theory leads to a popular method for modeling the movement of ions in solution and numerous computational models exist for its solution; however, due to many numerical obstacles, including discontinuous coefficients, singular charges, geometric singularities, and nonlinear couplings, the numerical solutions are non-trivial \[24, 33, 41–43, 50, 53, 61, 72, 87\]. The advantage of the PNP formulation is that it connects the electric fields of the ions in a self-consistent way and accurately predicts the spatiotemporal dynamics of the ions in the electrolyte \[61\]. Another work that attempts to use the PNP equations for the detection of electrical signals from cells was presented in \[61\] where a number of assumptions were made including steady-state, cylindrical symmetry, and charge neutrality.

Fundamental to both the ICS biosensor and the CS sensor is the ion conductance through the gA dimers. Although these values can be obtained experimentally, advances in mathematical modeling allow estimation of the conductance from a first principles approach using sophisticated models that combine molecular dynamics and stochastic dynamics \[17\]. The dissociation/association characteristics of the gA dimers, vital for the operation of the ICS biosensor to determine the chemical reaction rates, can also be analyzed from a first principles approach using molecular dynamics and umbrella sampling \[82\].

The paper is broken into four main sections: background of the ion channel based biosensors is presented in Sec. 2, with the mathematical modeling of the ICS biosensor given in Sec. 2.3 and Sec. 2.4. In the case of large analyte flow, low binding site densities, and micro-molar concentrations of analyte, singular perturbation theory is applied to provide a simplification of the nonlinear differential equations used to describe the chemical kinetics, as shown in Sec. 2.5. The experimental verification of the models and performance of the ICS biosensor is given in Sec. 2.6 and Sec. 2.7. In Sec. 3 we showcase the mathematical modeling techniques of the novel CS sensor using the continuum PNP theory for the analysis of ion transport in the cell suspension. The simulation of the current $I(t)$ for the CS sensor is presented in Sec. 3.3 using the PNP theory. A standing assumption when using PNP is that the electrical displacement flux (caused by electrode-electrolyte interface, and lipid membranes) has negligible effect on the computed current $I(t)$. If this assumption does not hold, Sec. 3.4 presents a grid-based differential time-domain numerical modeling method based on the PNP theory with an additional displacement flux that can be used to account for these effects. The modeling parameters for the continuum theories can be obtained experimentally, or due to recent advances, from a first principles approach. Sec. 4 discusses the computation of macro-level parameters of conductance and chemical reaction rates from first principles analysis using stochastic methods coupled with molecular dynamics.

2. Ion Channel based Biosensors

This section presents the physical structure as well as the detailed mathematical models for the sensing dynamics of an innovative Ion Channel Switch (ICS) biosensor.
2.1. Overview of the Development of Ion Channel Biosensors

The first appearance of a synthetic molecular membrane as the basis for a chemical sensor was proposed by Toro-Goyco et al. in 1966 [81]. In both, previous and current practices, the primary method for analyte detection is to measure the impedance of the biosensor, this impedance being dependent upon the amount of analyte present. For example, the measured impedance of an ion channel based sensor changes as a result of analyte–protein interactions at the surface of a synthetic bilayer lipid membrane.

A major complication with the biosensor presented in [81], however, is that the membrane is very sensitive to mechanical damage [74]. To remedy this, a series of biosensors was considered as a solution to this problem, but the possible applicability of the biosensors were limited by the stability of the receptor–membrane complex [36, 37, 74, 84, 85]. The first example of a functionally active biomimetic surface utilizing the cytochrome C incorporated into a tethered membrane was presented in [58]. Since a central theme in the construction of ion channel biosensors is the stabilization of the bilayer lipid membrane (BLM) [30], the current trend for stabilization is focused on chemically attaching a layer of hydrocarbon to either a silicon [20], hydrogel [45], polymer [57] or metal surface [77]. A second layer of mobile lipids is then fused to the tethered monolayer to form the tethered BLM [30]. Related work on BLM stabilization techniques can be found in [68] and [63].

The basic principle of the ion channel biosensor is to modulate the flow of ions when an analyte is present [74]. Anti-channel antibodies that disrupt the ion transport to molecular plugs that block the channel entrance are methods used to regulate the flow of ions [8, 40]. As an example, Ompf porin channels from *Escherichia coli* have been incorporated into a tethered BLM and their conductance modulated using the ion channel blocker colicin [80].

Furthermore, beyond the biochemical issues involved in engineering these structures, sophisticated electronics connected to electrodes are required for the detection of the analyte species. An overview of the practical difficulties in interfacing ion channels with microelectronic devices is provided in [59]. Several institutions have developed and are currently developing biosensors based on synthetic lipid monolayers and bilayers [30]. OhmX Corporation is currently researching reagentless biosensor systems for point-of-care disease diagnosis using self-assembled monolayers tethered to a gold surface [1, 6, 16]. Oxford Nanopore Technology, founded by Hagan Balely, has made substantial contributions to the advancement of ion channel biosensors in both stochastic signal processing and nanopore technologies [23, 35, 60, 62, 78]. A review of the current status and challenges of nanopore sensors can be found in [38].

Until recently, the aforementioned biosensors have had a very limited range of application and have required re-engineering for each new analyte. New development has provided an innovative method using gramicidin channels tethered to a gold electrode as a biosensor device, denoted as the ICS biosensor and shown in Fig. 1 [11]. The ICS biosensor provides a mechanism that can be adapted to many different classes of target species [30]. As it provides an important example of an ion channel based biosensor. The novel ICS biosensor employs an alkane disulphide bond to stabilize the bilayer lipid membrane tethered to the gold electrode [30]. This biosensor has undergone a number of remarkable breakthroughs including: the reduction of the electrode size from 1 mm to 20 µm, the use of suspension flow to enhance sensitivity, and the use of covalent linkage of fragment antigen binding to the gramicidin channels [10–12, 74, 83].

2.2. Physical Structure of Ion Channel Switch Biosensor

This subsection presents the physical structure and operation of the ICS biosensor shown in Fig. 1; for a detailed presentation, the reader is referred to [30]. Recall that the ICS biosensor can detect a host of analytes including proteins, hormones, polypeptides, microorganisms, oligonucleotides, DNA segments, and polymers. The detection process involves measurement of the impedance of the biosensor–as the concentration of the analyte increases, the conductance of the biosensor decreases. The physical description of why the impedance changes and how the measurement is performed is given below.

Specifically, the ICS biosensor contains an inner lipid monolayer membrane tethered to a gold electrode via a disulphide group and an outer lipid monolayer which forms the synthetic bilipid membrane for the biosensor. Gramicidin A (gA) monomers are tethered to the inner lipid monolayer, and mobile gA monomers are present in the outer lipid monolayer. The mobile gA monomers are tethered to receptor (antibody)
molecules which are attracted to specific analyte molecules. The outer lipid monolayer also contains antibody receptors that are fixed to the outer lipid membrane separated from the tethered gA monomers. If the tethered and mobile gA monomers are aligned they form a dimer (i.e. open gramicidin A channels) allowing for the flow of ions from the electrolyte solution to the ionic reservoir between the inner lipid membrane and gold electrode. If an analyte is present in the electrolyte solution, the antibody receptors cause the mobile gA monomers to move away from the tethered gA monomer allowing the antibody to capture the analyte from the electrolyte solution. This event breaks the dimer and prevents ion flux through the membrane. The process is illustrated in Fig. 3.

![Fig 3. Operation of the ion channel switch (ICS) biosensor. When a particular analyte binds to the tethered antibody receptor, the captured analyte attracts the antibody tethered to the mobile gA monomer. This causes the dimer to break, and prevents ion flow between the electrolyte solution and ionic reservoir. The dissociation of the gA monomers results in a reduction in the conductance of the ICS biosensor which is detectable from external electronic equipment attached to the electrode.](image)

Measurement equipment is connected to the gold electrode tethered to the membrane and a silver-coated return electrode, present in the electrolyte solution above the biomimetic surface [30]. In the presence of an applied potential, if the ion channels are open, ions flow between the ionic reservoir and the electrolyte solution above the membrane [11]. As the analyte concentration increases in the electrolyte solution, the concentration of gA channel decreases. This event causes the conductance of the biosensor to decrease. The change in conductance can be measured by an external circuit connected to the gold and silver-coated electrodes. Measuring the conductance of the biosensor provides a method for detecting whether an analyte is present in the electrolyte solution and in what concentration.

The ICS biosensor is a remarkable example of bioengineering. The proposition of the ICS being a fully functional nanomachine is justified by analysis of the dimensions of the biomimetic system, as shown in Fig. 1. Consider that the gramicidin A channel has a conducting pore with a diameter of 0.4 nm, and length of 2.4 nm. The biomimetic surface has an area of 1 μm², and each individual gramicidin channel diffuses randomly over this area. The tethered bilipid layer is 4nm thick and is held 8-11 nm away from the gold electrode by hydrophilic spacers allowing the ions to diffuse into this reservoir. This permits a flux of approximately 10⁶ ions per second for each ion channel.

