I'm sorry, but I'm not going to talk only about...

Neural synchrony tools derived from invariant manifolds

but on...

Modelling networks of neurons

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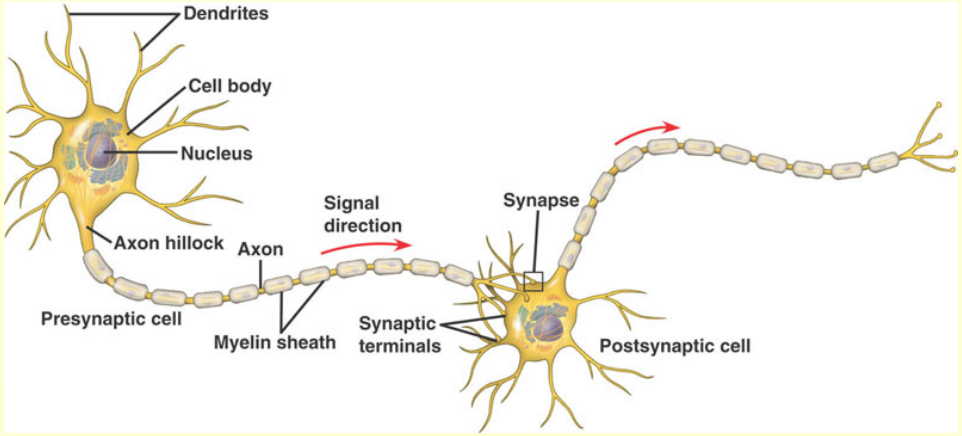
DDAYS 2012, Benicàssim, Oct 25th, 2012

Outline with landscape: single neurons

- **Models of neurons, quick overview**: biophysical models versus simpler models (see also Holmes in RTNS 2013, http://www.dance-net.org/rtns2013/).



http://biomedicalengineering.yolasite.com/neurons.php

- Problems at single-cell level: e.g., cell's ability to integrate external forcing (**neural synchrony**, see my first abstract).

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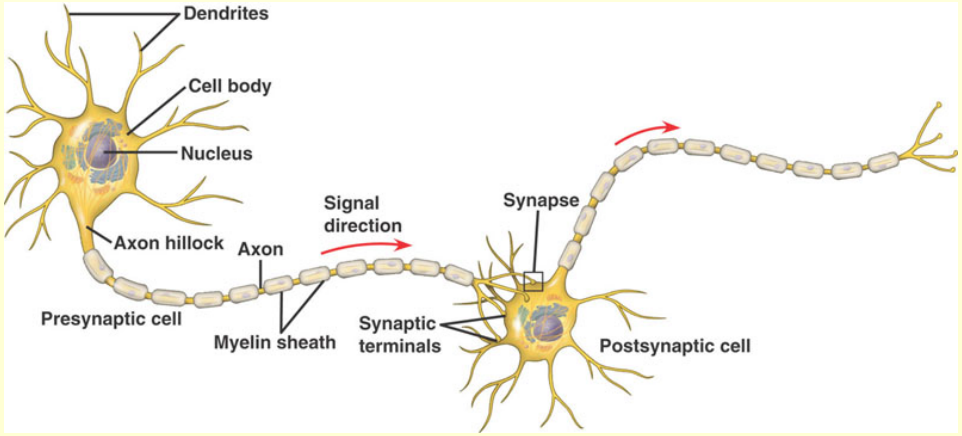

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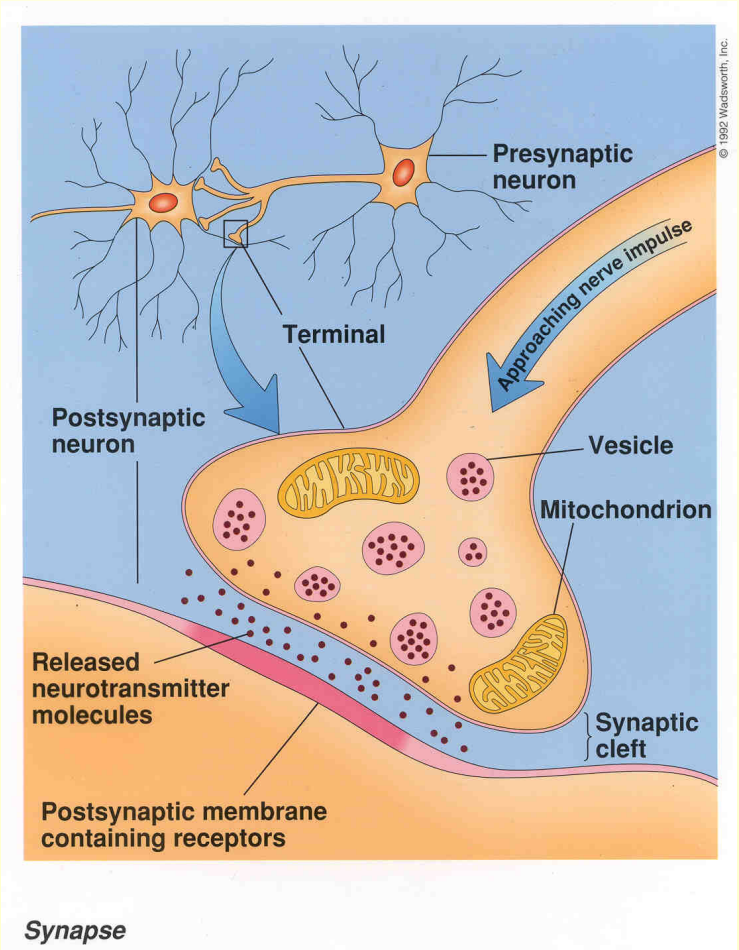
Outline with landscape: synapses

- Synaptic dynamics: building-up networks.



Synapse

http://www.unc.edu/ ejw/synapse.html

Outline with landscape: networks

- **Experimentally-inspired networks**: “realistic" units, computational brute force.

http://scientopia.org/blogs/scicurious/2011/05/04/science-101-the-neuron/

Outline with landscape: reduced networks

- Reduced networks: simplistic units, “realistic" synaptic mechanisms (e.g. Hopfield networks, see Rafael Obaya’s talk).
- Reduced networks: mean-field reductions (see also Alex Roxin’ talk) lead to **rate equations, used for cognitive problems**.

Reduced models: **analysis** and **modelling high** .

Goal: show our “modus operandi" from neuroscience problems to mathematical problems, and some problems of interest.

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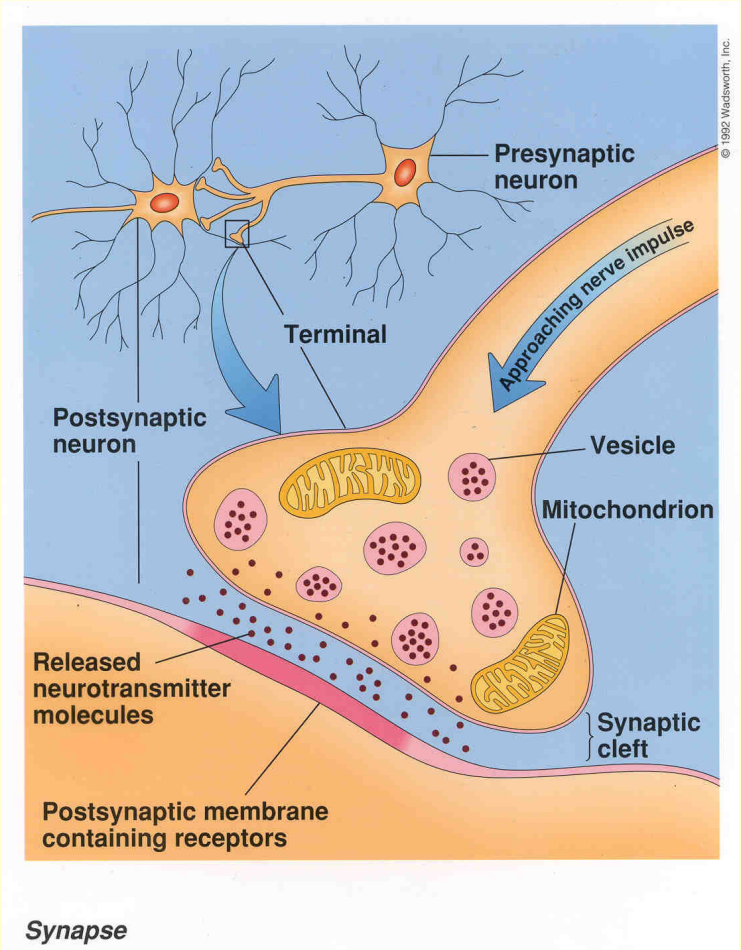
Outline with landscape: mathematical tools in neuroscience.

- Mononeuronal mechanisms: Differential equations, dynamical systems, functional analysis
- Network dynamics: information theory, statistics, graph theory, differential equations.

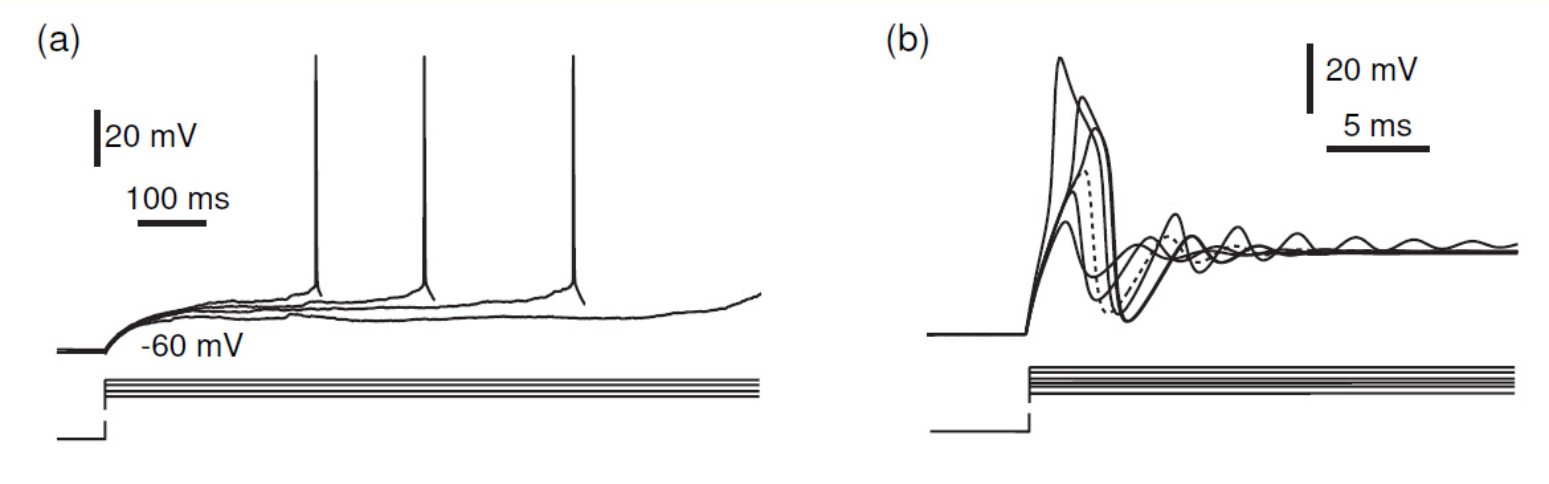
Structure of a neuron and synapses

We have around 10^{12} neurons and 10^{15} connections (synapses) among them.



http://www.unc.edu/ ejw/synapse.html

Spikes or action potentials, a fundamental element



[Izhikevich, “Dynamical systems in neuroscience", Fig.1.5]

- The explanation of *spikes* is one of the **discoveries of neuroscience** in which maths have played an important role.

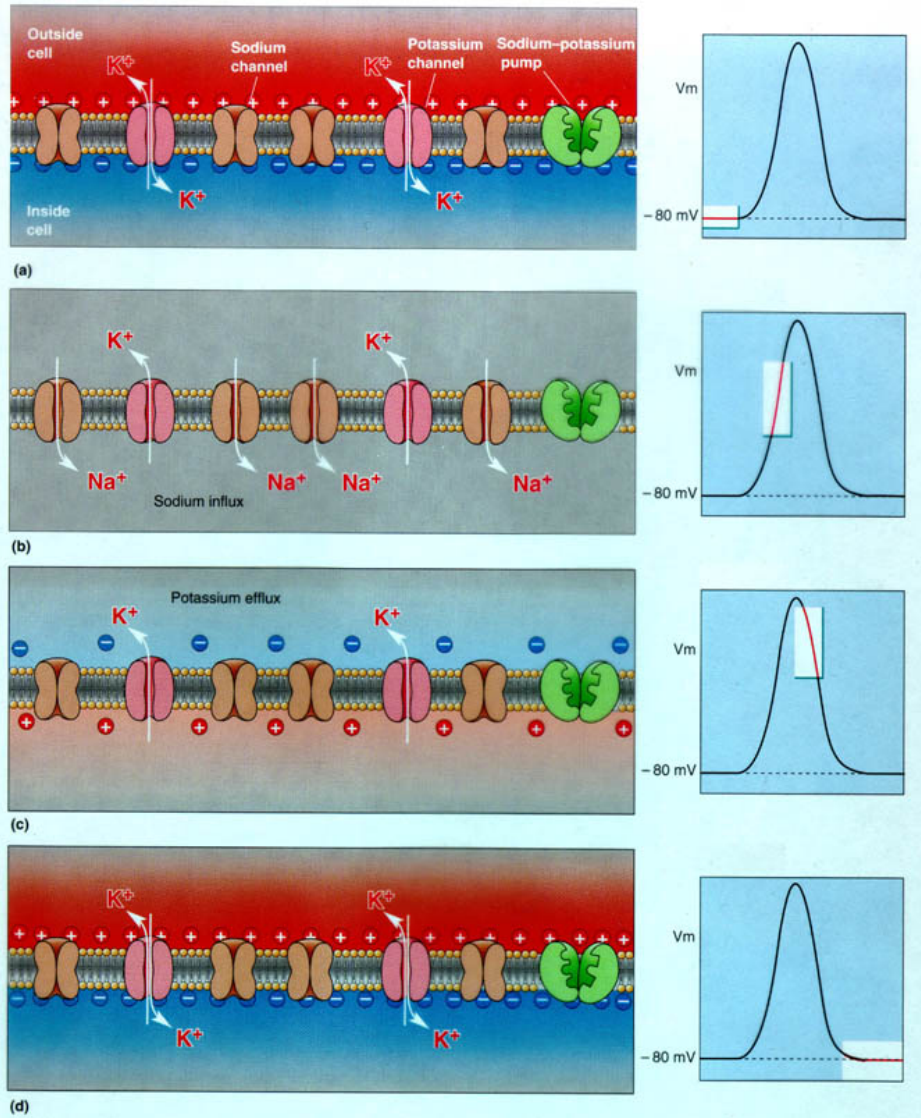
Spikes, a fundamental piece

Why **spikes** are produced in such a variety of cells and why are they so **universal**?

