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Numerical study of pressure response to action potential by water permeation with ion transports

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Abstract

While the permeation mechanism of solute (e.g., ions and glucose) through biological membrane has been studied extensively, the mechanical role of water transport in intracellular phenomena has not received much attention. In the present study, to investigate the effect of water permeation on the intracellular pressure response, a novel permeation flux model through a biological membrane is developed by incorporating the coupling permeabilities (between water and ion fluxes) as the water–ion interaction in the ion channels. The proposed model is applied to a two–dimensional permeation problem of water and ions in a closed cell separated by a thin membrane. The permeation flux model reproduces the typical time response of intracellular pressure to action potentials with reasonable agreement with experimental results in the literature, indicating that the pressure response can be characterized by the following three parameters: water permeability, the mass ratio of water and ion, and the ratio of the permeation fluxes of water and ion. In particular, the permeation flux ratio plays an essential role in intracellular phenomena; depending on the value of the permeation flux ratio, the time lag between the action potential and the pressure response is 0.1 times smaller than that expected by the previous researchers, indicating that water transport associated with ions may trigger a pressure response. This study demonstrates the importance of water permeation in intracellular mechanical response through coupling of the fluid motion and electric fields.

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1 Introduction

Permeations of sodium and potassium ions from/to inside and outside through the respective ion channels induce action potential on the membrane, which is observed as a transient response of membrane potential. Hodgkin and Huxley proposed a parallel conductance model to explain the ion permeation by treating the axon membrane as a capacitor. They developed a set of time evolution equations for the membrane potential (i.e., the intracellular electric potential with respect to the extracellular potential), Hodgkin–Huxley (H–H) equations [1, 2, 3, 4, 5]. Although their model successfully reproduced the membrane excitation of axons with phenomenological permeation laws, the model did not include the effect of water molecules transported with ions on the axon membrane, and indeed it was later pointed out that membrane excitation in a number of phenomena may involve water permeation. For example, Hill et al. [6] reported a small radial contraction of crayfish axons in response to the generation of action potential. Furthermore, Tasaki and Iwasa [7, 8], Iwasa et al. [9], and Terakawa [10, 11] revealed that increases and decreases in intracellular pressure correspond to the depolarization and repolarization of the action potential (see Appendix A), respectively. Although it was known that solvent water molecules also permeate axon membranes at that time, the previous studies [7, 8, 9, 10, 11] concluded that the intracellular pressure response was caused by structural changes in the axon membrane and/or of cytoplasm, rather than by the permeation of water molecules, which was supported only recently [12].

The significance of water permeation has not drawn attention for the following two backgrounds: (1) only the number of water molecules permeating the membrane was focused on and not considered in terms of the fluid dynamics coupling mass and momentum fluxes, and (2) there was no model describing the water–ion interaction in the ion channels. There were several hypotheses regarding the factors that cause intracellular pressure to respond, and Tasaki and Iwasa [8] proposed verifying these hypotheses by measuring the time lag between the peaks of the membrane potential and the pressure rise. However, the generation mechanism of the pressure response is not clearly understood.

Some studies [13, 14, 15] indeed indicated that membrane permeation of water molecules causes intracellular pressure response. Kim et al. [13] recorded a transient volume change in nerve terminals induced by water transport associated with sodium inflow during the spike change of the action potential. However, they did not discuss water–ion interactions during permeation because the membrane proteins that transport water molecules were unclear.

Meanwhile, recent molecular dynamics studies [16, 17] have clarified the tertiary structure of the ion channels. Potassium ions pass through potassium channels in the completely dehydrated state [16], while sodium ions pass through sodium channels in the incompletely dehydrated state [17, 18]. The completely or incompletely dehydrated state of the ions suggests that the permeation molar fluxes of water and ions interact with each other in the ion channels. Based on these findings, Oiki et al. [19] successfully measured the molar permeation flux ratio, called the coupling ratio of water–ion flux, in a potassium channel. Their measurement of the flux ratio clarified the average distribution of water molecules and potassium ions in the channel.

In light of the above, by expressing the water–ion interaction in the ion channel with the coupling ratio of water–ion flux, the present study develops a new model of the water permeation flux associated with the sodium and potassium ion transports, through coupling with the equation of motion for a fluid as a continuous phase (i.e., Navier–Stokes equation). According to the phenomenological laws, water permeation flux is driven by intracellular pressure, membrane potential, and differences in ion concentration on the membrane. Whereas the time dependence of the membrane potential is described by the parallel conductance model of Hodgkin and Huxley [5], the intracellular pressure and difference in ion concentration are calculated from the flow and electric fields of fluid and ions adjacent to the membrane. Thus, we set up a fundamental system consisting of water and ions with the water–ion interaction in the continuous phase together with the permeation flux model; however ion–ion interactions are not considered. In addition, for simplicity, the present study does not address membrane deformation and changes in membrane thickness associated with the generation of action potentials. To discretize the fluid equation, our original discrete forcing immersed boundary (DF–IB) method [20, 21, 22, 23] is used to accurately calculate the trans–membrane flux with consistently coupled pressure and incompressible velocity fields, and the same discretization strategy is applied to solve the equations for the electric potential and concentration fields.

In this study, we focus on the water transportation in association with ions in the process of solute–solvent permeation through a membrane. After showing that water–ion transportation can be characterized by a small number of parameters, the significance of water permeation flux on the time responses of intracellular pressure and action potential is discussed.

2 Modeling

The governing equations for water, ions, and membrane potential are described in this section. In the following, the subscript γ is used to represent ion species. In the present study, γ takes either Na or K, and the summation convention is not applied to repeating γ indices. Hereafter, averaged variable across membrane is represented with a bar over a symbol (e.g. $\bar{\phi}$), except for ion conductance g_γ (see Appendix A).

2.1 Permeation flux model

Hodgkin and Huxley [5] reproduced the action potential by modeling the permeation currents of sodium and potassium ions in two steps: (i) following the phenomenological laws, the difference between the membrane potentials $\llbracket\psi\rrbracket$ and the equilibrium potential E_γ^0 is assumed to be the driving force inducing the ion permeation current I_γ , and the ion permeation current is linearly related to the driving force with conductance g_γ :

$$I_\gamma = g_\gamma(\llbracket\psi\rrbracket - E_\gamma^0),$$

and (ii) the conductance g_γ is identified based on the experimental results using the giant axon of squid. Here, the jump value $\llbracket\phi\rrbracket$ on the membrane for an arbitrary ϕ is defined as $\llbracket\phi\rrbracket = \phi_1 - \phi_2$, where ϕ_1 and ϕ_2 are the values on the membrane in the inner and outer sides of the axon.

In the present study, the permeation flux model for three-component electrolyte solutions is derived in the same steps as above by adopting the conductance of the H-H equations into that of the ion permeation current, which will be explained subsequently.

2.1.1 Permeation fluxes and driving forces

Because the phenomenological laws are derived from the second law of thermodynamics, the irreversible phenomena inside the membrane are focused on establishing a relation between the three-component permeation fluxes and the driving forces that induce them. If local equilibrium is assumed inside the membrane, the Gibbs equation yields the dissipation function (entropy generation) Φ as follows [24]:

$$\Phi = J_w \llbracket\mu_w\rrbracket + J_{Na} \llbracket\tilde{\mu}_{Na}\rrbracket + J_K \llbracket\tilde{\mu}_K\rrbracket, \quad (1)$$

where J_w and J_γ are the molar fluxes of water and ions relative to the motion of the membrane, respectively, and $\llbracket\mu_w\rrbracket$ and $\llbracket\tilde{\mu}_\gamma\rrbracket$ are the chemical potential jump of water and the electrochemical potential jump of ions

across the membrane, respectively. Assuming that membrane pores are filled with a dilute solution, the electrochemical potential jump $[[\tilde{\mu}_\gamma]]$ is expressed by the pressure jump (intracellular pressure) $[[p]]$, the electric potential jump (membrane potential) $[[\psi]]$, and the ion concentration jump $[[c_\gamma]]$ as follows:

$$[[\tilde{\mu}_\gamma]] = \bar{V}_\gamma [[p]] + z_\gamma \mathcal{F} [[\psi]] + RT \frac{[[c_\gamma]]}{\bar{c}_\gamma}, \quad (2)$$

where $\bar{V}_\gamma$ is the molar volume of ions, z_γ the valence of ions, $\mathcal{F}$ the Faraday constant, R the general gas constant, T the absolute temperature, and $\bar{c}_\gamma (\simeq (c_{\gamma 1} + c_{\gamma 2})/2)$ the ion concentration inside the membrane. Furthermore, the chemical potential jump of water $[[\mu_w]]$ can also be expressed from the Gibbs–Duhem equation using the jump values $[[p]]$, $[[\psi]]$ and $[[c_\gamma]]$ as follows:

$$[[\mu_w]] = \bar{V}_w \left[[[p]] - (z_{\text{Na}} \mathcal{F} \bar{c}_{\text{Na}} + z_{\text{K}} \mathcal{F} \bar{c}_{\text{K}}) [[\psi]] - RT ([[c_{\text{Na}}]] + [[c_{\text{K}}]]) \right], \quad (3)$$

where $\bar{c}_w \bar{V}_w \simeq 1$ is used according to the dilute solution assumption inside the membrane. Substituting Eqs.(2) and (3) into Eq.(1), the dissipation function is given as follows:

$$\begin{aligned} \Phi = & u_p [[p]] + \frac{I_{\text{pNa}}^d}{\bar{\rho}_{e\text{Na}}} \left[\bar{\rho}_{e\text{Na}} ([[\psi]]) - [[E_{\text{Na}}]] \right] \\ & + \frac{I_{\text{pK}}^d}{\bar{\rho}_{e\text{K}}} \left[\bar{\rho}_{e\text{K}} ([[\psi]]) - [[E_{\text{K}}]] \right], \end{aligned} \quad (4)$$

where u_p is the total permeation flux given as $u_p = J_w \bar{V}_w + J_{\text{Na}} \bar{V}_{\text{Na}} + J_{\text{K}} \bar{V}_{\text{K}}$, $\bar{\rho}_{e\gamma} (= z_\gamma \mathcal{F} \bar{c}_\gamma)$ the charge density inside the membrane, and $I_{\text{p}\gamma}^d$ and $[[E_\gamma]]$ are the ion permeation diffusion current and the equilibrium potential jump, respectively, defined as

$$\begin{aligned} I_{\text{p}\gamma}^d &= z_\gamma \mathcal{F} \left(J_\gamma - \frac{\bar{c}_\gamma}{\bar{c}_w} J_w \right), \\ [[E_\gamma]] &= - \frac{k_B T}{z_\gamma e} \frac{[[\rho_{e\gamma}]]}{\bar{\rho}_{e\gamma}}, \end{aligned}$$

where k_B and e are the Boltzmann constant and the electric elementary quantity, respectively, and $\rho_{e\gamma}$ is the charge density outside the membrane. Considering that the ion permeation velocity $J_\gamma \bar{V}_\gamma$ can be assumed significantly smaller than the water permeation velocity $J_w \bar{V}_w$, we can reasonably accept $u_p \simeq J_w \bar{V}_w$. Hereafter, the total permeation flux is referred to as water permeation velocity.

In the nonequilibrium thermodynamics, the dissipation function is the sum of the products of the permeation fluxes and the corresponding driving forces. For each term in the right-hand side of Eq.(4), the

permeation flux and corresponding driving force are paired, and the following phenomenological law relates the fluxes and forces:

$$\begin{pmatrix} u_p \\ I_{pNa}^d / \bar{\rho}_{eNa} \\ I_{pK}^d / \bar{\rho}_{eK} \end{pmatrix} = \mathbf{L} \begin{pmatrix} \llbracket p \rrbracket \\ \bar{\rho}_{eNa} (\llbracket \psi \rrbracket - \llbracket E_{Na} \rrbracket) \\ \bar{\rho}_{eK} (\llbracket \psi \rrbracket - \llbracket E_K \rrbracket) \end{pmatrix}, \quad (5)$$

where

$$\mathbf{L} = \begin{pmatrix} L_{ww} & L_{wNa} & L_{wK} \\ L_{NaW} & L_{NaNa} & L_{NaK} \\ L_{Kw} & L_{KNa} & L_{KK} \end{pmatrix}. \quad (6)$$

Eq.(5) is the permeation flux model proposed in this study, and Eq.(6) is the permeability matrix. The off-diagonal components of the permeability matrix represent the magnitude of interaction with the other components, and these components are referred to as coupling permeability coefficients, hereafter.

2.1.2 Modeling of permeability coefficients

Mathematical expressions for the permeability coefficients in Eq.(6) are derived specifically for the axon membrane in a form that corresponds to the H-H equations.

