Hippocampal Interneurons: Model Development Strategies

Frances K. Skinner

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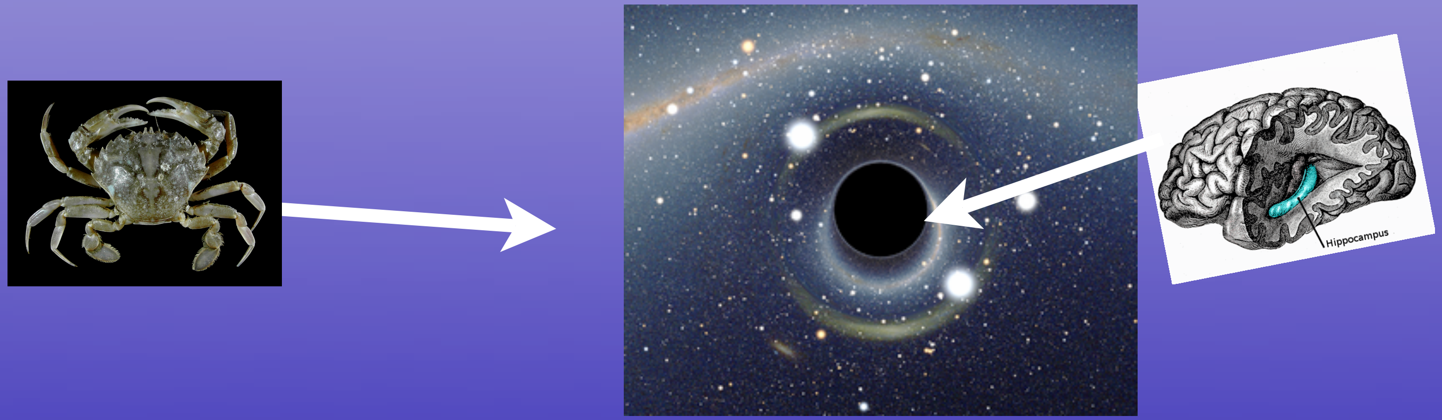
HBP Hippocamp CA1: Collaborative and Integrative Modeling of Hippocampal Area CA1

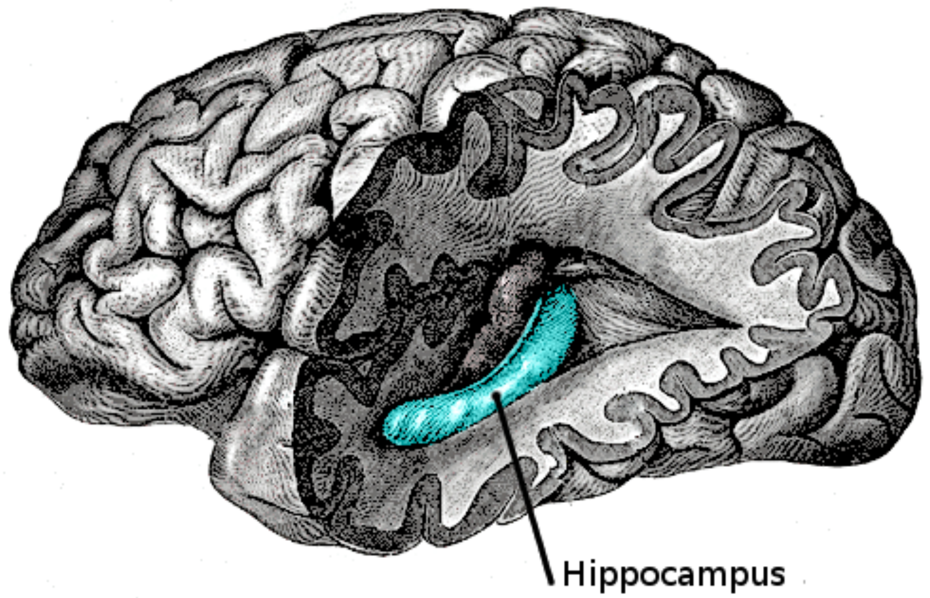
31st March-1st April 2015, London, United Kingdom



images: wikipedia

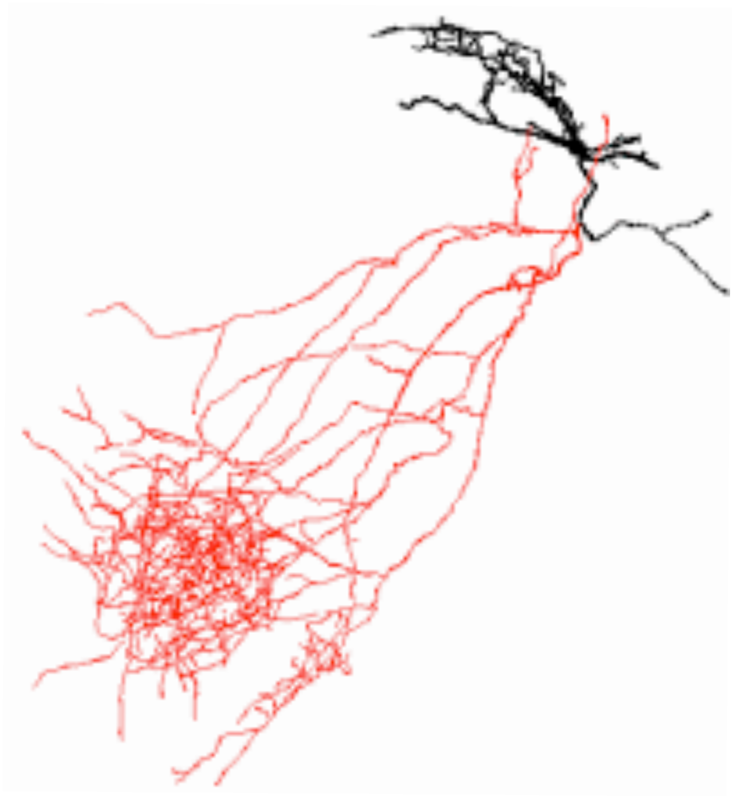
TALK OUTLINE

- brief intro
- cellular-based modeling features
- existing inhibitory models (briefly)
- some of our modeling (briefly)
- opinion/suggestions

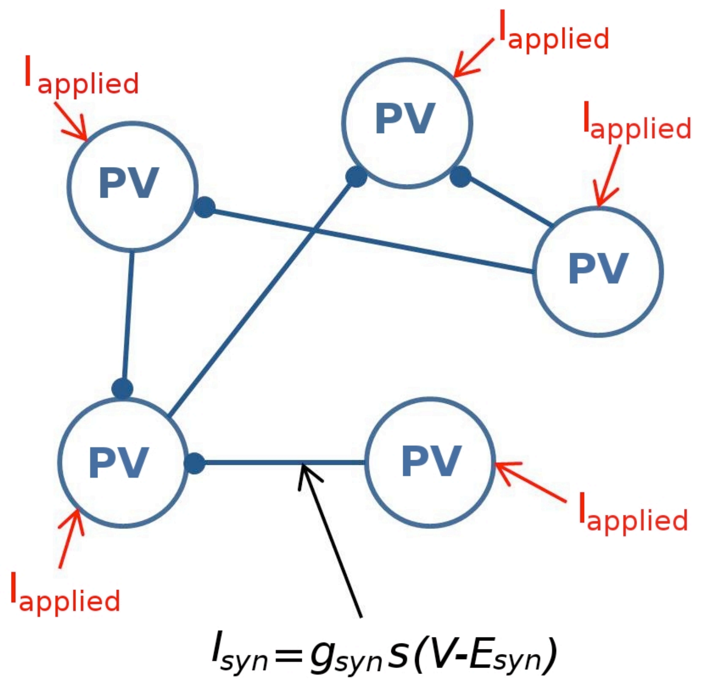


Two Research Prongs in my Lab

Detailed multi-compartment models of inhibitory cells



Population activities in inhibitory (and excitatory) networks



from Scholarpedia, "Hippocampus" - Buzsaki (2011)

"The **hippocampus** is a part of the forebrain, located in the medial temporal lobe. It is critical for the formation of those kinds of memories, which can be consciously *declared*. Due to its self-generated network patterns, newly acquired memories are gradually transferred to neocortical stores through the process of memory consolidation."

"Nearly all *hippocampal functions* are performed in collaboration with several of its partners, of which the most prominent is the entorhinal cortex, and strongly influenced by subcortical neuromodulators."

Function of hippocampal subregions

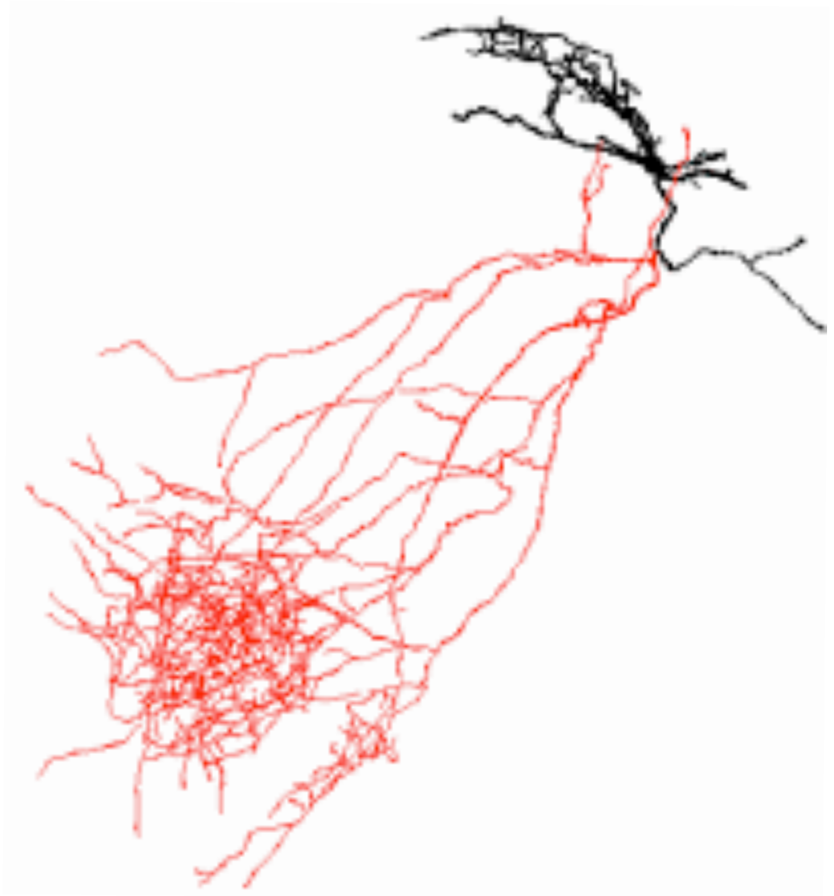
from Scholarpedia, "Models of Hippocampus" - Hasselmo (2011)

Region CA1

"In contrast to region CA3, region CA1 has little excitatory recurrent connectivity, and receives primarily feedforward input from region CA3 and medial entorhinal cortex layer III. Some models have proposed that region CA1 functions as a comparator of the input from entorhinal cortex layer III with the output from region CA3....."

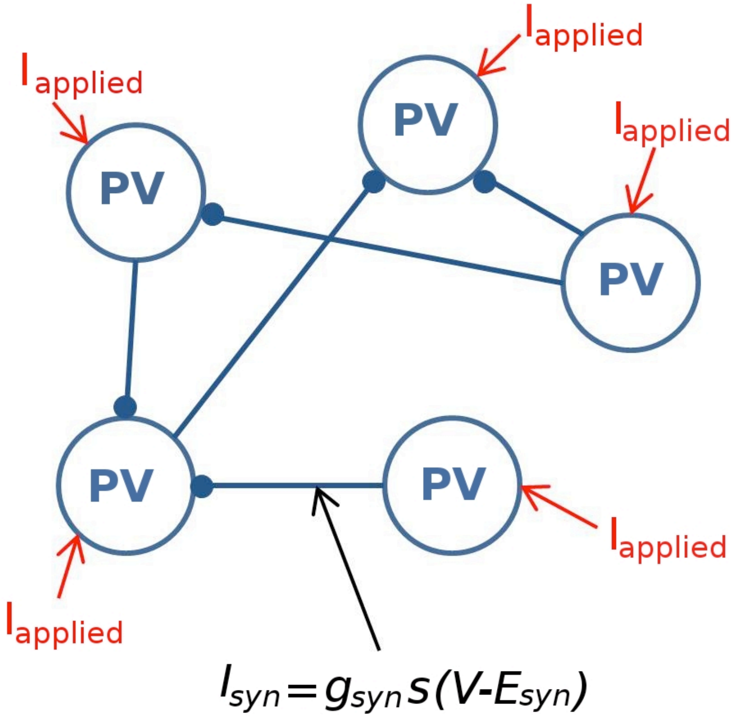
Two Research Prongs in my Lab

Detailed multi-compartment models of inhibitory cells



Experimental Collaborators (present):
J.J. Lawrence, L. Topolnik

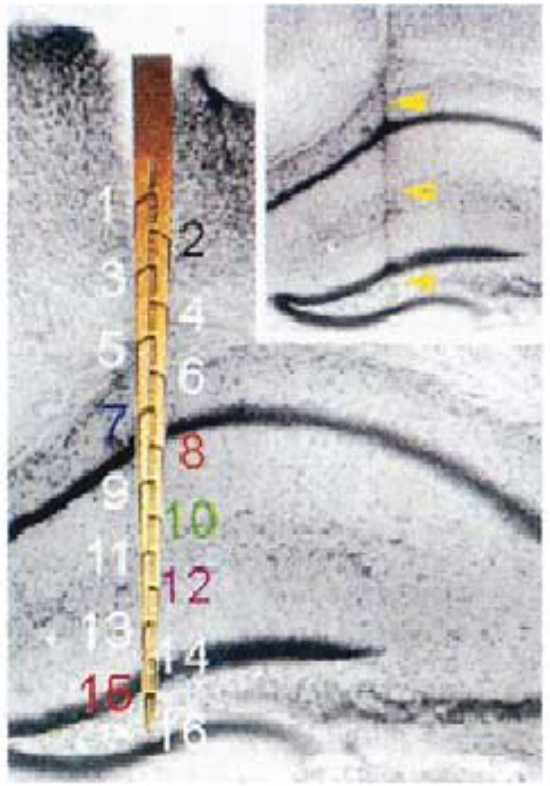
Population activities in inhibitory (and excitatory) networks



