Generalized travelling wave solutions for a microscopic chemotaxis model

P. M. Tchepmo Djomegni

UNIVERSITY OF
KWAZULU-NATAL

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This dissertation is submitted in fulfilment of the academic requirements for the degree of Doctor of Philosophy in Applied Mathematics to the School of Mathematics, Statistics and Computer Science, College of Agriculture, Engineering and Science, University of KwaZulu-Natal, Durban.

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As the candidate's supervisor, I have approved this dissertation for submission.

Professor K S Govinder ..... November 2014

Abstract

In biology cell migration is one of the most critical processes, for it is decisive in the mechanisms leading to the beginning of life. The collective migration of cells via wave motion plays a key role in understanding many essential steps in developmental processes. It is often modelled as a system of partial differential equations (PDEs). We investigate in a one-dimensional microscopic model, the formation of travelling bands (via wave motion) of bacteria E coli, caused by the chemotactic response of cells to a signal moving with constant speed. We also look at the impact of cell growth and unbiased turning rate on the behaviour of our system. The model derives from the experimental observation reported in Budrene and Berg (1991, 1995).

In the first problem we tackle, we overlook the proliferation of the cells and we search for travelling wave solutions in the case where the cells do not starve. We show that, using a group theoretical approach, a larger class of travelling wave solutions than that obtained from the standard ansatz is possible. By applying realistic initial and boundary conditions, we restrict the general solutions appropriately. This is the first time that explicit travelling wave solutions have been obtained for this system of equations. In particular, we treat the full system, including non-zero diffusivity terms, unlike previous approaches. Importantly, we provide biologically relevant solutions.

The second problem focuses on the metabolism effect in the case of starvation. It was observed experimentally that a low concentration of nutrients may not cause the band to break up, but rather impel the cells to consume the excreted signal. Here cell growth is allowed with constant rate. We use asymptotic methods to prove the existence of travelling wave solutions in both the case of diffusivity and non diffusivity. Significant results have been obtained.

In the last problem we incorporate the proliferation of the cells in the case of non-limiting

resources. Constant cell growth and a nutrient dependent proliferation rate are considered. We combine a dynamical systems analysis with other analytic methods to investigate the behaviour of the solutions. Travelling wave solutions have been obtained both for high chemotactic sensitivity, and also in the case of no chemotaxis. Explicit, biologically and pertinent solutions have been provided, confirming the validation of the model.

Preface

I declare that the contents of this dissertation are original except where due reference has been made. It has not been submitted before for any degree to any other institution.

P. M. Tchepmo Djomegni

November 2014

Declaration 1 - Plagiarism

I, Patrick Mimphis Tchepmo Djomegni, declare that

1 The research reported in this thesis, except where otherwise indicated, is my original research.

2 This thesis has not been submitted for any degree or examination at any other university.

3 This thesis does not contain other persons data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4 This thesis does not contain other persons writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

   a Their words have been re-written but the general information attributed to them has been referenced

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5 This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the References sections.

Signed

Declaration 2 - Publications

Details of contribution to publications presented in this thesis:

Chapter 2

P. M. T. Djomegni and K. S. Govinder. Generalized travelling wave solutions for hyperbolic chemotaxis PDEs. *Math. Biosciences* (2014), Submitted.

Chapter 3

P. M. T. Djomegni and K. S. Govinder. Travelling wave solutions in chemotaxis: starvation. *J. Math. Biol.* (2014), Submitted.

Chapter 4

P. M. T. Djomegni and K. S. Govinder. Asymptotic analysis of travelling wave solutions in Chemotaxis with nutrients dependent cell growth. *J. Theor. Biol.* (2014), Submitted.

Acknowledgments

" Except the Lord build the house, they labour in vain that build it; except the Lord keep the city, the watchman waketh but in vain." **Psalm 127, 1 (KJV)**

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Dedication

To my Saviour and my redeemer, the Lord Jesus Christ, for the grace He has given me to accomplish this work

To my dear admirable father Mr Djomegni Hubert for his multiple support

To Mr Robin Moodley and his wife Jennifer for their love, and for the spiritual and emotional support

" Remember the Lord your God. He is the one giving you power to be successful, in order to fulfil the covenant he confirmed to your ancestors with an oath." **Deut 8, 18(NLT)**

*"If you confess with your mouth the Lord Jesus and believe in your heart that God has raised him from dead, you will be saved."***Rom 10,9 (NKJV)**

Contents

Chapter 1

Introduction

1.1 Differential equations and its importance in Biology

The endeavour to understand and predict physical phenomena gave birth to mathematical models, represented in the form of differential or difference equations. Differential equations were formulated for the first time in the mid $17th$ century by Leibniz and Newton, and were applied to solve problems in geometry and mechanics [49].

In systems biology, modeling differential equations has played a remarkable role. Its has helped to study population dynamics [66], spread of infectious diseases [38, 48], intracellular dynamics [39, 111], drug delivery [53, 90], tumour growth [37, 35] and scar formation [20] amongst others. Malthus [66] was the first to propose a model for population dynamics. Verhulst [103] later improved the model by considering limiting carrying capacity. Lotka [59, 60] and Volterra [106] later proposed a model to describe the interaction between two populations. This approach is widely used in epidemiology to study the spread of diseases.

Partial differential equations (PDEs) are often employed to model complex mechanism in Biology, for they consider multivariational parameters (time, space, intracellular variational). They can be used to study the time-space distribution of cell migration, tumour growth, and pattern formation [63, 64, 29]. Fisher's equation is one of the most used models to describe the spread of a species from a macroscopic (population-based) level. It was formulated by Fisher [31] as

follws:

$$\frac{\partial u}{\partial t} = ru(1-u) + D\frac{\partial^2 u}{\partial x^2}, \tag{1.1}$$

where u represents the density of the specie, D is the diffusion coefficient, x is the position, t the time and r a constant. From a microscopic (individual-based) level, the convection equation is commonly used to describe the transport mechanisms of particles. A typical example is the transport equation describing the velocity-jump process given by

$$\frac{\partial p}{\partial t} + \nabla(vp) = R, \tag{1.2}$$

where $p(x, v, t)$ stands for the particle density at the position x, moving with velocity v at time t, and R describes sources or sinks. In the above equation, it is assumed that there is no interaction between particles.

Given the role that PDEs play in understanding complex phenomena, methods for solving PDEs are vital. With the outstanding work of Lie, group theory via symmetry analysis became the most useful method for finding exact solutions of PDEs. Lie symmetries are used to reduce the numbers of variables and the order of the system, to determine invariant solutions [76, 86]. Although the applications of Lie symmetry analysis involved lengthy expressions, the development of software packages has simplified its implementation.

Depending on the complexity of the equations under study, instead of looking at the exact state of solutions at any position, one may only be interested in the long term behaviour. This approach gave birth to dynamical systems analysis, in which the qualitative behaviour of the solutions are analyzed [96]. We have utilized both approaches in this work.

Despite the methods developed to analyse PDEs, many nonlinear PDEs cannot be solve explicitly. As a result, only particular classes of solutions have been explored. Travelling wave solutions are a special type of solution that have great utility. Their particularity is that they move with constant speed and they preserve their shape profile. Importantly, travelling waves have been observed in chemotaxis [1, 8, 25, 84] – the subject of this work.

1.2 Partial differential equations in chemotaxis

Chemotaxis is the orientation of species in response to chemoattractants. It plays an important role in the collective migration of cells. It contributes to the recruitment of cells into sites of inflammation or infection, and speeds up the metastasis and atherosclesis process of diseases [18, 21, 34, 70, 71]. Understanding the key factors facilitating chemotaxis enables us to control and predict the trajectory of cells, their self-organization, mutual defense and response to extracellular signaling.

Travelling bands (via wave motion) was observed in chemotaxis systems for the first time in the late 1800s by Engelmann [25, 26], Pfeffer [84] and Beyenrinck [8]. Over the past fifty years, the noteworthy work of Adler [1, 2] has made bacterial chemotaxis one of the better-documented systems in Biology. Adler [1, 2, 3] introduced a population of cells in a capillary tube containing oxygen and nutrients. He observed the formation of two bands of cells. The first band consumed some nutrients and all the oxygen, while the second band consumed the residual nutrients. In both bands, cells move towards higher concentrations. The formation of the bands of cells was also observed without the addition of nutrients [2].

From the macroscopic perspective, Keller and Segel [44, 45, 46] formulated the first model (the K-S model) for chemotaxis depicting the chemotactic behaviour of slime molds. The general form of the K-S model is given by:

$$\frac{\partial b}{\partial t} = \nabla.\left(\mu(s)\nabla b\right) - \nabla.\left(k_2(b,s)b\nabla s\right) + f(b,s), \tag{1.3}$$

$$\frac{\partial s}{\partial t} = D\nabla^2 s - g(b,s), \tag{1.4}$$

where $b(x,t)$ represents the bacteria density, $s(x,t)$ is the concentration of the critical substrate, $k_2(b,s)$ is the chemotactic sensitivity function, $f(b,s)$ is the cell proliferation rate function, $g(b,s)$ represents the uptake of substrates by cells or degradation, and $\mu(s)$ and D are the diffusion coefficients of bacteria and the substrates, respectively.

Often growth and death are neglected in the mathematical analysis of (1.3)–(1.4) due to their long relative time scale. However, the consideration of this biological process has proved to be important in the behaviour of the system. Lapidus *et al* [55] observed that zero growth did

not prevent cells from aggregating, but rather reduced the wave speed. Some classes of growth functions were provided by Kennedy *et al* [47] leading to travelling wave solutions of constant speed. Biologically, Budrene and Berg [13, 14] observed the formation of new bands of bacteria caused by the proliferation of cells.

The global existence of the solutions of (1.3)–(1.4) was proved under different forms of the chemotactic sensitivity function k_2 [39, 40, 77]. A singularity in the function k_2 was required for the existence of travelling wave solutions in the zero growth scenario [44, 45, 46]. Such a restriction is not realistic in certain contexts, for it can cause the bands of cells to move with unlimited velocity [111]. Nadin *et al* [73] overcame this unnecessary restriction by adding logistic growth terms.

From the microscopic (cell-based) perspective, Patlak [83] proposed the first model for chemotaxis describing a random walk process of a particle with persistence of direction and external bias. For the case of particles moving independently by alternating run and tumble, Alt [4] and Othmer *et al* [80] formulated a model describing the velocity-jump processes, written as follows:

$$\frac{\partial}{\partial t}p(x,v,t) + v.\nabla p(x,v,t) = \lambda \int_V T(v,v')p(x,v',t)dv', \tag{1.5}$$

where $p(x,v,t)$ is the particle density at position x and time t, moving with velocity v, λ is the turning rate, and $T(v,v')$ is the turning kernel representing the probability of a velocity jump (if a jump occurs) from v' to v.

Intracellular dynamics describing the response of cells to chemical have been represented in general in the form of ODEs as follows [5, 28, 29, 93, 95]:

$$\frac{dy}{dt} = f(y,S), \tag{1.6}$$

where $y = (y_1, ..., y_M) \in \mathbb{R}^M$ are internal state variable, S is the concentration of the stimuli detected, and f is a vector function describing the process. Recently, Xue *et al* [111] proposed a model that considers the interplay between chemoattractants and nutrients. They also represented in their model signal transduction and metabolism processes. Their model can be used in a variety of biological systems to describe the conflict between two species of a microscopic level (individual behaviour). Under the scenario of zero cell growth and non diffusion

of substrates, Xue *et al* [111] obtained travelling wave solutions (without requiring a singular sensitivity). Franz *et al* [32] considered growth in the situation of starvation. They assumed that cells consumed chemoattractants only (which do not diffuse). They demonstrated the existence of travelling wave solutions, but required a minimal wave speed.

1.3 Model formulation

The model studied in this thesis is inspired by the experimental work of Budrene and Berg [13, 14], Brenner *et al* [11], and Woodward *et al* [110]. Moving in a semi solid containing a carbon source of succinate (the nutrient), it was observed that bacteria *E coli* consume succinate and secrete a signal gradient of aspartate, then aggregate in response to the signal, and form different geometric patterns. The size of the aggregate increased as the succinate concentration increased. When the concentration of succinate becomes low, the aggregation does not break up; cells consume aspartate.

Within the cells, mechanisms are developed to enable them to communicate and to respond to stimuli. Such mechanism is called the signal transduction. It is well understood in *E coli*, whereby cells detect signaling via their transmembrane receptors. In response to the signaling, an enzyme will be excreted within the cell and will facilitate the direction of the movement of the cell [7]. The phosphorylation of CheY (caused by chemorepellents) will result to clockwise rotation of the flagella, and will cause the cell to tumble. The dephosphorylation of CheY (caused by chemoattractants) will drive counter-clockwise rotation of the flagella, and will propel the cell forward [23, 65]. We note that the protein CheY facilitates the issuance of the signal from chemoreceptors to flagella, and that *E coli* moves by alternating runs and tumbles with constant speed $s = 10 - 20\mu m/sec$ [82]. In the mathematical representation of this intracellular dynamic, two main factors are always considered: fast excitation (rapid decrease in the phosphorylated protein), and slower adaptation (slow return to the prestimulus level). The model describing this process can be formulated as follows [5, 28, 30, 78, 95]:

$$\frac{dy_1}{dt} = f_1(y, S) = \frac{g(S) - (y_1 + y_2)}{t_e}, \quad \frac{dy_2}{dt} = f_2(y, S) = \frac{g(S) - y_2}{t_a}, \tag{1.7}$$

where the variable $y = (y_1, y_2)$ describes the signal transduction, $S(x, t)$ is the concentration of

the signal at position x and time t, the function g encrypts the first step of signal transduction, and t_e and t_a are the time scale for excitation and adaptation respectively.

In the absence (or at low concentration) of the nutrients, cells consume the excreted signal. A well organized metabolism process takes place within the cells allowing them to survive when resources are limited, and to respond to their surroundings. To model this mechanism, Xue *et al* [111] assumed that after consuming the nutrient F a variable z_1 is responsible for the secretion of the signal S via the pathway

$$F \to z_1 \to S. \tag{1.8}$$

A low level of nutrients catalytically causes z_1 to give rise to a starving variable z_2 via the pathway

$$\phi \xrightarrow{z_1} z_2 \to \phi, \tag{1.9}$$

where ϕ represent the reactants/products assumed to be in excess. The model description of this intracellular metabolism is formulated as follows [111]:

$$\frac{dz_1}{dt} = g_1(z, F) = \frac{F(x,t) - z_1}{t_f}, \quad \frac{dz_2}{dt} = g_2(y, S) = \frac{z_1 - z_2}{t_m}, \tag{1.10}$$

where the variable $z = (z_1, z_2)$ represents the metabolism process, and t_f and t_m are the characteristic time scale for the production of the variable z_1 and z_2, respectively.

From a cell-based point of view, the cell distribution can be described via transport equations for velocity-jump processes as follows:

$$\frac{\partial p^+}{\partial t} + s\frac{\partial p^+}{\partial x} + \sum_{i=1}^{2} \frac{\partial}{\partial y_i}(f_i(y,S)p^+) + \sum_{i=1}^{2} \frac{\partial}{\partial z_i}(g_i(z,F)p^+) = -\lambda\left(-\frac{\partial S}{\partial x}\right)p^+ + \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(F)p^+, \tag{1.11}$$

$$\frac{\partial p^-}{\partial t} - s\frac{\partial p^-}{\partial x} + \sum_{i=1}^{2} \frac{\partial}{\partial y_i}(f_i(y,S)p^-) + \sum_{i=1}^{2} \frac{\partial}{\partial z_i}(g_i(z,F)p^-) = \lambda\left(-\frac{\partial S}{\partial x}\right)p^+ - \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(F)p^-, \tag{1.12}$$

where $p^{\pm}(x, y, z, t)$ represents the cell density at the position x, time t and internal state $[y, z]$, moving with velocity $\pm s$, h is the proliferation rate of the cells, and λ is the turning rate function of the cells. We will choose the turning rate proposed by Xue *et al* [111] given as

$$\lambda\left(\frac{\partial S}{\partial x}\right) = \lambda_0\left(1 + \frac{\frac{\partial S}{\partial x}}{k + |\frac{\partial S}{\partial x}|}\right) = \lambda_0\left(1 + \chi\frac{\partial S}{\partial x}\right), \tag{1.13}$$

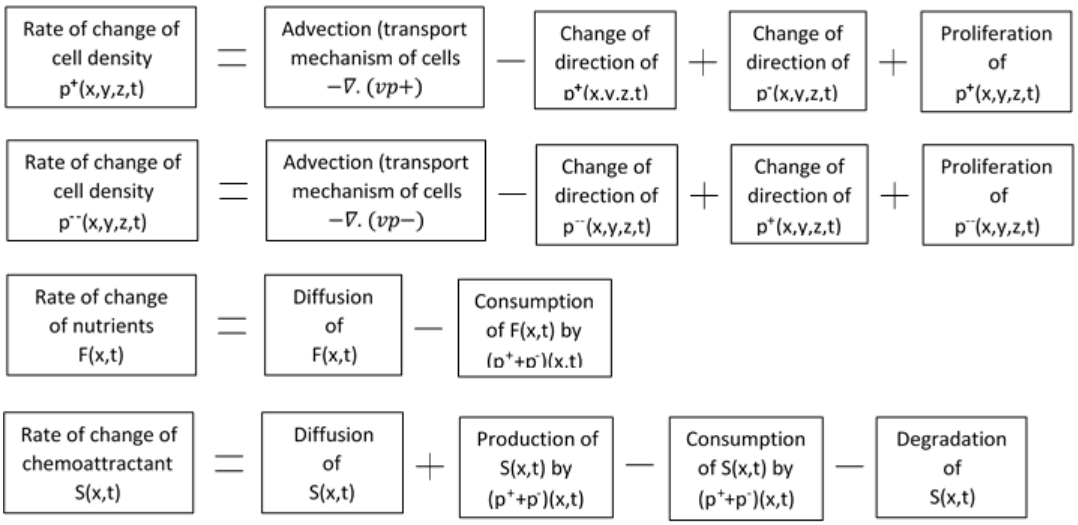


Figure 1.1: Diagram describing the time-space distribution of cells and substrates in chemotaxis

with λ_0 being the unbiased turning rate ($\lambda_0 > 0$), χ the chemotactic sensitivity and k the sensitivity coefficient.

We can describe using diffusion equations the distribution of substrates as follows [111]:

$$\frac{\partial F}{\partial t} = D_F \frac{\partial^2 F}{\partial x^2} - \alpha_1 F \int_{\mathbb{Z}} \int_{\mathbb{Y}} w(z_2)(p^+ + p^-) dy dz, \tag{1.14}$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + \alpha_2 F \int_{\mathbb{Z}} \int_{\mathbb{Y}} w(z_2)(p^+ + p^-) dy dz - \alpha_1 S \int_{\mathbb{Z}} \int_{\mathbb{Y}} (1 - w(z_2))(p^+ + p^-) dy dz - \gamma S, \tag{1.15}$$

where α_1 and α_2 are respective the consumption and production rate of substrates per cell, γ is the degradation rate of the signal, and w is a switch function given by

$$w(z_2) = \begin{cases} 0 & \text{for } z_2 \leq z_c, \\ 1 & \text{for } z_2 > z_c, \end{cases} \tag{1.16}$$

where z_c is a critical concentration of succinate that facilitates metabolism. The systems (1.11)–(1.12) and (1.14)–(1.15) can be interpreted from the diagram in Figure 1.1.

Diffusion of substrates and cell growth and death have often been ignored in chemotaxis models due to the complexity of the analysis. (For instance, the diffusion term involves a higher spatial order in the system, and its non representation reduces the order of the system.) These restrictions are justified in certain experimental settings (*in vivo* experiments, duration of experiment

taking place before the proliferation process, low diffusion of substrates, etc). However, in many situations they have a significant impact on the behaviour of the system. It was experimentally observed in *E coli* that the proliferation of cells causes the formation of new bands of cells [14]. Moreover, Elliot *et al* [24] controlled the migration and the proliferation of *E coli* cells to invade and interact with tumor cells. Mathematically, it has been proved that allowing diffusion in the model can contribute to the stabilization of the steady state of the system [88].

1.4 Outline

The main objective of this work is to investigate the observed formation of bands of bacteria in our model, via the study of the existence of travelling wave solutions. Unlike previous approaches, we will allow for diffusivity and signal degradation. We will undertake the investigation under the scenarios of growth and of zero growth, and in situations of high sensitivity and non sensitivity to the signal. The effect of microscale parameters such as cell speed, cell growth and unbiased turning rate on the macroscopic behaviour of the system will be examined. Group theoretical analysis will be used to generate a larger class of travelling wave solutions (via new invariants) than that obtained from the standard ansatz. Only relevant invariants will be considered. The coefficients resulting from the Lie symmetry analysis will play a stabilizing role in the boundedness study of the solutions, confirming our previous findings on the links between group theory and dynamical systems analysis [97]. Generalized travelling wave solutions will be demonstrated, with explicit solutions provided in most of the cases for the first time.

In Chapter 2, we examine the case of non starvation under zero growth. Here, it is assumed that there are enough resources, cells consume nutrients (the succinate) only, and excrete a gradient of signal (the aspartate). We will provide, for the first time, a general form of diffusing solutions. Realistic initial and boundary conditions will be applied to restrict them appropriately, and to provide biologically relevant travelling wave solutions.

In Chapter 3, we introduce growth and death in the model for non starving cells. Two forms of proliferation rates are considered: constant growth rate and linear growth rate depending on

the concentration of nutrients. The constant growth is motivated by the observation of Budrene and Berg [14] in which *E coli* cells grew at a constant rate over the range of $0.5 - 7mM$ of succinate concentration. The linear growth rate incorporates both growth and death. We will combine the stability analysis results with asymptotic methods to investigate the behaviour of the system.

In Chapter 4, we look at the scenario of starvation. Starvation in this context depicts the total depletion (or very low concentration) of nutrients. Cells here consume signal only (as observed in [2]). We note that Xue *et al* [111] in their interpretation of starvation (under zero growth), assumed the possibility of nutrients to be consumed by cells (when the signal concentration becomes the lowest). We here consider the limiting situation of survival (the signal is not produced). We will conduct our analysis under both the cases of zero and constant growth. Unlike previous approaches, we allow for diffusivity and signal degradation. We will provide explicit solutions in the limiting cases of no chemotaxis and high chemotactic sensitivity.

In Chapter 5, we summarize the results obtained in our analysis. We highlight some limitations to be explored in future work.

Chapter 2

Travelling wave solutions in chemotaxis under zero growth: no starvation

2.1 Introduction

In biology cell migration is one of the most critical process, for it is decisive in the mechanisms leading to beginning of life. In fact, the signalling of the female reproductive tract is essential in the regulation of sperm motility; most of male sterility results from poor sperm motility [27]. In addition, cell migration is crucial in the growth and maintenance of multicellular organisms via developmental morphogenesis, tissue repair and regeneration as well as tumour metastasis. It is important to study the collective migration of cells via wave motion, as this plays a key role in understanding many essential steps in developmental processes [108]. For example, in the wound healing process, cells are required to move together in particular directions to specific locations. Additionally, tumor invasion is boosted by proliferation and significant migration of cells into the surrounding tissue [27].

Some bacteria are attracted by nutrients (sugar, amino acids, etc.) and repelled by noxious substances. This phenomenon is called chemotaxis, whereby cells move in response to a chemical gradient (depending on the effect on the cells, the chemical is defined as chemoattractant or chemorepellent) [23]. The chemical activates a receptor at the surface of the cell, which

results in a physiological response – there is a signal transduction. A well-studied example of this is found in *E coli*, where bacteria sense the environment and detect chemicals (the signal), mediated by transmembrane chemoreceptors located at the poles. Chemorepellents produce phosphorylation of CheY, which induce clockwise rotation of the flagella, whereas chemoattractants result in CheY dephosphorylation and induce counter-clockwise rotation of the flagella [65]. The chemotaxis protein CheY is involved in the issuance of the signal from the chemoreceptors to the flagella motors [82]. The counter-clockwise rotation pushes the bacterium forward (it is called a "run"), and the clockwise rotation causes the bacterium to tumble, which prevents it from moving toward repellents. In the absence of chemical stimuli, bacteria alternate between run and tumble modes. In Adler's experiments [1, 2, 3], travelling bands of *E coli* were observed when a number of cells were introduced at one end of a capillary tube containing oxygen and an energy source. As the amount of oxygen was insufficient to oxidize all the energy sources, two sharp bands of cells, visible to the naked eye, were seen. Cells in the first band consumed the oxygen, excreted and hence caused a gradient in the concentration of oxygen, then moved (at a constant speed) toward higher concentrations. However, in the second band, cells created a gradient in the concentration of the energy source, and moved toward higher concentrations as well. Such phenomena have been formulated by mathematicians in terms of partial differential equations (PDEs) to describe the evolution of cell density and the changes in concentration of chemicals. The established models are classified as linear or nonlinear, discrete or continuous, deterministic or stochastic.

From the macroscopic (population-based) viewpoint, Keller and Segel [44, 45, 46] were the first to propose a continuum model to picture the formation of the chemotactic bands of cellular slime molds *Dictyostelium discoideum* in response to the chemical. Subsequently, other authors [20, 67, 69] developed discrete models, but the continuum Keller-Segel (K-S) model remained the most popular and the widest used for chemotaxis on population based perspective. The generalized K-S model is written as follows:

$$\frac{\partial b}{\partial t} = \nabla.\left(\mu(s)\nabla b\right) - \nabla.\left(k_2(b,s)b\nabla s\right) + g(b,s) - h(b,s), \tag{2.1}$$

$$\frac{\partial s}{\partial t} = D\nabla^2 s - f(b,s), \tag{2.2}$$

where at the position x and time t, $b(x,t)$ stands for the density of bacteria, $s(x,t)$ for the

concentration of the critical substrate, $\mu(s)$ is the diffusion coefficient of bacteria, $k_2(b,s)$ the chemotactic function, $g(b,s)$ and $h(b,s)$ account for the cell growth and death rate functions, D is the diffusion coefficient of the substrate, and $f(b,s)$ is the degradation rate of the substrate.

Often the growth and death terms in (2.1)–(2.2) are overlooked. This is due to the fact that in most cases, these events take place much later than the duration of many *in vivo* experiments [101]. However, some authors have studied the impact of those terms on the behaviour of the distribution [47, 55, 57, 75]. For instance, Lapidus *et al* [55] noticed that the absence of bacteria growth did not prevent the aggregation of the cells, but instead decreased the speed of the wave. Kennedy *et al* [47] identified some classes of functions (standing for the cell growth) which led to travelling wave solutions of constant speed. Lauffenburger *et al* [57] emphasised the diffusion coefficient, and found that the impact of relative changes in the diffusion coefficient of the population is higher than the relative changes in the growth rate. A large set of models emerged from (2.1)–(2.2) (with zero growth and death terms). In the minimal model ($k_2(b,s) = \chi$, where χ is the chemotactic coefficient), it was shown that the behaviour of solutions depends on the dimension of the space [40]. Recently Osaki *et al* [77] proved the global existence of solutions in one dimension. In the signal-dependent sensitivity models (here $k_2(b,s) = \chi/(1+\alpha s)^2$ for the receptor model, or $k_2(b,s) = \chi(1+\beta)/(s+\beta)$ for the logistic model), the one-dimensional solutions are global in time. Regarding the density-dependent sensitivity models (with $k_2(b,s) = \chi(1-b/\gamma)$ for the volume filling model, or $k_2(b,s) = \chi/(1+\epsilon b)$, where γ stands for the maximum cell density), Hillen *et al* [39] have shown the global existence of solutions in all space dimensions. The steady states investigated by Rascle [87] showed that unstable eigenvalues are exponentially small. Wang [107] investigated the existence, stability and chemical diffusion limits of travelling wave solutions (2.1)–(2.2) with logarithmic sensitivity.

From the microscopic (cell-based) viewpoint, modelling chemotaxis started with Patlak [83]. His model described a random walk with persistence of direction (i.e., the probability to move in a specific direction has to be the same for all the directions, and depend on the previous direction), and external bias (i.e., the movement can be influenced by an external force). Later, his model was improved by Alt [1] and Othmer *et al* [80] who derived a transport equation based on velocity-jump process. In addition, numerous stochastic approaches have been undertaken to

model the behaviour of individual cells in response to the external signalling [42, 79, 81, 102]. It was shown that the parabolic limit of the microscopic model (via transport equation) is the Keller-Segel model [61]. Recent work has focussed on the description of the microscopic behavior of individual cells, including the transduction of the signal (i.e, the response of a cell to the extracellular signalling). The intracellular dynamics of the cells was modelled in terms of a system of ordinary differential equations, as follows [6, 28, 29, 93, 95]:

$$\frac{dy}{dt} = f(y, S), \tag{2.3}$$

where $y = (y_1, y_2, ..., y_M) \in \mathbb{R}^M$ are internal state variables, $S = (S_1, S_2, ..., S_N) \in \mathbb{R}^N$ are concentrations of external signals detected, and $f : \mathbb{R}^M \times \mathbb{R}^N \longrightarrow \mathbb{R}^M$ is a function. In 2011, Xue *et al* [111] improved the model by incorporating a metabolism effect. Their model accurately describes the experiments in [11, 13, 14], in which cells consume succinate and secrete aspartate that in turn will be used as a food and as a signal.

Our analysis is based on the model for bacteria chemotaxis formulated by Xue *et al* [111], consistent with current biology, that employs a transport equation for velocity-jump processes. It has been shown that travelling wave solutions are possible in chemotaxis models incorporating the growth of the cells [54, 72]. Xue *et al* [111] tried to show whether travelling wave solutions exist in the case of non proliferation of the cells, and without the unbounded velocity coming from a singularity in the chemotactic sensitivity. It was assumed that the substrate and the attractant do not diffuse along the space. As a result, the order of the system was reduced to one. In our case, we allow for diffusivity and thus analyse a more involved, realistic model. We will show that the resulting (complicated) equations are still tractable, and we will prove the existence of travelling wave solutions, with explicit solutions being demonstrated. In §2.2, we briefly introduce the reduced model. The Lie analysis is applied to the model in §2.3. This helps us to reduce the PDEs into ordinary differential equations (ODEs) which subsequently are fully analysed. We conclude this work with a discussion in §2.4.

2.2 Reduced Model

In the experiments reported in [9, 13, 14, 110], it was observed that bacteria cells, swimming in a semi solid agar, consume the substrate succinate and excrete attractant aspartate, then aggregate in response to gradients of the aspartate, and form different spatial patterns (in *E coli*, aggregates form in the wake of a travelling circular band [5]). The density of the aggregate and the attractant production increase as the succinate concentration increases [13, 14]. A low concentration of the succinate may impel the cells to consume attractant instead [11]. In the context of this experiment, Xue *et al* [111] formulated, in one-dimensional space, a model for the chemotaxis of *E coli*, based on the transport equation for a velocity jump process (more details about the model can be obtained in [111]). In the case where cells do not starve and consume only succinate, assuming a fast signal transduction (i.e. no explicit representation for the internal signal transduction variable) and that the cells are purely-chemotactic (i.e. no proliferation of the cells), they reduced their model to

$$n_t + j_x = 0, \tag{2.4}$$

$$j_t + s^2 n_x - s\lambda_1\left(\frac{\partial S}{\partial x}\right) n + 2\lambda_0 j = 0, \tag{2.5}$$

$$F_t - D_F F_{xx} + \beta F n = 0, \tag{2.6}$$

$$S_t - D_S S_{xx} - \alpha F n + \gamma S = 0, \tag{2.7}$$

where $n(x,t)$ is the macroscopic cell density, $j(x,t)$ the cell flux, $F(x,t)$ the concentration of the succinate, $S(x,t)$ the concentration of the aspartate (all at position x, and time t), β is the consumption rate of the succinate, α is the production rate of the aspartate, γ is the degradation rate of the aspartate, λ_0 is the unbiased turning rate (with $\lambda_0 > 0$), $s = 10\mu m/sec$ is the speed of a single cell, and λ_1 is given by

$$\lambda_1\left(\frac{\partial S}{\partial x}\right) = \begin{cases} -2\lambda_0, & \partial S/\partial x < 0, \\ 0, & \partial S/\partial x = 0, \\ 2\lambda_0, & \partial S/\partial x > 0. \end{cases} \tag{2.8}$$

Note that n and j can be disaggregated as follows:

$$n(x,t) = n^+(x,t) + n^-(x,t), \quad j(x,t) = sn^+(x,t) - sn^-(x,t), \tag{2.9}$$

where n^+ (respectively n^-) stands for the cell density moving to the right (respectively to the left), and $\lambda_1(\zeta)$ results from the cells' turning rate function

$$\lambda(\zeta) = \lambda_0 \left(1 + \frac{\zeta}{k + |\zeta|}\right), \tag{2.10}$$

in the limiting case $k \to 0$, where k stands for the sensitivity coefficient. From numerical investigations, Xue *et al* [111] observed that travelling wave solutions exist, but with a single peak of S and n for certain parameters. They tried to prove this conjecture analytically by assuming that nutrients do not diffuse (i.e., $D_F = D_S = 0$), and by constructing the following set of solutions

$$\begin{aligned} Y_S = \{f \in \mathbb{C}^1(\mathbb{R}); f(u) \text{ is monotonically increasing for } u < 0 \\ \text{and decreasing for } u > 0, \quad \lim_{u\to\infty} f(u) = 0\}. \end{aligned}$$

For the remainder of this work, we will investigate the existence of travelling wave solutions in the case of the diffusivity of the food and the attractant (i.e., $D_F \neq 0$ and $D_S \neq 0$). We will undertake the investigation using the Lie symmetry analysis for it has proved to be a powerful tool for analytically solving nonlinear differential equations [43]. Travelling wave solutions arise naturally in this analysis. We recall, in this context, that travelling wave solutions are continuous, positive, bounded solutions to (2.4)–(2.7) [61, 111].

2.3 Lie analysis and travelling wave solutions

Recall that a *kth* order partial differential equation [10]

$$E(x, y, \partial y, ..., \partial^k y) = 0, \tag{2.11}$$

where $\partial^k y$ stands for the components of all *kth* order partial derivatives of y with respect to x, with $y(x) = (y^1(x), ..., y^m(x))$, and $x = (x_1, ..., x_n)$, admits

$$X = \xi_i(x, y)\frac{\partial}{\partial x_i} + \eta^\nu(x, y)\frac{\partial}{\partial y^\nu}, \tag{2.12}$$

as symmetry if

$$X^{[k]}E \mid_{E=0} = 0 \tag{2.13}$$

holds, where $\xi_i(x,y)$ and $\eta^\nu(x,y)$ are the infinitesimals of the Lie group of transformation of (2.11), and $X^{[k]}$ is the kth extension of X.

Applied to the system (2.4)–(2.7) (with λ_1 treated as a constant), the operation of (2.13) leads to

$$X = \partial_t + c\partial_x + a_2 F\partial_F + a_2 S\partial_S + a_3 \mathrm{e}^{-\lambda_2 t}\partial_j, \qquad X_\infty = d(t,x)\partial_S \tag{2.14}$$

as symmetries, where d is the solution of

$$-D_S\frac{\partial^2 d}{\partial x^2} + \frac{\partial d}{\partial t} + \gamma d = 0, \tag{2.15}$$

and c, a_2 and a_3 are arbitrary real parameters. X_∞ is an infinite-dimensional symmetry that always arises when one is analysing linear equations. The characteristic equations associated with the finite-dimensional symmetry are [10]

$$\frac{dt}{1} = \frac{dx}{c} = \frac{dF}{a_2 F} = \frac{dS}{a_2 S} = \frac{dj}{a_3 \mathrm{e}^{-2\lambda_0 t}} = \frac{dn}{0}. \tag{2.16}$$

Thus we get the following invariants

$$u = x - ct, \tag{2.17}$$

$$F = p(u)\mathrm{e}^{a_2 t}, \tag{2.18}$$

$$S = q(u)\mathrm{e}^{a_2 t}, \tag{2.19}$$

$$j = J(u) - \frac{a_3}{2\lambda_0}\mathrm{e}^{-2\lambda_0 t}, \tag{2.20}$$

$$n = N(u). \tag{2.21}$$

From the form of the new independent variable (2.17) we see that it is possible to obtain travelling wave solutions. Here, c represents the speed of the wave. Since there is no external force to quicken the motion of the cells, the speed of the wave should not be greater than the speed of a single cell (recall that $c < 0$ means the wave is moving to the left), i.e., we have the constraint

$$-s \leq c \leq s. \tag{2.22}$$

We note that the arbitrary parameter a_2 has an interesting role. When $a_2 = 0$ we reduce to the expected classical travelling wave *ansatz*. However, for non-zero a_2 we could have growing ($a_2 >$

0) or damped ($a_2 < 0$) travelling wave solutions. Further, we observe that j has a travelling wave component together with an additive purely timelike component. These nuances are all a result of performing a full group theoretical analysis of (2.4)–(2.7). Simply assuming that all the dependent variables in (2.4)–(2.7) depend on (2.17) would have also yielded travelling wave solutions, but those would be more restrictive that the results presented here (We note that (2.18)–(2.20) are generalized travelling wave solutions [85].).

Denoting by primes the derivatives with respect to u, and assuming N and J decay to zero at infinity, the system of PDEs (2.4)–(2.7) reduce to the system of ODEs

$$J = cN, \tag{2.23}$$

$$(s^2 - c^2)N' - (s\lambda_1 - c\lambda_2)N = 0, \tag{2.24}$$

$$D_F p'' + cp' - (a_2 + \beta N)p = 0, \tag{2.25}$$

$$D_S q'' + cq' - (a_2 + \gamma)q + \alpha N p = 0. \tag{2.26}$$

The analysis splits naturally into two parts, each with subcases.

2.3.1 Case $c \neq \pm s$

In our study we will also consider the set

$$\begin{aligned} Y_S' = \{f \in \mathbb{C}(\mathbb{R}); f(u) \text{ is monotonically increasing for } u < 0 \\ \text{and decreasing for } u > 0, \quad \lim_{u\to\infty} f(u) = 0\}, \end{aligned} \tag{2.27}$$

and we will show for a specific case in the appendix that, the monotonically increasing and decreasing of the solution $q(u)$ requires $q'(u)$ to be discontinuous at the origin.

