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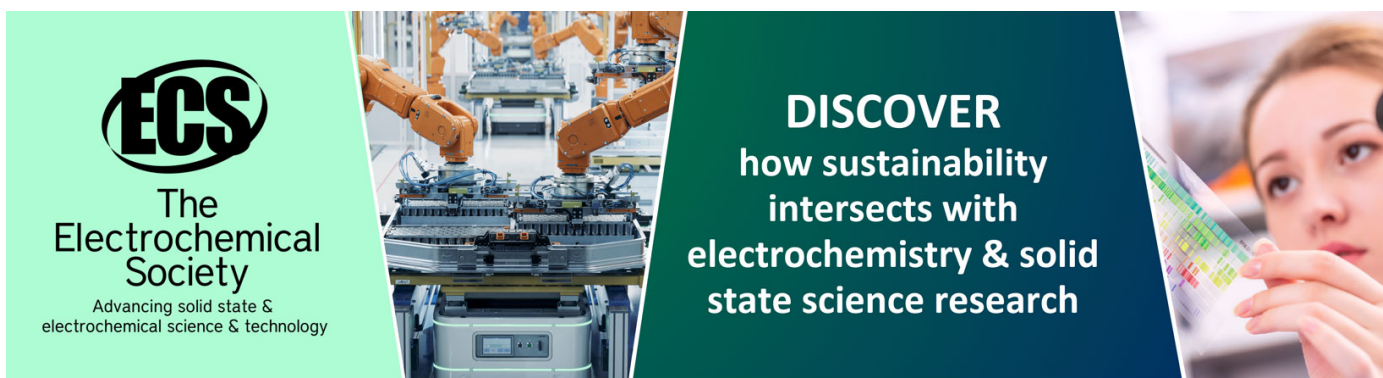
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The Rössler system as a model for chronotherapy

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Abstract. The biological systems are opened and are kept far from thermodynamics equilibrium. For these reasons, biological systems are always exposed to external perturbations, which may produce alterations on these rhythms as a consequence of coupling synchronization of the autonomous oscillator with perturbation. Coupling of therapeutic perturbations, such as drugs and radiation, on biological systems delivery to biological rhythms is known as chronotherapy. We used the Rössler system as a theoretical model for chronotherapy, generalized this formalism for chaotic behaviour. We found that when the Rössler is more dissipative, such as c increase, the systems become more robust to the perturbations.

1. Introduction

Rhythmic processes are common and very important to life: cyclic behaviour is present in heart beating, breath and circadian rhythms [1]. The biological systems are opened and are kept far from equilibrium. For these reasons, biological systems are always exposed to external perturbations, which may produce alterations on these rhythms as a consequence of coupling synchronization of the autonomous oscillator with perturbation. Coupling of therapeutic perturbations, such as drugs and radiation, on biological systems delivery to biological rhythms is known as chronotherapy. Cancer [2, 3], rheumatoid arthritis [4] and asthma [5, 6] are some of the diseases under study in this field because of their relation with circadian cycles. Mathematical models and numerical simulations are necessary to understand the functions of biological rhythms, to comprehend the transition from simple to complex behaviour and to delineate the conditions under which they arise [7].

Rössler system [8] has been widely used as a model of a chaotic system, because of its simplicity; it is the prototype for a great variety of chaotic behaviour, as in chemical chaos [9]. This system exhibits a chaotic behaviour at some values of its parameters. This behaviour can be modified if it is under some control chaos method.

Control chaos methods can be classified as internal control and external control. Internal Control could be executed by some types of feedback. It can be done through time dependent perturbations to the system parameters [10, 11, 12], or to variables [13], or by controlling the bifurcations [14].

External Control (Open-Loop Control) is applied through a time function perturbation, independent of the behaviour of the controlled process. In this category there are methods based in phase synchronization phenomena: synchronization of two or more chaotic systems [15, 16, 17], or synchronizing a chaotic system with a periodical external force [18, 19, 20].

It has been found that a model for the mechanism of circadian rhythms in *Neurospora* (three-variable model) develops nonautonomous chaos when is perturbed with a periodic forcing, and the dynamical behaviour depends on the forcing waveform (square wave to sine wave) [21, 22]. Instead, in a ten equations model of the circadian rhythm in *Drosophila*, autonomous chaos occurs in a restricted domain of parameter values, but this chaos can be suppressed by a sinusoidal or square wave forcing cycle [22, 23].

In previous work [24], we applied periodic perturbations on oscillating models, but these models do not exhibit chaotic behaviour. The objective of this work is to generalize this formalism for chaotic behaviour, using the Rössler system as a theoretical model for chronotherapy.

2. Experimental part

We perturbed the variable y of the Rössler autonomous system [8] adding the term $d \sin(2\pi t / T)$. The resulting non autonomous differential equations are:

$$\begin{aligned}\dot{x} &= -(y + z) \\ \dot{y} &= x + ay + d \sin \frac{2\pi}{T}t \\ \dot{z} &= b + z(x - c)\end{aligned}\tag{1}$$

It is well known that the Rössler system exhibit a chaotic behaviour when $a = 0.1$, $b=0.1$ and $c=18$ or $c=9$ (c is a control parameter). At these values of parameters a , b and c , it was applied the perturbation, changing the amplitude (d) from 0 to 18. The period, T , was fixed to the value of 6.066 ($c=9$) or $T=6.154$ ($c=18$), which corresponds to the dominant frequency in the power spectrum of the attractor for autonomous system.

