The Neuron as a Dynamical System

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Geometry of Neuroscience

References for this lecture:

- Eugene M. Izhikevich, *Dynamical Systems in Neuroscience*, MIT Press, 2007.
- G. Bard Ermentrout, David H. Terman, *Mathematical Foundations of Neuroscience*, Springer, 2010.
- Yakov Pesin, Vaugham Climenhaga, *Lectures on Fractal Geometry and Dynamical Systems*, American Mathematical Society 2009.
- Tanya Kostova, Renuka Ravindran, Maria Schonbek, *FitzHugh-Nagumo Revisited: Types of Bifurcations, Periodical Forcing and Stability Regions by a Lyapunov Functional*, Internat. J. Bifur. Chaos Appl. Sci. Engrg. 14 (2004), no. 3, 913–925

- interplay of electrophysiology, bifurcation mechanism of dynamical systems, and computational properties of neurons
- neuron in terms of ions and channels
- neuron in terms of input/output relations
- neuron as a nonlinear dynamical system

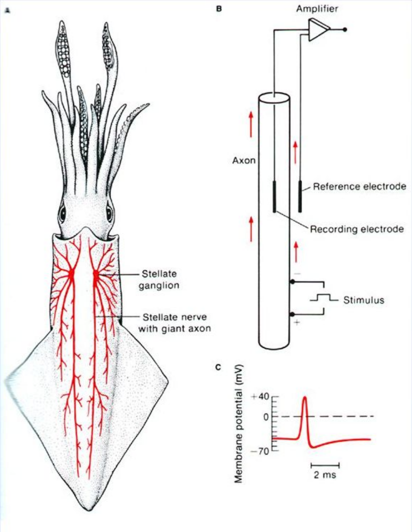
• dynamical system near a transition (bifurcation) resting/spiking activities

• deduce computational properties of neurons from studying *geometry* of phase portrait at the bifurcations of the nonlinear dynamical system

Properties of neurons

- about 10^{11} neurons in the human brain
- can transmit electric signals over long distances
- neuron receives input from more than 10^5 other neurons through synapses
- organized in neuronal circuits
- spikes main mean of communication between neurons
- firing threshold of neurons

Hodgkin-Huxley Model based on giant squid axon



Eckert: Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 5-21.

Deriving the Hodgkin-Huxley Equation

- all cells have a membrane potential $V_M = V_{in} - V_{out}$ difference of electric potential inside and outside the cell membrane
- resting potential = potential across the membrane when cell is at rest: typical neuron $-70mV$
- Sodium/Potassium channels: non-gated channels (always open) and voltage gated channels (open depending on conditions on membrane potential)
- inward current: positively charged ion entering membrane: Na^+ (raises membrane potential: depolarized)
- outward current: positively charged ion leaving the cell K^+, or negatively charged entering the cell Cl^- (hyperpolarized)

Nernst–Planck equation

- $C(x)$ concentration of some ion and $V(x)$ potential at some point $x \in M$ on membrane, diffusive flux J_{diff}, diffusion constant D (depends on size of molecules)

$$J_{diff} = -D \frac{\partial C}{\partial x}$$

  diffusion movement from high to low concentration

- Electrical drift: electric field $E = -\partial V / \partial x$, valence $z \in \mathbb{Z}$ of ion, μ mobility

$$J_{drift} = -\mu z C \frac{\partial V}{\partial x}$$

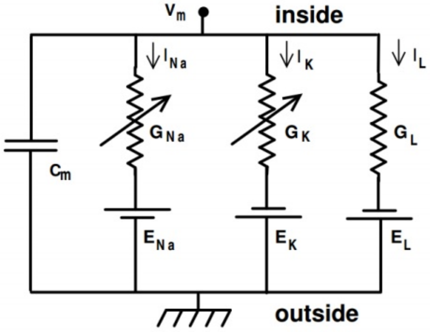
- total flux across membrane: $J = J_{diff} + J_{drift}$
- Einstein relation: mobility and diffusion coefficient

$$D = \frac{kT}{q} \mu$$

  Boltzmann constant k, temperature T, charge q

- corresponding current flux $=0$ is Nernst–Planck equation

Hodgkin-Huxley circuit



$$C_M \frac{dV_M}{dt} + I_{ion} = I_{ext}$$

- fraction p_i of open channels for ion i

$$\frac{dp_i}{dt} = \alpha_i(V)(1 - p_i) - \beta_i(V) p_i$$

Hodgkin-Huxley Equation

in Hodgkin-Huxley model of giant squid axon:

