Hybrid extension of a deterministic model for the Calcium-Inositol intracellular oscillations

V. Balan, I.R. Nicola, D. Opriş

Abstract. A deterministic mathematical model for intracellular Calcium oscillations which takes into consideration the Calcium-stimulated degradation of inositol 1,4,5-triphosphate by a 3-kinase is extended: the fuzzification and randomization of the original SODE allows considering a hybrid system of differential equations, as a perturbed derived model. The behavior of the hybrid system is investigated for given sets of parameters. Numerical simulations illustrate the obtained results.

M.S.C. 2010: 37G10, 37M20, 37N25, 92C45.
Key words: dynamical system, stationary points, fuzzification, randomization, hybrid system, oscillations, credibility space, chance space.

1 Introduction

It is well known that randomness is a basic type of uncertainty and probability theory is a branch of mathematics that deals with random phenomena. The axiomatic foundation of probability theory was given by Kolmogorov [4] in 1933 and is based on normality, nonnegativity and countable additivity.

Fuzziness mainly concerns with phenomena with vague and subjective information, mainly those having lack of or without history account. Therefore, fuzziness appears to be not an antagonist, but a complementary notion to randomness. The concept of *fuzzy set* was initially proposed by Zadeh [16] in 1965 by means of membership functions. In order to study the behavior of fuzzy phenomena, a new branch of mathematics entitled *credibility theory* was founded in 2004 and refined in 2007 by Liu ([6]). Different from other fuzzy theories, credibility theory is based on an axiomatic system, involving normality, monotonicity, self-duality and maximality axioms.

In many cases, the two basic types of uncertainty (*fuzziness and randomness*), simultaneously appear in a system. In order to express the quantities with fuzziness and randomness, Liu [6] introduces the notion of hybrid variable. To facilitate measuring of hybrid events, the concept of *chance measure* was introduced by Li and Liu [5].

BSG Proceedings 18. The Int. Conf. of Diff. Geom. and Dynamical Systems (DGDS-2010), October 8-11, 2010, Bucharest Romania, pp. 23-31.

The present work considers the extension of a deterministic mathematical model for intracellular Calcium oscillations, which studies the Calcium-stimulated degradation of inositol 1,4,5-triphosphate by a 3-kinase: namely, a perturbed derived model based on a hybrid system of differential equations, obtained by both fuzzification and randomization of the original SODE. The behavior of the hybrid system - investigated for given sets of parameters, is further illustrated by numerical Maple 12 software simulations.

We first introduce several considerations on credibility and chance spaces, and on hybrid variables.

Let Θ be a nonempty set, P be the power of Θ (i.e. all subsets of Θ) and Cr the credibility measure ([8], [14]). A fuzzy variable is a function from the credibility space (Θ, P, Cr) to the set of real numbers. If a fuzzy variable ξ is defined as a function on a credibility space, then we may get its membership function through

$$\mu(x) = (2Cr\{\xi = x\}) \wedge 1,\ x \in \mathbb{R}.$$

Suppose that (Θ, P, Cr) is a credibility space and $(\Omega, F, \Pr)$ is a probability space. The product $(\Theta, P, Cr) \times (\Omega, F, \Pr)$ is called a chance space. A *hybrid variable* is a measurable function, from a chance space $(\Theta, P, Cr) \times (\Omega, F, \Pr)$ to the set of real numbers, i.e. for any Borel set B of real numbers, the set $\{(\theta, \omega) \in \Theta \times \Omega |\ \xi(\theta, \omega) \in B\}$ is an event.

In the following, let T be an index set and let (Θ, P, Cr) be a credibility space. A *fuzzy process* C_t is a function from $T \times (\Theta, P, Cr)$ to the set of real numbers. A fuzzy process C_t is said to be a C process (or *Liu process*) if [7]:

a) $C_0 = 0$;

b) C_t has stationary and independent increments;

c) every increment $C_{s+t} - C_s$ is a normally distributed fuzzy variable with expected value $e_1 t$ and variance $\sigma^2 t^2$, whose membership function is

$$\mu(x,t) = 2\left(1 + \exp\left(\frac{\pi\,|x - e_1 t|}{\sqrt{6}\sigma t}\right)\right)^{-1},\ x \in \mathbb{R}.$$

We say that the process C is *standard* if $e_1 = 0$ and $\sigma = 1$. This process plays the role of Brownian motion.

