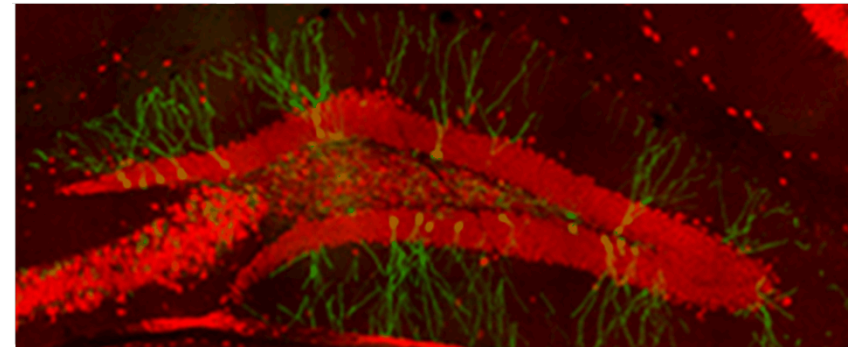
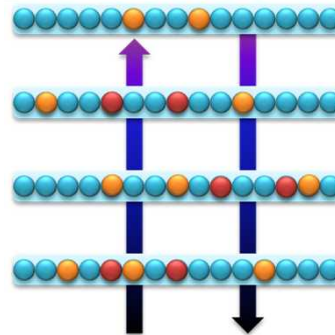
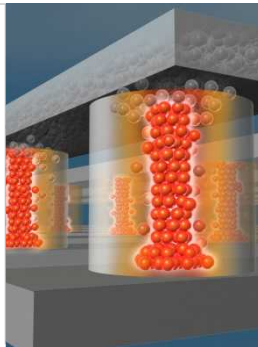


Exceptional service in the national interest



Modulating Neural Computation

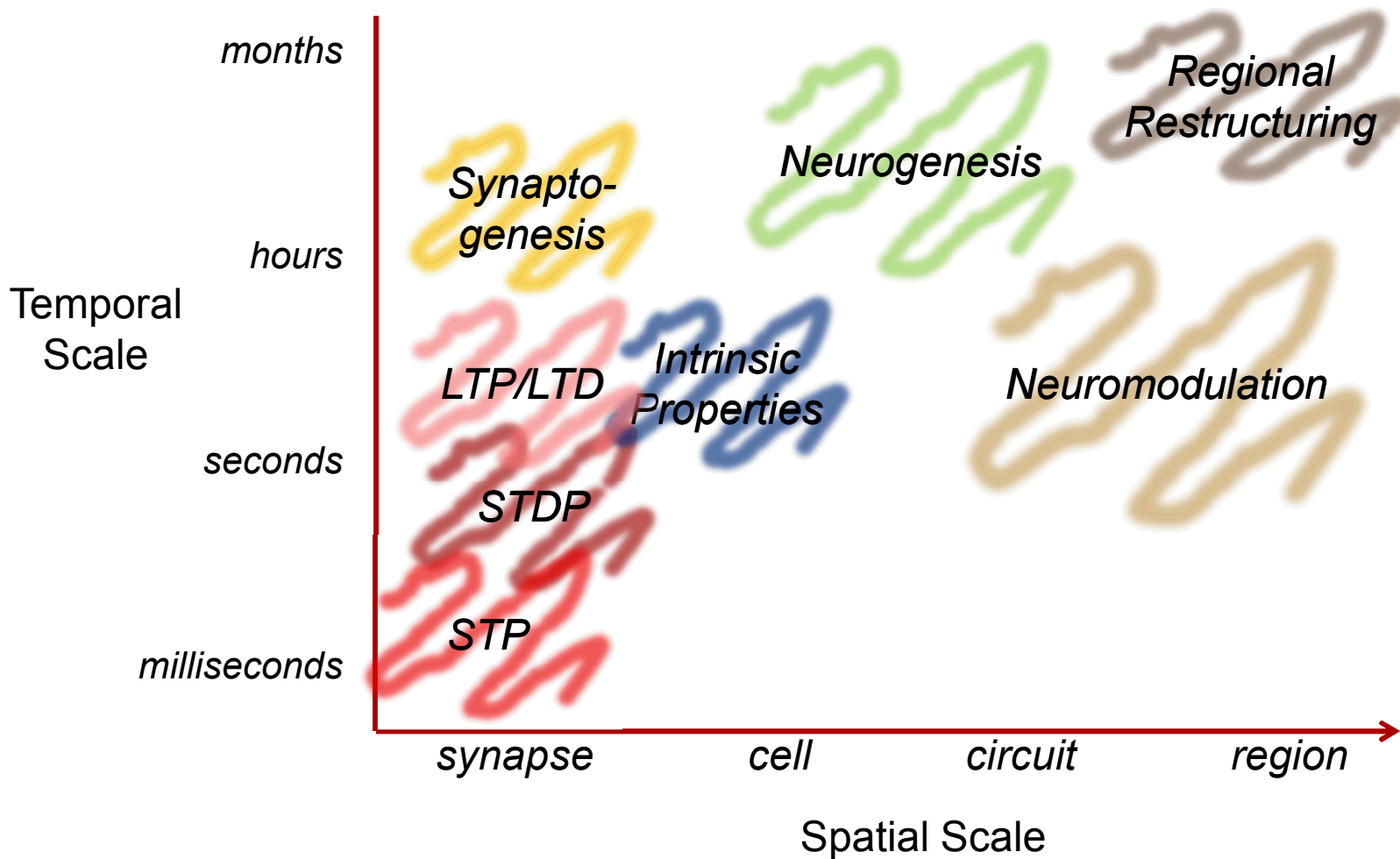
4th Annual NICE Workshop, Berkeley, CA 2016

Brad Aimone, Ph.D.
Sandia National Laboratories

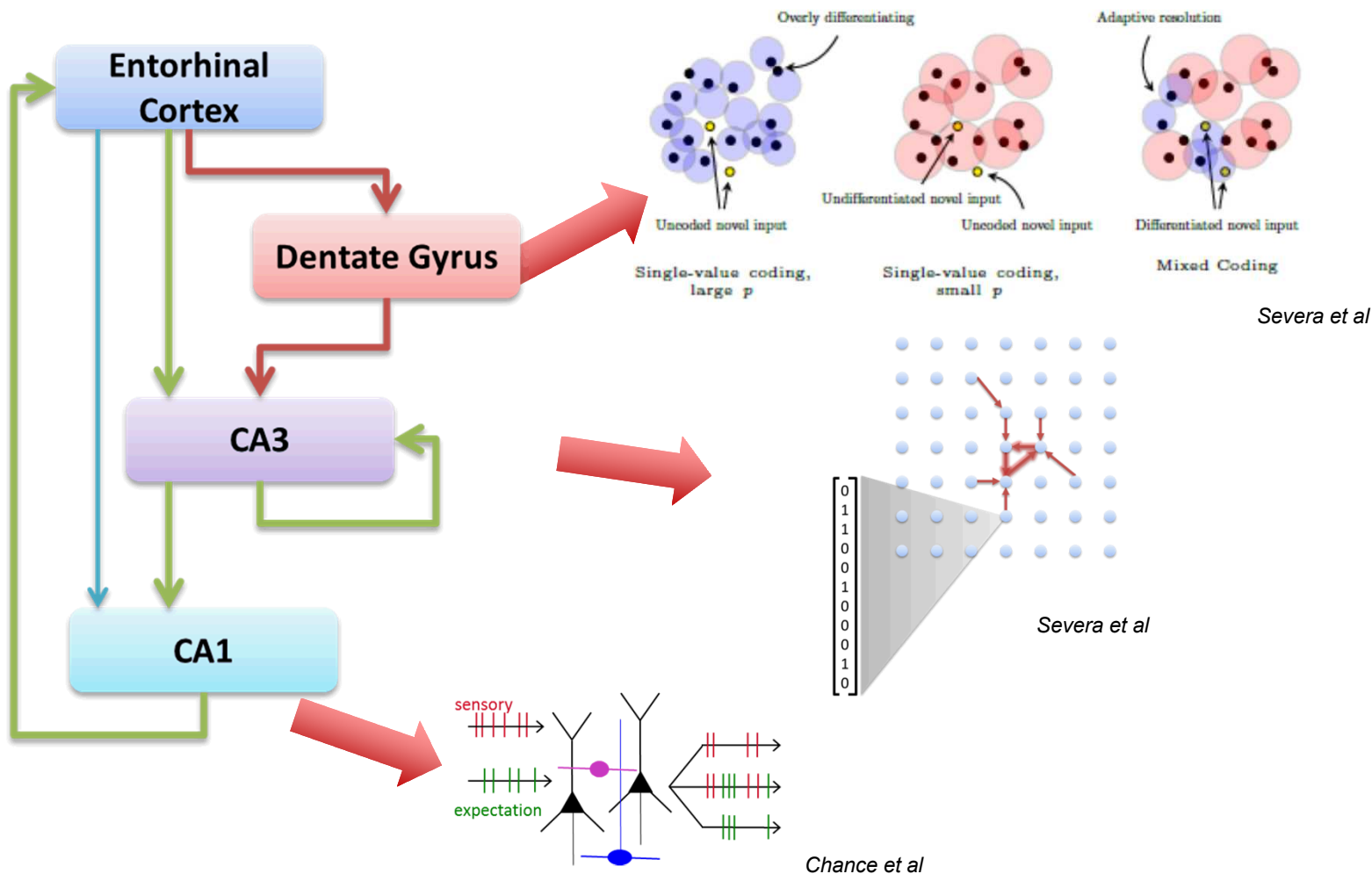


Sandia National Laboratories is a multi-program laboratory managed and operated by Sandia Corporation, a wholly owned subsidiary of Lockheed Martin Corporation, for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

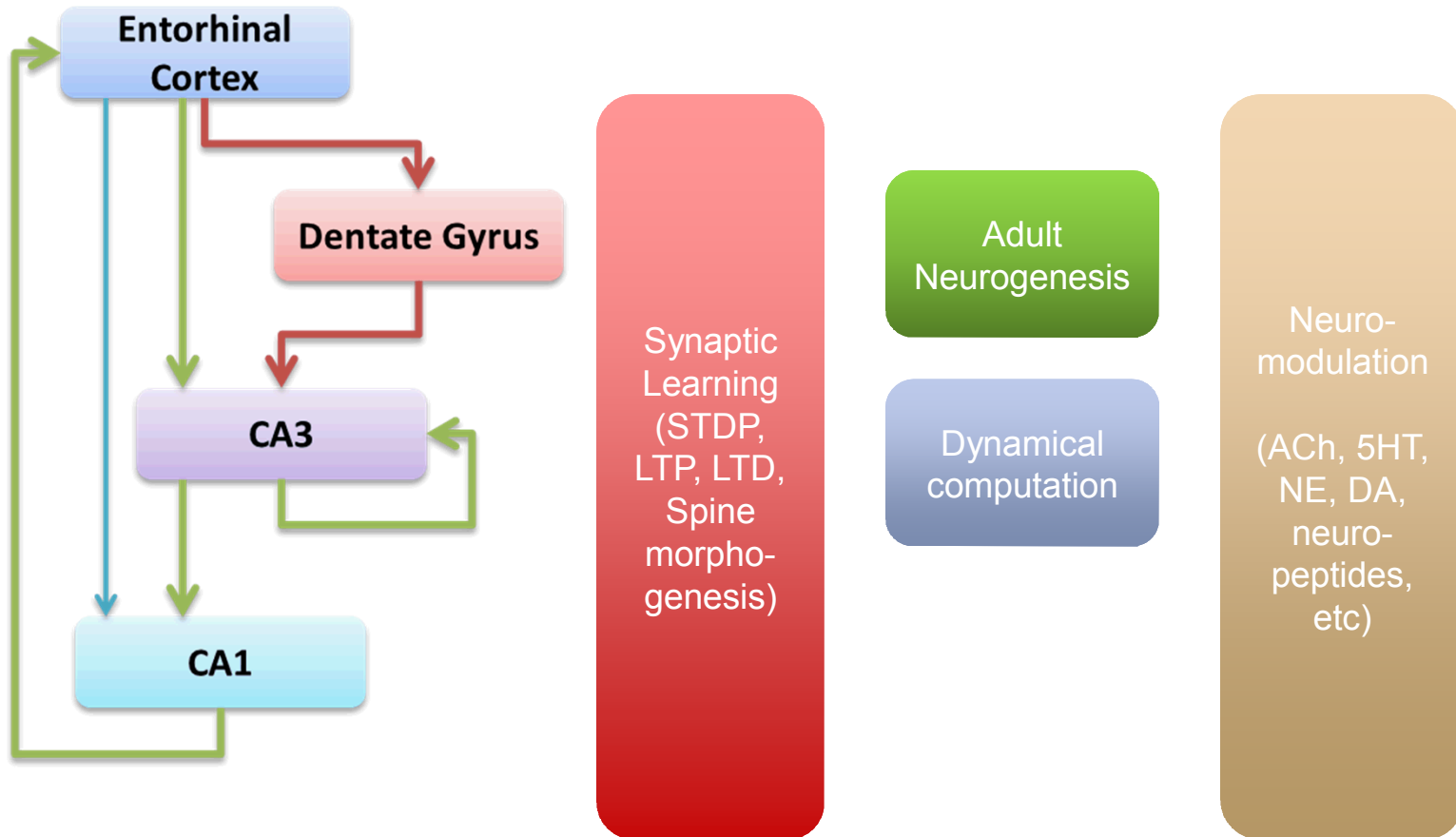
Neural plasticity influences neural computation at many spatial and temporal scales