The system (1) was numerically solved applying the Gear algorithm for stiff ordinary differential equations, using double precision and tolerance of 10^{-8} [25]. The obtained time series was analyzed by using the software Tisean 2.1 [26], using the following tools: *d2* and *c2t* (integral correlation and Takens-Theiler estimator for smoothing of the curves of integral correlation), *lyap_k* (maximal Lyapunov exponent, λ , by Kantz algorithm), *spectrum* (power spectrum) and *poincaré* (to obtain a Poincaré section). Poincaré section was constructed from embedding of x variable in three dimensions and cutting with a plane $x(t-2\tau) = 0$. The lag time, τ , was calculated with the *mutual* tool (this estimates the time delayed mutual information of the data).

3. Results and Discussion

The results of the application of periodical perturbations on the Rössler system are shown in two bifurcation diagrams (figure 1). In both, some periodical windows and period-doubling cascades are observed. As the system becomes more dissipative, that is, as c increases its value (for $c=9$, $\lambda=0.047$, and for $c=18$, $\lambda=0.058$), the system is more robust to the perturbation. In fact, it can be seen that the value of amplitude d where it is reached the period-1 window (d_p) is lower for $c=9$ ($d_p=7.46$) than for $c=18$ ($d_p=8.26$). And, it can be observed that the periodic regions are narrower for $c=9$ (d is between 7.46 and 8.88) than for $c=18$ (d is between 8.26 and 13.17).

These results obtained by Sanin *et al.* [27] confirmed this tendency to robustness of the Rössler system. When they perturbed the x variable of the Rössler system with the parameters $a=0.2$, $b=0.2$ and $c=2.6$, with a periodic function (cosine), $T=5.818$ (corresponding to the dominant frequency). They found periodic windows at low values of the amplitude d (analyzed between 0 and 2).

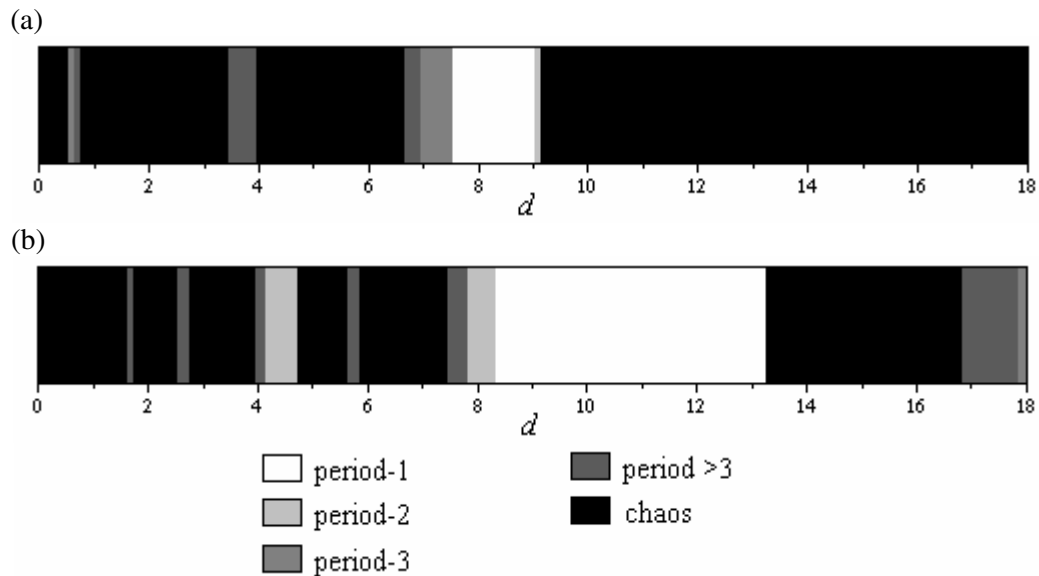


Figure 1. Bifurcation diagrams of perturbed Rössler system. The dynamical behaviour is represented by the gray bands. (a) $c = 9$, $T = 6.066$, and for autonomous system $\lambda = 0.047$; (b) $c = 18$, $T = 6.154$, and for autonomous system $\lambda = 0.058$

On the other hand, Pikovsky *et al.* [19, 28] perturbed the Rössler system to study synchronization with an external oscillator. They perturbed the x variable with a cosine function, with $a=0.5$, $b=0.4$ and $c=8.5$. They analyze synchronization when the amplitude d is between 0 and 1, but is mentioned the appearance of a narrow periodic window. Finally, using a modified Rössler system, Vadivasova *et al.* [29] perturbed the x variable, studying the effect of c (from 4.0 to near 7.0) and amplitude d (from 0.0 to near 0.07) on the synchronization, but they found periodic window with values of d as low as 0.005.

Although the Rössler system studied in this work could be controlled, transforming the chaotic behaviour into a periodic one, it can be noticed that the dominant frequency of the orbit remains invariable and the same of the original autonomous system.

We could be considering the autonomous Rössler model as the dynamic of a rhythmic disease (e.g. asthma or arthritis). It can be entrained to some cyclic behaviour to reduce its peaks. For example, if the pain peaks at an irregularly timing (chaos), the drug (or any suitable therapy) should be administered at an appropriate frequency (here, the dominant frequency). But the doses (amplitude) must be regulated to a level where the peaks synchronize with the frequency, so a period-1 behaviour can result. A higher period must be avoided, because implies more frequently pain peaks.

More work is needed to extend this model to other cases of perturbing frequency, so the dominant frequency can be maybe diminished.

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