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Inferring parameters for a lattice-free model of cell migration and proliferation using experimental data

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ABSTRACT

Collective cell spreading takes place in spatially continuous environments, yet it is often modelled using discrete lattice-based approaches. Here, we use data from a series of cell proliferation assays, with a prostate cancer cell line, to calibrate a spatially continuous individual based model (IBM) of collective cell migration and proliferation. The IBM explicitly accounts for crowding effects by modifying the rate of movement, direction of movement, and the rate of proliferation by accounting for pair-wise interactions. Taking a Bayesian approach we estimate the free parameters in the IBM using rejection sampling on three separate, independent experimental data sets. Since the posterior distributions for each experiment are similar, we perform simulations with parameters sampled from a new posterior distribution generated by combining the three data sets. To explore the predictive power of the calibrated IBM, we forecast the evolution of a fourth experimental data set. Overall, we show how to calibrate a lattice-free IBM to experimental data, and our work highlights the importance of interactions between individuals. Despite great care taken to distribute cells as uniformly as possible experimentally, we find evidence of significant spatial clustering over short distances, suggesting that standard mean-field models could be inappropriate.

1. Introduction

One of the most common *in vitro* cell biology experiments is called a *cell proliferation assay* (Bosco et al., 2015; Bourseguin et al., 2016; Browning et al., 2017). These assays are conducted by placing a monolayer of cells, at low density, on a two-dimensional substrate. Individual cells undergo proliferation and movement events, and the assay is monitored over time as the density of cells in the monolayer increases (Tremel et al., 2009). One approach to interpret a cell proliferation assay is to use a mathematical model (Warne et al., 2017). Calibrating the solution of a mathematical model to data from a cell proliferation assay can provide quantitative insight into the underlying mechanisms, by, for example, estimating the cell proliferation rate (Sengers et al., 2007; Tremel et al., 2009). A standard approach to modelling a cell proliferation assay is to use a mean-field model, which is equivalent to assuming that individuals within the population interact in proportion to the average population density and that there is no spatial structure, such as clustering (Maini et al., 2004; Sarapata and de Pillis, 2014; Sengers et al., 2007; Sherratt and Murray, 1990; Tremel et al., 2009). More recently, increased computational power has meant that individual based models (IBMs) have been used to directly model the cell-level behaviour (Binny et al., 2016a; Frascoli et al., 2013; Johnston et al., 2014). IBMs are attractive for modelling biological phenomena because they can be used to represent properties of individual agents, such as cells, in the system of interest (Binny et al., 2016a; 2016b; Frascoli et al., 2013; Peirce et al., 2004; Read et al., 2012; Treloar et al., 2013). Typical IBMs use a lattice, meaning that both the position of agents, and the direction of movement, are restricted (Codling et al., 2008). In contrast, lattice-free IBMs are more realistic because they enable agents to move in continuous space, in any direction. However, this extra freedom comes at the cost of higher computational requirements (Plank and Simpson, 2012).

