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A continuum approximation to an off-lattice individual-cell based model of cell migration and adhesion

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HIGHLIGHTS

- An off-lattice individual-cell based (IBM) model of cell migration and adhesion is developed.
- A commonly used PDE model of cell adhesion follows by ignoring cell–cell correlations in the IBM.
- We derive a novel continuum approximation to the IBM which does not neglect correlations.
- This approximation is accurate for a wide range of cell numbers and parameters.

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ABSTRACT

Cell–cell adhesion plays a key role in the collective migration of cells and in determining correlations in the relative cell positions and velocities. Recently, it was demonstrated that off-lattice individual cell based models (IBMs) can accurately capture the correlations observed experimentally in a migrating cell population. However, IBMs are often computationally expensive and difficult to analyse mathematically. Traditional continuum-based models, in contrast, are amenable to mathematical analysis and are computationally less demanding, but typically correspond to a mean-field approximation of cell migration and so ignore cell–cell correlations. In this work, we address this problem by using an off-lattice IBM to derive a continuum approximation which does take into account correlations. We furthermore show that a mean-field approximation of the off-lattice IBM leads to a single partial integro-differential equation of the same form as proposed by Sherratt and co-workers to model cell adhesion. The latter is found to be only effective at approximating the ensemble averaged cell number density when mechanical interactions between cells are weak. In contrast, the predictions of our novel continuum model for the time-evolution of the ensemble cell number density distribution and of the density–density correlation function are in close agreement with those obtained from the IBM for a wide range of mechanical interaction strengths. In particular, we observe 'front-like' propagation of cells in simulations using both our IBM and our continuum model, but not in the continuum model simulations obtained using the mean-field approximation.

1. Introduction

Mechanical interactions between cells underpin a considerable range of biological processes during tissue development and maintenance. Two pertinent examples are the collective migration of cohesive groups of cells, which occur during wound healing and cancer invasion (see for example Friedl and Wolf, 2003; Friedl and Gilmour, 2009; Rørth, 2009), and cell sorting, which may drive certain aspects of self-organisation and tissue pattern during embryo development (see Amack and Manning, 2012 for a review).

A number of mathematical models of cell–cell and cell–ECM adhesion have been developed. Broadly speaking, these can be classified as either continuum-based models or individual cell- (or agent-) based models (IBMs), although some incorporate features from both (and are typically referred to as hybrid models, for example see Jeon et al., 2010; Osborne et al., 2010 for an overview). Traditionally, continuum-based models are derived from a deterministic, top-down perspective, wherein the dynamics of a large population of cells is described in terms of locally averaged

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properties, such as the spatial distribution of the cell number density (which we shall refer to as the cell density distribution) (Armstrong et al., 2006; Maini et al., 2004; Keller and Segel, 1971; Sherratt and Murray, 1990). To derive these models, various conservation laws, in particular conservation of mass, are exploited (see for example Armstrong et al., 2006; Murray, 2003). This means that one must prescribe certain constitutive equations, such as how the flux of cells depends on the system variables (Murray, 2003). These, in turn, can be obtained either by analogy with well-established physical laws (Murray, 2003), or intuition (Armstrong et al., 2006). For this reason, the connection between the resulting macroscopic continuum-based description and the microscopic cell-scale processes is not always clear. Furthermore such continuum descriptions are typically based on the implicit assumption that statistical correlations between cells are negligible, i.e. a mean-field assumption (Grima, 2008). However, the behaviour of a cell is often determined by interactions between it and other nearby cells (via signals or mechanical forces), which in turn leads to strong cell–cell correlations. This was observed, for example, during collective cell migration (Trepat et al., 2009), where correlations in the cell velocities are driven in large part by mechanical interactions (Serra-Picamal et al., 2012).

