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Using fractional differential equations to model the Michaelis-Menten reaction in a 2-d region containing obstacles

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ABSTRACT: Features inside living cells are complex and crowded, and in such complex environments diffusion processes exhibit three different behaviours; Fickian diffusion, subdiffusion, and superdiffusion. This study aims to investigate the phenomenon of subdiffusion, which occurs when there is molecular crowding, by proposing a new continuous spatial model involving fractional differential equations. The anomalous diffusion parameter is introduced to represent the spatial crowdedness in the media. The equations are solved numerically using an implicit fractional trapezoidal method. Simulations applied to the particular case of the Michaelis-Menten reaction demonstrate that, as a result of anomalous diffusion or a crowded situation in low dimensional biological media, kinetics are of the fractal type. The model also predicts that increasing obstacle density results in reactant segregation, which is similar to that observed in in vivo conditions in cells.

KEYWORDS: anomalous diffusion, reaction-diffusion equation, *Ziziphus oenoplia*continuous simulation

INTRODUCTION

An important subject of interest is how we can understand the dynamics of cellular processes taking place on the cell membrane or within the cell. The inside of living cells can be characterized as disordered and 'crowded' and, as a consequence of the fractal kinetic type of behaviour of its molecules, it fails to obey the concepts of classical behaviour[1]. For instance, the high molecular crowding exhibited inside living cells has been shown to have significant impact on reaction rates and the thermodynamic properties of molecules within the cell[2]. It also results in the diffusion at the cell membrane being not only highly anomalous but occurring at a slower rate[3,4].

Modelling cellular processes based on the Law of Mass Action has proved to be excellent in simple, homogeneous, in vitro conditions. However, this law comes into question when used to describe the dynamics of molecules in more complex situations, such as in vivo conditions. This is because the law requires free diffusion and a homogeneous reaction environment, together with the ability to average together reactant densities over a large spatial domain in order to form a predictable picture of the system behaviour[1].

Two significant extensions to the deterministic approach model have been made. In the power law approach[5] reactant concentrations are raised to non-integer powers. However, it fails to describe many important biochemical effects such as saturation and sigmoidicity[6]. Another issue is that this approach has been proven analytically only for the simplest reactions, and no empirical results based on this approach extend to more complex systems.

The fractal kinetics approach[7] introduces time dependence to the rate constants. This approach can be used in fractal environments and non-classical simulations. However, these fractal-like kinetics have the problem of a singularity at $t = 0$, which raises issues of its validity as a deterministic approach[6].

The limitations of these approaches in implementation, especially in continuous spatial modelling, motivates this current study into an approach using fractional differential equations (FDEs) and Michaelis-Menten enzyme kinetics to model the behaviour of macromolecules in a two-dimensional disordered medium. It is assumed that the reaction environments are within the cell membrane because chemical reactions in membrane pores exhibit fractal-like kinetics. FDEs are used because they have properties that characterize obstacle density parameters. By using these properties, we can control the presence of obstacles within the reaction environment by either pure or anomalous diffusion. We also introduce a numerical method to solve the FDEs which we refer to as the implicit fractional trapezoidal method.

FRACTIONAL REACTION DIFFUSION EQUATIONS

In the last few decades, the theory of fractional derivatives has attracted significant attention in various areas, such as viscoelasticity [8], signal processing [9], biology [10,11]. In biology, one of its most prominent uses is in modelling diffusion processes [8,12], and the fractional model has been used to describe anomalous diffusion in complex environments [10,11].

Traditionally, in order to represent complex process at cell membranes, reaction diffusion equations have been used. The equations can be written as

$$\frac{\partial S}{\partial t} = K\nabla^2 S + \sum_{j=1}^{M} a_j(S)\gamma_j, \tag{1}$$

in which K is the diffusion coefficient, which is assumed to be constant, but could be a diagonal matrix and S is the concentration of species. In the case of Michaelis-Menten reactions $S = (S_1, S_2, S_3)$ where S_1, S_2, and S_3 are the concentrations of enzyme, substrate, and enzyme-substrate complex, respectively.

In a heterogenous medium or medium with anomalous diffusion, spatial crowding needs to be taken into account. Thus equation (1) needs to be modified by adding obstacle parameter densities. In order to do this, the reaction-diffusion problem is generalized to a reaction-subdiffusion problem [13]. We have used a fractional dynamic approach and replaced equation (1) with reaction-subdiffusion equations

$$\frac{\partial S}{\partial t} = KD_t^{1-\alpha}\nabla^2 S + \sum_{j=1}^{M} a_j(S)\gamma_j, \tag{2}$$

where $D_t^{1-\alpha}$ is the Riemann-Liouville derivative operator

$$D_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)}\frac{\partial}{\partial t}\int_0^t \frac{f(S)}{(t-S)^{1-\alpha}}\,\mathrm{d}S.$$

In this reaction-subdiffusion equation, the parameter α is a measure of the density of obstacles, assumed to be randomly scattered in the cell membrane. With increasing obstacles within the system, α approaches zero, and approaches 1 in the limit of no obstacles in which case (1) is recovered.

