Modeling fractal-like drug elimination kinetics using an interacting random-walk model

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We introduce an interacting random-walk model to describe the residence time of drug molecules undergoing a series of sojourn times in the body before being permanently eliminated under either homogeneous or heterogeneous conditions. We show that short-term correlations between drug molecules lead to Michaelis-Menten kinetics while long-term correlations lead to transient fractal-like kinetics. By combining both types of correlation, fractal-like Michaelis-Menten kinetics are achieved, and the simulations confirm previous analytical results.

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I. INTRODUCTION

Pharmacokinetics is the quantification of the course of a drug through the body [1]. Drug molecules undergo many processes during their residence in the body, including absorption, distribution, metabolism, and elimination. Because many spaces within the body are confined or heterogeneous, these processes are frequently nonlinear. An interacting random-walk model is developed to relate the macroscopic chemical kinetic behavior of the ensemble of drug molecules to the microscopic interactions between individual molecules. Previously, it was shown that geometric heterogeneity can lead to fractal pharmacokinetics [2]. The goal of this paper is to demonstrate that both long- and short-term interactions between drug molecules can also generate fractal-like kinetics.

II. ELIMINATION KINETICS

When a dose of drug is given as a bolus directly into the vascular system, the resulting plasma concentration-time curve decreases continuously from a maximum and is called a clearance curve. For drugs rapidly distributed throughout the body, the shape of the curve is determined predominantly by the rate of elimination through enzymatic biotransformation. The kinetics describing this elimination depend on the geometry of the reaction space and the degree of mixing of the drug within the plasma. In homogenous, well-mixed media, the rate of a chemical reaction is directly proportional to the product of the concentrations of the N reactants each raised to the reaction order n_i,

$$\dot{C}_i(t) = -k\prod_{i=1}^{N} C_i^{n_i}(t), \tag{1}$$

where C_i is the concentration of reactant i and k is the kinetic rate coefficient. The reaction order is the number of concentration terms that must be multiplied together to get the rate of the reaction [3]. For a single step, n_i is typically equal to the molecularity, which is the number of molecules that are altered during the reaction. When only one molecule is modified, the reaction is described by

$$\dot{C}(t) = -kC(t). \tag{2}$$

However, the rate of enzyme-catalyzed reactions can deviate from those predicted by Eq. (2). Michaelis-Menten kinetics [4] is the standard formalism for describing these reactions. At high concentrations, saturation of the enzymes limits the maximum reaction rate that can be achieved, while at low concentrations the rate of formation of the enzyme-substrate complex becomes significant and the reaction becomes dependent on the substrate concentration [5]. The rate of Michaelis-Menten kinetics is given by

$$\dot{C}(t) = -\frac{v_{\max}C(t)}{K_M + C(t)}. \tag{3}$$

The parameter $v_{\max}$ is the maximum rate of the reaction, and the Michaelis-Menten constant K_M is the substrate concentration at half the maximum rate.

In low-dimensional or heterogeneous spaces, Eqs. (2) and (3) do not hold [6]. In the case of transient reactions, the kinetic rate coefficient becomes time-dependent [7]:

$$k(t) = k_0 t^{-h}, \tag{4}$$

where

$$h = 1 - \frac{d_s}{2}. \tag{5}$$

The quantity d_s (where $0 \leqslant d_s \leqslant 2$) is the spectral dimension that describes the path of a random walker within the medium [8]. The classical case corresponds to $d_s = 2$. Because Eq. (4) has a singularity at $t=0$ for $h>0$, Schnell and Turner [9] have suggested a modified form of Eq. (4) based on the Zipf-Mandelbrot distribution, $k(t)=k_0(\tau+t)^{-h}$, where the constant τ is the critical time from which the rate constant is driven by fractal effects. However, if τ is very small, Eq. (4) is a good approximation. The corresponding reaction rate is

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$$\dot{C}(t) = -k_0 t^{-h} C(t). \tag{6}$$

Equation (6) has been incorporated into pharmacokinetics through both noncompartmental and compartmental models. The former includes the homogeneous-heterogeneous distribution model introduced by Macheras [10] to quantify the global and regional characteristics of blood flow to organs. The latter includes the fractal compartmental model developed by Fuite *et al.* [2] in which a classical compartment was used to represent the plasma while a fractal compartment was used to represent the liver. Equation (6) has also been incorporated into the Michaelis-Menten formalism, notably by Kosmidis *et al.* [11] with the result that

$$\dot{C}(t) = -\frac{v_{\max} C(t)}{K_{M0} t^h + C(t)}, \tag{7}$$

where K_{M0} is the modified Michaelis-Menten constant.

