Integration in Neuroscience from a Cellular-based Neuronal Network Perspective

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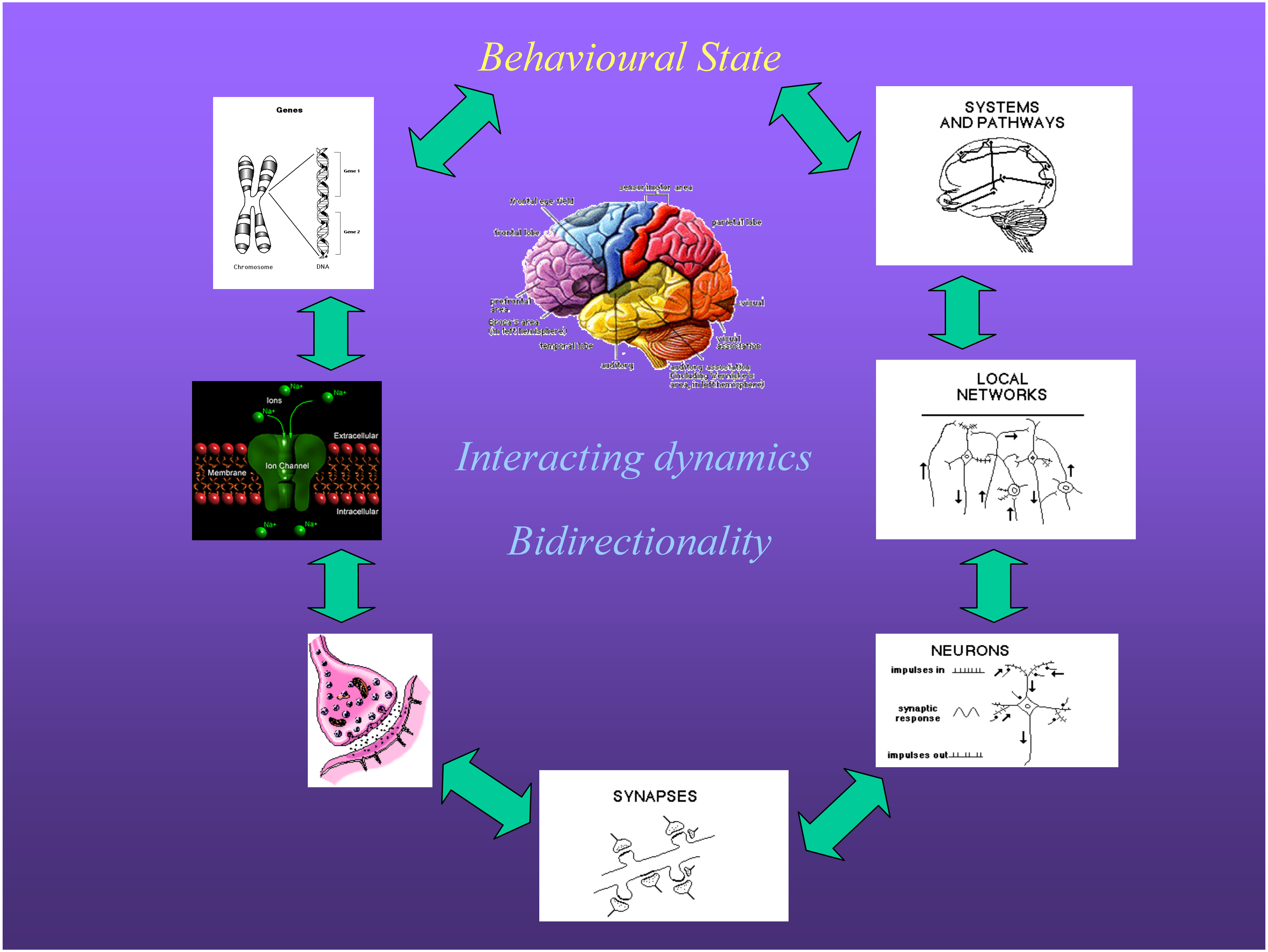
TALK OUTLINE

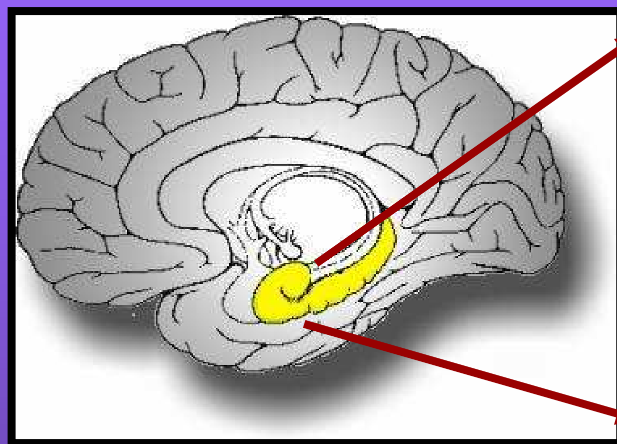
- *General introduction*
- *Hippocampus focus*
- *Experimental data focus*
- *Basket cell focus*
- *Modelling approach 1 – simulations and ad-hoc analyses (synaptic depression)*
- *Modelling approach 2 – simulations and linking to experimental data (gap junctions)*
- *Closing*

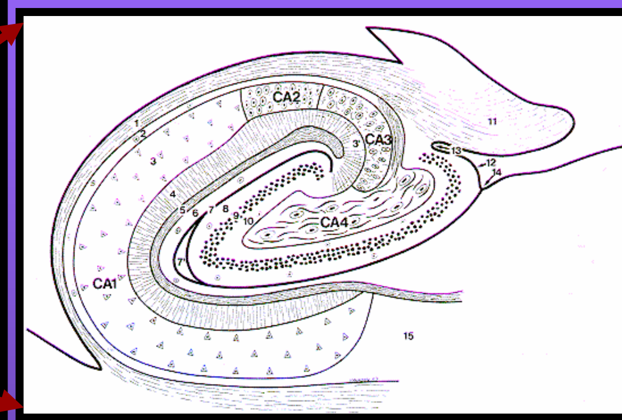


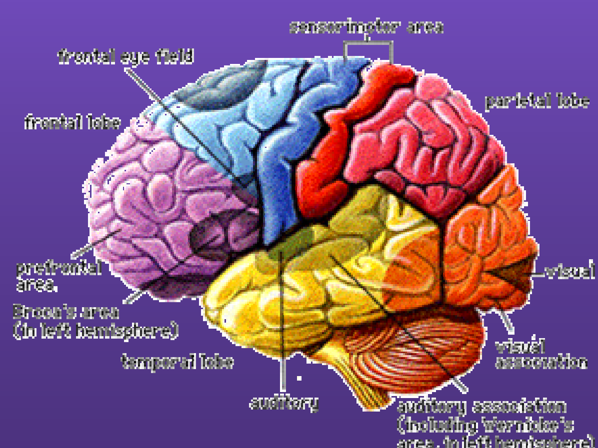
Behavioural State
Genes
Gene 1
Gene 2
Chromosome
DNA
SYSTEMS AND PATHWAYS
sensorimotor area
frontal eye field
parietal lobe
frontal lobe
prefrontal area
Broca's area (in left hemisphere)
temporal lobe
visual
visual association
auditory
auditory association (including Wernicke's area, in left hemisphere)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

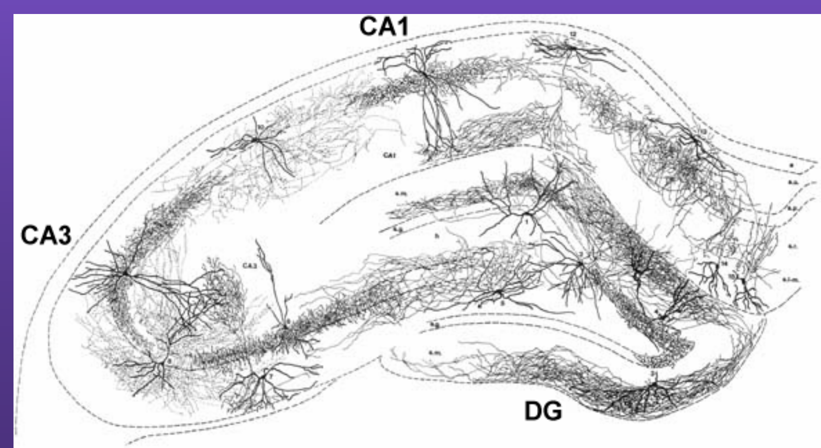
Focus and Context

"Welcome to the hippocampal world!" ☺









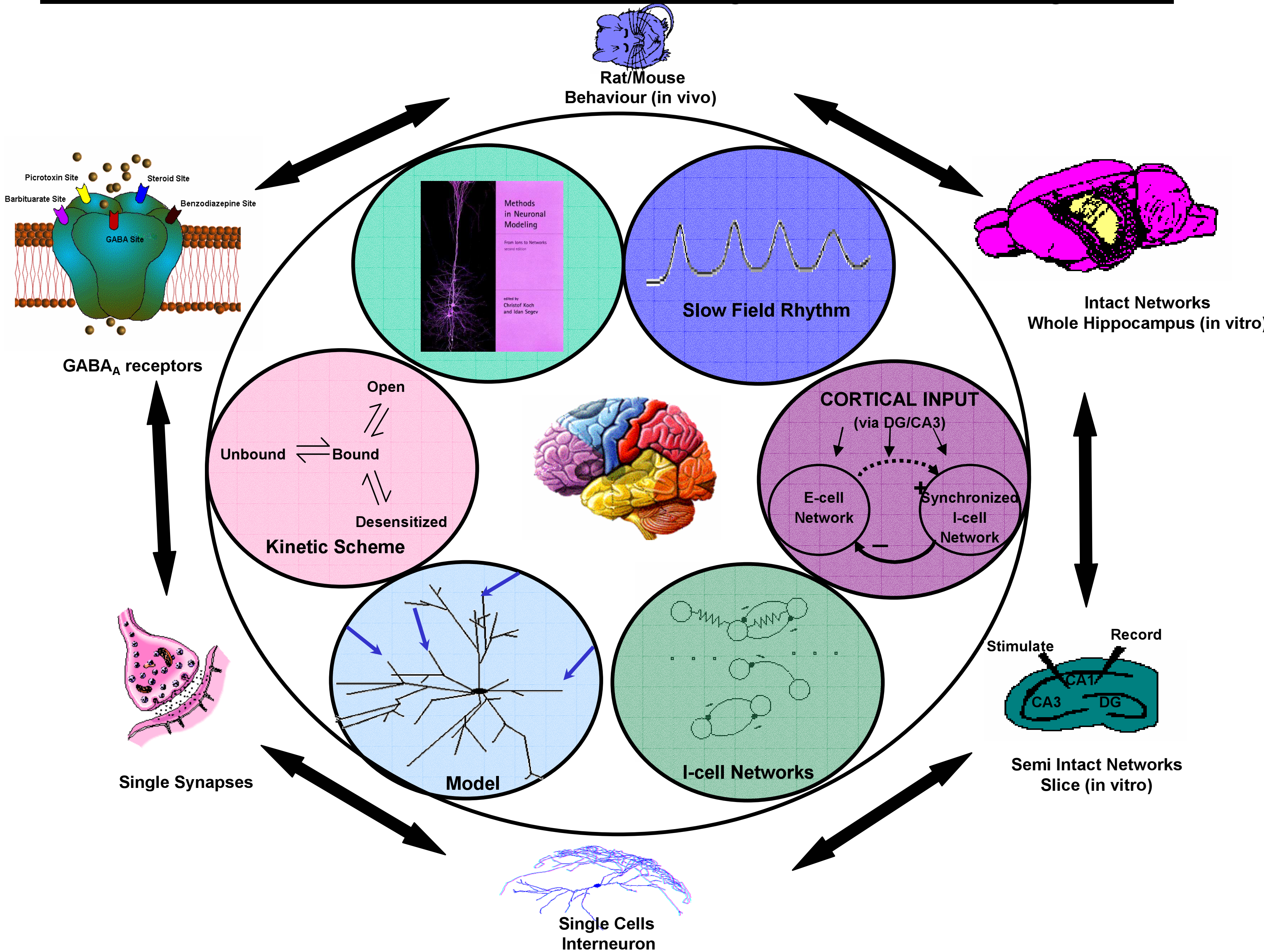
The hippocampal cortex is an intensely studied region of the brain because:

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

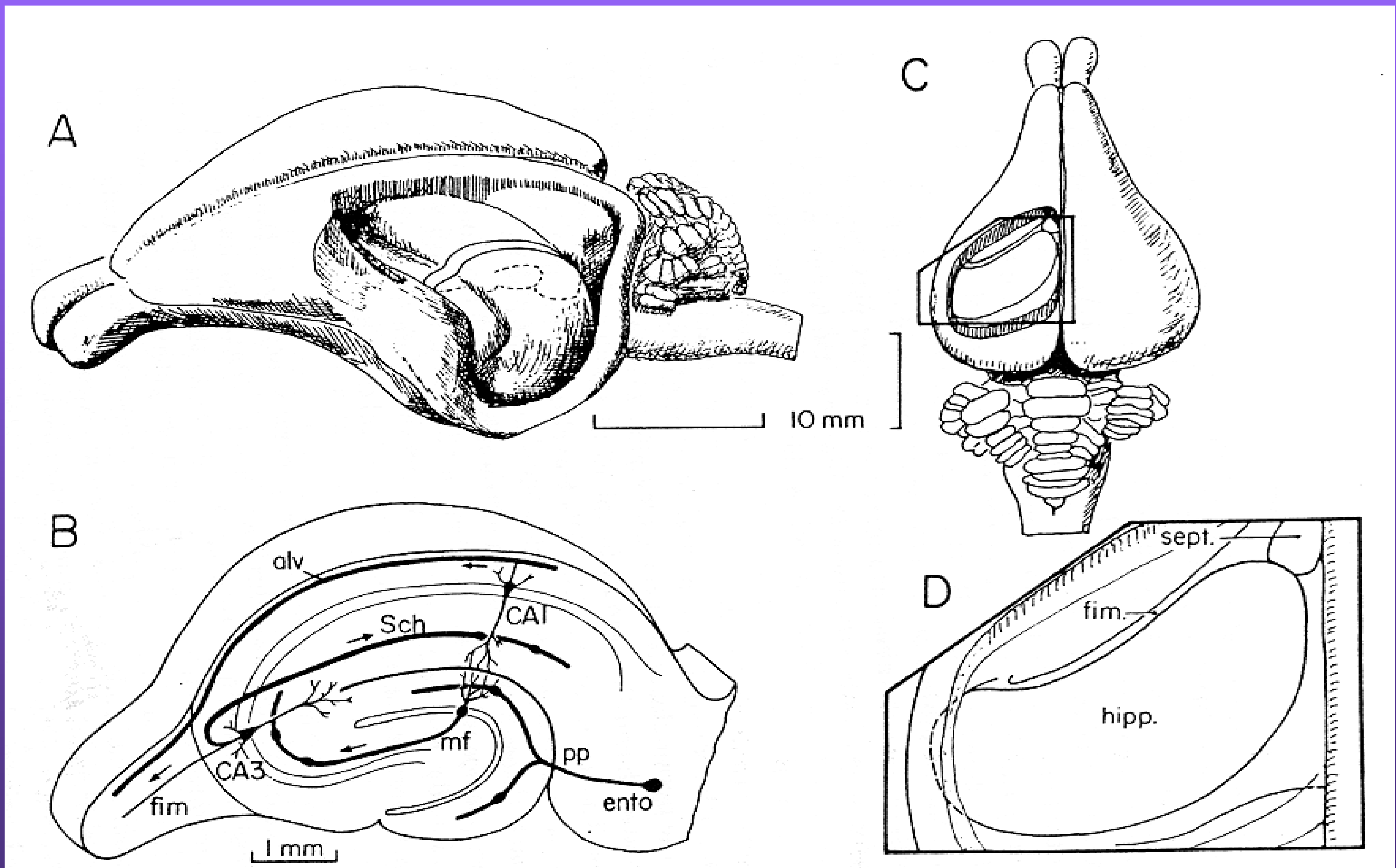
- *It is associated with memory and learning (i.e., LTP, LTD), epileptic seizures, and neurogenesis.*

