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Travelling waves in a minimal go-or-grow model of cell invasion

Carles Falcó*, Rebecca M. Crossley, Ruth E. Baker

Mathematical Institute, University of Oxford, OX2 6GG, Oxford, United Kingdom

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ABSTRACT

We consider a minimal go-or-grow model of cell invasion, whereby cells can either proliferate, following logistic growth, or move, via linear diffusion, and phenotypic switching between these two states is density-dependent. Formal analysis in the fast switching regime shows that the total cell density in the two-population go-or-grow model can be described in terms of a single reaction–diffusion equation with density-dependent diffusion and proliferation. Using the connection to single-population models, we study travelling wave solutions, showing that the wave speed in the go-or-grow model is always bounded by the wave speed corresponding to the well-known Fisher–KPP equation.

1. Introduction

Reaction–diffusion equations are widely used to describe the dynamics of invading species, such as cells, and often exhibit travelling wave solutions. A classic example is the Fisher–Kolmogorov–Petrovsky–Piskunov (FKPP) equation, which assumes that cells move via linear diffusion and proliferate following logistic growth [1,2]. In the last decade however, so-called go-or-grow models [3–7] have been suggested to describe the dichotomous behaviour observed in experiments whereby an individual cell either proliferates slowly and migrates quickly, or proliferates quickly and migrates slowly [8,9]. Under the go-or-grow hypothesis, cells are also able to transition between the migratory and proliferative states via a phenotypic switch. The mechanism underlying this switching behaviour is not yet fully understood [10,11], but could be due to a variety of factors such as surrounding cell density, pressure or environmental features, amongst others. One way to model heterogeneous populations of cells under the go-or-grow hypothesis is to use systems of reaction–diffusion equations. For specific forms of the phenotypic switching functions, previous works study approximations of the travelling wave solutions by combining the method introduced by Canosa [12] with qualitative theory and numerical simulations [5,6]. Interestingly, these studies revealed notable differences between the minimum travelling wave speed predicted analytically and the speed observed numerically. However, minimal progress has been made to understand how invasion phenomena depend on the switching functions more generally [7].

In this work, we study invasion phenomena in a minimal go-or-grow model, whereby cells either proliferate or migrate, and switching between phenotypic states occurs via general switching functions. After presenting this model in Section 2, we first demonstrate, via a formal fast reaction limit [13,14], the connection between a model involving phenotypically distinct populations and a model consisting of a single population of cells, that has density-dependent diffusion and proliferation terms. Interestingly, this analysis reveals a connection between multiple phenotype models with density-dependent switching functions, and degenerate diffusion models consisting of a single phenotype, for which the standard linear stability analysis does not yield accurate travelling wave speed predictions [15,16]. We then proceed in Section 3 to perform a travelling wave analysis of the minimal go-or-grow

* Corresponding author.

E-mail addresses: falcoigandia@maths.ox.ac.uk (C. Falcó), rebecca.crossley@maths.ox.ac.uk (R.M. Crossley), ruth.baker@maths.ox.ac.uk (R.E. Baker).

model presented in this work and show that the minimum travelling wave speed emitted from the model does not exceed that of the FKPP equation. Furthermore, we demonstrate that, for specific forms of the phenotypic switching function, solutions of the multiple phenotype model do not attain this minimum travelling wave speed. This analysis provides an explanation for the discrepancies observed in prior studies between the minimum wave speed predicted analytically and the numerically observed travelling wave speed [8].

2. A minimal go-or-grow model

We consider a heterogeneous cell population consisting of cells which are either proliferative or invasive. The density of the invasive population is represented by $\rho_1(\mathbf{x}, t)$ and the density of the proliferative population is given by $\rho_2(\mathbf{x}, t)$, for $(\mathbf{x}, t) \in \mathbb{R}^d \times [0, +\infty)$. For the sake of simplicity, we assume that invasive cells move via linear diffusion, and can switch to the proliferative phenotype at a rate given by the switching function $\Gamma_1(\rho)$, which depends on the total cell density $\rho = \rho_1 + \rho_2$. On the other hand, we assume that the proliferative cells follow logistic growth, and can switch to the invasive phenotype at a rate given by $\Gamma_2(\rho)$. With this, the model reads

$$\begin{aligned}\partial_t \rho_1 &= \Delta \rho_1 - \rho_1 \Gamma_1(\rho) + \rho_2 \Gamma_2(\rho), \\ \partial_t \rho_2 &= \rho_2 (1 - \rho) + \rho_1 \Gamma_1(\rho) - \rho_2 \Gamma_2(\rho).\end{aligned}\quad (1)$$

