1 The Single Neuron

Qualitative features of the dynamics of excitable/oscillatory processes are shared by broad classes of neuronal models. These features are expressed in models for single cell behavior and they include excitability and threshold behavior, beating and bursting oscillations, bistability and hysteresis, etc.

Our goal here is to illustrate, by exploiting specific models of excitable membrane, some of the concepts and techniques which can be used to understand, predict, and interpret these dynamic phenomena. The mathematical methods to be used include, graphical/geometric representation of the dynamics (phase plane analysis), and analytic formulae for characterizing thresholds and stability conditions. The concepts are from the qualitative theory of nonlinear differential equations and nonlinear oscillations, and from perturbation and bifurcation theory. The topics we will cover include steady states, trajectories, limit cycles, stability, domains of attraction, and bifurcation of solutions.

1.1 Models of the single neuron

Here we review some important models of single neuron dynamics and describe their behaviour to constant current injection.

Hodgkin-Huxley

The standard dynamical system for describing a neuron as a spatially isopotential cell with constant membrane potential V is based upon conservation of electric charge, so that

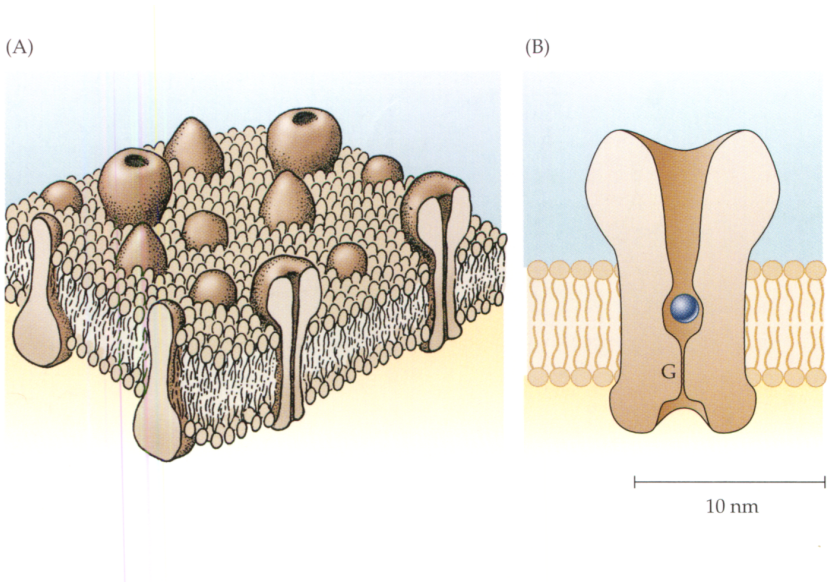
$$C\frac{dV}{dt} = -F + I_s + I$$

where C is the cell capacitance, F the membrane current, I_s the sum of external synaptic currents entering the cell and I describes any external injected currents. In the Hodgkin-Huxley model (1952) the membrane current arises mainly through the conduction of sodium and potassium ions through voltage dependent channels in the membrane. The contribution from other ionic currents is assumed to obey Ohm's law. In fact F is considered to be a function of V and of three time and voltage dependent conductance variables m, n and h:

$$F(V, m, n, h) = g_L(V - V_L) + g_K n^4(V - V_K) + g_{Na} h m^3(V - V_{Na})$$

where g_L, g_K and g_{Na} are constants and V_L, V_K and V_{Na} represent the constant membrane reversal potentials associated with the leakage, potassium and sodium channels respectively. The conductance variables m, n and h take values between 0 and 1 and approach the asymptotic values $m_\infty(V)$, $n_\infty(V)$ and $h_\infty(V)$ with time constants $\tau_m(V)$, $\tau_n(V)$ and $\tau_h(V)$ respectively. Summarizing, we have that

$$\tau_X(V)\frac{dX}{dt} = X_\infty(V) - X, \qquad \text{with } X \in \{m, n, h\}$$



Ionic gates are embedded in the cell membrane and control the passage of ions.

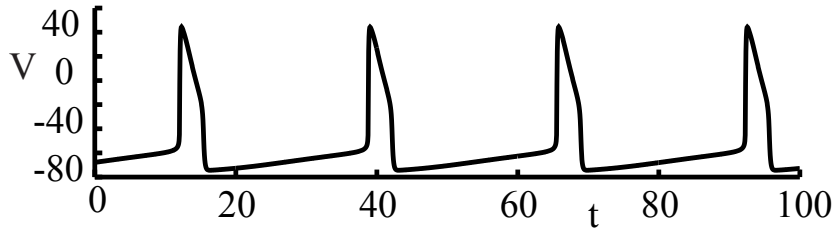
The six functions $\tau_X(V)$ and $X_\infty(V)$, $X \in \{m, n, h\}$, are obtained from fits with experimental data. It is common practice to write

$$\tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}, \qquad X_\infty(V) = \alpha_X(V)\tau_X(V)$$

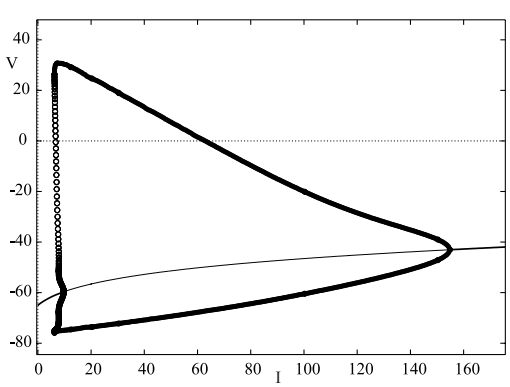
The details of the final Hodgkin-Huxley description of nerve tissue are completed with:

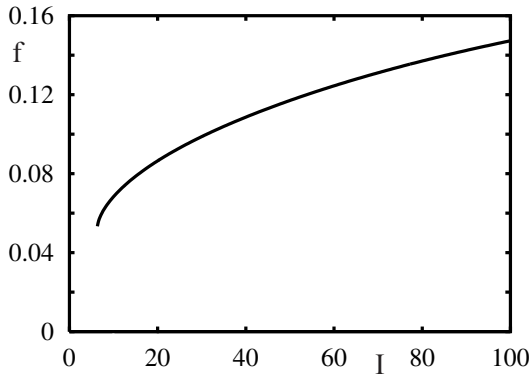
$$\alpha_m(V) = \frac{0.1(V+40)}{1-\exp[-0.1(V+40)]} \qquad \alpha_h(V) = 0.07\exp[-0.05(V+65)]$$
$$\alpha_n(V) = \frac{0.01(V+55)}{1-\exp[-0.1(V+55)]} \qquad \beta_m(V) = 4.0\exp[-0.0556(V+65)]$$
$$\beta_h(V) = \frac{1}{1+\exp[-0.1(V+35)]} \qquad \beta_n(V) = 0.125\exp[-0.0125(V+65)]$$

$C = 1\mu F\ cm^{-2}$, $g_L = 0.3mmho\ cm^{-2}$, $g_K = 36mmho\ cm^{-2}$, $g_{Na} = 120mmho\ cm^{-2}$, $V_L = -54.402mV$, $V_K = -77mV$ and $V_{Na} = 50mV$. (All potentials are measured in mV, all times in ms and all currents in μA per cm^2).



Periodic spike train that can be generated by the HH model under constant current injection.





Left: Bifurcation diagram of the Hodgkin-Huxley model as a function of the external drive I. Black circles show amplitude of stable limit cycle, open circles indicate unstable limit cycle behaviour. Solid line shows stable fixed point, thin line shows unstable fixed point behaviour. Right: Frequency of oscillation as a function of external drive.

Moris-Lecar

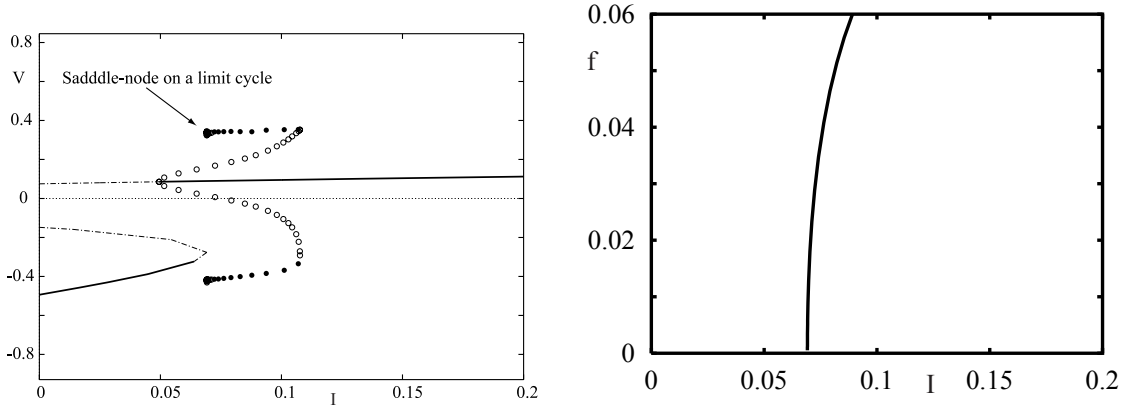
Under constant current injection barnacle muscle fibers respond with a host of oscillatory voltage waveforms. To describe this system Morris and Lecar (1981) introduced a set of coupled ODEs incorporating two ionic crrents: an outward going, noninactivating potassium current and an inward going, noninactivating calcium current. Assuming that the calcium currents operate on a much faster time scale than the potassium current one they formulated the following two dimensional system:

$$\frac{dV}{dt} = I - g_L(V - V_L) - g_K w(V - V_K) - g_{Ca} m_\infty(V)(V - V_{Ca}) \equiv I + f_1(V, w)$$
$$\frac{dw}{dt} = \lambda(V)(w_\infty(V) - w) \equiv f_2(V, w)$$

with

$$m_\infty(V) = 0.5(1 + \tanh[(V - V_1)/V_2])$$
$$w_\infty(V) = 0.5(1 + \tanh[(V - V_3)/V_4])$$
$$\lambda(V) = \phi \cosh[(V - V_3)/(2V_4)]$$

w represnts the fraction of K^+ channels open, and the Ca^{2+} channels respond to V so rapidly that we assume instantaneous activation. Here g_L is the leakage conductance, g_K, g_{Ca} are the potassium and calcium conductances, V_L, V_K, V_{Ca} are corresponding reversal potentials, $m_\infty(V)$, $w_\infty(V)$ are voltage-dependent gating functions and $\lambda(V)$ is a voltage-dependent rate. V_1, V_2, V_3, V_4 and ϕ are constants given by $V_k = -0.7$, $V_L = -0.5$, $V_{Ca} = 1$, $g_K = 2$, $g_L = 0.5$, $V_1 = -0.01$, $V_2 = 0.15$, $g_{Ca} = 1.33$, $V_3 = 0.1$, $V_4 = 0.145$ and $\phi = 1/3$.



