Modelling: principles & practise

LACONEU 2014

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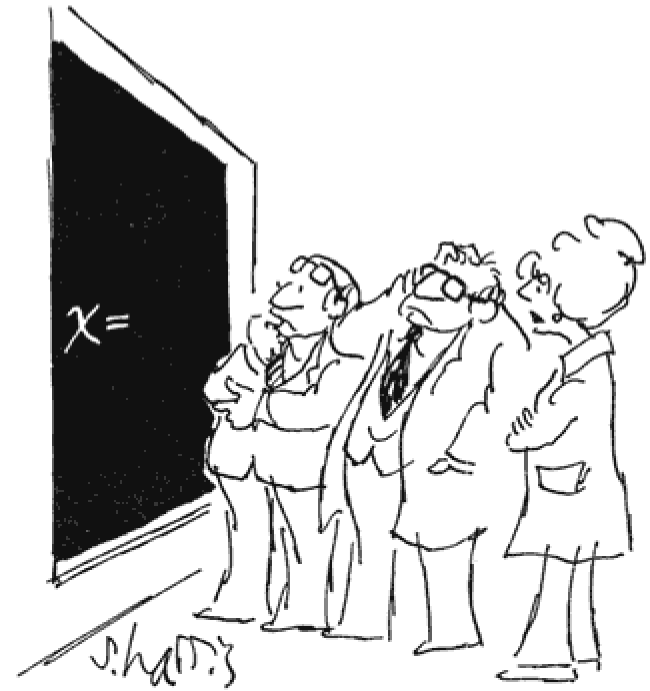
Motivation

- As funded scientists, we have a responsibility to the enterprise to pursue efficient routes to knowledge
- There are good and bad applications of tools
- A toolbox becomes a scientific arsenal when you know when to use what tool (which means knowing their limitations and how far beyond those limitations they can still be profitably used)

Outline

- Why theory and what is it?
- Neurophysiology case studies in modelling methodologies
    1. population coding in retina (Olivier & Agos)
    2. AP-onset rapidness (Brette)
    3. dendritic morphology
- Bonus part 1: Approximations and reductions
- Bonus part 2: Noise and variability



WHY THEORY?

16 October 1964, Volume 146, Number 3642

SCIENCE

(Hypothesis-based)

Strong Inference

Certain systematic methods of scientific thinking may produce much more rapid progress than others.

John R. Platt

practiced and taught. On any given morning at the Laboratory of Molecular Biology in Cambridge, England, the blackboards of Francis Crick or Sidney Brenner will commonly be found covered with logical trees. On the top line will be the hot new result just up from the laboratory or just in by letter or rumor. On the next line will be two or three alternative explanations, or a little list of "What he did wrong." Underneath will be a series of suggested experiments or controls that can reduce the number of possibilities. And so on. The tree grows during the day as one man or another comes in and argues about why one of the experiments wouldn't work, or how it should be changed.

i.e. why theory?

An upgrade to experimental science:

- Experimental research programs can become method-centric: the tools risk becoming the hypotheses.
- Beyond a handful of interacting elements, the human capacity to analyze a system through plain intuition and exhaustive enumeration of the possibilities breaks down.
- Concepts need an 'open source' framework to be useful to the community, not just mental pictures in an investigator's head or even in the paper.
- With models, we can explore parameter regimes not attainable experimentally for practical or ethical reasons

Pre-experiment:

- Manipulations in experimental protocols are extremely laborious, but with well written code, they can be made in a model with the push of a button.
- So models can often raise and discount hypotheses more quickly than experiments, letting us focus the experimental effort on the questions that are most informative or interesting.

Post-experiment:

- Theory can help interpret regularities in data in the common case when no obvious interpretation exist.
- While data can be context-dependent (e.g. cell prep is special) and incomplete (e.g. only for subsystem), models can integrate information about a various parts of a system obtained through various ways

Can’t this be automated?

Machine learning (e.g. classification and regression algorithms) applied to neural data to reveal hidden structure is essential to neuroscience…but, e.g.

03 (2012) PHYSICAL REVIEW LETTERS

Extracting Dynamical Equations from Experimental Data is NP Hard

So, don’t wait for an algorithm to do it for you.

Jorge Luis Borges, Collected Fictions

On Exactitude in Science:

how much detail?

…In that Empire, the Art of Cartography attained such Perfection that the map of a single Province occupied the entirety of a City, and the map of the Empire, the entirety of a Province. In time, those Unconscionable Maps no longer satisfied, and the Cartographers Guilds struck a Map of the Empire whose size was that of the Empire, and w… . The f… so f… eir Forebears had been, saw that that vast Map was Useless, and not without some Pitilessness was it, that they delivered it up to the Inclemencies of Sun and Winters. In the Deserts of the West, still today, there are Tattered Ruins of that Map, inhabited by Animals and Beggars; in all the Land there is no other Relic of the Disciplines of Geography.
—Suarez Miranda,Viajes de varones prudentes, Libro IV,Cap. XLV, Lerida, 1658

"we now use the country itself, as its own map, and I assure you it does nearly as well."-Lewis Carroll

Well, there
is
only
one
truth…

…so model bulldozers
with quarks?

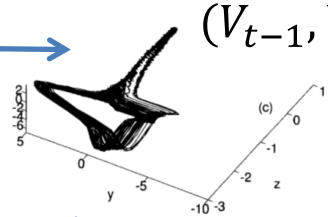
-Goldenfeld & Kadanoff, Science (1999)

Not all DOFs in a system are ‘active’ in the function under study

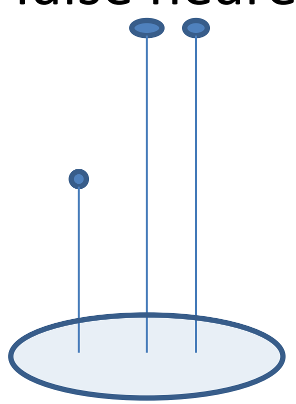
e.g. how many dimensions do you need to reconstruct the attractor of a lobster stomatogastric CPG neuron voltage trace?

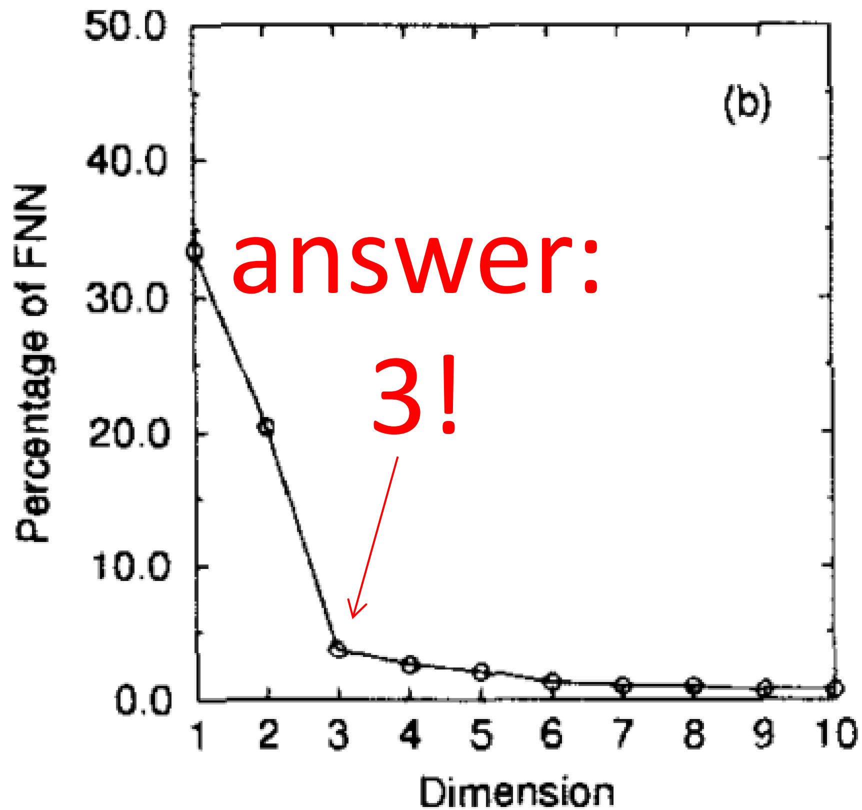
- Time-delay embedding

(V_{t-1}, V_t, V_{t+1})