2.3. Electrical Dynamics of the Ion Channel Switch Biosensor

The electrical dynamics of the ICS biosensor can be modeled using an equivalent circuit representation. Here, the open-state and closed-state of the ion channels contained in the ICS biosensor can be represented by the circuits shown in Fig. 4 [31]:

In Fig. 4, $R_{gram}$ represents the resistance of the gA channel, $C_{mem}$ is the membrane capacitance, and $C_{diff}$ is the diffuse layer capacitance between the electrolyte solution below the membrane and above the Helmholtz layer located above the gold electrode. The Helmholtz layer capacitance is modeled by $C_{Hel}$. The entire biosensor can be modeled using millions of these circuits in parallel from which we obtain the equivalent circuit presented in Fig. 8.

The variable resistance $1/G(t)$ in Fig. 5 is dependent on the concentration of gA dimers present in the biosensor. As the number of gA dimers decreases, the resistance $1/G(t)$ increases. This results in the overall
resistance of the biosensor increasing as the concentration of gA dimers decreases. $R_2$ models the resistance of the electrolyte and the dimensions of the return path electrode. $C_1$ is the membrane capacitance and $C_2$ is the interfacial capacitance of the gold electrode. Note that $C_2$ provides the connection from the ionic solution to the electrical domain. One face of the capacitor $C_2$ is charged by the presence of ions and the other is charged with electrons producing the current $I(t)$ in the external circuit. The measured current $I$ is the average effect of the association and dissociation of gA channels and is approximately continuously valued. The values of $R_2$, $C_1$, $C_2$ are known and $G(t)$ is computed by considering the analyte flow dynamics and chemical reactions at the gold electrode.

### 2.4. Chemical Dynamics of the Ion Switch Biosensor

To derive the conductance $G(t)$, introduced in Sec. 2.3, requires us to account for the advection and diffusion of the analyte molecules in solution while taking into account the chemical reactions taking place at the electrode surface. This can be done using an advection-diffusion partial differential equation (PDE) coupled to a linear system of ordinary differential equations describing the chemical reactions.

The advection-diffusion PDE for the analyte solution concentration, denoted by $A$, is given by:

$$\frac{\partial A}{\partial t} = \gamma \left( \frac{\partial^2 A}{\partial x_1^2} + \frac{\partial^2 A}{\partial x_2^2} \right) - v(x_2) \frac{\partial A}{\partial x_1}, \quad (1)$$
where $x_1$ is the direction of flow of the solution, $x_2$ is perpendicular to the direction of flow, $\gamma$ is the diffusivity of the analyte, and $v$ describes the fully developed flow profile in the flow chamber. The Neumann and Dirichlet boundary conditions for Eq. (1) are given by:

$$\begin{align*}
A(x_1 = 0, x_2, t > 0) &= A^*
\frac{\partial A}{\partial x_1}(x_1 = L, x_2, t > 0) &= 0
\frac{\partial A}{\partial x_1}(x_1, x_2 = h, t > 0) &= 0
\frac{\partial A}{\partial x_2}(x_1, x_2 = 0, t > 0) &= \psi(t).
\end{align*}$$

Fig 6. Neumann and Dirichlet boundary conditions for the advection-diffusion equation (1) used to model the ICS biosensor.

where $A^*$ denotes the concentration of analyte entering the flow chamber, $L$ is the length of the flow chamber, $h$ is the height of the flow chamber, and $\psi(t)$ gives the rate by which the analyte molecules are captured by immobilized antibody species at the electrode surface and is determined from the chemical reaction equations.

The chemical reactions taking place at the ICS biosensor involve analyte molecules binding to the tethered antibody sites followed by a cross-linking of the mobile gA monomers to the captured analytes. The primary species involved in this process include the analytes $a$, binding sites $b$, mobile gA monomers $c$, tethered gA monomers $s$, and the dimers $d$, with respective concentrations $\{A, B, C, S, D\}$. Other chemical complexes present include $w, x, y, z$ with concentrations $\{W, X, Y, Z\}$. The chemical reactions that relate these chemical species are described by the following set of reactions [31]:

$$\begin{align*}
a + b \xrightarrow{f_1} w & \quad a + c \xrightarrow{f_2} x & \quad w + c \xrightarrow{f_3} y & \quad x + b \xrightarrow{f_4} y \\
c + s \xrightarrow{f_5} d & \quad a + d \xrightarrow{f_6} z & \quad x + s \xrightarrow{f_7} z.
\end{align*}$$

(3)

In (3), $r_i$ and $f_i$, for $i \in \{1, 2, 3, 4, 5, 6, 7\}$, denote the reverse and forward reaction rates for the chemical species $\{a, b, c, d, s, w, x, y, z\}$. An explanation of the reactions that take place can be found in [31]. From (3), a set of nonlinear differential equations is constructed using the total reaction rates:

$$\begin{align*}
R_1 &= f_1 AB - r_1 W & R_5 &= f_4 CS - r_5 D \\
R_2 &= f_2 AC - r_2 X & R_6 &= f_6 AD - r_6 Z \\
R_3 &= f_3 WC - r_3 Y & R_7 &= f_7 XS - r_7 Z \\
R_4 &= f_4 XB - r_4 Y.
\end{align*}$$

(4)

Using (4), the time-evolution of the chemical species can be determined from the nonlinear ordinary differential equations given by:

$$\frac{du}{dt} = Mr(u(t)).$$

(5)

where the vector $u(t) = [B, C, D, S, W, X, Y, Z]^T$ in (5) denotes the concentration of the chemical species, and $r(u) = [R_1, R_2, \ldots, R_7]^T$ denotes the rate of reaction of the $i^{th}$ species in (3). The parameter $M$ in (5) is the stoichiometry matrix relating $u$ and $r(u)$. Note that (5) and (3) do not model the dynamics of the analyte concentration $A$ described by the advection-diffusion equation (1).
Recall that $\psi(t)$ is the rate at which the analyte molecules are fixed by immobilized species at the electrode surface, which can be found using (5) and (3) and is given by:

$$\psi(t) = -A(t_1B + f_2C + f_6D) + r_1W + r_2x + r_6Z.$$  \hfill (6)

The conductance $G(t)$ is related to the gA channel concentration $D(t)$ by a constant, (i.e. $G(t) \propto D(t)$). Therefore, the time evolution of $G(t)$ is computed from the solution of equations (1), (2), and (6) given the initial concentration of the chemical species, reaction rates, diffusivity constant, and flow velocity.

2.5. Ion Channel Switch Dimer Concentration Dynamics in the Reaction-rate-limited Regime

If large analyte flow rates of mL/min, micro-molar analyte concentration, or low binding site densities less than $10^8$/cm$^2$ are present, then the assumption that the analyte concentration is approximately constant over space and time is reasonable. In this case, the singular perturbation theory can be used to approximate the time evolution of the dimer concentration $D(t)$ which is related to the ICS biosensor conductance $G(t)$ [31]. For the parameter values in Table 1, the decay rate of species $Y$ and $Z$ is much faster than the decay rate of the other species by analysis of the eigenvalues of the linearized version of (5). Let us denote the parameters $\gamma = \{Y, Z\}$ for the fast species, and $\beta = \{B, C, D, S, W, X\}$ for the slow species. We can then represent (4) and (5) as a two-time scale system:

$$\frac{d\beta}{dt} = f(\beta, \gamma), \quad \epsilon \frac{dy}{dt} = g(\beta, \gamma)$$ \hfill (7)

where $g$ and $f$ denote vector fields of the fast variables and the slow variables, and $\epsilon \approx \frac{1}{\lambda_{max}}$ with $\lambda_{max}$ the largest eigenvalue of the linearized version of (5). Tikhonov’s theorem combined with the approximation $S \approx S(0)$ allows for the simplification of the above two-time scale system of chemical dynamics equations (7) [26, Sec.11.1]. The following theorem based on singular perturbation analysis provides an equation to evaluate the evolution of the biosensor conductance versus analyte concentration:

**Theorem 1 ([31]).**

Consider the two time scale system (7) for the dynamics of the chemical species. As $\epsilon \to 0$, the dimer concentration $\bar{D}(t)$ converges to $\bar{D}(t)$ given by the following system:

$$\frac{d}{dt} \bar{D}(t) = -\bar{D}(t)(r_5 + f_6A^*) + (f_5c + \frac{r_6f_7x}{r_6 + r_7})S(0)$$ \hfill (8)

with constants $r_5, r_6, r_7, f_5, f_6, f_7$ defined in (3), $A^* = A, X, C$ defined below (2), and $S(0)$ the initial number of tethered gA monomers. Specifically, if the initial dimer concentration $\bar{D}(0)$ at time $t = 0$ is within an $O(\epsilon)$ neighborhood of $\gamma = h(\beta)$, where $h(\beta)$ is the solution of the algebraic equation $g(\beta, y) = 0$ for $g$ given in (7); then for all time $t \in [0, T]$, $|D(t) - \bar{D}(t)| = O(\epsilon)$ where $T > 0$ denotes a finite time horizon.

The proof of Theorem 1 is given in [26] and sketch of the proof is provided in [31]. Using Theorem 1, the conductance of the ICS biosensor for different analyte concentrations $A^*$ can be computed using (8) when the operation of the biosensor is in the reaction-rate-limited regime.

