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The Fitzhugh-Nagumo model

a mathematical analysis of the nerve system

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Award date:
2004

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Bachelor Project

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Computational Science and Engineering

August-December 2004

Abstract

Nerve pulses are caused by flows of sodium and potassium through the membrane of a neuron axon. This phenomena can be modelled by the Hodgkin-Huxley model, but the equations of this model are quite difficult to solve. The Fitzhugh-Nagumo model is a simplification of the Hodgkin-Huxley model. It appears to be a perturbed problem with small variable ε, and solution methods will be discussed for the cases $\varepsilon = 0$ as well as $\varepsilon \neq 0$. The problem discussed in this paper is whether the Fitzhugh-Nagumo model is a good description of nerve pulses.

Contents

1 Introduction

1.1 Historical overview

Modern scientists have always tried to combine great theoretical work with physical results. Not only physics happened to be a pool of inspiration, but also increasingly chemistry, economics and biology. The latter area came into the picture somewhere at the end of the 18th century, when great progress was made in *electrophysiology* ([7]). Electrophysiology is the science that studies the interaction between biology and electromagnetic fields. Examples of electrophysiological results in the 19th century are the Leyden Jar, the frog experiment by Galvan and the Voltaic Pile. At the beginning of the 20th century, A.V. Hill received the noble prize for discovering that heat is produced during a nerve impulse. This gave him the opportunity to establish his own research center: Hill's interdisciplinary school at Cambridge. Two alumni of Hill's school were *A.L. Hodgkin* and *A.F. Huxley*. They published their model for the electric signalling of individual nerve cells ([1]) in 1952, for which they received the noble prize in 1963. They used a technique called "voltage clamp" on a axon of a giant squid named Loligo. The Hodgkin-Huxley system consists of a nonlinear partial differential equation, coupled to three ordinary differential equations which makes the system rather complicated. Various simplifications have been suggested, like the polyomial model, the van Capelle-Durrer model and the Fitzhugh-Nagumo model ([8], [3], [11]), the latter probably being the most famous. In the early 1960's Richard Fitzhugh analyzed the Hodgkin Huxley model and he applied some techniques he had learned from Russian applied mathematics journals. His work, combined with that by Nagumo, Arimoto, and Yoshizawa, became known as the Fitzhugh-Nagumo model which gave great insight in the complexity of the membrane potential process.

1.2 Problem setting and paper setup

The neural system is the "internet" of the human body, it sends all kinds of information throughout the body. This is obviously a biological process, so you could wonder why a mathematician would make an analysis of it. As a matter of fact, applied mathematicians are trained to model real life problems from physics, chemistry, electrotechnics and biology. Modelling of problems is important, because by using the right model the mathematician can communicate with other scientists. For example, nerve signals can be modelled by waves. The model Hodgkin and Huxley came up with was a rather complex one; calculation of these waves happened to be quite difficult for this model. The Fitzhugh-Nagumo model is a simplification of this model, but does it still give a good description of the nerve signals? To answer this question we need to check the following statement:

> Although the Fitzhugh-Nagumo model is a simplification of the Hodgkin-Huxley model, it still maintains all important properties.

This report is structured as follows: in section 2 a biological description of the nerve system is given. The neuron is analyzed and it becomes clear that sodium and potassium flows through the membrane are important for nerve signals. In section 3 the permeability of the membrane is analyzed, and the Nernst equation is derived which is of importance for the

Hodgkin-Huxley model (HH model). In section 4 the membrane is modelled and the cable equation is derived which forms the basis of the HH model. This is done by analyzing electrical circuits. Also the importance of ionic batteries is discussed. In section 5 the HH model is derived using the cable equation with ionic batteries and the experimental data Hodgkin an Huxley found ([1]). In section 6 the Fitzhugh-Nagumo model (FN model) is derived which appears to be a perturbed problem with small variable ε. The problem is analyzed for $\varepsilon = 0$ in section 7 and for $\varepsilon \neq 0$ in section 8. Conclusions drawn from both analysis are given in section 9.

2   Biology of the nerve system

As stated before, the nerve system is the information source of the human body. Using our nerves we can locate objects, feel temperature changes and be informed of pain throughout our body. We are interested in the process how all these signals are transmitted to the right target. An extended study of the nerve system can be found in [2], [3] and [4].

The nervous system consists of a *central* and a *peripheral system*. The central nervous system, consisting of the brain and the spinal cord, is the place where all the information is gathered and the peripheral system, containing *neurons* and nerve endings, is the source of all information. The nerve endings gain the information, such as light, sound, chemicals, or touch, which is transmitted by neurons. Since transmission is something mathematicians are acquainted to modelling, neurons play an important rôle in this report. A neuron consists of *dendrites*, a *cell body* (also called a *soma*), an *axon* and *axon terminals*, like in Figure 1. The dendrites receive information from another neuron or from a nerve ending. This information is then transmitted by the axon to the axon terminals. These axon terminals are connected to either dendrites (they are separated by a thin gap containing neurotransmitters, called *synapse*, as shown in Figure 2) or tissue, like for instance a muscle.
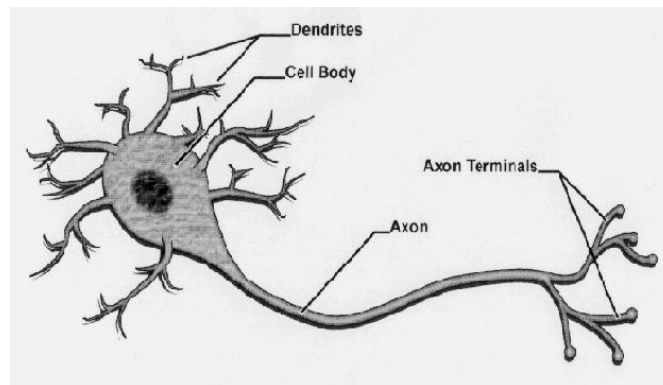

Figure 1: A schematic picture of a nerve cell

Nerve pulses transmitted by the axon are called *nerve action potentials*. This process appears to be a chemo-electrical process. The nerve action potentials are electrical signals sent out by the body, and their appearance depends on the concentration of ions around the nerve

Table 1: Typical values for intracellular and extracellular concentrations in nmol ([3])

	Squid Giant Axon	Frog Sartorius Muscle	Human Red Blood Cell
Intracellular conc.			
Na^+	50	13	19
K^+	397	138	136
Cl^-	40	3	78
Extracellular conc.			
Na^+	437	110	155
K^+	20	2.5	5
Cl^-	556	90	112

cell, basically sodium (Na^+) and potassium (K^+) ions. Although ions like chloride (Cl^-) and calcium (Ca^{2+}) have some importance, they turn out to yield only secondary effects. The signals take part in an all-or-nothing process which means that the signals only occur if a certain *depolarization threshold* is met. For example, a voltage of the order of 70 mV results in a resting state, while a voltage of the order of 100 mV gives a nerve action potential. This voltage does not depend on the strength of the incoming signal, but rather on factors like temperature, fatigue of the nerve, drugs, etc.

