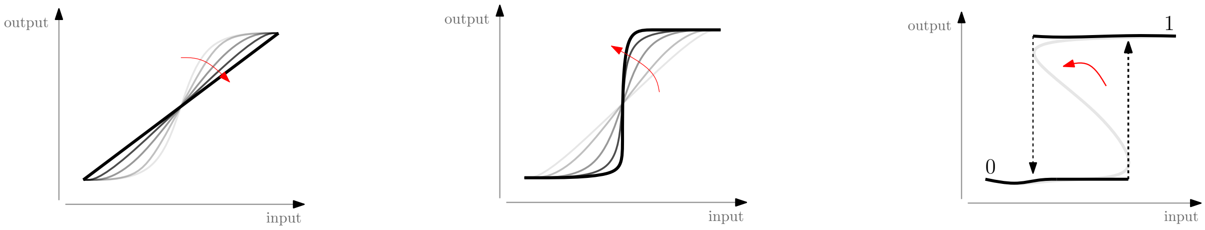
Switchlets : analysis and design of multi resolution sensitivity

R. Sepulchre -- University of Cambridge

ICMS 2017, Eindhoven

Feedback glocalizes

Negative feedback balanced by positive feedback



Regulating behaviors

Linear

exogenous

continuous

(feedback zooms out)

sensitivity resonance

(feedback zooms in)

Decision-making behaviors

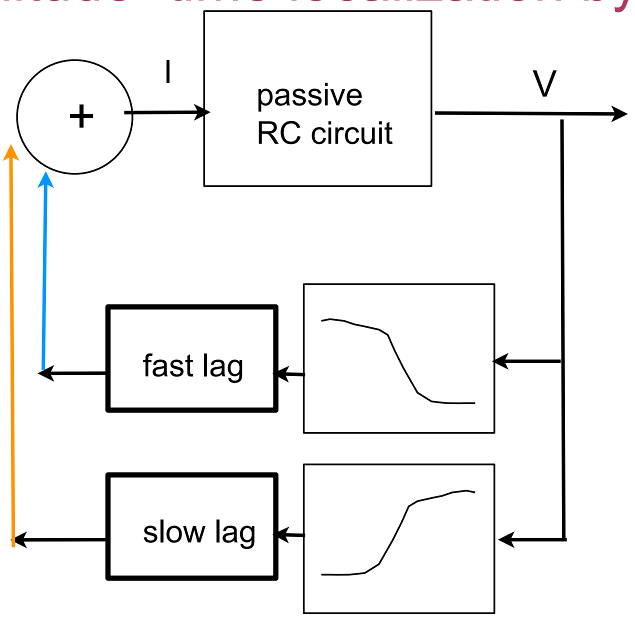
Switch

endogenous

discrete

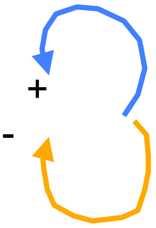
(feedback zooms out)

Robust amplitude+time localization by feedback



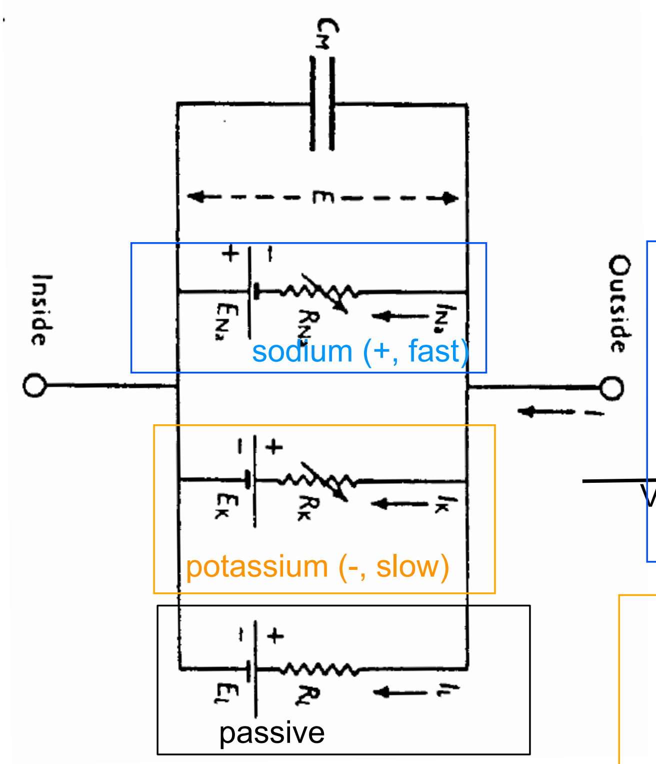
High frequency behavior:

Low frequency behavior:



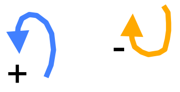
Necessary localization in some frequency range !

Hodgkin-Huxley model as localized behavior



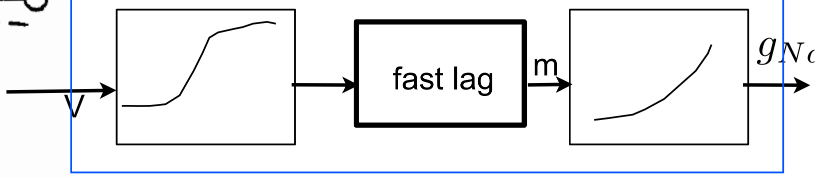
$$\underleftrightarrow{C\dot{V} + I_l} = -I_{Na} - I_K$$

passive



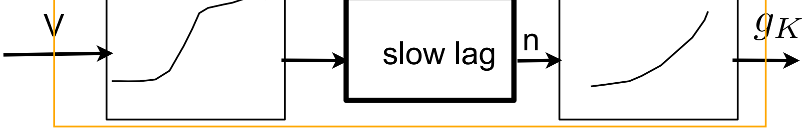
$$I_{Na} = \bar{g}_{Na}\, m^3\, h\, (V - V_{Na})$$

$$\tau_m(V)\dot{m} = -(m - m_\infty(V))$$



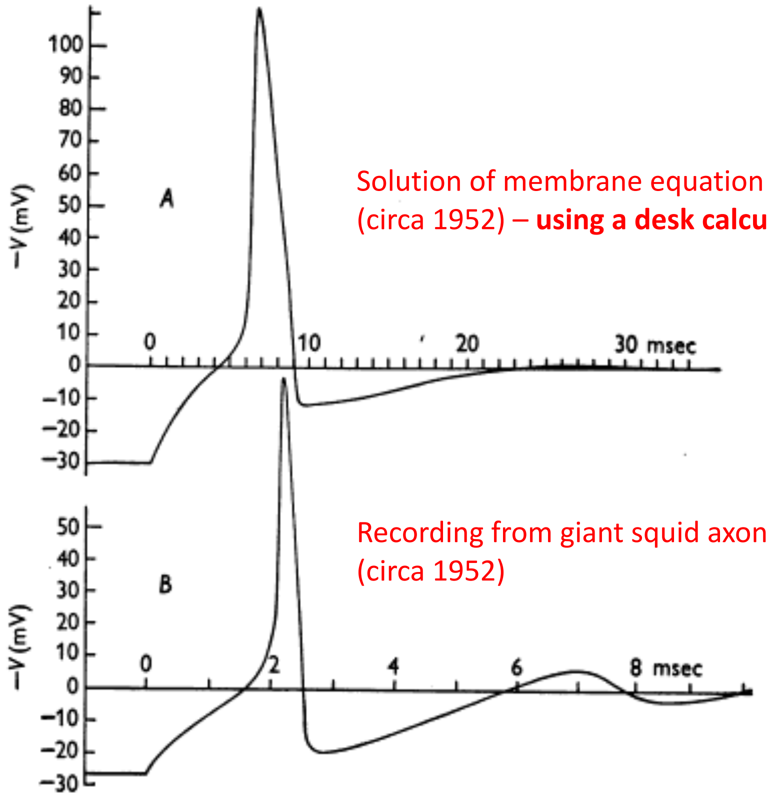
$$I_K = \bar{g}_K\, n^4\, (V - V_K)$$

$$\tau_n(V)\dot{n} = -(n - n_\infty(V))$$



$$(V_K < V < V_{Na})$$

Neuronal excitability is **very well understood**

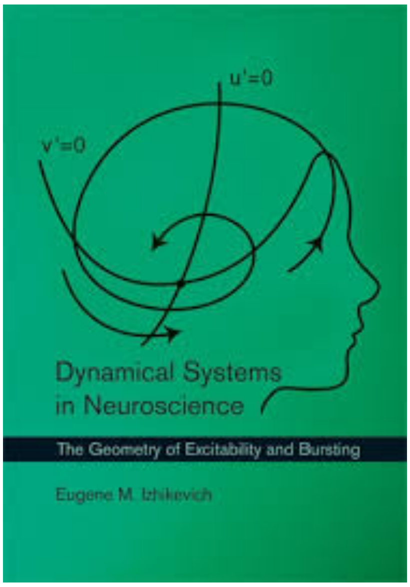


Solution of membrane equation
(circa 1952) – **using a desk calculator**!