Let T be an index set and $(\Theta, P, Cr) \times (\Omega, F, \Pr)$ a chance space. A *hybrid process* is a measurable function from $T \times (\Theta, P, Cr) \times (\Omega, F, \Pr)$ to the set of real numbers, i.e. for each $t \in T$ any Borel set B of real numbers, the set $\{(\theta, \omega) \in \Theta \times \Omega |\ X(t, \theta, \omega) \in B\}$ is an event.

Suppose B_t is a standard Brownian motion (or Wiener process), C_t is a standard C process (standard Liu process), and f, g, h are some given functions. Then:

$$dx(t) = f(t, x(t))dt + g(t, x(t))dB_t + h(t, x(t))dC_t \tag{1.1}$$

is called a *hybrid differential equation* ([7], [9], [14]). A solution is a hybrid process $x(t)$ that satisfies 1.1 in t identically.

2 The deterministic mathematical model for oscillations in Calcium concentration

Progresses in physiologic phenomena are mainly related to understanding the Calcium role in biological processes. The evolution of fluorescent samples which contained Ca^{2+} has led to finding oscillations in the intracellular Calcium concentration. The cytosolic Calcium oscillations were observed in a large variety of cellular types, where these appear spontaneously, or as effect of stimulation with a hormone or a neurotransmitter.

The temporal oscillations in the Calcium concentration from the cell cytosole (i.e., the matrix within the cell, in which the cell organites exist in suspension) have been described, when it became possible to study the Calcium evolution at the level of a single cell.

The cytosolic Calcium is involved in numerous cell functions, whereas its physiologic and pathophysiologic role are unanimously acknowledged.

The deterministic mathematical model studied in this paper was proposed by Houart et al. ([1]) in 1999. It derives from a biological model of intracellular Calcium oscillations based on the mechanism of Calcium-induced Calcium-release (CICR), that takes into consideration the Calcium-stimulated degradation of inositol 1,4,5-triphosphate (InsP_3) by a 3-kinase. This mathematical model contains three state variables: $x_1(t)$, $x_2(t)$ and $x_3(t)$, $t \geq 0$, where

- $x_1(t)$ is the concentration of free Calcium in cytosole;
- $x_2(t)$ is the Calcium concentration in the inner compartment of the cell;
- $x_3(t)$ is the concentration of $InsP_3$ (the 1,4,5-triphosphate inositol) which mediates the Calcium ions release.

The differential equations which describe the model are

$$(2.1)\quad \begin{cases} \dot{x}_1(t) = & -a_8 x_1(t) + a_{11} + a_1 a_{12} + a_9 x_2(t) - a_{13} \cdot \dfrac{x_1(t)^2}{a_2^2 + x_1(t)^2} + \\ & + a_{14} \cdot \dfrac{x_1(t)^m}{a_7^m + x_1(t)^m} \cdot \dfrac{x_2(t)^2}{a_6^2 + x_2^2(t)} \cdot \dfrac{x_3(t-\tau)^4}{a_4^4 + x_3(t-\tau)^4}, \\ \dot{x}_2(t) = & -a_9 x_2(t) + a_{13} \cdot \dfrac{x_1(t)^2}{a_2^2 + x_1(t)^2} - \\ & - a_{14} \cdot \dfrac{x_1(t)^m}{a_7^m + x_1(t)^m} \cdot \dfrac{x_2(t)^2}{a_6^2 + x_2(t)^2} \cdot \dfrac{x_3(t-\tau)^4}{a_4^4 + x_3(t-\tau)^4}, \\ \dot{x}_3(t) = & a_1 a_{15} - a_{16} \cdot \dfrac{x_3(t-\tau)^p}{a_3^p + x_3(t-\tau)^p} \cdot \dfrac{x_1(t)^n}{a_5^n + x_1(t)^n} - a_{10} x_3(t-\tau), \end{cases}$$

with the initial condition

$$x_1(0) = x_{10},\ x_2(0) = x_{20},\ x_3(\theta) = \varphi(\theta),\ \theta \in [-\tau, 0], \tau > 0,$$

where $\varphi : [-\tau, 0] \to \mathbb{R}$ is a smooth function and $m, n, p \in \mathbb{N}$.