The potential difference is governed by the influx and efflux of sodium and potassium through the *membrane* of the axon which is a very thin shell (about 5 to 10 nm). Table 1 shows the intracellular and extracellular concentrations of sodium, potassium and chloride for 3 different cell types. The influx of sodium is responsible for the depolarization of the membrane. After this depolarization, the neuron has to repolarize to its resting potential. This repolarization is influenced by the efflux of potassium. The influx and efflux occur by diffusion, and the depolarization/repolarization process is governed by *protein gates* .

There are three types of gates in the axon that influence the action potential: the m-, n- and
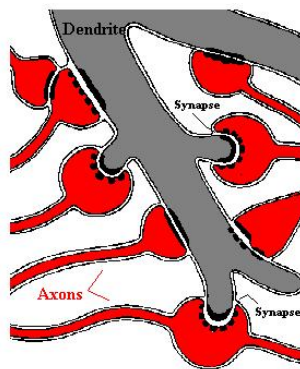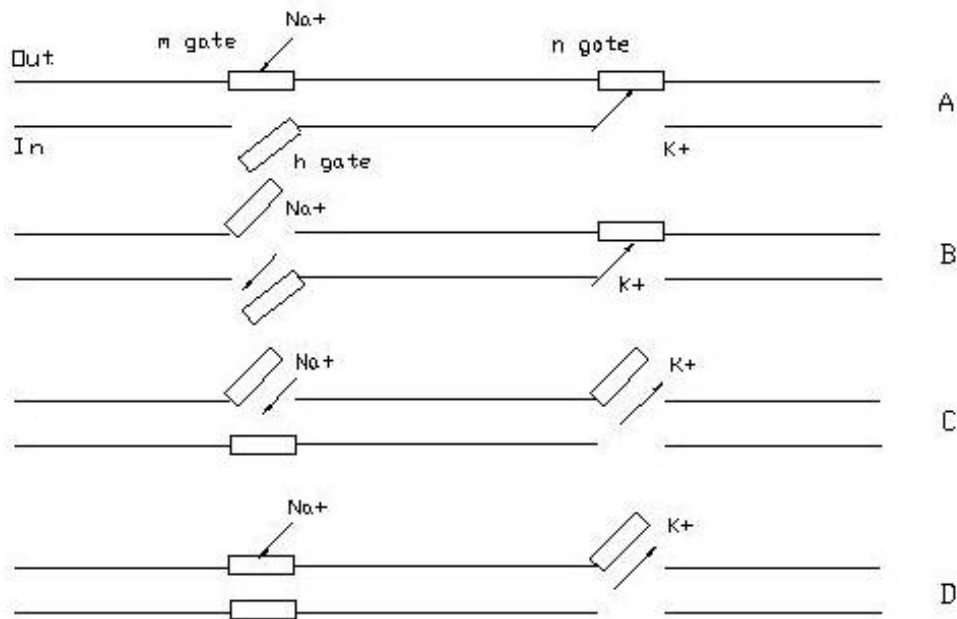

Figure 2: The synapse connections

Figure 3: The protein gates

h-gate. The m- and h-gates regulate the sodium flow, while the n-gates regulate the potassium flow. If the neuron is in resting state, both the m- and the n-gates are closed, and the h-gate is open. Therefore the outer shell of the membrane is closed, so there is no ion-flow. During depolarization, the n-gate is open, so the sodium can diffuse down its gradient. There is no potassium flow. During the repolarization, the h-gate is closed and the m-gate is open, so now there is a flow of potassium only. If the m-gate is open for too long, the potential of the cell drops below the resting rate. This situation is called *undershoot* . Figure 3 shows the different states of the protein gates: the normal state (A), the depolarization state (B), the repolarization state (C), and the undershoot state (D).

3   Membrane permeability

In the previous section we saw that the flow of certain ions through the membrane caused an action potential. Now we will try to calculate this action potential. See also [5]. Assume there are 2 compartments with unequal ionic concentrations, compartment 1 and compartment 2, and assume they have different electric potentials, V_1 and V_2 respectively. Also, assume that a small quantity of δn moles moves from compartment 2 to compartment 1 carrying an electric charge $\delta n z F$, where z is the valence of the material and F is Faraday's constant. In addition, assume that in this process the temperature T and the pressure p are constant. There are four types of energy that change during the flow: internal energy ($\delta n \Delta U$), heat energy ($\delta n T \Delta S$), work energy ($-\delta n p \Delta(p\varphi)$), and electrical energy ($-\delta n z F \Delta V$), with U the internal energy, S the entropy, and φ the volume per mole of the solution. The change in internal energy is

Table 2: Typical values for Nernst and resting potentials in mV ([3])

	Squid Giant Axon	Frog Sartorius Muscle	Human Red Blood Cell
Nernst potentials			
V_{Na}	+56	+55	+55
V_K	-77	-101	-86
V_{Cl}	-68	-86	-9
Resting potentials	-65	-99	-8

equal to the sum of the change in the other energies:

$$\delta n \Delta U = \delta n T \Delta S - \delta n \Delta(p\varphi) - \delta n z F \Delta V. \tag{1}$$

For the enthalpy H and the Gibbs energy G we have $H = U + p\varphi$ and $G = H - TS$ respectively. Then we can write (1) as

$$\Delta G + zF\Delta V = 0. \tag{2}$$

The Gibbs energy per mole of component p is denoted by $\mu[p]$. For $\mu[p]$ we have

$$\mu[p] = \mathbf{R}T \ln c[p], \tag{3}$$

where $\mathbf{R}$ is the gas constant and $c[p]$ is the concentration of component p. Applying (3) on compartment 1 and 2, and combining the result with (2) gives the *Nernst equation* :

$$\Delta V = \frac{\mathbf{R}T}{z(p)F} log \frac{c[t2]}{c[t1]} \tag{4}$$

With this result equilibrium potentials can be calculated which will appear in the HH model. Table 2 shows the Nernst potentials for three different cell types.

