

Degeneracy in detailed neuronal models



*Computational
Approaches to Memory
and Plasticity*

12th June 2016

"Just how many ways are there to skin a cat?"

Rishikesh Narayanan
Indian Institute of Science, Bangalore

What is Degeneracy?

Degeneracy and complexity in biological systems

Gerald M. Edelman* and Joseph A. Gally

PNAS | November 20, 2001 | vol. 98 | no. 24 | 13763–13768

Degeneracy is the ability of elements that are *structurally different* to perform the *same* function or yield the *same* output

Degeneracy is NOT redundancy!

Redundancy: same function is performed by *identical* elements.

Degeneracy: involves *structurally different* elements. May yield same or different functions depending on the context in which it is expressed.

Degeneracy is ubiquitous across scales of biological function

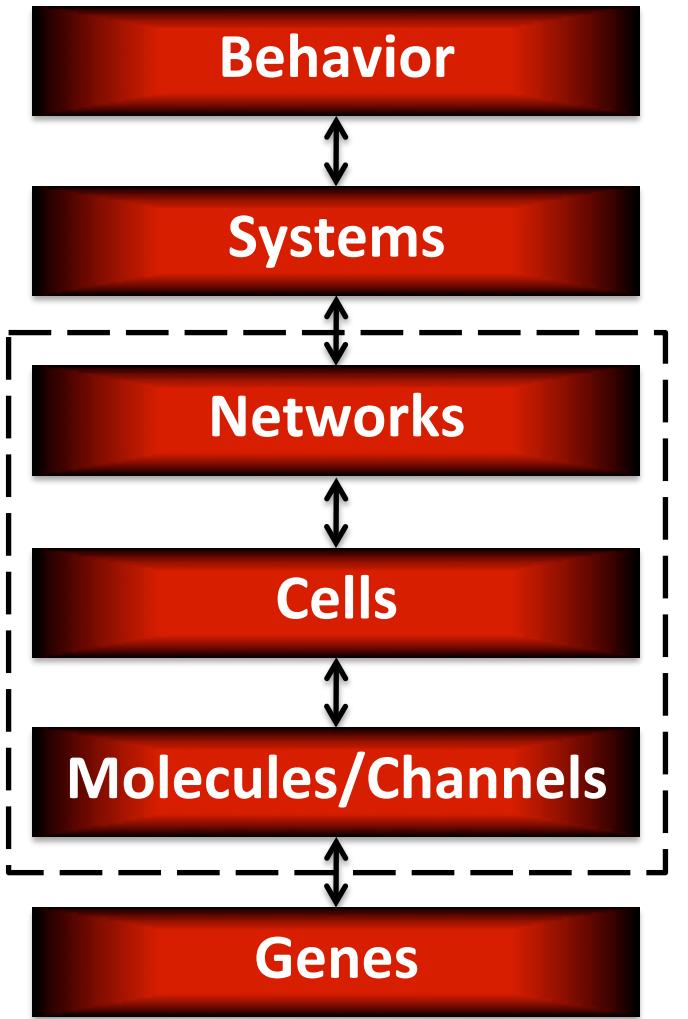


Table 1. Degeneracy at different levels of biological organization

1. Genetic code (many different nucleotide sequences encode a polypeptide)
2. Protein fold (different polypeptides can fold to be structurally and functionally equivalent)
3. Units of transcription (degenerate initiation, termination, and splicing sites give rise to functionally equivalent mRNA molecules)
4. Genes (functionally equivalent alleles, duplications, paralogs, etc., all exist)
5. Gene regulatory sequences (there are degenerate gene elements in promoters, enhancers, silencers, etc.)
6. Gene control elements (degenerate sets of transcription factors can generate similar patterns of gene expression)
7. Posttranscriptional processing (degenerate mechanisms occur in mRNA processing, translocation, translation, and degradation)
8. Protein functions (overlapping binding functions and similar catalytic specificities are seen, and "moonlighting" occurs)
9. Metabolism (multiple, parallel biosynthetic and catabolic pathways exist)
10. Food sources and end products (an enormous variety of diets are nutritionally equivalent)
11. Subcellular localization (degenerate mechanisms transport cell constituents and anchor them to appropriate compartments)
12. Subcellular organelles (there is a heterogeneous population of mitochondria, ribosomes, and other organelles in every cell)
13. Cells within tissues (no individual differentiated cell is uniquely indispensable)
14. Intra- and intercellular signaling (parallel and converging pathways of various hormones, growth factors, second messengers, etc., transmit degenerate signals)
15. Pathways of organismal development (development often can occur normally in the absence of usual cells, substrates, or signaling molecules)
16. Immune responses (populations of antibodies and other antigen-recognition molecules are degenerate)
17. Connectivity in neural networks (there is enormous degeneracy in local circuitry, long-range connections, and neural dynamics)
18. Mechanisms of synaptic plasticity (changes in anatomy, presynaptic, or postsynaptic properties, etc., are all degenerate)
19. Sensory modalities (information obtained by any one modality often overlaps that obtained by others)
20. Body movements (many different patterns of muscle contraction yield equivalent outcomes)
21. Behavioral repertoires (many steps in stereotypic feeding, mating, or other social behaviors are either dispensable or substitutable)
22. Interanimal communication (there are large and sometimes nearly infinite numbers of ways to transmit the same message, a situation most obvious in language)

Degeneracy in single neuron models

Variability, compensation, and modulation in neurons and circuits

Eve Marder¹

15542–15548 | PNAS | September 13, 2011 | vol. 108 | suppl. 3

Variability, compensation and homeostasis in neuron and network function

Eve Marder and Jean-Marc Goaillard

NATURE REVIEWS | NEUROSCIENCE

VOLUME 7 | JULY 2006 |

Multiple models to capture the variability in biological neurons and networks

Eve Marder^{1,2} & Adam L Taylor^{1,2}

NATURE NEUROSCIENCE VOLUME 14 | NUMBER 2 | FEBRUARY 2011

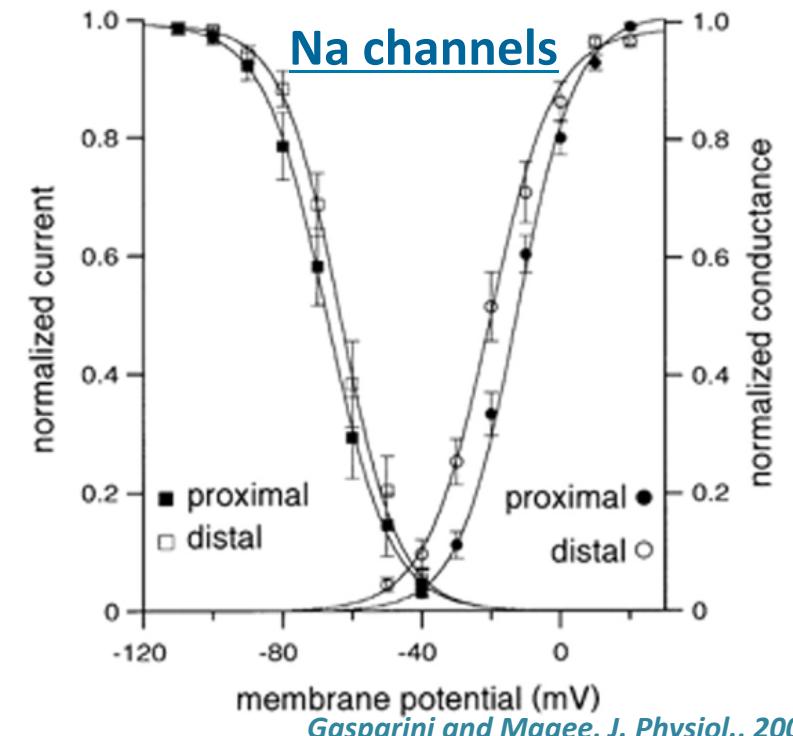
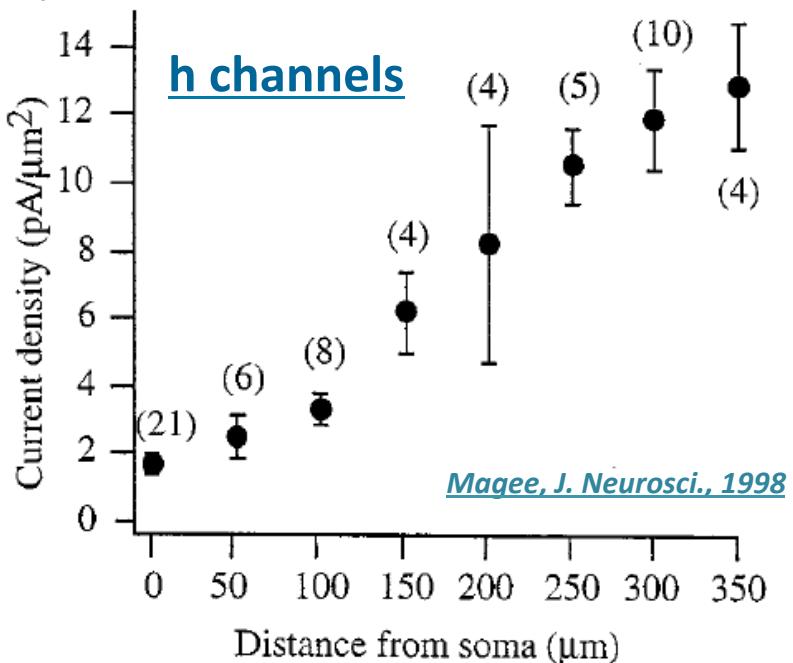
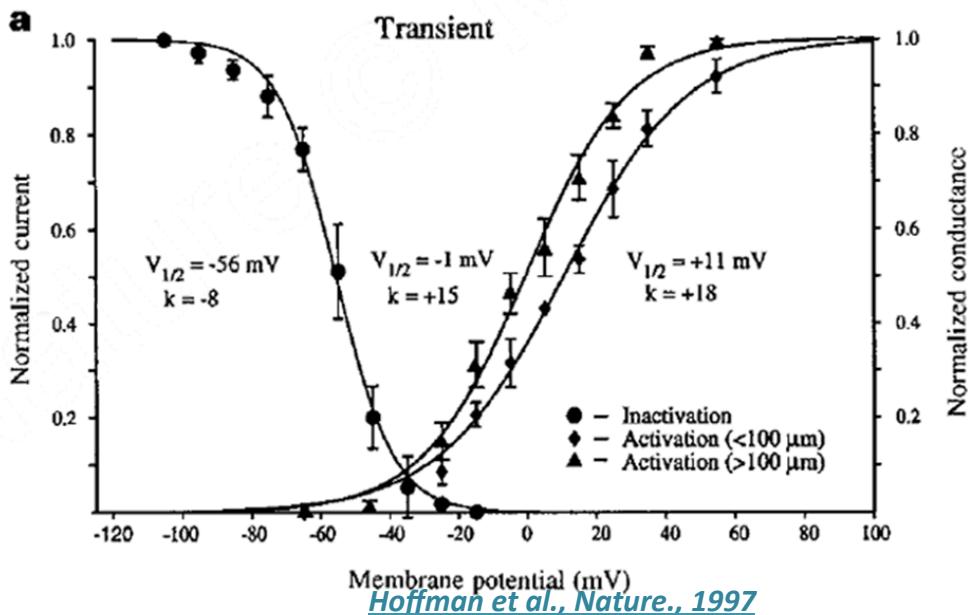
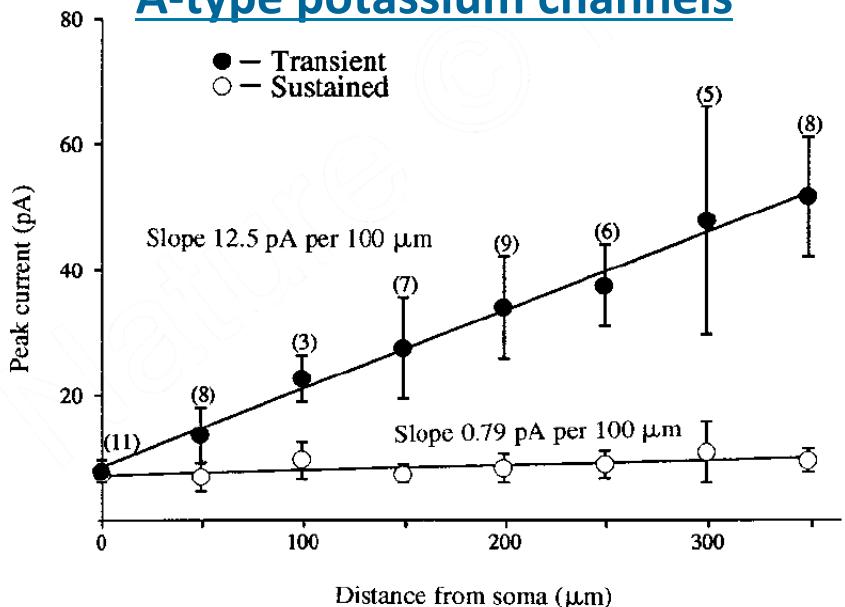
Computational implications of biophysical diversity and multiple timescales in neurons and synapses for circuit performance

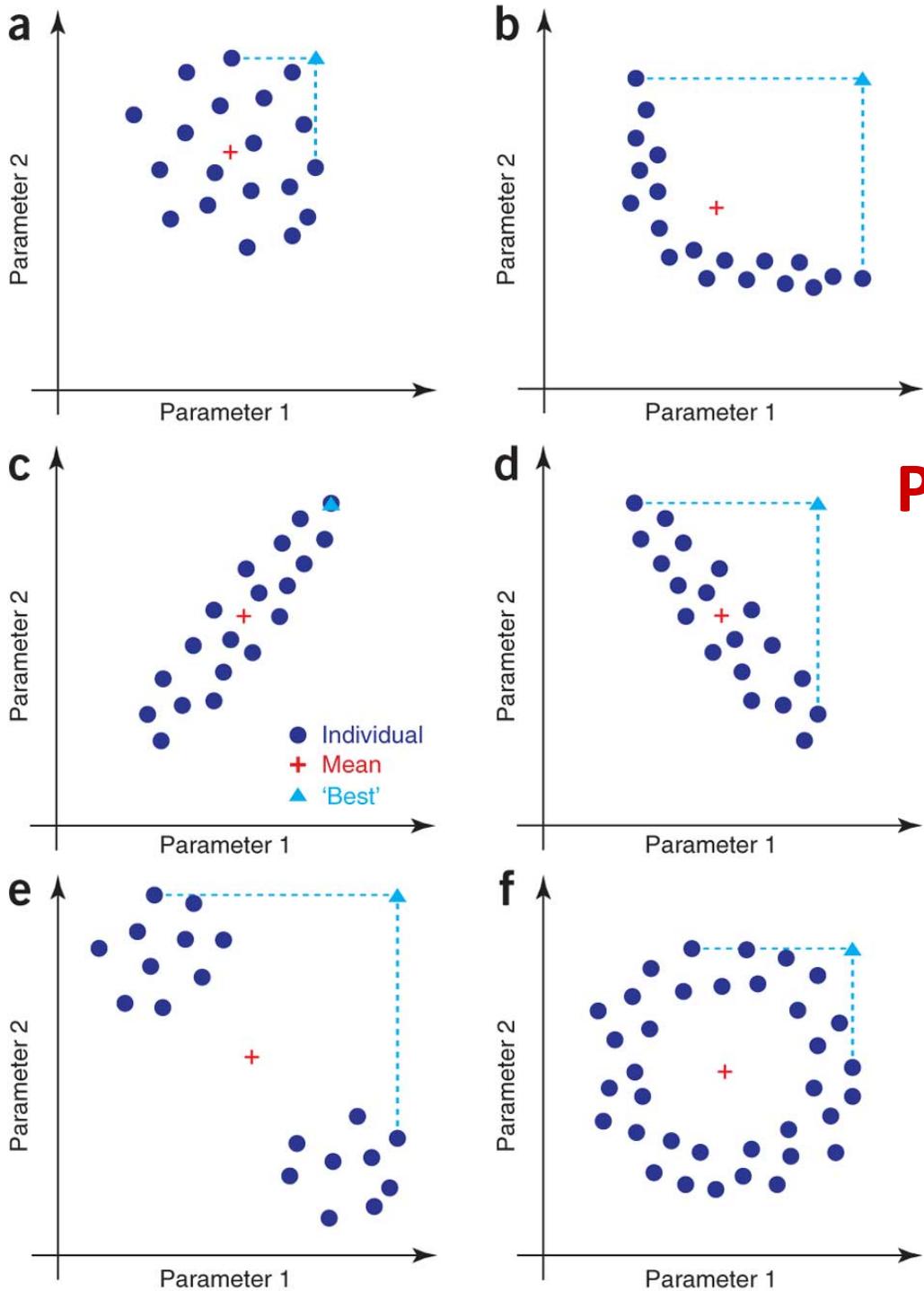
Julijana Gjorgjieva¹, Guillaume Drion^{1,2} and Eve Marder¹

Current Opinion in Neurobiology 2016, 37:44–52

Notice the error bars!

A-type potassium channels



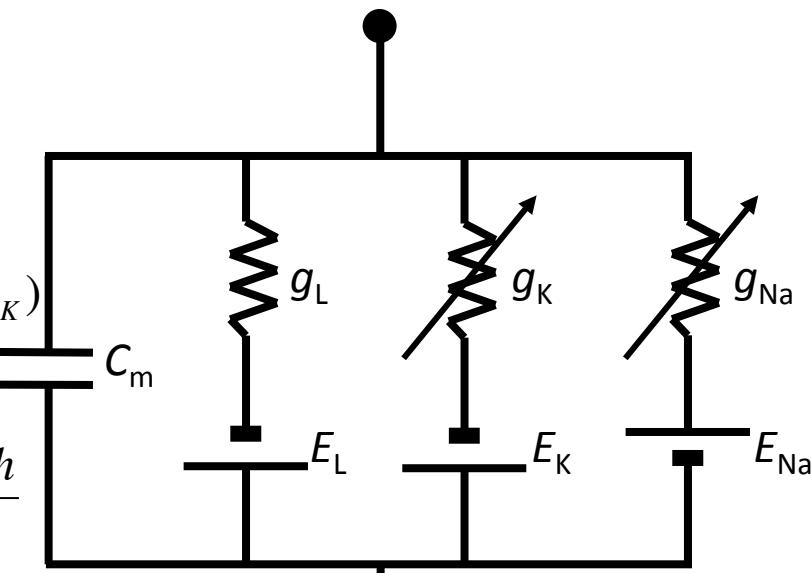


Problems with using mean or best values of the measured parameters!