Left: Bifurcation diagram of the type I Morris-Lecar model as a function of the external drive J. Black circles show amplitude of stable limit cycle, open circles indicate unstable limit cycle behaviour. Solid line shows stable fixed point, thin line shows unstable fixed point behaviour. Note the saddle-node on a limit cycle bifurcation at $I \approx 0.06925$. Right: Frequency of oscillation as a function of external drive.

Linearisation

Suppose that a is a fixed point of $\dot{x} = f(x)$ so that $f(a) = 0$. Expand f locally as a Taylor series in $u = x - a$:

$$\dot{u}_i = f_i(u + a) = f_i(a) + \sum_j \frac{\partial f_i}{\partial x_j}(a) u_j + O(u^2)$$

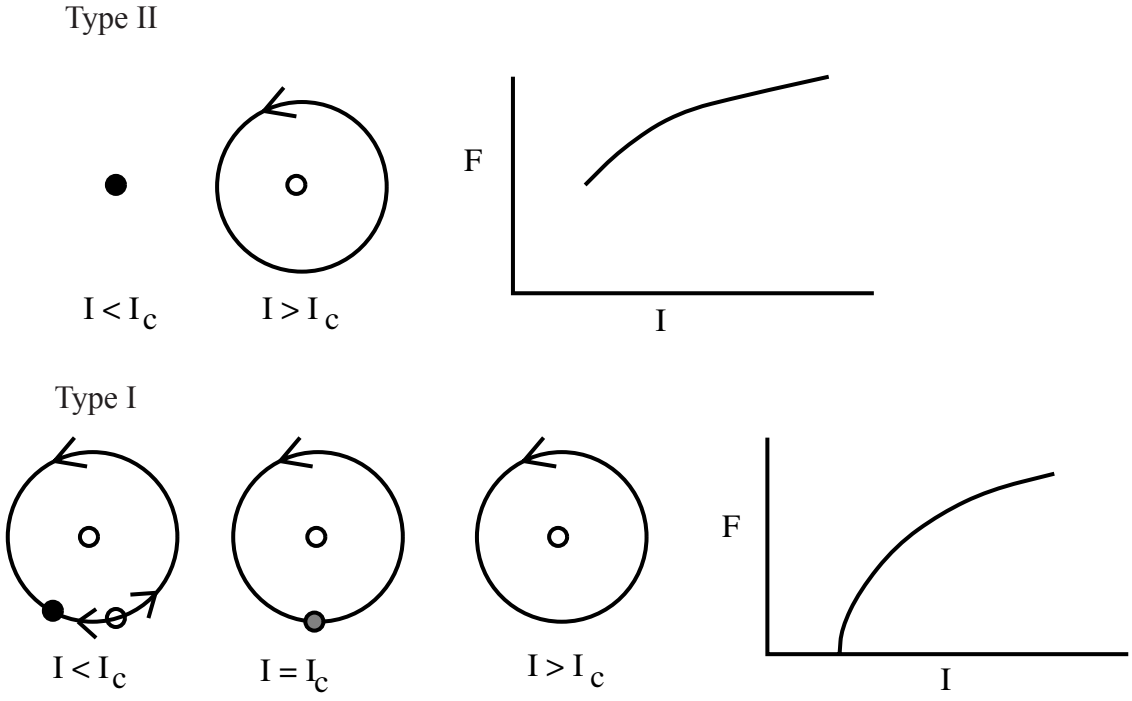
Since $f_i(a) = 0$ by assumption,

$$\dot{u} = Au + O(u^2), \quad A_{ij} = [Df(a)]_{ij} = \frac{\partial f_i}{\partial x_j}(a)$$

Theorem (linear stability): Suppose that $\dot{x} = f(x)$ has an equilibrium at $x = a$ and the linearisation $\dot{x} = Ax$. If A has no zero or purely imaginary eigenvalues then the local stability of the fixed point is determined by the linear system (hyperbolic fixed point). In particular, if all eigenvalues have a negative real part $\mathrm{Re}\ \lambda_i < 0$ for all $i = 1, \ldots, n$ then the fixed point is asymptotically stable.

1.2 Mathematical reductions and canonical models

A number of conductance based models can exhibit a saddle-node on a limit cycle bifurcation signalling a transition from an excitable to an oscillatory regime as the strength of applied current is increased (eg Moris-Lecar). Such behavior is an example of *Class I neural excitability* since oscillations with arbitrarily low frequency can occur in a neighborhood of the bifurcation point and is common to may cortical neuron models. The firing rate as a function of the current is $f \sim \sqrt{I - I_c}$ near the critical value I_c of the current. This should be contrasted with *Class II neural excitability* where the onset of repetitive firing is at a non-zero frequency as observed in the Hodgkin-Huxley equations, for example, when an excitable state loses stability via a subcritical Hopf bifurcation.



Firing rate functions of neurons and the onset of rhythmicity. Type II: Subcritical Hopf bifurcation. Type I: Saddle-node limit cycle bifurcation. (Solid points are stable, open are unstable nodes, and grey are saddles.)

Linear systems in $\mathbb{R}^2$

$$\dot{x}_1 = ax_1 + bx_2$$
$$\dot{x}_2 = cx_1 + dx_2$$

Introduce the vector $x = (x_1, x_2)^T$, then

$$\dot{x} = Ax, \qquad A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

Try a solution of the form $x = e^{\lambda t}x_0$. This leads to the linear homogeneous equation

$$(A - \lambda I_2)x_0 = 0$$

where I_2 is the 2×2 identity matrix. For the system above to have a non-trivial solution we require that

$$\boxed{\det(A - \lambda I_2) = 0}$$

which is called the *characteristic equation*. Substituting the components of A into the characteristic equation gives

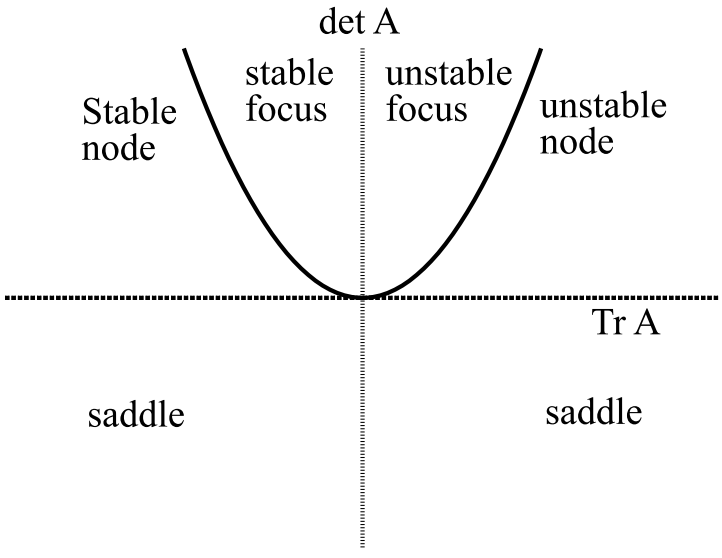
$$\lambda^2 - (a + d)\lambda + (ad - bc) = 0$$

so that

$$\boxed{\lambda_\pm = \frac{1}{2}\left[\operatorname{Tr} A \pm \sqrt{(\operatorname{Tr} A)^2 - 4 \det A}\right]}$$

We classify the different types of behaviour according to the values of $\operatorname{Tr} A$ and $\det A$.

- $\lambda_\pm$ are real if $(\operatorname{Tr} A)^2 > 4 \det A$.
- Real eigenvalues have the same sign if $\det A > 0$ and are positive if $\operatorname{Tr} A > 0$ (negative if $\operatorname{Tr} A < 0$) — **stable and unstable nodes**.
- Real eigenvalues have opposite signs if $\det A < 0$ — **saddle node**.
- Eigenvalues are complex if $(\operatorname{Tr} A)^2 < 4 \det A$ — **focus**.



