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THEORETICAL MODELS FOR CHRONOTHERAPY: PERIODIC PERTURBATIONS IN HYPERCHAOS

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Abstract. In this work, a hyperchaotic system was used as a model for chronotherapy. We applied a periodic perturbation to a variable, varying the period and amplitude of forcing. The system, five-dimensional, has until three positive Lyapunov exponents. As a result, we get small periodical windows, but it was possible to get large areas of hyperchaos of two positive Lyapunov exponents from a chaotic behavior. In this chronotherapy model, chaos could be considered as a dynamical disease, and therapy goal must be to restore the hyperchaotic state.

1. Introduction.

Dynamical diseases are these characterized by sudden changes in qualitative dynamics of the physiological process [7, 39]. Some pathologies are recognized as dynamical diseases as cardiac arrhythmias [20] and epilepsies [37], but there are others disorders too [12, 13, 33, 26, 47]. Some researchers claim that some of these dynamical diseases show a chaotic behavior [26, 46] or more complex than the healthy state one [28]. However, others have claimed that some excessive order (periodicity) is pathological [24, 51] and that the corresponding wealth dynamics is chaotic or simply more complex [51, 23, 32, 16, 22, 43, 1, 36]. In any case, the pathological dynamics is the deviation of the normal one [7].

Under controlled conditions in laboratory, chaotic behavior can be clearly observed in some biological systems [32, 10, 5], although it is more difficult to demonstrate a chaotic behavior *in vivo* due to difficulties as short time series, nonstationarity and noise [19, 31, 21]. Hyperchaos is even more difficult to be observed [30], but there is not theoretical reason for discard hyperchaotic dynamics in nature.

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It is believed that many dynamical diseases are characterized by a basically normal control system in a region of physiological parameters that produces pathological behavior [7, 39]. Chronotherapy, the coordination of the biological rhythms with medical treatment, is a logical choice for the treatment of a dynamical disease. There are chronotherapeutic studies and applications in some diseases as cancer [14, 42, 17, 34, 35, 11], rheumatoid arthritis [15] and asthma [40, 44]. By now, there is an ample variety of type of control of chaotic systems [9, 2, 3], but for a model of chronotherapy, a time function perturbation is more convenient as external control of dynamics. A biological system is always exposed to external perturbations. Under a critical level, the dynamics of this system is not appreciably modified, until this level is reached. Then, if the perturbation was an undesirable environmental stimulus, then, a disease could be produced. However, if the perturbation was a therapy, the goal would be to surpass the critical level to drive the system to a desired state.

The control of hyperchaos is not as feasible as chaos control, but there are some methods as adaptive control [8, 49], and modulation of system parameters [38], among others [50, 27, 45].

In previous work [6] we examined the effect of periodic perturbations on two types of chaotic behavior of Rössler system: spiral and funnel chaos, and it was find that the more irregular of both, the funnel chaos, is more robust to be controlled. The objective of this work is to generalize this formalism to a continuous system with hyperchaotic dynamics to be used as a theoretical model for chronotherapy.

2. Experimental part.

Let us consider the next system (Baier-Sahle) [4]:

$$\begin{aligned} \dot{x_1} &= -\left(x_2 + a x_1\right) \\ \dot{x_i} &= x_{i-1} - x_{i+1} \\ \dot{x_n} &= e + b x_n \left(x_{n-1} - d\right) \end{aligned} \tag{1}$$

From (1) we can get a five dimensional system:

$$\begin{aligned} \dot{x_1} &= -\left(x_2 + a x_1\right) \\ \dot{x_2} &= x_1 - x_3 \\ \dot{x_3} &= x_2 - x_4 \\ \dot{x_4} &= x_3 - x_5 \\ \dot{x_5} &= e + b x_5 \left(x_4 - d\right) \end{aligned} \tag{2}$$

A periodical term $M \sin \frac{2\pi t}{T}$ (the external perturbation) was added to the second equation of the system (2):

$$\begin{aligned}
\dot{x_1} &= -(x_2 + a x_1) \\
\dot{x_2} &= x_1 - x_3 + M \sin \tfrac{2\pi t}{T} \\
\dot{x_3} &= x_2 - x_4 \\
\dot{x_4} &= x_3 - x_5 \\
\dot{x_5} &= e + b x_5 (x_4 - d)
\end{aligned} \tag{3}$$

where M is the amplitude and T is the period of the perturbation.

