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Stimulation Of Retinal Ganglion Cells– A Genelarized Finite Element Model

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***Abstract*—Retinal stimulations that aim to compensate for defective photoreceptor cells bypass the initial visual processing system and directly stimulate the ganglion cells. The output of the ganglion cells is directed to the Lateral Geniculate Nucleus (LGN), the visual "gateway" to the brain.**
This paper numerically simulates part of the above process using the generalized finite element method.
The ganglion cell is modeled using the cable equation and the extracellular medium using a 3D formulation. The ionic current model used is the one built by Fohlmeister et al. for mammals. Relying on results from different branches of applied mechanics, as well as generalizing the interpolation functions to the capacitive and membrane currents, lead to compact matrices throughout the finite element formulation. This applies to the transient, steady-state, ionic as well as membrane current matrices.
The coupling between the extracellular/intracellular domains thru the extracellular potential and membrane current is also discussed.

Keywords— ganglion cells, extracellular/intracellular domains, action potential, membrane current, retinal stimulation.

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I. INTRODUCTION

A group of numerical simulations in the field of biomedical engineering aim to understand better the functioning of the different organs and to suggest alternative pathways to the defective ones [1-7]. Retinal simulations are a subset of such a group. The goal of these simulations is to find a way to compensate for defective photoreceptor cells by bypassing the initial retinal visual processing system and directly stimulating the ganglion cells. The ganglion cells are the output of the retina to the Lateral Geniculate Nucleus (LGN), the visual "gateway" to the brain.
Models that simulate this process range from the bidomain model, that assumes the extracellular and intracellular domains to coexist in the same physical space and averages the response of the ganglion cells [7], to the decoupled model of extracellular space-ganglion cell line model [3], passing by the coupled model of extracellular space-ganglion cell line model [4].

In this paper, a numerical simulation of part of the above process is attempted. It relies on results from different branches of applied mechanics that leads to compact finite element matrices. In addition, generalizing the interpolation functions to the ionic and membrane currents simplifies the time integration scheme. Several examples are presented that discusses the above approach.

One of the goals of the formulation in this paper is to allow the mesh of the extracellular space to be independently built from the mesh of the ganglion cell model.
The extracellular space is modeled using the 3D finite element method. The ganglion cells are modeled using 1D elements based on the cable equation.
The coupling between the extracellular and intracellular domains is thru the extracellular potential and the membrane current. The extracellular potential affects the membrane potential in the ganglion cell that generates membrane current that feed back into the extracellular potential. The extracellular potential is interpolated to determine the nodal values at the ganglion cell mesh. The nodal membrane currents at the ganglion cell mesh are extrapolated to the

extracellular nodes to determine their effects on the extracellular potential distribution. The last section in the paper discusses the formulation of such a process and an example is presented that illustrates the solution.

In most examples, the ionic current model proposed by Fohlmeister et al. for mammals was used [2-7].

II. Ganglion cells

Light that is reflected from objects passes first through the retina and is finally processed by the brain. The energy carried by the photons of light is chemically transformed into current by the photoreceptor cells. This current is then fed through several layers of cells, and end up at the ganglion cells. The output of the ganglion cells is directed to the Lateral Geniculate Nucleus (LGN), the visual "gateway" to the brain.

a. Ganglion Cell Ionic Current Model: Fohlmeister Model [2-7]

The model assumes the membrane current to be the sum of a capacitive part represented by $c_m . \partial V_m/\partial t$ and an Ionic part which is mainly the sum of Na, K, and Ca ionic currents. The equations of the ionic currents are generally the product of a nonlinear conductance term, and difference in potentials.

