Numerical Solutions of an Immunology Model Using Reaction-Diffusion Equations with Stochastic Source Terms

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Background

- Immune cells secrete **cytokines** in order to communicate with other immune cells. Cytokines are modeled continuously as **soluble factors**.
- A subset of cytokines called **chemokines** direct the motion of immune cells along their concentration gradient by a process known as **chemotaxis**. Cell motion is inherently **stochastic**.
- Based on these signals, the cells will group together to respond to an infection.

Reaction-Diffusion System for the Soluble Factors

For $i = 1, 2, \ldots, N$, let U_i be the concentration of soluble factor i.

$$\frac{\partial U_i}{\partial t}(\mathbf{x}, t) = \text{diffusion} + \text{reaction} + \text{source terms}$$

$$= D_i \Delta U_i(\mathbf{x}, t) - \left\{ \sum_{j=1}^{N} r_{ij} U_j(\mathbf{x}, t) + \lambda_i \right\} U_i(\mathbf{x}, t)$$

$$+ \sum_{\mu=1}^{M} J_{i\mu}(t) g_{s_\mu}(\mathbf{x} - \mathbf{x}_\mu(t)), \qquad \mathbf{x} \in \Omega$$

- D_i is the diffusion coefficient for U_i.
- r_{ij} is the rate at which U_i is removed by interaction with U_j.
- $\mathbf{x}_\mu(t)$ is the position of cell μ.
- g_{s_μ} is a smoothly cut-off Gaussian centered at $\mathbf{x}_\mu$.
- $J_{i\mu}(t)$ is the secretion rate of U_i by cell μ.

Stochastic Differential Equations for the Cell Motion

Cell motion is modeled by a Langevin process $X_t = (\mathbf{x}_t, \mathbf{v}_t)$

- Position: $d\mathbf{x}_t = \mathbf{v}_t\, dt$
- Velocity: $d\mathbf{v}_t = [h(\mathbf{U}(\mathbf{x}_t)) - \gamma \mathbf{v}_t]\, dt + \sigma(\mathbf{U}(\mathbf{x}_t))\sqrt{\gamma} d\mathbf{W}_t$
- The motion is biased toward the direction of $h(\mathbf{U}(\mathbf{x}_t))$ where

$$h(\mathbf{U}) = \sum_{i=1}^{N} \frac{\chi_i \nabla U_i}{h_0 + |\nabla U_i|}.$$

  Here χ_i is the chemotactic constant that controls how much the drift is influenced by the gradient of soluble factor i.
- The magnitude of the Wiener process depends on a soluble factor concentration by

$$\sigma(U) = \sum_{i=1}^{N} \sigma_0 \left(1 + \frac{U_i}{U_i^0}\right)^q e^{-\lambda U_i}$$

Operator Splitting

We can split the model into the following three problems for which there are well-known numerical methods:

1. The diffusion of the soluble factors,

$$\frac{\partial U_i}{\partial t}(\mathbf{x}, t) = D_i \Delta U_i + \sum_{\mu=1}^{n} J_{i\mu}(t) g_{s_\mu}(\mathbf{x} - \mathbf{x}_\mu(t)), \quad U_i(0) = u_i.$$

   Note: This is a now a decoupled set of *linear* PDEs.

2. The reactions of the soluble factors,

$$\frac{\partial U_i}{\partial t} = -\left\{ \sum_{j=1}^{m} r_{ij} U_j + \lambda_i \right\} U_i, \quad U_i(0) = u_i.$$

   Note: This is now a system of ODEs.

3. The motion of the cells,

$$d\mathbf{x}_t = \mathbf{v}_t dt, \quad \mathbf{x}(0) = \xi,$$
$$d\mathbf{v}_t = [h(\mathbf{u}(\xi)) - \gamma \mathbf{v}_t]\, dt + \sigma(\mathbf{u}(\xi))\sqrt{\gamma} d\mathbf{W}_t, \quad \mathbf{v}(0) = \nu.$$

Operator Splitting

For each time step:

1. Solve the diffusion using the initial concentrations and cell positions.
2. Solve the reaction the using the updated concentrations.
3. Move the cells according to the Langevin process using the updated concentrations and initial cell positions.

Important Estimates:

$$\sup_{0\leq t\leq \Delta t} \left|\mathbb{E}\left[\left\|U(t)-\overline{U}(t)\right\|_k + X_t - \overline{X}_t\right]\right| \leq C(\sup|u|, \|u\|_{(k+2)\vee 3})(\Delta t)^2.$$

$$\sup_{0\leq t\leq \Delta t} \mathbb{E}\left[\left\|U(t)-\overline{U}(t)\right\|_k^2 + |X_t - \overline{X}_t|^2\right]^{\frac{1}{2}} \leq C(\sup|u|, \|u\|_{(k+2)\vee 3})(\Delta t)^{\frac{3}{2}}.$$

