MASDOC Biomembranes RSG - Modelling the movement of a neutrophil chasing a bacterium

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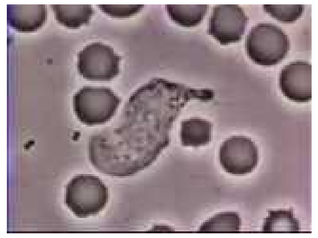
Introduction and Project Goals

Our project investigates the mechanisms by which a neutrophil (white blood cell) chases a bacterium by means of chemotaxis — the response of cells to chemical changes in their surroundings.



This project aims:-

- To simplify and adapt the model of Neilson *et al.* to use a mean curvature flow model for the movement of the neutrophil membrane, and propose a numerical simulation for this new model using finite element methods.
- To assess the probability of a nearby bacterium escaping a neutrophil in various situations using diffusion processes.
- To compare the results of our simulations with those of an empirical model by Li, Nørrelykke and Cox.

The Model of Neilson *et al.*

The chemotaxis model of Neilson, Mackenzie, Insall and Webb [2] is our starting point. The reaction-diffusion equations for this model are

$$\partial_t^\bullet a + a\nabla_{\Gamma(t)}\cdot v = D_a\Delta_{\Gamma(t)}a + f(a,b,c) - r_a a,$$
$$\partial_t^\bullet b + b\nabla_{\Gamma(t)}\cdot v = D_b\Delta_{\Gamma(t)}b - r_b b + r_b \fint_{\Gamma(t)} a\,\mathrm{d}x,$$
$$\partial_t^\bullet c + c\nabla_{\Gamma(t)}\cdot v = D_c\Delta_{\Gamma(t)}c - r_c c + b_c a$$

where

- v is the normal velocity of the neutrophil membrane $\Gamma(t)$.
- D_a, D_b, D_c, r_a, r_b and r_c are diffusion coefficients and decay rate constants for the chemoattractants.
- b_c determines the growth of c in the presence of a
- f is a non-linear stochastic term which incorporates the effect of the external signal and random fluctuations.

These are coupled to a PDE modelling the movement of the neutrophil membrane. This PDE is given by

$$u_t\cdot\nu = V_f - \lambda\kappa$$

where

- $u\cdot\nu$ represents the outward normal movement of the cell membrane.
- V_f represents the velocity contribution influenced by the presence of chemoattractant a, and stimulates protrusions in the direction of the bacterium's location.
- $\lambda\kappa$ regulates the cell movement so that the cell area does not increase, and the membrane does not bend too much. Smoother configurations have lower energy and are more preferable, so the motion of the membrane will resist increasing curvature.

Simplifying the Chemotaxis Model

Under suitable conditions, the equations for b and c can be normalised and reduced down to

$$b = \fint_{\Gamma(t)} a\,\mathrm{d}x \quad \text{and} \quad c = \frac{\widetilde{b}_c}{\widetilde{r}_c}a \approx 0.385a$$

These results are backed up by simulation data in the paper of Neilson *et al.* We are therefore left with just one equation governing the dynamics of the chemoattractant concentrations.

Neutrophil Membrane Movement - New Approach

The main issue with the Neilson *et al.* model is finding values of λ, which have to satisfy a non-linear ODE. We therefore propose an alternative model based upon mean curvature flow, given by the equation

$$V_f(x) = -\varepsilon H(x) + \delta a(x) + \bar{\lambda}.$$

where ϵ, δ are small, positive constants, $\bar{\lambda}$ is a Lagrange multiplier which constraints the area of the cell to remain constant and $H(x)$ is the mean curvature at point x.

Model Numerics

Curve approximation setup

- The smooth evolving surface $\Gamma(t)$ is approximated by a polyhedral surface $\Gamma_h(t)$, whose vertices are taken to sit on $\Gamma(t)$ so that it is an interpolation.
- $\Gamma_h(t)$ is parametrised by a smooth mapping $\mathbf{X}^h : \mathbb{R}\times[0,T]\to\mathbb{R}^2$ with periodicity condition $\mathbf{X}^h(p,t) = \mathbf{X}^h(p+1,t)$, $0\le t\le T, \forall p\in\mathbb{R}$.

