A model of the autonomic control of heart rate at the pacemaker cell level through G-proteins

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Abstract— **A mathematical model of the pacemaker cell of the mammal sinoatrial node, based upon the Yanagihara-Noma-Irisawa equations, is presented here. Its aim is to mimic the control of the pacemaker cell, as measured on the resulting heart rate, by both branches of the autonomic nervous system (ANS). It is a simplification of the original model by the suppression of some variables (but no ionic current being removed). It also uses a dynamical model of the G-proteins as actuators of this control in the system, and a construction of the sympathetic and vagal impulses, reflecting respiratory sinus arrhythmia and baroreflex influence. These characteristics make it a model compatible with what is known of the electrophysiological mechanisms of pacemaking at the single cell level, and with the observed spectral characteristics of short-term (respiratory) heart rate variability at the whole heart (electrocardiographic) level, thus partly bridging a gap between these two representation levels of the ANS.**

Keywords— **Electrophysiology, pacemaker cell, heart rate, G-proteins, autonomic nervous system**

I. Introduction

THE autonomic nervous system (ANS) has been for a long time assessed noninvasively by the analysis of heart rate variability. Spectral analysis of the RR signal evidences 2 main peaks in man and other mammals: on the one hand a high frequency one, reflecting the activity of the vagal branch of the ANS, mainly related to respiration, and neurochemically mediated by acetylcholine (ACh), and on the other hand a low frequency one, reflecting both the sympathetic branch of the ANS, strongly influenced by the baroreflex and mediated by norepinephrine (NE), and also, to a lesser extent, the vagal branch[1].

Relatively independently of these heart rate spectral analysis studies, mathematical models of the sinus node pacemaker cell have been proposed in the last 20 years. These models, among which the Yanagihara-Noma-Irisawa (YNI) model[2], usually incorporate the action of ACh on the action potential[2], [3], but seldom the action of NE. Nevertheless, recent studies have incorporated both ACh and NE, on the basis of the YNI model[4], of the Bristow-Clark model[5], or of a model involving less currents[6].

A satisfying model of the pacemaker cell incorporating the complete control by the ANS will be a major stepping stone towards an explicit model of the heart rate as a deterministic dynamical system, which might explain possible chaotic characteristics of it by bifurcation analysis studies (as in [7]), with control parameters linked to ACh and NE concentrations in the neuroeffector junction.

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II. Methods

The present model takes the YNI model as a basis; it first replaces the variables which give little contribution to the total depolarizing current (h, m, q, as evidenced by I-V plots, see e.g. [8]) by their equilibrium values, letting remain only d, f for the slow inward Ca current, p for the K current, and E for transmembrane potential as dynamic variables. It represents the actions of ACh and NE on the ionic currents by their effects on adenylate cyclase through a dynamic model of the intervention of G-proteins G_s (stimulating, NE-dependent), G_i (inhibiting, ACh-dependent) and G_k (directly active on the K_ACh channel), on the maximum intensity of currents, following ideas developed in [6]. Ach and NE concentrations are simulated according to a model recently proposed for ACh only[3]. Vagal and sympathetic pulse trains follow an original model including oscillations at fixed frequencies (respiratory and baroreflex-linked); the parameters of this last model have been tuned according to what is known of the discharge frequencies of the vagus[9] and of the sympathetic nerve[10]. No stochastic component has been included in the model. Units are milliseconds, millivolts, and nanomoles for ACh and NE concentrations.

Equations for the vagal impulse train are:

$$vag = exp(-5000{x_1}^2) \quad \text{where}$$
$$\dot{x}_1 = x_2, \qquad \dot{x}_2 = -(\tfrac{2\pi(6.5+3.5x_3)}{1000})^2 x_1,$$
$$\dot{x}_3 = x_4, \qquad \dot{x}_4 = -(\tfrac{2\pi\nu_R}{1000})^2 x_3,$$

with $\nu_R = 0.25$ Hz (respiratory frequency). Similar equations were designed for the sympathetic, with other parameters, including a baroreflex-linked frequency $\nu_B = 0.1Hz$.

The vagal impulse train is then used as input to the abovementioned model proposed for ACh[3] (2 more first-order equations, one for the releasable pool of ACh, one for free ACh concentration). The same is done for NE, with different parameters; but in this case, a presynaptic inhibiting factor ($\frac{80}{80+[ACh]}$, as in [6]) modulates the equilibrium value in the 1st-order differential equation for [NE]. Fixed parameters (to be identified) are the maximum increase in [ACh] and [NE] at each vagal or sympathetic pulse.

Then, as in [6], the resulting values of [ACh] and [NE] influence the equilibrium values G_∞ of G_s, G_i, G_k in the 3 1st-order equations $\dot{G} = \alpha(G_\infty - G)$, with time constants: $\alpha_s = 10^{-4}, \alpha_i = 5.10^{-4}, \alpha_k = 10^{-2}$.

Equilibrium values are represented homographically as: $G_{\infty,s} = \frac{[NE]+A_sK_s}{[NE]+K_s}$, $G_{\infty,i} = \frac{[ACh]}{[ACh]+K_i}$, $G_{\infty,k} = \frac{[ACh]A_k}{[ACh]+K_k}$, $A_s = 0.12$, $K_s = 600$, $K_i = 150$, $A_k = 0.6$, $K_k = 2100$.

