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Chaos in weakly coupled pacemaker cells

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A model of the rabbit sinoatrial action potential is introduced, based on a model by Morris and Lecar. One cell is described by two first order ordinary differential equations, with 10 constant parameters. The model is much simpler than most other models in use, but can reproduce perfectly experimentally recorded action potentials. The dynamics of two coupled cells, with and without the presence of periodic acetylcholine pulses, shows examples of bifurcations and strange attractors, mathematical phenomena characterizing chaotic motion. It remains to be clarified whether such dynamics is actually observed, for example in the small irregular variations of the normal heart rate.

I. INTRODUCTION

One of the motivations for the present paper is to demonstrate that simple models can account for many of the complex waveforms and rhythms that can be observed in heart tissue (Guevara, 1991; Clark *et al.*, 1991; Glass & Shrier, 1991; Endresen, 1995). The present model describes the main currents through the cell membrane. The slow inward Ca^{++} current (i_s) and the outward K^+ current (i_K) are the predominant membrane currents found in rabbit sinoatrial node cells (Wilders *et al.*, 1991; Irisawa & Noma, 1982). Voltage dependent Ca^{++} and K^+ channels are also found in barnacle giant muscle fibers, as observed in a well-known paper by Morris and Lecar (1981). By adjustment of some of the parameters in the mathematical model of Morris and Lecar, the action potential of slow rabbit sinoatrial node cells can be reproduced. The dynamic behavior of this model is more easily understandable than the complex fourteen-variable treatment of Noble and Noble, which has been used in earlier studies on coupling two cells together (Winslow *et al.*, 1993; Winslow *et al.*, 1994).

In this paper a model containing two differential equations is shown to perfectly fit recordings of rabbit sinoatrial action potential waveforms. It is then developed into a model of two coupled cells. For certain parameter values this model describes chaotic motion in terms of a strange attractor. The model is extended to include pulses from the vagus nerve. These periodic pulses succeed in controlling the system, except when it is in the chaotic state. Finally the consequences of the simulation results are discussed.

II. THE ACTION POTENTIAL MODEL

The enormous complexity of cardiac ion channels, involving many complex proteins (Catterall, 1995), makes it impossible to model this phenomenon from the first principles of physics. To reconstruct the shape of the action potential of the sinus pacemaker we modify the model of Morris and Lecar (1981) for the barnacle giant muscle fiber. The equations introduced in their model were derived empirically, fitting parameters in the well-known Boltzmann distribution law to voltage clamp recordings, a method first introduced in the Nobel-prize work of Hodgkin and Huxley (1952). Thus, the appearance of several exponential functions in these models is due to the Boltzmann exponential distribution. The model of Morris and Lecar has been shown to be close to recorded data in many totally different regimes of behavior. This suggests that the model accounts for the most important factors, namely the calcium current and the potassium current. The peak values of these currents are approximately ten times larger than for the other currents in the slow-type rabbit sinoatrial node cells (Wilders *et al.*, 1991). A further similarity between this model and earlier models of rabbit sinoatrial node cells, such as the model of Irisawa and Noma (1982), is the outward-going rectifying nonlinearity of the Ca^{++} conductance. The leak current and the applied current in the Morris-Lecar model are omitted. The resulting equations are:

$$\frac{dv}{dt} = -\frac{1}{C}(i_s + i_K + i_{K-AC} + i_j) \quad (1)$$

$$\frac{dw}{dt} = \lambda_w \cosh\left(\frac{v - v_3}{2v_4}\right) \left[\frac{1}{2}\left(1 + \tanh\left(\frac{v - v_3}{v_4}\right)\right) - w\right] \quad (2)$$

$$i_s = \frac{1}{2}g_s \left[1 + \tanh\left(\frac{v - v_1}{v_2}\right)\right](v - v_s) \quad (3)$$

$$i_K = g_K w (v - v_K), \quad (4)$$

with the parameters given in Table 1. Here v denotes the membrane potential, w the fraction of open K^+ channels, i_s the calcium current and i_K the potassium current. The two variables i_{K-AC} and i_j are not part of the model of Morris and Lecar, but introduced here. They are initially set to the constant value zero. Fig. 1 shows the model-generated and the experimentally recorded rabbit sinoatrial action potential waveform (a). The root mean square deviation between 400 data samples (2s of recording) and the fit is merely 0.035mV. The figure also displays the outward K^+ current (b) and the inward Ca^{++} current (c). These follow closely the model traces displayed in Fig. 6 in (Wilders *et al.*, 1991). The maximum value of