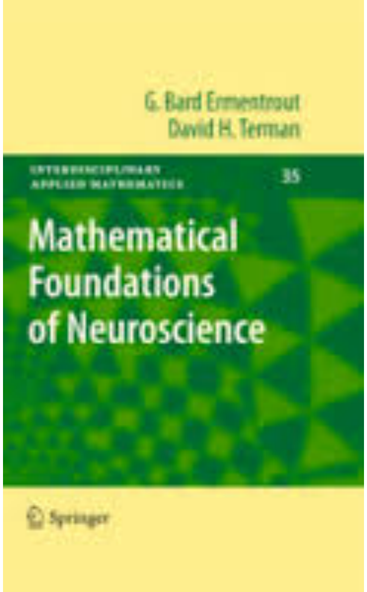
Recording from giant squid axon
(circa 1952)

Hodgkin & Huxley, J Physiol. (1952)

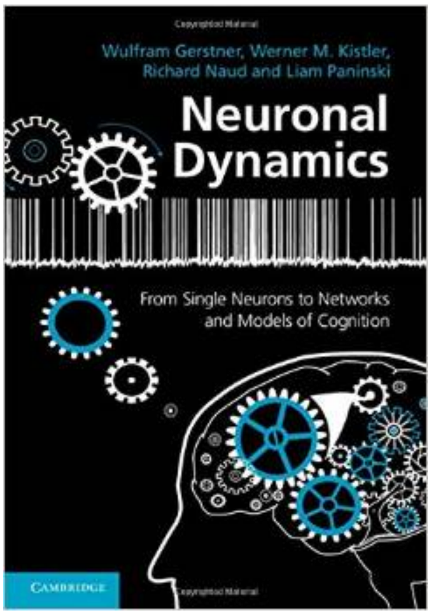
Dynamical systems neuroscience



2007



2010



2014

Learning the language of neurodynamics and neurophysiology

G. Drion, L. Massotte, V. Seutin, R. Sepulchre. How modeling can reconcile apparently discrepant experimental results : the case of pacemaking in dopaminergic neurons PLoS Computational Biology, 7(5), 1002050, 2011.

G. Drion, A. Franci, V. Seutin, R. Sepulchre. A Novel Phase Portrait for Neuronal Excitability, PLoS ONE 7(8) : e41806. 2012.

A. Franci, G. Drion, R. Sepulchre. An organizing center in a planar model of neuronal excitability. SIAM Journal on Applied Dynamical Systems, 11(4), pp. 1698-1722, 2012

G. Drion, A. Franci, V. Seutin, R. Sepulchre. A Balance Equation Determines a Switch in Neuronal Excitability, PLoS Computational Biology 9(5) : e1003040, 2013.

A. Franci, G. Drion, R. Sepulchre. Modeling the modulation of neuronal bursting: a singularity theory approach. SIAM J. Appl. Dyn. Syst. 13-2 (2014), pp. 798-829

G. Drion, A. Franci, J. Dethier, R. Sepulchre. Dynamic input conductances shape neuronal spiking. eNeuro, DOI: 10.1523/ENEURO.0031-14. 2015.

J. Dethier, G. Drion, A. Franci, R. Sepulchre. A positive feedback at the cellular level promotes robustness and modulation at the circuit level, Journal of Neurophysiology, 114(4), pp. 2472-2484, 2015.

2014 - excitable systems as behaviors

- What is an excitable system ? How is it regulated ?
- How can we study interconnections of excitable systems ?
- What makes those nonlinear systems tractable ?
- What makes those systems worth studying beyond their relevance in neuroscience?

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Excitability in a system theoretic language

G. Drion, T. O'Leary, J. Dethier, A. Franci, R. Sepulchre. *Neuronal behaviors: a control perspective.* 54th IEEE Conference on Decision and Control, Osaka, Japan, pp. 1923 - 1944, December 2015. Tutorial paper.

R. Sepulchre, G. Drion, A. Franci. *Excitable behaviors*, in “Emerging Applications of Control and System Theory” , workshop be held in honor of M. Vidyasagar in Dallas, TX, September 28-30, 2017.

What is excitability ?

From google …

Excitability | definition of excitability by Medical dictionary

ex·cit·a·bil·i·ty (ek-sīt'ă-bil'i-tē),

Having the capability of being excitable.

Farlex Partner Medical Dictionary © Farlex 2012

From google …

Excitability | definition of excitability by Medical dictionary

ex·cit·a·bil·i·ty (ek-sīt'ă-bil'i-tē),

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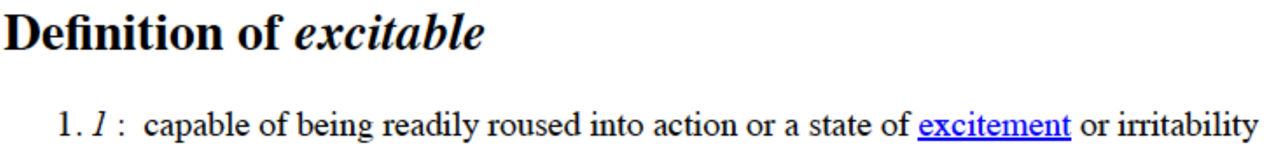
Farlex Partner Medical Dictionary © Farlex 2012



Definition of *excitable*

1. *1* : capable of being readily roused into action or a state of excitement or irritability

From google …

Excitability | definition of excitability by Medical dictionary

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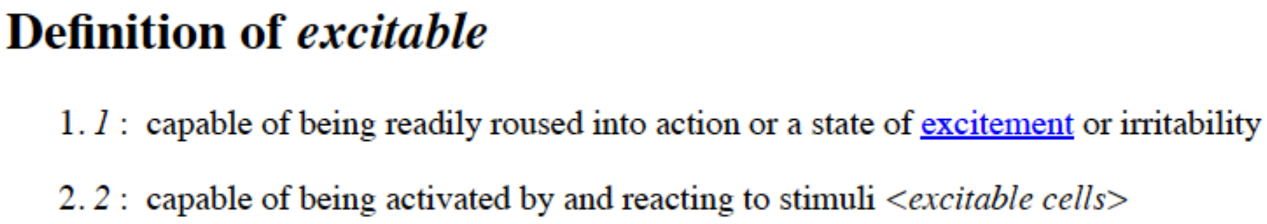
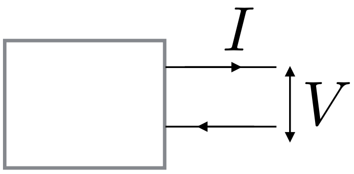
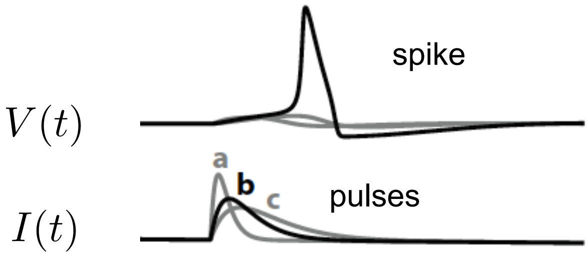


Definition of *excitable*

1. *1* : capable of being readily roused into action or a state of excitement or irritability
2. *2* : capable of being activated by and reacting to stimuli <*excitable cells*>

