Lecture 6

The FitzHugh-Nagumo Model

6.1 The Nature of Excitable Cell Models

Classically, it was known that the cell membrane carries a potential across the inner and outer surfaces, hence a basic model for a cell membrane is that of a capacitor and resistor in parallel. The model equation takes the form

$$C_m \frac{dV}{dt} = -\frac{V - V_{eq}}{R} + I_{appl}, \tag{6.1}$$

where C_m is the membrane capacitance, R the resistance, V_{eq} the rest potential, V the potential across the inner and outer surfaces, and I_{appl} represents the applied current. In landmark patch clamp experiments in the early part of the 20^{th} century, it was determined that many cell membranes are *excitable*, i.e., exhibit large excursions in potential if the applied current is sufficiently large. Examples include nerve cells and certain muscle cells, e.g., cardiac cells.

$>$From 1948-1952, Hodgkin and Huxley conducted patch clamp experiments on the giant squid axon, a rather large part of nerve tissue suitable for experimentation given the technology of the time. Based on their experiments, they constructed a model for the patch clamp experiment in an attempt to give mathematical explanation for the axon's excitable nature. A key part of their model assumptions was that the membrane contains channels for potassium and sodium ion flow. In effect, the $1/R$ factor in (6.1) became potential dependent for both channels. The underlying model equation is:

$$C_m \frac{dV}{dt} = -g_K n^4 (V - V_K) - g_{Na} m^3 h (V - V_{Na}) - g_L (V - V_L) + I_{appl}. \tag{6.2}$$

Here the subscripts K, Na, and L correspond to potassium, sodium, and leakage channels, respectively. The terms $g_K n^4$, $g_{Na} m^3 h$, and g_L are the conductances (reciprocal of resistances). The variables n, m, and h are hypothesized *potential dependent gating variables* whose dynamics were assumed to follow first order kinetics. The equations take the form

$$\tau_w(V)\frac{dw}{dt} = w_\infty(V) - w, \;\; w = n, m, h, \tag{6.3}$$

where $\tau_w(V)$ and $w_\infty(V)$ are the time constant and rate constant determined from the experimental data.

Taken together, (6.2) and (6.3) represent a four dimensional dynamical system known as the Hodgkin-Huxley model. It does provide a basis for qualitative explanation of the formation of action potentials in the giant squid axon. Moreover, the model structure forms a basis for virtually all models of excitable membrane behaviour.

6.2 FitzHugh Model Reduction

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, of the form

$$C_m\frac{dV}{dt} = -g_K n^4(V - V_K) - g_{Na}m_\infty^3(V)(0.8 - n)(V - V_{Na}) - g_L(V - V_L) + I_{appl}$$
$$n_w(V)\frac{dn}{dt} = n_\infty(V) - n.$$

In effect this provides a phase space qualitative explanation of the formation and decay of the action potential. (See Keener & Sneyd[1].)

A further observation due to FitzHugh was that the V-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

$$\begin{aligned} \frac{dv}{dt} &= v(v-\alpha)(1-v) - w + I \\ \frac{dw}{dt} &= \varepsilon(v - \gamma w). \end{aligned} \tag{6.4}$$

[1] J. Keener & J. Sneyd, *Mathematical Physiology,* Springer-Verlag (1998), p 133.

Here, the model has been put in dimensionless form, v represents the fast variable (potential), w represents the slow variable (sodium gating variable), α, γ, and ε are constants with $0 < \alpha < 1$ and $\varepsilon \ll 1$ (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 (6.4). Hence the equations (6.4) have become known as the FitzHugh-Nagumo model.

6.3 Simulations and Phase Plane

We assume the parameters are such that precisely one equilibrium point exists. Further, we translate the model to place this equilibrium at $(0, 0)$ as follows. Let

$$f(v) = v(v - \alpha)(1 - v),$$

and let (v_{eq}, w_{eq}) be the equilibrium point for (6.4). Then we can write the model equations in the form

$$\begin{aligned}\frac{dv}{dt} &= f(v + v_{eq}) - f(v_{eq}) - w \\ \frac{dw}{dt} &= \varepsilon(v - \gamma w).\end{aligned}$$

Here we will illustrate the behaviour of the FitzHugh-Nagumo model using "typical" values for the parameters. Two Hopf bifurcation phenomena will be illustrated by varying v_{eq} and by varying α.

In the first case, we take values: $\alpha = 0.139$, $\varepsilon = 0.008$, $\gamma = 2.54$. The plots are shown in Figures 6.1 and 6.2 where we have set $v_{eq} = 0.07$ and $= 0.15$, respectively. The phase portraits with nullclines are shown on the left. Note how the orbits are driven by the nullclines. Further, note the position of the knee of the v-nullcline in relation to the equilibrium point in the two figures. (In the limit cycle case, the knee is to the left.) Numerically, the actual bifurcation value is approximately $v_{eq} = 0.085$.

