Numerical approach to three-dimensional model of cellular electrophysiology by the method of fundamental solutions

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Abstract
A three-dimensional model of cellular electrophysiology, the 3D cable model, is numerically studied. Our numerical scheme is constructed based on the method of fundamental solutions, which is a meshfree numerical solver for homogeneous linear partial differential equations. We numerically show the existence of pulse-like traveling wave solutions for the model.

Keywords cellular electrophysiology, 3D cable model, method of fundamental solutions

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1. Introduction

Many mathematical models for cellular electrophysiology have been developed over the past 60 years. Among them, the Hodgkin-Huxley model [1] and the FitzHugh-Nagumo model [2] play essential roles in understanding various electrophysiological phenomena. However, they are not suitable when the shapes of cells are complex, and the effects of intracellular structures should be considered. Therefore, another mathematical model is required to take into account the information on the shapes of three-dimensional cells.

In [3], Mori and Peskin constructed a mathematical model which takes into account both geometric effects and ionic concentration dynamics and solved it based on the finite volume method. In the present paper, we adopt the following two-phase problem, known as the 3D cable model, proposed by Eisenberg and Johnson [4]. Although this is a rather simple mathematical model compared with the one proposed in [3], we can construct a straightforward numerical scheme; therefore we expect that this problem enables us to study fundamental phenomena in cellular electrophysiology. Let \( \Omega_e \) be a bounded open set in \( \mathbb{R}^3 \) with a finite number of connected components, and assume that its boundary \( \Gamma \) is smooth. The region \( \Omega_i \) represents the interior of a cell, or a finite collection of cells and the boundary \( \Gamma \) corresponds to the cellular membrane. The extracellular space \( \Omega_e = \mathbb{R}^3 \setminus (\Omega_i \cup \Gamma) \) is assumed to be connected. Then, the problem is stated as follows:

\[
\begin{align*}
\Delta v_i &= 0 \quad \text{in } \Omega_i \times (0, T), \\
\Delta v_e &= 0 \quad \text{in } \Omega_e \times (0, T),
\end{align*}
\]

Here, \( v_i \) and \( v_e \) denote the electrostatic potentials in \( \Omega_i \) and \( \Omega_e \), respectively, \( \sigma_i \) and \( \sigma_e \) are the electric conductivities of \( \Omega_i \) and \( \Omega_e \), respectively and \( \mathbf{n} \) denotes the unit outward normal vector on \( \Gamma \). The function \( v = v_i - v_e \) is the membrane potential which represents the jump in the electrostatic potential across the membrane, \( w \) is called a gating variable and is defined solely on the membrane, and the functions \( v_0 \) and \( w_0 \) are given initial functions. A typical example of the functions \( f \) and \( g \) is the following cubic FitzHugh-Nagumo kinetics:

\[
f(v, w) = v(1 - v)(v - \alpha) - w, \quad g(v, w) = \epsilon(v - \gamma w),
\]

where \( 0 < \alpha < 1, \epsilon > 0, \gamma > 0 \) are constants. See Fig. 1 for geometrical settings in the cylindrical case.

In [5], Matano and Mori proved the existence of global classical solutions of (1) and studied their asymptotic behavior. They rewrote the original problem (1) into the system of a pseudo-differential equation and an ordinary differential equation on the membrane \( \Gamma \). It is hard to study the problem analytically, and hence numerical studies become powerful tools to understand the prop-
agitation of nerve impulses in a cell. This paper aims to study the behavior of solutions of (1) from a numerical point of view. Among several numerical solvers for Laplace equations (1a) and (1b), we adopt the method of fundamental solutions since it frequently offers a highly accurate approximate solution for elliptic partial differential equations without any mesh generation [6]. In numerical examples, we observe pulse-like waves propagating on the membrane.

