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# Travelling waves for a velocity-jump model of cell migration and proliferation

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ABSTRACT

Cell invasion, characterised by moving fronts of cells, is an essential aspect of development, repair and disease. Typically, mathematical models of cell invasion are based on the Fisher–Kolmogorov equation. These traditional parabolic models cannot be used to represent experimental measurements of individual cell velocities within the invading population since they imply that information propagates with infinite speed. To overcome this limitation we study combined cell motility and proliferation based on a velocity-jump process where information propagates with finite speed. The model treats the total population of cells as two interacting subpopulations: a subpopulation of left-moving cells, $L(x,t)$, and a subpopulation of right-moving cells, $R(x,t)$. This leads to a system of hyperbolic partial differential equations that includes a turning rate, $\Lambda \geqslant 0$, describing the rate at which individuals in the population change direction of movement. We present exact travelling wave solutions of the system of partial differential equations for the special case where $\Lambda = 0$ and in the limit that $\Lambda \to \infty$. For intermediate turning rates, $0 < \Lambda < \infty$, we analyse the travelling waves using the phase plane and we demonstrate a transition from smooth monotone travelling waves to smooth nonmonotone travelling waves as $\Lambda$ decreases through a critical value $\Lambda_{crit}$. We conclude by providing a qualitative comparison between the travelling wave solutions of our model and experimental observations of cell invasion. This comparison indicates that the small $\Lambda$ limit produces results that are consistent with experimental observations.



## 1. Introduction

Cell invasion, characterised by moving fronts of cells, is an essential feature of development [42], tissue repair [20,21] and disease progression [24,31,41]. Moving fronts of cells can arise in systems that involve populations of motile cells that proliferate to a carrying capacity density. The combination of these two processes, cell motility and carrying capacity-limited proliferation, leads to invasion fronts that can move into vacant tissues leaving them uniformly occupied with cells behind the front.

Standard mathematical models of cell invasion are related to the Fisher–Kolmogorov equation [11,15], or extensions of the Fisher–Kolmogorov equation [4,8,26,27,41,53,54]. The Fisher–Kolmogorov equation is a parabolic reaction–diffusion model that supports travelling wave solutions [5,11,28] thought to represent constant speed moving cell fronts [20,21,48]. Other approaches to modelling moving fronts of cells include discrete position-jump models of cell movement [1,2,4,30,32,33,46,51] which, when combined with an appropriate carrying capacity-limited proliferation mechanism [4,44,48], can lead to invasion wave behaviour [45].

Advances in microscopy and imaging technologies mean that experimental measurements of cell invasion are becoming increasingly detailed and it is now possible to make measurements of the speed of individual cells within a bulk population of cells. For example, Britto [3] measured the speed of individual neurons within a population of neurons during development, comparing individual cell speed measurements in both wild-type and mutant mouse models. Kulesa [16] used detailed time lapse images within a developing mouse embryo to measure the speed of individual neural crest cells within an invading population with the aim of exploring whether the cell speed was related to the location of the cell. Nishiyama [29] also used time-lapse images to study individual neural crest cell movement within a developing mouse embryo and part of their study measured the velocity of individual cells. Similarly, Druckenbrod and Epstein used time-lapse images to study individual neural crest cell movement within an invasive population [9]. Druckenbrod and Epstein found that cells well behind the leading edge of the invading population were relatively immobile whereas cells at the leading edge tended to move in the same direction as the invading population [9]. Unfortunately, standard reaction–diffusion partial differential equations (PDEs) can not be used to make predictions of the speed of individual cells since these parabolic models imply that information propagates with infinite speed [50] even though information propagates with finite speed in the corresponding discrete position-jump process.

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To overcome this limitation of parabolic models, we will consider the continuum-limit PDE description of a discrete random walk model known as a velocity-jump process in which information propagates with finite speed [7,12–14,30]. Briefly, the discrete process in one-dimension involves considering a total population of cells to be composed of a subpopulation of left-moving cells and a subpopulation of right-moving cells [49]. Discrete simulations can be performed on a regular lattice with lattice spacing $\Delta$. During each discrete time interval, of duration $\tau$, each agent is given the opportunity to undergo a displacement of $v\tau$ with probability $P_m$, where $v$ is the agent velocity. This means that left-moving agents will attempt to step a distance $-v\tau$, and right-moving agents will attempt to step a distance of $+v\tau$. Agents are permitted to change velocity with probability $P_t$ per time step so that left-moving agents can convert into right-moving agents, and right-moving agents can convert into left-moving agents. Setting $P_t = 0$ gives purely ballistic motion, setting $P_t \ll 1$ gives persistent motion with occasional changes in direction, whereas setting $1 - P_t \ll 1$ gives essentially persistence-free motion. Agent proliferation can be incorporated by allowing each agent the opportunity to produce a daughter agent with probability $P_p$ per time step [50]. Other approaches are related to velocity-jump models, such as Carleman models [6,19,37], since these models also incorporate two different kinds of discrete particles that can move at different velocities and interact with each other in some way.

