Article review -

Dissipation of the excitation wavefronts

V. N. Biktashev University of Liverpool

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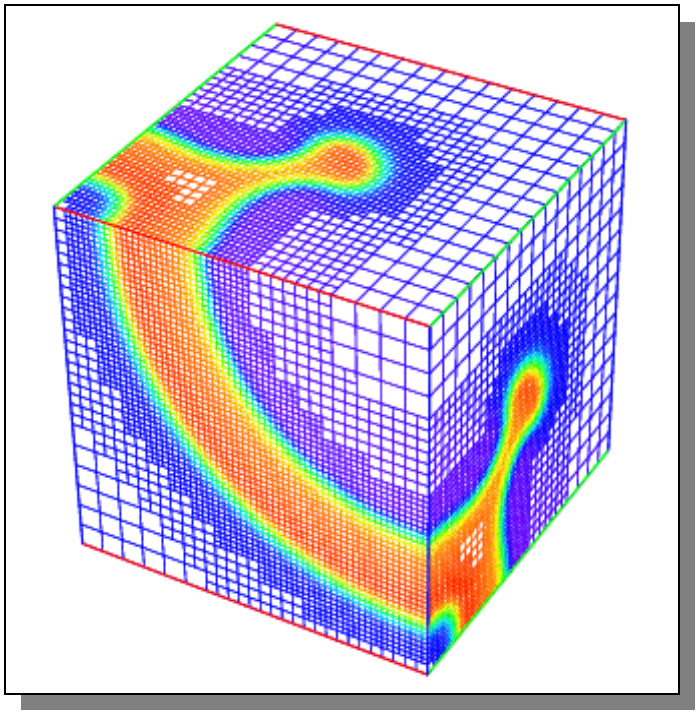

Written by: Ofer Fridman 03210248-5 (14/05/2008)

Course: 77838 - MEDICAL PHYSICS

Prof. L.D. Shvartsman

The Hebrew University of Jerusalem - Racah Institute of Physics.

* The front page figure is a FitzHugh-Nagumo Problem with AMR (3D) simulation[1].

Introduction

In this review we will draw the path from the detailed model for giant squid axon, achieved by Nobel Prize-winners Hodgkin & Huxley[2, 3] to the complex phenomena of "Dissipation of excitation wavefront" [4]. The needed assumptions and their results will be reviewed.

Hodgkin & Huxley axon model

In 1952 Alan Lloyd Hodgkin and Andrew Huxley described a model to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon. This squid axon was selected because of its size, up to 1 mm in diameter; typically around 0.5 mm, which enables experimental measurements using the equipment available at that time. The Hodgkin-Huxley model (HH) consists of a set of nonlinear ordinary differential equations. HH was the first model to use mathematical reconstruction of experimentally determined kinetics of ion channel transport and gating, rather than abstract equations.

$$
\begin{aligned}
\frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + g_{Na}(E_{Na} - E)m^3 h \\
&\quad + g_K(E_K - E)n^4 + g_l(E_l - E), \\
\frac{\partial m}{\partial t} &= (\overline{m}(E) - m)/\tau_m(E), \\
\frac{\partial h}{\partial t} &= (\overline{h}(E) - h)/\tau_h(E), \\
\frac{\partial n}{\partial t} &= (\overline{n}(E) - n)/\tau_n(E),
\end{aligned}
$$

Equation 1

Where E is the transmembrane voltage, $g_{Na.K,l}$ are maximal conductivities per membrane capacitance of Na, K, and leakage currents, $E_{Na,K,l}$ are their reversal potentials, m, h and n are fractions of open channel gates, m; h; n are their equilibria, and $\tau_{m,h,n}$ are their time scales[4].