- persistent voltage gated K^+ current four activation gates
- transient voltage gated Na^+ current three activation gates
- leak current Cl^-

activation variables n, m (probability of activation gate open), inactivation variable h (probability of inactivation gate open)

$$C_M \frac{dV_M}{dt} = -g_K n^4 (V_M - E_K) - g_{Na} m^3 h (V_M - E_{Na}) - g_L (V_M - E_L)$$

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

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

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

Propagation of the Action Potential $V = V_M(x,t)$

$$C\frac{\partial V}{\partial t} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} + I - I_K - I_{Na} - I_L$$

with a radius of axon, R resistance of axoplasm, and with currents as above $I = g m^a h^b (V - E)$ gate model

- nonlinearities in $\alpha(V)$ and $\beta(V)$

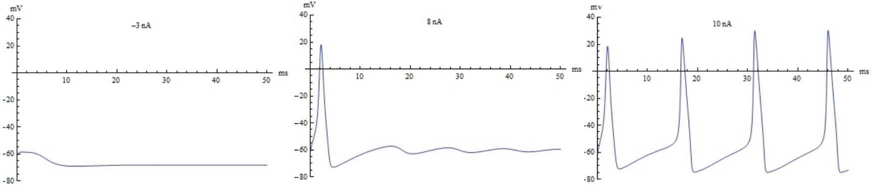
$$\alpha_n(V_m) = \frac{0.01(V_m+10)}{\exp\left(\frac{V_m+10}{10}\right)-1} \qquad \alpha_m(V_m) = \frac{0.1(V_m+25)}{\exp\left(\frac{V_m+25}{10}\right)-1} \qquad \alpha_h(V_m) = 0.07\exp\left(\frac{V_m}{20}\right)$$

$$\beta_n(V_m) = 0.125\exp\left(\frac{V_m}{80}\right) \qquad \beta_m(V_m) = 4\exp\left(\frac{V_m}{18}\right) \qquad \beta_h(V_m) = \frac{1}{\exp\left(\frac{V_m+30}{10}\right)+1}$$

numerical treatment of equations

Injected current I as bifurcation parameter

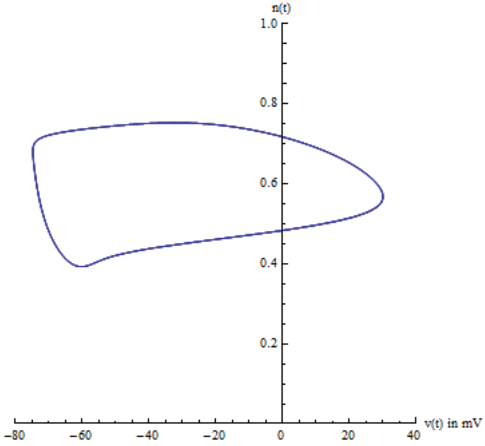
Shape of $V(t)$ for increasing I (in nanoamps): not firing, firing a single spike, cycle with train of spikes, sudden jump in amplitude not gradual increase (bifurcation phenomenon)



• Hodgkin–Huxley linearization at fixed point: two negative eigenvalues and two complex eigenvalues (small positive real part)

• eigenvectors of negative eigenvalues evolve to zero (large t)

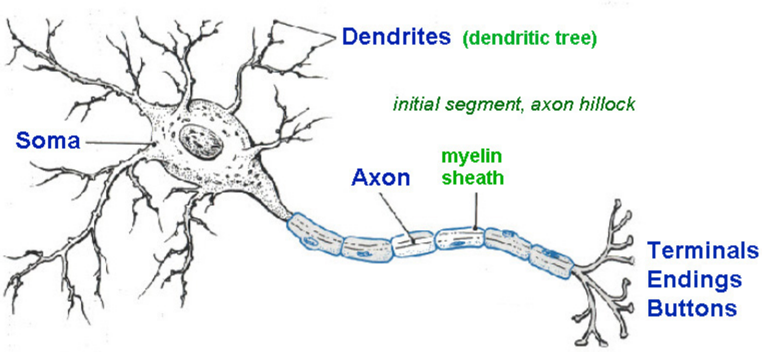
• eigenvectors of complex eigenvalue define center manifold: solutions in 4-dim system flow towards center manifold in 2-dim plane; limit cycle in center manifold plane



FitzHugh–Nagumo Model

(simplified version of the Hodgkin-Huxley dynamics, 1961)

• neuron receiving signals along dendrites, processed in the soma, single output along the axon



- voltage difference at one location in axon affects time evolution of voltage differences at nearby locations
- action potential propagates along the length of the axon
- model time evolution of the action potential at a given site on the axon
- model diffusion of action potential along axon

Heuristics on the form of the equation: $u(t)$ action potential at a particular site on the axon

