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Fractal geometry, fractal kinetics and chaos en route to biopharmaceutical sciences

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INTRODUCTION

Biopharmaceutics and pharmacokinetics have been developed and expanded, as have many other scientific subjects, based on conceptions of **homogeneity** and **linearity**.

Homogeneity or homogeneous conditions are a presupposition in almost all studies in this field of research. For example, the shape of a drug particle is assumed to be an ideal sphere and its surface smooth, the permeability of the intestinal complex membrane is considered constant along the gastrointestinal (GI) tract, the concentration of drug is postulated to be homogeneous in the GI fluids as well as in each of the hypothetical compartments of multicompartment models, etc. However, common intuition and scientific knowledge tell us that the drug particle is not an ideal sphere, while its surface is not smooth, the permeability of the GI wall is position and time dependent, the concentration homogeneity of drug in the GI tract and the peripheral compartments is synonymous with a well mixed system which is by far beyond the realms of reality.

Linearity is the basic principle of biopharmaceutics and pharmacokinetics. Formally, a system is linear if the output of an operation is proportional to the input. This property of proportionality along with the property of independence, i.e. the response of the system to an action is equal to the sum of the results of the values of the separate factors, are the fundamental features of linear systems. The biological systems we deal with are complicated systems, each of which consists of a number of factors. For example, GI absorption is a complicated process with many participating factors, such as solubility and dissolution rate of drug, volume, pH, composition and flow rate of GI fluids, biological membrane. However, a simple passive or active mechanism of drug transport is routinely used to model drug absorption. This approach is basically linear since the interaction of the variable of interest, i.e. the concentration of drug in the GI fluids with the other variables constituting the system, is considered weak or negligible. Nevertheless, the concentration of drug in the GI tract cannot be considered to be detached from the remainder of the system.

In various fields of research, e.g. physics, chemistry and physiology, scientists are increasingly finding that at the research level it is the nonlinear phenomena that control the game; physical or physiological heterogeneity is everywhere while heterogeneous conditions prevail in numerous physical, physiological and biochemical processes. Today's science shows that the real world is relentlessly nonlinear and, therefore, the techniques of nonlinear dynamics are required to analyse the nonlinear phenomena. In parallel, structural and functional heterogeneities can be described and understood with the concept of **fractals**.

Kinetic processes in various scientific fields are

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traditionally treated with classical kinetics. The latter is quite satisfactory for reactions and processes in well stirred media, i.e. under 'homogeneous' conditions. In fact, the kinetics of diffusion-controlled processes and reactions in three dimensional homogeneous systems obey the classical laws of diffusion where the rate constant of the process is linearly proportional to the diffusion coefficient. However, this proportionality is not valid for systems with smaller dimensions, fractal spaces, or disordered systems since the laws of transport are different in these media. Accordingly, fractal kinetics has been developed since classical kinetics was found to be unsatisfactory under dimensional constraints, e.g. phase boundaries, understirred media or membrane reactions.

The main objectives of this work are: (i) to present basic ideas of nonlinear dynamics and chaos, fractals and fractal kinetics; and (ii) to give some examples and applications in different areas relevant to drug research.

NON LINEAR DYNAMICS AND CHAOS

The dynamical systems theory is an important field of interest in many disciplines, such as physics, chemistry, biology, physiology, economics, etc. Dynamical systems are described with deterministic equations which can be linear or nonlinear differential (continuous) or difference (discrete) equations. In principle, the future behaviour of a dynamical system can be predicted from given initial conditions. However, predictability is ensured when the system's equations are linear but this is not always true when the equations are nonlinear. In the real world, most of the systems are described by nonlinear equations and the main goal is to predict the behaviour of a system after a long period of time. If this long term behaviour is unpredictable the system is characterised as chaotic.

Generally, deterministic chaos denotes the irregular or chaotic behaviour that is generated in nonlinear dynamical systems. Nonlinearity is a necessary, but not a sufficient, condition for a system to exhibit chaotic behaviour. A criterion for a system to be chaotic is its sensitivity dependence upon initial conditions; if two states of a system starting with slightly different initial conditions grow exponentially in time then the state of the system becomes essentially unknown after some time.

The sensitivity dependence on initial conditions was first recognised by Poincare (1) at the turn of the century who stated that small differences in the initial conditions can produce large differences in the final phenomena and thus prediction becomes impossible. However, it is well known today that the 'sensitivity' is not the only necessary condition for a system to be chaotic (2).