- Method of false nearest neighbors:





Abarbanel et al. Neuro. Comp. 1996

Approach depends on goal

Practical Models	Theoretical Models
Main goals are management, design, and prediction	Main goals are theoretical understanding and theory development
Numerical accuracy is desirable, even at the expense of simplicity	Numerical accuracy is not essential; the model should be as simple as possible
Processes and details can be ignored only if they are numerically unimportant	Processes and details can be ignored if they are conceptually irrelevant to the theoretical issues
Assumptions are quantitative representations of system processes	Assumptions may be qualitative representations of hypotheses about the system, adopted conditionally in order to work out their consequences
System and question specific	Applies to a range of similar systems

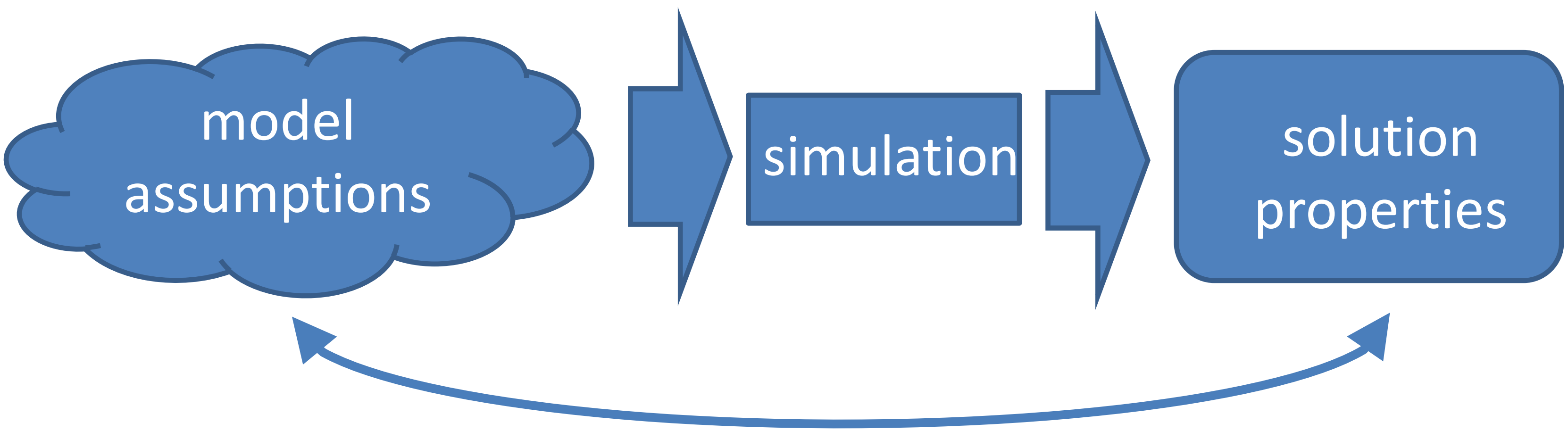
Ch.1, Ellner & Guckenheimer 2006

Theory models

- Einstein said:

  "A model should be as simple as possible but not simpler."
- He <u>*also*</u> said:

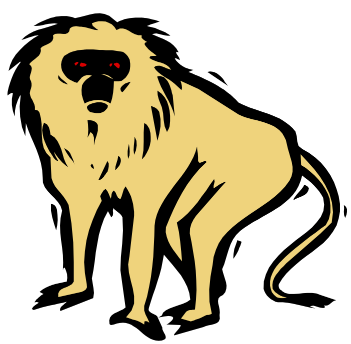
  "It is just as much an intellectual offense to include a detail that is unnecessary as to exclude one that is."



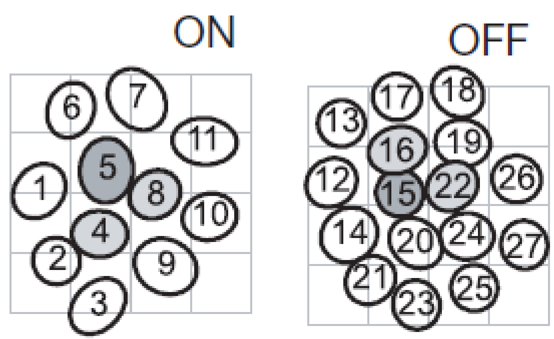
- All models are wrong; some are useful (i.e. those that are well chosen).

