Generalized Model For Chemotactic And Chemotropic Effects Coupled To Actin Dynamics:
A Phase Field Approach

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DEDICATION

To my parents, my brothers, my grandparents, and Rula who have taught me things never to be found in books,
To Jihad for showing me the way,
To Nour my ancient friend,
To Hiba my crutch along the road,
And to those who witnessed...
I will start by admitting that my stay here at Montreal has appreciably height-
ened my awareness towards how precarious life is. However, despite its unpredictabil-
ity, I have realized that with faith all its seemingly unsurmountable problems dissolve.
In the face of that Truth, I stand in awe.
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The ubiquity of free boundary problems in biology, with which we are mainly concerned, led us to adopt a mathematical technique to render them tractable and relatively easy to solve. The phase field method, used when dealing with dynamical systems with moving boundary condition, addresses arising difficulties involved with tracking those boundaries. In this work we model the motion of neutrophils, cells of the immune system, in response to chemical driving. Their morphology changes dynamically as they move to neutralize their target, a mechanism called chemotaxis. Additionally, we propose a model for neural cell growth, which is instigated by mediators, a process termed chemotropism. When coupled to an internal mechanism of actin polymerization, this induces the advancement of the axonal tip. Lastly, we used the method to build a generalized model from which both chemotactic and chemotropic models can be derived. These three problems were solved by the construction of free energy functionals $F$ that captured the main features of the dynamics, in relation to the order parameters $\phi$ that distinguished the phases of the system as well as their interfaces. We considered the membrane of the cells, their inside and outside, as well as their leading edges. The governing partial differential equations were obtained by a variational differentiation of $F$ with respect to the fields. Following this method, we were able to model cell morphodynamics in two and three dimensions. The major contribution of our work lies in the reduction of the complexity of those problems: we solve partial differential equations of fields coupled to the underlying dynamics at the molecular level, which are derived from a
closed form generalized functional describing both the cell motion, deformation and growth.
L'abondance des problèmes à interface libre dans la biologie auxquels nous sommes principalement intéressés, nous a conduits à adopter une technique qui les rend relativement faciles à résoudre. Phase Field Method, utilisée pour examiner des systèmes dynamiques possédants des conditions aux limites en mouvement, resoud la difficulté provenant de suivre leur évolution. Dans ce travail, on modèle le mouvement des neutrophiles qui sont des cellules du système immunitaire en réponse aux signaux chimiques. Leur morphologie change dynamiquement quand ils se déplacent pour neutraliser leur cible: ce mécanisme est appelé chimiotaxie. Également, on propose un modèle pour le développement des cellules nerveuses induit par des médiateurs. Ce processus est nommé chémotropisme. Ce dernier, quand il est lié au mécanisme interne responsable de la polymérisation de l'actine, induit l'avancement du bout de l'axone. Finalement, on a employé la méthode pour construire un modèle généralisé qui permet de dériver les deux modèles chimiotactique et chémotropique. Ces problèmes ont été résous en construisant des fonctionelles d'énergie libre $F$, capturant les caractéristiques principaux de la dynamique en fonction d'un paramètre d'order $\phi$ qui permet de distinguer les différentes phases du système aussi bien que les interfaces qui les séparent. Les équations aux dérivées partielles décrivant leur évolution sont déterminées en effectuant une différenciation variationnelle de $F$ par rapport au champs $\phi$. En suivant cette méthode, on était capable de reproduire la dynamique des morphologies en deux et trois dimensions. La contribution majeure
de notre travail réside dans la réduction de la complexité de ces problèmes en suivant les équations aux dérivées partielles. Ces dernières sont liées aux mécanismes internes au niveau moléculaire dérivés d'une fonctionnelle généralisée $\mathcal{F}$ qui décrit le mouvement de la cellule ainsi que sa déformation et sa croissance.
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1.1 Introduction

Cells exhibit dynamical processes at the molecular level, several of which entail exchange between the intracellular and extracellular domains, and some of which lead to a flow within a restricted region of the cell. Consequently their evolution is linked to the position of the membrane where the flux of matter occurs. These processes could of course leave the boundary unaffected, but in many cases they lead to alterations influencing the cell’s morphology. The latter category is a highly nonlinear class of systems, which involves moving boundary conditions, which itself relies on fundamental underlying mechanisms. Biology abounds with such systems, examples include neural cell growth, pollen tubes, neutrophils, and numerous others which can all be mathematically described as free boundary problems. Fig. 1–1 is an illustration of a typical situation, where the dynamics of a monomer depends on the position of a boundary, which itself depends on the flux of the monomers.

The morphodynamics of cells can then be thought of as out-of-equilibrium systems, with imposed free boundary conditions, and our understanding of their behavior relies on our understanding of fundamental properties of the most common states of matter: solid, liquid and gas, and of their behavior at equilibrium, and of the phase transitions that they undergo. To address this important phenomena, we present the
necessary background before embarking on the mathematical and biological details pertaining to the cells that we will model.

Figure 1–1: A migrating cell projects its actin cytoskeleton, called lamellipodium, and its leading edge moves as a result of monomer flux.

Numerous simulation-based methods can be used to model the evolution of such systems, examples include an atomistic approach, or a continuum one. The first treats the system as an $N$-body problem, as it is concerned with the particle level description. It relates the statistical averages to the thermodynamical properties. This explains why the large time scale behavior becomes inaccessible in this approach. These include Monte Carlo methods, as well as Molecular Dynamics simulations.

As for the continuum approach they follow a slowly varying macroscopic quantity by integrating out the irrelevant microscopic degrees of freedom. Hydrodynamics equations, for example, reflect the system’s conservations laws as well as its symmetries, and describes changes affecting solid or liquid systems. However, these might
become inaccurate at smaller length scales. The phase-field method, on the other hand inherently locates the position of the interface, and determines its shape. In the phase-field method, the atomistic lengths are overlooked at the expense of an order parameter, nearly constant in the bulk of the phases, and smoothly changing at the interface. It represents local orientations, concentrations, etc, which evolve as the thermodynamical driving changes. Then the thermodynamical description of interface morphology is implicit, as are relations between temperature, the boundary, its curvature, its velocity, surface tension and its anisotropies. One such example is that of a pure isotropic interface, separating two phases at equilibrium. Analogously, in out-of-equilibrium systems, and in order to determine the motion of the boundary, similar relations must be established between the shape of the interface, its velocity, and temperature, which model the atomic and the macroscopic levels of description of the physical problem. This can be achieved through the power of energy functionals.

The thermodynamical description depends on the details of the problems. For example, an isothermal system at fixed pressure will be appropriately portrayed by the Gibbs free energy. Alternatively, the Helmholtz free energy describes a system at constant temperature and volume. The free energies’ relation to thermodynamical variables, with the appropriate conservation laws, and equations of motion will determine the time evolution of the system. For simple heterogeneous systems, they can be constructed in terms of a scalar order parameter $\phi$ and its derivative $\nabla \phi$. Typically this parameter is given the values 1 and 0 each characterizing a phase, and a continuous transition between them marks the interface. The coefficients of this
expansion are controlled by the physical system’s symmetries. For instance, those multiplying the odd powers of $\nabla \phi$ must vanish since the physics should be invariant under coordinate reversal. The dynamics of the order parameter phenomenologically implicitly includes all the details regarding the interface morphology.

In thermodynamically irreversible processes, the specification of the rate of change of the order parameter also necessitates a connection between $\phi$ and the free energy. It is based on a fundamental thermodynamical observation for reversible processes, which entails equating the fluxes depicting the rates of change to the forces producing them. Similar relations govern irreversible processes. Explicitly, applying an infinitesimal forcing cannot be reversed. Consequently the free energy of such out-of-equilibrium system is dissipated.

The order parameter $\phi$ can represent a conserved quantity such as concentration, or a non-conserved one such magnetization. Consequently, its nature determines the equation governing the rate of change in $\phi$. We now move to describe the equations governing its evolution in relation to the free-energy functional.

### 1.2 Non-Conservative Dynamics

We now turn to the case where the order parameter involves a non-conserved macroscopic quantity characterizing the system. In this case, the rate of dissipation of the free energy $F$ as a function of time for an irreversible process must obey the following inequality:

$$\frac{d}{dt} \int F(\phi, T)d^3 \vec{x} \leq 0.$$ 

This is equivalent to $\int (\frac{\delta F}{\delta \phi}) \cdot (\frac{\partial \phi}{\partial T}) T d^3 \vec{x} \leq 0$, taken at constant temperature. Then we identify the conjugate force of the change in $\phi$ to be $(\frac{\delta F}{\delta \phi})$. This together with the
assumption that the flux of the rate of change in the parameter is proportional to the force producing it, leads to the following:

\[
\frac{\partial \phi}{\partial t} = -\Gamma \left( \frac{\delta F}{\delta \phi} \right),
\]

where \( \Gamma \) is the mobility. This gives \( -\Gamma \left( \frac{\delta F}{\delta \phi} \right)^2 \leq 0 \) in accordance with the initial inequality. Here we are neglecting the effects of additive noise.

This was done for a general functional without specifying its equation in terms of the field \( \phi \). It will become clear how to construct this functional relation in the following sections.

1.3 Conservative Dynamics

We now consider the case where \( \phi \) describes a conserved quantity, given by the continuity equation that follows:

\[
\frac{\partial \phi}{\partial t} = \nabla \cdot J.
\]

where \( J \) is the flux.

Similarly, we note that the rate of change of the free energy must satisfy the inequality \( \frac{\delta F}{\delta t} \leq 0 \). This translates into the condition on the integrand \( \left( \frac{\delta F}{\delta \phi} \right) \cdot \left( \frac{\partial \phi}{\partial t} \right) \leq 0 \), also taken at constant temperature. Now using the continuity equation we can write the later inequality as \( \left( \frac{\delta F}{\delta \phi} \right) \cdot (\nabla \cdot J) \leq 0 \). Also, we use the following identity

\[
B(\nabla \cdot A) = \nabla(AB) - A \cdot \nabla B
\]

to write:

\[
\left( \frac{\delta F}{\delta \phi} \right)(\nabla \cdot J) = \nabla[J \cdot \left( \frac{\delta F}{\delta \phi} \right)] + J \cdot \nabla(\frac{\delta F}{\delta \phi}).
\]

The first term on the right hand side is zero, since \( F \) is an integral over a volume, and can be changed by Gauss’s law into an integral over the bounding surface, where the flux is zero for a closed system. This then gives the following:
\[ J \cdot \nabla \left( \frac{\delta F}{\delta \phi} \right) < 0. \]

It is then clear that the conjugate force for the flux is \( \nabla \left( \frac{\delta F}{\delta \phi} \right) \), which together with the fundamental assumption that the flux is proportional to the force producing it, and with the continuity equation allow us to write:

\[ \frac{\partial \phi}{\partial t} = \nabla \cdot \left[ \Gamma \nabla \left( \frac{\delta F}{\delta \phi} \right) \right]. \]

Now that we have defined some key physical notions, we move on to the representation of the free energy and its relation to the order parameter, and to the nature of the dynamics.

### 1.4 Fokker-Planck Equation

The derivation of the nonconservative and conservative dynamics equations relied on a fundamental observation relating the rate of change of a field to its conjugate force. To make the formalism more rigorous, we show its equivalence to the Fokker-Planck equation, and therefore validate our assumptions.

We start with the Langevin Eq. 1.1 relating a variable \( m \) to a deterministic force \( v \), and a random one \( f(t) \). The latter is a Gaussian noise where the correlation defined as the second moment of the Gaussian by \( \langle f(t)f(t') \rangle = 2k_B T \Gamma \delta(t - t') \).

\[ \frac{\partial m}{\partial t} = v + f(t). \] (1.1)

In principle, one can describe the evolution of a system by setting and solving its equations of motion corresponding to its degrees of freedom. However, in systems involving a large number of degrees of freedom, the task become unfeasible. That is, given the equations of motion are known, it is impractical to have a knowledge
of all the initial conditions and of the system’s particles. Then one might deduce that systems with large number of particles do not display any regularity at the macroscopic level. However, its components appear to follow statistical laws, which are probabilistic in nature, as opposed to deterministic laws given in classical mechanics. Then for a given macroscopic state with $s$ degrees of freedom, we denote $q_i$ and $p_i$ the position and momenta of each particle in the $2s$-dimensional space, where $i = 1, ..., s$. Then at a given time, the state is defined by the values of $q_i$ and $p_i$, and it can be represented in this $2s$-dimensional space by a point. The time evolution of the system can be depicted by a trajectory in this phase space, which will be called a phase space trajectory. Then we denote $\Delta p \Delta q$ to be a phase space volume. Consequently the probability that this point lies between $q + dq$ and $p + dp$ is given by:

$$\rho(p, q)dp_i dq_i.$$ 

where $\rho$ is the probability density. The latter does not depend on the details of the initial conditions, since for long enough times their contribution will be outweighed. Then the movement of the phase point is a steady flow in the $2s$-dimensional phase space, since the points will be distributed according to the initial distribution function. Then by the Liouville theorem, it must obey the continuity equation given by:

$$\frac{d\rho}{dt} = \frac{\partial \rho}{\partial t} + v \cdot \nabla \rho = 0.$$ 

This means that the distribution along trajectories is constant. Noting that this macrostate can be divided into $N$ similar non-interacting substates, means that the
distribution is the multiplication of those of the substates. Which means that the logarithm of the distribution is additive:

$$\log \rho(p, q) = \log \rho_1(p, q) + \ldots \log \rho_s(p, q).$$

Additionally, independent additive variables characterizing systems, are nothing but integrals of motion, that is constants like the energy, momentum, and angular momentum. Then log $\rho = \beta E + \alpha P_{lm}$, where $\beta$, $\alpha$ are constant coefficients multiplying the energy $E$ and the linear momentum $P_{lm}$ respectively. Then clearly the mean values characterizing the substates define the macrostate, which allows us to write:

$$\rho(p, q) \propto \delta(E - \bar{E}) \cdot \delta(P_{lm} - \bar{P}_{lm}) \cdot \delta(m - \bar{M}).$$

where $\bar{E}$ and $\bar{P}_{lm}$ are respectively the average energy and linear momentum, and $M$ is a variable characterizing the system.

The micro-canonical probability distribution is given in relation to $M$, the solution of the Langevin equation, through : $\rho = \delta(m - M)$. The evolution of $\rho$ is given by

$$\dot{\rho} = -\dot{m} \frac{\partial \delta(m-M)}{\partial m} = -\frac{\partial (\bar{\rho}_{m})}{\partial m}. \text{This allows us to write} \rho(M, t) = \rho(M, 0) [e^{\int_{0}^{t} \frac{\partial (\bar{\rho}_{m})}{\partial m} |_{m=M} dt}].$$

Now we move to write an equation for the average distribution $P(M, t) = \langle \rho(m, t) \rangle$. Then we make use of the definition of $\dot{m}$ given in Eq. 1.1, and the correlation constraining $\bar{f}$ to write : $P(M, t) = e^{\int_{0}^{t} \frac{\partial \bar{f}}{\partial m} (-v + \Gamma k_B T \frac{\partial \varphi}{\partial m}) P(M, 0)}$. Consequently the change of $P$ as a function of time is given by Eq 1.2:

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial m}(-v + \Gamma k_B T \frac{\partial \varphi}{\partial m}) P(M, 0). \quad (1.2)$$

The steady state translates into $v = \Gamma k_B T \ln \frac{\partial P_{ss}}{\partial m}$. However, the distribution at steady state is related to the free energy through $P_{ss} = e^{-\varphi_{ss}}$. Therefore $v = -\Gamma \frac{\partial \varphi}{\partial m}$. This establishes an equivalence between the steady state of the Fokker-Plank
equation, and the Langevin equation. The argument allows us to specify the form of
the deterministic part in the Langevin equation, which led us to define the conjugate
force of the variable $m$ to be $-\Gamma \frac{\delta F}{\delta m}$. For a conserved system, $\Gamma$ becomes an operator,
such as $\Gamma \rightarrow (-\Gamma \nabla^2)$.

1.5 Mean Field

In a mean field formulation of a multiple phase system, $\phi$ will parametrize the
coexisting phases, in each of which it will assume a constant value. The free energy
density can be expanded in powers of the field: $f(\phi) = \Sigma a_n \phi^n$, assuming the
analyticity of $f(\phi)$. This expansion should guarantee that the values of $\phi$ character-
izing the phases minimize $f$, and that all the symmetries of the system are incorpo-
rated. The free energy density allows the construction of the energy functional via
$F = \int f(\phi) d^d x$. Then a variational differentiation is carried out with respect to $\phi$
allowing us to write its conjugate force $\frac{\delta F}{\delta \phi}$. The latter controls the dynamics of $\phi$
through this generalized equation [46]:

$$\frac{\partial \phi}{\partial t} = (-1)^{n+1}(\nabla^2)^n (\frac{\delta F}{\delta \phi}).$$

(1.3)

which reduce to the conservative and non-conservative dynamics in the case where
$n = 1$ and $n = 0$ respectively. This is the premise of this Ginzbrug-Landau formalism.
The phase transition that the system undergoes is driven by the local equilibrium
free energy that determines the dynamics.

The mean field treatment assumes that the fluctuations about the mean are
negligible. This is a valid approximation in many cases of first order phase transitions.
However in second order phase transitions, fluctuations become important, and the
Ginzburg-Landau energy functional $F$ should be amended with terms that are powers of $(∇φ)$.

$$F(φ, ∇φ) = \int [F(φ, 0) + \vec{L} \cdot ∇φ + ∇φ \cdot K∇φ + ...] d^d x,$$

where $\vec{L} = \frac{∂f}{∂(∂φ/∂x)} = 0$ since the free energy should be independent of the choice of coordinate system. While $K_{ij} = \frac{∂^2 f}{∂(∂φ/∂x_i)∂(∂φ/∂x_j)} = K_{ji}$, and $F(φ, 0) = \Sigma a_n φ^n = f(φ)$.

The latter equation can now be written :

$$F(φ, ∇φ) = \int [Σa_n φ^n + ∇φ \cdot K∇φ] d^d x.$$

Depending on the nature of the field, the dynamics will either be conservative, or non conservative, however the field will be driven in either cases by its conjugate force $∇(\frac{δF}{δφ})$, and $(\frac{δF}{δφ})$ respectively.

