SAND2012-3550P

The value of looking deeper – the what, why, and how of high fidelity adult neurogenesis modeling

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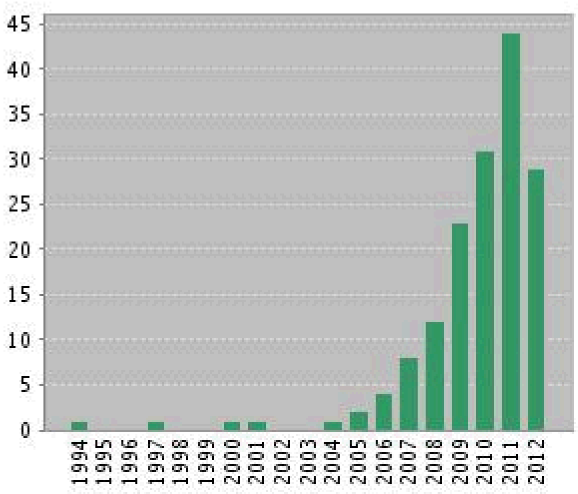
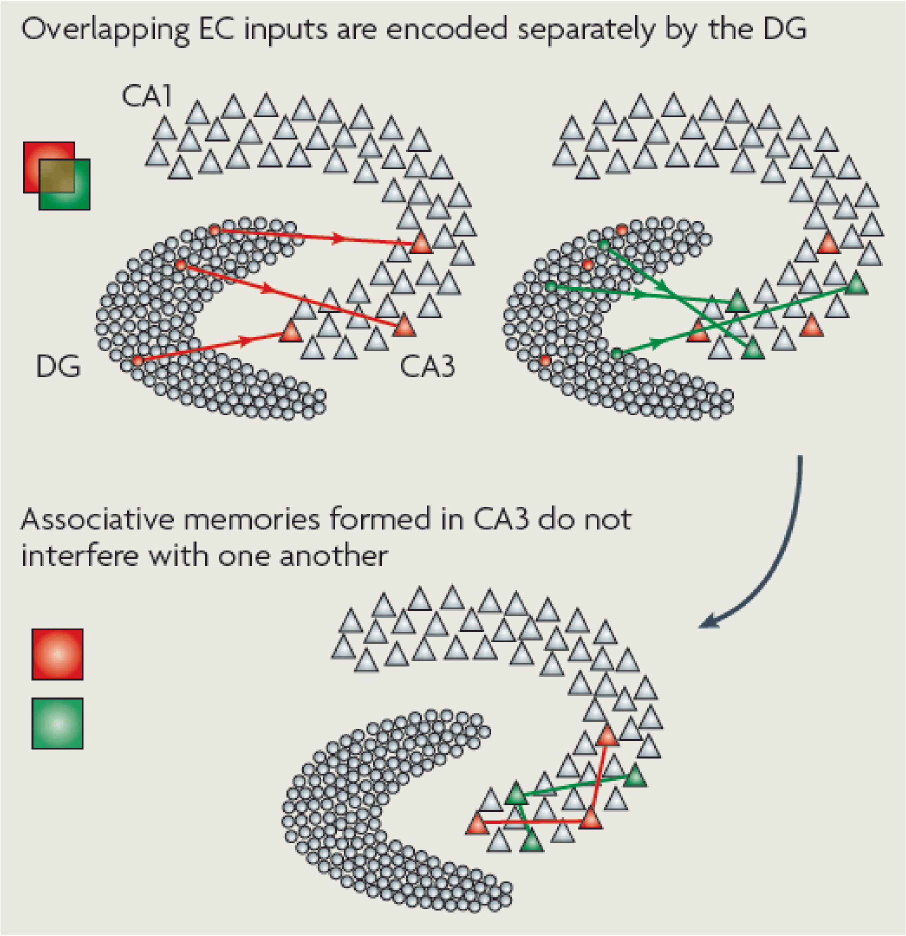
Sandia National Laboratories