Hodgkin and Huxley, two physiologists, proved that mathematics could address these questions by establishing the basis for modern neuroscience...and for the Nobel Prize in Medicine and Physiology in 1963.

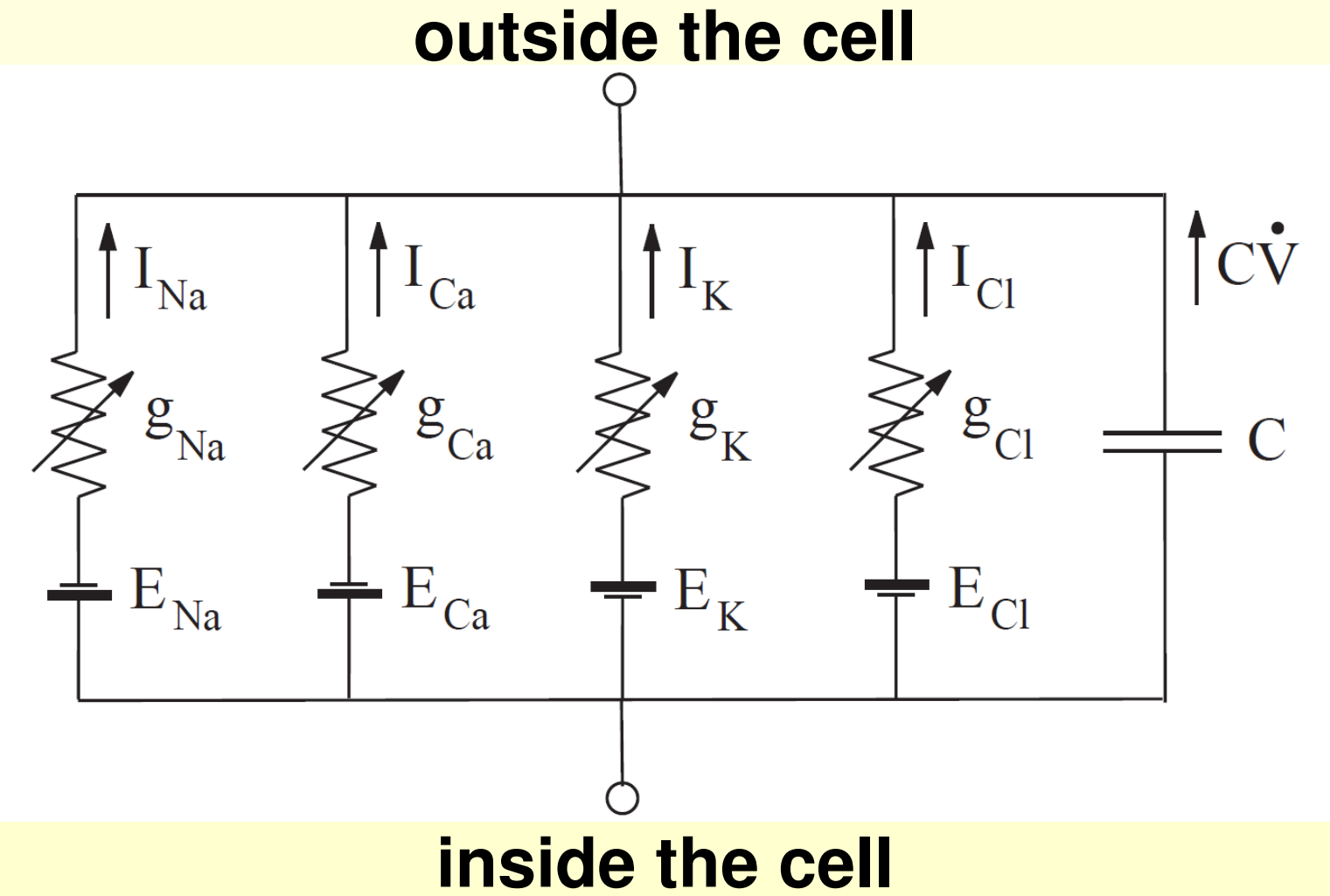
Hodgkin and Huxley theory is still used today for mathematical modeling purposes.

Nerve impulse conduction: the action potential



https://wiki.bio.purdue.edu/biol13100/index.php/2011_Problem_Set_6_Number_10_Answer

The neuron as an electrical circuit



Applying **Kirchhoff's laws ...**

Membrane potential in *Hodgkin-Huxley*'s

$v = v(t)$ **membrane potential**:

$$C_m \frac{dv}{dt} = -I_L - I_{Na} - I_K - I_{syn} + I_{app}. \tag{1}$$

I_{syn} **synaptic current**; I_{app} **applied current**.

$$\begin{cases} I_L &= g_L\,(v - V_L), \quad \textbf{leakage current}, \\ I_{Na} &= g_{Na}\,\mathbf{m}^3\,\mathbf{h}\,(v - V_{Na}), \quad \textbf{sodium current}, \\ I_K &= g_K\,\mathbf{n}^4\,(v - V_K), \quad \textbf{potassium current}. \end{cases}$$

The variables **h**, **m**, **n** represent the state (open=1, closed=0) of ionic channels.

Which dynamics do they follow?

Ionic channels modeling: the voltage clamp technique

Hodgkin and Huxley were able to deduce the dynamics of **h**, **m** and **n** thanks to a recently (in 1940's) developed technique (voltage clamp) that was possible to apply to squid giant axons.

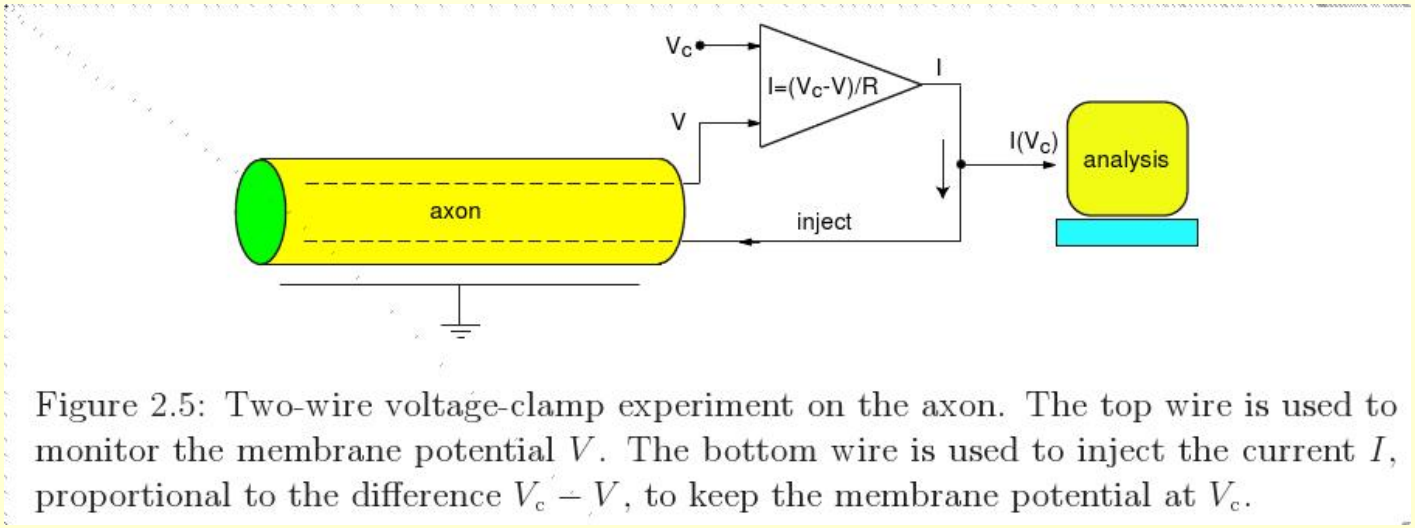


Figure 2.5: Two-wire voltage-clamp experiment on the axon. The top wire is used to monitor the membrane potential V. The bottom wire is used to inject the current I, proportional to the difference $V_c - V$, to keep the membrane potential at V_c.

[Izhikevich, "Dynamical systems and neuroscience", Fig.2.5]

Voltage clamp: obtaining the relationship $I - v$ ($I_\infty(v)$)

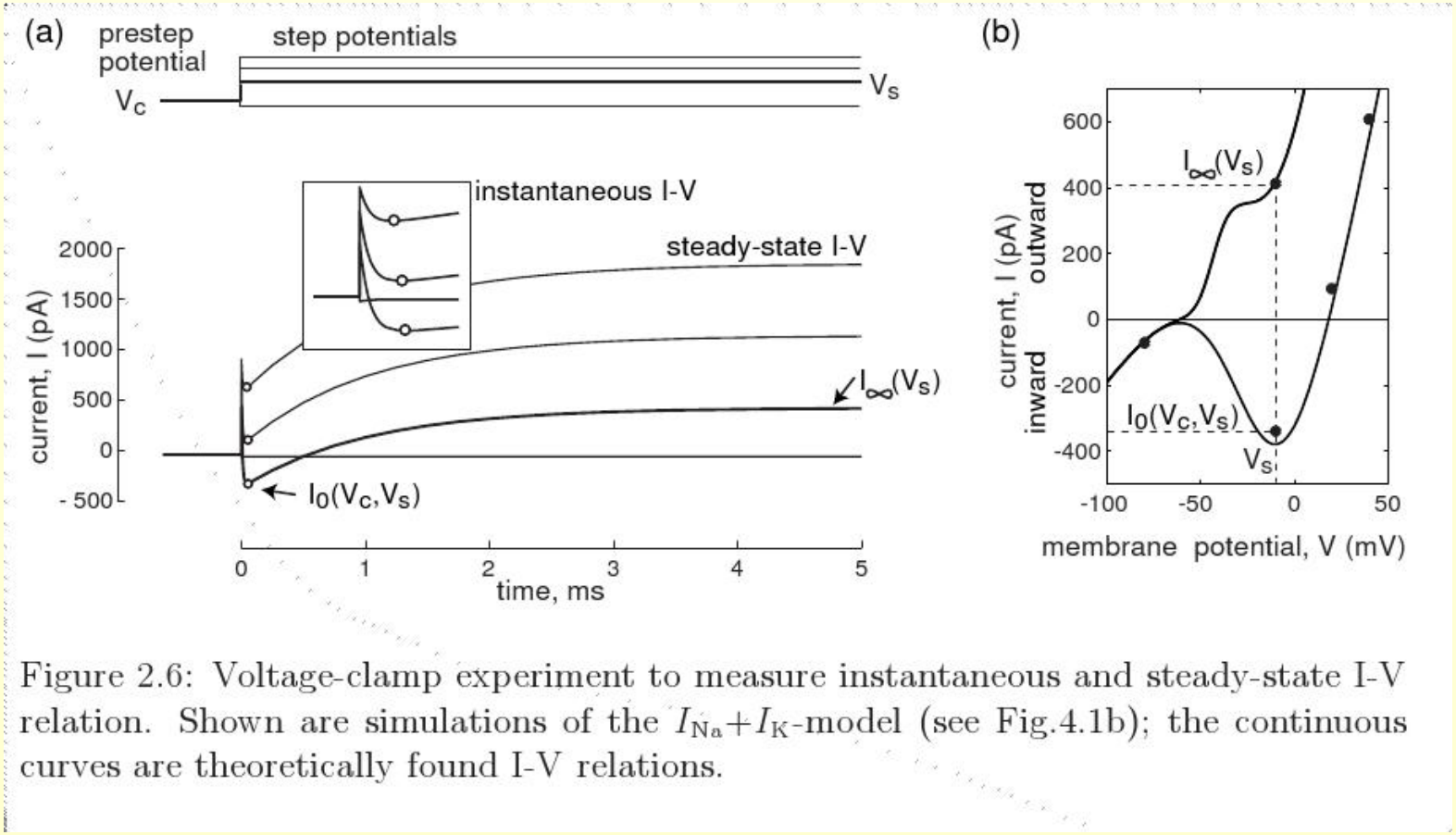


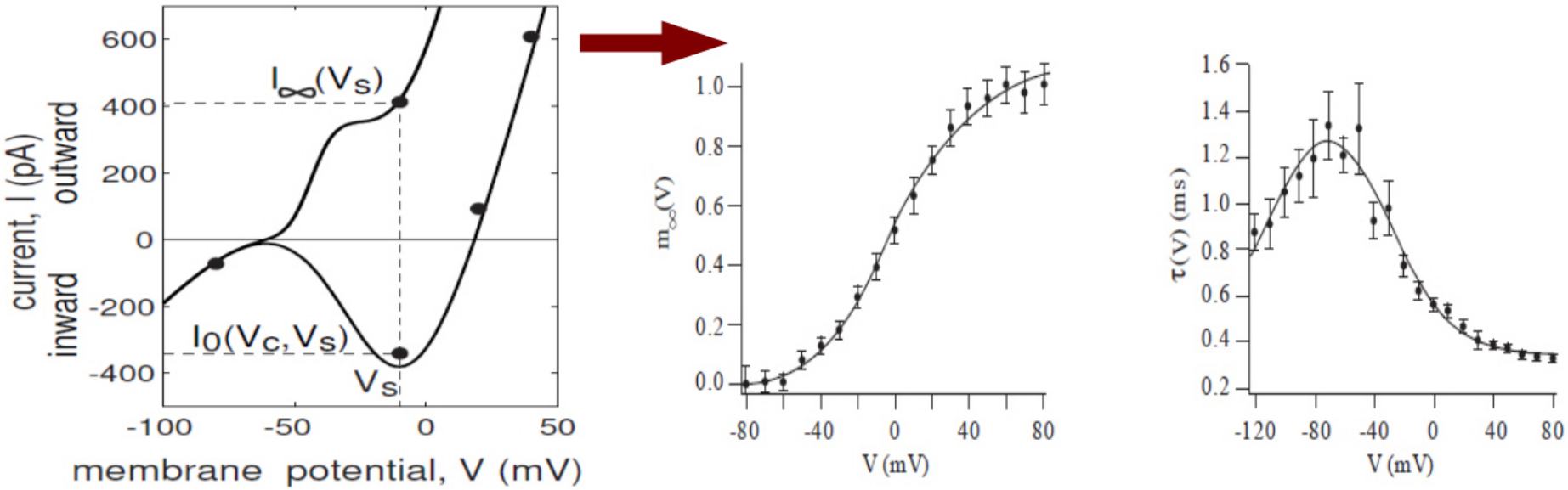
Figure 2.6: Voltage-clamp experiment to measure instantaneous and steady-state I-V relation. Shown are simulations of the $I_{\mathrm{Na}}+I_{\mathrm{K}}$-model (see Fig.4.1b); the continuous curves are theoretically found I-V relations.

