Advances in Applied Mathematics and Mechanics
Adv. Appl. Math. Mech., Vol. **9**, No. 5, pp. 1250-1270

DOI: 10.4208/aamm.OA-2016-0114
October 2017

Asymptotic Analysis of Travelling Wave Solutions in Chemotaxis with Growth

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Received 9 September 2016; Accepted (in revised version) 26 December 2016

Abstract. Mass migration of cells (via wave motion) plays an important role in many biological processes, particularly chemotaxis. We study the existence of travelling wave solutions for a chemotaxis model on a microscopic scale. The interaction between nutrients and chemoattractants are considered. Unlike previous approaches, we allow for diffusion of substrates, degradation of chemoattractants and cell growth (constant and linear growth rate). We apply asymptotic methods to investigate the behaviour of the solutions when cells are highly sensitive to extracellular signalling. Explicit solutions are demonstrated, and their biological implications are presented. The results presented here extend and generalize known results.

AMS subject classifications: 34D20, 37N25, 92B05

Key words: Lie symmetries, velocity-jump process, travelling waves, asymptotic methods.

1 Introduction

Chemotaxis is the process whereby cells direct their motion in response to extracellular signalling. The earliest recorded observation of chemotaxis of bacteria occurred in the late 1800s [5, 12, 13, 35]. In his experiment, Adler [1–3] 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. Mathematical models have been developed to describe chemotaxis.

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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. Cell proliferation was 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 [44]. Keller and Segel [21] shown that a singularity in the chemotactic coefficient is necessary in order to produce the band behaviour (travelling wave solutions) under zero cellular growth/death. To check the validity of the K-S model, Scribner et al. [37] performed numerical simulations and compared their results with Adler's (1966) experimental results under different initial conditions. They provided some forms of $\mu(s)$, $\chi(s)$ and $k(s)$, all dependent on a critical attractant concentration level a, that produced both uniform and non-uniform bands of bacteria. Many interesting results (both mathematics and applications) on travelling wave solutions in chemotaxis have recently been obtained by Wang [45].

From an individual perspective, Patlak [33] was the first to propose a chemotaxis model. His model portrayed the random walk process of a particle with persistence of direction, and external bias. In the case where the particles alternatively 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 [32]. In the case of no interaction between particles, Alt [4] and Othmer et al. [32] derived a model that employs a transport equation for velocity jump processes as follows:

$$\frac{\partial}{\partial t}p(x,v,t)+v\cdot\nabla p(x,v,t)=\lambda\int_V T(v,v')p(x,v',t)dv', \tag{1.1}$$

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 (1.1) that the choice of the new velocity does not depend on the run length. The intracellular dynamic of cells was later considered to study the signal transduction and metabolism effect [43, 47].

Cell growth and death have often been overlooked in many of the mathematical models of chemotaxis, though they play a biologically significant role in the behaviour of systems. In fact, Budrene et Berg [9] observed that cell growth is crucial for the propagation of the swarm ring and the formation of new aggregates (bands of cells). They also observed that *E coli* cells grow at an approximately constant rate over the concentration range of succinate $0.5-7$mM. Elliott et al. [11] 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 [22, 24–26, 30]. From the population perspective, Kennedy and Aris [22] found a certain growth function that gave birth to travelling wave solutions of constant speed. Unlike the Keller and Segel's [21] results, Lauffenburger et al. [25] 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. [16] also consid-

ered growth in their model. They assumed that cells grow only on the excreted signal, and they did not consider diffusion. They proved the existence of travelling wave solutions, and they observed that cell growth/death stabilises the wave profile. We note that cells most often grow on nutrients [9], or in some situations grow on higher concentrations of potential food present locally. Diffusion of substrates is also an important factor in biology to consider. It has been been shown that the diffusion of substrates plays a stabilizing role on the steady state of systems [36].

A new model that incorporates the interplay between the initial substrate and the excreted signal was recently formulated by Xue et al. [47]. Their model is noteworthy as it was the first attempt to describe the interactions between two substrates 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 they proved the existence of travelling wave solutions when substrates are not allowed to diffuse. Building on these results, we allowed for diffusion and cell growth, and we presented explicit solutions for the first time [42].

In this study we will investigate the existence of travelling wave solutions of a microscopic chemotaxis model. We will account for diffusivity, cell growth and death, signal degradation. This will be the first attempt to simultaneously consider growth (depending on nutrients) and the interaction between the nutrients and the excreted signal. We will examine the case of high sensitivity to signal. Additionally, we will also investigate the impact of cell growth/death on the behaviour of the bands of cells and substrates. In what follows, we will introduce the model in Section 2. There after we will apply the Lie symmetry approach in Section 3 to generate travelling wave invariants. We will present relevant theorems together with their biological interpretations in Section 4. The results are then discussed in Section 5.

2 Model formulation

The model is inspired by the self-organization of cells, their collective defense and their response to certain gradients of signal. It results from the experimental observations [8,9, 46] 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 were present in the wake of a travelling circular band [9]. 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 [7]. We focus on the case of non limiting nutrients.

Denoting by $n^{\pm}(x,t)$ the density of cells at the position x and the time t, moving with constant speed $\pm s$, the distribution of the cells can be described in one dimensional space

via the telegraph process [14, 18, 32]:

$$\frac{\partial n^+}{\partial t}+s\frac{\partial n^+}{\partial x}=-\lambda\left(-\frac{\partial S}{\partial x}\right)n^+ +\lambda\left(\frac{\partial S}{\partial x}\right)n^- +h(F)n^+, \tag{2.1a}$$

$$\frac{\partial n^-}{\partial t}-s\frac{\partial n^-}{\partial x}=\lambda\left(-\frac{\partial S}{\partial x}\right)n^+ -\lambda\left(\frac{\partial S}{\partial x}\right)n^- +h(F)n^-, \tag{2.1b}$$

where $F(x,t)$ is the concentration of the succinate, $S(x,t)$ is the concentration of the aspartate, and λ and h are respectively the turning and proliferation rate functions of the cells. We will use the form of turning rate function formulated in [47] defined as follows:

$$\lambda\left(\frac{\partial S}{\partial x}\right)=\lambda_0\left(1+\frac{\frac{\partial S}{\partial x}}{k+|\frac{\partial S}{\partial x}|}\right)=\lambda_0\left(1+\chi\frac{\partial S}{\partial x}\right), \tag{2.2}$$

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. It was shown that the parabolic limit of (2.1a)-(2.1b) in the absence of internal dynamics is the Keller-Segel model [27]. We will focus on the limiting case $k\to 0$, corresponding to unbounded (or high) sensitivity to the signal [47]. Then λ becomes the switch function

$$\lambda\left(\frac{\partial S}{\partial x}\right)=\begin{cases} 0, & \partial S/\partial x<0,\\ \lambda_0, & \partial S/\partial x=0,\\ 2\lambda_0, & \partial S/\partial x>0.\end{cases} \tag{2.3}$$

When k varies ($0<k<\infty$), travelling waves are difficult to analyse. However, Franz et al. [16] numerically demonstrated that increasing chemotactic responses causes an increase in the wave speed. When $k\to\infty$, there is no chemotaxis ($\chi=0$) and the advection is caused by the bias of turning.