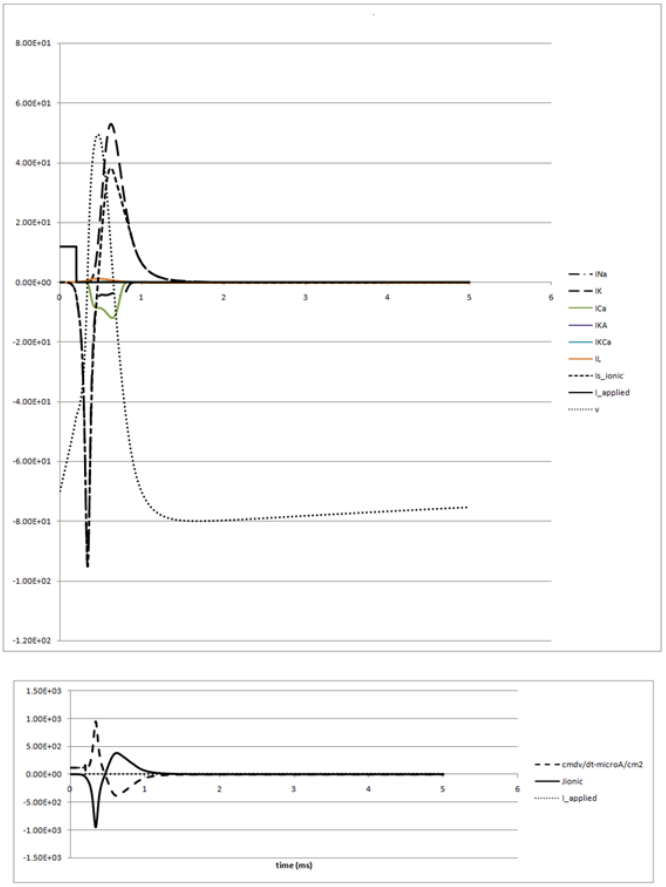


Fig. 1 Response of Ionic current model to a step current of 120 μA/cm^2 (Currents=10^7*μA/μm^2, Voltage=mV)

This is expressed by the equation:

$$I_m = c_m . \partial V_m/\partial t + J_{ionic} \quad (1)$$

where
I_m= membrane current (μA/μm^2)
c_m= capacitance of the membrane (μF/μm^2)
V_m= membrane potential (mV)
t = time (ms)
J_{ionic} = Ionic current (μA/μm^2)

The response of such a model to a step current of 120 μA/cm^2 is shown in Fig. 1. The properties used are similar to that of the soma in [2].

b. The Cable Equation-Constant Diameter

The cable equation is derived by applying the conservation of total current to a membrane electrical circuit, shown in Fig. 2.

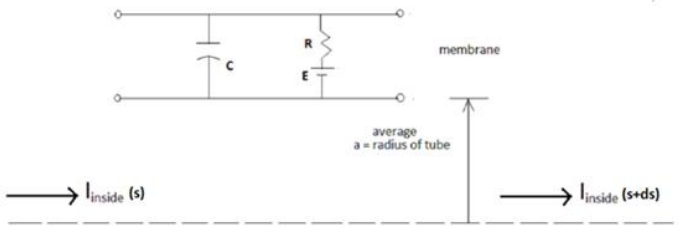


Fig. 2 Membrane electrical circuit

The conservation of total current leads to:

$$J_c + J_{ionic} = (a/2) . \sigma_{cytoplasm} \partial^2/\partial x^2 [V_{inside}] + I_{ext}(s,t)/(2* \pi *a) \quad (2)$$

where

V_I = Intracellular potential
V_E = Extracellular potential
V_m = membrane potential = V_{inside} -$V_{outside}$
$I_{ext}(s,t)$= external applied current (μA/μm)
$\sigma_{cytoplasm}$ =conductance of cytoplasm (mS/μm)
$R_{cytoplasm}$ =resistance of cytoplasm (kΩ.μm)
a= radius of tube (μm)

Expressing eq. (2) in terms of the membrane potential gives (in the absence of external current):

$$(c_m . \partial V_m/\partial t + J_{ionic}) - (a/2).\sigma_{cytoplasm} . \partial^2/\partial s^2 V_m(s,t) = (a/2).\sigma_{cytoplasm} . \partial^2/\partial s^2 V_E(s,t) \quad (3)$$