The six permeability coefficients in the second and third rows of the permeability matrix in Eq.(6) for the ion permeation diffusion currents $I_{p\gamma}^d$ are derived. The ion permeability coefficients L_{NaNa} and L_{KK} correspond to conductances in the H-H equations as follows:

$$L_{NaNa} = \frac{\bar{g}_{Na} m^3 h}{(\bar{\rho}_{eNa})^2}, \quad L_{KK} = \frac{\bar{g}_K n^4 + \bar{g}_l}{(\bar{\rho}_{eK})^2}, \quad (7)$$

where $\bar{g}_\gamma$, $\bar{g}_l$, m , h , and n are the parameters of the H-H equations; see Appendix A for details. The four permeability coefficients L_{NaK} , L_{KNa} , L_{NaW} , and L_{Kw} are zero as the ion-ion interactions and ion permeations by the intracellular pressure $\llbracket p \rrbracket$ are not considered in the present study.

Then, the remaining three permeability coefficients L_{ww} , L_{wNa} , and L_{wK} in the first row of the permeability matrix in Eq.(6) are modeled. The coupling permeability coefficients L_{wNa} and L_{wK} represent the water-ion interaction that are determined based on the distributions of water molecules and ions in the ion channels predicted by numerical studies [16, 17, 18]. According to Oiki et al. [19], the distribution of water molecules and ions in the ion channels can be modeled using the coupling ratio of water-ion flux

$$n_\gamma = \left(\frac{J_w}{J_\gamma} \right)_{\llbracket p \rrbracket=0}, \quad (8)$$

in the situations where the pressure jump is zero, which is equivalent to water molecules being transported only by ionic effects $\bar{\rho}_{e\gamma}(\llbracket\psi\rrbracket - \llbracket E_\gamma\rrbracket)$ across the ion channels. By introducing the coupling ratio of water-ion flux n_γ , the coupling permeation coefficients L_{wNa} and L_{wK} can be expressed using ion coefficients L_{NaNa} and L_{KK} as follows:

$$\frac{L_{w\gamma}}{L_{\gamma\gamma}} = \left(\frac{u_p}{I_{p\gamma}^d / \bar{\rho}_{e\gamma}} \right)_{\llbracket p\rrbracket=0} = \frac{J_w \bar{V}_w}{J_\gamma / \bar{c}_\gamma - J_w \bar{V}_w} \simeq n_\gamma \frac{\bar{c}_\gamma}{c_w}, \quad (9)$$

where it is assumed that the water concentration inside the membrane is equal to that outside the membrane c_w and that the ion concentration inside the membrane is dilute, i.e., $\bar{c}_\gamma / c_w \ll 1$. The water permeability coefficient L_{ww} is given as an independent parameter in this study.

In summary, the ion permeation coefficients L_{NaNa} and L_{KK} introduced by the model of Hodgkin and Huxley [5] are used in Eq.(5) to induce the ion permeation diffusion currents $I_{p\gamma}^d$ and in Eq.(7) to obtain the coupling permeation coefficients L_{wNa} and L_{wK} using Eq.(9), and together with the water permeation coefficients L_{ww} , the permeation flux model specific to axon membranes is completed.

In the subsequent sections, we refer to the electric potential jump $\llbracket\psi\rrbracket$ as membrane potential and the pressure jump $\llbracket p\rrbracket$ as intracellular pressure, following conventions in the field of neuronal cell biology.

2.2 Parallel conductance model

This study adopts the parallel conductance model developed by Hodgkin and Huxley [5], and the response of membrane potential to the external current is described by the following ordinary differential equation:

$$C_m \frac{d\llbracket\psi\rrbracket'}{dt} = I'_{\text{ext}} - I_{pNa} - I_{pK}, \quad (10)$$

where $\llbracket\psi\rrbracket'$ is the membrane potential relative to the resting potential -70 mV and I'_{ext} is explained in the following. In the present study, only potassium ions pass through the leak channels, and the equilibrium potentials are time-dependent unlike those in the H-H equations. These differences from the H-H equations can be adjusted by replacing I_{ext} with the following external current:

$$I'_{\text{ext}} = I_{\text{ext}} - g_{Na} \Delta E_{Na} - g_K \Delta E_K - g_l \Delta E_l, \quad (11)$$

where g_γ and g_l are ion conductances, and ΔE_γ and ΔE_l are, respectively, $\Delta E_\gamma = \llbracket E_\gamma\rrbracket - E_\gamma^0$ and $\Delta E_l = \llbracket E_K\rrbracket - E_l^0$, and I_{ext} is the external current adopted in the H-H equations. The ion concentration inside the membrane is sufficiently low that the convective terms ($\bar{\rho}_{e\gamma} u_p$) of ion permeation currents are negligible.

2.3 Governing equations in the continuous phase

The domains separated by the membrane are filled with water and ions (Na^+ and K^+), and those are treated as continuous phases.

Water is treated as an incompressible fluid, and its density and viscosity are assumed to be constant. The governing equations for the fluid are the equation of continuity and the Navier–Stokes (N–S) equation with electrostatic force and osmotic pressure terms:

$$\nabla \cdot \mathbf{u} = 0, \quad (12)$$

$$\begin{aligned} \rho_w \frac{\partial \mathbf{u}}{\partial t} + \rho_w \mathbf{u} \cdot \nabla \mathbf{u} \\ = -\nabla p + \eta_w \nabla^2 \mathbf{u} + \mathbf{f}_{\text{el}} + \mathbf{f}_{\text{osm}}, \end{aligned} \quad (13)$$

where ρ_w is the density, η_w the viscosity, and $\mathbf{u}$ the velocity of water. The electrostatic force $\mathbf{f}_{\text{el}}$ is expressed as follows:

$$\begin{aligned} \mathbf{f}_{\text{el}} &= \left(\sum_{\gamma} \rho_{e\gamma} - \rho_e^{\text{polar}} \right) \nabla \psi \\ &= \varepsilon_0 (\nabla \cdot \nabla \psi) \nabla \psi \\ &= \varepsilon_0 \nabla \psi \nabla^2 \psi, \end{aligned}$$

where ρ_e^{polar} is the polarization charge density and ε_0 is the permittivity of vacuum. For the osmotic pressure term $\mathbf{f}_{\text{osm}}$, the van't Hoff's law is applied:

$$\mathbf{f}_{\text{osm}} = - \sum_{\gamma} \frac{k_B T}{z_{\gamma} e} \nabla \rho_{e\gamma}.$$

The governing equations for ions are the Gauss' law and the Nernst–Planck (N–P) equation:

$$\nabla^2 \psi = -\frac{1}{\varepsilon_w} \sum_{\gamma} \rho_{e\gamma}, \quad (14)$$

$$\begin{aligned} \frac{\partial \rho_{e\gamma}}{\partial t} + \mathbf{u} \cdot \nabla \rho_{e\gamma} \\ = -\nabla \cdot D_{\gamma} \left(-\frac{z_{\gamma} e}{k_B T} \rho_{e\gamma} \nabla \psi - \nabla \rho_{e\gamma} \right), \end{aligned} \quad (15)$$

where ε_w is the permittivity of water and D_{γ} is the diffusion coefficient of ions.

The membrane potential calculated from the parallel conductance model is used as the boundary condition for the electric potential on the membrane. To apply the two-dimensional Gauss' law, a control

volume is considered to include part of the membrane as a boundary as shown in Fig. 1. Assuming that the electric potential gradient on the face normal to the membrane is zero, the following relation for the electric potential gradient on both sides of the membrane is obtained:

$$-\frac{\partial\psi}{\partial y}\bigg|_{\text{out}} + \frac{\partial\psi}{\partial y}\bigg|_{\text{in}} = \frac{b}{\varepsilon_w} \sum_{\gamma} \bar{\rho}_{e\gamma}, \quad (16)$$

where b is the membrane thickness. Along with Eq.(16), the membrane potential definition $[\psi] = -\psi|_{\text{out}} + \psi|_{\text{in}}$ is used to determine the electric potential field in the continuous phase.

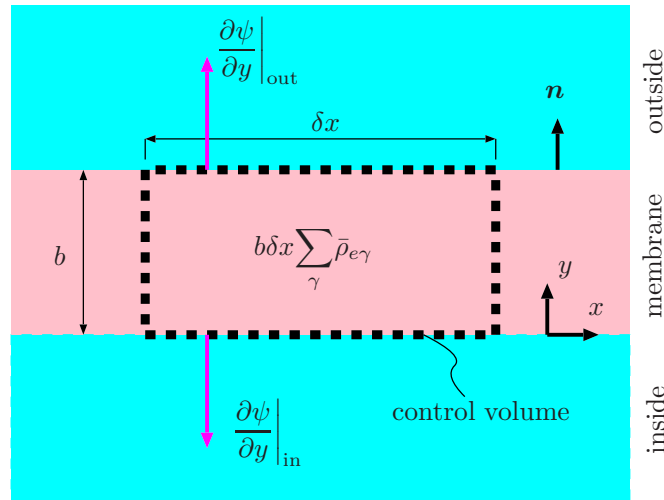


Figure 1: Schematic of the control volume that includes part of the membrane as a boundary to apply the Gauss' law in two dimensions.

2.4 Non-dimensionalization of the governing equations

The above governing equations are non-dimensionalized by the scaled variables, $x^* = x/H_0$, $y^* = y/H_0$, $t^* = t/t_0$, $\mathbf{u}^* = \mathbf{u}/U_0$, $p^* = p/(\rho_w U_0^2)$, $\psi^* = \psi/\psi_0$, $\rho_{e\gamma}^* = \rho_{e\gamma}/\rho_{e0}$, and $I_\gamma^* = I_\gamma/(\rho_{e0} U_0)$, where $U_0 = H_0/t_0$, H_0 the reference length, t_0 the reference time, ρ_{e0} the reference charge density, and ψ_0 the reference electric potential.

The non-dimensional parameters are as follows: $L_{ij}^* = L_{ij}/(H_0/\eta_w)$, $\mathcal{G}_\gamma = g_\gamma/(\rho_{e0} U_0/\psi_0)$, $M_0 = \rho_{e0} M_w/\rho_w \mathcal{F}$, $\mathcal{C}_m = C_m/(\rho_{e0} H_0/\psi_0)$, $\text{Re} = \rho_w H_0^2/\eta_w t_0$, $\mathcal{E}_l = \varepsilon_0 \psi_0^2 t_0/\eta_w H_0^2$, $\mathcal{O}_s = k_B T \rho_{e0} t_0/e\eta_w$, $\Psi_0 = e\psi_0/k_B T$, $\text{Pe} = H_0^2/D_0 t_0$, $\mathcal{D}_\gamma = D_\gamma/D_0$, $\epsilon_w = \varepsilon_w/\varepsilon_0$, and $\mathcal{L}_t = b/H_0$, where M_w is the molecular weight of water and D_0 is the characteristic diffusion coefficient.

The non-dimensional forms of the equations and parameters are summarized in the following.

The permeation flux model, Eq.(5):

$$\begin{pmatrix} u_p^* \\ I_{pNa}^d/\bar{\rho}_{eNa}^* \\ I_{pK}^d/\bar{\rho}_{eK}^* \end{pmatrix} = \mathbf{L}^* \begin{pmatrix} \text{Re}[\psi^*] \\ \bar{\rho}_{eNa}^* \mathcal{O}_s \Psi_0 ([\psi^*] - [E_{Na}^*]) \\ \bar{\rho}_{eK}^* \mathcal{O}_s \Psi_0 ([\psi^*] - [E_K^*]) \end{pmatrix}, \quad (17)$$

where

$$[E_\gamma^*] = -\frac{1}{z_\gamma \Psi_0} \frac{[\rho_{e\gamma}^*]}{\bar{\rho}_{e\gamma}^*}.$$

The ion permeability coefficients $L_{\gamma\gamma}$ in Eq.(7) and the ratio of $L_{w\gamma}^*$ to $L_{\gamma\gamma}^*$ in Eq.(9):

$$L_{NaNa}^* = \frac{1}{\mathcal{O}_s \Psi_0} \frac{\bar{\mathcal{G}}_{Na} m^3 h}{(\bar{\rho}_{eNa}^*)^2}, \quad L_{KK}^* = \frac{1}{\mathcal{O}_s \Psi_0} \frac{\bar{\mathcal{G}}_K n^4 + \bar{\mathcal{G}}_l}{(\bar{\rho}_{eK}^*)^2}, \quad (18)$$

$$\frac{L_{w\gamma}^*}{L_{\gamma\gamma}^*} = n_\gamma \frac{M_0 \bar{\rho}_{e\gamma}^*}{z_\gamma}, \quad (19)$$

and the remaining permeability coefficients are zero.

The parallel conductance model, Eq.(10):

$$\mathcal{C}_m \frac{d[\psi^*]'}{dt^*} = I_{\text{ext}}^* - I_{pNa}^* - I_{pK}^*. \quad (20)$$

The details of the parameters comprising the ion currents $I_{p\gamma}^*$ in the right-hand side are shown in Appendix A.

