Biomembranes RSG - Project Implementation

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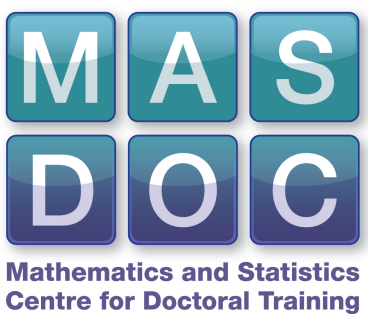

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Motivation

We are interested in the motion of a neutrophil (white blood cell) chasing a bacterium.

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(chase.mpg)

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- An SDE approach to model the escape probability of a bacterium.
- A statisical approach to examine the movement of the neutrophil and bacterium based on an empirical model.

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- As a starting point, we consider the chemotaxis model of Neilson *et al.* This model has two parts.
  - Dynamics of chemicals - governed by reaction-diffusion PDEs.
  - Membrane movement - governed by a PDE and a non-linear ODE.

Reaction-Diffusion System

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$$\partial_t^\bullet a + a\nabla_{\Gamma(t)} \cdot v = D_a \Delta_{\Gamma(t)} a + \frac{s(\frac{a^2}{b} + b_a)}{(s_c + c)(1 + a^2 s_a)} - r_a a.$$

$$\partial_t^\bullet b + b\nabla_{\Gamma(t)} \cdot v = D_b \Delta_{\Gamma(t)} b - r_b b + r_b \fint_{\Gamma(t)} a \, \mathrm{d}x.$$

$$\partial_t^\bullet c + c\nabla_{\Gamma(t)} \cdot v = D_c \Delta_{\Gamma(t)} c - r_c c + b_c a.$$

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- Cortical Torsion ("Bending").

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where:

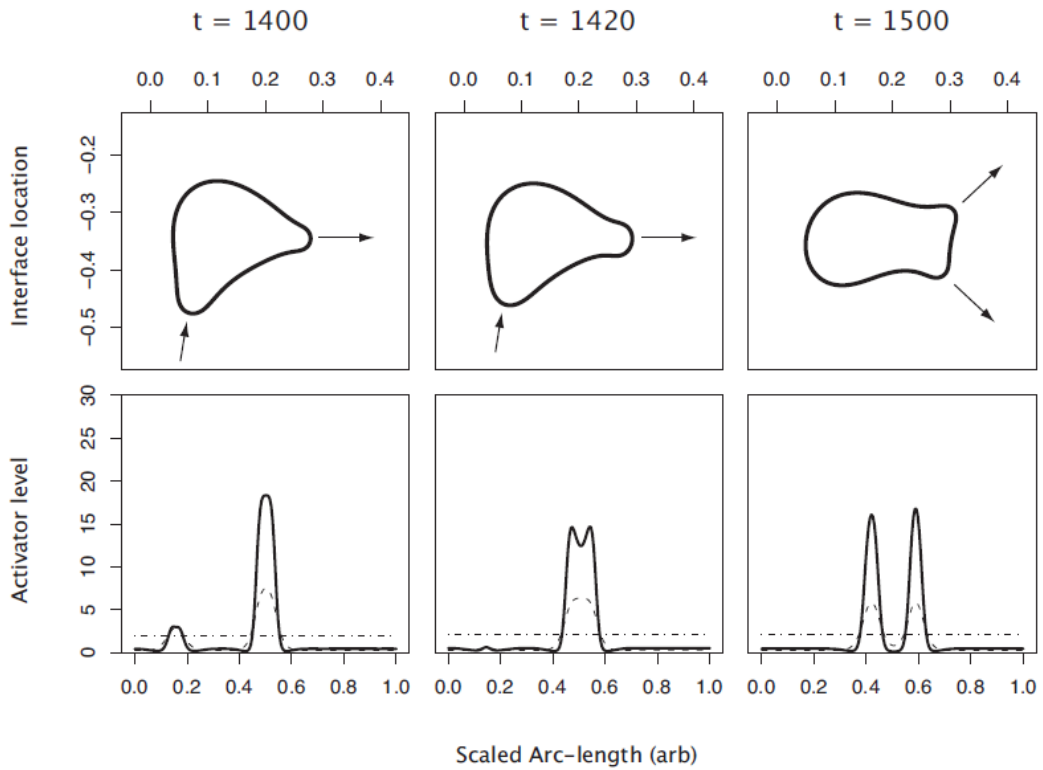
- $V_f = K_{\text{prot}} a$ with K_{prot} a positive parameter.
- κ represents cortical torsion
- λ ensures the area of the cell is controlled. In particular, it is a solution to the non-linear ODE

$$\frac{\mathrm{d}\lambda}{\mathrm{d}t} = \frac{\lambda_0 \lambda \left(A - A_0 + \frac{\mathrm{d}A}{\mathrm{d}t} \right)}{A_0 \left(\lambda + \lambda_0 \right)} - \beta\lambda$$

with λ_0 and β positive constants, $A(t)$ the area of the cell and A_0 the initial cell area.

