Physica A 442 (2016) 110–121

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Lattice-free models of directed cell motility

Carolyn Irons [a], Michael J. Plank [a,b,*], Matthew J. Simpson [c,d]

[a] School of Mathematics and Statistics, University of Canterbury, Christchurch 8140, New Zealand
[b] Te Pūnaha Matatini, a New Zealand Centre of Research Excellence, New Zealand
[c] Mathematical Sciences, Queensland University of Technology (QUT), GPO Box 2434, Brisbane, Queensland 4001, Australia
[d] Tissue Repair and Regeneration Program, Institute of Health and Biomedical Innovation, QUT, Brisbane, Queensland, Australia

HIGHLIGHTS

- A new lattice-free model for chemotaxis is presented and analysed.
- Derivation of a macro-scale description from the micro-scale behaviour.
- Key differences between the new model and existing lattice-based models explored.
- Investigation of how directional bias and crowding effects influence collective cell behaviour.

ARTICLE INFO

Article history:
Received 17 July 2014
Received in revised form 1 July 2015
Available online 8 September 2015

Keywords:
Advection
Chemotaxis
Biased random walk
Exclusion process
Nonlinear diffusion
Scratch assay

ABSTRACT

Directed cell migration often occurs when individual cells move in response to an external chemical stimulus. Cells can respond by moving in either the direction of increasing (chemoattraction) or decreasing (chemorepulsion) concentration. Many previous models of directed cell migration use a lattice-based framework where agents undergo a lattice-based random walk and the direction of nearest-neighbour motility events is biased in a preferred direction. Such lattice-based models can lead to unrealistic configurations of agents, since the agents always move on an artificial lattice structure which is never observed experimentally. We present a lattice-free model of directed cell migration that incorporates two key features. First, agents move on a continuous domain, with the possibility that there is some preferred direction of motion. Second, to be consistent with experimental observations, we enforce a crowding mechanism so that motility events that would lead to agent overlap are not permitted. We compare simulation data from the new lattice-free model with a more traditional lattice-based model. To provide additional insight into the lattice-free model, we construct an approximate conservation statement which corresponds to a nonlinear advection–diffusion equation in the continuum limit. The solution of this mean-field model compares well with averaged data from the individual-based model.

1. Introduction

Directed cell movement is essential for a variety of physiological processes including wound healing, angiogenesis, axon guidance and bacterial migration [1–5]. Typically, cells move in a particular direction in response to an external factor, such as a chemical stimulus. For example, white blood cells can move towards a site of infection in response to chemicals released by the bacteria causing the infection [5,6]. The directed movement of cells along a chemical gradient is called chemotaxis.

* Corresponding author at: School of Mathematics and Statistics, University of Canterbury, Christchurch 8140, New Zealand. Tel.: +64 3 3642699.
E-mail address: michael.plank@canterbury.ac.nz (M.J. Plank).

http://dx.doi.org/10.1016/j.physa.2015.08.049
0378-4371/

A chemical which acts as an attractant is called a chemoattractant, whereas a chemical which acts as a repellent is called a chemorepellent [5].

Cell motility is often studied using *in vitro* techniques, such as a scratch assay, where cells are grown in a two-dimensional monolayer before part of the population is scratched, leaving a region of unoccupied substrate that the remaining cells subsequently recolonise [7]. Other experiments are used to investigate chemotaxis specifically by, for example, investigating the relationship between the concentration of chemoattractant and the amount of directional bias cells exhibit [5].

Discrete random walk models are often used to study collective cell motion, including chemotaxis [1,2,8]. These models produce snapshots of the spreading population and movie-based data that are easy to compare with experimental images and time-lapse data [9]. There are two key classes of random walk model that have been used to represent collective cell migration processes.

