Modeling Action Potentials in Cell Processes

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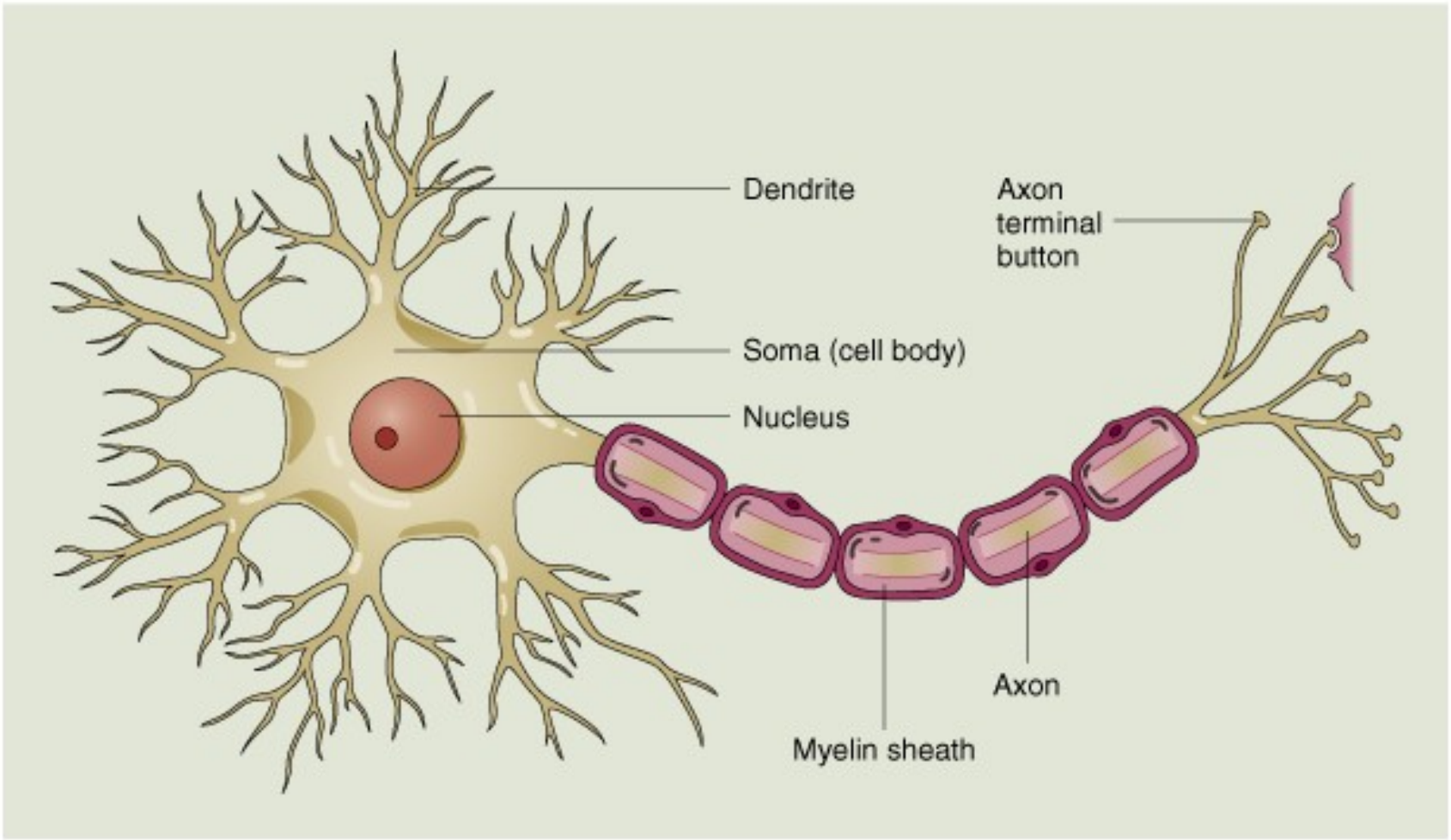
Action Potential

Why study nerve action potentials?

- Action potential describes how the body communicates and sends signals.



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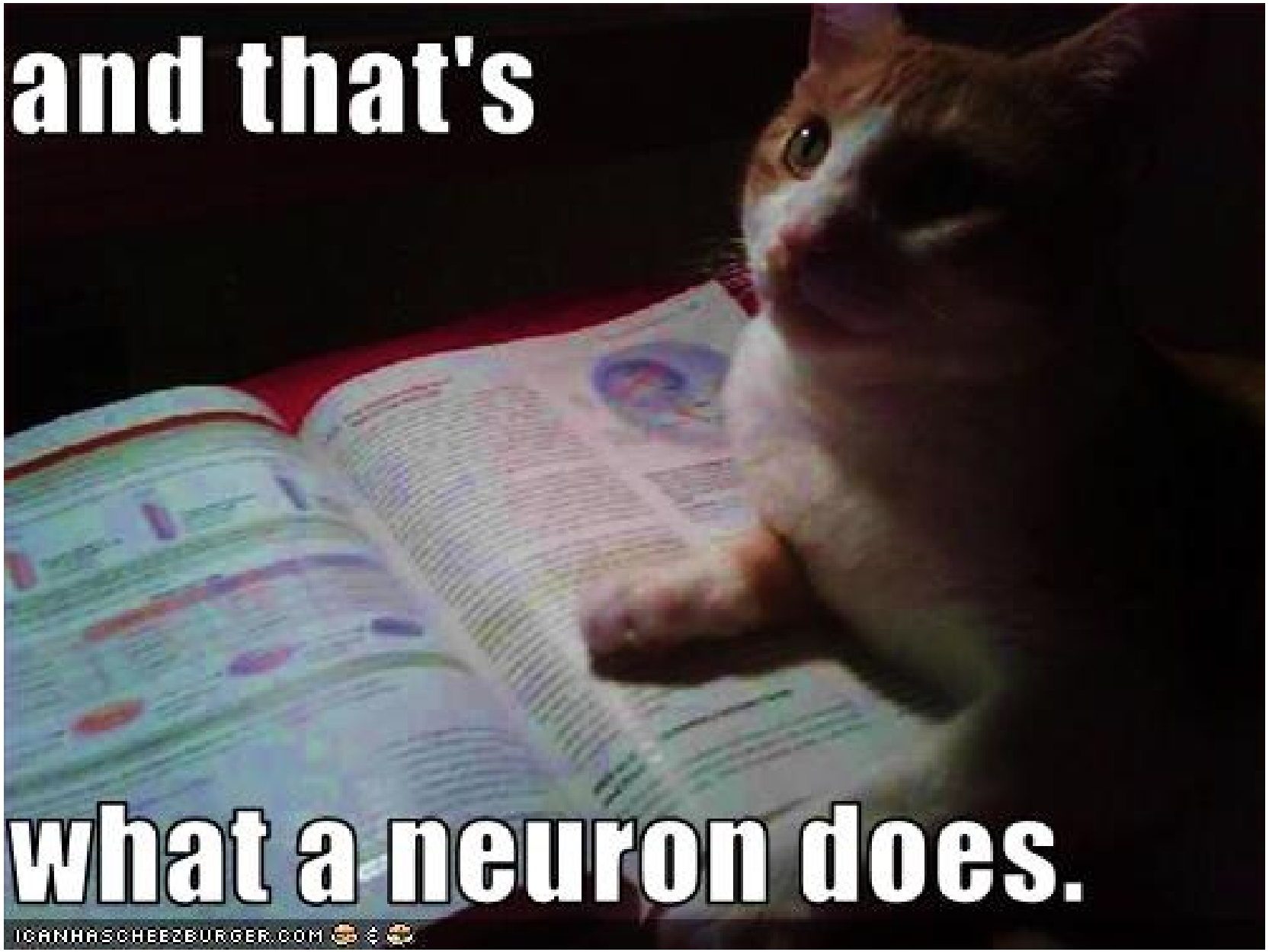
and that's
what a neuron does.
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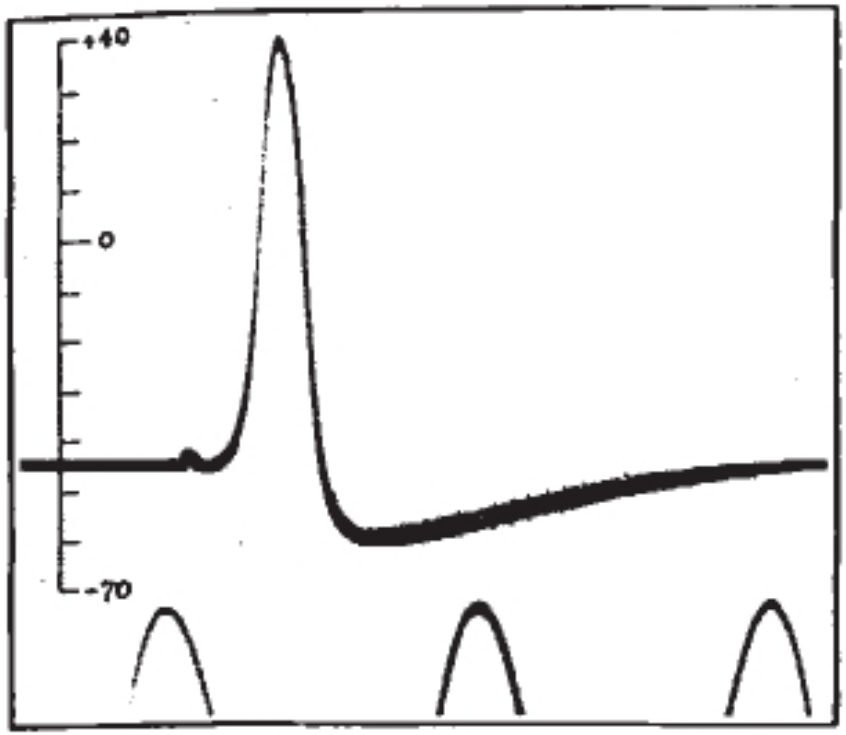
Nerve Impulse Transmission Models

- Hodgkin Huxley model (1952)
- Fitz-Hugh Nagumo model (1961)
- Morris-Lecar model (1981)



History of the Hodgkin-Huxley Model

Our present day understanding and methods of modeling neural excitability have been significantly influenced by the landmark work of Hodgkin and Huxley. In 1952, Hodgkin and Huxley published a series of articles, defining their research.

Derivation of the Hodgkin-Huxley Model

- The Hodgkin-Huxley model is based on the idea that the electrical properties of a segment of a cell membrane can be modeled by an equivalent circuit.