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

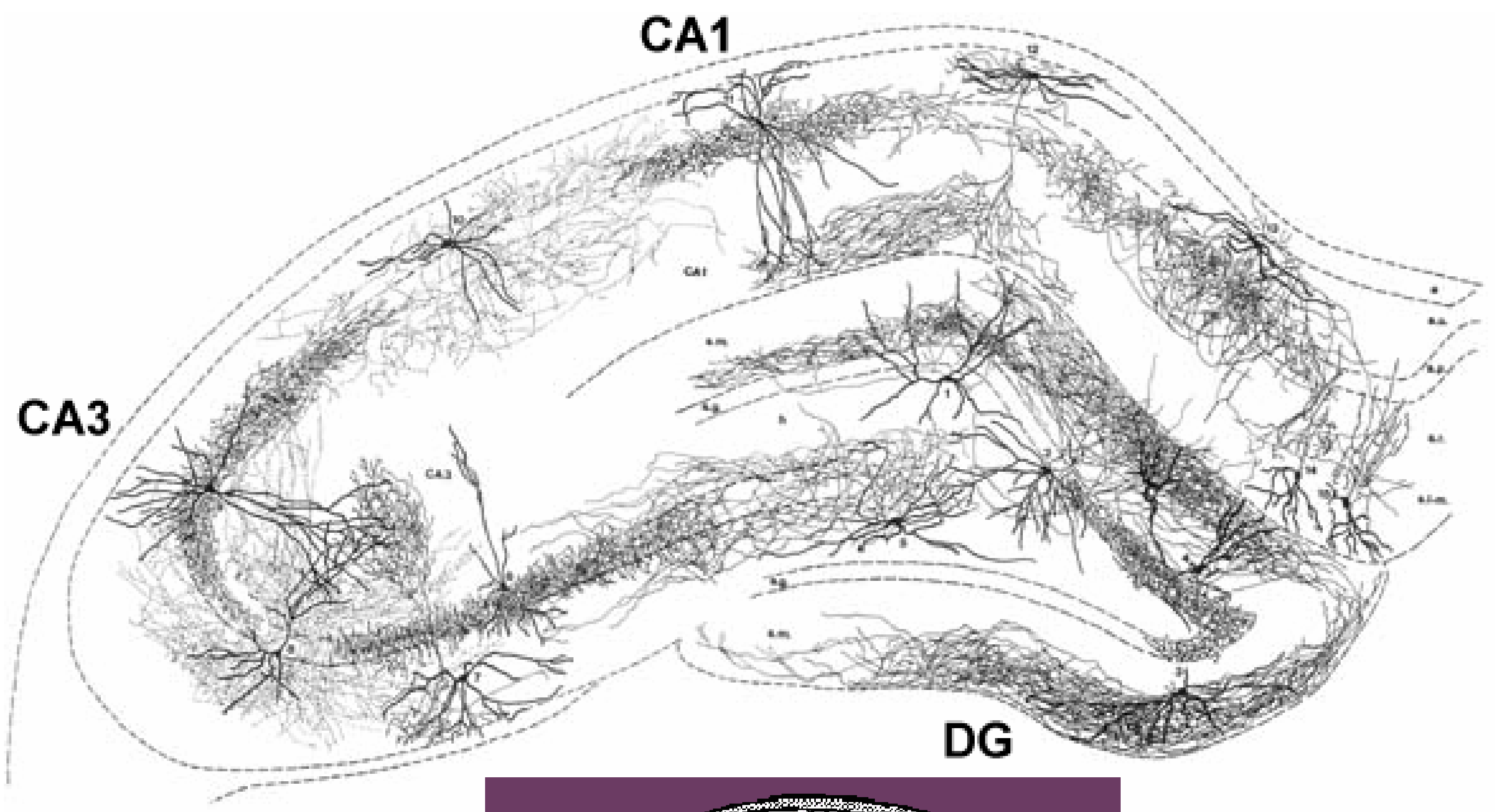
"Computational Road Maps to Dynamic Phenotypes"

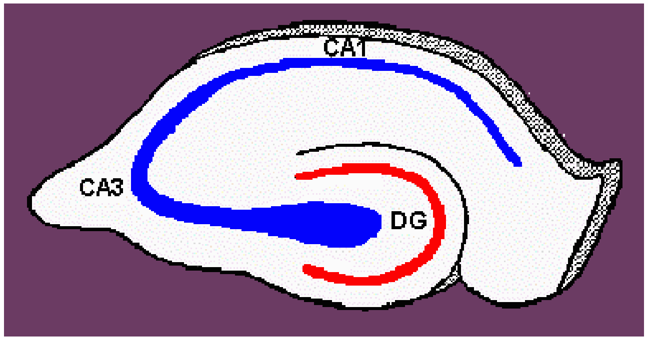


Hippocampus and conventional slice preparation



Layers, signal flow, cell types





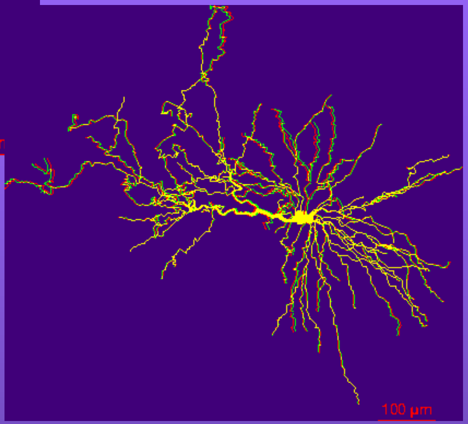
Interneurons

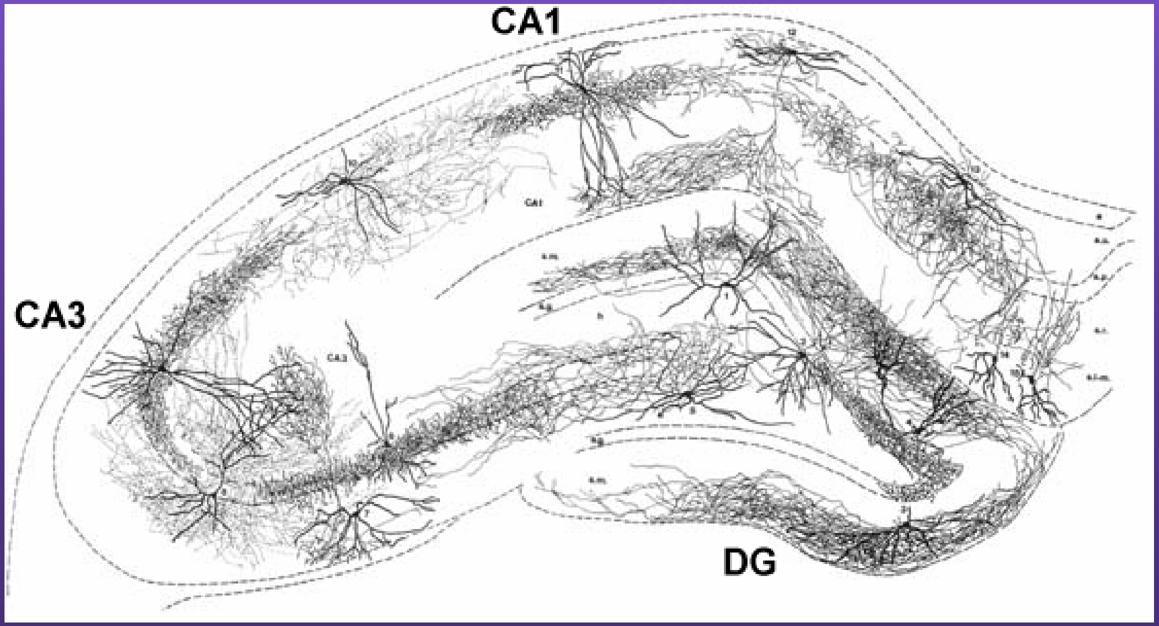
(GABAergic nonprincipal cells or Inhibitory neurons)

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

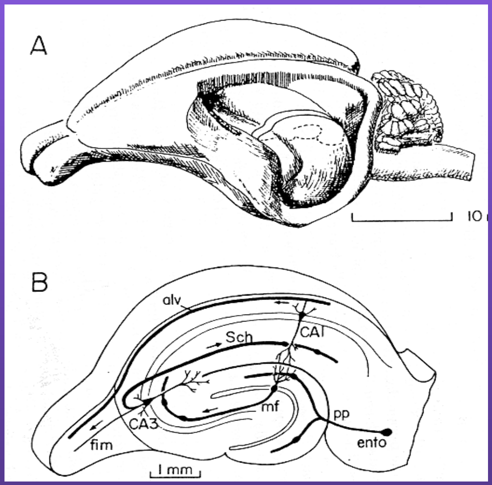
Freund and Buzsáki, Hippocampus 6:347-470, 1996

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



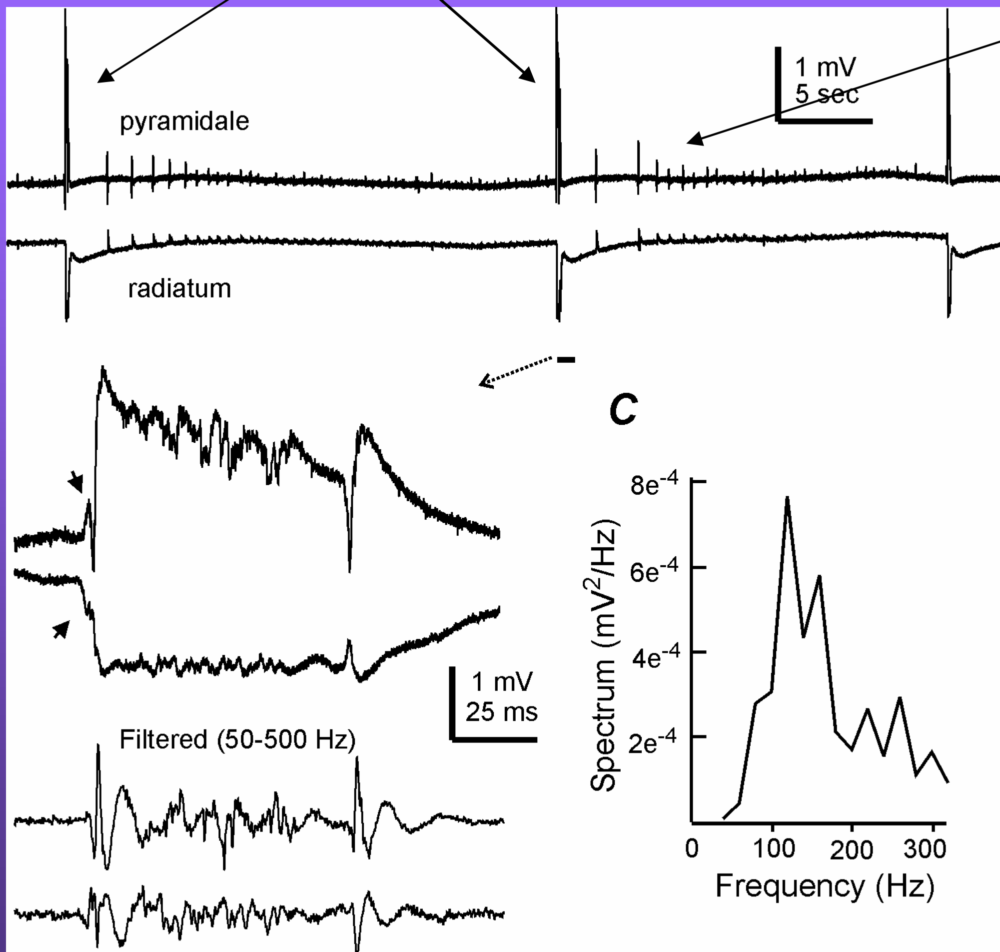


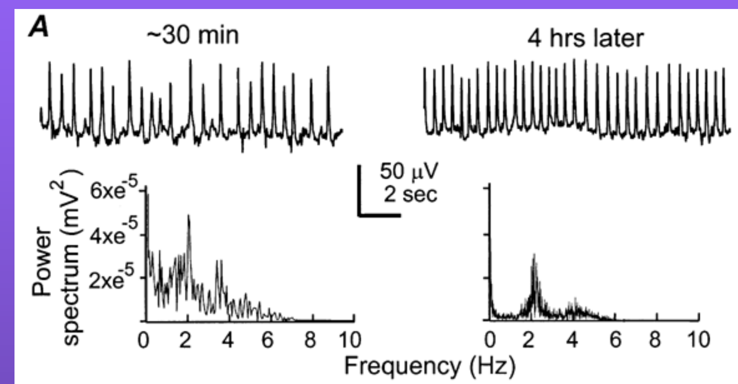
Two types of population activities obtained in whole hippocampus and thick slice preparations (...that critically depend on inhibitory cell participation)



- Spontaneous rhythmic field potentials (SRFPs)
- Sharp wave-ripples (SPW- ripples)

SPW-ripple *SRFP*



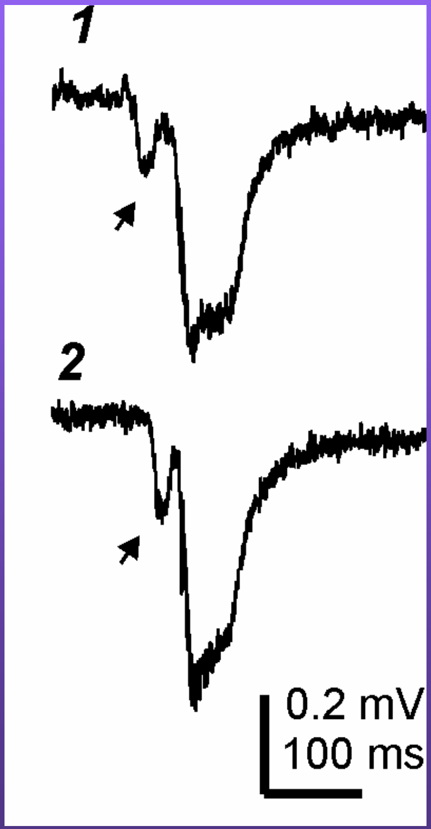


L.Zhang et al.

