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Identification of Cl(Ca) channel distributions in olfactory cilia

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SUMMARY

Identification of detailed features of neuronal systems is an important challenge in the biosciences today. Transduction of an odor into an electrical signal occurs in the membranes of the cilia. The Cl(Ca) channels that reside in the ciliary membrane are activated by calcium, allow a depolarizing efflux of Cl^- and are thought to amplify the electrical signal to the brain.

In this paper, a mathematical model consisting of partial differential equations is developed to study two different experiments; one involving the interaction of the cyclic-nucleotide-gated (CNG) and Cl(Ca) channels and the other, the diffusion of Ca^{2+} into cilia. This work builds on an earlier study (Mathematical modeling of the Cl(Ca) ion channels in frog olfactory cilia. *Ph.D. Thesis*, University of Cincinnati, Cincinnati, OH, 2006; *Math. Comput. Modelling* 2006; **43**:945–956; *Biophys. J.* 2006; **91**:179–188), which suggested that the CNG channels are clustered at about 0.28 of the length of a cilium from its open end. Closed-form solutions are derived after certain reductions in the model are made. These special solutions provide estimates of the channel distributions. Scientific computation is also used. This preliminary study suggests that the Cl(Ca) ion channels are also clustered at about one-third of the length of a cilium from its open end. Copyright © 2008 John Wiley & Sons, Ltd.

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1. INTRODUCTION

We model the behavior of cytoplasmic calcium, buffer and membrane potential in an olfactory cilium during experiments that involve the Cl(Ca) and cyclic-nucleotide-gated (CNG) channel types. The primary goal of this work is to elicit information on the distribution of the Cl(Ca) ion channels.

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The techniques for the experimental procedure have been developed by S. J. Kleene (see references in [1]). One olfactory cilium of a receptor neuron is drawn into an open-ended recording pipette. The mouth of the pipette becomes attached to the base of the cilium. Then the pipette with the cilium inside is excised from the rest of the neuron. The base of the cilium remains attached to the open end of the pipette with the full length of the cilium inside the pipette.

We model two distinct experimental protocols, referred to as the diffusion experiment and the interaction experiment. In order to control the concentration of calcium in the cilium, a buffered calcium solution is used with BAPTA in both the experiments. In the diffusion experiment, buffered calcium is allowed to diffuse into the cilium from the bath surrounding the pipette. As the mixture enters the cilium, some of the calcium molecules bind to Cl(Ca) channels. This allows the channels to open and initiate a transmembrane Cl^- current that is measured with electrodes placed inside and outside the pipette. The inside of the cilium is held at $-50\,\mathrm{mV}$, causing Cl^- ions to flow from the inside of the cilium to the outside. cAMP is eliminated from all of the solutions and so is unavailable to gate the CNG channels, which are also known to exist in these cilia. Li^+ is used in the place of Na^+ to disable, at least in part, the Na^+/Ca^{2+} exchanger.

In the interaction experiment, the cilium is immersed in a bath containing $100\,\mu\mathrm{M}$ cAMP. Initially, the membrane potential is held at 0 mV while the cAMP solution diffuses into the cilium and opens the CNG channels. Because the reversal potential is 0 mV, there is no current at this stage. Following this, the membrane potential is rapidly changed to -40, -60 and $-80\,\mathrm{mV}$. Two phases of current follow this voltage step. First, there is an instantaneous current carried by Na^+ and Ca^{2+} through the open CNG channels. (The increase in cytoplasmic Ca^{2+} is also expected to activate a current through the electrogenic Na^+/Ca^{2+} exchanger.) As Ca^+ accumulates, it becomes sufficiently concentrated to activate the Cl(Ca) channels and a secondary Cl^- current gradually appears.

In this paper we will develop mathematical models for the diffusion and interaction experiments, form reduced models from which we can derive approximate closed-form solutions and solve the original equation system numerically using a finite difference method. We note the following related studies of olfactory cilia: [2–4].

We now outline the rest of this paper. In Section 2 we introduce our mathematical model and simplify it using the rapid buffer approximation (RBA). In Section 3 we form a reduced model; the payoff for this is closed-form approximate solutions. In Section 4 we return to the full model and provide several finite difference Crank–Nicolson computational solutions. There is also a short discussion section and an Appendix with values for the final constants.

2. MATHEMATICAL MODEL

Our model consists of equations for the membrane potential $v=v(x,t)$ and calcium concentration $c=c(x,t)$, where $0<x<L$. The point where $x=0$ is the open end of the cilium and $x=L$ corresponds to the closed end. We assume that time t is in the range of several seconds.

The membrane potential satisfies

$$\frac{1}{r_a}\frac{\partial^2 v}{\partial x^2}=-J_T \tag{1}$$

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where r_a is ciliary intracellular resistance and J_T is the total of the transmembrane currents; for the diffusion experiments

$$J_T = J_{Cl} \tag{2}$$

and for the interaction experiments

$$J_T = J_{CNG} + J_{Cl} + J_X \tag{3}$$

where J_{CNG} and J_{Cl} are transmembrane current flows through CNG and Cl(Ca) channels and J_X is current through the Na^+/Ca^{2+} exchangers. We have assumed that the capacitance term is negligible as well as the background conductance (leak current). Physically, the calcium current is given by

$$J_{CNG}(x,t) = g_{CNG} P_{max} \rho_{CNG}(x) v(x,t)$$

where g_{CNG} is the single CNG channel conductance and the membrane potential $v(x,t)$ is the driving force for calcium given that the equilibrium potential for calcium is 0 mV. P_{max}, maximum open probability of CNG channels, is used because [cAMP] is always saturating everywhere and the CNG channel distribution, $\rho_{CNG}(x)$ is taken to be clustered in a small region [5]. The chloride current is given by

