MA916 RESEARCH STUDY GROUP

Biomembranes

Research Proposal

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1   Introduction

The movement of cells and the mechanisms by which they do so is one of the fundamental questions of biology and biochemistry. At a fundamental level, cells in an organism respond to their surroundings by reacting to chemical changes: this is known as *chemotaxis*. We wish to investigate mathematical models for how cells migrate under chemotaxis.

The difference between something being alive or dead is arguably its ability to move. In biological systems, living species sense their surroundings and respond to it: chemotaxis is "the influence of chemical substances in the environment on the movement of mobile species" [9].

For example, consider two cells, named cell A and cell B. Suppose cell A emits a chemical signal, and that cell B picks up on the signal. If cell B moves towards cell A then the chemical species is called a *chemoattractant*, and such chemical signal is referred to as *positive chemotaxis*. If cell B moves away from cell A, then the chemical species is called a *chemorepellent* or *chemoinhibitor*, and such chemical signal is referred to as *negative chemotaxis*. (Indeed, the word "chemotaxis" is derived from the Greek "taxis" which means to arrange.)

The behaviour of chemotaxis is best understood with the following analogy, taken from the paper [17]: a male tiger may enter into a new territory and detect the scent left by a female tiger. Hoping for an opportunity to breed, our tiger is drawn further into the new area. On the other hand, suppose the incoming male instead senses the scent left by another male tiger. He interprets the scent as a message that this territory belongs to another. If he is not up to fighting for hunting and breeding rights, he will retreat.

Experimental observations show that given a moving *Staphylococcus aureus* bacterium, one can observe that a human neutrophil (white blood cell) chases the bacterium and eventually envelops it. The remarkable video of this, filmed in the 1950s, is available at `http://www.biochemweb.org/neutrophil.shtml`. Upon viewing the above video clip, we notice that the migration of the neutrophil membrane is, in this setting, governed by three main factors: the external chemical stimulus from the bacterium, the geometry of the neutrophil cell and the forces induced by colliding with the passive red blood cells. We ignore this third factor to begin with by discarding these red blood cell 'obstacles'.

What exactly is happening from a biological viewpoint? Inside the cell membrane are receptors which detect shallow gradients of chemoattractants outside the cell, like those excreted by the bacterium. In turn, intricate signalling pathways somehow instruct the membrane to induce pseudopods in the direction of the gradients. These protrusions cause the remainder of the cell to retract under the cortical tension (the geometric factor) and therefore the cell migrates in the direction of the leading pseudopod. This 'signal centred' approach is widely accepted, and one we try to model. However, it should be noted that other explanations have been proposed, such as the 'pseudopod-centred' approach, where pseudopods form themselves: the chemoattractants influence internal pseudopod dynamics as opposed to pseudopod formulation (see, e.g., [10]).

In section 2, we review the model of Neilson *et al.* for chemotaxis on a moving cell. In section 3, we outline the two main ways in which we propose to extend the model. Section 4 contains supplementary questions to the main problem; section 5 contains a plan for how to proceed with the various tasks. Appendix A contains the necessary mathematical background to the problems.

2 Models for Chemotaxis

A number of models for chemotaxis have been proposed in recent years, dating as far back as 1970. Many of these chemotaxis models use population densities: however, we consider a *single* cell moving under the influence of one or more bacteria, as seen in figure 1. First, we outline some of the historical models used. The requisite mathematical background is outlined in appendix A.
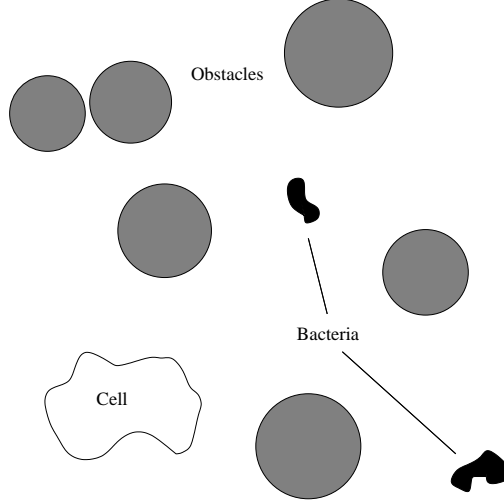

Figure 1: A diagram of the basic situation we wish to consider

2.1 Historical models

Hans Meinhardt developed a model of chemotaxis in [**13**], which was based (in part) on the Keller–Segel model (see [**11**] and [**17**]). He considers the following equations on n surface elements of a cell. Let a denote the surface density of a local autocatalytic activator (or attractant), b denote the surface density of a rapidly distributed global inhibitor and c denote the surface density of a local inhibitor. He postulates the following ODEs for the reaction kinetics:

$$\frac{\mathrm{d}a_i}{\mathrm{d}t} = \frac{s_i(\frac{a_i^2}{b} - b_a)}{(s_c + c_i)(1 + s_a a_i^2)} - r_a a_i \tag{2.1a}$$

$$\frac{\mathrm{d}b}{\mathrm{d}t} = r_b \sum_{i=1}^{n} \frac{a_i}{n} - r_b b \tag{2.1b}$$

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = b_c a_i - r_c c_i \tag{2.1c}$$

where $i = 1, \ldots, n$. The constants r_a, r_b and r_c denote decay rates of the local activator, global inhibitor and local inhibitor respectively, while s_a is a saturation coefficient, s_c is the Michaelis–Menten constant and b_a is a basal production rate of the activator. Note that the noise term is given in [**13**] as

$$s_i = r_a(1 + dy \cos\left(\frac{2\pi(i-j)}{n}a\right))(1 + dr\mathrm{RND})$$

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where dy and dr are parameters to be chosen and $\mathrm{RND} \in (0, 1)$ is a uniformly distributed random variable.

However, in [13] the model is postulated without derivation: further inspection shows that the model is discrete, in the sense that it is solved in n surface elements of the surface of the cell. This is a useful model, but we would like a model taking into account the diffusion of the chemoattractants, postulated on the surface of a cell.

2.2 The model of Neilson *et al.*

Neilson, Mackenzie, Webb and Insall proposed in [14] a model which incorporates the geometry of the cell: essentially, they propose a model for moving the cell, and then use a continuum version of equations 2.1 to yield a model for chemotaxis on a moving cell. As this model forms the basis of the project, which we propose to extend and improve in a number of ways, we summarise the details of the model here. We use the same notation as [14] wherever possible.

2.2.1 Deformation of the cell surface

For each $t \in [0, T]$ where $T > 0$ is fixed, let $\Gamma(t)$ be a smooth closed curve in $\mathbb{R}^2$, and let us use the notation of $\Gamma_0 := \Gamma(0)$. We consider the surface of the cell as $\Gamma(t)$, depending on time t, for which a material particle P located at $X_p(t)$ on $\Gamma(t)$ has velocity $\dot{X}_p(t)$, which is not necessarily normal to the surface: indeed, assume that there exists a velocity field u so that points P on $\Gamma(t)$ evolve with velocity

$$\dot{X}_p(t) = u(X_p(t), t).$$

The surface itself deforms according to the following equation for the surface velocity u:

$$u_t \cdot \bar{\nu} = V_f - \lambda \kappa, \tag{2.2}$$

where $\bar{\nu}$ is the normal to $\Gamma(t)$, V_f is the driving force due to the chemoattractant, κ is the cortical torsion, and λ is a phenomenological parameter which keeps the area approximately constant. Exact equations for V_f and λ are given below in section 2.2.3.