Finite element approximation

- Let $p_j = jh$, with $j = 0,\dots,N$, be a uniform grid, and define the piecewise linear finite element space

$$V_h = \{\phi\in C^0([0,1];\mathbb{R}) : \phi|_{[p_{j-1},p_j]}\in P_1, j=1,\dots,N; \phi(0)=\phi(1)\}.$$

- Find $a^h(\cdot,t)\in V_h$ such that for almost every $t\in(0,T)$,

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_0^1 a^h\phi\left|\mathbf{X}_p^h\right|\mathrm{d}p + D\int_0^1 \frac{a_p^h\phi_p}{\left|\mathbf{X}_p^h\right|}\mathrm{d}p = \int_0^1 f(a^h)\phi\left|\mathbf{X}_p^h\right|\mathrm{d}p \qquad (1)$$

  for every $\phi(\cdot,t)\in V_h$.
- Given $a^h(\cdot,t)\in V_h$, find $\mathbf{X}^h\in\mathbf{V}_h$ such that for almost every $t\in(0,T)$,

$$\int_0^1 [\mathbf{X}_t^h\cdot\varphi]\left|\mathbf{X}_p^h\right| + \frac{\varepsilon\mathbf{X}_p^h\cdot\varphi_p}{\left|\mathbf{X}_p^h\right|}\mathrm{d}p = \int_0^1 (\delta a^h + \bar{\lambda}^h)\varphi\cdot(\mathbf{X}_p^h)^\perp\,\mathrm{d}p \qquad (2)$$

  for every $\varphi(\cdot,t)\in\mathbf{V}_h$, subject to the area of the cell remaining constant, where $\bar{\lambda}^h$ is a discretised form of $\bar{\lambda}$.

Simulation Results

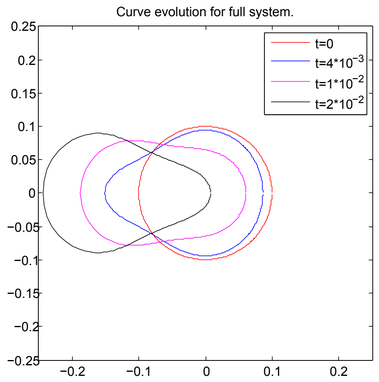


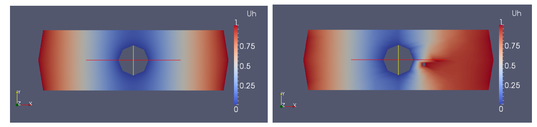
Figure: Curve Evolution under (1) and (2) with $\Delta t = O(h^2)$, $\varepsilon = 10^{-6}$ and final time $T = 10$, with the unit circle as the initial curve. The model constants are as in [2]

This figure illustrates the progression of the neutrophil membrane under the numerical method developed above.

- The initial condition $a_0 = 20\exp\left(\frac{-(p-0.5)^2}{0.0002}\right)$ represents the presence of a bacterium on the left hand side.
- The result is the formation of a protrusion towards the bacterium, driving the neutrophil to move in the same direction.

The Chase - When Does a Bacterium Escape?

- Given the movement of the neutrophil, what is the probability that a nearby bacterium escapes?
- The first figure shows the probability of escape in a capillary with reflective boundaries; the second figure is the same setting with an added obstacle.
- This is a function of the starting position of the bacterium relative to the neutrophil at the centre of the figure.



(a) Without obstacle (b) With obstacle

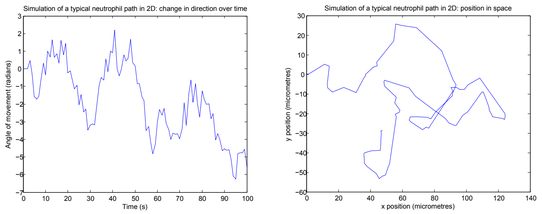
- Chemotaxis is a process based upon concentrations of amino acids in a fluid and the diffusions of these concentrations
- The effects of this process decay exponentially with distance.
- The bacterium thus significantly increases its chances of escaping by starting only a relatively small distance further from the neutrophil.

Comparison with an Empirical Model

Experimental data from Li *et al.* [1] suggests that neutrophils move in a rough zig-zag manner.

- The cell moves in a straight line for a random distance modelled by an Exp(5×10^{-6}) (metres) distribution before turning.
- It remembers the direction (left or right) it last turned and turns the opposite way approximately 2/3 of the time.
- The turn angle is distributed according to an Exp(0.67) (radians) distribution.

The graphs give details of a simulated cell movement in the plane, starting at the origin.



(c) (d)

- The theory suggests that a new pseudopod is most likely to form in the gap between the two most recent formations, which accounts for the zig-zag motion.
- The model of Nielson *et al.*, backs up these conclusions.
- The normalised reaction-diffusion model does not currently predict this long-term pseudopod behaviour (the choice of numerical scheme may also be a factor).
- There is scope to develop the model to better reflect the empirical data.

Acknowledgements

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References

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