Application of a random network with a variable geometry of links to the kinetics of drug elimination in healthy and diseased livers

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This paper discusses an application of a random network with a variable number of links and traps to the elimination of drug molecules from the body by the liver. The nodes and links represent the transport vessels, and the traps represent liver cells with metabolic enzymes that eliminate drug molecules. By varying the number and configuration of links and nodes, different disease states of the liver related to vascular damage have been simulated, and the effects on the rate of elimination of a drug have been investigated. Results of numerical simulations show the prevalence of exponential decay curves with rates that depend on the concentration of links. In the case of fractal lattices at the percolation threshold, we find that the decay of the concentration is described by exponential functions for high trap concentrations but transitions to stretched exponential behavior at low trap concentrations.

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I. INTRODUCTION

Pharmacokinetics is the study of the absorption, distribution, metabolism, and eventual elimination of a drug from the body [1]. Pharmacological data usually consist of discrete values of the concentration of a drug in the plasma or blood as a function of time. A plot of these values generates a concentration-time curve that first rises as absorption of the drug dominates and then decreases after a maximum concentration value is reached. This decline may be relatively short or may last for several days, and it is mainly governed by the rate of elimination (or clearance) of the drug from the body. In the case of a bolus intravenous dose, only the decline portion of the curve is observed, and the resulting concentration-time curve is called a clearance curve. The goal of pharmacokinetic modeling is to use these curves to describe, compare, and predict a drug's course in the body, as well as to determine optimum dosing regimens, potential toxicity, and drug-drug interactions.

The most common type of pharmacokinetic models are the compartmental models [2]. A compartment is defined as the number of drug molecules having the same probability of undergoing a set of chemical kinetic processes. The exchange of drug molecules between compartments is described by kinetic rate coefficients (in units of time^{-1}), which may be related to physiological parameters such as molecular binding rates and organ volumes.

The classical compartmental model is based on two main assumptions: (i) each compartment is homogeneous (i.e., there is instantaneous mixing) and (ii) the kinetic rate coefficients are all constant, such that the fraction of drug transferred between any two compartments does not vary with time. The system is described by coupled first-order differential equations whose solutions take the form of a sum of terms that are exponential in time. While compartmental models can provide adequate agreement with clinical pharmacokinetic data sets, they often fail to provide a good fit to the tail regions, where power-law or stretched-exponential time dependence can occur [3,4]. Since all data sets are finite in size, they can always be fitted with a sufficiently large number of compartments and an associated large number of adjustable parameters. However, this does not address the origin of the nonexponential behavior in pharmacokinetics.

It has been hypothesized that a cause of this anomalous behavior is the breakdown of the classical assumptions under physiological conditions, which are often confined and heterogeneous [5]. For example, one of the most prominent cardiovascular patterns in the body is the dichotomously branching tree, whose vessels become successively shorter and narrower to most effectively fill their embedding space of Euclidean dimension d. Such a pattern is exemplified by the blood vessels supplying the heart, lung, kidney, and liver [6]. Regional blood flow to these organs has been found to be heterogeneous in both space and time [7–9]. Heterogeneous conditions also occur within and between cells [10,11].

In this paper, we develop a relatively simple physical model for the liver that takes into account its heterogeneous structure under both healthy and pathological conditions, and we perform numerical simulations to demonstrate that the elimination of drugs from the body can exhibit nonexponential behavior when the organ of elimination is considered as a network of catalytic enzymes.