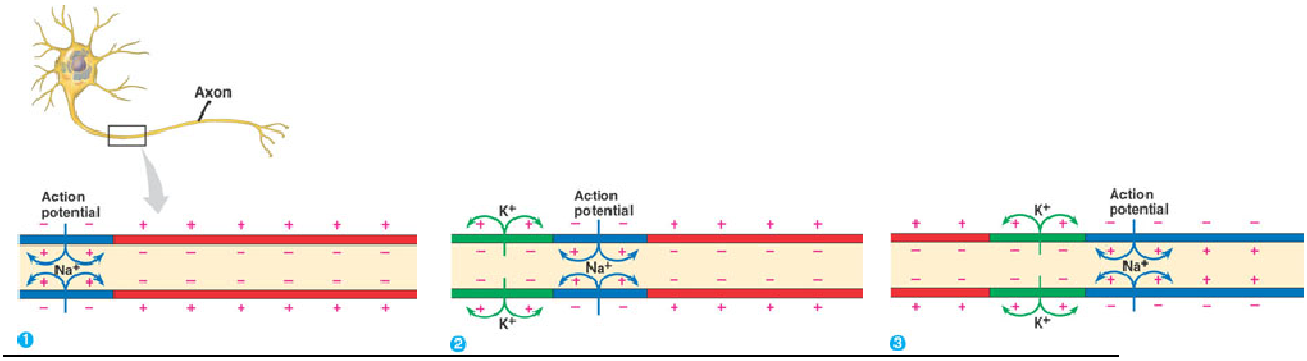

Figure 1 - axon ion channel and pumps action[5]

The HH realistic model is based on the physiological properties of the membrane but it has no analytical solution. This disadvantage led to a group

of simplified versions of the HH model, which analytical solutions can be applied to.

FitzHugh–Nagumo model[6]

In the mid-1950's, FitzHugh sought to reduce the Hodgkin-Huxley model to a two variable model for which phase plane analysis applies. His general observation was that the gating variables n and h have slow kinetics relative to m: Moreover, for the parameter values specified by Hodgkin and Huxley, n + h is approximately 0.8. This led to a two variable model, called the fast-slow phase plane model.

$$C_m \frac{\partial E}{\partial t} = -g_k^{n^4}\left(E - E_k\right) - -g_{Na}^{m_\infty^3}\left(E\right)\left(0.8 - n\right)\left(E - E_{Na}\right) - g_L\left(E - E_L\right) + I_{appl}$$

$$n_w\left(E\right)\frac{dn}{dt} = n_\infty\left(E\right) - n$$

Equation 2

In effect this provides a phase space qualitative explanation of the formation and decay of the action potential[7]. A further observation according to FitzHugh was that the E -nullcline had the shape of a cubic function and the n-nullcline could be approximated by a straight line, both within the physiological range of the variables. This suggested a polynomial model reduction of the form:

$$\frac{\partial E}{\partial t} = \left(a - E\right)\left(E - 1\right)E - v$$

$$\frac{\partial v}{\partial t} = \varepsilon\left(\beta E - \gamma v - \delta\right)$$

Equation 3

Here, the model has been put in dimensionless form, E represents the fast variable (potential), v represents the slow variable (sodium gating variable), α, γ and ε are constants with $0 < \alpha < 1$ and $\varepsilon << 1$ (accounting for the slow kinetics of the sodium channel). In 1964, Nagumo constructed a circuit using tunnel diodes for the nonlinear element (channel), whose model equations are those of FitzHugh. Hence the equations have become known as the FitzHugh-Nagumo model (FNH).

These rate equations of FNH don't have the needed spatial part in order to refine them we add:

$$\frac{\partial E}{\partial t} = \frac{\partial^2 E}{\partial x^2} + (a - E)(E - 1)E - v$$

$$\frac{\partial v}{\partial t} = \varepsilon(\beta E - \gamma v - \delta)$$

Equation 4

Where E corresponds to the transmembrane voltage and v represents all other, slow variables. This equation has analytical analysis, as well as simulation for one or more dimensions.

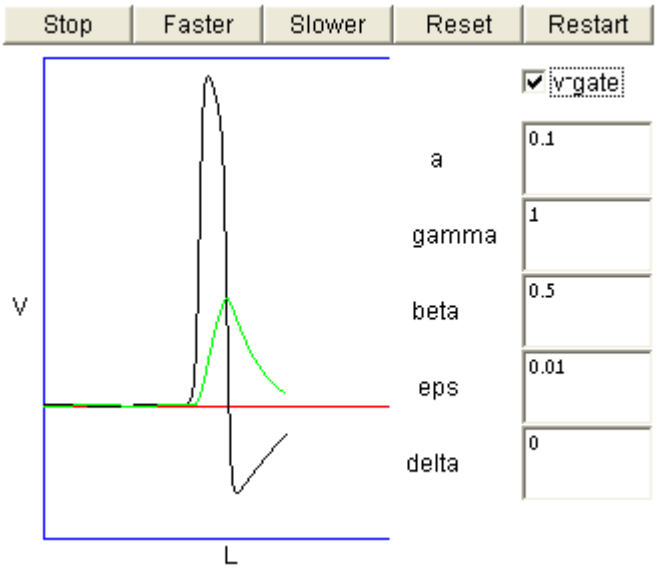

Figure 2 - FNH in one dimension model Simulation[8]