I_K is $114.6pA$, a value close to the experimentally recorded value of Ono and Ito (1995): $I_K = 103.4 \pm 9.4pA$ for a cell with a capacitance of $47pF$. The lowest value of I_s ($-88.2pA$), is not as low as the experimental values of Doerr, Denger and Trautwein (1989). This is due to the relatively low maximum value of the recorded membrane potential ($-8.49mV$), and hence a flatter upstroke (phase 0) than usually seen in cells from the rabbit sinoatrial node. The period of the oscillator is $381.9ms$. The Appendix contains an outline of the numerical implementation of this model, and of an extended model.

TABLE I. Parameter values used by Morris and Lecar, and parameter values estimated in this paper.

Parameter	Morris-Lecar	Endresen
C	20	$\mu F/cm^2$ 60.0000
g_s	4	mS/cm^2 382.9118
g_K	8	mS/cm^2 536.1093
v_s	100	mV 214.1429
v_K	-70	mV -259.0783
v_1	-1	mV -35.9358
v_2	15	mV 7.8589
v_3	10	mV -27.9375
v_4	14.5	mV 6.3210
λ_w	1/15	$(ms)^{-1}$ 20.7796

FIG. 1. Model-generated (solid line) and experimentally recorded (dashed line) rabbit sinoatrial action potential waveform (a), outward K^+ current (b) and inward Ca^{++} current (c).

Acetylcholine released at the vagus endings in the heart increases the potassium conductance by activation of specific K^+ channels. The following equations for the acetylcholine-activated potassium current, i_{K-ACH} , introduced by Irisawa and Noma (1982) are used to simulate acetylcholine pulses from the vagus nerve endings:

$$\frac{du}{dt} = \alpha(1 - u) - \beta u \quad (5)$$

$$\alpha = \frac{0.012332}{1 + 4.2 \cdot 10^{-6}/[ACH]} \quad (6)$$

$$\beta = 0.01 \exp[0.0133(v + 40)] \quad (7)$$

$$i_{K-ACH} = 0.27u(v + 90) \quad (8)$$

Here u denotes the gating variable of the acetylcholine-activated potassium channel. α and β are the rate constants of opening and closing of this channel and $[ACH]$ the concentration of acetylcholine released from the vagus nerve endings into the synaptic cleft. Fig. 2 shows the effect of a train of $10^{-6}M$ ACh pulses with period $400ms$. Each pulse has a duration of $50ms$, and the pulse was terminated in the same way as in (Michaels *et al.*, 1984), setting the opening rate constant α to zero. These pulses succeed in controlling the cell, locking the period to $0.4s$, as displayed in Fig. 2. Note that the amplitude of acetylcholine activated potassium current is small compared to the other currents. These findings are close to the results in (Michaels *et al.*, 1984) and (Dexter *et al.*, 1989)

FIG. 2. Effect of a train of acetylcholine pulses ($10^{-6}M$) with period $400ms$ on simulated sinus pacemaker. Membrane potential (a), i_{K-ACH} (b), i_K (c) and i_s (d).

To illustrate that the model results are close to experiments, we demonstrate that the spontaneous activity in the sinoatrial node can be abolished by the injection of a constant bias current, as suggested in (Guevara *et al.*, 1987). In Fig. 3 the action potential is plotted for 5 different values of the constant bias current. The spontaneous activity is abolished when i_{bias} is lower than $-2pA$.

FIG. 3. Effect on spontaneous activity of a constant depolarizing bias current. $i_{bias} = 0pA$ (a), $-0.5pA$ (b), $-1.0pA$ (c), $-1.5pA$ (d), and $-2.0pA$ (e).

