Fractal Space and Time - Sources of Nonlinearity in Drug Elimination

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Abstract

This paper is concerned with a new idea in the area of pharmacokinetics, namely the concept of fractality in both spatial and temporal domains. Physiological fractality is due to both the architecture of organs of drug elimination such as the vasculature of the liver and the time-dependent processess that exhibit self-similarity. Both diffusion on branched and porous media and chemical kinetics in such media result in new types of invasion and elimination characteristics. We illustrate the general features of pharmacokinetic fractality with two vastly different examples of data sets: one obtained for the heart medication called mibefradil and the other for the chemotherapeutic agent paclitaxel. While the sources of fractality in these two cases are quite different, one is due to spatial distribution and the other is due to protein binding, the results in both cases show power law time dependence which is a hallmark of fractality.

I. Introduction

Pharmacokinetics (PK) is the study of the absorption, distribution, metabolism, and eventual elimination of a drug from the body [1]. It is fundamental in developing dosing regimes, predicting the behaviour of new drugs, and estimating therapeutic effects. For some compounds, such as anesthetics, cardiac drugs, and chemotherapeutic drugs, quantitative knowledge about the interaction of the drug with the body is of vital importance.

Pharmacological data usually consist of the concentration of a drug in the plasma or blood as a function of time. Characteristic curves first rise as absorption of the drug dominates, and then after a maximum concentration value is reached, they tend to decrease in a long tail. This decline consists of some residual absorption but is mainly governed by the rate of elimination of the drug from the body. The elimination rate is a major determinant of the length of effect and the total dose delivered by the drug.

This paper discusses factors affecting the elimination tail as well as mathematical methods for its analysis. Two drugs with tails exhibiting similar fractal properties will be discussed, although it will be shown that very different mechanisms are responsible in each case.

Nonlinearity in Pharmacokinetics
Traditional pharmacokinetic models are based on the assumption of a linear relationship between the dose of a drug and its concentration. The body is divided into compartments, and a drug's journey between two different compartments is described by a rate coefficient [2]. In a linear model, these rate coefficients called *k* are assumed to be constant. The concentration in each compartment can be described by the following differential equation:

$$\frac{dC(t)}{dt} = kC(t) \tag{1}$$

Integrating it directly produces:

$$C(t) = C_0 e^{-kt} \tag{2}$$

Thus for multiple simultaneous processes in a number of compartments, a series of coupled differential equations is obtained. Since all of these equations are linear, it is easy to see that the outcome in terms of C(t) is a superposition of exponential funcitons. Thus exponential decay should dominate long-time behaviour. In numerous cases this is manifestly not so and there may be a number of reasons accounting for non-exponential asymptotics of PK data, one of which is the presence of nonlinearity and one form or another.

Nonlinear pharmacokinetics are said to exist when the parameters are dose- or time-dependent [3]. With dose-dependence, an increase in the administered dose results in a disproportionate increase in the absorbed dose. The most common type of dose-dependence discussed in the literature follows Michaelis-Menten kinetics, where the clearance of a drug changes with

concentration due to saturation of the drug action sites. References to time-dependent nonlinearity are much less frequent, though Levy [3] lists the following possible sources: absorption and elimination parameters, systemic clearance, enzymatic metabolic activity, plasma binding, renal clearance, and cerebrospinal fluid drug concentration. It is also worth mentioning that both dose and time dependencies can be present simultaneously.

Because the body is a complex system, the observed concentration values are the end product of many intricate interactions. In all likelihood, there is one dominant process responsible. In this paper, we discuss two unique such processes: the geometry of the eliminating organ and the distribution of the residence time of the drug within cells.

Power Laws and Fractals

A major advantage of complex systems is that in many cases they can be described by reasonably simple mathematics. For example, power laws have been found in ecology, biology, economics, chemistry, and physics [4]. They are given by the simple scaling relation:

$$g(x) = Ax^a \tag{3}$$

By taking the log of both sides, we obtain:

$$\log g(x) = \log A + a \log x \tag{4}$$

Thus when plotted on a log-log scale, this type of function produces a straight line with slope α. Power laws are attractive because they are scale-invariant. Multiplying the x-variable by a factor of a merely changes the constant of proportionality:

$$g(x) = A(ax^a) = (aA)x^a \tag{5}$$

The shape of such a system is the same irrespective of the scale. Because the characteristics of the system remain the same as we zoom in or out of the system, this allows us to extrapolate from shorter time or space intervals to longer ones and vice versa.

Fractals are objects that have non-integer power exponents. They can be described by the following equation:

$$L(d) \propto d^{1-D} \tag{6}$$

where D is the fractal dimension of the system and can be thought of as a measure of the space-filling properties of a structure [5,6].

Fractals describe systems behaving under constraints. For example, the circulatory system consists of a series of bifurcating vessels, and the time it takes for a circulating drug to reach its target will depend on the confines of its path. Similarly, most organs in the body are complex structures and the diffusion of a drug across them will be limited by the available surfaces.

Because their structure persists down to smaller and smaller scales, fractals have the unique ability to fill their available space as efficiently as possible.

