MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **4**, Number **2**, April **2007**

http://www.mbejournal.org/

pp. **177–186**

THEORETICAL MODELS FOR CHRONOTHERAPY: PERIODIC PERTURBATIONS IN FUNNEL CHAOS TYPE

Juvencio Alberto Betancourt-Mar

Laboratorio UNE-SAS, Universidad del Noreste
Prol. Ave. Hidalgo 6315, Tampico, Tams., México, C.P.89337

José Manuel Nieto-Villar

Department of Physical Chemistry, Faculty of Chemistry, University of Havana, Havana, Cuba
and "H. Poincaré" Complex Systems Division, University of Havana, Havana, Cuba

(Communicated by Stefano Boccaletti)

Abstract. In this work, the Rössler system is used as a model for chronotherapy. We applied a periodic perturbation to the y variable to take the Rössler system from a chaotic behavior to a simple periodic one, varying the period and amplitude of forcing. Two types of chaos were considered, spiral and funnel chaos. As a result, the periodical windows reduced their areas as the funnel chaos character increased in the system. Funnel chaos, in this chronotherapy model, could be considered as a later state of a dynamical disease, more irregular and difficult to suppress.

1. **Introduction.** Dynamical diseases are characterized by sudden changes in qualitative dynamics of the physiological process [8, 44]. Some of the pathologies recognized as dynamical diseases are the well-known cardiac arrhythmias [28] and epilepsies [43], but there are also hematological diseases [46, 22, 9, 16, 17], immunological diseases [40, 55, 23], some endocrinological disorders such as diabetes [35, 56, 50], and some pathological human behavior [58]. It has been claimed that some of these dynamical diseases show a chaotic behavior [35, 38, 57]. However, others have claimed that some excessive order (periodicity) is pathological [29, 60] and that the corresponding wealth dynamics is chaotic or at least irregular [60, 30, 51, 53, 39, 20]. In any case, the pathological dynamics is the deviation of the normal one [26].

Although it is difficult to unambiguously demonstrate a chaotic behavior in a biological system because of such difficulties as short time series, nonstationarity and noise [26, 27, 37], under controlled conditions in the laboratory, chaotic behavior can be clearly observed in some biological systems [39, 12, 33, 13].

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 [8, 44], and many models of these diseases support this claim [43, 9, 16, 17, 40, 23, 56, 50, 38, 57].

Chronotherapy is the coordination of the biological rhythms with medical treatment. There are chronotherapeutic studies and applications in some diseases as

2000 *Mathematics Subject Classification.* 92C50.
Key words and phrases. chronotherapy, chaotic chemical reactions, chronobiology, biological rhythm, non-linear dynamics, Rössler system, funnel chaos.

cancer [47, 18, 48, 21, 42], rheumatoid arthritis [19] and asthma [45, 54]. Chronotherapy is a logical choice for the treatment of a dynamical disease. By now, there is an ample variety of type of control of chaotic systems [11, 2, 3], but for a model of chronotherapy, a time function perturbation serves more conveniently as external control of dynamics. A biological system is always exposed to external perturbations. Until these perturbations reach a critical level, the dynamics of the system is not appreciably modified. Then, if the perturbation were an undiserable environmental stimulus, a disease could be produced. However, if the perturbation were a therapy, the goal would be to surpass the critical level.

For example, it has been found that a model for the mechanism of circadian rhythms in Neurospora (three-variable model) develops nonautonomous chaos when perturbed with a periodic forcing [32, 31]. In addition, in a ten-equations model of the circadian rhythm of Drosophila, autonomous chaos occurs in a restricted domain of parameter values, but this chaos can be suppressed by a forcing cycle [31, 41]. Drosophila circadian models has been used as a model of chronotherapy, by applying perturbations to get an entrainment of the oscillations with the external stimulus [14, 15].

Although the Rössler system is not a model of a specific disease (this is not our intention), it has been chosen because it is a minimal model for continuous-time chaos, and it has been used as a prototype for a large variety of chaotic behavior [24]. It exhibits the same basic complex behaviors that less simple systems do: periodic orbits, bifurcations and various types of chaotic dynamics [1].