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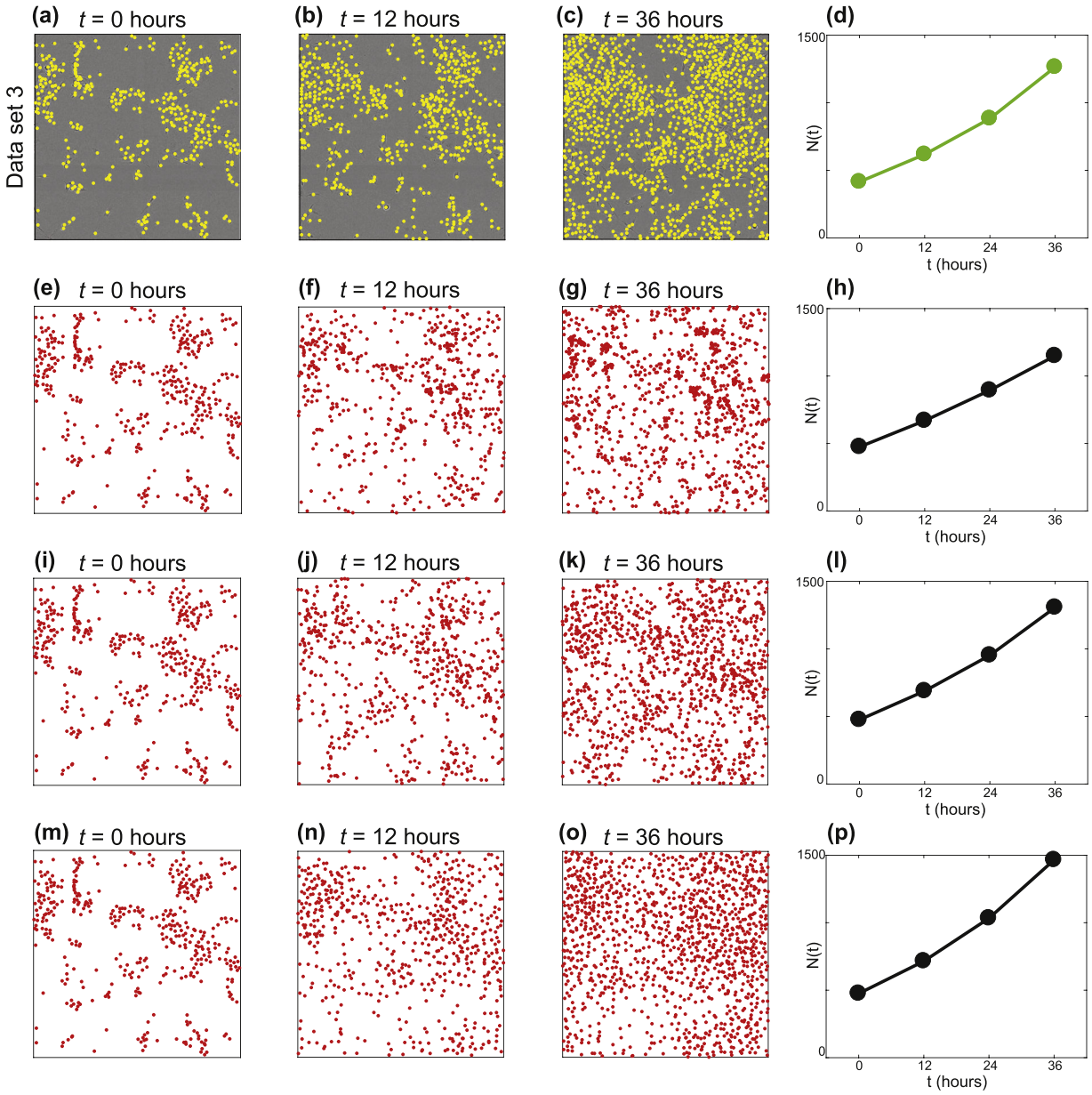

Fig. 1. (a)-(c) Experimental data set 3 at $t = 0$, 12 and 36 hours. The position of each cell is identified with a yellow marker. The field of view is a square of length 1440 μm. (d) Population size, $N(t)$ for experimental data set 3. (e)-(h) One realisation of the IBM with $\gamma_b = 0$ μm, leading to an overly clustered distribution of agents. (i)-(l) One realisation of the IBM with $\gamma_b = 6.0$ μm , leading to a distribution of agents with similar clustering to the experimental data. (m)-(p) One realisation of the IBM with $\gamma_b = 20$ μm, leading to an overly segregated distribution of agents. All IBM simulations are initiated using the same distribution of agents as in (a), with $m = 1.0$ /hour, $p = 0.040$ /hour, and $\sigma = 24$ μm.

In this work we consider a continuous-space, continuous-time IBM (Binny et al., 2016b). This IBM is well-suited to studying experimental data from a cell proliferation assay with PC-3 prostate cancer cells (Kaighn et al., 1979), as shown in Fig. 1(a)-(d). The key mechanisms in the experiments include cell migration and cell proliferation, and we note that there is no cell death in the experiments on the time scale that we consider. Therefore, agents in the IBM are allowed to undergo both proliferation and movement events. Crowding effects that are often observed in two-dimensional cell biology experiments (Cai et al., 2007) are explicitly incorporated into the IBM as the rates of proliferation and movement in the model are inhibited in regions of high agent density. In this study we specifically choose to work with the PC-3 cell line because these cells are known to be highly migratory, mesenchymal cells (Kaighn et al., 1979). This means that cell-to-cell adhesion is minimal for this cell line, and cells tend to migrate as individuals. We prefer to work with a continuous-space, lattice-free IBM as this framework gives us the freedom to identically replicate the initial location of all cells in the experimental data when we specify the initial condition in the IBM. In addition, lattice-free IBMs do not restrict the direction of movement like a lattice-based approach.

A key contribution of this study is to demonstrate how the IBM can be calibrated to experimental data. In particular, we use approximate Bayesian computation (ABC) to infer the parameters in the IBM. Four sets of experimental images (Supplementary Material 1), each corresponding to an identically-prepared proliferation assay, are considered. The experiments are conducted over a duration of 36 hours, which is unusual because proliferation assays are typically conducted for no more than 24 hours (Browning et al., 2017). Data from the first three sets of experiments (Fig. 2) are used to calibrate the IBM and data from the fourth set of images