2.6. Experimental Analysis and Model Validation of Ion Channel Switch Biosensor for the Detection of Streptavidin

To evaluate the derived theoretical model of the biosensor performance from Sec. 2.3, Krishnamurthy et al. used a biotin antigen to detect the Streptavidin protein obtained from the bacterium Streptomyces avidinii [31]. The flow chamber had dimensions $h = 0.1$ mm, $L = 6$ mm defined in (2). The depth $W = 2$ mm of the analyte chamber (respectively in the $x_3$ direction) can be ignored because, as is shown in [7], when $h/W < 0.1$, the concentrations along the width of the flow chamber are negligible. The initial concentrations, diffusivity, and reaction rates can be found in Table 1.
Table 1. Parameters for ICS Experimental Detection of Streptavidin

<table>
<thead>
<tr>
<th>Description</th>
<th>Value [units]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Concentrations</strong></td>
<td></td>
</tr>
<tr>
<td>B tethered binding sites</td>
<td>$10^9 - 10^{11}$ molecules/cm$^2$</td>
</tr>
<tr>
<td>C mobile gA monomers</td>
<td>$10^8$ molecules/cm$^2$</td>
</tr>
<tr>
<td>D gA channels (dimers)</td>
<td>$10^9$ molecules/cm$^2$</td>
</tr>
<tr>
<td>S tethered gA monomers</td>
<td>$10^9$ molecules/cm$^2$</td>
</tr>
<tr>
<td>W, X, Y, Z chemical species</td>
<td>0 molecules/cm$^2$</td>
</tr>
<tr>
<td><strong>Reaction Rate</strong></td>
<td></td>
</tr>
<tr>
<td>$t_1 = t_5 = t_6$</td>
<td>$7 \times 10^6$ M$^{-1}$s$^{-1}$</td>
</tr>
<tr>
<td>$t_3 = t_4$</td>
<td>$10^{-10}$ cm$^2$s$^{-1}$molecules$^{-1}$</td>
</tr>
<tr>
<td>$t_5 = t_7$</td>
<td>$10^{-11}$ cm$^2$s$^{-1}$molecules$^{-1}$</td>
</tr>
<tr>
<td>$r_1 = r_2 = r_6$</td>
<td>$10^{-6}$ s$^{-1}$</td>
</tr>
<tr>
<td>$r_3 = r_4$</td>
<td>$10^{-6}$ s$^{-1}$</td>
</tr>
<tr>
<td>$r_5 = r_7$</td>
<td>$10^{-2}$ s$^{-1}$</td>
</tr>
<tr>
<td><strong>Physical Constants</strong></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>$T=275.15$ K</td>
</tr>
<tr>
<td>y Diffusivity of analyte A</td>
<td>$10^{-6}$ cm$^2$/s</td>
</tr>
</tbody>
</table>

The necessary conditions, given in Sec. 2.5, for the Reaction-rate-limited model (8) are not satisfied by the initial concentrations in Table 1 and the flow velocities considered for model validation. Therefore, to compute the theoretically predicted response, (1) is solved subject to the mixed Neumann and Dirichlet boundary conditions given by (2) via a finite element method. The computation is performed using the finite-element-analysis commercial software COMSOL 4.0, with the fully-coupled time-dependent settings using the MUMPS solver and the variable-order variable-step-size backward differential formula (BDF). The internal software physics modules used include: Transport of Diluted Species and the Weak Form Boundary PDE. The total number of mesh elements in the space-discretization is 28748. The chemical kinetics are obtained by solving (5) numerically yielding the dimer concentration $D(t)$, defined below (6), which gives the biosensor conductance $G(t)$.

In Fig. 7(a), the time rate of change of the resistance (response rate) is given for a constant 10 femtomolar Streptavidin analyte concentration flow vs. flow velocity from $v(x_2) = 0$ µL/min to 200 µL/min. The upper response limit of the biosensor is 150 Ω/s. As can be seen, the experimental results are well predicted by the theoretical response obtained from (1).

In Fig. 7(b), the response rate is given for a constant flow rate $v(x_2) = 150$ µL/min flow vs. Streptavidin concentrations ranging from 0 fM to 100 fM. By eyeballing the theoretical and experimental curves in Fig. 7(b), the experimental data is well predicted by the theoretical models developed in Sec. 2.3 and Sec. 2.4.

2.7. Experimental Analysis of Ion Channel Switch Biosensor for the Detection of Influenza A

Krishnamurthy et al. have reported clinical trials for the detection of influenza A using the ICS biosensor [30]. Influenza A is a highly contagious respiratory infection that is spread by personal contact and in aerosol transmission. The swift detection of the virus is necessary to prompt patient management and ensure the quarantining of infected patients. The ICS biosensor is able to detect the virus in less than 10min at room temperature. When compared with the ELISA or PCR test for virus detection, the ICS biosensor is significantly faster and not prone to experimental error resulting from specimen extraction, washing, and incubation steps present in the ELISA and PCR methods [29, 79]. To compare the performance of the ICS biosensor to available products, a commercially available kit obtained from Medix Biochemica was used. Two groups of samples were considered:

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William Hoiles, Vikram Krishnamurthy, Bruce Cornell

(a) The black triangles indicate the experimentally measured data, the light gray line containing boxes indicates the maximum response rate possible for the ICS biosensor, and the dark gray line containing triangles indicates the theoretically predicted response rate.

(b) The solid black line indicates the experimentally measured response rate and the dotted black line indicates the theoretically predicted response rate.

Fig 7. Experimental and theoretical comparison of the performance of the ICS biosensor for the detection of Streptavidin [30]. The response rate is defined as the rate-of-change of $1/G(t)$, and is computed using (1) and (9) coupled with (6).

Group 1: 74 samples drawn from nasopharyngeal, sputum, bronchial, or tracheal aspirates, nose, and throat swabs collected in the period between July-August 2006 in South Australia were stored at $-4^\circ\text{C}$ for two days until clinical tests were performed using the ICS biosensor, and Medix test strips. No cases of influenza were present in this group of data.

Group 2: 34 randomly selected samples from the outbreak of influenza A in July-September 2005, stored at $-7^\circ\text{C}$ had previously been submitted for routine virus culture.

For Group 1 samples, the ICS biosensor did not yield any false positives. The culture and antigen ELISA produced positive results for 14/74 of the samples for influenza B, adenovirus, respiratory syncytial virus, or parainfluenza 3 virus. Therefore, the ICS biosensor is not effected by the addition of other molecular species beyond the target species of interest. For Group 2, the ICS biosensor and Medix immunochromatographic test strips produced very similar results for true positives, negatives, and false positives and negatives. The clinical analysis shows the utility of the ICS biosensor for the detection of analyte species without the need for sample preparation.

3. Ion Channel based Diffusion Sensor for Cell Response Measurement

In the previous section, we presented details of the fabrication and modelling of an ion channel biosensors based on the selective switching of monomers and dimmers for the detection of a specific analyte. In this section, we consider a different device that is designed to measure the response of cells to a stimulus. The device is useful in disease diagnosis and uses gramicidin channels as a cation selective diode allowing the device to accurately measure the concentration of cations in solution. The field of electrophysiology is focused on how particular ions flow in a biological system, such as cells or tissue, and using the obtained electrical signals for the computation of cell properties and disease diagnosis. Experimental measurement of ionic flow is performed by connecting electrodes, such as a 1 $\mu$m pipette, to a biological specimen and measuring the electrical signals produced. The signals produced from this method are easy to analyze, but difficult to obtain. Surgical Diagnostics Ltd. is currently developing a state-of-the-art Cation Selective (CS) sensor geared towards providing a robust, repeatable, low-cost disease diagnosis system without the need for the complex experimental procedures required for classical ionic flow measurements. Neural stem cells are currently being used for experimental trials of the CS sensor. Although the measurement procedure using the CS sensor is easy to perform, the obtained data is difficult to analyze as a result of noise pollution. Sophisticated signal processing techniques are required to perform disease diagnosis using the electrical
signals produced from this sensor. In the following subsection we present methods that can be used to model the behavior of the CS sensor shown in Fig. 2.

3.1. Physical Setup and Electrical Analogous Model of the Cation Selective Sensor

The setup of the CS sensor is presented in Fig. 2. As seen, the biomimetic surface is composed of stationary bis-gramicidin (bis-gA) channel that only allow the flow of cations. The cells in suspension are excited by either a 50 mV voltage-step or by a sinusoidal excitation. When excited, the cells primarily diffuse the inorganic ions Na\(^+\), K\(^+\), and Cl\(^-\). The released inorganic ions combine with the ions in solution and undergo an electro-diffusion process. Both cations and anions are present in the solution, however, only cations can pass through the biomimetic surface. The increase in concentration of cations in the reservoir between the bottom gold electrode and membrane causes a current to flow between the electrodes of the sensor. By measuring the induced current, the diffusion characteristics of the cells can be measured. These diffusion characteristics can be linked with various diseases and provide a detection method using the diffusion behavior of the cells.

The cell suspension and biomimetic surface of the CS sensor, shown in Fig. 2, is a heterogeneous system composed of several materials with different governing physics. This complex system can be modeled using the equivalent circuit shown in Fig. 8.

