Sensitivity analysis of neuronal behaviors

R. Sepulchre -- University of Cambridge

ICMS 2017, Eindhoven

An old fashioned concept

Sensitivity analysis

From Wikipedia, the free encyclopedia

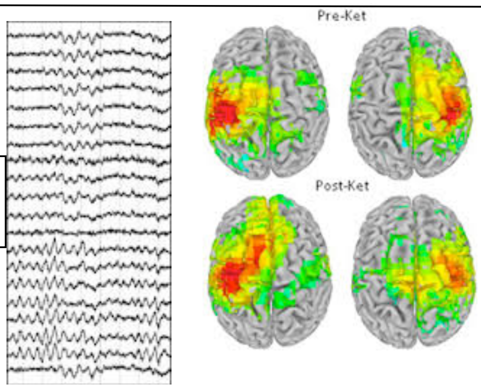
Sensitivity analysis is the study of how the uncertainty in the output of a mathematical model or system (numerical or otherwise) can be apportioned to different sources of uncertainty in its inputs.[1] A related practice is uncertainty analysis, which has a greater focus on uncertainty quantification and propagation of uncertainty. Ideally, uncertainty and sensitivity analysis should be run in tandem.

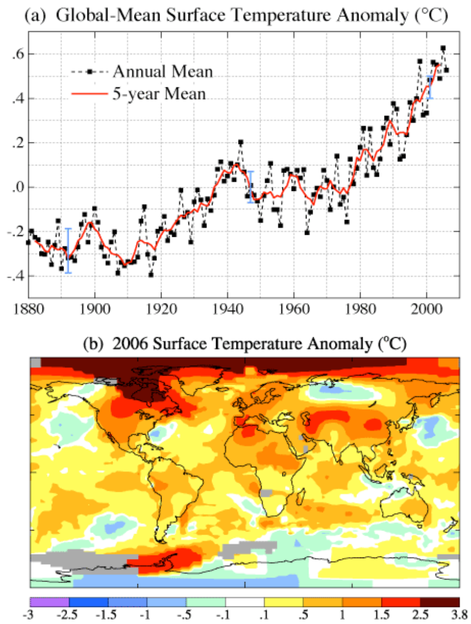
- 6 Applications
  - 6.1 Environmental
  - 6.2 Business
  - 6.3 Social Sciences
  - 6.4 Chemistry
  - 6.5 Engineering
  - 6.6 In meta-analysis
  - 6.7 Multi-criteria decision making
  - 6.8 Time-critical decision making

How does the small control the large ?

concentration signals

phase & intensity signals



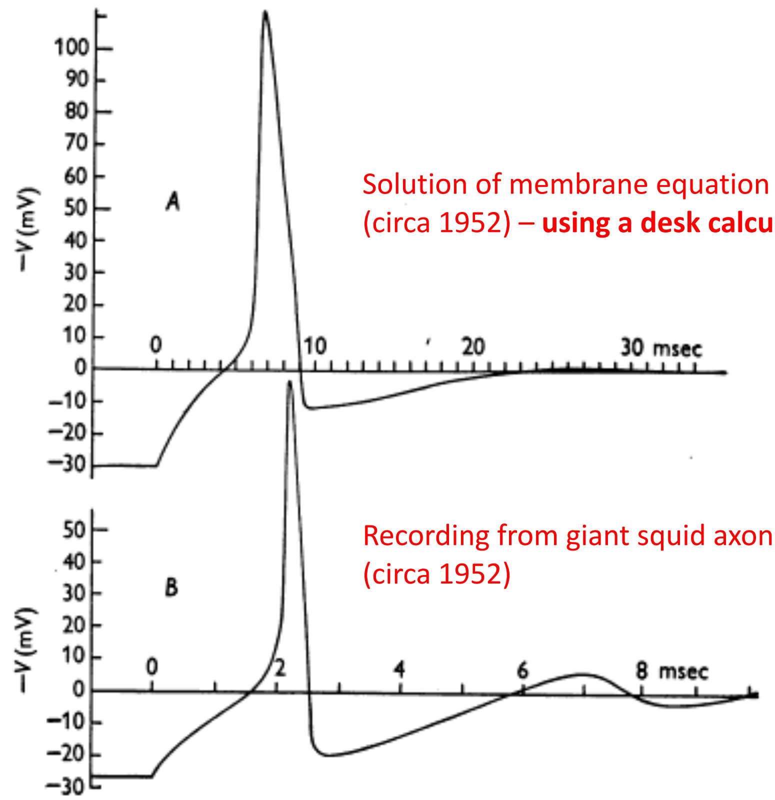


intensity signals

Sensitivity analysis across scales

- The brain champions robust signalling across scales
- Sensitivity analysis is at the core of robust control theory.
- How can the large be at the same time sensitive to the small (for controllability) and insensitive to the small (for robustness) ?

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)

Why neuronal excitability ?

- A unique example of biophysical modelling across scales.
  A unique pool of experimental data.

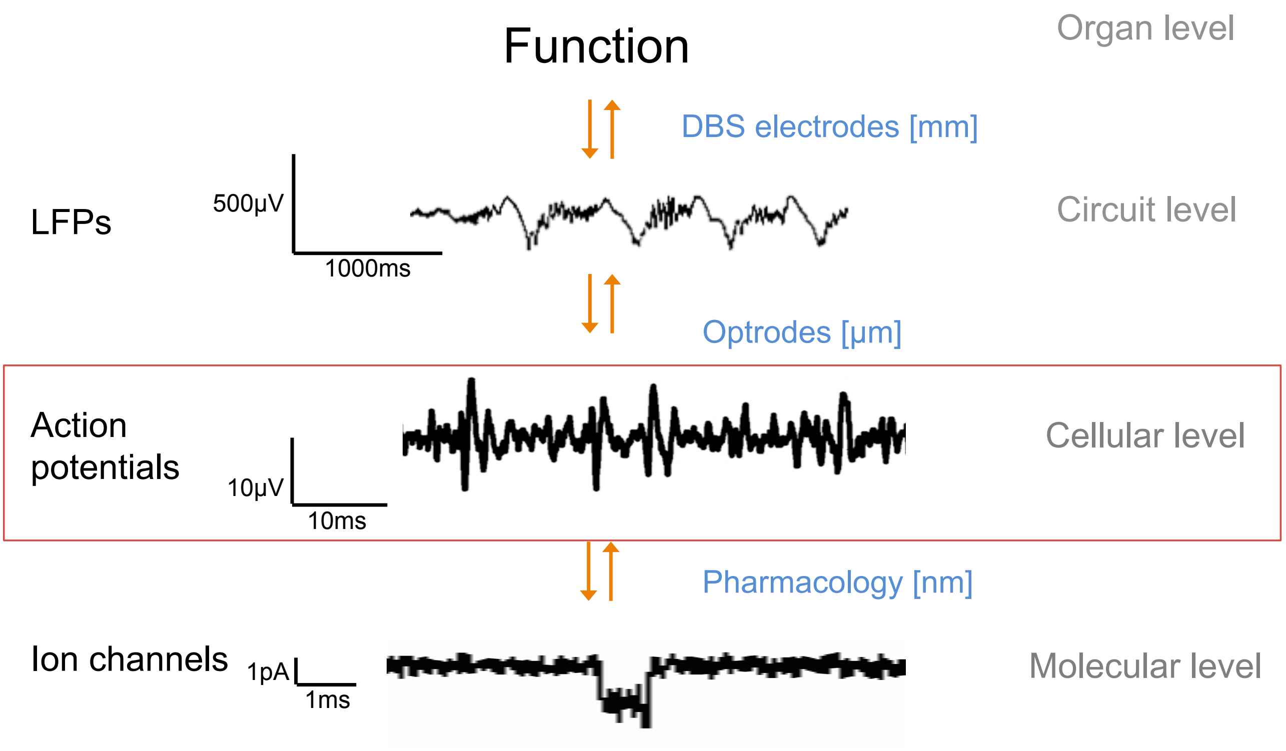
- Signalling and robustness across scales is a core question of neurophysiology.

- Questions and challenges seem analog at other scales.