The governing equations for the continuous phases, Eqs.(12), (13), (14), and (15):

$$\nabla^* \cdot \mathbf{u}^* = 0, \quad (21)$$

$$\begin{aligned} & \frac{\partial \mathbf{u}^*}{\partial t^*} + \mathbf{u}^* \cdot \nabla^* \mathbf{u}^* \\ &= -\nabla^* p^* + \frac{1}{\text{Re}} \nabla^{*2} \mathbf{u}^* \\ &+ \frac{\mathcal{E}_l}{\text{Re}} \nabla^* \psi^* \nabla^{*2} \psi^* - \frac{\mathcal{O}_s}{\text{Re}} \sum_\gamma \frac{1}{z_\gamma} \nabla^* \rho_{e\gamma}^*, \end{aligned} \quad (22)$$

$$\nabla^{*2} \psi^* = -\frac{\mathcal{O}_s \Psi_0}{\epsilon_w \mathcal{E}_l} \sum_\gamma \rho_{e\gamma}^*, \quad (23)$$

$$\begin{aligned} & \frac{\partial \rho_{e\gamma}^*}{\partial t^*} + \mathbf{u}^* \cdot \nabla^* \rho_{e\gamma}^* \\ &= -\nabla^* \cdot \frac{\mathcal{D}_\gamma}{\text{Pe}} \left(-z_\gamma \Psi_0 \rho_{e\gamma}^* \nabla^* \psi^* - \nabla^* \rho_{e\gamma}^* \right). \end{aligned} \quad (24)$$

The relation between the electric potential gradients on both sides of the membrane, Eq.(16):

$$-\left.\frac{\partial\psi^*}{\partial y^*}\right|_{\text{out}} + \left.\frac{\partial\psi^*}{\partial y^*}\right|_{\text{in}} = \frac{\mathcal{O}_s\Psi_0\mathcal{L}_t}{\epsilon_w\mathcal{E}_l} \sum_{\gamma} \bar{\rho}_{e\gamma}^*. \quad (25)$$

The time advancement of the entire system, Eq.(17) ~ Eq.(25), is performed using the standard numerical methods. For more detail, see Appendix B.

3 Validation

3.1 Problem statement

We set up a problem of the permeations of sodium and potassium ions and water through a straight axon membrane fixed in a two-dimensional rectangular domain of size $L_x \times L_y (= 2H_0 \times H_0)$ as shown in Fig. 2, where the value of the reference length H_0 is assumed to be $1 \mu\text{m}$ so that it is comparable to the size of a typical axon diameter and that the solution can be considered as a continuum. The permeable membrane is placed at the center of the computational domain along the x axis.

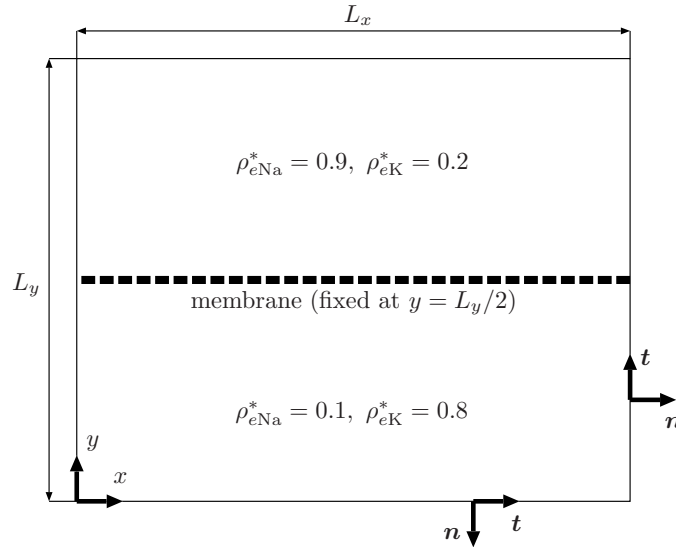


Figure 2: Schematic of the computational domain and initial condition for the ion concentration. The regions $y^* < L_y/2$ and $y^* > L_y/2$ are considered to be inside and the outside of the axon, respectively.

The initial conditions for the fluid velocity and pressure fields are $\mathbf{u}^* = \mathbf{0}$ and $p^* = 0$ throughout the computational domain. The initial conditions for the ion concentration field are as follows:

$$\begin{aligned} \rho_{eNa}^* &= 0.9, \quad \rho_{eK}^* = 0.2 & : & \text{outside the axon,} \\ \rho_{eNa}^* &= 0.1, \quad \rho_{eK}^* = 0.8 & : & \text{inside the axon,} \end{aligned}$$

and the membrane potential $[\psi^*] = -1$ is given uniformly along the membrane. An external current I_{ext}^* is uniformly imposed on the membrane.

The boundaries of the computational domain are treated as wall, and the fluid velocity and pressure obey the impermeable and non-slip boundary conditions and the Neumann boundary condition, respectively:

$$\mathbf{u}^*|_{\text{wall}} \cdot \mathbf{n} = 0, \quad \mathbf{u}^*|_{\text{wall}} \cdot \mathbf{t} = 0, \quad (26)$$

$$\nabla^* p^*|_{\text{wall}} \cdot \mathbf{n} = 0, \quad (27)$$

where $\mathbf{n}$ and $\mathbf{t}$ are the unit normal and tangent vectors on the boundary, respectively (see Fig. 2). The impermeable boundaries result in zero water permeation flux u_p^* from/to inside and outside axons. The boundary conditions for the currents and electric potential are the impermeable and the Dirichlet conditions, respectively:

$$\mathbf{I}_\gamma^*|_{\text{wall}} \cdot \mathbf{n} = 0, \quad (28)$$

$$\psi^*|_{\text{wall}} = 0. \quad (29)$$

On the membrane, the fluid flux parallel to the membrane is zero (i.e., non-slip boundary condition) and the pressure gradient normal to the membrane is zero although a pressure jump $[p]$ exists across membrane.

3.2 Simulation conditions

The simulation parameters are set as follows: the grid resolution is $\Delta = L_x/128 = L_y/64$, the time increment $\Delta t^* = 5 \times 10^{-7}$, the thickness of membrane $\mathcal{L}_t = 10^{-4}$, the coupling coefficients $\mathcal{E}_l = 0.01$, $\mathcal{O}_s = 0.01$, and $\Psi_0 = 1$, the diffusion coefficients $\mathcal{D}_{\text{Na}} = \mathcal{D}_{\text{K}} = 1$, the valence of ions $z_{\text{Na}} = z_{\text{K}} = 1$, and the relative permittivity of the fluid $\epsilon_w = 1$. The Reynolds and Peclet numbers are fixed at $\text{Re} = 1$ and $\text{Pe} = 1$, respectively. The magnitude of the applied external current is $I_{\text{ext}} = 4[\mu\text{A}/\text{cm}^2]$, which corresponds to the non-dimensional current of $I_{\text{ext}}^* = 4 \times 10^{-2}/(\rho_{e0}(H_0/t_0))$. Under this condition, an action potential emerges only once (see Appendix A) just as observed in the previous experiments [7, 8, 9, 10, 11]. The uniform and steady external current $I_{\text{ext}}^* = 4 \times 10^{-2}/(\rho_{e0}(H_0/t_0))$ is applied to the membrane after $t^* = 1$ when both fluid and ion fields are considered to reach steady state.

We investigate the changes in the pressure response to action potentials by varying the following parameters: the water permeability coefficient L_{ww}^* , the water-ion mass ratio M_0 , and the coupling ratios of water-ion flux n_{Na} and n_{K} .

3.3 Results

Fig. 3 shows the intracellular pressure at $x^* = L_x/2$ and the action potential under the condition of $L_{ww}^* = 1 \times 10^{-6}$, $M_0 = 1 \times 10^{-3}$, and $n_{Na} = n_K = 1$. The increasing and decreasing phases of the pressure in the figure correspond to the depolarization and repolarization, respectively, which are consistent with the results of previous experimental studies [7, 8, 9, 10, 11]. The figure shows the typical response of intracellular pressure to the emergence of an action potential, which will be explained subsequently.

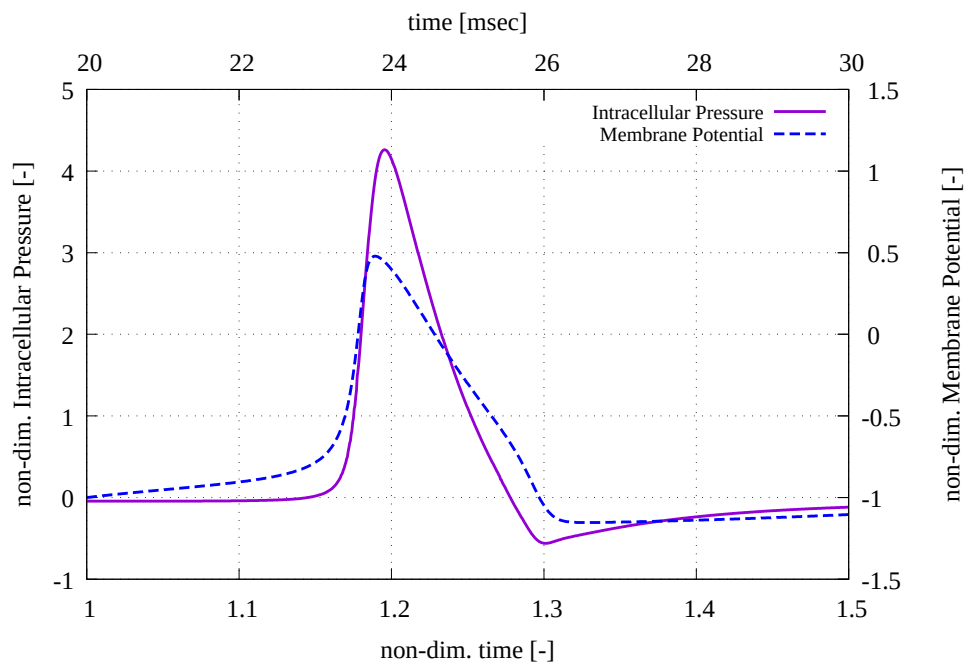


Figure 3: The typical time response of the intracellular pressure at $x^* = L_x/2$ associated with the generation of the action potential under the condition $L_{ww}^* = 1 \times 10^{-6}$, $M_0 = 1 \times 10^{-3}$, and $n_{Na} = n_K = 1$. The reference time is set as $t_0 = 20$ [msec], and the non-dimensional external current $I_{ext}^* = 4 \times 10^{-2}/(\rho_{e0}(H_0/t_0))$ is applied to the membrane uniformly at non-dimensional time $t^* = 1$ and kept constant thereafter.

We discuss the validity of the model of the coupling permeability coefficients L_{wNa}^* and L_{wK}^* in Eq.(19), which represent the water-ion interactions in the ion channels. Fig. 4 compares the pressure responses for the following four combinations of the permeability coefficients: (a) both L_{wNa}^* and L_{wK}^* are modeled by Eq.(19); (b) only L_{wNa}^* is modeled by Eq.(19) and L_{wK}^* is fixed at the constant value of 0.5×10^{-6} , which

is half the value of L_{ww}^* ; (c) only L_{wK}^* is modeled by Eq.(19) and L_{wNa}^* is fixed at the constant value of 0.5×10^{-6} ; and (d) both L_{wNa}^* and L_{wK}^* are fixed at the constant value of 0.5×10^{-6} . Note that case (a) is the same condition as in Fig. 3.

In case (a), both positive and negative intracellular pressures are generated as the membrane potential changes. In cases (b) and (c), only positive or negative intracellular pressure appears. In case (d), no intracellular pressure response is observed in response to the changes in membrane potential. The pressure responses in case (a) exhibit reasonable agreement with the experimental results in the previous studies [7, 8, 9, 10, 11], indicating the validity of the modeling of the coupling permeability coefficients L_{wNa}^* and L_{wK}^* in Eq.(19).