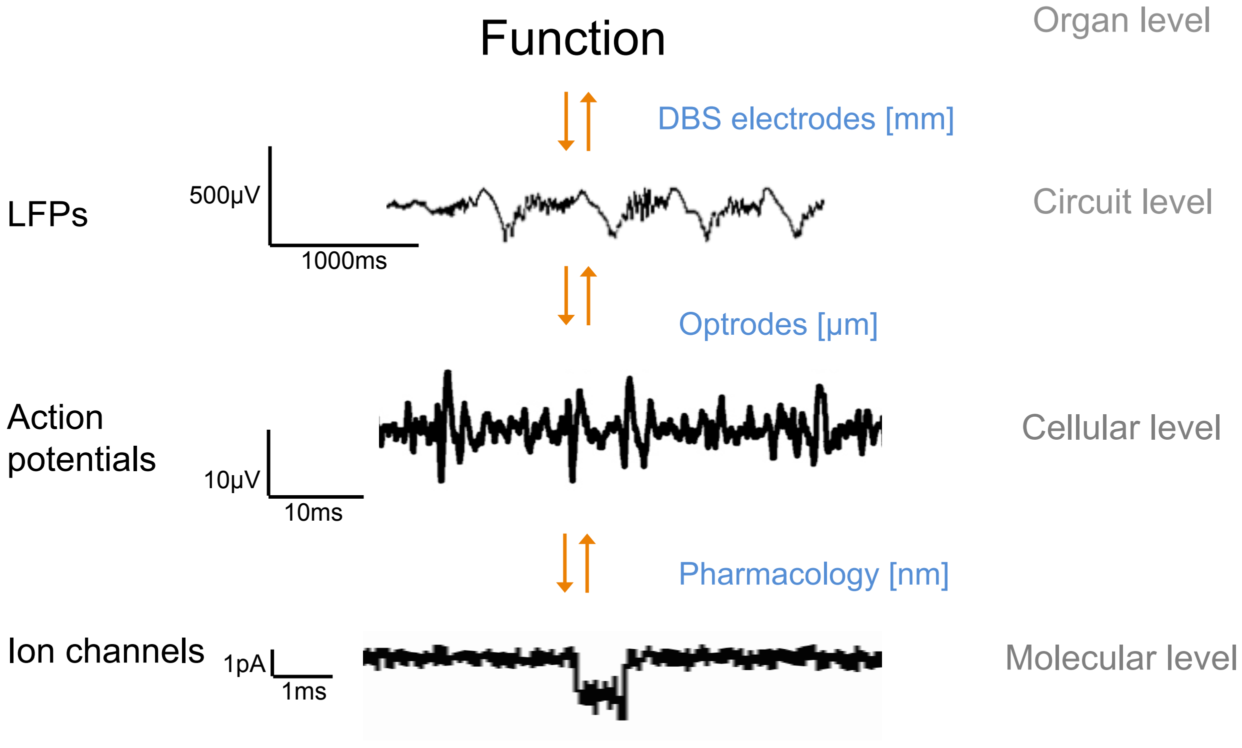
A behavioral property



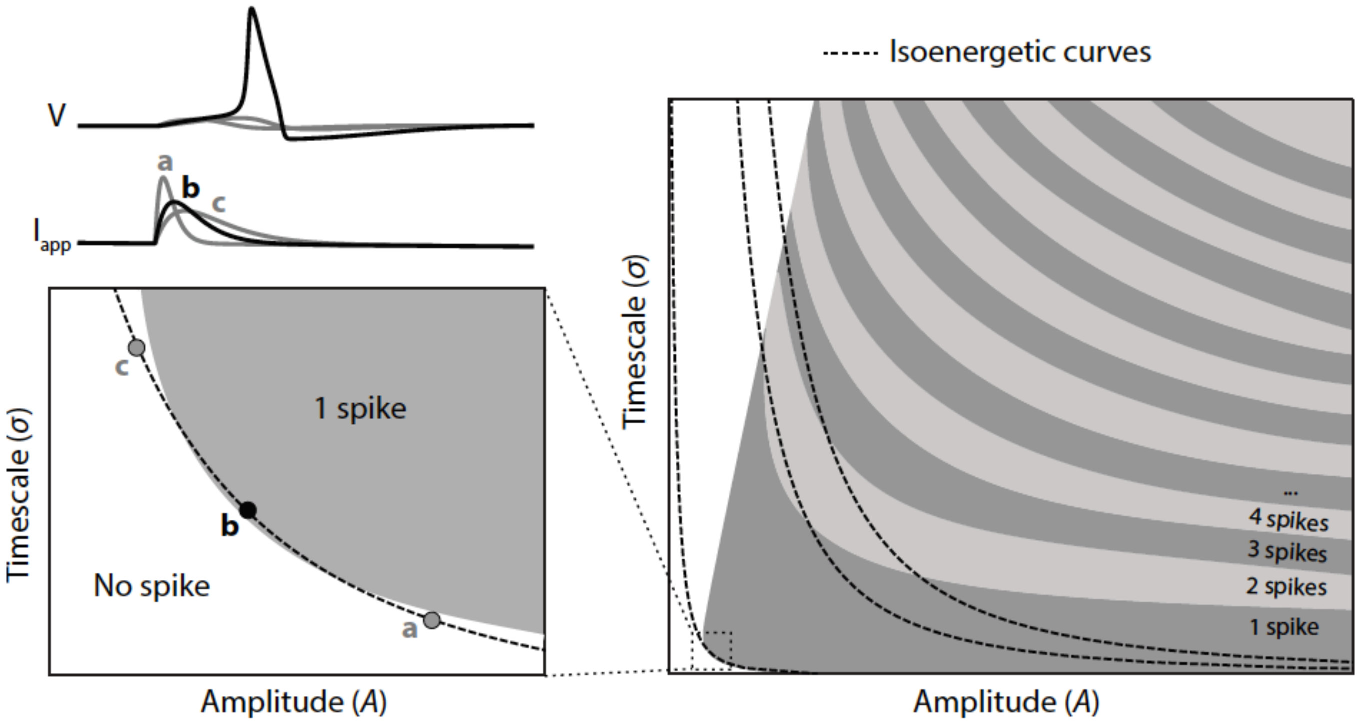


A family of trajectories characterised by current *pulses* and all-or-none voltage *spikes*

Electrical activity of the brain at many scales



A threshold phenomenon : *localised* sensitivity + *analog-digital* conversion



Excitable behaviors

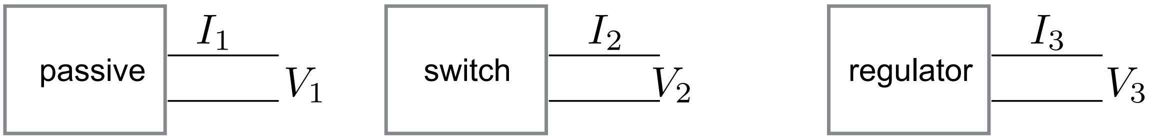
- Neuronal networks are interconnections of neurons and synapses. In neurons, the *current* is the input. In synapses, the *voltage* is the input.
- The all-or-none nature of the spike makes the behavior *nonlinear and hybrid.* Intractable ?
- Excitable behaviors have a *resolution*. Tractable ?

How ?

A circuit representation

An energy balance

A circuit representation



backbone

negative resistance device

localizes the switch

$$V = V_1 = V_2 = V_3$$

$$I = I_1 + I_2 + I_3$$

Fitzhugh Nagumo circuit

1962 *Nagumo, et al.: Transmissi*

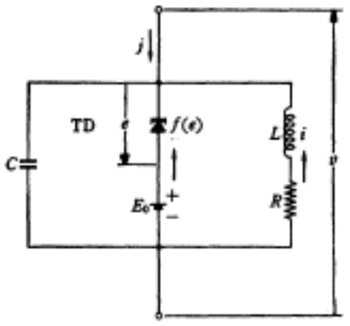


Fig. 2—An electronic simulator of the BVP model.

$$C\dot{V}_1 = I_1 \qquad I_2 = \frac{V_2^3}{3} - kV_2 \qquad L\dot{I}_3 + R_3 I_3 = V_3$$

passive switch regulator

Hodgkin Huxley circuit

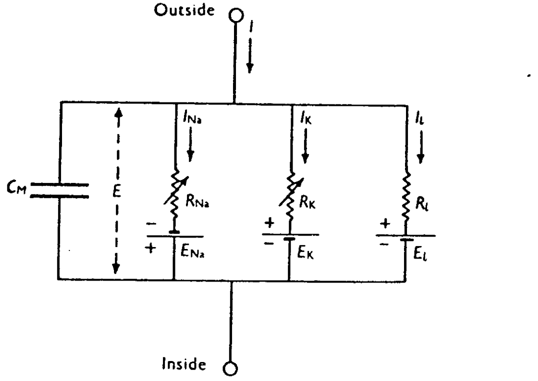


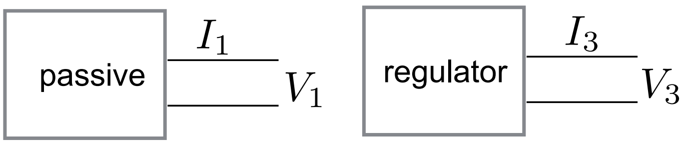
Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

passive membrane: $C\dot{V} + I_L$

The switch: sodium activation I_{Na}

The regulator: potassium current I_K

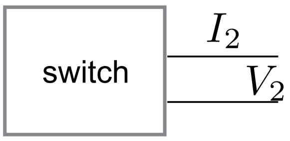
Dissipativity analysis



$\dot{S}_1 \leq V_1 I_1$ $\dot{S}_3 \leq V_3 I_3$

$S = S_1 + S_3$ storage

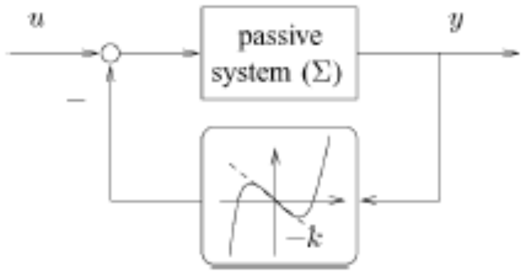
'analog'



negative resistance device

'discrete'

Dissipativity theory of locally active devices



A fundamental mechanism of oscillation

Bifurcations dictated by structure

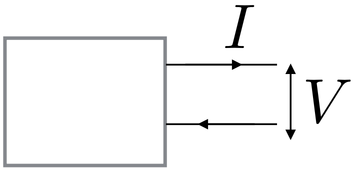
Synchronization theory through diffusive coupling

(Sepulchre & Stan 2005, Stan & Sepulchre 2007)

A bottleneck : state-space approach

Dissipativity of behaviors

(Willems, EJC 2009)



supply (power) : $s(t) =< I(t), V(t) >$

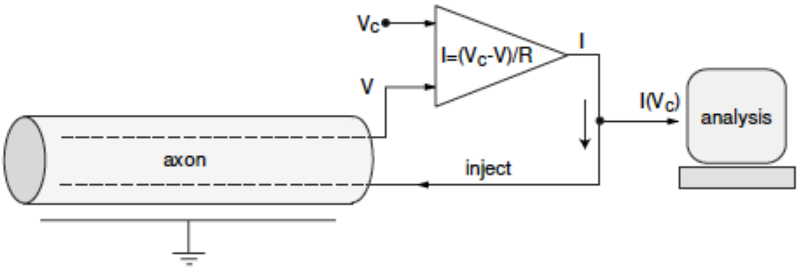
What can we infer for the behavior from the supply ?