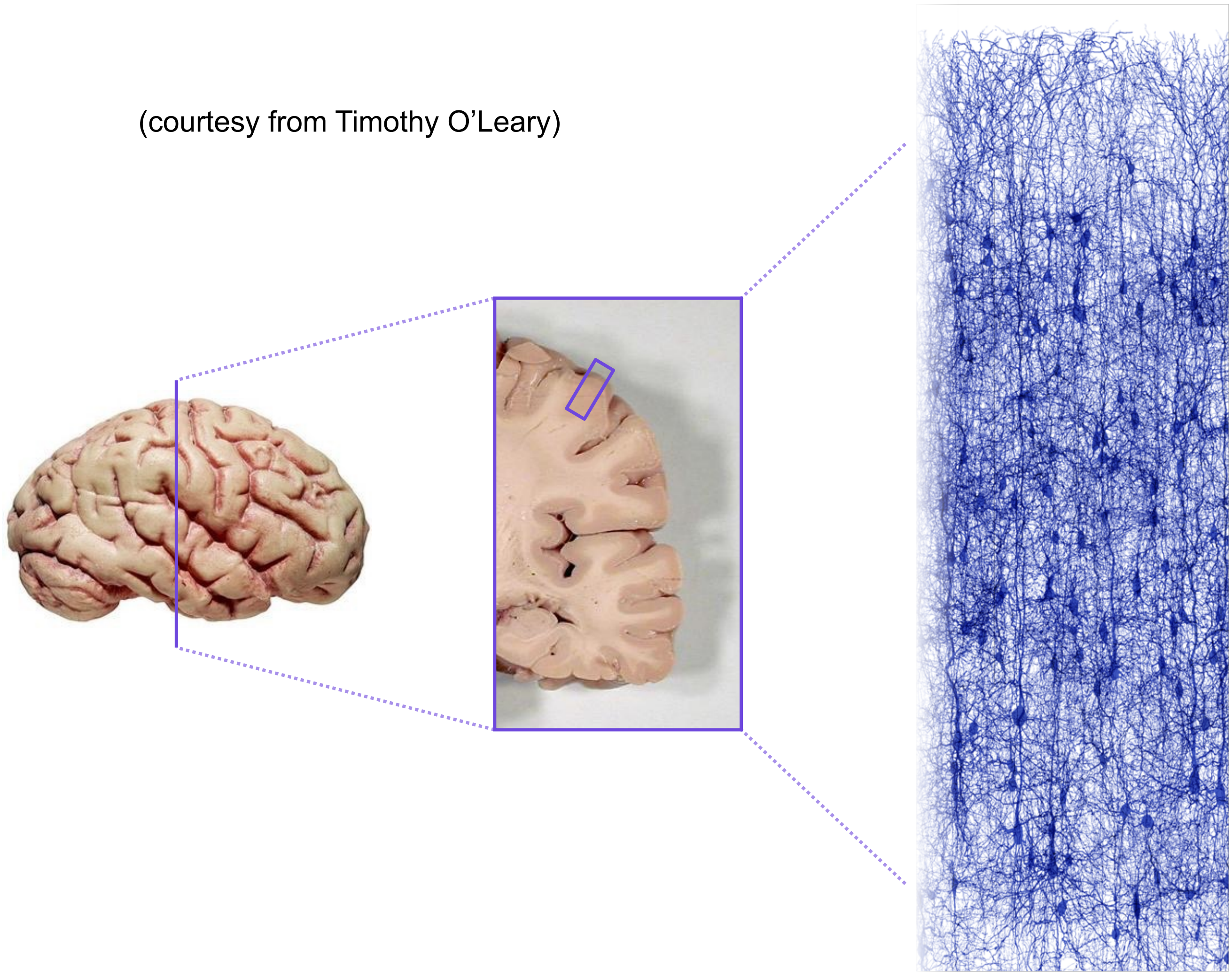
Outline

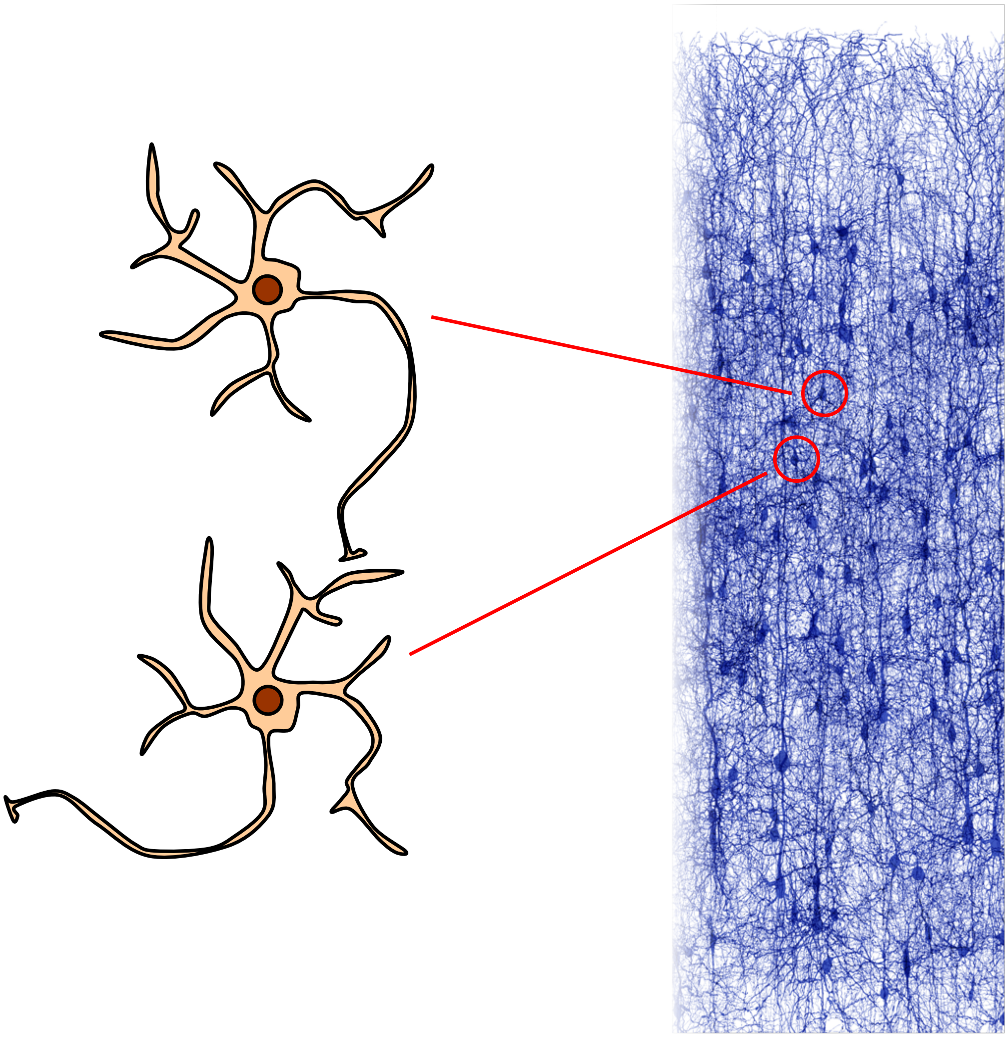
- I. A model across scales
- II. The fragility of sensitivity analysis across scales
- III. Sensitivity analysis: a local tool with global aims
- IV. Intractable questions and paradoxes across scales

