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About the topology of the intacellular sinusoidal pacing.

A.Rabinovitch[1], N.G.Gulko[2], I.Aviram[3]
[1] Physics Department Ben-Gurion University of the Negev, Beer-Sheva, 84105, Israel
[2] Center of Advanced Studies in Mathematics
at Ben-Gurion University of the Negev, Beer-Sheva, 84105, Israel
[3] 35 Sderot Yeelim, Beer-Sheva, 84730, Israel.
Email: avinoam@bgu.ac.il, gulko@math.bgu.ac.il

Abstract

Our cosideration: sinusoidal pacing of a sick sinus node in the heart is to be preferred over a train of pulses one. We concentrate on some stimulation on a BVP system , and on the complex Yanagihara-Noma-Irisawa system.

The interesting results obtained are: 1) For a range of forcing frequencies the phase trajectory deforms near the bottom left and the upper right corners which gradually develop into "bulges"; 2) The time spent in the part of the trajectory not including the bulges remains constant for a whole range of stimulating periods.

Introduction

The sinus node (SN) is the natural pacemaker of the heart. It operates as an oscillator - limit cycle (LC) device sending action potential pulses into the atria and the rest of the heart which operates as an excitable medium. Dysfunctions of the SN are quite frequent, either as a result of malfunctions of the controlling nervous system [1], or pathologies of the organ itself, or of heart transplant [2],[3]. In such situations, external pacing delivered into the SN itself may be called for.

We consider here such a pacing, and compare two possibile shapes: a train of δ-like pulses (TOP) [4], [5], and a continuous sinusoidal driving [6]. We use two mathematical models for the SN itself: (a) a simple FitzHugh Nagumo (FHN) system both, in the LC mode [7],[8],[9] and in the excitable regime for a sick SN , which can be easily analyzed in the components' phase space (activator vs. inhibitor); (b) the complex Yanagihara-Noma-Irisawa (YNI) system largely belived to be more realistic.

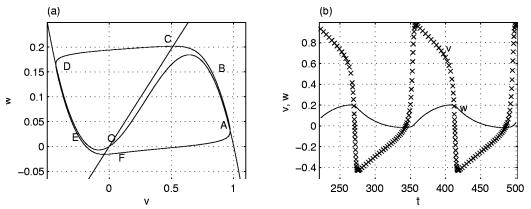

Figure 1: FHN: (a): The phase trajectory; (b): The action potential v, and the refractority w as a function of time for $Q = 0$. (FA) and (CD) are the fast parts of the phase trajectory; (AB) and (DE) are the slow parts of the phase trajectory, (EF) and (BC) are parts where deformations appear for a wide range of sinusoidal stimulating periods.

It is shown that sinusoidal pacing is much smoother than the TOP, and does not lead to a $n : 1$ malfunction as does the latter.

The models

A.To model a forced pacemaker we first use the simple FitzHugh-Nagumo or Bonhoeffer van der Pol system ([7])([12]) with an external stimulation Q.

$$\dot{v} = v(v-a)(1-v) - w + Q = f(v) - w + Q$$
$$\dot{w} = \varepsilon(v - bw) \tag{1}$$

where v can be looked at as a membrane potential or 'action potential', w is the 'refractority', ε is the ratio between the fast excitation and the slow recovery time constants, b is the ratio of the two major ion conductances. The parameter a is used as in [8] to measure the excitability range. Here we choose $a = -0.16$, and $a = 0.0016$ which put the system in the LC regime and the excitable mode respectively. Although equation (1) constitutes a simple model, it does contain the main basic qualitative properties needed to describe e.g. most of the phenomena appearing in the pulse propagation in the heart.

The initial conditions used in (1) at $t = 0$ are: $v = 0$, $w = 0$.

We choose $\varepsilon = 0.008$ and $b = 2.54$ ([13]). For $a = -0.16$ and the given set of parameters the phase trajectory Γ_0 of the unstimulated system ($Q = 0$ in (1)), is a stable limit cycle with a period T_0 of 142 time units (Fig. 1) which should be correlated with the regular interbeat interval ($\simeq 1$ sec) of the SN.