Hopf bifurcation theorem

The Hopf bifurcation involves a nonhyperbolic fixed point with linearised eigenvalues $\pm i\omega$, with a 2-D centre manifold and bifurcating solutions which are periodic rather than stationary. Consider the system

$$\dot{x} = \mu x - \omega y - (x^2 + y^2)x$$
$$\dot{y} = \omega x + \mu y - (x^2 + y^2)y$$

Linearising about the origin shows that the origin is a stable focus if $\mu < 0$ and an unstable focus if $\mu > 0$ (since the eigenvalues of the linearised flow are $\mu \pm i\omega$.) Hence, the origin is nonhyperbolic when $\mu = 0$ and a bifurcation is expected as μ passes through zero. This is easily analysed in polars where

$$\dot{r} = \mu r - r^3, \qquad \dot{\theta} = \omega$$

Consider a dynamical system of the form

$$\dot{x} = f(x, y, \mu), \qquad \dot{y} = g(x, y, \mu)$$

with $f(0, 0, \mu) = g(0, 0, \mu) = 0$. Suppose that the following conditions hold

A The Jacobian matrix

$$L = \begin{bmatrix} \partial_x f & \partial_y f \\ \partial_x g & \partial_y g \end{bmatrix}$$

evaluated at the origin when $\mu = 0$ has a pair of pure imaginary eigenvalues:

$$L = \begin{bmatrix} 0 & -\omega \\ \omega & 0 \end{bmatrix}$$

This is equivalent to the conditions

$$\mathrm{Tr} L = \partial_x f + \partial_y g = 0, \qquad \det L = \partial_x f \partial_y g - \partial_y f \partial_x g > 0$$

B If $\alpha(\mu) \pm i\omega(\mu)$ denotes the eigenvalues of $L(\mu)$ evaluated at the fixed point, then

$$\frac{d\alpha(\mu)}{d\mu} \neq 0 \qquad \text{transversality condition}$$

or equivalently

$$f_{\mu x} + g_{\mu y} \neq 0 \qquad \text{at } (x, y, \mu) = (0, 0, 0)$$

Then a limit cycle bifurcates from the origin with an amplitude that grows like $|\mu|^{1/2}$ whilst its period tends to $2\pi/\omega$ as $|\mu| \to 0$. The bifurcation is supercritical if $\sigma < 0$ and subcritical if $\sigma > 0$ where

$$\sigma = \frac{1}{16}[f_{xxx} + g_{xxy} + f_{xyy} + g_{yyy}]$$
$$+ \frac{1}{16\omega}\left(f_{xy}(f_{xx} + f_{yy}) - g_{xy}(g_{xx} + g_{yy}) - f_{xx}g_{xx} + f_{yy}g_{yy}\right)$$

The saddle-node bifurcation

As an example consider

$$\boxed{\dot{x} = \lambda - x^2}$$

In general a 1-D dynamical system $\dot{x} = f(x, \lambda)$ has a saddle-node bifurcation point at $(x, \lambda) = (0, 0)$ if the following holds

- $f(0, 0) = 0$, $f_x(0, 0) = 0$
- $f_{xx}(0, 0) \neq 0$
- $f_\lambda(0, 0) \neq 0$

If $f_\lambda f_{xx} < 0$ stable/unstable pair exists for $\lambda > 0$, whereas if $f_\lambda f_{xx} > 0$ then pair exists for $\lambda < 0$. For higher dimensional systems

$$\dot{x} = f(x, \lambda), \qquad x \in \mathbb{R}^m, \quad \lambda \in \mathbb{R}^l$$

we suppose that the system has an equilibrium defined by

$$f(\overline{x}, \overline{\lambda}) = 0.$$

The equilibrium is hyperbolic if the Jacobian matrix $L = D_x f$ (with eigenvalues $\mu_i \in \mathbb{C}$ and corresponding right (left) eigenvectors $v_i \in \mathbb{C}^m$ ($w_i \in \mathbb{C}^m$)) evaluated at the equilibrium has no eigenvalues with zero real part. It is nonhyperbolic if at least one eigenvalue has zero real part. A saddle-node bifurcation occurs when

- The equilibrium is nonhyperbolic with precisely one eigenvalue, say μ_1, with zero real part. This is guaranteed if
$$D_x f(\overline{x}, \overline{\lambda}) v_1 = 0$$
and $\mathrm{Re} D_x f(\overline{x}, \overline{\lambda}) v_i \neq 0$, $i = 2, \ldots, m$.
- The function $f(x, \overline{\lambda})$ has nonvanishing quadratic terms along the eigenvector v_1; that is
$$w_1 (D_x^2 f(\overline{x}, \overline{\lambda})(v_1, v_1)) \neq 0$$
where $D_x^2 f(\overline{x}, \overline{\lambda})(\cdot, \cdot) : \mathbb{C}^m \times \mathbb{C}^m \to \mathbb{C}^m$ is a bilinear vector-form.
- The n-dimensional vector
$$w_1 D_\lambda f(\overline{x}, \overline{\lambda}) \neq 0,$$
which is called the transversality condition.

Reduction of Hodgkin-Huxley

The mathematical forms chosen by Hodgkin and Huxley for the functions τ_X and X_∞, $X \in \{m, n, h\}$, are all transcendental functions. Both this and the high dimensionality of the model make analysis difficult. However, considerable simplification is attained with the following observations

- $\tau_m(V)$ is small for all V so that the variable m rapidly approaches its equilibrium value $m_\infty(V)$.
- The equations for h and n have similar time-courses. In fact the Na^+ channel closing, h, occurs at the same rate but in the opposite direction to K^+, n. Hence, n and h may be *slaved* together.

We mimic the slower approach of n and h to their asymptotic values by the replacement

$$X = X_\infty(U), \qquad X \in \{n, h\}$$

This equation can always be solved exactly for U since the functions X_∞ are monotonic and hence invertible. Hence, the reduced model is now two dimensional with a membrane current $f(V, U) = F(V, m_\infty(V), n_\infty(U), h_\infty(U))$. By demanding that the time-dependence of f in the reduced model mimic the time-dependence of F in the full model at constant V we have that

$$\frac{\partial F}{\partial h}\frac{dh(V)}{dt} + \frac{\partial F}{\partial n}\frac{dn(V)}{dt} = \left(\frac{\partial f}{\partial h_\infty}\frac{dh_\infty}{dU} + \frac{\partial f}{\partial n_\infty}\frac{dn_\infty}{dU}\right)\frac{dU}{dt}$$

Under the approximation that $h \approx h_\infty(U)$ and $n \approx n_\infty(U)$ we may solve for the time evolution of U to obtain

$$\begin{aligned} C\frac{dV}{dt} &= -f(V, U) + I_s + I \\ \frac{dU}{dt} &= g(V, U) \end{aligned}$$

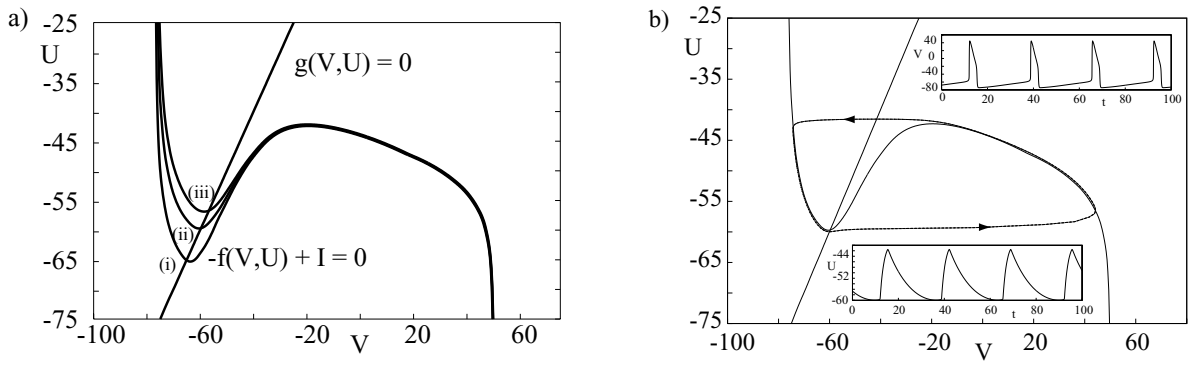
where

$$g(V, U) = \frac{\frac{\partial F}{\partial h}\left[\frac{h_\infty(V) - h_\infty(U)}{\tau_h(V)}\right] + \frac{\partial F}{\partial n}\left[\frac{n_\infty(V) - n_\infty(U)}{\tau_n(V)}\right]}{\frac{\partial f}{\partial h_\infty}\frac{dh_\infty(U)}{dU} + \frac{\partial f}{\partial n_\infty}\frac{dn_\infty(U)}{dU}}$$

and $\partial F/\partial h$ and $\partial F/\partial n$ are evaluated at $h = h_\infty(U)$ and $n = n_\infty(U)$. The variable V describes the capacitive nature of the cell whilst U describes the time-dependence of the membrane conductance. In fact U may be regarded as a variable responsible for the *refractory* period of a neuron.

The reduction to a two dimensional system allows a direct visualization of the dynamics by plotting the flow in the (V, U) plane. A plot of the nullclines $dV/dt = 0$ and $dU/dt = 0$ allows the visualization of both the fixed point (defined by the intersection of the two nullclines) and the flow. In the reduced model $g(V, V) = 0$ and the nullcline for dU/dt is simply the straight line $U = V$.

For zero external input the fixed point is found at $(V, U) = (V^*, U^*) = (-65, -65)$. Moreover, in this instance the fixed point is stable and the neuron is said to be *excitable*. When a positive external current is applied the low-voltage portion of the dV/dt nullcline moves up whilst the high-voltage part remains relatively unchanged. For sufficiently large constant external input the intersection of the two nullclines falls within the portion of the $dV/dt = 0$ nullcline with positive slope. In this case the fixed point is unstable and and the system may support a limit cycle. The system is said to be oscillatory as it may produce a train of action potentials. Action potentials may also be induced in the absence of an external current for synaptic stimuli of sufficient strength and duration.



(a) Nullclines of the reduced neuron model with (i) $I = 0$, (ii) $I = 10$ and (iii) $I = 20$. (b) The reduced neuron model in an oscillatory regime ($I = 10$) capable of generating a train of spikes (see inset for dynamics of V and the refractory variable U).

Saddle node on a limit cycle

We shall briefly indicate how to reduce equations of Moris-Lecar type to a phase model describing the universal behavior close to a saddle-node on a limit cycle bifurcation.

