Opinion TRENDS in Pharmacological Sciences Vol.25 No.3 March 2004

The heterogeneous course of drug transit through the body

Aristides Dokoumetzidis[1,3], Vangelis Karalis[1], Athanassios Iliadis[2] and Panos Macheras[1]

[1]School of Pharmacy, University of Athens, Panepistimiopolis, 15771 Athens, Greece
[2]Department of Pharmacokinetics, Faculty of Pharmacy, University of Mediterranean, 27 Jean Moulin, 13385 Marseilles Cedex 5, France
[3]Present address: School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK

Advances in mathematics and physics that deal with fractal geometry, fractal kinetics and chaotic dynamics have offered new insights for complex, kinetic and dynamical phenomena. These concepts can be applied to describe the heterogeneous nature of drug processes in the human body. Using these concepts, all processes related to gastrointestinal drug absorption (i.e. dissolution or release, transit and uptake) are considered to take place in non-homogeneous, disordered media. In pharmacokinetic modeling, fractal spaces and branching transport networks, or stochastic models, replace the classical compartmental models. Classical pharmacodynamics relies on the suppression or amplification of a steady-state baseline; however, the underlying physiological systems are often much more complex. Therefore, tools of nonlinear dynamics are used to analyze the drug effect.

Most research in biopharmaceutics and pharmacokinetics is based on the concept of homogeneity, which is thought to describe average kinetic behaviour. For example, in the field of dissolution testing a well-stirred (homogeneous) dissolution medium is used to mimic the *in vivo* conditions prevailing in the gastrointestinal lumen. The simplest model of pharmacokinetics – the one-compartment model – relies on the assumption that an instantaneous distribution equilibrium is reached after drug administration. Similarly, homogeneity is the prevailing concept for the drug concentration of each one of the compartments in multi-compartmental pharmacokinetic models. In pharmacodynamics, the application of the mass action law to describe drug–receptor interaction assumes perfect mixing in the microenvironment of the receptor. In addition, most pharmacodynamic systems are considered to be detached from the remainder of the biological system, ignoring the inherent complexity.

One can argue, however, that the assumptions of homogeneity and well-stirred media are in fact contrary to the evidence provided by the anatomical and physiological complexity of the human body. This means that drug diffusion is inhibited because the drug molecules cannot move in all directions and are constrained to locally available sites. In these 'under-stirred' regions, the rate constant of drug movement is not proportional to the diffusion coefficient of drug molecules and thus the classical Fick's laws of diffusion, which relate the concentration flux to the gradient of the concentration through proportionality, cannot be applied. A better description of transport limitations can be based on the principles of diffusion in disordered media [1]. Furthermore, biological systems are composed of numerous strongly interacting parts and thus can be nonlinear from a dynamical systems viewpoint. Disciplines such as physiology and biochemistry, which are closely related to pharmacology, have adopted concepts and ideas borrowed from mathematics and physics to achieve more realistic modeling of the complex, heterogeneous kinetic and dynamical phenomena. These concepts include fractal geometry, fractal kinetics and chaotic dynamics [2,3].

A brief introduction to the above theoretical concepts is presented in Boxes 1 and 2, and their drug-related applications are described below. Drug transit through the body can be roughly divided into the three phases. Figure 1 presents a pictorial contrast between the homogeneous and the heterogeneous approaches that are used to describe the phenomena involved in the time-course of a drug through the body.

Drug absorption

Drug dissolution, release, transit and uptake in the gastrointestinal tract are heterogeneous processes because they take place at interfaces of different phases (solid–liquid or liquid–membrane) under variable, understirred conditions. Confirmation of the inadequate mixing in the vicinity of the gastrointestinal membrane and the presence of fractal fingers in the mucus layer over the surface epithelium for HCl transport has been provided by *in vitro* and *in vivo* studies [4,5]. In addition, dissolution [6,7] and flow experiments [8] in topologically constrained media (ensuring a quasi two-dimensional space) using miscible fluids of different viscosity reveal that the interface ripples and becomes extremely meandering (fractal).

These observations, among many others, prompted the interpretation of drug absorption phenomena in terms of fractal concepts [9]. An important kinetic implication is

Corresponding author: Panos Macheras (macheras@pharm.uoa.gr).

 0165-6147/$ - see front matter doi:10.1016/j.tips.2004.01.008

Box 1. Fractal geometry and fractal kinetics

Ordinary geometrical objects have integer topological dimensions. However, objects of fractional dimensions are also defined, which are called fractals. The non-integer values for the dimensionality of these objects come from the infinitely fine detail of their structure. The main property of fractals is 'self-similarity under-scaling' (scale invariance). This means that a part of the object looks similar, or even identical, to the whole, and this continues for infinite levels of scaling. A classic example of a fractal object is the Sierpinski gasket, Figure Ia [2].

