The MPI Parallelization of the Diffusion-Drift Algorithm for Quantitative Analysis of Breast Tumor Electric Signals

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Introduction

Experimental measurements on MCF-7 cells, a standard breast cancer cell line, have demonstrated that the membrane potential varies with the different stages of cell division [1]. The membrane potential was found to depolarize, that is become more positive, at the beginning of the Gap 1 (G1) stage and hyperpolarize at the Gap 1/Synthesis (G1/S) transition. The extracellular electrical signals, electric current densities and biopotentials, generated due to these depolarizations and hyperpolarizations were calculated due to a single cell in [1].

This paper aims to expand the work in [1] by modeling breast tumors, containing a large number of cells, of different spatial distributions and division stages. Malignant breast tumors were found to exhibit an irregular shape whereas benign tumors were found to have a smooth circular shape [2]. Therefore, the goal of this work is to study the effect of the different cell configurations on the electric signals.

The results prove the concept, at a small scale, that different spatial arrangements of MCF-7 cells affect the generated electric signals. This is the motivation for exploring the more computationally expensive analysis of sizable tumors, ~1mm in diameter, with larger number of cells. The MPI parallelization of the algorithm is proposed to achieve this goal.

Formulations

Cells are typically encapsulated by a selectively permeable membrane which separates the extracellular and intracellular media. In addition, cells maintain a membrane potential via the active transfer of ions between the extracellular and the intercellular media [1]. These cellular dynamics create diffusion-drift forces which can be described by the Nernst-Plank, continuity and Poisson equations as [1]:

\[ \vec{J}_m = -D_m \nabla C_m - \mu_m C_m Z_m \nabla \phi + \vec{J}_{\mu m} \quad (1) \]

\[ \frac{\partial C_m}{\partial t} = -\nabla \cdot \vec{J}_m \quad (2) \]

\[ \nabla^2 \phi = -\frac{F}{e} \sum_m Z_m C_m \quad (3) \]

where for ion \( m \), \( \vec{J}_m \) is the flux or electric current density (moles/(cm\(^2\) × s)), \( D_m \) is the diffusion coefficient (cm\(^2\)/s), \( C_m \) is the concentration (moles/cm\(^3\)), \( \mu_m \) is the mobility of (cm\(^2\)/(volt × s)), \( Z_m \) is the signed charge, \( \phi \) is the electrostatic potential (V), \( J_{\mu m} \) is the
active electric current density due to ions pumps in the cell membrane, \( F \) is Faraday’s constant (96485 C/mol) and \( \varepsilon \) is the permittivity of the material (80 \( \varepsilon_0 \) for water under quasi static conditions). Three ions, potassium \( C_{\text{K}^+} \), sodium \( C_{\text{Na}^+} \), and chloride \( C_{\text{Cl}^-} \), will be considered in this work [1]. The active sodium and potassium electric current densities in (1), \( J_{a_{\text{Na}}} \) and \( J_{a_k} \), are non-zero only at the cell boundary and can be expressed as in [1].

Equation (1)-(3) vary with both the time and space and, therefore, are discretized both spatially and temporally. The implicit scheme described in [1] is employed for the temporal discretization whereas the non-uniform scheme described in [3] is employed for the spatial discretization. The non-uniform scheme is used due to the contrast in size between the cell length and the intercellular gap. The computational domain shown in Fig. 1 is used to simulate the MCF-7 cells. The left, right, top and bottom boundary conditions are set to Neumann, Dirichlet, periodic and periodic boundary conditions, respectively [1]. The parameters employed in the model such as the diffusion and mobility coefficients of the three ions are similar to those in [1]. In the depolarization transition, the active electric current density at the cells boundaries is decreased by four times. In addition, the diffusion and mobility coefficients of potassium ions at the cells boundaries are decreased by ten times [1]. To simulate the hyperpolarization transition, the change in the previous three parameters is reversed. The other model parameters such as the diffusion and mobility coefficients of sodium and chloride ions are maintained constant.

**Results**

Any two cells can be distributed spatially in various ways inside a tumor. Three different spatial arrangements of the two cells configuration are modeled: (i) Cell 1 and Cell 2 are separated by an internal gap of 0.25\( \mu \text{m} \) which is the average separation distance between MCF-7 cells as estimated in [4], (ii) Diagonally placed cells Cell 1 and Cell 3 and (iii) Cell 1 and 2 touching with no separation. As an example, the two cells are simulated to simultaneously hyperpolarize in the three cases but other cases will be presented in the conference. The biopotential difference \( V_i \) defined in Fig. 1a is plotted versus time in Fig.
1b for the three cases. The maximum $V_1$ dropped from 0.26 $\mu$V when Cell 1 and Cell 2 are simulated to 0.21 $\mu$V in the diagonal case. This drop can be attributed to the fact that Cell 3 is further from the position where $V_1$ is calculated in comparison to Cell 2. Therefore, the biopotential signals generated from Cell 3 decay more than Cell 2. In addition, the presence of the intercellular gap in the Cell 1 and Cell 2 configuration amplifies $V_1$ since the motion of the ions discharged in the intercellular gap is restricted to the horizontal direction only. The absence of the gap also reduces the maximum of $V_1$ to 0.19 $\mu$V when the two cells are touching as shown in Fig. 1b. In addition when the two cells are touching, they lose one of their four boundaries where they can exchange ions with the extracellular media. This can also be the reason that $V_1$ is lower and slower to converge to zero in the third configuration.

Fig. 2 shows the spatial distribution of the electrical current densities and the biopotentials, after 0.8 minutes from the start of the hyperpolarization at the instant marked in Fig. 1b. In Fig. 2, the cells are shown in dark blue whereas the color at the other pixels represents the biopotential at the extracellular media. The arrows directions and lengths represent the directions and magnitudes, respectively, of the electrical current densities. Fig. 2a shows the presence of a magnified electric current density in the intercellular gap which is absent in Fig. 2b-c. This is because any ions released by the two cells in the intercellular gap can only move in the horizontal direction.

**MPI Parallelization of the Model**

Each case in Fig. 1 and Fig. 2 required ~ 24 hours on a single 2.2GHz processor with 8GB of RAM. Expanding the computational domain to include larger tumors will require the MPI parallelization of the algorithm to keep the execution time realistic. At each time step, (1)-(3) above are discretized leading to four sparse system of equations, one for the biopotential and one for each of the three ions considered. The solution of these systems of equations composes most of the execution time of the algorithm. To reduce the
execution time the Portable, Extensible Toolkit for Scientific Computation, PETSc library [5] is utilized to parallelize the solution of the system of equations. Several iterative solvers in the PETSc library were tested and the optimum solver, which solved the system of equations in the least time, is the Enhanced Bi-conjugate Gradient stabilized (BiCGStab(L)) solver. The BiCGStab(L) iterative solver is used via calling the KSPSolve command. Preliminary results showing the speed up of solving the system of equations resulting from (3) above is shown in Fig. 3. Fig. 3 is obtained for a computational grid composed of 840×840 pixels which is the smallest grid that can accommodate a 1mm tumor. The speed up is normalized with respect to the execution time of 8 processors. The super linear speed up in Fig. 3 can be attributed to the cache effect [6]. Speed up from the parallelization of the overall algorithm versus different number of processors will be presented in the conference.

Conclusions

The electric signals generated by MCF-7 cells are found to vary considerably with their spatial distribution. The presence of an intercellular gap between the cells magnifies both the biopotentials and the electric current densities. Current work is in progress to investigate hundreds of cells composing ~ 1mm tumors.

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References