# Analysis of a Model for an Excitable Fiber with Myotonia or Periodic Paralysis

**By**

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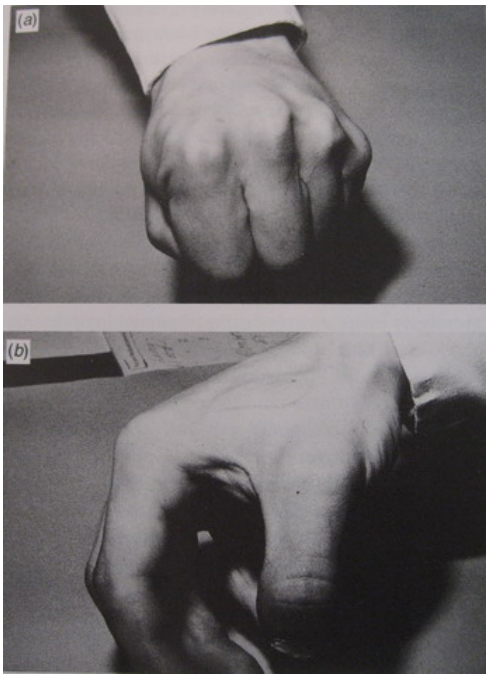



**Outline of Talk**

- Background on the disease
- Present the Cannon-Corey Model
- Reduction of model to a 3D system
- Use perturbation theory and simulation to describe cases of model behavior, and compare with predictions

# Myotonia and Periodic Paralysis (channelopathies)

Muscle disorders caused by ion channel abnormalities in peripheral skeletal muscles
(Mutations in the coding region of ion channel genes)

Myotonia characterized by repetitive discharging activity beyond a stimulus period, generally leading to muscle stiffness

Symptoms are episodic, severity varies greatly

Disease does not affect the muscle contractile mechanisms, or other neuromuscular systems

Individuals have elevated levels of serum $K^+$ concentration (Hyperkalemic)

More sever cases can lead to block of spike production in muscle, i.e.  periodic paralysis

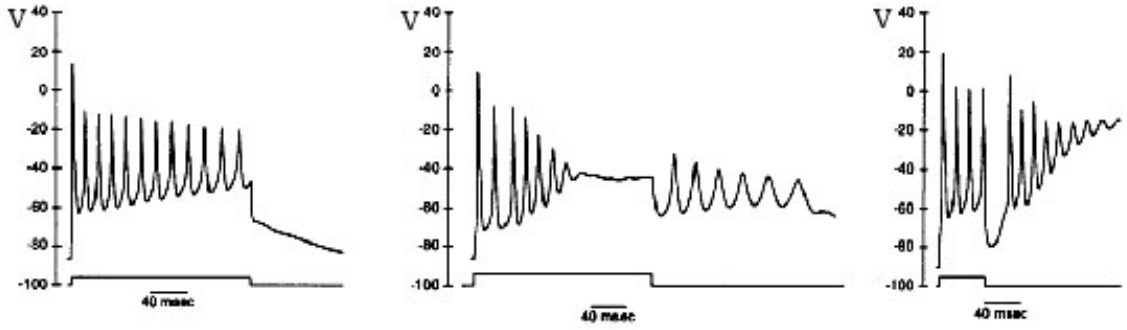
# Experimental/ Modeling of Cannon, et al

Using patch-clamp techniques, Cannon et al (Biophys. J. 65 (1993), 270) demonstrated role of defects in $Na^+$ channel inactivation

Hypothesis is that difference in shapes, form of action potentials is associated with myotonia and periodic paralysis

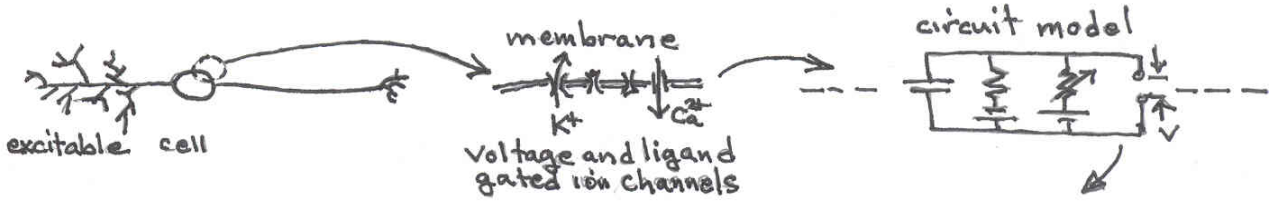
Muscle fibers with myotonia generate repetitive trains of spikes
Muscle fibers with paralysis generate large depolarizations and block spike production when $[K^+]_{ext}$ is elevated

Figure shows 3 forms of after-response observed in rat muscle with steps of depolarizing current applied to fibers exposed to 10 $\mu mol$ anemone toxin (ATXII) in vitro




