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Continuum approximations for lattice-free multi-species models of collective cell migration

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ABSTRACT

Cell migration within tissues involves the interaction of many cells from distinct subpopulations. In this work, we present a discrete model of collective cell migration where the motion of individual cells is driven by random forces, short range repulsion forces to mimic crowding, and longer range attraction forces to mimic adhesion. This discrete model can be used to simulate a population of cells that is composed of $K \geq 1$ distinct subpopulations. To analyse the discrete model we formulate a hierarchy of moment equations that describe the spatial evolution of the density of agents, pairs of agents, triplets of agents, and so forth. To solve the hierarchy of moment equations we introduce two forms of closure: (i) the mean field approximation, which effectively assumes that the distributions of individual agents are independent; and (ii) a moment dynamics description that is based on the Kirkwood superposition approximation. The moment dynamics description provides an approximate way of incorporating spatial patterns, such as agent clustering, into the continuum description. Comparing the performance of the two continuum descriptions confirms that both perform well when adhesive forces are sufficiently weak. In contrast, the moment dynamics description outperforms the mean field model when adhesive forces are sufficiently large. This is a first attempt to provide an accurate continuum description of a lattice-free, multi-species model of collective cell migration.

1. Introduction

In vivo cell migration involves many different cell types interacting with each other. For example, tumour invasion involves malignant cancer cells moving through normal surrounding tissues (Weinberg, 2009). Interactions between different cell types are also captured in certain *in vitro* experiments, such as the migration of malignant melanoma cells, which is thought to be enhanced when these cells are moving amongst skin cells (Eves et al., 2003). Multiple species of cells can also be created in experiments where some subpopulation of cells, amongst an otherwise identical subpopulation, are labelled and tracked over time (Simpson et al., 2006, 2007). While some mathematical models explicitly account for interactions between different subpopulations of cells (Painter and Sherratt, 2003), most mathematical models deal with a single population of cells only (Maini et al., 2004; Sherratt and Murray, 1990).

A common approach to modelling cell migration is to use a lattice-based random walk model. This approach captures details of the motion of individual cells, which is attractive because this kind of information can be linked to time lapse images from experiments. The continuum-limit description of such a lattice-based model can also be used to study the group behaviour. Although some previous lattice-based models account for interactions between different types of cells (Penington et al., 2011; Simpson et al., 2009), these lattice-based models are unrealistic because real cells do not move on regular lattice-based structures. Other limitations of lattice-based models include restrictions on cell size. For example, the diameter of a typical melanoma cell is approximately 18 μm (Treloar et al., 2013) whereas the diameter of a typical skin cell is approximately 25 μm (Simpson et al., 2013). In a model with both types of cells present, it is not possible to accommodate these differences in cell size if we use a standard lattice-based approach where each cell occupies a single lattice site (Binder and Simpson, 2016).

To address these limitations, we define a lattice-free model that can be used to describe the migration of a population of cells that is composed of many potentially distinct subpopulations. We adopt a modelling framework that is an extension of previous approaches by (Newman and Grima, 2004) and Middleton and co-workers (2014). The work by Newman and Grima considered a stochastic model of individual cell migration, with chemotactic effects, and

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they described the continuum limit using a Langevin formulation. The work of (Newman and Grima, 2004) was then extended by Middleton and co-workers (2014) who also considered a stochastic model of individual cell migration in terms of a Langevin formulation, however they considered both a traditional mean field continuum approximation as well as a more sophisticated moment closure continuum approximation that accounts for the spatial and temporal dynamics of pairs of agents. A key feature of both these previous models is that they are appropriate for studying the collective migration of a single populations of cells. However, many practical problems in development and disease progression involves multiple interacting subpopulations of cells. Therefore, the main aim of the current study is to develop a discrete model of collective migration where the total population of cells consists of an arbitrary number of interacting subpopulations. Our discrete model incorporates random cell motility, adhesion between cells and finite size effects (crowding). We allow for differences in cell size, cell motility and cell adhesion between the different subpopulations. In addition to producing stochastic realisations of the discrete model, we also analyse the continuum limit using both a standard mean field approximation and a more sophisticated moment dynamics approximation. Comparing averaged behaviour from the discrete simulations with the solution of the continuum models confirms that the mean field approach can be inaccurate when adhesion is sufficiently strong. This is important because almost all mathematical models of collective cell migration invoke the mean field approximation (Maini et al., 2004; Painter and Sherratt, 2003; Sherratt and Murray, 1990).

This manuscript is organised in the following way. In Section 2 we describe the discrete model. In Section 3.1, we analyse the discrete model, showing how we can obtain a continuum description of the average behaviour of the discrete model. In particular, we focus on two different continuum descriptions: (i) a mean field approximation; and (ii) a higher-order moment dynamics approximation. Results in Sections 3.2–3.3 compare solutions of both continuum approximations and averaged discrete results for problems involving one and two interacting subpopulations, with additional comparisons presented in the Supplementary Material. In Section 3.4 we investigate how the accuracy of the MFA and KSA approximations depends on the choice of model parameters. Finally, in Section 4, we summarise our work and highlight opportunities for future investigation.