Poincare's ideas were based on the study of a system of nonlinear differential equations (the equations of the famous three-body problem of celestial mechanics) introducing qualitative methods of geometry and topology instead of the strict analytical methods, to discuss the global properties of

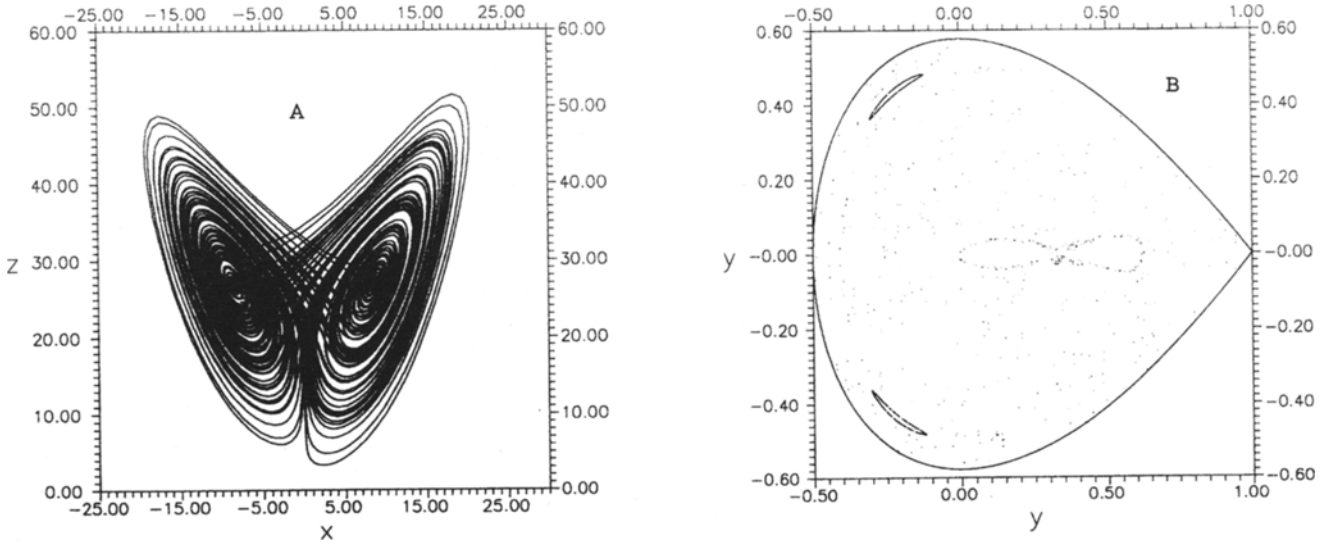

Fig. 1 : (*A*) The attractor solution to the Lorenz system of equations depicted in a 2-dimensional phase space (X,Z) [*see* (5)]. (*B*) Poincare surface of section x = 0, E(energy) = 1/6 for Henon-Heiles system [*see* (6)].

the system. Poincare's ideas were extended by Birckhoff (3) who demonstrated the importance of discrete systems (mappings) for a better understanding of the dynamics arising from differential equations.

The deterministic dynamical systems can be divided into two distinct classes, conservative and dissipative systems depending upon whether they preserve or not their volumes in the corresponding phase space (*see* Phase space, below). Both classes can be described by differential equations or maps (difference equations) and thus one can understand the behaviour of a given system by solving the corresponding equations and constructing the phase space portrait (3,4). Lorenz (5) and Henon-Heiles (6) were the first to identify chaotic behaviour by investigating the phase space of systems which describe the flow of air in the earth's atmosphere (dissipative system) and the motion of a star near the center of a flat galaxy (conservative system), respectively (Fig. 1).

Phase space

In equations describing physical systems there are typically one or more variables needed to describe the system, the environment, and their interaction. The most common way to simulate the system under study is with the use of differential equations describing how the variables change in time. Usually, a system of m independent variables is described by m-coupled differential equations of the general formula

$$d\mathbf{X}/dt = G\,[\mathbf{X}(t)] \qquad \text{Eq. 1}$$

where **X** is an m-component vector. The best way to study the evolution of the system in time is to integrate the equations (analytically or numerically). The solution is depicted by a curve in m-dimensional space (the **phase space**) where the coordinate axes correspond to the continuum of values of the components of vector **X**. Such a plot is a geometric construction which traces out the evolution of the system in time and is called a phase curve or a trajectory in phase space. Thus, a trajectory in phase space represents the evolution of the system and each point of the trajectory represents the state of the system at the corresponding time. Furthermore, because of the uniqueness of the solutions of differential equations, different phase space trajectories cannot cross each other.

The characteristic property of the preservation or not of the volume in the phase space is used for the discernment of the dissipative or conservative character of a dynamical system. This discernment is very important since several features are not common in these two types of systems. For example, important differences in the mechanisms leading to chaos exist between the dissipative and conservative systems. Furthermore, dissipative systems have attractors which in some cases are 'strange' while conservative systems do not have attractors. The fractal dimension (*see* Fractals, below) of the attractor is an integer number. When the dimension is not an integer then the corresponding attractor is called 'strange'. Finally, it should be mentioned that a chaotic system can consist of a single equation with one variable if it is discrete, or a set of coupled equations with at least three variables if it is continuous.

The dynamical behaviour of a system depends on the stability of its fixed points which can be either periodic orbits or equilibrium points. The study of the stability of its fixed points is accomplished by linearising at this point each of the equations of the dynamical system. The eigenvalues of the system of the linearised equations provide information about the stability of the corresponding fixed point. Furthermore, one can get an insight into the evolution of nearby trajectories. Since the stability of a fixed point and the calculated corresponding eigenvalues are dependant on the values of the parameters of the physical system, the stability can change as the values of the parameters change. Thus, dynamical systems can exhibit rich behaviour due to the stability characteristics of the fixed points.