II. GEOMETRY OF THE LIVER

Since the enzymatic metabolism of drug molecules occurs mainly in the liver, it is important to determine the role that the geometry of the liver and its supplying blood vessels play on the rate of drug removal from the body. The liver receives blood from both the hepatic artery and the portal vein [Fig. 1(a)] at pressures that are much lower than that of arterial blood [12]. The vessels bifurcate in a treelike formation [Fig. 1(b)] and deliver blood carrying both nutrients and toxins to the liver cells, called hepatocytes. The hepatocytes are the

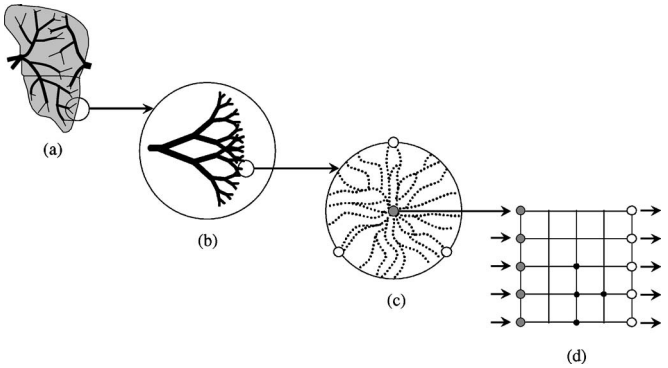

FIG. 1. The liver. (a) The macrostructure. The hepatic artery and portal vein bring blood rich in oxygen, nutrients, and drug molecules in from the left. (b) The vessels branch to form a tree of arterioles and venules. (c) The terminal vessel (shaded circle) empties into an acinus. The small black circles are hepatocytes, and the white spaces consist of sinusoids and extracellular space. The three white circles on the periphery are collecting vessels that lead to the hepatic vein though a tree similar to the supply one pictured in (b). (d) The equivalent network representation. The molecules enter the lattice from the left through a supply vessel (shaded circle) and leave from the right by a collecting vessel (open circle). In between, they perform a random walk. The black circles represent hepatocytes and the empty nodes represent acini and extracellular space.

sites of metabolic activity, and they are arranged radially around branches of the central vein. The cords of cells are separated by extracellular space and sinusoids, which play the role of capillaries in the liver. Each vein and its surrounding hepatocytes form a functional unit called the acinus [Fig. 1(c)].

The health of the liver can be compromised by viruses, hereditary diseases, and toxins such as alcohol [13]. Damage to or death of the hepatocytes leads to inflammation of the liver, called *hepatitis*. Although zones of necrosis can form when adjacent cells die, this damage is to some extent reversible, since the liver has the ability to regenerate. Thus hepatitis is typically characterized by waves of cell death and regeneration, leading to a mixture of necrotic areas and nodules of new hepatocytes. Because the architecture of the liver is often compromised, some cells may not receive normal levels of blood supply. Furthermore, as inflammation progresses, fibrous tissue may replace the normal hepatocytes, resulting in the irreversible condition of *cirrhosis*. The damage can be compounded because the formation of necrotic zones increases the resistance to blood flow, and *intrahepatic shunts* can occur in which blood vessels begin to bypass the liver altogether. Therefore, although the liver has the capacity to withstand and even correct a lot of damage, its ability to transport, absorb, and metabolize important nutrients and drug molecules can be compromised.

The complexity of the geometry of both healthy and diseased livers has been characterized using fractal analysis. Javaneau [14] used ultrasonic wave scattering to determine a fractal dimension of $d_f \approx 2$ for the liver. Because of the complexity of the liver structure and the irregularity introduced by fibrosis, various research groups have used fractal analysis to quantify the degree of fibrosis in the liver [15,16]. For example, Moal *et al.* [17] found that the value of d_f increases with increasing fibrosis, whether it is induced by disease or toxins.

III. KINETICS UNDER HETEROGENEOUS CONDITIONS

In this section, we explore how the complex geometry of the liver influences the transport and kinetic processes occurring within it. It has been shown that physical systems under geometric constraints exhibit both anomalous diffusion and anomalous reaction rates. The average mean-square displacement as a function of time of a particle diffusing through a heterogeneous medium is given by the power law [18]

$$\langle r^2(t)\rangle \sim t^{2/(d_f+2)}, \tag{1}$$

where d_f is the fractal dimension of the medium. Similarly, for heterogeneous chemical reactions (for example, ones that occur on or inside a fractal medium), the kinetic reaction rate has been found to be a decreasing power of time [19,20],