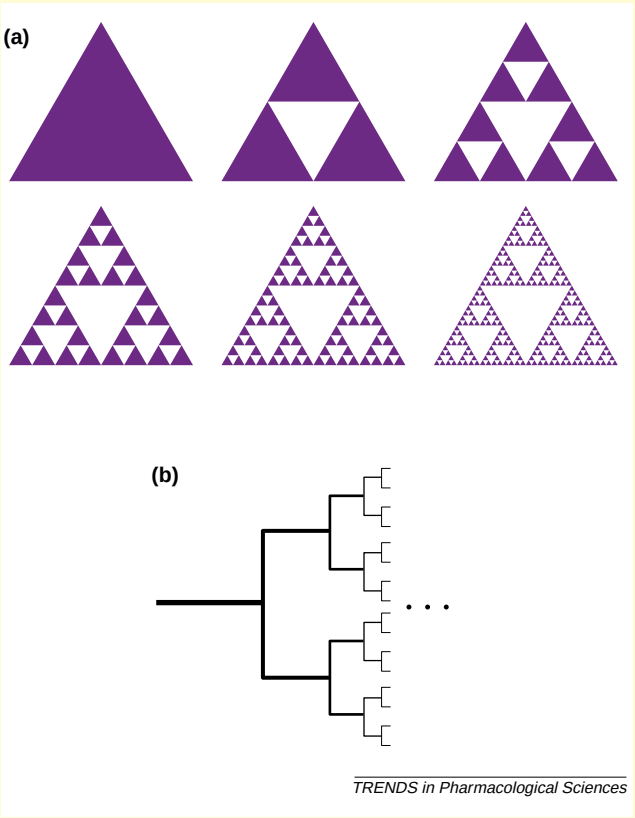

Figure I. (a) The Sierpinski gasket. This fractal object is created by considering an equilateral triangle that is divided into four equal parts. The middle part is discarded and the procedure is repeated iteratively for each one of the remaining parts, producing in this way a self-similar perforated object of infinite detail. **(b)** A schematic of the bifurcating vascular tree of mammals.

An appropriate measure of an ordinary object of integer dimension d can be the length for a curve, the area for a surface and so on. Magnifying the object by a factor l, this measure scales as l^d; for example, if a surface is doubled, its area is increased by $2^2 = 4$ times, which means that four of the original surfaces fit inside the magnified surface. By contrast, magnifying the Sierpinski gasket by a factor of 2 means that three Sierpinski gaskets of the original size can fit. This means that the relation $2^{df} = 3$ holds, where $d_f = \ln 3/\ln 2 \approx 1.585$ is the non-integer, fractal dimension of the Sierpinski gasket. This value is smaller than 2, which is the expected value for a surface. The 'shortage' of dimensionality compared with an ordinary surface comes from the infinite perforation of the object.

Fractals are not just strange mathematical objects. Self-similar structures are also very common in nature. Examples include leaves, snowflakes and physiological systems such the vascular system (Figure Ib) [2]. However, the difference between mathematical fractals and real-life fractals is that for the latter, the fractal properties apply only within a limited scale, which can be several orders of magnitude but do not extend infinitely.

In the field of classical chemical kinetics, reactions are considered to take place in homogeneous spaces. Homogeneity is ensured with continuous stirring of the system, which re-randomizes constantly the positions of the reactant molecules in the solution. However, when the stirring of the system is insufficient (e.g. in the gastrointestinal lumen) the processes or reactions take place in spaces that do not fulfill the topological conditions of homogeneity. The limiting step of heterogeneous reactions is non-classical or anomalous diffusion, which is slower than classical diffusion and is similar to the diffusion that takes place in porous media. Furthermore, in reactions with insufficient stirring, depletion zones are created that tend to enlarge as a result of the lack of re-randomization of positions of the reactant species. In these heterogeneous conditions it has been found [3] that the reaction rate coefficient is not constant but time dependent, following a power law of time:

$$K = k_1 t^{-h} (t \neq 0) \qquad \text{(Eqn I)}$$

where k_1 is a constant with units $(\text{time})^{h-1}$ and h is a dimensionless exponent. For example, when the reaction $A + A \rightarrow products$ takes place in a three-dimensional homogeneous space, its kinetics are second order and are characterized by a rate constant. However, when the reaction is considered to take place in the fractal space of the Sierpinski gasket, which has dimension 1.585, the rate coefficient, instead of being constant, follows a power law of time (Eqn I), where $h = 0.317$ [3].

that Fick's laws of diffusion are not valid in the heterogeneous milieu of the gastrointestinal lumen, and fractal-like kinetics [3] are more appropriate for the description of kinetic processes. Thus, the concept of the 'absorption rate coefficient', which originates from the fractal nature of the gastrointestinal drug processes and is compatible with the time-dependent character of these processes, was proposed to replace the classic notion of the 'absorption rate constant' [9]. Furthermore, the dissolution, transit and uptake of drugs in the gastrointestinal tract have been described probabilistically using Monte Carlo simulations [9–11], a tool that uses random numbers to generate a sample population of the system from which properties can be determined. Time-dependent absorption models have also been used to explain the gastrointestinal absorption of cyclosporin A [12] and propranolol from various formulations [13].

In the field of drug dissolution and release studies, a population growth model for dissolution was developed [14], based on a recurrence equation. This model, which does not rely on Fick's first law of diffusion and the time continuity assumption, described classical [14] and non-classical (supersaturated) [15] dissolution data well. Lansky and Weiss [16,17] published the continuous-time counterpart of the population growth model based on the non-constant fractional dissolution rate. The same authors [18] provided an index to quantify heterogeneity for the various dissolution models. Furthermore, the ubiquitous empirical use of the Weibull function [which is the exponential of a power law (i.e. a stretched exponential function)] in dissolution studies has been justified theoretically in terms of fractal kinetics considerations [19]. In parallel, physically based interpretations for the use of the Weibull function in drug release studies have been derived from Monte Carlo simulations [20,21].

Box 2. Chaotic dynamics

A dynamical system is a deterministic mathematical system that is represented by a set of variables. The set of these variables needed to describe the state of the system in a unique way forms a mathematical space called phase space [2] and their number is the dimension of the system. The time evolution, or trajectory, inside the phase space is described by mathematical rules, usually differential equations.

The trajectories of most dynamical systems, in the long run, are confined to a limited part of the phase space, which is called the attractor [2]. Every trajectory that starts outside the attractor approaches the attractor as time passes. An attractor is an object of lower dimension (e.g. a point or a circle) than the entire phase space. For example, a multidimensional phase space can have a point attractor (zero dimension; see the effect–concentration plot of Figure 1 in the main text), which means that all trajectories tend to concentrate in a specific point in the phase space, a steady state.