3 CASE STUDIES IN MODELLING METHODOLOGIES

Case study 1: assessing retinal population coding



macaque



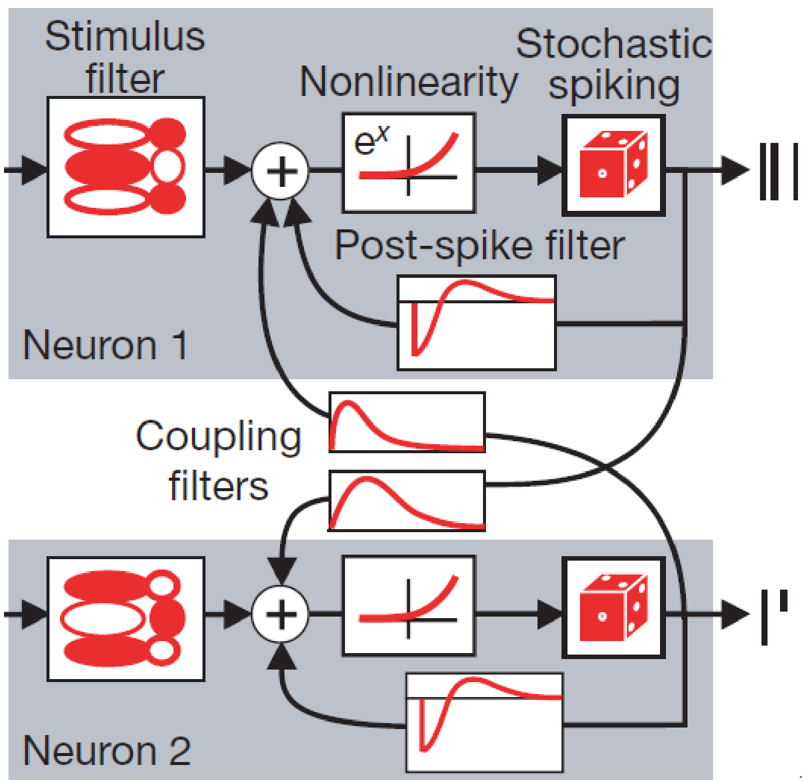
salamander

Case study 1: assessing retinal population coding

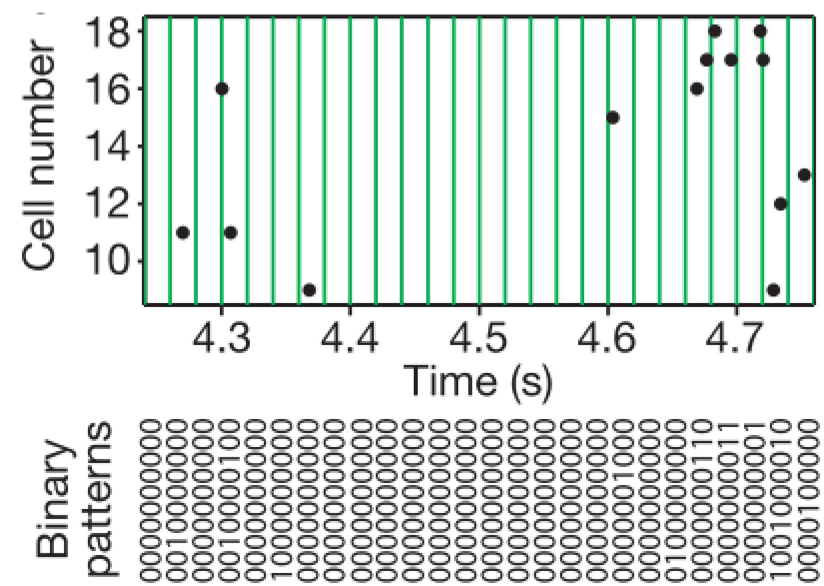
generalized linear models

Versus

maximum entropy models



Pillow et al., Nature 2008



$$P_2(\sigma_1, \sigma_2, \ldots, \sigma_N) = \frac{1}{Z} \exp\left[\sum_i h_i \sigma_i + \frac{1}{2} \sum_{i \neq j} J_{ij} \sigma_i \sigma_j\right] \qquad (1)$$

where the Lagrange multipliers $\{h_i, J_{ij}\}$ have to be chosen so that the averages $\{\langle\sigma_i\rangle, \langle\sigma_i\sigma_j\rangle\}$ in this distribution agree with experiment; the

Schneidman et al., Nature 2006

Case study 1

generalized linear models

Vs.

maximum entropy models

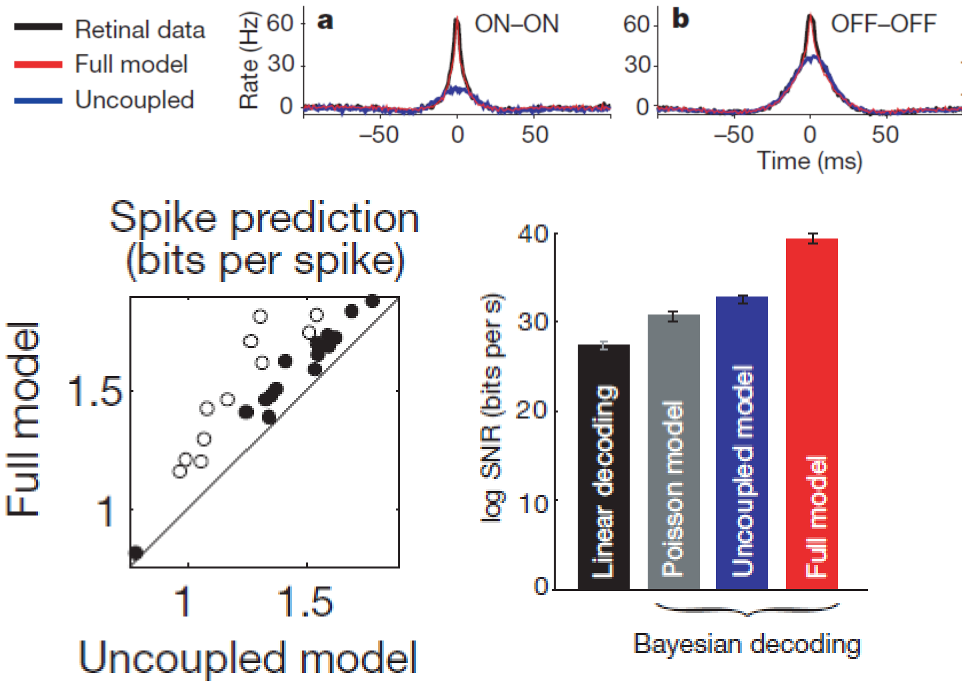
a generative model (generates output from input)	a statistical model (of pattern probabilities)
N_cells=27	N_cells=40
N_paras=70/filter *(4*27 filters)>5000	N_paras=55 (for N=10)
Fitted using maximum likelihood to 7min of spike responses	convex optimization constrained by 1st & 2nd order statistics
Test with no coupling	Test with conditional independence

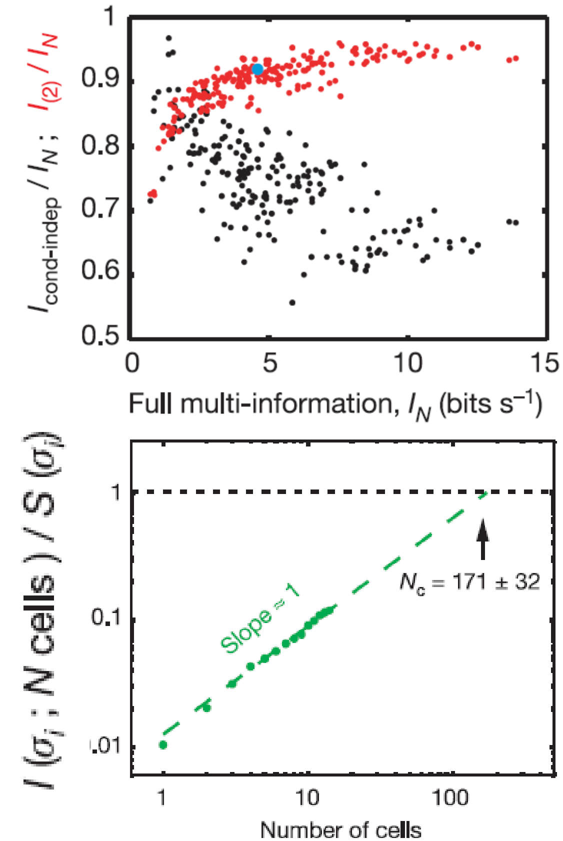
Case study 1

generalized linear models

Vs.

maximum entropy models





-gives temporal response and correlation
-weak estimate of information (via logSNR)
-lacks some observed features and only phenomenological

-compute information directly
-can extrapolate to larger networks
-can't assess stimulus dependence

Case study 1

Inquisitive Power

Vs.