To make things clearer, an analogy with a binary system is presented. The Ising model makes use of a discrete variable, $s = 0 \text{ or } 1$, that quantifies the total magnetization, and is a good representation for binary systems [46]. Its Hamiltonian in the presence of an external field $H$, in two dimensions can be written as such:

$$\mathcal{H} = \Sigma_i \Sigma_{j \neq i} s_i(1 - s_j) + H s_i,$$

where the sum is over all spins $n$. Now noting that the first term can be written as follows :

$$\Sigma_{j \neq i} s_i(1 - s_j) = \Sigma_{j \neq i} ((s_i - s_j)^2 - (s_i + s_j)^2 + 2s_i)/2.$$

and considering the nearest neighbors interaction, the last equation is then :

$$\Sigma_{j \neq i} (s_i - s_j)^2 - (s_i + s_j)^2 + 2s_i)/2 \approx \frac{a^2}{2} \frac{(s_i - s_j)^2}{a^2} + \frac{(s_i - s_l)^2}{a^2} + \frac{(s_i - s_T)^2}{a^2} + \frac{(s_i - s_B)^2}{a^2}
= \frac{a^2}{2} |∇s|^2.$$
Where R, L, T and B denote the right, left top and bottom nearest neighbors. Additionally, going from the discrete representation to the continuous one is done by changing $\sum_i \rightarrow \int \frac{d^d x}{a^d} = \int \frac{dV}{a^d}$ which together with the above manipulation give:

$$F = \int (\frac{1}{2} |K \nabla s|^2 + hs(1 - s) + Hs) dV$$

where $h = \frac{1}{2an^2}$ is equivalent to the energy per unit volume, $K$ is the energy per unit length. Then the interface width is given by $\xi = \sqrt{\frac{K}{h}}$.

Having constructed the functional encompassing all symmetries, interactions and external fields, the dynamics of $s$ can be derived. The change in the order parameter is proportional to its conjugate force. Identifying the latter as $\frac{\delta F}{\delta s}$, which is set by the nonconservative nature of the field, we obtain a partial differential equations, given by Eq. 1.3, where for a nonconserved field $n = 0$. $s$ being the magnetization, it is clearly a non conserved quantity, and therefore the equation of motion is:

$$\frac{\partial s}{\partial t} = K \nabla^2 s - (1 - 2s) - H.$$

### 1.6 Phase Field Method

Modeling microstructures’ evolution is a challenging task, and the prevailing technique was the sharp interface method, where the area dividing the system’s phases is regarded as a sharp boundary. The velocity of the interface, separating the phases, is specified by the boundary condition, and this involves instantaneous tracking of the moving surface. For such problems, numerical methods are required to replicate the physical aspect of the dynamics. However, this is a numerically exhaustive task in which the interface must be explicitly traced. On the other hand, a diffuse interface method offers a more tractable approach to the arising complexity.
The method can be generalized to systems with coexisting phases in the presence of an interface, where the details of the phase transition give rise to the dynamics of the boundary. The complexity of problems involving the phase transition lies in the interdependence between the solution and the boundary condition. These are called free-boundary problem, and only a handful of them can be solved analytically. Therefore numerical schemes have been devised to tackle that category of problems. Instead of the instantaneous tracking of the boundary, as is the case in the sharp interface method, the phase field method is introduced as a diffuse interface method, which reduces the complexity of the treatment to the dynamics of \( \phi \), governed for example by Eq. 1.3. A continuous change in its value designates the locus of the interface, and one need not undertake explicit boundary tracking.

It makes use of the fact that on the mesoscopic level, most materials are heterogeneous. These microstructures are composed of domains, which are set apart by their sizes, orientations, and chemical compositions. They control the mechanical as well as the physical properties of the material under scrutiny. However those microstructures are often metastable or unstable structures, and are continuously changing. Therefore continuous variables are assigned to the microstructure to describe the phases, the time evolution of which traces the changes the systems undergoes.

The computational time scales with the size of the interface following this relation \( t \propto \xi^{-d} \) where \( d \) is the space dimension. Therefore by increasing the width of the interface one gains efficiency, at the expense of accuracy. The latter is lost when the interface becomes broader, and some details are lost as shown in Fig. 1–2, 1–3. This can be overcome by the use of adaptive meshing algorithms.
This method has numerous applications, including solidification models, phase transitions, grain growth, coarsening, thin films and surfaces, crack propagation and so forth. The work we present generalizes the method, by making use of it in the context of living systems.

Phase field models are built to replicate the dynamics of an interface depicted by a sharp interface limit. In the limit where the interface width is much smaller than physical lengths of interest, the phase field formulation must reduce to the former. The later is recovered by expanding in powers of the interface’s nondimensionalized width, which is the ratio of the interface width \( \xi \) to the relevant physical length \( l \). The expansion is carried out in the interfacial region, which is called the inner expansion, and in the bulk, denoted by the outer expansion, and then the matching is performed order by order.
Figure 1–3: The order parameter varies sharply at the interface, whereas it varies smoothly in the diffuse interface method [48].

This leads to a partial differential equation, augmented by a set of boundary conditions. When compared with the sharp interface limit, this defines the values of the parameter of the phase field model.

1.7 Modeling Biological systems

Now that we have introduced the key physical notions that are pertinent to our treatment, we move on to show their connection to the biological systems that we are interested in modeling. Cell motion is the governing theme of those systems. The cell undergoes morphological changes as it moves, reflecting significant deformations of its membrane.

Typically, the cell’s interior and exterior can be seen as two different phases of the same material, and consequently a field $\phi$ can be attributed to the system. The phases are set apart by assigning different values of $\phi$; this is how the distinction will
be made between the cell’s interior and exterior. Those values of \( \phi \) should minimize the free energy, we therefore choose them to be \( \phi = 1 \), and \( \phi = 0 \) to characterize them respectively. Additionally, the presence of the interface will be mathematically incorporated in the description as a smooth transition between the values of the field.

### 1.8 Free-Boundary Problems

To illustrate the robustness, yet simplicity of the method in the context of biological systems involving moving boundaries, we present a phase field model involving diffusion between intra and extra-cellular domains [4], augmented with a no-flux boundary condition, in Dictyostelium amoeba following a chemo-attracting cyclic stimulation. The chemoattractant concentration \( c \) obeys:

\[
\frac{\partial c}{\partial t} = D \nabla^2 c,
\]

subject to \( n \cdot \nabla c = 0 \) at the boundary, where \( n \) is the unit vector normal to the surface.

First, we consider the case of a stationary boundary, where the cell’s domain defined between \( x = -a \), and \( x = a \) is given by \( \phi = \frac{1}{2} + \frac{1}{2} \tanh\left(\frac{a-x}{\xi}\right) \), and \( \xi \) is the width of the interface.

Alternatively, we restrict the validity of the diffusion equation to the previously defined domain, and rewrite it in a way that will incorporate the no-flux boundary condition. This phase field formulation provides an alternative to the boundary tracking technique, which was done by defining a modified diffusion equation [4]. We hereafter show their equivalence:

\[
\phi \frac{\partial c}{\partial t} = D \nabla (\phi \nabla c).
\]
This equation is derived from the functional $F(\phi,c) = \int \frac{1}{2} (\phi \nabla c)^2 dV$, by taking $rac{\partial c}{\partial t} = -\Gamma \left( \frac{\delta F}{\delta c} \right)$, and setting $\phi = \frac{1}{\Gamma}$. Now, integrate the modified diffusion equation at the boundary:

$$
D[\phi \nabla c] \bigg|_{a+\xi} - D[\phi \nabla c] \bigg|_{a-\xi} = \int_{a-\xi}^{a+\xi} \phi \frac{\partial c}{\partial t} dx = -v \int_{a-\xi}^{a+\xi} \phi \frac{\partial c}{\partial x} dx + O(\xi).
$$

However, $D[\phi \nabla c] \bigg|_{a+\xi} \approx 0$, since $\phi(a + \xi) \approx 0$. Also noting that $\phi(a - \xi) \approx 1$, and that $c$ is continuous, allow us to write the above equation as:

$$
D[\nabla c] \bigg|_{a-\xi} \approx O(\xi).
$$

which in the limit of a sharp interface $\xi \to 0$ is nothing but the no flux boundary condition.

A similar treatment is used in modeling wave propagation in realistic heart geometries [5], to study the transmembrane potential dynamics. This is an example of a moving boundary condition, driven by a velocity that depends on the value of $c$ at the interface, the equation of $c$ has to be augmented with the term $\phi \cdot \nabla c$, along with an equation governing the dynamics of $\phi$. We now assume for simplicity this to be conservative, that is $\frac{\partial \phi}{\partial t} = \Gamma \nabla^2 \frac{\delta F}{\delta \phi}$, where $\Gamma$ is the mobility, and $F = \int [\epsilon \frac{1}{2} (\nabla \phi)^2 + f(\phi)] dx$. Here $\epsilon$ is proportional to the surface tension, and $f(\phi)$ is a polynomial with homogeneous state $\phi = 1$, and $\phi = 0$. Writing the system in one dimension, we get:

$$
\begin{align*}
\phi \frac{\partial c}{\partial t} &= D \nabla \cdot (\phi \nabla c) + \phi \cdot \nabla c. \\
\frac{\partial \phi}{\partial t} &= \Gamma \nabla^2 \frac{\delta F}{\delta \phi}.
\end{align*}
$$

(1.4)

The boundary condition can now be recovered similarly:
\[
D[\phi \nabla c]_{a+\xi} - D[\phi \nabla c]_{a-\xi} = \int_{a-\xi}^{a+\xi} \phi [\frac{\partial c}{\partial t} - \nabla c] \, dx.
\]

\[
D[\nabla c]_{a-\xi} = c \Big|_{a-\xi} + O(\xi).
\]

Here the change in the concentration is proportional to the value of the concentration at the interface. This example shows that the phase field allows one to incorporate the boundary condition in its corresponding equation, without having to explicitly track its position; it is implicitly integrated in the governing equation. It is of particular interest to our problem, for the reason that the concentration at the boundary defines the velocity of the moving interface. However a more generalized, yet equivalent treatment of the problem will be presented for completeness.

The solidification of a pure substance [6], in which the latent heat defines the velocity of the boundary can be written as:

\[
\frac{\partial u}{\partial t} = D \nabla^2 u.
\]

subject to \( V = D (\partial_n u)_{-} - (\partial_n u)_{+} \), where \( u \) is the non-dimensionalized temperature defined as \( u = \frac{T - T_M}{L/c_p} \), where \( T \) is the temperature, \( T_M \) the melting temperature, \( L \) is the latent heat, \( c_p \) is the specific heat at constant pressure, and \( D \) is the diffusion coefficient. This is coupled to the liquid-solid order parameter \( \phi \) via:

\[
\begin{cases}
\frac{\partial u}{\partial t} = D \nabla^2 u + \frac{\partial \phi}{\partial t}, \\
\frac{\partial \phi}{\partial t} = \epsilon \nabla^2 \phi - f(\phi) - g_\phi \lambda u.
\end{cases}
\tag{1.5}
\]

where \( f(\phi) \) is the free energy, and \( g_\phi = \phi - \frac{2\phi^3}{3} - \frac{\phi^5}{5} \). Considering that \( \phi \) relaxes on a time scale much faster than \( u \), this allows us to write \( \frac{\partial \phi}{\partial t} = V \cdot \frac{\partial \phi}{\partial n} \), and \( \frac{\partial u}{\partial t} = V \cdot \frac{\partial u}{\partial n} \), which when replaced into Eq. (1.5), and integrated over the interface give:
\[ V - D(\partial_n u - \partial_n u) = V(u - u) = 0, \text{ given the continuity in } u \text{ at the interface. Then:} \]
\[ V = D(\partial_n u - \partial_n u). \]

This is a more generalized form of the moving boundary problem, in which \( V \) can be an arbitrary velocity, unlike that from the previous Dictyostelium example where \( V \) depended explicitly on the value of \( c(a - \xi) \).

Both treatments are equivalent, however we will be adopting the procedure followed in solving the Dictyostelium problem in tackling free boundary problems in this thesis.

1.9 Thesis Overview

Now that the theoretical framework has been introduced, we will present our original contributions. We will use the phase field method to model the motion of the neutrophil, a cell of the immune system, in response to external chemical cues. In addition, we present a model of the axonal growth resulting from reaction to attractants. These instigate growth cone protrusion mechanism allowing the formation of synaptic connections. In Chapter 2, we present the results of modeling the motion of a neutrophil as it detects the presence of an intruder cell, and show its morphological changes once it has been triggered. We also compare our result with experimental data using a time-lapse that shows the effect of chemotaxis on the neutrophil.

In Chapter 3, we use the method to model the growth of the axon, neglecting the internal underlying dynamics of actin. We present the two-dimensional as well as three-dimensional simulation of the growth triggered by a chemical cue. This is a mechanism termed chemotropism.
In Chapter 4, we adopt a simplified model for actin dynamics, and couple it to the previously formulated model of axon elongation. Therein, we make use of the phase field to include the moving boundary condition in the corresponding equations. This exercise shows the robustness of the method in solving free-boundary problem.

In Chapter 5, we present a generalized model for chemotaxis and chemotropism, from which all the results of this work can be derived. Finally in Chapter 6, we conclude by presenting our view on the limitations as well as the applicability of the method in the context of out-of-equilibrium systems.
CHAPTER 2
Neutrophil Morphodynamics

2.1 Introduction

Neutrophils, abundant in the blood stream, are part of the immune system first-responder cells to inflammations. The triggering by chemical cues, mainly Interleukin-8, is a process termed chemotaxis in which the cells are driven to the infection site in an attempt to neutralize what the immune system tags as an antigen. They have a diameter of $8 - 9\mu m$, and are the major component of the white blood cell population. Their shape remains approximately spherical in their non-operative mode, that is when they flow in the blood stream not subject to any alert or chemical signal. In that state, their lifespan is around 4 days on average, while it becomes 2 days subsequent to their activation.

Following activation, they morph into peculiar non-spherically shaped cells, and begin migrating. Their motion is accompanied by a continuous change in their configuration. The movement is due to their ability to detect the slightest chemical gradient in the medium induced by specific mediators. These mediators first instigate a polymerization mechanism at the leading edge of the cell, which together with an active cytoskeleton make the immobile neutrophil gain movement and cause its motion up or down the gradient, and drive it to the site of infection [8].
This remarkable activity of the neutrophil is a by-product of two consecutive mechanisms: the polymerization and actin dynamics. The first mechanism is a sensing process and is realized by reordering or activating lipids or proteins, in the plasma membrane, which then set a favorable direction for the cell’s motion. Moreover, it prevails when the cell is immobile suggesting its capability of performing spatial sensing [9] in a stationary condition [10][11][12]. The cell then needs an actin cytoskeleton in addition to the latter mechanism that biases its motility. The latter is a network of proteins with dynamic structure responsible for locomotion. A linear sensitivity to the chemical gradient detected by the cell sets the velocity field.

Experimental observations confirmed that neutrophils do chemotax, however the mechanism by which they move is still the subject of debate. In 1974, Zigmond [13] questioned the hypothesis of temporal sensing, in which cells are capable of measuring and comparing concentrations at successive times, which requires a single receptor at the cell’s membrane. He confirmed the premise of spatial sensing, that involves at least two receptors that enable the cell to detect gradients across its dimension. Additional investigations by Maher [14] and Wilkinson [15] confirmed the effect of the chemical gradient on the speed of the cell, a process termed chemokinesis.

A mathematical model of this behavior dates back in 1971 [16]. Keller and Seggel suggested an explanation of chemotaxis using a diffusion-convection model, where the velocity was related to the chemical concentration. Single cell models were also built to understand the cell’s motility and adhesion. In the model suggested by Hammer, the cell was modeled as a hard sphere covered with adhesive springs. It
succeeded in reproducing many observed mechanical properties. Those were also shown to be linked to the deformations the cell undergoes [17].

As well a fluid mechanistic approach was developed to model the motion, in which the cell was seen as a liquid drop [18]. The morphology was identified as a factor that controls the cell’s properties. The former was coupled to one of the cell’s intracellular properties: the lamellipodia extension and retraction’s oscillatory cycle.

The intricacy of modeling their motion lies in the dependence of their dynamics on a moving boundary; they exhibit notable changes in their membranes as they move towards the target. This falls in the category of free boundary problems and can be tackled using the phase-field method. It grounds itself on partitioning space into regions, each assigned a value of a field \( \phi \) characteristic of the distinct phases present in the system, and thus reduces the complexity of the treatment to the dynamics of \( \phi \). The governing partial differential equation can be attained by a variational method applied to the functional describing the physical system. To model the neutrophil dynamics, a quantity distinguishing between the cell’s interior and its surrounding needs to be identified. It will be denoted by \( \phi \), and assigned a value of 1 and 0 for the interior and exterior of the cell respectively, and a smooth transition between them on the interface. The functional will have a bulk free energy, a term accounting for interaction between the phases, and an applied external field. The cell will be tracked and alteration in its membrane will be captured.
2.2 The System’s Functional

The introduction of the phase field in the context of neutrophil dynamics serves as a visualization tool for the cell’s morphology and time evolution. The phase field is a measure by which the physical and mechanical properties of the system can be modeled. The cell and its environment have obvious dissimilarities on the macroscopic level, reflecting underlying differences on the mesoscopic one. We can conveniently divide functions between the intracellular and extracellular domains by assigning nearly constant values to a prescribed field in the bulk of these domains; the interface corresponds to a narrow region where the phase field undergoes a smooth transition between the bulk values.

This behavior is captured by the free energy functional. Specifically, the free energy density, as we have shown, is a Taylor expansion in powers of $\phi$, typically chosen to be a double-well function. In addition, a term accounting for the presence of the interface is reflected by including an expansion in powers of $\vec{\nabla}\phi$ in the equation of the functional. However the system must be invariant under space transformation, that is when $\vec{x} \rightarrow -\vec{x}$, where $\vec{x}$ is the space variable; this forces the coefficients multiplying the odd powers of $\vec{\nabla}\phi$ to vanish.

The neutrophil moves under the effect of a chemical cue. Its contribution can be accounted for in the construction of the functional by the introduction of an external field. These properties suffice as a minimal model to accurately portray the dynamics of the neutrophil [7].

In order to limit the values of $\phi$ to 0 and 1, a bulk free energy of the form $f = a\phi^2(1 - \phi)^2$ was introduced. The term $(\nabla\phi)^2$ will account for the interaction
between different phases of the system, mimicking heterogeneity and hence giving rise to a surface tension. Finally, the external field will be denoted by $H$ and will be related to the concentration of the chemical attractant. The free energy is of the form:

$$\mathcal{F} = \int \left[ \frac{\epsilon (\nabla \phi)^2}{2} + a \phi^2 (1 - \phi)^2 + H \phi \right] dV. \quad (2.1)$$

where $\epsilon$ is proportional to the surface tension.