Cannon et al proposed a mathematical model and did computer simulations to help explain disruption of Na channel inactivation as a possible cause of myotonia and periodic paralysis

# Conductance-based Models of Excitable Membranes




current conservation principle

**Hodgkin-Huxley** $C_m \frac{\partial v}{\partial t} + I_{ion} = I_e$

**formalism** capacitance + resistance = external current
current (ionic) current (applied, coupling,…)

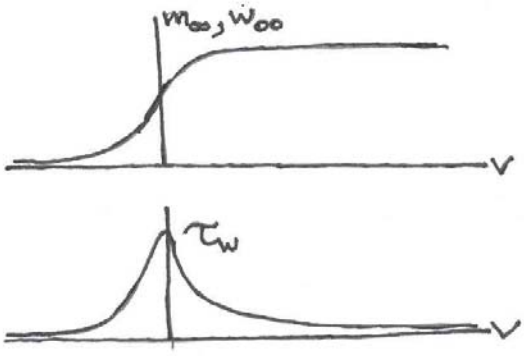
$$I_{ion} = \sum_{ion-species} I_j = \sum_j g_j (v - E_j)$$

$$g_j = \bar{g}_j m^a h^b$$

***Example*: *Morris-Lecar Model*** **(for barnacle muscle)**

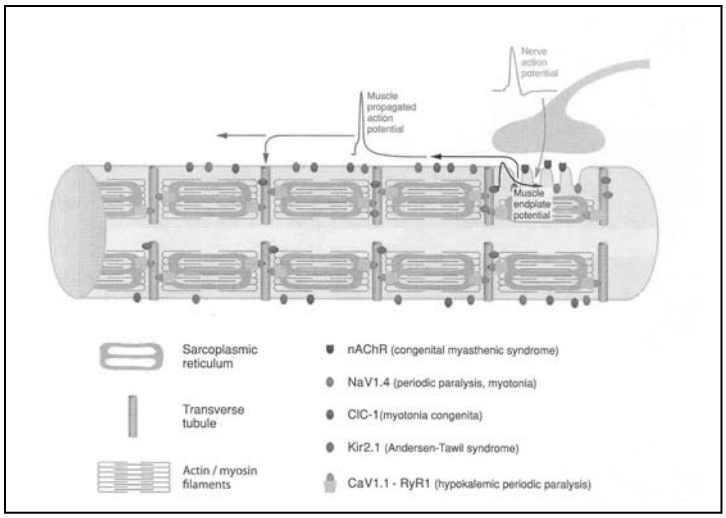
$$C_m \frac{dv}{dt} = I_e - \bar{g}_{Ca} m_\infty(v)(v - E_{Ca}) - \bar{g}_K w(v - E_K) - g_{lk}(v - E_{lk})$$

$$\frac{dw}{dt} = \frac{1}{\tau_w(v)}\{w_\infty(v) - w\}$$



## Cannon's two-compartment model (8 dimensional)

$V$ = surface membrane potential
$V_t$ = T-tubule membrane potential
$m, n, h, m_t, n_t, h_t$ are channel activation variables




$$C_m \frac{dV}{dt} = I_m - \bar{g}_{Na} m^3 [(1-f)h + f](V - E_{Na}) - \bar{g}_K n^4 (V - E_K) - g_l (V - E_l) - g_a (V - V_t)$$

$$C_m \frac{dV_t}{dt} = -\tilde{\eta}_{Na} \bar{g}_{Na} m_t^{\,3} [(1-f)h_t + f](V_t - E_{Na}) - \tilde{\eta}_K \bar{g}_K n_t^{\,4} (V_t - \tilde{E}_K) - \tilde{\eta}_l g_l (V_t - \tilde{E}_l) + \frac{g_a}{\gamma}(V - V_t)$$

$$\frac{dy}{dt} = \alpha_y(\nu)(1-y) - \beta_y(\nu) y = (\alpha_y + \beta_y)\left\{ \frac{\alpha_y}{\alpha_y + \beta_y} - y \right\} = \{ y_\infty(\nu) - y \} / \tau_y(\nu)$$

$$y = m, n, h, h_t, m_t, n_t \qquad \nu = V, V_t$$

$$\tilde{E}_K = \frac{RT}{Fz} \ln\left\{ \frac{[K^+]_t}{[K^+]_i} \right\} \qquad \tilde{E}_l = \frac{RT}{Fz} \ln\left\{ \frac{[K^+]_t + 0.01[Na^+]_o}{[K^+]_i} \right\}$$

$\gamma, \tilde{\eta}'s$ are scale factors accounting for the ratio of T-tubular membrane area to surface membrane area

