Journal of Pharmacokinetics and Pharmacodynamics (2019) 46:165–172
https://doi.org/10.1007/s10928-019-09625-8

ORIGINAL PAPER

Monte Carlo simulations in drug release

Kosmas Kosmidis[1] · George Dassios[2]

Received: 18 September 2018 / Accepted: 7 March 2019 / Published online: 18 March 2019

Abstract
We present methods based on simple sampling Monte Carlo simulations that are used in the study of controlled drug release from devices of various shapes and characteristics. The manuscript is part of a special tribute issue for Prof. Panos Macheras and we have chosen applications of the Monte Carlo method in the field of drug release that were pioneered by him and his research group. Thus, we focus on the investigation of diffusion based release and we present methods that go beyond the application of the classical fickian diffusion equation. We describe methods that have proven to be effective in illuminating the profound effects of the substrate heterogeneity on the drug release profiles and demonstrate some of the most powerful applications of agent based simulations and numerical methods in the field of pharmacokinetics.

Keywords Monte Carlo simulations · Numerical methods · Drug release

Introduction

It is often desirable, for therapeutical purposes, that a drug is delivered for a prolonged period of time after its administration and possibly at a constant rate [1]. Controlled drug release aims in regulating the amount of drug present in the human body and is obviously vital for effective therapy as well as for the development of new pharmaceutical products [2]. Thus, the understanding and modeling of the mechanisms involved in controlled release is a scientific field with considerable mathematical and practical importance. Several models have been proposed for the description of drug release [3–13] and all acknowledge the fact that diffusion plays a significant role in the drug release mechanisms. Monte Carlo simulation methods provide us with a way to understand diffusion based drug release in a microscopic level and elucidate several aspects of the release process that are otherwise difficult to comprehend. In this manuscript we will present the key ideas used in Monte Carlo simulations of drug release along with some examples of the successful application of the method in pharmacokinetics.

The Monte Carlo method is a very elegant numerical framework allowing the study of complex problems in statistical physics. Statistical mechanics provides a simple recipe for the study of systems with many degrees of freedom. One has to calculate the partition function Z of the system and the knowledge of this function Z is sufficient to determine all the thermodynamic properties of the system [14, 15]. In practice, however, the actual process of calculating the properties of a particular model is not a simple task. Exact solutions are very rare and computational methods are necessary.

The name "Monte Carlo" was coined by Nicolas Metropolis in 1949- and for many people, Monte Carlo simulation just means applying the famous Metropolis algorithm to the problem in hand [16]. The characteristic feature of the Monte Carlo method is that a system's evolution is simulated by drawing random numbers and deciding on the possible changes of the system's state based on these random numbers. Although the Metropolis algorithm is used for the simulation of systems in a heat bath, these equilibrium thermal Monte Carlo simulations is not the only field of application of the method.

Invited manuscript for the Special Tribute Issue for Panos Macheras.

✉ Kosmas Kosmidis
kosmask@auth.gr

George Dassios
gdassios@otenet.gr

[1] Division of Theoretical Physics, Physics Department, Aristotele University of Thessaloniki, 54124 Thessaloniki, Greece

[2] Division of Applied Mathematics, Department of Chemical Engineering, University of Patras, Patras, Greece

A system of particles that diffuses in space can also be studied using Monte Carlo methods and these kinetic Monte Carlo simulations are based in numerical studies of the concept of a random walk [17].

Simple sampling Monte Carlo methods: random walk simulations

What is a random walk? It is easy to reply to this question if you simply imagine a drunk outside a bar. Assume, furthermore, that he is so drunk that he practically cannot see where he is going. The probability of taking one step forward is equal to the probability of taking one step backward and the probability of taking one step to the left is equal to that taking one step to the right. Let him take several steps and record the way he moves. Then you have a very good example of what we call a random walk. If we want to be precise this is an example of an unbiased random walk on a two dimensional square lattice. There are several other types and generalizations of the above process that fall into the category of random walks, but the above example, the so called "drunkard's walk" [17] is rather comprehensive and simple. Despite this "frivolous" simplicity [18], the complete mathematical formulation of the random walk framework is rather sophisticated [19, 18]. Formally a random walk is a Markov chain with independent additive increments [20]. More precisely, a sequence of random variables Xn is a random walk if it satisfies

$$X_{n+1} = X_n + \epsilon_n \tag{1}$$

where $\epsilon_1, \epsilon_2, \ldots$ is a sequence of identically distributed random variables and is generated independently of $X_n, X_{n-1}, \ldots$. If the distribution of the ϵ_n is symmetric about zero, the sequence is called a symmetric random walk [21, 22].