2.2.2 Reaction–diffusion equations on the surface of the cell

The model for the chemotaxis in [14] is based on a system of reaction–diffusion equations, which emerged from the discrete model developed by Meinhardt outlined in section 2.1 above. As above, let a denote a local autocatalytic activator (or attractant), b denote a rapidly distributed global inhibitor and c denote a local inhibitor. Assume that the cell boundary $\Gamma(t)$ moves with velocity u. The equations take the form

$$\partial_t^\bullet a + a \nabla_{\Gamma(t)} \cdot u = D_a \Delta_{\Gamma(t)} a + \frac{s(\frac{a^2}{b} + b_a)}{(s_c + c)(1 + a^2 s_a)} - r_a a \tag{2.3a}$$

$$\partial_t^\bullet b + b \nabla_{\Gamma(t)} \cdot u = D_b \Delta_{\Gamma(t)} b - r_b b + r_b \fint_{\Gamma(t)} a \, \mathrm{d}x \tag{2.3b}$$

$$\partial_t^\bullet c + c \nabla_{\Gamma(t)} \cdot u = D_c \Delta_{\Gamma(t)} c - r_c c + b_c a. \tag{2.3c}$$

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The constants r_a, r_b and r_c denote decay rates of the local activator, global inhibitor and local inhibitor respectively. The corresponding diffusion coefficients are D_a, D_b and D_c. In equation (2.3a), s_a is a saturation coefficient, s_c is the Michaelis–Menten constant and b_a is a basal production rate of the activator. The constant b_c in equation (2.3c) determines the growth of the local inhibitor c in the presence of the activator a.

The effect of the external signal and random fluctuations are incorporated into the term s: in [**14**], they model the effect of the external signal and random fluctuations by

$$s(x,t) = r_a[(1 + dr\mathrm{RND}) + R_0(1 + dr\mathrm{RND})],$$

where dr is a positive parameter, and $\mathrm{RND} \in (0,1)$ is a uniformly distributed random variable. Note that this is different to [**13**]: in [**14**] (p.12) they say that "a biological objection to using [the noise term used by Meinhardt] is the need for cell wide comparison of individual receptors to define j and hence the direction towards the source of chemoattractant."

Note carefully that equation (2.3a) is in fact a surface stochastic partial differential equation: the terms $(1 + dr\mathrm{RND})$ and $R_0(1 + dr\mathrm{RND})$ model the noisy autocatalytic activation and noisy chemotactic signal respectively. The parameter R_0 is given in [**14**] by the following equation for the local concentration C of the chemoattractant in the bulk:

$$R_0 = \frac{C}{C + K_d},$$

where K_d is the disassociation constant. The reader should note that R_0 is not constant: if it were then, as RND is a uniformly distributed random variable, the concentration field given out by the bacterium would be constant and nothing would move.

In fact, it is postulated that this term arises from perhaps some solution of an equation of the type

$$-\Delta C = Q\delta(x)$$

where Q is a constant and δ is the Dirac delta function at point x in the bulk (i.e., x does not live on the surface of the cell but in the medium surrounding it). This is motivated from there being a point source of attractant coming from fixed point x in the bulk, modelling the position of the bacterium.

However, this choice of noise is fairly simple, and it may be of interest to look into Gaussian noise, which is perhaps a more realistic model of noise in biological processes.

2.2.3 The choice of V_f and λ

Recall the velocity equation (2.2). A priori it looks like the curve $\Gamma(t)$ evolves independently of equations (2.3), but this is in fact false. Experimental evidence suggests that the best choice for V_f is

$$V_f(x) = K_{\mathrm{prot}}a(x), \tag{2.4}$$

where K_{prot} is a positive parameter and a is a "solution" or numerical approximation (see section 4.5). Note "prot" stands for protrusive, as V_f is the protrusive (normal) velocity.

For λ, there are many possible forms ([**14**], p.13). One choice used in [**14**] is that which solves the following ODE:

$$\frac{\mathrm{d}\lambda}{\mathrm{d}t} = \frac{\lambda_0 \lambda (A - A_0 + \frac{\mathrm{d}A}{\mathrm{d}t})}{A_0 (\lambda + \lambda_0)} - \beta\lambda, \qquad (2.5)$$

where λ_0 and β are positive parameters and A_0 is the initial area of the cell.

This choice for λ is chosen for it "works well and is robust to changes in the parameters involved" ([**14**], p.13). From this, we see that the movement of $\Gamma(t)$ is coupled with the surface stochastic partial differential equation (2.3a).

2.3 Numerical Methods

Seeking an analytic solution for such a complicated problem as this is clearly not viable, so we must inevitably resort to numerical methods. We summarise the relevant methods here: the details are left to appendix A.4.

The first method for solving such a PDE was introduced in [**14**] and it involves using a level set method (LSM) to evolve the cell based on the solution of the reaction-diffusion equations, followed by an Arbitrary Lagrangian Eulerian surface finite element method (ALE-SFEM) to update the solution. In [**15**] the surface finite element method (SFEM) was introduced as a replacement for the LSM. The ALE-SFEM works by transforming the reaction-diffusion PDEs on the evolving surface to a PDE on a fixed reference frame, which changes at each time step. It can be solved on this reference frame using a SFEM. The SFEM parametrises the surface and again constructs finite elements to solve the equation governing the movement of the cell.

For SFEM, instead of the velocity equation (2.2), we consider a surface Γ in $\mathbb{R}^2$ moving with a flow whose normal velocity is defined as

$$\bar{\mathbf{x}}_t \cdot \bar{\nu} = \alpha(\bar{\mathbf{x}}, t)\kappa + \beta(\bar{\mathbf{x}}, t) \qquad (2.6)$$

where $\bar{\nu}$ is the unit normal to Γ, κ is the curvature, and $\bar{\mathbf{x}}$ is the position vector. The functions α and β represent retractions and protrusions respectively. In our case β depends on a spatio-temporal activator profile obtained from the system of reaction diffusion equations, while α is used to regulate the cell area, i.e. keep it roughly constant.

The SFEM has a number of advantages over the LSM. In particular, it allows the model to use just one mesh as the SFEM mesh can also be used for the ALE-SFEM and it does not rely on any toolboxes from Matlab. Therefore this approach is much more computational efficient and may even allow modelling in three dimensions. It is also more robust and so it will model the cell more accurately. The only drawback is that the SFEM finds it harder to deal with changes in topology; however, we are not currently dealing with situations involving cell splitting. Therefore we recommend that the model is implemented as in [**15**], i.e. using the SFEM for cell movement and the ALE-SFEM for solving the reaction-diffusion equations.

3 Main Research Problem

We wish to investigate two possible extensions and improvements to the model of Neilson *et al.*: firstly, by changing the equations by which the cell moves around; and secondly, by incorporating the movement of the bacterium into the model. In an ideal world, it would be possible to incorporate both changes, but it seems prudent to focus on each change individually, at least in the short term.

3.1 Alternative models for the deformation of the cell

3.1.1 Changing the model for the deformation of the cell

Task 1. *Modify the model in [**14**] so that the velocity V_f in equation (2.2) takes account of the curvature of the cell.*

In section 2.2.3, we described the choices of V_f and λ which Neilson *et al.* made in [**14**]: recall that they chose $V_f(x) = K_{\text{prot}} a(x)$ (see equation (2.4), so that the velocity depended on the concentration of the reactant a. However, the velocity itself takes no account of the curvature of the cell (though the other coefficient, λ, depends on the area of the surface).

