Introduction to Computational Neuroscience: Minimal Modeling

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General Biological Questions

- What accounts for the rhythmic activity?
- Under what circumstances do synaptic and intrinsic properties of neurons cooperate or compete?
- What effect do multiple time scales have?
- What are the underlying neural mechanisms that govern behavior?

Translation to mathematics

- What accounts for the rhythmic activity?

  Periodic solutions in phase space

- Under what circumstances do synaptic and intrinsic properties of neurons cooperate or compete?

  Effect of parameters on solutions

- What effect do multiple time scales have?

  Singular perturbation theory

- What are the underlying neural mechanisms that govern behavior?

  Deriving mathematically minimal models that reveal necessary and sufficient conditions

Short-term synaptic plasticity has been identified in the majority of synapses in the central nervous system.

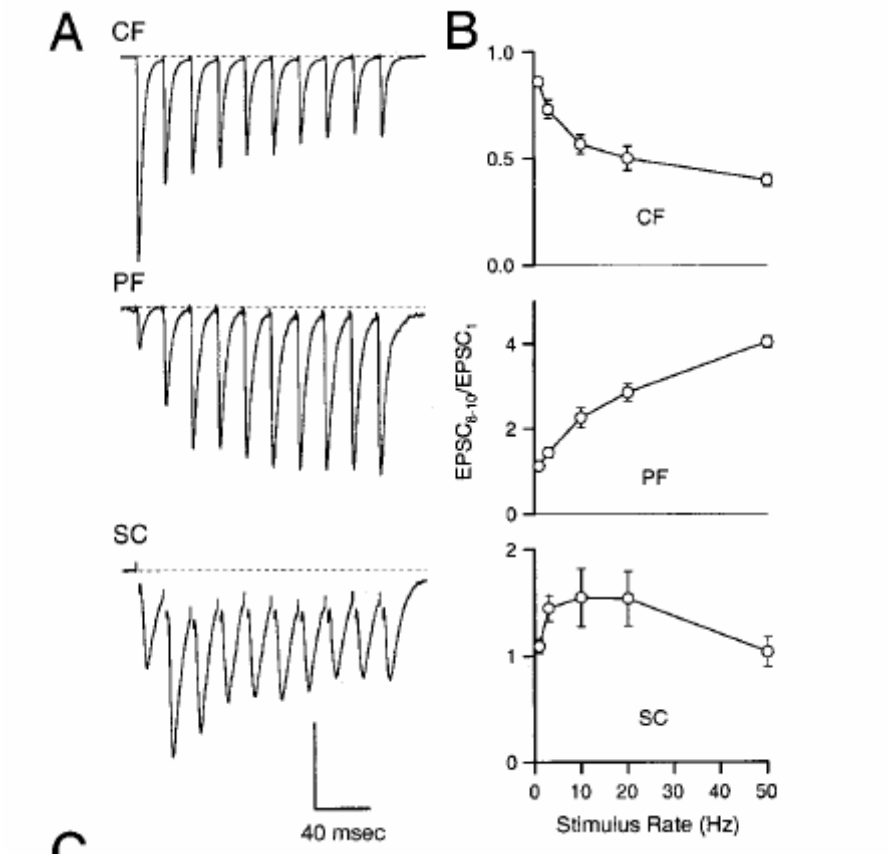


Figure 2. Diversity of short-term plasticity in the CNS. *A*, *Top*, Climbing fiber to Purkinje cell EPSCs (*CF*); *middle*, parallel fiber to Purkinje cell EPSCs (*PF*); *bottom*, CA3 to CA1 Schaffer collateral EPSCs (*SC*) recorded while stimulating afferents at 50 Hz for 10 stimuli at 34°C. Traces are averages of four to six trials each. Stimulus artifacts were suppressed for clarity. Vertical scale bar is 2, 400, and 60 pA for the CF, PF, and SC synapses, respectively. *B*, Average magnitude of the 8th–10th EPSC normalized by the first EPSC plotted as a function of stimulus frequency for the climbing fiber (*top*), the parallel fiber (*middle*), and the Schaffer collateral (*bottom*) synapses. Data are shown as mean ± SEM ($n = 4–5$).

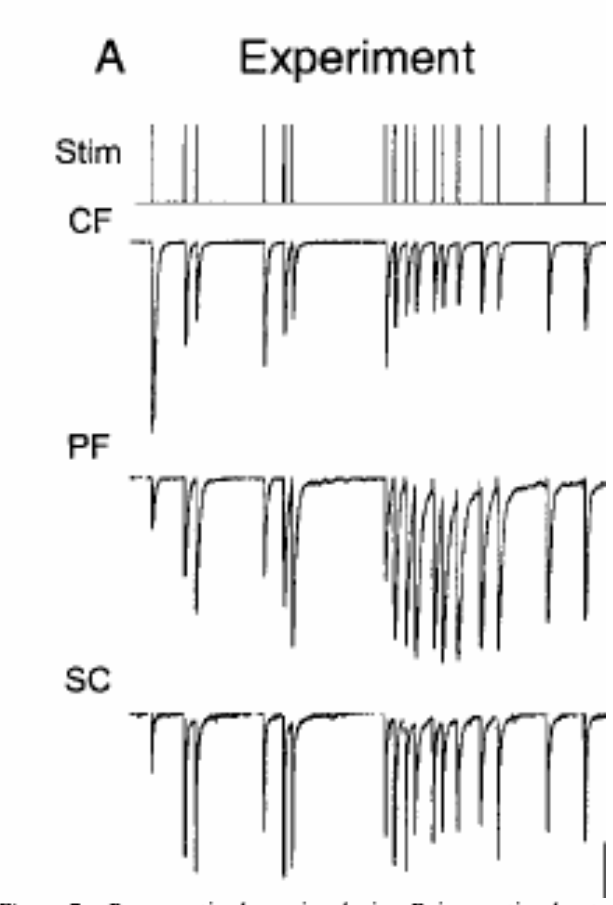
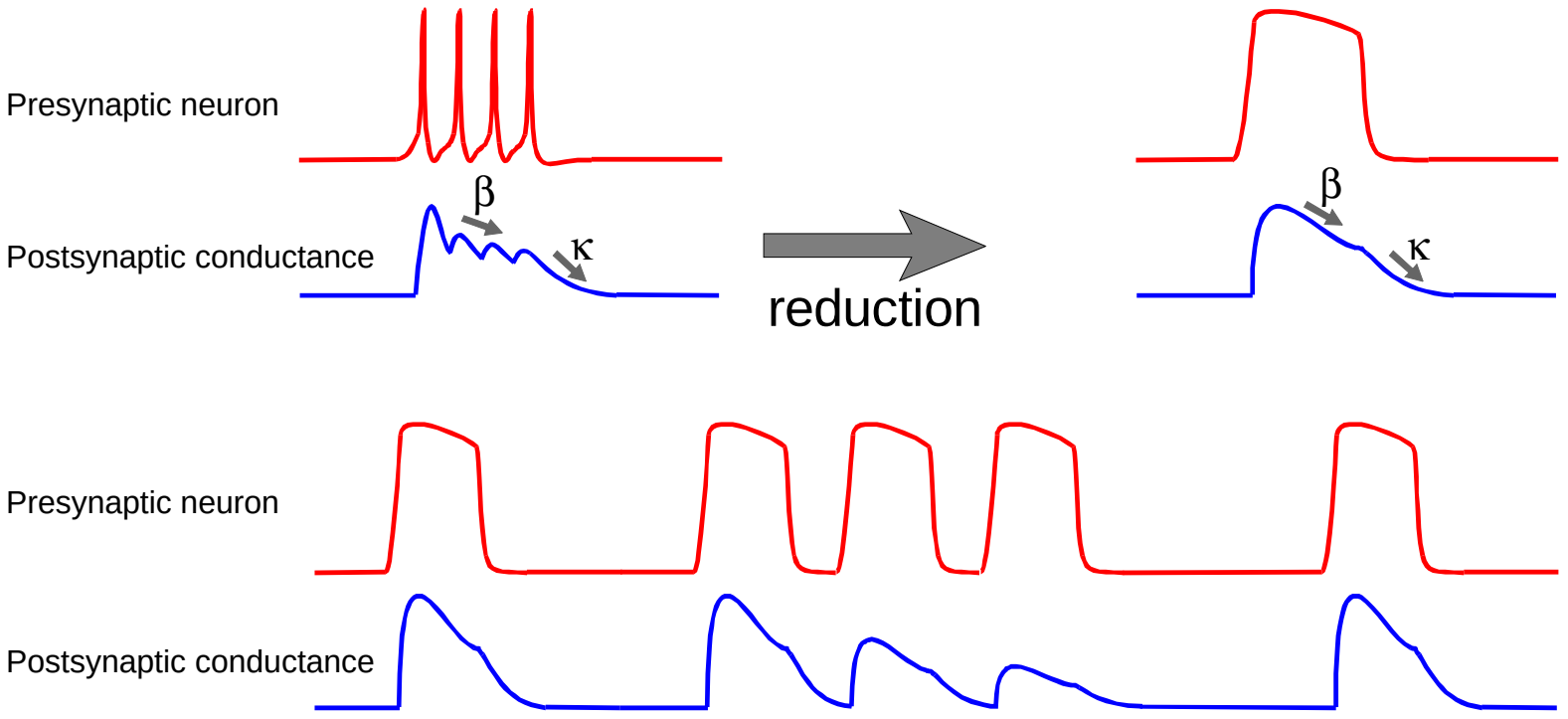


Figure 7. Presynaptic dynamics during Poisson stimulus trains. *A*, Examples of EPSCs recorded in response to an irregular stimulus train with average rate 20 Hz at the climbing fiber (*CF*), parallel fiber (*PF*), and Schaffer collateral (*SC*) synapses. Stimulus artifacts were suppressed for

From Dittman et al., J. Neurosci, 2000.

Dynamics of short-term synaptic depression



τ_κ = Inhibitory decay time constant

τ_β = Depression time constant

τ_α = Recovery from depression time constant

Plasticity: What's it good for?

In cortical circuits:

- Automatic gain control
- Network stabilization
- Population rhythm generation
- Direction selectivity
- Novelty detection
- Coincidence detection
- Generation of frequency-selective responses

Abbott, Nelson, Reyes, Markram, Tsodyks
Rinzel, Marder, Nadim etc…

In rhythm generating networks:

- Multistability
- Phase maintenance
- Episodic Bursting

Also:

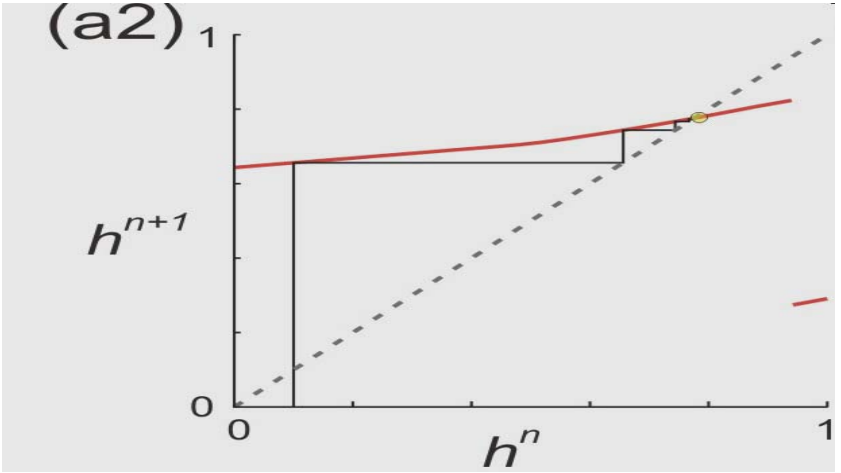
- Short-term habituation of the mammalian startle response
- Differential stimulus filtering
- On-off switching

What advantages does synaptic plasticity confer upon a rhythmic network?

- The answer is architecture dependent.
- Plasticity allows different parameters to be relevant to the network at different frequencies or at different moments in the rhythmic cycle.
- Plasticity can work synergistically with intrinsic neuronal properties.

We will discuss several biologically motivated minimal MATHEMATICAL examples:

We will also discuss in detail one model with no plasticity that leads to an interesting one-dimensional map.

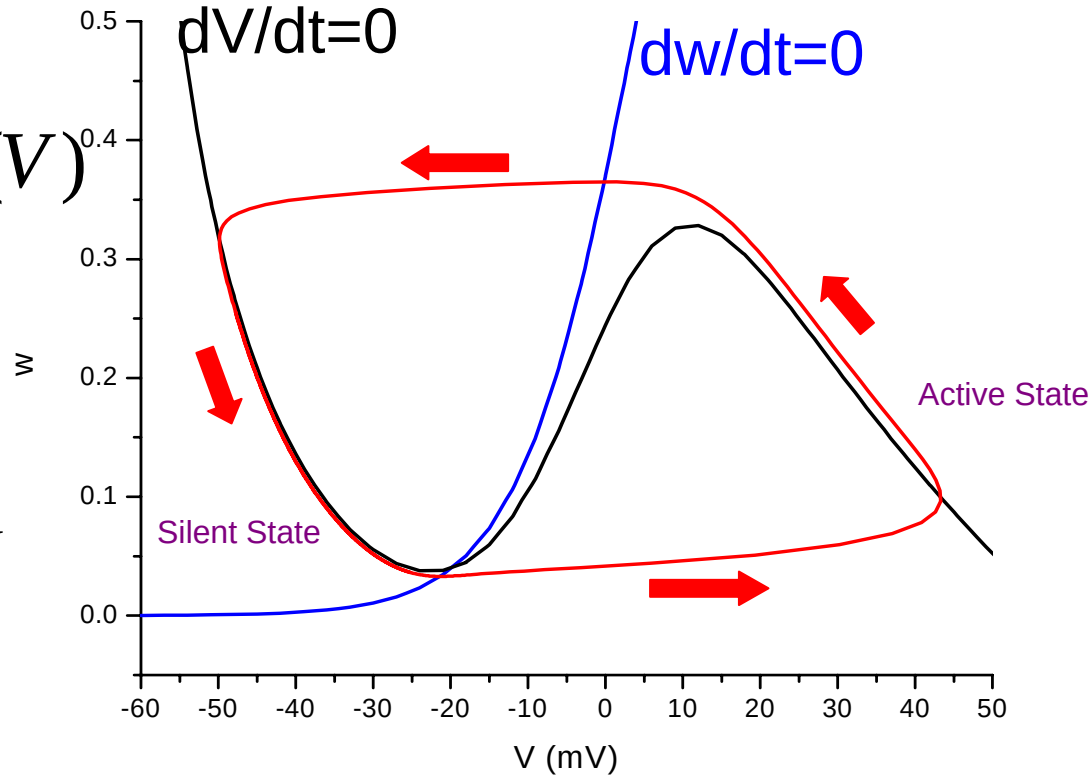


2-D model for single neurons

Based on Hodgkin-Huxley Formalism

$$\varepsilon V' = F(V, w)$$

$$w' = (w_\infty(V) - w) / \tau_w(V)$$



As $\varepsilon \to 0$ Geometric Singular Perturbation theory becomes applicable

Slow Equations

$$0 = F(V, w)$$

$$w' = (w_\infty(V) - w) / \tau_w(V)$$

Fast Equations $(t = \varepsilon\zeta)$

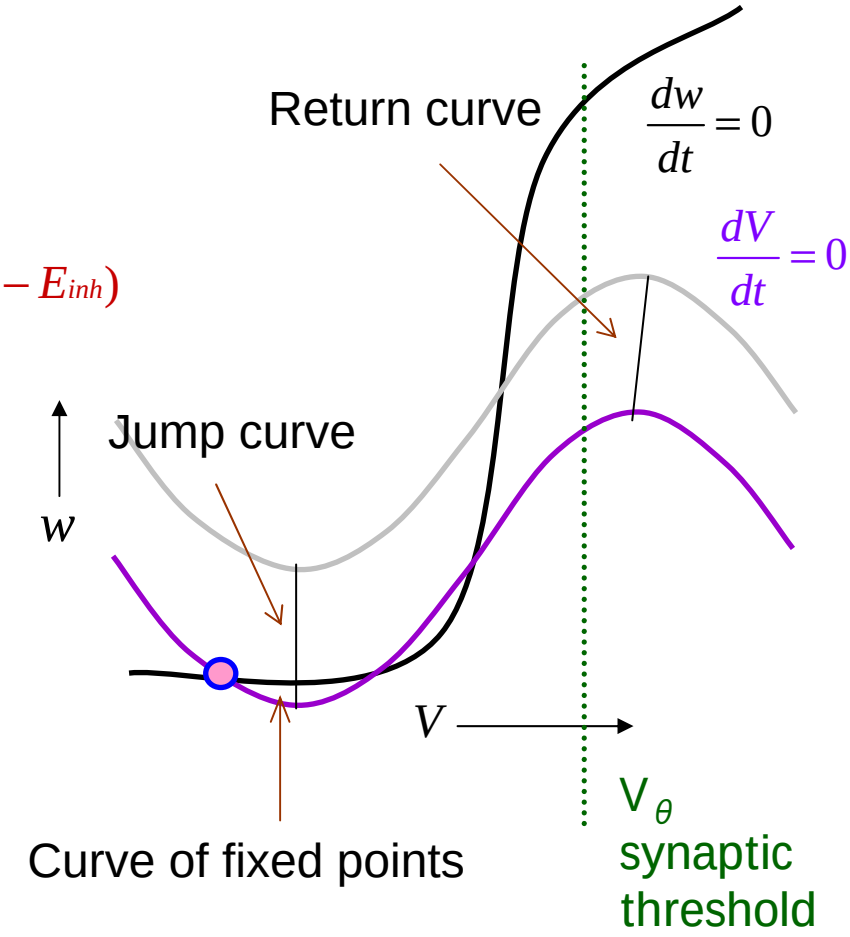
$$dV / d\zeta = F(V, w)$$

$$dw / d\zeta = 0$$

Model Effect of inhibition

$$\begin{cases} \varepsilon \dfrac{dV}{dt} = F(V,w) - \boldsymbol{I_{syn}} \\ \dfrac{dw}{dt} = \dfrac{w_\infty(V) - w}{\tau_w(V)}; \end{cases} \qquad I_{syn} = g_{\max} s(V_{pre})(V - E_{inh})$$