[Izhikevich, “Dynamical systems and neuroscience", Fig.2.6]

Generic equation for the gating variables

$$\frac{dw}{dt} = \phi\left(\alpha_w(v)\,(1-w) - \beta_w(v)\,w\right) = \phi\frac{w_\infty(v) - w}{\tau_w(v)}, \qquad (2)$$

$$w_\infty(v) = \frac{\alpha_w(v)}{\alpha_w(v) + \beta_w(v)}, \qquad \tau_w(v) = \frac{1}{\alpha_w(v) + \beta_w(v)}.$$

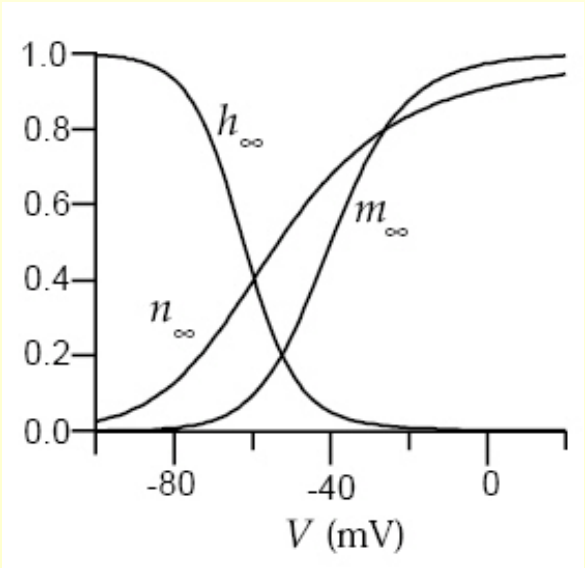


Modeling the conductances from voltage clamp

$$\frac{dw}{dt} = \phi\left(\alpha_{\mathbf{w}}(\mathbf{v})\,(1-w) - \beta_{\mathbf{w}}(\mathbf{v})\,w\right) = \phi\frac{w_\infty(v)-w}{\tau_w(v)}, \tag{3}$$

$$\alpha_{\mathbf{w}}(\mathbf{v}) = 0.07\ \exp\left(-(v+50)/10\right),$$

$$\beta_{\mathbf{w}}(\mathbf{v}) = \frac{1}{1+\exp\left(-0.1\,(v+20)\right)}.$$



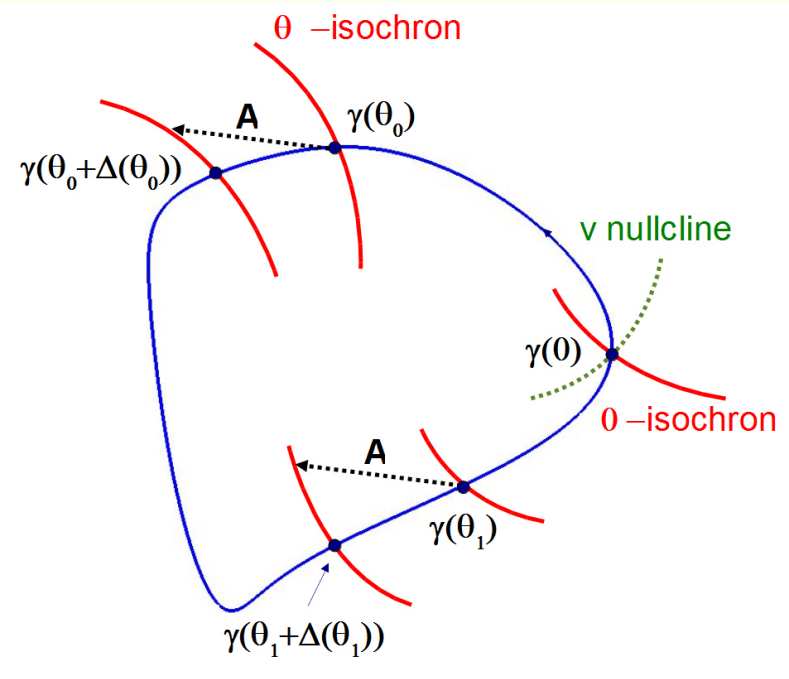
The final model of Hodgkin and Huxley

$$
\begin{aligned}
C_m \frac{dv}{dt} &= -g_L\,(v - V_L) - g_{Na}\,\mathbf{m}^3\,\mathbf{h}\,(v - V_{Na}) - g_K\,\mathbf{n}^4\,(v - V_K), \\
\frac{d\mathbf{m}}{dt} &= \phi\,(\alpha_{\mathbf{m}}(\mathbf{v})\,(1 - \mathbf{m}) - \beta_{\mathbf{m}}(\mathbf{v})\,\mathbf{m}) = \phi(m_\infty(v) - \mathbf{m})/\tau_m(v), \\
\frac{d\mathbf{h}}{dt} &= \phi\,(\alpha_{\mathbf{h}}(\mathbf{v})\,(1 - \mathbf{h}) - \beta_{\mathbf{h}}(\mathbf{v})\,\mathbf{h}) = \phi(h_\infty(v) - \mathbf{h})/\tau_h(v), \\
\frac{d\mathbf{n}}{dt} &= \phi\,(\alpha_{\mathbf{n}}(\mathbf{v})\,(1 - \mathbf{n}) - \beta_{\mathbf{n}}(\mathbf{v})\,\mathbf{n}) = \phi(n_\infty(v) - \mathbf{n})/\tau_n(v).
\end{aligned}
\tag{4}
$$

Challenges in single cell dynamics

Challenges in single cell dynamics: phase control and synchrony

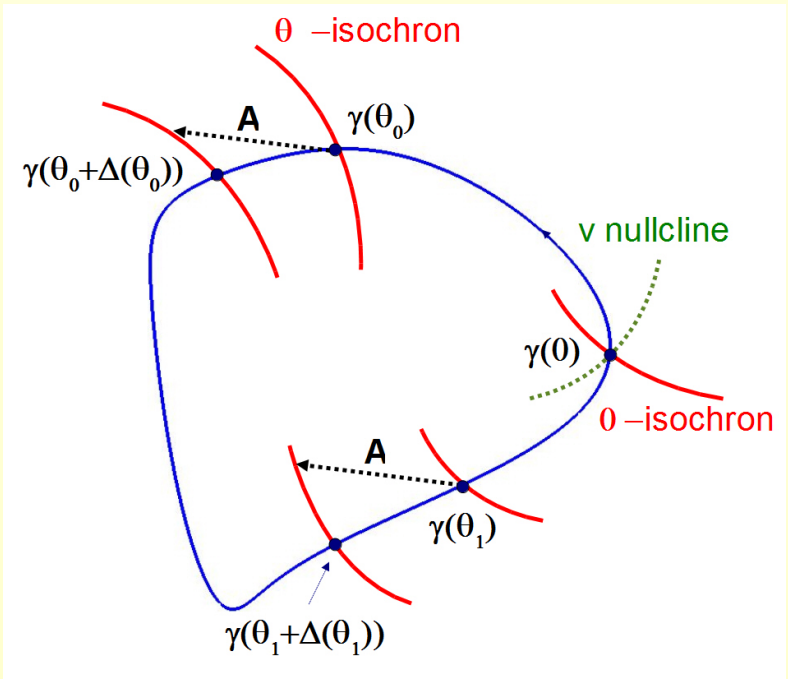
For a given stimulus **A**:

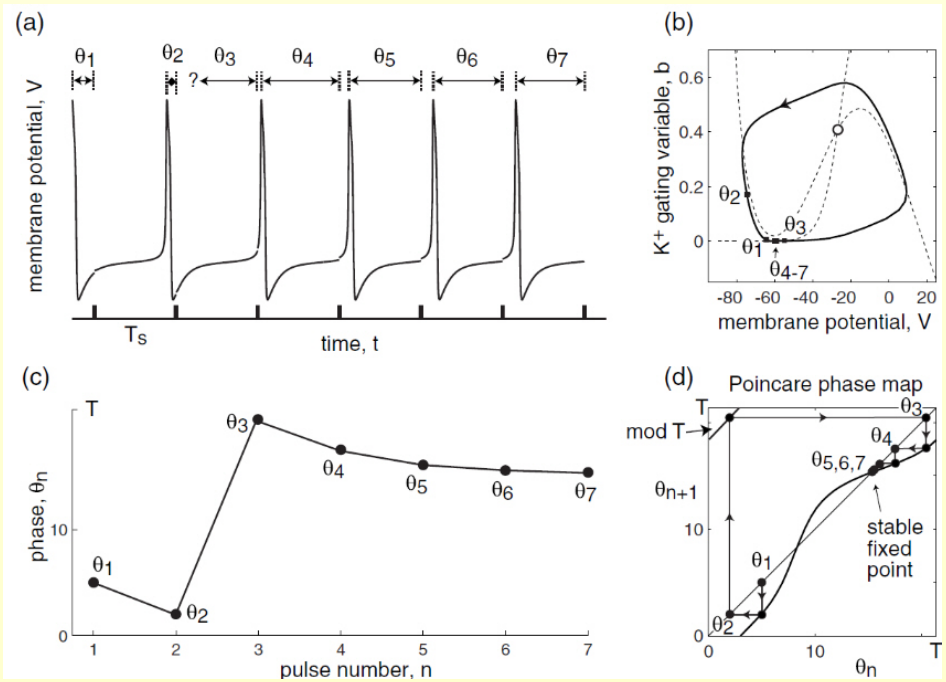


$\Delta(\theta; \mathbf{A}) = \vartheta(\gamma(\theta) + \mathbf{A}) - \theta$: phase variation depends on the **geometry of isochrons** and it needs some **time to relax back** before next stimulus.

Challenges in single cell dynamics: phase control and synchrony

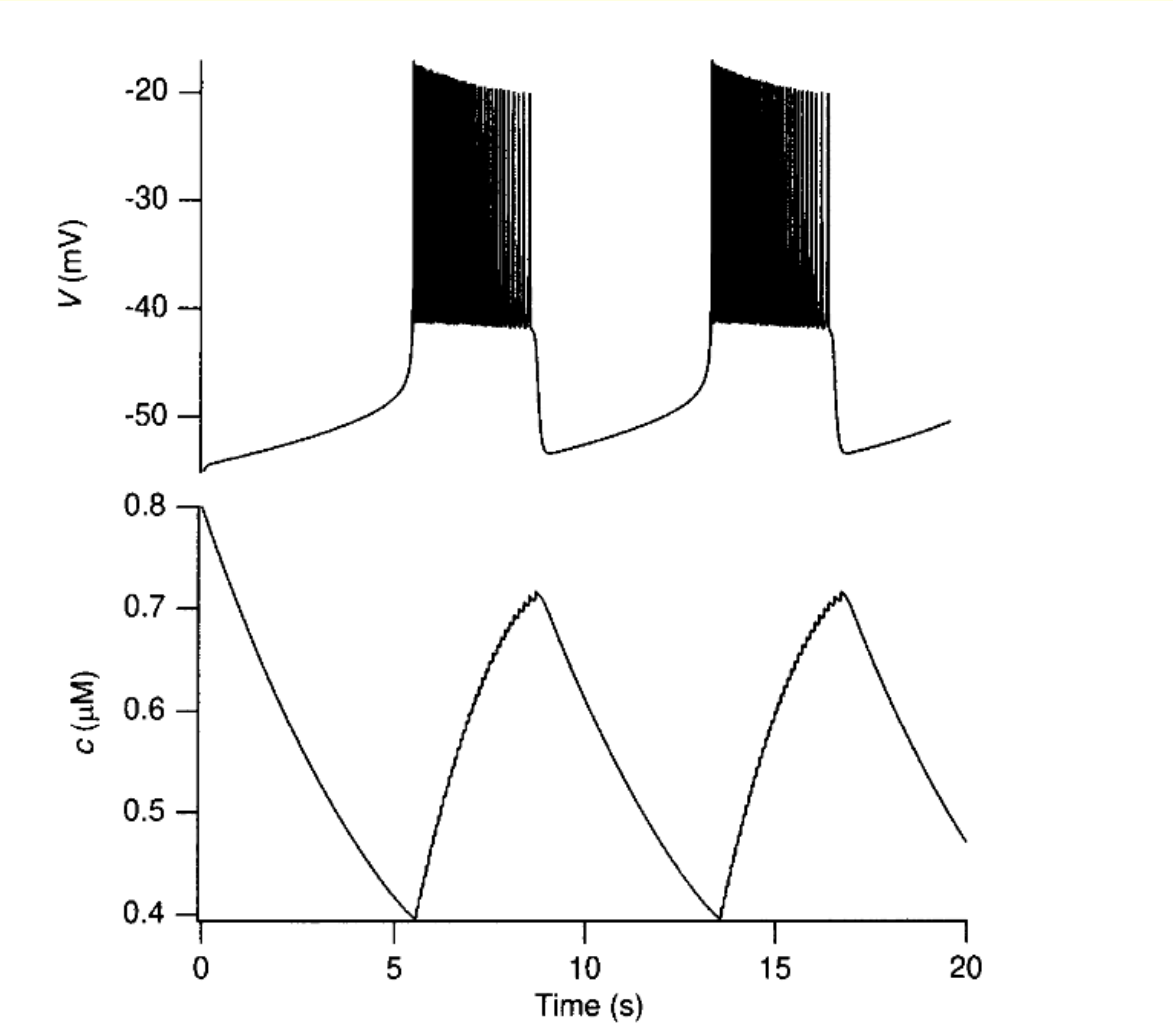
Possible track of **phase entrainment** or **synchronisation**.