Integrating (2.24) and assuming $q \in Y_S'$, then we have

$$n(x,t) = N(u) = \begin{cases} n_0 \mathrm{e}^{\sigma_1 u}, & u < 0, \\ n_0 \mathrm{e}^{-\sigma_2 u}, & u \geq 0, \end{cases} \tag{2.28}$$

where $u = x - ct$, $n_0 = N(0) = N_0\lambda_0/s$, $\sigma_1 = 2\lambda_0/(s + c)$ and $\sigma_2 = 2\lambda_0/(s - c)$, with N_0 standing for the total cell population initially introduced. Taking (2.28) into account, equation

(2.25) admits

$$p(u) = \begin{cases} \left[c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) + c_2^1 K_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)\right] \mathrm{e}^{-(c/(2D_F))u}, & u \leq 0, \\ \left[c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)\right] \mathrm{e}^{-(c/(2D_F))u}, & u \geq 0 \end{cases} \tag{2.29}$$

as solution, where the functions $I_{k_i}(v)$ and $K_{k_i}(v)$ are the two linearly independent solutions to the modified Bessel's equation, $\alpha_i = \sqrt{4n_0\beta D_F}/(D_F\sigma_i)$, $k_i = \sqrt{c^2 + 4a_2 D_F}/(D_F\sigma_i)$ (with $k_i > 0$), and c_1^1, c_2^1, c_1^2 and c_2^2 are arbitrary constants. In fact, if we let $v_1 = \alpha_1 \mathrm{e}^{(\sigma_1/2)u}$, $v_2 = \alpha_2 \mathrm{e}^{-(\sigma_2/2)u}$ and $p(u) = f_{k_i}(v_i)\mathrm{e}^{-(c/(2D_F))u}$ (with $i = 1, 2$), where f_{k_i} stands for either I_{k_i} or K_{k_i}, then it follows that (2.25) becomes the modified Bessel's equation

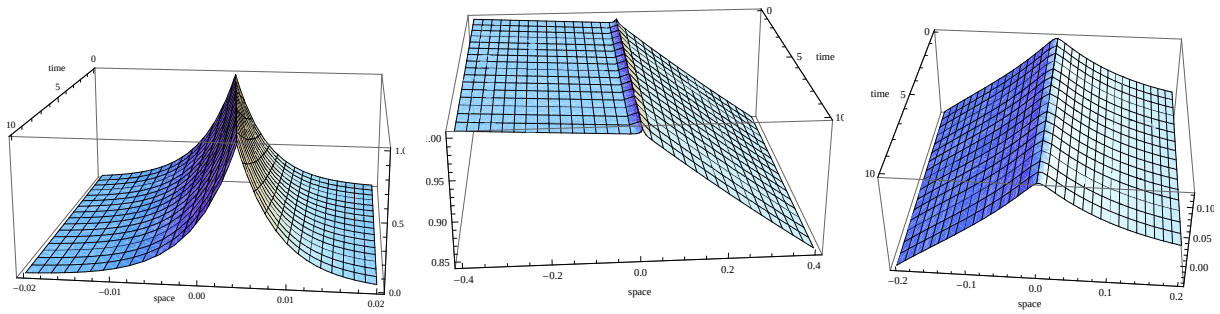
$$v_i^2 \frac{\partial^2 f_{k_i}(v_i)}{\partial v_i^2} + v_i \frac{\partial f_{k_i}(v_i)}{\partial v_i} - (v_i^2 + k_i^2) f_{k_i}(v_i) = 0. \tag{2.30}$$

Given that equation (2.26) is a nonhomogeneous second order differential equation (in $q(u)$) with constant coefficients, then the solutions $q(u)$ are obtained after a direct integration of (2.26). We conduct our analysis with different values of a_2, and to display the behaviour of solutions we plot them in three dimensions, keeping the values of the parameters as set in the experiment as follows [111]: $s = 10^{-2} mm/sec$, $D_F = D_S = 10^{-3} mm^2/sec$, $\alpha = \beta = 0.2/sec$, $\gamma = 0.05/sec$, $\lambda_0 = 1/sec$, $c = \pm 4.3 \times 10^{-4} mm/sec$, $p(0) = 1mM$, and $n_0 = \lambda_0 N_0/s = 10^3 cells/cm^3 = 1 cell/mm^3$. The sub-figures (a) depict the distribution of the cells, while sub-figures (b) and (c) depict the succinate and aspartate concentrations respectively. We note from the experiment that the α_i are very small (of order 10^{-2}).

Assume $0 < c < s$

Theorem 2.3.1. *When $a_2 = 0$, unique travelling wave solutions to (2.4)–(2.7) exist and are explicitly given by (2.28),*

$$F(x,t) = p(u) = \begin{cases} p(0)\mathrm{e}^{-(c/(2D_F))u} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) / I_{k_1}\left(\alpha_1\right), & u < 0, \\ p(0)\mathrm{e}^{-(c/(2D_F))u} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) / I_{k_2}\left(\alpha_2\right), & u \geq 0, \end{cases} \tag{2.31}$$



(a) (b) (c)

Figure 2.1: Non starvation travelling waves in the case of $a_2 = 0$ and $c > 0$. Cells are very slowly distributed over the space (see subfigure (a)), and excrete a low concentration of aspartate with respect to the succinate (see subfigures (b) and (c)).

and

$$S(x,t) = q(u) = \begin{cases} \gamma_8 \mathrm{e}^{-\gamma_1 u} + \gamma_9 \mathrm{e}^{\gamma_2 u} - \dfrac{\alpha n_0 p(0) \mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 p(0) \mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u < 0, \\ \gamma_8 \mathrm{e}^{-\gamma_1 u} + \gamma_9 \mathrm{e}^{\gamma_2 u} + \dfrac{\alpha n_0 p(0) \mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_6 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ \qquad - \dfrac{\alpha n_0 p(0) \mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_7 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, \quad u \geq 0, \end{cases} \tag{2.32}$$

where $u = x - ct$,

$$\begin{aligned} &\gamma_1 = (c+\gamma_3)/(2D_S), \quad \gamma_2 = (\gamma_3 - c)/(2D_S), \quad \gamma_3 = \sqrt{c^2 + 4\gamma D_S}, \\ &\gamma_4 = -c/(2D_F) + c/D_S + \gamma_2 + \sigma_1, \quad \gamma_5 = -c/(2D_F) + c/D_S - \gamma_1 + \sigma_1, \\ &\gamma_6 = -c/(2D_F) + c/D_S + \gamma_2 - \sigma_2, \quad \gamma_7 = -c/(2D_F) + c/D_S - \gamma_1 - \sigma_2, \\ &\gamma_8 = \frac{\alpha n_0 p(0)(\alpha_1/2)^{k_1}}{\gamma_3(\gamma_4 + c/(2D_F))\Gamma(1+k_1) I_{k_1}(\alpha_1)}, \quad \gamma_9 = \frac{-\alpha n_0 p(0)(\alpha_2/2)^{k_2}}{\gamma_3(\gamma_7 - c/(2D_F))\Gamma(1+k_2) I_{k_2}(\alpha_2)}, \end{aligned} \tag{2.33}$$

and c *is chosen so that*

$$\gamma_2\gamma_9 \leq \gamma_1\gamma_8, \quad \gamma_1 \leq \frac{c}{D_F} + \sigma_2, \quad \gamma_1\gamma_8 \mathrm{e}^{\sigma_1 u} \leq \gamma_2\gamma_9 \mathrm{e}^{\gamma_2 u}, \tag{2.34}$$

for any real $u < 0$. ■

(Note that the proofs of all theorems are given in the Appendix.)

From the experiments, note that the constraint (2.34) is realistic. In fact, Budrene *et al* [13] observed that the wave speed c is within the range $1-2mm/hour$, and the diffusion coefficients are of order $10^{-5}cm^2/sec$.

Now we assume $a_2 \neq 0$.

Theorem 2.3.2. *When $a_2 > 0$, non zero travelling wave solutions do not exist.* ■

Theorem 2.3.3. *For $\max(-c^2/(4D_F), -\gamma) < a_2 < 0$, travelling wave solutions exist and are given by (2.28),*

$$F(x,t) = F(0,0)\mathrm{e}^{a_2 t} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_2}(\alpha_2), \quad u \geq 0, \tag{2.35}$$

and

$$S(x,t) = \mathrm{e}^{a_2 t} q(u), \tag{2.36}$$

with

$$q(u) = \begin{cases} (1+\tau_2/\tau_1)\delta_1 \mathrm{e}^{\tau_2 u}, \quad u < 0, \\ \dfrac{\tau_2\delta_1}{\tau_1}\mathrm{e}^{-\tau_1 u} + \delta_1 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ \qquad - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_5 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, \quad u \geq 0, \end{cases} \tag{2.37}$$

where $u = x - ct$,

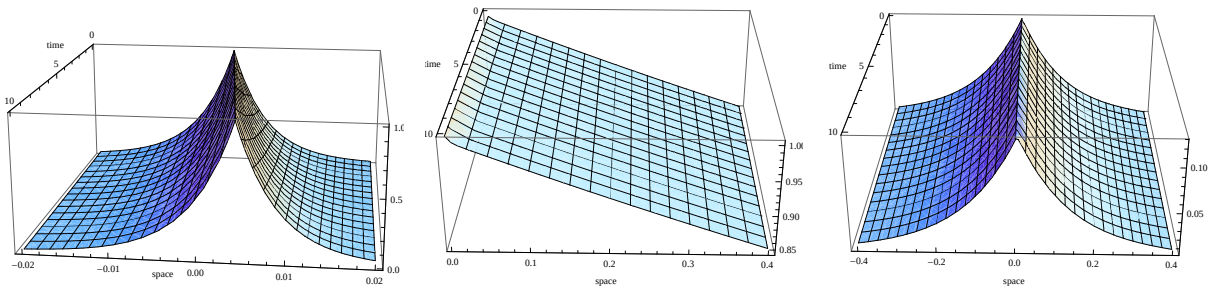
$$\begin{aligned} &\delta_1 = \frac{-\alpha n_0 F(0,0)(\alpha_2/2)^{k_2}}{\tau_3(-\sigma_2 k_2/2 + \tau_5)\Gamma(1+k_2) I_{k_2}(\alpha_2)}, \quad \tau_1 = (c+\tau_3)/(2D_S), \quad \tau_2 = (-c+\tau_3)/(2D_S), \\ &\tau_3 = \sqrt{c^2 + 4D_S(a_2+\gamma)}, \quad \tau_4 = -c/(2D_F) + c/D_S + \tau_2 - \sigma_2, \\ &\tau_5 = -c/(2D_F) + c/D_S - \tau_1 - \sigma_2, \end{aligned} \tag{2.38}$$

and c is chosen so that $\tau_1 \leq \sigma_2 k_2/2 + c/(2D_F) + \sigma_2$, i.e.,

$$\frac{c + \sqrt{c^2 + 4D_F(a_2+\gamma)}}{2D_S} \leq \frac{c + \sqrt{c^2 + 4a_2 D_F}}{2D_F} + \frac{2\lambda_0}{s-c}. \tag{2.39}$$

■

Likewise, we note from biological observations that (2.39) is a realistic constraint. The notation $max(a,b)$ stands for the maximum value between a and b.



(a) (b) (c)

Figure 2.2: Non starvation travelling waves in the case where $a_2 < 0$ and $c > 0$ ($a_2 = -10^{-5}$).

Theorem 2.3.4. *For* $max\,(-c^2/(4D_F), -\gamma) < a_2 < 0$, *travelling wave solutions exist and are given by (2.28),*

$$F(x,t) = \begin{cases} F(0,0)\mathrm{e}^{a_2 t} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \mathrm{e}^{-(c/(2D_F))u}/I_{k_1}(\alpha_1), & \alpha_0 t \le x < ct, \\ F(0,0)\mathrm{e}^{a_2 t} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-(c/(2D_F))u}/I_{k_2}(\alpha_2), & x \ge ct, \end{cases} \tag{2.40}$$

and

$$S(x,t) = \mathrm{e}^{a_2 t} q(u), \tag{2.41}$$

with

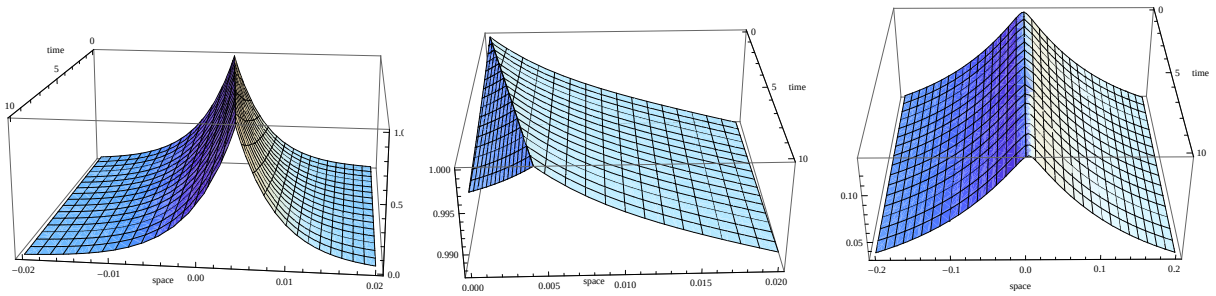
$$q(u) = \begin{cases} \delta_{11}\mathrm{e}^{-\tau_1 u} + \delta_1 \mathrm{e}^{\tau_2 u} - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, & u < 0, \\ \delta_{11}\mathrm{e}^{-\tau_1 u} + \delta_1 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_5 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, & u \ge 0, \end{cases} \tag{2.42}$$

where $u = x - ct$, τ_1, τ_2, τ_3, τ_4, τ_5 *and* δ_1 *are given in (2.38),* τ_{41}, τ_{51}, δ_{11} *and* α_0 *by*

$$\begin{aligned} &\tau_6 = -c/(2D_F) + c/D_S + \tau_2 + \sigma_1, \quad \tau_7 = -c/(2D_F) + c/D_S - \tau_1 + \sigma_1 \\ &\delta_{11} = \frac{\alpha n_0 F(0,0)(\alpha_1/2)^{k_1}}{\tau_3(\sigma_1 k_1/2 + \tau_6)\Gamma(1+k_1) I_{k_1}(\alpha_1)}, \quad \alpha_0 = \frac{-1}{2}\left(\sqrt{c^2 + 4a_2 D_F} - c\right), \end{aligned} \tag{2.43}$$

and c *holds*

$$-\frac{c}{(2D_F)} + \sigma_1 > 0, \tau_2\delta_1 \le \tau_1\delta_{11}, \tau_1 \le \frac{\sigma_2 k_2}{2} + \frac{c}{2D_F} + \sigma_2, \tau_1\delta_{11}\mathrm{e}^{(\sigma_1 k_1/2 - c/(2D_F) + \sigma_1)u} \le \tau_2\delta_1 \mathrm{e}^{\tau_2 u}, \tag{2.44}$$



(a) (b) (c)

Figure 2.3: Non starvation travelling waves in the case where $a_2 < 0$ and $c > 0$.

for any real $u < 0$. ■

Assume $-s < c < 0$

Theorem 2.3.5. *When* $a_2 = 0$*, travelling wave solutions to (2.4)–(2.7) exist and are explicitly given by (2.28),*

$$F(x,t) = p(u) = \begin{cases} p(0)\mathrm{e}^{-(c/(2D_F))u} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)/I_{k_1}(\alpha_1), & u < 0, \\ p(0)\mathrm{e}^{-(c/(2D_F))u} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)/I_{k_2}(\alpha_2), & u \geq 0, \end{cases} \tag{2.45}$$

and

$$S(x,t) = q(u) = \begin{cases} \gamma_{81}\mathrm{e}^{-\gamma_1 u} + \gamma_{91}\mathrm{e}^{\gamma_2 u} - \dfrac{\alpha n_0 p(0)\mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 p(0)\mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, & u \leq 0, \\ \gamma_{81}\mathrm{e}^{-\gamma_1 u} + \gamma_{91}\mathrm{e}^{\gamma_2 u} + \dfrac{\alpha n_0 p(0)\mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_6 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ \qquad - \dfrac{\alpha n_0 p(0)\mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_7 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, & u > 0, \end{cases} \tag{2.46}$$

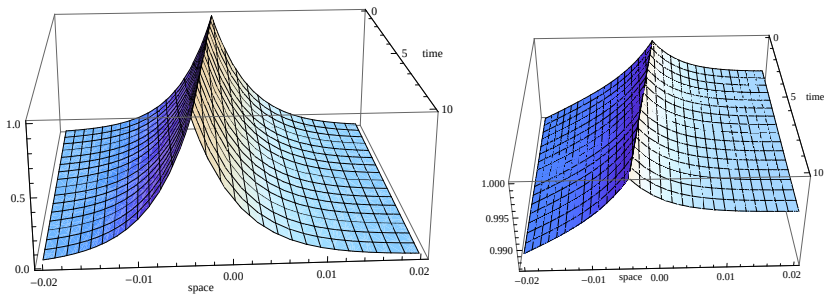
where $u = x - ct$*,* γ_1*,* γ_2*,* γ_3*,* γ_4*,* γ_5*,* γ_6*,* γ_7 *are given in (2.33), and* γ_{81}*,* γ_{91} *are given by*

$$\gamma_{81} = \frac{\alpha n_0 p(0)(\alpha_1/2)^{k_1}}{\gamma_3(\gamma_4 - c/(2D_F))\Gamma(1+k_1)I_{k_1}(\alpha_1)} \quad \gamma_{91} = \frac{-\alpha n_0 p(0)(\alpha_2/2)^{k_2}}{\gamma_3(\gamma_7 + c/(2D_F))\Gamma(1+k_2)I_{k_2}(\alpha_2)}, \tag{2.47}$$

and c *is chosen so that for any real* $u \geq 0$*,*

$$\gamma_1 \leq \sigma_2, \quad \gamma_1\gamma_{81}\mathrm{e}^{(-c/D_F+\sigma_1)u} \leq \gamma_2\gamma_{91}\mathrm{e}^{\gamma_2 u}. \tag{2.48}$$

■



(a) (b)

Figure 2.4: Non starvation travelling waves in the case of $a_2 = 0$ and $c < 0$.

Theorem 2.3.6. *When $a_2 > 0$, non zero continuous travelling wave solutions do not exist.* ■

Theorem 2.3.7. *For $max(-c^2/(4D_F), -\gamma) < a_2 < 0$, travelling wave solutions exist, and are given by (2.28),*

$$F(x,t) = F(0,0)\mathrm{e}^{a_2 t} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_1}(\alpha_1), \quad u \le 0, \tag{2.49}$$

and

$$S(x,t) = \mathrm{e}^{a_2 t} q(u), \tag{2.50}$$

with

$$q(u) = \begin{cases} \delta_{11}\mathrm{e}^{-\tau_1 u} + \dfrac{\tau_1 \delta_{11}}{\tau_2}\mathrm{e}^{\tau_2 u} - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u \le 0, \\ (1 + \tau_1/\tau_2)\delta_{11}\mathrm{e}^{-\tau_1 u}, \quad u > 0, \end{cases} \tag{2.51}$$

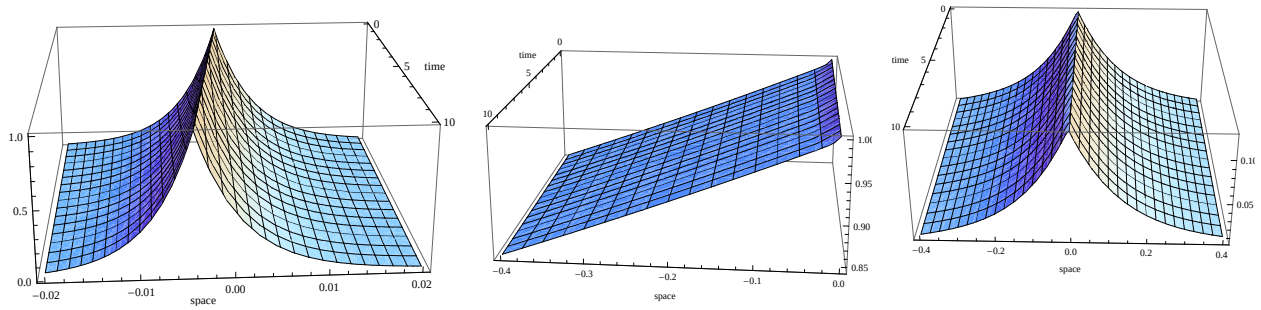
where $u = x - ct$, τ_1, τ_2, τ_3 are giving in (2.38), and τ_6, τ_7, δ_{11} are given in (2.43), and c is chosen so that

$$\tau_2 \le \frac{\sigma_1 k_1}{2} - \frac{c}{2D_F} + \sigma_1. \tag{2.52}$$

■

Theorem 2.3.8. *For $max\left(-c^2/(4D_F), -\gamma\right) < a_2 < 0$, travelling wave solutions exist and are given by (2.28),*

$$F(x,t) = \begin{cases} F(0,0)\mathrm{e}^{a_2 t} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_1}(\alpha_1), \quad x \le ct, \\ F(0,0)\mathrm{e}^{a_2 t} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_2}(\alpha_2), \quad ct < x \le \alpha_2 t, \end{cases} \tag{2.53}$$



(a) (b) (c)

Figure 2.5: Non starvation travelling waves in the case where $a_2 < 0$ and $c < 0$.

and

$$S(x,t) = \mathrm{e}^{a_2 t} q(u), \tag{2.54}$$

with

$$q(u) = \begin{cases} \delta_{11}\mathrm{e}^{-\tau_1 u} + \delta_1 \mathrm{e}^{\tau_2 u} - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u \le 0, \\ \delta_{11}\mathrm{e}^{-\tau_1 u} + \delta_1 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ - \dfrac{\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_5 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, \quad u > 0, \end{cases} \tag{2.55}$$

where $u = x - ct$, $\alpha_2 = (\sqrt{c^2 + 4a_2 D_F} + c)/2$, τ_1, τ_2, τ_3, τ_4, τ_5, δ_1 *are given in (2.38),* τ_6, τ_7, δ_{11} *are given in (2.43), and* c *holds*

$$\tau_2 \le \frac{\sigma_1 k_1}{2} - \frac{c}{(2D_F)} + \sigma_1, \quad \tau_2\delta_1 \le \tau_1\delta_{11}, \quad \tau_1\delta_{11}\mathrm{e}^{(\sigma_2 k_2/2 + c/(2D_F) + \sigma_2)u} \le \tau_2\delta_1\mathrm{e}^{\tau_1 u}, \tag{2.56}$$

for any $u > 0$. ■

There is a trivial connection between solutions obtained in §2.3.1 and solutions obtained in §2.3.1. In fact, their directions are just swapped over, while the piecewise functions constituting the solutions do not change (this result was predictable from (2.25)–(2.26), and is shown by comparing Figure 2.1 and Figure 2.4, and Figure 2.2 and Figure 2.5). Thus, we will not provide the proof for Theorem 2.3.5, Theorem 2.3.6, Theorem 2.3.7 and Theorem 2.3.8, given that they result from the proofs of the theorems in §2.3.1.

Assume $c = 0$

In this case there is no wave motion, and from (2.23), (2.20), and (2.9), the cell flux density $j(x,t)$ is zero; cells are symmetrically distributed about the origin ($n^+(x) = n^-(x)$). However, we are interested in the distribution of $F(x,t)$ and $S(x,t)$, for the cells are only spatially distributed (refer to (2.17) and (2.21)). When $a_2 > 0$, $F(x,t)$ and $S(x,t)$ in (2.18)–(2.19) are very large as $t \to +\infty$. On the other hand, when $a_2 < 0$, we have non real solutions (for from (2.29), the order, k_i, becomes a pure imaginary complex number). Therefore, we only look for solutions in the case of $a_2 = 0$.

Theorem 2.3.9. *When $a_2 = 0$, the solutions to (2.4)–(2.7) are explicitly given by*

$$n(x,t) = N(x) = \begin{cases} n_0 \mathrm{e}^{\sigma_0 x}, & x < 0, \\ n_0 \mathrm{e}^{-\sigma_0 x}, & x \geq 0, \end{cases} \tag{2.57}$$

$$F(x,t) = p(x) = \begin{cases} p(0) I_0\left(\alpha_0 \mathrm{e}^{(\sigma_0/2)x}\right) / I_0(\alpha_0), & x < 0, \\ p(0) I_0\left(\alpha_0 \mathrm{e}^{-(\sigma_0/2)x}\right) / I_0(\alpha_0), & x \geq 0, \end{cases} \tag{2.58}$$

and

$$S(x,t) = q(x) = \begin{cases} \gamma_9 \mathrm{e}^{-\gamma_1 x} + \gamma_9 \mathrm{e}^{\gamma_1 x} - \dfrac{\alpha n_0 p(0) \mathrm{e}^{-\gamma_1 x}}{\gamma_3 I_0(\alpha_0)} \displaystyle\int_x^0 \mathrm{e}^{-\gamma_4 u_1} I_0\left(\alpha_0 \mathrm{e}^{(\sigma_0/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 p(0) \mathrm{e}^{\gamma_1 x}}{\gamma_3 I_0(\alpha_0)} \displaystyle\int_x^0 \mathrm{e}^{-\gamma_5 u_1} I_0\left(\alpha_0 \mathrm{e}^{(\sigma_0/2)u_1}\right) du_1, & x < 0, \\ \gamma_9 \mathrm{e}^{-\gamma_1 x} + \gamma_9 \mathrm{e}^{\gamma_1 x} + \dfrac{\alpha n_0 p(0) \mathrm{e}^{-\gamma_1 x}}{\gamma_3 I_0(\alpha_0)} \displaystyle\int_0^x \mathrm{e}^{\gamma_5 u_1} I_0\left(\alpha_0 \mathrm{e}^{(-\sigma_0/2)u_1}\right) du_1 \\ \qquad - \dfrac{\alpha n_0 p(0) \mathrm{e}^{\gamma_1 x}}{\gamma_3 I_0(\alpha_0)} \displaystyle\int_0^x \mathrm{e}^{\gamma_4 u_1} I_0\left(\alpha_0 \mathrm{e}^{(-\sigma_0/2)u_1}\right) du_1, & x \geq 0, \end{cases} \tag{2.59}$$

where

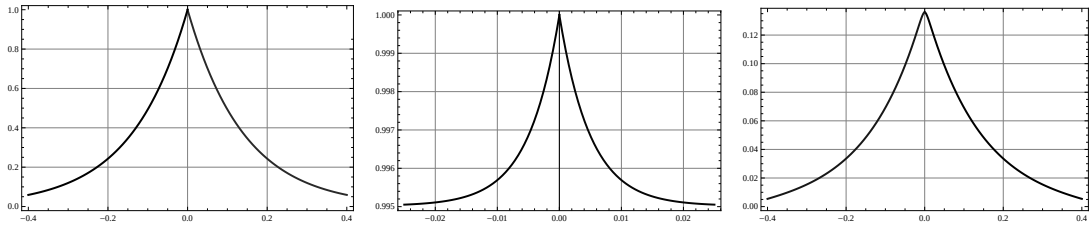
$$\sigma_0 = \frac{2\lambda_0}{s}, \gamma_1 = \frac{\gamma_3}{(2D_S)}, \gamma_3 = \sqrt{4\gamma D_S}, \gamma_4 = -\gamma_1 - \sigma_0, \gamma_5 = \gamma_1 - \sigma_0, \gamma_9 = \frac{-\alpha n_0 p(0)}{\gamma_3 \gamma_4 I_0(\alpha_0)}. \tag{2.60}$$

■

2.3.2 Case $c = \pm s$

We first assume that $c = s$. Then, from (2.24), we have

$$(\lambda_1(\partial S/\partial x) - 2\lambda_0)N = 0, \tag{2.61}$$



(a) (b) (c)

Figure 2.6: Non starvation travelling waves in the case where $a_2 = c = 0$.

which implies that either $\lambda_1(\partial S/\partial x) = 2\lambda_0$ and N is arbitrary, or $\lambda_1(\partial S/\partial x) \neq 2\lambda_0$ and $N = 0$. If $\lambda_1(\partial S/\partial x) = 2\lambda_0$, then from (2.8), the concentration of the attractant $S(x,t)$ is strictly increasing in space (i.e, $\partial S/\partial x > 0$). This result is not biologically relevant, for it requires the cell density to be spatially increasing (the attractants are produced only by the cells). However, if $\lambda_1(\partial S/\partial x) \neq 2\lambda_0$, then $n(x,t) = N(x - st) = 0$ – there is no travelling wave solution.

The same analysis is applied in the case of $c = -s$.

2.4 Discussion

In this paper, we investigated the existence of travelling wave solutions for microscopic bacterial (*E coli*) chemotaxis. The analysis was based on a model formulated by Xue *et al* [111] in which bacteria cells freely swim in a semi solid agar, consume only succinate $F(x,t)$ and excrete aspartate $S(x,t)$. We focused on the case where the cells do not starve (the concentration of succinate $F(x,t) \geq z_c$, where z_c stands for a critical threshold for conversion to a starving phenotype). Cell growth was disregarded in the model, and the turning rate function of the cells was chosen to allow them to react to infinite sensitivity signal (in the perspective to keep the wave undamped over the time). Unlike previous approaches we allowed substrates to diffuse along the space (which is a more realistic approximation of the scenario). The Lie symmetry analysis helped to reduce the full system of nonlinear second order PDEs into ODEs (This naturally led to traveling wave solutions via the group invariants obtained.). By analyzing the system of ODEs we proved the existence and uniqueness of travelling wave solutions, with

explicit solutions being demonstrated for the first time. In addition to the standard travelling waves we also obtained damped, pulse and front travelling wave solutions.

From the numerical investigation in the case of non diffusivity of substrates, Franz *et al* [32] observed oscillations in the wave motion of the hybrid model of chemotaxis. The same oscillations were also observed by Othmer and Schapp [78], and cannot be demonstrated using the mean-field theory. In this study, we considered the diffusion (for it was shown that diffusion plays a stabilizing role on the equilibrium of the system [88]), and we used the Lie analysis to construct a stabilizer coefficient a_2 which led to two damped travelling wave solutions in the case where $a_2 < 0$. When $a_2 > 0$, we noted that the growing solutions found blew up as t approaches ∞. Hence, realistic travelling wave solutions did not exist for this range of the parameter. We note also that when $c = \pm s$ (where $s = 10 - 20\mu m/sec$ is the speed of a single cell of *E coli*), travelling wave solutions do not exist. This result was expected, for it has been shown that the wave speed c is within the range $1 - 2mm/hour$ [13].

When the wave speed c is positive, we note from (2.28), that the cell density temporally decreases on the left (i.e, where $x < ct$) and increases on the right (i.e, where $x > ct$). Note also from §2.3.1, that the initial distribution of the food (succinate) highly influences the direction and the distribution of the wave. This result agrees with the experimental observations of Budrene *et al* [14], in which the pattern geometries of the wave depend on the initial conditions. In fact, from §2.3.1, the succinate is initially distributed on the right ($c > 0$). The wave motion enforces the substrates to diffuse to the right over the time. However, we notice the presence of the aspartate on the left – this is due to the turning rate function; after consuming succinate, some single cells have changed their direction, and then excreted aspartate (we can visualize the scenario in Figure 2.1 and Figure 2.2). The same scenario is observed in §2.3.1. (The time delay between the consumption of the succinate and the excretion of the aspartate is left for future investigation.)

The diffuse coefficients D_F and D_S do not really affect the distribution of the cells; this result was predictable from the formulation of the model (see equations (2.4) and (2.5)). Nevertheless it is not correct to ignore them, for they play an important role in the existence of the travelling wave solutions, and the distribution of the substrates. In fact, with the assumption $D_F = D_S =$

0, Xue *et al* [111] assumed that the spread of the substrates is only influenced by the motion of the cells, and obtained smooth solutions (for the substrates). However, we observe from the numerical solutions that the width of the substrates they obtained is higher than the ones obtained in this paper. We obtained in one case non-smooth solutions (that was expected regardless of the constraints on D_F and on D_S), given the discontinuity of the cells' turning rate function and the non-differentiability of $n(x,t)$ at $(t,ct)_{t>0}$; it seems that major collisions (or jumps) between cells happened at that point. Moreover, when $a_2 = 0$, our analysis shows a higher concentration of succinate on the left (see Figure 2.1(b)), whereas Xue *et al* [111] obtained higher concentrations of succinate on the right. Our results are more realistic given that cells move towards higher concentrations, and from the model cells are aggregated on the left irrespective of the presence of the diffusivity. Thus, taking heed of diffusivity can substantially change the behaviour of solutions and lead to different predictions.

For the future work, we will analyse the case of starvation (where the concentration of food is not enough to feed the cells); the metabolism effect will be considered.

In summary, we have produced analytic solutions to the system (2.4)–(2.7) for the first time in the case of nonzero diffusivity. The solutions provided are a good match to experimental evidence, thus confirming the validity of the model.

2.5 Appendix

We recall, in this context, that travelling wave solutions are continuous, positive, bounded solutions to (2.4)–(2.7) [61, 111]. In the course of our analysis, the following functions will be used:

$$v_1 = \alpha_1 \mathrm{e}^{(\sigma_1/2)u}, \quad v_2 = \alpha_2 \mathrm{e}^{-(\sigma_2/2)u}, \quad h(u) = \left(c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)\right), \tag{2.62}$$

where α_i and σ_i are given in §3.1. We first establish a useful Lemma for our analysis.

Lemma 1. *For $v \geq 0$, the modified Bessel functions $I_k(v)$ and $K_k(v)$, of order $k > 0$, are*

continuous and positive, and as v approaches zero [76, 68],

$$I_k(v) \approx \frac{(v/2)^k}{\Gamma(1+k)}, \quad K_k(v) \approx \frac{\Gamma(k)}{2}\left(\frac{2}{v}\right)^k. \tag{2.63}$$

Thus, $I_{k_1}(v_1)$ ($I_{k_2}(v_2)$) converges and $K_{k_1}(v_1)$ ($K_{k_2}(v_2)$) diverges as $u \to -\infty$ (respectively as $u \to +\infty$). ■

The proof follows directly from the definition of the functions I_k and K_k.

Theorem 2.3.1

We now prove two propositions that are necessary for the proof of Theorem 2.3.1.

Proposition 1. *For $a_1 > 0$ and $a_2 = 0$, the solution $p(u)$ in (2.29) is bounded if and only if $c_2^1 = 0$.*

Proof. Let $a_1 > 0$ and $a_2 = 0$. Recall from the previous lemma that $p(u)$ in (2.29) is always continuous everywhere except at zero (but $p(u)$ is finite as $u \to 0$). Therefore, the study of the boundedness of $p(u)$ on $(-\infty, +\infty)$ can be restristed to the case where $u \to \pm\infty$.

From (2.29), if $c_2^1 \neq 0$, then $p(u)$ diverges as $u \to -\infty$ (for $K_{k_1}(v_1)$ diverges as $u \to -\infty$). Now assume $c_2^1 = 0$. As $u \to -\infty$, we have

$$I_{k_1}(v_1) \approx \frac{(v_1/2)^{k_1}}{\Gamma(1+k_1)} \approx \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{(\sigma_1 k_1/2)u} \approx \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{(a_1/(2D_F))u}, \tag{2.64}$$

which implies that $p(u)$ converges as $u \to -\infty$, with

$$p_- = \lim_{u \to -\infty} p(u) = c_1^1 (\alpha_1/2)^{k_1}/\Gamma(1+k_1). \tag{2.65}$$

When $u \to +\infty$, then

$$K_{k_2}(v_2) \approx \frac{\Gamma(k_2)}{2}\left(\frac{2}{v_2}\right)^{k_2} \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \mathrm{e}^{(\sigma_2 k_2/2)u} \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \mathrm{e}^{(a_1/(2D_F))u}, \tag{2.66}$$

from which

$$p_+ = \lim_{u \to +\infty} p(u) = \frac{c_2^2 \Gamma(k_2)}{2(\alpha_2/2)^{k_2}}. \tag{2.67}$$

In this case ($c_2^1 = 0$), note that the initial condition at zero yields

$$c_1^1 = \frac{p(0)}{I_{k_1}(\alpha_1)}. \tag{2.68}$$

□

Proposition 2. *Let $a_1 > 0$, $a_2 = 0$, and*

$$q(u) = \begin{cases} b_1^1 \mathrm{e}^{-\gamma_1 u} + b_2^1 \mathrm{e}^{\gamma_2 u} - \dfrac{\alpha n_0 p(0) \mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 p(0) \mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u < 0, \\ b_1^2 \mathrm{e}^{-\gamma_1 u} + b_2^2 \mathrm{e}^{\gamma_2 u} + \dfrac{\alpha n_0 \mathrm{e}^{-\gamma_1 u}}{\gamma_3} \int_0^u \mathrm{e}^{\gamma_6 u_1} \left(c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right)\right) du_1 \\ \qquad - \dfrac{\alpha n_0 \mathrm{e}^{\gamma_2 u}}{\gamma_3} \int_0^u \mathrm{e}^{\gamma_7 u_1} \left(c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right)\right) du_1, \quad u \geq 0, \end{cases} \tag{2.69}$$

where γ_1, γ_2, γ_3, γ_4, γ_5, γ_6 and γ_7 are given in (2.33), c_1^2, c_2^2, b_1^1, b_2^1, b_1^2 and b_2^2 are arbitrary constants. Then $q(u)$ is bounded if and only if $b_1^1 = \gamma_8$ and $b_2^2 = \gamma_{91} + \gamma_{92}$, where γ_8 is given in (2.33), and γ_{91}, γ_{92} are given by

$$\gamma_{91} = \frac{-\alpha n_0 c_1^2 (\alpha_2/2)^{k_2}}{\gamma_3(\gamma_7 - a_1/(2D_F))\Gamma(1+k_2)}, \quad \gamma_{92} = \frac{-\alpha n_0 c_2^2 \Gamma(k_2)}{2\gamma_3(\gamma_7 + a_1/(2D_F))(\alpha_2/2)^{k_2}}. \tag{2.70}$$

Proof. Given that the modifiel Bessel functions I_{k_i} and K_{k_i} are continuous, then $q(u)$ in (2.69) is always continuous everywhere, except at zero depending on the value of the constants. Therefore, we only need to prove the boundedness of $q(u)$ as $u \to \pm\infty$.