- Inhibition lowers the V-nullcline
- If inhibition is strong enough, a curve of “fixed points” is introduced on the inhibited branches.
- Local minima form a jump curve



Inhibitory Synapse

Synaptic current: $I_{syn} = - g_{max}\, s\, (v_{post} - E_{syn})$, $E_{syn} < v_{rest}$

$$s' = \frac{1-s}{\tau_\gamma} H_\infty(V_{pre} - V_\theta) - \frac{s}{\tau_\kappa} H_\infty(V_\theta - V_{pre})$$

Slow Equations in the silent phase

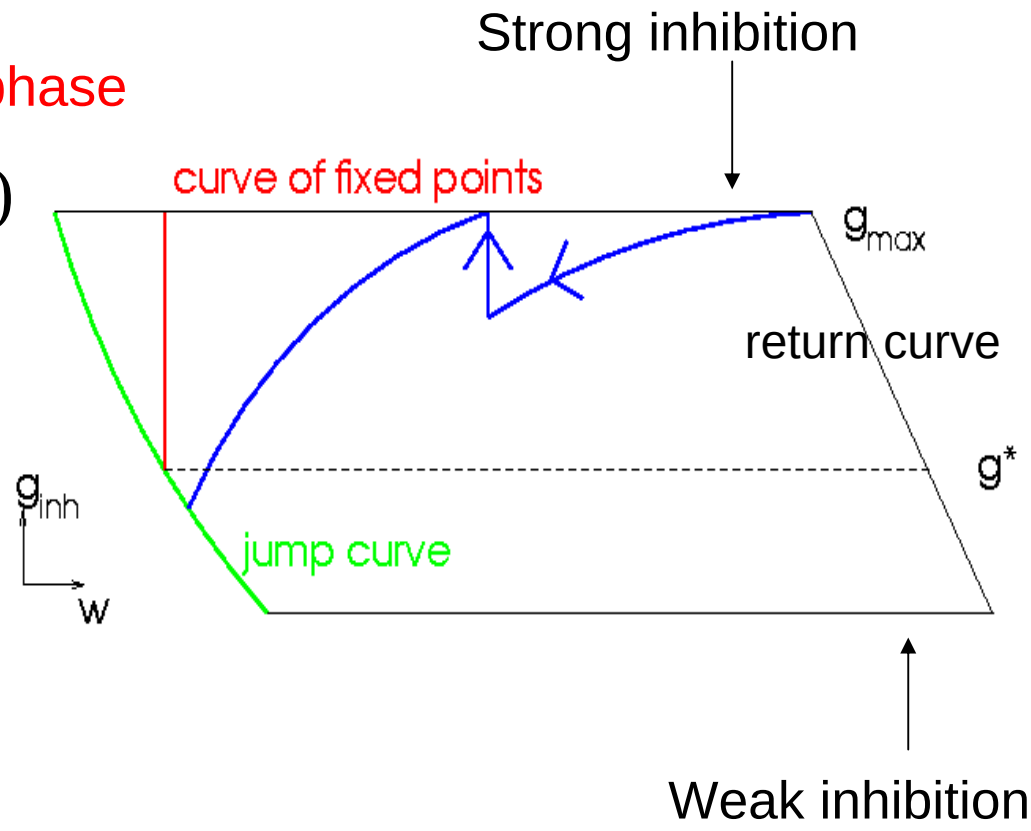
$$0 = F(V,w) - g_{\max}\, s(v - E_{syn})$$

$$w' = (w_\infty(V) - w) / \tau_w(V)$$

$$s' = -s / \tau_\kappa$$

$$g_{inh} = g_{\max}\, s$$

S is reset to 1 with a pre-synaptic spike



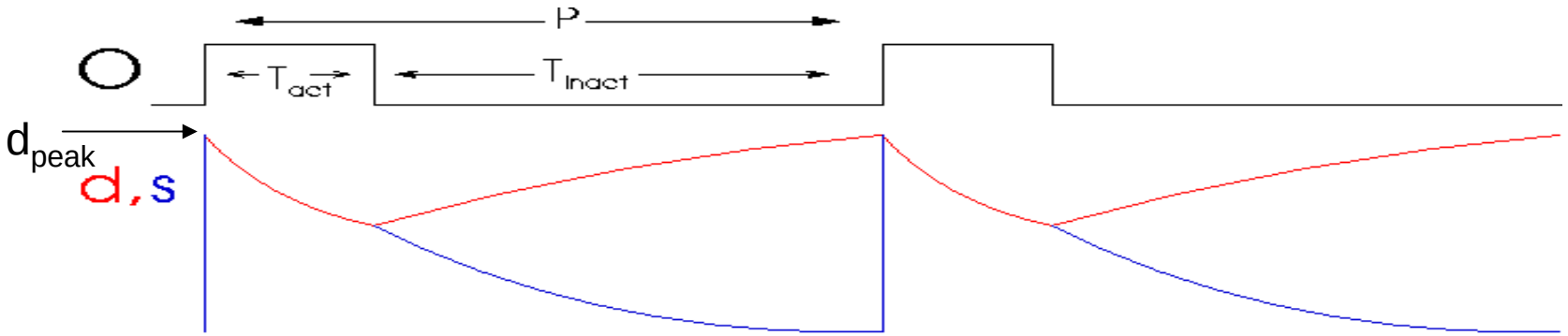
Models for depressing synapses

Like other phenomenological reset models of Abbot et al, Markram &Tsodyks

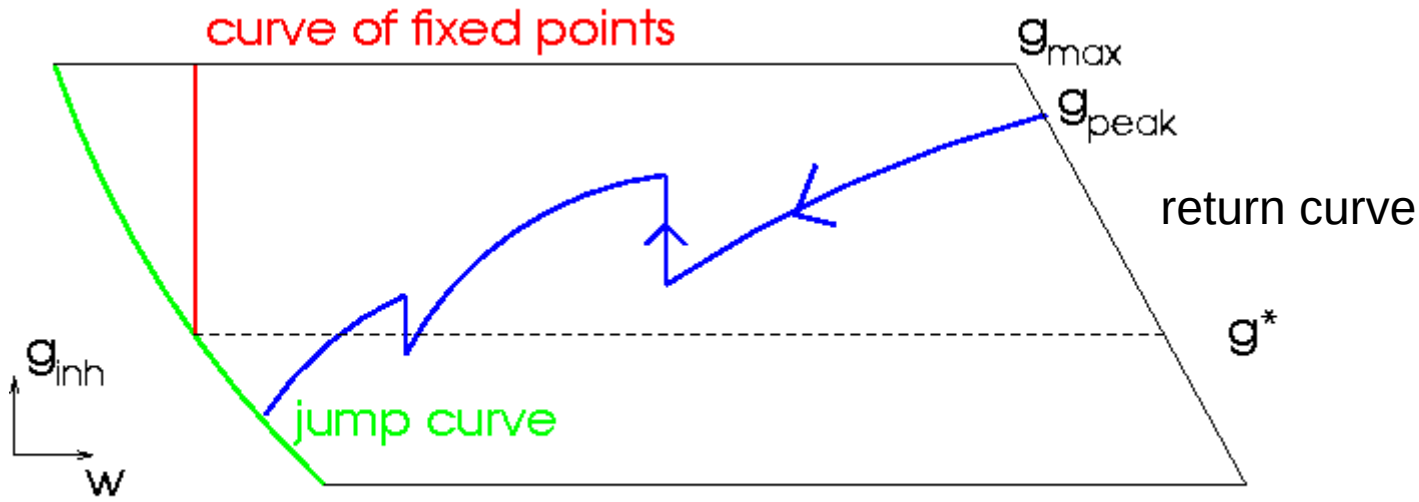
$$d' = \frac{1-d}{\tau_\alpha} H_\infty(V_\theta - V_{pre}) - \frac{d}{\tau_\beta} H_\infty(V_{pre} - V_\theta)$$

Depression

s is reset to the value of d at the moment of a presynaptic spike

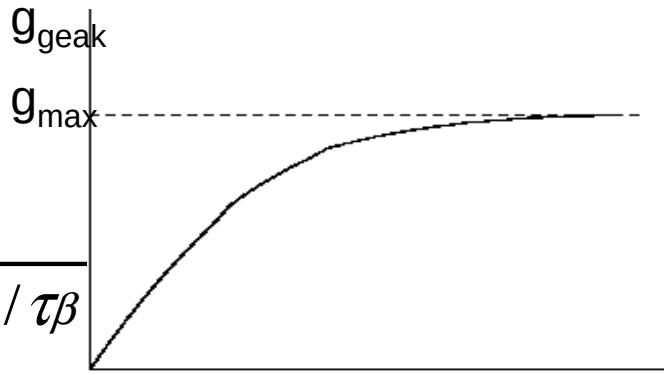


Effect of depression on post-synaptic cell



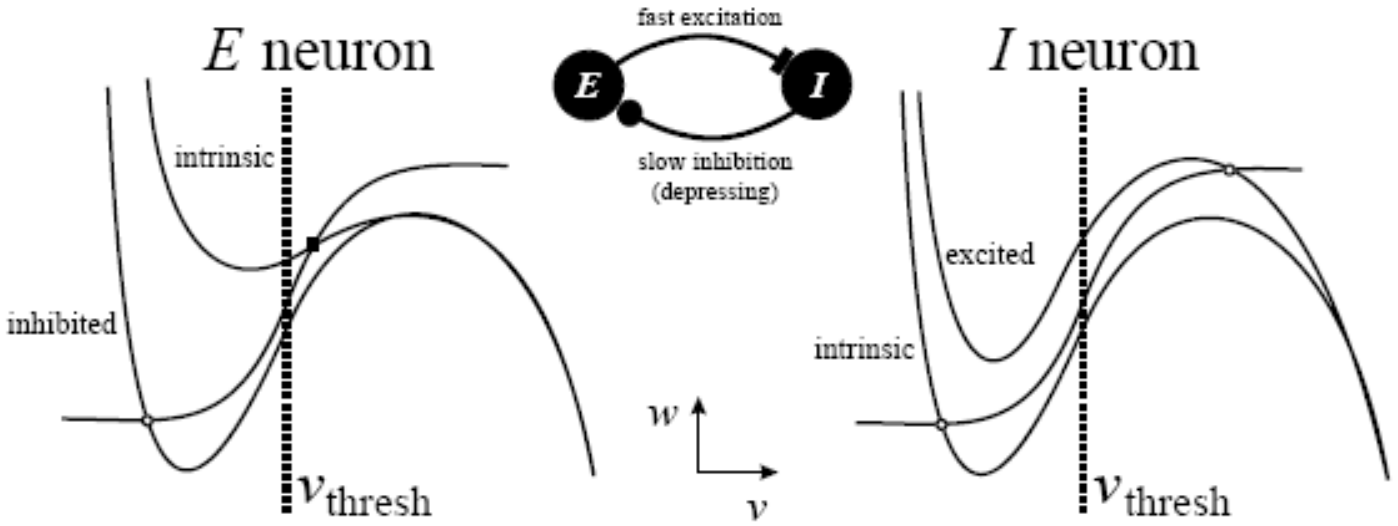
S is reset to current value of dg_{max} with each pre-synaptic spike

$$g_{\text{peak}} = g_{\text{max}} \frac{1 - e^{-T_{Inact} / \tau\alpha}}{1 - e^{-T_{Inact} / \tau\alpha} e^{-T_{Act} / \tau\beta}}$$

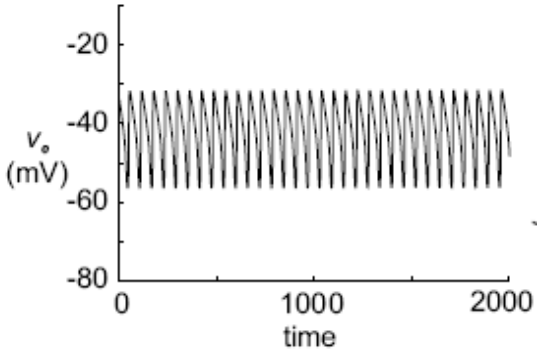


P (but increasing only T_{Inact})

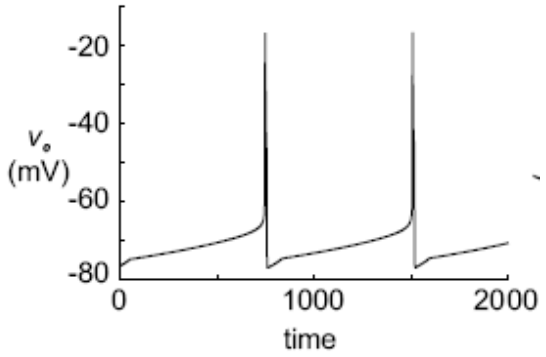
Bistability in feedback networks (B., Manor, Nadim, 2001)



Cell controlled



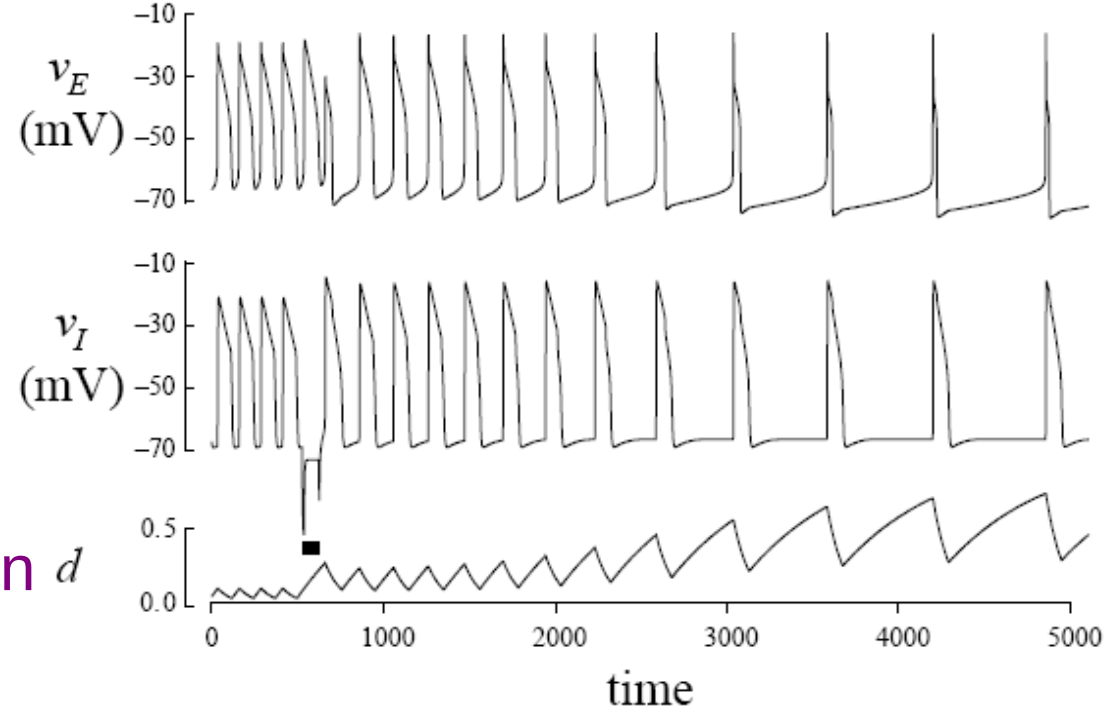
Synapse controlled



E-cell

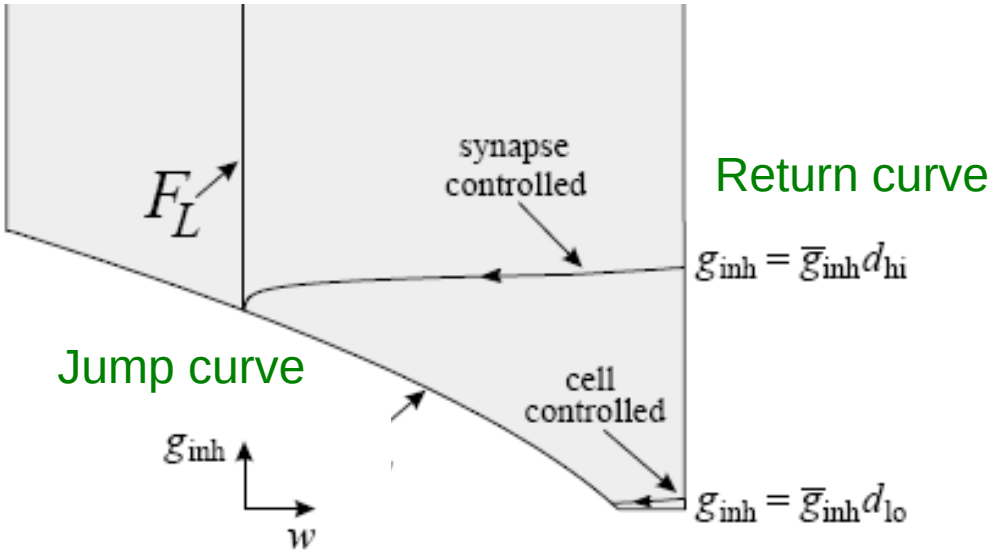
I-cell

depression d



Slow manifold for the silent state of the E neuron

We use a one-dimensional map to measures the value of d whenever E is on the return curve