Some of the numerical constants come from [6], others have been changed to adapt better to the YNI equations

or to the particular setting of the G-proteins variables, the action of which on maximum ionic currents is described by: $\overline{i_s} \rightarrow (1+3G_s)(1-G_i)\overline{i_s}$, $\overline{i_k} \rightarrow (1+G_s)(1-G_i)\overline{i_k}$, $\overline{i_h} \rightarrow (1+2G_s)(1-G_i)\overline{i_h}$, and $\overline{i_{k\_ACh}} \rightarrow G_k\overline{i_{k\_ACh}}$.

The resulting set of 1st-order equations has been numerically integrated on a Sun UNIX workstation with a BDF algorithm, dedicated to stiff sets of equations, using the public domain software SCILAB, developed at INRIA.

III. Results

An illustration of the model is shown on Fig. 1:

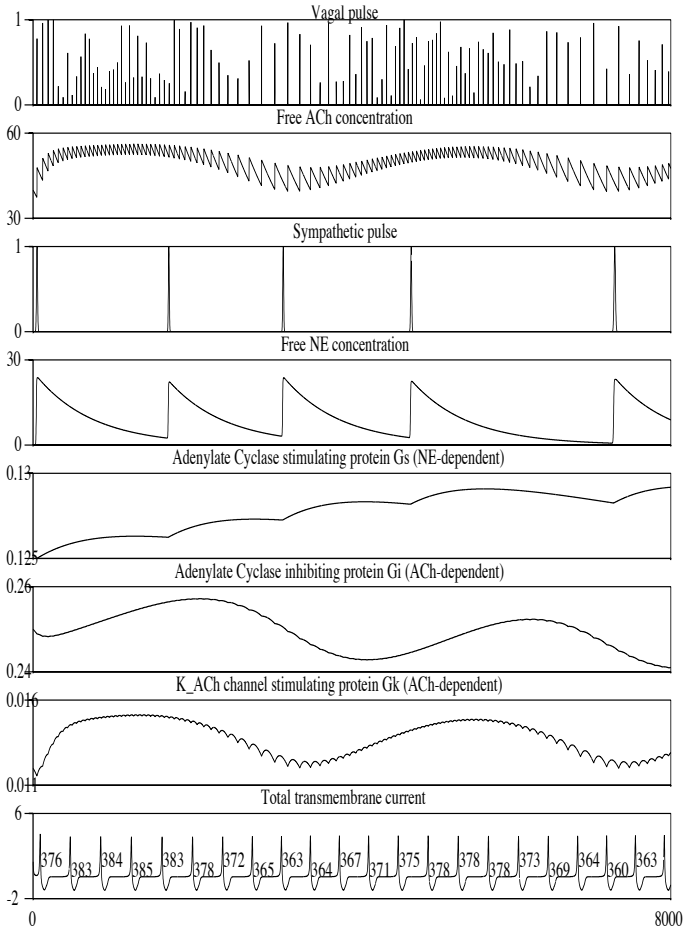

Figure 1. *Results of numerical integration in* SCILAB *of the main features of the model, on a time interval of 8 seconds. Units are milliseconds for time, μamperes for current, and nanomoles/l for concentrations.*

Then a FFT performed on the RR series obtained from the integration of the system over a longer time window (56 seconds) is shown on Fig. 2.

IV. Discussion

This model describes the action of the ANS on heart rate through G-proteins and the adenylate cyclase. It combines ideas published by Mokrane et al.[6], integrating both branches of the ANS, with an original design of the vagal and sympathetic trains, transformed in free [ACh] or [NE] in the neuroeffector junction according to a design proposed by Dexter et al.[3] for ACh, and with the original YNI equations[2].

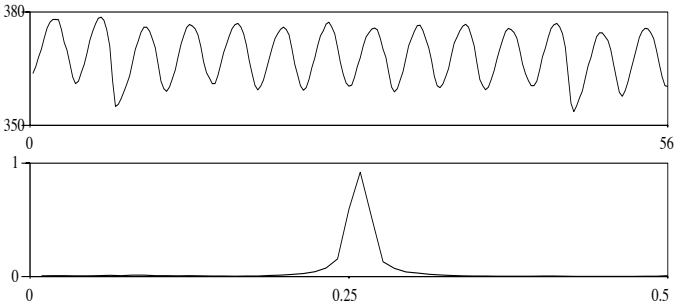

Figure 2. *RR signal resulting from the integration of the system over 56 seconds, and its spectral analysis by FFT. A high frequency peak is present at 0.25 Hz, representing respiratory sinus arrhythmia, but no peak representing baroreflex activity may be seen at the expected frequency of 0.1 Hz.*

The action of the vagal branch of the ANS on the single pacemaker cell is satisfactorily mimicked by this model, but not the action of the sympathetic branch. This shortcoming may be accounted for by unadapted representation of the sympathetic impulse, of the production and degradation of NE, of its influence on the equilibrium value of G_s, or of its action on the main current i_s. Most likely, the direct transposition to NE of the model chosen for ACh[3] is not completely accurate. But it also might be that NE should act on the constants α and β in the YNI equations (as in [4]) for the gating variables d, f, p. Physiological likelihood will lead us on this way to a next step of this model, to study the influence of both branches of the ANS on the pacemaker cell, as measured by heart rate variability.

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