Comments Concerning Models of Myelinated Fibers

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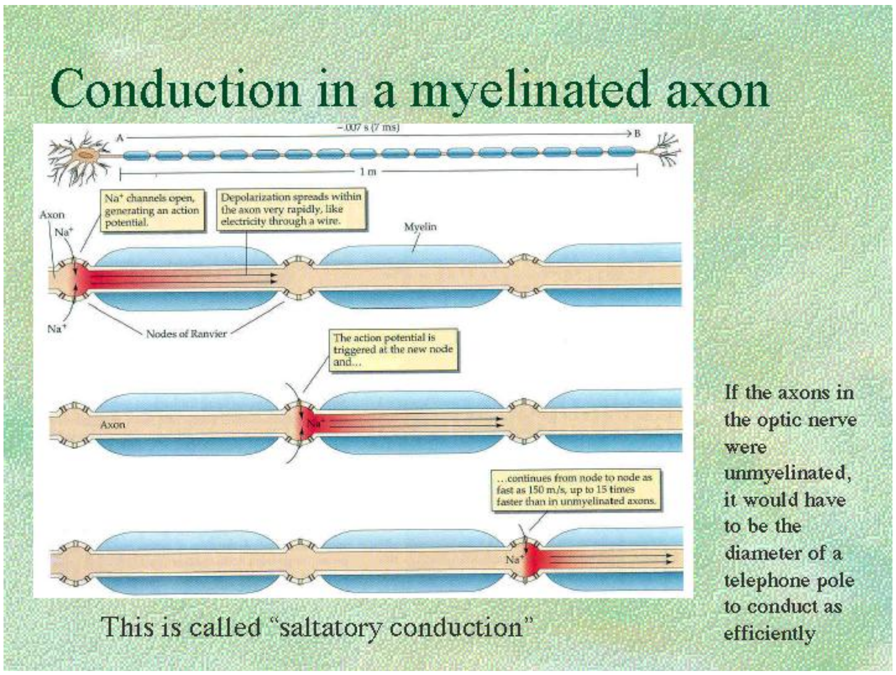
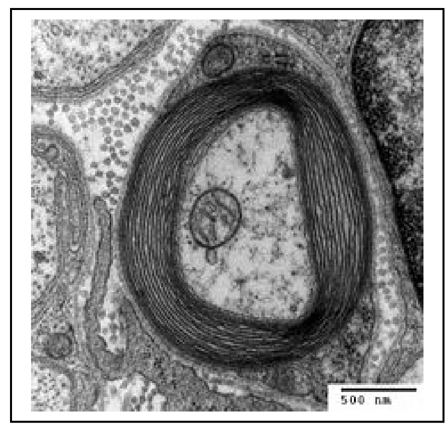
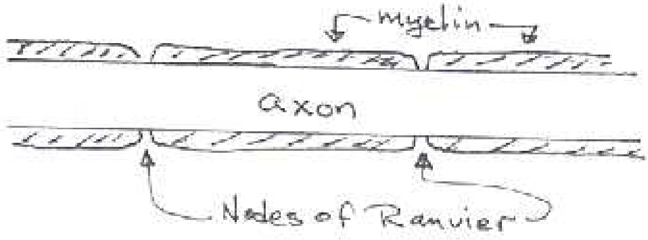




Outline:

1 Some background on myelinated neurons
2 Derivation of *Pure Saltatory Conduction* (PSC) model
3 Energy and Threshold results
4 Traveling wave solutions for PSC model without recovery
5 Some open questions
6 Derivation of *Lumped Myelinated Segment* (LMS) model
7 What has and has not been done on the LMS model
8 *Electrotonic diffusive* model
9 What has and has not been done on the this model

