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Review Article

Nonlinear Dynamics and Chaos Theory: Concepts and Applications Relevant to Pharmacodynamics

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

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The theory of nonlinear dynamical systems (chaos theory), which deals with deterministic systems that exhibit a complicated, apparently random-looking behavior, has formed an interdisciplinary area of research and has affected almost every field of science in the last 20 years. Life sciences are one of the most applicable areas for the ideas of chaos because of the complexity of biological systems. It is widely appreciated that chaotic behavior dominates physiological systems. This is suggested by experimental studies and has also been encouraged by very successful modeling. Pharmacodynamics are very tightly associated with complex physiological processes, and the implications of this relation demand that the new approach of nonlinear dynamics should be adopted in greater extent in pharmacodynamic studies. This is necessary not only for the sake of more detailed study, but mainly because nonlinear dynamics suggest a whole new rationale, fundamentally different from the classic approach. In this work the basic principles of dynamical systems are presented and applications of nonlinear dynamics in topics relevant to drug research and especially to pharmacodynamics are reviewed. Special attention is focused on three major fields of physiological systems with great importance in pharmacotherapy, namely cardiovascular, central nervous, and endocrine systems, where tools and concepts from nonlinear dynamics have been applied.

KEY WORDS: pharmacodynamics; chaos; cardiovascular drugs; CNS drugs; hormones.

INTRODUCTION

The values of the measured properties of many physiological systems look random. We are used to thinking that the determinants of variability are unknown because the factors affecting the phenomena studied are numerous. This idea relies on the classical view of randomness, which requires that a complex system has a large (perhaps infinite) number of degrees of freedom that are not directly observed but whose presence is manifested through fluctuations. However, over the last two decades, scientists from various fields of research have shown that randomness generated by deterministic systems (dynamical systems) exhibit spectra practically indistinguishable from spectra of pure random processes. This is referred to as *chaotic* behavior, a specific subtype of nonlinear dynamics, which is the science dealing with the analysis of dynamical systems (1,2).

The paradox with the term chaos is the contradiction between its meaning in colloquial use and its mathematical sense. Routinely, we use the word chaos in every day life as a synonym of randomness with (usually) catastrophic implications; in mathematics, chaos refers to irregular behavior of a system that appears to be random, *but is not.* Accordingly, this apparently random-looking behavior poses a fundamental dilemma for the origin of randomness in a set of irregular observations of a studied system: Is the system chaotic or not? In other words, does the irregular behavior of observations arise from noise or chaos? (Fig 1, A and B)

The key element in this complex, unpredictable, random-like behavior is nonlinearity. When a system consists only of linear terms, a result is proportional to its stimulus and the cumulative effect of two stimuli is equal to the summation of the individual effects of each stimulus. This is the superposition principle, which states that every linear system can be studied by analyzing it into its components, taking complexity out of the question. In contrast, for nonlinear systems, the superposition principle does not hold; the overall behavior of the system is not at all the same as the summation of the individual behaviors of its components, making complex, unpredictable behavior a possibility. Nevertheless, not every nonlinear system is chaotic, which means that nonlinearity is a necessary but not a sufficient element for chaos.

The basic ideas of chaos were introduced more than a hundred years ago; however, its significance and implications were realized relatively recently because chaos was studied in detail after the wide spread of computers in the seventies. Although its study started from the fields of mathematics, astronomy and physics, scientists from almost every field grew interest in these ideas. Life sciences are one of the most applicable areas for the ideas of chaos due to the complexity of biological systems, although many consider the advanced mathematics used, a drawback. The last 20 years the science

[1] School of Pharmacy, University of Athens, Athens, Greece.
[2] Department of Pharmacokinetics, University of Mediterranee, Marseilles, France.
[3] To whom correspondence should be addressed. (e-mail: macheras@pharm.uoa.gr)

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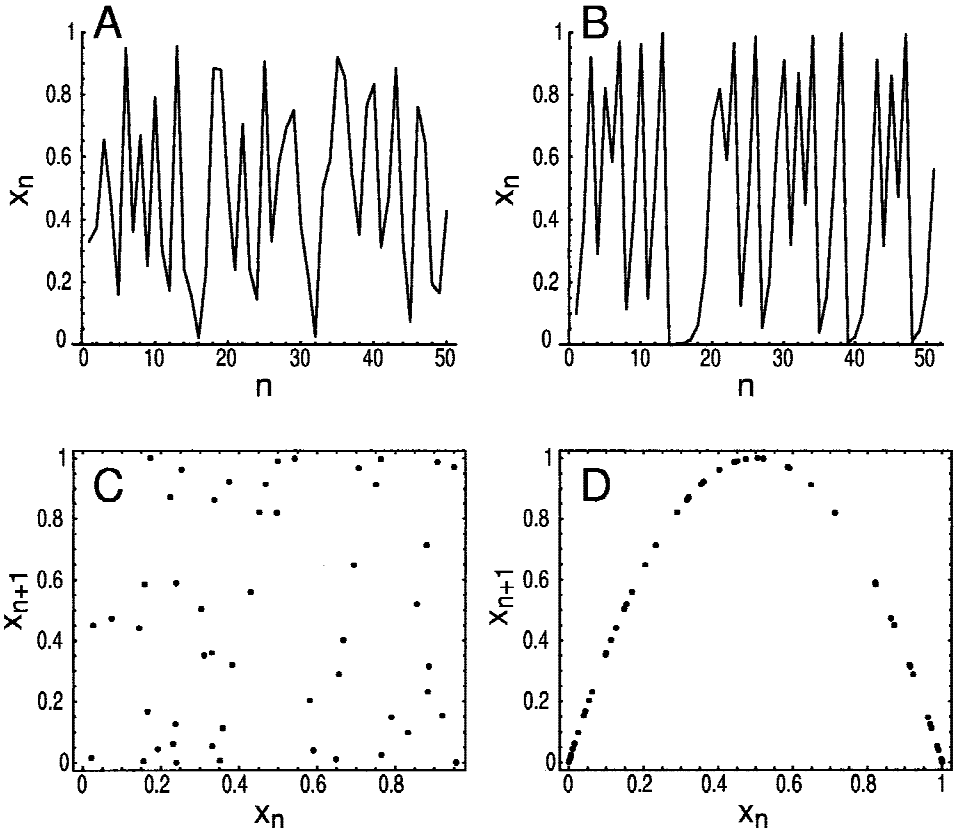

Fig. 1. (A) A series of uniformly distributed random numbers between 0 and 1. (B) Plot generated by the logistic map, a deterministic system of the form $\chi_{n+1} = 4\chi_n(1 - \chi_n)$. It is impossible to distinguish them visually (A or B). (C and D) The pseudophase plots of the two sequences of plots A and B, respectively. Each χ_n is plotted against its consequent χ_{n+1}. The random sequence (A) produces a pseudophase space of scattered points (C) showing that there is no correlation between successive points. On the contrary, the points of the deterministic sequence (B) lay in a well formed line (D).

of chaos has formed a truly interdisciplinary area of research which has changed the way people look at phenomena in every field of science.

