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Perturbation approximation of solutions of a nonlinear inverse problem arising in olfaction experimentation

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Abstract In this paper, a mathematical model of the diffusion of cAMP into olfactory cilia and the resulting electrical activity is presented. The model, which consists of two nonlinear differential equations, is studied using perturbation techniques. The unknowns in the problem are the concentration of cAMP, the membrane potential, and the quantity of most interest in this work: the distribution of CNG channels along the length of a cilium. Experimental measurements of the total current during this diffusion process provide an extra boundary condition which helps determine the unknown distribution function. A simple perturbation approximation is derived and used to solve this inverse problem and thus obtain estimates of the spatial distribution of CNG ion channels along the length of a cilium. A one-dimensional computer minimization and a special delay iteration are used with the perturbation formulas to obtain approximate channel distributions in the cases of simulated and experimental data.

Keywords Olfaction · Inverse problem · Cilia · Perturbation analysis · Computational neuroscience

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1 Introduction

Identification of detailed features of neuronal systems is an important challenge in the biosciences today. Cilia are long thin cylindrical structures that extend from the olfactory receptor neurons into the nasal mucus. Transduction of an odor into an electrical signal occurs in the membranes of the cilia. The cyclic-nucleotide-gated (CNG) channels which reside in the ciliary membrane are activated by cAMP, allow a depolarizing influx of Ca^{2+} and Na^{+}, and are thought to initiate the electrical signal [4].

In [2] a mathematical model for the diffusion of cAMP into an olfactory cilium from a grass frog is developed and used with numerical computations to determine plausible distributions of CNG ion channels. A key conclusion that is suggested in [2] and demonstrated more strongly in [3] is that the distribution of the ion channels, $\tilde{\rho}(\tilde{x})$, is heavily clustered in a short segment of the cilium, roughly 1/3 of the distance from the base (open end) to the tip (closed end).

As is typical of inverse problems this one appears to be highly ill-conditioned; certain matrices that arise in the numerical solution process have condition numbers as high as 10^{13}. Thus, even though the residuals and sample computations in [2] are quite accurate, it is desireable to develop solutions in a different way.

In this paper we use perturbation techniques to develop an approximate solution to the inverse problem. Based on previous work [3], we look for $\tilde{\rho}$ in the form of a *density pulse*: either a delta function or a tall Gaussian with a narrow base. Thus the problem reduces to finding the strength and position of each pulse. Using a simple one-dimensional numerical minimization and special delay iteration we develop accurate approximations using the perturbation solution to cases with simulated and experimental data. Below we describe the mathematical model.

Governing equations

We begin with the dimensional equations governing our model, which we obtain from [2]. We consider diffusion and reaction of cAMP molecules in solution, the (volume) concentration of which we denote by $\tilde{C}(\tilde{x}, \tilde{t})$. cAMP diffuses in the $\tilde{x}$-direction in a one-dimensional channel of length L. Conservation of mass of cAMP is then given by

$$\frac{\partial \tilde{C}}{\partial \tilde{t}} = D\frac{\partial^2 \tilde{C}}{\partial \tilde{x}^2} - \alpha\frac{\partial \tilde{S}}{\partial \tilde{t}}, \qquad 0 \le x \le L, \tag{1}$$

where D is the diffusion coefficient, $\tilde{S}(\tilde{x}, \tilde{t})$ is the concentration of bound cAMP, and α is a conversion factor. The equation for $\tilde{S}$ is given by

$$\tilde{S} = B_S \tilde{\rho} F(\tilde{C}),$$

where B_S (units of molecules per channel) is the number of binding sites that are needed to activate the channel, and $\tilde{\rho}(\tilde{x})$ is the density of channels along the surface of the cilium. (In the inverse problem, we are trying to solve for $\tilde{\rho}$.) $F(\tilde{C})$ is the dimensionless Hill function describing the binding process, given by

$$F(\tilde{C}) = \frac{\tilde{C}^n}{\tilde{C}^n + K_{1/2}^n},$$

where $K_{1/2}$ is the "half-maximal concentration", so-called because it is the value of $\tilde{C}$ at which $F = 1/2$. From the appendix, we see that $n = 1.7$. Note that upon substitution of $\tilde{S}$ into (1), we are left with a diffusion-type equation solely in $\tilde{C}$. Thus, it suffices to impose boundary and initial conditions only on $\tilde{C}$, not on $\tilde{S}$. Initially, the channel has no cAMP, so

$$\tilde{C}(\tilde{x}, 0) = 0. \tag{2}$$

At the exposed end of the cilium ($\tilde{x} = 0$), the concentration is the same as the value C_b in the bulk and there is no flux through the sealed end of the cilium ($\tilde{x} = L$):

$$\tilde{C}(0, \tilde{t}) = C_\mathrm{b} \quad \text{and} \quad \frac{\partial \tilde{C}}{\partial \tilde{x}}(L, \tilde{t}) = 0. \tag{3}$$

The binding initiates a change in the sodium current flux $\tilde{J}(\tilde{x}, \tilde{t})$ through the channels, which is governed by the following equation:

$$\tilde{J} = \frac{g_\mathrm{CNG} P \tilde{V} \tilde{S}}{B_S},$$

where g_CNG is the conductance of the channels, $\tilde{V}(\tilde{x}, \tilde{t})$ is the membrane potential, and P is the maximum open probability for the channel.

The membrane potential $\tilde{V}$ is also related to the current through standard cable theory:

$$\frac{1}{R_\mathrm{a}} \frac{\partial^2 \tilde{V}}{\partial \tilde{x}^2} = \tilde{J}, \qquad 0 \le \tilde{x} \le L, \tag{4}$$

where R_a is the (lineal) resistance density of the longitudinal current in the cilium. The form of (4) dictates that we impose two boundary conditions upon $\tilde{V}$. At the exposed end of the cilium ($\tilde{x} = 0$), the potential is the same as the value in the bulk, which we denote by $-V_\mathrm{b}$ because it is negative. Moreover, there is no change in potential at the sealed end of the cilium ($\tilde{x} = L$):

$$\tilde{V}(0, \tilde{t}) = -V_\mathrm{b} \quad \text{and} \quad \frac{\partial \tilde{V}}{\partial \tilde{x}}(L, \tilde{t}) = 0. \tag{5}$$

The quantity actually measured is $\tilde{I}(\tilde{t})$, the total current, which is simply the integral of $\tilde{J}$:

$$\tilde{I} = \int_0^L \tilde{J}\, d\tilde{x} = -\frac{1}{R_\mathrm{a}} \frac{\partial \tilde{V}}{\partial \tilde{x}}(0, \cdot), \tag{6}$$

where we have used (4) and (5). Thus, given current data $\tilde{I}(\tilde{t})$ and parameters D, α, B_S, $K_{1/2}$, C_b, g_CNG, P, R_a, and V_b we wish to find the functions $\tilde{C}$, $\tilde{V}$, and $\tilde{\rho}$. We specify that $\tilde{\rho}$ consists of a single narrow pulse; thus the real unknowns are the pulse position $\tilde{x}_0$ and its strength, which is equivalent to the number of channels. This is an inverse problem since the coefficient $\tilde{\rho}$ is unknown.

