Stability of a travelling nerve impulse

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Outline of the talk

1. The model studied and its features. Why Hodgkin-Huxley or FitzHugh-Nagumo?
2. A travelling wave solution: properties and features
3. Stability of a travelling wave: the Evans function and its construction.

Original references

Hodgkin-Huxley: 1952 **A quantitative description of membrane current** (J. Physiol)

Cole, Antosiewicz, Rabinovitz: **Automatic computation** 1955

FitzHugh, 1961: **Impuses and physiological states in theoretical models of nerve membrane**

Evans and Shank 1970: **Solution to axon equations** (Biophys. J)

Evans 1970-1975: **The stability of the nerve influx** (4 papers Indiana Math. J.)

Hastings 1975: **On travelling wave solutions of the HH eqs.**

1 Modeling of the problem

1.1 Electrophysiological model

Membrane current density $I = C_M \partial_t V + I_K + I_{Na} + I_l$:
Channel currents I_K, I_{Na}, I_l, Capacitance current $C_M \partial_t V$(the membrane being a dielectric with large conductivity), with
$I_K = \bar{g}_K n^4 (V - V_K), I_{Na} = \bar{g}_{Na} m^3 h (V - V_{Na}), I_l = \bar{g}_l (V - V_l)$.
The quantities n, m, h represent probabilities of fluxes of ions through the membrane, satisfying:

$$\partial_t n = \lambda_n(V)(n_\infty(V) - n)$$

$\lambda_n(V) = 0.1 \frac{1+\frac{V}{10}}{e^{1+\frac{V}{10}} - 1} + \frac{1}{8} e^{\frac{V}{80}}$, $(n_\infty(V))^{-1} = 1 + \frac{5}{4} e^{\frac{V}{80}} \frac{e^{1+\frac{V}{10}} - 1}{1+\frac{V}{10}}$
(similar expressions and relations for m and h).

Let $N_\infty(V) = (n_\infty(V), m_\infty(V), h_\infty(V))^T$

For $(n, m, h) = N_\infty(V)$**,** $I_K + I_{Na} + I_l = 0$ **iff** $V = 0$

Numerical values $\bar{g}_K = 36, \bar{g}_{Na} = 120, \bar{g}_l = 0.333,$
$V_K = 12mV, V_{Na} = -115mV, V_l = -10.613mV$
$n_\infty(0) = 0.317, m_\infty(0) = 0.0529, h_\infty(0) = 0.596$
$I_K = -4.36mAcm^{-2}$, $I_{Na} = 1.21mAcm^{-2}$, $I_l = 3.18mAcm^{-2}$
and $\bar{g}_K(n_\infty(0))^4 = 0.363mmho.cm^{-2}$,
$\bar{g}_{Na}(m_\infty(0))^3 h_\infty(0) = 0.0105mmho.cm^{-2}$.

Gauss law and application on the mean of the potential in the axoplasm

$$\frac{2}{\sigma r}\frac{\partial^2 V}{\partial x^2} = I.$$

1.2 Hodgkin-Huxley equation and PDE system

Introduce $g(n,m,h) = \bar{g}_K n^4 + \bar{g}_{Na} m^3 h + \bar{g}_l > 0$,
$S(n,m,h) = \bar{g}_K n^4 V_K + \bar{g}_{Na} m^3 h V_{Na} + \bar{g}_l V_l$,

$$\frac{2}{\sigma r} \frac{\partial^2 V}{\partial x^2} = C_M \partial_t V + g(n,m,h)V - S(n,m,h). \tag{1}$$

Introduce $N = (n,m,h)$, $\Lambda(V) = \mathrm{Diag}(\lambda_n(V), \lambda_m(V), \lambda_h(V))$.
System of Hodgkin-Huxley equations ($X = x\sqrt{\frac{\sigma r}{2}}$)

$$\left\{ \begin{array}{l} \partial_t V - \partial^2_{X^2} V = -g(n,m,h)V + S(n,m,h) = -g(N)V + S(N) \\ \partial_t N^T = \Lambda(V)(N_\infty(V) - N^T) \end{array} \right. \tag{2}$$

2 Aim of the study of this system

Q1: Stability at rest $V = 0$?