From the Hodgkin–Huxley axon to the heart model

Up to this point all of the presented models describe only the axon, while the main interest of this paper is the functioning of the heart model. In order to approach this subject, two parts are needed: The first is a biological mechanism, analog to the one in the axon; the second is a mathematical description of the phenomena in more than one dimension.
Experimentally based models of the heart have been developed since 1960, most of them assumed the HH like mechanisms [9].
The basic feature of the properties of excitable membranes in HH formulation is that the current is carried by ions moving down their respective electrochemical potential gradients. For example, the sodium current changes direction when the sodium electrochemical potential gradient is reversed, by changing either the membrane potential or the extracellular sodium concentration.
In cardiac muscle these HH like mechanisms were first discovered in 1963, when the Current-voltage relations of Purkinje fibres in sodium-deficient solution was described [10], and explored until 1979, when sodium current in cardiac Purkinje fibres was revealed [11]. After this more mechanisms were

discovered, the HH equations were adapted and a lot of simulations were conducted [12].
The transition from more than one dimension HH to the same in FNH is trivial (replace the x deviation by Laplace operator)

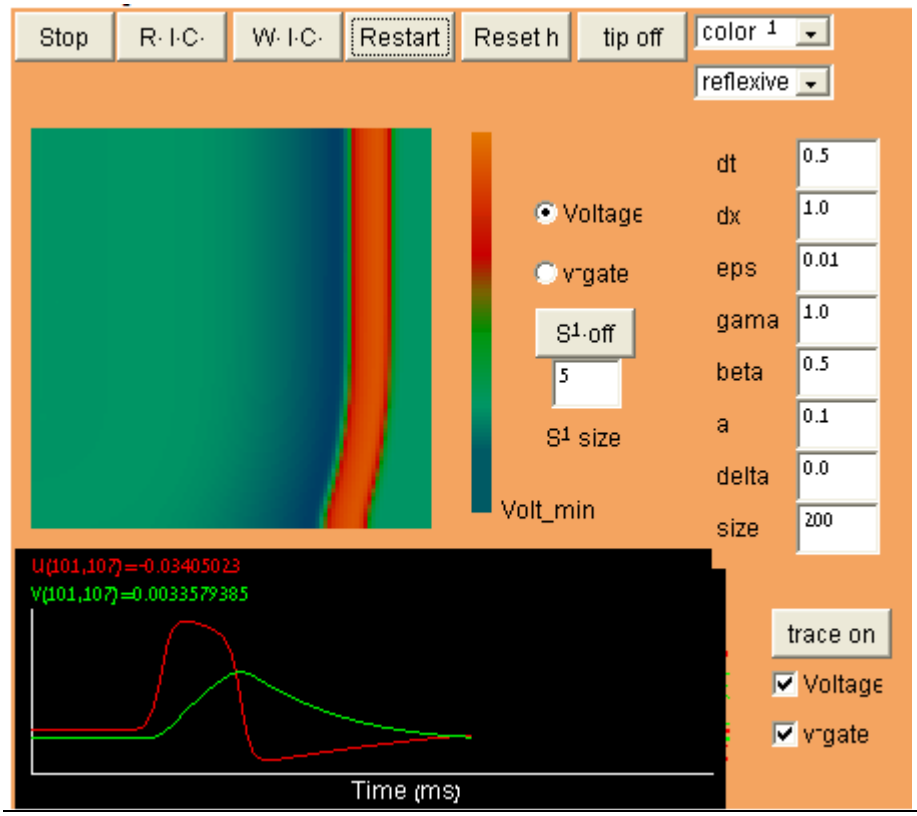

Figure 3 - FNH two dimensional simulations[13]

Dissipation of the Excitation Wave Fronts

Subject problem

Ventricular fibrillation (VF) remains the most common cause of sudden death in humans [14]. One of the factors causing this might be dissipation of the Excitation Wave Fronts. This phenomena cannot be adequately reproduced in the commonly used model, FHN-type system[4]. This can be shown using simulation in Figure 4: in FHN model, if the block lasts shorter than the action potential the wave does not dissipates.