$$J_{Cl}(x,t) = g_{Cl} \rho_{Cl}(x) F(c(x,t)) v(x,t)$$

where g_{Cl} is the single Cl(Ca) channel conductance. The Hill function

$$F(c) = \frac{c^2}{c^2 + K_{1/2}^2} \tag{4}$$

represents Ca^{2+} molecules binding and activating the Cl(Ca) channels. We propose the existence of a Na^+/Ca^{2+} exchanger that is in the same cluster as the CNG channels and has the following simplified current:

$$J_X = g_X \rho_X v(x,t)$$

where g_X is the exchanger conductance and ρ_X is the exchanger distribution that will be assumed to be localized near the CNG channels. To complete the description of the membrane potential problem we append the boundary conditions (BCs) below:

$$v(0,\cdot) = v_{Bulk} \quad \text{and} \quad \frac{\partial v}{\partial x}(L,\cdot) = 0 \tag{5}$$

where v_{Bulk} is the voltage at which the membrane potential is clamped at the open end.

The behavior of the cytoplasmic calcium and buffer complex $b(x,t) = [Ca\,B]$ can be modeled by the following initial/boundary value problems (see [6]):

$$\frac{\partial c}{\partial t} = D_{Ca} \frac{\partial^2 c}{\partial x^2} + (k_- b - k_+ c(B_T - b)) - F_{Ca} - \alpha \frac{\partial S}{\partial t} \tag{6}$$

$$\frac{\partial b}{\partial t} = D_B \frac{\partial^2 b}{\partial x^2} - (k_- b - k_+ c(B_T - b)) \tag{7}$$

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where F_{Ca} is the transmembrane calcium flow. For the diffusion experiments

$$F_{\mathrm{Ca}} = 0 \tag{8}$$

and for the interaction experiment

$$F_{\mathrm{Ca}} = q(f_{\mathrm{CNG}} J_{\mathrm{CNG}} + J_X) \tag{9}$$

where f_{CNG} reflects the fraction of the CNG current carried by Ca^{2+} and $q = (2FA)^{-1}$ is the factor that converts the local current into a flux of Ca^{2+}. (F is the Faraday constant and A is the cross-sectional area of the cilium.) We neglect any of the Ca^{2+} pumps as no ATP is supplied. B_T is the total concentration of buffer (complex plus free buffer) and

$$S(x,t) = B_S \rho_{\mathrm{Cl}}(x) F(c(x,t))$$

is the number of bound Ca^{2+} ions (to the Cl(Ca) ion channels) and B_S (molecules/channel) is the number of binding sites. We neglect any reactions with calmodulin; there is no evidence in our experimental current traces of a strong current decay that would be due to calcium–calmodulin feedback.

Assuming that the RBA is appropriate (buffer reaction is faster than the other processes involving calcium) we set $K = k_-/k_+$ then combine (6) and (7) to obtain (see [6])

$$\frac{\partial c}{\partial t} = \frac{1}{1+\theta}\left[\frac{\partial^2}{\partial x^2}\left(D_{\mathrm{Ca}} c + D_B B_T \frac{c}{K+c}\right) - F_{\mathrm{Ca}} - \alpha B_S \rho_{\mathrm{Cl}} F'(c)\frac{\partial c}{\partial t}\right] \tag{10}$$

where

$$b = \frac{B_T c}{K+c} \quad \text{and} \quad \theta = \frac{B_T K}{(K+c)^2}$$

The model for the evolution of calcium is complete after adding the BCs

$$c(0,\cdot) = c_{\mathrm{Bulk}} \quad \text{and} \quad \frac{\partial c}{\partial x}(L,\cdot) = 0 \tag{11}$$

and the initial condition (IC)

$$c(\cdot,0) = 0 \tag{12}$$

We have represented the fact that there is a free calcium concentration c_{Bulk} outside of the pipette (at the open end of the cilium) and initially the concentration inside is so small that we take it to be zero. We are especially interested in the behavior of the current,

$$I(t) = \int_0^L J_T(x,t)\,\mathrm{d}x$$

which is experimentally measurable.

Continuing to follow [6] we can reformulate our model by defining

$$w = \phi^{-1}(c) := D_{\mathrm{Ca}} c + D_B B_T \frac{c}{K+c}$$

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where ϕ^{-1} is a one-to-one function that we can invert by solving an intermediate quadratic equation in c to obtain

$$c=\frac{-(D_{\mathrm{Ca}}K-w+D_B B_T)+\sqrt{(D_{\mathrm{Ca}}K-w+D_B B_T)^2+4D_{\mathrm{Ca}}Kw}}{2D_{\mathrm{Ca}}}$$

As

$$\frac{\partial w}{\partial t}=\left(\frac{\mathrm{d}}{\mathrm{d}c}\phi^{-1}(c)\right)\frac{\partial c}{\partial t}=(D_{\mathrm{Ca}}+D_B\theta)\frac{\partial c}{\partial t}$$

we have

$$\frac{\partial w}{\partial t}=\frac{D_{\mathrm{Ca}}+D_B\theta}{1+\theta}\left[\frac{\partial^2 w}{\partial x^2}-F_{\mathrm{Ca}}(\phi(w),v)-\alpha B_S\rho_{\mathrm{Cl}}F'(\phi(w))\frac{\partial c}{\partial t}\right]$$

or

$$\frac{\partial w}{\partial t}=\frac{D_{\mathrm{Ca}}+D_B\theta}{1+\theta+\alpha B_S\rho_{\mathrm{Cl}}F'(\phi(w))}\left[\frac{\partial^2 w}{\partial x^2}-F_{\mathrm{Ca}}(\phi(w),v)\right] \tag{13}$$

