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The effect of domain growth on spatial correlations

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HIGHLIGHTS

- A method to include the effect of domain growth on the evolution of spatial correlations between proliferative and motile agents is presented.
- We demonstrate an approximation that allows domain growth to be included in continuum models in a tractable manner.
- A framework to study of the effects of domain growth on spatial correlations between agents for more complicated scenarios is established.

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ABSTRACT

Mathematical models describing cell movement and proliferation are important tools in developmental biology research. In this work we present methods to include the effects of domain growth on the evolution of spatial correlations between agent locations in a continuum approximation of a one-dimensional lattice-based model of cell motility and proliferation. This is important as the inclusion of spatial correlations in continuum models of cell motility and proliferation without domain growth has previously been shown to be essential for their accuracy in certain scenarios. We include the effect of spatial correlations by deriving a system of ordinary differential equations that describe the expected evolution of individual and pair density functions for agents on a growing domain. We then demonstrate how to simplify this system of ordinary differential equations by using an appropriate approximation. This simplification allows domain growth to be included in models describing the evolution of spatial correlations between agents in a tractable manner.

1. Introduction

Many important biological processes during development involve the movement and proliferation of cell populations on growing domains [1]. For example, cranial neural crest stem cells, a subset of a migratory cell population that give rise to a diverse lineage, have been shown to migrate along the developing cranofacial region in embryonic chickens [2–4]. Similarly melanoblasts, neural crest precursors to melanocytes, have been shown to migrate through the developing dorsal lateral epithelium in the embryonic mouse [5–7].

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In both of the aforementioned examples, individual-based models (IBMs) have played an important role in research into these cell migratory processes [3,4]. Studies involving IBMs have shown, in the case of melanoblasts, that the distribution of the migrating cells is thought to determine fur patterning and pigmentation defects such as piebaldism [8]. In the case of cranial neural crest stem cells, IBMs have helped to elucidate the mechanisms by which a cell becomes a 'leader' or a 'follower' in the collective cell migration process [2–4]. IBMs allow an intuitive representation of cells (referred to as 'agents' in the IBM), and allow for complex behaviours, such as cell–cell interactions and volume exclusion, to be easily assigned to agents in the model [9–12]. Importantly, IBMs can capture the effects of spatial correlations and heterogeneity in agent populations, and the ramifications spatial correlations can have on density-dependent processes such as cell migration and proliferation [13–23].

IBMs are also often amenable to approximation by population-level continuum models. Accurate continuum approximations of IBMs are important tools for understanding biological systems as, in contrast to IBMs, they generally allow for more mathematical analysis. This analysis can be crucial to form a mechanistic understanding of biological systems, which is not always apparent (or feasible) from simply studying the averaged results of a large number of repeats of an IBM. For example, using an IBM to conduct an exhaustive exploration of a large parameter space in order to examine a model's behaviour is often not possible. Analytical techniques can often be employed for this purpose. However, in certain scenarios standard mean-field partial differential equation (PDE) descriptions of IBMs, such as those describing the expected evolution of the population density, suffer from the limitation that they neglect to incorporate the impact of spatial correlations and clustering. Therefore, in order to derive accurate continuum approximations of IBMs it is often necessary to include the effects of spatial correlations in continuum models [14–22,24–29]. Furthermore, having the mathematical tools to directly compute spatial correlations allows them to be analysed, which can give important insights into the biological process being studied. For instance, spatial correlations indicative of different types of cell–cell interactions can be observed in cell populations [13,30,31], and spatial correlations between cells are thought to play an important role in tumour growth [32].

In this work we examine how domain growth affects the evolution of individual and pair density functions for agents in an IBM. A large body of literature already exists concerning the evolution of individual and pair density functions on static domains [14–23], the most striking examples of which show that standard mean-field PDE descriptions can be wholly insufficient approximations of the evolution of the agent density in IBMs in certain scenarios [14,17]. We therefore also display how to integrate the results presented here into pre-existing models. In doing so we simplify the implementation of the methods we present so that they can be more easily applied to the study of complex systems.

The outline of this work is as follows: to begin we introduce our one-dimensional IBM and domain growth mechanism in Section 2.1. We then define the individual and pair density functions, and derive a system of ordinary differential equations (ODEs) describing the evolution of the individual and pair density functions with respect to time on a growing domain in Section 2.2. To test the accuracy of this system of ODEs we compare its numerical solution with ensemble averages of the individual and pair agent densities from the IBM for a range of initial conditions and parameter values in Section 3. In Section 4 we integrate domain growth into existing models for calculating the evolution of pairwise spatial correlations. These models are typically used to correct mean-field approximations for the evolution of the agent density in an IBM by taking spatial correlations into account. In Section 5 we conclude with a discussion of the results presented.

2. Model

In this section we first introduce the IBM and the domain growth mechanism we employ throughout this work. We then introduce the individual and pair density functions and derive a system of ODEs describing the evolution of these functions in the IBM.

2.1. One-dimensional IBM and the domain growth mechanism

We use an agent-based, discrete random-walk model on a one-dimensional regular lattice with lattice spacing Δ [33] and length $L(t)$, where $L(t)$ is an integer describing the number of lattice sites. Throughout this work the lattice site spacing, Δ, is always equal to one.[1] All simulations are performed with periodic boundary conditions. Each agent is assigned to a lattice site, from which it can move or proliferate into an adjacent site. If an agent attempts to move into a site that is already occupied, the movement event is aborted. Similarly, if an agent attempts to proliferate into a site that is already occupied, the proliferation event is aborted. This process, whereby only one agent is allowed per site, is referred to as an exclusion process [33]. Time is evolved continuously, in accordance with the Gillespie algorithm [34], such that movement, proliferation and growth events are modelled as exponentially distributed 'reaction events' in a Markov chain. Attempted agent movement or proliferation events occur with rates P_m or P_p per unit time, respectively. That is, $P_m\delta t$ is the probability of an agent attempting to move in the next infinitesimally small time interval δt. Throughout this work the initial agent distribution for all simulations is achieved by populating lattice sites uniformly at random until the required initial density is achieved.[2]

[1] Note, however, that Δ does not have to be equal to one for the results presented here to hold.

[2] An alternative method to generate the same average initial density in the simulations would be to populate each lattice site uniformly at random with the probability of the initial density required. This method was also implemented and found to make no difference to the results (not shown).