# Model Reduction

Assumptions: **1**. quasi-steady state: $m \leftarrow m_\infty(v)$ ($\tau_m << \tau_h, \tau_n$),

$$m_t \leftarrow m_{t\infty}(v)$$

$$n_t \leftarrow r_\infty(w) = \frac{\alpha_{mt}}{\alpha_{mt} + \beta_{mt}}$$

**2**. $(1-f)h + f \leftarrow f$ (Similarly for $h_t$)

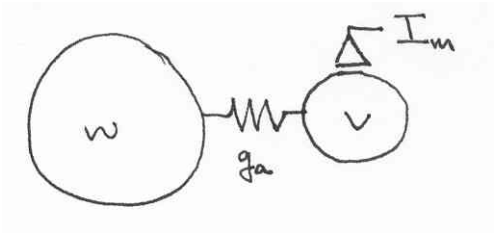
$v = V$ = surface membrane potential
$w = V_t$ = T-tubule membrane potential
$n$ = (dimensionless) potassium activation variable

$$\begin{cases} \dfrac{dv}{dt} = F(v,n,w) \\ \dfrac{dn}{dt} = \varepsilon G(v,n) \\ \dfrac{dw}{dt} = \varepsilon\delta H(v,w) \end{cases} \qquad 0 < \varepsilon, \delta << 1$$

$$F(v,n,w) \equiv \frac{1}{C_m}\left\{I_m - \bar{g}_{Na}\, f m_\infty{}^3(v)(v - E_{Na}) - \bar{g}_K n^4 (v - E_K) - g_l(v - E_l) - g_a(v - w)\right\}$$

$$G(v,n) \equiv \alpha_n(v)(1-n) - \beta_n(v)n$$

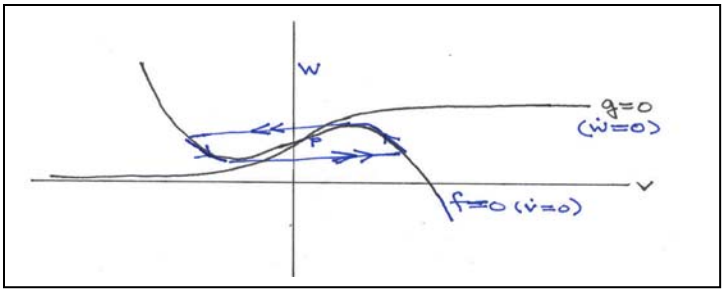
$$H(v,w) \equiv \frac{-1}{C_m}\left\{\eta_l g_l(w - \tilde{E}_l) + \eta_{Na}\bar{g}_{Na}\, f m_\infty{}^3(w)(w - E_{Na}) + \eta_K \bar{g}_K r_\infty{}^4(w)(w - \tilde{E}_K) + g_b(w - v)\right\}$$




***v*** has fastest dynamics, ***n*** intermediate dynamics, and ***w*** has the slowest dynamics, consistent with observations

# Geometric perturbation theory: "generic-cell" example

(1) $$\begin{cases} \dfrac{dv}{dt} = f(v,w) \\ \dfrac{dw}{dt} = \varepsilon g(v,w) \end{cases} \qquad 0 < \varepsilon << 1$$




**Assume**: the given nullcline geometry in figure; a single fixed point on middle branch of the cubic *v*-nullcline; $\dot{v} > 0$ (< 0) below (above) the *v*-nullcline; $\dot{w} > 0$ (< 0) below (above) the *w*-nullcline

Poincare-Bendixson $\Rightarrow \exists$ limit cycle for $\varepsilon$ sufficiently small
The limit cycle approaches a 4-piece *singular* limit cycle as $\varepsilon \to 0$:

(2) $$\begin{cases} \dfrac{dv}{dt} = f(v,w) \\ \dfrac{dw}{dt} = 0 \end{cases}$$

*w* = constant along solution path, trajectories are horizontal (*w* acts as a parameter in *v* equation …the **fast equation**)

Fixed point set is the whole cubic { *f = 0* }

Reduced system (2) gives good approximation to solution to (1) away from { *f = 0* }
Near { *f = 0* } introduce slow time scale $\tau = \varepsilon \cdot t$ ($\frac{d}{dt} = \varepsilon \frac{d}{d\tau}$), then let $\varepsilon \to 0$:

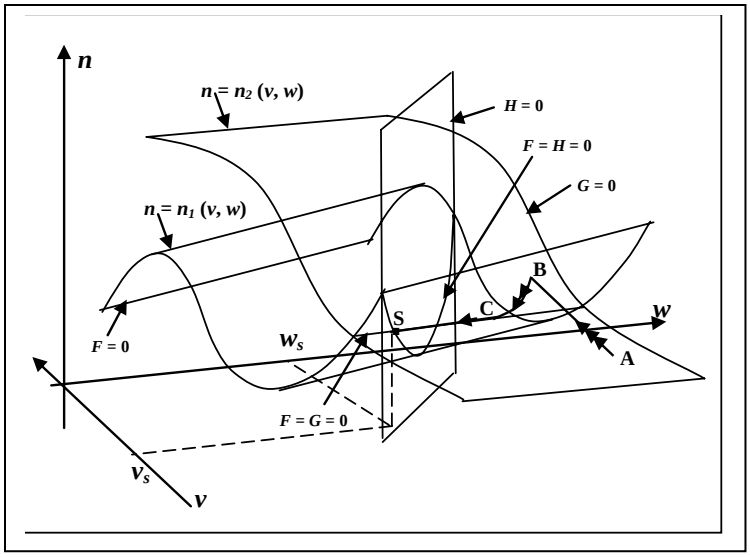
(3) $$\left.\begin{cases} 0 = f(v,w) \\ \dfrac{dw}{d\tau} = g(v,w) \end{cases}\right\} \quad \Rightarrow v = h_L(w), \quad v = h_R(w)$$