Assume $u < 0$. We note that $v_1 = \alpha_1 \mathrm{e}^{(\sigma_1/2)u}$ is very small (of order 10^{-2} as mentioned in §2.3.1). Then as $u \to -\infty$,

$$\int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \int_u^0 \mathrm{e}^{(\gamma_5 + a_1/(2D_F))u_1} du_1, \tag{2.71}$$

which implies that

$$\mathrm{e}^{\gamma_2 u} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx -\frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} u \mathrm{e}^{\gamma_2 u}, \tag{2.72}$$

if $\gamma_5 + a_1/(2D_F) = 0$, or

$$\mathrm{e}^{\gamma_2 u} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx \frac{(\alpha_1/2)^{k_1}}{(\gamma_5 + a_1/(2D_F))\Gamma(1+k_1)} \left(\mathrm{e}^{\gamma_2 u} - \mathrm{e}^{\sigma_1 u}\right), \tag{2.73}$$

if $\gamma_5 + a_1/(2D_F) \neq 0$. Therefore,

$$\lim_{u\to-\infty} \mathrm{e}^{\gamma_2 u} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 = 0. \tag{2.74}$$

Likewise, given that

$$\mathrm{e}^{-\gamma_1 u} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx \frac{(\alpha_1/2)^{k_1}}{(\gamma_4 + a_1/(2D_F))\Gamma(1+k_1)} \left(\mathrm{e}^{-\gamma_1 u} - \mathrm{e}^{\sigma_1 u}\right) \tag{2.75}$$

as $u \to -\infty$, then

$$\mathrm{e}^{-\gamma_1 u}\left(b_1^1 - \frac{\alpha n_0 p(0)}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1\right) \approx \gamma_8 \mathrm{e}^{\sigma_1 u} + \mathrm{e}^{-\gamma_1 u}\left(b_1^1 - \gamma_8\right), \tag{2.76}$$

where γ_8 is given in (2.33). Thus from (2.74) and (2.76), $q(u)$ is bounded (when $u < 0$) if and only if $b_1^1 = \gamma_8$, and

$$\lim_{u\to-\infty} q(u) = 0. \tag{2.77}$$

Now we assume $u \geq 0$, and note that

$$\lim_{u\to+\infty} \mathrm{e}^{-\gamma_1 u} \int_0^u \mathrm{e}^{\gamma_6 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 = 0 \tag{2.78}$$

(for $I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)$ is bounded, and $-\gamma_1 + \gamma_6 < 0$). As $u \to +\infty$,

$$\int_0^u \mathrm{e}^{\gamma_7 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \approx \frac{(\alpha_2/2)^{k_2}}{(\gamma_7 - a_1/(2D_F))\Gamma(1+k_2)} \left(\mathrm{e}^{(\gamma_7 - a_1/(2D_F))u} - 1\right) \tag{2.79}$$

(given that $v_2 = \alpha_2 \mathrm{e}^{-(\sigma_2/2)u}$ is very small), and

$$\int_0^u \mathrm{e}^{\gamma_7 u_1} K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \approx \frac{\Gamma(k_2)}{2(\gamma_7 + a_1/(2D_F))(\alpha_2/2)^{k_2}} \left(\mathrm{e}^{(\gamma_7 + a_1/(2D_F))u} - 1\right), \tag{2.80}$$

which imply that

$$\mathrm{e}^{\gamma_2 u}\left(b_2^2 - \frac{\alpha n_0}{\gamma_3} \int_0^u \mathrm{e}^{\gamma_7 u_1} h(u_1) du_1\right) \approx \gamma_{91} \mathrm{e}^{-(a_1/D_F + \sigma_2)u} + \gamma_{92} \mathrm{e}^{-\sigma_2 u} + \mathrm{e}^{\gamma_2 u}\left(b_2^2 - \gamma_{91} - \gamma_{92}\right), \tag{2.81}$$

where γ_{91}, γ_{92} are given in (2.70), and $h(u)$ is given by (2.62). Thus, when $u > 0$, $q(u)$ in (2.69), is bounded if and only if $b_2^2 = \gamma_{91} + \gamma_{92}$, and we have

$$\lim_{u\to+\infty} q(u) = 0. \tag{2.82}$$

□

Proof of Theorem 2.3.1 Let $a_2 = 0$ and $c_2^1 = 0$ (with $k_i = a_1/(D_F\sigma_i)$, and $c_1^1 = p(0)/I_{k_1}(\alpha_1)$). Assuming $q \in Y_S$, it is clear that N in (2.28) is a solution of (2.24) (see §2.3.1). Thus from (2.29) and Proposition 1, $p(u)$ is a bounded solution of (2.25) (the positivity will be discussed later). Substituting (2.28) and (2.29) into (2.26), and integrating, we obtain $q(u)$ given by (2.69). Taking $b_2^2 = \gamma_{91} + \gamma_{92}$ and $b_1^1 = \gamma_8$ (as set in Proposition 2), then $q(u)$ is bounded. We now show that for all real u, $q(u)$ in (2.32) is positive, with $q \in Y_S$. From (2.69),

$$q'(u) = \begin{cases} -\gamma_1 b_1^1 \mathrm{e}^{-\gamma_1 u} + \gamma_2 b_2^1 \mathrm{e}^{\gamma_2 u} + \dfrac{\gamma_1 \alpha n_0 p(0) \mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ \quad + \dfrac{\gamma_2 \alpha n_0 p(0) \mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u < 0, \\ -\gamma_1 b_1^2 \mathrm{e}^{-\gamma_1 u} + \gamma_2 b_2^2 \mathrm{e}^{\gamma_2 u} - \dfrac{\gamma_1 \alpha n_0 \mathrm{e}^{-\gamma_1 u}}{\gamma_3} \int_0^u \mathrm{e}^{\gamma_6 u_1} \left(c_1^2 I_{k_2}(v_2) + c_2^2 K_{k_2}(v_2)\right) du_1 \\ \quad - \dfrac{\gamma_2 \alpha n_0 \mathrm{e}^{\gamma_2 u}}{\gamma_3} \int_0^u \mathrm{e}^{\gamma_7 u_1} \left(c_1^2 I_{k_2}(v_2) + c_2^2 K_{k_2}(v_2)\right) du_1, \quad u \geq 0, \end{cases} \tag{2.83}$$

and the continuity of q at zero (i.e., $q(0^-) = q(0^+)$) and the differentiability at zero (i.e., $q'(0^-) = q'(0^+)$) give

$$b_1^2 = b_1^1 = \gamma_8, \quad b_2^1 = b_2^2 = \gamma_{91} + \gamma_{92}. \tag{2.84}$$

To guarantee $q(u)$ to be decreasing when $u \geq 0$, we take $c_2^2 = 0$. Thus, for $c_1^2 = p(0)/I_{k_2}(\alpha_2)$, $p(u)$ is positive and continuous at zero. As a result, when $u \geq 0$,

$$q'(u) \leq -\gamma_1\gamma_8 \mathrm{e}^{-\gamma_1 u} + \gamma_2\gamma_9 \mathrm{e}^{-(a_1/D_F + \sigma_2)u} - \frac{\gamma_1 \alpha n_0 p(0) \mathrm{e}^{-\gamma_1 u}}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_6 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, \tag{2.85}$$

and when $u < 0$,

$$q'(u) \geq -\gamma_1\gamma_8 \mathrm{e}^{\sigma_1 u} + \gamma_2\gamma_9 \mathrm{e}^{\gamma_2 u} + \frac{\gamma_2 \alpha n_0 p(0) \mathrm{e}^{\gamma_2 u}}{\gamma_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\gamma_5 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1. \tag{2.86}$$

where γ_8 and γ_9 are given in (2.33). In fact, $I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)$ is decreasing when $u \geq 0$, and $I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)$ is increasing when $u < 0$, with

$$\frac{(\alpha_2/2)^{k_2}}{\Gamma(1+k_2)} \mathrm{e}^{-(\sigma_2 k_2/2)u} \leq I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \leq I_{k_2}(\alpha_2), \tag{2.87}$$

and

$$\frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{(\sigma_1 k_1/2)u} \leq I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \leq I_{k_1}(\alpha_1). \tag{2.88}$$

Then from(2.81),

$$\gamma_2 \mathrm{e}^{\gamma_2 u} \left(\gamma_9 - \frac{\alpha n_0 p(0)}{\gamma_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\gamma_7 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1\right) \leq \gamma_2\gamma_9 \mathrm{e}^{-(\sigma_2 k_2/2 + a_1/(2D_F) + \sigma_2)u}, \tag{2.89}$$

and from (2.76),

$$-\gamma_1 \mathrm{e}^{-\gamma_1 u}\left(\gamma_8 - \frac{\alpha n_0 p(0)}{\tau_3 I_{k_1}(\alpha_1)}\int_u^0 \mathrm{e}^{\gamma_4 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1\right) \geq -\gamma_1\gamma_8 \mathrm{e}^{\sigma_1 u}, \tag{2.90}$$

which imply (2.85) and (2.86). Thus, for a_1 holding (2.34), $q(u)$ is increasing when $u < 0$ and decreasing when $u \geq 0$ (with $q(u)$ approaching zero as $u \to \pm\infty$), i.e., $q(u)$ is positive. Therefore, $q(u)$ in (2.32) is a positive, bounded solution to (2.26), with $q \in Y_S$. □

Theorem 2.3.2

We now state and prove the following proposition that will help us in the proof of Theorem 2.3.2.

Proposition 3. *Let a_1 and a_2 strictly positive, and $p(u)$ given by (2.29). Then $F(x,t) = \mathrm{e}^{a_2 t}p(u)$ is bounded if and only if $c_2^1 = c_2^2 = 0$ and ($c_1^1 = 0$ or $\frac{x}{t} \leq \frac{-1}{2}(\sqrt{a_1^2 + 4a_2 D_F} - a_1)$), and ($c_1^2 = 0$ or $\frac{x}{t} \geq \frac{1}{2}(\sqrt{a_1^2 + 4a_2 D_F} + a_1)$).*

Proof. As mentioned in the previous propositions, we will just look at the convergence at $\pm\infty$. Assume $u < 0$. If $c_2^1 \neq 0$, then $p(u)$ diverges as $u \to -\infty$, i.e., $F(x,t)$ diverges as $t \to +\infty$ and $x \to \pm\infty$ (with $x < a_1 t$). Suppose that $c_2^1 = 0$ and $c_1^1 \neq 0$, as $u = x - a_1 t \to -\infty$,

$$F(x,t) \approx \frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)}\mathrm{e}^{a_2 t}\mathrm{e}^{(\sigma_1 k_1/2 - a_1/(2D_F))(x-a_1 t)}, \tag{2.91}$$

$$\approx \frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)}\mathrm{e}^{x\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/(2D_F)}\mathrm{e}^{t\left(a_1^2+2a_2D_F-a_1\sqrt{a_1^2+4a_2D_F}\right)/(2D_F)}, \tag{2.92}$$

$$\approx \frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)}\mathrm{e}^{x\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/(2D_F)}\mathrm{e}^{t\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)^2/(4D_F)}, \tag{2.93}$$

$$\approx \frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)}\mathrm{e}^{\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)\left(x+t\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/2\right)/(2D_F)}. \tag{2.94}$$

Therefore $F(x,t)$ diverges as $t \to +\infty$ and $x \to \pm\infty$, if $\frac{-1}{2}(\sqrt{a_1^2 + 4a_2 D_F} - a_1) < \frac{x}{t} < a_1$, and converges if $\frac{x}{t} \leq \frac{-1}{2}(\sqrt{a_1^2 + 4a_2 D_F} - a_1)$.

Now we assume $u \geq 0$ (i.e., $x \geq a_1 t$). As $u \to +\infty$,

$$K_{k_2}(v_2)\mathrm{e}^{-(a_1/(2D_F))u} \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}}\mathrm{e}^{u\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/(2D_F)}. \tag{2.95}$$

If $c_2^2 \neq 0$, $p(u)$ diverges as $u \to +\infty$ (i.e., $F(x,t)$ diverges as $t \to +\infty$ and $x \to +\infty$). Suppose $c_2^2 = 0$ and $c_1^2 \neq 0$, as $t \to +\infty$ and $x \to +\infty$,

$$F(x,t) \approx \frac{c_1^2(\alpha_2/2)^{k_2}}{\Gamma(1+k_2)} \mathrm{e}^{-x\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)/(2D_F)} \mathrm{e}^{t\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)^2/(4D_F)}, \tag{2.96}$$

$$\approx \frac{c_1^2(\alpha_2/2)^{k_2}}{\Gamma(1+k_2)} \mathrm{e}^{\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)\left(-x+t\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)/2\right)/(2D_F)}. \tag{2.97}$$

Therefore, as $t \to +\infty$ and $x \to +\infty$, $F(x,t)$ diverges when $\frac{x}{t} < \frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1)$, and converges when $\frac{x}{t} \geq \frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1)$.

□

From Proposition 3, we have four possible cases of study, with $c_2^1 = c_2^2 = 0$ in each case.

1. If $c_1^1 \neq 0$ and $c_1^2 \neq 0$, then

$$F(x,t) = \begin{cases} c_1^1 \mathrm{e}^{a_2 t} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \mathrm{e}^{-a_1/(2D_F)}, & \frac{x}{t} \leq \frac{-1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1), \\ c_1^2 \mathrm{e}^{a_2 t} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-a_1/(2D_F)}, & \frac{x}{t} \geq \frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1). \end{cases} \tag{2.98}$$

   Therefore, continuous travelling wave solutions do not exist.

2. If $c_1^1 = 0$ and $c_1^2 \neq 0$, then taking into consideration Proposition 3, and substituting (2.28) and (2.29) into (2.26), and integrating we obtain

$$q(u) = \begin{cases} b_3^1 \mathrm{e}^{-\tau_1 u} + b_4^1 \mathrm{e}^{\tau_2 u}, & u < 0, \\ b_3^2 \mathrm{e}^{-\tau_1 u} + b_4^2 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 c_1^2 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \\ - \dfrac{\alpha n_0 c_1^2 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_5 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1, & u \geq \frac{1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1), \end{cases} \tag{2.99}$$

   where τ_1, τ_2, τ_3, τ_4 and τ_5 are given in (2.38), and b_3^1, b_4^1, b_3^2 and b_4^2 are constant. Therefore, continuous travelling wave solutions do not exist.

3. Likewise, if $c_1^1 \neq 0$ and $c_1^2 = 0$, there is no continuous travelling wave solutions.

4. If $c_1^1 = c_1^2 = 0$, the non zero travelling wave solutions do not exist.

Thus, when $a_2 > 0$, non zero continuous travelling wave solutions do not exist. □

Theorem 2.3.3 and Theorem 4.3.4

Here, we choose a_2 so that τ_2 in (2.38) remains positive (by taking $a_2+\gamma>0$), and $k_i>0$ (i.e., $a_2>-a_1^2/(4D_F)$).

Now we establish a few propositions for the proof of Theorem 2.3.3 and Theorem 4.3.4.

Proposition 4. *Let $a_1>0$, $a_2<0$ (with $a_2>-a_1^2/(4D_F)$) and $p(u)$ given by (2.29). Then $F(x,t)=\mathrm{e}^{a_2 t}p(u)$ is bounded if and only if ($c_2^1\neq 0$ with $\frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1)\leq\frac{x}{t}<a_1$), or ($c_2^1=0$, $c_1^1\neq 0$ with $\frac{-1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1)\leq\frac{x}{t}<a_1$), or ($c_1^1=c_2^1=0$).*

Proof. Assume $u<0$ and $c_2^1\neq 0$. As $u\to-\infty$,

$$c_2^1\mathrm{e}^{a_2t}K_{K_1}(v_1)\mathrm{e}^{\frac{-a_1}{2D_F}u}\approx\frac{c_2^1\Gamma(k_1)}{2(\alpha_1/2)^{k_1}}\mathrm{e}^{\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)\left(-x+t\left(\sqrt{a_1^2+4a_2D_F}+a_1\right)/2\right)/(2D_F)}. \tag{2.100}$$

Then $F(x,t)$ diverges as $t\to+\infty$ and $x\to\pm\infty$ if $\frac{x}{t}<\frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1)$, and converges if $\frac{1}{2}(\sqrt{a_1^2+4a_2D_F}+a_1)\leq\frac{x}{t}<a_1$. When $c_2^1=0$ and $c_1^1\neq 0$, as $u\to-\infty$,

$$F(x,t)\approx\frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)}\mathrm{e}^{\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)\left(x+t\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/2\right)/(2D_F)}. \tag{2.101}$$

Therefore, as $t\to+\infty$ and $x\to\pm\infty$, $F(x,t)$ diverges if $\frac{x}{t}<\frac{-1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1)$, and converges if $\frac{x}{t}\geq\frac{-1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1)$.

Now assume $u\geq 0$ (i.e., $x\geq a_1t$). As $u\to+\infty$,

$$c_2^2\mathrm{e}^{a_2t}K_{K_2}(v_2)\mathrm{e}^{-(a_1/(2D_F))u}\approx\frac{c_2^2\Gamma(k_2)}{2(\alpha_2/2)^{k_2}}\mathrm{e}^{\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)\left(x+t\left(\sqrt{a_1^2+4a_2D_F}-a_1\right)/2\right)/(2D_F)}. \tag{2.102}$$

Then, $F(x,t)$ always converges as $t\to+\infty$ and $x\to+\infty$ (since $\frac{x}{t}>a_1>\frac{-1}{2}(\sqrt{a_1^2+4a_2D_F}-a_1)$). Therefore, as pointed out in Proposition 1, the convergence at the boundaries implies the boundedness.

□

The following proposition study the boundedness of $q(u)$ in the case where $c_1^1=c_2^1=0$, and will be used for the proof of Theorem 2.3.3.

Proposition 5. *Let $a_1 > 0$, $max(-a_1^2/(4D_F), -\gamma) < a_2 < 0$, and*

$$q(u) = \begin{cases} b_5^1 \mathrm{e}^{-\tau_1 u} + b_6^1 \mathrm{e}^{\tau_2 u}, \quad u < 0, \\ b_5^2 \mathrm{e}^{-\tau_1 u} + b_6^2 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_4 u_1} \left(c_1^2 I_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) + c_2^2 K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) \right) du_1 \\ - \dfrac{\alpha n_0 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_5 u_1} \left(c_1^2 I_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) + c_2^2 K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) \right) du_1, \quad u \geq 0, \end{cases} \tag{2.103}$$

where τ_1, τ_2, τ_3, τ_4 and τ_5 are given in (2.38), and c_1^2, c_2^2, b_5^1, b_6^1, b_5^2 and b_6^2 are constant. Then $S(x,t) = \mathrm{e}^{a_2 t} q(u)$ is bounded if and only if ($b_6^2 = \delta_1 + \delta_2$, or $a_1 \leq \frac{x}{t} \leq \frac{a_1\tau_2 - a_2}{\tau_2}$), and ($b_5^1 = 0$, or $\frac{a_1\tau_1 + a_2}{\tau_1} \leq \frac{x}{t} < a_1$), where δ_1 given in (2.38) and δ_2 by

$$\delta_2 = \frac{-\alpha n_0 c_2^2 \Gamma(k_2)}{2\tau_3(\sigma_2 k_2/2 + \tau_5)(\alpha_2/2)^{k_2}}. \tag{2.104}$$

Proof. Assume $u \geq 0$. Since $\tau_4 - \tau_1 < 0$, then as in (2.78), we have

$$\lim_{u \to +\infty} \mathrm{e}^{-\tau_1 u} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) du_1 = 0. \tag{2.105}$$

As $u \to +\infty$,

$$\int_0^u \mathrm{e}^{\tau_4 u_1} K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) du_1 \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \int_0^u \mathrm{e}^{(\tau_4 + \sigma_2 k_2/2)u_1} du_1, \tag{2.106}$$

which implies that

$$\mathrm{e}^{-\tau_1 u} \int_0^u \mathrm{e}^{\tau_4 u_1} K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) du_1 \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} u \mathrm{e}^{-\tau_1 u}, \tag{2.107}$$

if $\tau_4 + \sigma_2 k_2/2 = 0$, or

$$\mathrm{e}^{-\tau_1 u} \int_0^u \mathrm{e}^{\tau_4 u_1} K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) du_1 \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}(\tau_4 + \sigma_2 k_2/2)} \left(\mathrm{e}^{(-a_1/(2D_F) - \sigma_2 + \sigma_2 k_2/2)u} - \mathrm{e}^{-\tau_1 u} \right), \tag{2.108}$$

if $\tau_4 + \sigma_2 k_2/2 \neq 0$ (with$-a_1/(2D_F) + \sigma_2 k_2/2 < 0$). Therefore, we always have

$$\lim_{u \to +\infty} \mathrm{e}^{-\tau_1 u} \int_0^u \mathrm{e}^{\tau_4 u_1} K_{k_2} \left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1} \right) du_1 = 0. \tag{2.109}$$

Given that $\tau_5 + \sigma_2 k_2/2 < 0$ (for $\tau_5 + \sigma_2 k_2/2 + \tau_2 < 0$, and $\tau_2 > 0$), as $u \to +\infty$,

$$\int_0^u \mathrm{e}^{\tau_5 u_1} h(u_1) du_1 \approx \frac{c_1^2 (\alpha_2/2)^{k_2}}{\Gamma(1 + k_2)} \int_0^u \mathrm{e}^{(\tau_5 - \sigma_2 k_2/2)u_1} du_1 + \frac{c_2^2 \Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \int_0^u \mathrm{e}^{(\tau_5 + \sigma_2 k_2/2)u_1} du_1, \tag{2.110}$$

where $h(u)$ is given by (2.62). Thus,

$$\mathrm{e}^{\tau_2 u}\left(b_6^2-\frac{\alpha n_0}{\tau_3}\int_0^u \mathrm{e}^{\tau_5 u_1}h(u_1)du_1\right)\approx \delta_1\mathrm{e}^{(-\sigma_2 k_2/2-a_1/(2D_F)-\sigma_2)u}+\delta_2\mathrm{e}^{(\sigma_2 k_2/2-a_1/(2D_F)-\sigma_2)u} +(b_6^2-\delta_1-\delta_2)\mathrm{e}^{\tau_2 u}, \quad (2.111)$$

where δ_1, δ_2 are respectively given in (2.38) and (2.104). Therefore from (2.105), (2.109) and (2.111), $S(x,t)$ converges to zero as $x\to+\infty$ and $t\to+\infty$, if $b_6^2=\delta_1+\delta_2$. However, if $b_6^2\neq\delta_1+\delta_2$, we remark from

$$(b_6^2-\delta_1-\delta_2)\mathrm{e}^{\tau_2 u}\mathrm{e}^{a_2 t}=(b_6^2-\delta_1-\delta_2)\mathrm{e}^{\tau_2 x}\mathrm{e}^{t(a_2-a_1\tau_2)}, \quad (2.112)$$

that $S(x,t)$ diverges when $\frac{x}{t}>\frac{-(a_2-a_1\tau_2)}{\tau_2}$, and converges when $a_1\leq\frac{x}{t}\leq\frac{-(a_2-a_1\tau_2)}{\tau_2}$, as $x\to+\infty$ and $t\to+\infty$.

Now we assume $u<0$, then $S(x,t)$ converges for $b_5^1=0$. If $b_5^1\neq 0$, $S(x,t)$ diverges when $\frac{x}{t}<\frac{a_1\tau_1+a_2}{\tau_1}$, and converges when $\frac{a_1\tau_1+a_2}{\tau_1}\leq\frac{x}{t}<a_1$. The proof follows from the fact that

$$b_5^1\mathrm{e}^{-\tau_1 u}\mathrm{e}^{a_2 t}=b_5^1\mathrm{e}^{-\tau_1 x}\mathrm{e}^{t(a_2+a_1\tau_1)}. \quad (2.113)$$

□

Proof of Theorem 2.3.3 Let $a_1>0$, $max(-a_1^2/(4D_F),-\gamma)<a_2<0$, and $c_1^1=c_2^1=0$. Substituting (2.28) and (2.29) in (2.26) and integrating, we get $q(u)$ given by (2.103). Choosing $b_5^1=0$ (because $q(u)$ should be increasing when $u<0$) and $b_6^2=\delta_1+\delta_2$, then $q(u)$ is bounded. We now show that $S(x,t)$ in (2.36) is a postive solution of (2.7), with $q\in Y_S'$ (we will show that $q\notin Y_S$).

The continuity of $q(u)$ at zero gives

$$b_6^1=b_5^2+b_6^2, \quad (2.114)$$

and the derivative is

$$q'(u)=\begin{cases}\tau_2 b_6^1\mathrm{e}^{\tau_2 u}, & u<0,\\ -\tau_1 b_5^2\mathrm{e}^{-\tau_1 u}+\tau_2 b_6^2\mathrm{e}^{\tau_2 u}-\dfrac{\tau_1\alpha n_0\mathrm{e}^{-\tau_1 u}}{\tau_3}\int_0^u \mathrm{e}^{\tau_4 u_1}\left(c_1^2 I_{k_2}(v_2)+c_2^2 K_{k_2}(v_2)\right)du_1 & \\ -\dfrac{\tau_2\alpha n_0\mathrm{e}^{\tau_2 u}}{\tau_3}\int_0^u \mathrm{e}^{\tau_5 u_1}\left(c_1^2 I_{k_2}(v_2)+c_2^2 K_{k_2}(v_2)\right)du_1, & u\geq 0.\end{cases} \quad (2.115)$$

If we assume that $q(u)$ is differentiable at zero (i.e., $q'(0^-) = q'(0^+)$), then from (2.114) and (2.115),

$$b_5^2 = 0, \quad b_6^1 = b_6^2. \tag{2.116}$$

In that case, $q(u)$ is not monotonically decreasing when $u > 0$, i.e., $q \notin Y_S$ (given that $q'(0) = \tau_2 b_6^2$ and $\lim_{u\to+\infty} q'(u) = 0$, with $b_6^2 > 0$). Thus, $q(u)$ is not differentiable at zero. This result is not surprising, given that the production term of the aspartate αNp in (2.26) is not differentiable at zero. To keep the peak at $u = 0$, we take $b_5^2 = \tau_2 b_6^2/\tau_1$ (i.e., $q'(0^+) = 0$), and from the continuity at zero, we have

$$b_6^1 = q(0) = b_5^2 + b_6^2 = (1 + \frac{\tau_2}{\tau_1})b_6^2. \tag{2.117}$$

To guarantee $q(u)$ to be monotonically decreasing when $u \geq 0$, we take $c_2^2 = 0$. Thus, for $c_1^2 = F(0,0)/I_{k_2}(\alpha_2)$, and from (2.111) and (2.115),

$$q'(u) \leq \tau_2\delta_1 \left(-\mathrm{e}^{-\tau_1 u} + \mathrm{e}^{(-\sigma_2 k_2/2 - a_1/(2D_F) - \sigma_2)u}\right) - \frac{\tau_1 \alpha n_0 F(0,0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_2)} \int_0^u \mathrm{e}^{\tau_4 u_1} I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1 \tag{2.118}$$

(the proof is similar with (2.89)). Thus, from (2.39), $q(u)$ is decreasing when $u > 0$, and note that $q(u)$ converges to zero as $u \to +\infty$. When $u < 0$, it is clear that $q(u)$ is increasing. As a result, $S(x,t)$ in (2.36) is a positive, bounded solution of (2.7), with $q \in Y_S'$. □

We will now use the following proposition in the proof of Theorem 4.3.4 (from proposition 5, we are studying the case where $c_2^1 = 0$ and $c_1^1 \neq 0$, with $\frac{-1}{2}\left(\sqrt{a_1^2 + 4a_2 D_F} - a_1\right) \leq \frac{x}{t} < a_1$).

Proposition 6. *Let $a_1 > 0$ (with $-a_1/(2D_F) + \sigma_1 > 0$), $max(-a_1^2/(4D_F), -\gamma) < a_2 < 0$, and*

$$q(u) = \begin{cases} b_5^1 \mathrm{e}^{-\tau_1 u} + b_6^1 \mathrm{e}^{\tau_2 u} - \dfrac{\alpha F(0,0) n_0 \mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ + \dfrac{\alpha F(0,0) n_0 \mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u < 0, \\ b_5^2 \mathrm{e}^{-\tau_1 u} + b_6^2 \mathrm{e}^{\tau_2 u} + \dfrac{\alpha n_0 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_4 u_1} \left(c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right)\right) du_1 \\ - \dfrac{\alpha n_0 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_5 u_1} \left(c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u_1}\right)\right) du_1, \quad u \geq 0, \end{cases} \tag{2.119}$$

where τ_1, τ_2, τ_3, τ_4 and τ_5 are given in (2.38), τ_{41} and τ_{51} in (2.43), and c_1^2, c_2^2, b_5^1, b_6^1, b_5^2 and b_6^2 are constant. Then $S(x,t) = \mathrm{e}^{a_2 t} q(u)$ is bounded if and only if ($b_5^1 = \delta_{11}$, or $\frac{a_1\tau_1 + a_2}{\tau_1} \leq \frac{x}{t} < a_1$),

and ($b_6^2 = \delta_1 + \delta_2$, or $a_1 \leq \frac{x}{t} \leq \frac{a_1\tau_2 - a_2}{\tau_2}$), where δ_{11}, δ_1 and δ_2 are respectively given in (2.43), (2.38) and (2.104).

Proof. Assume $u < 0$ (with $-a_1/(2D_F) + \sigma_1 > 0$), then

$$\lim_{u\to-\infty} \mathrm{e}^{\tau_2 u} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx \lim_{u\to-\infty} \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{\tau_2 u} \int_u^0 \mathrm{e}^{(\tau_7+\sigma_1 k_1/2)u_1} du_1 = 0 \quad (2.120)$$

(since $\tau_2 + \tau_7 > 0$). As $u \to -\infty$,

$$\mathrm{e}^{-\tau_1 u} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \approx \frac{(\alpha_1/2)^{k_1}}{(\tau_6 + \sigma_1 k_1/2)\Gamma(1+k_1)} \left(-\mathrm{e}^{(\sigma_1 k_1/2 - a_1/(2D_F)+\sigma_1)u} + \mathrm{e}^{-\tau_1 u}\right), \quad (2.121)$$

which implies that

$$\mathrm{e}^{-\tau_1 u}\left(b_5^1 - \frac{\alpha n_0 F(0,0)}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1\right) \approx \delta_{11} \mathrm{e}^{(\sigma_1 k_1/2 - a_1/(2D_F)+\sigma_1)u} + (b_5^1 - \delta_{11})\mathrm{e}^{-\tau_1 u}. \quad (2.122)$$

If $b_5^1 = \delta_{11}$, $S(x,t)$ converges to zero as $x \to \pm\infty$ and $t \to +\infty$. However if $b_5^1 \neq \delta_{11}$, $S(x,t)$ diverges if $\frac{x}{t} < \frac{a_1\tau_1 + a_2}{\tau_1}$, and converges if $\frac{a_1\tau_1+a_2}{\tau_1} \leq \frac{x}{t} < a_1$ (the proof is similar with the one in (2.113)).

The case where $x \geq a_1 t$ has already been studied in Proposition 5. □

Proof of Theorem 4.3.4 Let $a_1 > 0$ (with $-a_1/(2D_F) + \sigma_1 > 0$), $max(-a_1^2/(4D_F), -\gamma) < a_2 < 0$, and $c_2^1 = 0$. Then $F(x,t)$ in (2.40) is a positive, bounded solution of (2.6). Substituting (2.28) and (2.29) in (2.26) and integrating (with $c_1^1 = F(0,0)/I_{k_1}(\alpha_1)$), we get $q(u)$ given by (2.119), bounded. Choosing $b_5^1 = \delta_{11}$ and $b_6^2 = \delta_1 + \delta_2$, we now show that $S(x,t)$ in (2.41) is positive and solution of (2.7), with $q \in Y_S$.

From (2.119),

$$q'(u) = \begin{cases} -\tau_1\delta_{11}\mathrm{e}^{-\tau_1 u} + \tau_2 b_6^1 \mathrm{e}^{\tau_2 u} + \dfrac{\tau_1\alpha F(0,0) n_0 \mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1 \\ + \dfrac{\tau_2\alpha F(0,0) n_0 \mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \quad u < 0, \\ -\tau_1 b_5^2 \mathrm{e}^{-\tau_1 u} + \tau_2\delta_1 \mathrm{e}^{\tau_2 u} - \dfrac{\tau_1\alpha n_0 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_4 u_1}\left(c_1^2 I_{k_2}(v_2) + c_2^2 K_{k_2}(v_2)\right) du_1 \\ - \dfrac{\tau_2\alpha n_0 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_5 u_1}\left(c_1^2 I_{k_2}(v_2) + c_2^2 K_{k_2}(v_2)\right) du_1, \quad u \geq 0. \end{cases} \quad (2.123)$$

The continuity and the differentiability of $q(u)$ at zero give

$$b_5^2 = b_5^1 = \delta_{11}, \quad b_6^1 = b_6^2 = \delta_1 + \delta_2. \tag{2.124}$$

Here to guarantee $q \in Y_S$, we also take $c_2^2 = 0$ (and note that $c_1^2 = F(0,0)/I_{k_2}(\alpha_2)$, from the continuity). Then as in (2.85) and (2.86) , when $u < 0$,

$$q'(u) \geq -\tau_1\delta_{11}\mathrm{e}^{(\sigma_1 k_1/2 - a_1/(2D_F)+\sigma_1)u} + \tau_2\delta_1\mathrm{e}^{\tau_2 u} + \frac{\tau_2\alpha F(0,0)n_0\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_1)}\int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_1\mathrm{e}^{(\sigma_1/2)u_1}\right) du_1, \tag{2.125}$$

and when $u \geq 0$,

$$q'(u) \leq -\tau_1\delta_{11}\mathrm{e}^{-\tau_1 u} + \tau_2\delta_1\mathrm{e}^{-(\sigma_2 k_2/2 + a_1/(2D_F)+\sigma_2)u} - \frac{\tau_2\alpha n_0 F(0,0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_2)}\int_0^u \mathrm{e}^{\tau_5 u_1} I_{k_2}\left(\alpha_2\mathrm{e}^{-(\sigma_2/2)u_1}\right) du_1. \tag{2.126}$$

Then, for a_1 holding (2.44), $q(u)$ is increasing when $u < 0$ and decreasing when $u \geq 0$. As a result, $q \in Y_S$ and $S(x,t)$ in (2.41) is a positive, bounded solution of (2.7). □

Theorem 2.3.9

Proof of Theorem 2.3.9 Let $a_1 = a_2 = 0$. From (2.63), recall that $I_0(v_1)$ (respectively $I_0(v_2)$) converges to one, and $K_0(v_1)$ (respectively $K_0(v_2)$) diverges, as $u \to -\infty$ (respectively $u \to +\infty$). Therefore, $p(u)$ in (2.29) is bounded if and only if $c_2^1 = c_2^2 = 0$. Setting c_2^1 and c_2^2 to zero, and substituting (2.28) and (2.29) into (2.26), then integrating, we obtain

$$q(u) = \begin{cases} f_1^1\mathrm{e}^{-\gamma_1 u} + f_2^1\mathrm{e}^{\gamma_1 u} - \dfrac{\alpha n_0 c_1^1\mathrm{e}^{-\gamma_1 u}}{\gamma_3}\displaystyle\int_u^0 \mathrm{e}^{-\gamma_4 u_1} I_0\left(\alpha_0\mathrm{e}^{(\sigma_0/2)u_1}\right) du_1 \\ \qquad + \dfrac{\alpha n_0 c_1^1\mathrm{e}^{\gamma_1 u}}{\gamma_3}\displaystyle\int_u^0 \mathrm{e}^{-\gamma_5 u_1} I_0\left(\alpha_0\mathrm{e}^{(\sigma_0/2)u_1}\right) du_1, \quad u < 0, \\ f_1^2\mathrm{e}^{-\gamma_1 u} + f_2^2\mathrm{e}^{\gamma_1 u} + \dfrac{\alpha n_0 c_1^2\mathrm{e}^{-\gamma_1 u}}{\gamma_3}\displaystyle\int_0^u \mathrm{e}^{\gamma_5 u_1} I_0\left(\alpha_0\mathrm{e}^{-(\sigma_0/2)u_1}\right) du_1 \\ \qquad - \dfrac{\alpha n_0 c_1^2\mathrm{e}^{\gamma_1 u}}{\gamma_3}\displaystyle\int_0^u \mathrm{e}^{\gamma_4 u_1} I_0\left(\alpha_0\mathrm{e}^{-(\sigma_0/2)u_1}\right) du_1, \quad u \geq 0, \end{cases} \tag{2.127}$$

where γ_1, γ_3, γ_4, γ_5 are given in (2.60), and f_j^i are arbitrary constants. From the previous results, the above solution $q(u)$ is bounded if and only if $f_1^1 = -\alpha n_0 c_1^1/(\gamma_3\gamma_4)$ and $f_2^2 = -\alpha n_0 c_1^2/(\gamma_3\gamma_4)$. The continuity of $p(u)$ and $q(u)$ at zero, and the fact that $q'_+(0) = 0$ yield

$$c_1^1 = c_1^2 = p(0)/I_0(\alpha_0), \quad f_1^2 = f_2^2, \quad f_2^1 = q(0) - f_1^1 = f_2^2. \tag{2.128}$$

In (2.127), it is clear (from the proof of Theorem 2.3.1) that $q(u) \in Y_S$ and is positive. □

Chapter 3

Travelling wave solutions in chemotaxis: starvation

3.1 Introduction

Chemotaxis is orientation (or movement) of an organism in response to chemical signals. Cells, through membrane receptors located at their surface, sense the environment, detect chemicals, and then transfer information to their interior [7]. Depending on the nature of the information, an enzyme will be produced and will cause cells to respond accordingly (attraction or repulsion). The protein CheY facilitates the transmission of the signal from the chemoreceptors to the flagella motors in *E coli* [82]. The phosphorylation of CheY caused by chemorepellents will drive the flagella to rotate clockwise, and the dephosphorylation of CheY caused by chemoattractants will drive counter-clockwise rotation of the flagella [65, 23]. Counter-clockwise rotation of the flagella causes the cell to move forward, and clockwise rotation causes the cell to stumble (we note that *E coli* moves by jumping through the rotation of its flagella).

Progress made in cell biology shows that chemotaxis plays a vital role in reproduction, tissue repair, drug delivery and tumor invasion [27, 33, 91, 53, 90]. In fact, sperm cell motility is directed by chemoattractants resulting from signalling of female reproductive tract [27, 33]. In wound healing processes, chemotaxis facilitates the aggregation of immune system cells into site

of infection [91]. It is also involved in metastasis and atherosclesis states of diseases [18, 21, 34, 70, 71]. In pharmacology, chemotaxis is involved in drug delivery to the targeted defective area [53, 90]. The beauty of the dynamics of chemotaxis is that cells manifest harmonious behaviour, while behaving independently. This was observed independently by Engelmann [25, 26], Pfeffer [84] and Beyerinck [8]. With the remarkable work of Adler [1, 2] in the past fifty years, bacterial chemotaxis became one of the better-documented systems in Biology. Adler [1, 2, 3] observed travelling bands of bacteria when he introduced a population of cells (*E coli*) in a capillary tube accommodating oxygen and an energy source. Two bands of cells were formed; the first band consumed all the oxygen and the second band consumed the residual energy source. Bands were also observed without the adding of the energy source; cells consumed oxygen and excreted a gradient of energy source [2]. Bak *et al* [5] noticed that the bands were in a form of a circular ring. The complexity of the geometric patterns caused by chemotaxis cannot be intuitively explained from experiments [72]. As a result, mathematical modelling approaches have been proposed which have been able to predict the geometric shape of the pattern [44, 45, 46, 83, 92].

As we have said before, Keller and Segel [44, 45, 46] proposed, for the first time from a population-based perspective, a chemotaxis model (the K-S model) that describes the motion of *slime* and the formation of chemotactic bands of cells. The general form of the K-S model is written as follows:

$$\frac{\partial b}{\partial t} = \nabla \cdot (\mu(s)\nabla b) - \nabla \cdot (b\chi(s)\nabla s), \tag{3.1}$$

$$\frac{\partial s}{\partial t} = D\nabla^2 s - k(s)b, \tag{3.2}$$

where t represents the time, b is the cell density, s the concentration of the critical substrate, $\chi(s)$ the chemotactic sensitivity, $k(s)$ the consumption rate of substrates per cell, and $\mu(s)$ and D the diffusion coefficient of the bacteria and the substrates, respectively. Note that cell proliferation was ignored in the K-S model. A singularity in the chemotactic sensitivity was required to produce travelling wave solutions [44, 45, 92]. Such a hypothesis is problematic, given that it can cause the bands to move with unbounded velocity (we note that the speed of the band should not be larger that the speed of a single cell)[111]. This unnecessary restriction can be overcome by the consideration of other relevant factors. It was shown, for instance,

that adding of logistic growth terms can lead to travelling wave solutions (with non-singular sensitivity) [73].