Suppose there exists a unique asymptotically stable fixed point and a saddle-point with a one-dimensional unstable manifold whose branches form a closed loop. Assume further that when $I = I_c$ the node and saddle coalesce at the point $(V, w)^T = \mathbf{Z}_c$ forming a simple loop $\mathbf{Z}(t)$ which becomes a stable limit cycle for $I > I_c$. Introduce a small parameter η and decompose the applied current as $I = I_c + \eta^2 \Delta I$. The Moris-Lecar equations can then be written in the form

$$\frac{d\mathbf{Z}}{dt} = F(\mathbf{Z}) + \eta^2 \Delta I \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

with $F(\mathbf{Z}) = (I_c + f_1(V, w), f_2(V, w))^T$. Taylor expand about the saddle-node $\mathbf{Z}_c$ by writing $\mathbf{Z}(t) = \mathbf{Z}_c + \eta z(t)\mathbf{e}$ where $\mathbf{e}$ is the unit eigenvector associated with the simple zero eigenvalue of the Jacobian $D_{\mathbf{Z}}F(\mathbf{Z}_c)$ of F at $\mathbf{Z}_c$:

$$\eta \mathbf{e} \frac{dz}{dt} = F(\mathbf{Z}_c) + \eta z(t) D_{\mathbf{Z}} F(\mathbf{Z}_c)\mathbf{e} + D^2_{\mathbf{Z}} F(\mathbf{Z}_c)(\eta z(t)\mathbf{e}, \eta z(t)\mathbf{e}) + \eta^2 \Delta I \begin{pmatrix} 1 \\ 0 \end{pmatrix} + \dots$$

After projecting onto the left eigenvector, $\mathbf{w}$, ($\langle \mathbf{w}, \mathbf{e} \rangle = 1$) we obtain the normal form for saddle-node dynamics (to second order)

$$\frac{dz}{dt} = \eta \left(p + q z^2 \right)$$

with $p \propto \Delta I$ and q determined by the second order terms in the Taylor expansion (which is taken to be positive) since $F(\mathbf{Z}_c) = 0$ and $\mathbf{w} D_{\mathbf{Z}} F(\mathbf{Z}_c)\mathbf{e} = 0$ for a saddle-node. Finally, performing the change of co-ordinates $\tau = \eta t$ and $z = \tan(\theta/2)$ (so $\cos\theta = (1 - z^2)/(1 + z^2)$) we obtain the canonical phase model

$$\frac{d\theta}{d\tau} = q(1 - \cos(\theta)) + p(1 + \cos(\theta))$$

If q and p have opposite signs then the canonical phase model has two fixed points, one stable and the other unstable, and the neuron is in an excitable state. On the other hand, if q and p

have the same sign (which we take to be positive) then there are no fixed points and the phase monotonically increases with time. In fact, one can obtain the exact solution

$$\theta(\tau) = 2\tan^{-1}\left[\sqrt{\frac{p}{q}}\tan\left(\sqrt{pq}\tau + \phi\right)\right]$$

for some arbitrary phase ϕ. It follows that the frequency of rotation is $\omega = 2\sqrt{pq}$ (in units of the slow time τ). Each time $\theta(\tau)$ passes through π the amplitude $z(t)$ *blows up* thus signalling the firing of a single spike in the full system.

Parabolic bursters

A simple extension of the above canonical model of a Class I excitable neuron can be used to describe what is known as a parabolic burster. *Bursting* is the rhythmic generation of several action potentials during a short time, followed by a period of inactivity. There are a wide variety of burst phenomena, but it appears that many are due to a similar underlying mechanism. We first note that the various chemical and electrical dynamics of the neuron operate on many time-scales, and for some neurons we can *dissect* their full dynamics into a fast system coupled to a slowly oscillating sub-system. Typically the fast system has a time-scale of milliseconds and models the membrane potential, and hence spike generation. The slow sub-system operates on a time-scale of tens of seconds and models trans-membrane ionic currents. The fast system is modulated by the slow one, and has two parameter regimes: a stationary state or *resting potential*, and a periodic state during which action potentials are generated. Thus, for this *slow wave* bursting to occur, the slow variable must parameterise bifurcations in the fast system.

We consider parabolic bursting models of the general form

$$\begin{aligned} \dot{u} &= f(u) + \epsilon^2 g(u, v, \epsilon) \\ \dot{v} &= \epsilon h(u, v, \epsilon), \end{aligned}$$

$u \in \mathbb{R}^p$, $v \in \mathbb{R}^q$, for which the following two properties hold:

(i) when $\epsilon = 0$ the system $\dot{u} = f(u)$ has an attracting invariant circle and a single degenerate point, i.e. the system is at a saddle-node bifurcation on a limit cycle.

(ii) $\dot{v} = h(0, v, 0)$ has a limit cycle solution.

Here the vector u is identified with the vector of potentials contributing to the spiking mechanism and v describes the vector of potentials associated with the slow wave. In the weak-coupling limit $\epsilon \to 0$ the model reduces to the following canonical form

$$\begin{aligned} \dot{\phi} &= [1 - \cos(\phi)] + [1 + \cos(\phi)]\, g(0, v, 0) \\ \dot{v} &= \frac{1}{c}\bar{h}(0, v, 0) \end{aligned}$$

where $\phi \in \mathbb{S}^1$ is the transformed membrane potential, c is some constant, and $f()$, $g()$, $h()$ and $\bar{h}()$ are smooth functions of their arguments. Furthermore, the slow-dynamics of the transformed equations become de-coupled from the membrane potential. Hence, we effectively have a non-autonomous version of the canonical phase model with time-periodic coefficients that sweep the neuron back and forth through the saddle-node bifurcation resulting in parabolic bursting. [The name parabolic arises since interspike intervals are distributed along a parabola.]

Integrate-and-fire

The integrate-and-fire (IF) model provides a caricature of the capacitative nature of cell membrane at the expense of a detailed model of the refractory process. The IF model satisfies a current balance equation together with the condition that whenever the neuron reaches a threshold h, it fires and V is immediately reset to some reset potential potential V_{reset}:

$$C\frac{dV}{dt} = -F(V) + I_s + I, \quad T_m < t < T_{m+1}$$

supplemented by the reset condition

$$\lim_{\delta \to 0^+} V(T_m + \delta) = V_{\text{reset}}$$

The *firing times* T_n are determined iteratively according to

$$T_n = \inf\{t \mid V(t) \geq h \; ; \; t \geq T_{n-1}\}$$

A linear IF model can be obtained from the reduced Hodgkin-Huxley by eliminating the dynamics of the variable U by setting $U = V$ everywhere so that $g(U, U) = 0$ and hence $dU/dt = 0$. This is a quite severe approximation since U is never very close to V except at the fixed point. The largest value of V for which $F(V) = f(V, V) = 0$ determines the onset of the oscillatory regime and can be used to define the threshold h for firing, since $dV/dt > 0$ for larger values of V.

1.3 Analysis of excitable and oscillatory behaviour using dynamical systems techniques

Wilson-Cowan

Even network models in certain approximations can reduce to a few variables. One example is the Wilson-Cowan model

$$\dot{x} = -x + f(\rho_x + ax - by)$$
$$\dot{y} = -y + f(\rho_y + cx - dy)$$

for fixed *weights* a, b, c, d and bifurcation parameters ρ_x and ρ_y. Here f is a sigmoidal function, such as

$$f(u) = \frac{1}{1 + e^{-u}}$$

which satisfies the (Ricatti) equation $f' = f(1 - f)$.

We can find values of ρ_x and ρ_y corresponding to a Hopf bifurcation. The point (x, y) is an equilibrium if

$$x = f(\rho_x + ax - by) \qquad y = f(\rho_y + cx - dy)$$

or equivalently

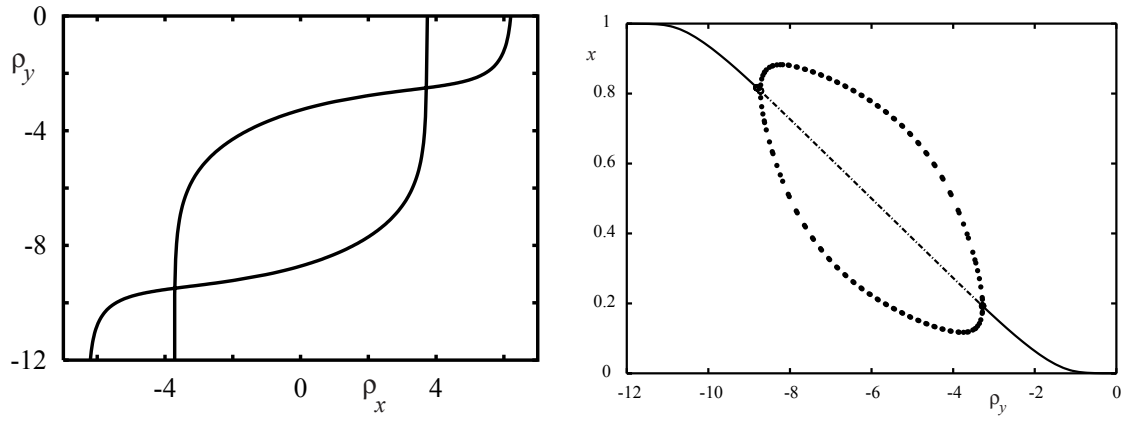
$$\rho_x = f^{-1}(x) - ax + by \qquad \rho_y = f^{-1}(y) - cx + dy$$

where $f^{-1}(u) = \ln(u/(1-u))$. The Jacobian matrix is therefore

$$L = \begin{bmatrix} -1 + af'(\rho_x + ax - by) & -bf'(\rho_x + ax - by) \\ cf'(\rho_y + cx - dy) & -1 - df'(\rho_y + cx - dy) \end{bmatrix} = \begin{bmatrix} -1 + ax(1-x) & -bx(1-x) \\ cy(1-y) & -1 - dy(1-y) \end{bmatrix}$$

Thus the conditions for a Hopf bifurcation are

$$\text{Tr}L = -2 + ax(1-x) - dy(1-y) = 0 \quad \text{and} \; \det L > 0$$



Left: Hopf bifurcation set of Wilson-Cowan oscillator for $a = b = c = 10$ and $d = -2$. Right: Bifurcation diagram for $\rho_x = 0$.

