Fields pre-CNS workshop and CNS 2007 in Toronto

- www.cnsorg.org
- Computational Neuroscience meeting
  - July 8th -12th
- http://www.fields.utoronto.ca/programs/scientific/07-08/neuroscience/
- Workshop on Perspectives for Future Directions in Computational and Mathematical Neuroscience
  - July 7th

‘Designing’ and ‘discovering’ cellular-based mechanisms underlying network dynamics

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Toronto Western Research Institute

University Health Network and

University of Toronto

March 30, 2007

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Jenni Chung
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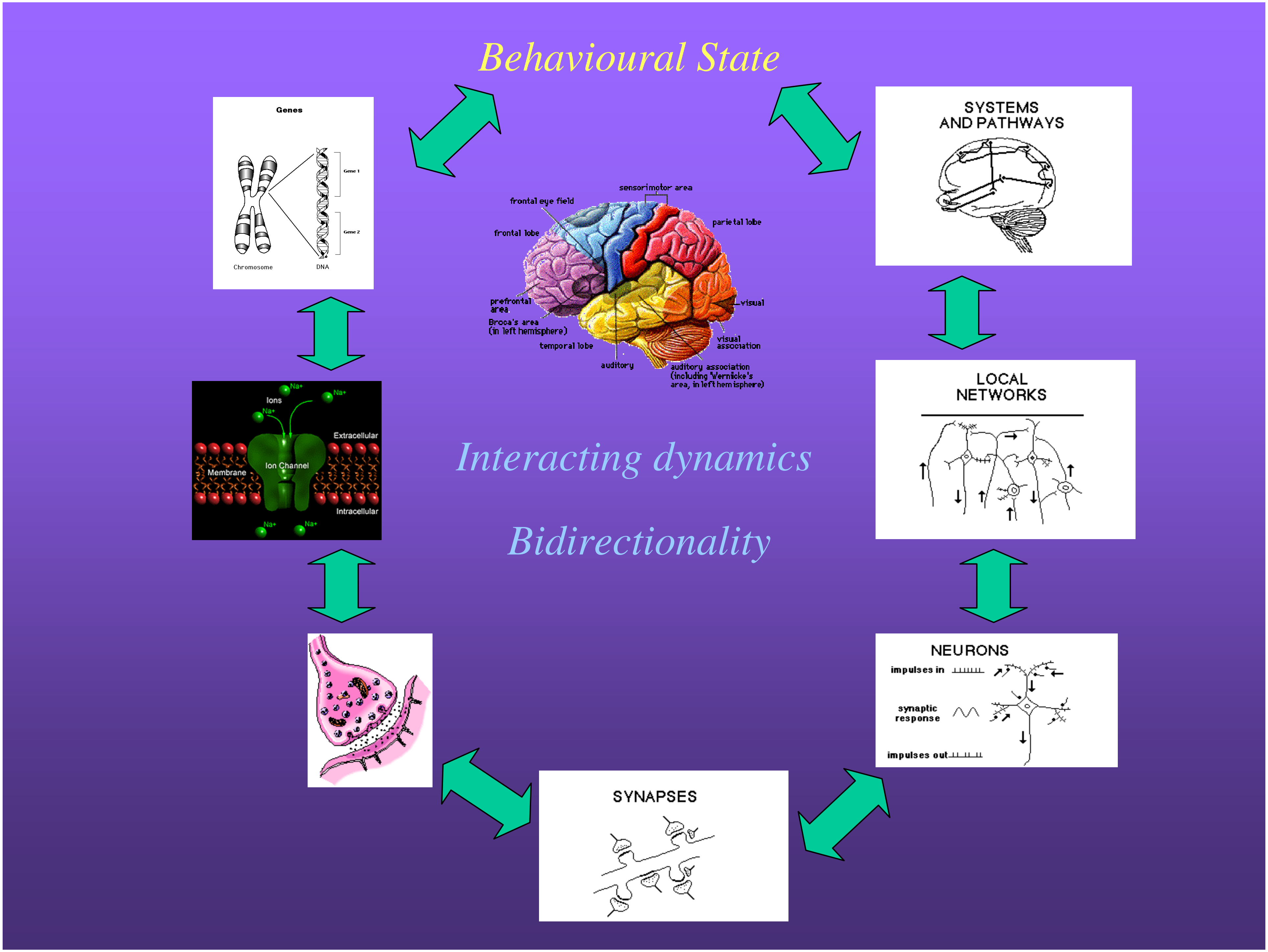
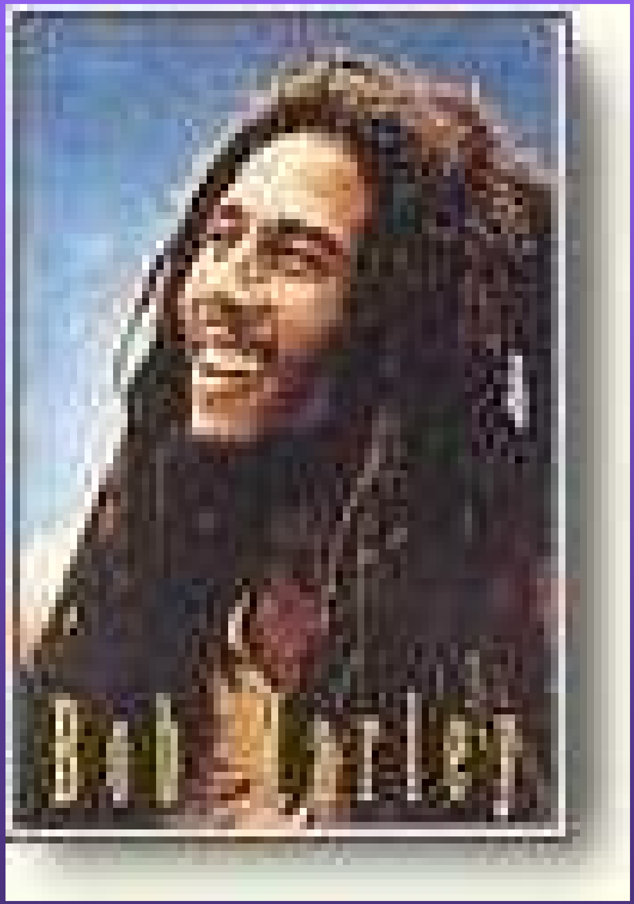


Behavioural State
Genes
Gene 1
Gene 2
Chromosome
DNA
sensorimotor area
frontal eye field
parietal lobe
frontal lobe
prefrontal area
visual
Broca's area (in left hemisphere)
temporal lobe
visual association
auditory
auditory association (including Wernicke's area, in left hemisphere)
SYSTEMS AND PATHWAYS
Ions
Na+
Extracellular
Membrane
Ion Channel
Intracellular
LOCAL NETWORKS
Interacting dynamics
Bidirectionality
NEURONS
impulses in
synaptic response
impulses out
SYNAPSES

From Deborah M. Gordon, Nature 8 March 2007

- *"A better route to understanding the dynamics of apparently self-organizing systems is to focus on the details of specific systems. This will reveal whether there are general laws…."*
- *"When we learn more about the specifics of such systems (such as ant colonies), we will see where analogies between them are useful and where they break down….."*
- *"Life in all its forms is messy, surprising and complicated…."*

“We got rhythm!”



From György Buzsáki's book, "Rhythms of the Brain" OUP 2006

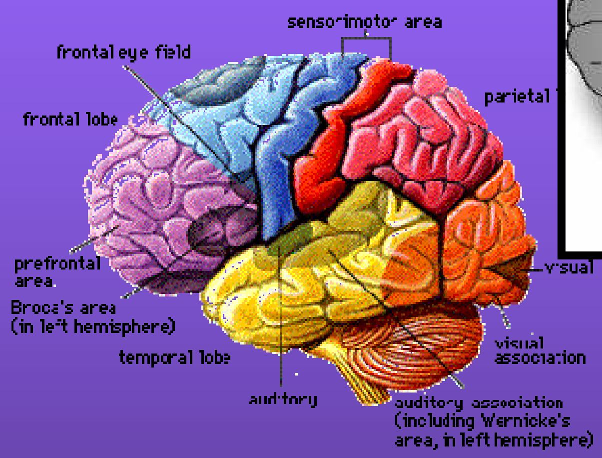
- *"... the most interesting thing we can learn about the brain is how its self-generated internal states, the potential source of cognition, are brought about."*
- *"... the disappointing "rule" of brain oscillators: coupling behavior depends on the details."*

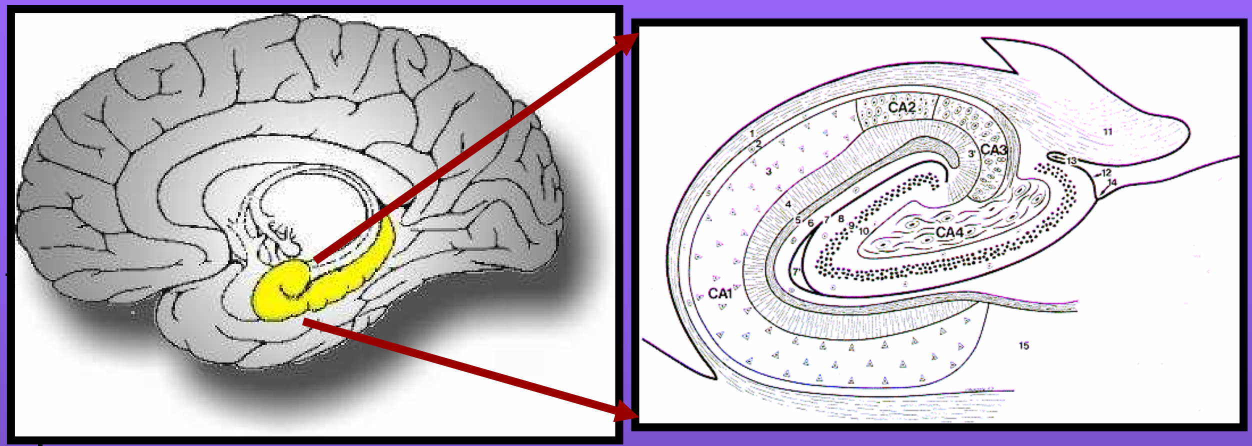
“Neither ignore the details nor be overwhelmed by them!”

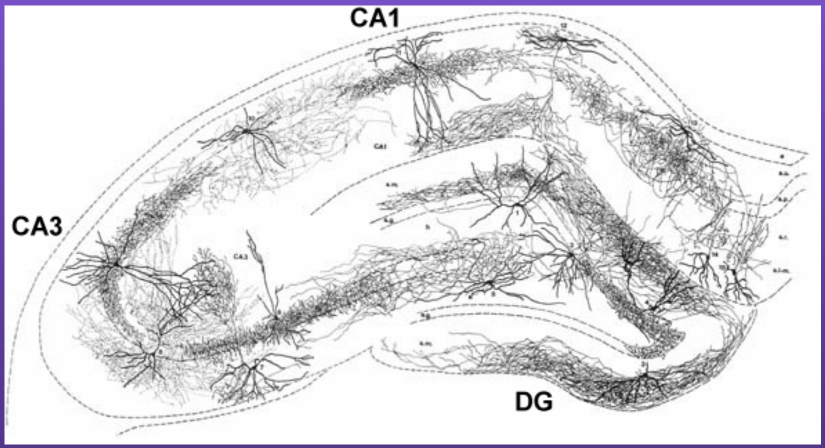
Outline

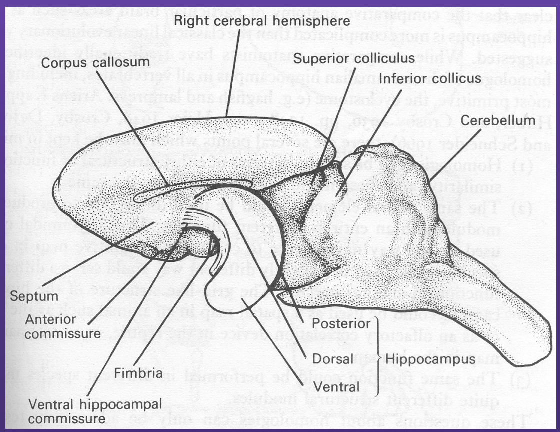
- *Background*
- *‘Design’ and ‘Discover’*
- *Ideas*
- *Future directions*

"Here comes the hippocampal world!" J









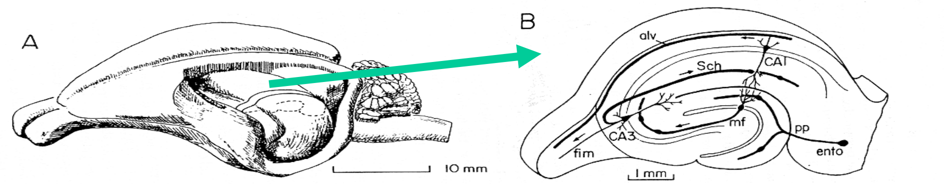
The hippocampal cortex is an intensely studied region of the brain because:

- *It is amenable to experiment, retaining its synaptic circuitry and thus population activities in the slice.*

- *It is associated with memory and learning (i.e., LTP, LTD), epileptic seizures, and neurogenesis.*

- *It exhibits a wide range of population rhythmic activity patterns (<1 to >200 Hz) that are associated with various behavioural states.*

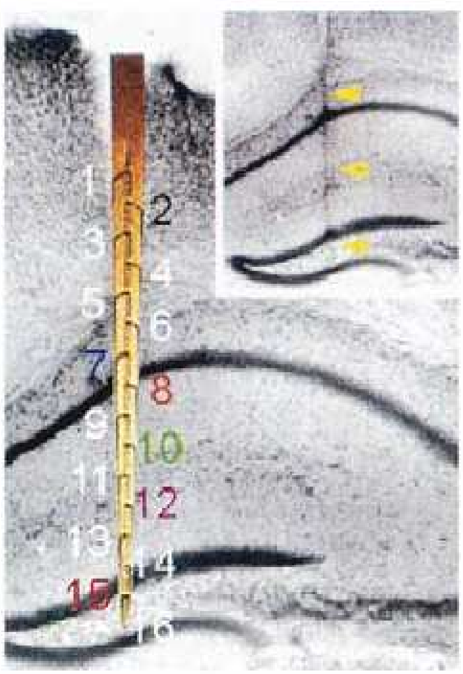
EEG activities of mouse hippocampus

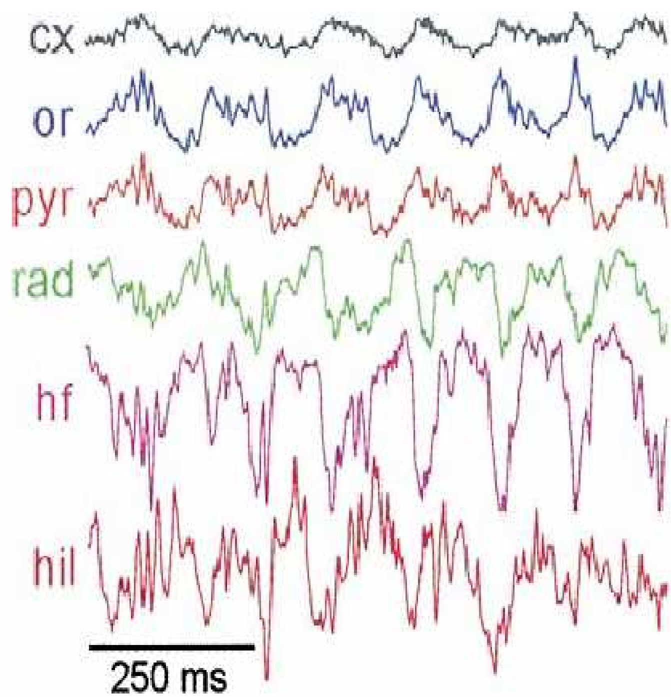


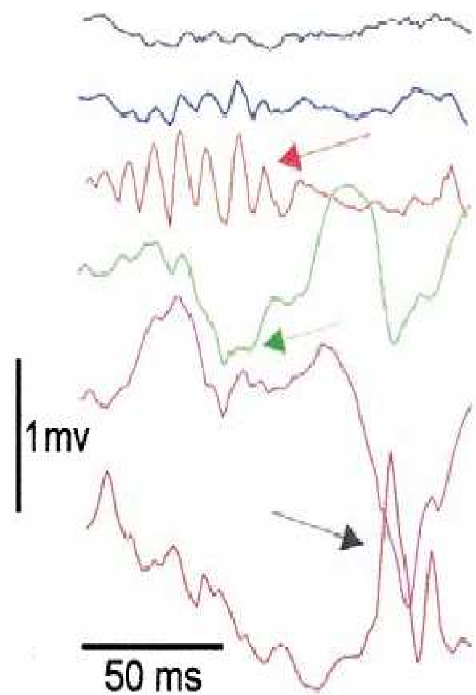
Electrode location

Theta-Gamma

SPW-ripples







S

G. Buzsáki et al. / Neuroscience 116 (2003) 201–211

Interneurons

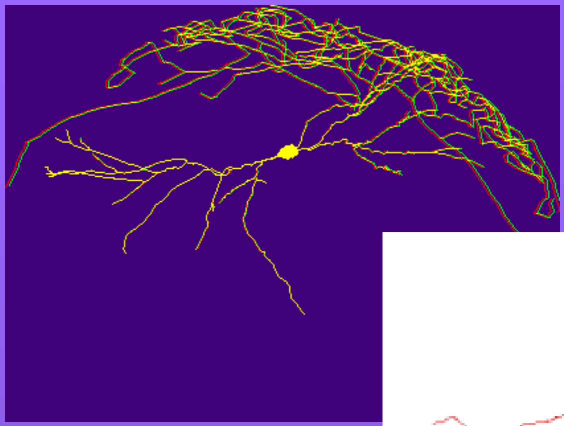
(GABAergic nonprincipal cells or Inhibitory neurons)

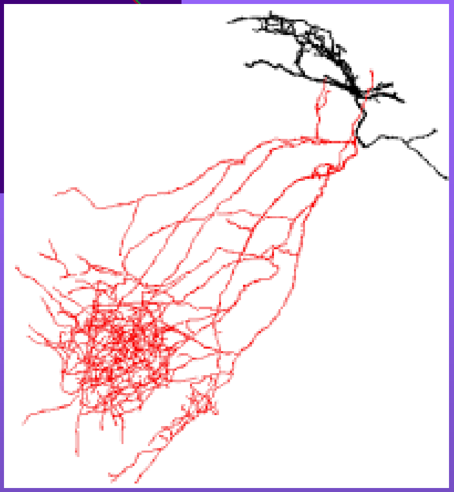
"Interneurons are part of an extensive inhibitory network which play an essential role in molding the synchronous rhythmic output of principal cells."

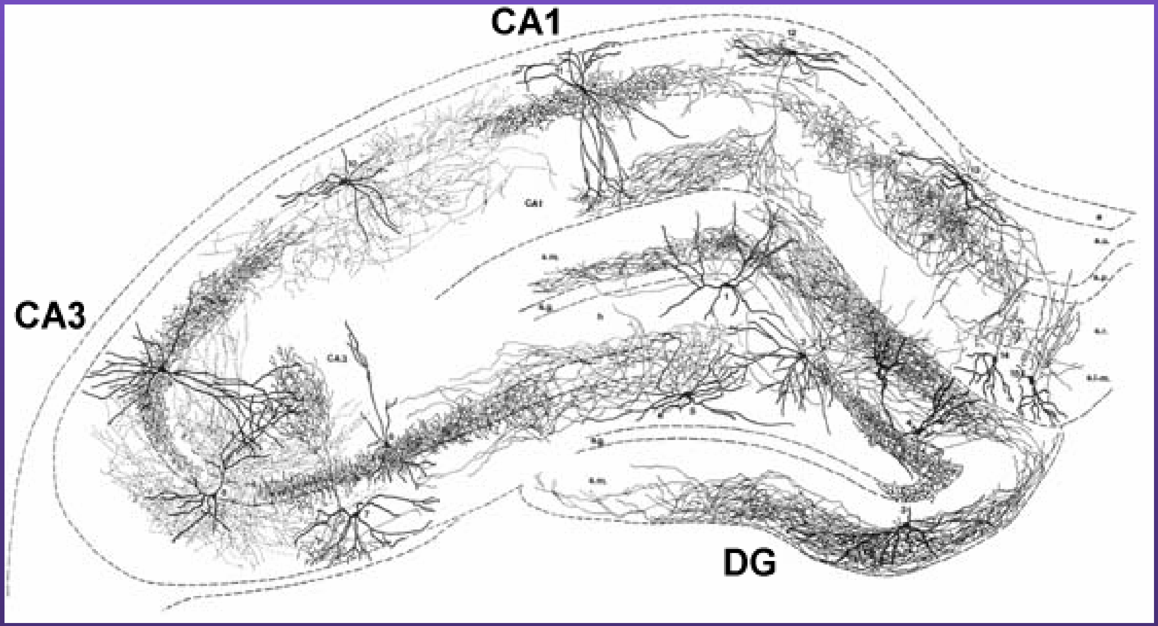
Freund and Buzsaki, Hippocampus 6:347-470, 1996

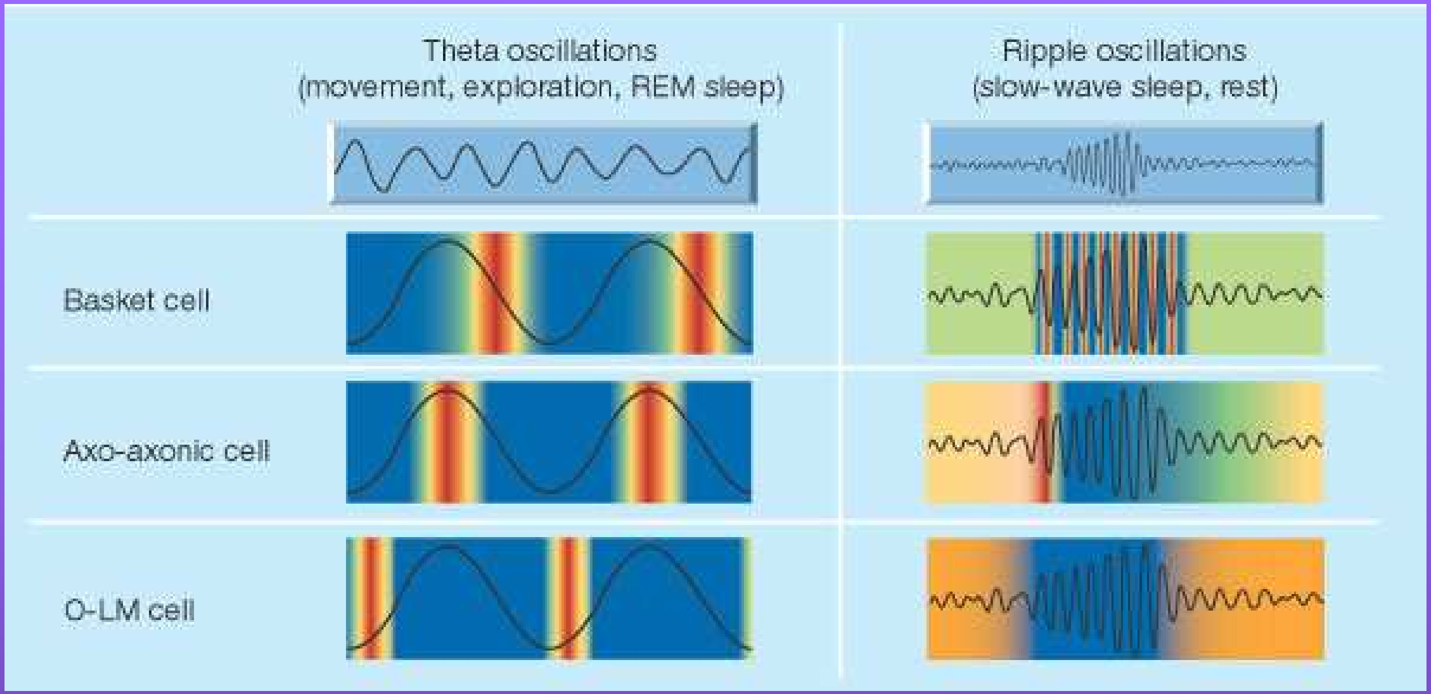
Interneurons represent 10-20% of the neuronal population but may provide the precise temporal structure necessary for ensembles of neurons to perform specific functions.

- Buzsáki and Chrobak, 1995









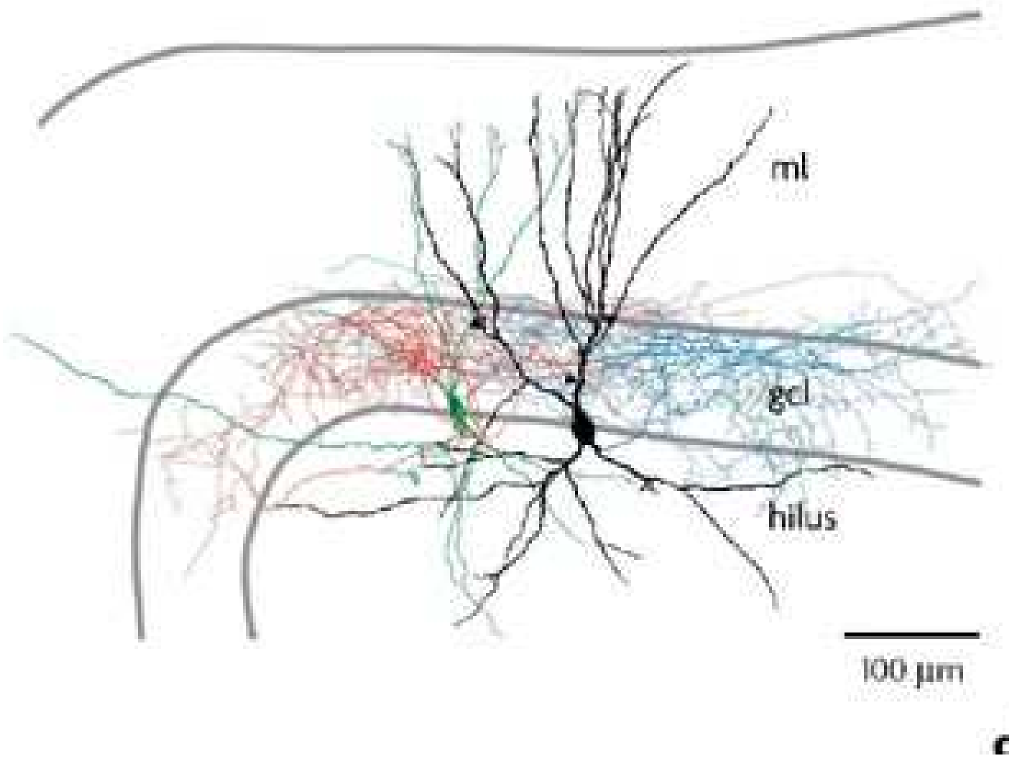
Interneurons and electrical oscillations.