As we mentioned earlier, cell growth is an important factor to consider in the dynamics of chemotaxis. We will consider two forms of h:

$$h(F)=\alpha_0 \quad \text{and} \quad h(F)=\beta_0(F-F_c), \tag{2.4}$$

where F_c is the minimum amount of succinate that produces 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 substrates can be described by the diffusion equations [47]

$$\frac{\partial F}{\partial t}=D_F\frac{\partial^2 F}{\partial x^2}-\alpha F(n^+ +n^-), \tag{2.5a}$$

$$\frac{\partial S}{\partial t}=D_S\frac{\partial^2 S}{\partial x^2}+\beta F(n^+ +n^-)-\gamma S, \tag{2.5b}$$

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

$$n(x,t)=n^+(x,t)+n^-(x,t), \quad j(x,t)=s(n^+(x,t)-n^-(x,t)), \tag{2.6}$$

then one transforms (2.1a), (2.1b), (2.5a) and (2.5b) into

$$\frac{\partial n}{\partial t}+\frac{\partial j}{\partial x}=h(F)n, \tag{2.7a}$$

$$\frac{\partial j}{\partial t}+s^2\frac{\partial n}{\partial x}=s\lambda^1 n-2\lambda_0 j+h(F)j, \tag{2.7b}$$

$$\frac{\partial F}{\partial t}=D_F\frac{\partial^2 F}{\partial x^2}-\alpha Fn, \tag{2.7c}$$

$$\frac{\partial S}{\partial t}=D_S\frac{\partial^2 S}{\partial x^2}+\beta Fn-\gamma S. \tag{2.7d}$$

The function $j(x,t)$ stands for the flux, and λ^1 is given by

$$\lambda^1\left(\frac{\partial S}{\partial x}\right)=\lambda\left(\frac{\partial S}{\partial x}\right)-\lambda\left(-\frac{\partial S}{\partial x}\right). \tag{2.8}$$

We will fully analyse the system (2.7a)-(2.7d) in the case of high sensitivity to the signal, and we will investigate the effect of cell growth on the behaviour of the bands. The Lie symmetry analysis will be used to generated (generalized) travelling wave solutions. The function λ^1 will be treated as a constant (since λ takes constant values on its subsdomains). We note that Lie symmetry analysis results have been used widely to describe invasion profiles [40].

3 Lie symmetry and travelling wave analysis

An *nth* order partial differential equation

$$E(x,y,\partial y,\cdots,\partial^n y)=0, \tag{3.1}$$

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

$$G=\xi_i(x,y)\frac{\partial}{\partial x_i}+\eta^\nu(x,y)\frac{\partial}{\partial y^\nu}, \tag{3.2}$$

as a symmetry, with $i=1,\cdots,N$ and $\nu=1,\cdots,m$, if [6]

$$G^{[n]}E\,|_{E=0}=0. \tag{3.3}$$

Here, $\xi_i(x,y)$ and $\eta^\nu(x,y)$ are the infinitesimals of the Lie group of invariant transformations of (3.1), and $G^{[n]}$ is the *nth* extension of G (refer to [6] for more details).

Applying the second extension operator $G^{[2]}$ to (2.7a)-(2.7d), we obtain

$$G_1=\partial_t+c\partial_x+\alpha_1 F\partial_F+\alpha_1 S\partial_S+\alpha_2 e^{(h-2\lambda_0)t}\partial_j,\quad G_\infty=d(t,x)\partial_S, \tag{3.4}$$

as symmetries if h is constant, and

$$G_2=\partial_t+c\partial_x,\quad G_\infty=d(t,x)\partial_S, \tag{3.5}$$

if $h(F)=\beta_0(F-F_c)$, with α_1, α_2 and α_3 arbitrary real parameters, G_∞ an infinite-dimensional symmetry, and d any solution of

$$D_S\frac{\partial^2 d}{\partial x^2}-\frac{\partial d}{\partial t}-\gamma d=0. \tag{3.6}$$

The characteristic equations associated with G_1 are [6]

$$\frac{dt}{1}=\frac{dx}{c}=\frac{dF}{\alpha_1 F}=\frac{dS}{\alpha_1 S}=\frac{dj}{\alpha_2 e^{(h-2\lambda_0)t}}=\frac{dn}{0}. \tag{3.7}$$

This leads to the new invariants

$$z=x-ct, \tag{3.8a}$$
$$F=F_1(z)e^{\alpha_1 t}, \tag{3.8b}$$
$$S=S_1(z)e^{\alpha_1 t}, \tag{3.8c}$$
$$j=J(z)+\frac{\alpha_2}{(h-2\lambda_0)}e^{(h-2\lambda_0)t}, \tag{3.8d}$$
$$n=N(z). \tag{3.8e}$$

The invariant (3.8a) corresponds to the usual travelling wave ansatz, with c being the speed of the wave. Since the speed of each cell cannot be less than the speed of the band, we consider $0<c\leq s$. It is interesting to observe that the more general form of the other invariants. Usually, after assuming z in the form (3.8a), one then further assumes that all the dependent variables are functions of z. Here, we see that a more general form of the dependent variables is possible. Therefore, performing a full group theoretical analysis of (2.7a)-(2.7d) has yielded the possibility of generalized travelling wave solutions (the restrictive case $\alpha_1=\alpha_2=0$ yields the standard travelling wave ansatz). We showed [42] 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. $\alpha_1>0$). Thus we will only consider the case where $\alpha_1\leq 0$. Further, we will ignore the additive purely timelike component of j (i.e., we set $\alpha_2=0$), as this does not add to the behaviour of the system. Substituting (3.8d) and (3.8e) into (2.7a) and (2.7b), we obtain

$$-cN'+J'=h(F)N, \tag{3.9a}$$
$$-cJ'+s^2N'=s\lambda^1N-2\lambda_0J+h(F)J, \tag{3.9b}$$

where the superscript $'$ denotes the total derivative with respect to the variable z. Thus, (3.9a)-(3.9b) can be rewritten as

$$(s^2-c^2)N'=(ch(F)+s\lambda^1)N+(h(F)-2\lambda_0)J, \tag{3.10a}$$
$$(s^2-c^2)J'=(s^2h(F)+cs\lambda^1)N+c(h(F)-2\lambda_0)J. \tag{3.10b}$$

Likewise, the substitution of (3.8b)-(3.8e) into (2.7c) and (2.7d) yields

$$D_F F_1'' + cF_1' - (\alpha_1 + \alpha N)F_1 = 0, \tag{3.11a}$$
$$D_S S_1'' + cS_1' + \beta F_1 N - (\alpha_1 + \gamma)S_1 = 0. \tag{3.11b}$$

When $c = s$, we remark that (3.10a) and (3.10b) coalesce, and (3.10a)-(3.11b) reduces to a system of three equations in the four unknown N, J, F_1 and S_1. The solutions in this case can depend on $N(z)$ or $J(z)$. For a constant distribution of $N(z)$ or $J(z)$, travelling wave solutions can be demonstrated under constant growth rate (The analysis for an exponential distribution (such as the Poisson or normal distribution) of $N(z)$ or $J(z)$ 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 $1-2$mm/h, while, for s, we have $10-20\mu$m/s [9,47]). As a result for the remainder of our work we will only consider $0 < c < s$, and study the existence of travelling wave solutions. We note that travelling wave solutions n, F and S in our context must be positive, continuous and bounded.