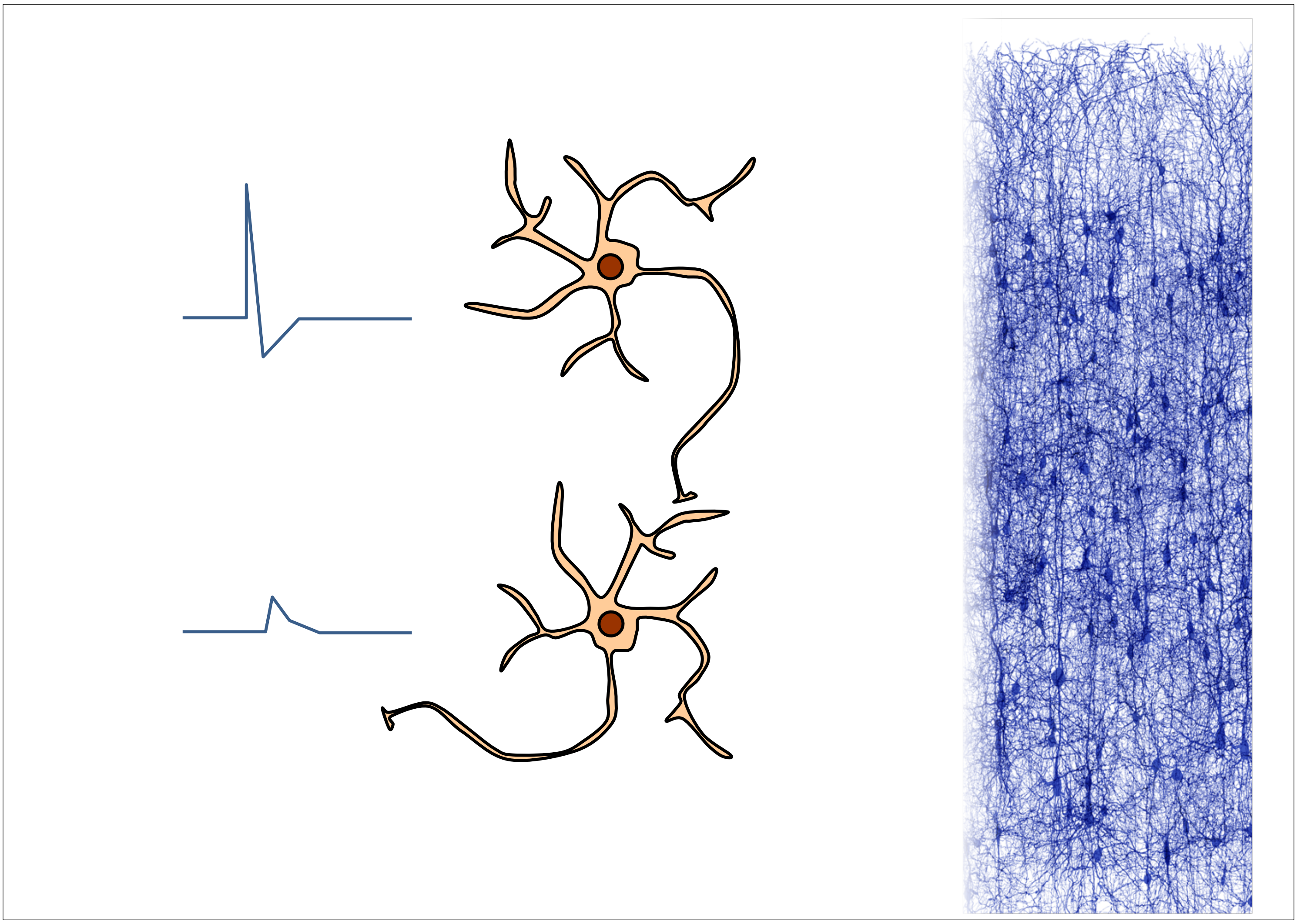
A multiresolution electrical behavior

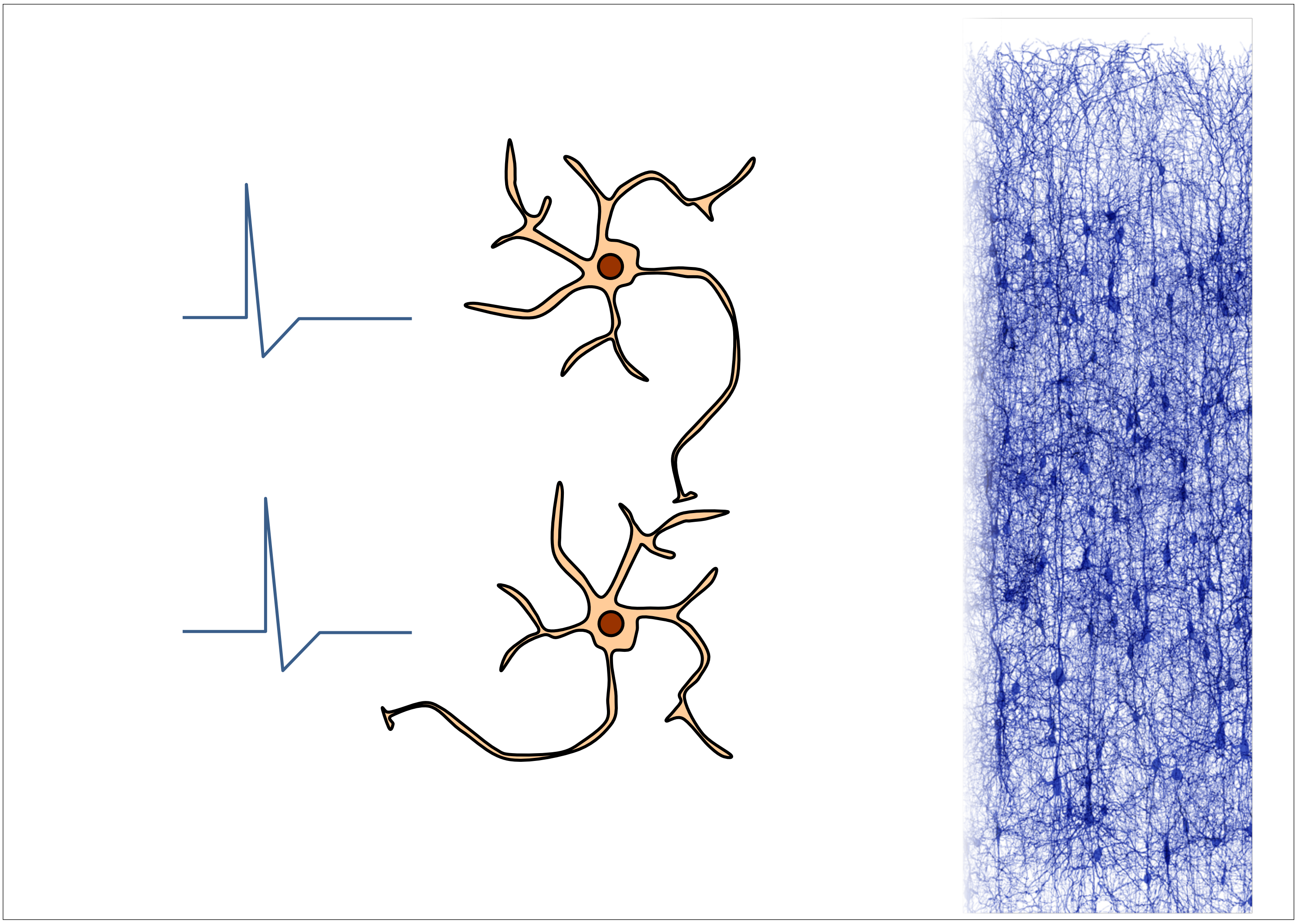


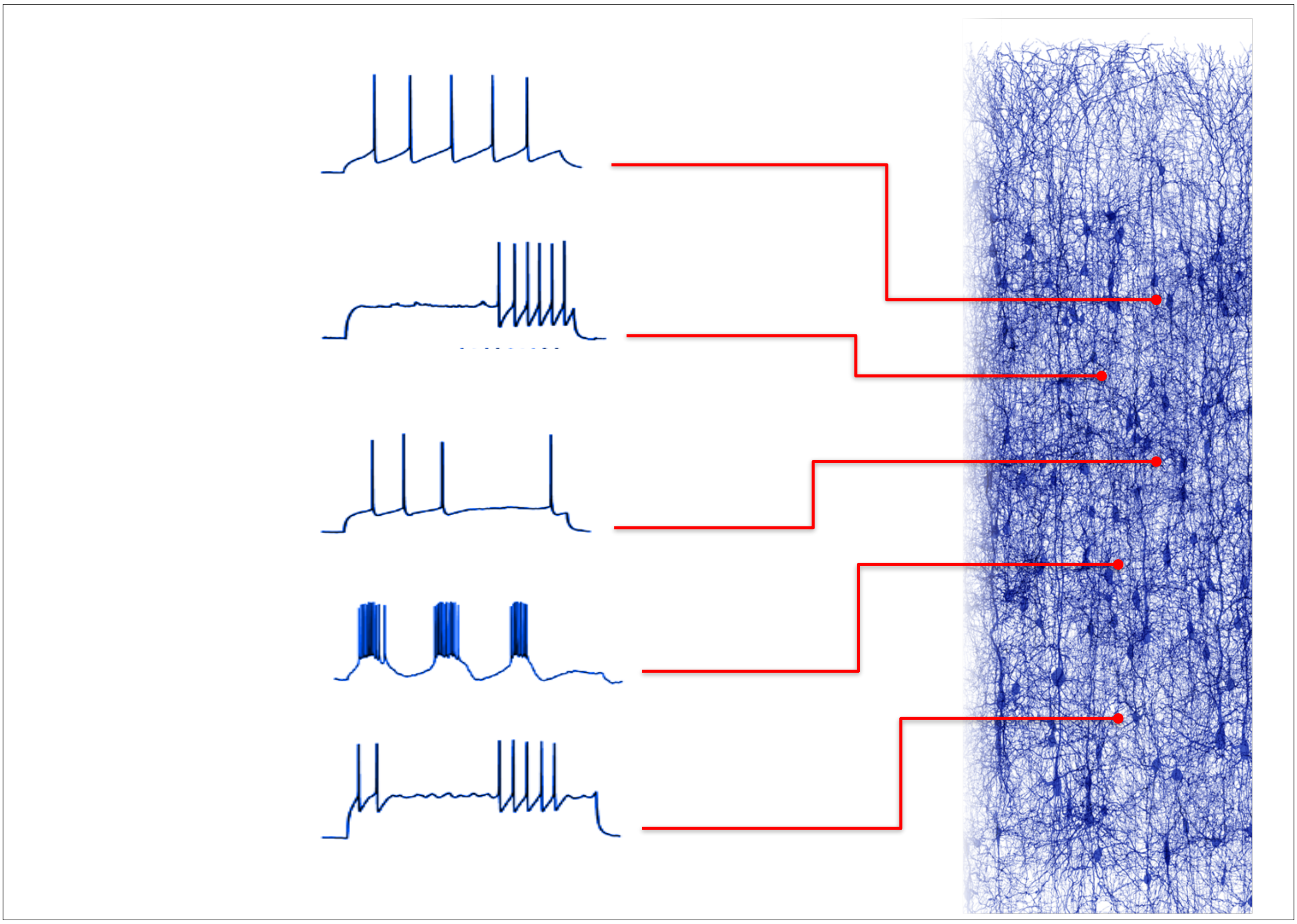
(courtesy from Timothy O'Leary)