In the case of steady state reactions, Anacker and Kopelman [6] found that the reaction rate is given instead by

$$\dot{C}(t) = -k_0 C(t)^X, \tag{8}$$

where X is the fractal reaction order related to the spectral dimension of the random walk. Because Michaelis-Menten kinetics occur within an environment with a pseudo-steady state drug concentration [5], Marsh and Tuszynski [12] proposed that

$$\dot{C}(t) = -\frac{v_{\max} C(t)^X}{K_M + C(t)^X} \tag{9}$$

for Michaelis-Menten reactions occurring within a heterogeneous or low-dimensional environment. It is important to note that the steady state condition can be achieved in different ways, even in the case of a single dose [12]. For example, the recycling of drug molecules between the plasma and the site of elimination can create a local steady state.

To summarize, any reaction for which $h>0$ or $X>m$ (where m is the molecularity of the reaction) is referred to as following fractal-like kinetics [13].

A. Asymptotic behavior

As well as being relevant to experimental and clinical situations, clearance curves represent the asymptotic behavior approached by systems with nonbolus administration. Even if a pharmacokinetic system is driven for an initial period (for example, through a continuous infusion or absorbed oral dose), the system's behavior is ultimately dissipative since the concentration will decrease towards zero as all the drug molecules ultimately leave the system. If we consider the behavior of the kinetics equations discussed in the previous section, the solution to Eq. (2) is simply an exponential in time, and the solution to Eq. (6) is a stretched exponential. For Michaelis-Menten kinetics [Eq. (3)], the solution is linear at high concentrations ($C \gg K_M$) and exponential at low concentrations ($C \ll K_M$). For transient fractal Michaelis-Menten kinetics [Eq. (7)], the solution transitions from an exponential to a stretched exponential. Finally, for steady state fractal Michaelis-Menten kinetics [Eq. (9)], an initial linear decrease is followed by a long-time power law tail of the form [12]

$$C(t) \sim t^{\gamma}. \tag{10}$$

The power exponent γ is negative and can be related to the fractal reaction order X through [12]

$$X = 1 - \frac{1}{\gamma}. \tag{11}$$

III. INTERACTING RANDOM-WALK MODEL

From a physical point of view, a group of drug molecules can be treated as a many-body system of identical molecules. The molecules are introduced into a confined, dissipative medium, and they undergo transport and kinetic processes until all of the molecules have been removed from the system. For drugs administered directly into the vascular system, the molecule residence time is determined predominantly by (i) the resistive effect of the temporary trapping of drug molecules in cells and tissues, and (ii) the conductive effect of permanent trapping due to metabolism and excretion.

Because the residence time of a drug molecule can be seen as the sum of many sojourn times within the body, we can consider the molecule as performing a random walk in time. In a simple random walk, a walker moves at every time step to one of its nearest-neighbor sites with equal probability. A more general process occurs when the length l of the steps, or flights, is not constant but rather drawn from a distribution $p(l)$. The properties of the random walk follow the central limit theorem if (i) the l values are not characterized by any long-range correlations, and (ii) the distribution $p(l)$ is not too broad [14]. If either of these conditions is not met, the walk can become anomalous. In this paper, we investigate the first case, and in a follow-up paper we will discuss the second scenario and model it using the continuous time random-walk (CTRW) formalism.

