Dominant-Scale Analysis for Hodgkin-Huxley Type Equations

Robert Clewley

rclewley@bu.edu

Center for Biodynamics, Boston University

Overview

- Motivation
- Hodgkin-Huxley type equations
- A model from neuroscience
- Quantifying dominance
- Dominant-scales and reduced models
- Attractor estimation
- Application to other systems

Supported by NSF grant #DMS-0211505

Motivation

- Systems of ODEs with intrinsic multiple time-scales ubiquitous in natural science
  - e.g. Van der Pol relaxation oscillator
- State-dependent coupling can introduce other time-scales
  - . . . not explicit in equations
  - e.g. impulses
- Complexity of high-dimensional systems limits intuition

Motivation

- Near orbits of interest, we’d like to know
  - which variables dominate its structure at what times?
  - what are its effective local degrees of freedom?
  - how *large* is its "attractor" basin?
  - what bifurcations are nearby?
- Analytical method for non-intuitive dynamics
  - partition orbits into successive ‘events’
  - low-dimensional approximate models
  - automated analysis tool (MATLAB code)

Form of H-H equations

Hodgkin-Huxley in class of conductance-based equations:

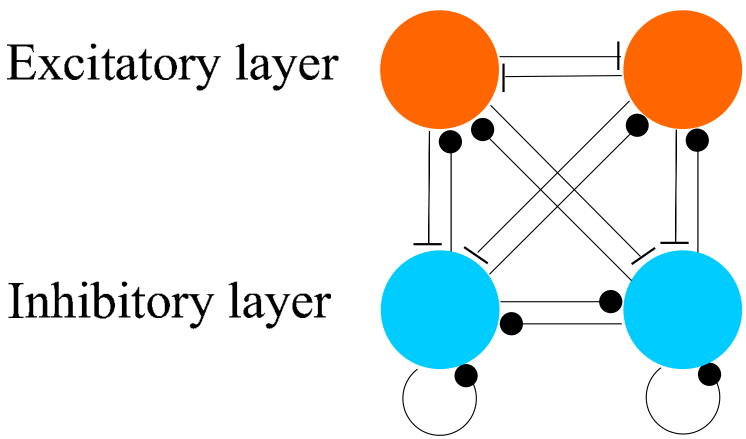
(everything is scalar)

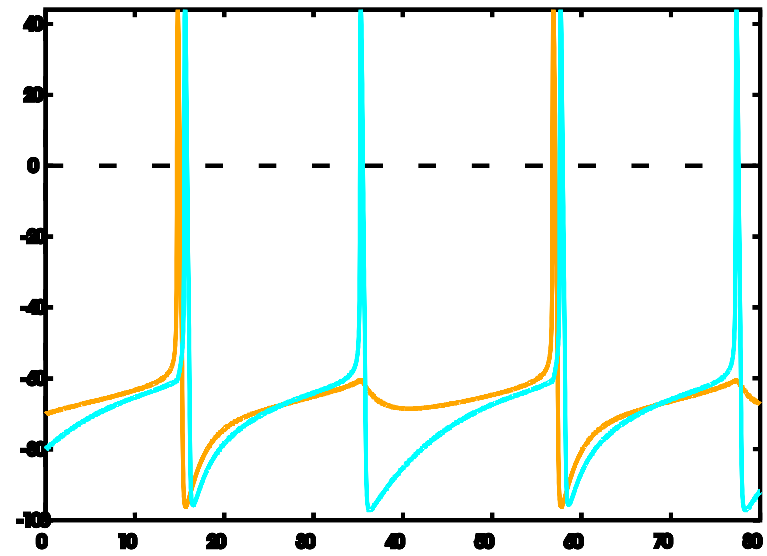
$$
\begin{aligned}
C\dot{V} &= \sum I_{\text{ionic}}(V,t) + \sum I_{\text{external}}(V,t) \\
\tau_g(V)\dot{g} &= g_\infty(V) - g \\
\vdots \quad &\quad \vdots
\end{aligned}
$$

- Membrane potential $V(t) \in [-100, 50]$ mV
- Gating variables $g(t) \in [0,1]$, etc.
- Ionic currents and some external currents $\bar{g}g(t)\,(V_{rev} - V)$
- External currents can also be directly additive $I(t)$

Example from neuroscience

- Two-layer network of cells in hippocampus
- Coherent network rhythm important [1]
- E cells synch. long-distance (due to modulation by I)
- Why? I cells fire twice per E cycle (*doublet*) [2]





[1] Traub, R., Whittington, M., *et al*, Nature (London) 328, 1996
[2] Ermentrout, G. B., Kopell, N. J., Proc. Nat. Acad. Sci. USA, 95, 1259–1264, 1998

