

CHAOS IN BIOLOGY

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Abstract

This paper presents a brief and pedagogical account of the relevance of chaos theory in biology. A few caveats to avoid misleading interpretations are underlined, for instance the required determinism and stationarity of the experimental time series. The selective advantage offered by a properly controlled chaotic dynamics is discussed on the examples of cardiac rhythm and brain dynamics.

1 Summary

Thirty years after the historical paper of May [1976] evidencing chaotic behaviors in a simple model of population dynamics, we present a brief and pedagogical account of the relevance of chaos theory in biology. We first raise simple but nevertheless essential caveats to avoid over-interpretation or even misleading conclusions. Mainly, before implementing any algorithm to estimate quantitative indices of chaos, one has to check that the dynamics is essentially deterministic and low-dimensional, and restrict to a time window where it is statistically stationary. We bring out the possible motivations for chaotic feature investigations in a biological context. We argue on two examples (cardiac rhythm, neural and brain dynamics) that a properly controlled chaotic dynamics offers a selective advantage. This explains the numerous observations of chaotic features in biological systems, but also the observed discrepancies from a pure chaotic dynamics, that are associated with their regulation.

Keywords : Chaos, determinism, reconstruction, cardiac rhythm, brain dynamics.

2 Introduction : primary observations

A step in the history of chaos theory has been the publication in 1976, by the physicist and ecologist Robert M. May, of a paper entitled ‘*Simple mathematical models with very complicated dynamics*’. This paper, probably one of the most cited as soon as one deals with chaos, presents a very simple model, being on purpose the most simple that one can devise to describe the dynamics of an insect population given the following minimal ingredients, May [1976] :

- generations do not overlap (that is, adults die before the eggs hatch);
 - adults reproduce with a rate $a > 0$;
 - resource limitation induces population saturation at a maximal value K ,
- that yields the following discrete-time evolution law :

$$X_{n+1} = aX_n \left(1 - \frac{X_n}{K} \right) \quad (1)$$

for the number X_n of individuals in the n -th generation. Introducing the relative population $x = X/K$ turns the evolution law into the following dimensionless form :

$$x_{n+1} = ax_n(1 - x_n) \quad (2)$$

This model is called the *logistic map*, in reference to the *logistic equation* $dz/dt = az(1 - z)$ proposed by Pierre-François Verhulst in 1846, accounting in the term $1 - z$ for the limited space (“*logis*” in french) constraint experienced by the population, turning the growth rate a into an effective rate $a(1 - z)$. But it is to be underlined that this continuous-time equation essentially differs from the discrete-time model introduced by May, and generates only a trivial behavior of convergence towards a stable fixed point $z^* = 1$ as soon as $z(t = 0) > 0$, Krivine et al. [2007]. Values $a < 0$ and $a > 4$ of the parameter are excluded because they lead to relative population values x lying outside the relevant interval $[0, 1]$. May thus studied (2) for $0 \leq a \leq 4$ and brought out an unsuspected wealth of different behaviors, among which erratic and long-term unpredictable ones now termed *chaotic*.

This article by May inspired much research work, dealing among other topics with cyclic or chaotic variations in populations of budworms, locusts, lemmings, sardines, or predator-prey systems (species are chosen according to either the occurrence of striking phenomena, like locusts invasions and lemmings “collective suicides”, or the availability of accurate and faithful data over a long period, typically more than a century, provided by the registers of fisheries and skin traders). But chaos studies in biology are not restricted to population dynamics, and other investigated domains are :

- epidemiology of some infectious diseases like measles and flu, Anderson and May [1992];
- cardiac rhythm;
- neurosciences, both at the neuron level (recording the electric activity of a single neuron and the spikes it emits and sends to all neurons connected downwards to its axon) and at the brain level (activity recorded by electroencephalogram);
- metabolism and intra-cellular rhythms, observed on concentrations of some species (for instance glucose, hormones, calcium or potassium ions). They illustrate and extend in vivo the chaotic behaviors observed in some chemical reactions, Goldbeter [1996].