In the current model, we define a temporal random walk on a one-dimensional finite lattice with periodic boundary conditions and two different kinds of lattice sites: plasma (P) transport sites and permanent elimination (E) traps. This is equivalent to assuming that the drug concentration in other tissues achieves equilibrium with the plasma in a relatively short time. Drug molecules are introduced onto P sites and undergo a sequence of sojourn times in P sites until they are removed from an E site. The residence time of a molecule is denoted by θ and can be expressed simply as

$$\theta = \sum_{i=1}^{N} \hat{\tau}_i, \tag{12}$$

where $\hat{\tau}_i$ is an individual sojourn time in a P site. Because θ is a macroscopic quantity and $\hat{\tau}$ is a microscopic quantity, Eq. (12) represents a simple statistical mechanical view of the drug residence time. In order to isolate the dynamics of the elimination process, the plasma sojourn time was taken to be constant and equal to three time steps. In addition,

molecules remained in E sites for one time step before being removed from the lattice. If the value of $\hat{\tau}_i$ is not constant but rather drawn from a probability distribution, the process becomes a CTRW.

If each walker is independent, the total number of walkers will decrease exponentially in time according to Eq. (2). However, if the walkers are allowed to interact, anomalous behavior can result. To test whether these interactions can reproduce fractal-like kinetics, both short-term and long-term correlations were introduced into the model using a saturable process and excluded volume effects.

This model can be mapped onto a stochastic compartmental model, with all the sites of a given type being interpreted as forming a "compartment" and the transfer between P and E sites being governed by a probability distribution function (PDF). However, the random walk model has a greater degree of flexibility in handling interactions between molecules.

A C++ program was written using Microsoft Visual C++.net (Redmond, WA) with a DrugMolecule class and a DrugSite class. An instance of the DrugMolecule class was created for each molecule to keep track of its plasma sojourn time, θ, number of plasma hits, N_P, and current location and site type. An instance of the DrugSite class was created for each lattice site to hold information about its location, type, and occupation status.

The Monte Carlo algorithm proceeds as follows.

(1) An L-length array $\{s_0, s_1, \ldots, s_L\}$ is created to represent the lattice, with s_i representing the type of site at the ith position. The site types are distributed randomly along the lattice according to the fractions f_i of the total number of sites of type i (equal to P or E).

(2) An N-length array $\{d_0, d_1, \ldots, d_N\}$ of drug molecules is created to track the position of each molecule.

(3) An M-length sorted list $\{t_0, t_1, \ldots, t_M\}$ is created to hold the update times of the molecules. The update time is equal to the current time plus the sojourn time associated with the type of site a molecule currently occupies. The list is sorted in increasing order in time, so that t_0 is the next time at which the system will advance.

(4) The clock, which runs in Monte Carlo time steps, is set to zero. The molecules are initially assigned to random P sites, and the sorted list is populated with update times equal to three time steps. Multiple occupancy of any site is not allowed.

(5) The clock is moved forward to equal t_0, and the molecule associated with that update time is selected.

(6) If the molecule is at an E site, it is removed from the system. Otherwise, a new site is chosen according to the sampling rules (cf. Sec. IV B). If the new site is unoccupied, the molecule moves to that site. If the site is occupied, the molecule remains at its current site. A new update time is generated for the molecule and added to the sorted list.

(6) Steps 5 and 6 are repeated until all of the molecules have been removed from the lattice.

At intervals of n_{update} moves, the elapsed time and occupation number, X_i, for each site type are recorded. The occupation number plays the role of the drug concentration. Unless otherwise indicated, the model parameters for the current study were chosen to be $L=200\,000$, $N=10\,000$,

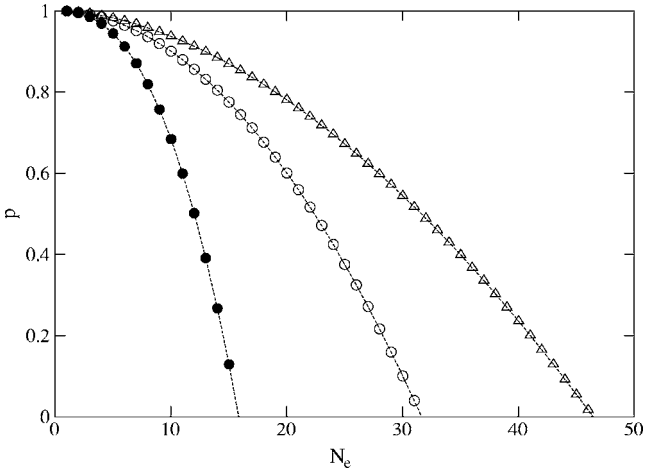

FIG. 1. The probability p that a molecule will move to an empty elimination (E) site, given the number N_e of currently populated E sites, with $N_e^{\max}=15$ (solid circles), $N_e^{\max}=30$ (open circles), and $N_e^{\max}=45$ (open triangles).