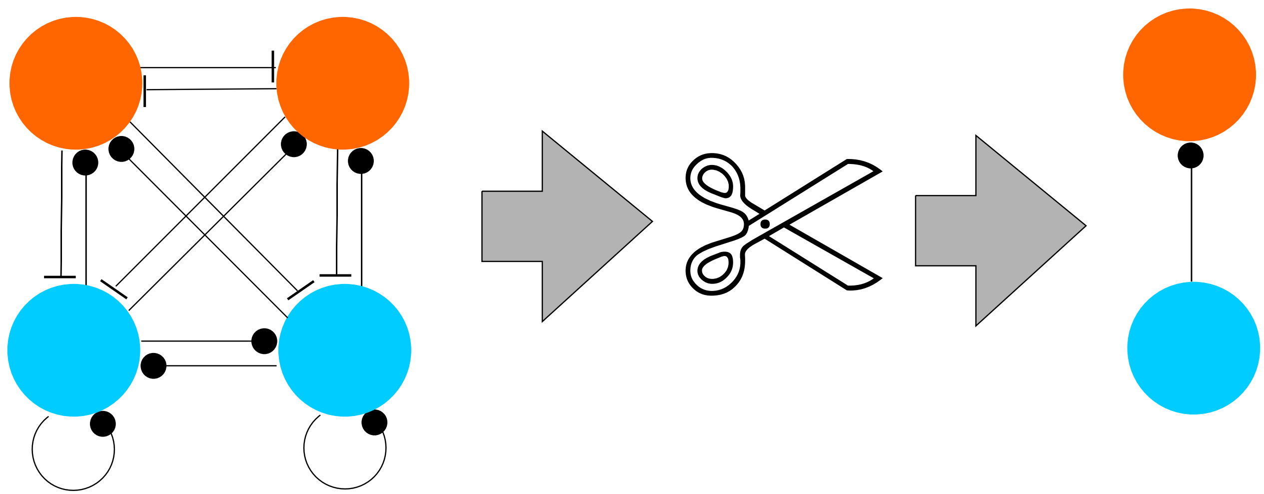
Effective low-dimensionality

- How does this 30-D system possess additional structure?
- Slaving, modulation, and independence between variables important
  - Threshold spike dynamics = almost unsuppressable fast cascade
  - Post-synaptic response slaved to pre-synaptic spiking V
  - Network topology $\Rightarrow$ variables not directly dependent on others
  - . . . etc.

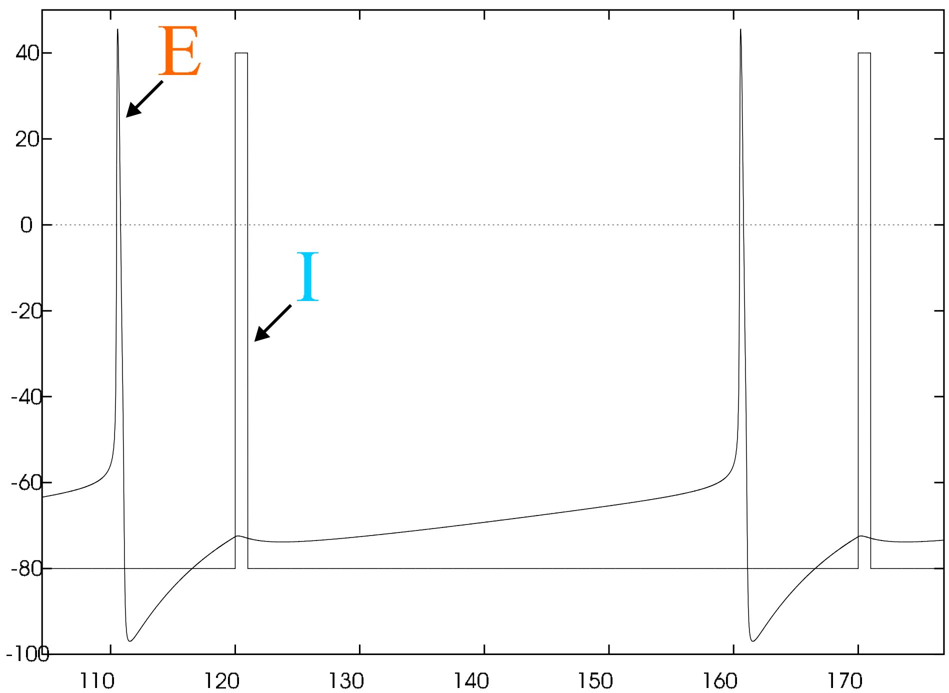
Spike Time Maps

- Ermentrout & Kopell [2] and others:
  - study successive “spiking times” (*near limit cycle*)
- Relationships through Spike Time Maps (e.g. 1D)
- STMs a good predictor of network synchronization properties
- Requires intuition and careful observation to understand dominance
- Maps have no guaranteed domain of existence, accuracy, or rigorous justification