Parsimony

-dimensionality a problem
-can ask more

-no curse of dimensionality
-stronger arguments
-fewer questions can be answered

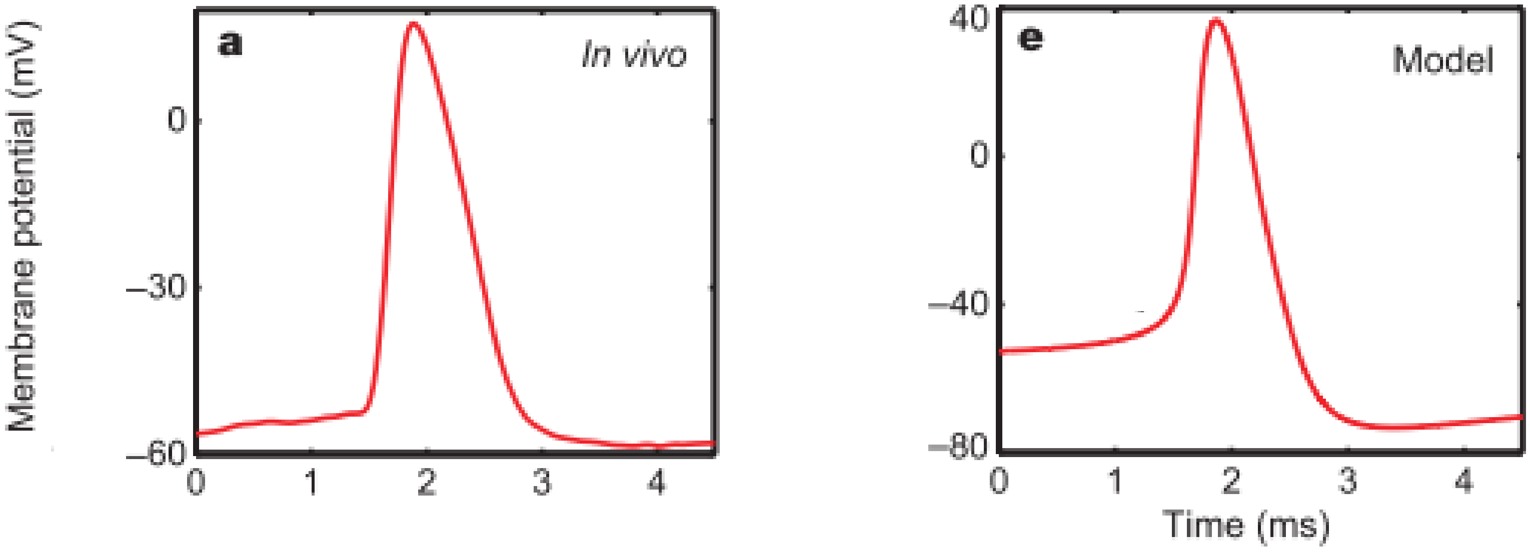
Trade-off between:

how much you can ask

and

how little you have to assume

Case study 2: causes and effects of action potential onset rapidness

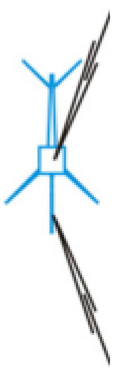


active AP-generation

Vs.

hard threshold

9 HH-like
Wang-Buszaki models



1-6, varying relevant parameters
7-9: added channel cooperativity,

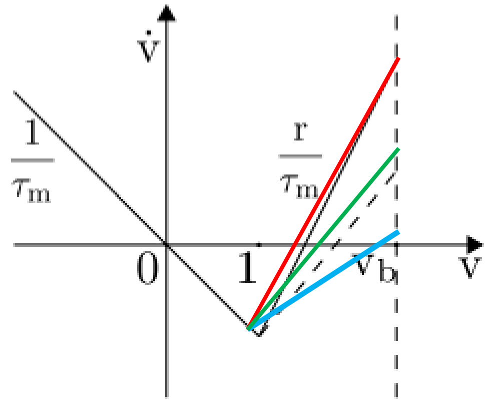
$$m_\infty(V) = \left[1 + \exp\left(-\frac{V - V_{\frac{1}{2}}}{k_A}\right)\right]^{-1}$$

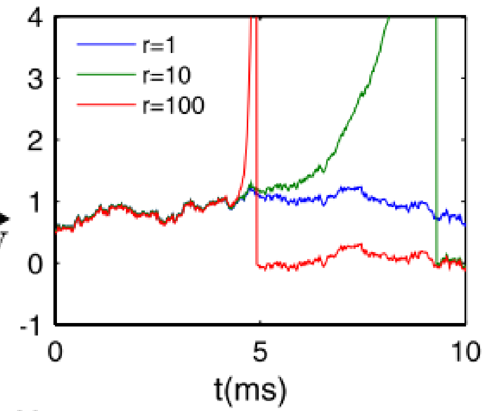
$$m_\infty^J(V) = m_\infty\left(V + KJ\left(m_\infty^J(V)\right)^x h\right)$$

GOAL:
provide a predictive & mechanistic explanation of the kink

Ilin et al., J. Neuro. 2013

Rapid LIF model



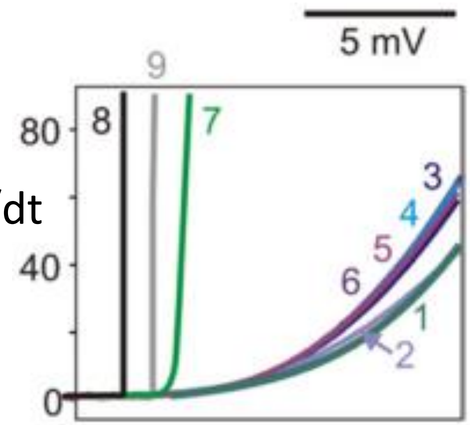


GOAL:
tractable model with variable rapidness to understand the consequences of the kink

Wei & Wolf, PRL 2011

active AP-generation Vs. hard threshold

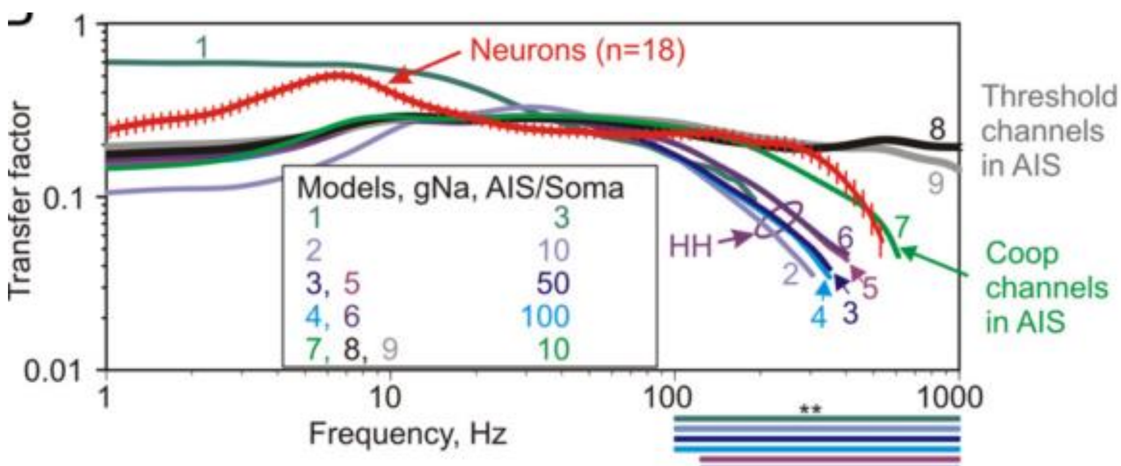
dV/dt

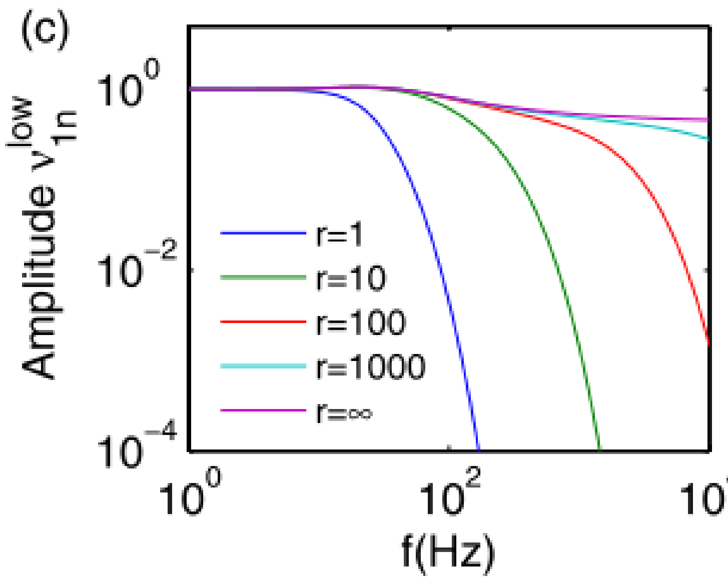


V

Rapid LIF-neuron

$$\nu_{1n}^{\mathrm{low}}(\omega) = \frac{i\omega(i\omega-1)}{(2-i\omega)(2+i\omega/r)} \frac{(1+1/r)(\frac{i\omega}{(1-i\omega)\sqrt{D}}\Phi_1 P_{01} + 2\Upsilon_1 P'_{01}) + \frac{\nu_0}{D}(2+i\omega/r)\Upsilon(v_r)e^{\Delta_0+i\omega\tau_r}}{\psi_1(v_r)e^{\Delta_0+i\omega\tau_r} + (Y_1\psi'_1 - Y'_1\psi_1)e^{\Delta_1}}$$