Schematic from E.I. Moser, Nature, 2003,
showing the activity profiles of three types of hippocampal interneurons during two brain states
(based on the findings of Klausberger et al., 2003).

Colours indicate the probability that a given interneuron will fire (maximum red, minimum blue). The variation within each group is small, suggesting that classes of interneurons exert precise control over distinct aspects of hippocampal network dynamics

Mutually inhibitory networks of basket cells, and….

Network models produce coherence at high frequencies

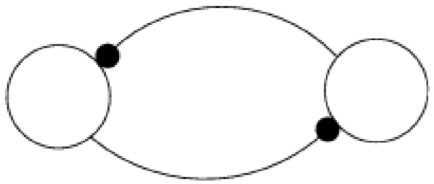


Bartos *et al. Nature Reviews Neuroscience* **8**, 45–56 (January 2007) | doi:10.1038/nrn2044

nature REVIEWS NEUROSCIENCE

…over a decade ago…

Theoretical Insight



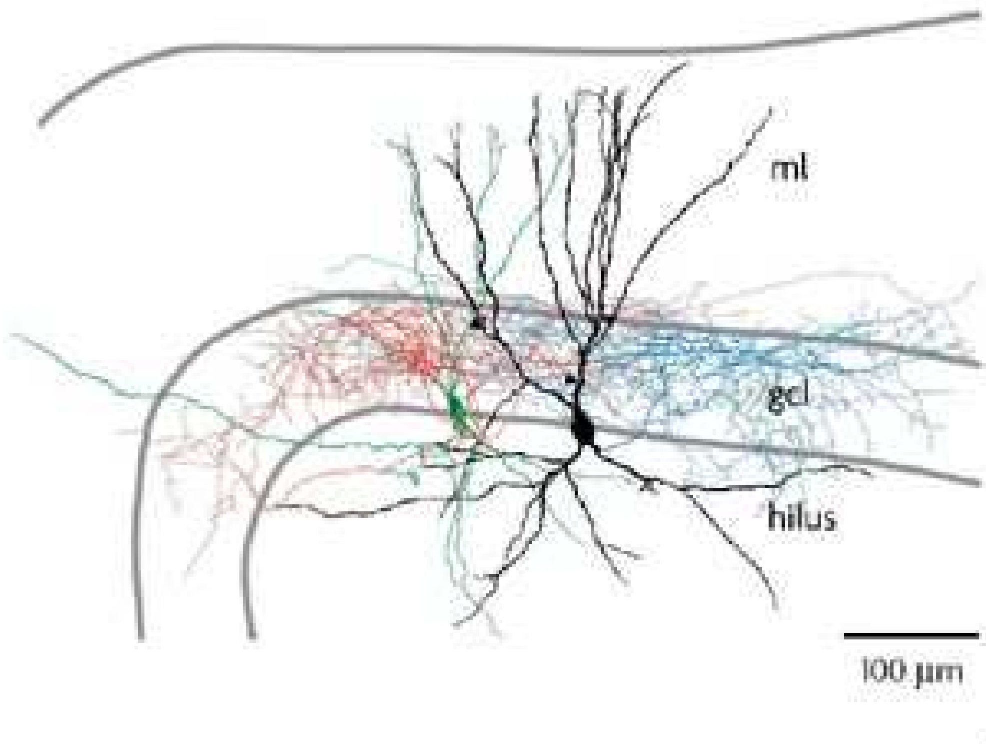
Mutual inhibition can synchronize oscillations if postsynaptic conductance decays sufficiently slowly

Wang & Rinzel, Neural Comput. 4:84-97, 1992
Wang & Rinzel, Neurosci. 53:899-904, 1993

…fast forward to today…

Mutually inhibitory networks of basket cells, and….

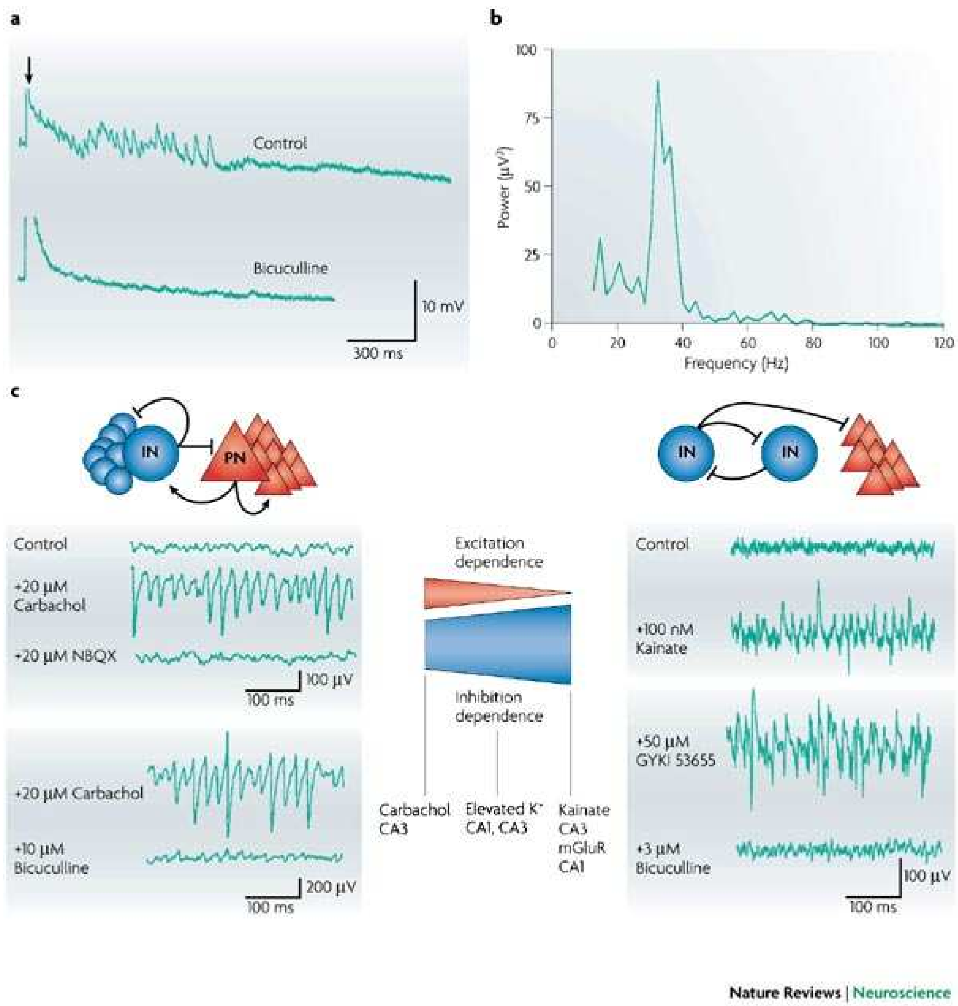
Network models produce coherence at high frequencies



Bartos *et al. Nature Reviews Neuroscience* **8**, 45–56 (January 2007) | doi:10.1038/nrn2044

nature REVIEWS NEUROSCIENCE

Context consideration….



Bartos *et al. Nature Reviews Neuroscience* **8**, 45–56 (January 2007) | doi:10.1038/nrn2044

‘Design’ and ‘Discover’

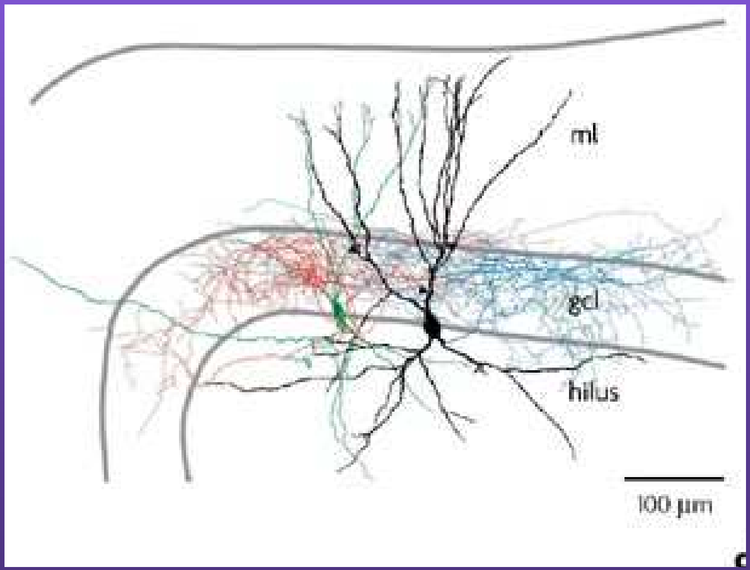
- Design: Invoke some underlying mechanism(s) of how the network output could be produced using smaller networks to allow a cellular perspective to be included.
- Use ideas and insight from experiment and theory.
- Take advantage of mathematical analyses to obtain dynamic understanding.
- Build larger networks using the understanding achieved in the smaller networks and experimental constraints.
- Discover: If resulting network output compares favourably with experimental manipulations, then the invoked mechanisms from design stage could be considered biologically plausible, and used to make further predictions.

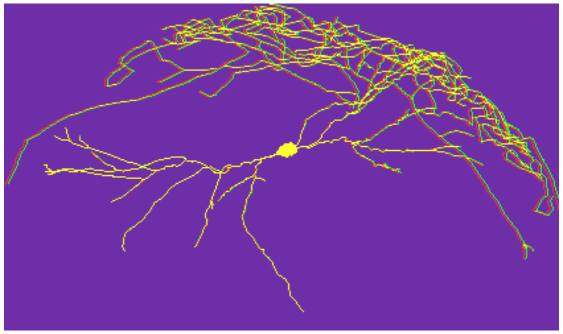
Hence, a designed discovery of the workings of biological networks

(in particular context)

Idea I

- Using heterogeneity to compare single compartment neuronal models

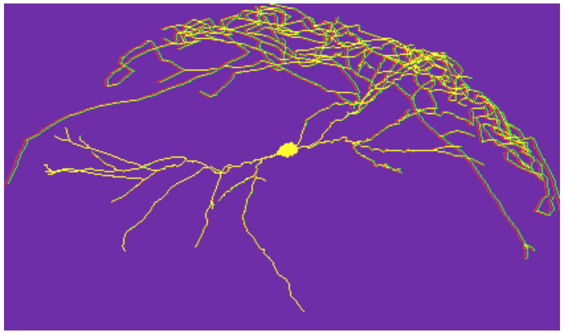




Wang and Buzsáki's (1996) model designed to represent a hippocampal interneuron cell:

$$
\begin{aligned}
C\frac{dV}{dt} &= I_{app} - g_{Na} m_\infty^3 h(V - V_{Na}) - g_K n^4 (V - V_K) \\
&\quad - g_L(V - V_L) \\
\frac{dh}{dt} &= \phi(\alpha_h(V)(1-h) - \beta_h(V)h) \\
\frac{dn}{dt} &= \phi(\alpha_n(V)(1-n) - \beta_n(V)n)
\end{aligned}
$$

$m_\infty = \alpha_m/(\alpha_m + \beta_m)$, where $\alpha_m(V) = -0.1(V+35)/(\exp(-0.1(V+35)) - 1)$, $\beta_m(V) = 4\exp(-(V+60)/18)$. $\alpha_h(V) = 0.07\exp(-(V+58)/20)$, $\beta_h(V) = 1/(\exp(-0.1(V+28))+1)$, $\alpha_n(V) = -0.01\exp(-(V+34)/\exp(-0.1(V+34)) - 1)$, $\beta_n(V) = 0.125\exp(-(V+44)/80)$, $\phi = 5$. Maximal sodium, g_{Na}, potassium, g_K, and leak, g_L, conductances are: 35, 9 and 0.1 mS/cm^2 respectively. Reversal potentials, V_{Na}, V_K, V_L, are 55, -90 and -65 mV respectively, and the capacitance, C, is 1 μF/cm^2.



