Degeneracy in hippocampal physiology & plasticity

Dynamics of Complex Systems 2017

I C T S

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wellcome trust DBT INDIA ALLIANCE

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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

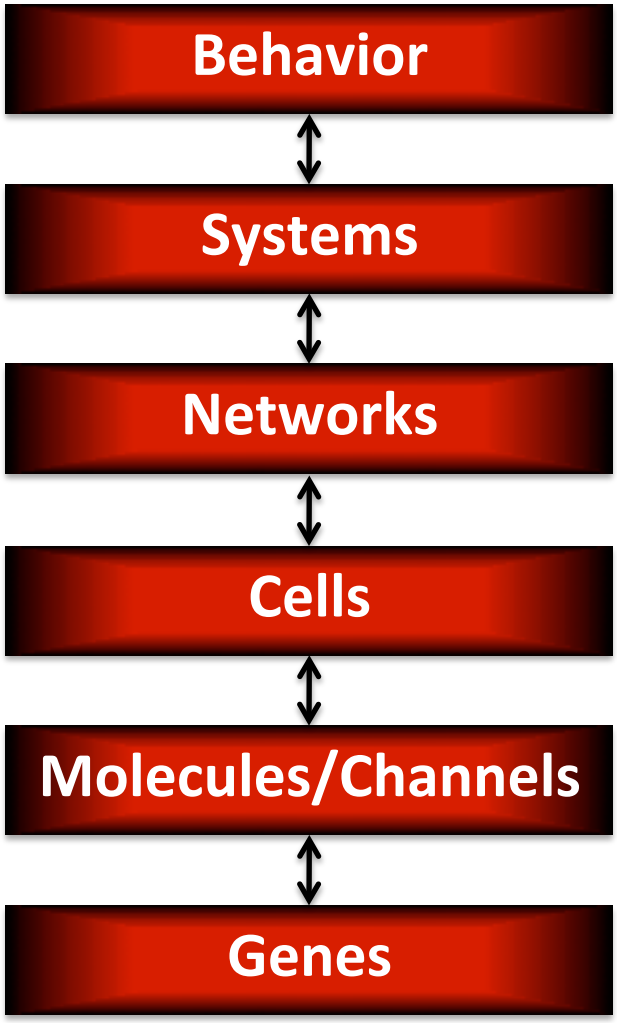


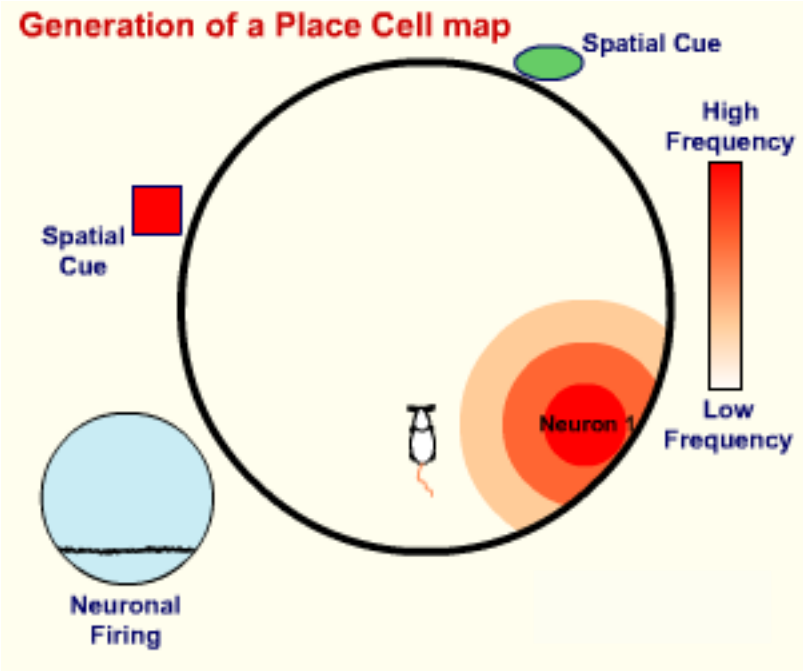
Table 1. Degeneracy at different levels of biological organization

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)

The hippocampus, spatial learning and memory

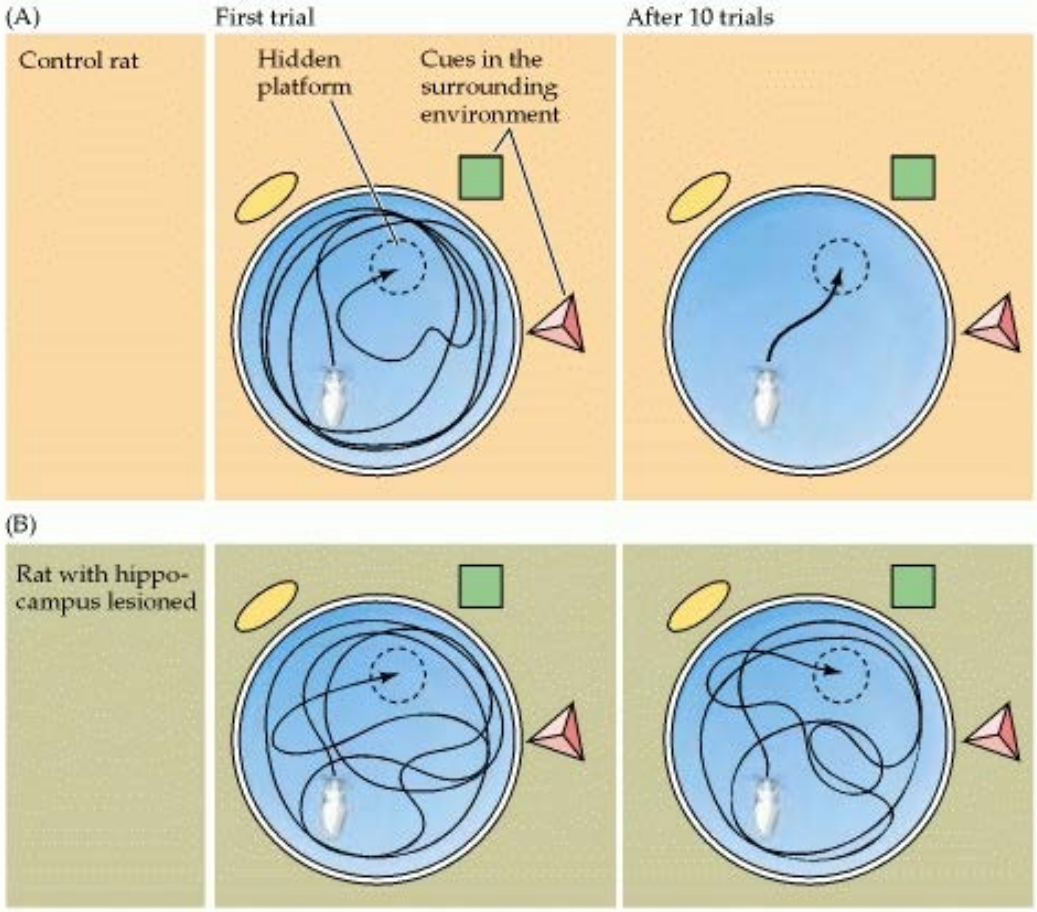
Place cells exhibit a high firing rate when an animal is in a specific location

O'Keefe and Dostrovsky, 1971



Nobel Prize in Physiology/Medicine, 2014

Hippocampal lesions impair the animal's ability to learn spatial tasks

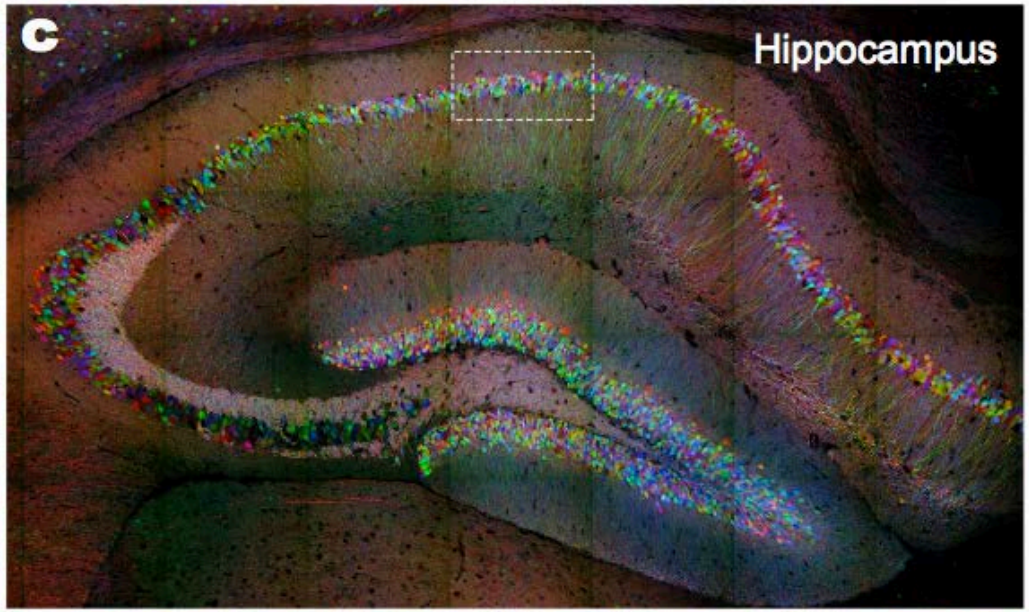


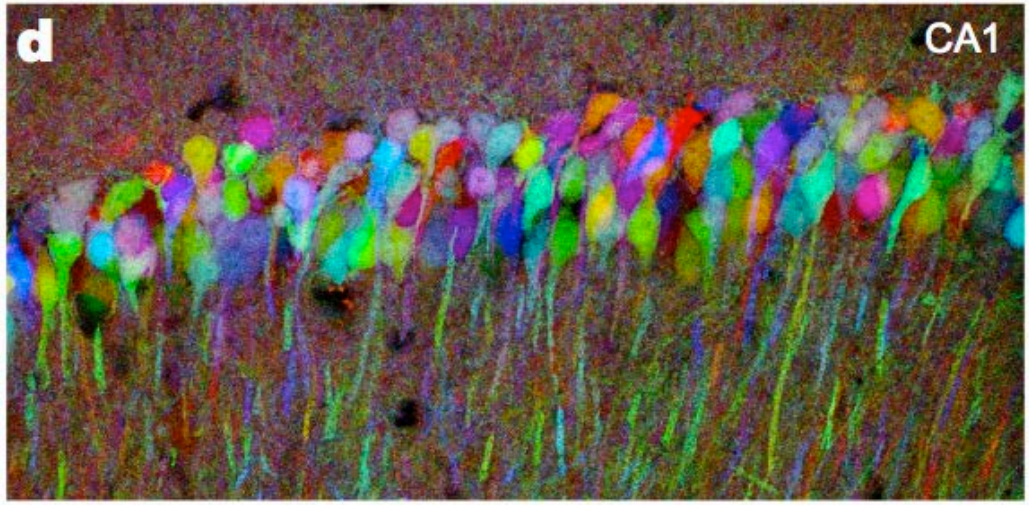
Morris et al., Nature, 1982

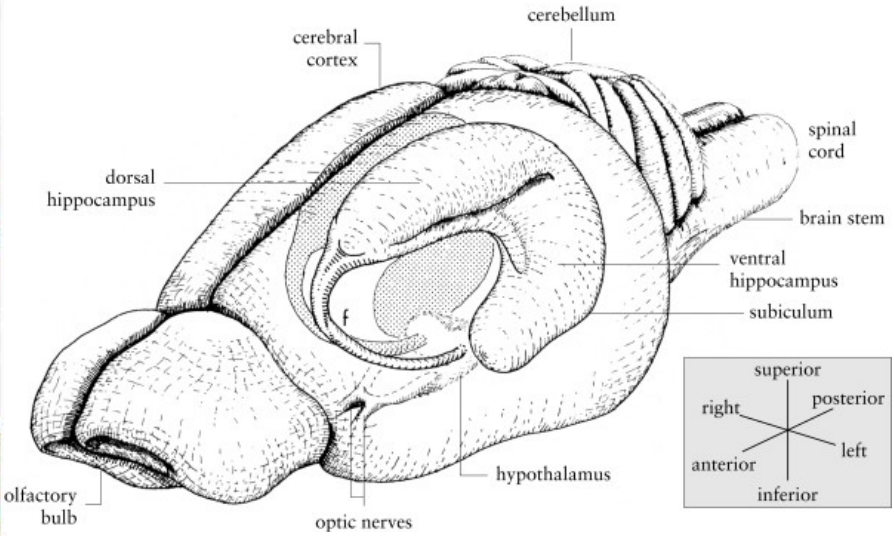
http://www.bris.ac.uk/synaptic/research/projects/memory/spatialmem.htm

Purves, Neuroscience Book

The hippocampus: Anatomical organization



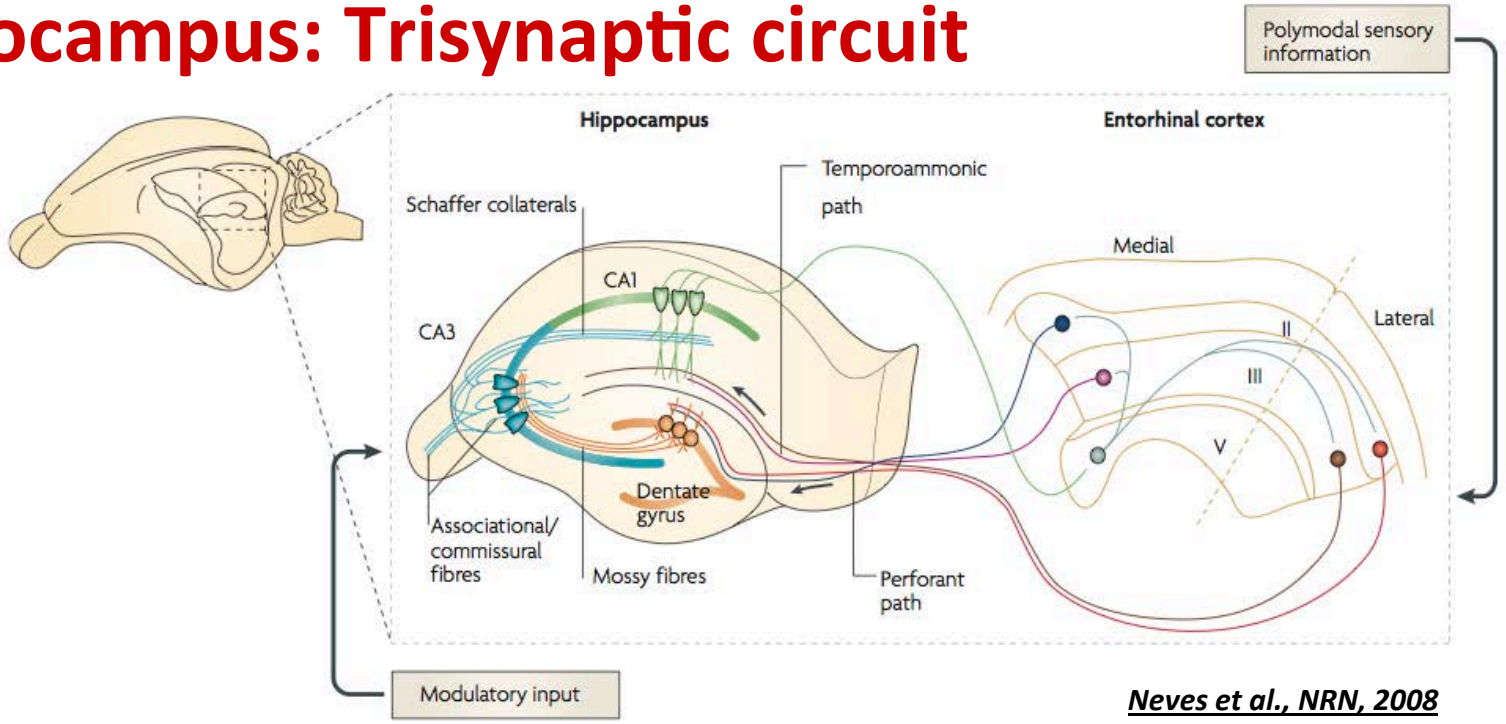




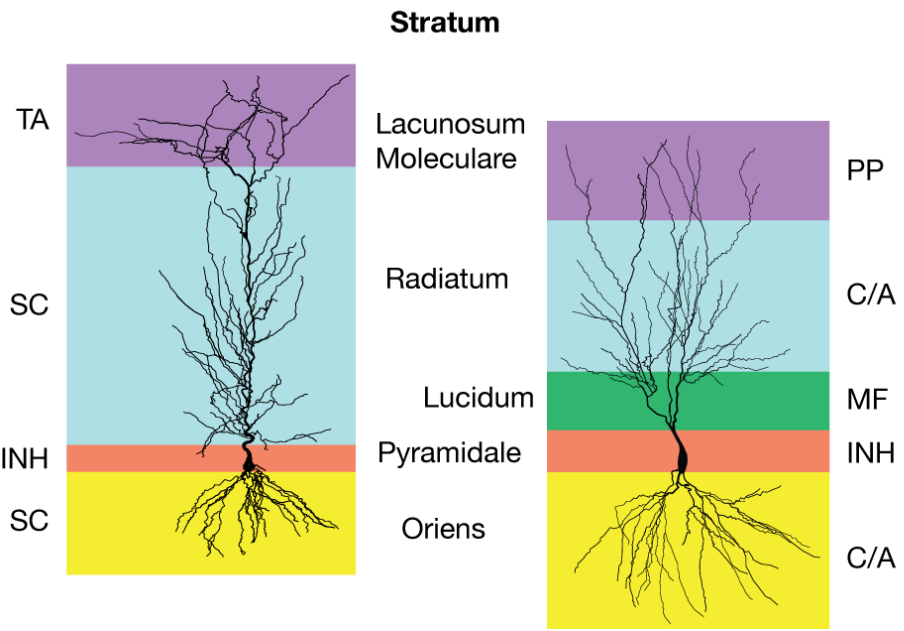
Brainbow mouse: each neuron has a different color!