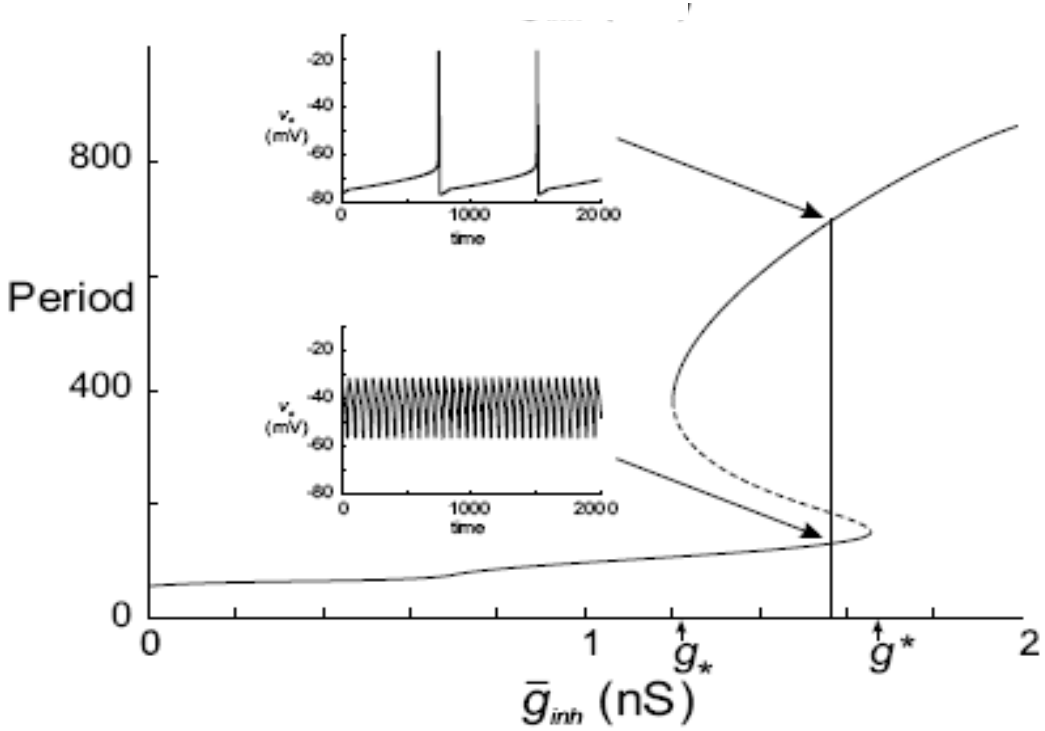


Return curve

Jump curve

Two modes of oscillations

- A cell-controlled high frequency mode (weak synapse)
- A synapse-controlled low frequency mode (strong synapse)

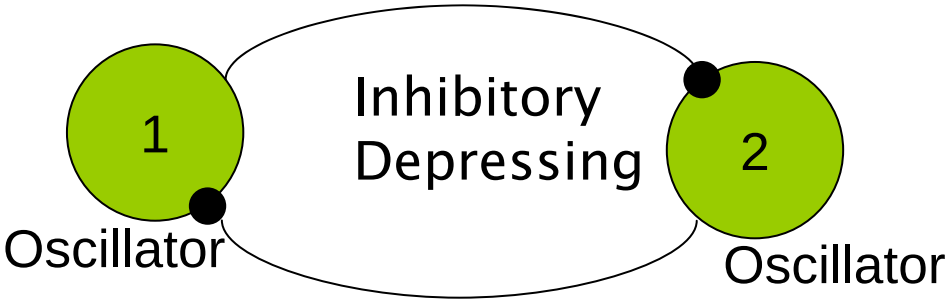


Feedback + plasticity forces the synaptic strength to **specific** values

We can use this observation in other contexts

Bistablity of anti-phase solutions

Motivated by experimental work of Nadim et al (2001,2005)



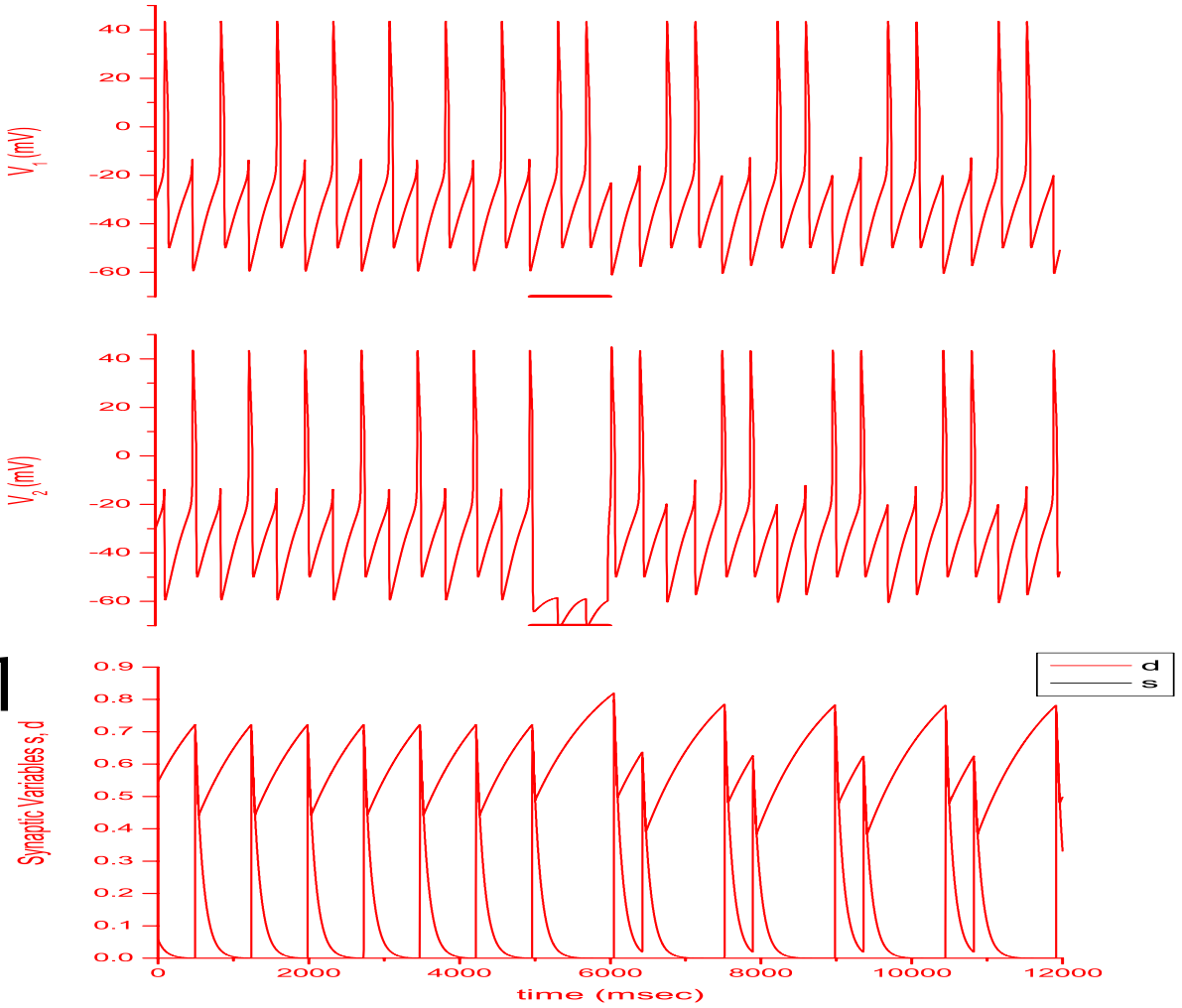
Commonly found solutions that arise in such networks are anti-phase spikes.

But what if we could get neuron 1 to fire two spikes in a row?

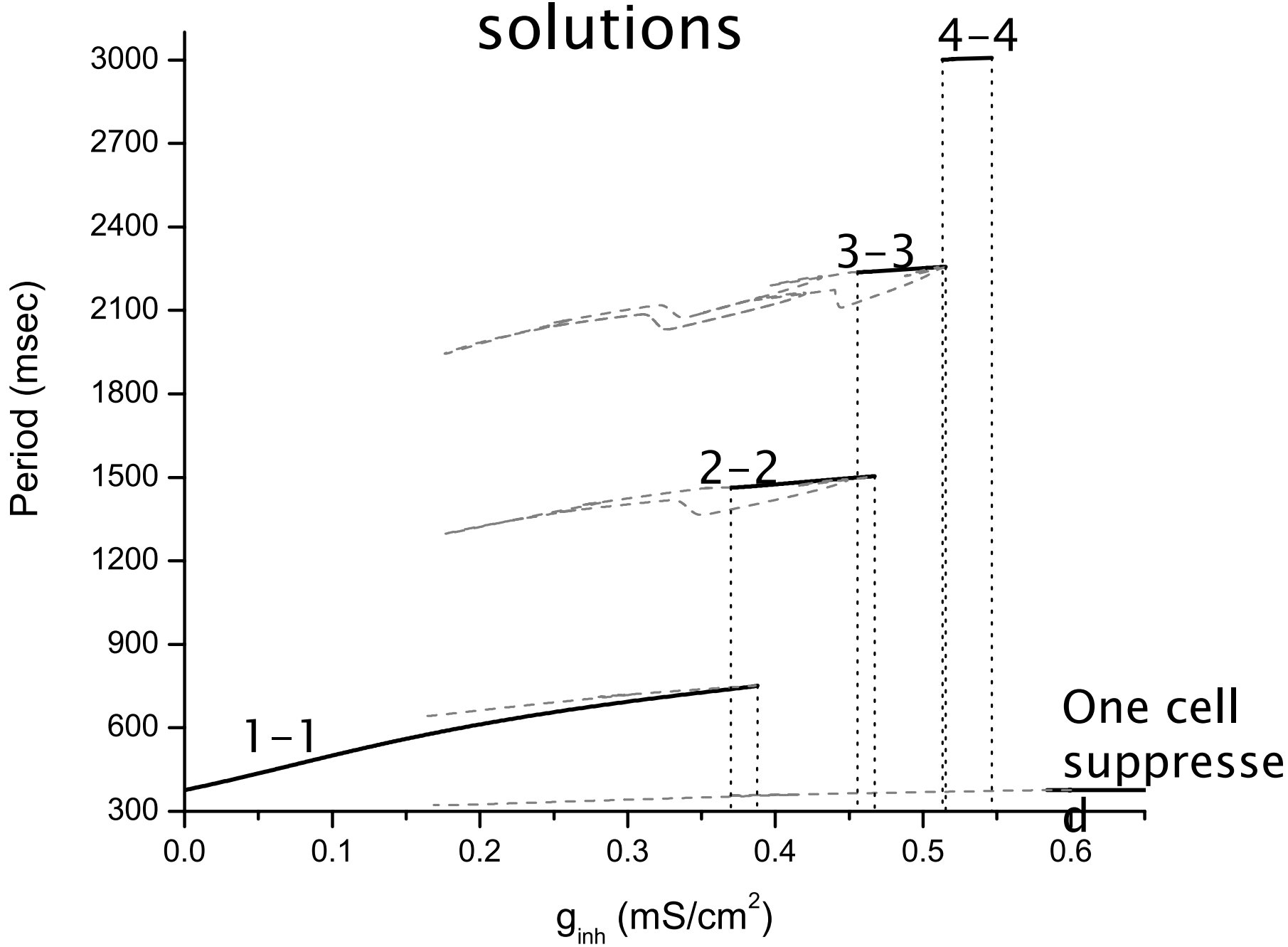
Bistability between 1-1 antiphase and 2-2 antiphase firing (Booth, B. 2009)

$g_{inh} = 0.38$ mS/cm^2

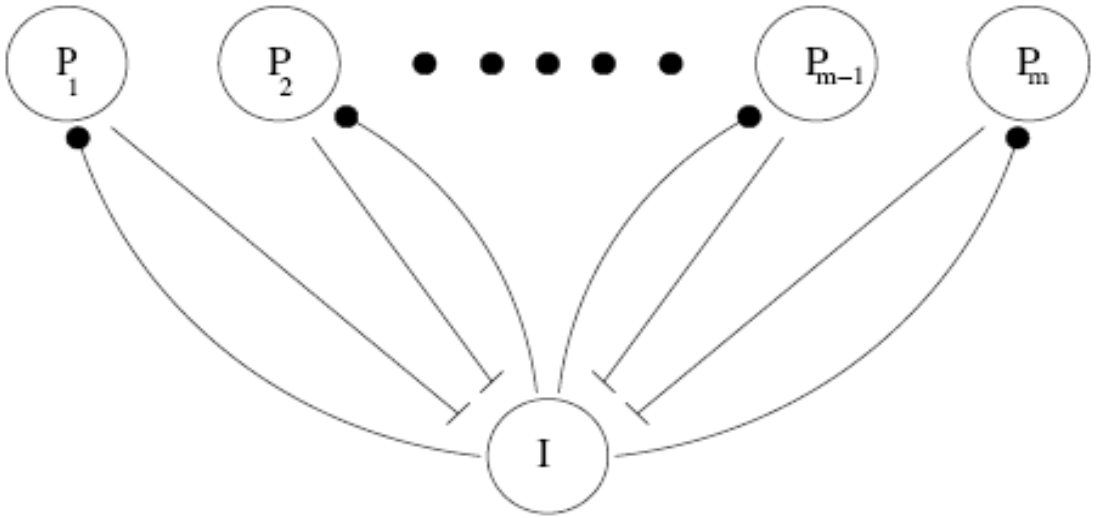
- Cell 2 is transiently inhibited allowing its synapse to recover more fully.
- Stronger inhibition to Cell 1 allows Cell 2 to spike twice.
- Cell 1 synapse also recovers



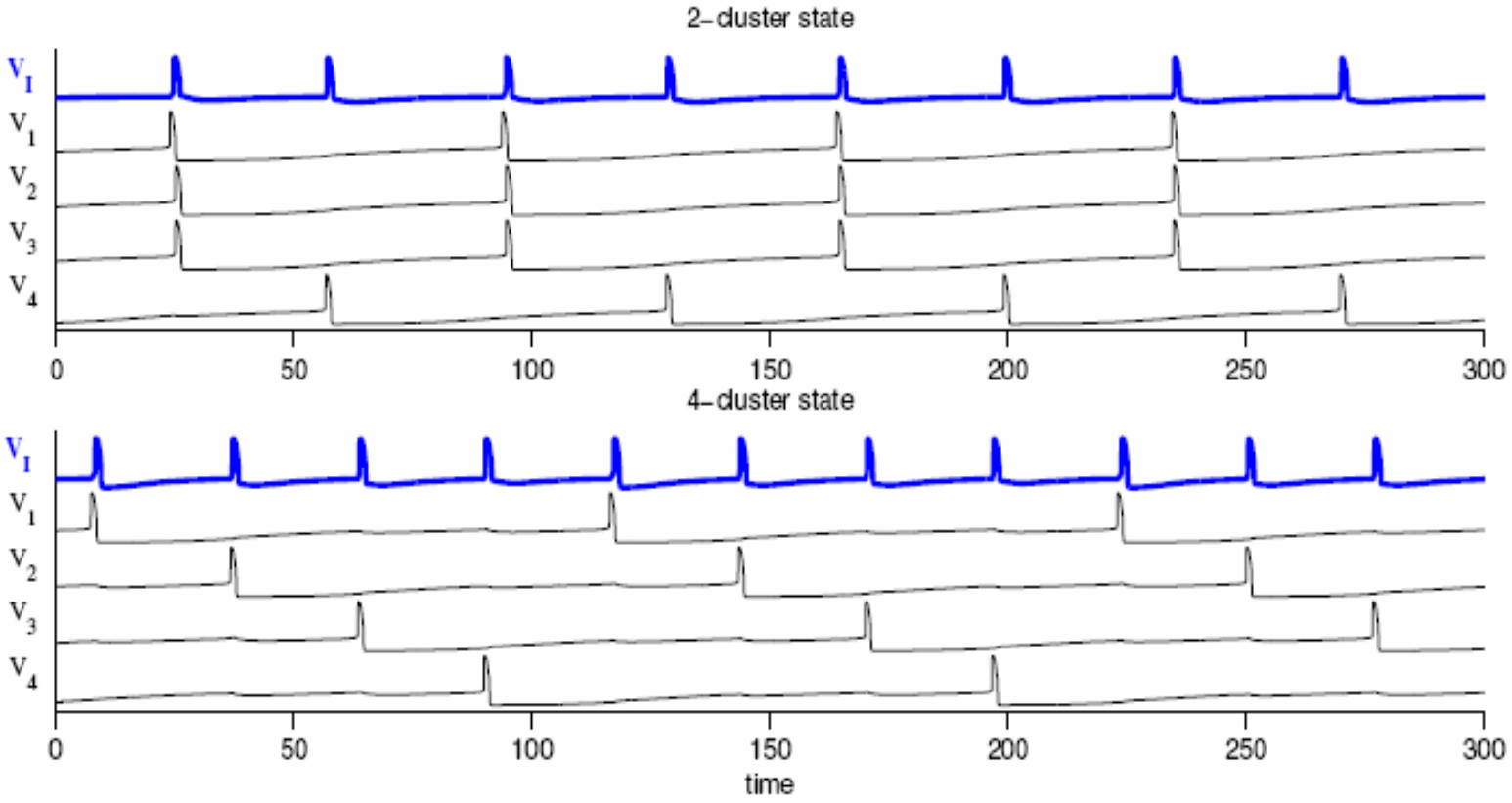
Bifurcation diagram of n-n antiphase solutions



Multistability and clustering in globally inhibitory networks (Chandrasekaran, Matveev, B. 2009)