The cell’s volume conserving dynamics implies $\phi$ is conserved. Therefore its rate of change should be related to a flux $J$. However this flux is proportional to its conjugate force $\nabla \frac{\delta \mathcal{F}}{\delta \phi}$. Therefore it is governed by Cahn-Hilliard like equation

$$\frac{d\phi}{dt} = \Gamma \nabla \cdot (\nabla \frac{\delta \mathcal{F}}{\delta \phi}).$$

The material derivative of $\phi$ is related to its partial derivatives with respect to time and space via: $\frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v \cdot \nabla \phi$, where $v$ is the velocity.

Furthermore, a linear sensitivity to the chemical attractant is assumed. The velocity vector $v = b \cdot \nabla c$ is presumed to be proportional to the gradient of the attractant’s concentration $c$, and controlled by the presence of an active actin cytoskeleton through $b$. This proportionality constant $b$ is non-zero, and reveals the existence of a functional actin mechanism. It is zero otherwise, and subsequently no motion is induced. This assumption follows because the dynamics of actin, once triggered, is fast compared to the other mechanisms. Therefore, its concentration in the cell is assumed to be the constant $b$. This approach is a simplification of a complex regulation mechanism between the detachment of myosin from the rear of the cell and polymerization of an actin network at its leading edge [19] [20].
Adding to the functional an external field contribution, the partial differential equation for $\phi$ can now be written as:

$$\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 (\epsilon \nabla^2 \phi - f_{\phi}) - b \cdot \nabla \phi + \Gamma \nabla^2 H$$

where $f = a(1 - \phi)^2$, and $f_{\phi}$ is its derivative. To guarantee the conservation of $\phi$, we note that $\Gamma \nabla \cdot (\nabla H) = -b\phi \nabla^2 c$, which then allows us to write $\frac{\partial \phi}{\partial t} = -\nabla \cdot G$, where $G$ is given by the following equation $G = \nabla \cdot [\Gamma (\epsilon \nabla^2 \phi - f') + b\phi \nabla c]$.

$$\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 (\epsilon \nabla^2 \phi - f') - b \nabla \cdot [\phi \nabla c] \quad (2.2)$$

A rigorous derivation of the equation is given in Appendix A. Following the dynamics of $\phi$ will allow us to track the cell, as well as the changes affecting its membrane under the effect of chemical signaling. This chemical gradient gains its functionality when the cell detects gradients as low as 1% across its dimension [13]. Also one crucial aspect in determining the level of orientation of the cell is the difference in the number of bound receptors across the cell’s dimension. Additionally if the cell receptors’ detachment speed is comparable to the mean of the concentration, then there will be an ultimate detection of the gradient. This latter mechanism was not incorporated within our model. However a similar concentration threshold was satisfied, equivalent to the condition of the fulfillment of 1% gradient across the cell’s dimension.

This then induces a heightened responsiveness at the front, and a reduced one at the back of the cell. However in the case of a change of the gradient’s orientation, the cell, rather than reorganizing its leading edge to face the new direction, drifts
in U-turns to direct itself towards the gradient. In order to include this feature, we introduce a field depicting the leading edge of the cell.

2.3 Polymerization Of The Leading Edge

The treatment described so far considers the cell’s interior as a homogeneous entity. This is very simplified as the internal structure is elaborate [21]. We therefore introduce another field which differentiates disparate regions within the cell’s interior, denoted by $\psi$, which will delineate the cell’s polymerized edge Fig.2–1. Experimental observations have shown that the site is persistently present in the region of the cell facing the highest concentration of the chemical cue, even in the absence of a functional actin cytoskeleton or cell’s motion [10]. Hence $\psi$ is localized near the cell’s membrane and is driven by the chemical gradient. It is initialized to 1 in that region, and to zero elsewhere. In order to derive the equation for the evolution of $\psi$, we add $\frac{\epsilon(\nabla \psi)^2}{2} + a\psi^2(1 - \psi)^2 + \frac{b\psi^2 \nabla \cdot (\phi \nabla c)}{2\Gamma'}$ to the equation of the functional Eq. (2.1), and note that the steady state of $\psi$ is reached when the cell attains the highest chemical concentration point. The choice of $\Gamma' \ll 1$ guarantees that the contribution of the term $\frac{b\psi^2 \nabla \cdot (\phi \nabla c)}{2\Gamma'}$ is negligible, and does not affect the conservation of $\phi$. Now $\psi$ is governed by $\frac{d\psi}{dt} = \frac{\partial \psi}{\partial t} + b' \phi \nabla c \cdot \nabla \psi = -\Gamma' \nabla^2 [\frac{d\psi}{dx}],$ which allows us to write:

$$\begin{align*}
\frac{\partial \phi}{\partial t} &= -\Gamma\nabla^2 (\epsilon \nabla^2 \phi - f'(\phi)) - b \nabla \cdot (\phi \nabla c) \\
\frac{\partial \psi}{\partial t} &= -\Gamma' \nabla^2 (\epsilon \nabla^2 \psi - f'(\psi)) - b' \nabla \cdot (\psi \phi \nabla c) \\
\frac{\partial c}{\partial t} &= D_1 \nabla^2 c - a_1.c.
\end{align*}$$

(2.3)

where $\Gamma$ and $\Gamma'$ are the mobilities of $\phi$ and $\psi$ respectively, $a_1$ is the chemical concentration’s degradation rate, and $D_1$ is the diffusion coefficient of the attractant.
The auxiliary field $\psi$ allows the incorporation of the turning of the cell as a whole, in order to have its leading edge face the new gradient’s direction, by adding an advective term to the equation of the concentration. Consequently this explains how the cell detects small changes, owing to the difference in sensitivity between the leading edge and trailing edges.

A closed form solution of the chemical concentration equation was attained. This allowed us to investigate the effect of multiple attractants, localized at different positions, on the cell’s dynamics.

A non-zero $b$ simplifies the complex regulation mechanism between the detachment of myosin and the polymerization of the actin network at the cell’s leading edge [19],[20]. This latter process occurs when the actin cytoskeleton is functional. We utilize a simplified approach where the dynamics of actin is assumed to be fast compared to other mechanisms.

The parameter $b$ acts as a switch for the cell’s motion. We respectively denote $c_{\text{max}}$ and $c_{\text{min}}$ the concentrations of the chemical cue at the cell’s leading edge located at $x$, and at its back located at $x - D_c$, where $D_c$ the cell diameter. Then we note that $c_{\text{max}} \propto e^{-\frac{x^2}{\xi}}$, and $c_{\text{min}} \propto e^{-\frac{(x-D_c)^2}{\xi}}$, where $\xi$ is the correlation length defined to be $D/v$, where $D$ is the diffusion coefficient of the chemical attractant, and $v = b\nabla c$.

Then we define the parameter $\delta = \frac{c_{\text{min}} - c_{\text{max}}}{c_{\text{max}}}$, to be the relative concentration difference across the cell’s dimension. Then we can write it as follows:

In the limit where $\frac{D_c}{\xi} \ll 1$, that is $\epsilon = \frac{D_c b \nabla c}{D} \ll 1$, $\delta \approx \frac{b \nabla c D_c (D_c - x)}{D} = O(\epsilon)$.

Hence the relative concentration difference across the cell’s dimension is small, which
induces an exponentially slow motion. However when $\delta = \mathcal{O}(1)$, which is satisfied when $\frac{D_x \delta \nabla c}{D} \gg 1$, the chemical gradient will drive the cell towards its target location.

Figure 2–1: This picture shows the agglomeration of actin at the leading edge of the cell [22].

2.4 Numerical Simulation

An explicit scheme was devised to solve Eqs. (2.3), which is a second-order accurate algorithm, whereas an Euler approach was used for the time derivative. The stability condition of the numerical scheme for the conserved model is given by the following inequality: $\frac{h_t}{h_x^2} < \frac{1}{2^{d+1}}$, where $d$ is the space dimension, $h_x$ is the space mesh size, and the time step size is $h_t$. A Guassian concentration was initialized to simulate the presence of a chemical attractant, and thus its gradient sets the velocity field. Also the field $\psi$ was initialized to $\Theta(-\nabla c \cdot \nabla \phi)$, where $\Theta$ is the Heaviside step
function. This mimics the emergence of structural changes in the plasma membrane, as seen in Fig. 2–1. This term is zero everywhere except at the region of the cell facing the highest chemical concentration, which is physically the locus of the plasma membrane.

The model was solved in 1D, 2D and 3D, and Fig. 2–2,2–3 are illustrative examples. The field $\phi$ shown in red in Fig. 2–3 tracks the neutrophils as it migrates towards the site of infection. Similarly in Fig. 2–2, the cell as well as its polymerized regions are followed in 2D.

Figure 2–2: The order parameter $\phi$, in orange, shows the evolution of the neutrophil as it moves towards the highest chemical concentration point, while the auxiliary field $\psi$ shown in red, characterizes its polymerized region.

Fig. 2–4 shows the response of a neutrophil to a chemical attractant diffusing in the medium, and inducing the crawling motion accompanied by the shape deformation of the cell. This can be seen in the three dimensional simulation of Fig. 2–3 where the cell migrates to the site of the highest chemical attractant concentration.
Figure 2–3: Multiple snapshots of the neutrophil’s motion are shown. The order parameter $\phi$, depicted in red, is traced at different positions in space, as the cell crawls its way to the highest concentration point.

Figure 2–4: Morphology of an active neutrophil in response to micropipet containing N-formyl-met-leu-phe localized at the white dot
showing the morphology alteration seen in physical systems Fig. 2–4. Additionally, Fig. 2–4 depicts the polymerized leading edge of the neutrophil, shown in red.

2.5 Velocity Field

Choosing the proper reference point is somewhat complicated. The neutrophil is not moving as a rigid body; different constituents and regions show dissimilar speeds. The leading edges moves at a different velocity than the rear of the cell owing to the fact that $v$ is proportional to the chemical gradient. We have decided to track its progress as a function of space.

For that purpose, a digression should be made regarding $v(\vec{x})$. Primarily, there are two approaches to track the motion in a flow, a Lagrangian and an Eulerian. The first follows the trajectory of a tracer, and marks the spatial changes of the quantity as time advances. For the second, we assume a fixed position in space at which the flow is computed. In what follows, we will adhere to the second definition, and find the flow at each mesh point in our domain as time elapses.

The one-dimensional version of the model was simulated, and the velocity field of the domain is plotted in Fig. 2–5. The initial position of the neutrophil is taken as a reference. The velocity showed a decaying behavior that fit to an exponential curve $v(0)e^{-\frac{\xi}{\lambda}}$. This result was carried out on a single experimental set up, and it is worthwhile confirming it on a larger, statistically more significant data set. Our study limited itself to the theoretical aspect in trying to model this biological system.

A velocity profile of that form hints that the dynamics is governed by a linear differential equation, since it was shown to be an exponentially decaying curve.
Assuming a predominantly diffusive dynamics for the chemical attractant concentration, and using $v = \nabla c$, Eq. (2.4) can be derived. Then, the dynamics of $v$ obeys:

$$\nabla^2 v + \frac{2}{l} \nabla \cdot v = 0.$$  \hspace{1cm} (2.4)

The explicit computation of the equation is carried out in Appendix A. The quantity $l$ in Eq. (2.4) is a diffusion length, expected to be $2\sqrt{D \cdot t}$. The solution Eq. (2.4) is an exponentially decaying curve, with decay scale $\frac{l}{2}$. The latter should be equal to the value of $\xi$ that fit the curve in Fig. 2–5. For that reason, a computational check was done to confirm the results. Taking $D = 1$, and $t = 11.55$, then the expected value of the diffusion length is $l_{expected} = 2\sqrt{D \cdot t} \approx 6.8$. On the other hand, the value of $\xi$ that fitted the data of the simulation for those chosen parameters was $\xi \approx 3.2 = \frac{l}{2}$, leading to $l = 6.30$ which agrees approximately with the value $l_{expected}$. Therefore,
this shows that the cell undergoes a predominantly diffusive motion despite the non-linearities present in the equation of motion of \( \phi \).

In order to test the validity of our results, a time-lapse video showing the motion of the neutrophil in response to a chemical cue was analyzed, and the velocity was measured at different locations following the cell’s motion. It shows an exponentially decaying behavior \( v(x)_{\text{experimental}} = v'(0)e^{-\frac{x}{\xi}} \). This verified our claim that the motion is predominantly diffusive. Additionally, this allowed us to retrieve the value of the diffusion length, \( l_d = 2 \times \frac{1}{\xi} \), as well as the diffusion coefficient \( D' = \frac{l_d^2}{2t'} \), where \( t' \) denotes the time needed to reach the steady state.

In Fig. 2–6 both the non-dimensionalized velocities were plotted as a function of the ratio of distance to half the diffusion length \( X = \frac{x}{\sqrt{D' t'}} = \frac{x}{\xi} \). The dots show the velocity of the cell at different positions predicted by our model, while the stars show the actual in vitro velocity of the neutrophil. This again gives good the perfect agreement of our results with experimental observations.

2.6 Other Mathematical Models

The one dimensional version of our model was implemented, and compared with the Keller and Segel minimal one-dimensional model (Eqs. 2.5). The latter expects cells to aggregate at the location of the zero chemical gradient, where the cell density shows a sharp boundary peak [23]. The equations of motion are:

\[
\begin{align*}
    u_t &= \nabla^2 u - \xi \nabla(u \nabla v) \\
    v_t &= \nabla^2 v + (u - 1).
\end{align*}
\]
Our model follows the evolution of a cell with linear sensitivity to chemical cues. A sharp peak is observed at steady state (Fig. 2–7), mimicking that of the model. Furthermore, the model exhibits a finite time blow up for dimensions $d \geq 2$, which are, in contrast, successfully portrayed by our model (Eqs. 2.3).
Efforts for to ameliorate this weakness of Keller and Segel’s model have been made [25]. Some other phenomenological models neglect the underlying workings at the molecular level, and focus on the individual or collective cell population behavior. They argue the direction of motion depends upon phenomenological parameters such as motility, or speed [24]. Other works have studied the persistence time, the time spent by the cell moving in a given orientation. Langevin’s Brownian motion models have been developed to depict the routes of single cells [26, 27, 28], based on the notion of persistence time.

However at this stage, we cannot predict how the neutrophil react in the case of multiple signals, and how the prioritization is made. We will however present in the coming section a possible mechanism by which the cell dynamically reacts in such situations.

2.7 Chasing a Bacterium

In this section, a full model will be built incorporating further features of the cell’s directional motility. First, the cell detects a chemical attractant, signaling the presence of an intruder cell. The cell then polymerizes accordingly and start moving up the gradient to neutralize the intruder. As the neutrophil moves, it secretes a chemical repellant felt by a sensing mechanism endowed to the chased cell [29]. Therefore, the latter’s velocity has the opposite sign of the chemical repellant’s gradient. Both the cues diffuse through the extracellular medium and their dynamics are governed by appropriate equations of motion. Their concentrations change with the cells displacements, following:
where \( \phi_1 \) and \( \phi_2 \) respectively denote the neutrophil and the chased cell’s fields, and \( c_i \) their respective attractant or repellant concentrations. \( \psi \) denotes the field of polymerized region of the neutrophil. \( \gamma_i \) is the mobility, \( \epsilon_i \) is the surface tension, \( D_i \) the diffusion coefficients, \( d_i \) sets the proportionality to chemical cue, and \( e_i \) is the degradation rates (for \( i = 1, 2 \) and 3), \( b_i \) was previously defined.

The model does not incorporate the target cell neutralization. This would involve a varying degradation rate of the chemical attractant reflecting the cessation of its production following the cell’s death.

### 2.8 Counteracting Velocity Fields

The cell’s morphodynamics accompanying its motion are controlled by a unique velocity field that simulates the presence of a chemical attractant. Therefore, at this stage it is natural to investigate the effect of more than one attractant located at different positions in space.
Figure 2–8: The neutrophil and the chased cell’s fields are both shown in the figure. The big cell, the neutrophil, experiences changes in its morphology as it moves and tries to capture the smaller one, the intruder cell.

The analytical solution, $c(x, t) = C \sqrt{\frac{m}{m+4D_1t}} e^{-a_1t} e^{-\frac{(x-x_0)^2}{m+4D_1t}}$, of Eq. 2.3 is given in Appendix A. Noting that $\frac{(x-x_0)^2}{m+4D_1t} \ll 1$, the concentration can be Taylor expanded. It behaves like a polynomial of order 2 in $x$.

In the $\phi$ equation of Eq. 2.3, the term $\nabla(\phi \nabla c) = \phi \nabla^2 c + \nabla c \nabla \phi$ requires interpretation. From the expansion, $\nabla c$ is approximately linear, and $\nabla^2 c$ has no $x$ dependence. Additionally, we argue that the linear term has a predominant effect,
since higher order terms are \( O(x^4) \ll O(x^2) \ll 1 \). Therefore, in the case of the presence of multiple attractant in the medium, \( \nabla c_i \) is calculated, where \( i \) is the chemical’s label. This is compared to other \( c_i \) in order to determine the dominating attractant.

For that purpose, we constructed a system where the neutrophil is under the effect of two chemical attractants located in the medium, we studied its behavior as a function of the ratio of \( \nabla c_i \). The governing equation is:

\[
(b \nabla c_1 + b_2 \nabla c_2) \nabla \phi = \left[ -2b_2 C \left( \frac{x-x_0}{m+4D_2} \right) e^{-a_2 t} - 2bC \left( \frac{x-x_0}{m+4D_1} \right) e^{-a_1 t} \right] \nabla \phi
\]

Then, up to \( O(x^3) \):

\[
\frac{b_2}{b} > -\frac{\nabla c_1}{\nabla c_2} = \Delta(x,t).
\]

The \( \Delta(x,t) \) equation defines a surface in the \((x,t)\) space, and according to the relative position of the ratio \( \frac{b_2}{b_1} \) to the curve, two behaviors were reproduced. One in which the neutrophil followed \( c_1 \) a gets attracted to the site where it is located, when \( \frac{b_2}{b_1} < 0 \), while in the other the cell followed \( c_2 \) when the inequality is reversed. In what follows we show snapshots portraying both behaviors. Fig. 2–10(a–d) show the the motion when \( c_1 > c_2 \), whereas Fig. 2–10 (e–h) show the opposite.