B. In order to give a wider validity to our results, we have also examined the Yanagihara-Noma-Irisawa model (YNI) of the sinus node [11], largely believed [10] to be quite realistic. This model includes four time dependent currents: a fast inward sodium current I_{Na}, and the potassium current I_K,a slow inward current I_S, and a delayed inward current I_h, activated by hyperpolarization. An additional current included in the model is a time-independent leak current I_l. The conservation of transmembrane current has a form:

$$C_m \frac{dV}{dt} = I_{Na} + I_K + I_S + I_h + I_l \tag{2}$$

Each current is a function of one, or more, of the six gating variables, each satisfying a 1st order differential equation [11].

We first examined both systems with a sinusoidal stimulation $Q(t) = A_1 \sin(2\pi t/T)$, added to Eq. (1), (2) and used $A_1 = 0.1$, and $A_1 = 1$ respectively and

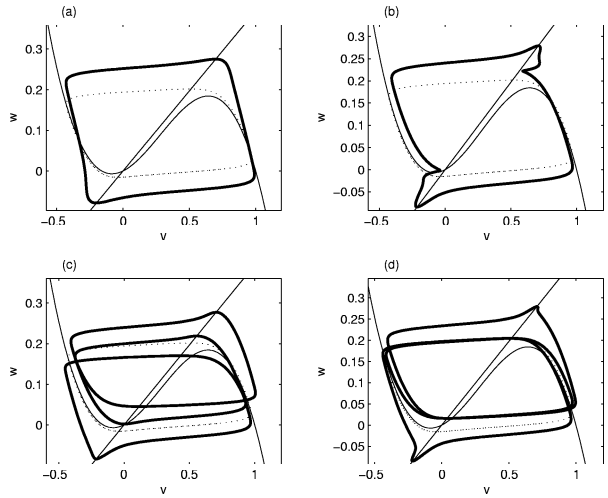

Figure 2: FHN: Set of phase trajectories for $A_1 = 0.1$ and different T's (a): $T = 300$, (b): $T = 700$, (c): $T = 720$, (d): $T = 1000$. Also shown are the nullclines (solid line) $\dot{w} = 0$ and $\dot{v} = 0$ and the phase trajectory of the unperturbed system (dotted).

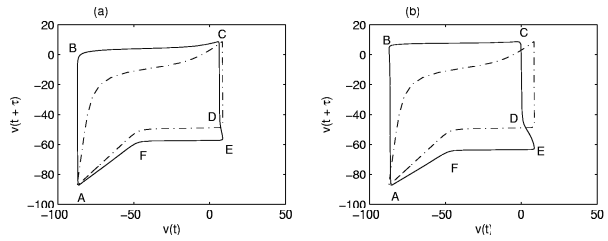

Figure 3: The stimulated YNI system (solid) and the unstimulated system (dash-dot) for $A_1 = 1$, and $\tau = 15$ (a): for $T = 300$, . (b): for $T = 500$.

stimulation period values T in the range: $T_0 < T < 7T_0$ where T_0 is the period of the nonstimulated systems, operating in a limit cycle mode.

Because of extreme difficulty to establish a natural, component based, phase space for YNI model, we opted to present the YNI results by using "artificial" phase space trajectory, obtained by an embedding procedure, whereby the voltage shifted in time $v(t+\tau)$ is plotted versus the unshifted voltage $v(t)$, both for the stimulated, and nonstimulated systems.

Results

Results are shown in Fig.2,3: For the FHN system they are as follows:

1. The phase trajectory remains strongly periodic in a wide interval of the driving frequencies (a wide $1:1$ entrainment region).

2. For $T_0 < T < T_{c_1}$ (e.g. for $A_1 = 0.1, T_{c_1} \simeq 700$)) the phase trajectory deforms, near its lower left and upper right corners, developing bulges.

3. A transition range appears for $T_{c_1} < T < T_{c_2}$ (for $A_1 = 0.1, T_{c_2} \simeq 720$)

4. Above $T > T_{c_2}$ the phase trajectory consists of three curves $(1:3)$ with bulges at the same locations as before.