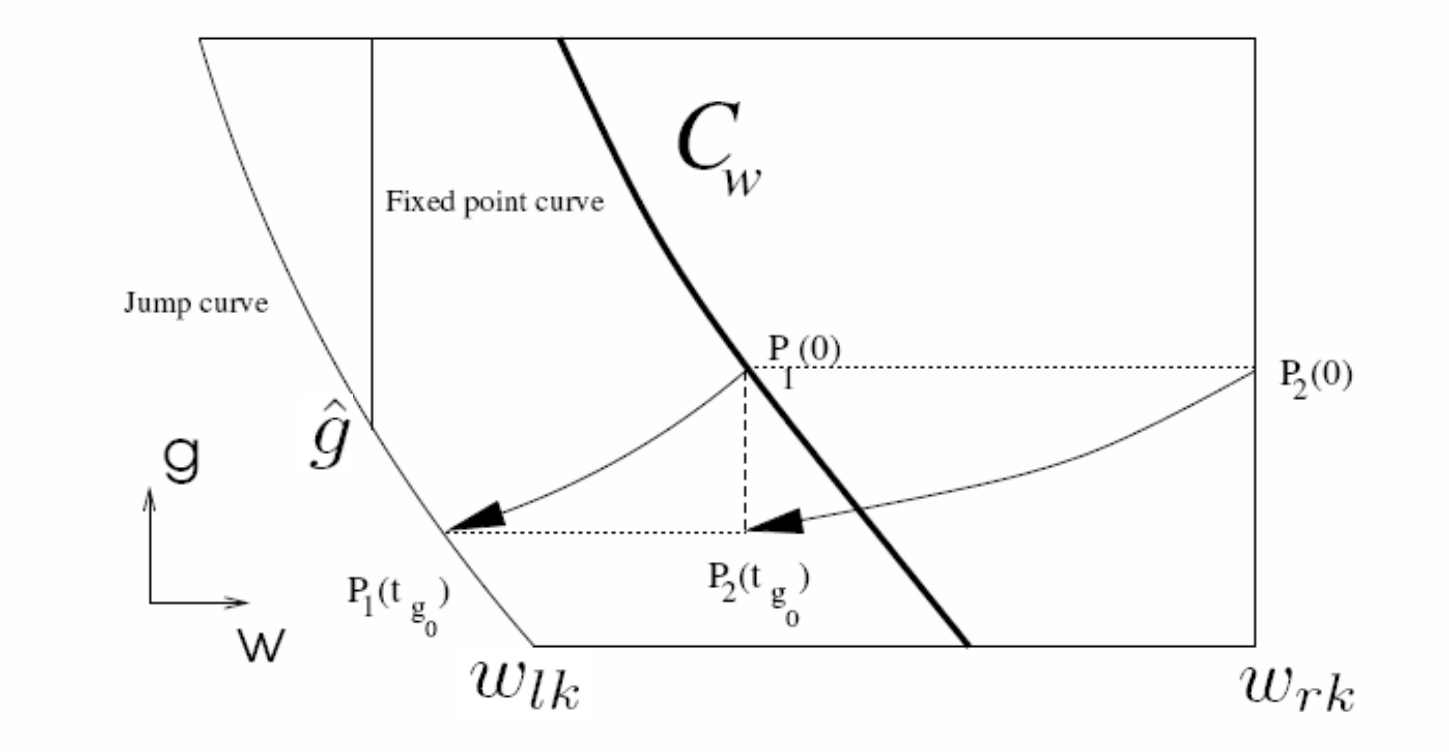


- Synapses from I to P are inhibitory and depressing
- Synapses from P to I are excitatory
- I fires whenever any P_k fires



- 1- and 3-cluster solutions also exist
- interspike interval of **I** decreases with number of clusters
- cluster solutions are periodic

Periodicity condition in *w*



$$g_0 e^{-t_{g0}/\tau_s} + \frac{\hat{g} w_{rk}}{w_{lk}} e^{-n t_{g0}/\tau_w} = \hat{g}$$

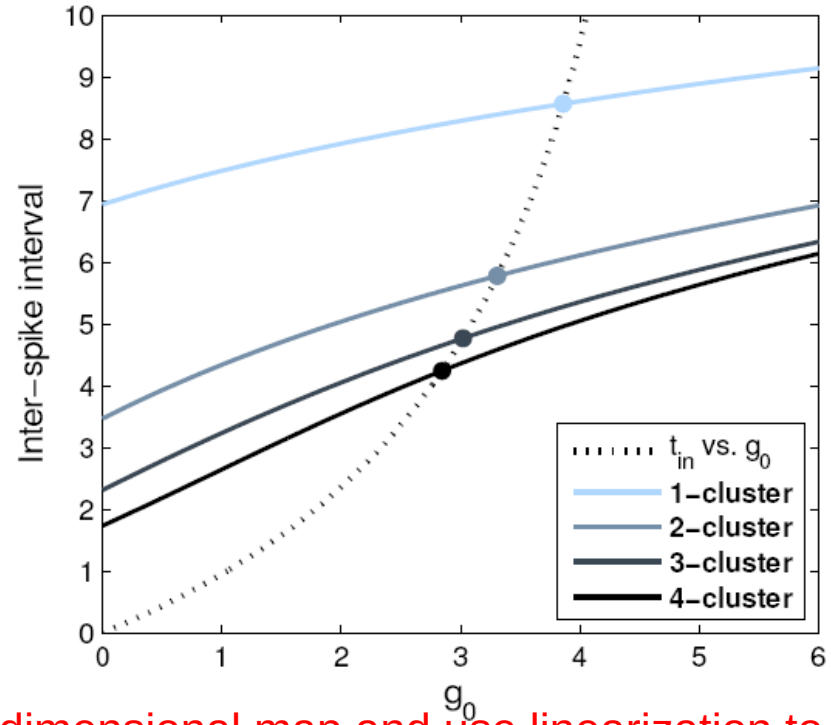
t_{g_0} is the time it takes the leading cell to reach the jump curve

n = number of clusters (*n*=2 shown above)

Periodicity condition in *g*

- If $g(0)=g_0$, what interspike interval t_{in} is needed to allow $g(t_{in})=g_0$.

$$t_{in}(g_0) = \tau_D \ln \frac{\bar{g} - r g_0}{\bar{g} - g_0} \qquad r = e^{-T_{act}/\tau_\beta}$$



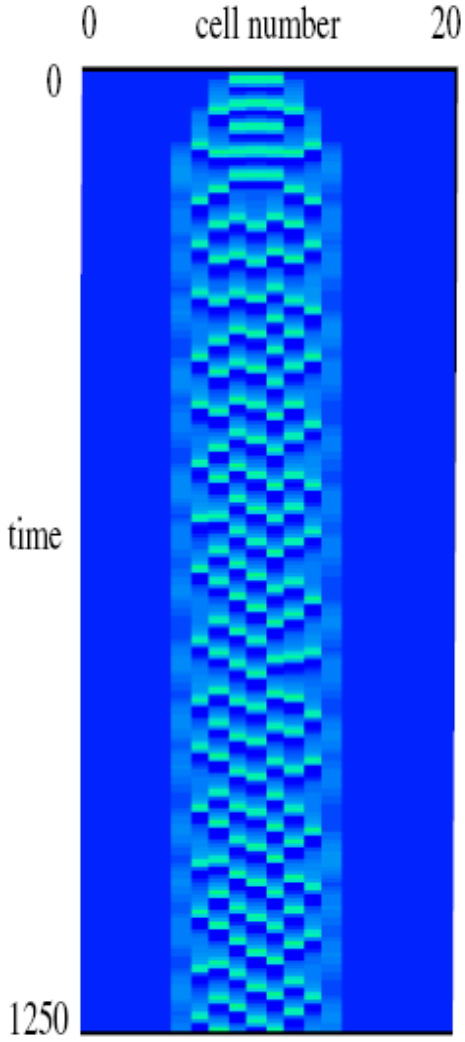
Discrete *g* values

We can derive an *n*-dimensional map and use linearization to prove stability of solutions

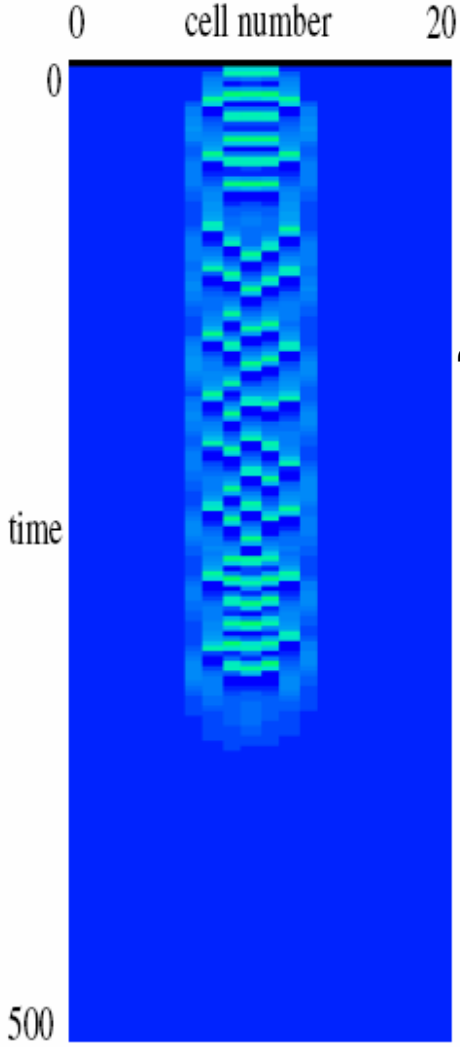
Localized Activity in Excitatory Networks

(Rubin, B. 2004, also see Drover and Ermentrout)

Bump – no depression



Toggle-switch – with depression



Strong synapses

“Weak” stable synapses

Depressed synapses

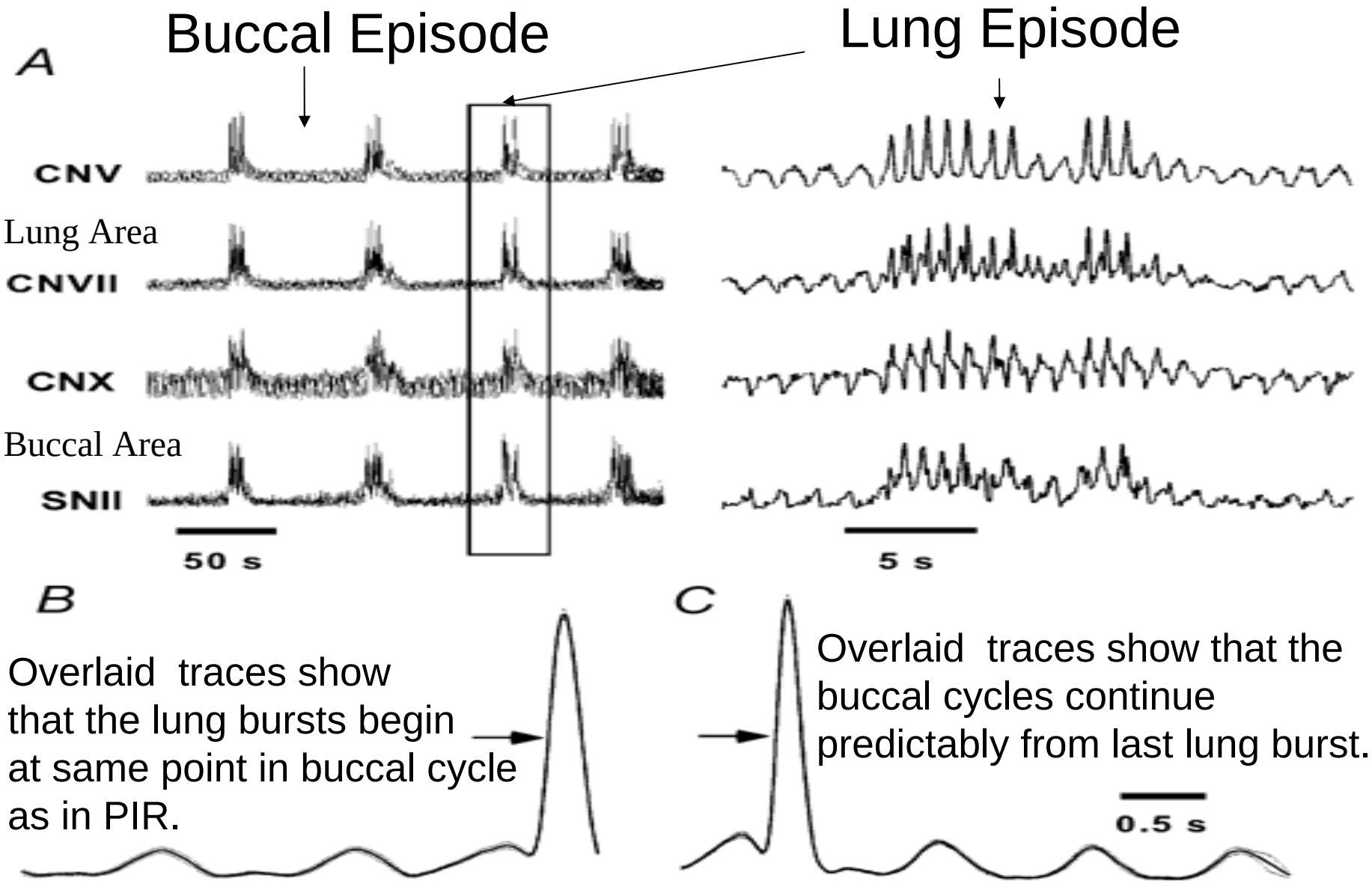
Episodic bursting in respiratory systems

Motivated by experimental work of Wilson (B., Lewis, Wilson, 2005)

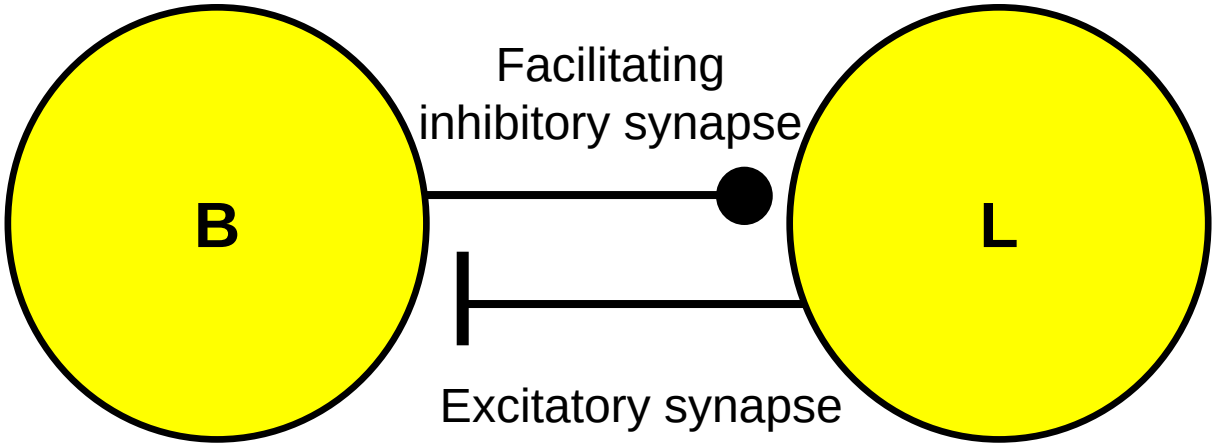
- Spontaneous population bursts are observed in cortex, hippocampus etc. and also during development (chick spinal cord, tadpole breathing)
- Tsodyks et al and O'Donovan & Rinzel's group have models for such behavior which involve synaptic plasticity.
- Our example is really, really basic.

Experimental Observations

Wilson et al 2002



A biologically constrained minimal model



$$v_L' = - I_{ion} - g_{inh} s_B [v_L - E_{inh}]$$

Morris-Lecar type equations

$$w_L' = [w_\infty(v_L) - w_L]/\tau(v_L)$$

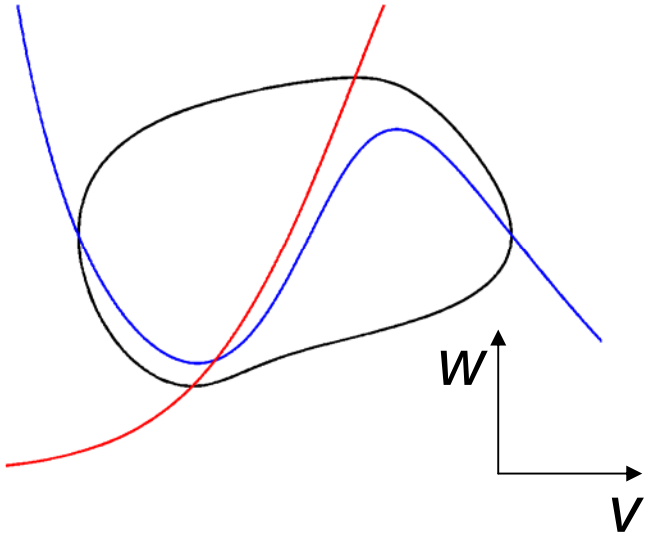
$$v_B' = - I_{ion} - g_{exc} s_L [v_B - E_{exc}]$$

$$w_B' = [w_\infty(v_B) - w_B]/\tau(v_B)$$

$$s_L' = \nu[1-s_L]s_\infty(v_L) - \eta s_L[1-s_\infty(v_L)]$$

$$s_B' = \gamma[d_B - s_B]s_\infty(v_B) - \kappa s_B[1-s_\infty(v_B)]$$

$$d_B' = [1-d_B]d_\infty(v_B)/\tau_\alpha - d_B[1-d_\infty(v_B)]/\tau_\beta$$

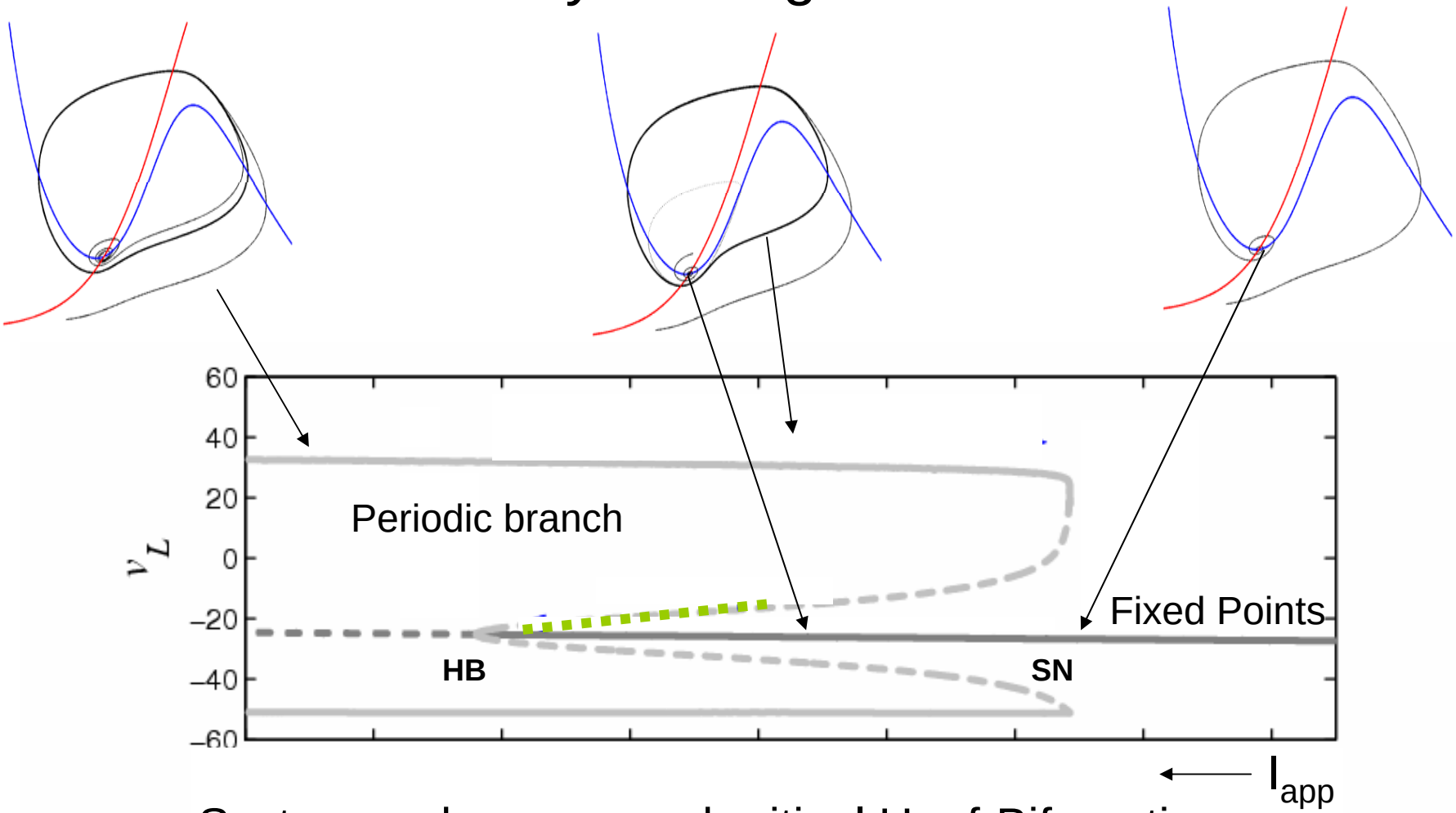


v_L = lung voltage, v_B = buccal voltage

s_L = excitatory synaptic gating

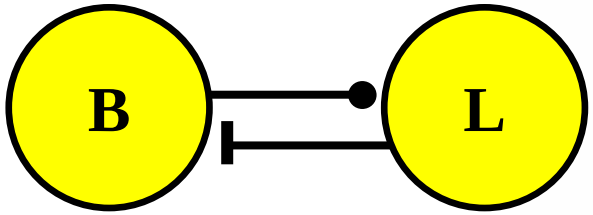
s_B = inhibitory synaptic gating, d_B = facilitation/de-facilitation gating