• damped harmonic oscillator (linear)

$$\ddot{u} + \zeta \dot{u} + cu = 0$$

ζ constant: measures how oscillations are damped

• first order form

$$\begin{aligned} \dot{u} &= -\zeta u - v \\ \dot{v} &= cu \end{aligned}$$

• more refined model: nonlinear damped harmonic oscillator: constant ζ replaced by function of u

$$\ddot{u} + \zeta(u^2 - 1)\dot{u} + cu = 0$$

van der Pol equation (circuits)

$$\dot{u} = -\zeta \left(u - \frac{u^3}{3} \right) - v$$
$$\dot{v} = cu$$

first order form, with $\dot{v} = -\ddot{u} + \zeta(\dot{u} - u^2 \dot{u})$

• FitzHugh–Nagumo model based on a version of the nonlinear damped harmonic oscillator

Bonhoeffer- van der Pol nonlinear damped harmonic oscillator

$$\dot{u} = u - \frac{u^3}{3} - v + I$$
$$\dot{v} = cu - \gamma - dv$$

with parameters γ, c, d to be set empirically, and external forcing term $I = I(t)$

• FitzHugh–Nagumo equation

$$\dot{u} = ag(u) - bv + I$$
$$\dot{v} = cu - dv$$

with $g(u)$ a cubic polynomial $g(u) = -u(u - \theta)(u - 1)$
• this only models action potential in time at a fixed site (no varying spatial dimension), to include dependence on spatial coordinate $u = u(x, t)$

$$\frac{\partial u}{\partial t} = ag(u) - bv + I + \kappa \frac{\partial^2 u}{\partial x^2}$$
$$\frac{\partial v}{\partial t} = cu - dv$$

used for propagation of signals (traveling waves) in excitable media

Discrete modeling of FitzHugh–Nagumo for numerical simulations

- fixed increment $\Delta > 0$
  - time derivative $\Delta^{-1}(u(x,t+\Delta) - u(x,t))$
  - space second derivative $\Delta^{-2}(u(x+\Delta,t) - 2u(x,t) + u(x-\Delta,t))$
- obtain a finite difference equation $u_k(n) = u(k\Delta, n\Delta)$

$$u_k(n+1) = u_k(n) - Au_k(n)(u_k(n)-\theta)(u_k(n)-1) - \alpha v_k(n) + \kappa U(n)$$
$$v_k(n+1) = \beta v_k(n) + \gamma v_k(n)$$

coefficients $A = a\Delta$, $\alpha = b\Delta$, $\beta = c\Delta$, $\gamma = 1 - d\Delta$ and diffusion term (from space second derivative)

$$U(n) = \Delta^{-1}(u_{k+1}(n) - 2u_k(n) + u_{k-1}(n))$$

without external forcing

- empirical assumption: α, β small, θ near $1/2$ and $\gamma < 1$ near one this type of discrete system: Coupled Map Lattice

- only u, v on a discrete set: lattice $\Delta\mathbb{Z} \times \Delta\mathbb{Z} \subset \mathbb{R} \times \mathbb{R}$
- any time step modeled by a local map $f = (f_1, f_2) : \mathbb{R}^2 \to \mathbb{R}^2$

$$f_1(u, v) = u - Au(u - \theta)(u - 1) - \alpha v$$
$$f_2(u, v) = \beta u + \gamma v$$

- local maps at each site coupled together by interaction terms like U

Coupled Map Lattices are a useful method for studying PDEs

Main problem is controlling the error term that can grow rapidly after a number of iterations

Local Map

$$f : (u, v) \mapsto \begin{cases} u - Au(u-\theta)(u-1) - \alpha v \\ \beta u + \gamma v \end{cases}$$

• Fixed point analysis: $(u, v) = (0, 0) = f(0, 0)$ fixed point for all values of parameters

$$v = \frac{\beta}{1-\gamma} u, \quad Au(u-\theta)(u-1) + \frac{\alpha\beta}{1-\gamma} u = 0$$

(real) solutions of second equation

$$u = \frac{1}{2}\left(\theta + 1 \pm \sqrt{(\theta-1)^2 - \frac{4\alpha\beta}{A(1-\gamma)}}\right)$$

discrimimant is nonnegative iff $A \geq A_0$

$$A_0 = \frac{4\alpha\beta}{(1-\gamma)(1-\theta)^2}$$

• $0 < A < A_0$ only one fixed point $(u, v) = (0, 0)$; $A = A_0$ one additional fixed point; $A > A_0$ origin and two more fixed points