And, in terms of the intracellular potential:

$$(c_m . \partial V_I/\partial t + J_{ionic}) - (a/2).\sigma_{cytoplasm} . \partial^2/\partial s^2 V_I(s,t) = c_m . \partial V_E/\partial t \quad (4)$$

c. Method of Weighted Residual- Finite Element Formulation

Applying the method of weighted residual to the cable equation (3) leads to:

$$\int c_m.\,\partial V_m/\partial t\,.\,\phi_i(s).\,ds + \int \phi_i(s).\,J_{ionic}(V_m).ds + \int (a/2).\sigma_{cytoplasm}\,.\,\partial V_m(s,t)/\partial s.\,\partial\phi_i(s)/\partial s.ds = -\int (a/2).\sigma_{cytoplasm}\,.\,\partial V_E(s,t)/\partial s.\,\partial\phi_i(s)/\partial s.ds + [\,-I_{inside}(s,t).\,(a/2).\,\phi_i(s)/A\,]^{s2}_{s1} \quad (5)$$

Similarly, when applied to eq.(4) gives:

$$\int c_m.\,\partial V_I/\partial t\,.\,\phi_i(s).\,ds + \int \phi_i(s).\,J_{ionic}(V_m).ds + \int (a/2).\sigma_{cytoplasm}\,.\,\partial V_I(s,t)/\partial s.\,\partial\phi_i(s)/\partial s.ds = \int c_m.\,\partial V_E/\partial t\,.\,\phi_i(s).\,ds + [\,-I_{inside}(s,t).\,(a/2).\,\phi_i(s)/A\,]^{s2}_{s1} \quad (6)$$

To derive the finite element equations, we start by space discretization of the membrane potential along an element

$$V_m(s,t) = \Sigma_j \phi_j(s).V_{mj}(t) \quad (7)$$

where $\phi_j(s)$ is the shape function of node "j" , $V_j(t)$ the potential at node "j" , "s" the distance along the dendrite/axon, and "A" the cross-sectional area of the tube.

Inserting (7) into eq. (5) results in:

$$C_{ij} * dV_{mj}(t)/dt + F_{Ionic\_i} + K_{ij} * V_{mj}(t) = -K_{ij} * V_{Ej}(t) + [\,-I_{inside}(s_2,t).\,(a/2).\delta_{i2}/A + I_{inside}(s_1,t).\,(a/2).\delta_{i1}/A\,] \quad (8)$$

where

$$C_{ij} = \int^{s2}_{s1} c_m\,.\phi_i(s).\,\phi_j(s).\,ds \quad (9)$$
$$K_{ij} = \int^{s2}_{s1} (a/2).\sigma_{cytoplasm}\,.\,\partial\phi_i(s)/\partial s.\,\partial\phi_j(s)/\partial s.\,ds$$
$$F_{Ionic\_i} = \int^{s2}_{s1} \phi_i(s).\,J_{ionic}(V_m(s,t))\,.\,ds$$
δ_{ij} = Kronecker's delta

If eq. (6) is used instead, this leads to:

$$C_{ij} * dV_{Ij}(t)/dt + F_{Ionic\_i} + K_{ij} * V_{Ij}(t) = C_{ij} * dV_{Ej}(t)/dt + [\,-I_{inside}(s_2,t).\,(a/2).\delta_{i2}/A + I_{inside}(s_1,t).\,(a/2).\delta_{i1}/A\,] \quad (10)$$

For a 2-node element with constant diameter, the matrices C_{ij}, K_{ij} and F_{Ionic_i} could be expressed as:

$$C_{ij} = (Cm*L/6)\begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$$

$$K_{ij} = (a/2).\sigma_{cytoplasm}/L\begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} \quad (11)$$

$$F_{Ionic} = \begin{bmatrix} \int^{s2}_{s1} \phi_1(s).\,J_{ionic}(v_m(s,t)).ds \\ \int^{s2}_{s1} \phi_2(s).\,J_{ionic}(v_m(s,t)).ds \end{bmatrix}$$