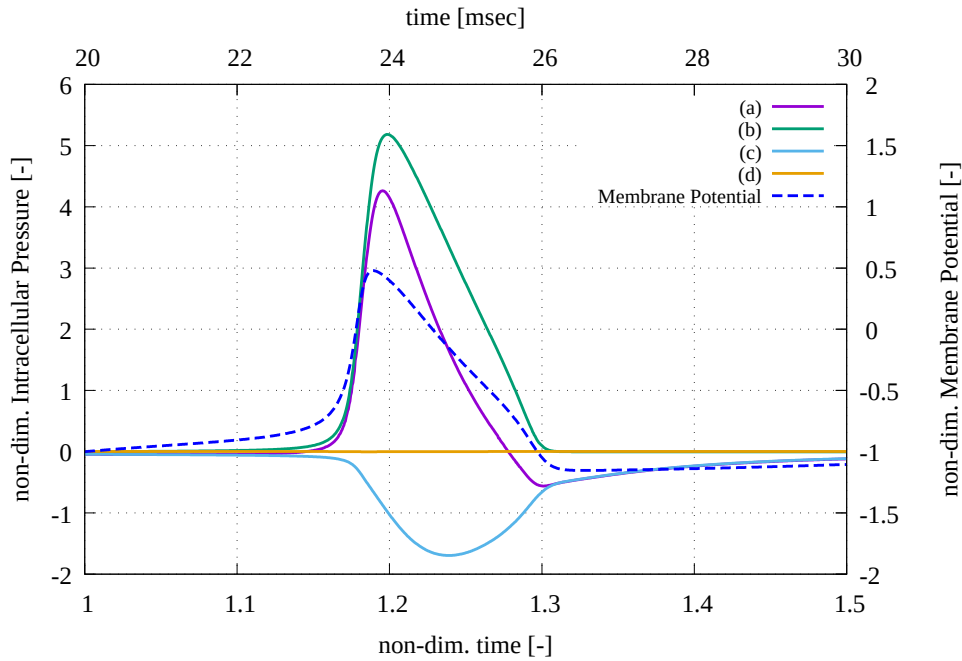


Figure 4: The pressure response to the action potential with or without the model described by Eq.(19) for the coupling permeability coefficients L_{wNa}^* and L_{wK}^* in the cases where (a) both L_{wNa}^* and L_{wK}^* are modeled by Eq.(19), (b) only L_{wNa}^* is modeled by Eq.(19), (c) only L_{wK}^* is modeled by Eq.(19), and (d) no model in Eq.(19) is given to any of them. The parameters are the same as Fig. 3.

Fig. 4 shows that the both rising and falling phases of pressure response emerge only when $L_{w\gamma}^*$ is modeled by Eq.(19), indicating that the pressure response is induced by the water inflow or outflow associated with the ion transports through the membrane. To investigate the contribution of each permeation flow to

water permeation flux u_p^* as expressed in Eq.(17), the time evolutions of the following three components (together with the net water permeation flux and action potential) are visualized in Fig. 5: the pressure-driven flow $L_{ww}^* \text{Re}[\psi^*]$, the Na^+ electroosmotic flow $L_{w\text{Na}}^* \bar{\rho}_{e\text{Na}}^* \mathcal{O}_s \Psi_0(\llbracket \psi^* \rrbracket - \llbracket E_{\text{Na}}^* \rrbracket)$, and the K^+ electroosmotic flow $L_{w\text{K}}^* \bar{\rho}_{e\text{K}}^* \mathcal{O}_s \Psi_0(\llbracket \psi^* \rrbracket - \llbracket E_{\text{K}}^* \rrbracket)$. Positive and negative values represent outflow and inflow, respectively. The figure shows that water molecules permeate with Na^+ and K^+ flow in and out of the axon, respectively. As the net water permeation is almost zero from the mass conservation law within the region enclosing the membrane, the pressure-driven flux is induced to counteract the sum of the electroosmotic flows. In addition, the Na^+ electroosmotic flow emerges earlier than the K^+ electroosmotic flow according to the mechanism of the H–H equations. Based on this time difference between the occurrences of two electroosmotic flows, we can also reasonably explain the correspondence of the depolarization and repolarization of the action potential to the increasing and decreasing phases of the pressure, respectively.

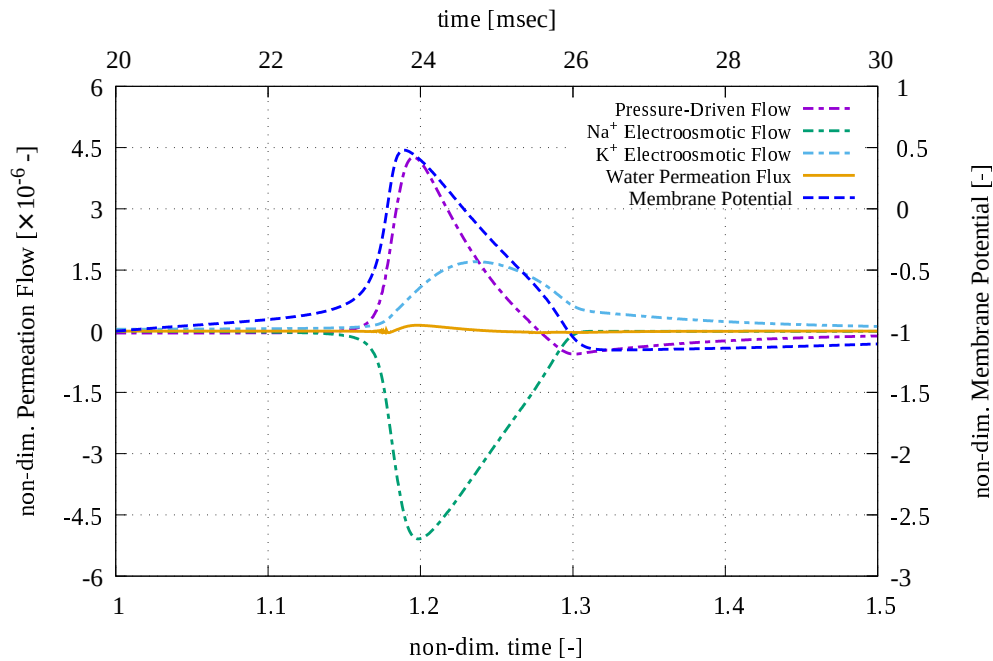


Figure 5: Comparison of the time evolutions of three permeation flows (i.e., pressure-driven flow and electroosmotic flows of Na^+ and K^+) and the water flux together with that of the action potential. The parameters are the same as Fig. 3.

4 Discussion

In this section, we investigate the effects of the water permeability coefficient L_{ww}^* , water-ion mass ratio M_0 and coupling ratio of water-ion flux n_γ on the pressure response and discuss the time lag between the action potential and pressure response.

4.1 Parameters affecting the pressure response

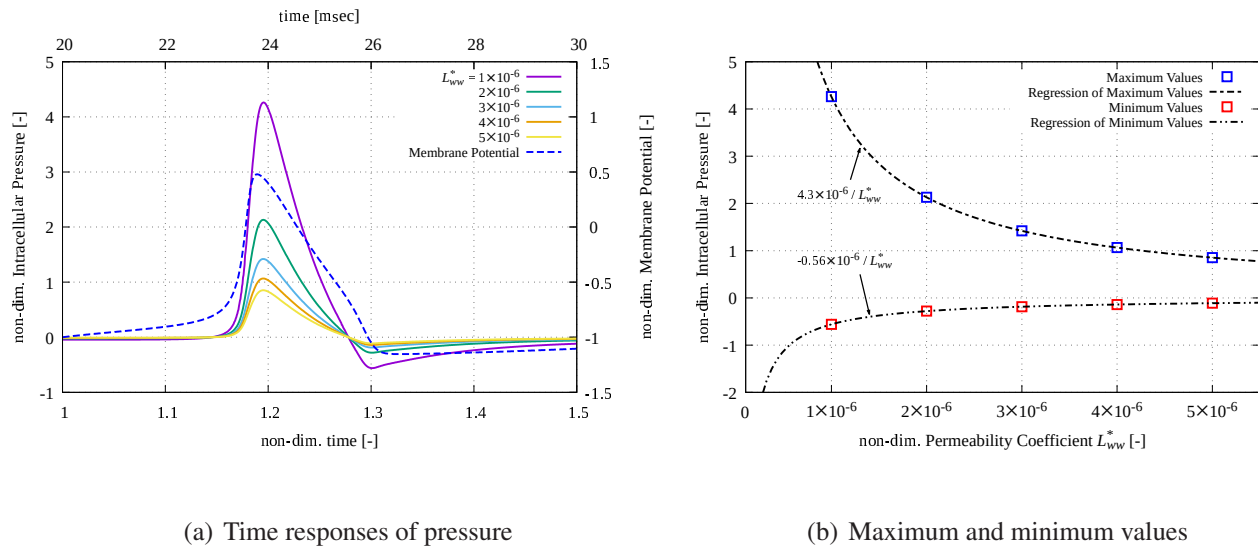


Figure 6: The effect of L_{ww}^* on the intracellular pressure. (a) Comparison of the time evolutions of the intracellular pressure (together with that of the action potential) for the following ranges of the water permeability coefficient: $L_{ww}^* = 1 \times 10^{-6}$, 2×10^{-6} , 3×10^{-6} , 4×10^{-6} , 5×10^{-6} . (b) The maximum and minimum values of the intracellular pressure for each water permeability coefficient L_{ww}^* in (a).

Fig. 6(a) compares the time responses of the pressure for the different water permeability coefficients in the following range: $L_{ww}^* = 1 \times 10^{-6}$, 2×10^{-6} , 3×10^{-6} , 4×10^{-6} , 5×10^{-6} . The values of M_0 and n_γ are fixed at 1×10^{-3} and 1, respectively. In the figure, the amplitudes of the pressure variation decrease as L_{ww}^* increases. The maximum and minimum values of the intracellular pressure are summarized in Fig. 6(b) as a function of L_{ww}^* . Both the maximum and minimum intracellular pressures are inversely proportional to the water permeability coefficient, and the absolute value of the ratio of the maximum to minimum intracellular pressures is 7.6 for all the L_{ww}^* cases. The result indicates that the magnitude of the pressure response is

primarily influenced by the water permeability coefficient and that the time–response profiles (Fig. 6(a)) are self–similar. This result is not surprising given that the intracellular pressure is generated to counteract the electroosmotic flows; as the electroosmotic flows induced by the membrane excitation are independent of the water permeability coefficient and the pressure–driven flow is modeled as the product of the water permeability coefficient and intracellular pressure (i.e., $L_{ww}^* \text{Re}[\llbracket p^* \rrbracket]$), the water permeability coefficient and the order of the magnitude of the intracellular pressure are inversely proportional to each other (to maintain the net zero water permeation flux):

$$\llbracket p^* \rrbracket = -\frac{M_0}{L_{ww}^* \text{Re}} \sum_{\gamma} \frac{n_{\gamma}}{z_{\gamma}} I_{p\gamma}^* , \quad (30)$$

which is obtained by fixing $u_p^* = 0$ in Eq. (17). In addition, effect of radial variation of membrane on the above equation is discussed in Appendix C.

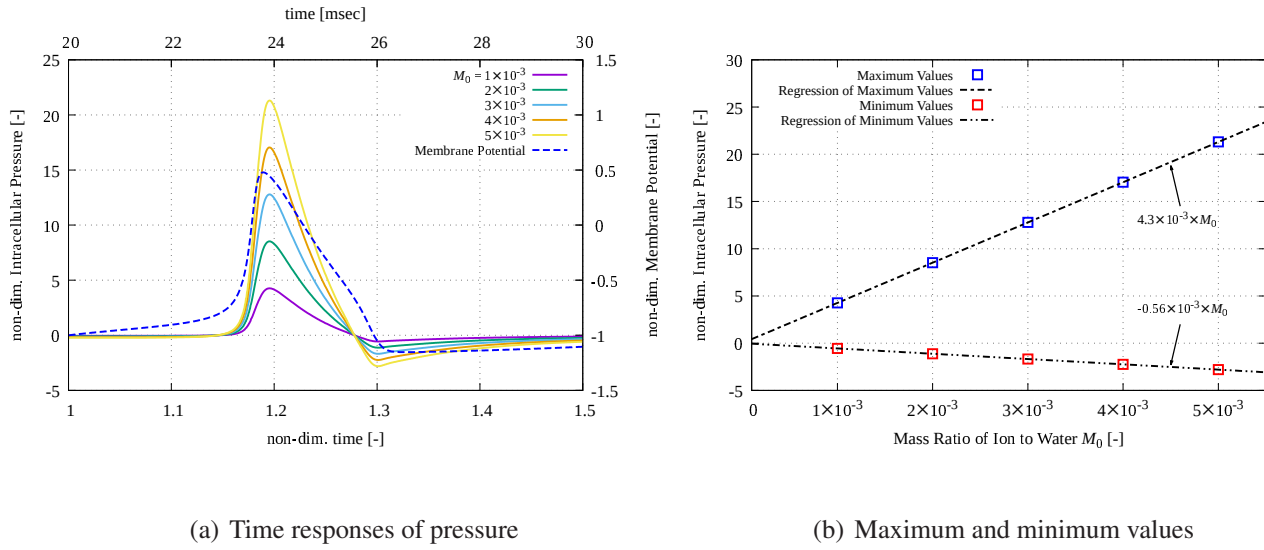


Figure 7: The effect of M_0 on the intracellular pressure. (a) The intracellular pressure (together with that of the action potential) for the following ranges of the mass ratio of ion to water: $M_0 = 1 \times 10^{-3}, 2 \times 10^{-3}, 3 \times 10^{-3}, 4 \times 10^{-3}, 5 \times 10^{-3}$. (b) The maximum and minimum values of the intracellular pressure for each mass ratio of ion to water M_0 in (a).