E.g. : dissipativity = integral of supply is *positive* along trajectories.

A feedback representation

A balance between positive and negative feedback

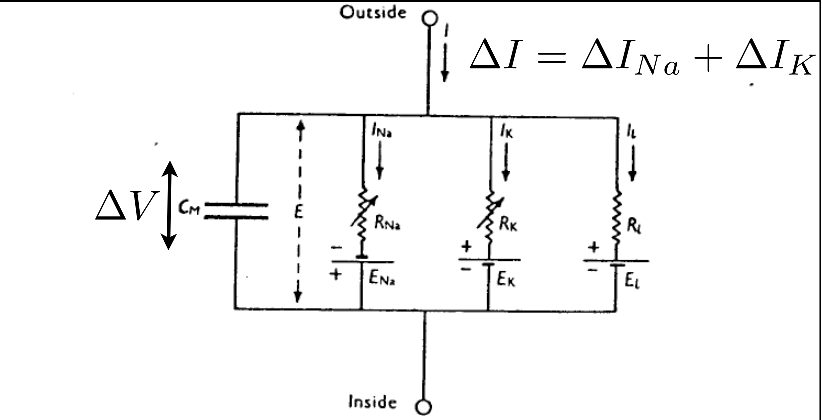
The voltage clamp experiment



The current response to a voltage step assesses the sign of the feedback gain in a given temporal and amplitude windows

---

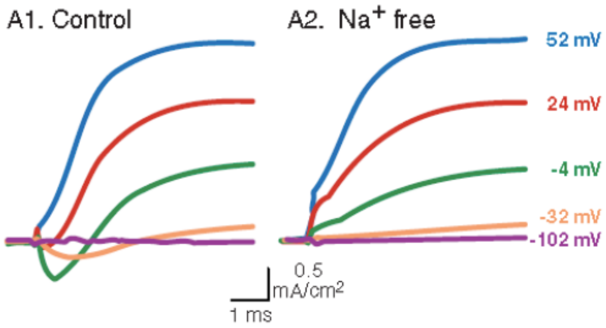
Assessing the localised positive feedback of I_Na

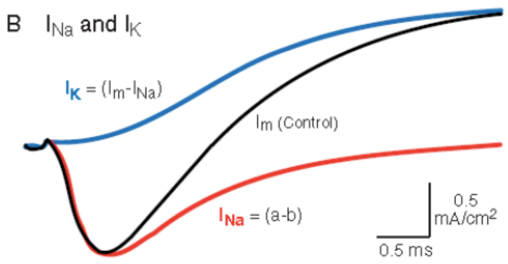


$$\Delta I = \Delta I_{Na} + \Delta I_K$$

Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

Measuring the time course of $\Delta I(t)$ for a given step change of ΔV





Dynamic input conductances

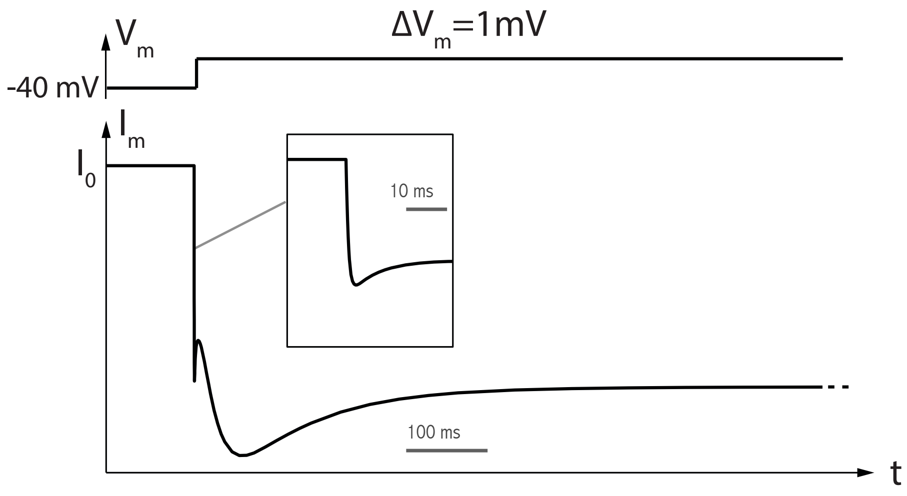
A local characterisation of excitability : $\frac{\Delta I}{\Delta V}(V; j\omega)$
the local admittance is negative real over a localised range of amplitude and frequency.

Because time scales are well separated in a spike, it is sufficient to compute the fast dynamic conductance $g_f(V)$ and the slow dynamic conductance $g_s(V)$.

The threshold and refractory period are well estimated from those quantities, which can be easily computed from a model or from an experiment.

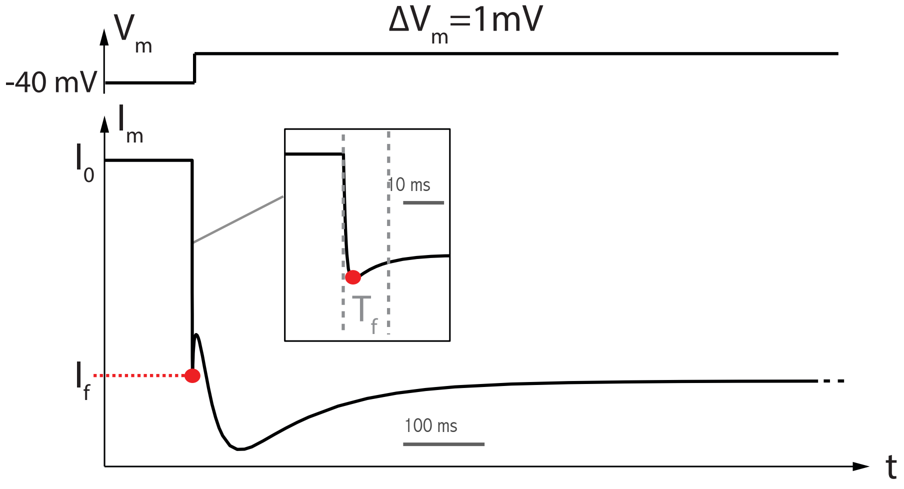
Decomposing the voltage step response into different timescales

- ☐ Most of neuron activity is shaped by the transient changes in membrane permeability.



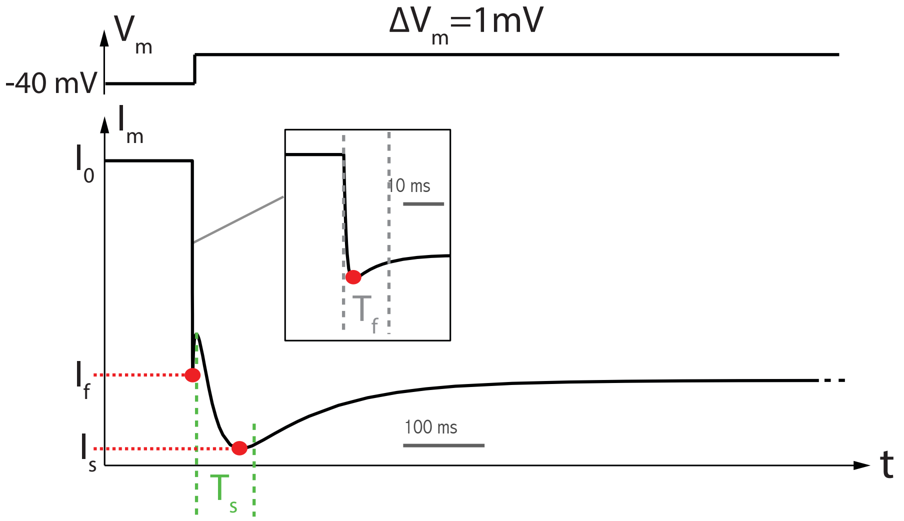
Decomposing the voltage step response into different timescales

- Most of neuron activity is shaped by the <u>transient</u> changes in membrane permeability.