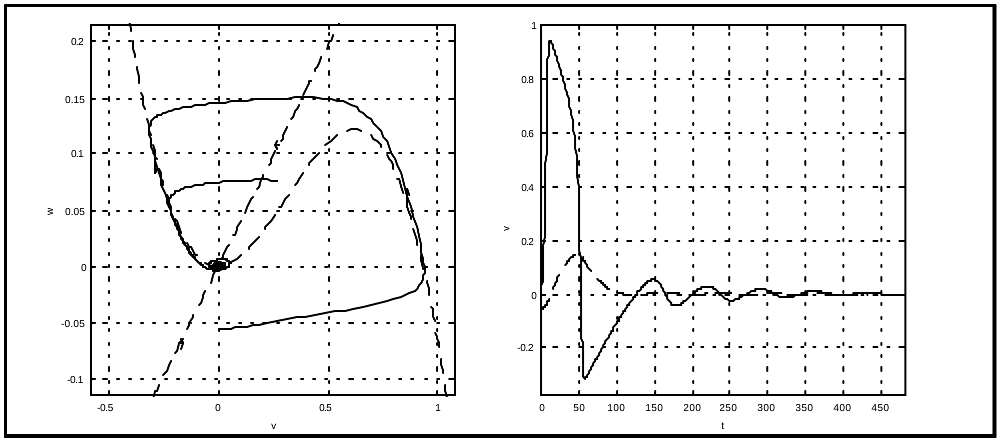

Figure 6.1: FitzHugh-Nagumo: $v_{eq} = 0.07$

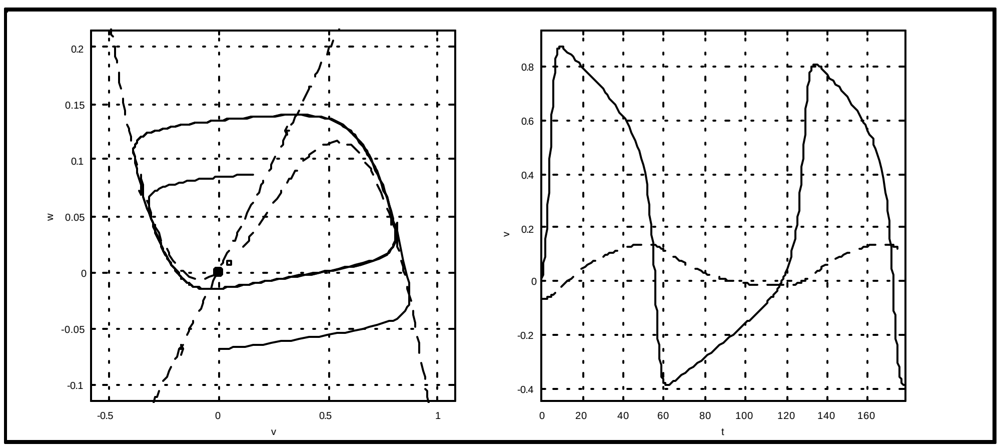

Figure 6.2: FitzHugh-Nagumo: $v_{eq} = 0.15$

In our second case we take $v_{eq} = 0$ and allow α to vary and take on negative values. The plots are shown in Figures 6.3 and 6.4 where we have set $\alpha = 0.139$ and $= -0.139$, respectively. The other parameters are $\varepsilon = 0.008$ and $\gamma = 1.5$. Again we note in the phase plots how the orbits follow the nullcline fields and the location of the knee of the v-nullcline for the limit cycle.