Contents

Normalisation



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We therefore want to normalise this model to see if this behaviour is described by the model.

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$$x = Lx', \quad t = Tt', \quad a = Aa', \quad b = Ab', \quad \text{and} \quad c = Ac'$$

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$$\partial^{\bullet}_{t'} a' + a' \nabla_{\Gamma'(t')} \cdot v' = T \left(\frac{D_a}{L^2} \Delta_{\Gamma'(t')} a' + \frac{s(\frac{a'^2}{b'} + \frac{b_a}{A})}{(s_c + Ac')(1 + A^2 (a')^2 s_a)} - r_a a' \right),$$

$$\partial^{\bullet}_{t'} b' + b' \nabla_{\Gamma'(t')} \cdot v' = T \left(\frac{D_b}{L^2} \Delta_{\Gamma'(t')} b' - r_b \left(b' - \fint_{\Gamma'(t')} a' \, \mathrm{d}x' \right) \right),$$

$$\partial^{\bullet}_{t'} c' + c' \nabla_{\Gamma'(t')} \cdot v' = T \left(\frac{D_c}{L^2} \Delta_{\Gamma'(t')} c' - r_c c' + b_c a' \right)$$

Reducing the System

Theorem - Reduced Reaction-Diffusion System

The system of normalised equations can be approximately reduced down to

$$\partial^{\bullet}_{t'} a' + a' \nabla_{\Gamma'(t')} \cdot v' = \Delta_{\Gamma'(t')} a' + \frac{Ts\left(\frac{a'^2}{b'} + \frac{b_a}{A}\right)}{(s_c + Ac')(1 + A^2 (a')^2 s_a)} - Tr_a a'$$

$$b' = \fint_{\Gamma'(t')} a' \, \mathrm{d}x',$$

$$c' = \frac{\widetilde{b_c}}{\widetilde{r_c}} a' \approx 0.385 a'.$$

Variational Formulation

($\mathbf{P}^{a}_{wk}$) Variational Formulation of Reaction-Diffusion Equations

Find $a(\cdot, t) \in V = H^1(\mathcal{G}_T)$ such that for almost every $t \in (0, T)$,

$$\frac{d}{dt}\int_{\Gamma(t)} a\phi + D\int_{\Gamma(t)} \nabla_{\Gamma(t)} a \nabla_{\Gamma(t)}\phi = \int_{\Gamma(t)} a\dot{\phi} + \int_{\Gamma(t)} f(a)\phi,$$

for every $\phi(\cdot, t) \in V$, where $\mathcal{G}_T = \cup_{t\in[0,T]}(\Gamma(t) \times \{t\})$ and

$$f(a) = T\left(\frac{s(\frac{a^2}{b} + \frac{b_a}{A})}{(s_c + Ac)(1 + A^2(a)^2 s_a)} - r_a a\right).$$

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Membrane Movement - Alternative Approach

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- We propose an alternative model that eliminates the $\lambda\kappa$ term and replaces the formula for V_f with a mean curvature flow model, given by

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

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

- Now let $\mathbf{X} \in C^2\left(\mathbb{R} \times [0, T], \mathbb{R}^2\right)$ be a parametrisation of $\Gamma(t)$.

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$$\mathbf{X}(p, t) = \mathbf{X}(p + 1, t), \ p \in \mathbb{R}, \ t \in [0, T].$$

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- The strong form of the PDE is

$$\mathbf{X}_t \left|\mathbf{X}_p\right| = \varepsilon \frac{\partial}{\partial p}\left(\frac{\mathbf{X}_p}{\left|\mathbf{X}_p\right|}\right) + (\delta a + \bar{\lambda})\mathbf{X}_p^{\perp} \quad \text{in } [0, 1] \times (0, T)$$
$$\mathbf{X}(\cdot, 0) = \mathbf{X}_0 \quad \text{in } [0, 1].$$

Variational Formulation

($\mathbf{P}^{\mathrm{m}}_{\mathrm{wk}}$) Variational Formulation of Membrane Movement PDE

Given $a \in H^1_{per}([0,1] \times [0,T]; \mathbb{R})$, find $\mathbf{X} \in H^1_{per}([0,1] \times [0,T]; \mathbb{R}^2)$ such that

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

subject to the area of the cell remaining constant, for all $\phi \in H^1_{per}([0,1]; \mathbb{R}^2)$.

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- $\Gamma_h(t)$ is a polyhedral surface whose vertices $\{\mathbf{X}_j(t)\}_{j=1}^N$ are taken to sit on $\Gamma(t)$.
- Let $\mathbf{X}^h : \mathbb{R} \times [0, T] \to \mathbb{R}^2$ be a smooth parametrisation of $\Gamma_h(t)$ with $\left|\mathbf{X}^h_p\right| > 0$, and periodicity condition $\mathbf{X}^h(p, t) = \mathbf{X}^h(p + 1, t)$, $0 < t \leq T$, $\forall p \in \mathbb{R}$.