We propose to model the velocity of the level set by

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

where $H(x)$ is the mean curvature of the surface at x, $a(x)$ is the concentration of the reactant a as before, and $\bar{\lambda}$ is a Lagrange multiplier subject to the constraint that the area of the cell remains constant. Using this model, it should be possible to replace equation (2.5) for λ with something considerably simpler.

3.1.2 Using Willmore flow to model the movement of the cell

Task 2. *Modify the model in [**14**] so that the cell moves according to an elastic surface energy to model the surface deformation.*

We wish to investigate how the cell moves when the cell moves according to the gradient flow of an elastic surface energy of the form $E = \frac{1}{2} \int_\Gamma F(a, H)$. For example, we consider *Willmore flow*, which moves points with normal velocity $u = f(H)$ where

$$f(H) := \Delta_{\Gamma(t)} H + H \|\nabla_{\Gamma(t)} \nu\|^2 - \frac{1}{2} H^3.$$

This is the L^2-gradient flow of the Willmore functional

$$\mathcal{W}(X) := \frac{1}{2} \int_\Gamma H^2 \, \mathrm{d}A, \tag{3.1}$$

where M is an n-dimensional reference manifold and $X \colon M \to \mathbb{R}^{n+1}$ is a smooth immersion with $\Gamma = X(M)$. We refer the reader to appendix A.3 for more of the technical details on Willmore flow itself.

The elastic energy flow is more biologically realistic: the pioneering work of Canham [**2**] and Helfrich [**7**] showed that the minimisers of energy (3.1) are (subject to volume and area constraints) exactly the shape of red blood cells.

It is thus biologically realistic to assume that the cell tries to minimise its Willmore energy while moving towards the bacterium. We thus believe that a more realistic and more accurate picture could be built up by using Willmore flow.

3.2 Modelling the movement of the bacterium

Task 3. *Extend the model in [**14**] to incorporate the movement of the bacterium into the model, without changing how the cell movement is modelled, nor the equations on the surface of the cell.*

On studying figure 8 in [**14**] (p. 18), one sees that the bacterium in which the cell is chasing is modelled as being fixed in space. In reality, the bacterium is moving around (it "runs away" from the chasing cell), and we wish to extend the model to incorporate this movement. We now discuss a way of mathematically achieving Task 3.

After one watches the video of the cell chasing the bacterium at `http://www.biochemweb.org/neutrophil.shtml`, one realises that the bacterium moves in a direction that is normal to cell boundary chasing it. We note also that the path of the bacterium is subject to some noise. It is natural to model such noise using Brownian motion. But how would one go about getting such a model of the movement of the bacterium? The reader must note that there should be some interaction between the cell and the bacterium.

A possible way of doing this is as follows: let $z(t) \in \mathbb{R}^2$ denote the position of the bacterium at time t and let $\Gamma(t)$ denote the cell surface at time t, which is evolving according to [**14**] equation (22) on p. 8. Project the point $z(t)$ onto $\Gamma(t)$ and call this point $x(t)$. Then a normal vector to the surface $\Gamma(t)$ at $x(t)$ is defined. Call such vector $\nu(x(t), t)$. Figure 2 shows the construction of such a normal vector ν.
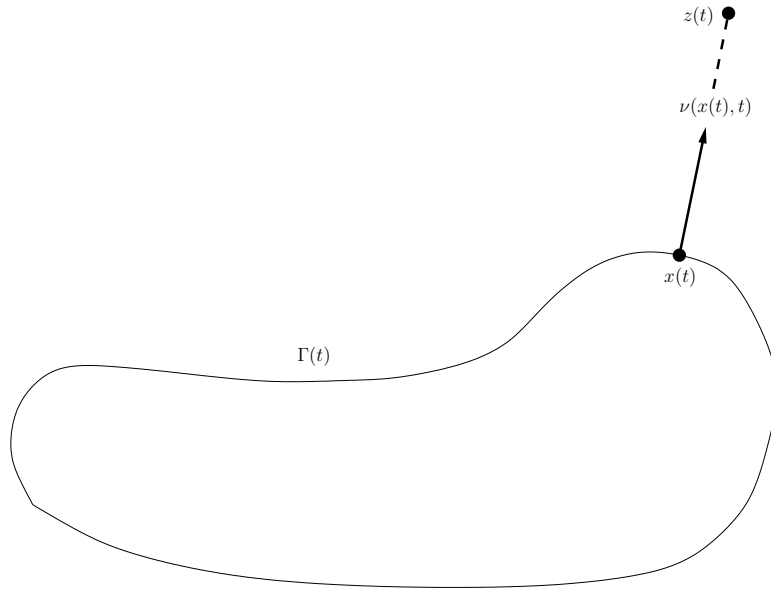

Figure 2: Construction of ν

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We suggest that the evolution of $z(t)$ should satisfy an stochastic differential equation (SDE) of the form

$$\begin{cases} \mathrm{d}z = f(x(t), z(t))\nu(x(t), t)\mathrm{d}t + \sigma(t)\mathrm{d}W & 0 < t \leq T \quad T < \infty \\ z(0) = z_0 \notin \Gamma(0) \end{cases} \qquad (3.2)$$

where W is two-dimensional Brownian motion; i.e. $W = (W_1, W_2)$ where W_i $(i = 1, 2)$ are one-dimensional Brownian motion with W_1 independent of W_2. It is up to the reader to decide what is best for the functions $f \colon \mathbb{R}^2 \to \mathbb{R}$, $\sigma \colon [0, \infty) \to \mathbb{R}$ and the initial starting point z_0. It maybe that σ need not depend on time.

Since there may not be an analytical solution to equation (3.2), one will need to use a numerical scheme to solve the SDE (see [8] for further details). For a more detailed survey of SDEs in general, Øksendal's book [16] is highly recommended.

4 Supplementary Research Problems

In addition to the main research problems, a number of other interesting questions arise as a result. They are outlined here in no particular order, and incorporate interesting problems from analysis, computation, probability and statistics.

4.1 Toy example for modelling bacterium movement

Related to the problem of modelling the bacterium movement into the model of [**14**], the following is a toy example in a simple setting to investigate what suitable drift one needs.

Task 4. *Fix $0 < T < \infty$. Consider the horizontal line segment in $\mathbb{R}^2$ from point $(-T, 0)$ to point $(T, 0)$. Suppose this line segment moves vertically upwards with velocity $v(t)$. Call this line $L(t)$. Let $z(t)$ be a point in $\mathbb{R}^2$ which evolves according to the Stochastic Differential Equation*

$$\begin{cases} \mathrm{d}z = f(x(t), z(t))\nu(x(t), t)\mathrm{d}t + \sigma(t)\mathrm{d}W & \forall t \in (0, T'], \\ z(0) = z_0 \notin L(0) = [-T, T]. \end{cases} \tag{4.1}$$

Note that W is two-dimensional Brownian motion. That is, $W = (W_1, W_2)$ where W_i (i = 1, 2) are one-dimensional Brownian motions with W_1 independent of W_2. Possible questions to answer are:

1. *What velocity v can/should we take?*

2. *How should we choose f to mimic the line $L(t)$ chasing a bacterium at point $z(t)$?*

3. *How far does z_0 need to be away from $L(0)$ to ensure (with probability 1) that $z(t)$ lies on $L(t)$*

4. *How large should T' be?*

5. *What is the first time $L(t)$ catches $z(t)$?*

The reader may object to the use of a finite length line segment with the argument that eventually the particle, which essentially undergoes Brownian motion with drift will eventually have x coordinate value $\pm T$. At such a point, the normal ν is no longer defined.