In Sect. 2 we scale (1)–(6). In Sect. 3 we solve the resulting system using perturbation techniques. Finally, in Sect. 4 we use the perturbation solution along with both simulated and real current data to determine an approximation for $\tilde{\rho}$. This last section involves some basic numerical computations.

2 Scaling

In this section we nondimensionalize the governing Eqs. (1)–(6); we will introduce scalings to simplify our problem and illustrate key physical ideas. We begin by scaling those variables for which characteristic values are self-evident:

$$C(x,t) = \frac{\tilde{C}(\tilde{x},\tilde{t})}{C_\mathrm{b}}, \quad V(x,t) = \frac{\tilde{V}(\tilde{x},\tilde{t})}{V_\mathrm{b}}, \qquad \text{and} \quad x = \frac{\tilde{x}}{L}.$$

For the Hill function we rescale to obtain

$$F(C) = \frac{C^n}{C^n + \epsilon} = \left(1 + \frac{\epsilon}{C^n}\right)^{-1} \quad \text{with} \quad \epsilon = \left(\frac{K_{1/2}}{C_\mathrm{b}}\right)^n.$$

We choose the letter ϵ because from the Appendix we see that $\epsilon \ll 1$. We note that $F(C) = O(1)$ for all C. We then scale the boundary and initial conditions:

$$C(x,0) = 0, \quad C(0,t) = 1, \qquad \frac{\partial C}{\partial x}(1,t) = 0, \tag{7}$$

and

$$V(0,t) = -1, \quad \frac{\partial V}{\partial x}(1,t) = 0. \tag{8}$$

Now we can determine the proper scale for the current. Letting

$$I(t) = \frac{\tilde{I}(\tilde{t})}{I_\mathrm{c}}$$

(where the subscript "c" refers to "characteristic value"), we have

$$I_\mathrm{c} I = -\frac{V_\mathrm{b}}{R_\mathrm{a} L}\frac{\partial V}{\partial x}(0,t) \quad \text{or} \quad I = -\frac{\partial V}{\partial x}(0,t) \quad \text{where} \quad I_\mathrm{c} = \frac{V_\mathrm{b}}{R_\mathrm{a} L}. \tag{9}$$

To scale $\tilde{\rho}$, we use its average value as the characteristic value ρ_c. Thus we have

$$\rho(x) = \frac{\tilde{\rho}(\tilde{x})}{\rho_c} \quad \text{where} \quad \rho_c = \frac{1}{L}\int_0^L \tilde{\rho}(\tilde{x})\, d\tilde{x}.$$

Using the definitions of $\tilde{J}$ and $\tilde{S}$ in (4) and then rescaling we obtain

$$\frac{\partial^2 V}{\partial x^2} = [b\rho F(C)]V, \quad \text{with} \quad b = R_a L^2 g_{CNG} P \rho_c. \tag{10}$$

Note that we have now eliminated $\tilde{J}$ from our equations completely. It is shown in the Appendix that $b = O(1)$. Though not necessary because of the form of (10), it will be convenient later to calculate $V(x, 0)$. Substituting $t = 0$ into (10), we obtain

$$\frac{\partial^2 V}{\partial x^2}(x, 0) = [b\rho F(C(x, 0))]\, V(x, 0) = 0,$$

where we have used (7). Then solving the above subject to (8), we have

$$V(x, 0) = -1. \tag{11}$$

Lastly, we may use our results to create a time scale. We substitute our formula for $\tilde{S}$ into (1) and using $t = \tilde{t}/t_c$ yields:

$$\frac{\partial C}{\partial t} = \frac{Dt_c}{L^2}\frac{\partial^2 C}{\partial x^2} - \frac{\alpha\rho_c}{C_b} B_S \rho \frac{\partial\,(F(C))}{\partial t}.$$

Choosing $t_c = L^2/D$, we find

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - a\rho\frac{\partial\,(F(C))}{\partial t} \quad \text{with} \quad a = \frac{\alpha\rho_c B_S}{C_b}. \tag{12}$$

It is shown in the Appendix that $a = O(1)$.

Because ρ is a function of x, in general equations (10) and (11) cannot be solved in closed form. Previous studies have assumed that $\tilde{\rho}$ is a constant, which is equivalent to $\rho = 1$. However, recent numerical work ([2], [3]) supports the hypothesis that the receptors occur in small regions of high density. This behavior occurs often in biological systems (see Sect. 8.1 of [1]). Thus, let us consider the case of a "density pulse" at a point x_0. For x near x_0, we let $\rho(x) = O(\epsilon^{-p})$ with $p > 0$. Because we have defined

$$\int_0^1 \rho(x)\, dx = 1, \tag{13}$$

the width of each pulse must be ϵ^p. Thus

$$\rho = \epsilon^{-p} r(\xi), \qquad \xi = \frac{x - x_0}{\epsilon^p}, \quad \text{and} \quad x_0 = O(1).$$

For the regions outside of the pulse, we take the density to be $o(1)$. It is most convenient to make the density transcendentally small. The pulses should be symmetric in ξ and nonnegative. Thus we define r as follows:

$$r(\xi) = h''(\xi), \qquad h''(\xi) \text{ transcendentally small as } |\xi| \to \infty, \tag{14}$$

where we use the h'' form for later algebraic convenience. Symmetry and positivity then require that

$$h'' \geq 0, \qquad h''(-\xi) = h''(\xi).$$

Now we integrate up to obtain additional facts about h. First, upon integrating from h'' to h', we obtain one arbitrary constant. Another constant may be chosen in order to specify the amplitude of the pulse. Therefore, we choose

$$h'(-\infty) = -\frac{1}{2}, \quad h'(\infty) = \frac{1}{2}. \tag{15}$$

If we integrate h' up to obtain h, we obtain an arbitrary constant, which we set equal to zero by requiring that

$$h(\xi) = -\frac{\xi}{2} + \text{transcendentally small terms as } \xi \to -\infty. \tag{16}$$

At first blush, it may look as if this implies more than the selection of a constant. However, if $h(\xi) \sim -\xi/2 + O(\xi^A)$, where $A < 1$, then taking the second derivative would lead to a term in h'' that decays algebraically, which would violate (14).