$f_E=0.05$, and $f_P=0.95$. The number of E sites was chosen to be much less than the number of P sites.

IV. REPRODUCING ELIMINATION KINETICS

A. Michaelis-Menten kinetics

In order to simulate Michaelis-Menten kinetics, molecules were allowed to jump anywhere on the lattice. However,

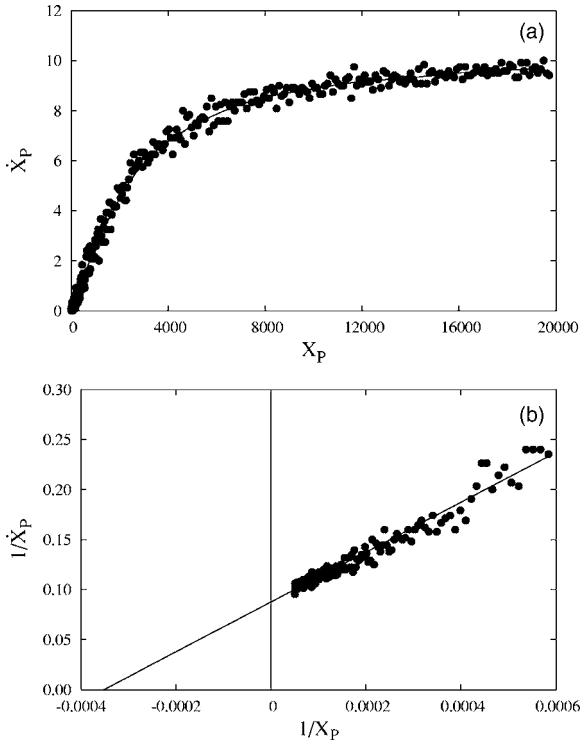

FIG. 2. (a) Reaction rate as a function of plasma occupation with $N_e^{\max}=30$. The solid line represents a moving-average trendline. (b) Reciprocal Lineweaver-Burk plot of the same data. The solid line represents the best-fit obtained by regression analysis, with corresponding values of $v_{\max}=1.14\pm0.01$ and $K_M=317\pm8$ ($R^2=0.958$).

although a molecule always moved to an empty P site, it was only moved to an empty E site if a random number drawn on [0,1] was less than the probability $p(N_e)$. The quantity N_e is the number of currently occupied E sites. To satisfy the condition that p is 1 for low values of N_e and 0 for $N_e=N_e^{\max}$, the probability distribution was chosen to have the form

$$p(N_e) = 1 - \left(\frac{N_e}{N_e^{\max}}\right)^2, \quad 0 \leqslant N_e \leqslant N_e^{\max}. \tag{13}$$

Figure 1 shows $p(N_e)$ for different values of $N_e^{\max}$. The effect of increasing $N_e^{\max}$ is to increase both $v_{\max}$ and K_M. Figure 2 confirms that this distribution produces the correct behavior; the plot of $\dot{X}_P$ as a function of X_P is hyperbolic and the Lineweaver-Burk plot [a linearization of Eq. (3)] is linear.

Figure 3 shows a plot of X_P following a bolus dose. As expected for Michaelis-Menten kinetics, the high-concentration behavior is linear and the low-concentration behavior is exponential. The transition occurs at approximately $X_P=2000$ molecules. Because this interaction only persists for the duration of the E site sojourn time (three time steps), this saturation effect is an example of a short-term correlation between the molecules.