Power laws and fractals can be generated in many different ways and can exist in both space and time. That is, a system characteristic can scale with either length or time. In pharmacokinetics, for example, the concentration of a drug can depend on the path it must follow through the body or on characteristic times such as diffusion or residence rates. It should be noted that both types of fractals can exist simultaneously in a system. In the following two sections, we will consider the calcium antagonist drug mibefradil, whose elimination is governed by the fractal geometry of its site of metabolism, as well as the chemotherapeutic drug paclitaxel, whose elimination is proposed to be governed by its residence time within the cells.

II. Mibefradil – Spatially-Induced Nonlinearity

Mibefradil is a calcium antagonist currently being developed to reduce ventricle fibrillation. It is orally administered, and its major site of elimination is the liver. In their studies done on chronically-instrumented dogs, Skerjanec *et al.* [7] concluded that observed nonlinear pharmacokinetics are due to dose- and time-dependent reduction of hepatic clearance of the drug. Fuite *et al.* [8] proposed that the source of this reduction is the fractal geometry of the liver. The circulation in the liver can be divided into the macrocirculation (including the hepatic artery and the hepatic and portal veins) and the microcirculation (consisting of the portal vein, hepatic arterioles, and the sinusoids) [9]. The microvasculature of the liver consists of vessels that bifurcate towards smaller and smaller daughter vessels. In fact, the vessels supplying the liver, lungs, kidney, and heart have been found to exhibit scaling relationships for branch diameter, branch length, pressure, and radius-to-length ratios [10, 11, 12]. Javanaud performed ultrasound scattering experiments and estimated the fractal dimension of the liver to be $d_f \approx 2$ [13].

Due to differences in the global and regional nature of blood flow to organs, Macheras developed a homogenous-heterogeneous distribution model [14]. The homogeneous conditions are considered "well-stirred", and the heterogeneous conditions near tissues are considered "under-stirred". Figure 1 illustrates this composite system.

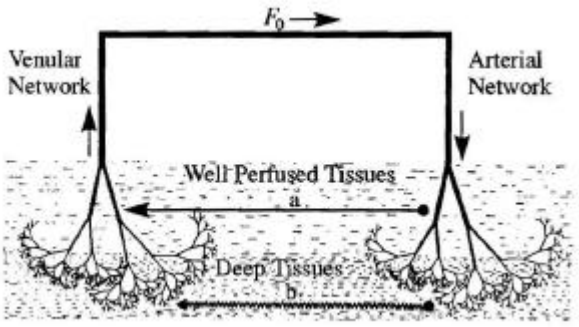

Figure 1. The vascular network divided into (a) homogeneous, well-perfused conditions, and (b) heterogeneous, fractal conditions in the deep tissues [14].

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 should display fractal kinetics. Essentially, the geometry of a surface where a chemical process is taking place affects the rate at which the process can occur. This reaction rate can be expressed as follows [15]:

$$k(t) \propto t^{-(1-d_S/2)} \tag{7}$$

Fuite *et al.* developed a theoretical model combining well-stirred Euclidean and fractal compartments, and analytical solutions for the time evolution of the drug concentration were obtained using perturbation analysis. The equations were then tested using mibefradil data from Skerjanec *et al.* [7]. The results for four dogs are shown in Figure 2. The spectral dimension for the dog liver estimated using the model was between 1.778 and 1.914, which compares favourably with the experimental result of 2 by Javanaud [13].

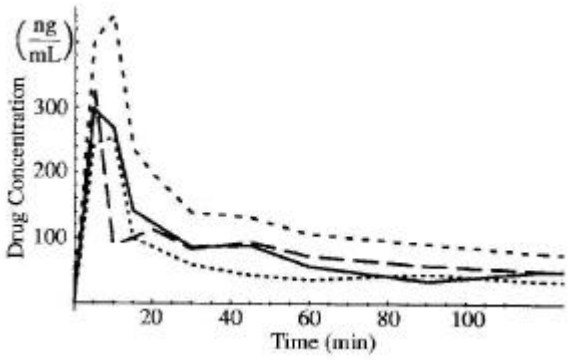

Figure 2. The early time behaviour of the concentration-time data for four different dogs [8].

III. Paclitaxel – Temporally-Induced Nonlinearity

Paclitaxel is a chemotherapeutic drug derived from the European Yew tree bark. It consists of a taxane nucleus with three rings, and it is poorly water-soluble [16]. The current formulation is a 6 mg/ml solution in a solvent consisting of 50% polyoxyethylated castor oil (Cremophor EL) and 50% dehydrated alcohol (USP) [17]. It is usually administered by intravenous infusion. Paclitaxel binds preferentially to microtubules, which are cellular components necessary for mitosis, intracellular transport, maintenance of cell shape, and cellular motility. It has been found that paclitaxel strongly inhibits cell replication by blocking cells in the G2 mitotic phase by stabilizing microtubules [18].

Paclitaxel is well-suited for pharmacokinetic studies because it is administered at high doses, it has a long residence time in the body, and it has been the subject of many dose escalation studies. It has shown a consistent disproportional increase in the maximum plasma concentration (C_{max}) and the area under the curve (AUC) [19]. Following the end of the infusion, a biphasic elimination has been noted [16].