Ilin et al., J. Neuro. 2013

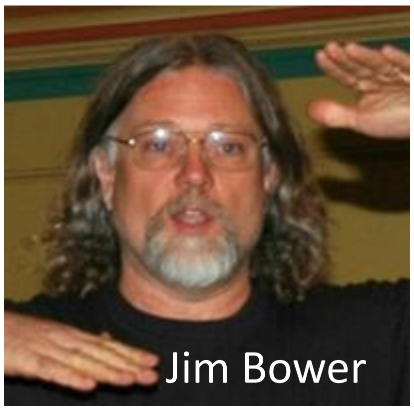
Wei & Wolf, PRL 2011

Case study 2

detail Vs. essence

detailed enough to provide some explanations of the mechanism

Simple enough to allow for deep understanding of the consequences



1st two directors of MBL course in 1988

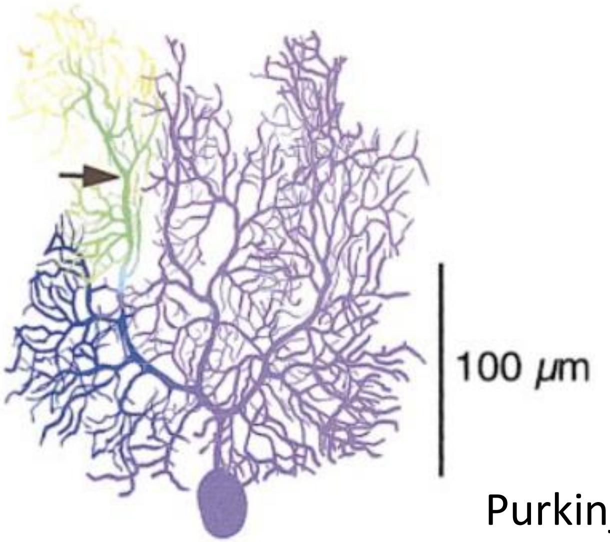
Trade-off between:

how much you can describe

and

how little you have to consider

Case study 3: fitting a compartmental neuron model



Purkinje cell

LP neuron

Case study 3

1500-compartment conductance-based model	4-compartment conductance-based model
implemented in NEURON	implemented in NEURON
2 cells: ~1500 compartments, 2 channels,	1 cell: 4 compartments, 10 channels
Parameters tuned to reproduce back-propagating AP, n=5	6x10^5 models with random parameter samples, selected 1300 using criteria from 3 simulations (nothing, step,periodic inhibition)

Property	Lower bound	Upper bound
Input conductance (nS)	36	132
Resting membrane potential (mV)	−47.5	−32.5
Resting spike rate (Hz)	13.1	30.6
Phase of burst onset (%)	32.0	44.0
Phase of burst offset (%)	61.7	74.9
Spike rate in burst (spikes/cycle)	16.3	30.2
Slow-wave amplitude (mV)	12.5	27.5
Peak slow-wave potential (mV)	−47.5	−32.5
ISI coefficient of variation in burst	0	0.25

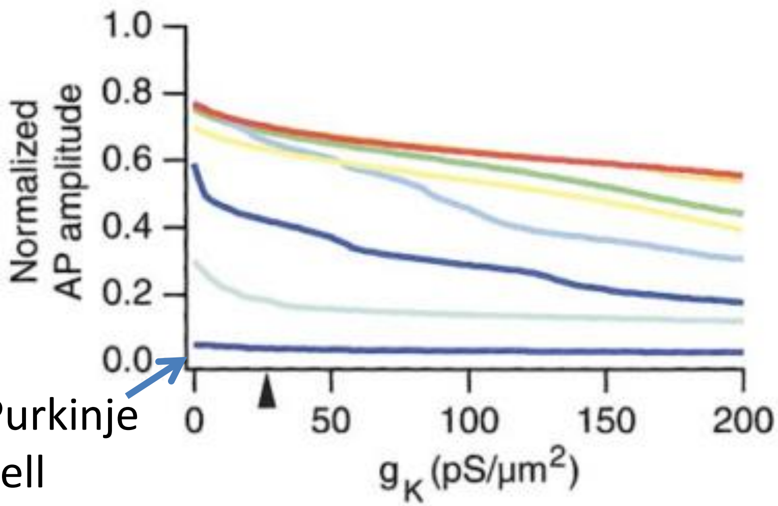
Vetter et al. J. Neurophysio. 2000

Taylor et al. Nat. Neuro. 2009

Case study 3

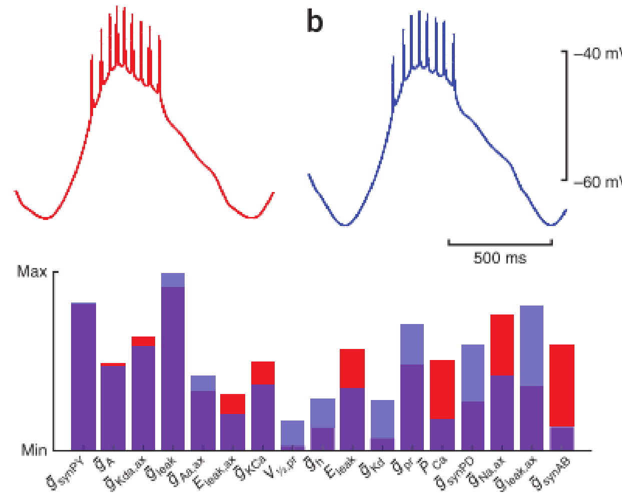
1500-compartment conductance-based model

4-compartment conductance-based model

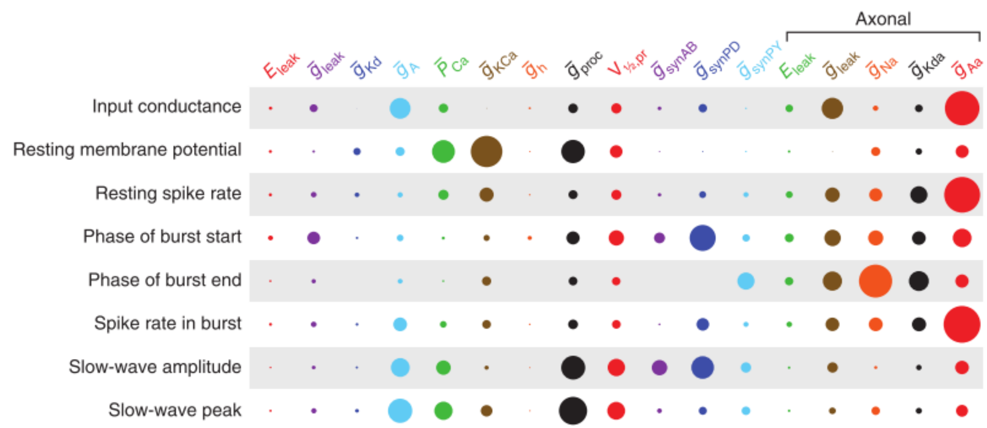


Purkinje cell

- Back-propagation absent
- insensitive to channel densities



Non-convex, but connected set of good models



Vetter et al. J. Neurophysio. 2000

Taylor et al. Nat. Neuro. 2009

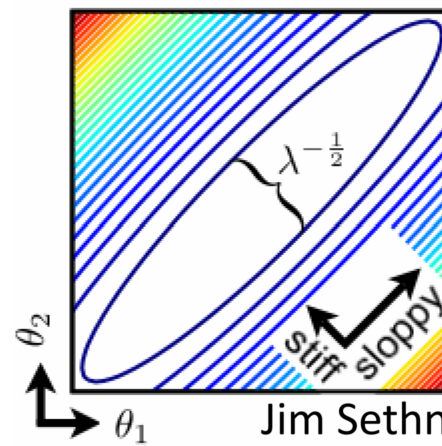
find 'the one' model

Vs.