B. Fractal-like kinetics

Transient fractal-like kinetics can be introduced into the model by limiting the movement of molecules along the lattice. For a simple random walk in which the molecules can jump to any site on the lattice, there is a constant probability (equal to f_E) that a molecule is eliminated at a given time. The probability is independent of the time that a molecule has spent in P sites, or its "age." In addition, the compartments are homogeneous and well-mixed, and the system lacks memory.

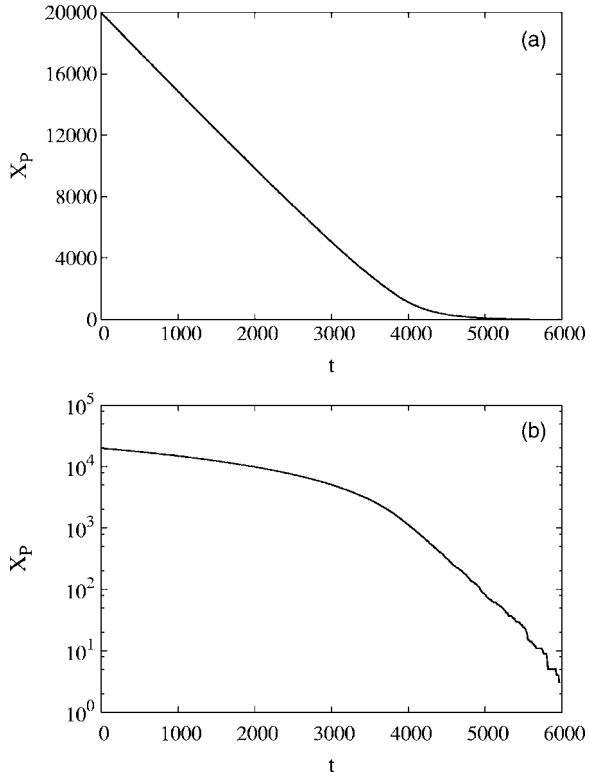

FIG. 3. (a) The plasma occupation following a bolus dose of 10 000 drug molecules undergoing short-term interactions ($N_e^{\max}=15$). (b) The decline is first linear and then transitions to exponential.

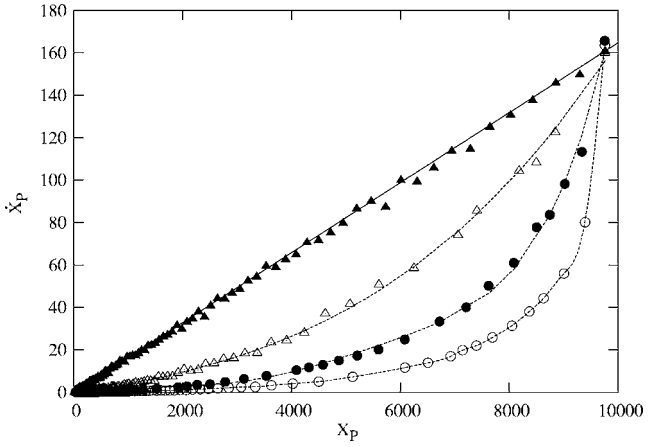

FIG. 4. Reaction rate as a function of plasma occupation following a bolus dose of 10 000 molecules undergoing short-term interactions with $N_e^{\max}=15$ and $\Omega=100$ (closed triangles), $\Omega=5$ (open triangles), $\Omega=2$ (closed circles), and $\Omega=1$ (open circles). The $\dot{X}_P$ and X_P values were averaged over five runs.