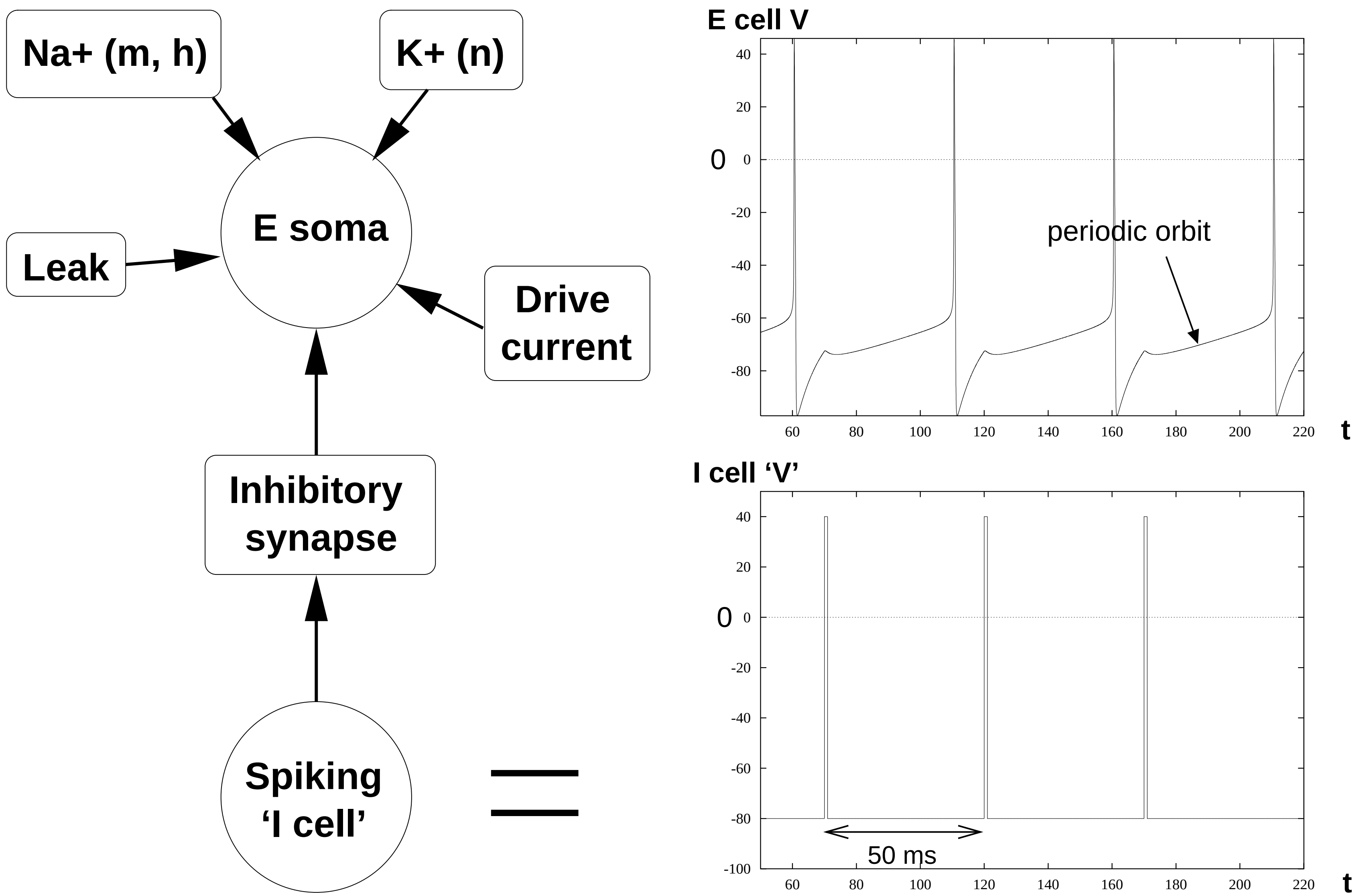
Focus on a simpler system



To understand concepts of ‘events’, ‘epochs’ & ‘dominance’ focus on a sub-system with uni-directional forcing I $\longrightarrow$ E



Variables' inter-relations



Equations for H-H system

Equations for excitatory cell:

$$
\begin{aligned}
\text{Membrane potential} \qquad \dot{V} &= g_{tot}(t)\left(V_\infty(t) - V\right) \\
&= \bar{g}_m m^3 h(V_m - V) + \bar{g}_n n^4 (V_n - V) \\
&\quad + \bar{g}_L (V_L - V) + \bar{g}_s s (V_s - V) + I \\
\text{Sodium activation} \qquad \dot{m} &= \frac{1}{\tau_m(V)}\left(m_\infty(V) - m\right) \\
\text{Sodium inactivation} \qquad \dot{h} &= \frac{1}{\tau_h(V)}\left(h_\infty(V) - h\right) \\
\text{Potassium activation} \qquad \dot{n} &= \frac{1}{\tau_n(V)}\left(n_\infty(V) - n\right) \\
\text{Inhibitory synapse} \qquad \dot{s} &= \frac{1}{\tau_s(V_{inhib})}\left(s_\infty(V_{inhib}) - s\right) \\
&= \alpha\Theta\left(V_{inhib}\right)(1 - s) - \beta s
\end{aligned}
$$

Notation

. . . defining the ‘target voltage’ (quasi-static fixed point)

$$V_\infty(t) = \frac{\sum_i \bar{g}_i g_i(t) V_i + I}{\sum_i \bar{g}_i g_i(t)}$$

and the total conductance

$$g_{tot}(t) = \sum_i \bar{g}_i g_i(t)$$

where $1/g_{tot}$ measures the timescale of V attraction to V_∞

- Note that $V_\infty(t)$ solves $dV/dt = 0$

Quantifying dominance

- Dominant influence of input terms over $V(t)$ underlies the structure of an orbit
  - Conductance inputs $\bar{g}_i g_i(t)$ affect *both* $V_\infty(t)$ and the relaxation timescale $1/g_{tot}(t)$
  - Direct current inputs affect only V_∞
- Unified way to compare influence of all inputs?
  - Relative size of terms in RHS is one way
  - We use a similar way that's helpful later . . .

Dominance defined

Our definition of dominance strength of a variable over V is

How much can a change in an input variable move V_∞?

e.g. for conductance-based input:

$$\begin{aligned} \Psi_k(t) &:= g_k(t) \left| \frac{\partial V_\infty}{\partial g_k}(t) \right| \\ &= \frac{\bar{g}_k g_k(t)}{g_{tot}(t)} \left| V_k - V_\infty(t) \right| \end{aligned}$$

due to conditional linearity of conductance-based ODEs

There is a corresponding formula for direct current inputs to V.