Eliminating y as

$$y_{\pm}(x) = \frac{1 \pm \sqrt{1 - 4(-2 + ax(1-x))/d}}{2}$$

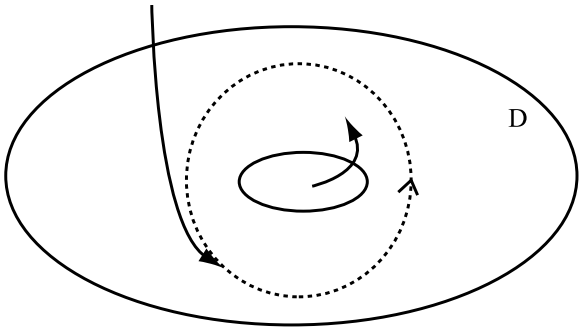
we can then plot the fixed point equation (parametrically) in the $(\rho_x(x), \rho_y(x))$ plane.

Poincaré Bendixson Theorem

It is generally difficult to establish the existence of a limit cycle. In 2-D one has the following useful theorem:

Theorem: Suppose that there exists a bounded region D of phase-space such that any trajectory entering D cannot leave D. If there are no fixed points in D then there exists at least one periodic orbit in D.

Typically, D will be an annular region with an unstable focus or node in the hole in the middle (so trajectories enter the inner boundary) and all trajectories cross the outer boundary inwards.



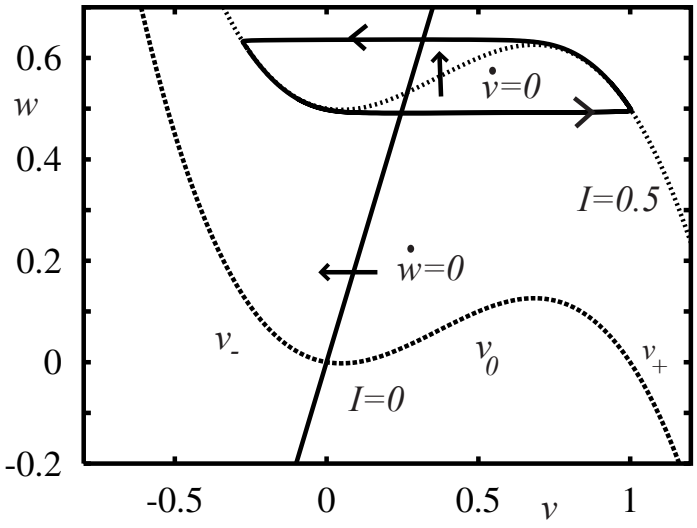
The Poincaré Bendixson theorem tells us that the dynamics of planar systems is severely limited — if a trajectory is confined to a closed, bounded region that contains no fixed points, then the trajectory must eventually approach a closed orbit. There is no *chaos* for planar systems!

FitzHugh-Nagumo model

The FitzHugh-Nagumo equations are the simplest equations that have been proposed for spike generation. They capture the essential features of the reduced Hodgkin-Huxley equations and are given by

$$\mu\dot{v} = f(v) - w + I \equiv f_1(v,w), \qquad f(v) = v(a-v)(v-1)$$
$$\dot{w} = v - \gamma w \equiv f_2(v,w)$$

where $0 < a < 1$ and $b, \gamma, \mu > 0$. Here v is like the membrane potential V, and w plays the role of a recovery variable incorporating the dynamics of the three variables m, n, h. Linear stability



Nullclines for the FitzHugh-Nagumo model with $a = 0.1$ and $\gamma = 0.5$. Periodic orbit with $I = 0.5$ and $\mu = 0.001$.

analysis: fixed point $(\overline{v}, \overline{w})$ is unique and defined by the real solution of the cubic equation

$$f(\overline{v}) - \frac{\overline{v}}{\gamma} + I = 0, \qquad \overline{w} = \frac{\overline{v}}{\gamma}$$

The Jacobian is given by

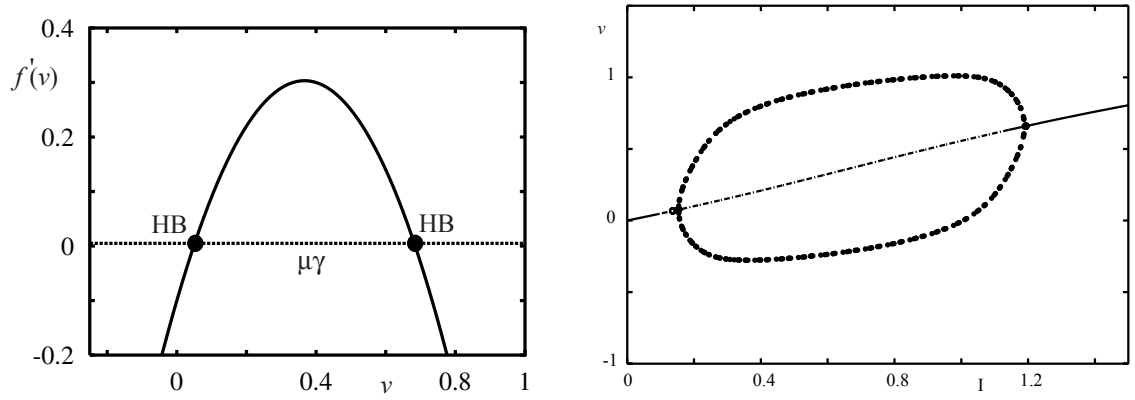
$$L = \begin{bmatrix} f'(\overline{v})/\mu & -1/\mu \\ 1 & -\gamma \end{bmatrix}, \qquad f'(v) = v(a-v) + v(1-v) + (v-a)(1-v)$$

For $I = 0$ $(\overline{v}, \overline{w}) = (0,0)$ and the fixed point is stable since $\mathrm{Tr}\, L = f'(0)/\mu - \gamma < 0$ (since $f'(0) = -a$) and $\det L = (1 + a\gamma)/\mu > 0$ and $(\mathrm{Tr}\, L)^2 - 4 \det L = (a/\mu - \gamma)^2 - 4/\mu > 0$ if $\mu \ll 1$.

With non-zero I we look for Hopf bifurcations defined by $\mathrm{Tr}\, L = 0$ and $\det L > 0$, which gives

$$f'(\overline{v}) = \mu\gamma$$

A plot of the quadratic $f'(v)$ shows that there may be two Hopf bifurcation points. Since for $I = 0$ the fixed point is stable we expect an instability of the fixed point with increasing I and a restabilisation for some even larger value of I. To prove the existence of a stable limit cycle when the fixed point is unstable we appeal to the Poincaré Bendixson theorem. If we pick a large enough box $(|v|, |w| \to \infty)$ then it is a simple matter to show that all trajectories are *inwards*.



Left: Conditions for Hopf bifurcation ($f'(\bar{v}) = \mu\gamma$). Right: Bifurcation diagram for $\mu = 0.01$, $\gamma = 0.5$.

The system is said to be *excitable* when the fixed point is stable and on the left branch of the cubic v nullcline and *oscillatory* when the fixed point is unstable and on the middle branch of the cubic v nullcline.

When $\mu \ll 1$ the variable v is said to be *fast* and w *slow*. This means that v may adjust rapidly and maintain a pseudo-equilibrium along the stable branches of $f_1(v, w) = 0$. Along these branches the dynamics of w are governed by the reduced dynamics

$$\dot{w} = f_2(v_\pm(w), w) = G_\pm(w)$$

When it is not possible for v to be in quasi-equilibrium, the motion is governed by

$$\frac{dv}{d\tau} = f_1(v, w), \qquad \frac{dw}{d\tau} = 0$$

where τ is the fast time scale $\tau = \mu t$. On this time scale w is a constant while v equilibrates to a solution of $f_1(v, w) = 0$.

The curve $v = v_0(w)$, the middle branch, is a *threshold* curve.

The period of oscillation of a stable orbit around an unstable fixed point on the middle branch can be approximated by the time spent on the slow branches. If we denote the value of w at the lower knee of the cubic by w_* and at the upper by w^* then the period of oscillation is given by

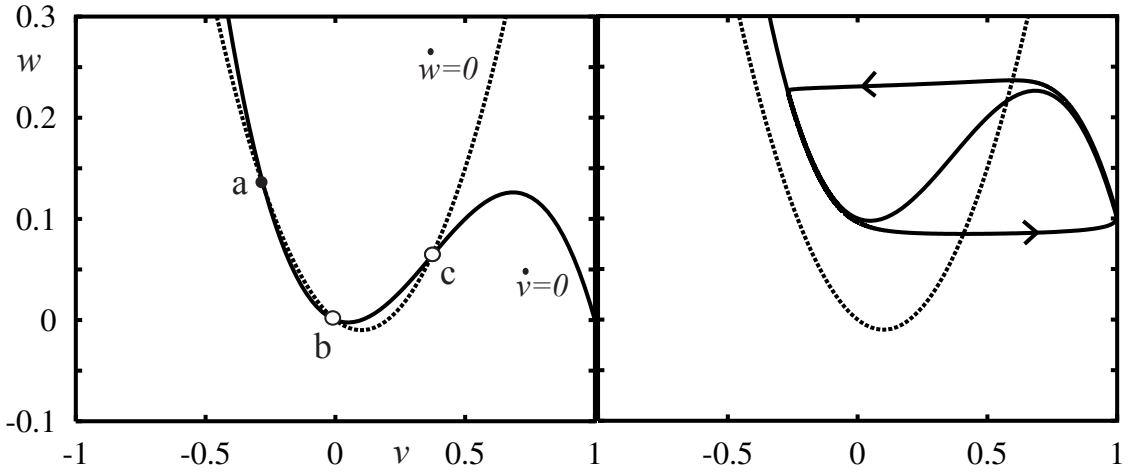
$$T = \int_{w_*}^{w^*} \left(\frac{1}{G_+(w)} - \frac{1}{G_-(w)} \right) dw$$