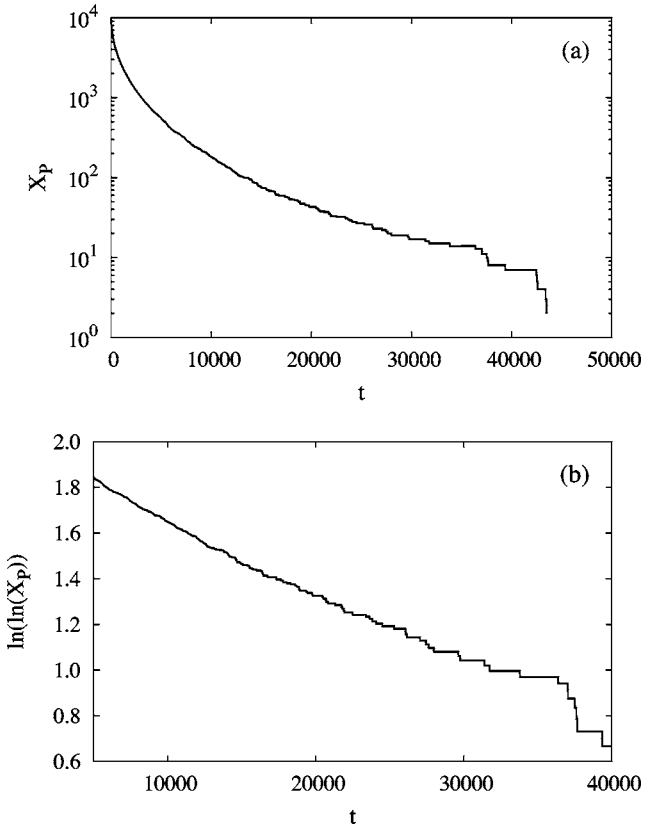

FIG. 5. (a) The plasma occupation following a bolus dose of 10 000 drug molecules undergoing long-term interactions ($\Omega=1$). (b) The decline follows a stretched exponential.

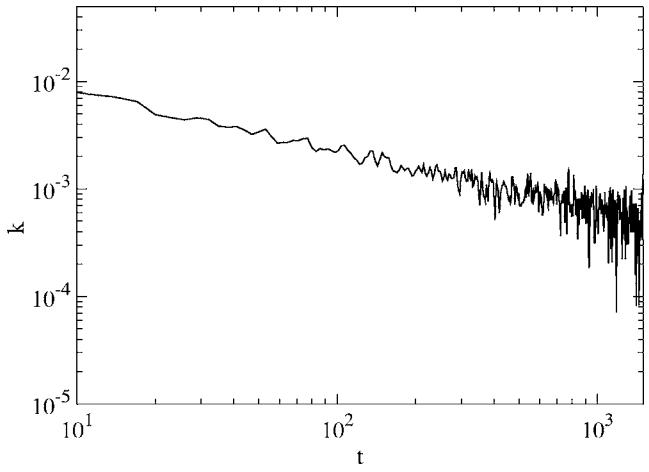

FIG. 6. The power law dependence of k on t for a lattice with long-term correlations ($\Omega=1$).

However, if the molecules are restricted to nearest-neighbor moves, the probability of elimination is no longer constant. Clusters of molecules will begin to form along the lattice, and the interior molecules will have limited mobility. The more interior a molecule is within a cluster, the more time must elapse before it will be able to move and access an E site. Therefore clustering creates an age-dependent effect. To implement this modification in the model, molecules were only allowed to move a maximum of Ω sites in either direction along the lattice. For large Ω (>50), classical kinetics were recovered.

This type of age discrimination in the elimination process mimics understirred compartments [15]. The lower the value of Ω, the less efficient the mixing process. A physiological analogy can be made to a drug that is transported through the bloodstream and eliminated from the liver. Access to an enzyme site in the liver will depend not only on the blood flow to the liver, but also on the degree of mixing within the blood. The rate of reactions occurring within poorly mixed environments has been shown to be slowed down in both regular and disordered environments [16–18].

Other stochastic models have been developed to study the effects of low-dimensional media on enzyme-mediated reactions. For example, Berry [19] and Kosmidis *et al.* [11] considered the spatial clustering of molecules within two-dimensional percolation lattices. Although Matis and Wehrly [20] used temporal clustering in their model, they used it to