Again we append BCs:

$$w(0,\cdot)=\phi^{-1}(c_{\mathrm{Bulk}})\quad\text{and}\quad\frac{\partial w}{\partial x}(L,\cdot)=0 \tag{14}$$

and IC

$$w(\cdot,0)=0 \tag{15}$$

3. ANALYTICAL SOLUTION

In this section we consider a reduced model. We are then able to construct approximate closed-form solutions to both the diffusion and interaction inverse problems. Among the simplifications, we neglect the binding of the cytoplasmic calcium to the Cl(Ca) ion channels, replace the Hill function in (4) for the Cl(Ca) activation by a Heaviside function and take $\rho_{\mathrm{CNG}}=T_{\mathrm{CNG}}\delta(\cdot-x_{\mathrm{CNG}})$, $\rho_{\mathrm{Cl}}=T_{\mathrm{Cl}}\delta(\cdot-x_{\mathrm{Cl}})$ and $\rho_X=T_X\delta(\cdot-x_{\mathrm{CNG}})$, where T_{CNG}, T_{Cl} and T_X are the total number of the CNG, Cl(Ca) channels and the Na^+/Ca^{2+} exchangers, respectively, and x_{CNG} and x_{Cl} are cluster points. Our computations in Section 4 indicate that our solutions do provide plausible answers to the inverse problems. For simplicity, we take $D_{\mathrm{Ca}}=D_B=D$. In addition, we assume that c takes on moderate values during the diffusion process before the Cl(Ca) channels are triggered. Substituting these assumptions into (13) we obtain

$$\frac{\partial w}{\partial t}=D\left[\frac{\partial^2 w}{\partial x^2}-F_{\mathrm{Ca}}(\phi(w),v)\right] \tag{16}$$

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3.1. The diffusion experiment

Considering (8) in (16) our reformulation becomes the heat equation for w:

$$\frac{\partial w}{\partial t} = D\frac{\partial^2 w}{\partial x^2} \tag{17}$$

with BC (14) and IC (15). For the membrane potential, by substituting these assumptions into (1) and (2), we have

$$\frac{1}{r_a}\frac{\partial^2 v}{\partial x^2} = g_{Cl}T_{Cl}\delta(\cdot - x_{Cl})H(c - K_{1/2})v \tag{18}$$

where we also impose (5). Note that the delta function has units of 1/Length. If we neglect the right end BC for w by assuming that the cilium is long we can derive the following error-function solution:

$$w(x,t) = \phi^{-1}(c_{Bulk})\left(1 - \mathrm{erf}\left(\frac{x}{\sqrt{4Dt}}\right)\right) \quad \text{where } \mathrm{erf}(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-\xi^2}\,\mathrm{d}z$$

Note that this solution form for w is a nonincreasing function in t for each fixed x. We define t_{Cl} so that $w(x_{Cl}, t_{Cl}) = \phi^{-1}(K_{1/2})$; this is the half activation time for the Cl(Ca) ion channels.

To match the singularity induced by the delta function we require for $t > t_{Cl}$

$$\left[\frac{\partial v}{\partial x}\right](x_{Cl},t) = r_a g_{Cl}T_{Cl}v_{Cl} \quad \text{therefore, } v(x,t) = \begin{cases} v_{Bulk} - (r_a g_{Cl}T_{Cl}v_{Cl})x & \text{for } x < x_{Cl} \\ v_{Cl} & \text{for } x > x_{Cl} \end{cases}$$

where $[\partial v/\partial x]$ is the jump in $\partial v/\partial x$ and v_{Cl} is yet to be determined constant such that it makes $v(x,t)$ continuous. The global current is

$$I(t) = g_{Cl}T_{Cl}\int_0^L \delta(\cdot - x_{Cl})H(c(\cdot,t) - K_{1/2})v(\cdot,t)\,\mathrm{d}x = g_{Cl}T_{Cl}H(t - t_{Cl})v_{Cl}$$

and thus for $t > t_{Cl}$ we have $v_{Cl} = I_{Cl}/(g_{Cl}T_{Cl})$. Therefore, we have

$$v(x,t) = \begin{cases} v_{Bulk} - r_a I_{Cl}x & \text{for } x < x_{Cl} \\ I_{Cl}/(g_{Cl}T_{Cl}) & \text{for } x > x_{Cl} \end{cases} \tag{19}$$

We now estimate x_{Cl} from t_{Cl}. From our solution formulas we see that

$$\frac{\phi^{-1}(K_{1/2})}{\phi^{-1}(c_{Bulk})} = 1 - \mathrm{erf}\left(\frac{x_{Cl}}{\sqrt{4Dt_{Cl}}}\right)$$

To obtain a full closed-form approximation we note that if $z_{Cl} := x_{Cl}/\sqrt{4Dt_{Cl}} \ll 1$ then we can make the linear approximation

$$\mathrm{erf}\left(\frac{x_{Cl}}{\sqrt{4Dt_{Cl}}}\right) \cong \mathrm{erf}(0) + \mathrm{erf}'(0)z_{Cl} = \frac{2}{\sqrt{\pi}}z_{Cl}$$