Lastly, we wish to point out some implications of our definition for h. First, we note that the integral of an even function is an odd function plus a constant. However, since $h'(-\infty) = -h'(\infty)$, we conclude that h' is odd. Moreover, we know that the integral of an odd function is even, so we have that

$$h(\xi) = \frac{\xi}{2} + \text{transcendentally small terms as } \xi \to \infty. \tag{17}$$

Here are a few simple choices for the pulse. First, we can choose it to be a δ-function, in which case we have

$$h''(\xi) = \delta(\xi), \quad h'(\xi) = H(\xi) - \frac{1}{2} \quad \text{and} \quad h(\xi) = \frac{|\xi|}{2}, \tag{18}$$

where $H(\xi)$ is the Heaviside step function. Alternatively, we could choose it as a Gaussian, in which case we have

$$h''(\xi) = \frac{1}{\sqrt{\pi}} \exp\left(-\xi^2\right),$$
$$h'(\xi) = \frac{\text{erf}(\xi)}{2}, \quad \text{and} \quad h(\xi) = \frac{1}{2}\left[\xi \text{erf}(\xi) + \frac{1}{\sqrt{\pi}} \exp\left(-\xi^2\right)\right]. \tag{19}$$

We should point out that one can examine the δ-function postulate for ρ independent of the ϵ^{-p} context, and it may be useful to do so in the future. The value of the perturbation approach is to be able to handle smooth pulses and provide corrections to the δ-function case.

The following re-formulation of the derivative term in (12) will be used in the next section:

$$\frac{\partial(F(C))}{\partial t} = -F^2(C)\frac{\partial}{\partial t}\left(\frac{\epsilon}{C^n}\right). \tag{20}$$

3 Perturbation solution

In this section we use perturbation techniques to solve the problem defined by the Eqs. (12), (10), (7), (8) and (9).

Solution of the cAMP diffusion problem

First we examine the effect of the pulses on C. (This will also establish a value for p.) Substituting (20) into (12), we obtain

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} + a\rho F^2(C)\frac{\partial}{\partial t}\left(\frac{\epsilon}{C^n}\right). \tag{21}$$

Motivated by the form of (21), in the outer region we let

$$C(x,t) = C_0(x,t) + O(\epsilon).$$

Substituting this into (21) and using our decay hypothesis about ρ, we have, to leading order,

$$\frac{\partial C_0}{\partial t} = \frac{\partial^2 C_0}{\partial x^2}, \tag{22}$$

which is not surprising. Biologically, we are stating that simple diffusion holds because there are no receptors in the outer region.

In the inner region we hypothesize the following perturbation expansion:

$$C(x,t) = c_0(\xi,t) + \epsilon c_1(\xi,t) + \epsilon^2 c_2(\xi,t) + o(\epsilon^2), \tag{23}$$

where the form is motivated by (21). Substituting this form and our definition for ρ into (21), we have, to leading order,

$$\frac{\partial c_0}{\partial t} = \epsilon^{-2p}\frac{\partial^2(c_0+\epsilon c_1+\epsilon^2 c_2)}{\partial \xi^2} + a\epsilon^{1-p} r F^2(c_0)\frac{\partial (c_0^{-n})}{\partial t},$$

from which we conclude

$$\frac{\partial^2 c_0}{\partial \xi^2} = 0, \tag{24}$$

$$\frac{\partial^2 c_1}{\partial \xi^2} = 0, \tag{25}$$

and

$$\frac{\partial c_0}{\partial t} = \epsilon^{2(1-p)}\frac{\partial^2 c_2}{\partial \xi^2} + a\epsilon^{1-p} r F^2(c_0)\frac{\partial (c_0^{-n})}{\partial t}, \tag{26}$$

where we have used the fact that $F(C) = O(1)$. Therefore, the dominant balance is given by $p = 1$.

The matching conditions for c_0 are

$$c_0(-\infty, t) = C_0(x_0^-, t), \qquad c_0(\infty, t) = C_0(x_0^+, t).$$

Solving (24) subject to the above yields

$$c_0(t) = C_0(x_0, t), \tag{27}$$

and hence there is no layer in C_0.

In the regions where $C = O(1)$ it is acceptable to use the following expansion

$$F(C) \sim 1 - \frac{\epsilon}{C^n} \tag{28}$$

for $C = O(1)$. The exact function and our approximation are shown in Fig. 1. Note that the agreement is quite good for a wide range of C values. However, it is not good for C small which would correspond to small t. In many, but not all, cases, the effects of the reaction term for t small are negligible. In Sect. 4 we develop a delay iteration to handle this difficulty.

If we now examine the spatial derivatives of the inner solution we have

$$\frac{\partial}{\partial x}(c_0 + \epsilon c_1 + \cdots)(\pm\infty, t) = \frac{\partial}{\partial x}(C_0 + \cdots)(x_0^{\pm}, t).$$

Since $\partial c_1/\partial x = (1/\epsilon)\partial c_1/\partial \xi$ and $\partial c_0/\partial \xi = 0$ from (27) we have

$$\frac{\partial c_1}{\partial \xi}(-\infty, t) = \frac{\partial C_0}{\partial x}(x_0^-, t) \quad \text{and} \quad \frac{\partial c_1}{\partial \xi}(+\infty, t) = \frac{\partial C_0}{\partial x}(x_0^+, t).$$