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- The surface gradient terms can thus be rewritten in terms of this parametrisation:

$$\nabla_{\Gamma_h(t)} F(p, t) = \frac{F_p(p, t)}{\left|\mathbf{X}^h_p(p, t)\right|} \frac{\mathbf{X}^h_p(p, t)}{\left|\mathbf{X}^h_p(p, t)\right|}$$

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- Let $p_j = jh$, with $j = 0, \ldots, N$, be a uniform grid with grid size $h = 1/N$. Define the finite element space

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

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$(\mathbf{P}_h^a)$ Semi-Discrete Problem

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

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

for every $\phi(\cdot, t) \in V_h$.

Finite Element Approximation for Reaction-Diffusion

- Denote the nodal basis functions by $\{\phi_j\}_{j=1}^N$ and let

$$a^h(p,t) := a^h(\mathbf{X}^h(p,t),t) = \sum_{j=1}^{N} A_j(t)\phi_j(p) \in V_h \subset V$$

where $\dim(V_h) = N < \infty$.

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  where $\dim(V_h) = N < \infty$.

- We can write the finite element approximation as follows:

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{j=1}^{N} A_j \int_0^1 \phi_j\phi_i \left|\mathbf{X}_p^h\right| \mathrm{d}p + D\sum_{j=1}^{N} A_j \int_0^1 \frac{\phi_{j,p}\phi_{i,p}}{\left|\mathbf{X}_p^h\right|}\mathrm{d}p$$
$$= \int_0^1 f(a^h)\phi_i \left|\mathbf{X}_p^h\right| \mathrm{d}p\,,\ i = 1,\ldots,N.$$

Fully Discrete Problem for Reaction-Diffusion

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- Let $t_m = m\Delta t$, $m = 0, \ldots, M$. Then the fully discrete system is given by

$$\left(\mathbf{M}^{m+1} + \Delta t \mathbf{S}^{m+1}\right) \mathbf{a}^{m+1} = \mathbf{M}^m \left(\Delta t \mathbf{F}^m + \mathbf{a}^m\right)$$

where

$$\mathbf{M}_{i,j}^m = \int_0^1 \phi_i \phi_j \left|\mathbf{X}_p^{h,m}\right| \, \mathrm{d}p \,, \; i,j = 1, ..., N,$$

$$\mathbf{S}_{i,j}^m = \int_0^1 \frac{\phi_{i,p}\phi_{j,p}}{|\mathbf{X}_p^{h,m}|} \, \mathrm{d}p \,, \; i,j = 1, ..., N,$$

$$\mathbf{a}^m = (A_1^m, ..., A_N^m),$$

$$\mathbf{F}_i^m = \int_0^1 f(\mathbf{a}^m)\phi_i \left|\mathbf{X}_p^{h,m}\right| \, \mathrm{d}p \,, \; i = 1, ..., N.$$

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- Similarly, the semi-discrete formulation for the neutrophil movement is given as follows:

$(\mathbf{P}_h^m)$ Semi-Discrete Problem

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

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

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 $\bar{\lambda}$.

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$$\mathbf{M}^m \mathbf{x}^{m+1} + \varepsilon \Delta t \mathbf{S}^m \mathbf{x}^{m+1} = \mathbf{M}^m \mathbf{x}^m + \Delta t \widetilde{\mathbf{M}}_{\mathbf{x}}^m \left(\delta a^m + \bar{\lambda}^m \mathbf{1} \right)$$
$$\mathbf{M}^m \mathbf{y}^{m+1} + \varepsilon \Delta t \mathbf{S}^m \mathbf{y}^{m+1} = \mathbf{M}^m \mathbf{y}^m + \Delta t \widetilde{\mathbf{M}}_{\mathbf{y}}^m \left(\delta a^m + \bar{\lambda}^m \mathbf{1} \right)$$

where

$$\left(\widetilde{\mathbf{M}}_{\mathbf{x}} \right)_{i,j}^m = \int_0^1 \phi_i \phi_j \left(\mathbf{X}_p^{h,m} \right)^\perp \cdot \mathbf{e}_1 \, \mathrm{d}p,$$
$$\left(\widetilde{\mathbf{M}}_{\mathbf{y}} \right)_{i,j}^m = \int_0^1 \phi_i \phi_j \left(\mathbf{X}_p^{h,m} \right)^\perp \cdot \mathbf{e}_2 \, \mathrm{d}p.$$

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First Attempt

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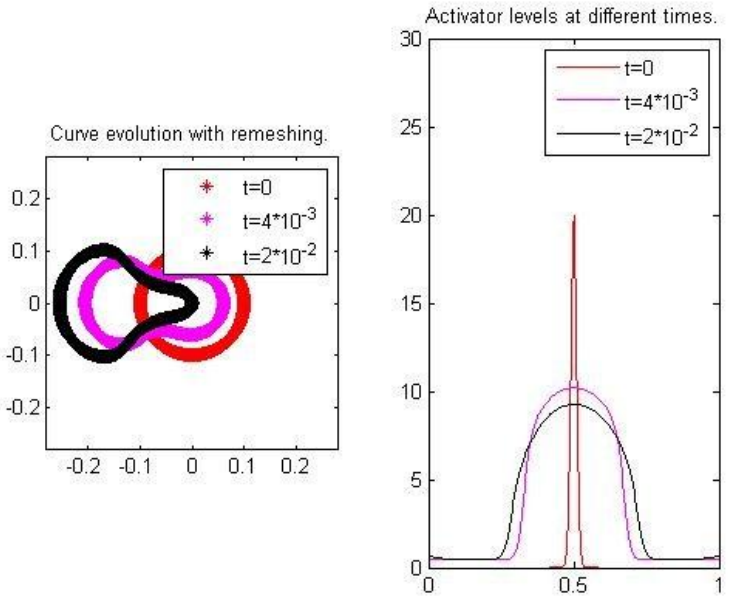