1st equation $\Rightarrow$ solution to (3) lies along { *f = 0* }
2nd equation $\Rightarrow$ determines evolution of the system along the *v*-nullcline. Thus

(4) $$\frac{dw}{d\tau} = g(h_q(w), w) \equiv G(w), \quad q = L, R$$ (**slow equation**)

# Channelopathy Model

$$\begin{cases} \dfrac{dv}{dt} = F(v,n,w) \\ \dfrac{dn}{dt} = \varepsilon G(v,n) \\ \dfrac{dw}{dt} = \varepsilon\delta H(v,w) \end{cases}$$




Fast manifold (mfd)

$F = 0 \Leftrightarrow n = n_1(v,w)$

$v > E_K \Rightarrow \dfrac{\partial n_1}{\partial w} > 0$; on $F = G = 0$ $\quad \dfrac{\partial v}{\partial w} > 0$

Intermediate mfd

$$G = 0 \Leftrightarrow n = n_2(v) \equiv \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)}$$

Slow mfd

$H = 0 \Leftrightarrow n = n_3(v)$

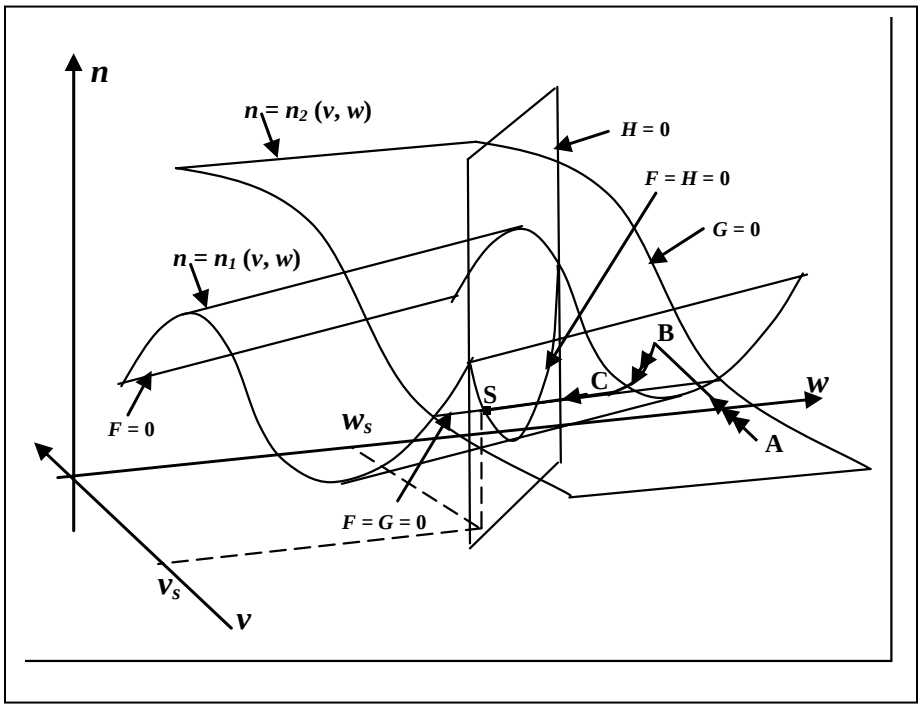
This intersects $F = F(v, n_2(v), w) = 0$ at the equilibrium point $(v_s, n_s, w_s)$ where $E_K < v_s, w_s < 0 < n_s < 1$

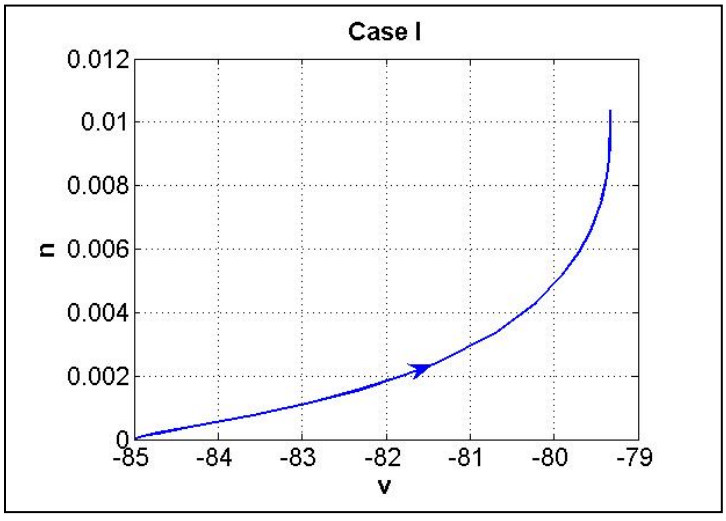
$H = 0$ intersects $F = 0$ along a curve $n = n_4(w) = n_2(n_3(w))$