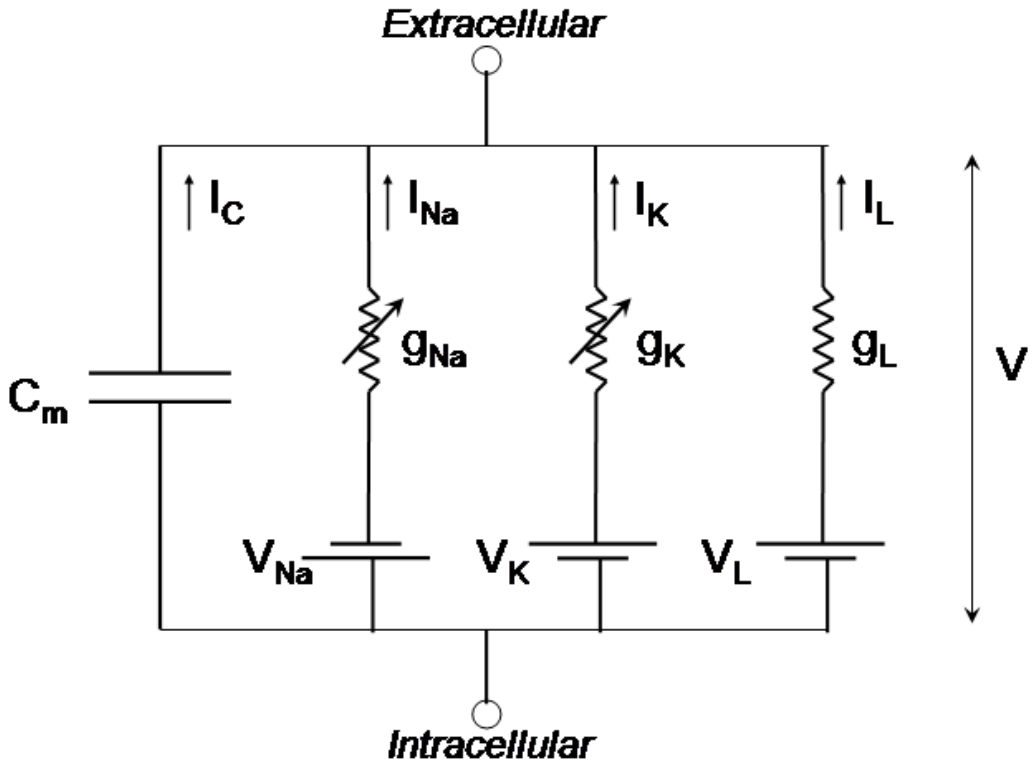


Figure: The equivalent circuit to a segment of the cell membrane
Image from http://thephysicsdomain.com/2013/03/28/047-hodgkin-huxley-hysteria/

Derivation of Hodgkin-Huxley

- Beginning with the basic physical principle of Capacitance: $C = \frac{Q(\mathbf{r},t)}{V(\mathbf{r},t)}$, where:
  - C is capacitance
  - $\mathbf{r} = \mathbf{r}(x, y, z)$ is the spatial coordinates vector
  - $Q(\mathbf{r}, t)$ is electrical charge as a function of space and time
  - $V(\mathbf{r}, t)$ is electric potential (or voltage) as a function of space and time
- Differentiating both sides with respect to time and solving for current gives us:
  - $C\frac{\partial V}{\partial t} = \frac{\partial Q}{\partial t} = I(V, \mathbf{r}, t)$
  - Where: $I(V, \mathbf{r}, t)$ is capacitave electric current as function of voltage, space, and time

- For a cell membrane, conservation laws dictate that the capacitive current would be defined as: $\frac{\partial Q}{\partial t} = C_m \frac{\partial V}{\partial t} = I(V, \mathbf{r}, t) = -\nabla \cdot \mathbf{J}(\mathbf{r}) + I_{ion}(V, t)$, where:
  - C_m is the membrane capacitance
  - $I_{ion}(V, t)$ is the ionic cell membrane current
  - $\mathbf{J}(\mathbf{r})$ is the spatially dependent membrane current vector
- Further, if we assume space clamps are applied at specific points along the membrane making the voltage uniform across the system, we can ignore all space dependence: $\nabla \cdot \mathbf{J}(\mathbf{r}) = 0$
- The system at rest is then: $C_m \frac{dV(t)}{dt} = I_{ion}(V, t)$

- Now consider the movement of an ion A across the membrane, moving transverse to $I_{ion}(V,t)$. This transverse potential drop across the membrane has two components:
  - The first is due to the concentration differences caused by this movement and is given by the Nernst Potential: $V_A = \frac{RT}{zF} \ln \frac{[A]_e}{[A]_i}$, where:
    - $[A]_e$ is the external concentration of ion A
    - $[A]_i$ is the internal concentration of ion A
    - R is the universal gas constant
    - T is absolute temperature
    - F is Faraday's constant
    - z is the charge of ion A
  - The second is due to a transverse electrical current: $V_\tau = \frac{I_\tau}{g}$, where:
    - g is membrane conductance
    - I_τ is transverse current
  - Put together, the potential drop across the membrane is: $V = V_A + V_\tau = V_A + \frac{I_\tau}{g}$

- Solving for transverse current: $I_\tau = g(V - V_A)$
- For multiple types of ion transfer with some leakage, the transverse current becomes: $I_\tau = \sum_j g_j(V - V_j)$, where j denotes each ion type as well as any ion leakage.
- Because Kirchoff's Current Law states that the sum of all currents in a closed system equals zero, we can deduce that:
  - $I_{ion} + I_\tau = 0$
  - $I_{ion} = -I_\tau = -\sum_j g_j(V - V_j)$
- Upon stimulation of the system, an external current (I_{app}) is applied: $I_{ion} = -\sum_j g_j(V - V_j) + I_{app}$
- Putting it all together yields: $C_m \frac{dV(t)}{dt} = -\sum_j g_j(V - V_j) + I_{app}$

Note: I_{app} could either be constant or a function of time.

For Sodium and Potassium Ion Channels

- For a system with sodium (Na) and potassium (K) ions passing across the cell membrane (with some ion leakage L), the equation for the time rate change of voltage is: $C_m \frac{dV(t)}{dt} = -\bar{g_{Na}}(V - V_{Na}) - \bar{g_K}(V - V_K) - g_L(V - V_L) + I_{app}$.
- The leakage conductance g_L is an experimentally determined constant. If the sodium conductance ($\bar{g_{Na}}$) and the potassium conductance ($\bar{g_K}$) are held constant, the model breaks down.

- Instead, Hodgkin and Huxley used gating variables to treat $\bar{g_{Na}}$ and $\bar{g_K}$ as functions of voltage and time:
  - $\bar{g_{Na}} = \bar{g_{Na}}(V, t)$
  - $\bar{g_{Na}} = \bar{g_{Na}}(V, t)$
- The gating variables chosen were:
  - $m(t)$: sodium gate activation
  - $h(t)$: sodium gate deactivation
  - $n(t)$: potassium gate activation
- These gating variables are functions of time and related to $\bar{g_{Na}}$ and $\bar{g_K}$ by the equations:
  - $\frac{\partial \bar{g_K}}{\partial t} = g_K n^4$
  - $\frac{\partial \bar{g_{Na}}}{\partial t} = g_{Na} m^3 h$
- The sodium ion channel has 3 steps to open and one step to close, hence $m^3 h$.
- The potassium ion channel has 4 steps to open and remains open, hence n^4.

- These gating variables satisfy the following differential equations:

$$\frac{dm(t)}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m \quad (1)$$

$$\frac{dh(t)}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h \quad (2)$$

$$\frac{dn(t)}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n, \quad (3)$$

  - Where:

$$\alpha_m(V) = \frac{(0.1)(25-V)}{e^{(\frac{25-V}{10})}-1}$$

$$\beta_m(V) = 4e^{\frac{-V}{18}}$$

$$\alpha_h(V) = (0.07)e^{\frac{-V}{20}}$$

$$\beta_h(V) = \frac{1}{e^{(\frac{30-V}{10})}+1}$$

$$\alpha_n(V) = \frac{(0.01)(10-V)}{e^{(\frac{10-V}{10})}-1}$$

$$\beta_n(V) = (0.125)e^{\frac{-V}{80}}$$

Final Hodgkin-Huxley Model

$$
\begin{aligned}
C_m \frac{dV(t)}{dt} &= -\bar{g_{Na}}(V - V_{Na}) - \bar{g_K}(V - V_K) - g_L(V - V_L) + I_{app} \\
\frac{dm(t)}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\frac{dh(t)}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h \\
\frac{dn(t)}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n
\end{aligned}
$$

Parameters and Initial Values

- Conductance Constants:

$$\begin{aligned} g_K &= 36\mu\text{S/cm}^2 \\ g_{Na} &= 120\mu\text{S/cm}^2 \\ g_L &= 0.3\mu\text{S/cm}^2 \end{aligned}$$

- Ion Voltage Constants:

$$\begin{aligned} V_{Na} &= 115\text{mV} \\ V_K &= -12\text{mV} \\ V_L &= 10.6\text{mV} \end{aligned}$$

- Membrane Capacitance Constant:

$$C_m = 1.0\mu\text{F/cm}^2$$

- Initial Values:

$$\begin{aligned} V(0) &= -70\text{mV} \\ m(0) &= 0 \\ h(0) &= 0 \\ n(0) &= 0 \end{aligned}$$

Once one has begun to research the Hodgkin-Huxley model, more in-depth, one can find that the instantaneous $I-V$ curves of Na^+ and K^+ are approximately linear. In this case, equation (1) becomes

$$C_m \frac{dv}{dt} = -g_K n^4 (v - v_K) - g_{Na} m^3 h (v - v_{Na}) - g_L (v - v_L) + I_{app} \tag{4}$$

Functions

Derivatives with respect to t:

- $\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m$
- $\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n$
- $\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h$

Functions

Equations of $\alpha(v)$ and $\beta(v)$

- $\alpha_m(v) = 0.1 \frac{25-v}{e^{\frac{25-v}{10}} - 1}$
- $\beta_m(v) = 4e^{\frac{-v}{18}}$
- $\alpha_n(v) = 0.01 \frac{10-v}{e^{\frac{10-v}{10}} - 1}$
- $\beta_n(v) = 0.125e^{\frac{-v}{80}}$
- $\alpha_h(v) = 0.07e^{\frac{-v}{20}}$
- $\beta_h(v) = \frac{1}{e^{\frac{30-v}{10}} + 1}$