Two types of chaotic behavior can be distinguished: one of them, spiral chaos, is very similar in its spectral and correlation properties to a harmonic oscillation in the presence of noise [4, 5, 6, 7]. The phase trajectory of the spiral attractor rotates with a high regularity around one saddle-focus, and the spectrum exhibits a narrow-band peak corresponding to the mean rotation frequency. Spiral chaos is called phase-coherent.

The other type of chaos, funnel (or screw) chaos, is very similar to a random process; the rate of mixing can not be considerably affected by noise [4, 5, 6, 7]. Phase trajectories on the funnel attractor make complicated loops around a saddle-focus and thus, demonstrate a non-regular rotation behavior, and the power spectrum does not contain sharp peaks.

It is well known that the Rössler system shows both types of chaos [24, 52]. Because of the differences between both types of chaos, we can not expect the same response to a periodic perturbation. To control chaos, it is not enough to know that the dynamics is chaotic; it is also necessary to know what type of chaos it is. A previous work applied periodic perturbations to the chaotic Rössler system [10]. With appropriate choice of the period and amplitude of perturbation, the chaotic dynamics of the system was controlled; but in that work, the parameters were restricted to a range where the system shows spiral chaos. The objective of this work is to generalize this formalism to a funnel chaos to be used as a theoretical model for chronotherapy.

2. **Experimental part.** Let us consider the chaotic chemical Rössler model [59]:

$$\begin{aligned} A + x &\rightleftharpoons 2x \\ x + y &\rightleftharpoons 2y \\ B + z &\rightleftharpoons 2z \\ C + y &\rightleftharpoons D \\ x + z &\rightleftharpoons E \end{aligned} \tag{1}$$

where x, y and z are the intermediates of the reactions. From the mass action law of chemical kinetics, the behavior of the concentrations of the intermediates x, y and z is described by the following adimensional autonomous system of ordinary differential equations:

$$\begin{aligned} \dot{x} &= -(y + z) \\ \dot{y} &= x + ay \\ \dot{z} &= b + z(x - c) . \end{aligned} \tag{2}$$

Working from system (2), we add a periodical term $d \sin \frac{2\pi t}{T}$ to the second equation (the external perturbation):

$$\begin{aligned} \dot{x} &= -(y + z) \\ \dot{y} &= x + ay + d \sin \tfrac{2\pi t}{T} \\ \dot{z} &= b + z(x - c) \end{aligned} \tag{3}$$

where d 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 [18, 42]. Moreover, a drug periodically administered by some common routes, such as oral or intramuscular, can produce a profile of plasma concentration over time roughly similar to a sinus function.

Two parameters were fixed: $b = 0.1$ and $c = 18$. When a is varied from 0.1 to 0.36, the chaotic behavior changes from spiral to funnel type. These values for the three parameters were chosen because the two types of chaos appear in these ranges (although there are other ranges with similar properties). For spiral chaos, the power spectrum was examined to find the sharp peak corresponding to the mean rotation frequency, to determine T_0, the period corresponding to that frequency. For funnel chaos, this sharp peak does not exist, so 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 a short interval around T_0.

The variation of the amplitude d was from 0 to the value where the solutions go to infinitum (with 40,000 points and interval of time of 0.04 in solutions of the differential equations). In some cases, inside periodic orbit regions, the iterations were extended to 100,000 points to remove the transients.

System (3) was numerically solved applying the Gear algorithm for stiff ordinary differential equations, using double precision and tolerance of 10^{-8} [25]. The time series obtained were analyzed by using the software Tisean 2.1 [34], using the following tools: *d2* and *c2t* (integral correlation and Takens-Theiler maximum likelihood estimator to obtain optimal values for correlation dimension), *lyap_k* (maximal Lyapunov exponent by Kantz algorithm), *spectrum* (power spectrum) and *poincare* (to obtain a Poincaré section). We applied *lyap_k* on the x variable. The Poincaré section was constructed from embedding of the 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). 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 2.7 software [36].

3. **Results and Discussion.** When the parameter a is below the critical value $a_c \approx 0.192$, the Rössler system always cycles around the saddle fixed point $(x_0, y_0) \approx (0, 0)$. This is the spiral chaos (Fig. 1a); but beyond a_c, sometimes the cycle around the fixed point is not completed and there are some maxima of $y < y_0$, characteristics of funnel chaos in Rössler system (Fig. 1b) [49]. Beyond $a_c \approx 0.36$, the system apparently does not have an attractor and the trajectories go to infinitum. Nevertheless, the transition from spiral chaos to funnel chaos as a is increased is smooth; the power spectrum gradually broadens as the sharp peak decreases and vanishes.