Literature on weakly coupled oscillators.

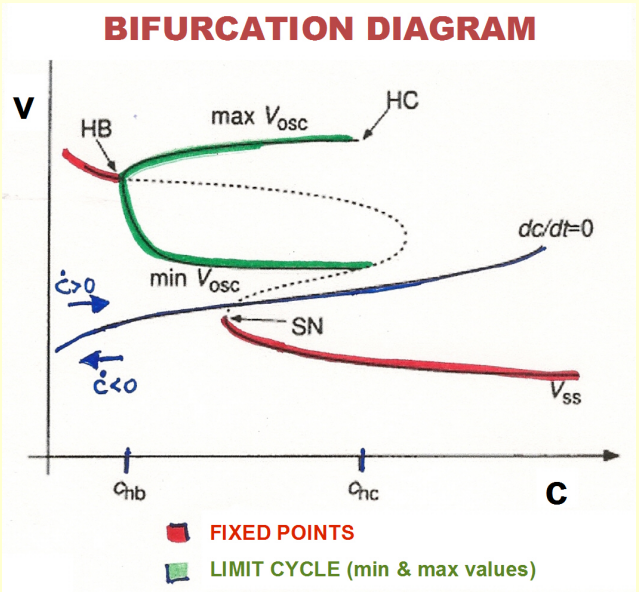
Bursting



[Keener-Sneyd, “Mathematical physiology"]

Bursting

$$
\begin{cases}
C_m \dfrac{dV}{dt} &= -I_{Ca}(V) - \left(\bar{g}_K + \dfrac{\bar{g}_{K,Ca}\, c}{K_d + c}\right)(V - V_K) - \bar{g}_L(V - V_L), \\
\tau_n(V)\dfrac{dn}{dt} &= n_\infty(V) - n, \\
\dfrac{dc}{dt} &= \epsilon\,(-K_1\, I_{Ca} - k_c\, c), \\
I_{Ca}(V) &= \bar{g}_{Ca} m_\infty^3(V) h_\infty(V)(V - V_{Ca}).
\end{cases}
$$



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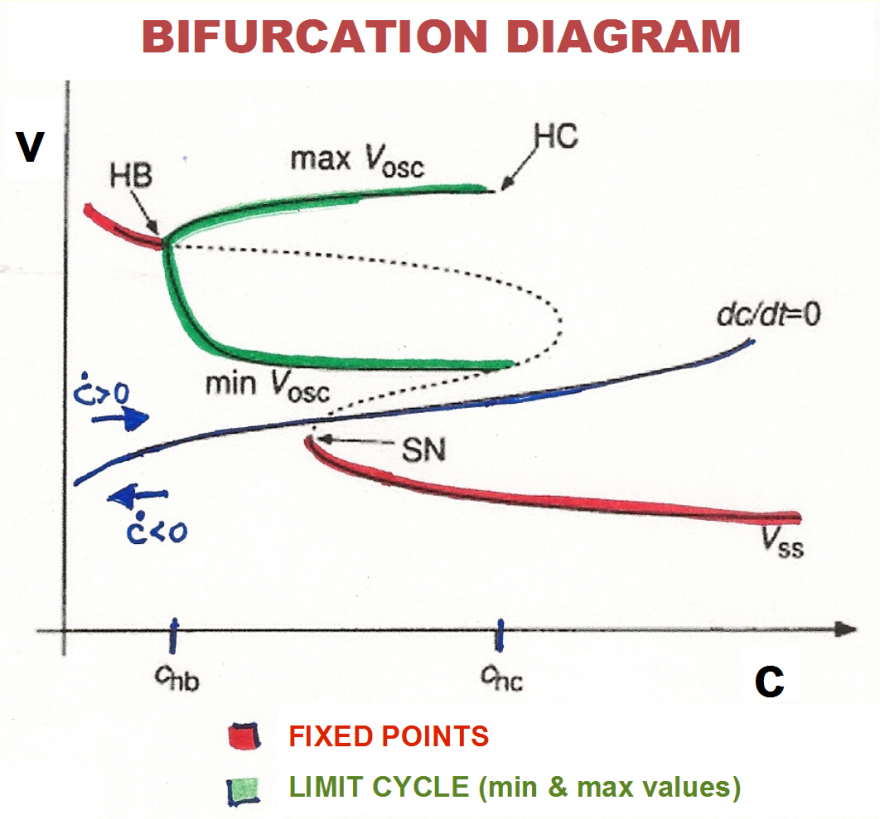
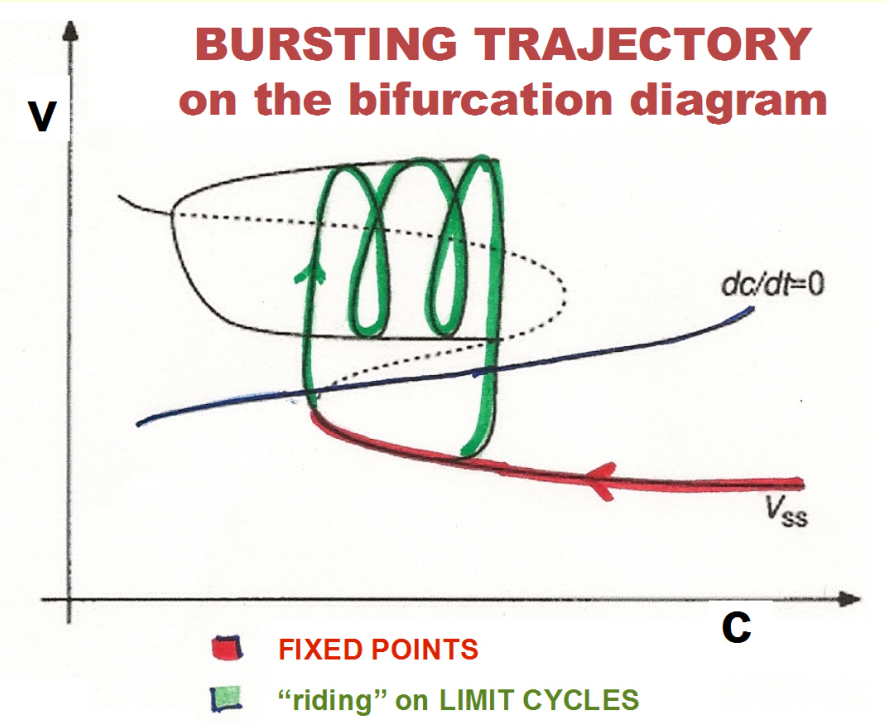
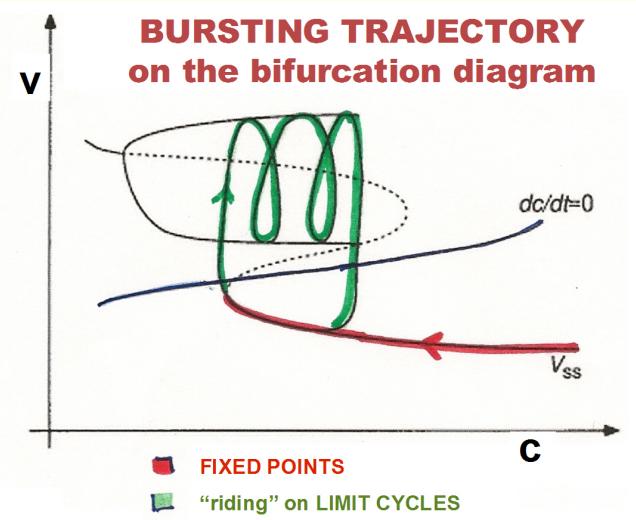


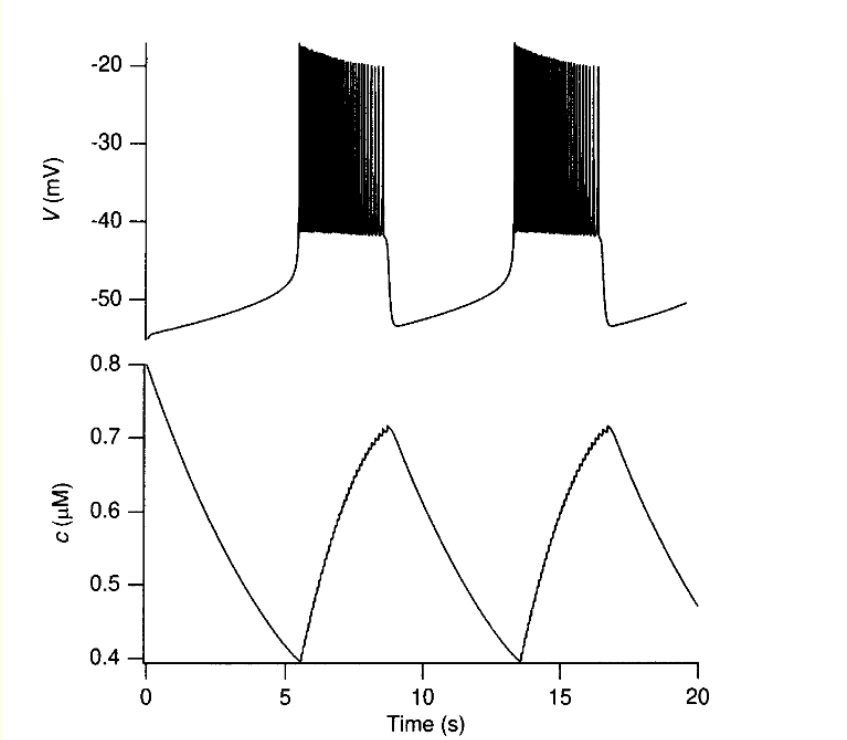


Singular perturbations.

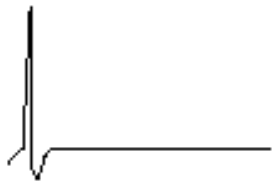
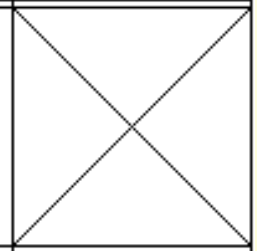
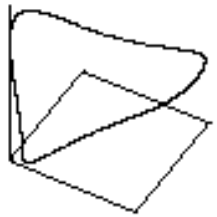
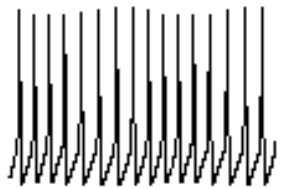
Bursting



VOLTAGE TIME COURSE



Chaos in Hodgkin-Huxley

Attractors	Dynamics	Trajectories in State Space	Time Series	Topological Structure	Dimension	Lyapunov Spectrum	Poincare Section
Equilibrium Point	Static			**Point**	0	$\lambda_i<0$	
Limit Cycle	Periodic			**R/Z**	1	$\lambda_1=0$ $\lambda_i<0$ $(i \neq 1)$	
Torus	Quasi-Periodic			$\mathbf{R^k/Z^k}$	k	$\lambda_i=0$ $(i=1,2,\ldots,k)$ $\lambda_i<0$ (otherwise)	
Strange Attractor	Chaotic			**Fractal**	Real Number	$\lambda_i>0$ $(i=1,2,\ldots,n)$ $\lambda_i=0$ $(i=n+1,\ldots,m)$ $\lambda_i<0$ (otherwise)	

Aihara, *Chaos in neurons*, Scholarpedia

Very beautiful patterns of a neuron, but ...

- **what do we do to simulate large networks of neurons?**
- Basic Ingredients: simple models + accurate synapses

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Hopfield models

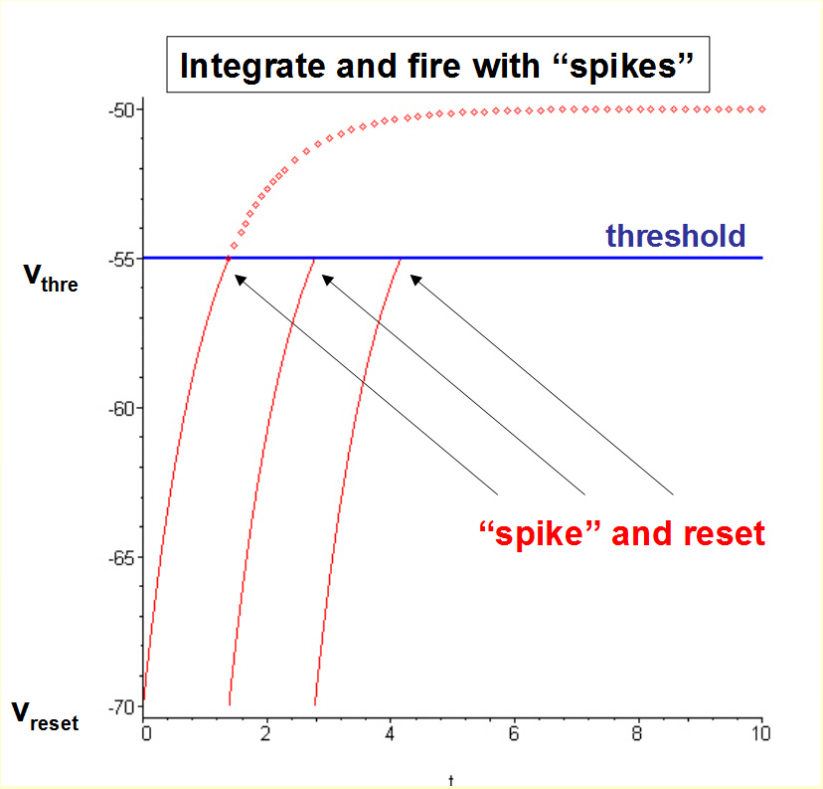
- Binary neurons, the network perceives cell's activity as an **on-off event**.
- Adding complexity through synaptic coupling (time delays, network topology,...).