Figure: Membrane progression and local activator concentration levels simulated by the full system.

Remarks

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- The reason for this may be due to our reduction of the original model.
- Our model reduced the local inhibitor to simply be a multiple of the activator. That was probably not a good idea...
- The extra diffusion provided by the local inhibitor and its influence on a larger part of the membrane may be the key for observing pseudopod splitting.

Full Model

without gradient

Full Model - with chemoattractant gradient

with chemoattractant gradient

Contents

Objectives of SDE modelling

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- Model the effects of chemotaxis on a cell's ability to capture a pathogen.

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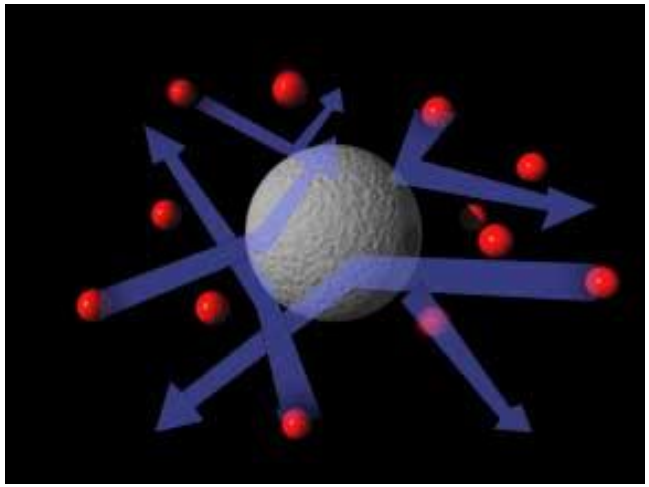
- Provide a reference for any simulation models
- Model the probability of a bacterium escaping a neutrophil as a function of the starting position of the bacterium relative to the neutrophil.

Formulating the Problem

Formulating the Problem

Bacterium

- Model the bacterium as a Brownian Motion



Formulating the Problem

Neutrophil

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Further Formulation

Formulating the Problem

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Further Formulation

- Bacterium escapes if it reaches escape radius

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Further Formulation

- Bacterium escapes if it reaches escape radius
- Neutrophil engulfing bacterium

Formulating the Problem

Neutrophil

- Acts under chemotaxical effects
- Path follows $b(Z_t, t)$ where Z_t is the path of the bacterium

Further Formulation

- Bacterium escapes if it reaches escape radius
- Neutrophil engulfing bacterium
- Neutrophil is centred at the origin