A remedy to this would be to have absorbing boundary conditions, that is once the x coordinate takes on such values, the particle remains at that x coordinate and moves solely in the y-direction. However, the motion is now solely in the y direction and so is not biologically applicable. Another possibly remedy is to take the above with $T' = +\infty$. However, there could be some implementation issues.

It should be noted that f should be chosen as in section 3.2, and to experiment as to which function works best. Thus this task is essentially a toy problem for the bigger problem.

The choice of v is free to that of the reader. Again, some experimenting would be ideal. In fact, if one chooses nice v and f one can actually solve

equation (4.1) analytically and answer most of the questions above straight off. The problem then arises for when one chooses f that satisfies properties for the biological accuracy of the model; i.e. choosing f like that in section 3.2

Task 4 is essentially a toy problem for generally modelling the bacterium into the model of [**14**]. It presents its own technicalities, but certainly some of the problem is reduced. For example the normal direction ν to a point $x(t)$ on $L(t)$ is trivial to compute and hence analytically tractable to use. This gives the group ample opportunity to implement some code to see graphically what is going on.

4.2 Multiple bacteria cells

Task 5. *Extend the model of [**14**] to the case where there is more than one bacterium in proximity to the neutrophil.*

The model of Neilson *et al.* incorporates a single bacterium. Imagine that, instead, there are two distinct bacteria cells in close proximity to a neutrophil cell. An obvious question arises: how does the neutrophil react? In order to consider this, first recall the SFEM, and in particular, equation (2.6), which models the movement of the neutrophil cell membrane. The velocity depends on the curvature of the cell membrane, κ and the chemoattractant - in this case, from the bacteria. The question of interest: how do we model this attractant force, f, given two bacteria cells?

Suppose the neutrophil is moving with normal velocity

$$v = \kappa + f(a) \tag{4.2}$$

where $a \colon \Gamma \to \mathbb{R}$ is a concentration field. Each bacterium is the centre of a concentration field for a chemoattractant. Assuming that the bacteria cells are identical, i.e. they have equal attracting properties, a suggestion would be to add the two concentration fields together. There will then be two source terms, one from each bacterium, in the reaction-diffusion equations:

$$\partial_t^\bullet a + a\nabla_{\Gamma(t)} \cdot v = S_1 + S_2 + D\Delta_{\Gamma(t)}a. \tag{4.3}$$

Obviously, S_1 should depend on the distance to bacterium number one, and S_2 should depend on the distance to bacterium number two. This intuitive approach would be a good development to the proposed model above for the movement of the bacterium.

The outlined problem of introducing multiple bacteria cells is a computational one, however, there are interesting 'toy' problems that look at it from an analytical and probabilistic viewpoint. Consider the real line and the open interval (a_1, a_2). Let $b_1 < a_1$ and $b_2 > a_2$. The interval represents the neutrophil and b_1 and b_2 represent the two bacteria cells (modelled as points). Using the equations talked about above, and those for the movement of a bacterium, i.e. Brownian motion with drift away from the neutrophil, set up SDEs to model the dynamics of this toy. These SDEs can then be solved to answer such questions as: what is the probability that both of the bacteria manage to escape the neutrophil (i.e. avoid contact with the neutrophil up to time T, say)?

4.3 Introducing obstacles

Recall that in the video clip at `http://www.biochemweb.org/neutrophil.shtml`, the neutrophil collides with 'obstacle' red blood cells: it would be interesting to further the model by incorporating these interactions.

Task 6. *Extend the model in [**14**] to incorporate the interactions between the neutrophil and the red blood cells and other obstacles.*

Assume the red blood cells are circular with centre y_0 and radius R. A point $x \in \Gamma$ will exert a force on the red blood cell when it comes into contact. Simultaneously, an equal and opposite force will act on x. (See figure 3.)

Note also, that this is not a hard collision: the neutrophil membrane and the red blood cell membrane are both elastic. It is intuitive to assume that the force acting between them, g, depends on the distance between x and y_0, which we will denote d. Obviously $g \equiv 0$ for $d > R$. The collision force, g will also depend on the momentum of the neutrophil.

We propose the following development of equation (4.2) to incorporate the obstacle red blood cells:

$$v = \kappa + f(a) - g(d) \text{ for } x \in \Gamma \tag{4.4}$$

The migration of each $x \in \Gamma$ is now influenced by three factors: the geometry of the cell, the chemoattractant, and any collisions with obstacles. The movement of the red blood cells is modelled by the following equation for y_0:

$$\dot{y}_0 = c \int_{x \in \Gamma} g(d). \tag{4.5}$$

Our assumptions are that the red blood cells are stationary before contact with the neutrophil, are moved under the colliding force during a collision and are again stationary when the collision has ended — this is representative of our viscous regime. Note that each point $x \in \Gamma$ will act on y_0. The suggested problem is to investigate suitable functions, g, to model this scenario.
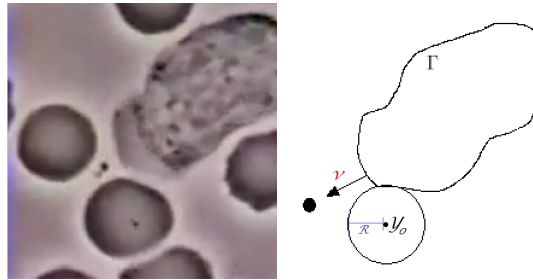

Figure 3: An illustration of the obstacle red blood cells that a neutrophil encounters while chasing the bacterium.

4.4 Existence and uniqueness of solutions to the surface chemotaxis equations

Consider equations (2.3) with no noise:

$$\partial_t^\bullet a + a\nabla_{\Gamma(t)} \cdot u = D_a\Delta_{\Gamma(t)}a - r_a a \tag{4.6a}$$

$$\partial_t^\bullet b + b\nabla_{\Gamma(t)} \cdot u = D_b\Delta_{\Gamma(t)}b - r_b b + r_b \fint_{\Gamma(t)} a \, \mathrm{d}x \tag{4.6b}$$

$$\partial_t^\bullet c + c\nabla_{\Gamma(t)} \cdot u = D_c\Delta_{\Gamma(t)}c - r_c c + b_c a. \tag{4.6c}$$

Task 7. *Discuss what it means for equations (4.6) to have a unique solution, with a view towards proving that they do indeed have a unique solution.*

As equations (4.6) are coupled, this is a somewhat difficult task, but useful to discuss nevertheless. First of all, as $\nabla_{\Gamma(t)} \cdot u$ is smooth, it might be worth considering the case where we assume D_a, D_b and D_c to be constants. So, as long as the forcing terms on the right-hand side are smooth, we will have weak solutions in H^1. This can be checked by multiplying through the equations by a smooth test function.

4.5 Rigorous formulation of SPDEs on (moving) surfaces

Consider equation (23) in [**14**]. We remind the reader of the equation here.

$$\frac{\partial a}{\partial t} + a\nabla_\Gamma \cdot u = D_a\Delta_\Gamma a + sf(a,b,c) - r_a a, \tag{4.7}$$

where f is some given function of a, b and c and s is given by

$$s(z,t) = r_a[(1 + dr\mathrm{RND}) + R_0(1 + dr\mathrm{RND})],$$

where z is the position of the bacterium, with R_0 given (as in section 2.2.2) by

$$R_0 = \frac{C}{C + K_d},$$

r_a and D_a constant, and RND is a uniformly distributed random variable. The s term is considered as noise; so, in fact, the above is a stochastic partial differential equation on an evolving surface. The problem is, even though this can be interpreted as such, in its current state it is not rigorously defined and this motivates the following.

