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Discrete and continuous models for tissue growth and shrinkage

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HIGHLIGHTS

- Introduce stochastic model of growing domain on which particles are situated.
- Derive coefficients of Fokker–Planck equation (FPE) describing particle density.
- Incorporate elemental death to model domain shrinkage and derive appropriate FPE.
- Outline computer-assisted methodology for approximating the coefficients of the FPE.
- Provide numerical simulations which verify our findings and demonstrate good agreement.

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ABSTRACT

The incorporation of domain growth into stochastic models of biological processes is of increasing interest to mathematical modellers and biologists alike. In many situations, especially in developmental biology, the growth of the underlying tissue domain plays an important role in the redistribution of particles (be they cells or molecules) which may move and react atop the domain. Although such processes have largely been modelled using deterministic, continuum models there is an increasing appetite for individual-based stochastic models which can capture the fine details of the biological movement processes which are being elucidated by modern experimental techniques, and also incorporate the inherent stochasticity of such systems.

In this work we study a simple stochastic model of domain growth. From a basic version of this model, Hywood et al. (2013) were able to derive a Fokker–Plank equation (FPE) (in this case an advection–diffusion partial differential equation on a growing domain) which describes the evolution of the probability density of some tracer particles on the domain. We extend their work so that a variety of different domain growth mechanisms can be incorporated and demonstrate a good agreement between the mean tracer density and the solution of the FPE in each case. In addition we incorporate domain shrinkage (via element death) into our individual-level model and demonstrate that we are able to derive coefficients for the FPE in this case as well. For situations in which the drift and diffusion coefficients are not readily available we introduce a numerical coefficient estimation approach and demonstrate the accuracy of this approach by comparing it with situations in which an analytical solution is obtainable.

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1. Introduction

There are many biological scenarios in which tissue growth plays a significant role in the distribution of migrating cells. Embryogenesis is one such process which provides numerous demonstrations of the importance of domain growth to the final positions of various cell types. At the same time as the embryo is growing the organisation of complex biological superstructures (such as limbs) is being orchestrated (Chevallier et al., 1977), therefore it is vital that the processes of cell migration and domain growth are coordinated with each other in order to achieve the correct results (Wolpert, 1969). For example, McLennan et al. (2012) examined how a subpopulation of neural crest cells travelled long distances and responded to growth of the underlying tissue. They found not only that cells are carried by the tissue growth but also that cellular velocity profiles correspond to the logistic tissue growth.

There have been several theoretical studies of the interplay between domain growth and pattern formation in both deterministic

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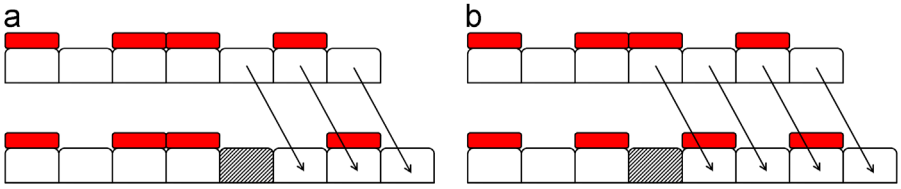

Fig. 1. Examples of growth and division events. Domain elements are white boxes and tracer particles are represented by smaller red boxes atop particular 'marked' elements. In each subfigure the top configuration shows a domain before a growth event and the bottom a domain configuration after a growth event. (a) An unmarked element is chosen to divide. It does so by pushing itself and the intervals to its right one element length, Δ. Tracer particles move with the elements and a new element (hatched) is inserted in the empty space. (b) A marked element is selected to divide. It undergoes the same movement procedure as for the unmarked element taking its tracer particle with it. Again a new element (hatched) is inserted in the vacant space. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this paper.)