$$k(t) = k_0 t^{-h}, \tag{2}$$

where h is the heterogeneity exponent and can be expressed in terms of the spectral dimension d_s as follows [21]:

$$h = 1 - \frac{d_s}{2}. \tag{3}$$

The spectral dimension is an intrinsic property of the fractal geometry of the structure and it characterizes the number of distinct sites visited by the random walker [22],

$$S(t) \sim t^{d_s/2}, \quad d_s < 2. \tag{4}$$

The spectral dimension is conjectured to be related to the geometry of the medium through

$$d_s = \frac{2d_f}{d_w}, \tag{5}$$

where d_w is the dimension of the random walk.

Fractal concepts have been incorporated into pharmacokinetics through both compartmental and noncompartmental models. The latter includes the homogeneous-heterogeneous distribution model introduced by Macheras [23] to quantify the global and regional characteristics of blood flow to organs. While the homogeneous portions of the circulatory system can be described using conventional kinetics, regional areas such as those feeding the liver are fractal and thus may be governed by fractal kinetics. Fuite *et al.* [24] incorporated these results into a fractal compartmental model to fit experimental data for the cardiac drug mibefradil. A Euclidean compartment was used to represent the plasma while a fractal compartment was used to represent the liver. The authors found a relationship between the heterogeneity exponent h and the fractal dimension d_f of the liver. Simulations of the model showed that h also plays a significant role in determining the shape of the concentration-time curve [25]. To gain further insight into this problem, we apply the theory of networks to investigate the effects of diseased states of the liver on its ability to clear a drug from the plasma.

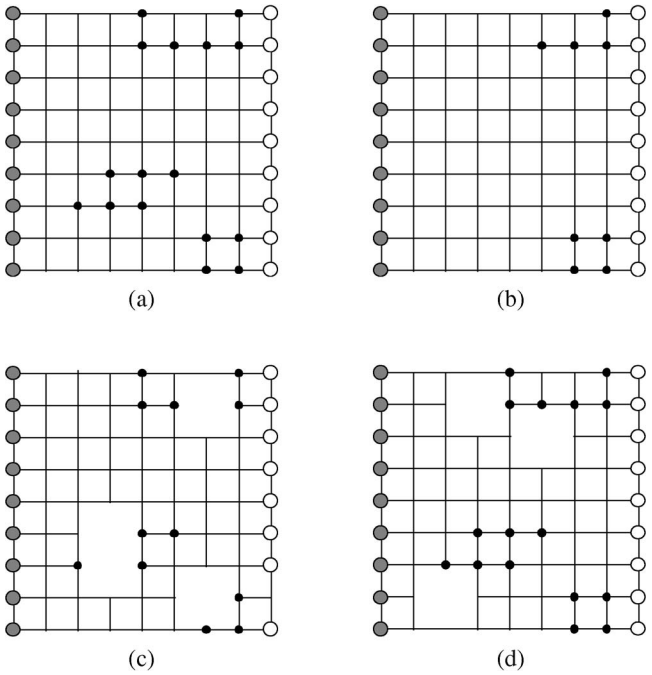

FIG. 2. The network model interpretation for (a) a healthy liver, (b) a liver with hepatitis, (c) a liver with necrotic cirrhosis, and (d) a liver with vascular damage. The shaded circles represent supply nodes, the open circles represent collecting nodes, the empty nodes represent S sites, and the black nodes represent H sites.

IV. FLOW NETWORK MODEL

The model consists of a two-dimensional 120×120 lattice of nodes connected by links [Fig. 2]. There are two types of nodes in this lattice: (i) N_h nodes of type H, which represent hepatocytes and absorb molecules, and (ii) N_s nodes of type S, which represent sinusoids and extracellular fluid. The first and last columns of the lattice are S nodes that act as supply and collecting vessels, respectively. The lattice has toroidal periodic boundary conditions in the direction of the flow and reflecting boundary conditions in the perpendicular direction. The number of random walkers was judiciously chosen to be 10^6. Moreover, N_h was fixed for every simulation on a given lattice. The probability E of a molecule being eliminated from an H node was fixed at 0.8 (incomplete absorption).