Some dynamical systems with three or more differential equations that include nonlinear terms can exhibit chaotic behaviour (i.e. trajectories follow complicated non-periodic patterns that resemble randomness). This behaviour only occurs for a specific range of the parameter values of the system. Hence, these systems exhibit qualitatively different behaviour for even a minor change of the parameter values. The main characteristic of chaotic dynamics is the sensitivity of the evolution of the system from initial conditions [2]. This means that a slight change in the initial conditions produces a completely different trajectory, which implies non-predictability of the time evolution of the system in the long run.

Like other dynamical systems, chaotic systems also have attractors. However, these attractors can be of non-integer, fractal dimension (Box 1). Thus, an attractor with infinite detail but confined in a finite space is defined and called a strange attractor [2]. The fractal topology of the strange attractors describes the complex, non-periodic behaviour of chaotic dynamics. Chaotic attractors are identified not only in mathematical models, but also in real-life experimental time series data, of which the exact dynamics are unknown.

Drug disposition

In classical pharmacokinetics, the description of drug time-course is accomplished using compartmental models (Figure 1). However, it is known that materials are distributed throughout the body by fractal networks of branching tubes [2] (Figure 1). Detailed analysis of the arterial and venular trees by West *et al.* [22,23] revealed that the allometric laws of biology originate from the fractal geometry of organisms. This fractal-like architecture of vascular trees was used for the development of a physiologically based model for the transport of the materials in the circulatory system [24] and used for the estimation of re-circulatory parameters [25]. Another important finding of the studies by West and colleagues [22,23] is that the internal surface areas of organisms for material exchange are 'maximally fractal'. Thus, the non-physiological values ($\gg 70$ l) of the apparent volume of distribution (V_{ap}) for most drugs [26] can be explained by an extremely high and effective exchange surface area in the internal structure of the organism. The body can be conceived, for drug distribution purposes, as a fractal object with an infinitely high surface to volume ratio (Figure 2). In this context, novel pharmacokinetic parameters have been proposed such as the fractal volume of drug distribution (v_f) and fractal clearance (CL_f) [27–30].

The simplified notion of the homogeneous compartments of pharmacokinetic models has been questioned in the literature [31–34] and attempts have been made to describe more realistically the heterogeneous character of drug distribution in the body. In this context, a heterogeneous model was proposed to interpret Ca^{2+} pharmacokinetics [35]. In this model, the kinetics of Ca^{2+} in deep tissues (under-stirred spaces) is described by a rate coefficient that decreases with time (fractal kinetics). In a similar vein, Weiss [36] explained the anomalous pharmacokinetics of amiodarone using fractal kinetic concepts, assuming non-exponential tissue trapping of the drug. These studies [35,36] seem to follow the same principles with the anomalous diffusion of water observed in biological tissues [37].

Another way to capture heterogeneity in pharmacokinetics is by stochastic modeling approaches, where the substance of interest is viewed as a set of molecules whose

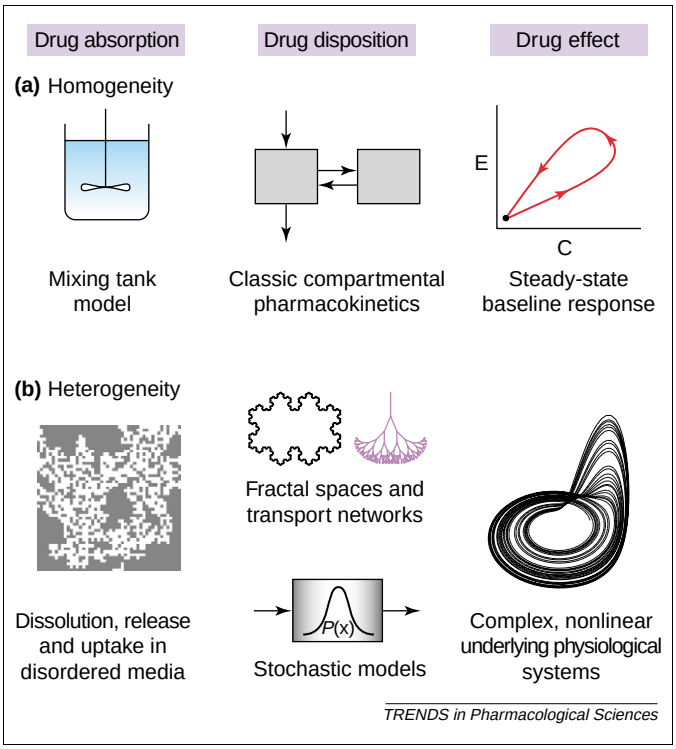

Figure 1. Homogeneous versus heterogeneous drug processes. The concepts of **(a)** homogeneous and **(b)** heterogeneous drug processes are contrasted. Classical pharmacokinetic modeling relies entirely on the concept of homogeneous compartments. Biopharmaceutic and pharmacodynamic modeling are considered as an extension of the compartmental pharmacokinetics, by adding compartments that either precede or follow the central pharmacokinetic compartment. In this vein, the mathematical basis for the description of drug processes relies on a unified compartmental approach, from the absorption phase up to the manifestation of drug effect. However, approaches that capture the heterogeneous nature of these processes have been proposed. Drug absorption: a mixing tank versus a percolation cluster [3]. Drug absorption, classically, is based on variations of the mixing tank model, although models with several compartments in series have also been used. The notion of heterogeneous gastrointestinal absorption can be considered by assuming that drug dissolution or release, transit and uptake take place in disordered media, such as the percolation cluster shown. Drug disposition: a scheme of a classical two-compartment model versus pictorial representations of fractal spaces and branching transport networks. In addition, a pictorial representation of a non-homogeneous compartment, used in stochastic mathematical models, is shown, whereas the drug quantities are described with probability distributions, $P(x)$. Drug effect: the classical counterclockwise hysteresis loop, of the effect (E) – plasma concentration (C) plot, which is a phase space with a point attractor (Box 2), versus a fractal attractor originating from chemical kinetic modeling. Classical pharmacodynamics relies on the suppression or the amplification of a steady-state baseline, resulting in a point attractor. By contrast, the underlying physiological systems are often much more complex than a steady-state baseline, exhibiting fractal strange attractors.