As can be seen in the bifurcation diagrams (Fig. 2 and Fig. 3), the oscillatory perturbation can suppress the chaotic behavior to obtain a periodic behavior, if we select the appropriate T and d. But if the amplitude d is too high for the system, the trajectories go to infinitum (no attractor); the critic value of d (d_c) for this behavior depends on T and the parameter a. Note that this attractor disappearance is more sensible to a: when a changes from 0.1 to 0.36, then d_c decreases in two orders.

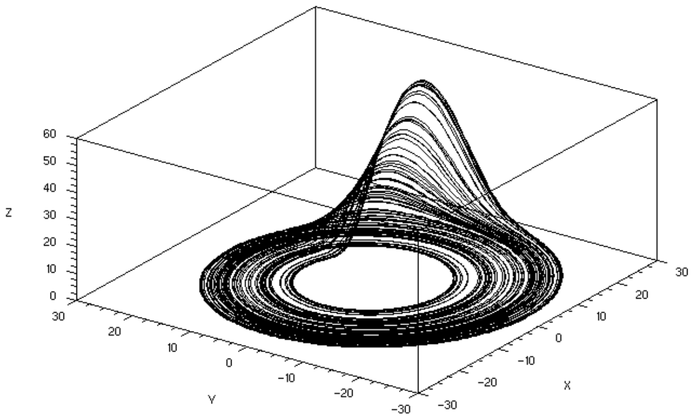
Although this work did not focus on the mechanisms of bifurcations presented, cascades of period-doubling bifurcation were observed at least for period 1 orbits when d decreased, in all cases.

Another important result derives from the periodic windows. As a increases from 0.1 to 0.36, the windows decrease their areas and vanish. In part, this can be produced by the fall of the d_c as a curtain that covers the areas of existence of some attractor, so the space *occupied* by the periodic areas decreases. However, we can see that the reduction of periodic areas is very important at $a = 0.2$, where d_c is not below the great periodic areas at $a = 0.1$ (Fig. 2). Therefore the most important cause of this shrinking of periodic areas is the change of parameter a; that is, the increase of the funnel character of the chaotic dynamics of the system. When $a = 0.36$, no periodic area is found and chaos can not be suppressed.

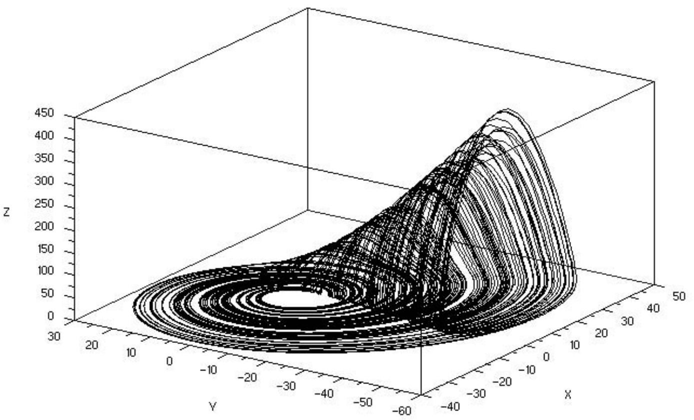
All the period 1 orbits are 1:1 phase-locked with the forcing oscillator, and the stable orbits generated by their period-doubling bifurcations are N:N phase-locked. However, in the $a = 0.1$ case, N:M phase-locked (N>M) orbits are observed when d is increased. For example, in the central periodic area above $d = 16$, there are 4:2 and 3:2 phase-locked orbits, and their corresponding period doubling bifurcations (Fig. 2). Below $d = 16$, almost all periodic orbits are N:N phase-locked, and most of the attracting orbits when $d > 16$ are N:M phase locked (N>M).

When $a = 0.1$, birhythmicity was detected in some cases, specifically where $d = 11.4$ and $T = 5.958$; in this case, an 11:7 and a 1:1 phase-locked orbit coexist in a small region of parameters (less than $\Delta d = 0.3$ and $\Delta T = 0.05$).