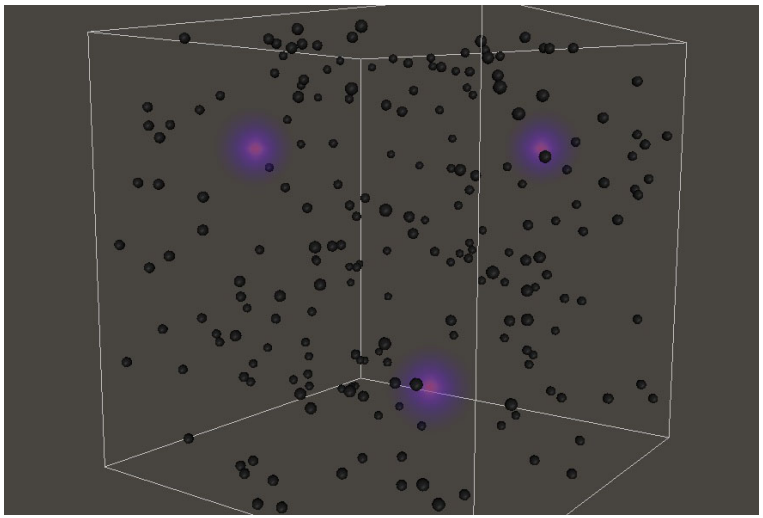
The resulting error using the two estimates above is $\mathcal{O}(\Delta t)$.

Numerical Methods

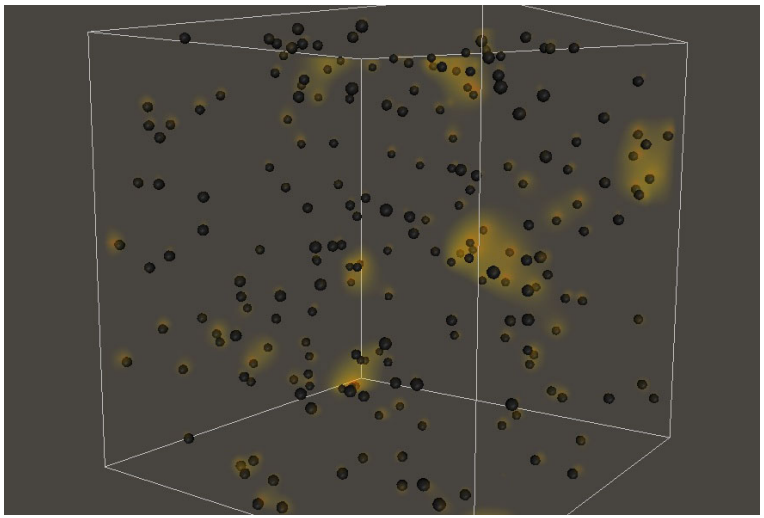
- Diffusion: Backward Euler with Multigrid
- Reaction: Simple ODE method
- Cell Motion: Hold the soluble factor concentration constant in space. Solve the Langevin process exactly.

All three methods are $\mathcal{O}(\Delta t)$.

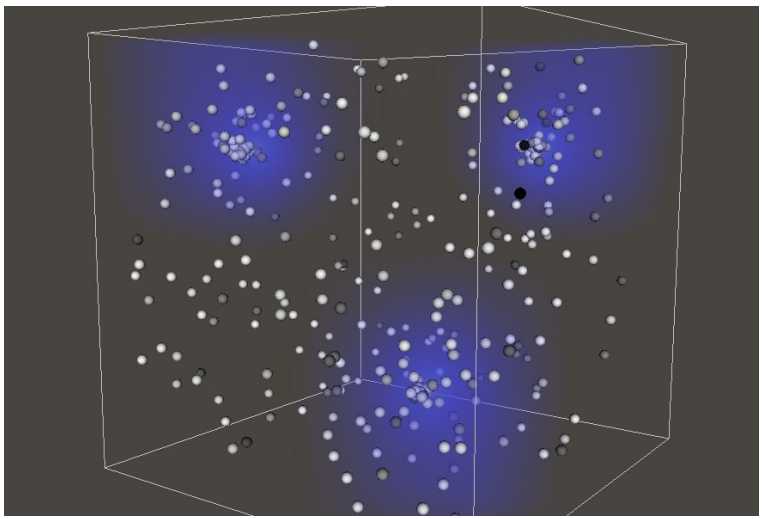
Numerical Simulation - Response to MCP1



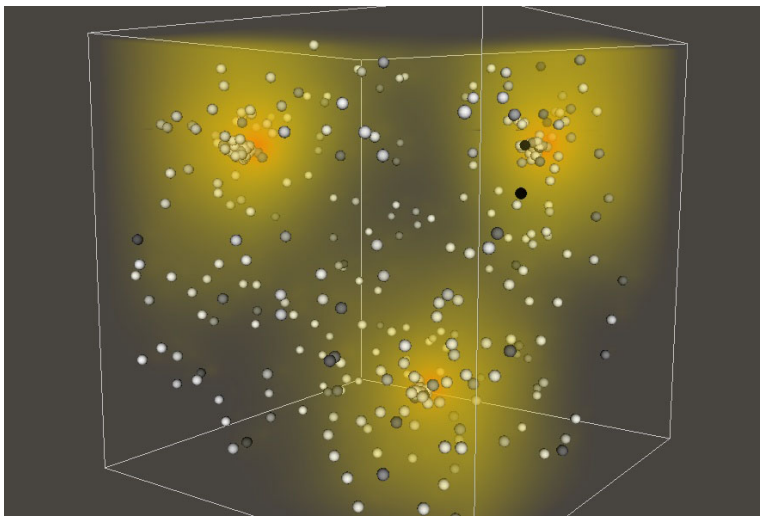
(a) Concentration of MCP1 at $t = 10$min



(b) Concentration of TNF at $t = 10$min



(c) Concentration of MCP1 at $t = 120$min



(d) Concentration of TNF at $t = 120$min

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