Chaos in the population paradigm using a difference equation

For a great number of biological systems the variables are not considered to be continuous function of time. For example, the growth of one population of a single species in a closed environment is a function of a discrete time index specifying successive generations. Such a system can be described by the **difference** equation:

$$x_{t+1} = f\,(x_t) \qquad \text{Eq. 2}$$

where x_t and x_{t+1} are the numbers of individuals in two successive generations, i.e. in time t and t+1, respectively, and f is a function that relates the value of x_{t+1} to x_t. To illustrate the population growth, the functional form of f in Equation 2 was assumed to be

a quadratic function (7):

$$x_{t+1} = rx_t(1 - x_t) \qquad \text{Eq. 3}$$

where r is the birth rate which relates proportionally to the numbers of individuals x_{t+1} and x_t while the term $(1 - x_t)$ denotes the restriction towards the unlimited growth due to limited resources. Equation 3 is one of the simplest nonlinear difference equations which is usually called 'quadratic or 'logistic' (7).

The discrete representation of a difference equation is called a **map** which provides the time evolution of the system and is based on the repeated application of the mapping operation (iteration) to the newly generated points. For Equation 3, the iteration requires only to assign a value for r which is inherently linked with the system under study, e.g. a high value for r means high fertility and/or rich feeding grounds.

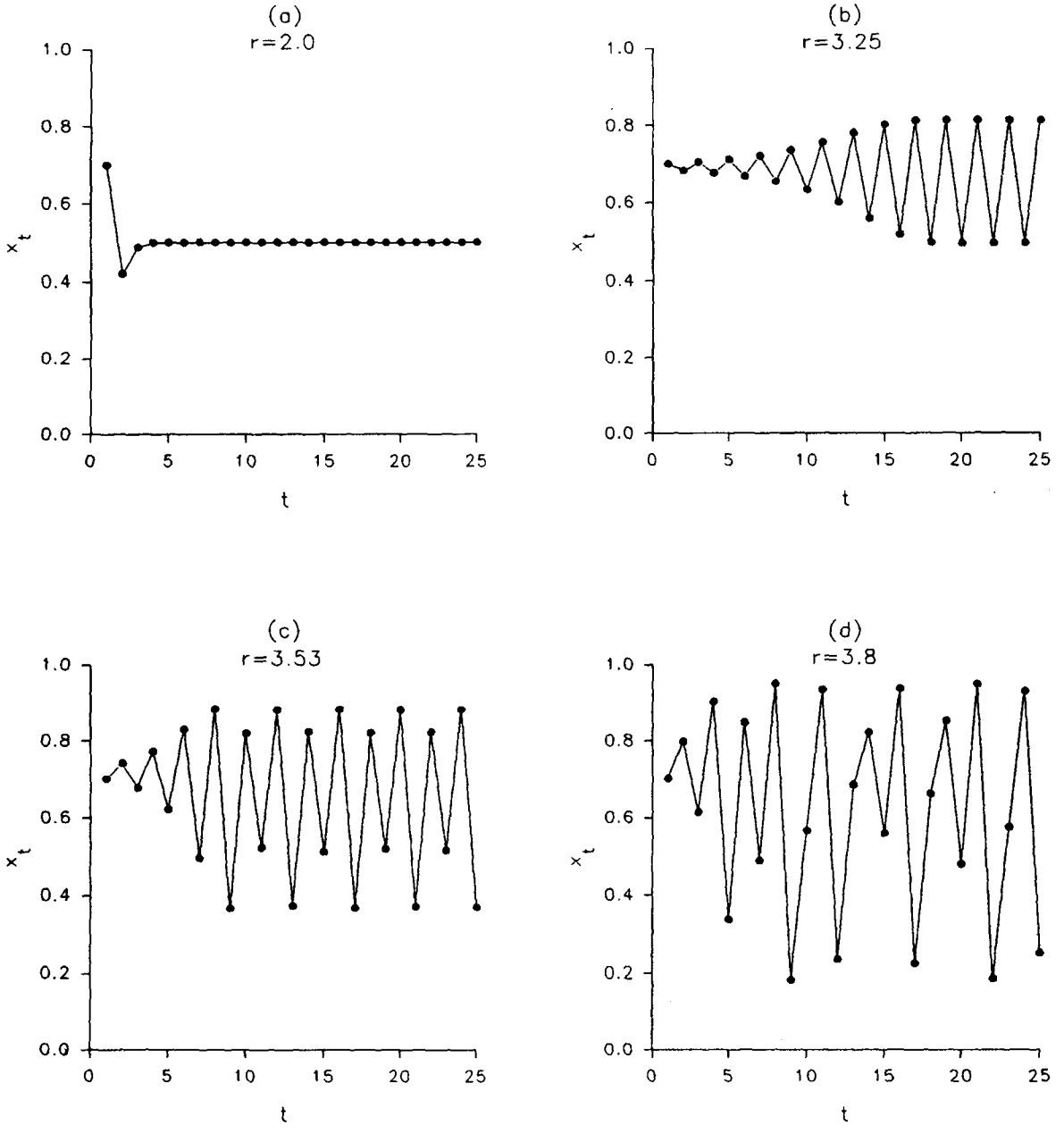

Fig. 2 : Various choices of the parameter r result in different solutions of the Equation 3 using in all cases the same initial point x_0 = 0.7. (*a*) The value of x_n after some iterations becomes constant, x_t = 0.5, for r = 2.0. (*b*) The value of x_n alternates between two values (2-cycle periodic orbit) for r = 3.25. (*c*) The value of x_n alternates between two large values and two small values (4-cycle periodic orbit) for r = 3.53. (*d*) The orbit is chaotic for r = 3.8.