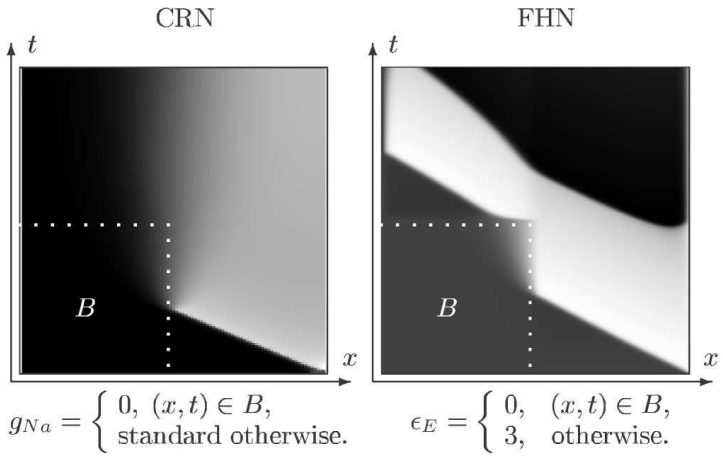

Figure 4 – Temporeary block of excitation front dose note produce dissipation in FHN model[4]

It might be considered as an option, to use the existing CRN, a detailed model of human atrial tissue [14], but there is a huge advantage to simplified models applying equations that can be analyzed analytically like in this case.

Methods

Based on HH (Equation 1), using assumptions on the front of the wave where E is rapidly raised, to describe the front only, we consider the limit of large g_{Na}, and disregard all ionic currents but Na. Another assumption regards the Values of $\tau_m(E)$ at the front, that are very small compared to other characteristic time scales of the problem. Thus m is always close to its quasistationary value <m(E)>. The differential equation for m is therefore eliminated.
Thus we get a system of two equations:

$$\frac{\partial E}{\partial t} = \frac{\partial^2 E}{\partial x^2} + I_{Na}(E)\overline{m}^3(E)h,$$
$$\frac{\partial h}{\partial t} = \frac{1}{\tau_h(E)}\left(\overline{h}(E) - h\right),$$

Equation 5

These equations describe the propagation of the excitation front (the fast process) only, leaving all other processes, such as action potential and recovery (the slow processes), out of the scope.
The last approximation regarding the m and h functions can be seen in Figure 5.

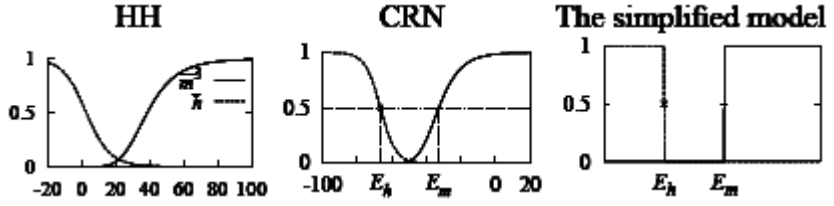

Figure 5 - Dependence of m and h in the detailed model and for this simplifid model

After rescaling and nondimensionalizations we obtain the system:

$$\frac{\partial E}{\partial t} = \frac{\partial^2 E}{\partial x^2} + \theta(E-1)h,$$
$$\frac{\partial h}{\partial t} = \frac{1}{\tau}\left(\theta(-E) - h\right),$$

Equation 6

This simplified model produces the "needed" Dissipation of the Excitation Wave Fronts (Figure 6) and can be used to analyze other parameters like speed or front shape. For an accurate quantitative description, a less simplified model (Equation 5) can be used.

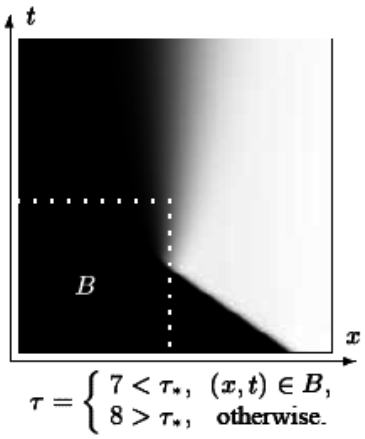

Figure 6- Temporary local block of the excitation front in the simplified model.

Personal attitude

First, it seems that a main part of the article (larger than I'd expect) is trying to aim at the obvious fact: that FHN model is insufficient for dealing with dissipation of wave fronts. This, instead of specifying the detailed advantages of this model relatively to other CRN-like models.
The second very strange thing, is the fact that this model aims at a very specific phenomena, that is not proven (at least not at the only referenced article provided for this reason[14]) to be the only or main reason for Ventricular fibrillation. This is much more peculiar if you consider the fact that the resulting model is not robust – it aims only at phenomena linked directly to the wave front.
Despite these two rather tactical comments, this article is a nice practical mathematical tools used on a medical problem, trying to reveal its secret mechanisms.

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