Likewise, from the cell-based perspective, Patlak [83] proposed the first model for chemotaxis to depict the random walk process of a particle with external bias and persistence of direction. This model was later improved by Alt [1] and Othmer *et al* [80]. Recently, Xue *et al* [111] formulated a model which takes into account the interaction between two substrates (nutrients and attractants). What is remarkable about their model is that it can be applied in a variety of biological situations, including population dynamics to describe the competition between two species from a microscopic level (the individual species behaviour). Variables describing intracellular processes such as metabolism and transduction of the signal were explicitly represented in the Xue *et al's* [111] model. Travelling wave solutions with a unique wave speed were demonstrated in the scenario of zero growth, without requiring a singularity in the chemotactic sensitivity. We [98, 99] extended these results by allowing for diffusivity and cell proliferation, and provided explicit solutions for the first time. Franz *et al* [32] studied the case of starvation. They assumed that cells consume chemoattractants only (which do not diffuse over the space), and considered a non constant growth of bacteria. They proved the existence of travelling wave solutions in the case of no chemotaxis.

In this paper, we will be looking at the individual behaviour of cells to understand the convergence and harmonization of their motion. The aggregation and movement (with constant speed) of cells are the centre of our study. We will focus on the case of low presence (or absence) of nutrients as the formation of bands of cells was observed in this situation [2, 11]. The existence of travelling wave solutions will be investigated. Unlike previous approaches, we will allow for diffusivity, and will account for signal degradation and constant cell growth. We will also study the impact of microscale parameters (such as cell growth rate, cell unbiased turning rate and cell speed) on the macroscopic behaviour of the system.

We introduce the model in Section 3.2. As symmetry analysis has proven to be very effective in finding useful solutions to PDEs [16], we utilise that approach for our system of PDEs. We generate a class of invariants that lead to generalized travelling wave solutions. In some cases, we utilise dynamical systems analysis to further investigate the behaviour of the solutions.

(This confirms our previous findings on the interplays between group theory and dynamical systems analysis [97].) Realistic initial and boundary conditions are then applied to obtain relevant solutions. We discuss our results in Section 3.3.

3.2 Reduced model and analysis

The model emanates from previous experiments [9, 13, 14, 110] in which bacteria (*E coli*) consume nutrients and excrete a signal gradient, then aggregate in different patterns formed in response to this gradient. We are concerned with the case of limited resources (low presence or absence of nutrients). In this scenario cells consume the excreted signal only. A set of chemical processes occur within the cells to enable them to survive and respond to their surroundings. Xue *et al* [111] developed a model to describe the intracellular metabolism, written as follows:

$$\frac{dz_1}{dt} = \frac{F(x,t) - z_1}{t_f}, \quad \frac{dz_2}{dt} = \frac{z_1 - z_2}{t_m}, \tag{3.3}$$

where $z = (z_1, z_2)$ depicts the cellular metabolism, $F(x,t)$ is the concentration of nutrients, and t_f and t_m are the characteristic time scales for the production of the immediate variables z_1 and z_2, respectively. In the above description, it is assumed that after consumption of succinate $F(x,t)$ a variable z_1 is involved to facilitate the production of the signal $S(x,t)$ via the pathway

$$F \to z_1 \to S. \tag{3.4}$$

The low level of nutrients will cause z_1 to catalytically influence the production of a starving variable z_2, via the metabolic pathway

$$\phi \xrightarrow{z_1} z_2 \to \phi, \tag{3.5}$$

where ϕ stands for the reactants/products assumed to be in excess [111].

We overlook the explicit representation of the variable z_1 (given that $t_f \lll t_m$), and we assume fast signal transduction (given that the adaptation time of the signal transduction $t_a \lll t_m$ [111]). Then the distribution of the cells (as introduced in Chapter 1) can be described in

one-dimensional space as follows:

$$\frac{\partial p^+}{\partial t} + s\frac{\partial p^+}{\partial x} + \frac{\partial}{\partial z}\left(\frac{F-z}{t_m}p^+\right) = -\lambda\left(-\frac{\partial S}{\partial x}\right)p^+ + \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(S)p^+, \tag{3.6}$$

$$\frac{\partial p^-}{\partial t} - s\frac{\partial p^-}{\partial x} + \frac{\partial}{\partial z}\left(\frac{F-z}{t_m}p^-\right) = \lambda\left(-\frac{\partial S}{\partial x}\right)p^+ - \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(S)p^-, \tag{3.7}$$

where $p^{\pm}(x,z,t)$ is the density of cells at the position x, the internal state $z = z_2$ and time t, moving with constant speed $\pm s$, λ and h are the turning rate function and the proliferation rate of the cells, respectively. We will consider the following turning rate function [111]:

$$\lambda(\xi) = \lambda_0\left(1 + \xi\chi(\xi)\right), \tag{3.8}$$

where λ_0 is the unbiased turning rate ($\lambda_0 > 0$) and $\chi(\xi) = (k + |\xi|)^{-1}$ is the chemotactic sensitivity function, with k being the sensitivity coefficient. By letting

$$n(x,t) = \int_{\mathbb{R}}(p^+(x,z,t) + p^-(x,z,t))dz, \quad j(x,t) = \int_{\mathbb{R}} s(p^+(x,z,t) - p^-(x,z,t))dz, \tag{3.9}$$

$$\lambda^1\left(\frac{\partial S}{\partial x}\right) = \lambda\left(\frac{\partial S}{\partial x}\right) - \lambda\left(-\frac{\partial S}{\partial x}\right), \quad \lambda^2\left(\frac{\partial S}{\partial x}\right) = \lambda\left(\frac{\partial S}{\partial x}\right) + \lambda\left(-\frac{\partial S}{\partial x}\right) = 2\lambda_0, \tag{3.10}$$

and integrating (3.6)–(3.7) over z, one can transform (3.6)–(3.7) into

$$\frac{\partial n}{\partial t} + \frac{\partial j}{\partial x} = h(S)n, \tag{3.11}$$

$$\frac{\partial j}{\partial t} + s^2\frac{\partial n}{\partial x} = s\lambda^1 n - 2\lambda_0 j + h(S)j. \tag{3.12}$$

The functions $n(x,t)$ and $j(x,t)$ are respectively the macroscopic cell density and the flux.

The equations describing the distribution of the signal can be given by

$$\frac{\partial S}{\partial t} = D_S\frac{\partial^2 S}{\partial x^2} - \alpha S n - \gamma S, \tag{3.13}$$

with α and γ standing for the consumption rate and degradation rate of the aspartate, respectively.

Note that the case $k = 0$ corresponds to unbounded sensitivity to the signal [111]. As a result, the function λ^1 becomes the switch function

$$\lambda^1\left(\frac{\partial S}{\partial x}\right) = \begin{cases} -2\lambda_0, & \partial S/\partial x < 0, \\ 0, & \partial S/\partial x = 0, \\ 2\lambda_0, & \partial S/\partial x > 0. \end{cases} \tag{3.14}$$

The situation of no chemotaxis (i.e., $\chi = 0$) takes place when $k \to \infty$, and we have $\lambda^1 = 0$. Here, cells are not sensitive to the signal. Since our investigations are restricted to these two limiting cases, the function λ^1 will be treated as a constant.

The system (3.11)–(3.13) was analysed in the case of no chemotaxis by Franz *et al* [32]. They assumed that $D_S = \gamma = 0$, and $h(S)$ is a linear function of S. Due to the complexity of the system, diffusivity has always been ignored in the mathematical analysis. It is important to note that diffusivity plays a stabilizing role in the behaviour of the system [88]. As a result, in our analysis, we will allow for diffusivity, and will investigate the existence of travelling wave solutions under zero growth and constant growth scenarios. The impact of the growth rate in the behaviour of the solutions will be explored.

3.2.1 Lie symmetry analysis

Examining the interplay between group theory and stability analysis, we found [98, 97] that the Lie symmetry analysis can generate new types of solutions (unlike the standard travelling wave ansatz) that play a significant role in the stability of the system. A partial differential equation of order n,

$$E(x, y, \partial y, ..., \partial^n y) = 0, \tag{3.15}$$

with $(x, y(x)) \in \mathbb{R}^N \times \mathbb{R}^M$, possesses

$$G = \xi_i(x, y)\frac{\partial}{\partial x_i} + \eta^\nu(x, y)\frac{\partial}{\partial y^\nu}, \tag{3.16}$$

as a symmetry if [10]

$$G^{[n]}E \mid_{E=0} = 0, \tag{3.17}$$

where $\xi_i(x, y)$ and $\eta^\nu(x, y)$ are the infinitesimals of the Lie group of invariant transformations of (3.15), and $G^{[n]}$ is the nth extension of G [10].

Applying (3.17) to (3.11)–(3.13), we obtain the symmetries

$$G_1 = \partial_t, G_2 = \partial_x, G_3 = \mathrm{e}^{-2\lambda_0 t}\partial_j, G_4 = S\partial_S, G_5 = \frac{-s\lambda^1}{2\alpha\lambda_0}\partial_j - \frac{1}{\alpha}\partial_n + tS\partial_S, \tag{3.18}$$

$$G_6 = \left(-\frac{st\lambda^1 + 2x\lambda_0}{2\lambda_0}\partial_j - \frac{1}{2\lambda_0}\partial_n - \frac{\alpha}{\lambda^2}S\partial_S\right)\mathrm{e}^{-2\lambda_0 t}, \tag{3.19}$$

in the case of zero growth (i.e., $h(S) = 0$). In the case of constant growth (with $h(S) = \alpha_0$), we have

$$G_1 = \partial_t, G_2 = \partial_x, G_3 = \mathrm{e}^{(\lambda_0 - 2\lambda_0)t}\partial_j, G_4 = S\partial_S, G_5 = \left(\frac{-s\lambda^1}{2\alpha\lambda_0}\partial_j - \frac{1}{\alpha}\partial_n + \frac{1}{\alpha}S\partial_S\right)\mathrm{e}^{\alpha_0 t}, \quad (3.20)$$

$$G_6 = \left(-\frac{st\lambda^1 + 2x\lambda_0}{\alpha}\partial_j - \frac{1}{\alpha}\partial_n - \frac{1}{\alpha_0 - 2\lambda_0}S\partial_S\right)\mathrm{e}^{(\alpha_0 - 2\lambda_0)t}, \quad (3.21)$$

for $\alpha_0 \neq 2\lambda_0$, and

$$G_1 = \partial_t, G_2 = \partial_x, G_3 = \partial_j, G_4 = S\partial_S, G_5 = -\frac{1}{\alpha}\partial_n + tS\partial_S, \quad (3.22)$$

$$G_6 = \frac{x}{\alpha}\partial_j + \frac{1}{2\alpha\lambda_0}\mathrm{e}^{-2\lambda_0 t}\partial_n + \frac{1}{4\lambda_0^2}S\mathrm{e}^{-2\lambda_0 t}\partial_S, \quad (3.23)$$

for $\alpha_0 = 2\lambda_0$. In the case of zero growth, the characteristic equations associated with

$$G = G_1 + cG_2 + c_1G_3 + c_2G_4 + c_3G_5 + c_4G_6 \quad (3.24)$$

using (3.18)–(3.19) are [10]

$$\frac{dt}{1} = \frac{dx}{c} = \frac{2\alpha\lambda_0\mathrm{e}^{2\lambda_0 t}dj}{2\alpha\lambda_0 c_1 - \alpha c_4(st\lambda^1 + 2x\lambda_0)} = \frac{-2\alpha\lambda_0 dn}{2\lambda_0 c_3 - \alpha c_4\mathrm{e}^{-2\lambda_0 t}} = \frac{4\lambda_0^2 dS}{(4\lambda_0^2 c_2 + 4\lambda_0^2 c_3 t - \alpha c_4\mathrm{e}^{-2\lambda_0 t})S}. \quad (3.25)$$

These lead to the new invariants

$$u = x - ct, \quad (3.26)$$

$$j = J(u) + \frac{\mathrm{e}^{-2\lambda_0 t}(4\lambda_0^2 c_4 u - 4c_1\lambda_0^2 + c_4(s\lambda^1 + 2c\lambda_0)(1 + 2\lambda_0 t))}{8\lambda_0^3}, \quad (3.27)$$

$$n = N(u) - \frac{c_3 t}{\alpha} - \frac{c_4\mathrm{e}^{-2\lambda_0 t}}{4\lambda_0^2}, \quad (3.28)$$

$$S = S_1(u)\exp\left(c_2 t + \frac{1}{2}c_3 t^2 + \frac{\alpha c_4\mathrm{e}^{-2\lambda_0 t}}{8\lambda_0^3}\right). \quad (3.29)$$

We note from (3.26), that travelling wave solutions can exist, with c being the speed of the wave. The invariants $N(u)$ and $S_1(u)$ will produce generalized travelling wave solutions [85], a wider type of solutions than obtained from the standard ansatz. As we require that solutions should not blow up as $x \to \pm\infty$ or $t \to \infty$, we take $c_3 = c_4 = 0$. Therefore, from the definition of the flux j (see (3.9)), we obtain $c_1 = 0$.

In the case of constant growth with $\alpha_0 \neq 2\lambda_0$, the characteristic equations associated with G, now using (3.20)–(3.21), are

$$\begin{aligned}\frac{dt}{1} = \frac{dx}{c} &= \frac{2\alpha\lambda_0 \mathrm{e}^{(2\lambda_0-\alpha_0)t}dj}{2\alpha\lambda_0 c_1 - sc_3\lambda^1 \mathrm{e}^{2\lambda_0 t} - 2\lambda_0 c_4(st\lambda^1 + 2x\lambda_0)} = \frac{-\alpha dn}{c_3\mathrm{e}^{\alpha_0 t} + c_4\mathrm{e}^{(\alpha_0-2\lambda_0)t}} \\ &= \frac{\alpha_0(\alpha_0-2\lambda_0)dS}{(\alpha_0(\alpha_0-2\lambda_0)c_2 + (\alpha_0-2\lambda_0)c_3\mathrm{e}^{\alpha_0 t} + \alpha_0 c_4\mathrm{e}^{(\alpha_0-2\lambda_0)t}))\,S}, \end{aligned} \tag{3.30}$$

and lead to the invariants

$$u = x - ct, \tag{3.31}$$

$$\begin{aligned} j &= J(u) + \frac{\mathrm{e}^{(\alpha_0-2\lambda_0)t}\left(s\lambda^1 c_3(\alpha_0-4\lambda_0)^2\mathrm{e}^{2\lambda_0 t} - 2\alpha\alpha_0 c_1\lambda_0(\alpha_0-2\lambda_0)\right)}{2\alpha\alpha_0(\alpha_0-2\lambda_0)^2\lambda_0} \\ &\quad + \frac{2\alpha_0\lambda_0 c_4(-1+t(\alpha_0-2\lambda_0)(s\lambda^1+2c\lambda_0))\mathrm{e}^{(\alpha_0-2\lambda_0)t} - c_4\mathrm{e}^{(\alpha_0-2\lambda_0)t}}{\alpha(\alpha_0-2\lambda_0)}, \end{aligned} \tag{3.32}$$

$$n = N(u) - \frac{(\alpha_0-2\lambda_0)c_3\mathrm{e}^{\alpha_0 t} + \alpha_0 c_4\mathrm{e}^{(\alpha_0-2\lambda_0)t}}{\alpha\alpha_0(\alpha_0-2\lambda_0)}, \tag{3.33}$$

$$S = S_1(u)\exp\left(\frac{\alpha_0^2 c_4\mathrm{e}^{(\alpha_0-2\lambda_0)t} + (\alpha_0-2\lambda_0)^2 c_3\mathrm{e}^{\alpha_0 t} + \alpha_0^2(\alpha_0-2\lambda_0)^2 c_2 t}{\alpha_0^2(\alpha_0-2\lambda_0)^2}\right). \tag{3.34}$$

As before, we take $c_1 = c_3 = c_4 = 0$ for physically viable solutions. The same conditions apply in the case of $\alpha_0 = 2\lambda_0$. As a result in our analysis we use the following invariants:

$$u = x - ct, \tag{3.35}$$

$$j = J(u), \tag{3.36}$$

$$n = N(u), \tag{3.37}$$

$$S = S_1(u)\mathrm{e}^{c_2 t}, \tag{3.38}$$

in all cases. Then the system (3.11)–(3.13) can be rewritten in term of the new invariants as follows:

$$(s^2-c^2)N' = (ch(S) + s\lambda^1)N + (h(S) - 2\lambda_0)J, \tag{3.39}$$

$$(s^2-c^2)J' = (s^2 h(S) + cs\lambda^1)N + c(h(S) - 2\lambda_0)J, \tag{3.40}$$

$$-cS_1' = D_S S_1'' - (\alpha N + \gamma + c_2)S_1, \tag{3.41}$$

where the superscript $'$ stands for the total derivative with respect to u. When $c = s$, (3.39)–(3.41) can be reduced to a system of two equations in three unknowns. Choosing $J(u)$ and $S_1(u)$

to depend on $N(u)$, we can demonstrate travelling wave solutions for a constant distribution of $N(u)$ (by simply solving the second order ODE with constant coefficients (3.41)). The analysis for the case of Poisson distribution (or normal distribution via asymptotic analysis) of $N(u)$ is similar to the analysis when $c \neq s$. We will focus in the rest of this work on the case of $c \neq s$ (with $0 < c < s$). Inspired by the numerical investigations of Xue *et al* [111], we will be looking for solutions admitting a single peak of S. We note that this restriction is less important when $k \to \infty$. Hence we assume $S_1 \in Y_S$, where

$$Y_S = \{f \in \mathbb{C}^1(\mathbb{R}); f(u) \text{ is monotonically increasing for } u < 0 \text{ and decreasing for } u > 0\}. \tag{3.42}$$

In our context, travelling wave solutions $n(x,t)$ and $S(x,t)$ must be positive, continuous and bounded, with $S_1 \in Y_S$.

3.2.2 Case of zero growth

Here $h(S) = 0$. Assuming that $N(u)$ and $J(u)$ decay to zero as $u \to \infty$, (3.39)–(3.41) can be reduced to

$$J = cN, \tag{3.43}$$

$$(s^2 - c^2)N' = (s\lambda^1 - 2c\lambda_0)N, \tag{3.44}$$

$$-cS_1' = D_S S_1'' - (\alpha N + \gamma + c_2)S_1. \tag{3.45}$$

In the case of high chemotactic sensitivity (the limiting case $k \to 0$), the turning rate function becomes a switch function and corresponds to unbounded sensitivity to the signal [111]. For $S_1 \in Y_S$, the solution $n(x,t)$ is given by

$$n(x,t) = N(u) = \begin{cases} N(0)\mathrm{e}^{\sigma_1 u}, & u < 0, \\ N(0)\mathrm{e}^{-\sigma_2 u}, & u \geq 0, \end{cases} \tag{3.46}$$

where $\sigma_1 = 2\lambda_0/(s+c)$ and $\sigma_2 = 2\lambda_0/(s-c)$. Here, the total cell population is given by $T = sN(0)/\lambda_0$ (obtained by integrating $N(u)$ over the whole line $\mathbb{R}$).

We assume $D_S = 0$, then $S_1(u)$ is positive and continuous. When $\gamma + c_2 \geq 0$, $S_1(u)$ is monotonically increasing ($S_1'(u) > 0$). As a result, $S_1 \in Y_S$ cannot hold. Since $S_1'(u)$ is continuous, for S_1 to hold in Y_S when $\gamma + c_2 < 0$, it is necessary that zero must be the only extremum point of $S_1(u)$ (the maximum), with $\alpha N(0) = -(\gamma + c_2)$ (because $S_1'(0) = 0$). Then, for $u < 0$,

$$cS_1'(u) = (\alpha N(u) + \gamma + c_2)S_1(u) = \alpha N(0)(\mathrm{e}^{\sigma_1 u} - 1)S_1(u) < 0. \tag{3.47}$$

Again $S_1 \notin Y_S$. Non-diffusing travelling wave solutions with a single peak of S do not exist.

In the case of diffusivity, substituting (3.46) into (3.45) and integrating, we obtain

$$S_1(u) = \begin{cases} \left[c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) + c_2^1 K_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)\right] \mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ \left[c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) + c_2^2 K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)\right] \mathrm{e}^{-(c/(2D_S))u}, & u \geq 0, \end{cases} \tag{3.48}$$

where $k_i = \sqrt{c^2 + 4D_S(\gamma + c_2)}/(D_S\sigma_i)$, $\alpha_i = \sqrt{4\alpha D_S N(0)}/(D_S\sigma_i)$, the coefficients c_j^i are constants of integration, and the functions $I_{k_i}(v)$ and $K_{k_i}(v)$ are the two linearly independent solutions to the modified Bessel's equation.

Proposition 7. *For $-\gamma < c_2 \leq 0$, the function $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where $S_1(u)$ is given by (3.48), is bounded if and only if $c_2^1 = c_2^2 = 0$.*

Proof. We choose $c_2 \leq 0$ in order to produce damped solutions. We note that the functions $I_{k_i}(v)$ and $K_{k_i}(v)$ given in (3.48) are continuous and positive [68, 76].

We assume $u = x - ct < 0$. Then $I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)$ converges to zero and $K_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)$ diverges, as $u \to -\infty$ [68, 76]. If $c_2^1 \neq 0$, $S(x,t)$ blows up as $x \to -\infty$. However, if $c_2^1 = 0$, as $u \to -\infty$,

$$I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \approx \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{\frac{\sigma_1 k_1}{2}u} \approx \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{\frac{\sqrt{c^2 + 4D_S(\gamma+c_2)}}{2D_S}u}. \tag{3.49}$$

This implies that

$$S_1(u) \approx \frac{c_1^1(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{\frac{\sqrt{c^2+4D_S(\gamma+c_2)}-c}{2D_S}u}, \tag{3.50}$$

and converges to zero as $u \to -\infty$ (provided $\gamma + c_2 > 0$). Then $S(x,t)$ converges to zero as $x \to \pm\infty$ or $t \to \infty$ (with $x - ct < 0$).

Now we assume $u \geq 0$. As $u \to \infty$,

$$K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \mathrm{e}^{\frac{\sigma_2 k_2}{2}u} \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \mathrm{e}^{\frac{\sqrt{c^2+4D_S(\gamma+c_2)}}{2D_S}u}, \tag{3.51}$$

which implies that

$$K_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-\frac{c}{2D_S}u} \approx \frac{\Gamma(k_2)}{2(\alpha_2/2)^{k_2}} \mathrm{e}^{\frac{\sqrt{c^2+4D_S(\gamma+c_2)}-c}{2D_S}u}, \tag{3.52}$$

as $u \to \infty$. Therefore, if $c_2^2 \neq 0$, $S(x,t)$ will blow up as $x \to \infty$ (with t fixed). However, if $c_2^2 = 0$, $S_1(u)$ converges to zero as $u \to \infty$ (given that $I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)$ converges to zero $u \to \infty$). As a result, $S(x,t)$ converges to zero as $x \to \infty$ or $t \to \infty$.

Given that $S_1(u)$ is continue in $(-\infty, 0)$ and $(0, \infty)$, and that $S_1(0^+)$ and $S_1(0^-)$ exist, then the convergence of $S(x,t)$ at the boundaries guarantees its boundedness. □

Theorem 3.2.1. *For $D_S \neq 0$ and $-\gamma < c_2 \leq 0$, travelling wave solutions for the system (3.11)–(3.13) (with $h(S) = 0$) exist and are explicitly given by (3.46), (3.43) and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where*

$$S_1(u) = \begin{cases} c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right) \mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right) \mathrm{e}^{-(c/(2D_S))u}, & u \geq 0, \end{cases} \tag{3.53}$$

with $c_1^1 = S_1(0)/I_{k_1}(\alpha_1)$ and $c_1^2 = S_1(0)/I_{k_2}(\alpha_2)$.

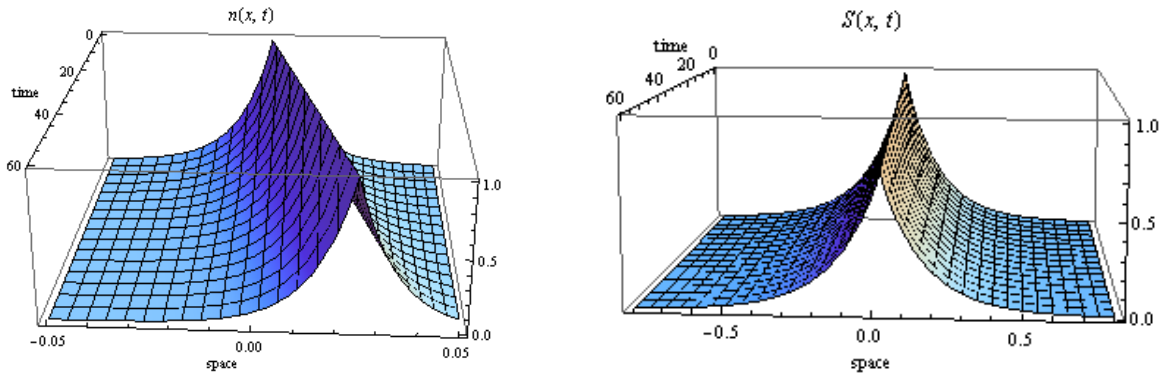
Proof. Invoking Proposition 7, we note that $n(x,t)$ and $S(x,t)$ are positive, continuous and bounded, and the function $\mathrm{e}^{-(c/(2D_S))u}$ is monotonically decreasing. We only need to show that $S_1 \in Y_S$.

When $u \geq 0$, the function $I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\sigma_2/2)u}\right)$ is decreasing. Therefore, $S_1(u)$ is also monotonically decreasing, and converges to zero as $u \to \infty$.

When $u < 0$, the function $I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right)$ is increasing, and from (3.49), we have

$$f(u) = \frac{(\alpha_1/2)^{k_1}}{\Gamma(1+k_1)} \mathrm{e}^{\frac{\sqrt{c^2+4D_S(\gamma+c_2)}}{2D_S}u} \leq I_{k_1}\left(\alpha_1 \mathrm{e}^{(\sigma_1/2)u}\right). \tag{3.54}$$

Given that the function $f(u)\mathrm{e}^{-(c/(2D_S)u}$ is monotonically increasing, then $S_1(u)$ is also monotonically increasing. Consequently, $S_1 \in Y_S$. □



(a) cells (b) signal

Figure 3.1: Distribution of cells and signal in the case of zero growth ($\lambda_0 = 1/sec$, $N(0) = 1$ and $S_1(0) = 1$).

An example of the travelling wave solutions indicated in Theorem 3.2.1 are illustrated in Figure 3.1 with $s = 20\mu m/sec$, $D_S = 10^{-5}cm^2/sec$, $\alpha = 1000/hour$, $\gamma = 0.05/sec$, $c = 1.5mm/hour$ [111] (these parameter values will be used in all future plots).

In the case of no chemotaxis (i.e., $\chi = 0$), we have $\lambda^1 = 0$. Then from (3.44), $N(u)$ blows up as $u \to -\infty$; cells can only aggregate in the half plane $u \geq 0$. Travelling wave solutions satisfying $S_1 \in Y_S$ do not exist. This is consistent with Xue *et al* [111]. However, if we relax the assumption on S_1, we can demonstrate travelling wave solutions.

Theorem 3.2.2. *In the absence of chemotaxis, generalized travelling wave solutions for the system (3.11)–(3.13) exist (without the restriction $S \in Y_S$) and are explicitly given in the case of non diffusivity ($D_S = 0$) by*

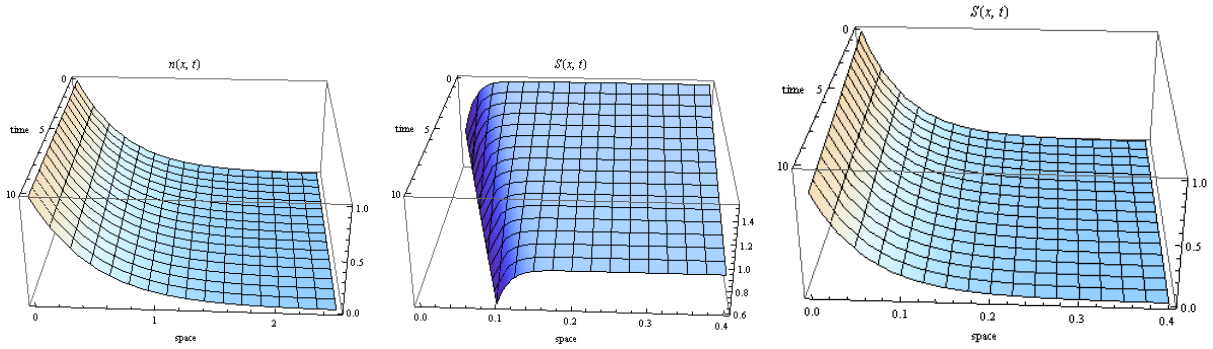
$$n(x,t) = N(u) = N(0)\mathrm{e}^{-\sigma_0 u}, \quad j(x,t) = J(u) = cN(0)\mathrm{e}^{-\sigma_0 u}, \tag{3.55}$$

and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where

$$S_1(u) = S_1(0)\exp\left(\frac{\alpha N(0)}{c\sigma_0}(1 - \mathrm{e}^{-\sigma_0 u}) + \frac{\gamma + c_2}{c}u\right), \tag{3.56}$$

with $u \geq 0$, $\sigma_0 = 2\lambda_0 c/(s^2 - c^2)$ and $c_2 \leq -\gamma$, and in the case of diffusivity ($D_S \neq 0$) by

$$S_1(u) = S_1(0)I_{k_0}\left(\alpha_{0,0}\mathrm{e}^{-(\sigma_0/2)u}\right)\mathrm{e}^{-(c/(2D_S))u}/I_{k_0}(\alpha_{0,0}), \tag{3.57}$$



(a) Cells (b) Aspartate ($D = 0$) (c) Aspartate ($D_S \neq 0$)

Figure 3.2: Distribution of cells in the absence of chemotaxis under zero growth (we used $c = 10\mu m/sec$ and $c_2 = -\gamma = -0.05/sec$, for $D_S = 0$, and $c = 1.5mm/hour$ and $c_2 = -0.02/sec$, for $D_S \neq 0$).

with $u \geq 0$, $k_0 = \sqrt{c^2 + 4D_S(\gamma + c_2)}/(D_S\sigma_0)$, $\alpha_{0,0} = \sqrt{4\alpha D_S N(0)}/(D_S\sigma_0)$ *and* $-\gamma < c_2 \leq 0$.

■

The proof follows the same procedure as Theorem 3.2.1. The solutions are illustrated in Figure 3.2.

3.2.3 Case of constant growth $h(S) = \alpha_0$

No chemotaxis ($k \to \infty$)

Here, $\chi = 0$. As a result, $\lambda^1 = 0$. Then (3.39)–(3.41) becomes

$$N' = f_1 N + g_1 J, \tag{3.58}$$

$$J' = f_2 N + c g_1 J, \tag{3.59}$$

$$-cS_1' = D_S S_1'' - (\alpha N + \gamma + c_2) S_1, \tag{3.60}$$

where

$$f_1 = \frac{c\alpha_0}{s^2 - c^2}, \quad g_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad f_2 = \frac{s^2\alpha_0}{s^2 - c^2}. \tag{3.61}$$

When $\alpha_0 = 2\lambda_0$ (i.e., $g_1 = 0$), $N(u)$ blows up as $u \to \infty$. In this situation, cells can only move in the half plane $u \leq 0$. As a result, S_1 cannot hold in Y_S.

Assuming $\alpha_0 \neq 2\lambda_0$, $N(u)$ and $J(u)$ are given by

$$\begin{pmatrix} N(u) \\ J(u) \end{pmatrix} = C_1 \begin{pmatrix} \gamma_3 \\ 1 \end{pmatrix} \mathrm{e}^{\lambda_1 u} + C_2 \begin{pmatrix} \gamma_4 \\ 1 \end{pmatrix} \mathrm{e}^{\lambda_2 u}, \tag{3.62}$$

where

$$\lambda_1 = \frac{-c(\lambda_0-\alpha_0)+\sqrt{\alpha_0^2 s^2 - 2\lambda_0\alpha_0 s^2 + c^2\lambda_0^2}}{s^2-c^2}, \quad \lambda_2 = \frac{-c(\lambda_0-\alpha_0)-\sqrt{\alpha_0^2 s^2 - 2\lambda_0\alpha_0 s^2 + c^2\lambda_0^2}}{s^2-c^2},$$

$$C_1 = \frac{N(0)-\gamma_4 J(0)}{\gamma_3-\gamma_4}, \quad \gamma_3 = \left(c\lambda_0 + \sqrt{s^2\alpha_0^2 - 2\alpha_0\lambda_0 s^2 + c^2\lambda_0^2}\right)/(\alpha_0 s^2), \tag{3.63}$$

$$C_2 = \frac{\gamma_3 J(0)-N(0)}{\gamma_3-\gamma_4}, \quad \gamma_4 = \left(c\lambda_0 - \sqrt{s^2\alpha_0^2 - 2\alpha_0\lambda_0 s^2 + c^2\lambda_0^2}\right)/(\alpha_0 s^2). \tag{3.64}$$

For $\alpha_0 < 2\lambda_0$, λ_1 and λ_2 have the same sign (we note that $\lambda_1\lambda_2 = -\alpha_0(\alpha_0 - 2\lambda_0)/(s^2 - c^2)$). Then $S_1 \notin Y_S$, because bounded solutions will be represented only in a half plane.

When $\alpha_0 > 2\lambda_0$, then $\lambda_1 > 0$ and $\lambda_2 < 0$. We will choose C_1 and C_2 so that $N(u)$ will not blow up as $u \to \pm\infty$. For $u < 0$, we will take $C_2 = 0$, and for $u \geq 0$, we will take $C_1 = 0$. This will require discontinuity of the flux at zero. Non-diffusing travelling wave solutions (admitting a single peak of S) do not exist. However, the requirement that $S_1 \in Y_S$ is less important in the case of no chemotaxis. We remark that Franz *et al's* [32] results reflected this relaxation. In our case we do find travelling wave solutions (see Figure 3.3).

Theorem 3.2.3. *Non-diffusing ($D_S = 0$) generalized travelling wave solutions for the system (3.11)–(3.13) exist without the restriction S_1 holding in Y_S (with $\chi = 0$). They are explicitly given by*

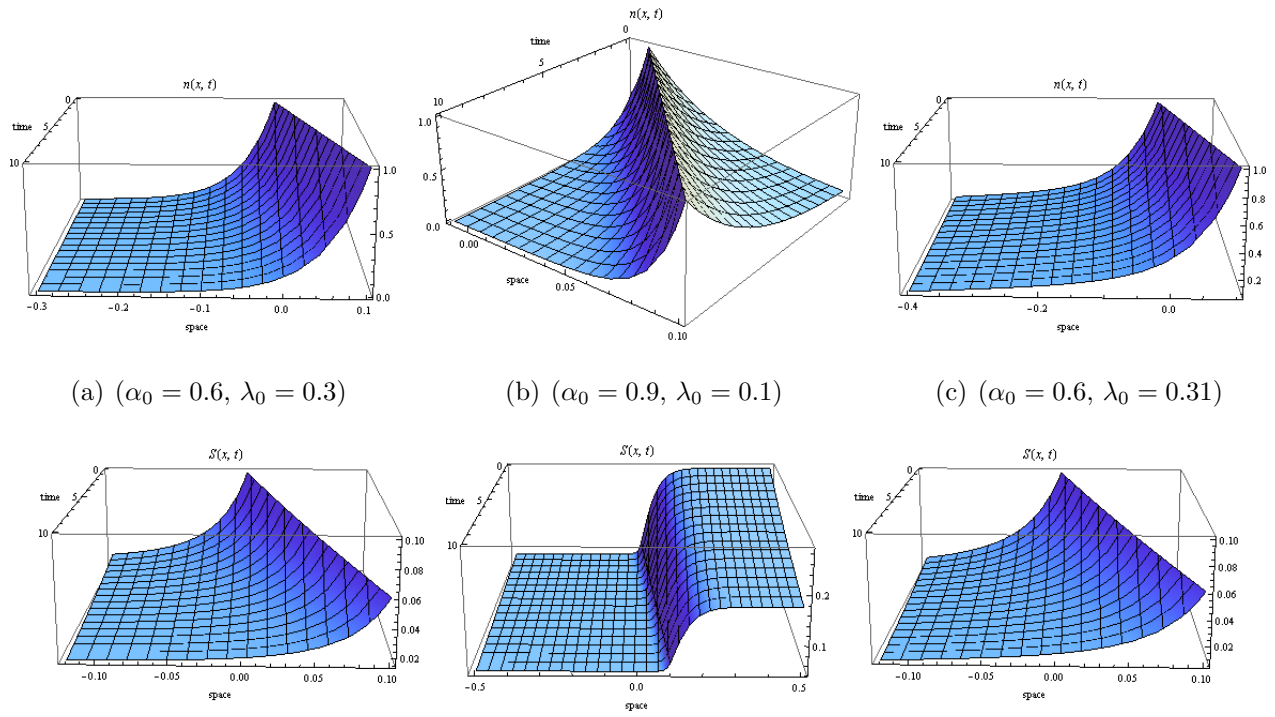
$$n(x,t) = N(u) = N(0)\mathrm{e}^{(c\alpha_0/(s^2-c^2))u}, \quad j(x,t) = J(u) = J(0) - \frac{s^2}{c}N(0)\left(1 - \mathrm{e}^{(c\alpha_0/(s^2-c^2))u}\right), \tag{3.65}$$

and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where

$$S_1(u) = S_1(0)\exp\left(\frac{\alpha N(0)(s^2-c^2)}{c^2\alpha_0}(\mathrm{e}^{(c\alpha_0/(s^2-c^2))u} - 1) + \frac{\gamma + c_2}{c}u\right), \tag{3.66}$$

for $\alpha_0 = 2\lambda_0$ (with $-\gamma \leq c_2 < 0$ and $u \leq 0$). In the case of $\alpha_0 \neq 2\lambda_0$, the solutions are given by

$$n(x,t) = N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_1 u}, & u < 0, \\ N(0)\mathrm{e}^{\lambda_2 u}, & u \geq 0, \end{cases} \quad j(x,t) = J(u) = \begin{cases} \frac{N(0)}{\gamma_3}\mathrm{e}^{\lambda_1 u}, & u < 0, \\ \frac{N(0)}{\gamma_4}\mathrm{e}^{\lambda_2 u}, & u \geq 0, \end{cases} \tag{3.67}$$



(a) $(\alpha_0 = 0.6,\ \lambda_0 = 0.3)$ (b) $(\alpha_0 = 0.9,\ \lambda_0 = 0.1)$ (c) $(\alpha_0 = 0.6,\ \lambda_0 = 0.31)$

(d) $(\alpha_0 = 0.6,\ \lambda_0 = 0.3)$ (e) $(\alpha_0 = 0.9,\ \lambda_0 = 0.1)$ (f) $(\alpha_0 = 0.6,\ \lambda_0 = 0.31)$

Figure 3.3: Distribution of cells (first row) and non-diffusing signal (second row) in the absence of chemotaxis (with the parameters set as follows: $c = 10\mu m/sec$, $c_2 = -\gamma = -0.05/sec$, $N(0) = 1$ and $S_1(0) = 0.1$).

and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, *where*

$$S_1(u) = \begin{cases} S_1(0)\exp\left(\frac{\alpha N(0)}{c\lambda_1}(\mathrm{e}^{\lambda_1 u} - 1)\right), & u < 0, \\ S_1(0)\exp\left(\frac{\alpha N(0)}{c\lambda_2}(\mathrm{e}^{\lambda_2 u} - 1)\right), & u \geq 0, \end{cases} \tag{3.68}$$

for $\alpha_0 > 2\lambda_0$ *(with* $c_2 = -\gamma$*), and by (3.62) and* $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, *where*

$$S_1(u) = S_1(0)\exp\left(\frac{\alpha\gamma_3 C_1}{c\lambda_1}(\mathrm{e}^{\lambda_1 u} - 1) + \frac{\alpha\gamma_4 C_2}{c\lambda_2}(\mathrm{e}^{\lambda_2 u} - 1) + \frac{\gamma + c_2}{c}u\right), \tag{3.69}$$

for $\alpha_0 < 2\lambda_0$ *(with* $u \leq 0$ *and* $-\gamma \leq c_2 < 0$*, if* $\lambda_1 > 0$*, or* $u \geq 0$ *and* $c_2 = -\gamma$*, if* $\lambda_1 < 0$*).* ■

The non-diffusing solutions $S_1(u)$ of Theorem 3.2.3 are obtained directly by integrating the first order system (3.58)–(3.60). We note that all of the solutions are bounded, for they are continuous and converge at the boundaries. A negative flux (see (3.65)) simply means that

most of the cells move to the left (recall that $j = s(n^+ - n^-)$). Unlike Franz *et al's* [32] results, we do not require a minimal wave speed. This therefore constitutes a generalization of their findings.