4   The cable equation

4.1   The axon model

To understand the structure of the HH model it is useful to study *the cable equation*, because the HH equation is a special form of this equation. The cable equation was first derived by William Thomson in 1854. It is based on the simple notion of transverse current leakage between the inner and outer conductor due to an imperfect insulator as a consequence of the longitudinal flow of current within the inner conductor. See also [5] and [6]. The insulator, in this model the membrane, is modelled as a long cylindrical boundary which separates the inner conductor from the outer conductor. The radius of the membrane is ρ. Since there are three media (the membrane, the inner and the outer conductor) the variables and parameters appearing in all media will be denoted by either $_m$ for the membrane, $_{in}$ for the inner conductor and $_{out}$ for the outer conductor. The current in the longitudinal direction is called $I(x, t)$ and the potential is called $V(x, t)$. We denote the current per unit length in the radial direction $K(x, t)$. r Is the resistance per unit length of the conductor. Figure 5 shows a fraction of an electrical circuit model of the interaction between the membrane and the conductors. What happens in the membrane is explained in subsection 4.3.
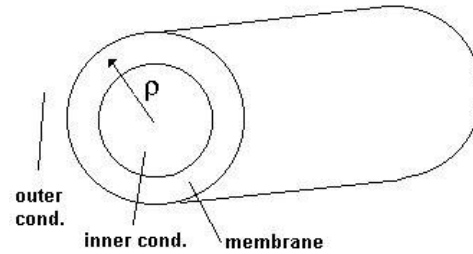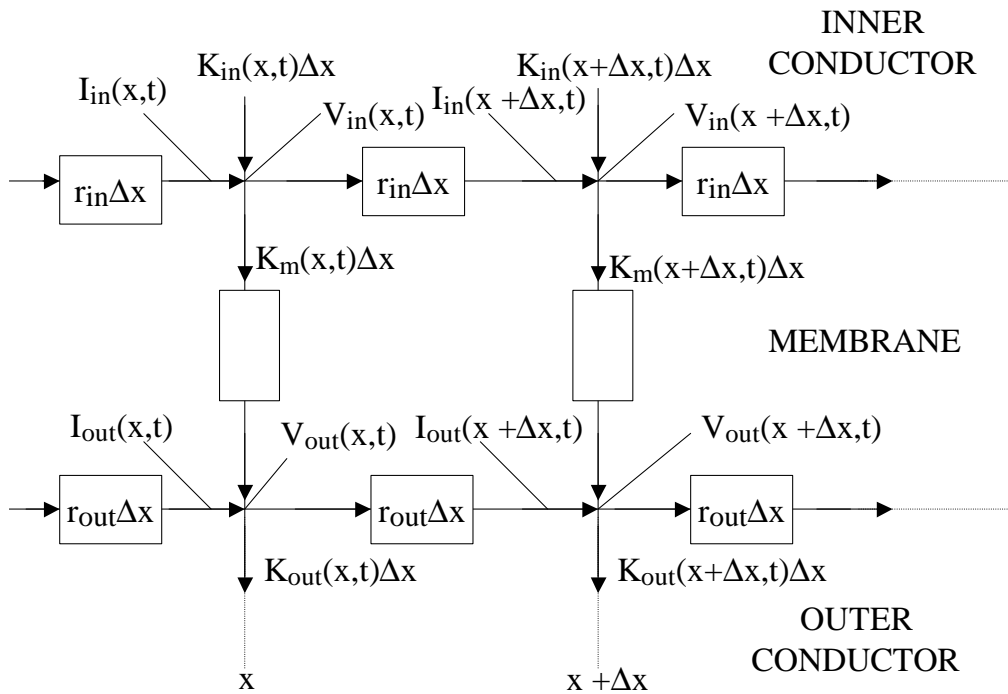
Figure 4: The axon

Figure 5: Electrical Circuit model of the membrane

4.2 The core-conductor equation

Kirchhoff's current law (conservation of current, (89)) applied to point x results in two balance equations

$$I_{in}(x,t) + K_{in}(x,t)\Delta x = I_{in}(x + \Delta x, t) + K_m(x,t)\Delta x, \tag{5}$$

$$I_{out}(x,t) + K_m(x,t)\Delta x = I_{out}(x + \Delta x, t) + K_{out}(x,t)\Delta x. \tag{6}$$

These equations can be rewritten into

$$\frac{I_{in}(x + \Delta x, t) - I_{in}(x,t)}{\Delta x} = K_{in}(x,t) - K_m(x,t), \tag{7}$$

$$\frac{I_{out}(x + \Delta x, t) - I_{out}(x,t)}{\Delta x} = K_m(x,t) - K_{out}(x,t). \tag{8}$$

By taking the limit $\Delta x \to 0$, two differential equations are formed

$$\frac{\partial I_{in}(x,t)}{\partial x} = K_{in}(x,t) - K_m(x,t), \tag{9}$$

$$\frac{\partial I_{out}(x,t)}{\partial x} = K_m(x,t) - K_{out}(x,t). \tag{10}$$

Such a derivation for the derivative of the current can also be done for the potential. Applying Ohm's law ((88)) on the network in figure 5 gives

$$V_{in}(x,t) - V_{in}(x + \Delta x, t) = r_{in}\Delta x I_{in}(x + \Delta x, t), \tag{11}$$

$$V_{out}(x,t) - V_{out}(x + \Delta x, t) = r_{out}\Delta x I_{out}(x + \Delta x, t). \tag{12}$$

Again, rewriting and taking the limit $\Delta x \to 0$, two differential equations are formed

$$\frac{\partial V_{in}(x,t)}{\partial x} = -r_{in} I_{in}(x,t), \tag{13}$$

$$\frac{\partial V_{out}(x,t)}{\partial x} = -r_{out} I_{out}(x,t). \tag{14}$$

Since $V_m = V_{in} - V_{out}$, the last two equations can be combined

$$\frac{\partial V_m(x,t)}{\partial x} = r_{out} I_{out}(x,t) - r_{in} I_{in}(x,t). \tag{15}$$

If we take the derivative with respect to x of this equation allows the substitution of (9) and (10) into this equation

$$\frac{\partial^2 V_m(x,t)}{\partial x^2} = (r_{out} + r_{in})K_m(x,t) - r_{out}K_{out}(x,t) - r_{in}K_{in}(x,t). \tag{16}$$

This result is called the *core-conductor equation*.