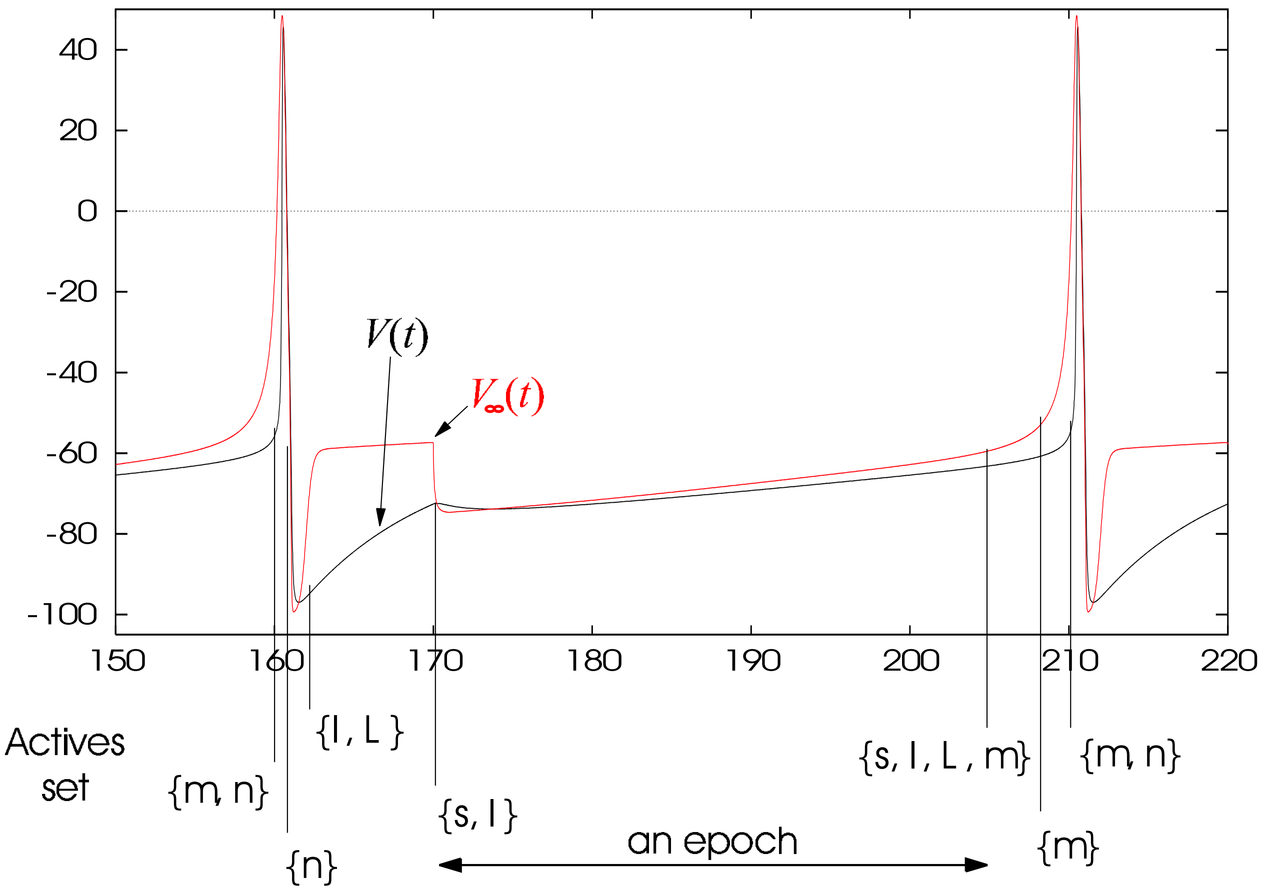
Computing dominant variables

- At each t, $\Psi_k(t)$ values compared in size, ranked
- Disregard weakest
  - when ratio to largest Ψ is smaller than a scale threshold σ
- Remaining dominant variables are called actives
- Candidate active variables are the inputs to the $V(t)$ equation
  - m, n, s, I (drive current), L (leak current)
  - treat h as part of $\bar{g}_m$ here