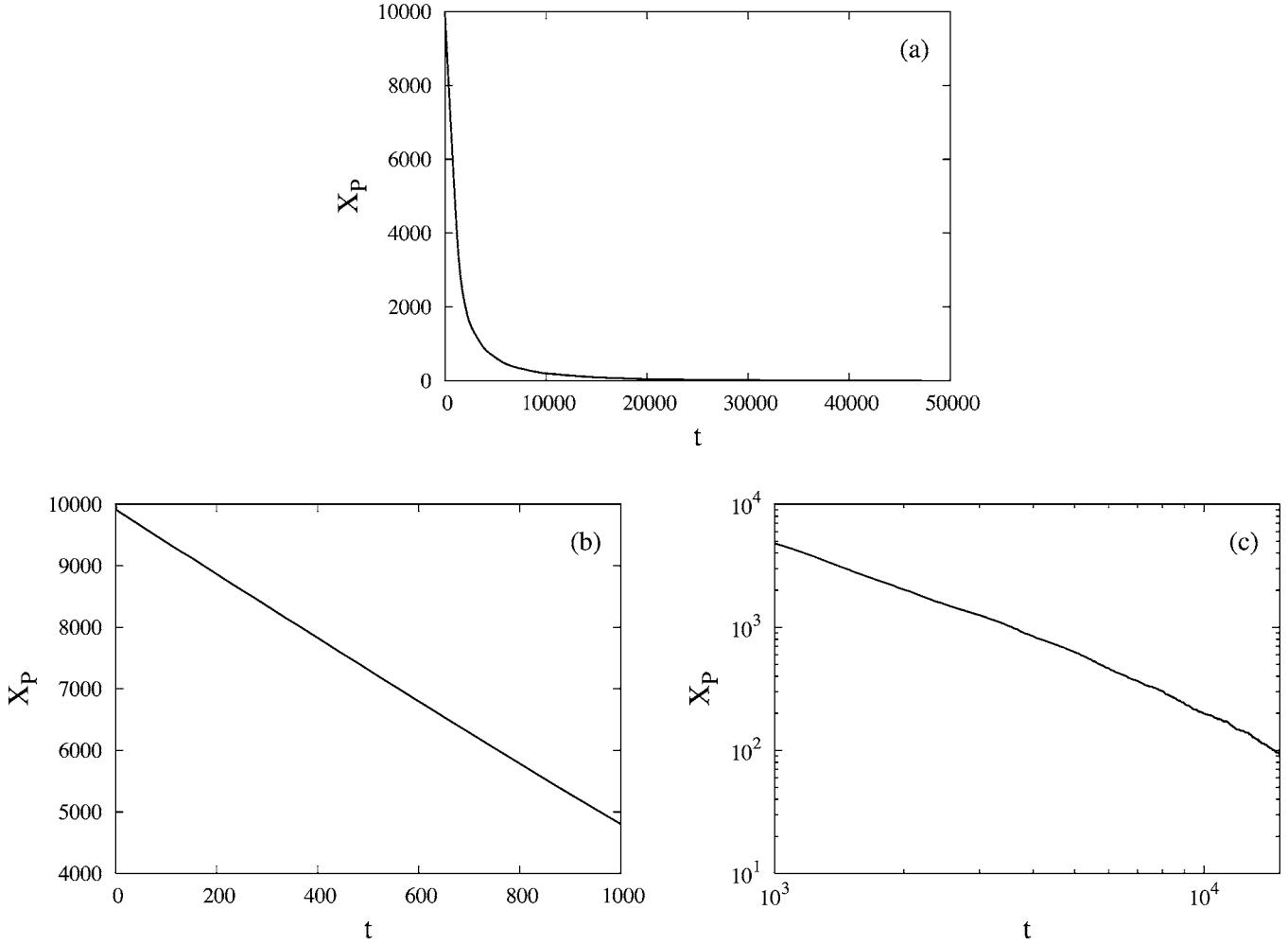

FIG. 7. (a) The plasma occupation following a bolus dose of 10 000 molecules undergoing both short-term and long-term correlations ($N_e^{\max}=15$ and $\Omega=1$). The decline is (b) first linear and then transitions to (c) a power law.