Q2: Existence of progressive solutions $V(t - \frac{X}{s})$?

Q3: Stability of such a progressive solution?

Why study FitzHugh-Nagumo system:

$$\begin{cases} \partial_t V - \partial^2_{X^2} V = c(y + V - \frac{V^3}{3}) \\ \partial_t y = -c^{-1}(V - a + by) \end{cases} ? \tag{3}$$

- give rise to a Hopf bifurcation when considering the associated system of ODE $\partial_t V = c(y + V - \frac{V^3}{3}), \partial_t y = -c^{-1}(V - a + by)$ under conditions $1 - \frac{2b}{3} < a < 1, 0 < b < 1, b < c^2$ for which there is only one equilibrium point which is a stable node.
- be the simplest non trivial nonlinear system appearing when taking into account the behavior of $\lambda_n(V)$ and $\lambda_h(V)$ (which are small) $\Rightarrow$ study of the system

$$\begin{cases} \partial_t V - \partial^2_{X^2} V = -g(n_\infty(V), m, h_\infty(V))V + S(n_\infty(V), m, h_\infty(V)) \\ \partial_t m = \lambda_m(V)(m_\infty(V) - m) \end{cases} \tag{4}$$

3 Study of the rest point $V = 0$

Linearized system at rest:

$$\begin{cases} \partial_t v - \partial^2_{X^2} v = -g(N_\infty(0))v + \nabla S(N_\infty(0)).\tilde{n} \\ \partial_n \tilde{n} = \Lambda(0)(N'_\infty(0)v - \tilde{n}) \end{cases}$$

For FitzHugh-Nagumo system one has

$$\begin{cases} \partial_t v - \partial^2_{X^2} v = c((1 - x_0^2)v + y) \\ \partial_t y = -c^{-1}(bv + y) \end{cases}$$

Exponential stability at rest and construction of the Evans function are consequences of the properties of the matrix

$$A(\tau) = \begin{pmatrix} -g(N_\infty(0)) - \tau & \nabla S(N_\infty(0)) \\ \Lambda(0) N'_\infty(0) & -\Lambda(0) \end{pmatrix}.$$

$$\text{(respectively)} A_f(\tau) = \begin{pmatrix} c(1-x_0^2) - \tau & c \\ -\frac{b}{c} & -\frac{1}{c} \end{pmatrix}.$$

Properties $A = A(0) = \begin{pmatrix} a & r \\ c & -\Lambda(0) \end{pmatrix}$ has four eigenvalues of negative real part. Moreover $A(\tau)$ has no imaginary eigenvalues for $\tau \geq 0$.

The eigenvalues or $A(\tau)$ are solution of

$R(\lambda) - \tau = -g(N_\infty(0)) - \tau - \lambda + \nabla S(N_\infty(0))(\Lambda(0) + \lambda I)^{-1} \Lambda(0) N'_\infty(0) = 0.$

Note that for $A_f(\tau)$ the result is similar.

Theorem 1 *The system (2) is exponentially stable at rest iff all eigenvalues of $A(\xi^2)$ stay in the half plane $\Re\lambda \leq -\kappa < 0$. It is equivalent to the exponential stability of the linearized system.*

This is the consequence of the properties of the eigenvalues and of the representation of the solution of the system as

$$W_\xi(t) = F \star D + \begin{pmatrix} 0 & 0 \\ 0 & e^{-t\Lambda} \end{pmatrix} D, D = W_\xi(0),$$

where $F(\xi, t) = e^{tA(\xi^2)} - \begin{pmatrix} 0 & 0 \\ 0 & e^{-t\Lambda} \end{pmatrix}$ is exponentially controlled,

hence

$$||W_\xi(t)|| \leq C||W_\xi(0)||e^{-\kappa t}.$$

4 Travelling wave construction

Q2: Travelling wave $(V_0(t-\frac{X}{s}), n_0(t-\frac{X}{s}), m_0(t-\frac{X}{s}), h_0(t-\frac{X}{s}))$.
Dynamical system

$$\begin{cases} V_0' - \frac{1}{s^2}V_0'' = -g(N_0)V_0 + S(N_0) \\ N_0' = \Lambda(V_0)(N_\infty(V_0) - N_0) \end{cases} \tag{5}$$