Experimental Collaborators (present):
S. Williams

Population Activities in rodent hippocampus

Electrode placement

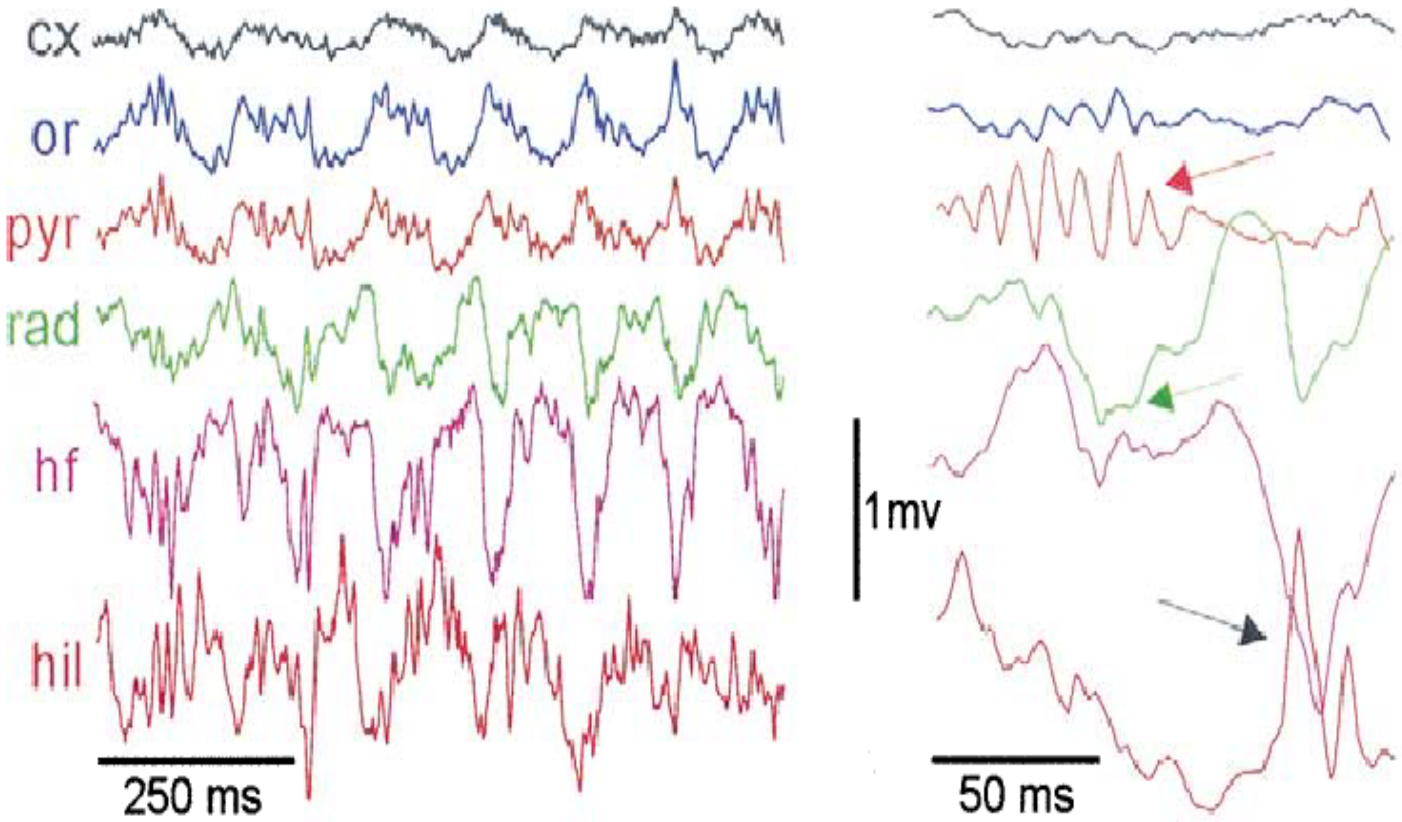


movement, exploration

Theta - gamma

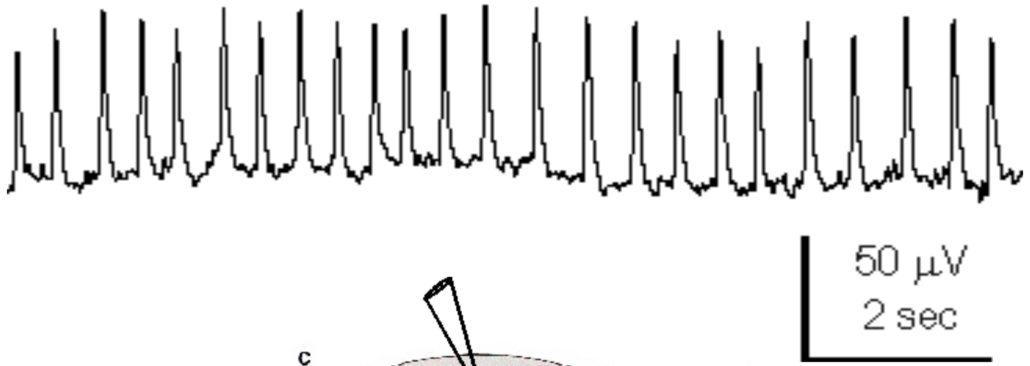
slow-wave sleep

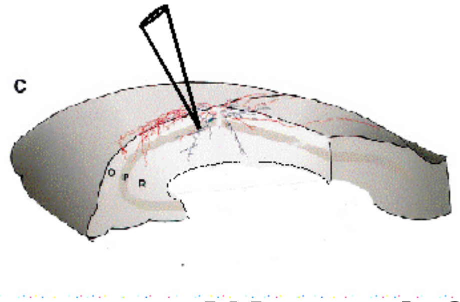
Sharp waves (SPW) - ripples



Buzsáki et al. 2003

mouse *in vivo*

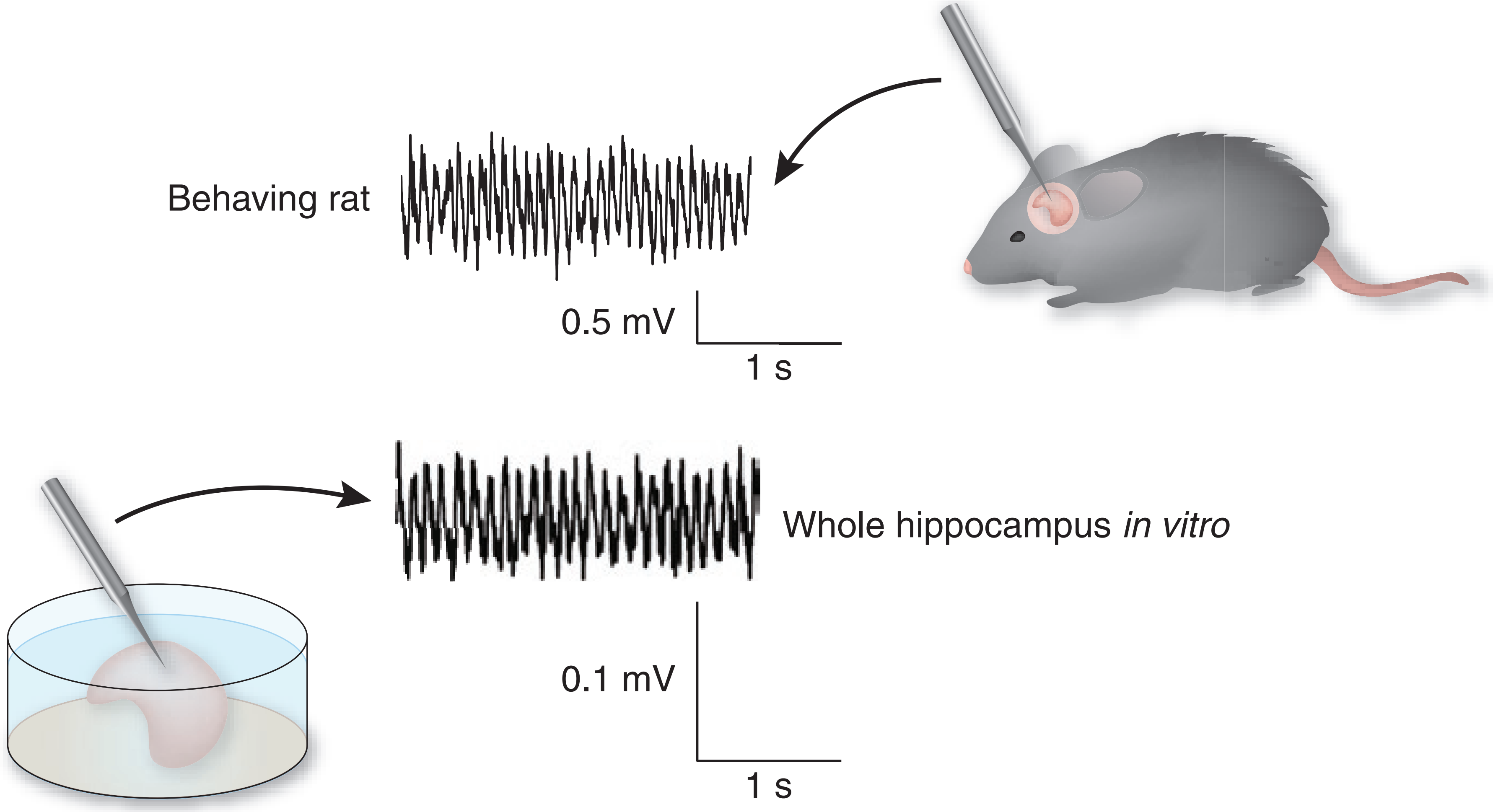




Wu et al. 2002, 2005

spontaneous GABAergic rhythms *in vitro*

Population Activities in rodent hippocampus (cont'd)



Theta (4-12 Hz) oscillations

Colgin and Moser 2009
based on Goutagny et al. 2009

behaviour and cognitive functioning

brain (macro-)circuits
(systems and pathways; cortical regions; distributed networks; large networks of neurons)

brain (micro-)circuits
(local circuits, networks of neurons)

cellular
- **single compartment**
- **multi-compartment**

(dendritic/axonal representation)

synaptic
(electrical, chemical)

molecular
(ion channels)

subcellular
(signalling pathways; internal/external concentrations; calcium dynamics; plasticity)

genetic

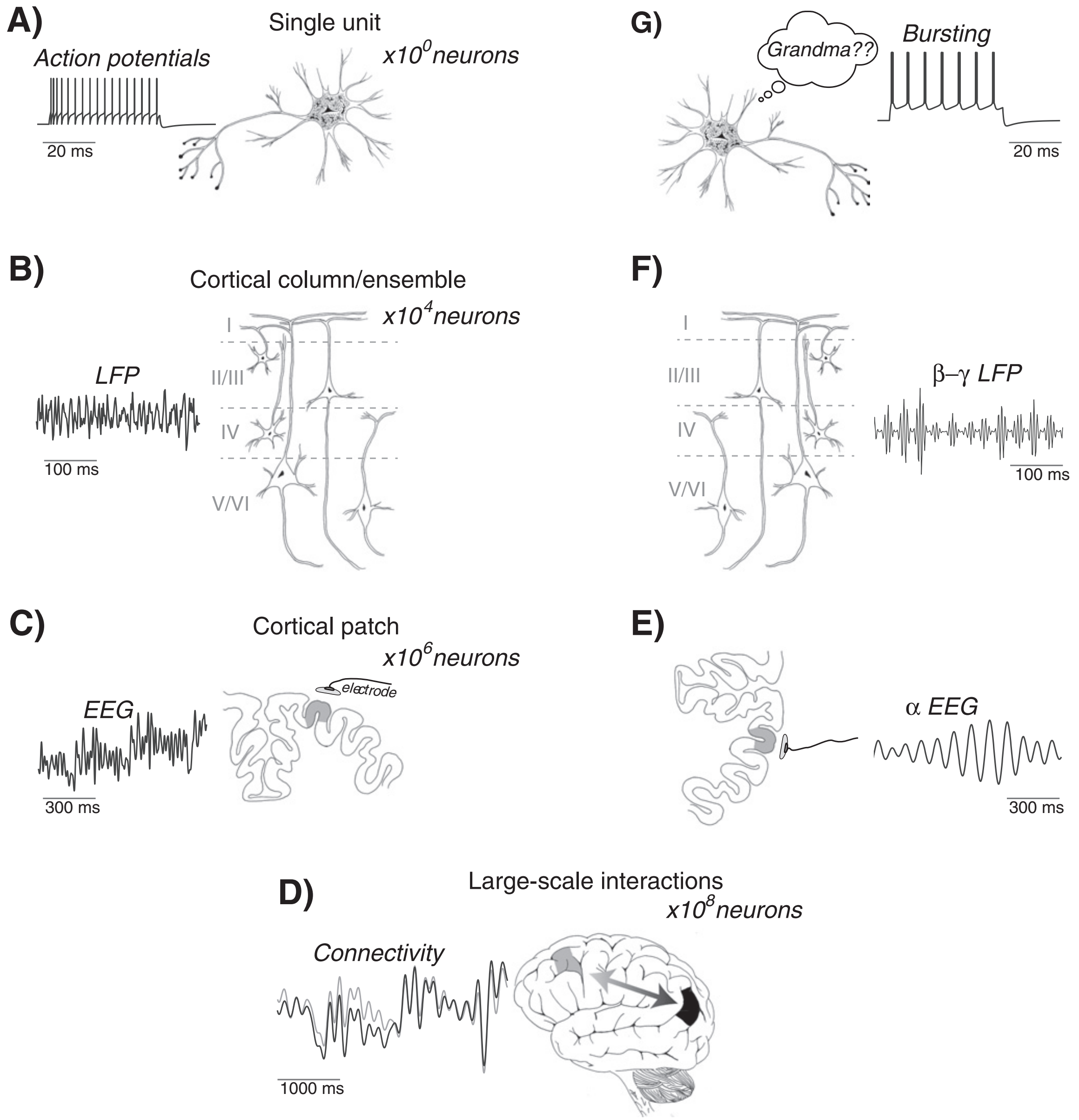
Skinner and Ferguson 2013

NeuroImage 85 (2014) 702–710

Review

Five methodological challenges in cognitive electrophysiology

Michael X Cohen [a,*], Rasa Gulbinaite [b]



"Spatial and temporal multiscale interactions are thought to be a defining feature of the brain."