Formalizing learning algorithm from the hippocampus requires consideration of wide range of neural plasticity

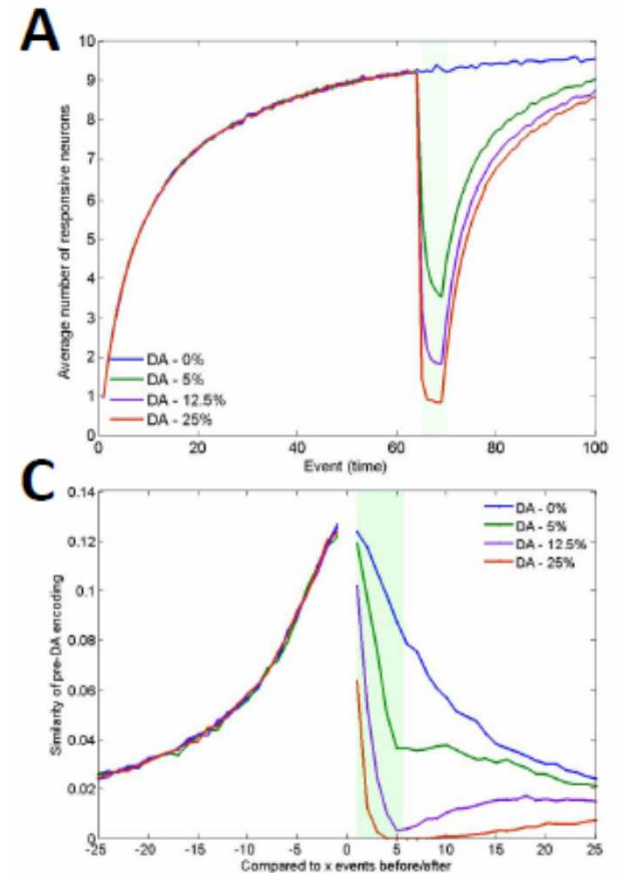


Formalizing hippocampal learning requires consideration of wide range of neural dynamics and plasticity



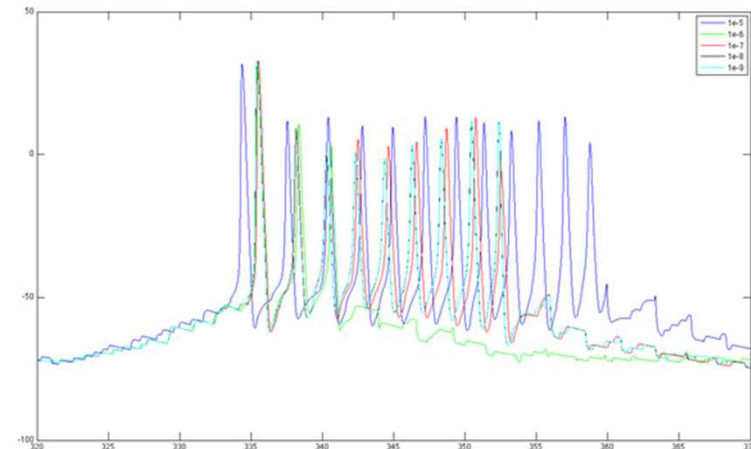
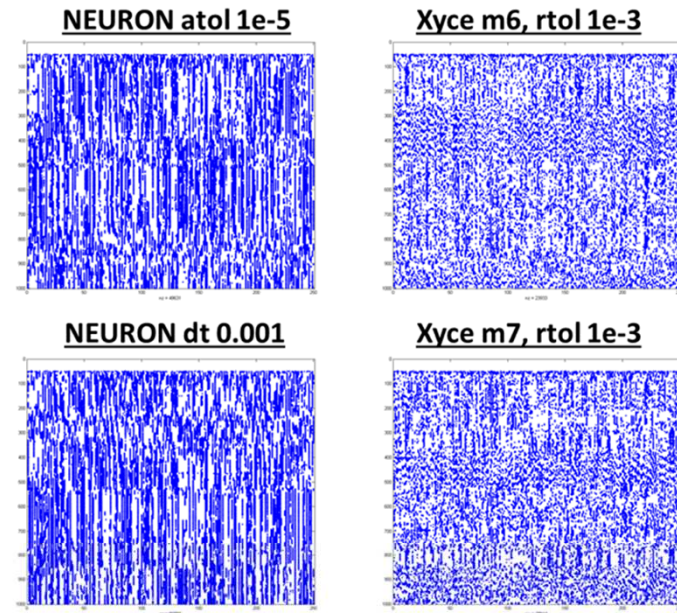
Dynamical neural computing and neuromodulation are tightly linked

- Modulatory systems are typically linked to setting global state or ascribing state to learned behaviors
 - Dopamine w/ reinforcement learning
 - Acetylcholine and serotonin w/ sleep & attention
- Modulators are well positioned to directly influence computation
 - Relatively global signal with highly heterogeneous receptors
 - Distinct interneuron populations often selectively activated
 - 5HT activates CCK basket cells while ACh activates PV basket cells
- Near-chaotic dynamics in cortical and hippocampal networks could make them highly sensitive to modulatory perturbation



A stable perspective to assess impact of neuromodulation

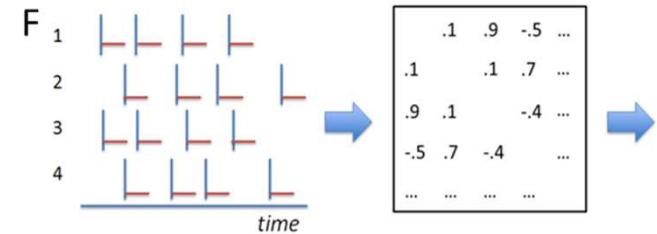
- Observation:
 Chaotic-like dynamics of identical recurrent networks yield vastly different behavior from different simulators...



A stable perspective to assess impact of neuromodulation

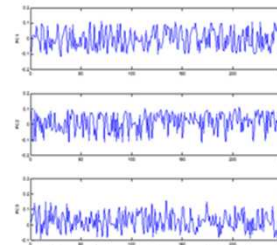
- Observation:
Chaotic-like dynamics of identical recurrent networks yield vastly different behavior from different simulators...

... but underlying correlational manifold is stable / consistent across simulations

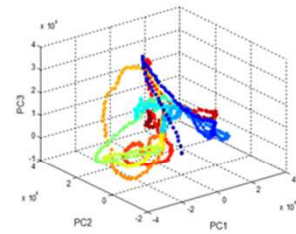


Filter spiking data to smooth temporal responses

Compute covariance matrix and determine eigenvectors (Principal Components Analysis)

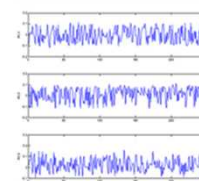
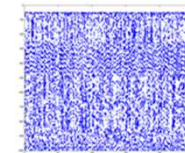


Principal components are orthogonal combinations of neurons and form new basis

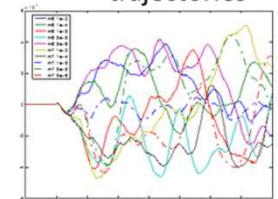


Dynamics of 250 neuron network can be observed as progression through PC space

G
Dynamics invariant PCs

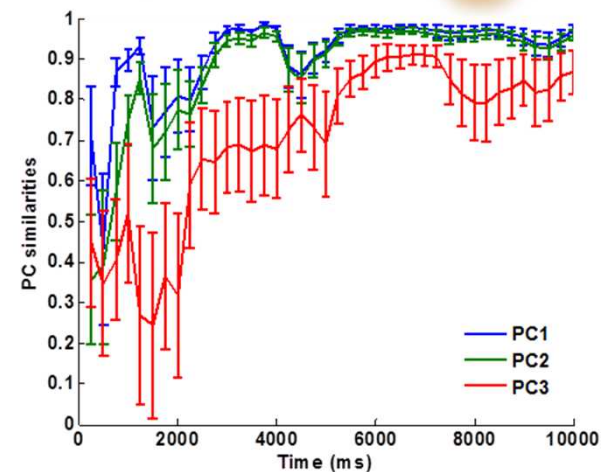
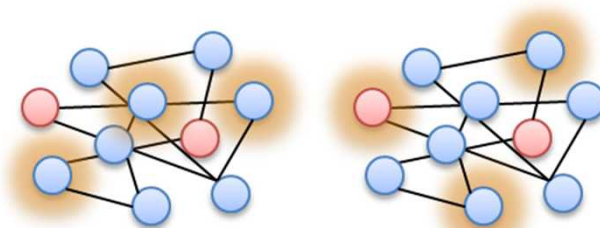


Temporally dynamic PC trajectories



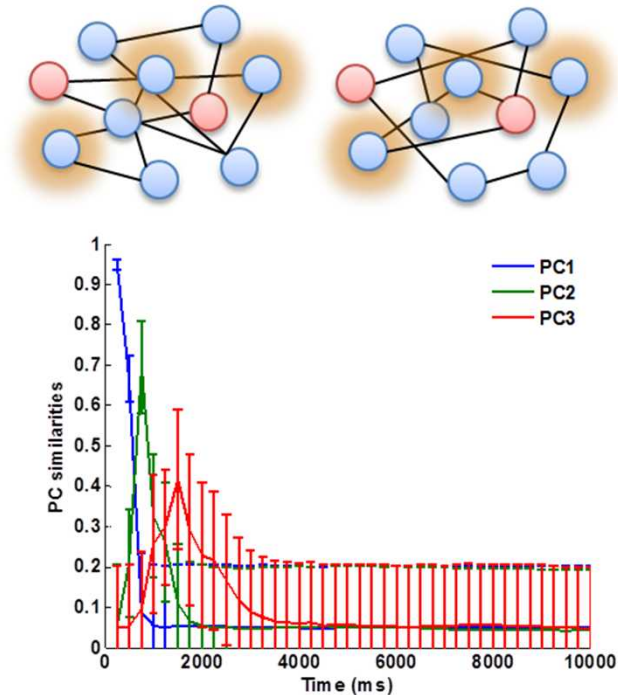
We can use principal components as readout of network perturbation

- Stable correlated neuron populations are not that surprising and consistent with STDP stories
- Different acute perturbations yield expected behaviors
 - Transient inputs displace correlated structure which eventually returns