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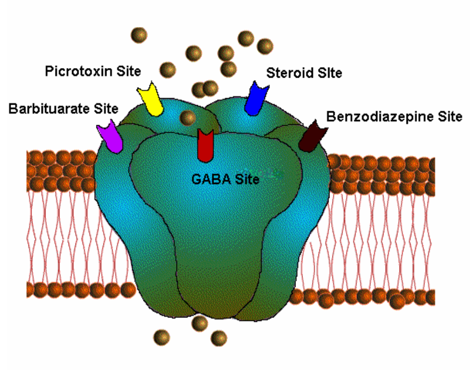
For the two-cell networks, the external drive to cell 1 or 2, respectively, is:

$$\begin{aligned} I_{app,1} &= I_{\mu} - \epsilon \quad \text{or} \\ I_{app,2} &= I_{\mu} + \epsilon \end{aligned}$$

Define the percent heterogeneity, %Het, as:

$$\%\text{Het} = \frac{(I.F.\text{ at } I_{app,2}) - (I.F.\text{ at } I_{app,1})}{I.F.\text{ at } I_{app,2}} \times 100\%$$

where $I.F.$ is the intrinsic frequency of the isolated cell.

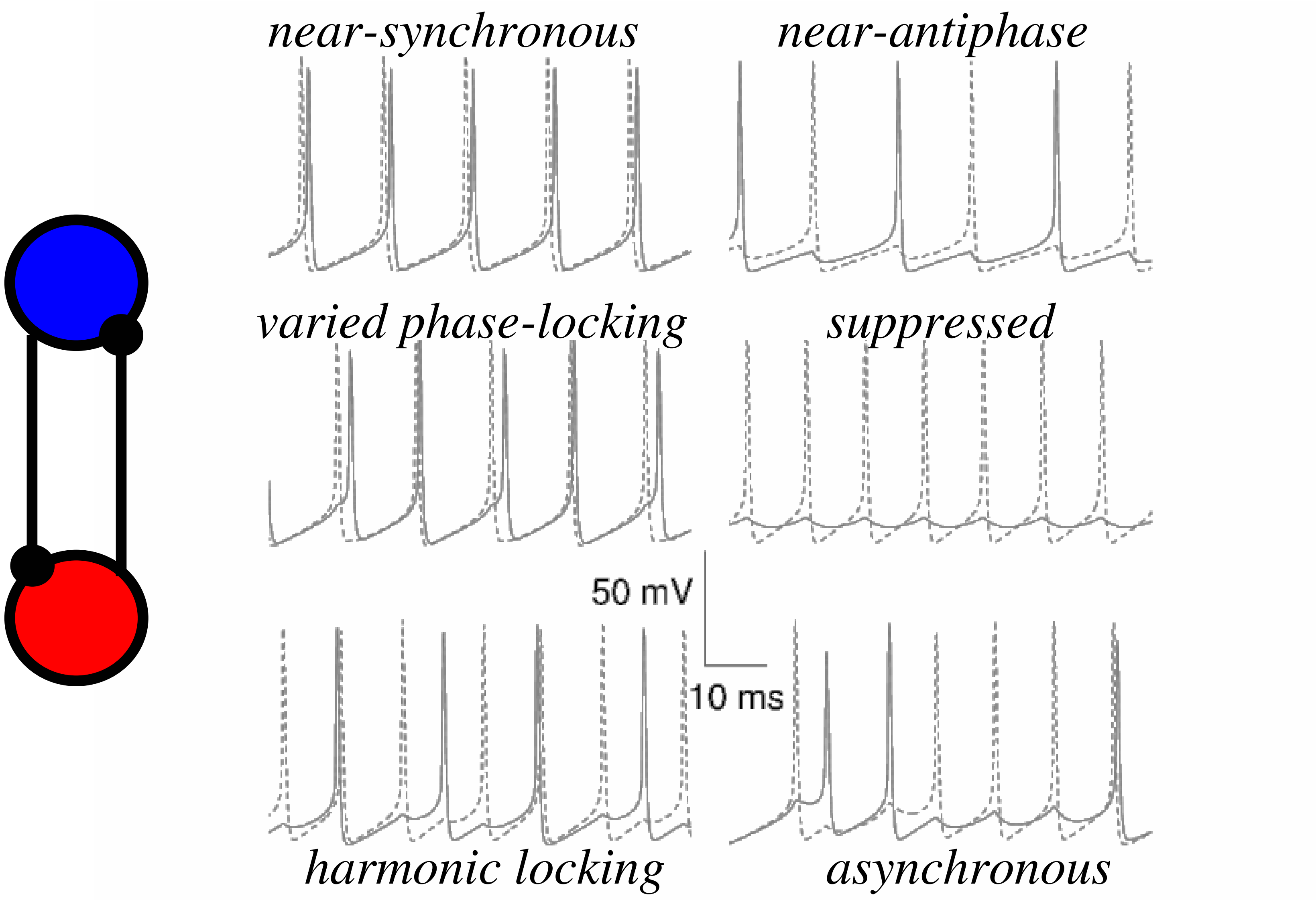


$$I_{syn} = g_{syn} s (V - V_{syn})$$

where

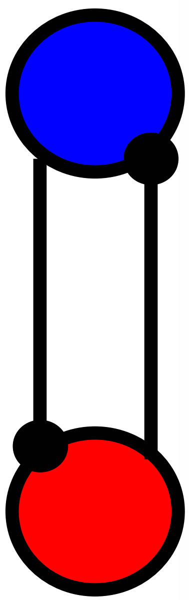
$$\begin{aligned} \frac{ds}{dt} &= \alpha T(V_{pre})(1-s) - \beta s \\ T(V_{pre}) &= \frac{1}{1+\exp(-V_{pre}/2)} \end{aligned}$$

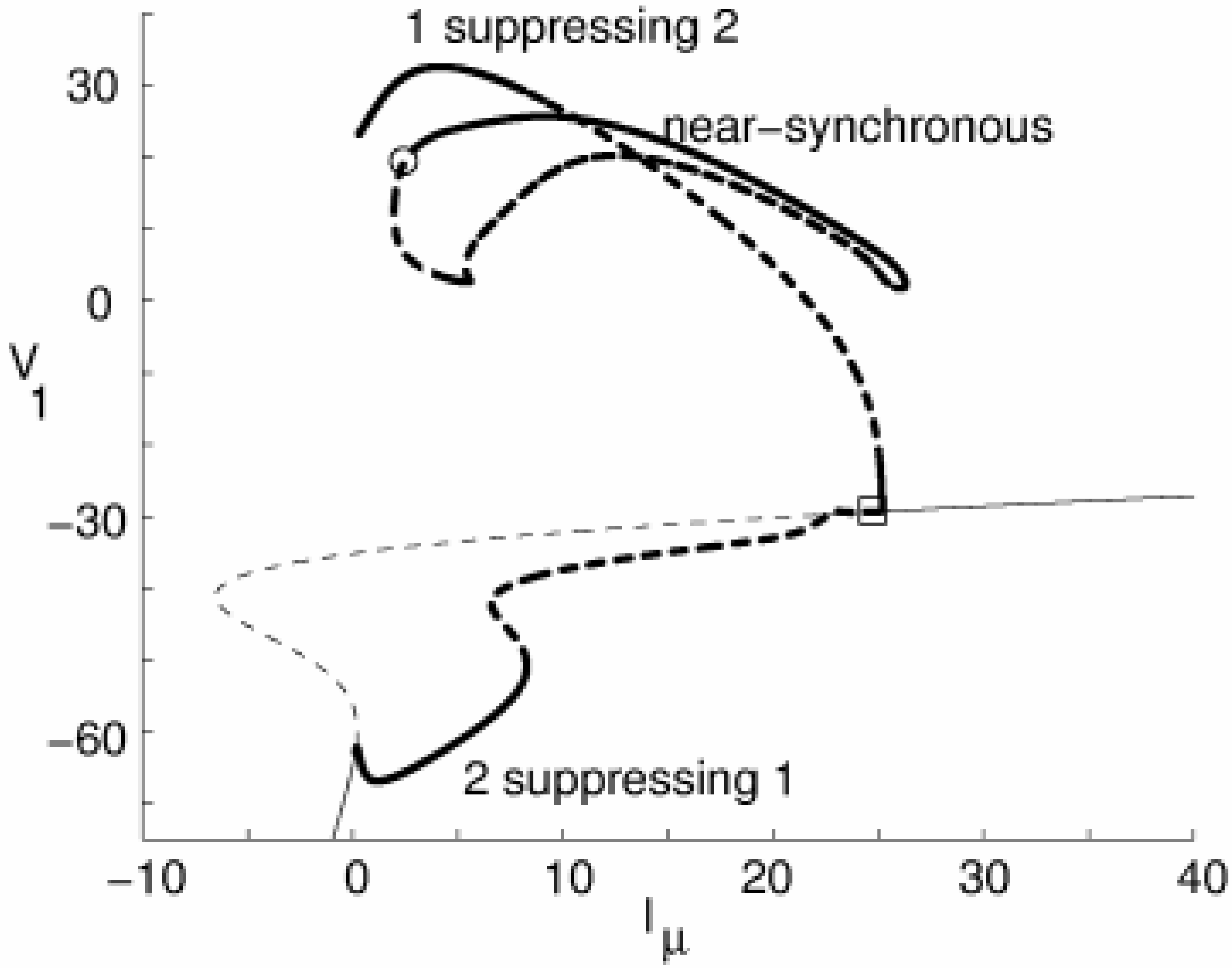
$V_{syn} = -75$ mV, $\alpha = 6.25$ ms^{-1}, β is the rate constant of the synaptic decay, $\tau_{syn} = 1/\beta$.