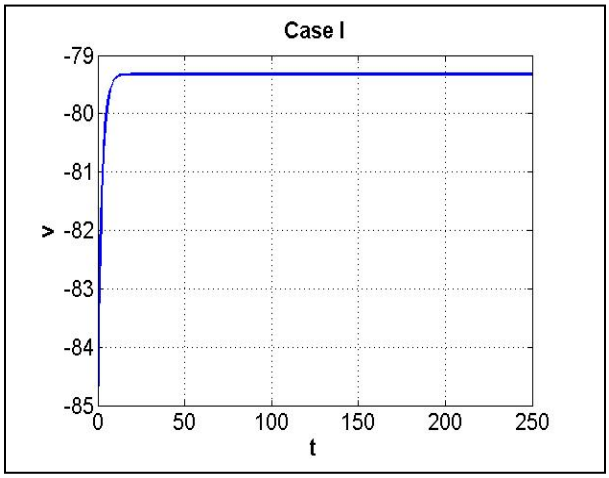
**Assume**: $n_2(0) > n_1(v_m, 0)$ where $v = v_m$ is rel. max. point of $n_1(v,0)$

Given this assumption, we have three physical cases.

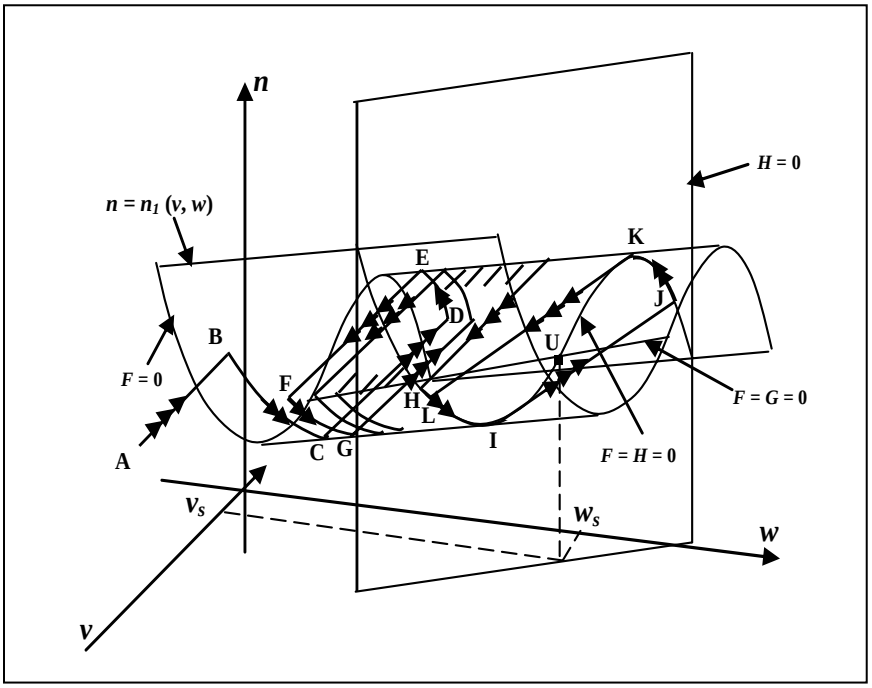
**Case I:** $F = G = 0$ curve lies in region where $F = 0$ is stable for all $w$ in region of interest. So $n_1(v,0) > n_1(v,w) \quad \forall w < 0$

