# Slow-fast Dynamical Systems from Mathematics to Biomedical Applications

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JP Françoise

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and ANR "ANAR".

ANAR consortium is devoted to the development in France of Mathematical physiology and of mathematical ecology. Its main characteristic is an approach which encompasses both the mathematical fundamental questions of bifurcation theory and the applications mainly devoted to modeling natural sciences.

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## Neuroendocrinology

It has been observed since long that several hormons are delivered in a complex way which alternates pulsating phases and surges. This is for instance the case for the GnRH which is an important neuroendocrine hormon. Untill recently modeling of such secretion patterns was not considered fully. Previous studies were only addressed to the understanding of the pulsatile regime. We made the following quite simple observation that if two populations of excitable cells, each of them being with different time scales of release, are coupled together in a simple way the final release pattern looks exactly like the one observed. In the special case of the GnRH this added some credibility to previous experimental contributions which suggested the existence of two different populations of GnRH neurons. It writes :

$$
\begin{aligned}
\epsilon\delta\dot{x} &= -y + f(x) && (1)\\
\epsilon\dot{y} &= a_0 x + a_1 y + a_2 + cX && (2)\\
\epsilon\gamma\dot{X} &= -Y + F(X) && (3)\\
\dot{Y} &= b_0 X + b_1 Y + b_2 && (4)\\
z(t) &= \chi_{\{y(t)>y_s\}}
\end{aligned}
$$

This is a fast-slow system and it has been discussed by Frédérique Clément (Inria Rocquencourt) and JPF (SIADS, 2008). Usual techniques of the bifurcation theory of fast-slow systems can be applied.

Equations (1) and (2) correspond to a fast system representing an average GnRH neuron, while equations (3) and (4) correspond to the slower system representing an average regulatory network. The $x, X$ variables represent the neuron electrical activities (action potential), while the $y, Y$ variables relate to ionic and secretory dynamics. The fast variables are assumed to have two stable stationary points separated by a saddle. Their bistability is accounted for by the cubic functions $f(x)$ and $F(x)$. The intrinsic dynamics of the slow variables follows a growth law of very small velocity ($a_1 \ll 1$ ). In each system, the fast and slow variables feedback on each other. The coupling between both systems is mediated through the unilateral influence of the slow regulatory neurons onto the fast GnRH ones ($cX$ term in equation (2)). The coupling term aggregates the global balance between inhibitory and stimulatory neuronal inputs onto the GnRH neurons. The global system exhibits 3 time scales given by $\epsilon\delta$, $\epsilon$ and $1$. Constant $\gamma$ is close to 1.

Our approach is adapted from the "geometrical dissection" that has been successfully applied to several models in Computational Neurosciences, especially those dealing with bursting oscillations.

In classical slow/fast systems, the slow variable is "frozen" and intervenes as a parameter in the study of the bifurcations of the fast system. In a similar way, we consider the fast 3 dimensional system with 2 time scales :

$$\begin{aligned} \delta\dot{x} &= -y + f(x) && (5) \\ \dot{y} &= a_0 x + a_1 y + a_2 + cX && (6) \\ \gamma\dot{X} &= -Y + F(X) && (7) \end{aligned}$$

where $Y$ acts as a varying parameter. This fast system breaks into an independent, 1D system (7), and a 2D system (5-6) forced by the 1D system.

Depending on $Y$ value, $Y = F(X)$ may have either one, two or three roots. Accordingly, equation (7) displays either one of the two possible attracting points (denoted respectively by $X_-(Y)$ and $X_+(Y)$), or both of them separated by a repulsive point (denoted by $X_0(Y)$). A saddle-node bifurcation occurs for the values of $Y$ corresponding to the ordinates of the local extrema of the cubic function : $(X, Y) = \pm(2/\sqrt{3}, 16/(3\sqrt{3}))$. Assuming $a_1 \approx 0$, we introduce $x_-(Y)$, $x_0(Y)$ and $x_+(Y)$ as the x values associated respectively with $X_-(Y)$, $X_0(Y)$ and $X_+(Y)$, from $x_i = -(a_2 + cX_i)/a_0, i = -, 0, +$.

– For $-\infty < Y < -16/(3\sqrt{3})$, equation (6) admits the attractive node $X_+(Y)$ as single stationary point, and $x_+(Y) > x_0^+ \approx 1.15$. It ensues that the 2D system (5)-(6) exhibits a stable focus, so that the 3D system displays one single stable stationary point.

– When $Y = -16/(3\sqrt{3}), X_+(Y) = 4\sqrt{3}, x_+(Y) \approx -3.60$, equation (5) undergoes a saddle-node bifurcation. The $X_0(Y)$ saddle and the $X_-(Y)$ attractive node appear and dissociate from the coincident point $X_0(Y) = X_-(Y) = -2/\sqrt{3}$, associated with $x_0(Y) = x_-(Y) = -0.032$. Both $x_0(Y)$ and $x_-(Y)$ belongs to the $\left[x_0^-; x_0^+\right]$ interval, for which the 2D system displays an unstable focus and a stable limit cycle. The 3D system thus exhibits simultaneously an attractive stationary point associated to $X_+(Y)$, an unstable stationary point together with an hyperbolic periodic orbit associated to $X_0(Y)$, and an hyperbolic stationary point together with an attractive periodic orbit associated to $X_-(Y)$. Hence $Y = -16/(3\sqrt{3})$ is also a bifurcation point for the 3D system, which triggers both a saddle-node bifurcation of periodic orbits and a saddle-node bifurcation of stationary points.