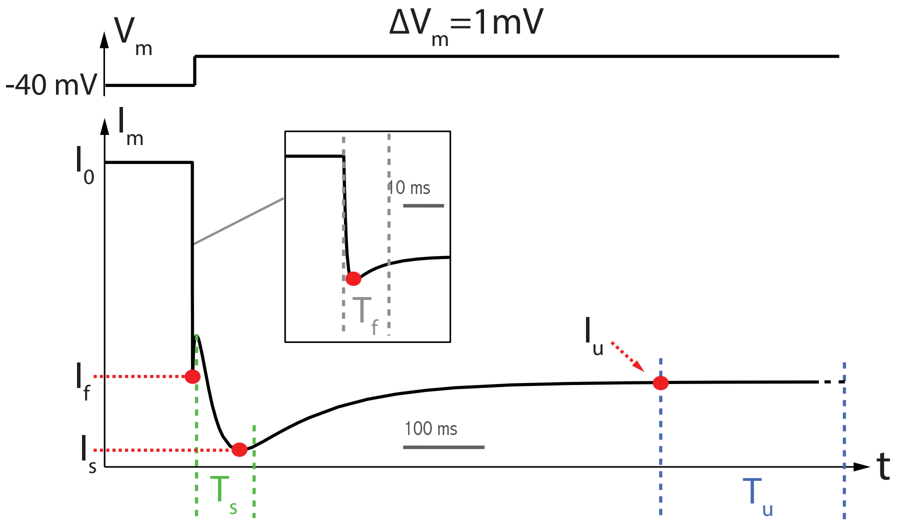
Decomposing the voltage step response into different timescales

- Most of neuron activity is shaped by the <u>transient</u> changes in membrane permeability.



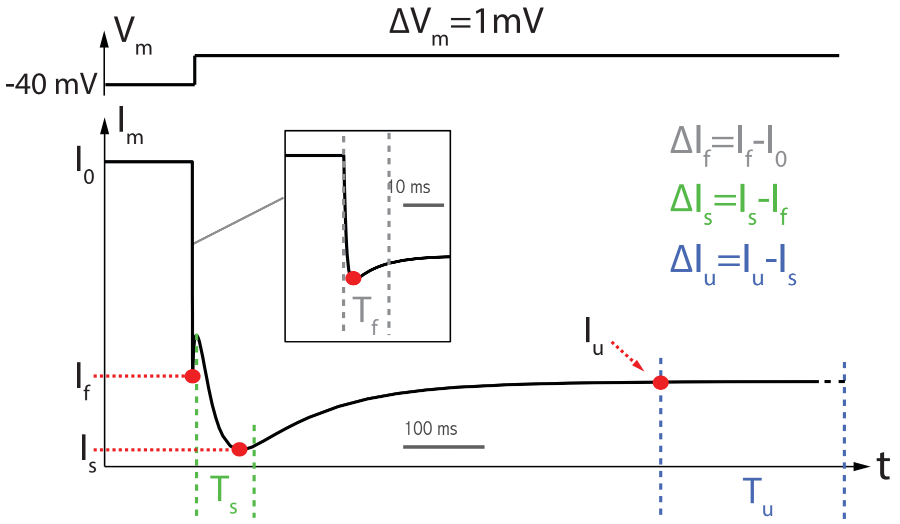
Decomposing the voltage step response into different timescales

☐ Most of neuron activity is shaped by the transient changes in membrane permeability.



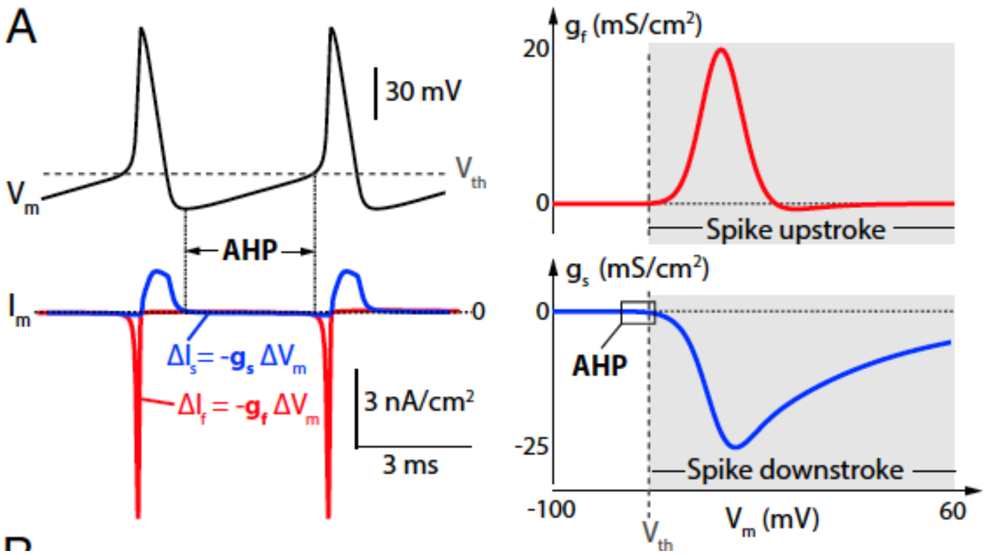
Decomposing the voltage step response into different timescales

☐ What really matters is not the value of the transmembrane current itself, but the value of the variations in transmembrane current ΔI_m that is induced by the variation of membrane potential ΔV_m at each period of time.



$$\Delta I_f = I_f - I_0$$
$$\Delta I_s = I_s - I_f$$
$$\Delta I_u = I_u - I_s$$

Dynamic input conductances of HH model



Excitable behaviors

A one port behavior made of spikes and pulses. All-or-none sensitivity in a localised amplitude and temporal range.

A behavioral characterisation : the localised energy balance of a switch regulated by a strictly passive circuit.

A feedback characterisation: a locally positive feedback amplifier regulated by negative feedback.

Tractability: the balance is localised in amplitude and frequency, hence amenable to local analysis tools.

What for ?

2014 - excitable systems as behaviors

- What is an excitable system ? How is it regulated ?
- How can we study interconnections of excitable systems ?
- What makes those nonlinear systems tractable ?
- What makes those systems worth studying beyond their relevance in neuroscience?

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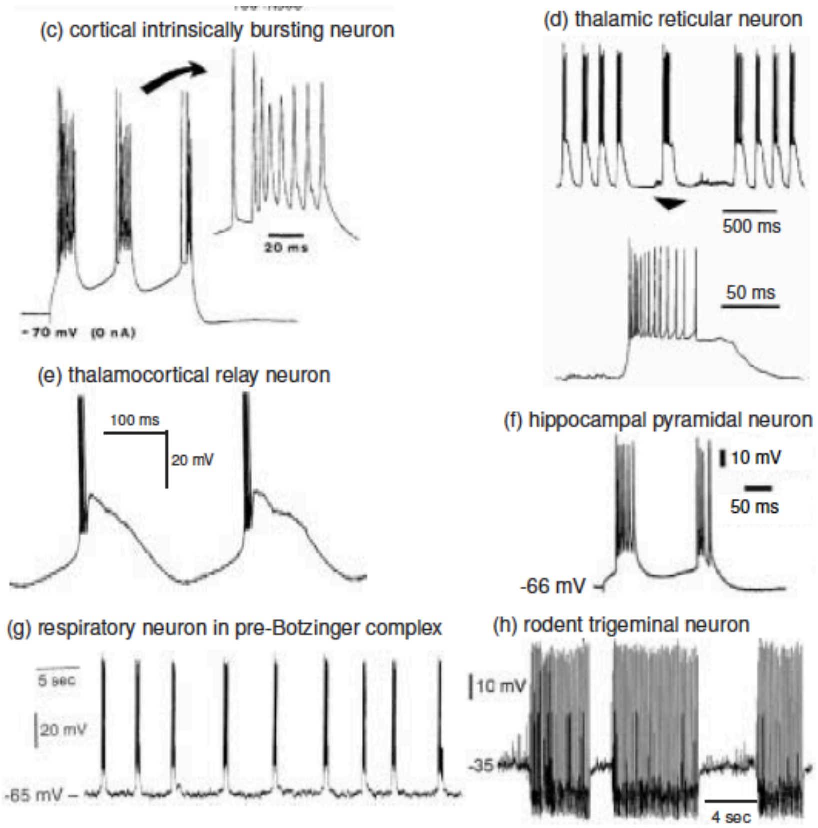
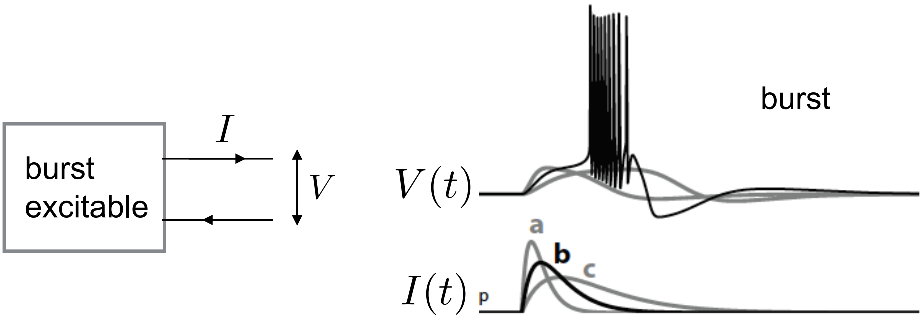
erc