Fig. 7(a) shows the time evolutions of the pressure for the different water–ion mass ratios in the following range: $M_0 = 1 \times 10^{-3}, 2 \times 10^{-3}, 3 \times 10^{-3}, 4 \times 10^{-3}, 5 \times 10^{-3}$. Throughout the simulations, the values of L_{ww}^* and n_{γ} are fixed at 1×10^{-6} and 1, respectively. A larger water–ion mass ratio causes a larger

variation in pressure. The maximum and minimum values of the intracellular pressure in Fig. 7(b) are in proportion to M_0 , and the absolute value of the ratio of the maximum to the minimum intracellular pressure is again found to be 7.6 for all the M_0 cases. The common scaling factor indicates that both L_{ww}^* and M_0 are major factors that determine the magnitude of the amplitude of the time response of the intracellular pressure $[[p^*]]$.

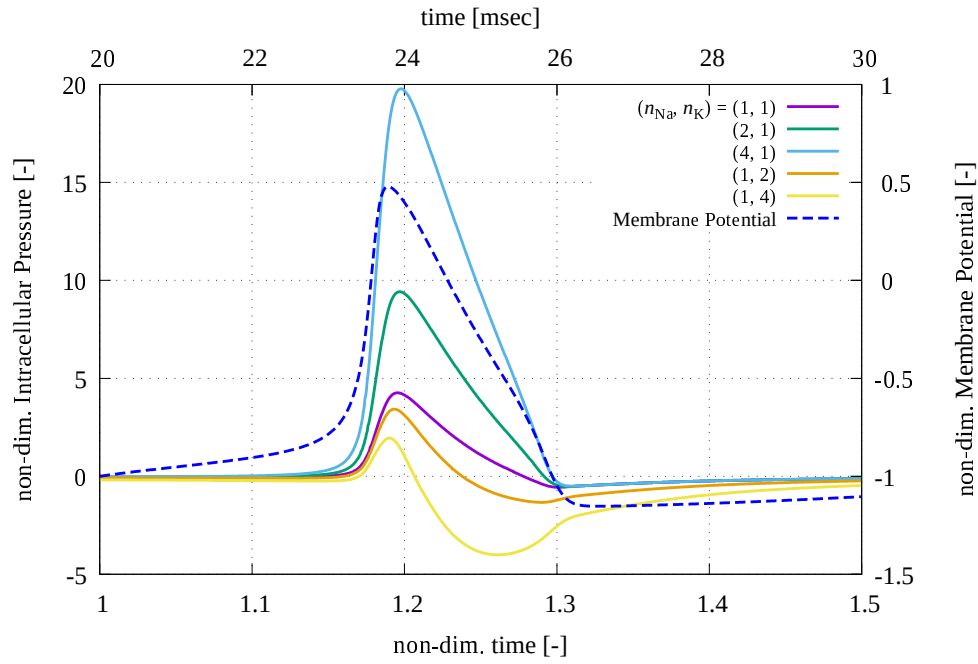


Figure 8: The pressure response to the action potential for the following combinations of the coupling ratios of water–ion flux: $(n_{Na}, n_K) = (1, 1), (2, 1), (4, 1), (1, 2), (1, 4)$. The parameters are the same as Fig. 3.

Finally, we investigate the effect of water–ion interactions in the ion channels on the pressure response. Fig. 8 shows the pressure responses for the following combinations of the coupling ratios of water–ion flux: $(n_{Na}, n_K) = (1, 1), (2, 1), (4, 1), (1, 2), (1, 4)$. In this attempt, L_{ww}^* and M_0 are fixed at the following values: $L_{ww}^* = 1 \times 10^{-6}$ and $M_0 = 1 \times 10^{-3}$. The trends in the pressure development in Fig. 8 may be summarized that the larger n_{Na} and n_K induce the stronger positive and negative phases in the pressure response, respectively. Fig. 9 compares the time developments of the permeation flows for the above cases of the coupling ratios except for $(n_{Na}, n_K) = (1, 1)$. Considering that the coupling ratio of water–ion flux (Eq. (8)) represents the number of water molecules that pass through an ion channel with respect to one ion

molecule, a larger coupling ratio induces a larger electroosmotic flow (Fig. 9(b)), and in return, the larger intracellular pressure to conserve the net water permeation flux u_p^* .

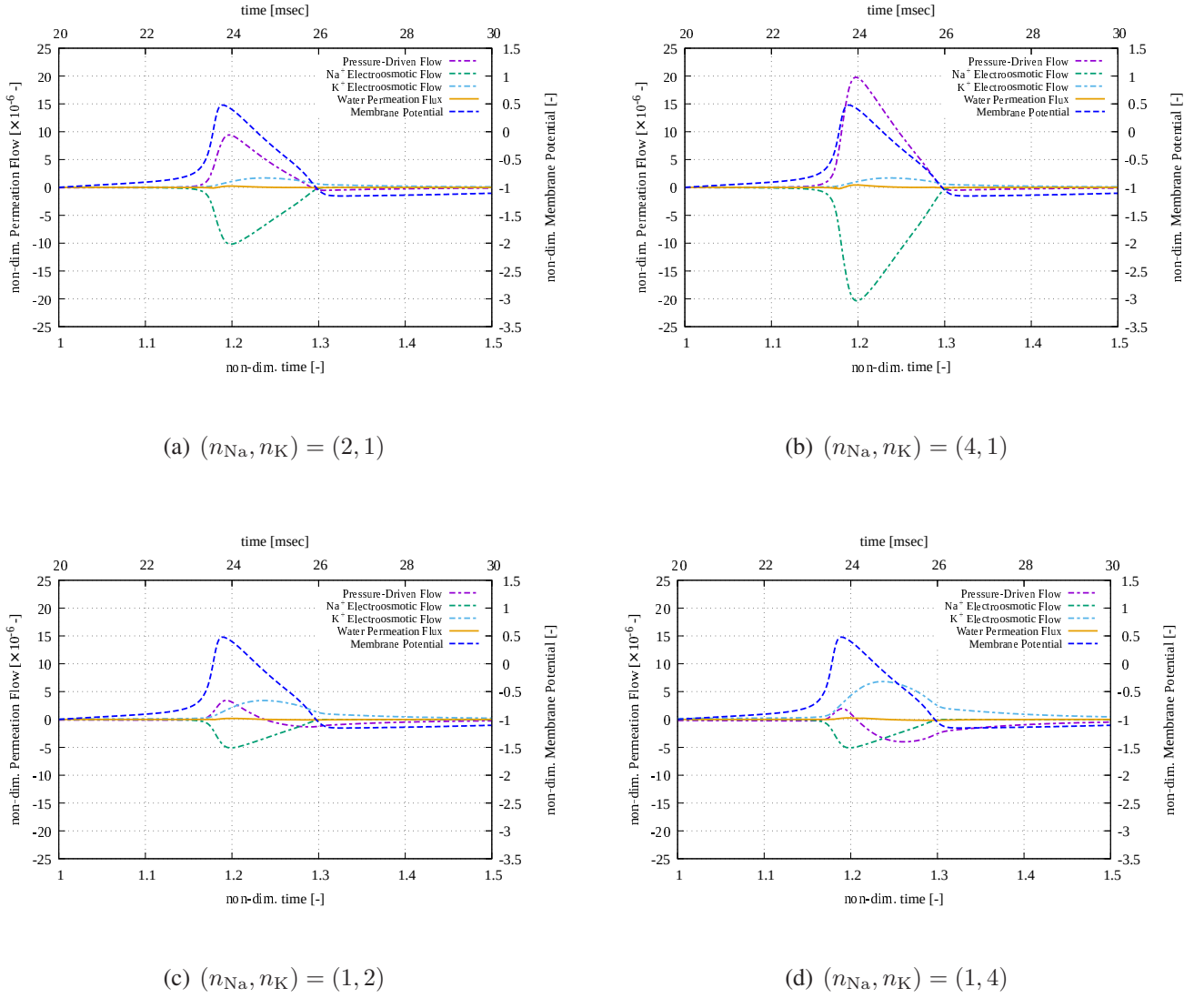


Figure 9: Permeation flows of water responding to the action potential for the same combinations of the coupling ratios of water-ion flux as in Fig. 8.

The above results suggest that the coupling ratio determines the amplitude ratio of the intracellular pressure $[p^*]$ during the depolarization and repolarization by adjusting the number of water molecules passing through the respective ion channels.

Table 1: The time lag [msec] between the maximum of the membrane potential and the peak of the pressure rise for varying combination of the coupling ratios n_γ under $L_{\text{ww}}^* = 1 \times 10^{-6}$ and $M_0 = 1 \times 10^{-3}$, where the reference time is 20 msec.

n_{Na}	Time lag ($n_{\text{K}} = 1$)	n_{K}	Time lag ($n_{\text{Na}} = 1$)
1	0.126	1	0.126
2	0.153	2	0.082
3	0.164	3	0.048
4	0.170	4	0.018
5	0.173	5	-0.011

4.2 Time lag between the action potential and pressure response

Tasaki and Iwasa [8] focused on the time lag between the membrane potential and the intracellular pressure to explain the generation mechanism of the pressure response to the action potential. They observed that the instant of the peak pressure is delayed with respect to that of the maximum membrane potential by approximately 0.05 msec, although their prediction of the time lag was one order of magnitude larger (0.5 msec) by assuming that the pressure response was purely caused by the electroosmotic flow of water [8]. This discrepancy was not surprising given the lack of knowledge about the water-ion interaction in the ion channels at that time. In this subsection, we show that a time lag smaller than that predicted by Tasaki and Iwasa [8] can be deduced and that the actual combination of coupling ratios on axons can be predicted by measuring the time lag.

In the previous subsection, the coupling ratio of water-ion flux n_γ is shown to influence the magnitude of the electroosmotic flow of the species γ . Considering that pressure is generated to counteract the sum of electroosmotic flows, we investigate the effect of the coupling ratios on the time lag. Hereafter, the non-dimensional time is multiplied by reference time (20 msec) and transformed into a dimensional value, assuming that the size of the system is identical to that of Tasaki and Iwasa [8].

Table 1 summarizes the time lags (measured at the instances of the maxima of the action potential and pressure) by varying the coupling ratios of water-ion flux n_γ in the ranges between 1 and 5 under $L_{\text{ww}}^* = 1 \times 10^{-6}$ and $M_0 = 1 \times 10^{-3}$.

By fixing n_{K} at 1, the increase in n_{Na} results in an increasing trend in the time lag because the magnitude of the pressure-driven flow counteracting the Na^+ electroosmotic flow becomes more dominant as n_{Na} increases. However, all the cases of n_{Na} (with $n_{\text{K}} = 1$) estimate larger values by one order of magnitude compared with the experimental result.

In contrast, by fixing $n_{\text{Na}} = 1$, the time lags exhibit a decreasing trend with n_{K} , which is caused by the attenuation of the intracellular pressure associated with larger magnitude of K^+ electroosmotic flow as n_{K} increases. Considering that the values of the time lag at $n_{\text{K}} = 2, 3, 4$ are of the same order of magnitude as those observed by Tasaki and Iwasa [8], their experimental results (i.e., the development of intracellular pressure in response to the action potential) may be explained by the water permeation mainly associated with the electroosmotic flows of K^+ .

Although the instantaneous coupling ratios of the ions may not be uniquely identified from a measurement of the time lag in more general situations of action potentials, the above results indicate that consideration of the involvement of water molecules may improve the understanding of the transport phenomena across ion channels.

5 Conclusions

To investigate the mechanical role of water permeation induced by ion transports in the intracellular pressure response from a fluid dynamics perspective, we developed a new water permeation flux model associated with sodium and potassium ion transports using the coupling ratio of water–ion flux.

The validity of the proposed permeation flux model was confirmed by comparing the simulation results with previous experimental results. In the present study, only when the water–ion interactions in the ion channels were taken into account, the rising and falling phases of the pressure response were found to correspond to depolarization and repolarization, respectively. These correspondences were explained by the pressure–driven flow that counteracted the sum of the two electroosmotic flows from the incompressibility of water. Therefore, the pressure response is affected by the coupling ratios of water–ion flux that determines the magnitude of the electroosmotic flows. These simulation results suggest that the water–ion interactions in the ion channels are involved in the generation mechanism of the pressure response. Moreover, investigation of the influence of the coupling ratio on the time lag between the membrane potential and pressure also supports the suggestion of a pressure–response mechanism.