Math ⟷ Biology

Consideration from a modeling perspective
Challenges quickly become apparent
Collaborations clearly required....

“Neither ignore the details nor be consumed by them!”

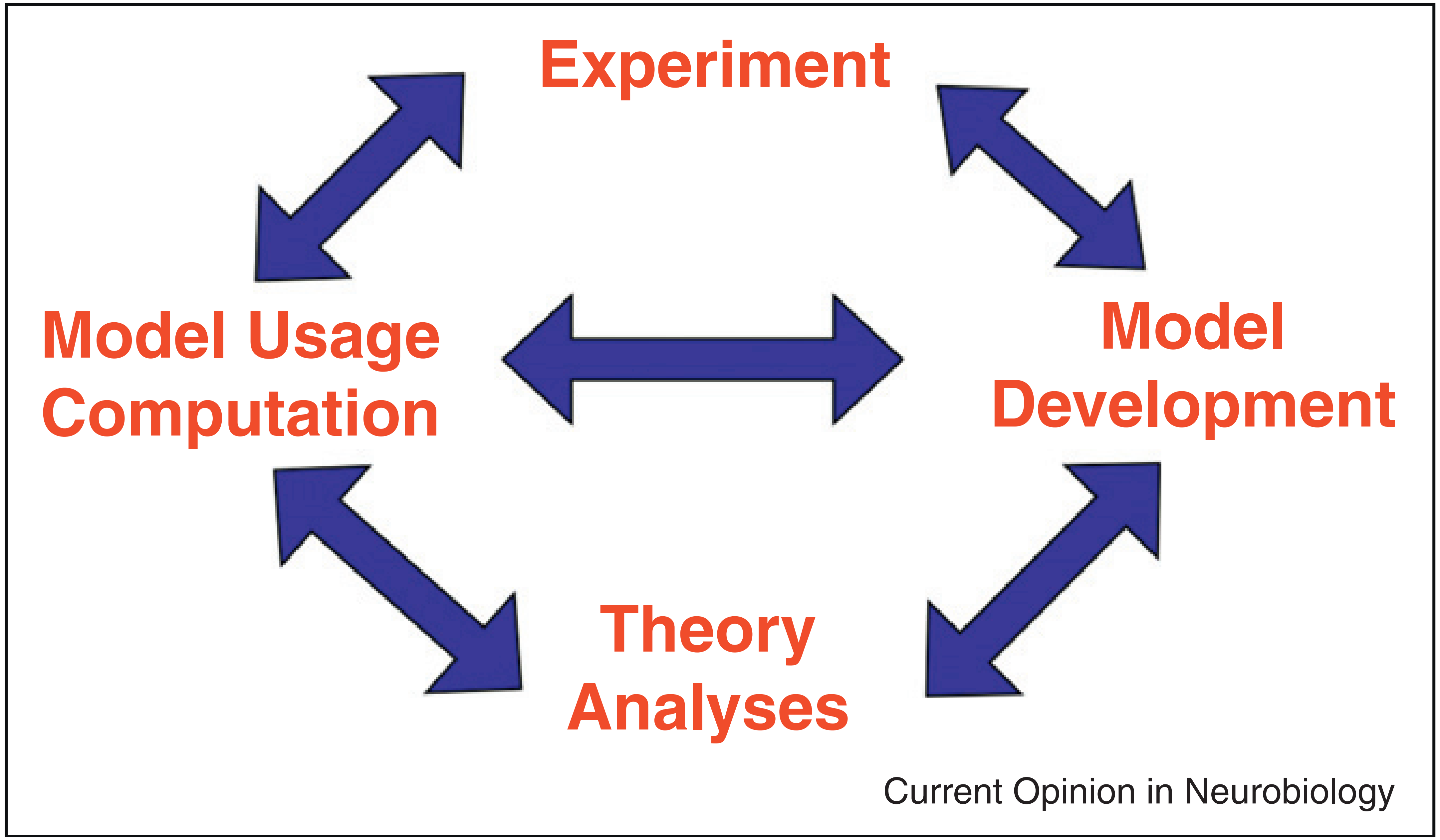
Brain Networks

context and function

size and architecture

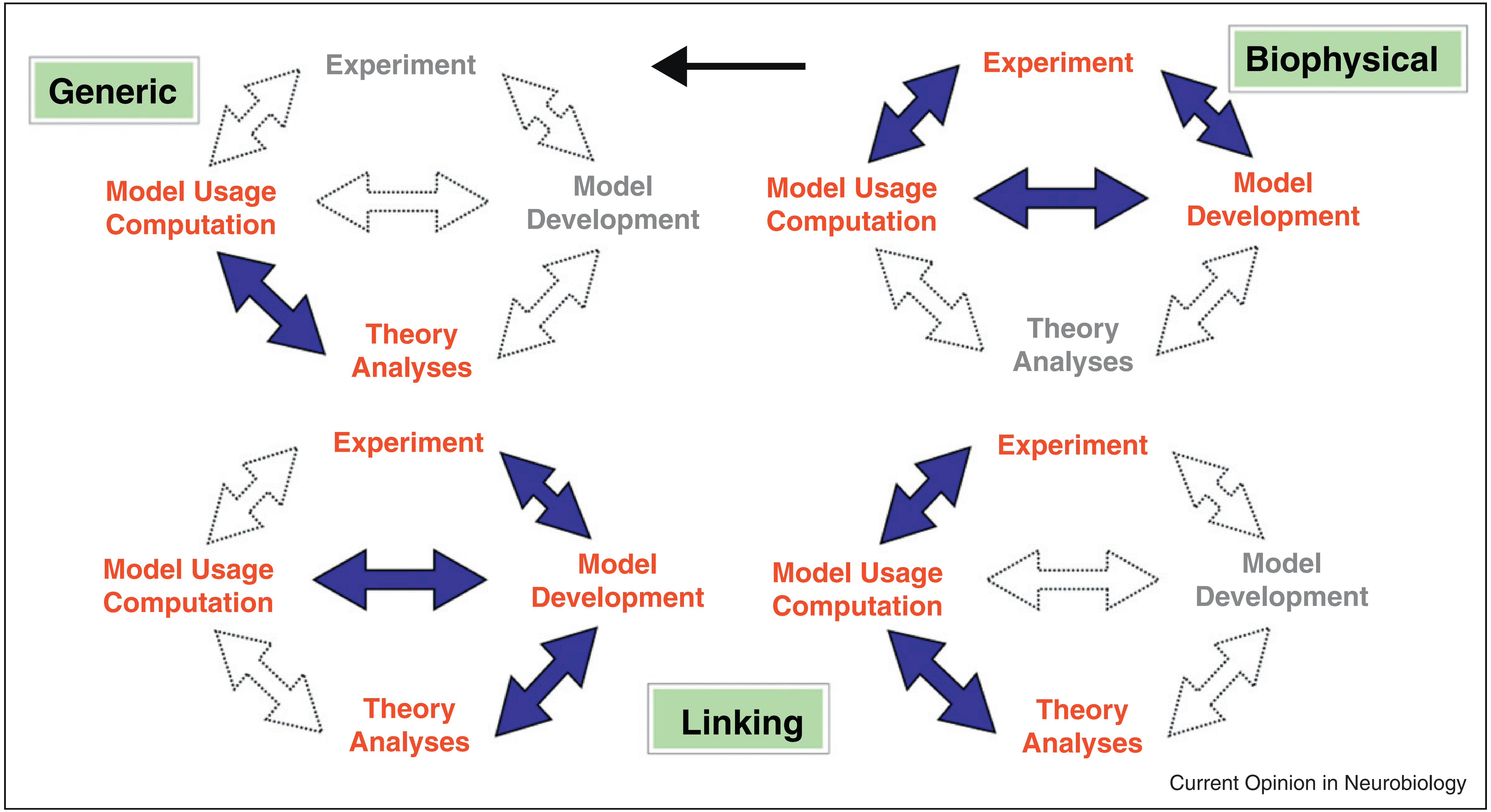
connectivity and cellular characteristics

“my balance and tight coupling”



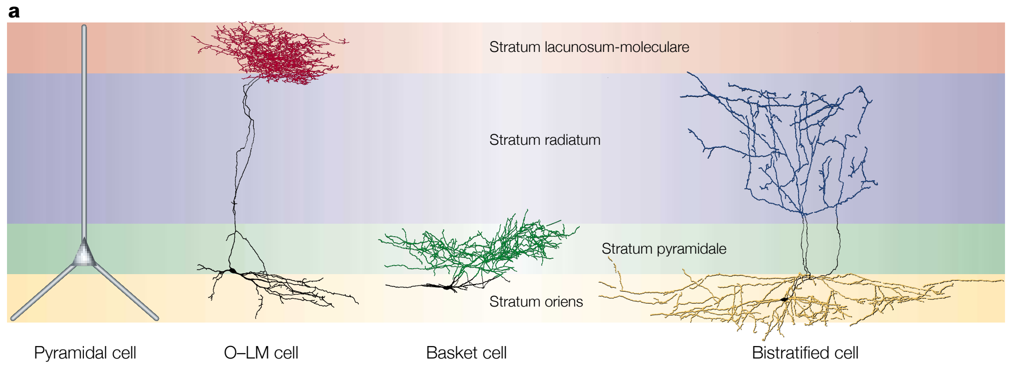
Cellular-based Modeling Features.

Skinner 2012



- possible useful organization to be clear about biological context of cellular models and to try to take best advantage of theoretical insights

- consider similar mathematical model structures, so interpretation is key



McBain and Fisahn 2001

Klausberger and Somogyi 2008

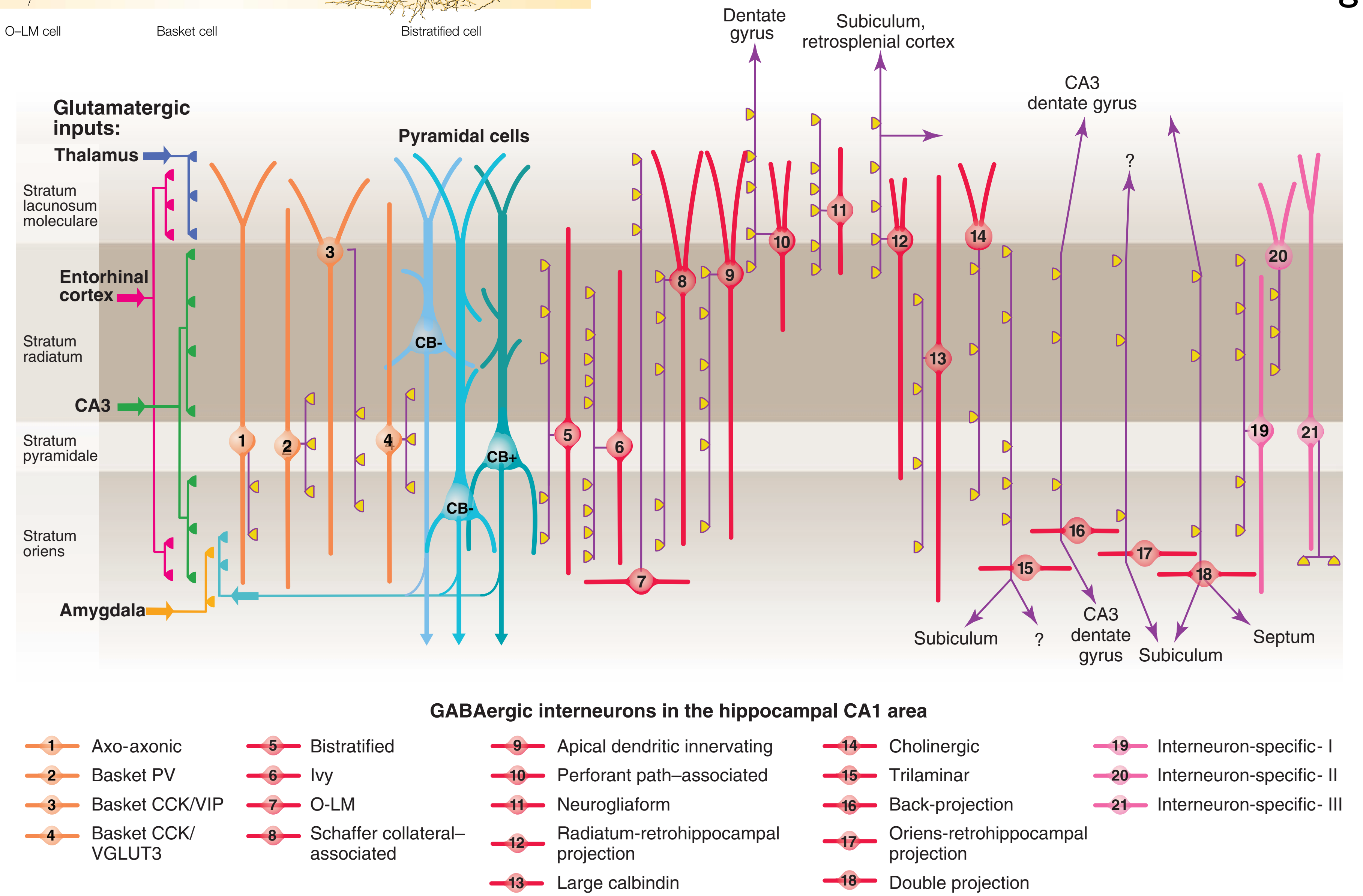


Fig. 1. Three types of pyramidal cell are accompanied by at least 21 classes of interneuron in the hippocampal CA1 area. The main termination of five glutamatergic inputs are indicated on the left. The somata and dendrites of interneurons innervating pyramidal cells (blue) are orange, and those innervating mainly other interneurons are pink. Axons are purple; the main synaptic terminations are yellow. Note the association of the output synapses of different interneuron types with the perisomatic region (left) and either the Schaffer collateral/commissural or the entorhinal pathway termination zones (right), respectively. VIP, vasoactive intestinal polypeptide; VGLUT, vesicular glutamate transporter; O-LM, oriens lacunosum moleculare.