Looking at the integral $\int^{s2}_{s1} \phi_i(s).\,J_{ionic}(v_m(s,t))\,.\,ds$

Assume that J_{ionic} is interpolated using the same shape function as V_m/V_I, i.e.,

$$J_{ionic}(s,t) = \phi_i(s).\,J_{ionic}(s_i,t) + \phi_j(s).\,J_{ionic}(s_j,t) \quad (12)$$

When replacing in eq. $(11)_3$, for a linear element,

$$F_{ionic\_i} = \int^{s2}_{s1}\,.\,\phi_i(s).*(\phi_i(s).\,J_{ionic}(s_i,t) + \phi_j(s).\,J_{ionic}(s_j,t)).ds \quad (13)$$

the above equation is written in matrix form as:

$$\begin{bmatrix} F_{ionic\_i} \\ F_{ionic\_j} \end{bmatrix} = (L/6)\begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}\begin{bmatrix} J_{ionic}(s_i,t) \\ J_{ionic}(s_j,t) \end{bmatrix} \quad (14)$$

Then, eq.(8) simplifies to

$$\underset{2x2}{C}\underset{2x1}{\begin{bmatrix} \dot{V}_{m1} \\ \dot{V}_{m2} \end{bmatrix}} + \underset{2x2}{K}\underset{2x1}{\begin{bmatrix} V_{m1} \\ V_{m2} \end{bmatrix}} + \underset{2x1}{F_{Ionic}} = -\underset{2x2}{K}\underset{2x1}{\begin{bmatrix} V_{e1} \\ V_{e2} \end{bmatrix}} + \underset{2x1}{\begin{bmatrix} (a/2)*I_{inside(S1,t)} \\ -(a/2)*I_{inside(S2,t)} \end{bmatrix}} \quad (15)$$

III. Extracellular space

a. Extracellular Potential 3D Equation

The extracellular potential distribution (V_E) over a medium with conductivity σ_e is given by the following equation, in case the transient term can be neglected:

$$\nabla.(-\sigma_e \nabla V_E) = I_{external} \quad (16)$$

where:

σ_e = local conductivity of the retinal layer (mS/μm)
V_E = the extracellular potential (mV)
$I_{external}$ = the external current per unit volume (μA/μm^3)

b. Method of Weighted Residual – Finite Element Formulation

Applying the weak form to the extracellular potential equation results in

$$\int_\Omega \nabla N_I.\,[\,(\sigma_e \nabla V_E)]\,d\Omega = \int_\Gamma N_I*[(\sigma_e \nabla V_E).\mathbf{n}\,]\,d\Gamma + \int_\Omega N_I*[\,I_{external}\,]\,dV \quad (17)$$

where N_I is the shape function for node "I".

Using the interpolation function for an 8-node element

$$V_E(X,Y,Z,t) = \Sigma^{8}_{J=1}\, N_J(X,Y,Z)\, .\, V_E^{J}(t) \qquad (18)$$

in eq.(17), leads to

$$\Sigma_J \{ \int_\Omega [\sigma_e \nabla N_I . \nabla N_J]\, d\Omega \}\, V_E^{J}(t) = \int_\Gamma N_I * [(\sigma_e \nabla V_E) \,.\mathbf{n}\,]\, d\Gamma + \int_\Omega N_I * [\, I_{external}\,]\, d\Omega \qquad (19)$$

