"Modelling Neurological Disease"

Frances K. Skinner
Toronto Western Research Institute, University Health Network
and University of Toronto

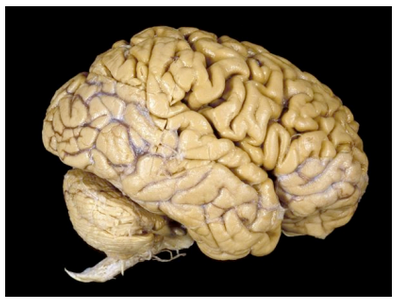
May 17, 2012

Fields Introductory Tutorial

part of Thematic Program:

"Towards Mathematical Modeling of Neurological Disease from Cellular Perspectives"

How do we model neurological disease?



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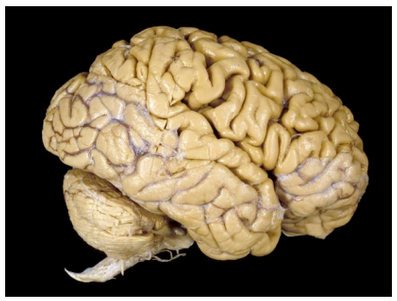
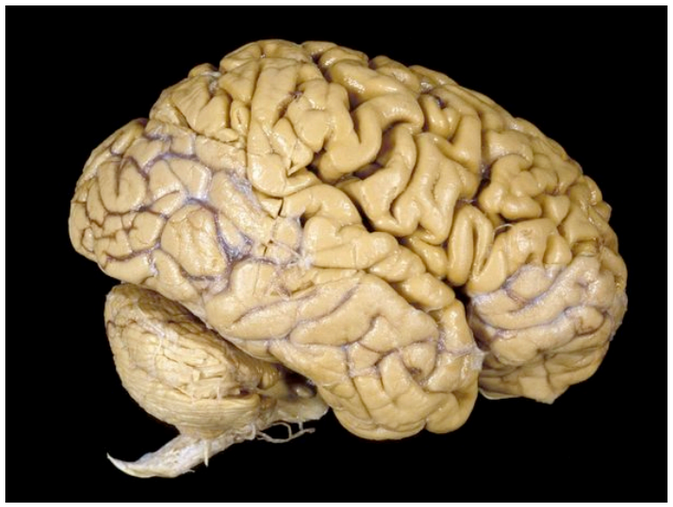
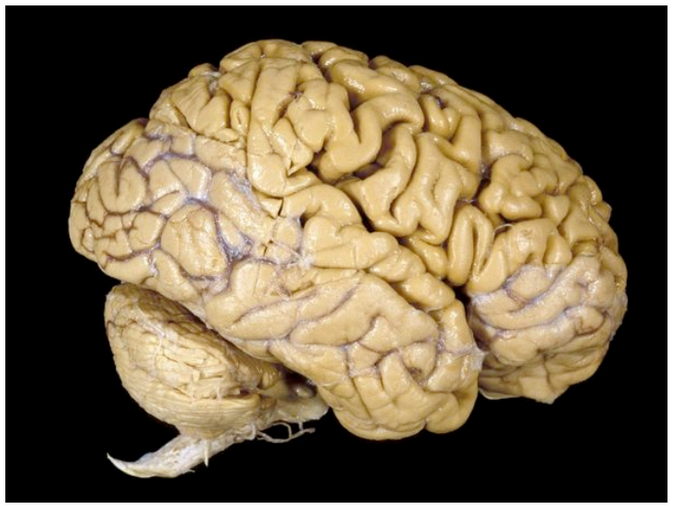


Short Answer: We don't know



Less short answer....

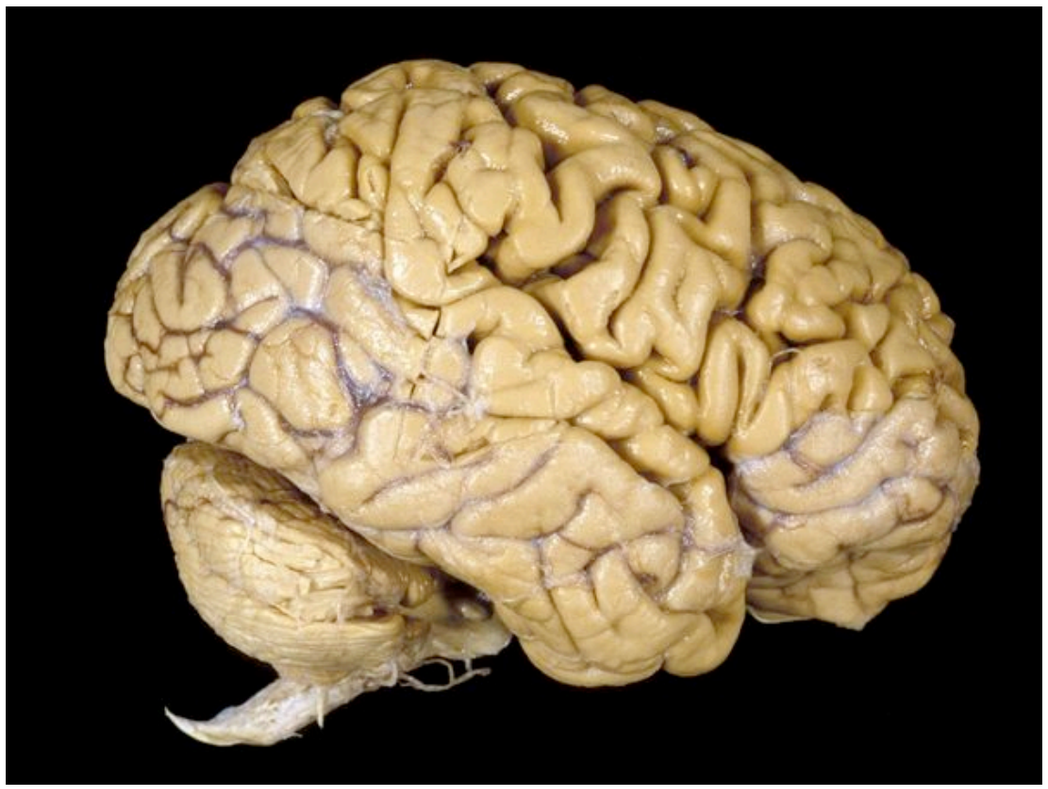


Less short answer....

"Towards mathematical modeling of neurological disease from cellular perspectives" - upcoming workshops!

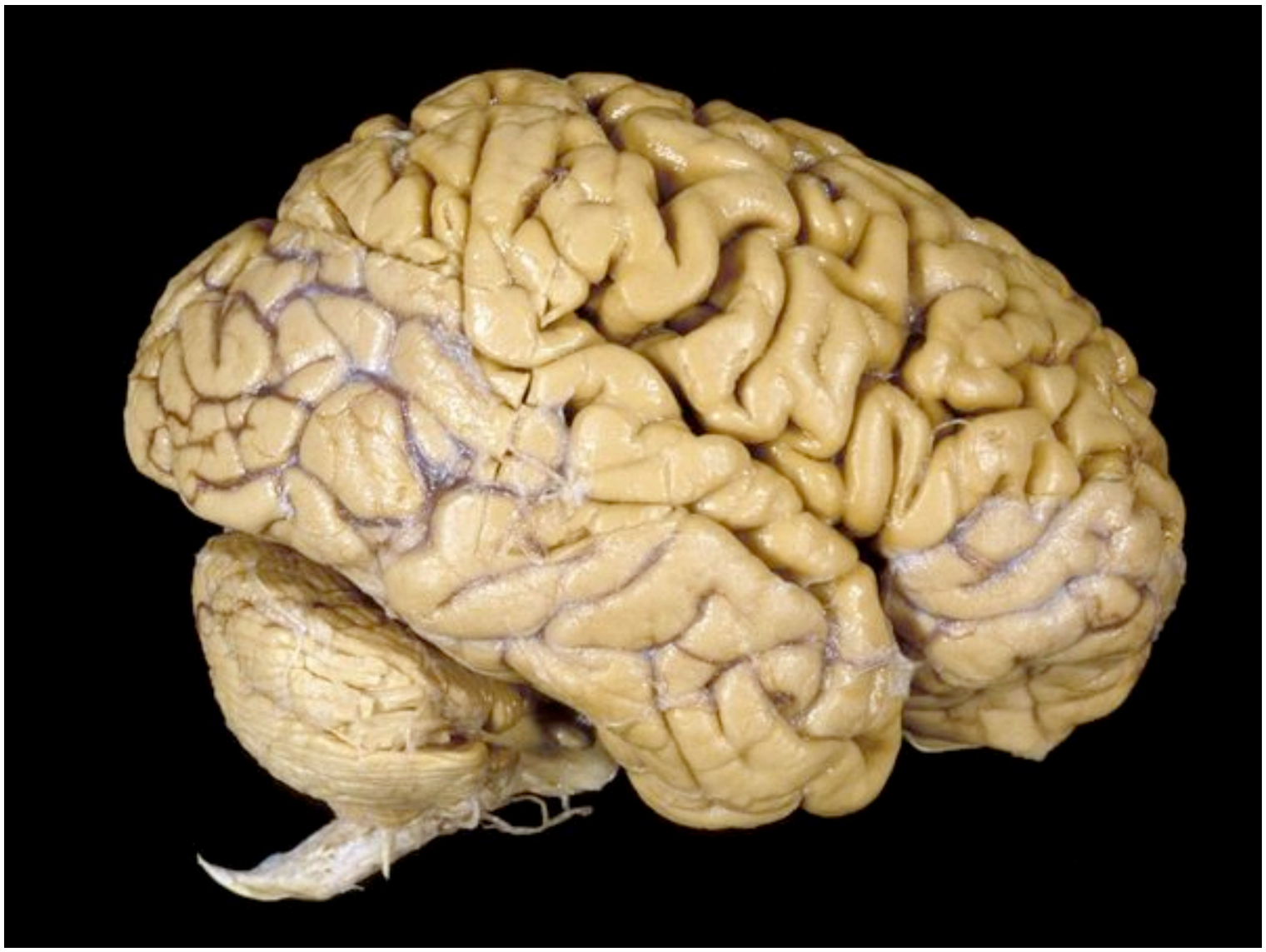
Neurological disease prevalence (US numbers):

4.5 million for Alzheimer's disease
2.2. million for Schizophrenia
2.3 million for Epilepsy
1.5 million for Parkinson's disease



Points to be illustrated and discussed in the lecture

- we need to consider a cellular basis (why?)
- context, context, context (under what situations is the disease considered?)
- neurological (experimental) models can be wide-ranging (what motivates the choice?)
- cellular-based (oscillatory) modeling



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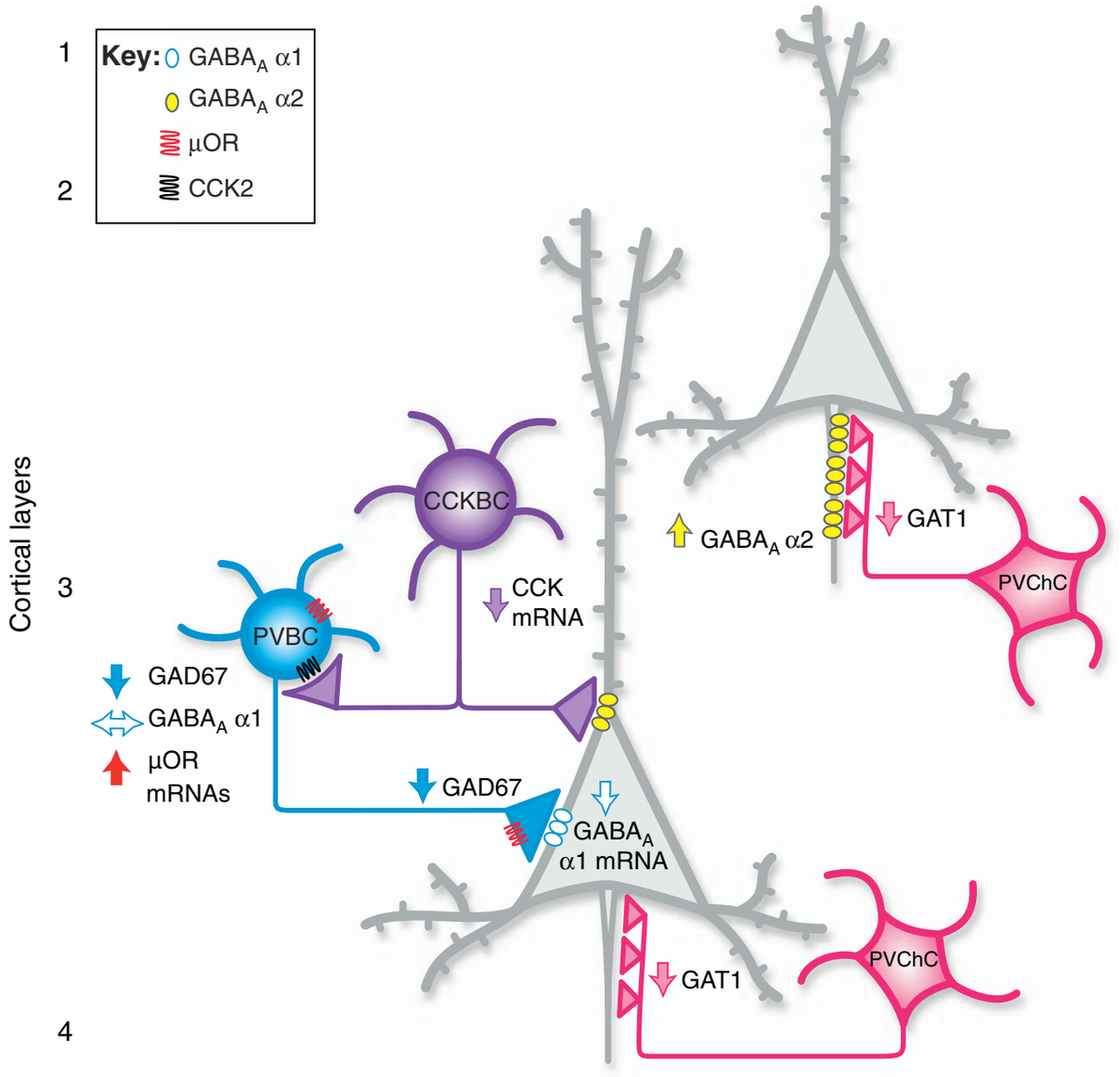
Trends in Neurosciences January 2012, Vol. 35, No. 1

Special Issue: Neuropsychiatric Disorders

Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia

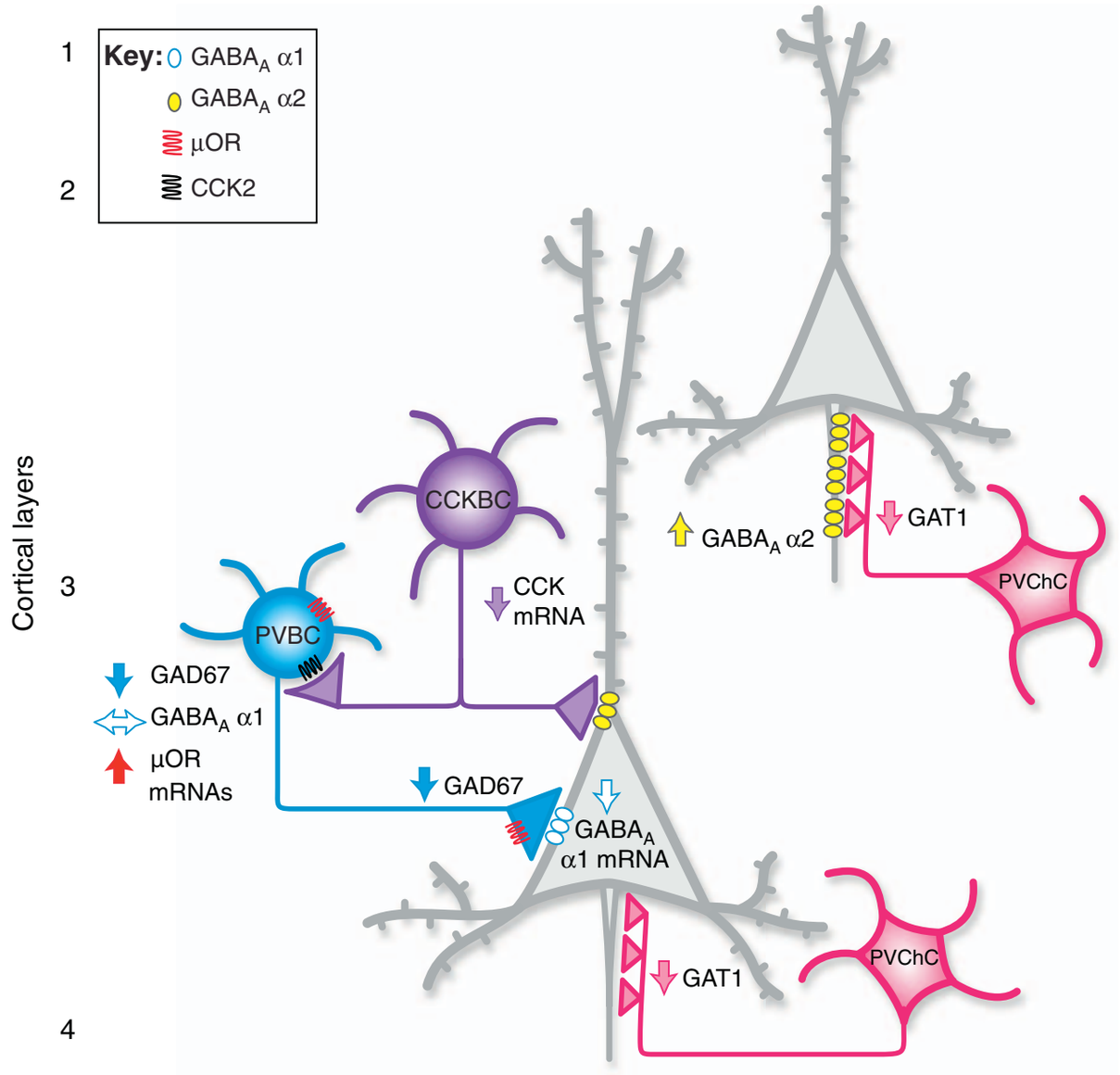
David A. Lewis, Allison A. Curley, Jill R. Glausier and David W. Volk

Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213, USA



Schematic summary of alterations in neuronal circuitry in layer 3 of the dorsolateral prefrontal cortex in subjects with schizophrenia

Lewis et al. 2012



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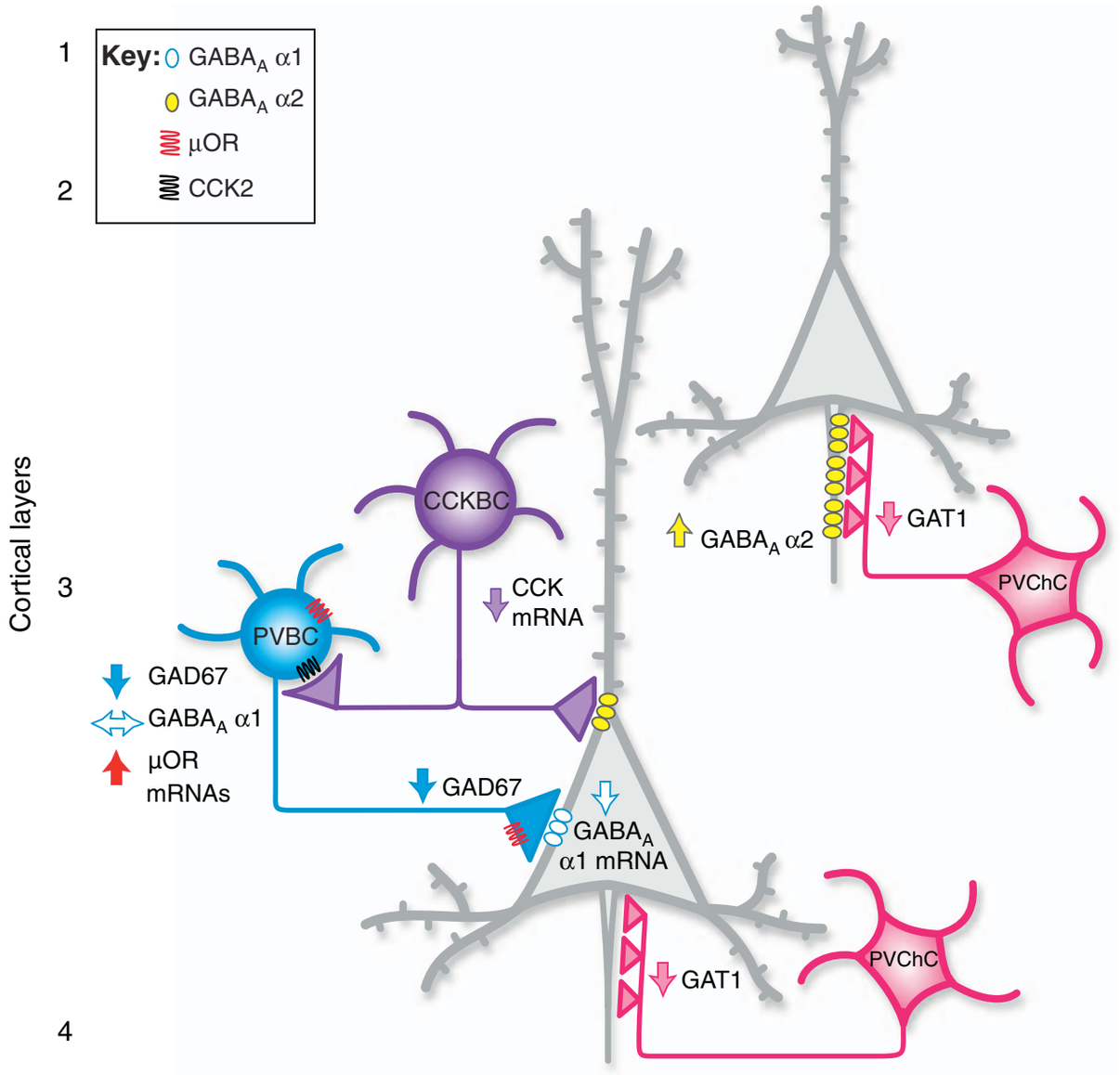

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Nature Reviews Neuroscience | AOP, published online 18 January 2012; doi:10.1038/nrn3155

Interneuron dysfunction in psychiatric disorders

Oscar Marín

Abstract | Schizophrenia, autism and intellectual disabilities are best understood as spectrums of diseases that have broad sets of causes. However, it is becoming evident that these conditions also have overlapping phenotypes and genetics, which is suggestive of common deficits. In this context, the idea that the disruption of inhibitory circuits might be responsible for some of the clinical features of these disorders is gaining support. Recent studies in animal models demonstrate that the molecular basis of such disruption is linked to specific defects in the development and function of interneurons — the cells that are responsible for establishing inhibitory circuits in the brain. These insights are leading to a better understanding of the causes of schizophrenia, autism and intellectual disabilities, and may contribute to the development of more-effective therapeutic interventions.

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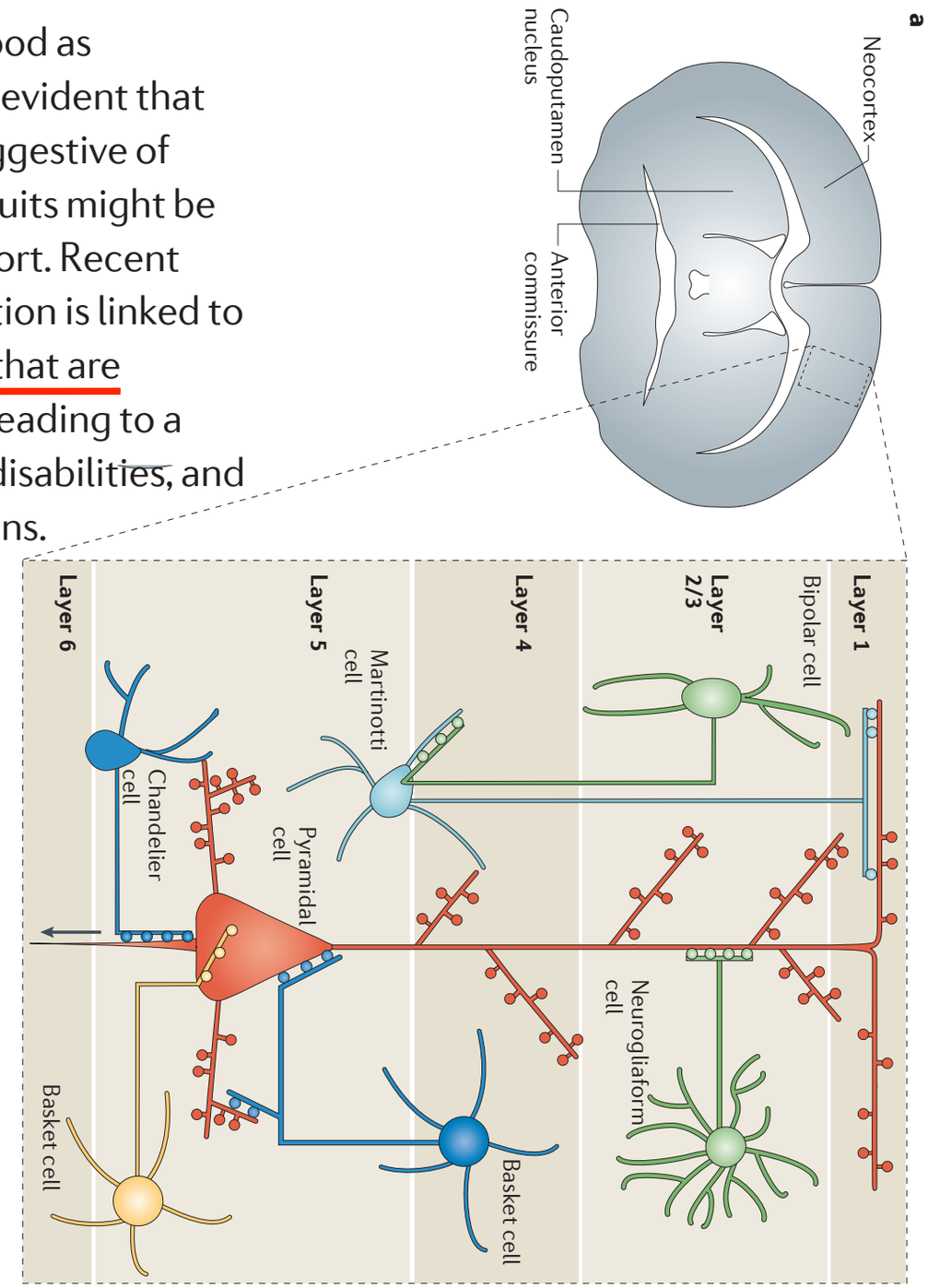

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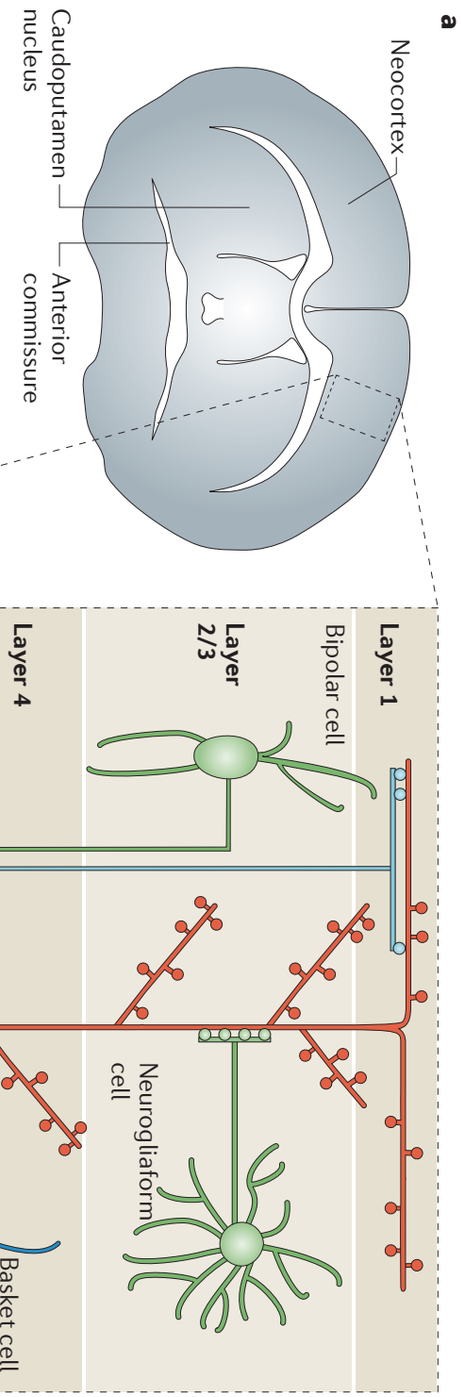
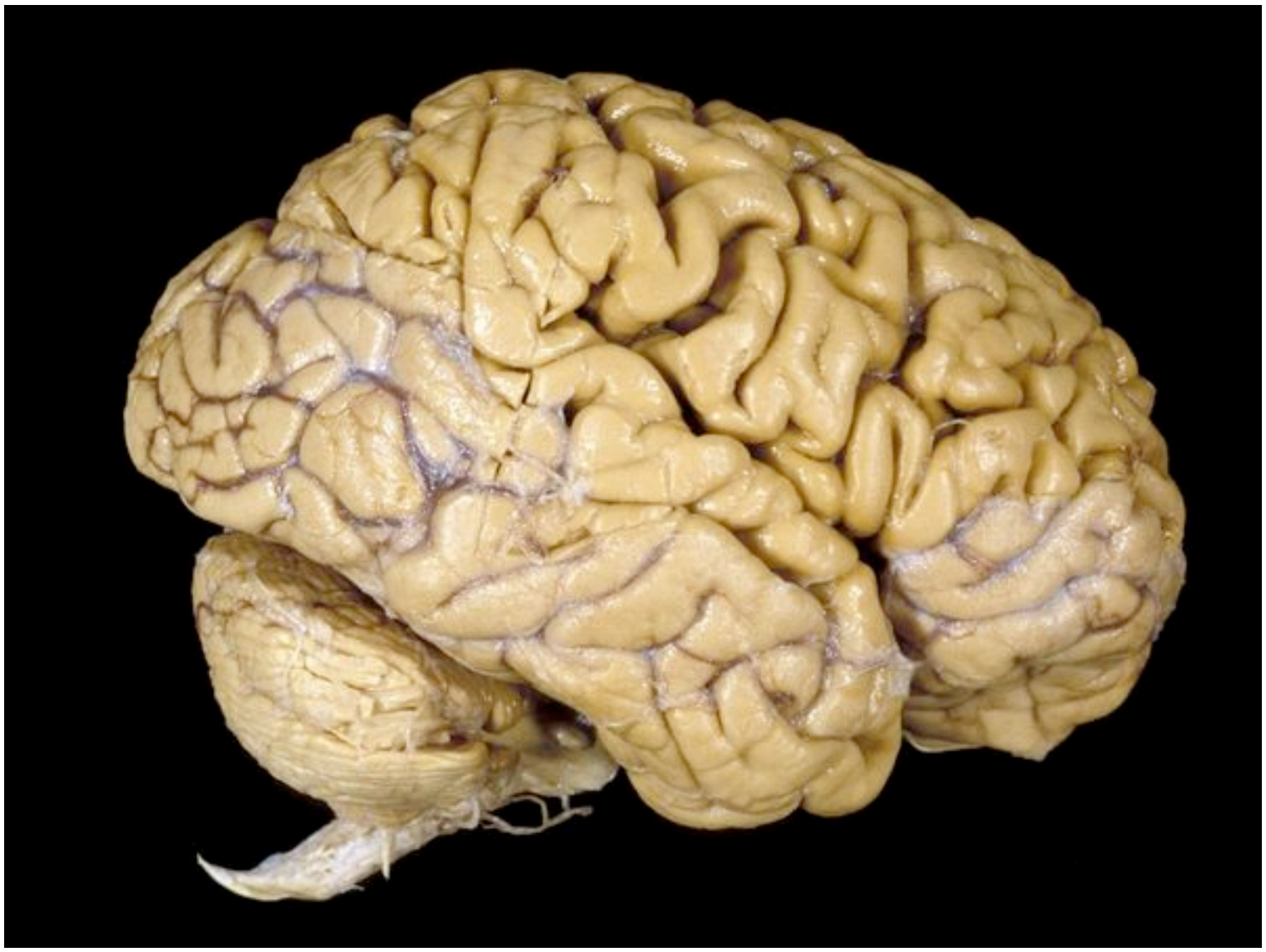
"....increasingly commonplace idea that the alteration of the excitatory-inhibitory balance is associated with various neuropsychiatric disorders"

"...contribution of interneurons to each unique pathophysiology..."





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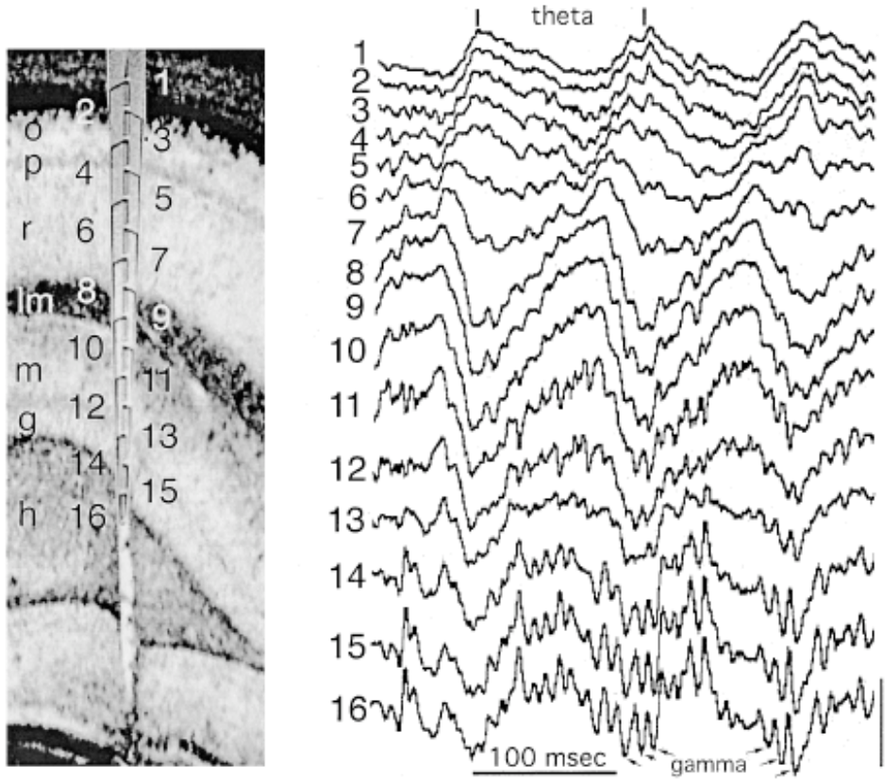
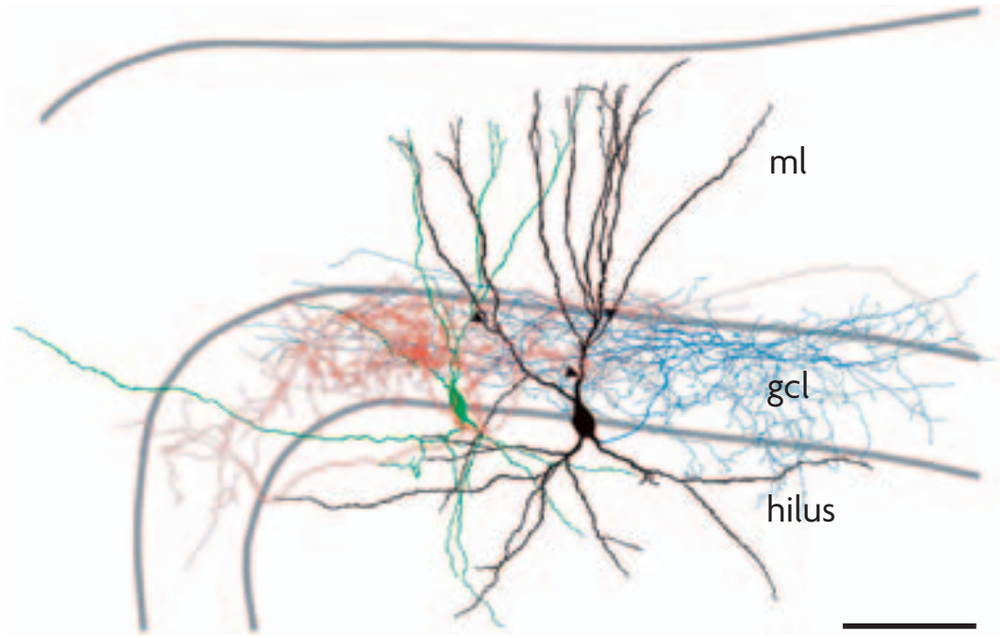
Gamma rhythms
(30-90 Hz, related to higher cognitive processing)