Livet et al., Nature, 2007

The hippocampus: Trisynaptic circuit

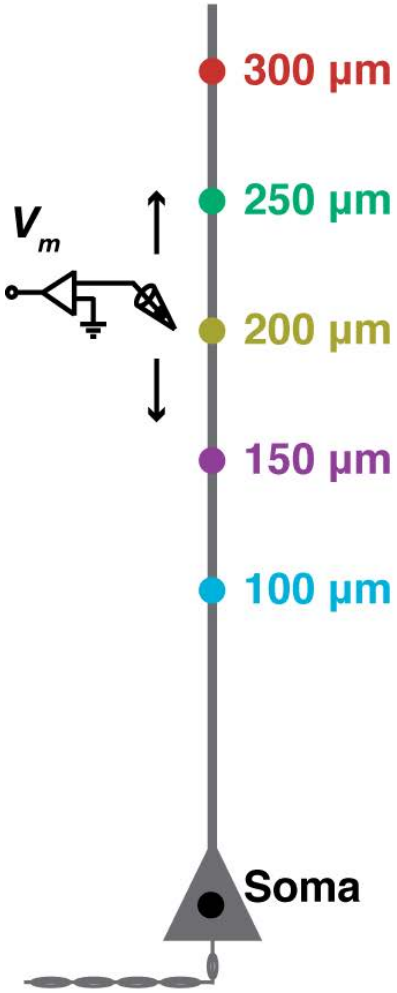


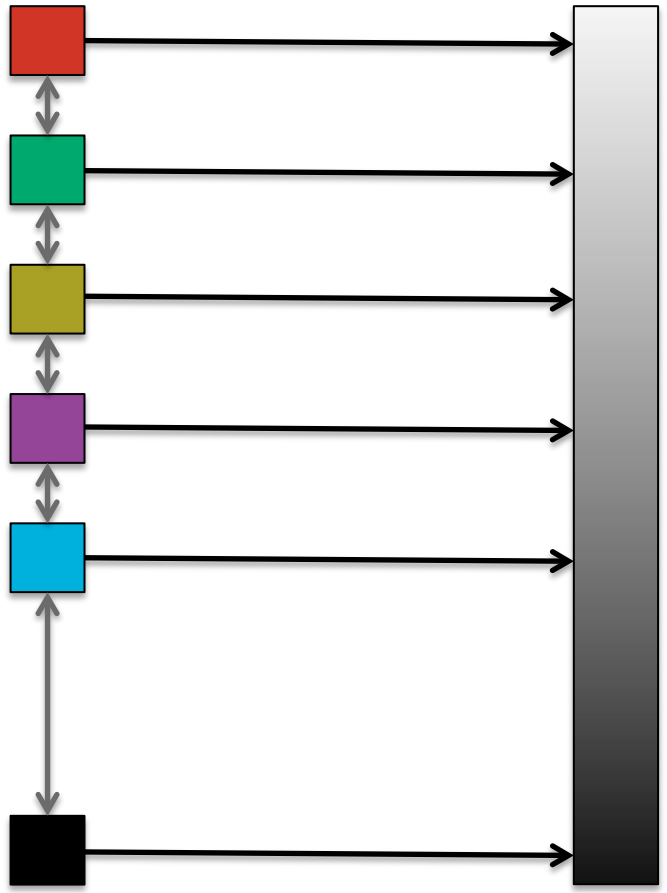
Neves et al., NRN, 2008



PP: Perforant pathway from entorhinal
C/A: Commissural/Associational inputs from CA3
MF: Mossy fiber inputs from DG
INH: Inhibitory inputs
SC: Schaffer collaterals from CA3
TA: Temporoammonic pathway from EC

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

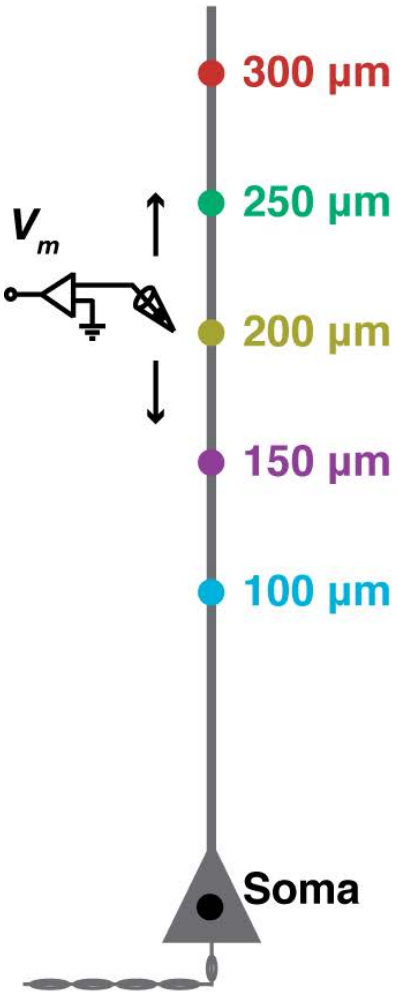


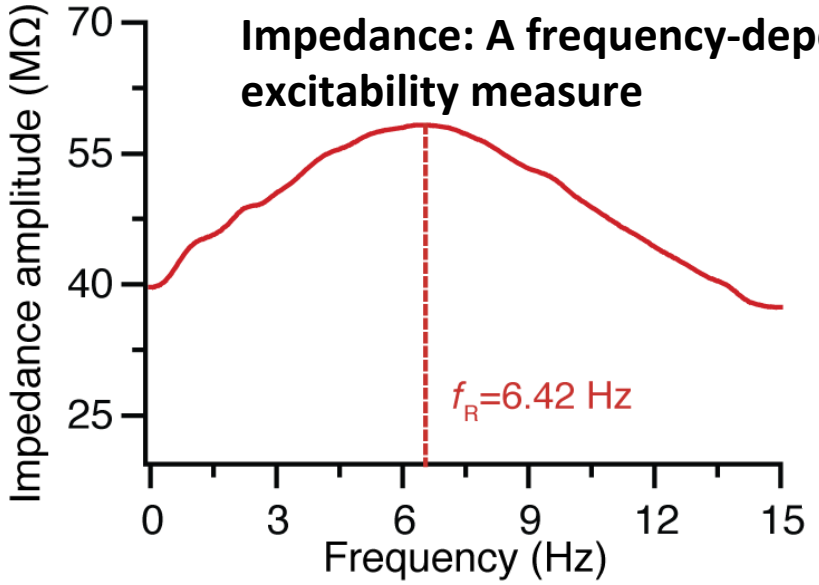


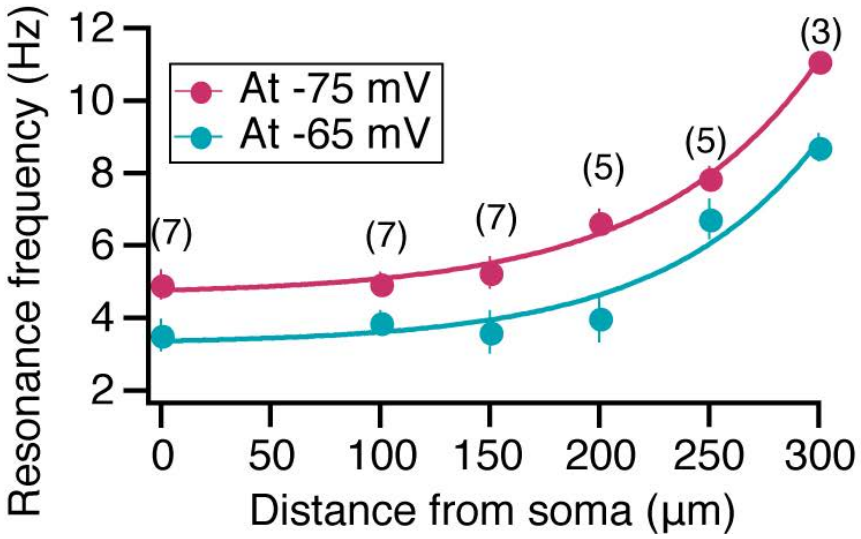
Spatial Topograph

Measurement Topograph

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



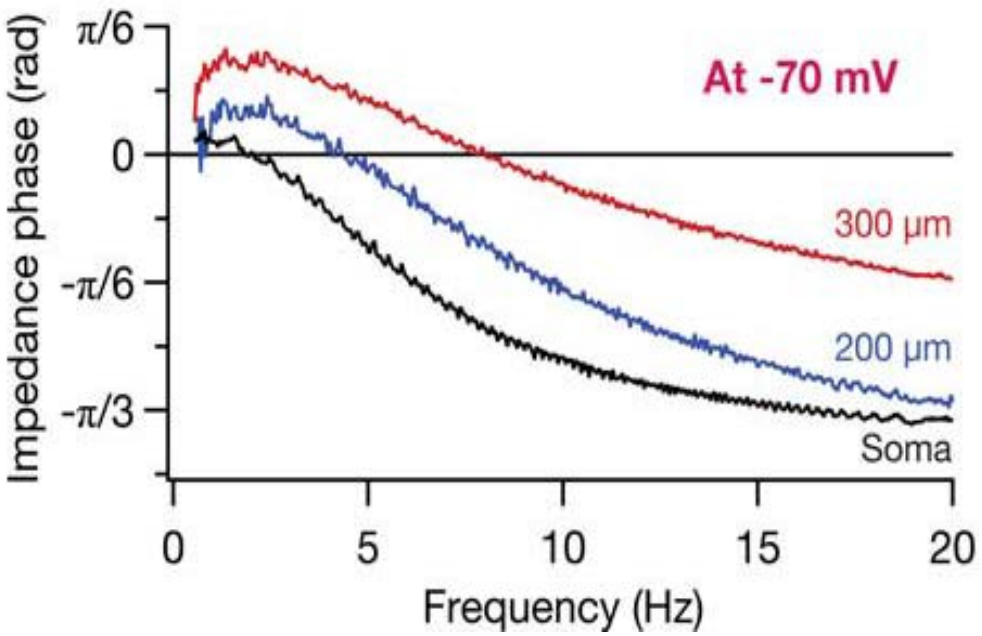


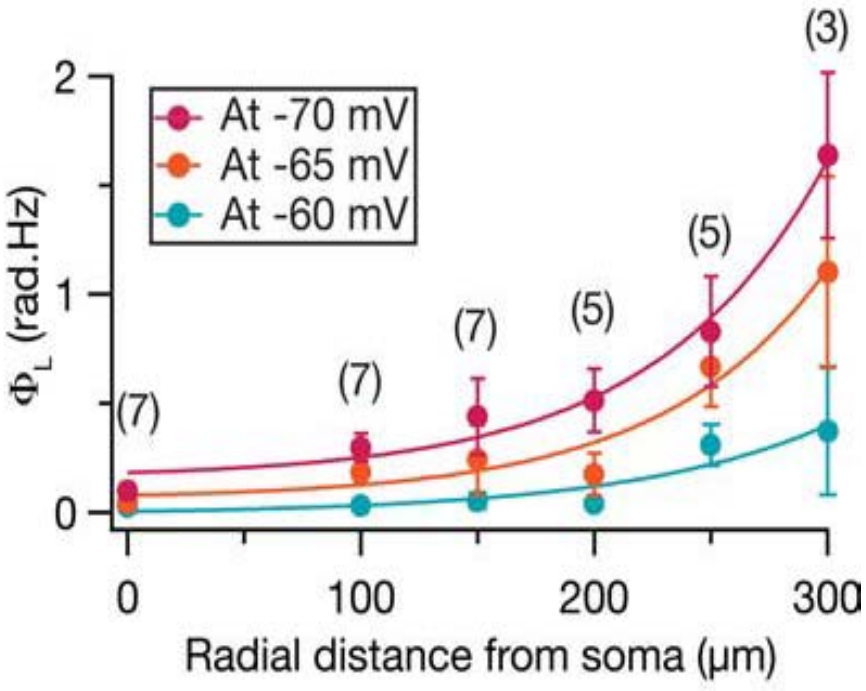


Narayanan and Johnston, Neuron, 2007

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

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





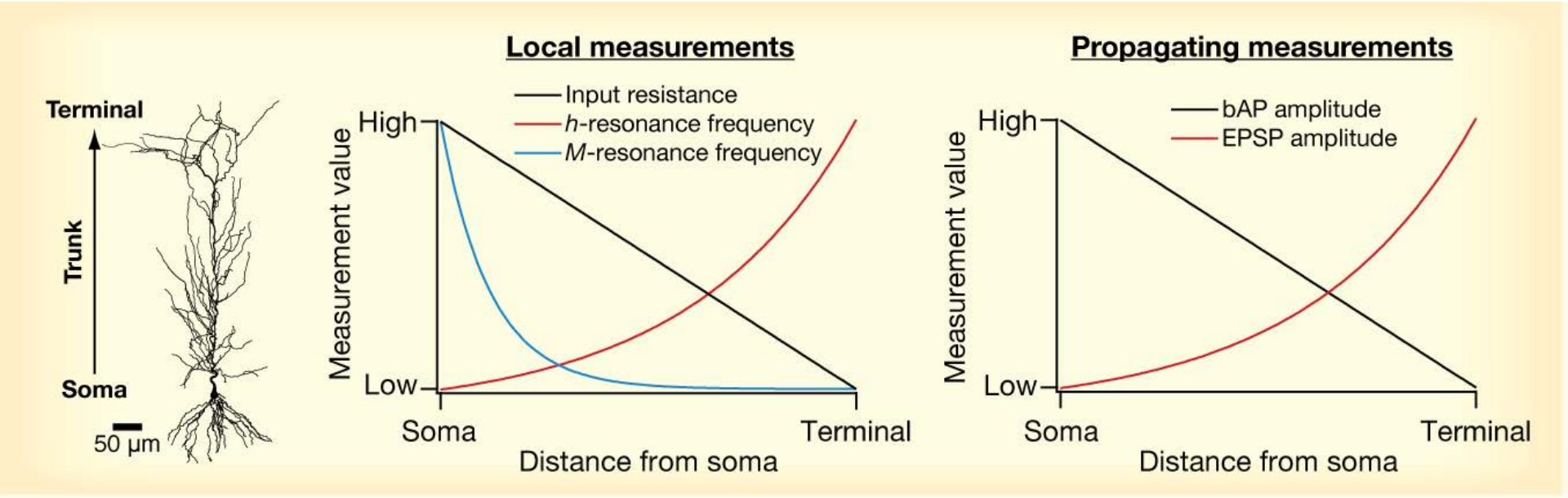
Narayanan and Johnston, J.Neurosci., 2008

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.