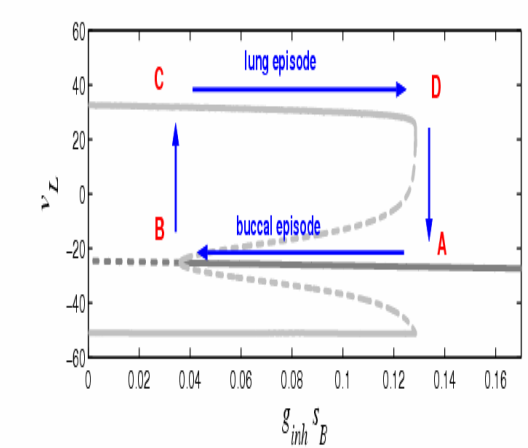
Bistability of Lung Oscillator

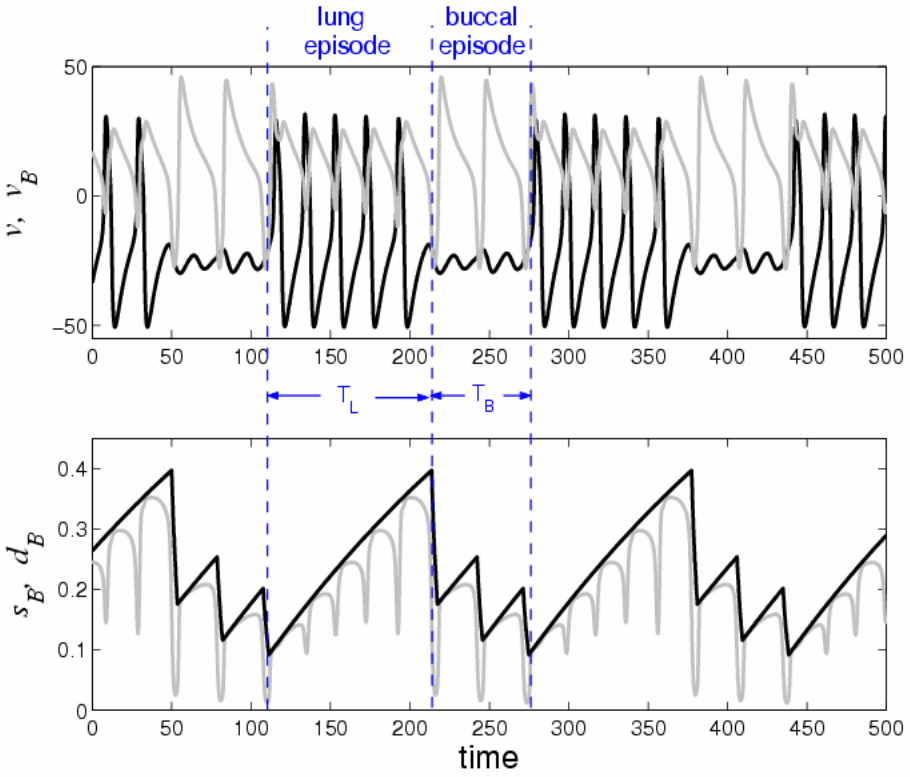


- System undergoes a subcritical Hopf-Bifurcation
- Oscillations arise/disappear via saddle-node bifurcations
- In between bifurcation points, there is a region of bistability
- Nothing special about I_{app}

Episodic nature of lung and buccal driven ventilation







V_L= black
V_B = gray

d_B= black
s_B = gray

T_L determined by the facilitation time constant τ_α.

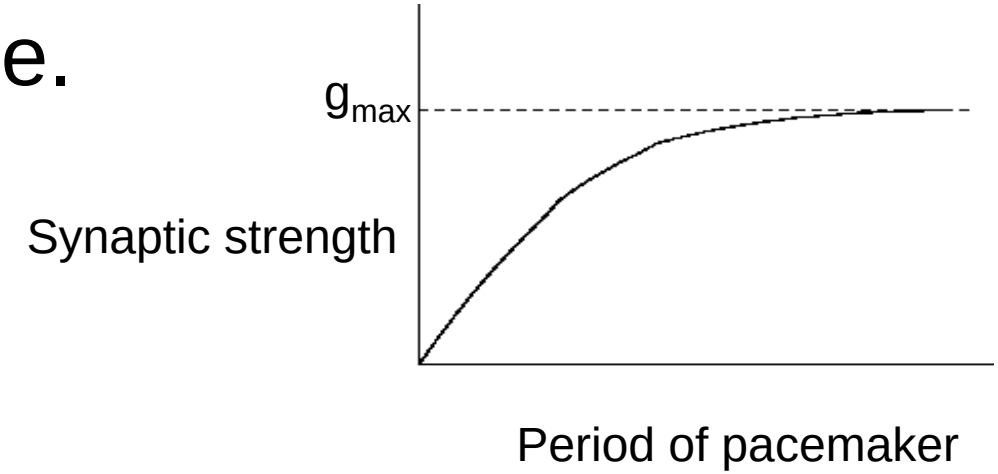
T_B determined by de-facilitation time constant τ_β.

Remarks about feedback networks

- Plasticity allows regeneration of synaptic currents.
- Plasticity plays a role in setting the network frequency and thereby forces the synapse to operate at a strength dictated by that frequency.
- Plasticity allows certain parameters to be relevant for certain solutions (synapse controlled or cell controlled)

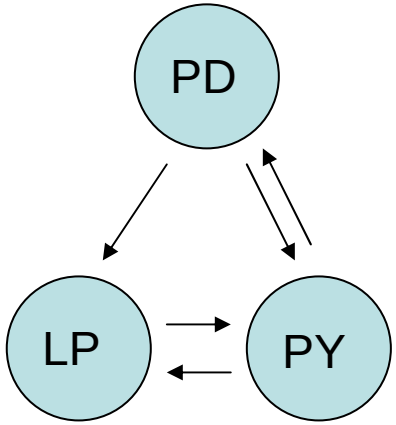
Feedforward Networks

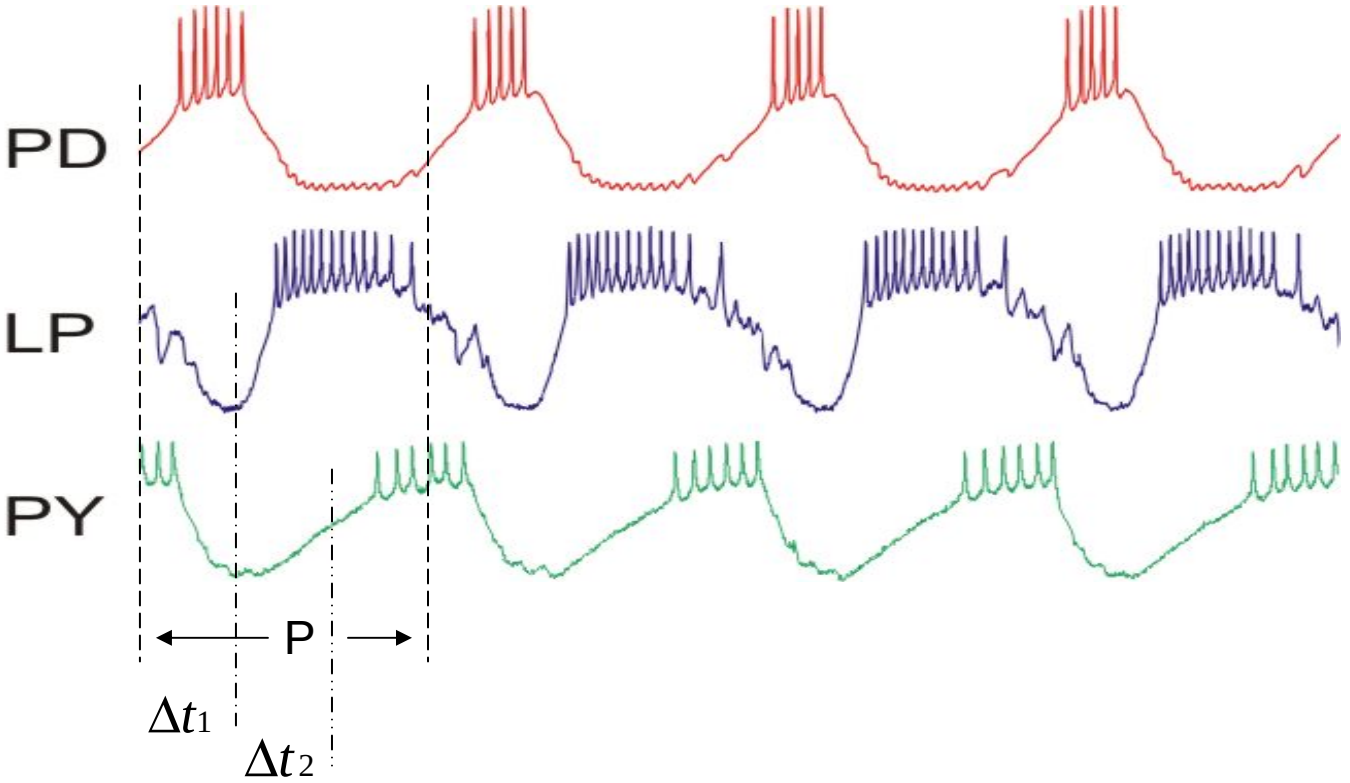
- Often these are driven by a pacemaker or external inputs.
- By controlling the period of these inputs, the level of plasticity in the network can be fine tuned – differs from the feedback case.



Phase control of the pyloric rhythm

(*Cancer borealis*)





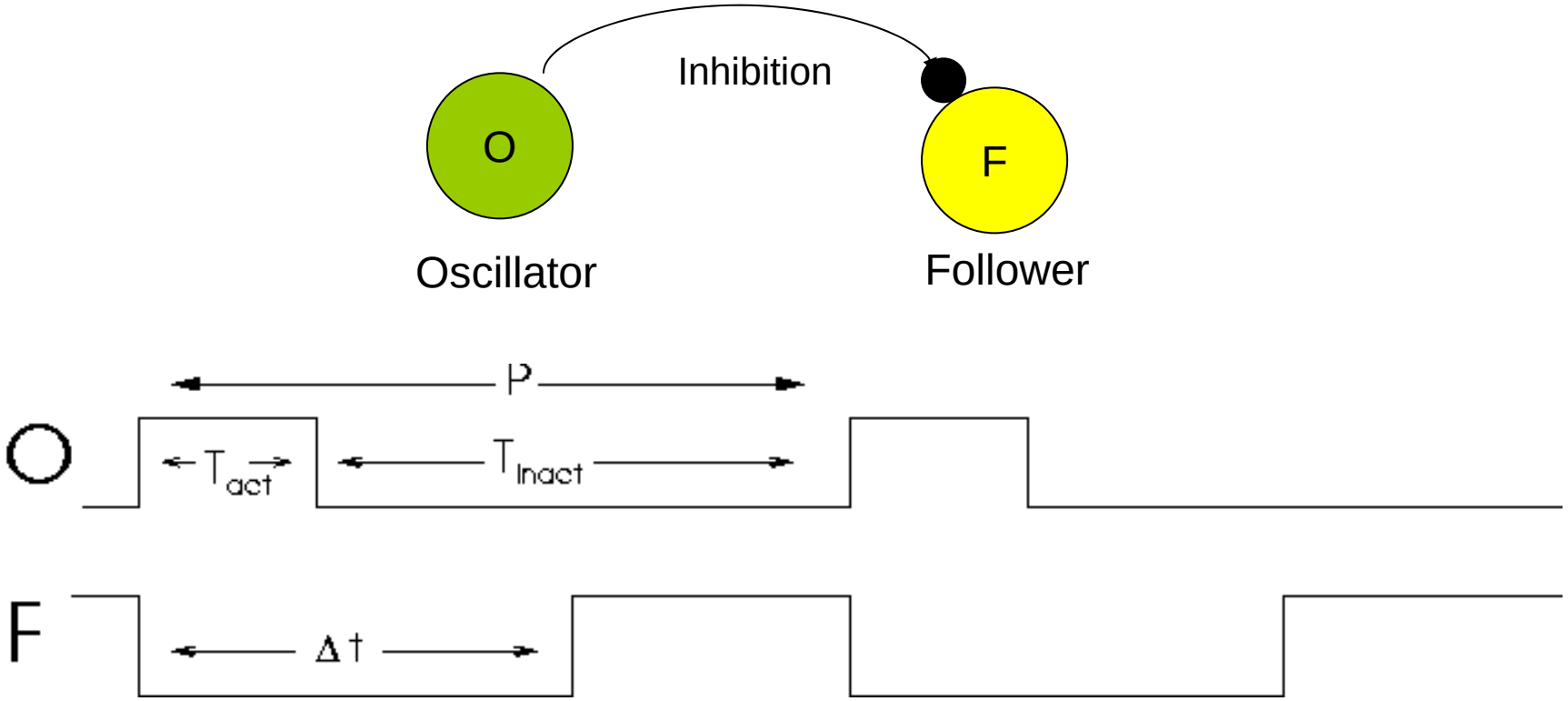
$$\phi_1 = \frac{\Delta t_1}{P}$$

$$\phi_2 = \frac{\Delta t_2}{P}$$

Phase of LP and PY remains constant as the period of the pacemaker PD changes (Hooper, 94,95).

What role does plasticity play in setting phase?

(Manor,B., Booth, Nadim, 2004)

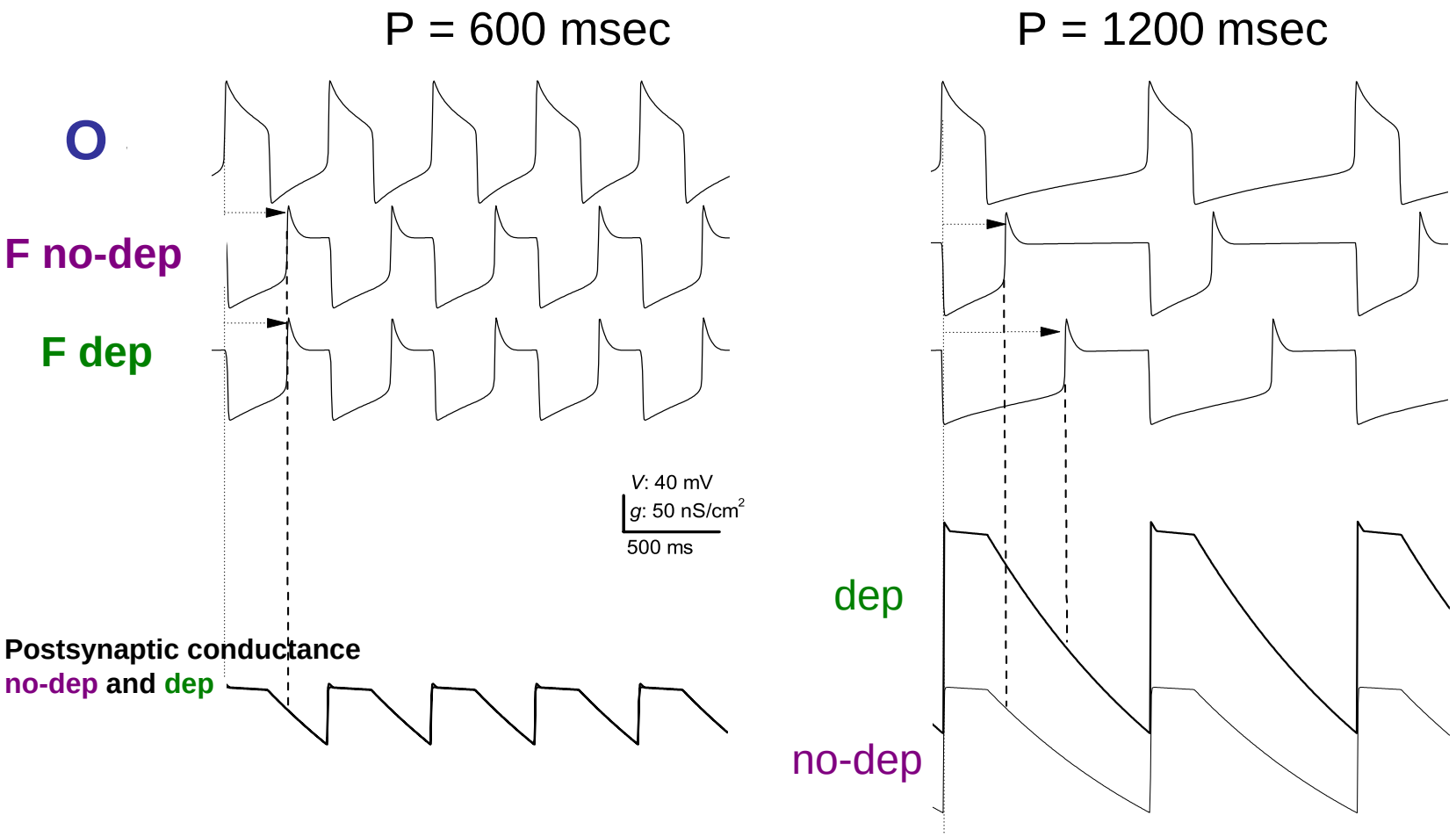


$$\phi = \frac{\Delta t}{P}$$

Which parameters determine the time Δ t at which F fires?