4 Travelling waves analysis

We are in the case of high sensitivity to signal ($k = 0$). Then λ^1 can be rewritten as

$$\lambda^1\left(\frac{\partial S}{\partial x}\right) = \begin{cases} -2\lambda_0, & \partial S/\partial x < 0, \\ 0, & \partial S/\partial x = 0, \\ 2\lambda_0, & \partial S/\partial x > 0. \end{cases} \tag{4.1}$$

Motivated by the numerical investigation's of Xue et al. [47], 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

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

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

For $S_1 \in Y_S$, (3.10a)-(3.11b) can be reduced to

$$N' = a_1 N + b_1 J, \tag{4.2a}$$
$$J' = a_2 N + c b_1 J, \tag{4.2b}$$
$$-cF_1' = D_F F_1'' - (\alpha_1 + \alpha N)F_1, \tag{4.2c}$$
$$-cS_1' = D_S S_1'' + \beta F_1 N - (\alpha_1 + \gamma)S_1, \tag{4.2d}$$

where

$$a_1 = \frac{c\alpha_0 - 2\lambda_0 s}{s^2 - c^2}, \quad b_1 = \frac{\alpha_0 - 2\lambda_0}{s^2 - c^2}, \quad a_2 = \frac{s^2\alpha_0 - 2\lambda_0 cs}{s^2 - c^2}, \tag{4.3}$$

for $z>0$, and

$$a_1=\frac{c\alpha_0+2\lambda_0 s}{s^2-c^2},\quad b_1=\frac{\alpha_0-2\lambda_0}{s^2-c^2},\quad a_2=\frac{s^2\alpha_0+2\lambda_0 cs}{s^2-c^2},\tag{4.4}$$

for $z<0$. The stability analysis of (4.2a)-(4.2d) around equilibrium points could be undertaken, but will restrict the results. For instance we will present a case of saddle point in which a suitable choice of initial conditions leads to convergent solutions. Moreover, for $\alpha_1=0$ or $\alpha_1=-\gamma$, a center manifold problem will arise and will make the analysis more complicated.

We assume first $\alpha_0=2\lambda_0$ (i.e., $b_1=0$), and we let $\lambda_1=\alpha_0/(s-c)$ and $\lambda_2=\alpha_0/(s+c)$. Then $N(z)$ and $J(z)$ are given by

$$N(z)=\begin{cases} N(0)\mathrm{e}^{\lambda_1 z}, & z<0,\\ N(0)\mathrm{e}^{-\lambda_2 z}, & z\geq 0,\end{cases}\qquad J(z)=\begin{cases} J(0)-sN(0)\left(1-\mathrm{e}^{\lambda_1 z}\right), & z<0,\\ J(0)+sN(0)\left(1-\mathrm{e}^{-\lambda_2 z}\right), & z\geq 0,\end{cases}\tag{4.5}$$

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

$$T=\int_{\mathbb{R}} N(z)dz=\int_{-\infty}^{+\infty} N(0)\mathrm{e}^{a_1 z}dz=\frac{2sN(0)}{\alpha_0}.\tag{4.6}$$

We note that the form of our system is mathematically similar to that analysed in the case of zero growth by [47] and [42], without and with diffusion respectively. The existence of travelling wave solutions has been established.

In the case when diffusion is ignored (i.e., $D_F=D_S=0$), the speed of the wave in our context is uniquely given by $c^*=s\gamma/(\gamma+\alpha_0\bar{\tau})$, and the travelling wave solutions $F_1(z)$ and $S_1(z)$ are given by (with $\alpha_1=0$)

$$F_1(z)=\begin{cases} F_1(0)\exp\left(\dfrac{\alpha N(0)}{c\lambda_1}(\mathrm{e}^{\lambda_1 z}-1)\right), & z<0,\\ F_1(0)\exp\left(\dfrac{\alpha N(0)}{c\lambda_3}(1-\mathrm{e}^{-\lambda_3 z})\right), & z\geq 0,\end{cases}\tag{4.7a}$$

$$S_1(z)=\mathrm{e}^{\frac{\gamma}{c}z}\left(S_1(0)-\frac{\beta}{c}\int_0^z N(z_1)F_1(z_1)\mathrm{e}^{\frac{-\gamma}{c}z_1}dz_1\right).\tag{4.7b}$$

For $\alpha_1\neq 0$, we note that continuous bounded travelling wave solutions do not exist. In fact from (4.2c),

$$F(x,t)=\mathrm{e}^{\alpha_1 t}F_1(z)=F_1(0)\mathrm{e}^{\frac{\alpha_1}{c}x}\mathrm{e}^{\frac{\alpha N(0)}{ca_1}(\mathrm{e}^{a_1 z}-1)}.\tag{4.8}$$

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

Likewise, when diffusion is considered ($D_S\neq 0$ and $D_F\neq 0$), the generalized travelling

wave solutions in our context are given by $F(x,t)=F_1(z)e^{\alpha_1 t}$ and $S(x,t)=S_1(z)e^{\alpha_1 t}$, where

$$F_1(z)=\begin{cases} F_1(0)I_{k_1}\left(\alpha_{0,1}e^{(\lambda_1/2)z}\right)e^{-(c/(2D_F))z}\Big/ I_{k_1}(\alpha_{0,1}), & z<0,\\ F_1(0)I_{k_2}\left(\alpha_{0,2}e^{-(\lambda_3/2)z}\right)e^{-(c/(2D_F))z}\Big/ I_{k_2}(\alpha_{0,2}), & z\geq 0,\end{cases} \tag{4.9a}$$

$$S_1(z)=\begin{cases} \delta_0^1 e^{-\tau_1 z}+\delta_0^2 e^{\tau_2 z}-\dfrac{\beta N(0)F_1(0)e^{-\tau_1 z}}{\tau_3 I_{k_1}(\alpha_{0,1})}\displaystyle\int_z^0 e^{\tau_{41}z_1}I_{k_1}\left(\alpha_{0,1}e^{(\lambda_1/2)z_1}\right)dz_1 \\ \qquad +\dfrac{\beta N(0)F_1(0)e^{\tau_2 z}}{\tau_3 I_{k_1}(\alpha_{0,1})}\displaystyle\int_z^0 e^{\tau_{51}z_1}I_{k_1}\left(\alpha_{0,1}e^{(\lambda_1/2)z_1}\right)dz_1, & z<0,\\ \delta_0^1 e^{-\tau_1 z}+\delta_0^2 e^{\tau_2 z}+\dfrac{\beta N(0)F_1(0)e^{-\tau_1 z}}{\tau_3 I_{k_2}(\alpha_{0,2})}\displaystyle\int_0^z e^{\tau_{42}z_1}I_{k_2}\left(\alpha_{0,2}e^{-(\lambda_3/2)z_1}\right)dz_1 \\ \qquad -\dfrac{\beta N(0)F_1(0)e^{\tau_2 z}}{\tau_3 I_{k_2}(\alpha_{0,2})}\displaystyle\int_0^z e^{\tau_{52}z_1}I_{k_2}\left(\alpha_{0,2}e^{-(\lambda_3/2)z_1}\right)dz_1, & z\geq 0,\end{cases} \tag{4.9b}$$

with $\max(-c^2/(4D_F),-\gamma)<\alpha_1<0$, and

$$\tau_1=\frac{c+\tau_3}{2D_S},\quad \tau_2=\frac{-c+\tau_3}{2D_S},\quad \tau_3=\sqrt{c^2+4D_S(\alpha_1+\gamma)},\quad \alpha_{0,1}=\frac{\sqrt{4N(0)\alpha D_F}}{\lambda_1 D_F}, \tag{4.10a}$$