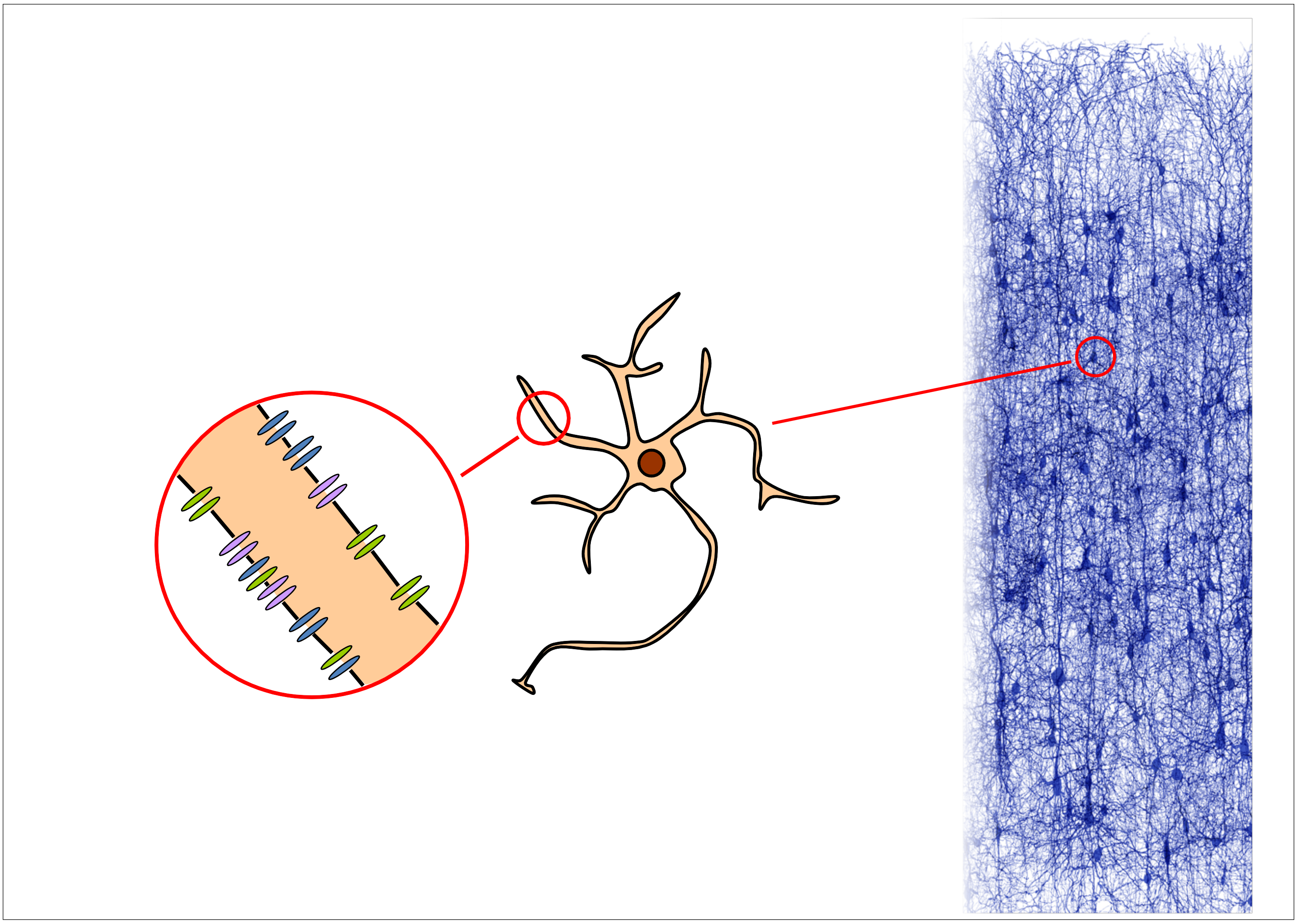


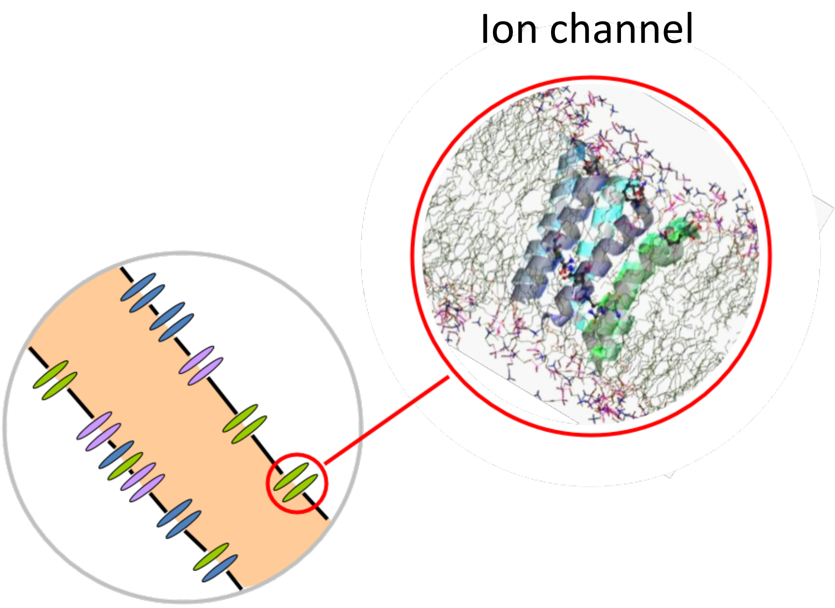


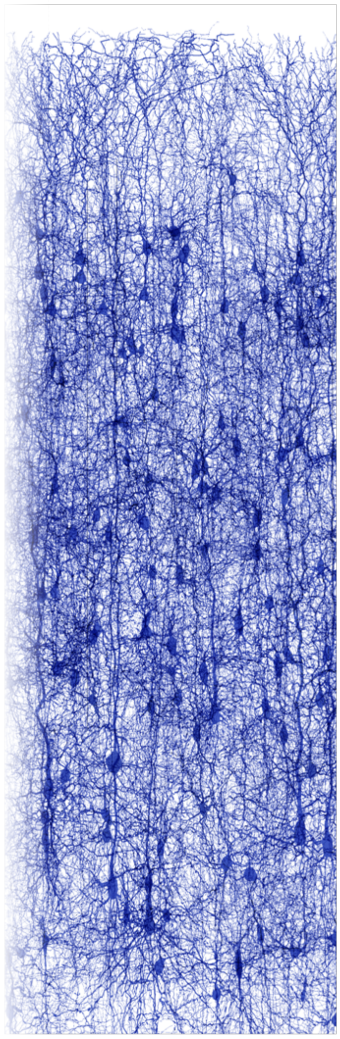




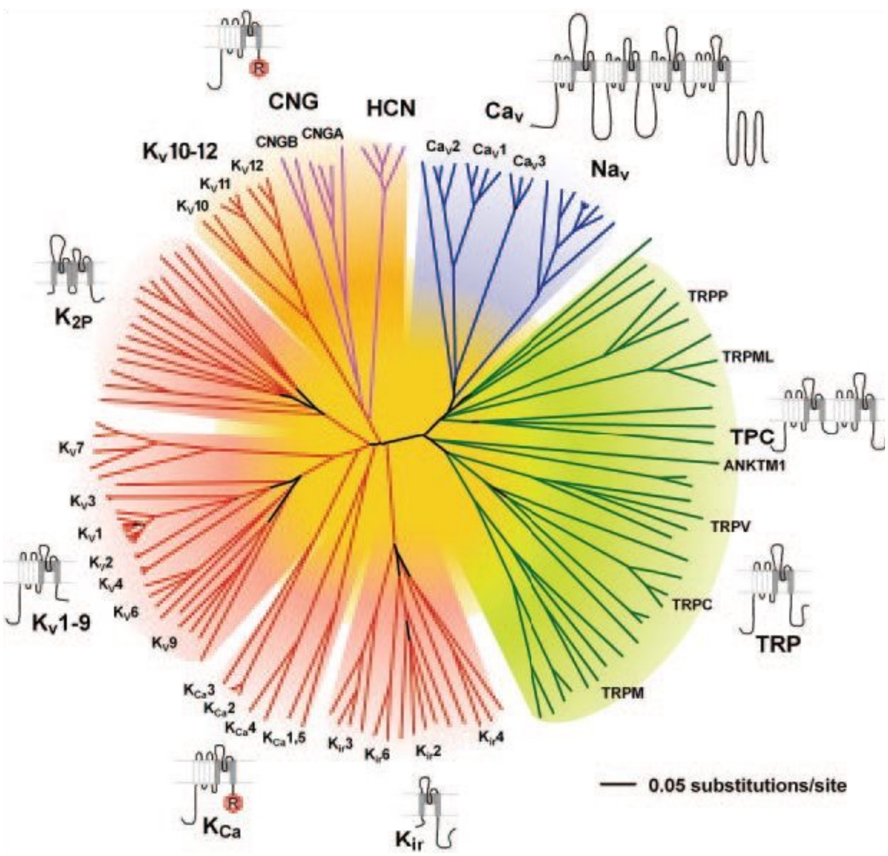








Ion channels are diverse

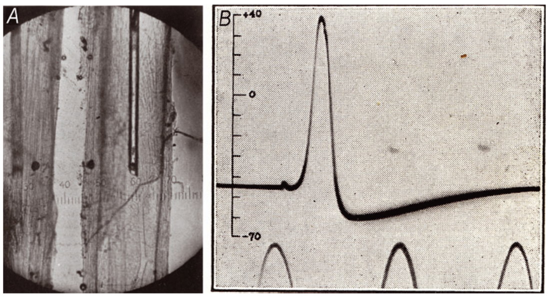


J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN and A. F. HUXLEY

A circuit model



The action potential

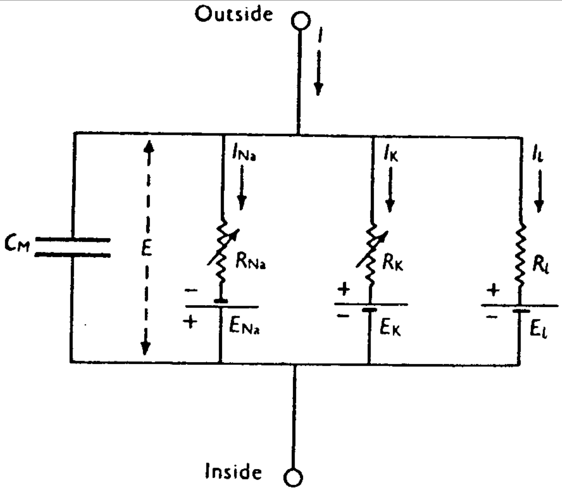
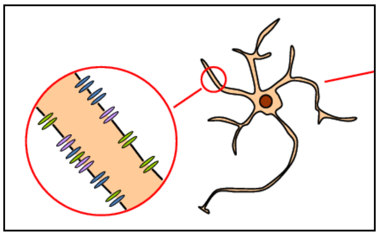
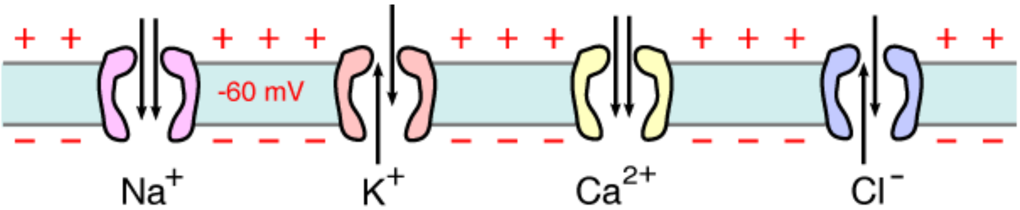
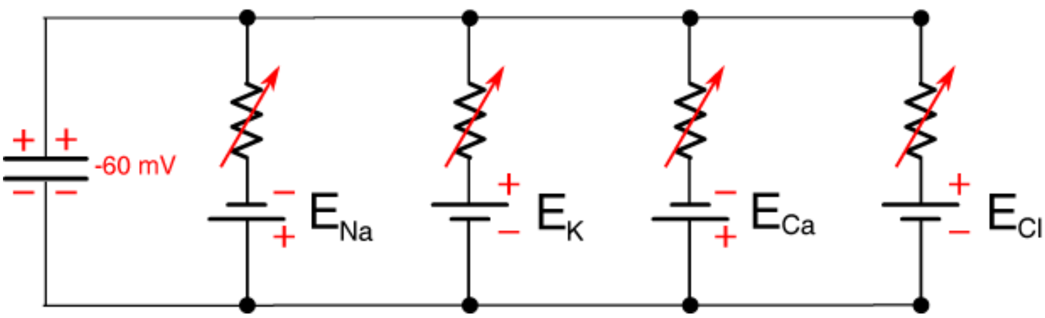


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_{Na} and R_K vary with time and membrane potential; the other components are constant.

A model across scales





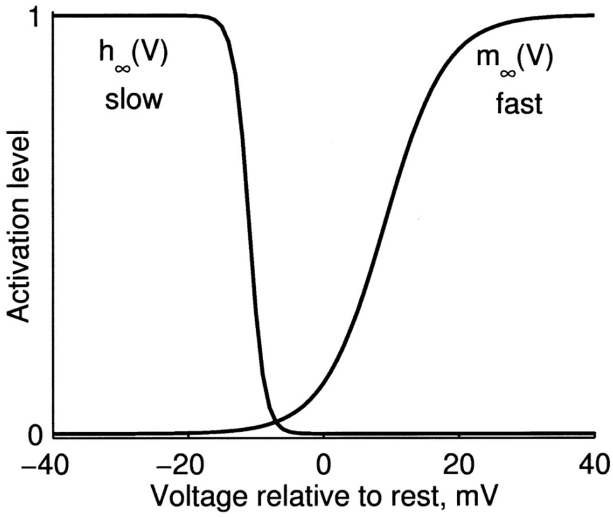


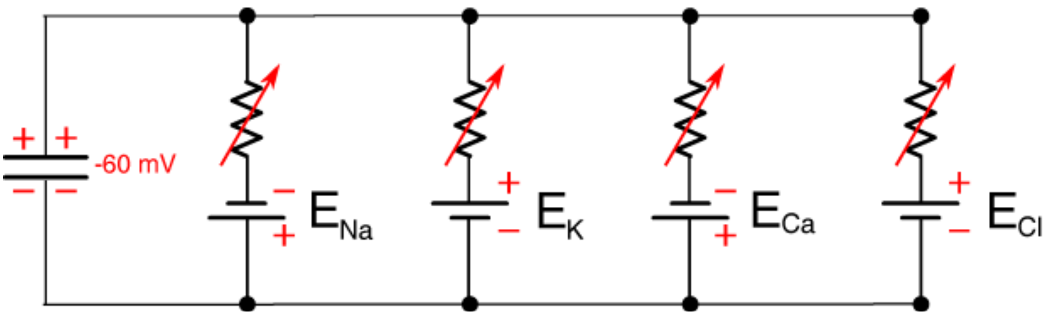
$$C\frac{dV}{dt} = \sum_i g_i(E_i - V)$$

$$g_i = \bar{g}_i m^p h^q$$

$$\tau_m(V)\frac{dm}{dt} = m_\infty(V) - m$$

$$\tau_h(V)\frac{dh}{dt} = h_\infty(V) - h$$

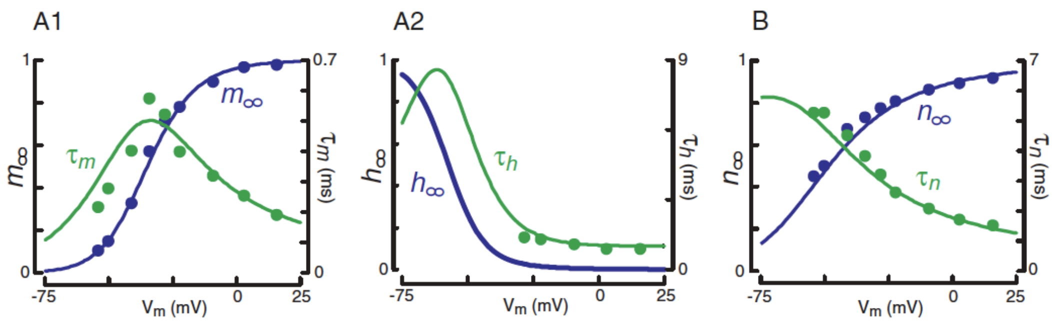




The Hodgkin-Huxley (HH) Model

- After curve fitting, Hodgkin and Huxley derived the following equations:

$$\begin{aligned}
C_m\dot{V}_m &= -\bar{g}_{Na}m^3h(V_m - V_{Na}) - \bar{g}_K n^4(V_m - V_K) - I_{leak} + I_{app} \\
\tau_m\dot{m} &= -(m - m_\infty) \\
\tau_h\dot{h} &= -(h - h_\infty) \\
\tau_n\dot{n} &= -(n - n_\infty)
\end{aligned}$$

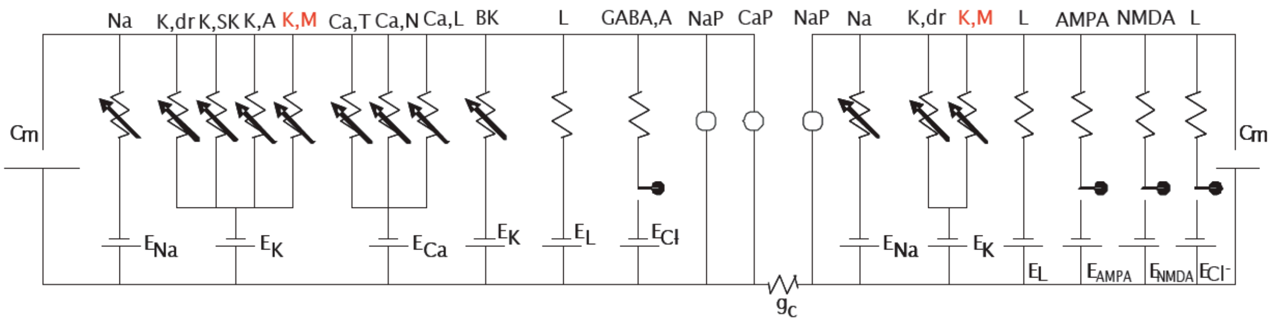


- m and n are the activation variables of sodium and potassium channels, respectively; and h is the inactivation variable of sodium channels.