Variables

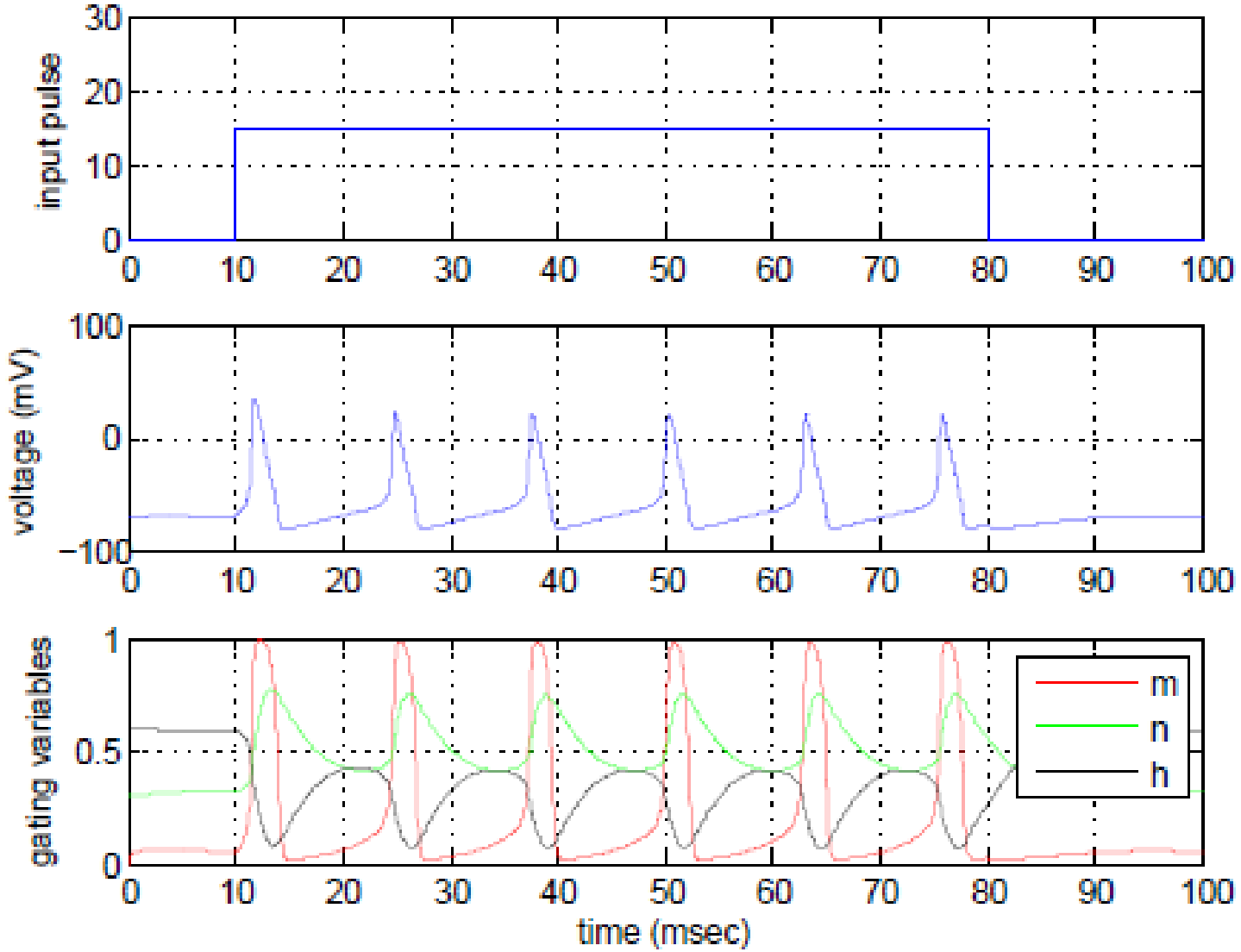
A list of the variables used in the model includes:

- C_m - Capacitance of the cell membrane
- g - Membrane conductance
- v - Voltage
- I_{app} - Applied current
- K - Potassium
- Na - Sodium

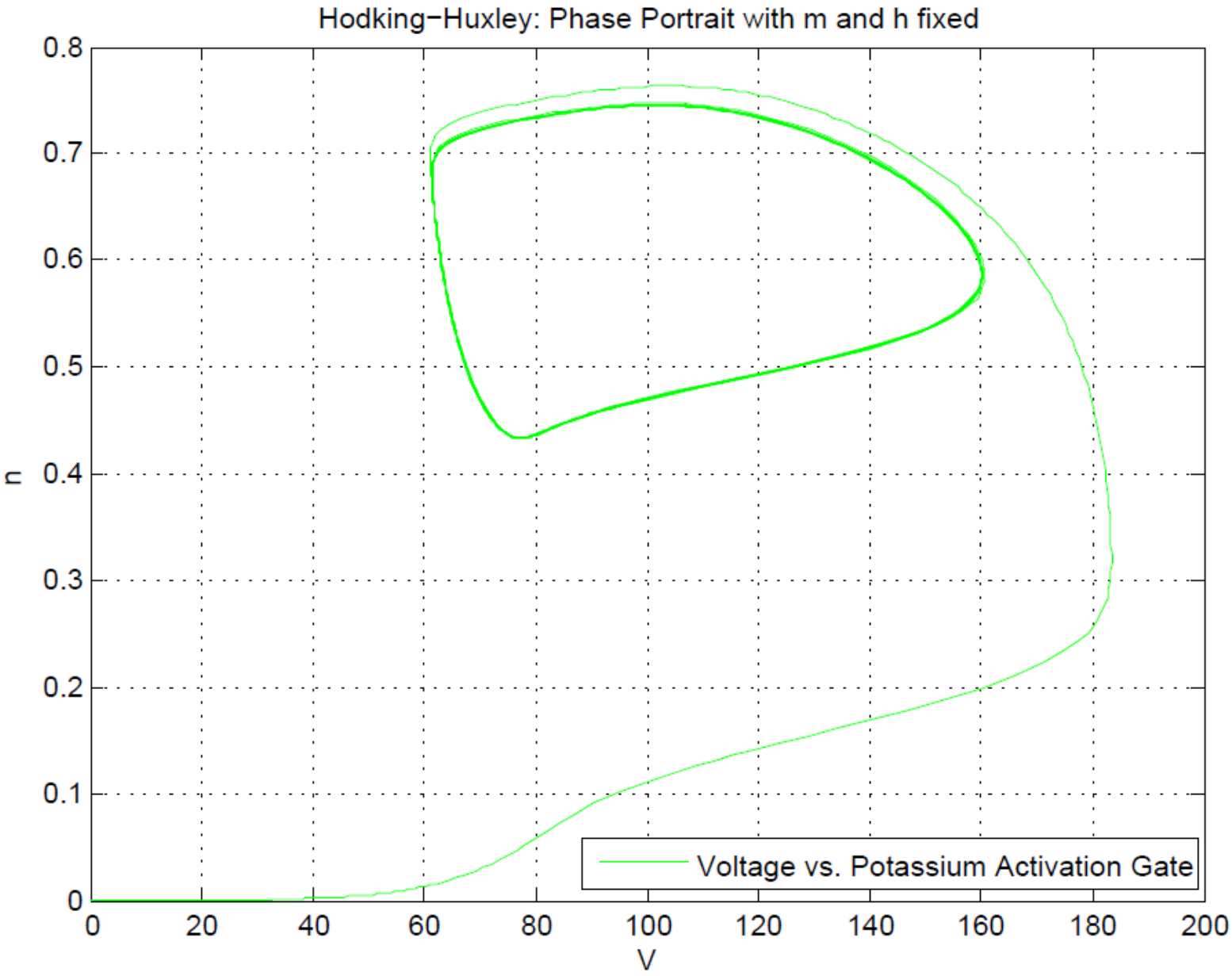
Some initial values that we use include:

- $g_K = 36$
- $g_{Na} = 120$
- $g_L = 0.3$
- $v_{Na} = 115$
- $v_K = -12$
- $I_{app} = 10.6$