The coefficients $a_i, i = \overline{1,16}$ admit physiological meanings ([1], [10], [13]). The mathematical model given by the SODE (2.1) allows the occurrence of simple (periodic) and complex Calcium oscillations for different sets of values of the parameters.

The periodicity suggests the existence of certain physiologic regulating mechanisms, hence of some reverse (feedback) auto-control mechanisms, which correspond to the experimental observations.

The complex oscillations are of explosive, chaotic or quasi-periodic type and are obtained for certain sets of values of the parameters.

For the explosive-type oscillations, from the numeric simulation we notice the existence of a Calcium high-amplitude peak, followed by small variations of the level, around a plateau. The chaotic-type oscillations are non-periodic and have a low amplitude. The quasi-periodic oscillations are characterized by the existence of multiple frequencies.

The qualitative analysis and the numerical simulation of the SODE (2.1) has been performed in [10] and [14]. Depending on the parameter x, there are studied the linear stability and the Hopf bifurcation around the stationary point of the SODE [13].

The stationary point is a solution for the system of equations which is obtained by the vanishing of the functions from the right hand side of (2.1). We have the following result:

Proposition 2.1. *The stationary point has the coordinates* x_{10}, x_{20}, x_{30}*, where* $x_{10} = (a_{11} + a_1 a_{12})/a_8$*,* x_{30} *is a positive root of the equation*

$$a_{10}x^{p+1} + (A_5 a_{16} - a_1 a_{15})x^p + a_{10}a_3^p x - a_1 a_{15} a_3^p = 0, \tag{2.2}$$

for $A_5 = \frac{x_{10}^n}{a_5^n + x_{10}^n}$*, and* x_{20} *is a positive root of the equation*

$$a_9 x^3 + (a_{14}B_4B_7 - a_{13}A_2)x^2 + a_9 a_6^2 x - a_{13}a_6^2 A_2 = 0, \tag{2.3}$$

for $A_2 = \frac{x_{10}^2}{a_2^2 + x_{10}^2}$*,* $B_4 = \frac{x_{30}^4}{a_4^4 + x_{30}^4}$*,* $B_7 = \frac{x_{10}^m}{a_7^m + x_{10}^m}$.

3 The hybrid model. Numerical simulation

The interaction between the concentrations of the variables of the model and of the parameters of the model, lead to model fuzzification and randomization. The fuzzification and the randomization of the model allow us to consider a hybrid system of differential equations, as a perturbed version of a deterministic SODE. The fuzzification is performed by considering the Liu processes from [7] $C(t, z_1)$, $C(t, z_2)$,$C(t, z_3)$, where z_1, z_2, z_3 are positive numbers which define the membership functions of the normal fuzzy distributions

$$\mu_i(z_i, t) = 2\left(1 + exp\frac{\pi|z_i|}{\sqrt{6}\sigma t}\right)^{-1}, \quad i = 1, 2, 3. \tag{3.1}$$

The randomization is performed by considering a Wiener process $B(t)$. The hybrid SODE associated to (2.1) is defined by ([9]):

$$\begin{aligned} dx_i(t) &= f_i(x_1(t), x_2(t), x_3(t-\tau))dt + \alpha_i dC(t, z_i) + \\ &\quad + \beta_i(x_i(t) - x_{i0})dB(t),\ i = 1, 2, 3 \\ x_1(0) &= x_{10},\ x_2(0) = x_{20},\ x_3(\theta) = \varphi(\theta),\ \theta \in [-\tau, 0], \tau > 0, \end{aligned} \tag{3.2}$$

with $\alpha_i \geq 0, \beta_i \geq 0,\ x_i(t) = x_i(t; z_i, \omega),\ i = 1, 2, 3,$ and where