Iterations based on Equation 3, reveal that the population can become extinct or the size of the population can be stable, oscillating or chaotic depending on the value of the rate parameter r (Fig. 2). It is interesting to see that when Equation 3 is written in the form using $x_t = x_{t+1} = x_{ss}$:

$$x_{ss}^2 + (1 - 1/r)x_{ss} = 0$$

two fixed points (steady-state solutions) $x_{ss} = 0$ and $x_{ss} = 1 - (1/r)$ are found. The population evolves as time passes to the steady-state values and becomes either extinct ($x_{ss} = 0$ for $r < 1$) or approaches the constant value $1 - r^{-1}$ when $1 < r < 3$. This means that whatever the size of the original population, the population will vanish if $r < 1$. In other words, for $r < 1$ and irrespective of the initial state of the system, all trajectories are attracted to zero because it is a stable point, $x = 0$, which is called an attracting fixed point or **attractor**. (Formally, an attractor is a set of points *S* such that for almost any point in the neighbourhood of *S* the dynamics approaches *S* as time approaches infinity.) When the birth rate is in the interval $1 < r < 3$, the population approaches the fixed point $x_{ss} = 1 - (1/r)$ which is another attractor since it is approached by all initial conditions, i.e. $0 < x_o < 1$. For example, for $r = 2$, $x_{ss} = 1 - (1/2) = 0.50$, i.e. half of the initial value of the population (Fig. 2a). These two steady states, $x = 0$ and $x = 1 - (1/r)$, are attractors with a very simple geometric structure, i.e. a point with dimension 0.

The most astonishing behaviour is observed with birth rates greater than three ($r > 3$) where the system looses its stability. Thus, when $r = 3.25$ the size of the population oscillates between two values, i.e. a fixed point of period 2 can be seen (Fig. 2b). This change in qualitative dynamics is called **bifurcation** since the fixed point for $r = 3$ becomes unstable and bifurcates into a new family of fixed points of period 2. Thus, the attractor is no longer the fixed point but a cycle of period 2. A slight increase of r, $r = 3.44$, produces a cycle of period 4. Accordingly, the cycle of period 4 becomes the attractor of the system (Fig. 2c). In general, as r increases in the range $3.0 < r < 3.57$ stable cycles of periods 2, 4, 8, 16, 32, 64, ... are generated. This pattern is called **pitchfork** or **period-doubling bifurcation** which is the classical 'route to chaos'. In fact, chaos occurs as r continues to increase in the range $3.57 < r < 4$. For $r = 3.57$, the system becomes aperiodic since the end point of the period doubling process is an orbit with an infinite period (zero frequency, Fig.2d). This behaviour which is generated from the deterministic system of Equation 3 for certain values of the parameter r is termed **chaotic** in an attempt to describe the geometric features of the attractor.

One might wonder now if the aforementioned analysis is relevant to drug research and biomedical sciences or it is restricted to the example considered. Possible applications of the difference equations (Eq. 2) of a single variable, x, may be the study of: (i) the change in the gene frequency in successive generations caused by a drug or disease; (ii) the number of individuals infected at various time intervals when studying the dynamics of epidemics; or (iii) the number of people using a dietetic as a result of a campaign at time t and the successive propagation of its use in the targeted population. In all these cases, appropriate definition of the function *f* should be made (*see* Eq. 2).

FRACTALS

Our understanding of nature has been based on the classical geometrical figures of smooth line, triangle, circle, cube, sphere, etc. Each one of these regular forms can be determined by a characteristic scale. For example, the length of a straight line can be measured with a ruler having a resolution finer than the entire length of the line. In general, each Euclidean object has a unique value for its properties (length, area or volume). It is also known that when these objects are viewed at higher magnification they do not reveal any new features.

In the real world, however, the objects we see in nature and the traditional geometric shapes do not bear much resemblance to one another. Benoit Mandelbrot (8) was the first to state the structural irregularity of the natural world: 'clouds are not spheres, mountains are not cones, coast lines are not circles, and bark is not smooth, nor does lightning travel in a straight line'. Mandelbrot (8) coined the word **fractal** for structures in space and processes in time that cannot be characterised by one spatial or temporal scale. In fact, the fractal objects and processes in time have multiscale properties, i.e. they continue to exhibit detailed structure over a large range of scales. Consequently, the value of a property of a fractal object or process depends on the spatial or temporal characteristic scale measurement ('ruler size') used.