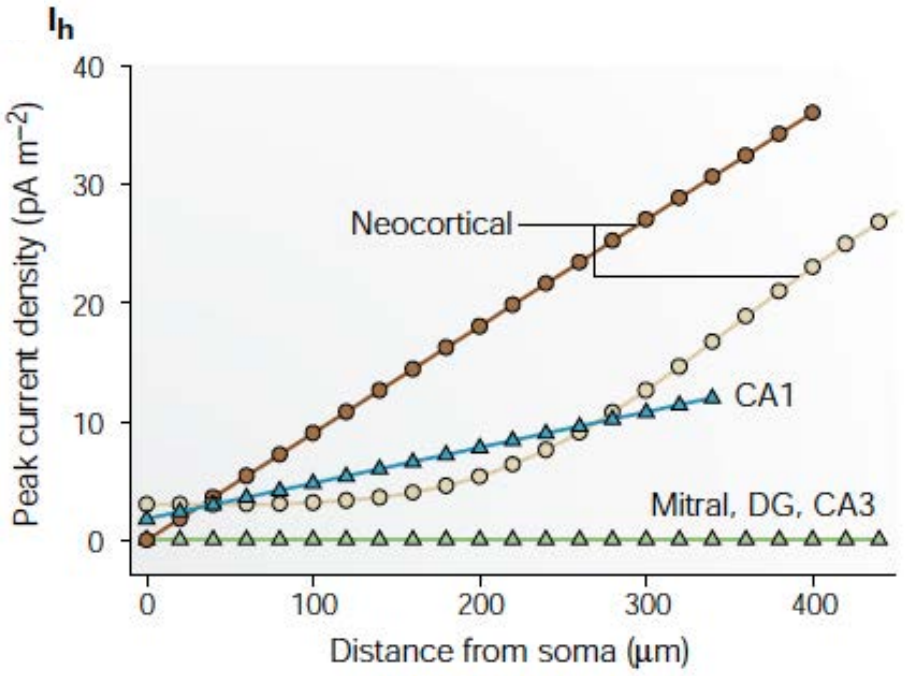
Functional maps within a single neuron

Rishikesh Narayanan[1] and Daniel Johnston[2]

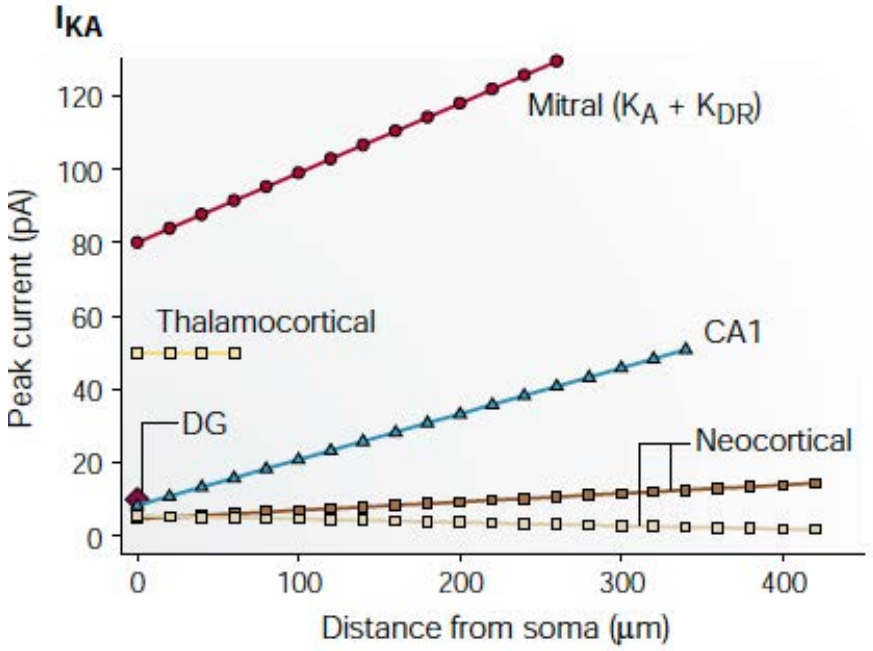


Channel/Receptor gradients actively mediate/ regulate intraneuronal functional maps

Resonance frequency map



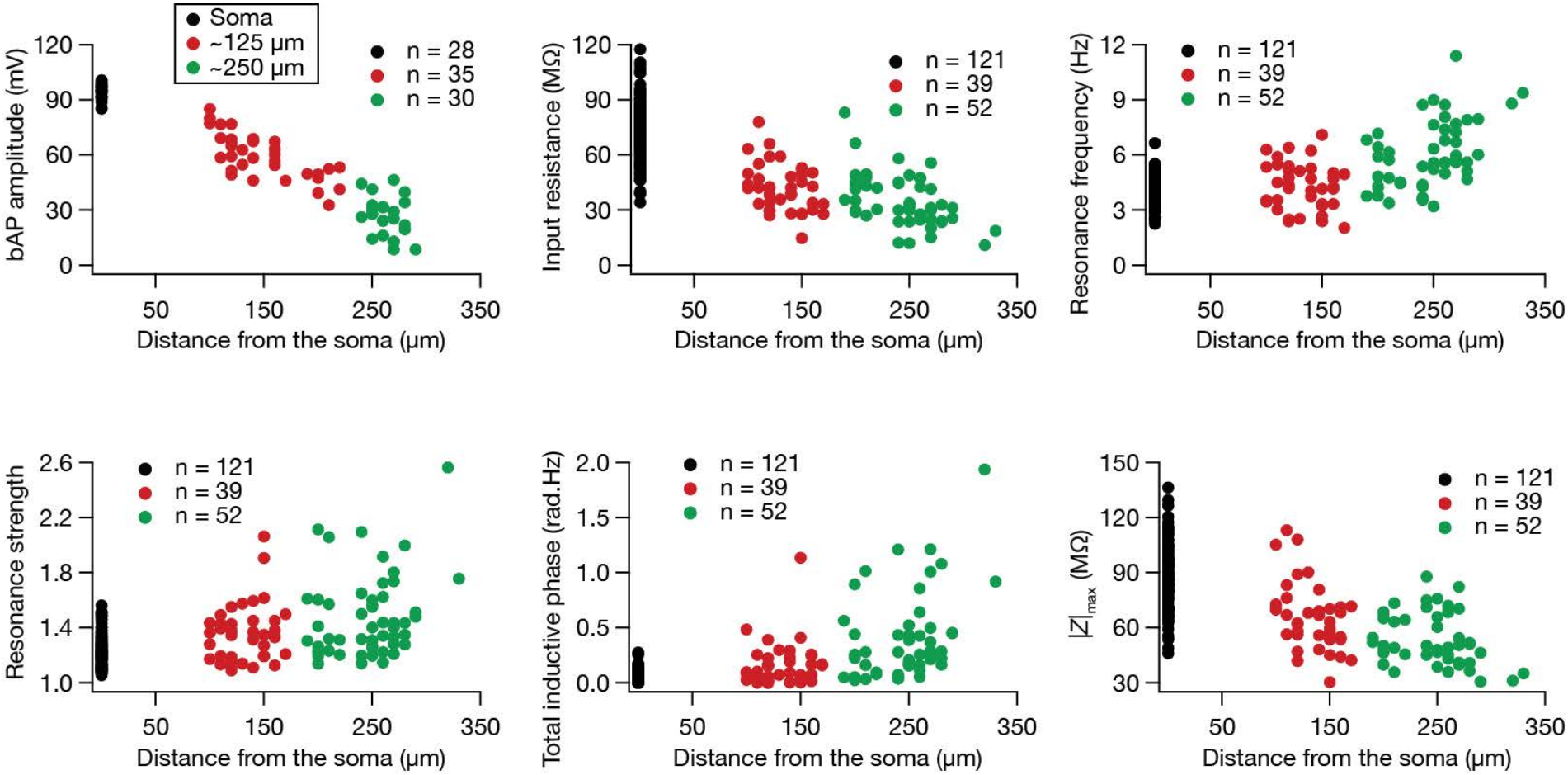
Backpropagating action potential (bAP) map



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

Migliore et al., Nature Rev. Neurosci., 2002

Experimental data on six different functional maps and their variability



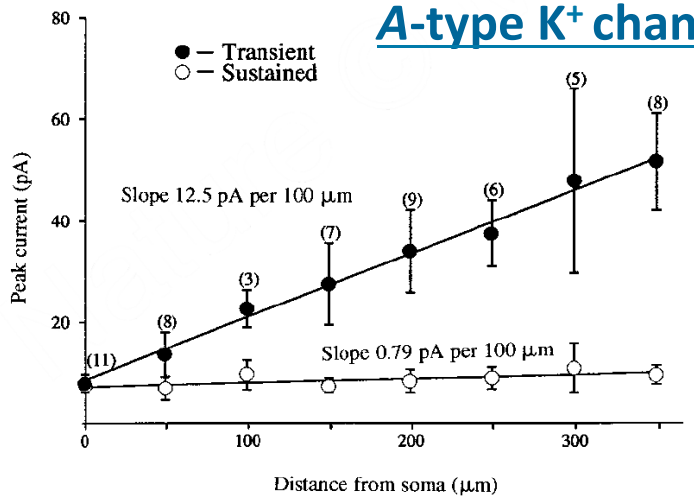
Experimental data from:

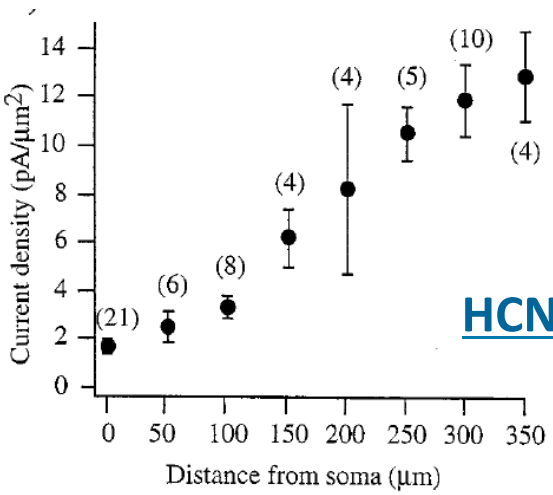
Narayanan and Johnston, Neuron, 2007;

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

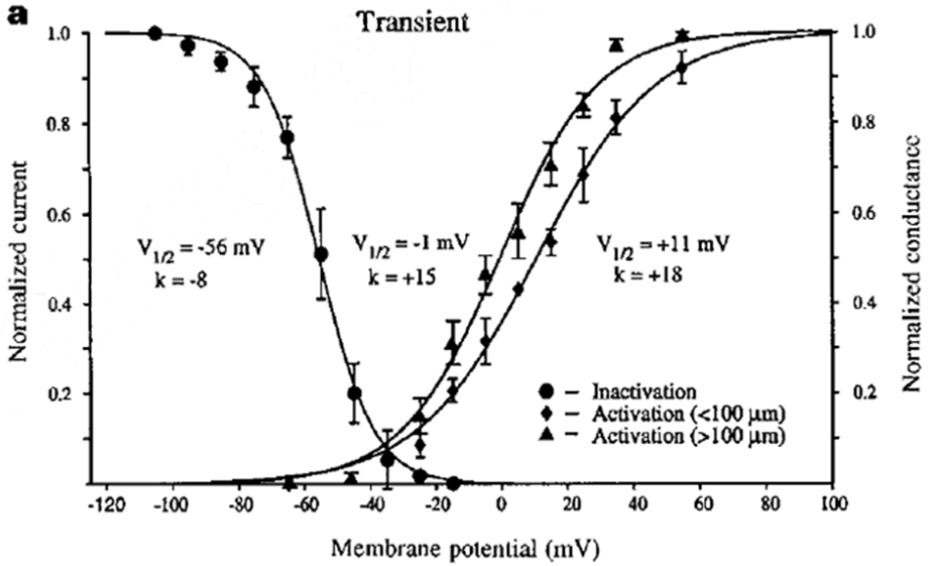
Experimental data on ion channel densities, their gradients and variability there

A-type K^+ channels

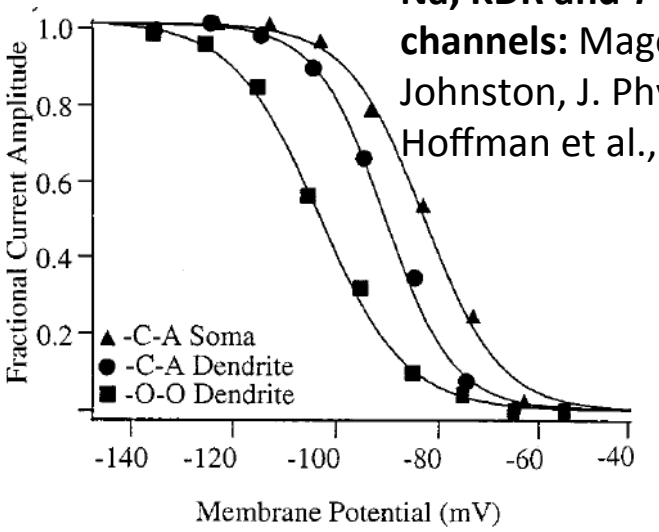




HCN channels



Na, KDR and *T*-type Ca^{2+} channels: Magee and Johnston, J. Physiol., 1995; Hoffman et al., Nature, 1997



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 on the *same* neuronal topograph?

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

Channelostasis (proteostasis for ion channels) is a complex puzzle in neurons

OPINION

Proteostasis in complex dendrites

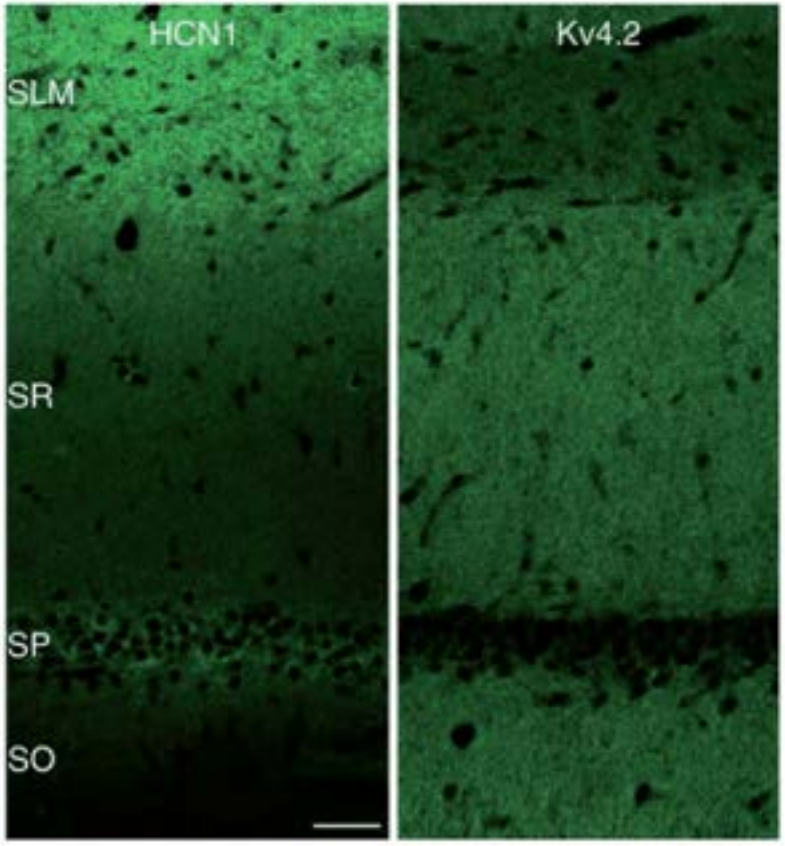
Cyril Hanus and Erin M. Schuman

Nature Reviews Neuroscience, 2013

Channelostasis, in pyramidal neurons is an extremely complex puzzle because:

(i) extensive dendritic arborization;

(ii) the combinatorial diversity of proteins that encode and regulate channel expression and localization.