Cellular details critical, interneurons in particular...

REVIEW

doi:10.1038/nature12983

Interneuron cell types are fit to function

Adam Kepecs[1] & Gordon Fishell[2]

Understanding brain circuits begins with an appreciation of their component parts — the cells. Although GABAergic interneurons are a minority population within the brain, they are crucial for the control of inhibition. Determining the diversity of these interneurons has been a central goal of neurobiologists, but this amazing cell type has so far defied a generalized classification system. Interneuron complexity within the telencephalon could be simplified by viewing them as elaborations of a much more finite group of developmentally specified cardinal classes that become further specialized as they mature. Our perspective emphasizes that the ultimate goal is to dispense with classification criteria and directly define interneuron types by function.

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REVIEW INSIGHT

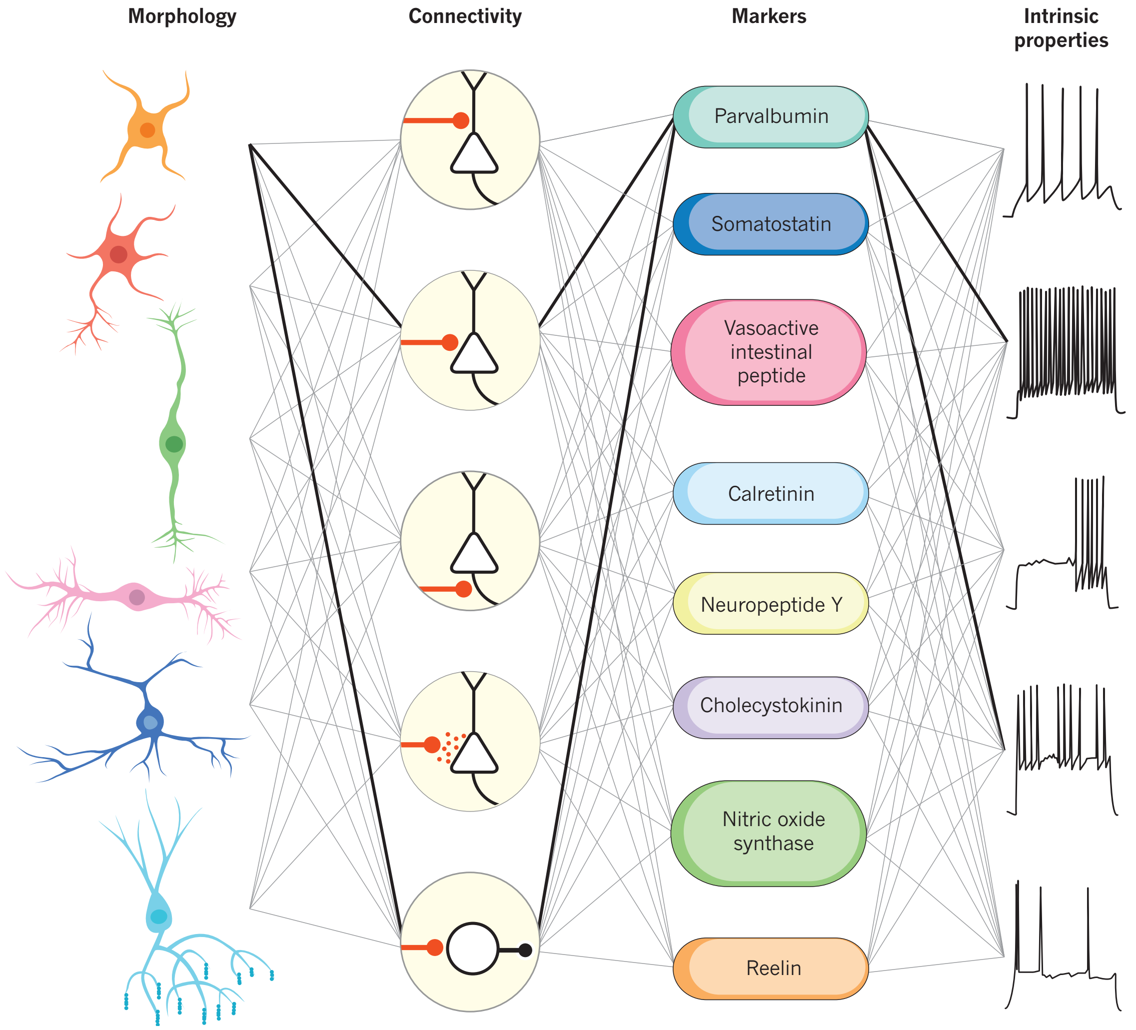

Figure 1 | Multiple dimensions of interneuron diversity. Interneuron cell types are usually defined using a combination of criteria based on morphology, connectivity pattern, synaptic properties, marker expression and intrinsic firing properties. The highlighted connections define fast-spiking cortical basket cells.

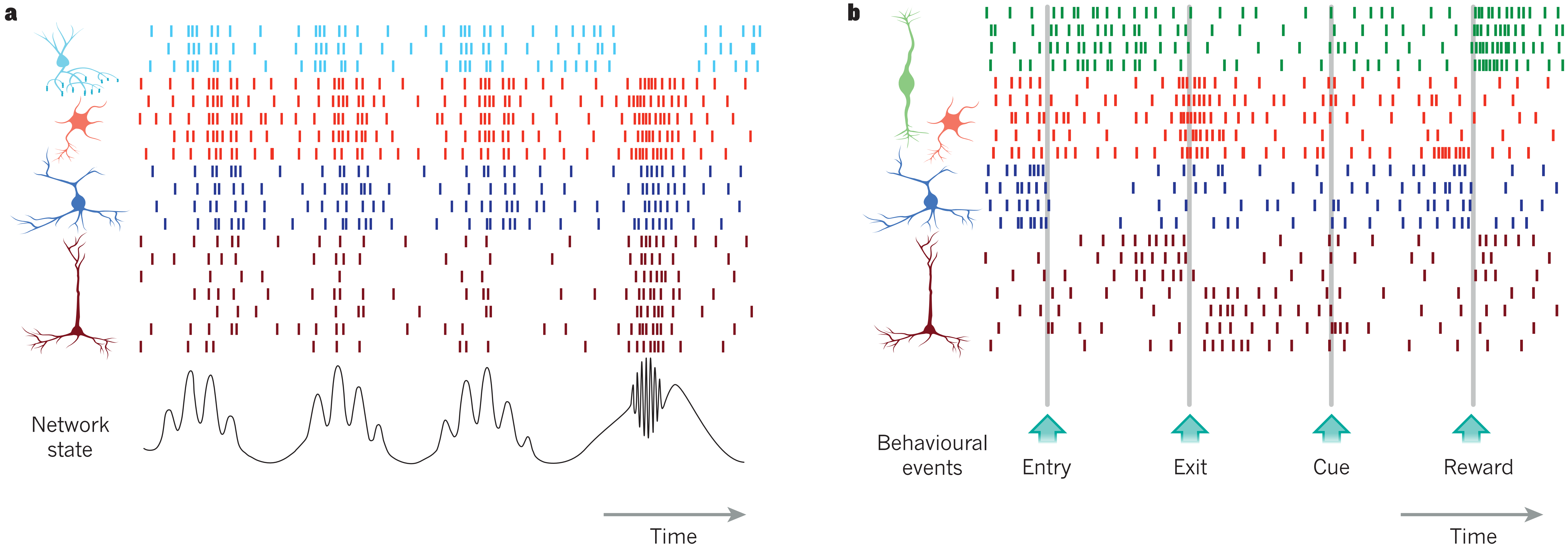

Figure 4 | Coordination and flow control hypotheses of recruitment. **a**, Coordination hypothesis. The bottom trace shows a local field potential representing the network state in the hippocampus. The firing of different neuron types (chandelier cell, light blue; basket cell, red; OLM cell, blue; pyramidal cell, brown) can be described in reference to the local field potential, both in terms of overall activity level and phase relationship[87,107,113]. **b**, Flow control hypothesis. The bottom arrows mark the timing of four behavioural events: entry, exit, cue and reward. The firing of different neuron types (vasointestinal peptide, green; parvalbumin, red; somatostatin, blue; pyramidal cell brown) can be described in reference to these events[84,102].

Encyclopedia of Computational Neuroscience
DOI 10.1007/978-1-4614-7320-6_29-1

Hippocampus, Model Inhibitory Cells

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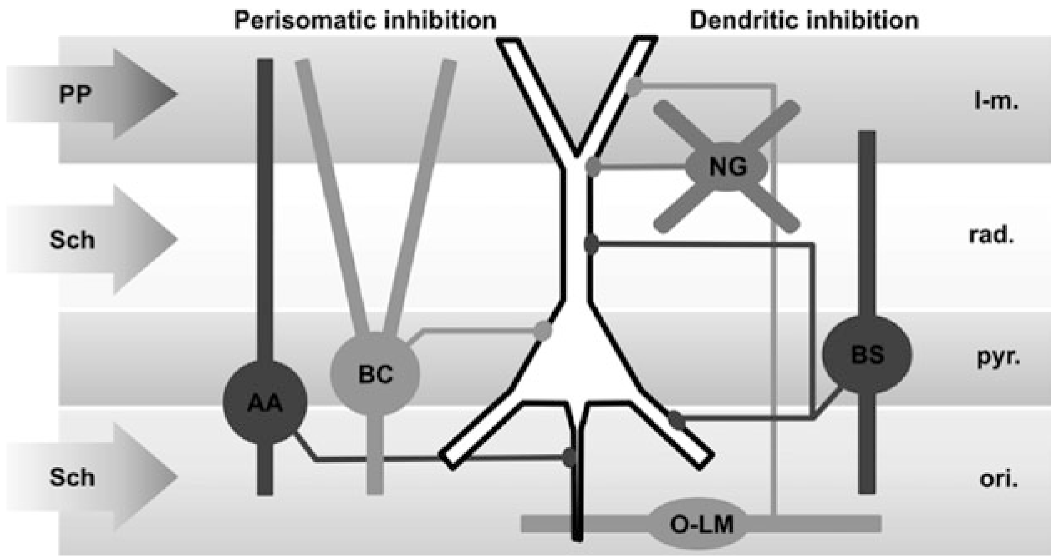
[b]Medicine (Neurology), University of Toronto, Toronto, ON, Canada
[c]Physiology, University of Toronto, Toronto, Ontario, Canada



Vida 2010

Table 1 Fast-spiking interneurons, basket cells

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA3 interneuron	Biophysical, multi- (Na, K-D)	Passive – generic Active – generic f-I – yes	Network (carbachol-driven population rhythms)	Traub et al. (1992)
CA3 SP interneuron	Biophysical, multi- (Na, K-DR, K-Ca, K-AHP, K-A, Ca-L)	Passive – generic Active – generic f-I – yes	Intrinsic (active, VGCs in dendrites, and spike transduction)	Traub and Miles (1995)
CA3 SP interneuron	Derivative, subsequent (Traub et al. 1995)		Network (population bursts with dendritic GJ coupling)	Traub (1995)
CA1[a] fast-spiking basket cell	Biophysical, single- (Na, K-DR)	Passive – generic Active – generic f-I – yes	Network (gamma rhythms)	Wang and Buzsáki (1996)
CA1 fast-spiking basket cell	Derivative, subsequent (Wang and Buzsáki 1996)		Network (gamma rhythms)	Bartos et al. (2007)[b]

etc.

Models of 'identifiable' hippocampal interneurons
- comprehensive list organized in 3 Tables, considering 5 aspects

Table 2 Horizontal dendrites, distal dendrite-targeting interneuron types

Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA1 O–LM interneuron	Biophysical, multi- (Na, K-DR, K-A, h-sag)	Passive – specific Active – specific f-I – yes	Intrinsic (active, VGCs in dendrites, and spike propagation)	Saraga et al. (2003)
CA1 O–LM interneuron	Derivative, simplification to single- (Saraga et al. 2003)		Network (theta/gamma rhythms)	Gloveli et al. (2005)[a]
DG HIPP interneuron	Biophysical, multi- (Na, K-DRf, K-A, K-Ca, K-AHP, Ca-L, h-sag)	Passive – specific Active – specific f-I – yes	Network (DG hyperexcitability, mossy fiber, and mossy cell changes)	Santhakumar et al. (2005)[b]
CA3 O–LM interneuron	Biophysical, single- (Na, Na-p, K-DR, h-sag)	Passive – generic Active – generic f-I – no	Network (theta-phase separation, encoding, and retrieval in CA3)	Kunec et al. (2005)
CA1 O–LM interneuron	Biophysical, single- (Na, Na-p, K-DR, h-sag)	Passive – generic Active – generic f-I – no	Network (theta rhythm)	Rotstein et al. (2005)