The physiological implications of the fractal concepts are serious since fractal structures and processes are ubiquitous in living things (9–12), e.g. the lung, the vascular system, neural networks, the convoluted surface of the brain, ion channel kinetics,

and the distribution of blood flow through the blood vessels. Besides, many applications of fractals are to the physics of surfaces, e.g. the surface area of a drug particle, surface reactions on proteins. Thus, fractal geometry allows scientists to develop alternative hypotheses for experimental observations which lead to more realistic explanations than the traditional approaches. The 'fractal hypotheses' can be expressed in quantitative terms by quantifying the fractal properties of the system under study as delineated below.

Properties of fractals

The most interesting property of fractals is the **geometric self-similarity** which means that the parts of a fractal object are smaller exact copies of the whole object. Geometrical fractals can be generated by a line replacement algorithm. For example, the Koch curve shown in Figure 3 can be produced after infinite recursions if the middle third of the length of the line at each stage is replaced by two lines of the same length. The biological objects with a fractal structure cannot be characterised by geometric self-similarity but rather they can be specified by **statistical self-similarity**. This is due to the fact that the parts of fractal biological objects resemble the whole object instead of being exact copies of the whole. Self-similarity has an important effect on the properties of fractal objects measured either on a part of the object or on the entire object. Thus, if one measures the value of a property $L(q)$ on the entire object at resolution q, the corresponding value at finer resolution $L(ar)$ with $a < 1$ measured on a piece of the object, will be proportional to $L(q)$, i.e. $L(aq) = KL(q)$.

The above delineated dependency of the values of the measurements on the resolution applied allows someone to infer that there is no **true** value for the measured property. Instead, a **scaling** relationship exists between the values measured and the corresponding resolutions utilised which mathematically has the form of a scaling power law:

$$L(q) = Aq^{\alpha} \qquad \text{Eq. 4}$$

where A and α are constants for the given fractal object or process studied. Equation 4 can be linearised:

$$\log L(q) = \log A + \alpha \log q \qquad \text{Eq. 5}$$

The last equation reveals that when measurements

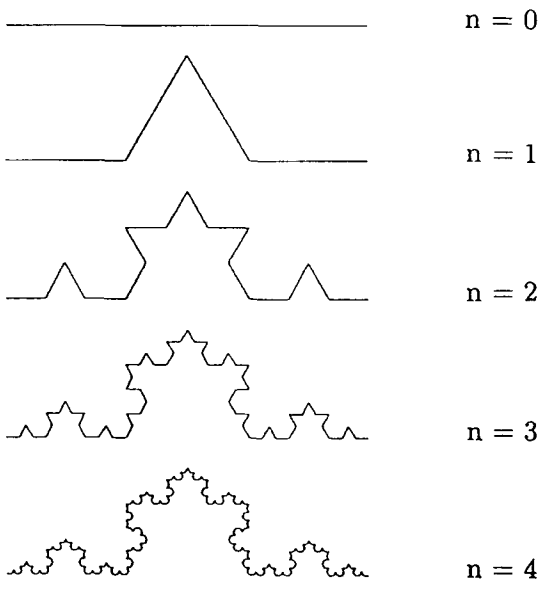

Fig. 3 : The first four iterations of the Koch curve. The fractal dimension is D = (log4/log3) = 1.2619.

for fractal objects or processes are carried out at various resolutions, the log–log plot of the measured property $L(q)$ and the scale q used are linearly related.

The degree of irregularity of a fractal object is quantified with the **fractal dimension**, D. This term is used to show that apart from the Euclidean integer dimensions (1 or 2 or 3) for the usual geometric forms, fractal objects have noninteger dimensions. For geometrically self-similar fractals, the fractal dimension can be determined either from self-similarity or from power law scaling (Eq. 4). The value of D can be derived from Equation 6 if we count the number N of the exact copies of the entire geometrical fractal which are observed when the resolution of scale is changed by a factor of F:

$$N = F^{D} \qquad \text{Eq. 6}$$

Thus, the value of D can be calculated from the equation:

$$D = \log N / \log F \qquad \text{Eq. 7}$$

For example, the fractal dimension of the Koch curve in Figure 3 is 1.2619 since four ($N = 4$) identical objects are found when the length scale is reduced by

a factor F = 3, i.e. D = log4/log3 = 1.2619. For statistically self-similar objects, the calculation of D is accomplished with various practical methods, the most common of which is called **box counting**. This method involves covering the object under study either with circles or spheres of various radii for two and three dimensional objects, respectively. Then, the minimum number of 'balls' (circles or spheres) N(q) of size q needed to cover the object are calculated. Finally, the fractal **box** dimension is calculated from the relationship:

$$D = \lim_{q \to 0} \frac{\log N(q)}{\log (1/q)} \qquad \text{Eq. 8}$$

FRACTAL KINETICS

In actual practice, many reactions and processes take place under dimensional or topological constraints. A diffusion process under such conditions is highly influenced, drastically changing its properties. A general, well-known, result is that in such constrained spaces diffusion is slowed down. This is manifested, for example, by the mean square displacement, which in normal spaces has a universal linear behaviour with time. It is now known that this behaviour is in fact sublinear (e.g. an exponent of 0.7 instead of 1) and causes the 'slowing-down' of the process. The same idea is manifested in chemical reactions, in which the reactants are treated as diffusing molecules, which can be spatially constrained by either walls or phase boundaries, depending on the system, with the end result that the reaction becomes **heterogeneous**. This holds for all types of bimolecular reactions, which are very common in our world (13).

