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Dynamical Systems

Liénard systems and potential-Hamiltonian decomposition III – applications

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Abstract

In the two previous Notes, we described the mathematical aspects of the potential-Hamiltonian (PH) decomposition, in particular for n-switches and Liénard systems. In the present Note, we give some examples of biological regulatory systems susceptible to be decomposed. We show that they can be modeled in terms of 2D-ODE belonging to n-switches and Liénard systems families. Although simplified, these models can be decomposed in a set of equations combining a potential and a Hamiltonian part. We discuss about the advantage of such a PH-decomposition for understanding the mechanisms involved in their regulatory abilities. We suggest a generalized algorithm to deal with differential systems having a second part of rational fraction type (frequently used in metabolic systems). Finally, we comment what can be interpreted as a precise signification in biological systems from the dynamical behaviors of both the potential and Hamiltonian parts. ***To cite this article: N. Glade et al., C. R. Acad. Sci. Paris, Ser. I 344 (2007).***

Résumé

Systèmes de Liénard et décomposition potentielle-Hamiltonienne III – applications. Dans les deux Notes précédentes, nous avons décrit la décomposition potentielle-Hamiltonienne pour des systèmes de type n-switch ou Liénard. Leurs équations sont bien adaptées à la modélisation des systèmes dynamiques en biologie. Nous donnons ici des exemples de systèmes de régulation biologique pouvant être écrits sous la forme d'équations de Liénard et également sous forme de systèmes n-switch. Nous discutons ensuite de l'intérêt de connaître les contributions potentielles et Hamiltoniennes de ces systèmes dans la compréhension de leurs mécanismes. Pour terminer, nous suggérons un algorithme prenant en compte des systèmes différentiels à second membre de type fraction rationnelle rencontrés dans les modèles métaboliques, pour lesquels les parties potentielle et Hamiltonienne ont des significations biologiques précises. On explique comment utiliser en pratique cette décomposition au voisinage de leurs attracteurs. ***Pour citer cet article : N. Glade et al., C. R. Acad. Sci. Paris, Ser. I 344 (2007).***

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Les systèmes de Liénard et les systèmes de type n-switch sont fréquemment utilisés pour modéliser des systèmes biologiques régulés, au niveau physiologique (système mono-organe comme le système cardiaque, respiratoire ou neural, et systèmes pluri-organes, comme le système végétatif, par couplage de systèmes de Liénard) ou au niveau moléculaire (processus morphogénétiques, où la composante n-switch représente la partie réactionnelle d'un système de diffusion–réaction). La décomposition potentielle-hamiltonienne [12,13] proposée pour traiter de tels systèmes permet de séparer leurs paramètres responsables de la bifurcation en régime oscillant en trois familles : l'une qui contrôle la période des oscillations (paramètres apparaissant dans la partie hamiltonienne), l'autre qui contrôle leur amplitude (paramètres apparaissant dans la partie potentielle), et la dernière qui contrôle à la fois la période et l'amplitude (paramètres apparaissant dans les deux parties de la décomposition potentielle-hamiltonienne). La signalisation des systèmes régulés fait en effet fréquemment appel à des modulations distinctes (de fréquence et d'amplitude) et il est essentiel de distinguer les paramètres responsables de ces modulations.

Un premier exemple d'application est constitué par les équations de Liénard, qui sont des Equations Différentielles Ordinaires de Dimension 2 (2D-EDO) du type : $\mathrm{d}x/\mathrm{d}t = y$, $\mathrm{d}y/\mathrm{d}t = -g(x) + yf(x)$, où f et g sont des polynômes. Par exemple, dans le système de van der Pol [25], nous avons : $g(x) = x$ et $f(x) = \mu(1 - x^2)$ et le système de FitzHugh–Nagumo [16,22,26] n'est qu'une variante de ce système de van der Pol, obtenue par un changement de variable (cf. Fig. 1). Les deux systèmes ont en particulier le même réseau isochrone (cf. Fig. 2).

L'intégration cardio-respiratoire, dans le système régulé végétatif, peut se modéliser par un couplage d'équations de van der Pol (cf. Fig. 4) :

$$\mathrm{d}x/\mathrm{d}t = y, \qquad \mathrm{d}y/\mathrm{d}t = -x + \varepsilon y\big(1 - x^2\big),$$
$$\mathrm{d}z/\mathrm{d}t = w, \qquad \mathrm{d}w/\mathrm{d}t = -z + \eta\big(1 - z^2\big)w + k(y)y,$$

où $k(y)$ représente le coefficient de couplage. Le calcul de la période d'entraînement du deuxième système de van der Pol par le premier, à travers ce couplage, donne la valeur :

$$T = 2\pi/\sqrt{\big(1 - \big(\eta\big(1 - \big(k(y)y\big)^2\big)\big)^2/4\big)}.$$

L'expression de T traduit l'influence du rythme respiratoire sur le rythme cardiaque (phénomène appelé arythmie respiratoire sinusale), dont la surveillance des variations est cruciale, pour vérifier l'intégrité du système végétatif de régulation cardio-respiratoire.