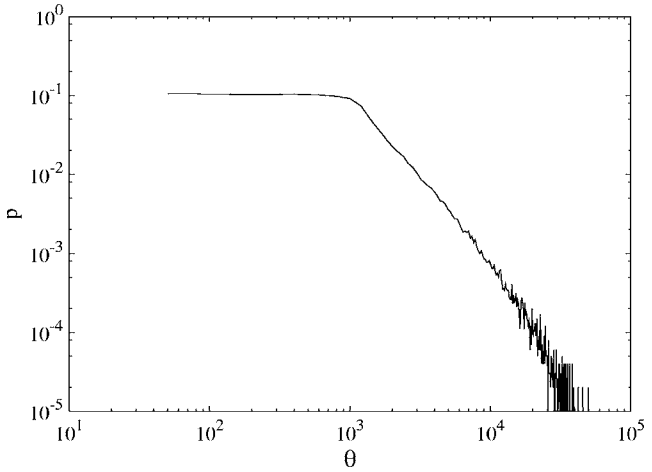

FIG. 8. The probability distribution of drug residence times θ for a system undergoing combined short- and long-term interactions ($N_e^{\max}=15$ and $\Omega=1$).

mimic situations in which drug molecules can adhere to each other or to a foreign object, and the elimination probability was the same for all molecules within a cluster. To the best of our knowledge, the stochastic pharmacokinetics model described here is unique in its use of both saturation and the temporal clustering of events.

Figure 4 shows the effect of Ω on the reaction rate. At the maximum plasma occupation, the rates are the same. However, as the concentration drops, the rate corresponding to $\Omega=100$ drops linearly, while the rates corresponding to lower Ω values decrease more drastically as clusters form and then eventually taper off as the clusters disperse. Because the rate never regains the value of the simple random walk, this suggest a long-time persistence of correlations between the molecules due to the formation and dispersion of clusters.

Figure 5 shows the plasma occupation curve following a bolus dose with $\Omega=1$. The curve exhibits a long-time tail that is best described by a stretched exponential in time. To confirm that this behavior is consistent with transient fractal-like kinetics, k [calculated as $(dX_P/dt)/X_P$] was plotted as a function of time (Fig. 6). A power law dependence was found, as predicted by Eq. (4), with $h=0.569\pm0.014$ ($R^2=0.965$).

C. Fractal-like Michaelis-Menten kinetics

When simulations were performed in the presence of both short-term and long-term interactions, the plasma occupation decreased in a triphasic manner (Fig. 7). There was an initial linear decline followed by a long-time power law tail and then a final exponential segment. The mean value of the power law tail exponent calculated between $t=1000$ and 13 400 and averaged over ten runs was $\gamma=-1.414\pm0.005$ ($R^2=0.995\pm0.005$). The power law transitioned to an exponential decay when less than 1% of the drug molecules remained in the system. Therefore these results are consistent with both Eq. (9) and experimental results found for the drug mibefradil [12], but indicate that the agreement breaks down at very small drug occupation levels.

The PDF for θ was calculated for the process illustrated in Fig. 7 using 100 000 drug molecules. The function had a long-time power law tail (Fig. 8) with an exponent of -2.46 ± 0.04 ($R^2=0.993$), which is equal to $\gamma+1$. The number of sojourn times will follow the same distribution, just scaled by the sojourn time. Furthermore, the area under the curve (AUC, a measure of the systemic exposure to the drug) exhibited a nonlinear dependence on the dose, N. In fact, the dependence followed a power law relationship for $N=5000-20\,000$ with a power exponent of -1.43 ± 0.02 ($R^2=0.997$). This value is consistent with γ and means that the long-time power law tail of the PDF is the main determinant of the pharmacokinetic behavior of a drug undergoing fractal-like Michaelis-Menten elimination.

V. CONCLUSION

A random walk with interactions was applied to investigate questions relevant to pharmacokinetics. Methods from statistical physics lend themselves well to problems in pharmacokinetics because the methods deal with large-scale, aggregated effects of the interaction between a large number of molecules, such as a dose of drug molecules. This work provides evidence that interactions between drug molecules can lead to anomalous, fractal-like kinetics. Using a combination of short-term and long-term interactions, we were able to reproduce various types of elimination kinetics and confirm our previously derived equation for Michaelis-Menten kinetics under heterogeneous conditions.

In future work, we plan to relax the assumption of a constant sojourn time at each site, thus transforming the interacting random walk into a general continuous time random walk. Furthermore, more than one type of temporary trapping site will be used to investigate the dose to a target site outside of the plasma. In this way, the model will become both hopping-controlled and trap-controlled.

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