It is equivalent to

$$\frac{d}{d\tau}\begin{pmatrix} V_0 \\ W_0 \\ N_0 \end{pmatrix} = \begin{pmatrix} s^2 W_0 \\ -g(N_0)V_0 + S(N_0) + s^2 W_0 \\ \Lambda_0(V_0)(N_\infty(V_0) - N_0) \end{pmatrix} \tag{6}$$

Linearized system around $(0,0,n_\infty(0),m_\infty(0),h_\infty(0))^t$,
$U=(\tilde{V},s^{-2}\tilde{V}',\tilde{n},\tilde{m},\tilde{h})^t$:

$$U'=\begin{pmatrix} 0 & s^2 & 0 & 0 & 0 \\ -a & s^2 & -r_1 & -r_2 & -r_3 \\ c_1 & 0 & -\lambda_1 & 0 & 0 \\ c_2 & 0 & 0 & -\lambda_2 & 0 \\ c_3 & 0 & 0 & 0 & -\lambda_3 \end{pmatrix} U = M(s^2)U.$$

The eigenvalues of this matrix are solution of $R(\lambda)=\frac{\lambda^2}{s^2}$, that is $\lambda\in\mathrm{Sp}(A(-\frac{\lambda^2}{s^2}))$. No imaginary eigenvalue. Only one eigenvalue $\lambda_0(s^2)>s^2$ in $\Re>0 \Rightarrow$ unstable manifold of dimension 1, stable manifold of dimension 4.

Construction of the unstable wave

Theorem 2 *For all $s \neq 0$ there exist two solutions $\phi_+(\tau)$ et $\phi_-(\tau)$ such that all solutions of (5) which go to 0 at $-\infty$ are $U = \phi_+(\tau - \tau_0)$ or $U = \phi_-(\tau - \tau_0)$.*

Constructive proof: The eigenvector E_+ associated with $\lambda_0(s^2)$ is

$$E_+ = (1, \frac{s^2}{\lambda_0(s^2)}, \frac{c_1}{\lambda_1 + \lambda_0(s^2)}, \frac{c_2}{\lambda_2 + \lambda_0(s^2)}, \frac{c_3}{\lambda_3 + \lambda_0(s^2)})^t$$

As (2) writes $U' = F'(U_\infty)(U - U_\infty) + R(U - U_\infty)$ construct a Picard sequence: $\begin{cases} Y^K_{n+1}(\tau) = U_\infty + \int_{-\infty}^{\tau} R(Y_n(\tau') - U_\infty)d\tau' \\ Y^K_0(\tau) = U_\infty + KE_+e^{\lambda_0(s^2)\tau} \end{cases}$. As $Y^K(\tau) = Y^1(\tau - \frac{1}{\lambda_+(s^2)} \ln|K|)$, we define the two solutions associated with $K > 0$ and $K < 0$.

Finding a travel speed

A travelling wave solution is in the intersection of the unstable manifold and the stable manifold.

- Stable manifold: dimension 4: implicit equation

$\Phi_{s^2}(V, W, n, m, h) = 0$.

Condition for the travel speed: $\Phi_{s^2}(\phi_+(\tau)).\Phi_{s^2}(\phi_-(\tau)) = 0$.

- Numerics: impossible as an IVP: stiff (large eigenvalues) problem.

Possible as a BVP: non zero solution satisfying the four conditions at $\tau = -T$ and one condition at $\tau = T$ (not yet done)

Remark: it is the solution of a minimization problem coupled with the ODEs (work in progress):

$$s^{-2}V'' = V' + g(N)V - S(N) \Leftrightarrow -s^{-2}u'' + (g(N) + \frac{s^2}{4})u = S(N)e^{-\frac{s^2}{2}t}$$

on $H^1([T_0, +\infty[)$. Coercivity constant $\alpha = min(s^{-2}, g_l + \frac{s^2}{4})$.