Outline

- I. A model across scales
- II. The fragility of sensitivity analysis across scales
- III. Sensitivity analysis: a local tool with global aims
- IV. Intractable questions and paradoxes across scales

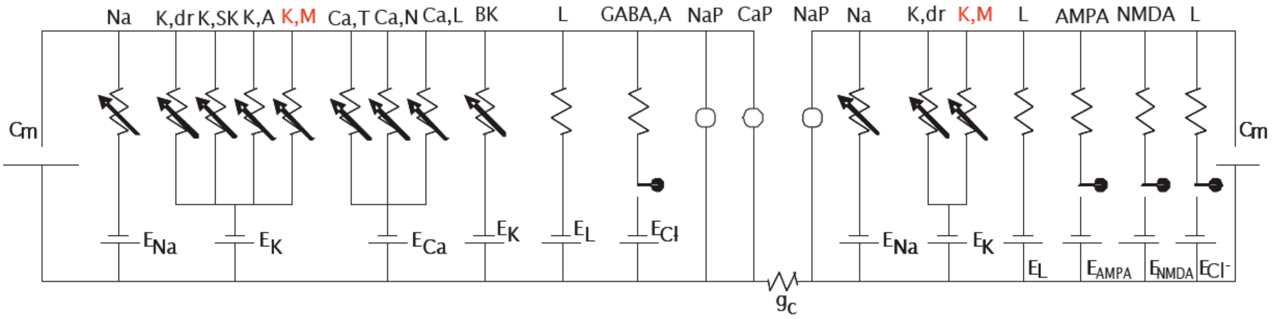
My first steps in electrophysiology: (a student project)



State-of-the art model of the dopaminergic neuron
About 130 state variables and 500 parameters (Canavier et al., 2006; Drion et al. 2010)

G. Drion master thesis (2008): adding a particular ionic current in the model; does the computational prediction match the experimental observation?

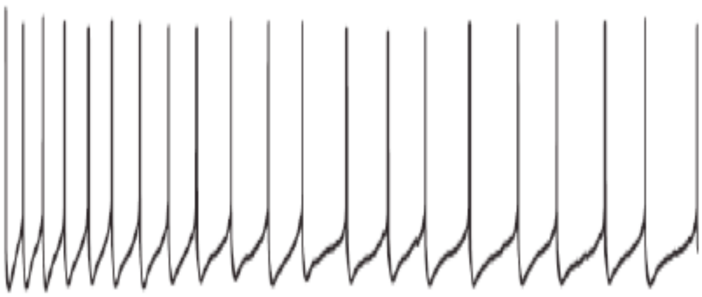
A nonlinear electrical circuit can be complicated...



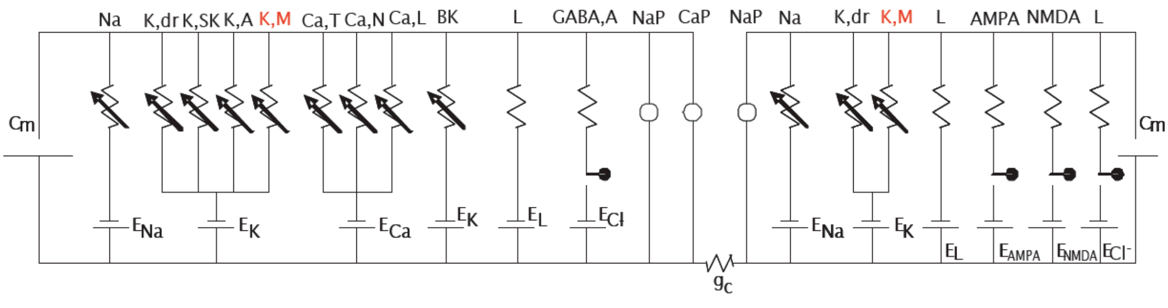
no general methodolgy to analyze 130 nonlinear differential equations with 500 parameters

and its behavior simple:

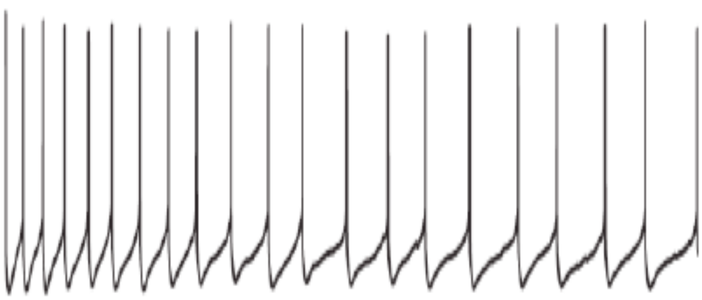
pacemaking behavior of midbrain dopaminergic neuron



Sensitivity analysis of neuronal behaviors: how does the small control the large?



- Why so many parallel branches in the circuit?
- Which ionic currents are the key players of the rhythm?



2009: the engineering approach

- We reduce the model to 5 states
- We hypothetize a systemic role for SK channels, possibly shared by many different neurons
- We submit our first 'systems' paper

SK Channels as Regulators of Synaptically Induced Bursting and Neural Synchrony

2010: the reviewers' response

- the systemic hypothesis is interesting but unsupported by experimental data
- the authors should focus on the DA neuron and not aim at generality
- the model predictions contradict several documented experimental observations about the role of L-type calcium channels.

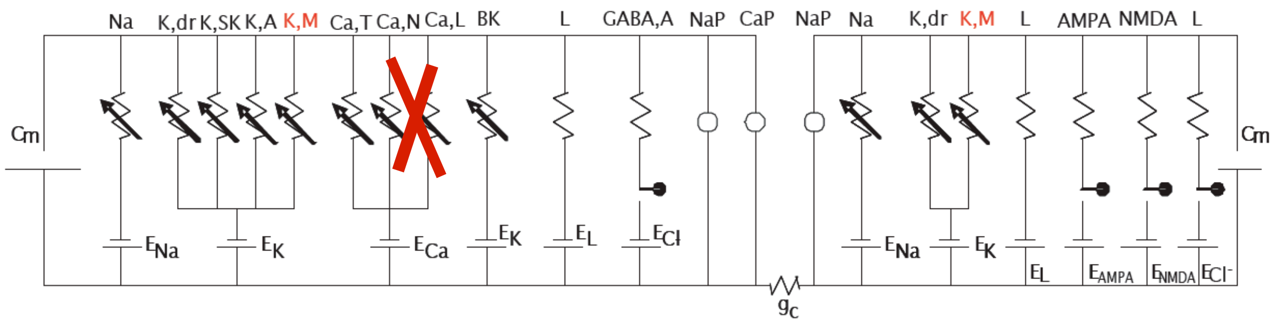
2010: an extensive literature review reveals a zoo of conflicting observations

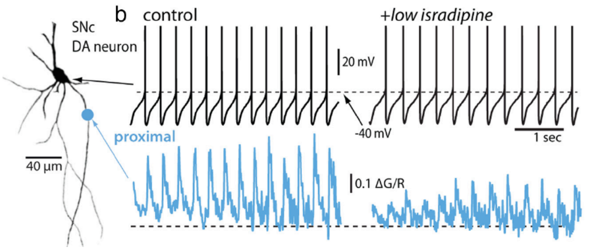
Table 1. Effect of manipulations that block voltage-dependent Ca^{2+} channels on the pacemaking of midbrain DA neurons *ex vivo* or *in vitro*.

Reference	Nature of the preparation	Agent used	Observed effect
Nedergaard et al., 1993	Slices from adult guinea-pigs, SNc, intracellular recordings.	nifedipine ($1-20$ μM)	Cessation of firing at undisclosed concentration.
Mercuri et al., 1994	Slices from adult Wistar rats, SNc and lateral VTA, intracellular recordings.	nifedipine and nimodipine ($0.3-30$ μM)	Decrease in the firing rate of about 50% with 1 μM of both drugs. Cessation of firing with $20-30$ μM of both drugs.
Puopolo et al., 2007	Acutely dissociated neurons from the SNc of juvenile (16 day-old) mice, whole cell recordings.	1.8 mM Co^{2+} in replacement of Ca^{2+} nimodipine (1 μM) ω-aga-IVA (200 nM)	Cessation of firing in all neurons (17/17). Firing rate decreased in 9/17 neurons. Firing rate decreased in 10/14 neurons.
Chan et al., 2007	Slices from juvenile mice (younger than P21), SNc, cell-attached and whole-cell recordings. Slices from young adult mice (older than P28), SNc, cell-attached and whole cell recordings.	isradipine (20 μM) and nimodipine (20 μM) isradipine (20 μM) and nimodipine (20 μM)	"Firing largely unaffected" (but firing reduced by an I_H blocker). Cessation of firing in all neurons (15/15): "plastic" phenomenon in "several" neurons (firing resumes during block > 1 hour in some neurons).
Guzman et al., 2009	Slices from both juvenile and young adult mice, SNc, cell-attached and whole cell recordings	isradipine (5 μM)	Firing unaffected.
Putzier et al., 2009	Slices from juvenile rats (younger than P21), SNc, whole cell recordings	nimodipine (10 μM)	Cessation of firing.
Khaliq and Bean, 2010	Slices from both juvenile and young adult mice, medial VTA, whole cell recordings	0 Ca^{2+}, 3 $mMMg^{2+}$	Firing increased three-fold.
Seutin et al., unpublished	Slices from adult (>6 week-old) rats, SNc, extracellular recordings)	nifedipine ($20-50$ μM) nimodipine ($5-20$ μM)	Firing unaffected (N = 5). Variable effects, no clear trend (N = 5).

SNc: substantia nigra, pars compacta; VTA : ventral tegmental area. Rodents are classified as juvenile (< P21), young adults (> P28) or adult (> 6 weeks).
doi:10.1371/journal.pcbi.1002050.t001

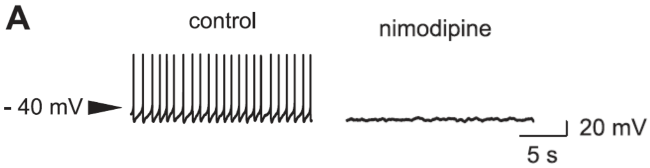
The knock-out experiment is fragile





Guzman et. al, 2009

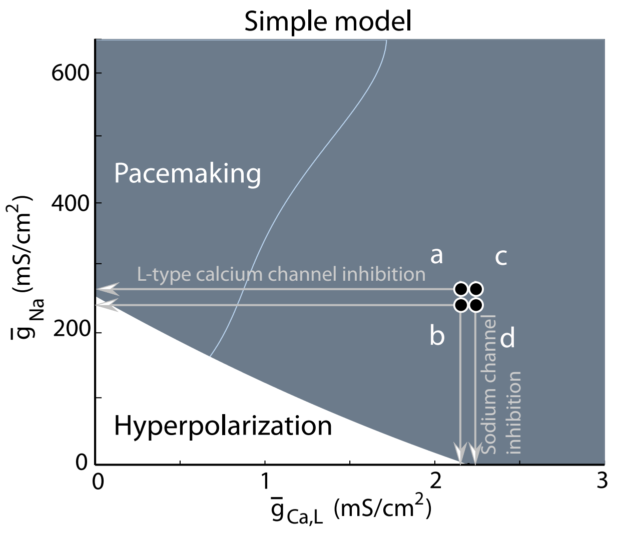
→ L-type calcium channels are not involved in the pacemaker activity of DA neurons.