$$\alpha_{0,2}=\frac{\sqrt{4N(0)\alpha D_F}}{\lambda_3 D_F},\quad \tau_{41}=\frac{-c}{2D_F}+\frac{c}{D_S}+\tau_2+\lambda_1,\quad \tau_{51}=\frac{-c}{2D_F}+\frac{c}{D_S}-\tau_1+\lambda_1, \tag{4.10b}$$

$$\tau_{42}=\frac{-c}{2D_F}+\frac{c}{D_S}+\tau_2-\lambda_3,\quad \delta_0^1=\frac{\beta N(0)F_1(0)(\alpha_{0,1}/2)^{k_1}}{\tau_3(\lambda_1 k_1/2+\tau_{41})\Gamma(1+k_1)I_{k_1}(\alpha_{0,1})}, \tag{4.10c}$$

$$\tau_{52}=\frac{-c}{2D_F}+\frac{c}{D_S}-\tau_1-\lambda_3,\quad \delta_0^2=\frac{-\beta N(0)F_1(0)(\alpha_{0,2}/2)^{k_2}}{\tau_3(-\lambda_3 k_2/2+\tau_{52})\Gamma(1+k_2)I_{k_2}(\alpha_{0,2})}, \tag{4.10d}$$

$$k_1=\frac{\sqrt{c^2+4\alpha_1 D_F}}{\lambda_1 D_F},\quad k_2=\frac{\sqrt{c^2+4\alpha_1 D_F}}{\lambda_3 D_F}. \tag{4.10e}$$

The functions I_{k_1} and I_{k_2} stand for the two linearly independent solutions of the modified Bessel's equation.

We remark that the speed c^* and the total population T of the band decrease for large growth rate α_0. 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 [9]. The destabilization (or dislocation) of the main aggregate affects its propagation speed. Moreover, we observe in comparison with the work done in the case of zero growth [42,47], similarity in the behaviour of travelling wave solutions for $\alpha_0=2\lambda_0$. The effect of growth can be compensated by the action of the turning rate.

The more interesting case is that of $\alpha_0\neq 2\lambda_0$. Here $N(z)$ and $J(z)$ are given by

$$N(z)=\begin{cases} \dfrac{C_1}{s}e^{\lambda_1 z}+\gamma_0 C_2 e^{\lambda_2 z}, & z<0,\\ \gamma_1 C_4 e^{-\lambda_4 z}-\dfrac{C_3}{s}e^{-\lambda_3 z}, & z\geq 0,\end{cases}\qquad J(z)=\begin{cases} C_1 e^{\lambda_1 z}+C_2 e^{\lambda_2 z}, & z<0,\\ C_3 e^{-\lambda_3 z}+C_4 e^{-\lambda_4 z}, & z\geq 0,\end{cases} \tag{4.11}$$

where

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

and $N(z)$ is continuous at zero.

When $\alpha_0>2\lambda_0$, we have $\lambda_2<0$ and $\lambda_4<0$; this correspond to the case of a saddle point in the stability analysis. To obtain unbounded 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 the discontinuity of the flux at zero. In this case, the solutions $N(z)$ and $J(z)$ are reduced to

$$N(z)=\begin{cases} N(0)\mathrm{e}^{(\alpha_0/(s-c))z}, & z<0,\\ N(0)\mathrm{e}^{-(\alpha_0/(s+c))z}, & z\geq 0,\end{cases}\qquad J(z)=\begin{cases} sN(0)\mathrm{e}^{(\alpha_0/(s-c))z}, & z<0,\\ -sN(0)\mathrm{e}^{-(\alpha_0/(s+c))z}, & z\geq 0.\end{cases}\tag{4.12}$$

(A negative flux simply means that most of the cells move to the left (for $j=s(n^+-n^-)$)). We observe that $N(z)$ has the same form as in (4.5). As a result $F_1(z)$ and $S_1(z)$ have the same form as in the case of $\alpha_0=2\lambda_0$ via (4.2c)-(4.2d). As stated above, diffusing and non-diffusing ($D_S=D_F=0$) travelling wave solutions exist. Here we note from (4.12), (4.2c) and (4.2d) that the sensitivity to the signal does not play a role in the aggregation of travelling band of cells. The cell distribution is dominated by the growth.

When $\alpha_0<2\lambda_0$, all the λ_i are positive and $N(z)$ and $J(z)$ given in (4.11) are bounded. If the constants C_1 (or C_2) and C_3 (or C_4) are zero, the analysis is also similar to the case of $\alpha_0=2\lambda_0$ (given the form of $N(z)$). Diffusing and non-diffusing travelling wave solutions exist.

We now assume that at most one of the constants C_i is zero. We will choose $C_3=0$ in what follows, and we note that the analysis with any of the C_i being zero is the same. We start first with the case of non diffusion.

Theorem 4.1. *For $\alpha_0<2\lambda_0$, $J(0^+)=N(0)/\gamma_1$ and*

i. $c=(1-\alpha_0/\lambda_0)s$, *or*

ii. $c>(1-\alpha_0/\lambda_0)s$ *and* ($sN(0)\geq J(0^-)$ *for* $s\gamma_0>1$, *or* $sN(0)\leq J(0^-)$ *for* $s\gamma_0<1$), *or*

iii. $c<(1-\alpha_0/\lambda_0)s$, $\alpha_0<\lambda_0$ *and* ($\gamma_0 J(0^-)\geq N(0)$ *for* $s\gamma_0>1$, *or* $\gamma_0 J(0^-)\leq N(0)$ *for* $s\gamma_0<1$),

non-diffusing ($D_S=D_F=0$) travelling wave solutions for $N(z)$, $F_1(z)$ and $S_1(z)$ exist and are

explicitly given by

$$N(z)=\begin{cases}\dfrac{C_1}{s}e^{\lambda_1 z}+\gamma_0 C_2 e^{\lambda_2 z}, & z<0,\\ N(0)e^{-\lambda_4 z}, & z\geq 0,\end{cases} \tag{4.13a}$$

$$F_1(z)=\begin{cases}F_1(0)e^{\frac{-\alpha C_1}{cs\lambda_1}(1-e^{\lambda_1 z})-\frac{\alpha\gamma_0 C_2}{c\lambda_2}(1-e^{\lambda_2 z})}, & z<0,\\ F_1(0)e^{\frac{\alpha N(0)}{c\lambda_4}(1-e^{-\lambda_4 z})}, & z\geq 0,\end{cases} \tag{4.13b}$$

and

$$S_1(z)=\begin{cases}e^{\frac{\gamma}{c}z}\left(S_1(0)+\dfrac{\beta}{c}\displaystyle\int_z^0 e^{-\frac{\gamma}{c}z_1}F_1(z_1)N(z_1)dz_1\right), & z<0,\\ e^{\frac{\gamma}{c}z}\left(S_1(0)-\dfrac{\beta}{c}\displaystyle\int_0^z e^{-\frac{\gamma}{c}z_1}F_1(z_1)N(z_1)dz_1\right), & z\geq 0,\end{cases} \tag{4.14}$$

with $S_1(0)=\beta F_1(0)N(0)/\gamma$.