Cortical neuron model

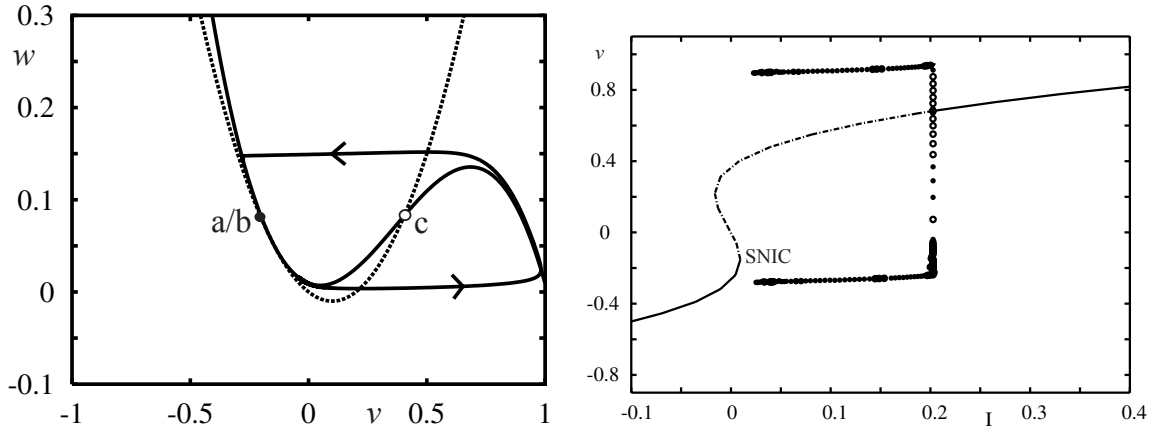
Many of the properties of real cortical neuron can be captured by making the equation for the recovery variable of the FitzHugh-Nagumo equations quadratic:

$$\dot{w} = \beta(v - v_1)(v - v_2) - \gamma w$$

In addition to the single fixed point of the FitzHugh-Nagumo model (denoted by (c)) it is possible to have another pair of fixed points denoted by (a) and (b). As I increases (a) and (b) can anhilate in a saddle node bifurcation For large enough I there is only one fixed point (c) on the middle branch of the cubic. In this instance an oscillatory solution occurs via the same mechanism as for the FitzHugh-Nagumo model.



Phase portrait for cortical neuron model with quadratic recovery variable, $\beta = \gamma = 0.5$, $v_1 = 0$,$v_2 = 0.2$. Left: I=0. Right: I=0.1, with stable limit cycle for $\mu = 0.01$.



Left: Saddle-node on invariant (limit) cycle (SNIC) bifurcation at $I_c \sim 0.009396$. Right: Full bifurcation diagram.

The atoll model

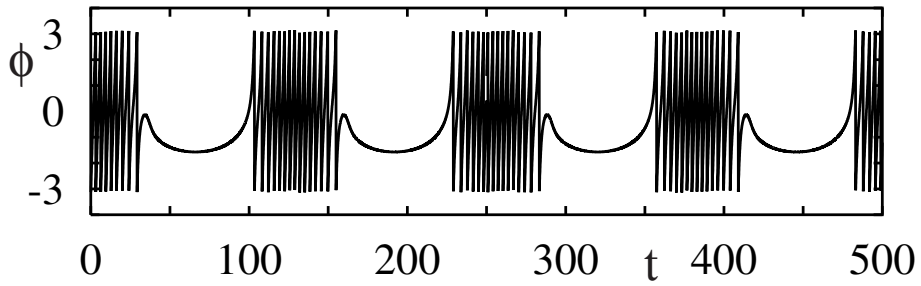
Any extra mechanism that can sweep the last neuron model back and forth through the saddle-node on a limit cycle bifurcation can result resulting in parabolic bursting. Hence, bursting neuron models typically have a phase space which is at least $\mathbb{R}^3$. However, as we already know there should be a change of coordinates to the torus $(\phi, \theta) \in \mathbb{S}^1 \times \mathbb{S}^1$. A typical example is the *atoll* model (obtained by setting $p = p(t) = \cos \omega t$ in the canonical phase model):

$$\begin{aligned} \dot{\phi} &= 1 - \cos\phi + (1 + \cos\phi)\cos\theta \\ \dot{\theta} &= \omega \end{aligned}$$

If $\cos\theta > 0$ then this guarantees that $\dot{\phi} > 0$. hence, for $0 < \theta < \pi/2$ and $3\pi/2 < \theta < 2\pi$, $\dot{\phi} > 0$ and there does not exist a fixed point. If $\cos\theta < 0$ then there exists two fixed points at the solution of

$$\pm|\cos\theta| = \frac{1 - \cos\phi}{1 + \cos\phi}$$

The name of the model stems from the fact that the set of equilibria of the fast subsystem is



Bursting orbit of atoll model with $\omega = 0.05$.

a circle, and the vector of activity $(\phi(t), \theta(t))$ *avoids* it. When the function $p(\theta)$ changes sign more than two times, there are many atolls on the torus.

1.4 Phase response curves and isochronal coordinates

Isochronal coordinates

Consider a limit cycle oscillation. Let $x(t)$ and $x'(t)$ be trajectories on and off the limit cycle respectively. If

$$\lim_{t\to\infty} d(x(t), x'(t)) = 0$$

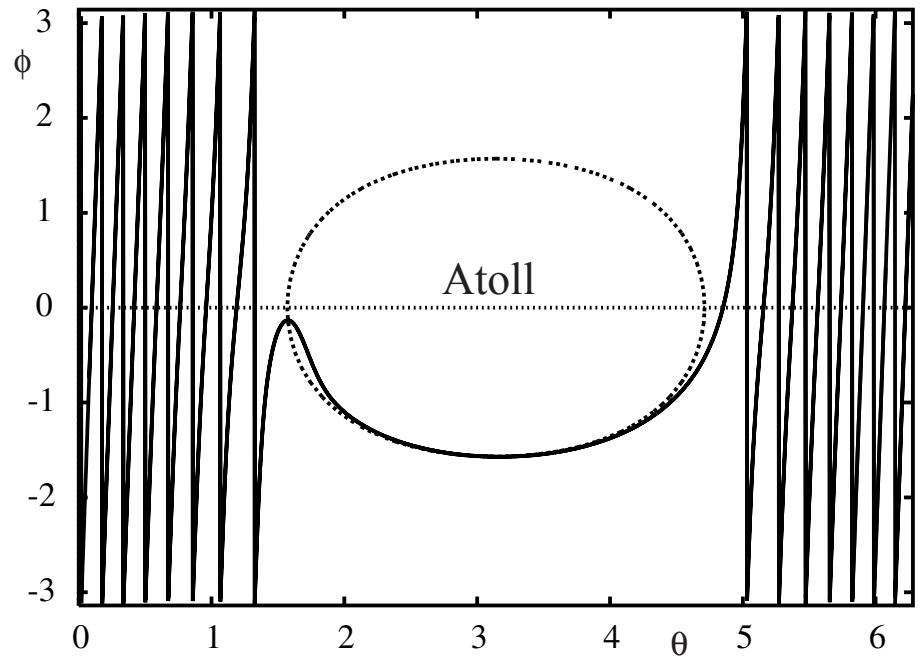
where d is the distance function, then $x(t)$ and $x'(t)$ are said to have the same *latent phase* Φ. The locus of all points with the same latent phase Φ is called an **isochron**.

Consider the dynamical system

$$\dot{r} = F(r), \qquad \dot{\theta} = \omega(r)$$

Suppose that there is a stable limit cycle at $r = 1$ with angular frequency $\omega = 1$. By polar symmetry, the equation for an isochron $\Phi =$ constant is

$$\boxed{\Phi = \theta - f(r), \qquad f(1) = 0}$$



Toroidal phase plane for atoll model, $(\phi, \theta) \in \mathbb{S}^1 \times \mathbb{S}^1$.

Differentiate with respect to t:

$$\dot{\Phi} \equiv 1 = \dot{\theta} - \frac{df}{dr}\dot{r}$$

Hence

$$\boxed{\frac{df}{dr} = \frac{\omega(r) - 1}{F(r)}}$$

As an example consider the dynamical system

$$\dot{r} = a(1-r)r, \qquad \dot{\theta} = 1$$

Then

$$\frac{df}{dr} = 0, \qquad \text{so } \Phi = 0 \text{ at } r = 1 \text{ and } \theta = 0$$

so the isochron is given by $\Phi = \theta$.

