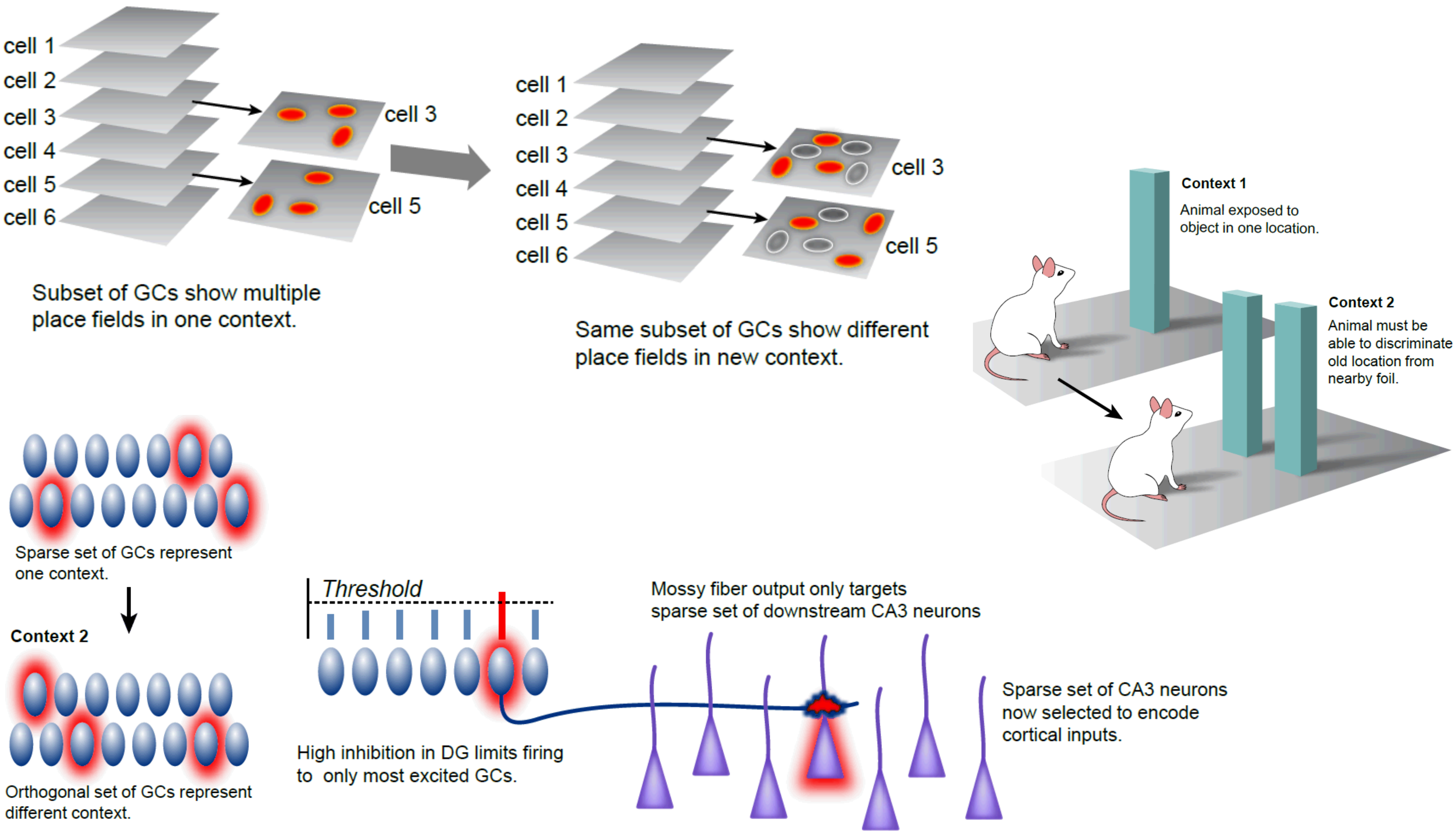
SAND2013-4112P

Large scale modeling of neurogenesis

Why it is more interesting and harder than it looks…

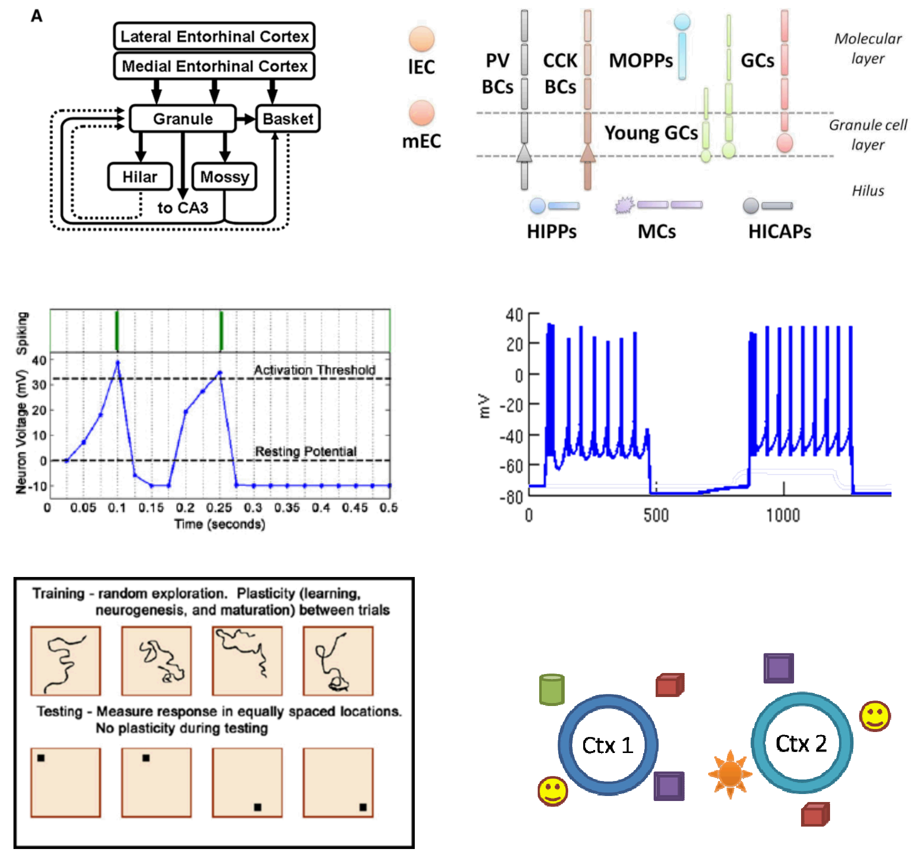
Brad Aimone

What is pattern separation?



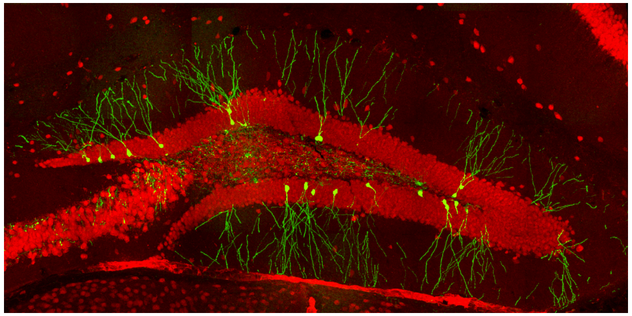
Limitations of past modeling work

- Between abstract and high fidelity
  - Time not particularly well represented
  - Details of DG architecture lost (e.g., feed-forward inhibition, modulatory inputs)
  - Experiment doesn't map to behavior

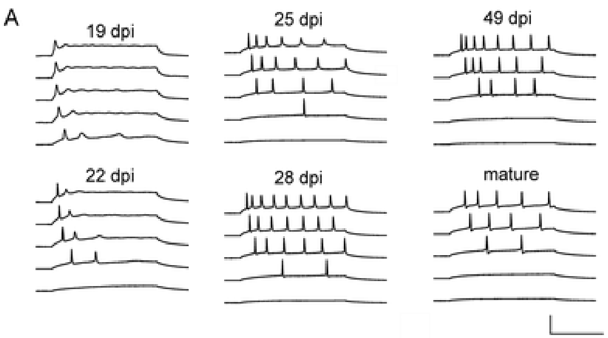


Aimone et al., Neuron 2009

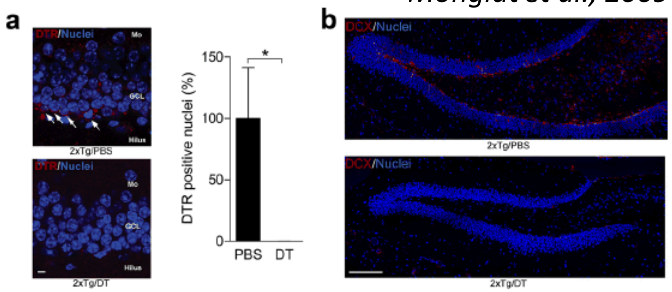
Modeling considerations



courtesy Chunmei Zhao



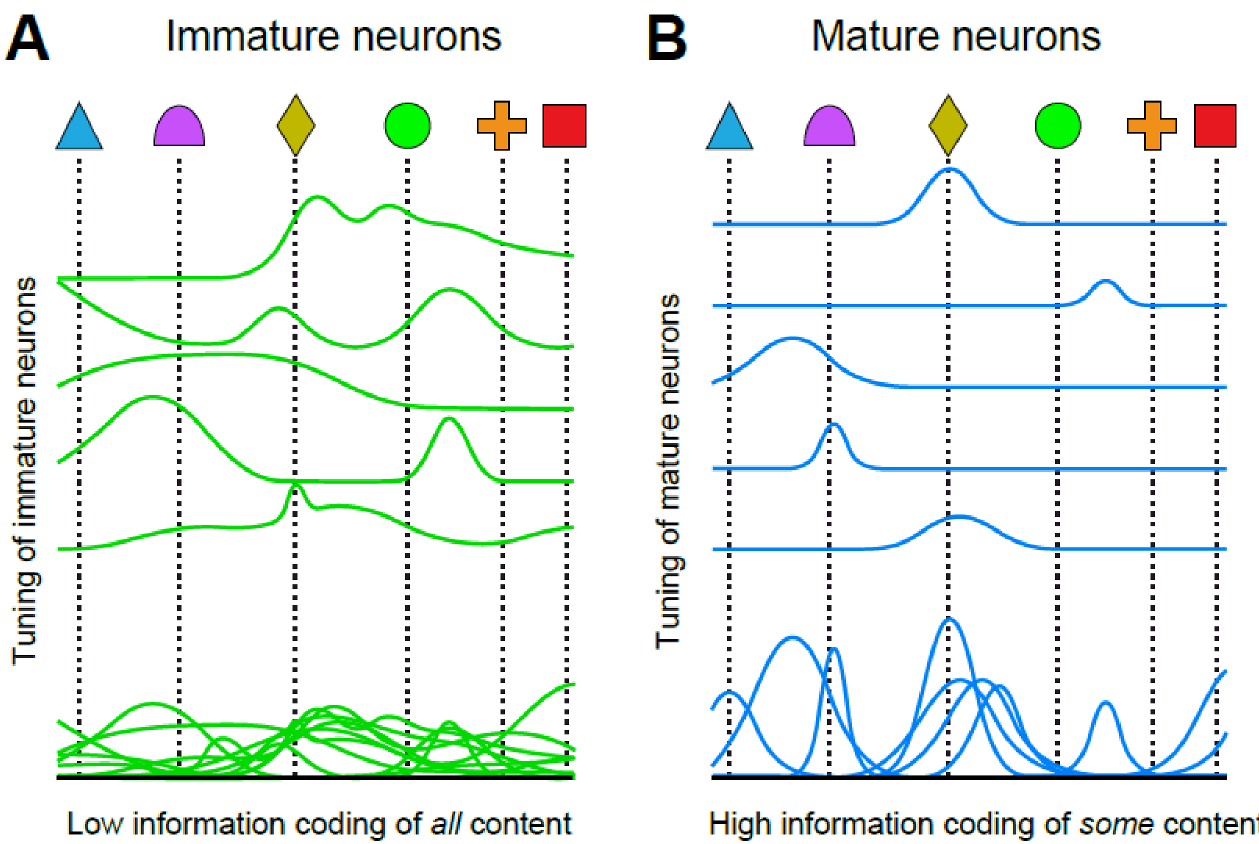
Mongiat et al., 2009



Arruda-Carvalho et al., 2011

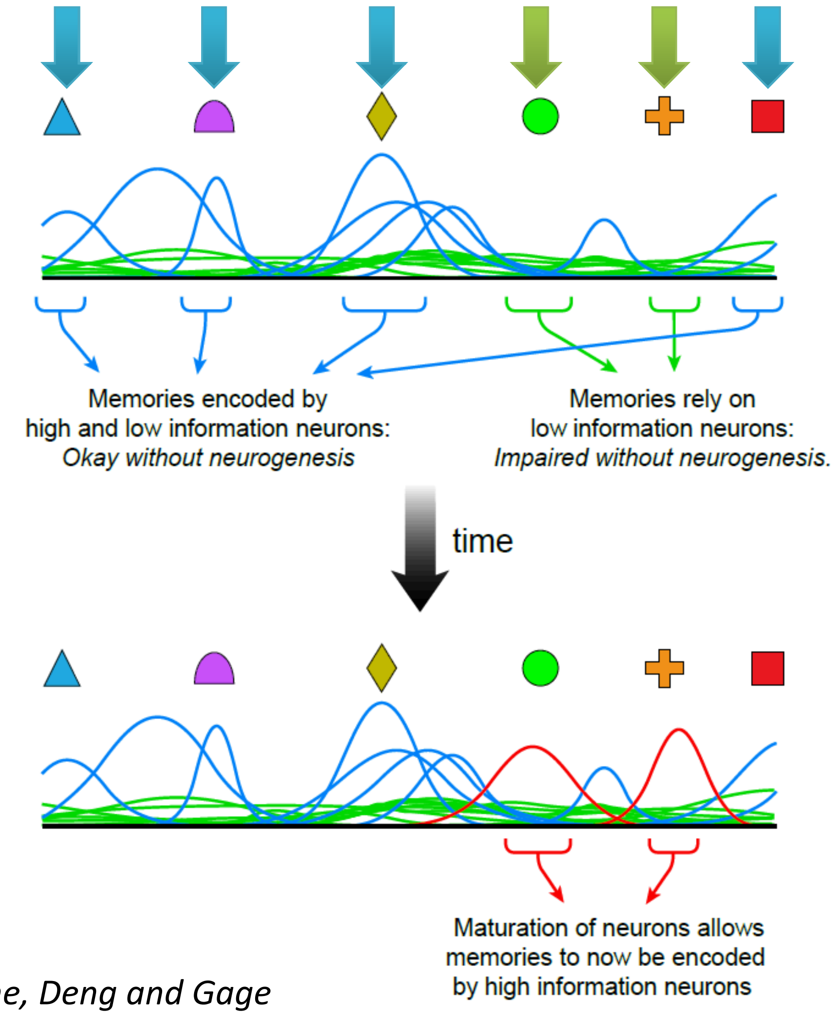
- Neuroanatomy
  - Circuit (principal neurons, interneurons, and how they are connected)
  - Maturation of new neurons
- Dynamics
  - Every neuron has unique dynamics
  - Neurogenesis results in many different forms of GC dynamics
- Behavior
  - *In vivo* and immediate early gene studies of neuron behavior
  - Behavior studies in lesion or knockdown animals