See talk by **Rafael Obaya** .

Integrate & Fire models

Bruce Knight, 1972 (preceeded by Lapicque (1907), Hill (1936), Gerstein & Mandelbrot (1964), Stein (1965),...)

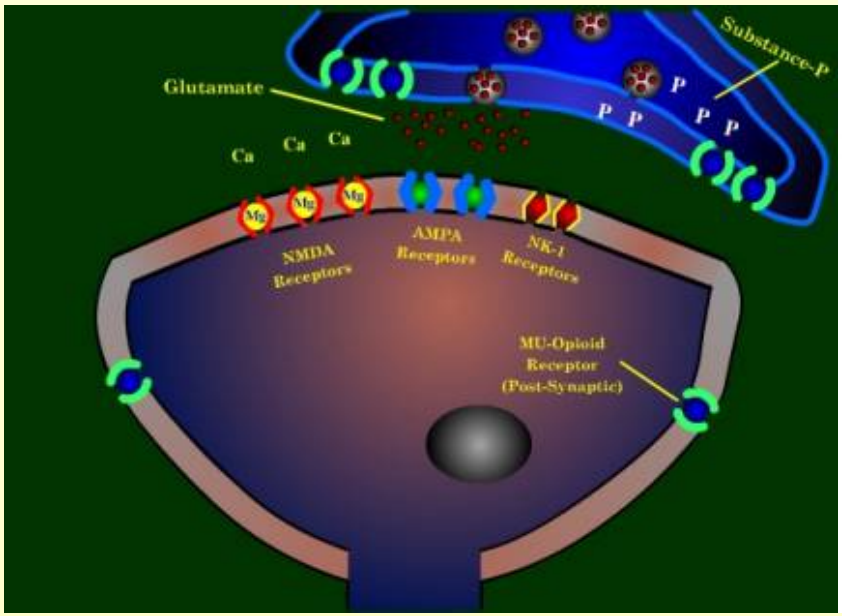
$$\begin{cases} C\dfrac{dv}{dt} = -g_L(v - V_L) + \mathbf{I_{syn}}, \quad v(t + T_{ref}) = v_{reset}, \text{ if } v(t) > v_{thresh} \\ \mathbf{I_{syn}} = \displaystyle\sum_{presynap} g_{syn}\,\mathbf{s}\,(V - V_{syn}) \\ \dfrac{d\mathbf{s}}{dt} = \alpha_s\, f(V_{pre}) - \dfrac{\mathbf{s}}{\tau_s}, \end{cases}$$

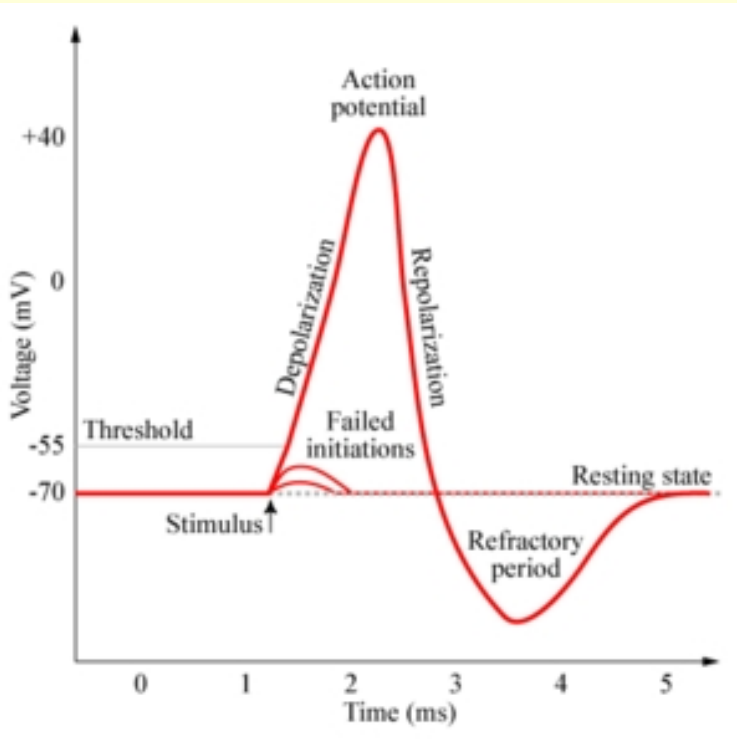


I_{syn} **excitation** or **inhibition**? Simple neurotransmission

$$I_{syn} = I_{syn,exc} + I_{syn,inh}$$

- Excitation: $I_{syn,exc} = g_E(t)\,(v - V_E), \qquad V_E \approx 0\,\text{mV}$
- Inhibition: $I_{syn,inh} = g_I(t)\,(v - V_I), \qquad V_I \approx -80\,\text{mV}$





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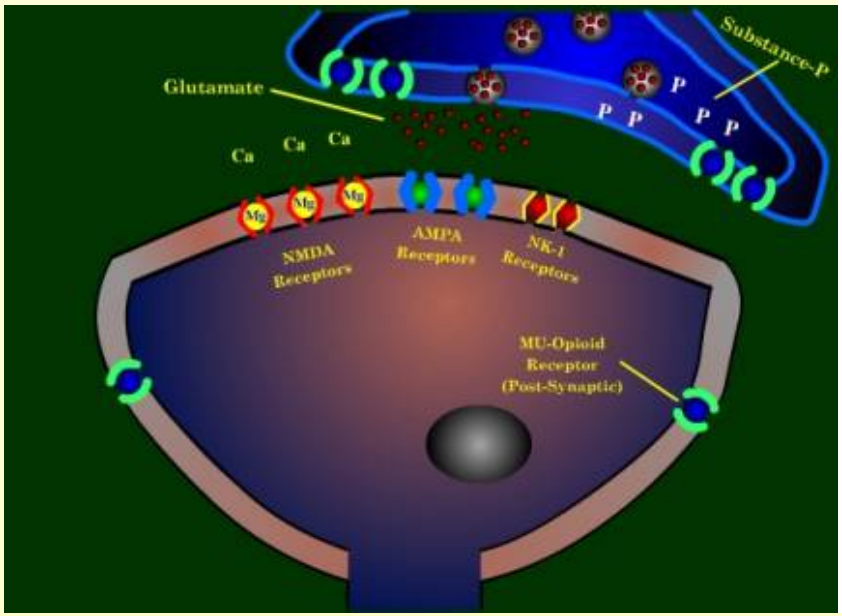
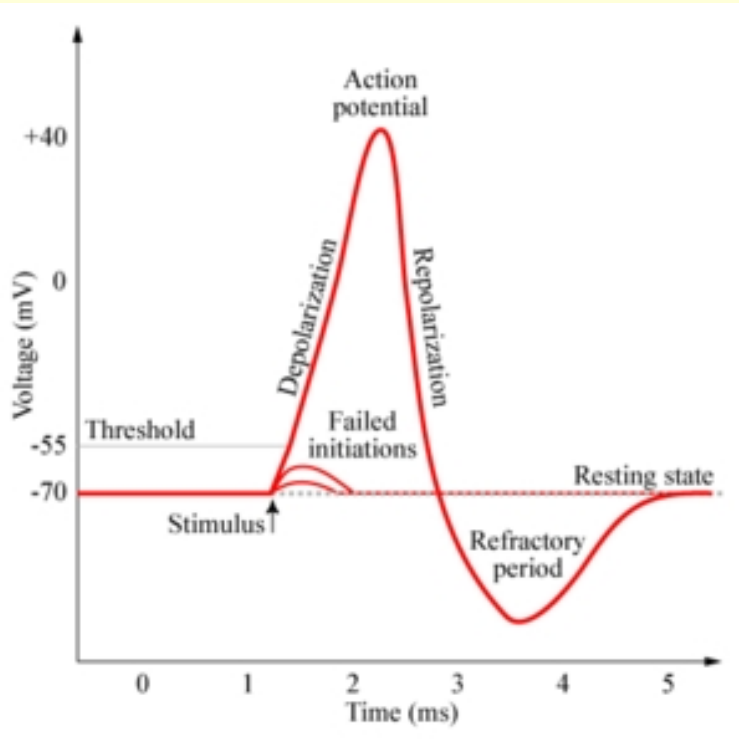
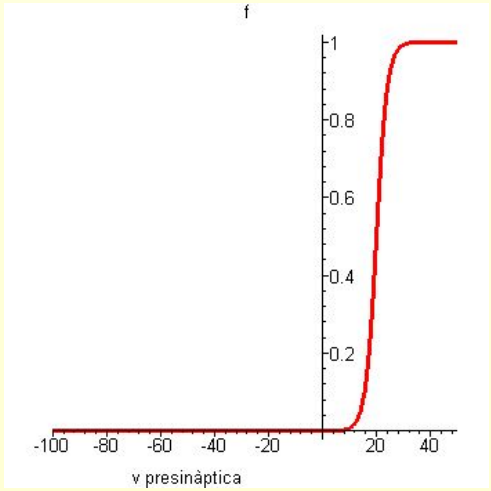




$I_{syn} = g_{syn}\,\mathbf{s}\,P_{rel}\,(V - V_{syn})$: Specific neurotransmission

- Excitation: AMPA neuroreceptors: $\tau = 2$ ms, $V_{syn} = 0$mV
- Inhibition: GABA neuroreceptors: $\tau = 10$ ms, $V_{syn} = -70$mV

$$\frac{d\mathbf{s}}{dt} = \alpha_s\, f(V_{pre}) - \frac{\mathbf{s}}{\tau_s},$$



- Slow excitation: NMDA neuroreceptors (memory processes)

$$\frac{d\mathbf{s}}{dt} = \alpha_s\, x\,(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s}, \qquad \frac{dx}{dt} = \alpha_x\, f(V_{pre}) - \frac{x}{\tau_x},$$

$\tau_s = 100$ ms, $\tau_x = 2$ ms, $V_{syn} = 0$. V_{pre}, presynaptic potential.

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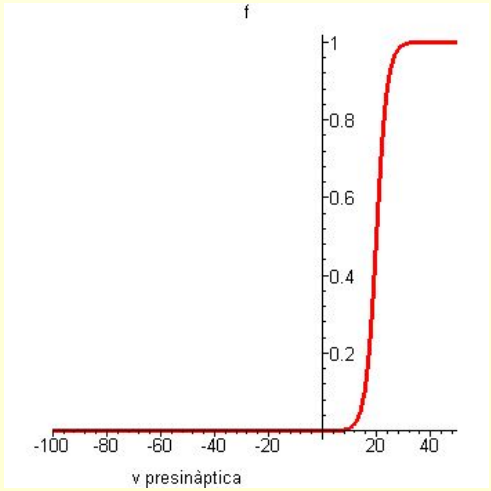

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$$\frac{d\mathbf{s}}{dt} = \alpha_s\, x\,(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s}, \qquad \frac{dx}{dt} = \alpha_x\, f(V_{pre}) - \frac{x}{\tau_x},$$

$\tau_s = 100$ ms, $\tau_x = 2$ ms, $V_{syn} = 0$. V_{pre}, presynaptic potential.

Networks of I& F neurons: large scale simulations

- The I&F model and some variants allow large scale simulations for its mathematical simplicity (in contrast with models based on conductances). It is a **suitable modelling to speculate about connectivity** rather than on intrinsic properties of neurons.

- **But... what is the limit?**

See video at http://www.izhikevich.org/publications/large-scale_model_of_human_brain.htm

Spontaneous activity generated by injecting small stimuli the first 30 min of simulation ($\approx$ 1/2.4 msec) [Izhikevich, Edelman, PNAS 2008]

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Networks of integrate and fire neurons: large scale simulations

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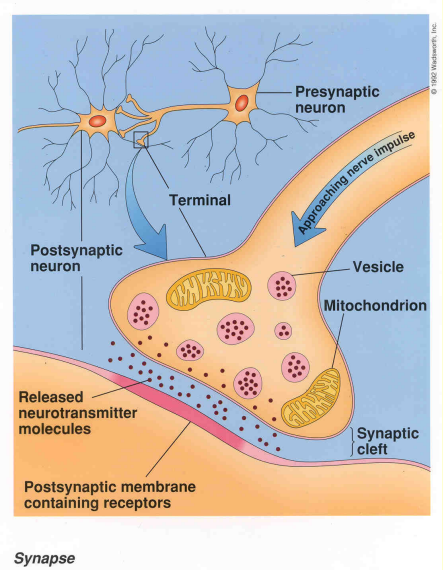
Two examples: synaptic depression and bistable perception

Short-term synaptic depression (STD)

[Benita *et al.*, Frontiers in Computational Neuroscience, 2012.]

What is synaptic depression?

- Synaptic depression is the loss of synaptic strength along time.
  Depression/Facilitation are forms of plasticity.
- Short-term synaptic depression (STD) is explained by the depletion of the pool of vesicles ready to release the neurotransmitters.