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and find that

$$z_{\mathrm{Cl}} \cong \frac{\sqrt{\pi}}{2}\left(1-\frac{\phi^{-1}(K_{1/2})}{\phi^{-1}(c_{\mathrm{Bulk}})}\right)$$

Now, using the facts that $K_{1/2}/B_T \ll D_B/D_{\mathrm{Ca}}$, $K/c_{\mathrm{Bulk}} \ll 1$ and $K/K_{1/2} \ll 1$ (for justifications see the Appendix),

$$1-\frac{\phi^{-1}(K_{1/2})}{\phi^{-1}(c_{\mathrm{Bulk}})} \cong 1-\frac{D_B/D_{\mathrm{Ca}}}{c_{\mathrm{Bulk}}/B_T + D_B/D_{\mathrm{Ca}}} \cong \frac{1}{1+D_B B_T (D_{\mathrm{Ca}} c_{\mathrm{Bulk}})^{-1}}$$

Thus,

$$x_{\mathrm{Cl}} \cong \frac{\sqrt{\pi D t_{\mathrm{Cl}}}}{1+D_B B_T (D_{\mathrm{Ca}} c_{\mathrm{Bulk}})^{-1}} \tag{20}$$

Once x_{Cl} is known we can find T_{Cl} by enforcing the continuity of v at $x = x_{\mathrm{Cl}}$:

$$v_{\mathrm{Bulk}} - r_{\mathrm{a}} I_{\mathrm{Cl}} x_{\mathrm{Cl}} = \frac{I_{\mathrm{Cl}}}{g_{\mathrm{Cl}} T_{\mathrm{Cl}}} \quad \text{or} \quad T_{\mathrm{Cl}} = \frac{I_{\mathrm{Cl}}}{g_{\mathrm{Cl}}(v_{\mathrm{Bulk}} - r_{\mathrm{a}} I_{\mathrm{Cl}} x_{\mathrm{Cl}})} \tag{21}$$

3.2. The interaction experiment

In this subsection we develop and solve a reduced model for the interaction experiment. Our main assumption, inspired by Lindemann [3], is to set the exchanger to absorb the considerable influx of Ca^{2+}. Substituting (9) into (16), we obtain

$$\frac{\partial w}{\partial t} = D\left(\frac{\partial^2 w}{\partial x^2} - q(f_{\mathrm{CNG}} g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} - g_X T_X)\delta(\cdot - x_{\mathrm{CNG}})v\right) \tag{22}$$

with BC (14) and IC (15). For the membrane potential, by substituting the assumptions we made into (1) and (3), we find

$$\frac{1}{r_{\mathrm{a}}}\frac{\partial^2 v}{\partial x^2} = ((g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X)\delta(\cdot - x_{\mathrm{CNG}}) + g_{\mathrm{Cl}} T_{\mathrm{Cl}} \delta(\cdot - x_{\mathrm{Cl}}) H(c - K_{1/2}))v \tag{23}$$

with BC and IC in (5). When $t < t_{\mathrm{Cl}}$ the second term in parentheses vanishes. Then matching the singularity induced by the delta function and continuity of $v(x,t)$, we find

$$v(x,t) = \begin{cases} v_{\mathrm{Bulk}} - r_{\mathrm{a}}(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} x & \text{for } x < x_{\mathrm{CNG}} \\ v_{\mathrm{Bulk}} - r_{\mathrm{a}}(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} x_{\mathrm{CNG}} & \text{for } x \geqslant x_{\mathrm{CNG}} \end{cases}$$

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Then setting $v_{\mathrm{CNG}} = v(x_{\mathrm{CNG}}, t)$ we find

$$v_{\mathrm{CNG}} = \frac{v_{\mathrm{Bulk}}}{1 + r_{\mathrm{a}}(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) x_{\mathrm{CNG}}} \tag{24}$$

If we define

$$I_{\mathrm{CNG}} + I_X = \int_0^L (J_{\mathrm{CNG}}(x,t) + J_X(x,t))\,\mathrm{d}x = (g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) \int_0^L \delta(\cdot - x_{\mathrm{CNG}}) v(\cdot, t)\,\mathrm{d}x$$

Then

$$I_{\mathrm{CNG}} + I_X = (g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} \tag{25}$$

and thus

$$v(x,t) = \begin{cases} v_{\mathrm{Bulk}} - r_{\mathrm{a}}(I_{\mathrm{CNG}} + I_X)x & \text{for } x < x_{\mathrm{CNG}} \\ v_{\mathrm{Bulk}} - r_{\mathrm{a}}(I_{\mathrm{CNG}} + I_X)x_{\mathrm{CNG}} & \text{for } x \geqslant x_{\mathrm{CNG}} \end{cases}$$

Now when $t > t_{\mathrm{Cl}}$ the defining equation (23) has two delta functions. Our preliminary results from the diffusion experiment indicate that typically $x_{\mathrm{CNG}} < x_{\mathrm{Cl}}$ and we assume that from here on. As above we find

$$v(x,t) = \begin{cases} v_{\mathrm{bulk}} - r_{\mathrm{a}}[(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} + g_{\mathrm{Cl}} v_{\mathrm{Cl}} T_{\mathrm{Cl}}]x, & 0 < x < x_{\mathrm{CNG}} \\ v_{\mathrm{bulk}} - r_{\mathrm{a}}[(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} x_{\mathrm{CNG}} + g_{\mathrm{Cl}} T_{\mathrm{Cl}} v_{\mathrm{Cl}} x], & x_{\mathrm{CNG}} < x < x_{\mathrm{Cl}} \\ v_{\mathrm{bulk}} - r_{\mathrm{a}}[(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} x_{\mathrm{CNG}} + g_{\mathrm{Cl}} T_{\mathrm{Cl}} v_{\mathrm{Cl}} x_{\mathrm{Cl}}], & x_{\mathrm{Cl}} < x < L \end{cases}$$