Following from standard rescalings of space and time, the diffusion coefficient and the intrinsic proliferation rate in Eqs. (1) have been set to one without loss of generality. We also note that this model does not account for cell death, however apoptosis can be readily incorporated into the model, as demonstrated in [5,6], without altering the analysis. The results in this work generalise directly to this scenario.

The model given in Eqs. (1) is studied in [5,6] for specific choices of switching functions, which facilitate analytic tractability. Here, and unless stated otherwise, we keep $\Gamma_1(\rho)$ and $\Gamma_2(\rho)$ general. Following the biological intuition that regions of high cell density lead to contact inhibition or nutrient limitation, and hence to inhibition of proliferation [17,18], typical switching functions are based on the assumption that $\Gamma_1(\rho)$ is non-increasing, and $\Gamma_2(\rho)$ is non-decreasing. We further assume that Γ_1 and Γ_2 are non-negative. While the model presented here is simpler, it remains closely related to those examined in [3,4], which consider density-dependent diffusion, and in [7], which further incorporates the influence of the extracellular matrix on cell invasion.

2.1. Connecting heterogeneous to single-population models

We investigate the fast phenotypic switching limit of Eqs. (1). In other words, we assume $\Gamma_1(\rho) = \tilde{\Gamma}_1(\rho)/\epsilon$, and $\Gamma_2(\rho) = \tilde{\Gamma}_2(\rho)/\epsilon$ where $\tilde{\Gamma}_1(\rho), \tilde{\Gamma}_2(\rho) \sim O(1)$ for $\epsilon \ll 1$. Upon formally taking the limit $\epsilon \rightarrow 0$ in Eqs. (1), we obtain $\rho_1 \tilde{\Gamma}_1(\rho) = \rho_2 \tilde{\Gamma}_2(\rho)$, and the two cell densities ρ_1 and ρ_2 can be related to the total cell density via

$$\rho_1 = \frac{\Gamma_2(\rho)}{\Gamma_1(\rho) + \Gamma_2(\rho)} \rho, \quad \rho_2 = \frac{\Gamma_1(\rho)}{\Gamma_1(\rho) + \Gamma_2(\rho)} \rho. \quad (2)$$

Consider now the equation governing the evolution of the total cell density over time,

$$\partial_t \rho = \Delta \rho + \rho_2 (1 - \rho). \quad (3)$$

Combining Eqs. (2) and (3) we obtain the following equation for the evolution of the total cell density

$$\partial_t \rho = \nabla \cdot (D(\rho) \nabla \rho) + r(\rho) \rho, \quad (4)$$

with the density-dependent diffusion coefficient $D(\rho)$, and proliferation rate $r(\rho)$, given by

$$D(\rho) = \frac{\Gamma_1(\rho) \Gamma_2'(\rho) - \Gamma_1'(\rho) \Gamma_2(\rho)}{(\Gamma_1(\rho) + \Gamma_2(\rho))^2} \rho + \frac{\Gamma_2(\rho)}{\Gamma_1(\rho) + \Gamma_2(\rho)}, \quad r(\rho) = \frac{\Gamma_1(\rho)(1 - \rho)}{\Gamma_1(\rho) + \Gamma_2(\rho)}.$$

In this case, assuming that Γ_1 is a non-increasing function of the total cell density is sufficient to show that the diffusion coefficient does not become negative, i.e. $D(\rho) \geq 0$ for any $\rho \geq 0$; and also that the per capita proliferation rate is a non-increasing function of density, i.e. $r'(\rho) \leq 0$. As mentioned earlier, this assumption on Γ_1 aligns with basic biological intuition. Moreover, under the assumption that cells remain proliferative at low densities, so that $\Gamma_2(0) = 0$, we obtain that the diffusion coefficient follows $D(\rho) \sim 2\Gamma_2'(0)/\Gamma_1(0)\rho + O(\rho^2)$ (for $\Gamma_2'(0) \neq 0$ and $\Gamma_1(0) \neq 0$), which resembles typical non-linear equations with degenerate diffusion.