The present study dared not consider membrane deformation to simplify the problem setting, and possible improvements are summarized in Appendix C. However, simulations that deal with the membrane deformation will give more significant impact on the field of neuronal cell biology. One example is axonal swelling associated with increased intracellular pressure. Barz et al. [14, 15] suggested that axonal swelling

associated with pressure waves can increase ion conductance and accelerate the propagation rate of action potentials. Furthermore, Wu et al. [26] modeled the ion diffusion in the axonal swelling region and visualized the blockage of action potential propagation using numerical simulations. Numerical studies on the intracellular pressure response considering membrane deformation will make essential contribution to the elucidation of electrical or mechanical phenomena that cannot be reproduced by the H–H equations alone.

Author contributions

All authors contributed to conceptualization, development of the mathematical models, and discussion. T. F. worked for validation. H. M. built the computer program, conducted numerical simulations, and played a leading role for verification and data mining. H. M., S. M., and S. T. wrote, edited, and reviewed the manuscript. S. T. took administrative role for resourcing and project management.

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Declaration of interests

The authors declare no competing interests.

Appendix

A Non-dimensionalization of the Hodgkin–Huxley equations

Based on the parallel conductance model as shown in Fig. A1, the generation of the action potential associated with the external current (input) is described by the following set of time evolution equations for the membrane potential, called H–H equations [5]:

$$\begin{aligned} C_m \frac{d[\psi]'}{dt} &= I_{\text{ext}} - I_{\text{Na}} - I_{\text{K}} - I_l, \\ \frac{dm}{dt} &= \alpha_m(1 - m) + \beta_m m, \\ \frac{dh}{dt} &= \alpha_h(1 - h) + \beta_h h, \\ \frac{dn}{dt} &= \alpha_n(1 - n) + \beta_n n, \end{aligned} \quad (\text{A1})$$

where C_m is the electrical capacitance of the membrane, $[\psi]'$ the membrane potential with reference to the resting potential -70 mV, I_{ext} the external current, t the time, m , h , n the parameters that determine the permeability of the corresponding ion channel, $I_{\text{Na}} = \bar{g}_{\text{Na}} m^3 h ([\psi]' - E_{\text{Na}}^0)$, $I_{\text{K}} = \bar{g}_{\text{K}} n^4 ([\psi]' - E_{\text{K}}^0)$, and $I_l = \bar{g}_l ([\psi]' - E_l^0)$, with E_{γ}^0 the equilibrium potential, $\bar{g}_{\text{Na}}$, $\bar{g}_{\text{K}}$, and $\bar{g}_l$ the maximum conductance values of sodium, potassium, and leak channels, respectively. The non-dimensional rate constants α^* and β^* at 6.3°C are functions of the membrane potential:

$$\begin{aligned} \alpha_m^* &= \tilde{t}_0 \times \frac{0.1(25 - \tilde{\psi}_0 [\psi^*]')}{\exp\left(\frac{25 - \tilde{\psi}_0 [\psi^*]'}{10}\right) - 1}, \\ \beta_m^* &= \tilde{t}_0 \times 4 \exp\left(-\frac{\tilde{\psi}_0 [\psi^*]'}{18}\right), \\ \alpha_h^* &= \tilde{t}_0 \times 0.07 \exp\left(-\frac{\tilde{\psi}_0 [\psi^*]'}{20}\right), \\ \beta_h^* &= \tilde{t}_0 \times \frac{\tilde{\psi}_0}{\exp\left(\frac{30 - \tilde{\psi}_0 [\psi^*]'}{10}\right) + 1}, \\ \alpha_n^* &= \tilde{t}_0 \times \frac{0.01(10 - \tilde{\psi}_0 [\psi^*]')}{\exp\left(\frac{10 - \tilde{\psi}_0 [\psi^*]'}{10}\right) - 1}, \\ \beta_n^* &= \tilde{t}_0 \times 0.125 \exp\left(-\frac{\tilde{\psi}_0 [\psi^*]'}{80}\right), \end{aligned} \quad (\text{A2})$$

where $\tilde{\psi}_0 = 10^3 \times \psi_0$ and $\tilde{t}_0 = 10^3 \times t_0$.

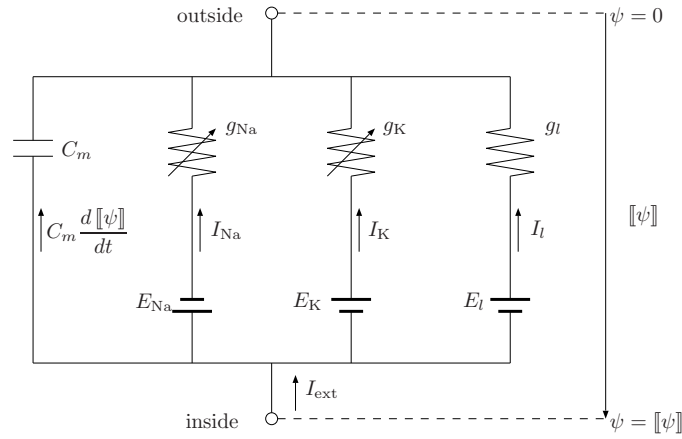


Figure A1: Schematic diagram of the parallel conductance model proposed by Hodgkin and Huxley.

Fig. A2 shows the numerical results of Eq.(A1), where the parameters in the above are set as follows: $C_m = 1.0 [\mu\text{F}/\text{cm}^2]$, $\bar{g}_{\text{Na}} = 120 [\text{mS}/\text{cm}^2]$, $\bar{g}_K = 36 [\text{mS}/\text{cm}^2]$, $\bar{g}_l = 0.3 [\text{mS}/\text{cm}^2]$, $E_{\text{Na}}^0 = 115.0 [\text{mV}]$, $E_K^0 = -12.0 [\text{mV}]$, and $E_l^0 = 10.613 [\text{mV}]$. From Fig. A2, a single pulse of the action potential is induced by the small external current, and an intermittent pulse of the action potential is induced by the large external current. This is due to the non-linearity of H–H equations for the membrane potential. The rising and falling phases of the membrane potential are called depolarization and repolarization, respectively.

B Details of the numerical simulations

B.1 Spatial discretization

In the present simulation, a second-order accurate central difference method is used for the discretization in space. The collocated arrangement of the variables is adopted for fluid velocity, pressure, charge densities, and electric potential. The velocity and pressure are coupled by the fractional step method. The motion of the membrane is not considered. For the discretization in time, the fourth-order Runge–Kutta method is adopted for the convection and viscous terms in the N–S equation, and the second-order Crank–Nicolson method for the N–P equation. The Bi–CGSTAB method is applied to solve the discretized algebraic equations of the pressure Poisson equation, the Gauss’ law, and the N–P equation.

The fluid–membrane interface is treated by the DF–IB method developed by the present authors [20, 21, 22, 23]. In the DF–IB method, based on the variable arrangement on the collocated points on a rectangular mesh, the discretization of the governing equations (i.e., the N–S equation, the pressure Poisson equation,

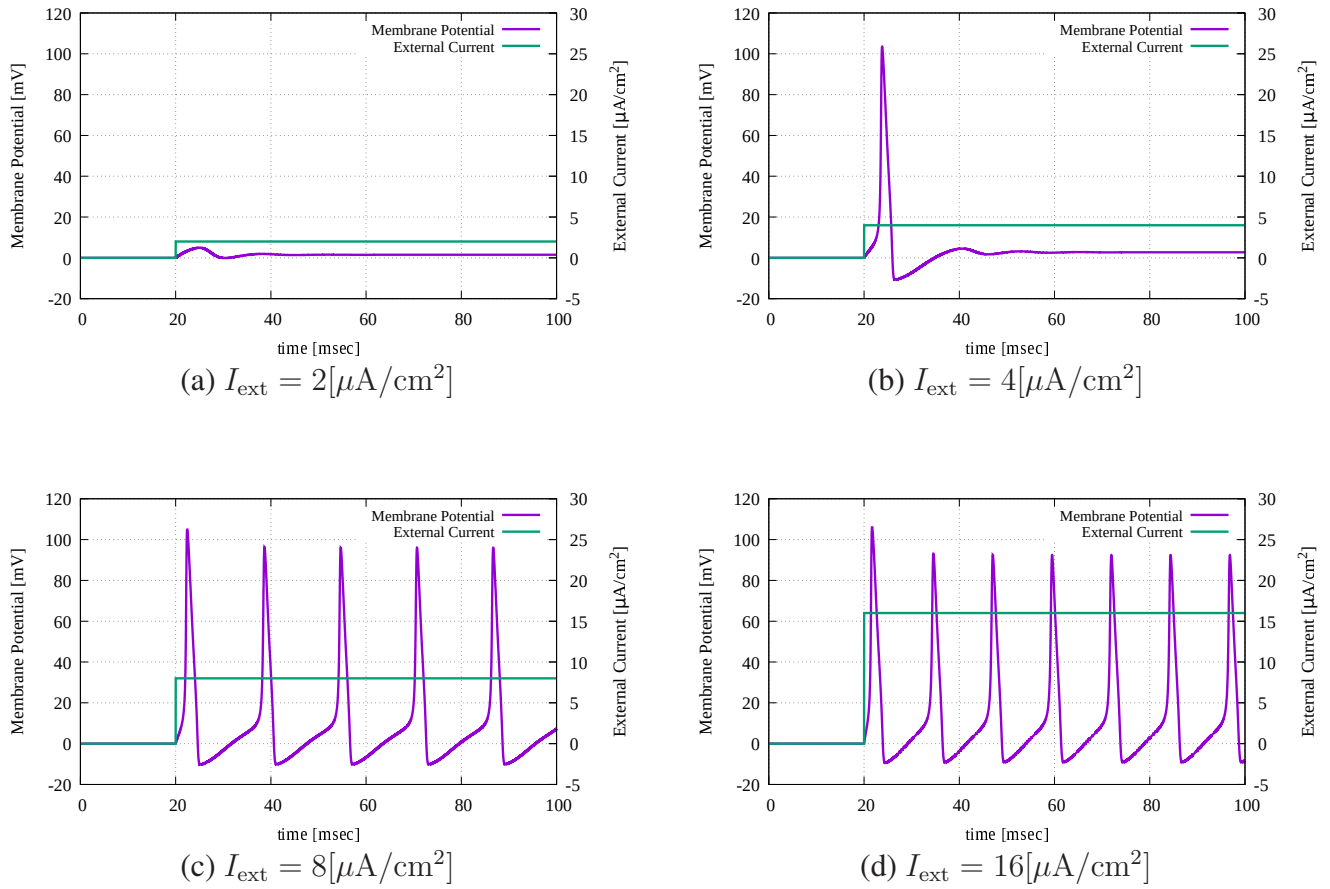


Figure A2: The response of membrane potential to external current. After 20 msec, the constant external current is applied. The membrane potential is computed with the resting potential set to zero.

and the velocity correction scheme) is carried out by taking the distance between the variable definition point and interface into account. The DF–IB method satisfies mass and momentum conservations in a discrete sense even in the computational cells adjacent to the interface, which enables capturing the interface sharply, and in turn, accurate calculation of the jump values of the variables across membrane. In the present study, the same interface treatment is applied for discretizing the Gauss' law and the N–P equation. For more details, Refs. [20, 21] describe the fundamental ideas of discretization for the DF–IB method, Ref. [22] explains the improvement for treating permeation flow through membrane, and Ref. [23] shows the extension to permeation problem with multi–component solution [23].

B.2 Time update of the system

The set of governing equations in the present study is time-updated in the following order. The superscript n represents the discrete time level.

B.2.1 Time update of the membrane potential

The membrane potential is updated by equations in Appendix A:

$$\begin{aligned}
 \mathcal{C}_m \frac{[\psi^*]^{n+1} - [\psi^*]^n}{\Delta t^*} &= I_{\text{ext}}^* - (I_{\text{pNa}}^*)^{n+\frac{1}{2}} - (I_{\text{pK}}^*)^{n+\frac{1}{2}}, \\
 (I_{\text{pNa}}^*)^{n+\frac{1}{2}} &= \bar{\mathcal{G}}_{\text{Na}}(m^{n+1})^3 h^{n+1} \left([\psi^*]^{n+\frac{1}{2}} - [E_{\text{Na}}^*]^{n+\frac{1}{2}} \right), \\
 (I_{\text{pK}}^*)^{n+\frac{1}{2}} &= (\bar{\mathcal{G}}_{\text{K}}(n^{n+1})^4 + \bar{\mathcal{G}}_l) \left([\psi^*]^{n+\frac{1}{2}} - [E_{\text{K}}^*]^{n+\frac{1}{2}} \right), \\
 \frac{m^{n+1} - m^n}{\Delta t^*} &= (\alpha_m^*)^n \left(1 - m^{n+\frac{1}{2}} \right) + (\beta_m^*)^n m^{n+\frac{1}{2}}, \\
 \frac{h^{n+1} - h^n}{\Delta t^*} &= (\alpha_h^*)^n \left(1 - h^{n+\frac{1}{2}} \right) + (\beta_h^*)^n h^{n+\frac{1}{2}}, \\
 \frac{n^{n+1} - n^n}{\Delta t^*} &= (\alpha_n^*)^n \left(1 - n^{n+\frac{1}{2}} \right) + (\beta_n^*)^n n^{n+\frac{1}{2}},
 \end{aligned} \tag{B3}$$

where

$$[E_{\gamma}^*]^{n+\frac{1}{2}} = -\frac{1}{z_{\gamma}\Psi_0} \frac{(3[\rho_{e\gamma}^*]^n - [\rho_{e\gamma}^*]^{n-1})/2}{(3(\bar{\rho}_{e\gamma}^*)^n - (\bar{\rho}_{e\gamma}^*)^{n-1})/2},$$

and others are $\phi^{n+\frac{1}{2}} = (\phi^{n+1} + \phi^n)/2$.