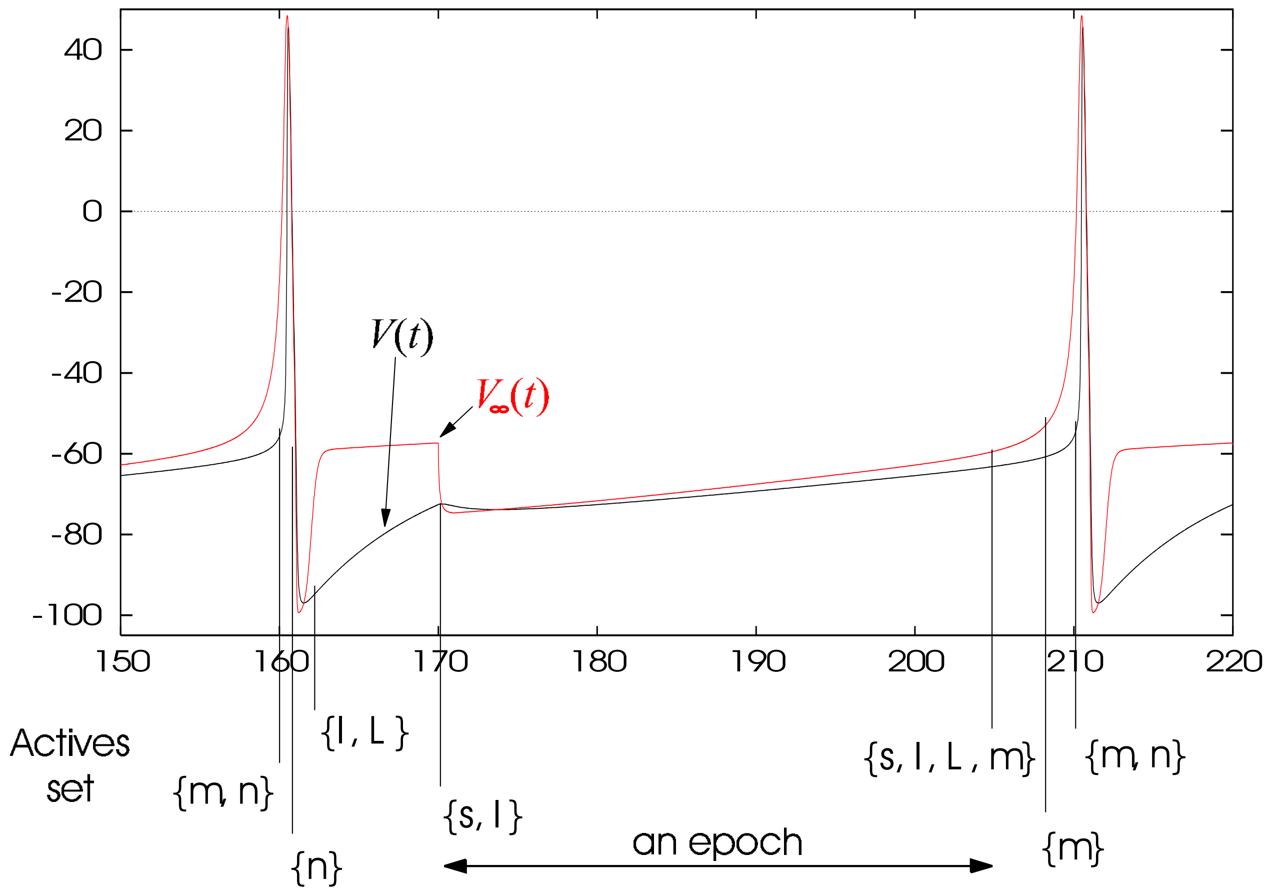
Partitioning orbit into epochs

- An event is a change in {actives}
- An epoch is the time interval between consecutive events
- Detect events using a MATLAB code
  - calculates $\Psi_k(t)$ values along a numerically computed orbit
  - uses term structure of the differential equations
- Partitions orbit into epochs accordingly . . .

Example epochs ($\sigma = 2.1$)



Example epochs ($\sigma = 2.1$)



Suppose for $t \in [208, 210)$ the m variable is the only active

What information does this give?

Asymptotic intuition

Use a helpful property of the *signed* dominance strengths Ψ^* to interpret the consequence:

$$
\begin{aligned}
\sum_k \Psi_k^* &= 0 \\
\Psi_m^* + \sum_{k \neq m} \Psi_k^* &= 0 \\
\Psi_m^* + \mathcal{O}(\varepsilon) &= 0 \qquad (\text{defining} \quad \varepsilon := 1/\sigma) \\
\frac{\bar{g}_m h m^3}{g_{tot}} (V_m - V_\infty) + \mathcal{O}(\varepsilon) &= 0 \\
V_\infty(t) - V_m &= \mathcal{O}(\varepsilon) \quad \text{provided } \bar{g}_m h m^3 \text{ is } \mathcal{O}(1)
\end{aligned}
$$

Local models

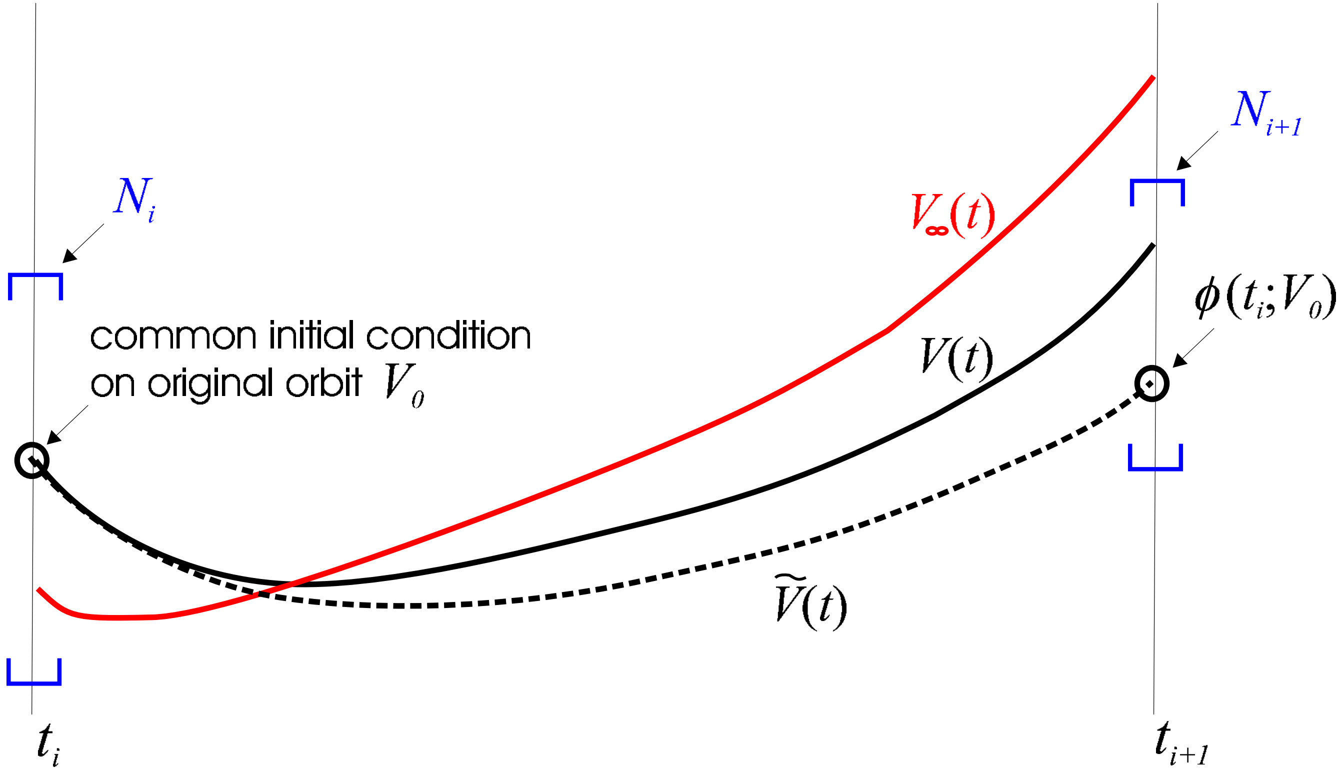
Therefore, over this epoch, $\mathcal{O}(\varepsilon)$-accurate local model is

$$\begin{aligned}
\dot{V} &= \bar{g}_m h m^3 \left(V_m - V\right) \\
\dot{m} &= \frac{1}{\tau_m(V)} \left(m_\infty(V) - m\right)
\end{aligned}$$