A sinus function was used because it is a simple rhythmic pattern and actually it has been used in cancer chronotherapy studies by drug infusion with programmable in-time pumps [34, 35]. Moreover, a drug periodically administered by some common routes as oral or intramuscular can produce a profile of plasma concentration along time roughly similar to sinus function.

For the system (3), three parameters were fixed: $b = 4$, $d = 2$ and $e = 0.1$. The parameter of control a is increased to get a dynamical behavior that changes from chaos to hyperchaos. It was examined the power spectrum to find the sharp peak corresponding to the mean rotation frequency, to determinate T_0, the period corresponding to that frequency. When it does not exist this sharp peak, T_0 was obtained by averaging sections (by binning) of the spectrum and selecting that of higher amplitude. Then, in both cases, T was varied for an interval around from $T_0/4$ to $3T_0$.

The variation of the amplitude M was from 0 to the value where the solutions go to infinitum (with 60000 points and interval of time of 0.5 in solutions of the differential equations). In some cases, inside periodic orbit regions, the iterations were extended to 100000 points to remove the transients.

The system (3) was numerically solved applying the Gear algorithm for stiff ordinary differential equations, using double precision and tolerance of 10^{-8} [18]. The obtained time series were analyzed by using the following Tisean 2.4 [25] tools: *d2* and *c2t* (integral correlation and Takens-Theiler maximum likelihood estimator to obtain optimal values for correlation dimension), *spectrum* (power spectrum) and *poincare* (to obtain a Poincaré section). Poincaré section was constructed from embedding of x variable in three dimensions and cutting with a plane $x(t - 2\tau)$ equal to average of the data. The lag time, τ, was calculated with the *mutual* tool (this estimates the time delayed mutual information of the data). The spectrum of Lyapunov exponents was determined by the Wolf algorithm [48]. The periodicity of the system was determined by the Poincaré section. The maximal Lyapunov exponent was used to determine if the behavior is chaotic (it is the case if its value is positive). The figures were constructed with Scilab 5.0 software [29].

3. **Results and discussion.** On one hand, for the system (2), if the control parameter is between $a \approx 0.075$and $a \approx 0.115$, the system has only one positive Lyapunov exponent ($\lambda_1 \approx 0.029$), and its correlation dimension is about 2. Between $a \approx 0.115$ and $a \approx 0.195$, the system has two positive Lyapunov exponents ($\lambda_1 \approx 0.045$, $\lambda_2 \approx 0.022$), and its correlation dimension is about 3. And above $a \approx 0.195$, three Lyapunov exponents are positive, ($\lambda_1 \approx 0.080$, $\lambda_2 \approx 0.053$, $\lambda_3 \approx 0.0036$), (and its