Bragin et al. 1995

Gamma rhythms nested in theta rhythms (movement, exploration)



Bartos et al. 2007

Key role in generation played by synchronous output from parvalbumin-positive interneurons (basket cells)

Dynamic Cooperation of Pyramidal Cells and Specific GABAergic interneurons in Cell Assemblies

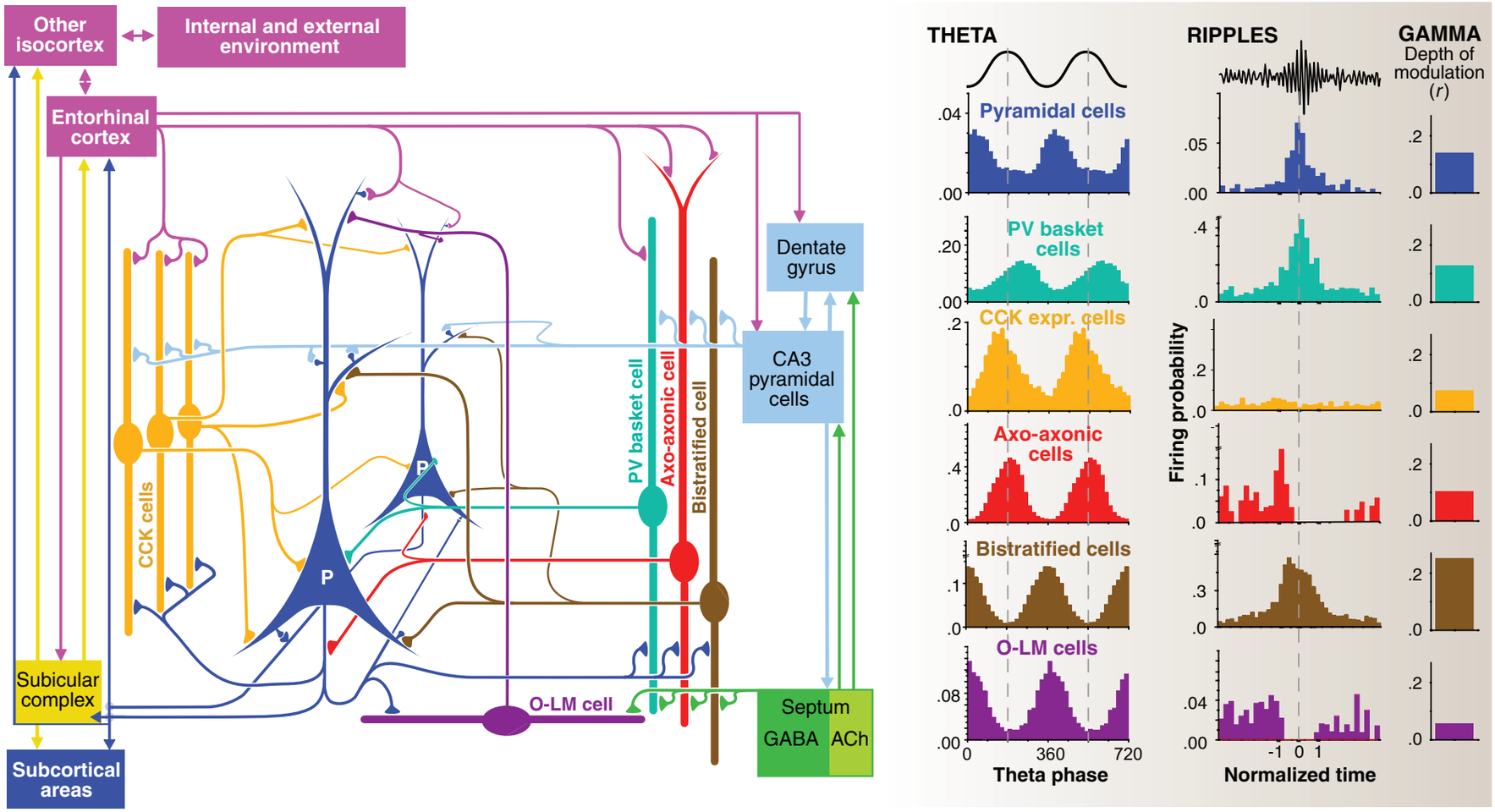
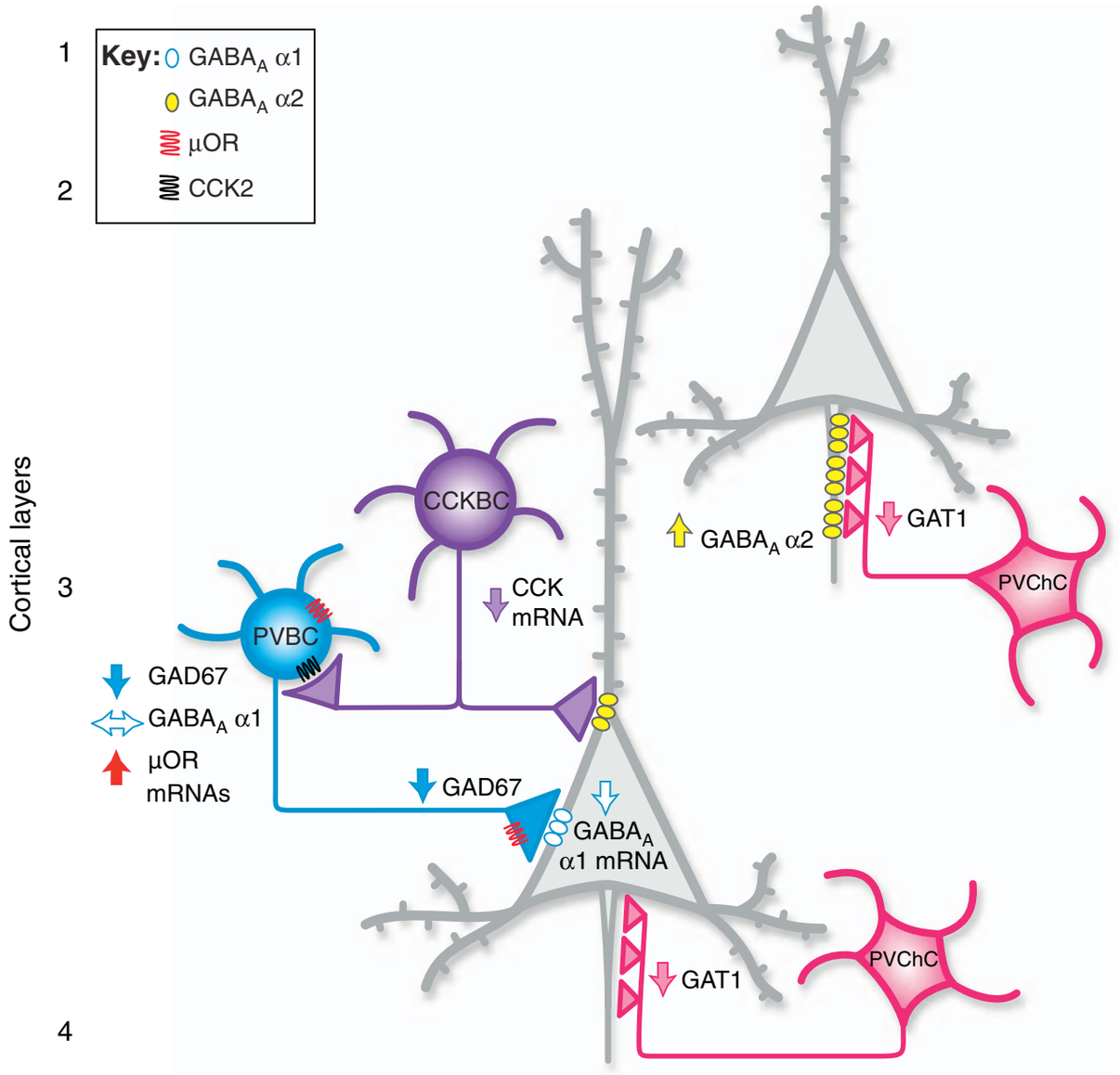


Fig. 2. Spatiotemporal interaction between pyramidal cells and several classes of interneuron during network oscillations, shown as a schematic summary of the main synaptic connections of pyramidal cells (P), PV-expressing basket, axo-axonic, bistratified, O-LM, and three classes of CCK-expressing interneurons. The firing probability histograms show that interneurons innervating different domains of pyramidal cells fire with distinct temporal patterns during theta and ripple oscillations, and their spike timing is coupled to field gamma oscillations to differing degrees. The same somatic and dendritic domains receive differentially timed input from several types of GABAergic interneuron (*18*, *19*, *23*, *30*). ACh, acetylcholine.

Klausberger and Somogyi 2008



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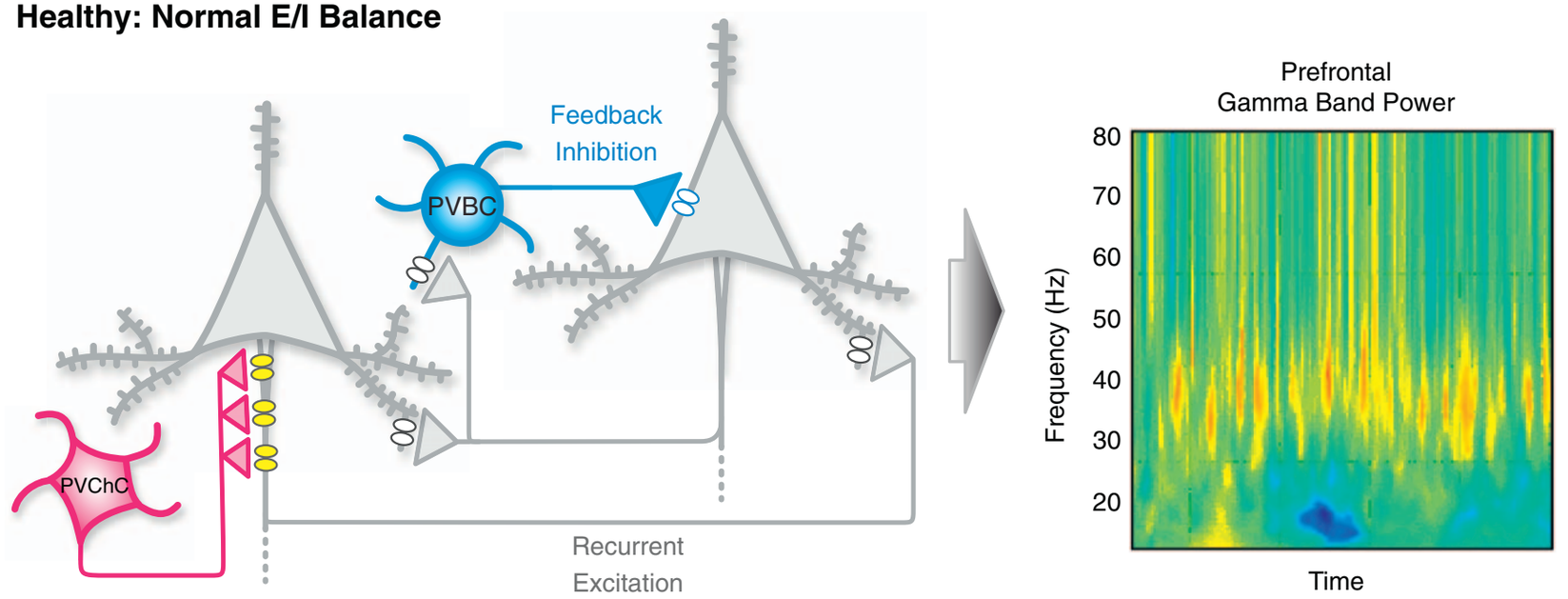
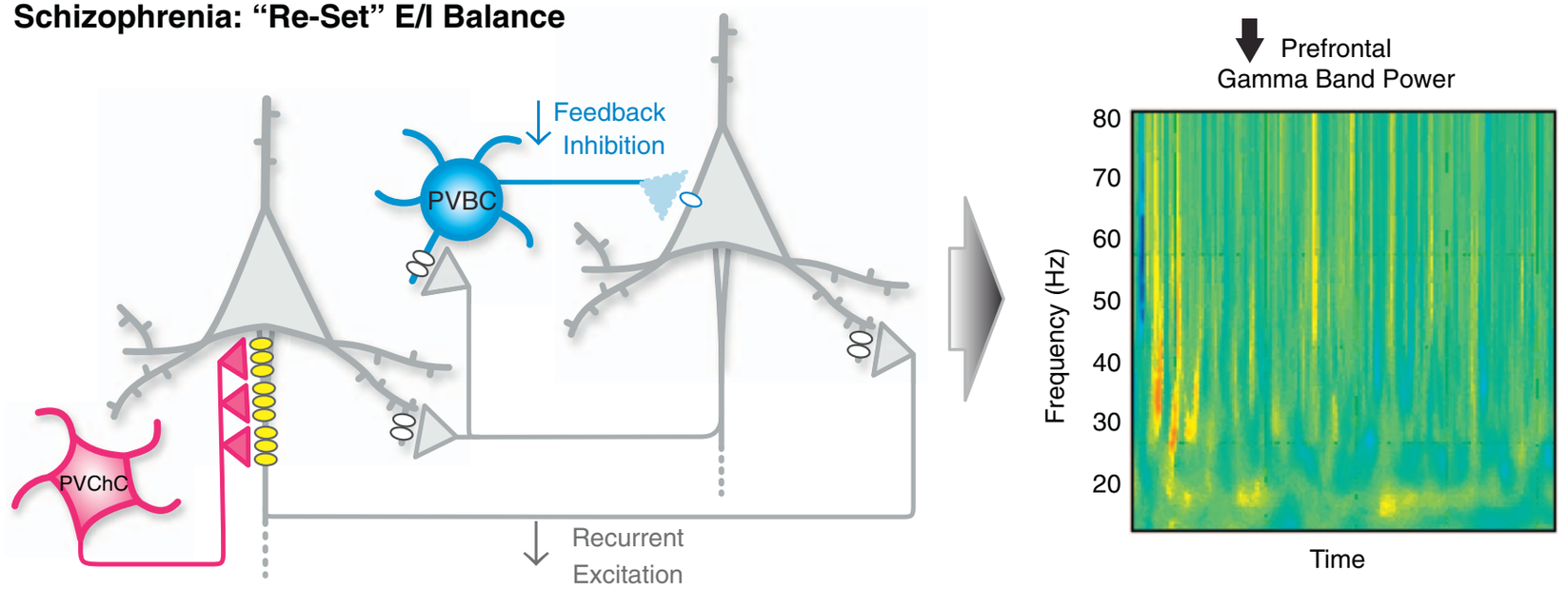
Healthy: Normal E/I Balance



Schizophrenia: "Re-Set" E/I Balance



Key: $GABA_A$ α2 Receptor $GABA_A$ α1 Receptor Glutamate Receptor

Lower recurrent excitation between P neurons	Lower feedback inhibition from PVBCs	Greater P neuron depolarization from PVChCs
• Smaller dendritic arbor • Fewer dendritic spines	• Reduced GABA synthesis • Increased suppression of GABA release • Fewer $GABA_A$ α1 receptors • Reduced chloride influx	• Reduced GABA re-uptake • More $GABA_A$ α2 receptors

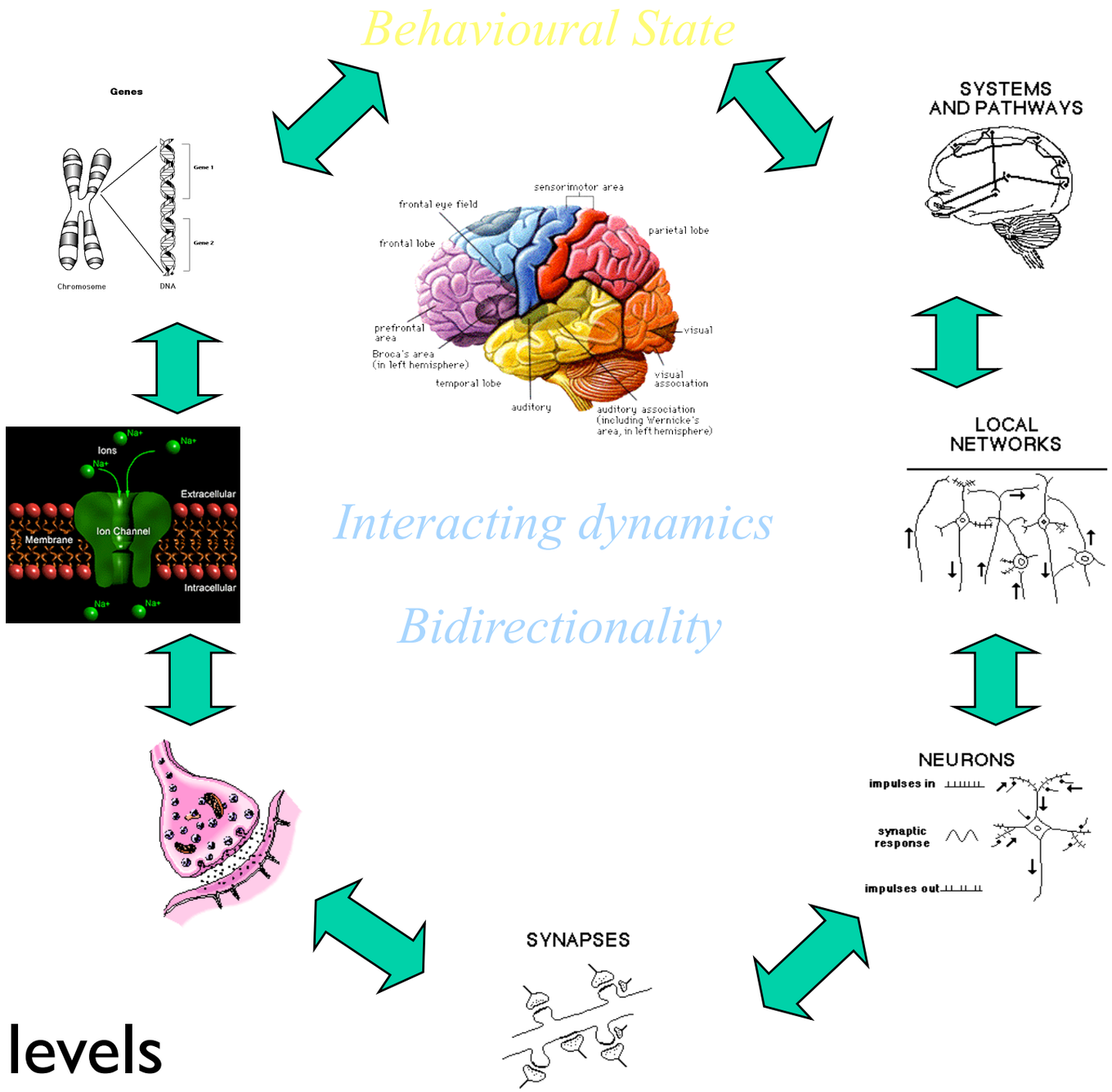
TRENDS in Neurosciences

"Thus, the multiple alterations that weaken PVBC inhibition of pyramidal cells could provide the neural substrate for the lower power of frontal lobe gamma band oscillations during cognitive control tasks."