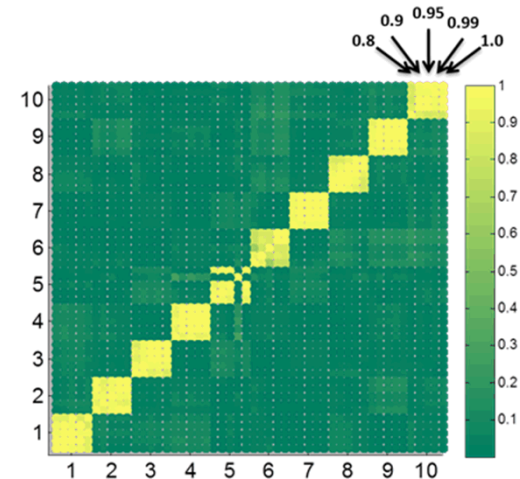
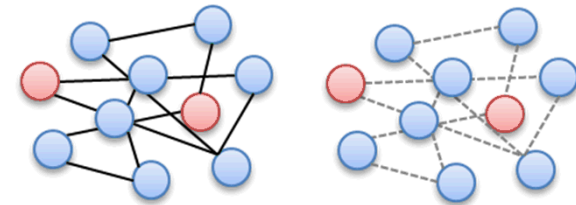
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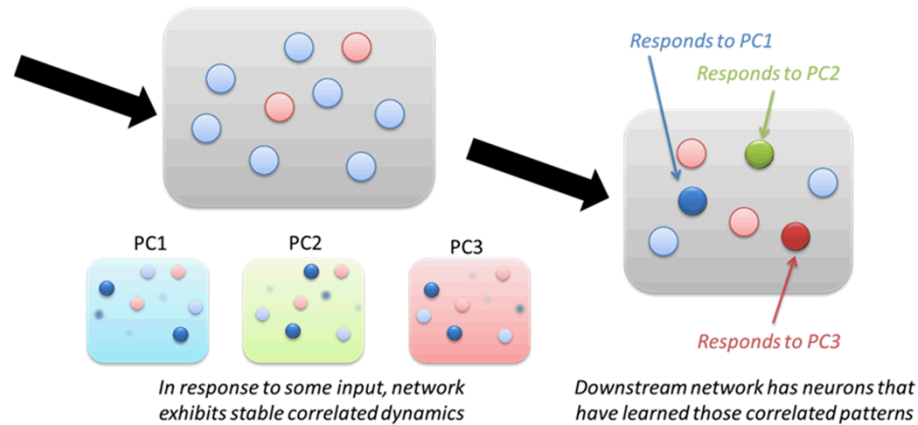
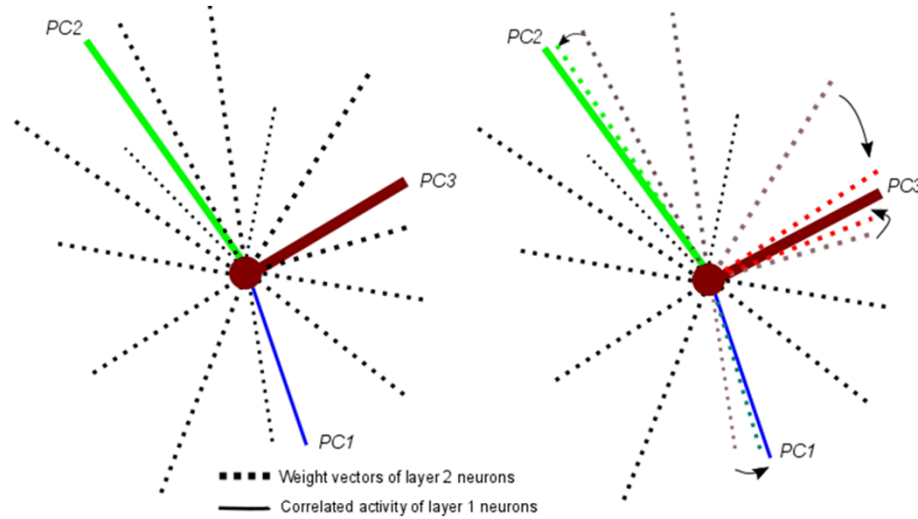


We can use principal components as readout of network perturbation

- Stable correlated neuron populations are not that surprising and consistent with STDP stories
- Different acute perturbations yield expected behaviors
 - Transient inputs displace correlated structure which eventually returns
 - Different networks have different manifolds in spite of “identical” inputs
 - Probabilistic synapses do not affect manifold stability

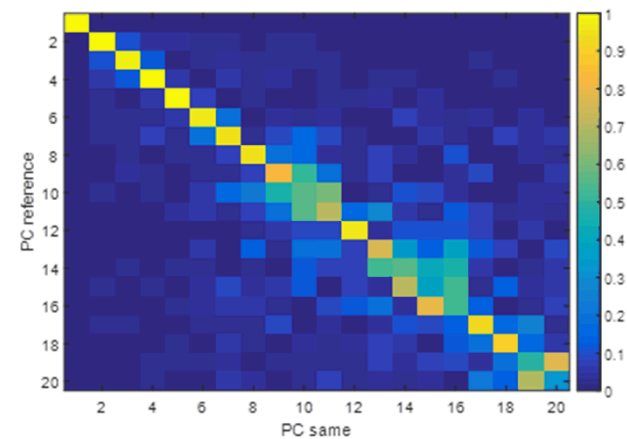
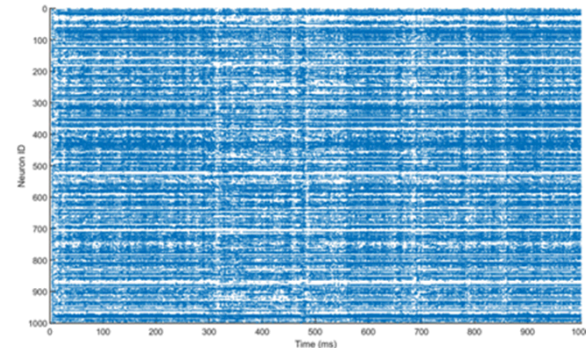


Correlated populations useful for learning and computation



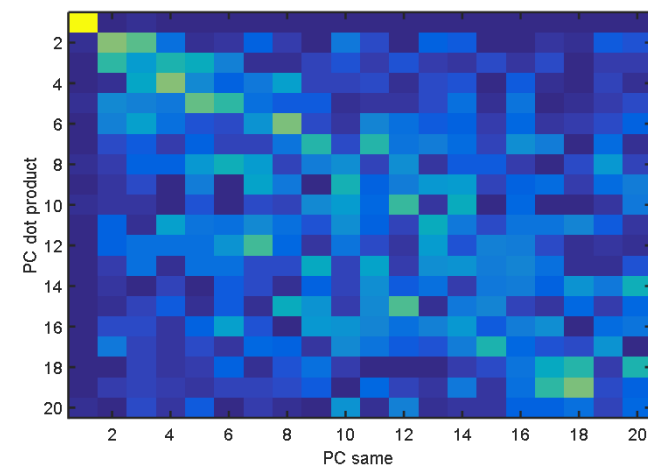
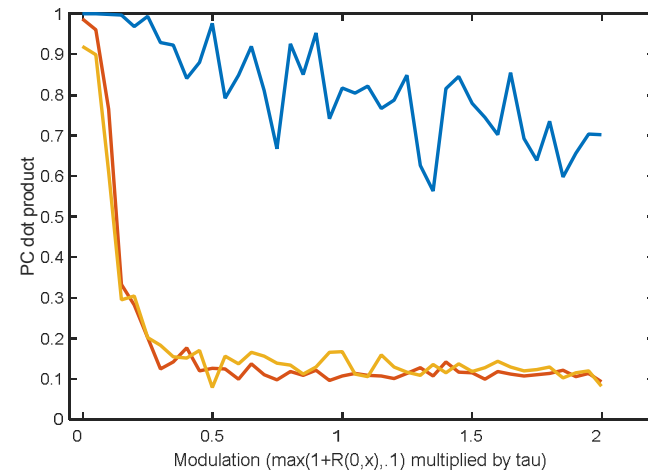
Neuromodulation can greatly impact dynamics

- Very simple LIF model
 - 80/20 E-I network
 - Neurons leak, integrate inputs, and spike above a threshold
- As before, reactivating same network yields consistent PCs



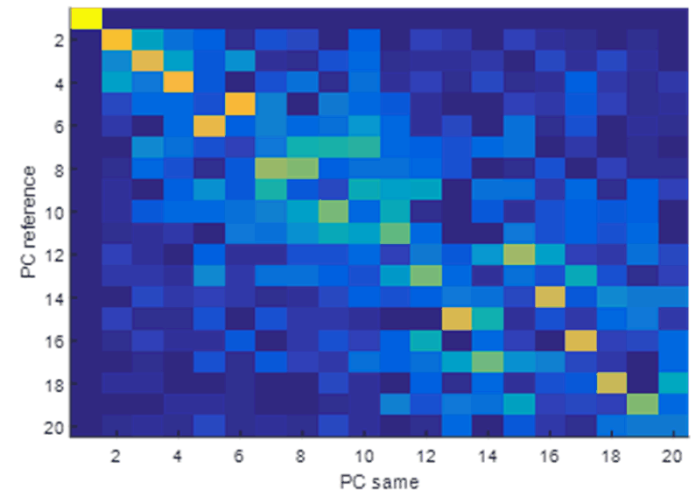
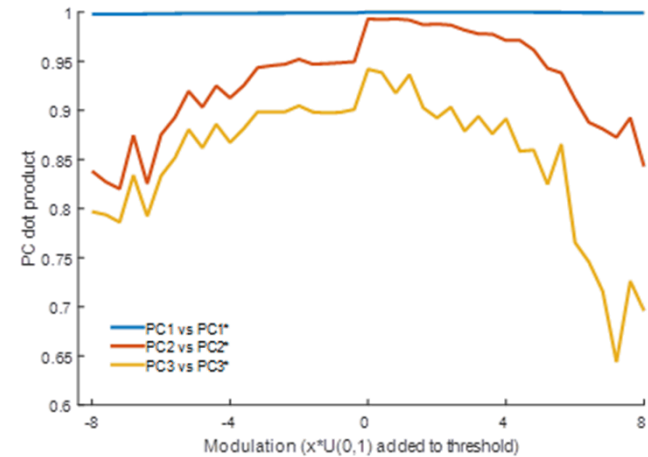
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 - Dramatic decorrelation of activity relative to before; especially for non-primary components