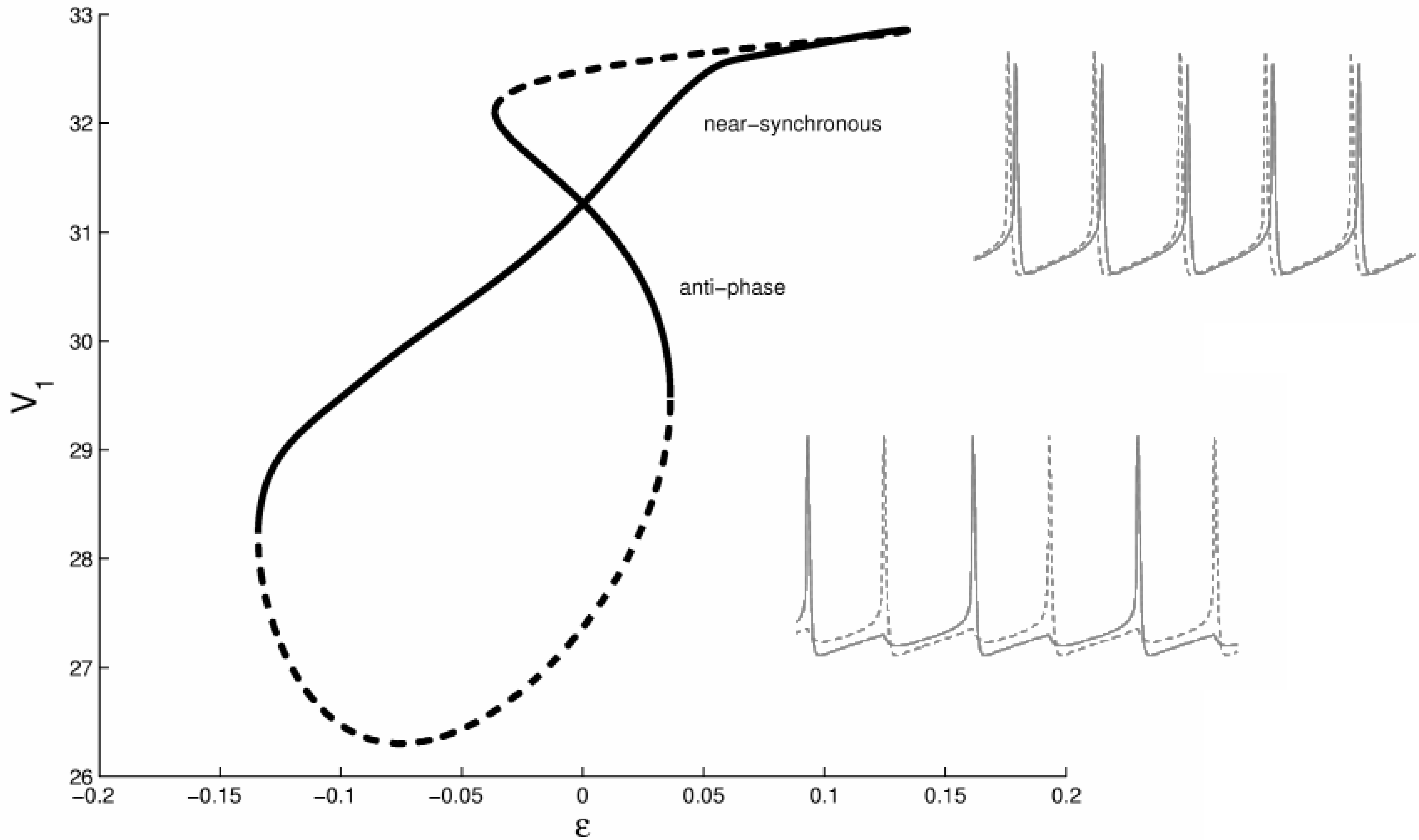
Skinner et al., J. Neurophysiol. 2005

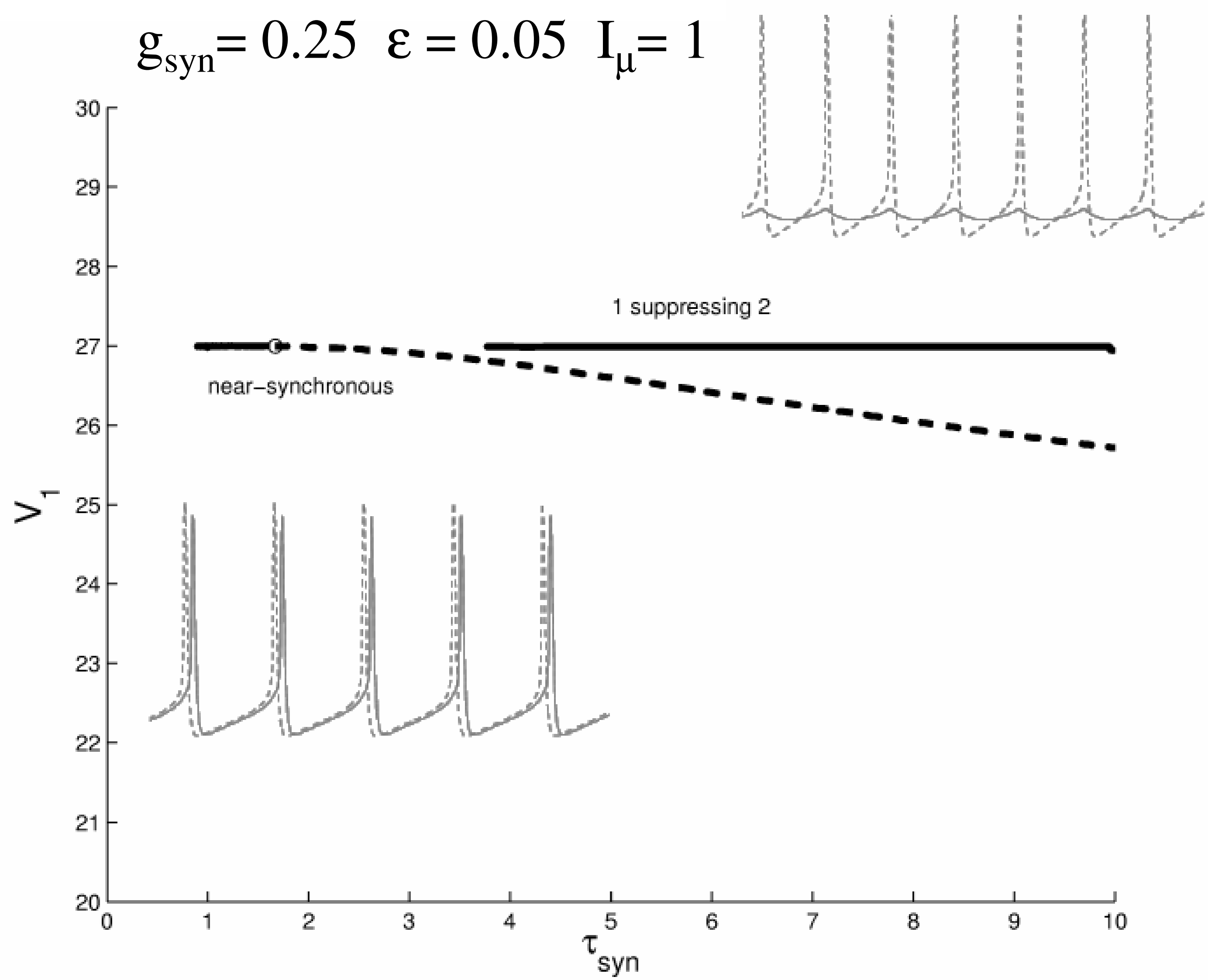
$g_{syn} = 0.5 \quad \varepsilon = 0.05 \quad \tau_{syn} = 10$





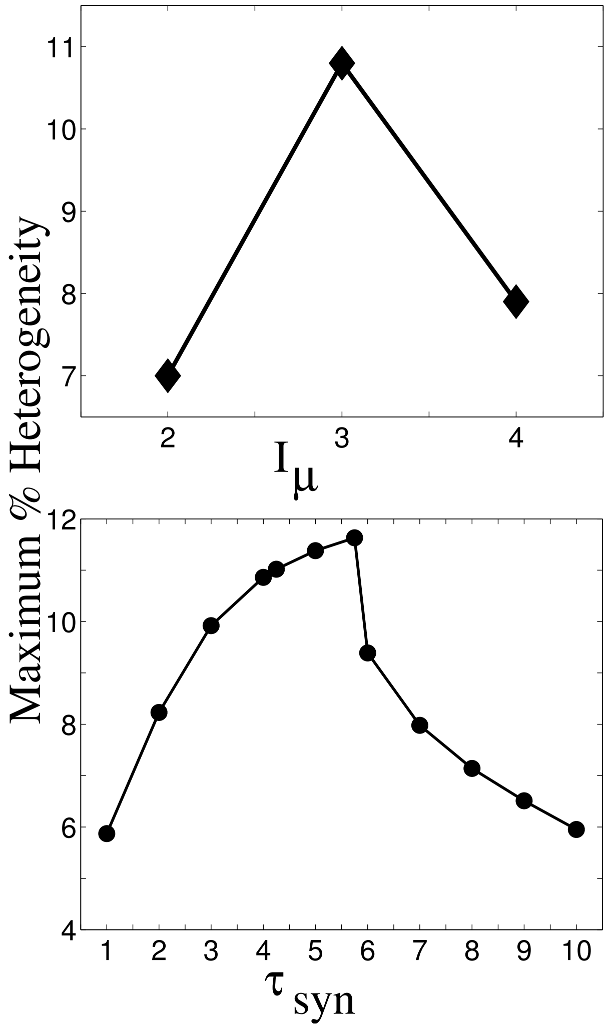
$g_{syn} = 0.25 \quad I_\mu = 3 \quad \tau_{syn} = 1$





g_{syn}= 0.25 ε = 0.05 I_μ= 1
1 suppressing 2
near−synchronous
V_1
τ_{syn}
30
29
28
27
26
25
24
23
22
21
20
0
1
2
3
4
5
6
7
8
9
10

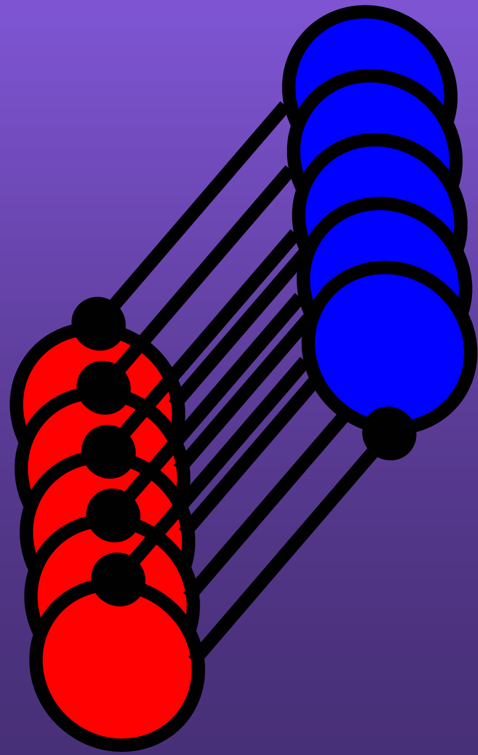
Max % Heterogeneity and Optimal Parameter Sets



quantitative evaluation of the importance of various intrinsic cellular details…

Idea II

- Using two-cell network model parameter values to constrain and predict N-cell network model outputs



***Parameter constraints in N-cell networks*?**

If one randomly distributes inputs to N cells of an N-cell inhibitory (all-to-all coupled) network in a range up to a maximal amount of heterogeneity, say $\%Het_{max}$

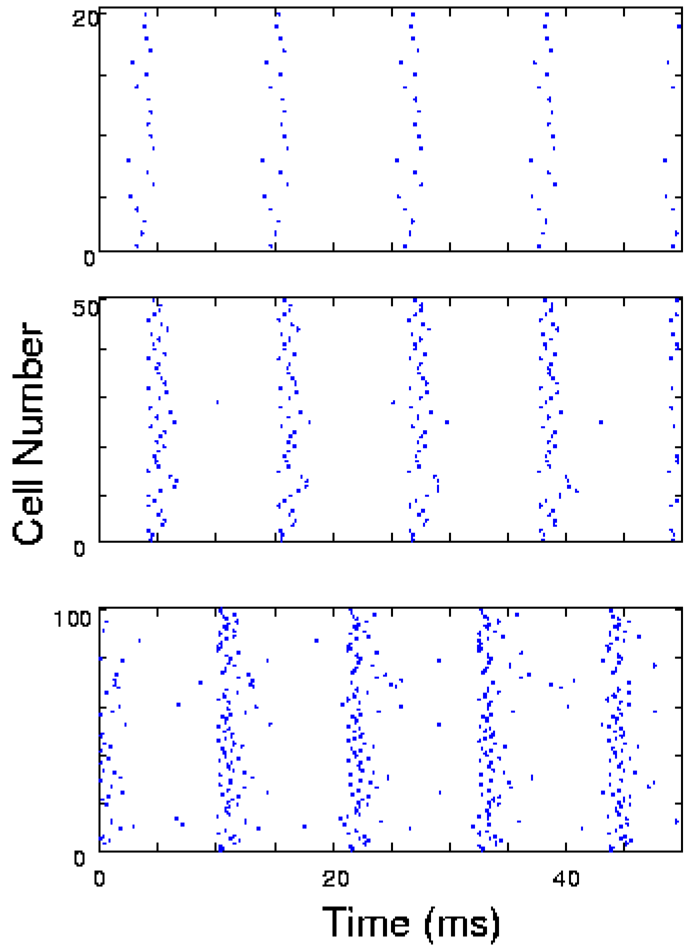
Then the possible patterns that the N-cell networks express include the patterns that the 2-cell networks express with

$$\%Het \leq \%Het_{max}$$

- Skinner et al., J. Comput. Neurosci. (2005)

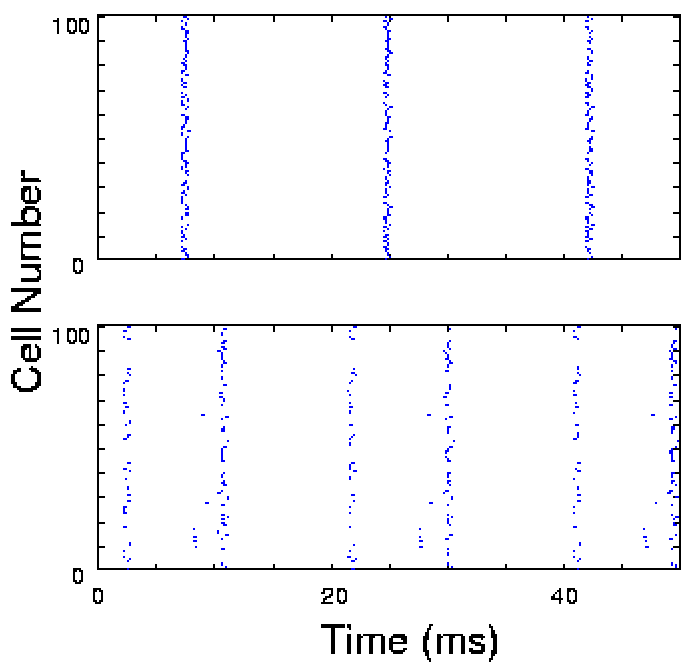
8%Het, τ_{syn}=6, I_{μ}=3

(near-synchronous solutions, but no multistability, as per 2-cell network bifurcation analyses)