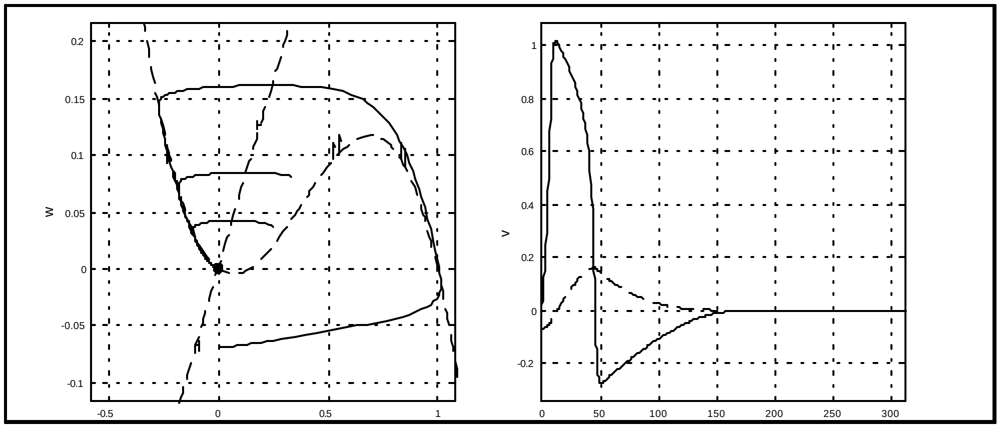

Figure 6.3: FitzHugh-Nagumo: $\alpha = 0.139$

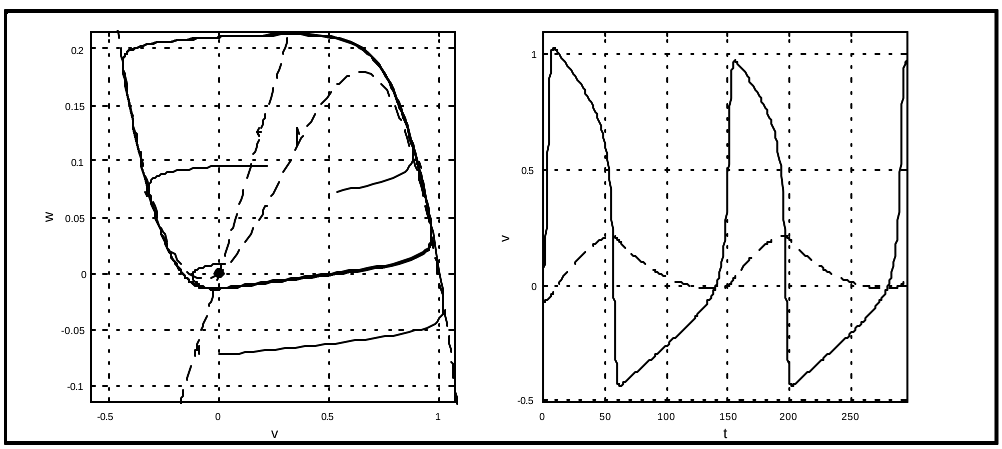

Figure 6.4: FitzHugh-Nagumo: $\alpha = -0.139$

6.4 Bifurcation Analysis

Here we will present the bifurcation analysis corresponding to Figures 6.3 and 6.4. We will see that the bifurcation point is $\alpha_0 = -\varepsilon\gamma$ with a limit cycle bifurcating for $\alpha < \alpha_0$.

Computing the Jacobian we have

$$J = J(0,0) = \begin{bmatrix} -\alpha & -1 \\ \varepsilon & -\varepsilon\gamma \end{bmatrix}.$$

Hence, $Tr(J) = -(\alpha + \varepsilon\gamma)$ and $\det(J) = \varepsilon(\alpha\gamma + 1)$. The eigenvalues are given by

$$\lambda = \frac{-(\alpha+\varepsilon\gamma) \pm \sqrt{(\alpha+\varepsilon\gamma)^2 - 4\varepsilon(\alpha\gamma+1)}}{2},$$

and the condition for the eigenvalues to be complex reads:

$$\varepsilon\gamma - 2\varepsilon^{1/2} < \alpha < \varepsilon\gamma + 2\varepsilon^{1/2}.$$

At $\alpha = -\varepsilon\gamma$, the eigenvalues are $\lambda = \pm i\eta$, where $\eta = \sqrt{\varepsilon(1-\varepsilon\gamma^2)}$. The corresponding eigenvectors are given by:

$$\begin{bmatrix} 1 \\ \varepsilon\gamma - i\eta \end{bmatrix} \text{ and } \begin{bmatrix} 1 \\ \varepsilon\gamma + i\eta \end{bmatrix}.$$

We can transform the model equations into suitable form using the transformation

$$T = \begin{bmatrix} 1 & 0 \\ \varepsilon\gamma & \eta \end{bmatrix}, \text{ with } T^{-1} = \frac{1}{\eta}\begin{bmatrix} \eta & 0 \\ -\varepsilon\gamma & 1 \end{bmatrix}.$$

Setting

$$\begin{bmatrix} v \\ w \end{bmatrix} = T \begin{bmatrix} x \\ y \end{bmatrix},$$

we obtain

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} \mu & -\eta \\ \frac{-\varepsilon\gamma\mu}{\eta} + \eta & 0 \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} (1-(\mu+\varepsilon\gamma)x^2 - x^3 \\ \frac{-\varepsilon\gamma(1-(\mu+\varepsilon\gamma)x^2+\varepsilon\gamma x^3}{\eta} \end{bmatrix}, \tag{6.5}$$

where we have set $\mu = -(\alpha + \varepsilon\gamma)$. This is the form appropriate to apply Theorem 5.4. We have

$$d = \frac{d}{d\mu}\mathrm{Re}\,\lambda\Big|_{\alpha=-\varepsilon\gamma} = \frac{1}{2} > 0.$$

Further, denoting the nonlinear terms in (6.5) by $f(x,y)$ and $g(x,y)$, then

$$\begin{aligned} a &= \frac{1}{16}f_{xxx} + \frac{1}{16\eta}\left(-f_{xx}g_{xx}\right)\Big|_{(0,0,-\varepsilon\gamma)} \\ &= -\frac{3}{8} + \frac{\gamma}{4}\frac{(1-\varepsilon\gamma)^2}{1-\varepsilon\gamma^2}. \end{aligned}$$

For the parameters given above ($\varepsilon = 0.008$, $\gamma = 1.5$) we have $a = -0.02.. < 0$. Consequently we can conclude that a limit cycle bifurcates for $\mu > 0$, i.e. $\alpha < -\varepsilon\gamma$. This is what was desired.