Jacobi stability of dynamical systems with applications to biology

Ileana Rodica Nicola and Vladimir Balan

Abstract

The paper investigates the structural stability of hepatocyte physiology in the case of bursting (explosive) behavior, based on the five KCC-invariants of the second-order canonic extension of the characterizing SODE.

Mathematics Subject Classification: 37N25, 92C45.
Key words: dynamical system, KCC-invariants, Jacobi stability.

1 Introduction.

It is well known that the SODE (system of ordinary diferential equations) which describes the intra-cell calcium variation in time exhibit a very rich and complex dynamical behavior.

In the present work we investigate the robustness and the fragility of a mathematical biological model which describes the Calcium variations in time in the living cell, by means of the deviation curvature tensor of the attached SODE (KCC or Jacobi stability). By robustness we mean both the relative insensitivity to alteration of their internal parameters and the ability to adapt to changes in their environment. From the mathematical point of view, the differential geometrical theory of variational equations studying the deviation of nearby trajectories allows us to estimate the admissible perturbation arround the steady states of the SODE. By admissible mean perturbations we have in view the ones which do not change the stability ranges of the system.

The applicative biological aspects of our model represent an important open question in the field, and are subject of further research.

The calcium variations in time model is based on the mechanism of calcium induced calcium release (CICR). This model takes into account calcium-stimulated degradation of inositol 1,4,5- triphosphate ($InsP_3$) by a 3-kinase.

Complex calcium (Ca^{2+}) variations in time have been observed in certain cell types, particularly in hepatocytes, as a response to stimulation by certain substances.

Proceedings of The 3-rd International Colloquium "Mathematics in Engineering and Numerical Physics" October 7-9 , 2004, Bucharest, Romania, pp. 195-201.

Because these cells are not electrically excitable, it is likely that these complex calcium variations rely on the interplay between two intracellular mechanisms capable of destabilizing the steady state. Two antagonistic effects are indeed at play: an increase in a substance called inositol is expected to lead to an increase in the frequency of calcium spikes, but at the same time the inositol induces rise in calcium, will also leads to increased inositol metabolisis due to the calcium activation of the inositol 3-kinase.

The model for calcium variations used in the present study containes three variables, namely the concentration of free Ca^{2+} in the cytosol (Z) and in the internal pool (Y), and the $InsP_3$ concentration (A). The time evolution of these variables is governed by the following SODE

$$
(1.1)\quad \begin{cases} \dfrac{dZ}{dt} = & -k\cdot Z + V_0 + \beta\cdot V_1 + k_f\cdot Y - V_{M_2}\cdot \dfrac{Z^2}{k_2^2+Z^2} + \\ & +V_{M_3}\cdot \dfrac{Z^m}{k_Z^m+Z^m}\cdot \dfrac{Y^2}{k_Y^2+Y^2}\cdot \dfrac{A^4}{k_A^4+A^4} \\ \dfrac{dY}{dt} = & -k_f\cdot Y + V_{M_2}\cdot \dfrac{Z^2}{k_2^2+Z^2} - V_{M_3}\cdot \dfrac{Z^m}{k_Z^m+Z^m}\cdot \dfrac{Y^2}{k_Y^2+Y^2}\cdot \dfrac{A^4}{k_A^4+A^4} \\ \dfrac{dA}{dt} = & \beta\cdot V_{M_4} - V_{M_5}\cdot \dfrac{A^p}{k_5^p+A^p}\cdot \dfrac{Z^n}{k_d^n+Z^n} - \varepsilon\cdot A, \end{cases}
$$

where

- V_0 refers to a constant input of Ca^{2+} from the extracellular medium;
- V_1 is the maximum rate of stimulus-induced influx of Ca^{2+} from the extracellular medium;
- β reflects the degree of stimulation of the cell by an agonist and thus only varies between 0 and 1;
- the rates V_2 and V_3 refer, respectively, to pumping of cytosolic Ca^{2+} into the internal stores and to the release of Ca^{2+} from these stores into the cytosol in a process activated by citosolic calcium (CICR); V_{M2} and V_{M3} denote the maximum values of these rates;
- parameters k_2, k_Y, k_Z and k_A are treshold constants for pumping, release, and activation of release by Ca^{2+} and by $InsP_3$;
- k_f is a rate constant measuring the passive, linear leak of Y into Z;
- k relates to the assumed linear transport of citosolic calcium into the extracellular medium;
- V_{M4} is the maximum rate of stimulus-induced synthesis of $InsP_3$;
- V_{M_5} is the rate of phosphorylation of $InsP_3$ by the 3-kinase;
- m, n and p are Hill coefficients related to the cooperative processes;
- ε is the phosphorilation rate of $InsP_3$ by the 5-phosphatase.