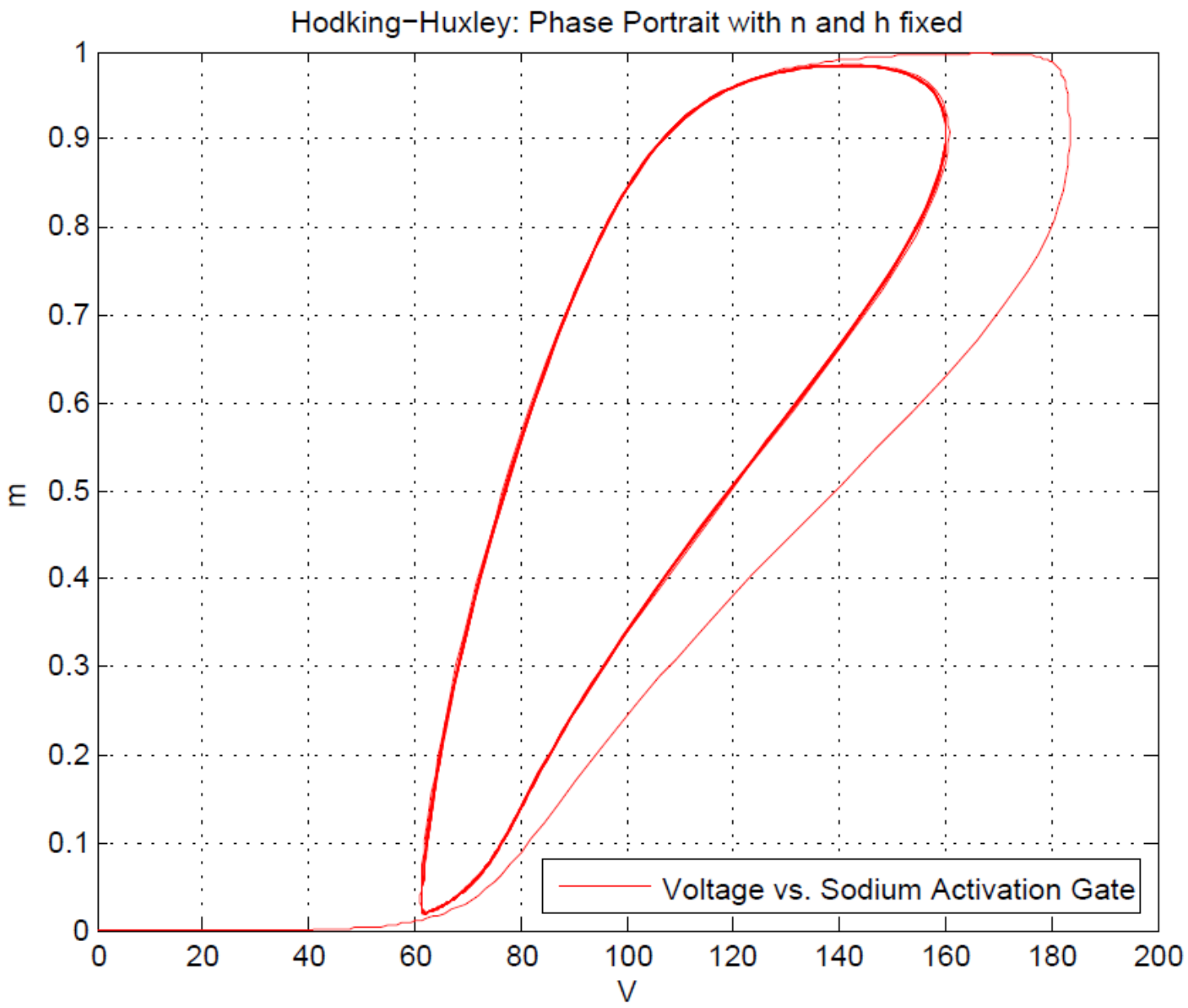
Analysis of Hodgkin-Huxley Model



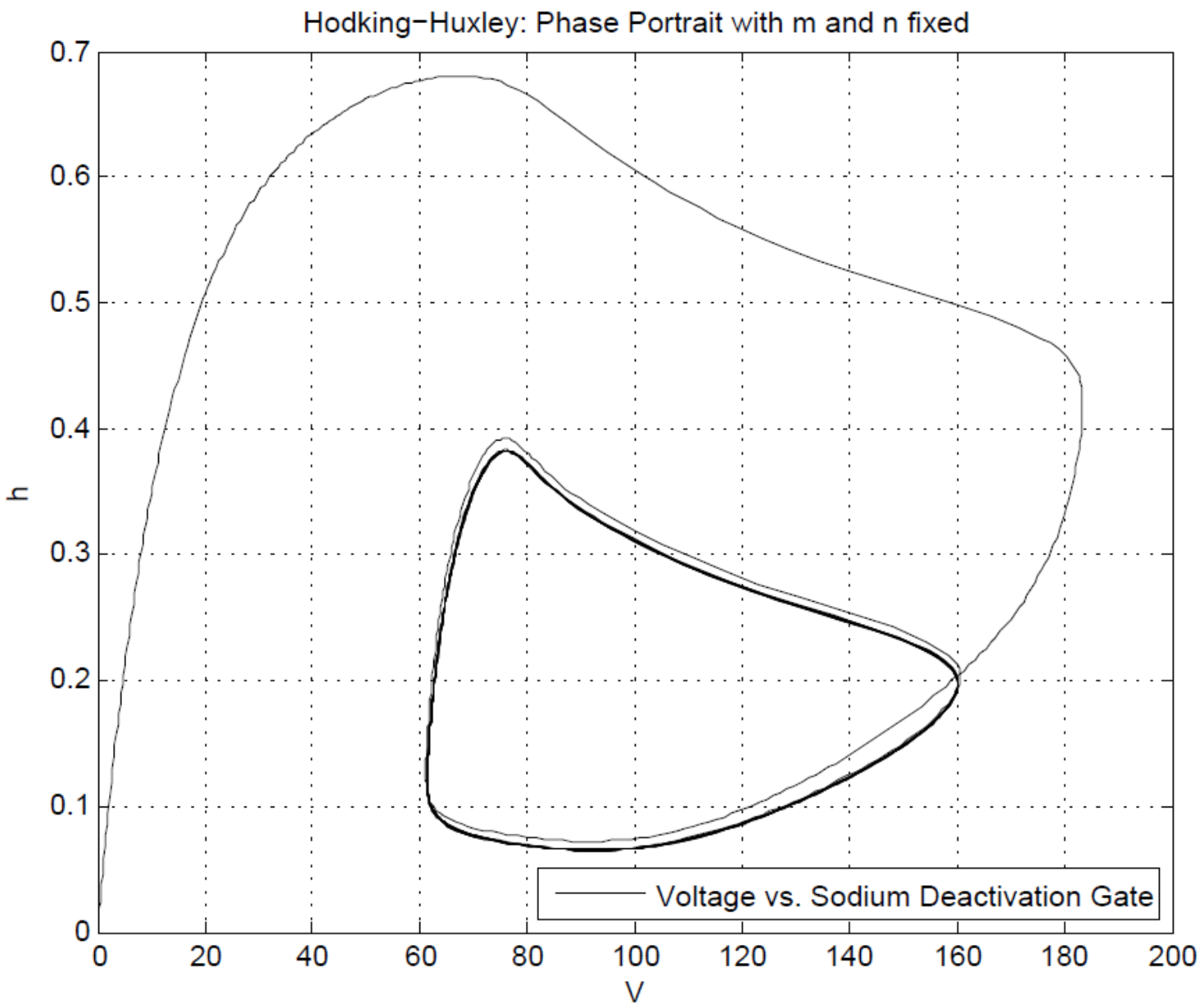
Analysis of Hodgkin-Huxley Model



Analysis of Hodgkin-Huxley Model



Analysis of Hodgkin-Huxley Model



General FHN Model

$$\varepsilon \frac{dv}{dt} = f(v, w) + I$$

and

$$\frac{dw}{dt} = g(v, w)$$

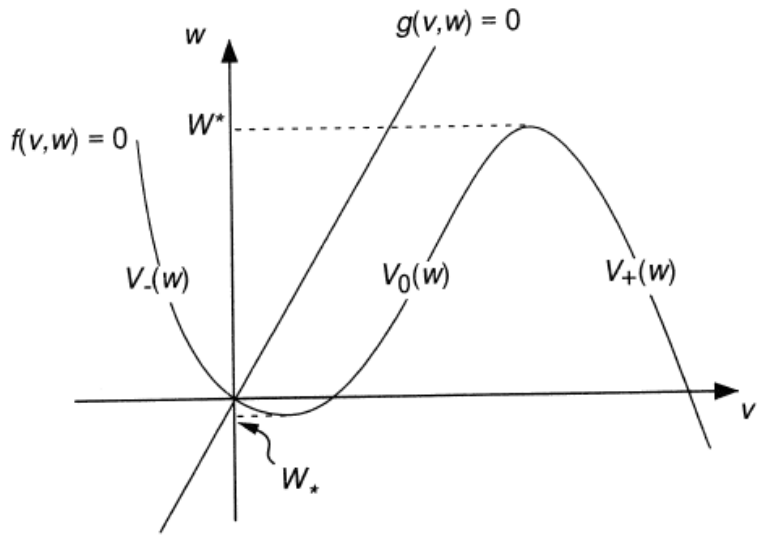
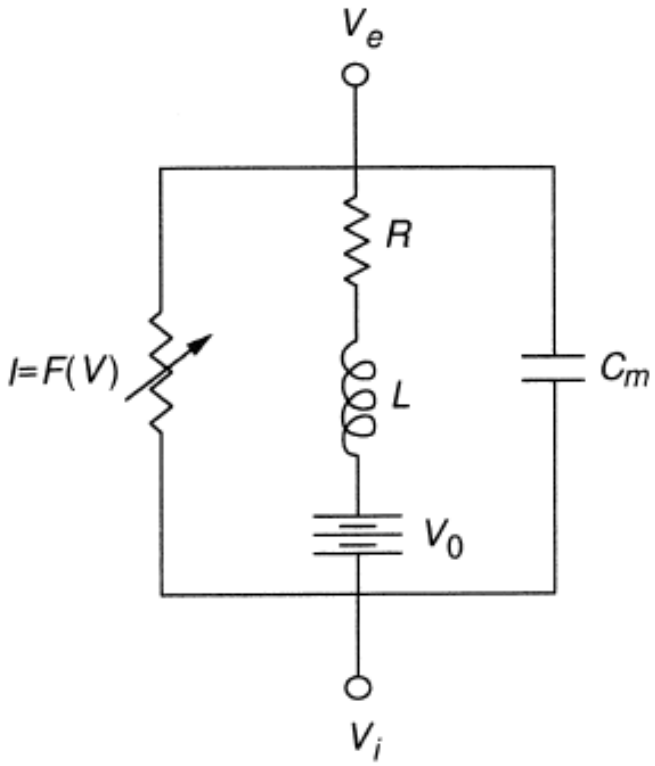


Figure : This image was taken from Sneyd and Keener's "Mathematical Physiology"

FHN Circuit

In 1960, Nagumo built a circuit having the same components as cell membrane using an inductor, resistor, and a battery.



Circuit Equations

Using Kirchoff's laws, the membrane circuit diagram can be modeled as:

$$C_m \frac{dV}{d\tau} + F(V) + i = -I_o \tag{5}$$

$$L \frac{di}{d\tau} + Ri = V - V_o \tag{6}$$

- I_o= Applied external current
- i= Current through the resistor, inductor, and battery
- V= Membrane potential
- V_0= Potential gain across the battery

Equations used to model FHN

$$A = \begin{cases} 0.01\dfrac{dv}{dt} = v(v-0.1)(1-v) - w + I \\ \dfrac{dw}{dt} = v - 0.5w \end{cases}$$

$$B = \begin{cases} 0.01\dfrac{dv}{dt} = v(v+0.1)(1-v) - w + I \\ \dfrac{dw}{dt} = v - 0.5w \end{cases}$$