4.3 The cable equation

In this subsection the membrane will be modelled as well. It can be modelled as an electrical circuit containing a capacitor and a resistor in parallel, like the one shown in Figure 6. Take $\hat{c}_m(\Delta x)$ to be the capacitance of a small section of the membrane with surface area equal to
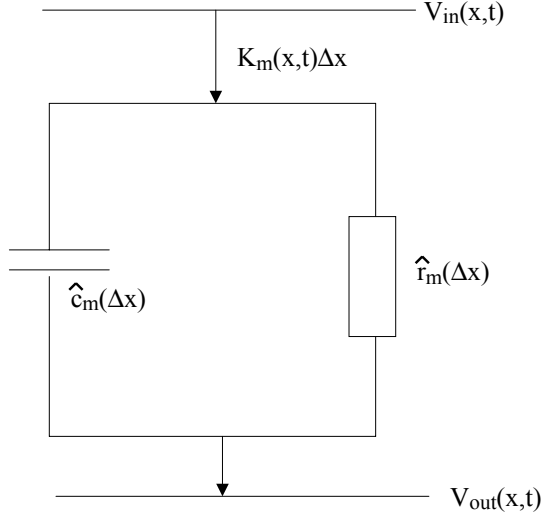
Figure 6: The electrical circuit of the membrane

$2\pi\rho\Delta x$ and $\hat{r}_m(\Delta x)$ to be the transmembrane resistance. Define $\hat{g}_m(\Delta x) := \frac{1}{\hat{r}_m(\Delta x)}$, where $\hat{g}_m$ is the conductance of the membrane. Both Ohm's law and the capacitor law ((90)) applied to Figure 6 give

$$K_m(x,t)\Delta x = \hat{c}_m(\Delta x)\frac{\partial V_m(x,t)}{\partial t} + \frac{V_m(x,t)}{\hat{r}_m(\Delta x)}). \tag{17}$$

To get rid of the Δx term we make an assumption concerning both $\hat{c}_m(\Delta x)$ and $\hat{g}_m(\Delta x)$. Take $\hat{c}_m(\Delta x) = c_m\Delta x$ and $\hat{g}_m(\Delta x) = g_m\Delta x$, where c_m and g_m are the capacitance and the conductance per unit length respectively. Now we can divide both sides of (17) by Δx which results into

$$K_m(x,t) = c_m\frac{\partial V_m(x,t)}{\partial t} + \frac{V_m(x,t)}{r_m}. \tag{18}$$

Substitution of this equation into the core-conduction equation gives the cable equation

$$r_m c_m \frac{\partial V_m(x,t)}{\partial t} = \frac{r_m}{r_{out} + r_{in}}(\frac{\partial^2 V_m(x,t)}{\partial x^2} + r_{out}K_{out}(x,t) + r_{in}K_{in}(x,t)) - V_m. \tag{19}$$

4.4 Adding ionic batteries

In section 2 we saw that the flux of certain ions have an impact on the potential difference. This process can also be included in an electrical circuit model with so called *ionic batteries* (Figure 7). Assume there are k ionic batteries. Let J be the current flow per unit area in the radial direction, G the conductance per unit area and C the capacitance per unit area. E is the equilibrium potential for a certain ion which is calculated by means of the Nernst equation (4).
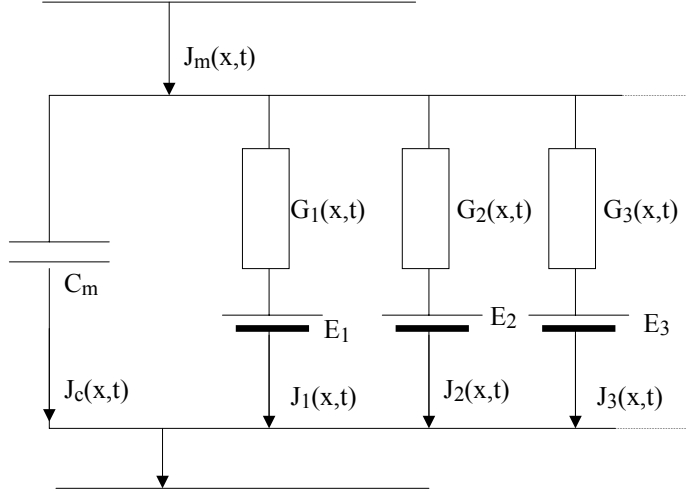
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Figure 7: The electrical circuit of the membrane including ionic batteries

From the definition it is clear that $2\pi\rho\Delta x J = \Delta x K$. Applying Kirchhoff's current law on the circuit in Figure 7 results in

$$J_m = J_c + \sum_{i=1}^{k} J_i. \tag{20}$$

For each battery the potential energy can be calculated

$$V_{in} - \frac{2\pi\rho J_i(x)\Delta x}{2\pi\rho G_i(x)\Delta x} - E_i = V_{out}. \tag{21}$$

Hence

$$J_i = (V_m - E_i)G_i. \tag{22}$$

Now we can find two equations for J_m

$$J_m = C_m\frac{\partial V_m}{\partial t} + \sum(V_m - E_i)G_i, \tag{23}$$

$$J_m = \frac{1}{2\pi\rho(r_{out} + r_{in})}\left(\frac{\partial^2 V_m}{\partial x^2} + r_{out}K_{out} + r_{in}K_{in}\right). \tag{24}$$

Eliminating J_m and assuming $r_{in} \gg r_{out}$ results in

$$\frac{1}{2\pi\rho r_{in}}\frac{\partial^2 V_m}{\partial x^2} = C_m\frac{\partial V_m}{\partial t} + \sum(V_m - E_i)G_i + J_{in}. \tag{25}$$

5 The Hodgkin-Huxley model

In this section the membrane-model will be applied to the axon described in section 2 and for the data Hodgin and Huxley found. Sodium and potassium did appear to be important for the membrane potential. Therefore there will be three batteries in the HH-model: a sodium, a potassium and a *leakage* battery. The leakage battery includes all ions excluding potassium and sodium.

In (25) the dimension is current per unit area. If ℓ is the unit length, then $2\pi\rho\ell$ is the unit area, so (25) can also be written as

$$\frac{1}{R_{in}}\frac{\partial^2 V_m}{\partial x^2} = \hat{c}_m\frac{\partial V_m}{\partial t} + (V_m - E_{Na})\hat{g}_{Na} + (V_m - E_K)\hat{g}_K + (V_m - E_L)\hat{g}_L + I_{app}, \tag{26}$$

where R_{in} is the resistance per unit area of the inner conductor. We can also define the *membrane resting potential* by

$$V_{eq} := \frac{\hat{g}_{Na}V_{Na} + \hat{g}_K V_K + \hat{g}_L V_L}{\hat{g}_{eff}}, \tag{27}$$

where $\hat{g}_{eff} := \hat{g}_{Na} + \hat{g}_K + \hat{g}_L$. The potassium and sodium conductances are found from experimental data. For the potassium conductance Hodgkin and Huxley tried $\hat{g}_K = \bar{g}_K n^4$, where n is a function of ν and $\nu = V_m - V_{eq}$. n Obeys the differential equation $n_t = \frac{(n_\infty(\nu) - n)}{\tau_n(\nu)}$, in which τ_n and n_∞ are experimentally determined. Usually, τ_n and n_∞ are written in terms of α_n and β_n