- Analysis reduced dimension to 3 (V, m, h) cf. original 5
- ε (not necessarily small) controls largest error
- Strong dissipation $\rightarrow$ no error accumulation
- Different to a center manifold reduction . . .
  - approximate model is valid only locally in time
  - may include *transient* decaying strong variables

Estimating attraction

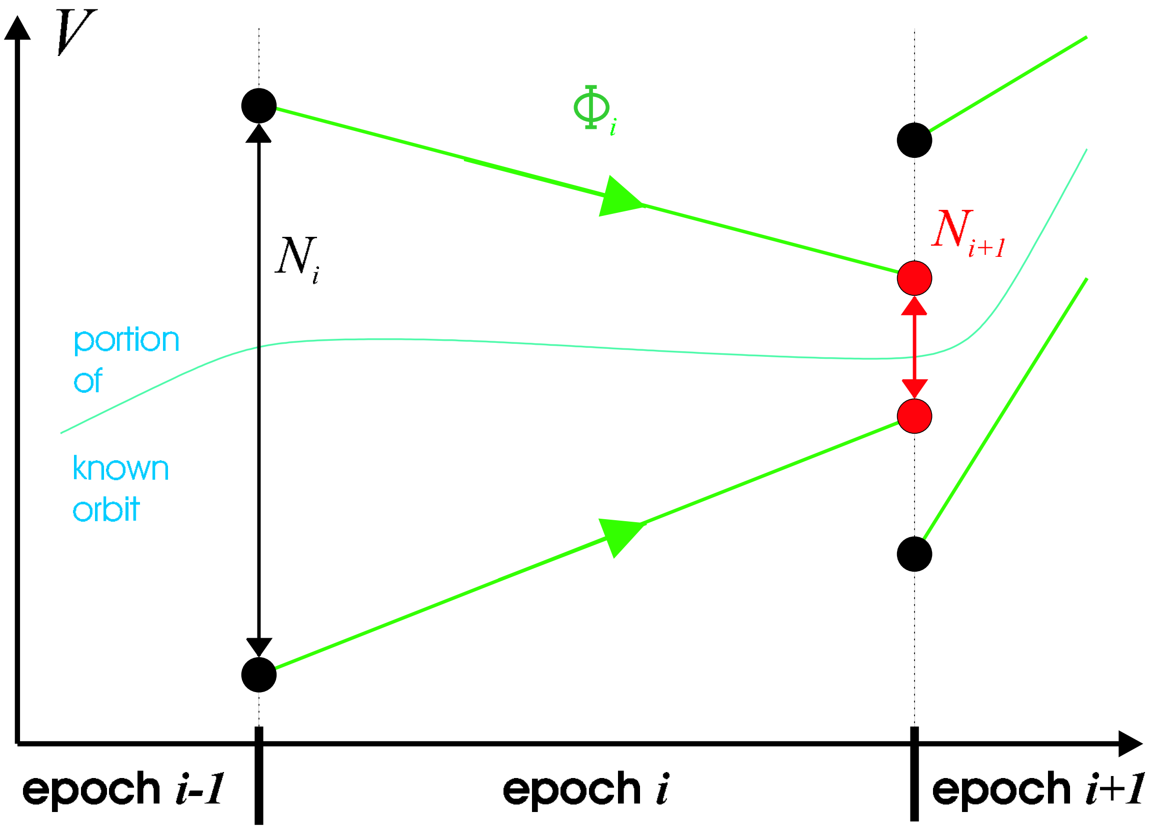
Now consider epoch with $\{s, I\}$ active, for $t \in [t_i, t_{i+1})$



- Solve reduced V equation using Variation of Constants
- Flow map $\phi_i\,(t_i; V_0) = \tilde{V}(t)$ is affine linear in V_0
- Define Φ_i to map a neighbourhood N_i of V_0 at t_i to that at t_{i+1} using ϕ_i