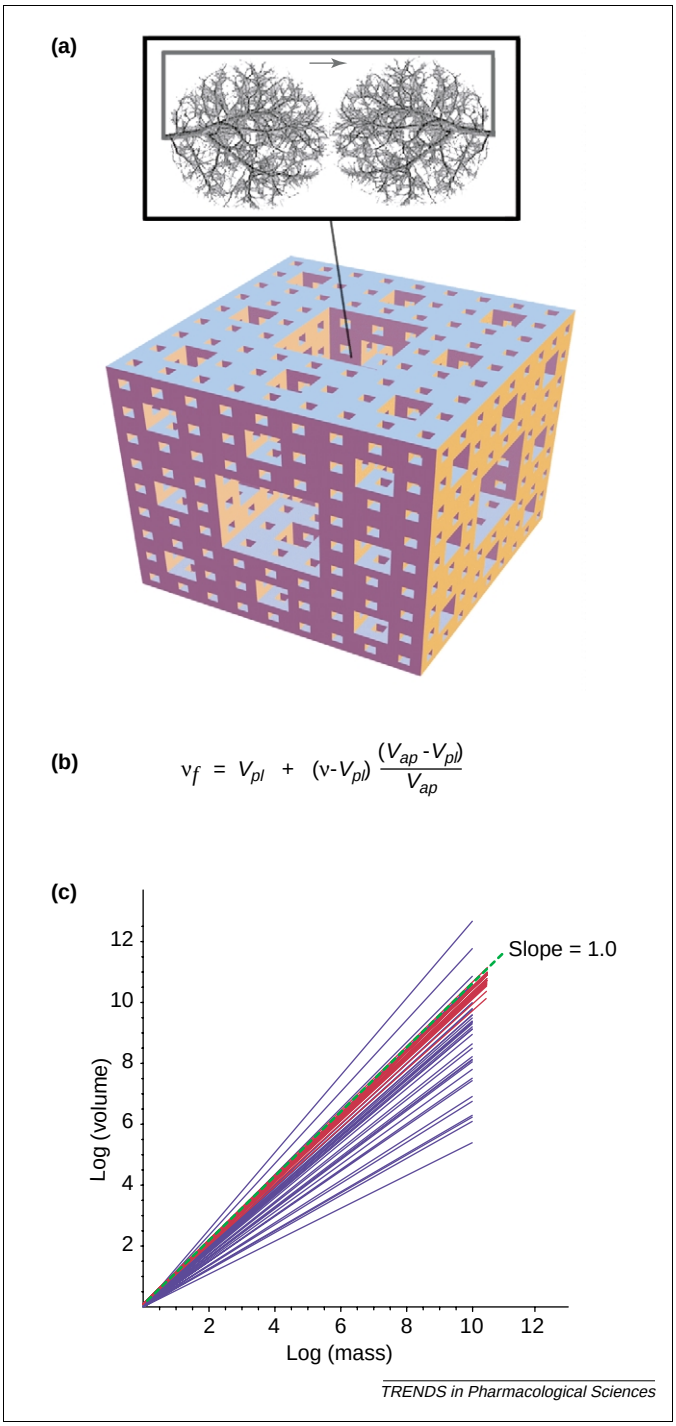

Figure 2. Drug distribution viewed in terms of fractal concepts. **(a)** Drug distribution is inextricably related to the internal exchange surface areas of the human body, which are 'maximally fractal' [22,23]. A 'biological–fractal' set characterizes the internal structure and includes the effective exchange area and the total volume of biologically active material (v). The upper limit of the volume of drug distribution is the fractal volume v (i.e. the body mass M of the species assuming a uniform constant density of 1 g ml^{-1}). The fractal three-dimensional parallelepiped in which the circulatory system is embedded provides a pictorial view of the volume v [27]. The cube, which corresponds to a modified Menger sponge [2] (i.e. a geometrically self-similar fractal with an infinitely high surface-to-volume ratio), is used to represent the part of the non-accessible experimentally 'biological–fractal' volume. Essential materials and drugs are transported through space-filling fractal networks of branching tubes of the circulatory system, which are supposed to occupy the empty spaces of the Menger sponge. **(b)** The fractal volume of drug distribution (v_f) corresponds to the portion of the volume v that is accessible to the drug. The value of v_f is determined by the physicochemical properties of drug and is estimated from V_{ap} values, where V_{pl} and V_{ap} are the plasma volume and the apparent volume of drug distribution, respectively [27]. **(c)** As a result of the anatomical and physiological similarities between mammalian species, the various types of volume of drug distribution can be expressed mathematically by allometric equations that have the general form: $Y = aM^b$, where M, a and b represent the species mass, the allometric constant and the allometric exponent, respectively, whereas Y denotes v_f or V_{ap}. The log–log plot of volume versus mass for several drugs is shown for v_f (red lines) and V_{ap} (blue lines) for the data presented in [27]. In general, volumes of drug distribution are expected to scale proportionally to body mass [i.e. $b = 1$ (dashed green line)]. In the great majority of cases the exponent b for v_f was found [27] to be either unity or very close to unity, whereas the b values for V_{ap} deviated from 1 considerably. This finding indicates that v_f is a physiologically sound concept.

random movement between compartments is based on probabilities of transfer. Various approaches in the formulation of stochastic models exist as Markov models, semi-Markov models, random hazard rate models and the use of Kolmogorov equations [33,38,39]. The first three approaches describe the random movement of homogeneous individual molecules whereas the last approach refers to heterogeneous molecules because of the inherent variability in their age, size or chemical composition. Although stochastic modeling is a compartmental approach, it describes the process uncertainty that does not exist in the deterministic compartmental models and supplies tractable forms that involve time-varying parameters. A stochastic pharmacokinetic model for cyclosporin has been developed recently [40].