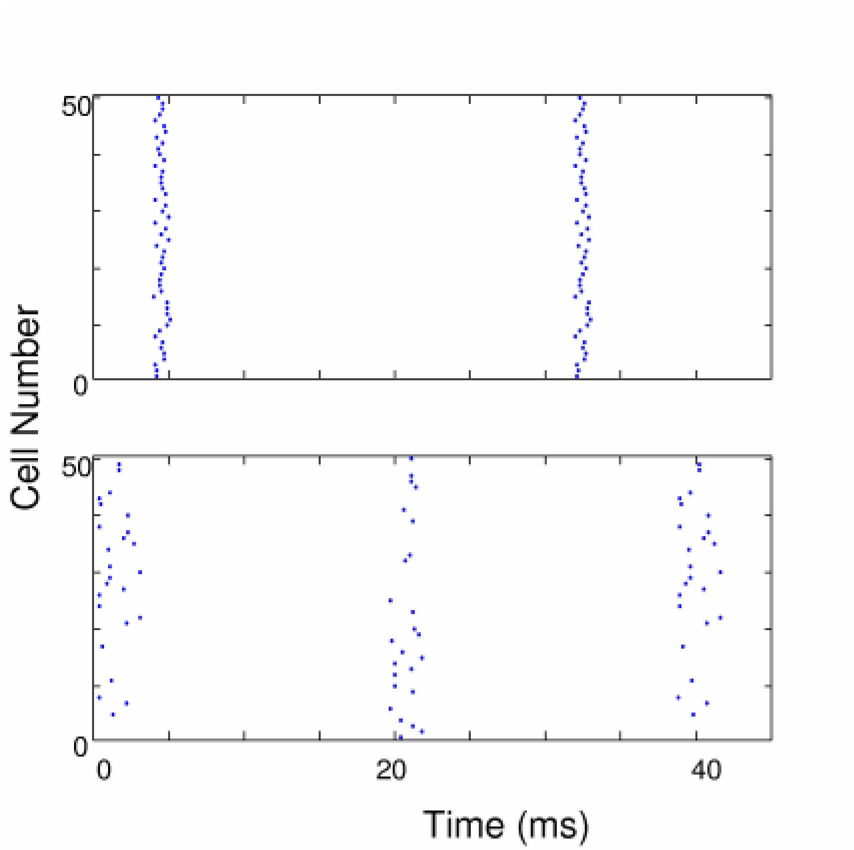
5%Het, τ_{syn}=1, I_μ=1

(bistable near-synchronous and near-antiphase solutions, as per 2-cell network bifurcation analyses)

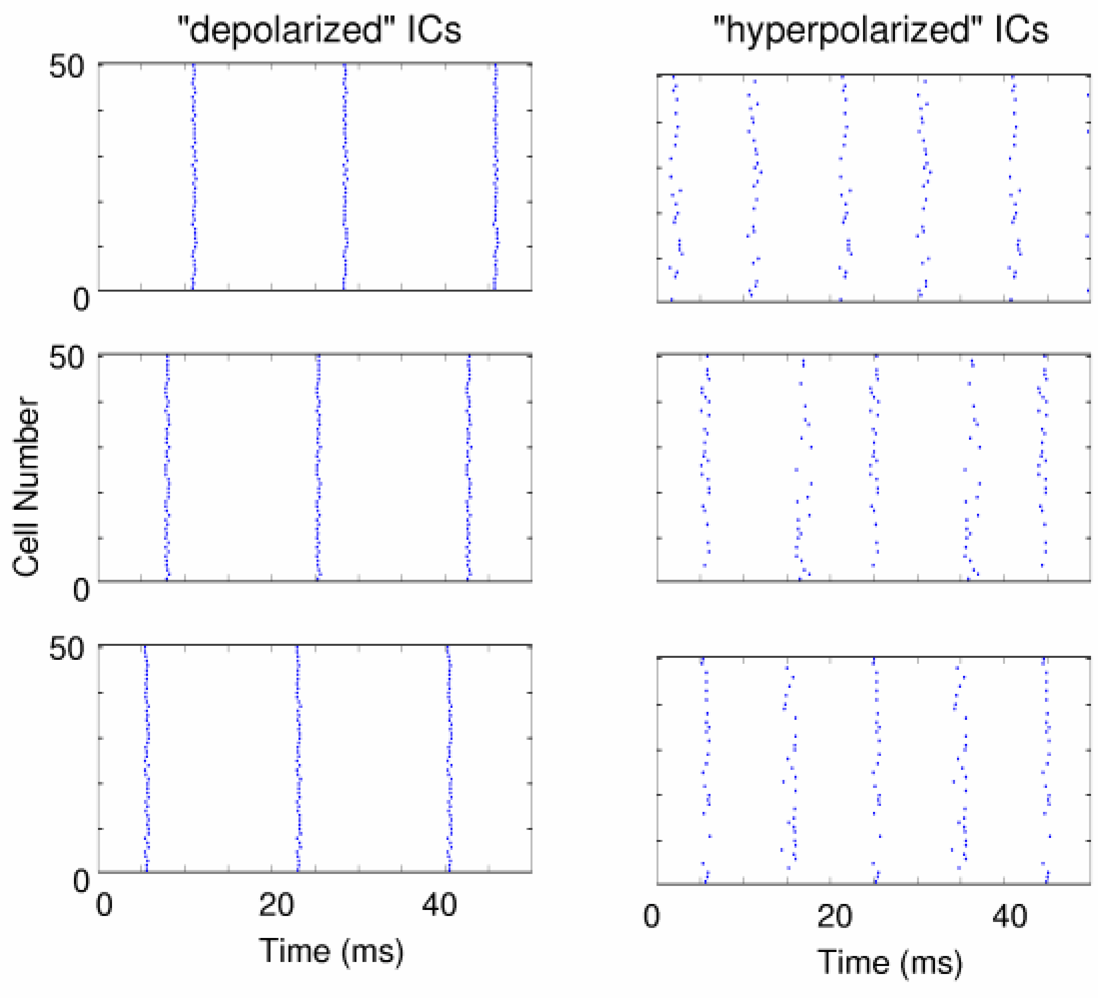


4%Het, τ_{syn}= 7, I_{μ}=1

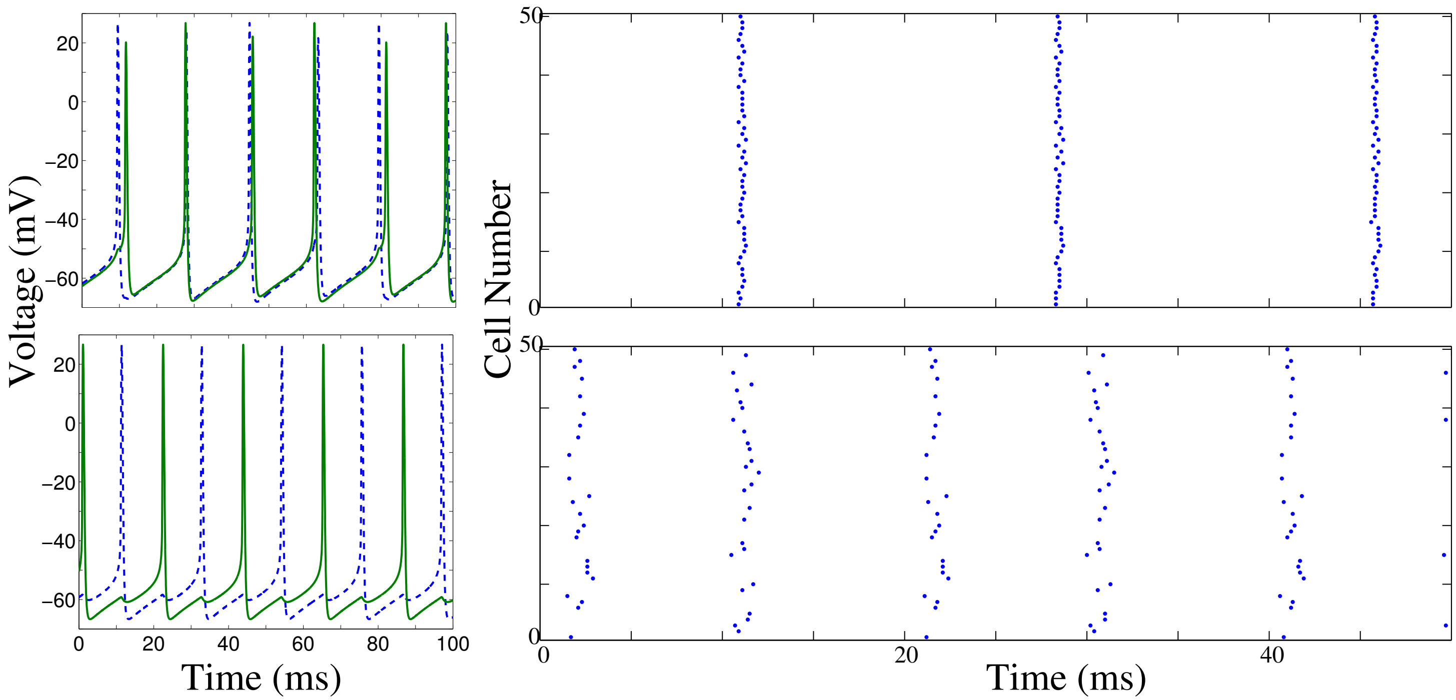
(bistable near-synchronous and suppressed solutions, as per 2-cell network bifurcation analyses)



Parameter preciseness
(4%Het, τ_{syn}= 1, I_{μ}=1)



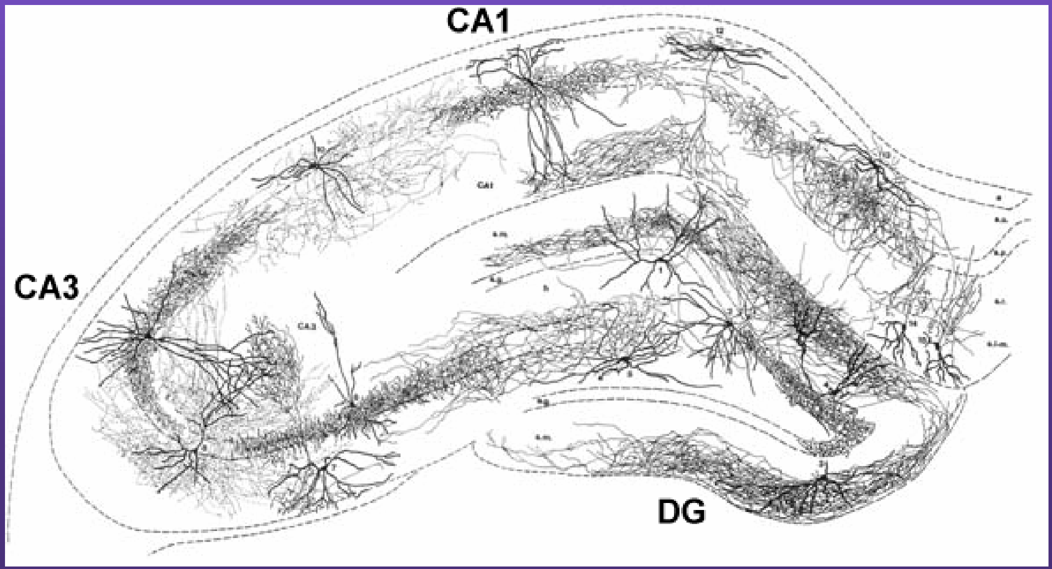
Two- to N-cell Network Output Correspondence



- *quantitative linkages occur*
- *multistability is manifest as distinct coherent patterns*

Idea III

- Estimating synaptic parameters from actual and virtual model networks… as a prelude to dealing with the experimental data



“VmD” method

“A Method to Estimate Synaptic Conductances from Membrane Potential Fluctuations”