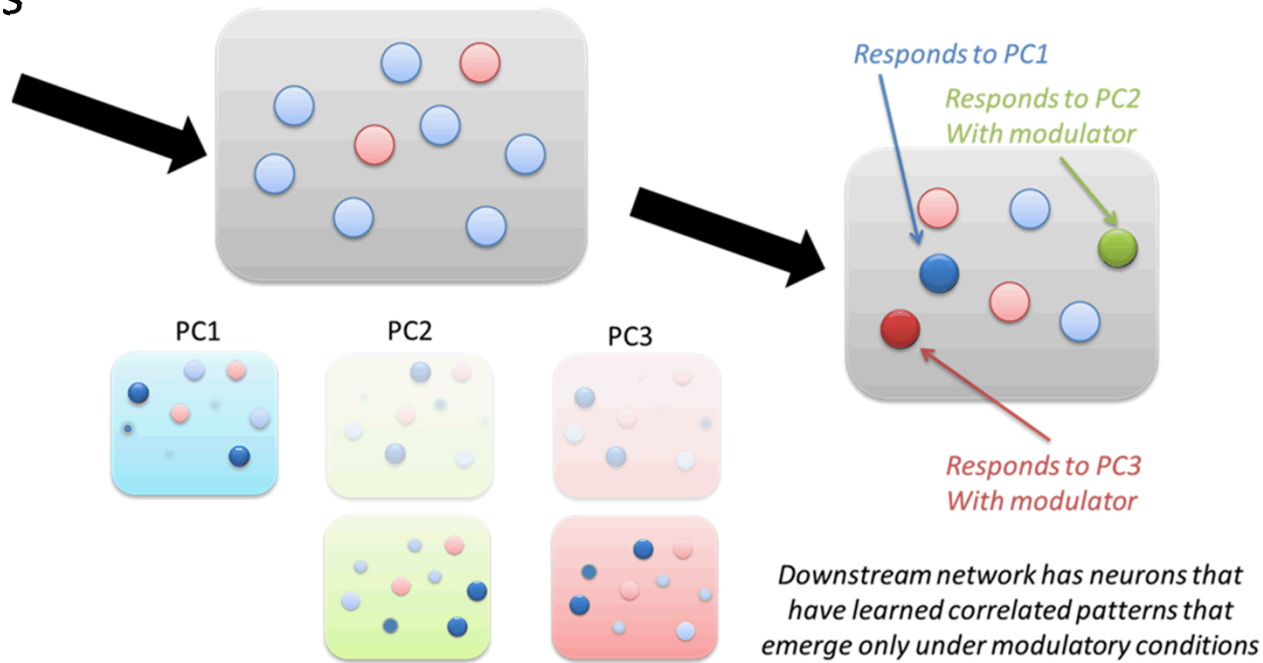
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 - Dramatic decorrelation of activity relative to before; especially for non-primary components
- Acetylcholine -> change v_{thresh}
 - Gradual decorrelation of activity



Modulation effects would propagate through coupled networks

- Highly simplified view of modulation and just scratching the surface
- Modulators are not independent and have highly complex effects

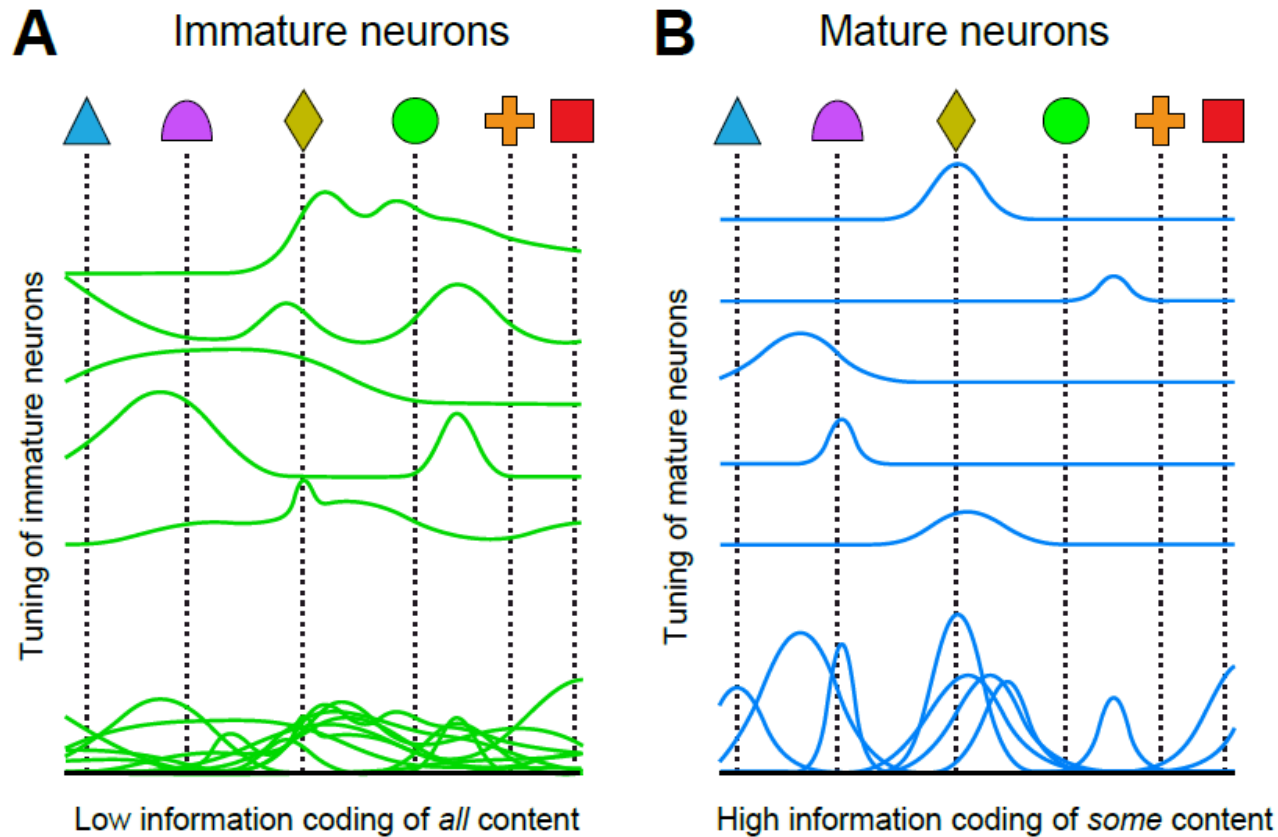


In response to modulation, correlated dynamics of network shift in cohesive manner

Thanks!

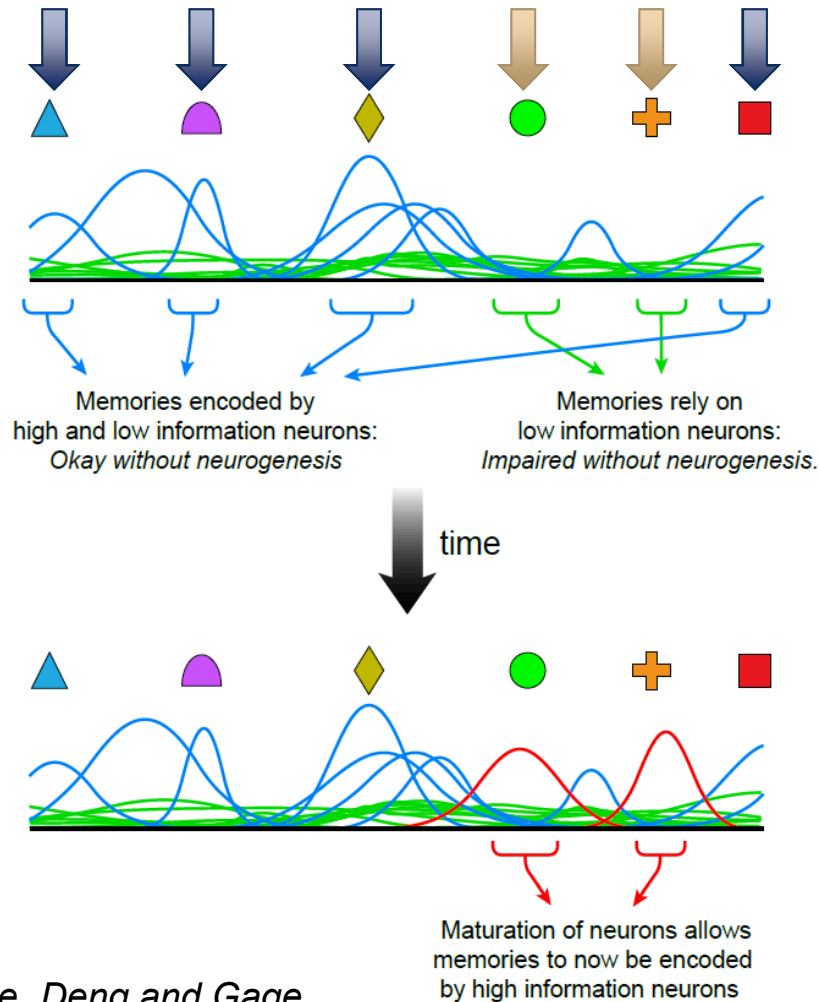
Backup slides...

Immature and mature neurons encode information differently



*Aimone, Deng and Gage
Neuron; 2011*

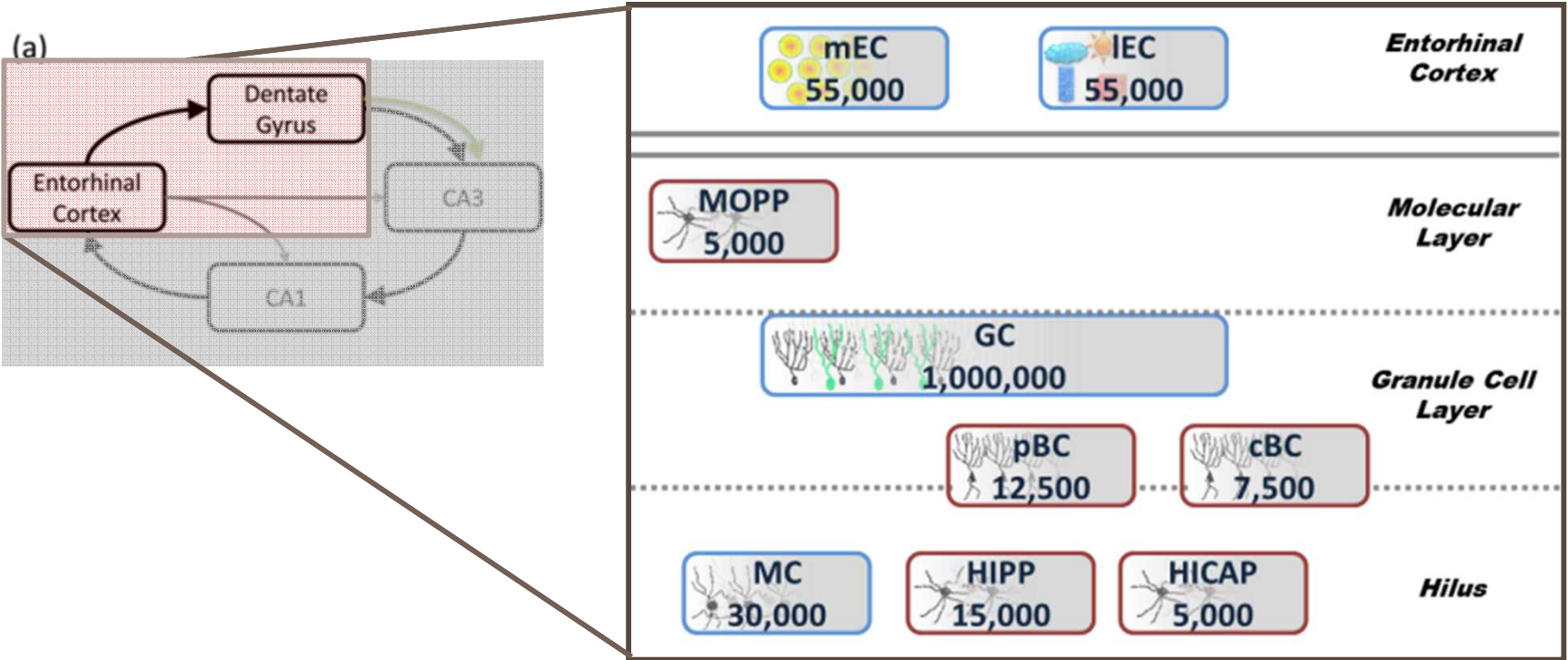
Mixed coding scheme in DG is potentially very powerful