3 Why looking for chaos ?

Beyond fashion and curiosity, what are the motivations for searching for chaos in a phenomenon, especially a biological phenomenon? The relevance of chaos theory comes first from the conceptual and quantitative tools that it offers for analyzing experimental time series, the main ones being phase space reconstruction from a one-dimensional signal, the computation of Lyapounov exponents that quantify the sensitivity to initial conditions, and the determination of the attractors and their dimension. Experimental data of interest are obtained by recording along the time the values of a few observables, for instance concentration of chemical species, population numbers, or electric signals by means of properly placed electrodes (electrocardiogram, electroencephalogram, or single neuron activity).

Looking for chaos in cardiac rhythm, brain or population dynamics has also the merit of replacing the study of such systems within the framework of *non linear dynamics*, where the adjective “non linear” contrasts it with the linear statistical methods based on the signal representation as a *linear superposition* of parameterized evolution laws (possibly stochastic processes), of standardized types, whose parameters and coefficients are estimated from the data. Such a linear representation often provides a very good and efficient fit of the data; it has in some case a good predictive value, but no explanatory value since it does not point at the actual underlying mechanisms, nor a regulatory value since it is not able to evidence control parameters of the observed behavior. Nonlinear dynamics viewpoint, on the contrary, considers the observed behavior as resulting from *coupled* dynamic processes. Established observation of chaos in a phenomenon reveals the presence of strong nonlinearities, mixing mechanisms and more technically specific phase space structure exhibiting in any point stable and unstable directions, originating from the coupling of a small number of essential degrees of freedom. Identification of chaos thus provides most useful informations to understand the origin of the observed dynamic behavior and to model them. Taking together data analysis and modeling, we bring out three objectives motivating to investigate the nature of the dynamics in biological systems, in particular their chaotic features if any :

- the *classification* of systems on the basis of their dynamic behavior, for *diagnosis*;
- the possible *predictions* about the system dynamics, for *prognosis*;

— the *explanation* of observed behavior, for *therapeutic purposes*.

4 How to evidence chaos from experimental data ?

In order to evidence chaotic behavior in a phenomenon, whether biological or not, two ways can be traveled. The first one is a direct analysis of experimental data, jointly with the development of algorithms for computing significant indices quantifying the dynamics features, Abarbanel [1996], Faure and Korn [2001]. The second one is the design, from the data, of models aiming at accounting for the essential mechanisms at work in the real system and explaining its leading behavior. The study then focuses on the model in order to unravel the possible behaviors, evidence the control parameters (and thus suggest therapeutic targets), investigate the robustness of the dynamics with respect to perturbations (and thus determine its response and/or adaptation after a change in external conditions), and develop integrative approaches describing collective properties (for instance, linking the neuron dynamics to the brain dynamics, a still largely open issue). The work of May [1976] presented in introduction is a typical example of this second approach, belonging to the field of “mathematical biology”, Murray [2002].

We shall focus on the first approach starting with an essential caveat : the value of a chaotic index, for instance a positive Lyapounov exponent or a non integral dimension for the attractor, cannot, hence *should never, be interpreted as a proof of the chaotic nature of the dynamics*. It provides a signature of chaos only once it is shown that the dynamics is *essentially deterministic and low-dimensional* : a chaotic dynamics, although long-term unpredictable and generating a statistically random trajectory, is perfectly predictable at short terms. In other words, the evolution can be represented over a small time interval Δt by means of a *map* f for a variable x *with only a few components*, explicitly $x_t \rightarrow f(x_t) = x_{t+\Delta t}$. In practice, this condition will be tested, with Δt being the time-step of the recording, by plotting the value x_{n+1} observed at time $t_{n+1} = (n+1)\Delta t$ as a function of x_n : one gets a curve (the graph of f) if the evolution is deterministic, or on the contrary a cloud of points if the evolution is random.