In a study of data from the literature currently being performed by the authors, preliminary results show not only biphasic elimination, but also a distinct power law relationship for each

phase. The first phase begins immediately after the end of the infusion and consists of a rapid decline lasting approximately one hour. The subsequent prolonged terminal phase can last up to 72 hours. Significantly, although the data span a wide range of age, sex, type of cancer, total dose, and infusion time, the power exponents for the two elimination phases seem to be approximately equal to -3.3 and -1.6, respectively. In addition, the time period corresponding to the uptake during the infusion also seems to obey a power law, but with a much larger range of exponents. Figure 3 shows a representative log-log plot for concentration-time data of paclitaxel.

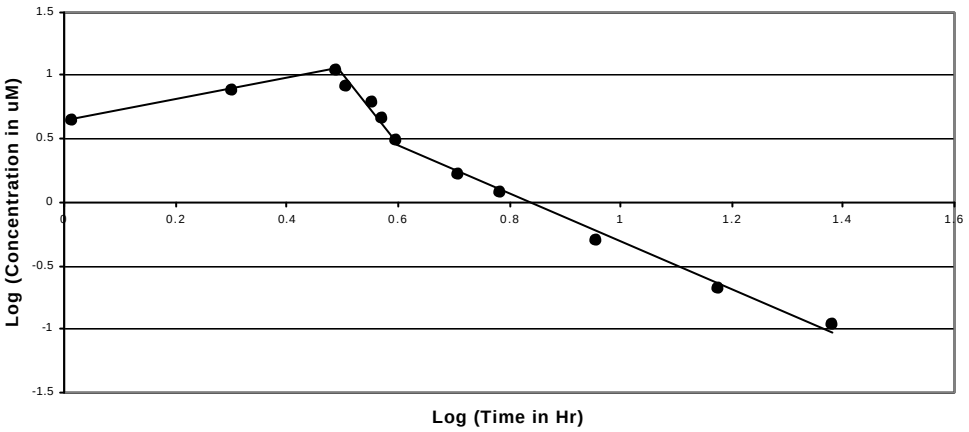

Figure 2. A typical log-log plot of concentration versus time for a three-hour infusion of 225 mg/m^2 of paclitaxel, measured over a 24-hour period. The biphasic elimination can be clearly seen. Data was taken from [19].

Various reasons have been proposed in the literature for the source of the nonlinearity of paclitaxel pharmacokinetics. The predominant explanation being offered is the high binding of paclitaxel molecules to the Cremophor EL vehicle and plasma proteins [20, 21]. However, a related drug docetaxel, which does not have Cremophor EL, has shown nonlinear behaviour in at least one paper [22]. In the study, 100 mg/m^2 of docetaxel was administered during a six-hour infusion. We found an exponent of -1.34 (with a correlation coefficient $R^2 = 0.9830$) for the period of 8 to 30 hours. In addition, pharmacokinetic studies of ABI-007, a Cremophor-free formulation of paclitaxel, demonstrated similar nonlinear behaviour. The data from one experiment [23] with ABI-007 produced an exponent of -1.60 (with $R^2 = 0.9469$), while in another study [24] the area under the curve scaled with dose with an exponent of -1.61 (with $R^2 = 0.9477$).

We propose that the nonlinearity and power law behaviour observed with paclitaxel is the result of trapping of the drug within both healthy and tumour cells. The residence times follow a probability distribution, where at each point in time, a drug molecule has a particular probability of being trapped in a cell and the complementary probability of being able to escape within a given time step. Because the total number of drug particles is very high, the statistics produce the consistent power law observed.

Several experiments provide support for this theory. Using data from an *in vitro* study looking at the cytotoxicity of paclitaxel and docetaxel in three cell lines [25], a power law relationship was

found between the IC_{50} and the exposure time. Interestingly, for one cell line, the exponent was found to be –1.62 (with $R^2 = 0.9957$). In addition, in another *in vitro* study of tumour cells in a supportive medium [26], the concentration of paclitaxel in the medium after four hours was related through a power law to the initial concentration with an exponent of –1.15 (with $R^2 = 0.998$).

The results from our study and a more in-depth analytical analysis will be offered in a future paper.

IV. Discussion

Biological systems are complex, but the advantage of such systems is the relatively simple mathematical description that seems to consistently emerge from their behaviour. Mibefradil is an orally-administered calcium antagonist with a relatively short elimination time, while paclitaxel is an intravenously-administered anticancer drug that can remain in the body for over three days. Nevertheless, the elimination curves of both drugs can be accurately described using a similar power law relationship. Each relationship leads to a different physical interpretation of the process of drug elimination but both cases involve nonlinear characteristics at variance with the standard linear multi-compartment PK modelling.

Whether the behaviour is generated by complexity in the space or time domain, the mathematical consequences are equivalent. The benefit of such a result is that a single pharmacokinetic methodology can be developed that has a wide range of applicability. In addition, the corresponding power exponents may prove to be useful pharmacokinetic parameters. This work is still in progress and we intend to extend the scope of analysis to other drugs including anesthetics.

Acknowledgements

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