IV. Time Integration Scheme: Interaction of the Extracellular space with the Ganglion Cells

a. Decoupled case

Using the forward Euler integration scheme, namely,

$$dV_{mi}(t_n)/dt = [V_{mi}(t_{n+1}) - V_{mi}(t_n)]/dt \qquad (20)$$

into eq. (15) leads to:

$$C\begin{bmatrix} V_{m1} \\ V_{m2} \end{bmatrix}_{n+1} = C\begin{bmatrix} V_{m1} \\ V_{m2} \end{bmatrix}_n - K\begin{bmatrix} V_{m1} \\ V_{m2} \end{bmatrix}_n \Delta t - F_{Ionic}\Big|_n \Delta t - K\begin{bmatrix} V_{e1} \\ V_{e2} \end{bmatrix}_n \Delta t + \begin{bmatrix} (a/2)*I_{inside(S1,t)}/A \\ -\,(a/2)*I_{inside(S2,t)}/A \end{bmatrix}_n \Delta t \qquad (21)$$

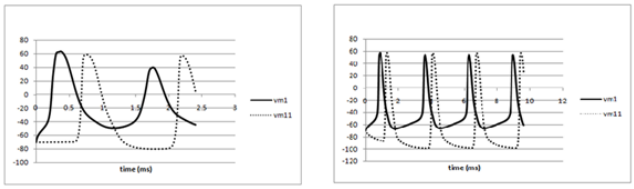
Similarly, for the intracellular potential the equation is written as:

$$C\begin{bmatrix} V_{i1} \\ V_{i2} \end{bmatrix}_{n+1} = C\begin{bmatrix} V_{i1} \\ V_{i2} \end{bmatrix}_n - K\begin{bmatrix} V_{i1} \\ V_{i2} \end{bmatrix}_n \Delta t - F_{Ionic}\Big|_n \Delta t + C\begin{bmatrix} \dot{V}_{e1} \\ \dot{V}_{e2} \end{bmatrix}_n \Delta t + \begin{bmatrix} (a/2)*I_{inside(S1,t)}/A \\ -\,(a/2)*I_{inside(S2,t)}/A \end{bmatrix}_n \Delta t \qquad (22)$$

Example I - Action Potential Initiation and Propagation due to Input Current/Extracellular Potential

As an example, a ganglion cell meshed using ten linear elements is subjected to two types of loading and boundary conditions:
(i) A current of 10^{-4}μA at the left end and insulated at the right end.
(ii) An external cathodic current source 50μm from above. This causes an extracellular potential variation along the length of the cell. Both ends of the mesh are insulated.

The radius of the element used is 0.3μm, representative of part of an axon, and the properties of gNa conductance is 3 times the gNa of Soma to represent an increase similar to the Sodium Channel Band (SOCB) (higher values could still be used [2,3]). As mentioned, ten linear elements were used with eleven nodes. The initiation and propagation of the membrane action potentials are shown in Fig. 3 (a) and (b) for nodes 1 and 11.



(a) (b)

Fig. 3 (a) Membrane potential of case (i) versus time
(b) Membrane potential of case (ii) versus time

b. Membrane Current

For the retina ganglion cell (RGC), the total membrane current I_m of element "e", as shown in Fig. 4, is given by

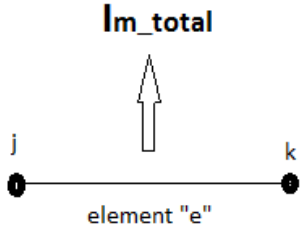


Fig. 4 Ganglion cell element with total membrane current

$$I_m(t)\_total = \int^{sk}_{sj} 2*\pi*a*I_m(s,t).ds = \int^{sk}_{sj} 2*\pi*a*(\,J_c + J_{ionic}\,).ds \qquad (23)$$

where J_c is the capacitive current.