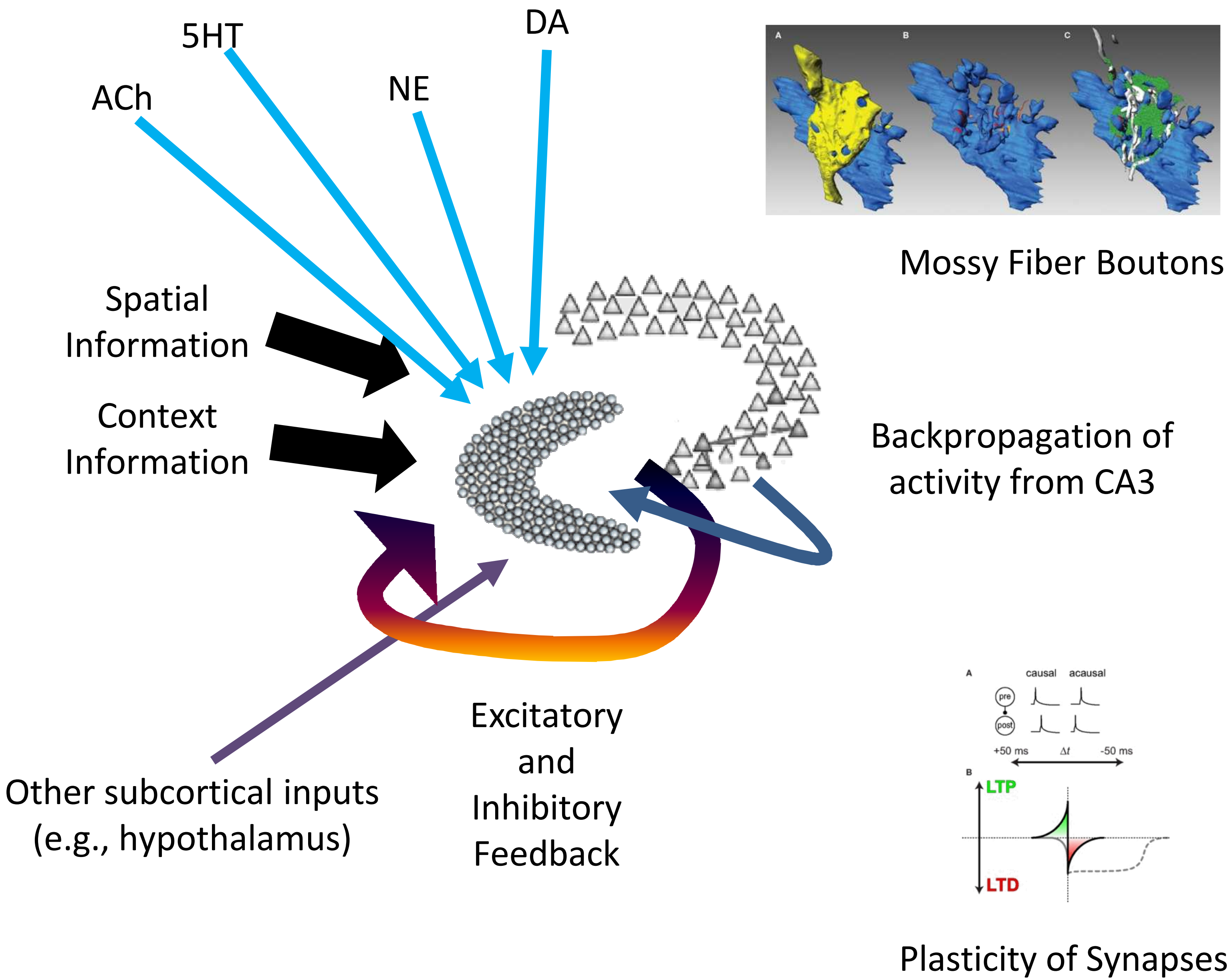
The need for modeling



ISI Papers with
"Pattern Separation" &
"Dentate Gyrus" as
keywords*

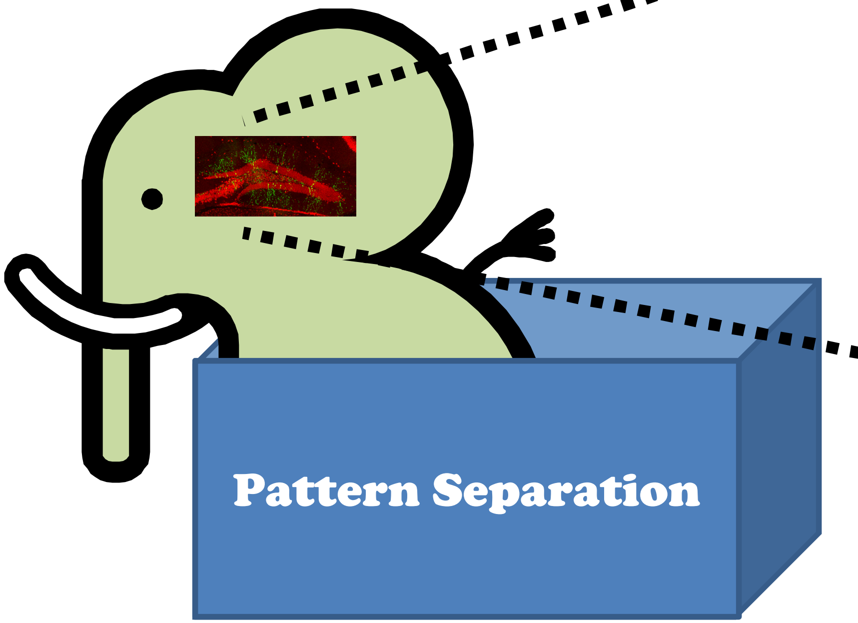


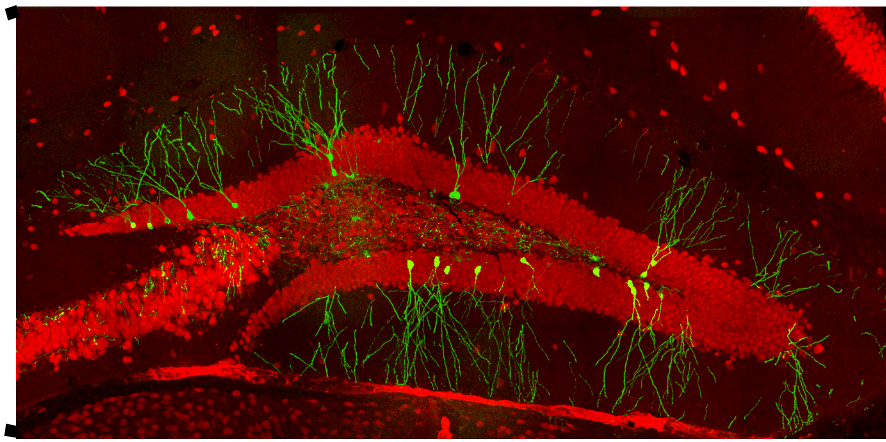
** yes, I am responsible for a non-trivial fraction of these*



ACh
5HT
NE
DA
Spatial Information
Context Information
Other subcortical inputs (e.g., hypothalamus)
Excitatory and Inhibitory Feedback
Backpropagation of activity from CA3
A
B
C
Mossy Fiber Boutons
A
causal
acausal
pre
post
+50 ms
Δt
-50 ms
B
LTP
LTD
Plasticity of Synapses

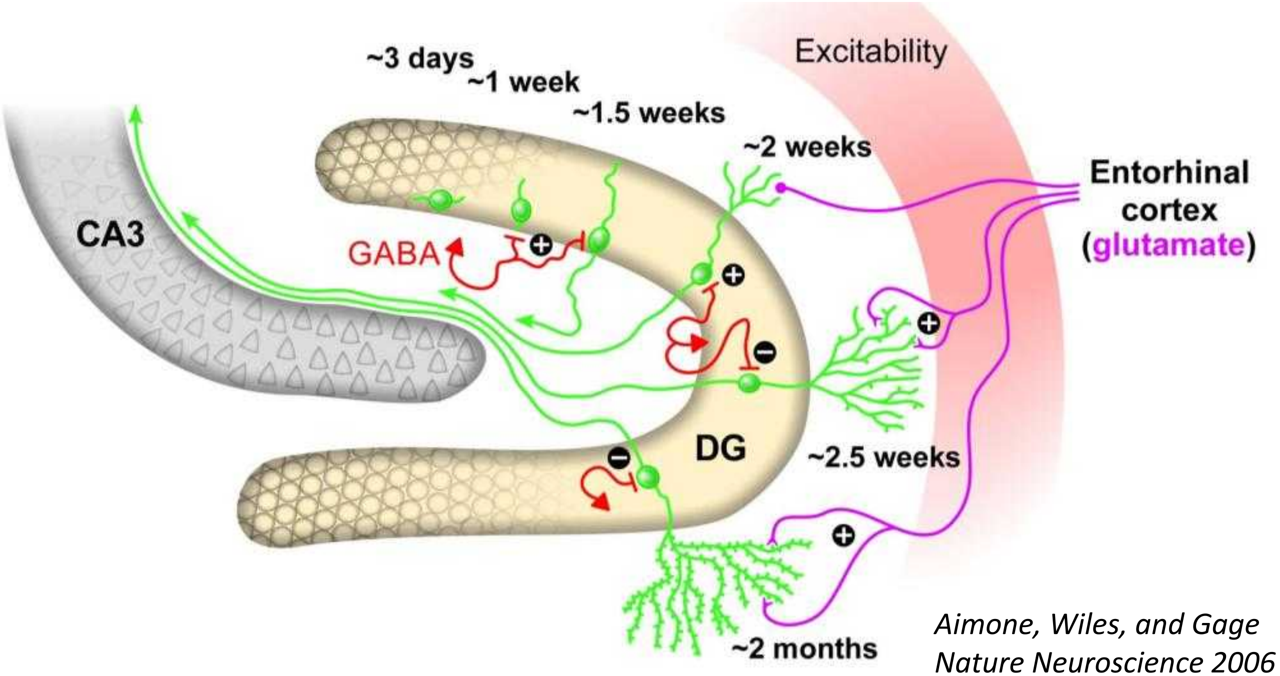
The real elephant in the room…





What are all those new neurons doing?