M. Rudolph, Z. Piwkowska, M. Badoual,

T. Bal and A. Destexhe

J. Neurophysiol. 91:2884-2896, 2004

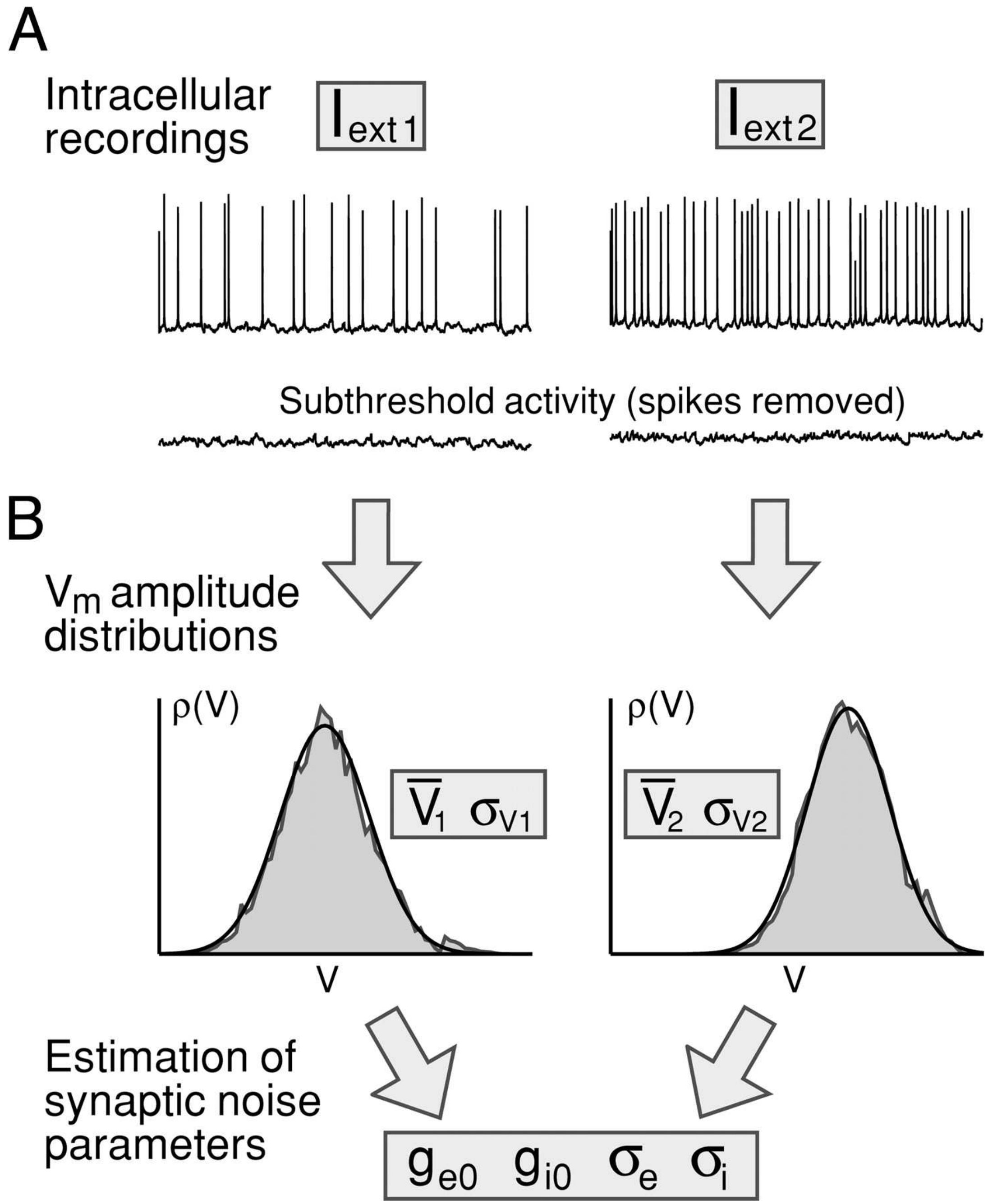
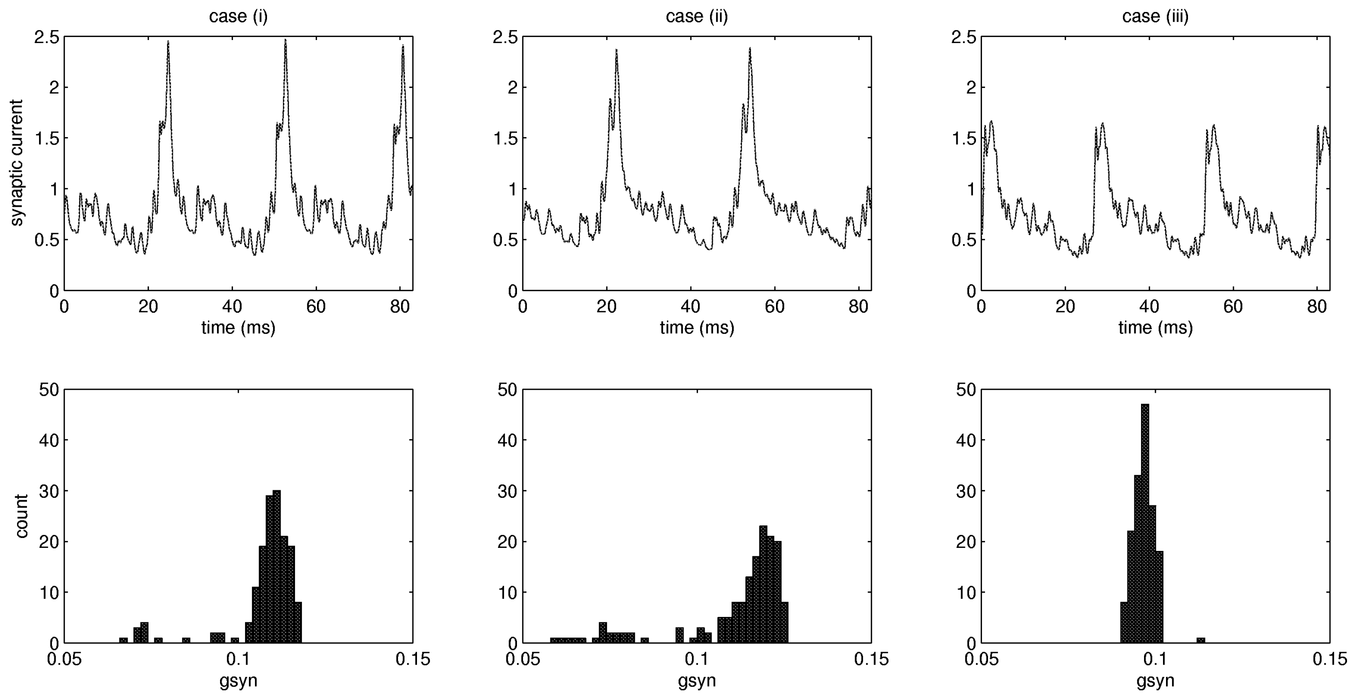


Illustration of VmD method

Figure 2
from Rudolph et al. (2004)

‘spike-free’ data from network models

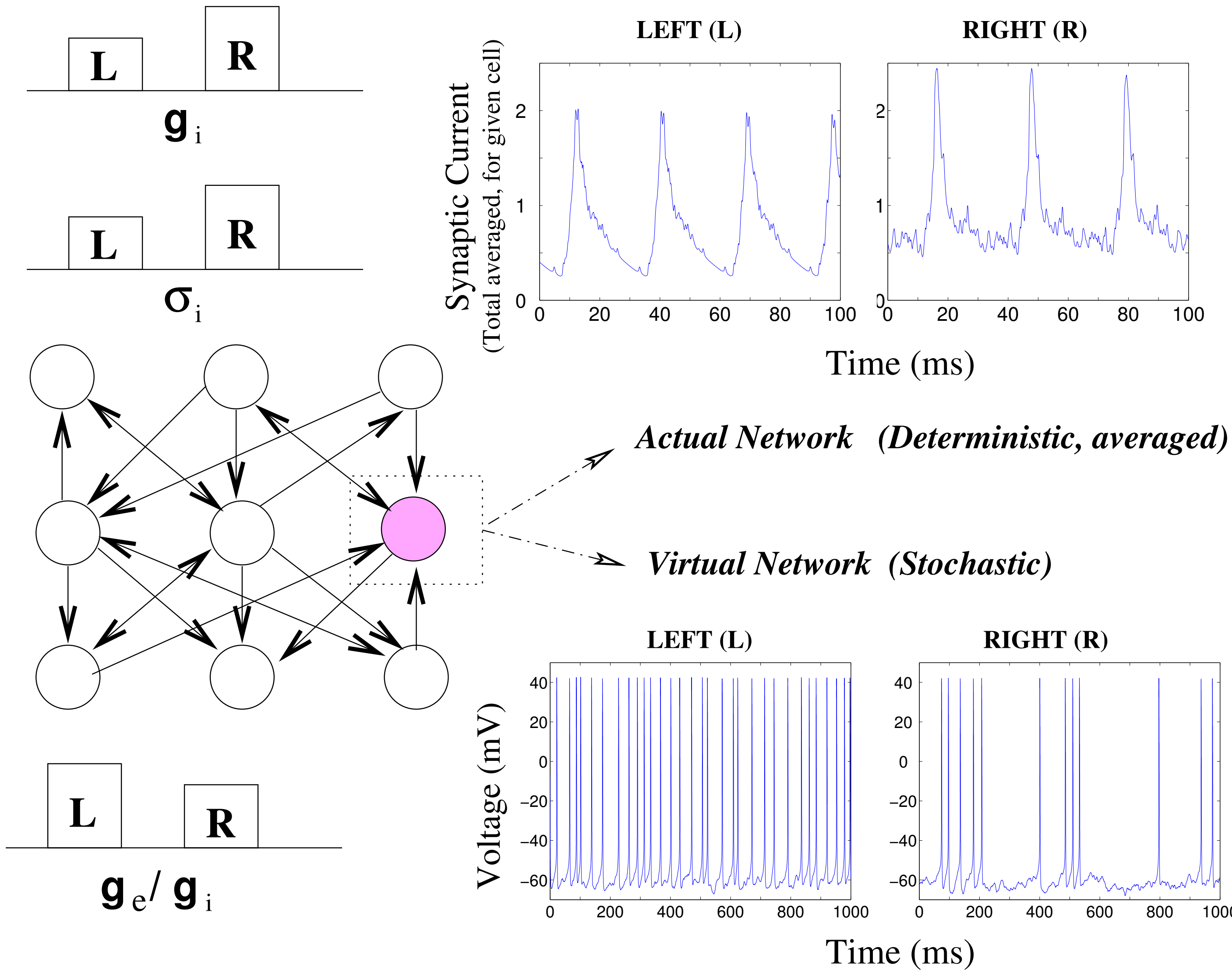
variable patterning can be captured by averaging across many deterministic simulations in which ICs and heterogeneity are varied



50-cell networks, 4% Het, 200 sets

g_{syn}= (i) 0.25, (ii) 0.25, (iii) 0.20; τ_{syn}= (i) 7, (ii) 9, (iii) 7

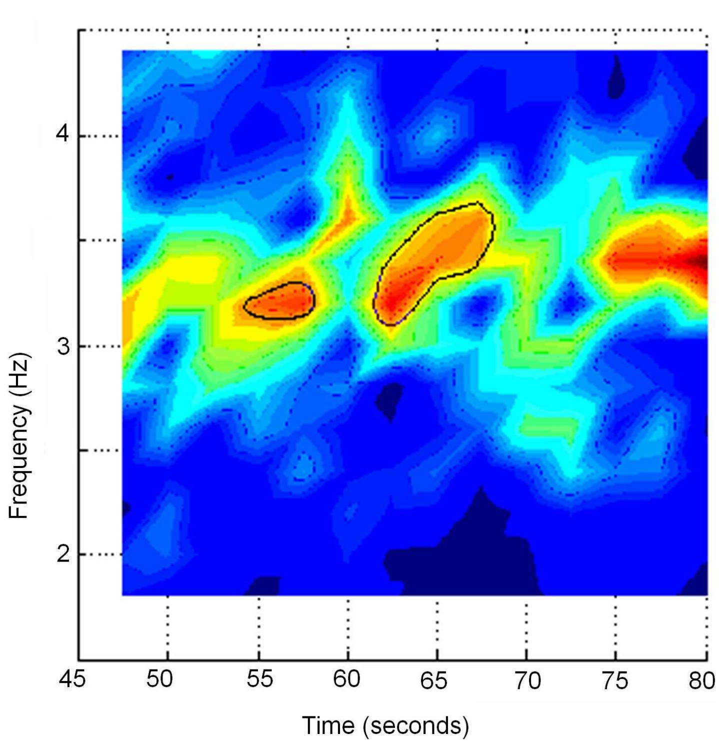
Synaptic parameter estimation from model networks



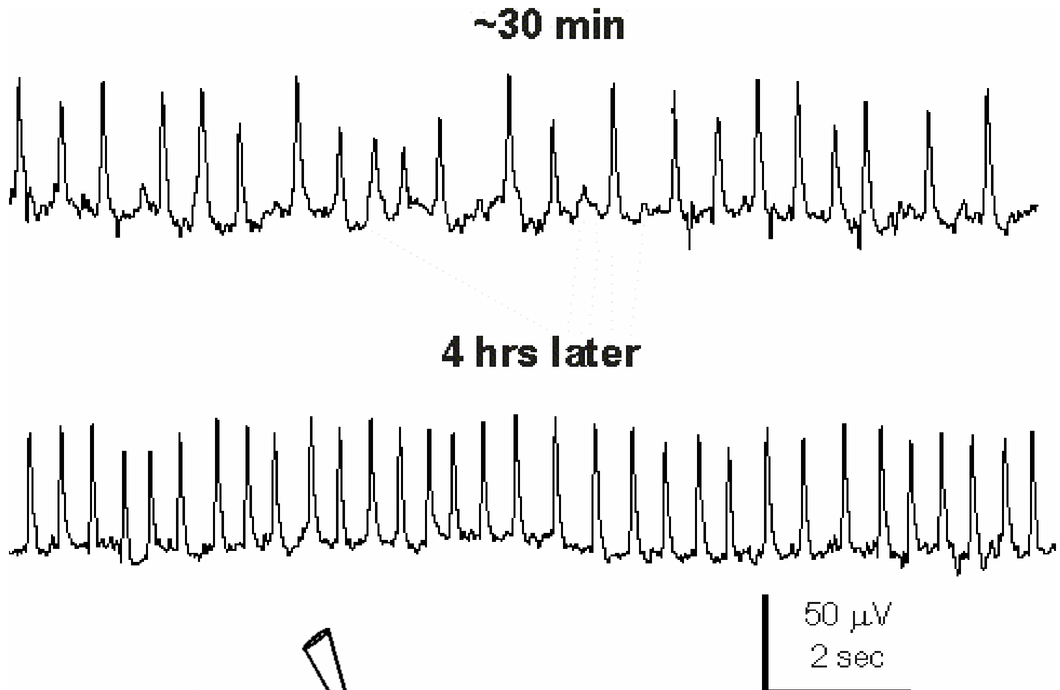
Review and onward….