For the nodal membrane current IN_{mj} at node "j" of element "e", the following equation assumes that each node of the element will acquire a membrane current weighted by the shape function of that node, thus,

$$IN_{mj}(t) = \int^{sk}_{sj} \phi_j(s).\, 2*\pi*a*(\,J_c + J_{ionic}\,).ds \qquad (24)$$

Assume that J_c and J_{ionic} are interpolated using the same shape functions as V_m/V_I, i.e.,

$$J_c(s,t) = \phi_j(s).J_c(s_j,t) + \phi_k(s).J_c(s_k,t) \qquad (25)$$

$$J_{ionic}(s,t) = \phi_j(s).J_{ionic}(s_j,t) + \phi_k(s).J_{ionic}(s_k,t) \qquad (26)$$

Replacing in eq. (24) leads to

$$IN_{mj} = 2*\pi*a*\int^{sk}_{sj} \phi_j(s).\,(\phi_j(s).J_c(s_j,t) + \phi_k(s).J_c(s_k,t) + \phi_j(s).J_{ionic}(s_j,t) + \phi_k(s).J_{ionic}(s_k,t)\,).ds$$

$$IN_{mj} = 2*\pi*a*\int^{sk}_{sj} \phi_j(s).\,(\{\phi_j(s).J_c(s_j,t) + \phi_j(s).J_{ionic}(s_j,t)\} + \{\phi_k(s).J_c(s_k,t) + \phi_k(s).J_{ionic}(s_k,t)\}).ds$$

For a linear element, the above equation is written as:

$$IN_{mj} = (2\pi.a.L/6)*\{2[J_c(s_j) + J_{ionic}(s_j)] + [J_c(s_k) + J_{ionic}(s_k)]\} = 2*\pi*a*(\,2*I_{mj}(s_j,t) + I_{mk}(s_k,t))*L/6 \qquad (27)$$

where $I_{mj}(s_j,t)$ is the membrane current "density" at node "j".

Similarly,

$$IN_{mk} = 2*\pi*a*(I_{mj}(s_j,t)+ 2*I_{mk}(s_k,t))*L/6 \quad (28)$$

Example II - Closed Form Solution: Membrane Potential and Membrane Current

This example deals with stimulating a single ganglion cell element by an external current source in the extracellular space, as shown in Fig. 5 below.
The external potential was built up over time to steady-state value at node "1" and assumed constant throughout the element to simplify the closed form solution.

The boundary condition (b.c.) on the left of the element is of the Neumann type (insulated).
On the right, the b.c. is of the mixed type given by

$$I_2 = g_r*(V_{i2}-V_r) \quad (29)$$

where
g_r = conductance (mS), V_r = voltage (mV)

The ionic current model used was the passive leaky current model.
A closed form solution was derived and compared with the results of a finite element mesh of one/ten elements. Fig. (6) compares the nodal membrane current at node "1" and total element current from the finite element solution with the closed form solution.
The total membrane current is equal to $(-I_2)$ in this case.

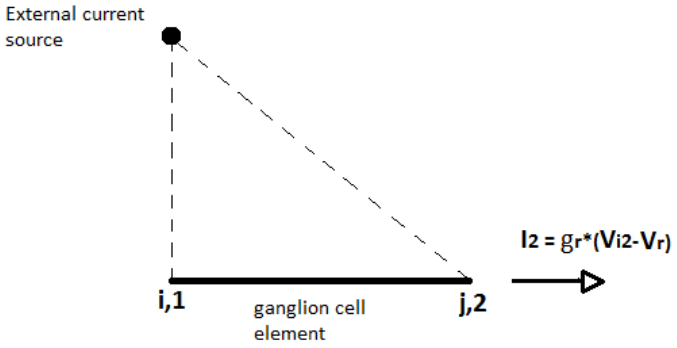
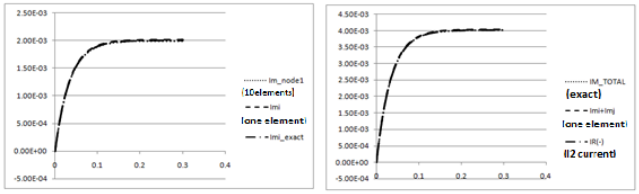