Graphic Solutions

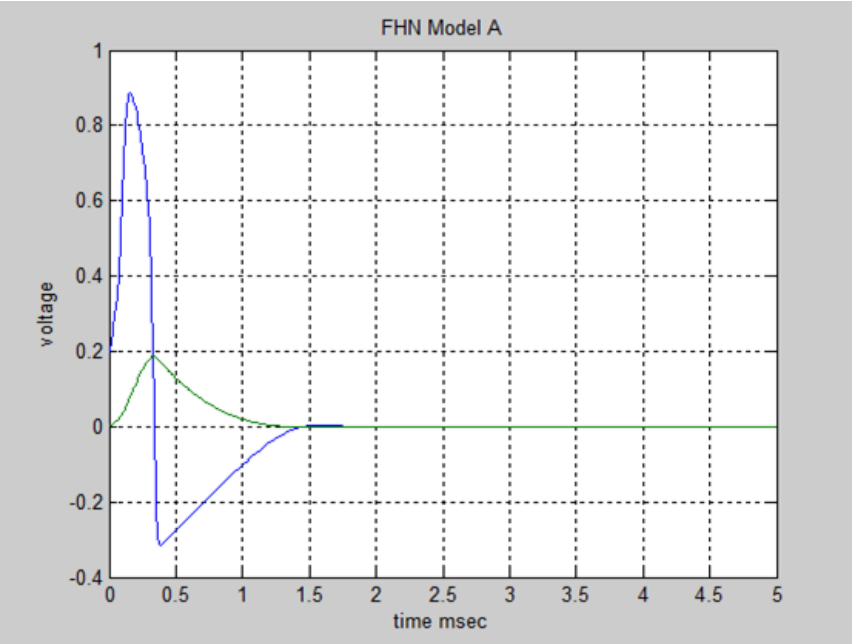


Figure : Graph of ***A***

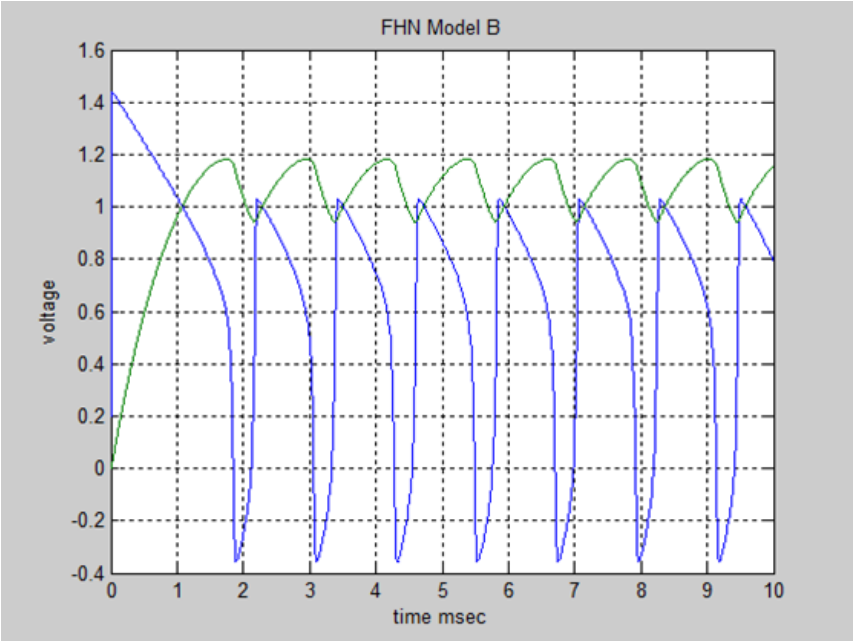


Figure : Graph of ***B***

- ***A*** has only spike and ***B*** has spontaneous oscillation
- No applied current

Phase Portrait of Nullclines with the Orbit

$$A = \begin{cases} w = -v^3 + 1.1v^2 - 0.1v \\ w = \frac{v}{0.5} \end{cases}$$

$$B = \begin{cases} w = -v^3 + 0.9v^2 + 0.1v \\ w = \frac{v}{0.5} \end{cases}$$

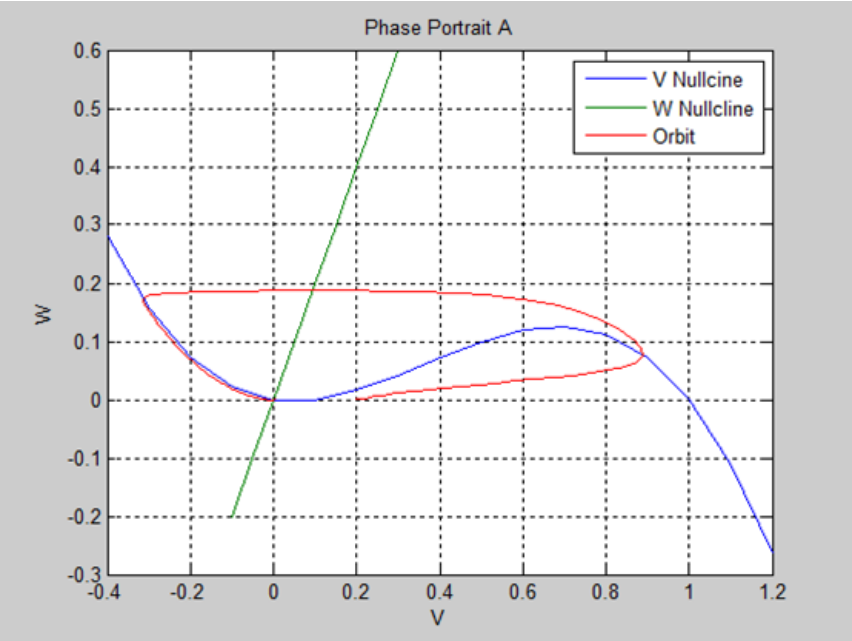


Figure : Phase portrait of ***A***

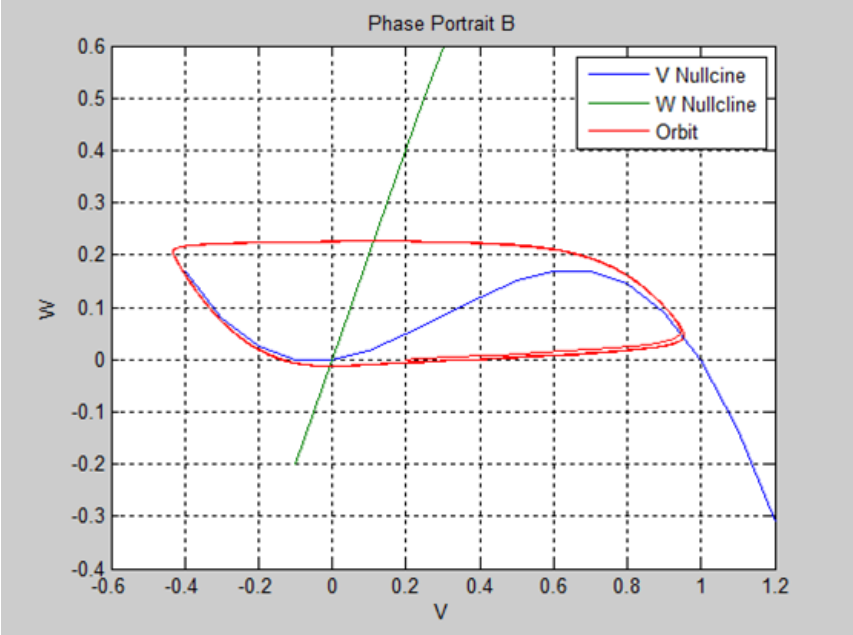


Figure : Phase portrait of ***B***

Critical Points

$$\mathbf{J}(\mathbf{0},\mathbf{0}) = \begin{pmatrix} -0.1 & -1 \\ 1 & -0.5 \end{pmatrix}$$

- The nullclines intersect at (0,0), which is the only critical point.
- In order to see the stability of the critical point, we computed the Jacobian at (0,0).
- The eigenvalues for this matrix are $\lambda = -0.3 + 0.9798i$ and $\lambda = -0.3 - 0.9798i$.
- This means that the critical point is stable and spiral.

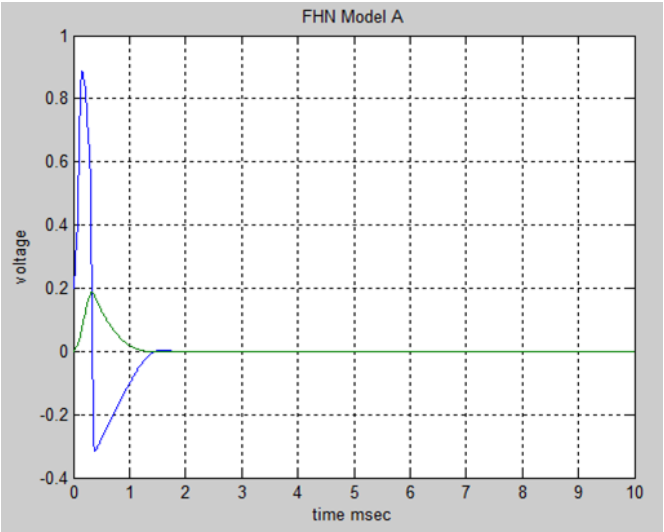
Bifurcation Analysis

$$A = \begin{cases} f(v,w) = \dfrac{1}{\varepsilon} v(v-\alpha)(1-v) - w + I \\ \\ g(v,w) = v - \gamma w \end{cases}$$