Formulating the Problem

Formulating the Problem

Diffusion describing motion of bacterium

$$\mathrm{d}Z_t = -b(Z_t, t)\mathrm{d}t + \sigma \mathrm{d}B_t$$

Z_t – the position of the bacterium

$b(Z_t, t)$ – the drift of the neutrophil

σ – constant variance of the Brownian Motion process

Theorem

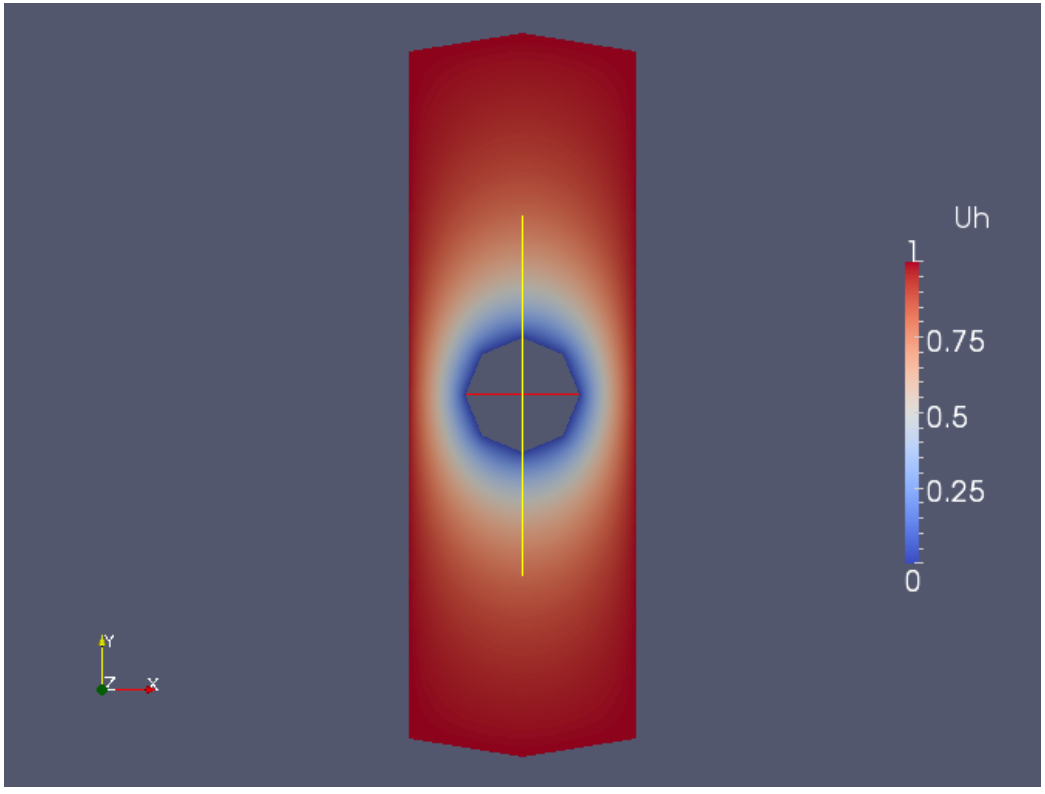
If a neutrophil and a bacterium are modelled as above and the bacterium begins at a point $R < |\beta| < kR$, where R and kR are the cell radius and escape radius respectively, then the probability of the bacterium escaping is given by $f(\beta, 0)$ where f is the solution in $C^2([0,\infty) \times \mathbb{R})$ to:

$$\begin{aligned} &\partial_s f - b(x,s) \cdot \nabla f - \frac{1}{2}\sigma^2 \Delta f = 0 \\ &f = 0 \qquad in \quad \partial B_R(0) \times (-T, 0) \\ &f = 1 \qquad in \quad \partial B_{kR}(0) \times (-T, 0) \\ &f = u(x) \qquad in \quad \Omega \times \{-T\} \end{aligned}$$

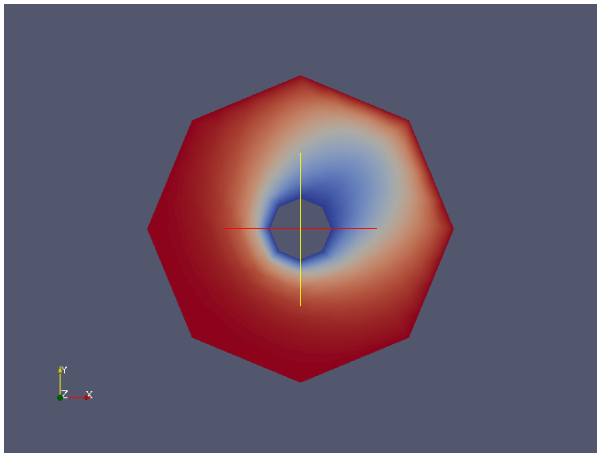
where we assume that the neutrophil's strategy has diminishing explicit time-dependence over time and tends to some function $u(X_t)$.

