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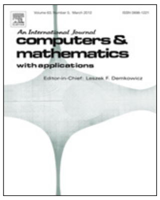

Discrete and continuous approaches to modeling cell movement in the presence of a foreign stimulus

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ABSTRACT

Cell movement is a complex process. Cells can move in response to a foreign stimulus in search of nutrients, to escape predation, and for other reasons. Mathematical modeling of cell movement is needed to aid in achieving a deeper understanding of vital processes such as embryogenesis, angiogenesis, tumor metastasis, and immune reactions to foreign bodies. In this work we consider cell movement that can be separated into two parts: one part is in direct response to a stimulus and the other is due to uncertainties and other reasons for the movement. In order to deal with the deterministic and random aspects of cell movement, an individual based model is created to simulate cells moving in the presence of heterogeneously distributed stimulus molecules. The model is then upscaled, starting with an analysis of the transition probabilities of individuals at each site, to obtain a continuous partial differential equation model. Finally, the two models are numerically compared to each other for a variety of different parameter values.

1. Introduction

The study of cell movement is essential to the understanding of a wide variety of human processes. Individuals or cells move in response to foreign stimuli such as external sources of nutrients, and chemical gradients, or to escape from predators. Their movement, however, is not always entirely directed and has an uncertainty component. It might also not be completely continuous, admitting periods of "rest". Most of the existing mathematical models do not take into consideration these important characteristics of movement.

There exist a wide variety of biological processes which depend on cells moving in response to a foreign stimulus. For example, during the gestation process, cells determine their position within each body segment by communicating with one another through signaling molecules [1,2]. The ability of cells to move and locate themselves in response to other cells' signaling molecules is vital to the creation of a healthy individual. Better understanding of this process will aid in the prevention of malformations in newborns [1]. Another example of individual movement in response to external stimuli can be found in the process called angiogenesis. Angiogenesis is the growth of new blood vessels from pre-existing vessels and it plays a vital role in tumor growth and tumor metastasis [3,4]. New blood vessels are created following growth factors like FGF (fibroblast growth factor) and VEGF (vascular endothelial growth factor) [3,2]. Their growth factors control the direction in which the new vessels are formed. Mathematical modeling of angiogenesis could potentially help prevent tumors from growing. A third example of individual movement in response to external stimuli can be found in the immune system response to foreign bodies such as bacteria or medical implants [5–7]. When an intruder is detected by the immune system, phagocytic cells move towards the site of invasion. The ability of the immune cells to recognize the foreign body

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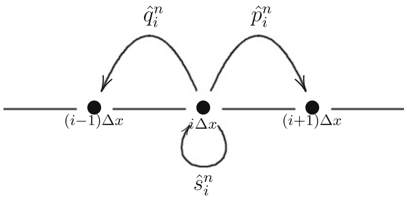

Fig. 1. A diagram of the transition probabilities for cells in a 1D grid.

and accordingly direct their movement plays a fundamental role in infection control. Better insight into this process can aid in the manufacture of safer implants and in the development of infection control strategies.

In order to model the complex movement of individuals in response to a foreign stimulus, we first start by developing a discrete individual based model (IBM). We use discrete mathematical models since they are able to capture extremely complex systems and all types of cell behavior can be added to the model relatively easily. The IBM model includes a parameter that controls the percentage of random, and consequently of directed, movement. It is important to include a random component and a directed component since biological models are clearly far from being deterministic and cells do not necessarily behave in the same way in identical situations. In addition, the discrete model includes parameters that account for how strongly cells "want" to remain in their current position as opposed to moving to another position. This desire to "stay" may be in response to the foreign stimulus or in response to the environment itself.

However, discrete individual based models are computationally expensive and in most cases only a very limited number of individuals, in comparison to the number in real life problems, can be modeled at the same time. To deal with large number of individuals, continuous models become more appropriate. In order to address situations where millions of individuals move at the same time, we upscale the individual based model by considering the transition probabilities of each site from one state to another and then taking appropriate limits as space and time steps tend to zero [8,9]. This approach leads to a continuous partial differential equation (PDE) model that captures the complex movement of cells in response to the stimulus. In the last section of the paper, we compare the discrete IBM and continuous PDE models through a series of numerical simulations under a variety of different stimulus distributions and parameter values.

Previous works have also considered similar upscaling of discrete models of cell movement [9,10,8,11–13]. However, none have included collectively a random component of the movement, the ability of cells to stay in their current position, a stimulus that varies in time and space, and a parameter controlling how strong the cells' predisposition is for staying in their own place. This not only significantly complicates the corresponding mathematical models but also helps represent more general and realistic classes of biological systems.

2. The individual based model

Consider an initial fixed number of individuals or cells and a fixed number of stimulus molecules (a chemical, for example), which are distributed on a line grid with a uniform distance between nodes given by Δx. Define $Z_i^n = Z(i\Delta x, n\Delta t)$ as the number of cells in position $i\Delta x$ at time $n\Delta t$, where Δt is the size of the discrete time steps, and $R_i^n = R(i\Delta x, n\Delta t)$ as the number of stimulus molecules at position $i\Delta x$ and time $n\Delta t$ with $i \in \{\dots, -3, -2, -1, 0, 1, 2, 3, \dots\}$ and $n \in \{0, 1, 2, 3, \dots\}$. Each site in the lattice is empty, or occupied by cells, or occupied by stimulus molecules, or occupied by both. We assume that several individuals can occupy a single site at the same time. At any moment $n\Delta t$ in time, cells and stimuli can reallocate in space. Then, at time $n\Delta t$, a cell at position i in the grid can do one of the following (Fig. 1):

- move rightward to position $(i+1)\Delta x$ with probability $\hat{p}_i^n$;
- remain at its current position i with probability $\hat{s}_i^n$;
- move leftward to position $(i-1)\Delta x$ with probability $\hat{q}_i^n$,

where $\hat{p}_i^n + \hat{q}_i^n + \hat{s}_i^n = 1$.

Cell movement can be divided into two parts: a random part and a part that depends completely on the spatial gradient of the stimulus distribution. In order to mathematically describe this model, we start by considering the random walk process for a single individual on the set $\{\dots, -3, -2, -1, 0, 1, 2, 3, \dots\}$. Let $a(n)$ be a random variable that describes the position of cell at time t_n. Then, for our one-dimensional model we define:

- $\hat{p}_i^n = P(a(n+1) = (i+1)\Delta x | a(n) = i\Delta x) = \left(\frac{3-\alpha}{6}\right)\theta + (1-\theta)p_i^n$ as the probability that an individual is at position $(i+1)\Delta x$ at time $(n+1)\Delta t$ given that it was at position $i\Delta x$ at time $n\Delta t$, i.e., the probability that an individual at position $i\Delta x$ at time $n\Delta t$ will move to the right;
- $\hat{q}_i^n = P(a(n+1) = (i-1)\Delta x | a(n) = i\Delta x) = \left(\frac{3-\alpha}{6}\right)\theta + (1-\theta)q_i^n$ as the probability that an individual is at position $(i-1)\Delta x$ at time $(n+1)\Delta t$ given that it was at position $i\Delta x$ at time $n\Delta t$, i.e., the probability that an individual at position $i\Delta x$ at time $n\Delta t$ will move to the left;
- $\hat{s}_i^n = P(a(n+1) = i | a(n) = i)$ as the probability that an individual is at position $i\Delta x$ at time $(n+1)\Delta x$ given that it was at position $i\Delta x$ at time $n\Delta t$, i.e., the probability that an individual at position $i\Delta x$ at time $n\Delta t$ will not move.