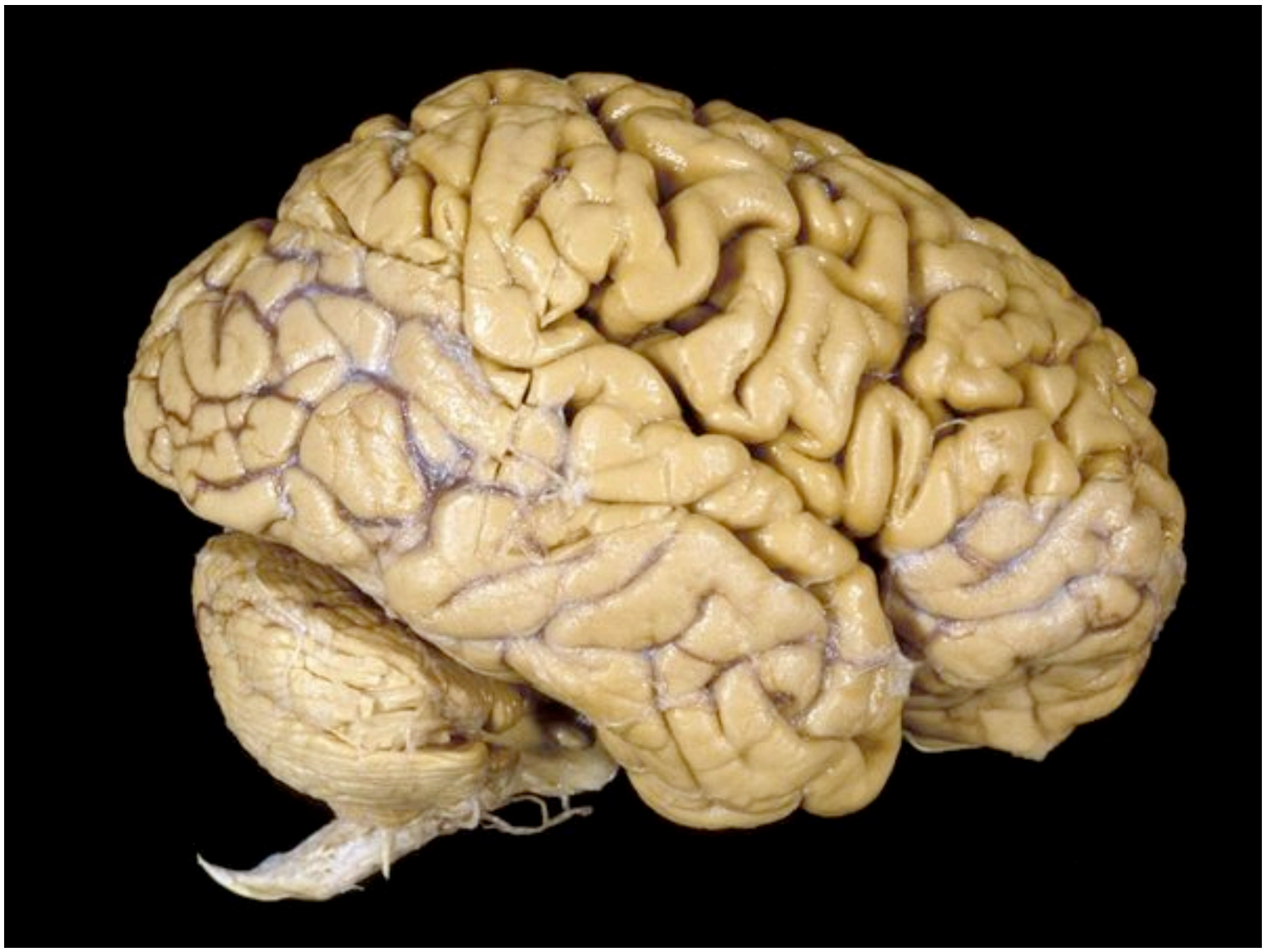
"..focus on only a limited portion of cortical circuitry; a full accounting of the pathophysiology underlying cognitive control deficits in schizophrenia requires better knowledge of the patterns of connectivity within the DLPRC and more sensitive methods for assessing the functional integrity and compensations of these connections in the illness." - Lewis et al, 2012

i.e., trying to put the pieces together....

while including a cellular perspective...



challenges of multiple levels and interpretations...



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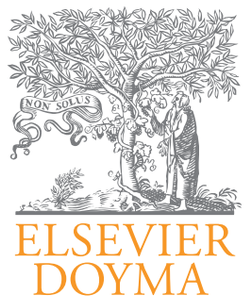

NEUROLOGÍA

www.elsevier.es/neurologia

REVIEW ARTICLE

Experimental models in epilepsy

M.E. Garcia Garcia*, I. Garcia Morales and J. Matías Guiu

Abstract

Introduction: Epilepsy is one of the neurological pathologies with the highest rate of incidence and with a significant number of negatives consequences. Current pharmacological treatments have an antiepileptic effect, allowing control over 70% of the patients, but they are not able to prevent the development of Epileptogenesis from occurring.

Method: We have reviewed the most relevant publications for experimental animal models with epilepsy by using the PubMed data base.

Results: We found a large number of publications related to different kinds of experimental models, both genetic (transgenic, genetically determined) and lesional, which appeared to resemble the different types of human epilepsy.

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"...a great variety of models that try to represent the different types of epilepsy that exist in humans.... each model presents a number of advantages and disadvantages, but the ideal model has not yet been found. At present, we select it depending on the design and purpose - target of the study."

Models of epilepsy

Ghanim Ullah and Steven J. Schiff (2009), Scholarpedia, 4(7):1409.

Epilepsy is a chronic neurological disorder characterized by occurrence and recurrence of seizures; epilepsy is thus a seizure disorder.

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"Despite an extraordinary amount of interest in understanding the dynamics of seizures, we still lack a unifying dynamical definition of what a seizure is (Soltesz and Staley, 2008). The extraordinary variety of experimental preparations and human epilepsies makes the quest for unifying principles especially difficult. Epilepsy is a good example of a dynamical disease where theory and computation must work hand-in-hand with experiment to bring us a deeper understanding and more rational therapeutics."

J Neurophysiol 92: 1116–1132, 2004.
First published March 31, 2004; 10.1152/jn.00529.2003.

Potassium Model for Slow (2-3 Hz) In Vivo Neocortical Paroxysmal Oscillations

M. Bazhenov,[1] I. Timofeev,[2] M. Steriade,[2] and T. J. Sejnowski[1,3]
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High extracellular K elicits seizures
(anesthetized cats)

European Journal of Neuroscience, Vol. 13, pp. 639–640, 2001

SHORT COMMUNICATION
Lowering the extracellular potassium concentration elicits epileptic activity in neocortical tissue of epileptic patients

Ali Gorji, Rüdiger Köhling, Heidrun Straub, Jörg-Michael Höhling and Michael Madeja
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Epilepsy is a common disease of the brain affecting 0.5–1% of the population (Lowenstein, 1998). Several strategies and models have been developed in order to elicit epileptic activity and to investigate the basic mechanisms of epileptogenesis. A well-established and widely distributed model is the increase in the extracellular potassium concentration ($[K^+]_o$, the so-called high-potassium model of epilepsy; Zuckermann & Glaser, 1970; Rutecki *et al*., 1985; Korn *et al*., 1987). Thus, epileptiform events arise in hippocampal slices when the $[K^+]_o$ is raised from around 4 mmol/L to >7 mmol/L. As underlying mechanisms, excitatory actions of potassium ions are considered, which include the reduction of the electromotive driving force, the impairment of γ-aminobutyric acid receptor-mediated inhibition and the shrinkage of the extracellular space due to glial cell swelling (for a review see McBain *et al*., 1993).

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The finding that reducing $[K^+]_o$ can induce epileptic activity has two consequences: (i) due to the fact that in contrast to the well-established, and intensively studied, high potassium model of epilepsy, the opposite change in $[K^+]_o$ also elicits epileptic activity, the hypotheses of epileptogenesis by changes in ionic concentration have to be reconsidered; and (ii), because returning $[K^+]_o$ to normal levels abolished the epileptic activity, thus representing an anti-epileptic effect, it can be assumed that the methods in traditional Iranian medicine to increase $[K^+]_o$ might indeed be of benefit for some epileptic patients.

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Institut für Physiologie, Westfälische Wilhelms-University Münster, Robert-Koch-Strasse 27a, D-48149 Münster, Germany

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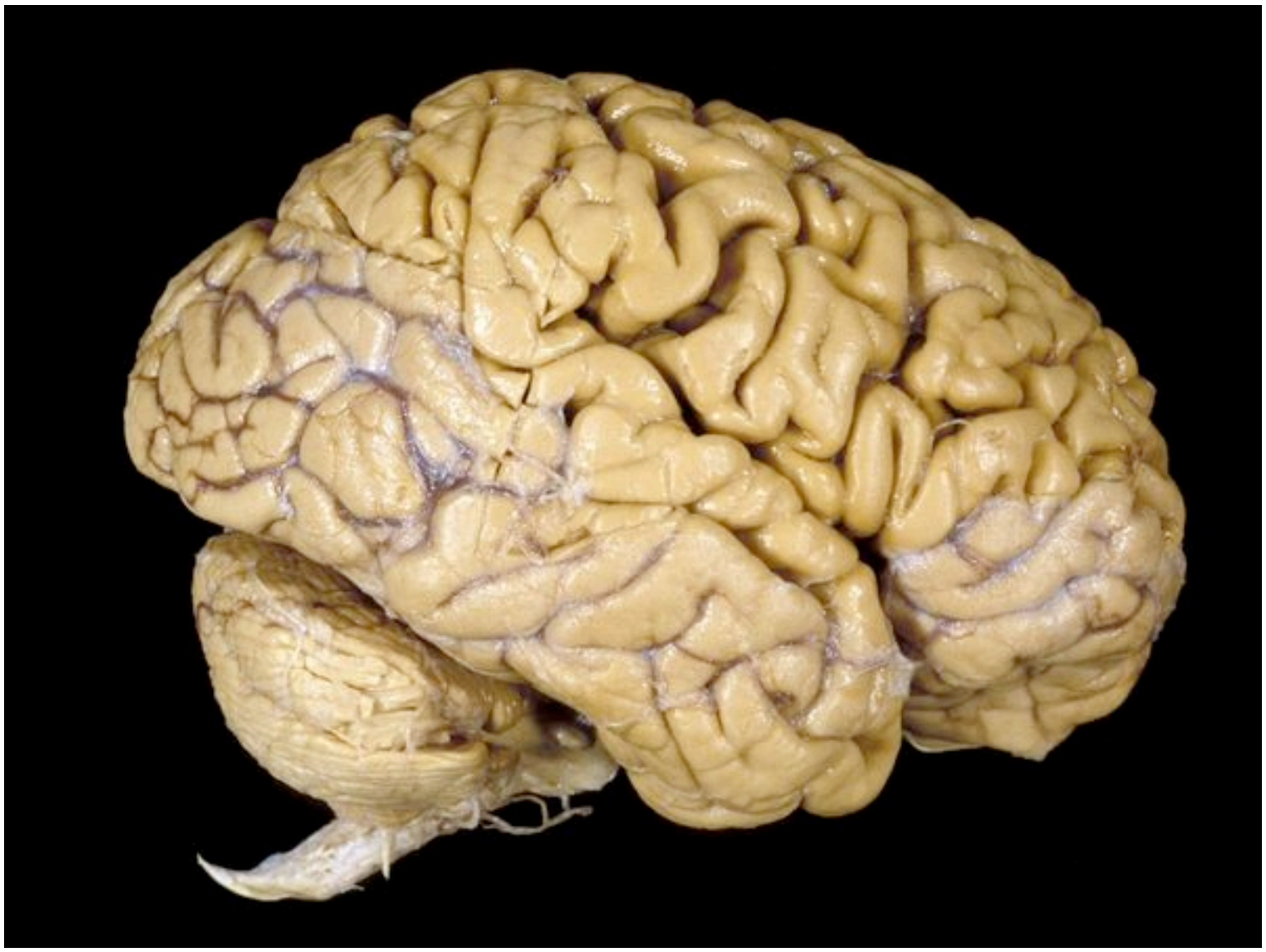
The finding that reducing $[K^+]_o$ can induce epileptic activity has two consequences: (i) due to the fact that in contrast to the well-established, and intensively studied, high potassium model of epilepsy, the opposite change in $[K^+]_o$ also elicits epileptic activity, the hypotheses of epileptogenesis by changes in ionic concentration have to be reconsidered; and (ii), because returning $[K^+]_o$ to normal levels abolished the epileptic activity, thus representing an anti-epileptic effect, it can be assumed that the methods in traditional Iranian medicine to increase $[K^+]_o$ might indeed be of benefit for some epileptic patients.

Low extracellular K elicits epileptic activity (human brain slices in vitro)



Points to be illustrated and discussed in the lecture

- we need to consider a cellular basis (why?)
- context, context, context (under what situations is the disease considered?)
- neurological (experimental) models can be wide-ranging (what motivates the choice?)
- cellular-based (oscillatory) modeling

BMC Systems Biology

Commentary

Computational disease modeling – fact or fiction?

Jesper N Tegnér*†[1], Albert Compte*†[2], Charles Auffray[3], Gary An[4], Gunnar Cedersund[5], Gilles Clermont[6], Boris Gutkin[7], Zoltán N Oltvai[8], Klaas Enno Stephan[9,10], Randy Thomas[11] and Pablo Villoslada[12]

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BMC Systems Biology

BioMed Central

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Open Access

Computational disease modeling – fact or fiction?

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commentary based on an exploratory workshop

two conceptual traditions in biological computational modeling noted:

- use of complex intracellular molecular models - systems biology community
- use of modeling strategy that selects features of relevance to the phenomena and combines available data in models of modest complexity

> *"a successful strategy in computational neuroscience has been to identify minimal models that adequately describe and predict the biology, but at the potential price of selecting a too narrowly focused model."*

***conclusion* - diverse scientific modeling cultures exist, intense cross-talk should occur to make progress on clinically relevant problems**

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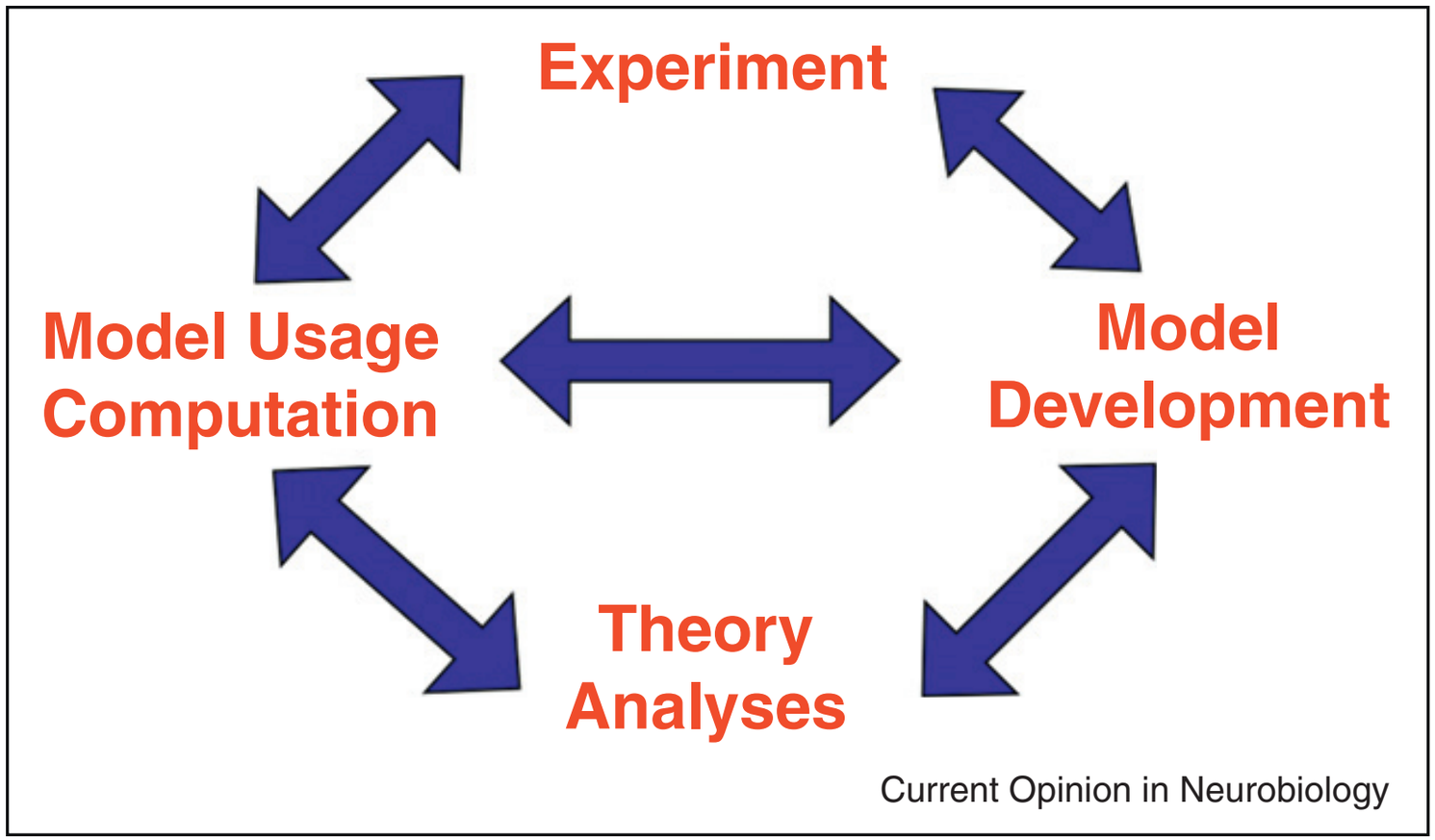
Current Opinion in Neurobiology 2012