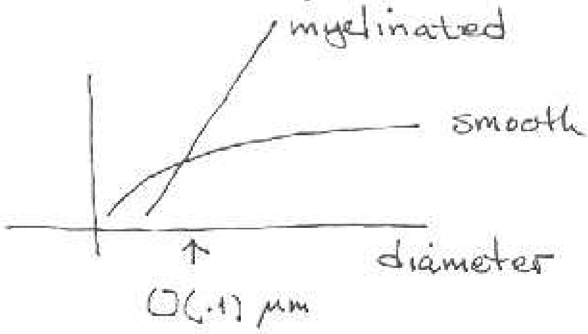
Myelination



1 At development stage axon, or dendrite, gets wrapped with Schwan cells, leaving "gaps" called nodes of Ranvier.

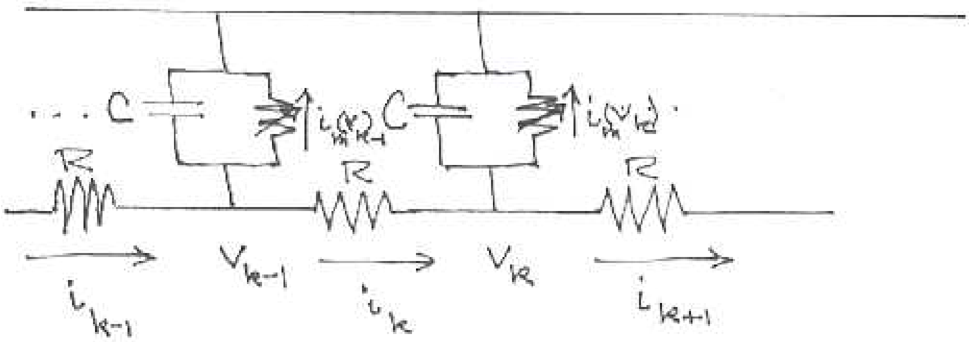
2. The nodes have high concentrations of potassium, sodium, and calcium ion channels. The internodes have relatively few channels.

3. Myelination allows longitudinal currents to excite only a very small percentage of active membrane, hence, increasing energy efficiency and propagation speed of impulses by orders of magnitude.



4. Demyelination associated with Alzheimers, Picks and other neurological diseases leading to dementia

Pure Saltatory Conduction (PSC) model



$$v_{k-1} - v_k = R i_k \qquad i_k - i_{k+1} = i_m(v_k) \doteq C\frac{dv_k}{dt} + I(v_k)$$

$$\rightarrow \quad C\frac{dv_k}{dt} + I(v_k) = \frac{1}{R}(v_{k-1} - 2v_k + v_{k+1})$$

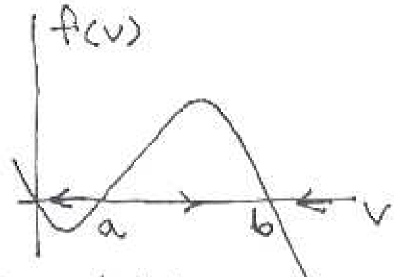
example dynamics : Fitz Hugh-Nagumo

$$(1) \quad \left\{ \boxed{\begin{aligned} \frac{dv_k}{dt} - f(v_k) + w_k &= v_{k-1} - 2v_k + v_{k+1} \\ \frac{dw_k}{dt} &= \sigma v_k - \gamma w_k \end{aligned}} \right.$$

or without recovery ($w_k \equiv 0$):

$$(2) \quad \boxed{\frac{dv_k}{dt} = f(v_k) + v_{k-1} - 2v_k + v_k}$$

remark: $v \equiv 0, a, b$ are equilibrium solutions



bistable

Sample results : $f(v) = v(1-v)(v-a)$ $F(v) \doteq \int_0^v f(s)ds$

Model (1)

Let $\{v_k, w_k\}$ = solution (1) and let

$$E_0(t) \doteq \sum_k \left\{ \frac{p}{2}(v_k - v_{k-1})^2 - pF(v_k) + \frac{d}{2}v_k + \frac{1}{2}(v_k + w_k)^2 + \frac{1}{2}K(v_k^2 + w_k^2) \right\}$$