• change of behavior of the equation at the threshold $A = A_0$

• Stability of fixed points: $Df = (\frac{\partial f_i}{\partial x_j})_{ij}$ Jacobian matrix describes linear approximation in neighborhood of fixed points

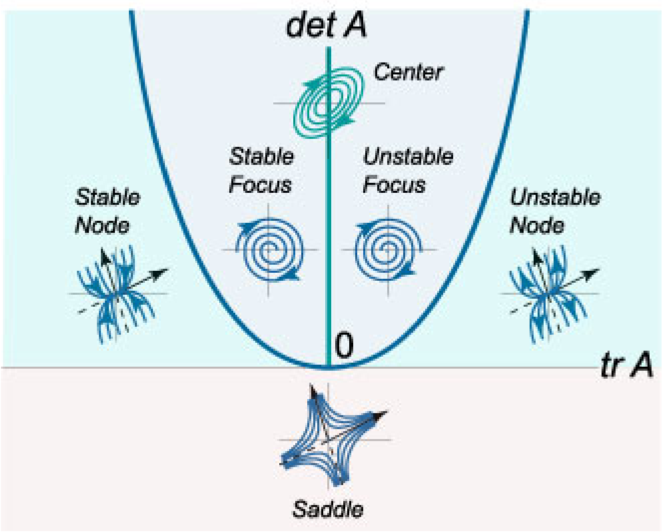
$$f(\underline{x}) = f(\underline{p}) + Df(\underline{p})(\underline{x} - \underline{p}) + R(\underline{x} - \underline{p})$$

error term R (nonlinearities) sufficiently small if sufficiently near fixed point $\underline{p}$

• Two dimensional cases: $T : \mathbb{R}^2 \to \mathbb{R}^2$ linear map, with eigenvalues μ, λ not on unit circle

- $|\lambda| \leq |\mu| < 1$: attractive fixed point $(0, 0)$
- $|\lambda| < 1 < |\mu|$: saddle point $(0, 0)$
- $1 < |\lambda| \leq |\mu|$: repelling fixed point $(0, 0)$

Behavior changes across discriminant curve $\mathrm{Tr}(A)^2 - 4\det(A) = 0$



Fixed point stability for two dimensional systems $A = Df(\underline{p})$

FitzHugh–Nagumo linearization

$$Df(u,v) = \begin{pmatrix} 1 - A\theta + 2A(1+\theta)u - 3Au^2 & -\alpha \\ \beta & \gamma \end{pmatrix}$$

eigenvalues at (u,v) of fixed point give stability

• if α, β sufficiently small eigenvalues approximated by γ and value of $1 - A\theta + 2A(1+\theta)u - 3Au^2$ at fixed point

• at fixed point $(u,v) = (0,0)$ eigenvalue close to γ and $1 - A\theta$: have $|1 - A\theta| < 1$ for $0 < A < 2/\theta = A_1$

- for $0 < A < A_1$ and $\gamma < 1$: attracting fixed point $(0,0)$
- for $A > A_1$ and $\gamma < 1$: saddle point $(0,0)$
- have $A_1 > A_0$ so when stability of $(0,0)$ changes have already two more fixed points

• stability at other fixed point: approximate location of fixed points and approximate value of Df

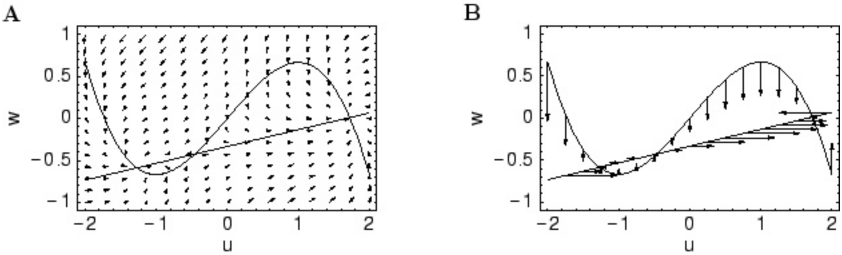
• fixed points on cubic $v = -\frac{A}{\alpha} u(u-\theta)(u-1)$: points of intersection of this cubic curve with the line $v = u\beta/(1-\gamma)$

• if β very small (compared to $1-\gamma$) line almost horizontal and fixed points approximated by intersection of cubic curve with $v = 0$: fixed points approximated by $(0,0)$, $(\theta, 0)$, $(1,0)$

• at $(\theta, 0)$: eigenvalues of linearization Df approximately γ and $1 + A\theta - A\theta^2$, since $0 < \theta < 1$, second eigenvalue > 1 and saddle point for all A