In the field of hepatic drug elimination, Michaelis–Menten (MM) kinetics is being used extensively. The foundation of MM formalism relies on the mass-action law as applied to enzymatic reactions, assuming a well-stirred medium. However, theoretical approaches based on fractal principles have been used to describe enzyme kinetics in low-dimensional disordered media [41–43]. Recently, Berry [44], using Monte Carlo simulations for the enzymatic reaction in two-dimensional lattices, showed that one of the microconstants of the reaction is not constant throughout the reaction course. It crosses over from a constant region at short times to a power law decrease at longer times, the hallmark of fractal kinetics. A direct application of fractal concepts to the hepatic elimination of mibefradil was reported by Fuite *et al.* [45]. These authors proposed that the fractal structure of the liver, with attendant kinetic properties of drug elimination, can explain the unusual nonlinear pharmacokinetics of mibefradil. Again, kinetics of the fractal type were considered to be due to topological constrains.

Drug effect

Pharmacodynamics is the most complex process during the presence of the drug in the human body. The drug can interact with various physiological systems and thus it is not uncommon for the pharmacodynamic response to be, in reality, nonlinear and governed by mechanisms that have not been studied extensively. However, the state of the art in pharmacodynamic modeling handles these complicated mechanisms with effect site compartment(s), as an extension of compartmental pharmacokinetic modeling [46]. The baseline of the pharmacodynamic response (i.e. the underlying physiological system) is generally considered as the steady state (Figure 1), which the drug either suppresses or enhances. Furthermore, the inherent