III. THE DYNAMICS OF TWO COUPLED CELLS

We determined the dynamics of two coupled cells. The intrinsic period of one of the cells and the coupling conductance between them are varied to achieve this. The intrinsic period T of the cell increases by reducing the parameter λ_w . Fig. 4 shows how the period T varies with λ_w . Values of λ_w larger than $\lambda_w \simeq 0.0223$ stopped the oscillator. The coupling current (Torre, 1976):

$$i_j^A = -i_j^B = g_j(v^A - v^B), \quad (9)$$

is introduced to model the gap junctions between two coupled cells. We use the notation A and B for the two cells, where A is the cell with unchanged intrinsic period.

FIG. 4. Intrinsic period of the reconstructed pacemaker as a function of the parameter λ_w .

FIG. 5. Resultant period T^B of pacemaker cell (cell B) with variable intrinsic period, as a function of λ_w^B , when the coupling conductance (g_j) to the neighbor cell (cell A) is varied. The initial conditions are $v = -52.71830mV$ and $w = 0.01898$ for both cells.

When the period of the second cell (cell B) is altered, the resultant period of both cells depends on the strength g_j of the coupling between the cells. At low coupling conductances there are small variations in the period. Fig. 5 shows how the period of cell B varies with different values of the coupling. Bifurcations arise for coupling values in the range $1pS < g_j < 60pS$. Anumonwo *et al.* (1992) has reported that the mean gap junction conductance between two rabbit sinus node cells is between $2062pS$ and $3439pS$, and that the conductance required for synchronization is only $142pS$. This implies that the complex oscillations found here might be present in rabbit sinoatrial node cells that are weakly coupled.

FIG. 6. The state space variables of both cells when the *intrinsic* periods are 381.9ms (cell A) and 581.7ms (cell B). Coupling conductance values are 50pS (a), 100pS (b), 300pS (c) and 500pS (d), respectively. The initial conditions are $v = -52.71830mV$ and $w = 0.01898$, for both cells, and the motion in the time interval 5s to 10s is shown.

In Fig. 6 the attractors of two weakly coupled cells is displayed. The initial conditions for these simulations are, for both cells, $v = -52.71830mV$ and $w = 0.01898$. The intrinsic period of cell B is adjusted to 581.7ms with $\lambda_w^B = 19.1172s^{-1}$, and the coupling conductance is set to 50pS (a), 100pS (b), 300pS (c) or 500pS (d), respectively. Varying the simulation time from 5s to 1000s does not significantly affect these phase plots. The only noticeable effect of the prolonged simulation time is that the orbits in Fig. 6(a) become more dense, indicating the presence of a strange attractor (shorter time step do not affect this!), and that the motion in Fig. 6(b) become closer to the stable fixed point.

FIG. 7. The state space variables of cell A as functions of the strength of the acetylcholine pulse, when the *intrinsic* periods are 381.9ms (cell A) and 581.7ms (cell B), and $g_j = 50 pS$. The acetylcholine concentration are: 0.1mM (a), 1.0mM (b), 3.0mM (c) and 3.5mM (d).

The strange attractor displayed in Fig. 6(a) is of special interest. Here the conductance is 50pS, the mean value for one gap junction (Anumonwo *et al.* 1992). Periodic pulses of ACh do not succeed in controlling these two unstable cells, and this might not be so important since the conductance is small compared to physiologically measured values. It is also a question whether vagal ACh has a larger effect on i_s than on i_K . Fig. 7 displays the chaotic motion of cell A for four values of the ACh concentration: 0.1mM (a), 1.0mM (b), 3.0mM (c) and 3.5mM (d). The period of the applied pulse is 400ms. Variation of the pulse duration and the ACh concentration does not affect this result. Enlarged ACh concentration directs the cell to a fixed point with coordinates $v = -89.99mV$ and $w = 0.00$ (see Fig. 7(d)), hence the chaos can not be directed to a desired orbit by a periodic pulse with enlarged amplitude.

A dynamical system is characterized by its Lyapunov exponents. If one or more of these are positive chaotic dynamics is present. The largest Lyapunov exponent is always the numerically easiest to determine, and this was calculated for various values of the coupling conductances g_j . The result is presented in Fig. 8 (b) (solid line), and demonstrates four distinct dynamical behaviour restricted to the regimes:

1. Quasiperiodic and chaotic motion in the range $0pS < g_j < 60pS$. See Fig. 6 (a).
2. Periodic “one low amplitude” motion in the range $60pS < g_j < 245pS$. See Fig. 6 (b).
3. A stable fixed point in the range $245pS < g_j < 319pS$. See Fig. 6 (c).
4. Periodic synchronized motion for $g_j > 319pS$. See Fig. 6 (d).