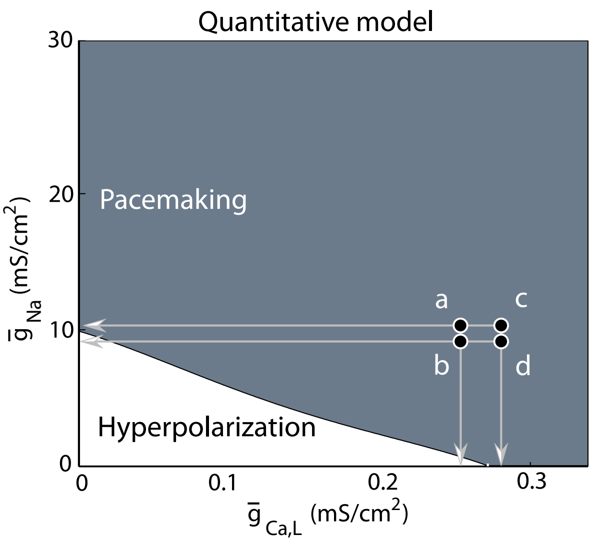


Putzier et. al, 2009

→ L-type calcium channels are critical for the pacemaker activity of DA neurons.

A two-parameter sensitivity analysis of the conductance-based model shows the fragility of the experimental protocol





AND : The model prediction is verified experimentally

2011: the rewarding stage

➡ The arguments for rejection of our previous paper led to a novel paper:

"How Modeling Can Reconcile Apparently Discrepant Experimental Results: The Case of Pacemaking in Dopaminergic Neurons."

The new paper is much better received!

➡ The validating experiment was a key factor of appreciation

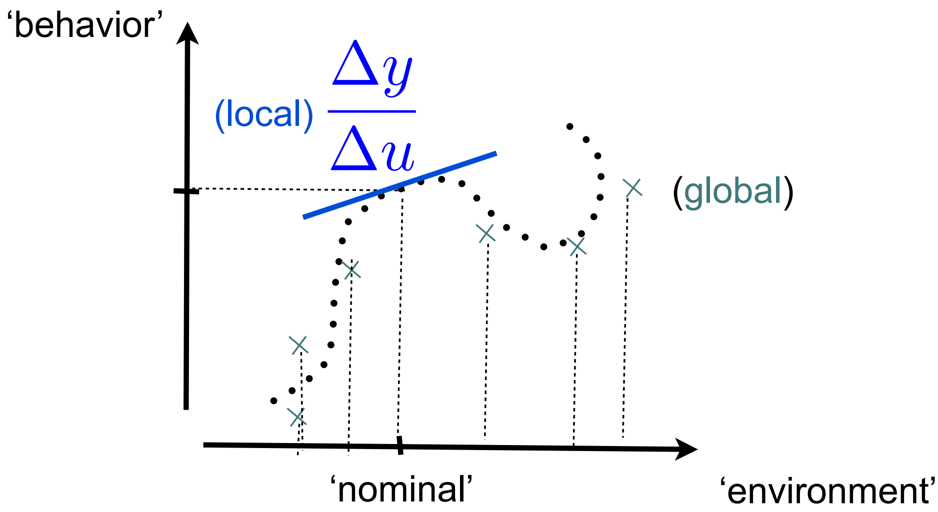
➡ One reviewer comments: *the study will help to sensitize the experimental community about the large effects on firing pattern induced by subtle changes in channel composition*

➡ Another reviewer comments: *Additionally, many other neurons possess multiple oscillatory mechanisms, and the paper presents one of the pioneering studies that will lead to more general understanding of pacemaking generated by interacting oscillatory mechanisms. Thus, presented results should be very interesting for a general reader and beyond the investigation of the dopaminergic neuron.*

Lessons from an anecdote

- Experimentalists (and reviewers) ask the right questions; we should provide them with the right tools
- Conductance-based modeling is incredibly predictive.
- Our analysis methods are completely ad hoc
- Knock-out experiments are ubiquitous; they can be fragile.

Sensitivity analysis



- Local = tractable, analytical, but short-sighted
- Global = desirable and comprehensive, but intractable

Outline

- I. A model across scales
- II. The fragility of sensitivity analysis across scales
- III. Sensitivity analysis: a local tool with global aims
- IV. Intractable questions and paradoxes across scales

State-of-the art: ‘global’ sensitivity analysis by extensive simulations

J Neurophysiol 90: 3998–4015, 2003.
First published August 27, 2003; 10.1152/jn.00641.2003.

innovative methodology

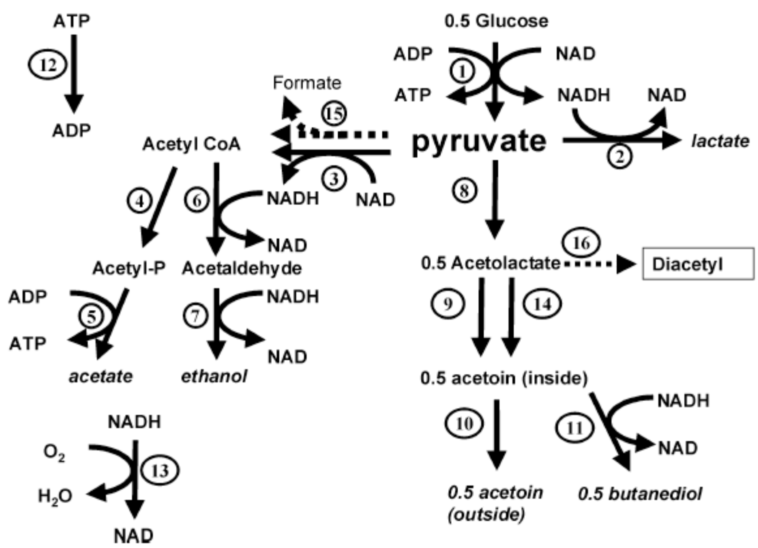
Alternative to Hand-Tuning Conductance-Based Models: Construction and Analysis of Databases of Model Neurons

Astrid A. Prinz, Cyrus P. Billimoria, and Eve Marder

Conventionally, the parameters of neuronal models are hand-tuned using trial-and-error searches to produce a desired behavior. Here, we present an alternative approach. We have generated a database of about 1.7 million single-compartment model neurons by independently varying 8 maximal membrane conductances based on measurement from lobster stomatogastric neurons (STG).

Metabolic control analysis : a success of local sensitivity analysis

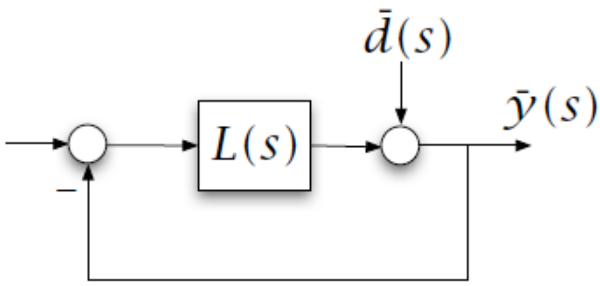
? Limiting step in a metabolic pathway ?



Control coefficients measure static relative change in flux in response to a relative change in enzyme activity

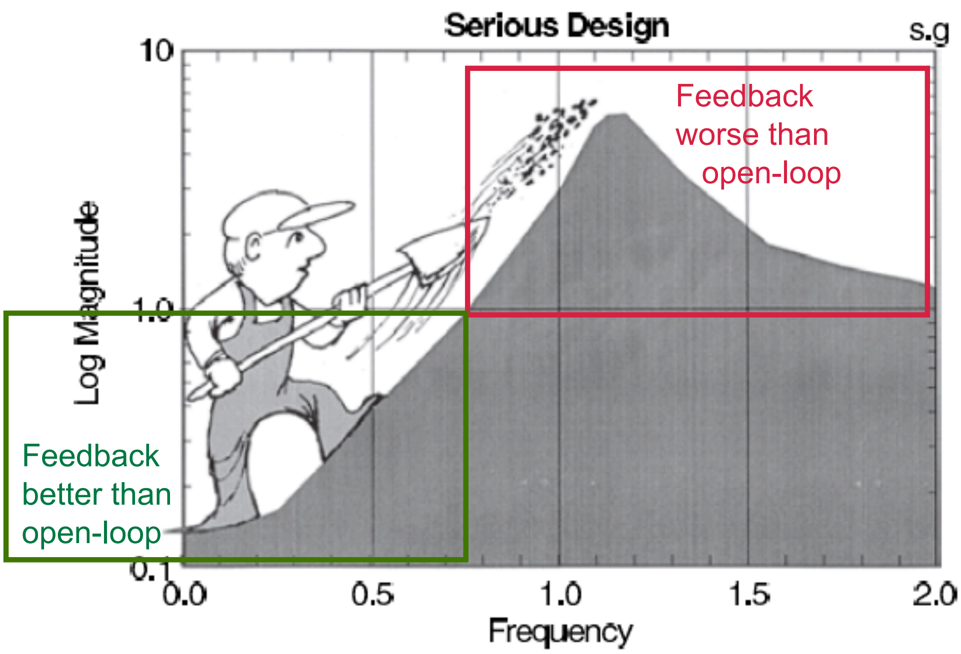
linear control theory:
a success of local sensitivity analysis

? How much does feedback reduce the effect of environment ?



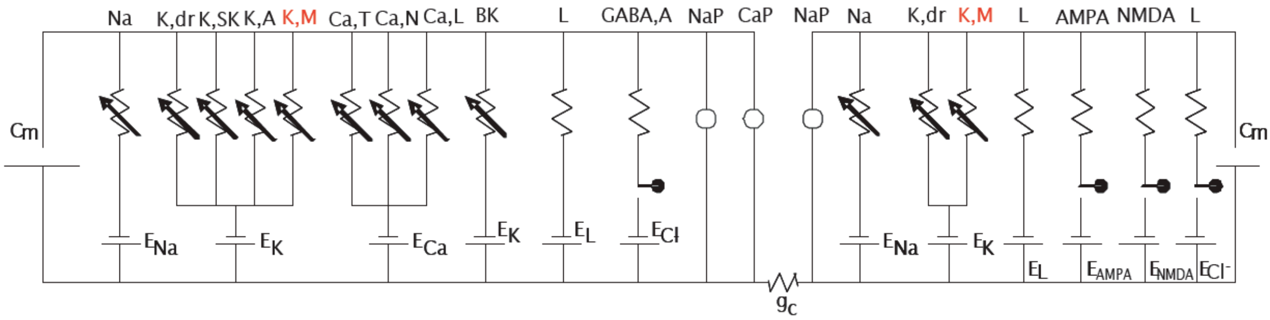
The sensitivity analysis function S(s) measures the relative change in closed-loop in response to a relative change in open-loop

Loop-shaping of the sensitivity function:
a key insight of control theory



A feedback controller shapes the sensitivity function, at each frequency, and the entire sensitivity analysis of the dynamical system can be inferred from a single curve.

Could local sensitivity analysis be relevant for neuronal behaviors?



Analogy 1 (metabolic control analysis): channel expression modulates ion flux

Analogy 2 (linear control theory): each ionic current acts as a feedback loop which alters the sensitivity of the open-loop behavior (i.e. the passive membrane)

BUT: neuronal behaviors look quite dynamic and quite nonlinear

A historical hint

The typical regulator system can frequently be described, in essentials, by differential equations of no more than perhaps the second, third or fourth order. …In contrast, the order of the set of differential equations describing the typical negative feedback amplifier used in telephony is likely to be very much greater. As a matter of idle curiosity, I once counted to find out what the order of the set of equations in an amplifier I had just designed would have been, if I had worked with the differential equations directly. It turned out to be 55.