Lemma 1: Suppose for some $t_0 \geq 0$, $\sup_k |v_k(t_0)| < a$, $E_0(t_0)^{1/2} < a$, then there is a set of parameters such that $\lim_{t \to \infty} v_k(t) = 0$ $\forall k$

$$E_1(t) \doteq \sum_k \left\{ \frac{1}{2}(v_k - v_{k-1})^2 - F(v_k) + \frac{1}{2}Av_k^2 - Bv_k w_k + \frac{1}{2}Cw_k^2 \right\}$$

Lemma 2: A, B, C can be chosen such if $\gamma^2 \geq \sigma$ and for some $t_0 \geq 0$ $E_1(t_0) < 0$, then for each $t \geq t_0$, $\exists\, l \in \mathbb{Z}$ such that $v_l(t) > a$.

Therefore, $\{v_k, w_k\} = \{0, 0\}$ is a local, but not global equilibrium solution.

Model (2) PSC model without recovery

By comparison principle arguments, if $\{v_k\}$ = solution to (2)

Lemma 3: If for some some $t_0 \geq 0$, $0 \leq v_k(t_0) \leq a_1$ for some $a_1 \in [0, a)$, then $\lim_{t \to \infty} v_k(t) = 0$ $\forall k \in \mathbb{Z}$.

Let $m \doteq \inf_{0 \leq v \leq 1} f(v)$ $M \doteq \sup_{0 \leq v \leq 1} f(v)$

Lemma 4: Suppose $\exists\, \alpha, \beta$, $a < \alpha < \beta < 1$, such that $2v - f(v) = 0$ for $v = \alpha, \beta$, $2v - f(v) < 0$ for $\alpha < v < \beta$. Suppose one of the following holds: (i) $2\alpha + m \leq \beta$; or (ii) $\alpha + 1 + M \leq 2\beta$. If $v_k(t_0) \geq 0$ $\forall k \in \mathbb{Z}$, and $v_l(t_0) \geq \alpha$ for some $l \in \mathbb{Z}$, then $\lim_{t \to \infty} v_k(t) = 1$ $\forall k \in \mathbb{Z}$.

Propagation for PSC model: $\frac{dv_k}{dt} = f(v_k) + v_{k-1} - 2v_k + v_{k+1}$

Assume $v_k(0) \in [0,1]$ $\forall k \in \mathbb{Z}$, $v_k(0) = 0$ for $|k| > J \geq 0$, $\lim_{t\to\infty} v_k(t) = 1$, $\forall k \in \mathbb{Z}$

mild conditions $\Rightarrow$ $\exists\, \bar{\theta} > 0$ such that $\theta > \bar{\theta} \Rightarrow \lim_{t\to\infty} v_{k \pm [\theta t]}(t) = 0$

$\exists\, \underline{\theta} > 0$ such that for $\theta < \underline{\theta} \Rightarrow v_{k\pm[\theta t]}(t) \to 1$

Suppose a threshold response has been initiated

Wave jumps from node to node

each succeeding node responds exactly like the previous node except for some time delay $\tau > 0$. $\therefore$

$$v_{k-1}(t) = v_k(t+\tau) \qquad i_{k-1}(t) = i_k(t+\tau) \qquad \forall k \ \forall t$$

$$\Rightarrow \frac{dv_k}{dt}(t) + I(v_k(t)) = v_{k-1}(t) - 2v_k(t) + v_{k+1}(t)$$

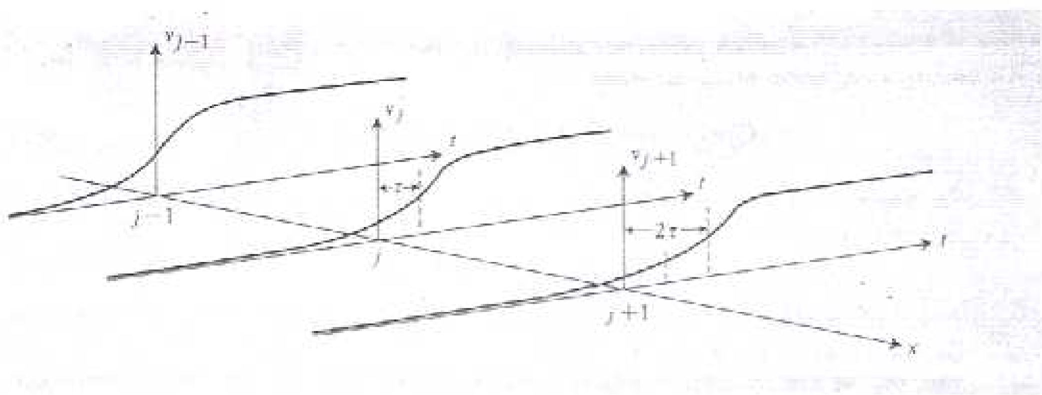
$$= v_k(t+\tau) - 2v_k(t) + v_k(t-\tau)$$