Si le couplage d'équations de Liénard met en jeu plus de deux systèmes, on peut être amené, à la limite, à étudier une Equation aux Dérivées Partielles (EDP) de type Burger, pour mettre par exemple en évidence des ondes progressives.

Si l'on considère enfin des systèmes métaboliques périodiques, régis par des cinétiques classiques de type michaëlien ou de type allostérique, on peut également obtenir une décomposition potentielle-hamiltonienne au voisinage de leurs cycles-limites, si ceux-ci sont proches de la bifurcation qui leur a donné naissance.

1. Introduction

Liénard and n-switches systems have served as paradigm or toy models for many biological regulatory systems (cardiac, respiratory, neural, ...) and morphogenetic processes (e.g. in embryogenesis and neogenesis) presenting a periodic temporal behavior with relaxation waves for excitable cells isolated or connected in functional tissues and spatio-temporal patterns if they belong to regulatory and/or morphogenetic networks. In tissues, these interacting cells can cause solitary waves or periodic spatial structures stationary in time (participating to the determination of the anatomy of the tissue by generating the morphology of the corresponding organ). They can also produce periodic structures in time, acting as intercellular or tissular signal triggers, e.g. provoking a collective behavior, the best example being the cardiac tissue in the heart. These systems are frequently used and we give here some examples of their use.

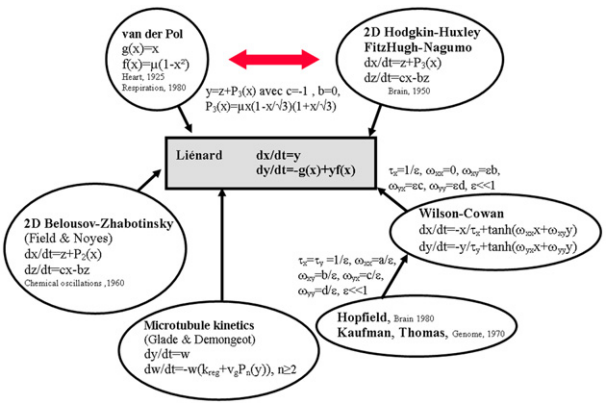

Fig. 1. An overview of Liénard systems in biological models.

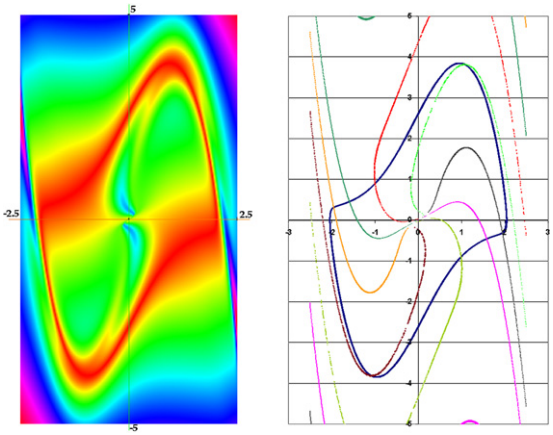

Fig. 2. False color representation of the velocity vectors norm for a van der Pol system (left) and isochronal fibration (right) (for $\mu = 2$, limit cycle period $T \simeq 7.642$).

2. Liénard systems as a paradigmatic model for biological regulatory systems

2.1. Classical examples of Liénard systems in biological modeling

Liénard equations are 2D-ODEs defined by: $\mathrm{d}x/\mathrm{d}t = y$, $\mathrm{d}y/\mathrm{d}t = -g(x) + yf(x)$, where g and f are polynomials. They have been used in physiology to simulate both the heart and respiratory system (van der Pol equations original [25] and modified [19]) and the nerve impulse (FitzHugh–Nagumo equations [14,18]). FitzHugh–Nagumo equations are just a 2D approximation of the Hodgkin–Huxley equations, fundamental in neurobiology [16,22,26].