Simple premise: Δ t should be a function of synaptic strength.

Depressing vs. non-depressing synapse in an O-F network



- Period P changed by varying O's interburst interval

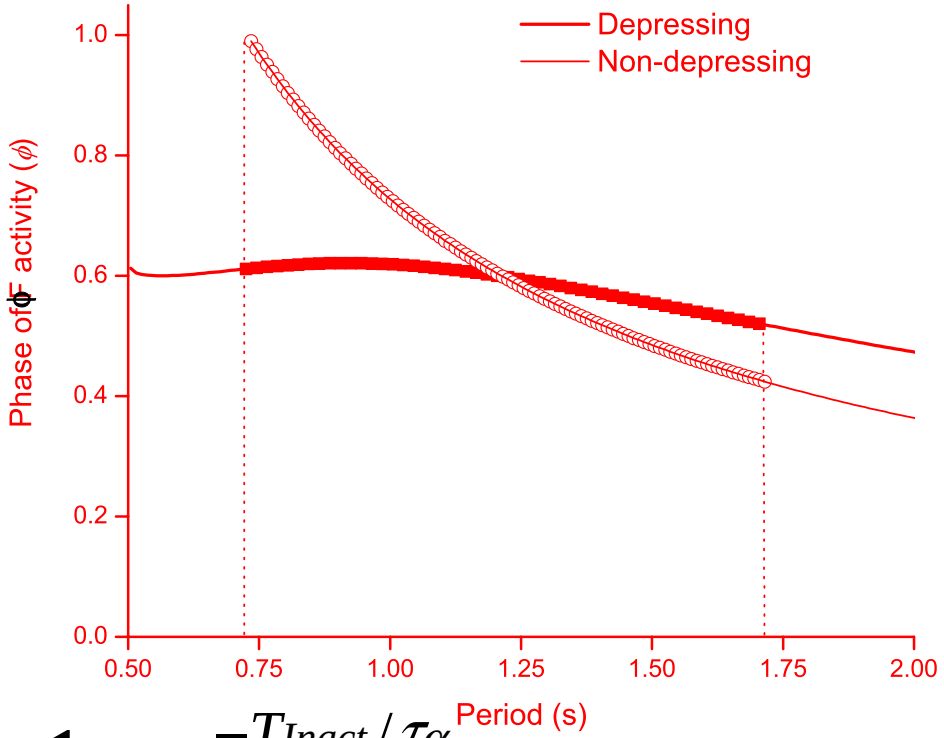
Phase vs. period in O-F network

For non-depressing synapse:

- Time delay Δt is constant
- Phase $\phi = \Delta t / P$ decreases like 1/P

For depressing synapse:

- At small P (weak inhibition), intrinsic properties of F determine ϕ
- At larger P (stronger inhibition), ϕ determined by synaptic properties



$$g_{\text{peak}} = g_{\max} \frac{1 - e^{-T_{Inact} / \tau_\alpha}}{1 - e^{-T_{Inact} / \tau_\alpha} e^{-T_{Act} / \tau_\beta}}$$

$$c_1 g_{\text{peak}} e^{-\Delta t / \tau_\kappa} + c_2 e^{-\Delta t / \tau_w} = g^*$$

Remarks about feedforward networks

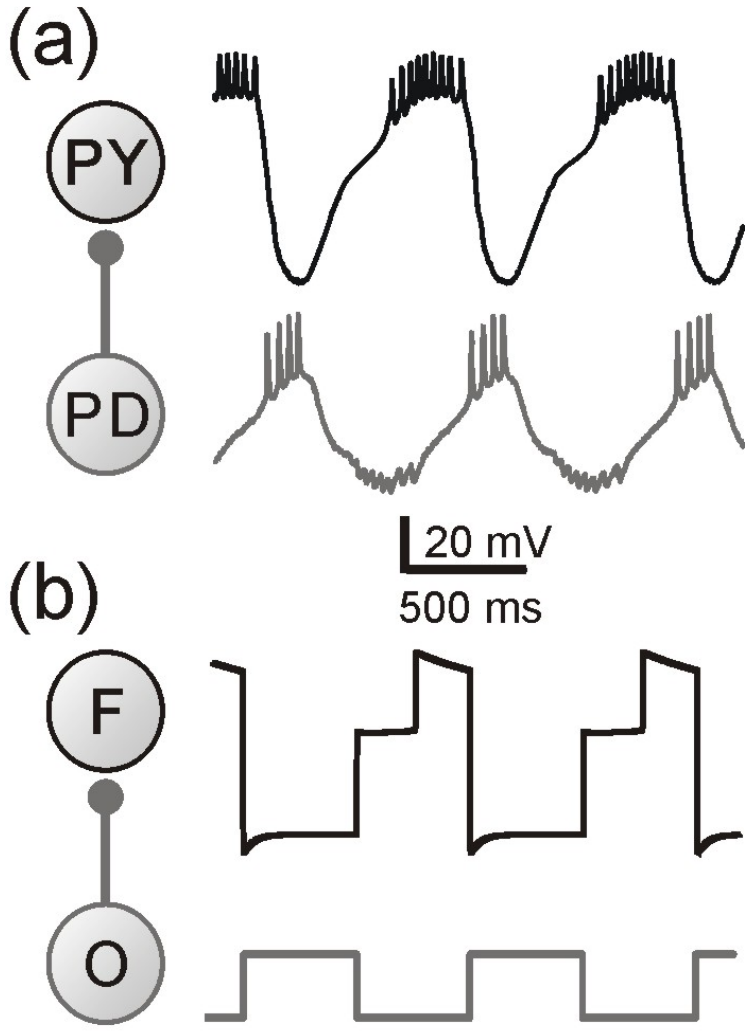
- In a feed forward network, the period of the oscillator and thus the strength of its synapse can be fine tuned.

- For phase control, without depression, phase can be chosen at exactly one value of the period. Depression creates a range of periods for which the phase of the postsynaptic cell can be assigned.

- Plasticity again allows certain parameters, intrinsic or synaptic, to be relevant to the network at different frequencies.

Mathematically intersting example based on pyloric CPG

- Oscillator-follower network governed by inhibition without plasticity
- PY contains an A-current that delays the first spike of the burst
- What effect does A-current have on the dynamics of the feed-forward network?
- Joint work with Farzan Nadim and Yu Zhang 2009

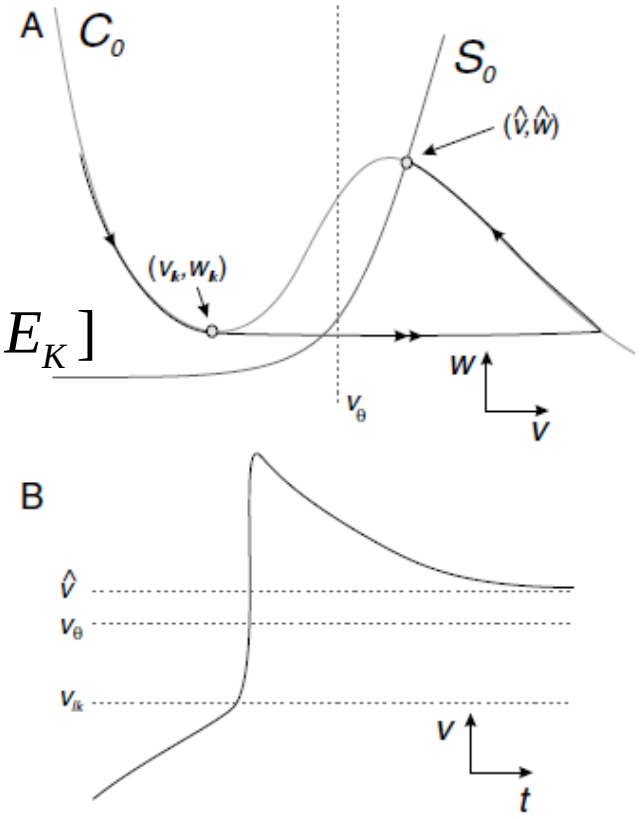


Morris-Lecar Model for F

$$\varepsilon \frac{dv}{dt} = f(v,w)$$

$$\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_w(v)}$$

$$f(v,w) = I_{ext} - g_L[v - E_L] - g_{Ca} m_\infty(v)[v - E_{Ca}] - g_K w[v - E_K]$$



- Let $\varepsilon \ll 1$, use singular perturbation theory

- Define sets of slow and fast equations to govern flow on slow manifold and the fast transitions between the branches of the slow manifold

- In the absence of input, F is boring – interaction between F and synaptic input from O is what will make the problem interesting.

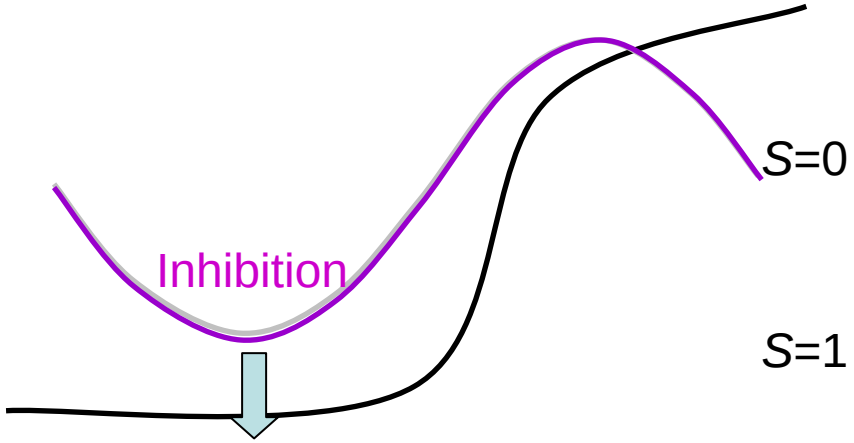
Effect of O's inhibition on F

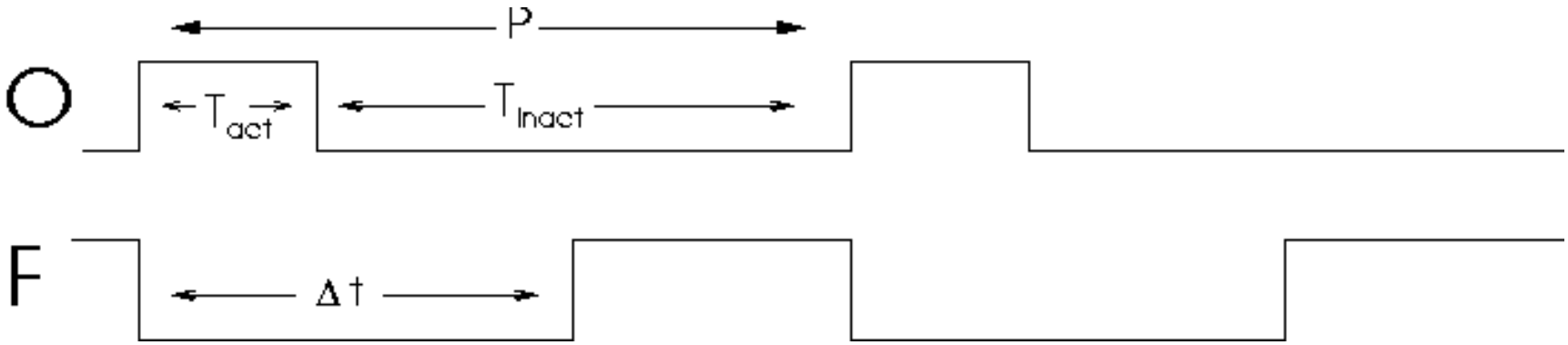
$$\varepsilon \frac{dv}{dt} = f(v, w) - g_{syn}\, s(v - E_{syn})$$

$$\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_w(v)}$$

$s = 0$ when O is inactive

$s = 1$ when O is active





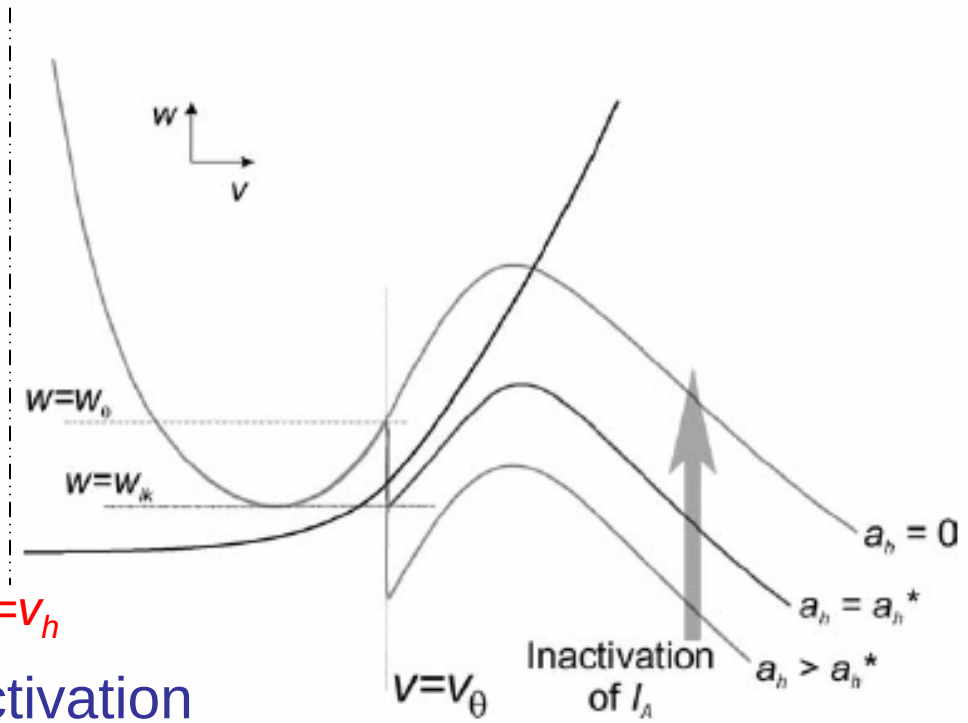
- Inhibition lowers the V-nullcline

Effect of A-current on F

$$\varepsilon \frac{dv}{dt} = f(v,w) - g_A n_\infty(v) h\,[v - E_K]$$

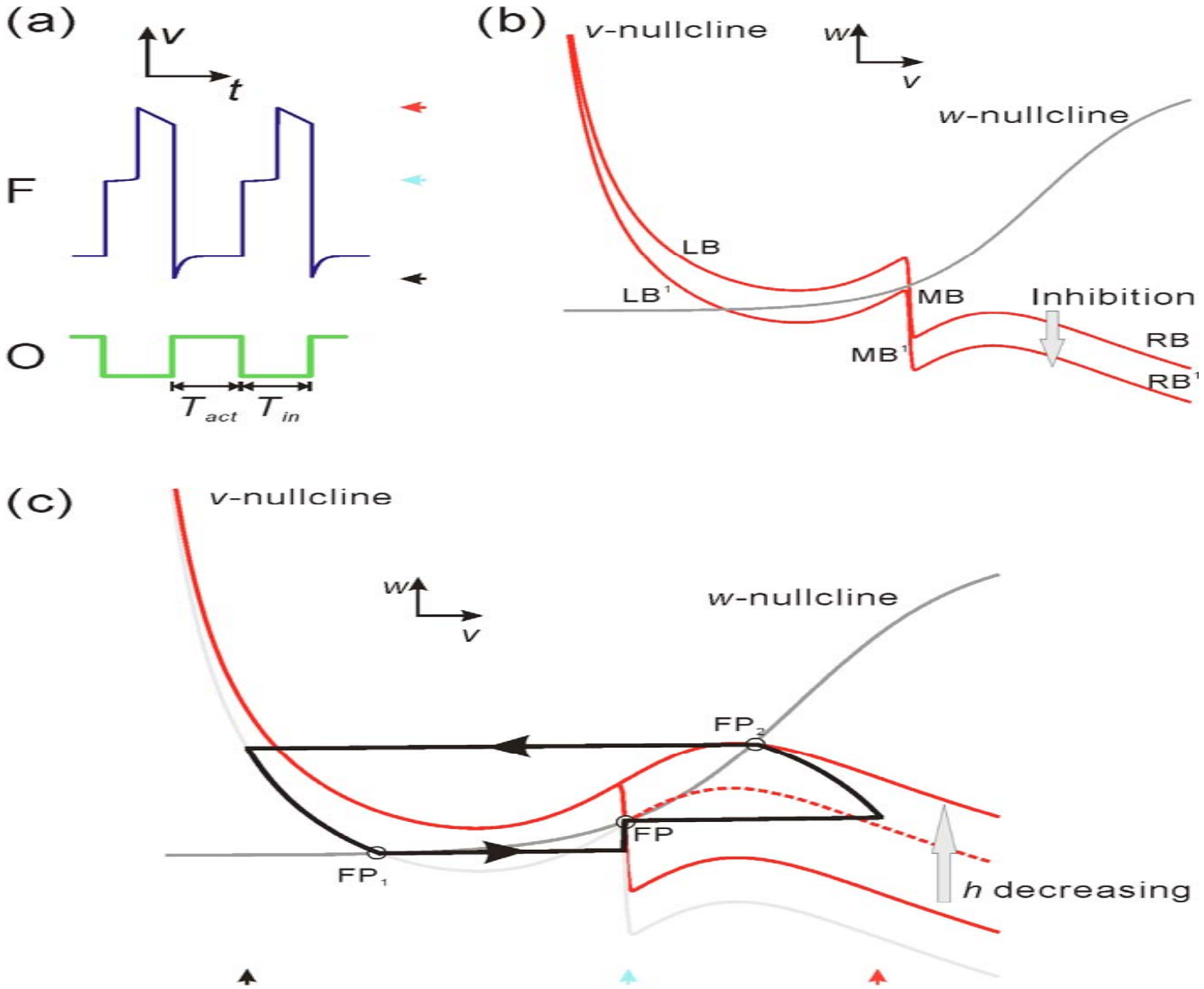
$$\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_w(v)}$$

$$\frac{dh}{dt} = \begin{cases} \dfrac{1-h}{\tau_{hl}} & \text{if } v < v_h \\ \dfrac{-h}{\tau_{hm}} & \text{if } v > v_h \end{cases}$$