In order to simulate a random walk in two dimensions we use a simple sampling Monte Carlo method [23, 14]. We initially place our walker in a 2-dimensional square lattice of size L. This practically means that we choose two integers in the range [1, L]. These are the coordinates of the initial position of the walker on the square lattice. The first one corresponds to the x coordinate of the walker and the second to the y coordinate. Next, we draw a random number z, typically in the range between [0, 1] using a reliable random number generator. If $z<1/4$ the walker takes a step to the left i.e. we decrease the x coordinate by 1 unit. if $1/4<z<1/2$ the walker takes a step to the right which means that we increase the x coordinate by 1 unit. If $1/2<z<3/4$ the walker takes a step downwards meaning that we decrease the y coordinate by 1 unit. Finally if $z > 3/4$ the walker takes a step upwards meaning that we increase the y coordinate by 1 unit. The process continues by drawing a new random number to decide about the next step of the walker and ends when the desired number of steps is completed.

The random walk model is a plausible microscopic description of the movement of a molecule that diffuses in a solid volume. The molecule moves more or less freely in a certain direction for a distance roughly equal to its mean free path. Then it collides with the molecules of the substrate's lattice. After the collision the molecule starts moving to an arbitrary direction until the next collision etc.

Thus, the above described algorithm is the base that allows us to investigate the following important question. How do drug molecules escape from a release device?

The answer to this important problem is a key element of controlled drug release and several groups have applied the Monte Carlo method to understand it.

Figure 1 shows an example of a random walk of 100,000 steps on a 2D square lattice. In this case the random walker starts at site (395, 395). The walker's final position is site (281, 242). The distinct number of sites visited by the walker is equal to 25,256. Notice the characteristic pattern with areas of the lattice that are almost fully explored by the walker, interwoven with large areas that remain completely unexplored.

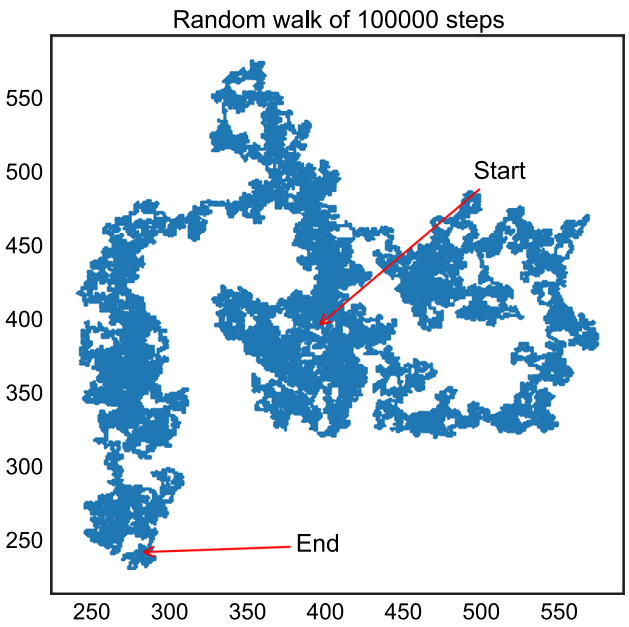

Fig. 1 A random walk of 100,000 steps on a 2D square lattice. The random walker starts at site (395, 395). The walker's final position is site (281, 242). The distinct number of sites visited by the walker is equal to 25256

Monte Carlo methods for drug release from euclidean matrices

The above idea was used by Prof. Panos Macheras [24] in order to simulate the release profile of drug molecules from regularly ordered substrates. We will describe the Monte Carlo method, used there to simulate release from cylindrical and spherical matrices, which has pretty much become the standard way of dealing with similar problems. The drug molecules are assumed to move inside the solid volume by performing random walks with excluded volume interactions. This means that each molecule occupies a volume V (one lattice site) where no other molecule can be at the same time.

Initially one considers a three-dimensional cubic lattice with size L i.e. with L^3 sites. A site is uniquely defined by its 3 coordinates i, j, k. Inside this cubic lattice one must define a cylinder or a sphere depending on the geometry of the problem that one needs to simulate. For a cylinder with radius r the condition for a site to belong to the interior of the cylinder is $i^2 + j^2 < (r-1)^2$. Sites whose i, j, k coordinates satisfy the previous inequality are sites that host drug molecules. If, on the other hand, the inequality $i^2 + j^2 > r^2$ holds, then this site is outside the cylinder. It is, thus, a restricted area and particles are not allowed to go there.

In order to define a sphere of radius r the process is similar, the difference being that the condition for a site to belong to the interior of the sphere is $i^2 + j^2 + k^2 < (r-1)^2$ and such sites can host drug molecules. If the inequality $i^2 + j^2 + k^2 > r^2$ holds, then this site is outside the sphere and labeled as a restricted area.