Immature and mature neurons encode information differently



Aimone, Deng and Gage
Neuron; 2011

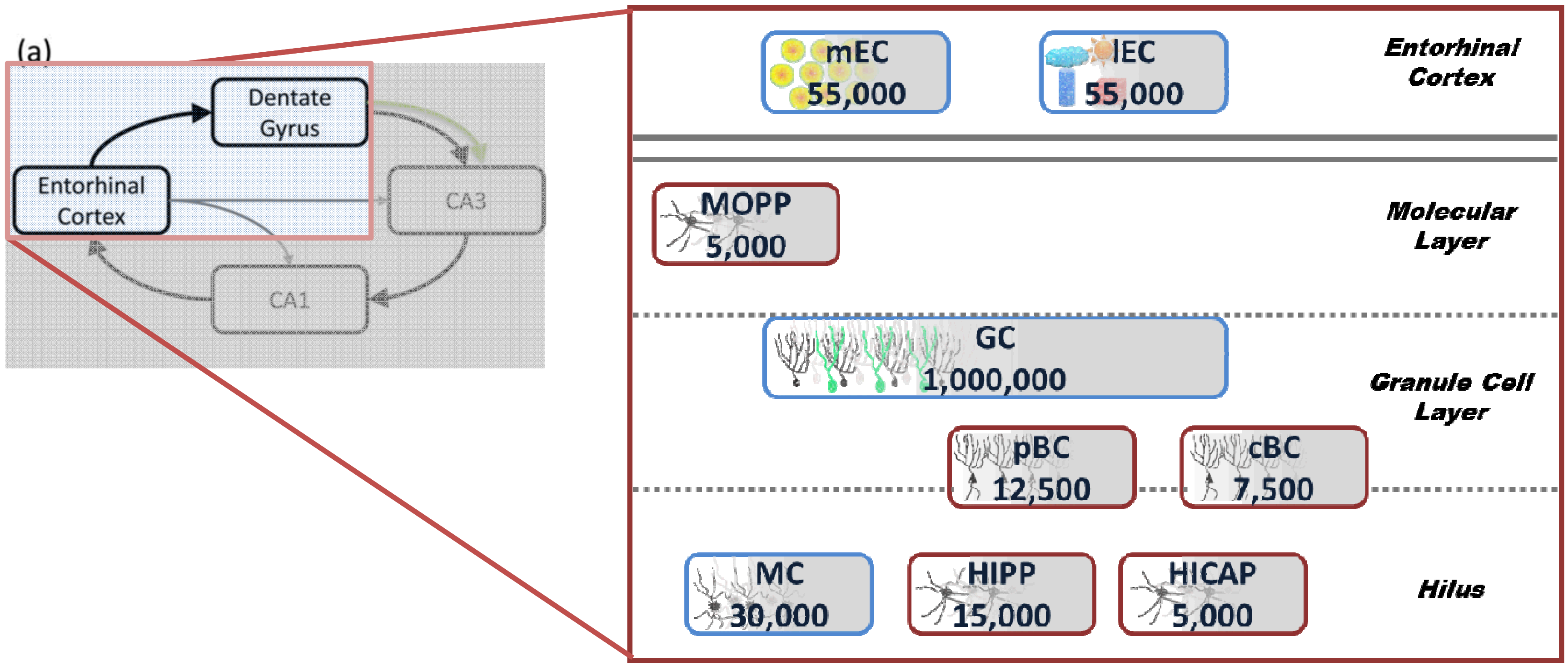
Mixed coding scheme in DG is potentially very powerful



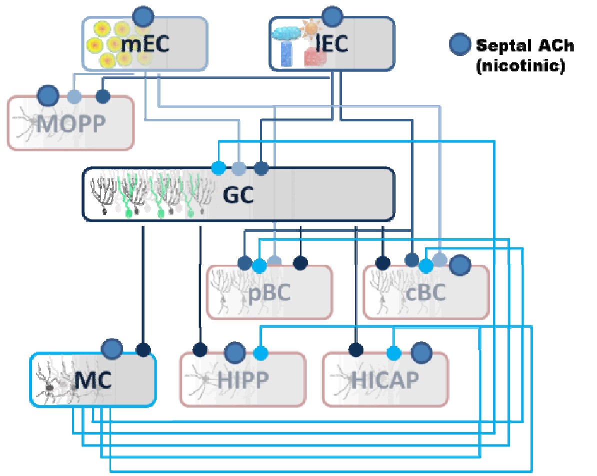
Aimone, Deng and Gage
Neuron; 2011

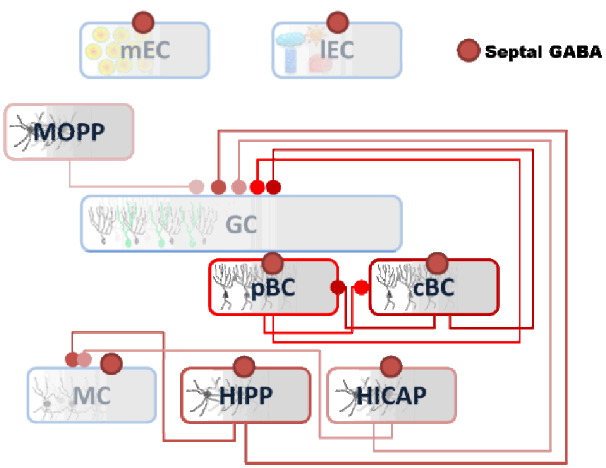
- Dentate Gyrus performs sparse coding for episodic memories
- Mature neurons are tightly tuned to specific features
  - *Not all events will activate mature neurons*
- Immature neurons are broadly tuned
  - *All events will activate some immature neurons*
- Neurons mature to be specialized to those events later
  - *Coding range of network gets more sophisticated over time*