5. The time spent at the part of the trajectory not including the bulges *remains a constant for a wide range of T's which depends on the amplitude of the driving sinus.*

Results for the YNI system (Fig.3) also show a localization of the time changes in a portion of the artificial phase trajectory.

Next, we compared the FHN system under above threshold pacing both sinusoidal and TOP. For the latter we chose $Q(t) = A_1 \sum_n \delta(t - nT)$ where δ is the Dirac delta function. For the TOP pacing the stimulating amplitude was 2 while for the sinusoidal one $A_1 = 0.2$.

When the SN is in a LC mode,(Fig 4), it is observed that the sinusoidal pacing (Fig 4(1)-(4)) leads to smooth responses for every frequency, due to the long periods of time the trajectories can spend near the foci (note however the changes in the action potential duration, and in the diastolic interval) , while for the TOP we obtain a $2:1$ response appearing for $T = 80$ (Fig 4(1)c,d); for $T = 174$ (Fig 4(2)c,d) the pacing just enhances the amplitude of the action

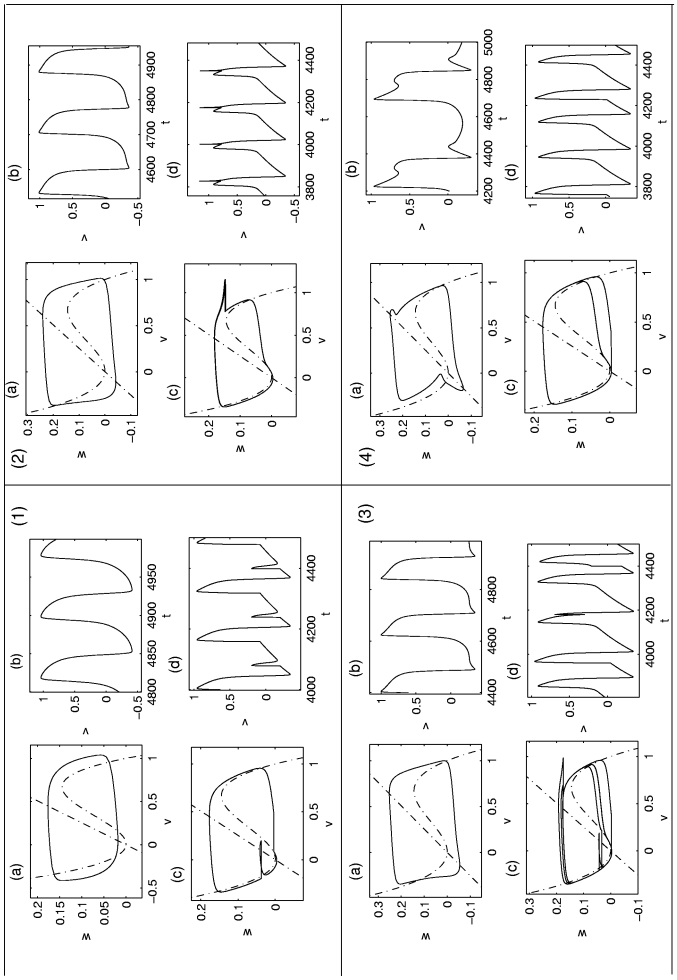

Figure 4: Phase space (full line) with nullclines (dash-dot), and time series for Eq. 1 in a limit cycle mode ($a = -0.0163$); (a),(b): Phase space and time series of $v(t)$ for the sinusoidal forcing, respectively, (c),(d) same for TOP forcing; (1): $T = 80$, (2):$T = 174$, (3): $T = 220$,(4): $T = 470$.

potential; for lower frequencies the system develops alternans (Fig 4(3),(4)c,d for $T = 230, 470$).

For a weaker SN, already in the excitable mode, the situation (not presented graphically) is somewhat similar although less dramatic. While the response to a sinusoidal stimulation remains smooth, the responses to the TOP pacing are as follows: For $T = 80$ the $2:1$ behavior is again obtained; for periods at or around the "natural" one, responses are "adequate": (e.g. for $T = 133$); for lower frequencies (e.g. for $T = 470$), unwanted oscillations appear between action potential pulses.

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