Solution

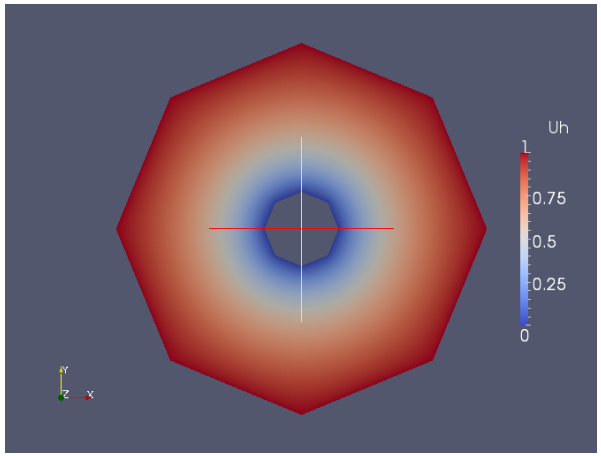
Solution in an approximated capillary



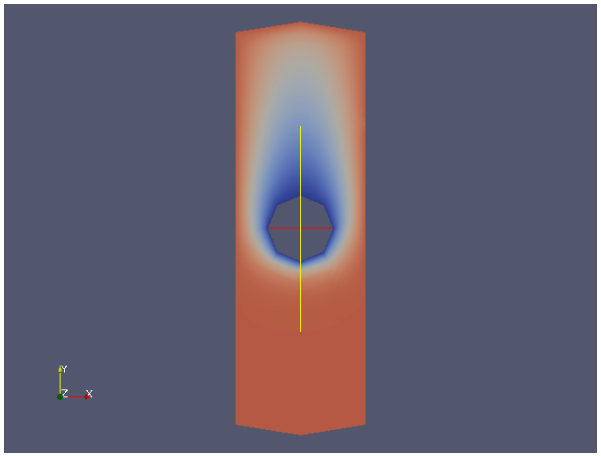
Comparison of Strategies



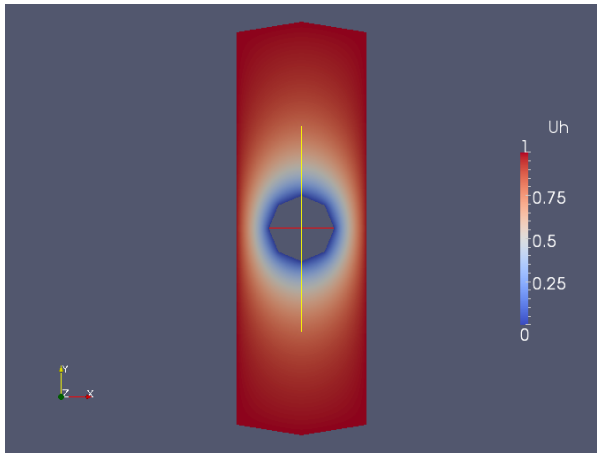
(a)



(b)

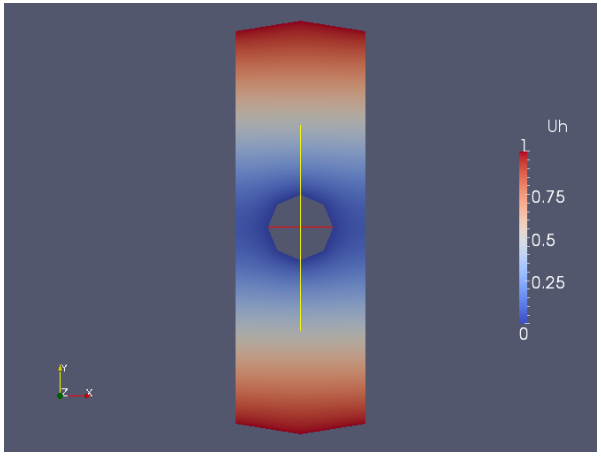


(c)

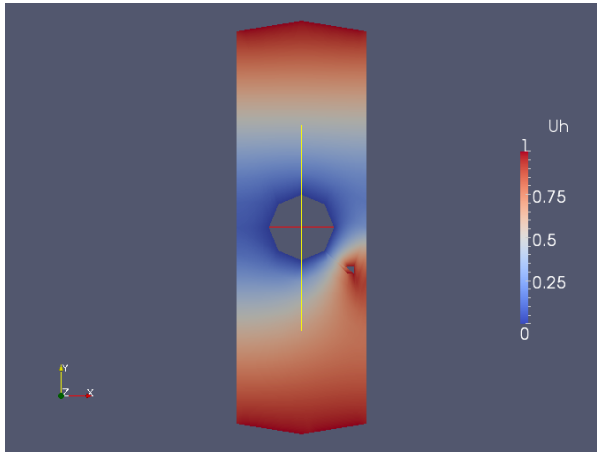


(d)

Further Comparison



(e)



(f)

Contents

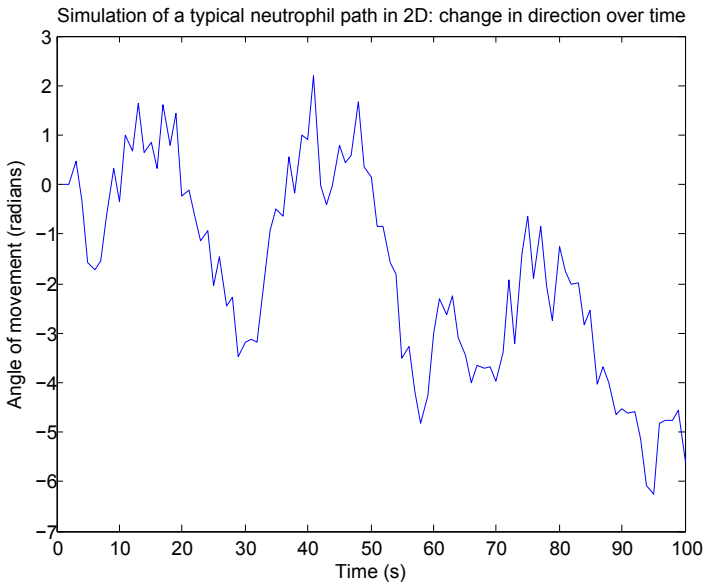
An empirical model for neutrophil movement

- Alternative model for cell movement in the absence of a chemoattractor
- Based on experimental data from Li *et al.*
- Models the cell as a point in the plane