$$n_\infty(\nu) = \frac{\alpha_n(\nu)}{\alpha_n(\nu) + \beta_n(\nu)}, \tag{28}$$

$$\tau_n(\nu) = \frac{1}{\alpha_n(\nu) + \beta_n(\nu)}, \tag{29}$$

which gives

$$n_t = \alpha_n(\nu)(1 - n) - \beta_n(\nu)n. \tag{30}$$

The sodium conductance is described similarly, except that the sodium flow depends on both the m-gate and the h-gate. Hodgkin and Huxley found that $\hat{g}_{Na} = \bar{g}_{Na}hm^3$, with m and h depending on ν and obeying the same differential equation as n. This result completes the Hodgkin-Huxley model:

$$\nu_{xx} = R[\hat{c}_m\nu_t + \bar{g}_K n^4(\nu - \nu_K) + \bar{g}_{Na}m^3 h(\nu - \nu_{Na}) + \bar{g}_L(\nu - \nu_L)], \tag{31}$$

$$n_t = \alpha_n(\nu)(1 - n) - \beta_n(\nu)n, \tag{32}$$

$$m_t = \alpha_m(\nu)(1 - m) - \beta_m(\nu)m, \tag{33}$$

$$h_t = \alpha_h(\nu)(1 - h) - \beta_n(\nu)h, \tag{34}$$

where

$$\alpha_n = 0.01\frac{10-\nu}{e^{\frac{10-\nu}{10}}-1}, \tag{35}$$

$$\beta_n = 0.125e^{\frac{-\nu}{80}}, \tag{36}$$

$$\alpha_m = 0.1\frac{25-\nu}{e^{\frac{25-\nu}{10}}-1}, \tag{37}$$

$$\beta_m = 4e^{\frac{-\nu}{18}}, \tag{38}$$

$$\alpha_h = 0.07e^{\frac{-\nu}{20}}, \tag{39}$$

$$\beta_h = \frac{1}{e^{\frac{30-\nu}{10}}+1}, \tag{40}$$

$$\bar{g}_{Na} = 120, \tag{41}$$

$$\bar{g}_K = 36, \tag{42}$$

$$\bar{g}_L = 0.3, \tag{43}$$

$$\nu_{Na} = 115, \tag{44}$$

$$\nu_K = -12, \tag{45}$$

$$\nu_L = 10.6. \tag{46}$$

6 The Fitzhugh-Nagumo model

The system of differential equations in the HH model is quite complicated, so many scientists tried to find a simpler model. Fitzhugh came up with a model in which there is a distinction between slow and fast variables. Both m and ν are fast variables which means that the potential changes quickly, and the sodium channel activates fast. Additionally, both n and h are slow variables which means that the sodium channel deactivates slowly, and the potassium channel activates slowly. By fixing two variables the problem now becomes one with the other two variables. The final FN model consists of a fast (ν) and a slow variable (w). It can be constructed by analyzing the electrical circuit in figure 8.

This model has an additional coil with self-inductance L_m and conductance G_m which represents the the slow transport of ions. The coil with the function $F(V)$ represents the fast transport of ions, in which the function $F(V)$ is non-linear. Nagumo came up with the idea to use a tunnel diode as the nonlinear element. Applying Kirchhoff's current law on the circuit in Figure 8 shows that

$$J_m = J_c + J_L + J_F. \tag{47}$$

For J_L we can use the equation for inductors ((91)) and Ohm's law

$$V_m = L_m 2\pi\Delta x\frac{\partial J_L}{\partial t} + \frac{J_L}{G_L}. \tag{48}$$

Using the cable equation and substituting J_c and J_F gives the following system

$$\frac{1}{2\pi\rho r_{in}}\frac{\partial^2 V_m}{\partial x^2} = C_m\frac{\partial V_m}{\partial t} + J_L + J_{in} + F(V_m), \tag{49}$$

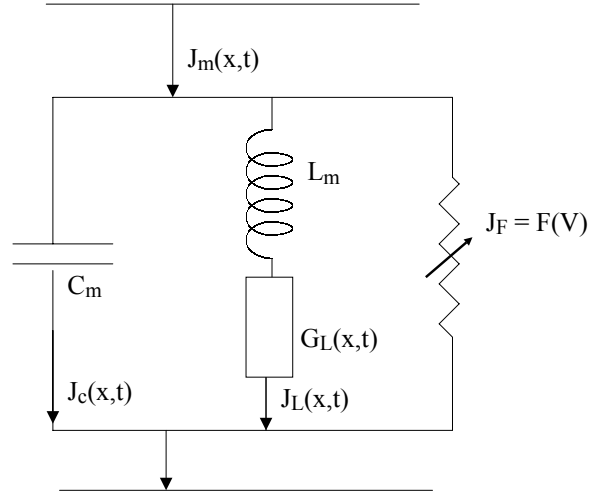$$V_m = L_m\frac{\partial J_L}{\partial t} + \frac{J_L}{G_L}. \tag{50}$$

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Figure 8: The electrical circuit of the Fitzhugh-Nagumo model

Setting J_{in} equal to zero and defining $W := J_L$ gives the differential equations in dimensional form of the Fitzhugh-Nagumo model:

$$\frac{1}{2\pi\rho r_{in}}\frac{\partial^2 V_m}{\partial x^2} = C_m\frac{\partial V_m}{\partial t} + W + F(V_m), \tag{51}$$

$$V_m = L_m\frac{\partial W}{\partial t} + \frac{W}{G_L}. \tag{52}$$

We prefer this system to be dimensionless. To accomplish this we need a characteristic value for the current and the voltage drop. The equilibrium potential can be calculated by taking all derivatives equal to zero. This leads to the equation

$$V_E + \frac{F(V_E)}{G_L} = 0. \tag{53}$$

To find a characteristic value R_E for the resistor we need to solve

$$R_E = [(\frac{df}{dV})_{V=V_E}]^{-1} \tag{54}$$

Using V_E and R_E we find the dimensionless quantities

$$t^* := (\frac{1}{C_m R_E})t, \tag{55}$$

$$x^* := (\sqrt{\frac{R_E}{2\pi\rho r_{in}}})x, \tag{56}$$

$$V^* := (\frac{1}{V_E})V_m, \tag{57}$$

$$W^* := (\frac{R_E}{V_E})W, \tag{58}$$

$$f^*(V^*) := -(\frac{R_E}{V_E})F(V_m). \tag{59}$$

Substitution of these quantities in the system yields:

$$\frac{1}{2\pi\rho r_{in}}\frac{\partial^2 V_m}{\partial x^2} = C_m\frac{\partial V_m}{\partial t} + W + F(V_m) \Longrightarrow \tag{60}$$

$$\frac{1}{2\pi\rho r_{in}}\frac{2\pi\rho r_{in}V_E}{R_E}\frac{\partial^2 V^*}{\partial x^{*2}} = C_m\frac{V_E}{C_m R_E}\frac{\partial V^*}{\partial t^*} + \frac{V_E}{R_E}W^* + \frac{V_E}{R_E}f^*(V^*) \Longrightarrow \tag{61}$$

$$\frac{\partial^2 V^*}{\partial x^{*2}} = \frac{\partial V^*}{\partial t^*} + W^* + f^*(V^*), \tag{62}$$

and

$$V_m = L_m\frac{\partial W}{\partial t} + \frac{W}{G_L} \Longrightarrow \tag{63}$$

$$V_E V^* = L_m\frac{V_E}{R_E}\frac{1}{C_m R_E}\frac{\partial W^*}{\partial t^*} + \frac{V_E}{R_E}\frac{W^*}{G_L} \Longrightarrow \tag{64}$$

$$\frac{\partial W^*}{\partial t^*} = \varepsilon(V^* - \gamma W^*), \tag{65}$$

where $\varepsilon := \frac{C_m R_E^2}{L_m}$ and $\gamma := \frac{1}{G_L R_E}$. If we substitute measured values for C_m, R_E, L and G_L we find that $\varepsilon \ll 1$ and $\gamma \approx 1$. Because ε is very small, the FN system is singularly perturbed. In the next section the reduced problem will be discussed, with the assumption that $\epsilon = 0$.

7 The reduced problem

The FN equations will now be analyzed further. In section 2, the nerve potential was discussed. This nerve potential was some kind of wave, which only propagates if a certain threshold is met. This process is analyzed from a mathematical point of view in this section.

We take a look at the reduced problem. Since $\varepsilon = 0$, W^* is constant, so the FN system reduces to (we omit the superscript)

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + f(V) \tag{66}$$

If $f(V) = 0$, then (66) becomes the heat equation. This equation can be solved with a similarity approach. Now take $f(V) \neq 0$. The nerve potential was a pulse shaped like a wave, so we try to find solutions of the form of *traveling waves*. To accomplish this we need to assume that $V(x,t) = u(\eta)$, with $\eta = x + ct$. In this case, c is the wave speed. We choose $c > 0$, since the problem is invariant for the substitution $x \to -x$. Define $\mathbf{y} := (y_1, y_2)^T := (u, \frac{du}{d\eta})^T$. Then (66) becomes

$$\dot{\mathbf{y}} = \begin{pmatrix} y_2 \\ cy_2 - f(y_1) \end{pmatrix}. \tag{67}$$

This system has the Jacobian matrix

$$\mathbf{J}(y_1) := \begin{pmatrix} 0 & 1 \\ -f'(y_1) & c \end{pmatrix}. \tag{68}$$

This matrix has eigenvalues

$$\lambda_{\pm} := \frac{c}{2} \pm \sqrt{\frac{c^2}{4} - f'(y_1)} \tag{69}$$

and eigenvectors

$$\mathbf{v}_{\pm} := \begin{pmatrix} 1 \\ \lambda_{\pm} \end{pmatrix}. \tag{70}$$

In order to calculate wave solutions, the function $f(u)$ has to be specified. Two examples of such a function are discussed: Fisher's f function and Nagumo's f function.

7.1   Fisher's f function

Fisher's f function is the simplest case of the nonlinear reaction diffusion equation ([11], [8]). The function reads

$$f(y_1) = y_1(1 - y_1). \tag{71}$$

This system has two singular points, $X_1 = (0,0)^T$ and $X_2 = (1,0)^T$. Substitution of these points into (69) gives

$$X_1 : \qquad \lambda_{\pm} := \frac{c}{2} \pm \sqrt{\frac{c^2}{4} - 1}, \tag{72}$$

$$X_2 : \qquad \lambda_{\pm} := \frac{c}{2} \pm \sqrt{\frac{c^2}{4} + 1}. \tag{73}$$

For point X_2 we find that λ_+ is positive and λ_- is negative. Hence, X_2 is a saddle point. The stability of point X_1 depends on the value of c. If $c \geq 2$ then $\lambda_{\pm}$ is always positive, which means that for those values of c, X_1 is a unstable node. If $c < 2$ then $\lambda_{\pm}$ is a complex number, with $Re(\lambda_{\pm}) > 0$, so X_1 is a unstable spiral. We neglect values of $c < 2$, because an unstable spiral implies that the solution would spin around the origin, leaving the first quadrant. This is not allowed, because concentrations can not be negative.
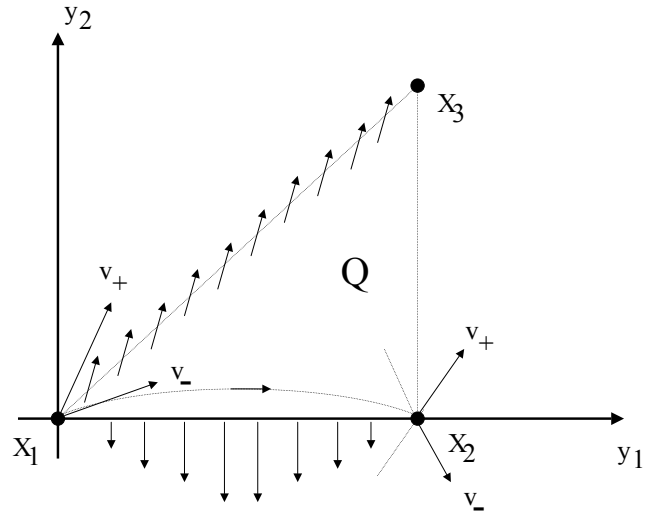
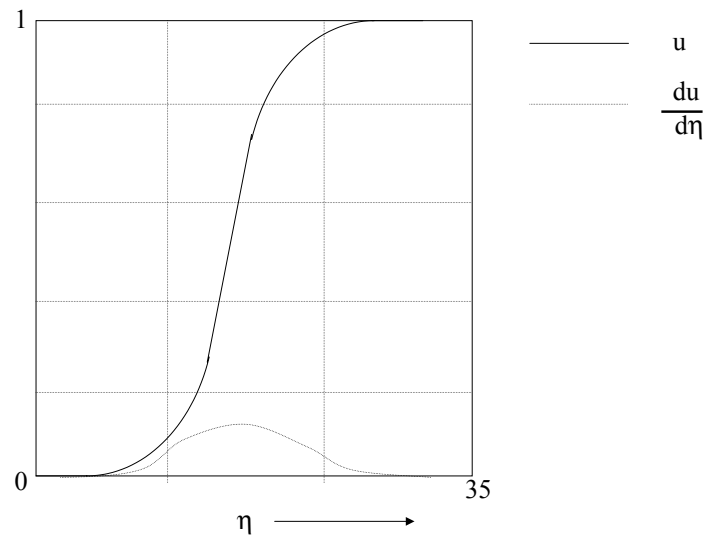Figure 9: Phase plane using Fisher's function