What consequences may be extracted for chronotherapy? If a chaotic behavior were considered a pathological one, the goal would be to transform this behavior into 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



(a) $a = 0.1$

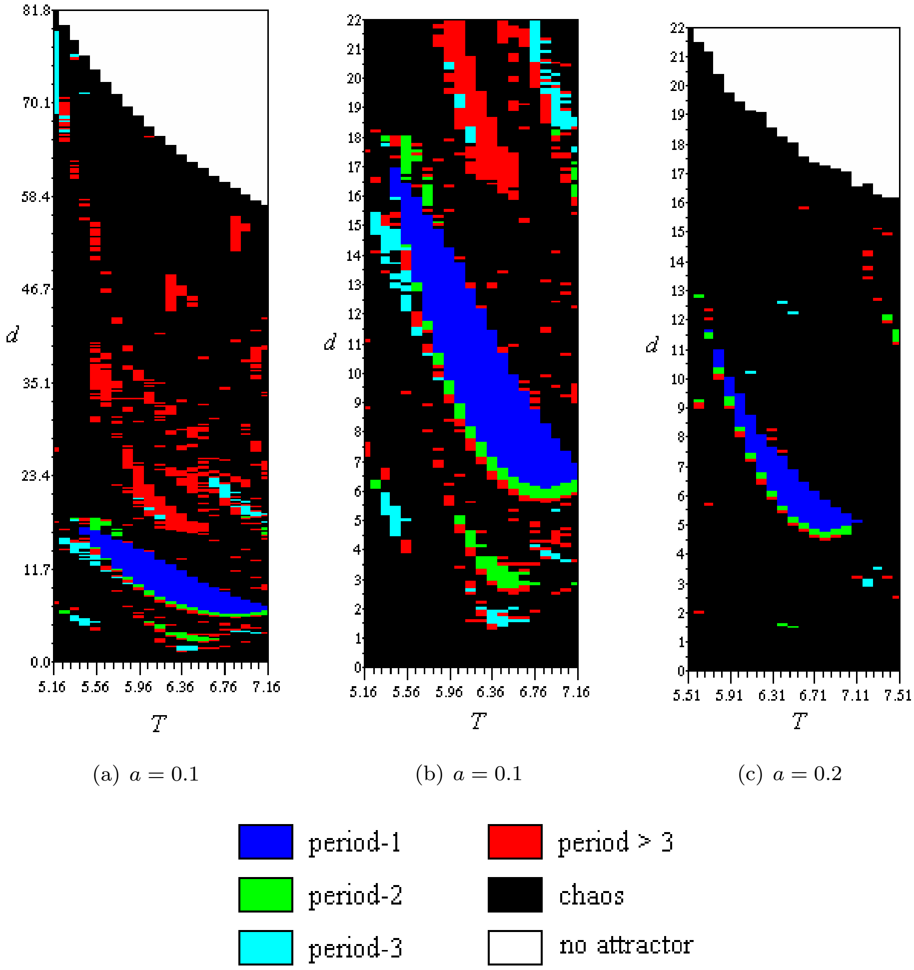


(b) $a = 0.36$

FIGURE 1. Phase space representation of the two types of chaotic dynamics of Rössler system; a) spiral type, where $a = 0.1$; and b) funnel type, where $a = 0.36$

eliminated by reduction of the harmful external periodic force. For example, suppose the dynamics of a rhythmic disease (such as asthma or arthritis) were 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 into a periodic, preferably of short frequency (for example, period 1 orbits). In our model, T is the period of the therapy and d is the quantity of dose. For a secure therapy it is necessary to have periodic areas (in bifurcation diagram) as large as possible.

On one hand, a period 2 area could be interesting, too, if it is a 2:2 phase-locked orbit (as is the case in the central region seen in Fig. 2, around $d = 3$ when $a = 0.1$), because it is geometrically similar to a 1:1 orbit and the average rate of the rotation (measured by time between two maxima of z) is the same. Higher periodicity N:N phase-locked orbits exist when $a = 0.1$ in Fig. 2, but the areas covered by them are small. On the other hand, N:M phase locked orbits (N>M) are risky if they are