Experimental data are typically a time record $(x_t)_{t \geq 0}$ of a *single* variable :

- the number of individuals in a population at generation t ;
- the number of infected individuals (e.g. with measles) at time t ;
- the concentration of a given chemical species (glucose, hormones, ions, ...) at time t ;
- the time interval between the t -th and $(t+1)$ -th heart beat ;
- the potential between two electrodes in an electroencephalogram ;
- the membrane potential of an axon at time t ;
- the time interval between the t -th and $(t+1)$ -th spike emitted by a neuron.

Time is necessarily discrete in experimental records. Discretization might be intrinsic : non overlapping generations in insect populations, single hence countable events like heart beats and neural spikes ; in this case, discretization does not put a limit on the information available about the system. More often, time discretization is imposed by the experimental protocol : the apparatus should relax to a reference state before being able to perform a new recording ; this imposes a minimal time interval between two successive observations, the longer the larger apparatus inertia is.

An additional difficulty arises : not only we have only a single trajectory at our disposal (the recording performed in the given experimental conditions) but, all the more, we observe only one variable, sometimes a few, but never all those defining the system state (its position in the phase space). In order to test the low-dimensionality condition and show that a small number d of degrees of freedom is enough to explain the observations (otherwise we would leave the domain of chaos to enter that of turbulence), we have to *reconstruct the dynamics and its phase space*. The privileged method to reconstruct a m -dimensional trajectory from a the recorded scalar sequence $(x_n)_{n \geq 1}$ uses *delays* : $X_n^{(m)} = (x_n, x_{n+1}, \dots, x_{n+m-1})$. To obtain a reconstructed dynamics that is topology equivalent to the real one, m should be enough large, at least larger than the number d of essential degrees of freedom. In practice, this number is unknown (one of our aims is precisely to determine it). A method to estimate its value is based on the

following remark : neighboring points in dimension m might no longer be so in dimension $m+1$ (and then termed “false neighbors”). An example is provided by a 8-shaped curve in space, that crosses itself when projected on the plane but whose two branches might remain at a finite distance when considered in the 3-dimensional space ; by contrast nothing changes further when it is considered in a higher-dimensional space. This shows that the *embedding dimension* of a self-avoiding 8-shaped curve is $d = 3$, whereas it reduces to $d = 2$ in case of a self-crossing curve (topologically equivalent to its typical plane projections). In the present case, we shall analyze the sequences $[X_n^{(m)}]_{n \geq 1}$ for increasing values of m and determine the value m^* beyond which the number of neighboring pairs (points at a distance smaller than a given threshold) do not decrease any more. This value m^* provides a lower bound to the searched dimension d (the bound can be strict if the observed sequence is short and finite-size effects prevent from unraveling all the directions, simply because the sample of neighbors is too small). Another criterion is to consider that a suitable value of m is reached once the values of the chaotic indices (topology and dimension of the attractors, Lyapounov exponents, entropy) do not vary any more when m is further increased. In case of a chaotic dynamics, Floris Takens [1981] rigorously proved the condition $m > 2D$, where D is the attractor dimension, for the reconstructed dynamics to be equivalent to the original dynamics.

Another method to discriminate a chaotic dynamics from a random dynamics is to perform a random shuffle of the data (one speaks of *surrogate data*) and to compare the pseudo-evolution thus generated with the observed one, Schreiber and Schmitz [2000]. Such a shuffle preserves the range of the data, their mean, their variance (in fact their whole distribution) but not their temporal structure : any feature associated with deterministic chaos will be lost after the shuffle, whereas all the features of a random evolution will remain unchanged.