analysis of parameter space

- No best model, only better models (model selection)
- principled approaches include noise model to avoid over-fitting

- degeneracy: multiple solutions produce similar outputs (Edelmen & Gally, PNAS 2002)
- Explore in minimum (Fisher information), across minimums
- Bifurcations/phase transitions



Jim Sethna

Trade-off between:

conciseness

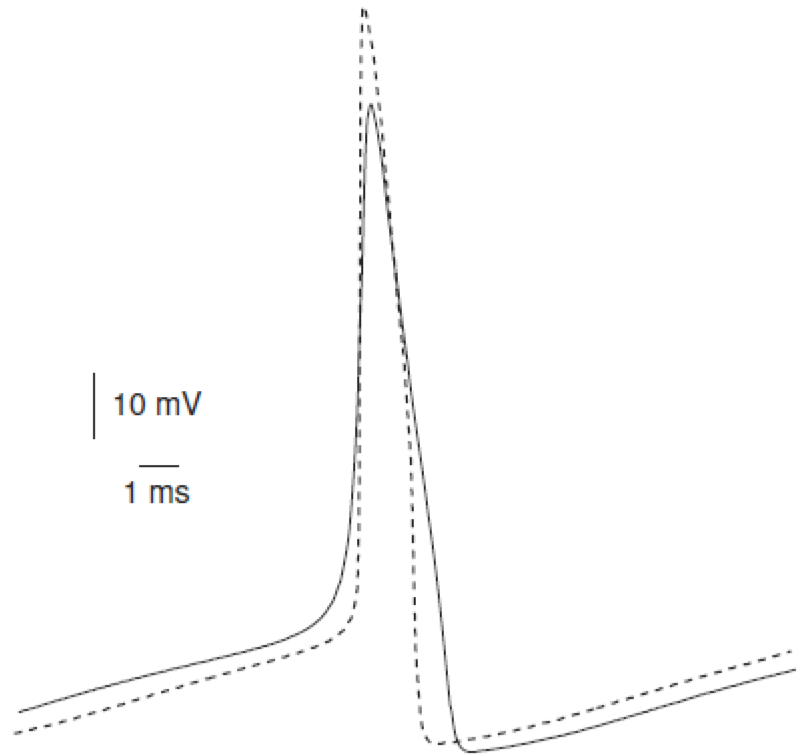
Vs.

robust results

(Eve) Marder & Taylor, Nat. Neuro. 2011

What have we learned from these case studies?

- Approach depends on question and style
- How much you get out depends on how much put in (garbage in, garbage out)
- Detail and essence both have their roles in model building
- fine-tuning may not be the way to go



REDUCTIONS AND APPROXIMATIONS

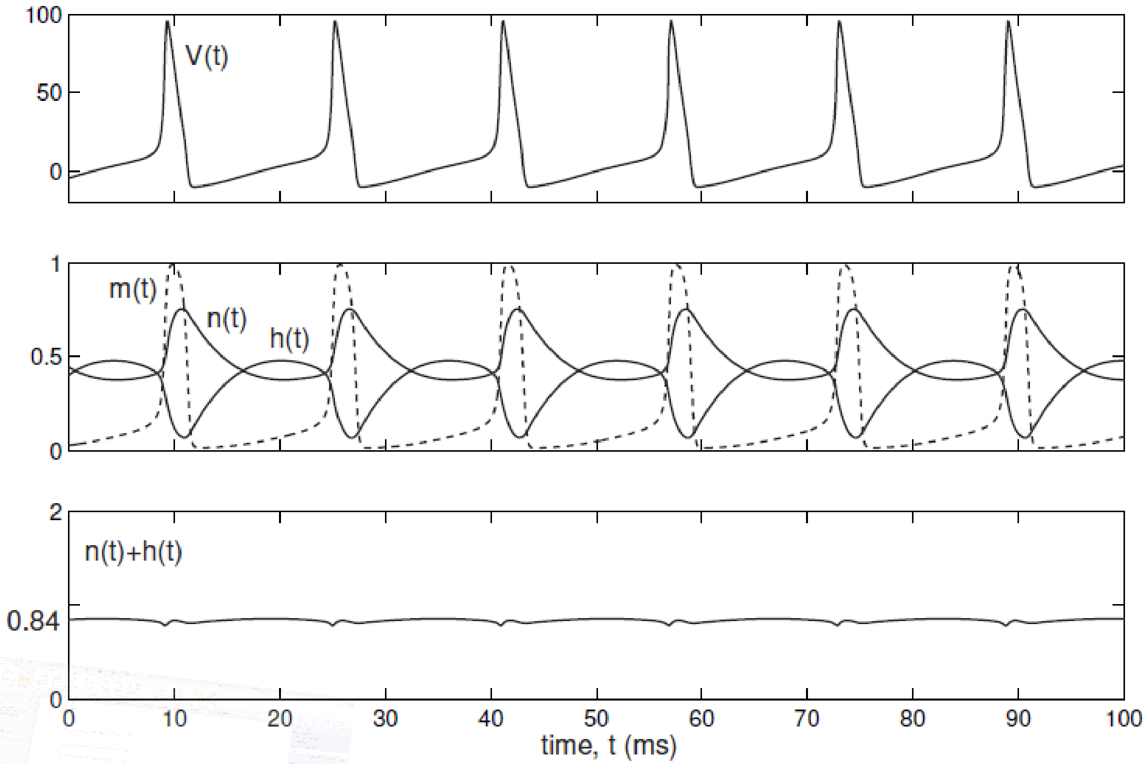
Don't neglect Billy!

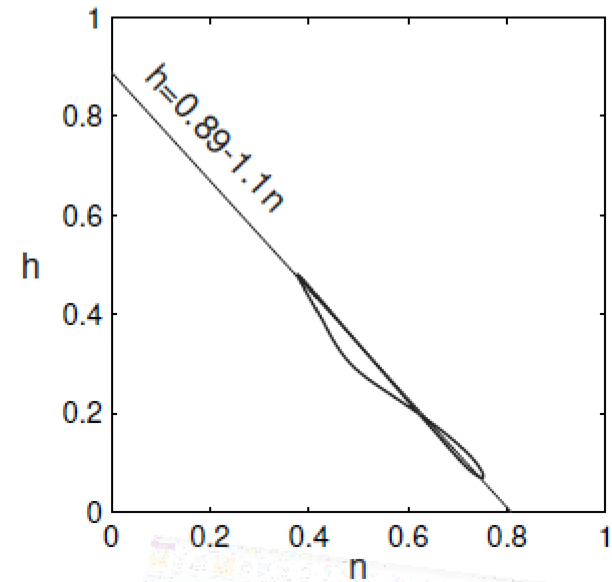
Well, it depends.