Map concatenation

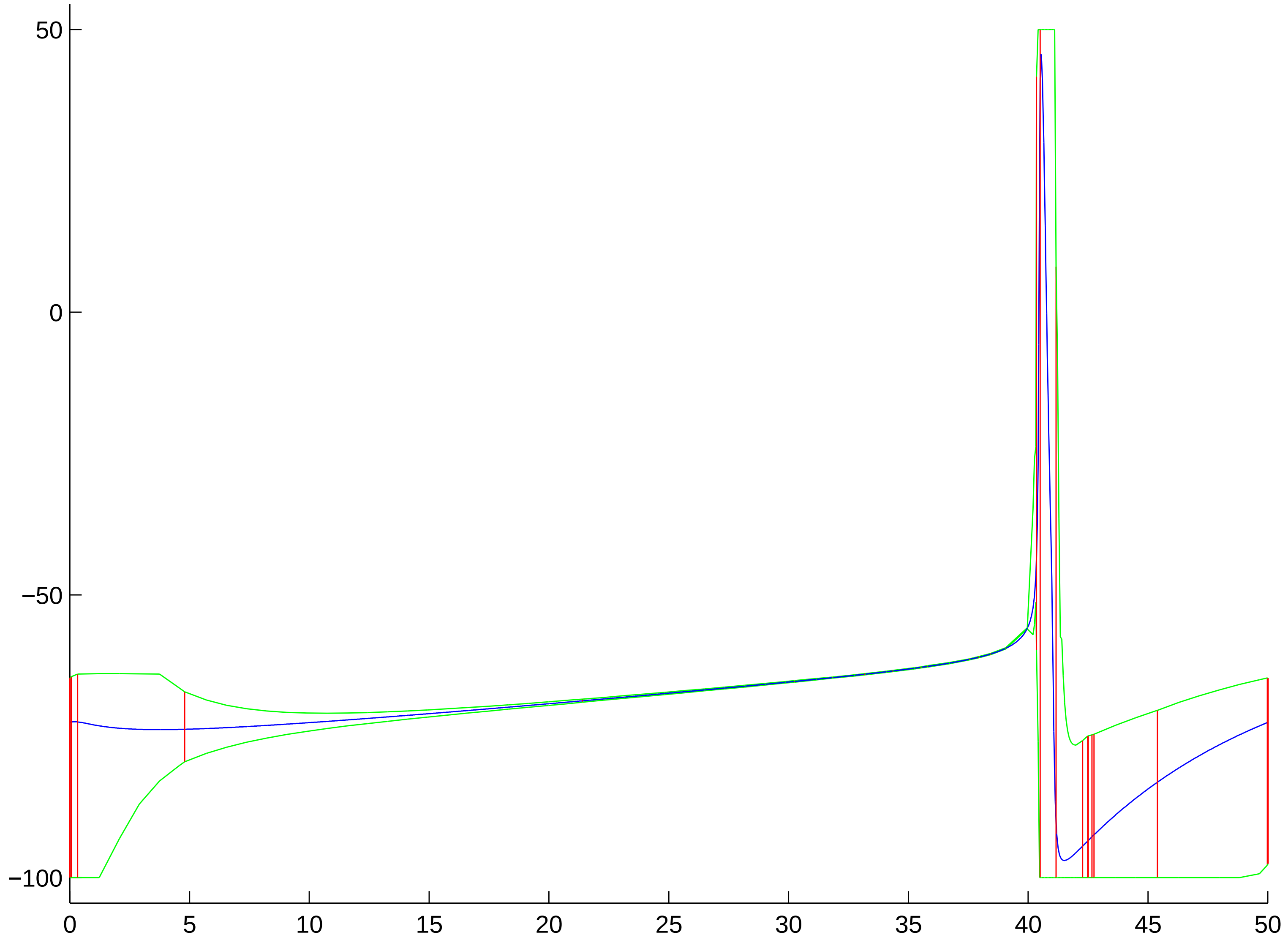
- Epoch's linear flow map Φ_i: initial interval $N_i \longrightarrow$ final interval N_{i+1}
- Φ_i a contraction due to dissipative voltage eq$^{\mathrm{n}}$, but not necessary
- Contraction rate is Floquet-like multiplier
- $(\Phi_P \circ \cdots \circ \Phi_1)(N_1)$ approximates Poincaré map *(with known domain)*



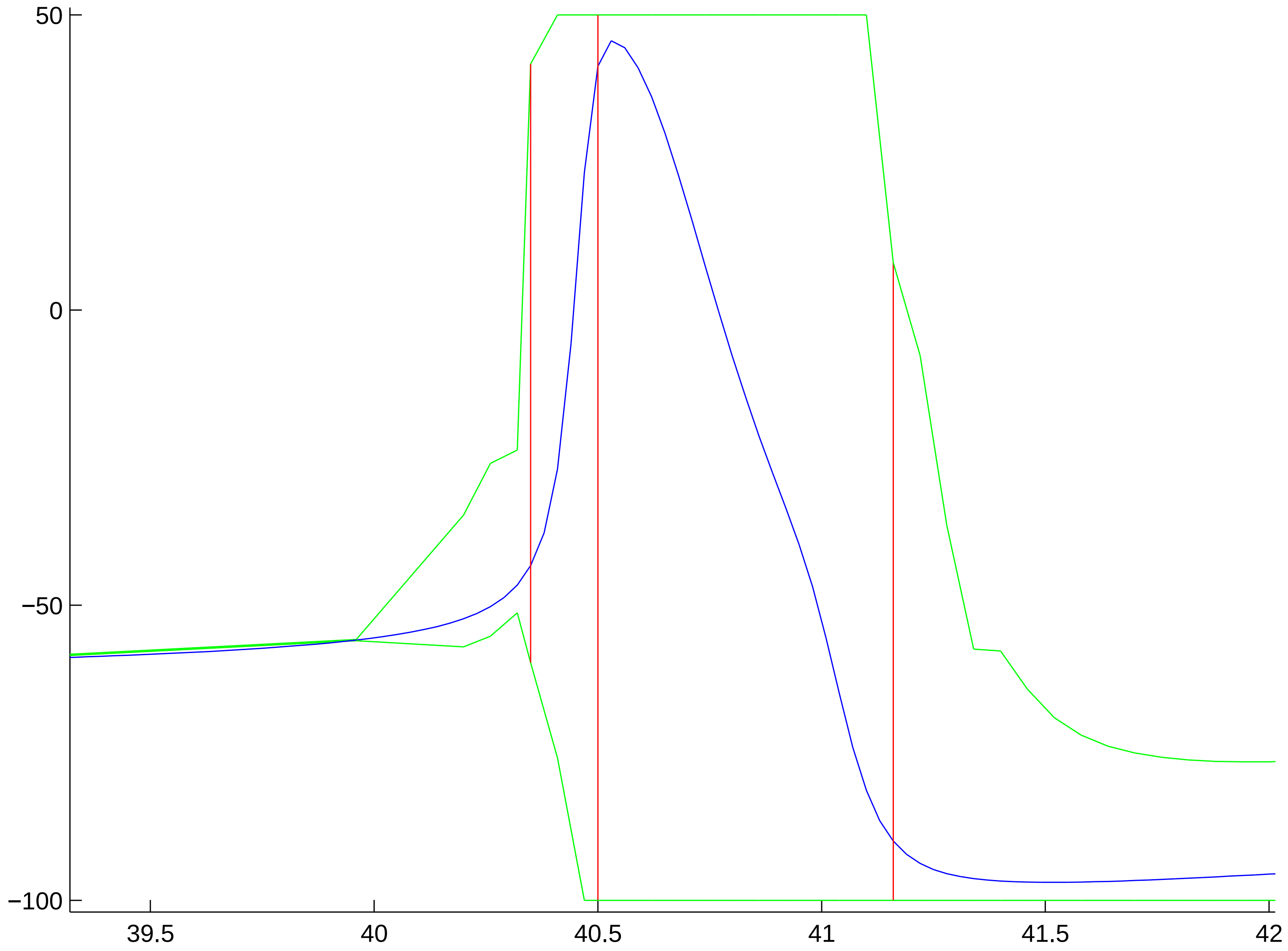
Estimating attractor basin around $V(t)$