Adult Neurogenesis

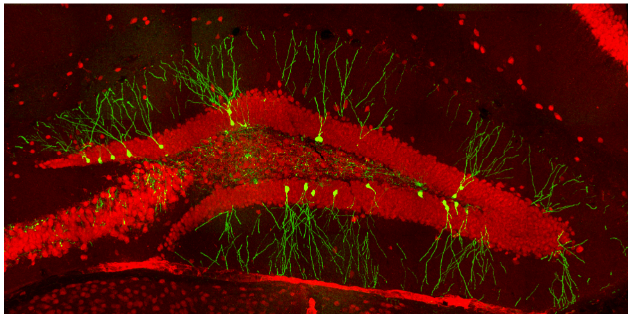


Aimone, Wiles, and Gage
Nature Neuroscience 2006

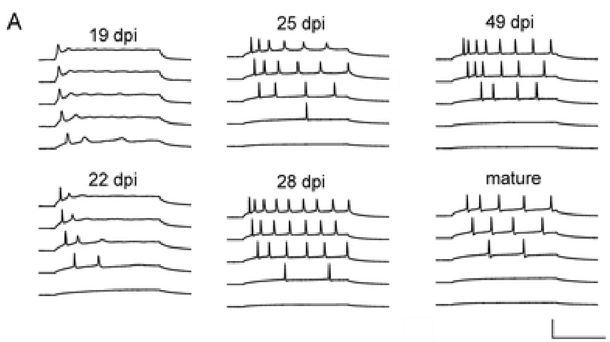
Neurogenesis → Pattern Separation is not a satisfying argument

It has to be more interesting than that…

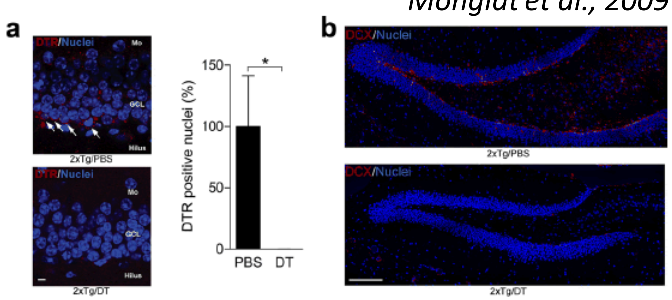
Modeling considerations



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

Spectrum of modeling: the added value of complexity

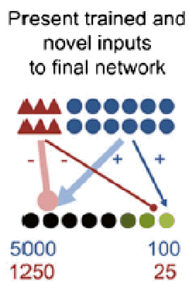
- Abstract
  - Assumptions in design and dynamics are very clear
  - Observed behaviors are easy to attribute to specific design principals
  - Relatively straightforward to do
- High Fidelity
  - Incorporates features whose importance is yet unclear
  - Highlights where biology data is strong and weak
  - Can reveal behaviors that were not a priori considered
  - Results can often be directly compared to biology

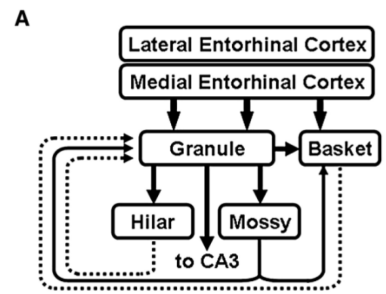
Levels of modeling neurogenesis

ABSTRACT

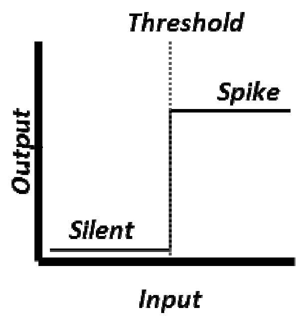
HIGH FIDELITY

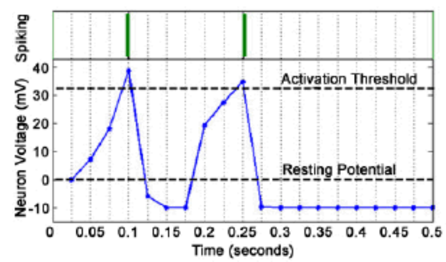
Anatomy



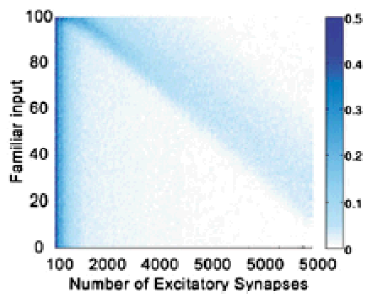


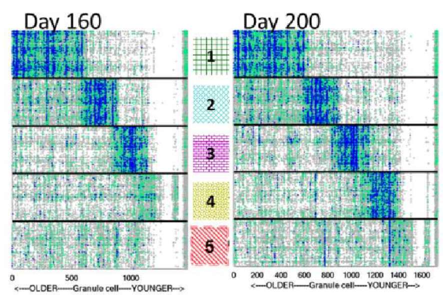
Dynamics





Behavior





Li et al., PNAS 2012

Aimone et al., Neuron 2009

Abstract models have been effective

- 2009 Neuron model (intermediate complexity)
  - Made three specific predictions that are being tested experimentally by many groups
    - Pattern Integration (*Marin-Burgin, Science 2012*)
    - Temporal Pattern Separation (Kesner lab, ongoing)
    - Long-term Specialization (Rangel et al., submitted ; *Alme et al., Hippocampus 2010; Frankland Lab*)
- 2012 PNAS model (very abstract)
  - Predicts that the difference in synapses number between young and mature neurons could sufficient for explaining function
  - Can clearly demonstrate the effects of perturbation on NG and DG function (e.g., effect of dopamine/reward)

Why look deeper?