Classical homogeneous kinetics assumes that the reactants are located in a 3-dimensional vessel, and that during the reaction process the system is constantly stirred, thus causing the positions (locations) of the reactants to be constantly re-randomized as a function of time. If/when such stirring does not take place, correlations begin to develop between the particle positions, which subsequently have a profound effect on the rate of the reaction. The build-up of such correlations is strongly dependent on the dimensionality, being more pronounced the further one gets from D = 3. This is so because quantitatively the parameter values in the diffusion laws are very different in different dimensionalities. In addition, if the space where the reaction takes place is not smooth, but highly irregular, this has an added effect on the building of such correlations. This happens if the space is a fractal structure characterized by its own dimensionality, which as discussed above, could be different from 1, 2, or 3.

The particle correlations result in building a depletion zone around each reactant, which grows steadily with time. This means that in the close neighbourhood of each particle there is a void, a space that is empty of particles. Naturally, the reaction slows down as particles must get further apart, to longer distances to find another particle to react with. A very 'curious' effect now is that the rate constant of the reaction is not 'constant' anymore, but depends on the growth of this depletion zone and, consequently, is time dependent. This modifies the kinetic differential equations and their solutions. For example, for the reaction A + A → Products, which is a prototype bimolecular reaction, the classical rate is :

$$\text{Rate} = k[A]^2 \qquad \text{Eq. 9}$$

the exponent 2 signifying the bimolecular character of the reaction. It turns out that on a fractal surface that has a dimensionality of 4/3 instead of 2, the rate for this reaction becomes:

$$\text{Rate} = k[A]^{2.5} \qquad \text{Eq. 10}$$

Furthermore, the 'constant' k now becomes:

$$k(t) = k_1 t^{-h} \qquad \text{Eq. 11}$$

where h = 1/3. Similar changes take place in other reactions and other spaces. Such findings are well established today, and they have been observed both experimentally and theoretically. Also, data for Monte-Carlo simulations (a powerful tool in this field) are in very good agreement with these findings.

APPLICATIONS OF FRACTALS, FRACTAL KINETICS AND CHAOS IN DRUG RESEARCH AND RELEVANT TOPICS

Fractal applications

Although the first review article in the pharmaceutical literature related to fractals was written in 1993 by Koch (14), the pioneering work of Avnir and his coworkers during the last 15 years revealed the fractal nature of molecule–surface interactions and reactions such as dissolution and adsorption. In a series of

studies, scaling laws, which describe quantitatively molecule–surface interactions, in adsorption were developed (15–19). Furthermore, the concept of fractal reaction dimension D_R was introduced to define the fractal dimension of the sub-set of reactive surface sites in adsorption (15,19) and dissolution (20,21).

Most of the recent applications of fractal geometry in drug research focus on the surface morphology of drug particles and their relevant properties (22). Leuenberger et al. (23) reviewed the application of percolation theory and fractal geometry to tablet compaction. In another study (24), the perimeter fractal dimension of insulin zinc crystals was assessed according to the walk-around step procedure. It was found that small changes in morphic features of insulin zinc crystals produced during crystallization and dissolution can be quantitatively assessed by this parameter (24). The fractal dimensions of lactose (25) and modified lactoses (26) were also measured to study the effect of particle morphology on the flow and packing properties of these materials. In addition, studies on fractal morphology of drug aggregates in aerosol propellant suspensions have shown that aggregation follows a diffusion limited cluster–cluster mechanism (27). It was also shown that the morphology of aggregates is significantly altered in the presence of a surfactant (27). In another field of research, Goetze and Brickhmann (28) have determined the fractal dimension of the surface of 53 proteins since the morphology of a protein's surface is associated with drug–receptor interactions or, in general, with molecular recognition. They found that the proteins have a surface fractal dimension ranging from 2.45–2.65 and self-similar surfaces within a range of 1.5–15 Å.

It is not only the surface of the materials or molecules to which the fractal concept has been applied. Kontturi et al. (29) have studied the effect of penetration enhancers on the fractal dimension of human skin and found that the enhancers increase the heterogeneity of skin surface. Applications of the fractal theory to pharmacokinetics and pharmacodynamics have been also published. Thus, the determination of fractal dimension of blood concentration-time curves and excretion-time profiles have been suggested (30,31) instead of the common practice of 'smoothing out' the unevenness of curves by fitting procedures. In parallel, Ragazzi (32,33) has discussed aspects of fractal theory relevant to pharmacodynamics.

Fractal kinetics applications

Fractal kinetics has been applied to enzyme kinetics described by the well known Michaelis-Menten equation. It is suggested (34,35) that under dimensionally-restricted conditions, the reaction of substrate–enzyme does not follow classical mass-action kinetics, but fractal kinetics. The modified 'fractal' Michaelis-Menten relationships can be more suitable for in vivo reactions which are confined to 2-dimensional membranes or 1-dimensional channels. Besides, the same concept has been applied (36) to carrier mediated transport studies which obey the Michaelian formalism under homogeneous conditions. The modified equation derived (36), which adheres to a transport process under dimensional constraints, seems to nicely describe experimental data, previously interpreted on the basis of a combined mechanism of passive and active transport.

