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Stochastic models of cell invasion with fluorescent cell cycle indicators

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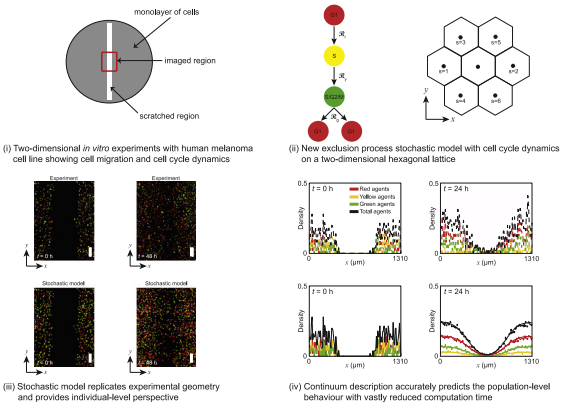
HIGHLIGHTS

- New stochastic model of cell invasion including fluorescent cell cycle indicators.
- Stochastic model treats total population of cells as three subpopulations.
- Stochastic model replicates experimental images from a recent set of scratch assays performed with human melanoma cells.
- Continuum limit is a novel system of three coupled nonlinear PDEs.
- For biologically relevant parameter choices, the PDEs accurately approximate averaged data from the stochastic model.

GRAPHICAL ABSTRACT



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ABSTRACT

Fluorescent cell cycle labelling in cell biology experiments provides real time information about the location of individual cells, as well as the phase of the cell cycle of individual cells. We develop a stochastic, lattice-based random walk model of a two-dimensional scratch assay where the total population is composed of three distinct subpopulations which we visualise as red, yellow and green subpopulations. Our model mimics FUCCI technology in which cells in the G1 phase of the cell cycle fluoresce red, cells in the early S phase fluoresce yellow, and cells in the S/G2/M phase fluoresce green. The model is an exclusion process so that any potential motility or proliferation event that would place an agent on an occupied lattice site is aborted. Using experimental images and previous experimental measurements we explain how to apply the stochastic model to simulate a scratch assay initialised with a low to moderate density monolayer of human melanoma cell line. We obtain additional mathematical insight by deriving an approximate partial differential equation (PDE) description of the stochastic model, leading to a novel system

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of three coupled nonlinear reaction diffusion equations. Comparing averaged simulation data with the solution of the continuum limit model confirms that the PDE description is accurate for biologically-relevant parameter combinations.

1. Introduction

Cell invasion involves moving fronts of populations of cells. The movement of these fronts is driven by combined cell migration and cell proliferation [1]. Such moving fronts play an important role in tissue repair [2,3], malignant spreading [4–6] and embryonic development [7,8]. Cell invasion is most commonly studied *in vitro* using a scratch assay [9,10], where a monolayer of cells is grown on a two-dimensional substrate and a portion of the population is scratched away using a sharp-tipped instrument. After the scratch has been made, individual cells in the population migrate and proliferate, with the net result being the formation of a moving front of cells that closes the scratch [9,10].

Cell invasion involves combined cell migration and cell proliferation. Cell proliferation is often conceptualised as a sequence of four phases: gap 1 (G1); synthesis (S); gap 2 (G2); and the mitotic (M) phase [11]. Together, the G1, S and G2 phases are referred to as *interphase*, which involves cells undergoing preparation for division. Following interphase, cells enter the mitotic phase, during which they divide into two daughter cells. Traditional scratch assays provide no means of distinguishing between different cell phases within the population. However, in 2008, fluorescent ubiquitination-based cell cycle indicator (FUCCI) technology [12] was developed and this technology allows us to visualise the cell cycle for individual cells within a population of cells [11–15]. FUCCI involves two fluorescent probes in the cell which emit red fluorescence when the cell is in the G1 phase, or green fluorescence when the cell is in the S/G2/M phase. FUCCI is important because it allows us to visualise cell cycle transitions in real time. FUCCI technology has many important applications, including developmental biology and cancer biology [16,17]. For example, in cancer biology, many important drugs involve interrupting the cell cycle [18,19]. Therefore, it is useful to be able to visualise, in space and time, how cells progress through the cell cycle.

In this work we describe a new stochastic random walk model of cell migration and cell proliferation that can be used to mimic, interpret and design scratch assay experiments performed with FUCCI technology. We begin by presenting images from a recent scratch assay performed with a human melanoma cell line. In these experiments, cells have been transfected with FUCCI so that each cell fluoresces either red, yellow or green [15]. Images in Fig. 1(a)–(b) show a population of 1205Lu melanoma cells, with each cell fluorescing either red, yellow or green. The image in Fig. 1(a) corresponds to $t = 0$ h, just after the scratch has been made in the uniform monolayer of cells. The image in Fig. 1(b) shows the same field of view at $t = 48$ h, after the wound has essentially closed. To describe this kind of data, we propose a lattice-based random walk model that treats the total population of cells as three interacting subpopulations: (i) a subpopulation of red agents; (ii) a subpopulation of yellow agents; and (iii) a subpopulation of green agents. Each agent in each subpopulation undergoes a nearest neighbour random walk at a particular rate [20] and is permitted to progress through the cell cycle as red agents transition to yellow agents, and yellow agents transition to green agents, before green agents eventually divide into two red daughter agents. The final transition from green agents into two red agents is permitted only when there is sufficient space available. A schematic of this cell cycle progression is shown in Fig. 1(c). Since the random walk model is an exclusion process [21], each lattice site cannot be occupied by more than one agent. Therefore, potential motility events or potential transition events that would place an agent onto an occupied lattice site are aborted [20,22,23]. This means that the model incorporates both contact inhibition of migration and contact inhibition of proliferation, which are both known to be important in two-dimensional scratch assays [24].

In addition to describing the stochastic model, we also derive a mean field continuum limit description of the stochastic model. This kind of approach has been pursued in many previous studies, with both single-species lattice-based stochastic models (including [25,26] for example) and single-species lattice-free stochastic models [27–31]. In contrast, the experimental system we consider here leads us to treat the population of agents in the discrete model as three subpopulations. Therefore, the continuum limit description is a novel system of three coupled nonlinear partial differential equations (PDE). This approach of having both an individual-level stochastic description and a population-level continuum description of the same underlying process is useful for interpreting cell biology experiments as some experimental data are most naturally interpreted using population-level measurements and properties, while other experimental data from the same experiment are best interpreted in a stochastic, individual-based framework [32–36]. To explore how well the continuum limit PDE describes the stochastic model, we generate a suite of identically prepared realisations of the stochastic model and explore how well the average behaviour of the stochastic model is accurately described by the solution of the system of PDEs. We conclude by presenting some parameter sensitivity of the continuum–discrete match, and outline how the new models presented here can be extended in future studies.

This work is an extension of our previous work which focuses exclusively on the heuristic development of continuum models to simulate collective cell migration with FUCCI technology [15]. However, we note that working with continuum models alone provides no opportunity to generate insight into cellular-level behaviours, and continuum models cannot