Since the problem of interest is the release of drug molecules from such a "device" we have to identify some sites on the surface of the cylinder or the sphere as leak sites meaning that when a drug molecule reaches such a site it is removed from the release device i.e. goes permanently out of the releasing solid volume. The fraction of the surface sites that are characterized as leak sites is a controllable parameter of the simulation and may be chosen to be in the range from one site to the complete surface. If, for example, we want to simulate the release process from a cylinder leaking from its round surface but not from its top or bottom we have to label as leak sites those with indices $(r-1)^2 < i^2 + j^2 < r^2$. Similarly if we want to simulate release from the complete surface of a sphere we have to label as leak sites those with indices $(r-1)^2 < i^2 + j^2 = k^2 < r^2$.

As a next step, we randomly place a number of particles on the sites of the cylinder, according to an initial particle concentration c, avoiding double occupancy. This means that on average a fraction c of the sites are initially occupied by particles, and the rest are empty. We can do that by repeatedly drawing random numbers. We "scan" the L^3 sites of our cubic lattice sequentially. If the site is a leak site or a restricted area we continue to the next site. If not we draw a random number z. If $z < c$ then we label the site as occupied by a drug molecule otherwise we label it as empty. We stop when we have completed the process for all sites of the lattice.

The diffusion process is simulated by selecting a particle at random and moving it to a randomly selected nearest neighbor site using the random walk algorithm that is described above. If the new site is an empty site, then the move is allowed, and the particle is moved to this new site. If the new site is already occupied, the move is rejected.

As soon as a particle migrates to a site labeled as a leak site it is removed from the system. And, thus, we are able to monitor the time evolution of this system. Our main quantity of interest is the number of molecules N that are inside the release device as a function of time. This brings us to the vital question of how to define the time for such simulations in a plausible way proportional to the actual time. The obvious choice is to define a variable t and to increment its value by one unit after each particle moves. This is not the wisest choice since in reality particles move simultaneously and not sequentially. Sequential updates in this case would introduce non-existent correlations between particles forcing, for example, particle number n to move only after particles $n-1, n-2, \ldots$ have moved. Such correlations may lead to artificial results and are know to cause difficulties in, for example, forest fire models [25]. Random updates [26] are preferred in this case and the typical approach used in Monte Carlo simulations of random walks [27] to rectify the artificially sequential time increments is that after each particle move the time is incremented not by one unit but by an amount of $1 / N$, where N is the number of particles remaining in the system. This is particularly important for drug release simulations, where the number of particles continuously decreases. With this, seemingly strange choice for the time increment, all drug molecules in the system are statistically allowed to move once in one time unit. Or to state it differently, the time unit characterizing the system is the mean time required for all N particles to move one step. The simulation continues until only a predetermined number of drug molecules remains in the system. A common choice is to wait long enough so that $N = 0$ i.e. for all drug molecules to escape the release device. It should be noted, however, that the choice between random and sequential updates in a Monte Carlo simulation is not always straightforward. For example, in Marcov Chain Monte Carlo simulations of the 1-hit metropolis algorithm

sequential updates are shown to lead to lower integrated autocorrelation time [26] and are, thus, preferable to random updates for that algorithm.

Since the Monte Carlo method simulates the evolution of the system stochastically, performing the above simulation only once is, obviously, of limited importance. We have to repeat the process multiple times and calculate averages of the quantities of interest. Thus, normally, we average our results using different initial random configurations but the same parameters.

Monte Carlo methods for drug release from fractal matrices

It is very interesting to understand how the presence of an heterogeneous substrate changes the diffusion profile of drug molecules and, consequently, to understand how the release profile is affected. In short, we need to find out what happens when the drug molecules diffuse on a highly disordered—fractal-substrate instead of the normal euclidean space of the interior of a cylinder or a sphere. Such studies were performed, among others, in [28–30]. For simplicity we will describe how these simulations are performed for a well known two dimensional random fractal, the percolation fractal [25]. This process can ,and has been extended to the three dimensional case in a straightforward manner.

Consider a two dimensional square lattice of length L. For each of the L^2 sites of the lattice draw a random number $x \in [0, 1]$. If this random number x is less than a predetermined constant $p \in [0, 1]$ then the site is labeled to be "open". Otherwise it is considered "closed". When all of the L^2 sites are labeled we examine the size of the clusters of "open" sites that have been formed. An isolated open site is a cluster of size one. If two "open" sites are neighboring sites then they belong to the same cluster. We keep only the largest cluster and disregard all the rest. When the number p is small (close to zero) then the largest cluster is small. When $p \simeq 1$ all "open" sites belong to the largest cluster. There is a critical value of p, known in the literature as p_c where the largest cluster connects opposite sizes of the lattice. This critical value for the 2D square lattice is known to be $p_c = 0.5927$ and the largest cluster at this particular critical value is known to be a fractal with fractal dimension $d_f = 91/48$. Moreover it is a random fractal because if one performs the same process with different random numbers will end up with a largest cluster consisting of different sites as opposed to other fractal structures as the Sierpinski gasket or the famous Mandelbrot set that are deterministic fractals [31]. Figure 2 shows an example of the percolation cluster. More specifically, we depict the largest cluster of a 1000×1000 square lattice at p_c. The number of sites comprising the largest cluster shown in the figure is equal to 281,706. The characteristic fractal landscape is rather obvious. There are holes of all length scales and diffusion on such a complex landscape is worth studying.