Stable population activities and relationship between SRFPs and SPWs

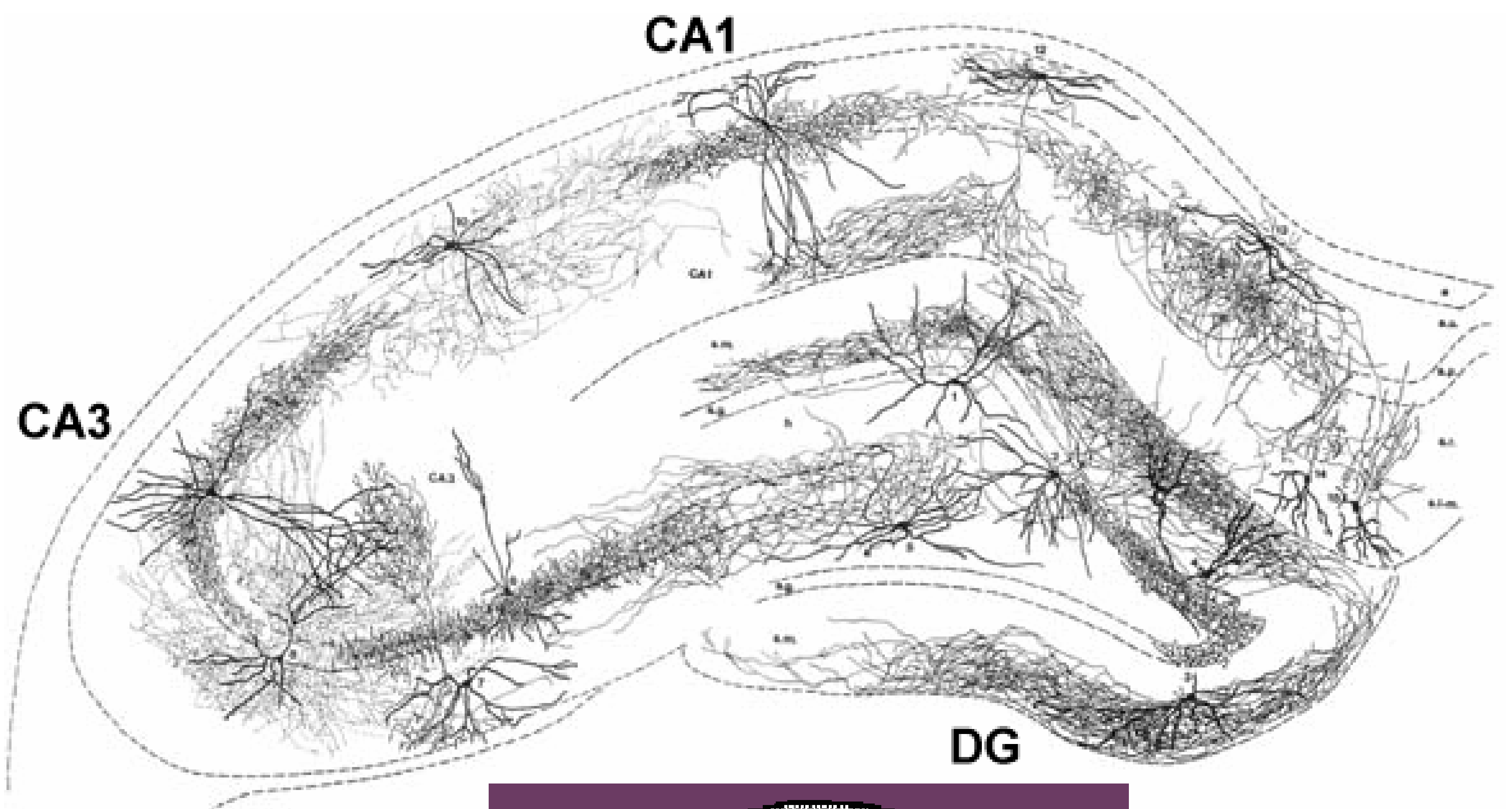
Initial time →

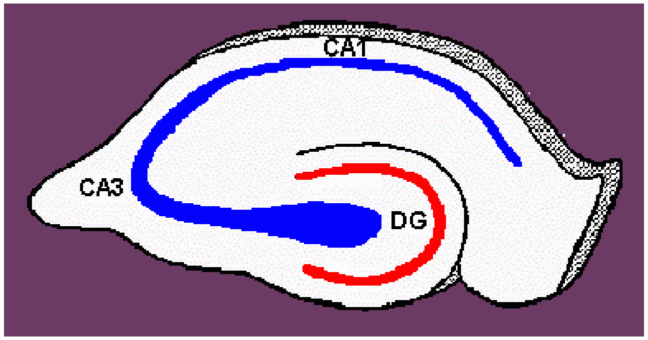
An hour and a half later →



What are the cellular and network mechanisms underlying these population activities?
(i.e., interactions between intrinsic and synaptic dynamics need to be understood.)

What model(s) to build?





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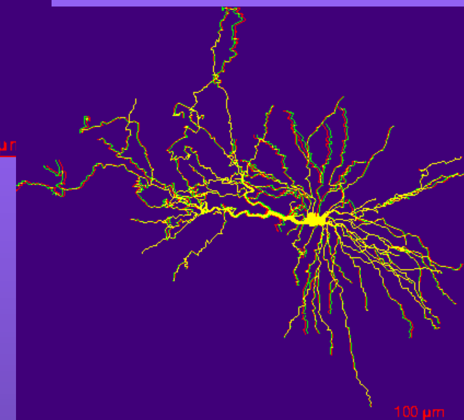
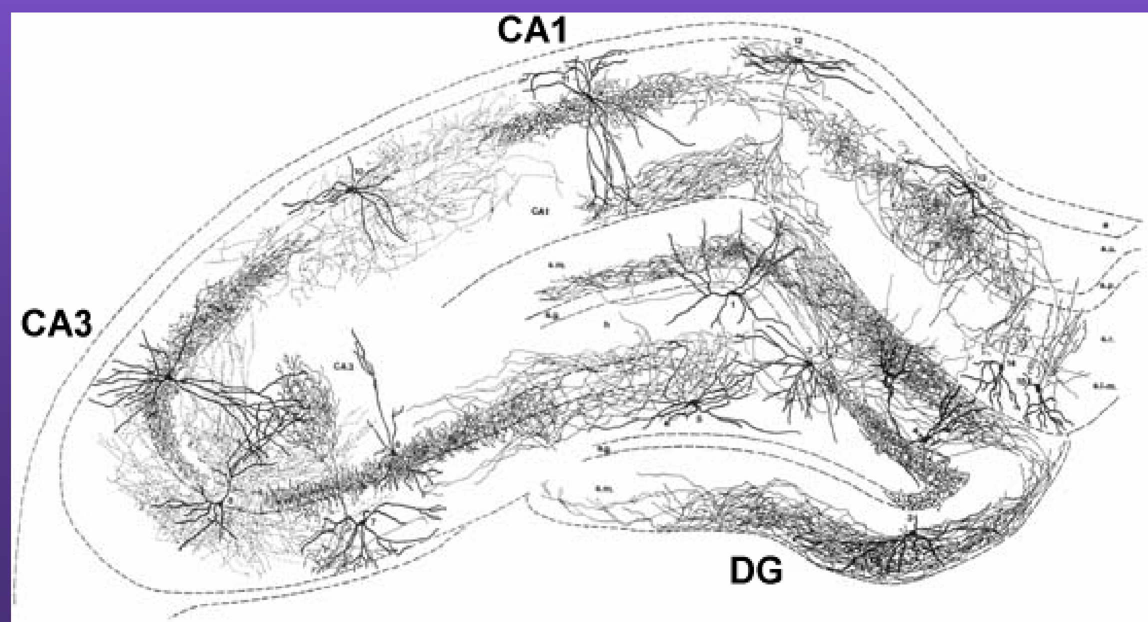
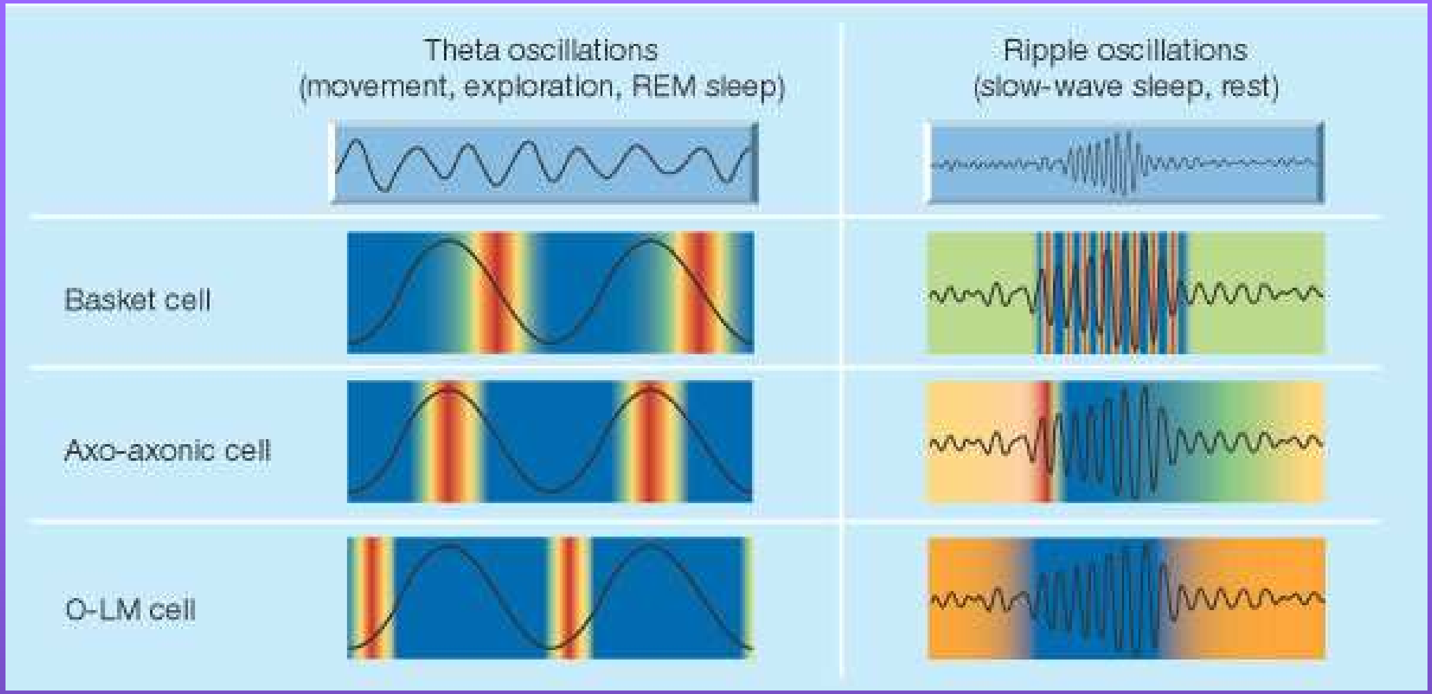


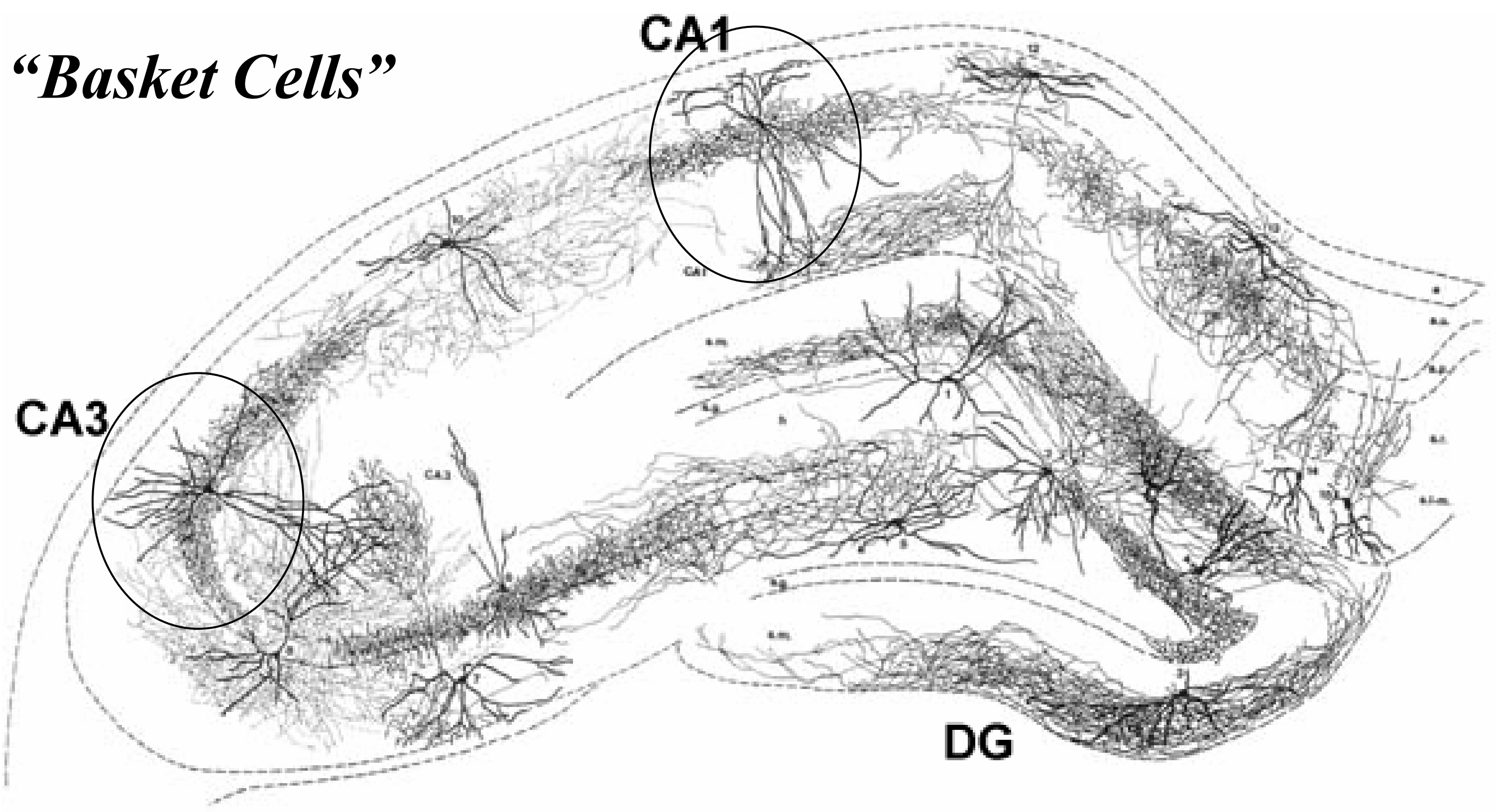




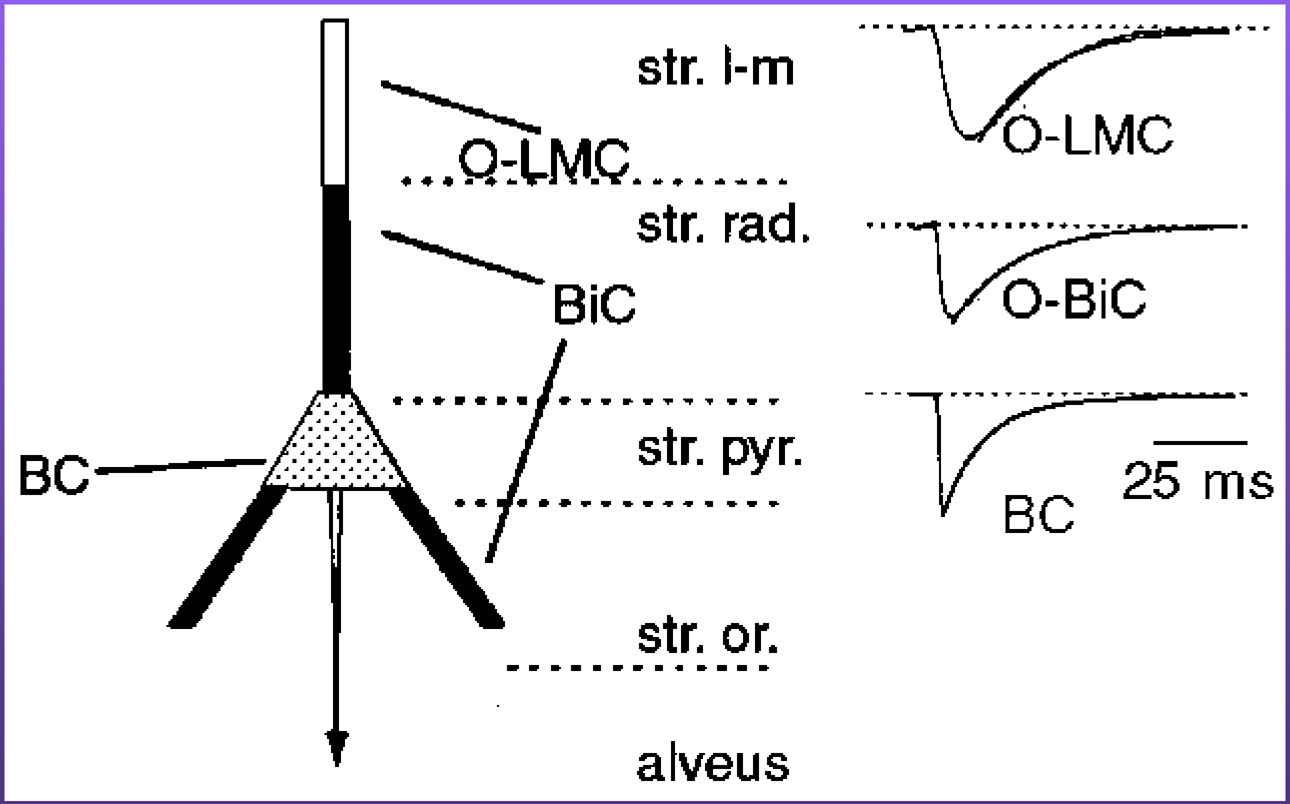
Interneurons and electrical oscillations.