As another example consider

$$\dot{r} = 5(1-r)r^2, \qquad \dot{\theta} = r$$

Thus

$$\frac{df}{dr} = \frac{r-1}{5r(1-r)r} = -\frac{1}{5r^2}$$

so

$$f(r) = \frac{1}{5r} + \text{constant}$$

and the isochron is given by

$$\Phi = \theta - \frac{1}{5r} + \frac{1}{5}$$

Poincaré maps

Consider an n-dimensional system $\dot{x} = f(x)$. Let S be an $n-1$ dimensional surface of section. S is required to be transverse to the flow $\phi(x,t)$, $f(x) \cdot n(x) \neq 0$ for all $x \in S$.
The Poincaré map P is a mapping from S to itself, obtained by following trajectories from one intersection with S to the next. Define P on an open set $U \subset S$ according to $P(x) = \phi(x, \tau(x))$ where $\phi(x, \tau(x)) \in S$ and $\phi(x,\tau) \notin S$ for $0 < \tau < \tau(x)$. If $x_k \in S$ denotes the kth intersection then the Poincaré map is defined as

$$x_{k+1} = P(x_k)$$

Let x^* be the point of intersection of a periodic orbit with S. Then x^* is a fixed point of the Poincaré map:

$$x^* = P(x^*)$$

We can determine the stability of a periodic orbit by looking at the behaviour of P near x^*. Linearising the Poincaré map gives, for $\nu = x - x^*$,

$$\boxed{\nu_{k+1} = DP(x^*)\nu_k + O(|\nu|^2)}$$

A periodic orbit is stable if the eigenvalues of $DP(x^*)$, λ_k, $k = 1, \ldots, n-1$ satisfy $|\lambda_k| < 1$.

$$\boxed{\lambda_k = e^{\sigma_k T}}$$

A situation where Poincaré maps arise in a natural way is the study of forced equations of the form

$$\dot{x} = f(x,t), \qquad f(x, t+T) = f(x,t)$$

If we let $\theta = t$ then

$$\dot{x} = f(x,\theta), \qquad \dot{\theta} = 1, \qquad f(x, \theta + T) = f(x,\theta)$$

and we have an autonomous ODE on $\mathbb{R}^n \times \mathbb{S}^1$. If we choose $S = \{(x_0, \theta), \theta = \theta_0\}$ then we can define the associated return map by

$$P(x_0) = x(x_0, T + \theta_0)$$

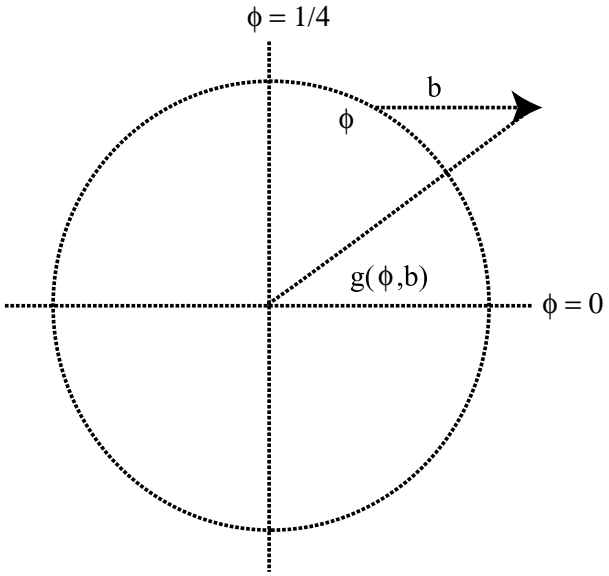
where $x(x_0, t)$ is the solution satisfying initial conditions $x(x_0, 0) = x_0$.

Phase response curves

Here we focus upon a standard model for entrainment in limit cycle oscillators of the form

$$\dot{\Phi} = 1, \qquad \dot{r} = ar(1-r)$$

with **phase** $\phi = \Phi \mod 1$. We now consider instantaneous perturbations in the form of impulses of strength b and instantaneous relaxation back to the limit cycle ($a \to \infty$).



The new phase on the limit cycle is a function of the phase at the time of stimulation and the strength of the perturbation and is denoted $g(\phi, b)$. If we sample the system just after every perturbation then we have a map on the circle given by

$$\phi_{n+1} = g(\phi_n, b) + \tau \mod 1$$

where τ is the time between stimuli and $\phi_n = \phi(n\tau)$.

The **P**hase **R**esponse **C**urve (or response function) is the function $g(\phi, b)$, which may be derived from the model or computed from experiment.

As an example we compute the PRC of the IF model. Suppose that an IF neuron (with $V_{reset} = 0, h = 1, C = 1$) operates as an oscillator such that the inter-spike interval $T^{m+1} - T^m =$ constant $= \Delta$ is fixed in the absence of synaptic inputs ($I_s = 0$). It is then possible to recast the dynamics in terms of a *phase* variable $\theta(t)$ with the following nonlinear transform:

$$\theta(t) \mod 1 \equiv \Psi(V) = \frac{1}{\Delta}\int_0^{V(t)} \frac{dV}{I - F(V)}, \qquad \Delta = \int_0^1 \frac{dV}{I - F(V)}$$

For non-zero I_s, the IF model may now be written

$$\frac{d\theta}{dt} = \frac{1}{\Delta}\frac{1}{I - F(V(\theta))}\frac{dV}{dt} = \frac{1}{\Delta} + I_s(t)R(\theta)$$

with $\theta(T^n) = n$. It is easy to see that if $I_s(t) = \delta(t - n\tau)$ then the new phase after stimulation is simply $R(\theta_n)$, ie $R(\theta)$ is the PRC. The PRC of the IF oscillator is given simply by

$$R(\theta) = \frac{1}{\Delta\,[I - F \circ \Psi^{-1}(\theta)]}, \qquad R(\theta + k) = R(\theta) \text{ for all } k \in \mathbb{Z}$$

The linear IF model, $F(V) = V$, has a PRC given simply by

$$R(\theta) = \frac{e^{\theta\Delta}}{\Delta I}, \qquad \Delta = \ln[I/(I-1)]$$

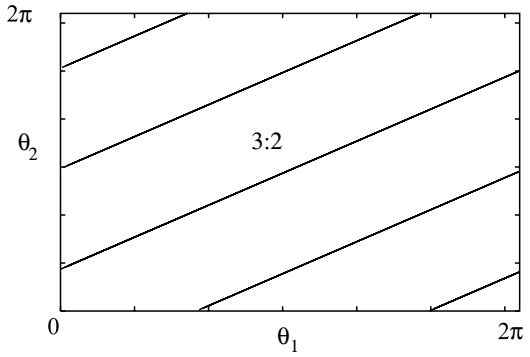
PRCs are of type I if they are always positive (positive stimulation decreases the distance to threshold) and of type II if they can cross zero and take on both positive and negative values.

1.5 Mode-locking to periodic stimuli

First suppose that $b = 0$ (no forcing). Then

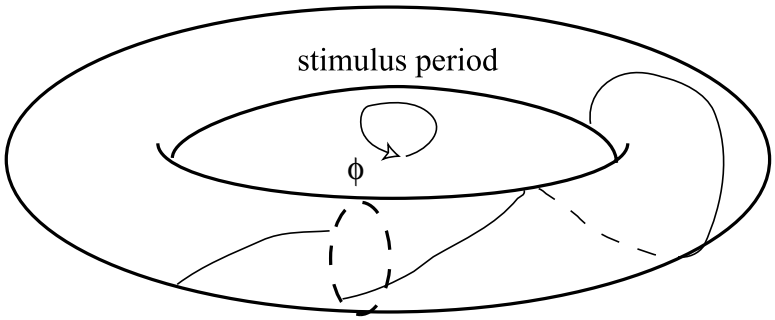
$$\phi_{n+1} = \phi_n + \tau \mod 1$$

If $\tau = M/N$ $(M, N \in \mathbb{Z})$ then every orbit is **periodic**: after N applications of the stimulus the orbit completes M full rotations. True for any rational value of τ. If τ is irrational then any orbit is dense on the circle: **quasiperiodic**.



Now consider the following example of the Poincaré section of flow on a Torus with

$$g(\phi, b) = \phi + b \sin 2\pi\phi$$

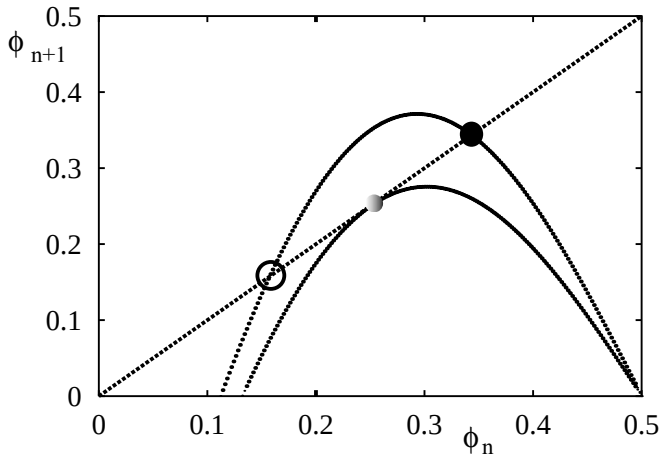


For $b < 1/2\pi$ the map is invertible. The (τ, b) plane has distinct regions called Arnold tongues which correspond to stable mode-locking in some ratio $N : M$. Inside the $N : M$ Arnold tongue

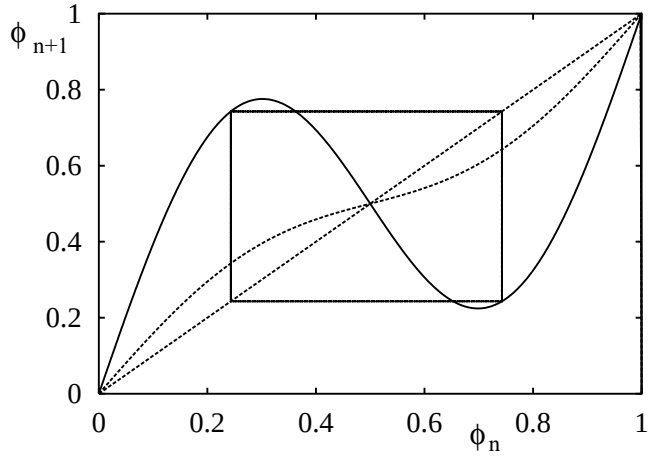
all orbits asymptotically approach a stable $N : M$ mode-locking pattern. For each such orbit there is a rotation number:

$$\rho = \lim_{N\to\infty} \frac{1}{N} \sum_{n=1}^{N} \phi_{n+1} - \phi_n$$

which measures the average rotation between stimuli.