Realistic scale model

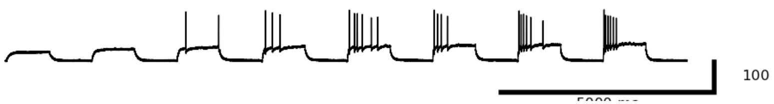


Realistic connectivity and dynamics

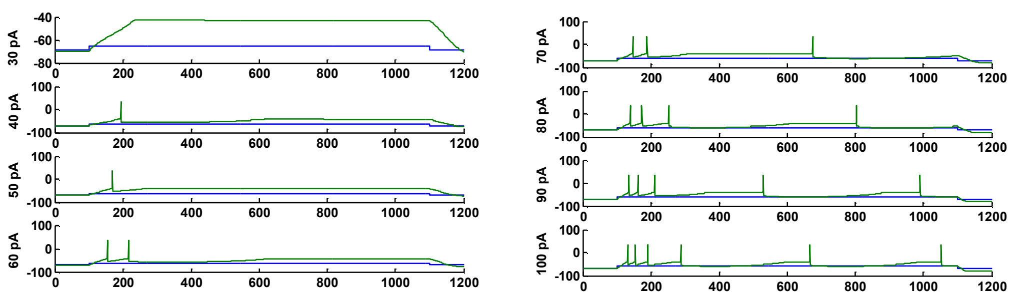




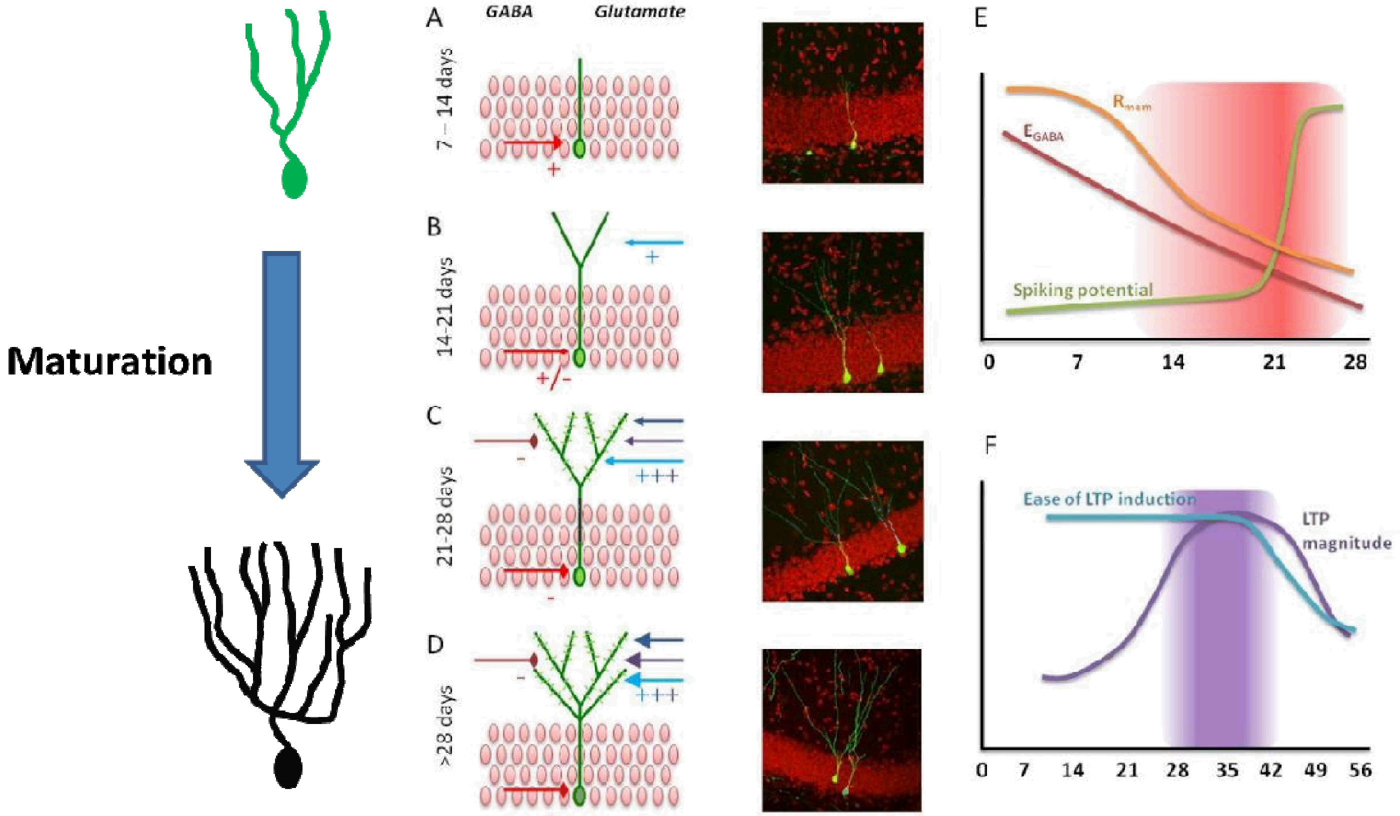
Physiology data



Modeled neuronal dynamics

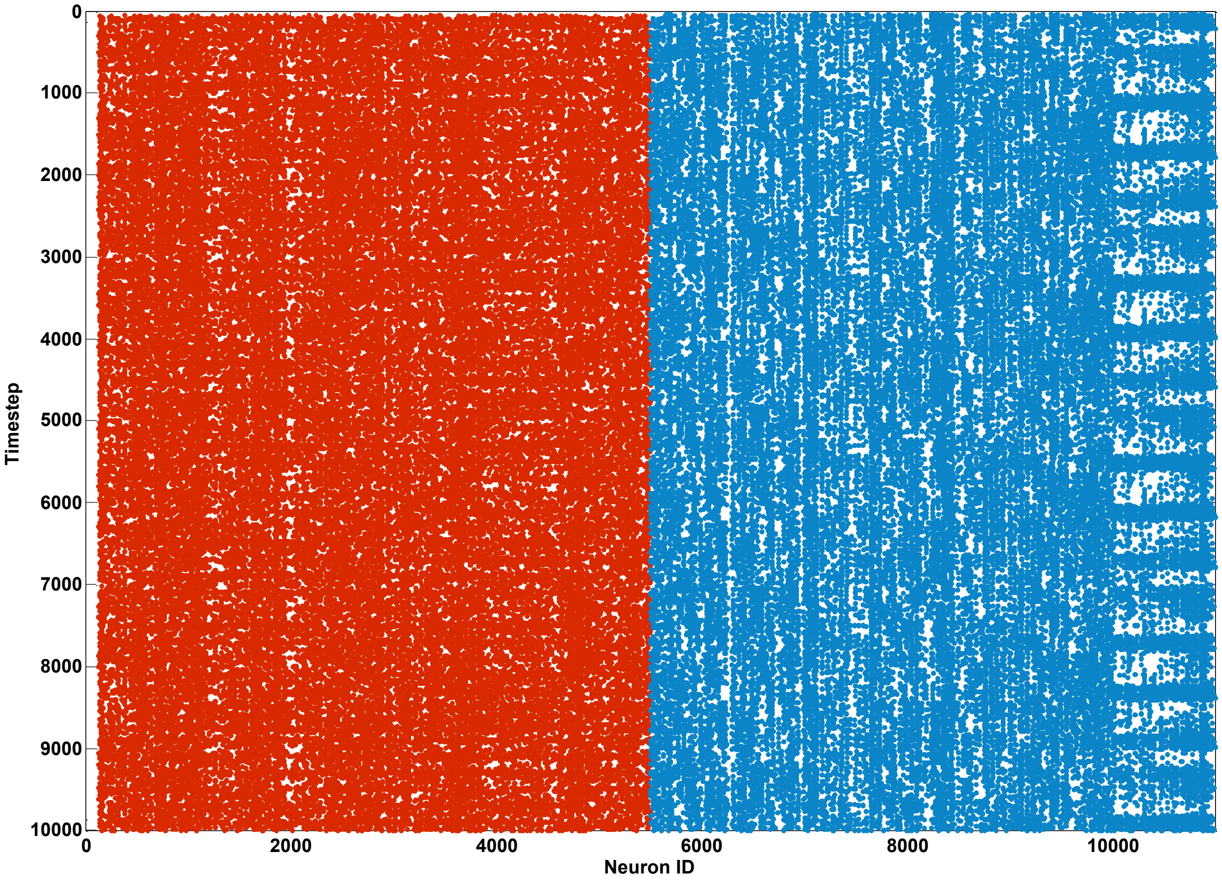


Neurogenesis Process

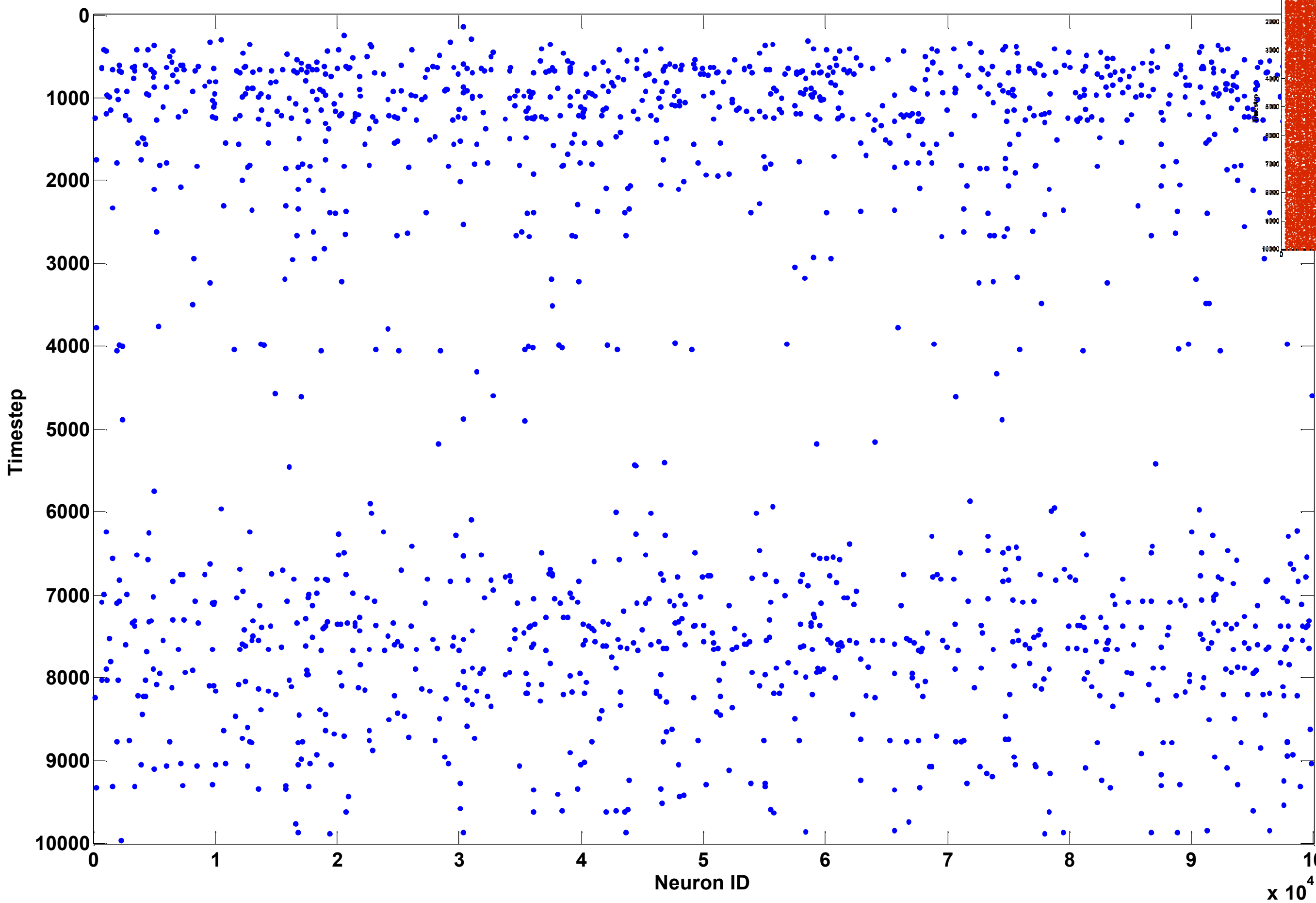


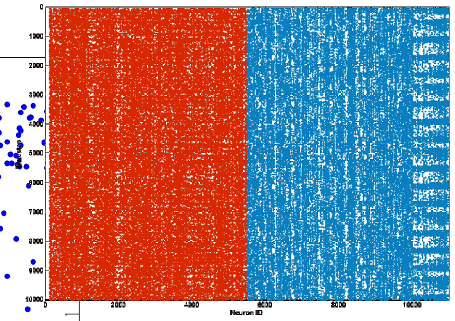
Aimone, Deng, and Gage
Trends in Cog. Sci. 2010

Activity of network – EC Inputs

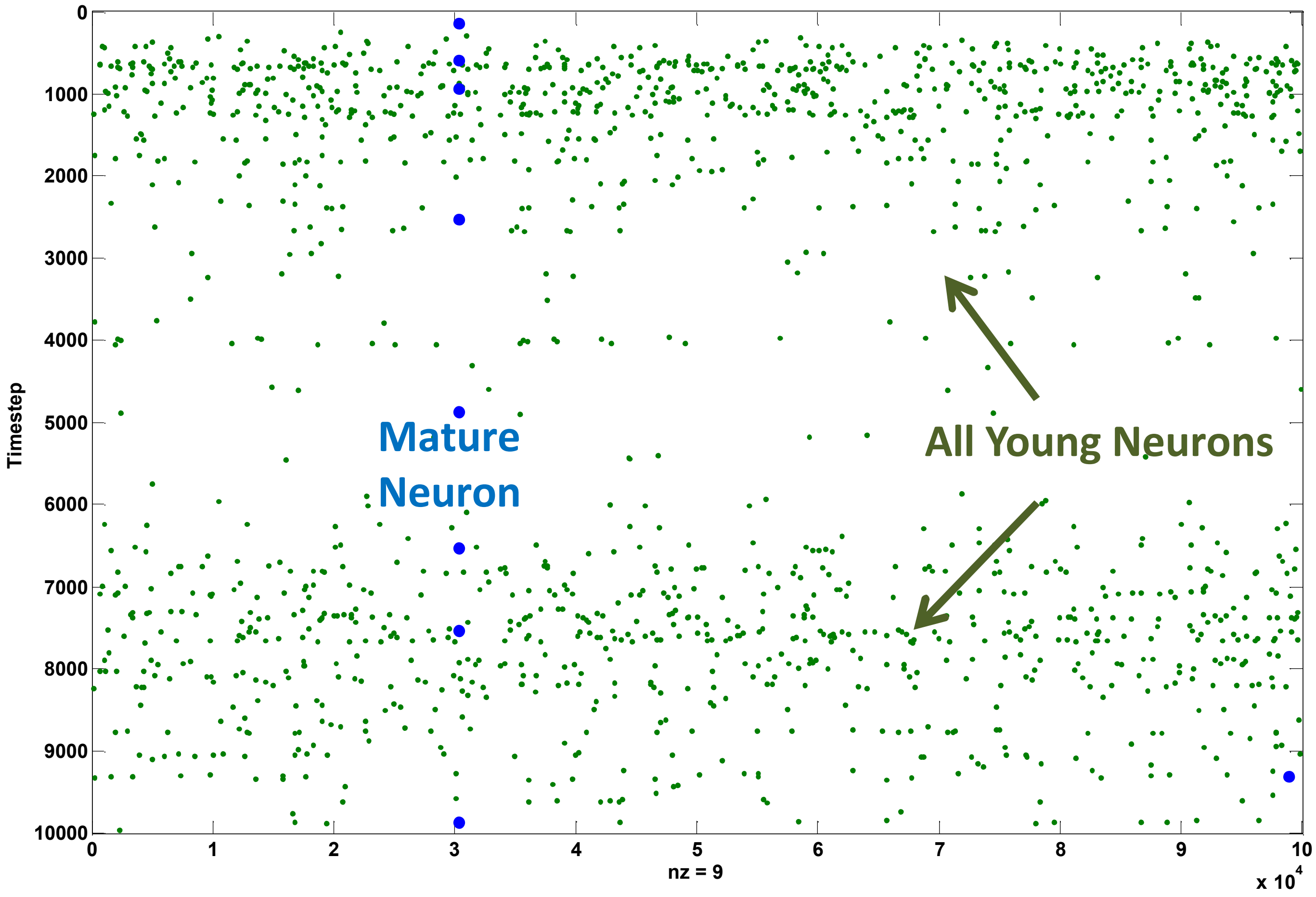


Activity of network – GC Outputs

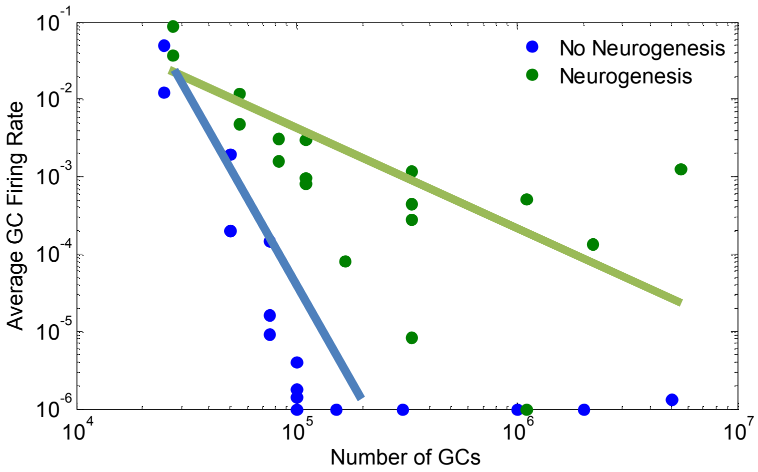




Young GCs dominate

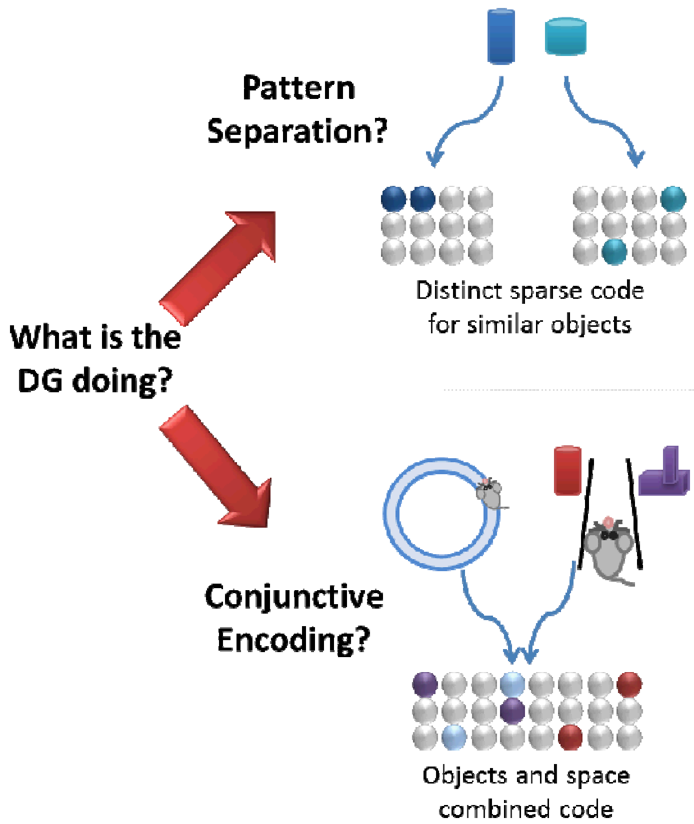


Lack of neurogenesis in large networks correlates with much lower activity



- Neurogenesis networks show activity to novel information at much higher scales
- As we approach human scales, mature neurons appear essentially silent in response to novel information
- Signal (immature) to noise (mature) is amplified in larger networks

Metrics for understanding NG model



- Pairwise correlation / dot product

$$Sim_{t1,t2} = \frac{\|f_{GC,t1} \cdot f_{GC,t2}\|}{\|f_{GC,t1}\|\|f_{GC,t2}\|}$$

- Average covariance

$$\sigma_{t1,t2} = \sum_{GC} (f_{GC,t1} - f_{t1}) \cdot (f_{GC,t2} - f_{t2})$$

How to combine over observations?

- **Linear compressability**

$$\kappa_{GC} = \sum_{i=1..d}(\sigma_i - \lambda_i) \Big/ \sum_{i=1..d} \sigma_i$$

- Average firing rate

$$f_{GC} = 1/N_{GC} \sum_{GC} N_{spikes}/T$$

- Total variance

$$\sigma_{GC} = \sum_{T} \sigma_{GC,T}$$

- Information Content

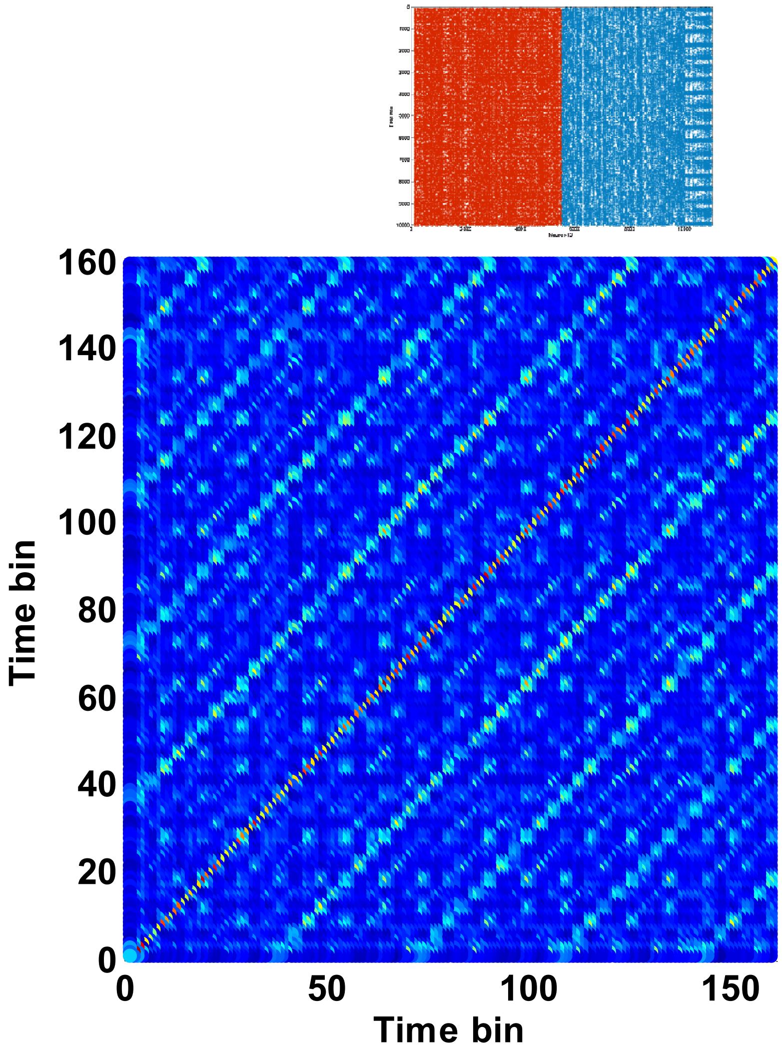
$$I = \sum_{ctx} p_{ctx} \, f/f \, \log_2 f/f$$

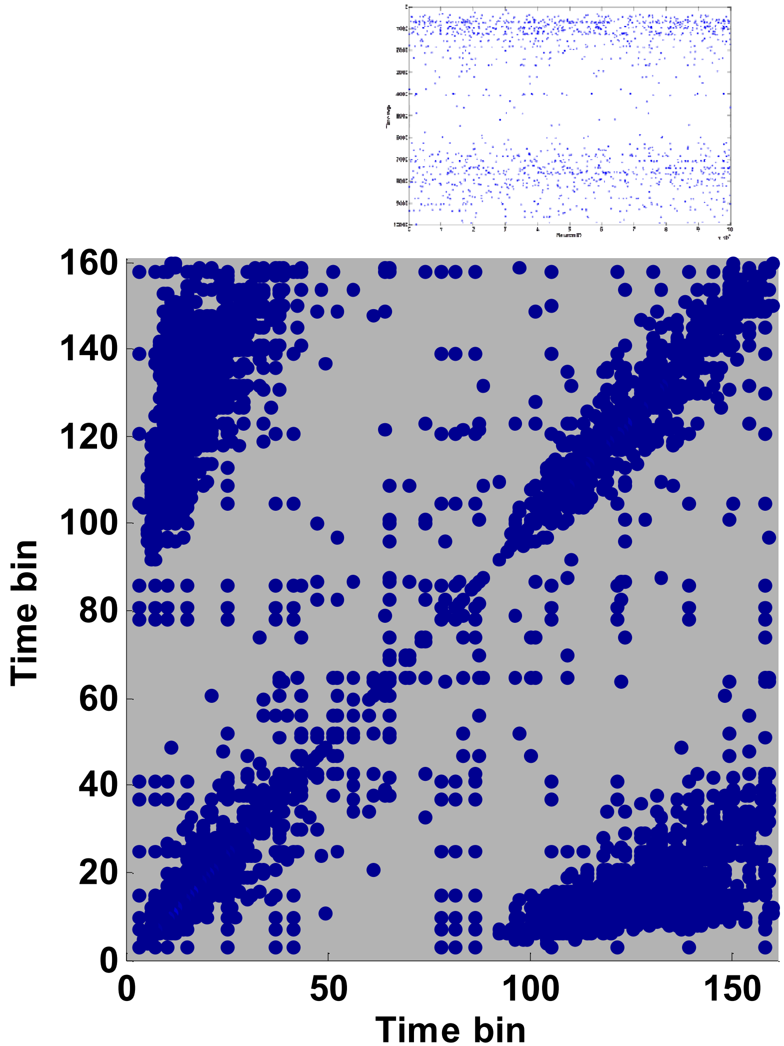
How to combine over neurons?