- Investigate interaction of unique physiology dynamics
  - *Example*: Do young neurons fire before or after mature cells in response to novel or familiar inputs?
- Explore interaction of complex actors
  - *Example*: Serotonin alters K^+ conductance thus membrane resistance in GCs (via 5ht1a receptors) - what does this mean for new neuron function?
- More sophisticated readout
  - *Example*: Directly compare to and predict *in vivo* metrics of behavior (i.e., place cells, oscillations)

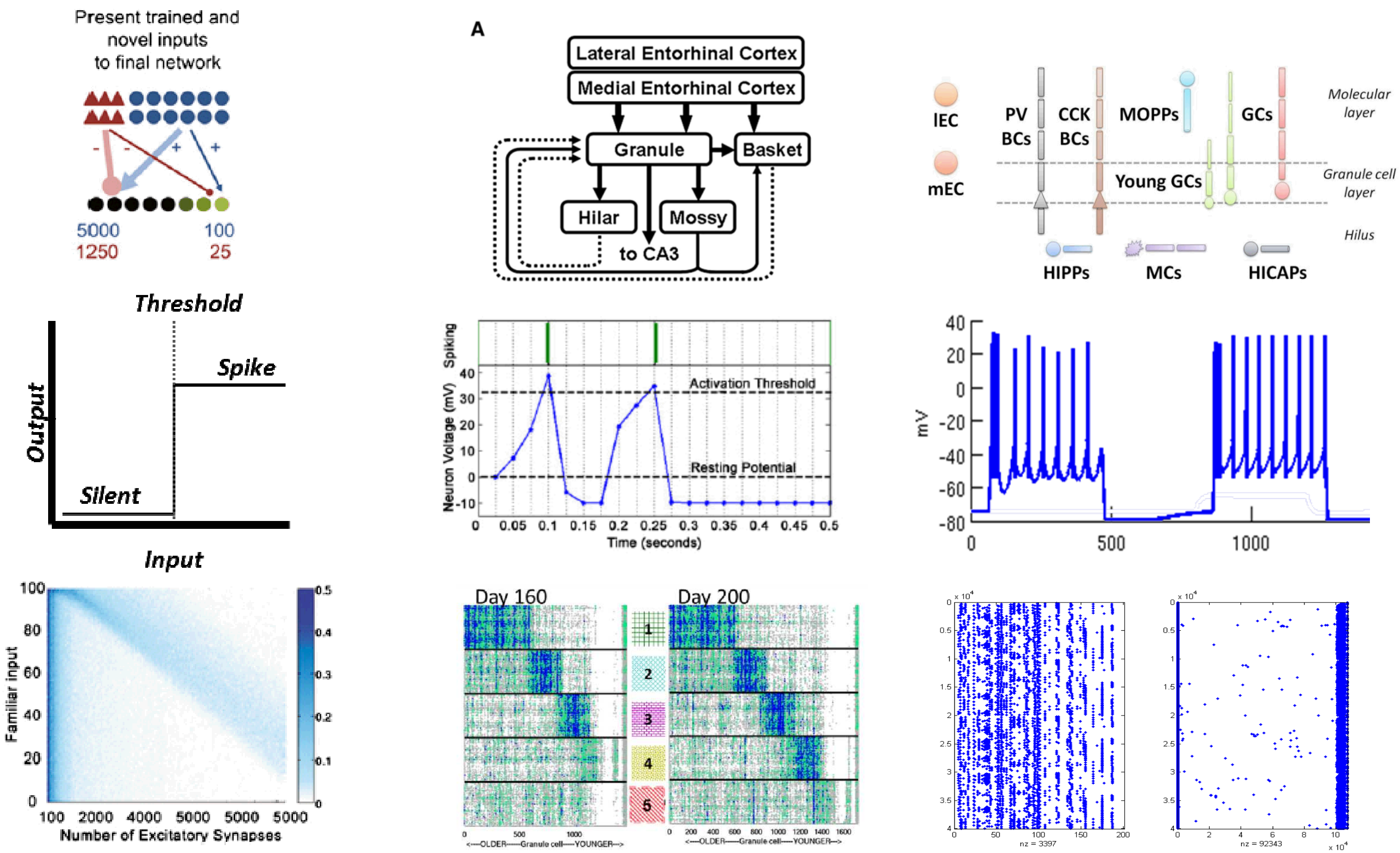
Levels of modeling neurogenesis

ABSTRACT — HIGH FIDELITY

Anatomy

Dynamics

Behavior

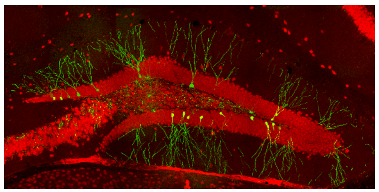


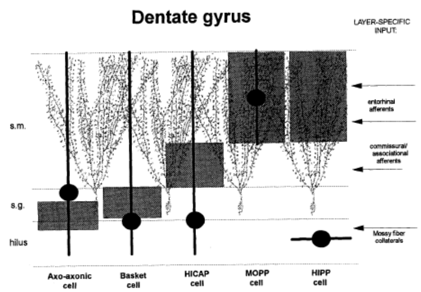
Li et al., PNAS 2012

Aimone et al., Neuron 2009

Anatomy

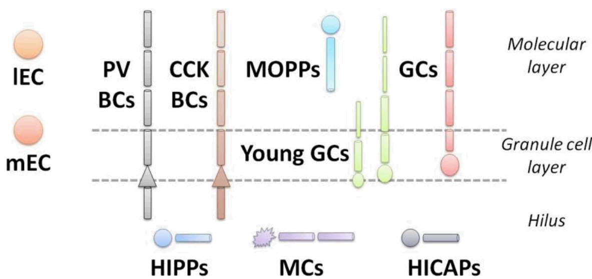
Actual

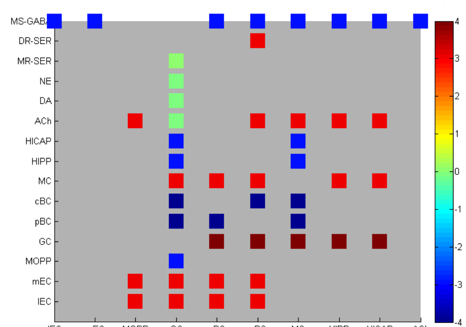


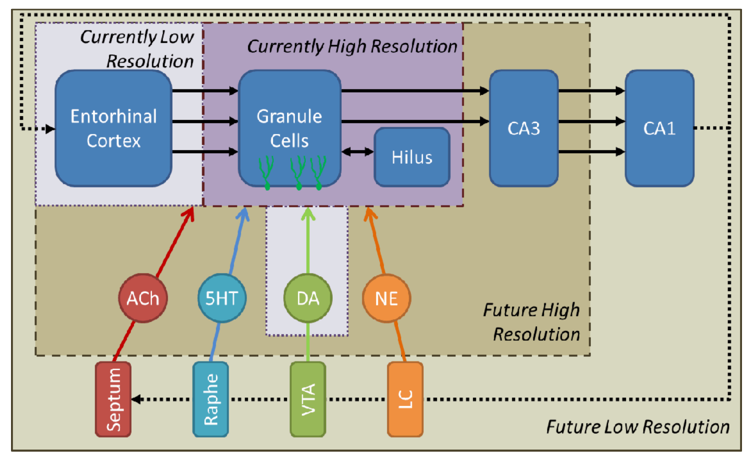


Goal: Implement biologically realistic neuron types, connectivity, **and scale**
Scope: Current focus on DG, ideally extend to CA3 and neuromodulatory systems