- Goal interval N_P at end of P^{th} epoch
- Maximize initial intervals such that $\Phi_i(N_i) \subset N_{i+1}$
  - ...use inverse mapped interval $\Phi^{-1}(N_{i+1})$
- Self-consistency conditions:
  - intervals must exclude V values that violate epoch's { actives }
  - use relative timescales of variables here
- Attractor basin estimate is $\{N_i\}_{i=1,\ldots,P}$
- Caveats:
  - accept some controllable error in Φ_i maps
  - do not expect to find all states that converge to the attractor

V attractor basin



V attractor basin (close-up of spike)



Benefits of this method

- Avoids expensive shooting method to determine the actual nearby orbits that meet epoch conditions
- MATLAB algorithm
  - needs few sample points (fast and efficient)
  - tunable accuracy
- Explictly indicates role of dominant variables
- Indicates degree of robustness of dynamics w.r.t. perturbation in V or its inputs
- Identification of bifurcation scenarios? (then use AUTO)

Potentially active inputs

- $\Psi_k(t)$ can also be used to find input variables that *would* be actives if their value changed
- These are called potentials
  - (can be solved for explicitly in H-H equations)
- A lack of potentials at time t indicates robustness of local model of V dynamics during that epoch
- {potentials} indicates directions of instability for the orbit
  - i.e. to perturbations of inputs (rather than of V)
- Potentials help guide determination of analysis regimes

Dominant-scale analysis

- Partition a known high-D trajectory into epochs
- Epochs: low-D approximate model & linear Φ flow map
- Φ measures local contraction of vector field
- Self-consistency conditions and Φ
  - estimate local attractor basin
- Epochs and {potentials} $\longrightarrow$ reduced model regimes
- Overall contraction $\longrightarrow$ diminishing approximation error

Summary

- Computational method to study dynamical structure of a high-dimensional coupled H-H system near known orbits
  - no *a priori* reduction of system needed
  - helps computational neuroscientists simplify detailed models
  - guides further experiments to focus on active components
  - automatic Spike Time Maps and synchrony analysis using concatenated Φ maps?
- Method implemented in MATLAB 'DSSRT' code
  - available at my CBD website
- Applications to other nonlinear coupled systems

Example nonlinear system

FitzHugh-Nagumo oscillator:

$$\begin{aligned} x' &= ax\left(1 - bx^2\right) - y + I + gs(t)\left(x_r - x\right) \\ y' &= \left(\tanh(5x) - y\right)/\tau \end{aligned}$$

Model of FHN (pseudo-linearize u equation):

$$\begin{aligned} u' &= au - bw^2u - v + I + gs(t)\left(u_r - u\right) \\ v' &= \left(\tanh(5u) - v\right)/\tau \\ w' &= (u - w)/\tau_w \end{aligned}$$

or $\ldots w = u\left(t - \tau_w\right)$, where τ_w is small.

FHN example continued

- FHN equations not ‘conditionally linear’
- For small τ_w, model tracks FHN system closely
- Sacrifice a dimension for conditional linearity of u equation
- Quasi-static fixed point is an attractor and repeller, in different epochs
- Bounds on dynamical variables not explicit
- Φ maps are not always contracting

Flow map Φ derivation

Suppose for some epoch $t \in [t_i, t_{i+1})$, approximate model for V is

$$
\begin{aligned}
\dot{V} &= \sum_k \bar{g}_k g_k(t)\,(V_k - V) + I, \quad V(t_i) = V_0 \\
&= A(t)V + B(t) \qquad\qquad A(t),\ B(t) \text{ known} \\
\therefore \quad V(t) &= \exp\left(\int_{t_i}^{t} A(r)\,\mathrm{d}r\right) V_0 \\
&\qquad + \int_{t_i}^{t} [A(u) + B(u)] \exp\left(\int_{r}^{t} A(r)\,\mathrm{d}r\right) du \\
&= P(t)V_0 + Q(t) \\
&= \phi_i\,(t; V_0) \qquad \text{affine linear in } V_0
\end{aligned}
$$

Define $\Phi_i : \mathbb{R} \to \mathbb{R},\ \Phi_i = v \mapsto \phi_i\,(t_{i+1}; v) + \Delta_{i+1}$

More on asymptotics

$$\sum_k \frac{\Psi_k^*}{p_k} = \frac{\bar{g}_m m^3 h}{g_{tot}}(V_m - V_\infty) + \frac{\bar{g}_n n^4}{g_{tot}}(V_n - V_\infty)$$
$$+ \frac{\bar{g}_s s}{g_{tot}}(V_s - V_\infty) + \frac{I}{g_{tot}} + \frac{\bar{g}_L}{g_{tot}}(V_L - V_\infty)$$
$$= \frac{\bar{g}_m m^3 h V_m + g_n n^4 V_n + \bar{g}_s s V_s + V_L + I}{g_{tot}}$$
$$- \frac{\bar{g}_m m^3 h + \bar{g}_n n^4 + \bar{g}_s s + g_L}{g_{tot}} V_\infty$$
$$= V_\infty - \frac{g_{tot}}{g_{tot}} V_\infty$$
$$= 0$$

using the definitions of g_{tot} and V_∞