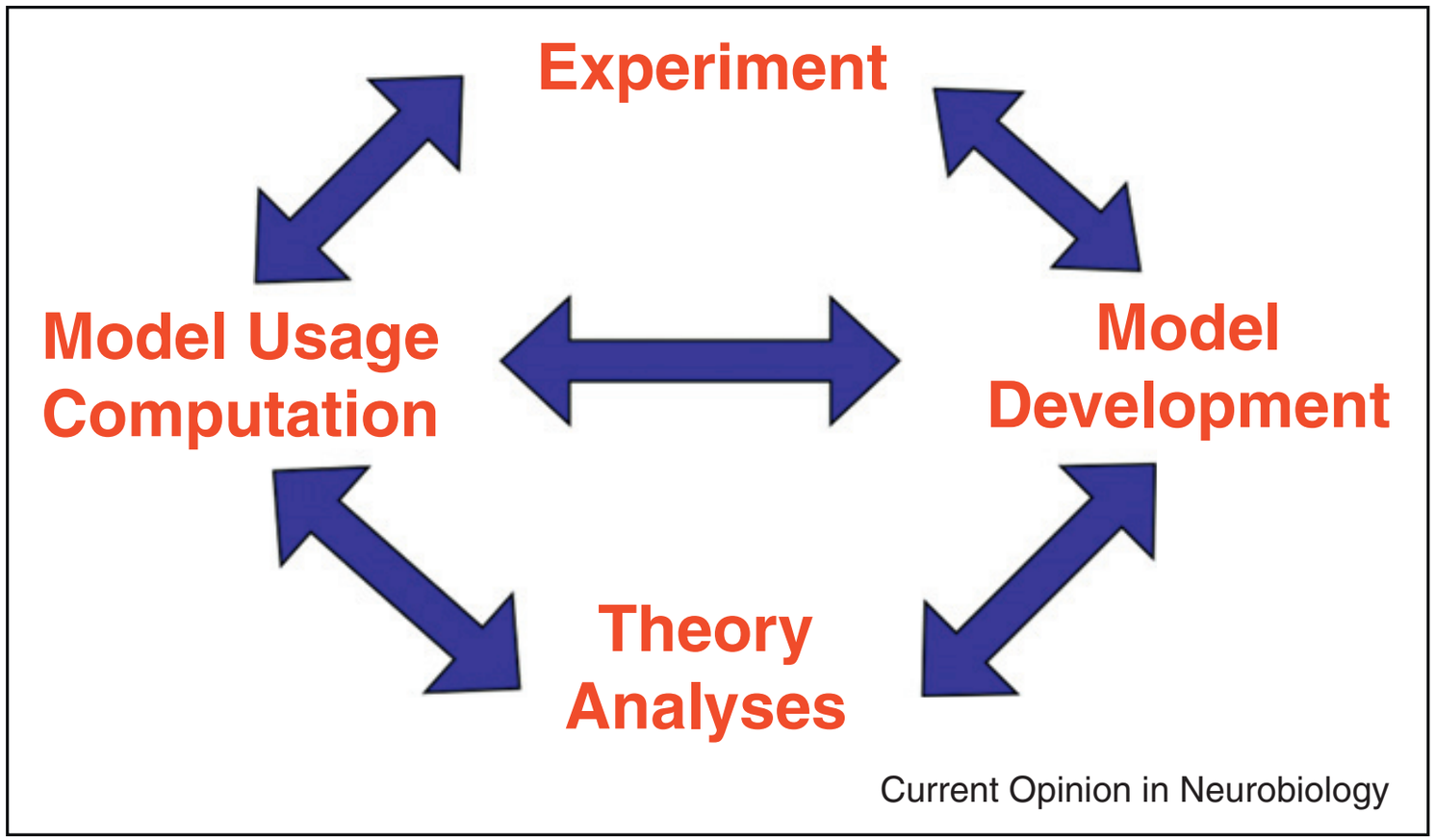
Cellular-based modeling of oscillatory dynamics in brain networks

Frances K Skinner

Oscillatory, population activities have long been known to occur in our brains during different behavioral states. We know that many different cell types exist and that they contribute in distinct ways to the generation of these activities. I review recent papers that involve cellular-based models of brain networks, most of which include theta, gamma and sharp wave-ripple activities. To help organize the modeling work, I present it from a perspective of three different types of cellular-based modeling: 'Generic', 'Biophysical' and 'Linking'. Cellular-based modeling is taken to encompass the four features of experiment, model development, theory/analyses, and model usage/computation. The three modeling types are shown to include these features and interactions in different ways.

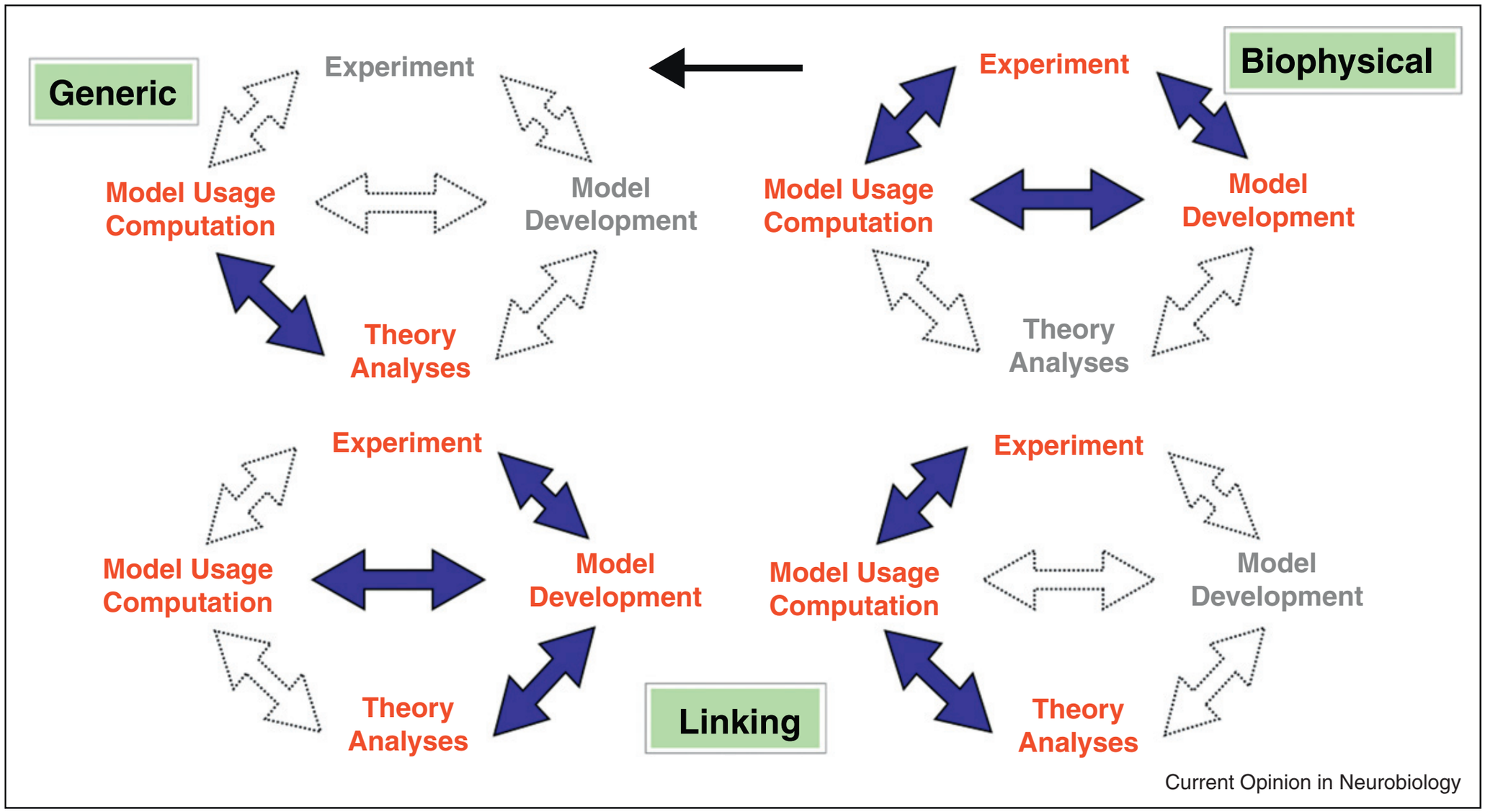


Cellular-based Modeling Features.

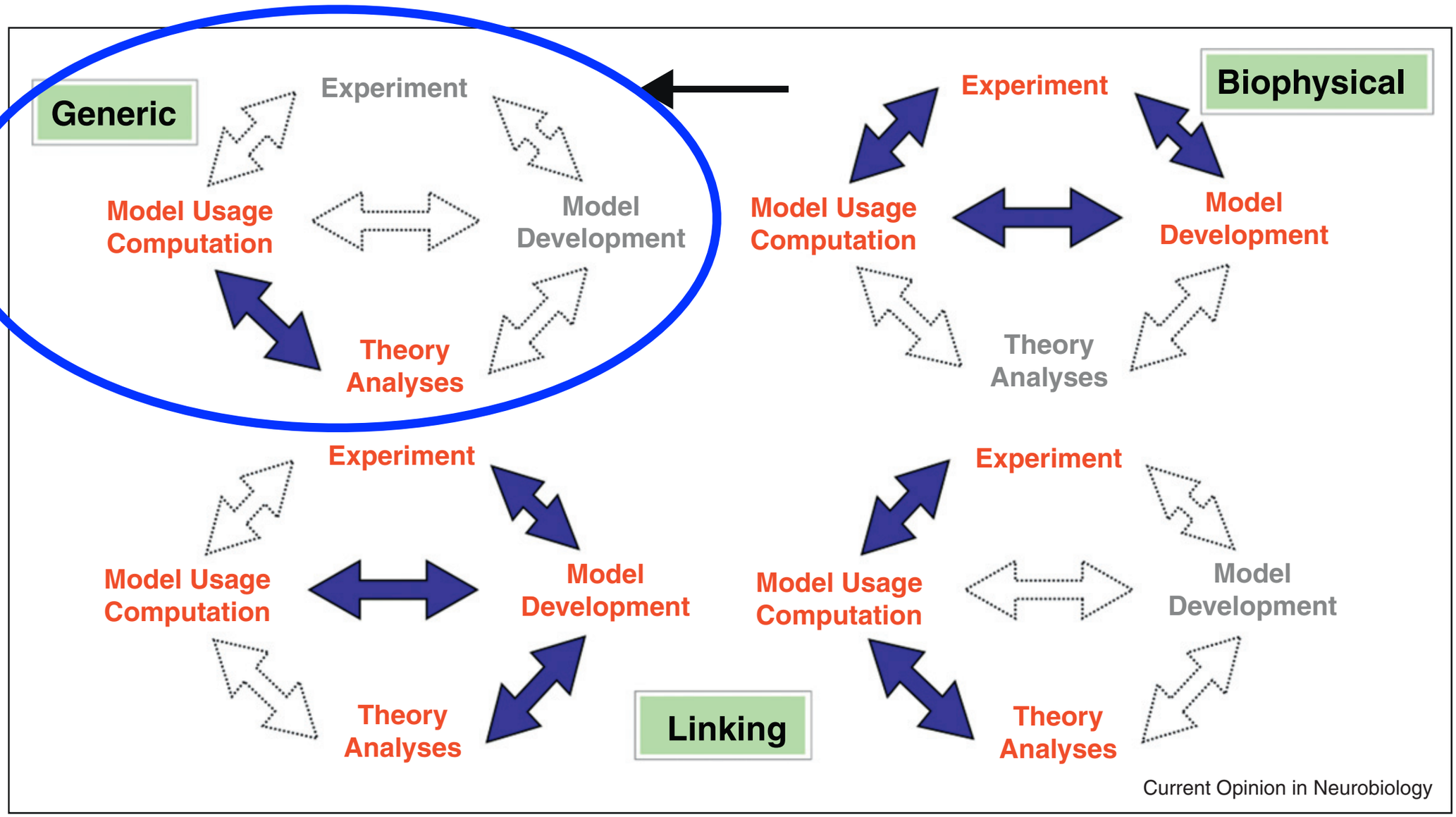


Cellular-based Modeling Features.

"... size and architecture, along with connectivity and cellular characteristics as dictated by context and function need to be taken into consideration."



Current Opinion in Neurobiology



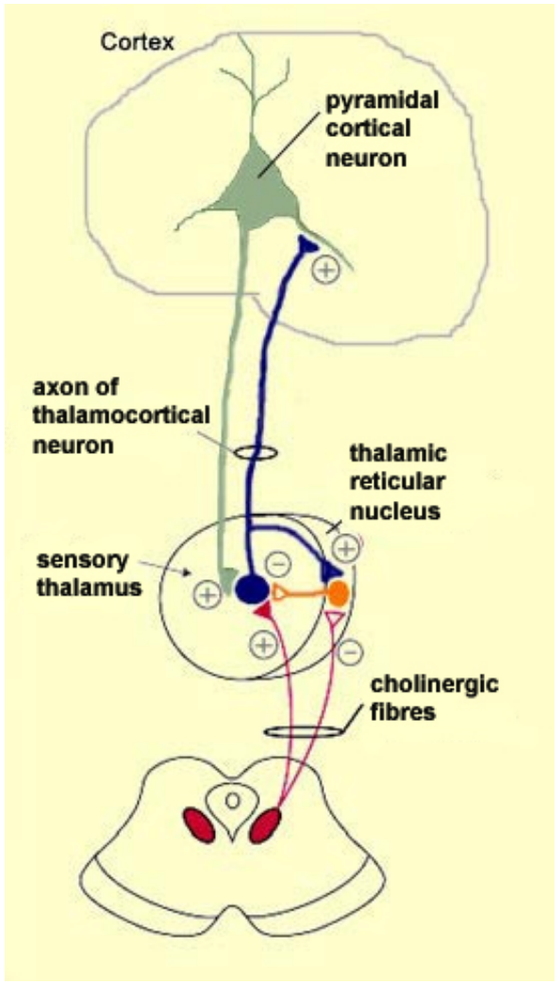
Current Opinion in Neurobiology

Neural Computation 1992

Alternating and Synchronous Rhythms in Reciprocally Inhibitory Model Neurons

Xiao-Jing Wang*
John Rinzel
Mathematical Research Branch, NIDDK, Bldg. 31, Rm. 4B-54, National Institutes of Health, Bethesda, MD 20892 USA

- reticular thalamic nucleus which has interacting inhibitory cells which have a low-threshold T-type calcium current (post-inhibitory rebound (PIR) ionic mechanism).