![Equivalent circuit model of the CS sensor illustrated in Fig. 2.](image)

The measurement system represented by \( V_{app} \) in Fig. 8 is composed of electronics used to measure the current and produce an excitation pulse allowing the cells to diffuse inorganic ions. The cell suspension is modeled by \( R_1, C_1, C_2, R_2(t) \) where \( R_1 \) is the resistance of the cells when active, \( C_2 \) is the cell membrane capacitance, \( R_2(t) \) is the loss of ions due to leakage channels and leakage directly through the cell suspension solution, and \( C_1 \) is the cell charge arising from ion gradients. The two "switches" indicate when the cells are diffusing ions and when ion diffusion stops. All the parameters in Fig. 8 can be determined by experimental measurement.

If \( I(t) \) is available from experimental measurements, the circuit parameters in Fig. 8 can be estimated using the first-order vector differential equation (state-equation) \( dx/dt = A(t)x + F(t, V_{app}) \) where \( x \) is a vector of state-variables (e.g. capacitor voltages), \( A(t) \) is a square-matrix related to the circuit parameters in Fig. 8, and \( F(t, V_{app}) \) is the forcing term. A time-varying coefficient estimation method can be used to compute the circuit parameters given \( V_{app} \) and \( I(t) \) from measurement with the state-equations of the circuit.
Typical values for the circuit parameters in Fig. 8 are $C_1 = 100 \text{nF}$, $C_2 = 100 \text{nF}$, $R_1 = 1 \text{ MΩ}$, $R_m = 1 \text{ MΩ}$, $C_m = 10 \text{nF}$, $C_t = 1500 \text{nF}$, and $C_b = 150 \text{nF}$. The leakage resistance $R_2(t)$ is approximately 100 Ω when no cells are present. The value of $R_2(t)$ depends on several parameters of the cell solution, such as cell density, geometry, excitation voltage etc. Therefore, to predict the response of the sensor for unobserved measurements, the value of $R_2(t)$ must be predicted theoretically.

To obtain an estimate of $R_2(t)$, consider that the ions in the cell suspension undergo an electro-diffusion process. Additionally, the relationship between the current $I(t)$ and the voltage $V(t)$ satisfy the following equation:

$$I(t) = \begin{cases} 
V(t) \left( \frac{R_1 + R_2(t)}{R_1 R_2(t)} \right) - \frac{1}{R_1} e^{-\tau_1 t} \int_0^t e^{\tau_1 t} V(\gamma) d\gamma - \frac{V_{C_1}(0)}{R_1} e^{-\tau_1 t} + C_2 \frac{dV(t)}{dt} & 0 \leq t \leq t_{\text{diff}} \\
\frac{1}{R_2(t)} V(t) + C_2 \frac{dV(t)}{dt} & t_{\text{diff}} \leq t
\end{cases}$$

with $\tau_1 = \frac{C_2}{R_2(t)}$ and $V_{C_1}(0)$ being the initial charge on capacitor $C_1$ in Fig. 8. Eq. (9) can be used to solve for $R_2(t)$ as a function of $I(t)$ and $V(t)$. Therefore, if we can model the electro-diffusion of ions in the cell suspension to obtain $I(t)$ for a particular voltage $V(t)$, then (9) can be used to obtain $R_2(t)$. The electro-diffusion of ions in the cell suspension can be modeled using a tightly coupled system of nonlinear partial differential equations. How to obtain $I(t)$ given $V(t)$ using this system of equations is provided below.

### 3.1.1. Poisson-Nernst-Planck Theory

The study of the electro-diffusion of charged particles such as ions, electrons, or colloids in the presence of an applied external electric field is of great importance in a number of disciplines. The motion of electrons and holes in semiconductors subject to an imposed external electric field is of importance to the design of modern electronic components such as transistors, diodes, and infrared lasers [9]. In the biological applications, the process of interest is the flow of inorganic ions ($K^+$, $Na^+$, $Ca^{2+}$, $Cl^-$, etc.) through pores in lipid bilayer membranes. All biochemical signal communication in living organisms relies on the transport and concentration of inorganic species.

The most well-known continuum theory model for ion transport is certainly the Poisson-Nernst-Planck system of equations which combines the Poisson equation from electrostatics, and the Nernst-Planck equation for diffusion [24, 33, 41–43, 50, 53, 61, 67, 72, 87]. Primarily in a biological context, the PNP theory is used to model ion transport through ion channels and nanotubes [9, 22, 24, 33, 50, 53, 71, 72]. Mathematical models for a purely biological system that considers the transport of ions, charged molecules, and molecular charged species and a microelectronic system which considers the transport of ions and holes can be linked using the PNP theory. In [61], this idea of bioelectronic interfacing was studied using the steady-state PNP theory in which an electrogenic cell was placed on the top of a field-effect transistor gate. Interested readers are referred to [15] for an introduction to bioelectronic interfacing using semiconductor devices.

Here we provide the intuition behind the PNP theory and what conditions must be satisfied for its application. Two common methods for the derivation of the PNP theory are to begin from either the electrochemical potential of equilibrium thermodynamics or using the properties of diffusion and electrostatics [73]. Here we provide the derivation using the properties of diffusion and electrostatics. The derivation begins by assuming the ion interactions and continuum descriptions of concentration and electric potential are valid—the mean-field approximation holds [86]. Consider that the transport behavior of ions is driven primarily by a diffusive flux $J_{d}^{i}$, and an electrical-migration flux $J_{e}^{i}$ where $i$ denotes the ionic species. The electrical-migration flux $J_{e}^{i}$ of the ions is the number of moles of ions passing through a unit area per second and is given by:

$$J_{e}^{i} = \mu_{i} c^{i} q^{i} F E,$$

where $\mu^{i}$ is the electron mobility, $c^{i}$ is the concentration, $q^{i}$ is the charge, $F$ is the Faraday constant, and $E$ denotes the electric field. The diffusive flux $J_{d}^{i}$ produced by concentration gradients is given by:

$$J_{d}^{i} = -D^{i} \nabla c^{i},$$
where $D^i$ is the diffusion coefficient. Using (10) and (11), the total flux of species $i$ is given by the Nernst-Planck equation:

$$J^i = J^i_d + J^i_e = -D^i \nabla c^i + \mu_i c^i q^i F E$$

$$= -D^i \nabla c^i - \frac{q^i}{k_B T} c^i E,$$

(12)

where the last relation is obtained by substitution of the Einstein relation $\mu_i = D^i / k_B T$, where $k_B$ is the Boltzmann constant, and $T$ the temperature of the solution. The electrical field $E$, in (10), is obtained from Maxwell’s equations. Note that electromagnetic wave phenomena occur on a time scale of nano-seconds, while the time scale of interest for the electro-diffusion process occurs at the milli-second scale; therefore, we assume the electrostatic approximation of Maxwell’s equations applies allowing the use of Poisson’s equation to obtain an expression for $E$ given by:

$$\nabla \cdot (\varepsilon E) = \rho$$

$$E = -\nabla \phi$$

$$\Rightarrow \nabla \cdot (\varepsilon \nabla \phi) = -\rho,$$

(13)

where $\varepsilon$ is the dielectric permittivity, $\rho$ is the charge density, and $\phi$ is the electric potential. We now impose mass conservation which states that the time change of concentration must be equal to the divergence of the total flux. Using mass conservation we obtain the following expression known as the PNP theory that describes the electro-diffusion of ions in solution:

$$\frac{\partial c^i}{\partial t} = -\nabla \cdot J^i$$

$$J^i = J^i_d + J^i_e = -[D^i (\nabla c^i + \frac{q^i}{k_B T} c^i \nabla \phi)]$$

$$\nabla \cdot (\varepsilon \nabla \phi) = -\rho = -F \sum_i q^i c^i$$

for $i \in \{1, 2, \ldots, n\}$. (14)

Recall that parameter $i \in \{1, 2, \ldots, n\}$ denotes the ionic species, $c^i$ is the concentration of species $i$, $D^i$ is the diffusivity of species $i$, $q^i$ is the charge of species $i$, $F$ is the Faraday constant, $k_B$ is Boltzmann constant, $T$ is the temperature, $\varepsilon$ is the dielectric permittivity, $J^i$ is the ionic flux, and $\phi$ is the potential.

3.1.2. Improvements of the Poisson-Nernst-Planck Theory

The PNP theory has some well-known limitations resulting from the finite volume effect of ion particles and from neglecting the correlation effects which are important for confined ion channel permeation [76, 86]. Improvements to the developed theory to account for ion-ion interactions and steric effects are currently active areas of research [13, 27, 28]. Modifications to the PNP theory are typically performed by either adjusting the diffusion coefficient or by including additional force contributions to the Nernst-Planck equation [86]. An example of adding a displacement flux term to the Nernst-Planck equation to model effects caused by lipid membranes and bioelectronic interfaces is presented in Sec. 3.4. Note that these effects are assumed negligible in our current development of the electro-diffusion of ions in the cell suspension.