Proof. We assume that $D_F=D_S=0$, $\alpha_0<2\lambda_0$ and $C_3=0$ (i.e., $J(0^+)=N(0)/\gamma_1$). Then from (4.11), $N(z)$ is given by (4.13a). As a result, the solutions presented in (4.13b) and (4.14) are obtained directly by substituting (4.13a) into (4.2c)-(4.2d) and integrating (with $\alpha_1=0$). Since $N(z)$ and $F_1(z)$ are continuous and bounded, and $F_1(z)$ is positive, to prove the existence of travelling wave solutions, it suffices to prove the positivity of $N(z)$ and $S_1(z)$, the boundedness of $S_1(z)$, and then that $S_1\in Y_S$. We first start with the positivity of $N(z)$.

It is trivial to show the positivity of $N(z)$ when $z\geq 0$. We assume $z<0$ and note that

$$\lambda_1-\lambda_2=\frac{2(\alpha_0 s+\lambda_0 c-\lambda_0 s)}{s^2-c^2}. \tag{4.15}$$

For $c>(1-\alpha_0/\lambda_0)s$, we have $\lambda_1>\lambda_2$ and $\gamma_0 C_2 e^{\lambda_2 z}$ is the leading behaviour of $N(z)$ as $z\to-\infty$. To guarantee the positivity of $N(z)$ as z approaches $-\infty$, C_2 must be positive. If $s\gamma_0>1$ (respectively $s\gamma_0<1$), then $sN(0)\geq J(0^-)$ (respectively $sN(0)\leq J(0^-)$ must hold and the positivity of $N(z)$ is guaranteed for all $z<0$ (given that $C_2>0$ and $\gamma_0 C_2+C_1/s=N(0)>0$). Likewise for $c<(1-\alpha_0/\lambda_0)s$ (with $\alpha_0<\lambda_0$), $\lambda_1<\lambda_2$ and the term $(C_1/s)e^{\lambda_1 z}$ leads the behaviour as $z\to-\infty$. To guarantee the positivity of $N(z)$ as z approaches $-\infty$, C_1 must be positive. If $s\gamma_0>1$ (respectively $s\gamma_0<1$), then $\gamma_0 J(0^-)\geq N(0)$ (respectively $\gamma_0 J(0^-)\leq N(0)$ must hold and the positivity of $N(z)$ is guaranteed for all $z<0$. The case of $c=(1-\alpha_0/\lambda_0)s$ (i.e., $\lambda_1=\lambda_2$) is evident.

Now we prove the positivity of $S_1(z)$. From (4.2d), $S_1'(z)$ is continuous (given the continuity of $N(z)$, $F_1(z)$ and $S_1(z)$). 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

$$f(z)=S_1(0)-\frac{\beta}{c}\int_0^z e^{-\frac{\gamma}{c}z_1}F_1(z_1)N(z_1)dz_1, \tag{4.16}$$

then there exists a constant $z_2>0$ such that as $z\to\infty$,

$$f(z)\approx S_1(0)-\frac{\beta}{c}\int_0^{z_2}\mathrm{e}^{-\frac{\gamma}{c}z_1}F_1(z_1)N(z_1)dz_1-\frac{\beta F_+}{c}\int_{z_2}^{z}\mathrm{e}^{-\frac{\gamma}{c}z_1}N(z_1)dz_1. \tag{4.17}$$

The existence of z_2 comes from the fact that $F_1(z)\approx F_+$ as $z\to\infty$, with $F_+=F_1(0)\mathrm{e}^{\alpha N(0)/(c\lambda_4)}$. Therefore, (4.17) implies that

$$\begin{aligned} f(z)&\approx f(z_2)+\frac{\beta F_+N(0)(\mathrm{e}^{(-\lambda_4-\gamma/c)z}-\mathrm{e}^{(-\lambda_4-\gamma/c)z_2})}{\gamma+c\lambda_4}\\ &\approx f(z_2)-\frac{\beta F_+N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)z_2}}{\gamma+c\lambda_4}+\frac{\beta F_+N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)z}}{\gamma+c\lambda_4}. \end{aligned} \tag{4.18}$$

Choosing the wave speed and the initial conditions so that

$$f(z_2)=\frac{\beta F_+N(0)\mathrm{e}^{(-\lambda_4-\gamma/c)z_2}}{\gamma+c\lambda_4}, \tag{4.19}$$

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

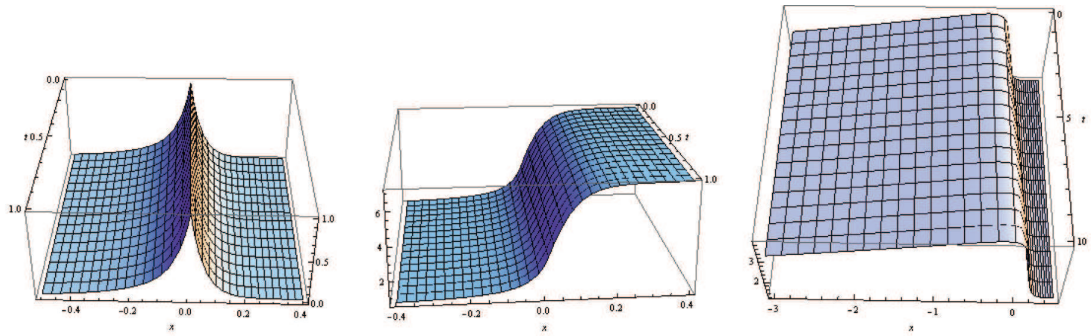
Showing that $S_1\in Y_S$, requires showing that $z=0$ is the only extremum point (from $S_1'(0)=0$ as indicated early), with $S''(0^-)\leq 0$ and $S''(0^+)\leq 0$. From (4.2c),

$$S_1''(z)=\frac{1}{c}\left(\gamma S_1'(z)-\frac{\beta\alpha}{c}F_1(z)N^2(z)-\beta F_1(z)N'(z)\right). \tag{4.20}$$

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

$$S_1''(z_*)=-\frac{\beta}{c^2}F_1(z_*)\left(\alpha N^2(z_*)+cN'(z_*)\right). \tag{4.21}$$

For $z<0$, $N'(z)$ given in (4.2a) is positive (given that $N(z)$ and $J(z)$ are positive); as a result $S_1''(z_*)<0$ (and $S_1''(0)<0$). If there exists a local extremum $z_0<0$, then it cannot be either a point of inflection or a local minimum. Suppose now that z_0 is a local maximum, then we can find $z_1\in(z_0,0)$ (given that $S_1''(0^-)\leq 0$) such that $S_1'(z_1)=0$ and $S_1''(z_1)\geq 0$ (a local minimum). This is a contradiction. For $z\geq 0$, $N'(z)$ is negative. Then $S_1''(z_*)<0$ if $z_*\in[0,z_1)$, and $S_1''(z_*)>0$ if $z_*\in(z_1,\infty)$, with $z_1=\lambda_4^{-1}\log(\alpha N(0)/(c\lambda_4))$. When $z\in[0,z_1)$, $z=0$ is the only extremum point (the local maximum). When $z\in(z_1,\infty)$, a local maximum or inflection point cannot exist. Suppose that there exists a local minimum $z_2>z_1$. Then $S_1(z)$ is increasing for $z\geq z_2$, and $S_1(z_2)\leq 0=\lim_{z\to\infty}S_1(z)$. This is a contradiction. Therefore, $z=0$ is the only extremum point of $S_1(z)$, and $S_1\in Y_S$. □



(a) (b) (c)

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

Remark 4.1. In the above theorem we do not consider the case $\alpha_1\neq 0$ because $F_1(z)$ will blow up as $z\to\infty$ (or as $z\to-\infty$) when $\alpha_1>0$ (or $\alpha_1<0$). Therefore, unbounded solutions will only exist in one region (the half plane $z\geq 0$, or $z\leq 0$) and S_1 cannot be in Y_S.