The HH parallel-conductance model parameters

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K)$$

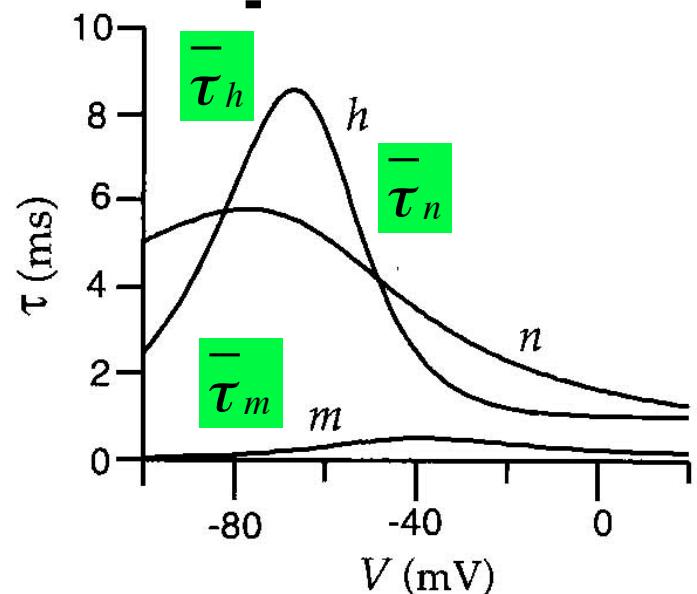
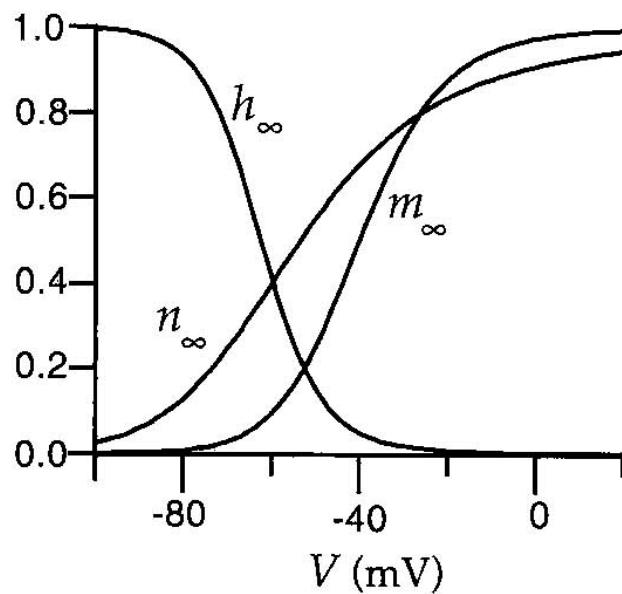
$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad \frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \quad \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$



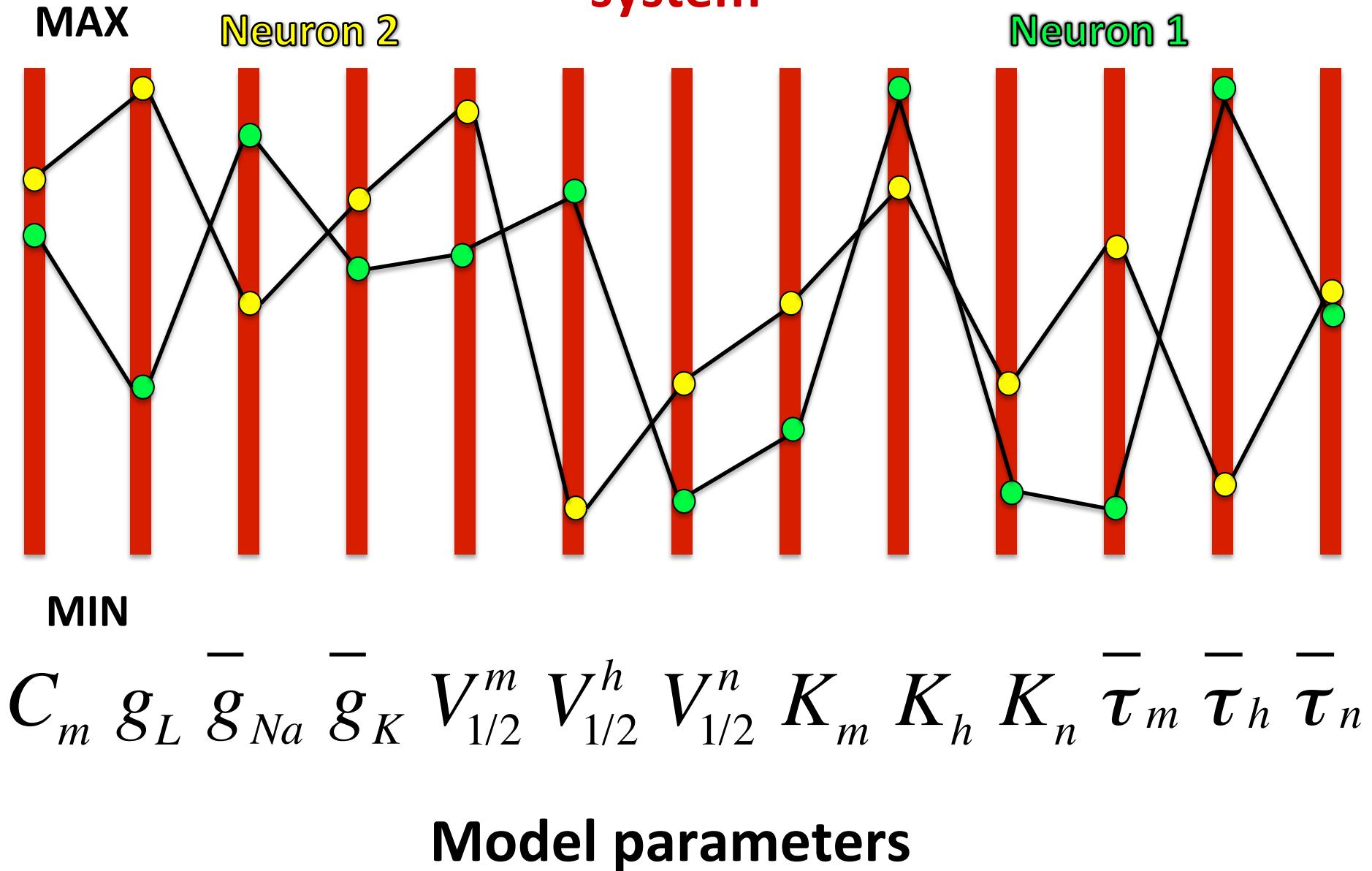
$$m_\infty(V) = \left(1 + \exp\left(\frac{V_{1/2}^m - V}{K_m}\right)\right)^{-1}$$

$$n_\infty(V) = \left(1 + \exp\left(\frac{V_{1/2}^n - V}{K_n}\right)\right)^{-1}$$

$$h_\infty(V) = \left(1 + \exp\left(\frac{V_{1/2}^h - V}{K_h}\right)\right)^{-1}$$



Global sensitivity analysis: Illustration with the HH system

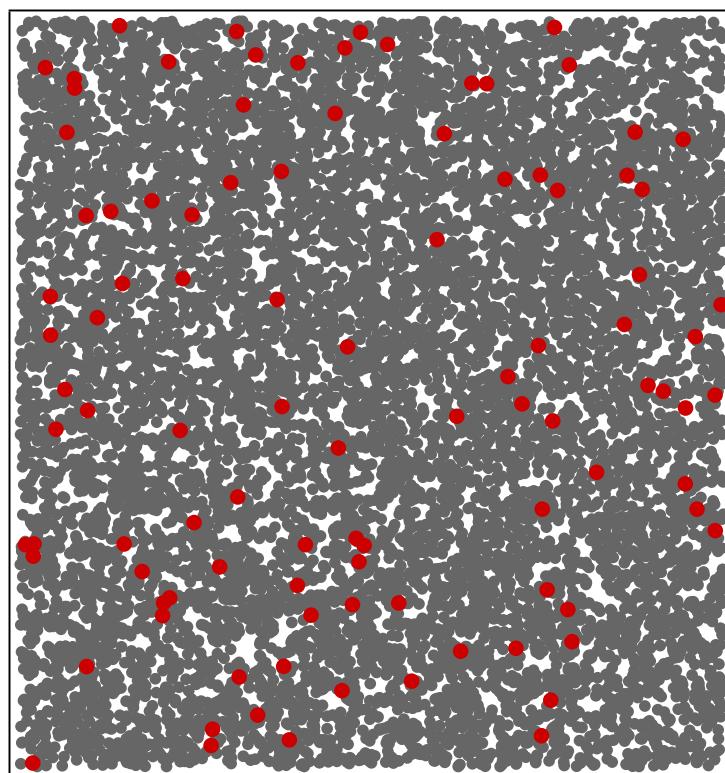


Global sensitivity analysis: Illustration with the HH system

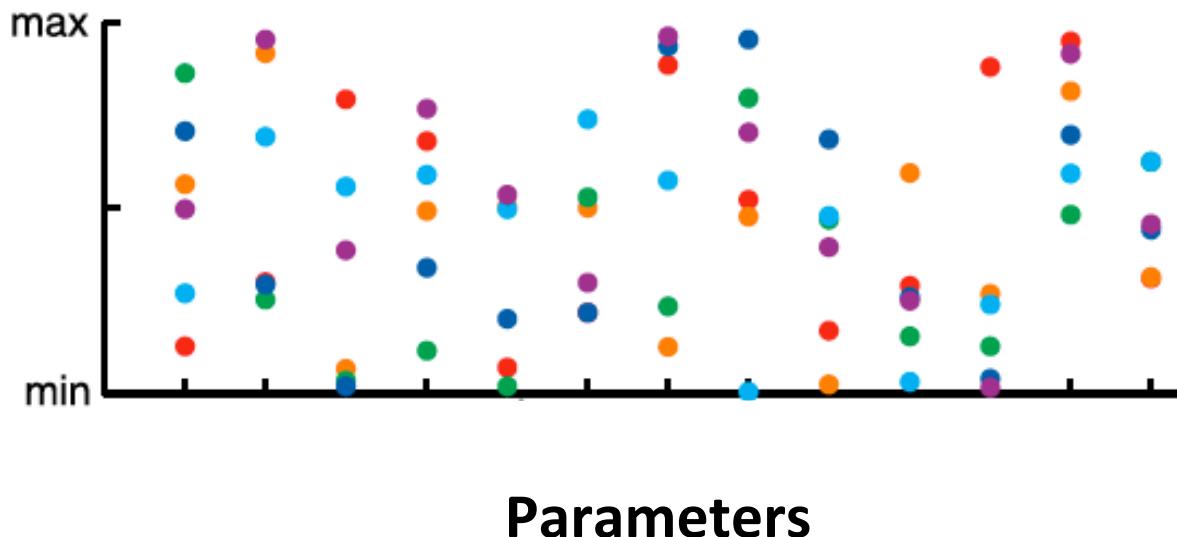
Generate N such models by sampling these parameters

Obtain measurements from them, and apply bounds on these measurements (e.g., Input resistance, firing rate, AP amplitude, etc.) from corresponding experiments

You will find a very small percentage of these N models matching these constraints: Valid models

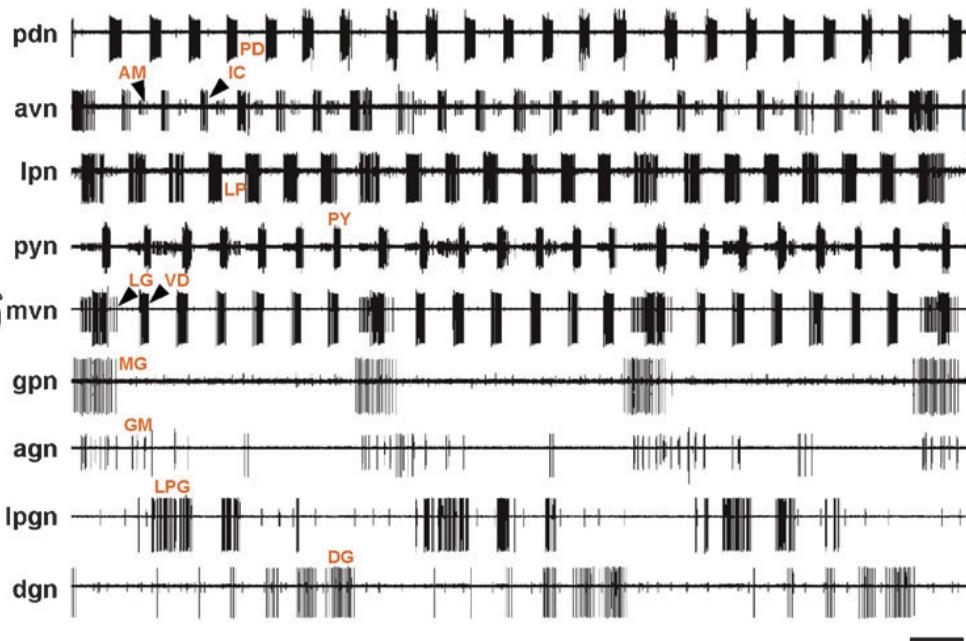
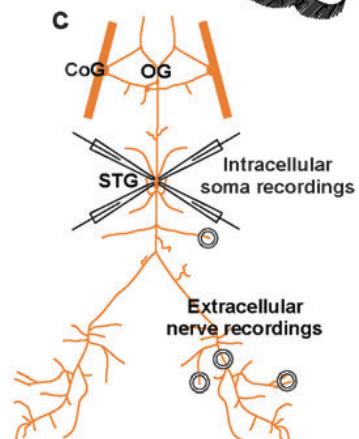
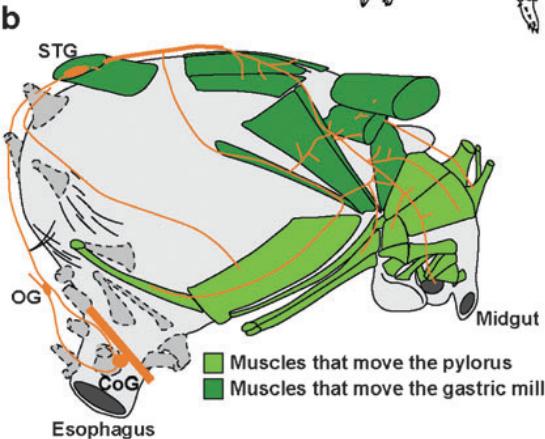
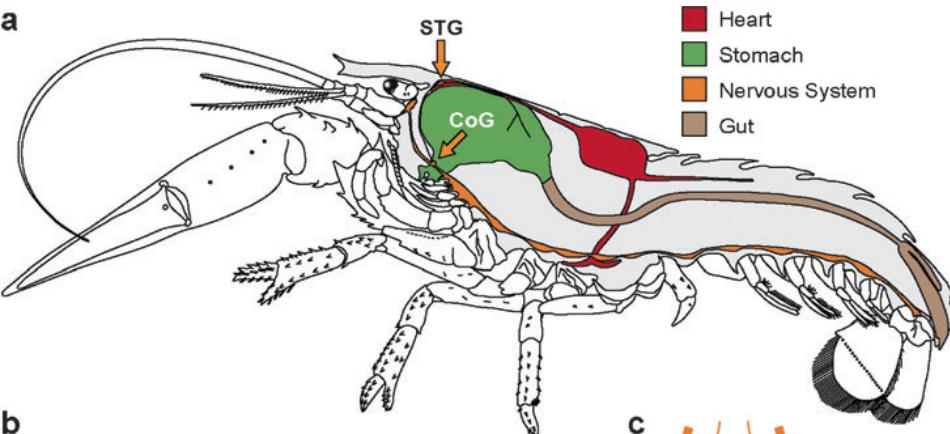


Analyzing the valid model parameters will reveal that you could obtain them with several non-unique channel combinations



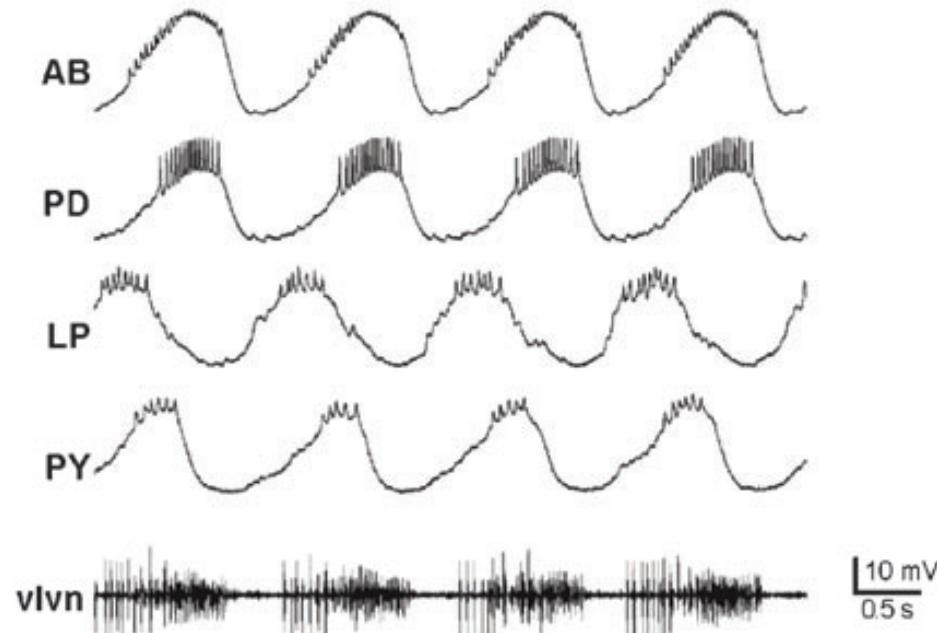
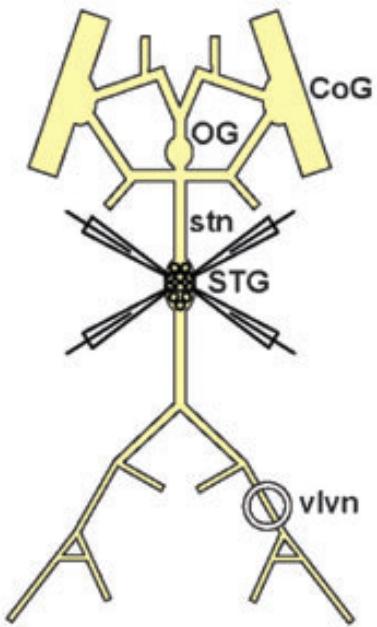
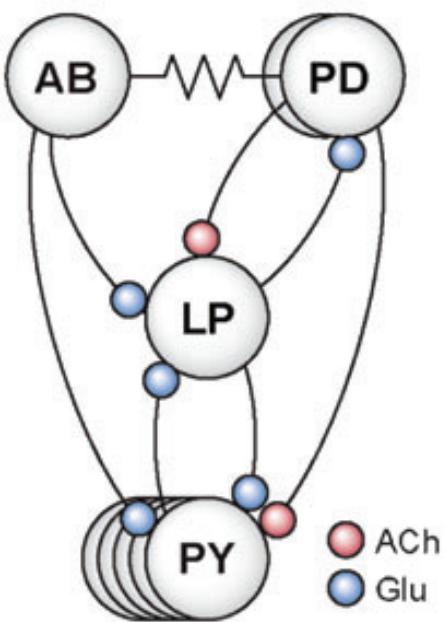
The pyloric rhythm in the crab

Pyloric: relating to or affecting the region where the stomach opens into the duodenum (small intestine)

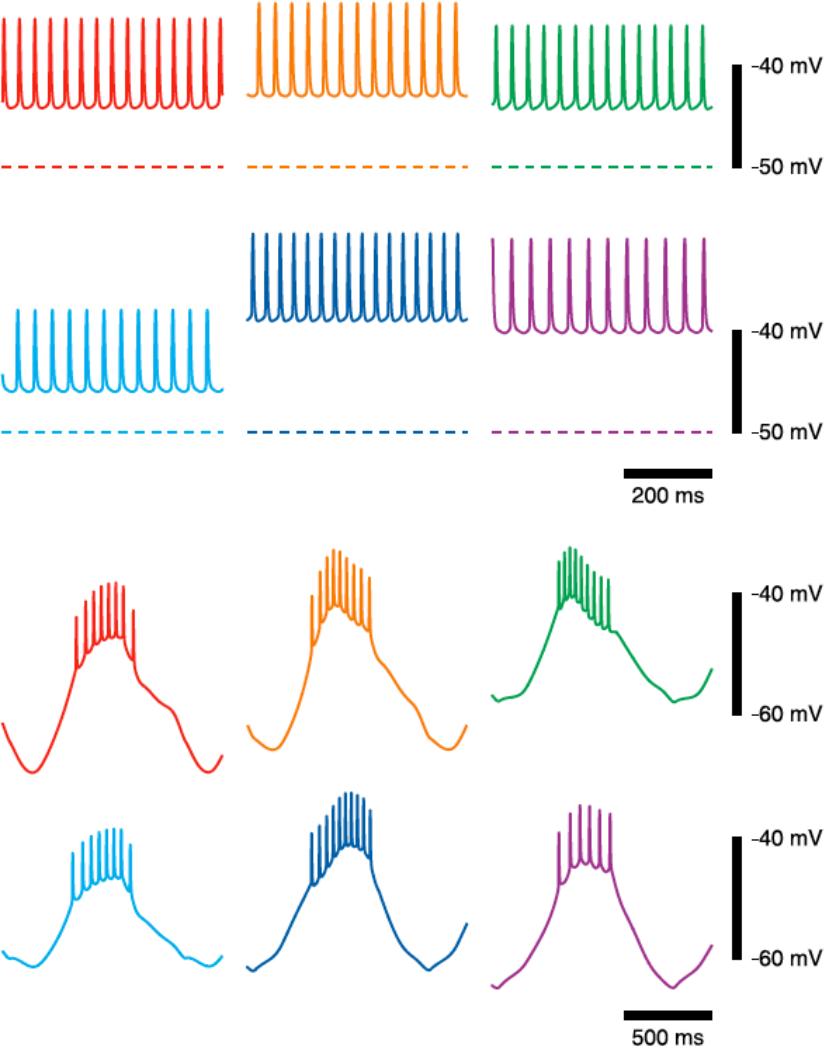


STG: Stomatogastric Ganglion

The pyloric rhythm in the crab

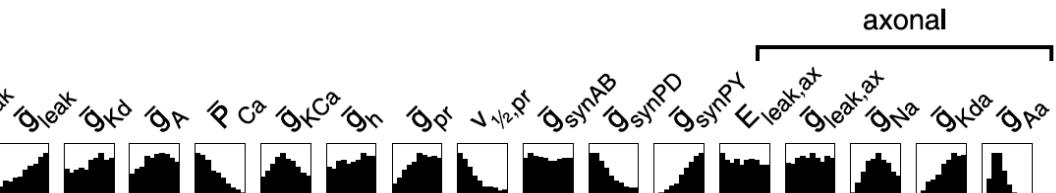
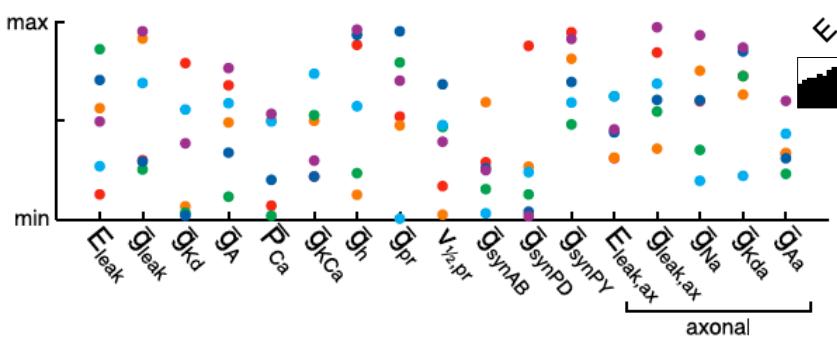