Construction of the stable manifold:

Let P_{s^2} be the matrix of eigenvectors of $M(s^2)$ (in the order positive e.v. and e.v. of negative real part). Let us write $F = P_{s^2}^{-1}U$. The dynamical system writes $F' = D(s^2)F + g(F, s^2)$, F solution of

$$\begin{aligned} F(t) &= U_1(t)(a_1, a_2, a_3, a_4, 0)^T + \int_0^t U_1(t-t')g(F(t'), s^2)dt' \\ &- \int_t^{+\infty}(0,0,0,0,g_5(F(t'), s^2))^T e^{\lambda_0(s^2)(t-t')}dt'. \end{aligned} .$$

This functional equation has a unique solution when initial value $(a_1, a_2, a_3, a_4, 0)^T$ is given. One has $F_5(0, a) = -\int_0^\infty g_5(F(t', a), s^2)e^{\lambda_0(s^2)(t-t')}dt'$ (equation of the stable manifold).

Q3: Stability of solutions of

$$\left\{\begin{array}{l} v_0' + s^{-2}v_0'' + (-g(n_0)v_0 + S(n_0)) = 0 \\ n_0' + \Lambda_\infty(v_0)(n_\infty(v_0) - n_0) = 0 \end{array}\right. ?$$

System in the adapted variables: $\xi = \frac{x}{s} - t$, t

$$\left\{\begin{array}{l} \partial_\xi v + s^{-2}\partial^2_{x^2} v + [-g(n)v + S(n)] = \partial_t v \\ \partial_\xi n + \Lambda_\infty(v)(n_\infty(v) - n) = \partial_t n \end{array}\right. \tag{7}$$

If one derivates the system on v_0, n_0 one gets

$$\left\{\begin{array}{l} v_0'' + s^{-2}v_0''' - g(n_0)v_0' + (-g'(n_0)v_0 + S'(n_0))n_0' = 0 \\ n_0'' + [\Lambda_\infty'(v_0)(n_\infty(v_0) - n_0) + \Lambda_\infty(v_0)n_\infty'(v_0)]v_0' - \Lambda_\infty(v_0)n_0' = 0. \end{array}\right.$$

This system writes

$$\begin{pmatrix} v_0' \\ n_0' \end{pmatrix}' + s^{-2}\begin{pmatrix} v_0' \\ 0 \end{pmatrix}'' + B(\xi)\begin{pmatrix} v_0' \\ n_0' \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \text{ where}$$

$B(\xi) = A(0) + P(\xi)$, $P(\xi) \to 0$ for $|\xi| \to +\infty$.

The linearization of (7) is

$$T_0\begin{pmatrix}\tilde v\\ \tilde n\end{pmatrix}=\begin{pmatrix}\tilde v\\ \tilde n\end{pmatrix}'+s^{-2}\begin{pmatrix}\tilde v\\ 0\end{pmatrix}''+B(y)\begin{pmatrix}\tilde v\\ \tilde n\end{pmatrix}=\partial_t\begin{pmatrix}\tilde v\\ \tilde n\end{pmatrix}.$$

Spectrum of operator T_0 gives the stability of the travelling wave. Introduce T_0^a the adjoint operator of T_0. The kernel of T_0^a is of dimension 1 (because (v_0', n_0') is in the kernel of T_0 and the dimension is 1). Denote by $\gamma(\xi)$ a function in $KerT_0^a$.

Evans showed that $\int \gamma(\xi).(v_0'(\xi), n_0'(\xi))d\xi = 0$ is equivalent to the existence of a ψ solution of $T_0\psi = (v_0'(\xi), n_0'(\xi))^T$.

Main result:

The system is exponentially stable at $\begin{pmatrix}v_0'(\xi)\\ n_0'(\xi)\end{pmatrix}$ iff

$\int \gamma(\xi).\begin{pmatrix}v_0'(\xi)\\ n_0'(\xi)\end{pmatrix}d\xi \neq 0$ and the maximum of the real parts of the $\lambda \neq 0$ such that $T_0\psi = \lambda\psi$ has a bounded solution is negative.

