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Comparing methods for modelling spreading cell fronts

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AUTHOR-HIGHLIGHTS

- We examine three different methods for modelling spreading cell fronts.
- We compare these methods to results from averaged discrete simulations.
- The transient and the asymptotic behaviour are both taken into account.
- We deduce which methods are best suited to specific parameter regimes.
- We discuss examples of which methods may be suitable for some biological phenomena.

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ABSTRACT

Spreading cell fronts play an essential role in many physiological processes. Classically, models of this process are based on the Fisher–Kolmogorov equation; however, such continuum representations are not always suitable as they do not explicitly represent behaviour at the level of individual cells. Additionally, many models examine only the large time asymptotic behaviour, where a travelling wave front with a constant speed has been established. Many experiments, such as a scratch assay, never display this asymptotic behaviour, and in these cases the transient behaviour must be taken into account. We examine the transient and the asymptotic behaviour of moving cell fronts using techniques that go beyond the continuum approximation via a volume-excluding birth-migration process on a regular one-dimensional lattice. We approximate the averaged discrete results using three methods: (i) mean-field, (ii) pair-wise, and (iii) one-hole approximations. We discuss the performance of these methods, in comparison to the averaged discrete results, for a range of parameter space, examining both the transient and asymptotic behaviours. The one-hole approximation, based on techniques from statistical physics, is not capable of predicting transient behaviour but provides excellent agreement with the asymptotic behaviour of the averaged discrete results, provided that cells are proliferating fast enough relative to their rate of migration. The mean-field and pair-wise approximations give indistinguishable asymptotic results, which agree with the averaged discrete results when cells are migrating much more rapidly than they are proliferating. The pair-wise approximation performs better in the transient region than does the mean-field, despite having the same asymptotic behaviour. Our results show that each approximation only works in specific situations, thus we must be careful to use a suitable approximation for a given system, otherwise inaccurate predictions could be made.

1. Introduction

Advancing fronts of cells are frequently observed experimentally (Simpson et al., 2007b, 2013b; Maini et al., 2004a,b). For example, in Fig. 1, we see an advancing front of murine fibroblast 3T3 cells from an *in vitro* experiment (Todaro and Green, 1963; Simpson et al., 2013b). This phenomenon is essential in many physiological processes: embryonic development hinges on the spatial advancement of cells (Simpson et al., 2007b), and wounds could not heal without it (Maini et al., 2004a,b). Additionally, it is important in tissue engineering (Sengers et al., 2007, 2009), which relies on the ability of fronts of cells to move into empty space. Less desirably, moving fronts of cells are a major factor in disease progression, most notably in cancer (Allred, 2010; Swanson et al., 2003; Gatenby and Gawlinski, 1996). An important clinical feature is the sharpness of the front, which is determined

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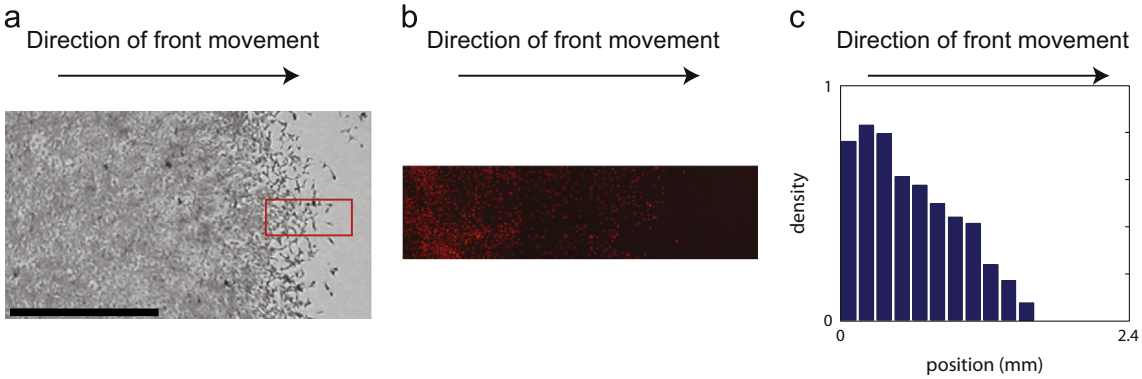

Fig. 1. Experimentally observed moving front of murine fibroblast cells. In (a) we see a snapshot of the cells invading the space to the right, whilst in (b), we see the highlighted region from (a) where the cell nuclei have been stained. In (c), we have the calculated density profile showing the shape of the front. The experimental details for producing images such as these can be found in Simpson et al. (2013b).

by the relative rates of migration and proliferation; a shallow front can lead to difficulties when surgically removing a tumour (Swanson et al., 2003). Given their importance biologically, it is hardly surprising that moving cell fronts have been the focus of many mathematical modelling studies.