Finally, we highlight that in the case of constant switching rates ($\Gamma_1' = \Gamma_2' = 0$), we have $D(\rho) = \theta := \Gamma_2/(\Gamma_1 + \Gamma_2)$ and $r(\rho) = (1 - \theta)(1 - \rho)$ where $\theta \in (0, 1)$ is a constant. Hence, we recover the well-known FKPP equation [15],

$$\partial_t \rho = \theta \Delta \rho + (1 - \theta)\rho(1 - \rho). \quad (5)$$

Equations of this type often exhibit travelling wave solutions in one spatial dimension such that $\rho(x, t) = U(x - ct)$, where $c \geq 0$ corresponds to the wave speed. In particular, the FKPP equation (Eq. (5)) admits travelling wave solutions with constant speed $c \geq c_{\min} = 2\sqrt{\theta(1 - \theta)}$. We note that $c_{\min} \leq 1$ for $\theta \in (0, 1)$, which we use as a reference to compare with the speed of propagation of travelling wave solutions to Eqs. (1).

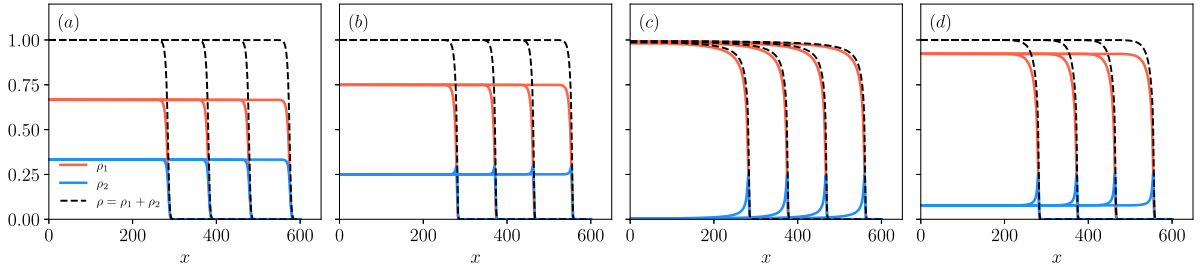


Fig. 1. Numerical solutions to Eqs. (1) subject to the initial conditions $\rho_1(x, 0) = \rho_2(x, 0) = 0.2$ for $0 \leq x < 100$, and $\rho_1(x, 0) = \rho_2(x, 0) = 0$ for $x \geq 100$, and for different choices of the switching functions F_1, F_2 . Solutions are plotted at times $t = 200, 300, 400, 500$. Chosen switching functions are as follows: (a) $F_1(\rho) = 0.5, F_2(\rho) = 1$; (b) $F_1(\rho) = 0.5, F_2(\rho) = 1.5\rho$; (c) $F_1(\rho) = 0.5(1 - \rho), F_2(\rho) = 1.5\rho$; (d) $F_1(\rho) = 0.5(1 - \rho^2/(0.5^2 + \rho^2)), F_2(\rho) = 1.5\rho^2/(0.5^2 + \rho^2)$.

3. Travelling wave analysis for heterogeneous populations

We now revisit Eqs. (1) in one spatial dimension to analyse travelling wave solutions of the form: $\rho_1(x, t) = U_1(x - ct)$, and $\rho_2(x, t) = U_2(x - ct)$. Fig. 1 shows travelling wave solutions of Eqs. (1) subject to different choices of the switching functions. Based on the biological intuition that high cell densities often lead to contact inhibition of proliferation, we chose F_1 to be a non-increasing function and F_2 to be a non-decreasing function of the total cell density ρ . By defining $z = x - ct \in (-\infty, +\infty)$, and writing Eqs. (1) in travelling wave coordinates we obtain

$$\begin{aligned} c \frac{dU_1}{dz} + \frac{d^2U_1}{dz^2} - U_1 F_1(U) + U_2 F_2(U) &= 0, \\ c \frac{dU_2}{dz} + U_2(1 - U) + U_1 F_1(U) - U_2 F_2(U) &= 0, \end{aligned} \quad (6)$$

where $U(z) = U_1(z) + U_2(z)$. Next, we look at steady states of Eqs. (6).