From Theorem 4.1, we remark that the formation of travelling bands of cells with continuous flux is possible if we take $J(0)=J(0^-)=N(0)/\gamma_1$. Is this case, the speed of the bands is uniquely given by $c=(1-\alpha_0/\lambda_0)s$. We also note the existence of travelling bands with various speeds, provided a good choice of the initial flux distribution is made. In contrast to the case of $\alpha_0<2\lambda_0$, here the unbiased turning rate plays an important role in the distribution of cells and substrates, and the speed of the band of cells. Due to the constraint on the initial conditions, most of cells initially move to the left ($J(0^+)<J(0^-)$). As a result, there is a greater concentration of succinate consumed in the left half plane and less in the right half plane. This causes high and low production of aspartate in the planes $z<0$ and $z>0$ respectively. An illustration of solutions from Theorem 4.1 is given in Fig. 1.

The case of diffusivity ($D_F\neq 0$ and $D_S\neq 0$) is more complicated. For instance, when $C_3=0$, the Eq. (4.2c) cannot be solved explicitly for F_1, given the form of $N(z)$ when $z<0$ (see (4.13a)). As a result, Eq. (4.2d) also cannot be solved explicitly for S_1. We will undertake an asymptotic analysis to investigate the long time behaviour of $F_1(z)$ and $S_1(z)$ in this case (again with at most one of the constants C_i is equal to zero). We note that $S_1(z)$ can be obtained explicitly given $N(z)$ and $F_1(z)$.

Again we assume that $C_3=0$ (i.e., $J(0^+)=N(0)/\gamma_1$). Depending on the value of α_0, λ_0 and c, one of the exponential terms in (4.11) is the leading behaviour of $N(z)$ when z approaches $-\infty$ (for instance, if $c>(1-\alpha_0/\lambda_0)s$, then $\lambda_2<\lambda_1$ and $\gamma_0C_2e^{\lambda_2 z}$ dominates the

behaviour of $N(z)$ as z approaches $-\infty$). Therefore, $N(z)$ is approximately equivalent to

$$N(z)\approx\begin{cases}\delta_1 e^{\mu_1 z}, & z<0,\\ N(0)e^{-\lambda_4 z}, & z\geq 0,\end{cases} \tag{4.22}$$

as $z\to\pm\infty$, where $\mu_1=\min(\lambda_1,\lambda_2)$ and δ_1 is the coefficient of the leading term $e^{\mu_1 z}$. Substituting (4.22) into (4.2c) and integrating thereafter one obtains as solution as $z\to\pm\infty$,

$$F_1(z)=\begin{cases}\left[\alpha_1^1 I_{k_1}\left(\alpha_{1,1}e^{(\mu_1/2)z}\right)+\alpha_2^1 K_{k_1}\left(\alpha_{1,1}e^{(\mu_1/2)z}\right)\right]e^{-(c/(2D_F))z}, & z<0,\\ \left[\alpha_1^2 I_{k_2}\left(\alpha_{2,2}e^{-(\lambda_4/2)z}\right)+\alpha_2^2 K_{k_2}\left(\alpha_{2,2}e^{-(\lambda_4/2)z}\right)\right]e^{-(c/(2D_F))z}, & z\geq 0,\end{cases} \tag{4.23}$$

where $k_1=\sqrt{c^2+4\alpha_1 D_F}/(D_F\mu_1)$, $k_2=\sqrt{c^2+4\alpha_1 D_F}/(D_F\lambda_4)$ (with $k_i>0$), $\alpha_{1,1}=\sqrt{4\delta_1\alpha D_F}/(D_F\mu_1)$, $\alpha_{2,2}=\sqrt{4N(0)\alpha D_F}/(D_F\lambda_4)$, and α_1^1, α_2^1, α_1^2 and α_2^2 are arbitrary constants. We have previously studied [42] the continuity and boundedness of (4.23) and we obtained the constraints $\alpha_2^1=\alpha_2^2=0$, $\alpha_1^2=F_1(0)/I_{k_2}(\alpha_{2,2})$, and, for $-\alpha_0 t<z<0$, (with $\alpha_0=(\sqrt{c^2+4\alpha_1 D_F}+c)/2$), $\alpha_1^1=F_1(0)/I_{k_1}(\alpha_{1,1})$. We note that $c/(2D_F)$ can be interpreted as the wave number (its unit is m^{-1}); this is the magnitude of the wave vector, which helps to describe the wave. Taking into account the continuity and boundedness conditions, then substituting (4.22) and (4.23) into (4.2d) and integrating, we obtain

$$S_1(z)=\begin{cases}\delta_1^1 e^{-\tau_1 z}+\delta_2^1 e^{\tau_2 z}-\dfrac{\beta\delta_1\alpha_1^1 e^{-\tau_1 z}}{\tau_3}\displaystyle\int_z^0 e^{\tau_6 z_1} I_{k_1}\left(\alpha_{1,1}e^{(\mu_1/2)z_1}\right)dz_1\\ \qquad+\dfrac{\beta\delta_1\alpha_1^1 e^{\tau_2 z}}{\tau_3}\displaystyle\int_z^0 e^{\tau_7 z_1} I_{k_1}\left(\alpha_{1,1}e^{(\mu_1/2)z_1}\right)dz_1, & z<0,\\ \delta_1^2 e^{-\tau_1 z}+\delta_2^2 e^{\tau_2 z}+\dfrac{\beta N(0)\alpha_1^2 e^{-\tau_1 z}}{\tau_3}\displaystyle\int_0^z e^{\tau_8 z_1} I_{k_2}\left(\alpha_{2,2}e^{-(\lambda_4/2)z_1}\right)dz_1\\ \qquad-\dfrac{\beta N(0)\alpha_1^2 e^{\tau_2 z}}{\tau_3}\displaystyle\int_0^z e^{\tau_9 z_1} I_{k_2}\left(\alpha_{2,2}e^{-(\lambda_4/2)z_1}\right)dz_1, & z\geq 0,\end{cases} \tag{4.24}$$

where δ_1^1, δ_2^1, δ_1^2 and δ_2^2 are integration constants, τ_1, τ_2 and τ_3 are given in (4.10), and

$$\tau_6=\frac{-c}{2D_F}+\frac{c}{D_S}+\tau_2+\mu_1, \qquad \tau_7=\frac{-c}{2D_F}+\frac{c}{D_S}-\tau_1+\mu_1, \tag{4.25a}$$

$$\tau_8=\frac{-c}{2D_F}+\frac{c}{D_S}+\tau_2-\lambda_4, \qquad \tau_9=\frac{-c}{2D_F}+\frac{c}{D_S}-\tau_1-\lambda_4. \tag{4.25b}$$

We have also proved [42] the boundedness of (4.24), and we found that $S_1(z)$ is positive and converges (only to zero) as $z\to\pm\infty$ if and only if

$$\delta_1^1=\frac{\beta\delta_1\alpha_1^1(\alpha_{1,1}/2)^{k_1}}{\tau_3(\mu_1 k_1/2+\tau_6)\Gamma(1+k_1)}, \quad \delta_2^2=\frac{-\beta N(0)\alpha_1^2(\alpha_{2,2}/2)^{k_2}}{\tau_3(-\lambda_4 k_2/2+\tau_9)\Gamma(1+k_2)}. \tag{4.26}$$