We note that the discontinuity of the flux at zero does not necessarily imply $N(u)$ to be discontinuous at zero. In fact, for $J(u) = sN(u)$ and the initial conditions given by $N^+(0^+) > N^+(0^-)$, $N^-(0^-) = N^+(0^+)$ and $N^-(0^+) = N^+(0^-)$, we have

$$N(0^+) - N(0^-) = N^+(0^+) + N^-(0^+) - N^+(0^-) - N^-(0^-) = 0, \tag{3.70}$$

and

$$J(0^+) - J(0^-) = s(N^+(0^+) - N^-(0^+) - N^+(0^-) + N^-(0^-)) = 2s(N^+(0^+) - N^+(0^-)) \neq 0. \tag{3.71}$$

Theorem 3.2.4. *For $D_S \neq 0$, $\alpha_0 > 2\lambda_0$, $-\gamma < c_2 \leq 0$ and $\gamma_3 J(0^-) = \gamma_4 J(0^+) = N(0)$, travelling wave solutions (with $S_1 \in Y_S$) for the system (3.11)–(3.13) exist and are explicitly given by*

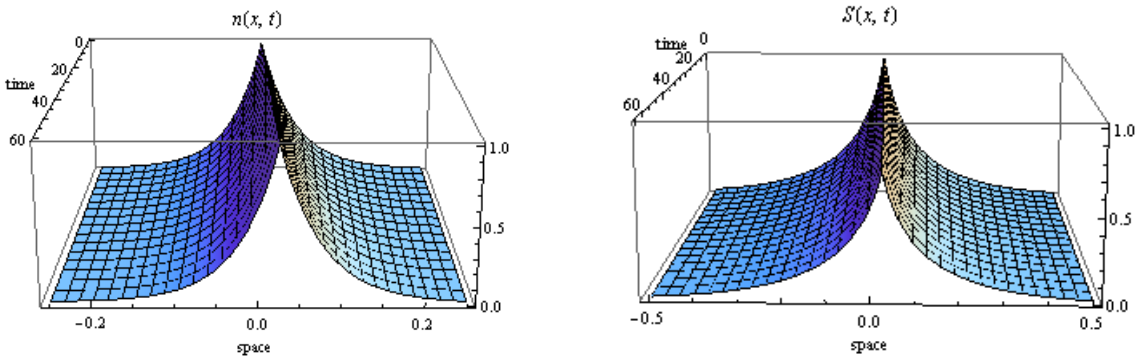
$$n(x,t) = N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_1 u}, & u < 0, \\ N(0)\mathrm{e}^{\lambda_2 u}, & u \geq 0, \end{cases} \qquad j(x,t) = J(u) = \begin{cases} \frac{N(0)}{\gamma_3}\mathrm{e}^{\lambda_1 u}, & u < 0, \\ \frac{N(0)}{\gamma_4}\mathrm{e}^{\lambda_2 u}, & u \geq 0, \end{cases} \tag{3.72}$$

and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where

$$S_1(u) = \begin{cases} c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\lambda_1/2)u}\right)\mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{(\lambda_2/2)u}\right)\mathrm{e}^{-(c/(2D_S))u}, & u \geq 0, \end{cases} \tag{3.73}$$

with $u = x - ct$, $k_1 = (\sqrt{c^2 + 4D_S(\gamma + c_2)}/(\lambda_1 D_S)$, $k_2 = -\sqrt{c^2 + 4D_S(\gamma + c_2)}/(\lambda_2 D_S)$,
$\alpha_1 = \sqrt{4\alpha D_S N(0)}/(\lambda_1 D_S)$, $\alpha_2 = -\sqrt{4\alpha D_S N(0)}/(\lambda_2 D_S)$, and $c_1^1 I_{k_1}(\alpha_1) = c_1^2 I_{k_2}(\alpha_2) = S_1(0)$.
■

The proof of the above theorem is similar to the proof of Theorem 3.2.1. See Figure 3.4 for an illustration of the solutions.



(a) cells (b) signal

Figure 3.4: Spread of cells and signal in the case of no chemotaxis under growth ($\lambda_0 = 0.3$, $\alpha_0 = 0.8$, $N(0) = 1$ and $S_1(0) = 1$).

High chemotactic sensitivity ($k \to 0$)

Here λ^1 is given by (3.14). For $S_1 \in Y_S$, the system (3.39)–(3.41) becomes

$$N' = a_1 N + b_1 J, \tag{3.74}$$

$$J' = a_2 N + c b_1 J, \tag{3.75}$$

$$-cS_1' = D_S S_1'' - (\alpha N + \gamma + c_2) S_1, \tag{3.76}$$

where

$$a_1 = \frac{c\alpha_0 - 2\lambda_0 s}{s^2 - c^2}, \quad b_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad a_2 = \frac{s^2\alpha_0 - 2\lambda_0 cs}{s^2 - c^2}, \tag{3.77}$$

for $u > 0$, and

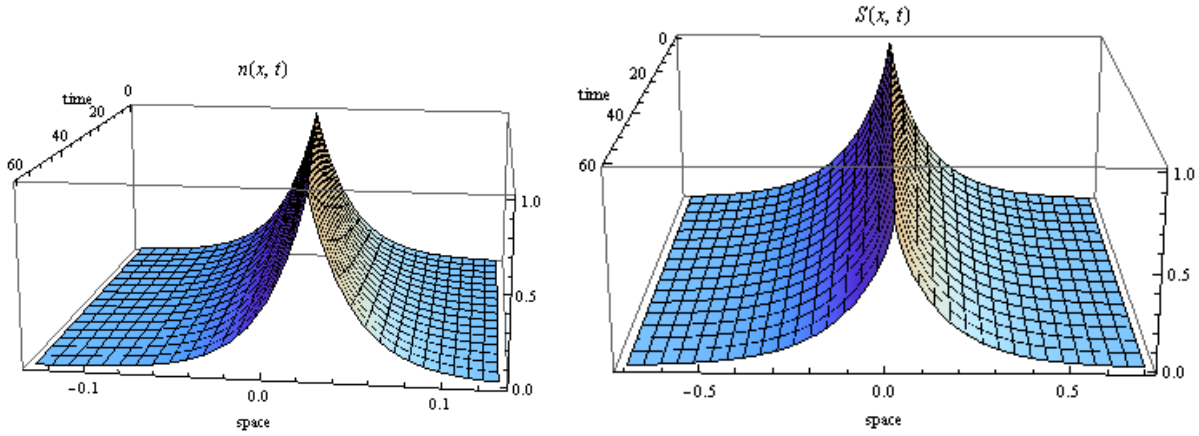
$$a_1 = \frac{c\alpha_0 + 2\lambda_0 s}{s^2 - c^2}, \quad b_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad a_2 = \frac{s^2\alpha_0 + 2\lambda_0 cs}{s^2 - c^2}, \tag{3.78}$$

for $u < 0$.

When $\alpha_0 = 2\lambda_0$, the coefficient b_1 vanishes and we obtain

$$N(u) = \begin{cases} N(0)\mathrm{e}^{\frac{\alpha_0}{s-c}u}, & u < 0, \\ N(0)\mathrm{e}^{-\frac{\alpha_0}{s+c}u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} J(0) - sN(0)\left(1 - \mathrm{e}^{\frac{\alpha_0}{s-c}u}\right), & u < 0, \\ J(0) + sN(0)\left(1 - \mathrm{e}^{-\frac{\alpha_0}{s+c}u}\right), & u \geq 0. \end{cases} \tag{3.79}$$

We note that the total cell population is given by $T_2 = 2sN(0)/(2\lambda_0 - \alpha_0)$, and the flux can be negative. This simply means that most of the cells move to the left (we recall that



(a) cells (b) signal

Figure 3.5: Spread of cells and signal in the case of high chemotactic sensitivity (with $\lambda_0 = 0.4$ and $\alpha_0 = 0.8$, $N(0) = 1$ and $S_1(0) = 1$).

$j = s(n^+ - n^-)$). The analysis in this situation is mathematically similar to the case of zero growth in §3.2.2. Travelling wave solutions satisfying $S_1 \in Y_S$ exist only in the case of diffusivity, underlying the importance of introducing this biological process into the model.

Theorem 3.2.5. *For $D_S \neq 0$, $\alpha_0 = 2\lambda_0$ and $-\gamma < c_2 \leq 0$, travelling wave solutions for the system (3.11)–(3.13) exist and are given by (3.79) and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where*

$$S_1(u) = \begin{cases} c_1^1 I_{k_1}\left(\alpha_1 \exp\left(\frac{\alpha_0}{2(s-c)}u\right)\right)\mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ c_1^2 I_{k_2}\left(\alpha_2 \exp\left(-\frac{\alpha_0}{2(s+c)}u\right)\right)\mathrm{e}^{-(c/(2D_S))u}, & u \geq 0, \end{cases} \tag{3.80}$$

with $u = x - ct$, $k_1 = (s-c)\sqrt{c^2 + 4D_S(\gamma + c_2)}/(\alpha_0 D_S)$, $k_2 = (s+c)\sqrt{c^2 + 4D_S(\gamma + c_2)}/(\alpha_0 D_S)$, $\alpha_1 = (s-c)\sqrt{4\alpha D_S N(0)}/(\alpha_0 D_S)$, $\alpha_2 = (s+c)\sqrt{4\alpha D_S N(0)}/(\alpha_0 D_S)$, and $c_1^1 I_{k_1}(\alpha_1) = S_1(0)$ and $c_1^2 I_{k_2}(\alpha_2) = S_1(0)$. ■

The proof of the above theorem is similar to the proof of Theorem 3.2.1. The solutions are depicted in Figure 3.5.

Now we assume $\alpha_0 \neq 2\lambda_0$, then

$$N(u) = \begin{cases} \frac{C_1}{s}\mathrm{e}^{\lambda_1 u} + \gamma_0 C_2 \mathrm{e}^{\lambda_2 u}, & u < 0, \\ -\frac{C_3}{s}\mathrm{e}^{-\lambda_3 u} + \gamma_1 C_4 \mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} C_1 \mathrm{e}^{\lambda_1 u} + C_2 \mathrm{e}^{\lambda_2 u}, & u < 0, \\ C_3 \mathrm{e}^{-\lambda_3 u} + C_4 \mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{3.81}$$

where

$$\lambda_1 = \frac{\alpha_0}{s-c}, \lambda_2 = \frac{2\lambda_0 - \alpha_0}{s+c}, \lambda_3 = \frac{\alpha_0}{s+c}, \lambda_4 = \frac{2\lambda_0 - \alpha_0}{s-c}, \gamma_0 = \frac{2\lambda_0 - \alpha_0}{s\alpha_0 + 2c\lambda_0}, \tag{3.82}$$

$$\gamma_1 = \frac{2\lambda_0 - \alpha_0}{2\lambda_0 c - s\alpha_0}, C_1 = \frac{s(\gamma_0 J(0^-) - N(0))}{s\gamma_0 - 1}, C_2 = \frac{sN(0) - J(0^-)}{s\gamma_0 - 1}, \tag{3.83}$$

$$C_3 = \frac{s(\gamma_1 J(0^+) - N(0))}{s\gamma_1 + 1}, C_4 = \frac{sN(0) + J(0^+)}{s\gamma_1 + 1}. \tag{3.84}$$

When C_1 (or C_2) and C_3 (or C_4) are zero, travelling wave solutions are possible.

Theorem 3.2.6. *For $D_S \neq 0$, $\alpha_0 < 2\lambda_0$, $-\gamma < c_2 \leq 0$ and $\gamma_0 J(0^-) = \gamma_1 J(0^+) = N(0)$, travelling wave solutions for the system (3.11)–(3.13) exist and are explicitly given by*

$$n(x,t) = N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_2 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \quad j(x,t) = J(u) = \begin{cases} \frac{N(0)}{\gamma_0}\mathrm{e}^{\lambda_2 u}, & u < 0, \\ \frac{N(0)}{\gamma_1}\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{3.85}$$

and $S(x,t) = S_1(u)\mathrm{e}^{c_2 t}$, where

$$S_1(u) = \begin{cases} c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\lambda_2/2)u}\right)\mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\lambda_4/2)u}\right)\mathrm{e}^{-(c/(2D_S))u}, & u \geq 0, \end{cases} \tag{3.86}$$

with $u = x - ct$, $k_1 = (\sqrt{c^2 + 4D_S(\gamma + c_2)}/(\lambda_2 D_S)$, $k_2 = \sqrt{c^2 + 4D_S(\gamma + c_2)}/(\lambda_4 D_S)$,
$\alpha_1 = \sqrt{4\alpha D_S N(0)}/(\lambda_2 D_S)$, $\alpha_2 = \sqrt{4\alpha D_S N(0)}/(\lambda_4 D_S)$, and $c_1^1 I_{k_1}(\alpha_1) = c_1^2 I_{k_2}(\alpha_2) = S_1(0)$. ■

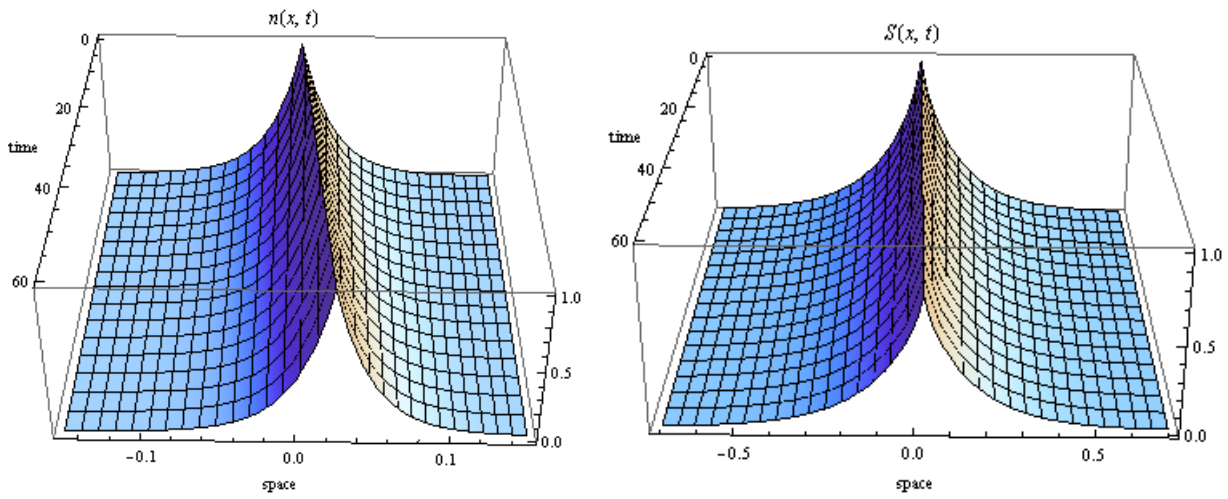
In the above theorem, the total cell population is given by $T_3 = 2N(0)/\alpha_0$. We illustrate the solutions in Figure 3.6.

When at most one of the constants C_i is zero (for instance C_2), equation (3.76) is difficult to solve explicitly for $S_1(u)$ (given the form of $N(u)$ when $u > 0$). In this situation, we only look at the asymptotic behaviour of the solutions as $u \to \pm\infty$. We note that the origin is the only equilibrium point of the system (3.74)–(3.76), and the determinant of the corresponding Jacobian matrix around the origin is given by

$$\Delta = \frac{\alpha_0(c_2 + \gamma)(\alpha_0 - 2\lambda_0)}{D_S(s^2 - c^2)}. \tag{3.87}$$

We consider $\alpha_0 < 2\lambda_0$ to guarantee the stability of $N(u)$ and $J(u)$(see (3.82)). The eigenvalues dictating the behaviour of $S_1(u)$ are given by

$$\lambda_{11} = \frac{-c + \sqrt{c^2 + 4D_S(c_2 + \gamma)}}{2D_S}, \quad \text{and} \quad \lambda_{22} = -\frac{c + \sqrt{c^2 + 4D_S(c_2 + \gamma)}}{2D_S}. \tag{3.88}$$



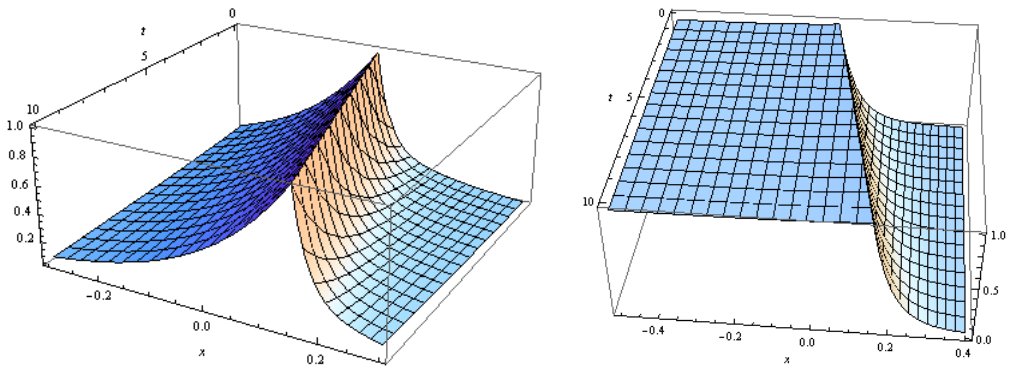
(a) cells (b) signal

Figure 3.6: Spread of cells and signal in the case of unbounded sensitivity to the signal, with $\alpha_0 < 2\lambda_0$ ($\lambda_0 = 0.8$, $\alpha_0 = 0.8$, $N(0) = 1$ and $S_1(0) = 1$).

For $c_2 + \gamma < 0$, λ_{11} and λ_{22} are both negative; non growing solutions are possible only in the half plane $u \geq 0$. Then S_1 cannot hold in Y_S. For $c_2 + \gamma > 0$, λ_{11} and λ_{22} have opposite signs. To obtain convergence, we will choose the initial data so that the behaviour of $S_1(u)$ will be controlled only by λ_{22} and λ_{11} as u approaches $+\infty$ and $-\infty$, respectively (this method was also applied in §3.2.3). In this situation $S_1(u)$ is positive, since none of the eigenvalues is complex (We note that the nonlinear term does not affect the stability of S_1, given that the eigenvalues are nonzero.). The challenge in getting explicit solutions for $S_1(u)$ prevents us from checking whether the restriction $S_1 \in Y_S$ holds for all real u or not. However, this restriction can be guaranteed as $u \to \pm\infty$. In fact, from (3.81), as $u \to \pm\infty$,

$$N(u) \approx \begin{cases} \delta_1 \mathrm{e}^{\mu_1 u}, & u < 0, \\ \delta_2 \mathrm{e}^{-\mu_2 u}, & u > 0, \end{cases} \tag{3.89}$$

where $\mu_1 = \min(\lambda_1, \lambda_2)$, $\mu_2 = \min(\lambda_3, \lambda_4)$, and δ_1, δ_2 are coefficients of the dominant terms $\mathrm{e}^{\mu_1 u}$ and $\mathrm{e}^{-\mu_2 u}$. Substituting (3.89) into (3.76) then integrating, and taking into consideration the



(a) cells (b) signal

Figure 3.7: Spread of cells and signal in the case of unbounded sensitivity to the signal, with $\alpha_0 < 2\lambda_0$ and only $C_1 = 0$ ($\lambda_0 = 0.2$, $c = 0.015$, $\alpha_0 = 0.21$, $N(0) = 1$, $S_1(0) = 1$).

boundedness conditions, one obtains, as $u \to \pm\infty$,

$$S_1(u) \approx \begin{cases} c_1^1 I_{k_1}\left(\alpha_1 \mathrm{e}^{(\mu_1/2)u}\right) \mathrm{e}^{-(c/(2D_S))u}, & u < 0, \\ c_1^2 I_{k_2}\left(\alpha_2 \mathrm{e}^{-(\mu_2/2)u}\right) \mathrm{e}^{-(c/(2D_S))u}, & u > 0, \end{cases} \tag{3.90}$$

where $k_i = (\sqrt{c^2 + 4D_S(\gamma + c_2)})/(\mu_i D_S)$, $\alpha_i = \sqrt{4\alpha D_S \delta_i}/(\mu_i D_S)$, and c_1^1 and c_1^2 are positive constants. We previously proved that $S_1 \in Y_S$. Asymptotic travelling wave solutions are possible. The asymptotic behaviour of $S_1(u)$ is illustrated in Figure 3.7(b).

3.3 Discussion

In this paper we studied the existence of travelling wave solutions (with a single peak for the signal) of a microscopic model for chemotaxis. We focused on the case of starvation; cells in this situation consume signal only. The effect of microscale parameters in the stability of the system was examined. Unlike previous approaches, we allowed for degradation of signal ($\gamma \neq 0$). While we will compare our results to those previously obtained, it must be borne in mind that this important biological process was not considered in other results. We performed a Lie symmetry analysis to generate a large class of invariants leading to generalized travelling wave solutions. Only relevant invariants were considered, but we believe that rich information

could have been extracted from the full form of invariants in different contexts. We provided explicit solutions, many for the first time.

We first considered the case of zero growth. Such a scenario is possible if the time interval is shorter than the period required for cell proliferation. When we imposed no chemotaxis, we could not find travelling wave solutions satisfying $S_1 \in Y_S$. We note that Xue *et al* [111] also indicated the absence of travelling wave solutions when there is no chemotaxis. However, their results held in the case of no diffusivity ($D_S = 0$). We have shown here that these results also hold in the diffusing case. However, when we relaxed the restriction on S_1 (less important in the absence of chemotaxis), we obtained both diffusing and non-diffusing travelling wave solutions, distributed in a half plane (see Figure 3.2).

If we now consider the high chemotactic limit, we find that non-diffusing ($D_S = 0$) travelling wave solutions do not exist. This is in contrast to Xue *et al's* [111] results in which they were found to exist. The degradation of the signal removed this possibility in our results. However, as evidenced in Theorem 3.2.1, the incorporation of diffusion does allow for the existence of travelling wave solutions. It is interesting to note that diffusion, in a sense, counteracts the wave eradication effect of the degradation of the signal.

In order to model the behaviour of cells over more realistic time frames, we incorporated cell growth into our model. As a first attempt we assumed constant growth. In general, with no chemotaxis, non-diffusing ($D_S = 0$) travelling wave solutions do not exist. However, we observe that this occurs due to the requirement that $S_1 \in Y_S$. This is not necessary in the case of no chemotaxis. Relaxing this restriction leads to non-diffusing travelling wave solutions (see Theorem 3.2.3). Note that, unlike Franz *et al* [32], we dot not require a minimal wave speed. We are also able to find diffusing travelling wave solutions (with a discontinuous flux) provided the growth rate dominates the dynamics (see Theorem 3.2.4).

If we consider the high chemotactic limit we find that non-diffusing travelling wave solutions do not exist. However, incorporating diffusivity leads to the possibility of travelling wave solutions (see Theorems 3.2.5, Theorem 3.2.6 and Corollary **??**). Note that these are the first results in the case of high chemotaxis with non-zero growth. In contrast to Keller and Segel's [44, 45] results in the macroscopic model under zero growth, none of our travelling wave solutions

required a singularity in the chemotactic sensitivity.

When cells are highly sensitive to signals, allowing for diffusivity, we observe for $\alpha_0 < 2\lambda_0$ that the total cell population (given by $T_2 = 2sN(0)/(2\lambda_0 - \alpha_0)$) increases as the growth rate α_0 becomes large; here most of the new born cells remain in the band. For $\alpha_0 = 2\lambda_0$, the growth rate controls the behaviour of the system (see §3.2.3). In this case, the total cell population (given by $T_3 = 2sN(0)/\alpha_0$) decreases as α_0 is large. This is due to the local depletion of the signal; some cells will move towards regions with higher concentrations of signal (this is typical in chemotactic systems). The aggregated cells here do not disperse as we demonstrated the existence of travelling wave solutions in this situation. However, for $\alpha_0 > 2\lambda_0$, we notice instability. The cell growth rate controls the behaviour of the system, and prevents formation of the aggregation.

The inverse phenomenon is observed in the limiting case where cells are not sensitive to the signal gradient; they move randomly in this situation. For $\alpha_0 \leq 2\lambda_0$, we obtained instability in the system, travelling wave solutions do not exist. However, for $\alpha_0 > 2\lambda_0$, the stability of the solutions is controlled by the growth rate α_0. We imposed restrictions on the initial conditions in order to foster a collective behaviour. Travelling wave solutions then resulted. This result is in agreement with Lauffenburger *et al's* [56] findings (in the macroscopic model), in which travelling wave solutions exist due to the balance of growth, death and random motility.

As result of our investigation, we remark that cell growth and cell unbiased turning rate play an important role in the stability of the system and the aggregation of cells. We also remark that the total cell population in the case of zero growth (T_1) is less than that of the case of constant growth (T_2 and T_3). The wider band of cells is obtained in the case of no chemotaxis (we recall that here the growth rate α_0 controls the stability of the system, the absence of sensitivity to stimuli keep most of cells in the band). The distribution of cells are displayed in Figures 3.1(a), 3.2(a), 3.3(a), 3.3(d), 3.4(a), 3.5(a) and 3.6(a). We also note that the total cell population T_i decreases as λ_0 becomes large; the permanent change of direction does not necessarily destabilize the formation of bands of bacteria.

We have shown that it is crucial to consider the individual response of cells when studying their macroscopic behaviour. This helps us to capture microscale information which play a

$h(S)$	k	D_S	TWS	Restriction on α_0
0	∞	0	$\times$ (or $\surd$ if $S_1 \notin Y_S$)	–
		$\neq 0$	$\times$ (or $\surd$ if $S_1 \notin Y_S$)	–
	0	0	$\times$	–
		$\neq 0$	$\surd$	–
α_0	∞	0	$\times$ (or $\surd$ if $S_1 \notin Y_S$)	– (or arbitrary)
		$\neq 0$	$\surd$	$\alpha_0 > 2\lambda_0$
	0	0	$\times$	–
		$\neq 0$	$\surd$	$\alpha_0 \leq 2\lambda_0$

Table 3.1: Table summarizing our findings on the existence of travelling wave solutions (TWS)

significant role in the system. Our results can be summarized in Table 3.1. For future work, we will consider a linear growth rate, for it involves both growth and death. The geometric shape of bands of bacteria will also be investigated.

Chapter 4

Asymptotic analysis of travelling wave solutions in chemotaxis with nutrients dependent growth rate

4.1 Introduction

Many physical problems arising in physical, social, natural, behavioural and applied sciences can be formulated as differential or difference equations. The solutions of these equations will describe the evolution of the relevant process. Understanding differential or difference equations and their solutions is crucial to understanding key phenomena in the system or the behaviour of the system. Differential equations have a long history in modelling biological systems, beginning with the remarkable work of Malthus [66] in 1798, who proposed the first principle of population dynamics. Subsequently, Verhulst [103] considered the case of limiting resources such as carrying capacity and he introduced the logistic equation. Gompertz [35] accounted for the mortality in his model, and assumed that the growth ends at a finite period of time. In the case of competition between species, the logistic equation was extended by Lotka [59, 60] and Volterra [106] to the Lotka-Volterra predator-prey model. More recently population dynamics has been incorporated in epidemiology to study the spread of infectious [38, 48]. In cell and molecular biology, various models have been proposed to study intracellular

dynamics [52], scar formation [20], tumor growth [104] and drug therapy [74]. Partial differential equations (PDEs) are often used to capture microscale information, for it considers both spacial and temporal variational (also intracellular variational). They help us to understand complex mechanisms in biology. As said before, one popular model employing PDEs is Fisher's equation, used to describe the spread of advantageous genes, given by [31]

$$\frac{\partial u}{\partial t} = ru(1-u) + D\frac{\partial^2 u}{\partial x^2}, \tag{4.1}$$

where $u(x,t)$ is the density of the specie at the position x and time t, D is the diffuse coefficient of the specie. General solutions of (4.1) cannot usually be obtained (for $r \neq 0$). However, some specific forms of solutions have be found.

Given the difficulty in solving nonlinear PDEs in general, special types of solutions have been investigated. Travelling wave solutions are a particular type of solution that tend to be relevant in modelling biological systems. They are usually seen as invariant solutions (that maintain their shape), moving with constant speed [105]. In cell biology, travelling waves have been observed in chemotaxis, whereby cells direct their motion in response to extracellular signalling (we note that the chemotaxis of bacteria was observed first in the late 1800s [8, 25, 26, 84]). In his experiment, Adler [1, 2, 3] observed the formation of travelling bands of bacteria when he injected a population of cells (*E coli*) at one end of a capillary tube containing oxygen and nutrients. Cells consumed nutrients and excreted a gradient of signal; thereafter moving in response to the signal. As the concentration of the oxygen was inadequate to oxidise all the nutrients, two sharp bands of cells, visible to the naked eye, formed. The first band of cells created a gradient in the concentration of oxygen, while the second band did so for the concentration of nutrients. Both bands swum towards higher concentrations. Patlak [83] and Keller and Segel [44, 45] independently proposed the first mathematical model of chemotaxis.

The continuum Keller-Segel (K-S) model has become the most common way to represent the chemotactic behaviour on a macroscopic (population-based) point of view. Its general form can be written as follow:

$$\frac{\partial b}{\partial t} = \nabla \cdot (\mu(s)\nabla b) - \nabla \cdot (b\chi(s)\nabla s), \tag{4.2}$$

$$\frac{\partial s}{\partial t} = D\nabla^2 s - k(s)b, \tag{4.3}$$

where b denotes the cell density, s is the concentration of the critical substrate, $\mu(s)$ is the diffuse coefficient of the bacteria, $\chi(s)$ is the chemotactic sensitivity (measuring the strength of the signal), $k(s)$ is the rate of consumption of the substrate per cell, D is the diffuse coefficient of the substrate, and t is time. We note that cell proliferation is not included in the K-S model, as it occurs in some cases over a longer timescale than the duration of many *in vivo* experiments [100]. A singularity in the chemotactic coefficient has been found by Keller and Segel [46] to be necessary in order to produce band behaviour (travelling wave solutions) under zero cellular growth/death. To check the validity of the K-S model, Scribner *et al* [92] performed numerical simulations and compared their results with Adler's [1, 2] experimental results under different initial conditions. They provided some forms of $\mu(s)$, $\chi(s)$ and $k(s)$, all dependant on a critical attractant concentration level a, that produced both uniform and non-uniform bands of bacteria.

Patlak [83] was the first to propose a chemotaxis model (stochastic) from a micro-scale (cell-based) perspective. His model portrayed the random walk process of a particle with persistence of direction, and external bias. In the case where the particles alternate run (to move forward) and tumble (probably to change the direction), the velocity jump process derived from the stochastic process is appropriate to describe the motion [80]. When there is no interaction between particles, Alt [1] and Othmer *et al* [80] derived a model that employs a transport equation for velocity jump processes as follows:

$$\frac{\partial}{\partial t}p(x,v,t) + v \cdot \nabla p(x,v,t) = \lambda \int_V T(v,v')p(x,v',t)dv', \tag{4.4}$$

where $p(x,v,t)$ is the density of particles at position $x \in \Omega \subset \mathbb{R}^N$, moving with velocity $v \in V \subset \mathbb{R}^N$ at time $t \geq 0$, λ is the turning rate, and $T(v,v')$ is the turning kernel standing for the probability of a velocity jump from v' to v if a jump occurs. It was assumed in (4.4) that the choice of the new velocity does not depend on the run length.

The response of cells to extracellular signalling (the transduction of the signal) has been studied through the intracellular dynamics of the cells. These dynamics have been modelled as the system of ordinary differential equations [6, 28, 29, 93, 95]:

$$\frac{dy}{dt} = f(y,S), \tag{4.5}$$

where $y = (y_1, ..., y_M) \in \mathbb{R}^M$ are internal state variable, S is the concentration of external signals detected, and $f : \mathbb{R}^{M+1} \longrightarrow \mathbb{R}^M$ is a function. Thus, the chemotaxis model with internal dynamics can be read as follows [101]:

$$\frac{\partial p^+}{\partial t} + v\frac{\partial p^+}{\partial x} + \sum_{i=1}^{M} \frac{\partial}{\partial y_i}\left[f_i(y,S)p^+\right] = \lambda(y)(-p^+ + p^-), \tag{4.6}$$

$$\frac{\partial p^-}{\partial t} - v\frac{\partial p^-}{\partial x} + \sum_{i=1}^{M} \frac{\partial}{\partial y_i}\left[f_i(y,S)p^-\right] = \lambda(y)(p^+ - p^-), \tag{4.7}$$

$$\frac{\partial S}{\partial t} = D_S\frac{\partial^2 S}{\partial x^2} + r(S, p^+, p^-)(p^+ + p^-), \tag{4.8}$$

where $p^{\pm}(x, y, t)$ is the density of particles at position x, with the internal state y, moving at time $t \geq 0$ to the right (left), and the function r describe the production, consumption or degradation of signals S. Recently, Xue *et al* [111] formulated a model that incorporates the interplay between the initial substrate and the excreted signal. Their model is noteworthy as it was the first attempt to describe the interactions between two populations from the individual-based perspective. This ground-breaking approach has allowed further progress to be possible in this field. They assumed non proliferation of cells and proved the existence of travelling wave solutions in the case of non diffusivity. Building on these results, we presented explicit solutions for the first time in the case of diffusivity [98].

The chemotaxis of *E coli* is one of the better studied systems for signal transduction. This is due to *E coli* being readily cultivated in a laboratory setting. It is important in microbiology and biotechnology to create recombinant DNA, and to transfer DNA via bacteria conjugation and transduction [12, 58, 89]. Even though cell growth and death plays a biologically significant role in the behaviour of the system, they have often been overlooked in many of the mathematical models of chemotaxis. In fact, Budrene and Berg [14] observed that the cell growth induces the formation of new aggregates (bands). Elliott *et al* [24] engineered a 3D *in vitro* novel tumor model that allowed the proliferation and spreading of *E coli* cells to invade and interact with bacterial-tumor cells. The effects of cell growth on the behaviour of the solutions has also received a mathematical treatment [55, 57, 56, 47, 75]. From the population perspective, Kennedy and Aris [47] found a certain growth function that gave birth to travelling wave solutions of constant speed. Unlike the Keller-Segel [46] results, Lauffenburg *et al* [56] included

bacterial growth and death, and assumed that bacteria move by diffusion. They obtained travelling wave solutions (in non *in vivo* experiments) irrespective of the chemotactic coefficient.

From the cell-based perspective, Franz *et al* [32] assumed that substrates do not diffuse and the cell proliferation depends only on the concentration of the extracellular signal. They proved the existence of travelling wave solutions and observed that the cell growth/death stabilises the wave profile. Their assumptions are very restrictive, for it has been shown that the diffusion of substrates plays a stabilizing role on the steady state of the system [88]. Moreover, cells most often grow on nutrients, or in some situations grow on higher concentrations of potential food present locally [14].

In this study, we will allow for diffusivity, and will consider a cell proliferation rate depending on nutrients. Additionally, we will account for the interaction between the nutrients and the signal. We will be specifically looking at the impact of cell growth/death on the behaviour of the bands and the substrates. Travelling wave solutions will be investigated in both the case of chemotaxis and of no chemotaxis. In what follows, we will introduce the model in §4.2. The Lie symmetry analysis will be used to generate damped travelling wave solutions in §4.3. Various relevant theorems will be presented. A full discussion will be given in §4.4.

4.2 Model formulation

Our model is motivated by the self-organization of cells, their collective defense and their response to certain gradients of signal. It results from the experimental observations [13, 14, 110] in which bacteria move in a semi solid agar containing nutrients (the carbon source is succinate), consume succinate and excrete a signal attractant (aspartate), then assemble and form different spatial patterns in response to gradients of the signal. It was observed that the patterns form within a certain range of succinate concentration, and *E coli* aggregates present in the wake of a travelling circular band [14]. The cells grow on succinate. The density of the aggregate within the swarm ring and the production of aspartate increase as the concentration of succinate is large. At low concentrations of succinate the aggregate may not break up as the gradient of aspartate becomes dominant and is consumed by cells [11]. We focus on the case of non limiting

nutrients.