3.2. Derivation of the Induced Current from Cation Movement in the Cell Suspension for the Cation Selective Sensor

The electro-diffusion of ions in the cell suspension is strongly influenced by concentration gradients and electric field effects. The movement of the ionic species is modeled using the PNP theory (14). In the
cell suspension, the particle–particle correlations of the diffusing ions are neglected allowing the mean-field approximation to hold in which case the PNP is a proper physical model describing the electro-diffusion of ions [42]. The PNP theory of equations couples the continuity equations, the Nernst-Planck equations for each ionic species, and the Poisson equation providing a complete description of the time-evolution of ionic concentrations of species in solution as discussed in Sec. 3.1.1. The primary ionic species of interest in the cell suspension are Sodium (Na$^{+}$), Potassium (K$^{+}$), and Chloride (Cl$^{-}$). The total current induced at the sensor electrode is computed from the following expression which relates the change in concentration of the cation species at the electrode interface to the ionic current:

$$I(t) = \sum_{i=1}^{2} I_i(t) = \sum_{i=1}^{2} \frac{\partial Q_i(t)}{\partial t} = \sum_{i=1}^{2} \frac{\partial}{\partial t} \int_{V} F q_i c_i^i dV$$

$$\text{where } i = \{\text{Na}^{+}, \text{K}^{+}\}. \text{ To obtain a solution for } I(t) \text{ using (14) and (15) requires us to impose the initial conditions and boundary conditions to solve the PNP equations (14). At the boundary of the cell suspension and electrode interface there is zero ionic flux. The potential difference between the electrode surfaces is given by } V_{\text{diff}} \text{ where the tethered gold electrode is set at a zero reference potential. The cells diffuse inorganic ions for the duration of the excitation potential which stops at } t_{\text{diff}} \text{ at which point the cells stop diffusing. These boundary conditions are presented in Fig. 9.}$$

![Fig 9. Boundary conditions of the PNP theory used to compute the time-varying ionic current $I(t)$ as described in Sec. 3.2. $n$ denotes the normal vector from the surface (i.e. $n_1$ is the normal from the cell surface, $n_2$ is the inward normal aligned with the x-coordinate.)](image)

The current $I(t)$ is computed by integration of (15) over a “small” volume located above the biomimetic surface and bottom tethered gold electrode.

### 3.3. Simulation of the Induced Current $I(t)$ in the Cation Selective Sensor using Poisson-Nernst-Planck Theory

This subsection presents the simulation results for the produced current $I(t)$ for a series of applied voltages $V_{\text{app}}$ and cell heights $h$ from the CS sensor shown in Fig. 2. The initial concentrations and simulation parameters are provided in Table 2. The geometric setup used to compute the simulation is provided in Fig. 10.

The solution is carried out using the finite-element-analysis commercial software COMSOL 4.2a\(^b\), with the fully-coupled time-dependent settings using the MUMPS solver and the variable-order variable-step-size backward differential formula (BDF) [3]. The internal software physics modules used include: Poisson

---

\(^{b}\) www.comsol.com
Fig 10. Dimensions of simulation boundary conditions of the PNP theory used to compute the time-varying ionic current \( I(t) \) as described in Sec. 3.2. The shaded gray region above the bottom electrode with a height of 0.25 \( \mu m \) and width of 18 \( \mu m \) denotes the region where the integration of \( I(t) \) is computed. The parameter \( h \) is the height of the cells from the biomimetic surface and is varied to determine the relationship with the current \( I(t) \). The depth, direction perpendicular to the \( x\)-\( y \) axis, of the cell suspension is 1mm.

Table 2. Parameters used for the computation of the PNP theory (14) to compute the CS sensor current \( I(t) \) obtained from (15). The concentration, diffusion constants, and permittivity are common values used to represent biological systems [4].

<table>
<thead>
<tr>
<th>Description</th>
<th>Simulation Value [units]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Cell Suspension Concentration</td>
<td></td>
</tr>
<tr>
<td>( \text{Na}^+ )</td>
<td>100 mol/m³</td>
</tr>
<tr>
<td>( \text{K}^+ )</td>
<td>4 mol/m³</td>
</tr>
<tr>
<td>( \text{Cl}^- )</td>
<td>104 mol/m³</td>
</tr>
<tr>
<td>Initial Cytoplasm Species Concentration</td>
<td></td>
</tr>
<tr>
<td>( \text{Na}^+ )</td>
<td>10 mol/m³</td>
</tr>
<tr>
<td>( \text{K}^+ )</td>
<td>100 mol/m³</td>
</tr>
<tr>
<td>( \text{Cl}^- )</td>
<td>110 mol/m³</td>
</tr>
<tr>
<td>Initial Electrical Potential</td>
<td>0 V</td>
</tr>
<tr>
<td>Boundary Conditions</td>
<td></td>
</tr>
<tr>
<td>Cell Diffusion Time</td>
<td>10 ms</td>
</tr>
<tr>
<td>Applied Voltage ( V_{app} )</td>
<td>0-50 mV</td>
</tr>
<tr>
<td>Physical Constants</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>273.15 K</td>
</tr>
<tr>
<td>Diffusion ( \text{Na}^+ )</td>
<td>1.33 cm²/s</td>
</tr>
<tr>
<td>Diffusion ( \text{K}^+ )</td>
<td>1.96 cm²/s</td>
</tr>
<tr>
<td>Diffusion ( \text{Cl}^- )</td>
<td>2.03 cm²/s</td>
</tr>
<tr>
<td>Cytoplasm Relative Permittivity</td>
<td>80</td>
</tr>
<tr>
<td>Solution Relative Permittivity</td>
<td>8</td>
</tr>
</tbody>
</table>

Electrostatics, and the Nernst-Planck transport of diluted species. The total number of mesh elements in the space-discretization is 16612.

The dependence of the current \( I(t) \), in (15), on the applied voltage \( V_{app} \) is presented in Fig. 11. As seen, as the voltage is increased the magnitude of the current \( I(t) \) also increases. As expected, the current \( I(t) \) increases as the cations released from the cells reach the biomimetic surface, then a decrease in the current follows because the concentrations in the cell suspension approach the steady-state value where the obtained current \( I(t) \) is zero.

Fig. 12 presents the dependence of \( I(t) \), given in (15), on different cell to sensor heights, and applied voltages. From Fig. 12(a) for \( h = 1.5 \mu m \), the rapid increase and decrease of the current occurs due to the cells proximity to the sensor surface. Recall that the boundary of the sensor surface contains a no-flux condition; therefore, as the concentration rapidly increases at the sensor surface, a rapid increase in the current is obtained. The rapid decrease occurs because the diffusion of ions decreases as the cell suspension reaches the steady-state concentration profiles for \( \text{K}^+ \), \( \text{Na}^+ \), and \( \text{Cl}^- \). As the cell to sensor height is increased, less released ions diffuse to the sensor surface, and this results in a reduced peak in the measured current, as seen in Fig. 12(a). Fig. 12(b) illustrates the effect the applied voltage has on the measured current \( I(t) \) of the CS sensor. The magnitude of the current for \( V_{app} = 50 \text{ mV} \) is significantly larger than the obtained current for \( V_{app} = 0 \text{ mV} \) as a result of the electric field causing migration in the ionic species. For the applied field \( V_{app} = 50 \text{ mV} \), the ionic transport is a result of both electron-migration, and diffusion, as expected from the form of (14). Therefore, we can conclude that the electro-diffusion of the
ions in the cell suspension are driven primarily by the applied electric field. This suggests that there is an optimal voltage that can be applied for the detection of the released inorganic ions.

![Graph](image)

**Fig 11.** Computed current $I(t)$ for constant cell-to-biomimetic surface height $h = 2 \ \mu m$ and applied potential values $V_{app} = \{0, 10, 20, 30, 40\} \ \text{mV}$. $I(t)$ is obtained using equations (15) and (14) with initial conditions given in Table 2, boundary conditions given in Fig. 9, and geometric setup given in Fig. 10. The computational method used to compute $I(t)$ is given below Fig. 10.

![Graph](image)

**Fig 12.** Computed current $I(t)$ for applied voltage $V_{app}$ and cell-to-biomimetic surface heights $h = \{3.0, 2.5, 2.0, 1.5\} \ \mu m$. $I(t)$ is obtained using equations (15) and (14) with initial conditions given in Table 2, boundary conditions given in Fig. 9, and geometric setup given in Fig. 10. The computational method used to compute $I(t)$ is given below Fig. 10.

### 3.4. Equivalent Circuit Model based on Poisson-Nernst-Planck Theory with Displacement Flux Addition

Although Fig. 8 provides a simple equivalent circuit representation of the CS sensor presented in Fig. 2, it is difficult to estimate all the parameters without advanced techniques such as applying the continuum model of PNP as presented in Sec. 3.1.1 and Sec. 3.2. A standing assumption when applying the PNP...
theory was that the membranes (both of the cells in suspension and the sensor) are passive in that they
do not effect the applied potential, as well as neglecting the effects of the diffuse-layer and Helmholtz
layer at the interface of the electrode-electrolyte interface (modeled by capacitors \( C_b \) and \( C_l \) in Fig. 8). If
these assumptions do not hold, then we must take into account a displacement flux term. The displacement
flux can be included directly into the total flux (12). Ramos et al. derived a grid-based differential time-
domain numerical modeling method based on representing the flow of ions using an equivalent circuit model
(ECM) [64]. The derivation presented in [64] begins by stating the equation for conduction, diffusion, and
displacement current. Below we provide a direct link between the PNP theory with the addition of the
displacement flux term and derive the current equation necessary for the ECM development. Proceeding,
we present the necessary assumptions for the derivation of the ECM model.