First note that the origin $(U_1, U_2) = (0, 0)$ is always a steady state, and we assume $U_1, U_2 \rightarrow 0$ as $z \rightarrow +\infty$. The other steady states, corresponding to $z \rightarrow -\infty$, depend on the choice of phenotypic switching functions (see Fig. 1) and belong to the set $\{(U_1, U_2) \in [0, 1]^2 : U_1 F_1(U) = U_2 F_2(U), U_2(1 - U) = 0\}$. From the second condition, $U_2(1 - U) = 0$, we must either have $U_2 = 0$ or $U = 1$. If $U_2 = 0$, the first condition becomes $U_1 F_1(U) = 0$, and a steady state with $U_1 \neq 0$ can only occur if there exists a $U^* > 0$ such that $F_1(U^*) = 0$. In this case, we obtain

$$(U_1, U_2) = (U^*, 0).$$

This is confirmed by numerical simulations in Fig. 1c when F_1 decreases linearly with the density.

On the other hand, if $F_1(U) > 0$ for all $U > 0$, then we must have $U = 1$, and we obtain

$$(U_1, U_2) = \left(\frac{F_2(1)}{F_1(1) + F_2(1)}, \frac{F_1(1)}{F_1(1) + F_2(1)} \right).$$

This second case corresponds to panels (a), (b) and (d) in Fig. 1.

3.1. Dispersion relation and minimum travelling wave speed

When seeking an expression for the travelling wave speed, c , it is often commonplace to perform a linear stability analysis centred around the origin, which yields a lower bound on the speed: $c \geq c_{\min}$, for some minimum wave speed $c_{\min} \geq 0$. Unfortunately, for the model presented in this work, analytical progress following this approach is limited and instead we shift the investigation to identify the dispersion relation, which relates the travelling wave speed with the dynamics at the leading front. We observe that at the leading front, cell densities are small, and hence we can linearise Eqs. (6) to give

$$\begin{aligned} c \frac{dU_1}{dz} + \frac{d^2U_1}{dz^2} - \gamma_1 U_1 + \gamma_2 U_2 &= 0, \\ c \frac{dU_2}{dz} + \gamma_1 U_1 + (1 - \gamma_2) U_2 &= 0, \end{aligned} \quad (7)$$

where we denote $\gamma_i = F_i(0)$ for $i = 1, 2$. By substituting the ansatz $U_1(z) \sim A e^{-\sigma z}$, $U_2(z) \sim B e^{-\sigma z}$, for $z \gg 1$ and $A, B \geq 0$ constants, we obtain

$$\underbrace{\begin{pmatrix} -c\sigma + \sigma^2 - \gamma_1 & \gamma_2 \\ \gamma_1 & -c\sigma + 1 - \gamma_2 \end{pmatrix}}_M \begin{pmatrix} A \\ B \end{pmatrix} = 0.$$

In order to ensure $A, B \neq 0$, we require $\det M = 0$, which gives

$$c^2 - c \left(\sigma + \frac{1 - \gamma_1 - \gamma_2}{\sigma} \right) + 1 - \gamma_2 - \frac{\gamma_1}{\sigma^2} = 0.$$