For the current simulations, the only parameter being varied was the fraction of links, which ranged from $p=1.0$ for a healthy liver to $p=0.5$ for a liver with vascular damage. It is possible that a drop-off in p may also reduce N_s; however, this effect will be minor due to the imposed periodic boundary conditions.

The algorithm proceeds as follows. Drug molecules, represented by a set of random walkers, enter the lattice on a supply node from the left side of the lattice. At each time step, every walker makes a nearest-neighbor move in a direction driven by a set of probabilities, w_i, which obey the natural condition $w_f+w_l+w_r+w_b=1$. We chose $w_f=0.75$, $w_l=0.1$, $w_r=0.1$, and $w_b=0.05$. Because of vascular flow and pressure, movement along the lattice has the highest probability, resulting in a biased random walk. The moves are made under excluded volume constraints, such that only one molecule can occupy a node at a given time. As the concentration of links reaches the percolation threshold, a greater amount of so-called dead-ends (links terminated by a single node) arises in the lattice. Therefore, a reparametrization of the transition probabilities was performed by taking into account the fact that increasing the value of parameter w_b raises the chance that a random walker will be able to escape a dead-end.

TABLE I. Description of how the flow network model can be modified to simulate different liver pathologies.

Pathology	Network modification
Vascular damage	Removal of a fraction of S node and their associated links.
Hepatitis	Conversion of a fraction of H nodes to S nodes
Cirrhosis	Removal of a fraction of H nodes and their associated links.
Intrahepatic shunts	A fraction of molecules circulate for an extra time τ instead of reentering the lattice.

A drug molecule exits the lattice if it lands on an empty H node and a random number drawn on $(0,1)$ is greater than a threshold value E. If a drug molecule reaches a collecting node, it enters the general circulation. It reenters the lattice after a lag time drawn from a Gaussian distribution with mean τ and standard deviation σ. Here, we used $\tau=120.0$ s and $\sigma=20$ s. The algorithm proceeds until all of the drug molecules have been eliminated from the system. The goal is to study the decay of the number of random walkers present on the lattice (by analogy, the number of drug molecules present in the liver) as a function of time.

The following assumptions were made in developing this model.

(i) The blood supply from the portal vein and the hepatic artery is the same.

(ii) Every acinus is the same (same pressure, rate of blood flow, etc.).

(iii) The two-dimensionality of the system is justified because each H node represents a sheet of hepatocytes and each S node can be thought of as a portal vein traveling into the page. Therefore, the liver is made up of a stack of identical copies of the lattice, such that a drug molecule sees the same 2D landscape no matter where it emerges out of the vasculature.

(iv) Due to the arrangement of cords of hepatocytes and sinusoids, lone H nodes are improbable; rather, H nodes will occur in clusters.

Although the simulations discussed in this paper explore the effects of vascular damage to the liver, other effects of disease, infections, and toxins can be simulated by making the modifications listed in Table I.

V. RESULTS

The most general formula describing the evolution of the drug concentration in disordered media through dispersive

kinetics is given by the modified kinetic equation,

$$\frac{d}{dt}C(t) = -k(t)C(t), \tag{6}$$

where the kinetic rate coefficient k has been replaced by the time-dependent coefficient $k(t)$. The solution of Eq. (6) leads to the following formula:

$$C(t) = C_0 \exp\left(-\int_0^t k(\tau)d\tau\right), \tag{7}$$

where C_0 is the initial concentration of drug molecules (the bolus dose). In the specific case of homogeneous media, where the kinetic rate coefficient is constant, the classical exponential formula is obtained,

$$C(t) = C_0 \exp(-k_0 t). \tag{8}$$

In the context of our flow network model, Eq. (8) is the simplest formula for the survival probability of random walkers evolving on a lattice with a specified number of traps (absorbing nodes). However, it is well known that for networks that exhibit self-similar geometries, the relation between a concentration of random walkers and time follows a stretched-exponential formula. This relation follows directly when Eq. (2) is inserted into Eq. (7) and the result is integrated,

$$C(t) = C_0 \exp(-kt^{\alpha}), \tag{9}$$

with $k=2k_0/d_s$ and time exponent $\alpha=d_s/2$.