This work is divided into two sections. In the first section the basic principles of dynamical systems are presented. In the second part, applications of nonlinear dynamics in topics relevant to drug research are reviewed.

BASIC PRINCIPLES OF DYNAMICAL SYSTEMS

A dynamical system is a deterministic mathematical system whose state is defined at any time by the values of N variables $\chi_1, \chi_2, \ldots, \chi_N$, and its evolution in time is determined by a set of rules. These rules, given a set of initial conditions $\chi_1(t_0), \chi_2(t_0), \ldots, \chi_N(t_0)$, determine the time evolution of the system in a unique way. This set of rules can be either differential equations of the form:

$$\frac{d\chi_i}{dt} = f_i[\chi_1, \chi_2, \ldots, \chi_N, t; a], \quad i = 1,2,\ldots,N \tag{1}$$

and then the system is called a flow, or discrete equations where every consequent generation of the variable χ_i is given by an equation of the form

$$\chi_{i,n+1} = f_i[\chi_{1,n}, \chi_{2,n}, \ldots, \chi_{N,n}; a], \quad i = 1,2,\ldots,N \tag{2}$$

where $\chi_{i,n}$ stands for the nth generation of the ith variable, and then the system is called a map. In the above definitions a represents a set of dynamical parameters of the system, having constant values. These parameters are also called *control parameters.* The set of the system's variables forms a mathematical space called *phase space* (1). A point in the phase space represents a unique state of the dynamical system. Thus the evolution of the system in time is represented by a curve in the phase space called *trajectory.* The number of variables needed to describe the system's state, which is the number of initial conditions needed to determine a unique trajectory, is the *dimension* of the system. There are also dynamical systems that have infinite dimension. Such systems are usually described by differential equations with partial derivatives or time delay differential equations, which can be considered as a set of infinite in number ordinary differential equations. The main property of the phase space is that trajectories can never intersect themselves or each other due to the uniqueness of the solutions. The phase space is a valuable tool in dynamical systems analysis since it is easier to analyze the properties of a dynamical system by determining topological properties of the phase space rather than analyzing the time series of the values of the variables directly.

Dynamical systems are classified in two main categories: the conservative and the non-conservative systems. The conservative systems have the major property of conserving the volume that is formed by an initial set of points in the phase space as times goes by, although the shape of the volume may change. In other words, a volume in the phase space re-

sembles an incompressible liquid. On the other hand, nonconservative systems do not possess this property and an initial volume in the phase space, apart from changing its shape, it may also grow or shrink. In the latter case (when the volume shrinks) the system is called more specifically, dissipative. Most systems in nature, including biological systems, are dissipative.

The trajectories of dissipative dynamical systems, in the long run, are confined in a subset of the phase space, which is called *attractor* (1), i.e., the set of points in phase space where the trajectories converge. An attractor is usually an object of lower dimension than the entire phase space (a point, a circle, a torus, etc). For example, a multidimensional phase space may have a point attractor (dimension 0), which means that the asymptotic behavior of the system is a steady state, or a limit cycle (dimension 1) which corresponds to a periodic asymptotic behavior, an oscillation. Even the solutions of systems with infinite dimension, like systems described by partial differential equations, may lie on attractors of low dimension (1). A phase space of a system may also have more than one attractors. In this case the asymptotic behavior, i.e., to which attractor a trajectory ends up, depends on the initial conditions. Thus, each attractor is surrounded by an *attraction basin,* which is the part of the phase space in which every initial condition gives a trajectory that ends up to the specific attractor. Schematic representations for the point, the limit cycle and the torus attractors, are depicted in Figure 2, whereas the point attractor of a classical pharmacokinetic-pharmacodynamic system is shown in Figure 3.

A dynamical system may exhibit qualitatively different behavior for different values of its control parameters. Thus, a system which has a steady state (point attractor) for some value of a parameter, may oscillate (limit cycle) for some other value. The critical value where the behavior changes, is called a *bifurcation point* and the process, *bifurcation* (1). More specifically this kind of bifurcation, i.e. the transition from a point attractor to a limit cycle, is referred to as *Hopf bifurcation.*

The most widely known bifurcation is *pitchfork bifurcation.* Consider the one-dimensional map

$$\chi_{n+1} = f[\chi_n] = a\chi_n[1 - \chi_n] \quad (3)$$

This difference equation is called *logistic map,* and represents a simple deterministic system, where given a χ_n one can calculate the consequent point χ_{n+1} and so on. It was introduced by May to describe the dynamics of a single species population (1). For values of the control parameter a between 1 and 3, Eq. 3 exhibits two steady states which can be considered of period 1, namely $\chi_{s,1a} = (a - 1)/a$ and the trivial $\chi_{s,1b} = 0$. These steady states are the solutions of the algebraic equation $\chi = f[\chi] = a\chi(1 - \chi)$. Although the steady states are two, for any initial condition different than $\chi = 0$ the system after a few steps will end up to $\chi_{s,1a}$ (Fig. 4A). This is so because steady state $\chi_{s,1a}$ is *stable,* while steady state $\chi_{s,1b}$ is *unstable.* The stability of steady state $\chi_{s,1a}$ means that a small change in the initial condition will not influence the final state of the trajectory, which will end up at $\chi_{s,1a}$. On the other hand, steady state $\chi_{s,1b}$ is *unstable* since a small change in the initial condition $\chi = 0$ will lead the trajectory away from $\chi_{s,1b} = 0$, and towards the stable steady state $\chi_{s,1a} = (a - 1)/a$, although for initial condition exactly $\chi = 0$ the system will remain always at $\chi = 0$.

For values of a higher than 3 the steady state $\chi_{s,1a}$ becomes unstable and gives birth to a new steady state of period 2, namely

$$\chi_{s,21},\chi_{s,22} = \frac{a + 1 \pm \sqrt{a^2 - 2a - 3}}{2a}$$

which is a solution of the equation $\chi = f[f[\chi]] = a^2\chi\ (1 - \chi)[(1 - a\chi\ (1 - \chi))]$. What happens now is that for any initial condition, except $\chi = 0$ and $\chi = (a - 1)/a$, the system after a few steps will end up forming a never-ending succession of the two values of $\chi_{s,21}$ and $\chi_{s,22}$ (Fig. 4B). This type of bifurcation is called *pitchfork bifurcation.* It must not be confused with Hopf bifurcation, since both attractors are of the same dimension, only the period is doubled. For an even higher value of a, namely $a > 1 + \sqrt{6}$ the stable steady state of period 2 becomes unstable and a new stable steady state of period 4 is born (Fig. 4C). The procedure of period doubling bifurcation continues as the value of the parameter a grows (Fig. 5). The difference between the values of a at which two successive bifurcations take place decreases (Fig. 5). It was actually found that the ratio of two successive intervals of a between