Henrik Bode, Feedback: the history of an idea, 1960

Bode developed loop-shaping analysis to overcome the intractability of sensitivity analysis of electrical circuits aimed at signal transmission

Sensitivity analysis: lessons from the past

- Sensitivity analysis is a methodology with global ambitions but local means.
- Sensitivity analysis should be a tractable methodology to solve an intractable problem, not the other way around.
- Sensitivity analysis provides key insight when the behavior is captured by a curve.

Outline

- I. A model across scales
- II. The fragility of sensitivity analysis across scales
- III. Sensitivity analysis: a local tool with global aims
- IV. Intractable questions and paradoxes across scales

In silico neurophysiology

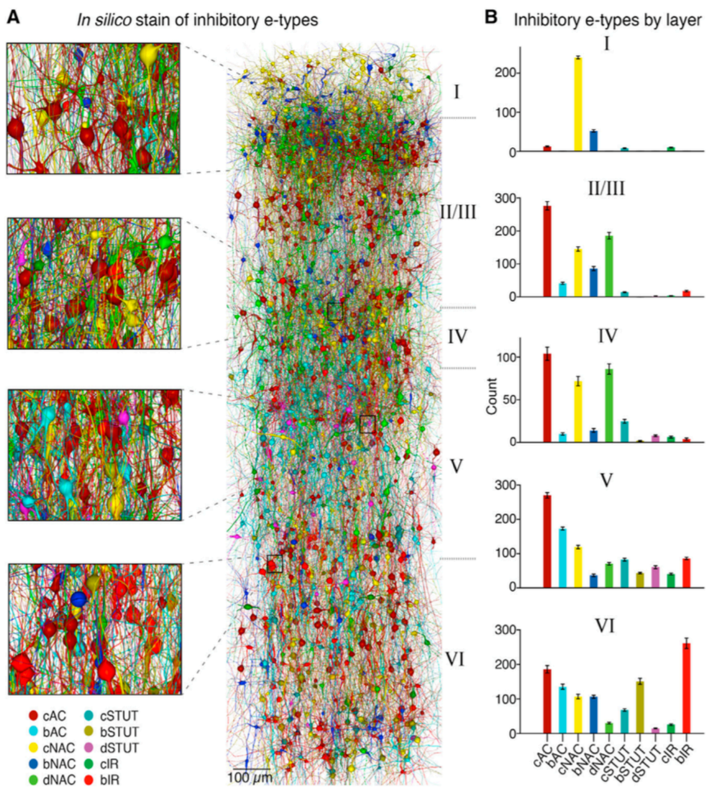
Reconstruction and Simulation of Neocortical Microcircuitry

Henry Markram,[1,2,19,*] Eilif Muller,[1,19] Srikanth Ramaswamy,[1,19] Michael W. Reimann,[1,19] Marwan Abdellah,[1] Carlos Aguado Sanchez,[1] Anastasia Ailamaki,[16] Lidia Alonso-Nanclares,[6,7] Nicolas Antille,[1] Selim Arsever,[1] Guy Antoine Atenekeng Kahou,[1] Thomas K. Berger,[2] Ahmet Bilgili,[1] Nenad Buncic,[1] Athanassia Chalimourda,[1] Giuseppe Chindemi,[1] Jean-Denis Courcol,[1] Fabien Delalondre,[1] Vincent Delattre,[2] Shaul Druckmann,[4,5] Raphael Dumusc,[1] James Dynes,[1] Stefan Eilemann,[1] Eyal Gal,[4] Michael Emiel Gevaert,[1] Jean-Pierre Ghobril,[2] Albert Gidon,[3] Joe W. Graham,[1] Anirudh Gupta,[2] Valentin Haenel,[1] Etay Hay,[3,4] Thomas Heinis,[1,16,17] Juan B. Hernando,[8] Michael Hines,[12] Lida Kanari,[1] Daniel Keller,[1] John Kenyon,[1] Georges Khazen,[1] Yihwa Kim,[1] James G. King,[1] Zoltan Kisvarday,[13] Pramod Kumbhar,[1] Sébastien Lasserre,[1,15] Jean-Vincent Le Bé,[2] Bruno R.C. Magalhães,[1] Angel Merchán-Pérez,[6,7] Julie Meystre,[2] Benjamin Roy Morrice,[1] Jeffrey Muller,[1] Alberto Muñoz-Céspedes,[6,7] Shruti Muralidhar,[2] Keerthan Muthurasa,[1] Daniel Nachbaur,[1] Taylor H. Newton,[1] Max Nolte,[1] Aleksandr Ovcharenko,[1] Juan Palacios,[1] Luis Pastor,[9] Rodrigo Perin,[2] Rajnish Ranjan,[1,2] Imad Riachi,[1] José-Rodrigo Rodríguez,[6,7] Juan Luis Riquelme,[1] Christian Rössert,[1] Konstantinos Sfyrakis,[1] Ying Shi,[1,2] Julian C. Shillcock,[1] Gilad Silberberg,[18] Ricardo Silva,[1] Farhan Tauheed,[1,16] Martin Telefont,[1] Maria Toledo-Rodriguez,[14] Thomas Tränkler,[1] Werner Van Geit,[1] Jafet Villafranca Díaz,[1] Richard Walker,[1] Yun Wang,[10,11] Stefano M. Zaninetta,[1] Javier DeFelipe,[6,7,20] Sean L. Hill,[1,20] Idan Segev,[3,4,20] and Felix Schürmann[1,20]

[1]Blue Brain Project, École polytechnique fédérale de Lausanne (EPFL) Biotech Campus, 1202 Geneva, Switzerland
[2]Laboratory of Neural Microcircuitry, Brain Mind Institute, EPFL, 1015 Lausanne, Switzerland
[3]Department of Neurobiology, Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[4]The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[5]Janelia Farm Research Campus, Howard Hughes Medical Institute, Ashburn, VA 20147, USA
[6]Laboratorio Cajal de Circuitos Corticales, Centro de Tecnología Biomédica, Universidad Politécnica de Madrid, 28223 Madrid, Spain
[7]Instituto Cajal (CSIC) and CIBERNED, 28002 Madrid, Spain
[8]CeSViMa, Centro de Supercomputación y Visualización de Madrid, Universidad Politécnica de Madrid, 28223 Madrid, Spain
[9]Modeling and Virtual Reality Group, Universidad Rey Juan Carlos, 28933 Móstoles, Madrid, Spain
[10]Key Laboratory of Visual Science and National Ministry of Health, School of Optometry and Opthalmology, Wenzhou Medical College, Wenzhou 325003, China
[11]Caritas St. Elizabeth's Medical Center, Genesys Research Institute, Tufts University, Boston, MA 02111, USA
[12]Department of Neurobiology, Yale University, New Haven, CT 06510 USA
[13]MTA-Debreceni Egyetem, Neuroscience Research Group, 4032 Debrecen, Hungary
[14]School of Life Sciences, University of Nottingham, Nottingham NG7 2UH, United Kingdom
[15]Laboratoire d'informatique et de visualisation, EPFL, 1015 Lausanne, Switzerland
[16]Data-Intensive Applications and Systems Lab, EPFL, 1015 Lausanne, Switzerland
[17]Imperial College London, London SW7 2AZ, UK
[18]Department of Neuroscience, Karolinska Institutet, Stockholm 17177, Sweden
[19]Co-first author
[20]Co-senior author
*Correspondence: henry.markram@epfl.ch
http://dx.doi.org/10.1016/j.cell.2015.09.029

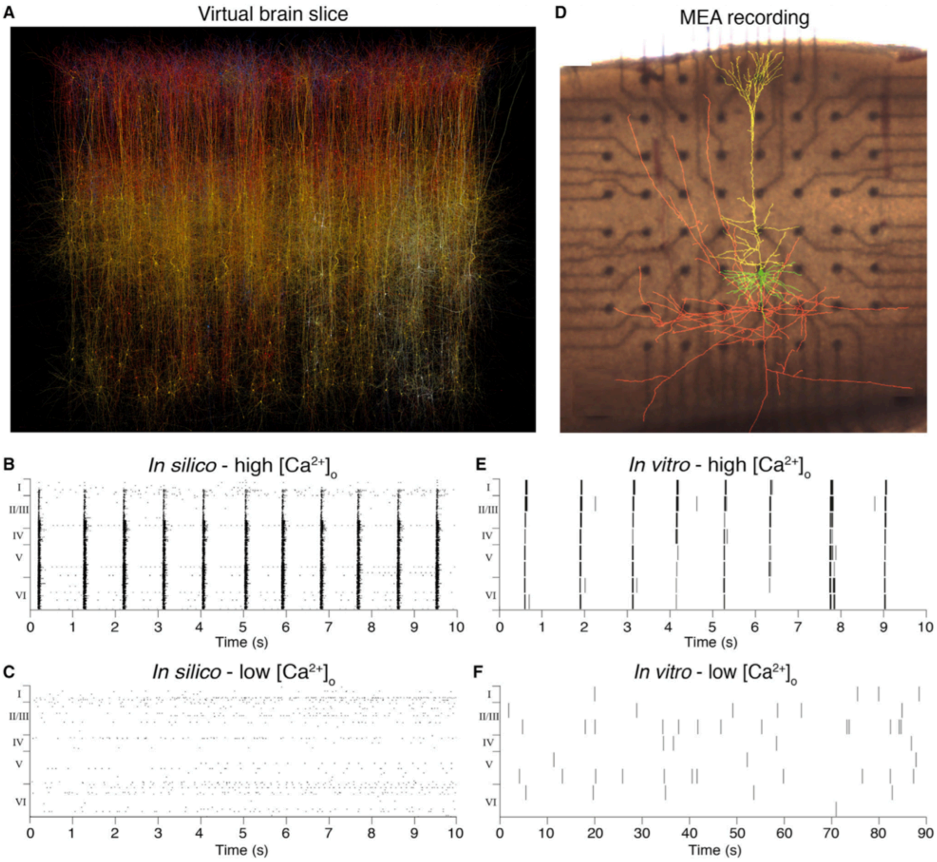
Markram et al., 2015

In silico neurophysiology



Markram et al., 2015

In silico neurophysiology

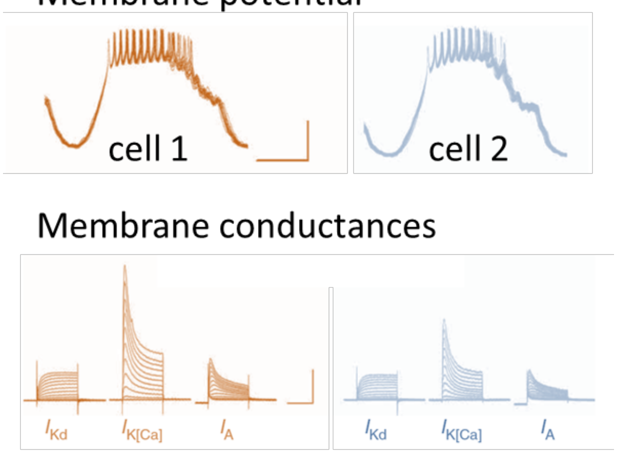


Markram et al., 2015

Neurons maintain a stable signal in spite of variable conductances

(Courtesy of Tim O'Leary)