then, $v_{\mathrm{Cl}} = v(x_{\mathrm{Cl}}, t)$, we find

$$v_{\mathrm{Cl}} = \frac{v_{\mathrm{Bulk}} - r_{\mathrm{a}}(g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} + g_X T_X) v_{\mathrm{CNG}} x_{\mathrm{CNG}}}{1 + r_{\mathrm{a}} g_{\mathrm{Cl}} T_{\mathrm{Cl}} x_{\mathrm{Cl}}} \tag{26}$$

and

$$v_{\mathrm{CNG}} = \frac{v_{\mathrm{Bulk}} - r_{\mathrm{a}} g_{\mathrm{Cl}} T_{\mathrm{Cl}} v_{\mathrm{Cl}} x_{\mathrm{CNG}}}{1 + r_{\mathrm{a}}(g_{\mathrm{CNG}} T_{\mathrm{CNG}} + g_X T_X) x_{\mathrm{CNG}}} \tag{27}$$

and

$$v(x,t) = \begin{cases} v_{\mathrm{bulk}} - r_{\mathrm{a}}(I_{\mathrm{CNG}} + I_X + I_{\mathrm{Cl}})x, & 0 < x < x_{\mathrm{CNG}} \\ v_{\mathrm{bulk}} - r_{\mathrm{a}}((I_{\mathrm{CNG}} + I_X)x_{\mathrm{CNG}} + I_{\mathrm{Cl}} x), & x_{\mathrm{CNG}} < x < x_{\mathrm{Cl}} \\ v_{\mathrm{bulk}} - r_{\mathrm{a}}((I_{\mathrm{CNG}} + I_X)x_{\mathrm{CNG}} + I_{\mathrm{Cl}} x_{\mathrm{Cl}}), & x_{\mathrm{Cl}} < x < L \end{cases} \tag{28}$$

where $I_{\mathrm{Cl}} = g_{\mathrm{Cl}} T_{\mathrm{Cl}} v_{\mathrm{Cl}}$.

Now, to solve for w in the concentration equation we neglect the BC (14) (here we have $c_{\mathrm{Bulk}} = 0$) and view w on the entire real line:

$$\frac{\partial w}{\partial t} = D \frac{\partial^2 w}{\partial x^2} + Q(t)\delta(\cdot - x_{\mathrm{CNG}})$$

where

$$Q(t) = -Dq(f_{\mathrm{CNG}} g_{\mathrm{CNG}} P_{\max} T_{\mathrm{CNG}} - g_X T_X) v(x_{\mathrm{CNG}}, t)$$

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Using the Fourier transform we find

$$w(x,t)=\int_0^t Q(s)\frac{\exp\left(-\dfrac{(x-x_{\mathrm{CNG}})^2}{4D(t-s)}\right)}{\sqrt{4\pi D(t-s)}}\,\mathrm{d}s$$

At $t=t_{\mathrm{Cl}}$ we have

$$c(x_{\mathrm{Cl}},t_{\mathrm{Cl}})=K_{1/2}$$

As $v(x_{\mathrm{CNG}},t)$ is constant on $0<t<t_{\mathrm{Cl}}$ we have

$$\phi^{-1}(K_{1/2})=-Dq(f_{\mathrm{CNG}}g_{\mathrm{CNG}}P_{\max}T_{\mathrm{CNG}}-g_XT_X)v_{\mathrm{CNG}}\int_0^{t_{\mathrm{Cl}}}\frac{\exp\left(-\dfrac{(x_{\mathrm{Cl}}-x_{\mathrm{CNG}})^2}{4D(t_{\mathrm{Cl}}-s)}\right)}{\sqrt{4\pi D(t_{\mathrm{Cl}}-s)}}\,\mathrm{d}s \tag{29}$$

To simplify the integral in (29) we let

$$\sigma=\frac{\Delta x}{\sqrt{4Dt_{\mathrm{Cl}}}}\quad\text{where }\Delta x=x_{\mathrm{Cl}}-x_{\mathrm{CNG}}$$

The computations in Section 4 suggest that typical values are $\Delta x=3\,\mu\mathrm{m}$ and $t_{\mathrm{Cl}}=0.7\,\mathrm{s}$; therefore, $\sigma=0.179\ll 1$. Then

$$\int_0^{t_{\mathrm{Cl}}}\frac{\exp\left(-\dfrac{(x_{\mathrm{Cl}}-x_{\mathrm{CNG}})^2}{4D(t_{\mathrm{Cl}}-s)}\right)}{\sqrt{4\pi D(t_{\mathrm{Cl}}-s)}}\,\mathrm{d}s=\sqrt{\frac{t_{\mathrm{Cl}}}{4\pi D}}\int_0^{t_{\mathrm{Cl}}}\frac{\exp\left(-\dfrac{\sigma^2}{1-s/t_{\mathrm{Cl}}}\right)}{\sqrt{1-s/t_{\mathrm{Cl}}}}\frac{\mathrm{d}s}{t_{\mathrm{Cl}}}=\sqrt{\frac{t_{\mathrm{Cl}}}{4\pi D}}\int_0^1\frac{\exp(-\sigma^2/s)}{\sqrt{s}}\,\mathrm{d}s$$