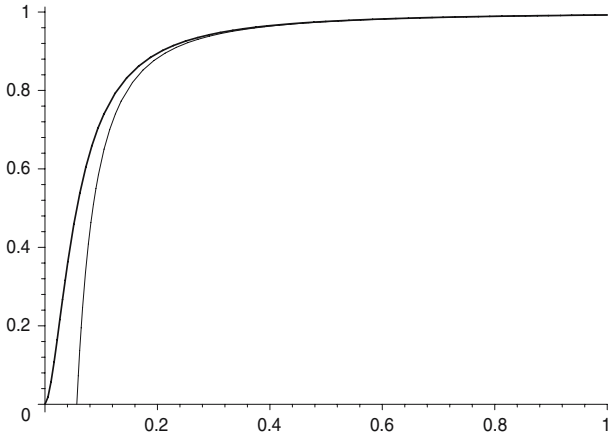

Fig. 1 Plot of F and a perturbation approximation

From (25) and the above

$$c_1(\xi, t) = \xi \frac{\partial C_0}{\partial x}(x_0, t) + A(t) \tag{29}$$

and hence there is no layer in $\partial C_0/\partial x$, either (Note that $A(t) = C_1(x_0, t)$.). So no measurable layer occurs in the $O(1)$ outer solution, subject to the small-t restrictions.

Thus we may simply solve (22) on the domain $0 \leq x \leq 1$, subject to the boundary and initial conditions (7) written in our new variable:

$$C_0(x, 0) = 0, \qquad C_0(0, t) = 1, \qquad \frac{\partial C_0}{\partial x}(1, t) = 0, \tag{30}$$

Biologically, we are saying that since the threshold concentration for reaction is so small ($O(\epsilon)$) that once $C = O(1)$ the reaction has already progressed to completion and it no longer affects the diffusion process.

There are two ways to solve our system: a Fourier series and a "Laplace series", based on an expansion of a Laplace transform solution. The latter works best for small t, which is where we will be mistrustful of our solution. Thus we derive the standard Fourier series solution and obtain

$$C_0(x, t) = 1 - \sum_{j=0}^{\infty} \frac{4}{(2j+1)\pi} \exp\left(-\left[\frac{(2j+1)\pi}{2}\right]^2 t\right) \sin\left(\frac{x(2j+1)\pi}{2}\right). \tag{31}$$

Note that for $t = O(1)$, our expression can be approximated well by only a few terms in the Fourier series.

Solution of the membrane potential equations

Now we turn our attention to V. In the outer region, motivated by our previous choice of $p = 1$, we let

$$V(x,t) = V_0(x,t) + \epsilon V_1(x,t) + o(\epsilon). \tag{32}$$

Substituting (32) into (10) and (8) and using our hypothesis about ρ, we have, to leading orders,

$$\frac{\partial^2 V_0}{\partial x^2} = 0, \quad V_0(0,t) = -1, \quad \frac{\partial V_0}{\partial x}(1,t) = 0, \tag{33}$$

and

$$\frac{\partial^2 V_1}{\partial x^2} = 0, \qquad V_1(0,t) = \quad 0, \qquad \frac{\partial V_1}{\partial x}(1,t) = 0. \tag{34}$$

From the above we see that in the outer region we have a time-varying series of linear profiles which matches the numerical solution in Fig. 2b of [2].

For the inner regions, we hypothesize the following perturbation expansion,

$$V(x,t) = v_0(\xi,t) + \epsilon v_1(\xi,t) + \epsilon^2 v_2(\xi,t) + o(\epsilon^2). \tag{35}$$

Substituting our expansions into (10), we have, to leading three orders,

$$\epsilon^{-2}\frac{\partial^2(v_0 + \epsilon v_1 + \epsilon^2 v_2)}{\partial \xi^2} = b\epsilon^{-1} r F(c_0 + \epsilon c_1)(v_0 + \epsilon v_1 + \epsilon^2 v_2).$$

So,

$$\frac{\partial^2 v_0}{\partial \xi^2} = 0, \tag{36}$$

and, noting that $c_0 = C_0$,

$$\frac{\partial^2 v_1}{\partial \xi^2} = bh'' F(C_0) v_0, \tag{37}$$

as well as

$$\frac{\partial^2 v_2}{\partial \xi^2} = bh''[F(C_0)v_1 + c_1 F'(C_0)v_0]. \tag{38}$$

Now we carefully consider the implications of our equations. In order to estimate the parameters in the inverse problem, we need to use all the time-dependent data we have been given. Thus, we needed to expand to $O(\epsilon^2)$ in the above in order to get time

dependence in our problem through C_0. In particular, we see that nowhere does C_0 enter into our equations for the leading order of V. Without C_0, there is no way for t to enter the problem. Hence we determine that V_0 and v_0 are independent of t. The matching conditions for v_0 are then given by

$$v_0(-\infty) = V_0(x_0^-), \qquad v_0(\infty) = V_0(x_0^+).$$

Solving (36) subject to the above yields

$$v_0 = V_0(x), \tag{39}$$

and hence there is no layer in V_0. Rather, the layer is in the *x-derivative* of V, just as is seen in Fig. 2b of [2]. (Note that the value of V_0 at the pulse is currently undetermined.)

Next we continue by examining v_1. The matching conditions for v_1 are given by matching to our outer solution:

$$\frac{\partial v_1}{\partial \xi}(-\infty, t) = \frac{dV_0}{dx}(x_0^-), \qquad \frac{\partial v_1}{\partial \xi}(\infty, t) = \frac{dV_0}{dx}(x_0^+). \tag{40}$$

Next we substitute V_0 in for v_0 in (37), then integrate once with a specific endpoint of $\xi = -\infty$ to obtain

$$\frac{\partial v_1}{\partial \xi}(\xi, t) - \frac{\partial v_1}{\partial \xi}(-\infty, t) = bV_0F(C_0)[h'(\xi) - h'(-\infty)]$$

Now, from (15) and (40),

$$\frac{\partial v_1}{\partial \xi}(\xi, t) - \frac{dV_0}{dx}(x_0^-) = bV_0F(C_0)\left[h'(\xi) + \frac{1}{2}\right]. \tag{41}$$

By substituting $\xi = \infty$ into the above we obtain a jump condition on dV_0/dx:

$$\frac{dV_0}{dx}(x_0^+) - \frac{dV_0}{dx}(x_0^-) = bV_0F(C_0) \tag{42}$$

using (40) again. Note that as far as the jump condition is concerned, the actual *form* of h does not come into play. Also note that (42) is exactly what we would obtain had we taken ρ to be a δ function without any consideration of ϵ.