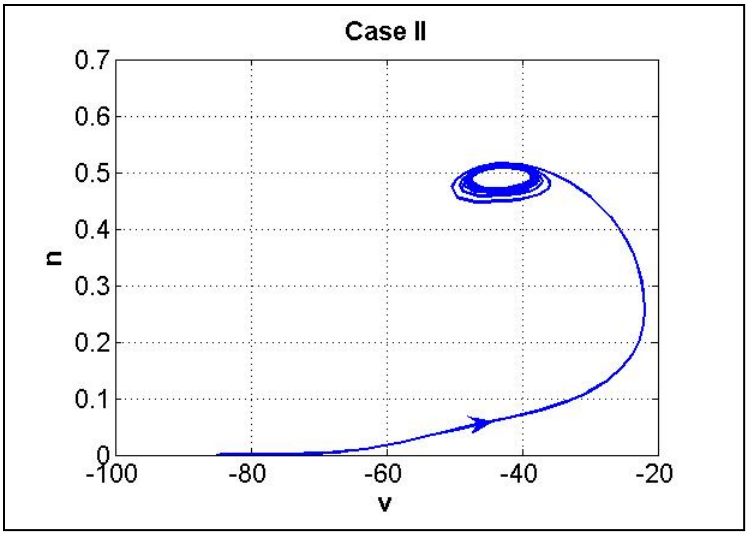


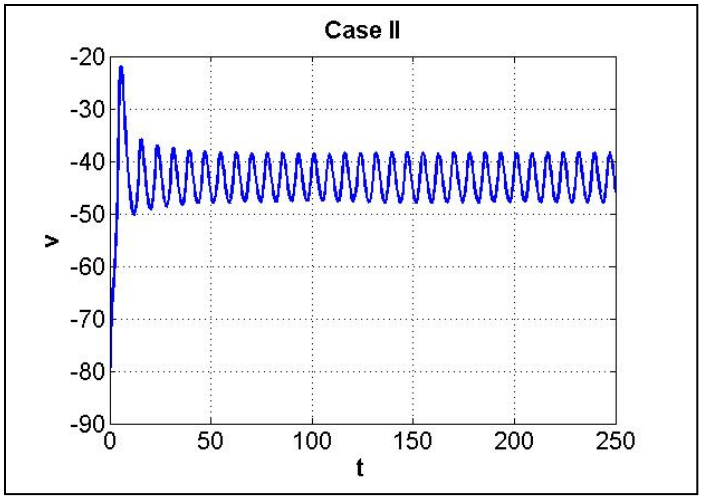



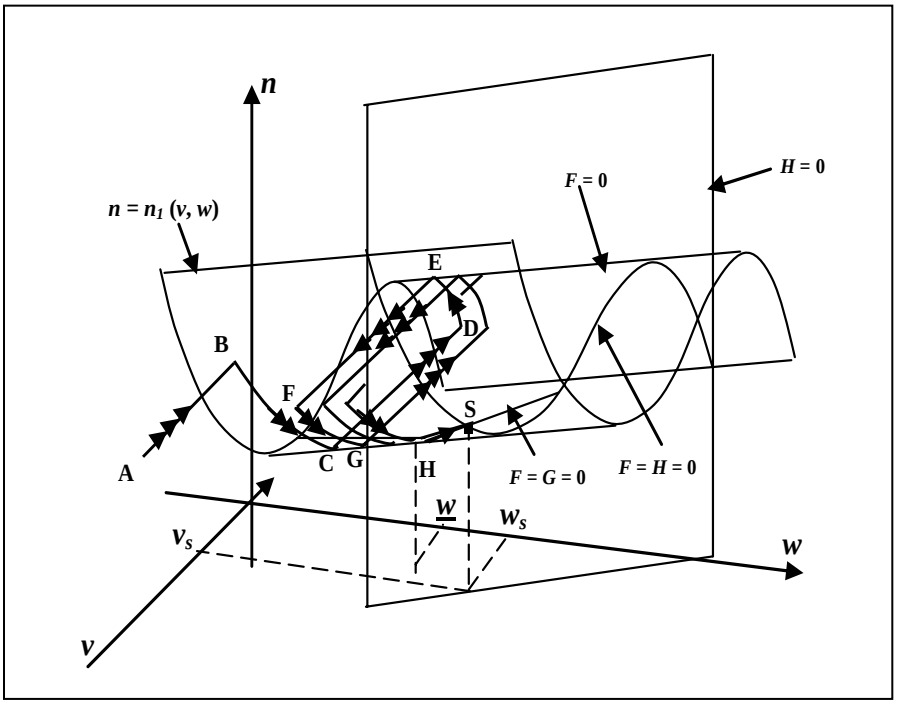
**Case II:** $F = G = 0$ lies in a region where mfd $F = 0$ is unstable for all $w \in I \equiv (w_s - \delta, w_s + \delta)$. Shapes and relative position of equilibrium manifolds depicted below.