Looking at single cell behaviour, models have been formulated to represent the dynamics of the elements within cells facilitating signal transduction. The main constituents are fast excitation (the rapid decrease in the motor control protein CheY_p), followed by slower adaptation (the slow return to the prestimulus level). It can be described in the form of a system of ordinary differential equations as follows [6, 28, 30, 78, 95]:

$$\frac{dy_1}{dt} = f_1(y, S) = \frac{g(S) - (y_1 + y_2)}{\tau_e}, \quad \frac{dy_2}{dt} = f_2(y, S) = \frac{g(S) - y_2}{\tau_a}, \tag{4.9}$$

where $y = (y_1, y_2) \in \mathbb{R}^2$ is the internal state variable describing the signal transduction, g encodes the first step of signal transduction, $S(x,t)$ is the concentration of the aspartate at the position x and the time t, τ_e and τ_a are respectively the time scale for excitation and adaptation. Denoting by $p^{\pm}(x,y,t)$ the density of cells in a band at the position x in the state y, moving with constant speed $\pm s$, then the distribution of the cells can be described in one dimensional space via the telegraph process [28, 80, 41]

$$\frac{\partial p^+}{\partial t} + s\frac{\partial p^+}{\partial x} + \sum_{i=1}^{2} \frac{\partial}{\partial y_i}\left(f_i(y,S)p^+\right) = -\lambda\left(-\frac{\partial S}{\partial x}\right)p^+ + \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(F)p^+, \tag{4.10}$$

$$\frac{\partial p^-}{\partial t} - s\frac{\partial p^-}{\partial x} + \sum_{i=1}^{2} \frac{\partial}{\partial y_i}\left(f_i(y,S)p^-\right) = \lambda\left(-\frac{\partial S}{\partial x}\right)p^+ - \lambda\left(\frac{\partial S}{\partial x}\right)p^- + h(F)p^-, \tag{4.11}$$

where $F(x,t)$ is the concentration of the aspartate, λ and h are respectively the turning rate function and the proliferation rate of the cells. We will use the form of turning rate function formulated in [32, 111] defined as follows:

$$\lambda\left(\frac{\partial S}{\partial x}\right) = \lambda_0\left(1 + \frac{\frac{\partial S}{\partial x}}{k + |\frac{\partial S}{\partial x}|}\right) = \lambda_0\left(1 + \chi\frac{\partial S}{\partial x}\right), \tag{4.12}$$

where λ_0 is the unbiased turning rate ($\lambda_0 > 0$), k the sensitivity coefficient and $\chi = (k + |\frac{\partial S}{\partial x})|)^{-1}$ the chemotactic sensitivity. In the limiting case $k \to 0$, we note that λ becomes the switch function

$$\lambda\left(\frac{\partial S}{\partial x}\right) = \begin{cases} 0, & \partial S/\partial x < 0, \\ \lambda_0, & \partial S/\partial x = 0, \\ 2\lambda_0, & \partial S/\partial x > 0. \end{cases} \tag{4.13}$$

This corresponds to unbounded sensitivity to the signal [111]. When $k \to \infty$, there is no chemotaxis ($\chi = 0$).

The proliferation term involves growth and death. *E coli* cells grow at an approximately constant rate over the concentration range of succinate $0.5 - 7mM$ [14]. We will consider two forms of h:

$$h(F) = \alpha_0, \quad \text{and} \quad h(F) = \beta_0(F - F_c), \tag{4.14}$$

where F_c is the minimum amount of succinate that facilitates growth, and α_0 and β_0 are positive constants. When the concentration of succinate is greater than F_c, $h(F)$ is positive and the population increases. However, when it is below F_c, the population decreases.

The distribution of the succinate and aspartate can be described by the diffusion equations

$$\frac{\partial F}{\partial t} = D_F \frac{\partial^2 F}{\partial x^2} - \alpha F \int_{\mathbb{R}^2} (p^+(x,y,t) + p^-(x,y,t))dy, \tag{4.15}$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + \beta F \int_{\mathbb{R}^2} (p^+(x,y,t) + p^-(x,y,t))dy - \gamma S, \tag{4.16}$$

where α is the consumption rate of succinate by cells, β is the production rate and γ the degradation rate, of the aspartate. Letting

$$n(x,t) = \int_{\mathbb{R}^2} (p^+(x,y,t) + p^-(x,y,t))dy, \quad j(x,t) = \int_{\mathbb{R}^2} s(p^+(x,y,t) - p^-(x,y,t))dy, \tag{4.17}$$

and integrating (4.10) and (4.11) over y, one transforms (4.10), (4.11), (4.15) and (4.16) into

$$\frac{\partial n}{\partial t} + \frac{\partial j}{\partial x} = h(F)n, \tag{4.18}$$

$$\frac{\partial j}{\partial t} + s^2 \frac{\partial n}{\partial x} = s\lambda^1 n - 2\lambda_0 j + h(F)j, \tag{4.19}$$

$$\frac{\partial F}{\partial t} = D_F \frac{\partial^2 F}{\partial x^2} - \alpha F n, \tag{4.20}$$

$$\frac{\partial S}{\partial t} = D_S \frac{\partial^2 S}{\partial x^2} + \beta F n - \gamma S. \tag{4.21}$$

The functions $n(x,t)$ and $j(x,t)$ stand for the total cell density of the band and the flux respectively, while λ^1 is given by

$$\lambda^1 \left(\frac{\partial S}{\partial x} \right) = \lambda \left(\frac{\partial S}{\partial x} \right) - \lambda \left(-\frac{\partial S}{\partial x} \right). \tag{4.22}$$

Cells growth is an important factor to consider, for its plays an influential role during the propagation of the swarm ring and the formation of new aggregates [14]. Many authors overlooked it, while others assumed a signal dependant growth rate. We will investigate in our situation, the effect of cell growth in the behaviour of the band. Travelling wave solutions will be explored in the both cases of high and no sensitivity to the signal. As a result, the function λ^1 will be treated as a constant in the Lie symmetry analysis.

4.3 Lie symmetry and travelling wave analysis

An nth order partial differential equation

$$E(x, y, \partial y, ..., \partial^n y) = 0, \tag{4.23}$$

where $\partial^k y$ stands for the components of all kth order partial derivatives of y with respect to x, $y(x) = (y^1(x), ..., y^m(x))$, and $x = (x_1, ..., x_N)$, admits

$$G = \xi_i(x, y)\frac{\partial}{\partial x_i} + \eta^\nu(x, y)\frac{\partial}{\partial y^\nu}, \tag{4.24}$$

as a symmetry if (Bluman and Anco, 2002)

$$G^{[n]}E \mid_{E=0} = 0. \tag{4.25}$$

Here, $\xi_i(x, y)$ and $\eta^\nu(x, y)$ are the infinitesimals of the Lie group of invariant transformations of (4.23), and $G^{[n]}$ is the nth extension of G (Bluman and Anco, 2002).

Applying the operation (4.25) to (4.18)–(4.21), we obtain as symmetries

$$G_1 = \partial_t + c\partial_x + \alpha_1 F\partial_F + \alpha_1 S\partial_S + \alpha_2 \mathrm{e}^{(h-2\lambda_0)t}\partial_j, \qquad G_\infty = d(t, x)\partial_S, \tag{4.26}$$

if h is constant, and

$$G_2 = \partial_t + c\partial_x, \qquad G_\infty = d(t, x)\partial_S, \tag{4.27}$$

if $h(F) = \beta_0(F - F_c)$, with a_1, a_2 and a_3 arbitrary real parameters, G_∞ an infinite-dimensional symmetry, and d a solution of

$$D_S\frac{\partial^2 d}{\partial x^2} - \frac{\partial d}{\partial t} - \gamma d = 0. \tag{4.28}$$

The characteristic equations associated with G_1 are (Bluman and Anco, 2002)

$$\frac{dt}{1} = \frac{dx}{c} = \frac{dF}{\alpha_1 F} = \frac{dS}{\alpha_1 S} = \frac{dj}{\alpha_2 \mathrm{e}^{(h-2\lambda_0)t}} = \frac{dn}{0}. \tag{4.29}$$

This leads to the new invariants

$$u = x - ct, \tag{4.30}$$

$$F = F_1(u)\mathrm{e}^{\alpha_1 t}, \tag{4.31}$$

$$S = S_1(u)\mathrm{e}^{\alpha_1 t}, \tag{4.32}$$

$$j = J(u) + \frac{\alpha_2}{(h-2\lambda_0)}\mathrm{e}^{(h-2\lambda_0)t}, \tag{4.33}$$

$$n = N(u). \tag{4.34}$$

The equation (4.30) justifies the possible existence of travelling wave solutions, c being the speed of the wave (with $0 < c \leq s$). Therefore, performing a full group theoretical analysis of (4.18)–(4.21) yields generalized travelling wave solutions (the restrictive case $\alpha_1 = \alpha_2 = 0$ yields the standard travelling wave solutions). We showed (in Tchepmo Djomegni and Govinder, 2014b) that the coefficient α_1 plays a stabilizing role on the system, and can produce damped (resp. growing) travelling wave solutions for $\alpha_1 < 0$ (resp. $\alpha_1 > 0$). We will only consider the case where $\alpha_1 \leq 0$, and only standard travelling wave solutions will be investigated in the case of non constant proliferation rate ($\alpha_1 = 0$). We will overlook the additive pure timelike component of j (i.e., $\alpha_2 = 0$), as this does not add to the behaviour of the system. Substituting (4.33) and (4.34) into (4.18) and (4.19), we obtain

$$-cN' + J' = h(F_1)N, \tag{4.35}$$

$$-cJ' + s^2 N' = s\lambda^1 N - 2\lambda_0 J + h(F_1)J, \tag{4.36}$$

where the superscript $'$ denotes the total derivative with respect to the variable u. Thus, (4.35)–(4.36) can be rewritten as

$$(s^2 - c^2)N' = (ch(F_1) + s\lambda^1)N + (h(F_1) - 2\lambda_0)J, \tag{4.37}$$

$$(s^2 - c^2)J' = (s^2 h(F_1) + cs\lambda^1)N + c(h(F_1) - 2\lambda_0)J. \tag{4.38}$$

Likewise, the substitution of (4.31)–(4.34) into (4.20) and (4.21) yields

$$D_F F_1'' + cF_1' - (\alpha_1 + \alpha N)F_1 = 0, \tag{4.39}$$

$$D_S S_1'' + cS_1' + \beta F_1 N - (\alpha_1 + \gamma)S_1 = 0. \tag{4.40}$$

When $c = s$, we remark that (4.37) and (4.38) are the same, and (4.37)–(4.40) becomes a system of three equations for four unknown N, J, F_1 and S_1. The solutions in this case can depend on $N(u)$ or $J(u)$. For a constant distribution of $N(u)$ or $J(u)$, travelling wave solutions can be demonstrated under constant growth rate (The analysis for an exponential distribution (such as the Poisson or normal distribution) of $N(u)$ or $J(u)$ is similar to the case of $c \neq s$). However, from experimental evidence, c is less than s (In particular, in *E coli*, it was observed that c is in the range $1 - 2mm/hour$, while, for s, we have $10 - 20\mu m/sec$ (Budrene and Berg, 1995; Xue et al., 2011).). As a result for the reminder of our work we will only consider $0 < c < s$, and study the existence of travelling wave solutions in the limiting cases of k, and under different forms of h. We note that travelling wave solutions in our context must be positive, continuous and bounded.

4.3.1 High chemotactic sensitivity ($k = 0$)

In this case, λ^1 can be rewritten as

$$\lambda^1\left(\frac{\partial S}{\partial x}\right) = \begin{cases} -2\lambda_0, & \partial S/\partial x < 0, \\ 0, & \partial S/\partial x = 0, \\ 2\lambda_0, & \partial S/\partial x > 0. \end{cases} \tag{4.41}$$

Motivated by the numerical investigation's of Xue et al. (2011), we will be looking for solutions admitting a single peak of S. In this context, travelling wave solutions $n(x,t)$, $F(x,t)$ and $S(x,t)$ are continuous, positive and bounded solutions in which $S_1 \in Y_S$, where

$$Y_S = \{f \in \mathbb{C}^1(\mathbb{R}); f(u) \text{ is monotonically increasing for } u < 0 \text{ and decreasing for } u > 0\}.$$

Constant cell growth rate $h(F) = \alpha_0$

For $S_1 \in Y_S$, (4.37)–(4.40) can be reduced to

$$\begin{aligned} N' &= a_1 N + b_1 J, && (4.42)\\ J' &= a_2 N + c b_1 J, && (4.43)\\ -cF_1' &= D_F F_1'' - (\alpha_1 + \alpha N) F_1, && (4.44)\\ -cS_1' &= D_S S_1'' + \beta F_1 N - (\alpha_1 + \gamma) S_1, && (4.45) \end{aligned}$$

where

$$a_1 = \frac{c\alpha_0 - 2\lambda_0 s}{s^2 - c^2}, \quad b_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad a_2 = \frac{s^2\alpha_0 - 2\lambda_0 cs}{s^2 - c^2}, \tag{4.46}$$

for $u > 0$, and

$$a_1 = \frac{c\alpha_0 + 2\lambda_0 s}{s^2 - c^2}, \quad b_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad a_2 = \frac{s^2\alpha_0 + 2\lambda_0 cs}{s^2 - c^2}, \tag{4.47}$$

for $u < 0$.

We assume first $\alpha_0 = 2\lambda_0$ (i.e., $b_1 = 0$). Then $N(u)$ and $J(u)$ are given by

$$N(u) = \begin{cases} N(0)\mathrm{e}^{(\alpha_0/(s-c))u}, & u < 0, \\ N(0)\mathrm{e}^{-(\alpha_0/(s+c))u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} J(0) - sN(0)\left(1 - \mathrm{e}^{(\alpha_0/(s-c))u}\right), & u < 0, \\ J(0) + sN(0)\left(1 - \mathrm{e}^{-(\alpha_0/(s+c))u}\right), & u \geq 0, \end{cases} \tag{4.48}$$

and the total population of the band of cells is given by

$$T = \int_{\mathbb{R}} N(u)du = \int_{-\infty}^{+\infty} N(0)\mathrm{e}^{a_1 u}du = \frac{2sN(0)}{\alpha_0}. \tag{4.49}$$

In the case of non diffusivity (i.e., $D_F = D_S = 0$), the form of our system when $\alpha_1 = 0$ is mathematically similar to the one analysed by Xue et al. (2011) when they assumed non proliferation. The existence of travelling wave solutions has been proved, with the speed of the wave given in our context by $c = s\gamma/(\gamma + \alpha_0\bar{\tau})$ (Xue et al., 2011). When $\alpha_1 \neq 0$, continuous bounded travelling wave solutions do not exist. In fact from (4.44),

$$F(x,t) = \mathrm{e}^{\alpha_1 t}F_1(u) = F_1(0)\mathrm{e}^{\frac{\alpha_1}{c}x}\mathrm{e}^{\frac{\alpha N(0)}{ca_1}(\mathrm{e}^{a_1 u} - 1)}. \tag{4.50}$$

As a result $F(x,t)$ diverges as $x \to \infty$ (resp. $x \to -\infty$) when $\alpha_1 > 0$ (resp. $\alpha_1 < 0$).

For large α_0, the speed and the population of the band decrease. This matches with experiments, for the variation in the local concentration of aspartate increases and induces the formation of new aggregates, and some cells will move towards the new aggregates (Budrene and Berg, 1995). The destabilization (or dislocation) of the main aggregate affects its propagation speed. Moreover, the concentration of aspartate and succinate change as α_0 changes.

In the case of diffusivity, we studied a similar system in (Tchepmo Djomegni and Govinder, 2014b) and we obtained generalized travelling wave solutions.

Now we assume $\alpha_0 \neq 2\lambda_0$, then $N(u)$ and $J(u)$ are given by

$$N(u) = \begin{cases} \frac{C_1}{s}\mathrm{e}^{\lambda_1 u} + \gamma_0 C_2 \mathrm{e}^{\lambda_2 u}, & u < 0, \\ -\frac{C_3}{s}\mathrm{e}^{-\lambda_3 u} + \gamma_1 C_4 \mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} C_1 \mathrm{e}^{\lambda_1 u} + C_2 \mathrm{e}^{\lambda_2 u}, & u < 0, \\ C_3 \mathrm{e}^{-\lambda_3 u} + C_4 \mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{4.51}$$

where

$$\lambda_1 = \frac{\alpha_0}{s-c}, \lambda_2 = \frac{2\lambda_0 - \alpha_0}{s+c}, \lambda_3 = \frac{\alpha_0}{s+c}, \lambda_4 = \frac{2\lambda_0 - \alpha_0}{s-c}, \gamma_0 = \frac{2\lambda_0 - \alpha_0}{s\alpha_0 + 2c\lambda_0},$$
$$\gamma_1 = \frac{2\lambda_0 - \alpha_0}{2\lambda_0 c - s\alpha_0}, C_1 = \frac{s(\gamma_0 J(0^-) - N(0))}{s\gamma_0 - 1}, C_2 = \frac{sN(0) - J(0^-)}{s\gamma_0 - 1},$$
$$C_3 = \frac{s(\gamma_1 J(0^+) - N(0))}{s\gamma_1 + 1}, C_4 = \frac{sN(0) + J(0^+)}{s\gamma_1 + 1}.$$

We took for granted the continuity of $N(u)$ at zero.

When $\alpha_0 > 2\lambda_0$, we have $\lambda_2 < 0$ and $\lambda_4 < 0$. To obtain bounded solutions, the initial conditions must be chosen so that $C_2 = C_4 = 0$ (i.e., $J(0^-) = sN(0)$ and $J(0^+) = -sN(0)$). This will require discontinuity of the flux at zero. In this case, the solutions $N(u)$ and $J(u)$ are reduced to

$$N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_1 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_3 u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} sN(0)\mathrm{e}^{\lambda_1 u}, & u < 0, \\ -sN(0)\mathrm{e}^{-\lambda_3 u}, & u \geq 0. \end{cases} \tag{4.52}$$

(A negative flux simply means that most of the cells move to the left, given that $j = s(n^+ - n^-)$.) Given the form of $N(u)$, the analysis here is mathematically similar to the case of $\alpha_0 = 2\lambda_0$. Diffusing and non-diffusing ($D_S = D_F = 0$) travelling wave solutions exist.

When $\alpha_0 < 2\lambda_0$, all the λ_i are positive and $N(u)$ and $J(u)$ given in (4.51) are bounded. We assume first non-diffusing substrates with at most one of the constants C_i being zero.

Theorem 4.3.1. *For $\lambda_0 < \alpha_0 < 2\lambda_0 c/s$, $J(0^+) = N(0)/\gamma_1$ and $0 < J(0^-) \leq s\gamma_1 J(0^+)$ for $s\gamma_0 - 1 > 0$, or $s\gamma_1 J(0^+) \leq J(0^-)$ for $s\gamma_0 - 1 < 0$, non-diffusing ($D_S = D_F = 0$) travelling wave solutions for $N(u)$, $F_1(u)$ and $S_1(u)$ exist and are explicitly given by*

$$N(u) = \begin{cases} \frac{C_1}{s}\mathrm{e}^{\lambda_1 u} + \gamma_0 C_2 \mathrm{e}^{\lambda_2 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{4.53}$$

$$F_1(u) = \begin{cases} F_1(0)\mathrm{e}^{\frac{-\alpha C_1}{cs\lambda_1}(1-\mathrm{e}^{\lambda_1 u}) - \frac{\alpha\gamma_0 C_2}{c\lambda_2}(1-\mathrm{e}^{\lambda_2 u})}, & u < 0, \\ F_1(0)\mathrm{e}^{\frac{\alpha N(0)}{c\lambda_4}(1-\mathrm{e}^{-\lambda_4 u})}, & u \geq 0, \end{cases} \tag{4.54}$$

and

$$S_1(u) = \begin{cases} \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) + \frac{\beta}{c}\int_u^0 \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1\right), & u < 0, \\ \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) - \frac{\beta}{c}\int_0^u \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1\right), & u \geq 0, \end{cases} \tag{4.55}$$

with $S_1(0) = \beta F_1(0)N(0)/\gamma$ and the wave speed c restricted to guarantee the convergence of $S_1(u)$ to zero as $u \to \infty$.

Proof. We note that (4.54) and (4.55) are obtained directly by substituting (4.53) into (4.44)–(4.45) and integrating (with $\alpha_1 = 0$ and $D_S = D_F = 0$). Given that $N(u)$ and $F_1(u)$ are continuous and bounded, and $F_1(u)$ is positive, it suffices to prove the positivity of $N(u)$ and $S_1(u)$, the boundedness of $S_1(u)$, and then that $S_1 \in Y_S$. We first start with the positivity of $N(u)$.

For $\lambda_0 < \alpha_0$ and $s\alpha_0 < 2\lambda_0 c$, we have $\lambda_1 > \lambda_2$ and $\gamma_1 > 0$. When $u < 0$, $\gamma_0 C_2 \mathrm{e}^{\lambda_2 u}$ is the leading behaviour as $u \to -\infty$. To guarantee the positivity of $N(u)$ as u approaches $-\infty$, C_2 must be positive. We note that

$$C_2 = \frac{sN(0) - J(0^-)}{s\gamma_0 - 1} = \frac{s\gamma_1 J(0^+) - J(0^-)}{s\gamma_0 - 1}. \tag{4.56}$$

If $s\gamma_0 > 1$ (respectively $s\gamma_0 < 1$), then $s\gamma_1 J(0^+) \geq J(0^-)$ (respectively $s\gamma_1 J(0^+) \leq J(0^-)$ must hold and the positivity of $N(u)$ is guaranteed for all $u < 0$ (given that $C_2 > 0$ and $\gamma_0 C_2 + C_1/s = N(0) > 0$). Moreover, for $J(0^-) > 0$, the positivity of $J(u)$ is also guaranteed, with $J(0^-) = C_1 + C_2$.

Now we prove the positivity of $S_1(u)$. From (4.45), $S_1'(u)$ is continuous (given the continuity of $N(u)$, $F_1(u)$ and $S_1(u)$). Then, for S_1 to be in Y_S, it is necessary that $S_1'(0) = 0$ (i.e., $S_1(0) = \beta F_1(0)N(0)/\gamma$). Letting

$$f(u) = S_1(0) - \frac{\beta}{c}\int_0^u \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1, \tag{4.57}$$

then there exists a constant $u_2 > 0$ such that as $u \to \infty$,

$$f(u) \approx S_1(0) - \frac{\beta}{c}\int_0^{u_2} \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1 - \frac{\beta F_+}{c}\int_{u_2}^u \mathrm{e}^{-\frac{\gamma}{c}u_1} N(u_1)du_1. \tag{4.58}$$

The existence of u_2 comes from the fact that $F_1(u) \approx F_+$, with $F_+ = F_1(0)\mathrm{e}^{\alpha N(0)/(c\lambda_4)}$, as $u \to \infty$. Therefore, (4.58) implies that

$$f(u) \approx f(u_2) + \frac{\beta F_+ N(0)(\mathrm{e}^{(-\lambda_4-\gamma/c)u} - \mathrm{e}^{(-\lambda_4-\gamma/c)u_2})}{\gamma + c\lambda_4}, \tag{4.59}$$

$$\approx f(u_2) - \frac{\beta F_+ N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)u_2}}{\gamma + c\lambda_4} + \frac{\beta F_+ N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)u}}{\gamma + c\lambda_4}. \tag{4.60}$$

Choosing the wave speed and the initial conditions so that

$$f(u_2) = \frac{\beta F_+ N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)u_2}}{\gamma + c\lambda_4}, \tag{4.61}$$

the functions $f(u)$ and $S_1(u)$ converge to zero as $u \to \infty$. As a result, they are both positive (given that $f(u)$ is decreasing). When $u < 0$, $S_1(u)$ is positive and converges as $u \to -\infty$ (given the boundedness of $N(u)$ and $F_1(u)$). Thus, $S_1(u)$ is positive, continuous and bounded.

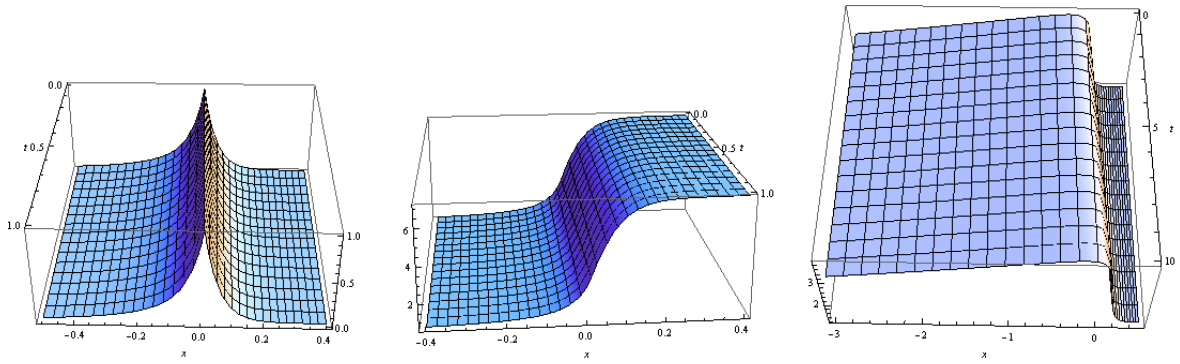
Showing that $S_1 \in Y_S$, requires showing that $u = 0$ is the only extremum point (from $S_1'(0) = 0$ as indicated early), with $S''(0^-) \leq 0$ and $S''(0^+) \leq 0$. From (4.44),

$$S_1''(u) = \frac{1}{c}\left(\gamma S_1'(u) - \frac{\beta\alpha}{c}F_1(u)N^2(u) - \beta F_1(u)N'(u)\right). \tag{4.62}$$

Then at a local extremum u_* (i.e., $S_1'(u_*) = 0$),

$$S_1''(u_*) = -\frac{\beta}{c^2}F_1(u_*)\left(\alpha N^2(u_*) + cN'(u_*)\right). \tag{4.63}$$

For $u < 0$, $N'(u)$ given in (4.42) is positive (given that $N(u)$ and $J(u)$ are positive); as a result $S_1''(u_*) < 0$ (and $S_1''(0) < 0$). If there exist a local extremum $u_0 < 0$, then it cannot be either a point of inflection or a local minimum. Suppose now that u_0 is a local maximum,



(a) Cell density (b) Succinate (c) Aspartate

Figure 4.1: Distribution of cell and non-diffusing substrates in the case of high sensitivity to the signal, and the scenario of constant growth rate α_0 (we used $s = 20\mu m/sec$, $\lambda_0 = 0.2/sec$, $\alpha = 0.2/sec$, $\beta = 0.17/sec$, $\alpha_0 = 0.21$, $N(0) = 1$, $F_1(0) = 3$, $\gamma = 0.17/sec$, $c = 11\mu m/sec$ and $J(0^- = 0.03)$).

then we can find $u_1 \in (u_0, 0)$ (given that $S_1''(0^-) \leq 0$) such that $S_1'(u_1) = 0$ and $S_1''(u_1) \geq 0$ (a local minimum). This is a contradiction. For $u \geq 0$, $N'(u)$ is negative. Then $S_1''(u_*) < 0$ if $u_* \in [0, u_1)$, and $S_1''(u_*) > 0$ if $u_* \in (u_1, \infty)$, with $u_1 = \lambda_4^{-1} \log(\alpha N(0)/(c\lambda_4))$. When $u \in [0, u_1)$, $u = 0$ is the only extremum point (the local maximum). When $u \in (u_1, \infty)$, a local maximum or inflection point cannot exist. Suppose that there exist a local minimum $u_2 > u_1$. Then $S_1(u)$ is increasing for $u \geq u_2$, and $S_1(u_2) \leq 0 = \lim_{u\to\infty} S_1(u)$. This is a contradiction. Therefore, $u = 0$ is the only extremum point of $S_1(u)$, and $S_1 \in Y_S$. □

Remark: In the above theorem we do not consider the case $\alpha_1 \neq 0$ because $F_1(u)$ will blow up as $u \to \infty$ (or as $u \to -\infty$) when $\alpha_1 > 0$ (or $\alpha_1 < 0$). As a result, unbounded solutions will only exist in one region (the half plane $u \geq 0$, or $u \leq 0$). In this situation, $S_1 \notin Y_S$. An illustration of solutions in Theorem 4.3.1 can be viewed in Figure 4.1.

The case of diffusivity ($D_F \neq 0$ and $D_S \neq 0$) is more complicated. For instance, if we consider $C_3 = 0$ (i.e., $J(0^+) = N(0)/\gamma_1$) and allow for diffusivity, then equation (4.44) cannot be solved explicitly for F_1, given the form of $N(u)$ when $u < 0$. As a result, equation (4.45) also cannot be solved explicitly for S_1. We will undertake an asymptotic analysis to investigate the long term behaviour of $F_1(u)$ and $S_1(u)$ in this case (again with at most one of the constants $C_i = 0$).

We note that $S_1(u)$ can be obtained explicitly (given $N(u)$ and $F_1(u)$) by a direct integration of the second order non homogeneous equation (4.45) with constant coefficients as follows:

$$S_1(u) = \begin{cases} \delta_1^1 \mathrm{e}^{-\tau_1 u} + \delta_2^1 \mathrm{e}^{\tau_2 u} - \dfrac{\beta \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_u^0 \mathrm{e}^{\tau_1 u_1} F_1(u_1) N(u_1) du_1 \\ \qquad + \dfrac{\beta \mathrm{e}^{\tau_2 u}}{\tau_3} \int_u^0 \mathrm{e}^{-\tau_2 u_1} F_1(u_1) N(u_1) du_1, \quad u < 0, \\ \delta_1^2 \mathrm{e}^{-\tau_1 u} + \delta_2^2 \mathrm{e}^{\tau_2 u} + \dfrac{\beta \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_1 u_1} F_1(u_1) N(u_1) du_1 \\ \qquad - \dfrac{\beta \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{-\tau_2 u_1} F_1(u_1) N(u_1) du_1, \quad u \geq 0, \end{cases} \tag{4.64}$$

where δ_j^i are constants of integration, and

$$\tau_1 = \frac{c + \tau_3}{2D_S}, \quad \tau_2 = \frac{-c + \tau_3}{2D_S}, \quad \tau_3 = \sqrt{c^2 + 4D_S(\alpha_1 + \gamma)}. \tag{4.65}$$

If we transform (4.42)–(4.45) into a six dimensional first order system, the solutions of the corresponding system exist on a finite interval, given the initial conditions. We will use asymptotic analysis to investigate the behaviour of $F_1(u)$ and $S_1(u)$ as $u \to \pm\infty$.

We assume that $C_3 = 0$. Depending on the value of α_0 and c, one of the exponential terms in (4.51) is the leading behaviour of $N(u)$ when u approaches $-\infty$ (for instance, if $\lambda_0 < \alpha_0 < 2\lambda_0 c/s$, then $\lambda_2 < \lambda_1$ and $\gamma_0 C_2 \mathrm{e}^{\lambda_2 u}$ dominates the behaviour of $N(u)$ as u approaches $-\infty$). Therefore, $N(u)$ is approximately equivalent to

$$N(u) \approx \begin{cases} \delta_1 \mathrm{e}^{\mu_1 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{4.66}$$

as $u \to \pm\infty$, where $\mu_1 = \min(\lambda_1, \lambda_2)$ and δ_1 is the coefficient of the leading term $\mathrm{e}^{\mu_1 u}$. Substituting (4.66) into (4.44) and integrating thereafter, one obtains as $u \to \pm\infty$,

$$F_1(u) = \begin{cases} \left[\alpha_1^1 I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u}\right) + \alpha_2^1 K_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u}\right)\right] \mathrm{e}^{-(c/(2D_F))u}, & u < 0, \\ \left[\alpha_1^2 I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u}\right) + \alpha_2^2 K_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u}\right)\right] \mathrm{e}^{-(c/(2D_F))u}, & u \geq 0, \end{cases} \tag{4.67}$$

as solution, where the functions $I_{k_i}(v)$ and $K_{k_i}(v)$ are the two linearly independent solutions of the modified Bessel's equation, $\alpha_{1,1} = \sqrt{4\delta_1 \alpha D_F}/(D_F \mu_1)$, $\alpha_{2,2} = \sqrt{4N(0)\alpha D_F}/(D_F \lambda_4)$, $k_1 = \sqrt{c^2 + 4\alpha_1 D_F}/(D_F \mu_1)$, $k_2 = \sqrt{c^2 + 4\alpha_1 D_F}/(D_F \lambda_4)$ (with $k_i > 0$), and α_1^1, α_2^1, α_1^2 and α_2^2 are arbitrary constants. We have previously studied (Tchepmo Djomegni and Govinder, 2014b)

the continuity and boundedness of (4.67) and we obtained the constraint $\alpha_2^1 = \alpha_2^2 = 0$, $\alpha_1^2 = F_1(0)/I_{k_2}(\alpha_{2,2})$, and, for $-\alpha_0 t < u < 0$, (with $\alpha_0 = (\sqrt{c^2 + 4\alpha_1 D_F} + c)/2$), $\alpha_1^1 = F_1(0)/I_{k_1}(\alpha_{1,1})$. Therefore, substituting (4.66) and (4.67) into (4.45) and integrating, we obtain

$$S_1(u) = \begin{cases} \delta_1^1 \mathrm{e}^{-\tau_1 u} + \delta_2^1 \mathrm{e}^{\tau_2 u} - \dfrac{\beta\delta_1\alpha_1^1 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\beta\delta_1\alpha_1^1 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u_1}\right) du_1, \quad u < 0, \\ \delta_1^2 \mathrm{e}^{-\tau_1 u} + \delta_2^2 \mathrm{e}^{\tau_2 u} + \dfrac{\beta N(0)\alpha_1^2 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_8 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right) du_1 \\ \qquad - \dfrac{\beta N(0)\alpha_1^2 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_9 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right) du_1, \quad u \geq 0, \end{cases} \tag{4.68}$$

where τ_1, τ_2 and τ_3 are given in (4.65), and

$$\tau_6 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 + \mu_1, \tau_7 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 + \mu_1, \tau_8 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 - \lambda_4,$$
$$\tau_9 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 - \lambda_4. \tag{4.69}$$

We have also proved (Tchepmo Djomegni and Govinder, 2014b) the boundedness of (4.68), and we found that $S_1(u)$ converges (only to zero) as $u \to \pm\infty$ if and only if

$$\delta_1^1 = \frac{\beta\delta_1\alpha_1^1(\alpha_{1,1}/2)^{k_1}}{\tau_3(\mu_1 k_1/2 + \tau_6)\Gamma(1+k_1)}, \quad \delta_2^2 = \frac{-\beta N(0)\alpha_1^2(\alpha_{2,2}/2)^{k_2}}{\tau_3(-\lambda_4 k_2/2 + \tau_9)\Gamma(1+k_2)}. \tag{4.70}$$

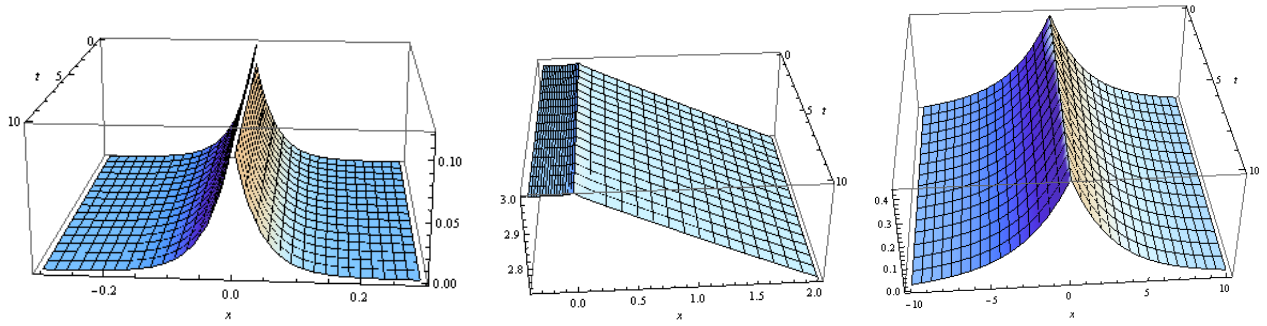
Giving the difficulty in producing explicit solutions for $F_1(u)$, we will not prove for all real u, the positivity of $F_1(u)$ and $S_1(u)$, and that $S_1 \in Y_S$. However, they hold as $u \to \pm\infty$.

Theorem 4.3.2. *For $\alpha_0 < 2\lambda_0$ and $J(0^+) = N(0)/\gamma_1$, asymptotic diffusing travelling wave solutions exist and are explicitly given by*

$$N(u) = \begin{cases} \delta_1 \mathrm{e}^{\mu_1 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{4.71}$$

$F(x,t) = F_1(u)\mathrm{e}^{\alpha_1 t}$ and $S(x,t) = S_1(u)\mathrm{e}^{\alpha_1 t}$, where

$$F_1(u) = \begin{cases} F_1(0) I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_1}(\alpha_1), & u < 0, \\ F_1(0) I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u}\right) \mathrm{e}^{-(c/(2D_F))u} / I_{k_2}(\alpha_2), & u \geq 0, \end{cases} \tag{4.72}$$



(a) Cell density (b) Succinate (c) Aspartate

Figure 4.2: Distribution of cell and diffusing substrates in the case of high sensitivity to the signal (we set the parameters as follows: $D_F = D_S = 9 \times 10^{-5} cm^2/sec$, $s = 20\mu m/sec$, $\lambda_0 = 0.5/sec$, $\alpha = \beta = 0.1/sec$, $\alpha_0 = 0.5$, $N(0) = 0.1$, $F_1(0) = 3$, $\gamma = 0.001/sec$, $\alpha_1 = 0$, $c = 1.5mm/hour$ and $J(0^-) = 0.0021$).

$$S_1(u) = \begin{cases} \delta_1^1 \mathrm{e}^{-\tau_1 u} + \delta_2^2 \mathrm{e}^{\tau_2 u} - \dfrac{\beta\delta_1\alpha_1^1 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u_1}\right) du_1 \\ \qquad + \dfrac{\beta\delta_1\alpha_1^1 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\mu_1/2)u_1}\right) du_1, \quad u < 0, \\ \delta_1^1 \mathrm{e}^{-\tau_1 u} + \delta_2^2 \mathrm{e}^{\tau_2 u} + \dfrac{\beta N(0)\alpha_1^2 \mathrm{e}^{-\tau_1 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_8 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right) du_1 \\ \qquad - \dfrac{\beta N(0)\alpha_1^2 \mathrm{e}^{\tau_2 u}}{\tau_3} \int_0^u \mathrm{e}^{\tau_9 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right) du_1, \quad u \geq 0, \end{cases} \tag{4.73}$$

with $\mu_1 = \min(\lambda_1, \lambda_2)$, $\max(-\gamma, -c^2/(4D_F)) < \alpha_1 \leq 0$, *and* δ_1^1 *and* δ_2^2 *given by (4.70).* ■

In the above Theorem 4.3.2, $N(u)$ and $F(x,t)$ are positive and bounded, and $F(x,t)$ is continuous (we note that $N(u)$ is not continuous at zero). The asymptotic solution $S_1(u)$ is mathematically similar to that of zero growth with positivity and $S_1 \in Y_S$ already demonstrated (Tchepmo Djomegni and Govinder, 2014b). An illustration of the asymptotic behaviour of the solutions presented in Theorem 4.3.2 is displayed in Figure 4.2. The asymptotic similarity to the zero growth case is not surprising as both models have the same boundary conditions as $u \to \pm\infty$.

If we choose the initial conditions so that C_1 (or C_2) and C_3 (or C_4) are zero, then we can explicitly demonstrate diffusing travelling wave solutions.