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

Parvalbumin-containing GABAergic interneuronal networks may be a fundamental structure of the cerebral cortex (Fukuda and Kosaka, 2000)



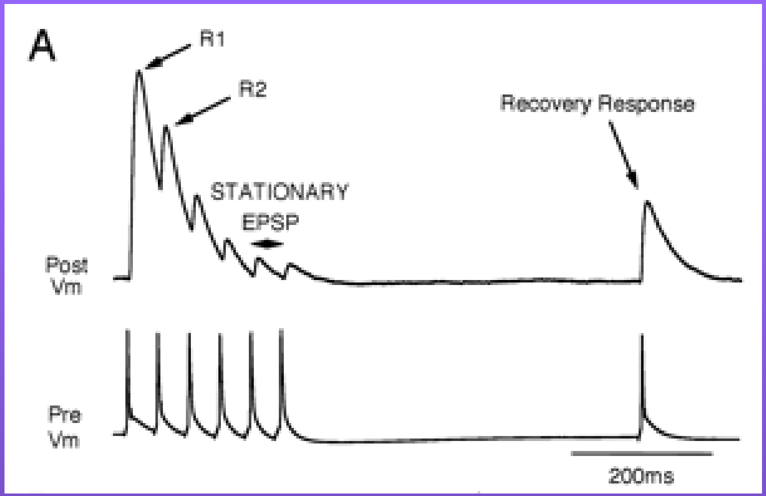
Basket cells (BCs) exhibit synaptic depression (Maccaferri et al., 2000)

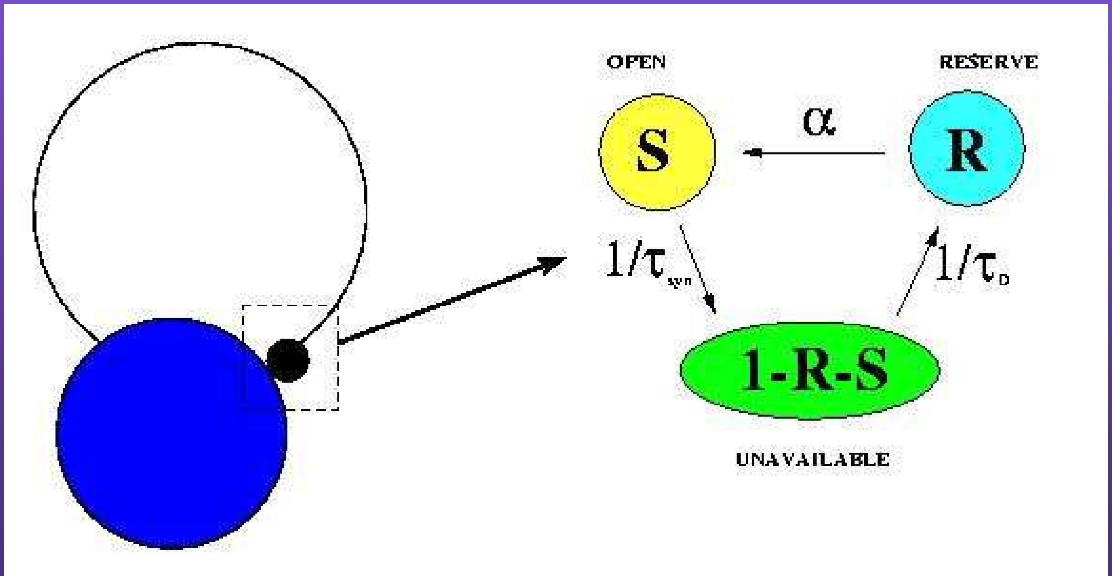


McBain Perspective

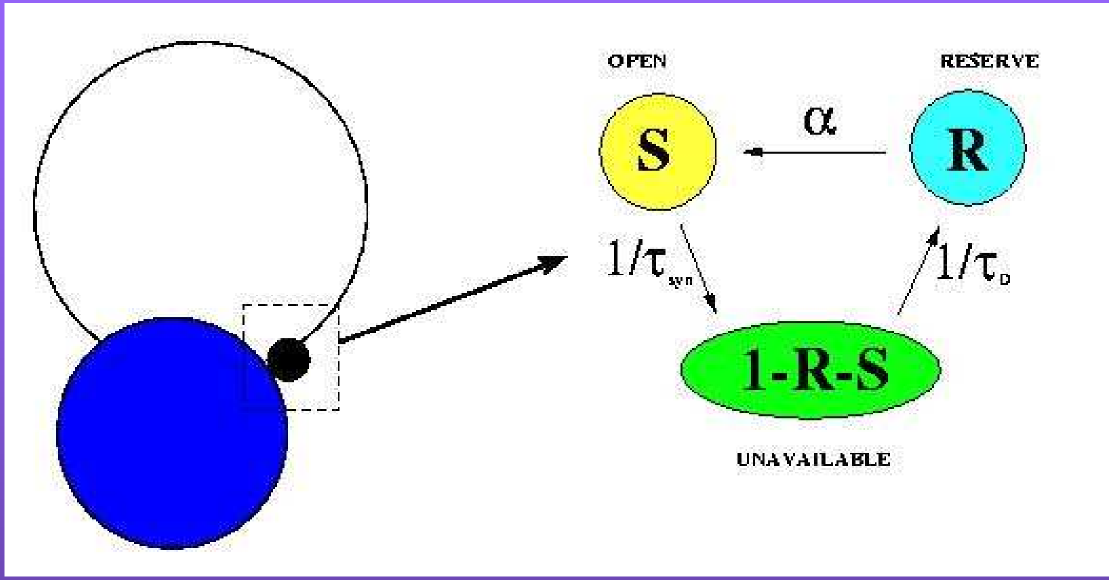
Short-term Plasticity: phenomenological model

(Tsodyks and Markram, 1997)





Synaptic Depression (short-term plasticity) model



$$I_{syn} = \bar{g}_{syn}\, S\, (V - V_{syn})$$

where

$$\frac{dS}{dt} = U_{SE}\, F(V_{pre})\, R - \frac{S}{\tau_S}$$

$$\frac{dR}{dt} = \frac{1 - S - R}{\tau_D} - U_{SE}\, F(V_{pre})\, R$$

and

$$F(V_{pre}) = 1/(1 + \exp(-(V_{pre}))$$

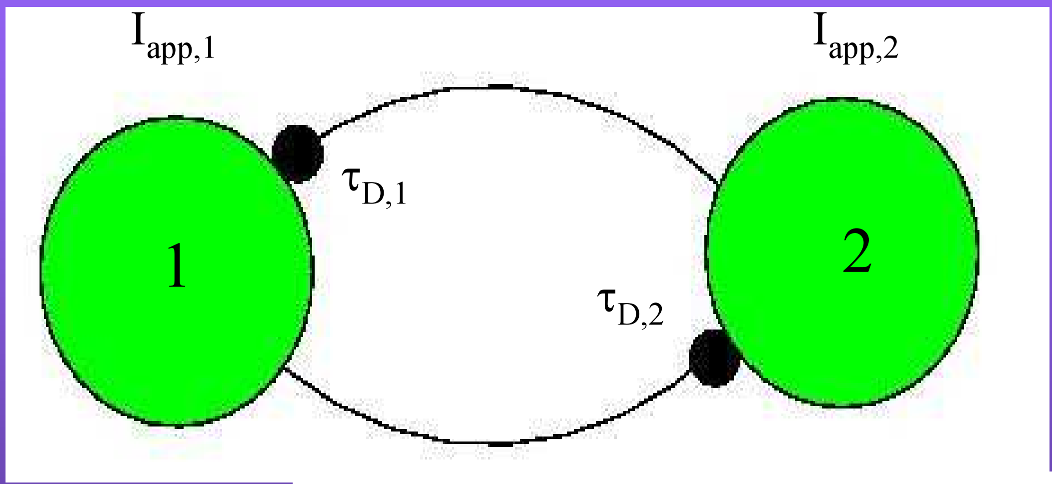
R is the synaptic resource in its recovered state

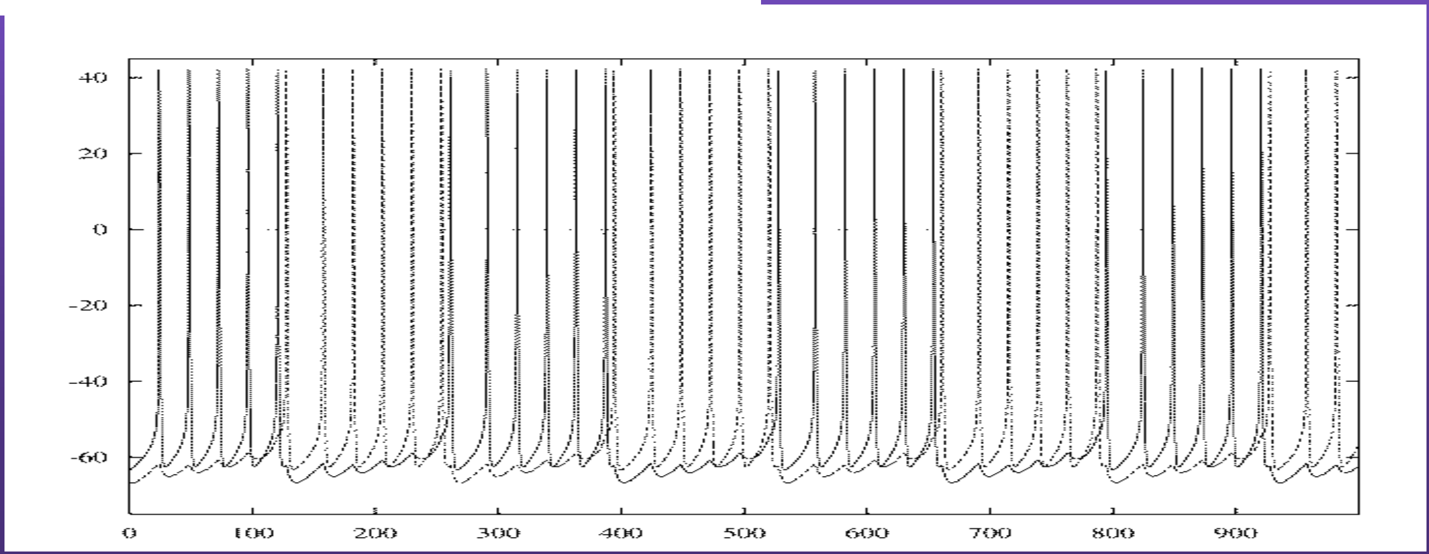
S is the active or effective synaptic resource

U_{SE} is the utilization of synaptic efficacy

"Novel Bursting Patterns Emerging from Model Inhibitory Networks with Synaptic Depression"

Jalil, Grigull and Skinner, submitted





Intrinsic Properties

$$C \frac{dV}{dt} = I_{app} - [\, \bar{g}_{Na}\, m_\infty^3\, h\, (V - V_{Na}) + \bar{g}_K\, n^4 + \bar{g}_L\, (V - V_L) + I_{syn} \,]$$

Synaptic Properties

$$I_{syn} = \bar{g}_{syn}\, S\, (V - V_{syn})$$

where

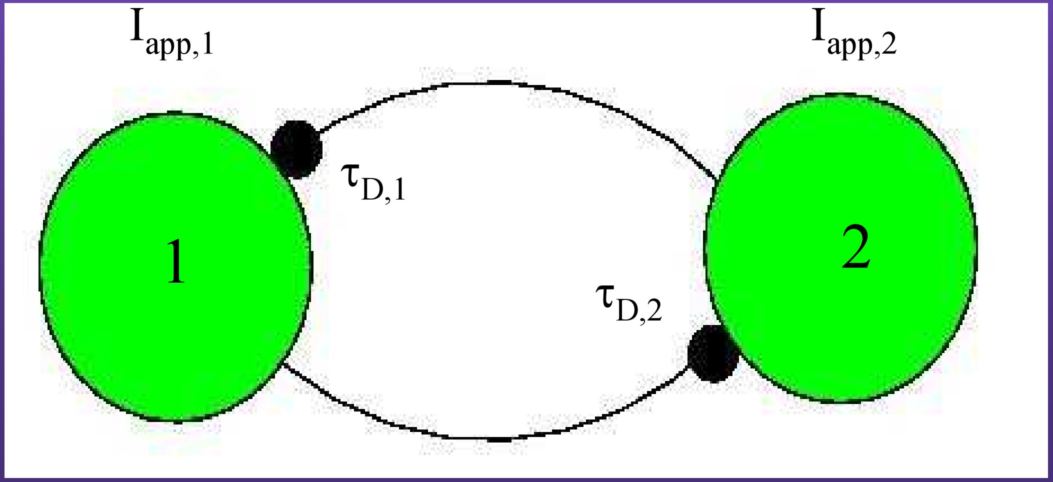
$$\frac{dS}{dt} = U_{SE}\, F(V_{pre})\, R - \frac{S}{\tau_S}$$

$$\frac{dR}{dt} = \frac{1 - S - R}{\tau_D} - U_{SE}\, F(V_{pre})\, R$$

and

$$F(V_{pre}) = 1/(1 + \exp(-(V_{pre}))$$

Full two-cell system would be a 10-dimensional Nonlinear system of ODEs



Use a strategy of embedding and extrapolation….

$$C\,\frac{dV}{dt} = I_{app} - [\,\bar{g}_{Na}\, m_\infty^3\, h\,(V - V_{Na}) + \bar{g}_K\, n^4 + \bar{g}_L\,(V - V_L) + I_{syn}\,]$$

$$I_{syn} = \bar{g}_{syn}\, S\,(V - V_{syn})$$

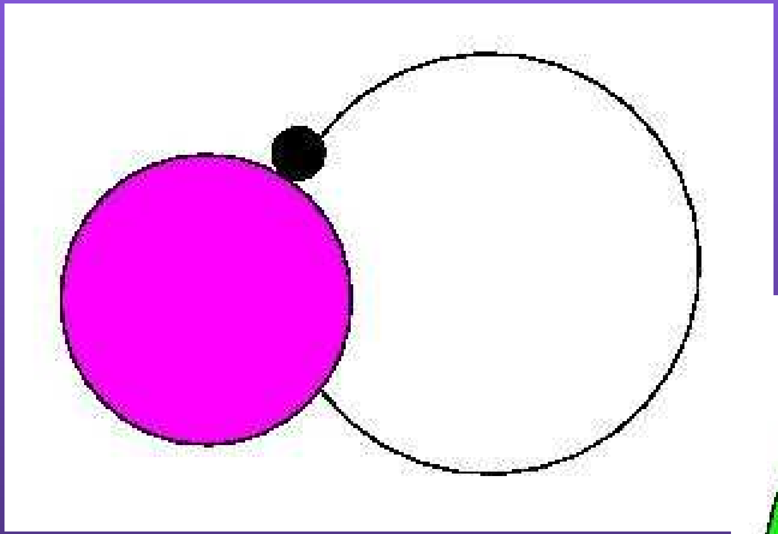
where

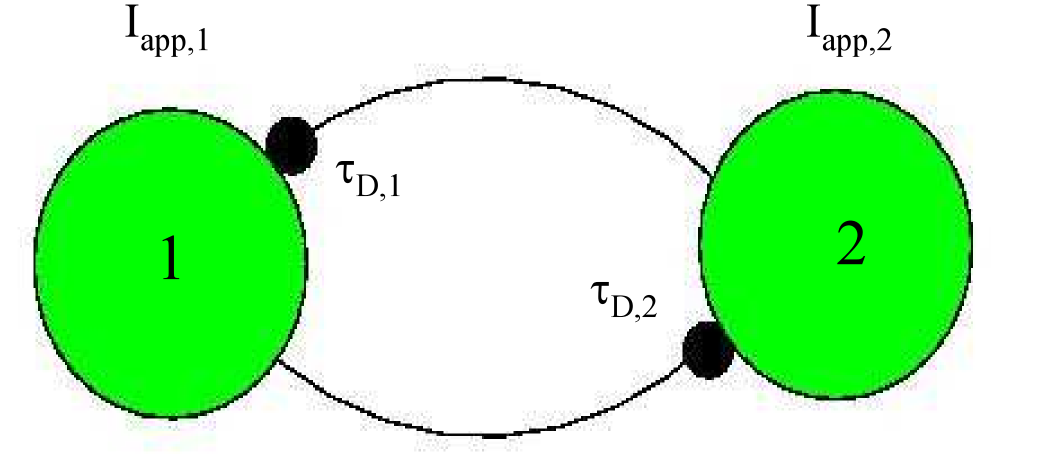
$$\frac{dS}{dt} = U_{SE}\, F(V_{pre})\, R - \frac{S}{\tau_S}$$