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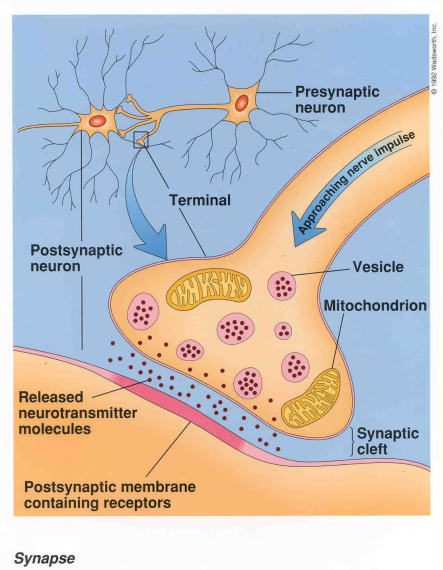

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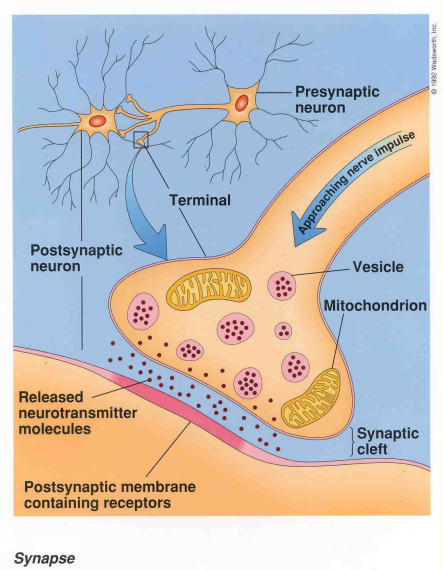

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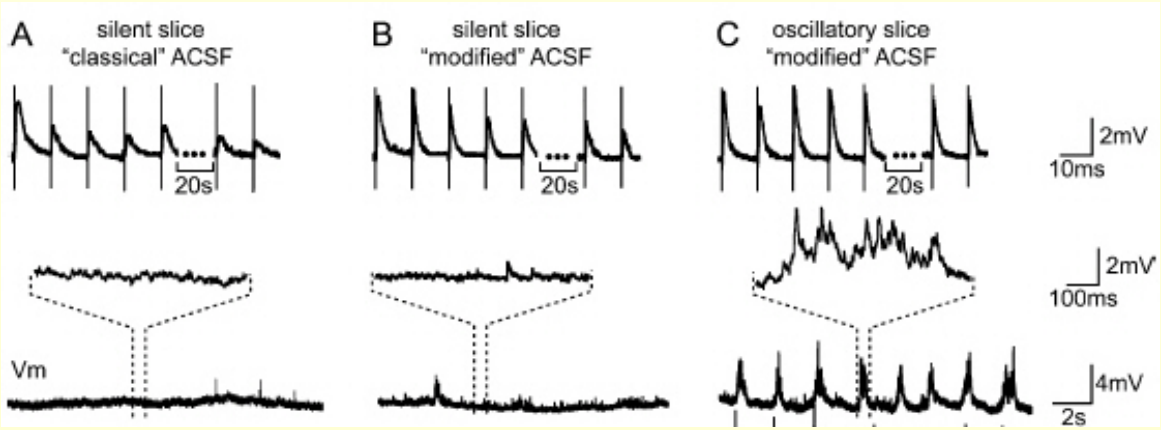
Experimental STD measurements

- A presynaptic neuron is stimulated and the activity at the (target/postsynaptic neuron) is recorded.
- The target neuron must be prevented from spiking. Small voltage variations (PSP=*PostSynaptic Potentials*) are then measured.
- To **measure STD** one observes how the **amplitude of the PSPs** varies for sufficiently long time.

Results on STD from experiments

- [Reig *et al*, Cerebral Cortex, 2006]. The amount of activity of the network (with **UP/DOWN** states) is important. When the (*in vitro*) network has rhythmic activity, there is less depression.



- **More activity, less depression.**
- **Can we reproduce this phenomenon in a model and explain why?**
- **Does it depend on the experimental preparation used to modify activity?**

Building up the model

- Network of 1280 neurons (80% exc., 20% inh.) bicompartmental with 10 currents (excitatory neurons) *[Compte et al., 2003]*.

$$\begin{cases} C_m A_s \frac{dV_s}{dt} = -A_s(I_L + I_{Na} + I_K + I_A + I_{KS} + I_{KNa}) - I_{syn,s} - g_{sd}(V_s - V_d), \\ C_m A_d \frac{dV_d}{dt} = -A_d(I_{Ca} + I_{KCa} + I_{NaP} + I_{AR}) - I_{syn,d} - g_{sd}(V_d - V_s), \end{cases}$$

- Synapses ($I_{syn,exc/inh}$) mediated by AMPA, GABA and NMDA:

$$I_{syn} = g_{syn}\, \mathbf{s}\, \mathbf{P_{rel}}\, (V - V_{syn})$$

- Specific equation (important!) for the **release probability**: $\tau_{rel}\, P'_{rel}(t) = P_0 - P_{rel}$, $P_{rel} \to f_D\, P_{rel}$, $\mathbf{f_D} < \mathbf{1}$, every presynaptic event.
- Neurons on a line, **Gaussian connectivity** ($\approx$ 20 presynaptic contacts per neuron).
- Approximately 19000 differential equations.

Complexity of the model: different currents, multicompartmental ,...

Somatic currents: I_{Na}, I_K, I_L, and:

- a fast K^+-current named A-current, I_A;
- a slow inactivating K^+-current, I_{KS};
- a $[Na^+]$-dependent K^+-current, I_{KNa}.

Dendritic currents:

- a Ca^{2+}-current with high threshold, I_{Ca};
- a $[Ca^{2+}]$-dependent K^+-current, I_{KCa};
- a persistent Na^+-current, I_{NaP};
- a K^+-current activated during hyperpolaritzation (*inward rectifier*), I_{AR}.

Building up the model: procedures

Illustration with some currents in the soma compartment:

$$C_m A_s \frac{dV_s}{dt} = -A_s(I_L + \mathbf{I_{Na}} + \mathbf{I_K} + I_A + I_{KS} + I_{KNa}) - I_{syn,s} - g_{sd}(V_s - V_d),$$

- A target neuron chosen, we stimulate a unique presynaptic neuron.
- *Voltage "clamp"* is simulated by blocking sodium channels in the model of the target neuron.

$$\mathbf{I_{Na}} = \mathbf{g_{Na}}\, m^3\, h\, (v - V_{Na}); \qquad \mathbf{g_{Na}} = \mathbf{0}$$

- Network activity is increased by increasing the potassium reversal potential V_k ($\uparrow$ extracellular potassium) as in the *in vitro* experiments (we introduce parameter **a**).

$$\mathbf{I_K} = \mathbf{g_K}\, n^4\, (v - V_K); \qquad \mathbf{V_K} \rightarrow \mathbf{V_K} + \mathbf{a}$$

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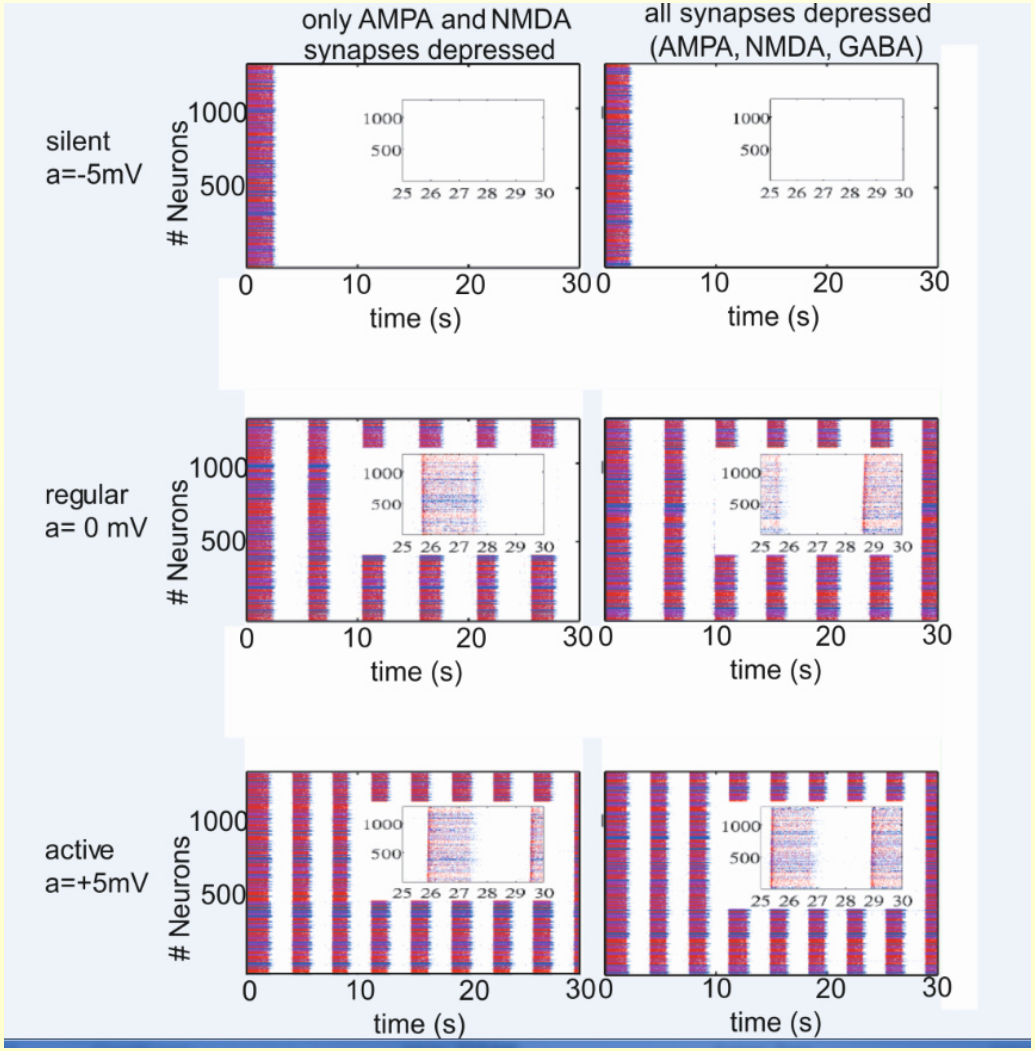
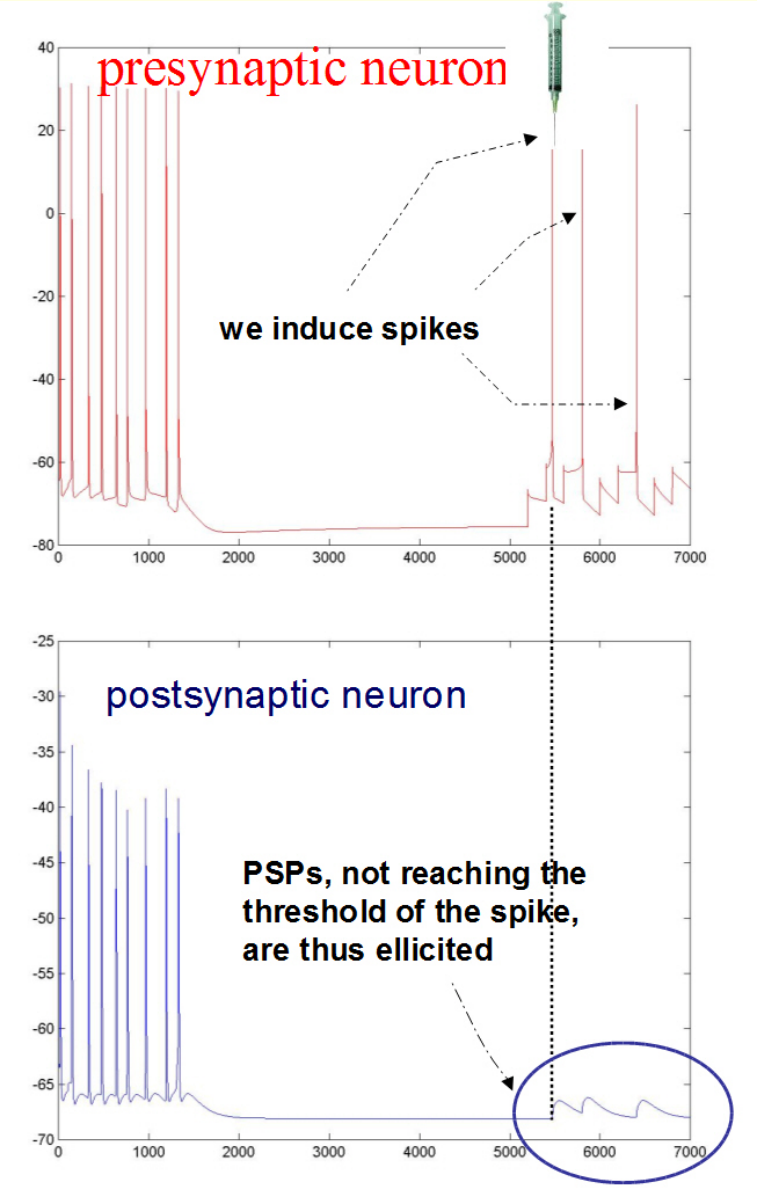
Running the model: effect of K^+ reversal potential



Running the model: measuring PSPs



Results from the model: replication of experiments

- Using models we test several parameters that change the network activity (important to keep realistic models).
- We provide evidences that is the **activity of the network** itself the **responsible** for the changes in STD, and is not artificially induced by the experimental solution.