- **Independent variance**

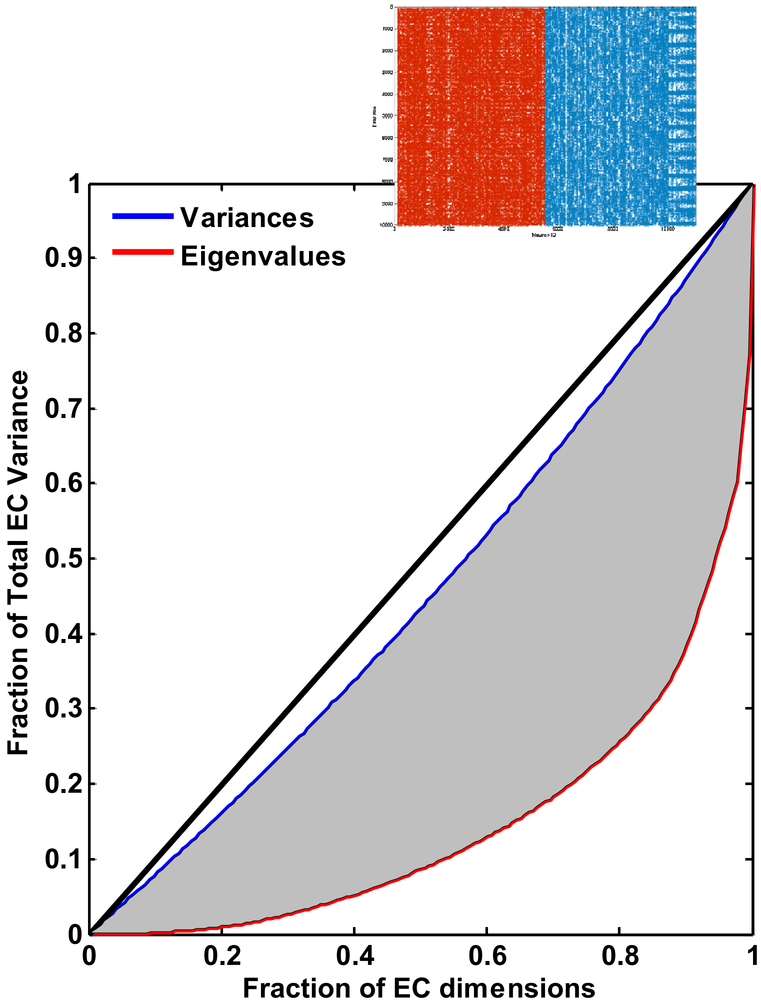
$$\varphi_{GC} = \sigma_{GC} \times \kappa_{\lambda}$$

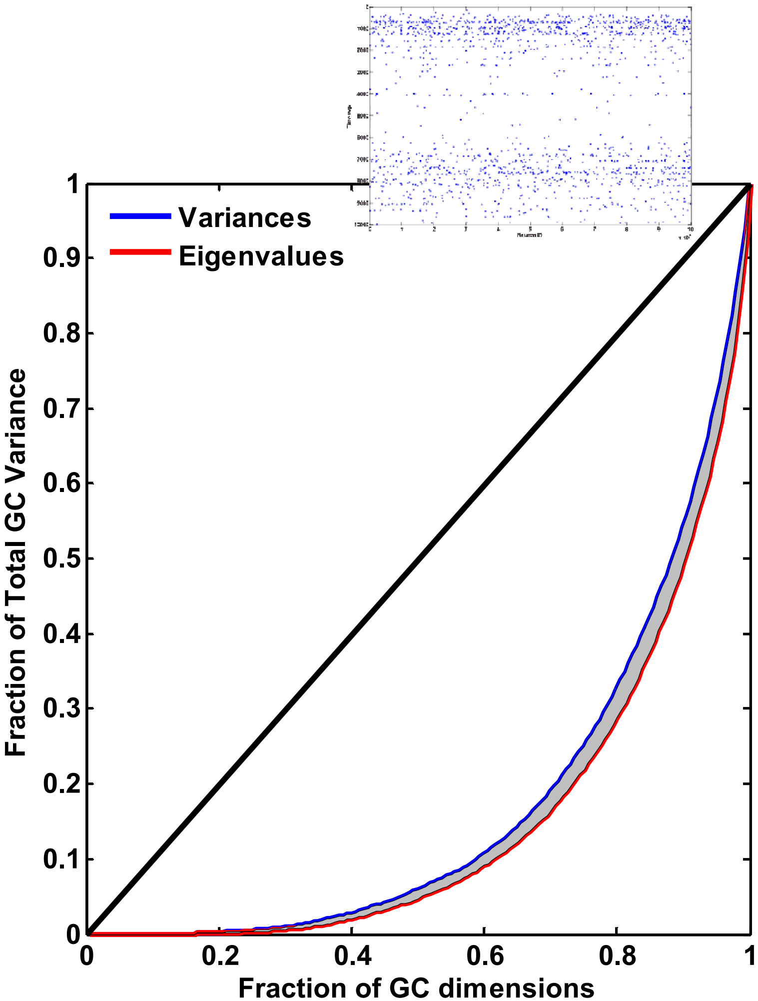
Information processing in large networks



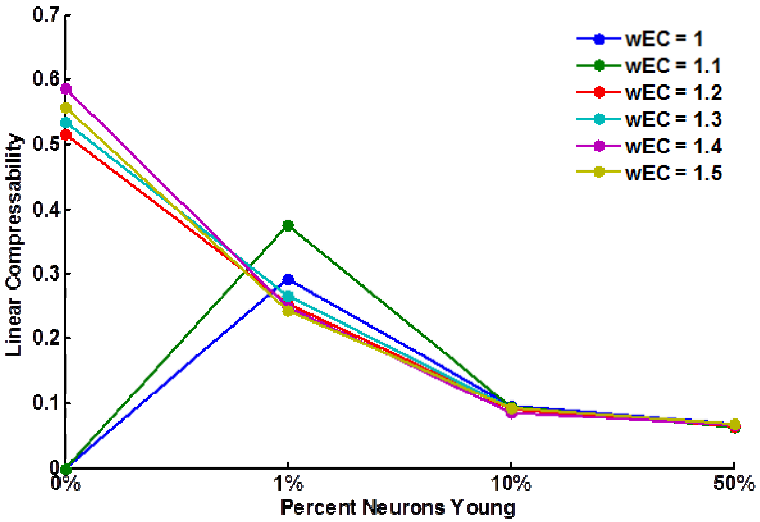


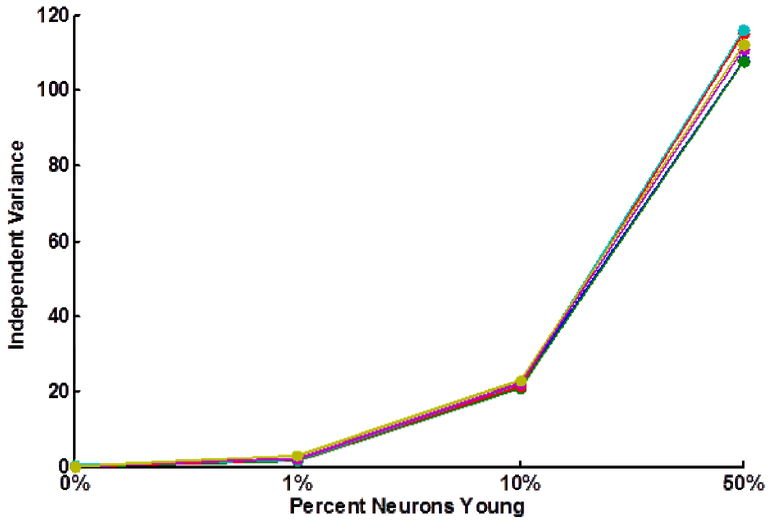
Information processing in large networks



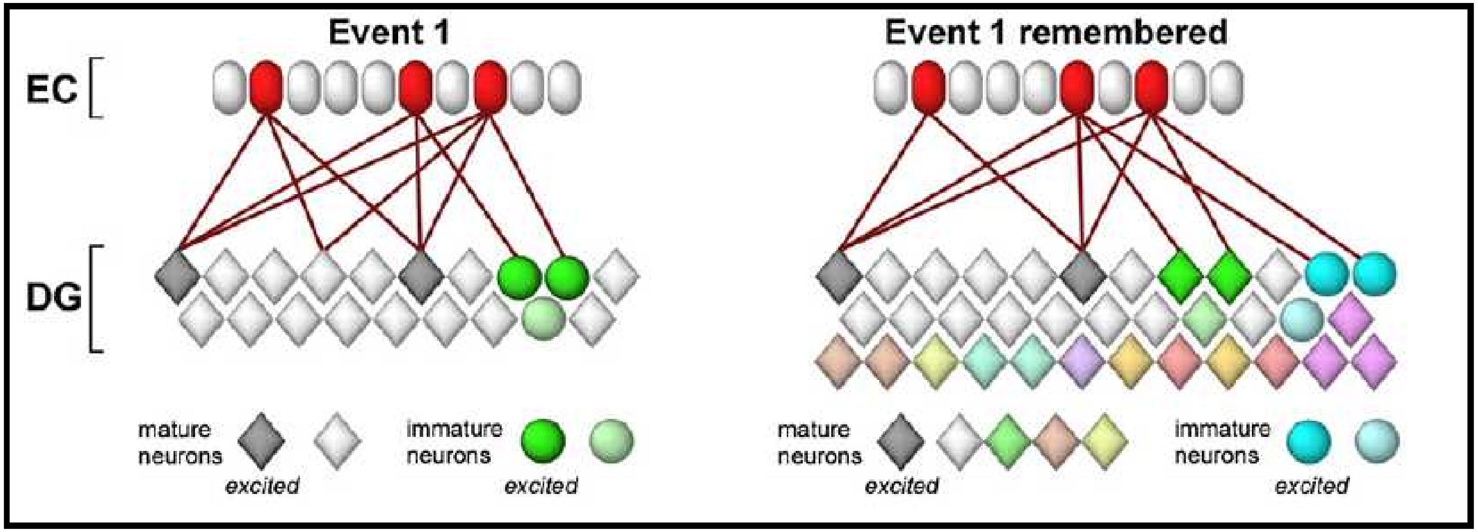


Neurogenesis decreases compressibility and increases total representation





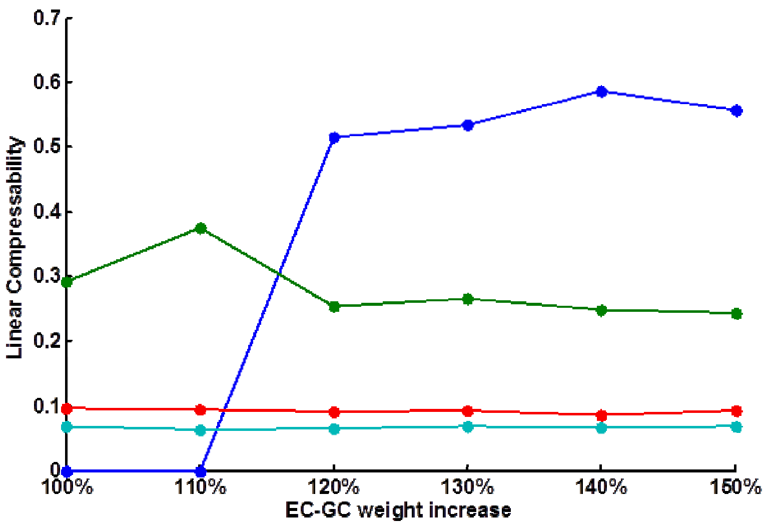
Environmental commitment of adult-born neurons

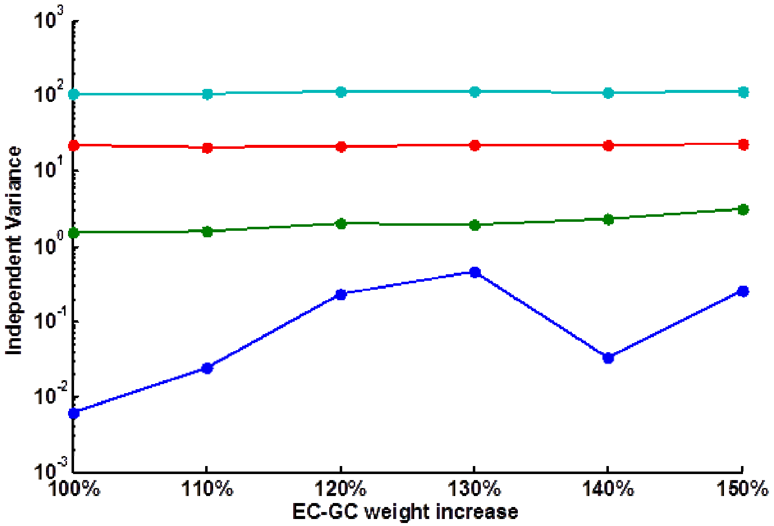


Aimone et al., Neuron 2009

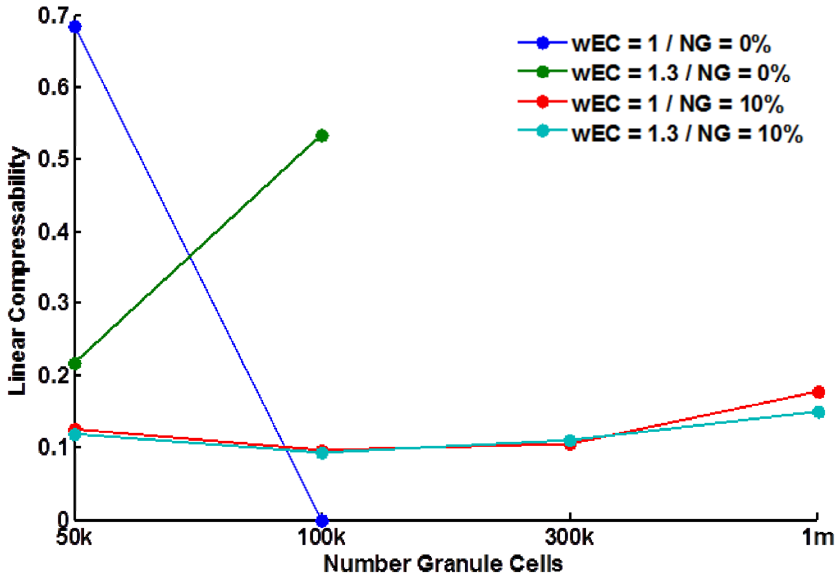
Hypothesis: The specialization of young neurons to the environments present during maturation allows improved encoding of new memories that relate to previously experienced contexts.