FitzHugh–Nagumo equations can be approached by the Wilson–Cowan system [10,23]. It has, in certain parametric circumstances, the same behavior than the Hopfield equations. In addition, the kinetics of the in vitro self-assembly of populations of microtubules, major elements of the cell skeleton, can be approached by Liénard systems by considering assembled (microtubules) and non-assembled (free tubulin molecules) species. Finally, Liénard systems are used for modeling oscillatory chemical reactions, for example the Belousov–Zhabotinsky reaction (Noyes equations [15,24]). These examples illustrate the universality of the Liénard systems (Fig. 1), which definitively constitute the natural mathematical framework in which many biological and chemical equations can be embedded.

As presented in the previous Notes [12,13], one of their main properties is their ability to modelize periodic behaviors with simple isochronal patterns (Fig. 2) susceptible to explain the entrainment of biological systems by instantaneous periodic stimulations.

2.2. The example of the regulon

The regulon structure is frequently observed in biology. It is made of a loop of activation and inhibition between two components A and B, with a self-activation of A. One can observe it for example in the CRO operon of the phages λ and μ, or in excitable networks such as the hippocampus, the bulbar respiratory center, the heart, ... (Fig. 3). The regulon can have two stable steady states (due to the presence of the positive loop for the multi-attractority and of the negative one for the stability [3,4]). One can note that a Liénard system is a regulon, where A (resp. B) is represented by the variable y (resp. x), if g, $f > 0$ and $-g' + yf' < 0$.

2.3. Examples in cardiac and respiratory coupled systems

To represent the vegetative control system of the cardiac and respiratory functions, let's consider two regulon-type coupled oscillators in interaction [2,11]. Indeed to simplify, we consider I, a set of inspiratory neurons (a center firing synchronously with the phrenic nerve) having a self-activatory loop and interacting with E, a set of expiratory neurons

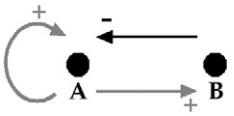

Fig. 3. Regulon scheme. Grey arrows are activatory (+) whereas the black one is inhibitory (−). A activates the formation of B and its own formation (self-catalysis), whereas B inhibits the formation of A.

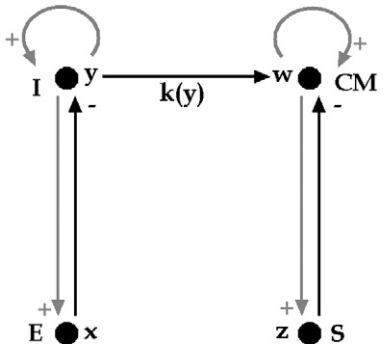

Fig. 4. Coupling between the respiratory oscillator (left) and the cardiac oscillator (right).

(a center firing during the phrenic silence); E is activated by I (via the pleural stretch receptors) and E inhibits I (through intra-bulbar connections) (Fig. 4).

We neglect in this simplified description other classical groups of neurons corresponding to the Richter classification. Taking them into account leads to a system of higher dimension having the same qualitative dynamical properties, in particular the entrainment ability [19]. In the same way, by neglecting the peripheral Aschow–Tawara node, we consider the cardiac control system as made of 2 groups of excitable cells, one located in the bulb, composed of neurons and called the cardio-modulator center CM, and the other located in the heart septum, called the sinusal node S (Fig. 4).

The van der Pol system representing the rhythmic respiratory activity is $\mathrm{d}x/\mathrm{d}t = y$, $\mathrm{d}y/\mathrm{d}t = -x + \varepsilon y(1 - x^2)$, where ε represents the anharmonic parameter. This oscillator has a free run (proper period) τ equal (near the bifurcation of the van der Pol limit cycle obtained for $\varepsilon = 0$), to the ratio $\tau = 2\pi/Im$, where $Im = \sqrt{1 - \varepsilon^2/4}$ is the imaginary part of the eigenvalues of the Jacobian matrix J of the van der Pol system:

$$J = \begin{bmatrix} 0 & 1 \\ -1 - 2\varepsilon xy & \varepsilon(1 - x^2) \end{bmatrix} \quad \text{taken at the stationary point } (x = 0,\ y = 0).$$

The van der Pol system representing the rhythmic cardiac activity is $\mathrm{d}z/\mathrm{d}t = w$, $\mathrm{d}w/\mathrm{d}t = -z + \eta(1 - z^2)w + k(y)y$, where η is the anharmonic parameter and $k(y)$ is the coupling intensity between I and CM. The entrained period of the cardiac oscillator is approximately equal (if η is small) to:

$$T = 2\pi/\sqrt{1 - \big(\eta\big(1 - \big(k(y)y\big)^2\big)\big)^2/4}.$$

Values of ε et η are fixed by the proper periods of the respiratory (4 seconds) and cardiac (1 second) oscillators. $k(y)$ is obtained by measuring the instantaneous cardiac period T (inter-beats duration) and calculating the slope of the regression line between T and the inspiratory activity y^2 (y being represented by the local inspiratory time counted from the beginning of an inspiration, when the cardiac beat of period T is occurring). This slope is approximated by $-\pi(\eta k(y))^2/2$, if η and $k(y)$ are small, and is estimated by the correlation coefficient ϱ between T and y^2 [2,11] multiplied by the ratio between standard deviations of T and y^2.