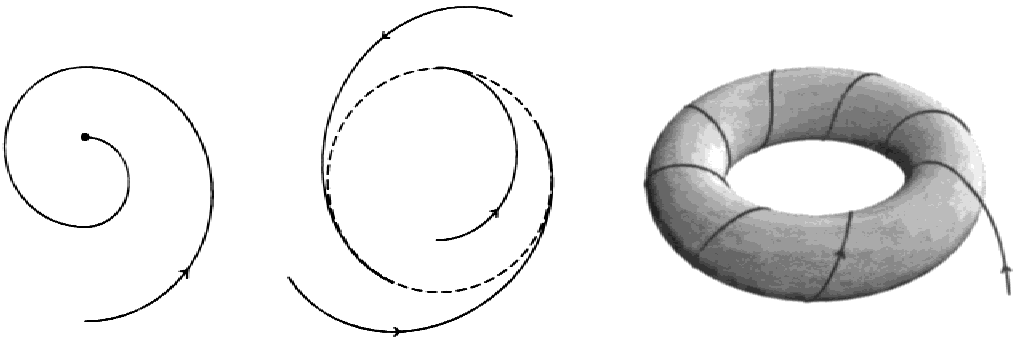

Fig. 2. A schematic representation of the various types of attractors. Left: the point attractor. Regardless the initial conditions, the system ends up to the same steady state. Middle: A limit cycle. The system always ends up doing a specific oscillation. Right: A torus attractor. The torus is the two-dimensional (2D) equivalent of a circle. In fact, a circle can be called a 1-torus, the 2D torus can be called a 2-torus and there is also the 3-torus and generally the n-torus. The trajectory on a 2-torus is a 2D oscillation with the ratio of the frequencies of the two oscillations being non-rational. Because the trajectory never passes from the same point twice, in infinite time fills the entire surface of the torus. This type of trajectory is called quasiperiodic. Being an attractor, the torus attracts all trajectories to fall on its surface and follow the quasiperiodic behavior.

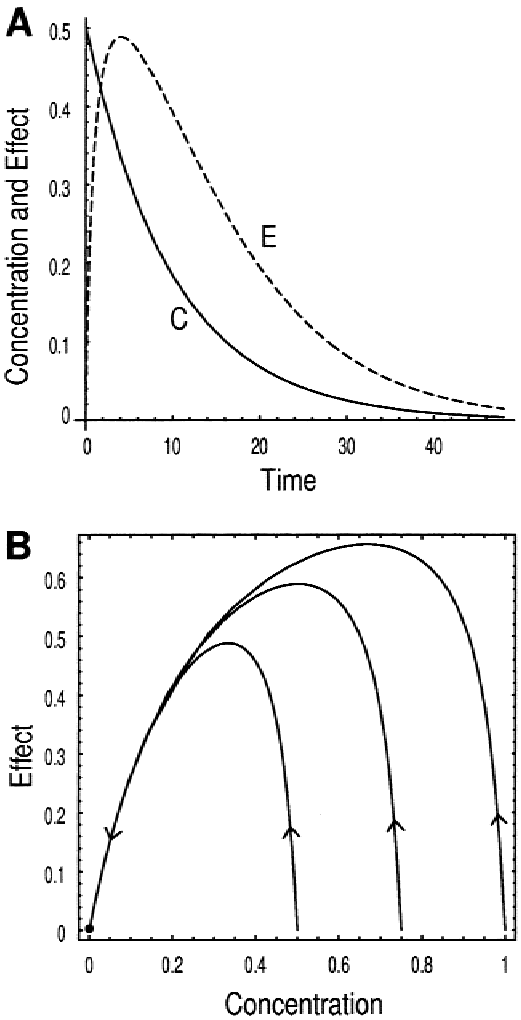

Fig. 3. (B) A typical example of a two dimensional phase space plot is the Concentration (C) over Effect (E) counter clockwise hysteresis loop plot, which is used in pharmacokinetics/pharmacodynamics. Here the two variables, C and E, are used to construct the phase space of a system of a one compartment indirect link model with bolus intravenous injection. The arrow indicates the time flow. Each point represents a uniquely defined state and only one trajectory may pass from it. The phase space has a point attractor, i.e., a steady state, which is obviously the point ($C = 0$, $E = 0$) reached at theoretically infinite time. Three different initial conditions of the form (C = dose, $E = 0$), are used to generate three different trajectories which all end up to the point attractor. The integrated equations of the system are

$$C = \frac{D}{V} \cdot e^{-k_{10}t},\ E = \frac{D \cdot E_{\max}\,(e^{-k_{10}t} - e^{-k_E t})}{C_{E_{50}} V(k_{10} - k_E) + D(e^{-k_{10}t} - e^{-k_E t})}$$

where $D = 0.5$, 0.75, and 1 (from left to right) are the doses, $V = 1$ is the volume of distribution, $k_{10} = 0.1$ is the elimination rate constant, $k_E = 0.5$ is the effect site dissipation rate constant, $E_{max} = 1$ is the maximum effect, and $C_{E_{50}} = 0.7$ is the concentration at which the 50% of the maximum effect is observed (all units are arbitrary). (A) The classical time profiles of the two variables, C and E,for D = 0.5, are shown.

successive bifurcations is universally constant, namely $\delta = 4.66$, not only for this specific system, but for all systems of this kind and it is referred to as *Feigenbaum constant* (1).

The period doubling sequence continues asymptotically as a approaches a critical point around $a = 3.6$, where the period goes to infinity. So, for $a > 3.6$ there exist infinite unstable steady states of period 1, 2, 4, 8, . . . and no stable steady states (Fig. 5). This means that almost any initial condition leads to a non periodic trajectory which looks random (Fig. 4D). This behavior is called *chaotic.*

So, apart from the regular behavior, which is either steady state, periodic, or quasiperiodic behavior (trajectory on a torus, Fig. 2), some dynamical systems, exhibit chaotic behavior, i.e., trajectories follow complicated non-periodic patterns that resemble randomness. Necessary but not sufficient conditions in order for chaotic behavior to take place in a system described by differential equations, is that it must have dimension at least 3, and it must contain nonlinear terms. However, it is not certain for three nonlinear differential equations to exhibit chaotic behavior. This kind of behavior may not take place at all, and when it does, it usually occurs only for a specific range of the system's control parameters.

The main characteristic of chaotic behavior is the *sensitivity to initial conditions.* This means that nearby trajectories, whose initial conditions are slightly different, follow completely different evolution in time (Fig. 4D). This property has the implication of nonpredictability of the time evolution of the system in the long run due to our inability to know the initial conditions with infinite accuracy. The deviation of two initially neighboring trajectories increases exponentially with time i.e. proportional to $exp(\lambda t)$, where the exponent λ is called *Lyapunov exponent* (1). The Lyapunov exponent is an indicator of the chaotic behavior of the system. A dynamical system has the same number of Lyapunov exponents as its dimension. The Lyapunov exponents express the deviation of initially nearby trajectories in each "direction." So, a Lyapunov exponent may be negative for a stable "direction," which expresses the exponential approach of two nearby trajectories, zero for a nonexponential deviation and positive for exponential deviation. A system of high dimension may have Lyapunov exponents of all signs and is considered chaotic if at least one of them is positive, which states that at least in one "direction" there exists sensitivity to the initial conditions.