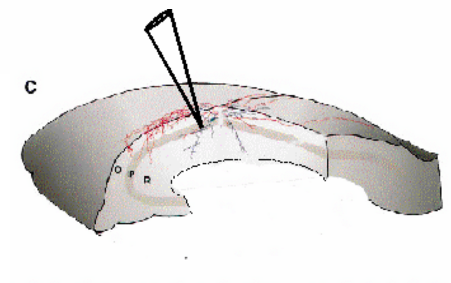
- I: quantitative evaluation of cellular details
- II: 2- to N-cell insights
- III: model and experiment network links

Spontaneous Rhythmic Field Potentials (SRFPs)
(Wu et al. 2002, 2005)



Gillis et al., J. Neurosci. Meth. (2005)





‘Design’ and ‘Discover’

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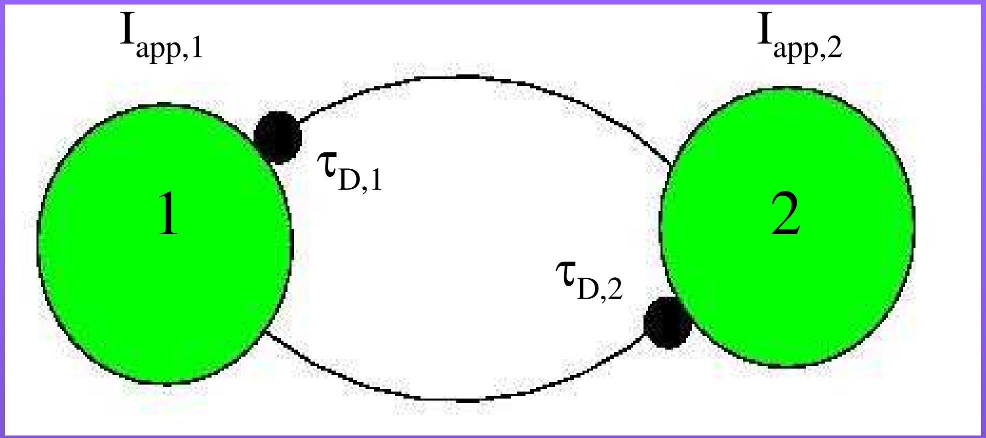
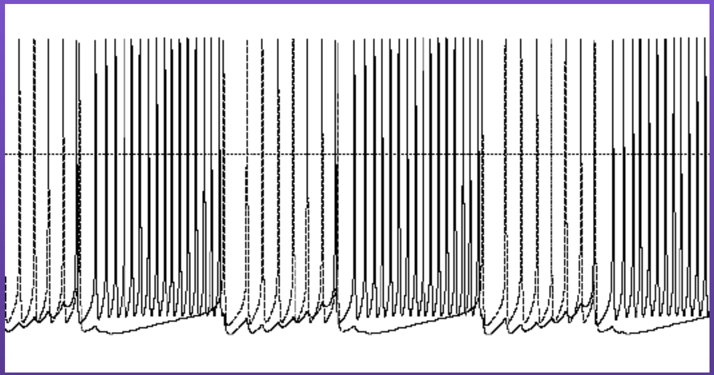
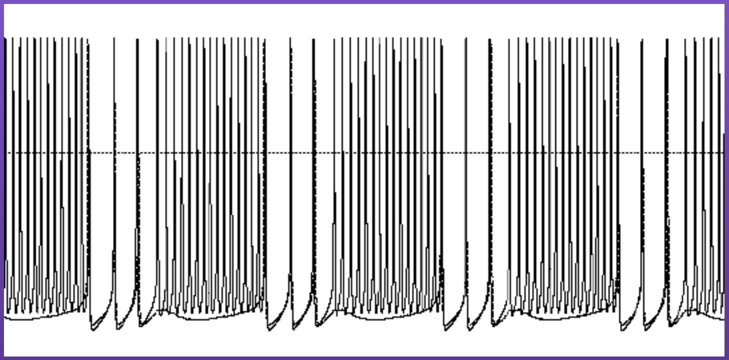




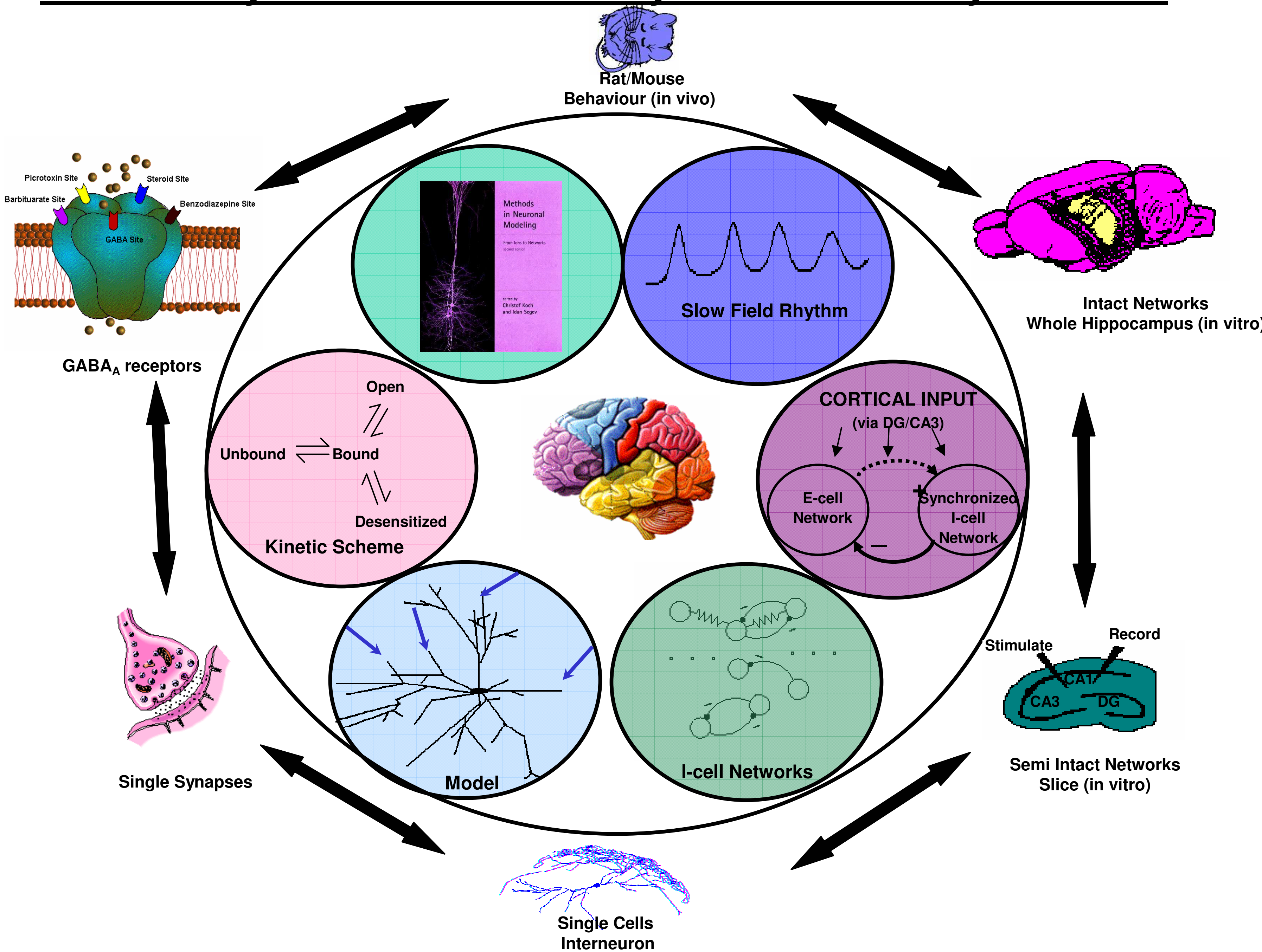
Alternating Bursting



Emergent Synchrony

- Jalil et al., J. Comput. Neurosci. 17:31-45, 2004

“Inhibitory Networks and Rhythmic Brain Dynamics”



Acknowledgements

All Present and Past Lab Members!

All Present and Past Collaborators!

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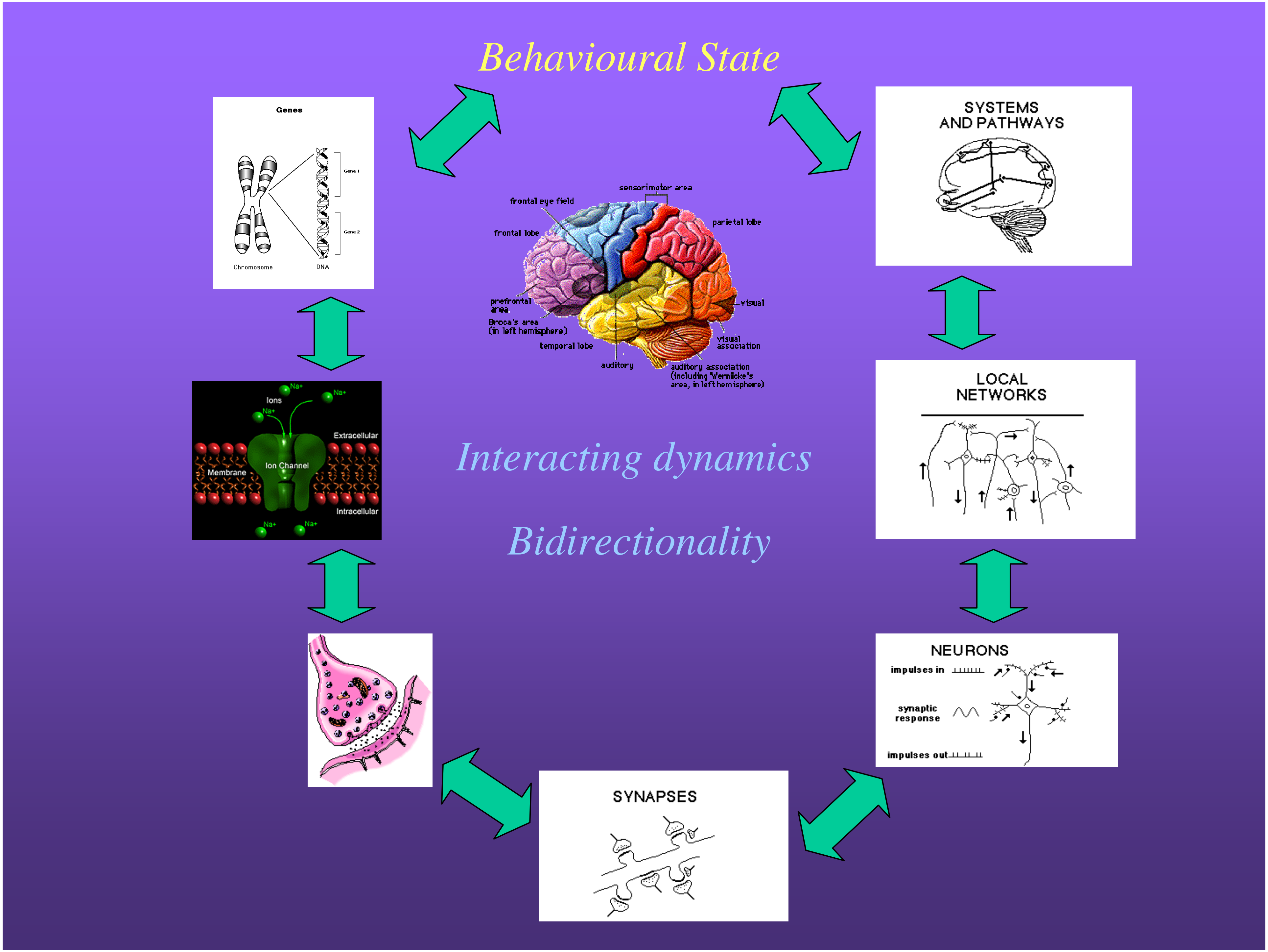
From Deborah M. Gordon, Nature 8 March 2007

- *"A better route to understanding the dynamics of apparently self-organizing systems is to focus on the details of specific systems. This will reveal whether there are general laws…."*
- *"When we learn more about the specifics of such systems (such as ant colonies), we will see where analogies between them are useful and where they break down….."*
- *"Life in all its forms is messy, surprising and complicated…."*


Behavioural State
Genes
Gene 1
Gene 2
Chromosome
DNA
sensorimotor area
frontal eye field
frontal lobe
parietal lobe
prefrontal area
visual
Broca's area (in left hemisphere)
temporal lobe
visual association
auditory
auditory association (including Wernicke's area, in left hemisphere)
SYSTEMS AND PATHWAYS
Ions
Na+
Extracellular
Membrane
Ion Channel
Intracellular
Interacting dynamics
LOCAL NETWORKS
Bidirectionality
NEURONS
impulses in
synaptic response
impulses out
SYNAPSES

The end