• at $(1,0)$: eigenvalues of linearization Df approximately γ and $1 + A\theta - A$; second eigenvalue > 1 when $0 < A < 2/(1-\theta) = A_2$, for $A < A_2$ attractive fixed point, for $A > A_2$ saddle

cubic curve and line and stability of fixed points

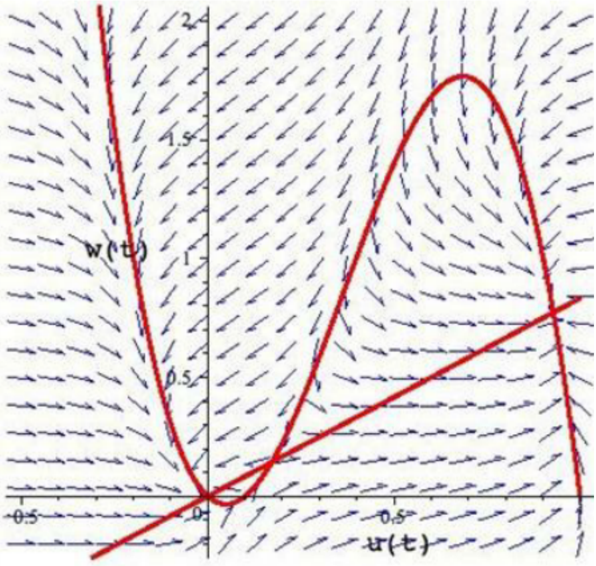


Cases:

- $A_0 < A < \min\{A_1, A_2\}$: three fixed points: origin stable, first fixed point saddle and second stable; trajectory approaching first fixed point *separatrix* between basins of attraction of origin and second fixed point

- value before A_1 where second eigenvalue $1 - A\theta$ at origin changes sign, reverses direction of left/right motion of trajectories near origin
- similar reversal at second fixed point near $A \sim 1/(1-\theta)$
- if $A_1 < A_2$ origin changes behavior to saddle before second fixed point
- in this range what happens to trajectories now leaving the origin in near horizontal direction? first fixed point also saddle repelling in horizontal direction...
- fixed point linear approximation incomplete picture: also look at behavior of periodic orbits! trajectories leaving origin attracted by a periodic orbit period 2, $f(f(u,v)) = (u,v)$, that appears around origin when $A > A_1$

• Morse-Smale system: a dynamical system where finitely many periodic orbits (including fixed points) and all orbits converge to a periodic orbit



2
1.5
1
0.5
0
-0.5
0.5
w(t)
u(t)

Period Doubling

• FitzHugh-Nagumo model is a Morse–Smale dynamical system in range of parameter A discusses above

• when further increasing the value of the parameter A beyond $\max\{A_1, A_2\}$ orbit of order 2 stops being attractive, two further points of order 4 appear near each (now unstable) order 2 point: new attractive period 4 orbit

• cascade of period doubling: the period 4 orbits becomes unstable giving rise of a stable period 8 orbit etc. with stable period 2^n becoming unstable and new stable period 2^{n+1} orbit emerging from the bifurcation

• numerical estimates indicate bifurcation values A_n of the parameter A converge to a value A_∞ when $n \to \infty$

• the dynamical system is Morse–Smale in the range $A < A_\infty$

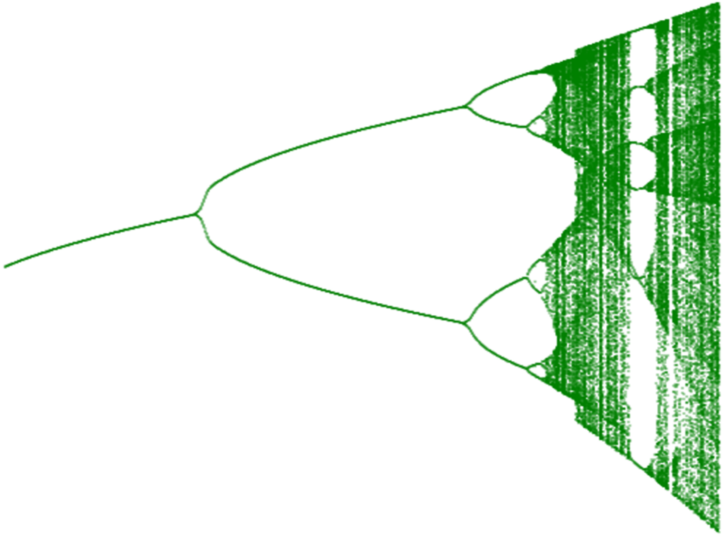
• in fact two sequences of such periodic orbits: one around $(0,0)$ to the left of the stable curve through the first fixed point $\sim (\theta, 0)$ and one for the second fixed point $\sim (1,0)$ to the right of the stable curve through the first fixed point