Task 8. *Rigorously formulate what it means for a stochastic partial differential equation to exist on a (possibly moving) prescribed smooth surface. In answering this, one should:*

1. *prescribe what noise one is considering and investigate how one constructs such noise on the surface;*

2. *state what it means to have a solution to such an equation.*

It should be understood that the above is not exhaustive, but certainly both are important to answer.

For the discussion and for the project, it would be best to have a specific example in mind. Consider the following, which is the heat equation on a fixed non-moving prescribed smooth surface Γ

$$\begin{cases} \partial_t u(x,t) = \Delta_\Gamma u(x,t) + W(x,t) & (x,t) \in \Gamma \times (0,T) \quad T < \infty \\ u(0,x) = g(x) & x \in \Gamma \end{cases} \tag{4.8}$$

where g is a given deterministic function, W is some noise and Δ_Γ is the Laplace–Beltrami operator (see appendix A.1). We can think of u as the temperature and W as some random perturbation, such as a heat source or heat sink. Possibly the easiest case for the noise W would be taking it as a Gaussian process; that is, the finite-dimensional distributions having a Gaussian probability density function. Thus, all we need to prescribe is the covariance of W. A good discussion of this type of noise used for stochastic partial differential equations on the flat space is given in [6], with particular interest in page 24.

4.6 Simulation of cell movement using random walks

It has been observed that amoeboid cells move in a random walk but with a high degree of persistence. As a result they turn more slowly and cover more territory in a given time than a random walk. This is sometimes referred to as a persistent random walk (see figure 4). In [12] it is suggested that this search strategy improves the cell's chance of finding and locking on to a bacterium relative to performing a standard random walk.

Suppose we have a number of bacteria uniformly distributed over a large domain. We assume that once the cell locks onto the trail of chemoattractant left by a bacterium it will be able to catch the bacterium relatively easily. Suppose the chemoattractant trail extends a distance δ from the bacterium. To see how long it takes the cell to catch a bacterium using a particular search strategy we can see how long it takes for the cell to enter a ball of radius δ around a bacterium. Denote this time T. Alternatively T could be the time it takes for the cell to catch multiple bacteria. A good quantity for a search strategy to minimise may be $\mathbb{E}[T]$. In the situation of an infinite domain with uniformly distributed bacteria we would achieve this by having the cell move in a straight line.

However there are many variants to the situation described above. In [12] the authors conclude that instead of choosing turns randomly in amplitude and
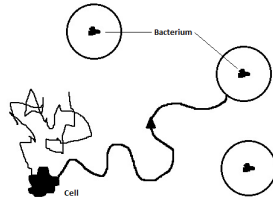

Figure 4: We can see that the random walk (left) is so volatile that it takes the cell a long time to cover any distance. The persistent random walk (right) turns less frequently and therefore explores the space better.

direction (a random walk) the cells bias their motion by remembering their last turn. They also choose turn amplitudes randomly from an exponential distribution rather than a Gaussian distribution. The paper [18] suggests that this helps to optimise search efficiency when targets are randomly distributed in a patch of finite size.

Task 9.   *1. Simulate cell movement using the model presented in [12] on finite domains to establish if indeed exponential turn amplitudes lead to better search efficiency.*

2. Suppose now that the bacteria themselves move around randomly. How does this search strategy fair in this case?

3. If each bacteria can split into two bacteria after a time step T_s, where T_s is fairly large, does this affect the optimal search strategy?

4.7   Statistics to compare models and experiments

In [14] the model of cell movement in the absence of chemoattractant is compared with the observed trajectories of cell centroids in order to see how similar the behaviour of the model is with that of real cells. In Figure 5, which is taken from that paper, the simulated and experimental paths appear similar by eye. However this is not very rigorous. We may struggle to determine which of a number of fairly good models best resemble the experimentally observed cell movement, or which choice of parameters give a model the best fit.
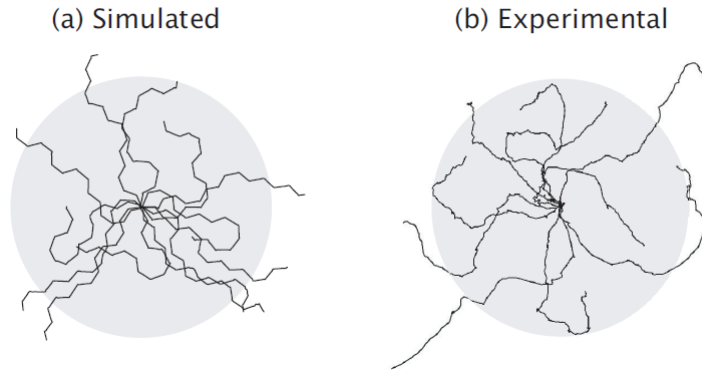

(a) Simulated   (b) Experimental

Figure 5: This figure from [14] shows the paths of cell centroids in the absence of chemoattractant for simulated cells and real cells. In this case they match quite closely, which suggests the model is good.

Task 10. *Formulate a method for determining whether the path of the cell produced by your model is 'similar' to experimental data. For example, 'similar' may mean the expected distance from the origin is comparable at all times; however, this is not sufficient to get a good match with the data. Simulated paths should also have a similar volatility and should change direction with a similar frequency as the experimental cell paths, but how do we measure this? Note that this problem is intentionally quite open.*

5 Action Plan

The following is a suggestion as to how the project could be approached.

- Firstly reading of [**14**] is very important. Most of the tasks involve modifying [**14**] or adding to it in some way. It should not be so important as to understand all the fine details on the first reading, but a general understanding should be grasped upon.

- Decide which task(s) the group wishes to do. It should be emphasised that not all the tasks should be attempted. The high number of tasks are there for the group to chose which ones they like best, and to be tailored to the skills of individual group members.

- Read the material in the appendix as appropriate. Regular meetings with Prof. C. Elliott and Dr B. Stinner are necessary and they will point out additional material, supplementary to material in the appendix and bibliography.

- On deciding the task and reading the appropriate material as required, break up the work load in a way that complements the skills and talents of the group. Start on the task by making small steps and remember that there is plenty of time to implement the project, but hard work is a necessity.

5.1 What tasks should the group look at first?

The main task is split into two different directions.

Firstly tasks 1 and 2 modifies how the curve is evolved. We incorporate geometry into the velocity of the points on the surface in task 1 whereas in task 2 the curve is evolved using a different gradient flow, called Willmore flow. This should give a more realistic model, as biomembranes seem to wish to minimise the Willmore energy functional. Modification to the numerics to come up with essentially a new numerical scheme, based upon [**14**], will be needed. Close collaboration with Prof. C. Elliott and Dr B. Stinner is highly recommended for this part of the project.

Alternatively, the group may wish to take on task 3 which essentially leaves [**14**] model as it is, but incorporates the movement of the bacterium into the model, noting that this is not done in [**14**]. Here, experimentation with what dynamics one should model the bacterium movement with are necessary. This leads to looking at the toy problem (task 4) which removes many of the possible problems the group may come across in task 3. A variation on task 3, would be to take task 1 or task 2 and incorporate the movement of the bacterium. Of course, time may not permit this and this could be a possible MSc thesis topic.

The tasks in section 4 are essentially self-contained subproblems. These have arisen from breaking down the main problem into smaller problems. These can be attacked independently as well as being incorporated into the main project. Indeed, these may be the only task(s) completed or even attempted in the project. The choice is there so that every group member has something to do and is interested in what they do.