Mediates I_h **Mediates I_{KA}**

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, $|Z|_{max}$, Φ_L)

11 differential equations per compartment

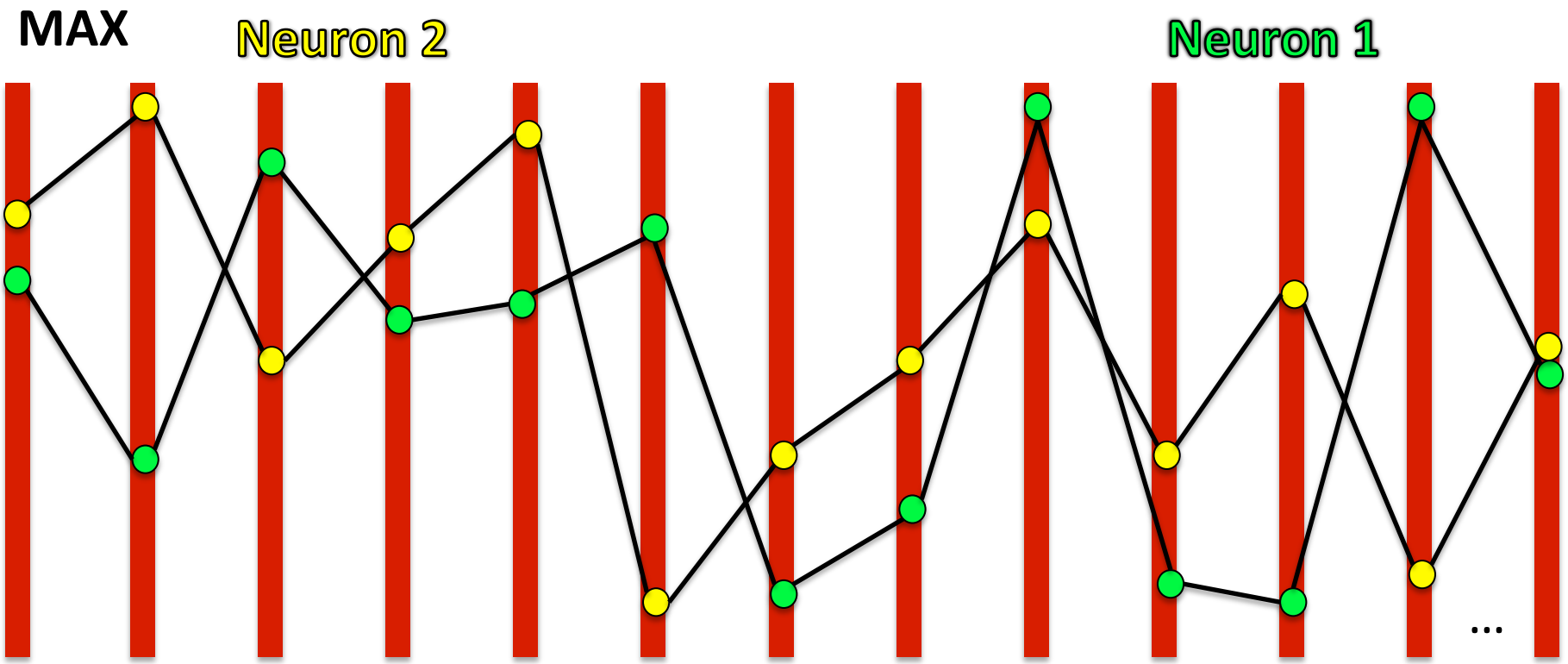
750–950 compartments per neuron

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

Rathour and Narayanan, PNAS, 2014

Global Sensitivity Analysis: Stochastic Sampling

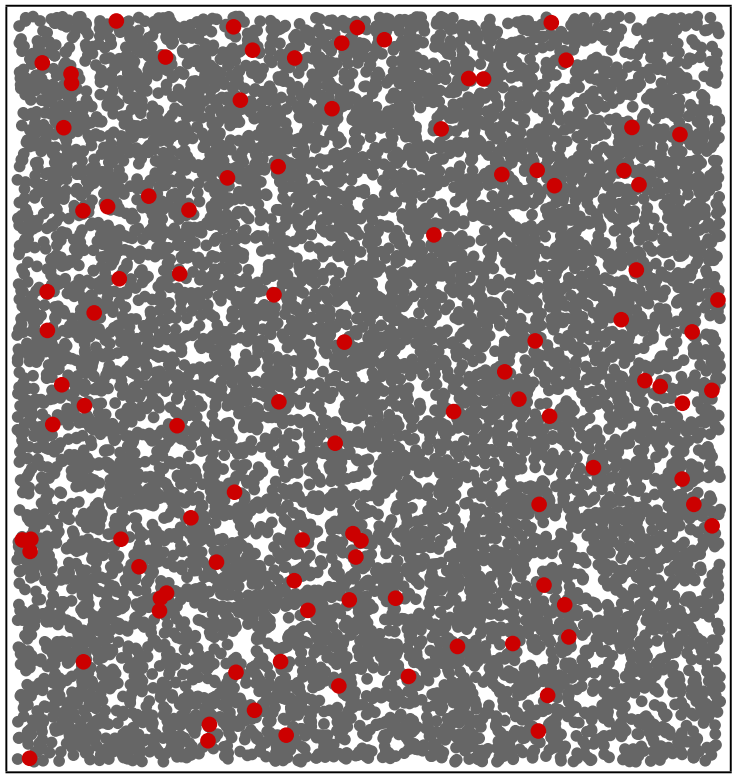


32 Model parameters

$$C_m \; g_L \; \bar{g}_{Na} \; \bar{g}_K \; V_{1/2}^m \; V_{1/2}^h \; V_{1/2}^n \; K_m \; K_h \; K_n \; \bar{\tau}_m \; \bar{\tau}_h \; \ldots \; \bar{\tau}_n$$

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

Global sensitivity analysis: Model Validation



Generate *N* such models by sampling these parameters

Obtain map measurements from them, and apply bounds on these measurements (e.g., Input resistance, resonance frequency, AP amplitude, etc.) from corresponding electrophysiological experiments

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

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.

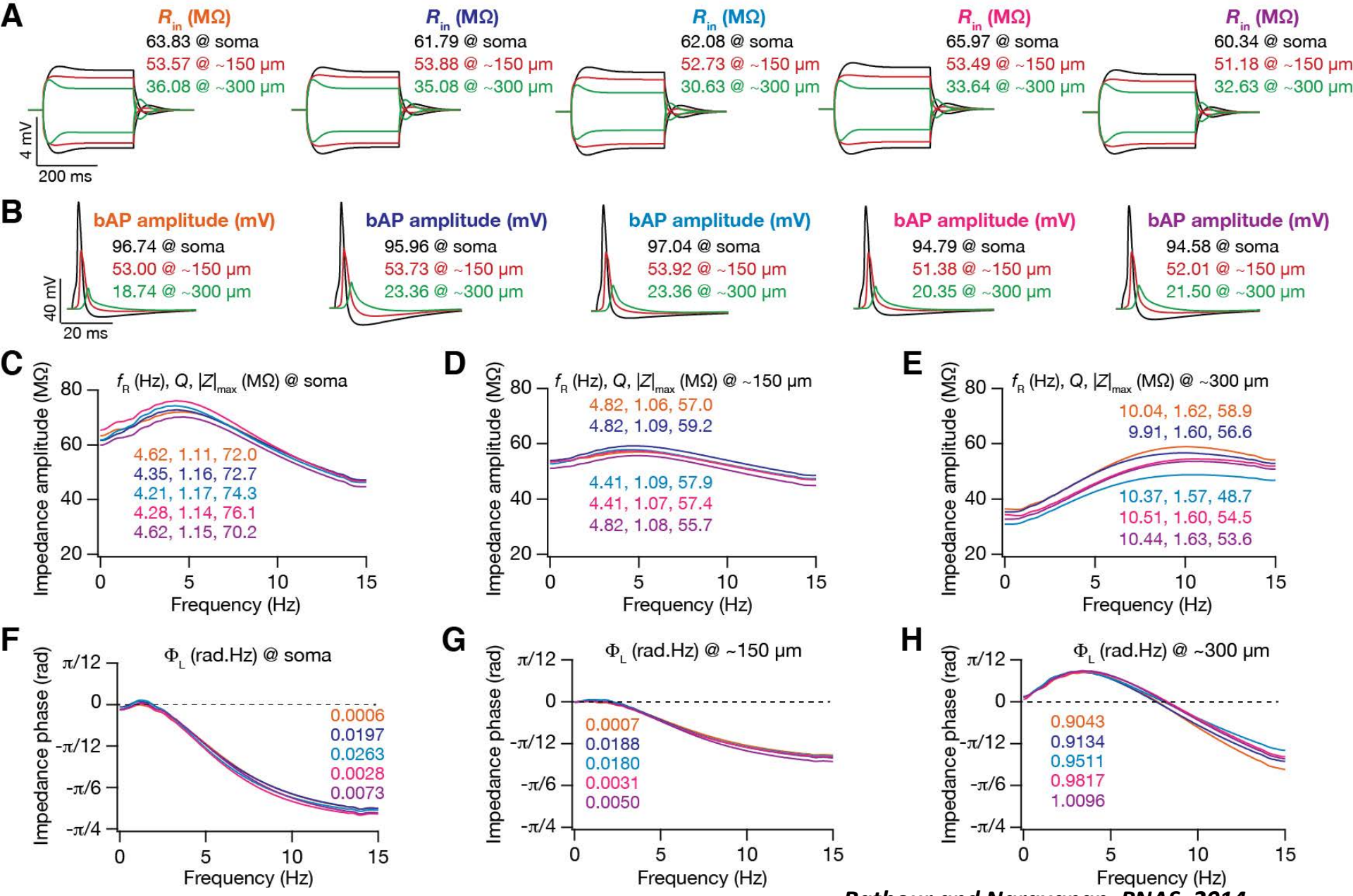
~80% of individual experimental variability covered by these bounds

Measurement	Soma		~150 µm		~300 µm	
	Lower	Upper	Lower	Upper	Lower	Upper
bAP Amplitude (mV)	90	105	40	70	10	25
Input resistance, R_{in}, (MΩ)	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, $\|Z\|_{max}$, (MΩ)	50	110	35	80	30	70

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

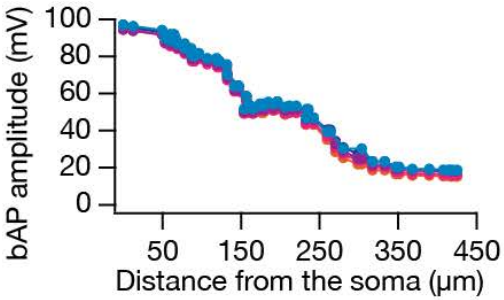
Rathour and Narayanan, PNAS, 2014

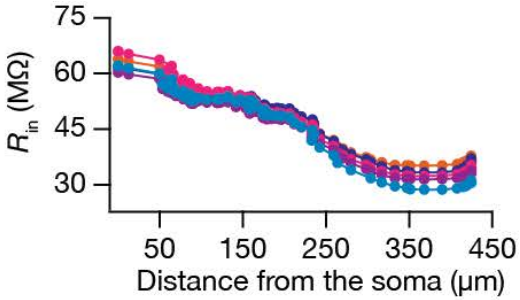
Let's take 5 valid models and compare their measurements,

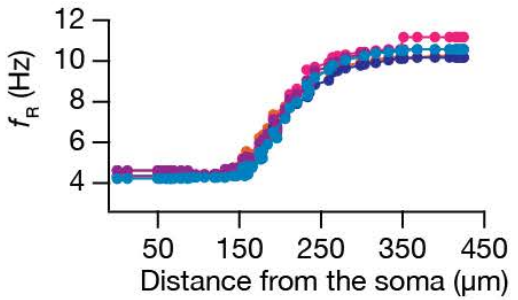


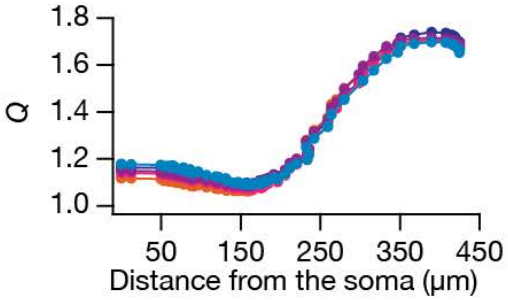
Rathour and Narayanan, PNAS, 2014

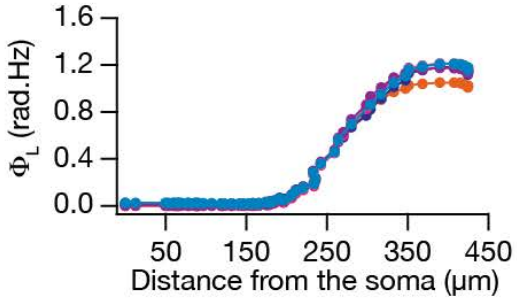
… their maps …

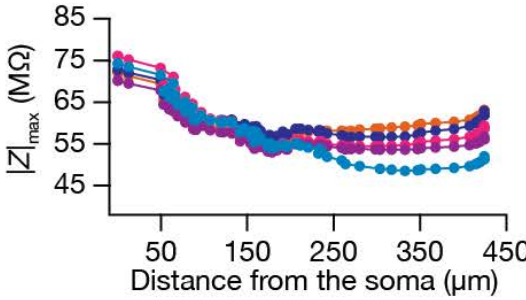










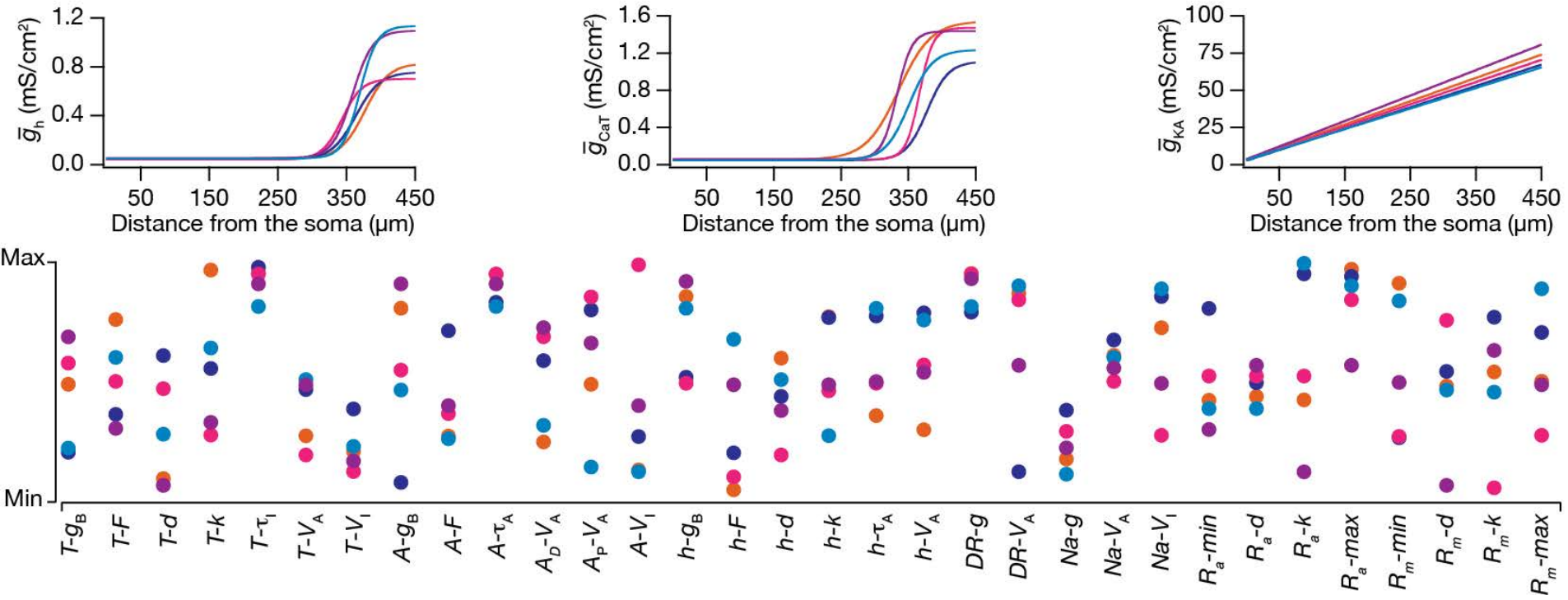


Maps are continuously constrained across valid models despite imposing constraints on only three locations