(3.3)

$$\begin{cases} f_1(x_1, x_2, x_3) = & -a_8 x_1 + a_{11} + a_1 a_{12} + a_9 x_2 - a_{13} \cdot \dfrac{x_1^2}{a_2^2 + x_1^2} + \\ & +a_{14} \cdot \dfrac{x_1^m x_2^2 x_3^4}{(a_7^m + x_1^m)(a_6^2 + x_2^2)(a_4^4 + x_3^4)} \\ f_2(x_1, x_2, x_3) = & -a_9 x_2 + a_{13} \cdot \dfrac{x_1^2}{a_2^2 + x_1^2} - a_{14} \cdot \dfrac{x_1^m x_2^2 x_3^4}{(a_7^m + x_1^m)(a_6^2 + x_2^2)(a_4^4 + x_3^4)} \\ f_3(x_1, x_2, x_3) = & -a_{10} x_3 + a_1 a_{15} - a_{16} \cdot \dfrac{x_3^p x_1^n}{(a_3^p + x_3^p)(a_5^n + x_1^n)}. \end{cases}$$

The numerical simulation of the hybrid SODE is performed by considering $\sigma = 1$ and using the system with differences ([14]):

$$\begin{aligned} x_i[j] = & \ x_i[j-1] + h f_i(x_1[j-1], x_2[j-1], x_3[j-1-\tau]) \\ & + \alpha_i L_i(j, z_i) + \beta_i(x_i[j-1] - x_{i0})G(h), \end{aligned} \tag{3.4}$$

with $i = 1, 2, 3,\ \ j = 1, \ldots, N$, where h is the iteration step and

$$\begin{cases} L_i(j, z_i) = 2\left(1 + exp\left(\dfrac{\pi|z_i|}{h\sigma\sqrt{6}S_i(j)}\right)\right)^{-1}, i = 1, 2, 3; \\ S_i(j) = b_i \displaystyle\sum_{k=1}^{j-1} x_i[k], \quad G(h) = \text{random[normald}[0, \sqrt{h}]](1). \end{cases} \tag{3.5}$$

For the values m, p, n and a_i given in the following table we obtain the orbits $(j, x_i(j, z_i, \omega))$, $i = 1, 2, 3$ of the system (3.2):

Parameters	n	m	p	a_1	a_2	a_3	a_4
Quasi-periodicity	4	2	2	0.51	.1	.3	.2
Explosion	2	4	1	0.46	.1	1	.1
Chaos	4	2	1	0.65	.1	.3194	.1
	a_5	a_6	a_7	a_8	a_9	a_{10}	
Quasi-periodicity	.5	.2	.5	.1667	.0167	.0017	
Explosion	.6	.2	.3	.1667	.0167	.0167	
Chaos	1	.3	.6	.1667	.0167	.2167	
	a_{11}	a_{12}	a_{13}	a_{14}	a_{15}	a_{16}	
Quasi-periodicity	.0333	.0333	.1	.3333	.0833	.5	
Explosion	.0333	.0333	.1	.3333	.0417	.5	
Chaos	.0333	.0333	.1	.5	.05	.8339	

Examining the three considered cases, the coordinates of the stationary point exhibit significant differences, especially for chaos case - in x_1, for both chaos and quasi-periodicity cases - in x_2 and for quasi-periodicity case - in x_3:

Stationary point	x_{10}	x_{20}	x_{30}
Quasi-periodicity	.3016376725	4.880410966	.4725167799
Explosion	.2916496701	4.475499124	.1989819160
Chaos	.3296040792	5.125545897	.1365437815

4 Hybrid and classic numeric simulations

Aiming to have a better visual understanding of how hybridization affects the classical model, we plotted the trajectories of the initial SODE and the trajectories of the hybrid system obtained after randomization and fuzzification, for $\tau = 3$, the step iteration $h = 0.001$ and $k = 400$ iterations (Fig. 1 a-c).