Integrating (41) (but this time doing an indefinite integral), we have

$$v_1(\xi, t) = \xi \frac{dV_0}{dx}(x_0^-) + bV_0F(C_0)\left[h(\xi) + \frac{\xi}{2}\right] + A(t), \tag{43}$$

where $A(t)$ is unknown for now. The matching conditions for v_1 are more subtle. Expanding (32) near x_0, we have

$$V(x_0 \pm \epsilon\xi, t) = V_0(x_0) + \epsilon\xi \frac{dV_0}{dx}(x_0^{\pm}) + \epsilon V_1(x_0^{\pm}, t) + o(\epsilon)$$

Since $V(x_0 + \epsilon\xi, t) \cong v_0(\xi) + \epsilon v_1(\xi, t)$ we find that for $\xi \to -\infty$ at the $O(\epsilon)$ level

$$v_1(\xi, t) \cong \xi \frac{dV_0}{dx}(x_0^-) + V_1(x_0^-, t). \tag{44}$$

Similarly, we have for $\xi \to +\infty$

$$v_1(\xi, t) \cong \xi \frac{dV_0}{dx}(x_0^+) + V_1(x_0^+, t). \tag{45}$$

So, letting $\xi \to -\infty$ and using (43) with (44), we have

$$\xi \frac{dV_0}{dx}(x_0^-) + bV_0F(C_0)\left[h(-\infty) + \frac{\xi}{2}\right] + A(t) - \xi \frac{dV_0}{dx}(x_0^-) = V_1(x_0^-, t)$$

so

$$A(t) = V_1(x_0^-, t), \tag{46}$$

where we have used (16). Letting $\xi = +\infty$ in (43) and using (45), we have

$$\frac{dV_0}{dx}(x_0^-)\xi + bV_0F(C_0)\left[h(\infty) + \frac{\xi}{2}\right] + A(t) - \xi \frac{dV_0}{dx}(x_0^+) = V_1(x_0^+, t).$$

Now, solving for $\frac{dV_0}{dx}(x_0^-)$ in (42) and substituting in the above,

$$\xi \frac{dV_0}{dx}(x_0^+) - bV_0F(C_0)\xi + bV_0F(C_0)\xi + A(t) - \xi \frac{dV_0}{dx}(x_0^+) = V_1(x_0^+, t)$$

where we used (17), so

$$A(t) = V_1(x_0^+, t). \tag{47}$$

From (46) and (47), we see that V_1 is continuous at x_0, just as V_0 is. Therefore there is no boundary layer in V_1. Rather, the layer is in the *x-derivative* of V_1, just as in V_0. In addition, our solution for v_1 may be written as

$$v_1(\xi, t) = \xi \frac{dV_0}{dx}(x_0^-) + bV_0F(C_0)\left[h(\xi) + \frac{\xi}{2}\right] + V_1, \tag{48}$$

where as before we now drop the arguments on V_1 since we know it is uniquely defined at x_0 and independent of ξ.

Substituting our formulas for v_0 and v_1, (39) and (48) into (38), we obtain

$$\frac{\partial^2 v_2}{\partial \xi^2} = bh'' \left\{ F(C_0) \left[\xi \frac{dV_0}{dx}(x^-) + bV_0 F(C_0)(h(\xi) + \frac{\xi}{2}) + V_1 \right] + \left(\xi \frac{\partial C_0}{\partial x} + C_1 \right) F'(C_0) V_0 \right\}. \tag{49}$$

As was done in (40) we find that

$$\frac{\partial v_2}{\partial \xi}(\infty, t) - \frac{\partial v_2}{\partial \xi}(-\infty, t) = \frac{\partial V_1}{\partial x}(x_0^+, t) - \frac{\partial V_1}{\partial x}(x_0^-, t). \tag{50}$$

Therefore, we may simply integrate (38) from $\xi = -\infty$ to $\xi = \infty$ to obtain a jump condition for V_1:

$$\frac{\partial v_2}{\partial \xi}(\infty, t) - \frac{\partial v_2}{\partial \xi}(-\infty) = b \int_{-\infty}^{\infty} h'' \left[F(C_0)(bV_0 F(C_0) h(\xi) + V_1) + F'(C_0) C_1 V_0 \right] d\xi,$$

where we have used the fact that h'' is even. Continuing to simplify, we have from (50)

$$\frac{\partial V_1}{\partial x}(x_0^+, t) - \frac{\partial V_1}{\partial x}(x_0^-, t) = b^2 F^2(C_0) V_0 \gamma + b(F(C_0) V_1 + F'(C_0) C_1 V_0) \quad \text{with} \quad \gamma = 2 \int_0^{\infty} h'' h \, d\xi \tag{51}$$

where we used the fact that $\int_{\infty}^{-\infty} h'' \, d\xi = 1$. Note that it is at this order that the actual behavior of h, rather than just its behavior as $|\xi| \to \infty$, becomes important.

We now examine the parameter γ. For the two choices of h, the delta function and Gaussian, we have

$$h'' = \delta(\xi) \qquad \Longrightarrow \qquad \gamma = 0,$$

and

$$h'' = \frac{1}{\sqrt{\pi}} \exp\left(-\xi^2\right) \qquad \Longrightarrow \qquad \gamma = \frac{1}{\sqrt{2\pi}}.$$

We now obtain several helpful jump conditions for $V \cong V_0 + \epsilon V_1$ by combining (42) and (51):

$$\frac{\partial (V_0 + \epsilon V_1)}{\partial x}(x_0^+, t) - \frac{\partial (V_0 + \epsilon V_1)}{\partial x}(x_0^-, t) = b(V_0 + \epsilon V_1) F(C_0) + \epsilon b^2 F^2(C_0) V_0 \gamma + \epsilon F'(C_0) C_1 V_0.$$

We note from (28) that $F'(C_0) = O(\epsilon)$. Then dropping the $O(\epsilon^2)$ terms, we have

$$\frac{\partial V}{\partial x}(x_0^+, t) - \frac{\partial V}{\partial x}(x_0^-, t) = bVF(C_0)(1 + \epsilon bF(C_0)\gamma). \tag{52}$$

From (33) and (34) we have that V is piecewise linear. Using the BC's we have

$$\frac{V(x_0, t) + 1}{x_0} = \frac{\partial V}{\partial x} \quad \text{on} \quad 0 \le x < x_0 \quad \text{and} \quad \frac{\partial V}{\partial x} = 0 \quad \text{on} \quad x_0 < x \le 1. \tag{53}$$

Using the above in (52) and solving for $V(x_0, t)$, we obtain

$$V(x_0, t) = \frac{1}{1 + bx_0F(C_0)(1 + \epsilon bF(C_0)\gamma)}.$$

Now, from (9) and (53) we have

$$I = -\frac{\partial V}{\partial x}(0, t) = -\frac{\partial V}{\partial x}(x_0^-, t) = \frac{bF(C_0)(1 + \epsilon bF(C_0)\gamma)}{1 + bx_0F(C_0)(1 + \epsilon bF(C_0)\gamma)}, \tag{54}$$

where we have used our expression above for V.