Tangent bifurcation



Period doubling bifurcation

Stability of fixed point at ϕ^*

$$\text{Tangent bifurcation } \left.\frac{\partial \phi_{n+1}}{\partial \phi_n}\right|_{\phi^*} = 1$$

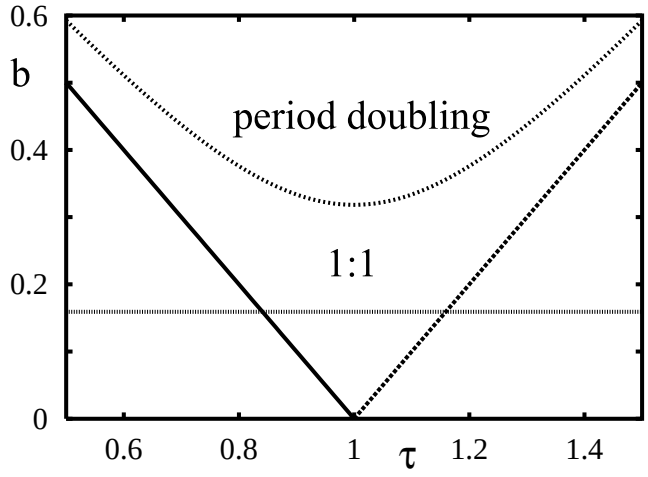
$$\text{Period doubling bifurcation } \left.\frac{\partial \phi_{n+1}}{\partial \phi_n}\right|_{\phi^*} = -1$$

Construction of Arnold tongues: eg for $\rho = 1$ (so that $\phi_{n+1} - \phi_n = 1$)

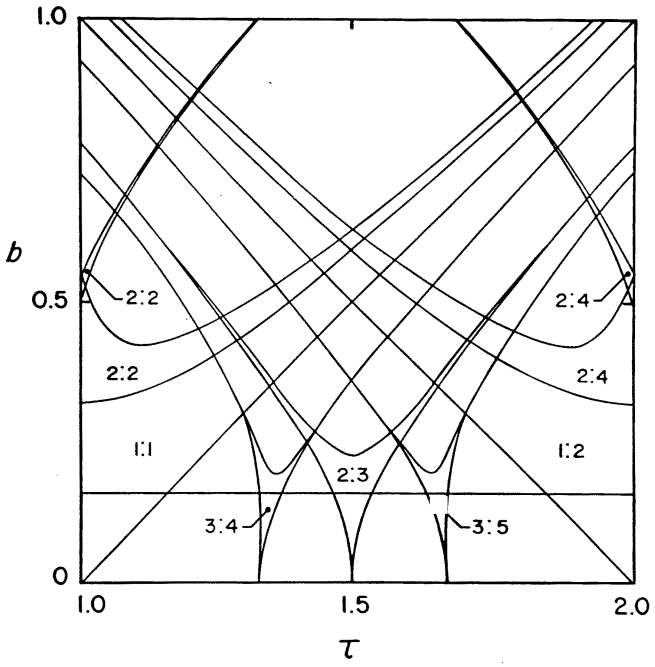
$$1 + \phi^* = g(\theta^*, b) + \tau, \qquad \text{or } \frac{1-\tau}{b} = \sin(2\pi\phi^*)$$

Sub into border conditions (tangent: $\cos 2\pi\phi = 0$ or $\sqrt{1-\sin^2 2\pi\phi} = 0$ so $\sin 2\pi\phi = \pm 1$, doubling: $1 - \sin^2 2\pi\phi = \pi^{-2}b^{-2}$) to find

$$b = \pm(\tau - 1), \qquad b^2 = \pi^{-2} + (\tau - 1)^2$$



Arnold tongue structure for 1:1 mode-locking.



Full Arnold tongue structure for other $N : M$ orbits. Note the existence of $N + N' : M + M'$ orbits between orbits of type $N : M$ and $N' : M'$.

1:1 mode-locking of the periodically forced IF neuron

Consider an IF neuron with threshold at 1 and reset level 0 being driven by a Δ periodic signal $A(t) = A(t+\Delta)$:

$$\dot{v} = -\frac{v}{\tau} + A(t), \qquad T_n < t < T_{n+1}$$

An implicit map of the firing times may be obtained by integrating between reset and threshold:

$$e^{T_{n+1}/\tau} = \int_{T_n}^{T_{n+1}} A(s)e^{s/\tau}ds = \left(\int_{-\infty}^{T_{n+1}} - \int_{-\infty}^{T_n}\right) A(s)e^{s/\tau}ds$$

Introducing the function

$$G(t) = \int_{-\infty}^{0} e^{s/\tau}A(t+s)ds, \qquad G(t) = G(t+\Delta)$$

gives

$$e^{T_{n+1}/\tau}[G(T_{n+1}) - 1] = e^{T_n/\tau}G(T_n)$$

Defining

$$F(t) = e^{t/\tau}[G(t) - 1]$$

we obtain

$$\boxed{F(T_{n+1}) = F(T_n) + e^{T_n/\tau}}$$

If F is invertible ($F'(t) \neq 0$ for all t) and F^{-1} is defined on the range of $F(t) + e^{t/\tau}$ then we have an explicit map of the form

$$T_{n+1} = \Psi(T_n), \qquad \Psi(t) = F^{-1}[F(t) + e^{t/\tau}]$$

Since

$$G'(t) = A(t) - \frac{G}{\tau}, \qquad \text{then } F'(t) = e^{t/\tau}[A(t) - 1/\tau]$$

so that $F'(t) \neq 0$ if $A(t) \neq 1/\tau$. A 1:1 mode-locked solution is defined by $T_n = (n+\phi)\Delta$, giving a fixed point equation

$$\boxed{G(\phi\Delta) = \frac{1}{1 - e^{-\Delta/\tau}}}$$

Stability is examined by considering perturbations of the form $T_n \to T_n + \delta_n$, giving

$$F(T_{n+1}) + F'(T_{n+1})\delta_{n+1} = F(T_n) + F'(T_n)\delta_n + e^{T_n/\tau}[1 + \delta_n/\tau]$$

When $F'(T_{n+1}) \neq 0$ (ie the firing map is explicit)

$$\delta_{n+1} = \kappa(\phi)\delta_n$$

$$\boxed{\kappa(\phi) = \left.\frac{F'(T_n) + e^{T_n/\tau}/\tau}{F'(T_{n+1})}\right|_{T_n=(n+\phi)\Delta} = e^{-\Delta/\tau}\frac{A(\phi\Delta)}{A(\phi\Delta) - 1/\tau}}$$

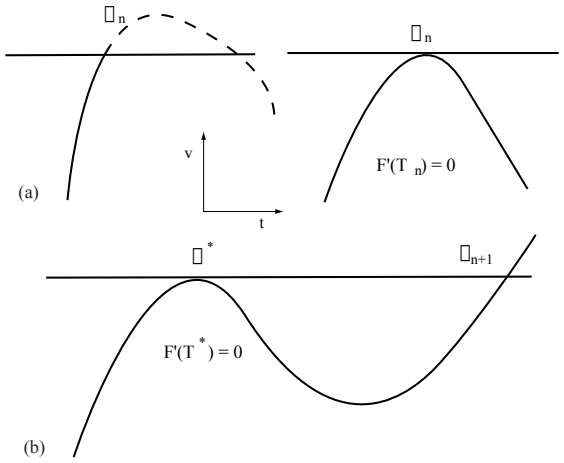
Solutions are stable if

$$|\kappa(\phi)| < 1$$

The borders of the regions where 1:1 solutions become unstable are defined by $\kappa(\phi) = 1$ (tangent bifurcation) and $\kappa(\phi) = -1$ (period doubling bifurcation).

When the firing map is only available implicitly solutions may lose stability in a non-smooth fashion. (a) There is a tangential intersection of the trajectory with the threshold value such

that upon variation of the bifurcation parameter the local maxima of the IF trajectory passes through threshold from above. They are defined by $\dot{v} = -v/\tau + A = 0$, so that $A(T_n) = 1/\tau$ or equivalently $F'(T_n) = 0$. (b) A sub-threshold local maxima increases through threshold leading to the creation of a new firing event at some earlier time than usual. They are defined by $F(T^*) = F(T_n) + e^{T_n/\tau}$ and $F'(T^*) = 0$ with $T^* < T_{n+1}$ and T_{n+1} is the solution to $F(T_{n+1}) = F(T_n) + e^{T_n/\tau}$.



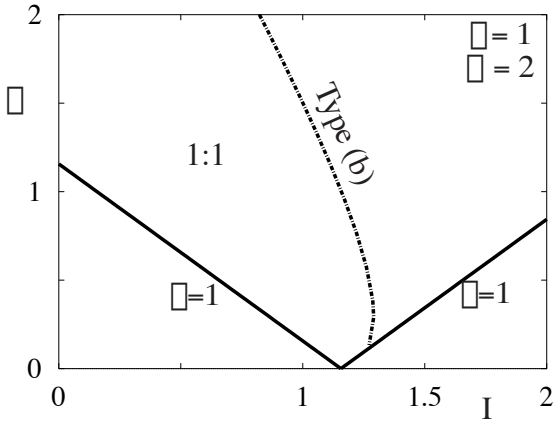
Loss of solution via a non-smooth bifurcation where a local maxima decreases through threshold. (b) Creation of solution, in a non-smooth bifurcation, as a local maxima increases through threshold.

As an example consider the case

$$A(t) = I + \begin{cases} +\epsilon & 0 \leq t < \Delta/2 \\ -\epsilon & \Delta/2 < t < \Delta \end{cases}$$

Conveniently the border condition $|\kappa(\phi)| = 1$ becomes independent of ϕ, since $A(\phi) = I \pm \epsilon$. A tangent bifuraction occurs when the map is explicit and $\kappa = 1$:

$$\pm\epsilon = -I + \frac{1/\tau}{1 - e^{-\Delta/\tau}}$$



S Coombes 2008