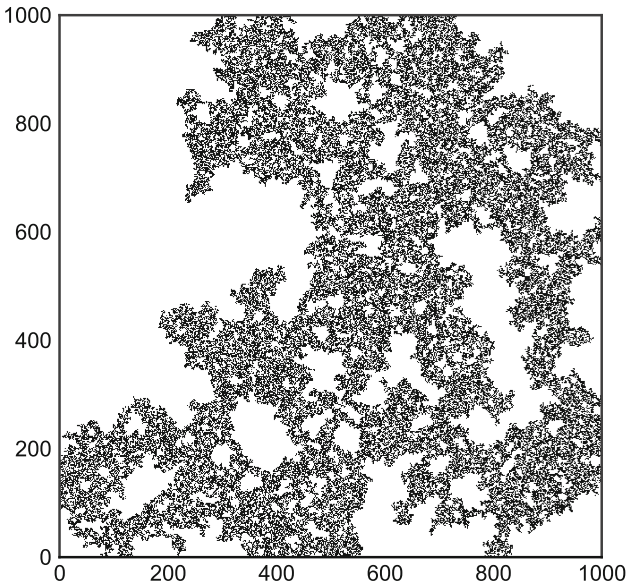

Fig. 2 Percolation cluster: the largest cluster of a 1000 squared lattice at $p_c = 0.5927$. The shape is known to be a fractal with fractal dimension $d_f = 91/48$. The number of sites comprising the largest cluster shown in the figure is equal to 281,706

The previous method of simulating random walks in the interior of a sphere or cylinder can be used to simulate random walks on the percolation fractal. We start by generating a percolation fractal using the method described above. The sites of the percolation fractal are filled with a predetermined fraction c of random walkers and the sites of the percolation fractal that are part of the square lattice's boundary are termed as leak sites.

One may initially think that the existence of such a disordered substrate has merely the effect of slowing down the diffusive process. After all at a regular square lattice a random walker has four nearest neighbors (Von Neumann neighborhood) to move at each step while in the fractal case there are, more often than not, less that four "open" neighboring sites and as a result the walkers will stay immobile more frequently than in the case of a euclidean environment. Thus, one might hope that the end result will be a normal diffusion with a smaller diffusion coefficient D. This is actually the case for random walks using the Moore neighborhood of a square lattice (i.e. eight nearest neighbors) or even using a continuous range of angles for the direction of the walker [32]. In all these cases the classical result that the mean squared displacement of a random walker is proportional to the number of steps is valid [17]. But for a fractal environment nothing could be

farther from the truth! It turns out (and the Monte Carlo method absolutely confirms it) that the existence of inaccessible areas in all length scales that characterizes a fractal structure [31] changes drastically the diffusive process and one refers to this phenomenon as anomalous diffusion [33]. The theoretical study of anomalous diffusion is challenging and quite sophisticated attempts have been made towards its understanding, most notably fractal [33] and fractional kinetics [34, 35].

Monte Carlo methods for drug release from matrices with high and low areas

We are interested in understanding how the release rate is changed, when the release device consists of a mixture of areas with high D_h and low D_l diffusion coefficients. Monte Carlo simulations have been used for studying drug release from random mixtures of high and low diffusivity areas (random mixing) [36] as well as from periodic layers of high and low diffusivity [37]. How can we modify the random walk model to effectively simulate faster or slower diffusion? It turns out that there is a simple way to do so. For a normal symmetric random walk, a walker located at a site with n neighbors jumps to one of the neighboring sites with probability $1 / n$. If, however, there is a probability q that the walker remains immobile at his position, instead of jumping to one of his closest neighboring sites, then the mean squared displacement of the random walker is decreased and one can rigorously demonstrate [36] that this corresponds to diffusive motion with a decreased diffusion constant. To be more specific, a lattice is considered and some lattice sites are labeled as high diffusivity areas while others as low diffusivity areas. If the moving particle is found at a high diffusion site, then we assume that $q = 0$ and that the diffusion coefficient is D_h. For a low diffusivity site we assume there is a non-zero q and taht the diffusion coefficient is D_l. It can be shown [36] that

$$\frac{D_l}{D_h} = 1 - q \tag{2}$$

The above Eq. (2) connects one quantity that is easily controlled in a Monte Carlo simulation to the ratio of the diffusion coefficients of the different mobility areas. Monte Carlo simulations of the above type have shown [36] that a release device covered by a thin film with diffusion coefficient D_l three orders of magnitude lower that the coefficient D_h of the rest of the device, will release drug at constant rate for almost the complete duration of the release process, a result of considerable practical importance.