Because chaotic systems may have both negative and positive Lyapunov exponents, their asymptotic behavior can be limited in an attractor as well, where the negative exponents express the convergence to the attractor and the positive the exponential divergence (chaotic behavior) within the attractor. These chaotic attractors are not elementary topological entities with integer dimensions, like a point, a circle or a torus. Instead they have a *fractal dimension,* which defines an extremely complicated object of infinite detail, being confined though in a finite space. This kind of attractor is called a *strange attractor* (1), and the integer dimension of the entire phase space in which the attractor lives, is called *embedding dimension* of the attractor (Fig 6A). The two concepts of the exponential divergence of initially neighboring trajectories and the confinement in a compact space, look controversial. However, the fractal structure of the strange attractor makes their coexistence feasible.

The concepts of nonlinear dynamics do not only apply in abstract mathematical systems that are described by maps or differential equations. Useful results can be obtained for real life data as well. Real life data, like biological signals, are usually time series of measured quantities. Instead of studying a time series statistically the idea is to consider it as if it came out of a dynamical system. Then, one tries to reconstruct its

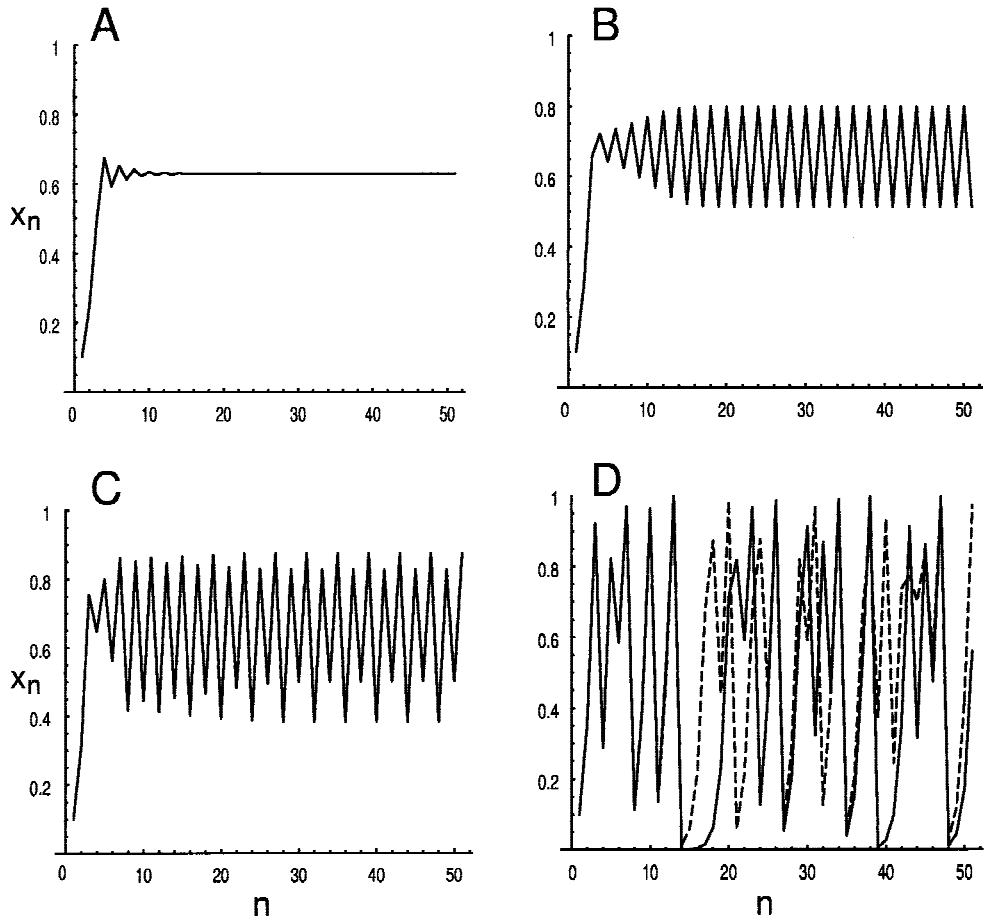

Fig. 4. The logistic map, for various values of the parameter *a.* (A) a steady state of period 1 for $a = 2.7$; (B) a steady state of period 2 for $a = 3.2$; (C) a steady state of period 4 for $a = 3.5$; (D) Two chaotic trajectories for $a = 4$ are coplotted. Only the initial conditions of the two trajectories differ slightly. For the solid line the initial condition is $\chi = 0.1$, whereas for the dashed line it is $\chi = 0.10001$. Although the difference is extremely small, the effect is not at all negligible. The orbits follow an indistinguishable route only for the first 10 steps. Right after, they deviate dramatically. Thus, the sensitivity from the initial conditions, together with its main consequence of long term unpredictability, are exhibited. The initial condition for all solid line plots (A to D) is $\chi = 0.1$.

phase space (pseudophase space) and see if any structure is detectable, either visually or using certain mathematical and numerical tools. The absence of any structure in the phase space, that is scattered points, means that it is not a real phase space and the system is stochastic (Fig. 1C). However, the presence of structure is an evidence of the dynamical origin of the time series and the existence of an attractor (Fig. 1D). The dimension of the attractor can give us information for the dynamical behavior of the whole system. If, for example the dimension of the attractor is not an integer, it corresponds to a strange attractor and the system exhibits chaotic behavior. The embedding dimension of the attractor, which is actually the dimension of the reconstructed phase space and in the case of a strange attractor should be the next greater integer of the fractional dimension, gives the least number of independent variables, or quantities, needed to describe the system.

The phase space reconstruction of a time series is accomplished by the method of delays. An embedding dimension N is chosen, plus a time delay τ, and then the phase space is constructed using as variables $\chi(t)$, $\chi(t + \tau), \ldots, \chi(t + (N - 1)\tau)$, for all t (Fig. 6). It is evident that the choice of N and τ is crucial for the reconstruction. There are certain theorems and tests that help in the proper choice of these parameters, but also experience and trial are always valuable tools. It must be mentioned though that due to the automated character of the algorithms, the danger of misleading results always exists. During the past years an overuse of these techniques was noticed and many of the results obtained by this rationale were either wrong or led to erroneous conclusions due to poor application of the techniques and algorithms.

The estimation of the dimensionality of a time series, which comes out as a result from the phase space reconstruction procedure, is important information for the prospect mathematical modeling of the system. A key factor in the mathematical modeling is parameter estimation. One usually needs to fit the established mathematical model to experimental data in order to estimate the control parameters of the system both for simulation and comparative purposes. However, a task so common in a classical system is quite difficult in a chaotic one. The sensitivity of the system's behavior from the initial conditions and the control parameters, makes it

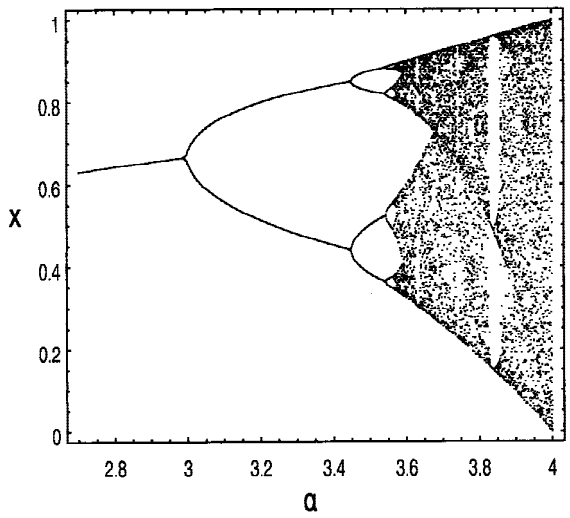

Fig. 5. The bifurcation diagram of the logistic map. The stable steady state of χ as a function of the parameter a is plotted. Below $a = 3$ the steady state is of period 1 and then following the Feigenbaum sequence, the period doubles repeatedly and goes to infinity as a approaches the critical point $a \cong 3.6$. This type of bifurcation is referred to as pitchfork due to the shape of this plot. Above $a = 3.6$ all steady states are unstable and the system is chaotic.

very hard to assess the parameters using tools such as least square fitting, however efforts have been made to deal with this problem (3).