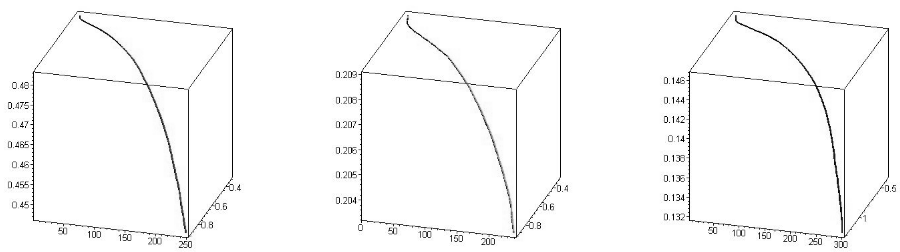

Fig. 1. Superposed hybrid/classic paths:
a) quasiperiodicity, b) explosion c) chaos

The plotted diagrams of the components of the unperturbed model for all three cases (quasiperiodicity, explosion and chaos) are the following:

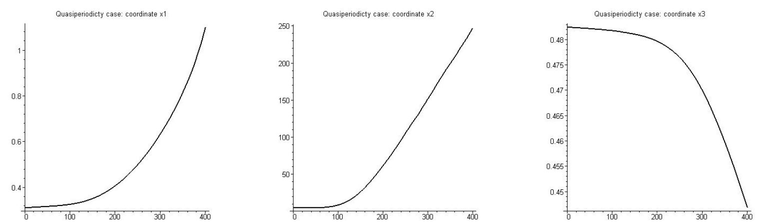

Fig. 2. Concentrations in the unperturbed quasiperiodicity case:
x_1 **-** Ca^{2+} **in cytosole,** x_2 **-** Ca^{2+} **in inner cell,** x_3 **-** $InsP_3$**.**

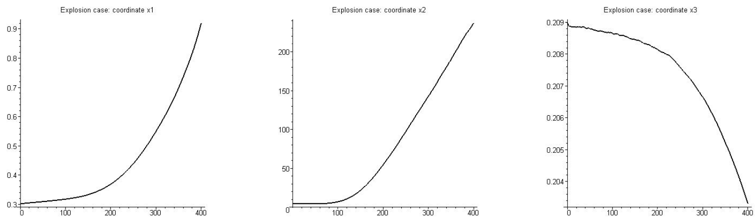

Fig. 3. Concentrations in the unperturbed explosion case:
x_1 **-** Ca^{2+} **in cytosole,** x_2 **-** Ca^{2+} **in inner cell,** x_3 **-** $InsP_3$**.**

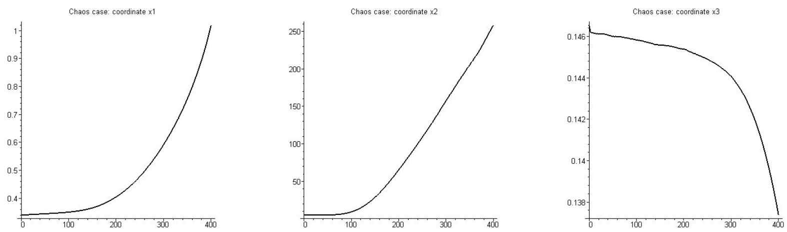

Fig. 4. Concentrations in the unperturbed chaos case:
x_1 **-** Ca^{2+} **in cytosole,** x_2 **-** Ca^{2+} **in inner cell,** x_3 **-** $InsP_3$**.**

The computer simulations for the hybrid model reveal that, for three sets of values of the parameters corresponding to three typical cases - quasiperiodicity, explosion and respectively chaos, the trajectories of the two systems (hybrid and classic) almost coincide. Namely, the plots exhibit rare line thickening, which occurs at corresponding points on the two integral curves, where deviation becomes significant. It is noteworthy to remark that the largest deviation - of order 1.6, between the trajectories of the initial SODE and the hybrid system is achieved in the case of the variable x_2, which characterizes the Ca^{2+} concentration in the inner compartment of the cell, while the other two deviations are much smaller.