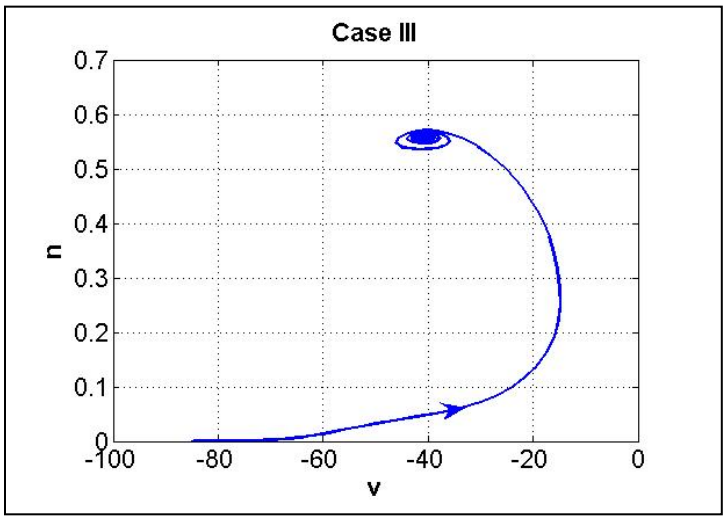


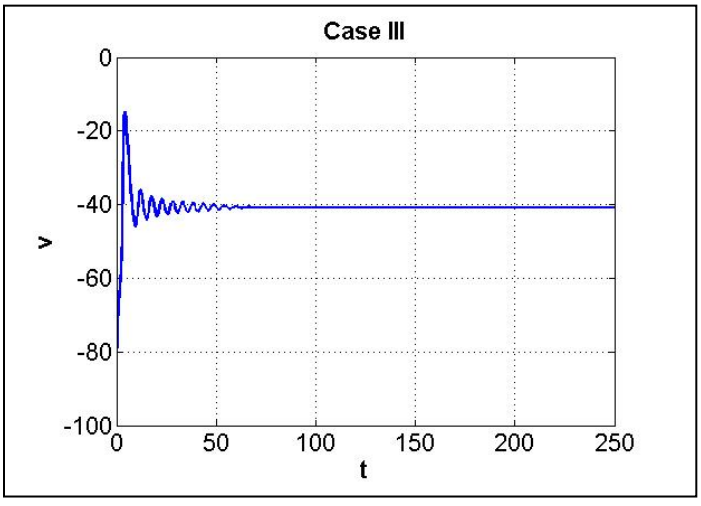



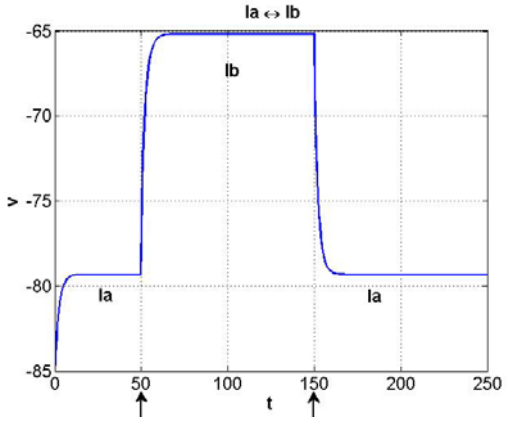



**Case III:** $F = G = 0$ lies in a region where mfd $F = 0$ is unstable for all $w < w_*$ for some $w_* < w_s < 0$, and passes to the region where the mfd $F = 0$ is stable for $w > w_*$ . Shapes and relative position of equilibrium manifolds depicted below.