Degeneracy in a four-compartment model of the LP neuron



Parameters exhibited weak pairwise correlations

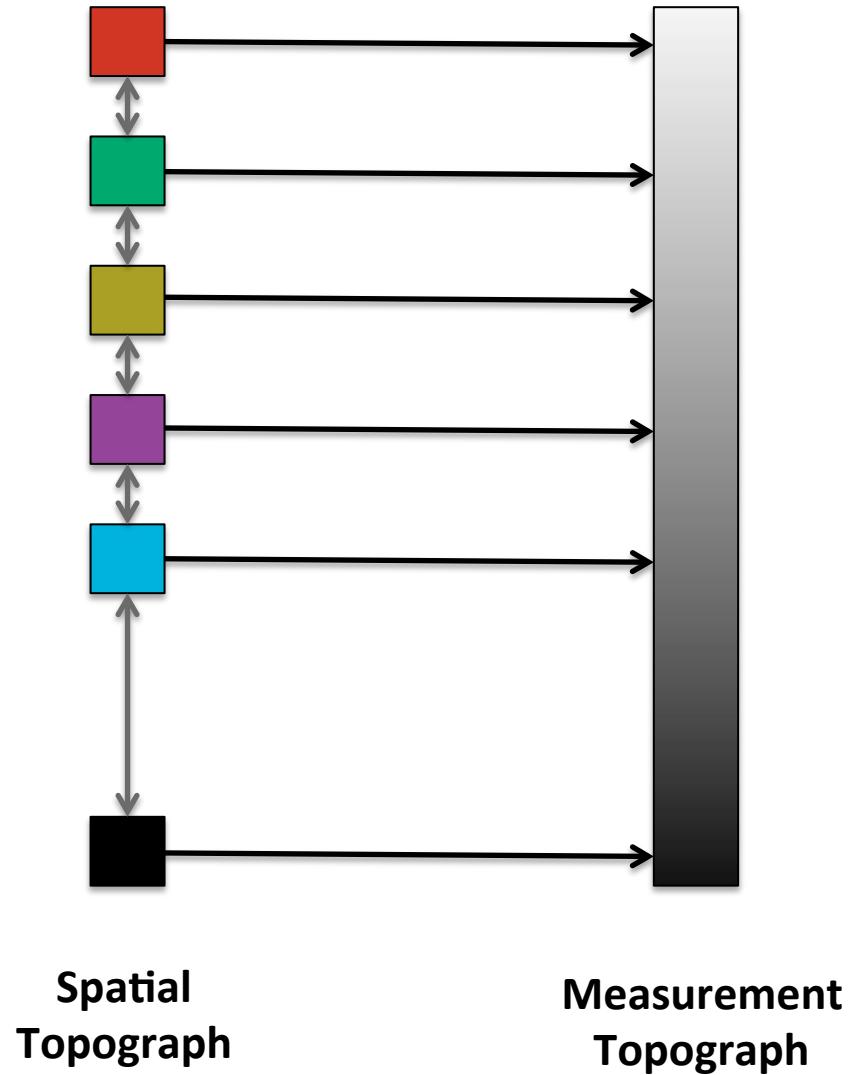
See reviews and papers from Eve Marder's lab for several lines of experimental evidence



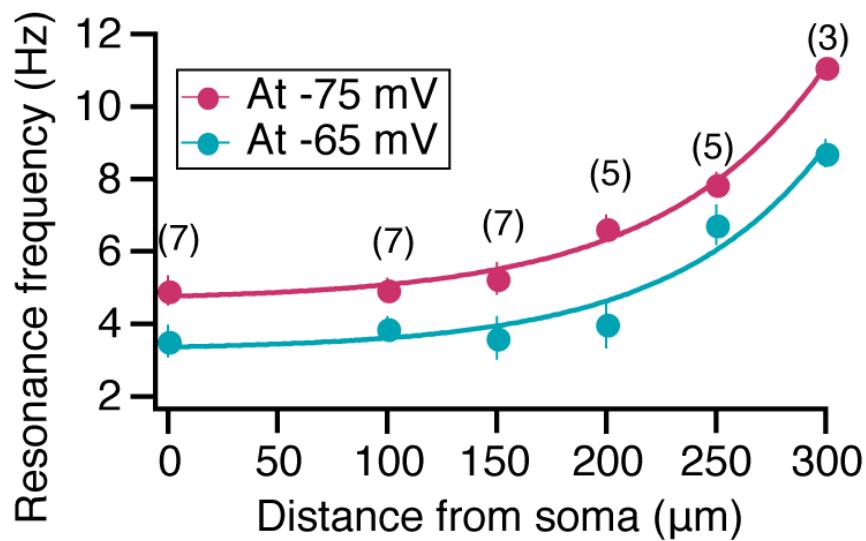
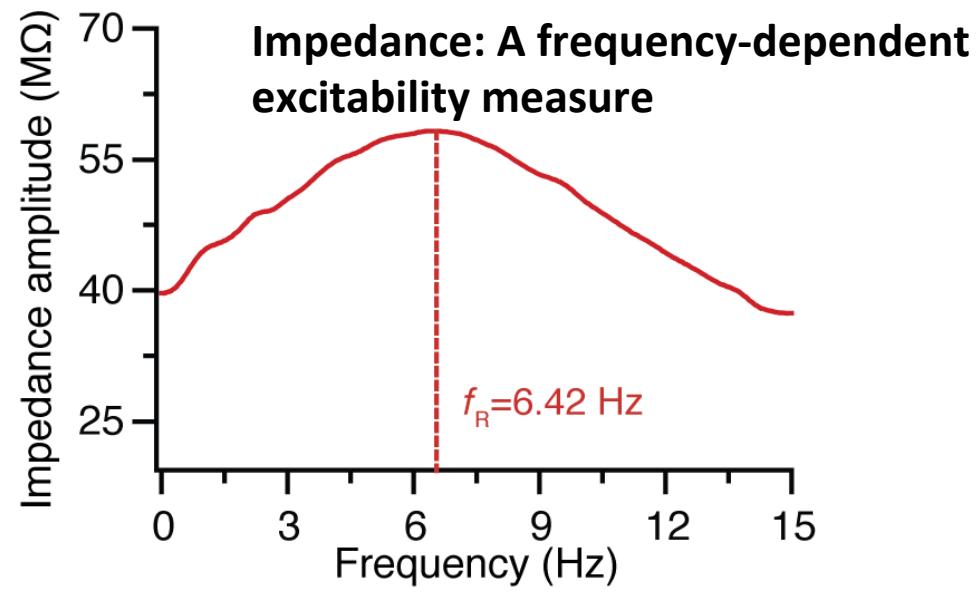
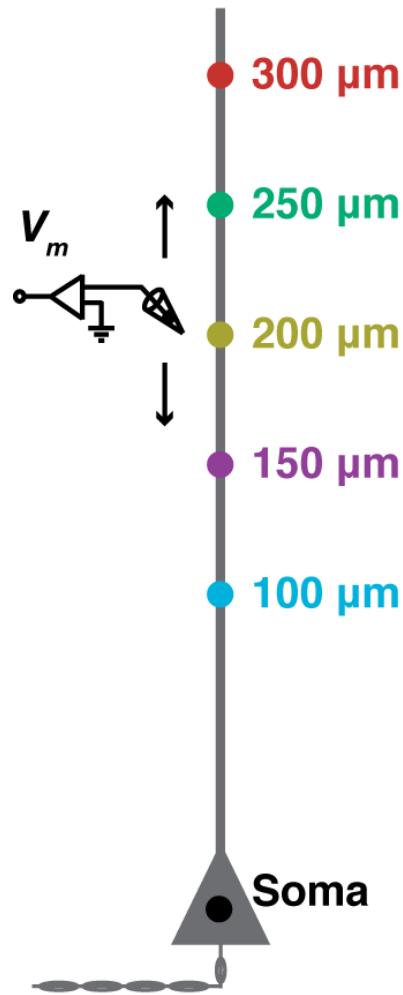
Taylor et al, J Neuroscience, 2009

Degeneracy in somato-dendritic functional maps

Several functional *maps* express within a hippocampal neuron: What is a map?

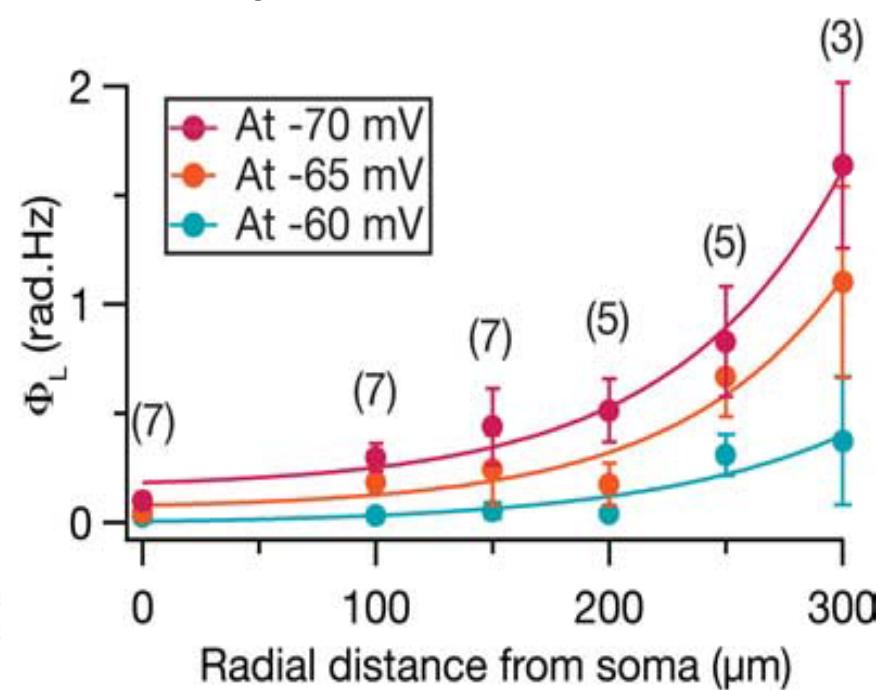
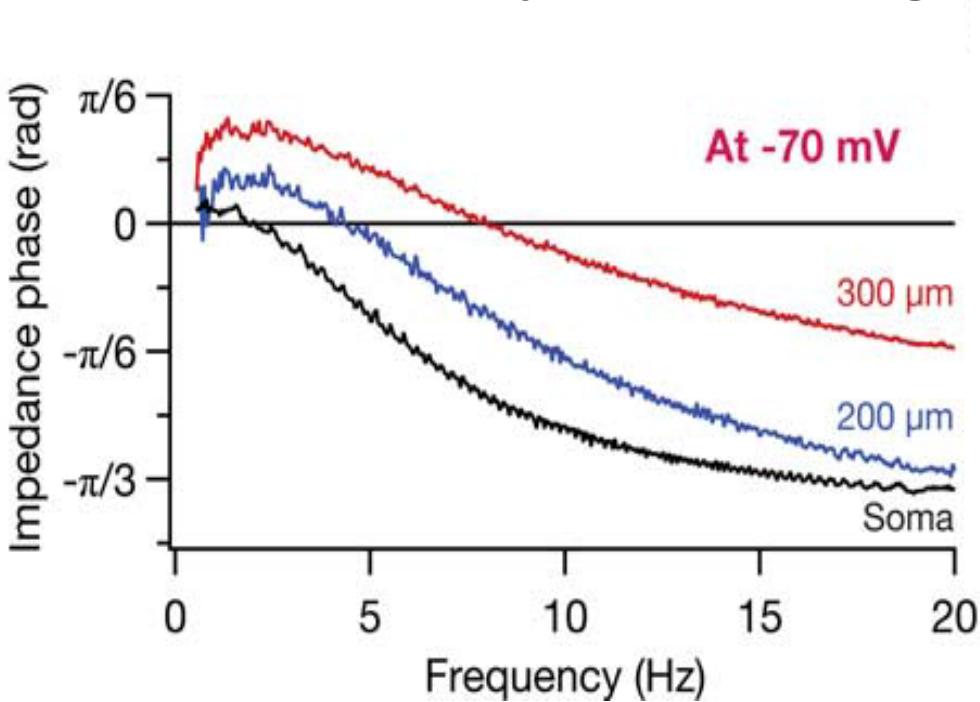


Several functional *maps* express within a single hippocampal neuron: Resonance frequency



Several functional maps express within a single hippocampal neuron: Inductive phase lead

Impedance: A frequency-dependent excitability measure, that also provides timing relationships!

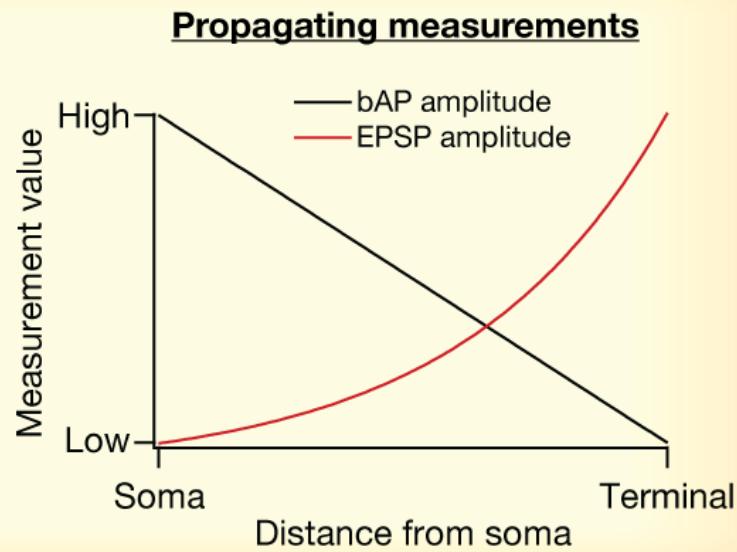
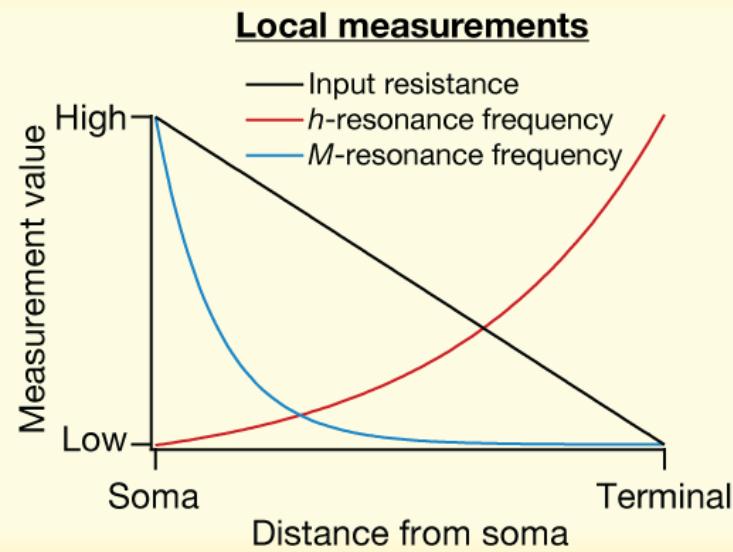
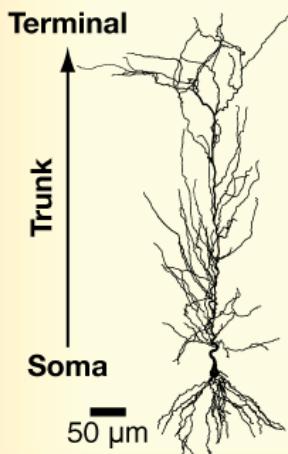


Several functional *maps* express within a single hippocampal neuron

J Neurophysiol 108: 2343–2351, 2012.
First published August 29, 2012; doi:10.1152/jn.00530.2012.

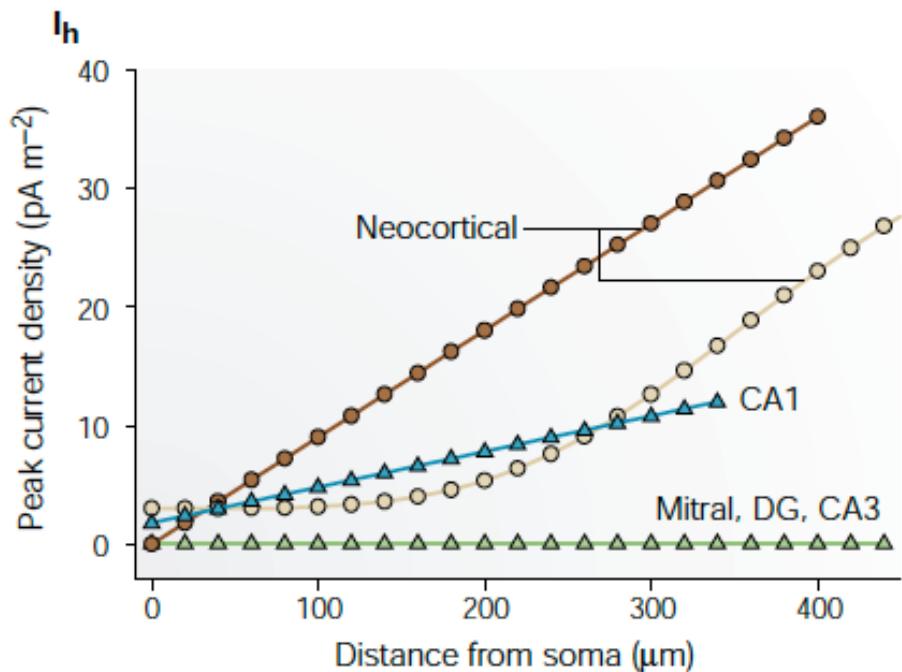
Functional maps within a single neuron

Rishikesh Narayanan¹ and Daniel Johnston²

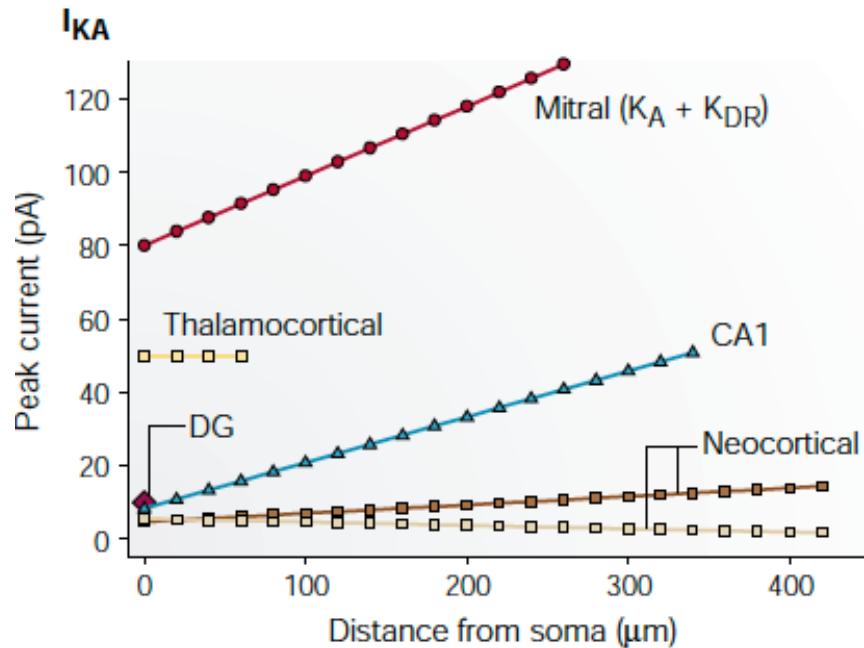


Channel/Receptor gradients actively mediate/ regulate intraneuronal functional maps