Consider the Michaelis-Menten reaction system with three molecular species and three reaction channels

$$A + B \xrightarrow{k_1} C\,, \quad C \xrightarrow{k_2} A + B\,, \quad C \xrightarrow{k_3} A + P.$$

where k_1, k_2, k_3 are the rate coefficients. If these reactions take place in a region of size $L \times L$ and there are obstacles present which inhibit diffusion, the reaction-diffusion equations are described by the fractional differential equations

$$\begin{aligned}
\frac{\partial A}{\partial t} &= D_t^{1-\alpha}(K\nabla^2 A - k_1 AB) + (k_2 + k_3)C,\\
\frac{\partial B}{\partial t} &= D_t^{1-\alpha}(K\nabla^2 B - k_1 AB) + k_2 C,\\
\frac{\partial C}{\partial t} &= D_t^{1-\alpha}(K\nabla^2 C + k_1 AB) - (k_2 + k_3)C,
\end{aligned} \tag{3}$$

where A, B, C denote concentrations, and K is the generalized diffusion coefficient. Note that the bimolecular reaction is inside the fractional operator, as bimolecular reactions are inhibited by obstacles whereas unimolecular reactions are not.

NUMERICAL METHOD

Consider the fractional differential equation of the form

$$\begin{aligned}
&\frac{\mathrm{d}y(t)}{\mathrm{d}t} = D_t^{1-\alpha} f(y(t)) + g(y(t)), t \in [0, T],\\
&y(0) = y_0, \quad y_0 \in \mathbb{R}^m,
\end{aligned} \tag{4}$$

where $0 < \alpha < 1$. The Caputo fractional derivative is given by

$$\widehat{D}_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)}\int_0^t \frac{f'(s)}{(t-s)^{1-\alpha}} ds. \tag{5}$$

If $f(t)$ is continuous and $f'(t)$ is integrable in the interval $[0, T]$, then for every $0 < \alpha < 1$ the Riemann-Liouville and the Caputo fractional derivatives satisfy [9]

$$D_t^{1-\alpha} f(t) = \widehat{D}_t^{1-\alpha} f(t) + \frac{t^{\alpha-1}}{\Gamma(\alpha)} f(0), \quad t > 0. \tag{6}$$

A number of authors, e.g., Diethelm et al [14,15] and Ford et al [16], consider the numerical solution of so-called Caputo FDEs that take the form $\widehat{D}_t^{\alpha} y(t) = f(y(t))$, but here the preferred form is (4), as it is more naturally allied to problems discussed in this paper. This form also appears in solving problems in systems biology arising from the anomalous diffusion and chemical kinetics of molecular species in crowded environments [10,11].

To solve problem (4), we introduce the implicit fractional trapezoidal method

$$\begin{aligned}
y_{n+1} = y_n &+ \frac{h}{2}(D_t^{1-\alpha}(f(y_n) + f(y_{n+1})))\\
&+ \frac{h}{2}(g(y_n) + g(y_{n+1})),
\end{aligned} \tag{7}$$

where h is the time step size. In order to implement such a method, numerical approximations to the fractional derivative operator are required. Here, the approximation by Diethelm et al[17] when approximating the Caputo fractional derivative operator is used. Hence

$$D_t^{1-\alpha} f(y_n) \approx \frac{h^{\alpha-1}}{\Gamma(1+\alpha)} \sum_{j=0}^{n} c_{jn} f(y_j), \qquad (8)$$

where $h = T/n$ is the integration stepsize, $t_j = jh$, y_n is an approximation to exact solution $y(t_n)$, and

$$c_{jn} = \begin{cases} \alpha n^{\alpha-1} - n^\alpha + (n-1)^\alpha, & \text{if } j = 0, \\ (n-j+1)^\alpha - 2(n-j)^\alpha + (n-j-1)^\alpha, & \\ \qquad\qquad \text{if } j = 1, 2, \ldots, n-1, & \\ 1, \qquad \text{if } j = n. & \end{cases}$$

We use the method of lines to discretize equations (3). Space is discretized with mesh points $x_i = i\Delta x, y_j = j\Delta x, 0 \leqslant i \leqslant m$, $0 \leqslant j \leqslant m$, and $\Delta x = L/m$. Then

$$\frac{dA_{ij}}{dt} = D_t^{1-\alpha}\Big(K\frac{A_{i+1,j} + A_{i-1,j} + A_{i,j+1} + A_{i,j-1}}{(\Delta x)^2} - K\frac{4A_{ij}}{(\Delta x)^2} - k_1 A_{ij} B_{ij}\Big) + (k_2 + k_3) C_{ij},$$