2. Numerical scheme

Let $\tau$ be a given time increment and define $t_n = n \tau$ for $n = 0, 1, 2, \ldots$. Hereafter, $F^n$ denotes the approximation of a function $F = F(t)$ at $t = t_n$. First, using the method of fundamental solutions (MFS for short), we seek approximations of the harmonic functions $v_i$ and $v_e$ satisfying the boundary conditions (1c), (1d) and (1g). MFS offers approximate solutions for linear partial differential equations of the form $Lu = 0$ by a linear combination of the fundamental solution $E$ of $L$ with singularities being located outside the problem region. For the three-dimensional Laplace operator $L = \Delta$, the fundamental solution $E$ is given by $E(x) = 1/(4\pi|x|)$. Therefore, following the idea in [7], we see that $v_i(\cdot, t_n)$ and $v_e(\cdot, t_n)$ are respectively approximated by $v_i^n$ and $v_e^n$ of the forms

$$v_i^n(x) = Q_{i,0}^n + \sum_{k=1}^K Q_{i,k}^n E_{i,k}(x), \quad v_e^n(x) = \sum_{k=1}^K Q_{e,k}^n E_{e,k}(x),$$

where

$$E_{i,k}(x) = \left| \frac{z_{i,k} - y_{i,k}}{4\pi|x - y_{i,k}|} \right|, \quad E_{e,k}(x) = \left| \frac{z_{e,k} - y_{e,k}}{4\pi|x - y_{e,k}|} \right|,$$

in which $\{y_{i,k}\}_{k=1}^K \subset \Omega$ and $\{y_{e,k}\}_{k=1}^K \subset \Omega$ are singular points, and $\{z_{i,k}\}_{k=1}^K \subset \Omega$ and $\{z_{e,k}\}_{k=1}^K \subset \Omega$ are other points which we call dummy points. Note that $v_e^n$ naturally satisfies the boundary condition (1g).

Remark 1 In the usual formulation of MFS, a harmonic function is approximated by

$$\sum_{k=1}^K Q_k E(x - y_k),$$

This approximate solution is not invariant under scaling and translation of coordinates. For the two-dimensional case, Murota’s invariant scheme [8,9] gives an invariant approximate solution of the form

$$Q_0 + \sum_{k=1}^K Q_k E(x - y_k), \quad \sum_{k=1}^K Q_k = 0.$$

However, this does not work for the three-dimensional problem, since the above invariant scheme makes fully use of properties of the logarithmic function, the fundamental solution of the two-dimensional Laplace equation.

The coefficients $\{Q_{i,k}^n\}_{k=0}^K$ and $\{Q_{e,k}^n\}_{k=1}^K$ are determined by using the collocation method. We construct the collocation equations from (1c) and (1d). Taking collocation points $\{x_j\}_{j=1}^K$ on $\Gamma$, from (1c), we obtain

$$\sigma_i \frac{\partial v^{n+1}}{\partial n}(x_j) = \sigma_e \frac{\partial v^{n+1}}{\partial n}(x_j), \quad j = 1, 2, \ldots, K,$$

which is equivalent to

$$\sum_{k=1}^K Q_{i,k}^{n+1} \sigma_i \frac{\partial E_{i,k}}{\partial n}(x_j) - \sum_{k=1}^K Q_{e,k}^{n+1} \sigma_e \frac{\partial E_{e,k}}{\partial n}(x_j) = 0,$$

for $j = 1, 2, \ldots, K$. Concerning (1d), we adopt the following semi-implicit scheme:

$$\frac{v^{n+1}(x_j) - v^n(x_j)}{\tau} - \sigma_i \frac{\partial v^{n+1}}{\partial n}(x_j) = f(v^n(x_j), w^n(x_j)) = - \sigma_i \frac{\partial v^{n+1}}{\partial n}(x_j), \quad j = 1, 2, \ldots, K; \quad v^n := v_i^n - v_e^n,$$

from which we obtain the following:

$$Q_{i,0}^{n+1} + \sum_{k=1}^K Q_{i,k}^{n+1} \left( E_{i,k}(x_j) + \tau \sigma_i \frac{\partial E_{i,k}}{\partial n}(x_j) \right)$$

$$- \sum_{k=1}^K Q_{e,k}^{n+1} E_{e,k}(x_j) = v^n(x_j) + \tau f(v^n(x_j), w^n(x_j)) =: b^n_j, \quad j = 1, 2, \ldots, K.$$