4 Numerical computations with the perturbation solution

We now use our perturbation solution approach to solve problems with simulated data and with real data from S. J. Kleene's lab (see [2] or [3] for more information on the experiments). We examine the case where $\rho \sim \delta$ and thus $\gamma = 0$. In this case we have from (54)

$$I(t) = \frac{bF(C_0(x_0, t))}{1 + bF(C_0(x_0, t))x_0}. \tag{55}$$

When considering situations with real data we note that the dimensional data current, $\tilde{I}(\tilde{t})$ tends to a limiting value as $\tilde{t} \to \infty$, so it is natural to define

$$I_\infty = \lim_{\tilde{t}\to\infty} \left[\frac{\tilde{I}(\tilde{t})}{I_c} \right].$$

Rewriting (55) with our form for F, we have

$$I(t) = \frac{b}{1 + bx_0 + \epsilon C_0^{-n}(x_0, t)}$$

so it is natural to take $I_\infty = b(1+bx_0)^{-1}$ in the perturbation expansion, which implies $b = I_\infty(1 - I_\infty x_0)^{-1}$. The only unknown in $I(t)$ in (55) now is the parameter x_0. We use current data to find a value for x_0 that minimizes the sum of squares (over the

available data points) of the differences between $I(t)$ and the perturbation formula in (55).

Thus there are two parts of our numerical computation. First, C_0 in (55) is computed. We used a sufficient number of terms in the separation of variables expansion (31) to ensure an accurate representation of C_0. The more major numerical computation in our procedure is the one-dimensional minimization. After determining an appropriate $\tilde{x}_0 = Lx_0$ we find a correction to b by noting that the experimental solutions tend to reach a steady state after $t = 1$. Therefore, we estimate I_∞ with data at that time:

$$I_\infty \cong \frac{b}{1 + bx_0 + \epsilon C_0^{-n}(x_0, 1)} \quad \text{so} \quad b \cong \frac{I_\infty}{1 - I_\infty x_0}(1 + \epsilon C_0^{-n}(x_0, 1)).$$

Below we detail our results for a simulated example where we know the cilium's channel distribution and an example with real data.

Example 1 (*Simulated*) Here we created current data by first solving a forward problem with $\tilde{\rho}(\tilde{x}) \sim \delta(\tilde{x} - \tilde{x}_0)$ where $\tilde{x}_0 = 1.7 \times 10^{-3}$ cm. We set $\tilde{\rho}$ so it has 400 CNG channels and the cilium length is $L = 5.0 \times 10^{-3}$ cm. The current resulting from this forward problem was used as data for our perturbation solution procedure. We took $C_\mathrm{b} = 40\ \mu$M.

Our procedure found $\tilde{x_0} = 1.76 \times 10^{-3}$ cm and, from the b-value, the total number of channels;

$$\text{Total number of channels} = \frac{b}{R_\mathrm{a} L g_\mathrm{CNG} P} \cong 409 \ \text{ Channels}.$$

Figure 2 has the true and perturbation currents which compare favorably in this case.

Example 2 Figure 3 displays the results from a case with real data. Here the perturbation procedure determined there were 290 channels and located the delta function distribution at $\tilde{x}_0 = 1.04 \times 10^{-3}$ cm.

These two examples show results that are quite common. However, in some cases, especially for cilia with larger numbers of channels, the current residuals were not as small.

Introducing a delay

As indicated above, the current from our perturbation approximation is not always accurate. This is primarily because at no time do we take into account the binding. Though it does occur only in a small region near the pulse for a small time, it does have an effect on the concentration (particularly the flux) for a time in the neighborhood of the pulse.

Handling the binding correctly would involve a complicated nonlinear boundary condition on the flux. But our simulations show that in effect, the binding delays the diffusive process. In particular, we note that once enough time has elapsed, C reaches a value where the approximation in (27) holds and then the binding can be neglected.

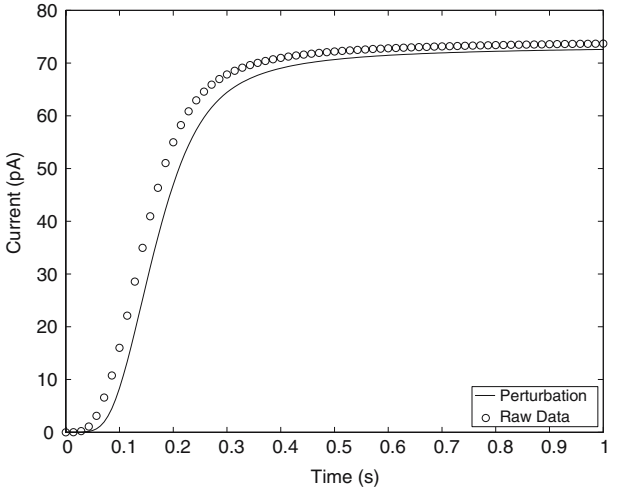

Fig. 2 The 400 channel simulated case described in Example 1. Comparison of true current and approximated current. Here $C_b = 40\mu M$ and $L = 5.0 \times 10^{-3}$ cm

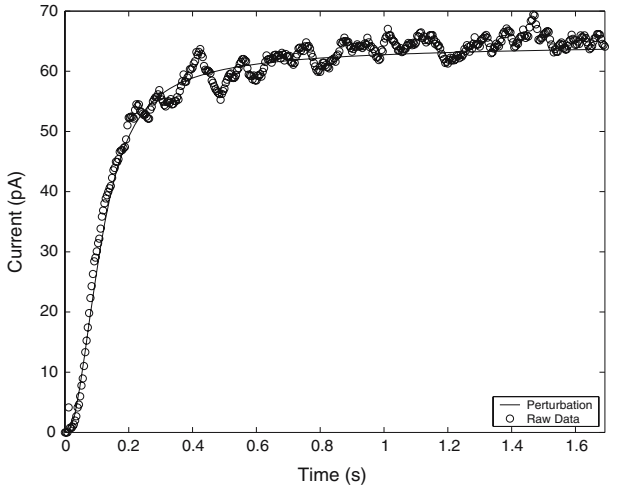

Fig. 3 Example 2 real data case. Here $C_b = 10\ \mu M$ and $L = 5.0 \times 10^{-3}$ cm. Comparison of true current and approximated current

The correct nonlinear boundary condition on C would require numerical solution, as discussed above.