A Mathematical Background

In this appendix we review some of the mathematical background required for this project. Much more can be found in the review paper of Deckelnick, Dziuk and Elliott [**3**].

A.1 Evolving surfaces

Denote by $\Gamma = \{\Gamma(t)\}_{t \in [0,T]}$ an evolving surface in $\mathbb{R}^3$. We assume that for each t fixed $\Gamma(t)$ is a smooth, connected and oriented surface in $\mathbb{R}^3$. Furthermore, we assume that $\partial\Gamma(t)$ is a smooth boundary for any $t \in [0,T]$ and $t \mapsto \Gamma(t)$, $t \mapsto \partial\Gamma(t)$ are smooth maps. Denote by ν the normal vector field on Γ. We assume in the following that $n = 3$. We keep n in to show the generalisation to n dimensional surfaces (cf. Gauss–Green formula below).

Definition A.1 (Surface gradient)**.** *For $f : \Gamma(t) \to \mathbb{R}$ smooth, define*

$$\nabla_{\Gamma(t)} f := \nabla f - (\nabla f \cdot \nu(t))\nu(t).$$

To define ∇f, an extension of f away from Γ is needed. We assume this exists in a thin layer around $\Gamma(t)$. Indeed, one can show that this extension for the surface gradient is irrelevant.

Further, a natural definition of the Laplacian on Γ called the Laplace–Beltrami operator is defined as

$$\Delta_{\Gamma(t)} u := \nabla_{\Gamma(t)} \cdot \nabla_{\Gamma(t)} u.$$

An important concept in differential geometry in the notion of curvature. Indeed, as we will see, curvature plays an important role in making surfaces move.

In [**14**] the boundary of the domain (a model for a cell) is moved using a level set method; solving an equation which in fact involves curvature. Hence their movement is due to mean curvature flow. We will see more of this in the following section.

Definition A.2. *The* curvature *or* mean curvature *is defined as*

$$\kappa(t) := -\nabla_{\Gamma(t)} \cdot \nu(t).$$

We will later call the mean curvature H as in the literature. So we have $2H = -\kappa$. We use the same sign convention as ([**3**], p.141) and take H positive for spheres.

Definition A.3. *The* curvature vector *is defined as*

$$\boldsymbol{\kappa}(t) := \kappa(t)\nu(t).$$

From vector analysis one should recall Green's formula: for surfaces, we have

Lemma A.4. *Let Γ be as above. Then, for suitably smooth $f : \Gamma \to \mathbb{R}$ we has*

$$\int_{\Gamma(t)} \nabla_{\Gamma(t)} f \, \mathrm{d}\mathcal{H}^{n-1} = -\int_{\Gamma(t)} f\boldsymbol{\kappa}(t) \, \mathrm{d}\mathcal{H}^{n-1} + \int_{\partial\Gamma(t)} f\boldsymbol{\mu}(t) \, \mathrm{d}\mathcal{H}^{n-2},$$

where $\mathcal{H}^k$ is the k-dimensional Hausdorff measure, $\boldsymbol{\mu}$ is the co normal to ν. (This is basically a mathematical formulation of the right hand grip rule from physics).

We will always assume that a smooth material velocity field

$$v \colon \{(t, \Gamma(t)) : t \in [0, T]\} \to \mathbb{R}^n$$

exists and describes the evolution of the surface. In other words, the trajectories $y(t, x_0)$ given as solutions to the ODEs

$$\partial_t y(t, x_0) = v(t, y(t, x_0))$$
$$y(0, x_0) = x_0 \in \Gamma(0),$$

define the surface via

$$\Gamma(t) = \{y(t, x_0) : x_0 \in \Gamma(0)\}.$$

For a given evolving surface, there is no unique such v, since the only normal portion $v \cdot \nu$ has to coincide with the normal motion, apart from the boundary points. Indeed, in applications, tangential contributions are associated with transport of material along the surface.

This leads to the notion of material derivative.

Definition A.5. *Suppose $f \colon [0, T] \times \Gamma \to \mathbb{R}$ is a given function on the evolving surface Γ. Then the* material derivative *of f is denoted by $\partial_t^\bullet f$, and is defined by*

$$\partial_t^\bullet f(t, x) := \frac{\mathrm{d}}{\mathrm{d}t} f(\cdot, y(\cdot, x_0))|_t,$$

where x_0 is a suitable point such that

$$y(t, x_0) = x \in \Gamma(t).$$

Indeed, one has by the chain rule that:

Lemma A.6. *For f above and extended smoothly away from Γ,*

$$\partial_t^\bullet f = \partial_t f + v \cdot \nabla f.$$

By considering conservation of mass we obtain the following, called the transport identities.

Lemma A.7 (Transport identity). *For suitable f as above, we have*

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Gamma(\cdot)} f(\cdot, x) \, \mathrm{d}\mathcal{H}^{n-1}(x) \Big|_t = \int_{\Gamma(t)} (\partial_t^\bullet f(t, x) + f(t, x) \nabla_{\Gamma(t)} \cdot v(t, x)) \, \mathrm{d}\mathcal{H}^{n-1}(x).$$

Lemma A.8 (Divergence theorem for evolving surfaces). *For a smooth vector field w on a closed evolving surface Γ, we have*

$$\int_{\Gamma(t)} \nabla_{\Gamma(t)} \cdot w \, \mathrm{d}\mathcal{H}^{n-1} = \int_{\partial\Gamma(t)} w \cdot \mu \, \mathrm{d}\mathcal{H}^{n-2} - \int_{\Gamma(t)} \boldsymbol{\kappa}(t) \cdot w \, \mathrm{d}\mathcal{H}^{n-1},$$

where μ is co-normal (as defined above).

The question remains as to how one actually specifies a moving surface. In [14], they use the level set method [3] of describing a surface. The idea is to consider a smooth level set function $\phi = \phi(x,t)$ so that

$$\Gamma(t) = \{x \in \mathbb{R}^2 : \phi(x,t) = 0\}.$$

This particular approach enables one to define an inside and an outside, by choosing a suitable function ϕ. The most common choice, as in [14], is to use the signed distance function:

$$\mathrm{d}(x, \Gamma(t)) := \inf_{y \in \Gamma(t)} \|x - y\|,$$

and so ϕ is taken to be

$$\phi(x,t) = \begin{cases} -\mathrm{d}(x, \Gamma(t)) & \text{if} \quad x \in S \\ \mathrm{d}(x, \Gamma(t)) & \text{if} \quad x \notin S \\ 0 & \text{if} \quad x \in \Gamma(t). \end{cases}$$

S identifies the area occupied within the curve $\Gamma(t)$. The orientation of $\Gamma(t)$ is set by taking the normal n to Γ to be in the direction of increasing ϕ. So, naturally we have

$$n(x,t) := \frac{\nabla\phi(x,t)}{\|\nabla\phi(x,t)\|}.$$

Taking this definition of the normal, we recall definition A.1 for the surface gradient, now with $\nu = n$.

A.2   Modelling conservative quantities

It is important to model quantities that are conserved. From chemical reactants on a surface to mass, we have already seen all the maths needed.

Example A.9. *Consider the energy*

$$|\Gamma(t)| := \int_{\Gamma(t)} 1.$$

Then

$$\frac{\mathrm{d}}{\mathrm{d}t}|\Gamma(t)| = -\int_{\Gamma(t)} v(t) \cdot \boldsymbol{\kappa}(t) \, \mathrm{d}\mathcal{H}^{n-1}.$$

To see the above, expand the left hand side with $f = 1$ using lemma A.7. From lemma A.6 we see that the material derivative vanishes. Now we argue that $v \cdot \mu = 0$, as μ is orthogonal to the normal direction and tangential direction of the velocity v. Now we are done.