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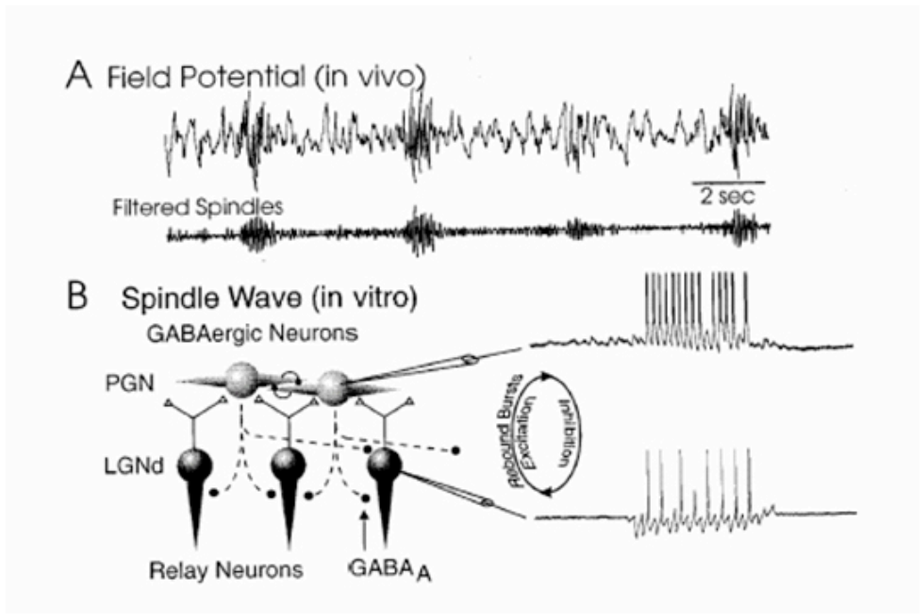

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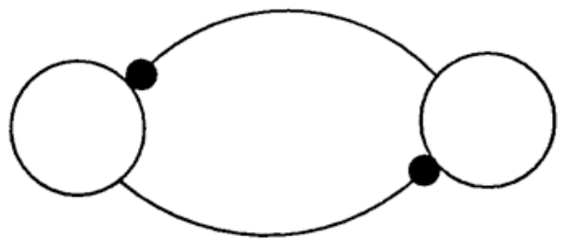
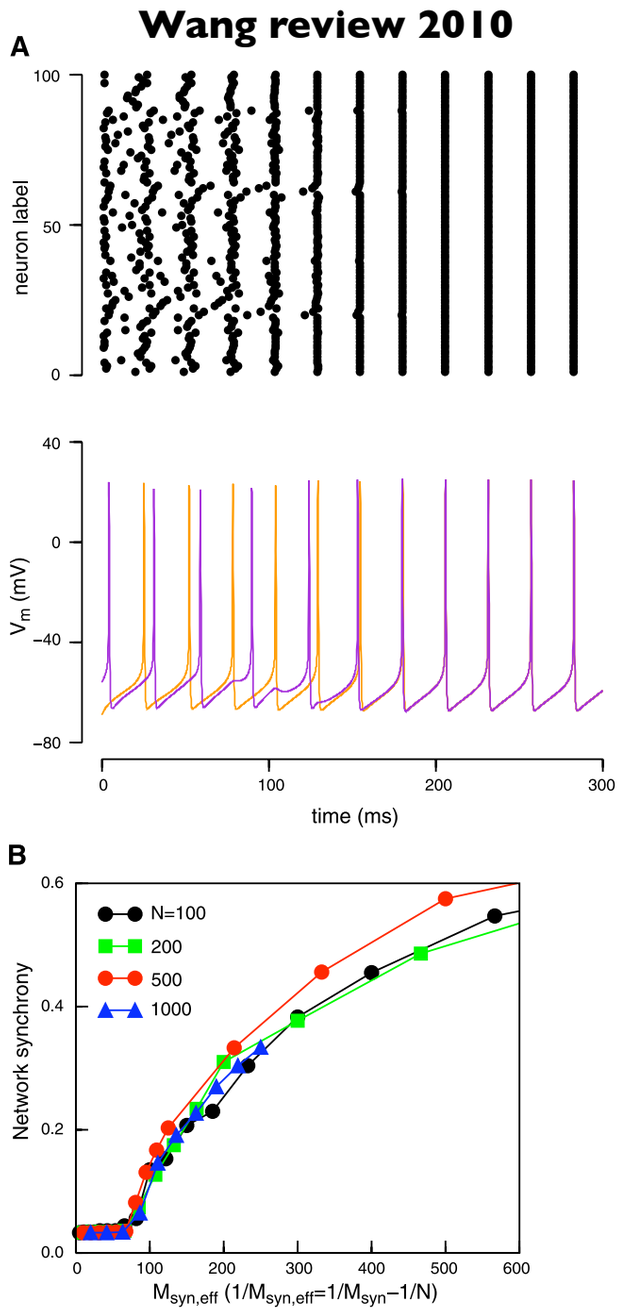


Mutual inhibition can synchronize oscillations
if postsynaptic conductance decays
sufficiently slowly

Two-cell network, phase plane analyses



Hippocampal inhibitory network models ...as based on Wang and Buzsaki 1996

...as mechanistically based on Wang and Rinzel 1992

Model neuron. Each interneuron is described by a single compartment and obeys the current balance equation:

$$C_m \frac{dV}{dt} = -I_{\mathrm{Na}} - I_{\mathrm{K}} - I_{\mathrm{L}} - I_{\mathrm{syn}} + I_{\mathrm{app}}, \tag{2.1}$$

where $C_m = 1\ \mu\mathrm{F/cm}^2$ and I_{app} is the injected current (in $\mu\mathrm{A/cm}^2$). The leak current $I_{\mathrm{L}} = g_{\mathrm{L}}(V - E_{\mathrm{L}})$ has a conductance $g_{\mathrm{L}} = 0.1\ \mathrm{mS/cm}^2$, so that the passive time constant $\tau_0 = C_m/g_{\mathrm{L}} = 10$ msec; $E_{\mathrm{L}} = -65$ mV.

The spike-generating Na^+ and K^+ voltage-dependent ion currents (I_{Na} and I_{K}) are of the Hodgkin–Huxley type (Hodgkin and Huxley, 1952). The transient sodium current $I_{\mathrm{Na}} = g_{\mathrm{Na}} m_\infty^3 h(V - E_{\mathrm{Na}})$, where the activation variable m is assumed fast and substituted by its steady-state function $m_\infty = \alpha_m/(\alpha_m + \beta_m)$; $\alpha_m(V) = -0.1(V + 35)/(\exp(-0.1(V + 35)) - 1)$, $\beta_m(V) = 4\exp(-(V + 60)/18)$. The inactivation variable h obeys a first-order kinetics:

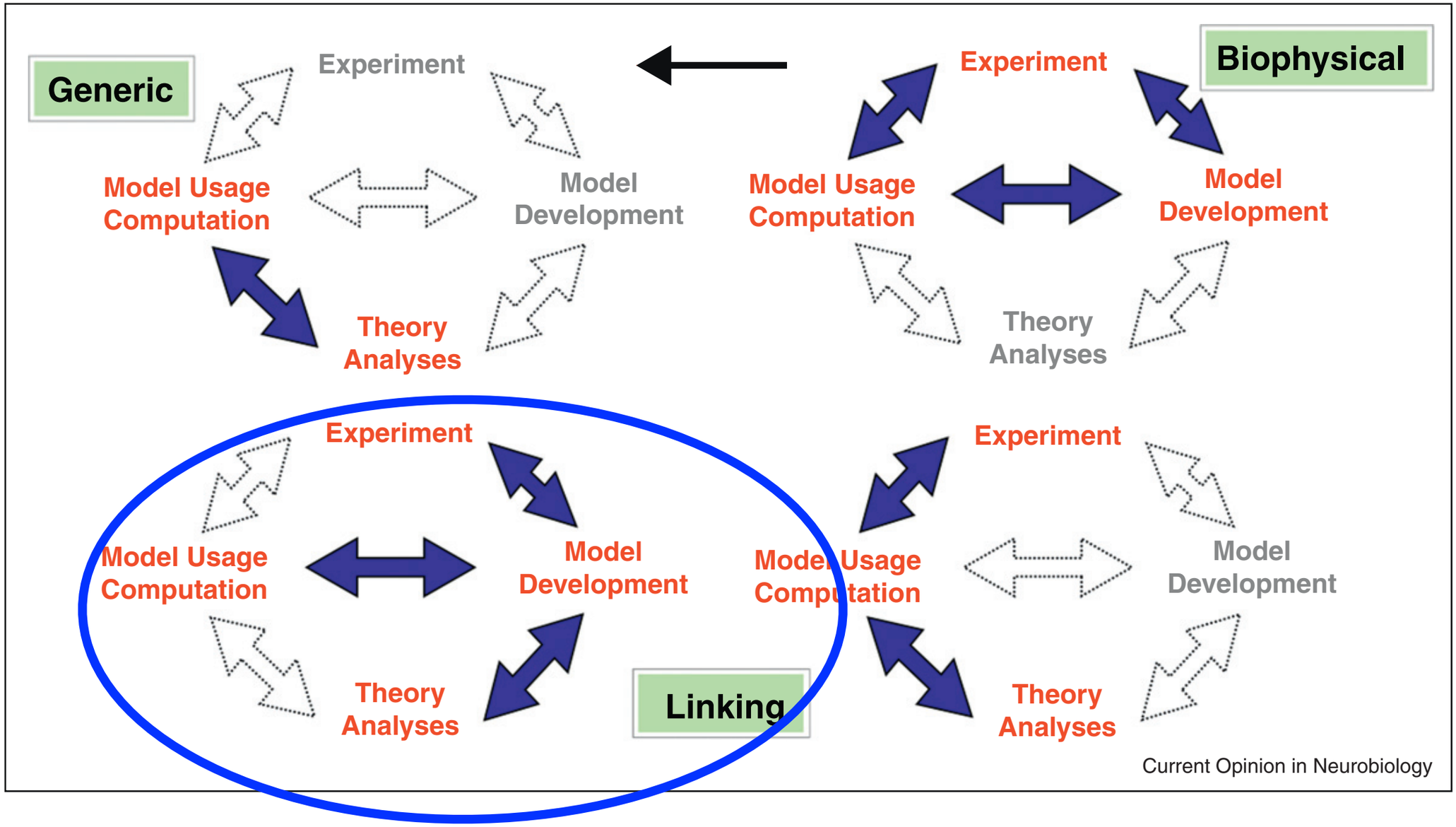
$$\frac{dh}{dt} = \phi(\alpha_h(1 - h) - \beta_h h) \tag{2.2}$$

where $\alpha_h(V) = 0.07\ \exp(-(V + 58)/20)$ and $\beta_h(V) = 1/(\exp(-0.1(V + 28)) + 1)$. $g_{\mathrm{Na}} = 35\ \mathrm{mS/cm}^2$; $E_{\mathrm{Na}} = 55$ mV, $\phi = 5$.

The delayed rectifier $I_{\mathrm{K}} = g_{\mathrm{K}} n^4\ (V - E_{\mathrm{K}})$, where the activation variable n obeys the following equation:

$$\frac{dn}{dt} = \phi(\alpha_n(1 - n) - \beta_n n) \tag{2.3}$$

with $\alpha_n(V) = -0.01(V + 34)/(\exp(-0.1(V + 34)) - 1)$ and $\beta_n(V) = 0.125\ \exp(-(V + 44)/80)$; $g_{\mathrm{K}} = 9\ \mathrm{mS/cm}^2$, and $E_{\mathrm{K}} = -90$ mV.



Current Opinion in Neurobiology

J Comput Neurosci
DOI 10.1007/s10827-011-0372-6

Network bursting using experimentally constrained single compartment CA3 hippocampal neuron models with adaptation

Muhammad Dur-e-Ahmad · Wilten Nicola · Sue Ann Campbell · Frances K. Skinner

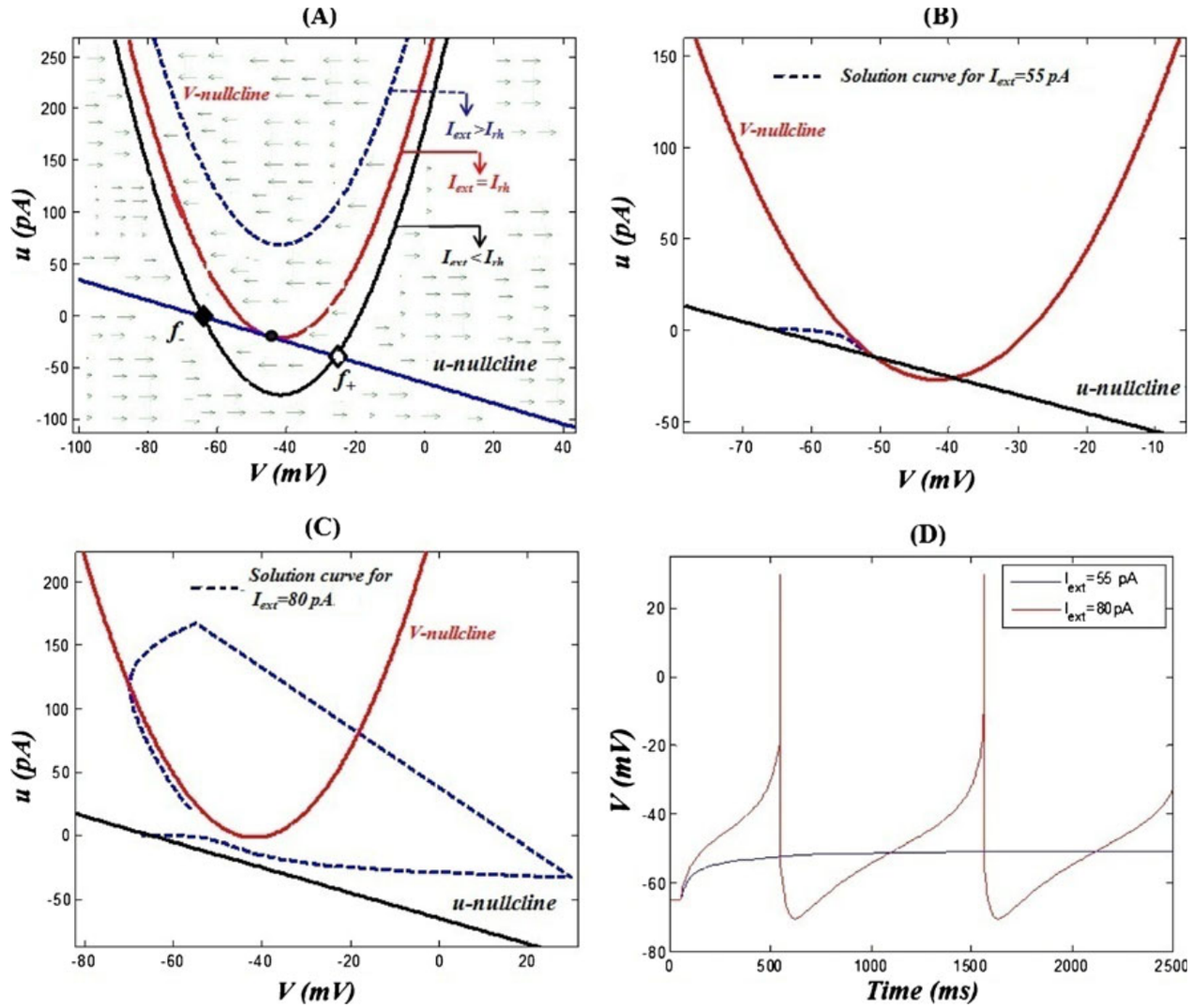
While $V < v_{\text{peak}}$:

$$C\dot{V} = k(V - v_r)(V - v_t) - u + I_{\text{ext}}$$

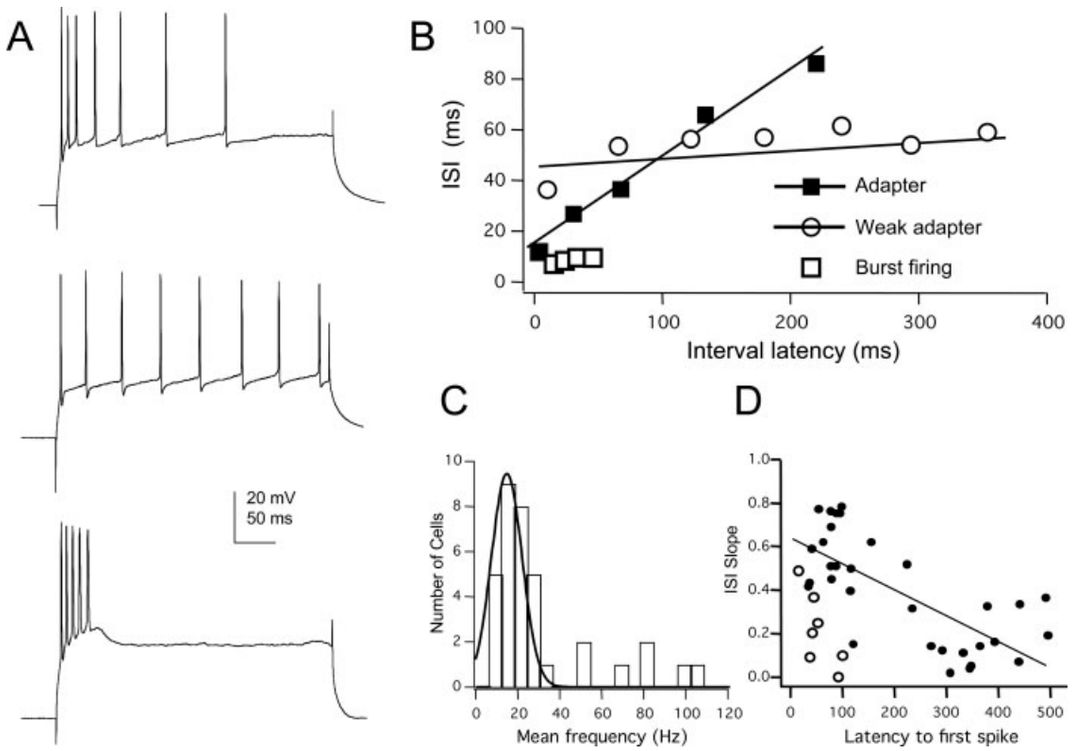
$$\dot{u} = a[b\,(V - v_r) - u].$$

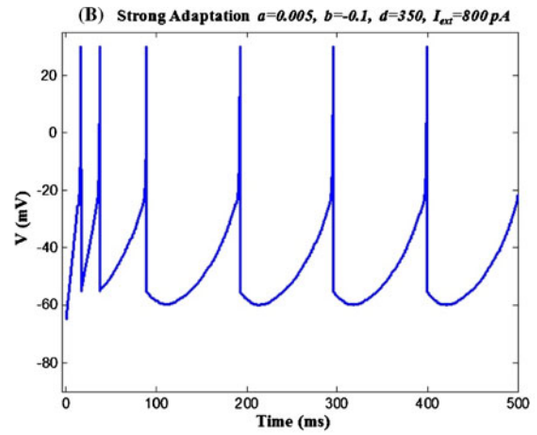
When V crosses v_{peak} from below:

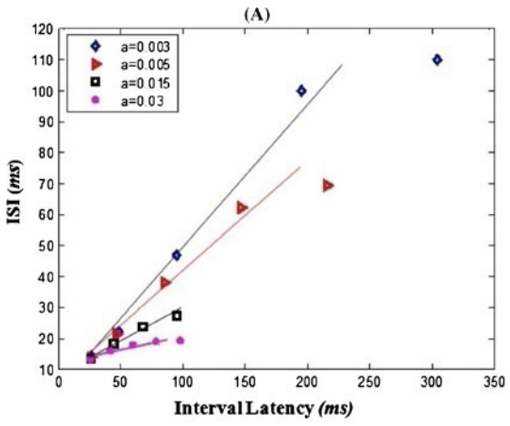
$$V \to c$$
$$u \to u + d$$

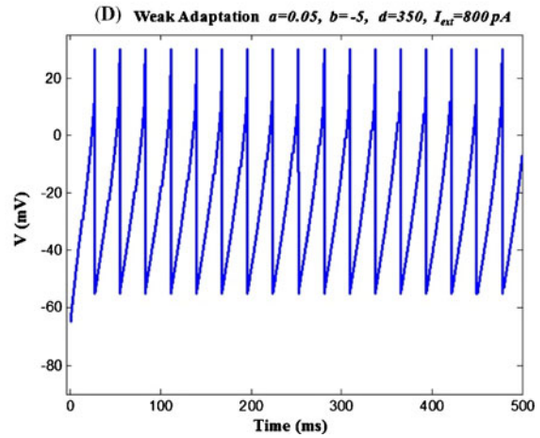


Hemond et al. 2008









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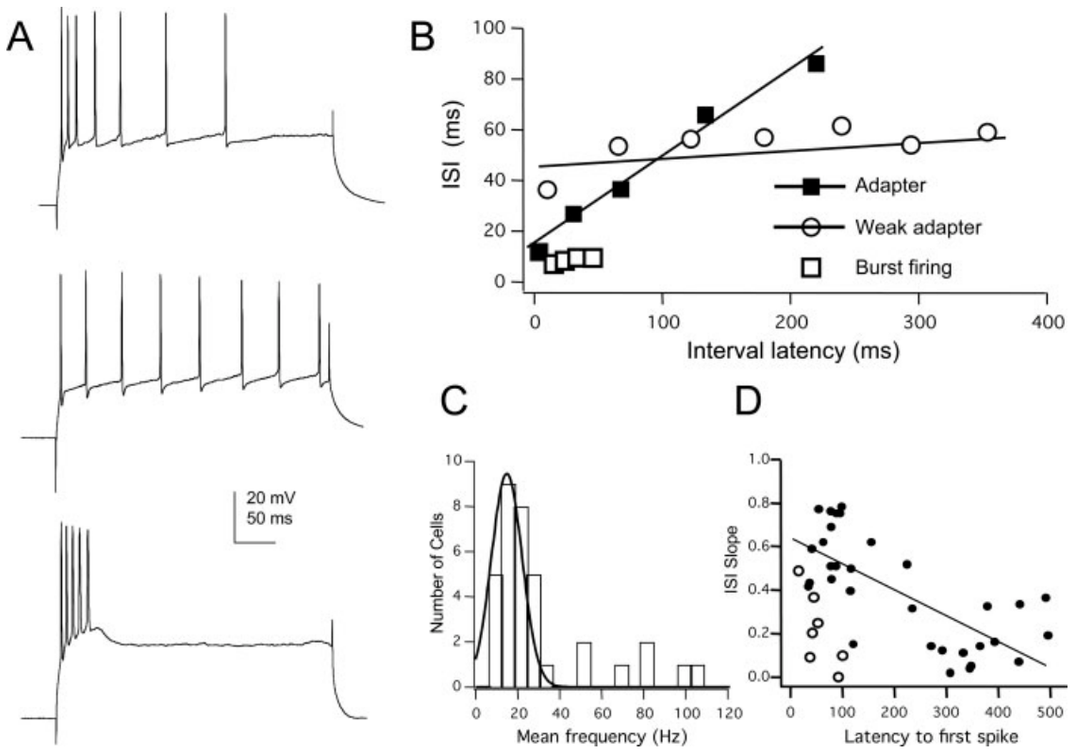
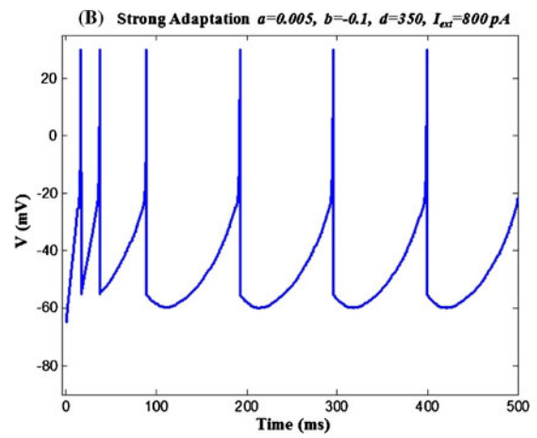
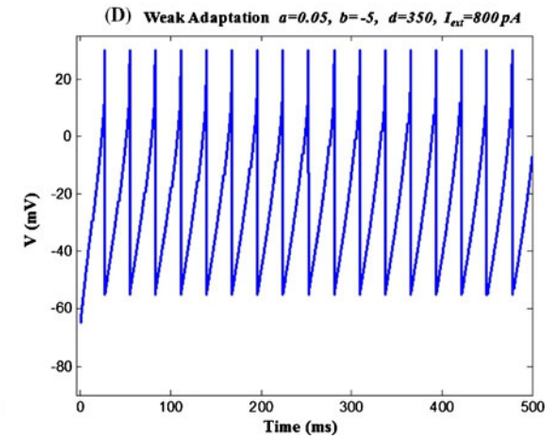
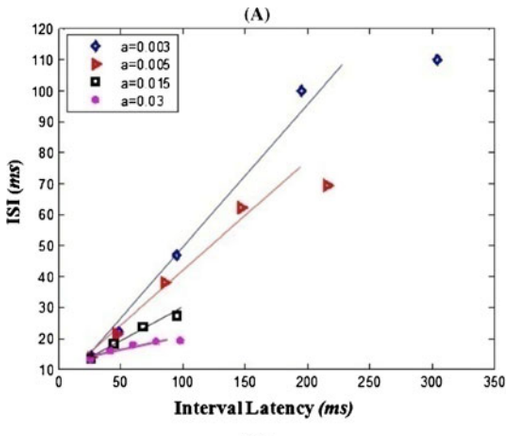
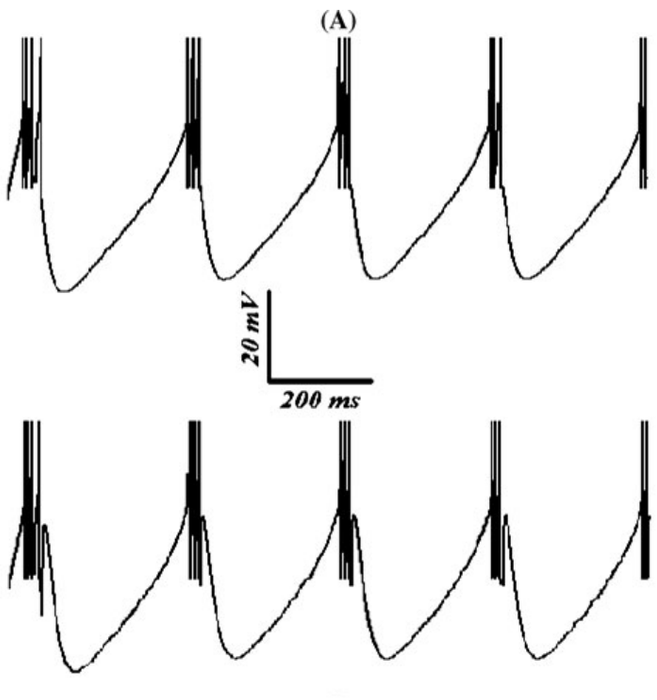


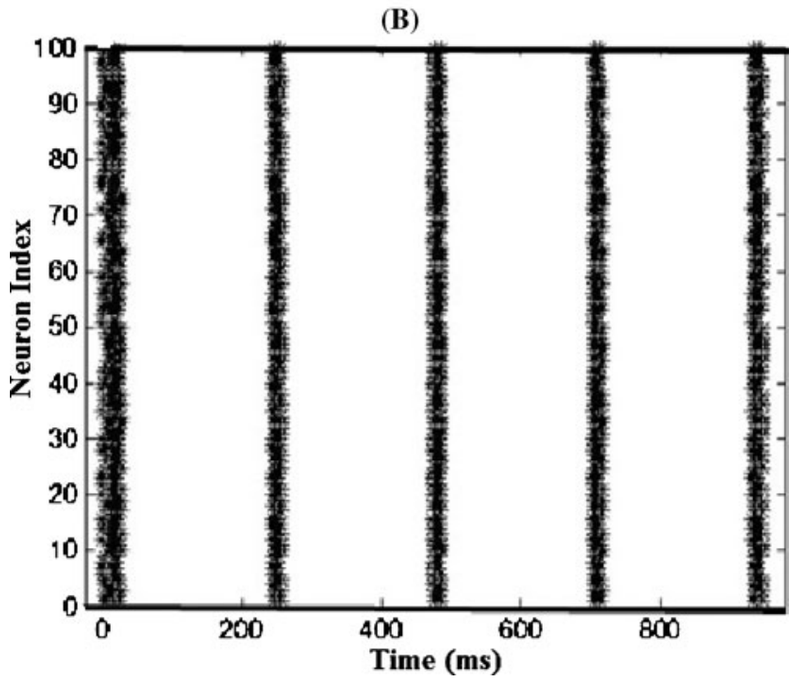


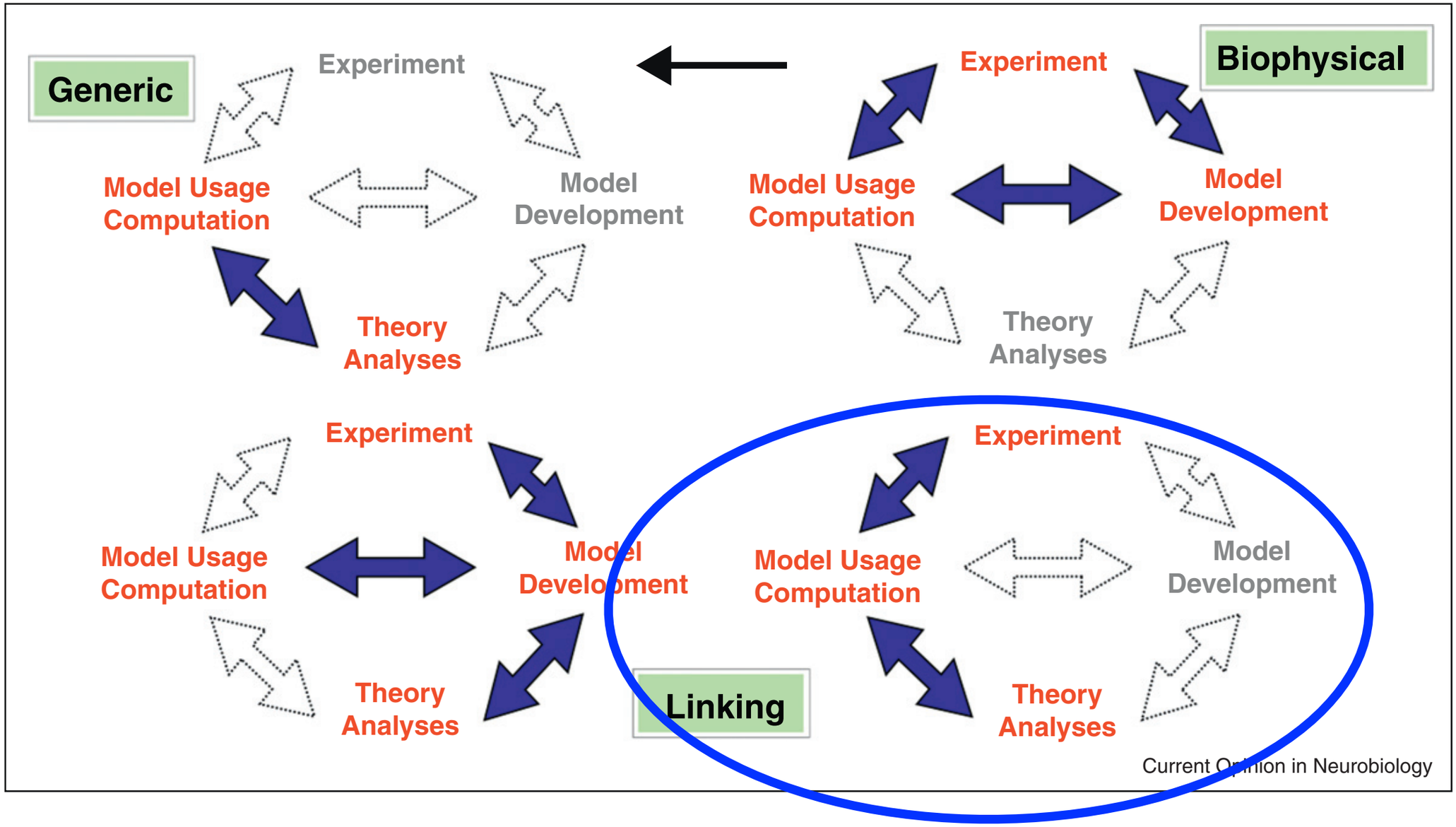




Dur-e-Ahmad et al. 2011







Current Opinion in Neurobiology

Linking Example - method of dynamic clamp

Cellular/Molecular

Cell Type-Specific Control of Neuronal Responsiveness by Gamma-Band Oscillatory Inhibition

Stephani Otte,[1,2]* Andrea Hasenstaub,[1]* and Edward M. Callaway[1]

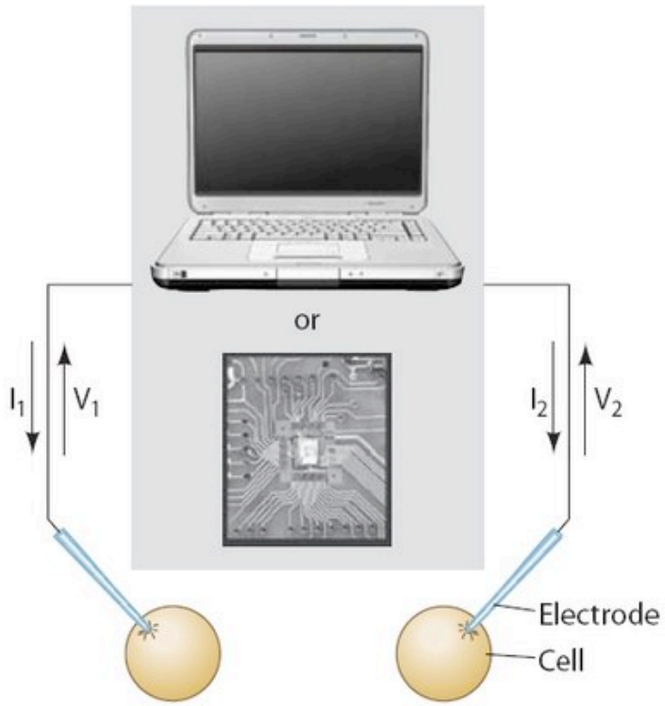
[1]Crick–Jacobs Center for Theoretical and Computational Biology, Salk Institute for Biological Studies, La Jolla, California 92037, and [2]Neurosciences Graduate Program, Division of Biological Studies, University of California at San Diego, La Jolla, California 92093