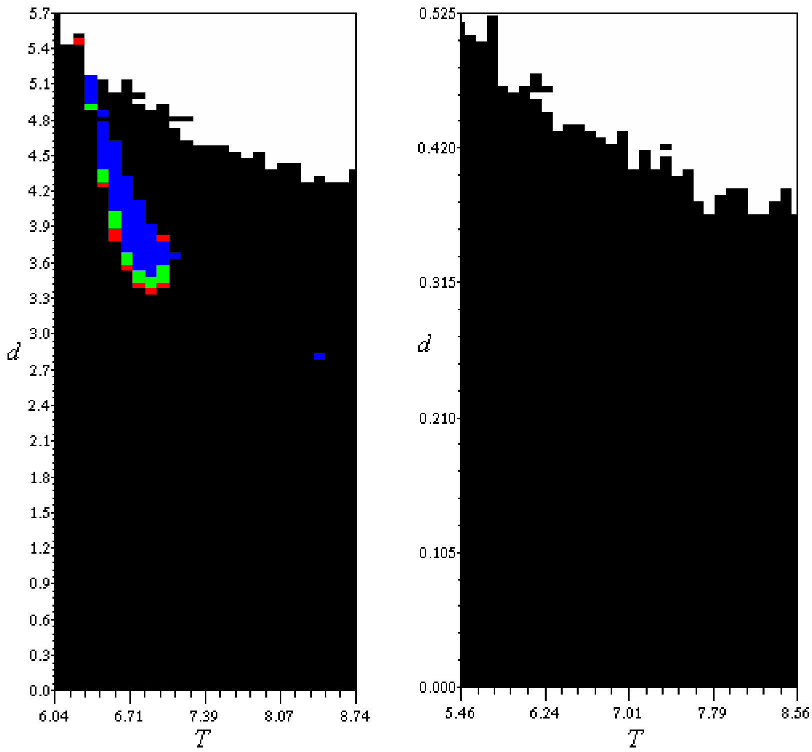


(a) $a = 0.1$ (b) $a = 0.1$ (c) $a = 0.2$

FIGURE 2. Bifurcation diagrams of the perturbed Rössler, varying amplitude d and period T. The control parameters are $b = 0.1$ and $c = 18$. In a) and b) $a = 0.1$ (spiral chaos regime), at different scales of the vertical axis; in c), $a = 0.2$ (funnel chaos regime).

considered in chronotherapy, because of their faster rate of rotation. For example, a 3:1 phase-locked orbit, as seen around $d = 75$ and $T = 5.16$ when $a = 0.1$ (Fig. 2), can imply in a rhythmic disease a very high frequency of peaks of attacks or crises compared with the original chaotic, but of lower rate dynamics.

In most of cases of attracting periodic orbits found in this work, the system approaches them in a few number of iterations, but with some T, d and a values, there are long transients, depending on initial conditions. In these cases, the chronotherapeutic approach would be to wait for appropriate initial conditions before apply the chronotherapy. Instead, we could force these appropriate initial



(a) $a = 0.3$ (b) $a = 0.36$

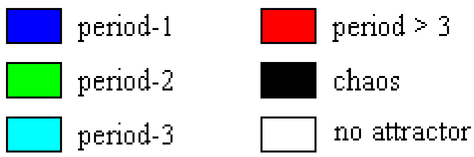


FIGURE 3. Bifurcation diagrams of the perturbed Rössler in funnel chaos regime, varying amplitude d and period T. The control parameters are $b = 0.1$ and $c = 18$. In a) $a = 0.3$; in b), $a = 0.36$. Note the scales of vertical axis of these diagrams are different.

conditions, by means of another therapy that could be a more conventional one or through another chaos control method.

Another important fact that must be taken into account in chronotherapy is that birhythmicity should be avoided as far as possible. If birhythmicity is unavoidable, we can force or wait for the appropriate initial conditions, too.

Nevertheless, for a successful therapy in a chronic disease, knowing the actual dynamical state of the disease may be of primary importance. Plausibly, a chronic disease is not stationary. If it is worsening, its dynamics may be growing more disorderly, more difficult to control. Funnel chaos could represent a pathological state more irregular than spiral chaos, possibly as a consequence of evolution of a chronic disease from more benign states. In this hypothetical scenario, the initial states, where spiral chaos is present, are very similar to the periodic states with some noise, whereas the final states, where funnel chaos is present, are more similar to random fluctuations. The evolution of the chronic disease is controlled by a control parameter, as a in Rössler system.

As a consequence, chronotherapy may not be as effective in a funnel chaos-type disease as in a spiral chaos-type one. If a disease is chronic, it may be evolving toward a more complex dynamics, with the result that the possibility of a successful treatment is decreasing with time.