Rathour and Narayanan, PNAS, 2014

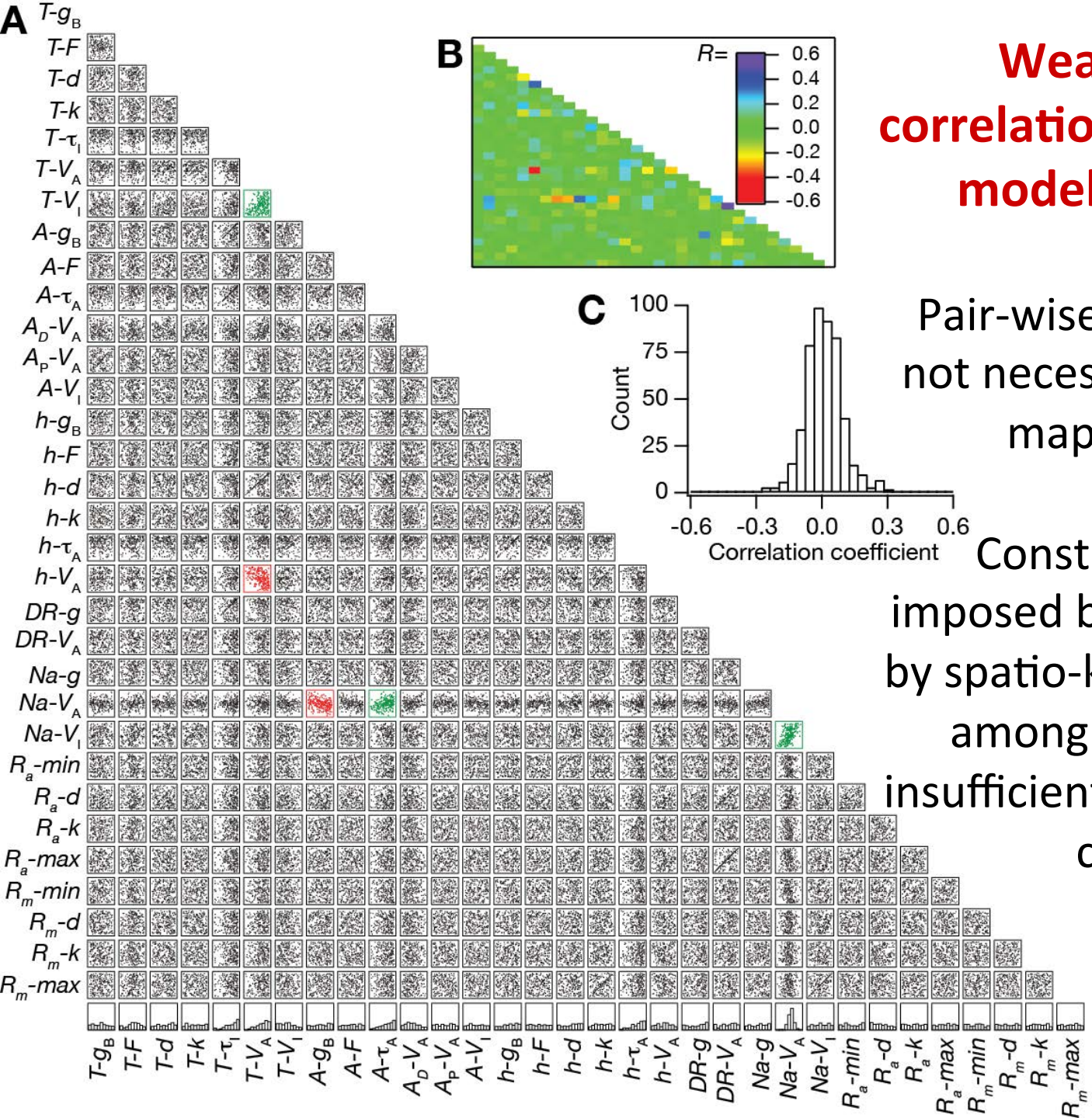
… and their ion channel gradients

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

Rathour and Narayanan, PNAS, 2014



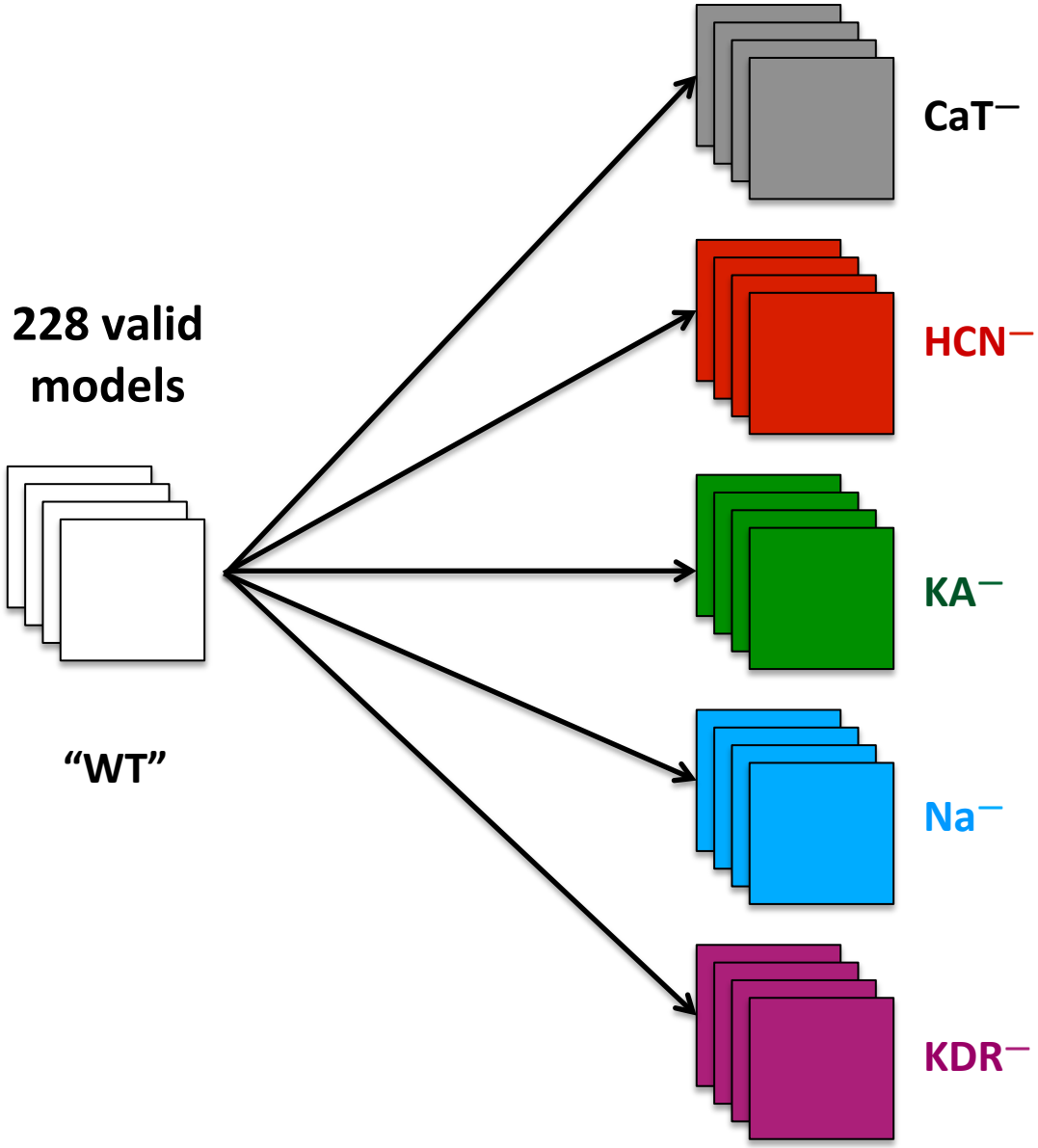
Weak pairwise correlations among valid-model parameters

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

Rathour and Narayanan, PNAS, 2014

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

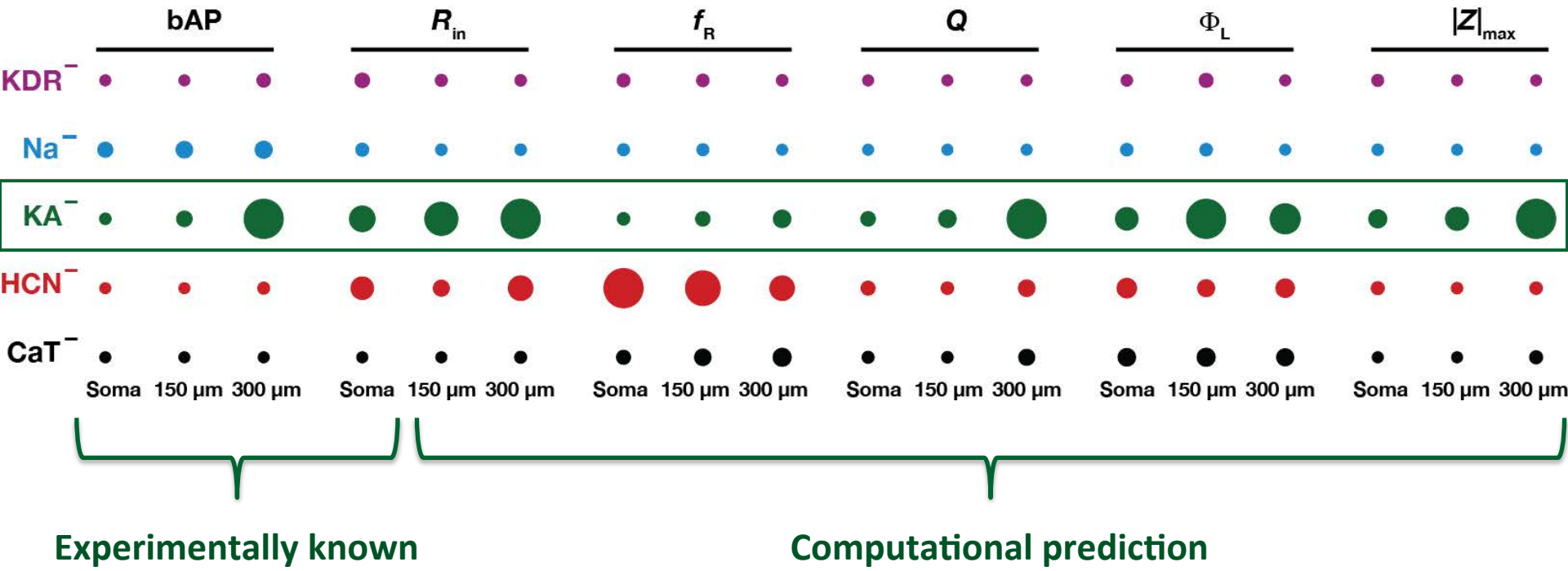


Virtual Knockout Models (VKM)

Obtain 18 map measurements (for all six maps) from each of these (228 × 5) VKMs and compare them with their "WT" counterparts

Relative dependence of individual measurements on different channels

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

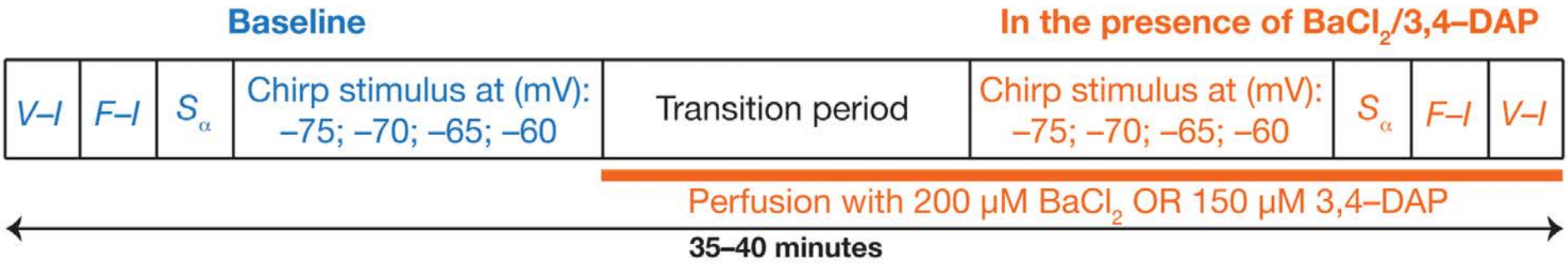


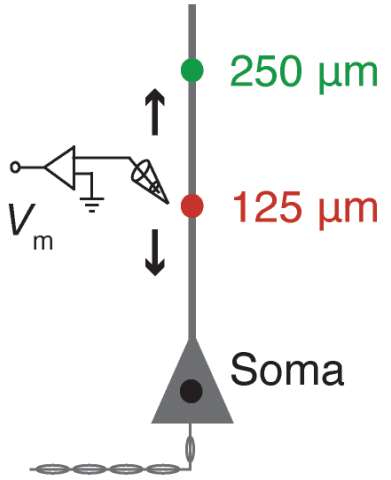
Experimentally known **Computational prediction**

Rathour and Narayanan, PNAS, 2014

Testing the computational prediction electrophysiologically!

Prediction: Blocking *A*-type K^+ channels would <u>decrease resonance frequency</u> but <u>increase input resistance</u> across the dendritic tree.





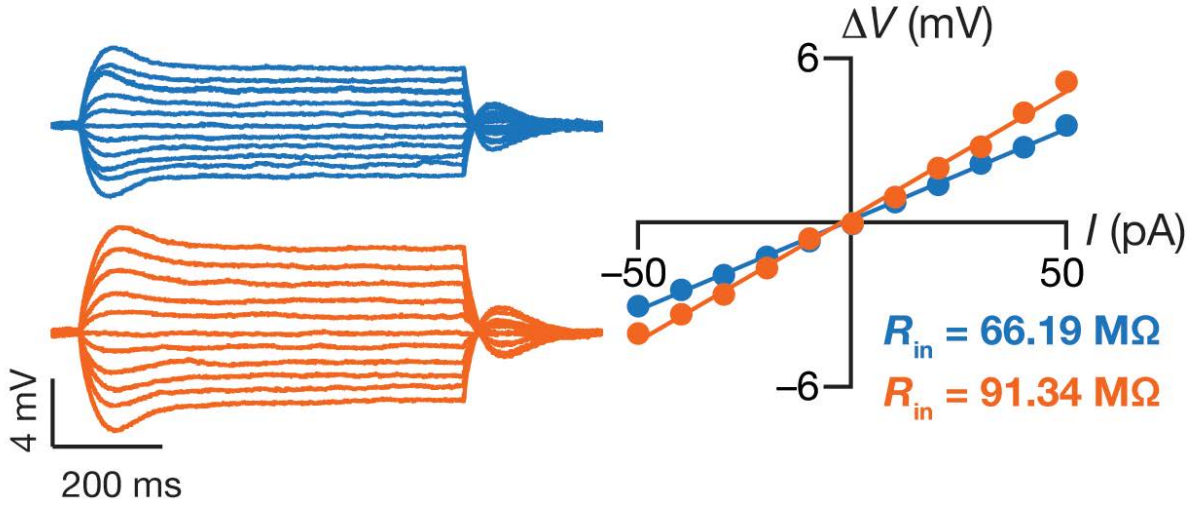
Recordings are from male sprague dawley rats

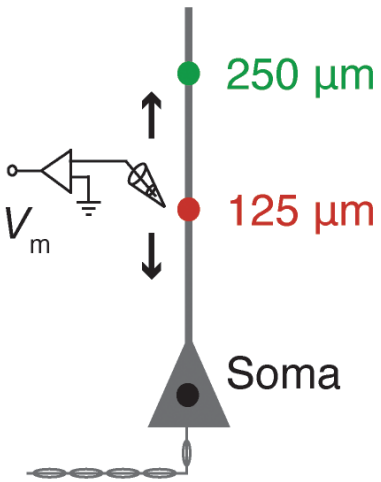
Recordings spanned up to 300 µm along the somatoapical axis of hippocampal pyramidal neurons