Figure 10: Wave solution of Fisher's function for velocity $c = 2.1$

The instability of the origin does not agree with the experimental data. The measured wave should become completely flat and should vanish when $\eta \to \pm\infty$. This means that the solution in the phase plane should be *homoclinic* which means that it should start and finish at the same singular point. This is impossible if the origin is an unstable node. There is, however, a travelling wave possible starting at X_1 and finishing at X_2. The orbit corresponding with this solution is called *heteroclinic* . To accomplish this result we need to define a new point $X_3 := (1, b)^T$, also drawn in Figure 9. Q Will be defined as the triangle $X_1 X_2 X_3$ and b is the slope of the hypothenuse between X_1 and X_3 which must be steeper then v_-. The vector field along both lines starting at X_1 points outwards of Q. This is very important, because if we now start in X_2 when $\eta = \infty$ and leave X_2 in the v_- direction the orbit has to go to the left, and since it can not leave Q though $X_1 X_2$ and $X_1 X_3$ it has to converge to X_1 for $\eta \to -\infty$. So there is a heteroclinic wave possible if $c \geq 2$. Figure 10 shows both u and $\frac{du}{d\eta}$ as functions of η for $c = 2.1$.

7.2   Nagumo's f function

Nagumo's function is a third degree polynomial ([11], [8]):

$$f(y_1) = y_1(y_1 - 1)(a - y_1), \tag{74}$$

with $0 < a < \frac{1}{2}$. This system has three singular points, $X_1 = (0, 0)^T$, $X_2 = (1, 0)^T$, and $X_3 = (a, 0)^T$. Substitution of these points into (69) gives

$$X_1: \qquad \lambda_\pm \quad := \quad \frac{c}{2} \pm \sqrt{\frac{c^2}{4} + a}, \tag{75}$$

$$X_2: \qquad \lambda_\pm \quad := \quad \frac{c}{2} \pm \sqrt{\frac{c^2}{4} - a + 1}, \tag{76}$$

$$X_3: \qquad \lambda_\pm \quad := \quad \frac{c}{2} \pm \sqrt{\frac{c^2}{4} - a + a^2}. \tag{77}$$

X_1 and X_2 are clearly saddle points, since $\sqrt{\frac{c^2}{4} + \zeta} > \frac{c}{2}$ for $0 < \zeta < 1$. X_3 acts the same as point X_1 in the Fisher case. The sign of $\dot{y}_1$ is always positive in the first quadrant, so all orbits move from the left to the right. Therefore, in this case there is also no homoclinic solution possible, only a heteroclinic one. So we look for a solution starting at X_1 and finishing at X_2, which is tangent to $\mathbf{v}_+$. The slope of $\mathbf{v}_+$ depends on the value of λ_+, which is a monotonically increasing function of c. Define point $X_5 := (1, b)^T$. Q is now defined as the triangle $X_1 X_2 X_5$ and b is the slope of $X_1 X_5$. If we take c very large, then the slope of $\mathbf{v}_+$ is bigger then b. Now define the slope r of the vector field along $X_1 X_5$

$$r(y_1) := c - \frac{(a - y_1)(y_1 - 1)}{b}. \tag{78}$$

Hence, $r(y_1) > b$ if $0 \leq y_1 \leq 1$, which means that an orbit starting in A with slope bigger then b will always stay above the line $X_1 X_5$. This will never give the required solution. Now take $c = 0$ instead. Then (67) becomes $\ddot{y}_1 = -f(y_1)$. This is an ordinary differential equation of the Hamiltonian type. See [8] for more information on Hamiltonian equations. In this case the Hamiltonian is the sum of the kinetic and potential energy

$$H := \frac{1}{2} y_2^2 + P(y_1), \tag{79}$$

with potential

$$P(y_1) := \int_0^{y_1} f(y)dy. \tag{80}$$

In our starting point X_1 we have $H \equiv 0$, so $y_2(y_1) = \sqrt{-2P(y_1)}$. The Nagumo function makes sure that $P(y_1)$ is positive for small values of y_1, but there is a point in the interval, say $\bar{y}_1$, where $P(\bar{y}_1) = 0$, which implies that $y_2(\bar{y}_1) = 0$. Define $X_4 := \bar{y}_1$ and take $c_0 > 0$ such that the orbit that starts at X_1 goes through X_5 if $y_1 = 1$. Since orbits with different values cannot cross each other there must be a c_1 with $0 \leq c_1 \leq c_0$ such that the orbit finishes at X_2. This orbit must be tangent to $\mathbf{v}_-$ in X_2. So there exists a heteroclinic, solitary wave traveling from X_1 to X_2.
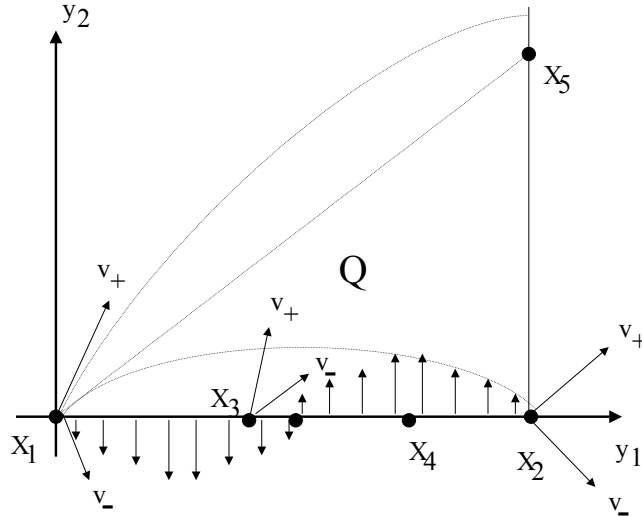