Resonance frequency map

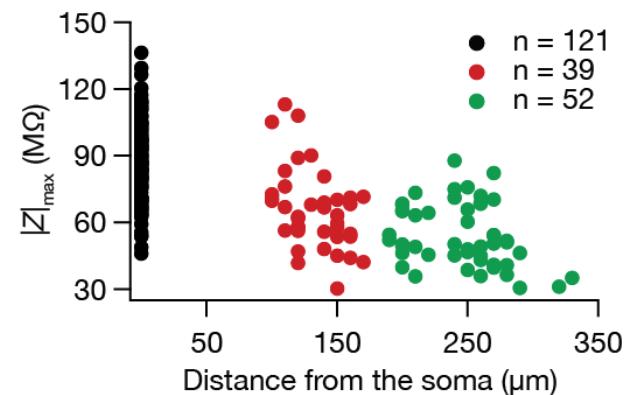
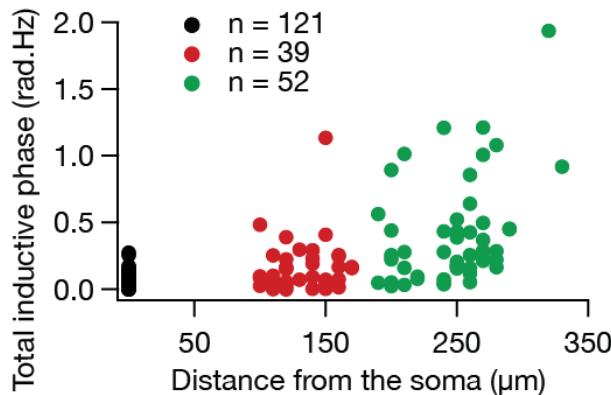
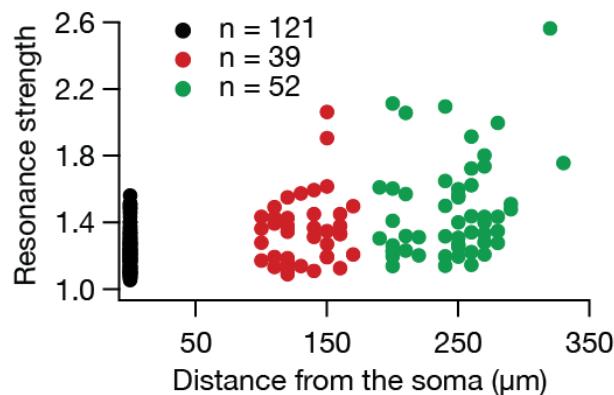
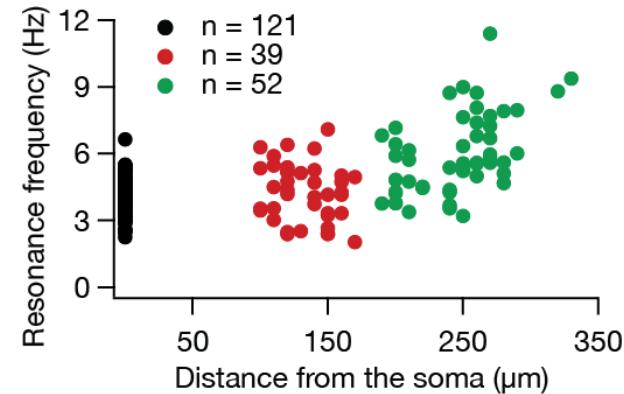
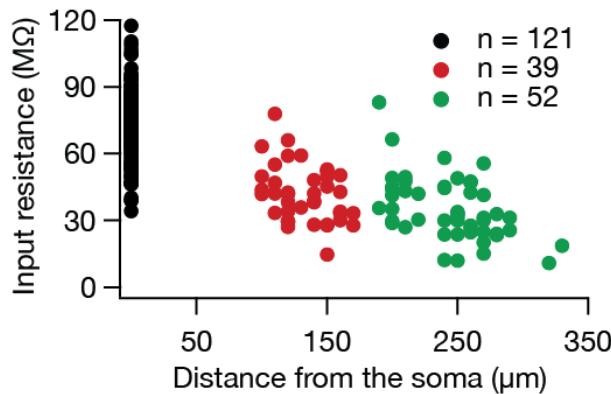
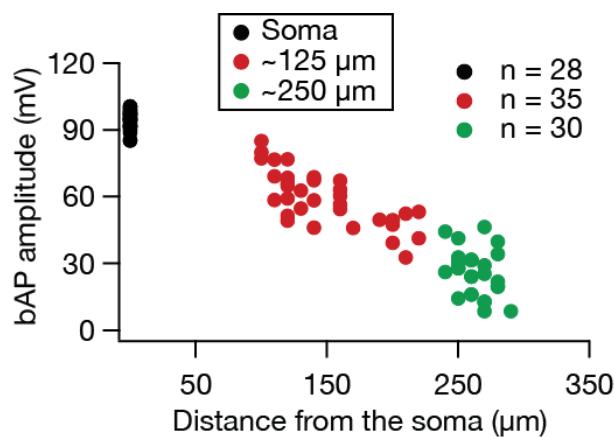


Backpropagating action potential
(bAP) map



Blocking HCN or KA channels respectively abolishes the expression
of the resonance frequency map and the bAP map

Experimental data on six different functional maps and their variability

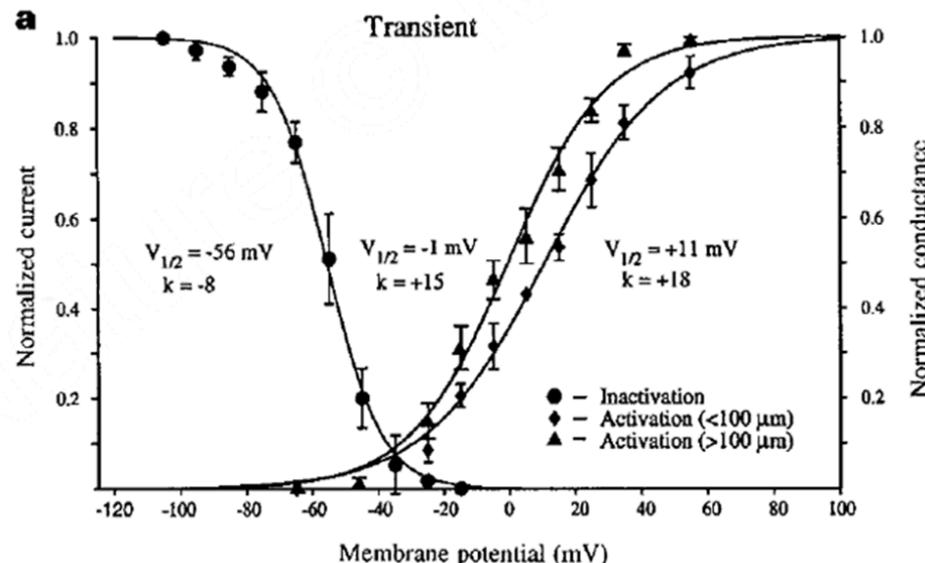
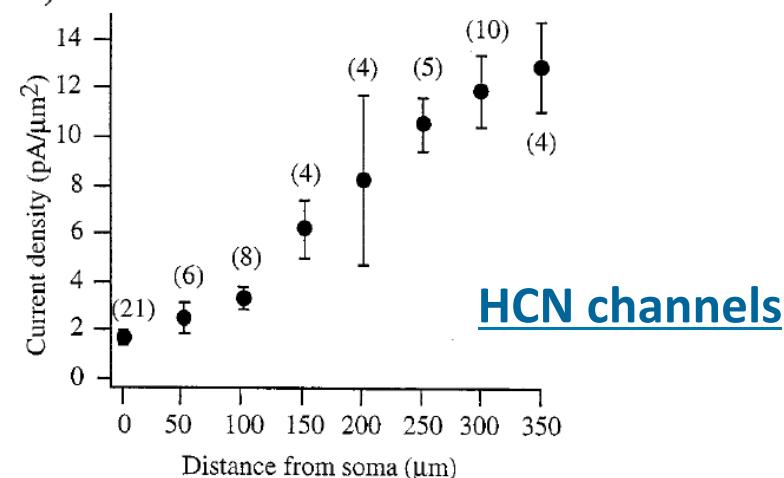
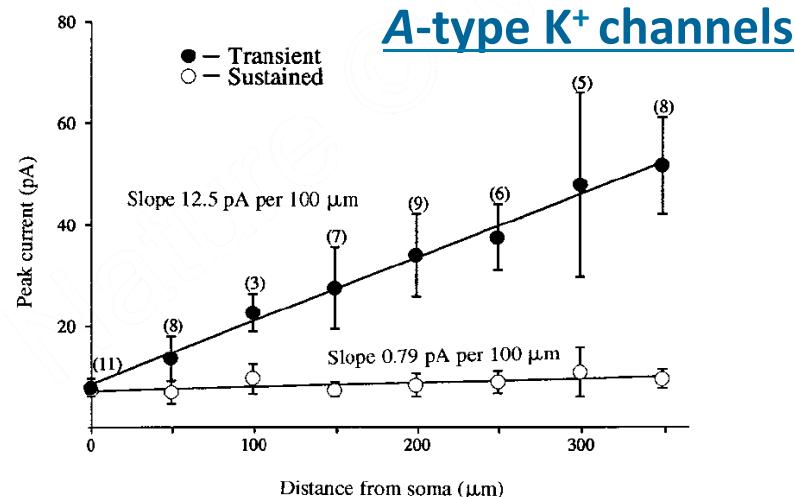


Experimental data from:

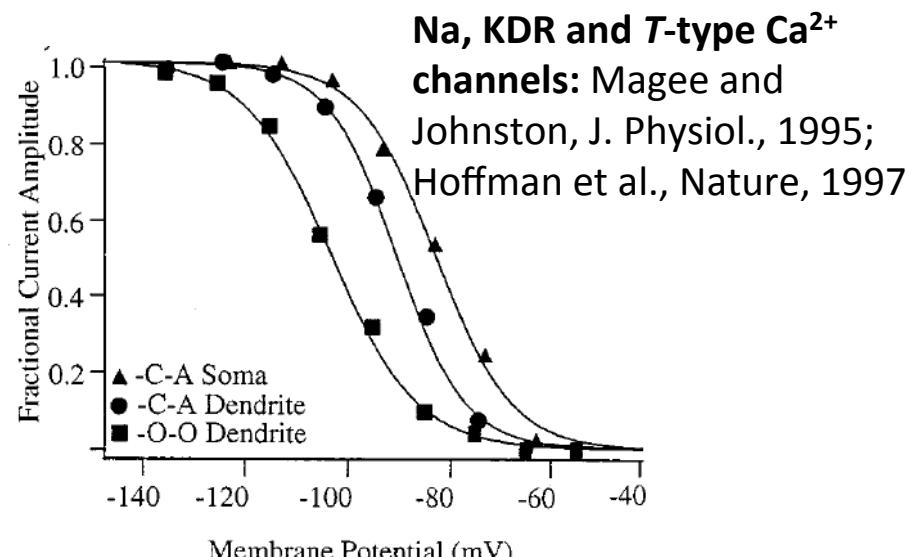
Narayanan and Johnston, Neuron, 2007;

Narayanan and Johnston, J. Neurosci., 2008; Narayanan et al., Neuron, 2010

Experimental data on ion channel densities, their gradients and variability there



Hoffman et al., Nature., 1997



Magee, J. Neurosci., 1998

Homeostasis of functional maps: Questions

How do these functional maps maintain homeostasis in the face of variability in underlying ion channel gradients?

Is it required that individual channels are maintained at specific densities to achieve robust *coexpression* of all these functional maps?

Does the requirement for these maps to express on the same structure impose specific constraints on channel-localization profiles?

What channel localization and targeting strategy should a neuron follow towards maintenance of these functional maps?

Global Sensitivity Analysis: Model Generation

Impose experimental variability on underlying parameters and generate a large set of models

The numbers:

5 ion channels (Na^+ , KDR, *T*-type Ca^{2+} , *A*-type K^+ , HCN)

6 functional maps along the somatoapical trunk (R_{in} , f_R , Q , bAP amplitude, $|Z|_{\text{max}}$, Φ_L)

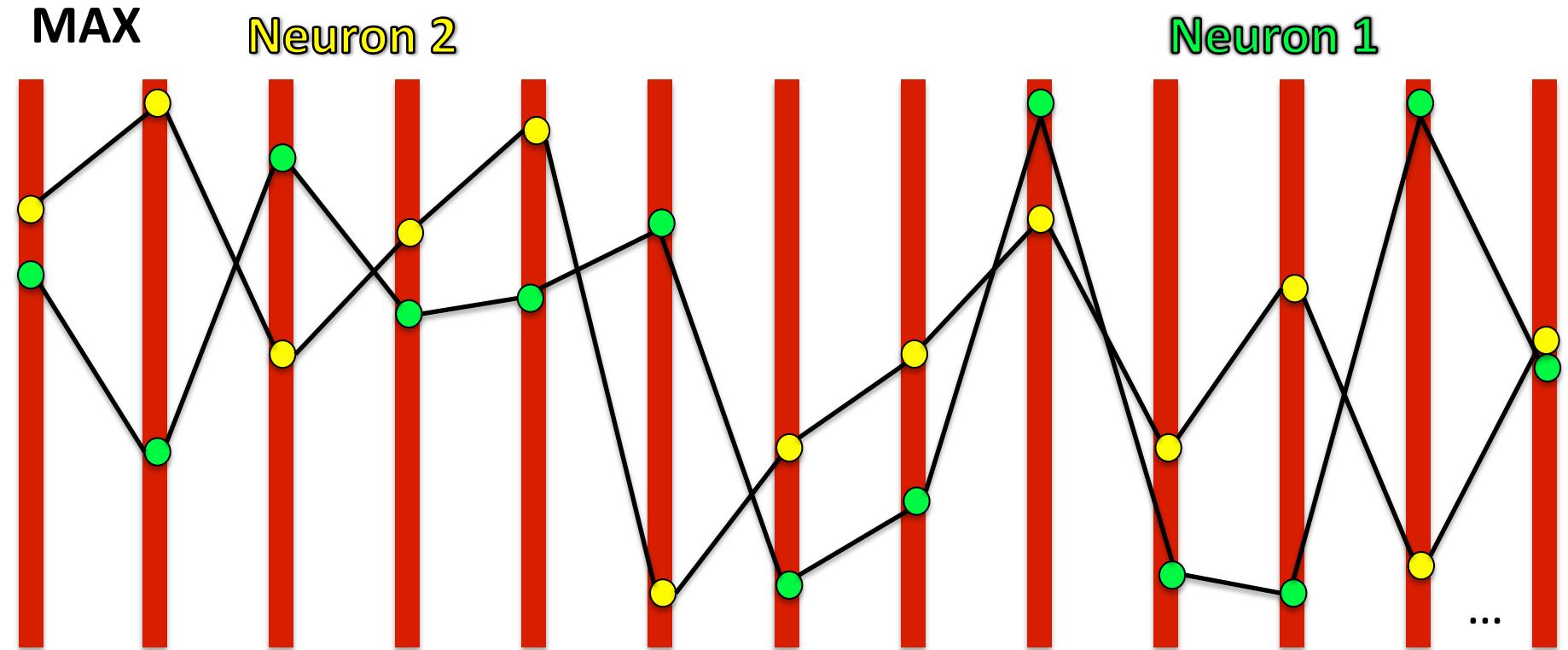
11 differential equations per compartment

750–950 compartments per neuron

32 parameter global sensitivity analysis (governing density, distribution, kinetics and voltage-dependence of the channels and associated passive properties)

20420 total models generated through uniform sampling of each of these 32 underlying parameters

Global Sensitivity Analysis: Random Sampling



C_m g_L g_{Na} g_K $V_{1/2}^m$ $V_{1/2}^h$ $V_{1/2}^n$ K_m K_h K_n τ_m τ_h ... τ_n

See Goldman et al., J. Neuroscience, 2001 and reviews by Eve Marder

Global Sensitivity Analysis: Model Validation

Assess validity of these models by comparing their maps with experimental counterparts

The numbers

18 different measurements employed to impose constraints to assess validity.

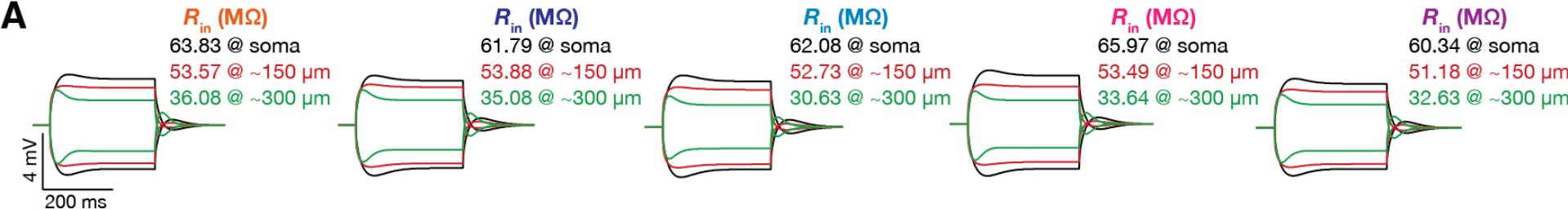
~80% of individual experimental variability covered by these bounds

Measurement	Soma		$\sim 150 \text{ }\mu\text{m}$		$\sim 300 \text{ }\mu\text{m}$	
	Lower	Upper	Lower	Upper	Lower	Upper
bAP Amplitude (mV)	90	105	40	70	10	25
Input resistance, R_{in} , ($M\Omega$)	45	90	30	55	10	50
Resonance frequency, f_R , (Hz)	2	5.5	3	6.5	5	11
Resonance strength, Q	1.01	1.5	1.01	1.9	1.2	2.6
Total inductive phase, Φ_L , (rad Hz)	0	0.15	0	0.3	0.15	2
Maximum impedance amplitude, $ Z _{max}$, ($M\Omega$)	50	110	35	80	30	70

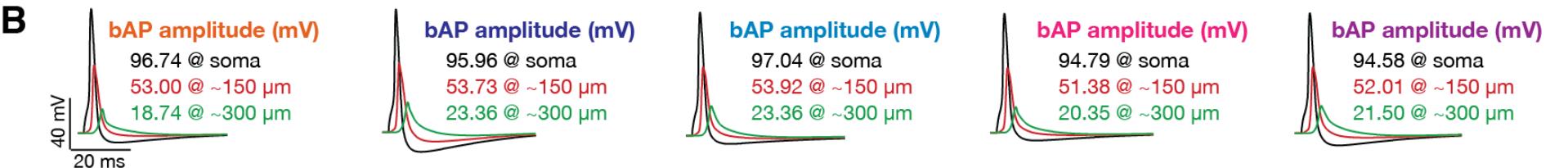
228 valid models (~1% of 20420 models generated)