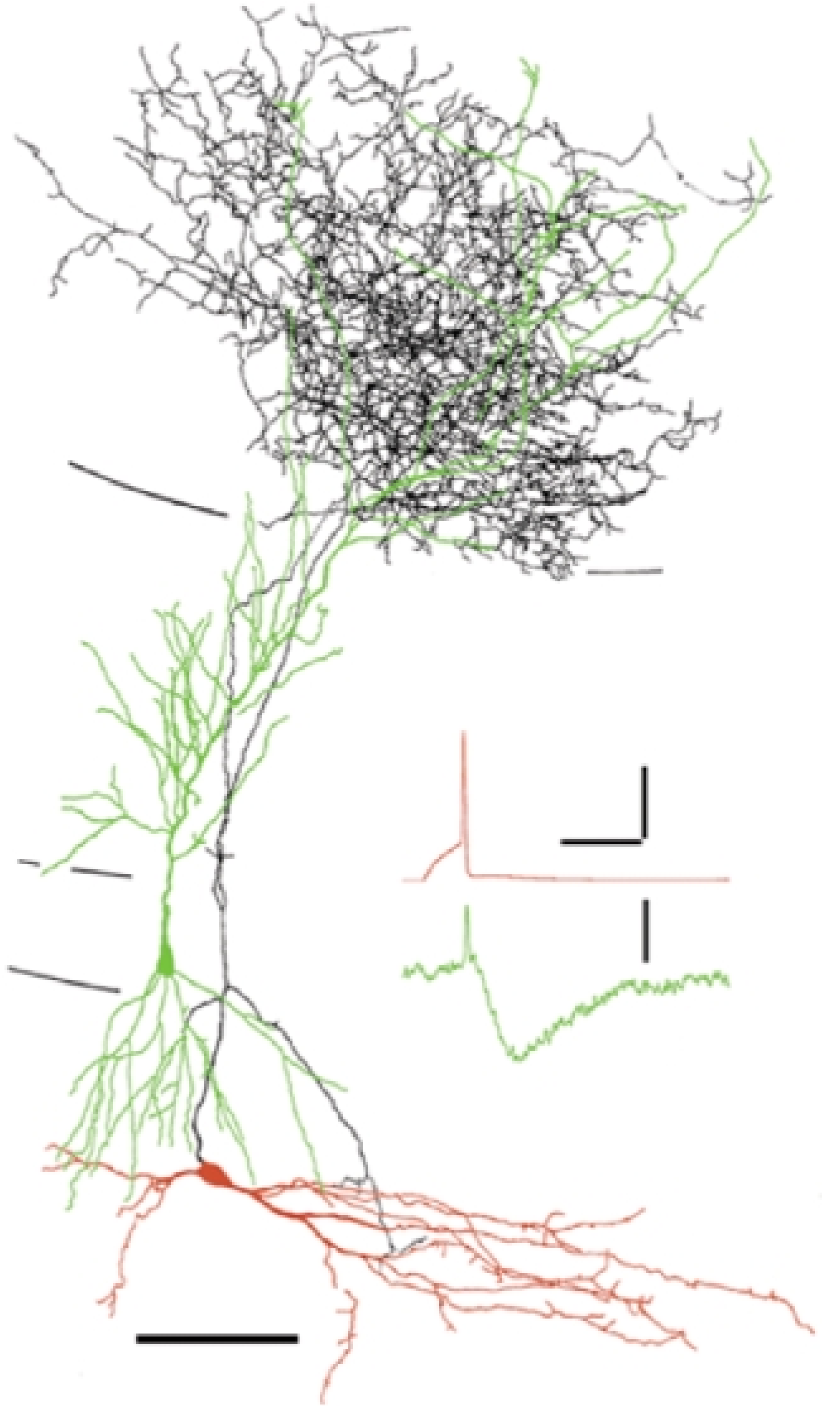
etc.

Table 3 Other interneuron types

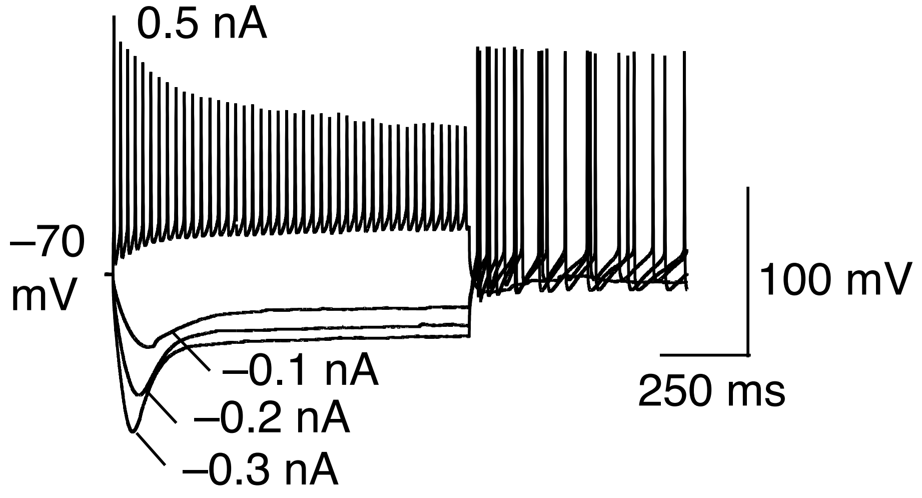
Interneuron type	Mathematical model type	Experimental basis	Functional aspects	References
CA1 O/A interneuron	Biophysical, single- (Na, Na-p, K-DR, K-D)	Passive – generic Active – generic f-I – no	Network (synchronized bursting with GJ and inhibitory coupling)	Skinner et al. (1999)
CA1 O/A interneuron	Derivative, expansion to multi- (Skinner et al. 1999)	f-I – yes	Intrinsic (K-D current control of bursting)	Saraga and Skinner (2002)
CA1[a] O/A CB+ interneuron	Biophysical, single- (Na, K-DR, K-Ca, Ca-L, h-sag)	Passive – generic Active – generic f-I – no	Network (septo-hippocampal theta rhythms)	Wang (2002)[b]
CA1 LM/RAD interneuron[c]	Biophysical, single- (Na, Na-p, K-DRf, K-DRs, K-A, K-D)	Passive – specific Active – specific f-I – no	Intrinsic (subthreshold MPO generation)	Morin et al. (2010)
CA1 LM/RAD interneuron	Derivative, subsequent (Morin et al. 2010)	f-I – yes	Network (reliable theta-frequency spiking in virtual networks)	Sritharan and Skinner (2012)

etc.

Oriens lacunosum-moleculare (OLM) interneuron



Maccaferri and Lacaille 2003

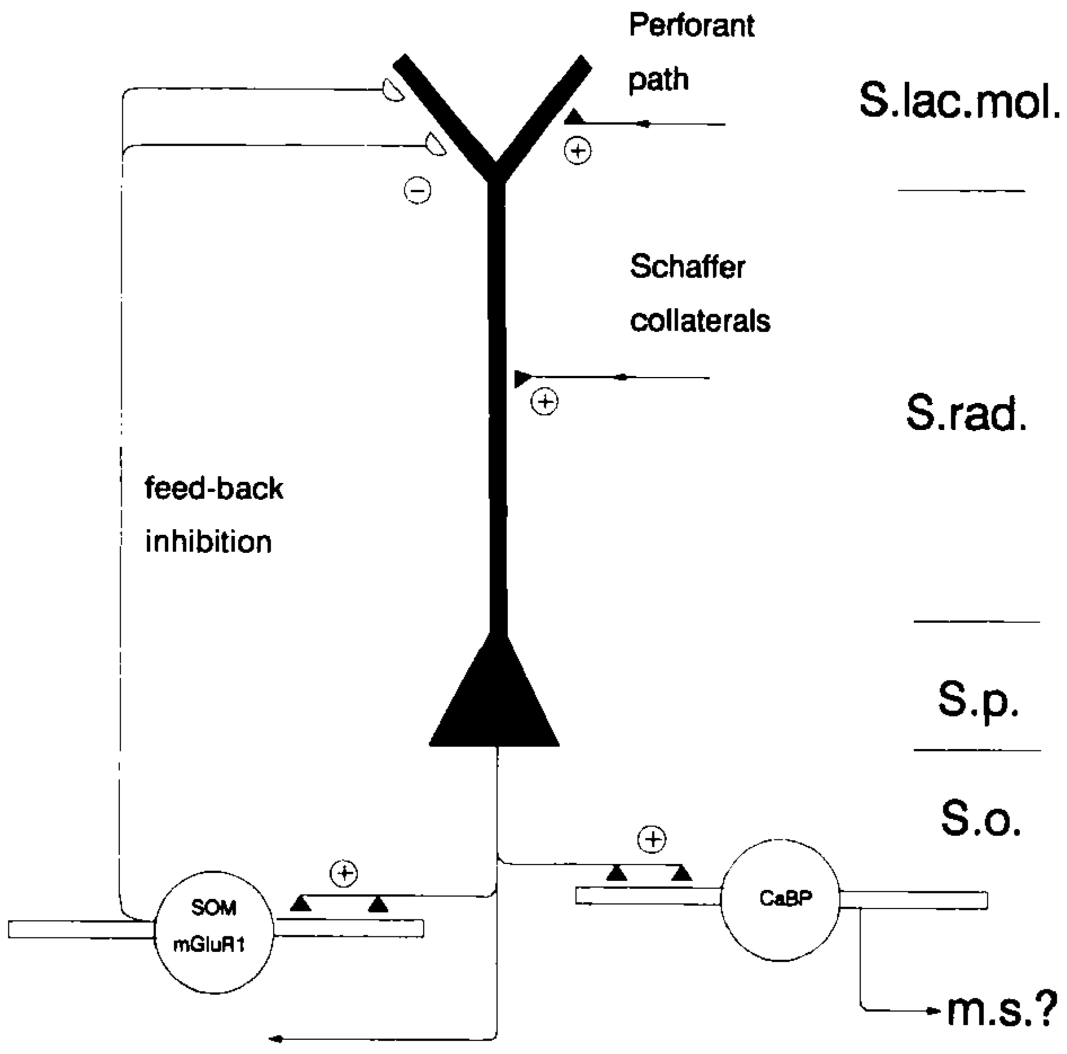


Long-term potentiation in hippocampal oriens interneurons: postsynaptic induction, presynaptic expression and evaluation of candidate retrograde factors

Elizabeth Nicholson and Dimitri M. Kullmann

UCL Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK

Phil. Trans. R. Soc. B 2014 **369**, 20130133, published 2 December 2013



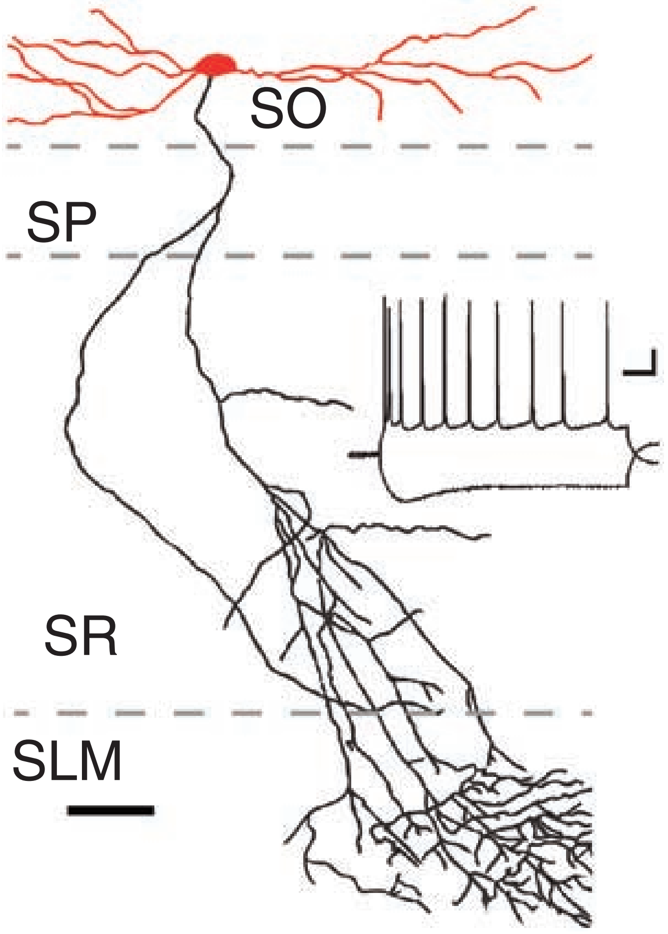
Blasco-Ibanez and Freund 1995

VOLUME 15 | NUMBER 11 | NOVEMBER 2012 NATURE NEUROSCIENCE

OLM interneurons differentially modulate CA3 and entorhinal inputs to hippocampal CA1 neurons

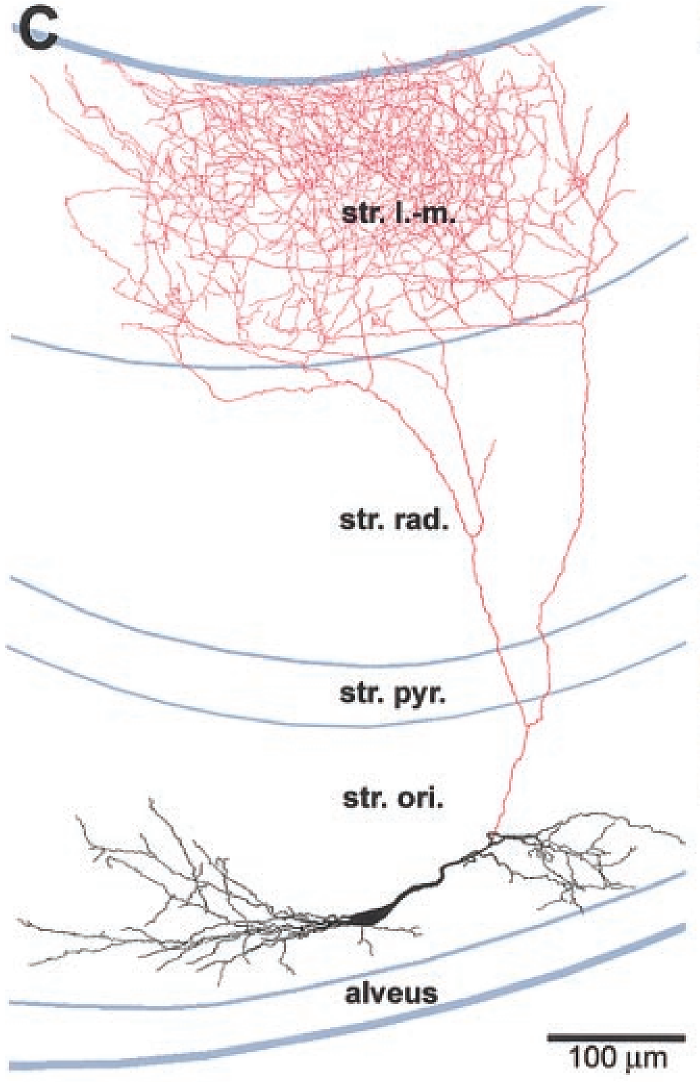
Richardson N Leão[1,2], Sanja Mikulovic[1], Katarina E Leão[1,2], Hermany Munguba[2], Henrik Gezelius[1], Anders Enjin[1], Kalicharan Patra[1], Anders Eriksson[1], Leslie M Loew[3], Adriano B L Tort[2] & Klas Kullander[1,4]

The vast diversity of GABAergic interneurons is believed to endow hippocampal microcircuits with the required flexibility for memory encoding and retrieval. However, dissection of the functional roles of defined interneuron types has been hampered by the lack of cell-specific tools. We identified a precise molecular marker for a population of hippocampal GABAergic interneurons known as oriens lacunosum-moleculare (OLM) cells. By combining transgenic mice and optogenetic tools, we found that OLM cells are important for gating the information flow in CA1, facilitating the transmission of intrahippocampal information (from CA3) while reducing the influence of extrahippocampal inputs (from the entorhinal cortex). Furthermore, we found that OLM cells were interconnected by gap junctions, received direct cholinergic inputs from subcortical afferents and accounted for the effect of nicotine on synaptic plasticity of the Schaffer collateral pathway. Our results suggest that acetylcholine acting through OLM cells can control the mnemonic processes executed by the hippocampus.