The implementation of these methods (and all the other ones inspired by non linear dynamics and chaos theory) is less straightforward than their theoretical principles, in particular because the recorded signal is in general noisy (by side phenomena or experimental noise). Another limitation comes from the finite and often short length of the signal, preventing from a faithful reconstruction since only a small and presumably non representative region of the phase space will be sampled. This limitation is strengthened by the possible non-stationarity of the signal : frequently the statistical features of the system dynamics evolve between the beginning and the end of the recording (we are considering living systems that can be affected by the measurement protocol or withstand experiment only for a limited duration), requiring to restrict the exploited series to finite windows where this drift can be ignored.

More basically, one should keep in mind that the distinction between a chaotic dynamics and a random evolution from the sole knowledge of an experimental time series is a very delicate and sometimes meaningless task : according to the observation scale (the microscope magnification rate), the same phenomenon might appear to be either deterministic and chaotic, or stochastic. A current example is provided by Brownian motion : the Brownian particle dynamics appears deterministic and chaotic at scales $l < \lambda$ where λ is the mean-free-path of the particle surrounded by water molecules ; on the contrary, it appears as a diffusive motion at larger scales. A more abstract example is provided by the series generated by the logistic map $x \rightarrow f(x) = 4x(1 - x)$: it is perceived as a deterministic evolution at the elementary time scale ($\delta t \sim 1$) and if the variable x is observed with enough fine resolution ($\delta x \ll 1$) ; on the contrary, if only the position of x with respect to $1/2$ is recorded, the ensuing binary sequence does not differ in its behavior (nor, more quantitatively, in its statistical properties) from a sequence generated by independent coin tossings. Besides one of the interests of the notion of chaos is to reconcile the appearance of erratic motions with the determinism of the underlying mechanisms.

In tunable experimental settings, a different and faithful test of chaos is to observe a bifurcation (or a sequence of bifurcations) leading to chaos ; in other words, when varying a control parameter a , to observe a regular regime for $a < a_c$ and a chaotic regime for $a > a_c$. Such a clear signature of chaos is for instance provided by the observation of a cascade of period-doubling bifurcations (this cascade is only one of the possible scenarios to chaos but it has the advantage to be unambiguously recognizable, even in noisy systems or in case of noisy measurements).

Let us finally mention a simpler approach to analyze experimental data. The basic step is to reduce the recorded signal to a symbolic sequence, then to analyze it within the framework of information theory developed by Claude Shannon [1948]. Typically, one codes x_t by $\omega_t = 0$ if $x_t \leq x^*$ or by $\omega_t = 1$ if $x_t > x^*$, where x^* is a suitable threshold, chosen by invoking extrinsic arguments and knowledge of the system, or determined as the value that optimizes the robustness of the results; for instance, x^* can be chosen so that $\langle \omega \rangle = 1/2$, or equal to a physiological threshold, or given by $x^* = \langle x_t \rangle$. To cite an example, in studying electric activity of single neurons, one might distinguish short and long inter-spike intervals, exactly as in the Morse alphabet. The ensuing binary sequence is then analyzed, e.g. its entropy is computed, with tools developed to quantify information carried by a coded message or a computer program written in binary code, Badii and Politi [1997].

5 Chaos in the cardiac rhythm.

Several studies inspired by chaos theory have been conducted on the cardiac rhythm observed in electrocardiograms. Results for patients suffering for cardiac diseases were compared with those obtained for healthy patients. The main conclusion (it would of course require more shades) is that healthy cardiac rhythm exhibits a chaotic component whereas very regular rhythms are associated with pathologies.

Explanation originates in the fact that an exactly periodic rhythm would not be robust: the slightest perturbation would disrupt it. What about a chaotic regime? The sensitivity to initial conditions of chaotic dynamics, responsible of their long-term unpredictability, also appears as an exploitable advantage insofar as a minute external input is enough to qualitatively modify the behavior. This remark led to the idea of controlling a chaotic dynamics by means of carefully tuned external perturbations, Garfinkel et al. [1992]. This notion of *control of chaos* is relevant for artificial systems, where the proper servo-control can be determined for instance by learning algorithms. But it might also be relevant as regards biological systems, where the proper regulatory mechanisms might have settled during the course of evolution, by means of natural selection. It seems plausible that cardiac rhythm illustrates this possibility to stabilize a chaotic regime on a roughly periodic trajectory, while keeping at disposal all the richness and sensitivity of the chaotic dynamics as a reservoir of possible solutions to respond to stresses and rapidly adapt to changes in the surroundings.