Fig. 5 Finite element with extracellular potential and boundary conditions

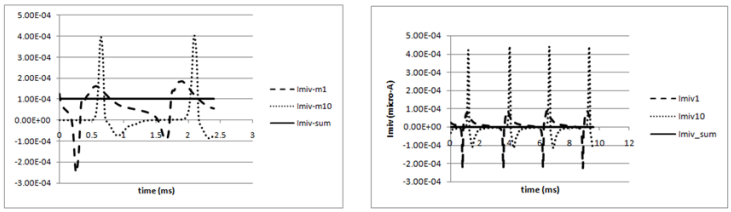
Membrane Currents of Example I
Fig. 7(a) shows the element membrane current versus time for elements 1 and 10 as well as the sum of elements membrane current for case (i). The sum of elements membrane current equals the input current in this case.

Fig. 7(b) shows the element membrane current versus time for elements 1 and 10 as well as the sum of elements membrane current for case (ii). The sum of elements membrane current equals zero in this case.



(a) (b)

Fig. 6 (a) Nodal membrane current at node "1"
(b) Total membrane current
Closed form solution vs. finite element solution



(a) (b)

Fig. 7 (a) Element membrane current/sum of elements membrane current for case (i) (μA)
(a) Element membrane current/sum of elements membrane current for case (ii) (μA)

c. Coupling terms

i). Extrapolation of membrane nodal currents to the extracellular mesh
The concentrated current IN_{mj} is located within a solid extracellular element with nodes K=1,…,8, if an 8-node element is used in the extracellular mesh, as shown in Fig. 8.

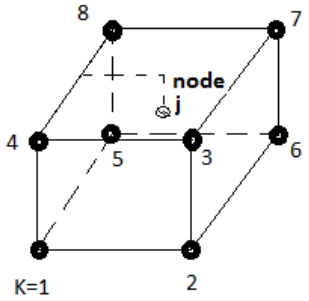


Fig. 8 8-node 3D extracellular element with ganglion node "j"

The concentrated nodal membrane current IN_{mj} within a solid extracellular element is distributed to the nodes of the extracellular mesh according to the weights of

the shape functions as detailed in eq. (30), with each node "K" getting a current I_{mKj} .

$$I_{mKj} = \{ N_K(x_j,y_j,z_j)/[\Sigma^{8}_{L=1} N_L(x_j,y_j,z_j)] \}* IN_{mj} \quad (30)$$

Since $\Sigma^{8}_{L=1} N_L(x_j,y_j,z_j) = 1$,

$$\Rightarrow \quad I_{mKj} = N_K(x_j,y_j,z_j)* IN_{mj} \quad (31)$$

ii) Interpolation of the extracellular potential to nodal values on the ganglion cell mesh

In solving the cable equation, the extracellular potential is needed at the nodes of the meshed cable. This could be obtained by interpolation, such as:

For the value of V_{Ei} , if node "i" lies in element "E", then

$$V_{Ei} = \Sigma^{8}_{K=1} N_K(x_i,y_i,z_i) \, . \, V_{EK}(t) \quad (32)$$

d. Coupled case (as an example, use multiple isolated elements each with two nodes)

Since time does not appear explicitly in the extracellular equation, but rather implicitly in $I_{applied}(t)$ and $I_m(t)$, the principle of superposition is assumed to apply.

The extracellular potential at a point is then the sum of extracellular potential due to the applied current in addition to the effects of membrane currents. This could be expressed by the following relation:

$$\mathbf{V}e(t) = \mathbf{V}eo + \mathbf{V}e_{ij}*\mathbf{IN_m}(t) \quad (33)$$

where

$\mathbf{V}e(t)$ = vector of nodal extracellular potential at nodes of the ganglion mesh

$\mathbf{V}eo$ = vector of nodal extracellular potential due to applied current

$\mathbf{V}e_{ij}$ = matrix of extracellular potential at node "i" due to a unit membrane current at node "j"

$\mathbf{IN_m}(t)$ = vector of membrane nodal currents in ganglion mesh

The vector $\mathbf{V}eo$ and the matrix $\mathbf{V}e_{ij}$ could be determined a priori before time integration.