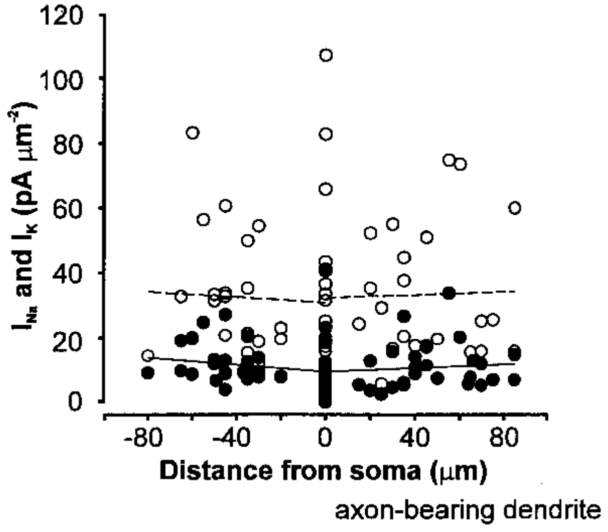
Models and Motivation

www.sciencemag.org SCIENCE VOL 287 14 JANUARY 2000



Distal Initiation and Active Propagation of Action Potentials in Interneuron Dendrites

Marco Martina,[1] Imre Vida,[2] Peter Jonas[1]*

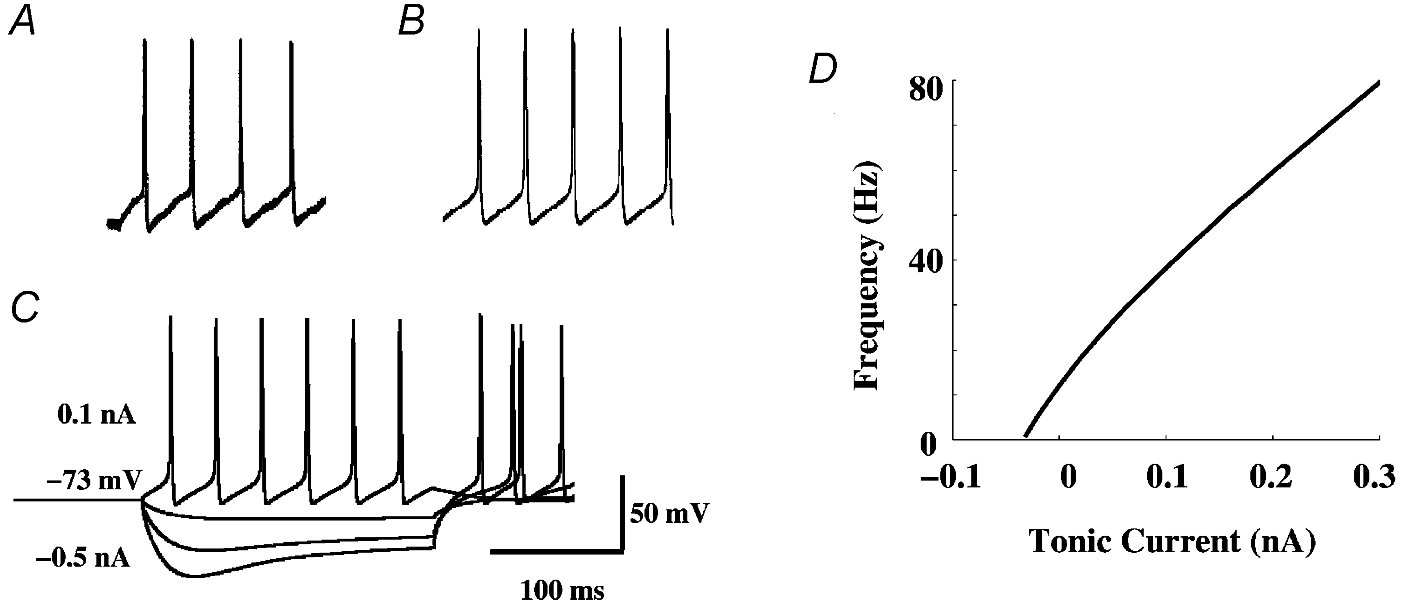


J Physiol (2003), 552.3 pp. 673–689
DOI: 10.1113/jphysiol.2003.04(
www.jphysiol

Active dendrites and spike propagation in multi-compartment models of oriens-lacunosum/moleculare hippocampal interneurons

F. Saraga*‡, C. P. Wu*, L. Zhang*† and F. K. Skinner*†‡§

*Toronto Western Research Institute, University Health Network, Departments of †Medicine (Neurology) and ‡Physiology and §Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada M5T 2S8



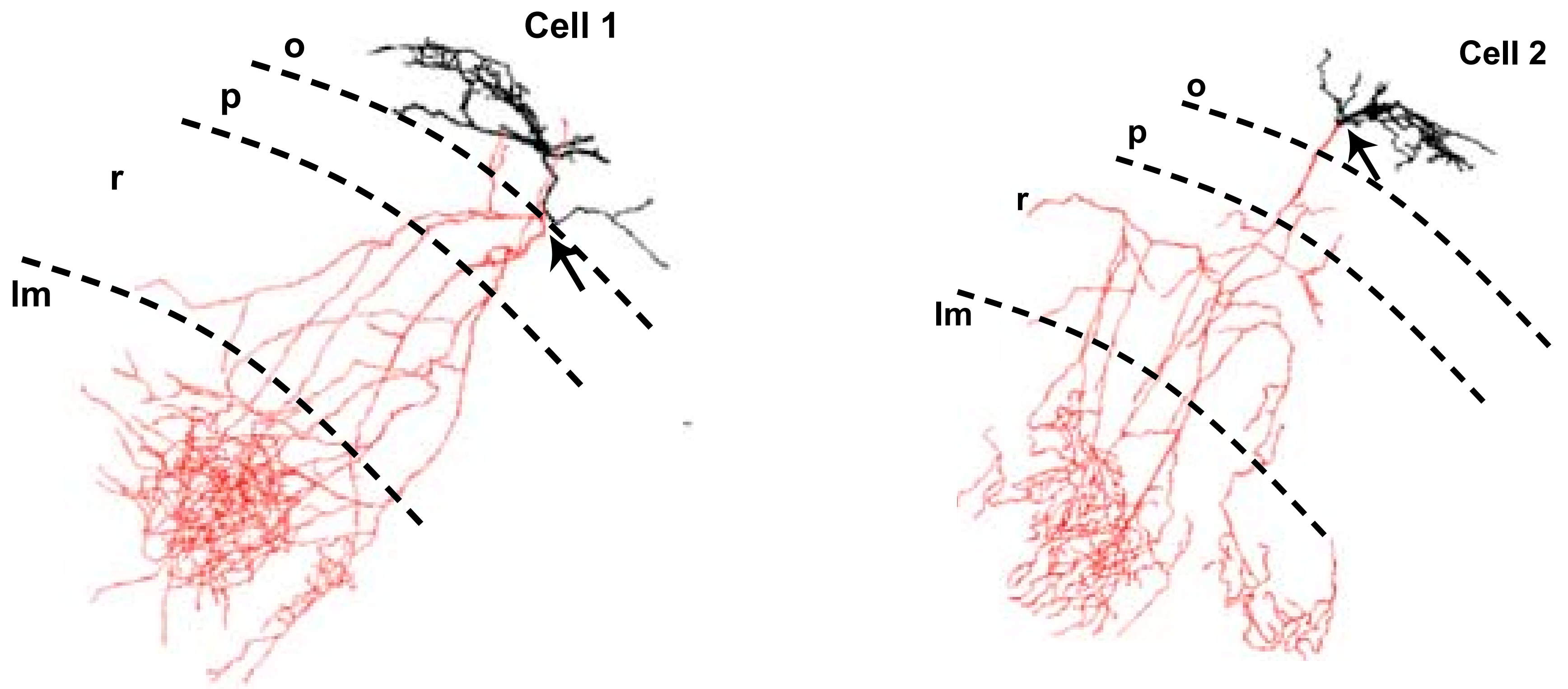
The Journal of Neuroscience, November 22, 2006 • 26(47):12325–12338 • **12325**

Cellular/Molecular

Somatodendritic Kv7/KCNQ/M Channels Control Interspike Interval in Hippocampal Interneurons

J. Josh Lawrence,[1]* Fernanda Saraga,[2,3,4]* Joseph F. Churchill,[1] Jeffrey M. Statland,[1] Katherine E. Travis,[1] Frances K. Skinner,[2,3,4,5] and Chris J. McBain[1]

[1]Laboratory of Cellular and Synaptic Neurophysiology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, [2]Toronto Western Research Institute, University Health Network, [3]Department of Physiology, [4]Department of Medicine (Neurology), and [5]Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada M5T 2S8



Using Multi-compartment Ensemble Modeling as an Investigative Tool of Spatially Distributed Biophysical Balances

...taking advantage of previous works and insights

Step 1

(i) Develop reference multi-compartment model(s).
(ii) Design database to address specific question.
(iii) Perform simulations.

Step 2

(i) Build databases for model and experimental comparisons
(ii) Extract appropriate models

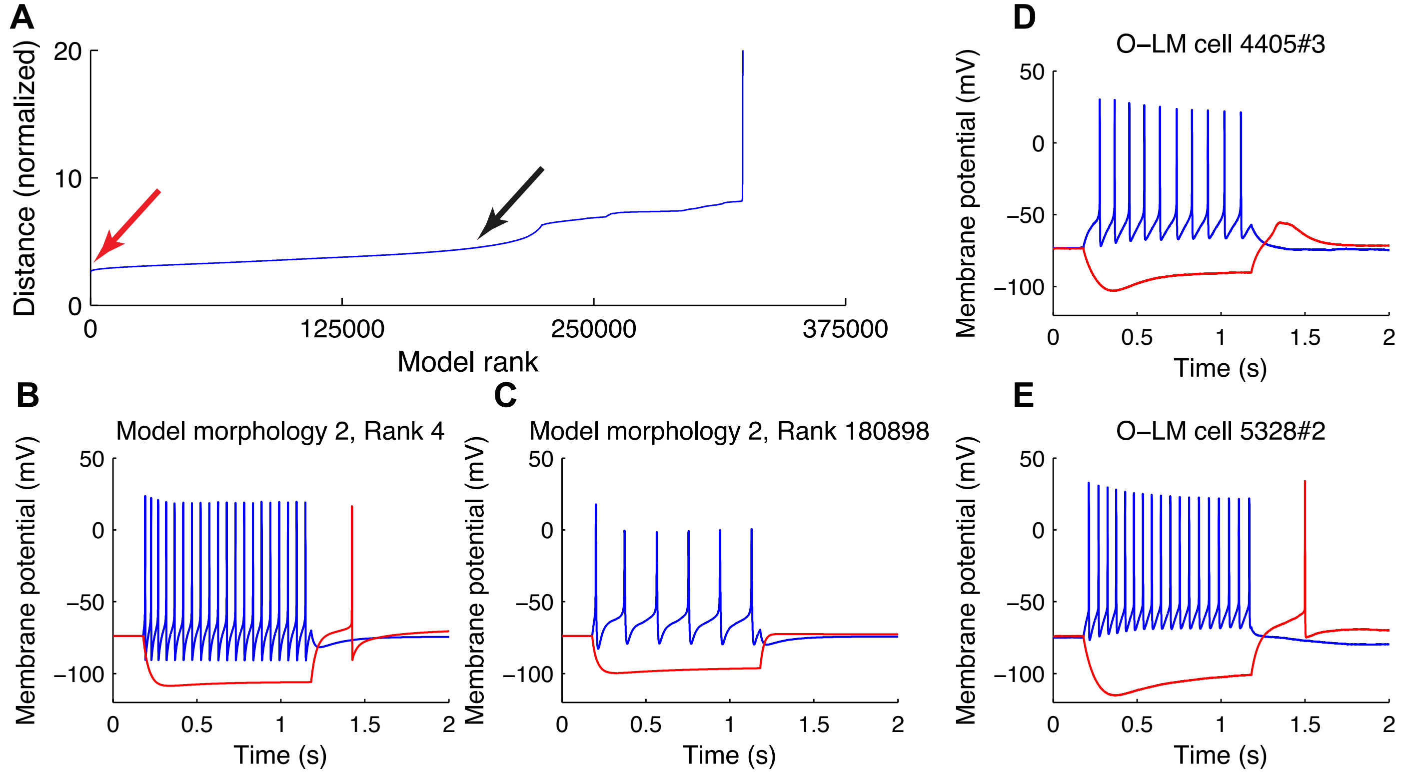
Step 3

Analyze good models

Step 4

(i) Examine specific question
(ii) Determine limitations
(iii) Suggest and design experiments

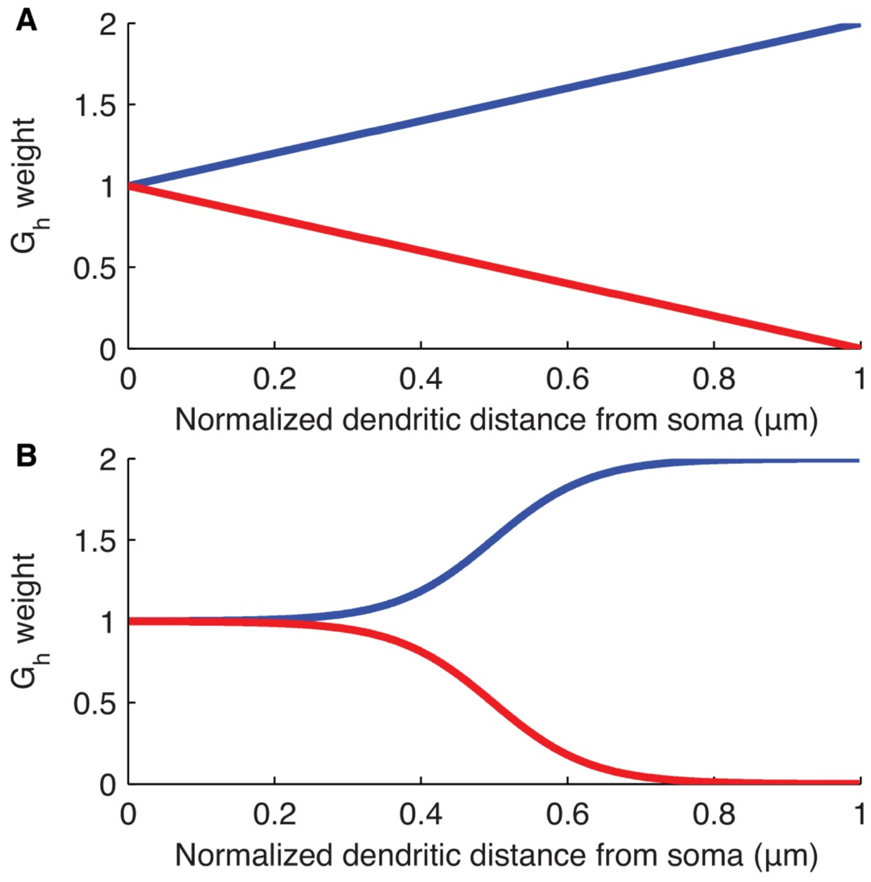
"The question of biological correctness and appropriateness is an evolving process, especially concerning densities, kinetics, and distributions of voltage-gated channels..."