Constructing Bifurcation Diagrams

- Fix a value of parameter A and an initial condition (u, v) (near origin)
- Compute a sufficiently large number of iterates
- Plot resulting position $f^n(u, v)$
- Repeat for other values of A
- Repeat whole process for other initial conditions (near second fixed point, near other fixed points where expect to find period doubling cascade)

Typically one such bifurcation diagram (near one of the fixed points involved) looks like the following picture

Bifurcation Diagrams



Cascade Bifurcations and Chaos Theory

• What is happening in these diagrams beyond the period doubling series, for $A \geq A_\infty$: see a much more complicated behavior and periodic orbits of periods other than 2^n; also find orbits dense in a Cantor set, not approaching periodic orbit

• universal behavior: $A_n - A_{n-1} \sim C\delta^n$ Feigenbaum constant δ (universal constant)

• Sharkovsky's ordering of the natural numbers:

$$3 < 5 < 7 < 9 < 11 < \cdots$$

$$< 2 \cdot 3 < 2 \cdot 5 < 2 \cdot 7 < 2 \cdot 9 < 2 \cdot 11 < \cdots$$

$$< 2^n \cdot 3 < 2^n \cdot 5 < 2^n \cdot 7 < 2^n \cdot 9 < 2^n \cdot 11 < \cdots$$

$$\cdots < 2^n < 2^{n-1} < \cdots < 8 < 4 < 2 < 1$$

• Sharkovsky's theorem: if a continuous map $h : \mathbb{R} \to \mathbb{R}$ has a periodic point of period $m \in \mathbb{N}$, then it also has periodic points of any period $n \in \mathbb{N}$ where $n > m$ in the Sharkovsky's ordering

• if a map $h : \mathbb{R} \to \mathbb{R}$ has only finitely many periodic orbits then all have periods powers of 2

• the result requires $h : \mathbb{R} \to \mathbb{R}$ (based on Mean Value Theorem), not true for maps $h : \mathbb{C} \to \mathbb{C}$ (for instance, eg $h(z) = e^{2\pi i/n} z$ where all periodic orbits period n)

• Sharkovsky's theorem very useful result to explain cascade period doubling phenomena by reducing to a one-dimensional dynamics

• Tien-Yien Li; James A. Yorke, *Period Three Implies Chaos*, The American Mathematical Monthly, Vol. 82, No. 10. (Dec., 1975), pp. 985–992

• period three implies infinitely many periodic orbits of arbitrary periods in $\mathbb{N}$ and sensitive dependence on initial conditions for orbits (which do not necessarily converge to a periodic orbit anymore)

• typical behavior past $A \geq A_\infty$ at the end of the period doubling cascade: chaos region with arbitrary periodic orbits

Bifurcation Diagrams in the FitzHugh–Nagumo model varying A

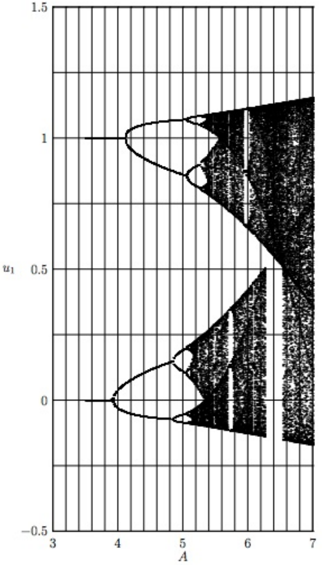
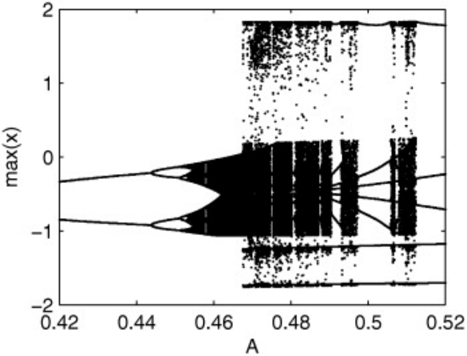


FIGURE 31. The bifurcation diagram for the discrete FitzHugh–Nagumo model (76) with $\theta = .51$, $\alpha = .01$, $\beta = .02$, and $\gamma = .8$, as A varies from 3 to 7.