The solution is obtained by replacing the above equation into the cable equation, namely,

$$\mathbf{C}.d\mathbf{V}_m/dt + \mathbf{F}_{ionic} + \mathbf{K}.\mathbf{V}_m = -\mathbf{K}.\mathbf{V}_e + \mathbf{I}(end) \quad (34)$$

and integrating thru time.

Example III - Coupling between Extracellular/ Intracellular Potentials: A Grid of 110 elements

To investigate the effect of coupling the membrane currents and the extracellular potential the following example is discussed.

A 35.85μA cathodic point current source is injected into an extracellular domain, 50μm above a layer of 110 independent ganglion cells, 2-node elements, as shown in Fig. 9.

The layer size is 300μmx100μm. It is estimated that the ganglion cell density is around 2000 cells/mm^2 [7].

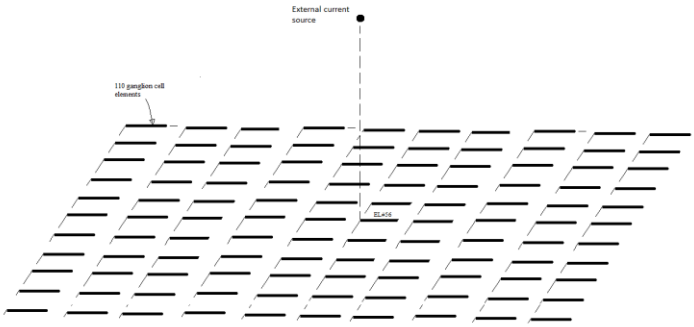


Fig. 9 Grid of 110 ganglion cell elements

Each element is subjected to the extracellular potential with boundary conditions similar to Example II. The length of each element is 30μm with ionic properties same as Example I.

In this example, the nodal currents from each element are fed back into the solution of the extracellular potential.

Fig. 10 shows the time variation of the nodal membrane currents of element #56.

For this particular problem, the membrane current seems to have a small effect on the extracellular potential.

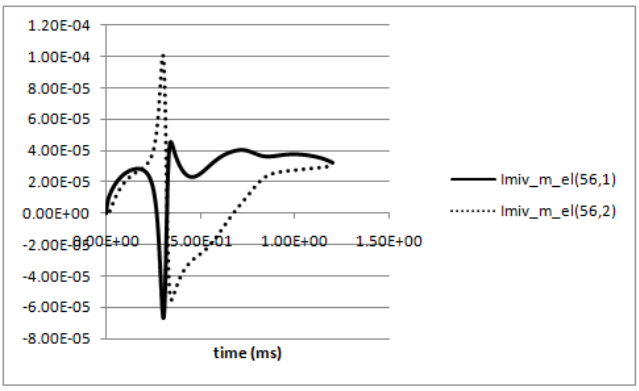


Fig. 10 Nodal membrane currents of element #56 versus time (μA)

V. Conclusions

Stimulating the ganglion cells directly with electrodes attached to the extracellular domain aims to circumvent a damaged photoreceptor system.

This paper built on our previous publication in using the finite element method with its various tools from applied mechanics to model the response of ganglion cells under extracellular potential. The ganglion cells were modeled using the 1D cable equation with the Fohlmeister ionic model for mammals. The extracellular space was modeled as a 3D domain.

The interaction of the extracellular space and the ganglion cell-cable is thru the extracellular potential and the membrane current. Closed form solutions as well as generalized finite element interpolations were used to investigate these interactions.

One of the aims of such formulation is to extend it to large scale problems were the number of individual ganglion cells modeled is large "independent" of the size of the extracellular mesh.

In addition, the effect of the membrane current from these ganglion cells is easily fed back into the extracellular mesh and readily accounted for.

VI. REFERENCES

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