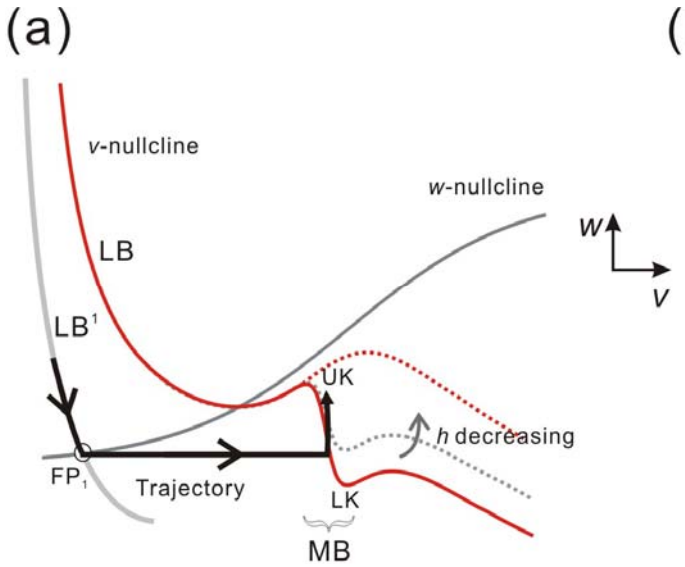


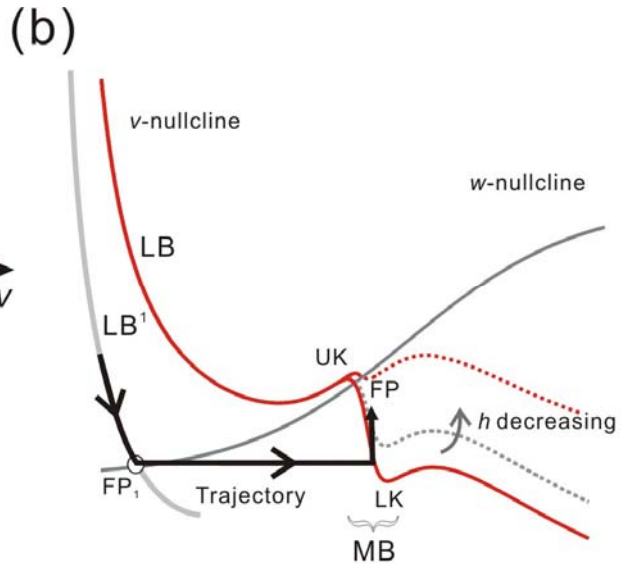
- Low voltage activation & inactivation thresholds $v=v_h$
- Creates a new stable middle branch
- *h* variable decays along middle and right branches
- *h* and *w* are slow, *v is fast*

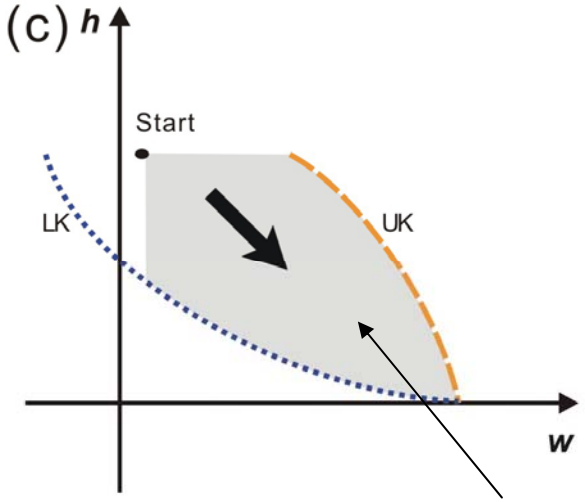
Effect of A-current and O's inhibition on F

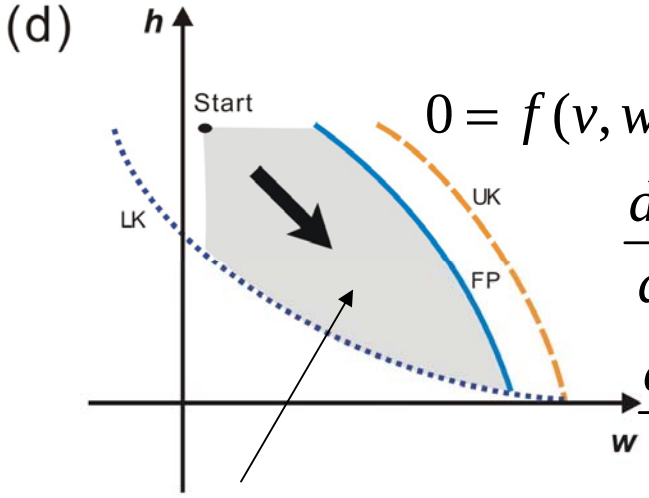


w-h slow manifold









$$0 = f(v,w) - g_A n_\infty(v)\, h\, [v - E_K]$$

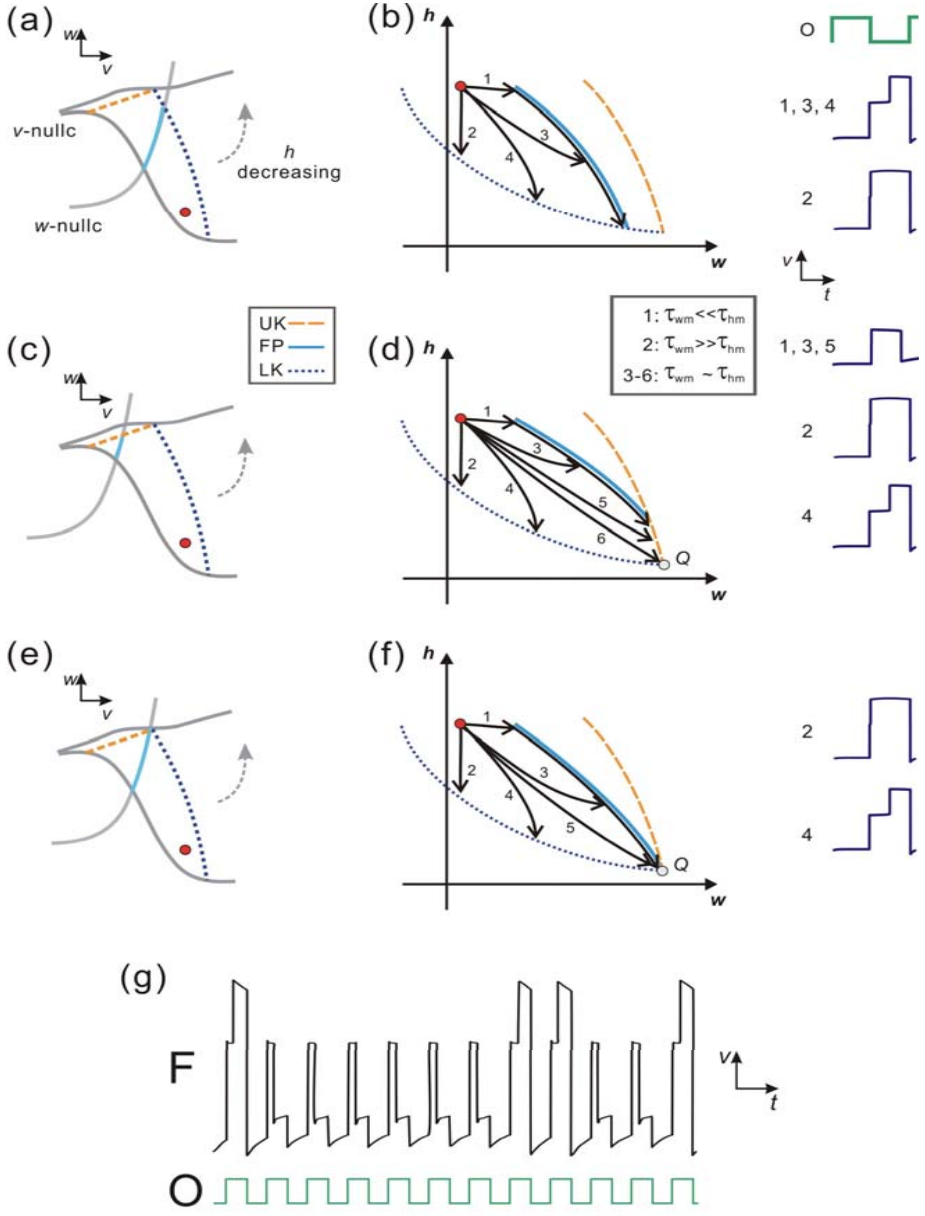
$$\frac{dw}{dt} = \frac{w_\infty(v) - w}{\tau_{wm}}$$

$$\frac{dh}{dt} = \frac{-h}{\tau_{hm}}$$

Positively invariant relative
to the slow manifold

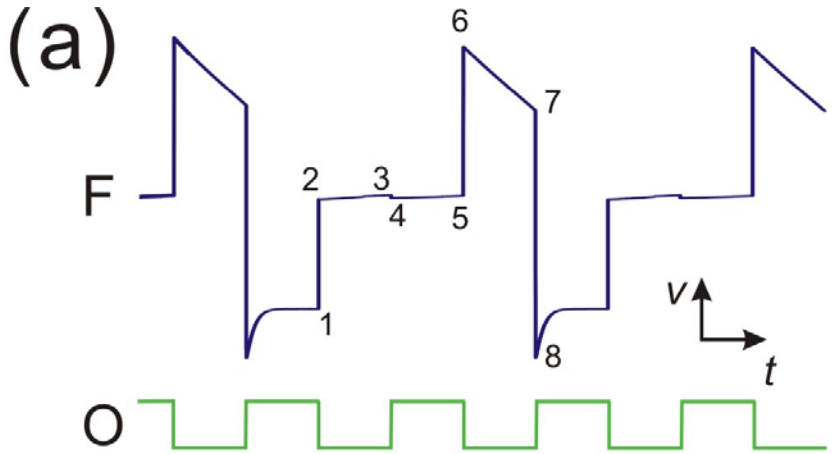
Trajectories on *w-h* slow manifold

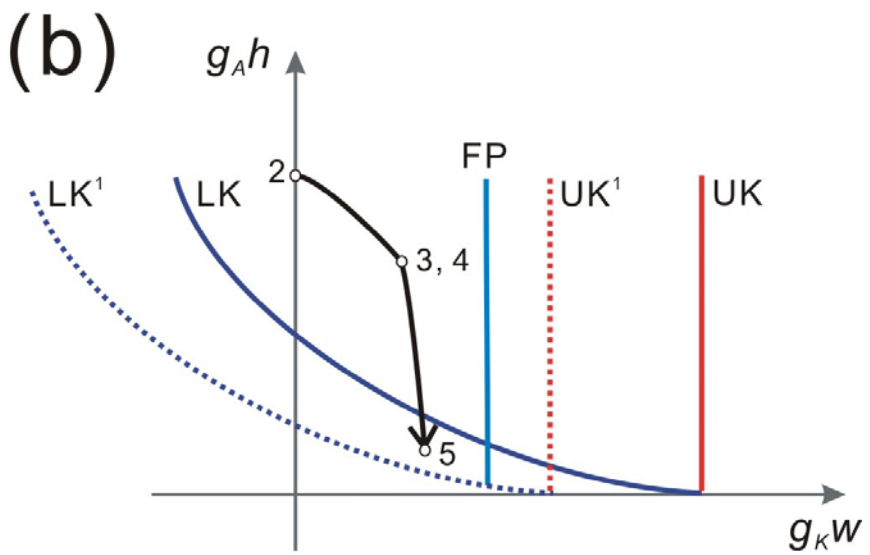
- Parameters determine location of the fixed point curve
- *w* and *h* time constants determine flow on slow manifold
- Exit through UK implies return to LB, exit through LK implies jump to RB
- When UK, LK, FP all intersect at one point, then singular flow is inconclusive (f), (g)



n:m periodic solutions

- By changing time constant for *h* on MB and/or maximal conductance g_A of A-current, trajectory can spend more time on MB
- Here the trajectory spends a full O cycle on MB
- We call this a 2:1 solution, 2 cycles of O for 1 cycle of F





Deriving a one-dimensional map

- Variables to start with (*v, w, h, s,* v_O) *(5)*
- Singular perturbation takes care of *v (4)*
- *s* is slaved to v_O (3)
- on MB, assume *w* dynamics faster than *h* dynamics (2)
- Record the value of *h* every time inhibition is removed, i.e. when *s* changes from 1 to 0 (1)
- Plus a few more small assumptions yields the one-dimensional map.

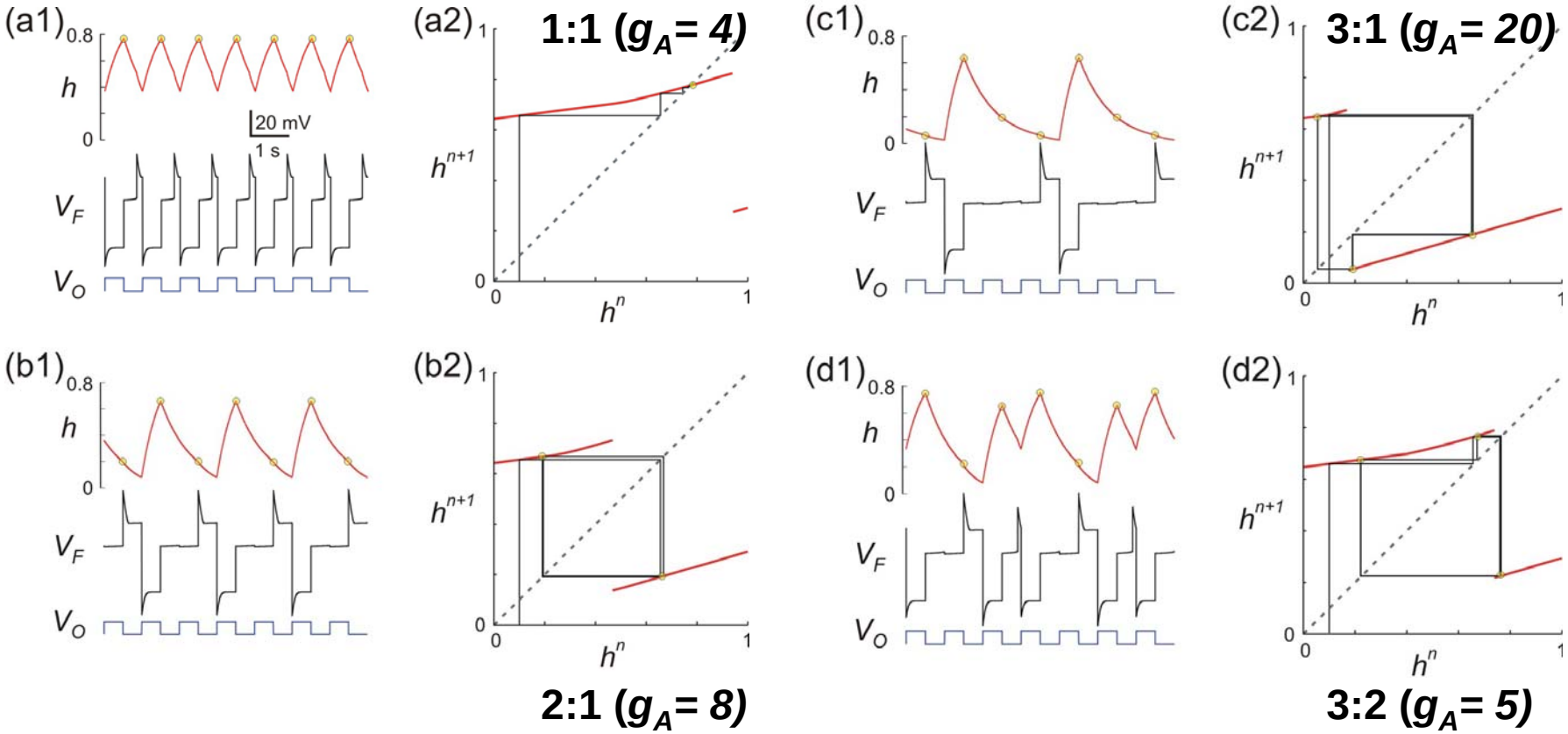
$$h^n = \begin{cases} 1+[h^{n-1}\exp(-\frac{T_{in}}{\tau_{hh}}+(\frac{1}{\tau_{hh}}-\frac{1}{\tau_{hm}})t_m{}^n)-1]\exp(-\frac{T_{act}}{\tau_{hl}}) & \text{if } t_m{}^n < T_{in} \quad \text{(a)} \\ h^{n-1}\exp(-\frac{P}{\tau_{hm}}) & \text{if } t_m{}^n > T_{in} \quad \text{(b)} \end{cases}$$

$$t_m{}^n = \tau_{hm}\ln\frac{g_A h^{n-1}[v_\theta - E_K]}{f(v_\theta, w_{FP})} \quad \text{(c)}$$