Figure 11: Phase plane using Nagumo's function

8 Miura's approach

R.M. Miura ([10]) analyzed the problem without the assumption $\varepsilon = 0$. He took $\varepsilon = 0.08$, $\gamma = 0.8$ and the f function $f(V) = 0.33V^3 - 1.20V^2 + 0.44V$. The traveling wave approach, with $V(x,t) = u(\eta)$ and $W(x,t) = w(\eta)$ ($\eta = x + ct$), gives the following system

$$cu' = u'' - w - 0.33u^3 - 1.20u^2 + 0.44u \tag{81}$$
$$cw' = 0.08(u - 0.8w), \tag{82}$$

with boundary conditions

$$\lim_{|\eta| \to \infty} u = 0 = \lim_{\eta \to \infty} w \tag{83}$$

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There are 2 problems with this system. The first is that if one finds a solution for η, then any translation in η is also a solution. The second problem is that c is unknown. This can be solved by treating c as a variable and adding the equation $c' = 0$ with boundary condition $u(0) = u_0 \neq 0$. As a consequence, the trivial solution is now not longer possible. The u_0 should be taken close to the maximum slope of $u(\eta)$, because that will minimize the numerical error. Miura discussed three different methods to compute the stable solitary wave solution which is shown in Figures 12 and 13 for a certain wave speed, but they will not be discussed in this paper. See [10] for details.
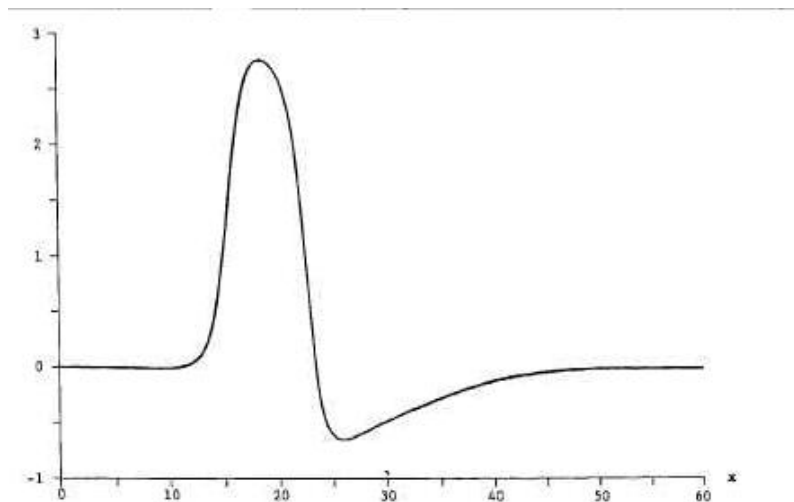

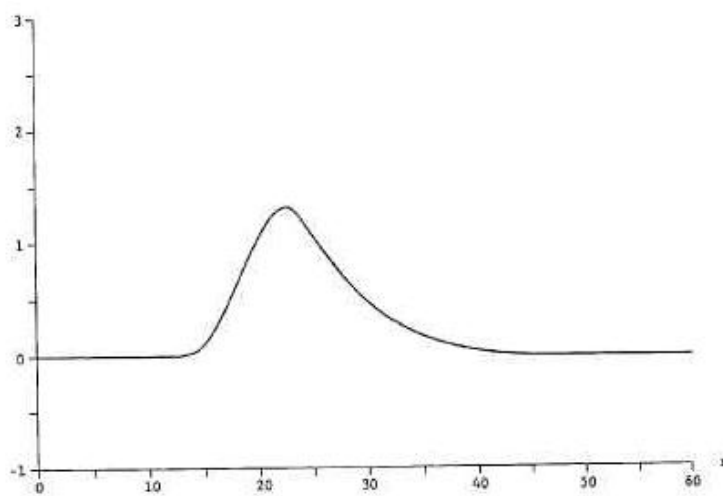Figure 12: Stable wave solution for u with c = 0.8117656369181

Figure 13: Stable wave solution for w with c = 0.8117656369181

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9 Conclusion

The functions we examined for the reduced problem did not give very good results. Although wave solutions are possible, they appeared to be heteroclinic, while the experiments done by Hodgkin and Huxley required a homoclinic wave. Fisher's f function has an additional flaw, because we found infinitely many possible values for c, while, according to the experiments, an unique wave velocity is necessary, like in the case of Nagumo's f function. These results tell us that the assumption $\varepsilon = 0$ was not a very good one. Miura's study shows that homoclinic solitary waves can be calculated for $\varepsilon \neq 0$. The choice of method depends on the result wanted, such as speed, profile, and or initiation time of the wave. Miura's results show that the FN model is a quite good model to describe nerve pulses. Therefore we can conclude that the research statement which says that the FN model maintains all important properties of the HH model, is correct. In addition, the Fitzhugh-Nagumo equations have evolved into a class of equations which are called the *generalized Fitzhugh-Nagumo equations*. This system is given by

$$\epsilon \frac{dV}{dt} = f(V, W) + I \tag{84}$$

$$\frac{dW}{dt} = g(V, W). \tag{85}$$

A famous example of a variant of this system is the van der Pol equation which was of great importance for the understanding of oscillations. The generalized system is an active area of research, see e.g. [12] and [13].

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A Notations and equations

A.1 Notations

$[p]$ = concentration of component p (mol)

$\hat{c}, c, C$ = capacitance, per unit length, per unit area respectively (F, Fm^{-1}, Fm^{-2})

E = equilibrium potential of a certain ion (V)

φ = volume per mole $(m^3 mol^{-1})$

F = constant of Faraday $(9,64853 \cdot 10^4 Cmol^{-1})$

$\hat{g}, g, G$ = conductance, per unit length, per unit area respectively (S, Sm^{-1}, Sm^{-2})

H = enthalpy (J)

I = longitudinal current(A)

J = radial current density flow (Am^{-2})

K = radial current per unit length (Am^{-1})

L = inductivity per unit area (Hm^2) $\mu[p]$ = Gibbs energy per mole of component p $(Jmol^-1)$

p = pressure (Pa)

ρ = radius of the membrane (m)

$\hat{r}, r$ = resistance, per unit length respectively $(\Omega, \Omega m^{-1})$

$\mathbf{R}$ = gas constant: $(8,3145 \ Jmol^{-1}K^{-1})$

S = entropy (JK^{-1})

T = temperature (K)

U = internal energy (J)

V = potential (V)

Z = valence of a certain ion

A.2   Equations and physical law's

Membrane potential:

$$V_m = V_{in} - V_{out}. \tag{86}$$

Nernst equilibrium potential:

$$E_m = -2,3 \frac{\mathbf{R}T}{ZF} log \frac{c[ion_{out}]}{c[ion_{in}]}. \tag{87}$$

Ohm's law:

$$V = IR. \tag{88}$$

Kirchhoff's current law:

$$\sum I = 0. \tag{89}$$

at any junction.

Capacitor law:

$$I = C \frac{dV}{dt}. \tag{90}$$

Inductor law:

$$V = L \frac{dI}{dt}. \tag{91}$$