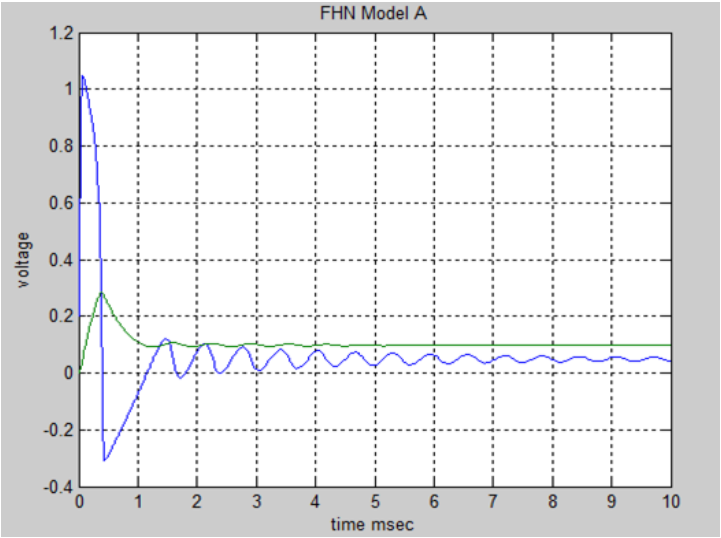
Bifurcation Analysis

$0.11 < I < 1.2$

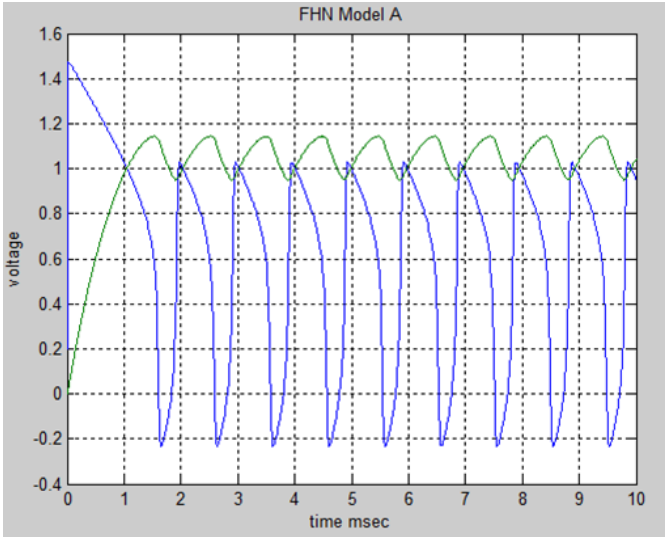
$I = 0$



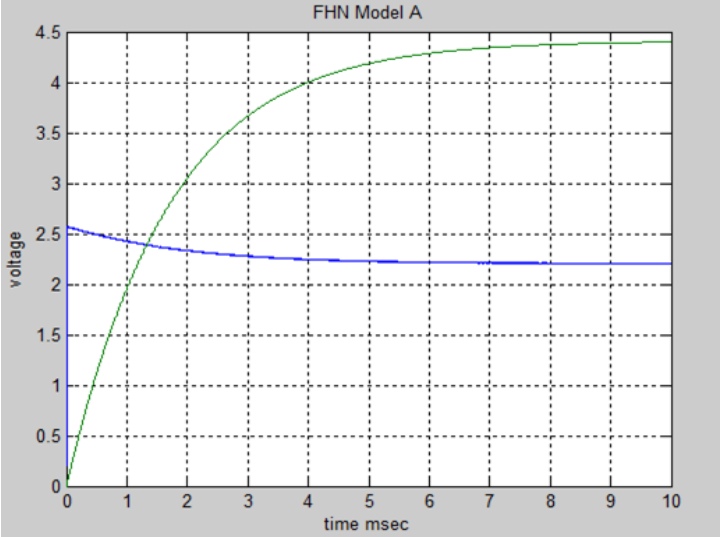
$I = 0.1$



$I = 1$



$I = 1$

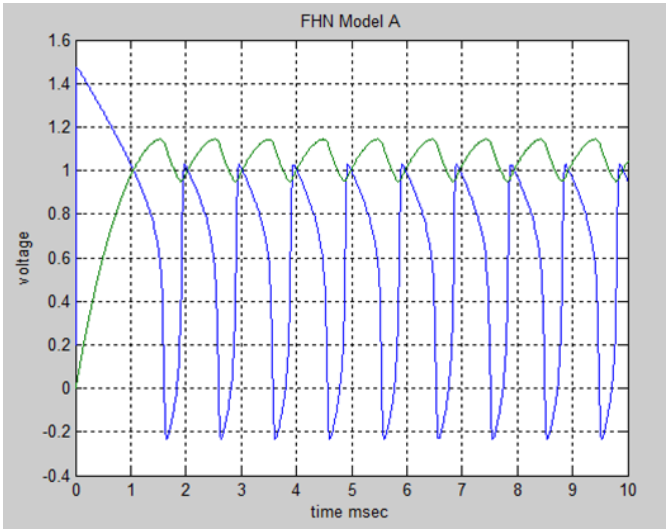


Bifurcation Analysis

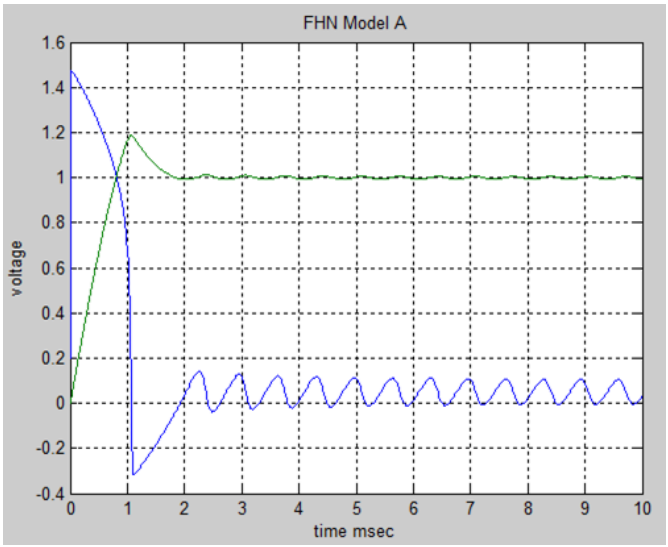
$0.05 < \gamma < 0.6$

With a constant applied current of $I = 1$, changing values of γ gives the following changes to the graph of $\boldsymbol{A}$:

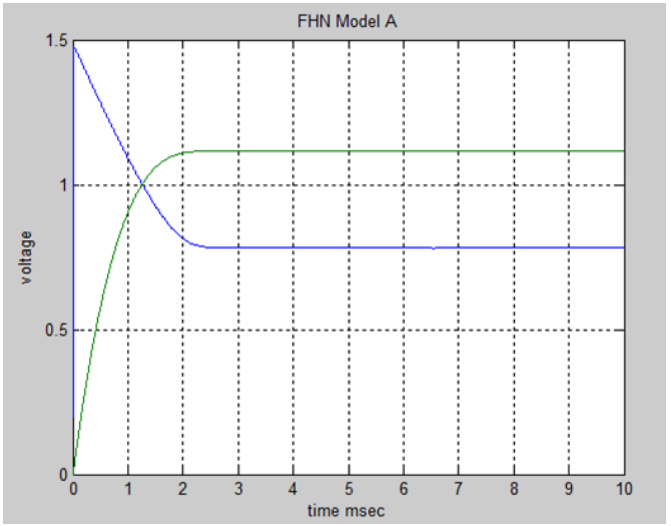
$\gamma = 0.5$



$\gamma = 0.05$



$\gamma = 0.7$

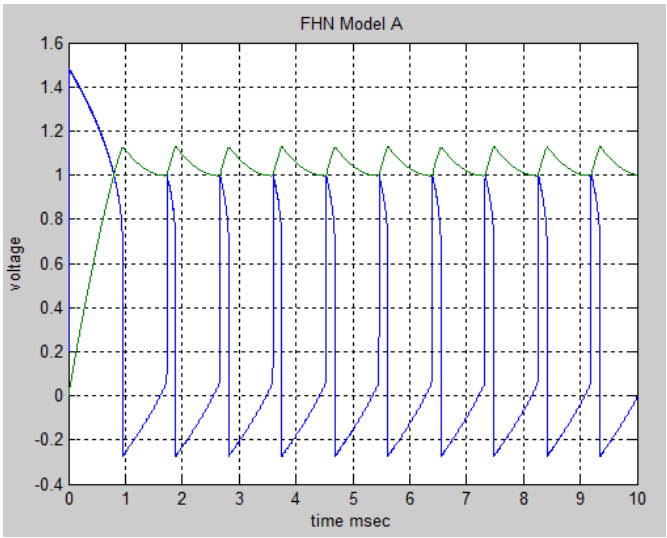


Bifurcation Analysis

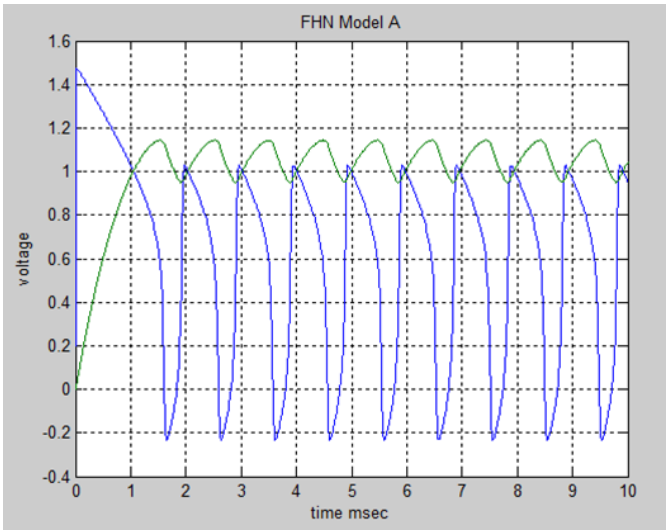
$\varepsilon < 0.1$

With a constant applied current of $I = 1$ and constant $\gamma = 0.5$, changing values of ε gives the following changes to the graph of ***A***.

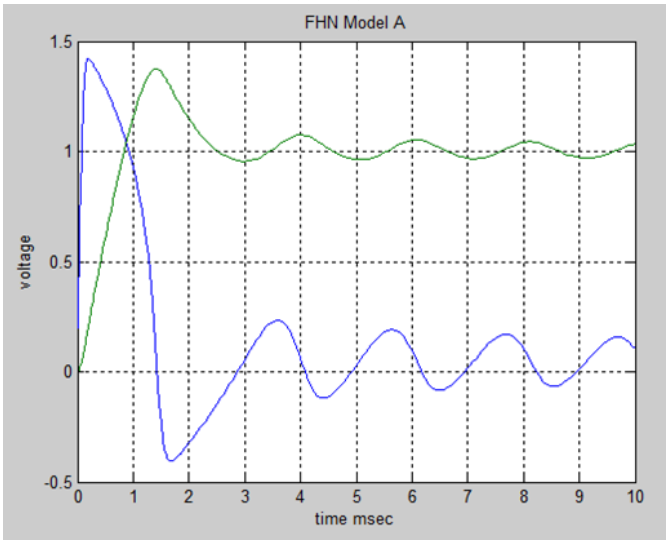
$\varepsilon = 0.0001$



$\varepsilon = 0.01$



$\varepsilon = 0.1$



Modified FHN Model

$$A = \begin{cases} f(v,w) = \frac{1}{\varepsilon} sin(v) - w + I \\ g(v,w) = v - \gamma w \end{cases}$$