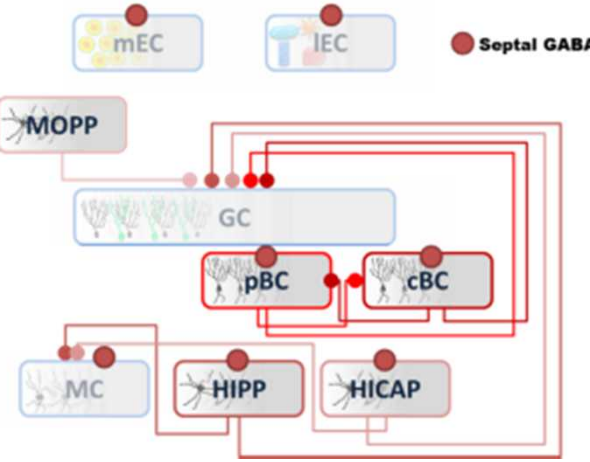
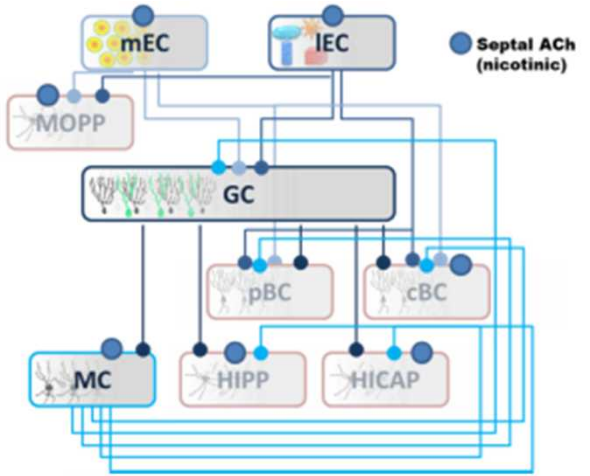
Aimone, Deng and Gage
Neuron; 2011

- 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*

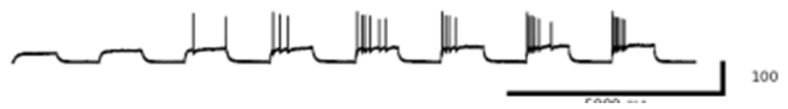
Realistic scale model



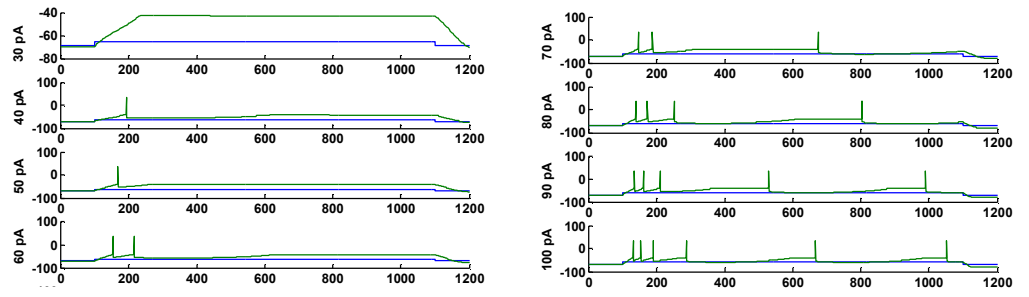
Realistic connectivity and dynamics



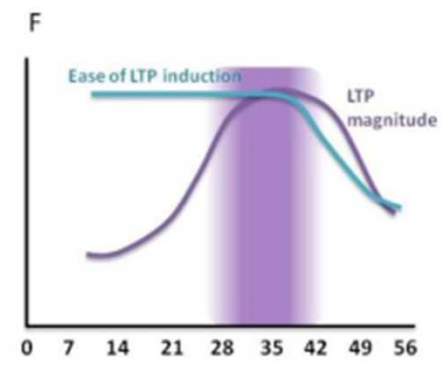
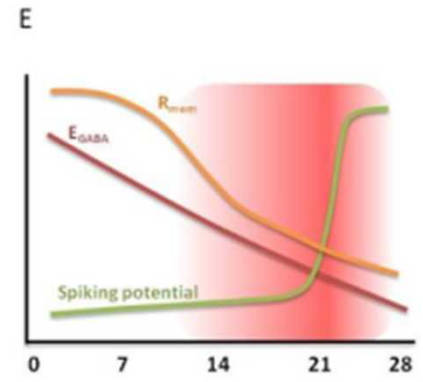
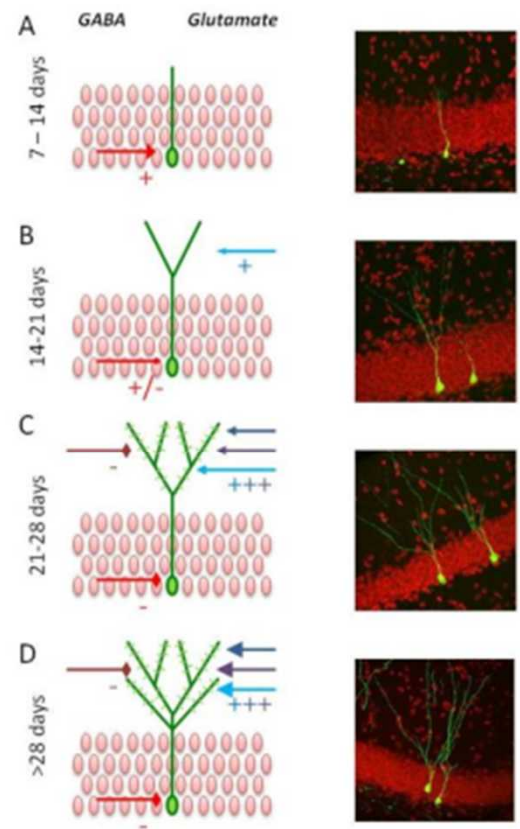
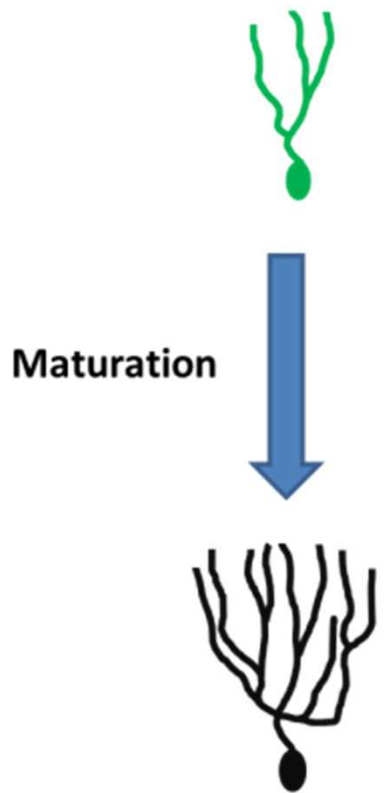
Physiology data



Modeled neuronal dynamics



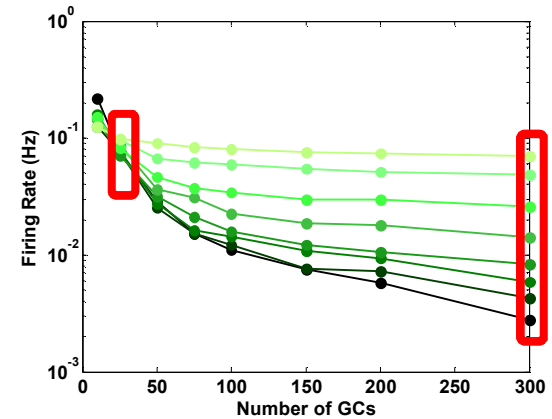
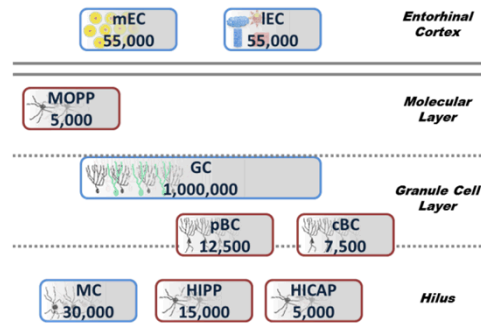
Neurogenesis Process



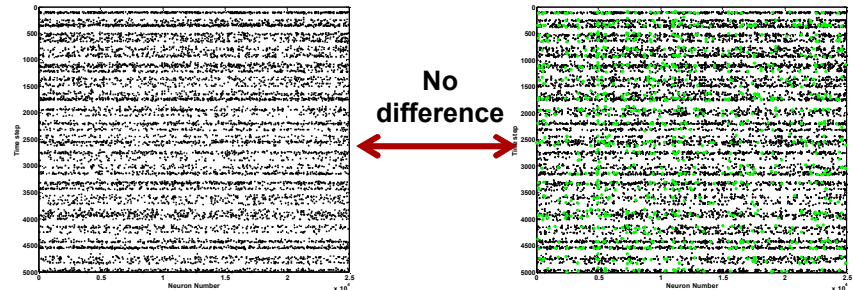
*Aimone, Deng, and Gage
Trends in Cog. Sci. 2010*

Large scale neural simulations are required to observe of realistic neural functions

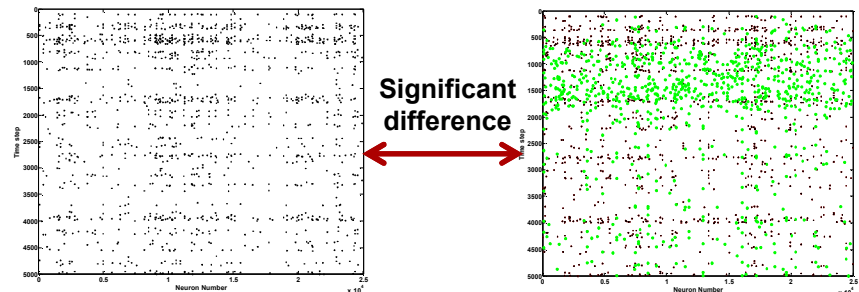
- Neural systems are highly non-linear and can involve complex feedback
- Scaling down neural simulations can have unintended implications
 - Example: Sharp increase in activity of reduced models shown here obfuscates experimental difference
- Models scale at number of interactions (roughly $O(N^2)$) and require substantial node-node communication



1/10th scale

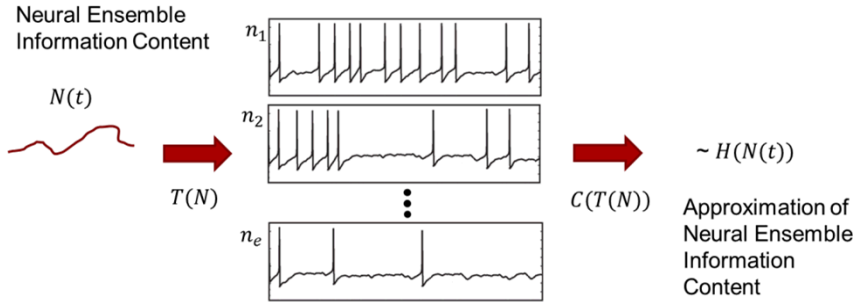


Full mouse-brain scale



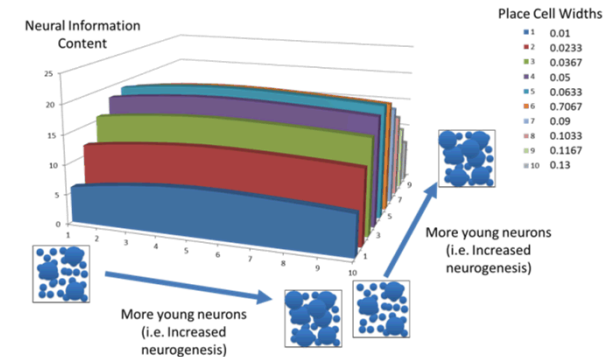
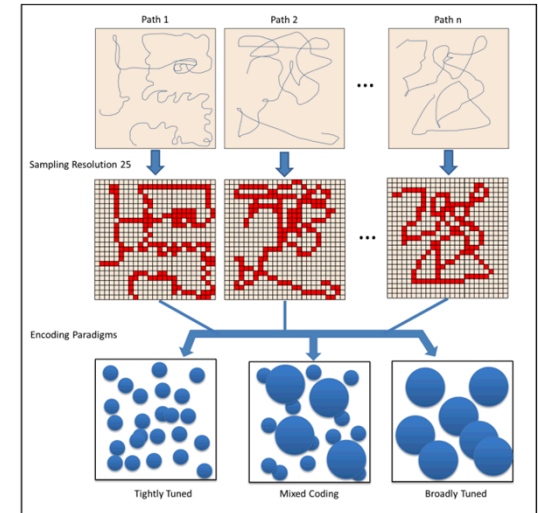
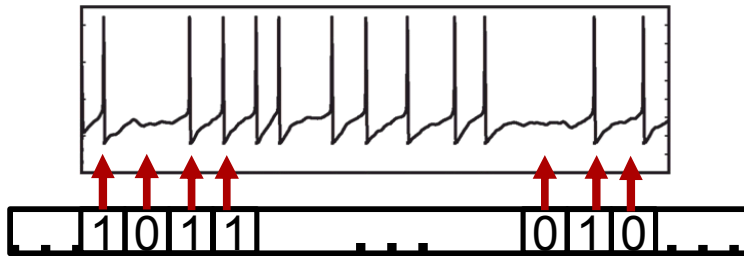
Carlson, Aimone et al., in preparation