Of particular interest is the application of fractal kinetics to ion channel kinetics in the cell membrane (37). It has been found that the ion channel proteins have discrete conformational states which are linked by physical mechanisms that result in fractal scaling (37–39). In this field of research, Li et al. (40) have shown that fractal mechanisms are associated with the allosteric effects of proteins and enzymes. It was proven that the Hill coefficient of the Hill equation, used in cooperative binding, is related to the fractal and spectral dimension of the protein (40).

Finally, theoretical aspects of fractal kinetics on controlled diffusion-limited drug release from a leaky matrix has been reported (41). It was found that the nature of drug release depends drastically on the dimension of the matrix and is dependent on whether the matrix is an Euclidean space or a fractal material (41).

Applications of chaos theory

Although the applications of chaos theory (or, better, of nonlinear dynamics) are very limited in drug research, the article of van Rossum et al. (42) with the intriguing title *Chaos and illusion* demonstrates clearly the potential applications of nonlinear dynamics to pharmacotherapy. It is clearly stated that the human body is a dynamic system with a large number of variables operating simultaneously. Therefore, the 'effect' induced by a drug should not be viewed as a single entity, but rather as a change of several variables which are interrelated nonlinearly. The group of van Rossum (43) was the first to introduce the

concept of attractor in the pharmaceutical literature, suggesting that pharmacokinetics is a simple case of chaos theory since it is dominated by a point attractor. However, their analysis was restricted to classical decay curves of drug in plasma.

In the field of basic research, analysis of the mass-action binding based on the fundamental ligand-receptor interaction using the techniques of nonlinear dynamics has been recently reported by Tallarida (44–48). In this series of articles, a common approach is adopted, i.e. the intensity of the feedback signal is modelled as a term which is a function of the concentration of ligand-bound receptors. The solution of the system of differential equations reveal chaotic behaviour as the values of the parameters are varied.

Analysis of time series data both from electrocardiograms and electroencephalograms exhibit irregular and apparently unpredictable or random behaviour. The application of nonlinear dynamics to drug effects on the activity of cardiac pulses and the brain are in its infancy. A characteristic example of application is the chaotic cycling of excitation blocking the sodium pump induced by a high dosage of ouabain on the isolated perfused rabbit interventricular septum (49).