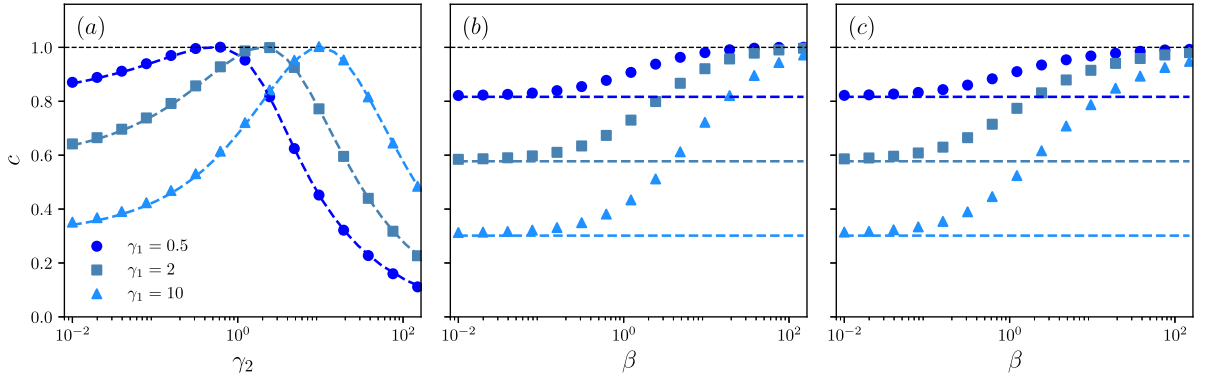


Fig. 2. Relationship between the estimated numerical speed (dots) of travelling wave solutions to Eqs. (1), and the minimum wave speed predicted by Eq. (8) (dashed lines). Numerical wave speed estimated using a trapezoidal rule applied to the expression $c = \int_{-\infty}^{+\infty} U_2(z)(1 - U(z)) dz$, which follows from Eq. (6) (note that the integrand $U_2(z)(1 - U(z))$ is exponentially small outside a narrow region near the front of the wave). Eqs. (1) are solved on a domain of length 7000, for a maximum simulation time of 6500, and initial conditions given by $\rho_1(x, 0) = \rho_2(x, 0) = 0.2$ if $0 \leq x < 100$ and $\rho_1(x, 0) = \rho_2(x, 0) = 0$ if $x \geq 100$. Chosen switching functions are as follows: (a) $\Gamma_1(\rho) = \gamma_1$, $\Gamma_2(\rho) = \gamma_2$; (b) $\Gamma_1(\rho) = \gamma_1$, $\Gamma_2(\rho) = \beta\rho$; (c) $\Gamma_1(\rho) = \gamma_1(1 - \rho^2/(0.5^2 + \rho^2))$, $\Gamma_2(\rho) = \beta\rho^2/(0.5^2 + \rho^2)$.

The travelling wave speed, c , can then be solved for as a function of σ , giving the dispersion relation:

$$c(\sigma) = \frac{1}{2} \left(f(\sigma) + \sqrt{f(\sigma)^2 - 4(1 - \gamma_2) + \frac{4\gamma_1}{\sigma^2}} \right), \quad f(\sigma) = \sigma + \frac{1 - \gamma_1 - \gamma_2}{\sigma}, \quad (8)$$

where we used that $c \geq 0$. The expression above predicts the existence of a minimum travelling wave speed, c_{\min} for $\sigma = \sigma^*$, such that $c_{\min} = c(\sigma^*)$. Finding the minimum speed analytically is challenging; we tried differentiating with respect to σ and it did not yield any progress. Instead we observe that $c(1) = 1$, and by differentiating $c(\sigma)$ with respect to σ and evaluating at $\sigma = 1$, we obtain

$$\left(\frac{dc}{d\sigma} \right)_{\sigma=1} = \frac{\gamma_2 - \gamma_1}{\gamma_1 + \gamma_2}.$$

Thus, for $\gamma_1 = \gamma_2$, $\sigma^* = 1$ yields the minimum wave speed, and in this case it is given by $c_{\min} = 1$. On the other hand, when $\gamma_1 > \gamma_2$ we have $(dc/d\sigma)_{\sigma=1} < 0$, and $\sigma^* > 1$ with $c_{\min} < 1$. An analogous argument yields $\sigma^* < 1$ and $c_{\min} < 1$ for $\gamma_1 < \gamma_2$. Hence, the minimum travelling wave speed displayed by Eqs. (1) is bounded from above by the minimum travelling wave speed corresponding to the FKPP model, Eq. (5). Fig. 2a shows an excellent agreement between the numerically observed speed and the prediction from Eq. (8) for a fully linear model with constant switching functions.

However, in the case of a nonlinear model with non-constant switching functions, we observe that the achieved wave speed exceeds the prediction from the linear stability analysis (see Fig. 2b–c). These differences arise from nonlinear effects within the model. In particular, increasing levels of nonlinearity (represented by increasing β in the figure) result in larger discrepancies. In contrast with the case of constant switching functions, here we observe that the wave speed is nonlinearly selected [19–21].