Assuming that $\sigma\ll 1$ and noting that the integrand $\to 0$ as $s\to 0$ we use

$$\exp(-\sigma^2/s)\cong 1-\sigma^2/s\quad\text{for } s>\sigma^2 \tag{30}$$

and estimate

$$\text{Integral}\cong\sqrt{\frac{t_{\mathrm{Cl}}}{4\pi D}}\int_{\sigma^2}^1(s^{-1/2}-\sigma^2s^{-3/2})\,\mathrm{d}s\cong\sqrt{\frac{t_{\mathrm{Cl}}}{\pi D}}(1-\sigma)^2$$

Figure 1 shows how the approximate and exponential integrands above compare for $\sigma=0.179$. Therefore, from (29) we now have

$$\phi^{-1}(K_{1/2})\cong -q(f_{\mathrm{CNG}}g_{\mathrm{CNG}}P_{\max}T_{\mathrm{CNG}}-g_XT_X)v_{\mathrm{CNG}}\sqrt{\frac{t_{\mathrm{Cl}}D}{\pi}}\left(1-\left(\frac{\Delta x}{\sqrt{4Dt_{\mathrm{Cl}}}}\right)^2\right) \tag{31}$$

Given data curves from Figure 3, values for v_{Bulk}, current values and Cl(Ca) open times t_{Cl}, as well as choice for $x_{\mathrm{CNG}}=0.28L$ [1, 5], we can determine estimates for T_{CNG}, x_{Cl} and T_{Cl}.

Combining (24) and (25) and setting $T_X=T_{\mathrm{CNG}}$ we can show

$$v_{\mathrm{CNG}}=v_{\mathrm{Bulk}}-r_{\mathrm{a}}x_{\mathrm{CNG}}(I_{\mathrm{CNG}}+I_X)$$

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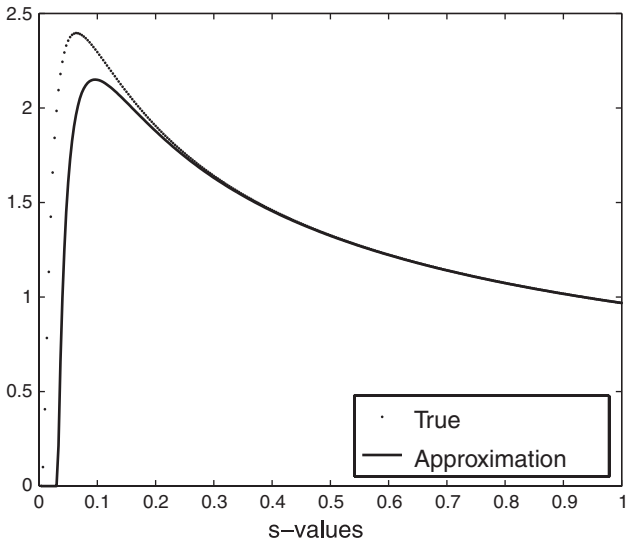

Figure 1. Comparison of true, $\exp(-\sigma^2/s)/\sqrt{s}$, and approximate, $s^{-1/2}-\sigma^2 s^{-3/2}$, integrands for $\sigma=0.179$ that lead to the simplification in (30).

and

$$T_{\mathrm{CNG}}=\frac{I_{\mathrm{CNG}}+I_X}{(1+f_{\mathrm{CNG}}f_X)g_{\mathrm{CNG}}P_{\max}v_{\mathrm{CNG}}}$$

Thus, starting with $x_{\mathrm{CNG}}.28L$ we can formulate guesses for v_{CNG} and T_{CNG}.

Now, from Equation (31) we can find Δx noting that $\phi^{-1}(K_{1/2})\cong D_B B_T$:

$$\Delta x=2\left(Dt_{\mathrm{Cl}}\left[1+\sqrt{\frac{\pi}{Dt_{\mathrm{Cl}}}}\left(\frac{D_B B_T}{q(1-f_X)f_{\mathrm{CNG}}g_{\mathrm{CNG}}P_{\max}T_{\mathrm{CNG}}v_{\mathrm{CNG}}}\right)\right]\right)^{1/2}$$

and thus $x_{\mathrm{Cl}}=x_{\mathrm{CNG}}+\Delta x$. Using the solution for v from (28) we can, in turn, determine v_{CNG}, $I_{\mathrm{CNG}}+I_X$, I_{Cl}, v_{Cl} and then $T_{\mathrm{Cl}}=I_{\mathrm{Cl}}/(g_{\mathrm{Cl}}v_{\mathrm{Cl}})$.

4. NUMERICAL AND ANALYTICAL SOLUTION PREDICTIONS

In this section we provide a sampling of finite difference Crank–Nicolson approximate solutions to (1), (5) and (13)–(15). We choose the channel and exchanger parameters in order to match the data from our lab under the assumption that the channel distributions (and exchanger distribution in the interaction experiment) are narrow Gaussian functions (4–5 μm). We also use our reduced model solutions with the data to predict the channel distributions.

In Figure 2 the results for the diffusion experiment are displayed. The channel distributions are chosen ahead of time to be narrow Gaussian distributions. We determined values for T_{Cl} and x_{Cl} by trial and error to obtain close fits to the current data. In the computation we had 100 spatial subintervals and 100 time steps.