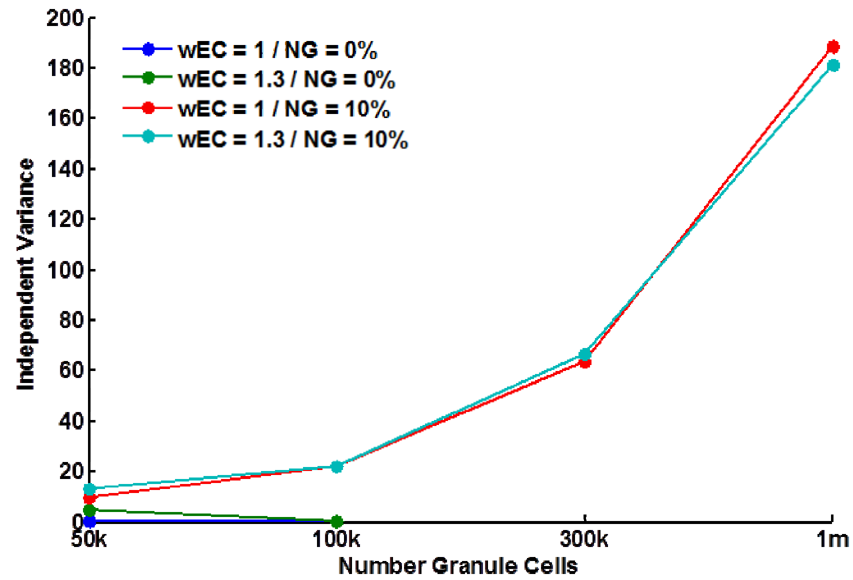
Increasing EC-GC weights impairs separation without improving coding



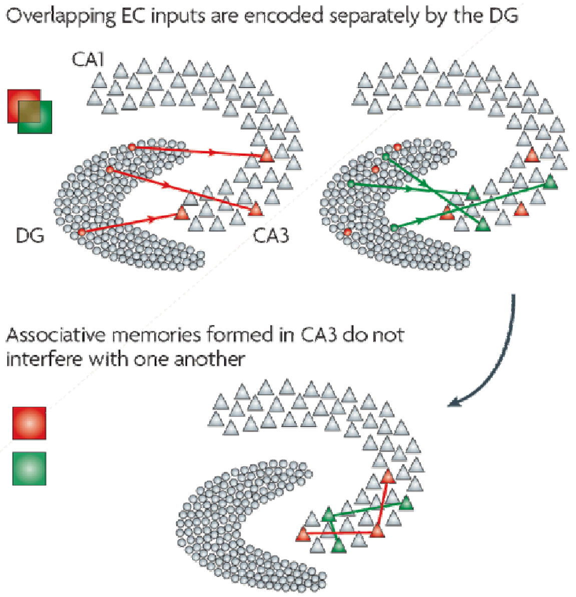


Increased size networks need neurogenesis for balancing separability and representations



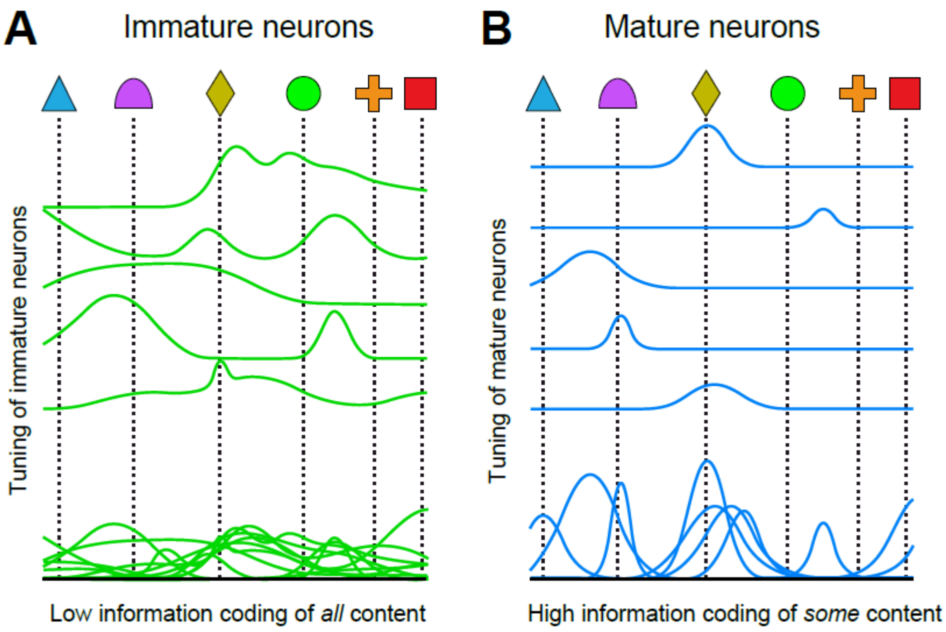


So which is right?

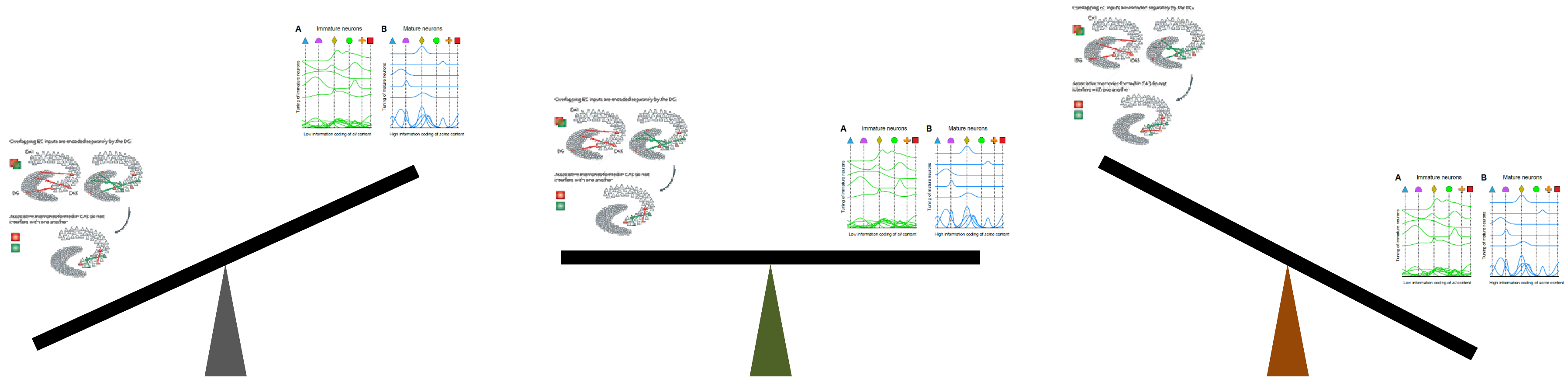


Pattern separation?

Or memory resolution?



Neurogenesis strikes a balance



No neurogenesis yields very little activity
DG representations are separate but very sparse

Neurogenesis increases activity while preserving separation
DG representations increase their resolution but avoid interference

Increasing activity directly ruins pattern separation
DG representations are dense and informative but potentially interfere with each other

So what needs to happen?

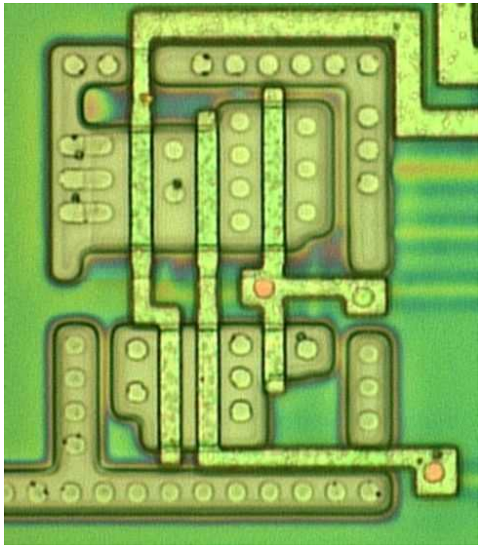
Neurons to Algorithms (N2A)
A Neural Modeling Tool

PI	Fred Rothganger
PM	Phil Bennett
Team	Christy Warrender Derek Trumbo Brad Aimone Corinne Teeter

Sandia National Laboratories is a multi-program laboratory managed and operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Corporation, for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000. SAND 212-8455P

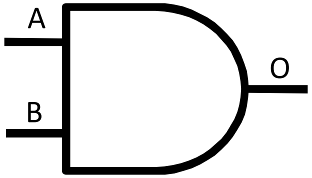
Original Motivation

Describe the ***function*** of each brain circuit.

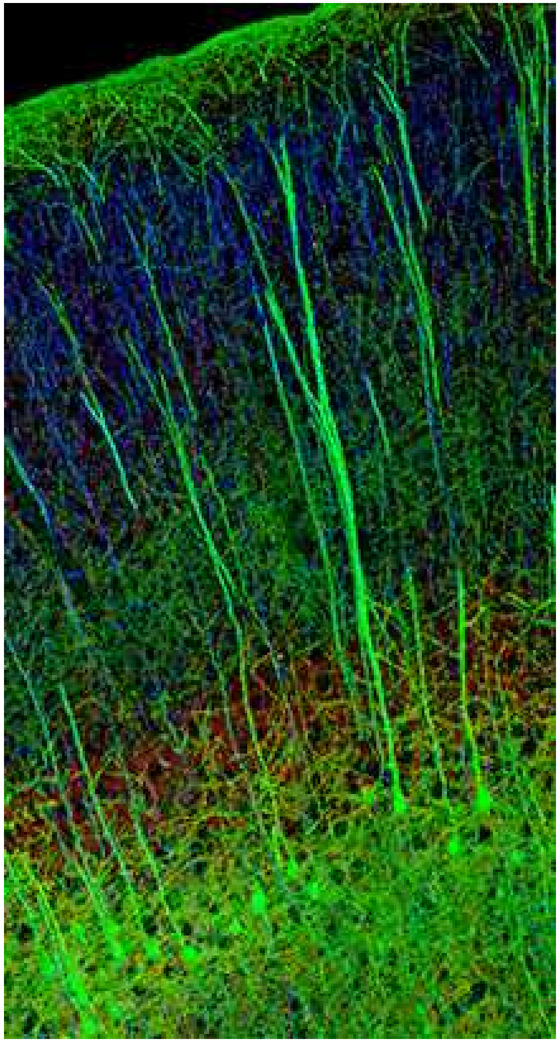


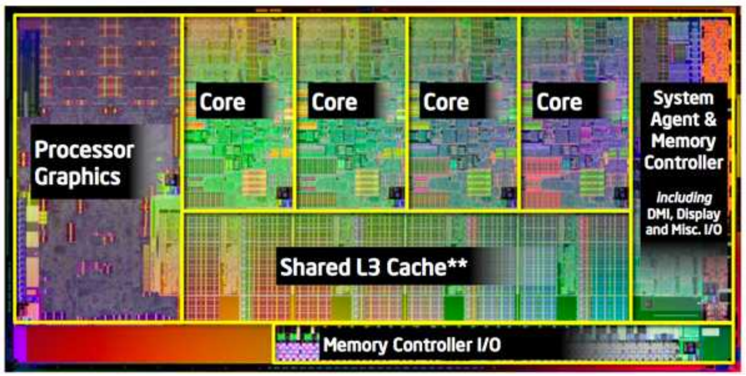
AND gate [Kömmerling & Kuhn 99]

Abstract away physical details to explain what something does or how it interacts with other things.

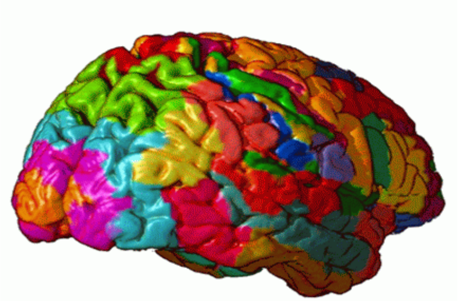


A	B	O
F	F	F
F	T	F
T	F	F
T	T	T





Sandy Bridge die [Intel Corp.]



Brodmann Areas

Neocortical (brain) slice [Stephen Smith Lab at Stanford]

The Challenge

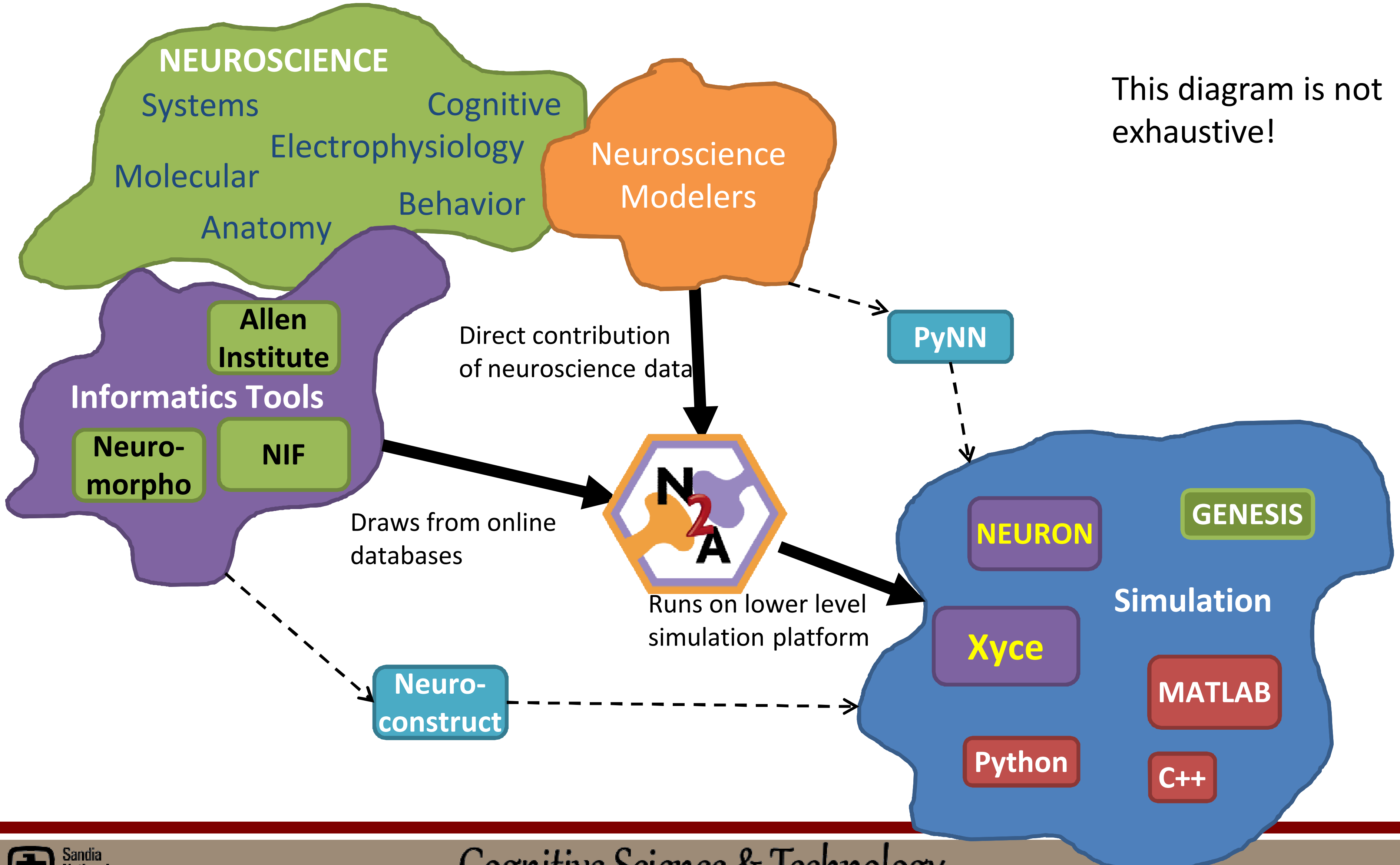
Society for Neuroscience
>30,000 scientists attend
>1,000 topic areas presented

Need to integrate all this knowledge. Beyond capacity of anyone to comprehend.