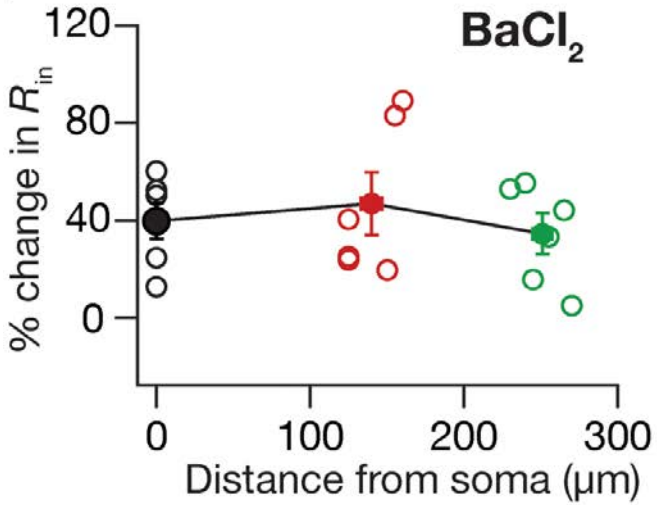
Rathour et al. Scientific Reports, 2016

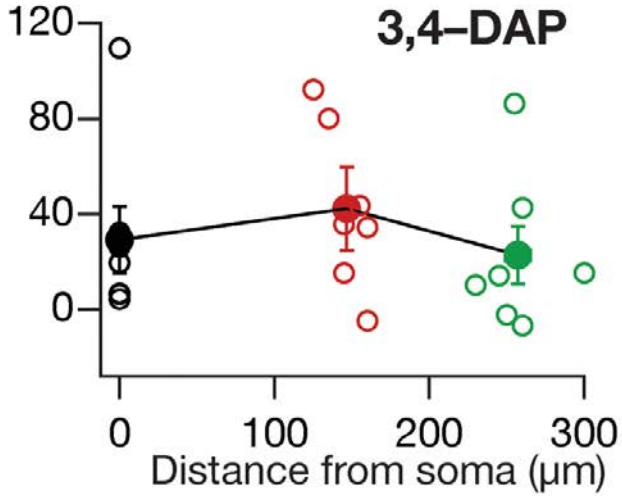
Input resistance increased at all locations with blockade of transient potassium channels

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





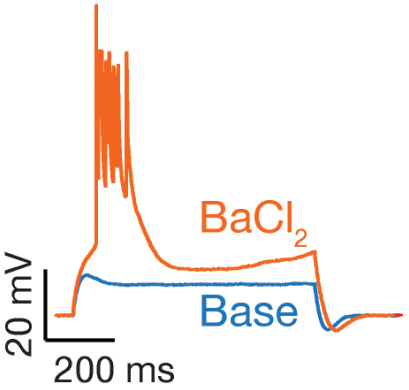


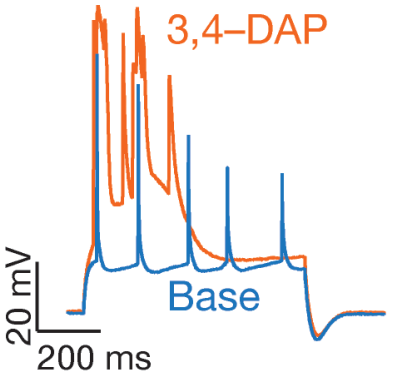


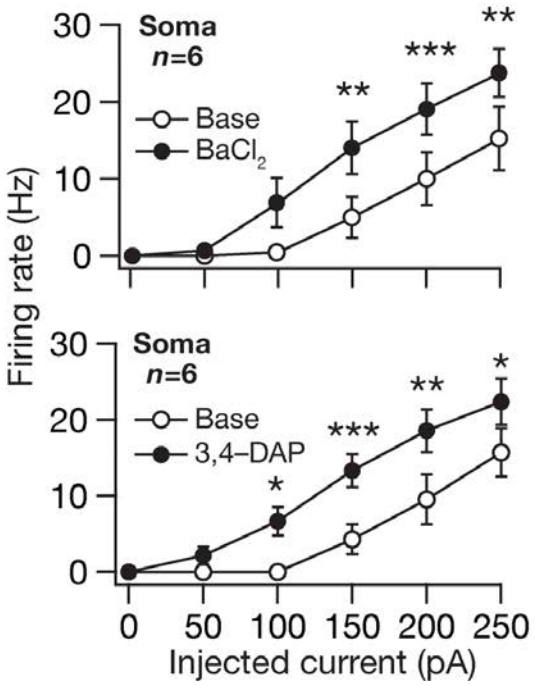
Rathour et al. Scientific Reports, 2016

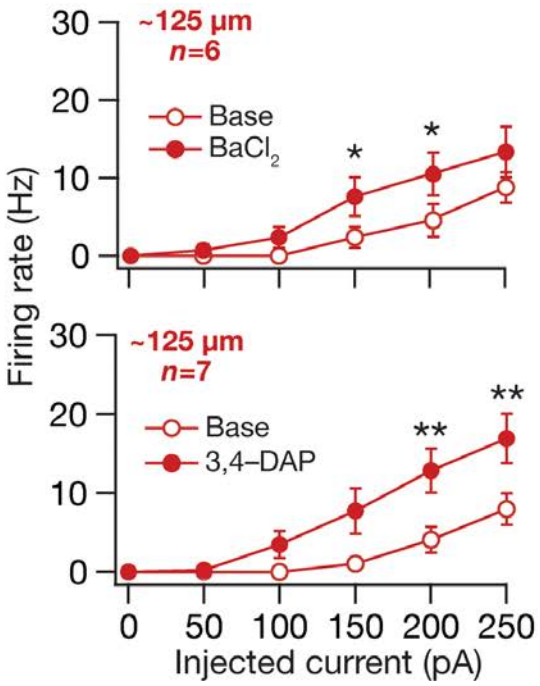
Consequently, firing rate increased at all locations with blockade of transient potassium channels

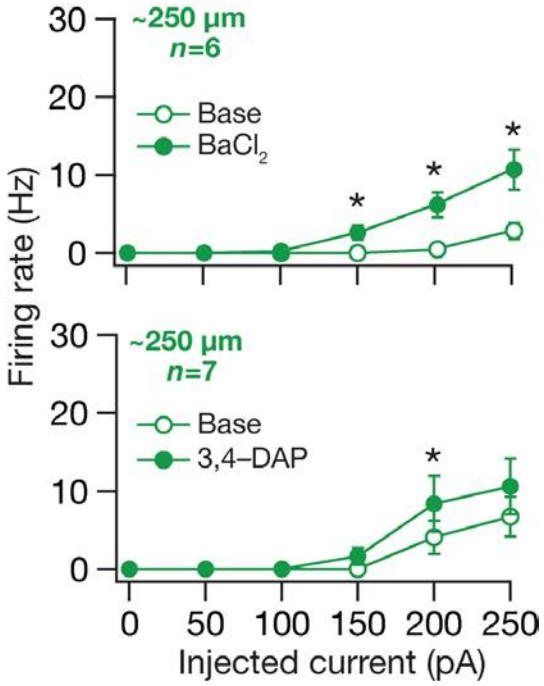
Prediction: Blocking *A*-type K^+ channels would <u>increase input resistance</u> (translating to increase in firing rate) across the dendritic tree.







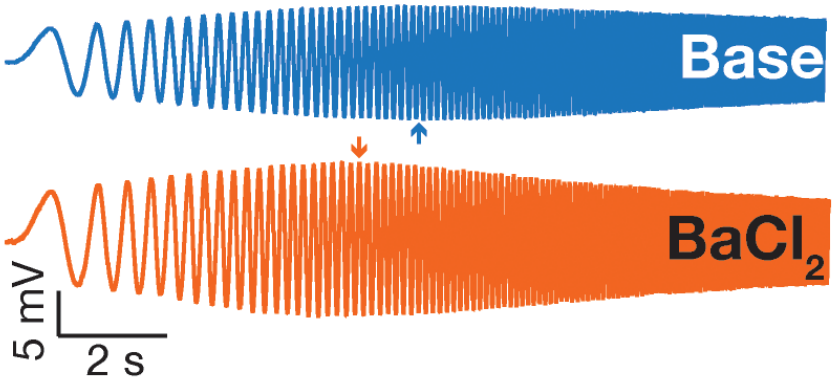


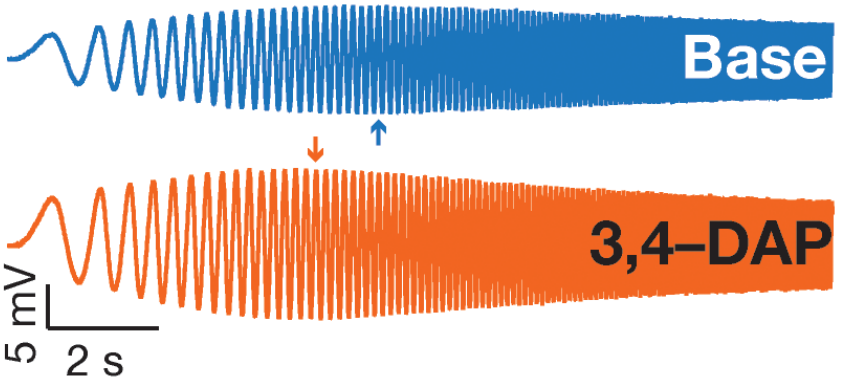


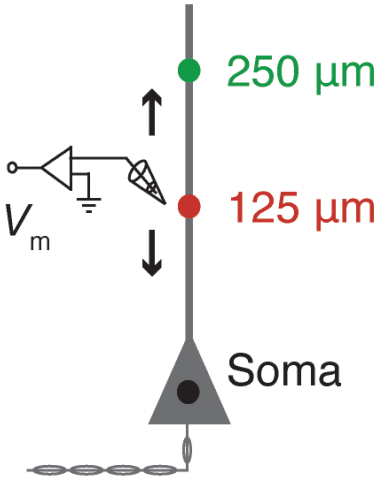
Rathour et al. Scientific Reports, 2016

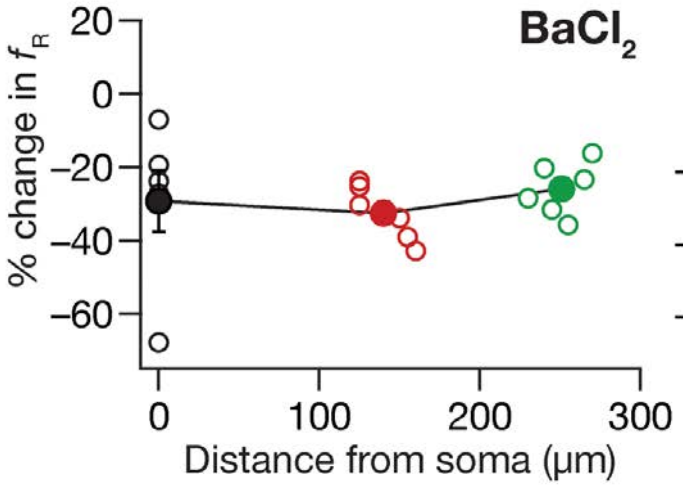
Resonance frequency decreased at all locations after blockade of transient potassium channels

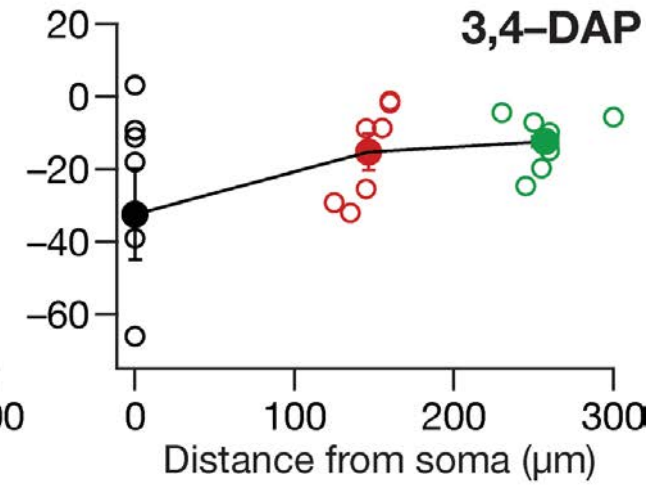
Prediction: Blocking *A*-type K^+ channels would decrease resonance frequency across the dendritic tree.











Rathour et al. Scientific Reports, 2016

Degeneracy in synaptic plasticity profiles

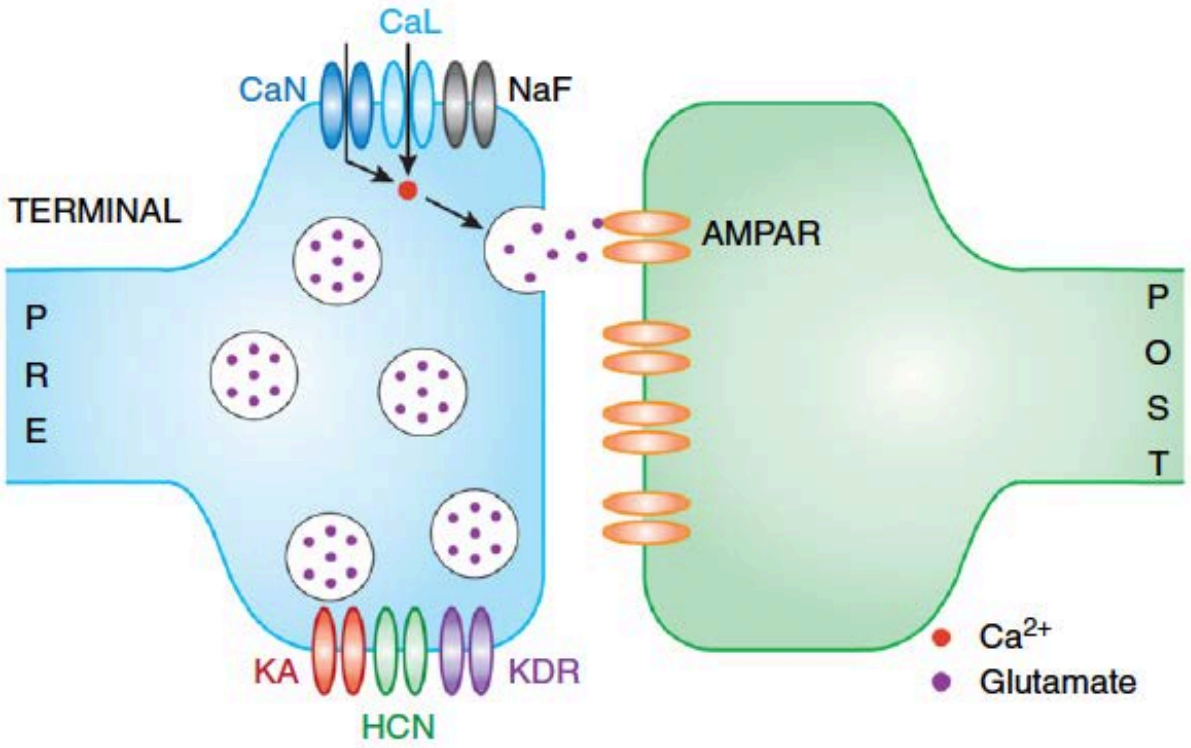
Degeneracy in short-term plasticity profiles

Degeneracy in the regulation of short-term plasticity and synaptic filtering by presynaptic mechanisms

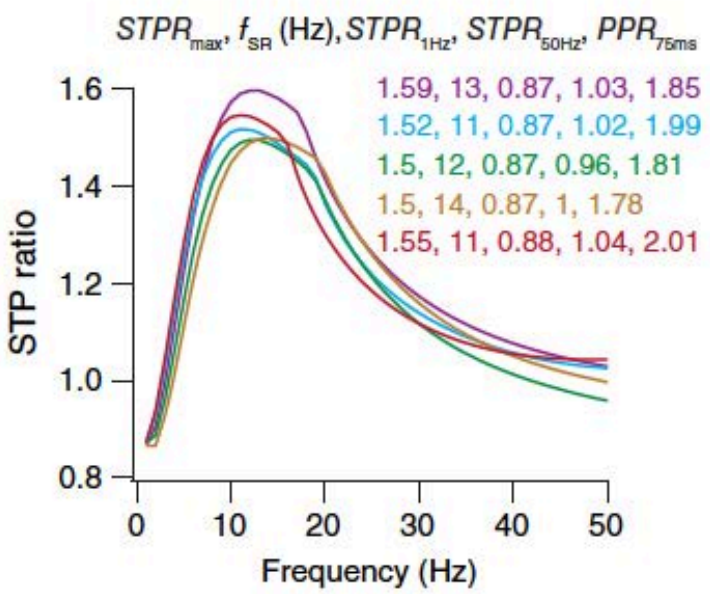
Chinmayee L. Mukunda and Rishikesh Narayanan