Let's take 5 valid models and compare their measurements,

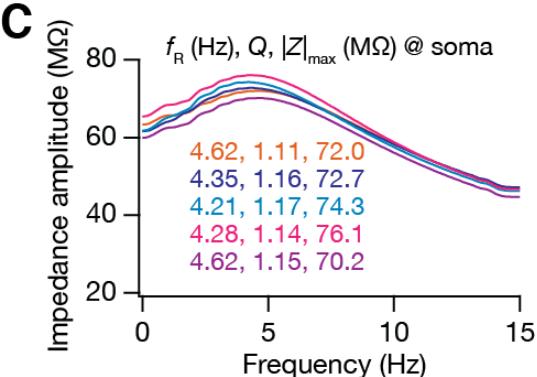
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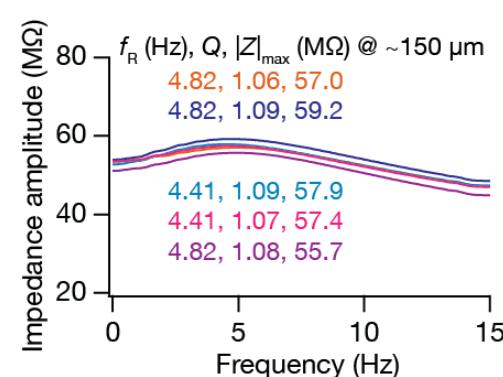
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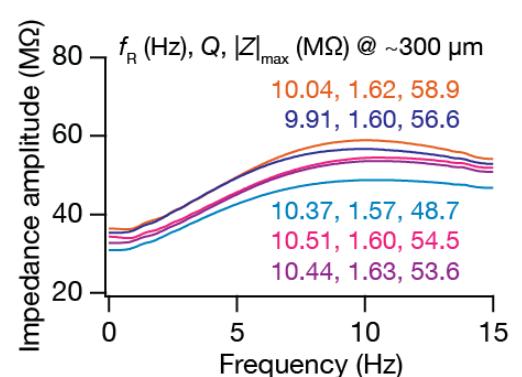
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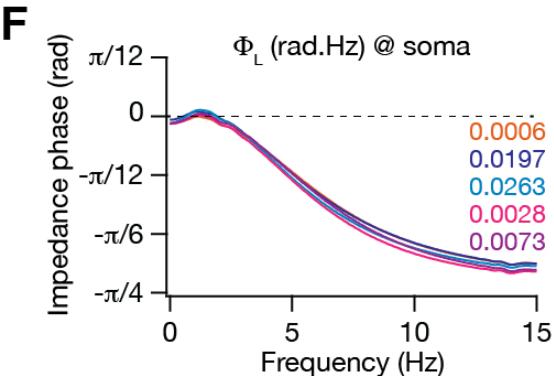
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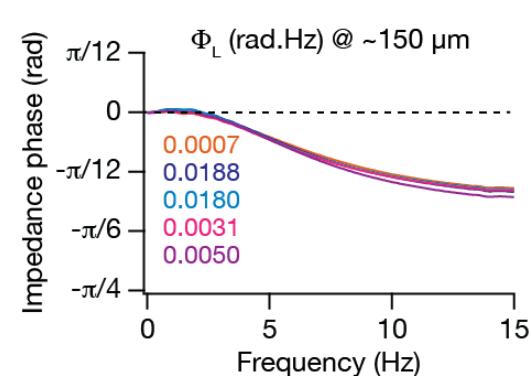
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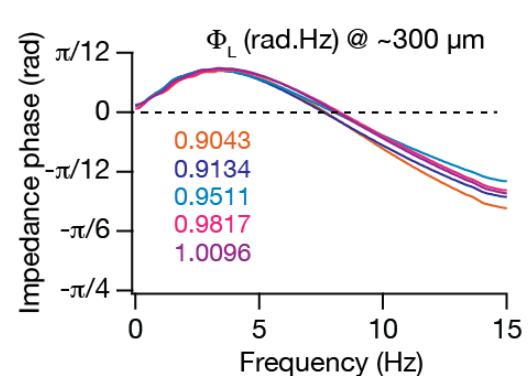
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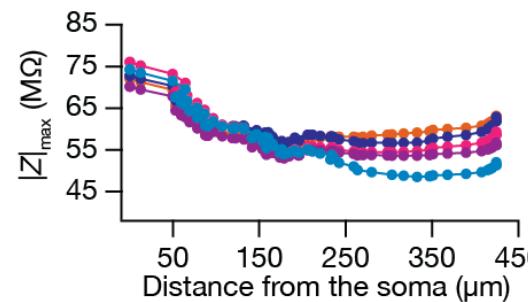
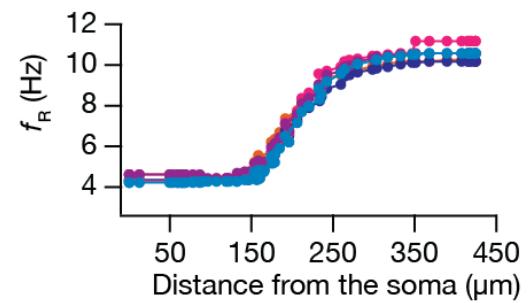
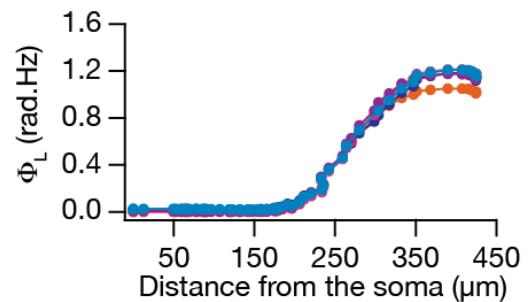
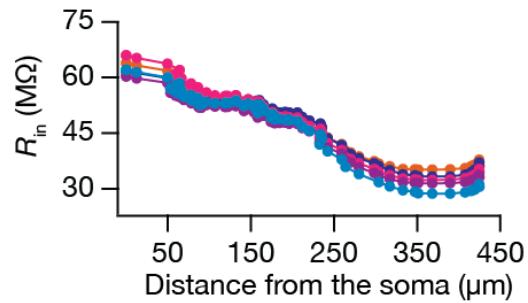
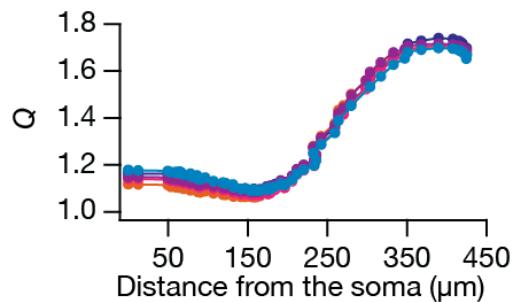
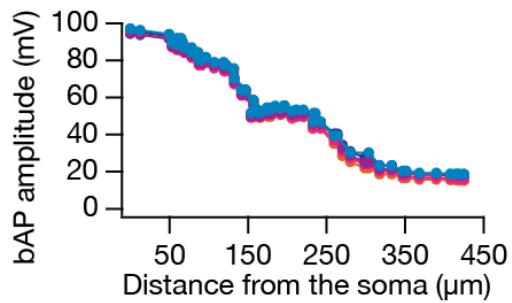
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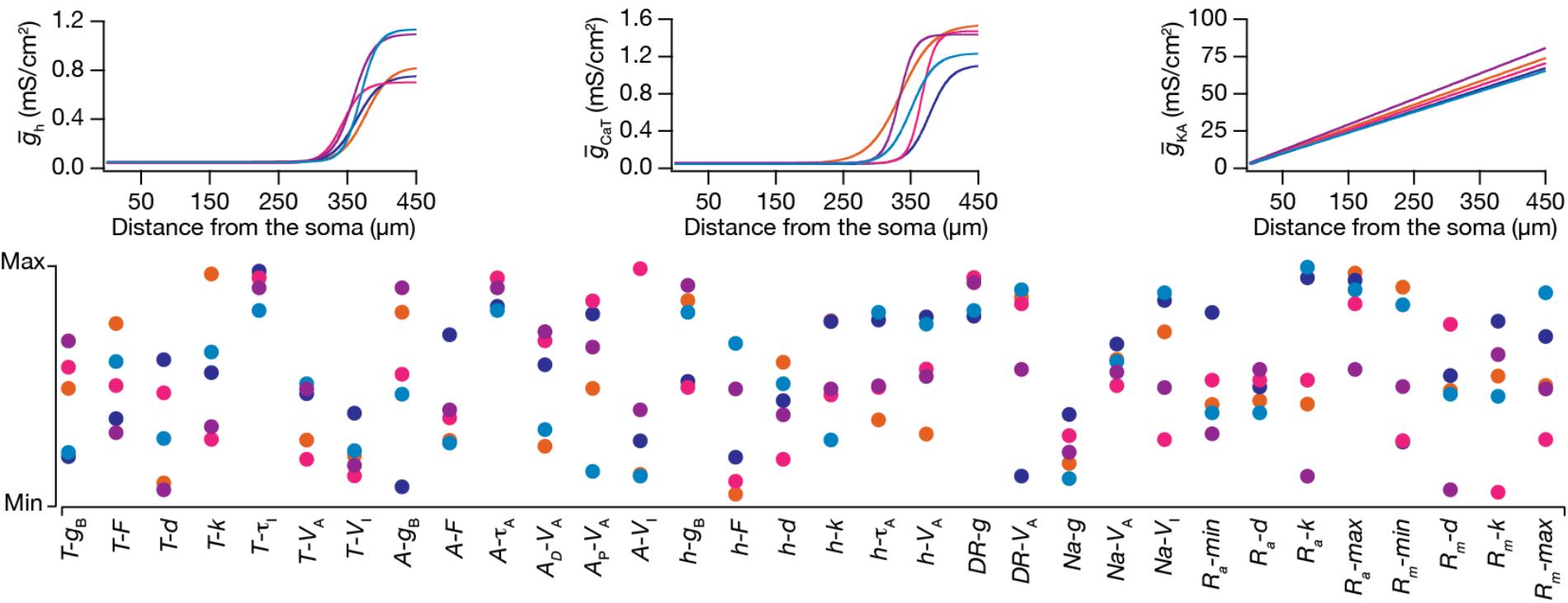
... their maps ...



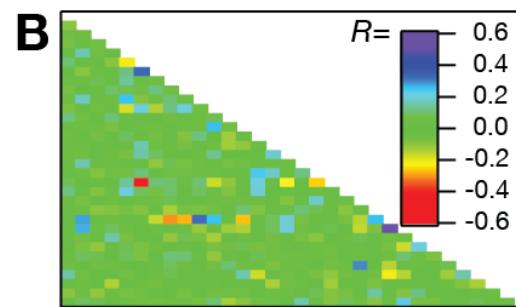
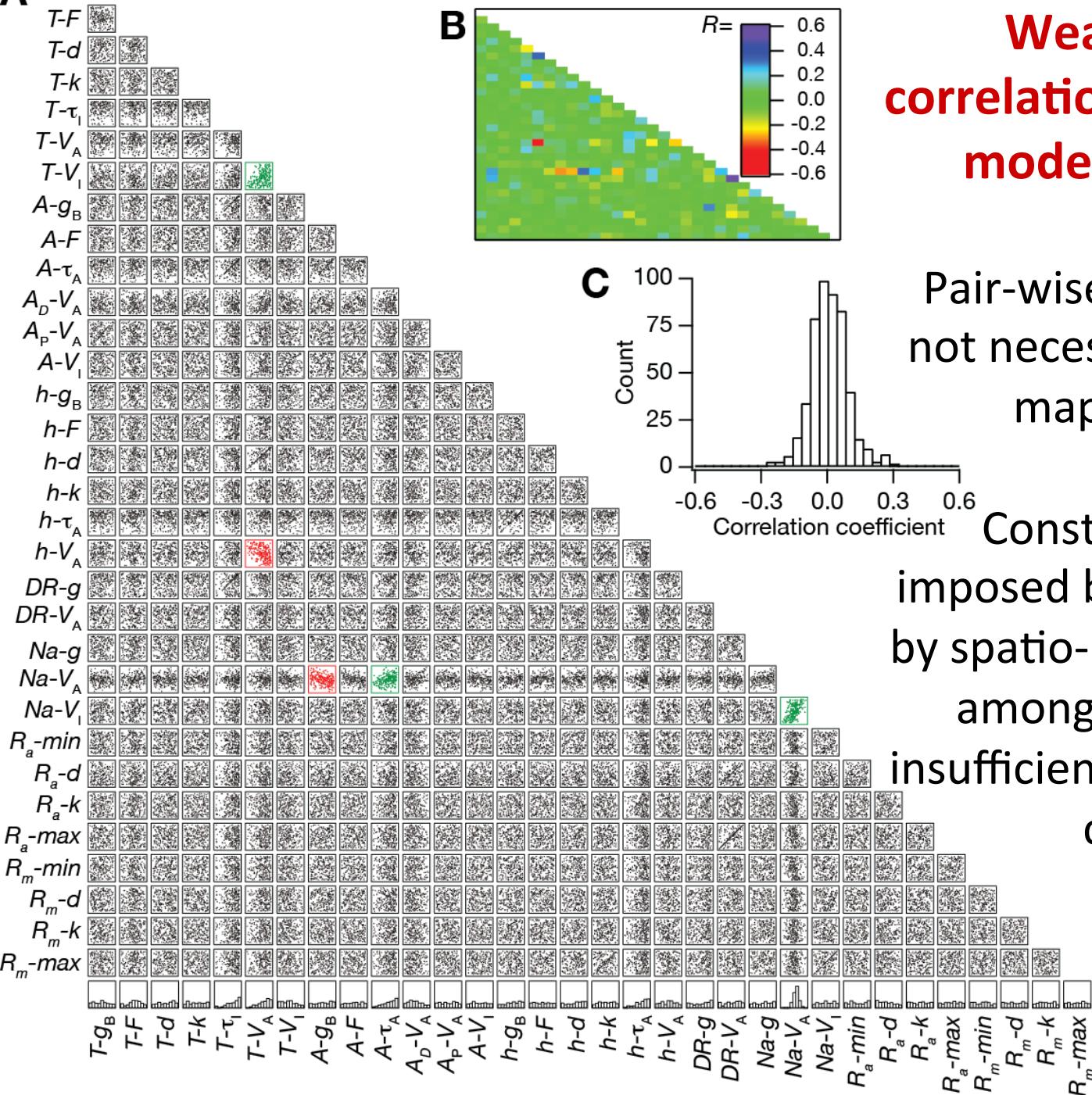
**Maps are continuously constrained across valid models
despite imposing constraints on only three locations**

... and their ion channel gradients

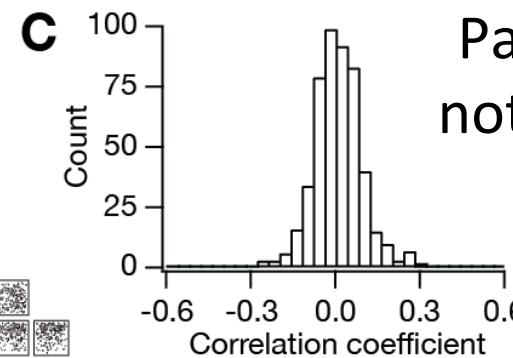
Underlying channel gradients and other parameters were distinct, implying degeneracy in the formation of the coexistent maps



Individual channels need not be maintained at specific conductance values for functional map homeostasis

A

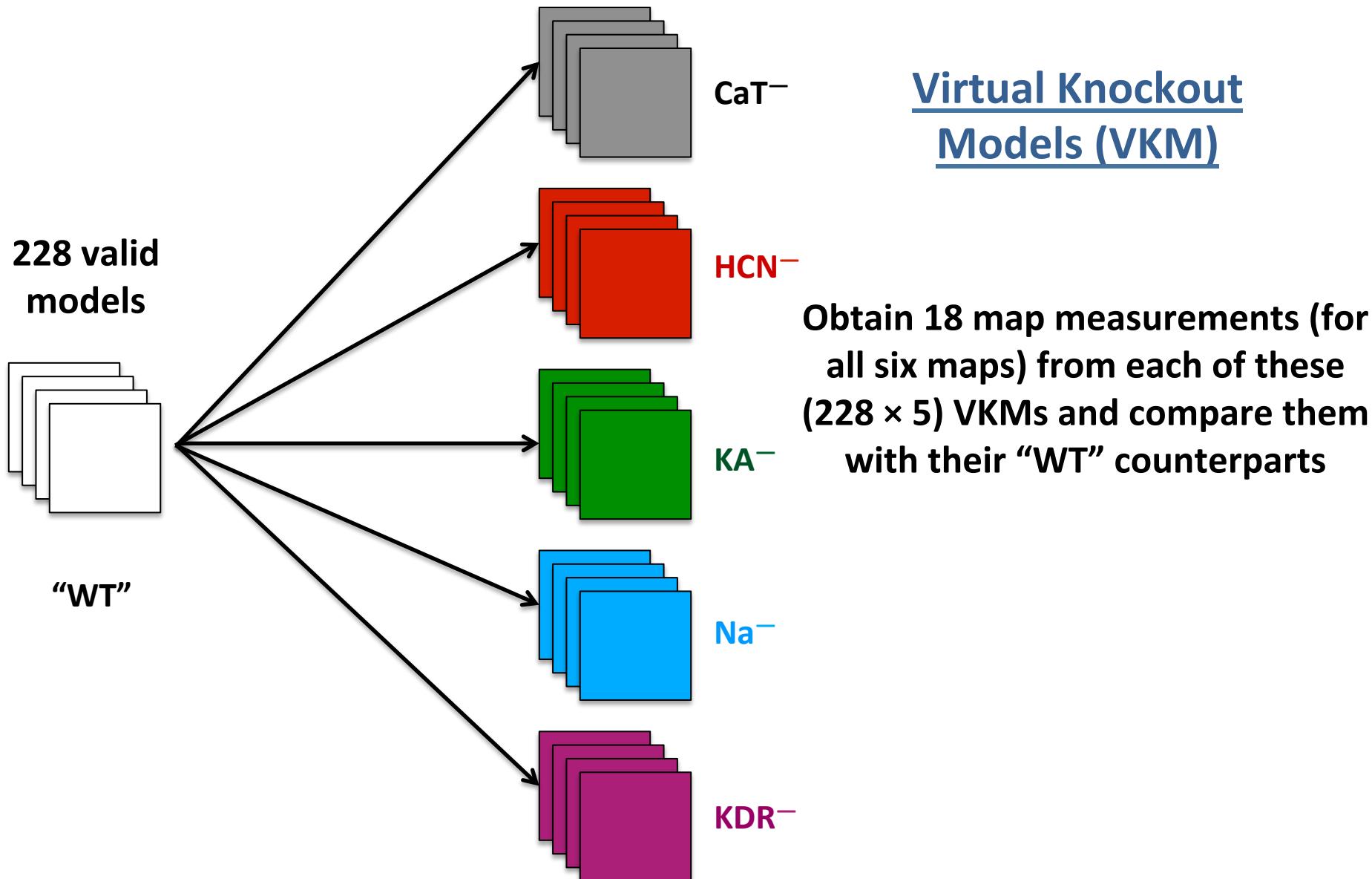
Weak pairwise correlations among valid-model parameters



Pair-wise channelostasis is not necessary for functional map homeostasis

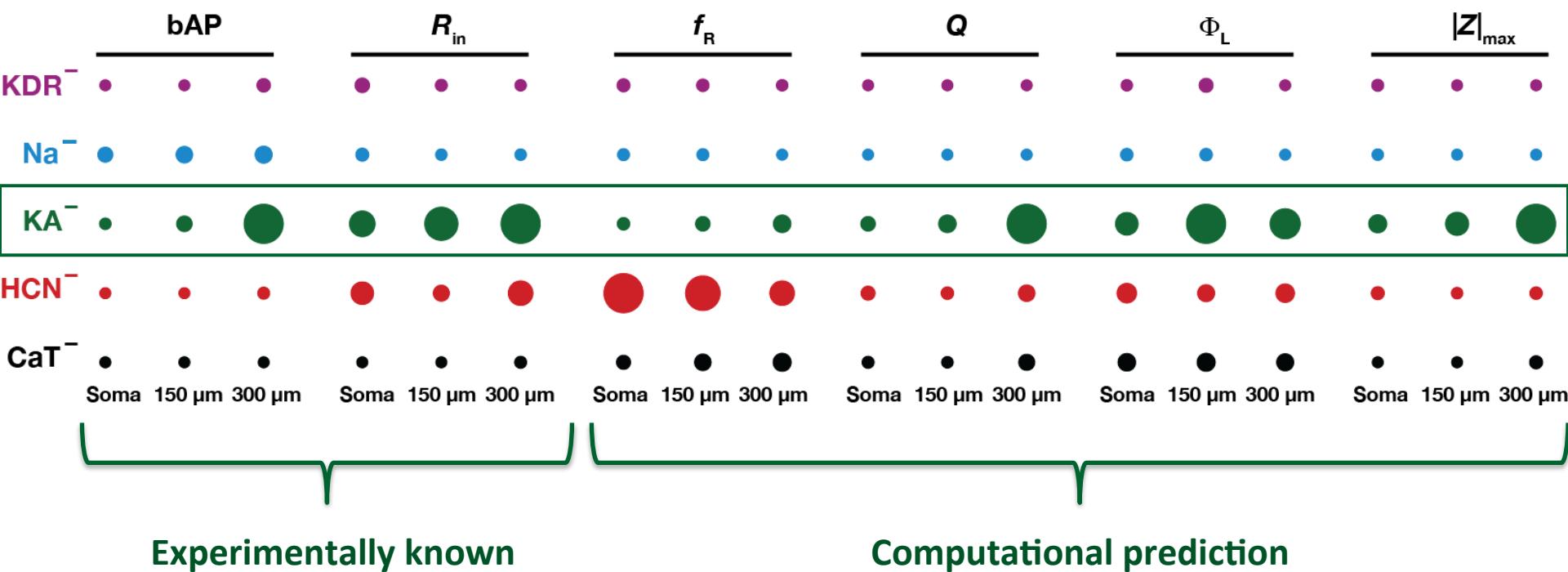
Constraints on the maps imposed by morphology and by spatio-kinetic interactions among ion channels were insufficient to enforce strong correlations among parameters

In this framework of collective channelostasis, how much are individual channels responsible for specific measurements?



Relative dependence of individual measurements on different channels

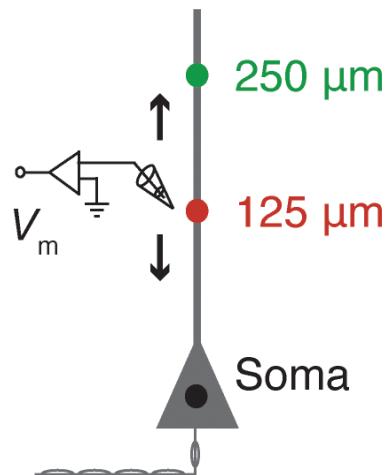
Prediction: Inactivating subthreshold channels are important modulators of impedance-based measurements



Testing the computational prediction electrophysiologically!