The following will prove crucial in modelling the cell movement and the equations below are found in [14] and other papers.

Let $u \colon \Gamma \to \mathbb{R}$ be the density of a conserved quantity. For example, it may be mass density of a chemical species. We neglect reactions with other species and allow for diffusion along the surface. We postulate a tangential flux of the form

$$q(t) = -D\nabla_{\Gamma(t)}u(t),$$

where D is a constant. Consider a source term $f \colon \Gamma \to \mathbb{R}$. On an arbitrarily small portion $G \subset \Gamma$ with moving velocity v with external unit co-normal μ the mass balance of u reads

$$
\frac{\mathrm{d}}{\mathrm{d}t} \int_{G(\cdot)} u(\cdot, x) \, \mathrm{d}\mathcal{H}^{n-1}(x) \Big|_t
$$
$$
= - \int_{\partial G(t)} q(t, x) \cdot \mu(t, x) \, \mathrm{d}\mathcal{H}^{n-2}(x) + \int_{G(t)} f(t, x) \, \mathrm{d}\mathcal{H}^{n-1}(x),
$$

which should be thought of as

Change in mass in $G = -$net flux across boundary $+$ source contribution.

Using lemma A.7 to deal with the left hand side and lemma A.8 to deal with the boundary integration, one ends up with

$$
\int_{G(t)} \partial_t^{\bullet} u + u \nabla_{\Gamma(t)} \cdot v \, \mathrm{d}\mathcal{H}^{n-1} = \int_{G(t)} f(t, x) \, \mathrm{d}\mathcal{H}^{n-1}
$$
$$
- \int_{G(t)} -D\boldsymbol{\kappa} \cdot \nabla_{\Gamma(t)} u \, \mathrm{d}\mathcal{H}^{n-1} - \int_{G(t)} -D\Delta_{\Gamma(t)} u \, \mathrm{d}\mathcal{H}^{n-1}.
$$

Since G was an arbitrary small surface, and the above has to hold for all such G we conclude that the following global PDE holds:

$$
\partial_t^{\bullet} u + u \nabla_{\Gamma(t)} \cdot v = f + D\Delta_{\Gamma(t)} u. \tag{A.1}
$$

These equations form the basis of chemotaxis models. Indeed, in [**14**], they consider three equations of the type (A.1) coupled for an autocatalytic activator, a rapidly distributed global inhibitor and a local inhibitor, each equation with different source terms f.

A.3   Introduction to Willmore flow

Here, we consider so called Willmore flow. Recall mean curvature flow, where points on the surface moving with velocity $u = -H$ in the normal direction. Willmore flow moves points with velocity $u = f(H)$ where

$$
f(H) := \Delta_{\Gamma(t)} H + H \|\nabla_{\Gamma(t)} \nu\|^2 - \frac{1}{2} H^3.
$$

Note again that this is in the normal (ν) direction. Indeed, the reader my agree that this is a considerably more complex flow. We will look at the derivation according to ([**3**], p. 215).

Define the Willmore functional

$$
\mathcal{W}(X) := \frac{1}{2} \int_{\Gamma} H^2 \, \mathrm{d}A,
$$

where M is an n-dimensional reference manifold and $X \colon M \to \mathbb{R}^{n+1}$ is a smooth immersion with $\Gamma = X(M)$. Consider variations

$$
X_{\varepsilon}(p) = X(p) + \varepsilon\phi(p) \quad p \in M,
$$

where $\phi\colon M \to \mathbb{R}^{n+1}$ is smooth and vanishes near ∂M.

Then

$$\begin{aligned}
\langle E'(X), \phi \rangle &= \frac{\mathrm{d}}{\mathrm{d}\varepsilon} E(X_\varepsilon)\Big|_{\varepsilon=0} \\
&= \int_\Gamma \Delta_\Gamma X (\Delta_\Gamma \phi + 2\nu \nabla_\Gamma \nu \cdot \nabla_\Gamma \phi) + \frac{1}{2} \int_\Gamma H^2 + \nabla_\Gamma X \cdot \nabla_\Gamma \phi \\
&= \int_\Gamma \nabla_\Gamma (H\nu) \cdot \nabla_\Gamma \phi - 2H \nabla_\Gamma \nu \cdot \nabla_\Gamma \phi + \frac{1}{2} \int_\Gamma H^2 \nabla_\Gamma X \cdot \nabla_\Gamma \phi
\end{aligned}$$

using integration by parts and the fact that $-\Delta_\Gamma X = H\nu$, by ([**3**], p.152). Willmore flow then arises as the L^2 gradient flow of the Willmore functional. That is,

$$\int_\Gamma X_t \cdot \phi \, \mathrm{d}A = -\langle E'(X), \phi \rangle.$$

So by integration by parts one obtains

$$X_t = \Delta_\Gamma (H\nu) - 2\nabla_\Gamma \cdot (H\nabla\nu) + H\nabla_\Gamma H - \frac{1}{2} H^3 \nu.$$

We now take the scalar product with ν and observe that

$$\Delta_\Gamma \nu \cdot \nu = -\|\nabla_\Gamma \nu\|^2,$$

we obtain

$$u = \Delta_\Gamma H + H\|\nabla_\Gamma \nu\|^2 - \frac{1}{2} H^3,$$

on $\Gamma(t)$ in the normal (ν) direction.

Note that it is not so important to be able to derive this result, and that many steps are missed out. The important thing to note is that one should consider points P moving according to the ODEs are mentioned in section 1; that is the trajectories $y(t, x_0)$ given as solutions to the ODEs

$$\begin{aligned}
\partial_t y(t, x_0) &= \boldsymbol{u}(t, y(t, x_0)) \\
y(0, x_0) &= x_0 \in \Gamma(0),
\end{aligned}$$

define the surface via

$$\Gamma(t) = \{y(t, x_0) : x_0 \in \Gamma(0)\},$$

where $\boldsymbol{u} = (\Delta_\Gamma H + H\|\nabla_\Gamma \nu\|^2 - \frac{1}{2}H^3)\nu$. It is interesting to note that u arises from the first variation of an energy. This energy is important in mathematical biology.

It is important to note that when the surface is parametrised, the curvature is given by the second derivative of the parametrisation, with respect to arc length ([**1**], p.2). That is, let $x\colon I \to \mathbb{R}^d$ be a smooth parametrisation of a smooth curve Γ in $\mathbb{R}^d$, where I is a suitable interval. Then

$$x_{ss} = \boldsymbol{\kappa},$$

where s is arclength and $\boldsymbol{\kappa}$ is the curvature vector as given in definition A.3. Hence, using the notation that

$$\boldsymbol{\kappa}(t) = -2H\nu(t)$$

we see that
$$H\nu(t) = -\frac{1}{2}x_{ss}.$$

With this in mind, one sees that Willmore flow gives rise to a fourth order PDE.

A.4   The surface finite element method (SFEM)

Here, we describe the surface finite element method (SFEM) for simulating chemotaxis on a moving cell, as introduced in [**15**] (though it is referred to as the parametrised finite element method, or PFEM, there). More details of the mathematical background may be found in [**4**] and [**5**].