Let $\varphi(t) = v_k(t) \qquad w(t) = w_k(t)$

$$(3) \quad \boxed{\begin{cases} \frac{d\varphi}{dt}(t) - f(\varphi(t)) + w(t) = \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau) \\ \frac{dw}{dt}(t) = \sigma\varphi(t) - \gamma w(t) \end{cases}}$$

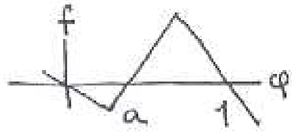
Special case: $w \equiv 0$ (no recovery)

$$(4) \quad \boxed{\frac{d\varphi}{dt}(t) = f(\varphi(t)) + \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau)}$$



I. Analytic solution : Let

$$f(\varphi) = \begin{cases} -\rho & \varphi < \frac{a\omega}{\omega+\rho} \\ \omega(\varphi - a) & \frac{a\omega}{\omega+\rho} < \varphi < \frac{\sigma + a\omega}{\omega+\sigma} \\ \sigma(1-\varphi) & \frac{\sigma+a\omega}{\omega+\sigma} < \varphi \end{cases}$$



Then a monotone solution to (4) with $\varphi(-\infty) = 0$, $\varphi(+\infty) = 1$ can be constructed from use of (i) boundary conditions at $\pm\infty$; (ii) continuity conditions for φ , $d\varphi/dt$ at $t = 0, t_1$; (iii) $\varphi(0) = \frac{a\omega}{\omega+\rho}$, $\varphi(t_1) = \frac{\sigma+a\omega}{\sigma+\omega}$ for determining 6 parameters plus t_1, τ

II. Numerical monotone solution for (4) :

$$\begin{cases} \frac{d\varphi}{dt}(t) = f(\varphi(t)) + \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau) \\ \varphi(-\infty) = 0 \ , \ \varphi(+\infty) = 1 \\ f(\varphi) = B\varphi(\varphi - a)(1-\varphi) \ , \ a \in (0, \tfrac{1}{2}] \end{cases}$$

1. Pick interval $[-L, L]$ to have (4) hold. Fix $\varphi(0) = 0.5$ to fix phase of wave solution

2. Develop asymptotic formulas for $\varphi(t)$ as $t \to \pm\infty$ so have high order approximations for $\varphi(\pm L)$

3. Pick a uniform step size h and a high-order approximation scheme for $d\varphi/dt$

4. For the delay/advance terms employ cubic interpolation $\varphi(t-\tau) \approx C_4\varphi(t-Mh-2h) + C_3\varphi(t-Mh-h) + C_2\varphi(t-Mh) + C_1\varphi(t-Mh+h)$ $M =$ integer part of τ/h . Do same for $\varphi(t+\tau)$.

5. Develop a nested iteration scheme, where τ is fixed during an inner loop. The outer loop is the solution to an equation $g(\tau) = 0$, which is solved via a secant method.

6. To converge to a good approximation, use a homotopy method by embedding problem in a one-parameter family of problems

$$(5)\quad \begin{cases} \dfrac{d\varphi}{dt}(t) = f_\alpha(\varphi(t)) + \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau) \\ \varphi(-\infty) = 0, \ \varphi(+\infty) = 1 \\ f_\alpha(\varphi) = \alpha f_\theta(\varphi) + (1-\alpha) f(\varphi) \qquad \alpha \in [0,1] \end{cases}$$

varying α from 1 to 0

$f_\alpha(\varphi)$ is defined so we have an exact solution to (5) when $\alpha = 1$.