B.2.2 Time update of the electric fields of ions

The N–P equation has a term including the product of the charge density $\rho_{e\gamma}^*$ and the electric potential ψ^* . This non-linearity is dealt with by using the electric potential at the intermediate time as $(\psi^*)^{n+\frac{1}{2}}$ [25].

Firstly, the electric potential $(\psi^*)^{n+\frac{1}{2}}$ is obtained by solving the Gauss' law:

$$\nabla^{*2}(\psi^*)^{n+\frac{1}{2}} = -\frac{\mathcal{O}_s\Psi_0}{\epsilon_w\mathcal{E}_l} \sum_{\gamma} \frac{3(\rho_{e\gamma}^*)^n - (\rho_{e\gamma}^*)^{n-1}}{2}. \tag{B4}$$

Next, the charge density $(\rho_{e\gamma}^*)^{n+1}$ is time-updated for each species according to the N–P equation:

$$\begin{aligned}
 &\frac{(\rho_{e\gamma}^*)^{n+1} - (\rho_{e\gamma}^*)^n}{\Delta t^*} \\
 &= -\nabla^* \cdot (\mathbf{I}_{\gamma}^{\text{d}*})^{n+\frac{1}{2}} - (\mathbf{u}^*)^{n+\frac{1}{2}} \cdot \nabla^* (\rho_{e\gamma}^*)^{n+\frac{1}{2}},
 \end{aligned} \tag{B5}$$

$$\begin{aligned}
 &(\mathbf{I}_{\gamma}^{\text{d}*})^{n+\frac{1}{2}} \\
 &= \frac{\mathcal{D}_{\gamma}}{\text{Pe}} \left(-z_{\gamma}\Psi_0(\rho_{e\gamma}^*)^{n+\frac{1}{2}} \nabla^* (\psi^*)^{n+\frac{1}{2}} - \nabla^* (\rho_{e\gamma}^*)^{n+\frac{1}{2}} \right),
 \end{aligned} \tag{B6}$$

where $(\rho_{e\gamma}^*)^{n+\frac{1}{2}} = ((\rho_{e\gamma}^*)^{n+1} + (\rho_{e\gamma}^*)^n)/2$ and $(\mathbf{u}^*)^{n+\frac{1}{2}} = (3(\mathbf{u}^*)^n - (\mathbf{u}^*)^{n-1})/2$. At the computational cells located at the boundary, the ion permeation current is specified instead of $\mathbf{I}_\gamma^{\text{d}*}$. Finally, the time-update of the electric potential $(\psi^*)^{n+1}$ is completed by solving the following equation of Gauss' law:

$$\nabla^{*2}(\psi^*)^{n+1} = -\frac{\mathcal{O}_s \Psi_0}{\epsilon_w \mathcal{E}_l} \sum_{\gamma} (\rho_{e\gamma}^*)^{n+1}. \quad (\text{B7})$$

By the end of the process, the electrostatic and osmotic pressure terms, $\mathbf{f}_{\text{el}}^*$ and $\mathbf{f}_{\text{osm}}^*$, are also updated.

B.2.3 Time update of the fluid motion

For the coupling of velocity and pressure, the fractional step method is used. Firstly, the fourth-order Runge-Kutta method is adopted for the convection term ($\mathbf{C}^* = -\mathbf{u}^* \cdot \nabla^* \mathbf{u}^*$) and the viscous term ($\mathbf{D}^* = \nabla^{*2} \mathbf{u}^* / \text{Re}$) to obtain the fractional step velocity $(\mathbf{u}^*)^F$:

$$\begin{aligned} & \frac{(\mathbf{u}^*)^F - (\mathbf{u}^*)^n}{\Delta t^*} \\ &= \mathbf{C}^* + \mathbf{D}^* + \frac{(\mathbf{f}_{\text{el}}^*)^{n+1} + (\mathbf{f}_{\text{el}}^*)^n}{2} + \frac{(\mathbf{f}_{\text{osm}}^*)^{n+1} + (\mathbf{f}_{\text{osm}}^*)^n}{2}. \end{aligned} \quad (\text{B8})$$

Then, the pressure is updated by solving the pressure Poisson equation:

$$\nabla^{*2}(p^*)^{n+1} = \frac{\nabla^* \cdot (\mathbf{U}^*)^F}{\Delta t^*}, \quad (\text{B9})$$

where $(\mathbf{U}^*)^F$ is the fractional step velocity at the computational cell face, which is obtained by an interpolation of $(\mathbf{u}^*)^F$. Finally, the velocity update is completed by accelerating with the pressure gradient:

$$(\mathbf{U}^*)^{n+1} = (\mathbf{U}^*)^F - \Delta t^* \nabla^* (p^*)^{n+1}. \quad (\text{B10})$$

C 1-D intracellular pressure and swelling model

In the main body of this paper, we formulated the mechanism of intracellular pressure generation acting on non-deformed axons with Eq.(30) in association with the incompressibility of water inside the axon, and predicted the parameters that affect the time response of the intracellular pressure. Here, we discuss mechanisms of intracellular pressure and swelling for a case of deformable axon membranes. In particular, a one-dimensional mathematical model of the intracellular pressure and axonal swelling induced by water fluxes associated with ion transport is developed. Here, the 1-D mathematical model refers to equations of motion of the membrane in the axon radial direction. In addition, parameters that affect the intracellular pressure and axonal swelling are discussed.

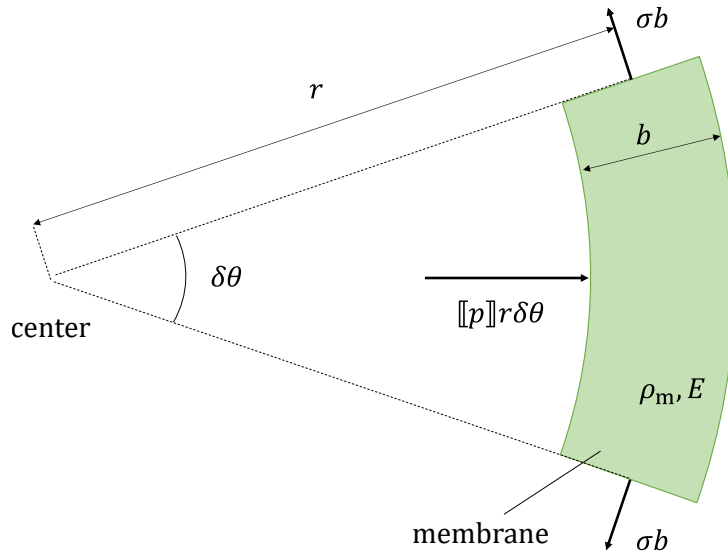


Figure C3: Schematic of forces acting on a portion of the axon membrane. Tension and intracellular pressure act uniformly on the membrane.

C.1 Modeling

The main assumptions for modeling are summarized as follows:

1. The axon cross-section is always circular (axis-symmetric deformation).
2. The change in radius due to swelling is small relative to the initial radius r_0 .
3. Water is an incompressible fluid.
4. Ionic conductance follows the H-H equations and is not affected by swelling.
5. Membrane density and thickness do not change with swelling.
6. Tension of the axon membrane follows a linear spring model.
7. Shear and bending stresses acting on the axon membrane are neglected.

From the homogeneity in the circumferential direction by Assumption 1, only a part of the membrane is considered, as shown in Fig. C3, and its equation of motion in the radial direction is given with a linear

spring model (Assumption 6) for the tension σ , as follows:

$$\begin{aligned}\rho_m b r \delta \theta \frac{d^2 r}{dt^2} &= \llbracket p \rrbracket r \delta \theta - 2 \sigma b \sin \frac{\delta \theta}{2} \\ &\simeq \llbracket p \rrbracket r \delta \theta - \sigma b \delta \theta \\ &= \llbracket p \rrbracket r \delta \theta - E \frac{\Delta r}{r_0} b \delta \theta ,\end{aligned}$$

and through rearranging with $\Delta r = r - r_0$ and the small-deformation assumption $r r_0 \simeq r_0^2$ (Assumption 2), the time-dependent equation for the radial variation finally takes the following form:

$$\rho_m \frac{d^2 \Delta r}{dt^2} = \frac{1}{b} \llbracket p \rrbracket - \frac{E}{r_0^2} \Delta r . \quad (\text{C11})$$

From Assumption 3, the axon swelling rate dV/dt (V : volume inside axon) is equal to the volumetric flow rate $-u_p \cdot 2\pi r$ of water permeating through the membrane and entering the axon:

$$\frac{dV}{dt} = -u_p \cdot 2\pi r . \quad (\text{C12})$$

The small-deformation assumption allows approximation of $dV/dt = 2\pi r dr/dt$, and Eq. (C12) is simplified as follows:

$$\frac{dr}{dt} = -u_p \quad (\text{C13})$$

Based on the assumption that ion conductance is not affected by swelling (Assumption 4), the following 1-D intracellular pressure and swelling model can be obtained by applying the permeation flux model of Eq.(5) to the right side of Eq.(C13), and then by coupling it with Eq.(C11):

$$\begin{aligned}\rho_m \frac{d^2 \llbracket p \rrbracket}{dt^2} + \frac{1}{b L_{ww}} \frac{d \llbracket p \rrbracket}{dt} + \frac{E}{r_0^2} \llbracket p \rrbracket \\ = - \sum_{\gamma} \frac{1}{L_{ww}} \frac{n_{\gamma} M_w}{z_{\gamma} \mathcal{F} \rho_w} \left(\rho_m \frac{d^2 I_{p\gamma}}{dt^2} + \frac{E}{r_0^2} I_{p\gamma} \right) ,\end{aligned} \quad (\text{C14a})$$

$$\begin{aligned}\rho_m \frac{d^2 \Delta r}{dt^2} + \frac{1}{b L_{ww}} \frac{d \Delta r}{dt} + \frac{E}{r_0^2} \Delta r \\ = - \sum_{\gamma} \frac{1}{b L_{ww}} \frac{n_{\gamma} M_w}{z_{\gamma} \mathcal{F} \rho_w} I_{p\gamma}\end{aligned} \quad (\text{C14b})$$

Using the dimensionless quantities and parameters defined in § 2.4 and others: $r_0^* = r_0/H_0$, $\Delta r^* = \Delta r/H_0$, $\mu_m = \rho_m b/\rho_w H_0$, and $K_s = E b t_0^2/\rho_w H_0^3$, the Eq.(C14) is non-dimensionalized as follows:

$$\begin{aligned} \mu_m \frac{d^2 \llbracket p^* \rrbracket}{dt^{*2}} + \frac{1}{L_{ww}^* \text{Re}} \frac{d \llbracket p^* \rrbracket}{dt^*} + \frac{K_s}{r_0^{*2}} \llbracket p^* \rrbracket \\ = - \sum_{\gamma} \frac{1}{L_{ww}^* \text{Re}} \frac{n_{\gamma} M_0}{z_{\gamma}} \left(\mu_m \frac{d^2 I_{p\gamma}^*}{dt^{*2}} + \frac{K_s}{r_0^{*2}} I_{p\gamma}^* \right), \end{aligned} \quad (\text{C15a})$$

$$\begin{aligned} \mu_m \frac{d^2 \Delta r^*}{dt^{*2}} + \frac{1}{L_{ww}^* \text{Re}} \frac{d \Delta r^*}{dt^*} + \frac{K_s}{r_0^{*2}} \Delta r^* \\ = - \sum_{\gamma} \frac{1}{L_{ww}^* \text{Re}} \frac{n_{\gamma} M_0}{z_{\gamma}} I_{p\gamma}^*, \end{aligned} \quad (\text{C15b})$$

where E is Young's modulus of the membrane.

To simplify the problem, the 1-D intracellular pressure and swelling model treats the solution as a bulk solution. Therefore, the equilibrium potential $\llbracket E_{\gamma}^* \rrbracket$ in Eq.(17) remains constant.