APPLICATIONS OF NONLINEAR DYNAMICS RELEVANT TO DRUG RESEARCH

Biopharmaceutics–Pharmacokinetics

Pharmacokinetic (PK) studies are in general less variable than pharmacodynamic (PD) studies (4). This is so since simpler dynamics are associated with pharmacokinetic processes. According to van Rossum and de Bie (5), the phase space of a pharmacokinetic system is dominated by a point attractor since the drug leaves the body, i.e., the plasma drug concentration tends to zero. Even when the system is as simple as that, tools from dynamical systems theory are still useful. When a system has only one variable a plot referred to as *phase plane* can be used to study its behavior. The phase plane is constructed by plotting the variable against its derivative. The most classical, quoted even in textbooks, phase plane is the *dC/dt vs. C* plot of the ubiquitous Michaelis–Menten kinetics (Fig. 7). In the pharmaceutical literature the phase plane plot has been used for the discernment of absorption kinetics and the estimation of the elimination rate constant (6,7).

To the best of our knowledge, only one model exhibiting chaotic behavior has been published in the pharmaceutical literature (8,9). This is the population growth model of dissolution, which is based on a recursion equation and was used to describe both classical and supersaturated dissolution profiles. This model, for specific ranges of values of the control parameters can exhibit chaotic behavior which mimics adequately the supersaturated dissolution profiles.

Another topic in which there is a potential use of dynamical systems theory is the analysis of variability encountered in PK studies with highly variable orally administered formulations (10). For example, the dissolution of a sparingly soluble drug takes place in the continuously changing environment of the gastrointestinal (GI) lumen (11). Because of the interactive character of the three principal physiological variables that affect drug dissolution i.e., the motility of intestines, the composition, and volume of GI contents, a dynamical system of low dimension can be envisaged. If this is a valid hypothesis a significant portion of the high variability encountered in the GI absorption studies (10) can be associated with the dynamics of the physiological variables controlling drug dissolution, transit and uptake. However, the inaccessibility of the region and thus the difficulty to obtain detailed information for the variables of interest, impose one to infer that the observed variability (10) originates exclusively from classical randomicity. Finally, the heterogeneous dynamical picture of the GI tract becomes even more complicated, by the coexistence of either locally or centrally driven feedback mechanisms e.g., avitriptan (12). Experimental observations indicate (12) that when avitriptan blood levels exceed a certain threshold level, a centrally driven feedback mechanism which affects gastric emptying is initiated. Consequently, the presence or absence of double or multiple peaks of avitriptan blood levels is associated with the dynamical system describing the dissolution, uptake of drug as well as the feedback mechanism controlling the functioning of the pylorus. It can be concluded that the use of nonlinear dynamics in GI absorption studies can provide a tool for the interpretation of variability and the understanding of unpredictability in situations where single, double or multiple peaks are observed and classical explanations, e.g., enterohepatic cycling, are not applicable.

Ligand–Receptor Interaction

Pharmacodynamics traditionally has been based on the mass action law which governs the drug-receptor interaction. This consideration leads to the classical E_{max} model, which is used routinely in most PD studies. However, deviations from this behavior can be anticipated when an endogenous substance e.g., a hormone or a neurotransmitter, is considered and a feedback mechanism, induced by the formation of a ligand–receptor complex, operates to maintain a basal ligand value. Indeed, Tallarida (13) has analyzed such a system using techniques of nonlinear dynamics and has shown that this system can be either dynamically stable or unstable, depending on the values of the parameters involved. These theoretical results were confirmed experimentally in a quantitative study of the control of dopamine release by negative feedback in the rat striatum (14). A consequence of this model is that competitive antagonists augment dopamine release, whereas competing agonists reduce such release. A new quantitative concept that describes the feedback control of the dopaminergic system is introduced, the control curve. Once known, the ligand's control curve has predictive value that may be useful in the design of efficient drug tests. These findings may be of a more general importance because baseline parameters are crucial in determining PD responses (15) whereas feedback mechanisms are frequently involved in the physiological processes e.g., the secretion of hormones, the recurrent inhibitory pathway for γ-aminobutyric acid (GABA) in the hippocampus, which has been described in almost every type of

