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Modelling the movement of interacting cell populations: A moment dynamics approach

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HIGHLIGHTS

- New moment dynamics model to describe the movement of interacting cell populations.
- Moment dynamics model applied to mimic two different cell biology experiments.
- Moment dynamics predictions outperform traditional mean-field PDE descriptions.
- Provide guidance regarding situations where the moment dynamics model is required.

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ABSTRACT

Mathematical models describing the movement of multiple interacting subpopulations are relevant to many biological and ecological processes. Standard mean-field partial differential equation descriptions of these processes suffer from the limitation that they implicitly neglect to incorporate the impact of spatial correlations and clustering. To overcome this, we derive a moment dynamics description of a discrete stochastic process which describes the spreading of distinct interacting subpopulations. In particular, we motivate our model by mimicking the geometry of two typical cell biology experiments. Comparing the performance of the moment dynamics model with a traditional mean-field model confirms that the moment dynamics approach always outperforms the traditional mean-field approach. To provide more general insight we summarise the performance of the moment dynamics model and the traditional mean-field model over a wide range of parameter regimes. These results help distinguish between those situations where spatial correlation effects are sufficiently strong, such that a moment dynamics model is required, from other situations where spatial correlation effects are sufficiently weak, such that a traditional mean-field model is adequate.

1. Introduction

Biological and ecological processes often involve moving fronts of interacting subpopulations. For example, in a biological setting, malignant spreading occurs when tumour cells interact with, and move through, the stroma (Bhowmick and Moses, 2005; De Wever and Mareel, 2003; Gatenby et al., 2006; Li et al., 2003). In an ecological setting, the spreading of an invasive species involves moving fronts, that, in some cases, is coupled with a retreating front of that species' prey (Hastings et al., 2005; Phillips et al., 2007; Skellam, 1951).

Fig. 1 shows images of two different types of cell biology experiments involving moving fronts of interacting subpopulations. Fig. 1(a)–(c) shows images of a co-culture scratch assay (Oberringer et al., 2007). This assay is constructed such that initially we have two subpopulations present in a certain region of the domain that is adjacent to a vacant region. As time proceeds, the two subpopulations spread into the vacant space. The image in Fig. 1(c) indicates that one of the subpopulations is clustered, whereas the other subpopulation is more evenly distributed. The image in Fig. 1(d) shows a subpopulation of initially confined melanoma cells that are spreading into a surrounding subpopulation of fibroblast cells (Li et al., 2003). These images demonstrate that collective cell spreading processes can involve moving fronts of interacting subpopulations. Given the importance of collective cell spreading processes to a range of biological applications, including wound healing and malignant spreading, it is relevant for us to develop robust mathematical and computational tools that can

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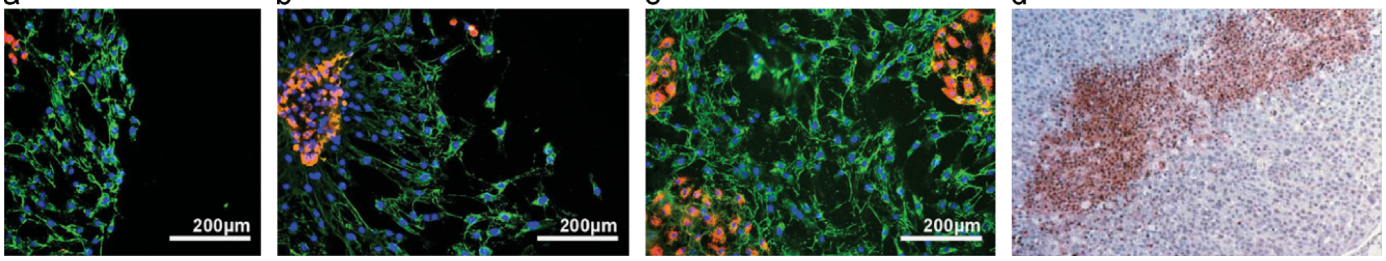

Fig. 1. Co-culture scratch assay containing human dermal microvascular endothelial cells (red) and human dermal fibroblasts (green) at (a) 0 hours, (b) 24 hours and (c) 48 hours. Adapted from Oberringer et al. (2007). (d) Human fibroblasts (blue) and TGF-β1 transduced 451Lu melanoma cells (brown), 19 days after subcutaneous injection into immunodeficient mice. Adapted from Li et al. (2003). (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this paper.)

accurately describe the motion of these kinds of multispecies moving front problems.