In the transitions between these regimes, the dynamics sometimes switches discontinuously between several of these four types of behaviour. The positive Lyapunov exponent visible in the range $40pS < g_j < 60pS$, confirms the presence of chaotic motion. The ranges with periodic stable motion is indicated by the dashed line in Fig. 8 (b), which represent the second largest Lyapunov exponent in the ranges where the largest exponent is zero and all of the other exponents are negative. The motion is sometimes quasiperiodic for conductances lower than $40pS$, which is the case when two or more Lyapunov exponents are zero, and all the other are negative.

FIG. 8. The period of cell B as a function of the coupling conductance g_j (a). In (b) the largest Lyapunov exponent (solid line) and the second largest Lyapunov exponent (dashed line). The second largest exponent is only plotted in the ranges where the largest exponent is zero and all of the three other exponents are negative. In this calculations the *intrinsic* periods are $381.9ms$ (cell A) and $581.7ms$ (cell B), and i_{K-ACH} is zero.

From a theoretical point of view the dynamics in Fig. 6(a) can be controlled by tiny aperiodic pulses. A chaotic system is highly susceptible to control, and can be directed to a desired state by tiny “butterfly” perturbations (Ott *et al.* 1994). It remains to be clarified if the vagus nerve is “intelligent” enough to produce such advanced pulses. However, it is tempting to conclude that this model simulates the variable heart beat; the normal heart rate varies subtly from beat to beat in an aperiodic manner. In particular the aperiodic motion in Fig. 7(b) resembles that observed in the heart; a frequency that is unstable but still restricted to a well-defined range.

IV. DISCUSSION

A simple model of rabbit sinoatrial action potential has been introduced. The results of the simulations done with this model are close to experimentally recorded waveforms from rabbit sinoatrial node. However, it remains to be seen whether the numerically determined phenomena, many complex and strange, will be found experimentally. These features the complex dynamics of two coupled cells and the strange behavior of two coupled cells that are paced with a periodic acetylcholine pulse. The model introduced here cannot be viewed as an physically accurate model, but instead as one of many possible theoretical models that describe some of the typical phenomena observed experimentally. It is important to notice that the parameters in Table 1 are estimated numerically; they are relatively speculative from a physiological point of view.

No evidence for chaotic dynamics in single rabbit sinoatrial node cells is found experimentally or theoretically (Guevara *et al.* 1987). It is possible that this is because, as suggested here, the dynamics of one such cell is autonomous and essentially two-dimensional, thus excluding the possibility for chaotic motion. Chaotic motion is only possible in a system of at least three differential equations, or of two equations with a time dependent driving term. For two coupled cells however, such dynamics can occur, since the number of differential equations in such a system is four.

Further research must clarify whether even simpler models can fit experimental recordings of periodic and aperiodic sinoatrial node action potentials. The transformation of a model of barnacle giant muscle fibers to a model of rabbit sinoatrial action potential, is surely fascinating. Perhaps it is possible to develop a universal model which, by adjusting a few parameters, can be fitted to action potential recordings from any type of tissue.

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APPENDIX: COMPUTATIONAL DETAILS

The Matlab (Copyright 1984-94 The MathWorks, Inc.) routine *leastsq* solves nonlinear least squares problems. This routine was used for estimating the parameters $g_s, g_K, v_s, v_K, v_1, v_2, v_3, v_4$ and λ_w as well as the initial conditions $v(0)$ and $w(0)$. The routine compared the computed curves with recorded data from the rabbit sinoatrial node. The estimation time was drastically reduced by letting an external c program compute the action potential for each new set of parameters. The c program contained a fourth order Runge-Kutta algorithm with a constant time step of 0.01ms. We used a Silicon Graphics computer IP19 and the Matlab version 4.2.c. The program that simulated two coupled cells for various coupling conductances and intrinsic periods, and the program that calculated the Lyapunov exponent for various coupling conductances, was optimized for the vector computer CRAY J90. The 8 plates in Fig. 5 were calculated simultaneously, each with a computer speed of approximately 110 Mflops.

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