Integral equation models for the inverse problem of biological ion channel distributions

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Abstract. Olfactory cilia are thin hair-like filaments that extend from olfactory receptor neurons into the nasal mucus. Transduction of an odor into an electrical signal is accomplished by a depolarizing influx of ions through cyclic-nucleotide-gated channels in the membrane that forms the lateral surface of the cilium. In an experimental procedure developed by S. Kleene, a cilium is detached at its base and drawn into a recording pipette. The cilium base is then immersed in a bath of a channel activating agent (cAMP) which is allowed to diffuse into the cilium interior, opening channels as it goes and initiating a transmembrane current. The total current is recorded as a function of time and serves as data for a nonlinear integral equation of the first kind modeling the spatial distribution of ion channels along the length of the cilium. We discuss some linear Fredholm integral equations that result from simplifications of this model. A numerical procedure is proposed for a class of integral equations suggested by this simplified model and numerical results using simulated and laboratory data are presented.

1. Introduction

In [4] a nonlinear integral equation model is developed for determining the spatial distribution of ion channels along the length of frog olfactory cilia. The essential nonlinearity in the model arises from the binding of the channel activating ligand to the cyclic-nucleotide-gated ion channels as the ligand diffuses along the length of the cilium. In this paper we investigate a linear model of this process in which the binding mechanism is neglected, leading to a particular type of linear Fredholm integral equation of the first kind with a “diffusive” kernel. The linear mathematical model consists of finding \(\rho = \rho(x)\) such that

\[
I(t) = \int_0^L \rho(x) F(c(x,t)) \, dx
\]

and

\[
\rho \geq 0
\]

where \(c\) is the solution of the initial/boundary value problem

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}, \quad x \in [0, L], \quad t \in [0, T]
\]
with boundary conditions (BCs)

\[ c(0, \cdot) = c_{Bulk} \quad \text{and} \quad \frac{\partial c}{\partial x}(L, \cdot) = 0 \]  

and initial condition

\[ c(\cdot, 0) = 0. \]  

Here

\[ F(c) = \frac{c^n(x, t)}{c^n(x, t) + K_{1/2}^{n}} \]

is a “Hill” function with positive constants \( K_{1/2} \) and \( n \), where \( K_{1/2} \) is the half-bulk concentration and \( n \) is an experimentally determined parameter. The function \( \rho \) is an unknown ion channel density function (channels/length), \( c \) is the concentration of a channel activating ligand that is diffusing from left-to-right in a thin cylinder (the interior of the cilium) of length \( L \) with diffusivity constant \( D \) (length\(^2\)/time), \( I(t) \) is a given total transmembrane current, the constant \( J_0 \) has units of current/length, and \( c_{Bulk} \) is the maintained concentration at the open end of the cylinder (while \( x = L \) is considered the closed end).

This problem arises in models of diffusion in tiny tubular biological structures such as rod photoreceptor cells [6] or frog olfactory cilia (see [1], [4], or [5]). In physical experiments a ligand (cGMP for the rods; cAMP for the cilia), which is held at constant concentration \( c_{Bulk} \) at the open end, diffuses into the rod or cilia and binds to ion channels (CNG for cilia) opening the channels and thereby allowing an ionic influx which initiates a local transmembrane current. The model (1)-(5) does not include terms modeling the binding or changes in membrane potential. However, if the quantity of ion channels is small these effects will be negligible.

Frog olfactory cilia have diameters of about 0.28\( \mu \)m and length around 40\( \mu \)m and are connected to the knobs at the ends of the dendrites of the olfactory receptor neurons. The Hill function in the experiments modeled here typically has exponent \( n = 1.7 \) and half-concentration \( K_{1/2} = 1.7 \mu M \). Here \( J_0 = g_{CNG}Pv_{Bulk} = 0.232 \) pA/channel \((g_{CNG} = 8.3 \) pS/Channel, \( P = 0.70 \) is the maximal open probability, and \( v_{Bulk} = -40 \) mV is the membrane potential).

Further motivation for this study comes from the emerging belief that cilia are far more prevalent than previously realized (see [7]).

2. Analytical Solution

In this section we derive an analytical solution of a simplified version of problem (1)-(5).

To that end we assume:

(i) The influence of the no-flux boundary condition for \( c \) at the closed end is negligible (or equivalently that the cilium is very long).

Neglecting the boundary condition at the closed end the diffusion equation has the closed form solution

\[ c(x, t) = c_{Bulk} \text{erfc}(x/(2\sqrt{Dt})) \]

where \text{erfc} is the complementary error function

\[ \text{erfc}(z) = 1 - \frac{2}{\sqrt{\pi}} \int_0^z \exp(-\tau^2) d\tau. \]

Therefore, curves of the form \( t \propto x^2 \) are level curves for the concentration function \( c \).
The Hill function exponent $n$ is large.