Let us consider the physical meaning of the Eq.(C13). In the equation, $d\Delta r^*/dt^*$ is the membrane velocity and u_p^* is the water permeation velocity (flux) relative to the membrane velocity. It implies that $u_p^* + d\Delta r^*/dt^*$ is the absolute velocity of water, and thus Eq.(C13) means that water remains in place and permeates the membrane in response to the axon membrane motion associated with action potentials. Therefore, as in the main body of this paper, there is no net motion of water through membrane. From this fact, we can obtain an equation that relates the mass transports, intracellular pressure, and axonal swelling:

$$L_{ww}^* \text{Re} \llbracket p^* \rrbracket + \frac{d\Delta r^*}{dt^*} = - \sum_{\gamma} \frac{n_{\gamma} M_0}{z_{\gamma}} I_{p\gamma}^*. \quad (\text{C16})$$

Since the case of non-deformed axons implies $d\Delta r^*/dt^* = 0$, Eq.(C16) covers Eq.(30).

C.2 Numerical simulations with 1-D model

Based on the above modeling, the numerical results of Eq.(C15) are shown in Figs. C4(a) and C4(b). The reference length H_0 is set to be $100 \mu\text{m}$, and the water permeability coefficient is $L_{ww}^* = 10^{-6}$, Reynolds number is $\text{Re} = 1$, water-ion mass ratio is $M_0 = 10^{-3}$, water-film mass ratio is $\mu_m = 10^3$, elastic modulus is $K_s = 10^5$, the water-ion flux couple ratio is $n_{\gamma} = 1$, and the ionic valence is $z_{\gamma} = 1$. The initial radius is $r_0^* = 0.05$, and the ion concentration field is given as follows:

$$\begin{aligned} \rho_{e\text{Na}}^* &= 0.9, \quad \rho_{e\text{K}}^* = 0.1 & : & \text{outside the axon,} \\ \rho_{e\text{Na}}^* &= 0.1, \quad \rho_{e\text{K}}^* = 0.9 & : & \text{inside the axon.} \end{aligned}$$

Although Eq.(C15) is a simple model that does not handle the fields of water and ions (i.e., hydrodynamics, electrical, and concentration fields) on either side of the membrane, the model well captures the essential trends of both pressure and radial responses at a comparable level with the previous experimental results [7, 8, 9, 10, 11].

Fig. C4(c) shows the membrane velocity $d\Delta r^*/dt^*$, the water permeate flow (pressure driven flow, Na^+ and K^+ electroosmotic flow), water permeate flux u_p^* and absolute water velocity $u_p^* + d\Delta r^*/dt^*$. As mentioned earlier, the equilibrium potential $\llbracket E_\gamma^* \rrbracket$, which constitutes the ion permeation current $I_{p\gamma}^*$, is always constant. Fig. C4(c) visualizes that the Eq.(C13) serves as a constraint that causes the mechanical response of the axon membrane.

C.3 Physical meaning of parameters in 1-D model

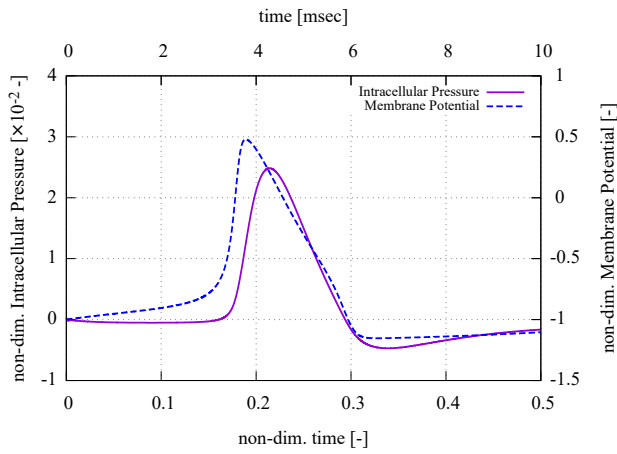
Eq.(C15) is found to have the same form as the equation of motion of a mass–spring–damper system with the external force on the right–hand side; μ_m , $1/L_{ww}^*$ Re, and K_s/r_0^{*2} are regarded as the mass, damping constant, and spring constant, respectively. Therefore, by varying the values of the parameters L_{ww}^* and K_s , their effects on the intracellular pressure and swelling are discussed for the time histories shown in Fig. C5 and C6. In the following, the second and third terms on the left– and the right–hand sides of Eq.(C15) are referred to as the damping, tension and external force terms, respectively.

In the case of a fixed axon membrane, $1/L_{ww}^*$ is a coefficient connecting the electroosmotic flow and the intracellular pressure, as shown by Eq. (30), and the intracellular pressure was generated without any time delay to the onset of the electroosmotic flow. On the other hand, in the case of considering the axon deformation, $1/L_{ww}^*$ has the role of inducing a time delay in the intracellular pressure response to the onset of the electroosmotic flow. Therefore, as Fig. C5 shows, smaller values of L_{ww}^* result in delays in the response time of intracellular pressure and swelling to follow the action potential. This can be intuitively understood as the reciprocal of the phenomenological coefficient L_{ww}^* in non–equilibrium thermodynamics. In Fig. C5, smaller values of L_{ww}^* result in larger amplitudes of intracellular pressure and swelling, because L_{ww}^* influences the external force term as well as the damping term.

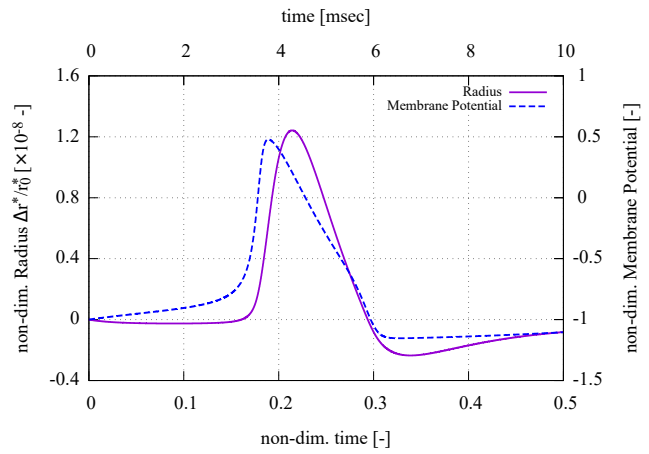
As the elastic modulus K_s affects the tension term, larger values of K_s result in faster response times to the maximum and minimum values of intracellular pressure and swelling, as shown in Fig. C6, which is reasonably accepted. However, the K_s dependence of the maximum and minimum amplitudes shows the

opposite trend for the time variation of the intracellular pressure and radius. This is because K_s appears in the external force term of the intracellular pressure equation (Eq. (C15a)) but not in the external force term of the radius equation (Eq. (C15b)).

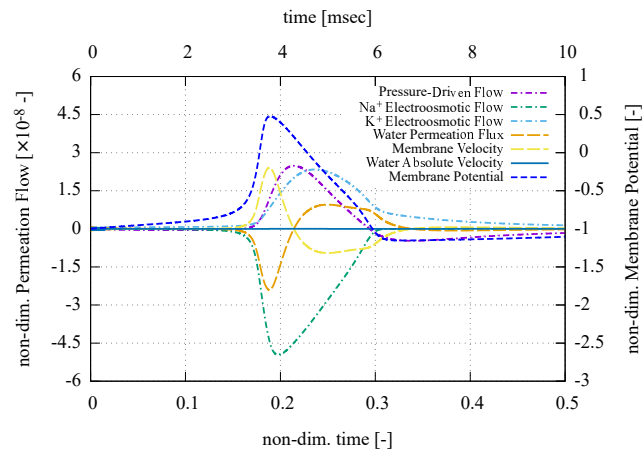
On the other hand, we find that the parameters M_0 and n_γ discussed in the main body of this paper affect both external force terms in Eq.(C15).



(a) Time response of intracellular pressure

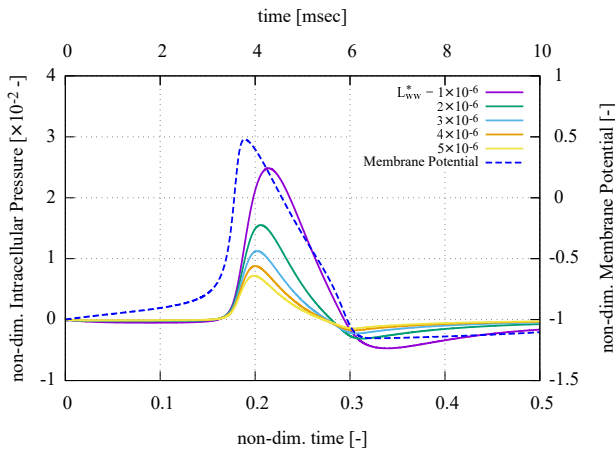


(b) Time response of axon radius

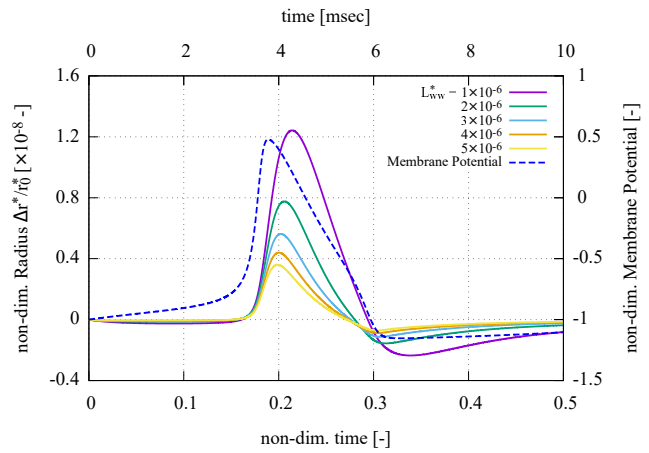


(c) The time responses of the three flows (Pressure-Driven Flow, Na^+ and K^+ EO Flow) and Water Flux u_p^* and Water Absolute Velocity $u_p^* + d\Delta r^*/dt^*$.

Figure C4: Mechanical effects of water permeation on axons and water permeation flow through the membrane using a 1-D intracellular pressure and swelling model. Axon radius normalized by initial radius $r_0^* = 0.05$.

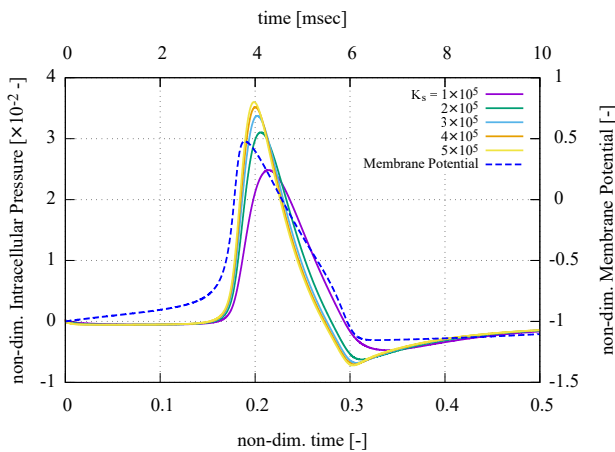


(a) Time response of intracellular pressure

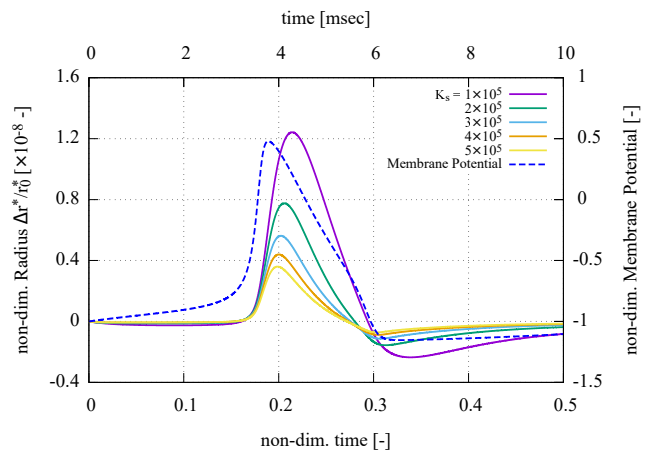


(b) Time response of axon radius

Figure C5: Time response of intracellular pressure and swelling when water transmission coefficient is varied in the following values: $L_{wv}^* = 1 \times 10^{-6}$, 2×10^{-6} , 3×10^{-6} , 4×10^{-6} , and 5×10^{-6} . Axon radius is normalized by the initial radius $r_0^* = 0.05$.



(a) Time response of intracellular pressure



(b) Time response of axon radius

Figure C6: Time response of intracellular pressure and swelling when the elastic modulus is varied in the following ranges: $K_s = 1 \times 10^5$, 2×10^5 , 3×10^5 , 4×10^5 , and 5×10^5 . Axon radius normalized by the initial radius $r_0^* = 0.05$.

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