Motivation

- Why reduce the dimension of a model?
- What is the risk?
- Often, direct application of classical analytical tools fail for complex systems.
  - One can simplify the model to fit the tool
  - One can still use the tool if the conditions fail mildly and the results are approximately correct
- Sometimes, understandable/derivable limiting scenarios can be used to describe much of the phenomena

Reduction 1: HH to Morris-Lecar





$$
\begin{aligned}
C\dot{V} &= I - \overbrace{g_{\mathrm{K}} n^4 (V - E_{\mathrm{K}})}^{I_{\mathrm{K}}} - \overbrace{g_{\mathrm{Na}} m_\infty^3(V)(0.89 - 1.1n)(V - E_{\mathrm{Na}})}^{\text{instantaneous } I_{\mathrm{Na}}} - \overbrace{g_{\mathrm{L}}(V - E_{\mathrm{L}})}^{I_{\mathrm{L}}} \\
\dot{n} &= (n_\infty(V) - n)/\tau_n(V) \, ,
\end{aligned}
$$

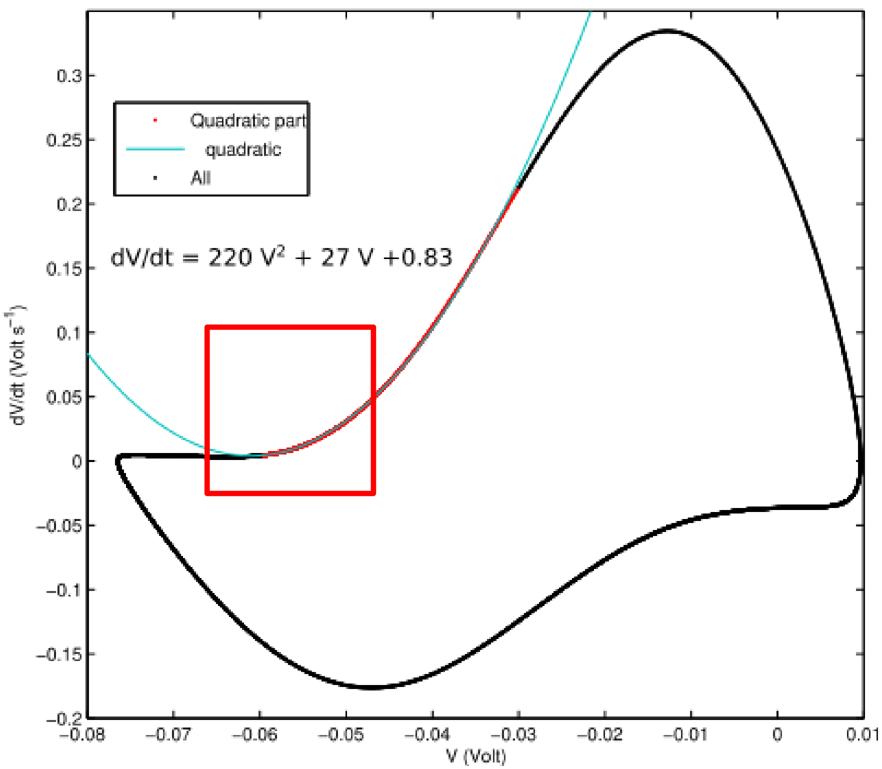
2D=> Phase plane analysis!

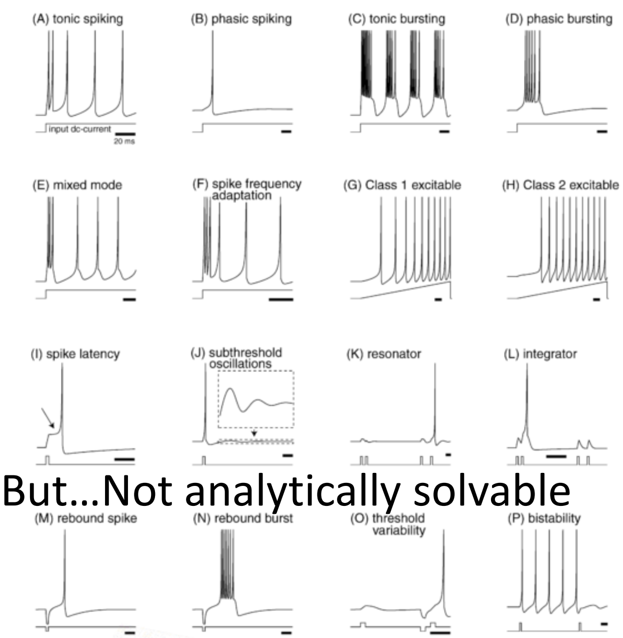
Reduction 2: Morris-Lecar to simple model

- Izhikevich's simple model

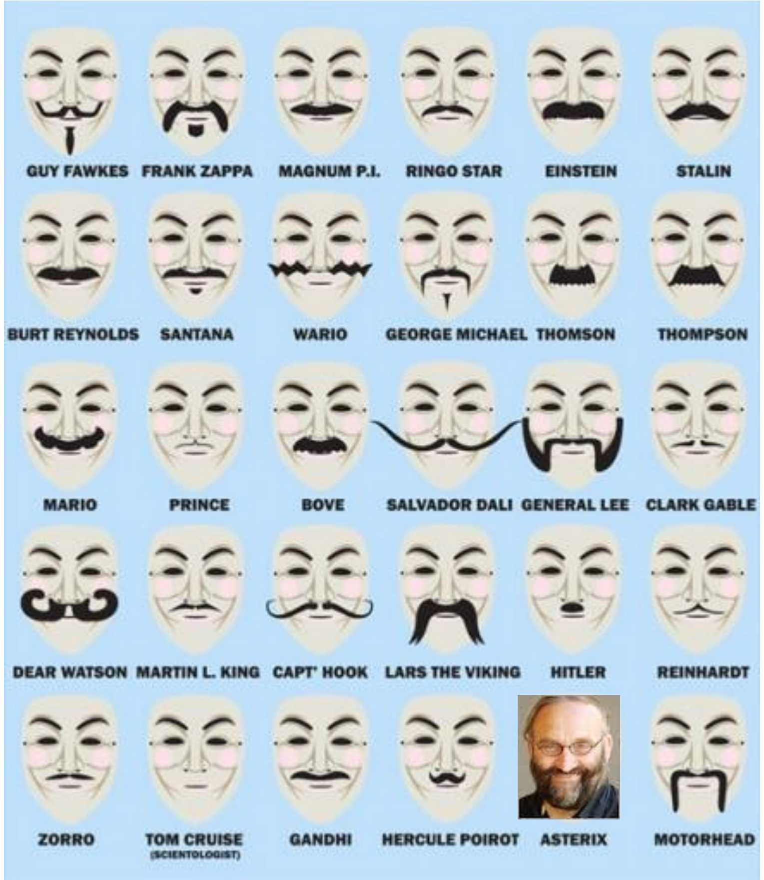
$$\dot{v} = I + v^2 - u \qquad \text{if } v \geq 1, \text{ then}$$

$$\dot{u} = a(bv - u) \qquad v \leftarrow c,\, u \leftarrow u + d$$





But…Not analytically solvable



NOISE AND VARIABILITY

Variability and noise

- Noise and variability often used interchangeably, but:

- **Variability** is an *ensemble* property of what we are studying
  - e.g. across trials in experiment or in time across a time series
  - measured in various statistical ways, e.g. standard deviation