Classically, advancing fronts of cells have been modelled using the Fisher–Kolmogorov equation (Fisher, 1937; Kolmogorov et al., 1937), which has a travelling wave solution with constant shape and speed. The asymptotic wave speed (as $t\to\infty$), v_f, for initial conditions with compact support is $2\sqrt{D\lambda}$ where D is the diffusivity of the cells, and λ their effective proliferation rate (Murray, 2002). Measuring the wavespeed experimentally does not allow us to determine unique values for D and λ, making additional experimental observations necessary (Simpson et al., 2013b; Sengers et al., 2007). Moreover, even once the travelling wave has been established, the Fisher–Kolmogorov equation, which represents the mean-field behaviour, is not always an accurate representation of the behaviour of a moving front of cells, due to the stochastic nature of these processes (Lewis, 2000; Khain et al., 2011). Thus, whilst it may be possible to fit experimental data to solutions of the Fisher–Kolmogorov model, this does not necessarily lead to accurate parameter estimation; something that is frequently overlooked in models of moving cell fronts (Sengers et al., 2007; Tremel et al., 2009). This has led to the development of alternative methods for modelling moving cell fronts, some of which we shall now discuss.

Using agent-based models, each cell is modelled explicitly thus retaining a description of the individual behaviour whilst still enabling observation of the population as a whole (Codling et al., 2008). Discrete models have been used to examine moving cell fronts in many areas of cell biology (Cheng et al., 2006; Dormann and Deutsch, 2002; Mani et al., 2002). They are also often used in conjunction with continuum models to provide a multiscale modelling framework (Simpson et al., 2007a). Discrete models are not confined to any particular region of parameter space, but are limited by their computational cost, and lack of analytical tractability. Thus, ideally, we would like to have simpler, more tractable methods approximating the behaviour of moving cell fronts.

When cells proliferate significantly more rapidly than they migrate, we expect a sharp front (Swanson et al., 2003) with the region behind the front almost completely filled with cells. Under these conditions, we are able to predict the asymptotic front speed using the one-hole approximation (OHA) (Callaghan et al., 2006). This method uses series expansions to provide a correction term to the front speed for the case without migration, which can be calculated exactly. The OHA agrees well with discrete simulations when cells proliferate significantly faster than they migrate, and can be extended to deal with more than one hole behind the front. However, the method of Callaghan et al. (2006) is only given for constrained systems where a cell either attempts to move or proliferate at every time step, without ever resting. Additionally, experimental results do not always produce the asymptotic travelling front behaviour. The following three assays highlight some of the different experiments which can be used to obtain data for travelling fronts:

1. A single moving front is allowed to develop over a long period of time (>100 h) (Maini et al., 2004a,b). These experiments are likely to allow for travelling front behaviour to be produced. However, they are not as straightforward to carry out as the same experiment over shorter timescales due to difficulties with keeping the cells alive for long periods of time, and maintaining a constant environment.
2. A single moving front is allowed to develop over a short period of time (<24 h). The results of these experiments are not on long enough timescales to produce asymptotic travelling front behaviour (Sengers et al., 2009), but are more feasible experimentally.
3. Two opposingly directed fronts come together. For instance, when a thin strip (Liang et al., 2007; Valster et al., 2005; Rodriguez et al., 2005; Young et al., 2012) or small hole (Young et al., 2012) of cells is removed from a monolayer. In this set-up, the artificially created gap is closed, thus the system may never reach the asymptotic travelling front speed. For example, the protocol in Liang et al. (2007) allows between 8 and 18 h for the scratch to close. Given that typical cell doubling times are of a similar order, we do not expect the asymptotic speed to have been reached before the fronts from either side of the scratch become interwoven. We see an example of this in Fig. 2, where a scratch assay is performed with 3T3 cells. Within 30 h, we see the two fronts meeting.

As many experiments follow the second and third methods, it is often important to be able to predict the transient behaviour as well as the asymptotic speed.

Moment dynamics models incorporate increasingly greater degrees of information into the mean-field model by taking into account the dynamics of cell pairs, triplets, and so forth. Pairwise models are generally the most common, requiring the use of an appropriate closure approximation for any triplet terms in the model (Dieckmann and Law, 2000). The use of moment dynamics models has been well documented in various biological scenarios (Baker and Simpson, 2010; Simpson and Baker, 2011; Ascolani et al., 2013; Law et al., 2003; Murrell et al., 2004; Sharkey, 2011). Specifically, Simpson and Baker (2011) develop a pairwise approximation (PWA), using the Kirkwood Superposition Approximation