Traditional velocity-jump models ignore crowding effects so that multiple agents are permitted to reside at the same location in space and agents are permitted to step across other agents [7,10,12–14,55]. For applications in cell biology, cells have a finite size and do not occupy the same location in space [47]. Motivated by this observation, we previously introduced crowding effects into existing discrete velocity-jump models so that each lattice site could be occupied by, at most, only one agent [49]. We modified the usual motility and proliferation mechanisms to ensure that potential motility and proliferation events that would place more than one agent per site were aborted, and we showed that the resulting PDE description of these interacting velocity-jump processes is different to the usual PDE description of noninteracting velocity-jump models without crowding effects [49]. In particular, we showed that the governing PDEs for the proliferative velocity-jump process with crowding effects appears to give rise to solutions with moving fronts that tend to travelling waves as time increases [50].

Our aim in this work is to describe travelling wave solutions of a set of PDEs that can be used to describe cell invasion. We begin with the PDE models derived previously for an interacting velocity-jump model with proliferation [49,50]. The travelling wave solutions are presented for three cases: (i) Case 1, no turning (ii) Case 2, fast turning, and (iii) Case 3, intermediate turning rates. We analyse the governing system of PDEs using a combination of exact and numerical techniques, and we catalogue a range of travelling wave solutions that includes a transition from smooth monotone travelling waves to smooth nonmonotone travelling waves. The PDE solutions are quantitatively compared with several properties of the corresponding heteroclinic orbits in the phase plane. We conclude by comparing our travelling wave results with experimental observations of cell invasion. This qualitative comparison indicates our velocity jump model with small turning rates leads to travelling wave solutions that recapitulate several key aspects of the experiments.

## 2. Partial differential equation model

Our previous work described a discrete model of a proliferative velocity-jump process with crowding effects [50]. In one dimension, we showed that the system of PDEs governing this process is given by

$$\frac{\partial R}{\partial t'} = -v\frac{\partial}{\partial x'}[R(1-S)] + \lambda(L-R) + \theta R(1-S), \tag{1}$$

$$\frac{\partial L}{\partial t'} = +v\frac{\partial}{\partial x'}[L(1-S)] + \lambda(R-L) + \theta L(1-S), \tag{2}$$

where $L(x',t')$ is the density of left-moving cells, $R(x',t')$ is the density of right-moving cells and $S(x',t') = L(x',t') + R(x',t')$ is the total cell density. The parameters in the system of PDEs are the cell velocity $v$, the turning rate $\lambda$ and the proliferation rate $\theta$. These parameters are related to the parameters in the corresponding discrete process, $P_m$, $P_t$ and $P_p$, respectively [50].

The systems of PDEs, Eqs. (1) and (2), correspond to the continuum-limit description of a proliferative velocity jump discrete process. In brief, this system involves a population of agents on a one-dimensional lattice with lattice spacing $\Delta$. The population is composed of a left-moving subpopulation and a right-moving subpopulation. Motility events take place by allowing agents to move at some velocity, and crowding effects are incorporated into the system by allowing, at most, one agent to occupy each lattice site. This motility mechanism leads to the nonlinear flux terms in Eqs. (1) and (2) in the limit that $\Delta \to 0$ and $\tau \to 0$, where $\tau$ is the time step in the discrete model. Agents also undergo turning events whereby left-moving agents convert into right-moving agents, and right-moving agents convert into left-moving agents with some specified probability per time step. These turning events lead to the source terms in Eqs. (1) and (2) that are proportional to $\lambda$. Agents in the discrete model also undergo proliferation events with some specified probability per time step. A proliferative agent at some site will attempt to deposit a daughter agent at a nearest neighbouring lattice site provided that the target site is vacant. The proliferation events in the discrete model give rise to the source terms in Eqs. (1) and (2) that are proportional to $\theta$. More detail of the discrete mechanism and the derivation of the PDE description is presented in our earlier work [50].

To simplify the dimensional governing equations, Eqs. (1) and (2), we introduce the nondimensional variables $t = t'/T$ and $x = x'/X$, with $T = 1/\theta$ and $X = v/\theta$ to obtain,

$$\frac{\partial R}{\partial t} = -\frac{\partial}{\partial x}[R(1-S)] + \Lambda(L-R) + R(1-S), \tag{3}$$

$$\frac{\partial L}{\partial t} = +\frac{\partial}{\partial x}[L(1-S)] + \Lambda(R-L) + L(1-S), \tag{4}$$

where we have only one dimensionless parameter, $\Lambda$, which represents the ratio of the turning rate to the proliferation rate, $\Lambda = \lambda/\theta$.

For a typical application of Eqs. (3) and (4) to describe some experimental observations, such as a scratch wound assay [4,20,21], we would consider applying the PDE model on a finite domain with an initial condition describing some region of the domain initially containing cells, say $S(x,0) = 1$, and the remainder of the domain being vacant, $S(x,0) = 0$. As our focus is to observe travelling wave solutions, we instead consider an infinite domain $-\infty < x < \infty$ and apply initial conditions of the form,

$$L(x,0) \equiv 0, \quad R(x,0) = \begin{cases} 1, & x \leqslant 0, \\ \exp(-\xi x), & x > 0, \end{cases} \tag{5}$$

where $\xi > 0$ is a constant. This initial condition represents a dense mass of right-moving cells for $x < 0$ whose concentration decays exponentially fast in the positive $x$-direction. Regardless of $\Lambda$, our numerical solutions of Eqs. (3) and (4) with (5) evolve so that a front of right-moving cells moves in the positive $x$-direction, tending to travelling waves as $t \to \infty$. For $\Lambda > 0$, a similar behaviour is observed for the $L(x,t)$ subpopulation. We note that while $L(x,t)$ rep-