Neural information content metrics make quantifying neural computing concrete



- Use complexity as a measure of compressibility in order to estimate entropy to quantitatively assess the information content of a signal

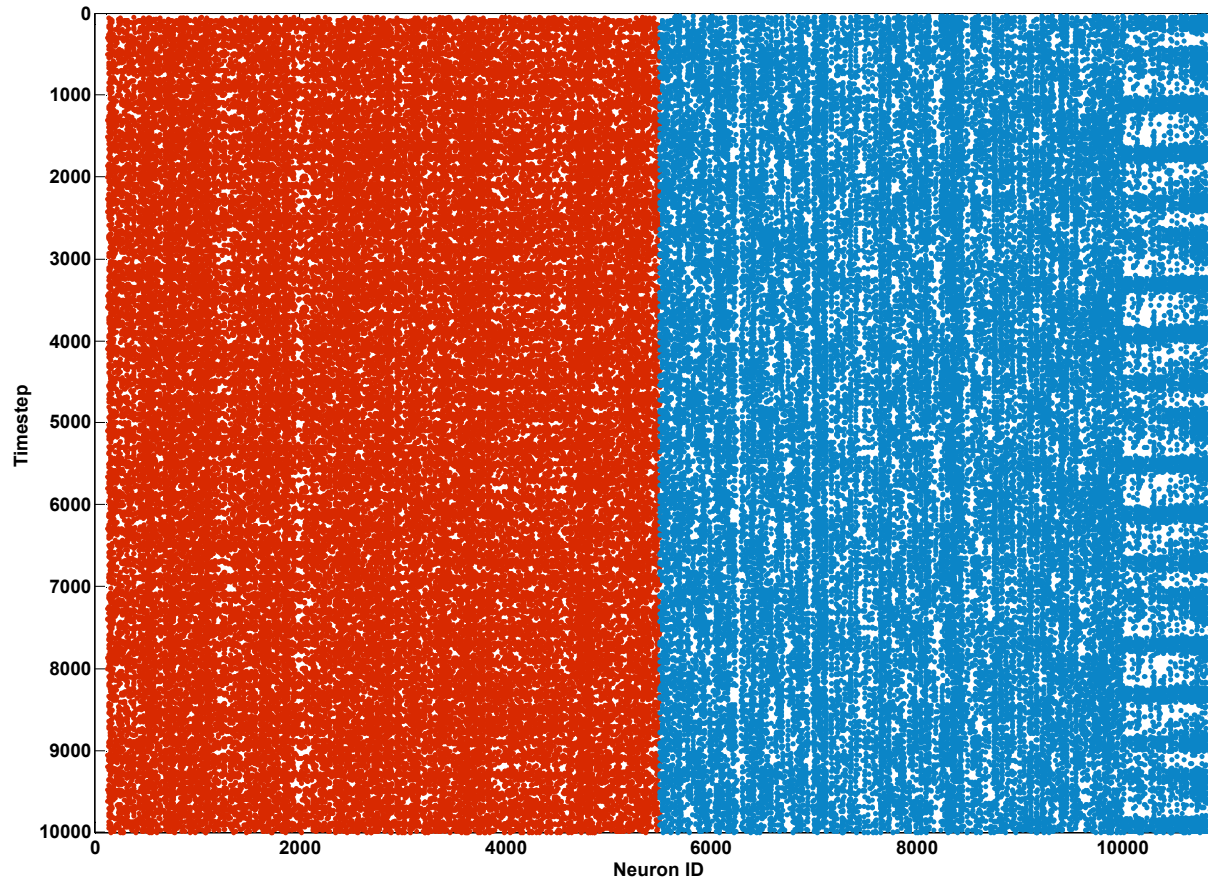
$$c_\alpha(x^n) = \frac{C_\alpha(x^n)}{n} * \log_\alpha n$$



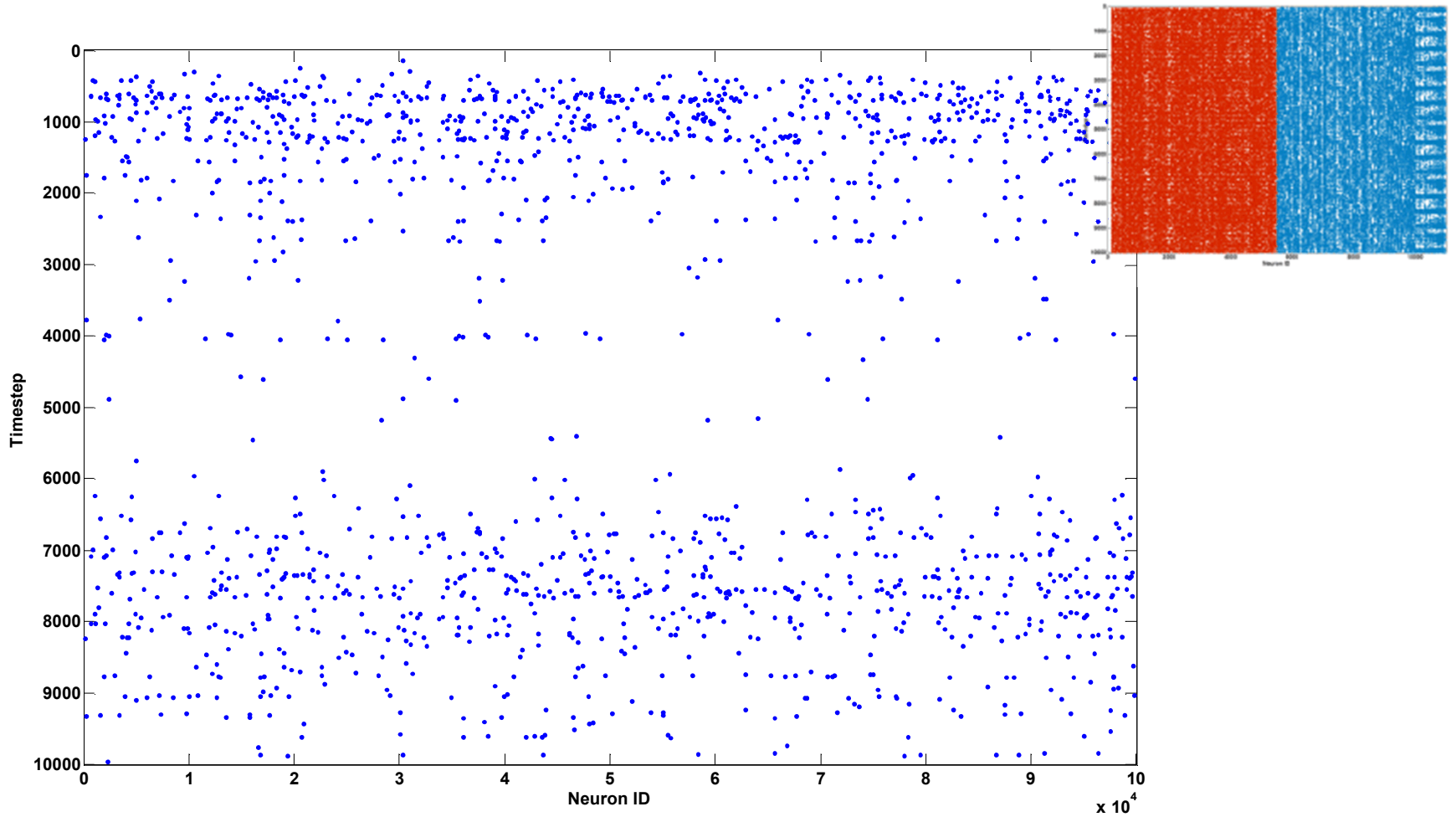
Vineyard, Craig M., et al. "Adult Neurogenesis: Implications on Human And Computational Decision Making." *Foundations of Augmented Cognition*. Springer Berlin Heidelberg, 2013. 531-540.

Vineyard, Craig M., et al. "Quantifying Neural Information Content: A Case Study of the Impact of Hippocampal Adult Neurogenesis" (Submitted)