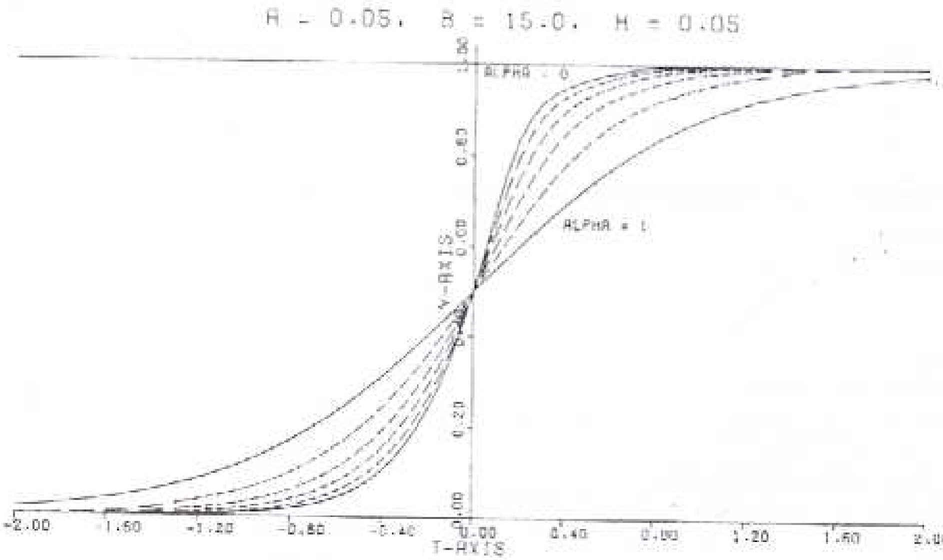


Fig. 4. Graph of solution changes when approaches to target problem from test problem with $\theta = 0.35$, $h = 0.05$, $a = 0.05$, $b = 15.0$

II. Another Analytic approach.

<u>Theorem</u> (Pedro and Lima, 2012): Consider a system of two mixed-type functional differential equations of the form

$$(*) \qquad \frac{dx}{dt} = A\,x(t-r) + B\,x(t+\tau) + D\,x(t) \qquad t \in \mathbb{R}$$

where A, B and D are 2x2 real-valued matrices, r & τ are positive constants. Suppose the following conditions are satisfied

1. $\det A = \det B = 0$

2. trace(A) and trace(B) are different from 0 and have the same sign.

Then system (*) has at least one nonoscillatory solution.

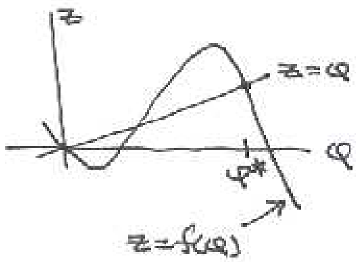
This is applicable to (3)

$$(3)\quad \begin{cases} \frac{d\varphi}{dt}(t) = f(\varphi(t)) - w(t) + \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau) \\ \frac{dw}{dt}(t) = \sigma\,\varphi(t) - \gamma\,w(t) \end{cases}$$

$$\varphi(-\infty) = 0 = w(-\infty), \quad \varphi(+\infty) = \varphi^*, \quad w(+\infty) = w^* \doteq \sigma\varphi^*/\gamma$$

$$\varphi^* = f(\varphi^*)$$

linearize system about $(\varphi, w) = (0,0), (\varphi^*, w^*)$



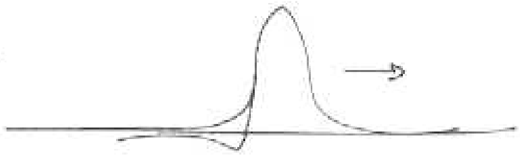
$$A = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}, \quad D = \begin{bmatrix} -2+c & -1 \\ \sigma & -\gamma \end{bmatrix}$$

where c is either $f'(0)$ or $f'(\varphi^*)$.