Take a closed surface Γ in $\mathbb{R}^2$. Consider a flow in which the normal velocity is defined as
$$\bar{\mathbf{x}}_t \cdot \bar{\nu} = \alpha(\bar{\mathbf{x}}, t)\kappa + \beta(\bar{\mathbf{x}}, t) \tag{A.2}$$

where $\bar{\nu}$ is the unit normal to Γ, κ is the curvature, and $\bar{\mathbf{x}}$ is the position vector. The functions α and β represent retractions and protrusions respectively. In our case β depends on a spatio-temporal activator profile obtained from the system of reaction diffusion equations, while α is used to regulate the cell area, i.e. keep it roughly constant.

Suppose we have a piecewise linear curve representing the edge of the cell at time t_m, which we will denote
$$\bar{X}^m = (\bar{X}_1^m, ..., \bar{X}_N^m)^T$$

with $\bar{X}^m = (x_j(t_m), y_j(t_m))$, $j = 1, ..., N$. To update the cell edge from time t_m to t_{m+1} [**14**] constructs a discretised weak formulation of (A.2), and solves the resulting system of linear equations

$$\Lambda^m \begin{pmatrix} \kappa^{m+1} \\ \delta\bar{\mathbf{X}}^{m+1} \end{pmatrix} = b^m.$$

where $\delta\bar{\mathbf{X}}^{m+1} = \bar{\mathbf{X}}^{m+1} - \bar{\mathbf{X}}^m$ and $\kappa^{m+1} = (\kappa_1^{m+1}, ..., \kappa_N^{m+1})^T$ are the vectors of coefficients with respect to the standard basis. The exact forms of Λ^m and b^m are defined in [**15**].

In addition to being linear this system of equations has structure that allows it to be solved efficiently. The coordinates of the new cell boundary at time t_{m+1} are then given by
$$\bar{\mathbf{X}}^{m+1} = \bar{\mathbf{X}}^m + \delta\bar{\mathbf{X}}^{m+1}.$$

With the original algorithm However, by replacing the LSM with the SFEM, we now only need one mesh because the SFEM uses the same mesh as the ALE-SFEM. As a result the algorithm simplifies to the following two step procedure for approximating the solution at time t_{m+1}:

Step 1: *Evolve the cell interface* — to do this we:

  (a) use the solution of the reaction-diffusion equations to determine β^m; and

  (b) use the SFEM to compute the new interface, $\bar{\mathbf{X}}^{m+1}$, by solving the linear system of equations.

Step 2: *Update the solution of the reaction-diffusion equations using the ES-FEM..*

The original algorithm in [**14**] was more complicated: they suppose that the surface is given in terms of some level set function ϕ: that is,

$$\Gamma(t) = \{x \in \mathbb{R}^2 : \phi(x,t) = 0\}.$$

The movement of the domain boundary is then achieved by solving a level set equation of the form

$$\frac{\partial \phi}{\partial t} + [V_f(x) - \lambda(t)\kappa(x)]\|\nabla\phi\| = 0, \tag{A.3}$$

where $V_f(x)$ represents a normal velocity of the level set of $\phi(x,t)$, $\lambda(t)$ is a time dependent but spatially constant parameter and $\kappa(x)$ denotes the curvature of the local level set of $\phi(x,t)$.

In [**14**], they required two different meshes: a Cartesian mesh for the LSM and a finite element mesh for the ALE-SFEM. The initial LS/ALE-SFEM approach taken by Neilson *et al.* in [**14**] was compared to SFEM in [**15**]: for the latter paper, both algorithms were implemented on Matlab and the SFEM was found to be around 10 times quicker than the LS/ALE-SFEM. In addition, as the SFEM is not dependent on the TOOLBOXLS toolbox in Matlab it was possible to implement it in GNU Fortran, leading to a 1000 times speed up.

The SFEM beats the LS/ALE-SFEM in terms of both efficiency and robustness, as well as being easier to implement and requiring few changes to extend to higher dimensions. That said, one advantage of the LS/ALE-SFEM approach is that the LSM can more easily deal with changes in topology, for example in cell splitting. However, this functionality is probably not required for the current situation we are modelling, and we therefore suggest use of the SFEM approach for implementation in this project.

References

1. John W. Barrett, Harald Garcke, and Robert Nürnberg. Numerical approximation of gradient flows for closed curves in $\mathbb{R}^d$. *IMA J. Numer. Anal.*, 30 (1):4–60, 2010.

2. P. B. Canham. The minimum energy of bending as a possible explanation of the biconcave shape of the human red blood cell. *Journal of Theoretical Biology*, 26(1):61–81, January 1970.

3. Klaus Deckelnick, Gerhard Dziuk, and Charles M. Elliott. Computation of geometric partial differential equations and mean curvature flow. *Acta Numer.*, 14:139–232, 2005.

4. Gerhard Dziuk. Finite elements for the Beltrami operator on arbitrary surfaces. In *Partial differential equations and calculus of variations*, volume 1357 of *Lecture Notes in Math.*, pages 142–155. Springer, Berlin, 1988.

5. Gerhard Dziuk and Charles M. Elliott. Finite elements on evolving surfaces. *IMA J. Numer. Anal.*, 27(2):262–292, 2007.

6. Martin Hairer. Lecture notes: An introduction to stochastic PDEs. *arXiv.org*, 0907.4178v1, 2009.

7. W. Helfrich. Elastic properties of lipid bilayers: Theory and possible experiment. *Zeitschrift für Naturforschung C*, 28(11):693–703, November–December 1973.

8. Desmond J. Higham. An algorithmic introduction to numerical simulation of stochastic differential equations. *SIAM Rev.*, 43(3):525–546 (electronic), 2001.

9. D. Horstmann. From 1970 until present: the Keller-Segel model in chemotaxis and its consequences II. *Jahresber. Deutsch. Math.-Verein.*, 106(2): 51–69, 2004.

10. Robert Insall. Understanding eukaryotic chemotaxis: a pseudopod-centred view. *Nat. Rev. Mol. Cell Bio.*, 11:453–458, June 2009.

11. Evelyn F. Keller and Lee A. Segel. Model for chemotaxis. *J. Theor. Biol.*, 30(2):225–234, 1971.

12. Liang Li, Simon F. Nørrelykke, and Edward C. Cox. Persistent cell motion in the absence of external signals: A search strategy for eukaryotic cells. *PLoS ONE*, 3(5):e2093, May 2008.

13. H. Meinhardt. Orientation of chemotactic cells and growth cones: models and mechanisms. *J. Cell Science*, 112(17):2867–2874, 1999.

14. Matthew P. Neilson, John A. Mackenzie, Steven D. Webb, and Robert H. Insall. Modelling cell movement and chemotaxis using pseudopod-based feedback. *Uni. Strathclyde Math. Stat. Res. Report*, 5:1–21, 2010.

15. Matthew P. Neilson, John A. Mackenzie, Steven D. Webb, and Robert H. Insall. Use of the parameterised finite element method to robustly and efficiently evolve the edge of a moving cell. *Integr. Biol.*, 2:687–695, 2010.

16. Bernt Øksendal. *Stochastic differential equations.* Universitext. Springer-Verlag, Berlin, sixth edition, 2003. ISBN 3-540-04758-1. An introduction with applications.

17. L. R. Ritter. A short course in modelling of chemotaxis, 2004. URL `www.iac.rm.cnr.it/~natalini/mathbio/courseritter.pdf`.

18. Peter J. M. Van Haastert. A model for a correlated random walk based on the ordered extension of pseudopodia. *PLoS Comput. Biol.*, 6(8):e1000874, August 2010.