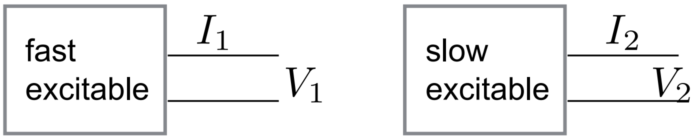
Bursting, an essential component of neuronal signalling



Bursting as interconnection of excitable systems



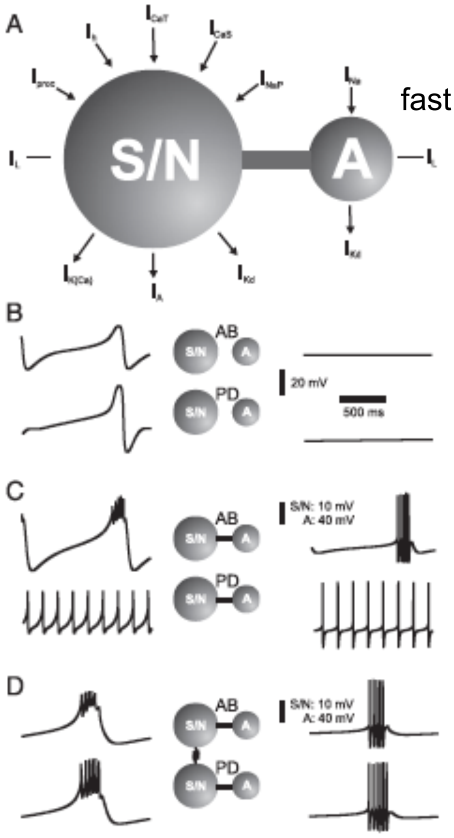
$$\equiv$$



$$I = I_1 + I_2$$

$$V = V_1 = V_2$$

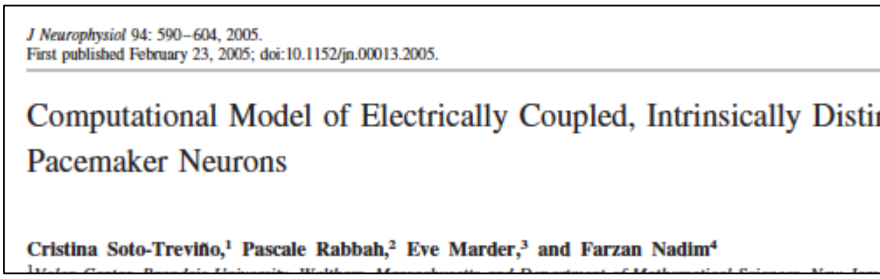
An ‘obviously’ correct picture …



slow excitable

fast excitable

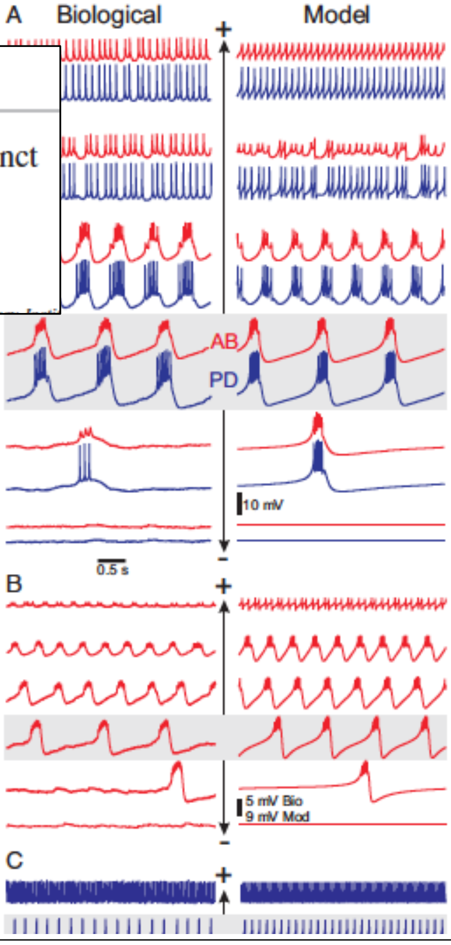
… without a theory



J Neurophysiol 94: 590–604, 2005.
First published February 23, 2005; doi:10.1152/jn.00013.2005.

Computational Model of Electrically Coupled, Intrinsically Distinct Pacemaker Neurons

Cristina Soto-Treviño,[1] Pascale Rabbah,[2] Eve Marder,[3] and Farzan Nadim[4]



A formidable experimental and computational achievement

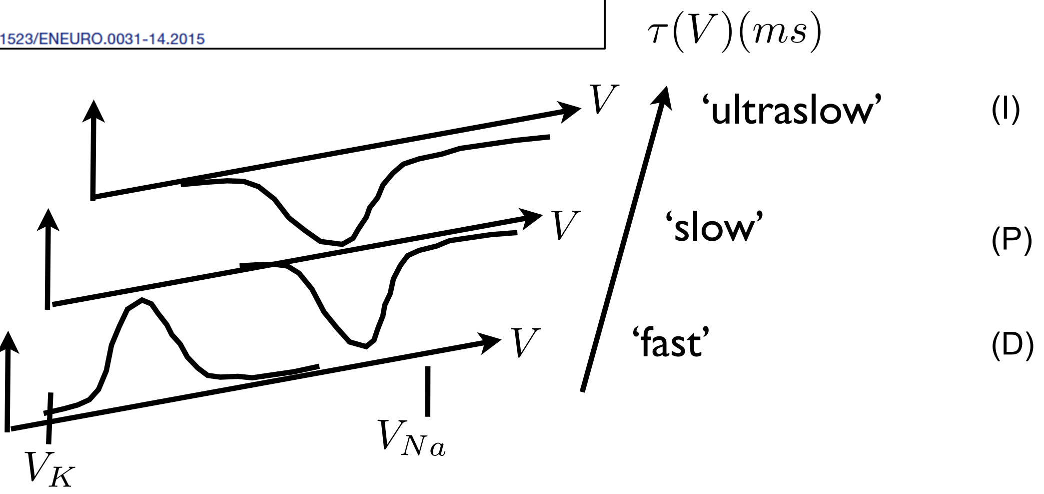
40 years of experience

A loop-shaping view of neuronal activity

Dynamic Input Conductances Shape Neuronal Spiking[1,2]

Guillaume Drion,[1,2,3] Alessio Franci,[1,4] Julie Dethier,[1,5] and Rodolphe Sepulchre[1,4]

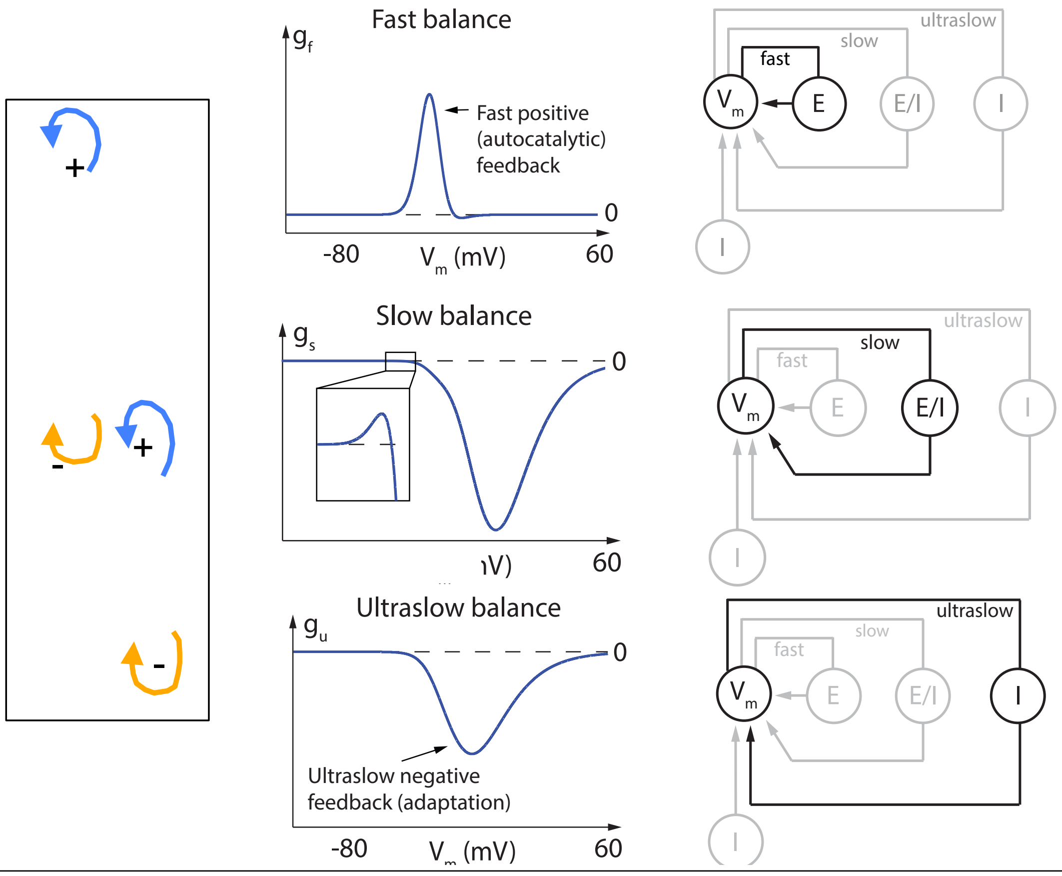
DOI:http://dx.doi.org/10.1523/ENEURO.0031-14.2015