Some Questions

example system (3) $\begin{cases} \dfrac{d\varphi}{dt} = f(\varphi(t)) - w(t) + \varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau) \\ \dfrac{dw}{dt} = \sigma\varphi(t) - \gamma w(t) \end{cases}$

1. non-nonoscillatory solutions
   and traveling wave solutions
   $(\varphi(t), w(t)) \to (0,0)$ as $t \to \pm\infty$



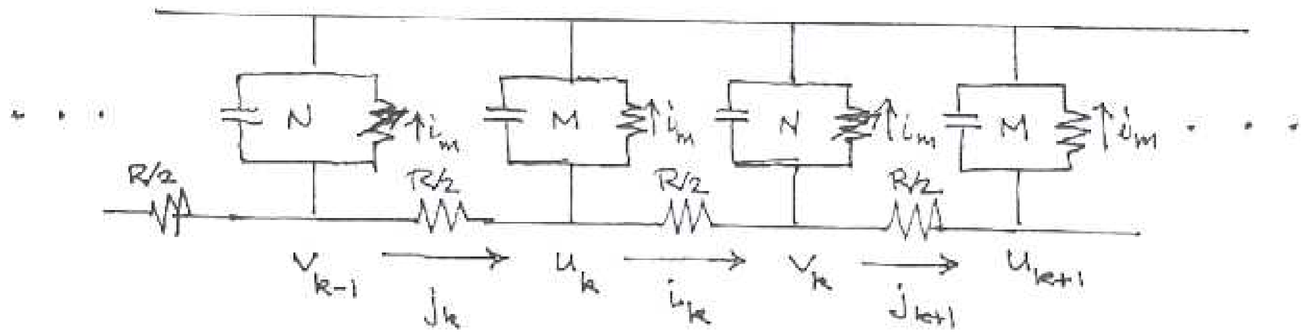
   existence
   stability and parameter dependence

2. traveling wave trains $(\varphi(t), w(t))$ periodic
   anything about them

3. Safety factor "kill" one or more successive nodes
   still get successful propagation
   of signals ?

4. More general dynamics, other applications, etc.

Lumped Myelinated Segment (LMS) model



$u_k - v_k = \frac{R}{2} i_k$ $\qquad\qquad$ $j_k - i_k = i_m(u_k)$

$v_{k-1} - u_k = \frac{R}{2} j_k$ $\qquad\qquad$ $i_k - j_{k+1} = i_m(v_k)$ $\qquad \Longrightarrow$

$$(6) \quad \begin{cases} \frac{2}{R}(v_{k-1} - 2u_k + v_k) = i_m(u_k) \doteq C_M \frac{du_k}{dt} + I_M(u_k) \\ \frac{2}{R}(u_k - 2v_k + u_{k+1}) = i_m(v_k) \doteq C_N \frac{dv_k}{dt} + I_N(v_k) \end{cases}$$

$I_N(v) = -f(v) + w$ $\qquad\qquad$ $I_M(u) = gu$

Observe: $g \to 0$, $C_M \to 0$ $\quad \Rightarrow \quad u_k = \frac{v_{k-1} + v_k}{2}$ so

$$u_k - 2v_k + u_{k+1} = \frac{v_{k-1} + v_k}{2} - v_k \quad \Longrightarrow$$

$$\frac{1}{R}(v_{k-1} - 2v_k + v_{k+1}) = C_N \frac{dv_k}{dt} + I_N(v_k)$$

i.e. recover PSC model

Travel wave solutions for LMS model, FitzHugh dynamics without recovery

at arbitrary node k $\qquad \varphi(t) = V_k(t)$ $\qquad G = 2/R$

$\qquad\qquad\qquad\qquad\qquad \psi(t) = u_k(t)$

$$(7) \quad \boxed{\begin{cases} \dfrac{d\varphi}{dt}(t) = f(\varphi(t)) + G\{\psi(t) - 2\varphi(t) + \psi(t-\tau)\} \\[2mm] \dfrac{d\psi}{dt}(t) = -g\psi(t) + G\{\varphi(t+\tau) - 2\psi(t) + \varphi(t)\} \end{cases}} \qquad t \in \mathbb{R}$$