In order to illustrate the above, in Fig. 3, we present Monte Carlo simulation results of the main quantity of interest in drug release studies, namely the fraction of the drug molecules that have escaped from the release device. This quantity is typically symbolized as M_t/M_∞. Thus, Fig. 3 depicts drug release versus time. Dotted points are results of Monte Carlo simulations. Blue circles show the release from a sphere of radius $r = 20$ sites. Orange squares show release from percolation fractals of a 200×200 squared lattice. Green triangles show release from a 100×100 lattice with randomly mixed (at a 50% ratio) of areas with high and low diffusivity and $D_l/D_h = 0.7$. Red polygons show release from a 100×100 lattice with its surface covered with a slow diffusivity layer with $D_l/D_h = 0.2$. The x-axis (Time) is in logarithmic scale- the distance between 10^1 and 10^3 is equal to the distance between 10^3 and 10^5. Time is measured in Monte Carlo steps.

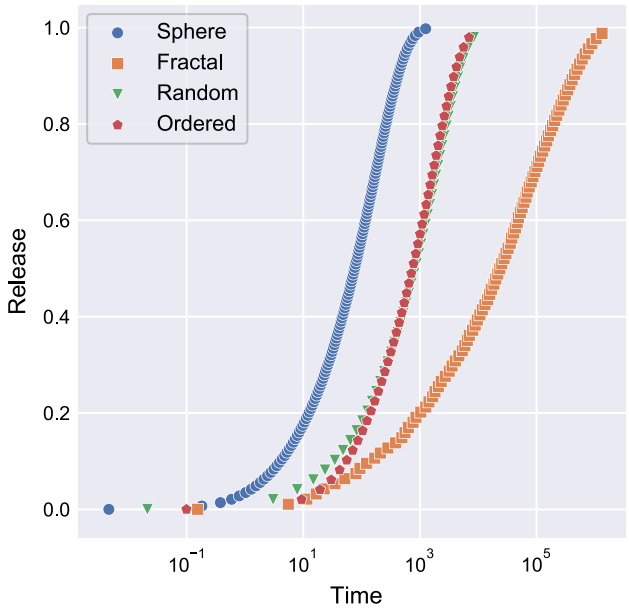

Fig. 3 (Color online) Drug release M_t/M_∞ versus time. Dotted points are results of Monte Carlo simulations. Blue circles show the release from a sphere of radius $r = 20$ sites. Orange squares show release from percolation fractals of a 200×200 squared lattice. Green triangles show release from a 100×100 lattice with randomly mixed (at a 50% ratio) of areas with high and low diffusivity and $D_l/D_h = 0.7$. Red polygons show release from a 100×100 lattice with it's surface covered with a slow diffusivity layer with $D_l/D_h = 0.2$. The time axis is in logarithmic scale. Time is measured in Monte Carlo steps

A generalized Fick's law and its implications

From the above, it becomes clear that kinetic Monte Carlo simulations based on the random walk model offer a method to study diffusive processes which is complementary to the solution of the classical diffusion equation. This

famous partial differential equation is typically derived from Fick's law (3)

$$\mathbf{J} = -D\nabla c \tag{3}$$

where c: the concentration of a substance, $\mathbf{J}$: flux of the substance and D: the diffusion coefficient [38]. The constant D denotes the quantity of a substance that is diffusing from one region to another and passes through each unit time when the volume-concentration gradient is equal to one. In addition to (3) the law of concervation of mass

$$\nabla \cdot \mathbf{J} + \frac{\partial c}{\partial t} = 0 \tag{4}$$

Inserting (3) into (4) we arrive at the diffusion equation

$$D\nabla^2 c = \frac{\partial c}{\partial t} \tag{5}$$

Thus, in Cartesian coordinates we will have the well known expression

$$D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) = \frac{\partial c}{\partial t} \tag{6}$$

reducing simply to

$$D\frac{\partial^2 c}{\partial x^2} = \frac{\partial c}{\partial t} \tag{7}$$

if the diffusion is one dimensional i.e. if there is a gradient of concentration only along the x-axis.

Equation 5 is a parabolic PDE [39] which implies an infinite speed of propagation of the quantity c. Indeed, the fundamental solution (Green's function) of (5) has the form (1-dimension)

$$G(x,t) = \frac{1}{\sqrt{4\pi D t}} e^{-\frac{x^2}{4Dt}} \tag{8}$$

which is positive for every $x \in \mathbb{R}$ and $t > 0$ [39]. Hence, any unit excitation at any point of $\mathbb{R}$ at any moment will affect the whole real line instantly. That means infinite speed of propagation of every effect on c. According to extended irreversible thermodynamics [40] and other local non-equilibrium approaches [41–44] ,one can correct this physically unrealistic phenomenon by generalizing Fick's law including the time derivative of the flux, i.e

Generalized Fick's law

$$\tau\frac{\partial \mathbf{J}}{\partial t} + \mathbf{J} = -D\nabla c \tag{9}$$

This means that any concentration gradient will cause a change not only on the flux but also on the way that flux changes with time. The constant τ is the relaxation time and represents the time lag needed to establish steady -state conduction of the substance in an element of volume when a concentration gradient is suddenly applied to that element (i.e. intravenous drug intake).