The model presented by Stokes [27] suggests that the mechanism of prioritization in the case of the presence of multiple chemoattractant is related to the number of bound receptors, which is itself linearly dependent on the concentration of the chemical cue. That is, the number of receptor-lingand complexes is responsible for biasing the motion in one direction rather than another. This is modeled by setting the appropriate ratio of \( b \) to \( b_2 \). This encodes the number of bound receptor, the asymmetry in the cell, and controls the position of the leading edge, and thus the
Figure 2–9: The figure shows the curve that defines the predominant chemical, above which the cue defined by $c$ will attract the cell towards its zero gradient.

 initialization of the $\psi$ field. Therefore, the definition of $b$ not only expresses the presence of an active actin cytoskeleton, but it also guides the cell towards the dominant chemical attractant.
Figure 2–10: Two scenarios of motion are shown in the presence of counteracting velocity fields. Figures a-b-c the cell is lead to the upper left corner while, d-e-f it is lead to the lower right corner.
2.9 Degradation Rate Effect

The chemical attractant degradation rate $a_1$ was shown to have a pivotal role in the dynamics of the cell. Generally, if $a_1$ is fast compared to the speed of the neutrophil, then the latter will move for some time, but it will soon be located outside the domain of attraction of the cue. Therefore we showed rigorously how the speed of the cell, in relation to the degradation rate, induces a motion that leads the cell to its target position. The leading edge of the cell should be moving with a velocity faster than that of the concentration: $\min(b \cdot \phi \cdot \nabla c) > \frac{dc}{dt}$ as shown in Fig. 2–11. The minimum allows the depiction of the cell’s leading edge; the closer the cell is to the target, the smaller the gradient. The above condition is translated as a condition relating the parameters:

$$a_1 > 2(x - x_0)b - \frac{2D}{(m+4D\eta)^{3/2}} + \frac{D(x-x_0)^2}{(m+4D\eta)^2}.$$  

This defines a curve in three dimensions, and if $a_1$ lies above it then the cell will reach its target position, otherwise it will move shortly and then stop.
Figure 2–11: Chemical concentrations level curves, with relative position to the cell \( \phi \).
2.10 Conclusion

The model presented here successfully portrays the motion of a Neutrophil induced by the presence of a chemical attractant. The one-dimensional model showed the same steady state solution as in previous work [16]. However, unlike the latter which exhibits a finite-time blow-up in dimensions $d \geq 2$, our model remains stable for all dimensions. When the chemical attractant concentration was coupled with the intruder cell’s field, a more complex model was built that captured the main features of the dynamics of a neutrophil’s chase. It depicts the morphological changes that the cell undergoes during the chase of a bacterium, as well as its ability to reorient itself in compliance with the position of the chased cell. This was confirmed by comparison to experiments. In particular the imaging of the directional sensing was captured. The image processing shows a high pixel intensity in the region of the cell that faces the highest chemical concentration [30]. Additionally, the cell is motile if clear-cut shape deformations are discernible, even without resort to time lapse procedures [31]. The appearance of a tail, a contracted region, indicates the posterior part of the cell, while the growing area marks its anterior. Tracking the neutrophil as it crawls allows one to find the velocity [32]. To additionally test for the validity of our model, we analyzed a time-lapsed video of the motion of the neutrophil.

The actin polymerization dominance over the retrograde flow was simplified, and is described by a constant which takes non zero values in that case, and zero when the cytoskeleton is not active. A more complex dynamics governs actin polymerization and thus a modification of the model to account for that process is a subject for a chapter 4. It is summarized in the following diagram in Fig. 2–12.
Figure 2–12: The underlying actin dynamics leading to polymerization of the cell’s leading edge [33].
CHAPTER 3
Neural Cell Growth

We now move to neural cell growth. The underlying mechanism responsible for the growth dynamics can be attributed to the presence of an active actin cytoskeleton and external chemical cues. A main distinction between the cell motion discussed in the previous chapter, and the neural cell should be noted before introducing the mathematical model [34]. Recall that chemotaxis is the action of driving the whole cell, by chemically defining its route. Chemotropism is the action of targeting a part of the cell by means of chemical mediators and cues, and subsequently delimiting the pathway that it will undertake. In a neural cell, this results in a rearrangement in the proteins and lipids of the plasma membrane to initiate axonal elongation. The latter being an interface puts the system in the category of free boundary problems. Therefore, the phase field method will be adopted to model growth in which chemotropic forcing is coupled to actin dynamics. Additionally, retraction of the axon is also portrayed, which takes place when the cell fails to form a synaptic connection.

Neural cell growth is attributable to two main mechanisms, one intracellular and another extracellular: the actin network formation, and the chemotropic driving. The former is indispensable for the filopodia protrusion at the growth cone, a process by which the latter explores its surroundings while seeking a synaptic connection. The motion of the growth cone is guided by cues, such as Netrins, Ephrins, and so forth. These will activate receptors which instigate the transport of actin to the leading
The active actin cytoskeleton will cause the axon to grow in the favored direction of motion [35][36].

The growth cone acts as a motor and detector for the neural cell, and is the region where most of the dynamics is taking place. It attaches to the extracellular matrix (ECM), an action that induces its intracellular processes, causing the filopodia’s forwards propulsion. The latter is gradually followed by engorgement and consolidation [36], and is directly linked to the actin dynamics, although not exclusively. In particular, F-actin, the constituent of the filopodia, is subject to an interplay between a retrograde flow and a polymerization responsible for the motion [37][36][38]. This happens when the growth cone clutches to the ECM causing the slowing down of the retrograde flow and allows the growth. Thus the adherence of the filopodia provides the necessary force for the movement. In addition to the growth cone-ECM complex, chemotropic cues steer the elongating axon through the medium.

The previously described interaction of the cell with the ECM is mediated by the plasma membrane, which is an arrangement of proteins and lipids responsible for signal transduction. Recent studies have shown a formation of micro-domains, lipid rafts, are confined to the region facing the highest chemical cue. The asymmetry in their localization is responsible for the growth cone pathway [39][40].

In trying to model the outgrowth of the axon, one faces the problem of the dependence of the dynamics on a moving boundary. Free boundary problems can be approached using phase field method, where the dynamics of an order parameter distinguishing the cell’s interior from its exterior can be tracked. Again, this can be
done by building a free energy functional $\mathcal{F}[\phi]$, from which the conjugate force of the field can be computed, that defines the equation governing the evolution of $\phi$ in time.

### 3.1 The Free Energy Functional

Analogous to the previous chapter, the field $\phi$ designates the neural cell, as well as its surrounding. Similarly, the dynamics of the rate of change in $\phi$, is controlled by a conjugate force. This requires the construction of a functional that encompasses all the features of the system. As was the case with the neutrophil, we require a free-energy density term, the minima of which designates the phases of the system. An external field plays the role of the chemical cue that sets the growth’s pathway. The interaction between the phases involves an expansion in powers of $\nabla \phi$ within the energy. The coefficient of the $(\nabla \phi)^2$ term is related to the surface tension. Recall that the functional of a binary system was given in the introductory chapter by:

$$\mathcal{F} = \int \left[ \epsilon \left( \nabla \phi \right)^2 + g(\phi) \right] dx,$$

where $g(\phi)$ is a double-well function. Again this is chosen to be $a\phi^2(1 - \phi)^2$. The steady state of the nonconservative dynamics of $\phi$ is given by $\frac{\delta \mathcal{F}}{\delta \phi}|_{\phi_{ss}} = 0$, where $\phi_{ss}$ is the steady state solution. This translates into $\phi_{ss} = \frac{1}{2}[1 + \tanh(\xi)]$, where $\xi = \sqrt{\frac{\epsilon}{a}}$.

We note that the surface tension [41] is given by:

$$\sigma = \int [\epsilon \left( \frac{\phi_{ss}}{dx} \right)^2] dx \propto \sqrt{\epsilon}$$

Then any anisotropy in the membrane should be included in the definition of $\epsilon$, which will bias the dynamics of the interface, and cause an inhomogeneity in the growth.

We further specify our choice of $\epsilon$ to address the elongation of the axon. A nuance between neuronal and non neuronal cells should be made. The spherical
shape of a cell is a result of a minimization of the surface area, mathematically equivalent to the minima of the free energy functional assuming constant surface tension. For a neural cell, however a force term in the functional allows for the axon to grow, which affects a region with zero surface tension. Therefore, in the case of a neural cell surface tension will no longer be homogenous, in view of the fact that the membrane itself witnesses a structural change.

A rearrangement in the proteins and lipids of cell’s plasma membrane is observed prior to motion [42][43][44]. This is where the protrusion force predominates and it is assigned an auxiliary field $\psi$, corresponding to phase separation, and describing the reorganization in the membrane. Also, this region is facing the highest chemical concentration $c$ which is responsible for the driving of the growth cone. The field was initialized as: $\phi = (1 + \tanh(x/\xi))/2$, whereas $\psi = \Theta(-\nabla c \cdot \nabla \phi)$, where $\Theta$ is the Heaviside step function. These choices of the fields will guarantee that $\phi$ smoothly changes between 1 and 0, the values it takes inside and outside of cell, respectively. Also $\psi$ is 1 at the leading edge and 0 elsewhere. The dependence of the cell on an active actin cytoskeleton gives rise to its response to external cues, and must also be incorporated so that the model captures the main features of the dynamics.

The surface tension will be zero in the region where the highest chemical concentration is, and where the field $\psi = 1$. Therefore $\epsilon \to \epsilon(\nabla c)^2(1 - \psi)$, and the functional was rewritten as such:

$$\mathcal{F} = \int \left[ \frac{\epsilon(\nabla c)^2(1 - \psi)(\nabla \phi)^2}{2} + g' \right] dV$$

where $g = a\phi^2(1 - \phi)^2$, and $g'$ is its derivative with respect to $\phi$. 

3.2 The Dynamics of The Fields

As the plasma membrane is persistent even in the absence of an active actin cytoskeleton, $\psi$ follows conservative dynamics, so that $\frac{d\psi}{dt} = \frac{\partial \psi}{\partial t} + v_{cone} \cdot \nabla \psi = -\Gamma' \frac{\delta F}{\delta \psi} \approx 0$, where we are considering the limit where this field’s mobility $\Gamma' \ll 1$, and $v_{cone}$ is the velocity of the growth cone, which must be proportional to the gradient of the chemical cue. We similarly obtain the time dependence of $\phi$ as $\frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v_{axon} \cdot \nabla \phi$, with $\frac{d\phi}{dt} = \Gamma \nabla^2 [\delta F / \delta \phi]$, where $\Gamma$ is the mobility, $F$ is defined in Eq. 3.1, and $v_{axon}$ is the velocity of the moving part of the cell. Equivalently, $v_{axon}$ the velocity of the axon which is led by the growth cone under the effect of chemical cues. Hence the governing partial differential equations are:

$$\left\{ \begin{align*}
\frac{\partial \phi}{\partial t} &= -\Gamma \nabla^2 [\epsilon (\nabla c)^2(1 - \psi) \nabla^2 \phi - g'] - v_{axon} \cdot \nabla \phi \\
\frac{\partial \psi}{\partial t} &= -v_{cone} \cdot \nabla \psi.
\end{align*} \right.$$  

(3.2)

It remains to obtain forms for $v_{axon}$ and $v_{cone}$.

Chemotactic effects give rise to the velocity $v_{axon}$ which must be mapped to the chemical cue concentration gradient, and coupled to the auxiliary field $\psi$. Additionally, the dependence of the cell on an active actin cytoskeleton is critical to its response to external cues. It should also be included so that the model captures the main features of the dynamics. Explicitly, the region driven by the chemical attractant is also the locus of the rearrangement in the plasma membrane. Therefore $v_{axon} = v_{axon}(\psi, \nabla c)$ should bear a dependence on the field $\psi$ as well as the
chemical gradient, and the underlying molecular processes give rise to the time dependence. Additionally, the latter together with the chemical concentration controls the cone’s velocity $v_{\text{cone}} = v_{\text{cone}}(\nabla c)$. To capture this, we define $v_{\text{cone}} \propto \nabla c$, and $v_{\text{axon}} \propto \psi \nabla c$. We utilize the fact that the concentration $c$ is slowly varying on the time scale of the growth. Hence it can be approximated as a time-independent Gaussian: $c \propto e^{-(x-x_0)^2/l}$, where $l$ is the width, and $x_0$ denotes the position of the highest chemical concentration.

The formalism described so far presumed the existence of a functional actin cytoskeleton responsible for the motion, and assumes no time dependence.

### 3.3 Actin Dynamics

The model should additionally portray the treadmilling effect in the actin dynamics. Our formalism presumes the existence of a functional actin cytoskeleton responsible for the motion, and the rate of actin flow to the leading edge controls the direction of motion of the axon and of the growth cone. The latter remains idle when the actin retrograde flow balances out the polymerization at the barbed end of the actin filament, leading to the treadmilling effect. Consequently the length of the polymer stays constant and no protrusion is detected. However, when the growth cone clutches to the ECM, inducing an attenuation in the F-actin retrograde flow, the filopodia protrudes and the growth cone advances.

These counteracting mechanisms can be modeled by introducing a time dependence in the definitions of the velocities. If polymerization dominates, then the actin filament will grow, and the axon together with the growth cone will move towards the target. Additionally, we assume that the polymerization is fast on the time scale
of the growth, and set $v_{\text{cone}} = \nabla c$ and $v_{\text{axon}} = \psi \nabla c$ as noted above. When actin is abundant, and can flow to the leading edge, these definitions are complete. However when actin becomes scarce, and the retrograde flow starts to dominate, a change in the direction of motion must be included. Further, when the rates of the retrograde flow and polymerization are equal, no motion is induced. For that purpose we introduce a simple switch $G(t)$, which changes velocity directions on a time scale assumed to be faster than the motion of the constituent phase fields. The switch has the following properties: $G(t) = b$ for time $t \leq t_{\text{target}}$, $G(t) = -b$ for $t_{\text{target}} < t < 2t_{\text{target}}$, and $G(t) = 0$ for longer times, where $t_{\text{target}}$ is controlled by the distance $d$ separating the tip of the cone from its target, as well as the choice of the chemical gradient. This is mathematically secured by noting $v_{\text{cone}} = \frac{dx}{dt} \approx a \cdot x$, from the lowest-order expansion of $c$. This then allows us to write $x = x_0 e^{at}$, where $x_0$ is the position of the tip of the growth cone. Finally this gives the critical time needed to reach the highest chemical concentration point as $\frac{1}{a} \cdot \log \frac{x_0 + d}{x_0}$. Then if $t_{\text{target}}$ equals or exceeds this time, the axon will make its synaptic connection, otherwise it will move forwards and retract as shown in Fig. 3–1.

Figure 3–1: The fields $\psi$ and $\phi$, depicted respectively in red and orange, show the two-dimensional growth of a neuron, followed by retraction.
This aforementioned dependence on actin, which is essential for protrusion, can be translated by mapping $v_{\text{cone}}$ and $v_{\text{axon}}$ to $G(t)$ displaying the interplay between polymerization and depolymerization of actin. Then $v_{\text{cone}} = \nabla c \cdot G(t)$, and $v_{\text{axon}} = \psi \cdot \nabla c \cdot G(t)$. Hence, if the period between growth and retraction is sufficiently long, the growth cone will make its synaptic connection before any switch in direction; otherwise the growth cone will advance forwards, followed by a retraction.

Now Eq. 3.2 can be written as:

$$\begin{cases}
\partial \phi / \partial t = -\Gamma \nabla^2 [\epsilon (\nabla c)^2 (1 - \psi) \nabla^2 \phi - g'] - G(t) \psi \nabla c \cdot \nabla \phi. \\
\partial \psi / \partial t = -G(t) \nabla c \cdot \nabla \psi.
\end{cases}$$

(3.3)

This set of partial differential equations will allow for protrusion as well as retraction, therefore portraying the interaction between the retrograde flow and the polymerization, as well as the lipid rearrangement at the leading edge.

We note that the definition of the velocities $v_{\text{axon}}$ and $v_{\text{cone}}$ are compatible. The dependence on $\psi$ in the definition of $v_{\text{axon}}$ reflects the exclusivity of the motion of the cell to its leading edge, while the soma remains at rest. This can be seen by noting that $v_{\text{axon}} = G(t) \psi \nabla c \approx G(t) \nabla c = v_{\text{cone}}$, where $\psi = 1$ and zero elsewhere.

Also the choice of $b$ being a constant, although it represents a dynamical process, can be justified by considering the relative growth rate to that of the filament at the leading edge. The movement rate ranges from $1\mu m/min$−$10\mu m/min$ [45]. At the same time, the rate of advance of the lamellipodium, which depends on the arrangement of profilin-ATP-G-actin at the leading edge due to polymerization, is
as quick as $10 - 100$ monomer per second. This is rapid on the time scale of the growth, and therefore the assumption that it reaches a steady state is valid. Although the distribution is not uniform [59], it shows a spatial dependence which can be approximated as a linear function of space. This follows from the definition of $\nabla c$. Therefore the chemical concentration in this formulation sets the direction of motion, and includes the effect of the profilin-ATP-G-actin concentration across the cell’s growing region, which we will show later to be responsible for producing the forwards motion. The concentrations of actin complexes at steady state are given in Fig. 3–2.

![Figure 3–2: The concentration of actin complexes at steady state.](image)

This shows that the concentration of actin complexes that causes the protrusion can be approximated by a linear function of space, which is shown in red in Fig. 3–2. Then our assumption that $v \propto \nabla c \propto x$ is equivalent to $v \propto a \propto x$. Now it
becomes clear that the velocity of the leading edge should have an orientation set by the gradient, which in turn, being proportional to $x$, includes the effect of the profilin-ATP-G-actin leading to protrusion.

### 3.4 Side Branching

To fully describe the neural cell, one needs to include in the formulation, in addition to the cell body and the axon, another dynamical part consisting of the dendrites. These are structures that branch along the axon or the cell body.

In order to conduct a signal, the dendrite must make a synaptic connection, and therefore a neural cell experiences multiple branching, responding to multiple signals. Those delineate the pathway of the dendrite and lead it to its target position.