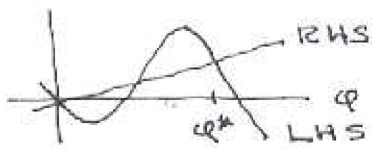
equilibrium states (φ^*, ψ^*): $2G(\psi^* - \varphi^*) + f(\varphi^*) = 0 = 2G(\varphi^* - \psi^*) - g\psi^*$

so

$$(8) \qquad \varphi(-\infty) = 0, \quad \psi(-\infty) = 0, \quad \varphi(+\infty) = \varphi^*, \quad \psi(+\infty) = \psi^*$$

$\psi^* = \dfrac{2G\varphi^*}{g+2G}$, $\varphi^* \in (0,1)$ is the largest solution to

$f(\varphi^*) = 2g\,\varphi^*/(g+2G)$



What has been done:

A. For the piecewise linear f given above, a smooth monotone solution to (7)-(8), $(\varphi(t), \psi(t))$, can be constructed.

$$\psi^* = \frac{2\sigma G}{2G(\sigma+g)+\sigma g} \qquad \text{and for } \varphi^*$$

solvability condition: $\dfrac{2gG}{g+2G} \leq \dfrac{\sigma\omega(1-a)}{\sigma+a\omega}$

B. The numerical scheme for the PSC model was modified to obtain approximate solutions $(\varphi(t), \psi(t), \tau)$ to LMS model.

<u>Electrotonic</u> <u>Diffusive</u> model (FitzHugh circuit)

$$(9)\quad \left\{ \boxed{\begin{array}{l} C_M \frac{\partial u}{\partial t} + g u = \frac{1}{R}\frac{\partial^2 u}{\partial x^2} \\ C_N \frac{\partial v_n}{\partial t} + I(v_n) = [\![\frac{\partial u}{\partial x}]\!]_{x_n} \end{array}} \right. \quad \begin{array}{l} x \in \mathbb{R},\ x \neq x_n = nL,\ n \in \mathbb{Z},\ t > 0 \\ t > 0,\ n \in \mathbb{Z}, \\ v_n(t) = \lim_{x \to x_n} u(x,t) \quad \forall t \end{array}$$

Let $I(v) = -f(v)$

By comparison principle argument

if $u(x,0) \in [0,\alpha]$ for $\alpha \in [0,a)$ $\forall$ all x

then $u, v_n \to 0$ as $t \to \infty$ (for all x)

There exists at "large" solution to

$$0 = \frac{d^2 q}{dx^2} - Rg\, q = 0 \qquad x \neq x_n$$

$$0 = f(q) + [\![\frac{dq}{dx}]\!]_{x_n} \qquad n \in \mathbb{Z}$$

say $Q_f(x)$

Then we have conditions such that

$$\lim_{t \to \infty} u(x,t) = Q_f(x) \qquad \forall x$$

Let $\sigma \doteq \sup_{0<v<1} \{ f(v)/v \}$

Let $\bar{\theta} \doteq \sigma / \sqrt{g+\sigma}$

if $\theta > \bar{\theta}$, then $\lim_{t \to \infty} u(x \pm [\theta t], t) = 0$

We have also derived conditions for "$u(x \pm [\theta t], t) \to Q_f(x)$" as $t \to \infty$.

Final Comments ! ?

I. LMS model

a. What new behavior can come from LMS vs PSC model?

b. PSC – reduced $\dot{\varphi}(t) = f(\varphi(t)) + d\{\varphi(t-\tau) - 2\varphi(t) + \varphi(t+\tau)\}$
if d too small $\nexists$ traveling wave front solution
same for LMS model ?

c. existence of various types of solutions
qualitative results

II. Electrotonic Diffusion model

essentially nothing known rigorously about the model.