We remind that from biological point of view, this SODE is based on the mechanism of Calcium release induced by Calcium influenced by the inozitol 1,4,5-triphosphate (IP_3) degradation by a 3-kynase. This model may exhibit various types of variations as: explosion, chaos, quasi-periodicity, depending on the values assigned to the parameters.

2 KCC-theory and Jacobi stability

We recall first some basics of KCC-theory ([17], [1], [2]). Let $x = (x^1, ..., x^n)$,

$$\dot{x} = \left(\frac{dx}{dt}\right) = \left(\frac{dx^1}{dt}, \frac{dx^2}{dt}, \ldots, \frac{dx^n}{dt}\right) \tag{2.1}$$

and t be the $2n+1$ coordinates of an open connected subset $\Omega \subset \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^1$. We consider a second order system of differential equations of the form

$$\frac{d^2x^i}{dt^2} + g^i(x, \dot{x}, t) = 0, \quad i \in \overline{1, n}, \tag{2.2}$$

where each function $g^i(x, \dot{x}, t)$ is smooth in a neighborhood of some initial conditions $(x_0, \dot{x}_0, t_0) \in \Omega$. In order to find the basic differential invariants of the system (2.2) (see Kosambi [10], E. Cartan [7] and S.S.Chern [8]) under the non-singular coordinate transformations

$$\overline{x}^i = f^i(x^1, \ldots, x^n), i \in \overline{1, n}, \overline{t} = t, \tag{2.3}$$

we define the KCC-covariant differential of a contravariant vector field $\xi^i(x)$ on the open subset Ω via

$$\frac{D\xi^i}{dt} = \frac{d\xi^i}{dt} + \frac{1}{2} g^i_{;r} \xi^r, \tag{2.4}$$

where ";" indicates partial differentiation with respect to $\dot{x}$, and the Einstein summation convention is used throughout. Using (2.4), the system (2.2) becomes

$$\frac{D\dot{x}^i}{dt} = \frac{1}{2} g^i_{;r} \dot{x}^r - g^i = \varepsilon^i, \tag{2.5}$$

where ε^i defined here is a contravariant vector field on Ω and is called *the first KCC-invariant*, which is interpreted as an external force [1]. The functions $g^i = g^i(x, \dot{x}, t)$ are 2 homogeneous in $\dot{x}$ if and only if $\varepsilon^i = 0$. In other words, $\varepsilon^i = 0$ is a necessary and sufficient condition for a semispray to be a spray. It is obvious that for the geodesic spray of a Riemannian or Finsler manifold, the first invariant vanishes.

It can be easily seen that, since the system is of the form $\dot{x} = X(x)$, the first invariant has the components $\varepsilon^i = \frac{1}{2} \frac{\partial X^i}{\partial x^r} \dot{x}^r$, and hence this vanishes for null velocities, i.e. on the stationary points of the field X. We shall further use for the SODE (1.1) the set of parameter values commonly used in the case of "explosion" (bursting),

$$\begin{aligned}
&\beta = 0.46,\ n = 2,\ m = 4,\ p = 1,\ K_2 = 0.1\mu M,\ k_5 = 1\mu M,\\
&k_A = 0.1\mu M,\ k_d = 0.6\mu M,\ k_Y = 0.2\mu M,\\
&k_Z = 0.3\mu M,\ k = 0.1667 s^{-1},\ k_f = 0.0167 s^{-1},\ \varepsilon = 0.0167 s^{-1},\\
&V_0 = 0.0333\mu M \cdot s^{-1},\ V_1 = 0.0333\mu M \cdot s^{-1},\ V_{M_2} = 0.1\mu M \cdot s^{-1},\\
&V_{M_3} = 0.3333\mu M \cdot s^{-1},\ V_{M_4} = 0.0417\mu M \cdot s^{-1},\ V_{M_5} = 0.5\mu M \cdot s^{-1}.
\end{aligned} \tag{2.6}$$