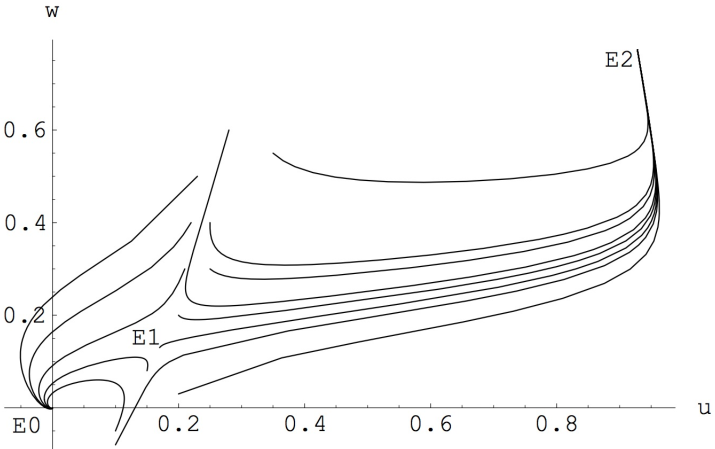
Bifurcation Diagram in the FitzHugh–Nagumo model for electric potential $x = u$ as function of varying parameter A



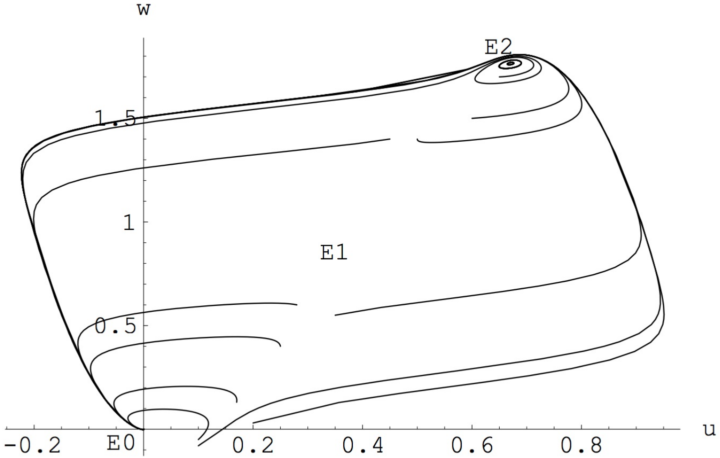
from

http://iopscience.iop.org/article/10.1088/1367-2630/12/5/053040

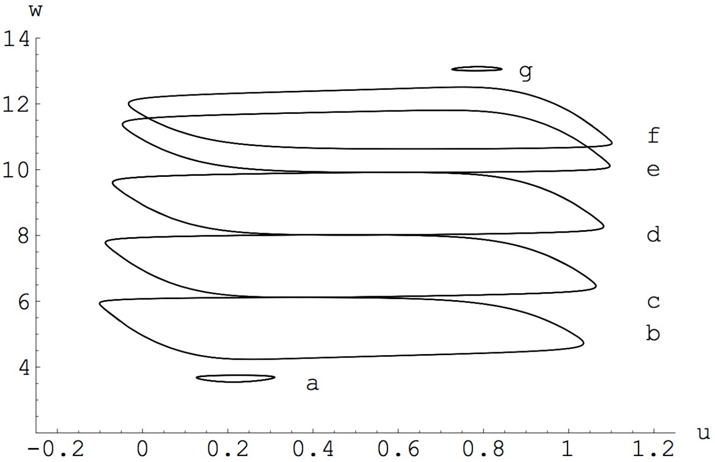
In terms of trajectories $(u(t), v(t))$ of the original continuous FitzHugh–Nagumo ODE



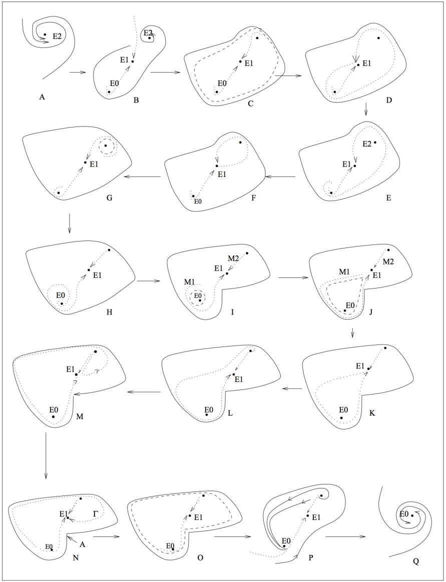
fixed points E_0 and E_2 are stable and E_1 is unstable