REFERENCES

1. Poincare H. (1892) : Les methodes nouvelles de la mechanique Celeste. Paris, Gauthier-Villars.
2. Devaney R.L. (1986) : An introduction to chaotic dynamical systems. Menlo Park, Benjamin-Cummings.
3. Schuster H.G. (1989) : Deterministic chaos. An introduction. 2nd edn. Weinheim, VCH Verlagsgesellschaft.
4. Baker G.L., Gallab J.P. (1990) : Chaotic dynamics. Cambridge, Cambridge University Press.
5. Lorenz E.N. (1963) : Deterministic nonperiodic flow. J. Atmos. Sci., 20, 282-293.
6. Henon M., Heiles C. (1964) : The applicability of the third integral of motion: some numerical results. Astron. J., 69, 73-79.
7. May R.M. (1976) : Simple mathematical models with very complicated dynamics. Nature, 261, 459-467.
8. Mandelbrot B.B. (1982) : The fractal geometry of nature. San Fransisco, W.H. Freeman.
9. West B., Goldberger A. (1987) : Physiology in fractal dimensions. Am. Sci., 75, 354-365.
10. Goldberger A., Rigney D.R., West B. (1990) : Chaos and fractals in human physiology. Sci. Am., 37, February.
11. Weibel E.R. (1991) : Fractal geometry: a design principle for living organisms. Am. J. Physiol., 261, L361-L369.
12. Elbert T., Ray W.J., Kowalik Z.J., Skinner J.E., Graf E.K., Birbaumer N. (1994) : Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol. Rev., 74, 1-47.
13. Kopelman R. (1988) : Fractal reaction kinetics. Science, 241, 1620-1626.
14. Koch H.P. (1993) : The concept of fractals in the pharmaceutical sciences. Pharmazie, 48, 643-659.
15. Farin D., Avnir D. (1989) : The fractal nature of molecule-surface interactions and reactions. In: Avnir D. (Ed.) The Fractal Approach to Heterogeneous Chemistry: Surfaces, Colloids, Polymers. New York, Wiley, pp 271-293
16. Avnir D., Farin D., Pfeifer P. (1984) : Molecular fractal surfaces. Nature, 308, 261-263.
17. Avnir D., Farin D., Pfeifer P. (1985) : Surface geometric irregularity of particulate materials: the fractal approach. J. Coll. Interf. Sci., 103, 112-123.
18. Farin D., Avnir D. (1987) : Reactive fractal surfaces. J. Phys. Chem., 91, 5517-5521.
19. Farin D., Avnir D. (1988) : The reaction dimension in catalysis of dispersed metals. J. Am. Chem. Soc., 110, 2039-2045.
20. Farin D., Avnir D. (1992) : Use of fractal geometry to determine effects of surface morphology on drug dissolution. J. Pharm. Sci., 81, 54-57.
21. Valsami G., Macheras P. (1995) : Determination of fractal reaction dimension in dissolution studies. Eur. J. Pharm. Sci., 3, 163-169.
22. Carstensen J.T., Francini M. (1993) : The use of fractal geometry in pharmaceutical systems. Drug Dev. Ind. Pharm., 19, 85-100.
23. Leuenbeerger H., Leu R., Bonny J.D. (1992) : Application of percolation theory and fractal geometry to tablet compaction. Drug Dev. Ind. Pharm. 18, 723-766.
24. Kocova S. El-Arini, R. Tawashi. (1994) : Morphological and fractal-based methods describing insulin zinc crystal habits. Drug Dev. Ind. Pharm., 20, 1-10.
25. Cartilier L.H., Tawashi R. (1994) : Effect of particle morphology on the flow and packing properties of lactose. STP Pharma-Sci., 3, 213-220.
26. Holgado M.A., Fernandèz-Hervas M.J., Fernandez-Arevalo M., Rabasco A.M. (1995) : Use of fractal dimensions in the study of excipients: application to the characterization of modified lactoses. Int. J. Pharm., 121, 187-193.
27. Bower C., Wasington C., Purewal T.S. (1995) : Fractal morphology of drug aggregates in aerosol propellant suspensions. Int. J. Pharm., 118, 229-235.
28. Goetze T., Brickhmann J. (1992) : Selfsimilarity of protein surfaces. Biophys. J., 61, 109-118.
29. Kontturi K., Murtomaki L., Hirvonen J., Paronen P., Urtii A. (1993) : Electrochemical characterization of human skin by impedance spectroscopy: the effect of penetration enhancers. Pharm. Res., 10, 381-385.
30. Koch H.P., Zacek H. (1991) : Fractals also in pharmacokinetics? Pharmazie, 46, 870-871.
31. Zacek H., Koch H.P. (1992) : Tentative heuristic statistical testing of self-similarity of fractals in pharmacokinetics. Pharmazie, 47, 376-378.
32. Ragazzi E. (1992) : Fractal dimension in pharmacology. Pharmacol. Res., 25, 21-24.
33. Ragazzi E. (1995) : Hidden fractals in pharmacodynamics. Pharmazie, 50, 66-68.
34. Lopez-Quintela M.A., Casado J. (1989) : Revision of the methodology in enzyme kinetics: a fractal approach. J. Theor. Biol., 139, 129-139.
35. Savageau M.A. (1995) : Michaelis-Menten mechanism reconsidered: implications of fractal kinetics. J. Theor. Biol., 176, 115-124.
36. Macheras P. (1995) : Carrier mediated transport can obey fractal kinetics. Pharm. Res., 12, 541-548.
37. Liebovitch L.S., Sullivan J.M. (1987) : Fractal analysis of a voltage-dependent potassium channel from cultured mouse

hippocampal neurons. Biophys. J., 52, 979-988.
38. Liebovitch L.S., Toth T.I. (1990) : Using fractals to understand the opening and closing of ion channels. Ann. Biomed. Eng., 18, 177-194.
39. Liebovitch L.S., Czegledy. (1992) : A model of ion channel kinetics based on deterministic, chaotic motion in a potential with two local minima. Ann. Biomed. Eng., 20, 517-531.
40. Li H., Chen S., Zhao H. (1990) : Fractal mechanisms for the allosteric effects of proteins and enzymes. Biophys. J., 58, 1313-1320.
41. Bunde A., Havlin S., Nossal R., Stanley H.E., Weiss G.H. (1985) : On controlled diffusion-limited drug release from a leaky matrix. J. Chem. Phys., 83, 5909-5913.
42. Van Rossum J.M., de Bie J.E.G.M. (1991) : Chaos and illusion. Trends Pharmacol. Sci., 12, 379-383.
43. Van Rossum J.M., de Bie J.E.G.M., van Lingen G., Teeuwen H.W.A. (1989) : Pharmacokinetics from a dynamical systems point of view. J. Pharmacokinet. Biopharmacol., 17, 365-392.
44. Tallarida R.J. (1990) : On control and stability of ligand receptor reactions according to the mass action law. Drug Dev. Res., 19, 257-274.
45. Tallarida R.J. (1990) Further characterisation of a control model for ligand-receptor interaction: phase plane geometry, stability and oscillation. Ann. Biomed. Eng., 18, 671-684.
46. Tallarida R.J. (1990) : Oscillation and control of ligand-receptor interactions according to the law of mass action. Life Sci., 46, 1559-1568.
47. Tallarida R.J., Freeman K. (1991) : Control and stability of ligand-receptor interactions in the presence of a competitive compound. Life Sci., 48, L19-L24.
48. Tallarida R.J., Freeman K. (1994) : Chaos and control in mass-action binding of endogeneous compounds. Ann. Biomed. Eng., 22, 153-161.
49. Garfinkel A., Spano M.L., Ditto W.L., Weiss J.N. (1992) : Controlling cardiac chaos. Science, 1230-1235.