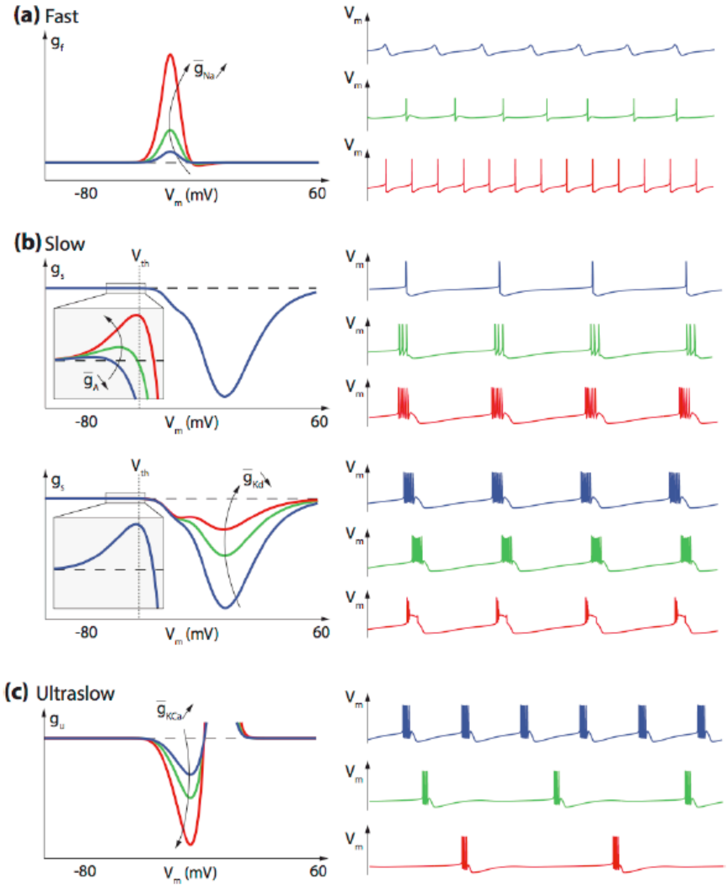
A neuronal rhythm is determined by its dynamic conductance, i.e its loop gain in localised ranges

The loop gain depends on amplitude and frequency.

A bridge between the quantitative and the qualitative



Dynamic conductances shape behavior



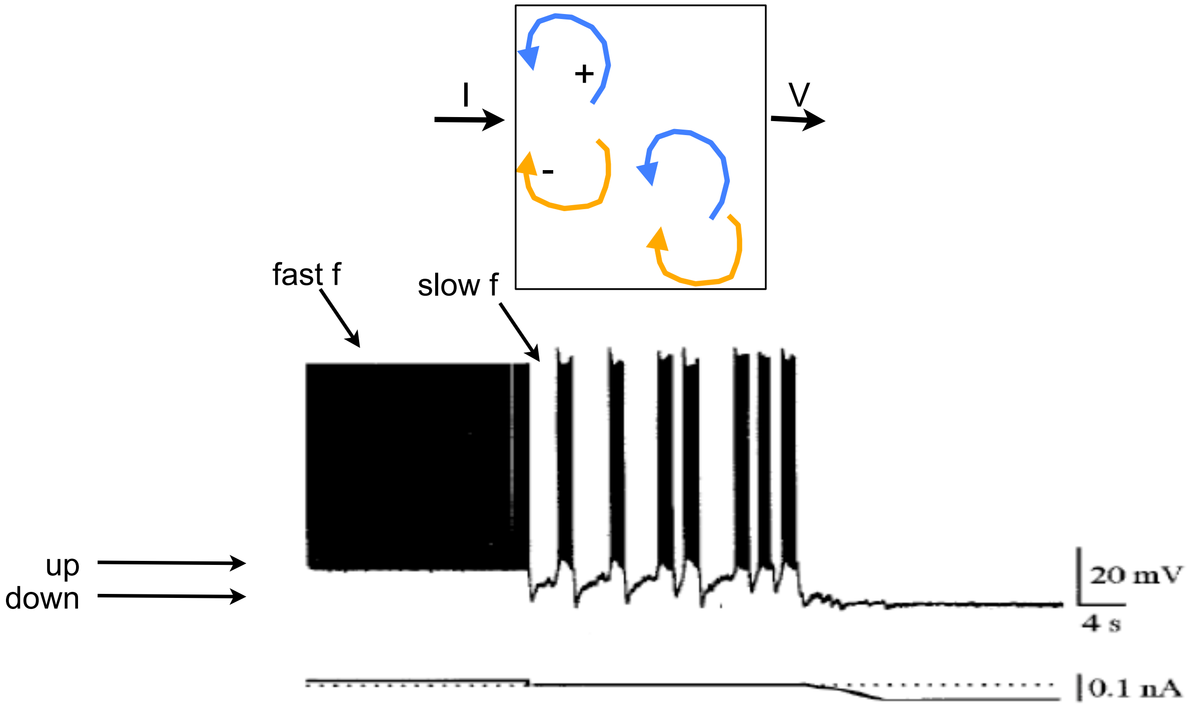
spike amplitude

intraburst frequency

burst type

interburst frequency

The firing modes of an endogenous burster

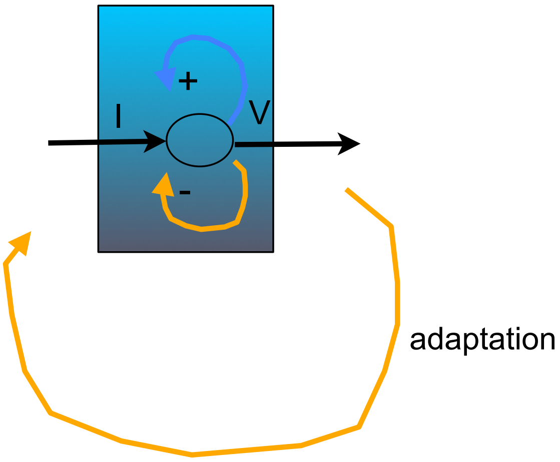


fast excitability
high state

fast+slow excitability
high+low state

hyperpolarized
low-state

The dominant bursting model of neurodynamics



Endogenous bursting : Slow negative feedback (adaptation) provides the driving oscillating input to the excitable model

Izhikevich, Chapter 9
Terman and Ermentrout, Chapter 5
Keener and Sneyd, Chapter 9

The dominant model of neurodynamics

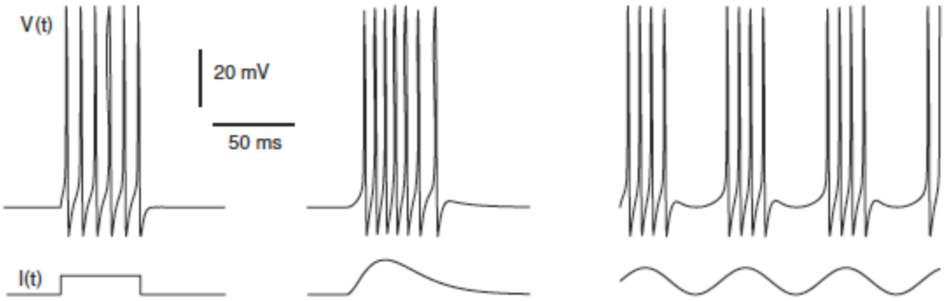
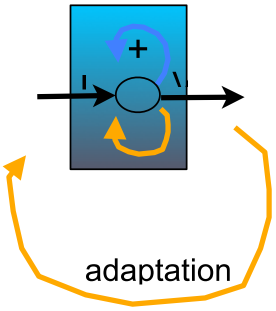
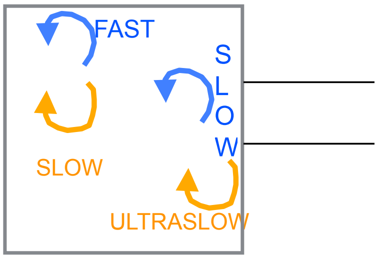


Figure 9.3: Forced bursting in the $I_{\mathrm{Na,p}}+I_{\mathrm{K}}$-model with parameters as in Fig.4.1a and time-dependent injected current $I(t)$. (Izhikevich)

Should we care ?