$t_m{}^n$ is the time on MB in the n^{th} cycle

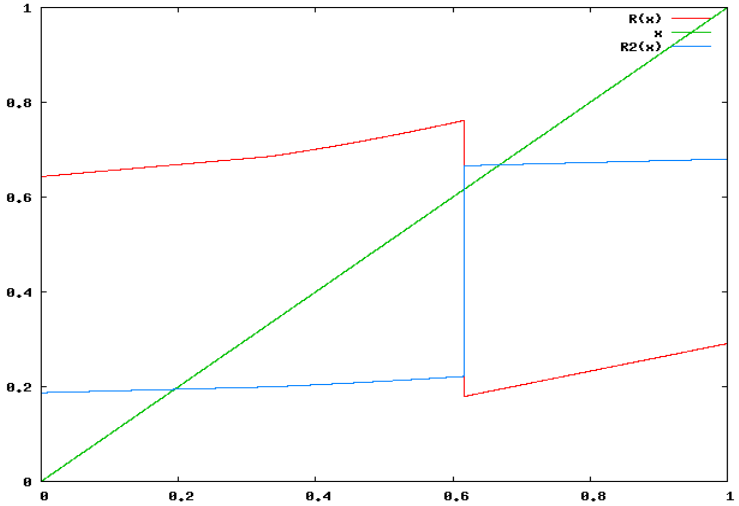
Dynamics of the map

- For different values of g_A, we obtain different solutions
- Discontinuity moves left as g_A is increased
- Global bifurcation when fixed point disappears
- One-dimensional map accurately captures dynamics of full system

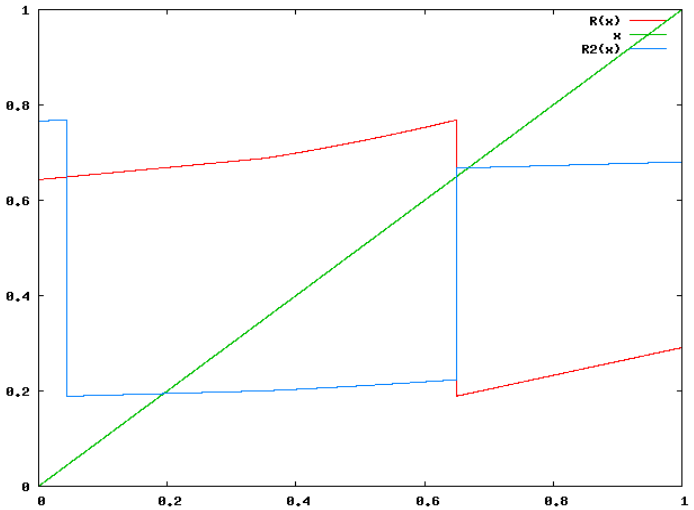


Iterates of the map

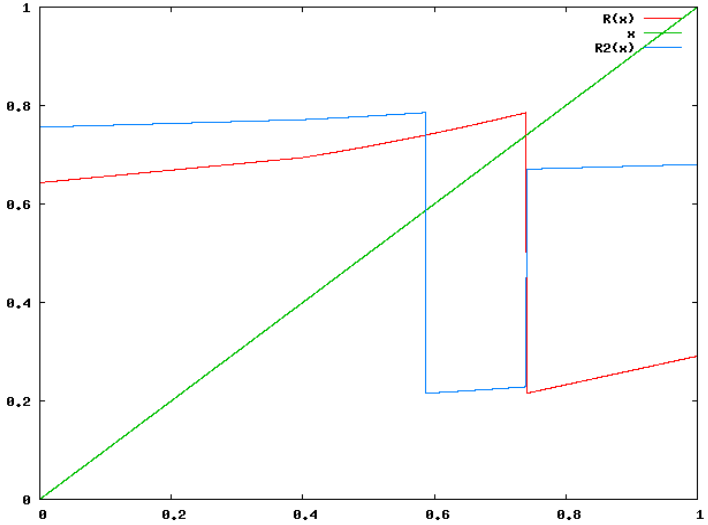
$g_A = 6.0$
Period 2



$g_A = 5.7$
Period 2



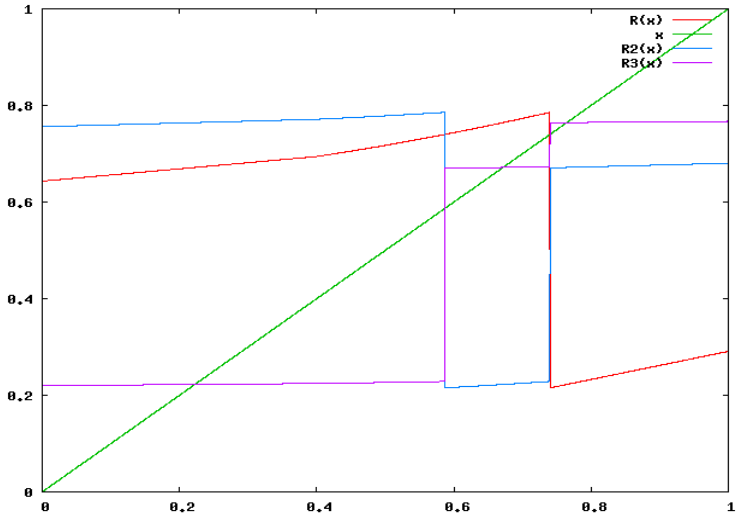
$g_A = 5.0$
No Period 2



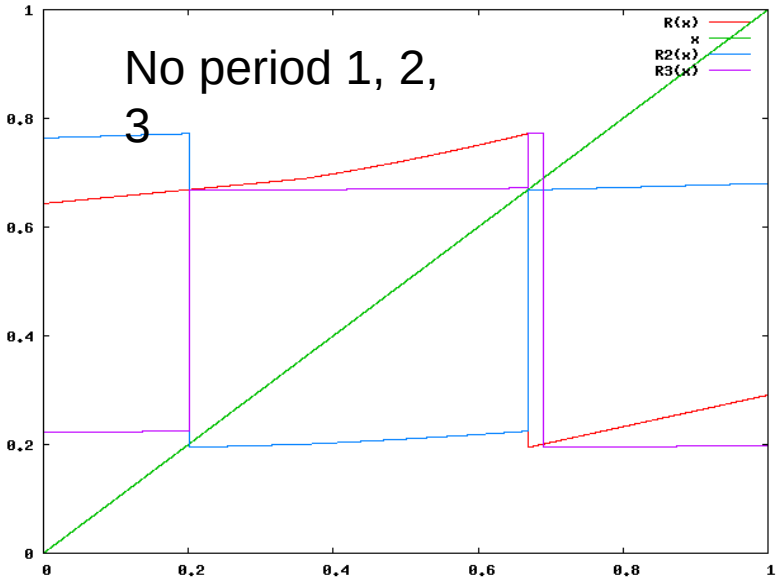
There must be something other than period 1 and 2!

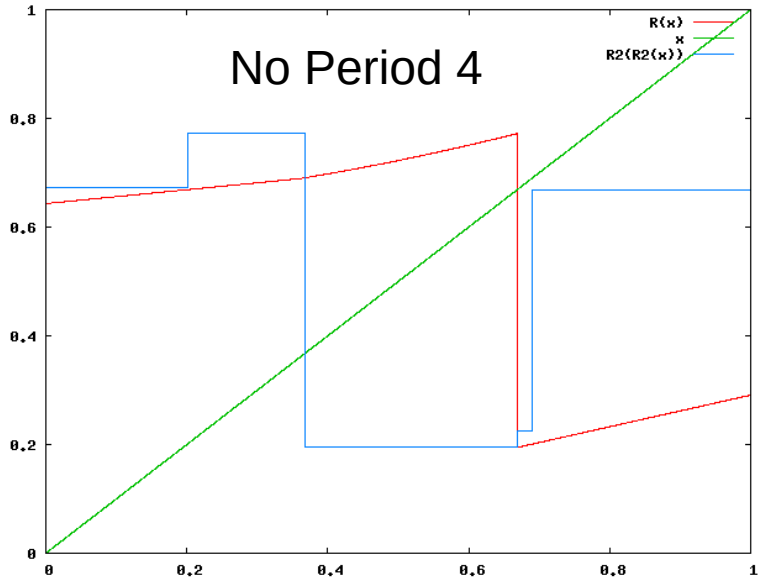
Bifurcations arise when fixed points of iterates disappear

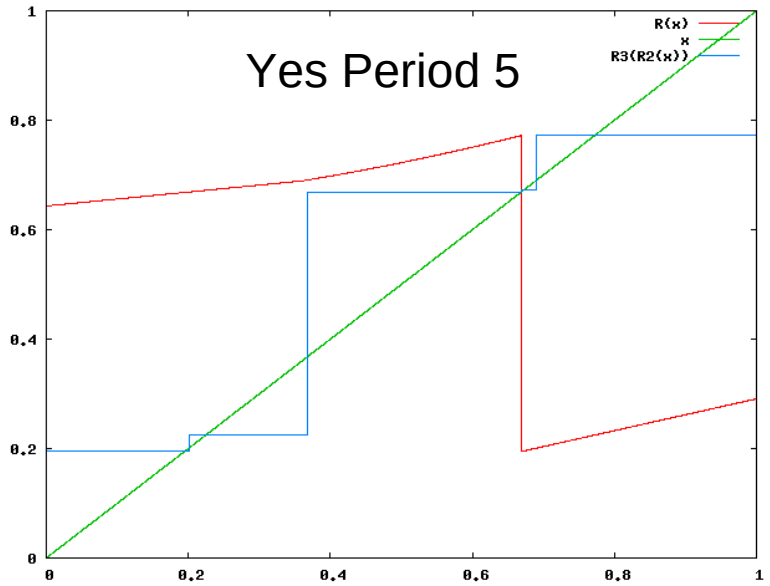
$g_A = 5.0$
Period 3



The case $g_A = 5.53$





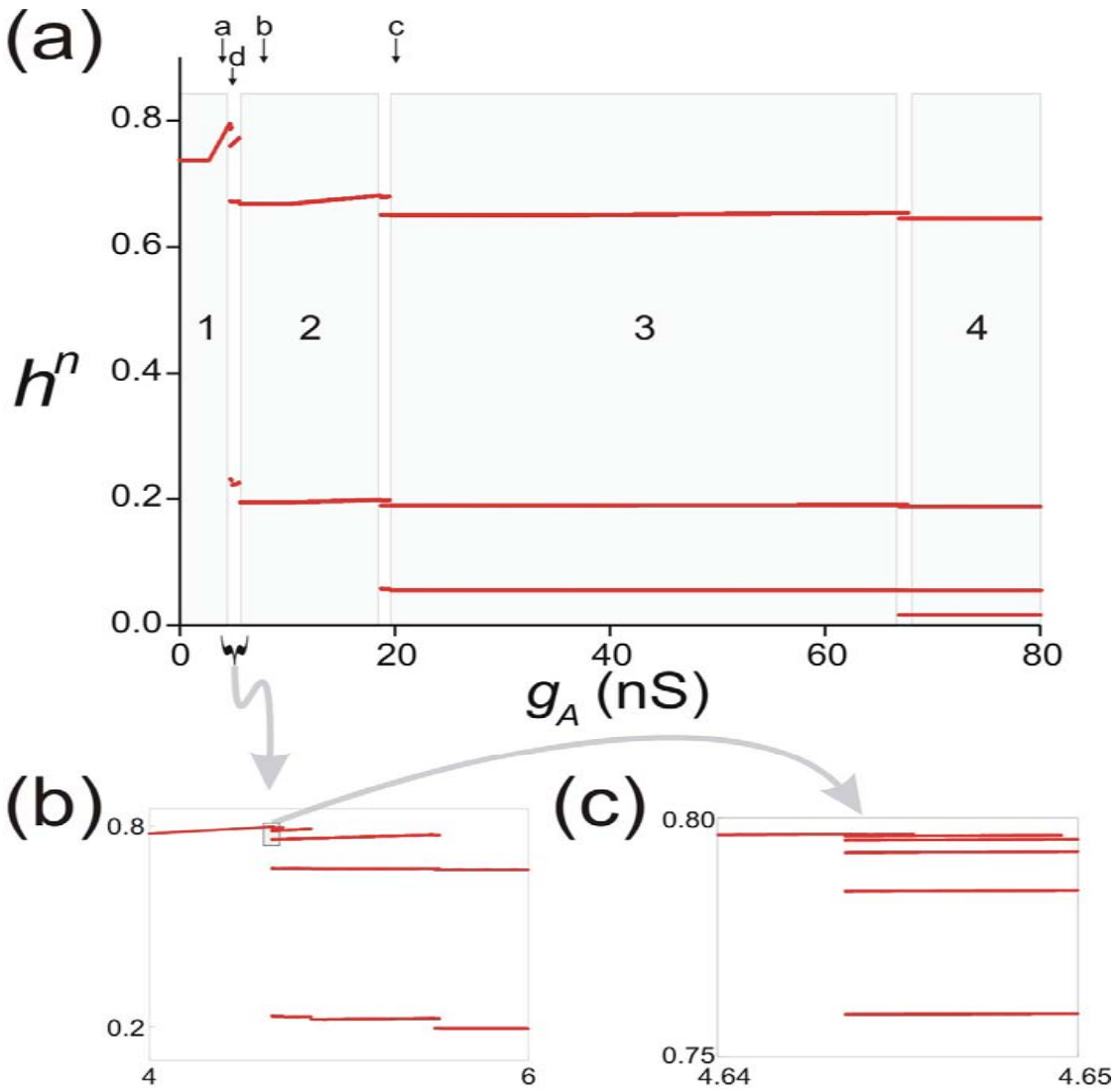


How many different solutions are there?

Can we predict what kinds of solutions will arise?

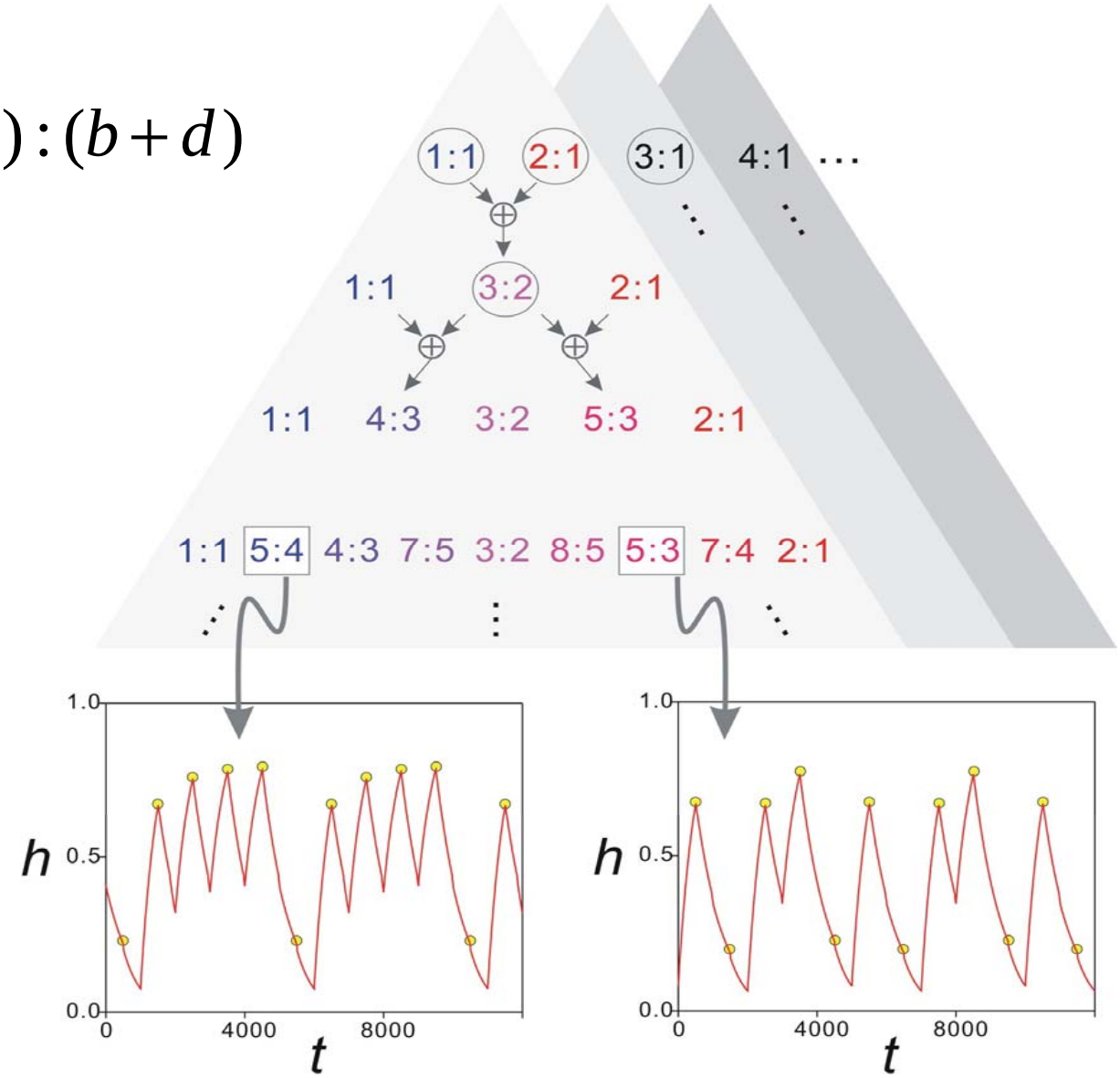
Bifurcation diagram

- Reveals a rich variety of *n:m* periodic solutions



Generalized Pascal Triangle

- Farey Rule
  $a:b \oplus c:d = (a+c):(b+d)$
- Between each *n*:*1* interval lies a countable infinity of periodic orbits
- Related to border collision bifurcations (Yorke et al).
- Biological relevance?



Remarks

- Interaction between A-current of F cell with the synaptic current from O responsible for interesting dynamics.
- Simple feed-forward model gave rise to a one-dimensional map with rich bifurcation structure, that in some parameter regimes described the dynamics of full five-dimensional system.
- Geometric singular perturbation theory and dynamical systems techniques ideal for studying small neuronal networks.

Conclusion

- Plasticity expands the dynamic capabilities of a network.
- In particular, it allows different parameters to control the network at different frequencies or at different moments in the cycle.
- How plasticity is used depends both on network architecture and on intrinsic properties of neurons.
- Mathematical modeling and analysis can provide insights that are not readily seen from experiments alone.
- Modeling also gives rise to interesting mathematical problems
- On-going work on a variety of related problems.
- Work supported by National Science Foundation (US) and Fulbright-Nehru Program (US & India)