Where we're at

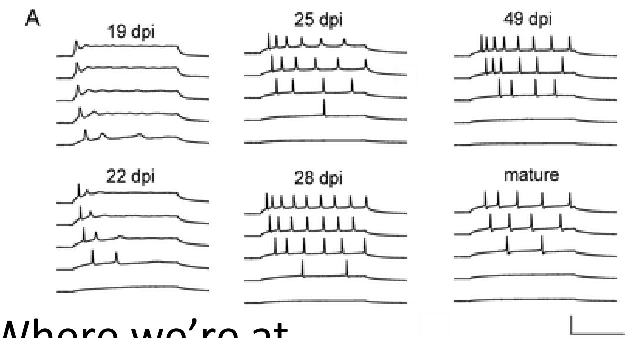




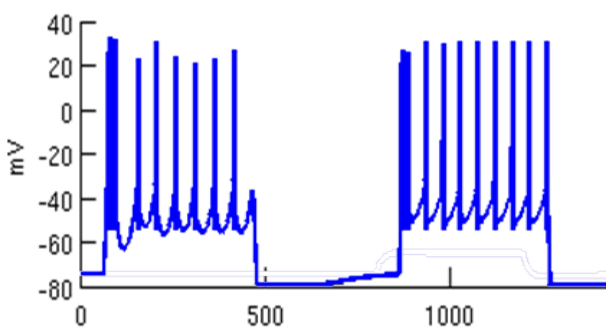


Physiology dynamics

Actual



Where we're at



$$\frac{dv}{dt} = \frac{1}{C}\left(k(v) \times (v - v_r) \times (v - v_t) - u + I_{syn} + I_{comp}\right)$$

where ...

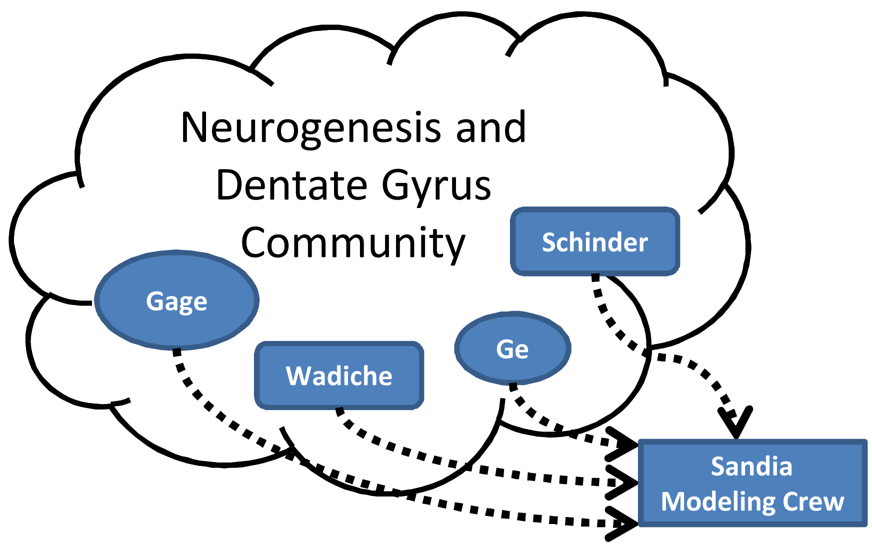
$$k(v) = k_N \times \left(k_a + k_b \times (v - v_t)\right)$$

$$\frac{du}{dt} = a \times (b \times (v - v_r) - u)$$

$$\begin{aligned} &if\ v > 35 \\ &u \leftarrow u + d \\ &v \leftarrow c \end{aligned}$$

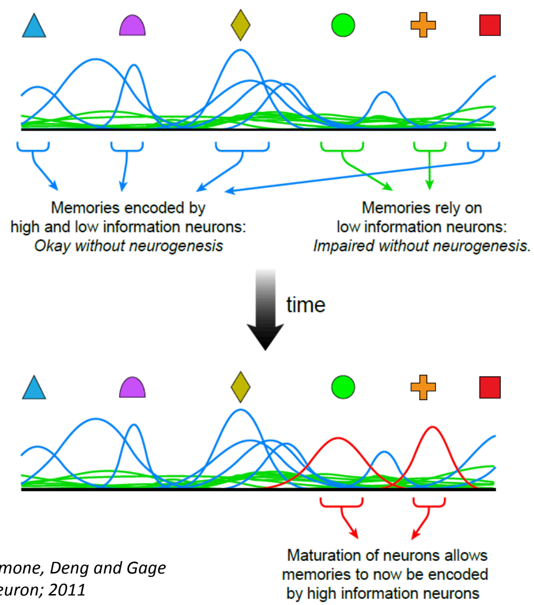
Goal: Algorithmically fit implement biologically realistic neuron dynamics for each neuron type; including changing dynamics as neurons mature

Scope: Current goal is a multi-compartment version of the *Izhikevich* class of neuron models. Will consider increasing to biophysically realistic (conductance based).



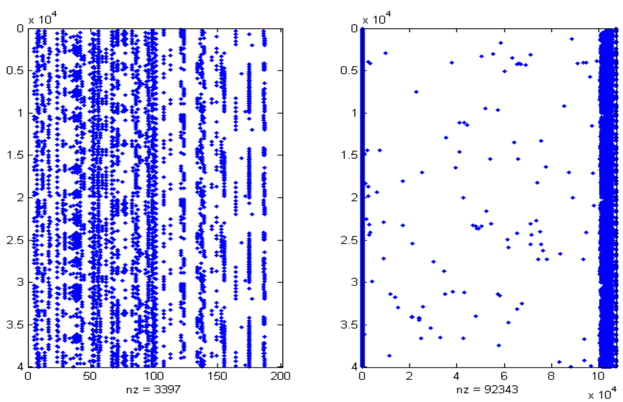
Behavior

Actual



Aimone, Deng and Gage Neuron; 2011

Where we're at



Goal: Explore more sophisticated theories of neurogenesis function (e.g., *memory resolution*). Hopefully, this will help radically disparate concepts of pattern separation and related network behaviors.

Further goals include directly relating function to behavioral tasks simultaneously being run.