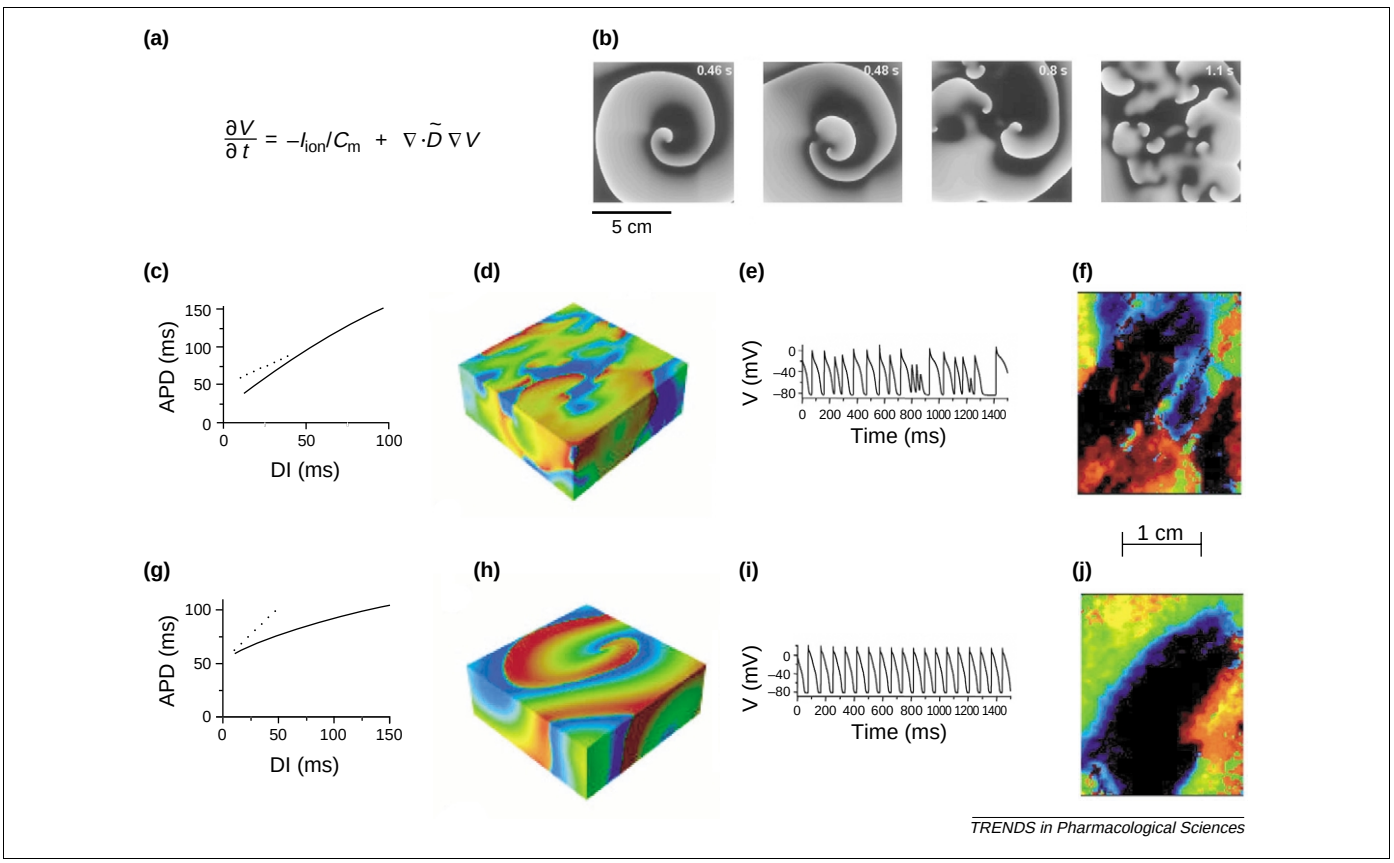

Figure 3. Study of ventricular fibrillation. The electrical activity of the heart and the initiation of ventricular fibrillation has been studied by using a diffusion reaction equation **(a)** (where V is the transmembrane voltage, I_{ion} is the total ionic current density, C_m is the capacitance and $\tilde{D}$ is the diffusion tensor), and found to produce spiral waves, an unstable structure that eventually breaks up and leads to chaotic, turbulent patterns **(b)**. The spiral waves (or scroll waves, which is their three-dimensional equivalent) have been identified in cases of ventricular tachycardia whereas the chaotic regime has been identified in cases of ventricular fibrillation. Antiarrhythmic drugs aim to prevent tachycardia and to succeed in this task in 80% of cases [51]. However, their action is based on separate cells and does not address the spatiotemporal effects and the formation of spiral waves that lead to fibrillation. In fact, it has been found that these drugs attenuate the instability of spiral waves. Thus, given that fact, the remaining 20% of cases in which the drugs fail to prevent the initiation of tachycardia makes them extremely dangerous. Therefore, antiarhythmic drugs must also have antifibrillatory properties to prevent the breakup of spiral waves, taking into account the parameters that play a key role in the instability of these structures, such as the slope of the action potential duration restitution (APDR), which is the slope of the action potential duration (APD) versus the diastolic interval (DI) and determines the stability of the spiral waves. In **(c)** the APDR slope is >1 (dotted line is slope 1) and small perturbations in DI amplify APD, resulting in turbulent behaviour as shown in simulated tissue **(d)**, the respective voltage versus time of the simulation **(e)** and the optical snapshot of real pig heart during fibrillation **(f)**. By contrast, when the APDR slope is <1 **(g)** the spiral waves are stable, as shown in simulated tissue **(h)**, the respective voltage versus time of the simulation **(i)** and the optical snapshot of real pig heart exhibiting spiral waves and where the restitution has been flattened by administration of bretylium **(j)**. Part (b) is reproduced, with permission, from [51] and parts (c–j) are reproduced, with permission, from [52].

variability of the pharmacodynamic response is routinely treated as 'noise'. Nevertheless, extensive experimental evidence, in addition to physiological modeling, indicate that the underlying physiological systems often are nonlinear dynamical systems (Figure 1) [47,48]. Such systems can exhibit qualitatively variable behaviour and in certain conditions even chaotic behaviour (Box 2). In these cases, the asymptotic behaviour of the system in the phase space is confined to a fractal structure called a strange attractor, instead of a steady state (i.e. a point attractor). Thus, the pharmacodynamic response can be a perturbation of the underlying nonlinear system and not just a suppression or attenuation of a steady state.

Nonlinear dynamics are usually applied in physiological systems and to the relevant drug action in two general directions: (i) the analysis of experimental or clinical data; and (ii) the construction of mathematical models. The analysis of real-life time series, experimental or clinical, is based on the hypothesis that the corresponding data originate from an unknown nonlinear dynamical system [2,48] that can form a strange attractor. Then, using certain tools (e.g. phase space reconstruction [2]), the validity of this hypothesis is tested, accounting also for the origin of variability, attributed to either noise or underlying dynamics. In addition, various relevant and useful measures, such as fractal dimensions of the attractor or of the time series itself, can be calculated, which are complementary to the usual statistical measures and help to discriminate qualitatively different conditions or to quantify the drug effect. In the case of mathematical modeling, the incorporation of nonlinear dynamics, where there is evidence of such presence, is neither complementary nor alternative to the classical approach. In such systems, the appropriate mechanistic mathematical modeling should be adapted to incorporate the nonlinearity features (Box 2), not for improved accuracy or detailed description, but to introduce a completely different rationale that cannot be approached classically.

Although the application of nonlinear dynamics in physiological systems is extensive, the application to relevant drug action is limited. Some of the most representative applications of nonlinear dynamics in

cardiovascular, central nervous and endocrinal systems, with the presence of drugs and the study of their action, are reviewed.

One of the major fields in which the theory of nonlinear dynamics has been widely applied is the dynamics of the heart. Recent applications of nonlinear dynamics focusing on methods of analyzing experimental recordings include work by Yambe and colleagues [49], who studied fractal attractors of time series of ventricular elastance (Emax), which is a parameter that is indicative of cardiac performance, in goats following the administration of various drugs. Furthermore, Tulppo *et al.* [50] studied the variability in heart rate, in the light of fractal analysis, in healthy subjects following the administration of various adrenergic and vagal drugs. However, the most promising application of nonlinear dynamics to the heart is the mathematical modeling of its electrical activity, which has revealed the causes of ventricular fibrillation and also the disappointing performance of some antiarhythmic drugs (Figure 3) [51–53].

Another important application of nonlinear dynamics is dealing with the action of CNS drugs. The analysis is focused mainly on the processing of electroencephalogram (EEG) recordings, introducing novel measures to quantify brain activity from EEG data. Comparison of several measures of EEG recordings, both classical and nonlinear, is made in the work by Widman *et al.* [54] for the anaesthetic drug sevoflurane. Examples of the application of nonlinear dynamics techniques to time-series analysis of EEG data from studies with CNS drugs include the investigation of the influence of anticonvulsive [55] and antiepileptic [56] drugs in epilepsy, the investigation of the electrophysiological effects of the neurotoxin 5,7-dihydroxytryptamine [57] and the study of epileptiform bursts in rats after administration of penicillin and K^+ ions [58].

The pulsatility of hormone secretion is widely acknowledged, whereas there is evidence that this is of dynamical origin and not random. It is believed that the interplay of various hormones form nonlinear oscillators through feedback mechanisms that can exhibit chaotic behaviour [59]. Recent examples of pharmacological interest include studies on parathyroid hormone and its impact on osteoporosis [60], the dynamics of insulin and glucose interaction [61], the secretion of cortisol and its suppression by corticosteroids [62], and the proposed set-point model for the prediction of the time-course of 8-hydroxy-(di-n-propylamino) tetralin-induced hypothermia [63]. Moreover, several investigations are focused on the study of hormone time series using the tools of nonlinear dynamics. Such examples include the glucose–insulin [64] and the cortisol–growth hormone systems [65]. Finally, a measure of pulsatility of time series, which is referred to as approximate entropy (ApEn), has been applied extensively to hormonal data [66]. An indicative recent example is the study of growth hormone with estradiol supplementation [67].