3.2. Explicit expressions for the minimum travelling wave speed

Fully analytical expressions for c_{\min} can be obtained under the assumption that $\gamma_1 = 0$ or $\gamma_2 = 0$. We present first the $\gamma_2 = 0$ case as it represents a more biologically realistic scenario where cells remain proliferative at low densities. In this case, Eq. (8) simplifies to

$$c(\sigma) = \frac{1}{2} \left(\sigma + \frac{1 - \gamma_1}{\sigma} + \frac{|\sigma^2 - 1 - \gamma_1|}{\sigma} \right).$$

Note then that $c(\sigma)$ increases for $\sigma > \sqrt{1 + \gamma_1}$, and decreases for $\sigma < \sqrt{1 + \gamma_1}$. Hence, $\sigma^* = \sqrt{1 + \gamma_1}$, and

$$c_{\min} = \frac{1}{\sqrt{1 + \gamma_1}}. \quad (9)$$

When $\gamma_1 = 0$, a similar argument yields the minimum wave speed

$$c_{\min} = \begin{cases} \sqrt{1 - \gamma_2} & \text{for } \gamma_2 < 1, \\ 0 & \text{for } \gamma_2 > 1. \end{cases}$$

3.3. The minimum wave speed is not attainable when $\Gamma_2(0) = 0$.

Based on the behaviour observed in Fig. 2b–c, we focus on the case $\gamma_2 = \Gamma_2(0) = 0$, with $\Gamma_2 \neq 0$ to ensure that travelling wave solutions exist. By linearising Eqs. (6) subject to $\Gamma_2(0) = 0$, representing the region near the invading front where cell densities are

low, we obtain

$$c \frac{dU_1}{dz} + \frac{d^2U_1}{dz^2} - \gamma_1 U_1 = 0, \\ c \frac{dU_2}{dz} + \gamma_1 U_1 + U_2 = 0.$$

Solving this system of equations, subject to $U_1, U_2 \rightarrow 0$ as $z \rightarrow \infty$, yields

$$U_1(z) = Ae^{-\lambda(c)z}, \quad U_2(z) = \frac{\gamma_1}{c\lambda(c) - 1} Ae^{-\lambda(c)z}, \quad \lambda(c) = \frac{1}{2} \left(c + \sqrt{c^2 + 4\gamma_1} \right),$$

for an arbitrary constant $A > 0$. Note that here we used that both populations have the same wave speed, and hence $U_1, U_2 \sim e^{-\lambda(c)z}$ as $z \rightarrow +\infty$. Positivity of travelling wave solutions (i.e. $U_1, U_2 \geq 0$ for all $z \in \mathbb{R}$) requires $c\lambda(c) - 1 > 0$, which is only satisfied when $c > c_{\min}$ (as in Eq. (9)). In particular, we obtain that travelling wave solutions for $F_2(0) = 0$ exhibit a wave speed exceeding c_{\min} , i.e. $c > c_{\min}$ when $F_2(0) = 0$, that is, the wave speed is nonlinearly selected.

4. Discussion and open problems

In this work, we examined a minimal go-or-grow model, where cells can either proliferate following logistic growth or move through linear diffusion. Via a formal fast reaction limit in the fast phenotypic switching regime, we revealed a connection between heterogeneous models and single-population models. This relationship implies an approximate equivalence between phenotypically distinct cell population models and models where diffusion and proliferation rates are determined by cell density. Our analysis also suggests that the invasion speed in travelling wave solutions of heterogeneous models is bounded by the wave speed of solutions to single-populations models.

Furthermore, our travelling wave analysis also reveals a lower bound on the invasion speed of travelling wave solutions to go-or-grow models. This estimate, based on a linear stability analysis, breaks down for nonlinear models (see Fig. 2b–c), and is also observed in similar models [5,16,22,23]. Numerically, we observe that $c_{\min} \leq c \leq 1$ for the model given by Eqs. (6), and that $c \rightarrow 1$ as the nonlinear switching rates increase. Although this behaviour intuitively makes sense when considering the connection to single-population models, we do not currently have a rigorous proof. The application of previously utilised techniques for addressing linear and nonlinear wave speed selection could provide valuable insights for our model [19–21]. We leave these conjectures for further investigation.

Data availability

No data was used for the research described in the article.

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