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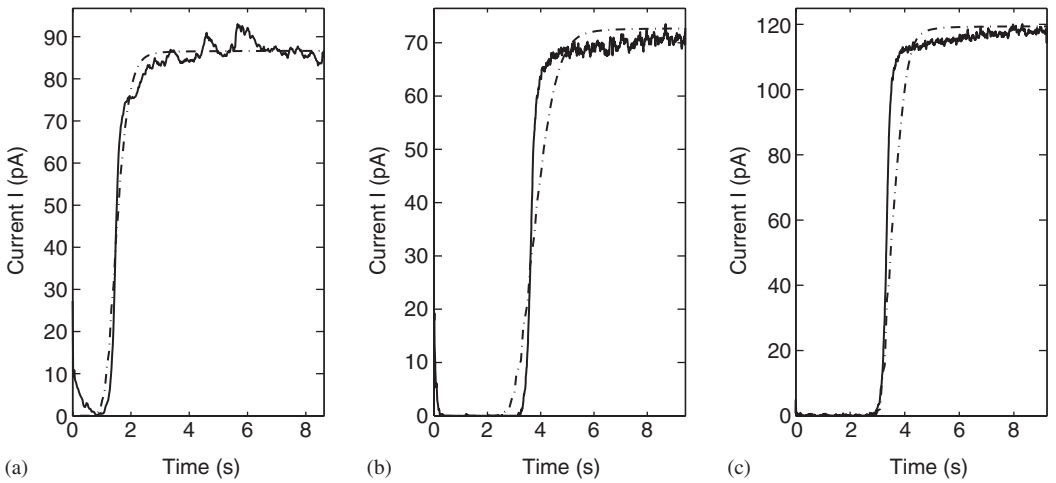

Figure 2. Plot of experimental (solid lines) and numerical (dashed lines) currents. In this and in Figure 3, currents are inward but are shown as positive for simplicity. Numerical currents are from the model with narrow (4–5 μm) Cl(Ca) ion channel Gaussian distributions and total channels T_{Cl} clustered at x_{Cl}: (a) $T_{\mathrm{Cl}}=2658$ channels clustered at $x_{\mathrm{Cl}}=7.5\,\mu\mathrm{m}$ with cilium length $L=50\,\mu\mathrm{m}$; (b) $T_{\mathrm{Cl}}=2437$ channels clustered at $x_{\mathrm{Cl}}=12.0\,\mu\mathrm{m}$ with length $L=50\,\mu\mathrm{m}$; and (c) $T_{\mathrm{Cl}}=5184$ channels clustered at $x_{\mathrm{Cl}}=12.0\,\mu\mathrm{m}$ with length $L=40\,\mu\mathrm{m}$.

Table I. Preliminary experimental data and predictions from the reduced model for the diffusion experiment.

Figure	t_{Cl}	I_{Cl}	x_{Cl}	T_{Cl}
2(a)	1.7	83	10.4	2803
2(b)	3.4	75	14.7	2802
2(c)	3.4	110	14.7	5342

Table I has values for the time of the onset of the Cl(Ca) current (t_{Cl}) and maximum current level (I_{Cl}), which were estimated from the experimental data above (Figures 2(a)–(c)). The table also has predictions for the Cl(Ca) channel distribution (x_{Cl} and T_{Cl}) from Equations (20) and (21).

The predictions made in Table I by the reduced model for x_{Cl} and T_{Cl} are plausible and close to those found by trial and error in the computations displayed in Figure 2.

In Figure 3 our computational results for the interaction experiments are displayed on a cilium of length 50 μm. In these examples we took $T_X=T_{\mathrm{CNG}}$ and $x_{\mathrm{CNG}}=0.28$, $L=14\,\mu\mathrm{m}$. Again, we chose values for the parameters (T_{CNG}, x_{Cl} and T_{Cl}) by trial and error. Here we had 200 spatial intervals and the same number of time steps.

In Table II we again set $x_{\mathrm{CNG}}=14\,\mu\mathrm{m}$ for data from [7], which is displayed in Figure 3. Here, we estimated, from Figure 3, the CNG and X currents (I_{CNG} and I_X) before the Cl(Ca) channel amplification, the onset time of the Cl(Ca) current (t_{Cl}) and the current level from both channel types and the exchanger ($I_{\mathrm{CNG}}+I_X+I_{\mathrm{Cl}}$). Then we used the procedure outlined in Section 4 to estimate T_{CNG}, x_{Cl} and T_{Cl} as displayed in Table II for the three different data sets. We note that

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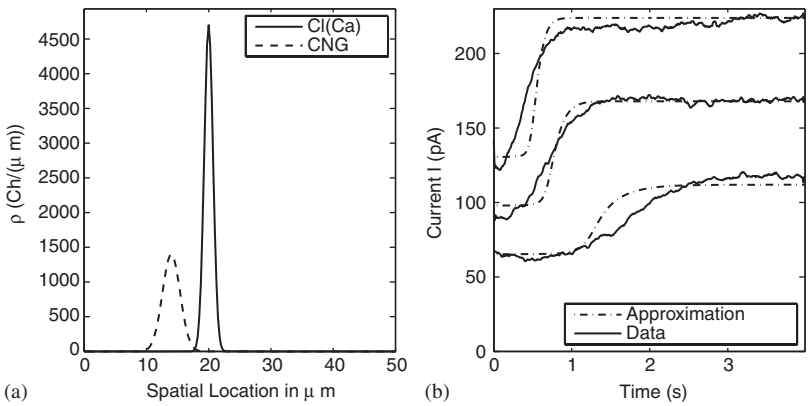

Figure 3. Experimental [7] and computational data for the interaction experiment: (a) CNG and Cl(Ca) channel distributions and (b) Current curves at each of the three clamped membrane potentials with $v_{\text{Bulk}} = -40\,\text{mV}$ (bottom), $-60\,\text{mV}$ (middle) and $-80\,\text{mV}$ (top). Here we had $x_{\text{CNG}} = 14\,\mu\text{m}$, $T_{\text{CNG}} = 4963$, $x_{\text{Cl}} = 20\,\mu\text{m}$ and $T_{\text{Cl}} = 8331$.