To incorporate side branching we introduce other detected chemical concentrations, denoted with the index $i$, so that $\psi \rightarrow \psi_i$ and $c \rightarrow c_i$ giving:

$$
\begin{align*}
\frac{\partial \phi}{\partial t} &= -\Gamma \nabla^2 \left[ \epsilon (\nabla c_i)^2 (1 - \psi_i) \nabla^2 \phi - g' \right] - \Gamma(t) \psi_i \nabla c_i \cdot \nabla \phi, \\
\frac{\partial \psi_i}{\partial t} &= -\Gamma(t) (\nabla c_i \cdot \nabla \psi_i).
\end{align*}
$$

(3.4)

Consequently the parameter $t_{\text{target}}$ in the definition of $G(t)$ controls the velocity.

For dendrites $t_{\text{dendrite}} < \frac{1}{a} \cdot \log \frac{x_0 + d}{x_0}$, so the side-branches move forwards and then retract, unlike the axon that succeeds in making its connection where its $t_{\text{axon}} > \frac{1}{a} \cdot \log \frac{x_0 + d}{x_0}$.

### 3.5 Numerics

A finite difference algorithm was compiled to solve Eq. (3.4) in two and three dimensions. The stability of the scheme was guaranteed by choosing the proper ratio
of time to space step sizes; this is set by the following inequality \( \frac{h_t}{h_x} < \frac{1}{2^{d+1}} \), where \( d \) is the space dimension [46]. The chemical concentration was assumed to be a Gaussian, the range of which guarantees the contact with the cell’s plasma membrane, in order to invoke the rearrangement of its lipids and proteins, explicitly inducing a non zero \( \psi \).
Figure 3–3: The tip of the elongating axon of an embryonic cortical neuron [49] is tracked as it moves to the highest chemical concentration point.

Fig. 3–4 shows the solution of the three-dimensional version of the model at steady state. The aspect ratio of the width of the axon to the diameter of the cell was fixed to match the experimentally measured one, which is approximately 1/7. This was done by choosing a diffusion length of the chemical concentration that instigate a polymerized region with the appropriate diameter, controlled through $\psi = \Theta(-\phi \nabla c)$.
Figure 3–4: The cell's auxiliary fields $\phi$ and $\psi$ are respectively shown in yellow and red replicating a 3D neural cell growth.
3.6 Bifurcation Diagram

In the definition of the axonal velocity, as well as that of the growth cone, we have introduced the notion of $t_{\text{target}}$. Its choice has been shown to have an effect on the dynamical morphology of the neural cell. We have defined a critical value above which the cell gives rise to an axon that succeeds in reaching its synaptic connection, and below which it would retract. This was secured by the following combination of parameters $\frac{1}{a} \cdot \log \frac{x_0 + d}{x_0}$ showing its dependence on the distance separating the growth cone from the point of highest chemical concentration $d$, as well as the choice of the signal gradient controlled by $a$.

Additionally we have assumed that the definition of the velocity contains a dependence of the profilin-ATP-G-actin complex responsible for the motion through a linear term $ax$, incorporated in the description of $c$ which also controls the directionality of the growth. Therefore any change in the value of $a$ reflects a change in the concentration of actin at the leading edge, and translates into a control parameter responsible for the state of the axon.

Varying the concentration of actin to measure its effect on the maximum distance the axon reaches before starting to retract will allow us to determine the threshold value $c_{at}$. This signals a bifurcation in the dynamics of the cell’s morphology based on the value of $c_a = a$. The axon’s tip has therefore two fixed points: one at zero, and the other at the site where the chemical concentration is highest. The two fixed points, therefore interchange stability for values of $c_a > c_{at}$, which is a transcritical bifurcation.
Figure 3–5: Maximum forward distance traveled by the axon as a function of the choice of the chemical gradient $c_a$

Figure 3–6: Transcritical bifurcation depicting the change in stability
3.7 Velocity Field

A time lapse of a growing embryonic cortical neuron was analyzed, and the velocity of the tip was shown in Fig. 3–3. We measured the velocity of the leading edge of the $\psi$ field, and find it comparable to experimental data resulting from tracking the tip of the axon in Fig. 3–3. We tracked the tip of an elongating axon in the presence of a chemical cue, and calculated its velocity, as shown in Fig. 3–7. We found that $v_{\text{cone}}$ depends linearly on the distance, as expected.

![Graph showing velocity vs. distance](image)

Figure 3–7: The velocity of the tip of the axon is calculated for both an in vitro growing neural cell, and for that of a numerical simulation of our model, shown respectively in blue and red dashed line.

The red dashed line and the blue solid line in Fig. 3–7 are respectively the velocity versus distance, in units of cell diameter per second $d_c/s$, of our model and representative experimental data of an in-vitro growing neuron. The slope of the
blue solid line is about 33, while that of the red dashed line is approximately 39, showing that our model has faithfully captured aspects of neural growth.

3.8 Conclusion

The bifurcation in the dynamics of the tip shows that synaptic connections can be made if actin inside the cell is abundantly available. More precisely, if the retrograde flow is impaired, the rate of polymerization will predominate and axons can reach their target site. Mathematically this can be achieved in our model by imposing a long period for the velocity term responsible for the chemotropic effects. Additionally, this approach allows us visualize the growth, and track the motion of the tip of the axon along with the plasma membrane.
CHAPTER 4
Actin Dynamics Coupled to Phase-Field

4.1 Introduction

Early studies have shown that a correlation exists between the rate of forwards movement of the growth cone, which is responsible for the guidance of the axon towards its postsynaptic target, and its morphology. In particular, there is a link between the actin cytoskeleton, termed lamellipodium, the filopodia, the former’s cytoplasmic projections beyond its leading edge, and the shape dynamics [51, 52]. It has also been established that the growth cone witnesses a retrograde flow from its distal region to its leading edge. The flow consists of the formation of fine structures, lamellipodia and filopodia, followed by forwards projection of the latter, and subsequently by retraction.

These three stages were later identified [53] as protrusion, engorgement and consolidation. The experimental work of Yamada [54] produced evidence that related the outgrowth to microtubules and to the F-actin polymer. They exposed neural cells to cytochalasin B and colchicine, which respectively cause the depolymerization of F-actin and microtubules. The first induced a misdirection of the growth cone, while the second induced a retraction of the filopodia, consequently preventing the axonal outgrowth. These observations lead to the following conclusion: the F-actin provides the guidance mechanism, and the microtubules in the structural composition are
necessary for the elongation. Additionally further studies were carried out to study
the interplay between the two mechanisms.

The actin network, the main component in the filopodia’s cytoskeleton, is re-
sponsible for producing the protrusion force at the leading edge of the cell, and
therefore constitutes the motor element in the growth cone’s search for synaptic
connections. The underlying dynamics controlling its formation are complex and
intertwined. There exist over twenty proteins that can bind with actin. These actin
binding proteins can be grouped into categories depending on their functions.

There is the type of actin binding protein that binds the actin monomers, that
which caps the barbed end, which is the region pointing towards the cell’s mem-
brane, or which caps the positive end. Other proteins function as anticapping at the
barbed end. In addition, there are those which detach F-actin, and those responsible
for anchoring the F-actin to specified regions of the cell’s membrane. Modeling the
orchestration and regulation of these proteins is somewhat intricate and requires sim-
plifications [56] . One study [57] considers actin network as a contractile viscoelastic
gel. Actin in that model acts under the effect of diffusive and convective forces.

There are two main approaches to modeling actin dynamics: a time dependent
one, or time independent. The first is concerned with solving a set of differential
equations, and describing the effect of these parameters on the steady state of its
dynamics, such as the prediction of the nucleotide behavior. Time dependent models
include Monte Carlo simulations which follow the evolution of actin filaments. Those
stochastic models have helped to understand the evolution of the filaments, their
lengths as well as the distribution of the latter. These also uncovered the role of annealing and fragmentation [58].

A simplified model [59] suggests that they can be reduced to four main molecular processes taking place at the growing edge of the cell. The actin filament involves a rod-like polymer with a positive end, called the barbed end, that points towards the membrane, and a negative end that points towards the cell’s interior. The Profilin-ATP-G actin is assembled at the barbed end as long as the end is uncapped, otherwise its capping restrains the formation of the complex near the boundary. Two mechanisms dampen the aggregation of Profilin-ATP-G actin complex, and thus control its concentration at the boundary which defines the protrusion velocity. The Profilin-ADP-actin is sequestered by cofilin, a binding protein that prevents its transformation into Profilin-ATP-actin complex. Also thymosin \( \beta_4 \) can bind to ATP-G actin by breaking the Profilin-ATP-G actin complex. However, the monomer flux is guaranteed by their transfer from the negative to the barbed ends, a mechanism termed tread-milling. At steady state the rates are equal.

The interplay between these molecular mechanisms gives rise to a clustering of the Profilin-ATP-G-actin complex near the membrane [59]. The dynamics of the latter is governed by a partial differential equation with a boundary condition imposed at the moving membrane. The model was solved in the moving frame of the system, where the boundary is kept at the origin. This could be done since the protrusion velocity is given by \( V = k_{on} \delta a(0) e^{f/k_B T} \), where \( k_B \) is the Boltzmann constant, \( T \) is the temperature, \( a(0) \) is the actin concentration at the interface, \( f \) is the free energy, \( \delta \) the filament length increment per monomer, and \( k_{on} \) the rate of
actin assembly. Thus it is shown to be proportional to $a(0)$, the concentration of Profilin-ATP-actin complex at the membrane, and attenuated by the surface tension effect that counteracts the forwards motion.

The equations were defined in the moving frame of the interface, and accordingly the boundary condition was defined. Consequently the interface is tracked instantaneously. However, in the phase-field method the interface is the locus of the smooth transition between zero and one, the values assigned to the field respectively for the exterior and interior domains of the growing region, and therefore is numerically less exhaustive since it does not require the boundary tracking.

These intracellular mechanisms could not have been triggered without the presence of a chemical cue which drives the axon towards the target position, when the actin cytoskeleton is functional. Therefore the presence of the chemical attractant must be included in the formulation of the problem, and the velocity should be redefined accordingly.

4.2 Methods

We use phase field method to model the growth of the neural cell, subject to a chemical attractant that drives the intracellular actin dynamics [50]. As done previously, to delineate the cell’s interior and exterior, auxiliary fields are given a value of 1 on the inside of the region of interest and zero outside it. The cell is assigned the field $\phi$, the part of it facing the highest chemical concentration is denoted by the field $\psi$, and $\phi_2$ pinpointed the initial position of the cell. Consequently the growing part of the cell is given by the auxiliary field $\tilde{\phi} = \phi - \phi_2 + \psi \cdot \phi \cdot \phi_2$, as depicted in Fig. 4–1.
Figure 4–1: A scheme showing the cell’s growing region given as a function of the cell’s initial position $\phi_2$, the cell at arbitrary time depicted by $\phi$, and the leading edge $\psi$. 
The presence of a chemical attractant biases the interface homogeneity, and gives rise to structural changes in the plasma membrane, described by non zero $\psi$. There, the surface tension is counteracted by protrusion, allowing the forward motion of the membrane. Additionally, the region persists in the presence of a chemical attractant, therefore its auxiliary field $\psi$ obeys conservative dynamics.

The cell as a whole is growing, therefore $\phi$ is not conserved. The chemotactic effects drive only the region of the cell where the surface tension is minimal. This is translated by introducing a $\psi$ dependent surface tension $\epsilon(\psi) = \epsilon \cdot (1 - \psi)$, and a $\psi$ dependent velocity $V(\psi)$.

The actin dynamics equations given by Mogilner’s model [59], can now be modified in the following way:

\[
\begin{align*}
\tilde{\phi} \frac{\partial \phi}{\partial t} &= D \nabla [\tilde{\phi} \nabla s] + \tilde{\phi} [k_{-3}s + k_{-1}p + J_d(x)] \\
\tilde{\phi} \frac{\partial p}{\partial t} &= D \nabla [\tilde{\phi} \nabla p] + \tilde{\phi} [k_1s - k_{-1}p - k_2p] \\
\tilde{\phi} \frac{\partial \beta}{\partial t} &= D \nabla [\tilde{\phi} \nabla \beta] + \tilde{\phi} [-k_{-3}\beta + k_3a] \\
\tilde{\phi} \frac{\partial a}{\partial t} &= D \nabla [\tilde{\phi} \nabla a] + \tilde{\phi} [k_{-3}\beta - k_3a + k_2p] - \delta k_m e^{-\frac{f_0}{kT}} \frac{B(t)}{\delta \eta} \nabla (a \cdot \tilde{\phi} \cdot \nabla c)
\end{align*}
\]

(4.1)

where $a$ is the concentration of profilin ATP-G-actin complex, $p$ is that of profilin ADP-G-actin complex, $\beta$ is that of thymosin ATP-G-actin, and $s$ is that of the cofilin ATP-G-actin complex. Multiplying by $\tilde{\phi}$ restricts the reaction diffusion equations
to the growing region of the cell, and guarantees the no-flux boundary conditions as required in the first three equations. In the equation for $a$ the addition of the term \( \frac{B(t)}{\delta \eta} \nabla (a \cdot \tilde{\phi} \cdot \nabla c) \) is equivalent to imposing the boundary condition at the tip \( \left. \frac{da}{dx} \right|_{L-\xi} = \frac{B}{\delta \eta} V. \)

Without loss of generality, integrating the $\beta$ equation over the interface of thickness $2\xi$, located at $L$ gives:

\[
D[\tilde{\phi} \nabla \beta] \bigg|_{L+\xi} - D[\tilde{\phi} \nabla \beta] \bigg|_{L-\xi} = \int_{L-\xi}^{L+\xi} \tilde{\phi} \left[ \frac{\partial \beta}{\partial t} + k_{-3}\beta - k_{3}a \right] dx.
\]

However, \( \tilde{\phi}(x) \bigg|_{L+\xi} \approx 0 \), while \( \tilde{\phi}(x) \bigg|_{L-\xi} \approx 1 \)

Then:

\[
D[\nabla \beta] \bigg|_{L-\xi} \approx \int_{L+\xi}^{L-\xi} \tilde{\phi} \left[ \frac{\partial \beta}{\partial t} + k_{-3}\beta - k_{3}a \right] dx \approx O(\xi).
\]

The latter boundary condition becomes zero in the limit of sharp interface.

By the same token:

\[
D[\nabla a] \bigg|_{L-\xi} \approx \int_{L+\xi}^{L-\xi} \tilde{\phi} \left[ \frac{\partial a}{\partial t} - k_{-3}\beta + k_{3}a - k_{2}p \right] dx - \int_{L-\xi}^{L+\xi} \left[ \delta k_{on} e^{\frac{-f}{k_BT}} \frac{B}{\delta \eta} \nabla (a \cdot \tilde{\phi} \cdot \nabla c) \right] dx.
\]

\[
D[\nabla a] \bigg|_{L-\xi} \approx O(\xi) - \int_{L-\xi}^{L+\xi} \left[ \delta k_{on} e^{\frac{-f}{k_BT}} \frac{B}{\delta \eta} \nabla (a \cdot \tilde{\phi} \cdot \nabla c) \right] dx.
\]

$B$ is homogenous and bears no spatial dependence. Therefore:

\[
D[\nabla a] \bigg|_{L-\xi} \approx O(\xi) - \int_{L-\xi}^{L+\xi} \left[ \delta k_{on} e^{\frac{-f}{k_BT}} \frac{B}{\delta \eta} \nabla (a \cdot \tilde{\phi} \cdot \nabla c) \right] dx.
\]

\[
D[\nabla a] \bigg|_{L-\xi} \approx O(\xi) - \delta k_{on} e^{\frac{-f}{k_BT}} \frac{B}{\delta \eta} \tilde{\phi} \cdot a \cdot \nabla c \bigg|_{L+\xi} + \delta k_{on} e^{\frac{-f}{k_BT}} \frac{B}{\delta \eta} \tilde{\phi} \cdot a \cdot \nabla c \bigg|_{L-\xi}.
\]

\[
D[\nabla a] \bigg|_{L-\xi} \approx \frac{B}{\delta \eta} V.
\]

The first term drops out since \( \tilde{\phi} \approx 0 \) for $x \in [L, L+\xi]$, where $V = \delta k_{on} a(L-\xi) e^{\frac{-f}{k_BT}} \nabla c$. 

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This result is reached by identifying the driving velocity of \(a\) to be proportional to \(\nabla c\). Then the material derivative of \(a(x, t)\) is related to its partial derivatives with respect to \(t\) and \(x\) via \(\frac{da}{dt} = \frac{\partial a}{\partial t} + \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \nabla c \cdot \nabla a\).

In what follows we will write the system functional as:

\[
F(a, \beta, s, p, \phi, \psi, \phi_2) = F_1(a, \phi, \psi, \phi_2) + F_2(\beta, \phi, \psi, \phi_2) + F_3(s, \phi, \psi, \phi_2) + F_4(p, \phi, \psi, \phi_2) + F_5(\phi, \psi) + F_6(\phi_2).
\]

We write the functional as a summation of terms that depend on a combination of auxiliary fields and concentration given by \(F_1, F_2,\) and \(F_3,\) which will generate the restricted diffusion equations, and on the auxiliary fields exclusively given \(F_4,\) and \(F_5,\) which will mainly generate the equation of motion of the fields.

Now we write

\[
F_1 = \int \frac{D}{2} (\tilde{\phi} \nabla a)^2 + H \frac{a^2}{2} dV.
\]

The equation governing the dynamics of \(a\) can be derived:

\[
\tilde{\phi} \frac{\partial a}{\partial t} = \tilde{\phi} \frac{\partial a}{\partial t} + \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \tilde{\phi} \nabla c \cdot \nabla a = -\frac{\delta F}{\delta a} + \sigma
\]

where \(\sigma\) accounts for terms that are sources or sinks, which is controlled by to those converted from \(\beta\) to \(a\) with rate \(k_{-3}\), and from \(p\) to \(a\) with rate \(k_2\), and are lost with rate \(k_3\) respectively, restricted to the \(\tilde{\phi}\) area. Then \(\sigma = (k_3a - k_{-3}\beta - k_2p) \cdot \tilde{\phi}\), and the equation of \(a\) can be written as follows:

\[
\tilde{\phi} \frac{\partial a}{\partial t} + \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \tilde{\phi} \nabla c \cdot \nabla a = D \nabla [\tilde{\phi} \nabla a] + \tilde{\phi} [k_{-3}\beta - k_3a + k_2p] - Ha
\]

\[
\tilde{\phi} \frac{\partial a}{\partial t} = D \nabla [\tilde{\phi} \nabla a] + \tilde{\phi} [k_{-3}\beta - k_3a + k_2p] - \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \tilde{\phi} \nabla c \cdot \nabla a - Ha
\]

We set \(H = -\delta k_{on} e^{\frac{f_{ls}}{k_B T}} \nabla (\tilde{\phi} \cdot \nabla c)\) and obtain:

\[
\tilde{\phi} \frac{\partial a}{\partial t} = D \nabla [\tilde{\phi} \nabla a] + \tilde{\phi} [k_{-3}\beta - k_3a + k_2p] - \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \tilde{\phi} \nabla c \cdot \nabla a - \delta k_{on} e^{\frac{f_{ls}}{k_B T}} \nabla (\tilde{\phi} \cdot \nabla c)a
\]

The last two terms can be written as \(\delta k_{on} e^{\frac{f_{ls}}{k_B T}} \nabla (a \cdot \tilde{\phi} \cdot \nabla c)\), and this is the term that
guarantees the boundary condition at the tip, as shown above.