We first investigated the case of random walkers with drift in the presence of a high concentration of H nodes ($N_h=50$) homogeneously distributed on the lattice, with the intent of determining the relationship between the kinetic rate coefficient k and the concentration of links p in the range from $p=1.0$ (noncritical region) to $p=0.5$ (percolation threshold). Here, p can be considered as a measure of the degree of vascular damage to the liver. The resulting concentration-time curves are linear on a log-linear plot [Fig. 3]; therefore, they follow the classical exponential form, even at the percolation threshold.

Linear regression analysis of the results for the homogeneous systems led to the quantitative determination of the coefficient k as a function of the probability p. This is shown in Fig. 4, where k depends on p through the power-law relationship

$$\log_{10} k = -2.6175 + 8.9272 \log_{10} p. \tag{10}$$

The number of traps and their distribution on a lattice have a crucial influence on the slopes of the lines in Fig. 4. The greater the number of traps, the greater the sensitivity of the random-walk process to their spatial distribution. The more inhomogeneous the distribution of the traps, the longer the time that a random walker survives on the lattice. Conversely, the order of the concentration curves can be used to determine the uniformity of the trap distribution, or analogously, the health of the liver.

In Fig. 5, we show the results of computer simulations performed for random walks on the 120×120 network of nodes close to the percolation threshold ($p_c=0.5$) with both a low and a high concentration of perfectly absorbing traps inhomogeneously distributed on the lattice. In the low-concentration case, the evolution of the drug concentration follows a stretched-exponential decay with $\alpha=0.667$. In contrast, the high-concentration case leads to exponential behavior. Therefore, if there is a significant number of elimination sites, drug elimination can exhibit classical behavior, even in an inhomogeneous medium.

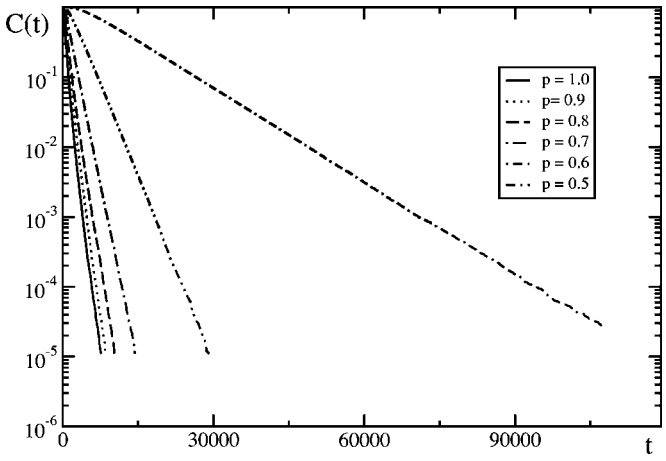

FIG. 3. A log-lin plot of the concentration as a function of time for various values of the probability p that bonds are removed in the case of a 120×120 lattice with 50 traps.

VI. SCALING RELATIONS AT THE PERCOLATION THRESHOLD

For the percolation lattice with a low concentration of traps, the kinetic rate coefficient is given by

$$k(t) \sim t^{-\alpha}, \quad \alpha = \frac{d_s}{2}. \tag{11}$$

We can determine a relationship between k and p using the scaling law from percolation theory [26] for p close to $p_c=0.5$,