No modulation (no route to burst)	the slow negative conductance controls the modulation between spike and burst
No robustness (fragile to noise and time scale separation)	The motif is as robust as the spiking motif
No interconnections	Interconnection based approach
Classification based on bifurcations	No classification ; loop shaping regulation

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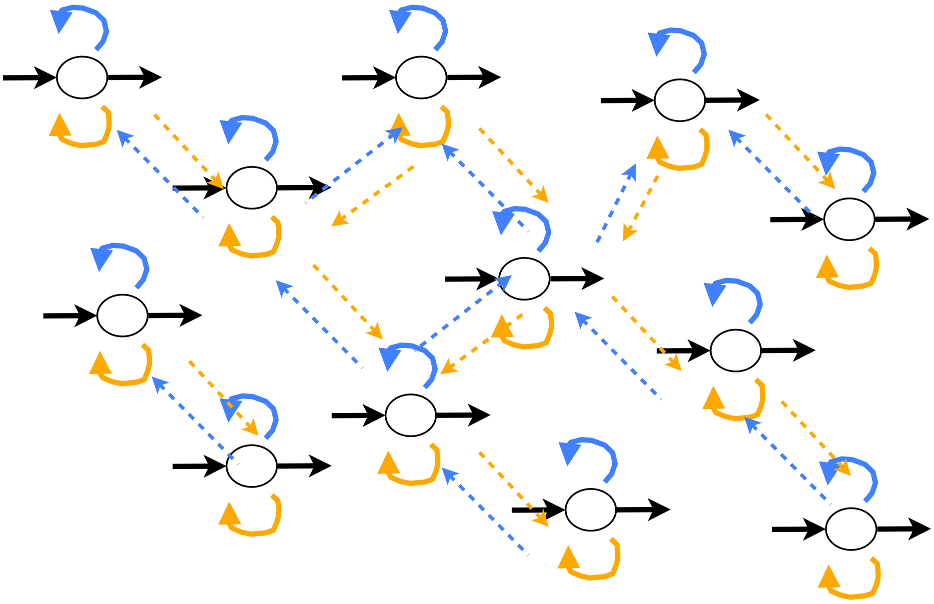
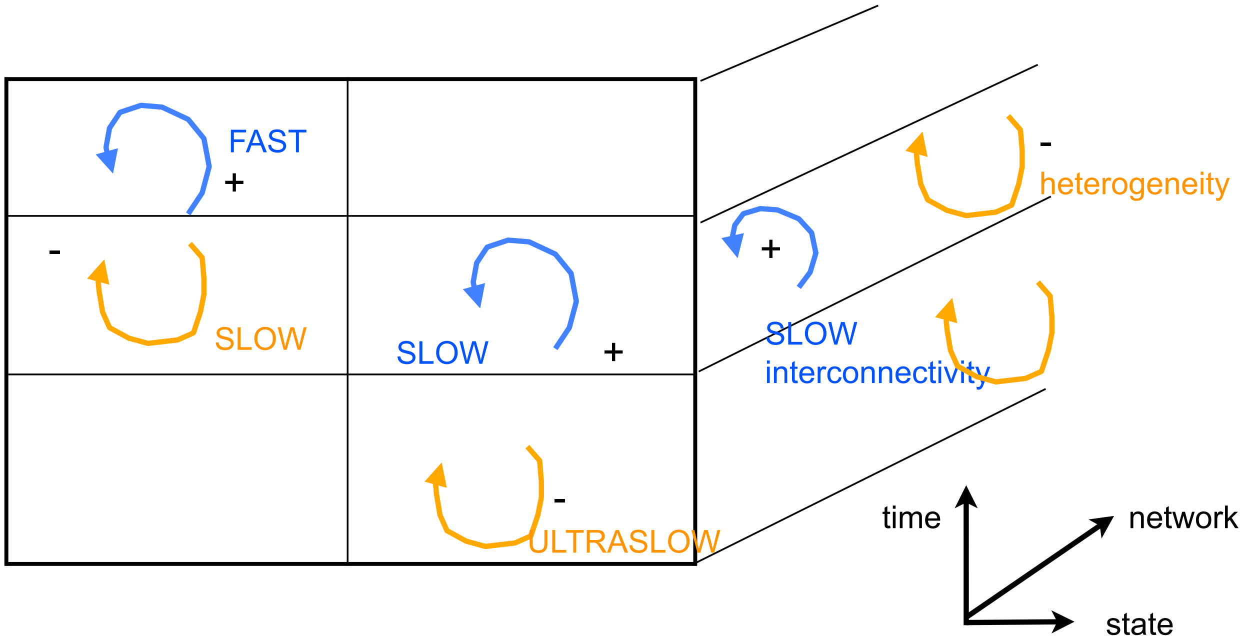
Networks of excitable bursters



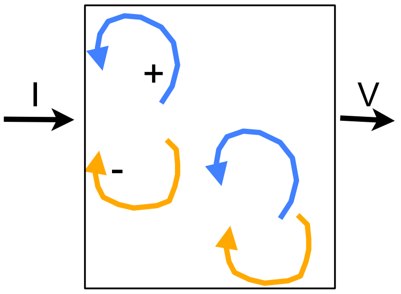
A feedback motif to localize *across* scales



Population of two-level individual behaviors interconnected in the slow time scale:

Anything between a heterogenous population of spiking individuals
and a homogenous population of synchronized bursters

A two-mode cellular behavior



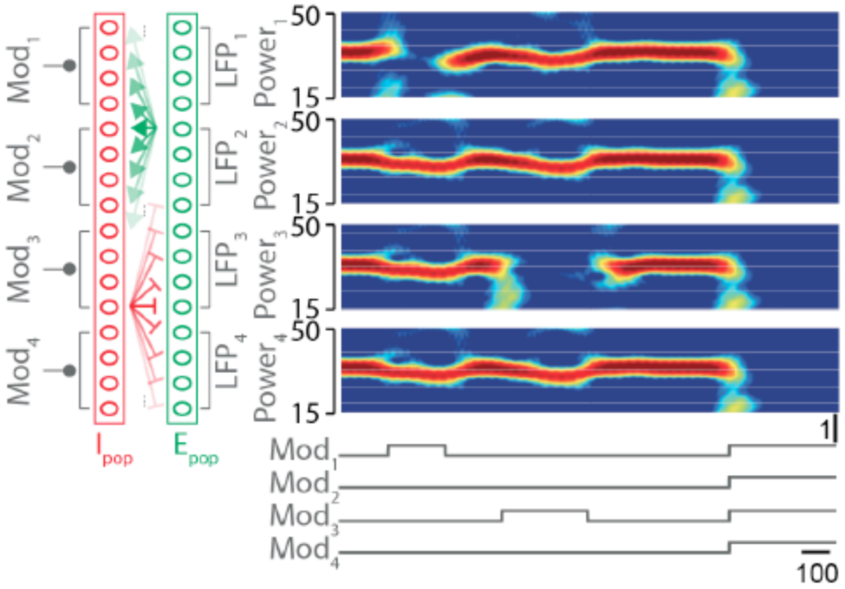
fast excitable
"spiker"

slow excitable
"burster"

fine-grained behavior is
exogenous

fine-grained behavior is
endogenous

Localization across scales



Red = synchronized network oscillations leading to LFPs

Blue = no LFP despite similar spiking activity in network

Conclusions

Why ?

Neurophysiologists study neuronal circuits as systems.
But there is a lack of systems methodology to study (state-space) conductance-based models.

What ?

An excitable behavior is a relationship between spikes and pulses.
The threshold phenomenon is a sensitivity localised in amplitude and time.

How ?

An energy balance between localised activation and global dissipation

What for ?

Interconnections : signalling properties of neuronal circuits

Complexity and simplicity of neuronal behaviours

Lecture 1

Complexity is an evolving concept about how the tiny interacts with the large.
Feedback is a zooming principle. It changes the resolution of a behavior.
Sensitivity is a local analysis tool at the core of robustness and controllability.

Lecture 2

Neuronal excitability is a unique modelling an experimental platform to study sensitivity across scales.
Some of the simplest questions appear to be intractable, both experimentally and computationally.

Lecture 3

An excitable behaviour has a localised sensitivity window regulated by a balance of positive and negative feedback.

Interconnections of excitable behaviours are tractable and provide a paradigm to analyse robust signalling across scales.

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