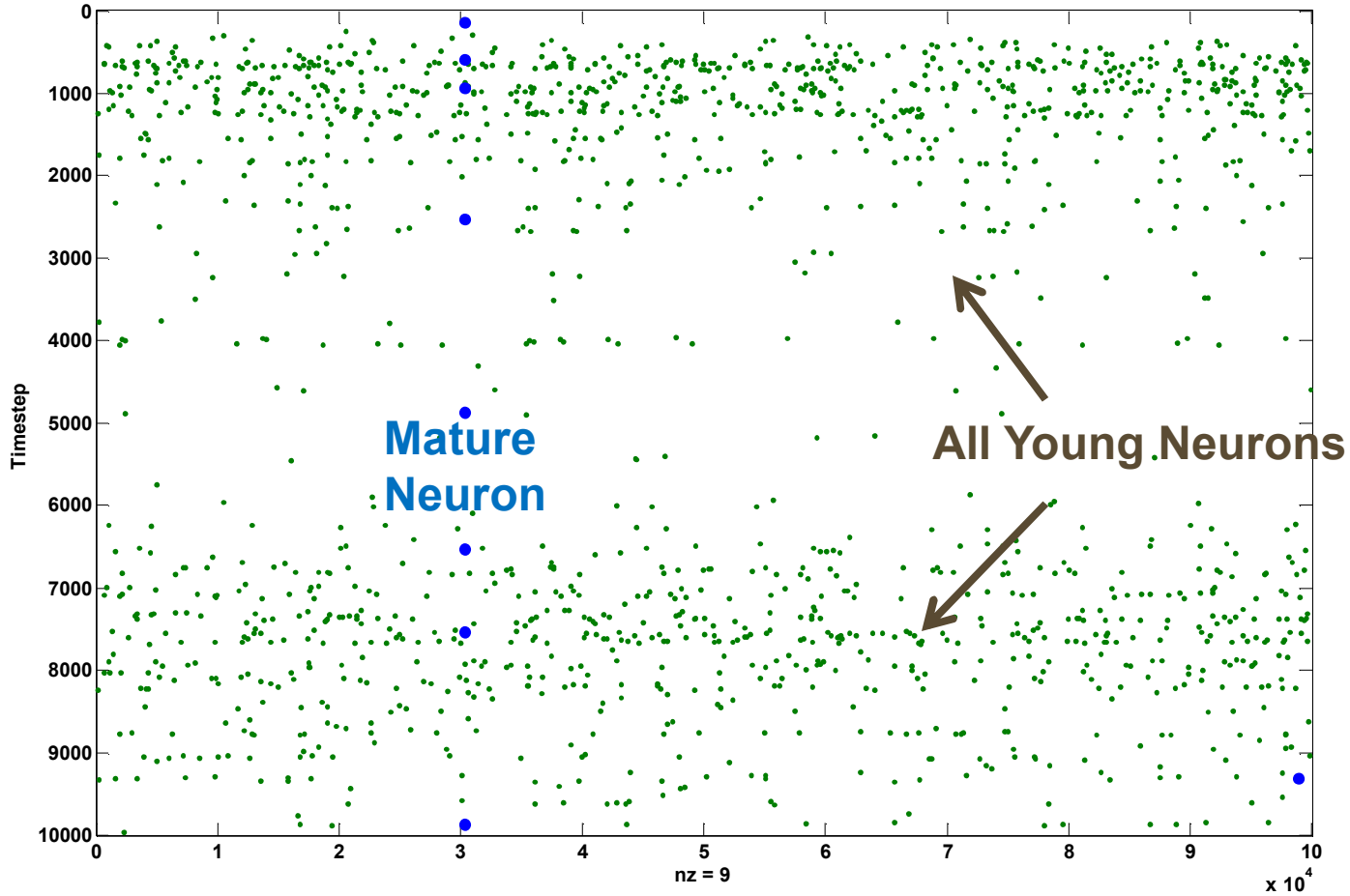
Activity of network – EC Inputs



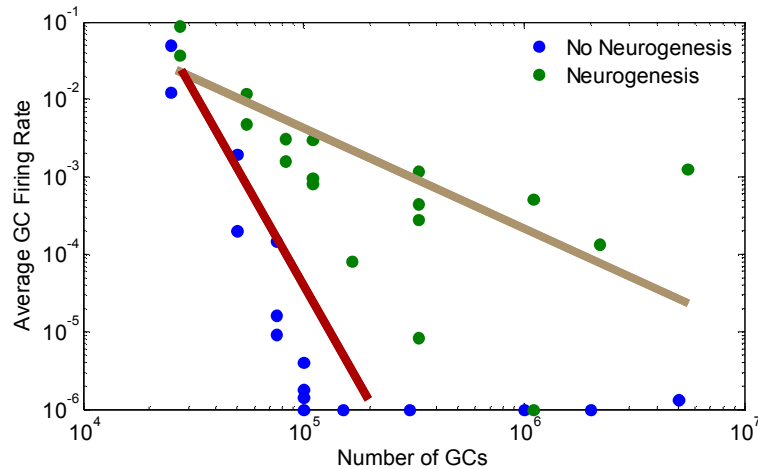
Activity of network – GC Outputs



Young GCs dominate



Lack of neurogenesis in large networks correlates with much lower activity

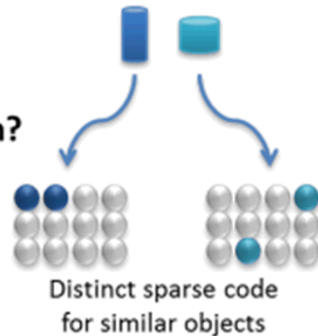


- Neurogenesis networks show activity to novel information at much higher scales
- As we approach human scales, mature neurons appear essentially silent in response to novel information
- Signal (immature) to noise (mature) is amplified in larger networks

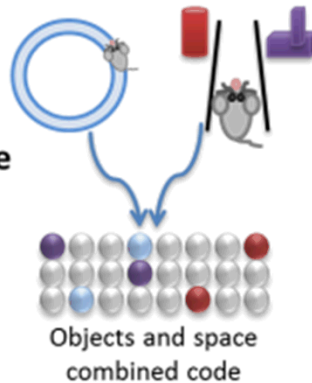
Metrics for understanding NG model Sandia National Laboratories

What is the DG doing?

Pattern Separation?



Conjunctive Encoding?



- Pairwise correlation / dot product

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

- Average covariance

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

How to combine over observations?

- Linear compressability

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

- Average firing rate

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

- Total variance

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

How to combine over neurons?

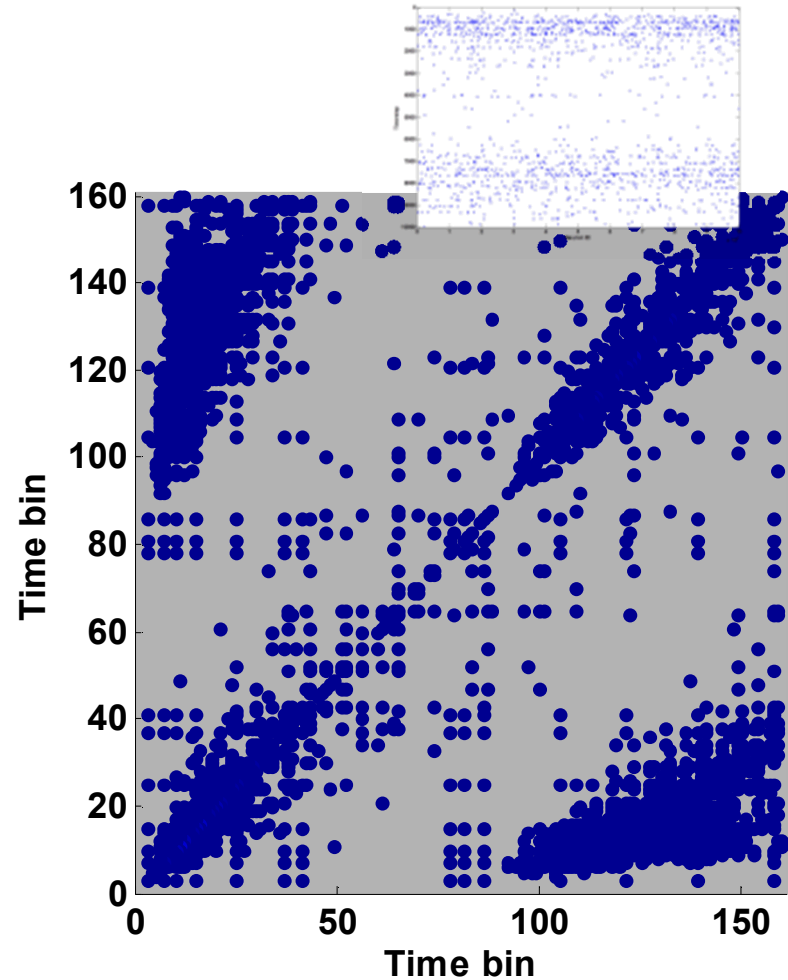
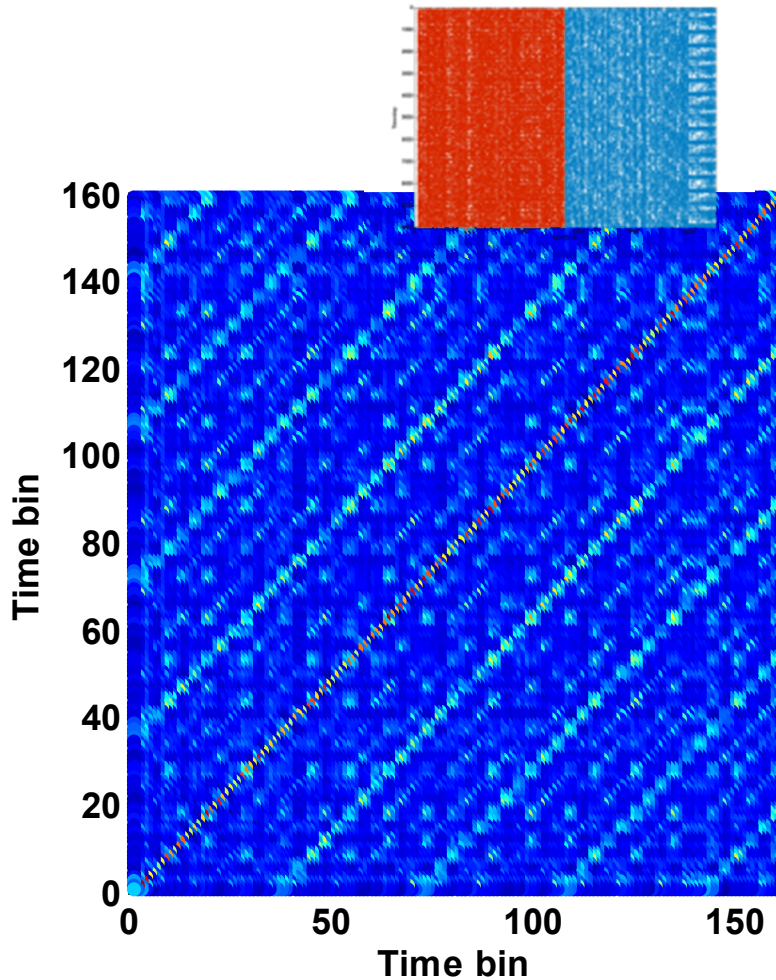
- Information Content

$$I = \sum_{ctx} p_{ctx} \frac{f}{f'} \log_2 \frac{f}{f'}$$

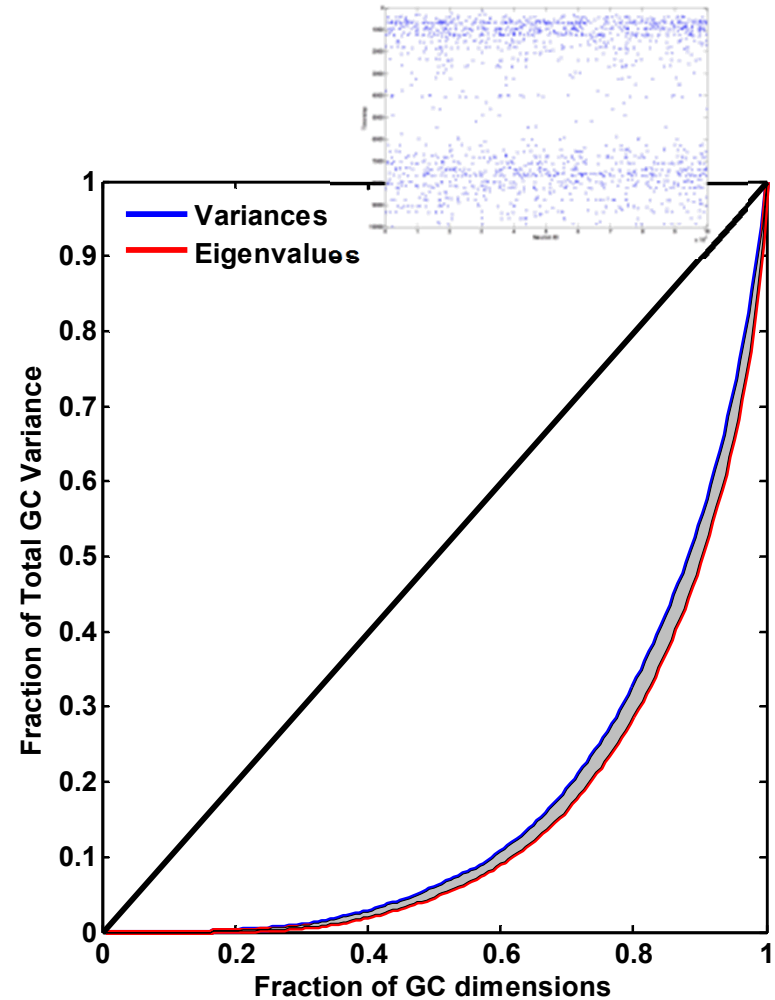
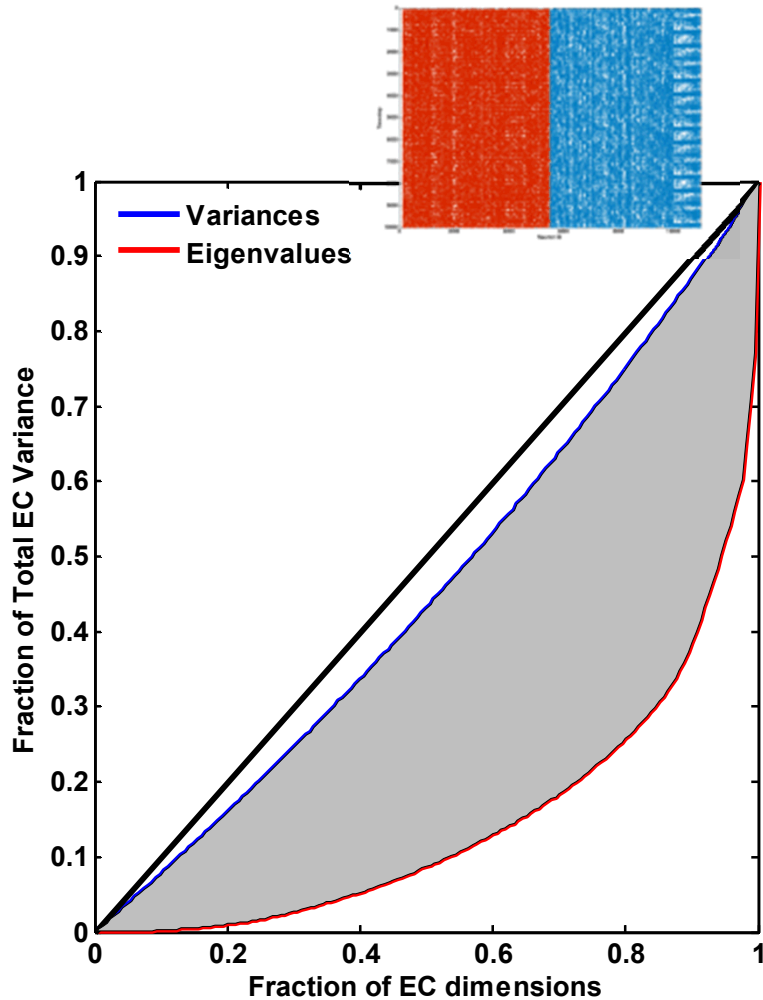
- Independent variance