Sekulić et al. 2014

Cycling Process: Hyperpolarization-activated inward currents (I_h) in dendrites?

Non-uniform distributions of I_h and different kinetics could better reproduce experimental results



....morphology and experimental recordings from the same cell needed (ongoing)

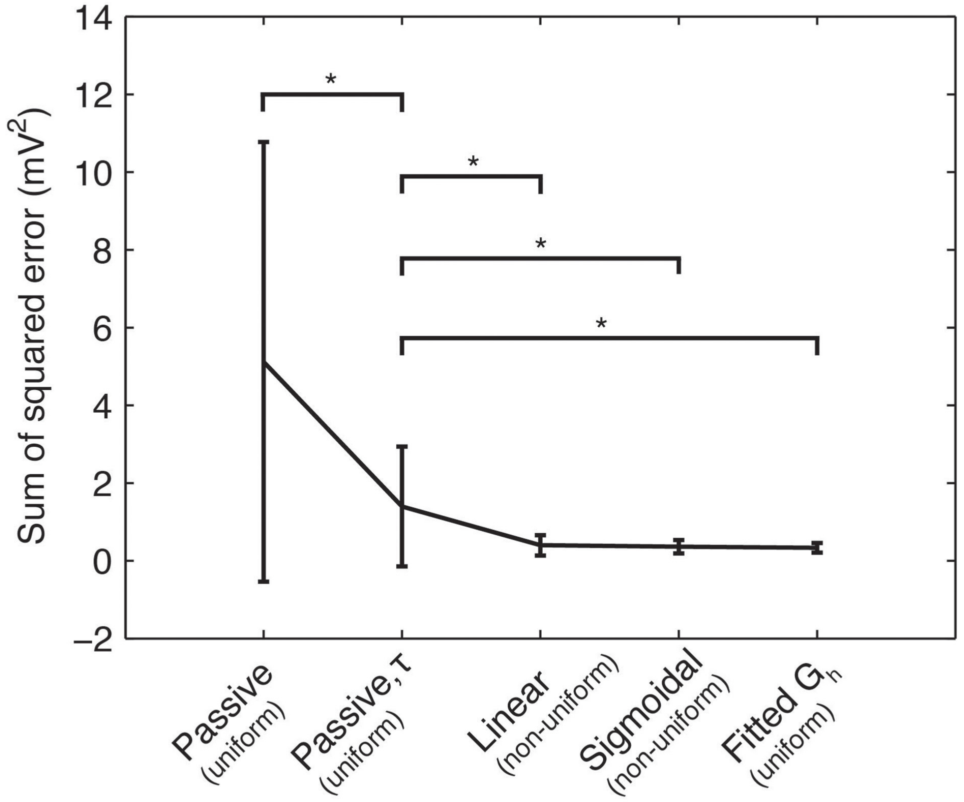
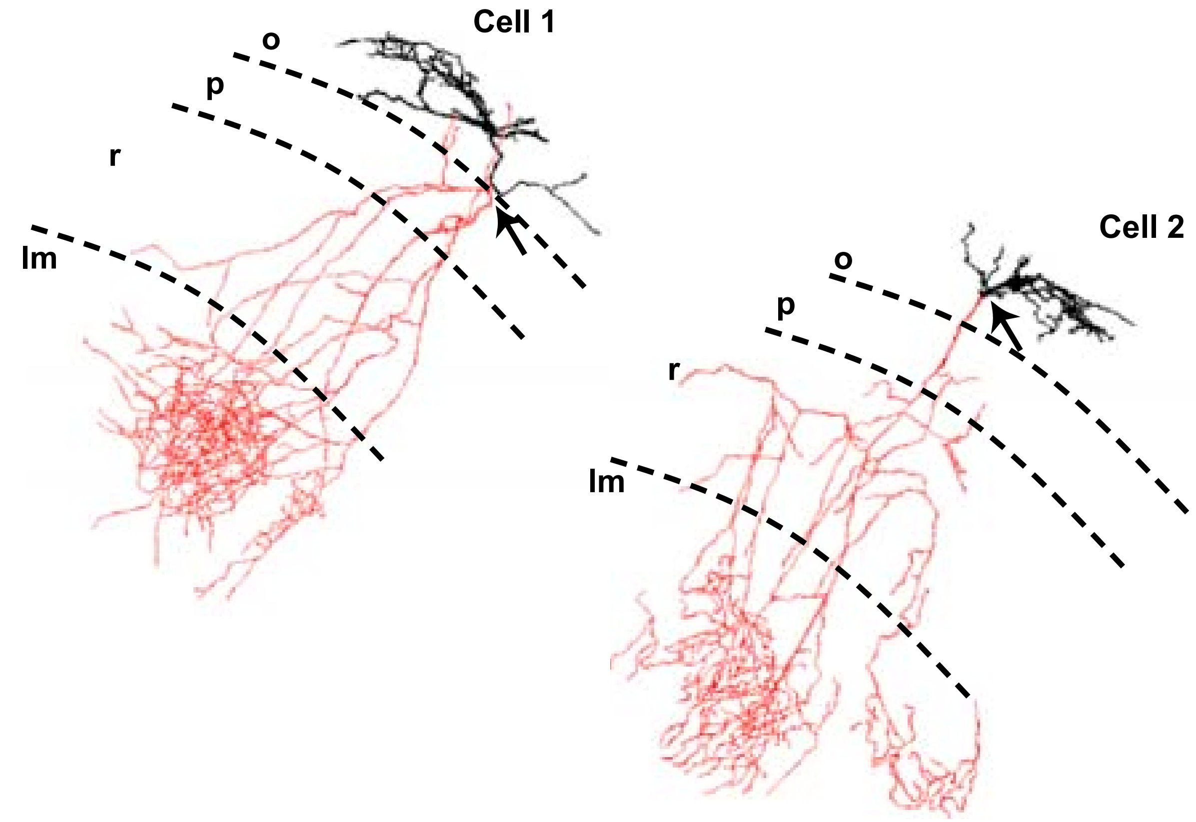


FIGURE 4 | Sum of squared errors between the model and experimental traces across different optimization procedures. Means



Sekulić et al. 2015

...back to theta oscillations and OLM cells

VOLUME 15 | NUMBER 11 | NOVEMBER 2012 **NATURE NEUROSCIENCE**

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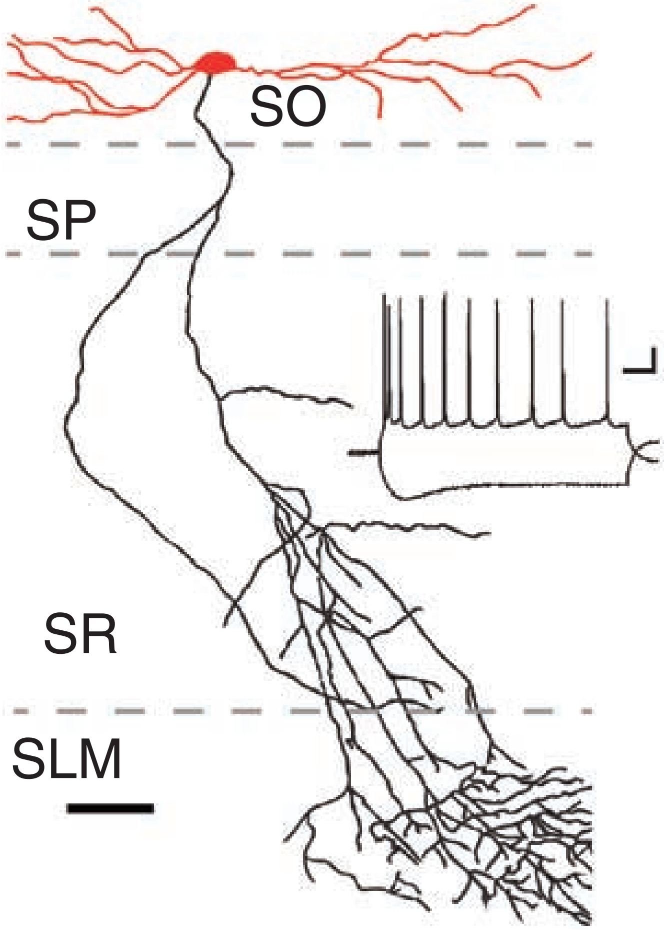
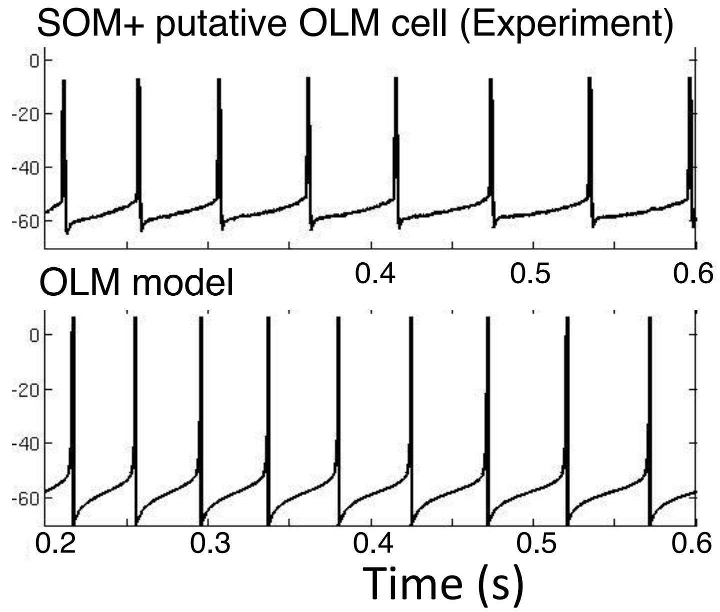
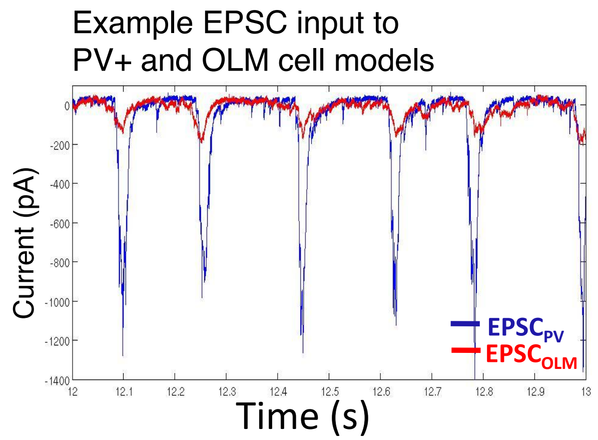


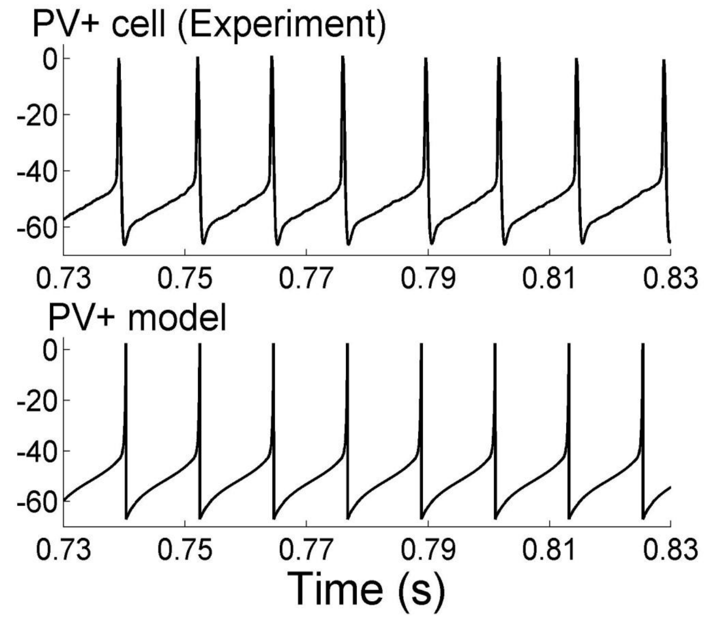
...back to theta oscillations and OLM cells