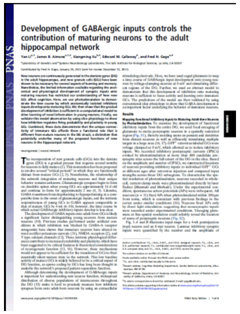
Scope: Current approach is to implement biologically realistic input behaviors (spatial/object tasks where EC inputs change over time). Will basic EC representations on grid (e.g., Moser lab) and object cell (e.g., Knierem lab) representations

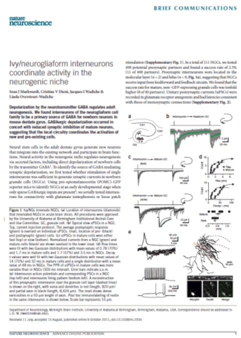
New tools for analyzing real-scaled spiking networks with population coding will likely be necessary

How do we build a realistic model

- Details matter

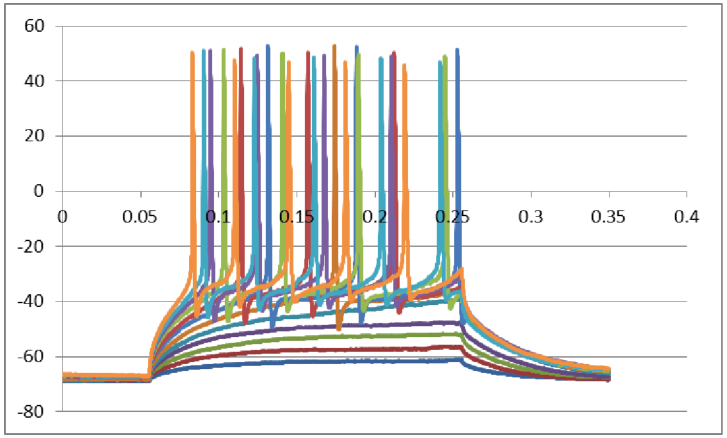
  Extract biological data from many disciplines

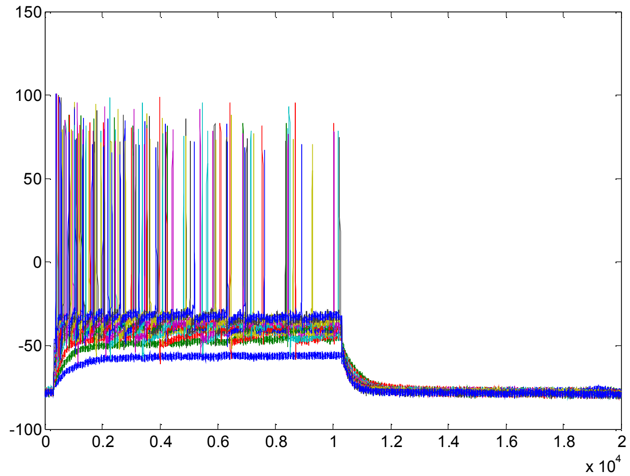




How do we build a realistic model

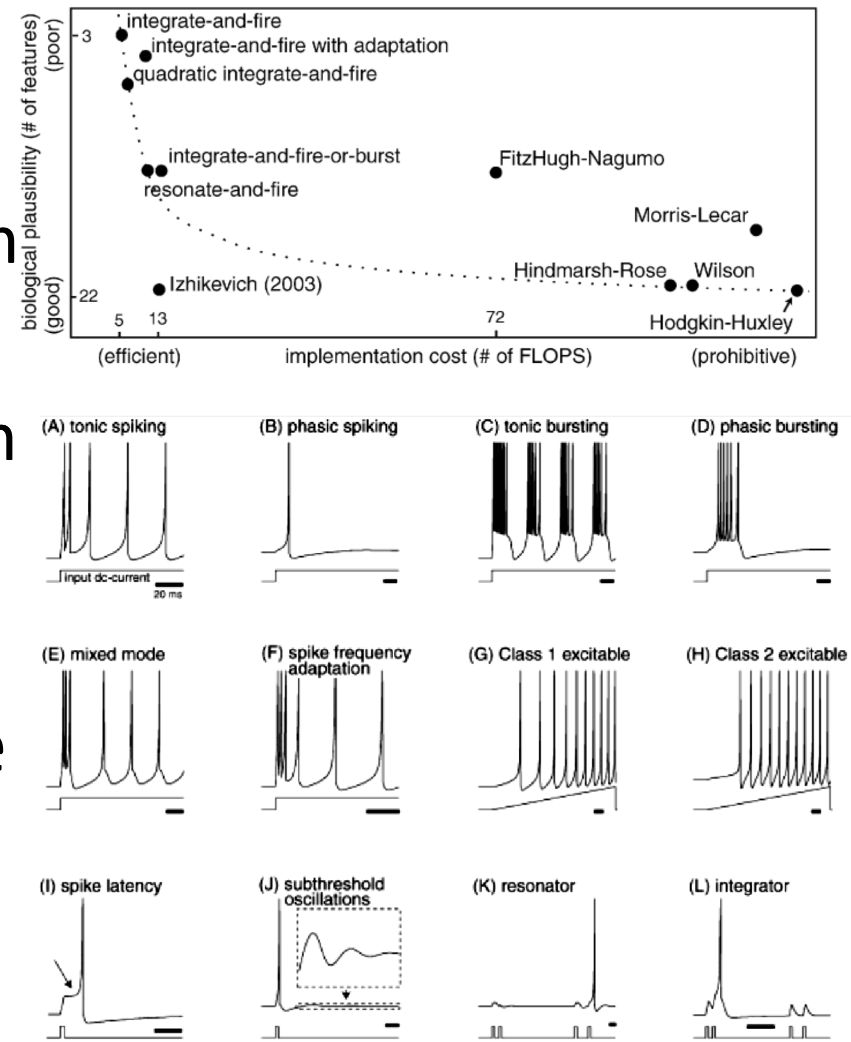
- Details matter
  - Extract biological data from many disciplines
  - Ask (beg) for raw data from electrophysiologists





How do we build a realistic model

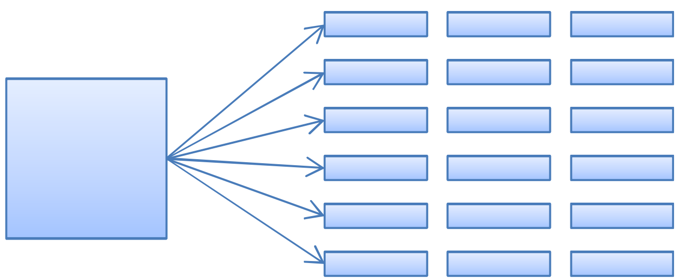
- Details matter
  - Extract biological data from many disciplines
  - Ask (beg) for raw data from electrophysiologists
- Select neuron and synapse models that are realistic, tractable, and "fittable"



