Sensitivity analysis of neuronal behaviors

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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. 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?

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

Function

- LFPs
- 500µV
- 1000ms

DBS electrodes [mm]

- Optrodes [µm]

- Action potentials
- 10µV
- 10ms

Circuit level

Organ level

- Cellular level

- Pharmacology [nm]

Molecular level

- Ion channels
- 1pA
- 1ms
Ion channels are diverse
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

The action potential

A circuit model

Fig. 1. Electrical circuit representing membrane. \( R_{Na} = 1/g_{Na} \); \( R_{K} = 1/g_{K} \); \( R_{L} = 1/g_{L} \). \( R_{K} \) vary with time and membrane potential; the other components are constant.

A model across scales
The Hodgkin-Huxley (HH) Model

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

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

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

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

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

m and n are the activation variables of sodium and potassium channels, respectively; and h is the inactivation variable of sodium channels.
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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 methodology 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 hypothesize 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>
<thead>
<tr>
<th>Reference</th>
<th>Nature of the preparation</th>
<th>Agent used</th>
<th>Observed effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nederhaug et al., 1993</td>
<td>Slices from adult guinea-pigs, SNc, intracellular recordings.</td>
<td>nifedipine (1–20 μM)</td>
<td>Cessation of firing at undisclosed concentration.</td>
</tr>
<tr>
<td>Mercuri et al., 1994</td>
<td>Slices from adult Wistar rats, SNc and lateral VTA, intracellular recordings.</td>
<td>nifedipine and nimodipine (0.3–3 μM)</td>
<td>Decrease in the firing rate of about 50% with 1 μM of both drugs.</td>
</tr>
<tr>
<td>Paepke et al., 2007</td>
<td>Acutely dissociated neurons from the SNc of juvenile (16 day-old) mice, whole cell recordings.</td>
<td>1.8 mM Ca²⁺ in replacement of Ca²⁺, nifedipine (1 μM) + aga-IVA (200 nM)</td>
<td>Cessation of firing in all neurons (17/17), Firing rate decreased in 9/17 neurons. Firing rate decreased in 10/14 neurons.</td>
</tr>
<tr>
<td>Chan et al., 2007</td>
<td>Slices from juvenile mice (younger than P21), SNc, cell-attached and whole-cell recordings.</td>
<td>nifedipine (20 μM) and nimodipine (20 μM)</td>
<td>“Firing largely unaffected” (but firing reduced by an I_{Ca} blocker). Cessation of firing in all neurons (15/15); “plastic” phenomenon in “several” neurons (firing resumes during block &gt; 1 hour in some neurons).</td>
</tr>
<tr>
<td>Guzman et al., 2009</td>
<td>Slices from both juvenile and young adult mice, SNc, cell-attached and whole cell recordings.</td>
<td>nifedipine (5 μM)</td>
<td>Firing unaffected.</td>
</tr>
<tr>
<td>Putzier et al., 2009</td>
<td>Slices from juvenile rats younger than P21, SNc, whole cell recordings.</td>
<td>nimodipine (10 μM)</td>
<td>Cessation of firing.</td>
</tr>
<tr>
<td>Khalil and Bann, 2010</td>
<td>Slices from both juvenile and young adult mice, medial VTA, whole cell recordings.</td>
<td>0 Ca²⁺, 3 mM Mg²⁺</td>
<td>Firing increased three-fold.</td>
</tr>
<tr>
<td>South et al., unpublished</td>
<td>Slices from adult (&gt; 6 week-old), SNc, extracellular recordings</td>
<td>nifedipine (20–50 μM) and nimodipine (5–20 μM)</td>
<td>Firing unaffected (N=5). Variable effects, no clear trend (N=5).</td>
</tr>
</tbody>
</table>

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.1003505.001
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

\[
\frac{\Delta y}{\Delta u}
\]

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

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

First published August 27, 2003; 10.1152/jn.00641.2003.

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

Control coefficients measure \textbf{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.

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Reconstruction and Simulation of Neocortical Microcircuitry

Henry Markram,1,2,19* Elfie Muller,1,19 Srikanth Ramaswamy,1,19 Michael W. Reimann,1,19 Marwan Abdellaah,1 Carlos Aguado Sanchez,1,2 Anastasia Almairac,1,6 Lidia Alonso-Nanci,1,6 Nicolas Antille,1 Selim Arsever,1 Guy-Antoine Arsenaké Kinou,1 Thomas K. Berger,1 Ahmet Biligi,1 Nerad Buncic,1 Athanasia Chailourouda,1 Giuseppe Chindenti,1 Jean-Denis Couroul,1 Fabien Delalonde,1 Vincent Delattre,1 Shaul Dran,1,2 Raphael Dumusc,1,2 James Dyne,1 Stefan Ellemann,1 Eyal Gal,1 Michael Emiel Gevaert,1 Jean-Pierre Ghobril,2 Albert Gidon,1 Joe W. Graham,1 Annuith Gupta,1 Valentin Haenel,1 Eddy Hay,1 Thomas Heiris,1,16,17 Juan B. Hernandez,8 Michael Hines,12 Lida Kanari,1 Daniel Keller,1 John Kenyon,1 Georges Khazen,1 Yiwha Kim,1 James G. King,10 Zoltan Kisvarday1,19 Pramod Kumbhar,1 Sébastien Lasserre,1,18 Jean-Vincent Le Bée,1 Bruno R.C. Magalhaes,1 Angel Merchán-Pérez,5,7 Julie Meyste,2 Benjamin Roy Monica,1 Jeffrey Muller,1 Alberto Muñoz-Gómez,5,7 Shruti Muralidharan,2 Koertjan Muthurasa,1 Daniel Nachbau,1 Taylor H. Newton,1 Max Nolte,1 Aleksandrs Ovcharenko,1 Juan Palaiclos,6 Luis Pastor,7 Rodrigo Perin,1 Rajnish Ranjan,13 Imaad Raihchi,1 José-Rodrigo Rodríguez,8,7 Juan Luis Riquelme,1 Christian Rüscher,1 Konstantinos Sfakakis,1 Ying Shi,1,2 Julian C. Shillcock,1 Glad Silberberg,18 Ricardo Silva,1 Farhan Taubed,1,19 Martin Tieleman,1 Maria Toledo-Rodriguez,14 Thomas Träningk,1 Werner Van Geit,1 Jafet Villarancha Diaz,1 Richard Walker,1 Yun Wang,10,11 Stefano M. Zanimet,1 Javier DeFelipe,6,7,9 Sean L. Hill,20

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20Co-senior author

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http://dx.doi.org/10.1016/j.cell.2015.09.029

Markram et al., 2015
Neurons maintain a stable signal in spite of variable conductances

(Courtesy of Tim O’Leary)

Membrane potential

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<tr>
<th>Membrane conductances</th>
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</tr>
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<tbody>
<tr>
<td>cell 1</td>
<td>cell 2</td>
</tr>
</tbody>
</table>

Membrane conductances at +15 mV

- $I_{Kd}$
- $I_{K[Ca]}$
- $I_A$

3 – 5 fold range!

Markram et al., 2015

Schulz et al. Nature Neurosci 2006
models suggest sensitivity of function to conductances

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

(Courtesy of Tim O’Leary)
Sensitivity of a circuit to neurotransmitters

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