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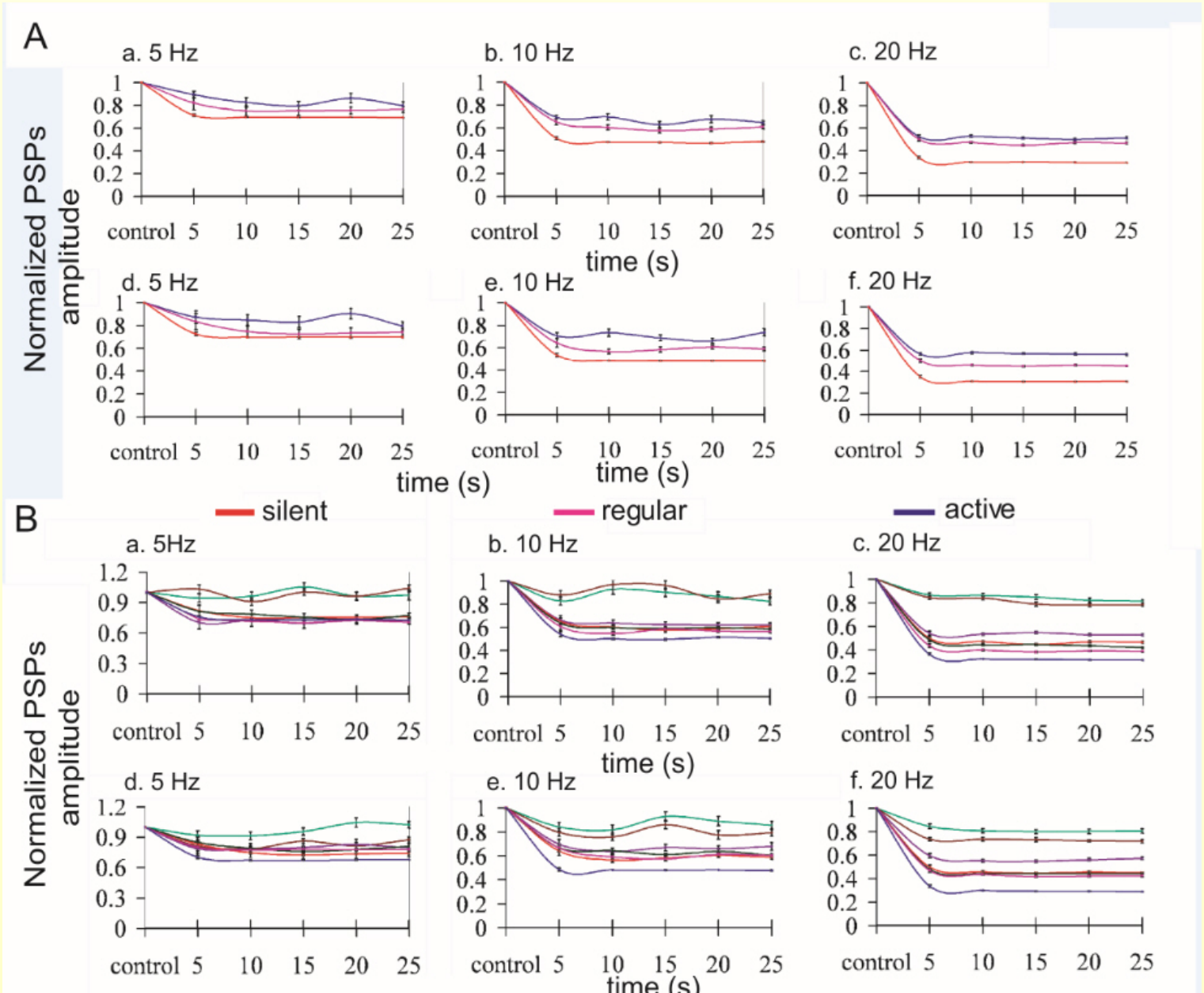
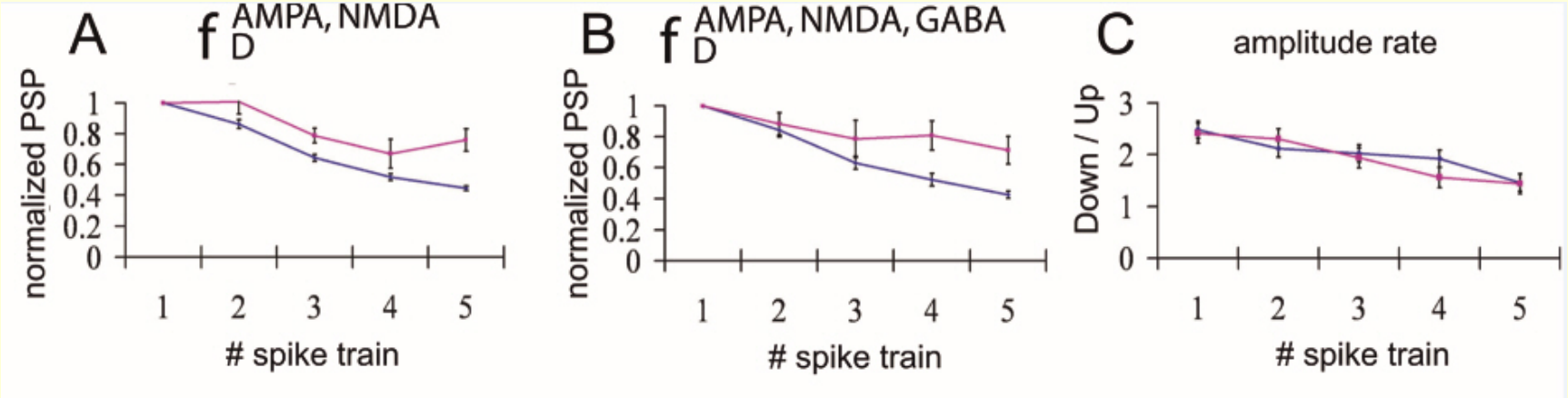


Results from the model: testable predictions

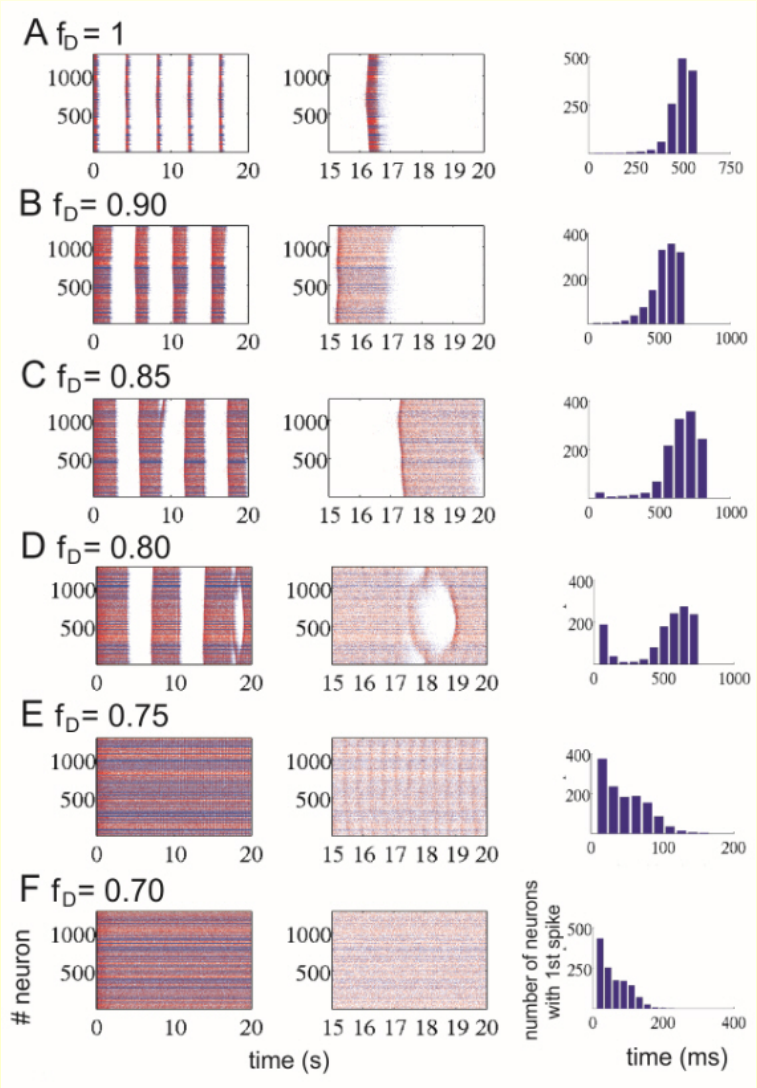
Different behaviour in UP and DOWN states of the network.



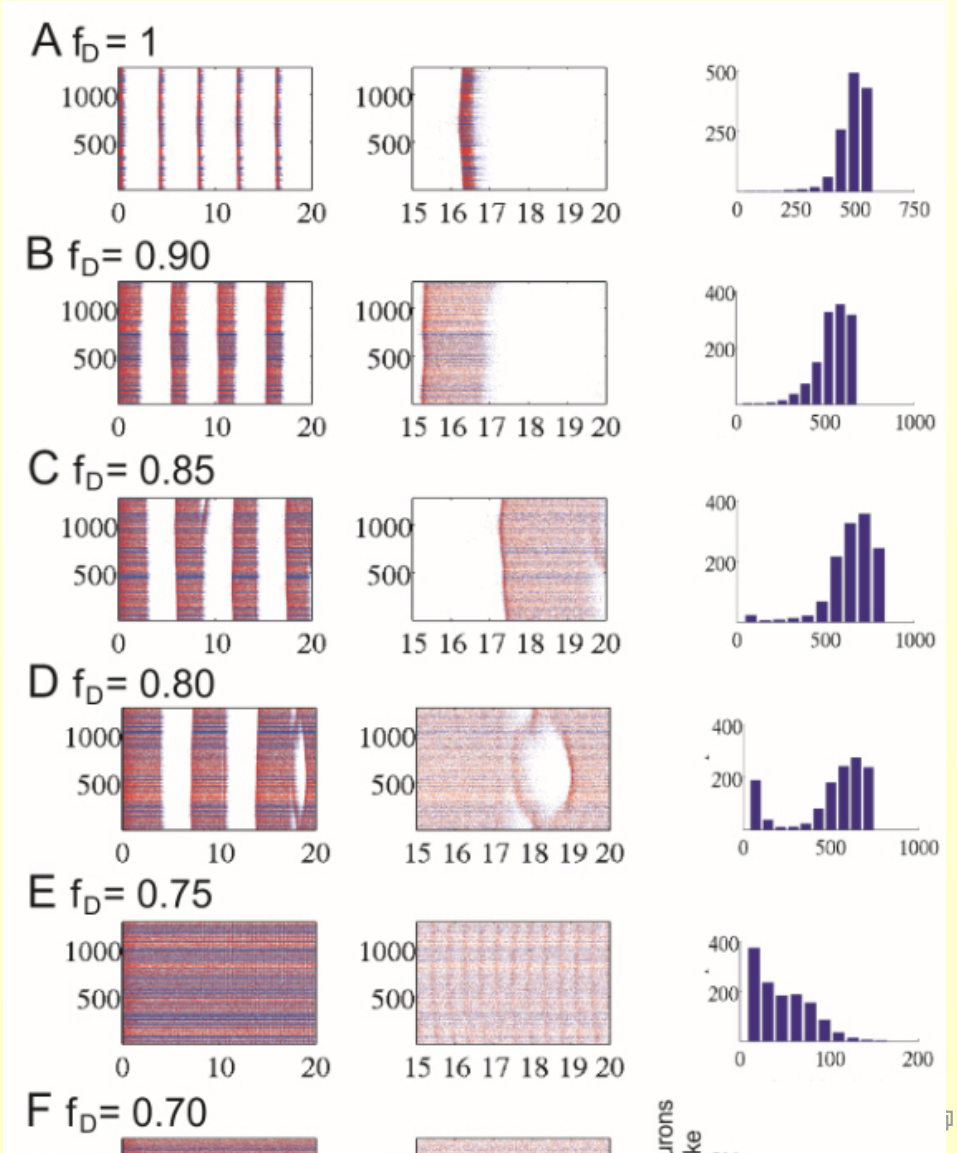
Depression at UP versus DOWN states.

Results from the model: non-testable predictions

Reciprocal result: **influence of STD** on the network activity.



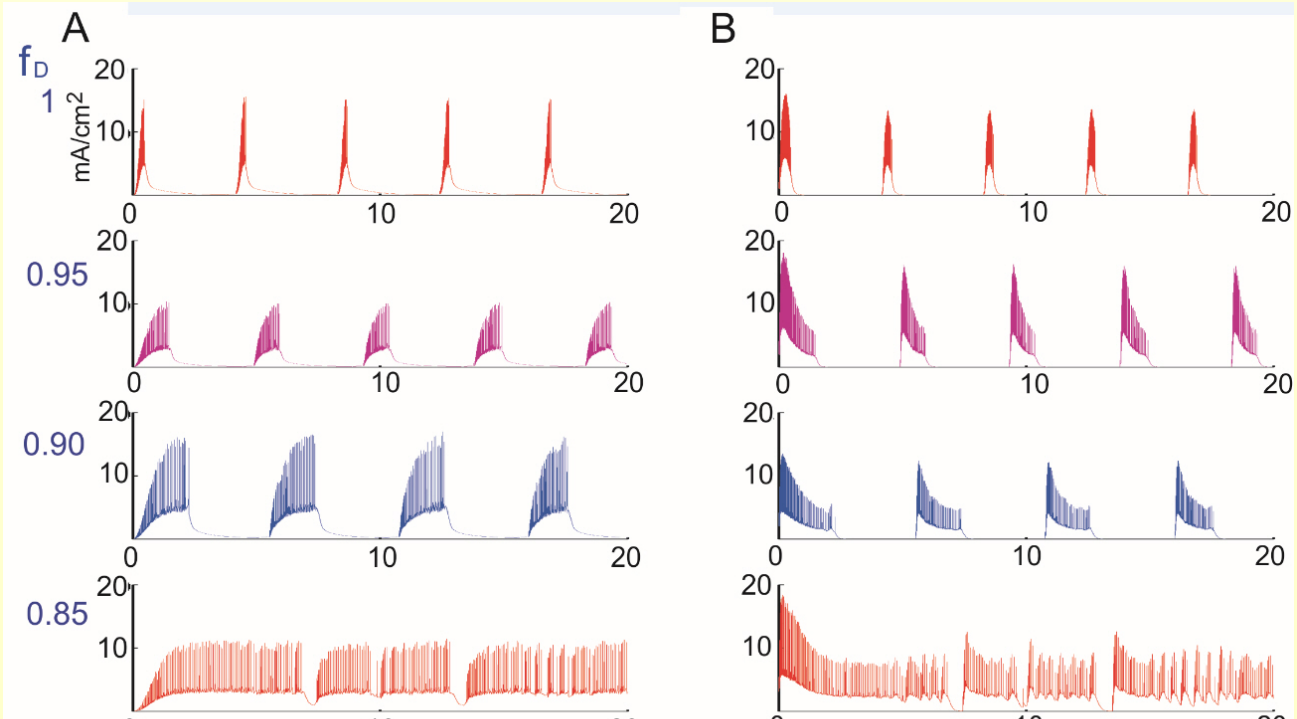
Non-testable predictions: influence of STD on network activity.



Results from the model: non-testable predictions, explanations

Calcium/sodium buffering (responsible of ending UP states) gets slower with depression.

$$I_{KNa} = g_{KNa} w([Na+])(v - V_K), \; I_{KCa} = g_{KCa} \frac{[Ca^{2+}]}{[Ca^{2+}] + K_D}(v - V_K),$$



Further steps

- Measures to **describe the bifurcation**.
- Reproduce the results with **network of more simplified neuron models** (containing a spiking mechanism, different time-scales allowing buffering) with similar synapse dynamics.
- Reduce the network to a **mean-field*** model where P_{rel} still plays a role to be able to do some analysis and state the explanations in a more consistent way.