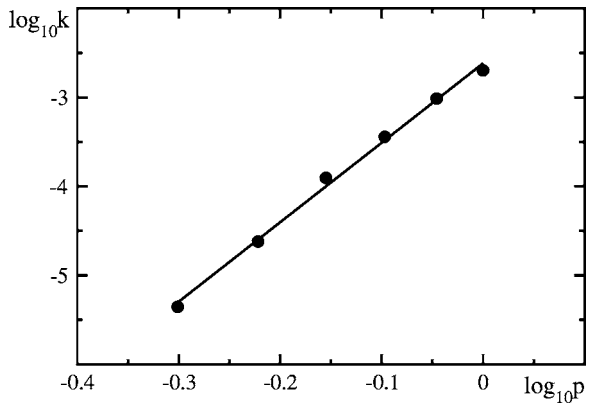

FIG. 4. The relationship between the kinetic rate constant k and the probability p.

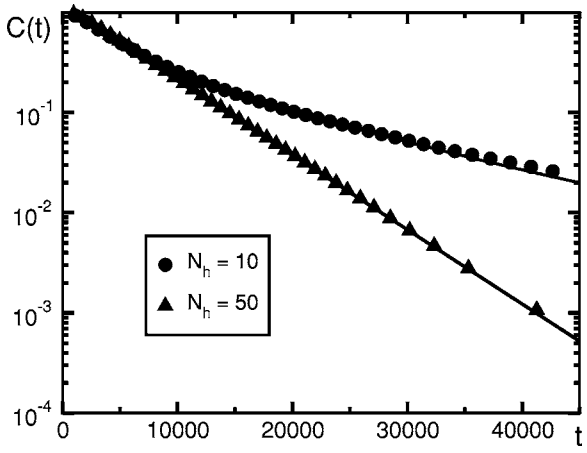

FIG. 5. Fit of Eq. (9) (solid lines) to the concentration data from computer simulations in the case of a percolation cluster with a low number and a high number of traps.

$$t \sim |p - p_c|^{-\gamma}, \quad \gamma = \frac{2\nu d_f}{d_s} \tag{12}$$

in the limit of short times. Therefore, the relation between the kinetic coefficient and the critical fraction of links in a cluster takes the following form:

$$k(p) \sim |p - p_c|^{\eta}, \quad \eta = \alpha\gamma = \nu d_f. \tag{13}$$

For a percolating cluster embedded in two-dimensional Euclidean space, it has been shown that $d_f = 91/48$ and $\nu = 4/3$. Therefore, $\eta = 2.5278$. In our simulations for a 120×120 lattice at the percolation threshold, we found $\eta = 2.4684$, which is consistent with this value.

VII. CONCLUSION

It is of significant importance to be able to quantify the ability of the liver to metabolize drug molecules under a range of conditions that reflect both normal and pathological conditions. The random network model developed in this paper can be used to investigate how the pharmacokinetics of a drug can depend on pathological conditions such as drug- and alcohol-related damage, viral hepatitis, cystic fibrosis, and tuberculosis.

Fractality can occur in pharmacokinetic systems through either the geometry of the eliminating organ or anomalous diffusion in constricted spaces. We have recently shown [25] that there is a direct relationship between the shape of the elimination tail and the fractal exponent α; in the case of very small α, the relationship is linear. While small deviations from classical kinetics still retain exponential behavior, there is a value of α where a transition to a power law occurs. In this paper, we showed the existence of another transition that occurs when the concentration of elimination sites is small. At low trap concentrations, the effects of the geometry of the lattice are significant, and the decay of the drug concentration becomes hindered. Accordingly, the concentration follows stretched exponential rather than exponential behavior. For large trap concentrations, however, the concentration curve regains the classical exponential behavior. This is because the inhomogeneous nature of the lattice is not being probed by the walkers due to the high probability of elimination. The geometry no longer determines the reaction rate.

A potentially important application of this work is in quantifying the correlation between the body's pharmacokinetic response and its state of health. Using a numerical approach, we have shown that self-similarity can lead to stretched-exponential behavior. This can occur in a regular geometrical fractal or a random network at the percolation threshold. In the noncritical case of the random network studied, we demonstrated that the elimination exponent satisfies a simple relationship with the probability p for removing a link.

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