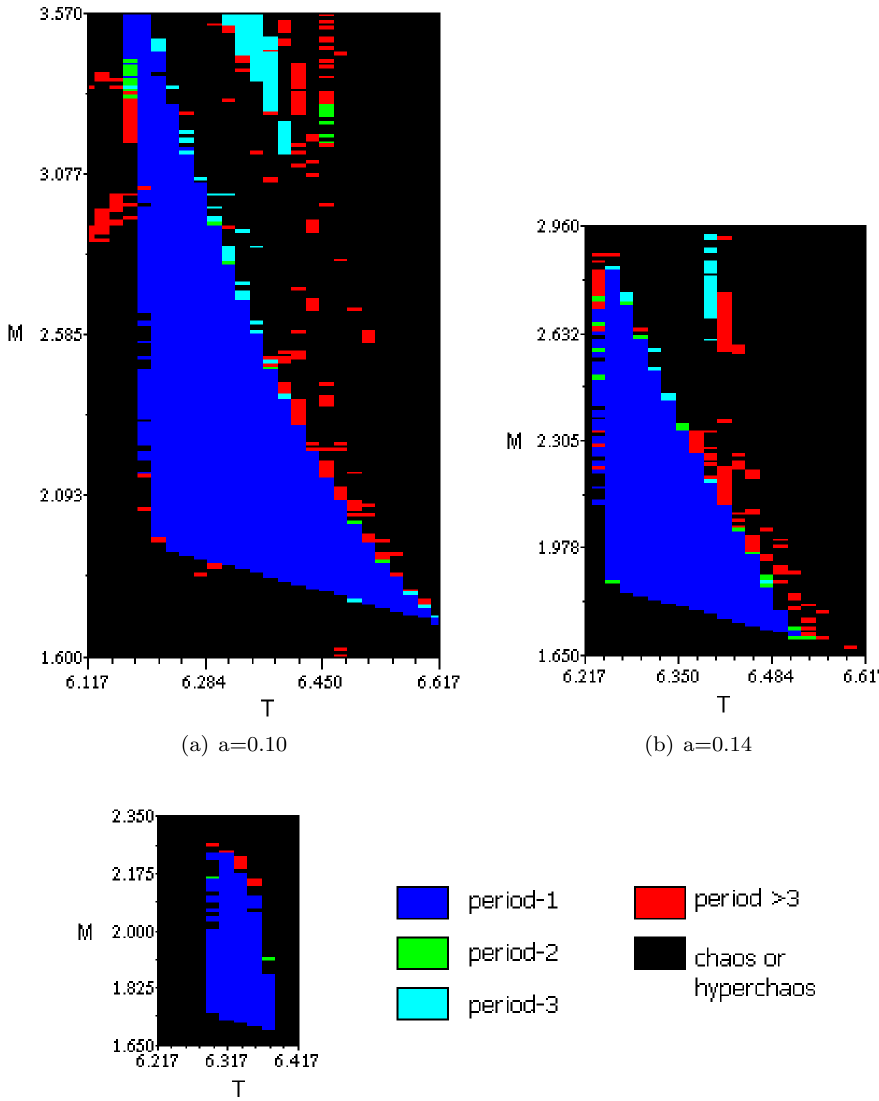
correlation dimension is about 4), in concordance with [41]. If we apply the perturbation, as in system (3), when $a = 0.1$, some little periodic windows can be seen. The original system, with one Lyapunov positive exponent, changes from chaotic to periodic. (Fig. 1) shows the evolution of a periodic window in bifurcation diagrams. At $a = 0.14$, the hyperchaotic case with two positive Lyapunov exponents, the respective periodic window is smaller. This window still exists at $a = 0.20$, a case with three positive Lyapunov exponents; but the area of this window is a little fraction of the others. In any case, the periodic windows are tiny areas in comparison with the chaotic or hyperchaotic areas. The windows are predominantly of period one orbits, they are 1:10 phase locked with the forcing oscillator. Regardless the Kolmogorov-Sinai entropy approaches a limit value for large n dimension of the system [41], as the system increases its number of positive Lyapunov exponents, it seems that is more difficult to control hyperchaos to a periodic orbit with this method.

On the other hand, it was possible to transform the chaotic behavior in a hyperchaotic one, by applying the external perturbation. As can be seen in (Fig. 2), with $a = 0.10$, the area of hyperchaos is very large, as the periodical ones are tiny. In this bifurcation diagram is visible too an area of no attractor, when the orbit escapes to infinity. It was possible to transform chaos to hyperchaos of two positive Lyapunov exponents, but, in appearance, we can not transform the hyperchaos of two positive Lyapunov exponents to one of three positive Lyapunov exponents, in any of the three values under study of parameter a.

What consequences could be extracted for chronotherapy? If a chaotic behavior was considered a pathological one, the goal would be to transform this behavior in a periodical one by means of a periodic therapy (the external periodic force). Nevertheless, if the healthy state was the chaotic, the periodic rhythm could be eliminated by reduction of the harmful external periodic force. Maybe, the dynamics of a rhythmic disease (as asthma or arthritis) was chaotic and presented peaks of attacks or crises. In this case the dynamics could be regulated by a periodic therapy to transform the chaotic behavior in a periodic, preferably of short frequency (for example, period 1 orbits). In our model, T is the period of the therapy and M is the dose. For a secure therapy it is necessary to have periodic areas (in bifurcation diagram) as big as possible, so in all the former cases the chronotherapy may be ineffective.