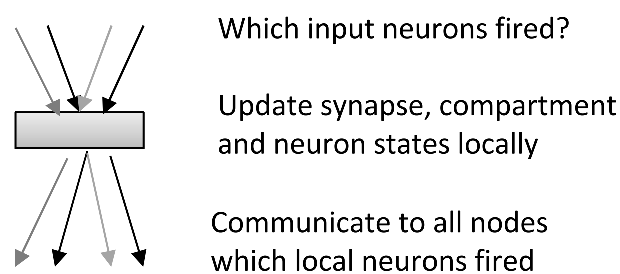
Izhikevich 2004

How to simulate … at relevant scales

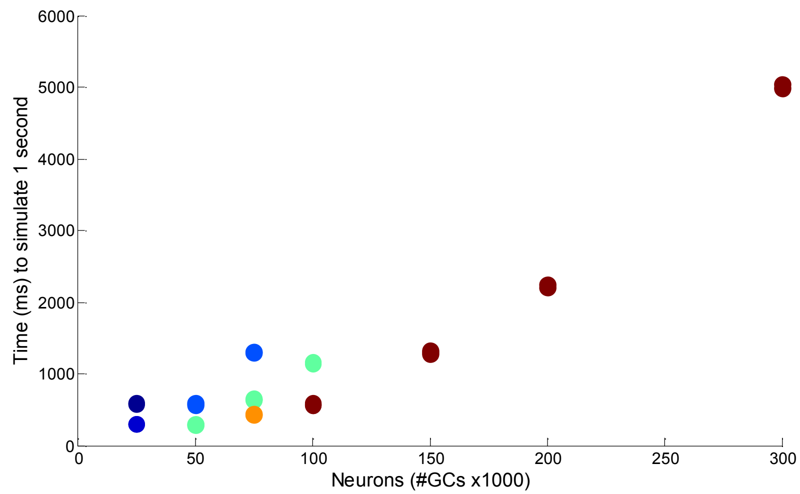
- Preliminary evidence suggests that reduced scale models can often be misleading and potentially simply wrong
- Intrinsically parallel code
- Run on supercomputer / cloud resources

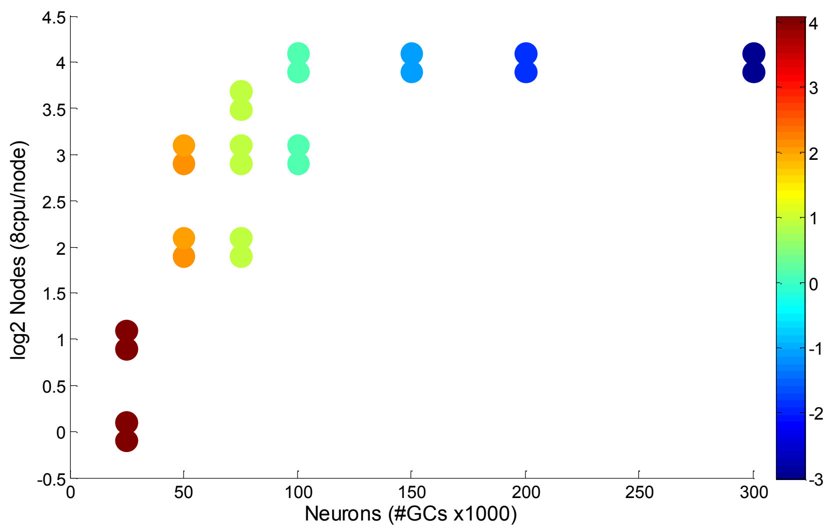


Distribute neurons and synapses across nodes



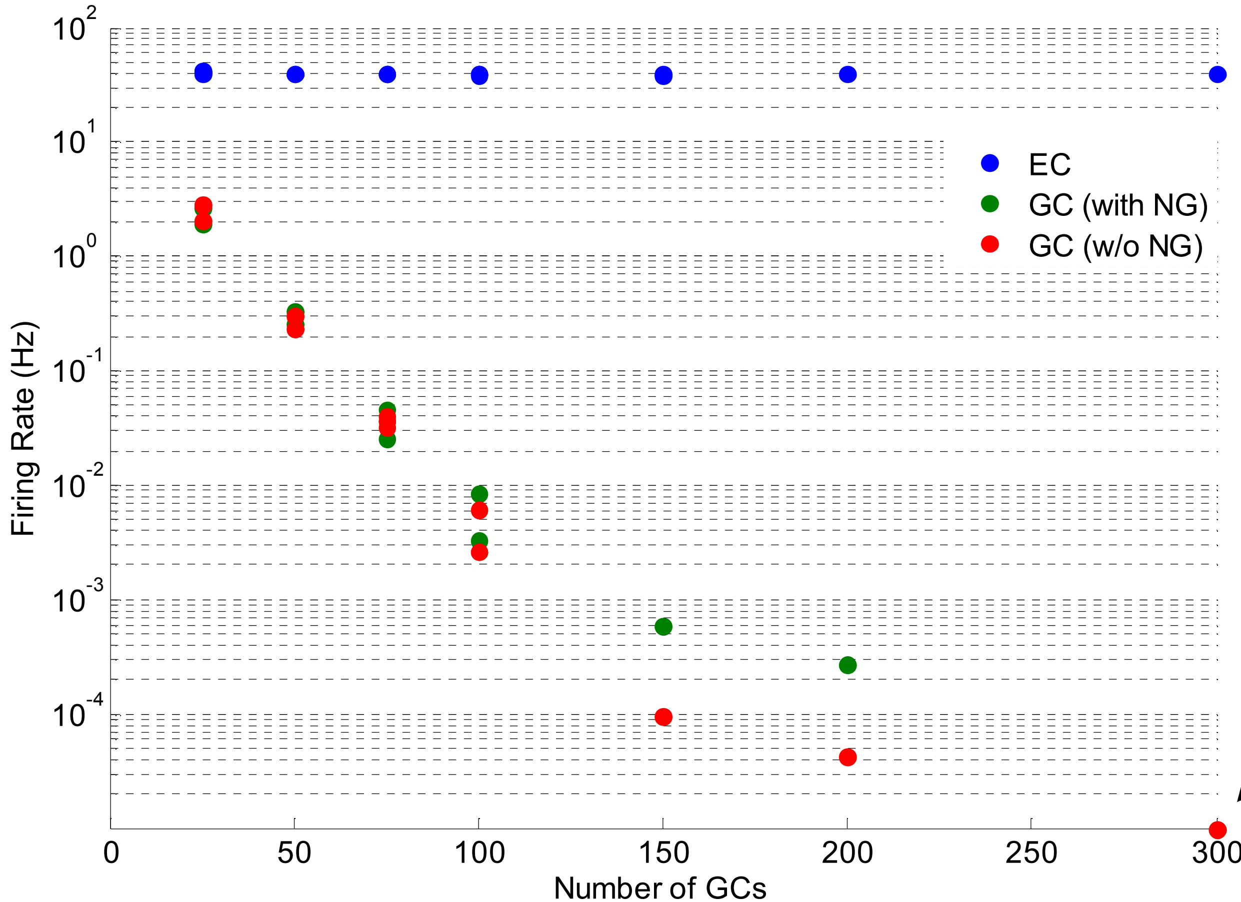
How simulations currently scale





- Takes a long time to simulate realistic sized networks
  - >1 hour to simulate mouse-sized network
- Considerably faster for smaller networks
  - How small is sufficient?
- Little overhead lost due to parallelization
  - Code appears to distribute efficiently