5 Evans function construction and formulation

5.1 Construction of the bounded solutions at ±∞ of the linearized system

$$\frac{d}{d\xi}\begin{bmatrix}\tilde{V}\\ \tilde{W}\\ \tilde{N}\end{bmatrix}+\begin{pmatrix}0 & s^2 & 0\\ a(\xi)-\lambda & -s^2 & r(\xi)\\ c(\xi) & 0 & -\Lambda(\xi)-\lambda I\end{pmatrix}\begin{bmatrix}\tilde{V}\\ \tilde{W}\\ \tilde{N}\end{bmatrix}=0 \quad (8)$$

$$-\frac{d}{d\xi}\begin{bmatrix}\tilde{V}^*\\ \tilde{S}^*\\ \tilde{N}^*\end{bmatrix}+\begin{pmatrix}0 & a(\xi)-\lambda & c^T(\xi)\\ s^2 & -s^2 & 0\\ 0 & r^T(\xi) & -\Lambda(\xi)-\lambda I\end{pmatrix}\begin{bmatrix}\tilde{V}^*\\ \tilde{S}^*\\ \tilde{N}^*\end{bmatrix}=0 \quad (9)$$

Uniqueness of the eigenvalue $\nu(\lambda)$ of positive real part of

$$\begin{pmatrix} 0 & s^2 & 0 \\ a-\lambda & -s^2 & r \\ c & 0 & -\Lambda-\lambda I \end{pmatrix}$$, $\Re\lambda > \delta_0 > 0$, eigenvector

$B_+ = (1, \frac{\nu(\lambda)}{s^2}, (\Lambda + (\lambda + \nu(\lambda))I)^{-1}c)^T$

and the eigenvector for the adjoint matrix

$B_- = (1 + \frac{\nu(\lambda)}{s^2}, 1, (\Lambda + (\lambda + \nu(\lambda))I)^{-1}r^T)^T$

Construction of the associated solution at $-\infty$ for the direct system (8) and the adjoint system (9) with a prescribed behavior at infinity:

$$||\beta(\lambda,\xi) - e^{\nu(\lambda)\xi}B_+|| + ||\beta^*(\lambda,-\xi) - e^{\nu(\lambda)\xi}B_-|| \leq Ce^{(\nu(\lambda)+\epsilon_0)\xi}$$

5.2 Definition of the Evans function

$$D(\lambda) = \beta(\lambda, \xi).\beta^*(\lambda, \xi), \forall \xi, \text{ independant of } \xi. \tag{10}$$

Properties:

Theorem 3 *a) The function* $D(\lambda)$ *is an analytic function, such that* $D(0) = 0$*.*
b) The system (2) is exponentially stable for the profile V_0 *with speed* s_0 *iff* $D(\lambda) \neq 0$ *for* $\lambda, \Re\lambda \geq 0, \lambda \neq 0$ *and* $\frac{\partial D}{\partial \lambda}(0) \neq 0$*.*
c) If $\frac{\partial D}{\partial \lambda}(0) > 0$*, no stability. If* $\frac{\partial D}{\partial \lambda}(0) < 0$*, one cannot conclude.*
d) The sign of $\frac{\partial D}{\partial \lambda}(0) > 0$ *is the sign of*

$$lim_{\xi \to -\infty} e^{\lambda_+(s_0^2)\xi} \begin{pmatrix} 1 + \frac{\lambda_+(s_0^2)}{s_0^2} \\ 1 \\ (\Lambda + (\lambda_+(s_0^2))I)^{-1} r^T \end{pmatrix} \partial_s U(s_0, \xi).$$

Note: λ root of order m of D iff λ eigenvalue of multiplicity m of T_0.

6 Conclusion and next steps

- Some physiological conclusions easy from a mathematical point of view (reversibility, invariance by translation,generation of this spontaneous influx with a small adapted disturbance)
- Numeric calculations of the 50' not convincing (cannot be reproduced easily with the methods of HH)
- Work in progress from a theoretical point of view and a numerical point of view
- Powerfulness of the Evans function and of the analysis of the stable manifold
- One feature of the Hodgkin-Huxley system has been forgotten: the equation of diffusion is linear in v.
- What about Evans formulation for FitzHugh-Nagumo?