Prediction: Blocking A-type K⁺ channels would decrease resonance frequency but increase input resistance across the dendritic tree.

Baseline			In the presence of BaCl ₂ /3,4-DAP		
V-I	F-I	S _α	Chirp stimulus at (mV): -75; -70; -65; -60	Transition period	Chirp stimulus at (mV): -75; -70; -65; -60
<hr/> <p>Perfusion with 200 µM BaCl₂ OR 150 µM 3,4-DAP 35–40 minutes</p> <hr/>					
S _α	F-I	V-I			

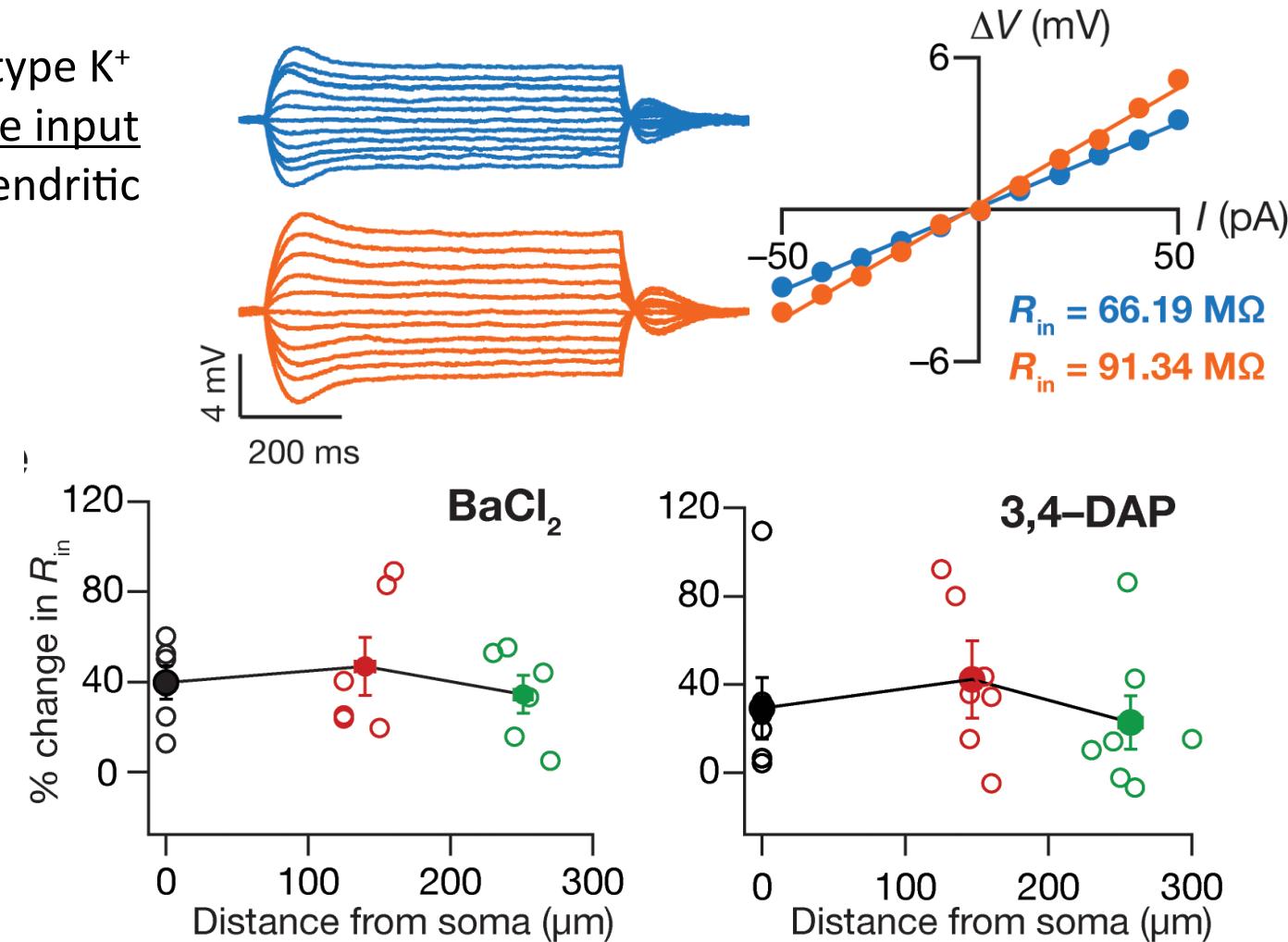
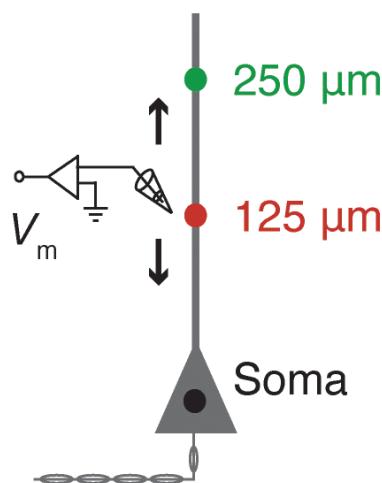


Recordings are from male sprague dawley rats

Recordings spanned up to 300 µm along the somatoapical axis of hippocampal pyramidal neurons

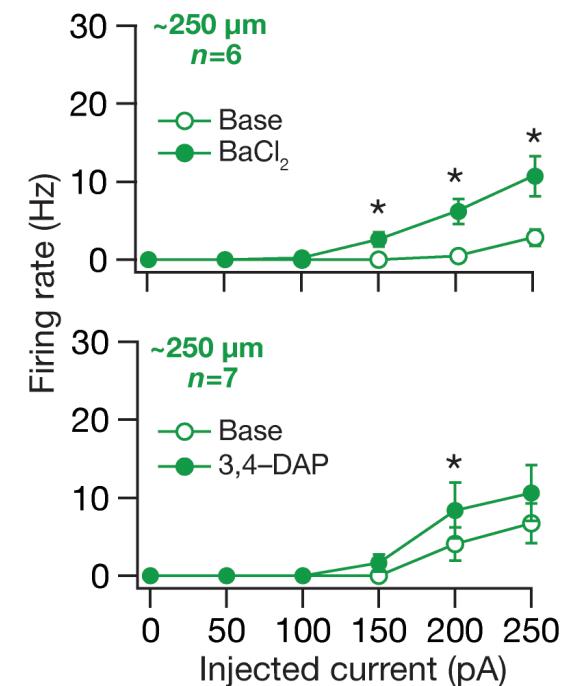
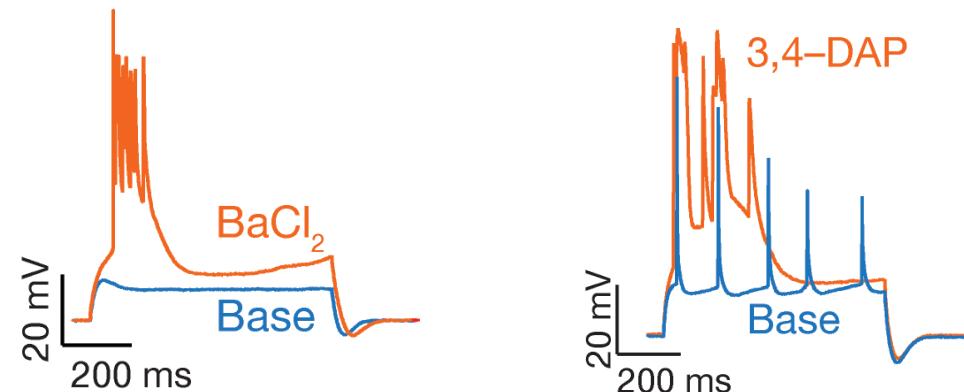
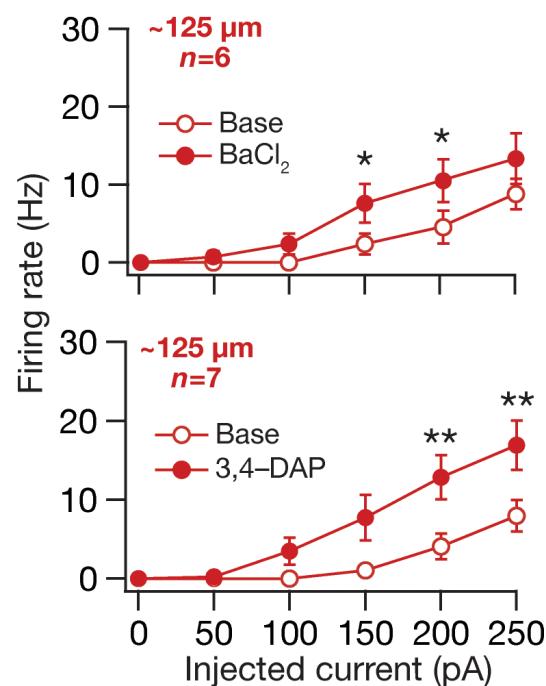
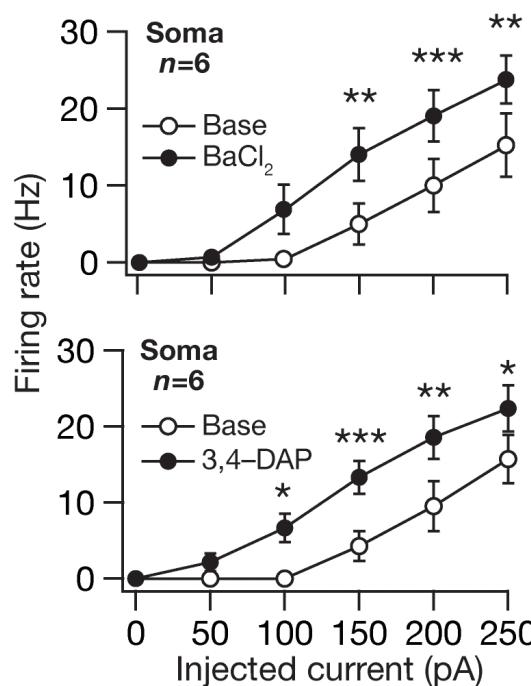
Input resistance increased at all locations with blockade of transient potassium channels

Prediction: Blocking A-type K⁺ channels would increase input resistance across the dendritic tree.



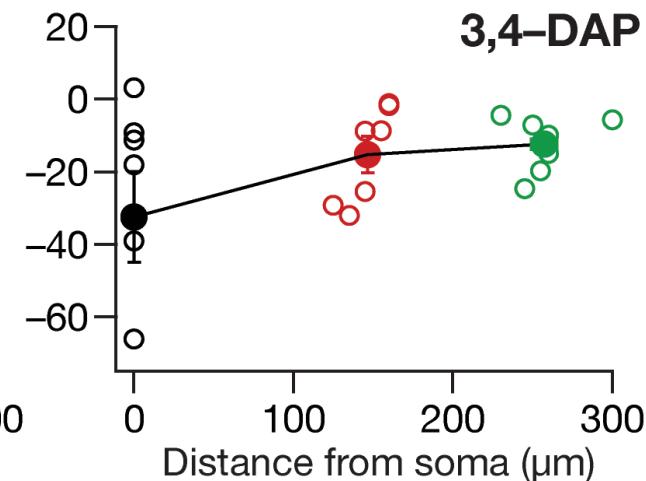
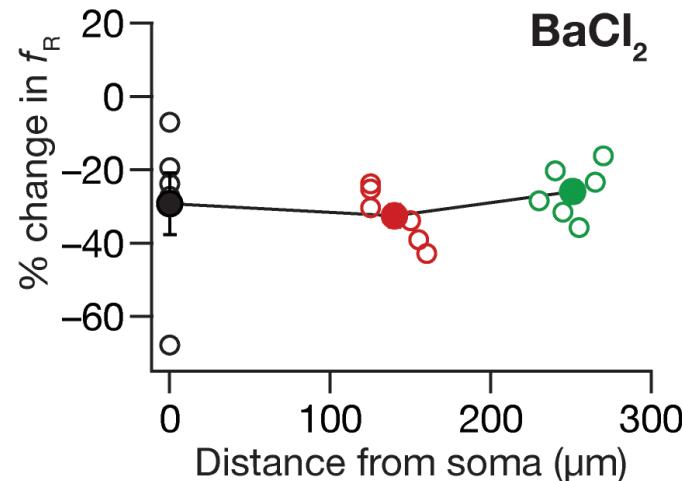
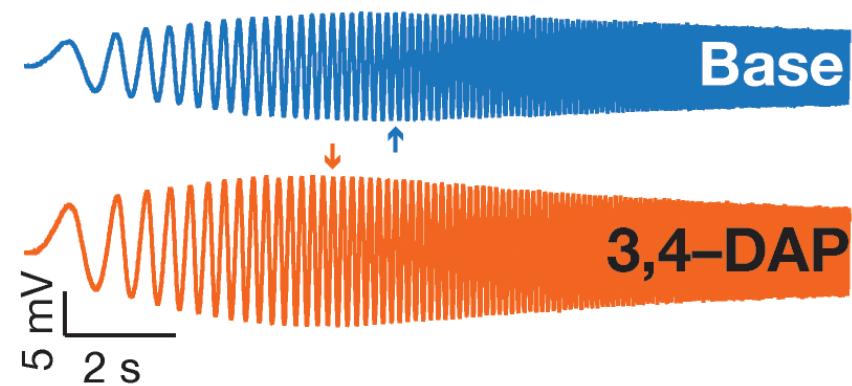
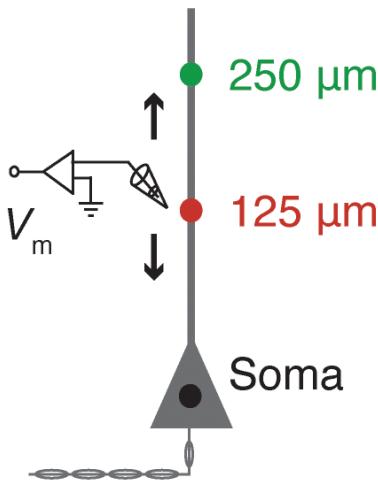
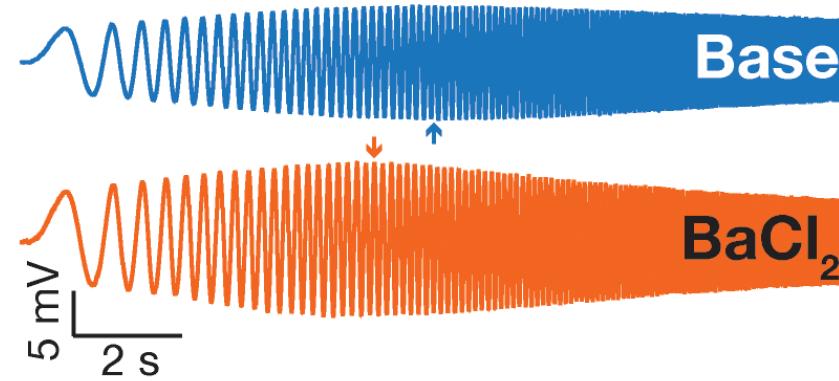
Consequently, firing rate increased at all locations with blockade of transient potassium channels

Prediction: Blocking A-type K⁺ channels would increase input resistance (translating to increase in firing rate) across the dendritic tree.



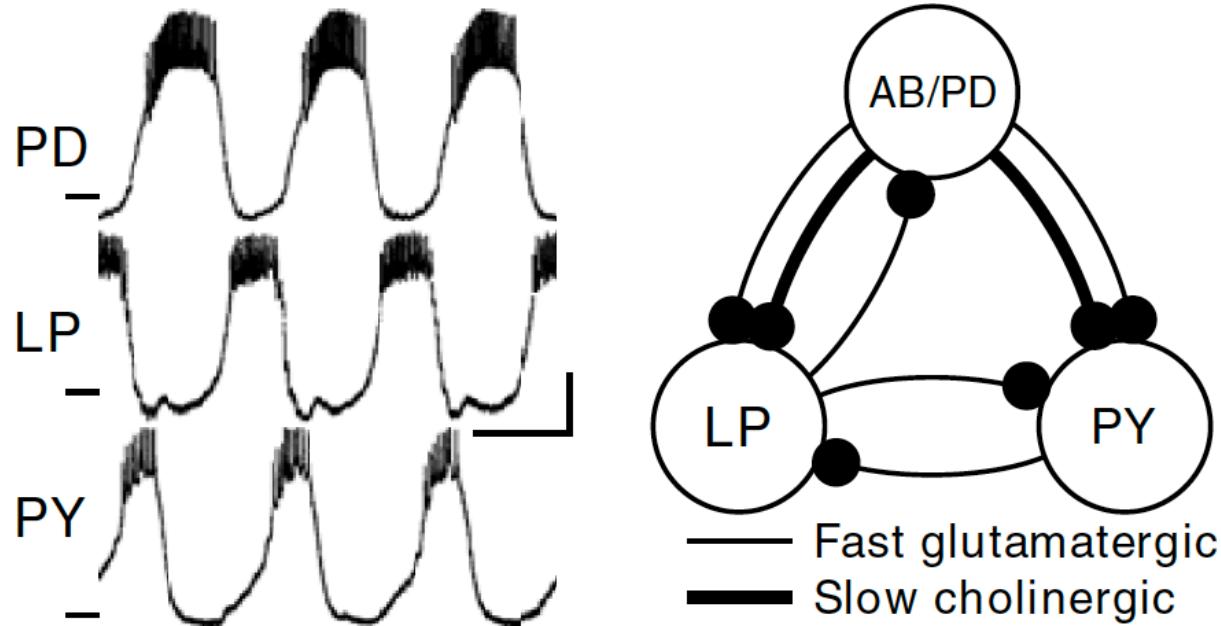
Resonance frequency decreased at all locations after blockade of transient potassium channels

Prediction: Blocking A-type K⁺ channels would decrease resonance frequency across the dendritic tree.



Degeneracy in network physiology

The pyloric rhythm in the crab: Model



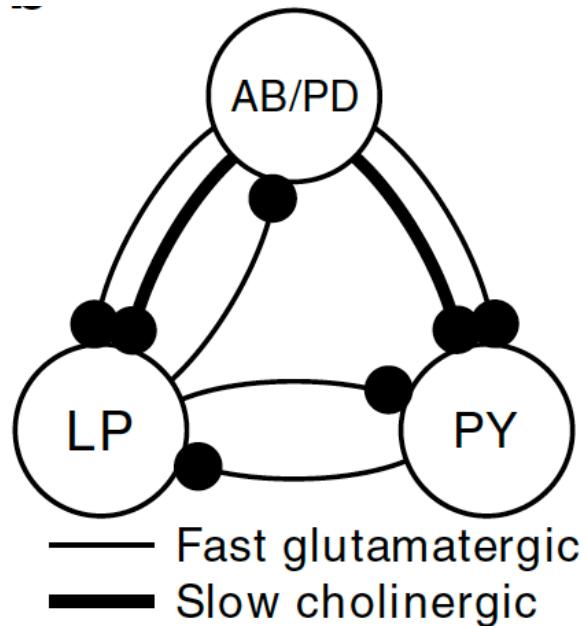
The pyloric rhythm in the crab: Model neurons

Table 2 Maximal conductance densities of model neurons

Arrived using GSA.