The integrity of the coupling between the 2 Liénard systems [17] allows the bulbar vegetative control system to adapt to the effort: first the breathing is entrained by a muscular activity and secondarily entrains the heart. Such a capacity of adaptation disappears in degenerative diseases like Parkinson or diabetes. Watching a parameter like ϱ is then interesting in elderly people surveillance and the at home watching systems will conversely permit the emergence of a new knowledge about the vegetative regulation and the improvement of the at home rehabilitation systems.

More generally, the study of series of coupled oscillators is necessary to explain synchronization, desynchronization and entrainment phenomena [23]. According to the previous example, we can establish the series of oscillators:

$$i = 1, \ldots, N, \quad \mathrm{d}x_i/\mathrm{d}t = y_i, \quad \mathrm{d}y_i/\mathrm{d}t = -g(x_i) + g(x_{i-1}) + y_i f(x_i).$$

The continuous limit in i leads to the partial differential equation (PDE):

$$\partial^2 x/\partial t^2 = f(x)\partial x/\partial t - g'(x)\partial x/\partial s.$$

This new class of PDE is an extension of Burger's equation (by exchanging the role of s and t [21]) and has to be studied in future articles (existence and unicity of solutions, traveling waves, conservative properties, ...).

2.4. Extension to metabolic systems

In genetic or metabolic regulatory systems, we can sometimes extract a potential and a Hamiltonian part [4,5,8,12,13]. If we suppose that enzyme kinetics are of Michaëlian or allosteric type, a polynomial $P(x_i)$ exists of order n (called 'cooperativity'), where x_i is the concentration of the substrate catalyzed by the ith enzyme of the metabolic system, then the degradation rate of x_i is given – if no other metabolite contributes to its catabolism – by $(-\partial \log P(x_i)/\partial \log x_i)/n$. In general, the corresponding differential system has a principal potential part (the system tends to become a gradient system when $\|x_i\|$ tends to infinity [8]), in particular because of the saturation of terms like $\partial \log P(x_i)/\partial \log x_i$. Then we can prove easily by denoting $y_i = \log x_i$ (the de Donder chemical affinity [6,7]) that if there are 2 enzymes in the metabolic system with the same cooperativity n and if the substrate x enters with a constant flux σ, we have:

$$\mathrm{d}y_1/\mathrm{d}t = \exp(-y_1)(\sigma - \partial \log P_1/\partial y_1)/n, \qquad \mathrm{d}y_2/\mathrm{d}t = \exp(-y_2)(\partial \log P_1/\partial y_1 - \partial \log P_2/\partial y_2)/n.$$

This system is PH-decomposable into two analytic parts in the neighborhood of a fixed point or of a just bifurcating limit cycle for which $\exp(-y_i)$'s can be considered as constant, with the potential $P = (\log P_1 + \log P_2)/n$ and the Hamiltonian $H = \sigma y_2 - \log P_1/n$.

An advantage of this decomposition is the parting of the set of parameters into 3 distinct families: amplitude controlling parameters (appearing in P only, like P_2 parameters), period controlling parameters (appearing in H only, like σ, which is also involved in the values of the stationary states) and mixed parameters (appearing both in P and H, like P_1 parameters). Although the PH-decomposition is not unique, this parting of the parameters can be crucial to understand the origin and the control of the cell signaling or tissue morphogenesis.

3. Conclusion

In the two previous Notes [12,13] we developed a new method for algebraically approximating limit cycles of classical dynamical systems like n-switches, Lotka–Volterra and Liénard systems, allowing us to separate the flow into two parts, a dissipative one called potential (or gradient) and a conservative one called Hamiltonian, whose parameters have different roles, with more amplitude modulating in the dissipative part and more frequency modulating in the conservative one. The specific power of each parameter will be evaluated in the future from generalization of the control strengths, currently available only in case of stationary states or of relaxation oscillations [1,9,20]. It will allow a practical use of the present approach in all biological applications described in this Note and in others of the same type in narrow fields (population dynamics, genetic control, immunologic response, ...).