Complete model of human cognition *cannot* exist as an idea in one person's mind.

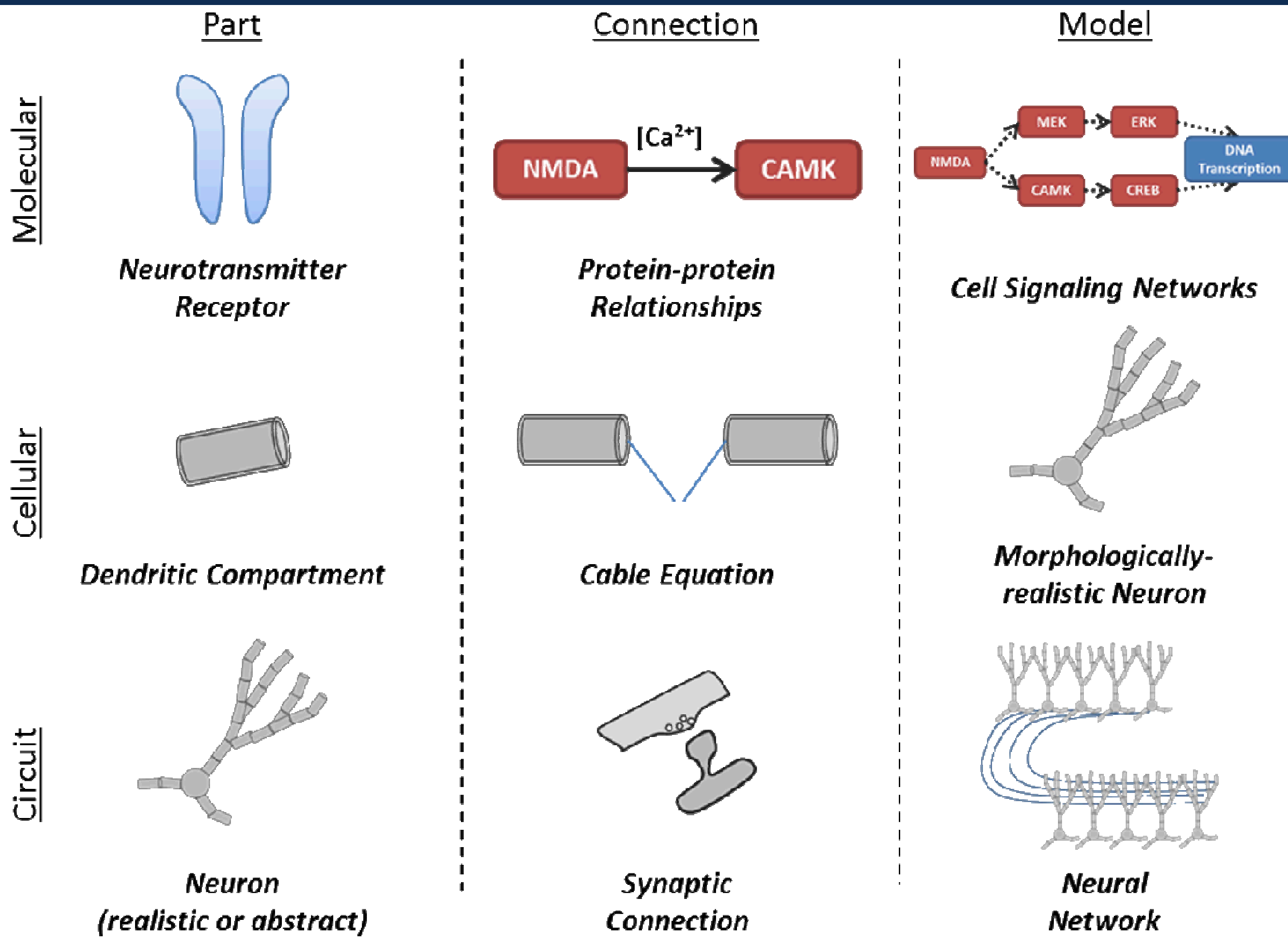
Must be an information structure held in a large computer system.

Where N2A Fits



This diagram is not exhaustive!

Scale agnostic



Workflow

- Contributed models
- Neurophysiology literature
- Online databases

Database of Neural Structure & Dynamics

Simulate

Xyce
PARALLEL ELECTRONIC SIMULATOR

DAKOTA

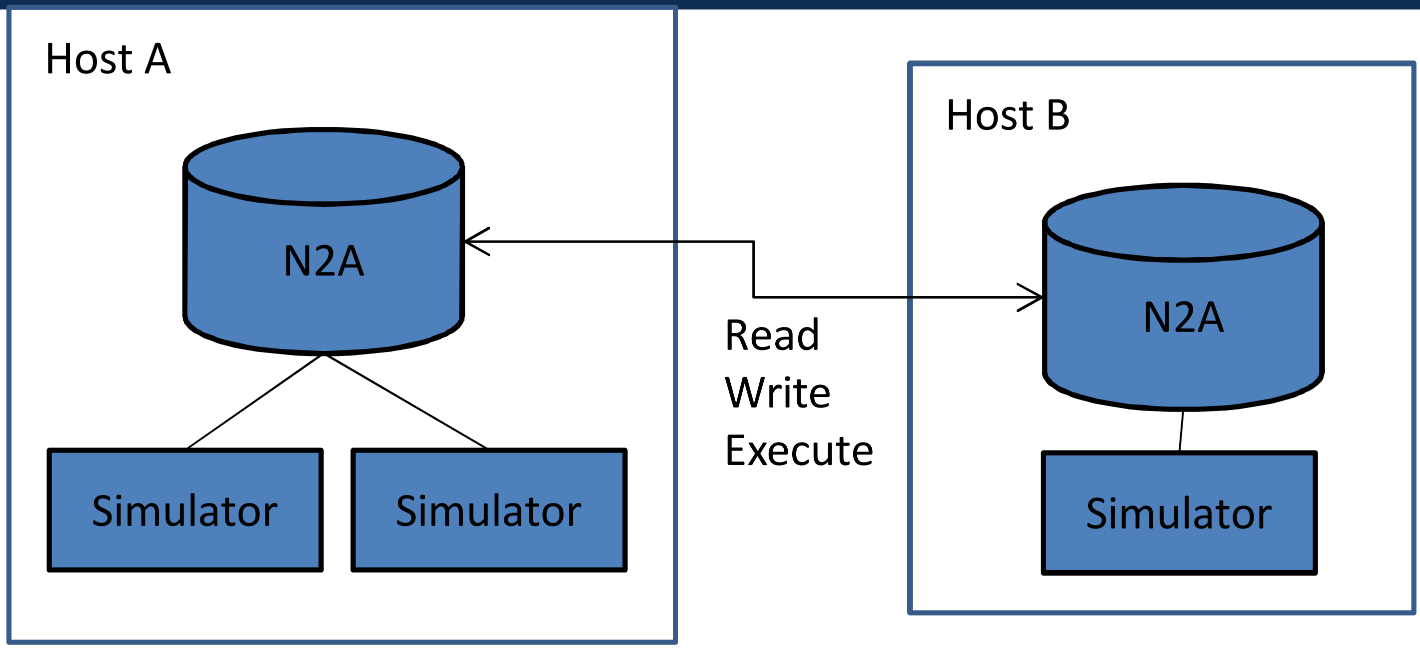
Fit parameters

Characterize model behavior

- Visualization
- Automatic analysis

Algorithmic motifs

Vision: P2P Sharing



A remote system may be another desktop, a cluster-computer, or a “cloud” service.

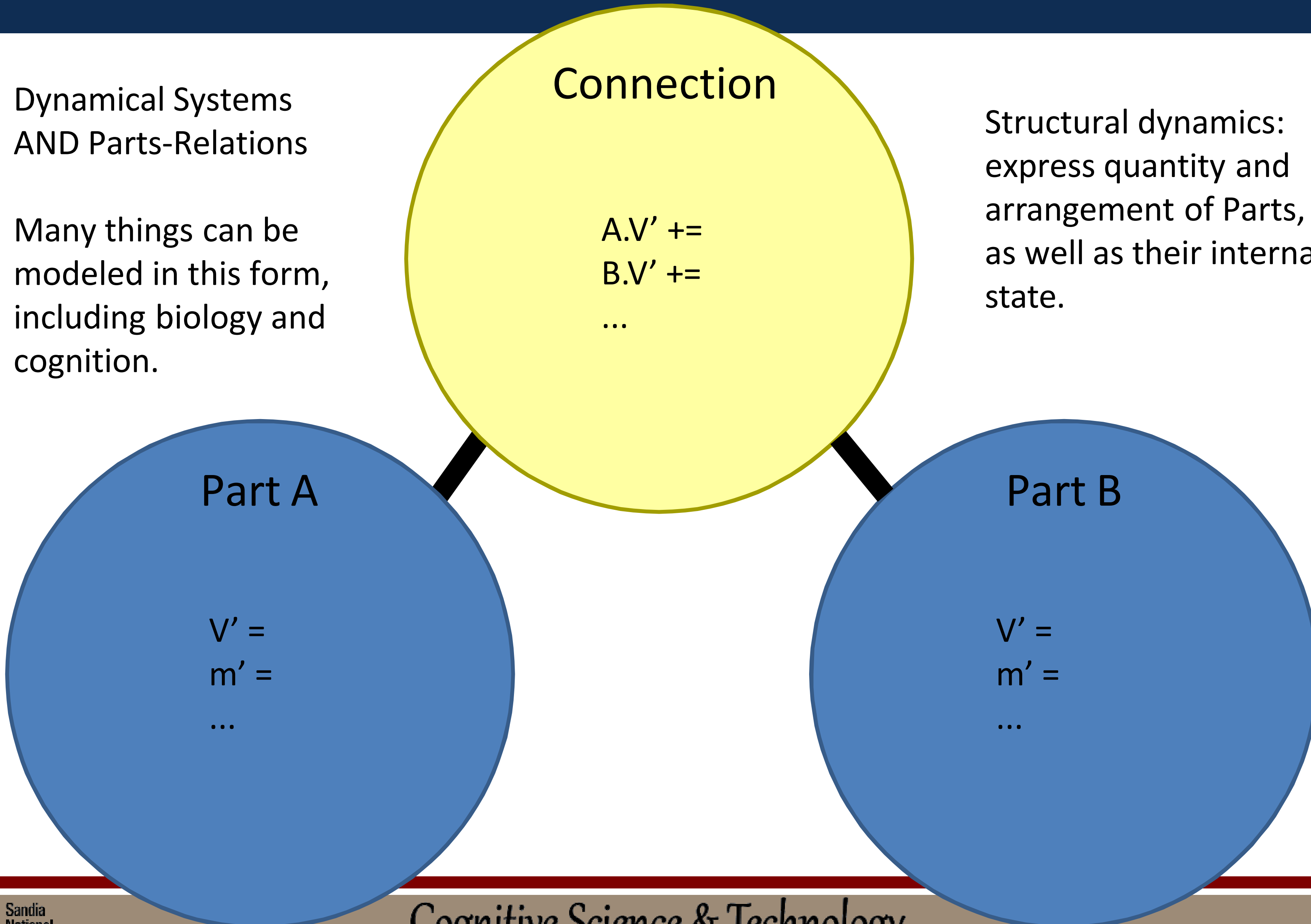
You may upload your models to another N2A system,
download models from it,
or ask it to simulate a model on your behalf.

Simulator may be any tool (Xyce, Neuron, PyNN, Brian, ...) for which there is a backend wrapper.

Model Structure

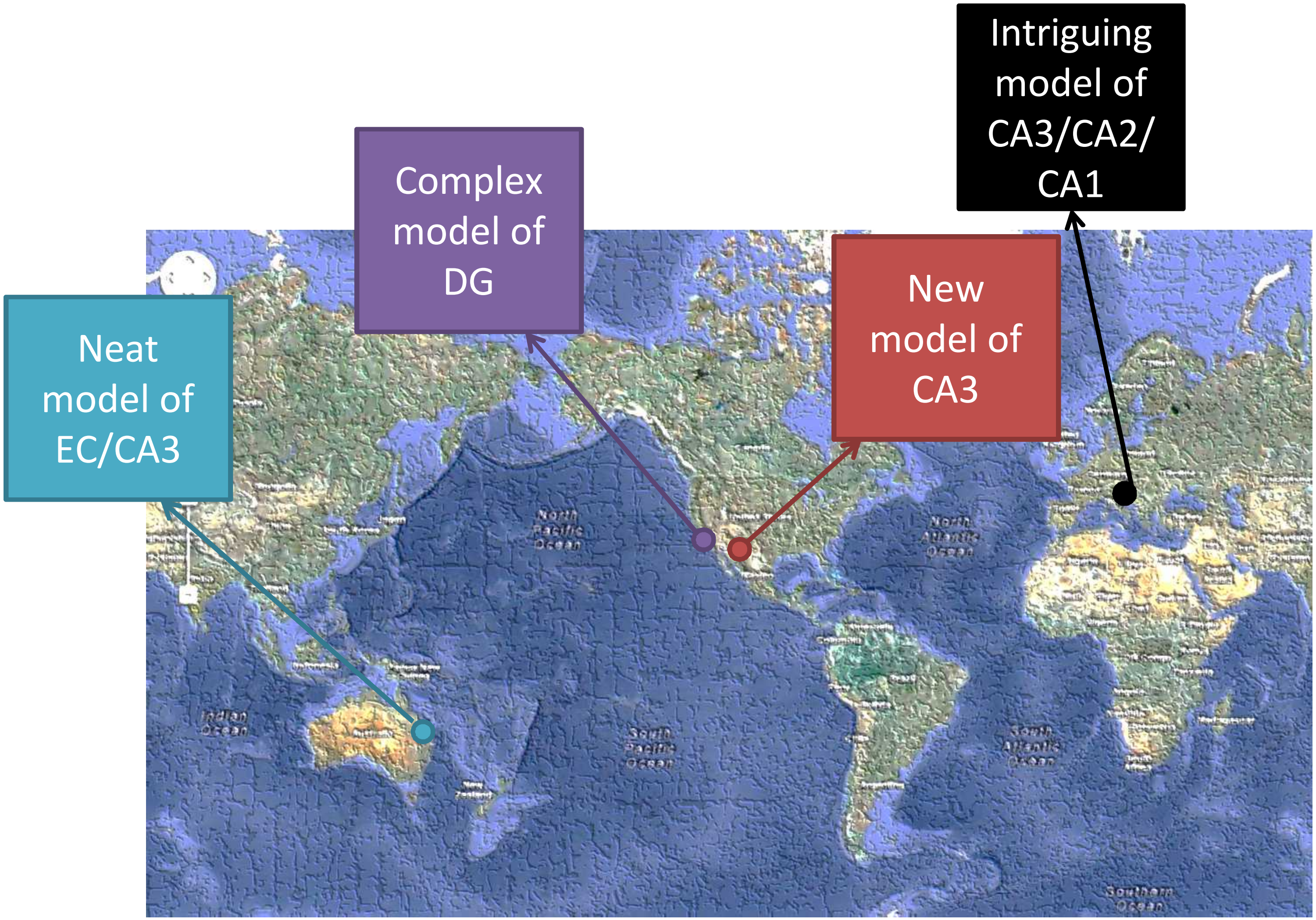
Dynamical Systems
AND Parts-Relations

Many things can be modeled in this form, including biology and cognition.