$$\frac{dR}{dt} = \frac{1 - S - R}{\tau_D} - U_{SE}\, F(V_{pre})\, R$$

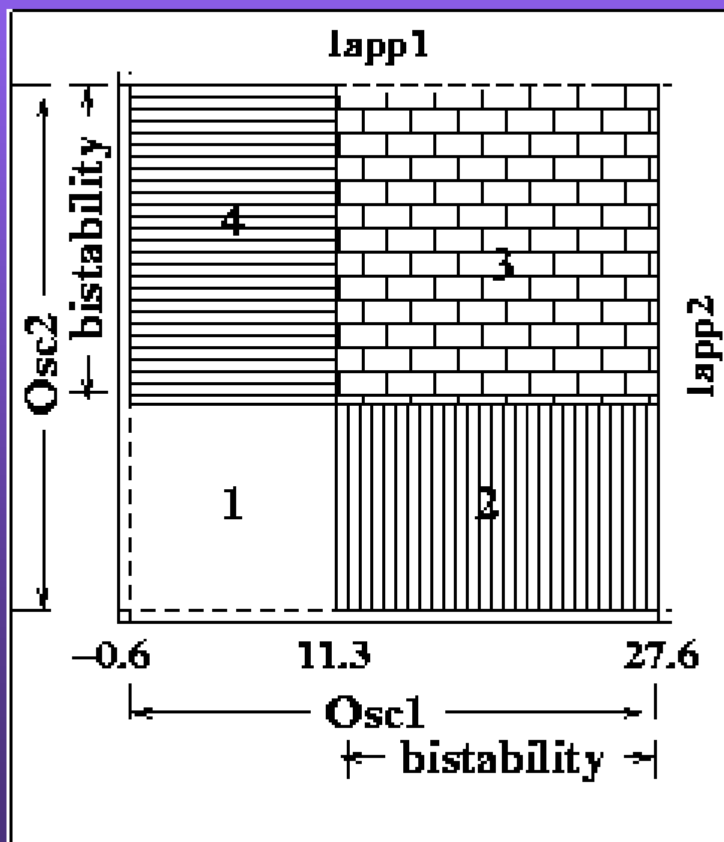
and

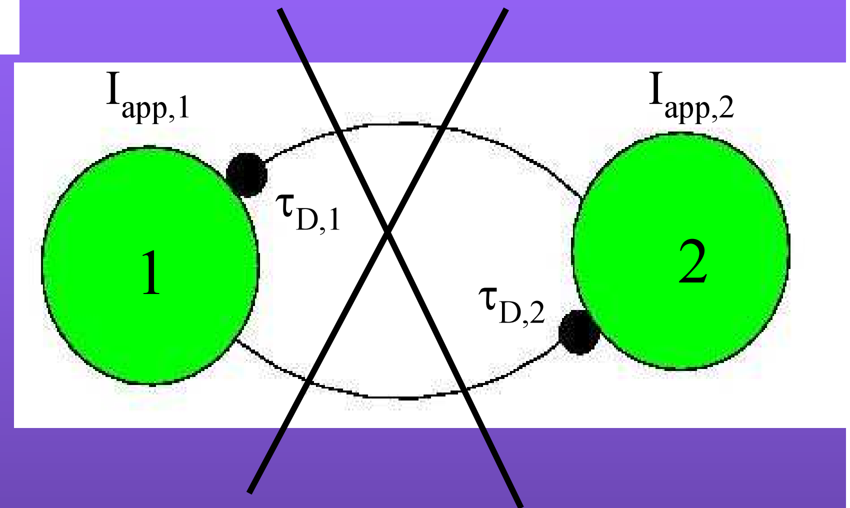
$$F(V_{pre}) = 1/(1 + \exp(-(V_{pre}))$$

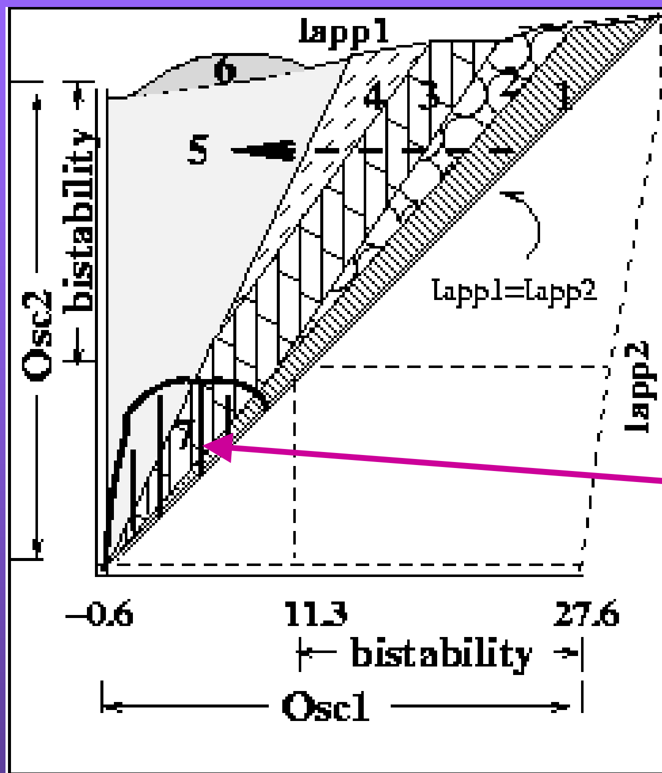


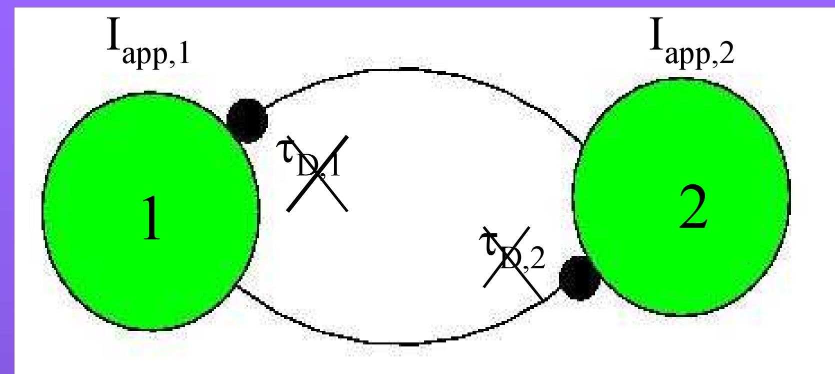


$$C\,\frac{dV}{dt} = I_{app} - [\,\bar{g}_{Na}\,m_\infty^3\,h\,(V - V_{Na}) + \bar{g}_K\,n^4 + \bar{g}_L\,(V - V_L) + I_{syn}\,]$$

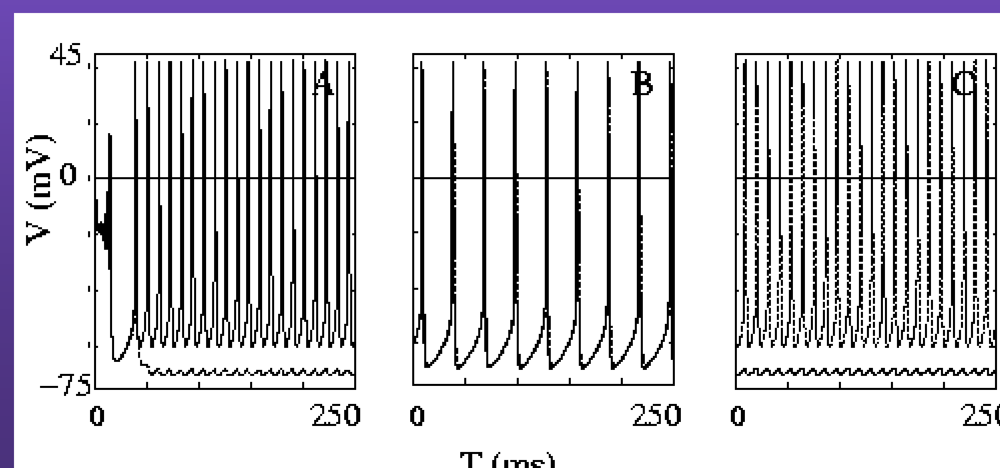


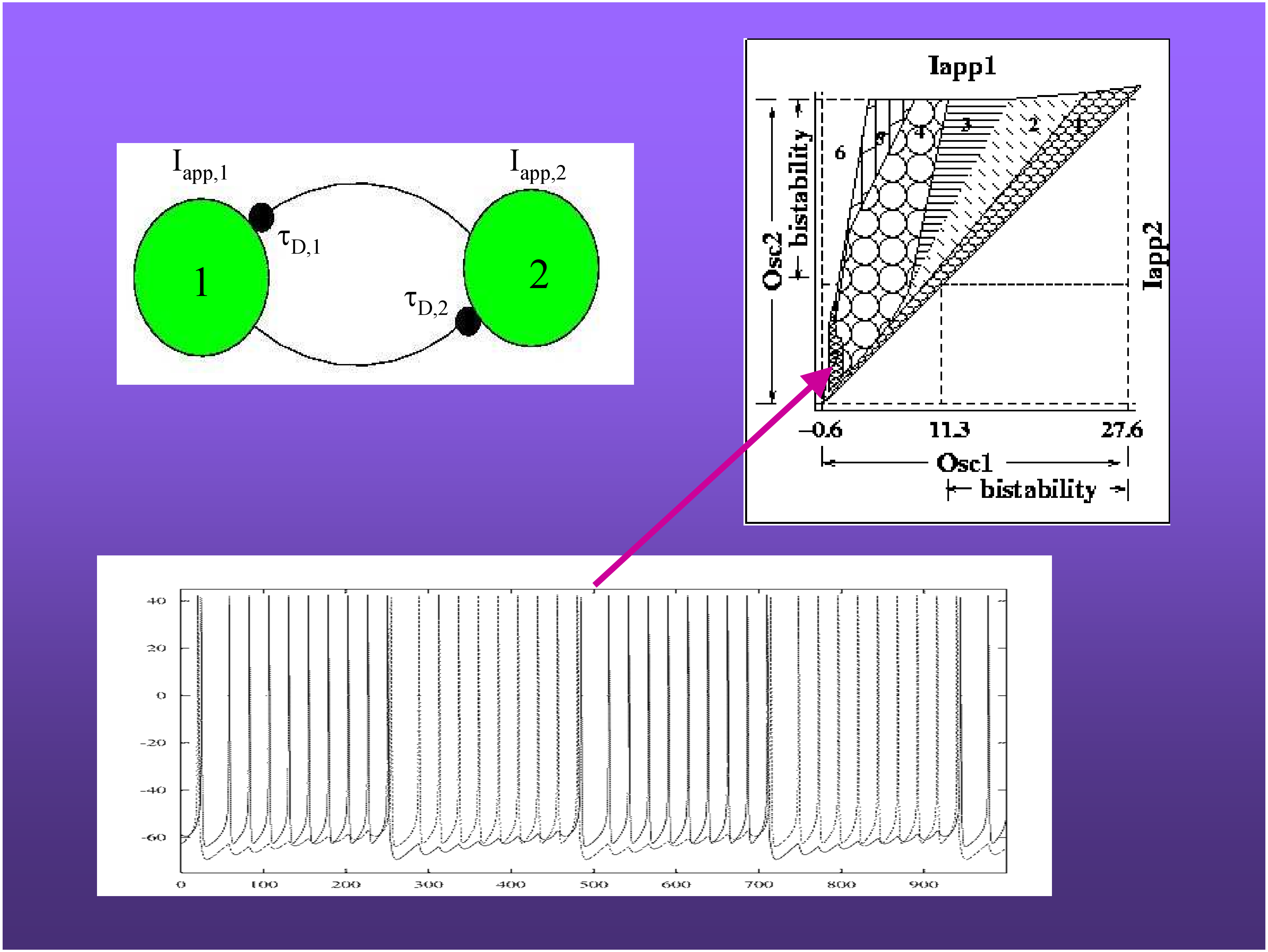






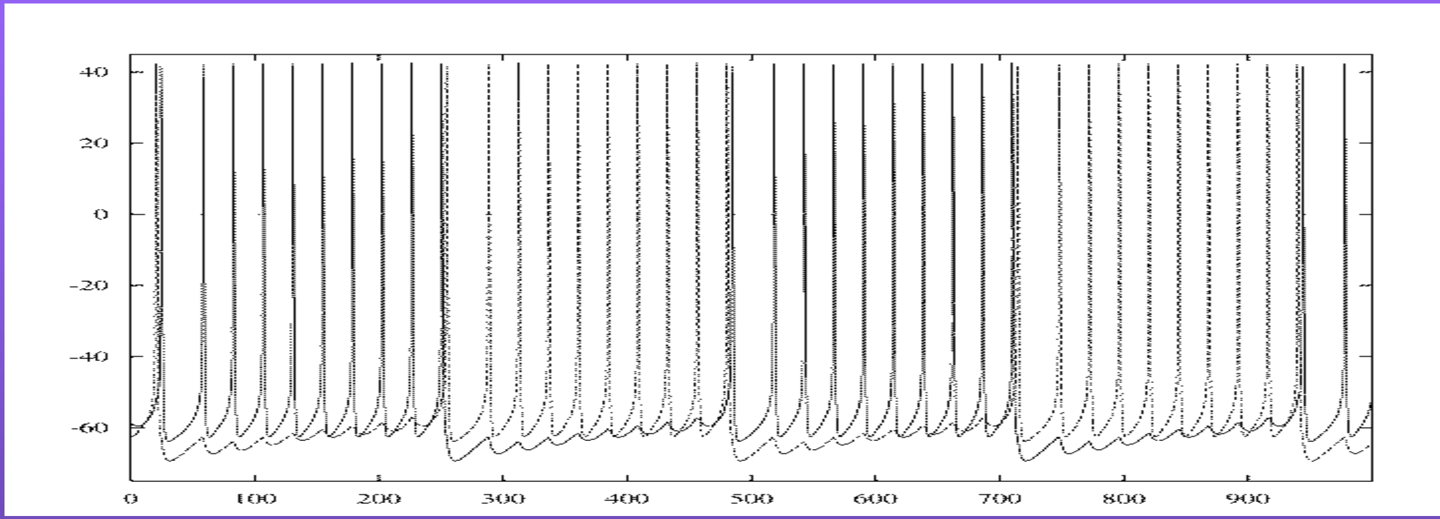
"Tristability"

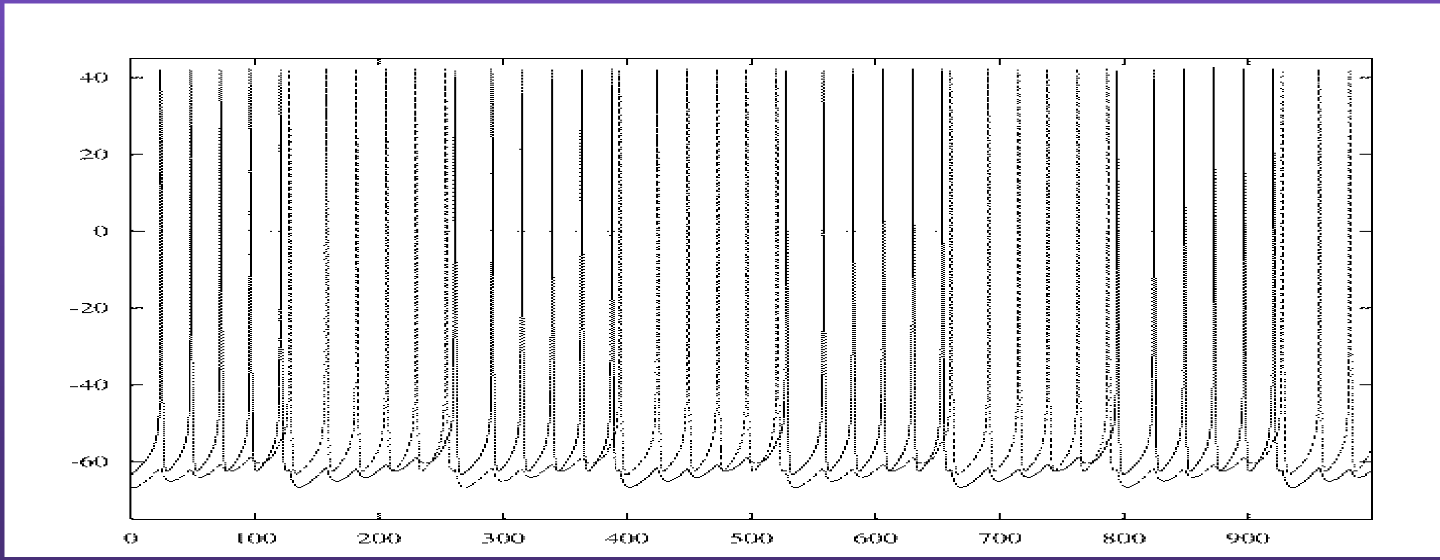



Iapp,1
Iapp,2
1
2
τD,1
τD,2
Iapp1
Iapp2
Osc2
bistability
6
5
4
3
2
1
–0.6
11.3
27.6
Osc1
bistability
40
20
0
-20
-40
-60
0
100
200
300
400
500
600
700
800
900