This assumption leads to the following simplification:

$$F(c(x, t)) = \frac{c(x, t)^n}{c(x, t)^n + K_{1/2}^n} \\ \approx H(c(x, t) - K_{1/2}) \\ = H(\beta^2 t - x^2)$$

where $H$ is the Heaviside unit step function centered at the origin

$$H(s) = \begin{cases} 
0 & s < 0 \\
1/2 & s = 0 \\
1 & s > 0 
\end{cases}$$

and $\beta \sim \sqrt{D}$ is given implicitly in terms of the half bulk concentration by the equation

$$K_{1/2} = c_{\text{bulk}} \text{erfc}(\beta/(2\sqrt{D}t)). \quad (6)$$

This type of assumption has also been made in the study of calcium sparks (see Section 8.11 of [3]).

Using these assumptions we now have

$$I(t) = J_0 \int_0^L H(\beta^2 t - x^2) \rho(x) \, dx = J_0 \int_0^{\beta\sqrt{t}} \rho(x) \, dx.$$

Differentiating yields

$$I'(t) = \frac{1}{2} \beta t^{-1/2} J_0 \rho(\beta\sqrt{t}).$$

Letting $y = \beta\sqrt{t}$, we obtain

$$\rho(y) = \frac{2I'(y/\beta^2)^2}{J_0 \beta^2}.$$

In this over simplified model, the channel density is given analytically in terms of the derivative of the total current and a parameter $\beta$ that is obtained by solving equation (6) numerically, e.g. by a bisection method. If the current is a sigmoidal function with short delay (Figure 1B), which is similar to the profiles in some applications (see [1], [5] or [6]), and we model the total current by the function

$$I(t) = \begin{cases} 
0 & 0 < t < t_{\text{Delay}} \\
I_{\text{Max}} [1 + (K_I/(t - t_{\text{Delay}}))^n_I]^{-1} & t > t_{\text{Delay}} 
\end{cases} \quad (7)$$

with $t_{\text{Delay}} = 30$ ms, $n_I \cong 2.2$, $I_{\text{Max}} = 150$ pA and $K_I \cong 100$ ms, then we obtain the solution as shown in Figure 1A. In this figure one sees that the gross features of the solution of this over-simplified model are consistent with those obtained with a much more sophisticated nonlinear model (see [4]).
3. Numerical Method

We now develop a numerical scheme for (1) when the kernel has a “diffusive” character as exemplified in Figure 2. The specific mathematical assumptions on the kernel are $K(\cdot, \cdot) \in C^1([0, L] \times [0, \infty))$ satisfies $K(x, 0) = 0$ and

$$\frac{\partial K}{\partial x}(x, t) < 0 < \frac{\partial K}{\partial t}(x, t).$$

Under these conditions, given $\epsilon > 0$ sufficiently small, there is a unique $T = T(L, \epsilon)$ satisfying

$$K(L, T) = \epsilon.$$

Also, for each $t \in (0, T)$ satisfying $K(0, t) > \epsilon$, there is a unique $x(t) \in (0, L)$ satisfying

$$K(x(t), t) = \epsilon.$$

Furthermore, the function $t \mapsto x(t)$ is strictly increasing. Under these assumptions, which are valid for the cilium model studied here, the times $\{t_j\}$ and nodal points $\{x_j\}$ defined below exist and are uniquely determined.

We compute $\rho$ sequentially as the ligand enters the cilia. Here, we think of $c = c(x, t)$ as a wave in the direction of increasing $x$. The plot of the $K(x, t) = F(c(x, t))$ (Figure 2) provides the main inspiration for this interpretation. Small increments in time lead to small changes in the spatial variable and movement of the “wavefront”.

The “flat” portion of the kernel, that is, that part of the kernel corresponding to the $x$-region in which $K(x, t)$ is small, tends to result in a loss of information about the density $\rho$ in the corresponding region. The equation is in this sense ill-posed. We now propose a kind of “regularization” procedure (see e.g., [2]) that leads to an approximation method for the solution. Given a small number $\epsilon > 0$ and a positive integer $N$ we define a time $T = T(\epsilon)$ by the formula $K(L, T) = \epsilon$, a partition of $[0, T]$ given by

$$0 < t_1 < \ldots < t_N = T, \quad t_j = j \frac{T}{N},$$

and a sequence of wavefront points $x_j = x_j(t_j)$ given by;

$$K(x_j, t_j) = \epsilon.$$
Essentially, at time $t_j$, we define $x_j$ as the point beyond which the “wave” $K(\cdot, t_j)$, is within $\epsilon$ of zero. Our approximation of $\rho$ is a piecewise constant on the spatial grid