Using Maple computer techniques, the condition of having the first invariant null on nonzero sections of the tangent space $T\mathbb{R}^3$ is equivalent to the vanishing of the determinant of the Jacobi matrix of the SODE vector field, i.e.,

$$
\begin{aligned}
&-1.\cdot(.5167000000\cdot Z^2+.3340000000e-1\cdot A\cdot Z^2+.6012000000e^2+.1202400000e^{-1}\cdot A+\\
&+.6012000000e^{-2}\cdot A^2+.1670000000e-1\cdot A^2\cdot Z^2)\cdot(.3607921440e^{-11}+\\
&+.3607921440e^{-7}\cdot A^4+.1803960720e^{-9}\cdot Y^2+.1803960720e^{-5}\cdot Y^2\cdot A^4+\\
&+.2254950900e^{-8}\cdot Y^4+.2254950900e^{-4}\cdot Y^4\cdot A^4+.4454224000e^{-9}\cdot Z^4+\\
&+.4454224000e^{-5}\cdot Z^4\cdot A^4+.2227112000e^{-7}\cdot Z^4\cdot Y^2+.2227112000e^{-3}\cdot Z^4Y^2A^4+\\
&+.2783890000e^{-6}\cdot Z^4\cdot Y^4+.2783890e^{-2}\cdot Z^4\cdot Y^4\cdot A^4+.444488880e^{-2}\cdot Z^4\cdot Y\cdot A^4)\cdot\\
&\cdot[(.360000+Z^2)(1+A)^2(.100000e^{-3}+A^4)(.4e^{-1}+Y^2)^2(.81000e^{-2}+1.\cdot Z^4)]^{-1}=0.
\end{aligned}
$$

This strongly nonlinear equation does not depend on velocities, and admits no solutions in the first octant of the position variables. But in the general extended case, when $(Z,Y,A)\in\mathbb{R}^3$ there exists a region in $T\mathbb{R}^3$ where the first invariant cancels: this is the total space of a vector subbundle (E,π_1,Σ) of rank one of $(T\mathbb{R}^3,\pi,\mathbb{R}^3)$, having as basis a surface Σ.

On the other hand, it is known that if the trajectories $x^i(t)$ of (2.2) are varied into nearby ones with respect to x as $\bar{x}^i(t)=x^i(t)+\xi^i(t)\eta$ with the parameter η small, one gets the variational equations

$$\frac{d^2\xi^i}{dt^2}+g^i_{;r}\frac{d\xi^r}{dt}+g^i_{,r}\xi^r=0, \tag{2.7}$$

where "," indicates partial differentiation with respect to x. Using now the KCC-covariant differential (2.4), one obtains (2.7) in the covariant form

$$\frac{D^2\xi^i}{dt^2}=P^i_r\xi^r, \tag{2.8}$$

where

$$P^i_j=-g^i_{,j}-\frac{1}{2}g^rg^i_{;r;j}+\frac{1}{2}\dot{x}^rg^i_{,r;j}+\frac{1}{4}g^i_{;r}g^r_{;j}+\frac{1}{2}\frac{\partial g^i_{;j}}{\partial t} \tag{2.9}$$

is called *the second KCC-invariant* of the system (2.2), or *deviation curvature tensor*. Its eigenstructure is an alternative to the Floquet Theory, with the eigenvalues of P^i_j replacing the characteristic multipliers (also called Floquet exponents, [15], [3]). In our case, it has the generic form

$$P^i_j=\frac{\partial^2X^i}{\partial x^j\partial x^r}\dot{x}^r+\frac{1}{4}\frac{\partial X^i}{\partial x^r}\frac{\partial X^r}{\partial x^j}.$$

Note that (2.8) is the Jacobi field equation when the starting system (2.2) are geodesic equations in either Finsler or Riemannian geometry. This justifies the usage of the term Jacobi stability for KCC-Theory.

On the other hand, the Jacobi equation (2.8) of the Finsler manifold (M,F) can be written in the scalar form

$$\frac{d^2v}{ds^2}+K\cdot v=0, \tag{2.10}$$

where $\xi^i=v(s)\eta^i$ is a Jacobi field along $\gamma: x^i=x^i(s)$, η^i is the unit normal vector field along γ; K is the flag curvature of (M,F) ([4]).