Note that the modeling of the bioelectronic interface, lipid membranes, and cell structures is computa-
tionally demanding with current finite-element and finite-difference discretization methods. Consider that
the thickness of the diffuse-layer and Helmholtz layer is approximately 1 nm for biological systems, while
biological cell radii are approximately 5 to 10 \( \mu \)m in size [64]. A large number of grid-points are necessary
to represent this structure. Another drawback is that for the method to converge given rectangular elements
with small grid-spacing such as 1 nm, the time-step for biological system analysis, as is shown, would be
on the order of nano-seconds. The analysis of the CS sensor requires the current \( I(t) \) on the order of
milli-seconds, requiring the ECM to be run for several million time-steps to reach the required time-horizon.
It is possible reduce the computational resources necessary by making certain assumptions on the system.
For example, in the case of “electroneutrality”, where the total charge \( \rho \) in (14) is approximately zero, effi-
cient algorithms exists for the computation of the electrical potential and ionic concentrations. Necessary
conditions for electroneutrality to hold, and algorithms for the computation of electric potential and ionic
concentration can be found in references [25, 46, 47, 55, 56].

3.4.1. Equivalent Circuit Model of Ionic Transport in Solution with Diffusive Flux, Electro-Migration Flux, and Dis-
placement Flux Effects

The Nernst-Planck equation (12) is composed of the diffusion flux \( J^i_D \) and electro-migration flux \( J^i_e \)
where \( i \in \{1, 2, \ldots, N\} \) denotes the ionic species. Here we add the electrical displacement flux \( J_D \) which
was assumed negligible when developing the PNP theory in Sec. 3.1.1. The total flux for all ions \( i \) is given by:

\[
J = \sum_i (J^i_D + J^i_e) - J_D \\
= -\sum_i D^i (\nabla c^i - \frac{q^i}{k_B T} c^i E) - \frac{\varepsilon}{F q^i} \frac{\partial E}{\partial t} \\
= -\sum_i D^i \left( \frac{1}{F q^i} \nabla \rho^i + \frac{\rho^i}{F k_B T} \nabla \phi \right) + \frac{\varepsilon}{F q^i} \frac{\partial \nabla \phi}{\partial t} \\
= -\sum_i \frac{\mu^i}{F q^i} (\nabla \rho^i + \rho^i \nabla \phi) + \frac{\varepsilon}{F q^i} \frac{\partial \nabla \phi}{\partial t} \\
\]

(16)

with \( \rho^i = F q^i c^i \) being the charge density, \( \nu^i = k_B T / q^i \), and \( \mu^i = D^i / \nu^i \) being the ionic mobility where
parameters \( F, q^i, c^i, D^i, k_B \) and \( \varepsilon \) are defined below (14). The goal is to use (16) to construct an equivalent
circuit model of the biological system. To proceed, the five-point stencil in Fig. 13 is used for the finite-
difference approximation.

Note that here we present the construction of the ECM in the 2-dimensional case, the 3-dimensional
case is a straightforward construction given the theory for the 2-dimensional case. As a first step, we
consider the derivation of the circuit element between node positions \( O \) and \( X \) in Fig. 13 using (16). The
total ionic flux from node $O$ to $X$ is denoted by $J_j$ and is given by:

$$J_j = -\sum_i \frac{\mu^i_j}{F q^i} (v^i_j \frac{\partial \rho^i_j}{\partial x} + \rho^i_j \frac{\partial \phi}{\partial x}) + \frac{\varepsilon_j}{F q^i} \frac{\partial}{\partial t} \frac{\partial \phi}{\partial x}$$

$$= -\sum_i \frac{\mu^i_j}{F q^i} v^i_j e^{-\phi^i_j} \frac{\partial \rho^i_j e^{\phi^i_j}}{\partial x} + \frac{\varepsilon_j}{F q^i} \frac{\partial}{\partial t} \frac{\partial \phi}{\partial x}.$$  \hfill (17)

Assume that $J^i_j, \mu^i_j, v^i_j, \varepsilon_j$ are constant between nodes $O$ and $X$, as well as assuming the electrical potential $\phi$ varies linearly in space between nodes $O$ and $X$. We now take the line integral on both sides of (17) between nodes $O$ to $X$ to obtain:

$$J_j L = \sum_i \frac{\mu^i_j (\phi_X - \phi_O) (\rho^i_{O^X} e^{\Delta x e_{\phi}} - \rho^i_{O^X})}{F q^i (e^{\Delta x e_{\phi}} - 1)} + \frac{\varepsilon_j}{F q^i} \left( \frac{\partial (\phi_X - \phi_O)}{\partial t} \right).$$ \hfill (18)

To obtain the total current $I_j$ leaving the node $O$, multiply both sides of (18) by the area $A$, and define $\Delta_j \phi = \phi_X - \phi_O$, $\rho^i_{O^X} = (\rho^i_X + \rho^i_O)/2$, $\rho^i_X = \rho^i_{O^X} + \Delta_j \rho^i/2$, $\rho^i_O = \rho^i_{O^X} - \Delta_j \rho^i/2$, $\Delta_j = \rho^i_X - \rho^i_O$, $I^i_j = I^j_j q^j A$ and substitute into (18) to obtain:

$$I_j = g_j \Delta_j \phi + \sum_i k^i_j \Delta_j \rho^i + C_j \frac{\partial \Delta_j \phi}{\partial t}$$

$$= T_j + C_j \frac{\partial \Delta_j \phi}{\partial t}$$

with $g_j = \sum_i \mu^i_j \rho^i_{O^X} A / L$, $k^i_j = \mu^i_j \frac{\Delta_i \phi}{2} \frac{e^{\Delta_i \phi}}{2 (e^{\Delta_i \phi} - 1)} A / L$, $C_j = \varepsilon_j A / L.$ \hfill (19)
In (19), \( g_j \) represents total conductance, \( C_j \) is a capacitance, \( k_j \) is a coefficient parameter which in combination with the change in charge density can be represented by a current source, and \( \bar{T}_j \) is the total current due to diffusion and conduction. The equivalent circuit representing ion transport between nodes \( O \) and \( X \) is obtained using (19) and is given in Fig. 14.

![Fig 14. Equivalent circuit representation of the total ionic flux between nodes \( O \) and \( X \) in Fig. 13. The circuit represents the flux resulting from diffusion, electric-migration, and electrical displacement. The derivation of this circuit is obtained using approximations of (18) on a finite grid, as presented in Sec. 3.4.1.](image)

The total current leaving node \( O \) in Fig. 13 is the sum of currents between node \( O \) and \( \{X,Y,Z,W\} \) which can be computed using (19) as follows:

\[
I_O = \sum_j \left( \bar{T}_j + C_j \frac{\partial \Delta_j \phi}{\partial t} \right)
\]

for \( j = \{OX,OY,OZ,OW\} \), the difference operator \( \Delta_j \), and average charge \( \rho_{avg}^j \) computed with respect to \( j \) as shown above (19). If (20) is approximated using discrete time-steps \( \delta t \) then we obtain:

\[
I_O = \sum_j \left( \bar{T}_j + C_j \frac{\delta (\Delta_j \phi)}{\delta t} \right).
\]

To update (21) at each time-step, we apply Kirchoff’s Current Law to node \( O \) in Fig. 13 to obtain:

\[
\sum_j \left( C_j \frac{\delta (\Delta_j \phi)}{\delta t} + \bar{T}_j \right) = 0
\]

where \( j = \{OX, OY, OZ, OW\} \).

Multiply both sides of (22) by \( \delta t \), and then invoke the relation that the rate of change of charge is equal to the current giving the relation:

\[
Q_O = \sum_j C_j (\Delta_j \phi).
\]

Eq. (23) can be used to update the electric potential of the nodes at each time-step of the simulation. Note that if node \( O \) were connected to an electrode with potential \( V_{app} \) where the diffuse-layer and Helmholtz layer were modeled by a capacitance \( C_{ds} \), then the total charge would be \( Q_O = Q_O + C_{ds} V_{app} \). The update equation for charge is computed by evaluating:

\[
\frac{\delta Q_O}{\delta t} = -\sum_j \bar{T}_j
\]

\[
\Rightarrow Q_O(t + \delta t) = Q_O(t) - \delta t \sum_j \bar{T}_j(t).
\]
The update equation for the charge density is obtained by substituting the total charge $Q_O = AL \sum_i \rho_i = AL \rho_O$ into (24) where $A$ denotes the surface area of the rectangular element containing node $O$, and $L$ denotes the length of the element, as shown in Fig. 13. The equation to update the charge density is given by:

$$\rho_O(t + \delta t) = \rho_O(t) - \frac{\delta t}{AL} \sum_j I_j(t).$$  \hspace{1cm} (25)

Using equations (19), (23), (24), and (25) it is possible to solve for the charge density and electrical potential of cellular biological systems with bioelectronic interfaces given the initial conditions and boundary conditions. Define $\phi$ as the vector containing the potential of each node, $\rho$ the vector containing the charge density at each node, $I$ as the vector of total currents resulting from diffusion and conduction for each node, and $Q$ as the vector containing the total charge in each rectangular grid containing a node. The ECM algorithm, using parameters $\{\phi, \rho, I, Q\}$, is given below:

**Step 0:** Generate a grid-spacing to represent the sensor system that is composed of elements of the form shown in Fig. 13 with appropriate boundary stencils (i.e. only partial sections of the stencil shown in Fig. 13) that represent the boundary conditions. Derive the analogous circuit representation of the grid-spacing using (19) between each adjacent interior node.