Similarly the β equation can be derived from the functional:
\[ F_2 = \int \frac{D}{2}(\tilde{\phi}\nabla\beta)^2 dV \]
Also, \( \tilde{\phi}\frac{\partial \beta}{\partial t} = -\frac{\delta F}{\delta \beta} + \sigma_2 \). Here the terms proportional to \( \beta \) contributing as sources in the \( a \) equation, should act as sinks in the \( \beta \) equations.
\[ \tilde{\phi}\frac{\partial \beta}{\partial t} = D \nabla[\tilde{\phi}\nabla\beta] - k_{-3}\beta + k_3 a \]
Also those of \( s \) and \( p \) are derived likewise from these functionals respectively \( F_3 = \int \frac{D}{2}(\tilde{\phi}\nabla s)^2 dV \), and \( F_4 = \int \frac{D}{2}(\tilde{\phi}\nabla p)^2 dV \). These give:
\[ \tilde{\phi}\frac{\partial p}{\partial t} = D \nabla[\tilde{\phi}\nabla p] - \tilde{\phi}[k_1 s + k_{-1} p - k_2 p] \]
\[ \tilde{\phi}\frac{\partial s}{\partial t} = D \nabla[\tilde{\phi}\nabla s] - \tilde{\phi}[k_1 s + k_{-1} p + J_d(x)] \]
Having redefined the internal dynamics, we turn to formulating the phase field equations. The functional \( F \) controls the fields’ conjugate forces, which in turn control the dynamics of their corresponding fields.
\[ F_5 = \int \left( \frac{\epsilon(\psi)}{2}(\nabla \phi)^2 + f(\phi) + \frac{\epsilon'}{2}(\nabla \psi)^2 + f(\psi) + H \psi \right) dV \]
where \( f(\phi) = a\phi^2(1 - \phi)^2 \). The material derivative of \( \phi \) is related to its partial derivatives with respect to time and space via:
\[ \frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + \nabla(V_1(\psi, a(\xi), \nabla c) \cdot \nabla \phi) \]
This allows us to write:
\[ \frac{\partial \phi}{\partial t} = -\Gamma \nabla^2[\epsilon(1 - \psi)\nabla^2 \phi - f_\phi] - V_1(\psi, a(\xi), \nabla c) \cdot \nabla \phi = \Gamma \nabla^2 \delta F_{\phi} \]
The dynamics of \( \psi \) is then given by:
\[ \frac{d\psi}{dt} = \frac{\partial \psi}{\partial t} + V_2(a(\xi), \nabla c) \cdot \nabla \psi = \Gamma \nabla^2 \delta F_{\psi} \]
\[ \frac{\partial \psi}{\partial t} = -\Gamma \nabla^2[\epsilon' \nabla^2 \psi - f_\psi] - V_2(a(\xi), \nabla c) \cdot \nabla \psi + \Gamma' \nabla^2 H \]
Forcing \( \Gamma' \nabla^2 H = \psi \cdot \nabla V \), will make the field conserved. Then the equation becomes:
\[ \frac{\partial \psi}{\partial t} = -\Gamma \nabla^2[\epsilon' \nabla^2 \psi - f_\psi] - \nabla(V_2(a(\xi), \nabla c) \cdot \psi). \]
The field $\phi_2$ is pinpoints the cell’s original configuration, therefore it should obey conservative dynamics:

$$F_6 = \int \frac{\epsilon_2}{2} (\nabla \phi_2)^2 + f(\phi_2) \, dV.$$  
$$\frac{\partial \phi_2}{\partial t} = -\Gamma_2 \nabla^2 [\epsilon \nabla^2 \phi_2 - f \phi_2]$$

The chemotropic effect will force only the part of the cell where $\psi \neq 0$, and $\phi \neq 0$ to move. With the chemical driving in the medium, the Profilin-ATP-G actin complex accumulates near the membrane. Then the velocity assigned to $\phi$ is:

$$V_1 = \delta k_{on} a(\xi) e^{\frac{-f}{k_B T}} \cdot \psi \cdot \vec{n}.$$  
However $\psi$ moves as a whole:

$$V_2 = \delta k_{on} a(\xi) e^{\frac{-f}{k_B T}} \cdot \vec{n}.$$  

where $\vec{n} = \frac{\nabla c}{|\nabla c|}$.

This model, when compared to that of the previous chapter, show an obvious resemblance with the equation of the cell’s field $\phi$. There, the velocity was $b \psi \nabla c$, where $\nabla c \approx A \psi x$. We argued that this is analogous to including the dynamics of actin in the definition of the velocity.

We hereafter show that the steady state of actin, mainly that of the profilin-ATP-G-actin concentration, displays a linear dependence on space, and when multiplied with the normalized vector $\vec{n}$, is directed towards the highest chemical concentration point. This is then equivalent to the assumption we made in the previous chapter.
In summary, the coupled equations of motions are:

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= \Gamma_1 \nabla \left[ \epsilon (1 - \psi) \nabla^2 \phi - f \phi \right] - V_1 \cdot \nabla \phi \\
\frac{\partial \phi_2}{\partial t} &= \Gamma_2 \nabla \left[ \epsilon_2 \nabla^2 \phi_2 - f \phi_2 \right] \\
\frac{\partial \psi}{\partial t} &= \Gamma' \nabla \left( \epsilon' (\nabla \psi)^2 - f \psi \right) - \nabla \cdot \left( V_2 \psi \right) \\
\frac{\tilde{\phi}}{\partial t} s &= D \nabla [\tilde{\phi} \nabla s] + \tilde{\phi} \left[ -k_1 s + k_{-1} p + J_d(x) \right] \\
\frac{\tilde{\phi}}{\partial t} p &= D \nabla [\tilde{\phi} \nabla p] + \tilde{\phi} \left[ k_1 s - k_{-1} p - k_2 p \right] \\
\frac{\tilde{\phi}}{\partial t} \beta &= D \nabla [\tilde{\phi} \nabla \beta] + \tilde{\phi} \left[ -k_{-3} \beta + k_3 a \right] \\
\frac{\tilde{\phi}}{\partial t} a &= D \nabla [\tilde{\phi} \nabla a] + \tilde{\phi} \left[ k_{-3} \beta - k_3 a + k_2 p \right] - \delta k_{on} \frac{f \theta}{\delta \eta} B(t) \nabla (a \cdot \tilde{\phi} \cdot \nabla c)
\end{align*}
\]

where $\tilde{\phi} = \phi - \phi_2 + \psi \cdot \phi \cdot \phi_2$

4.3 Results

As in the previous chapters we made use the field $\phi$ to visualize the actual morphodynamics. We show in Fig. 4–2 the steady state configuration $\phi$ in orange, together with $\psi$ in red.

For that purpose, we compare the velocities of the tip of the axon for both models
Figure 4–2: The neural cell growth is shown in orange. The figure depicts the steady state of $\phi$.

In addition, we follow the steady state concentration and their spatial variation, and compare those with their behavior as given in the original model. This confirms our assumption in the previous chapter regarding the fast dynamics of actin, which is equivalent to the treatment presented in this chapter. The two velocity profiles fall close to each other, and are set apart by the choice of the coefficient multiplying the first order power of $x$.

Again we stress that choosing $v \propto \nabla c \propto x$ in the model of Chapter 3, is analogous to choosing $v \propto a_{interface} \cdot \vec{n} \propto x$. In other words $a(x)$ being linearly
Figure 4–3: The velocity of the tip of the axon is plotted as a function of distance for an in vitro growing neuron, and compared to the velocity of the tip for the simplified chemotropic model of Chapter 3, and to that of model of Chapter 4 shown in blue, red, and green respectively.

...dependent on space produces the same effective force as that produced by choosing \(v \propto x\).

We note that the concentration of profilin-ADP-G-actin complex shows a close equivalence to that given by the original model. Also the thymosin-ATP-G-actin shown by the dashed blue line falls close to the blue curve. However there appears to be a discrepancy between the dashed green curve and the solid line green curve, which are those of cofilin-ADP-G-actin complex. The discrepancy can be depicted in the
value of $a$ near the membrane, however at the distal part its behavior is comparable to the expected one.

This could be explained by the choice of the term added to the equation of $a$ to recover the original boundary condition.

### 4.4 Conclusion

In this chapter we have adopted a simplified model to the underlying actin dynamics. This, together with the introduction of phase fields describing the cell, its original position, as well as its leading edge, helped construct a functional that
successfully portrayed the system. The coupling between the fields and actin was
made through the mapping of the formers’ velocities to the concentration of profilin-
ATP-G-actin at the leading edge.

We then verified our reformulation by comparing it with the expected behavior of
the actin complexes, which turned out to behave analogously, although there were
certain discrepancies in their values.

We also investigated the assumption made in the previous chapter regarding the
validity of taking the velocity of the cell’s field to be a linear function of space. It
turned out that including the concentration of actin in the definition of the velocity,
together with a directional vector pointing towards the postsynaptic connection,
is analogous to choosing a velocity which was dependent on the gradient of the
concentration of the chemical attractant.
5.1 Introduction

Directed motion and growth involve particular sensing of external signals, followed by structural rearrangement of the cytoskeleton to induce the proper effect. The translation of the cue into intracellular mechanisms is common to both types of dynamics. Dictyostelium motion represents an appropriate model for chemotaxis. It is able to detect a concentration gradient with the aid of G-protein coupled receptors, and generates a directed motion accordingly. On the other hand, the budding yeast’s response to chemical mating signals, which moves under chemotactic effects, is also achieved through the help of G-protein-coupled receptors, which direct the growth towards its target localized at the zero of the concentration gradient, which leads to the pear-like shape of the yeast. Studies suggest that the apparent differences in the fast motion of the Dictyostelium, and the relatively slow growth of the yeast can be reduced to a similar mechanism of signal transduction, which is translated by directional movement of growth [60].

Models for directional motility assume that the cell is related to the ligand binding receptors across its membrane. Then, in uniform concentrations, the cell motion is controlled by the stochastic behavior by which fluctuations in the ligand binding receptors set the favored direction of motion. These include both the temporal as well as the spatial sensing of the gradients, since the former is a time dependent
process. However in this work we have adopted the hypothesis of spatial sensing neglecting the effect of noise on the orientation and guidance of the cell.

The receptors’ occupancy, in our model of Chapter 2 and 3, is related to the emergence of the field $\psi$ reflecting their concentration. Therefore the definition of the velocity in Chapter 3 indicates that dependance. The growth cone can discern concentration gradient of the order of $1 - 10\%$ across their membrane [60], which is of the order of $10\mu$m, and subsequently redirects the elongation. This feature was observed in our model. We obtained an analytical result in the case of the neutrophil, where the condition is given by $\frac{D_b \nabla c}{D} \gg 1$. In chemotropism, the condition should be satisfied by both fields $\psi$ and $\phi$. Also, there should be a surface, where the occupied receptors are present, whose dimension is large enough to instigate the growth. Further, investigation needs to be done to determine that critical area.

Reduced sensitivity of the cell as it progresses to the attractant is observed in both systems under chemotropic or chemotactic effects. This feature was included in both our models through the introduction of a degradation rate in the equation governing the chemical concentration.

Similarities between the models presented in this work can be readily observed. The underlying molecular processes responsible for the growth as well as the motion can be reduced to the dynamics of actin. This, in addition to the morphological changes the cells undergo subject to a chemical signal, are the points of similarities between the dynamical processes. These observations imply that these two mechanisms might be explained as aspects of a generalized process. The similarities can be summarized in the diagram Fig. 5–1.
In chemotaxis, the cell as a whole is targeted by the chemical cue, instigating its

Figure 5–1: The diagram summarizes the similarities between chemotaxis and chemotropism
cytoskeletal dynamics. However, in chemotropism, the signal is directed at a part of
the cell which is then led with the help of the filopodia to make its synaptic connec-
tion. We identify the cell with the field $\phi$, its polymerized region with the field $\psi$, and $\phi_2$ will keep track of the cell’s original configuration. The part of the cell where
the actin dynamics is taking place will be denoted by $\varphi$.

The auxiliary field $\varphi$ depicted in both Fig. 5–2, 5–3 delineates the leading edge or
the axonal tip for a crawling cell or a neural cell respectively. It is related to the
previously defined fields through $\varphi = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2)^n \cdot \psi^{1-n}$. For $n = 0$, $\varphi = \psi$ which is confirmed graphically as being the region where the polymerization arises.

Also for $n = 1$, the region with $\varphi = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2)$ is the growing region of the
cell.
Figure 5–2: The fields $\phi$, $\phi_2$ and $\psi$ denote respectively the cell, its original configuration, and its polymerized region. $\varphi = \psi$ denotes its leading edge.

5.2 Generalized Functional

Having established the similarities between both mechanism, we are now in a position to suggest that they can both be derived from a more comprehensive model.
Figure 5–3: The fields $\phi$, $\phi_2$ and $\psi$ denote respectively the cell, its original configuration, and its polymerized region. $\varphi = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2)$ denotes its growth cone.
which includes all the symmetries and features that we have so far described.

We conjecture that this generalized functional $F[\phi, \phi_2, \psi]$ in Eq. 5.1 can explain both mechanisms with the appropriate choice of the parameter $n$, and external fields $H$ and $H_2$:

$$F = \int \left[ \epsilon (\nabla^n c)^2 (1 - n \psi) (\nabla \phi)^2 + a \phi^2 (1 - \phi)^2 + (1 - n) H \phi 
\right. \\
+ \epsilon (\nabla \phi_2)^2 + a \phi_2^2 (1 - \phi_2)^2 + \epsilon' (\nabla \psi)^2 + a \psi^2 (1 - \psi)^2 + H_2 \psi \right] dx$$

(5.1)

where $\epsilon$, $\epsilon'$ are proportional to surface tension, $c$ is the chemical concentration of the attractant, $H$ and $H_2$ are external fields, and $a$ is an energy density. The claim is that, for $n = 0$ the functional describes chemotaxis, while $n = 1$ describes chemotropism.

The dynamics of $\phi$ is controlled by $\frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v \cdot \nabla \phi = \Gamma \nabla^2 \left( \frac{\delta F}{\delta \phi} \right)$, where we defined $v = \frac{\psi^n \nabla c \cdot (\delta k_{on} a(\xi) e^{-f_\delta/k_B T})}{|\nabla c|}$, and $\Gamma$ is the mobility. The expression of $v$ has terms related to the gradient of the chemical cue, and the concentration of actin at the leading edge $a(\xi)$ which corporate to induce the forward motion. This protrusion is counteracted by the surface tension contribution which is incorporated in the expression of the velocity by the introduction of the term $e^{-f_\delta/k_B T}$, where $k_B$ is the Boltzmann factor and $T$ is the temperature. In chemotropism, only the polymerized region of the cell is targeted by the chemical cue, and therefore the term $\psi$ takes into account that effect. In chemotaxis, the cell as a whole moves as it detects a chemical gradient, and therefore the term $\psi$ should not be included. This gives rise to the power $n$ for $\psi$. Also in the chemotropic model, the growth cone is led by the chemical gradient, and the former pulls the cell to the highest chemical concentration point.

Similarly the equation of $\psi$ is controlled by $\frac{d\psi}{dt} = \frac{\partial \psi}{\partial t} + v_2 \cdot \nabla \psi = \Gamma' \nabla^2 \left( \frac{\delta F}{\delta \psi} \right)$, where
$v_2 = \frac{\nabla c}{|\nabla c|} \cdot \delta k_{on} a(\xi) e^{-f\delta/k_B T}$, and $\Gamma'$ is the mobility. Here the equation of the velocity differs from that of the $\phi$ field by the absence of $\psi$. This means that the leading edge should move as a whole when it senses a chemical gradient, whether in chemotaxis or in chemotropism.

The original position of the cell is retained by the introduction of the variable $\phi_2$, which equation becomes $\frac{\partial \phi_2}{\partial t} = \Gamma \nabla^2 (\frac{\delta F}{\delta \phi_2})$.

For $n = 0$ with the appropriate choices of $H$ and $H_2$, the functional reduces to that of the chemotaxis model, while for $n = 1$ and for a proper selection of $H_2$ the functional reduces to the chemotropic model. To make things more rigorous, we derive the governing equation for each case.

5.3 Chemotaxis Model

We start by recovering the chemotaxis model from the generalized functional. This is the case when $n = 0$. First the functional becomes:

$$\mathcal{F} = \int [\epsilon (\nabla \phi)^2 + a \phi^2 (1 - \phi)^2 + H \phi + \epsilon (\nabla \phi_2)^2 + a \phi_2^2 (1 - \phi_2)^2 + \epsilon' (\nabla \psi)^2 + a \psi^2 (1 - \psi)^2 + H_2 \psi] \, dx.$$  

From this functional, we can now derive the equations of both fields $\phi$, and $\psi$:

$$\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 (\epsilon \nabla^2 \phi - f\phi - \nabla^2 H) - v \cdot \nabla \phi.$$  

This together with the appropriate choice of $H$ given by $\Gamma \nabla^2 H = -\phi \cdot \nabla v$, which allows us to write:

$$\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 (\epsilon \nabla^2 \phi - f\phi) - \nabla \cdot (v \phi).$$

where $v = \psi^n \cdot \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f\delta/k_B T}) = \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f\delta/k_B T}).$

Similarly, the equation of $\psi$ is given by:
\[ \frac{\partial \psi}{\partial t} = -\Gamma'[\epsilon' \nabla^2 \psi - f \psi - \nabla^2 H_2] - v_2 \cdot \nabla \psi. \] 

Then defining \( \Gamma' \nabla^2 H_2 = -\psi \cdot \nabla v_2 \), we write:

\[ \frac{\partial \psi}{\partial t} = -\Gamma' \nabla^2 [\epsilon' \nabla^2 \psi - f \psi] - \nabla \cdot (v_2 \psi). \]

where \( v_2 = \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f \delta / k_B T}). \)

Finally we write the equation of \( \phi_2 \) given by:

\[ \frac{\partial \phi_2}{\partial t} = -\Gamma [\epsilon \nabla^2 \phi_2 - f \phi_2] \varphi = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2)^n \cdot \psi^{1-n} = \psi \]
Now that the equations of the fields are defined, we couple them to the actin complexes equations, which now reduce to the chemotaxis model defined in Eq. (5.2).