We need an additional condition to determine the coefficients uniquely. In this paper, we adopt the following linear equation:

$$\sum_{k=1}^K Q_{i,k}^{n+1} = 0.$$

Summarizing the above, we obtain the following linear system:

$$GQ^{n+1} = b^n,$$

where

$$G = \begin{bmatrix} 0 & 1^T_K & 0^T_K \\ 0_K & G_{11} & G_{12} \\ 1_K & G_{21} & G_{22} \end{bmatrix},$$

$$G_{11} = \begin{bmatrix} \sigma_i \frac{\partial E_{i,k}}{\partial n}(x_j) & j, k = 1, 2, \ldots, K \end{bmatrix},$$

$$G_{12} = \begin{bmatrix} -\sigma_e \frac{\partial E_{e,k}}{\partial n}(x_j) & j, k = 1, 2, \ldots, K \end{bmatrix},$$

$$G_{21} = \begin{bmatrix} E_{i,k}(x_j) + \tau \sigma_i \frac{\partial E_{i,k}}{\partial n}(x_j) & j, k = 1, 2, \ldots, K \end{bmatrix},$$

$$G_{22} = \begin{bmatrix} -E_{e,k}(x_j) & j, k = 1, 2, \ldots, K \end{bmatrix}.$$
\[ Q^{n+1} = (Q^{n+1}_{1,0}, Q^{n+1}_{1,1}, \ldots, Q^{n+1}_{i,K}, Q^{n+1}_{i+1,1}, \ldots, Q^{n+1}_{i+1,K})^T, \]
\[ b^n = (0, 0^T, b^0_i, \ldots, b^0_K)^T, \]
\[ b^0_i = v^n(x_j) + \tau f(v^n(x_j), w^n(x_j)). \]

Solving the above linear system and discretizing (1f), we obtain approximations \( v^{n+1} \) and \( w^{n+1} \) as follows:
\[ v^{n+1}(x) = Q^{n+1}_{i,0} + \sum_{k=1}^{K} Q^{n+1}_{i,k} E_{i,k}(x) - \sum_{k=1}^{K} Q^{n+1}_{i,k} E_{i,k}(x), \]
\[ w^{n+1}(x) = w^n(x) + \tau g(v^n(x), w^n(x)). \]

3. Numerical examples

We demonstrate numerical examples when \( \Omega_i \) is a cylinder defined by
\[ \Omega_i = \left\{ x = (x, y, z)^T \mid -\frac{L}{2} < x < \frac{L}{2}, y^2 + z^2 < \rho^2 \right\}, \]
where \( L \) and \( \rho \) are positive numbers. We choose singular points, dummy points and collocation points in the following way (see Fig. 2 for graphic representations of these points):
\[ x_k = \left( \frac{L}{2} + \left( i - \frac{1}{2} \right) \Delta x, \rho \cos(j \Delta \theta), \rho \sin(j \Delta \theta) \right)^T, \]
\[ y_{i,e},k = \left( \frac{L}{2} + \left( i - \frac{1}{2} \right) \Delta x, R_{i,e} \cos(j \Delta \theta), R_{i,e} \sin(j \Delta \theta) \right)^T, \]
\[ z_{i,e},k = \left( \frac{L}{2} + \left( i - \frac{1}{2} \right) \Delta x, R_{i,e} \cos(j \Delta \theta), R_{i,e} \sin(j \Delta \theta) \right)^T, \]
\[ x_{MN+1} = \left( \frac{L}{2}, 0, 0 \right)^T, \quad x_{MN+2} = \left( \frac{L}{2}, 0, 0 \right)^T, \]
\[ y_{0,MN+1} = \left( \frac{L}{2} + (\kappa - 1)\rho, 0, 0 \right)^T, \]
\[ y_{0,MN+2} = -y_{0,MN+1}, \]
\[ y_{1,MN+1} = \left( \frac{L}{2} + (1 - \frac{1}{\kappa}) \rho, 0, 0 \right)^T, \]
\[ y_{1,MN+2} = -y_{1,MN+1}, \]
\[ z_{1,MN+1} = \left( \frac{L}{2} + (\kappa^2 - 1)\rho, 0, 0 \right)^T, \]
\[ z_{1,MN+2} = -z_{1,MN+1}, \]
\[ z_{0,MN+1} = \left( \frac{L}{2} + (1 - \frac{1}{\kappa^2}) \rho, 0, 0 \right)^T, \]
\[ z_{0,MN+2} = -z_{0,MN+1}, \]