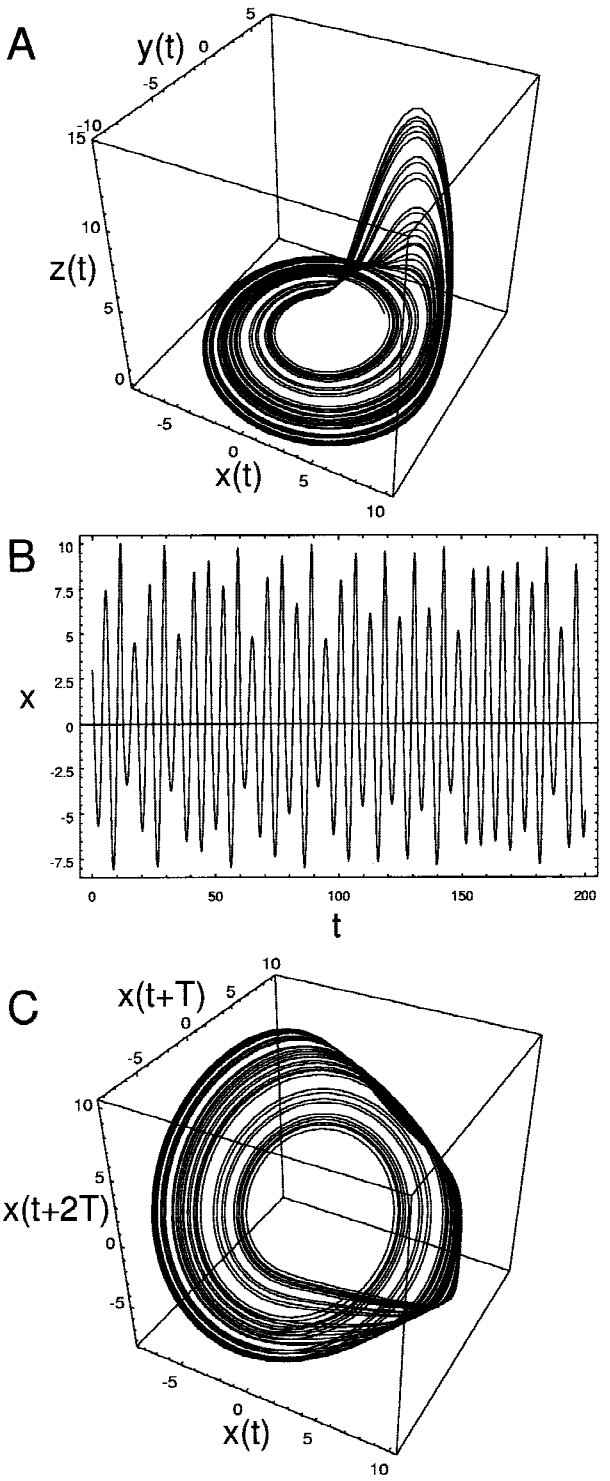

Fig. 6. (A) the Rossler strange attractor (1). The system is $d\chi/dt = -y - z$, $dy/dt = \chi + 0.2y$, $dz/dt = 0.4 + \chi z - 5.7z$, with initial conditions $\chi(0) = 3$, $y(0) = 3$, $z(0) = 0$. The single trajectory plotted, never passes from the same point a second time without however leaving a compact volume, thus forming a fractal object of infinite detail (fractal dimension $\cong 2.07$). (B) the χ variable of the same trajectory is plotted as a function of time, exhibiting its obvious nonperiodicity. (C) the Rossler attractor is reconstructed with the method of delays, making use only of the data from the χ variable, as it would be if χ was an observable quantity and nothing more of the underlying dynamics was known. Of course, here the dimension of the system is also known and one does not have to try other dimension values. Every value of $\chi(t)$ is plotted against $\chi(t + T)$ and $\chi(t + 2T)$ with lag time $T = 1$. The reconstructed phase space is not identical to the original one, however, the main topology and features are depicted adequately.

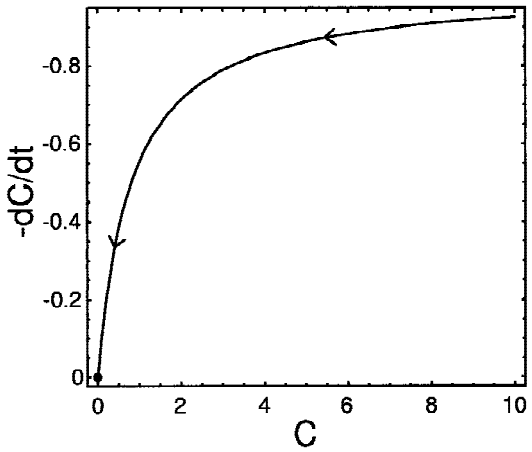

Fig. 7. A $-dC/dt$ *vs* C plot of a one compartment model with bolus i.v. input and Michaelis–Menten elimination. The arrows indicate the time flow. This widely used type of plot is actually a phase plane plot. Michaelis–Menten kinetics is the first thing that comes in the mind of a pharmaceutical scientist regarding nonlinear differential equations. This type of non-linear differential equations, however, are associated with regular behavior in every day experience. Indeed, the fact that they are usually used in systems of a single variable, takes chaotic behavior out of the question. But even if one uses three or more coupled differential equations, including nonlinear terms of any type, chaotic behavior is not guaranteed. The behavior of a system may still be regular in the region of the control parameters that there is interest in, or even in the whole region of control parameters space.

neural tissue, ranging from the lowest invertebrates through humans (16), and the production of biotech products in humans (17). As a matter of fact, the state of the art in PK/PD studies relies heavily on the concept of indirect response (15), which is based on our ignorance of the detailed nature of drug–receptor interaction in the biophase and in particular, of the "post-receptor events" (4) after the formation of drug-receptor complex. Recent research on the signaling between receptors (18) indicates that the "response" can be, in several cases, much more complex than it is supposed in PK/PD models.

In the next paragraphs three major fields of physiological systems with great importance in pharmacotherapy, namely cardiovascular, central nervous, and endocrine systems, and where tools and concepts from nonlinear dynamics have been applied, will be discussed.

Cardiovascular System

Numerous applications of nonlinear dynamics and chaos theory to cardiac physiology have been published (19). Many techniques, either statistical (like spectral analysis) or dynamical (like phase space reconstruction) applied to electrocardiogram (ECG) data clearly indicate that the frequency of the heartbeat is essentially irregular. The ECG was in fact, one of the first biological signals studied with the tools of nonlinear dynamics. Studies applying concepts from chaos theory to ECG data, regarding the effects of drugs on the dynamics of cardiac physiology, have also been published.

Examples include the effect of atropine on cardiac interbeat intervals (20), the induction of cellular chaos during quinidine toxicity (21), the attempt to control cardiac chaos using ouabain (22), and the effect of anticholinergic drugs on heart rate variability (23).

Another very successful application of nonlinear dynamics to the heart is through mathematical modeling. An example in which a simple model based on coupled oscillators describes the dynamics of agonist induced vasomotion is in the work of de Brouwer *et al.* (24), where the route to chaos in the presence of verapamil, a class IV antiarrhythmic drug, is studied.

Undoubtedly, the most promising modeling of the cardiac dynamics is associated with the study of the spatial evolution of the cardiac electrical activity. The cardiac tissue is considered to be an excitable medium of which the electrical activity is described both in time and space by reaction–diffusion partial differential equations (25). This kind of system is able to produce, spiral waves, which are the precursors of chaotic behavior. This consideration explains the transition from normal heart rate to tachycardia, which corresponds to the appearance of spiral waves, and the following transition to fibrillation, which corresponds to the chaotic regime after the breaking up of the spiral waves (Fig. 8). The transition from the spiral waves to chaos is often characterized as electrical turbulence due to its resemblance to the equivalent hydrodynamic phenomenon. These concepts have been successfully applied to the effect of antiarrhythmic drugs as well. It is widely known that although class II antiarrhythmic drugs, like isoproterenole, have shown satisfactory results (26), class I and III agents, such as encainide, flecainide, and moricizine, have been shown even to increase sudden death rate caused by ventricular fibrillation (27). Although it is unclear how to integrate the drug action in the excitable media models, successful attempts have been made to simulate, mainly, two-dimensional cardiac tissue (28,29). Also three-dimensional (3D) cardiac tissue has been simulated as well (30), where the 3D equivalent of spiral waves appear, the scroll waves. These models explain how a drug can exhibit antiarrhythmic action in a single cell system, which ignores the spatial evolution, while acting as proarrythmic in a system of a whole cardiac tissue of spatial dimension 2 or 3. This has given rise to a new approach to antiarrhythmic drug evaluation based on the chaotic dynamics of the transition from tachycardia to fibrillation (29–31), which is also supported by experimental evidence (30). The results of these recent studies (31) indicate that the failure to predict long-term efficacy of classs I and III antiarrhythmic agents in patients with ischemic heart disease (27) may be associated with the limitations of the classical approach which is based only on the suppression of premature ventricular polarization on the electrocardiogram i.e., the initiation of tachycardia. Sudden cardiac death resulting from ventricular fibrillation, however, is separated into two components: initiation of tachycardia and degeneration of tachycardia to fibrillation. It is proposed by these studies that a new antiarrhythmic drug classification scheme must be adopted which should incorporate the antifibrillatory profile based on results from excitable media modeling, together with the classical antitachycardiac profile (classes I to IV scheme). Also, the drug bretylium is proposed as a prototype for future development of antifibrillatory agents (30).