It is also known that the sign of K influences the geodesic rays ([4]). Indeed, if $K>0$, then the geodesic bunch together (are Jacobi stable), and if $K<0$, then they disperse (are Jacobi unstable).

Hence negative flag curvature is equivalent to positive eigenvalues of P^i_j, and positive flag curvature is equivalent to negative eigenvalues of P^i_j. It is known the following

Theorem 1. ([2], [1]) *The trajectories of (2.2) are Jacobi stable if and only if the real parts of the eigenvalues of the deviation tensor P^j_i are strict negative everywhere, and Jacobi unstable, otherwise.*

The notion of Jacobi stability presented until here can be extended to the general case of the SODE (2.2) using the Theorem above as the definition for the Jacobi stability of the traiectories of a SODE. The third, fourth and fifth invariants of the system (2.2) are respectively

$$R^i_{jk} = \frac{1}{3}(P^i_{j;k} - P^i_{k;j}), \quad B^i_{jkl} = R^i_{jk;l}, \quad D^i_{jkl} = g^i_{;j;k;l}. \tag{2.11}$$

A basic result of the KCC-theory which points out the role of the five invariants is the following:

Theorem 2. ([1]) *Two SODE's of form (2.2) on Ω can be locally transformed, relative to (2.3), one into another, if and only if their five invariants $\varepsilon^i, P^i_j, R^i_{jk}, B^i_{jkl}, D^i_{jkl}$ are equivalent tensors. In particular, there are local coordinates $(\overline{x})$ for which $g^i(x, \dot{x}, t) = 0$ if and only if all five KCC-tensors vanish.*

Based on Maple computations, we can infer straightforward that for our SODE subject to the requirement of having real (positive) solutions (Z, Y, A), there exists no coordinate change such that the coefficients of the new second order SODE-semispray do all vanish, i.e., the trajectories of the second-order extended system (including the field lines of the initial SODE) can never be lines, whatever coordinate system one might choose.

3 MAPLE numerical results on Linear and KCC-stability

Proposition 1. *In the "explosion" subcase, i.e., the parameter values below, the deviation curvature tensor P^i_j has the positive eigenvalue $\lambda_1 = 0.001326818690$ and the two complex conjugate eigenvalues with negative real part $\lambda_{2,3} = -0.01505325754 \pm 0.001930995461\sqrt{3}I$. Hence the field lines of the system are Jacobi unstable.*

Considering the parameter k_Y variable within the interval $(0, 1)$ and the other parameters taking the values in (2.6), we get the following results regarding linear stability and Jacobi stability.

Proposition 2. *For $k_Y \in (0, 1)$ the system (1.1) admits a "positive" equilibrium point (Z_0, Y_0, A_0) and the discriminant of the characteristic polyomial of the Jacobi matrix attached to (1.1) is positive and depends discontinously on k_Y. There exists a set of pairs $0 < \varepsilon_1 < \delta_1 < \ldots < \varepsilon_n < \delta_n < 1$, $n \in \mathbf{N}$ such that the Jacobi matrix has a real eigenvalue and two complex conjugate eigenvalues for $k_Y \in (\varepsilon_i, \delta_i)$.*

Proposition 3. *There exist a positive constant $\varepsilon \in (0.11, 0.12)$ such that for $k_Y \in (\varepsilon, 1)$ the deviation curvature tensor P^i_j has a real positive eigenvalue and two complex conjugate eigenvalues, hence the field lines of (1.1) are Jacobi unstable.*

For $k_Y \in (0, \varepsilon)$, the deviation curvature tensor P^i_j has three real eigenvalues, of which one is positive; hence for this case the field lines are Jacobi unstable.

In the following we consider the parameter V_{M3} varying freely in the interval $(0, 1)$; the effect on this paths of the SODE (1.1) is described by the following results:

Proposition 4. For $V_{M3} \in (0, 1)$ the system (1.1) admits a "positive" equilibrium point (Z_0, Y_0, A_0). There exists a real constant $\varepsilon \in (0.45, 0.46)$ such that, for $V_{M3} \in (0, \varepsilon)$, Y_0 continuously depends on V_{M3}. For $V_{M3} \in (\varepsilon, 1)$, Y_0 exibits singularities.