In contrast to continuum-based models, IBMs treat cells as discrete entities. At the coarsest scale, each variable in the IBM corresponds to the centre of mass position of an individual cell; for finer-scale descriptions, variables can instead correspond to sub-elements of a cell. The positions of cells or cell elements can either be restricted to specific lattice sites (these being lattice-based models; for example cellular automata Von Neumann, 1966), or be off-lattice (i.e. so that cells or cell elements occupy positions in continuous space). In lattice-based models for which a cell only spans a single site, cell movement is captured by prescribing certain transition probabilities (this being the probability of a cell jumping from one site to another). These transition probabilities can be made to depend on whether a particular site is already occupied by another cell. In this way, other biologically relevant effects can be incorporated into the model: volume exclusion is captured by assuming that each lattice site is occupied by at most one cell (Khain et al., 2009; Simpson et al., 2010b, 2010a); cell adhesion by assuming that the probability of a cell vacating a site is lower if another adherent cell occupies a neighbouring site (Khain et al., 2009; Simpson et al., 2010b; Deroulers et al., 2009). The coarseness of the lattice means that any two cells can either occupy neighbouring lattice sites (and therefore adhere to one another), or be one or more cell diameters apart. Hence, this approach can only provide a phenomenological description of mechanical interactions between cells. Furthermore, the coarseness of the lattice spacing prevents it from realistically capturing local correlations in the relative positions and velocities of neighbouring cells (although the model may still be an improvement over a mean-field description). To overcome these issues, the model can be altered so that a cell spans multiple lattice points (such as in the Cellular Potts Model or CPM). Alterations in cell size, shape or location (as a consequence of these interaction forces) are reflected by changes in the system's potential energy. The model evolves by moving from one state to another, energetically more favourable state. This approach has been successfully applied to a number of different problems associated with cell–cell adhesion and movement (Turner and Sherratt, 2002; Turner et al., 2004), including cell-sorting (Graner and Glazier, 1992; Glazier and Graner, 1993; Mombach, 1999). Of course, increasing the spatial resolution of the lattice increases the computational cost of the model, although artefacts can still arise as a consequence of imposing a lattice (Grima and Schnell, 2006; Deutsch and Dormann, 2005).

An alternative to lattice-based models are off-lattice ones. Again, model variables can either correspond to the positions of individual cells (treated as point masses) (Drasdo et al., 1995; Palsson and Othmer, 2000; Newman and Grima, 2004; Sepúlveda et al., 2013), or subcellular cell elements (as used in the subcellular element model or SEM) (Newman, 2005; Sandersius and Newman, 2008). In this case, positions of cells or cell-elements are governed by either stochastic (where stochasticity is adopted to capture random cell movement) or ordinary differential equations. One advantage of an off-lattice model is that, even for the coarsest description where model variables correspond to cell positions, this approach allows one to more realistically capture mechanical interactions between cells than a lattice-based model. In particular, it was recently demonstrated by Sepúlveda et al. (2013) that a coarse off-lattice model (wherein cells are treated as point masses) could accurately capture the cell-velocity and cell–cell correlations that arise during collective migration of Madin–Darby Canine Kidney (MDCK) cells.

Being able to provide a direct mapping between discrete and continuum based models has a number of clear advantages. In the case where IBMs are stochastic, the model will require many realisations in order to analyse its properties. Moreover, the computational cost of solving an IBM typically scales quadratically with the number of cells or sub-cellular elements being considered, whereas for continuum based models, the problem scales with the required resolution necessary to capture variations of interest. The additional computational cost associated with numerically analysing IBMs is particularly acute when one wants to study effects from varying different parameters in the model (which may be the case, for example, if one wants to fit the model to the available data). Finally, the study of IBMs and continuum-based approximations can help clarify how traditional continuum-based models (derived using a top-down approach) and IBMs relate to one another (Murray et al., 2012).

Continuum approximations have been derived for coarse-grained lattice-based models of cell adhesion and motility (Johnston et al., 2012; Simpson and Baker, 2011). Importantly, the authors found that the so-called mean field approximation (MFA) is not adequate to describe the behaviour of the IBM when adhesion effects are strong. Instead, to describe the correlations, the authors adopted the so-called Kirkwood Superposition Approximation (KSA). However, coarseness of the lattice meant that cells only span a single lattice point, and so it is unlikely that such models will accurately capture correlations in relative cell neighbour positions. Continuum approximations to CPM-based models (where cells instead span multiple grid points) have been derived (Lushnikov et al., 2008; Alber et al., 2007). These consider cells that physically interact (via volume exclusion and interaction with the extracellular matrix) and move along a chemical gradient (chemotaxis). Mean-field based approximations to the CPM take into account cell–cell adhesion (Alber et al., 2007); however the latter is neglected by current continuum models that go beyond the mean-field approximation (Lushnikov et al., 2008).

In general, an off-lattice approach offers a better description of the underlying correlations (Sepúlveda et al., 2013). Previous attempts to relate the behaviour of these models to partial differential equation (PDE) based models include fitting the continuum-based model (and hence estimating parameters) to averaged simulations obtained from an IBM (Young et al., 2001). Of course, this is numerically rather cumbersome; being able to obtain an accurate continuum approximation to an off-lattice model would allow (for example) a rapid exploration of the model's parameter space. Other attempts to derive continuum approximations from discrete off-lattice models can be found in the works of Fozard et al. (2010) and Murray et al. (2009, 2012), however these ignore stochasticity.

In this work, we address the above considerations by exploring continuum approximations to an off-lattice IBM that is based on Langevin equations, building on the work of Newman and