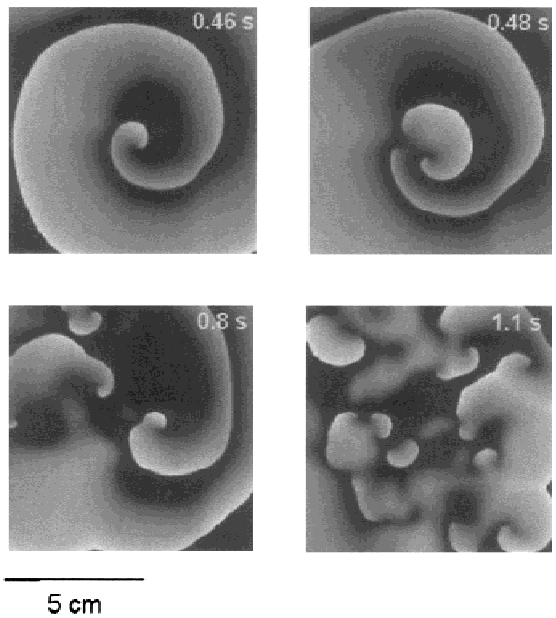

Fig. 8. The four snapshots show the evolution and break up of a spiral wave pattern in 2D simulated cardiac tissue (300 × 300 cells). The chaotic regime shown in the final snapshot, corresponds to fibrillation. [From (31) with permission.]

In the pharmaceutical literature (32), the pharmacodynamics of antiarrhythmic drugs are treated with the classical models, E_{max}, indirect link with effect compartment, etc. Variability, wrong dosage scheme, narrow therapeutic index and lack of individualization of treatment are the dominant interpretations for the failure of these drugs. Another factor held responsible for the failure in treatment with antiarrhythmics is the possible non-bioequivalency of the generics used (33). However, classical bioequivalence studies, are based only on the comparison of pharmacokinetic parameters of the formulations (C_{max}, area under the curve [AUC]); although testing for therapeutic equivalence is implied, pharmacodynamics are not taken into account at all. Thus, classical bioequivalence studies may be inappropriate to assess the effects of antiarrhythmic drugs if their mechanism of action relies on a nonlinear dynamical system as the studies of the UCLA team (29–31) indicate.

Central Nervous System (CNS)

The application of non-linear dynamics to brain electrical activity offers new information about the dynamics of the underlying neuronal networks and formulated the brain disorders on the basis of qualitatively different dynamics (34). Once again, most of studies in this field applying non-linear tools are based on experimental electroencephalogram (EEG) recordings and demonstrate the irregular behavior of the brain electrical activity. Various metrics have been used to assess the EEG variability, using phase space reconstruction techniques or even calculating the fractality of the EEG recording in real time (35). These tools, apart from pointing out the obvious complexity of the brain electrical signals, offer supplemental information to the classical techniques, such as Fourier analysis, to distinguish qualitatively different EEG recordings, e.g., in epileptic seizures (36), in Parkinson's disease (37), or in schizophrenia (38). In the same context, low doses of ethanol have been found to reduce the non-linear structure of brain activity (39). Most of the PK/PD studies of

centrally acting drugs rely on quantitative measures of EEG parameters (40). However, an ideal EEG parameter to characterize the CNS effect of drugs has not been found as yet. To the best of our knowledge, time series analysis of EEG data of PD studies with CNS drugs using techniques of non-linear dynamics are limited. Examples include investigations of the influence of anticonvulsive (41) and antiepileptic (42) drugs in epilepsy, the study of sleep EEG under lorazepam medication (43), the study of the effects of pregnenolone sulfate and ethylestrenol on rat behavior (44), the investigation of the electrophysiological effects of the neurotoxin 5,7-dihydroxytryptamine (45), and the study of epileptiform bursts in rats after administration of penicillin and K^+ ions (46).

Modeling in the brain is targeted mainly to the general qualitative principles underlying the various phenomena, such as epileptic seizures (47) and not of course to quantitative assessment and forecasting as one would expect to achieve in simpler systems. For example in (16), modeling recurrent inhibition and epilepsy, is studied and also penicillin is considered, as a GABA inhibitor.

The analysis of brain activity using tools from chaos theory can provide important information with regard to the underlying dynamics if one takes into consideration that the qualitative EEG changes, induced by centrally acting drugs e.g., ketamine, thiopental, etomidate, propofol, fentanil, alfentanil, sulfentanil, and benzodiazepines differ considerably (40). This exercise can also unmask the sources of extremely high variability (the coefficient of variation for model PD parameters of benzodiazepines in humans ranges from 30 to 100%) (40). A plausible interpretation for the extremely high variability of PD parameters of benzodiazepines may be associated with the dynamical behavior of the underlying system i.e., the recurrent inhibitory pathway of GABA (16).

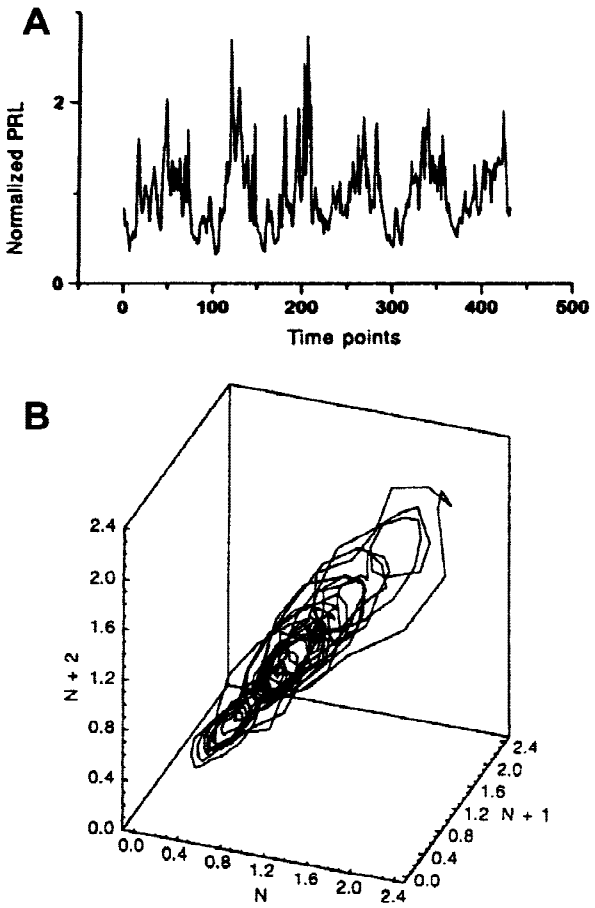

Fig. 9. (A) A composite prolactin time series that consists of six individual 24-hour profiles making a total of 432 data points. (B) Sketch of the 3D attractor of prolactin generated by the data of plot A. The dimension of the attractor was found to be fractional, namely $D_0 = 1.66$, indicating that diurnal prolactin secretion is governed by nonlinear dynamics. [From (50) with permission.]