fixed points E_0 and E_2 are stable, with an unstable periodic orbit around E_2

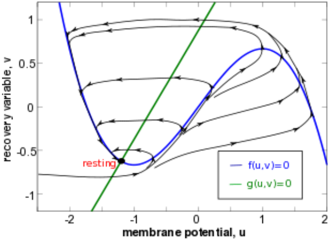


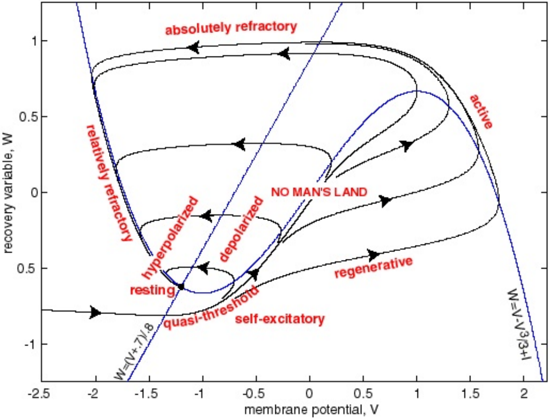
with also an external forcing I: limit cycle appears through Hopf bifurcation near E_0, moves upward with increasing I and disappears in another Hopf bifurcation near E_2

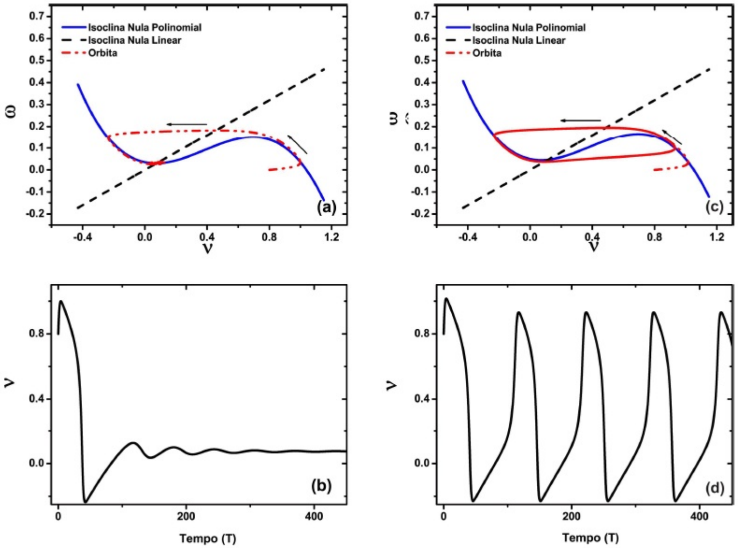


a sequence of orbits for descrasing values of I

Resulting picture of the model






Isoclina Nula Polinomial
Isoclina Nula Linear
Orbita
(a)
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ω
ν
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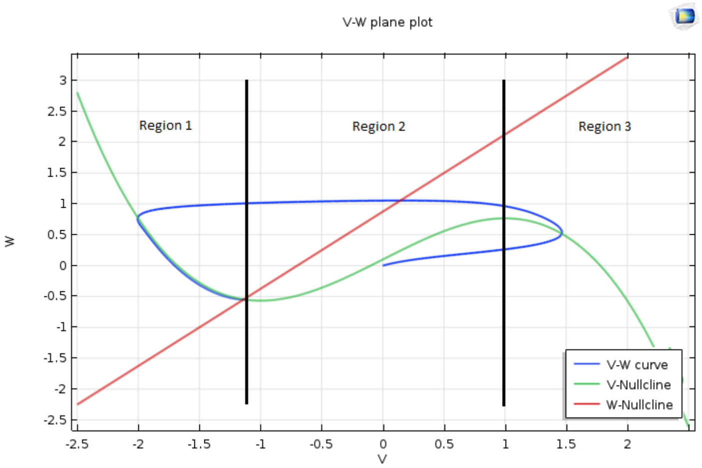
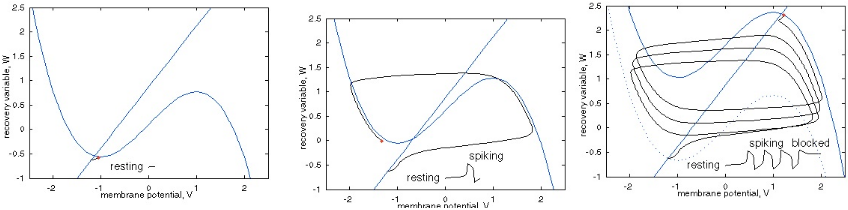
Tempo (T)



with external forcing term I move the cubic curve and the intersections with line

Varying external forcing



Conclusion

- Single neuron is a complicated nonlinear dynamical system
- Spiking behavior arises from bifurcation pattern and stability properties of equilibria (fixed points) and occurrence of limiting cycles
- Varying parameters (injected current J and parameter A) creates pattern of bifurcations
- Possibility of bifurcation cascades and chaos

We will later deal with larger neuronal architectures beyond single neuron case