Theorem 4.3.3. *For $\alpha_0 < 2\lambda_0$, $J(0^-) = N(0)/\gamma_0$ and $J(0^+) = N(0)/\gamma_1$, diffusing travelling wave solutions $N(u)$, $F_1(u)$ and $S_1(u)$ exist and are given by*

$$N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_2 u}, & u < 0, \\ N(0)\mathrm{e}^{-\lambda_4 u}, & u \geq 0, \end{cases} \tag{4.74}$$

$F(x,t) = F_1(u)\mathrm{e}^{\alpha_1 t}$ and $S(x,t) = S_1(u)\mathrm{e}^{\alpha_1 t}$, where

$$F_1(u) = \begin{cases} F_1(0)I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_2/2)u}\right)\mathrm{e}^{-(c/(2D_F))u}/I_{k_1}(\alpha_{1,1}), & u < 0, \\ F_1(0)I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u}\right)\mathrm{e}^{-(c/(2D_F))u}/I_{k_2}(\alpha_{2,2}), & u \geq 0, \end{cases} \tag{4.75}$$

$$S_1(u) = \begin{cases} \delta_1^1\mathrm{e}^{-\tau_1 u} + \delta_2^2\mathrm{e}^{\tau_2 u} - \dfrac{\beta N(0)F_1(0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_{1,1})}\int_u^0 \mathrm{e}^{\tau_6 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_2/2)u_1}\right)du_1 \\ \qquad + \dfrac{\beta N(0)F_1(0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_{1,1})}\int_u^0 \mathrm{e}^{\tau_7 u_1} I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_2/2)u_1}\right)du_1, \quad u < 0, \\ \delta_1^1\mathrm{e}^{-\tau_1 u} + \delta_2^2\mathrm{e}^{\tau_2 u} + \dfrac{\beta N(0)F_1(0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_{2,2})}\int_0^u \mathrm{e}^{\tau_8 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right)du_1 \\ \qquad - \dfrac{\beta N(0)F_1(0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_{2,2})}\int_0^u \mathrm{e}^{\tau_9 u_1} I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{-(\lambda_4/2)u_1}\right)du_1, \quad u \geq 0, \end{cases} \tag{4.76}$$

with τ_1, τ_2 and τ_3 given in (4.65), $\max(-c^2/(4D_F), -\gamma) < \alpha_1 < 0$, and

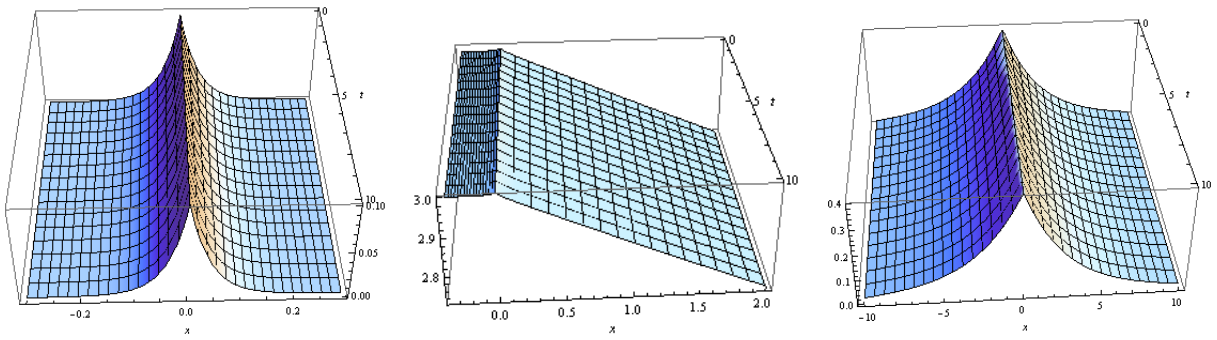
$$\tau_6 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 + \lambda_2, \tau_7 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 + \lambda_2, \tau_8 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 - \lambda_4,$$

$$\tau_9 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 - \lambda_4, \delta_1^1 = \frac{\beta N(0)F_1(0)(\alpha_{1,1}/2)^{k_1}}{\tau_3(\lambda_2 k_1/2 + \tau_6)\Gamma(1+k_1)I_{k_1}(\alpha_{1,1})}, \tag{4.77}$$

$$\delta_2^2 = \frac{-\beta N(0)F_1(0)(\alpha_{2,2}/2)^{k_2}}{\tau_3(-\lambda_4 k_2/2 + \tau_9)\Gamma(1+k_2)I_{k_2}(\alpha_{2,2})}. \tag{4.78}$$

■

We have proved the boundedness of the solutions $F_1(u)$ and $S_1(u)$ in Theoorem 4.3.3. The restriction $S_1 \in Y_S$ has already been demonstrated (Tchepmo Djomegni and Govinder, 2014b). An illustration of the solutions of Theorem 4.3.3 is displayed in Figure 4.3.



(a) (b) (c)

Figure 4.3: Distribution of cell and diffusing substrates in the case of high sensitivity to the signal, with $C_1 = C_3 = 0$ (we set the parameters as follows: $D_F = D_S = 9 \times 10^{-5} cm^2/sec$, $s = 20\mu m/sec$, $\lambda_0 = 0.5/sec$, $\alpha = \beta = 0.1/sec$, $\alpha_0 = 0.5$, $N(0) = 0.1$, $F_1(0) = 3$, $\gamma = 0.001/sec$, $\alpha_1 = 0$ and $c = 1.5mm/hour$).

Nutrient dependent cell growth rate $h(F) = \beta_0(F - F_c)$

Only standard travelling wave solutions are considered in this section. For $S_1 \in Y_S$, (4.37)–(4.40) can be written as follows:

$$N' = c_1 N + d_1 J + \frac{\beta_0 c}{s^2 - c^2} F_1 N + \frac{\beta_0}{s^2 - c^2} F_1 J, \tag{4.79}$$

$$J' = c_2 N + c d_1 J + \frac{\beta_0 s^2}{s^2 - c^2} F_1 N + \frac{\beta_0 c}{s^2 - c^2} F_1 J, \tag{4.80}$$

$$-cF_1' = D_F F_1'' - \alpha F_1 N, \tag{4.81}$$

$$-cS_1' = D_S S_1'' + \beta F_1 N - \gamma S_1, \tag{4.82}$$

where

$$c_1 = \frac{-\beta_0 c F_c - 2\lambda_0 s}{s^2 - c^2}, \quad d_1 = \frac{-(\beta_0 F_c + 2\lambda_0)}{s^2 - c^2}, \quad c_2 = \frac{-\beta_0 s^2 F_c - 2\lambda_0 cs}{s^2 - c^2}, \tag{4.83}$$

for $u > 0$, and

$$c_1 = \frac{-\beta_0 c F_c + 2\lambda_0 s}{s^2 - c^2}, \quad d_1 = \frac{-(\beta_0 F_c + 2\lambda_0)}{s^2 - c^2}, \quad c_2 = \frac{-\beta_0 s^2 F_c + 2\lambda_0 cs}{s^2 - c^2}, \tag{4.84}$$

for $u < 0$.

Rewriting (4.79)–(4.81) as a first order system, we note that at least one of the eigenvalues of the corresponding linearised system around the equilibria is zero (it emanates from (4.81));

there is a center manifold. As the plane $N = J = 0$ is an invariant manifold, the Taylor expansion does not help to determine the flow on the center manifold. We will express $F_1(u)$ in terms of $N(u)$ and $J(u)$, and substitute back into (4.79)–(4.80) to obtain an autonomous system in $N(u)$ and $J(u)$ only. The stability analysis will help us to investigate the asymptotic behaviour of $N(u)$ and $J(u)$. Thereafter we will deduce the behaviour of $F_1(u)$ and $S_1(u)$.

We assume $D_S = D_F = 0$. From (4.79)–(4.80) and (4.81),

$$N(u) = \frac{1}{(cc_1 - c_2)} \left(cN'(u) - J'(u) + \beta_0 F_1(u) N(u) \right), \tag{4.85}$$

$$= \frac{1}{\beta_0 F_c} \left(cN'(u) - J'(u) + \frac{\beta_0 c}{\alpha} F_1'(u) \right). \tag{4.86}$$

This implies that

$$\int_0^u N(u_1) du_1 = \frac{cN(u) - J(u) + (\beta_0 c/\alpha) F_1(u) - (cN(0) - J(0) + (\beta_0 c/\alpha) F_1(0))}{\beta_0 F_c}. \tag{4.87}$$

Then, from (4.81),

$$F_1(u) = F_1(0) \exp\left(\frac{\alpha}{c} \int_0^u N(u_1) du_1 \right) = F_{00} \exp\left(\frac{\alpha(cN(u) - J(u)) + \beta_0 c F_1(u)}{\beta_0 c F_c} \right), \tag{4.88}$$

where

$$F_{00} = F_1(0) \exp\left(-\frac{\alpha(cN(0) - J(0)) + \beta_0 c F_1(0))}{\beta_0 c F_c} \right). \tag{4.89}$$

Thus the function $F_1(u)$ can be implicitly given by

$$F_1(u) \mathrm{e}^{-(1/F_c) F_1(u)} = F_{00} \exp\left(\frac{\alpha(cN(u) - J(u))}{\beta_0 c F_c} \right), \tag{4.90}$$

and explicitly given by

$$F_1(u) = f(N(u), J(u)) = -F_c \times W\left(\frac{-F_{00}}{F_c} \exp\left(\frac{\alpha(cN(u) - J(u))}{\beta_0 c F_c} \right) \right), \tag{4.91}$$

where W stands for the Product logarithm function (also called *Lambert W function*) (Corless et al., 1996). If $N(u)$ and $J(u)$ converge as $u \to \pm\infty$, then from (4.90), $F_1(u)$ converges to a non zero value as $u \to \pm\infty$. In fact, the convergence of $N(u)$ and $J(u)$ causes the function $g(u) = F_1(u) \mathrm{e}^{-(1/F_c) F_1(u)}$ to converge to $l \neq 0$. Consequently, $F_1(u)$ cannot diverges nor converge to zero as $u \to \pm\infty$ (given from(4.88) that $F_1(u)$ is positive).

We now examine the stability of $N(u)$ and $J(u)$. Substituting (4.91) into (4.79)–(4.80), we obtain an autonomous system of differential equations in N and J written as follows:

$$N' = c_1 N + d_1 J + \frac{\beta_0 c}{s^2 - c^2} N f(N, J) + \frac{\beta_0}{s^2 - c^2} J f(N, J), \tag{4.92}$$

$$J' = c_2 N + c d_1 J + \frac{\beta_0 s^2}{s^2 - c^2} N f(N, J) + \frac{\beta_0 c}{s^2 - c^2} J f(N, J). \tag{4.93}$$

The possible equilibria of the above system $(0, 0)$ and $(0, J^*)$, where

$$J^* = \frac{\beta_0 c F_c}{\alpha} \log \left(\frac{\beta_0 F_{00}}{\beta_0 F_c + 2\lambda_0} \exp(\frac{\beta_0 F_c + 2\lambda_0}{\beta_0 F_c}) \right). \tag{4.94}$$

At the vicinity of $(0, 0)$, the linearised system associated with (4.92)–(4.93) is given by

$$N' = \left(c_1 + \frac{\beta_0 c}{s^2 - c^2} f(0,0) \right) N + \left(d_1 + \frac{\beta_0}{s^2 - c^2} f(0,0) \right) J, \tag{4.95}$$

$$J' = \left(c_2 + \frac{\beta_0 s^2}{s^2 - c^2} f(0,0) \right) N + c \left(d_1 + \frac{\beta_0}{s^2 - c^2} f(0,0) \right) J, \tag{4.96}$$

the determinant of the Jacobian matrix is

$$\Delta_1 = \frac{(-(\beta_0 F_c + 2\lambda_0) + \beta_0 f(0,0)) (\beta_0 F_c - \beta_0 f(0,0))}{s^2 - c^2}, \tag{4.97}$$

and the corresponding eigenvalues are

$$\lambda_6 = \frac{\beta_0 (f(0,0) - F_c)}{s - c}, \quad \text{and} \quad \lambda_7 = \frac{\beta_0 F_c + 2\lambda_0 - \beta_0 f(0,0)}{s + c}, \tag{4.98}$$

if $u < 0$, and

$$\lambda_8 = \frac{\beta_0 (F_c - f(0,0))}{s + c}, \quad \text{and} \quad \lambda_9 = \frac{-(\beta_0 F_c + 2\lambda_0) + \beta_0 f(0,0)}{s - c}, \tag{4.99}$$

if $u \geq 0$, where $f(0,0) = -F_c \times W(-F_{00}/F_c)$.

Given that $F_c > f(0,0)$ (since $W(-F_{00}/F_c) > -1$), then $\Delta_1 < 0$ and the origin is a saddle point (with $\lambda_6 < 0$, $\lambda_7 > 0$, $\lambda_8 > 0$ and $\lambda_9 < 0$). As a result, $(0, J^*)$ is unstable. If we choose the initial conditions so that only the stable manifolds will control the behaviour of $N(u)$ and $J(u)$ (with the eigenspace E_{λ_7} leading the behaviour in the half plane $u \leq 0$, and E_{λ_9} leading the behaviour in the half plane $u \geq 0$), then it will require discontinuity of $N(u)$ and $J(u)$ at zero. Travelling wave solutions in this situation are not possible.

4.3.2 No Chemotaxis ($k \to \infty$)

In this case the chemotactic sensitivity $\chi = 0$; then $\lambda^1(\partial S/\partial x) = 0$.

Constant cell growth rate $h(F) = \alpha_0$

The system (4.37)–(4.40) can be reduced to

$$N' = f_1 N + g_1 J, \tag{4.100}$$

$$J' = f_2 N + c g_1 J, \tag{4.101}$$

$$-cF_1' = D_F F_1'' - (\alpha_1 + \alpha N) F_1, \tag{4.102}$$

$$-cS_1' = D_S S_1'' + \beta F_1 N - (\alpha_1 + \gamma) S_1, \tag{4.103}$$

where

$$f_1 = \frac{c\alpha_0}{s^2 - c^2}, \quad g_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad f_2 = \frac{s^2 \alpha_0}{s^2 - c^2}. \tag{4.104}$$

When $\alpha_0 = 2\lambda_0$ (i.e., $g_1 = 0$), unbounded solutions exist only in the half plane $u \leq 0$ (because $f_1 > 0$). Then (4.100)–(4.103) is mathematically equivalent to (4.42)–(4.45) (with $\alpha_0 = 2\lambda_0$). Travelling wave solutions exist.

We now assume $\alpha_0 \neq 2\lambda_0$. The determinant of the Jacobian matrix of (4.100)–(4.101) is given by

$$\Delta = -\frac{\alpha_0(\alpha_0 - 2\lambda_0)}{s^2 - c^2}, \tag{4.105}$$

and the eigenvalues associated are given by

$$\lambda_1 = \frac{-c(\lambda_0 - \alpha_0) + \sqrt{\alpha_0^2 s^2 - 2\lambda_0 \alpha_0 s^2 + c^2 \lambda_0^2}}{s^2 - c^2}, \quad \lambda_2 = \frac{-c(\lambda_0 - \alpha_0) - \sqrt{\alpha_0^2 s^2 - 2\lambda_0 \alpha_0 s^2 + c^2 \lambda_0^2}}{s^2 - c^2}. \tag{4.106}$$

Therefore, $N(u)$ and $J(u)$ are explicitly given by

$$\begin{pmatrix} N(u) \\ J(u) \end{pmatrix} = C_1 \begin{pmatrix} \gamma_3 \\ 1 \end{pmatrix} \mathrm{e}^{\lambda_1 u} + C_2 \begin{pmatrix} \gamma_4 \\ 1 \end{pmatrix} \mathrm{e}^{\lambda_2 u}, \tag{4.107}$$

where

$$C_1 = \tfrac{N(0) - \gamma_4 J(0)}{\gamma_3 - \gamma_4}, \quad \gamma_3 = \left(c\lambda_0 + \sqrt{s^2\alpha_0^2 - 2\alpha_0\lambda_0 s^2 + c^2\lambda_0^2}\right)/(\alpha_0 s^2), \tag{4.108}$$

$$C_2 = \tfrac{\gamma_3 J(0) - N(0)}{\gamma_3 - \gamma_4}, \quad \gamma_4 = \left(c\lambda_0 - \sqrt{s^2\alpha_0^2 - 2\alpha_0\lambda_0 s^2 + c^2\lambda_0^2}\right)/(\alpha_0 s^2). \tag{4.109}$$

When $\alpha_0 > 2\lambda_0$, then $\Delta < 0$ and we have $\lambda_1 > 0$ and $\lambda_2 < 0$. We will choose C_1 and C_2 so that the solutions will not blow up at the boundaries. This will require discontinuity of $J(u)$ at zero, but does not imply $N(u)$ to be discontinuous at zero. For $u \geq 0$, we take $J(0^+) = N(0)/\gamma_4$ (i.e., $C_1 = 0$ and $C_2 = J(0^+)$), and for $u < 0$ we take $J(0^-) = N(0)/\gamma_3$ (i.e., $C_2 = 0$ and $C_1 = J(0^-)$). Then in this situation,

$$N(u) = \begin{cases} N(0)\mathrm{e}^{\lambda_1 u}, & u < 0, \\ N(0)\mathrm{e}^{\lambda_2 u}, & u \geq 0, \end{cases} \quad J(u) = \begin{cases} \frac{N(0)}{\gamma_3}\mathrm{e}^{\lambda_1 u}, & u < 0, \\ \frac{N(0)}{\gamma_4}\mathrm{e}^{\lambda_2 u} & u \geq 0, \end{cases} \tag{4.110}$$

and the total cell population is given by

$$T_1 = \int_{\mathbb{R}} N(u)du = \frac{N(0) \times \sqrt{s^2\alpha_0^2 - 2\alpha_0\lambda_0 s^2 + c^2\lambda_0^2}}{\alpha_0(\alpha_0 - 2\lambda_0)}. \tag{4.111}$$

Theorem 4.3.4. *For $\alpha_0 > 2\lambda_0$ and $\gamma_3 J(0^-) = \gamma_4 J(0^+) = N(0)$, travelling wave solutions exist and are explicitly given in the case of non diffusivity (with $\alpha_1 = 0$) by (4.110),*

$$F_1(u) = \begin{cases} F_1(0)\mathrm{e}^{\frac{\alpha N(0)}{c\lambda_1}(\mathrm{e}^{\lambda_1 u}-1)}, & u < 0, \\ F_1(0)\mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}(\mathrm{e}^{\lambda_2 u}-1)}, & u \geq 0, \end{cases} \tag{4.112}$$

and

$$S_1(u) = \begin{cases} \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) + \frac{\beta F_1(0)N(0)}{c}\int_u^0 \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_1}(\mathrm{e}^{\lambda_1 u_1}-1)+(\lambda_1-\gamma/c)u_1}du_1\right), & u < 0, \\ \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) - \frac{\beta F_1(0)N(0)}{c}\int_0^u \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}(\mathrm{e}^{\lambda_2 u_1}-1)+(\lambda_2-\gamma/c)u_1}du_1\right), & u \geq 0, \end{cases} \tag{4.113}$$

and in the case of diffusivity by (4.110), $F(x,t) = F_1(u)\mathrm{e}^{\alpha_1 t}$ and $S(x,t) = S_1(u)\mathrm{e}^{\alpha_1 t}$, where

$$F_1(u) = \begin{cases} F_1(0)I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_1/2)u}\right)\mathrm{e}^{-(c/(2D_F))u}/I_{k_1}(\alpha_{1,1}), & u < 0, \\ F_1(0)I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{(\lambda_2/2)u}\right)\mathrm{e}^{-(c/(2D_F))u}/I_{k_2}(\alpha_{2,2}), & u \geq 0, \end{cases} \tag{4.114}$$

and

$$S_1(u) = \begin{cases} b_1^1\mathrm{e}^{-\tau_1 u} + b_2^2\mathrm{e}^{\tau_2 u} - \dfrac{\beta N(0)F_1(0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_1}(\alpha_{1,1})}\int_u^0 \mathrm{e}^{\tau_6 u_1}I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_1/2)u_1}\right)du_1 \\ \qquad + \dfrac{\beta N(0)F_1(0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_1}(\alpha_{1,1})}\int_u^0 \mathrm{e}^{\tau_7 u_1}I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_1/2)u_1}\right)du_1, & u < 0, \\ b_1^1\mathrm{e}^{-\tau_1 u} + b_2^2\mathrm{e}^{\tau_2 u} + \dfrac{\beta N(0)F_1(0)\mathrm{e}^{-\tau_1 u}}{\tau_3 I_{k_2}(\alpha_{2,2})}\int_0^u \mathrm{e}^{\tau_4 u_1}I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{(\lambda_2/2)u_1}\right)du_1 \\ \qquad - \dfrac{\beta N(0)F_1(0)\mathrm{e}^{\tau_2 u}}{\tau_3 I_{k_2}(\alpha_{2,2})}\int_0^u \mathrm{e}^{\tau_5 u_1}I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{(\lambda_2/2)u_1}\right)du_1, & u \geq 0, \end{cases} \tag{4.115}$$

with $max(-\gamma, -c^2/(4D_F)) < \alpha_1 \leq 0$,

$$k_i = \frac{\sqrt{c^2+4\alpha_1 D_F}}{D_F|\lambda_i|}, \alpha_{i,i} = \frac{\sqrt{4N(0)\alpha D_F}}{D_F|\lambda_i|}, \tau_3 = \sqrt{c^2+4D_S(\alpha_1+\gamma)}, \tau_1 = \frac{c+\tau_3}{2D_S}, \tau_2 = \frac{-c+\tau_3}{2D_S},$$
$$\tau_4 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 + \lambda_2, \tau_5 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 + \lambda_2, \tau_6 = \frac{-c}{2D_F} + \frac{c}{D_S} + \tau_2 + \lambda_1,$$
$$\tau_7 = \frac{-c}{2D_F} + \frac{c}{D_S} - \tau_1 + \lambda_1, b_1^1 = \frac{\beta N(0) F_1(0)(\alpha_{1,1}/2)^{k_1}}{\tau_3(\lambda_1 k_1/2 + \tau_6)\Gamma(1+k_1) I_{k_1}(\alpha_{1,1})},$$
$$b_2^2 = \frac{-\beta N(0) F_1(0)(\alpha_{2,2}/2)^{k_2}}{\tau_3(\lambda_2 k_2/2 + \tau_5)\Gamma(1+k_2) I_{k_2}(\alpha_{2,2})}. \tag{4.116}$$

Proof. The solution $N(u)$ in (4.110) is positive, continuous and bounded.

Assuming non diffusivity and $\alpha_1 = 0$, (4.112)–(4.113) derive directly from the integration of (4.102) and (4.103), with $F_1(u)$ positive, continuous and bounded. We do not consider the case $\alpha_1 \neq 0$, otherwise

$$F_1(u) = \begin{cases} F_1(0) \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_1}(\mathrm{e}^{\lambda_1 u}-1)+\alpha_1 u}, & u < 0, \\ F_1(0) \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}(\mathrm{e}^{\lambda_2 u}-1)+\alpha_1 u}, & u \geq 0, \end{cases} \tag{4.117}$$

will blow up at $-\infty$ if $\alpha_1 < 0$, or at ∞ if $\alpha_1 > 0$. Now we study the positivity and boundedness of $S_1(u)$. We assume $u \geq 0$ and we let

$$m(u) = \mathrm{e}^{-(\gamma/c)u} S_1(u) = S_1(0) - \frac{\beta F_1(0) N(0)}{c} \int_0^u \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}(\mathrm{e}^{\lambda_2 u_1}-1)+(\lambda_2-\gamma/c)u_1} du_1. \tag{4.118}$$

Then, as $u \to \infty$, there exist $u_2 > 0$ such that

$$m(u) \approx S_1(0) - \frac{\beta F_1(0) N(0)}{c} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}} \left[\int_0^{u_2} \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}\mathrm{e}^{\lambda_2 u_1}+(\lambda_2-\gamma/c)u_1} du_1 + \int_{u_2}^u \mathrm{e}^{(\lambda_2-\gamma/c)u_1} du_1 \right]. \tag{4.119}$$

(This comes from the fact that $\mathrm{e}^{(\alpha N(0)/(c\lambda_2))\mathrm{e}^{\lambda_2 u}} \approx 1$ as $u \to \infty$). Therefore, as $u \to \infty$,

$$m(u) \approx m(u_2) - \frac{\beta F_1(0) N(0)}{c} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}} \left(\frac{\mathrm{e}^{(\lambda_2-\gamma/c)u} - \mathrm{e}^{(\lambda_2-\gamma/c)u_2}}{\lambda_2 - \gamma/c} \right), \tag{4.120}$$
$$\approx m(u_2) - \frac{\beta F_1(0) N(0)}{\gamma - c\lambda_2} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}+(\lambda_2-\gamma/c)u_2} + \frac{\beta F_1(0) N(0)}{\gamma - c\lambda_2} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}} \mathrm{e}^{(\lambda_2-\gamma/c)u}. \tag{4.121}$$

For $S_1(0)$ given by

$$S_1(0) = \frac{\beta F_1(0) N(0)}{c} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}} \int_0^{u_2} \mathrm{e}^{\frac{\alpha N(0)}{c\lambda_2}\mathrm{e}^{\lambda_2 u_1}+(\lambda_2-\gamma/c)u_1} du_1 + \frac{\beta F_1(0) N(0)}{\gamma - c\lambda_2} \mathrm{e}^{-\frac{\alpha N(0)}{c\lambda_2}+(\lambda_2-\gamma/c)u_2}, \tag{4.122}$$

the functions $m(u)$ and $S_1(u)$ converge to zero as $u \to \infty$. As a result, $m(u)$ and $S_1(u)$ are positive, given that $m(u)$ is decreasing. We have therefore proved the existence of $S_1(0)$.

When $u < 0$, we note that $S_1(u)$ is positive and bounded. In fact, from (4.113),

$$\begin{aligned} 0 < S_1(u) &\leq \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) + \frac{\beta F_1(0)N(0)}{c}\int_u^0 \mathrm{e}^{-\frac{\gamma}{c}u_1}du_1\right), && (4.123)\\ &\leq S_1(0)\mathrm{e}^{\frac{\gamma}{c}u} + \frac{\beta F_1(0)N(0)}{\gamma}\left(1-\mathrm{e}^{\frac{\gamma}{c}u}\right), && (4.124)\\ &< S_1(0) + \frac{\beta F_1(0)N(0)}{\gamma}. && (4.125)\end{aligned}$$

Thus for all real u, $S_1(u)$ is positive, continuous and bounded. Non-diffusing travelling wave solutions exist.

In the case of diffusivity, substituting (4.110) into (4.102) and integrating, we obtain

$$F_1(u) = \begin{cases} \left[\alpha_1^1 I_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_1/2)u}\right) + \alpha_2^1 K_{k_1}\left(\alpha_{1,1}\mathrm{e}^{(\lambda_1/2)u}\right)\right]\mathrm{e}^{-(c/(2D_F))u}, & u < 0,\\ \left[\alpha_1^2 I_{k_2}\left(\alpha_{2,2}\mathrm{e}^{(\lambda_2/2)u}\right) + \alpha_2^2 K_{k_2}\left(\alpha_{2,2}\mathrm{e}^{(\lambda_2/2)u}\right)\right]\mathrm{e}^{-(c/(2D_F))u}, & u \geq 0, \end{cases} \quad (4.126)$$

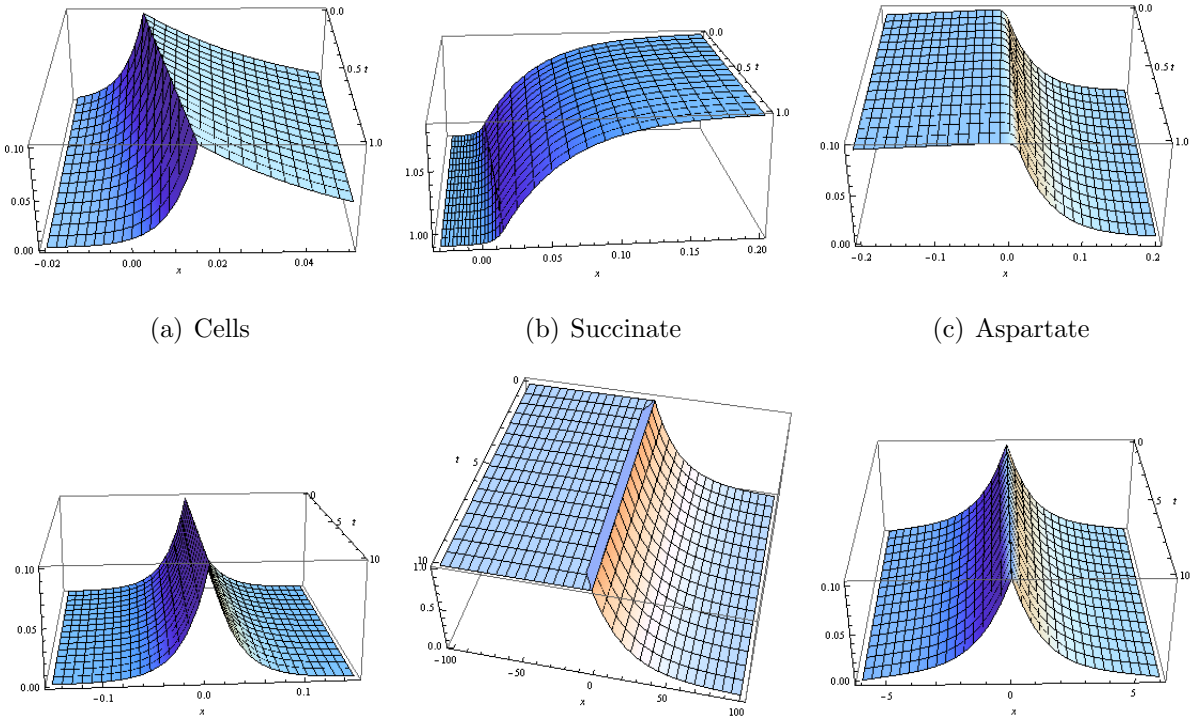
where k_i and $\alpha_{i,i}$ are given in (4.116), and α_j^i are integration constants. We have proved (Tchepmo Djomegni and Govinder, 2014b) the boundedness of (4.126), with $\alpha_2^1 = \alpha_2^2 = 0$. The continuity of $F_1(u)$ at zero gives $\alpha_1^1 = F_1(0)/I_{k_1}(\alpha_{1,1})$ and $\alpha_1^2 = F_1(0)/I_{k_2}(\alpha_{2,2})$. Then $F_1(u)$ in (4.114) is positive, continuous and bounded.

Substituting (4.110) and (4.114) into (4.103), and integrating, one obtains (4.115). We also proved (Tchepmo Djomegni and Govinder, 2014b) the boundedness and positivity of (4.115), with b_1^1 and b_2^2 given in (4.116). Thus, $F(x,t) = F_1(u)\mathrm{e}^{\alpha_1 t}$ and $S(x,t) = S_1(u)\mathrm{e}^{\alpha_1 t}$ are positive, continuous and bounded. Generalized diffusing travelling wave solutions exist. □

The solutions of the above theorem are illustrated in Figure 4.4. Under the same experimental settings, we observe a very slow distribution (of cells and substrates) when substrates are not allowed to diffuse, requiring a large wave speed.

When $\alpha_0 < 2\lambda_0$, $\Delta > 0$ and the eigenvalues have the same sign. To avoid oscillations about the origin, the wave speed should satisfy the constraint

$$s\sqrt{\alpha_0(2\lambda_0 - \alpha_0)/\lambda_0^2} \leq c < s, \quad (4.127)$$



(a) Cells (b) Succinate (c) Aspartate

(d) Cells (e) Succinate (f) Aspartate

Figure 4.4: Cell and substrates distribution in the absence of chemotaxis with constant growth rate $\alpha_0 > 2\lambda_0$ (we considered the biological settings (Xue et al., 2011): $D_F = D_S = 9 \times 10^{-5} cm^2/sec$, $s = 20\mu m/sec$, $\lambda_0 = 0.1/sec$, $\alpha = \beta = 1000/hour$, $\gamma = 18/hour$, $\alpha_0 = 0.9$, $N(0) = 0.1$, $F_1(0) = 1$, and $c = 15\mu m/sec$ in the case of non-diffusivity, and $c = 1.5mm/hour$ in the case of diffusivity). The first row represents the non-diffusing distribution, and the second row represents the diffusing distribution.

with $\lambda_0 \neq \alpha_0$ (from (4.106). If $\alpha_0 < \lambda_0$, λ_1 and λ_2 in (4.106) are both negative, whereas if $\alpha_0 > \lambda_0$ they are both positive. Therefore, cells aggregate only in one region (either in the plane $u \geq 0$, or in the plane $u \leq 0$) depending on the value of α_0 and λ_0. We previously studied the existence of travelling wave solutions for the form of $N(u)$ given in (4.107) (se §4.3.1 in the case where $\alpha_0 \neq 2\lambda_0$). Thus, travelling wave solutions exist with minimum speed $c^* = s\sqrt{\alpha_0(2\lambda_0 - \alpha_0)/\lambda_0^2}$.

Nutrient dependant cell growth rate $h(F) = \beta_0(F - F_c)$

In this case, (4.37)–(4.40) becomes

$$\begin{aligned} N' &= f_3 N + g_3 J + \frac{\beta_0 c}{s^2 - c^2} F_1 N + \frac{\beta_0}{s^2 - c^2} F_1 J, && (4.128)\\ J' &= f_4 N + c g_3 J + \frac{\beta_0 s^2}{s^2 - c^2} F_1 N + \frac{\beta_0 c}{s^2 - c^2} F_1 J, && (4.129)\\ -c F_1' &= D_F F_1'' - \alpha F_1 N, && (4.130)\\ -c S_1' &= D_S S_1'' + \beta F_1 N - \gamma S_1, && (4.131) \end{aligned}$$

where

$$f_3 = \frac{-\beta_0 c F_c}{s^2 - c^2}, \quad g_3 = \frac{-(\beta_0 F_c + 2\lambda_0)}{s^2 - c^2}, \quad f_4 = \frac{-\beta_0 s^2 F_c}{s^2 - c^2}. \tag{4.132}$$

We assume non diffusivity (i.e., $D_S = D_F = 0$) and we let $f(N, J) = F_1$, where F_1 is given by (see (4.91))

$$F_1(u) = -F_c \times W\left(\frac{-F_{00}}{F_c} \exp\left(\frac{\alpha(cN(u) - J(u))}{\beta_0 c F_c}\right)\right), \tag{4.133}$$

with

$$F_{00} = F_1(0) \exp\left(-\frac{\alpha(cN(0) - J(0)) + \beta_0 c F_1(0))}{\beta_0 c F_c}\right). \tag{4.134}$$

Then (4.128)–(4.129) becomes the autonomous system

$$\begin{aligned} N' &= f_3 N + g_3 J + \frac{\beta_0 c}{s^2 - c^2} N f(N, J) + \frac{\beta_0}{s^2 - c^2} J f(N, J), && (4.135)\\ J' &= f_4 N + c g_3 J + \frac{\beta_0 s^2}{s^2 - c^2} N f(N, J) + \frac{\beta_0 c}{s^2 - c^2} J f(N, J). && (4.136) \end{aligned}$$

This system admits two possible steady states: $(0, 0)$ and $(0, J^*)$, where J^* is given by

$$J^* = \frac{\beta_0 c F_c}{\alpha} \log\left(\frac{\beta_0 F_{00}}{\beta_0 F_c + 2\lambda_0} \exp(\frac{\beta_0 F_c + 2\lambda_0}{\beta_0 F_c})\right). \tag{4.137}$$

The linearised system associated with (4.135)–(4.136) around the origin is given by

$$\begin{aligned} N' &= (f_3 + \frac{\beta_0 c}{s^2 - c^2} f(0, 0))N + (g_3 + \frac{\beta_0}{s^2 - c^2} f(0, 0))J, && (4.138)\\ J' &= (f_4 + \frac{\beta_0 s^2}{s^2 - c^2} f(0, 0))N + c(g_3 + \frac{\beta_0}{s^2 - c^2} f(0, 0))J, && (4.139) \end{aligned}$$

the determinant of the corresponding Jacobian matrix by

$$\Delta_2 = \frac{(\beta_0 F_c - \beta_0 f(0, 0))\,(\beta_0 f(0, 0) - \beta_0 F_c - 2\lambda_0)}{s^2 - c^2}, \tag{4.140}$$

and the associated eigenvalues by

$$\lambda_3 = \frac{-c(\beta_0 F_c + \lambda_0 - \beta_0 f(0,0)) - \sqrt{s^2(\beta_0 F_c + \lambda_0 - \beta_0 f(0,0))^2 - \lambda_0^2(s^2 - c^2)}}{s^2 - c^2}, \tag{4.141}$$

and

$$\lambda_4 = \frac{-c(\beta_0 F_c + \lambda_0 - \beta_0 f(0,0)) + \sqrt{s^2(\beta_0 F_c + \lambda_0 - \beta_0 f(0,0))^2 - \lambda_0^2(s^2 - c^2)}}{s^2 - c^2}, \tag{4.142}$$

provided $s^2(\beta_0 F_c + \lambda_0 - \beta_0 f(0,0))^2 - \lambda_0^2(s^2 - c^2) \geq 0$, where $f(0,0) = -F_c \times W(-F_{00}/F_c)$.

Given that $F_c > f(0,0)$, then $\Delta_2 < 0$ and the origin is a saddle point (with $\lambda_3 < 0$ and $\lambda_4 > 0$). As a result, $(0, J^*)$ is unstable.The system is still tractable, we can choose the initial conditions so that only the stable manifold will control the behaviour of the system in a half plane (see Figure 4.5). Then the solutions $N(u)$ and $J(u)$ will converge to zero in that plane; as a result, $F_1(u)$ will converge as well.

We analyse the behaviour of $S_1(u)$ as $u \to \pm\infty$. For given $N(u)$ and $F_1(u)$, we note that $S_1(u)$ is explicitly given by

$$S_1(u) = \begin{cases} \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) + \frac{\beta}{c}\int_u^0 \mathrm{e}^{-\frac{\gamma}{c}u} F_1(u_1)N(u_1)du_1\right), & u < 0, \\ \mathrm{e}^{\frac{\gamma}{c}u}\left(S_1(0) - \frac{\beta}{c}\int_0^u \mathrm{e}^{-\frac{\gamma}{c}u} F_1(u_1)N(u_1)du_1\right), & u \geq 0. \end{cases} \tag{4.143}$$

For the half plane $u \geq 0$, we choose the initial conditions so that λ_3 controls the stability of $N(u)$ and $J(u)$. In this case, $N(u)$ and $J(u)$ converge to zero as $u \to \infty$. For given $N(u)$ and $J(u)$ positive and continuous, the solution $F_1(u)$ given by (4.162) is positive, continuous and bounded. There exist a constant $C_1 > 0$ such that as $u \to \infty$,

$$N(u) \approx C_1 \mathrm{e}^{\lambda_3 u}. \tag{4.144}$$

(We note that the linearized system dominates the behaviour of $N(u)$ and $J(u)$ around the steady state, given that none of λ_3 or λ_4 is zero). Letting

$$n(u) = \mathrm{e}^{-(\gamma/c)u} S_1(u) = S_1(0) - \frac{\beta}{c}\int_0^u \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1, \tag{4.145}$$

as $u \to \infty$, there exist $u_2 > 0$ such that

$$\begin{aligned} n(u) &\approx S_1(0) - \frac{\beta}{c}\int_0^{u_2} \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1 - \frac{\beta F_+ C_1}{c}\int_{u_2}^{u} \mathrm{e}^{(\lambda_3-\gamma/c)u_1}du_1, \quad (4.146)\\ &\approx n(u_2) - \frac{\beta F_+ C_1}{c}\left(\frac{\mathrm{e}^{(\lambda_3-\gamma/c)u} - \mathrm{e}^{(\lambda_3-\gamma/c)u_2}}{\lambda_3 - \gamma/c}\right), \quad (4.147)\\ &\approx n(u_2) - \frac{\beta F_+ C_1}{\gamma - c\lambda_3}\mathrm{e}^{(\lambda_3-\gamma/c)u_2} + \frac{\beta F_+ C_1}{\gamma - c\lambda_3}\mathrm{e}^{(\lambda_3-\gamma/c)u}, \quad (4.148)\end{aligned}$$

where $F_+ = \lim_{u\to\infty} F_1(u)$. For $S_1(0)$ given by

$$S_1(0) = \frac{\beta}{c}\int_0^{u_2} \mathrm{e}^{-\frac{\gamma}{c}u_1} F_1(u_1)N(u_1)du_1 + \frac{\beta F_+ C_1}{\gamma - c\lambda_3}\mathrm{e}^{(\lambda_3-\gamma/c)u_2}, \quad (4.149)$$

the functions $n(u)$ and $S_1(u)$ converge to zero as $u \to \infty$. Consequently, they are both positive (given that $n(u)$ is decreasing).

