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Modeling transport through an environment crowded by a mixture of obstacles of different shapes and sizes

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HIGHLIGHTS

- Stochastic simulations of individual and collective motion through a crowded environment.
- Crowded environments populated by mixtures of obstacles of different shapes and sizes.
- Transport properties depend on the obstacle volume fraction and details of the obstacle shape and size distribution.
- Standard fractional diffusion equation descriptions ought to be used with care.

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ABSTRACT

Many biological environments are crowded by macromolecules, organelles and cells which can impede the transport of other cells and molecules. Previous studies have sought to describe these effects using either random walk models or fractional order diffusion equations. Here we examine the transport of both a single agent and a population of agents through an environment containing obstacles of varying size and shape, whose relative densities are drawn from a specified distribution. Our simulation results for a single agent indicate that smaller obstacles are more effective at retarding transport than larger obstacles; these findings are consistent with our simulations of the collective motion of populations of agents. In an attempt to explore whether these kinds of stochastic random walk simulations can be described using a fractional order diffusion equation framework, we calibrate the solution of such a differential equation to our averaged agent density information. Our approach suggests that these kinds of commonly used differential equation models ought to be used with care since we are unable to match the solution of a fractional order diffusion equation to our data in a consistent fashion over a finite time period.

1. Introduction

Many biological environments, such as those shown in Fig. 1(a)–(b), are crowded by macromolecules, organelles and cells of varying size and shape. Experimental and computational evidence suggests that crowding effects may impede the transport of macromolecules and cells in such environments [1–7]. Therefore, the development of reliable mathematical models of this transport process is very important. Several previous studies have sought to describe crowded transport processes using either random walk simulation models [8–18] or fractional order diffusion equation (FDE) models [19–29].

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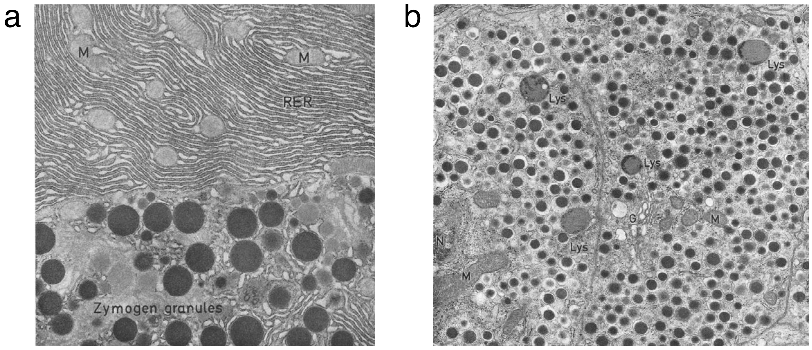

Fig. 1. (a) Intracellular image of mouse pancreatic acinar cells [34]. (b) Intracellular image of alpha cells from a diabetic mouse [34]. Images (a)–(b) are reproduced with kind permission from Springer.

Although some previous studies have considered the effect of different obstacle shapes and sizes in detail [30–33], others have simply focused on studying transport through environments in which a single type of obstacle is present [14,15]. Here, we focus on environments containing a mixture of different types of obstacles since experimental images (Fig. 1(a)–(b)) indicate that many biological environments contain multiple types of obstacles, whose sizes vary considerably.

In this work, we examine the transport of both individual agents and populations of agents through crowded environments using a lattice-based unbiased nearest neighbor random walk model. We simulate crowding effects by randomly populating the lattice with immobile obstacles of different shapes and sizes, whose relative densities are specified by a particular distribution. By holding the density of lattice sites occupied by obstacles, ϕ, constant, and varying the relative density of each individual obstacle type, we are able to create different crowding environments. Some of these environments are dominated by small obstacles, whilst others are dominated by large obstacles.

Although the idea of studying transport through a crowded environment using random walk simulations has become well-established since Saxton's original studies over twenty years ago [12,13], this area of research remains active with many recent studies making valuable contributions. For example, recent theoretical advancements have extended Saxton's lattice-based results to lattice-free frameworks [30,35,36], including studying the role of obstacle orientation [37]. Progress has also been made by combining experimental and theoretical approaches, for example, studying overlapping circular and elliptical obstacles [38] and studying more complicated environments containing up to 15 different types of obstacles [31]. Other more experimentally oriented studies have sought to interpret trajectory data describing the motion of individual cells or molecules using various mathematical frameworks [32,33,39].

In addition to this collection of studies which explicitly focus on motion through crowded environments, other researchers have made progress towards the development, application and solution of FDE models that are thought to implicitly represent crowded transport. Such FDE models have been analyzed in various biological settings including chemical reactions [23], reaction fronts [22,24] and reaction–diffusion mechanisms [25]. We would like to emphasize that the group of studies described here, focusing explicitly on motion through crowded environments using experimental and simulation data [30–33,35–39], have not attempted to interpret their results using any kind of FDE framework. Conversely, the group of studies described here focusing on FDE models [21–25] have not attempted to connect the solution of any FDE model to measurements from any simulation or experiment which explicitly represents transport through a crowded environment. Therefore, given the discrepancy between these two active areas of the literature, one of the aims of the present study is to consider a stochastic model of transport through a crowded environment containing a mixture of different obstacle shapes and sizes and to use averaged data from the stochastic model to examine whether it is possible to represent the transport process using a simpler FDE framework. Although there is a current debate in the literature about how to discriminate between obstructed diffusion, CTRWs and FDEs, and fractional Brownian motion [40], we concentrate on CTRWs and FDEs in this work.

2. Stochastic simulations

We consider a two-dimensional square lattice, with lattice spacing Δ, where we index sites (i, j), with $0 \le i \le M$ and $0 \le j \le N$, so that each site has location $(x, y) = (i\Delta, j\Delta)$. The dimension of the lattice is $0 \le x \le L_x$ and $0 \le y \le L_y$, where $L_x = (M + 1)\Delta$ and $L_y = (N + 1)\Delta$. At the start of a simulation we randomly populate the lattice with immobile obstacles to a specified, spatially uniform density, ϕ. We then place either a single motile agent (Section 3) or a population of motile agents (Section 4) on vacant sites. These agents undergo an unbiased nearest neighbor random walk in which we enforce a simple exclusion condition [41]. Potential motility events that would lead to an agent occupying the same site as another agent or an obstacle are aborted. We use the Gillespie algorithm [42] to advance the simulation until we reach some time T. We always average our results over K identically prepared realizations. The initial location of the motile agent is randomly chosen in each realization. To minimize the computational expense, we regenerate the obstacle field every R