$$\rho_A(x) = \rho_j^A \quad \text{for} \quad x \in [x_{j-1}, x_j],$$

and can be found sequentially as the cAMP diffuses into the cilia. So, since $K(x, t_1) \leq \epsilon$ for $x_1 \leq x \leq L$, we have

$$I(t_1) \approx J_0 \int_0^{x_1} K(x, t_1) \rho_1^A \, dx$$

or, since $\rho_1^A$ is constant,

$$\rho_1^A = \frac{I(t_1)}{J_0 \int_0^{x_1} K(x, t_1) \, dx}. \quad (8)$$

Now, we suppose that $\rho_1^A, \ldots, \rho_{j-1}^A$ are known. Since $K(x, t_j) \leq \epsilon$ for $x_j \leq x \leq L$ we have

$$I(t_j) \approx J_0 \int_0^{x_{j-1}} K(x, t_j) \rho_j^A \, dx + J_0 \rho_j^A \int_{x_{j-1}}^{x_j} K(x, t_j) \, dx$$

and thus

$$\rho_j^A = \frac{I(t_j) / J_0 - \int_0^{x_{j-1}} K(x, t_j) \rho_j^A \, dx}{\int_{x_{j-1}}^{x_j} K(x, t_j) \, dx} \quad (9)$$

for $j = 2, \ldots, N$. This provides an explicit procedure to compute $\rho_A$.

We now argue that the residual, defined as the true current minus the current $I_A$ obtained from $\rho_A$ through the definition

$$I_A(t) = J_0 \int_0^{L} \rho_A K(x, t) \, dx$$

is bounded by a term of order $O(N^{-1} + \epsilon)$, if the computed approximation $\rho_A$ satisfies

$$0 \leq \rho_A(x) \leq M \quad \text{for} \quad 0 \leq x \leq L. \quad (10)$$
Unfortunately, we cannot, a priori, guarantee these conditions on $\rho^A$. We also define the following bounds:

$$C_1 = \max_t |I'(t)| \quad \text{and} \quad C_2 = \max_{(x,i)} \left| \frac{\partial K}{\partial t} \right|.$$  

(11)

First we demonstrate that

$$\left| I(t_i) - J_0 \int_0^L \rho^A K(x, t_i) \, dx \right| \leq J_0 M L \epsilon \quad \text{for} \quad i = 1, 2, \ldots, N.$$  

(12)

We start by dividing the expression in the absolute value bars;

$$\left| I(t_i) - J_0 \int_0^L \rho^A K(x, t_i) \, dx \right| \leq \left| I(t_i) - J_0 \int_0^{x_i} \rho^A K(x, t_i) \, dx - \rho_i^A \int_{x_{i-1}}^{x_i} K(x, t_i) \, dx \right|$$

$$+ \quad J_0 \int_{x_i}^L |\rho^A||K(x, t_i)| \, dx$$

The first term on the right side of the inequality is zero by the definition of $\rho^A$ (from (8) and (9)) and $|K(\cdot, t_i)| \leq \epsilon$ on the interval $[x_i, L]$. So, using our assumed bound, (10), on $\rho^A$,

$$\left| I(t_i) - J_0 \int_0^L \rho^A K(x, t_i) \, dx \right| \leq J_0 \epsilon \int_{x_i}^L |\rho^A| \, dx \leq J_0 M L \epsilon.$$  

(13)

Now we seek to find the full residual bound at an arbitrary value of $t \in [0, T]$;

$$\left| I(t) - J_0 \int_0^L \rho^A K(x, t) \, dx \right| \leq \left| I(t) - I(t_i) \right| + \left| I(t_i) - J_0 \int_0^L \rho^A K(x, t_i) \, dx \right|$$

$$+ \quad J_0 \left| \int_0^L \rho^A(K(x, t_i) - K(x, t)) \, dx \right|$$

where we choose $t_i$ so that $|t - t_i| \leq 1/N$. Then, using the mean value theorem on the function $I$, with the first assumed inequality in (11) and the result (13), we have

$$\left| I(t) - J_0 \int_0^L \rho^A K(x, t) \, dx \right| \leq C_1 \frac{1}{N} + J_0 M L \epsilon + \int_0^L |\rho^A||K(x, t_i) - K(x, t)| \, dx.$$  

Using now the upper bound on $\rho^A$ and the mean value theorem on $K(\cdot, t)$, along with the second assumed bound in (11), we find

$$\left| I(t) - J_0 \int_0^L \rho^A K(x, t) \, dx \right| \leq (C_1 + C_2 J_0 M L) \frac{1}{N} + J_0 M L \epsilon$$

which completes our argument that the residual is small under the assumption (10) about $\rho^A$.