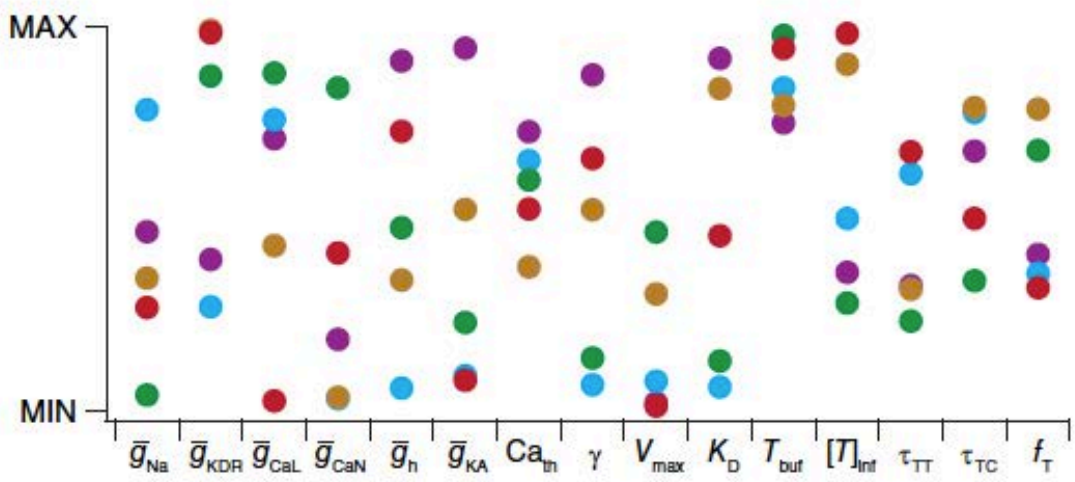
Cellular Neurophysiology Laboratory, Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India

The Journal of Physiology, April 2017



Degeneracy in short-term plasticity profiles





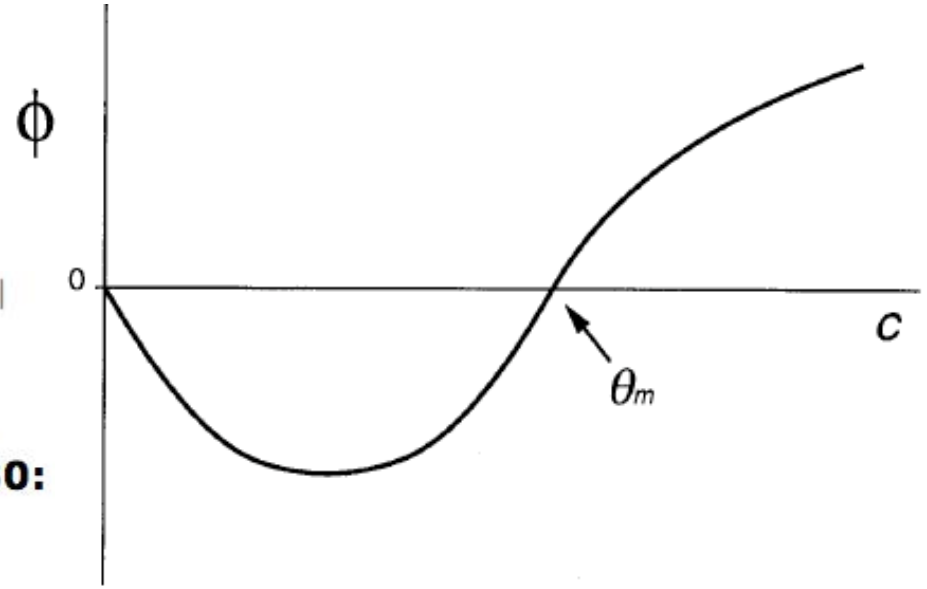
The BCM rule and hippocampal plasticity

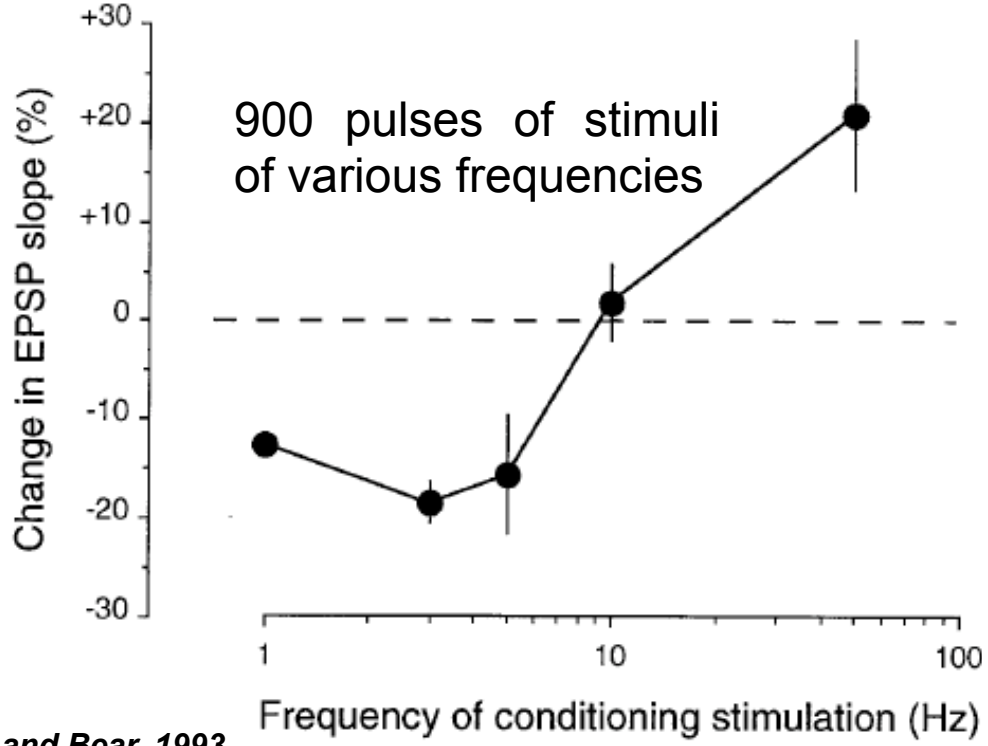
Nature Reviews Neuroscience **13**, 798-810 (November 2012) |
doi:10.1038/nrn3353

OPINION

The BCM theory of synapse modification at 30: interaction of theory with experiment

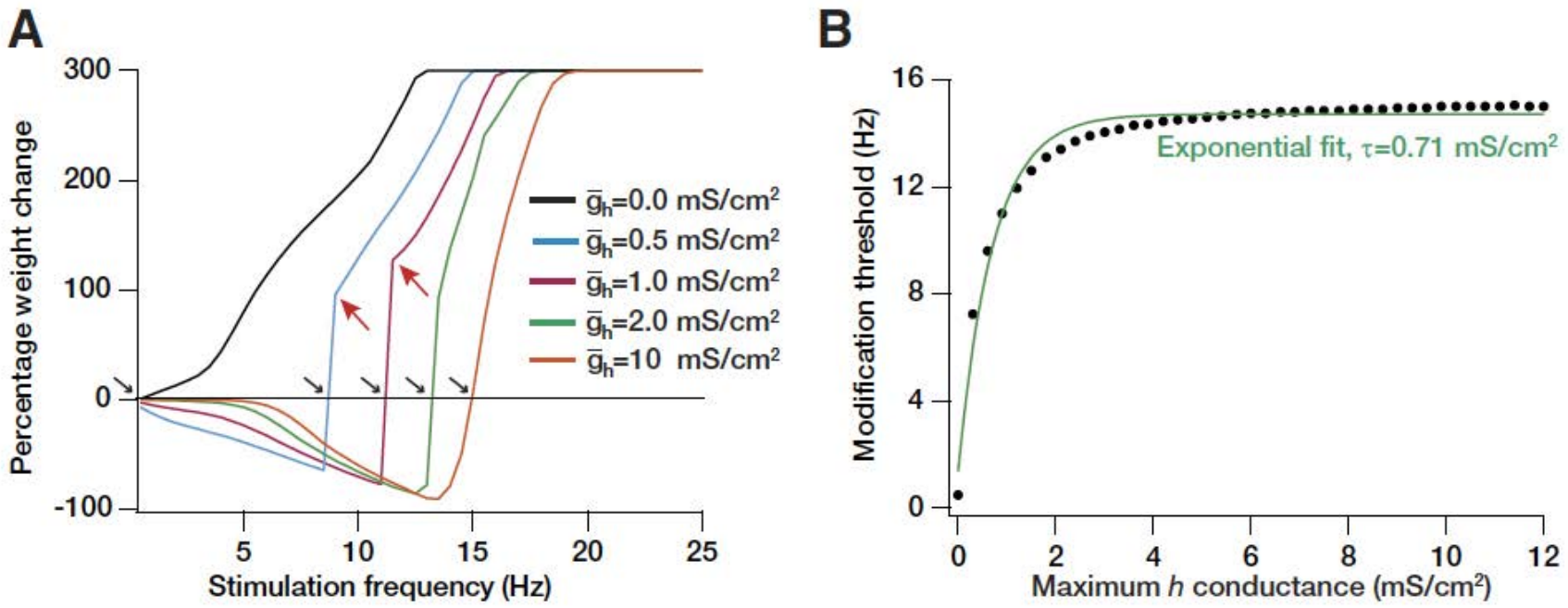
Leon N Cooper[1] & Mark F. Bear[2] About the authors





Dudek and Bear, 1993

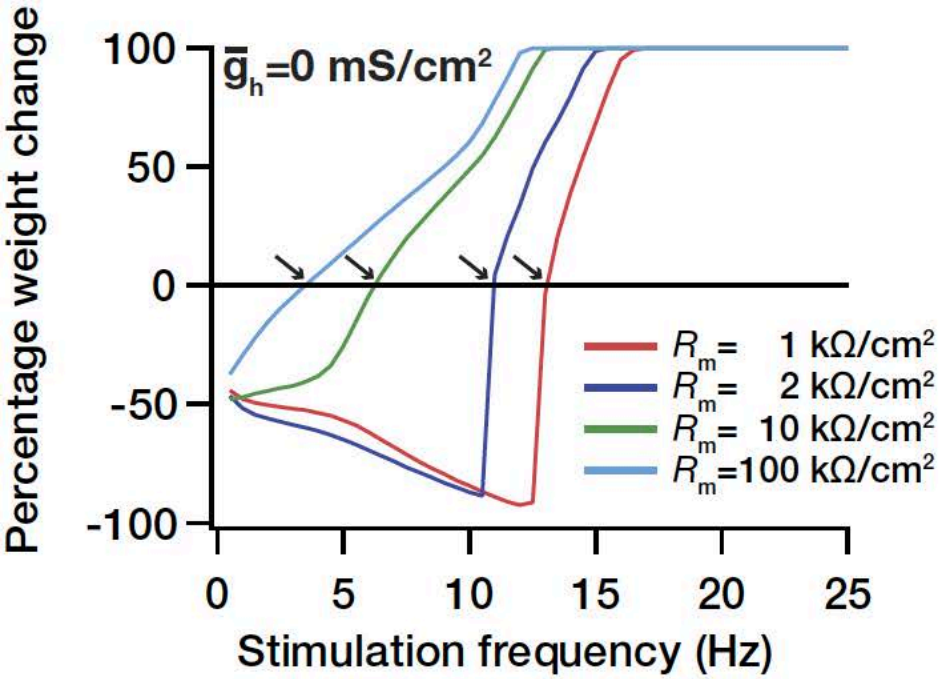
HCN channels alter synaptic plasticity rules

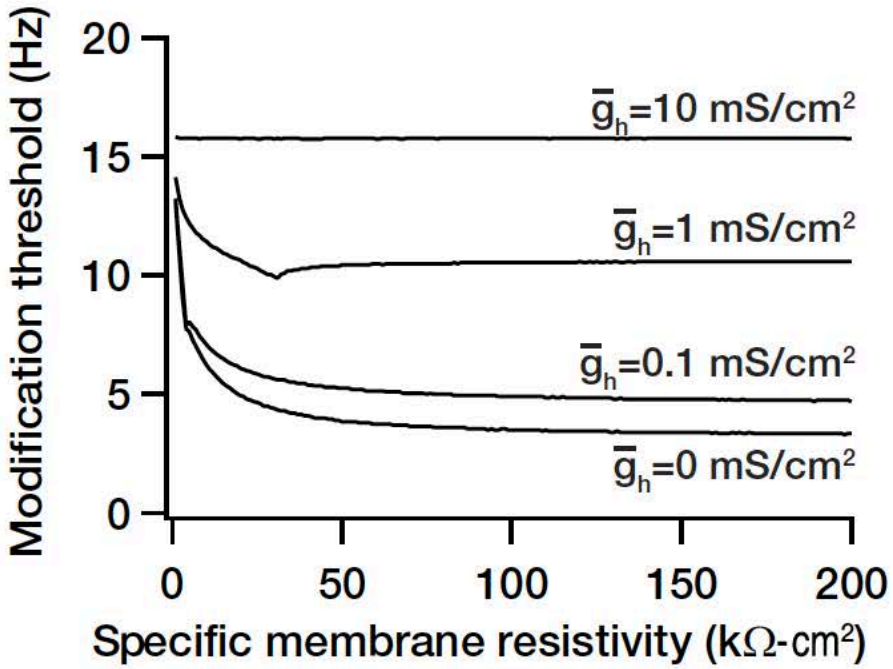


Narayanan and Johnston, J. Neurophys, 2010

Leak channels also alter synaptic plasticity rules!!