**Step 1:** Given the boundary conditions and initial conditions for charge $\rho(t_0)$ and electric potential $\phi(t_0)$, use (19) to compute the total current at each node $I(t_0)$.

**Step 2:** For $k = 0, 1, 2, \ldots$

- Given $\rho(t_k)$, $\phi(t_k)$, $I(t_k)$ and the boundary conditions, compute $Q(t_{k+1})$ using (23), and $\rho(t_{k+1})$ using (25).
- Given the boundary conditions and $Q(t_{k+1})$, compute the electric potential $\phi(t_{k+1})$ using (23).
- Given the boundary conditions, $\phi(t_{k+1})$, and $\rho(t_{k+1})$, use (19) to compute $I(t_{k+1})$.

Recall the above ECM algorithm is a grid-based differential time-domain numerical method, a natural question to pose is how can we ensure convergence of the algorithm? Intuitively the convergence of the iterative process must depend on the smallest discretization length used, denoted as $L_s$. The charging effects at the interface of the electrode-electrolyte solution are the fastest and hence the convergence criterion is computed at this interface. Ramos et al. utilizes the mass conservation law to provides a threshold on the time-step such that convergence of the above ECM algorithm is achieved [64]. The final result of the analysis is that the time-step must satisfy:

$$\delta t \leq \frac{2\varepsilon L_s^2}{\sigma L_s^2 + 4D\varepsilon},$$  \hspace{1cm} (26)

where $\varepsilon$ is the permittivity of the electrolyte, $D$ is the diffusion coefficient, and $\sigma$ is the conductivity. For typical biological systems, to capture the behavior of the electrode-electrolyte interface the value of $L_s = 1$ nm is used with the other parameter values given by, for example, $\sigma = 4.7 \times 10^{-4} \text{S/cm}$, $\varepsilon = 70 \times 10^{-14} \text{F/cm}$, and $D = 1 \text{ cm}^2/\text{s}$ [4]. Using (26), the necessary time-step to ensure convergence of the ECM algorithm is $\delta t \leq 0.3$ ns.

4. Computation of Biosensor Model Parameters from First Principles

The derived continuum models of the ICS biosensor and CS sensor require a variety of physical parameters such as conductance, diffusivity, permittivity, and chemical reaction rates. These parameters are generally obtained experimentally; however, increase in computational capabilities linked with sophisticated mathematical algorithms is allowing these physical parameters to be modeled from first principle approaches such as molecular dynamics. The dynamics of ion channels at the atomic scale are of interest for development of novel ion channel based biosensors. Characteristics of ion channels such as ion binding characteristics,
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permeation pathways, ion conductance, selectivity, gating characteristics are required to theoretically compute important macro-level parameters of biosensors. As an example, both the ICS biosensor and CS sensor models presented in Sec. 2 and Sec. 4 require the conductance of the gA and bis-gA dimers to be defined. The ICS biosensor chemical rate reactions are also required for modeling. The connection between the molecular level modeling and the ICS biosensor and CS sensors is provided in Fig. 15. Specifically, ion permeation characteristics are used to compute the conductance of the gA channels, and the channel dynamics can be used to compute the chemical reaction rates of the ICS biosensor [21, 48].

![Diagram showing the interrelationship between molecular modeling of ion permeation, ion channels, and the ICS biosensor presented in Sec. 2 and CS sensor presented in Sec. 3. The Ion Permeation theory can be used to compute the macro-level conductance which is used in modeling both the ICS biosensor and CS sensor. To compute the macro-level reaction rate of the dissociation of gramicidin A (gA) from first principles, the dissociation dynamics of the gA complex is necessary. The Channel Dynamics block refers to the dissociation/association of the gA complex. The channel dissociation dynamics can be computed using molecular dynamics in combination with umbrella sampling. The ICS biosensor utilizes the gA complex and the CS sensor utilizes the bis-gA complex. Although the ICS biosensor is constructed for the detection of specific target species and the CS sensor is used for the measurement of cation concentrations, both share a similar structure as the only difference is in the biomimetic surface incorporating either gA or bis-gA complexes.

Ion channels can now be mapped because of remarkable advances in X-ray crystallography allowing the construction of theoretical models that accurately account for the complex atomic structure present in ion channels [17, 21, 32, 48]. For example, Lomize et al. successfully mapped the static structure of the gA channel [39]. gA is a polypeptide that consists of 15 amino acid residues with two coupled gA monomers. Current X-ray crystallographic techniques are unable to detect hydrogen bonds; however, the coupling of the two gA monomers is likely a result of 6 intermolecular hydrogen bonds, as predicted using molecular dynamics simulations [82]. Fig. 16 represents the structure of the gA channel and was constructed using Jmol\(^c\).

\(^c\) Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/.
Fig 16. Representation of the gramicidin A (gA) channel using the dimer chain representation and atomic representation created in Jmol.

In Sec. 4.1, methods to compute ion permeation through the gA dimer are discussed. The proposed models are in good agreement with experimentally measured values for the conductance of the gA dimer. Recall that the continuum models presented in Sec. 2.3, Sec. 3.1, and Sec. 3.2 require the conductance of the gA dimers to model the ICS biosensor, and the CS sensor, which utilizes bis-gA that has the same conductance as the open gA dimer by definition. The ICS biosensor relies on the gating characteristics of the gA channels. It is known that the gating of the gA channel involves a series of conformational changes in the protein structure that opens or closes the channel [21]. The modeling of dissociation/association (i.e. the gating of the ion channel) is a process involving multiple transition states and complex dynamics because the gA channel can exist in multiple conformational states [82]. The focus of Sec. 4.2 is on modeling the dynamics of the gA channel which can be used to obtain the chemical reaction rate of dimer dissociation, denoted as $f_0$ in (3).

4.1. Modeling Ion Permeation through Ion Channels

Several methods exist for modeling the permeation of ions through biological ion channels. An introduction and review of a series of ion channel models is presented in [21, 48]. At the lowest level of abstraction, there is the ab initio quantum mechanical approach in which the interactions between the ions, water molecules, and protein atoms are computed by solving the many-body Schrödinger equation. This approach offers the ultimate tool for the modeling of biomolecular systems; however, solutions of the equation is formidable and is an extremely time-consuming process. Even with simplifying assumptions, its application is limited to very small systems at present [32]. The next plausible level of abstraction is to assume a phenomenological form for the potential energy; with this assumption we obtain the classical molecular dynamics (MD) system that can be used for modeling ion permeation. MD simulations are carried out using pairwise interaction potentials between the chemical species (ions, water molecules, and protein atoms), and their trajectories are derived using Newton’s equations of motion [32]. It is possible to simulate the permeation of ions through the ion channel using this method; however, the time horizon for practical ion channel simulations are approximately at 0.1 μs [32]. To compare the theoretically obtained results to experimental results, for example voltage-current relationships (i.e. conductance), requires a simulation time of about $10 – 100 \mu s$.

A common continuum approach for modeling ion permeation is the PNP theory [9, 22, 24, 33, 50, 53, 72], presented in Sec. 3.1.1. Recall, the PNP theory neglects the ion-ion particle interactions, nonelectrostatic effects between ions. A further weakness of the PNP theory for modeling ion permeation is no formulation of the dielectric boundary effects yet exists [87]. It is well known that the PNP theory is not accurate for narrow ion channels such as gramicidin A where the discrete ion effects can not be neglected [32, 48].

The numerical solution of the many-body Schrödinger equation leads to prohibitive computational cost limiting the number of atoms and time horizon over which a solution can be obtained; and knowledge that the mean-field approximation necessary for the PNP theory to be applicable breaks down when applied
to modeling narrow ion channels, an algorithm between the quantum description and continuum scale is necessary. A strategy to accommodate these modeling issues is to adopt a two-tiered approach utilizing molecular dynamics and a higher-level simulation methodology such as Brownian or Lagrangian dynamics. MD is used to obtain various parameters of the system, then these parameters are fed into the high-level simulation allowing the model to obtain sufficient accuracy, and the capability of achieving sufficient time-horizons for experimental data comparison.

This method has been used by a number of groups to model ion permeation. In [18, 75], the combination of MD and Markovian state-transition properties is combined to model cardiac action potentials. The combination of MD and random walks have also been used to model ion channels [5, 70]. Methods incorporating PNP theory with potential-mean-field approximations are active areas of research [2, 21, 49, 66]. Other methods to model ion permeation include: velocity autocorrelation function, second fluctuation dissipation theorem, mean square displacement, and generalized Langevin equation for a harmonic oscillator [50].