4. Gauss-Seidel Type Iterations

The procedure described in Section 3 provides a special set of grid points $x_0, x_1, \ldots, x_N$ once the time nodes $t_0, t_1, \ldots, t_N$ are chosen. The work in Section 3 also gives some assurance that such a procedure will succeed. In this section, to increase accuracy, we include the omitted terms in the integrals that correspond to spatial regions where the kernel is very small and flat. We solve the resulting systems sequentially by using a Gauss-Seidel procedure in which previously computed density values are used in these tail regions where the kernel is small. In this way a sequence of iterates, or guess piecewise constant functions $\rho^{(m)}$, for $m = 1, 2, \ldots$ is obtained. Assuming the same partition as in Section 3 we look for

$$\rho^{(m)}(x) = \rho^{(m)}_j \quad \text{for} \quad x \in [x_{j-1}, x_j].$$
Further, assuming we have computed \( \rho^{(m-1)} \) and \( \rho_1^{(m)}, \ldots, \rho_{j-1}^{(m)} \), then the usual Gauss-Seidel procedure leads to

\[
I(t_j)/J_0 = \int_0^{x_{j-1}} K(x, t_j) \rho^{(m)} dx + \rho_j^{(m)} \int_{x_{j-1}}^{x_j} K(x, t_j) dx + \int_{x_j}^{L} K(x, t_j) \rho^{(m-1)} dx
\]

and thus, taking the positive part to enforce the constraint (2), we set

\[
\rho_j^{(m)} = \max \left\{ \frac{I(t_j)/J_0 - \int_0^{x_{j-1}} K(x, t_j) \rho^{(m)} dx - \int_{x_j}^{L} K(x, t_j) \rho^{(m-1)} dx}{\int_{x_{j-1}}^{x_j} K(x, t_j) dx}, 0 \right\}
\]

for \( j = 1, \ldots, N \). In our numerical approximations we found it advantageous to use a nonuniform mesh for \( t \) with \( t_j = (j/N)^{1.5} T \) for \( j = 0, 1, \ldots, N \).

5. Computational Examples

In this section we display the results of the algorithm described in Section 3. In the first two examples, we have created a channel distribution \( \rho \) and then derived, by solving the full system of equations numerically, the associated current \( I \) (i.e., we solved a forward problem to create the "true" current). We then used our algorithm to find an approximate \( \rho \) (i.e., we solved the inverse problem) and then numerically computed an approximate current (another forward problem). We denote this approximate current \( I_{\text{Appx}} \); and use an \( L_1 \) norm to compute a relative residual:

\[
\text{Relative Residual} = \frac{\sum_{i=1}^{N} |I(t_i) - I_{\text{Appx}}(t_i)|}{\sum_{i=1}^{N} |I(t_i)|}
\]

Below we describe the results for four different example computations. The first two have known or created channel distributions from which the current profile \( I \) was derived numerically. In the last two examples we have used current data obtained from laboratory experiments. The approximate channel distribution \( \rho^A \) is a piecewise constant function and the current derived

**Figure 3.** Graphical results for example 1. A. True and approximate \( \rho \) functions. B. True and approximate current profiles.
Figure 4. Graphical results for Example 2. A. True and approximate ρ functions. B. True and approximate current profiles.

from it are displayed in Figures 3-6. The actual data points are indicated by an ‘o’. In Examples 1 and 2 we have $c_{Bulk} = 30 \, \mu M$ and $L = 40 \mu m$.

**Example 1:** Here we consider the case of a cilium with a smooth distribution of channels centered around 20\(\mu m\). Figure 3 has the created ρ labeled “True” and the approximate ρ obtained by the algorithm is the piecewise constant function. We set $N = 18$ in this example.

**Example 2:** We study the case where ρ is has two narrow but tall peaks. Here we had $N = 18$; the results are displayed in Figure 4.

In Examples 3 and 4 we use data from our lab in experiments with grass frog olfactory cilia. Noise is mitigated by averaging the raw data and defining $I$ by numerical integration.

**Example 3:** Here the length of the cilium is 70\(\mu m\) and the concentration of cAMP used in the experiment was $c_{Bulk} = 20 \, \mu M$. We used $N = 18$; the results are displayed in Figure 5.

**Example 4:** Here the length of the cilium is 40\(\mu m\) and the concentration of cAMP used in the experiment was $c_{Bulk} = 300 \, \mu M$. We used $N = 18$; the results are displayed in Figure 5.

The condition numbers for the matrix $A$ in these examples ranged from $1.9 \times 10^3$ in Example 4 to a high of $7.7 \times 10^6$ in Example 3.

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Figure 5. Graphical results for Example 3. A. Approximate $\rho$ functions. B. True and approximate current profiles.

Figure 6. Graphical results for Example 4. A. Approximate $\rho$ functions. B. True and approximate current profiles.

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