Model neuron	Maximal membrane conductance density in mS/cm ²							
	g(I_{Na})	g(I_{CaT})	g(I_{CaS})	g(I_A)	g($I_{K(Ca)}$)	g(I_{Kd})	g(I_H)	g(I_{leak})
AB/PD 1	400	2.5	6	50	10	100	0.01	0.00
AB/PD 2	100	2.5	6	50	5	100	0.01	0.00
AB/PD 3	200	2.5	4	50	5	50	0.01	0.00
AB/PD 4	200	5.0	4	40	5	125	0.01	0.00
AB/PD 5	300	2.5	2	10	5	125	0.01	0.00
LP 1	100	0.0	8	40	5	75	0.05	0.02
LP 2	100	0.0	6	30	5	50	0.05	0.02
LP 3	100	0.0	10	50	5	100	0.00	0.03
LP 4	100	0.0	4	20	0	25	0.05	0.03
LP 5	100	0.0	6	30	0	50	0.03	0.02
PY 1	100	2.5	2	50	0	125	0.05	0.01
PY 2	200	7.5	0	50	0	75	0.05	0.00
PY 3	200	10.0	0	50	0	100	0.03	0.00
PY 4	400	2.5	2	50	0	75	0.05	0.00
PY 5	500	2.5	2	40	0	125	0.01	0.03
PY 6	500	2.5	2	40	0	125	0.00	0.02

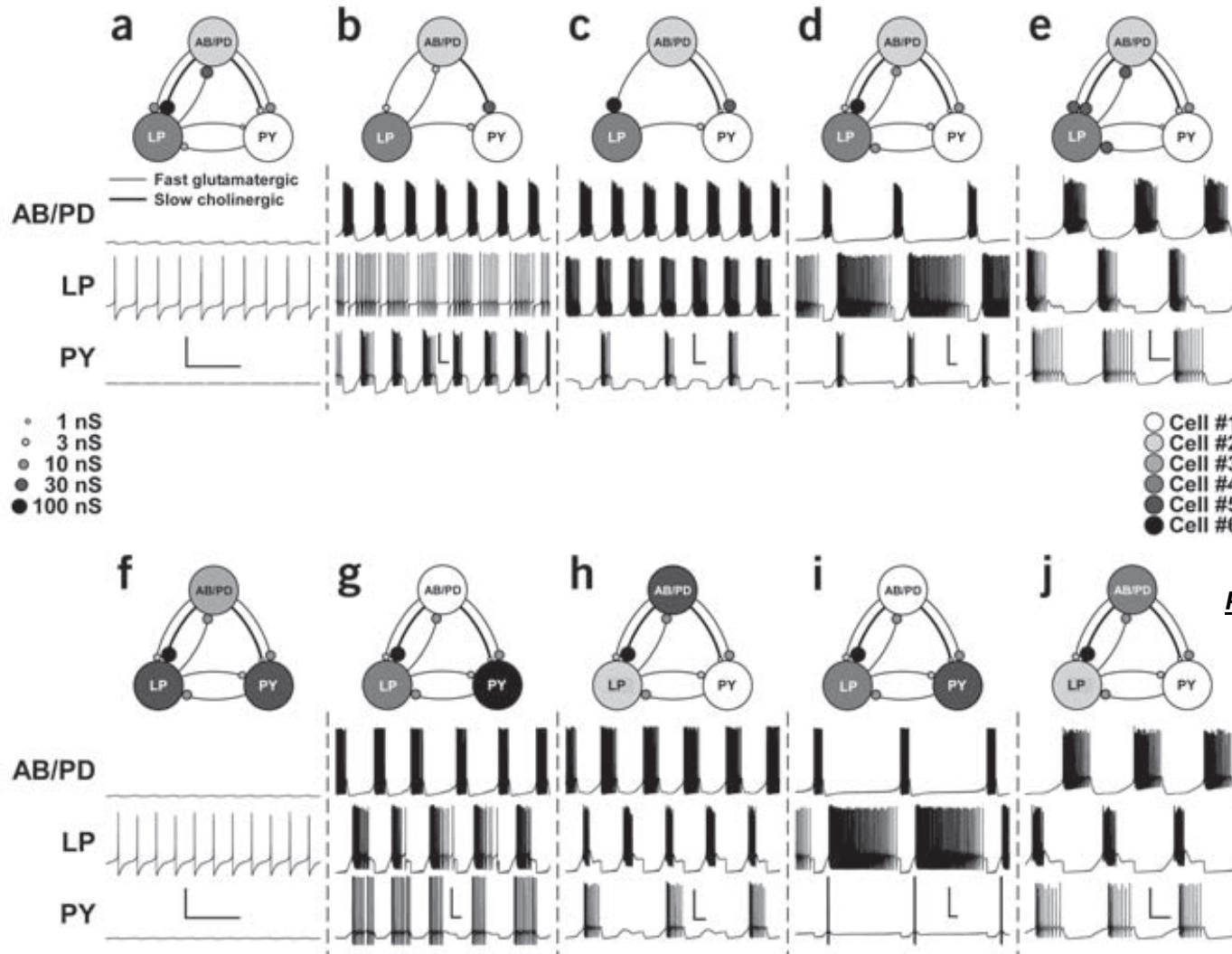
The pyloric rhythm in the crab: Conductance-based model synapses



Independently vary the strengths of the seven synapses in the pyloric circuit model, with each synapse taking one of five or six different strengths: 0 nS, 3 nS, 10 nS, 30 nS, 100 nS and, for synapses onto PY, 1 nS, covering the entire functionally relevant range of synaptic conductances.

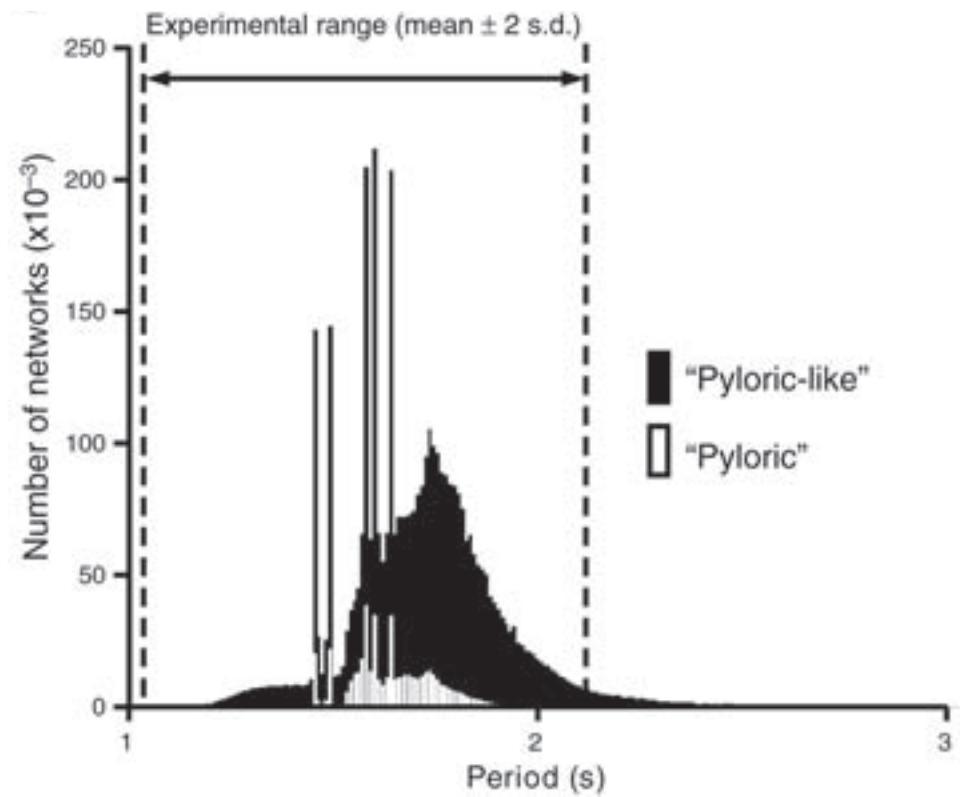
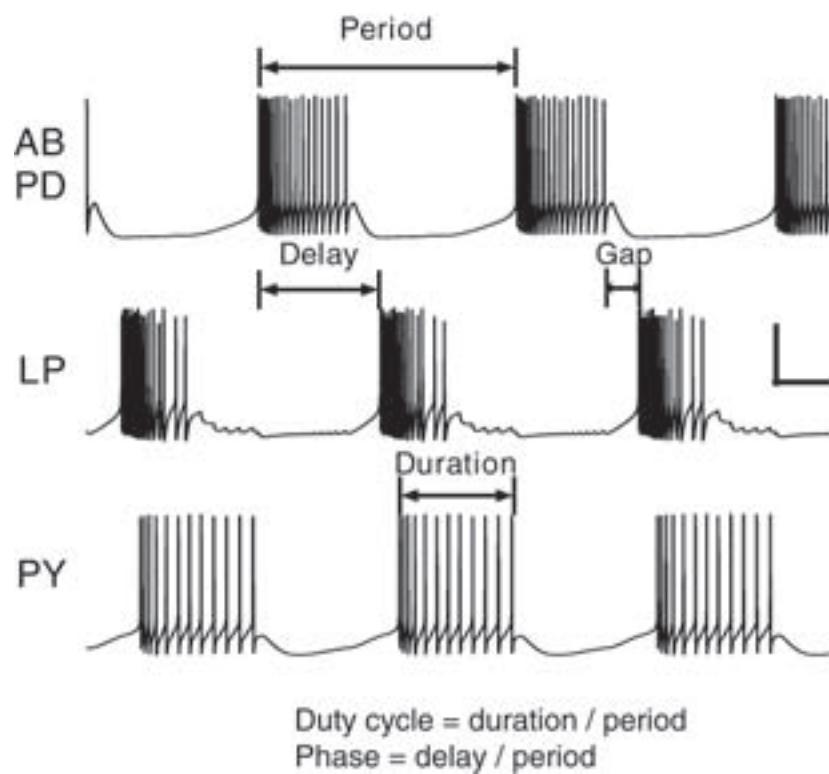
The pyloric rhythm in the crab: Example outputs

Generate a database of more than 20,250,000 model pyloric circuits by spanning the range of neurons and synapses



Prinz et al., Nature Neuroscience, 2004

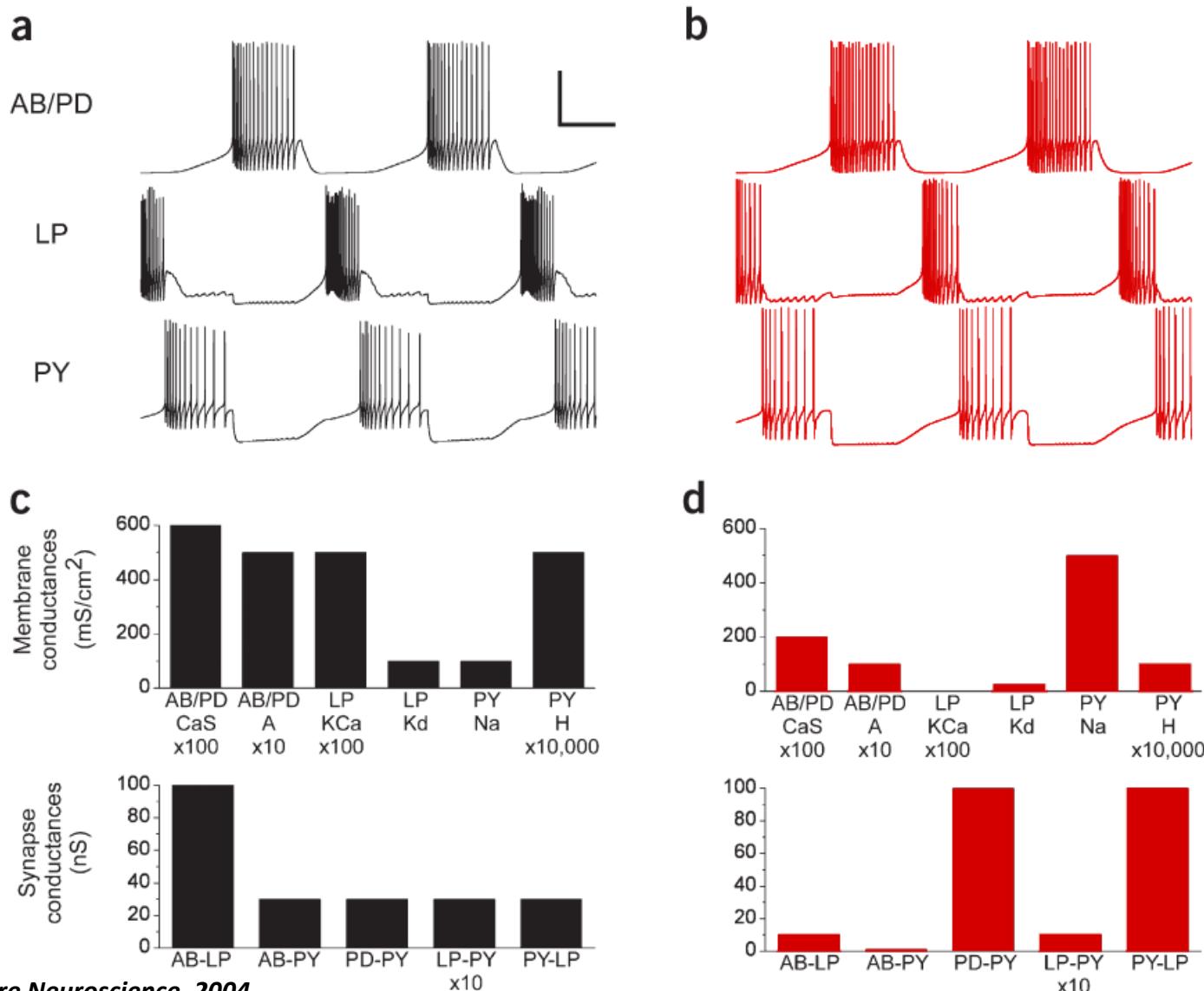
The pyloric rhythm in the crab: Check validity



'Pyloric-like': In every cycle, the LP burst began before the start of the PY burst and finished before the end of the PY burst; and the AB/PD burst finished before the start of the LP burst, creating a gap in firing activity.

Out of the 20,250,000 networks in the database, 4,047,375 (20%) were pyloric-like by these criteria

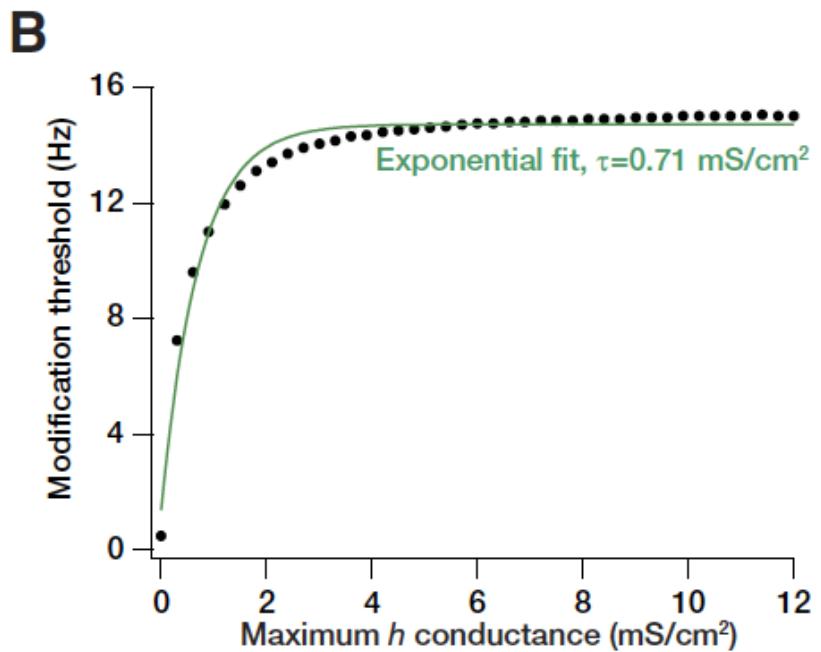
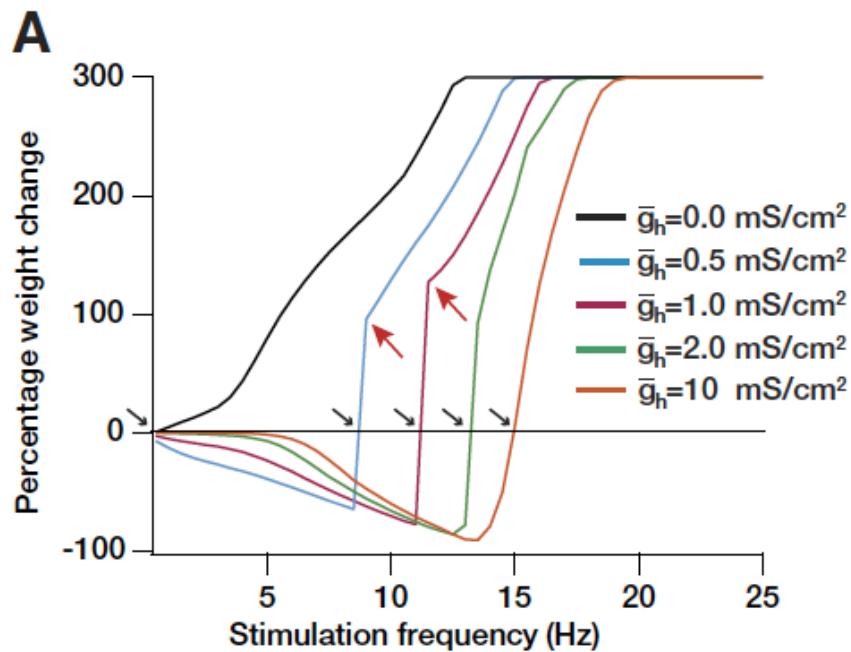
Degeneracy in network function, spanning both intrinsic and synaptic properties



Degeneracy in synaptic plasticity profiles

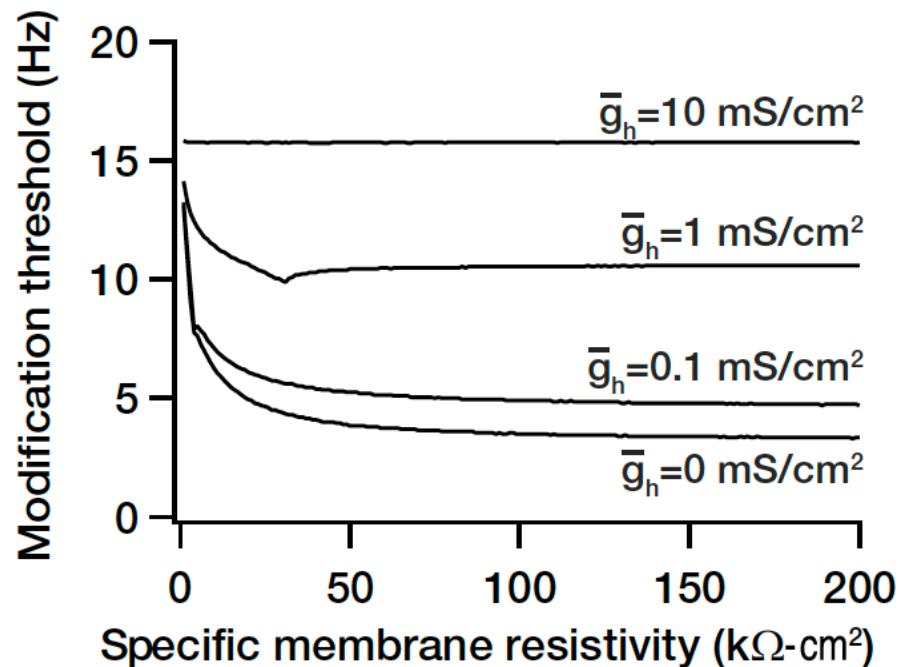
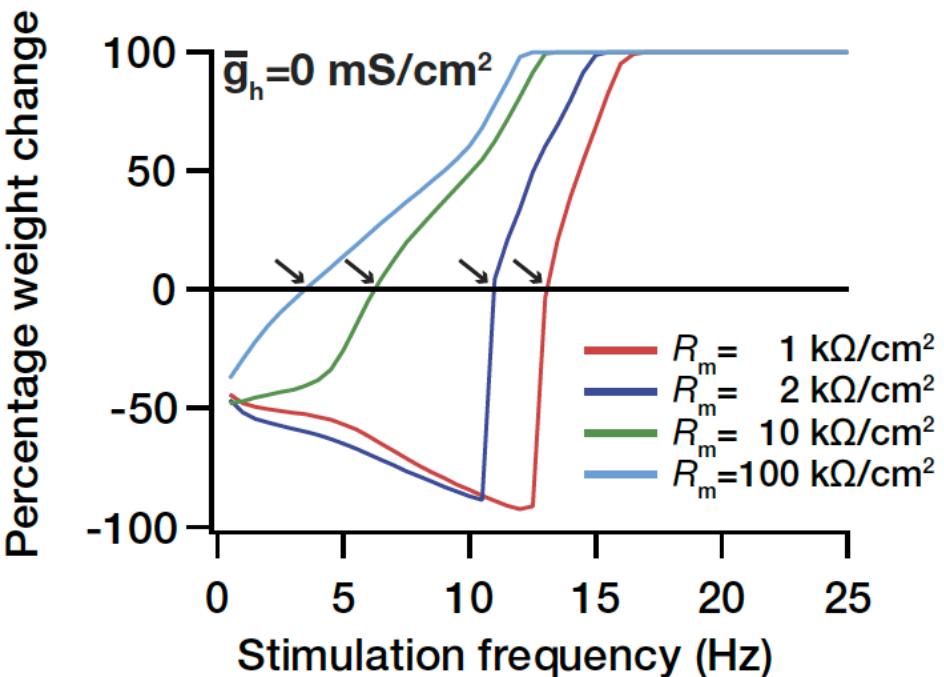
HCN channels alter synaptic plasticity rules