Impact of intrinsic properties/plasticity on synaptic plasticity rules

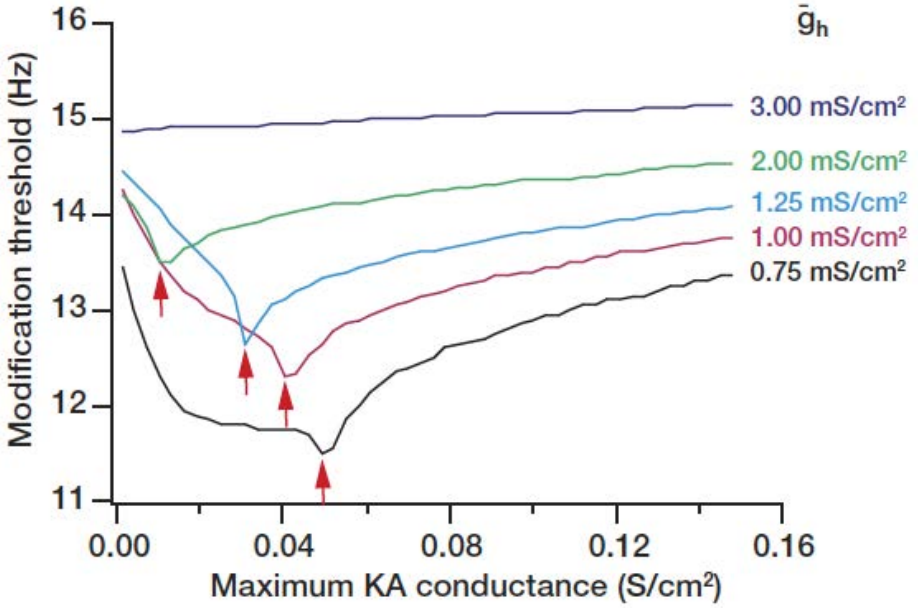


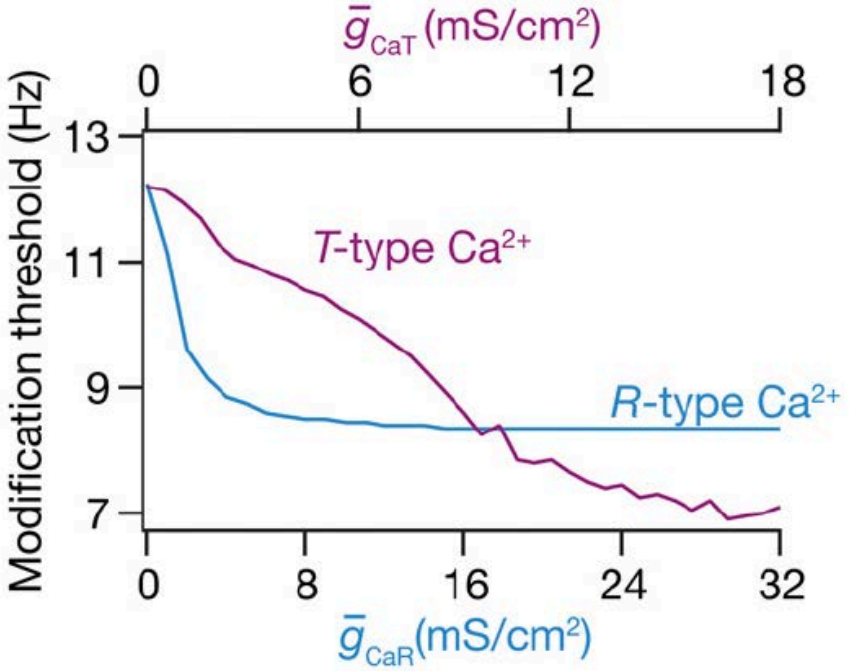


Narayanan and Johnston, J. Neurophys, 2010

So do *A*-type K^+ channels, *R*- and *T*-type Ca^{2+} channels

Impact of intrinsic properties/plasticity on synaptic plasticity rules



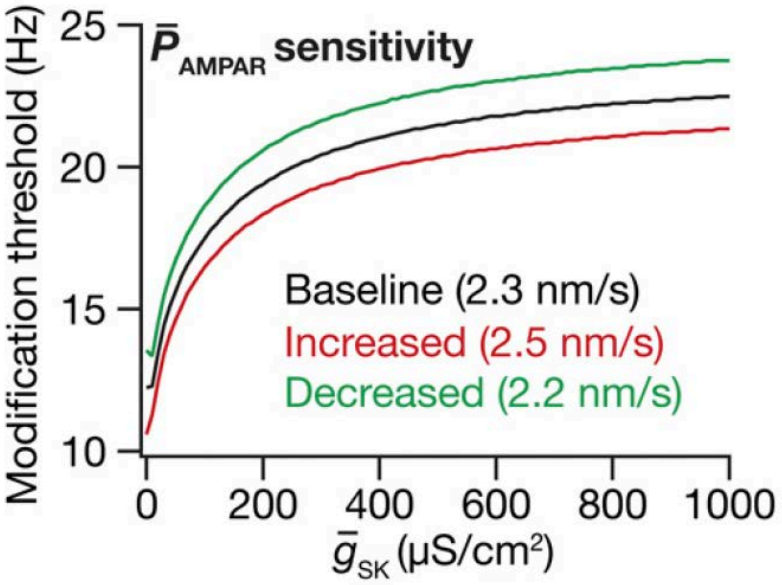


Narayanan and Johnston, J. Neurophys, 2010

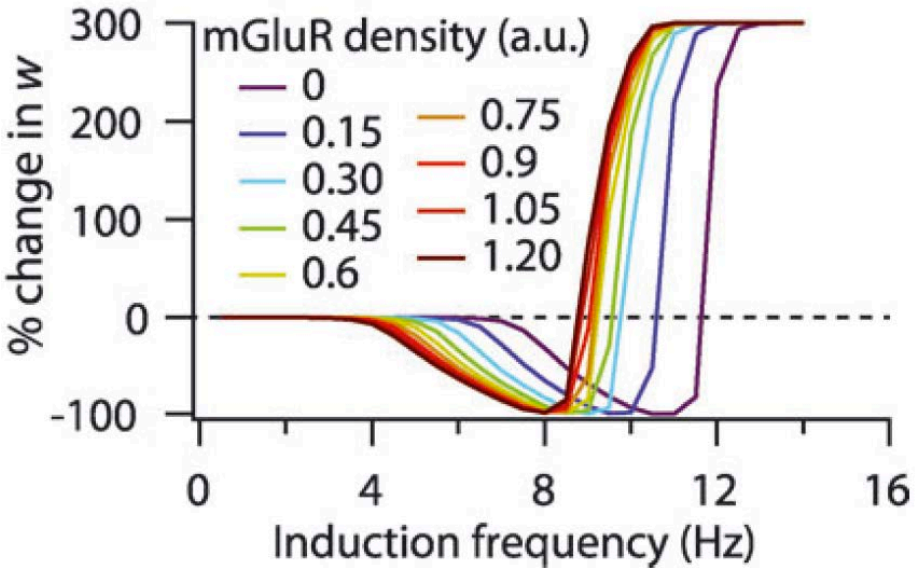
Anirudhan and Narayanan J. Neurosci, 2015

So do SK channels and mGluR receptors!!!

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



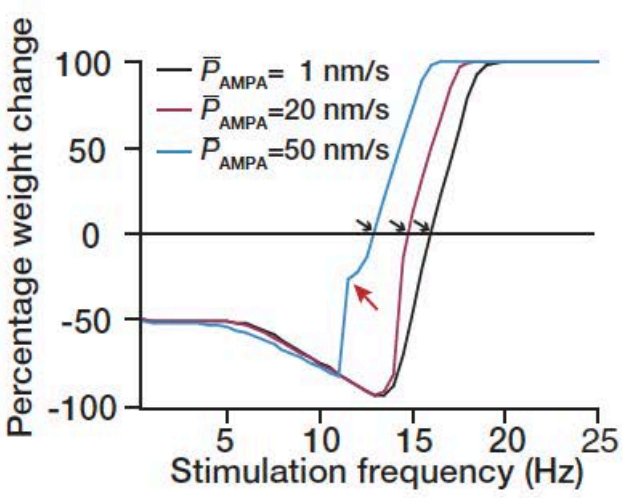
Anirudhan and Narayanan J. Neurosci, 2015

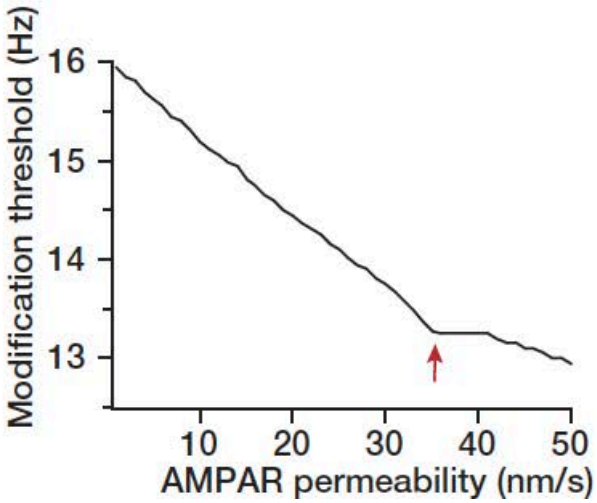


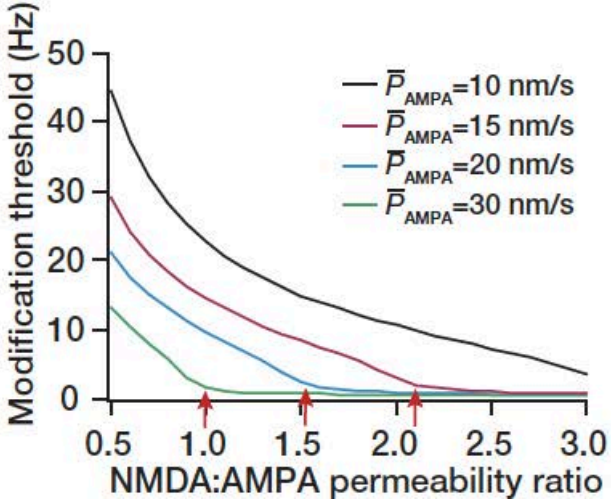
Ashhad and Narayanan J. Physiol, 2013

So do AMPA and NMDA receptors!!!

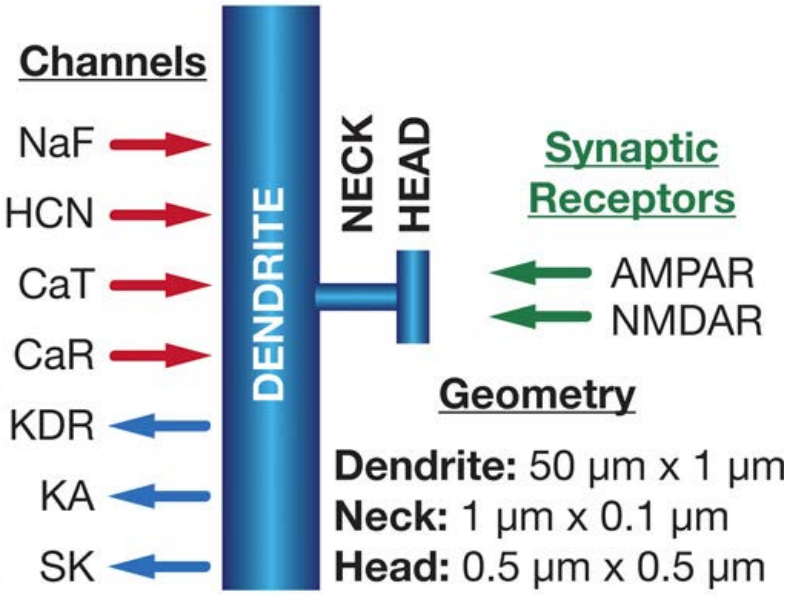
Impact of receptor plasticity on synaptic plasticity rules







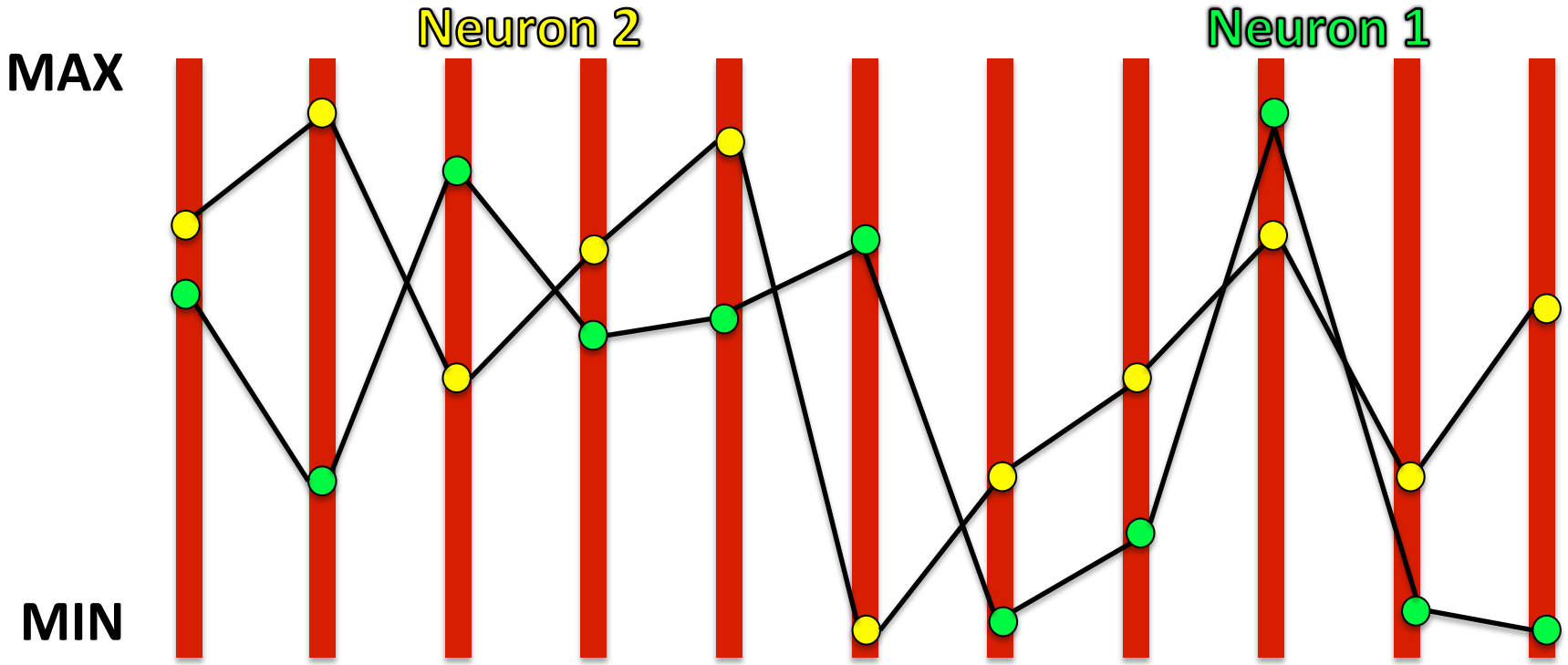
Narayanan and Johnston, J. Neurophys, 2010



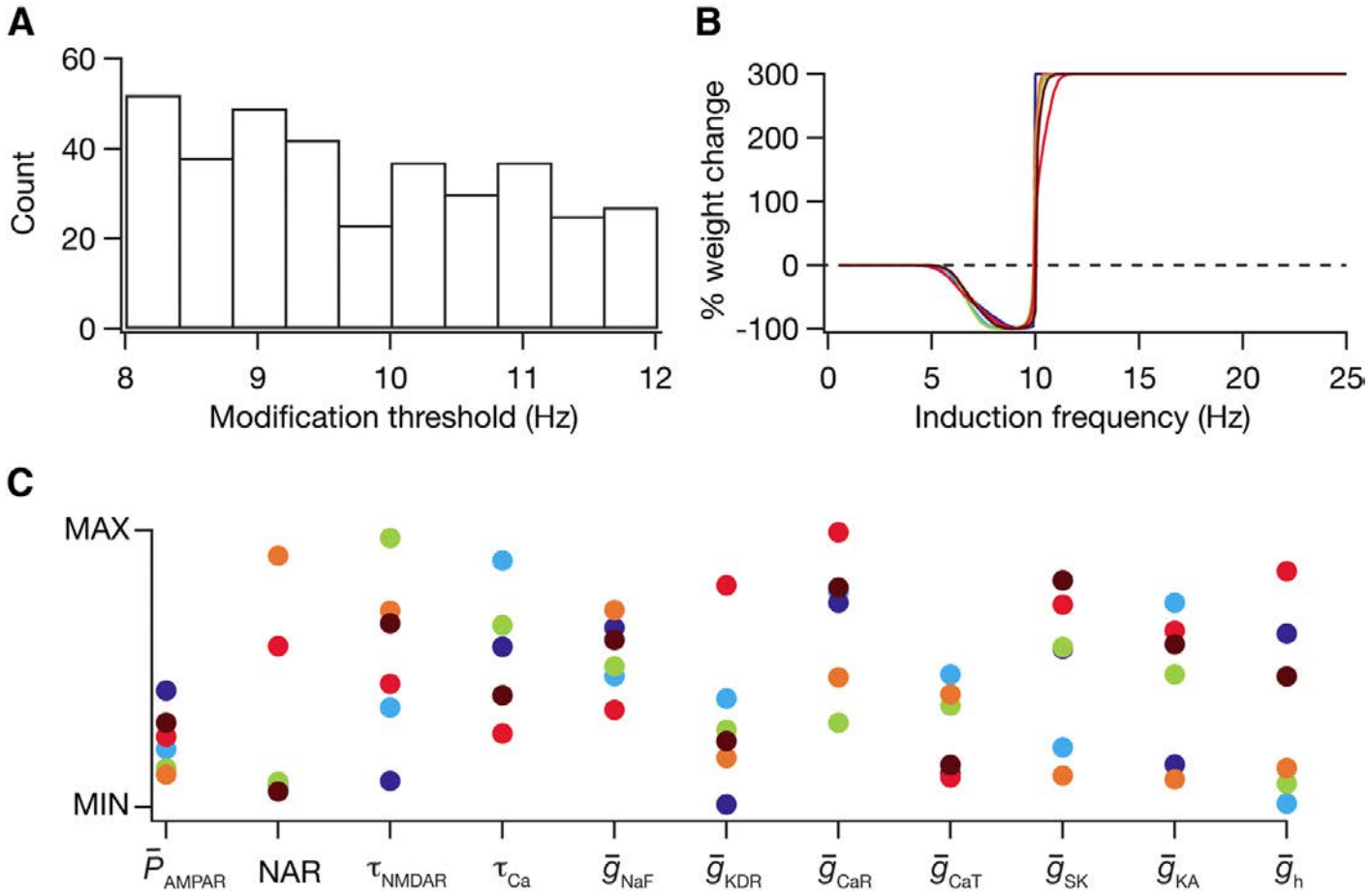
So, are there several ways to achieve the same plasticity profile?

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

Anirudhan and Narayanan J. Neurosci, 2015

Summary

Nothing in physiology 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.

Degeneracy and the underlying complexity are necessary for, and an inevitable outcome of, natural selection.

Complexity in biological systems should not be viewed from the limited perspective of curse-of-dimensionality, but from the evolutionarily advantageous perspective of achieving functional robustness through degeneracy.