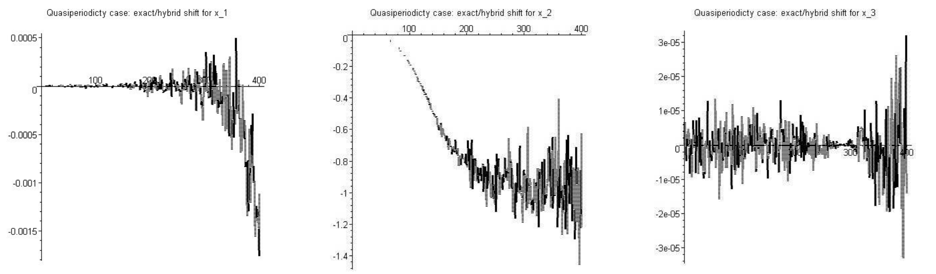

Fig. 5. Quasiperiodicity case: classic/hybrid rheonomic deviations of concentration
(x_1 **- of** Ca^{2+} **in cytosole,** x_2 **- of** Ca^{2+} **in inner cell,** x_3 **- of** $InsP_3$**)**

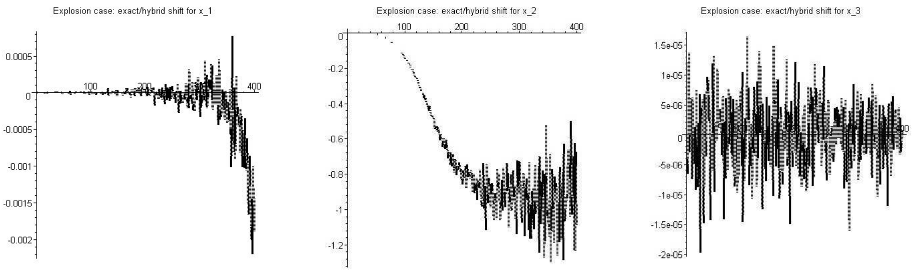

Fig. 6. Explosion case: classic/hybrid rheonomic deviations of concentration (x_1 - of Ca^{2+} in cytosole, x_2 - of Ca^{2+} in inner cell, x_3 - of $InsP_3$)

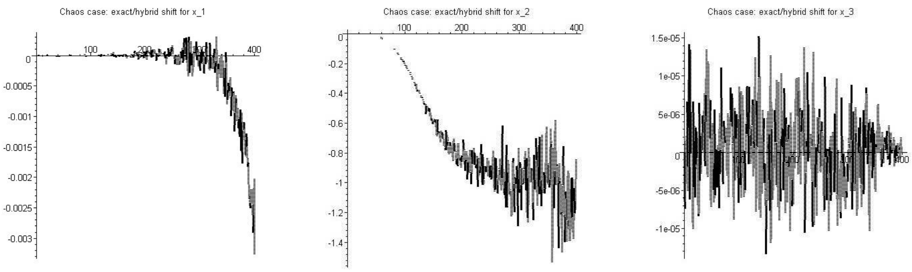

Fig. 7. Chaos case: classic/hybrid rheonomic deviations of concentration (x_1 - of Ca^{2+} in cytosole, x_2 - of Ca^{2+} in inner cell, x_3 - of $InsP_3$)

Analyzing the behavior of Ca^{2+} in cytosole and inner cell, and of $InsP_3$, we conclude that the differences between the simulated hybrid/non-hybrid paths for the three sets of value of parameters corresponding to quasiperiodicity, explosion and respectively chaos (Fig. 5, 6 and 7) exhibit the most significant deviation in the case of quasiperiodicity - which is the most affected by hybridization. Moreover, the same behavior was observed for the alternative lower delay $\tau = 2$, in all the three investigated cases. An open problem is the effect of hybridization on dynamical systems which exhibit specific particular features (e.g., Shimizu-Morioka [2, 3]). A forecoming paper will address the qualitative study of the hybrid differential system (3.2), which is subject of ongoing research.