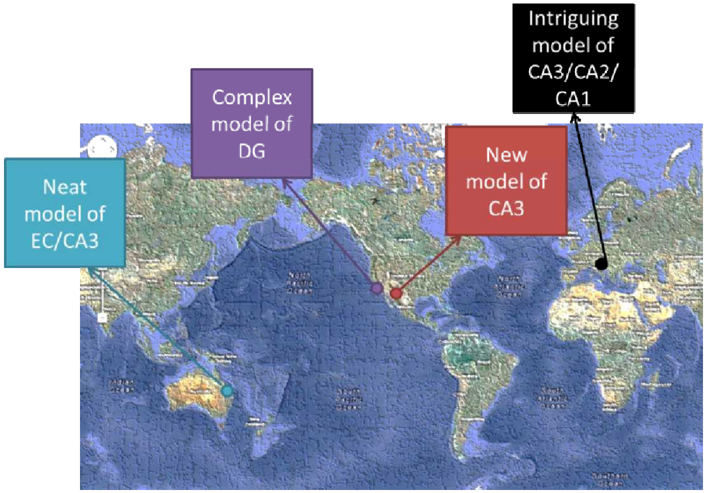


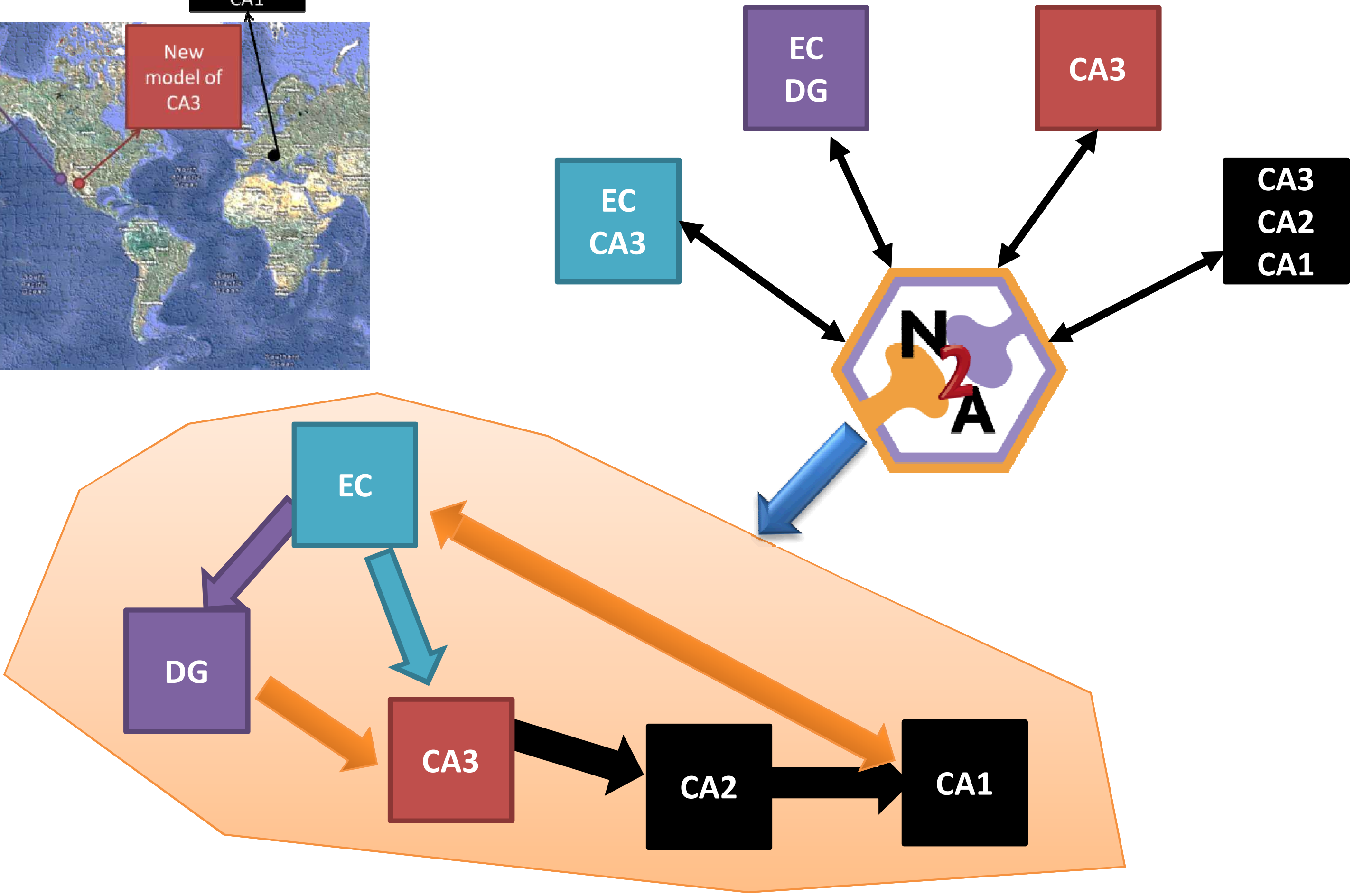
Structural dynamics: express quantity and arrangement of Parts, as well as their internal state.

Example…


Intriguing model of CA3/CA2/ CA1
Complex model of DG
New model of CA3
Neat model of EC/CA3