"Alternating Bursting Pattern"

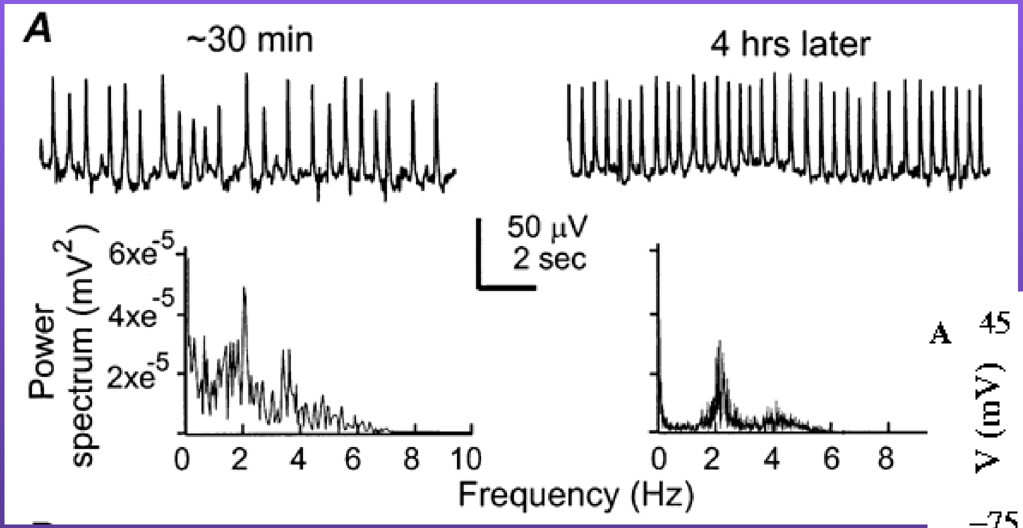
(increasing depression time constant, 300 to 400 msec)

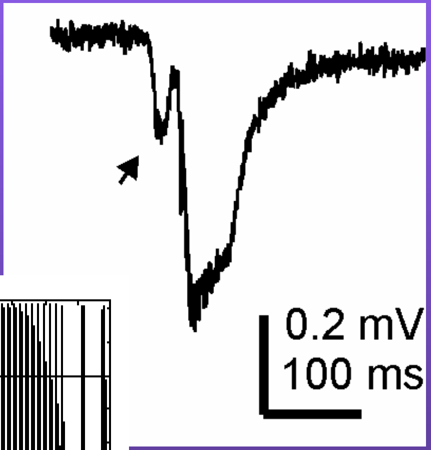


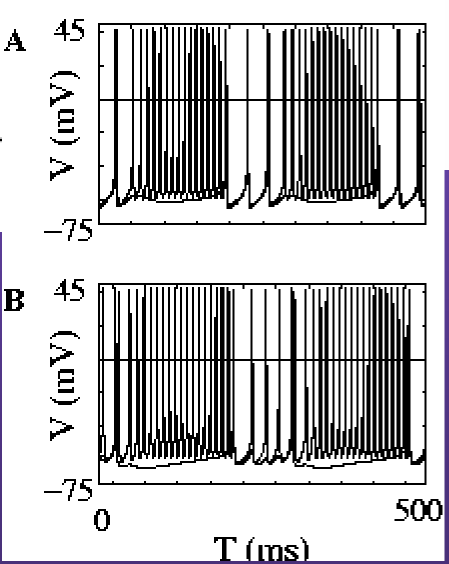


SRFP and relationship between SRFPs/SPWs :

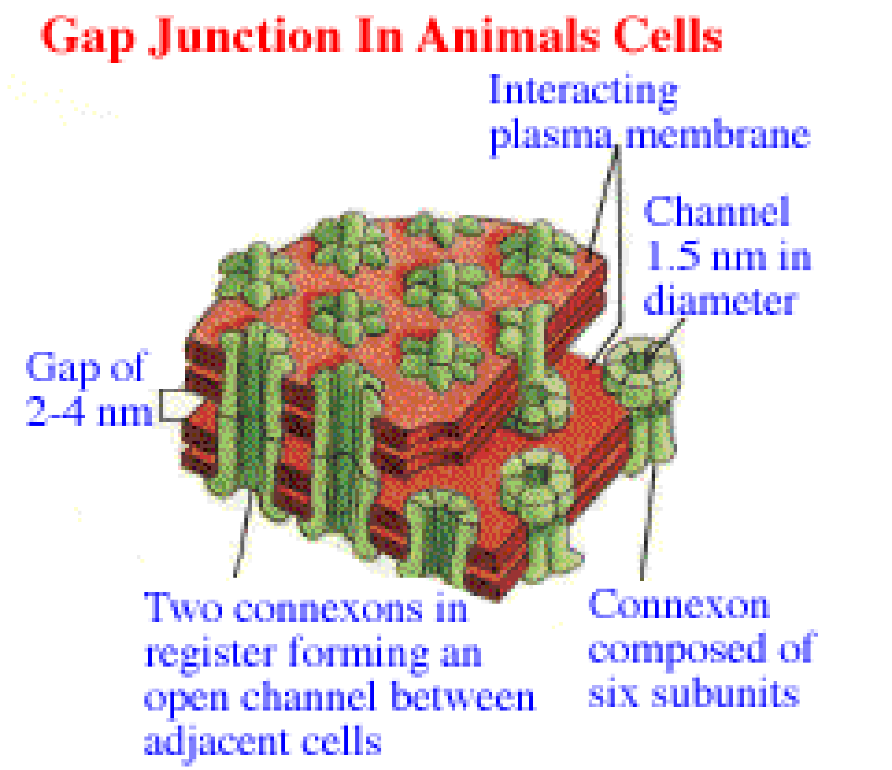
Speculation and Suggestions from Modelling Work

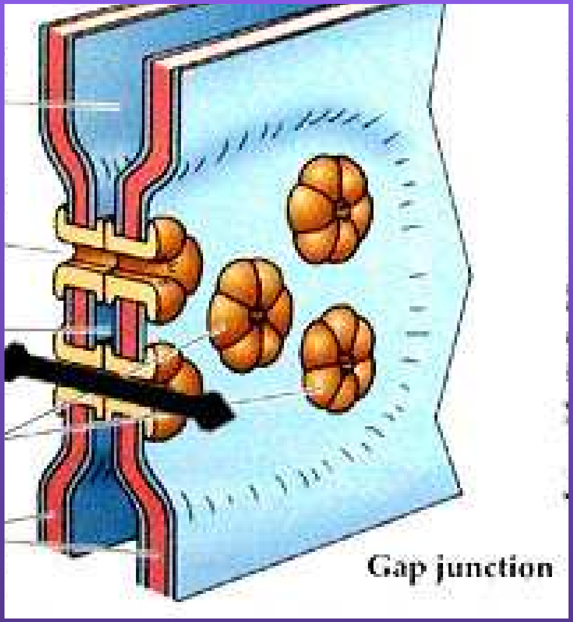






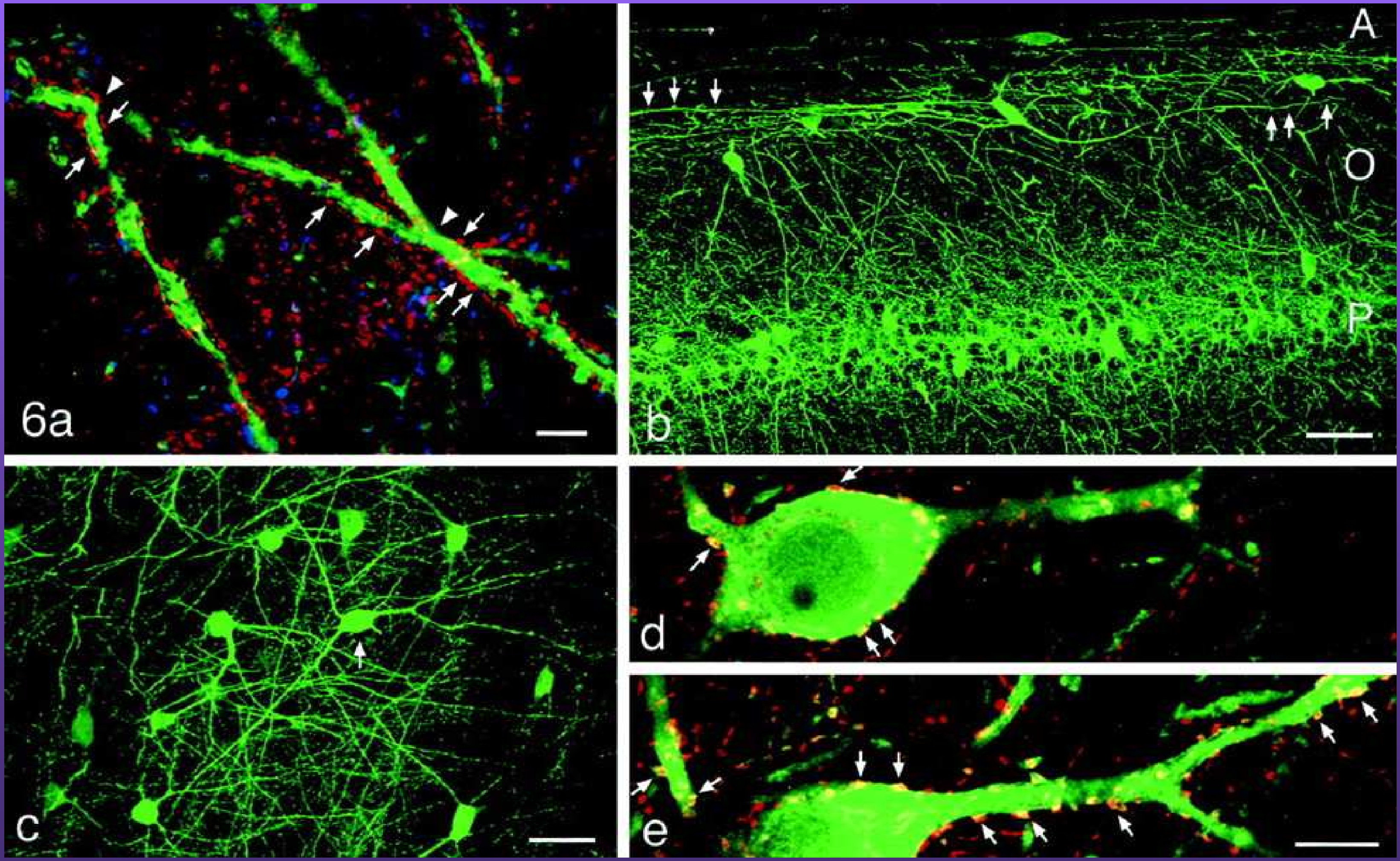
In addition to chemical inhibitory synapses, electrical connections or gap junctions (GJs) are also present between basket cell inhibitory networks



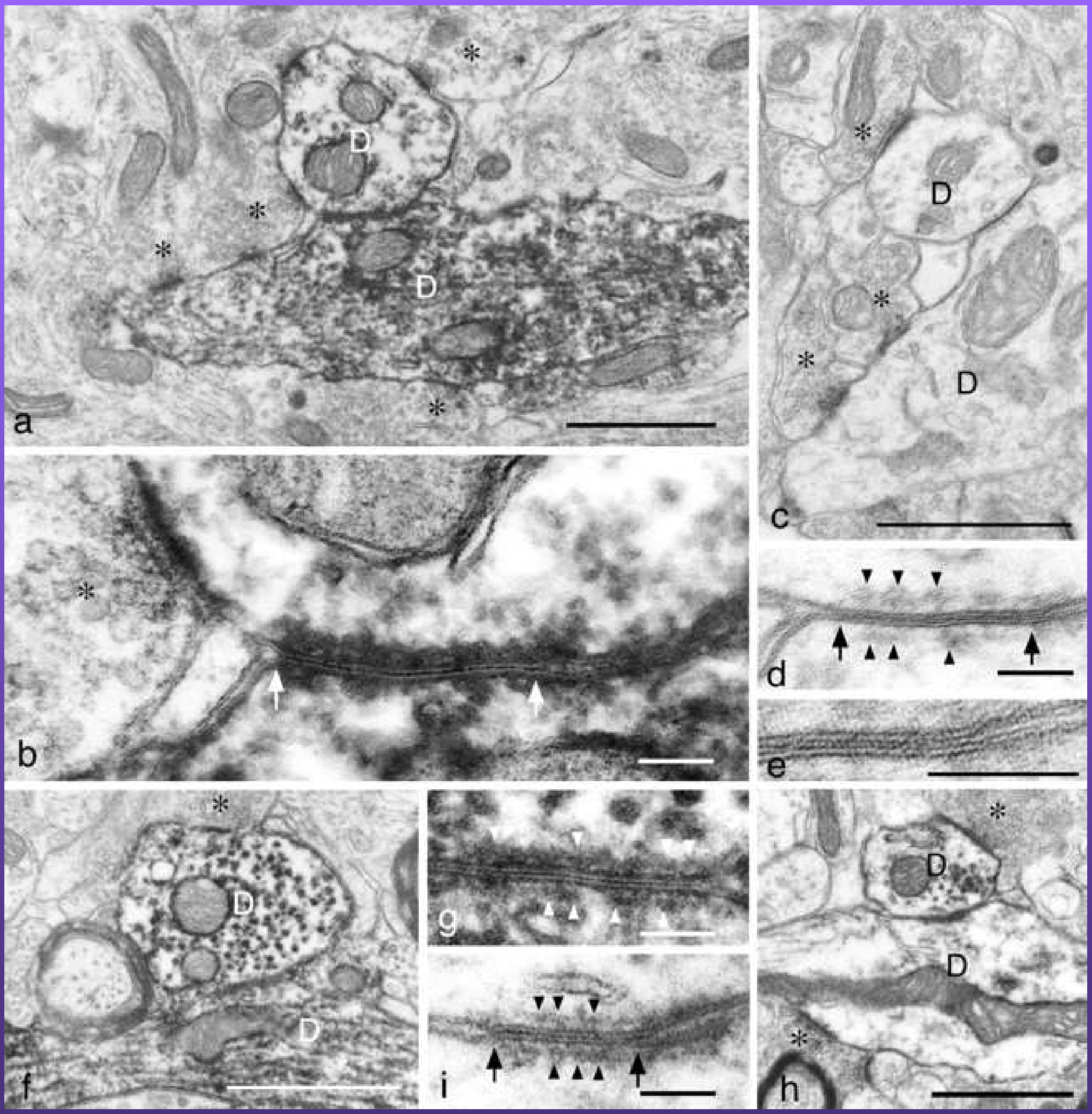


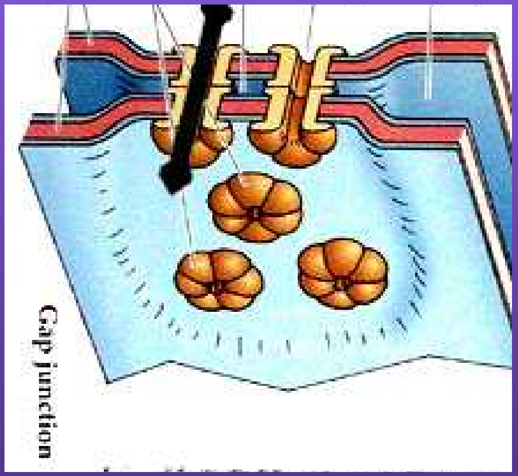
Hippocampal GABAergic neurons form dual networks connected by chemical (axosomatic) and electrical (dendrodendritic) synapses