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

Acknowledgments. This work was supported by the agreement between Universidad del Noreste and Laboratorio SAS from Tampico, Mxico.

REFERENCES

[1] K. T. Alligood, T. D. Sauer and J. A. Yorke, "Chaos in differential equations" In CHAOS- AN INTRODUCTION TO DYNAMICAL SYSTEMS, Springer, New York, 1996, pp. 273-327

[2] B. R. Andrievskii and A. L. Fradkov, CONTROL OF CHAOS: METHODS AND APPLICATIONS. I. METHODS. Automation and Remote Control 64 (2003) 679-713.

[3] B. R. Andrievskii and A. L. Fradkov, CONTROL OF CHAOS: METHODS AND APPLICATIONS. II. APPLICATIONS. Automation and Remote Control 65 (2004) 505-33.

[4] V. S. Anishchenko, T. E. Vadivasova, A. S. Kopeikin, G. I. Strelkova and J. Khurts, SPECTRAL AND CORRELATION ANALYSIS OF SPIRAL CHAOS. Fluctuations and Noise Letters 3 (2003) L213-21.

[5] V. S. Anishchenko, T. E. Vadivasova, G. A. Okrokvertskhov and G. I. Strelkova, CORRELATION ANALYSIS OF DYNAMICAL CHAOS. Physica A 325 (2003) 199-212.

[6] V. S. Anishchenko, T. E. Vadivasova, G. I. Strelkova and G. A. Okrokvertskhov, STATISTICAL PROPERTIES OF DYNAMICAL CHAOS. Mathematical Biosciences and Engineering 1 (2004) 161-84.

[7] V. S. Anishchenko, G. A. Okrokvertskhov, T. E. Vadivasova and G. I. Strelkova, MIXING AND SPECTRAL-CORRELATION PROPERTIES OF CHAOTIC AND STOCHASTIC SYSTEMS: NUMERICAL AND PHYSICAL EXPERIMENTS. New J. Phys. 7 (2005) 76.

[8] J. Bélair, L. Glass, U. A. der Heiden and J. Milton, DYNAMICAL DISEASE: IDENTIFICATION, TEMPORAL ASPECTS AND TREATMENT STRATEGIES OF HUMAN ILLNESS. Chaos 5 (1995) 1-7.

[9] S. Bernard, J. Bélair and M. C. Mackey, BIFURCATIONS IN A WHITE-BLOOD-CELL PRODUCTION MODEL. C. R. Biologies 327 (2004) 201-10.

[10] J. A. Betancourt-Mar, I. S. Alarcn-Montelongo and J. M. Nieto-Villar, THEORETICAL MODELS IN CHRONOTHERAPY: II. PERIODIC PERTURBATIONS IN A CHAOTIC CHEMICAL REACTION. Biological Rhythm Research. 37 (2006) 131-6.

[11] S. Boccaletti, C. Grebogi, Y. C. Lai, H. Mancini and D. Maza, THE CONTROL OF CHAOS: THEORY AND APPLICATIONS. Physics Reports 329 (2000) 103-97.

[12] T. V. Bronnikova, V. R. Fed'nika, W. M. Schaffer and L. F. Olsen, PERIOD-DOUBLING BIFURCATIONS AND CHAOS IN A DETAILED MODEL OF THE PEROXIDASE-OXIDASE REACTION. J. Phys. Chem. 99 (1995) 9309-12.

[13] T. V. Bronnikova, W. M. Schaffer, M. J. B. Hauser and L. F. Olsen, ROUTES TO CHAOS IN THE PEROXIDASE-OXIDASE REACTION. 2 THE FAT TORUS SCENARIO. J. Phys. Chem. B 102 (1998) 632-40.

[14] D. Claude, J. Clairambault and F. Levi, RYTHMES BIOLOGIQUES ET CHRONOTHRAPEUTIQUE: COMPARAISON ENTRE DES SCHMES D'ADMINISTRATION THORIQUES ET DES THRAPEUTIQUES APPLIQUES EN CANCROLOGIE. ESAIM: PROCEEDINGS 9 (2000) 119-137.

[15] D. Claude and J. Clairambault, PERIOD SHIFT INDUCTION BY INTERMITTENT STIMULATION IN A DROSOPHILA MODEL OF PER PROTEIN OSCILLATIONS. Chronobiol. Int. 17 (2000) 1-14.