(Painter et al., 1999; Crampin et al., 2002a, 1999, 2002b; Crampin and Maini, 2001a; Kulesa et al., 1996) and stochastic (Woolley et al., 2011) regimes. Others investigations have specifically focussed on the targeted migration of cells on growing domains and have again covered both the deterministic (Landman et al., 2003; Simpson et al., 2006) and stochastic (Binder et al., 2008; Binder and Landman, 2009) scenarios and indeed mechanisms in order to segue between the two (Baker et al., 2010; Yates et al., 2012). The two types of modelling regime traditionally focus on different scales, with stochastic models able to incorporate experimental scale details and the inherent noisiness of the biological system, while deterministic, continuum models tend to focus on the macroscale, ensemble properties and give a clear overview of the behaviour of the system. A multiscale understanding of the complex processes involved in cell migration can be achieved by linking these two modelling regimes together in an 'equivalence framework', which provides insight into the interplay between the individual-level and population-level models. Employing such an equivalence framework allows us to make use of either modelling regime in order to investigate the relevant properties of the system.

Recently Hywood et al. (2013) have initiated such a framework by analysing a discrete, stochastic, on-lattice domain growth model in which the domain is made up of elements which may proliferate independently and with equal probability. Using the infinitesimal moments of the underlying stochastic process (Gillespie, 1992; Karlin and Taylor, 1981) the authors were able to derive the coefficients of a Fokker–Planck equation (FPE) which approximates the spatio-temporal evolution of the expected occupancy of the lattice sites in the case of an exponentially growing domain. The work of Hywood et al. (2013) is itself an extension of the work of Binder and Landman (2009) who consider a similar process on a deterministically growing domain.

In Section 2 we review the work of Hywood et al. (2013) and describe how it might be extended to include time-dependent proliferation rates and to incorporate elemental death. Using this reformulated model we are able to extend this equivalence framework, in Section 3, to cases where the domain does not grow exponentially in the mean-field. By deriving the infinitesimal moments of the stochastic process which underlies domain growth we are able to incorporate several biologically-motivated types of domain growth including exponential, linear and logistic. Importantly, in Section 4 we also consider the case in which individual elements are allowed to die as well as proliferate. We derive the drift and diffusion coefficients of the FPE which describes the expected marker density on the growing/contracting domain. Not only does this allow for the more realistic representation of domain growth processes in which apoptosis may occur, but it also enables the representation of domain shrinkage which may be important for biological processes such as wound healing (Greenhalgh, 1998; Grinnell et al., 1999). In each situation we confirm our theoretical findings by comparisons of the mean tracer density (over many realisations of the individual-level model) to numerical solutions of the derived FPEs.

There are situations in which the drift and diffusion coefficients of the underlying stochastic process are not readily available. In order to deal with these situations, in Section 5, we present a Fokker–Plank coefficient estimation approach (Yates et al., 2009) which is reminiscent of the equation-free technique (Kevrekidis et al., 2003). We utilise this approach in order to find computationally the coefficients of the assumed FPE and we verify our findings through further numerical simulations.

We conclude in Section 6 with a brief discussion summarising our findings and suggesting areas into which this work may be extended.

2. An equivalence framework

In this section we introduce the individual-based model and the continuum representation between which we hope to derive an equivalence framework. We extend the basic individual-based model to incorporate time-dependent proliferation rates and elemental death and present the FPE which we expect to describe the mean-field tracer density.

2.1. The individual-based model

We begin by introducing the basic stochastic model upon which the rest of the results of this paper are based. Consider a one-dimensional domain made up initially of N_0 contiguous elements each of length Δ. We incorporate growth and shrinkage into this individual-level model by allowing these elements to undergo 'proliferation events' and 'death events' which are analogous to biological cell division and cell death events.[1] In continuous time a domain element is chosen, uniformly among all the elements, to proliferate or to die with exponentially distributed waiting time. We extend the work of Hywood et al. (2013) by introducing time-dependence of the parameter, $b(t)$, of the exponential waiting time distribution for birth events. This allows us to incorporate a variety of different types of domain growth in addition to the standard exponential domain growth resultant from a time-independent waiting time distribution. In addition we incorporate the possibility of a time-dependent rate of death, $d(t)$ into the model.

If domain element i is chosen to proliferate then it does so by pushing all the elements to its right (including itself) a distance Δ to the right in order to make room for an identical daughter element which is placed in its original position (see Fig. 1). If element i is selected to die then it is removed from the lattice and all the elements to its right shift Δ to the left in order to fill the

[1] We note that biological cells do not instantaneously disappear, grow or divide, nor do they have exponentially distributed waiting times between divisions. These are, however, mathematical idealisations that we have made in order to render the model tractable.

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