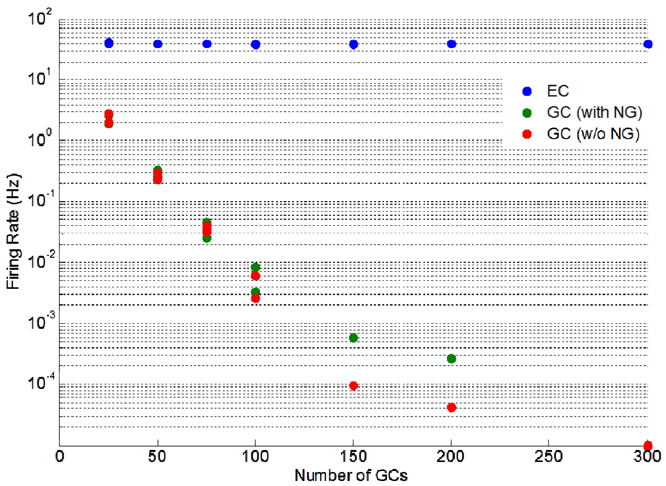
Preliminary data shows GC activity decreases with scale

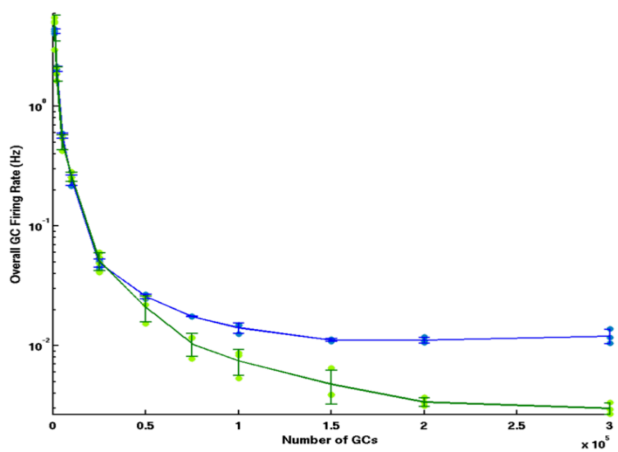


No activity in mouse sized networks

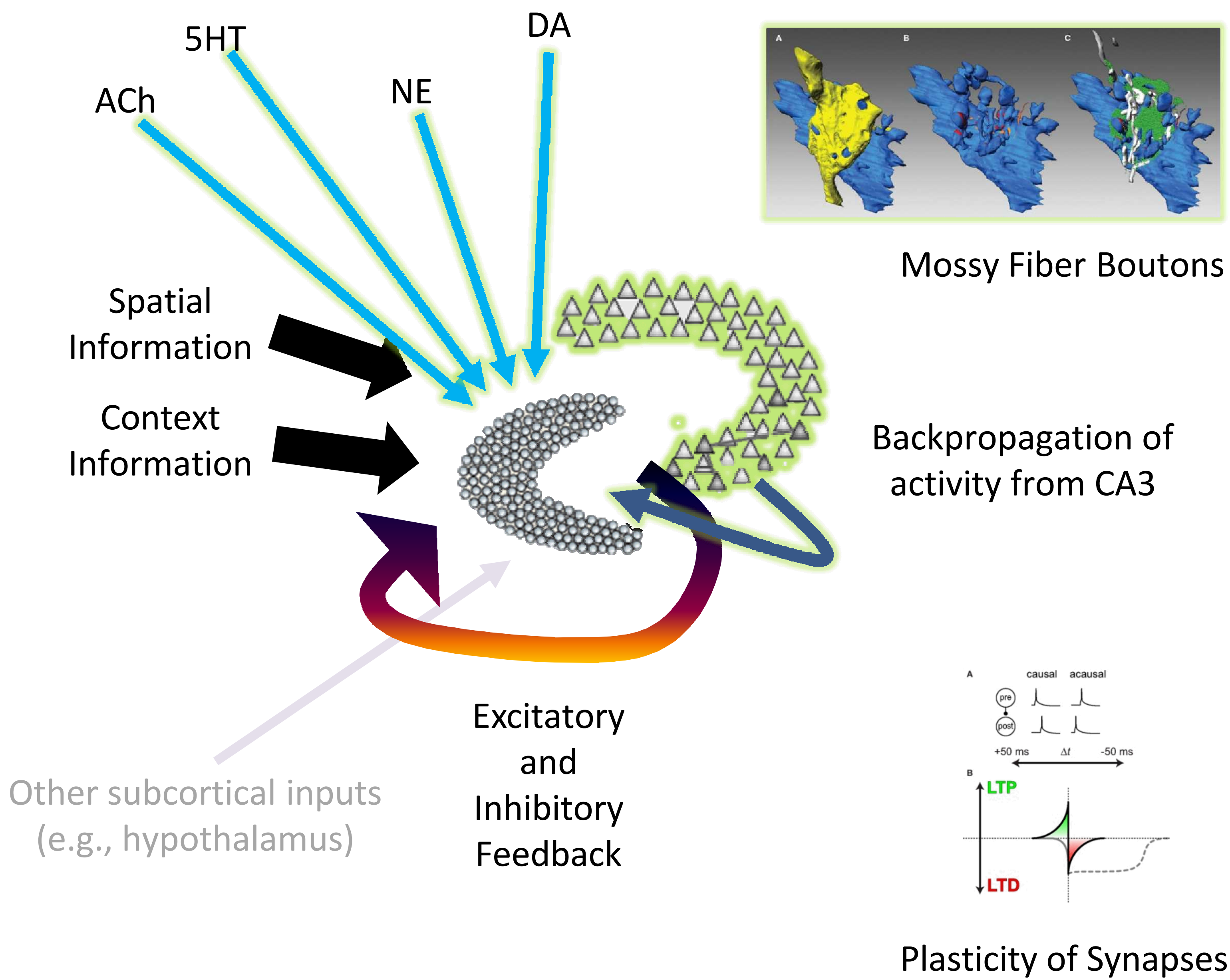
Presence of immature neurons boosts activity particularly in large scale

Notes on preliminary scaling result





- Very consistent with observation in previous iteration of model
- Still early
  - Needs improved fitting of neuron dynamics
  - Longer simulation epochs
- This looks only at *novel* encoding, familiar may be fundamentally different



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Plasticity of Synapses

Questions to ask of realistic model

- How does model DG respond to realistic behavioral training task?
- Memory resolution over time; difference in novel vs familiar information encoding
- Pattern separation – what makes DG unique?
- Does scaling affect function?
- Network dynamics
  - Relationship of neuron activity to network dynamics (e.g., oscillations)
  - Neuromodulation