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

Theorem 4.2. *For $\alpha_0 < 2\lambda_0$ and $J(0^+) = N(0)/\gamma_1$, asymptotic diffusing travelling wave solutions exist and are explicitly given by*

$$N(z) = \begin{cases} \delta_1 e^{\mu_1 z}, & z < 0, \\ N(0) e^{-\lambda_4 z}, & z \geq 0, \end{cases} \tag{4.27}$$

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

$$F_1(z) = \begin{cases} F_1(0) I_{k_1}\left(\alpha_{1,1} e^{(\mu_1/2)z}\right) e^{-(c/(2D_F))z} \Big/ I_{k_1}(\alpha_1), & z < 0, \\ F_1(0) I_{k_2}\left(\alpha_{2,2} e^{-(\lambda_4/2)z}\right) e^{-(c/(2D_F))z} \Big/ I_{k_2}(\alpha_2), & z \geq 0, \end{cases} \tag{4.28a}$$

$$S_1(z) = \begin{cases} \delta_1^1 e^{-\tau_1 z} + \delta_2^2 e^{\tau_2 z} - \dfrac{\beta\delta_1\alpha_1^1 e^{-\tau_1 z}}{\tau_3} \displaystyle\int_z^0 e^{\tau_6 z_1} I_{k_1}\left(\alpha_{1,1} e^{(\mu_1/2)z_1}\right) dz_1 \\ \qquad + \dfrac{\beta\delta_1\alpha_1^1 e^{\tau_2 z}}{\tau_3} \displaystyle\int_z^0 e^{\tau_7 z_1} I_{k_1}\left(\alpha_{1,1} e^{(\mu_1/2)z_1}\right) dz_1, & z < 0, \\ \delta_1^1 e^{-\tau_1 z} + \delta_2^2 e^{\tau_2 z} + \dfrac{\beta N(0)\alpha_1^2 e^{-\tau_1 z}}{\tau_3} \displaystyle\int_0^z e^{\tau_8 z_1} I_{k_2}\left(\alpha_{2,2} e^{-(\lambda_4/2)z_1}\right) dz_1 \\ \qquad - \dfrac{\beta N(0)\alpha_1^2 e^{\tau_2 z}}{\tau_3} \displaystyle\int_0^z e^{\tau_9 z_1} I_{k_2}\left(\alpha_{2,2} e^{-(\lambda_4/2)z_1}\right) dz_1, & z \geq 0, \end{cases} \tag{4.28b}$$

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 (4.26).

In the above Theorem 4.2, $N(z)$ and $F(x,t)$ are positive and bounded, and $F(x,t)$ is continuous (we note that $N(z)$ is not continuous at zero). The asymptotic solution $S_1(z)$ is mathematically similar to that of zero growth, with positivity and $S_1 \in Y_S$ already demonstrated [42]. The similarity to the zero growth case is not surprising as both models have the same boundary conditions as $z \to \pm\infty$. Given that the Bessel functions I_{k_1} and I_{k_2} in (4.28a) are bounded, the wave number $c/(2D_F)$ controls the asymptotic distribution of the succinate concentration $F_1(z)$. However, the asymptotic distribution of cells is controlled by the unbiased turning rate λ_0 and the growth rate α_0. Graphically, we observe low consumption of succinate and low production of aspartate (see Fig. 2); diffusion affects the activity of cells.

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

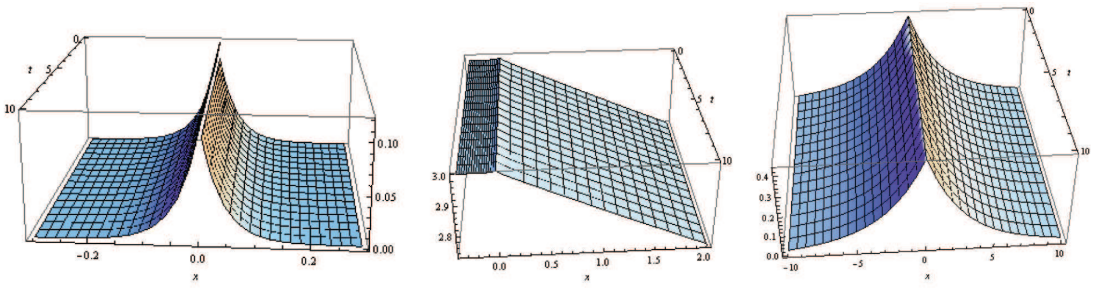
Given the form of G_1, only standard travelling wave solutions can be considered in this case (i.e., $\alpha_1 = 0$). For $S_1 \in Y_S$, (3.10a)-(3.11b) can be written as follows:

$$N' = c_1 N + d_1 J + \frac{\beta_0 c}{s^2 - c^2} F_1 N + \frac{\beta_0}{s^2 - c^2} F_1 J, \tag{4.29a}$$

$$J' = c_2 N + c d_1 J + \frac{\beta_0 s^2}{s^2 - c^2} F_1 N + \frac{\beta_0 c}{s^2 - c^2} F_1 J, \tag{4.29b}$$

$$-c F_1' = D_F F_1'' - \alpha F_1 N, \tag{4.29c}$$

$$-c S_1' = D_S S_1'' + \beta F_1 N - \gamma S_1, \tag{4.29d}$$



(a) (b) (c)

Figure 2: Distribution of cell density (see (a)) and diffusing substrates (see (b) for succinate concentration, and (c) for aspartate concentration) in the case of high sensitivity to the signal (we set the parameters as follows: $D_F = D_S = 9\times10^{-5}\text{cm}^2/\text{s}$, $s = 20\mu\text{m/s}$, $\lambda_0 = 0.5/\text{s}$, $\alpha = \beta = 0.1/\text{s}$, $\alpha_0 = 0.5$, $N(0) = 0.1$, $F_1(0) = 3$, $\gamma = 0.001/\text{s}$, $\alpha_1 = 0$, $c = 1.5\text{mm/h}$ and $J(0^-) = 0.0021$).

where

$$c_1 = \frac{-\beta_0 c F_c - 2\lambda_0 s}{s^2 - c^2}, \quad d_1 = \frac{-(\beta_0 F_c + 2\lambda_0)}{s^2 - c^2}, \quad c_2 = \frac{-\beta_0 s^2 F_c - 2\lambda_0 cs}{s^2 - c^2}, \tag{4.30}$$

for $z > 0$, and

$$c_1 = \frac{-\beta_0 c F_c + 2\lambda_0 s}{s^2 - c^2}, \quad d_1 = \frac{-(\beta_0 F_c + 2\lambda_0)}{s^2 - c^2}, \quad c_2 = \frac{-\beta_0 s^2 F_c + 2\lambda_0 cs}{s^2 - c^2}, \tag{4.31}$$

for $z < 0$.

Rewriting (4.29a)-(4.29c) 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 (4.29c)); 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 $F_1(z)$ in terms of $N(z)$ and $J(z)$, and substitute back into (4.29a)-(4.29b) to obtain an autonomous system in $N(z)$ and $J(z)$ only. The stability analysis will help us to investigate the asymptotic behaviour of $N(z)$ and $J(z)$. Thereafter we will deduce the asymptotic behaviour of $F_1(z)$ and $S_1(z)$.