Another possibility is in the case that the healthy state is the hyperchaotic one, maybe the two positive Lyapunov exponents one (i.e. $a = 0.14$). The hyperchaotic behavior is difficult to remove by an external periodical perturbation, so the healthy state is robust. In special cases, the system can be driven to a periodical state (disease) or a resonant catastrophic state with no attractor (death). A diminution of complexity can be considered as a dynamical disease, as in the case when the control parameter a changes from 0.14 to 0.10 and the system exhibits chaotic behavior (only one positive Lyapunov exponent). The chronotherapy (the external perturbation) can impose a hyperchaotic behavior (two positive Lyapunov exponent) in most of possible combinations of dose and frequency of application (although some of them must be avoided as they drive the system to periodical state or to escape to infinity; worst disease or death, respectively).

As the Baier-Sahle system is only a minimal model, for a more realistic and detailed analysis it is necessary to work with specific models of physiological systems.



(a) a=0.10

(b) a=0.14

(c) $a = 0.20$

FIGURE 1. Bifurcation diagrams of the perturbed Baier-Sahle system (3), varying amplitude M and period T. The control parameter $a = 0.1$ to $a = 0.20$ (resolution of T and M are both 0.02). Without perturbation, Lyapunov positive exponents are: for $a = 0.1$, $\lambda_1 \approx 0.029$; for $a = 0.14$, $\lambda_1 \approx 0.045$, $\lambda_2 \approx 0.022$, and for $a = 0.20$, $\lambda_1 \approx 0.080$, $\lambda_2 \approx 0.053$, $\lambda_3 \approx 0.0036$.

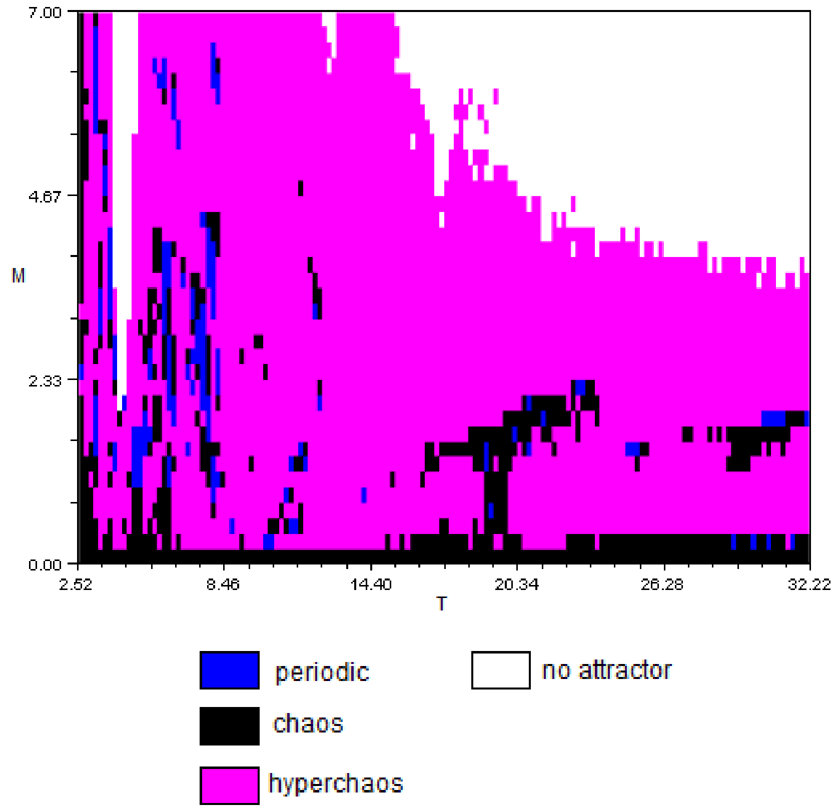


Figure 2. Bifurcation diagram of the perturbed Baier-Sahle system (3), varying amplitude M and period T. The control parameter $a = 0.10$. It shows the number of positive Lyapunov exponents: periodic has 0, chaos has one, hyperchaos, has two. The white zone is for no attractor: the systems apparently goes to infinity (resolution of T and M are both of 0.5).

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