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References

[1] P. Baconnier, P. Pachot, J. Demongeot, An attempt to generalize the control coefficient concept, J. Biol. Systems 1 (1993) 335–347.
[2] S. Ben Lamine, P. Calabrese, H. Perrault, T.P. Dinh, A. Eberhard, G. Benchetrit, Individual differences in respiratory sinus arrhythmia, Am. J. Physiol. Heart Circ. Physiol. 286 (2004) 2305–2312.
[3] O. Cinquin, J. Demongeot, Positive and negative feedback: striking a balance between necessary antagonists, J. Theor. Biol. 216 (2002) 229–241.
[4] O. Cinquin, J. Demongeot, Positive and negative feedback: mending the ways of sloppy systems, C. R. Biologies 325 (2002) 1085–1095.
[5] O. Cinquin, J. Demongeot, High-dimensional switches and the modeling of cellular differentiation, J. Theor. Biol. 233 (2005) 391–411.
[6] T. de Donder, Sur la théorie des invariants intégraux, Ph.D. thesis ULB, Brussels, 1899.
[7] T. de Donder, Thermodynamic Theory of Affinity: A Book of Principles, Oxford Univ. Press, Oxford, 1936.

[8] J. Demongeot, Existence de solutions périodiques pour une classe de systèmes différentiels gouvernant la cinétique de chaînes enzymatiques oscillantes, in: Lecture Notes in Biomath., vol. 41, 1981, pp. 40–62.
[9] J. Demongeot, F. Esteve, P. Pachot, Comportement asymptotique des systèmes : applications en biologie, Rev. Int. Syst. 2 (1988) 417–442.
[10] J. Demongeot, M. Kaufmann, R. Thomas, Positive feedback circuits and memory, C. R. Acad. Sci. Paris, Ser. III 323 (2000) 69–79.
[11] J. Demongeot, G. Virone, F. Duchêne, G. Benchetrit, T. Hervé, N. Noury, V. Rialle, Multi-sensors acquisition, data fusion, knowledge mining and alarm triggering in health smart homes for elderly people, C. R. Biologies 325 (2002) 673–682.
[12] J. Demongeot, N. Glade, L. Forest, Liénard systems and potential-Hamiltonian decomposition I – methodology, C. R. Acad. Sci. Paris Ser. I, 10.1016/j.crma.2006.10.016.
[13] J. Demongeot, N. Glade, L. Forest, Liénard systems and potential-Hamiltonian decomposition II – algorithm, C. R. Acad. Sci. Paris Ser. I, doi:10.1016/j.crma.2006.10.013.
[14] R. Fitzhugh, Impulses and physiological states in theoretical models of nerve membranes, Biophys. J. 1 (1961) 445–466.
[15] P. Glansdorff, I. Prigogine, Thermodynamic Theory of Structure, Stability and Fluctuations, Wiley, New York, 1971.
[16] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. 117 (1952) 500–544.
[17] J.D. Murray, Mathematical Biology, Springer, Berlin, 1989.
[18] J. Nagumo, S. Arimoto, S. Yoshizawa, An active pulse transmission line simulating nerve axons, Proc. IRL 50 (1960) 2061–2070.
[19] T. Pham Dinh, J. Demongeot, P. Baconnier, G. Benchetrit, Simulation of a biological oscillator: the respiratory rhythm, J. Theor. Biol. 103 (1983) 113–132.
[20] P. Ruoff, M.K. Christensen, J. Wolf, R. Heinrich, Temperature dependency and temperature compensation in a model of yeast glycolytic oscillations, Biophysical Chemistry 106 (2003) 179–192.
[21] S. Thibault, L. Heyer, G. Benchetrit, P. Baconnier, Ventilatory support: a dynamical systems approach, Acta Biotheoretica 50 (2002) 269–279.
[22] R. Thom, Topological models in biology, Topology 8 (1969) 313–335.
[23] A. Tonnelier, S. Meignen, H. Bosch, J. Demongeot, Synchronization and desynchronozation of neural oscillators: comparison of two models, Neural Networks 12 (1999) 1213–1228.
[24] J.J. Tyson, The Belousov–Zhabotinskii Reaction, Lecture Notes in Biomath., vol. 10, 1976.
[25] B. van der Pol, J. van der Mark, The heartbeat considered as a relaxation oscillation and an electrical model of the heart, Philos. Mag. 6 (1928) 763–775.
[26] C. Zeeman, Differential equations for the heartbeat and nerve impulse, in: Dynamical Systems Symposium Univ. Bahia, Academic Press, New York, 1973, pp. 683–741.