Thus, what we wish to do instead is introduce a delay into the concentration as used in the computation of the current. In other words, since the current will depend on the *true* concentration at time t, it will depend on the *computed* concentration (which does not include the delay) at some time $t - \Delta t$, where Δt is the delay. Mathematically, we wish to replace (55) by

$$I_0 = -\frac{bF(C_0(x, t-\Delta t))}{1 + bF(C_0(x, t-\Delta t))x_0}. \tag{56}$$

To estimate the delay, we integrate (12) across the pulse:

$$0 = \left[\frac{\partial C}{\partial x}\right]_{x_0^-}^{x_0^+} - a\frac{\partial(F(C(x_0, t)))}{\partial t}, \tag{57}$$

where we have used the definition of ρ.

Next we examine the gradient terms. We assume that binding uses up all the flux into the pulse during this short delay period, so the gradient at x_0^+ is zero. On the left, computations of the concentration show an almost linear profile from $C(0, t) = 1$ to a very small value at $x = x_0$. Thus we may estimate the gradient at x_0^- by $-1/x_0$. Substituting these results into (57), we have

$$a\frac{\partial(F(C(x_0, t)))}{\partial t} = \frac{1}{x_0}.$$

Then integrating this equation to our delay time Δt, we have

$$a[F(C(x_0, \Delta t) - F(C(x_0, 0))] = \frac{\Delta t}{x_0}$$

so

$$\Delta t = aF(C(x_0, \Delta t))x_0, \tag{58}$$

where we have used the initial condition for C.

Thus the computation of the delay really calls for a choice of a threshold value of F. Thus we wish to select a value of F corresponding to a C above (which is equivalent to a time past) which binding is a minimal effect. The first choice might be to pick the value of F corresponding to maximum binding. Since the binding term in (12) may be written as

$$F'(C)\frac{\partial C}{\partial t},$$

(where the second term is assumed to be roughly the same size throughout the interval $(0, \Delta t)$), this corresponds to a maximum in $F'(C)$, or the value of F at which $F'' = 0$.

We hence calculate F'' in terms of F:

$$F'' = \frac{nF(1-F)}{C^2}\left[n(1-2F) - 1\right].$$

Therefore, the value of F at the inflection point of interest is given by

$$F = \frac{n-1}{2n}.$$

For the value of n we have chosen, this corresponds roughly to $F \approx 0.21$. Then we would substitute this value into (58) to obtain an estimate for Δt.

Simulations show that while this value of Δt does improve the fit, it is still too small. And upon reflection, we see that by choosing F at the inflection point, we are ignoring only the first half of the binding (up to the maximum of F'). Therefore, what we now wish to do is calculate the F corresponding to the latter inflection point *of* F'. This would then allow us to ignore much more of the binding.

Calculating $F^{(3)}$, we have

$$F^{(3)} = \frac{nF(1-F)}{C^3}\left[6n^2F^2 + 6n(1-n)F + n^2 - 3n + 2\right].$$

Therefore, the latter value of F at which $F^{(3)} = 0$ is given by

$$F = \frac{3(n-1) + \sqrt{3n^2 - 3}}{6n}.$$

For the value of n we have chosen, this corresponds roughly to $F \approx 0.44$. We found that the value 0.44 was too high and, therefore, used the value $1/3$ which is intermediate to the earlier estimate of 0.21 and this new 0.44.

Now we can devise the following iterative scheme. Given a problem with no delay ($\Delta t_0 = 0$), use our algorithm to compute estimates for b and x_0. This can be done as in Examples 1 and 2. ρ_c (and hence a) may be calculated from the computed b value. Once a and x_0 are calculated, a new Δt is calculated using (58):

$$\Delta t_{n+1} = F_* a(\Delta t_n) x_0(\Delta t_n) \equiv \mathcal{F}(\Delta t_n), \tag{59}$$

where we have chosen $F_* = 1/3$. This iteration should then have a fixed point Δt_* which will give better estimates for b and x_0 than $\Delta t = 0$. Unfortunately, we have found that the iterative scheme in (59) has very slow convergence, with oscillations about the fixed point Δt_*. Thus we replace the scheme (59) with

$$\Delta t_{n+1} = (1-\omega)\mathcal{F}(\Delta t_n) + \omega \Delta t_n. \tag{60}$$

(Note that fixed points of (60) are fixed points of (59).) We took $\omega = 1/2$ to speed convergence. We found that, typically, after 3–5 iterations the Δt_n's stabilized.

Below we have two examples where we have used this delay procedure. We evaluate a residual error for the current outputs for each case;

$$\text{Residual} = \frac{\sum_i |I_{\text{Data}}(t_i) - I_{\text{Appx}}(t_i)|}{\sum_i |I_{\text{Data}}(t_i)|}$$

where t_i are the data points.