2. Discrete model

We consider a population of N cells that is composed of an arbitrary number of subpopulations, $K \geq 1$. Illustrative schematics showing interactions between individuals in a population with $K = 1$ and $K = 2$ subpopulations are given in Fig. 1(a) and (b), respectively.

We begin by assuming that each individual cell is a point mass and that its movement can be described by an equation of motion. For simplicity, from this point on, we restrict our attention to a one-dimensional geometry, and in Section 4 we discuss how the framework can be adapted to higher dimensions. To begin describing the collective motion, we assume that the motion of each cell is governed by Newton's second law,

$$m_i \frac{\mathrm{d}^2 x_i}{\mathrm{d}t^2} = \mathcal{V}_i + \sum_{j \neq i} R_{ij} + \zeta_i, \qquad i = 1, \ldots, N, \tag{2.1}$$

where x_i is the position of the ith cell, m_i is its mass, and R_{ij} is an interaction force between the ith and jth cells. $\mathcal{V}_i$ is the viscous force between the cell and the surrounding medium, and ζ_i is the stochastic force associated with random Brownian motion. According to Stokes' law, the viscous force on a small spherical particle moving in a viscous fluid is given by

$$\mathcal{V}_i = -\mu \frac{\mathrm{d}x_i}{\mathrm{d}t}, \tag{2.2}$$

where $\mu > 0$ is the drag coefficient. If we neglect inertial forces and invoke Stokes' law (Middleton et al., 2014), we arrive at a system of Langevin stochastic differential equations (SDEs) given by

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \sum_{j \neq i} F_{ij} + \xi_i, \qquad i = 1, \ldots, N, \tag{2.3}$$

where $R_{ij} = \mu F_{ij}$ and $\zeta_i = \mu \xi_i$.

In summary, according to Eq. (2.3), the collective migration of cells is determined by a balance between cell-to-cell interactions (short-range crowding and longer range adhesion), stochastic forces, and viscous forces. Collective cell migration that is driven by unbiased stochastic forces is thought to be relevant in many applications, such as collective cell spreading in many single-species *in vitro* experiments (Simpson et al., 2013). Therefore, we focus on unbiased stochastic forces by sampling ξ_i from a Gaussian distribution with zero mean and zero auto-correlation (Middleton et al., 2014).

It is biologically reasonable to model the interaction forces between cells, F_{ij}, to have different amplitudes for subpopulations of cells. This is relevant if we wish to specify different adhesion forces between different subpopulations (Steinberg, 1996). For simplicity, we assume $F_{ij} = F_{ji}$, and we specify the interaction force to be

$$F_{ij} = f_0 \mathcal{Z}(r) \operatorname{sgn}(x_i - x_j), \tag{2.4}$$

where f_0 is the dimensional amplitude of the interaction force, $\mathcal{Z}(r)$ is the dimensionless force law function that depends on the separation distance, and $r = |x_i - x_j|$. The function sgn is the *signum* function. The particular choice of $\mathcal{Z}(r)$ depends on phenomenological cellular behaviour we wish to model. Several force laws have been suggested, including a linear spring model (Murray et al., 2009) and non-linear force laws such as Morse

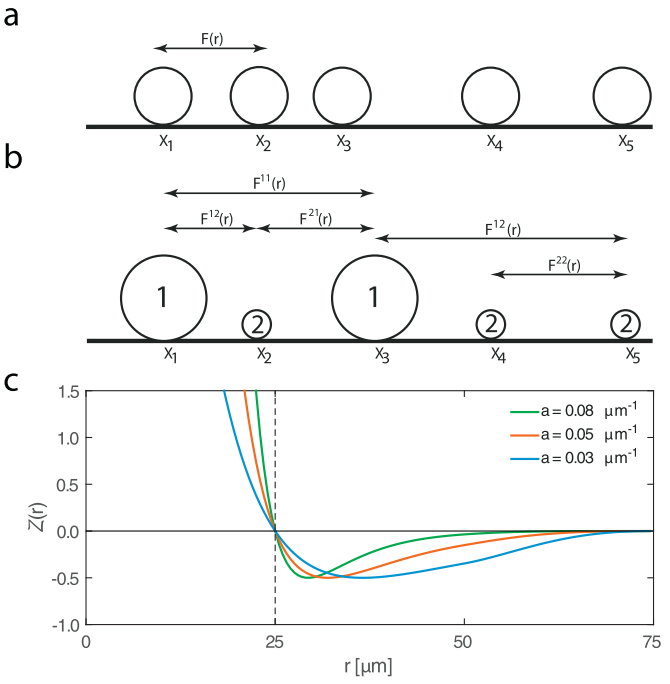

Fig. 1. (a) and (b) Representative plot of single- and multi-species systems of cells, respectively. In (a) we show the intraspecies force, $F(r)$, and in (b) we show both intraspecies forces, $F^{11}(r)$ and $F^{22}(r)$, and interspecies forces, $F^{12}(r)$ and $F^{21}(r)$. Here, r is the distance between cells. (c) Dimensionless force law function $\mathcal{Z}(r)$, given by Eq. (2.5), for various values of a. Here, $\delta = 25$ μm corresponds to a typical cell diameter.