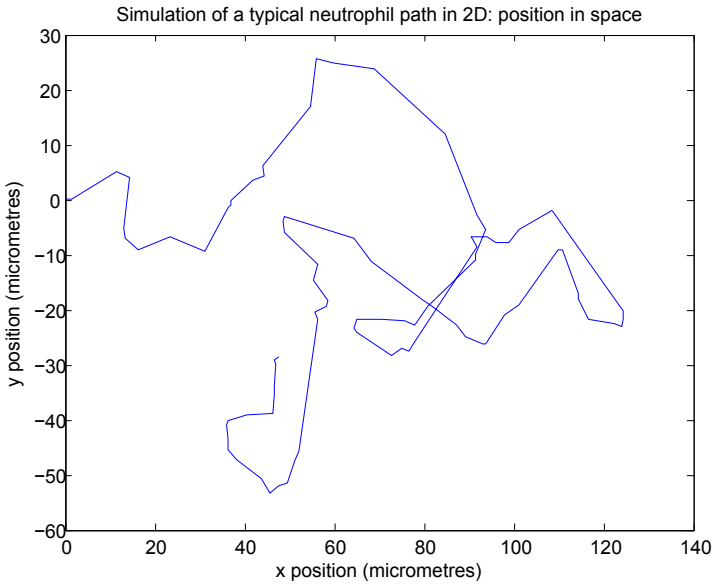
The model

- Cell moves in a straight line for Exp(5) micrometres
- Constant speed $7.46 \times 10^{-6} \text{ms}^{-1}$
- Cell then turns Exp(0.67) radians
- Turn history is a Markov process
- Ratio of [opposite-to-previous]:[same-as-previous] turning pairs is 2.1:1
- Result is a roughly zig-zag shaped path

Simulation of a typical cell motion



(g) Turn history



(h) Corresponding path of cell

Aims for the empirical model

1. • The PDE model also predicts neutrophil motion (based on pseudopod formation)
   • The simpler empirical model fits the experimental data well
   • We should expect the PDE model to produce similar neutrophil paths
2. Useful in its own right as a way of analysing the search strategy

Comparing the PDE and empirical models

- PDE model shows the cell moving in the direction of the extended pseudopod
- Pseudopods eventually split into two others
- One of these dominates and forms a fully grown pseudopod while the other shrinks back

Comparing the PDE and empirical models

- Experimental data also relate pseudopod formation to direction of movement
- Zig-zag motion shows pseudopods must be forming in alternating left-right cycle
- It is suggested that the dominant pseudopod (usually) forms between two most recent extensions
- PDE model could be extended to examine this behaviour
- With further work, PDE model could produce paths on the timescale of the empirical model

Is the search strategy efficient?

- Cells have been around (evolving) a long time!
- Existence of a particular search strategy suggests it improves efficiency
- Random walks, Levy processes...

What makes a good search strategy

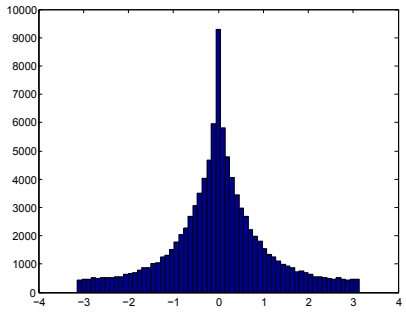
- Primary goal: seek out as many bacteria as possible
- A good strategy should
  - explore areas quickly and efficiently
  - avoid covering the same area within a short space of time
  - not get the neutrophil stuck where it cannot be of any use

What makes a good search strategy

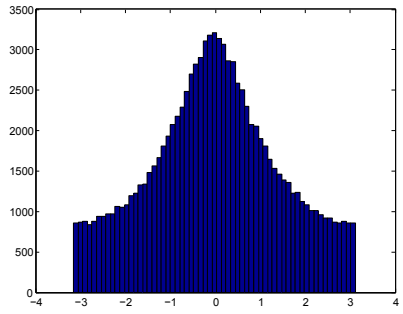
Condition the first step of every path to be in the positive x direction. We consider

- the angle at which the neutrophil exits a circle of given radius r
- the mean time taken for the cell to first exit the circle

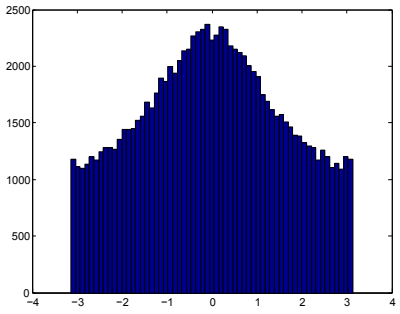
Exit angle distributions



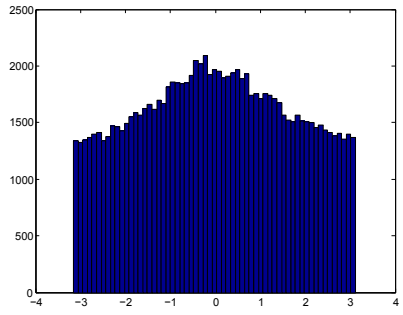
(i) $r = 20$



(j) $r = 50$



(k) $r = 100$



(l) $r = 200$

Figure: Histograms comparing the distribution of exit angles for radii r = 20, 50, 100 and 200, based on 100,000 simulations each.