This law combined with equation (4) leads to a more realistic physical model of diffusion governed by the equation

Generalized diffusion equation

$$D\nabla^2 c = \frac{\partial c}{\partial t} + \tau\frac{\partial^2 c}{\partial t^2} \tag{10}$$

Equation (10) is a hyperbolic equation [39] having finite speed of propagation (realistic model) [43] where the term $\partial c/\partial t$ acts as a dissipation term. Note also that the operator $\tau\frac{\partial}{\partial t}$ is dimensionless, as it should be in order to be compatible with the term $\mathbf{J}$.

In order to clarify the above we present as an example the solution of a "model" one dimensional case. More specifically we solve numerically Eqs. (5, 10) for a 1D rod of length $l = \pi$ and initial drug concentration distribution $c(x, t = 0)) = \sin(x)$ and with boundary conditions $c(x = 0, t) = 0$ and $c(x = \pi, t)) = 0$.

We present the results of this numerical solution in Fig.4. More specifically, Fig.4 (Top Left) a three-dimensional plot of the concentration $c(x, t)$ at the z-axis as a function of the spatial coordinate of the rod x and the time t. Obviously, the variable $x \in [0, \pi]$ and we examine the case of $\tau = 0$ which is equivalent to the classical diffusion Eq. (5). Fig. 4(Bottom Left) shows the same for $\tau = 0.5$ which is the actual non-trivial generalized diffusion equation (Eq. 10) case . (Top Right) Spatial concentration distribution $c(x, t = 0.5)$ for $\tau = 0$ (solid line) and $\tau = 0.5$ (dashed line). (Bottom Right) Evolution of the concentration $c(x = 0.5, t)$ versus time for $\tau = 0$ (solid line) and $\tau = 0.5$ (dashed line). All quantities are in arbitrary units (a.u).

Numerical solutions of Eq.10 like those presented here can be compared to Monte Carlo simulation results as well as to experimental results with an aim to determine the optimal value of the relaxation constant τ for a particular system. Obviously, large values of τ signify that a classical diffusion description is not adequate.

Conclusions

We have presented, in a fairly detailed manner, how numerical methods and in particular kinetic Monte Carlo simulation methods can be used to study controlled drug release from release devices of various shapes and characteristics when diffusion is the main underlying release mechanism. Our focus has been on the detailed investigation of diffusion based release and we presented a set of methods that are important in the study of the release process, go beyond the application of the classical fickian