$$\frac{dB_{ij}}{dt} = D_t^{1-\alpha}\Big(K\frac{B_{i+1,j} + B_{i-1,j} + B_{i,j+1} + B_{i,j-1}}{(\Delta x)^2} - K\frac{4B_{ij}}{(\Delta x)^2} - k_1 A_{ij} B_{ij}\Big) + k_2 C_{ij},$$

$$\frac{dC_{ij}}{dt} = D_t^{1-\alpha}\Big(K\frac{C_{i+1,j} + C_{i-1,j} + C_{i,j+1} + C_{i,j-1}}{(\Delta x)^2} - K\frac{4C_{ij}}{(\Delta x)^2} + k_1 A_{ij} B_{ij}\Big) - (k_2 + k_3) C_{ij},$$

where A_{ij}, B_{ij}, C_{ij} are approximations to $A(x_i, y_j, t)$, $B(x_i, y_j, t)$, $C(x_i, y_j, t)$, respectively. Periodic boundary conditions were used. Values of $K = 10^{-5}$, $k_1 = 0.01$, $k_2 = 0.02$, $k_3 = 0.03$, $L = 1$, $m = 10$ and $T = 600$ were chosen. The initial values were chosen randomly from a uniform distribution $U(0, 1)$ and we used $h = 0.6$.

NUMERICAL RESULTS

The concentrations of enzyme molecules A vary depending on the level of heterogeneity within the system (Fig. 1). A significant difference in the concentration distribution for $\alpha = 0.25$ and $\alpha = 0.95$ can be seen. The concentration at $\alpha = 0.25$, 0.5 and 0.75 varies a lot between 0 and 2. At this stage, molecular diffusion is significantly slowed. The presence of immobile obstacles or crowding agents may also trap the molecules for the some period, producing a longer diffusion time. As can be seen with $\alpha = 0.95$, in which the system is close to pure diffusion, the concentration at most points has already reached the equilibrium value of 1.

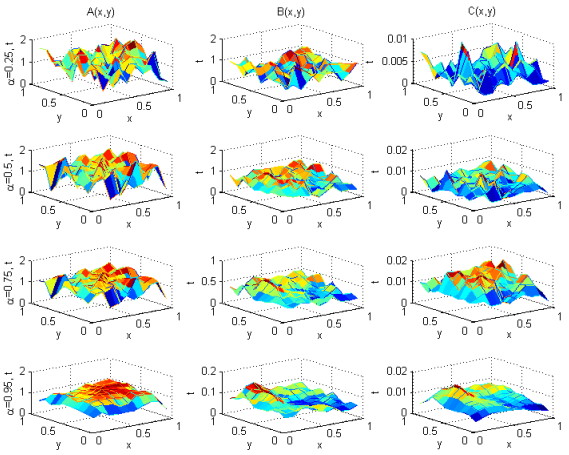

Fig. 1 Concentrations of A, B, and C at $T = 600$ for various values of α.

As the level of crowdedness in the system increases, particularly for α between 0.25 and 0.75, it can be seen that concentrations of molecule B (the substrate) vary a lot between 0 and 1. At this stage, molecular diffusion is obstructed by immobile crowding agents and structures that cause molecules to become trapped or require them to travel longer distances before reaching other molecules. For $\alpha = 0.95$, the concentration distribution is much smoother and close to zero.

In pure diffusion, the concentration of C (the complex) will eventually decay to zero. For $\alpha = 0.25$, the level of heterogeneity in the system is very high and the diffusion process is slowed. The concentration levels fluctuate between 0 and 0.005. For larger α, the concentrations of C increase and fluctuate between 0 and 0.01. We also see that concentrations fluctuate rapidly for $\alpha = 0.25, 0.5, 0.75$. It should be pointed out that a value of $\alpha = 0.25$ is not biologically reasonable, as usually $\alpha \geqslant 0.5$[1,4], but these results are included to demonstrate the strong crowding effects at this value.

Fig. 2a shows that as we reduce α, the concentration at a given point takes longer to diffuse away. Fig. 2b and Fig. 2c show that the diffusion of concentration at a point slows as the system becomes more crowded. On decreasing the heterogeneity in the system, particularly from $\alpha = 0.5$ to $\alpha = 0.95$, the concentration at a point nearly reach zero which is

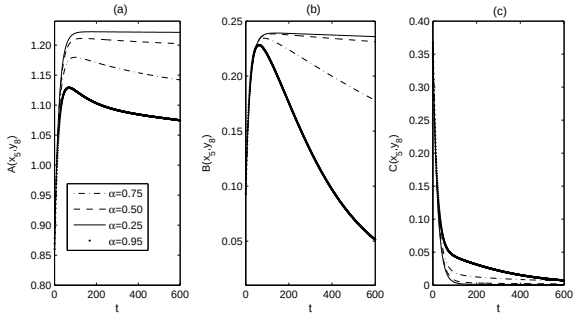

Fig. 2 Variation of A, B, and C concentrations at (x_5, y_8) over time for various values of α.

close to pure diffusion.

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