[16] C. Colijn and M. C. Mackey, A MATHEMATICAL MODEL OF HEMATOPOIESIS: I. PERIODIC CHRONIC MYELOGENOUS LEUKEMIA. J. Theor. Biol. 237 (2005) 117-32.

[17] C. Colijn and M. C. Mackey, A mathematical model of hematopoiesis: II. cyclical neutropenia. J. Theor. Biol. 237 (2005) 133-46.

[18] B. Coudert, G. Bjarnasonb, C Focanc, E. Donato di Paola and F Lvie, It is time for chronotherapy! Pathologie Biologie 51 (2003) 197-200.

[19] M. Cutolo, B. Seriolo, C. Craviotto, C. Pizzorni and A. Sulli, Circadian rhythms in RA. Ann. Rheum. Dis. 62 (2003) 593-6.

[20] D. Delignières, M. Fortes and G. Ninot, The fractal dynamics of self-esteem and physical self. Nonlinear Dynamics in Psychology and Life Sciences 8 (2004) 497-510.

[21] M. Eriguchi, F. Levi, T. Hisa, H. Yanagie, Y. Nonaka and Y. Takeda, Chronotherapy for cancer. Biomedicine & Pharmacotherapy 57 (2003) 92s-5s.

[22] P. Fortin and M. C. Mackey, Periodic chronic myelogenous leukaemia: spectral analysis of blood cell counts and aetiological implications. British Journal of Haematology 104 (1999) 336-45.

[23] U. Foryś, Marczuk's model of immune system dynamics with application to tumour. J. Theor. Medicine 4 (2002) 85-93.

[24] P. Gaspard, "Rssler systems" In Encyclopedia of nonlinear science, edited by A. Scott, Routledge, New York, 2005 pp. 808-11

[25] C. W. Gear,"The automatic integration of stiff ordinary differential equations" In Processing 68: Proceedings of the IFIP Congress 68, edited by A J H Marvel, North-Holland, New York, 1968, pp 187-193

[26] L. Glass, Synchronization and rhythmic processes in physiology. Nature 410 (2001) 277-84.

[27] L. Glass and D. Kaplan, Time series analysis of complex dynamics in physiology and medicine. Med. Prog. Technol. 19 (1993) 115-28.

[28] L. Glass, "Dynamical disease - the impact of nonlinear dynamics and chaos on cardiology and medicine" In The impact of chaos on science and society, edited by C. Grebogi and J. A. Yorke, United Nations University Press, New York, 1997, pp. 219-231

[29] A. L. Goldberger, L. A. N. Amaral, J. M. Hausdorff, P. Ch. Ivanov and C. K. Peng, Fractal dynamics in physiology: alterations with disease and aging. Proc. Natl. Acad. Sci. USA 99 (2002) 2466-72.

[30] A. L. Goldberger, Is the normal heartbeat chaotic or homeostatic?. News Physiol. Sci. 6 (1991) 87-91.

[31] A. Goldbeter, D. Gonze, G. Houart, J.-C. Leloup, J. Halloy, and G. Dupont, From simple to complex oscillatory behavior in metabolic and genetic control network. Chaos 11 (2001) 247-60.

[32] D. Gonze D and A. Goldbeter, Entrainment versus chaos in a model for a circadian oscillator driven by light-dark cycles. J. Stat. Phys. 101 (2000) 649-63.

[33] M. J. B. Hauser, L. F. Olsen, T. V. Bronnikova and W. M. Schaffer, Routes to chaos in the peroxidase-oxidase reaction: period-doubling and period-adding. J. Phys. Chem. B 101 (1997) 5075-83.

[34] R. Hegger H. Kantz and T. Schreiber, Practical implementation of nonlinear time series methods: The TISEAN package. Chaos 9 (1999) 413-35.

[35] T. A. Holt, A chaotic model for tight diabetes control. Diabetic Medicine 19 (2002) 274-8.

[36] INRIA, Scilab. Ver 2.7 (2003). A free scientific software package for numerical computations. Available from: http://www.scilab.org

[37] H. Kantz and T Schreiber, The human ecg-nonlinear deterministic versus stochastic aspects. IEE Proc. Sci. Measurement Technol. 145 (1998) 279-84.