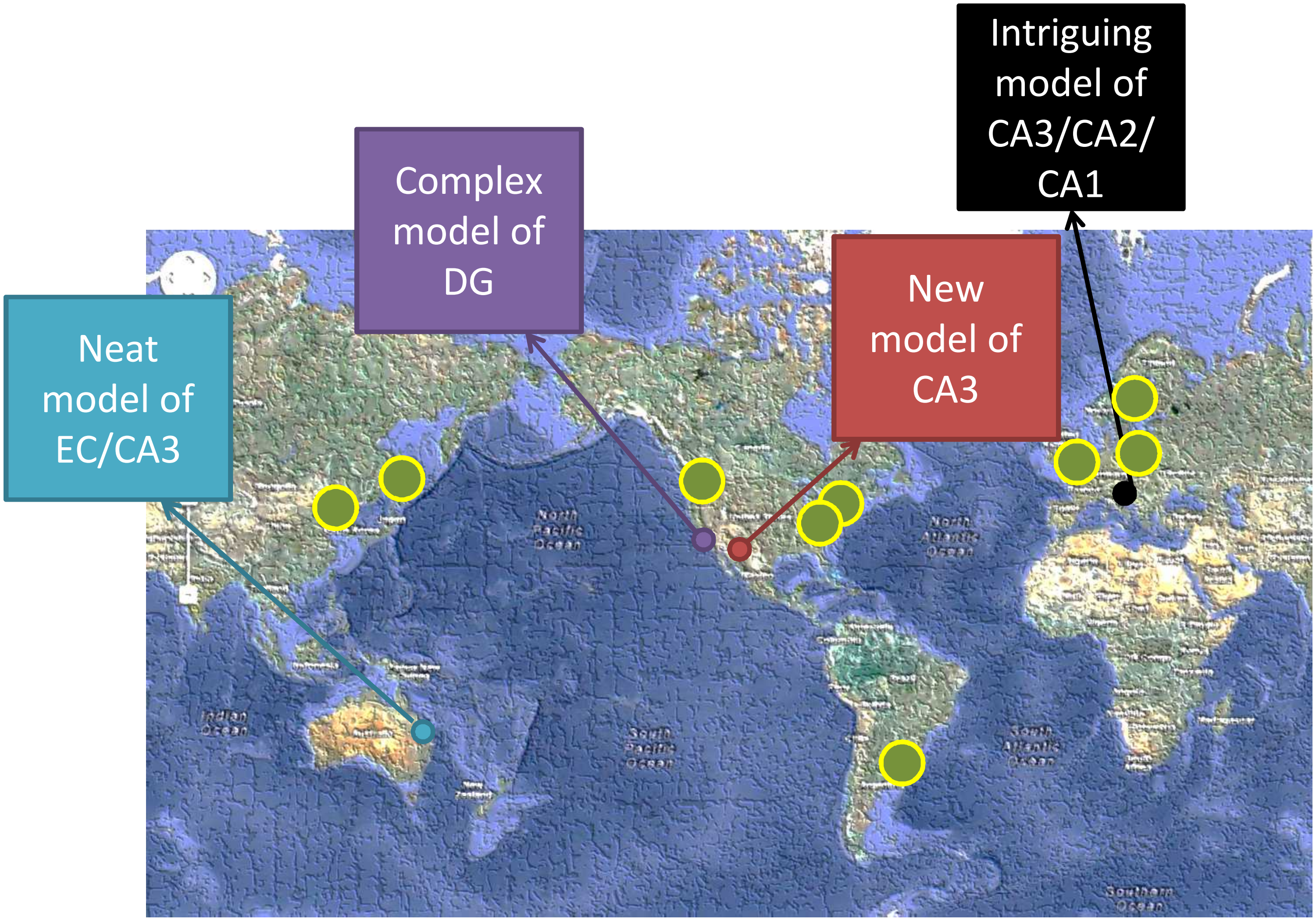
Unifying models from across sources



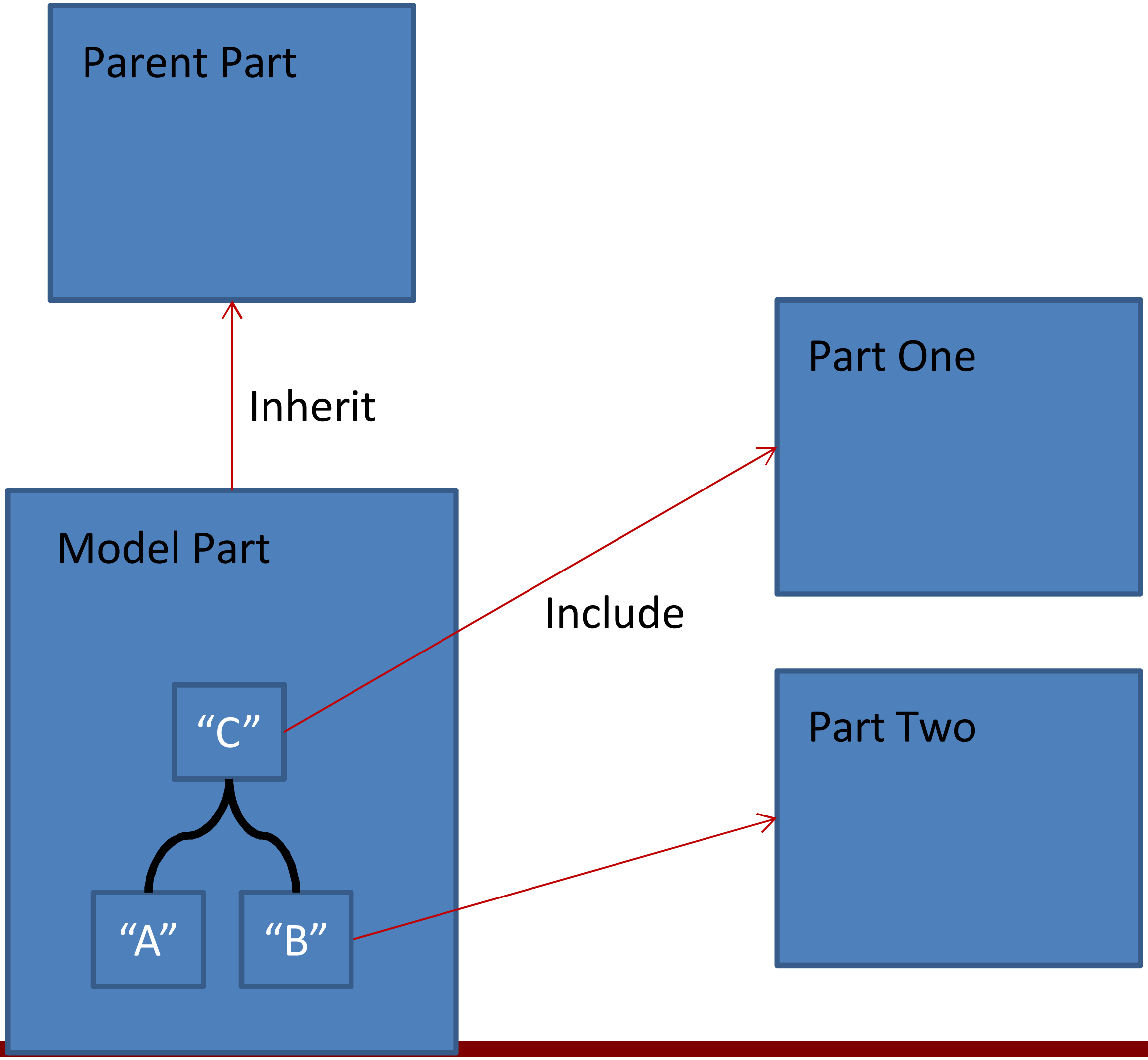


New hybrid model

It can go beyond models – experimental data can be represented as well



Hierarchical Composition

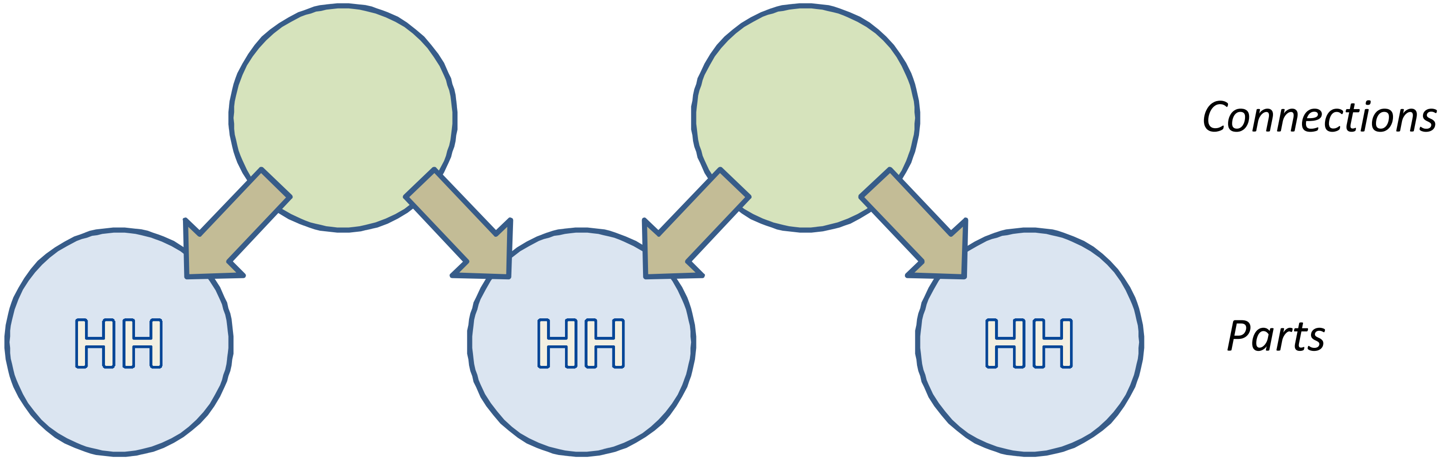


Example

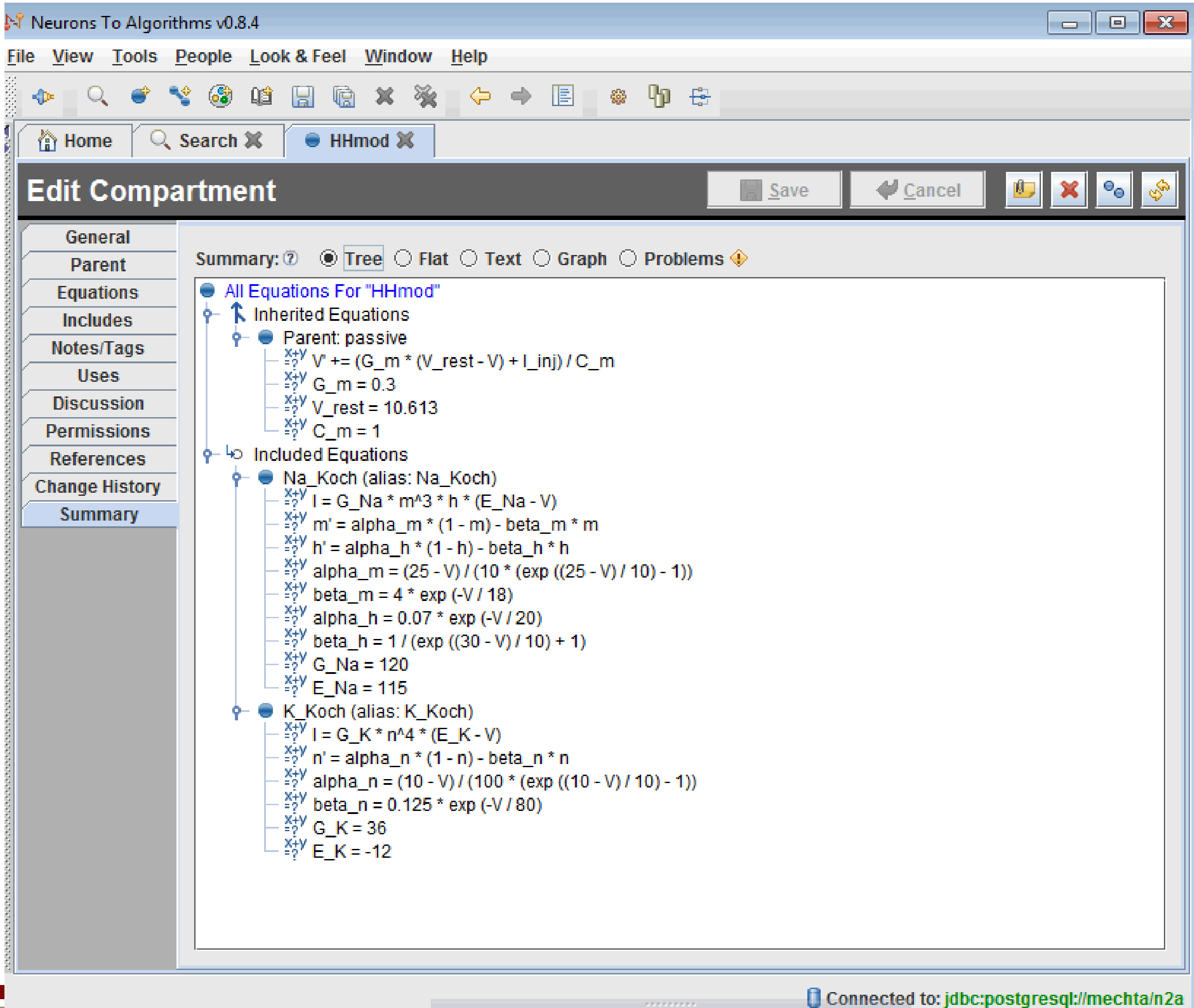
Measure Spike Propagation through Multi-Segment Hodgkin-Huxley Cable

Neuroscience Representation:

N2A Representation:

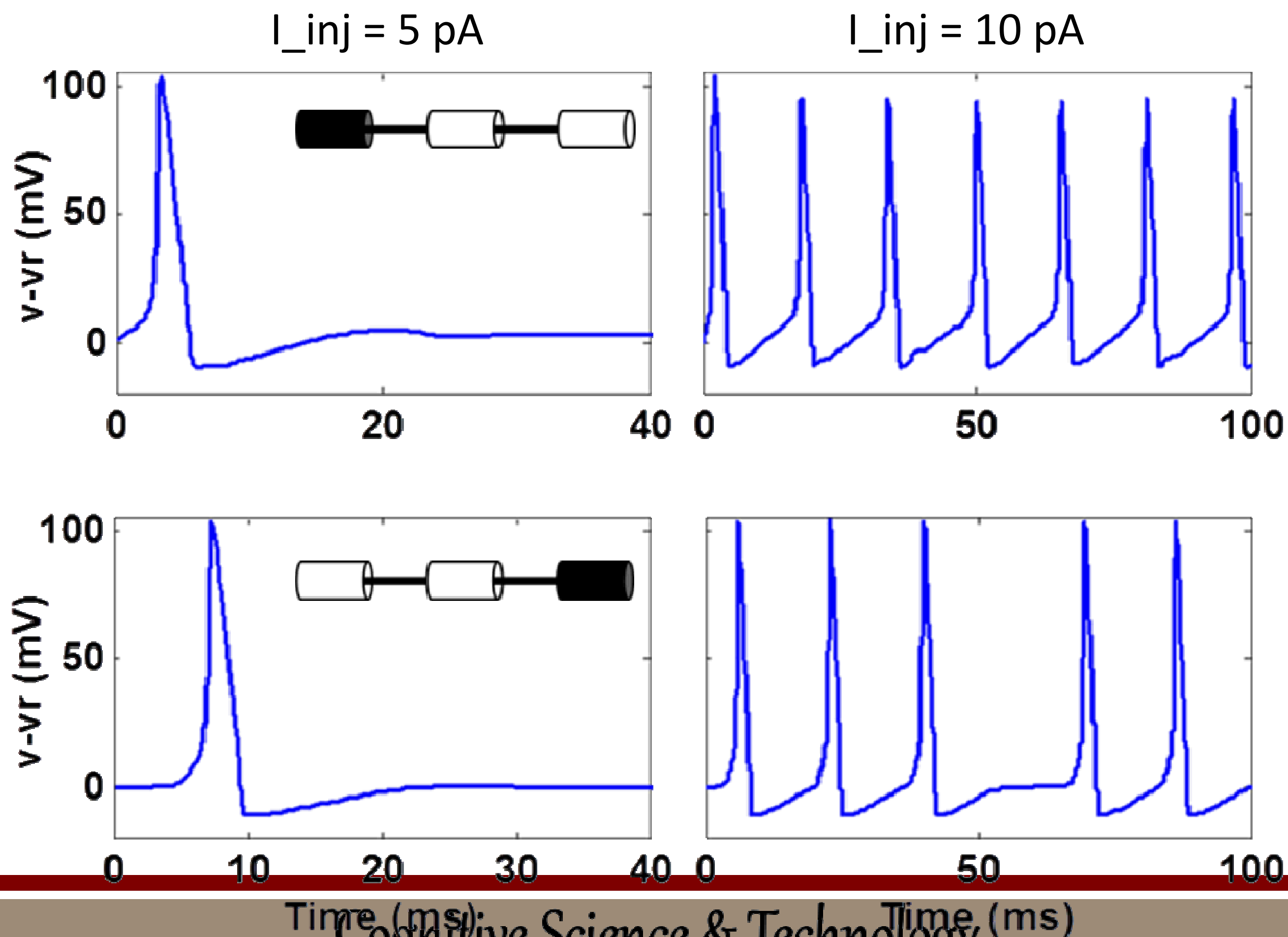


Demo

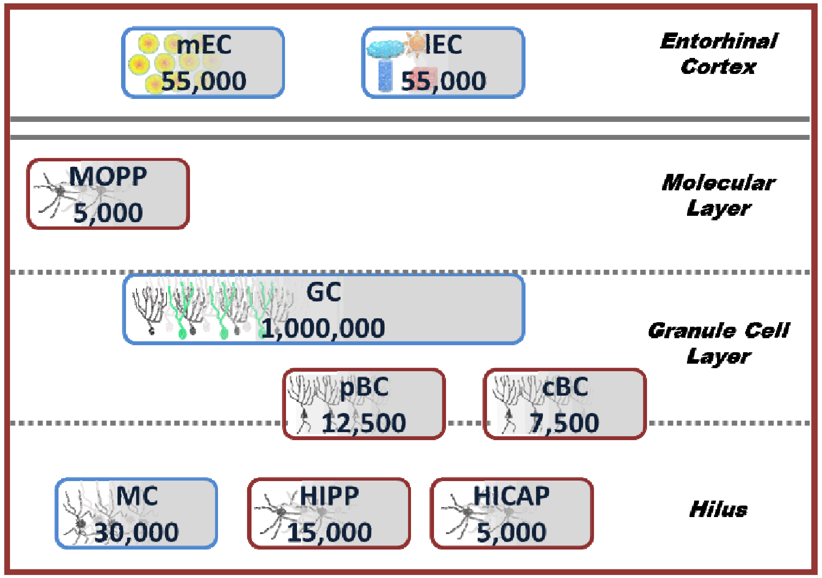

Neurons To Algorithms v0.8.4
File View Tools People Look & Feel Window Help
Home
Search
HHmod
Edit Compartment
Save
Cancel
General
Parent
Equations
Includes
Notes/Tags
Uses
Discussion
Permissions
References
Change History
Summary
Summary: Tree Flat Text Graph Problems
All Equations For "HHmod"
Inherited Equations
Parent: passive
V' += (G_m * (V_rest - V) + I_inj) / C_m
G_m = 0.3
V_rest = 10.613
C_m = 1
Included Equations
Na_Koch (alias: Na_Koch)
I = G_Na * m^3 * h * (E_Na - V)
m' = alpha_m * (1 - m) - beta_m * m
h' = alpha_h * (1 - h) - beta_h * h
alpha_m = (25 - V) / (10 * (exp ((25 - V) / 10) - 1))
beta_m = 4 * exp (-V / 18)
alpha_h = 0.07 * exp (-V / 20)
beta_h = 1 / (exp ((30 - V) / 10) + 1)
G_Na = 120
E_Na = 115
K_Koch (alias: K_Koch)
I = G_K * n^4 * (E_K - V)
n' = alpha_n * (1 - n) - beta_n * n
alpha_n = (10 - V) / (100 * (exp ((10 - V) / 10) - 1))
beta_n = 0.125 * exp (-V / 80)
G_K = 36
E_K = -12
Connected to: jdbc:postgresql://mechta/n2a

Results

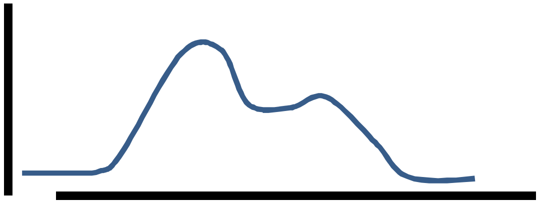

I_inj
V_1
V_3


I_inj = 5 pA
I_inj = 10 pA
v-vr (mV)
100
50
0
0
20
40
0
50
100
v-vr (mV)
100
50
0
0
10
20
30
40
0
50
100
Time (ms)
Time (ms)

Measuring parameter sensitivity in neural systems



Hundreds of parameters
Millions(?) of perturbations



N2A demo

Backup

Summary

- Easy to create / extend / share parts
  - Inherit or include existing parts
  - References and credit go with parts
- Easy to build Models
  - Large hippocampus model accidentally got deleted.
  - Took 5 minutes to recreate! (All parts were still in DB.)
- Easy to run simulations
  - Simple equation language controls all aspects
  - Don’t need to know arcane details of simulator
- (soon) Easy analysis of results
  - Automatic generation of multiple simulations to explore parameters
  - Stores record of each experiment, so it can be reproduced
  - Link out to favorite data analysis tools (Matlab, etc.)

Equations Create "Variables"

Passive Compartment

```
V'     = (G * (V_rest - V) + I_inj) / C
G      = 0.3
V_rest = 10.613
C      = 1
```

"Variables"

```
V'
V       <-- Created implicitly by differential equation V'
G       ┐
V_rest  ├ Constants
C       ┘
```

Note that I_inj is unresolved. It must be provided before the part is instantiated. Usually the model specifies such missing values.

Inheritance

Ion Channel

```
V' += I / C
```

Potassium Channel → Ion Channel

```
V'      += I / C
I        = G * n^4 * (E - V)
n'       = alpha_n * (1 - n) - beta_n * n
alpha_n = (10 - V) / (100 * (exp ((10 - V) / 10) - 1))
beta_n   = 0.125 * exp (-V / 80)
G        = 36
E        = -12
```

Only the green equations are specified in the "Potassium Channel" part.

Inclusion

Active Compartment → Passive Compartment + Potassium Channel “K”

```
V'         = (G * (V_rest - V) + I_inj) / C
G          = 0.3
V_rest     = 10.613
C          = 1
V'        += K.I / C
K.I        = K.G * K.n^4 * (K.E - V)
K.n'       = K.alpha_n * (1 - K.n) - K.beta_n * K.n
K.alpha_n  = (10 - V) / (100 * (exp ((10 - V) / 10) - 1))
K.beta_n   = 0.125 * exp (-V / 80)
K.G        = 36
K.E        = -12
```

“Boxing” – Prepend the alias of an included part to all the variables it explicitly creates, except for “+=” equations.

Effect of “+=”

```
V' = (G * (V_rest - V) + I_inj) / C + K.I / C
```

Unordered Evaluation

Variables are double-buffered

V'_0
$V_0 = \int(V'_0)dt$
$K.I_0$
$K.n'_0$
$K.n_0 = \int(K.n'_0)dt$
$K.alpha\_n_0$
$K.beta\_n_0$

V'_1
V_1
$K.I_1$
$K.n'_1$
$K.n_1$
$K.alpha\_n_1$
$K.beta\_n_1$

Constants are not buffered

G
V_rest
C
K.G
K.E
I_inj

First exchange buffers and integrate implicit variables.

$V'_1 = (G * (V\_rest - V_0) + I\_inj) / C + K.I_0 / C$
$K.I_1 = K.G * K.n_0\wedge 4 * (K.E - V_0)$
$K.n'_1 = K.alpha\_n_0 * (1 - K.n_0) - K.beta\_n_0 * K.n_0$
$K.alpha\_n_1 = (10 - V_0) / (100 * (exp ((10 - V_0) / 10) - 1))$
$K.beta\_n_1 = 0.125 * exp (-V_0 / 80)$

Then update all regular variables.

Conditional Evaluation

Izhikevich Neuron

```
v' = 1/C*(k*(v-vr)*(v-vt)-u+I)
v  = c @ v > 35
u' = a*(b*(v-vr)-u)
u  = d @ v > 35
vt = -0.04
vr = -0.07
k  = 0.1e-6
I  = 0
a  = 100
b  = -0.1e-9
c  = -0.045
d  = 100e-12
```

Reset when voltage exceeds threshold. (Otherwise integrate v' and u')

Special Variables