$$\mathbf{J(0,0)} = \begin{pmatrix} 0.8 & -1 \\ 1 & -0.5 \end{pmatrix}$$

$$\lambda_{1,2} = 0.15 \pm 0.759934i$$

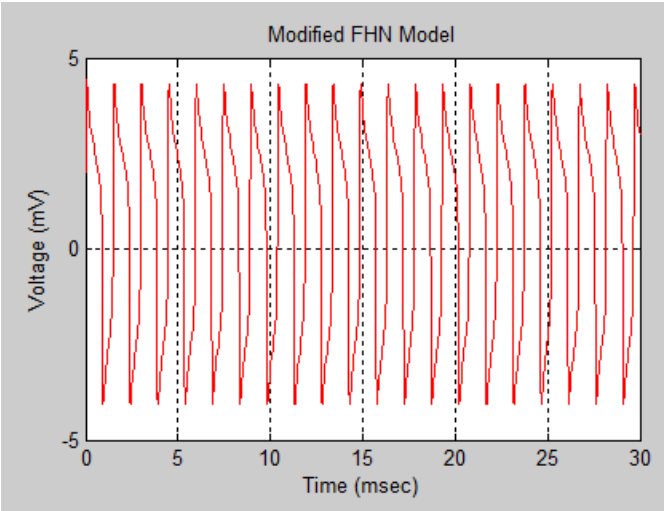


Figure : Modified FHN Model Graph

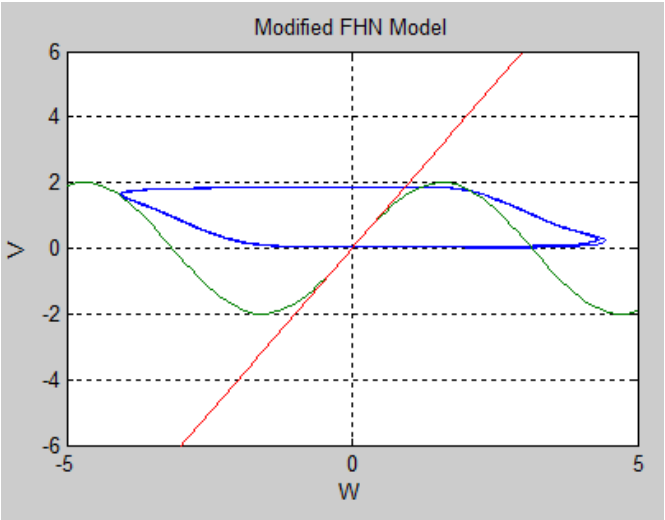
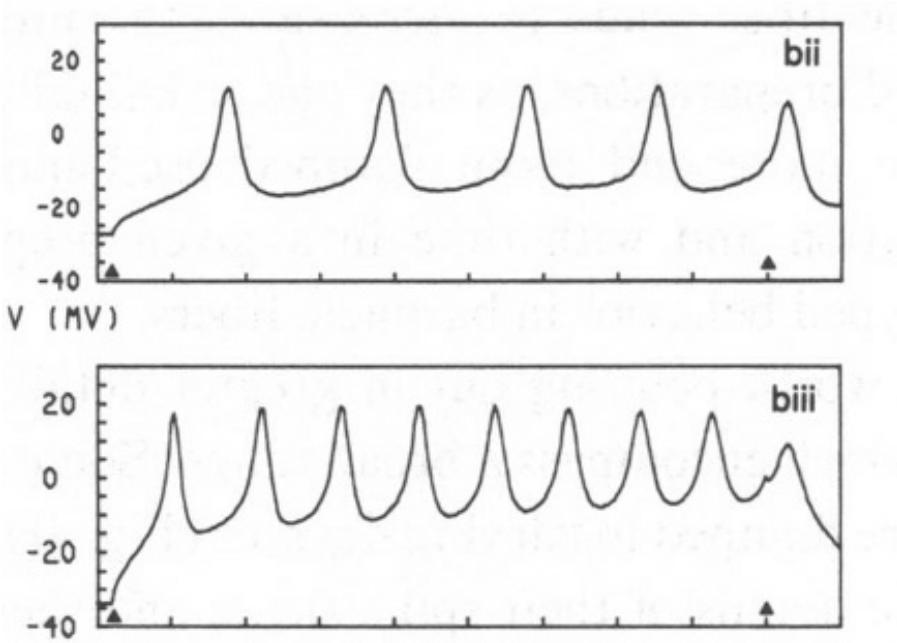


Figure : Modified FHN Model Phase Plane

The Morris-Lecar Model

- Introduced in 1981 by Dr. Harold Lecar and Dr. Catherine Morris
- The Morris-Lecar model is a biological neuron model used to reproduce the variety of oscillatory behaviors between the Calcium and Potassium ions in the barnacle giant muscle fiber.



Principle Assumptions

The principal assumptions underlying the Morris-Lecar model include:

- Conductance-based model, where all of the ion channels are activated by voltage.

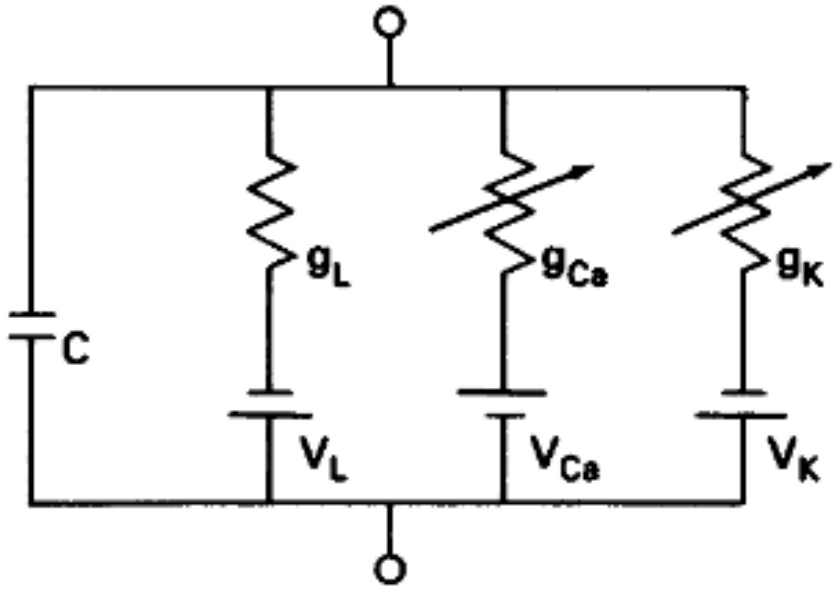


FIGURE 1 Equivalent circuit for a patch of space-clamped barnacle sarcolemma.

- In excitable systems, there are two different types of gated ion channels for one species of ions in the membrane.
- The open and closed states of the channels are partitioned according to a Boltzman distribution.

Variables and Parameters

- V - Membrane Potential (mV)
- W - Recovery Variable (mV)
- I_{app} - Applied Current Stimulus($\frac{\mu A}{cm^2}$)
- T - Time (ms)
- C_m - Membrane Capacitance($\frac{\mu F}{cm^2}$)
- g - Instantaneous(or maximum) Membrane Conductance($\frac{mmho}{cm^2}$)
- V_{Ca}, V_K, V_L - Equilibrium potential corresponding to leak, Ca^{2+}, and K^+, respectively (mV)
- v_1 - Potential (mV)
- v_2 - Reciprocal of slope of voltage dependence (mV)
- v_3 - Potential (mV)
- v_4 - Reciprocal of slope of voltage dependence (mV)
- g_K - Conductance of Potassium Ions (mS)
- g_{Ca} - Conductance of Calcium Ions (mS)
- g_L - Conductance of Leaked Ions (mS)

The Morris-Lecar model is written as

$$C_m \frac{dV}{dt} = -g_{Ca} M_\infty(V)(V - V_{Ca}) - g_K W(V - V_k) - g_L(V - V_L) + I_{app} \tag{7}$$

$$\frac{dW}{dt} = \frac{W_\infty(V) - W}{T_W(V)} \tag{8}$$

Where M_∞ , N_∞ and T_W are represented as

$$M_\infty(V) = \frac{1}{2}(1 + tanh(\frac{V - V_1}{V_2})) \tag{9}$$

$$W_\infty(V) = \frac{1}{2}(1 + tanh(\frac{V - V_3}{V_4})) \tag{10}$$

$$T_W = cosh\frac{V - V_3}{2V_4} \tag{11}$$

Non-Dimensionalization

The first task was to find a non-dimensional representation of the Morris-Lecar equations in terms of these scaling variables.

- $v = \frac{V}{V_{Ca}}$
- $t = \frac{g_K T}{2C_m}$
- $w = W$

The non-dimensional parameters are:

- $\overline{V_1} = \frac{V_{Ca}}{V_2}, \overline{V_2} = \frac{V_1}{V_2}, \overline{V_3} = \frac{V_{Ca}}{V_4}, \overline{V_4} = \frac{V_3}{V_4}, \overline{V_5} = \frac{V_K}{V_{Ca}}, \overline{V_6} = \frac{V_L}{V_{Ca}}$
- $a = \frac{g_{Ca}}{g_K}, b = \frac{2g_L}{gK}, c = \frac{2}{g_K * v_{Ca}}, d = \frac{\theta * g_K}{2C_m}$

Non-dimensional Equations

The reassigned values of the original model using the non-dimensional functions gives a new model to analyze:

$$\frac{dv}{dt} = -a(1 + tanh(\overline{V_1}v - \overline{V_2})) - 2w(v - \overline{V_5}) - b(v - \overline{V_6}) + cI_{app} \tag{12}$$

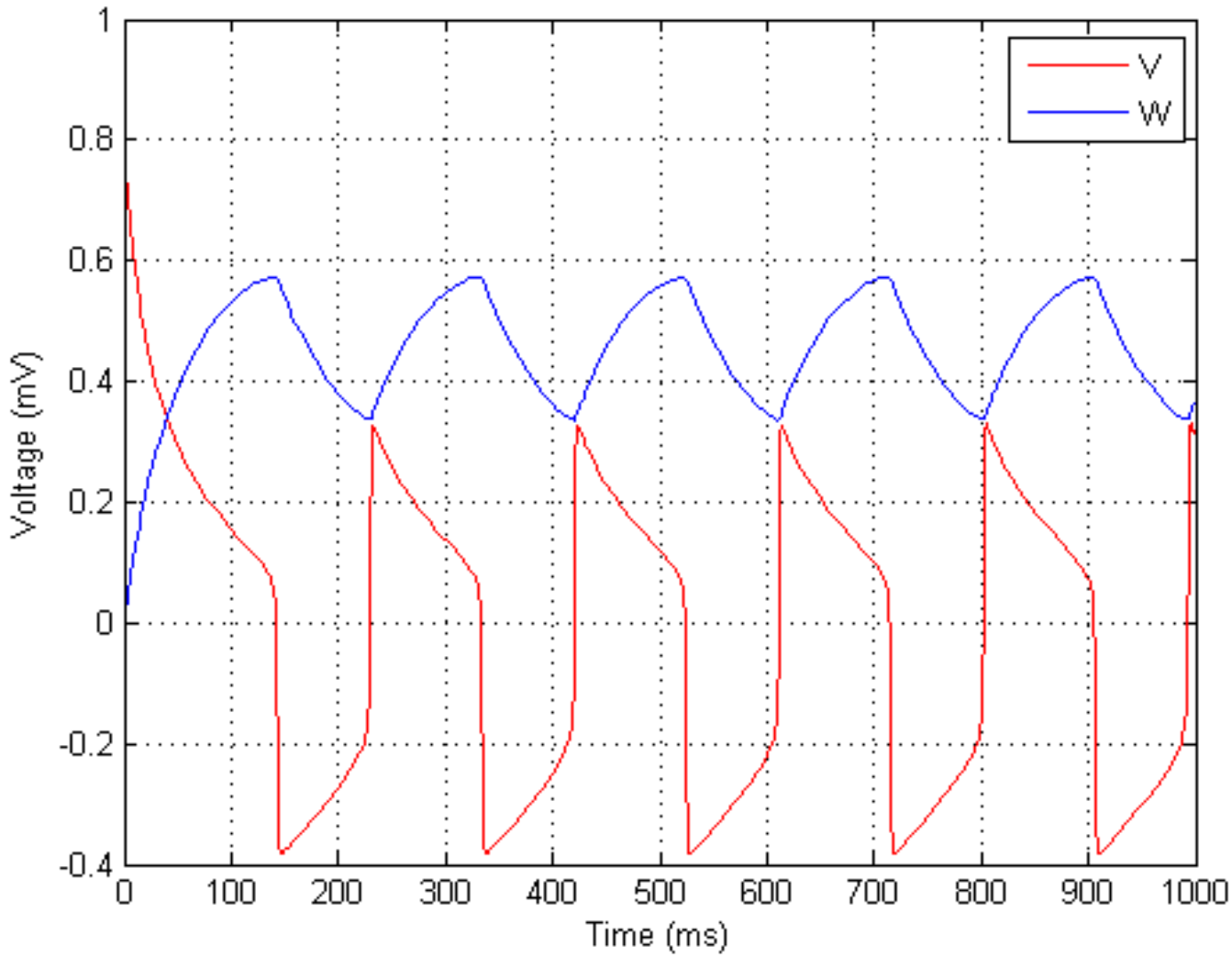
$$\frac{dw}{dt} = acosh(\frac{1}{2}(\overline{V_3}v - \overline{V_4}))[\frac{1}{2}(1 + tanh(\overline{V_3}v - \overline{V_4})) - w] \tag{13}$$