Electrical coupling

$I_1 = g^*(V_2 - V_1)$ $I_2 = g^*(V_1 - V_2)$

Synaptic coupling

$I_1 = g(V_2)^*(V_1 - E)$ $I_2 = g(V_1)^*(V_2 - E)$

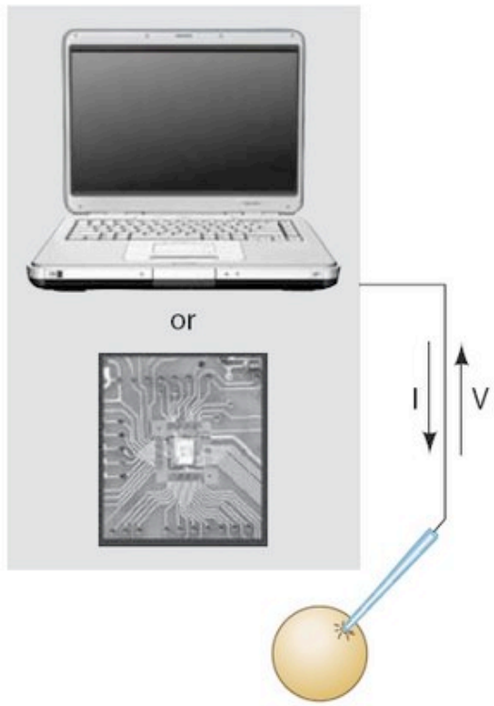


Voltage-dependent conductance

$I = g(V)^*(V - E)$

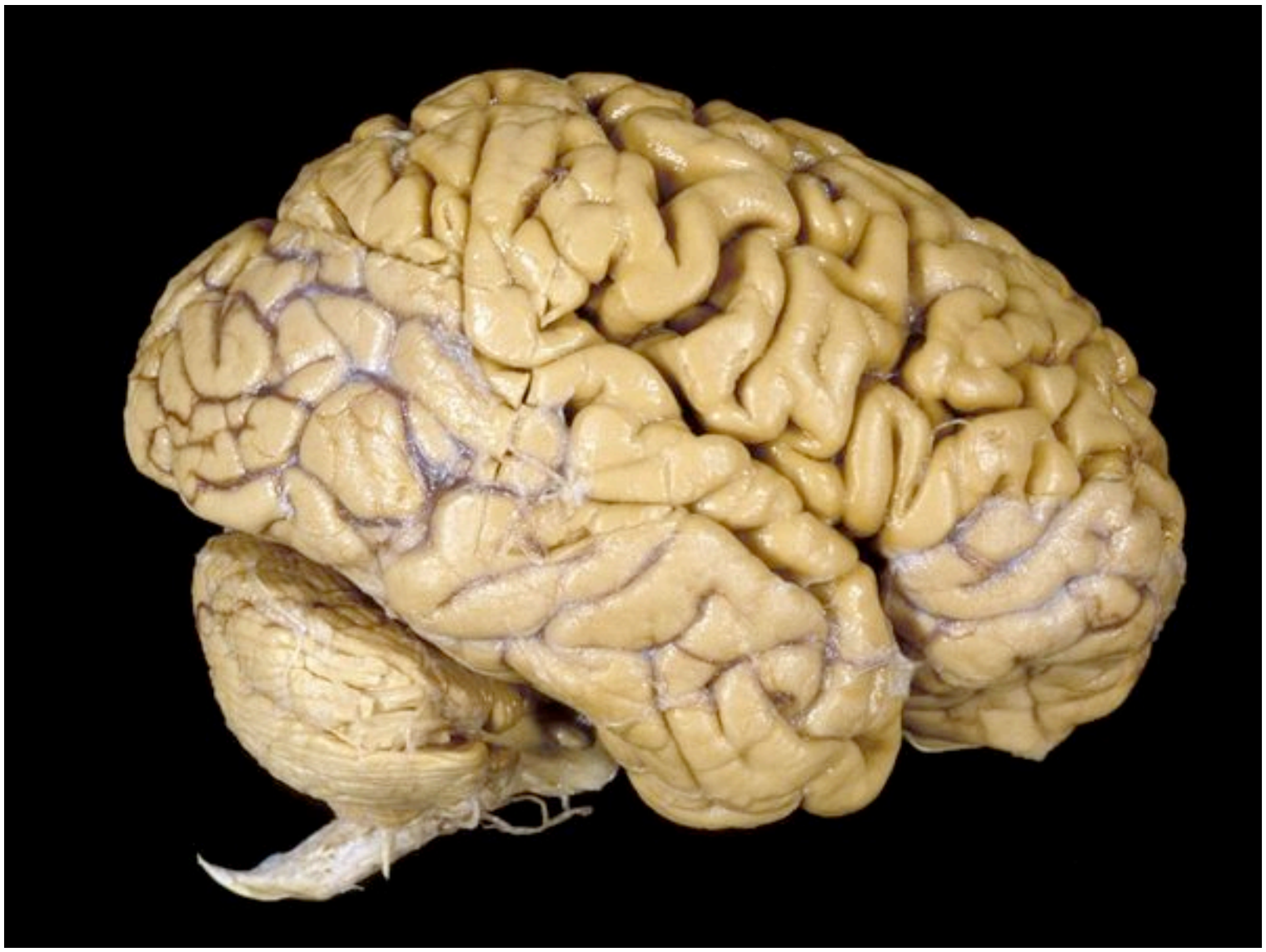
Synapse

$I = g^*(V - E)$



Dynamic Clamp Methodology

from Prinz and Cudmore Scholarpedia 2011



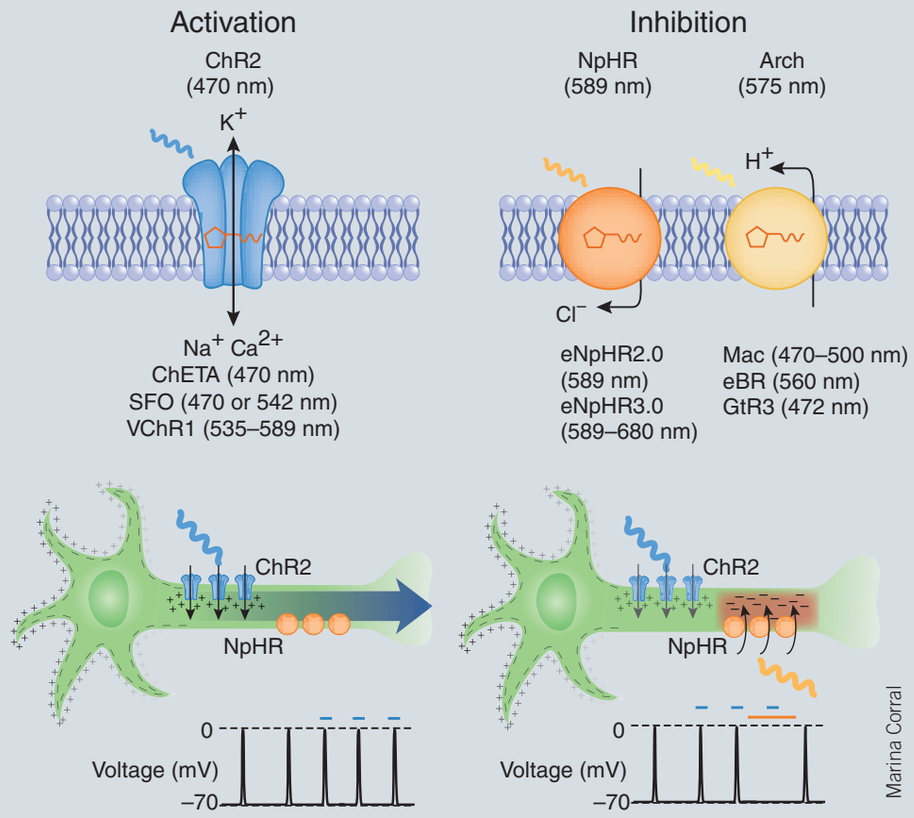
Take Home Messages

- we need to consider a cellular basis (why?)
- context, context, context (under what situations is the disease considered?)
- neurological (experimental) models can be wide-ranging (what motivates the choice?)
- cellular-based (oscillatory) modeling

Concluding Comments

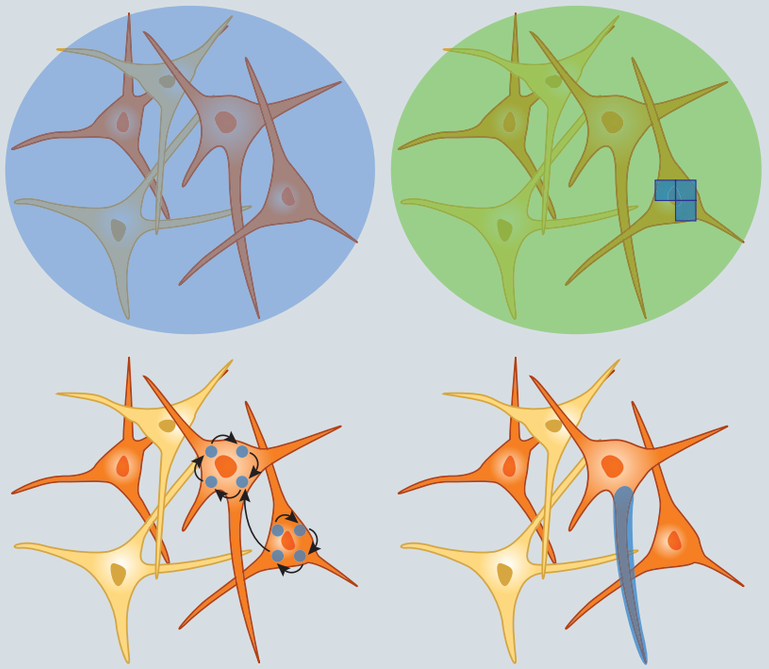
Optogenetics: controlling cell function with light

A brief description of the basic steps required to control cellular function with optogenetics is presented.



Optogenetic tools for modulating membrane volage potential.

First step: light-activated proteins - the toolbox
Second step: delivering the genes
Third step: controlled illumination
Fourth step: reading the outcome



Illumination of target cells using widefield, patterned and scanned light.

"Optogenetic tools have now changed the way neuroscience is conducted owing to a convergence over the past 2 years of the intrinsic tractability of the single-component tools with rapid advances in the associated enabling technologies."

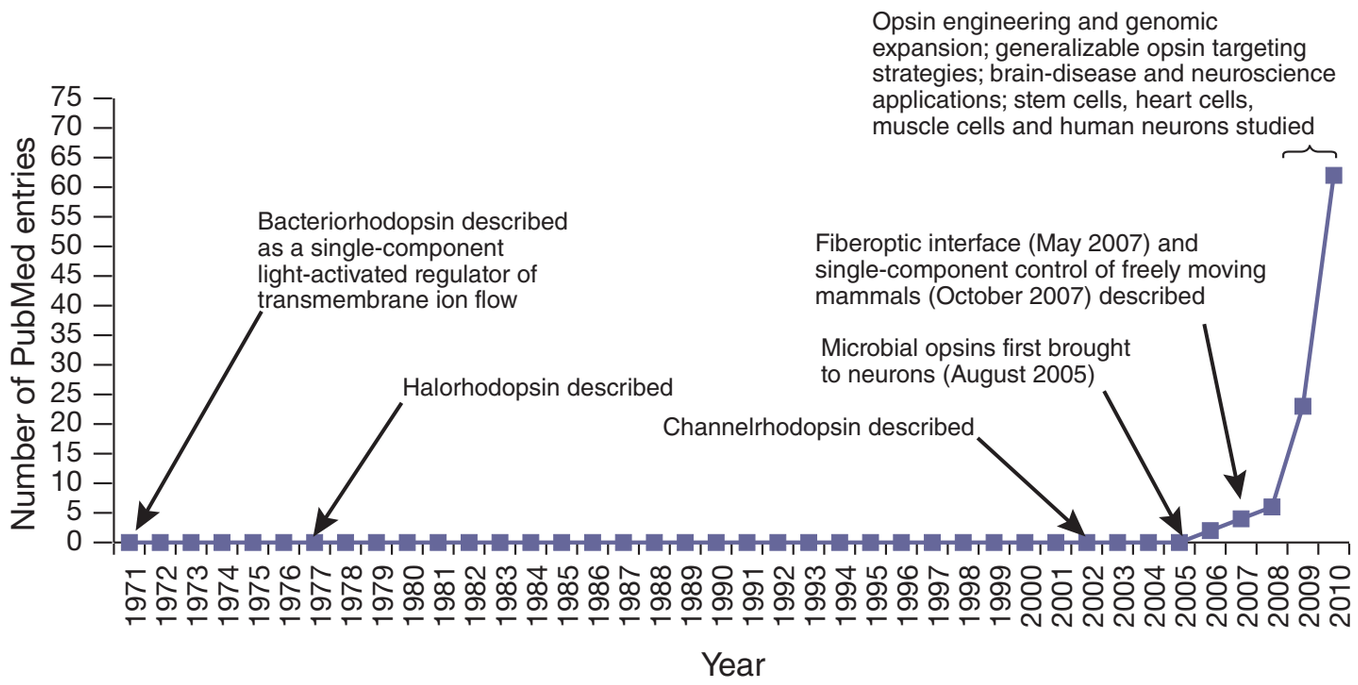


Figure 1 | Graphical illustration of 'optogenetics' emerging in the scientific literature. Demonstration of single-component optogenetic control of neurons with microbial opsins[4] was followed by corresponding optogenetic terminology[2] in October 2006, and corresponding optogenetic control of freely moving mammals using microbial opsins and the fiberoptic neural interface[9,10]. Also marked are identifications of bacteriorhodopsin[3], halorhodopsin[5] and channelrhodopsin[6], all of which were much later (2005–2010) shown to function as fast, single-component optogenetic tools in neurons. Numbers indicate only publications searchable by 'optogenetics' or derivatives thereof on 1 December 2010.

Although it arose from neuroscience, optogenetics addresses a much broader unmet need in the study of biological systems: the need to control defined events in defined cell types at defined times in intact systems. Such analyses are important because cellular events are typically meaningful only in the context of other events occurring in the rest of the tissue, the organism and the environment as a whole.

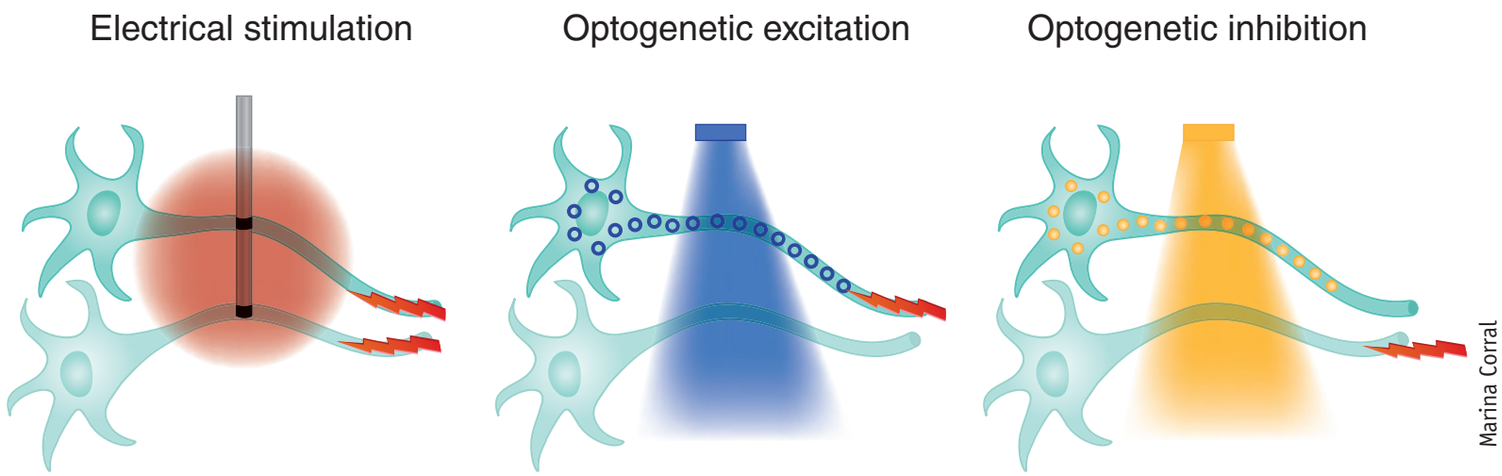


Figure 2 | Principle of optogenetics in neuroscience. Targeted excitation (as with a blue light–activated channelrhodopsin) or inhibition (as with a yellow light–activated halorhodopsin), conferring cellular specificity and even projection specificity not feasible with electrodes while maintaining high temporal (action-potential scale) precision.

NEURAL CIRCUITS

Optogenetic investigation of neural circuits underlying brain disease in animal models

Kay M. Tye[1,2] and Karl Deisseroth[1,3,4,5]

Abstract | Optogenetic tools have provided a new way to establish causal relationships between brain activity and behaviour in health and disease. Although no animal model captures human disease precisely, behaviours that recapitulate disease symptoms may be elicited and modulated by optogenetic methods, including behaviours that are relevant to anxiety, fear, depression, addiction, autism and parkinsonism. The rapid proliferation of optogenetic reagents together with the swift advancement of strategies for implementation has created new opportunities for causal and precise dissection of the circuits underlying brain diseases in animal models.

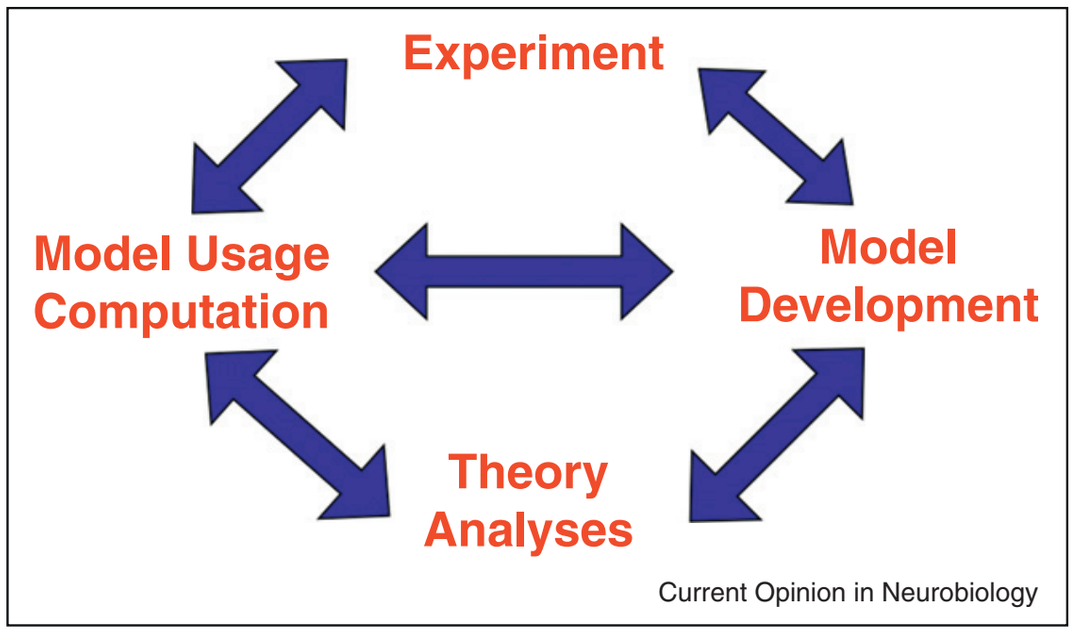
Physiol Rev 90: 1195–1268, 2010;
doi:10.1152/physrev.00035.2008.

Neurophysiological and Computational Principles of Cortical Rhythms in Cognition

XIAO-JING WANG

Department of Neurobiology and Kavli Institute of Neuroscience, Yale University School of Medicine, New Haven, Connecticut

Wang X-J. Neurophysiological and Computational Principles of Cortical Rhythms in Cognition. *Physiol Rev* 90: 1195–1268, 2010; doi:10.1152/physrev.00035.2008.—Synchronous rhythms represent a core mechanism for sculpting temporal coordination of neural activity in the brain-wide network. This review focuses on oscillations in the cerebral cortex that occur during cognition, in alert behaving conditions. Over the last two decades, experimental and modeling work has made great strides in elucidating the detailed cellular and circuit basis of these rhythms, particularly gamma and theta rhythms. The underlying physiological mechanisms are diverse (ranging from resonance and pacemaker properties of single cells to multiple scenarios for population synchronization and wave propagation), but also exhibit unifying principles. A major conceptual advance was the realization that synaptic inhibition plays a fundamental role in rhythmogenesis, either in an interneuronal network or in a reciprocal excitatory-inhibitory loop. Computational functions of synchronous oscillations in cognition are still a matter of debate among systems neuroscientists, in part because the notion of regular oscillation seems to contradict the common observation that spiking discharges of individual neurons in the cortex are highly stochastic and far from being clocklike. However, recent findings have led to a framework that goes beyond the conventional theory of coupled oscillators and reconciles the apparent dichotomy between irregular single neuron activity and field potential oscillations. From this perspective, a plethora of studies will be reviewed on the involvement of long-distance neuronal coherence in cognitive functions such as multisensory integration, working memory, and selective attention. Finally, implications of abnormal neural synchronization are discussed as they relate to mental disorders like schizophrenia and autism.



Cellular-based Modeling Features.

Physiol Rev 90: 1195–1268, 2010;
doi:10.1152/physrev.00035.2008.

Neurophysiological and Computational Principles of Cortical Rhythms in Cognition

XIAO-JING WANG

Department of Neurobiology and Kavli Institute of Neuroscience, Yale University School of Medicine, New Haven, Connecticut

"Remarkable progress has been made over the last two decades in our understanding of the physiological basis of synchronous oscillations such as gamma and theta rhythms, which occur in the cerebral cortex of awake behaving mammals. We have learned that there is a wide diversity of cellular and circuit mechanisms underlying the generation of such rhythms; at the same time some unifying themes and general principles have begun to emerge."

NEXT - Some In Depth Examples

NEXT - Some In Depth Examples

THEN

onward to...

Workshops

"Towards mathematical modelling of neurological disease from cellular perspectives"

THE END
(is it ever?)