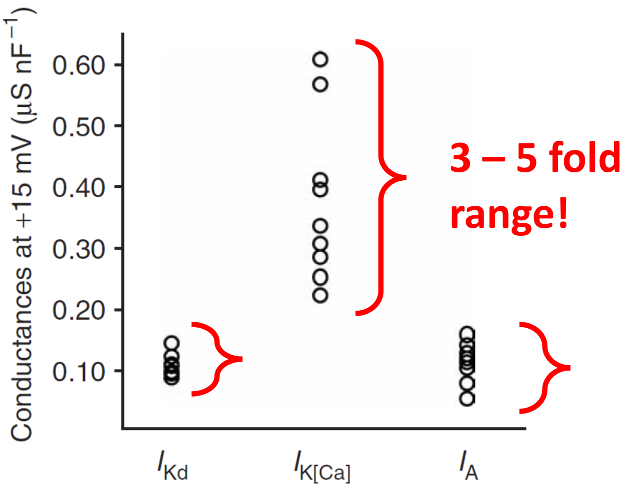
Membrane potential



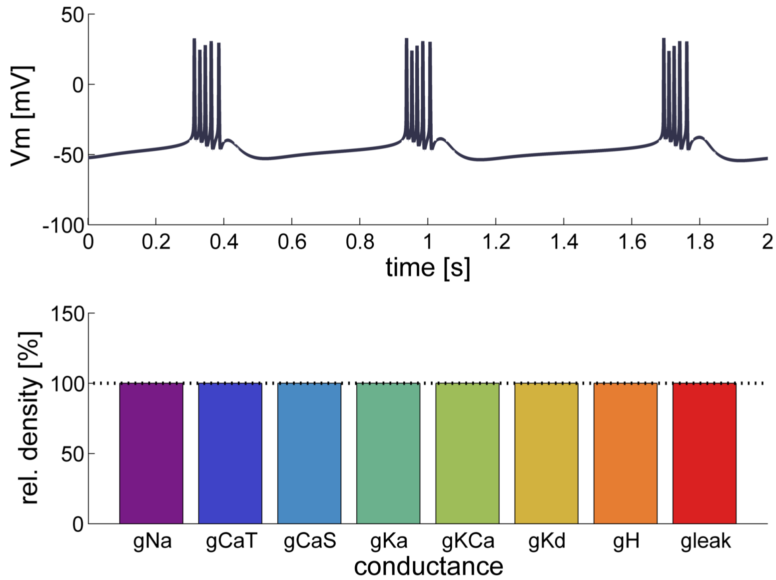
Membrane conductances

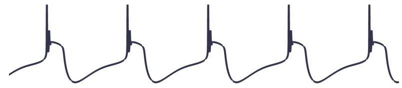
cell 1 cell 2

Membrane conductances (multiple cells)

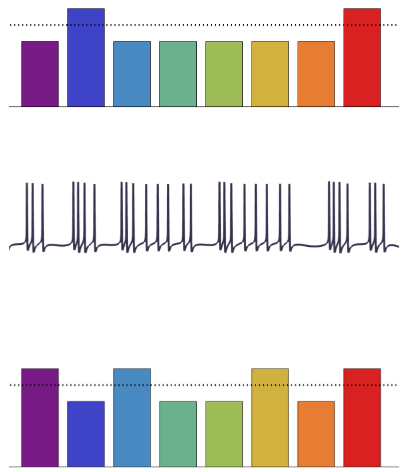


Schulz et al. Nature Neurosci 2006

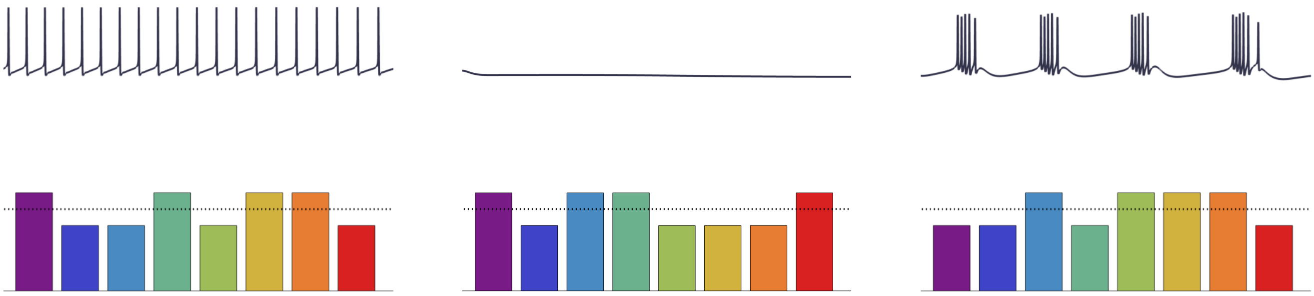




(Courtesy of Tim O'Leary)



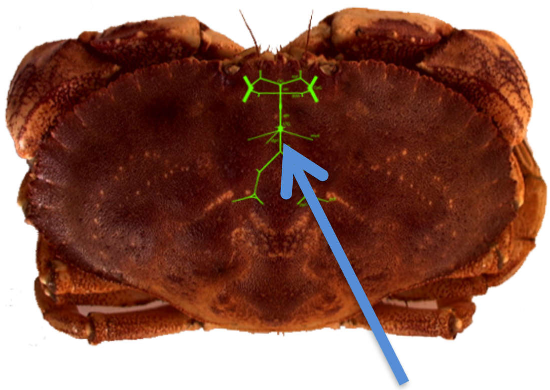
models suggest sensitivity of function to conductances



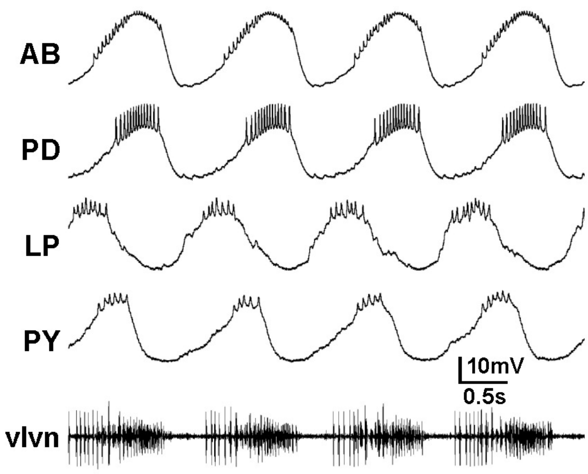
A well-defined neural circuit! The crustacean **stomatogastric ganglion.**

(Courtesy of Tim O'Leary)

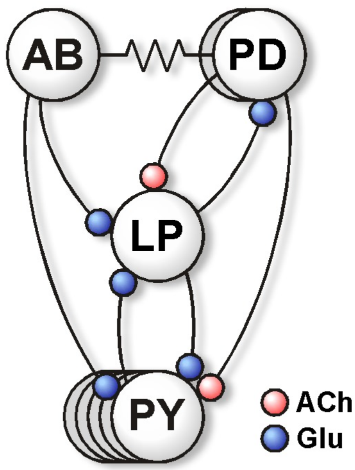
(courtesy of
Timothy O'Leary)



Pyloric rhythm



Pyloric circuit



Sensitivity of a circuit to neurotransmitters

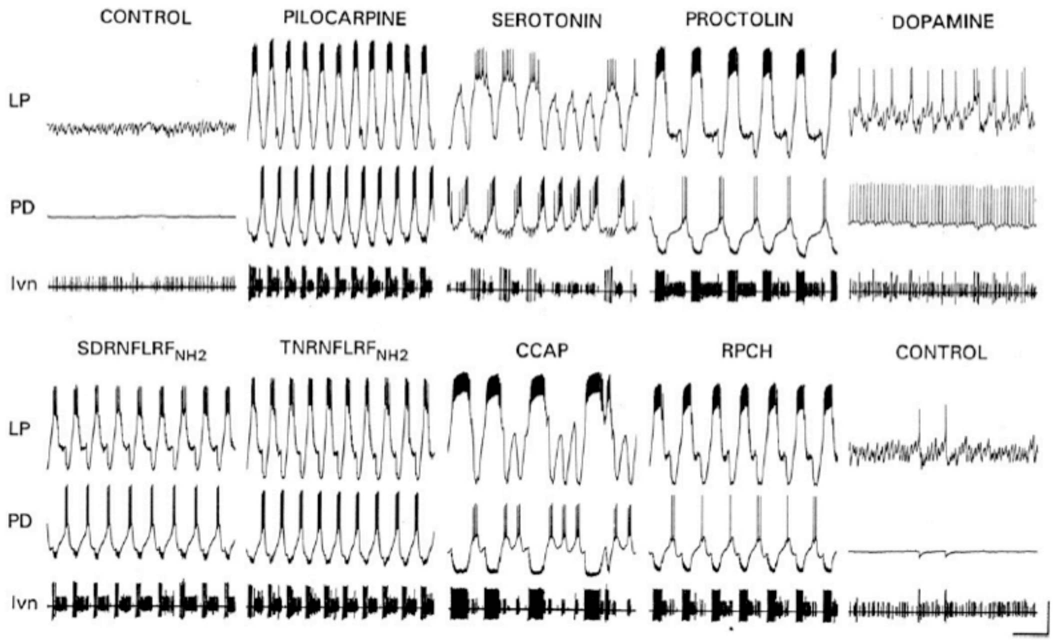


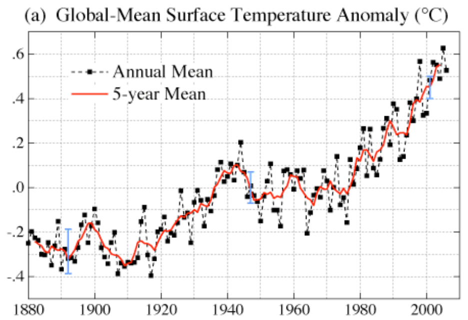
Figure 3. Multiple Neuromodulators Can Activate Different Forms of the Pyloric Rhythm
In each panel the top two traces are intracellular recordings from the lateral pyloric (LP) and pyloric dilator (PD) neurons. The bottom trace is an extracellular recording from the lateral ventricular nerve (lvn) that carries the axons of the LP, PD, and pyloric (PY) neurons (Marder and Weimann, 1992).

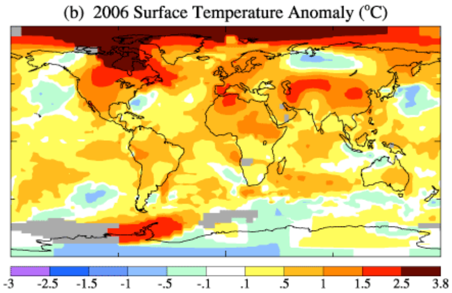
The complexity of sensitivity analysis across scales

- No signalling across scales without sensitivity of the large to the small
- No robustness across scales without insensitivity of the large to the small
- An seemingly intractable question even in the presence of detailed modelling of the small.

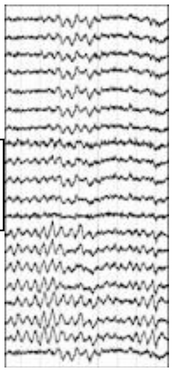
How does the small control the large ?

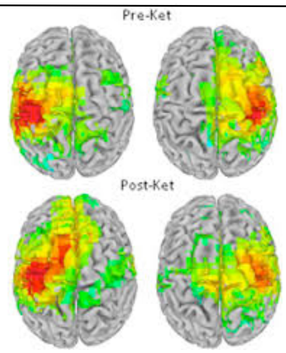
concentration signals





phase & intensity signals





intensity signals