In the previous lecture, we saw



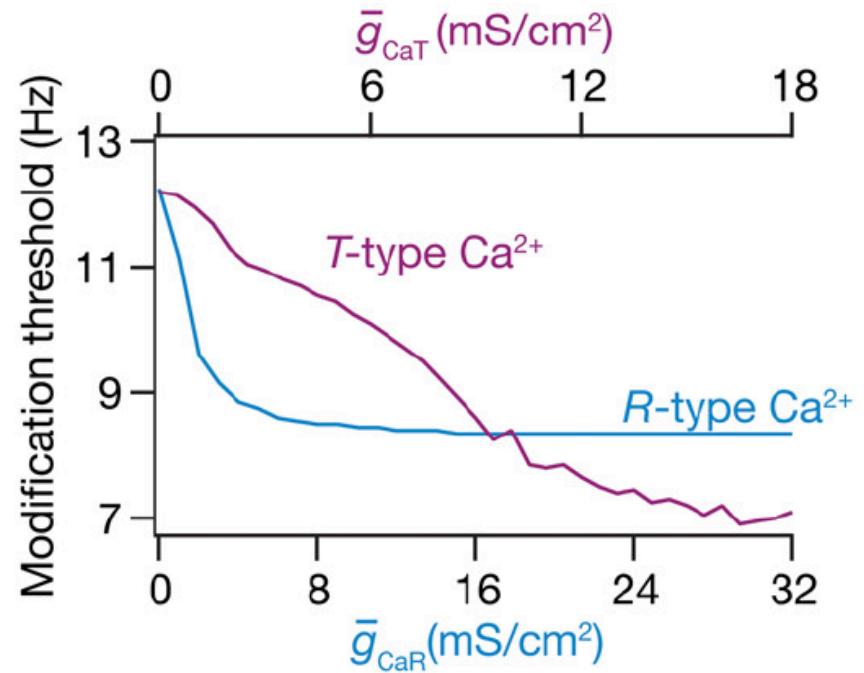
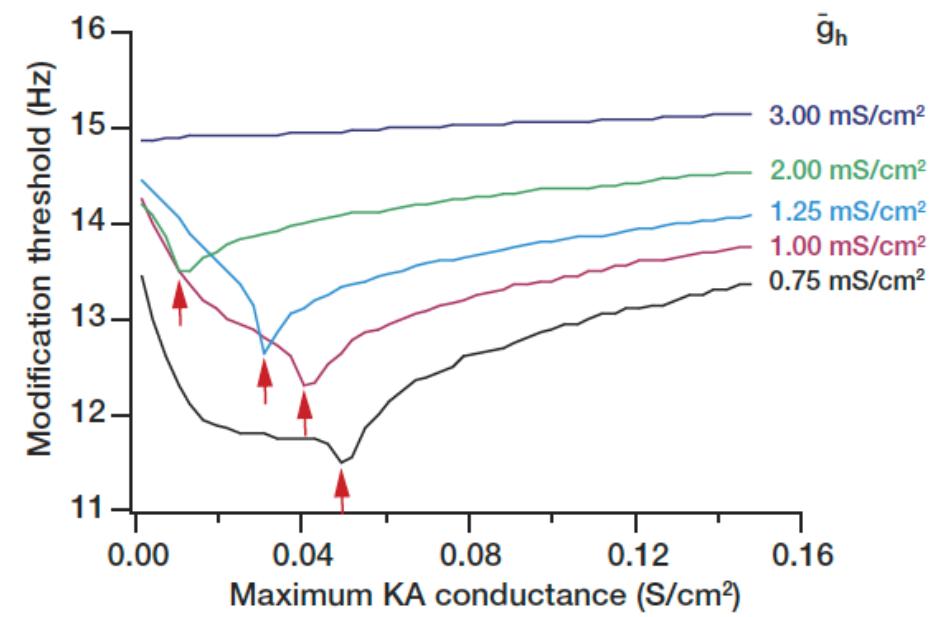
Leak channels also alter synaptic plasticity rules!!

Impact of intrinsic properties/plasticity on synaptic plasticity rules



So do A-type K⁺ channels, R- and T-type Ca²⁺ channels

Impact of intrinsic properties/plasticity on synaptic plasticity rules

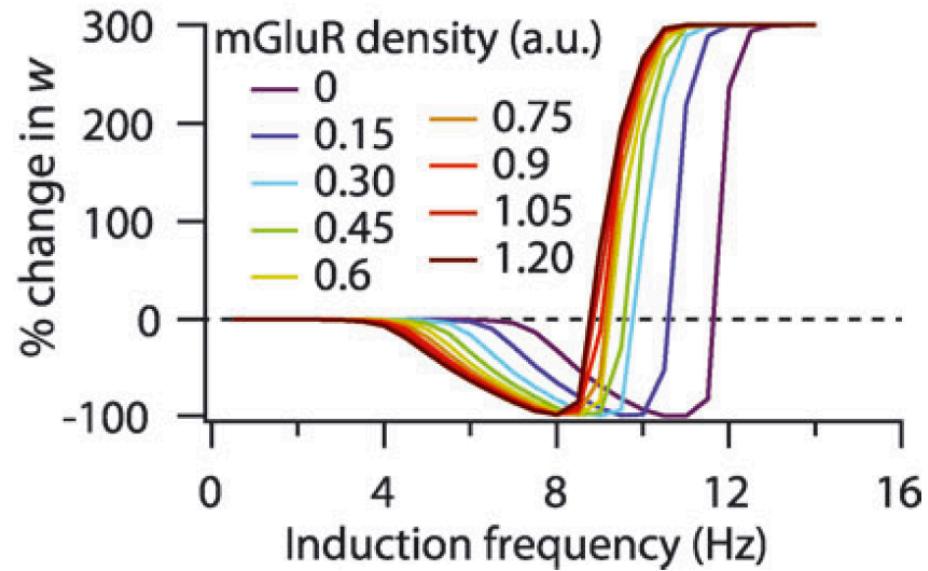
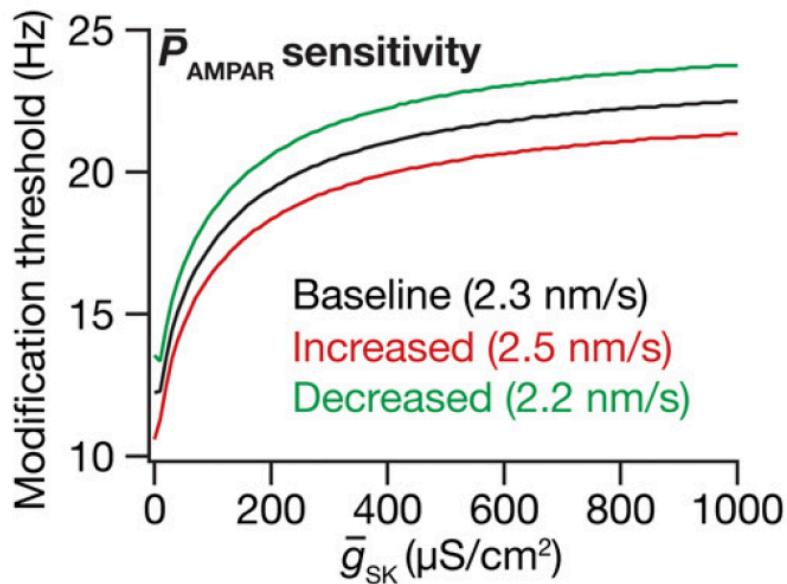


Narayanan and Johnston, J. Neurophys, 2010

Anirudhan and Narayanan J. Neurosci, 2015

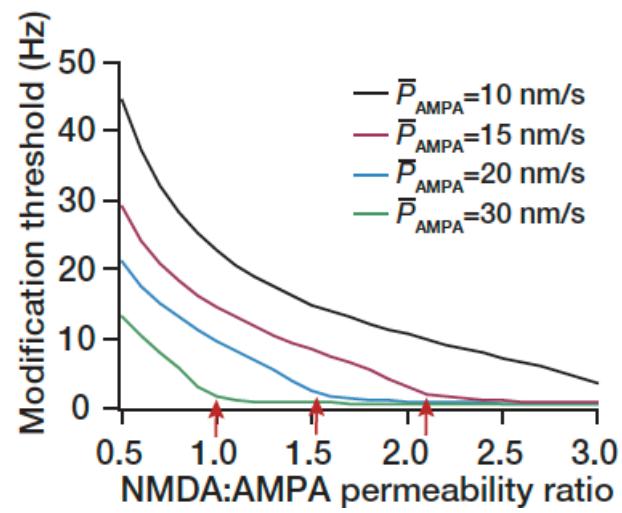
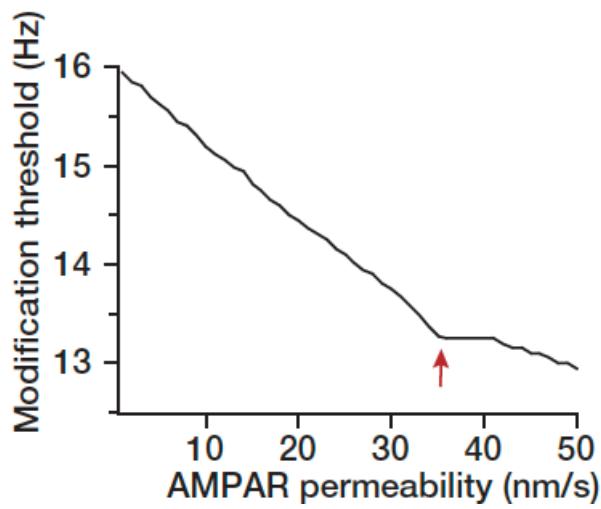
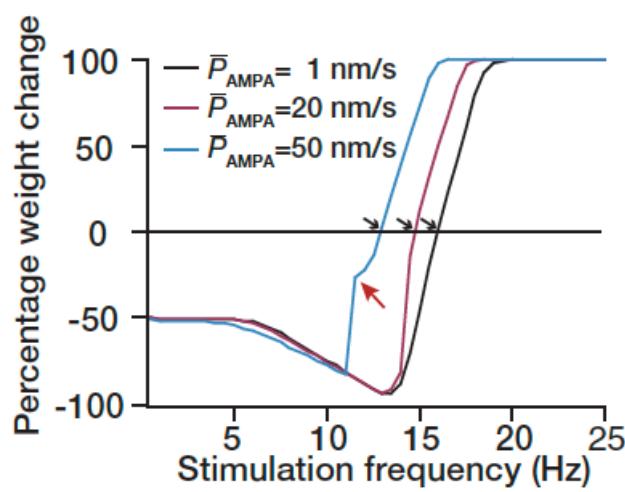
So do SK channels and mGluR receptors!!!

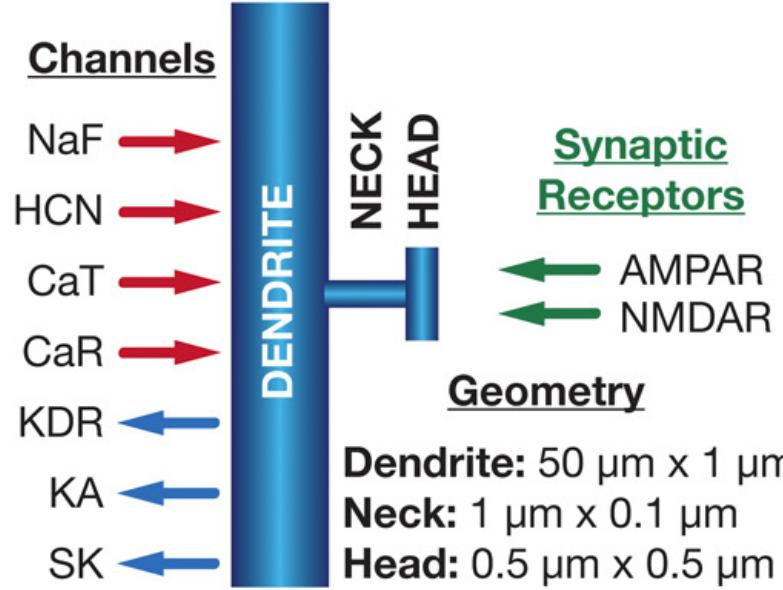
Impact of intrinsic/receptor properties/plasticity on synaptic plasticity rules



So do AMPA and NMDA receptors!!!

Impact of receptor plasticity on synaptic plasticity rules





So, are there several ways to achieve the same plasticity profile?

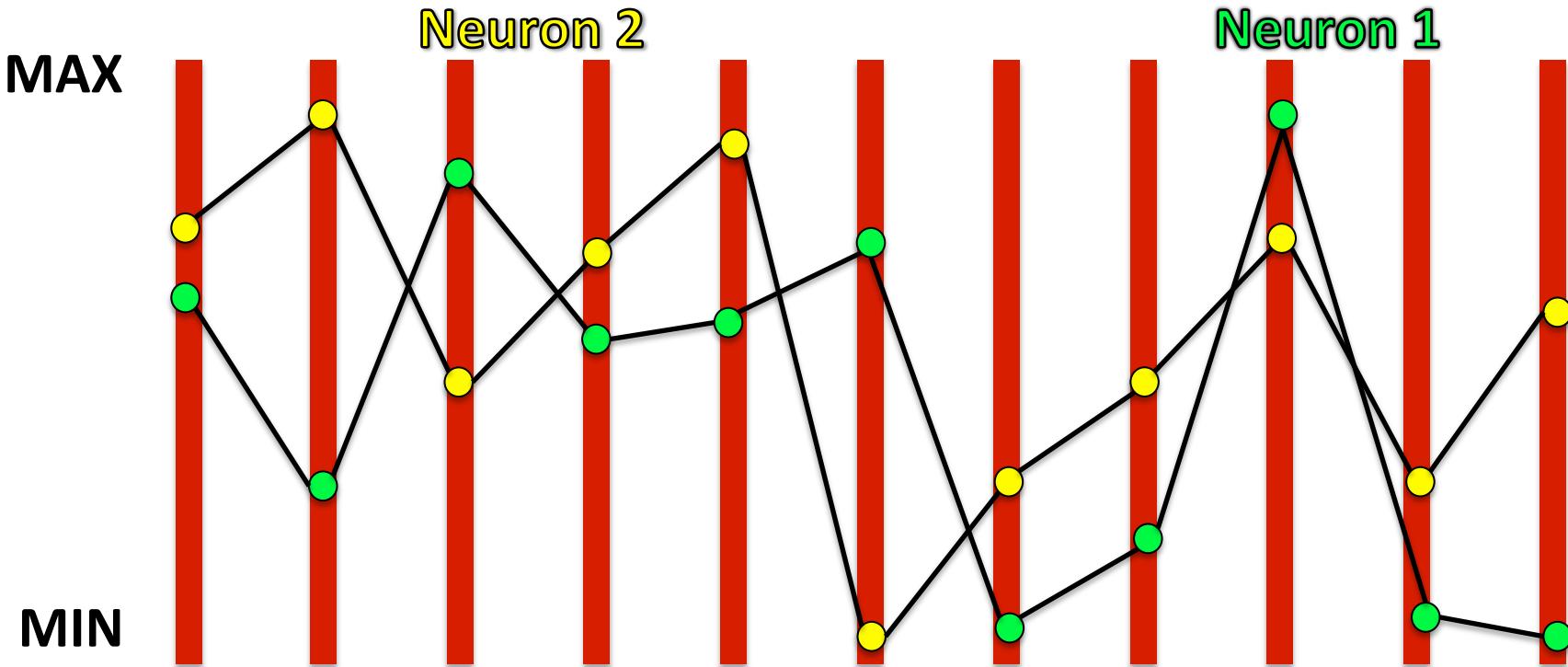
9 Channels/Receptors

Eleven Parameters

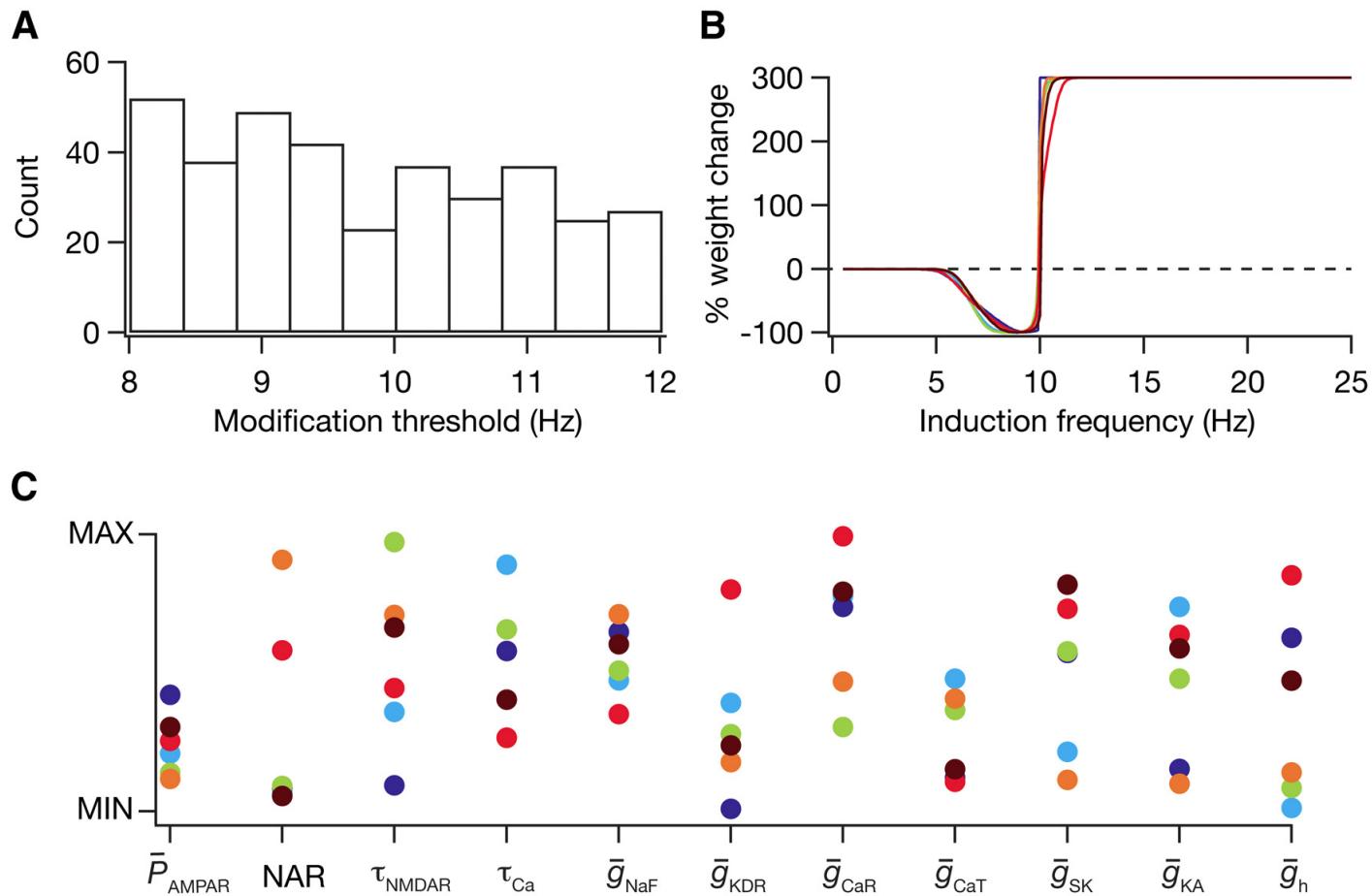
20,000 plasticity profiles

360 valid models

Anirudhan and Narayanan J. Neurosci, 2015



Analogous Synaptic Plasticity Profiles Emerge from Disparate Channel Combinations



Parameters exhibited weak pair-wise correlations here as well

Summary

Nothing in biology makes sense except in the light of degeneracy!

— Modified from Theodosius Dobzhansky

Degeneracy and complexity in biological systems

Gerald M. Edelman* and Joseph A. Gally

PNAS | November 20, 2001 | vol. 98 | no. 24 | 13763–13768

Degeneracy is a ubiquitous biological property; it is a feature of complexity at genetic, cellular, system, and population levels.

It is both necessary for, and an inevitable outcome of, natural selection.



<http://www.youtube.com/watch?v=b240PGCMwV0>

RICHARD FEYNMAN

“Now I’m going to discuss how we would look for a new law. In general, we look for a new law by the following process. **First, we guess it** (audience laughter), no, don’t laugh, that’s the truth. **Then we compute the consequences of the guess**, to see what, if this is right, if this law we guess is right, to see what it would imply and **then we compare the computation results to nature or we say compare to experiment or experience**, compare it directly with observations to see if it works.

If it disagrees with experiment, it's WRONG. In that simple statement is the key to science. It doesn’t make any difference how beautiful your guess is, it doesn’t matter how smart you are, who made the guess, or what his name is... If it disagrees with experiment, it’s wrong. That’s all there is to it.”