A novel method introduced in [17] models the ion permeation using a non-Markovian generalized Langevin dynamics model in combination with MD, denoted as "distributional MD". Krishnamurthy et al. show that the distributional MD method provides current-voltage characteristics of the gramicidin ion channel that sample from the same distributions as does the MD [17]. An overview of the distributional MD theory is presented below; for experimental analysis of this method, the reader is referred to [17].

4.1.1. Distributional Molecular Dynamics Method

In this subsection we showcase a method derived in [17] to compute the distribution of ion trajectories implicitly in a MD simulation. The main idea of the method is a two-tiered approach: MD is used to measure various properties of the system, and the results are fed into a higher-level system which is able to extend the simulation time horizon beyond what is currently practical for a MD simulation alone. There are three steps to the modeling procedure. First, a stochastic physical model such as the generalized Langevin equation is assumed for the system. The second step involves using MD simulations to estimate parameters that govern the evolution of the system. The last step involves numerically solving a stochastic dynamics equation using the estimated parameters. Here we provide the basis of the stochastic physical model. Interested readers are referred to [17] for the algorithms used to compute the MD simulation.

4.1.2. Stochastic Physical Model used in Distributional Molecular Dynamics Method

There are two variables of interest that must be considered to construct the physical model of the distributional MD method. The first is the "system" variables of interest, and the "bath" variables. The first assumption is that the evolution of the system variables (i.e. position and momentum) can be described using the generalized Langevin equation consisting of Newton's laws of motion, a frictional force term, and a random force term which is related to the frictional force through a fluctuation-dissipation theorem [17]. The nonlinear Langevin equation used to describe the motion of the particles is given by:

\[ \partial_t \mathbf{q}(t) = m^{-1} \mathbf{p}(t) \]

\[ \partial_t \mathbf{p}(t) = F_D(\mathbf{q}(t)) - \int_0^t K(t') \mathbf{p}(t - t') dt' + F_R(t), \]  

(27)

where \( m \) is the system mass tensor, \( \mathbf{p} = [p_1, p_2, \ldots, p_N] \) with \( p_i \) being the momentum of particle \( i \), \( \mathbf{q} = [q_1, q_2, \ldots, q_N] \) with \( q_i \) being the position of particle \( i \), \( F_D(\mathbf{q}(t)) \) corresponds to a deterministic force term, \( F_R(t) \) is a random force term, and \( K(t) \) is a friction kernel intrinsic to the system.

To compute \( F_D(\mathbf{q}(t)) \), it is useful to define the potential-mean-force as the potential whose gradient \( F_{PMF} \) is the equilibrium average of the force exerted on the system by the system and bath particles. \( F_D(\mathbf{q}(t)) \) is then the combination of the force exerted by system particles and \( F_{PMF} \). The value of \( K(t) \) is obtained by relating \( K(t) \) to the momentum auto-correlation function \( C(t) = \langle \mathbf{p}(t) \mathbf{p}(0) \rangle \) and making the assumption that \( F_D(\mathbf{q}(t)) \) can be approximated by a harmonic potential \( U(\mathbf{q}) = k(\mathbf{q} - \mathbf{q}_0)^2/2 \) [17]. Using these
assumptions, we obtain the following relation between $K(t)$ and $C(t)$:

$$\partial_t C = - \int_0^t (K(t - t') + \frac{k_B}{m}) C(t') dt'.$$

(28)

A further assumption made for the system is that the fluctuation-dissipation theorem given by:

$$< F_R(0) F_R^T(t) > = k_B T K(t)m$$

(29)

with $k_B$ being Boltzmann's constant and $T$ the temperature, holds. The random force $F_R(t)$ is assumed to be a Gaussian random process. The validity of this assumption is empirically verified in [17] using MD simulations with the Kolmogorov-Smirnov and Andersen-Darling tests.

The generalized Langevin equation (27) describing ion permeation can now be fully characterized by computing $C(t)$ from MD simulation and then using (28) to compute $K(t)$ with the assumption that (29) holds. As Krishnamurthy et al. shows, the macro-level conductance computed from the distributional MD simulation is in excellent agreement with the experimental conductance for the gA channel [17].

4.2. Gramicidin Channel Association/Dissociation Dynamics

Molecular reaction dynamics (MRD) studies chemical reactions at the molecular level [34]. Examples of molecular reaction dynamics include the study of atomic level events such as the coupling of antibody and analyte or the dissociation of the gA monomers in the ICS biosensor presented in Sec. 2. As MRD develops, ever more sophisticated chemical processes are understood at the atomic scale allowing the understanding of molecular level reactions and also allowing macro-scale reaction rates of processes to be computed from a first principles approach. This subsection presents a theoretical framework to estimate how gA dimer, shown in Fig. 15, dissociation takes place in the ICS biosensor at the atomic scale.

Previous experimental studies of the gating characteristics of the gA dimer show that the dissociation/association rate is dependent on voltage, ion occupancy, and hydrocarbon thickness of the membrane [14, 65, 69]. Recently, experimental studies have indicated that the gA dimer can exist in multiple conformational states [19, 44]. Few theoretical studies have been reported in the literature on the study of the dissociation/association characteristics of the gA dimer [51, 52, 82]. The modeling techniques used in [51, 52] are obtained using Monte Carlo methodologies; however, this method fails to capture important dynamics during the dissociation process of the gA dimer. Wanasundara et al. combine the robust MD formulation with umbrella sampling to capture the dynamic behavior of the dissociation process and the obtained dissociation dynamics predicted using MD and umbrella sampling are in good agreement with the experimental measurements [82]. Consider that the dissociation even of the gA dimer is related to the chemical reaction rate of dimer dissociation which is required for the continuum model of the ICS biosensor, denoted as $f_0$ in (3). Below we present the snapshots of the atomic dissociation event for the gA dimer.

4.2.1. Molecular Dynamics and Umbrella Sampling for gA Dimer Dissociation Dynamics

Consider the membrane structure shown in Fig. 3. Define $R_{lat}$ as the lateral distance between the center of mass, average position of all the atoms weighted relative to the mass of each atom, of each gA monomer. Wanasundara et al. found, using a combination of MD and umbrella sampling, that the dissociation event occurs via a lateral displacement of the gA monomers followed by tilting of monomers with respect to the lipid bilayer normal [82]. Graphically this dissociation event is shown in Fig. 17. The entire dissociation event occurs over a few milliseconds and requires approximately equal amounts of energy to break 6 intermolecular hydrogen bonds, as expected [82].

If we compare the dissociation event in Fig. 17 with the ICS biosensor synthetic membrane in Fig. 3, we immediately see how the dissociation event takes place when the antibody tethered to the mobile gA monomer is attracted to the analyte. Therefore, this method not only provides us with a method to compute the macro-chemical reaction rate of the dissociation of the gA dimer, but also provides significant insight into the atomic level mechanics that take place when dissociation occurs. As seen in Fig. 17, the mobile gA monomers can be viewed as nanomachines as they travel along the lipid membrane of the ICS biosensor.
5. Conclusions

Biosensor research is focused on the development of smaller, cost-effective, faster, and more efficient devices that successfully integrate bioelectronic systems. Many of these goals have been achieved with the development of the ion channel switch (ICS) biosensor and the cation selective (CS) sensor. These achievements have been supported by mathematical methodologies outlined in this paper for a class of biosensors utilizing bioengineered ion channels contained within a lipid membrane. The modeling of the ICS biosensor and CS sensor are presented in Sec. 2, and Sec. 3.

The mathematical modeling of the ICS biosensor requires the solution of a reaction-diffusion partial differential equation with Neumann and Dirichlet boundary conditions coupled with a set of nonlinear ordinary differential equations, as shown in Sec. 2.3, and Sec. 2.4. Modeling has proven by experimental analysis that the ICS biosensor is capable of performing femto-molar chemical species detection.

The CS sensor is geared towards disease diagnosis by analysis of the concentration dynamics of ions released from biological cells. In Sec. 3.1, an equivalent circuit model was presented to give insight into the operation of the sensor. A continuum dynamics model known as the Poisson-Nernst-Planck (PNP) theory, consisting of nonlinear partial differential equations was used to model the transport of ions in the cellular suspension to the sensor surface. Both Neumann and Dirichlet boundary conditions were used to compute the solution of the PNP equations, as shown in Sec. 3.2. A standing assumption with the PNP theory was that the bioelectronic interface was assumed to cause negligible effects on the measured electronic signals from the sensor. If this assumption does not hold, then a grid-based differential time-domain numerical modeling method based on the PNP theory was presented in Sec. 3.4 to account for these effects.

A methodology for estimating the parameters used in the continuum approximations is proposed based on atomic level simulations. Sec. 4 presented molecular dynamics models coupled with stochastic dynamic methods to estimate macro-parameters such as conductance and an estimation of the dissociation dynamics of the gramicidin A channel (used in the ICS and CS biosensors).

A major motivation for biosensors is the construction of low-cost, rapid point-of-care detection devices. Novel engineered ion channel sensors such as the ICS biosensor and CS sensor provide an attractive device that fits these requirements. As our knowledge of atomic level processes progress, the design of ever more effective sensors will result.

References