This analysis is performed with the following initial values:

- $g_{Ca} = 4.4\frac{mS}{cm^2}, g_K = 8\frac{mS}{cm^2}, g_L = 2\frac{mS}{cm^2}$
- $V_1 = -1mV, V_2 = 15mV, V_3 = 0mV, V_4 = -40mV$
- $V_{Ca} = 100mV, V_K = -70mV, V_L = -50mV$
- $C_m = 20\frac{\mu F}{cm^2}, I_{app} = 0.06\frac{mA}{cm^2}, \theta = 0.040(ms)^{-1}$

Solutions

With the new non-dimenstional equations, MATLAB can then be used to analyze the new model numerically and provide the following graph



Solutions Cont'd

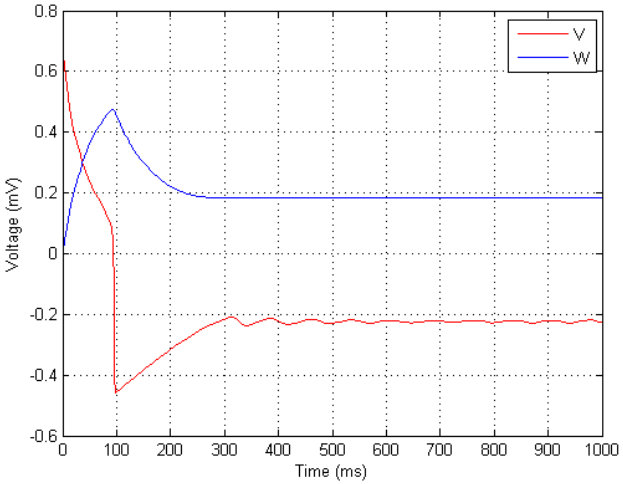


Figure : Lower boundary of I_{app}

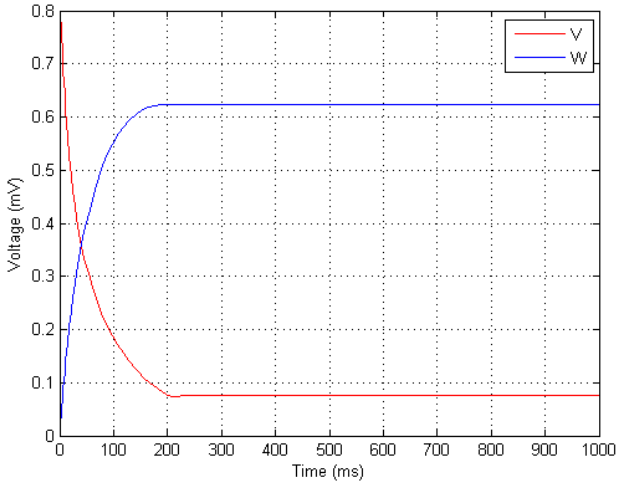
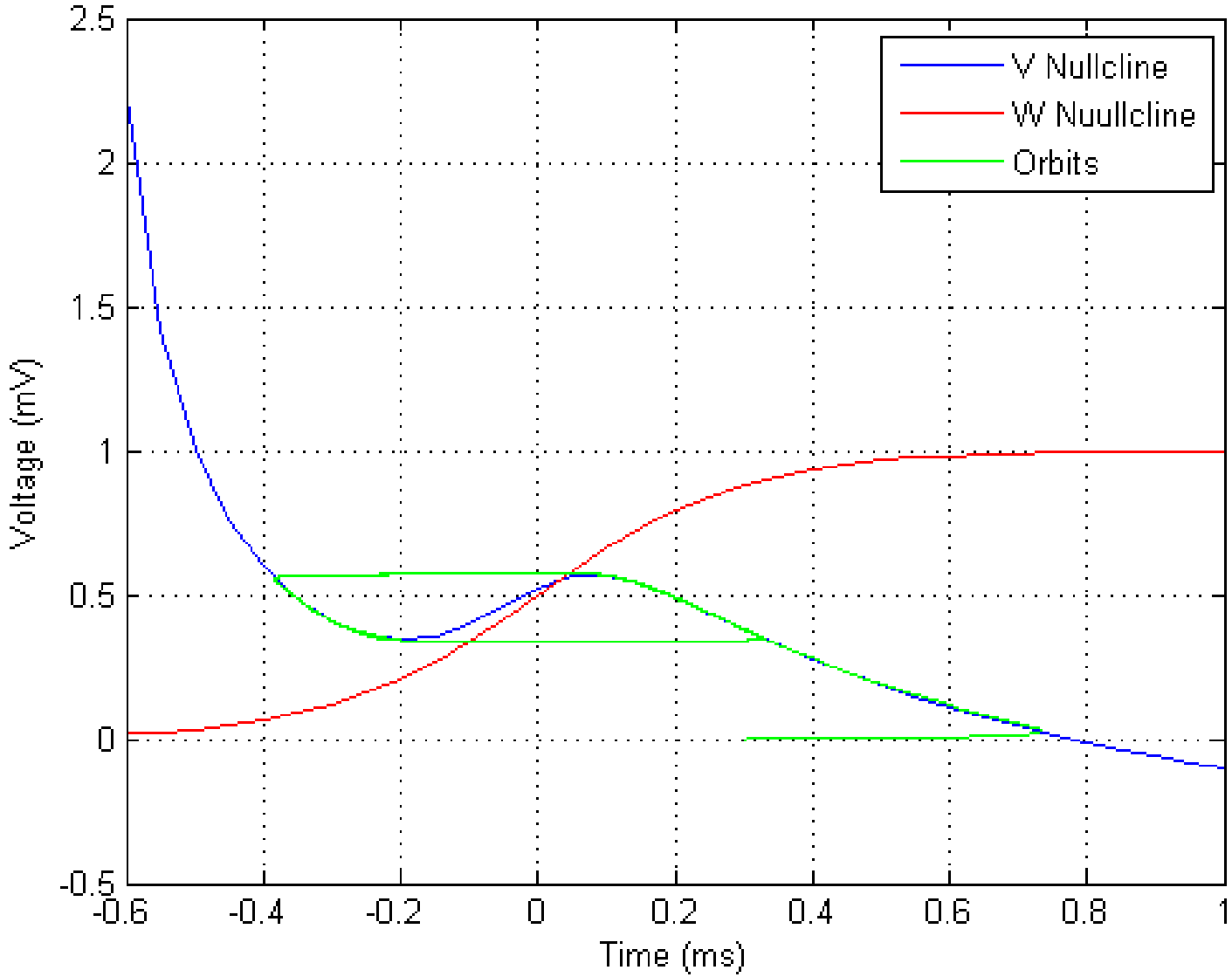


Figure : Upper boundary of I_{app}

Phase Portrait Analysis



Jacobian and Eigenvalues

Using MATLAB commands, the critical points of the phase portrait analysis were found out to be $(.0333, .5553)$. After calculating the Jacobian matrix at the critical point for our model, this is the resulting matrix:

$$\begin{bmatrix} -4.987 & -0.0666 \\ 2.6871 & -0.5508 \end{bmatrix}$$

Because of the form of this matrix, this system of equations is deemed stable and from this matrix the Eigenvalues are:

$$\lambda_1 = -4.9463 \tag{14}$$

$$\lambda_2 = -0.5915 \tag{15}$$

Conclusion

In conclusion,

- The Hodgkin-Huxley model is very accurate, but hard to analyze.
- The FitzHugh-Nagumo model is mathematically correct, but hard to explain biologically.
- The Morris-Lecar model combines the simplicity of the FitzHugh-Nagumo model, while maintaining some biological meaning.

References

- http://hbcudigest.com/tennessee-state-takes-right-path-on-homecoming-parade-route-issue/
- http://www.webbiology.com/the-nervous-system
- https://www.boundless.com/#microbiology/bacteria-archaea-and-eukaryote-cell-structure/transport-across-the-cell-membrane/active-transport/
- http://cheezburger.com/2748402944
- http://en.wikipedia.org/wiki/Hodgkin%E2%80%93Huxley_model
- https://en.wikipedia.org/wiki/FitzHugh%E2%80%93Nagumo_model
- http://www.scholarpedia.org/article/Morris-Lecar_model
- http://www.psy.plymouth.ac.uk/research/Wsimpson/misc/hh.html
- Fall, Christopher P., Eric S. Maryland, John M. Wagner, and John J. Tyson. *Computational Cell Biology*. Vol. 20. New York: Springer, 2002. Print.
- Kenner, James, James Sneyd. *Mathematical Physiology I: Cellular Physiology (Interdisciplinary Applied Mathematics)*. New York: Spinger, 2008. Print.