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A MINIMALIST MODEL OF CALCIUM-VOLTAGE COUPLING IN GnRH CELLS.

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1. INTRODUCTION

We present a minimalist model to understand the interplay between burst firing and calcium dynamics in GnRH (Gonadotropin-releasing hormone) neurons. GnRH neurons are located in the basal hypothalamus, and are responsible for the production of the GnRH decapeptide. The episodic release of this hormone into the portal system stimulates the pituitary release of gonadotropins, LH and FSH, which drive sexual development and control the female menstrual cycle and male spermatogenesis. The detailed mechanisms governing GnRH release dynamics are still unknown, and the investigation of those mechanisms could provide some clues to understand central aspects of life such as maturation and fertility.

Based on experimental data recorded by the group of Herbison in GnRH-Pericam transgenic mice [1, 2], Duan *et al* constructed a detailed model for the behavior of GnRH neurons [2]. Duan's model relies on the specific molecular components participating in the control of membrane potential and intracellular calcium concentrations, and accurately reproduces the results obtained by Herbison *et al*. Moreover, the model was tested for different pharmacological conditions, and it was used to predict the existence of a slow activated long-duration potassium current (UCL-2077 sensitive sI_{AHP}), which was later identified experimentally.

However, the extremely high dimensionality of the system (due to the many gating variables and variables describing the states of the different channels and pumps), make it very difficult to undertake a dynamical analysis of the model in the usual way. Namely, it is not clear at all which variables evolve in a slow scale and which variables evolve in a fast scale, and therefore there is not a straightforward way to perform a bifurcation analysis.

In this work, we attempt to approach Duan's model starting from an essentially simplified framework. In order to capture only the excitable feature of both the membrane potential and calcium dynamics, and the fact that spiking activ-

ity in GnRH neurons not only drives calcium transients (as is known to be the case) but it is itself also driven by the latter, we put aside the detailed underlying biology and represent both burst firing and intracellular calcium via two coupled FitzHugh-Nagumo-like dynamical systems, and only one (calcium-dependent) gating variable controlling voltage. For such a simplified model, we can set the time scales according to the experimental findings (a fast evolution of the voltage, superimposed on a slow evolution of the calcium concentration). We find that the calcium subsystem drives burst firing by making the fast subsystem to undergo a Hopf-Bifurcation. Specifically, fast relaxation-oscillations occur in a specific region of the $c-z$ plane (c being the calcium concentration, and z the calcium-dependent gating variable mentioned above). Slow oscillations, instead, are carried by the fast subsystem by a transitory shift of the steady state, whose stability remains however unchanged (but has yet the net effect of a perturbation). For this simple description, we can obtain analytically the full bifurcation structure of the model. This allows us to systematically repeat the analysis for the different pharmacological conditions described in [2].

Finally, we discuss to what extent our model can provide an insight to elucidate the intricate dynamics of Duan's model, and what are its intrinsic limitations.

2. THE MODEL

As mentioned in the introduction, our model is given by two FitzHugh-Nagumo-like dynamical systems. The first system concerns the voltage dynamics, and it reads,

$$\epsilon_1 \frac{dv}{dt} = v(\theta_1 - v)(v - \alpha_1) - w_1 + I(c, z) \quad (1.a)$$

$$\frac{dw_1}{dt} = \beta_1(v - \gamma_1 w_1) \quad (1.b)$$

$$\tau_z(c) \frac{dz}{dt} = z_\infty(c) - z, \quad (1.c)$$

where

$$I(c, z) = z \left(1 - \frac{c^{n_1}}{Kd_1^{n_1} + c^{n_1}} \right),$$

$$z_\infty(c) = \exp \left(-\frac{(c-p)^2}{b} \right), \text{ and } \tau_z(c) = f \exp(-dc).$$

This system is coupled with a second system representing the slow dynamics of the calcium concentration,

$$\epsilon_2 \frac{dc}{dt} = (c - 0.1)(\theta_2 - c)(c - \alpha_2) - w_2 + q(v) \quad (2.a)$$

$$\frac{dw_2}{dt} = \beta_2(c - \gamma_2 w_2), \quad (2.b)$$

where

$$q(v) = h \left(\frac{v^{n_2}}{Kd_2^{n_2} + v^{n_2}} \right).$$

The time scales of both subsystems are set by choosing suitable values for the parameters ϵ_1 , ϵ_2 , and β .