where
\[ k = (i - 1)M + j, \quad i = 1, 2, \ldots, N, \quad j = 1, 2, \ldots, M, \]
\[ \Delta x = \frac{L}{N}, \quad \Delta \theta = \frac{2\pi}{M}, \quad R_1^d = \kappa \rho, \quad R_2^d = \kappa^{-1} \rho, \]
\[ R_1^d = \kappa^2 \rho, \quad R_2^d = \kappa^{-2} \rho, \]
and \( \kappa > 1 \) is a parameter, which is determined by trial and error and its optimal choice is not clear at this stage.

Fig. 2. Configurations of singular points, dummy points and collocation points with \( i = 2, j = 1, 2, \ldots, M, M = 8 \).

Fig. 3. Snapshots of time evolutions of \( v \) and \( w \) with initial values given by (3).

We set parameters as
\[ L = 40, \quad \rho = \frac{2}{3}, \quad \sigma_1 = \sigma_e = 0.1, \quad \tau = 0.02, \]
\[ M = 30, \quad N = 60, \quad \kappa = 3, \]
and the nonlinearities \( f \) and \( g \) are given by
\[ f(v, w) = v(1 - v)(v - 0.1) - w, \quad g(v, w) = 0.005(v - 3w). \]

In the above setting, we numerically find pulse-like traveling wave solutions to the problem (1). In all the following numerical examples, the linear system (2) is solved by using LU decomposition, and we take \( w^0 \equiv 0 \).

In the first example, \( v^0 \) is given by
\[ v^0(x, y, z) = \begin{cases} 0.5, & -\frac{L}{5} < x < \frac{L}{5}, \\ 0, & \text{otherwise}, \end{cases} \]

(3)
In this case, from both sides of the edges, two pulse-like traveling waves appear and they head for the center of the cylinder. See Fig. 4.

We finally consider the case where \( v^0 \) is given by

\[
v^0(x, y, z) = \begin{cases} 
0.5, & x > \frac{2L}{3}, \\
0, & \text{otherwise}.
\end{cases}
\]  

(5)

In this case, one pulse-like traveling wave appear near the support of \( v^0 \), and it heads for the other edge of the cylinder. See Fig. 5.

4. Concluding remarks

In this paper, we have developed a numerical scheme for solving the 3D cable model (1) based on the method of fundamental solutions and have verified its effectiveness by several numerical experiments. For future works, it would be required to compare our numerical results with ones using the one-dimensional FitzHugh-Nagumo system. Furthermore, it would be interesting to study how the shape of \( \Omega \) affects the behavior of solutions from the numerical point of view. Besides, if we overcome difficulties of general theoretical analysis of MFS, such as solvability and convergence, then it would be one of the powerful meshfree solvers of elliptic PDEs. Moreover, it is crucial to study the stability and the convergence analysis of this scheme mathematically. It is also vital to improve our numerical scheme so that it can solve the problem (1) where the problem region \( \Omega \) has a more complex configuration.

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