Example 3 (*Simulated with 1,600 channels*) Figure 4 displays our results for data created from a delta function distribution located, as in Example 1, at 1.7×10^{-3} cm

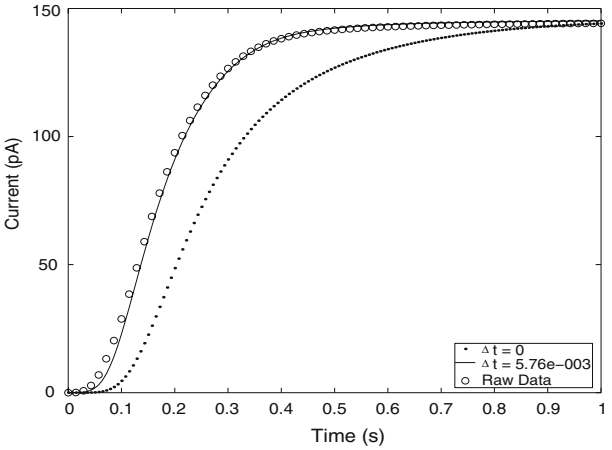

Fig. 4 Example 3 simulated data case. Here $C_\mathrm{b} = 40\ \mu$M and $L = 5.0 \times 10^{-3}$ cm

and with 1,600 channels. The location and channel count found with delay $\Delta t = 0$ s was $\tilde{x}_0 = 2.1 \times 10^{-3}$ cm with 4993 channels. However, 4 steps of the delay iteration procedure we found $\Delta t = 5.76 \times 10^{-3}$ s and an accurate estimate of the channel distribution with $\tilde{x}_0 = 1.66 \times 10^{-3}$ cm with 1685 channels. Figure 4 reveals the significant improvement in the residual by using this delay procedure. The residual for the $\Delta t = 0$ case was 0.137 while, after the iteration, with $\Delta t = 5.76 \times 10^{-3}$ was 0.012; which is a tenfold improvement.

Example 4 (*Real Data from the Kleene Lab*) Figure 5 displays our results for real data using the iteration scheme with 3 iterations. The cilium in this example was 7×10^{-3} cm and we had $C_\mathrm{b} = 20\ \mu$M. Again the delay iteration produced an improved approximation with final $\Delta t = 5.17 \times 10^{-3}$ s. Here we had $\tilde{x}_0 = 1.70 \times 10^{-3}$ cm and

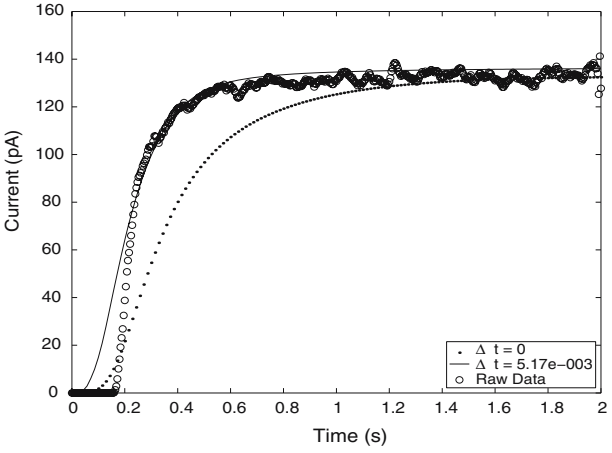

Fig. 5 Example 4 real data case. Here $C_\mathrm{b} = 20\ \mu$M and $L = 7.0 \times 10^{-3}$ cm

1385 channels. The residual for the $\Delta t = 0$ case was 0.099 while, after the iterations, the residual was 0.040 and the calculated delay was $\Delta t = 5.17 \times 10^{-3}$.

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Appendix

Now we use typical physical parameters to estimate our dimensionless parameters. The references for the physical constants throughout are [2] and [3]. We choose $C_\mathrm{b} = 30$ μM from the following range of values used in experiments:

$$5\,\mu\mathrm{M} \le C_\mathrm{b} \le 300\,\mu\mathrm{M}.$$

For $K_{1/2}$ and n, we have

$$K_{1/2} = 1.7\,\mu\mathrm{M} \quad \text{and} \quad n = 1.7.$$

Thus, ϵ is

$$\epsilon = \left(\frac{K_{1/2}}{C_\mathrm{b}}\right)^n = 7.60 \times 10^{-3}.$$

In order to calculate the characteristic current I_c, we need the following parameters:

$$V_\mathrm{b} = 50\ \mathrm{mV} = 5 \times 10^{-2}\ \mathrm{V}, \quad \text{and} \quad R_\mathrm{a} = 1.49 \times 10^{11}\ \frac{\Omega}{\mathrm{cm}}.$$

In the calculation of R_a, we note that the intracellular resistance is given by $R_\mathrm{a} = R_\mathrm{i}/A$, where A is the cross-sectional area. The intracellular resistivity R_i is known to be 91.7 Ω-cm. We took the diameter of the cilium to be 2.8×10^{-5} cm. We chose $L = 3 \times 10^{-3}$ cm from the following experimental range:

$$3 \times 10^{-3}\ \mathrm{cm} \le L \le 10 \times 10^{-3}\ \mathrm{cm}.$$

Then for the characteristic current we have

$$I_\mathrm{c} = \frac{V_\mathrm{b}}{R_\mathrm{a} L} = 112\ \mathrm{pA}.$$

For the characteristic density, experimental values range between

$$1.4 \times 10^5\ \frac{\mathrm{channel}}{\mathrm{cm}} \le \rho_\mathrm{c} \le 10^6\ \frac{\mathrm{channel}}{\mathrm{cm}}.$$

Again, we use a typical value, $\rho_\mathrm{c} = 3 \times 10^5$ channels/cm (900 channels).

To calculate b, we also need the following values, given in the text: $g_{\mathrm{CNG}} = 8.3 \times 10^{-12}(\Omega \cdot \text{channel})^{-1}$ and $P = 0.7$. We thus obtain the following value for b:

$$b = R_{\mathrm{a}} L^2 g_{\mathrm{CNG}} P V_{\mathrm{b}} \rho_{\mathrm{c}} = 2.35.$$

We may calculate the characteristic time scale once we have the following value: $D = 2.7 \times 10^{-6}\,\mathrm{cm}^2/\mathrm{s}$. Thus

$$t_{\mathrm{c}} = \frac{L^2}{D} = 3.33\ \mathrm{s}.$$

Note that this value is somewhat long compared to the time scale evident in the numerical simulations, but right on par with the physical experiments.

To calculate a, the only remaining parameter we need is α, which is given by

$$\alpha = \frac{1}{N_A A} = 2.7 \times 10^{-6} \frac{\mu\mathrm{M} \cdot \mathrm{cm}}{\mathrm{molecule}}$$

where $N_A = 6.0 \times 10^{23}$ molecules/mole is Avogadro's number. We also assign $B_S = 1.7$ molecules/channel (number of binding sites needed to activate the CNG channel current). With this we can now obtain the dimensionless parameter a,

$$a = \frac{\alpha \rho_{\mathrm{c}}}{C_{\mathrm{b}}} B_S = 4.6 \times 10^{-2}.$$

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