Previous mathematical modelling of problems involving moving fronts of multiple interacting subpopulations have typically involved studying systems of reaction–diffusion partial differential equations (PDEs) (Gatenby and Gawlinski, 1996; Painter and Sherratt, 2003; Sherratt, 2000; Simpson et al., 2007a,b; Smallbone et al., 2005). For example, Sherratt (2000) considers a two-species model of tumour growth. In this model, the movement of the tumour cell subpopulation, $v(x,t)$, is inhibited by the stroma subpopulation, $u(x,t)$. Cell proliferation is also influenced by crowding, since the rate of proliferation is a decreasing function of the total cell density, $u(x,t)+v(x,t)$ (Sherratt, 2000). More generally, Painter and Sherratt (2003) suggest that the motion of interacting cell subpopulations depends on the gradient of each particular species' density, as well as the gradient of the total cell density. Focusing specifically on tumour invasion, Gatenby and Gawlinski (1996) propose a three-species model, where the density of normal tissue decreases due to an excess concentration of H^+ ions. Smallbone et al. (2005) extend the Gatenby and Gawlinski three-species model by including a necrotic core within the tumour, which is more consistent with biological observations. However, while these models provide valuable insight into the interaction of multiple cell subpopulations, they are limited in two ways. First, each of these PDE models relies on invoking a mean-field assumption. That is, these models implicitly assume that individuals in an underlying stochastic process interact at a rate that is proportional to the average density (Grima, 2008). This assumption amounts to the neglect of any spatial structure present in the subpopulations (Law and Dieckmann, 2000). Second, these PDE models describe population-level behaviour, and do not explicitly consider individual-level information that could be relevant when dealing with certain types of experimental data (Simpson et al., 2013).

Instead of working directly with PDEs, mean-field descriptions of collective cell behaviour have been derived from discrete individual-level models (Binder and Landman, 2009; Codling et al., 2008; Fernando et al., 2010; Khain et al., 2012; Simpson et al., 2009, 2010). These discrete models, which can also incorporate crowding (Chowdhury et al., 2005), can be identified with corresponding mean-field continuum PDE models that aim to describe the average behaviour of the underlying stochastic process. Using this kind of approach gives us access to both discrete individual-level information as well as continuum population-level information. For example, to model the migration of adhesive glioma cells, Khain et al. (2012) derive a mean-field PDE description of a discrete process which incorporates cell motility, cell-to-cell adhesion and cell proliferation. However, while the relationship between the averaged discrete data and the solution of the corresponding mean-field PDE description is useful in certain circumstances, it is well-known that the assumptions invoked when deriving mean-field PDE descriptions are inappropriate in certain parameter regimes, due to spatial correlations between the occupancy of lattice sites (Baker and Simpson, 2010; Johnston et al., 2012; Simpson and Baker, 2011). The impact of spatial correlation is relevant when we consider patchy or clustered distributions of cells, such as in Fig. 1(b) and (c). Baker and Simpson (2010) partly address this issue by developing a moment dynamics model that approximately incorporates the effect of spatial correlation. Markham et al. (2013) extend this work, but focus on problems where the initial distribution of cells is spatially uniform, meaning that the modelling and computational tools developed by Markham et al. (2013) are not suitable for studying the motion of moving fronts of various interacting subpopulations.

In this work we consider a discrete lattice-based model for describing the motion of a population of cells where the total population is composed of distinct, interacting subpopulations. To understand how our work builds on previous methods of analysis, we derive a standard mean-field description of the discrete model and demonstrate that, in certain parameter regimes, the mean-field model does not describe the averaged discrete behaviour. By considering the dynamics of the occupancy of lattice pairs, we derive one- and two-dimensional moment dynamics descriptions that incorporate an approximate description of the spatial correlation present in the system. Motivated by the geometry of the two typical cell biology experiments in Fig. 1, we apply our model to two case studies. The first case study is relevant to co-culture scratch assays and the second case study is relevant to the invasion of one subpopulation into another subpopulation, thereby mimicking tumour invasion processes. Through these case studies we demonstrate that our moment dynamics model provides a significantly more accurate description of the averaged discrete model behaviour. Finally, we discuss our results and outline directions for future work.

2. Methods

2.1. Discrete model

We consider a lattice-based random walk model where each lattice site may be occupied by, at most, one agent (Chowdhury et al., 2005). The model is presented for situations where there are two subpopulations, denoted by superscripts G and B, and we note that the framework could be extended to include a larger number of subpopulations if required. The superscripts G and B correspond to the colour scheme in our figures where results relating to the G subpopulation are given in green and results relating to the B subpopulation are given in blue. The discrete process takes place on a one-dimensional lattice, with lattice spacing Δ, where each site is indexed $i \in [1, X]$. Agents on the lattice undergo movement, proliferation and death events at rates P_m^G, P_p^G, P_d^G and P_m^B, P_p^B, P_d^B per unit time, for subpopulations G and B, respectively. During a potential motility event, an agent at site i attempts to move to site $i \pm 1$, with the target site chosen with equal probability. This potential event will be successful only if the target site is vacant. A proliferative agent at site i attempts to place a daughter