ELECTROPROTEINAMIZING MODELING AT CELL SCALE

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MODELING PRINCIPLE

Extracellular medium $Q$ and cytoplasm $O$ separated by the cell membrane $\Gamma$ are considered as homogeneous isotropic media, with the respective conductivities $\sigma$, and $\epsilon$. $S_0$ and $C_m$ denote the membrane's surface conductivity and capacitance.

When the pulse $g(t)$ applied to the cell, the electric potential $\varphi$ verifies

\[
\begin{align*}
\nabla \cdot (\sigma \nabla \varphi) &= 0 & &\text{in} \ O, \ C_m, \\
\frac{\partial \varphi}{\partial n} &= 0 & &\text{on} \ \Gamma, \\
\varphi &= \Phi_0, & &\text{in} \ \Gamma, \\
\varphi &= \varphi_0 & &\text{on} \ \Gamma.
\end{align*}
\]

In the model of Neu and Krasowska the EP is described through a highly nonlinear current term, which depends on a large number of parameters. Here we take the EP into account through the membrane conductivity $S_0 + S_m + \epsilon \nabla \cdot \varphi$, in $\Omega$. $S_0$ is the membrane conductivity when no pulse is applied, whereas $S_m$ is its value when fully depolarized.

A sliding door model:

\[
\begin{align*}
\frac{\partial \varphi}{\partial t} &= \max \left( \frac{\partial \Phi_0}{\partial t} \right) \left( \Phi_0 - \varphi \right) & &\text{in} \ \Omega, \\
\Phi_0 &= 0 & &\text{on} \ \Gamma.
\end{align*}
\]

PRELIMINARY RESULTS

Electric potential and electroproteinamizing coefficients in a single cell under the influence of a uniform electric field.

COMPARISON WITH KRASOWSKA MODEL

In order to make the link between the numerical results and the survival rates given by the experiments, a GO drug model is set up. Assuming that the flow of molecules through the membrane is proportional to the EP coefficient $\alpha$, the bleomycin concentration $B$ follows the ODE

\[
\frac{d B}{d t} = \alpha \int \left( \Phi_0 - \varphi \right) d \Omega,
\]

where $\alpha$ is a parameter which has to be calibrated with the experiments.

It is known that passed a given intracellular concentration of bleomycin, apoptosis is very likely to happen. Moreover, a too important value of the cell membrane conductivity considerably affects the membrane's structure. We propose the following cell survival probability:

\[
S(\varphi, B) \sim \left( 1 - \tilde{H}_0 \left( \frac{B}{B_0} \right) \right) \left( 1 - \tilde{H}_m \left( \varphi \right) \right),
\]

meaning that the concentration $B$ must not exceed the threshold $B_0$ and the same for the average of $\Phi_0$ with $\varphi$. Several simulations were simultaneously run on cells with different characteristic sizes to compute survival rate of a distributed cell population.

It is also possible to derive a spatial diffusion model from Fick's law, with a similar resolution than the potential equation.

BLEOMYCIN DIFFUSION

SECOND ORDER FINITE DIFFERENCES CARTESIAN METHOD

The method used to accurately discretize the fluxes and the jump conditions on $\Gamma$ is based on the insertion of additional unknowns on each side of the interface. The points neighbouring the interface are treated with specific stencils to approximate the Laplacian term below (left panel). These $\nabla \cdot g$ put on the interface points are discretized at the second order in each direction (middle panel). If the obtained stencil contains non-admissible points (i.e., it is not a valid stencil), the stencil is shifted as shown on the right panel.

It is possible to derive an analytic solution of the linear problem (3), when studying a circular cell in a field of the form (1). Compared to this solution, our scheme achieves a second order convergence. The order is lower when EP is taken into account.

DYNAMIC VS STATIC MODEL

Simulations were run up to several millisecond, the order of $\tau_m$, in order to reach the steady state. The static equations, in which the electric term $\nabla \cdot g$ is neglected, is also solved with the same parameters. The steady state and the transient results can be compared (left panel). One can note that estimation on $\Phi_0$ given by a static model are too pessimistic when well-stressed pulse are applied.

REFERENCES


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