A decrease of the chaoticity of the cardiac rhythm is thus an alarming clinical signature, pointing at a decreased adaptability and decreased robustness. Estimation of the correlation dimension is besides used as a diagnosis tool in some medical centers. Nevertheless, we here encounter an example of the shades that accompany the notion of chaos in biology: more often, the observed dynamic regimes will be more complicated than pure chaotic dynamics, with many other superimposed features coming from the dynamics regulation.

6 Chaos in neurons and brain?

Some stochasticity is unavoidable in neural system dynamics, due to external inputs (for instance variations in the metabolic fluxes) and to the randomness of the elementary events participating in the propagation of the nerve impulse. Hence, looking for chaos in neural dynamics makes sense only once the question has been more precisely delineated. One can thus investigate whether the activity of a single neuron, reflecting in the spikes it emits, is chaotic; or whether the effective macroscopic dynamics reconstructed from an electroencephalogram exhibits a chaotic component. These two questions have been studied intensively for long, Faure and Korn [2001, 2003].

Data on the electric activity of a neuron are obtained by recording the variations of the membrane potential of its axon. They are then filtered insofar as only the times where the neuron emits a spike (a brief and sharp increase of its membrane potential) are kept. Established chaotic behaviors have been observed for instance in neurons having a pacemaker role, or belonging to well-identified small functional networks, like the 'central pattern generators' involved in some motor activities; intermittent behavior

have also been observed, Faure and Korn [2003]. A first issue is to characterize the dynamics of the neuron, in particular for identification and classification purposes if several different neurons are investigated and the issue without knowing in advance whether they are of the same type or not. A second motivation is to infer the functional role of the neuron and to determine how its activity will influence the behavior of the network in which it is embedded; it opens on the fundamental question of understanding how information is coded and carried by neurons. A third one could be to observe the influence of a drug or a neuro-receptor mutation on the basic activity of neurons, hence to predict and possibly control their overall consequences. It is to note that the length of spike records is bounded by the signal stationarity condition (over a too long duration, the observed neuron will either adapt or suffer damages); since the time discretization is here intrinsic, fixed by the spikes, the number of points exploitable in the analysis is limited, in an inescapable way.

At the level of neural networks, remarkable experiments have been performed in which real neurons have been coupled to artificial electronic ones hence precisely controlled and tunable. It has thus been possible to investigate the modifications experienced by a real neuron as a function of the strength and temporal patterns of the inputs it received from its (here artificial) neighbors. Strikingly, this study has clearly evidenced that the dynamic potentialities of a neuron are strongly modified by its embedding within a network : dynamic regimes (oscillations, spike trains) might be observed whereas they never occur in the isolated neuron. Conversely, the embedding of a neuron in a network (provided suitable conditions on the inwards connections are satisfied) might stabilize an intrinsic irregular behavior. We here encounter a selective advantage of chaos : neurons having a chaotic basic regime bring a great flexibility in the implementation of a functional network since a chaotic neuron can potentially be stabilized in a large number of different regimes, Schiff et al. [1994], Rabinovich and Abarbanel [1998].