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= \Gamma \nabla^2 [\epsilon \nabla^2 \phi - f \phi] - \nabla \cdot (v \phi) \\
\frac{\partial \phi_2}{\partial t} &= \Gamma \nabla^2 [\epsilon \nabla^2 \phi_2 - f \phi_2] \\
\frac{\partial \psi}{\partial t} &= \Gamma' \nabla^2 (\epsilon' (\nabla \psi)^2 - f \psi) - \nabla \cdot (v_2 \psi) \\
\phi \frac{\partial s}{\partial t} &= D \nabla [\phi \nabla s] + \phi [k_{-3}s + k_{-1}p + J_d(x)] \\
\phi \frac{\partial p}{\partial t} &= D \nabla [\phi \nabla p] + \phi [k_1 s - k_{-1}p - k_2 p] \\
\phi \frac{\partial \beta}{\partial t} &= D \nabla [\phi \nabla \beta] + \phi [-k_{-3}\beta + k_3 a] \\
\phi \frac{\partial a}{\partial t} &= D \nabla [\phi \nabla a] + \phi [k_{-3} \beta - k_3 a + k_2 p] - \delta k_{on} e^{\frac{-E_2}{k_B T}} \frac{B(t)}{\delta \eta} \nabla (a \cdot \phi \cdot \psi \cdot \nabla c)
\end{align*}
\]

(5.2)

where \( \phi = \psi, s, p, \beta \) and \( a \) are respectively cofilin-ADP-G-actin, profilin-ADP-G-actin, thymosin-ATP-G-actin, and profilin-ATP-G-actin complexes. Multiplying the actin complexes equations by \( \phi \) will restrict their validity to the region defined by nonzero \( \phi \). In addition, this formulation takes into account their correct boundary conditions as shown in Chapter 4. It differs from the one we presented in Chapter 86.
2 as it includes the actin dynamics equations. In Chapter 2, we assumed that the molecular processes are fast on the time scale of the motion so that \( a(\xi) \) assumes a constant value. Therefore this model is a more complete one, as it encompasses the aforementioned aspect of the motion.

### 5.4 Chemotropic Model

Similarly, we now derive the equations when \( n = 1 \), which reduces to the chemotropic model. We start by redefining the functional:

\[
\mathcal{F} = \int \left[ \epsilon (\nabla c)^2 (1 - \psi) (\nabla \phi)^2 + a \phi^2 (1 - \phi)^2 + \epsilon (\nabla \phi_2)^2 + a \phi_2^2 (1 - \phi_2)^2 + \epsilon' (\nabla \psi)^2 + a \psi^2 (1 - \psi)^2 + H_2 \psi \right] dx.
\]

From which we derive the equation for \( \phi \) given by:

\[
\frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 \left[ \epsilon (\nabla c)^2 (1 - \psi) \nabla^2 \phi - f_\phi \right] - v \cdot \nabla \phi.
\]

where \( v = \psi \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f_\delta/k_B T}) = \psi \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f_\delta/k_B T}). \)

Now the equation of \( \psi \) is given by:

\[
\frac{\partial \psi}{\partial t} = -\Gamma' \left[ \epsilon' (\nabla^2 \psi - f_\psi - \nabla^2 H_2) - v_2 \cdot \nabla \psi \right].
\]

with \( \Gamma' \nabla^2 H_2 = -\psi \cdot \nabla v_2 \).

\[
\frac{\partial \psi}{\partial t} = -\Gamma' \nabla^2 \left[ \epsilon' (\nabla^2 \psi - f_\psi) - \nabla \cdot (v_2 \psi) \right].
\]

where \( v_2 = \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f_\delta/k_B T}) = \frac{\nabla c}{|\nabla c|} \cdot (\delta k_{on} a(\xi) e^{-f_\delta/k_B T}). \)

Finally, the equation of \( \phi \) is given by:

\[
\frac{\partial \phi}{\partial t} = -\Gamma \left[ \epsilon (\nabla^2 \phi_2 - f_{\phi_2}) \right].
\]

The definition of \( \varphi \) follows: \( \varphi = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2)^n \cdot \psi^{1-n} = (\phi - \phi_2 + \psi \cdot \phi \cdot \phi_2) \).

When we couple these to the equations of actin its reduces to the chemotactic model defined by Eq. 5.3, we obtain:
\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= \Gamma_1 \nabla^2 [\epsilon(1 - \psi) \nabla^2 \phi - f_\phi] - v \cdot \nabla \phi \\
\frac{\partial \phi_2}{\partial t} &= \Gamma_2 \nabla^2 [\epsilon_2 \nabla^2 \phi_2 - f_{\phi_2}] \\
\frac{\partial \psi}{\partial t} &= \Gamma' \nabla^2 (\epsilon' (\nabla \psi)^2 - f_\psi) - \nabla \cdot (v_2 \psi) \\
\varphi \frac{\partial s}{\partial t} &= D \nabla [\varphi \nabla s] + \varphi [k_{-3}s + k_{-1}p + J_a(x)] \\
\varphi \frac{\partial p}{\partial t} &= D \nabla [\varphi \nabla p] + \varphi [k_1 s - k_{-1}p - k_2 p] \\
\varphi \frac{\partial \beta}{\partial t} &= D \nabla [\varphi \nabla \beta] + \varphi [-k_{-3} \beta + k_3 a] \\
\varphi \frac{\partial a}{\partial t} &= D \nabla [\varphi \nabla a] + \varphi [k_{-3} \beta - k_3 a + k_2 p] - \delta k_{on} e^{-\frac{ta}{B(t)}} B(t) \nabla (a \cdot \varphi \cdot \psi \cdot \nabla c)
\end{align*}
\]

where \( \varphi = \phi + \psi \cdot \phi_2 \), and the details of the model are presented in chapter 4.

### 5.5 Conclusion

The similarities, both chemotropic and chemotactic effects have on the cell, can be summarized by the following influences: a directional sensing which is translated in an asymmetry affecting the number of protein binding receptors across the membrane, which leads to structural changes in the cell’s cytoskeleton, followed by motion...
or growth. Additionally, they both exhibit forms of desensitization, that can be seen by the degradation of the chemical attractant.

Finally we have shown that both mechanisms can be explained by this generalized functional. With appropriate choices of $H$ and $H_2$, the model describes chemotaxis when $n = 0$, while it explains chemotropism for $n = 1$. This was motivated by the similarities between the processes at the underlying molecular level as well as the external cue that guides the motion or the growth.

Within the literature, no mathematical model combines both effects. Additionally the advantage of our formulation is that it provides a visualization of the effective cellular dynamics, in addition to the underlying mechanics at the molecular level. Therefore this method not only encompasses symmetries of the physical system, it also includes the effect of the chemical signaling as well as the actin polymerization dynamics.

It also provided insights on the necessary conditions to induce the motion or the growth, by relating the concentrations to the parameters that defined the velocity. In addition to the assumption that these mechanisms are triggered exclusively by spatial sensing, which can be modified to include temporal effects one by including noise, it is straightforward to incorporate stochastic contributions reflecting the fluctuations in protein binding receptors at the membrane.

Desensitization was incorporated by including a degradation rate in the equation governing the chemical attractant. As the model faithfully displays all the main features that we have just described, this generalized functional can be used to a multitude of other cells that move under the effect of chemotaxis such as Dictyostelium,
sperms, Amoeba, and those which are affected by chemotropism such as budding yeast, pollen tubes, and so forth.
In summary, the study of chemotactic and chemotropic effects on the neutrophil and the neuron, relied on statistical laws which defined their evolution. That was achieved by the construction of the energy functional $F$ encompassing the physical system’s symmetries. Consequently, the evolution of the system, or its rate of change, was mapped to a generating force. The latter was attained by a variational differentiation of $F$ with respect to the field $\phi$ that characterized the phases of the system under scrutiny. At the macroscopic level the systems phases are distinguishable, which is reflected by an appropriate choice of the field’s values. The bulk of the phases, which is in our work identified as the extracellular and intracellular domain, was respectively assigned the values 0 and 1, while the interface is marked by a smooth transition between the two.

Consequently the nature of the identified field defined the conjugate force. Therefore conserved $\phi$ restricts the force to be of the form $\nabla^2 \frac{\delta F}{\delta \phi}$, while that of a non conserved $\phi$ is of the form $\frac{\delta F}{\delta \phi}$. As a result the dynamics of the phases is depicted by the changes affecting $\phi$.

The advantage of the method is that it assumes a diffuse interface in contrast to a sharp interface approach to dynamically evolving systems. These problems are governed by partial differential equations with moving boundary conditions. The latter depends of the details of the dynamics, and hence the highly nonlinear aspect
of the problem arises. The difficulty lies in the necessity of instantaneous tracking of the boundary which is an exhaustive approach. The phase field method serves as an alternative technique to solve the arising difficulty. The smooth transition in the value of $\phi$ portrays the interface.

In this work, we have employed the phase-field method to model the morphodynamics of neutrophils. Assigning distinct values to the field $\phi$ to distinguish the cell’s interior and exterior allowed us to build a functional describing the system. Being an out of equilibrium system, we used notions previously described to portray the dynamics. The functional, as expected, defines a conjugate force that specifies the time evolution of $\phi$. In this model, we have used the fact that the cell is volume preserving, forcing $\phi$ to be conserved.

To additionally describe changes that the cell undergoes, we introduced the field $\psi$ describing the polymerized edge of the cell. In this treatment we have neglected the underlying molecular processes at the leading edge, mainly those of actin responsible for producing the motion, and assumed that they follow very fast dynamics on the time scale of the cell movement. Furthermore, we assumed a linear sensitivity to any external chemical cue that guides the neutrophil to the site of infection. This was translated in the choice of the external field $H$, which was restricted by the conservation of $\phi$.

These assumptions allowed us to follow the motion of the neutrophil in two and three dimensions, by simulating the morphological alterations of the cell. This approach allowed us to incorporate the effect of desensitization, by the introduction of a degradation rate in the equation governing the dynamics of the chemical cue.
In addition, it allowed us to include a conditional response of the cell to cues, based on the amplitude of the gradient. Also, the emergence of structural changes in the membrane reflected the alteration affecting the number of ligand binding receptors that are responsible for biasing the motion.

The results were then compared with those of an in-vitro neutrophil moving under the effect of a chemical cue. The velocity was retrieved as a function of space, and confirmed the findings of our model. This approach was adopted since the cell components move at different speed, and we reasoned the the velocity of its centroid might not be conclusive.

We then moved on to model a similar mechanism: the response of a neural cell to chemical guidance. The cell has a leading edge, which is the growth cone. In this case, however, its assigned field moves, and pulls with it part of the cell, while the rest, the soma cell, remains static. This observation allowed us to define the velocity of the $\phi$ field to be proportional to $\psi \nabla c$, unlike that in the chemotaxis model which was defined to be proportional to $\nabla c$. The $\psi$ dependence in the velocity reflects the chemotropic effect on the dynamics; only the part of the cell attached to the $\psi$ field will be endowed with a velocity. This element where $\psi \neq 0$ and $\phi \neq 0$ is the growth cone. Additionally, to incorporate side branching, we generalized the treatment to incorporate more that one field $\psi$, each assigned to an external chemical cue.

We were able to model the growth in two and three dimensions, and to follow the growth cone as well. The axonal tip was tracked, and the velocity was measured along the direction of motion. It was compared to an in-vitro growing neuron. The assumption of a fast underlying actin dynamics still needed to be verified.
The treatment was still incomplete in both the neutrophil’s motion and the neural growth, as it lacked the details of the actin dynamics at the molecular level. We then moved on to build a more general model encompassing the neglected mechanisms.

For that purpose we adopted a simplified model for actin dynamics that is concerned with the time evolution of the concentration of profilin-ATP-G-actin, profilin-ADP-G-actin, cofilin-ADP-G-actin, and thymosin-ATP-G-actin. This problem was solved initially in the moving frame of the axon, in view of the fact that the dynamics of the profilin-ATP-G-actin concentration depended on its value at the membrane.

Therefore, we identified this as a free boundary problem, and reformulated it with the help of the phase-field method. We generalized the definition of the axon velocity introduced previously to include a dependence on the concentration of profilin-ATP-G-actin, and modified the concentration equations to contain their corresponding boundary conditions. This was achieved by singling out the growing region of the cell, and assigning to it the field $\tilde{\phi}$.

This treatment was then compared with the original model, and the steady state concentrations of the actin complexes were plotted as a function $x$, the direction of growth. Our results proved to be in agreement with the simplified model.

We noted the resemblance between the mechanisms of motion and growth, and formulated a generalized model from which both processes originate. The definition of the auxiliary field $\tilde{\phi}$ was generalized to describe both the polymerized region of a moving cell, as well as the growing region of a neuron. This allowed us to couple the
fields that designate the cell, as well as its leading edge or its growth cone, to the
dynamics of actin responsible for producing the forwards motion.

This parameterized functional provided a generalized formulation of both chemotactic and chemotropic effects on the cells. This method is generalizable to model many other cell morphodynamics problems, such as cell division, red blood cells, and numerous other dynamical processes affecting the cell shape.

Having summarized the contributions of our work, we turn to the features that this model failed to portray in an attempt to direct future investigations concerned with some aspects of the dynamics involved. We turn to the chemotaxis model first, and explore the possible consequences of adding stochastic term on the dynamics. In the equation $\psi$, which is the part that biases the motion towards the favored direction based on the number of bound membrane receptors, the fluctuations in that number would depict the way the cell deals with signal to noise. Similar questions could be raised in the case of a growing neuron. This determining a critical area emerging in response to the chemical gradient, and leads to definite axonal elongation, as not all cues induce a guaranteed growth. In other words the area enclosed by $\psi$, initialized to $\Theta(-\nabla \phi \cdot \nabla c)$, is critical in inducing the growth. This can be done by examining the effect of the chemical gradient on the growth, and running an exhaustive simulation to measure its consequence on the morphology in order to identify the bifurcation in the morphology.

In all the models, we have assumed linear sensitivity on the chemical attractant, however this may not always be valid. Therefore one could investigate the effect of different regimes of velocity dependence on signals.
In the third model, where we included the contribution of the actin concentration in producing the protrusive force, we measured discrepancies with the original model. Investigations could be carried to find the optimal term that reproduces faithfully the behavior of the actin complexes.

Finally, we hope that the treatment presented in this work is a contribution to generalizing the method to the context of biological systems, and that it helped understand, and describe the physical properties of certain aspects of motion and growth. We trust that our attempt, with simplifications and assumptions, nevertheless recovers and replicates significant properties of the systems under scrutiny.
Appendix A

6.1 Field’s Equation

The Ginzburg-Landau energy functional is given by:

\[ F[\phi] = \int \left[ \frac{\epsilon(\nabla \phi)^2}{2} + a\phi^2(1-\phi)^2 + H\phi \right] dV. \] (6.1)

In order to find the equation of motion of the field \( \phi \), \( \frac{\delta F}{\delta \phi} \) is calculated.

\[ F[\phi + \delta \phi] = \int \left[ \frac{\epsilon(\nabla (\phi + \delta \phi))^2}{2} + a(\phi + \delta \phi)^2(1-\phi - \delta \phi)^2 + H \cdot (\phi + \delta \phi) \right] dV. \] (6.2)

Now expanding Eq. (6.2), and neglecting terms of order \((\delta \phi)^2\) we get:

\[ \frac{\epsilon(\nabla (\phi + \delta \phi))^2}{2} = \frac{\epsilon(\nabla \phi)^2 + 2\cdot(\nabla \phi) \cdot (\nabla \delta \phi) + (\nabla \delta \phi)^2}{2} \approx \frac{\epsilon(\nabla \phi)^2 + 2\cdot(\nabla \phi) \cdot (\nabla \delta \phi)}{2}. \]

Also,

\[ a(\phi + \delta \phi)^2(1-\phi - \delta \phi)^2 = a(\phi^2 + 2\cdot \phi \cdot \delta \phi + (\delta \phi)^2)(1-2\cdot \phi + \phi^2 - 2\delta \phi + 2\cdot \phi \cdot \delta \phi + (\delta \phi)^2) \approx a\phi^2 \cdot (1-\phi)^2 - 2a \cdot \phi \cdot (1-\phi) \delta \phi - 2a \cdot \phi \cdot (1-\phi) \cdot (\delta \phi)^2. \]

Now Eq. (6.2) becomes:

\[ F[\phi + \delta \phi] = \int \frac{\epsilon(\nabla \phi)^2 + 2\cdot(\nabla \phi) \cdot (\nabla \delta \phi)}{2} \cdot \delta \phi dV. \] (6.3)

We now subtract Eq. (6.3) from Eq. (6.1), and we get:
\[ F[\phi + \delta \phi] - F[\phi] = \int \epsilon \cdot (\nabla \phi) \cdot (\nabla \delta \phi) + a \cdot [2 \phi \cdot (1 - \phi)^2 - 2 \phi^2 \cdot (1 - \phi) + H] \cdot \delta \phi dV. \]

Noting that the second term in the last equation is \( f' \) where \( f = a \phi^2 \cdot (1 - \phi)^2 \), and integrating the first term by part we get:

\[ F[\phi + \delta \phi] - F[\phi] = \delta F = \int \left[ -\frac{\epsilon \nabla^2 \phi}{2} + f' + H \right] \delta \phi dV. \]  

(6.4)

Now the equation of motion of \( \phi \) is related to \( \frac{\delta F}{\delta \phi} \) by :

\[ \frac{d\phi}{dt} = \Gamma \nabla^2 \frac{\delta F}{\delta \phi} = -\Gamma \nabla^2 \left[ \frac{\epsilon \nabla^2 \phi}{2} - f' - H \right]. \]  

(6.5)

The material derivative is related to the partial derivatives with respect to time and space via:

\[ \frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v \cdot \nabla \phi. \]

This allows us to write Eq. (6.5) as :

\[ \frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 \left[ \frac{\epsilon \nabla^2 \phi}{2} - f' - H \right] - v \cdot \nabla \phi. \]