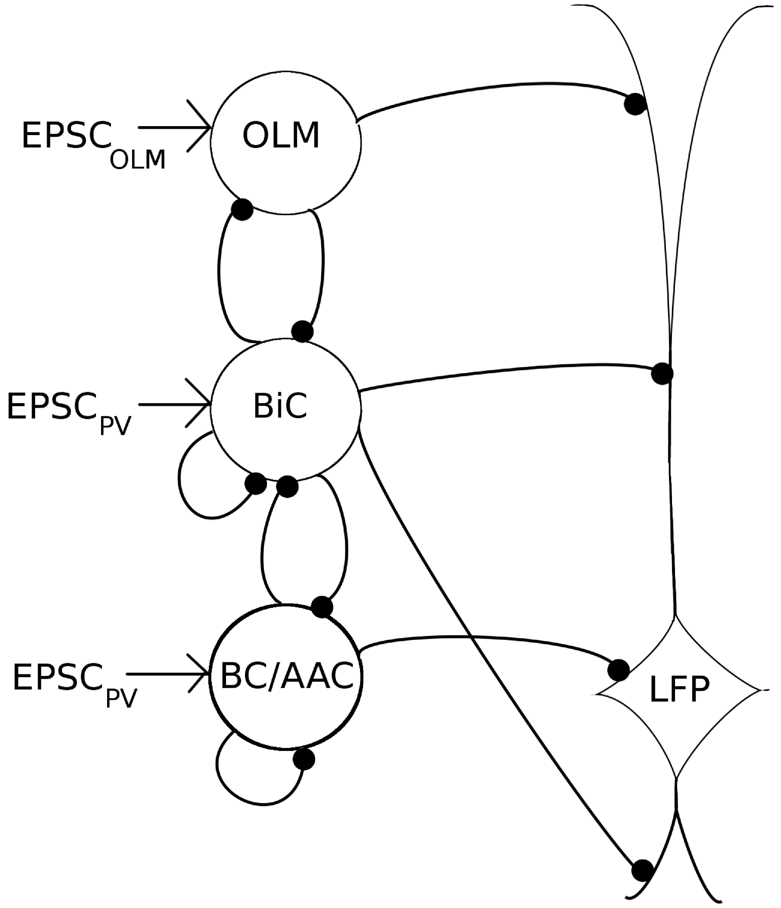
inhibitory cell numbers appropriate for microcircuit theta oscillation context, intrinsic cell models in same context, excitatory drive from experiment

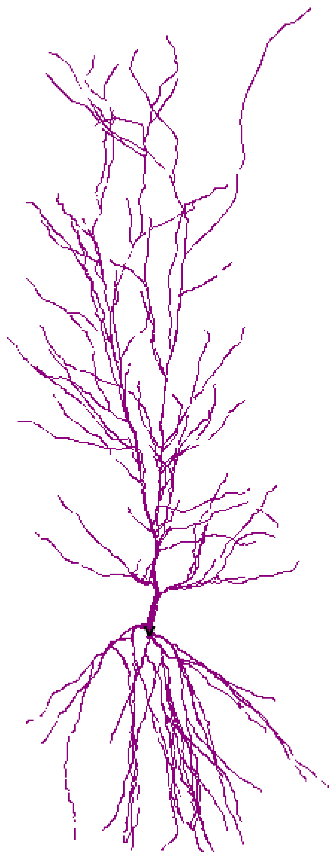
CA1 multi-compartment model used to integrate effects of cell firing at various layers



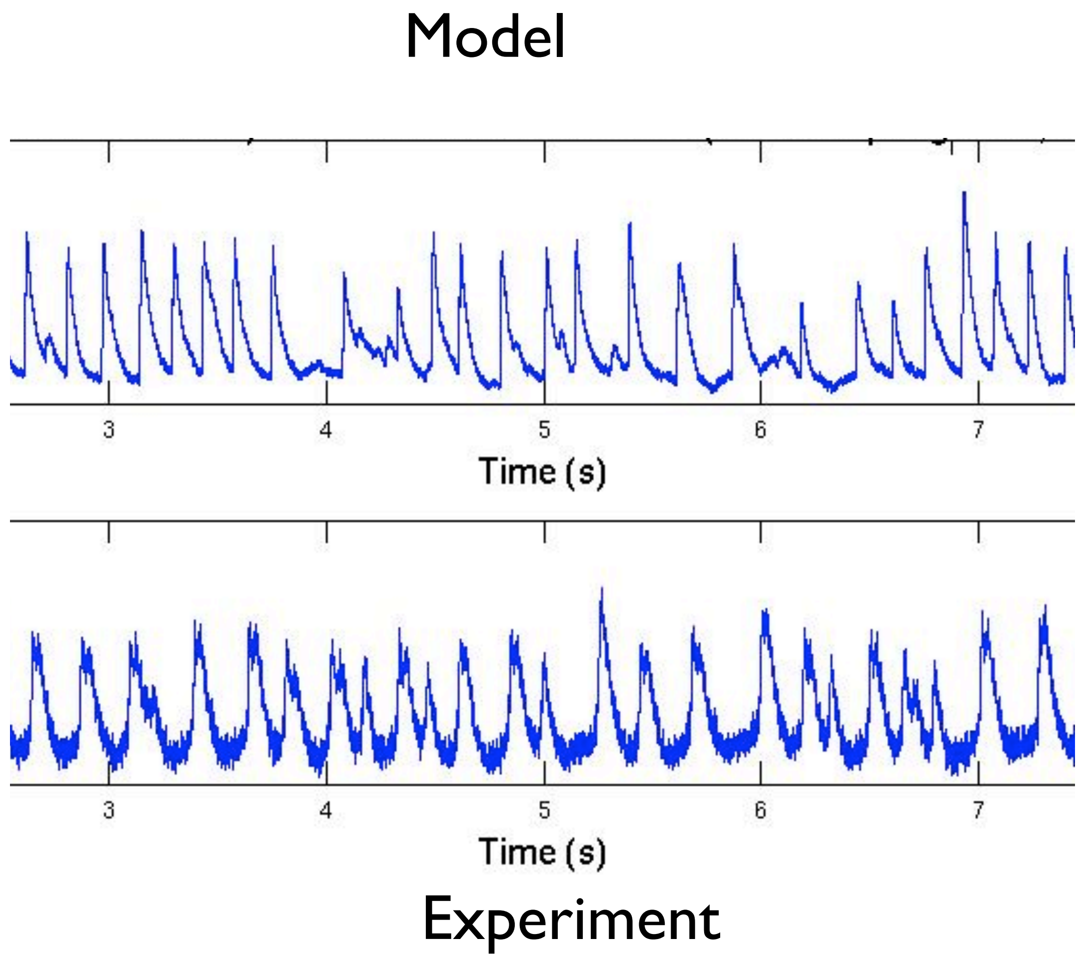






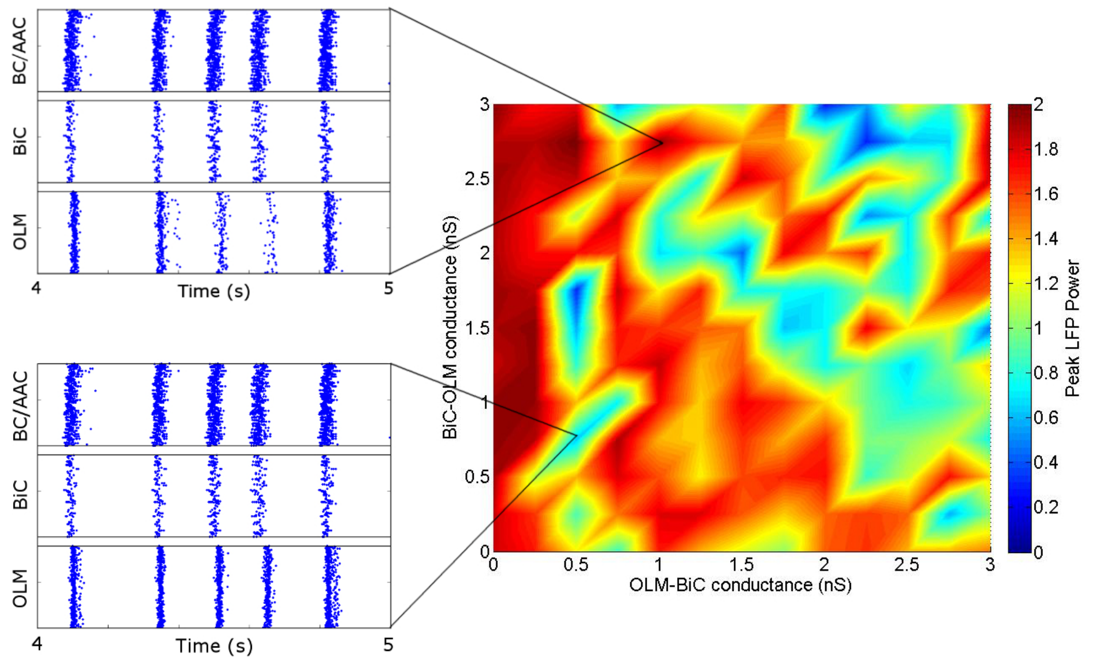


Migliore et al. (2005)

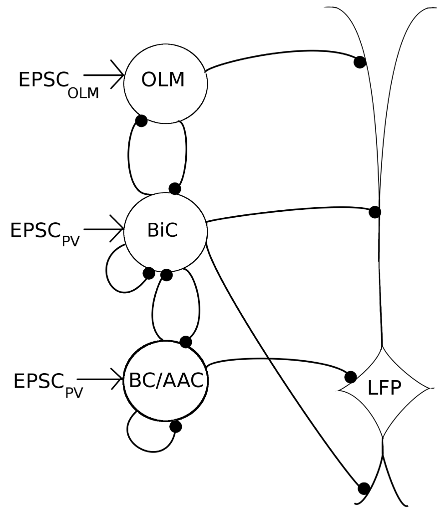


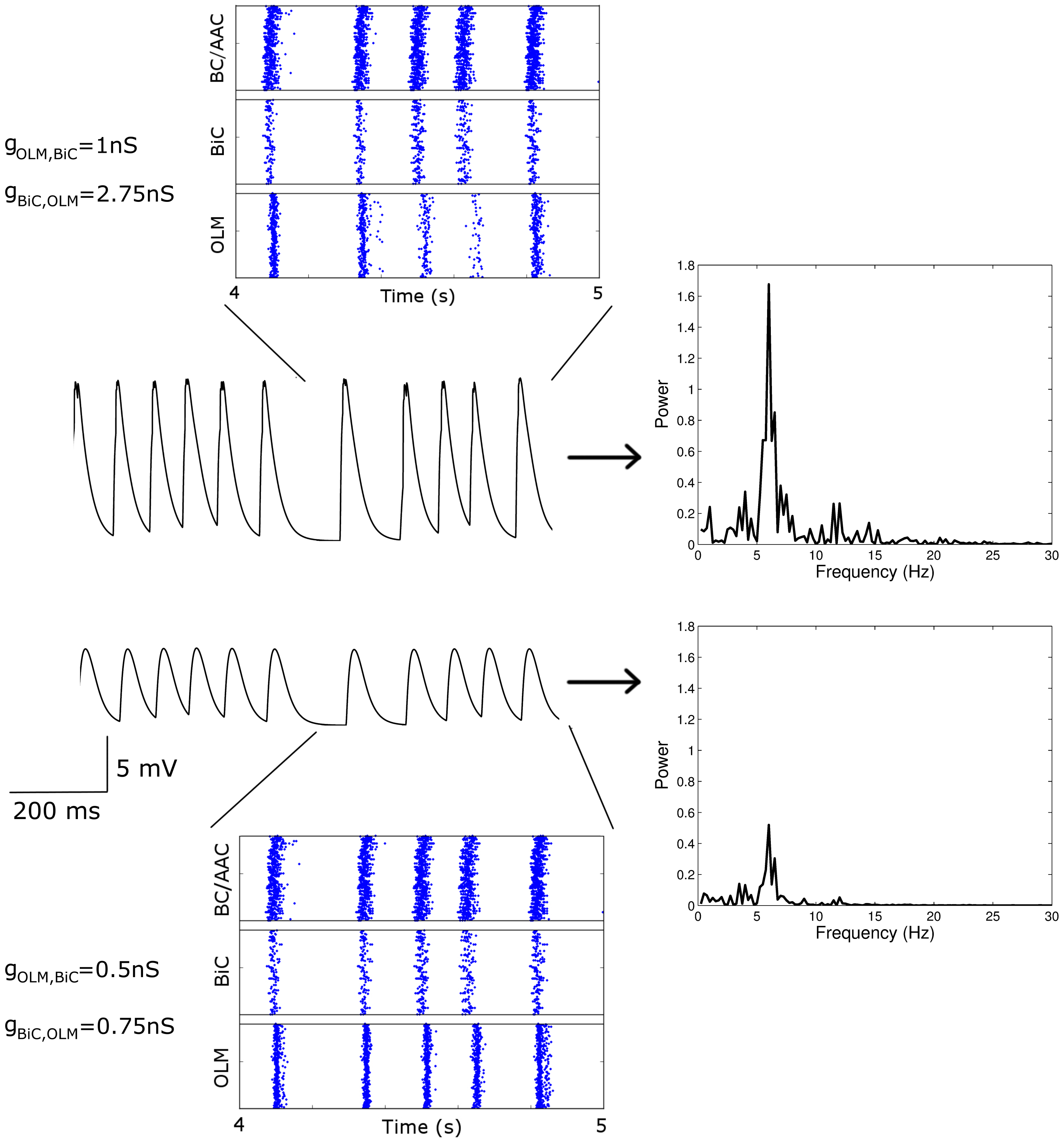
...different 'types' of experimentally linked OLM cell models

Two distinct regions in which OLM cells do or do not (red) affect theta power



(a) $c_{OLM,BiC} = 0.21,\ c_{BiC,OLM} = 0.13$





CA1 Hippocampal Model(s) - Can we do this?

Maybe.

We should definitely be sharing, but...

Models and their development should not and cannot really be separated from their context ('function')

Why not? (not as 'nice' as worms or crabs....)

Hippocampal function?

(e.g., not just CA1, and we're building the models to get biological/physiological insight...)

What to include? (unclear because of above)

CA1 Hippocampal Model(s) - Can we do this?
Suggestions

Determine and define common context/framework ***first***
(e.g., theta, gamma, SPWR, seizures, place cells/grid cells, phase precession, in vitro, in vivo aspects etc.)
Then build community

Ensure metadata is included given the above
(e.g., species, temperature, solutions, recording details, etc.)

Separate context-dependent and context-independent experimental data for model parameters
(e.g., synaptic decay time constants ok, but perhaps not reversal potentials;
channel kinetics ok but probably not channel conductances etc.)

Implementation - integrating models of different detail - I/O possibilities? and try to take advantage of theoretical aspects...
(e.g., Hedrick and Cox)