For the half plane $u \leq 0$, we choose the initial conditions so that λ_4 controls the stability of $N(u)$ and $J(u)$. In this case, the convergence of and boundedness of $N(u)$, $J(u)$ and $F_1(u)$ is established, with $F_1(u)$ positive. As a result, $S_1(u)$ is positive and bounded. Due to the nonlinearity in (4.128)–(4.129), we cannot prove the positivity of $N(u)$.

The case of diffusivity is more intricate. Equation (4.130) is a second order linear equation in F_1 with non constant coefficients. Its solutions depend on the form of $N(u)$, but the nonlinearity in (4.128)–(4.129) does not allow us to find an explicit (or implicit) form of $N(u)$. Moreover, writing

$$F_1(u) = F_1(0) + \int_0^u \mathrm{e}^{-\frac{c}{D_F}u_1}\left(F_1'(0) + \frac{1}{D_F(s^2-c^2)}\int_0^{u_1} \mathrm{e}^{\frac{c}{D_F}u_2}(F_c N - cN' + J')(u_2)du_2\right)du_1, \quad (4.150)$$

results in (4.128)–(4.129) becoming a nonlinear non-autonomous differential integral system in $N(u)$ and $J(u)$ (we obtained (4.150) by solving (4.128)–(4.129) in $F_1 N$, then substituting the result into (4.130) and integrating). The analysis in this situation is complicated. However, the system is tractable when we only allow the signal to diffuse. In fact, integrating (4.131) for $S_1(u)$ (with $D_S \neq 0$), one obtains

$$S_1(u) = \delta_1^1 \mathrm{e}^{-\tau_1 u} + \delta_1^2 \mathrm{e}^{\tau_2 u} + \frac{\beta \mathrm{e}^{-\tau_1 u}}{\tau_3}\int_0^u \mathrm{e}^{\tau_1 u_1} F_1(u_1)N(u_1)du_1 - \frac{\beta \mathrm{e}^{\tau_2 u}}{\tau_3}\int_0^u \mathrm{e}^{-\tau_2 u_1} F_1(u_1)N(u_1)du_1, \quad (4.151)$$

where $\tau_3 = \sqrt{c^2 + 4\gamma D_S}$, $\tau_1 = (c + \tau_3)/(2D_S)$, $\tau_2 = (-c + \tau_3)/(2D_S)$. For $D_F = 0$, we have earlier shown the boundedness of $N(u)$ and $F_1(u)$. Under the same initial conditions, we assume the positivity of $N(u)$, and we let

$$n_1(u) = \delta_1^2 - \frac{\beta}{\tau_3}\int_0^u \mathrm{e}^{-\tau_2 u_1} F_1(u_1)N(u_1)du_1, \quad n_2(u) = \delta_1^1 - \frac{\beta}{\tau_3}\int_u^0 \mathrm{e}^{\tau_1 u_1} F_1(u_1)N(u_1)du_1. \tag{4.152}$$

For $u \geq 0$, there exist $u_2 > 0$ and $C_1 > 0$ such that as $u \to \infty$ (see (4.146)),

$$\begin{aligned} n_1(u) &\approx \delta_1^2 - \frac{\beta}{\tau_3}\int_0^{u_2} \mathrm{e}^{-\tau_2 u_1} F_1(u_1)N(u_1)du_1 - \frac{\beta F_+ C_1}{\tau_3}\int_{u_2}^u \mathrm{e}^{(\lambda_3-\tau_2)u_1}du_1, && (4.153)\\ &\approx n_1(u_2) - \frac{\beta F_+ C_1}{\tau_3}\left(\frac{\mathrm{e}^{(\lambda_3-\tau_2)u} - \mathrm{e}^{(\lambda_3-\tau_2)u_2}}{\lambda_3 - \tau_2}\right), && (4.154)\\ &\approx n_1(u_2) - \frac{\beta F_+ C_1}{\tau_3(\tau_2-\lambda_3)}\mathrm{e}^{(\lambda_3-\tau_2)u_2} + \frac{\beta F_+ C_1}{\tau_3(\tau_2-\lambda_3)}\mathrm{e}^{(\lambda_3-\tau_2)u}. && (4.155)\end{aligned}$$

For δ_1^2 given by

$$\delta_1^2 = \frac{\beta}{\tau_3}\int_0^{u_2} \mathrm{e}^{-\tau_2 u_1} F_1(u_1)N(u_1)du_1 + \frac{\beta F_+ C_1}{\tau_3(\tau_2-\lambda_3)}\mathrm{e}^{(\lambda_3-\tau_2)u_2}, \tag{4.156}$$

the functions $n_1(u)$ and $\mathrm{e}^{\tau_2 u}n_1(u)$ converge to zero as $u \to \infty$. Therefore, they are both positive, given that $n_1(u)$ is decreasing. Since $F_1(u)$ and $N(u)$ are bounded, then $\mathrm{e}^{-\tau_1 u}\int_0^u \mathrm{e}^{\tau_1 u_1} F_1(u_1)N(u_1)du_1$ is also bounded. Consequently, $S_1(u)$ is positive (for $\delta_1^1 > 0$), continuous and bounded.

Likewise, for $u \leq 0$, there exist $u_3 < 0$ and $C_2 > 0$ such that, as $u \to -\infty$,

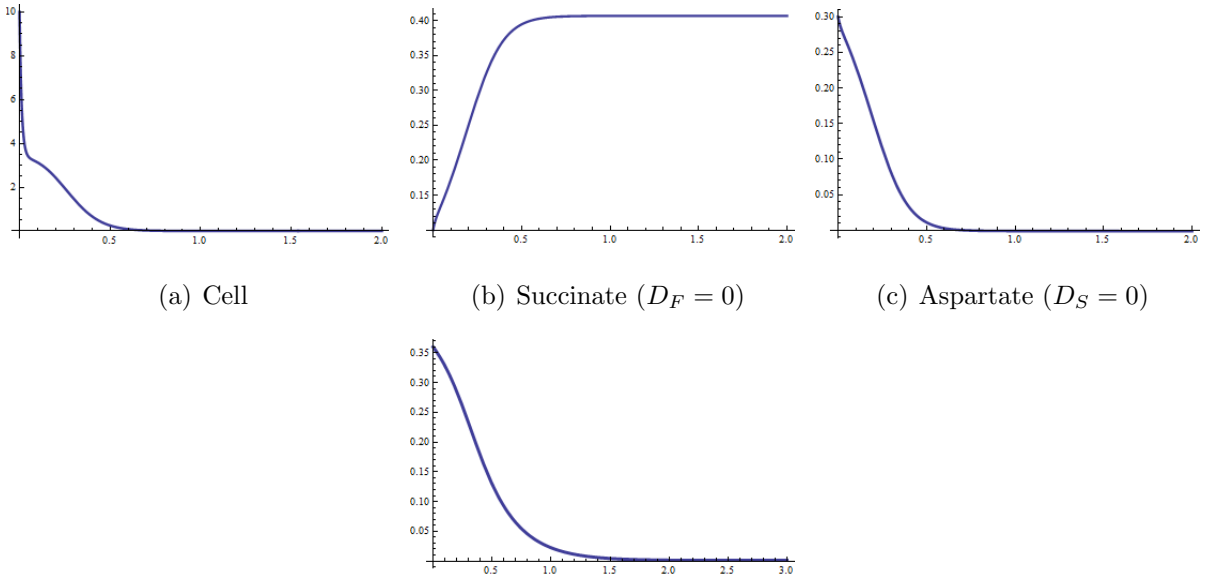
$$\begin{aligned} n_2(u) &\approx \delta_1^1 - \frac{\beta}{\tau_3}\int_{u_3}^0 \mathrm{e}^{\tau_1 u_1} F_1(u_1)N(u_1)du_1 - \frac{\beta F_- C_2}{\tau_3}\int_u^{u_3} \mathrm{e}^{(\lambda_4+\tau_1)u_1}du_1, && (4.157)\\ &\approx n_2(u_3) - \frac{\beta F_- C_2}{\tau_3}\left(\frac{\mathrm{e}^{(\lambda_4+\tau_1)u_3} - \mathrm{e}^{(\lambda_4+\tau_1)u}}{\lambda_4 + \tau_1}\right), && (4.158)\\ &\approx n_2(u_3) - \frac{\beta F_- C_2}{\tau_3(\tau_1+\lambda_4)}\mathrm{e}^{(\lambda_4+\tau_1)u_2} + \frac{\beta F_- C_2}{\tau_3(\tau_1+\lambda_4)}\mathrm{e}^{(\lambda_4+\tau_1)u}. && (4.159)\end{aligned}$$

For δ_1^1 given by

$$\delta_1^1 = \frac{\beta}{\tau_3}\int_{u_3}^0 \mathrm{e}^{\tau_1 u_1} F_1(u_1)N(u_1)du_1 + \frac{\beta F_- C_2}{\tau_3(\tau_1+\lambda_4)}\mathrm{e}^{(\lambda_4+\tau_1)u_2}, \tag{4.160}$$

the functions $n_2(u)$ and $\mathrm{e}^{-\tau_1 u}n_2(u)$ converge to zero as $u \to -\infty$, and $n_2(u)$ is positive, since $n_2(u)$ is decreasing. We note that the function $\mathrm{e}^{\tau_2 u}\int_u^0 \mathrm{e}^{-\tau_2 u_1} F_1(u_1)N(u_1)du_1$ is bounded, given that $F_1(u)$ and $N(u)$ are bounded. As a result, $S_1(u)$ is positive (for $\delta_1^2 > 0$) and converges to zero as $u \to -\infty$.

Putting these results together, we formulate the following conjecture.



(a) Cell (b) Succinate ($D_F = 0$) (c) Aspartate ($D_S = 0$)

(d) Aspartate ($D_S \neq 0$)

Figure 4.5: Cell and substrates distribution in the absence of chemotaxis with linear growth rate (we used $D_F = D_S = 4.2 \times 10^{-5} cm^2/sec$, $s = 20\mu m/sec$, $\lambda_0 = 0.5/sec$, $\alpha = \beta = 0.2/sec$, $\beta_0 = 0.4$, $N(0) = 10$, $F_1(0) = 0.1$, $F_c = 0.1$, $\gamma = 5/hour$, $c = 15\mu/sec$). We note that $F_c > f(0,0)$, with $f(0,0) = 0.007488$.

Conjecture 1. *For $D_F = 0$, travelling wave solutions $N(u)$, $F_1(u)$ and $S_1(u)$ exist (only in a half plane), with the speed of the wave c restricted via*

$$s^2(\beta_0 F_c + \lambda_0 + \beta_0 F_c \times W(-F_{00}/F_c))^2 - \lambda_0^2(s^2 - c^2) \geq 0. \tag{4.161}$$

Moreover, for given $N(u)$ and $J(u)$, $F_1(u)$ is given by

$$F_1(u) = -F_c \times W\left(\frac{-F_{00}}{F_c} \exp\left(\frac{\alpha(cN(u) - J(u))}{\beta_0 c F_c}\right)\right), \tag{4.162}$$

and $S_1(u)$ by (4.143) and (4.151) in both cases of non diffusivity and diffusivity, respectively. ■

An example of the solutions in Conjecture 1 are illustrated in Figure 4.5. We observe that the signal aspartate is highly concentrated (or produced) in the region where most of the cells are confined. The large value of $N(0)$ that we chose to plot the solutions is justified by the cell growth ($h(F) = \beta_0(F(u) - F_c) \geq 0$); death does not occur.

4.4 Discussion

Travelling solutions have always played an important role in understanding physical phenomena. In cell biology, it has helped to study the collective migration of cells, to understand the processes of wound healing, tumor invasion and tumor-immune interaction dynamics (Harley et al., 2004; Maini et al., 2004). In our study, we investigated in a chemotaxis model, the formation of bands of cells moving with constant speed. This was achieved via the study of the existence of travelling wave solutions. The model has been inspired by previous experimental results in (Budrene and Berg, 1991, 1995; Woodward et al., 1995). Given that travelling waves have mainly been analysed from the macroscopic point of view, we focused on the microscale level. We specifically looked at the effect of the cell growth and unbiased turning rate on the behaviour of the system, and at the fluctuation of information from a microscale perspective. Unlike previous approaches and motivated by (Budrene and Berg, 1995), we assumed that cells grew on nutrients only, and we allowed for the diffusion of substrates. We used the Lie symmetry analysis to produce a wider class of travelling wave solutions (a damping solution) than the standard *ansatz*. This is in line with our previous findings on the interplay between stability analysis and group theory (Tchepmo Djomegni and Govinder, 2014a).

In the case of high chemotactic sensitivity, we assumed that the aspartate concentration distributes with a single peak. This assumption was motivated by the results of the numerical investigation of Xue et al., 2011. Motivated by the experiment of Budrene et Berg (1995) in which it was observed that cells grew at a constant rate over a certain concentration of succinate, we considered first the scenario of constant cell growth rate α_0. For $\alpha_0 = 2\lambda_0$ (λ_0 being the unbiased turning rate), we observe that the speed and the width of the bands decrease as α_0 increases, and the distribution of succinate and aspartate changes significantly as α_0 changes. This agrees with experimental observations (Budrene and Berg, 1995) in which the proliferation of cells creates a large fluctuation in the local concentration of aspartate, which causes the formation of new aggregates. The new aggregates destabilize the swarm ring (the main band) and attract cells (Budrene and Berg, 1995). Recall that this situation is mathematically equivalent to the non starvation case (Xue et al., 2011; Tchepmo Djomegni and Govinder, 2014b) in which

cells consume succinate (the nutrient) only. The case $\alpha_0 \neq 2\lambda_0$ has also been analysed, with explicit solutions being demonstrated. Travelling wave solutions have been obtained in both cases of diffusivity and non diffusivity.

For the case of linear growth rate, we were able, in spite of the complexity of the model, to combine a dynamical system analysis with analytic methods to integrate the system and explore the behaviour of the solutions at the boundaries. This is in contract to Franz et al. (2014) who did not investigate the existence of travelling waves in the case of high chemotactic sensitivity (though they assumed a signal dependence growth rate). We showed that travelling wave solutions are not possible.

In the absence of chemotaxis (where $\chi = 0$ and $\lambda(\zeta) = \lambda_0 = \text{constant}$), travelling wave solutions have been demonstrated. This is an extension of Xue et al's (2011) results, wherein it was proved that the discontinuity at zero of the turning rate function $\lambda(\zeta)$ was a necessary condition for the existence of travelling wave solutions (with no cell proliferation). For constant growth rate $\alpha_0 > 2\lambda_0$, we notice that growth dominates the behaviour of cells in the band. The total cell population T_1 given by (4.111), increases as α_0 is small. Here, most of the new born cells remain in the band. However, as α_0 becomes large, T_1 decreases. This is due to the local depletion of substrates, cells move (randomly) towards regions with higher concentrations. When $\alpha_0 < 2\lambda_0$ (with $\alpha_0 \neq \lambda_0$), we obtained a minimum speed for the band, given by $c^* = s\sqrt{\alpha_0(2\lambda_0 - \alpha_0)/\lambda_0^2}$. For $\alpha_0 < \lambda_0$, c^* increases as λ_0 is small, and decreases as λ_0 becomes large. The constant change of direction of cells (depicting their inability in decision making at the individual level) affects their collective behaviour significantly. For $\alpha_0 > \lambda_0$, c^* increases as λ_0 is large, and decreases as λ_0 is small. We note that cells aggregate only in one region when $\alpha_0 \leq 2\lambda_0$.

In the case of linear growth rate, we obtained travelling wave solutioms with very restrictive conditions on the the wave speed and initial conditions (see (4.161)). This result was expected given that cells move randomly; they cannot detect extracellular signalling. Therefore, special experimental conditions should be established in order to foster a collective behaviour. We note that Franz et al. (2014) obtained travelling wave solutions gathering in one region, and moving with minimal speed $c^* = \sqrt{(2\lambda_0 - 1 + S_c)(1 - S_c)/\lambda_0^2}$.

In the light of our investigation, we observe, in comparison to the literature, significant changes

(loss, creation or fluctuation) of information while looking at a microscale angle to understand macro behaviours. In fact, unlike Keller and Segel's (1970,1971a) results, we found that a singularity in the chemotactic coefficient is not a necessary condition for the existence of travelling waves. This result has also been confirmed elsewhere (Xue et al., 2011). Moreover, we found a situation (case $\alpha_0 = 2\lambda_0$) in which the wave speed decreases as the cell growth rate α_0 increases. Furthermore, zero growth does not necessarily cause the wave speed, c, to decrease (refer in §4.3.1 and §4.3.2 to the case $\alpha_0 < 2\lambda_0$). This is in contrast to Lapidus et al. (1978) finding, in which the zero cell growth decreases the speed of the wave but does not prevent the cells to aggregate.

In the mathematical analysis of our model, intracellular dynamics variables were not represented explicitly, though they play a central role in the response of cells to extracellular signaling. For future work, we will consider higher dimensional spaces and will investigate the geometric pattern of the band.

Chapter 5

Conclusion

In this thesis we investigated the existence of travelling wave solutions of a one-dimensional microscopic model for chemotaxis. The wave motion in our context, describes the collective movement of cells (as a band), usually caused in response to extracellular signaling. We considered some important biologically factors such as cell growth, diffusion of substrates and degradation of the chemoattractant excreted by cells. We studied their effect on the behaviour of the solutions, and we presented their biological implications. We demonstrated in the limit cases of high and absence of sensitivity to stimuli, the existence of travelling wave solutions. A general form of solutions are provided in most of the cases, and for the first time when the diffusion process is allowed. The results obtained in this thesis contribute positively to the existing literature on chemotaxis. Indeed, they can be used to obtain solutions of many systems in modeling involving diffusion. They can also be used to investigate the asymptotic behaviour of the solutions of second order ODEs when they are unknown. We underline that the general solutions obtained in the analysis are studied in order to provide biologically relevant solutions.

The mathematical analysis of travelling wave solutions in the case of weak and of increasing chemotactic sensitivity (from a microscopic perspective), has not been given much consideration in the literature. This is due, in most cases, to the formulation of the cell turning rate function in one-dimensional space. However, it is important to note that the fluctuation of the chemotactic sensitivity is an important factor to consider. Its plays a vital role in wound healing, cancer treatment and drug delivery processes [22, 50, 51]. For future work, we will

extend the investigation to higher dimensional spaces in order to gain a better understanding of the chemotactic process. We also intend to study the geometric pattern of the bands of cells.

Bibliography

[1] J. Adler, Chemotaxis in bacteria, Science 153 (1966) 708-716.

[2] J. Adler, Effect of amino acids and oxygen on chemotaxis in escherichia coli, J. Bacteriol. 92 (1966) 121-129.

[3] J. Adler, Chemotaxis in bacteria, Annu. Rev. Biochem. 44 (1975) 341-356.

[4] W. Alt, Biased random walk models for chemotaxis and related diffusion approximations, J. Math. Biol. 9 (1980) 147-177.

[5] B. Bak, C. Tang, K. Wiesenfeld, Self-organized criticality: an explanation of $1/f$ noise, Phys. Rev. Lett. 59 (1987) 381-384.

[6] N. Barkai, S. Leibler, Robusness in simple biochemical networks, Nature 387 (1997) 913-917.

[7] J. M. Berg, J. L. Tymoczko, L. Stryer, Biochemistry 5th ed. (New York, 2002).

[8] M. Beyerinck, Ueber Spirillum desulfuricans als Ursache von Sulfatreduction, Zentralbl. Bakteriol. Parasitenkd. 1 (1895) 1-9.

[9] Y. Blat, M. J. Eisenbach, Tar-dependent and independent pattern formation by salmonella typhimurium, Bacteriology 177 (1995) 1683-1691.

[10] G. W. Bluman, S. C. Anco, Symmetry and integration methods for differential equations, Appl. Math. Sci., Springer-Verlag, New York,154 (2002).

[11] M. Brenner, L. Levitor, E. Brudrene, Physical mechanisms for chemotactic pattern formation by bacteria, Biophys. J. 74 (1998) 1677-1693.

[12] H. Brüssow, C. Canchaya, W. D. Hardt, Phages and the evolution of bacterial pathogens: from genomic rearrangements to lysogenic conversion, Microbiol. Mol. Biol. Rev. 68(3) (2004) 560-602.

[13] E. O. Budrene, H. C. Berg, Complex patterns formed by motile cells of escherichia coli, Nature 349 (1991) 630-633.

[14] E. O. Budrene, H. C. Berg, Dynamics of formation of symmetrical patterns by chemotactic bacteria, Nature 376 (1995) 49-53.

[15] J. Carr, Applications of Centre Manifold Theory, Springer-Verlag, New York (1981).

[16] P. A. Clarkson, Nonclassical symmetry reductions for the Boussinesq equation, Chaos, Solitons & Fractals 5 (1995) 2261-2301.

[17] P. Cluzel, M. Surette and S. Leibler, An ultrasensitive bacterial motor revealed by monitoring signaling proteins in single cells, Science 287(5458) (2000) 1652-1655.

[18] J. S. Condeelis, J. B. Wyckoff, M. Bailly, R. Pestell, D. Lawrence, J. Backer, J. E. Segall, Lamellipodia in invasion, Semin. Cancer Biol. 11 (2001) 119–128.

[19] R. M. Corless, G. H. Gonnet, D. E. Hare, D. J. Jeffrey, D. E. Knuth, On the Lamber W function, Adv. Comput. Math. 5 (1996) 329-359.

[20] J. Dallon, J.A. Sherratt, A mathematical model for fibroblast and collagen orientation, Bull. Math. Biol. 60 (1998) 101-130.

[21] P. Devreotes, C. Janetopoulos, Eukaryotic chemotaxis: distinctions between directional sensing and polarization, J. Biol. Chem. 278 (2003) 20445–20448.

[22] R. E. Durand, Chemosensitivity testing in V79 spheroids: drug delivery and cellular microenvironment, J Natl. Cancer Inst. 77(1) (1986) 247-52.

[23] M. Eisenbach, J. W. Lengeler, Chemotaxis, Imperial College Press, London, (2004).

[24] N. Elliott, T. Lee, L. You, F. Yuan, Proliferation behaviour of *E coli* in a three-dimensional in vitro tumor, Integrative Biology 3 (2011) 696-705.

[25] T. Engelmann, Neue methode zur untersuchung der sauerstoffaussheidung pflanzlicher und thierischer organismen, Pflugers Arch. Gesamte Physiol. 25 (1881a) 285-292.

[26] T. Engelmann, Zur biologie der schizomyceten, Pflugers Arch. Gesamte Physiol. 26 (1881b) 537-545.

[27] F. Entschladen, K. S. Zanker, Cell migration: signalling and mechanisms, Transl. Res. Biomed. Basel 2 (2002) 163-172.

[28] R. Erban, H. G. Othmer, From individual to collective behavior in bacterial chemotaxis, SIAM J. Appl. Math. 65 (2004) 361-391.

[29] R. Erban, H. G. Othmer, From signal transduction to spacial pattern formation in E. coli: a paradigm for multiscale modelling in biology, Multiscale Model. Simul. 3 (2005) 362-394.

[30] R. Erban and H. G. Othmer, Taxis equations for amoeboid cells, J. Math. Biol. 54 (2007)847-885.

[31] R. A. Fisher, The wave of advance of advantageous genes, Ann. Eugenics 7 (1937) 353-369.

[32] B. Franz, C. Xue, K. Painter, and R. Erban, Travelling waves in Hybrid Chemotaxis Models, Bull. Math. Biol. 76(2) (2014) 377-400.

[33] B. M. Friedrich, F. Jülicher, Chemotaxis of sperm cells, Proc. Natl. Acad. Sci. USA 104 (2007) 13256-13261.

[34] V. Gangur, N. P. Birmingham, S. Thanesvorakul, Chemokines in health and disease, Vet. Immunol. Immunopathol. 86 (2002) 127–136.

[35] B. Gompertz, On the Nature of the function expressive of the law of human mortality, and on a mew Mode of determining the value of life contingencies, Phil. Trans. R. Soc. 115 (1825) 513-585.

[36] L. Grüne, E. D. Sontag and F. R. Wirth, Asymptotic stability equals exponential stability, and ISS equals finite energy gain – if you twist your eyes, Systems & Control Letters 38 (1999) 127-134.

[37] K. Harley, P. van Heijster, R. Marangell, G. J. Pettel, M. Wechselberger, Existence of travelling wave solutions for a model of tumor invasion, Siam J. Apll. Dyn. Sys. 13(1) (2004) 366-396.

[38] H. W. Hethcote, The mathematics of infectious diseases, SIAM Rev. 42(4) (2000) 599-653.

[39] T. Hillen, K. J. Painter, Global Existence for a Parabolic Chemotaxis Model with Prevention of Overcrowding, Adv. Appl. Math. 26(4) (2001) 280-301.

[40] T. Hillen, K. J. Painter, A user's guide to PDE models for chemotaxis, J. Math. Biol. 58(1) (2009) 187-217.

[41] T. Hillen and H. G. Othmer, The diffusion limit of transport equation derived from velocity-jump processes, SIAM J. Appl. Math. 61 (2000) 751-775.

[42] E. Jabbarzadeh, C. F. Abrams, Chemotaxis and random motility in unsteady chemoattractant fields: a computational study, J. Theo. Biol. 235(2) (2005) 221-232.

[43] A. G. Johnpillai, A. Yildirim, A. Biswas, Chiral solutions with Bohm potential by Lie group analysis and travelling wave hypothesis, Rom. Journ. Phys. 57 (2012) 545-554.

[44] E. F. Keller, L. A. Segel, Initiation of slim mold aggregation viewed as an instability, J. Theo. Biol. 26 (1970) 399-415.

[45] E. F. Keller, L. A. Segel, Model for chemotaxis, J. Theo. Biol. 30(2) (1971a) 225-234.

[46] E. F. Keller, L. A. Segel, Travelling bands of chemotactic bacteria: a theoretical analysis, J. Theo. Biol. 30(2) (1971b) 235-248.

[47] C. R. Kennedy, R. Aris, Travelling waves in a simple population model involving growth and death, Bull. Math. Biol. 42 (1980) 397-429.

[48] W. O. Kermack, A. G. McKendrick, A contribution to the mathematical theory of epidemics, Proc. Roy. Soc. London Ser. A 115 (1927) 700-721.

[49] A. Korzybski, Science and sanity: an introduction to non-Aristotelian systems and general semantics (5th ed.), Institute of General Semantic, New York (1994).

[50] W. Kuai, Q. Wang, X. Yang, Y. Zhao, R. Yu, X. Tang, Interleukin-8 associates with adhesion, migration, invasion and chemosensitivity of human gastric cancer cells, World J Gastroenterol. 18(9) (2012) 979-985.

[51] L. Kucerova, S. Skolekova, M. Matuskova, M. Bohac, Z. Kozovska, Altered features and increased chemosensitivity of human breast cancer cells mediated by adipose tissue-derived mesenchymal stromal cells, BMC Cancer 13 (2013) 13-535.

[52] A. V. Kuznetsov, A. A. Avramenko, A macroscopic model of traffic jams in axons, Mathematical Biosciences 218(2) (2009) 142-152.

[53] E. Lajkó, I. Szabó, K. Andódy, A. Pungor, G. Mezö, L. Köhidai, Investigation on chemotactic drug targeting (chemotaxis and adhesion) inducer effect of GnRH-III derivatives in Tetrahymena and human leukemia cell line, J. Pept. Sci. 19(1) (2013) 46–58.

[54] K. Landman, G. Petter, D. Newgreen, Chemotactic cellular migration: smooth and discontinuous travelling wave solutions, SIAM J. Appl. Math. 63 (2003) 1666-1681.

[55] I. R. Lapidus, R. Schiller, A model for travelling bands of chemotactic bacteria, J. Theo. Biol. 22 (1978) 1-13.

[56] D. A. Lauffenburger, C. Kennedy and R. Aris, Travelling band of bacteria in the context of population growth, Bull. Math. Biol. 46(1) (1984) 19-40.

[57] D. A. Lauffenburger, R. Aris, K. Keller, Effects of random motility on growth of bacterial populations, Microb. Ecol. 7(3) (1981) 207-227.

[58] S. Y. Lee, High cell-density culture of Escherichia coli, Trends Biotechnol. 14(3) (1996) 98-105.

[59] A. J. Lotka, Contribution to the Theory of Periodic Reaction, J. Phys. Chem. 14(3) (1910) 271-274.

[60] A. J. Lotka, Elements of Physical Biology (Williams and Wilkins, Baltimore, 1925).

[61] R. Lui, Z. A. Wang, Travelling wave solutions from microscopic to macroscopic chemotaxis models, J. Math. Biol. 61 (2010) 739-761.

[62] P. K. Maini, D. L. S. McElwain, D. Leavesley, Travelling waves in a wound healing assay, Appl. Math. Letters 17 (2004) 575-580.

[63] P. K. Maini, D. L. Benson, J. A. Sherratt, Pattern formation in reaction-diffusion models with spatially inhomogeneoos diffusion coefficients, IMA J. Math. Applied in Med. & Biol. 9 (1992) 197–213.

[64] P. K. Maini, T. E. Woolley, R. E. Baker, E. A. Gaffney, S. S. Lee, Turings model for biological pattern formation and the robustness problem, Roy. Soc. Interface Focus 2(4) (2012) 487–496.

[65] N. Maki, J. E. Gestwicki, E. M Lake, L. L. Kiessling, J. Adler, Motility and chemotaxis of filamentous cells of escherichia coli, J. Bacteriol. 182 (2000) 4337-4342.

[66] T. R. Malthus, An Essay on the Principle of Population (in Oxford World's Classics reprint, Chapter V, p 39-45, 1798).

[67] A. F. Marée, P. Hogeweg, How amoeboids self-organize into a fruiting body: multicellular coordination in dictyostelium discoideum, Proc. Natl. Acad. Sci. USA 98(7) (2001) 3879-3883.

[68] N. W. McLachlan, Bessel functions for engineers *2nd Ed.* (Clarendon Press, Oxford, 1955).

[69] N. Mittal, E. O. Budrene, M. P. Brenner, A. Van Oudenaarden, Motility of escherichia coli cells in clusters formed by chemotactic aggregation, Proc. Natl. Acad. Sci. USA 100(23) (2003) 13259-13263.

[70] M. A. Moore, The role of chemoattraction in cancer metastases, Bioessays 23 (2001) 674–676.

[71] P. M. Murphy, Chemokines and the molecular basis of cancer metastasis, N. Engl. J. Med. 345 (2001) 833–835.

[72] J. Murray, Mathematical Biology (Springer, Berlin, 2002).

[73] G. Nadin, B. Perthame, L. Ryzhik, Traveling waves for the Keller-Segel system with Fisher birth term, Interfaces and Free Boundaries 10 (2008) 517–538.

[74] P. W. Nelson, J. D. Murray, A. S. Perelson, A model of HIV-1 pathogenesis that includes an intracellular delay, Math. Biosci. 163 (2000) 201-215.

[75] R. Nossal, Boundary movement of chemotactic bacterial populations, Math. Biosci. 13 (1972) 397-406.

[76] F. W. J. Olver, D. W. Lozier, R. F. Boisvert, C. W. Clark, NIST Handbook of Mathematical Functions (Cambridge University Press, 2010).

[77] K. Osaki, A. Yagi, Finite dimensional attractor for one-dimensional Keller-Segel equations, Funkcial. Ekvac. 44 (2001) 441-469.

[78] H. G. Othmer, P. Schapp, Oscillatory cAMP signalling in the development of dictyostelium discoideum, Comments Theo. Biol. 5 (1998) 175-282.

[79] H. G. Othmer, A. Stevens, Aggregation, blow-up and collapse: the ABCs of taxis in reinforced random walks, SIAM J. Appl. Math. 57 (1997) 1044-1081.

[80] H. G Othmer, S. R. Dunbar, W. Alt, Models of dispersal in biological systems, J. Math. Biol. 26 (1988) 263-298.

[81] E. Palsson, H. G. Othmer, A Model for individual and collective cell movement in dictyostelium discoideum, Proc. Natl. Acad. Sci. USA, 97(19) (2000) 10448-10453.

[82] K. Paul, V. Nieto, W. C. Carlquist, D. F. Blair, R. M. Harshey, The c-di-GMP binding protein YcgR controls flagellar motor direction and speed to affect chemotaxis by a "Backstop Brake" mechanism, Mol. Cell. 38 (2010) 128-139.

[83] C. S. Patlak, Random walk with persistence and external bias, Bull. Math. Biophys. 15 (1953) 311-338.

[84] W. Pfeffer, Über chemotaktische bewegungen von bacterien, flagellaten and volvocineen, Unt. Bot. Inst. Tübingen 2(III) (1888) 582-661.

[85] A. D. Polyanin, V. F. Zaitsev, Handbook of Nonlinear Partial Differential Equations (Chapman & Hall/CRC, Washington, 2004).

[86] Procesi C., *An Approach through Invariants and Representations* (Springer Science+Business Media, New York, 2007)

[87] M. Rascle, C. Ziti, Finite time blow up in some models of chemotaxis, J. Math. Biol. 33 (1995) 388-414.

[88] G. Rosen, Effects of diffusion on the stability of the equilibrium in multi-species ecological systems, Bull. Math. Biol. 39 (1977) 373-383.

[89] E. Russo, The birth of biotechnology, Nature 421(6921) (2003) 456-457.

[90] A. Sahari, M. A. Traore, B. E. Scharf, B. Behkam, Directed transport of bacteria-based drug delivery vehicles: bacterial chemotaxis dominates particle shape, Biomed. Microdevices 16(5) (2014) 717–725.

[91] L. Schneider, M. Cammer, J. Lehman, S. K. Nielsen, C. F. Guerra, I. R. Veland, C. Stock, E. K.Hoffmann, B. K Yoder, A. Schwab, P. Satir, S. T. Christensen, Directional cell migration and chemotaxis in wound healing response to PDGF-AA are coordinated by the primary cilium in fibroblasts, Cell Physiol. Biochem. 25(2-3) (2010) 279-292.

[92] T. Scribner, L. Segel, E. Rogers, A numerical study of the formation and the propagation of travelling bands of chemotactic bacteria, J. Theor. Biol. 46 (1974) 189-219.

[93] S. Setayeshgar, C. Gear, H. Othmer, L. Kevrekidis, Application of coarse integration to bacterial chemotaxis, Multiscale Model. Simul. 4(1) (2005) 307-327.

[94] V. Sourjik, Receptor clustering and signal processing in E. *coli* chemotaxis, TRENDS in Microbiology 12(12) (2004) 569-576.

[95] P. Spiro, J. Parkinson, H. Othmer, A model of excitation and adaptation in bacterial chemotaxis, Proc. Natl. Acad. Sci. USA 94(1997) 7263-7268.

[96] Strogatz S. H., Nonlinear Dynamics and Chaos with applications to Physics, Biology, Chemistry and Engineering, Perseus Books, New York, (1994).

[97] P. M. Tchepmo Djomegni, K. S. Govinder, The interplay of group and dynamical systems analysis: The case of spherically symmetric charged fluids in general relativity, Int. J. Non-Linear Mech. 62 (2014) 58-72.

[98] P. M. Tchepmo Djomegni, K. S. Govinder, Generalized Travelling Wave Solutions for Hyperbolic Chemotaxis PDEs, Preprint: SMSCS-University of KawZulu-Natal, Durban (2014).

[99] P. M. Tchepmo Djomegni, K. S. Govinder, Asymptotic analysis of travelling wave solutions in chemotaxis with nutrients dependant cell growth, Preprint: SMSCS-University of KwaZulu-Natal, Durban (2014).

[100] M. J. Tindall, S. Porter, P. Maini, G. Gaglia, J. Armitage, Overview of mathematical approaches used to model bacterial chemotaxis I: The single cell, Bull. Math. Biol. 70(6) (2008) 1525-1569.

[101] M. J. Tindall, P. K. Maini, S. L. Porter, J. P. Armitage, Overview of mathematical approaches used to model bacterial chemotaxis II: bacterial populations, Bull. Math. Biol. 70(6) (2008) 1570-1607.

[102] R. T. Tranquillo, D. A. Lauffenburger, S. H. Zigmond, A stochastic model for leukocyte random motility and chemotaxis based on receptor binding fluctuations, J. Cell Biol. 106(2) (1988) 303-309.

[103] P. F. Verhulst, Notice sur la loi que la population poursuit dans son accroissement, Correspondance mathématique et physique 10 (1838) 113-121.

[104] M. Villasana, A. Radunskaya, A delay differential equation model for tumor growth, J. Math. Biol. 47(3) (2003) 270-294.

[105] A. I. Volpert, Vit. A. Volpert, Vl. A. Volpert, Travelling solutions of parabolic systems, Translation of Mathematical Monographs 140 (1994), American Mathematical Society, Providence.

[106] V. Volterra, Variazioni e fluttuazioni del numero d'individui in specie animali conviventi, Mem. Acad. Lincei Roma 29 (1926) 31-113.

[107] Wang Z. A, Mathematics of travelling waves in chemotaxis, Discr. Cont. Dyn. Syst. B. 18 (2013) 601-641.

[108] Weijer C. J., Collective cell migration in development, J. Cell Sci. 122 (2009) 3215-3233.

[109] S. Wiggins, Introduction to Applied Nonlinear Dynamical Systems and Chaos, Springer-Verlag New York Berlin , (1990).

[110] D. E. Woodward, R. Tyson, M. R. Myerscough, E. O. Budrene, H. C. Berg, Spacio-temporal patterns generated by salmonella typhimurium, Biophys. 68 (1995) 2181-2189.

[111] C. Xue, H. J. Hwang, K. J. Painter, R. Erban, Travelling waves in hyperbolic chemotaxis equations, Bull. Math. Biol. 73 (2011) 1695-1733.