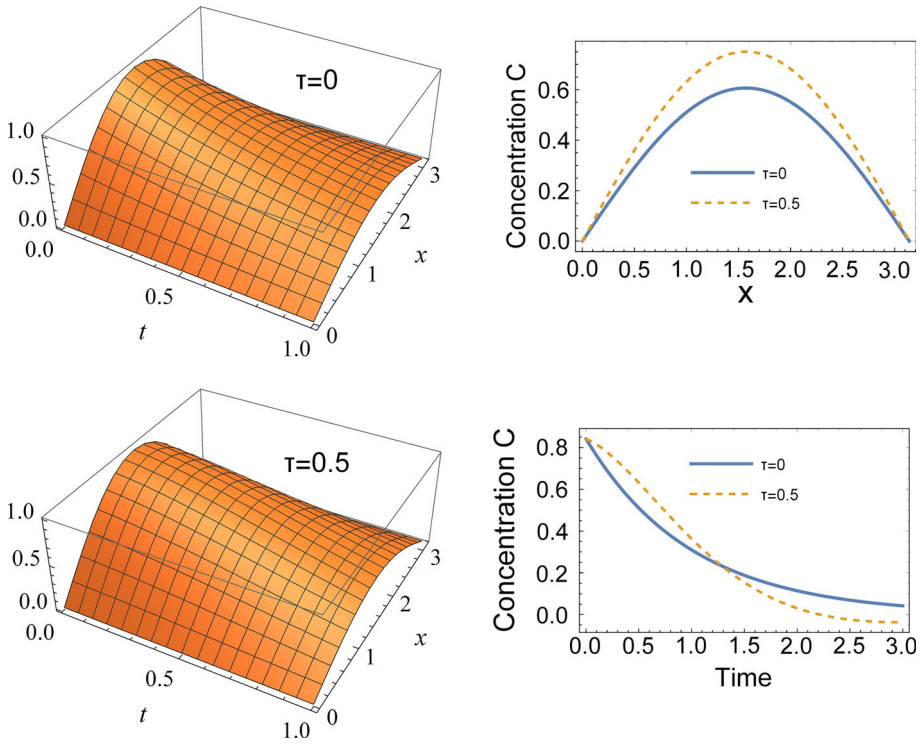

Fig. 4 Numerical solution of the generalized diffusion equation (Eq. 10) for a 1D rod of length $l = \pi$ and initial drug concentration distribution $c(x)) = \sin(x)$. (Top Left) The depicted surface is a three-dimensional plot of $c(x, t)$ for the case of $\tau = 0$ which is equivalent to the classical diffusion Eq. (5).(Bottom Left) The same for $\tau = 0$. (Top Right) Spatial concentration distribution $c(x, t = 0.5)$ for $\tau = 0$ (solid line) and $\tau = 0.5$ (dashed line). (Bottom Right) Evolution of the concentration $c(x = 0.5, t)$ versus time for $\tau = 0$ (solid line) and $\tau = 0.5$ (dashed line). All quantities are in arbitrary units (a.u)

diffusion equation and should be used in parallel with the classical approach. The implications of the results presented in the present manuscript are rather significant. First, based on the Monte Carlo methods described above it has been indicated that Fickian drug release from Euclidian or fractal matrices can be described with the Weibull function [28, 45] and this fact can be used for the discernment of drug release mechanisms [45].

Moreover, we note that Pharmacokinetics has been usually dealt with under the homogeneity assumption and the fact that biological systems are better understood as being inherently fractal is, thus, ignored. Drug molecules interact with metabolic enzymes or pharmacological receptors in unstirred, space-restricted, heterogeneous and geometrically fractal environments and the notion of the compartment as a homogeneous kinetic space must be modified [46, 10]. The study of diffusion in fractal spaces using of fractional calculus and Monte Carlo methods has lead, for example, in defining time-dependent rate constants with a characteristic fractal exponent [47, 6] . We are able to speak of Fractal Pharmacokinetics and realize that it is crucial that pharmacokinetic models incorporate rate laws based on fractal kinetics, which appear to reflect more accurately than mass-action kinetics the in vivo conditions.

The manuscript is not intended—not even remotely—to be a review of the published literature on numerical methods for controlled drug release. We merely want to demonstrate in a comprehensive manner a guide on how these methods can be used to augment our understanding of controlled drug release. The manuscript is part of a special tribute issue for Prof. Panos Macheras and this has been our guide for the selection of the presented material as it consists of applications of the Monte Carlo and numerical methods pioneered by him.

References

1. Perrie Y, Rades T (2012) FASTtrack Pharm. Pharmaceutical press, London
2. Macheras P, Iliadis A (2016) Modeling in biopharmaceutics, pharmacokinetics and pharmacodynamics. Springer, New York. https://doi.org/10.1007/978-3-319-27598-7
3. Bäckman P, Arora S, Couet W, Forbes B, de Kruijf W, Paudel A (2018) Advances in experimental and mechanistic computational models to understand pulmonary exposure to inhaled drugs. Eur J Pharm Sci 113:41–52
4. Kaoui B, Lauricella M, Pontrelli G (2018) Mechanistic modelling of drug release from multi-layer capsules. Comput Biol Med 93:149–157
5. Kosmidis K, Macheras P (2018) On the dilemma of fractal or fractional kinetics in drug release studies: a comparison between weibull and mittag-leffler functions. Int J Pharm 543(1–2):269–273
6. Kosmidis K, Karalis V, Argyrakis P, Macheras P (2004) Michaelis-menten kinetics under spatially constrained conditions: application to mibefradil pharmacokinetics. Biophys J 87(3):1498–1506
7. Marsh RE, Tuszyski JA (2006) Fractal michaelis-menten kinetics under steady state conditions: application to mibefradil. Pharm Res 23(12):2760–2767. https://doi.org/10.1007/s11095-006-9090-6