Although recording methods look similar, the analysis (in particular as regards the chaotic features) of the electroencephalogram is far more complicated than that of the electrocardiogram. The main reason is the obvious fact that brain, contrary to the heart, is not globally synchronized (such an overall synchronization would be highly pathological, as shown by epilepsy crises following from an instance of partial synchronization). Spatial dimension cannot be ignored, and dynamics a priori depart from the basic notion of deterministic low-dimensional chaos. The high dimension of the recorded signal (coming from an array of about a hundred of electrodes) precludes in practice a plain implementation of reconstruction methods and usual chaos criteria. These caveats have somehow put off the initial enthusiasm, Babloyantz et al. [1985], Skarda and Freeman [1897], and a lot of critical investigations have been conducted to delineate whether chaos is actually at work in brain, in which form, and how it is possible to detect and describe it from experimental data, Rapp [1993], Lehnertz et al. [1999], Kaneko and Tsuda [2001]. Nevertheless, it is possible to show using surrogate data method that deterministic non linear components are present in the electroencephalogram. Conclusions about chaos at the brain level are nevertheless not clear not consensual, moreover weakened by the hypotheses (determinism, stationarity) required by the analysis methods. The issue thus remains largely open and it is actively investigated by several teams.

7 Biological usefulness and exploitation of chaos

The examples of cardiac rhythm and neurons illustrate a more general conclusion : chaos offers both robustness and adaptation properties that provide a functional advantage hence a selective advantage. But in order to take profit of these properties, additional regulatory mechanisms have to settle, that appear as a specificity of living systems. Indeed, a major difference discriminates living systems, able to reproduce and experiencing natural selection from one generation to the other, and physical systems, where the only selection at work is associated with the stability, with respect to perturbations and noise, of equilibria and dynamic regimes. Living systems are thus more apt to explore the whole range of possible behaviors, through a slow adaptive tuning of the parameters controlling their dynamics, and a co-evolution of their sub-systems. Three remarkable properties follow :

- a thorough exploration of the parameter space yielding a larger panel of dynamic regimes and bifur-

cations ;

— a possible stabilization on thresholds, bifurcation points or other non generic situations (even those involving a joint tuning of several control parameters) that is achieved by selected feedbacks and control mechanisms ;

— a possible control of the chaotic regimes. We here mean the approximate and transient stabilization of the dynamics on one of the unstable periodic orbits embedded in any strange attractor, allowed by finely tuned feedbacks and regulatory mechanisms selected and settled during evolution. It is besides better that such a stabilization is only transient so that the system might shift to another regime (think for instance to brain dynamics), fulfill other function, or recover a sensitivity to other stimuli. This possibility to stabilize the system in a roughly periodic regime has the double interest of being very flexible (almost any period can be reached) and of low cost (because the amplitude of the regulatory perturbations to be applied to the original dynamics remains low). It is by contrast very costly in terms of information : biological systems ‘pay this cost’ step after step in the course of evolution, through the selected establishment of feedbacks achieving logical adaptive circuits. In nervous system (or brain in higher organisms), this process can be fulfilled at a far shorter time scale thanks to the learning performances of neural networks.

Furthermore, it should be noted that deterministic chaos is weakened or even suppressed by the presence of noise (random external perturbations). This is due to the fact that noise destroys the remarkable phase space structure associated with a chaotic dynamics : tangle of dilating and contracting directions, fractal structure of strange attractors, dense covering of these attractors with unstable periodic orbits with periods of arbitrary duration. On the other hand, chaotic behavior are robust within classes of deterministic dynamics, and a slight modification of the coupling constants or kinetic rates (as long as no bifurcation point is crossed) will preserve the qualitative features of the dynamics. Chaotic dynamics thus offer a delicate balance of sensitivity and robustness. When completed in the course of evolution by multiple regulation and control mechanisms, chaos endows living systems with an increased adaptability, larger than the adaptability offered by regular dynamics. This might explain the observation of chaos, or rather, chaotic features, in several biological systems.

In conclusion, we underline the following points :

— it is highly delicate to evidence chaos in experimental data, especially biological ones ;
— pure chaotic features, close to the mathematical notion of deterministic chaos, will be observed only at the level of isolated elements, for instance single neurons. At the system level, chaotic features will be partly modified by regulation and controlled mechanisms, settled in the course of evolution, so as to exploit the dynamics robustness and adaptability provided by a chaotic component.

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