Concluding remarks

New insights can be gained by the elucidation of the effects of the heterogeneous structure (geometric disorder of the medium) and of the imperfect mixing on the kinetics of the drug processes in the human body. Thus, new levels of understanding for drug absorption and disposition phenomena are anticipated using fractal concepts. In addition, the application of nonlinear dynamics to pharmacodynamics can unveil a qualitatively different interpretation for the mechanism(s) and/or the variability of drug effect(s) recordings.

References

1 ben-Avraham, D. and Havlin, S. (2000) *Diffusion and Reactions in Fractals and Disordered Systems*, Cambridge University Press
2 Bassingthwaighte, J.B. *et al.* (1994) *Fractal Physiology*, Oxford University Press
3 Kopelman, R. (1988) Fractal reaction kinetics. *Science* 241, 1620–1626
4 Bhaskar, K.R. *et al.* (1992) Viscous fingering of HCl through gastric mucin. *Nature* 360, 458–461
5 Holm, L. and Flemstrom, G. (1990) Microscopy of acid transport at the gastric surface *in vivo*. *J. Intern. Med. Suppl.* 732, 91–95
6 Lenormand, R. *et al.* (1987) Three-dimensional fractals: experimental measurements using capillary effects. *Phys. Rev. A.* 36, 1855–1858
7 Daccord, G. (1987) Chemical dissolution of a porous medium by a reactive fluid. *Phys. Rev. Lett.* 58, 479–482
8 Nittmann, J. *et al.* (1985) Fractal growth of viscous fingers – quantitative characterization of a fluid instability phenomenon. *Nature* 314, 141–144
9 Macheras, P. and Argyrakis, P. (1997) Gastrointestinal drug absorption: is it time to consider heterogeneity as well as homogeneity? *Pharm. Res.* 14, 842–847
10 Kalampokis, A. *et al.* (1999) Heterogeneous tube model for the study of small intestinal transit flow. *Pharm. Res.* 16, 87–91
11 Kalampokis, A. *et al.* (1999) A heterogeneous tube model of intestinal drug absorption based on probabilistic concepts. *Pharm. Res.* 16, 1764–1769
12 Caroli-Bosc, F.X. *et al.* (2000) Ursodeoxycholic acid modulates cyclosporin A oral absorption in liver transplant recipients. *Fundam. Clin. Pharmacol.* 14, 601–609
13 Higaki, K. *et al.* (2001) Time-dependent oral absorption models. *J. Pharmacokinet. Pharmacodyn.* 28, 109–128
14 Dokoumetzidis, A. and Macheras, P. (1997) A population growth model of dissolution. *Pharm. Res.* 14, 1122–1126
15 Valsami, G. *et al.* (1999) Modeling of supersaturated dissolution data. *Int. J. Pharm.* 181, 153–157
16 Lansky, P. and Weiss, M. (1999) Does the dose-solubility ratio affect the mean dissolution time of drugs? *Pharm. Res.* 16, 1470–1476
17 Lansky, P. and Weiss, M. (2001) Modeling heterogeneity of properties and random effects in drug dissolution. *Pharm. Res.* 18, 1061–1067
18 Lansky, P. and Weiss, M. (2003) Classification of dissolution profiles in terms of fractional dissolution rate and a novel measure of heterogeneity. *J. Pharm. Sci.* 92, 1632–1647
19 Macheras, P. and Dokoumetzidis, A. (2000) On the heterogeneity of drug dissolution and release. *Pharm. Res.* 17, 108–112
20 Kosmidis, K. *et al.* (2003) A reappraisal of drug release laws using Monte Carlo simulations: the prevalence of the Weibull function. *Pharm. Res.* 20, 988–995
21 Kosmidis, K. *et al.* (2003) Fractal kinetics in drug release from finite fractal matrices. *J. Chem. Phys.* 119, 6373–6377
22 West, G.B. *et al.* (1997) A general model for the origin of allometric scaling laws in biology. *Science* 276, 122–126
23 West, G.B. *et al.* (1999) The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science* 284, 1677–1679
24 Dokoumetzidis, A. and Macheras, P. (2003) A tube model for transport and dispersion in the circulatory system based on the vascular fractal tree. *Ann. Biomed. Eng.* 31, 284–293
25 Karalis, V. *et al.* (2004) A physiologically based approach for the estimation of recirculatory parameters. *J. Pharmacol. Exp. Ther.* 308, 198–205
26 Rowland, M. *et al.* (1995) *Clinical Pharmacokinetics: Concepts and Applications*, 3rd Edn, Williams & Wilkins, Lippincott
27 Karalis, V. *et al.* (2001) Fractal volume of drug distribution: it scales proportionally to body mass. *Pharm. Res.* 18, 1056–1060
28 Karalis, V. and Macheras, P. (2002) Drug disposition viewed in terms of the fractal volume of distribution. *Pharm. Res.* 19, 696–703
29 Karalis, V. *et al.* (2002) Multivariate statistics of disposition