Fukuda and Kosaka, J.Neurosci. 20:1519-1528, 2000

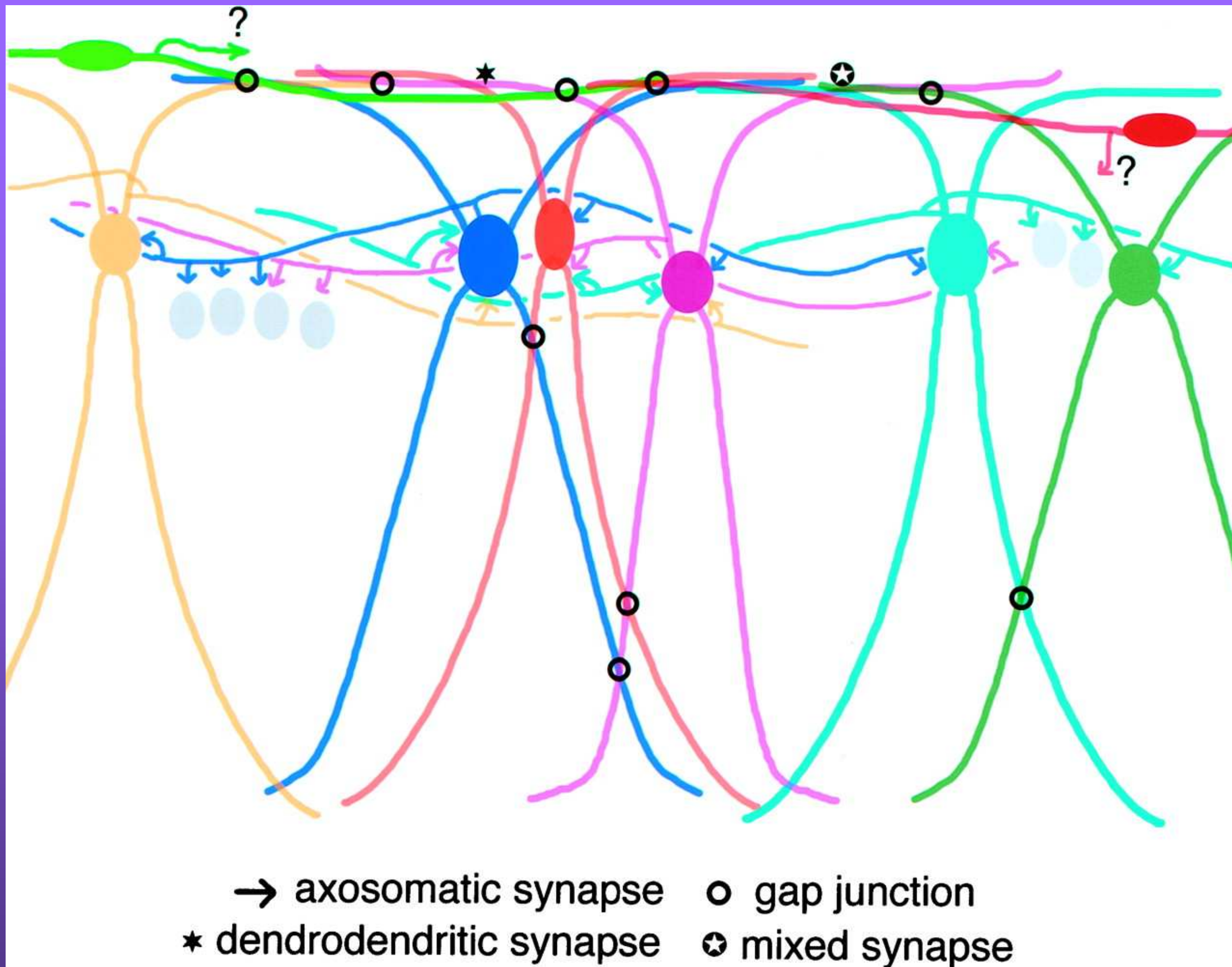


Dendrodendritic Gap Junctions





Fukuda and Kosaka, 2000



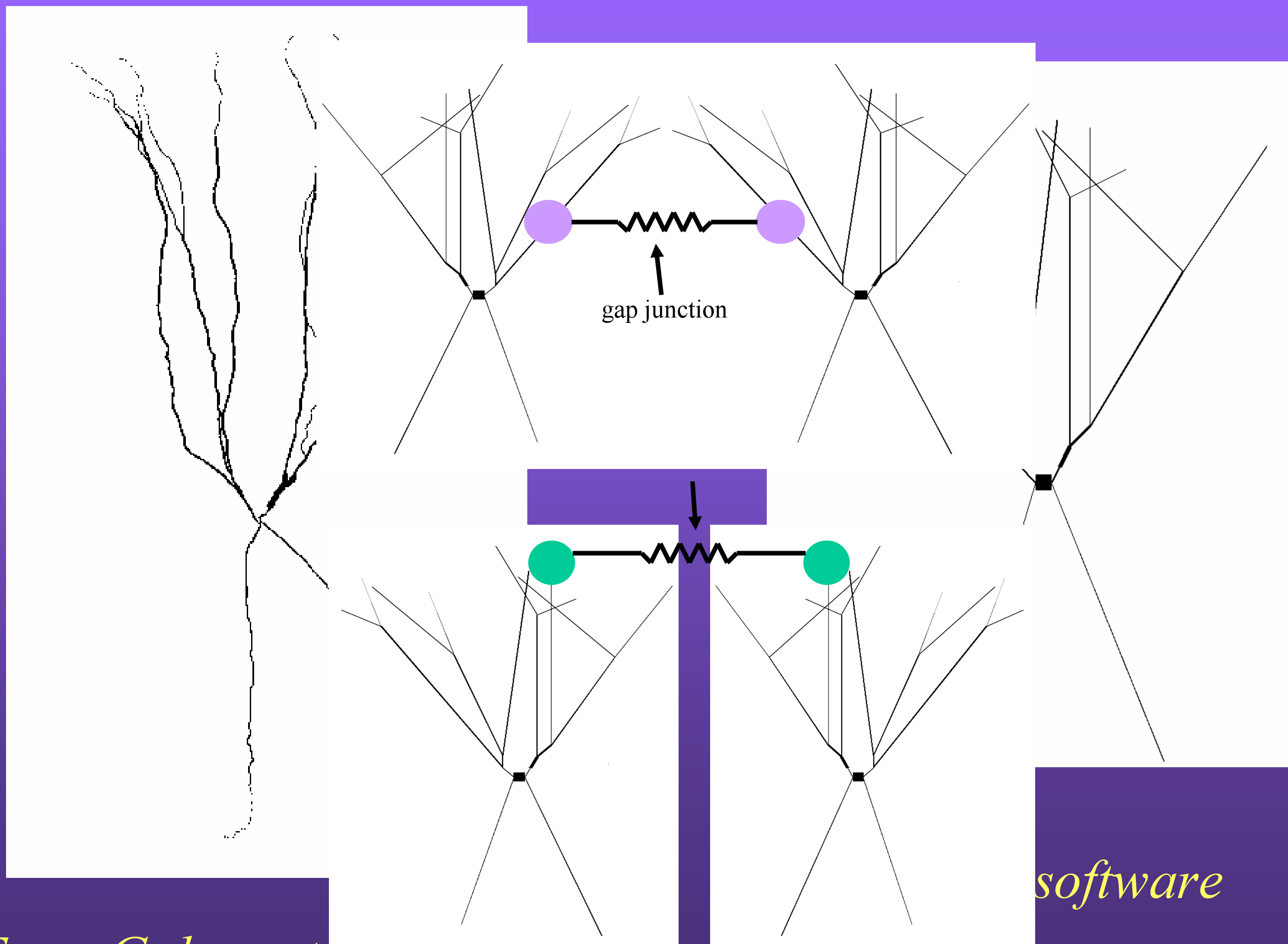
Fukuda and Kosaka, J.Neurosci. 20:1519-1528, 2000

Theoretical and modeling studies using simple neuronal caricatures clearly show that the effects of gap-junctional coupling are not straightforward.

Synchronous, anti-synchronous, phase-locked and bistable patterns can be produced in GJ-coupled networks depending not only on GJ strength, but also on details of the spike shape and frequency.

What parameter regimes are physiologically relevant?

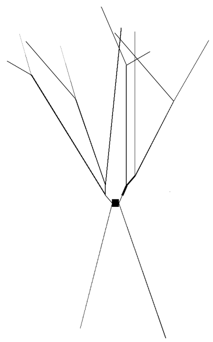
Multi-compartment representation of interneurons (basket cells)



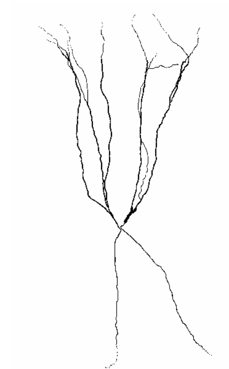
software

From Gulyas et al. 1999

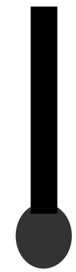
Ad-hoc Reduced Two-compartment Models



Multi-compartment Model Cell



CA1 Basket Cell



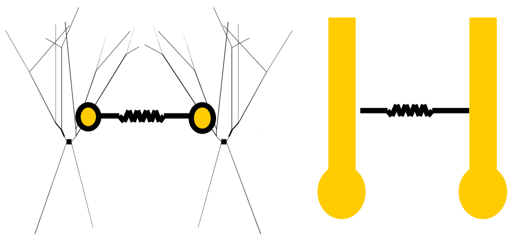
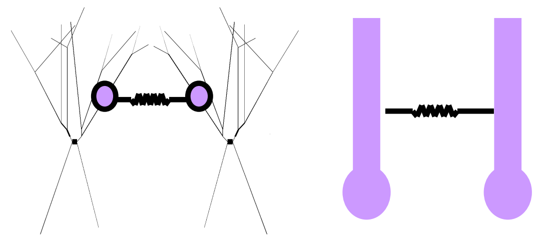
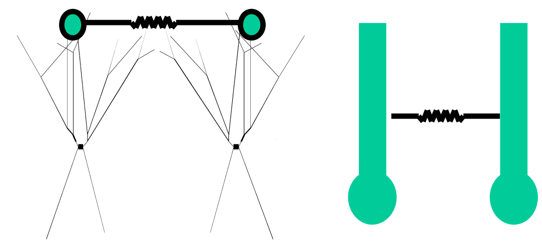
Reduced Two-compartment Model Cell

- A two-compartment model was constructed using the following equations:

$$C\frac{dV_S}{dt} = I_{app} - I_{Na} - I_K - I_L - g_{coup,D-S}(V_S - V_D)$$

$$C\frac{dV_D}{dt} = -I_L - g_{coup,S-D}(V_D - V_S) - I_{gap}$$

Two-cell Network Models

- Proximal Location

(~100 μm from soma)

- Middle Location

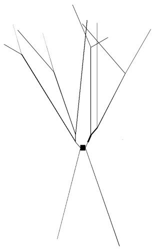
(~200 μm from soma)

- Distal Location

(~400 μm from soma)

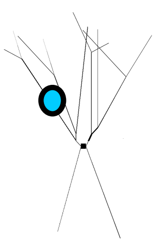
- Two-cell (homogeneous) networks of model cells coupled by GJs were constructed where the GJ current for cell *i*, I^i_{gap}, is given by $I^i_{gap} = g_{gap}(V^i_D - V^j_D)$ where $i \neq j$.
- Two-cell networks of the reduced model cells correspond to GJs being located at the selected sites in the full multi-compartment model.

Protocol

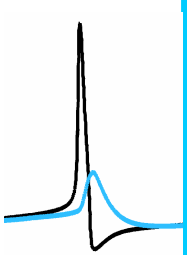


Create multi-compartment model.

Create two-compartment model such that the passive properties are the same as in the multi-compartment model.

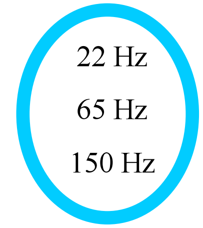


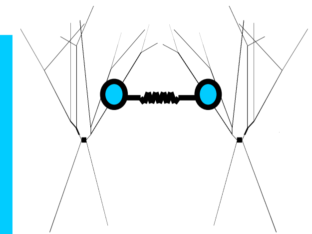
Choose a GJ location in multi-compartment model.

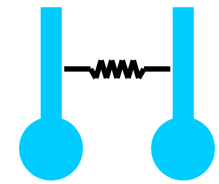


Choose $g_{coup.}$ values for two-compartment model such that the dendritic spike amplitudes are the same in both models.

Choose an intrinsic frequency



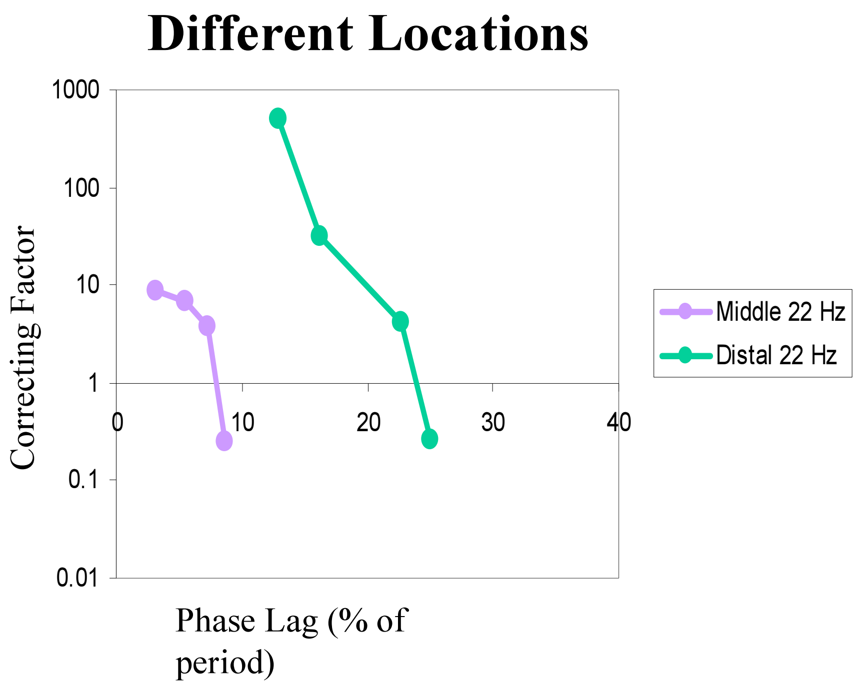


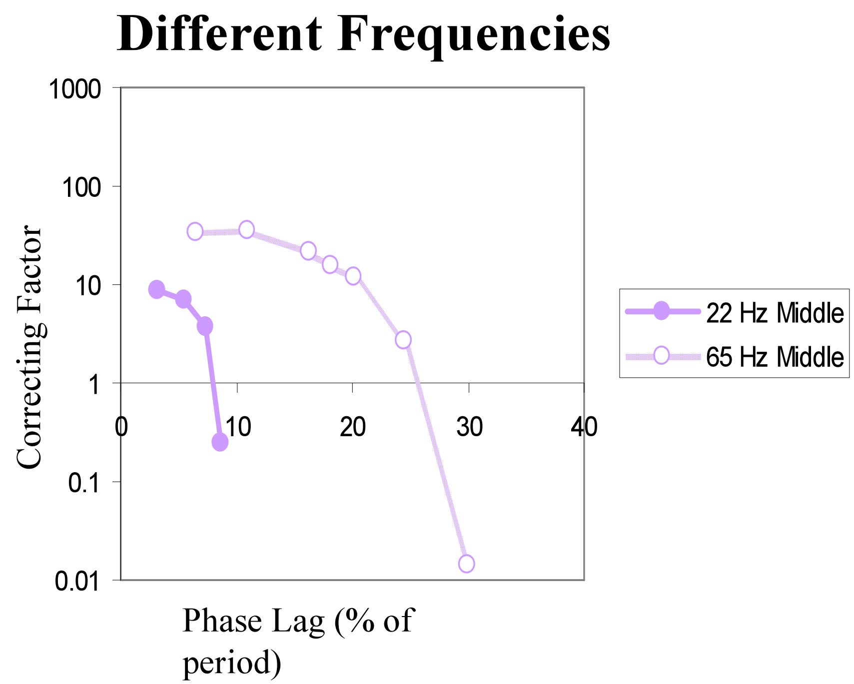


Build two-cell networks and perform simulations for a range of g_{gap} values in both models.

Compare phase-locked patterns in both models and quantify GJ conductances in two-compartment model.