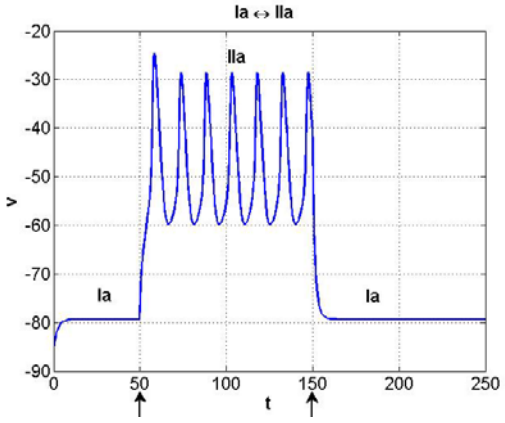


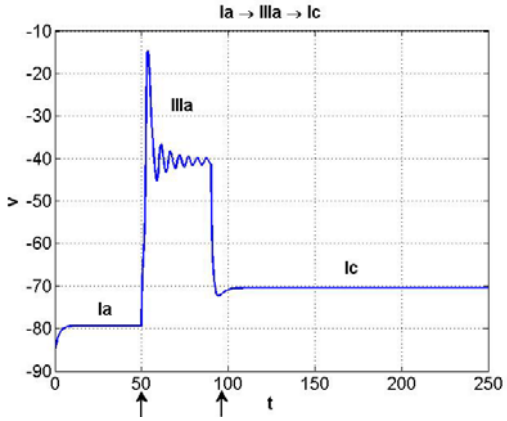





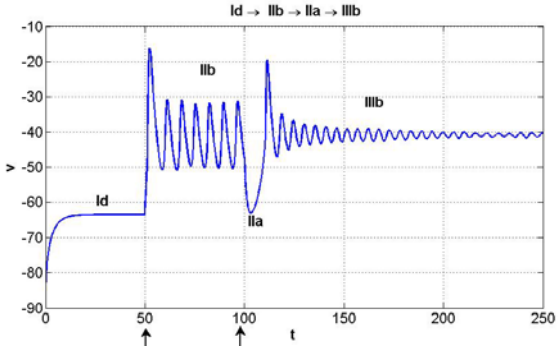

a) $f = 0.005, \quad I_m = 30$



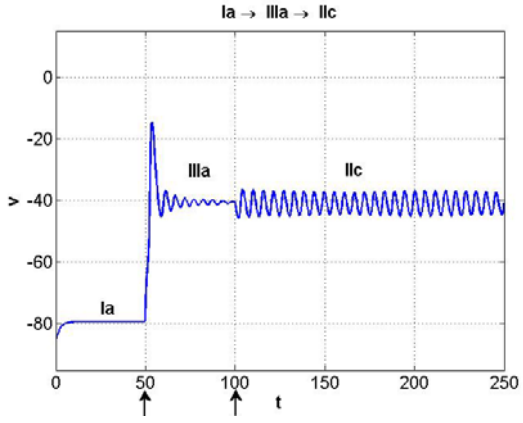

b) $f = 0.015, \quad I_m = 45$




c) $f = 0.02, \quad i_m = 65$

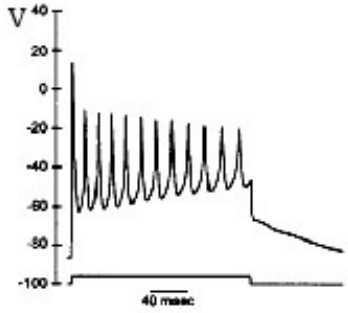



d) $f = 0.015, \quad I_m = 60$

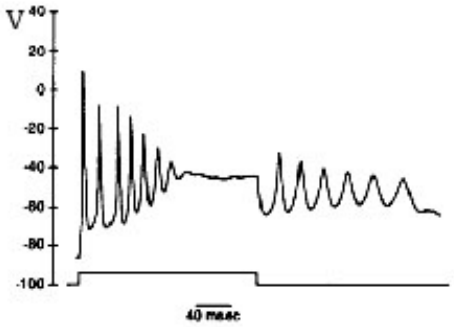



e) $f = 0.02, \quad I_m = 60$

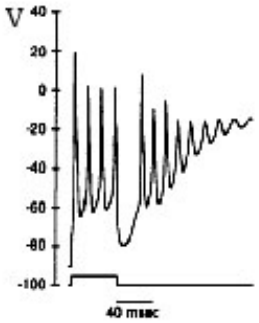
From the ATX II experiment on rat muscle




**1a)**




**1b)**




**1c)**

Note similarity between figure 1c) here and d) above
between figure 1b) and e) above

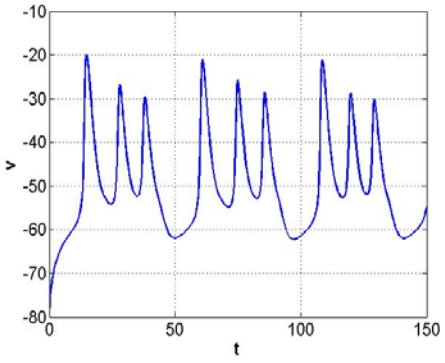
## Comments

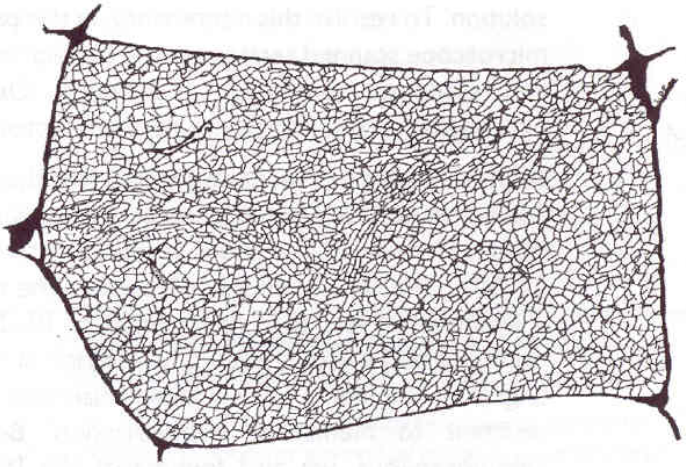
- ✓ The reduced model is capable of simulating a variety of relevant dynamical behavior along the lines of the full Cannon model, while being simple enough to do some analysis.
- ✓ It displays normal to myotonia to paralysis type pathological behavior. The reduced model is easier to give precise conditions for each behavior.

- ✓ We need to consider if the (reduced) model is capable of suggesting relationships, e.g., pre-onset electrical activity that might have clinical value.

- ✓ The two-compartment approach is a drastic reduction of the actual anisotropic, inhomogeneous nature of the transverse-tubular system.

- ✓ Three-time scale problems can lead to mixed-mode oscillations and other behavior needing further mathematical elaboration.



T system network reconstruction from frog sartorius muscle fiber (Peachy & Eisenberg, Biophys. J. 1978)