[38] R. King, J. D. Barchas and B. A. Huberman, Chaotic behavior in dopamine neurodynamics. Proc. Natl. Acad. Sci. USA 81 (1984) 1244-7.

[39] H. Korn and P. Faure, Is there chaos in the brain? II. Experimental evidence and related models. C. R. Biologies 326 (2003) 787-840.

[40] K. E. Kürten and F. Castiglione, Dynamical model of B-T cell regulation. International Journal of Modern Physics C 12 (2001) 367-75.

[41] J. C. Leloup and A. Goldbeter, Chaos and birhythmicity in a model for circadian oscillations of the PER and TIM proteins in Drosophila. J. Theor. Biol. 198 (1999) 445-59.

[42] F. Levi, Circadian chronotherapy for human. Lancet Oncol. 2 (2001) 307-15.

[43] F. Lopes da Silva, W. Blanes, S. N. Kalintzin, J. Parra, P. Suffczynski and D. N. Velis, Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. Epilepsia 44 (2003) 78-83.

[44] M. C. Mackey and l. Glass, Oscillations and chaos in physiological control systems. Science 197 (1977) 287-9.

[45] R. J. Martin and S. Banks-Schlegel, Chronobiology of asthma. Am. J. Respir. Crit. Care Med. 158 (1998) 1002-7.

[46] J. G. Milton and M. C. Mackey, Periodic haematological diseases: mystical entities or dynamical disorders?. Journal of Royal College of Physicians of London 23 (1989) 236-41.

[47] M. C. Mormont and F. Levi, Cancer chronotherapy: principles, applications, and perspectives. Cancer 97 (2002) 155-69.

[48] M. C. Mormont and F. Levi, Cancer chronotherapy: Principles, applications and perspectives. Cancer 97 (2003) 155-69.

[49] G. V. Osipov, B. Hu, C. Zhou, M. V. Ivanchenko and J. Kurths, Three types of transitions to phase synchronization in coupled chaotic oscillators. Phys. Rev. Lett. 91 (2003) 024101.

[50] M. G. Pedersen, R Bertram and A. Sherman, Intra- and inter-islet synchronization of metabolically driven insulin secretion. Biophysical Journal 89 (2005) 107-19.

[51] C. S. Poon and C. K. Merrill, Decrease of cardiac chaos in congestive heart failure. Nature 389 (1997) 492-95.

[52] O. E. Rössler, Chaos in abstract kinetics: Two prototypes. Bull. Math. Biol. 39 (1977) 275-89.

[53] M. Small, K. Judd, M. Lowe and S. Stick, Is breathing in infants chaotic? dimension estimates for respiratory patterns during quiet sleep. J. Appl. Physiol. 86 (1999) 359-76.

[54] C. M. Spengler and S. A. Shea, Endogenous circadian rhythm of pulmonary function in healthy humans. Am. J. Respir. Crit. Care Med. 162 (2000) 1038-46.

[55] Z. Szymańska, Analysis of immunotherapy models in the context of cancer dynamics. Int. J. Appl. Math. Comput. Sci. 13 (2003) 407-18.

[56] B. Topp, K. Promislow, G. deVries, R. M. Miura and D. T. Finegood, A model of beta-cell mass insulin and glucose kinetics: pathways to diabetes. J. Theor. Biol. 206 (2000) 605-19.

[57] M. V. Voitikova, Strange attractors in immunology of tumor growth. arXiv:chao-dyn/9708015 v1 21 Aug 1997

[58] K. Warren R. C. Hawkins and J. C. Sprott, Substance abuse as a dynamical system: evidence and clinical implications of nonlinearity in time series of daily alcohol. Addictive Behaviors 28 (2003) 369-74.

[59] K. D. Willianovski and O. E. Rössler, Irregular oscillations in a realistic abstract quadratic mass action system. Z. Naturforsch A 35 (1980) 317-8.

[60] R. M. Yulmetyev, S. A. Demin and P. Hänggi, "Manifestations of chaos in real complex systems: case of Parkinson's disease" In The logistic map and the route to chaos, edited by M. Ausloos and M. Dirickx, Springer-Verlag, Berlin, 2005, pp. 175-196.

Received on April 19, 2006. Accepted on November 18, 2006.

E-mail address: nolineal@spectroq.com
E-mail address: nieto@fq.uh.cu