8. Nygren H (1993) Nonlinear kinetics of ferritin adsorption. Biophys J 65(4):1508–1512. https://doi.org/10.1016/S0006-3495(93)81221-9
9. Ritger PL, Peppas NA (1987) A simple equation for description of solute release ii. Fickian and anomalous release from swellable devices. J Controll Release 5(1):37–42
10. Savageau MA (1995) Michaelis-menten mechanism reconsidered: implications of fractal kinetics. J Theor Biol 176(1):115–124. https://doi.org/10.1006/jtbi.1995.0181
11. Savageau MA (1998) Development of fractal kinetic theory for enzyme-catalysed reactions and implications for the design of biochemical pathways. Biosystems 47(1–2):9–36
12. Siepmann J, Peppas N (2001) Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (hpmc). Adv Drug Deliv Rev 48(2–3):139–157
13. Zhan W, Alamer M, Xu XY (2018) Computational modelling of drug delivery to solid tumour: understanding the interplay between chemotherapeutics and biological system for optimised delivery system. Adv Drug Deliv Rev 132:81–103
14. Landau DP, Binder K (2014) A guide to Monte Carlo simulations in statistical physics. Cambridge University Press, Cambridge
15. Reichl LE (2016) A modern course in statistical physics. Wiley, Hoboken
16. Newman M, Barkema G (1999) Monte Carlo methods in statistical physics. Oxford University Press, New York
17. Weiss G (2005) Aspects and applications of the random walk (random materials & processes S.). North-Holland
18. Hughes BD (1995) Random walks and random environments. Clarendon Press; Oxford University Press, Oxford
19. Feller W (2008) An introduction to probability theory and its applications, vol 1. Wiley, Hoboken
20. Fishman G (2013) Monte Carlo: concepts, algorithms, and applications. Springer, New York
21. Kroese DP, Taimre T, Botev ZI (2013) Handbook of monte carlo methods, vol 706. Wiley, Hoboken
22. Robert C, Casella G (2013) Monte Carlo statistical methods. Springer, New York
23. Kalos M, Whitlock P (2008) Monte Carlo methods, 2nd edn. WILEY-VCH Verlag GmbH & Co, KGaA, Weinheim
24. Kosmidis K, Argyrakis P, Macheras P (2003b) A reappraisal of drug release laws using monte carlo simulations: the prevalence of the weibull function. Pharm Res 20(7):988–995
25. Bunde A, Havlin S (2012) Fractals and disordered systems. Springer Science & Business Media, New York
26. Berg BA (2004) Markov chain Monte Carlo simulations and their statistical analysis: with web-based Fortran code. World Scientific Publishing Company, Singapore
27. Bunde A, Havlin S, Nossal R, Stanley H, Weiss G (1985) On controlled diffusion-limited drug release from a leaky matrix. J Chem Phys 83(11):5909–5913
28. Kosmidis K, Argyrakis P, Macheras P (2003a) Fractal kinetics in drug release from finite fractal matrices. J Chem Phys 119:6373
29. Villalobos R, Vidales AM, Cordero S, Quintanar D, Domínguez A (2006) Monte carlo simulation of diffusion-limited drug release from finite fractal matrices. J Sol-Gel Sci Technol 37(3):195–199
30. Villalobos R, Garcia E V, Quintanar D, Young P M (2017) Drug release from inert spherical matrix systems using Monte Carlo simulations. Curr Drug Deliv 14(1):65–72
31. Bunde A, Havlin S (2013) Fractals in science. Springer, New York
32. Landau RH, Páez MJ, Bordeianu CC (2015) Computational physics: problem solving with Python. Wiley, Hoboken
33. Havlin S, Ben-Avraham D (2002) Diffusion in disordered media. Adv Phys 51(1):187–292
34. Dokoumetzidis A, Macheras P (2009) Fractional kinetics in drug absorption and disposition processes. J Pharmacokinet Pharmacodyn 36(2):165–178. https://doi.org/10.1007/s10928-009-9116-x
35. Sokolov IM, Klafter J, Blumen A (2002) Fractional kinetics. Phys Today 55(11):48–54
36. Kosmidis K, Macheras P (2007a) Monte carlo simulations for the study of drug release from matrices with high and low diffusivity areas. Int J Pharm 343(1–2):166–172
37. Kosmidis K, Macheras P (2007b) Monte carlo simulations of drug release from matrices with periodic layers of high and low diffusivity. Int J Pharm 354:111
38. Crank J et al (1979) The mathematics of diffusion. Oxford University Press, Oxford
39. Morse PM, Feshbach H (1953) Methods of theoretical physics. Mc Graw-Hill Book, New York
40. Jou D, Casas-Vázquez J, Lebon G (1996) Extended irreversible thermodynamics. Springer, New York
41. Nettleton R, Sobolev SL (1995) Applications of extended thermodynamics to chemical rheological, and transport processes: a special survey part i. Approaches and scalar rate processes. J Non Equilib Thermodyn 20(3):205–229
42. Sobolev S (1994) Equations of transfer in non-local media. Int J Heat Mass Transfer 37(14):2175–2182
43. Sobolev S (2012) Local non-equilibrium diffusion model for solute trapping during rapid solidification. Acta Mater 60(6–7):2711–2718
44. Sobolev SL (1991) Transport processes and traveling waves in systems with local nonequilibrium. Sov Phys Uspekhi 34(3):217
45. Papadopoulou V, Kosmidis K, Vlachou M, Macheras P (2006) On the use of the weibull function for the discernment of drug release mechanisms. Int J Pharm 309(1–2):44–50
46. Pereira LM (2010) Fractal pharmacokinetics. Comput Math Methods Med 11(2):161–184
47. Fuite J, Marsh R, Tuszyński J (2002) Fractal pharmacokinetics of the drug mibefradil in the liver. Phys Rev E 66(2):021904