pharmacokinetic parameters for structurally unrelated drugs used in therapeutics. *Pharm. Res.* 19, 1827–1834
30 Karalis, V. *et al.* (2003) Quantitative structure pharmacokinetic relationships for disposition parameters of cephalosporins. *Eur. J. Pharm. Sci.* 20, 115–123
31 Rescigno, A. (2001) The rise and fall of compartmental analysis. *Pharmacol. Res.* 44, 337–342
32 Wise, M.E. and Borsboom, J.M. (1989) Two exceptional sets of physiological clearance curves and their mathematical form: test cases? *Bull. Math. Biol.* 51, 579–596
33 Matis, J.H. and Wehrly, T.E. (1998) A general approach to non-Markovian compartmental models. *J. Pharmacokinet. Biopharm.* 26, 437–456
34 Weiss, G.H. *et al.* (1994) A non-Markovian model for calcium kinetics in the body. *J. Pharmacokinet. Biopharm.* 22, 367–379
35 Macheras, P. (1996) A fractal approach to heterogeneous drug distribution: calcium pharmacokinetics. *Pharm. Res.* 13, 663–670
36 Weiss, M. (1999) The anomalous pharmacokinetics of amiodarone explained by nonexponential tissue trapping. *J. Pharmacokinet. Biopharm.* 27, 383–396
37 Kopf, M. *et al.* (1996) Anomalous diffusion of water in biological tissues. *Biophys. J.* 70, 2950–2958
38 Matis, J.H. and Kiffe, T.R. (2000) Stochastic population models. A compartmental perspective. In *Lecture Notes in Statistics* (Vol. 145) (Bickel, P. *et al.*, eds), pp. 17–37, Springer Verlag
39 Matis, J.H. *et al.* (1989) Some generalized stochastic compartment models for digesta flow. *Biometrics* 45, 703–720
40 Claret, L. *et al.* (2001) A stochastic model describes the heterogeneous pharmacokinetics of cyclosporin. *J. Pharmacokinet. Pharmacodyn.* 28, 445–463
41 López-Quintela, M. and Casado, J. (1989) Revision of the methodology in enzyme kinetics: a fractal approach. *J. Theor. Biol.* 139, 129–139
42 Savageau, M.A. (1995) Michaelis-Menten mechanism reconsidered: implications of fractal kinetics. *J. Theor. Biol.* 176, 115–124
43 Savageau, M.A. (1998) Development of fractal kinetic theory for enzyme-catalysed reactions and implications for the design of biochemical pathways. *Biosystems* 47, 9–36
44 Berry, H. (2002) Monte Carlo simulations of enzyme reactions in two dimensions: fractal kinetics and spatial segregation. *Biophys. J.* 83, 1891–1901
45 Fuite, J. *et al.* (2002) Fractal pharmacokinetics of the drug mibefradil in the liver. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 66, 021904
46 Derendorf, H. and Meibohm, B. (1999) Modeling pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. *Pharm. Res.* 16, 176–185
47 Dokoumetzidis, A. *et al.* (2001) Nonlinear dynamics and chaos theory: concepts and applications relevant to pharmacodynamics. *Pharm. Res.* 18, 415–426
48 van Rossum, J.M. and de Bie, J.E. (1991) Chaos and illusion. *Trends Pharmacol. Sci.* 12, 379–383
49 Yambe, T. *et al.* (2003) Chaos attractors of ventricular elastance to evaluate cardiac performance. *Artif. Organs* 27, 104–107
50 Tulppo, M.P. *et al.* (2001) Effects of pharmacological adrenergic and vagal modulation on fractal heart rate dynamics. *Clin. Physiol.* 21, 515–523
51 Weiss, J.N. *et al.* (1999) Chaos and the transition to ventricular fibrillation: a new approach to antiarrhythmic drug evaluation. *Circulation* 99, 2819–2826
52 Garfinkel, A. *et al.* (2000) Preventing ventricular fibrillation by flattening cardiac restitution. *Proc. Natl. Acad. Sci. U. S. A.* 97, 6061–6066
53 Fenton, F.H. *et al.* (2002) Multiple mechanisms of spiral wave breakup in a model of cardiac electrical activity. *Chaos* 12, 852–892
54 Widman, G. *et al.* (2000) Quantification of depth of anesthesia by nonlinear time series analysis of brain electrical activity. *Phys. Rev. E Stat. Phys. Plasmas Fluids Relat. Interdiscip Topics* 62, 4898–4903
55 Lehnertz, K. (1999) Non-linear time series analysis of intracranial EEG recordings in patients with epilepsy-an overview. *Int. J. Psychophysiol.* 34, 45–52
56 Elger, C.E. (2000) Nonlinear EEG analysis and its potential role in epileptology. *Epilepsia* 41, S34–S38
57 Di Mascio, M. *et al.* (1999) Decreased chaos of midbrain dopaminergic neurons after serotonin denervation. *Neuroscience* 92, 237–243
58 Ishizuka, S. and Hayashi, H. (1998) Spontaneous epileptiform bursts and long-term potentiation in rat CA3 hippocampal slices induced by chaotic stimulation of mossy fibers. *Brain Res.* 790, 108–114
59 Glass, L. and Mackey, M. (1988) *From Clocks to Chaos. The Rhythms of Life*, Princeton University Press
60 Rattanakul, C. *et al.* (2003) Modeling of bone formation and resorption mediated by parathyroid hormone: response to estrogen/PTH therapy. *Biosystems* 70, 55–72
61 Tolic, I.M. *et al.* (2000) Modeling the insulin-glucose feedback system: the significance of pulsatile insulin secretion. *J. Theor. Biol.* 207, 361–375
62 Dokoumetzidis, A. *et al.* (2002) Nonlinear dynamics in clinical pharmacology: the paradigm of cortisol secretion and suppression. *Br. J. Clin. Pharmacol.* 54, 21–29
63 Zuideveld, K. *et al.* (2001) A set-point model with oscillatory behavior predicts the time course of 8-OH-DPAT-induced hypothermia. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 281, R2059–R2071
64 Kroll, M.H. (1999) Biological variation of glucose and insulin includes a deterministic chaotic component. *Biosystems* 50, 189–201
65 Ilias, I. (2002) Complexity and non-linear description of diurnal cortisol and growth hormone secretory patterns before and after sleep deprivation. *Endocr. Regul.* 36, 63–72
66 Veldhuis, J.D. and Pincus, S.M. (1998) Orderliness of hormone release patterns: a complementary measure to conventional pulsatile and circadian analyses. *Eur. J. Endocrinol.* 138, 358–362
67 Veldhuis, J.D. *et al.* (2002) Impact of estradiol supplementation on dual peptidyl drive of GH secretion in postmenopausal women. *J. Clin. Endocrinol. Metab.* 87, 859–866