3. RESULTS

All calculations were performed in matlab. We show here the results corresponding to the physiological conditions.

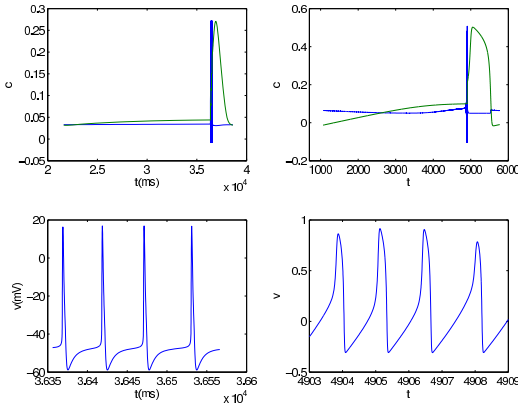


Figure 1 – The slow behavior of the calcium transients (top), and the fast burst firing (bottom), for Duan’s model (left), and the model described here (right). The burst firing is attached to the calcium plots to stress the fact that bursting turns on and off at certain values in the raising phase of the transients. v , c and t are represented in arbitrary units in our simulations. In Duan’s model, c is a measure of the calcium concentration relative to the baseline. In the two FitzHugh-Nagumo-like model the parameters are set to $\alpha_1 = 0.1$, $\theta_1 = 1$, $\beta_1 = 1$, $\epsilon_1 = 0.01$, $\gamma_1 = 0.5$, $\alpha_2 = 0.16$, $\theta_2 = 0.52$, $\beta_2 = 5.95 \cdot 10^{-5}$, $\epsilon_2 = 2$, $\gamma_2 = 1$, $Kd_1 = 0.5$, $n_1 = 4$, $h = 0.3$, $Kd_2 = 0.5$, $n_2 = 4$, $p = 0.132$, $b = 0.0005$, $f = 1400$, and $d = 20$.

4. CONCLUSIONS

As depicted in Figure 1, our model qualitative replicates the main features of Duan’s model simulations. Namely, the fact that calcium concentration drives burst firing is evident in the raising phase of the transient, where burst firing suddenly switches on and off. Moreover, even the temporal patterns can be reproduced very well (the duration of the calcium transients relative to the period of the calcium oscillations, the burst duration relative to the duration of the transients, and the number of spikes per burst). However, the shape of both transients and burst firing look different when compared with the simulations of Duan’s model. The

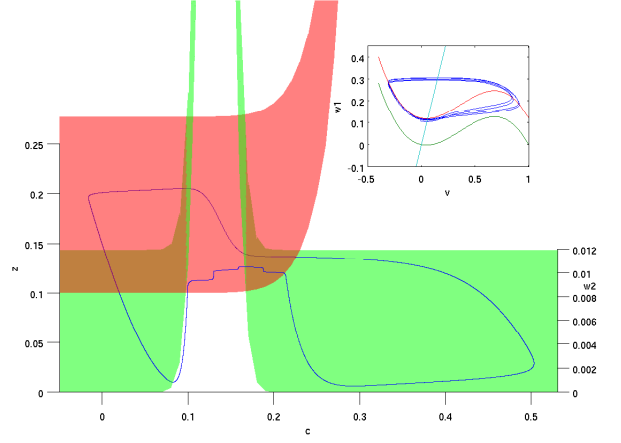


Figure 2 – Trajectory of the slow system in the $c-w_2-z$ space. The pink surface represents the Hopf Bifurcation of the fast system, which divides the slow space in two regions. In the upper region relaxation-oscillations exist, which develop burst firing. In the lower region the voltage asymptotically approaches a steady state. The green surface corresponds to the z -nullcline. In the inset, the phase plane of the fast system showing two fixed points with different stabilities. As the slow system ‘pushes’ the v -nullclines (green and red curves) upwards in the $v-w_1$ plane, the bifurcation occurs where the w_1 -nullcline (light blue curve) intersects the v -nullcline at its minimum.

latter limitation is due to the specific behavior of FitzHugh-Nagumo-like dynamical systems, and to overcome it, a refinement of the model is required. The most interesting fact, however, is that the simple model presented here allows us to undertake the full bifurcation analysis. The main features of the bifurcation structure are depicted in Figure 2, where it is possible to understand how the slow system and the gating variable interplay to generate an oscillatory regime for the fast system, by which burst firing switches on and off. We stress that this kind of behavior could be found even in Duan’s model.

ACKNOWLEDGMENTS

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