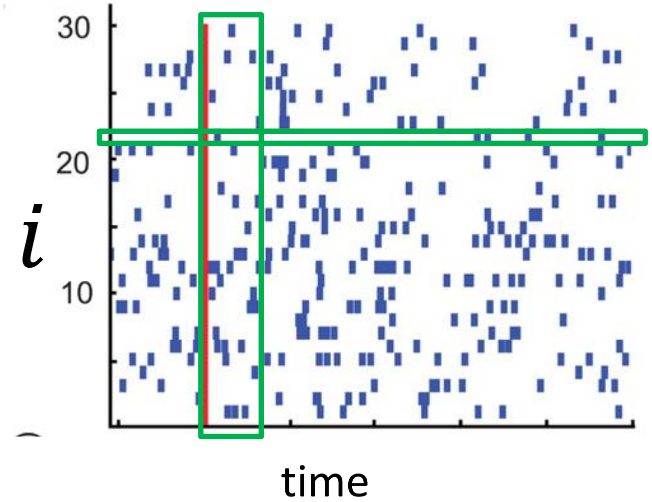
- **Noise** is a *semantic* label for the part of the observed variability that is not explicitly modelled
  - Environment is deterministic, but so complex it looks noisy
    - Complexity from many dimensions or chaotic dynamics or both
  - Signals are often split into a deterministic part and a stochastic part
    - E.g. coarse-grained models like Brownian motion

- Where to draw the line between system and environment?
  - determines the deterministic and stochastic part of your model

- How do deterministic and stochastic analyses come together?
  - How do they inform each other?

A example of drawing the line

- Fully deterministic network simulation in asynchronous, irregular state



- LIF receiving network input

$$\frac{dV}{dt} = -\frac{V}{\tau_m} + \frac{I(t)}{C} + \sum_{i,j}^{K} \omega_i \delta(t - t_{ij})$$

- As $\omega \to 0, K \to \infty$ (diffusion approximation)

$$\tau_m \frac{dV}{dt} = -V(t) + RI(t) + \xi(t)$$

Capocelli and Ricciardi 1971

- Study transfer properties as a function of the process (mean, variance, correlation time)

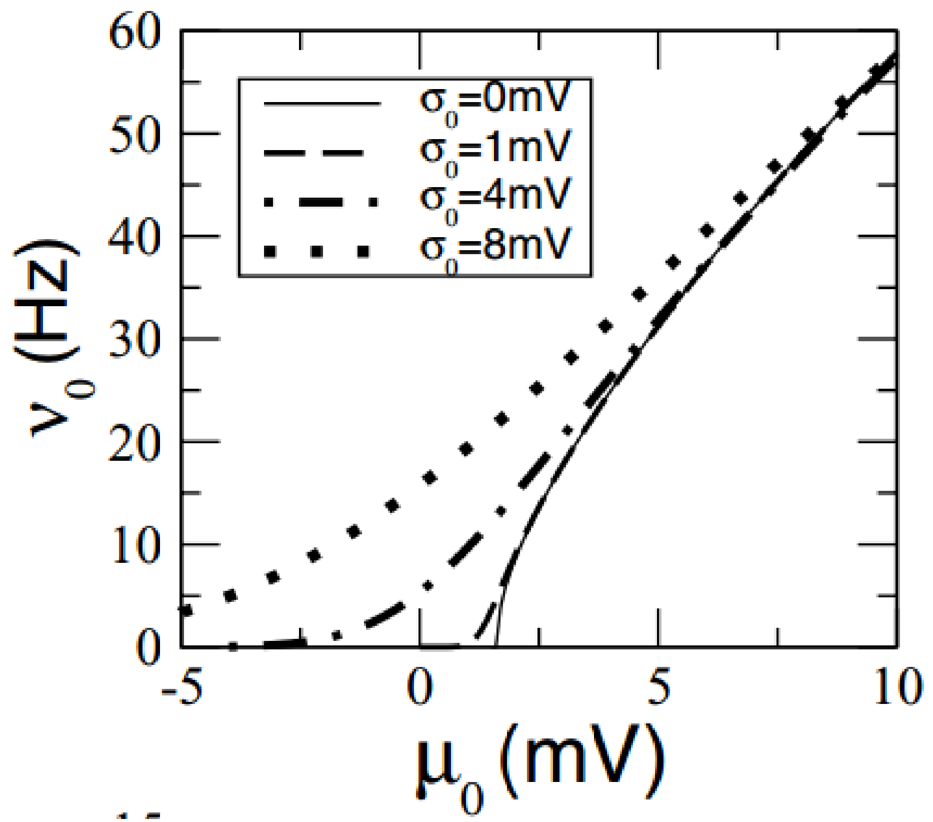
An example of a stochastic effect: fI-curve linearization by noise

$$C\frac{dV}{dt} = -g_L(V - V_L) + \psi(V) + I(t)$$

$$\psi(V) = g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right)$$

$$I(t) = g_L \mu(t) + \sigma(t)\sqrt{C g_L}\,\eta(t)$$

mean and std. dev.

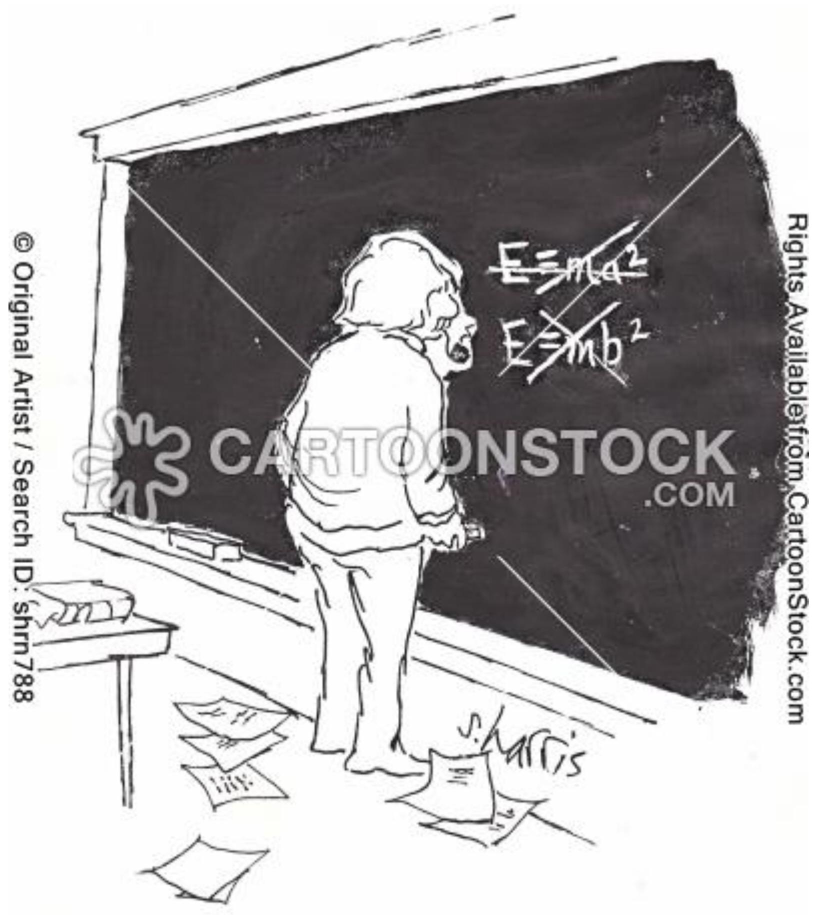


Concluding thoughts

- Any one who does science knows that there are many routes to knowledge and that the 'scientific method' of high school is an idealization.
- Nevertheless, every true master that innovates, knows the prescribed methods of their discipline even if they find them lacking.
- So, when learning a tool, try hard to understand it’s limits!

Acknowledgements

- Neurophysics Lab, MPIDS



How strict are your simplifying assumptions?

- Diffusion approximation

Excitatory inputs: conductance-based or current-based.

- State-dependent conductance is a pain.
- Since excitatory reversal potential far away,

Reductions

- In search of minimal DOFs