References

[1] G. Houart, G. Dupont and A. Goldbeter, *Bursting, chaos and birhytmicity originating from self-modulation of the inositol 1,4,5-triphosphate signal in a model for intracellular Ca^{2+} oscillations*, Bull. Math. Biol., 61 (1999), 507-530.

[2] C. Cattani, A. Ciancio, *Existence theorem for hybrid competition model*, BSG Proceedings 18, Geometry Balkan Press 2011, 32-39.

[3] N. Islam, H. P. Mazumdar and A. Das, *On the stability and control of the Schimizu-Morioka system of dynamical equations*, Diff. Geom. Dyn. Syst. 11 (2009), 135-143.

[4] A.N. Kolmogorov, *Foundations of Probability Theory*, 2nd ed., New York, USA, Chelsea Publishing Co., 1960 (originally published in 1933).

[5] X. Li, B. Liu, *Chance measure for hybrid events with fuzziness and randomness*, Soft Computing 13, 2(2009), 105-115.

[6] B. Liu, *Uncertainity Theory*, Springer-Verlag, Berlin, 1st ed. 2004; 2nd ed., 2007.

[7] B. Liu, *Fuzzy process, hybrid process and uncertain process*, Journal of Uncertain Systems 2, 1(2008), 3-16, http://orsc.edu.cn/liu.

[8] B. Liu, Y.K. Liu, *Expected value of fuzzy variable and fuzzy expected value models*, IEEE Transactions on Fuzzy Systems 10, 4 (2002), 445-450.

[9] G. Mircea, M. Neamţu, A.L. Ciurdariu, D. Opriş, *Numerical simulations for dynamic stochastic and hybrid models of internet networks*, WSEAS Transactions on Mathematics 12, 8(2009), 679-688.

[10] I.R Nicola, *Geometric Methods for the Study of Some Complex Biologic Processes* (in Romanian), Bren Eds., 2007.

[11] I.R. Nicola, *Stability of limit cycles in a calcium oscillations dynamics model*, ROMAI Journal 2, 1 (2006), 157-168.

[12] I.R. Nicola I.R., V. Balan, *Jacobi stability for dynamical systems with applications to biology*, BSG Proc. 12, Geometry Balkan Press 2005, Bucharest, 195-201.

[13] I.R. Nicola, C. Udrişte, V. Balan, *Appl. of dynamical systems with time-delay in the physilogy of the hepatocyte*, Ann. Univ. Bucharest 55, 1 (2005), 97-104.

[14] D. Opriş, T. Ceauşu, A. Şandru, *Wiener, Liu and Hybrid Processes. Applications in Economy, Biology and Geometric Mechanics. Numerical Simulations* (in Romanian), Mirton Eds., Timişoara 2009.

[15] C. Udrişte, V. Balan, I.R. Nicola, *Linear stability and Hopf bifurcations for time-delayed intra-cell calcium variation models*, BSG Proc. 12, Geometry Balkan Press, 2005, 272-283.

[16] L.A. Zadeh, *Fuzzy sets as a basis for a theory of posibility*, Fuzzy Sets and Systems 1 (1978), 3-28.

Authors' addresses:

Vladimir Balan
University Politehnica of Bucharest, Faculty of Applied Sciences,
Department of Mathematics-Informatics I, 313 Splaiul Independentei,
RO-060042 Bucharest, Romania. E-mail: vladimir.balan@upb.ro

Ileana Rodica Nicola
University "Spiru Haret" of Bucharest, Faculty of Mathematics and Informatics,
Ion Ghica Str. 13, RO-030045 Bucharest, Romania.
E-mail: nicola_rodica@yahoo.com

Dumitru Opriş
West University of Timişoara, Faculty of Mathematics and Computer Science,
Department of Mathematics, Bd. V. Parvan, nr. 4, RO-300223 Timişoara, Romania.
E-mail: opris@math.uvt.ro