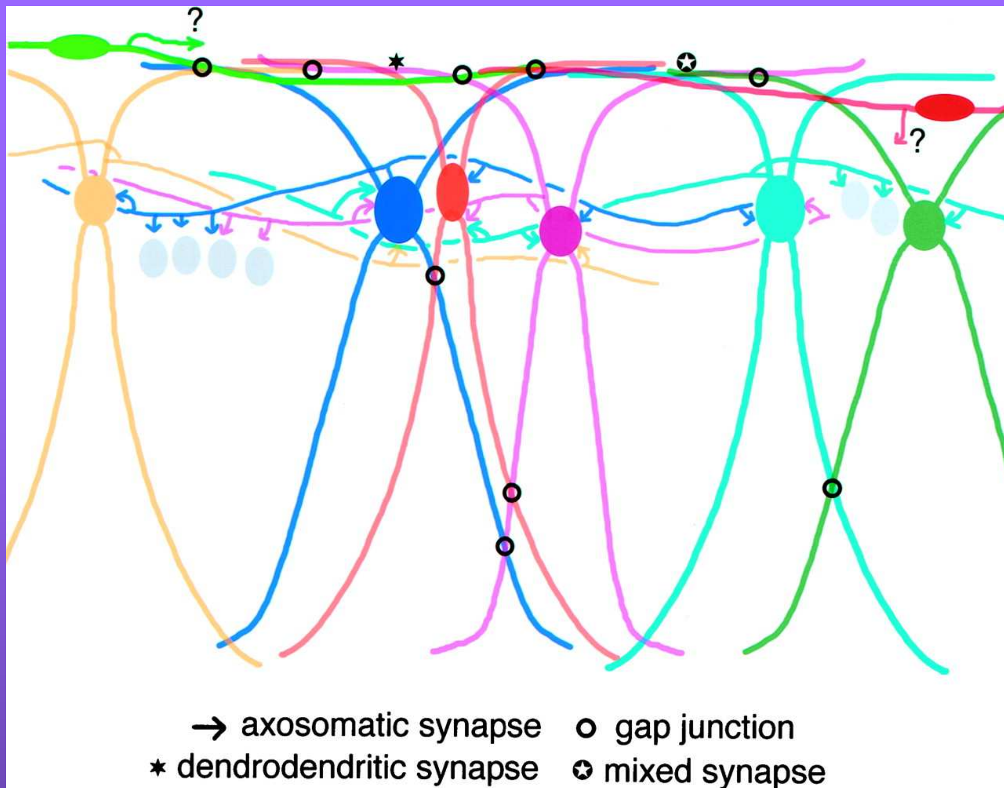
Quantifying GJ Conductances

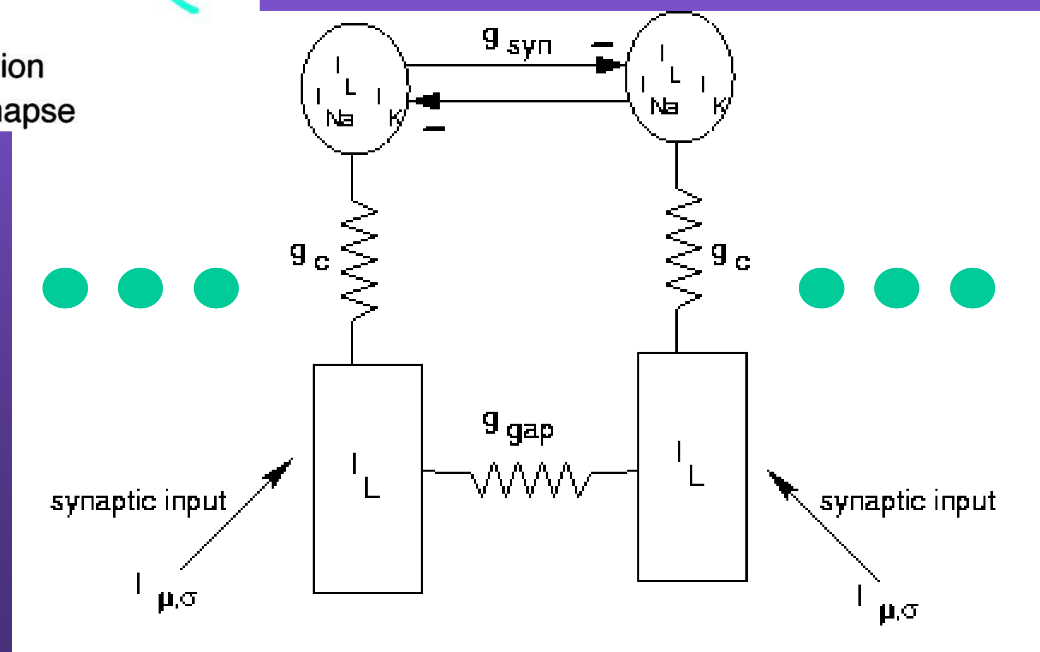




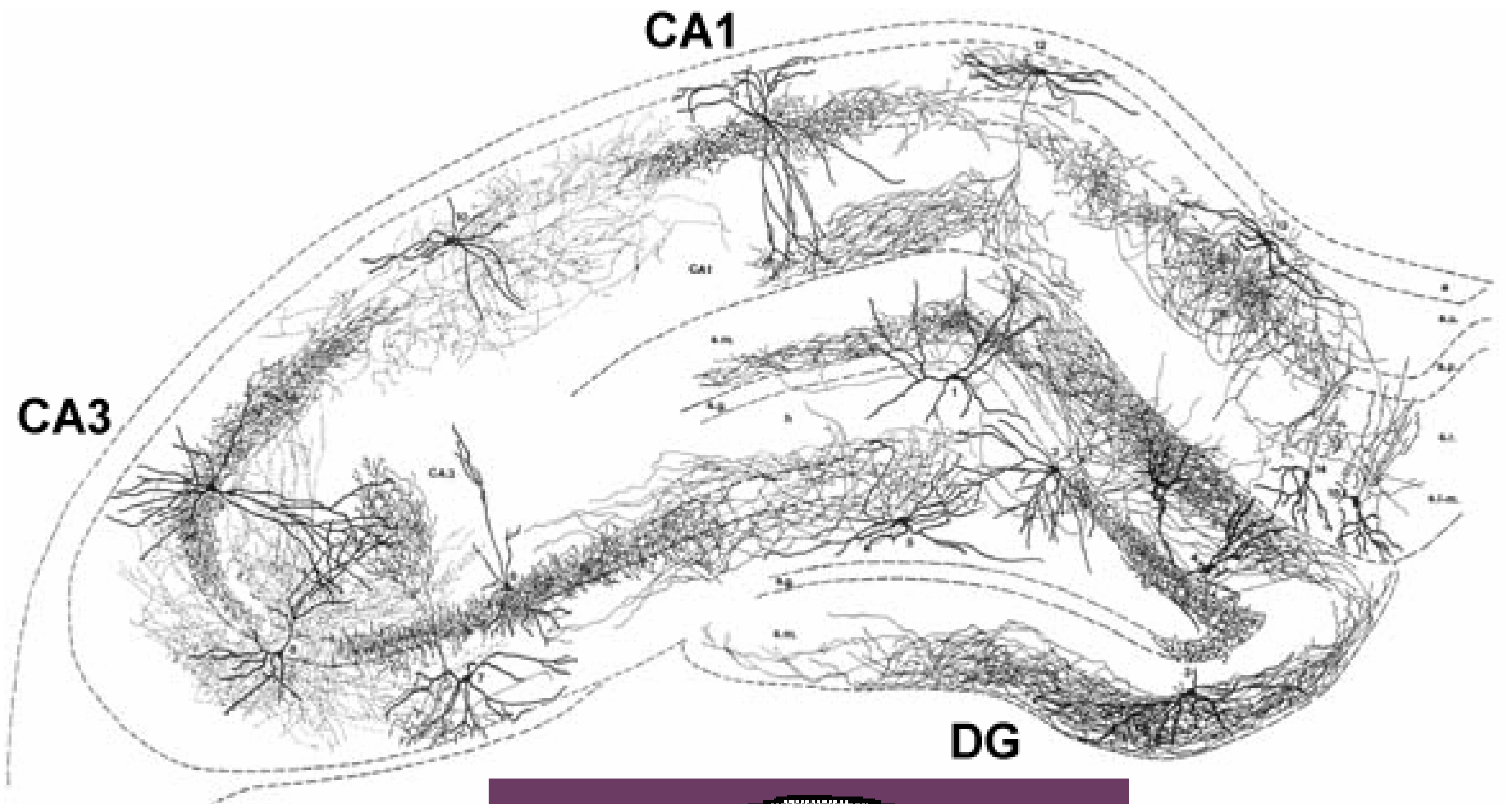
- For lower intrinsic frequencies and more proximal locations, GJ conductance values in the two-compartment models more closely approximate those in the multi-compartment model. The above plots indicate the appropriate correcting factor that needs to be applied.

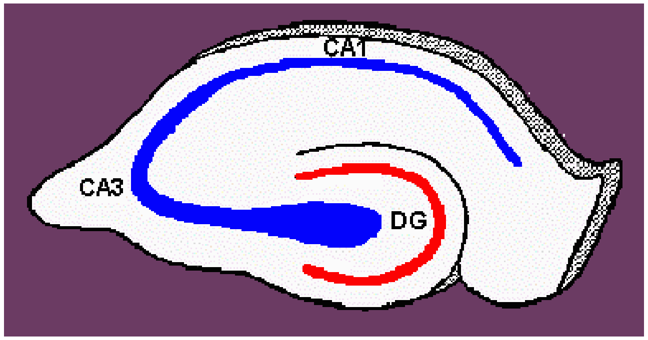
- In general, when physiological GJ conductances are in the 10 – 100 pS range, GJ conductances in the two-compartment models are appropriate.


?
?
→ axosomatic synapse
○ gap junction
✶ dendrodendritic synapse
✪ mixed synapse

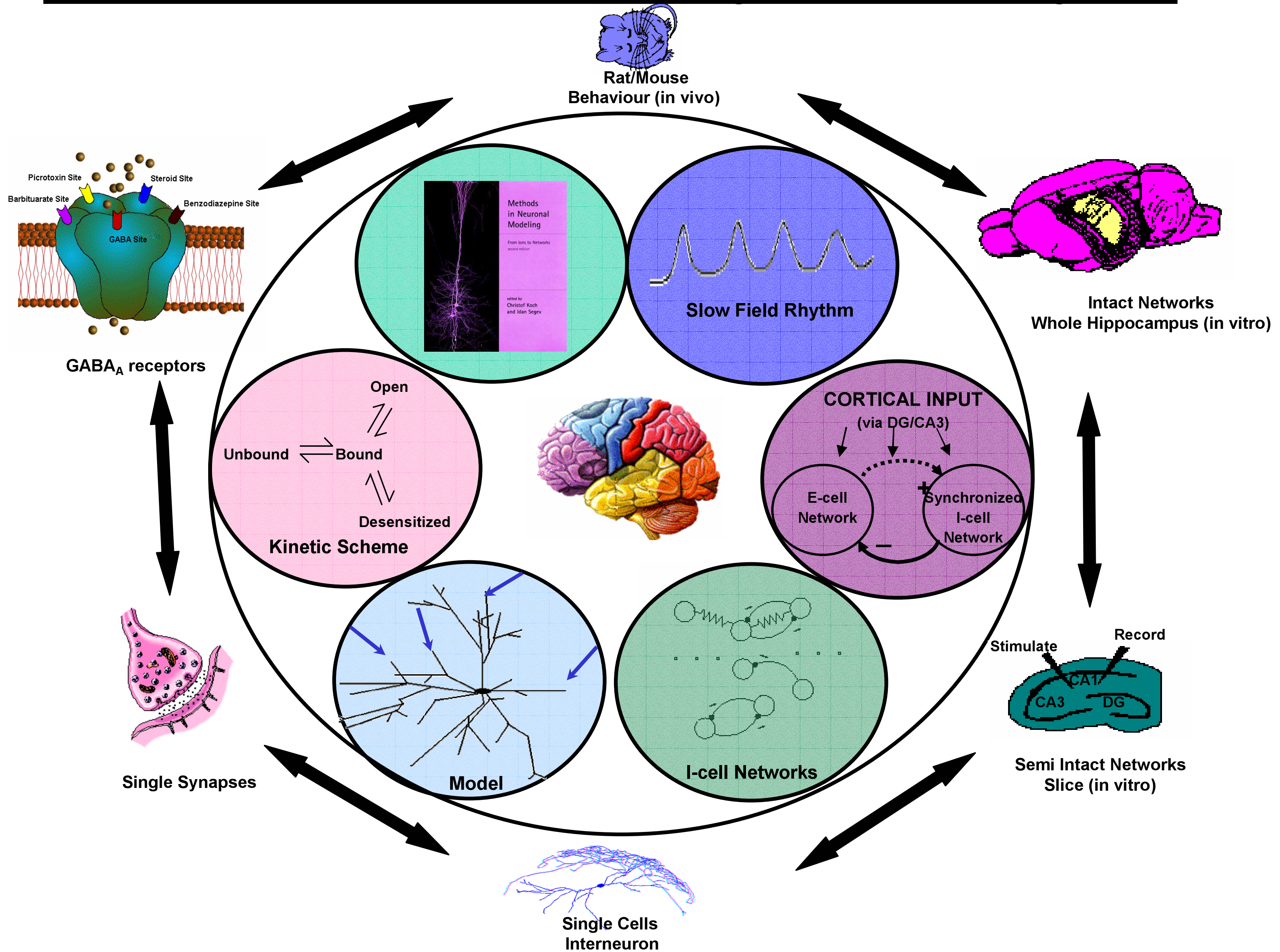

g syn
I L
I Na
I K
g c
g c
g gap
I L
I L
synaptic input
synaptic input
I μ,σ
I μ,σ

"Cellular-based network models"

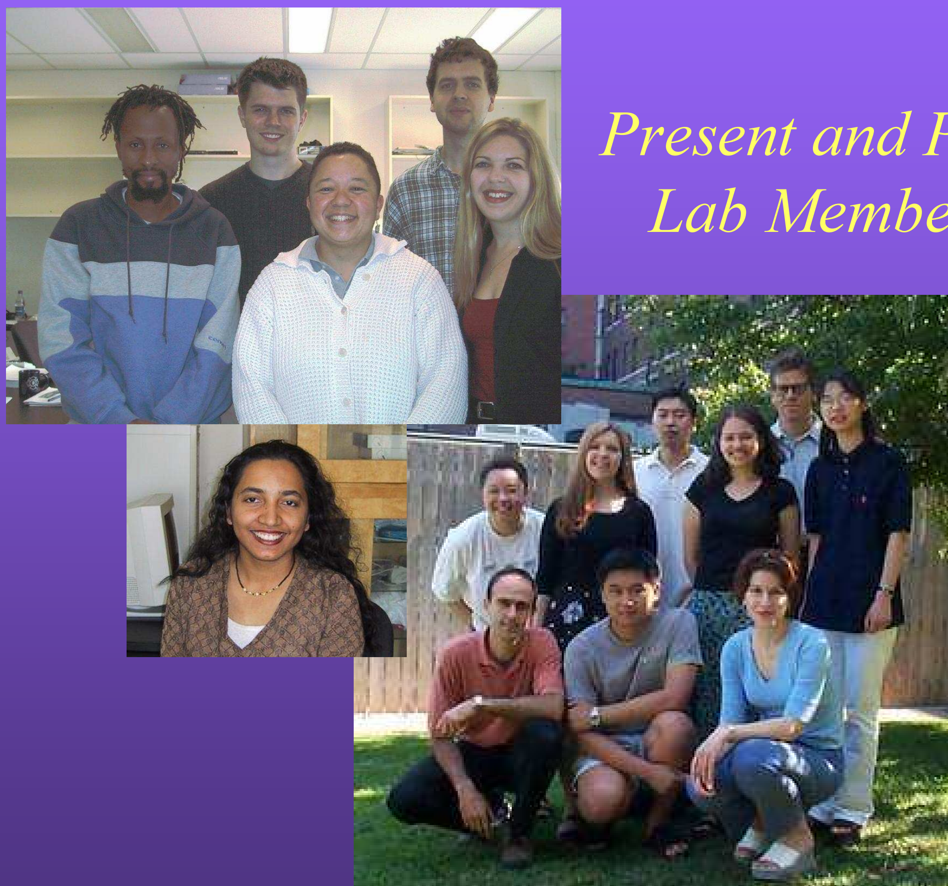




"Computational Road Maps to Dynamic Phenotypes"



Acknowledgements



Present and Past Lab Members

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