Since the cell conserves its volume all throughout, then we should be able to relate the change in time of \( \phi \) to a gradient of some current. This leads to the following \( \Gamma \nabla^2 H = - (\nabla \cdot v) \phi \). Finally the equation of motion of \( \phi \) can be written

\[ \frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 \left[ \frac{\epsilon \nabla^2 \phi}{2} - f' \right] - \nabla \cdot (v \phi). \]  

(6.6)

Now we chose a linear sensitivity to chemical cue, that is the velocity field is set to be proportional to the concentration gradient, and the neutrophil’s dynamics will be governed by :

\[ \frac{\partial \phi}{\partial t} = -\Gamma \nabla^2 \left[ \frac{\epsilon \nabla^2 \phi}{2} - f' \right] - b \nabla \cdot (\phi \nabla c). \]  

(6.7)
6.2 Velocity Equation

Starting with the equation of the chemical concentration

\[ \frac{\partial c}{\partial t} = D_1 \nabla^2 c_1 - ac. \]

And using the linear sensitivity assumption, \( v = b \nabla c \), and that \( a << 1 \) we get:

\[ \frac{\partial v}{\partial t} = D_1 \nabla^2 v - av \approx D_1 \nabla^2 v. \]  \hspace{1cm} (6.8)

Now we note that this approximation entails a conservation of the chemical concentration, and therefore its total derivative with respect to time is zero. This leads to

\[ \frac{dc}{dt} = \frac{\partial c}{\partial t} + v_c \nabla c = 0. \]

where \( v_c \) is the speed at which the concentration is moving. Then \( \frac{dc}{dt} = -v_c \nabla c \), which allows us to rewrite Eq. 6.8 as

\[ D_1 \nabla^2 v + v_c \nabla v = 0. \]  \hspace{1cm} (6.9)

Now setting \( l = \frac{2D_1}{v_c} \), we can now finally write:

\[ \nabla^2 v + \frac{2}{l} \nabla v = 0. \]  \hspace{1cm} (6.10)

6.3 Velocity Analysis

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= -\Gamma \nabla^2 (\epsilon \nabla^2 \phi - f'(\phi)) - b \nabla \cdot (\phi \nabla c) \\
\frac{\partial c}{\partial t} &= D_1 \nabla^2 c - d_1 c.
\end{align*}
\]  \hspace{1cm} (6.11)

The Fourier transform is defined to be:
\[
\hat{f} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} f(x, t)e^{-i\omega x} dx.
\]

Then identities:
\[
\mathcal{F}(f^{(n)}) = (i\omega)^n \mathcal{F}(f) = (i\omega)^n \hat{f}.
\]
\[
\mathcal{F}(x^n f) = i^n \hat{f}^{(n)}.
\]

Start by applying the Fourier transform on the equation of \( c(x, t) \), this gives:
\[
\frac{\partial \hat{c}}{\partial t} = D_1 (i\omega)^2 \hat{c} - d_1 \hat{c}.
\]
\[
\frac{\partial \hat{c}}{\partial \omega} = - (\omega^2 D_1 + d_1) \hat{c}.
\]

Therefore:
\[
\hat{c}(\omega, t) = \hat{c}_0 e^{-(D_1 \omega^2 + d_1)t}.
\]
\[
\hat{c}(\omega, t = 0) = \hat{c}_0 = \frac{1}{\sqrt{2\pi}} \int c_0(x, t)e^{-i\omega x} dx
\]

We initialized the concentration to be a Gaussian:
\[
c(x, 0) = C e^{-\frac{(x-x_0)^2}{m}}.
\]

Then \( \hat{c}_0(\omega, t) \) is:
\[
\hat{c}_0(\omega, t) = C \sqrt{\frac{m}{2}} e^{-\frac{m\omega^2}{4} + i\omega x_0}.
\]

This then allows us to write \( \hat{c}(\omega, t) \):
\[
\hat{c}(\omega, t) = C \sqrt{\frac{m}{2}} e^{-\frac{m\omega^2}{4} + i\omega x_0} e^{-(D_1 \omega^2 + d_1)t}.
\]

We now write the inverse Fourier transform of \( \hat{c}(\omega, t) \):
\[
c(x, t) = \frac{1}{\sqrt{2\pi}} \int \hat{c}(\omega, t) e^{i\omega x} d\omega.
\]
\[
c(x, t) = C \frac{\sqrt{m}}{\pi} e^{-d_1 t} \int e^{-\left(\frac{m}{4} + D_1 t\right)\omega^2 + i\omega(x + x_0)} d\omega.
\]

We can now finally write \( c(x, t) \):
\[
c(x, t) = C \frac{\sqrt{m}}{m + 4D_1 t} e^{-d_1 t} e^{-\frac{(x-x_0)^2}{m + 4D_1 t}}.
\]

In our domain: \( \frac{(x-x_0)^2}{m + 4D_1 t} \ll 1 \), we can therefore Taylor expand the exponential about \( x_0 \) in order to linearize the equation of \( c(x, t) \), which then becomes up to fourth order:
\[
c(x, t) \approx C \left[ 1 - \frac{(x-x_0)^2}{m + 4D_1 t} \right] \sqrt{\frac{m}{m + 4D_1 t}} e^{-d_1 t} + O(x^4).
\]

We now go back to (2.3) and apply the Fourier transform to the equation of \( \phi(x, t) \). First start by treating the convective term by taking the linearized \( c(x, t) \) of Eq. (6.13), then:
\[
\nabla(\phi \cdot \nabla c) = \phi \cdot \nabla^2 c + \nabla c \cdot \nabla \phi.
\]

We have:
\[
\nabla c = -2C \frac{(x-x_0)}{m + 4D_1 t} \sqrt{\frac{m}{m + 4D_1 t}} e^{-d_1 t},
\]
\[
\nabla^2 c = -2C \frac{x}{m + 4D_1 t} \sqrt{\frac{m}{m + 4D_1 t}} e^{-d_1 t}.
\]

Then we identify the velocity term to be \( b \nabla c \) since it multiplies \( \nabla \phi \). Now we assume that the cell is subject to another field, that is spatially varying \( \nabla c_2 = x \). Then there will be two counteracting velocities, and we need to determine which one will have the predominant effect.
\[
(b \nabla c + b_2 \nabla c_2) \nabla \phi.
\]
\[
(-2bC \frac{(x-x_0)}{m + 4D_1 t} \sqrt{\frac{m}{m + 4D_1 t}} e^{-d_1 t} + b_2 x) \nabla \phi.
\]

Then:
\[
-2bC \frac{(x-x_0)}{m + 4D_1 t} \sqrt{\frac{m}{m + 4D_1 t}} e^{-d_1 t} + b_2 x > 0.
\]
\[
\frac{b_2}{b} > \frac{2C (x-x_0)}{x} \frac{m}{m+4D_1 t} \sqrt{\frac{m}{m+4D_1 t} e^{-d_1 t}}.
\]

Then let \( \Delta(x, t) = \frac{2C (x-x_0)}{x} \frac{m}{m+4D_1 t} \sqrt{\frac{m}{m+4D_1 t} e^{-d_1 t}} \).

For our choice of \( \nabla c_2 \), \( \frac{b_2}{b} \) should be positive for the cell to be exclusively driven by the \( \nabla c_2 \), and visa versa. This was confirmed in the simulations, for a choice of \( b_2 > 0.006 \), the cell was primarily driven by \( \nabla c_2 \) and the cell moved away from the site of infection, while for a choice of \( b_2 = -0.03 \) the cell moved to the site mostly driven by \( \nabla c \). Now if we assume that \( \nabla c_2 \) is also governed by a diffusion equation, the same procedure could be carried out to get a linearization of \( c_2 \) about \( x_{02} \). Then:

\[
\nabla c_2 = -2C_2 \frac{(x-x_{02})}{m_2+4D_2 t} \sqrt{\frac{m_2}{m_2+4D_2 t} e^{-d_2 t}}.
\]

We can now compare the effect of both fields by noting

\[
(b\nabla c + b_2 \nabla c_2) \nabla \phi = \left[ -2b_2 C_2 \frac{(x-x_{02})}{m_2+4D_2 t} \sqrt{\frac{m_2}{m_2+4D_2 t} e^{-d_2 t}} - 2bC \frac{(x-x_0)}{m+4D_1 t} \sqrt{\frac{m}{m+4D_1 t} e^{-d_1 t}} \right] \nabla \phi
\]

\[
\frac{b_2}{b} > \frac{2C \frac{(x-x_{02})}{m_2+4D_2 t} \sqrt{\frac{m_2}{m_2+4D_2 t} e^{-d_2 t}}}{2C_2 \frac{(x-x_{02})}{m_2+4D_2 t} \sqrt{\frac{m_2}{m_2+4D_2 t} e^{-d_2 t}}} = \Delta(x, t).
\]

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Then the cell will be predominantly driven by $\nabla c$ and visa versa. For parameter values: $D_1 = D_2 = 1$, $C = C_2 = 20$, $d_1 = d_2 = 0.005$, $x_0 = 50$, $x_{02} = 60$ and $m_1 = 4 \times 10^2$, $m_2 = 5 \times 10^2$, we show a plot of $\Delta(x, t)$. Here for $\frac{b_2}{b} > 9.63$, then $\nabla c$ is predominant, and the converse is true; when $\frac{b_2}{b} < 9.63$, $\nabla c_2$ will dominate.

### 6.4 Numerical Scheme

The derivative with respect to time is defined by the forward Euler method:

\[
\frac{df}{dt} = \frac{f(t+h_t) - f(t)}{h_t}.
\]

where $h_t$ denotes the time step size.

The space derivative followed a second order accurate explicit algorithm defined as follows:

\[
\frac{df}{dx} = \frac{f(x+h_x) - f(x-h_x)}{2h_x}.
\]

where $h_x$ is the space mesh size.

Accordingly the second derivatives is given by:

\[
\frac{d^2f}{dx^2} = \frac{f(x-h_x) - 2f(x) + f(x+h_x)}{h_x^2}.
\]

The choice of the time and space step sizes is not arbitrary, it should guarantee the stability of the algorithm. It is therefore controlled by the space dimensionality $d$. Specifically for a conservative dynamics, it is given by the following relation:

\[
\frac{h_t}{h_x^2} < \frac{1}{2d^d+1}.
\]
Appendix B

The functional is given by

$$ F[\phi, \psi] = \int \left[ \frac{\epsilon (\nabla c)^2 (1 - \psi)(\nabla \phi)^2}{2} + a \phi^2 (1 - \phi)^2 \right] dV. \quad (6.14) $$

$$ F[\phi + \delta \phi, \psi] = \int \left[ \frac{\epsilon (\nabla c)^2 (1 - \psi)(\nabla \phi + \delta \phi)^2}{2} + a (\phi + \delta \phi)^2 (1 - \phi - \delta \phi)^2 \right] dV. \quad (6.15) $$

Now expanding Eq. (6.15), and neglecting terms of order \((\delta \phi)^2\) we get:

$$ \frac{\epsilon (\nabla c)^2 (1 - \psi)(\nabla \phi + \delta \phi)^2}{2} \approx \frac{\epsilon (\nabla c)^2 (1 - \psi)(\nabla \phi)^2 + 2 (\nabla \phi \cdot \nabla \delta \phi) + \nabla (\delta \phi)^2}{2} \approx \frac{\epsilon (\nabla c)^2 (1 - \psi)(\nabla \phi)^2 + 2 (\nabla \phi \cdot \nabla \delta \phi)}{2}. $$

Also

$$ a (\phi + \delta \phi)^2 (1 - \phi - \delta \phi)^2 = a (\phi^2 + 2 \phi \cdot \delta \phi + (\delta \phi)^2)(1 - 2 \phi + \phi^2 - 2 \delta \phi + 2 \phi \cdot \delta \phi + (\delta \phi)^2) \approx $$

$$ a (\phi^2 + 2 \phi \cdot \delta \phi)(1 - 2 \phi + \phi^2 - 2 \delta \phi + 2 \phi \cdot \delta \phi) = a (\phi^2 + 2 \phi \cdot \delta \phi)((1 - \phi)^2 - 2(1 - \phi) \cdot \delta \phi) = $$

$$ a \phi^2 \cdot (1 - \phi)^2 - 2a \cdot \phi^2 \cdot (1 - \phi) \delta \phi + 2a \cdot \phi \cdot (1 - \phi)^2 \delta \phi - 2a \cdot \phi \cdot (1 - \phi) \cdot (\delta \phi)^2 \approx $$

$$ a \phi^2 \cdot (1 - \phi)^2 + a \cdot [2 \phi \cdot (1 - \phi)^2 - 2 \phi^2 \cdot (1 - \phi)] \delta \phi. $$

Now Eq. (6.15) becomes:

$$ F[\phi + \delta \phi] = \int \frac{\epsilon (\nabla c)^2 (1 - \psi)((\nabla \phi)^2 + 2 \cdot (\nabla \phi) \cdot (\nabla \delta \phi))}{2} + a \phi^2 (1 - \phi)^2 + a \cdot [2 \phi \cdot (1 - \phi)^2 - 2 \phi^2 \cdot (1 - \phi)] \cdot \delta \phi dV. \quad (6.16) $$
Noting that the second term in the last equation is \( f' \) where \( f = a \phi^2 \cdot (1 - \phi)^2 \), and integrating the first term by part we get:

\[
\mathcal{F}[\phi + \delta \phi, \psi] - \mathcal{F}[\phi, \psi] = \delta F = \int \left[ -\frac{\epsilon(\nabla c)^2(1 - \psi)\nabla^2 \phi}{2} + f' \right] \delta \phi dV. \tag{6.17}
\]

Now the equation of motion of \( \phi \) is related to \( \frac{\delta F}{\delta \phi} \) by :

\[
\frac{d\phi}{dt} = \Gamma_1 \nabla^2 \left( \frac{\delta F}{\delta \phi} \right) = -\Gamma_1 \nabla^2 \left[ \frac{\epsilon(\nabla c)^2(1 - \psi)\nabla^2 \phi}{2} - f' \right]. \tag{6.18}
\]

The material derivative is related to the partial derivatives with respect to time and space via:

\[
\frac{d\phi}{dt} = \frac{\partial \phi}{\partial t} + v \cdot \nabla \phi.
\]

This allows us to write Eq. (6.18) as :

\[
\frac{\partial \phi}{\partial t} = -\Gamma_1 \nabla^2 \left[ \frac{\epsilon(\nabla c)^2(1 - \psi)\nabla^2 \phi}{2} - f' \right] - v \cdot \nabla \phi. \tag{6.19}
\]

Additionally, the equation of the field \( \psi \) can now be computed:

\[
\mathcal{F}[\phi, \psi + \delta \psi] = \int \left[ \frac{\epsilon(\nabla c)^2(1 - \psi - \delta \psi)|\nabla \phi|^2}{2} + a \phi^2 (1 - \phi)^2 \right] dV. \tag{6.20}
\]

We now subtract Eq. (6.20) from Eq. (6.14), and we get:

\[
\mathcal{F}[\phi, \psi + \delta \psi] - \mathcal{F}[\phi, \psi] = \int -\frac{\epsilon(\nabla c)^2(\nabla \phi)^2}{2} \cdot \delta \psi dV.
\]

But we have:

\[
\frac{d\psi}{dt} = \frac{\partial \psi}{\partial t} + v_2 \cdot \nabla \psi = -\Gamma_2 \frac{\delta F}{\delta \psi}.
\]
The equation of the $\psi$ is given by

$$\frac{\partial \psi}{\partial t} = -\Gamma_2 \frac{\delta F}{\delta \psi} - v_2 \cdot \nabla \psi.$$ 

This in turn gives:

$$\frac{\partial \psi}{\partial t} = \Gamma_2 \frac{\epsilon (\nabla c)^2 \cdot (\nabla \phi)^2}{2} - v_2 \cdot \nabla \psi. \quad (6.21)$$
Appendix C

The equation of the functional $F(a)$ is given by

$$F(a) = \int \frac{D\tilde{\phi} \cdot (\nabla a)^2}{2} - \frac{Ha^2}{2} \, dV.$$  \hspace{1cm} (6.22)

Similarly as in the previous appendices we write $\frac{\delta F}{\delta a}$, to derive the equation of $a$.

$$F(a + \delta a) = \int \frac{D\tilde{\phi} \cdot (\nabla a + \delta a)^2}{2} - \frac{H(a + \delta a)^2}{2} \, dV.$$  

Neglecting terms of the order $(\delta a)^2$ we write:

$$F(a + \delta a) = \int \frac{D\tilde{\phi} \cdot (\nabla a)^2 + 2\nabla a \cdot \nabla (\delta a))}{2} - \frac{H(a^2 + 2a\delta a + (\delta a)^2)}{2} \, dV.$$

Now:

$$F(a + \delta a) - F(a) = \int D\tilde{\phi} \cdot \nabla a \cdot \nabla (\delta a) - (H a \delta a) \, dV.$$  

Now integrating the first term by part by noting that $u = \tilde{\phi} \nabla a$ and $v' = \nabla (\delta a)$ we write:

$$\int [D\tilde{\phi} \cdot \nabla a \cdot \nabla (\delta a)] \, dV = D\tilde{\phi} \cdot \nabla a \cdot a - \int [D\tilde{\phi} \cdot \nabla a] \cdot \delta a \, dV.$$  

The first term is a vanishing surface term, then:

$$F(a + \delta a) - F(a) = - \int [D\tilde{\phi} \cdot \nabla a] \cdot \delta a \, dV - \frac{\delta F}{\delta a} \cdot \delta a \, dV.$$  

We can now write $\frac{\partial a}{\partial t} = \frac{\partial a}{\partial t} + v \cdot \nabla a = - \frac{\delta F}{\delta a} + \sigma$.

$$\frac{\partial a}{\partial t} = D\nabla (\tilde{\phi} \nabla a) + \tilde{\phi} \cdot (k_3 \beta - k_3 a + k_2 p) + H a - v \cdot \nabla a.$$  

Letting $H = -\nabla v$, we write:

$$\frac{\partial a}{\partial t} = D\nabla (\tilde{\phi} \nabla a) + \tilde{\phi} \cdot (k_3 \beta - k_3 a + k_2 p) - \nabla (v \cdot a).$$  

where $v = V_{Mogi} \frac{\partial}{\partial \eta} \tilde{\phi}$. Similarly, the equation of $\beta$, $s$ and $p$ follow.
References


[34] S. Najem and M. Grant. Phase Field Model For Neural Cell Chemotropism.