Endocrine System

It is widely appreciated that hormone secretion is characterized by pulsatility. The first experimental studies of the pulsatile nature of hormone secretion started more than thirty years ago. Hellman *et al.* reported in 1970 (48) that "Cortisol is secreted episodically by normal man." It was also realized that this pulsatility was not due to noise, but was actually associated with physiological processes. Indeed, the circadian clock, the interaction between hormones through feedback mechanisms, and the interaction of hormones with central and autonomic nervous systems are some of the reasons for this behavior. It has been apparent that the theory of dynamical systems is the right field to find useful tools for the study of hormonal systems. This has been done in two directions: experimental studies using tools from time series analysis and modeling with differential equations.

Experimental studies of hormonal systems utilizing tools from nonlinear dynamical systems theory started in the nineties. The phase space reconstuction approach, making use only of the hormone's plasma profiles, was utilized to assess the dimensionality and expose the chaotic nature of the underlying dynamics of various hormones. Such examples are, the work of Prank *et al.* (49) on parathyroid hormone, Papavasiliou *et al.* (50) on prolactin (Fig. 9), and Ilias *et al.* (51) on cortisol and growth hormone. In all the above studies, the reconstruction of the phase space gave attractors of fractal dimension showing evidence for the presence of nonlinear dynamics. Also, Pincus developed in 1991 a different method to quantify the hormone pulsatility, which is referred to as Approximate Entropy algorithm (ApEn) (52) and is based on the concept of Lyapunov exponents. This method has been applied for several hormones such as adrenocorticotropic hormone (ACTH), cortisol, prolactin, insulin, growth hormone (GH), testosterone and luteinizing hormone (LH), quantifying the observed pulsatility, and comparing it between different groups, such as sick against healthy, different age groups, etc. [(53) and references therein]. The experimental evidence of the chaotic nature of hormonal underlying dynamics clarify the origin of the pulsatility and act as a guide for proper modeling.

Smith in 1980 (54) used a mathematical model of three interacting hormones, namely testosterone, LH, and LH-releasing hormone, to describe qualitatively their behavior. The initial model was improved later by Cartwright and Husain (55), who introduced time-retarded terms of the three variables to make the system more realistic, exhibiting limit cycle solutions. Further improvements of the model were studied by Bing-Zheng and Gou-Min (56) and also by Das *et al.* (57). Apart from testosterone other efforts in the same

context have been made to model the secretion of hormones. Examples are the work of Lenbury and Pacheenburawana (58) in the system of cortisol, ACTH and corticotrophin-releasing hormone (CRF), the work of Topp *et al.* in the system of β-cell mass, insulin, and glucose (59) and also the work of Londergan and Peacock-Lopez (60). The latter is a general model of hormone interaction description with negative feedback, exhibiting very rich dynamics, even chaotic behavior.

Many drugs affect the normal hormonal secretion, either as their primary target of action or as a side effect. Many studies in the last years have considered models of hormonal secretion together with the dominant PK/PD concepts of drug action. Examples include the effect of corticosteroids on cortisol by Chakraborty *et al.* (61); the effect of the gonadotropin-releasing hormone antagonist on testosterone and LH by Fattinger *et al.* (62); the effect of the dopaminomimetic drug DCN 203-922 on prolactin by Francheteau *et al.* (63); the effect of the calcimimetic agent R-568 on parathyroid hormone by Lalonde *et al.* (64); and the effect of ipamorelin on GH by Gobburu *et al.* (65). All the above studies share a common element. The hormone secretion modeling is kept to the minimum, usually consisting of a single differential equation or even an algebraic equation that gives a simple smooth hormone baseline. Then, the PK/PD models like direct or indirect link and response (66), relate the inhibition or the stimulation of the baseline, with the drug concentration. In order to set the baseline, only the most obvious characteristics of the hormone profile are integrated, like a periodic circadian rhythm. The dynamical structure of the underlying physiology is practically ignored and so is pulsatility which is considered to be noise. The only studies, that pulsatility is considered as a feature of the profile, are the works of Francheteau *et al.* (63) for the effect of dopaminomimetic drug DCN 203-922 on prolactin and Chakraborty *et al.* (61) for the effect of fluticasone propionate on cortisol. However, even in these studies the pulsatility is integrated phenomenologically through spline terms or Fourier harmonics, respectively, and not through modeling of the dynamical origin of the pulsatility. It must be noted though that there are studies where the pulsatility does not play an important role, like in the study of Gobburu *et al.* (65) for the effect of ipamorelin on growth hormone, where the baseline of the hormone is reasonably considered zero due to the multifold amplification of the GH levels after the administration of the drug.

From the above presentation, it is evident that although significant progress has been made as far as the physiological modeling of hormonal systems is concerned, the relevant pharmacodynamic modeling, even in state of the art studies dealing with the effect of drugs on hormonal levels, practically ignores these findings. It is a necessity to develop new pharmacodynamic models for drugs related to hormonal secretion, compatible with the physiological modeling and the experimental findings that suggest low dimensional nonlinear dynamical behavior. This kind of modeling not only is it more realistic but integrates a new rationale as well. The notions of the sensitivity from the initial conditions and the qualitatively different behavior for different, even slightly, values of the control parameters, surely play an important role and must be taken into account in modeling since their presence is suggested by experiments.

EPILOGUE

The application of nonlinear dynamics in physiological systems proposes a new basis in the way certain pathological phenomena emerge. The main characteristic is that a pathological symptom is considered as a sudden qualitative change in the temporal pattern of an illness, i.e., a bifurcation takes place. This change can either be caused by endogenous factors or by an exterior stimulus that changes one or more critical control parameters. According to this rationale, therapeutic strategies should aim to invert the progress of the disease and restore normal physiological conditions by interfering with the control parameters. This is in contrast to the classical approach where the effort is focused in eliminating the symptoms with a linear rationale which relates the therapeutic stimulus with the effect through a proportionality. This is a general concept also referred to as *dynamic disease,* a term introduced by Mackey and Milton (2,67).

It is widely appreciated that chaotic behavior dominates physiological systems. Moreover, periodic or other non-chaotic states are considered pathological, whereas the chaotic behavior is considered to be the normal, healthy state. The reason of this has to be associated with a fundamental advantage of nonlinear systems over classical. Indeed, it is considered that the main characteristic of nonlinear dynamical systems, which is the different qualitative behavior for small variations of the control parameters may offer finer, more rapid, and more energy efficient controllability of the system compared to linear systems (68). This may be the reason why nature prefers chaos than regularity and of course the latter is a good enough reason for applied biological sciences such as pharmacodynamics to adopt this rationale in greater extent. We hope that this review article contributes to this direction, however it must be pointed out that it must not be considered exhaustive since pharmacodynamics are also strongly related to other systems where nonlinear dynamics are present, e.g., biochemical and immunological systems.

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