Lattice-based random walk models represent the spatial domain as a regular lattice. Individual cell motility events are usually modelled using a nearest-neighbour random walk process. Many relevant applications of collective cell spreading involve situations where interactions between neighbouring cells are important since experiments are often initiated at a relatively high cell density [10–12]. Experimental observations of the effects of cell-to-cell interactions [12] have motivated the development of random walk models which incorporate crowding effects, For example, in an exclusion process [13], each lattice site can be occupied by, at most, a single agent. In this type of model, individual movement events depend on the state of the system. For example, a motility event that would place an agent on an occupied site would be aborted and these aborted events are interpreted as a crowding effect [14–16]. Directional bias can be incorporated into these models by allowing the probabilities of choosing a target site for the nearest-neighbour random walk to be unequal [1,17], although other models of directed motion are also possible [18,19]. Lattice-based exclusion process models have been used to represent many processes in cell biology, including cancer cell migration [7,14], wound healing [20,21] and development [9]. In a lattice-based model, the direction of movement is chosen from a discrete set of directions corresponding to nearest-neighbour lattice sites, for example: left, right, up or down on a two-dimensional square lattice.

Images from experimental investigations clearly show that individual cells are not arranged on a regular lattice [7,12,22]. Lattice-free random walk models permit agents to reside within a continuous spatial domain and allow direction of movement to be a continuous variable [23]. Continuum limit approximations have been derived for a population of cells undergoing a biased position-jump process [24,25] or biased velocity-jump process [26], and can be either a chemotaxis equation or an anisotropic diffusion equation, depending on the strength of the bias [27]. However, these earlier results do not include cell-to-cell interactions and crowding effects, which are thought to have a major impact on collective behaviour [2]. More recently, cell-to-cell interactions have been incorporated into lattice-free models using various individual-level mechanisms. For example, Refs. [28,29] used a simple, unbiased random walk with an attempt-and-abort volume exclusion mechanism; this has been extended to the biased case [30]. Refs. [31,32] used Brownian motion plus drift to model agent motility with a hard disk collision mechanism for volume exclusion. Refs. [33,34] modelled crowding using a neighbour-dependent interaction force, rather than a strict volume exclusion mechanism. These models could include a global bias, as well as local neighbour-dependent bias, but the results presented applied to the case without global bias. The different individual-level mechanisms of Refs. [28,30,31,33,34] give rise to different nonlinear advection–diffusion equations or integro-differential equations for the average agent density.

There has been an increasing interest in deriving approximate mean-field (continuum-limit) descriptions of individual-based random walk models with cell-to-cell interactions. These often take the form of a partial differential equation (PDE) for agent density. Such descriptions can provide greater insight than is possible from simulations of an individual-based model alone. For example, the averaged behaviour of an unbiased lattice-based exclusion process can be described by the linear diffusion equation [13], whereas combining proliferation with unbiased motility in a lattice-based model leads to a reaction–diffusion PDE which is a generalisation of the Fisher–Kolmogorov equation [35–37]. Incorporating directional bias in a lattice-based exclusion process leads to a nonlinear advection–diffusion PDE [17]. Contact effects, such as cell-to-cell adhesion, can lead to a nonlinear diffusion equation [14,38,39], a nonlinear advection equation [40] or an equation of Cahn–Hilliard type [41,42]. However, the form of the nonlinearity can depend on the geometry of the lattice (e.g. square or triangular) [43], highlighting the fact that the choice of lattice is non-unique and can affect model predictions.

One of the key differences between lattice-based and lattice-free models is in the maximum density of agents. The highest density arrangement of circles in a plane is a hexagonal tessellation, giving an area occupancy of $\pi/\sqrt{12}$, which is greater than the area occupancy associated with a square lattice arrangement, $\pi/4$. However, random variations in agent locations mean that the lattice-free model is extremely unlikely to get close to its theoretical maximum density, whereas in a lattice-based model the agents are always arranged in a regular pattern, making it much easier to achieve the maximum density [28]. Because of this difference, cell proliferation in a lattice-free model leads to a source term in the PDE that is smaller than the corresponding source term in a lattice-based PDE description [44]. Another consequence of this difference is that a greater proportion of attempted motility events are aborted in a lattice-free model than a corresponding lattice-based model. These differences manifest in the mean-field PDE description since an unbiased lattice-based model leads to a linear diffusion PDE whereas an unbiased lattice-free model leads to a nonlinear diffusion PDE [45]. However, the appropriate mean-field PDE description of a lattice-free model incorporating crowding effects of directional bias have not yet been considered or compared with the equivalent results from a lattice-based model.

In this work we present and analyse a lattice-free model of biased cell motility that is an extension of previous models of unbiased cell motility [28,45]. We model directional bias at the individual agent level using a continuous circular distribution