– As $Y$ keeps on increasing, $x_0(Y)$ reaches the value of the abscissa of the $f(x)$ cubic local minimum, where $x_0(Y) = -2/\sqrt{3} \equiv x_0^-$,

$X_0(Y) \approx -0.024$ and $Y \approx -0.096$. The 2D system undergoes a Hopf bifurcation. In the 3D system, the hyperbolic periodic orbit and the unstable stationary point coalesce into an hyperbolic stationary point.

– As $Y$ increases further, $x_-(Y)$ reaches the value of the abscissa of the $f(x)$ cubic local maximum, where $x_-(Y) = 2/\sqrt{3} \equiv x_0^+$, $X_-(Y) \approx -2.22$ and $Y \approx 2.1$. The 2D system undergoes another Hopf bifurcation. In the 3D system, the attractive periodic orbit and the hyperbolic stationary point coalesce into an attractive stationary point.

– Finally, when $Y = -16/(3\sqrt{3})$, equation (7) undergoes a saddle-node bifurcation again. The $X_0(Y)$ saddle and the $X_+(Y)$ attractive node disappear beyond the coincident point $X_0(Y) = X_+(Y) = 2/\sqrt{3}$, associated with $x_0(Y) = x_-(Y) = -2.39$.

We now go back to the 4D system (1-4) to unravel the hysteresis loop underlying the sequence of phases.

- In phase 1, $Y$ remains almost constant and system (5-6) displays the single attractive point associated to $X_+(Y)$, corresponding to the ascending part of the surge ;
- As $X_+(Y)$ decreases slowly, the solution of the 4D system remains close to the attractive point, corresponding to the duration of the surge (phase 2), until this node disappears through a saddle-node bifurcation. Then the solution switches to the other attractive node $X_-(Y)$, corresponding to the decreasing part of the surge (phase 3) ;
- In phase 4, as $X_-(Y)$ increases slowly, the solution remains close to the attractive point associated to $X_-(Y)$, corresponding to the plateau. Eventually, this attractive point disappears into an attractive periodic orbit via a Hopf bifurcation, initiating the pulsatile phase ;
- As phase 1 starts again, $X$ speeds up and the pulse frequency increases. At some point the attractive periodic orbit disappears into a saddle-node of periodic orbits. The solution of the 4D system then jumps back to the single attractive node associated to $X_+(Y)$ and

recovers the ascending part of the surge.

On the hypothalamic level, only the variability in the frequency of GnRH pulses (rather than its control) has been up to now the focus of mathematical models based on nonlinear dynamics (Brown, 1997). Our modeling approach is comparable to these previous ones in the sense that it also considers the effect of the average activity of one group of neurons on the activity of another group. But the way by which this effect is introduced differs. They used as external inputs an impulsion train, whereas we assume that both groups can be represented by the same type of equations (of FitzHugh-Nagumo type) but with different time scales. Following a 3 time-scaled approach, we have not only managed to account for the alternating pulse and surge pattern of GnRH secretion, but also for the frequency increase in the pulsatile regime. We have also unraveled the possible existence of a pause before pulsatility resumption after the surge, which could be investigated from an experimental viewpoint. Hence the capacity of our model to display complex features interpretable against experimental evidence suggests that such a modeling approach may be a useful complement to experimental studies of neuroendocrine systems.

Recent joint contribution of Frédérique Clément and Alexandre Vidal discusses the possibility to fit the parameters of the model to the experimental data coming from various species collected from collaborative teams from INRA (Nozilly).

Some connections with the vast subject of “Bursting Oscillations”

(2+1)-systems or forced (1+1)-systems

Alexandre Vidal’s Thesis and article Doss-Francoise-Piquet, CompleXus.

Recently, we have also related our system to the mixed-modes oscillations generated by canards phenomena (1+2)-systems.

## Références

[1] Borisyuk, A. & Rinzel, J. [2004] "Understanding neuronal dynamics by geometrical dissection of minimal models," in *Methods and Models in Neurophysics*, Les Houches Summer School 1980 (Chow, C., Gutkin, B., Hansel, D. & C. Meunier), Elsevier New York, pp. 19–72.

[2] Clement, F. & Françoise, J.-P. [2007] "Mathematical modeling of the GnRH-pulse and surge generator," SIAM J. Applied Dynamical Systems **6**, 441–456.

[3] Clement, F. & Vidal, A. [2009] "Foliation-based parameter tuning in a model of the GnRH pulse and surge generator," SIAM Journal on Applied Dynamical Systems, 2009, 8(4) : 1591-1631.

[4] Desroches, M., Krauskopf, B. & Osinga, H. M. [2008] "Mixed-mode oscillations and slow manifolds in the self-coupled FitzHugh-Nagumo system," Chaos **18** (1).

[5] C. Doss-Bachelet, J.-P. Francoise and C. Piquet "Bursting oscillations in two coupled FitzHugh-Nagumo systems." ComPlexUs : 2, 101-111, (2003).

[6] Françoise, J.-P. [2005] *Oscillations en Biologie : Analyse qualitative et modèles*, Springer, Collection : Mathématiques et Applications, vol. 46.

[7] Vidal, A. [2006] "Stable periodic orbits associated with bursting oscillations in population dynamics," Lecture Notes in Control and Information Sciences **341**, 439–446.

[8] Vidal, A. [2007] "Periodic orbits of tritrophic slow-fast systems and double homoclinic bifurcations," Discrete and Continuous Dynamical Systems – Series B suppl. vol., 1021–1030.

## THANK YOU