Exit angle distributions

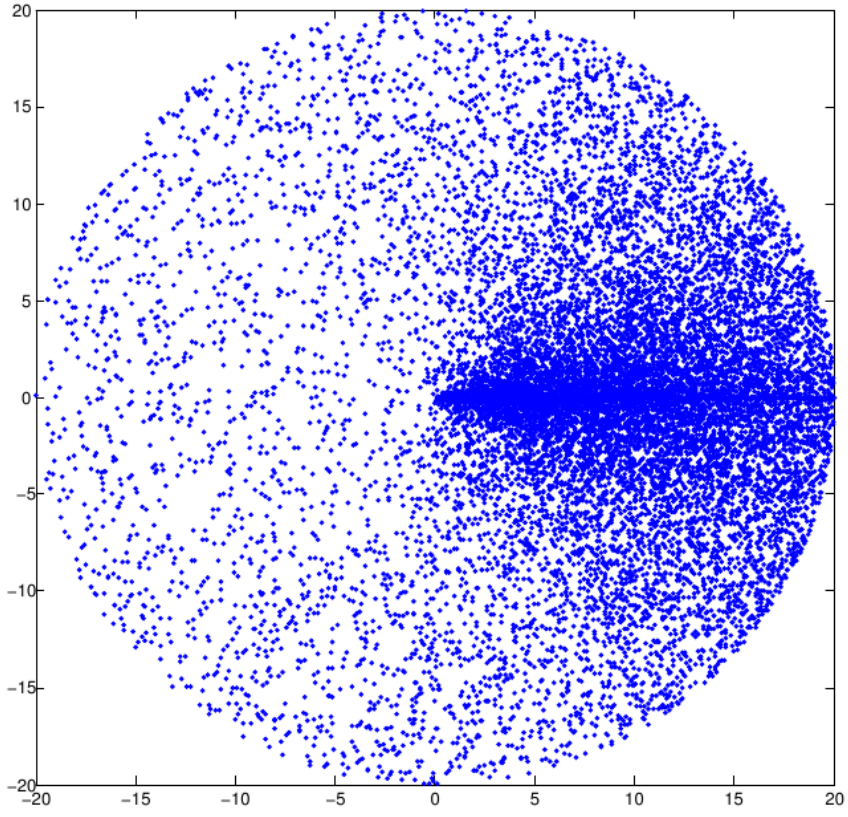


Figure: Plots of escape position for 200 uniformly spaced choices of circle radius from 0.1 - 20, 100 independent simulations per radius.

Mean exit time

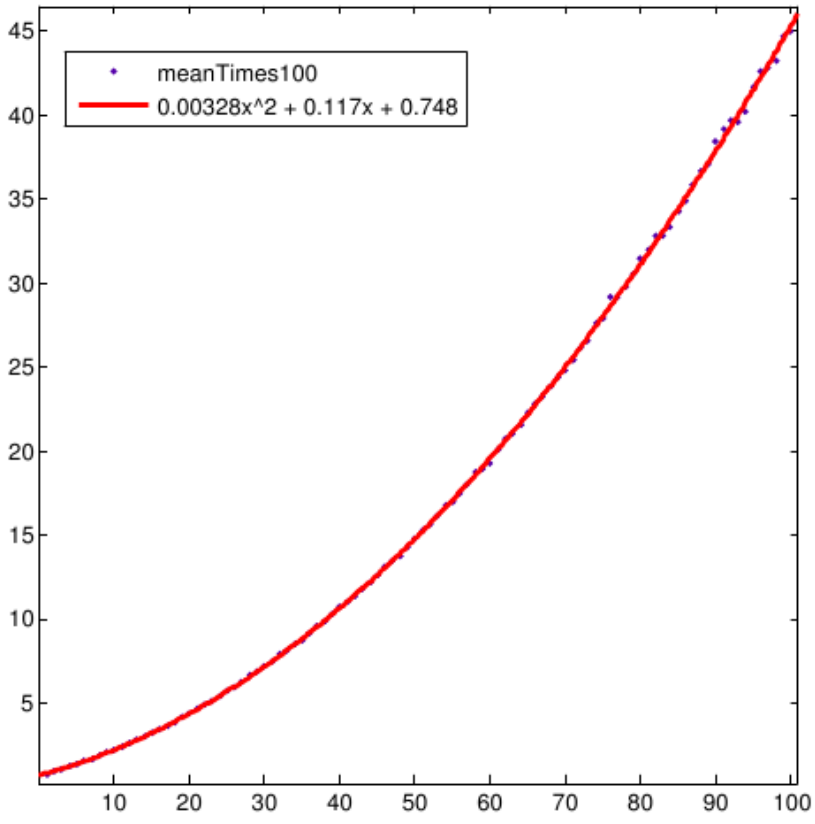


Figure: Mean escape times plotted against radius of the circle, based on 10,000 simulations per radius.

Summary

- Search strategy helps cell to scan local area quickly
- Persistence of initial direction diminishes over time
- Further things to take into consideration, *e.g.*
  - Why not (for example) a Levy process?
  - What is a reasonable cost function?

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- Therefore, our model gives the same results as in Neilson *et al.*, with some obvious benefits.

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- The high persistence of the neutrophil's motion, along with the zig-zag behaviour, means that it explores its local area more quickly than a standard random walk.

Further Work

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Acknowledgements

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Thank you for listening!