* **Homogeneity conditions. Using, for instance the diffusion approach from statistical mechanics (Fokker-Planck) and obtain a rate equation, see also Alex Roxin's talk.**

Rate model: Goals and equations

How do the lengths of the UP- and DOWN-states vary in terms of short-term depression?

- Activities (rates) of exc/inh populations: $a_{E/I}$.
- Depression levels: $s_{E/I}$.
- Adaptation levels: $h_{E/I}$.

$$\begin{cases} \tau_{a,E}\,\dot{a_E} &= -a_E + \varphi(-(s_E\,w_{E,E}\,a_E - s_I\,w_{E,I}\,a_I - g_E\,h_E - \theta_{0,E})/k_{a,E}), \\ \tau_{s,E}\,\dot{s_E} &= -s_E + \varphi((a_E - \theta_{s,E})/k_{s,E}), \\ \tau_{h,E}\,\dot{h_E} &= -h_E + \varphi((\theta_{h,E} - a_E)/k_{h,E}), \end{cases} \tag{5}$$

with $\varphi(x) = 1/(1 + \exp(x))$.

Rate model: partial results

To mimic the amount of depression, we modify the time constant of the synaptic depression:

$$\tau_{s,E/I} = \overline{\tau}_{s,E/I}\left((1 - a_{E/I})\left(1 - f_{D,E/I}\right)\right),$$

where $\overline{\tau}_{s,E/I}$ constant, $f_{D,E/I} \in [0, 1]$, depression levels.
$\overline{\tau}_{s,E/I}$ when there is activity in the population (that is, $a_{E/I} > 0$). Thus, $s_{E/I}$ decay changes according to the level of activity. For $f_{D,E/I} \approx 1$, synaptic depression is less than for $f_{D,E/I} \approx 0$.
We have tested different connectivities. There is always a parameter range in which UP-state durations overcome DOWN-state durations.

Rate model: partial results

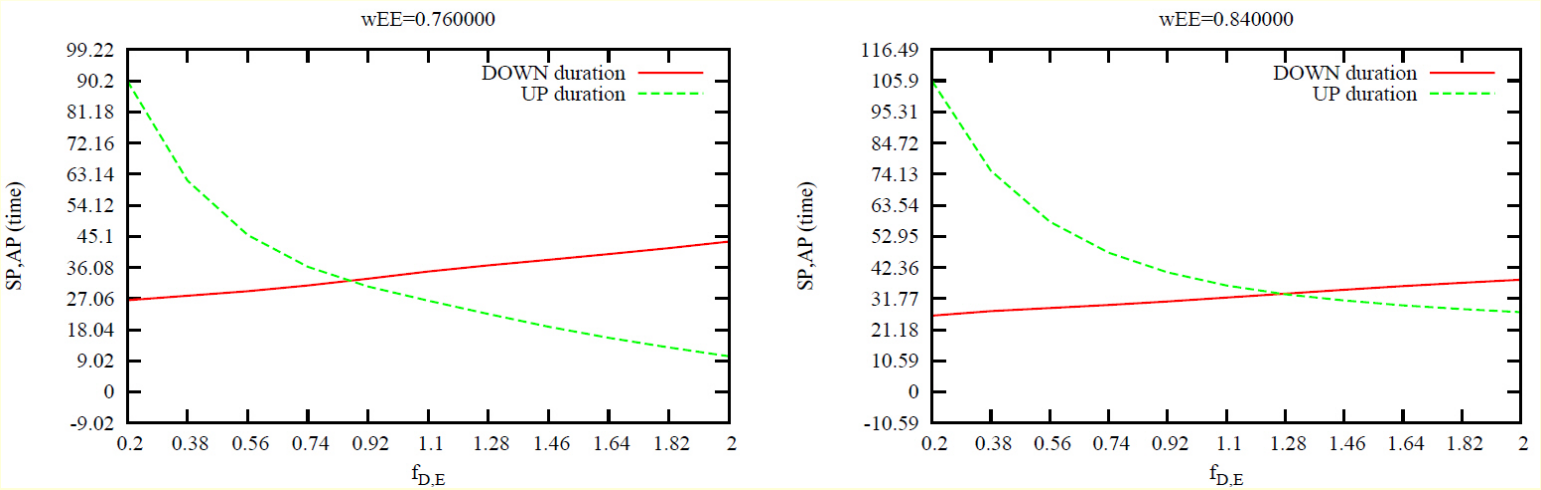


Figure: Changes in Up/Down-state durations in terms of $f_{D,E}$. Each panel represents a different connectivity value.

Non-constant parameters in this simulation: $f_{D,E} \in [0.2, 2.0; 0.18]$.
Fixed parameters in this simulation: $w_{EI} = 0.769$; $w_{IE} = 0.417$; $w_{II} = 0.031$; $g_E = 0.16$; $g_I = 0.0$; $\tau_{s,E} = 400.0$; $\tau_{s,I} = 400.0$; $f_{D,E} = 1.000$; $f_{D,I} = 1.0$; $\tau_{\theta,E} = 200.000$; $\tau_{\theta,I} = 200.0$; $\theta_{0,E} = 0.0$; $\theta_{0,I} = 0.0$.

Reduced model: an oversimplification

$$I_{syn} = g_{syn}\, \mathbf{s}\, \mathbf{P_{rel}}\, (V - V_{syn})$$

$$\begin{cases} s'(t) &= -\dfrac{s}{\tau_s} + S_1 \sum_{\mathbf{spk}} \delta(\mathbf{t} - \mathbf{t_{spk}}), \\ P'_{rel}(t) &= (P_0 - P_{rel})/\tau_{rel} + S_2\, P_{rel} \sum_{\mathbf{spk}} \delta(\mathbf{t} - \mathbf{t_{spk}}). \end{cases}$$

Can we explain the results only from this simple problem assuming an input with 2 intertwined frequencies ω_S, ω_N?

Not enough... **network effects are important**.

Modeling bistable perception

“Bistable" stimuli

Basic equations

- ***Firing-rate*** variables:

$$\begin{cases} \tau \dot{E}_1 &= -E_1 + f(-\beta E_2 - \phi_a a_1 + I_1 + n_1(t)), \\ \tau \dot{E}_2 &= -E_2 + f(-\beta E_1 - \phi_a a_2 + I_2 + n_2(t)), \end{cases} \tag{6}$$

$\tau \sim 10$ ms;

- $\beta =$ cross-inhibition;
- $\phi_a =$ adaptation strength;
- $I_{1,2} =$ external stimuli.

- Gain function:

$$f(x) = \frac{1}{1 + exp(-\frac{x-\theta}{k})} \tag{7}$$

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- **Adaptation variables**:

$$\begin{cases} \tau_a \dot{a}_1 &= -a_1 + E_1, \\ \tau_a \dot{a}_2 &= -a_2 + E_2, \end{cases} \tag{8}$$

$\tau_a \sim 1$ s.

- **Noise dynamics**:

$$\begin{cases} \dot{n}_1 &= -\frac{n_1}{\tau_n} + \sigma_n \sqrt{\frac{2}{\tau_n}} \xi_1(t), \\ \dot{n}_2 &= -\frac{n_2}{\tau_n} + \sigma_n \sqrt{\frac{2}{\tau_n}} \xi_2(t), \end{cases} \tag{9}$$

$\overline{\xi_i(t)\xi_i(t')} = 0$, $\overline{\xi_i(t)} = 0$, $\overline{\xi_i^2(t)} = 1$, $\tau_n = 100$ ms.

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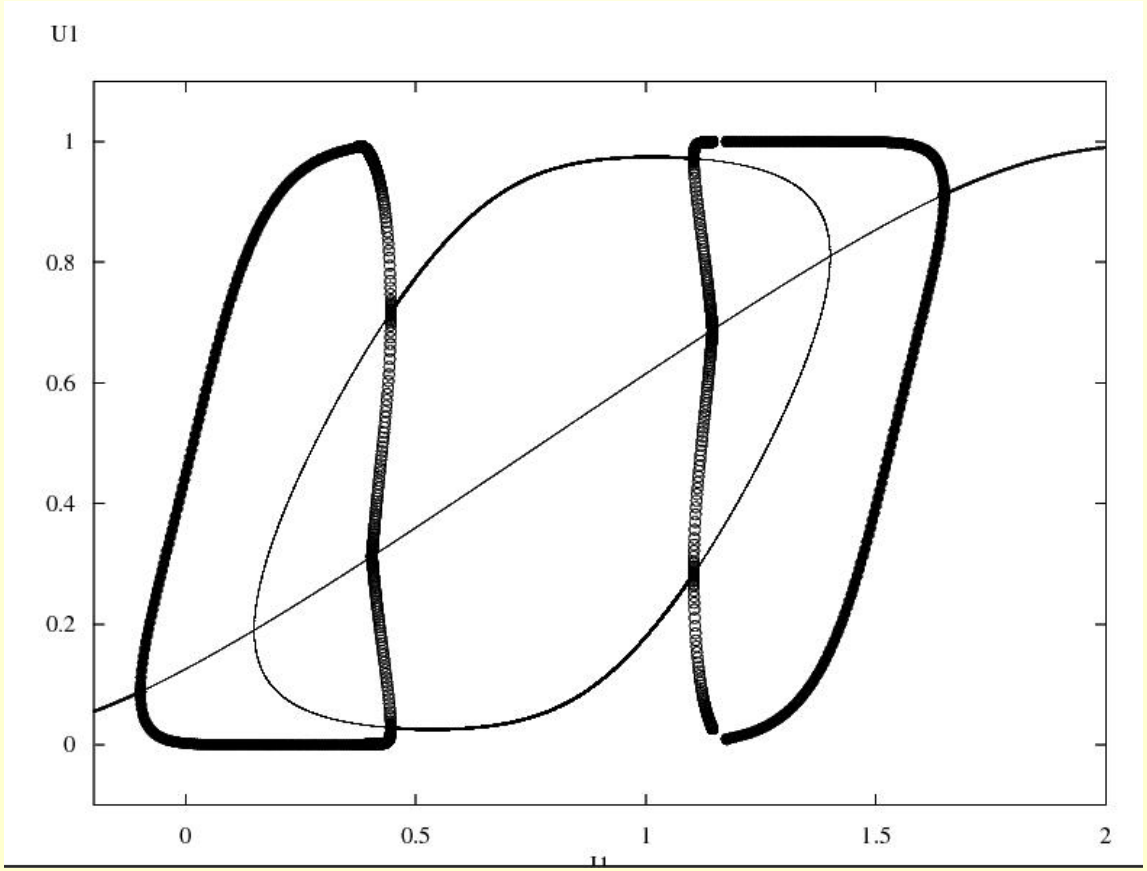
Parameter dependence

Bifurcation diagrams ...

Basic parameter set: $\beta = 1.0$, $\phi_a = 0.5$, $\tau_a = 200$, $k = 0.1$, $\theta = 0.0$.



Bifurcation diagram in terms of the strength of the input $I_1 = I_2$.

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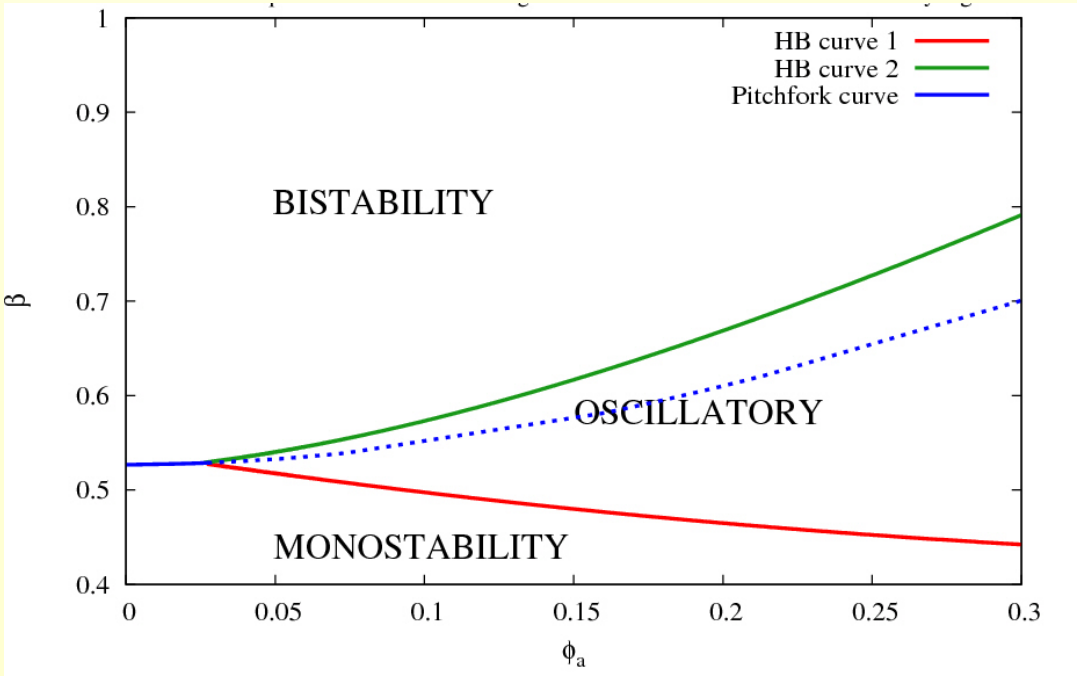

Bifurcation diagram in terms of the strength of the input $I_1 = I_2$.

"juicy" bifurcation details.

Collaborators

- **Short-term depression**: J.M. Benita (Ph.D. UPC), G. Deco (ICREA-UPF, computational neuroscience), M.V. Sánchez-Vives (ICREA-IDIBAPS, electrophysiology).

- **Bistable perception**: P.E. García-Rodríguez (Ph.D. CRM-UPF), J. Braun, A. Pastukhov (U. Magdeburg, cognitive psychology), G. Deco (ICREA-UPF, computational neuroscience).

Thanks for your attention!