Table II. Preliminary experimental data and predictions from the reduced model for the interaction experiment.

v_{Bulk} (mV)	$I_{\text{CNG}} + I_X$ $(t \leqslant t_{\text{Cl}})$ (pA)	t_{Cl} (s)	$I_{\text{CNG}} + I_X + I_{\text{Cl}}$ $(t > t_{\text{Cl}})$ (pA)	T_{CNG} (ch)	x_{Cl} (μm)	T_{Cl} (ch)
−40	−65	1.0	−115	5078	20	9204
−60	−95	0.4	−170	4883	18	8481
−80	−125	0.30	−220	4787	18	7224

the results in the T_{CNG}, x_{Cl} and T_{Cl} columns are plausibly close to those found by trial and error in Figure 3.

5. DISCUSSION

In this paper we have formed mathematical models for two related experiments involving the diffusion of buffered calcium in an olfactory cilium, the *diffusion* and *interaction* experiments. Because of the two current transitions in the interaction experiment it is sometimes referred to as the biphasic experiment. Because of the huge influx of current in the interaction experiment through the CNG channels we, following Lindemann [3], introduce a simple model for an exchanger and position it with the CNG channel cluster.

We focus on the inverse problems of computing the Cl(Ca) ion channel cluster from the current versus time data, which provides an extra BC to our evolution problems.

We analyze our models in two different ways. In the first we make several significant reductions. The payoffs for our simplifications are approximate closed-form solutions from which we can make predictions on the solutions to the inverse problems. An advantage of the formula is that the parameter dependencies are known explicitly. Sensitivities could then be estimated directly.

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We also solve the full problems numerically after making guesses on the channel cluster positions. Predictions for the reduced models based on given experimental data are provided in Tables I and II. The computational results (and data traces) are provided in Figures 2 and 3. The channel cluster distributions are estimated using trial and error in the computations. We found that our reduced model predictions compare favorably with those obtained numerically.

The diffusion problem is well defined as all parameters have been estimated experimentally. We intend to use this model with an inverse solver to produce a thorough study of the Cl(Ca) ion channel distribution.

The interaction model is not as well defined as little definitive is known about the exchanger. We note that adjustment of the exchanger parameters can change the outcomes of our analysis.

APPENDIX

Below we list the parameters and their definitions.

L	length of cilium. $40\,\mu\text{m} \leqslant L \leqslant 50\,\mu\text{m}$
r_c	ciliary radius. $0.15\,\mu\text{m}$
R_i	ciliary intracellular resistivity. $9.2\times10^5\,\mu\text{m/S}$
r_a	ciliary intracellular resistance. $r_a = R_i/\pi r_c^2 = 1.5\times10^{-2}/\text{nS}\,\mu\text{m}$
g_{CNG}	single CNG channel conductance. $5.0\times10^{-4}\,\text{nS/ch}$
g_{Cl}	single Cl(Ca) channel conductance. $8.0\times10^{-4}\,\text{nS/ch}$
$K_{1/2}$	half maximum concentration of Ca^{2+} to activate Cl(Ca) channels. $4.8\,\mu\text{M}$
P_{max}	maximum open probability of CNG channels. 0.7 no units
D_{Ca}	Ca^{2+}diffusion coefficient. 300 $(\mu\text{m})^2/\text{s}$ [1]
D_B	BAPTA diffusion coefficient. 95 $(\mu\text{m})^2/\text{s}$ [8]
D	approximated diffusion coefficient. 100 $(\mu\text{m})^2/\text{s}$
k_+	forward reaction rate constant. $600/\mu\text{M s}$ [8]
k_-	backward reaction rate constant. $100\,\text{s}^{-1}$ [8]
B_T	total concentration of BAPTA (complex plus free). $2000\,\mu\text{M}$
q	converting factor of transmembrane current. $q=(2\pi F r_c^2)^{-1}=8.45\times10^4\,\mu\text{M}\,\mu\text{m/pA s}$ [9]
α	conversion factor for binding. $2.7\times10^{-2}\,\mu\text{M}\,\mu\text{m/molecule}$
B_S	number of binding sites. 1 molecule/ch
f_{CNG}	fraction of the CNG current carried by Ca^{2+}. 0.4 no units [10]
f_X	computational parameter. 0.97 no units
g_X	single Na^+/Ca^{2+} exchanger conductance. $g_X = f_X f_{CNG} g_{CNG} P_{max} = 1.3\times10^{-4}\,\text{nS/ch}$
K	reaction dissociation constant. $K = k_-/k_+ = \frac{1}{6}\,\mu\text{M}$
T_{CNG}	total number of CNG channels. Units ch
T_{Cl}	total number of Cl(Ca) channels. Units ch
T_X	total number of Na^+/Ca^{2+} exchangers. Units ch
c_{Bulk}	free calcium concentration at the exposed end of the cilium. $c_{Bulk}=300\,\mu\text{M}$ for the diffusion experiment and for the interaction experiment $c_{Bulk}=0\,\mu\text{M}$
v_{Bulk}	voltage clamp. $v_{Bulk}=-50\,\text{mV}$ for the diffusion experiment and for the interaction experiment $v_{Bulk}=-40, -60$ and $-80\,\text{mV}$

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