Mathematical and computational modelling of cell clustering under the influence of a chemotatic signal

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1 Background

Chemotaxis is defined as the directed movement of cells in response to chemical stimuli. It is a crucial mechanism seen in various biological processes. The chemical stimuli can be food or oxygen that the cells tend to move towards, known as chemoattractant, or substances such as toxins that drive the cells away, known as chemorepellent. Cells of the same type like to come together to form clusters. Cell aggregation, which is the formation of tissues, arise from this process.

2 Model

The cell membrane is discretized as a polygon with given number of vertices (nodal points) connected by line segments. The movement of the cell is determined by the interaction of the different forces at each vertex. There are six mechanisms in total that determine the displacement of the cell:

1. Chemotaxis
2. Random Walk
3. Area Constraint on the cell
4. Surface Tension of Cell Membrane
5. Repulsion from Computational Domain's Boundary
6. Lennard-Jones Force Between Cells

2.1 Chemotaxis

The primary mechanism that determines the displacement of the cell is chemotaxis. Cells migrate in response to the gradient of a chemical substance. In this model, there is one single fixed point source on the computational domain. The source is constantly secreting chemoattractant that promotes cell movement in the gradient's direction. The distribution of the point source is modelled by Dirac Delta distribution:

$$\delta(x) = 0,\ \forall x \in \mathbb{R}^d,\ x \neq 0$$

$$\int_\Omega \delta(x) = 1,\ if\ \{0\} \in \Omega$$

Since the chemoattracnt is constantly being secreted by the point source and diffusing across the computational domain, reaction-diffusion system is used to determine the concentration of the chemoattractant. Combining this with the Dirac Delta distribution, the concentration of the chemoattractant follows:

$$\frac{\partial c(x,t)}{\partial t} - \nabla \cdot (D \nabla c(x,t)) = k\delta(x(t) - x_s), x \in \Omega, t > 0$$

where D is the diffusion rate and k is the secretion rate. Ω is the computational domain, which is circular and represents a petri dish in the model.

The Robin boundary condition on the computational domain is given by:

$$\frac{\partial c}{\partial n} + k_s c = 0,\ on\ \partial\Omega, t > 0$$

where k_s is the mass transfer coefficient. What this means that there is a balance between the flux through the boundary and flux coming from region far away from the domain.

The displacement due to chemotaxis is given by:

$$dx = \beta_c \frac{\nabla c(x_i j, t)}{||\nabla c(r_i, t)||} dt$$

where x_{ij} represents the jth node on the ith cell, and r_i is the centroid of the ith cell. Normalizing the gradient with the norm of gradient at the centroid leads to differences across nodes on the same cell. The nodes closer to the point source will have a stronger gradient, and leads to greater displacement. β_c is a parameter that determines the weight of chemotaxis, and dt is the time step of the model.

To solve the reaction-diffusion system in FeNiCs, given a test function ϕ, the weak formulation is:

$$\int_\Omega \frac{\partial c(x,t)}{\partial t} \cdot \phi - k(\phi\ \delta(x(t) - x_s)) + k_s c(x,t) = -\int_\Omega D(\nabla\phi \nabla c(x,t))$$

2.2 Random Walk

When chemotaxis is absent, cells exhibit disordered movement due to Brownian random walk, this is given by:

$$dx = \sigma_{rw} dW(t) dt$$

where σ_{rw} is the weight of random walk, and $dW(t)$ is the vector-Wiener process.

2.3 Area Constraint

Cell area tend to stay relatively constant regardless of other mechanisms. Therefore, an area control variable denoted by λ is taken into count. λ is a Lagrange multiplier that represents a constant force over the cell membrane. This force will counterbalance the effect that drastically changes the cell's area from the initial cell area. The displacement is given by:

$$dx = -\lambda \hat{n}\ dt$$

where λ follows:

$$\frac{d\lambda}{dt} = \frac{\beta_1 \lambda (A - A_0 + \frac{dA}{dt})}{A_0(\lambda + \beta_1)} - \beta_2 \lambda$$

A_0 is the initial area of the cell, A is the current area of the cell. $\hat{n}$ is the outward unit normal vector on the cell membrane. β_1, β_2 are parameters.

λ will fluctuate between positive and negative in the absence of other mechanisms. When cell area increases, λ increases and shrinks the cell area accordingly. When cell area decreases, λ becomes more negative and increases the cell area.

2.4 Surface Tension

To compensate the effect drastic deformation due to chemotaxis on the cell membrane, surface tension is included to maintain the relative smoothness of the cell membrane. Let $\Delta\tau_j$ denote the mean curvature at vertex j, the estimation for $\Delta\tau_j$ at timepoint $n+1$ is given by:

$$\Delta\tau_j^{n+1} = \frac{x_{j+1}^n - 2x_j^n + x_{j-1}^n}{d_1 d_2}$$

where x are the coordinates of the vertex and $d1$, $d2$ are the distances between neighboring vertices $(j-1, j)$ and $(j, j+1)$.

The surface tension is modelled by the mean curvature of the cell membrane. Mean curvature vector follows:

$$H = -\Delta_\tau x$$

The weak formulation with the test function w is given by:

$$\int_{\Gamma_t} wH = \int_{\Gamma_t} \nabla_\Gamma w \cdot \nabla_\Gamma x$$

where H is the mean curvature, $\Delta_\tau x$ is the Laplace-Beltrami operator of the cell membrane.

The displacement due to surface tension is given by:

$$dx = \alpha \Delta_\tau \, dt$$

where α is the strength of displacement due to surface tension.

2.5 Repulsion from Computational Domain's Boundary

The computational domain is a circular. Cells are not allowed to exit the computational domain. Therefore, a repulsive force from the domain's boundary is exerted on the cell membrane if the cell comes close to the boundary. The displacement is given by:

$$dx = \epsilon_r e^{\frac{1}{d}} \hat{n_{db}} \, dt$$

where ϵ_r is the strength of repulsion, d is the minimal distance from the vertex to the domain's boundary, and $\hat{n_{db}}$ is the inward unit normal vector on the boundary.

2.6 Lennard-Jones Force Between Cells

In this model, cell clustering happens at close promoxity but are not allowed to intersect with each other. This is similar to the intermolecular forces determined by Lennard-Jones potential. Cells attract each other when they are within a certain distance, and exerts repulsion force to prevent overlapping. The displacement is given by:

$$dx = 4 \, \epsilon_{lj} \left(\left(\frac{\sigma_{lj}}{d} \right)^{12} - \left(\frac{\sigma_{lj}}{d} \right)^{6} \right) \, dt$$

where d is the distance between pairs of nodes, σ_{lj} represents the cutoff distance which Lennard-Jones force switch from attraction to repulsion, and ϵ_{lj} is strength of Lennard-Jones potential.

3 Parameters

dt	D	k	k_s	β_c	σ_{rw}	λ_0	β_1	β_2	α	ϵ_r	ϵ_{lj}	σ_{lj}
0.05	233.2	2.5	100	1.5	1	0.5	0.2	0.001	0.5	0.5	0.7	0.02

Among the parameters, the ones that determine the weight of the mechanism: $\beta_c, \sigma_{rw}, \epsilon_{lj}, \sigma_{lj}$ are sensitive to change. β_c and σ_{rw} are kept relatively close to each other so that the effect of Lennard-Jones potential will not fail when the displacement is too large which leads to the cells overlapping.

References

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