We assume $D_S = D_F = 0$. From (4.29a)-(4.29b) and (4.29c),

$$\begin{aligned} N(z) &= \frac{1}{(cc_1 - c_2)}\left(cN'(z) - J'(z) + \beta_0 F_1(z) N(z)\right) \\ &= \frac{1}{\beta_0 F_c}\left(cN'(z) - J'(z) + \frac{\beta_0 c}{\alpha} F_1'(z)\right). \end{aligned} \tag{4.32}$$

This implies that

$$\int_0^z N(z_1)dz_1 = \frac{cN(z) - J(z) + (\beta_0 c/\alpha)F_1(z) - (cN(0) - J(0) + (\beta_0 c/\alpha)F_1(0))}{\beta_0 F_c}. \tag{4.33}$$

Then, from (4.29c),

$$F_1(z)=F_1(0)\exp\left(\frac{\alpha}{c}\int_0^z N(z_1)dz_1\right)=F_{00}\exp\left(\frac{\alpha(cN(z)-J(z))+\beta_0 cF_1(z)}{\beta_0 cF_c}\right), \tag{4.34}$$

where

$$F_{00}=F_1(0)\exp\left(-\frac{\alpha(cN(0)-J(0))+\beta_0 cF_1(0))}{\beta_0 cF_c}\right). \tag{4.35}$$

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

$$F_1(z)\mathrm{e}^{-(1/F_c)F_1(z)}=F_{00}\exp\left(\frac{\alpha(cN(z)-J(z))}{\beta_0 cF_c}\right), \tag{4.36}$$

and explicitly by

$$F_1(z)=f(N(z),J(z))=-F_c\times W\left(\frac{-F_{00}}{F_c}\exp\left(\frac{\alpha(cN(z)-J(z))}{\beta_0 cF_c}\right)\right), \tag{4.37}$$

where W stands for the Product logarithm function (also called *Lambert W function*) [10]. If $N(z)$ and $J(z)$ converge as $z\to\pm\infty$, then from (4.36), $F_1(z)$ converges to a non zero value as $z\to\pm\infty$. In fact, the convergence of $N(z)$ and $J(z)$ causes the function $g(z)=F_1(z)\mathrm{e}^{-(1/F_c)F_1(z)}$ to converge to $l\neq 0$. Consequently, $F_1(z)$ cannot diverge nor converge to zero as $z\to\pm\infty$ (given from (4.34) that $F_1(z)$ is positive). We also note that $F_1(z)$ is positive and bounded by F_c (since $-1\leq w(x)\leq 0$ when $x\leq 0$).

We now examine the stability of $N(z)$ and $J(z)$. Substituting (4.37) into (4.29a)-(4.29b), we obtain an autonomous system of differential equations in N and J written as follows:

$$N'=c_1N+d_1J+\frac{\beta_0 c}{s^2-c^2}Nf(N,J)+\frac{\beta_0}{s^2-c^2}Jf(N,J), \tag{4.38a}$$

$$J'=c_2N+cd_1J+\frac{\beta_0 s^2}{s^2-c^2}Nf(N,J)+\frac{\beta_0 c}{s^2-c^2}Jf(N,J). \tag{4.38b}$$

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

$$J^*=\frac{\beta_0 cF_c}{\alpha}\log\left(\frac{\beta_0 F_{00}}{\beta_0 F_c+2\lambda_0}\exp\left(\frac{\beta_0 F_c+2\lambda_0}{\beta_0 F_c}\right)\right). \tag{4.39}$$

At the vicinity of $(0,0)$, the linearised system associated with (4.38a)-(4.38b) is given by

$$N'=\left(c_1+\frac{\beta_0 c}{s^2-c^2}f(0,0)\right)N+\left(d_1+\frac{\beta_0}{s^2-c^2}f(0,0)\right)J, \tag{4.40a}$$

$$J'=\left(c_2+\frac{\beta_0 s^2}{s^2-c^2}f(0,0)\right)N+c\left(d_1+\frac{\beta_0}{s^2-c^2}f(0,0)\right)J, \tag{4.40b}$$

the determinant of the Jacobian matrix is

$$\Delta_1 = \frac{(-(\beta_0 F_c + 2\lambda_0) + \beta_0 f(0,0))(\beta_0 F_c - \beta_0 f(0,0))}{s^2 - c^2}, \tag{4.41}$$

and the corresponding eigenvalues are

$$\lambda_6 = \frac{\beta_0(f(0,0) - F_c)}{s-c}, \quad \text{and} \quad \lambda_7 = \frac{\beta_0 F_c + 2\lambda_0 - \beta_0 f(0,0)}{s+c}, \tag{4.42}$$

if $z < 0$, and

$$\lambda_8 = \frac{\beta_0(F_c - f(0,0))}{s+c}, \quad \text{and} \quad \lambda_9 = \frac{-(\beta_0 F_c + 2\lambda_0) + \beta_0 f(0,0)}{s-c}, \tag{4.43}$$

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

Given that $F_c > f(0,0)$ (since the *Lambert* function $W(x) > -1$), 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 $N(z)$ and $J(z)$ (with the eigenspace E_{λ_7} leading the behaviour in the half plane $z \leq 0$, and E_{λ_9} leading the behaviour in the half plane $z \geq 0$), then it will require discontinuity of $N(z)$ and $J(z)$ at zero. Travelling wave solutions in this situation are not possible. The concentration of succinate being bounded by F_c, cells do not reproduce ($h(F) < 0$). Therefore, the high sensitivity to extracellular signalling and the fluctuation of the death rate of cells, cause instability and prevent the formation of travelling band of cells with constant speed. This shows the importance of reproduction in the collective migration.

5 Discussion

In this 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 [8, 9, 46]. Given that travelling waves have mainly been analysed from the macroscopic point of view, we focused on the microscopic level. We additionally 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, 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 [41].

When cells are highly sensitive to the signal, we assumed that the aspartate concentration distributes with a single peak. This assumption was motivated by the results of the numerical investigation of [47]. We considered first the scenario of constant cell growth

rate α_0 (for it was observed that cells grew at a constant rate over a certain concentration of succinate [9]). For $\alpha_0 = 2\lambda_0$, 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 [9] 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 [9]. Recall that this situation is mathematically equivalent to the non starvation case [42, 47] 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. We found that the distribution of succinate is controlled by the wave number $c/(2D_F)$, whereas the distribution of cells is controlled by the unbiased turning rate λ_0 and the growth rate α_0, at the boundaries.

For the case of linear growth rate, we were able, in spite of the complexity of the model, to integrate the system and explore the behaviour of the solutions at the boundaries. This is in contrast to [16] 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 light of our investigation, we observe, in comparison to the literature, significant changes (loss, creation or fluctuation) of information while looking from a microscale angle to understand macro behaviours. In fact, unlike the [19, 20] 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 [47]. 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 Section 4.1 to the case $\alpha_0 < 2\lambda_0$). This is in contrast to the [24] finding in the macroscopic model, in which the zero cell growth decreases the speed of the wave but does not prevent the cells to aggregate.

We note that our model was only formulated in one-dimensional space. As a result, intracellular dynamic variables were not represented explicitly even though they play a central role in the response of cells to extracellular signalling. For future work, we will consider higher dimensional spaces and will also investigate the geometric patterns of bands of cells.

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