Proposition 5. *There exist three constants $\varepsilon_1 \in (0.023, 0.024)$, $\varepsilon_2 \in (0.124, 0.125)$ and $\varepsilon_3 \in (0.225, 0.226)$ such that:*

a) for $V_{M3} \in (\varepsilon_1, \varepsilon_2) \cup (\varepsilon_3, 1)$ the Jacobi matrix of the system (1.1) has a real eigenvalue and two complex conjugate eigenvalues; for $V_{M3} \in (\varepsilon_1, \varepsilon_2)$ the equilibrium point (Z_0, Y_0, A_0) is an attractor.

b) for $V_{M3} \in (0, \varepsilon_1) \cup (\varepsilon_2, \varepsilon_3)$ the Jacobi matrix of the system (1.1) admits three real eigenvalues.

Proposition 6. *For $V_{M3} \in (0, 1)$ the deviation curvature tensor P^i_j has a real positive eigenvalue and two complex conjugate eigenvalues, and hence the field lines of the system are Jacobi unstable.*

Acknowledgement. The present work was partially supported by the Grant CNCSIS MEN A1478/2004, MA51-04-01.

References

[1] P.L. Antonelli, *Equivalence problem for systems of second order ordinary differential equations*, Encyclopedia of Math., Kluwer Acad. Publ, 2000.

[2] P.L. Antonelli, R. Ingarden, M. Matsumoto, *The Theory of Sprays and Finsler Spaces with Applications in Physics and Biology*, Kluwer Acad. Publ, FTPH vol. 58, 1993.

[3] P.L.Antonelli, S. Rutz, V.S. Sabău, *A transient-state analysis of Tyson's model for the cell division cycle by means of KCC-theory*, Open System & information Dynamics, 9 (2002), 3, 223-238.

[4] D. Bao, S.S. Chern, Z. Shen, *An Introduction to Riemann-Finsler Geometry*, Springer, GTM 200, 2000.

[5] M. Berridge, P. Lipp, M. Bootman, *Calcium signalling*, Curr. Biol. 9, R157-R159, (1999).

[6] J. A. M. Borghans, G. Dupont, A. Goldbeter, *Complex intracellular calcium oscillations: A theoretical exploration of possible mechanisms*, Biophys. Chem. 66, 25-41, (1997).

[7] E. Cartan, *Observations sur le mémoir précédent*, Math. Zeitschrift 37 (1933), 619-622.

[8] S.S. Chern, Sur la geometrie d'un système d'equations differentialles du second ordre, Bull. Sci. Mat. 63 (1939), 206-212.

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

[10] D.D. Kosambi, *Parallelism and path space*, Math. Zeitschrift 37 (1933), 608-618.

[11] G.Mircea, M.Neamţu, D.Opriş, *Dynamical Systems in Economy, Mechanics, Biology Described by Differential Equations with Time-Delay* (Romanian), Mirton Press, Timişoara 2003.

[12] M.Neagu, I.R.Nicola, *Geometric dynamics of calcium oscillations ODE systems*, BJGA 9 (2004), 2, 36-67.

[13] I.R.Nicola, C.Udrişte, V.Balan, *Time-delayed flow of hepatocyte physiology*, Annals of the University of Bucharest, to appear.

[14] D.Opriş, C.Udrişte, *Pole shifts explained by a Dirac delay in a Stefanescu magnetic flow*, An. Univ. Bucureşti, LIII, 1 (2004), 115-144.

[15] C. Robinson, *Dynamical Systems: Stability, Symbolic Dynamics and Chaos*, CRC Press, 1995.

[16] J. A. Rottingen, J.G. Iversen, *Rulled by waves ? Intracellular and intercellular calcium signalling*, Acta Physiol. Scand. 169 (2000), 203-219.

[17] V.S. Sabău, *Systems biology and deviation curvature tensor*, preprint.

[18] G.Stefan, *Retarded Dynamical Systems. Stability and Characteristic Functions*, Longman Sci & Technical, England 1989.

[19] N.V.Tu, *Introductory Optimization Dynamics*, Springer Verlag, 1991.

[20] C.Udrişte, *Algebra, Geometry and Differential Equations* (Romanian), Editura Didactică şi Pedagogică, Bucharest, 2002.

Ileana Rodica Nicola and Vladimir Balan
Department Mathematics I, University Politehnica of Bucharest,
Splaiul Independentei 313, RO-060042, Bucharest, Romania,
email: nicola_rodica@yahoo.com, vbalan@mathem.pub.ro