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

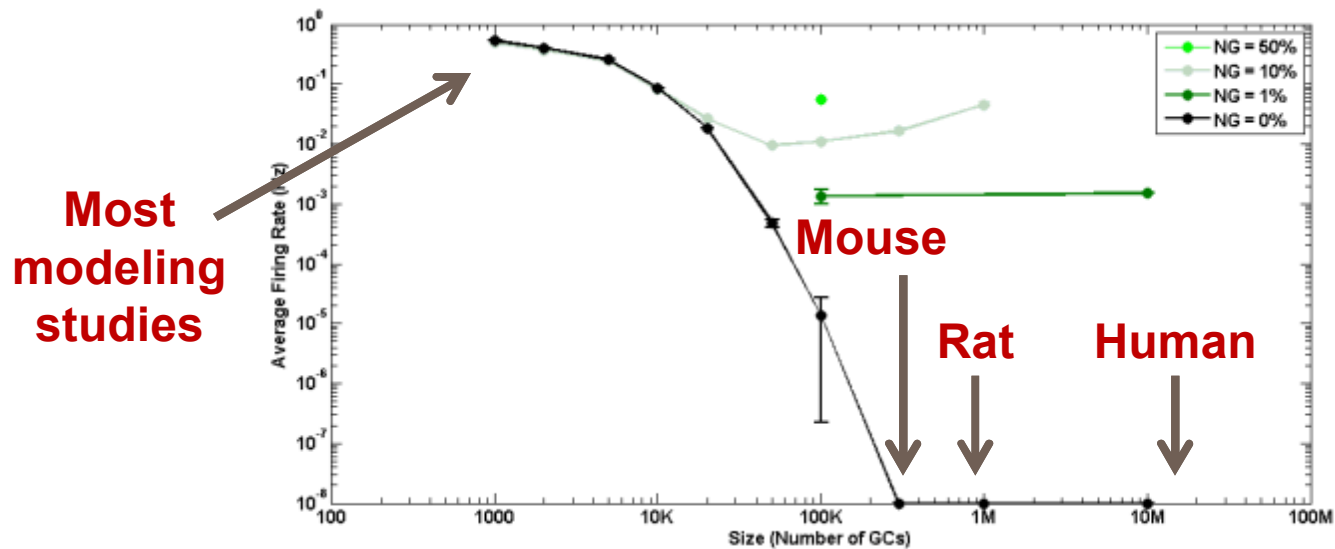
Information processing in large networks



Information processing in large networks

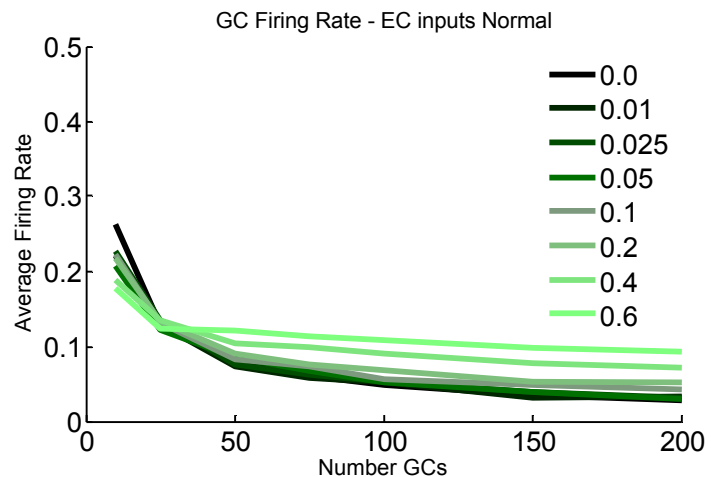
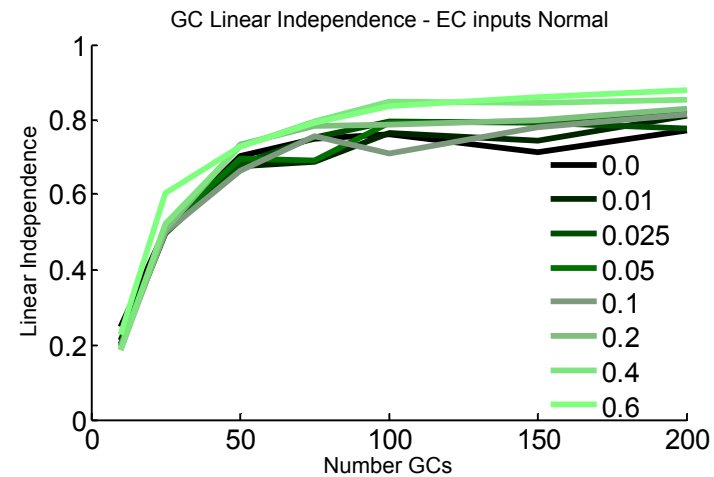
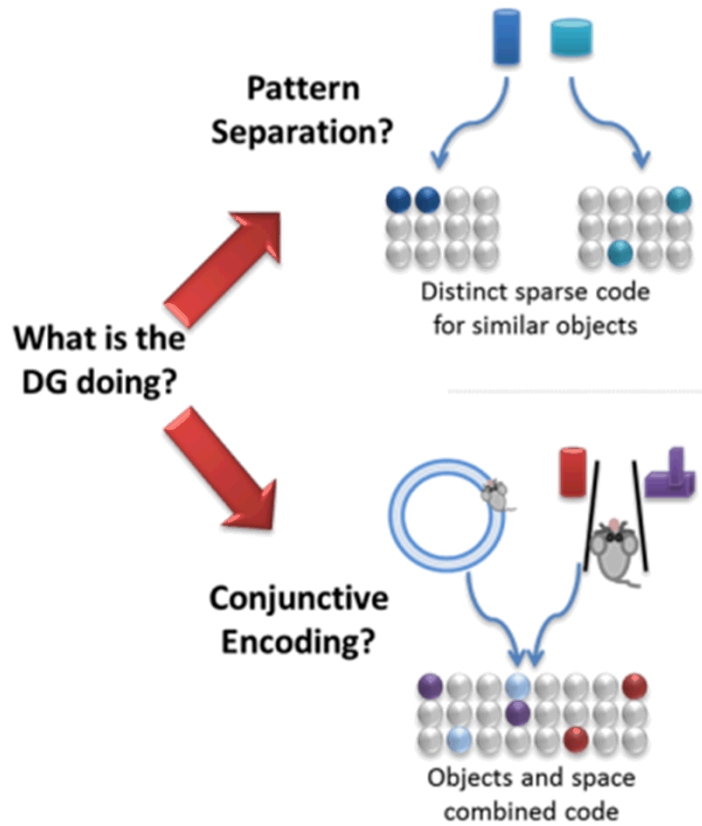


Function of neurogenesis is scale dependent...

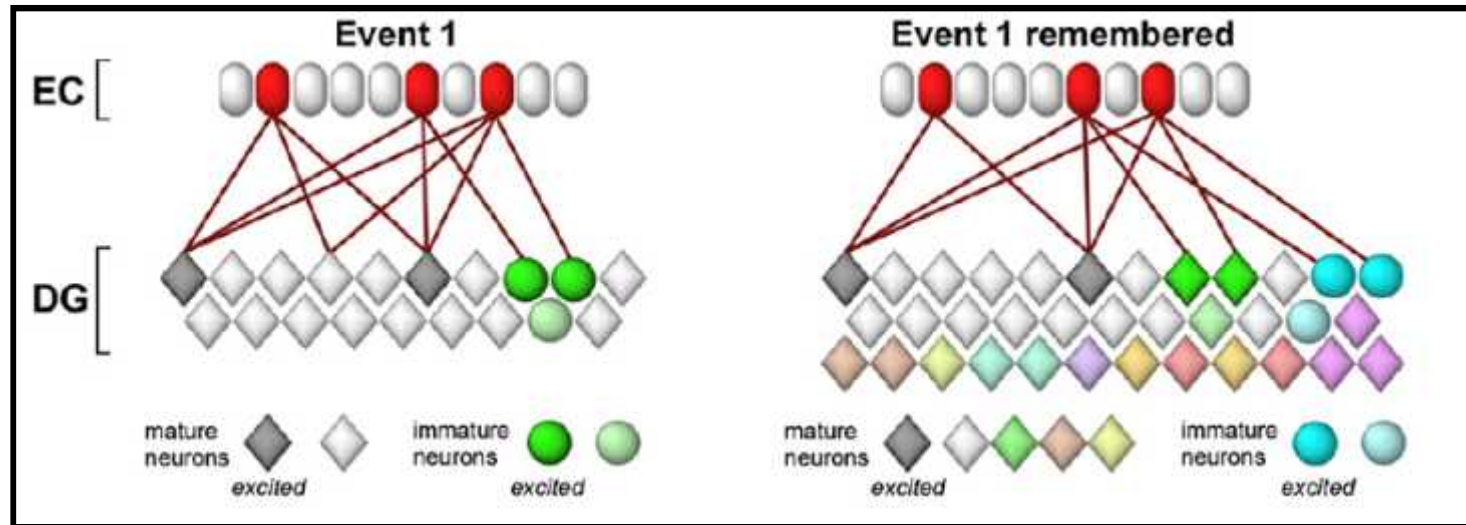


- Neurogenesis networks show activity to novel information at much higher scales
- As we approach human scales, mature neurons appear essentially silent in response to novel information
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Neurogenesis maintains compressibility and increases total representation



Environmental commitment of adult-born neurons



Aimone et al., Neuron 2009

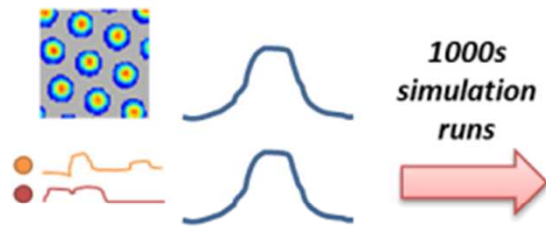
Hypothesis: The specialization of young neurons to the environments present during maturation allows improved encoding of new memories that relate to previously experienced contexts.

- >1000 parameters
 - ~10 neuron parameters
 - 9 neuron types
 - 56 GC ages
 - ~13 connection parameters
 - 44 connection types

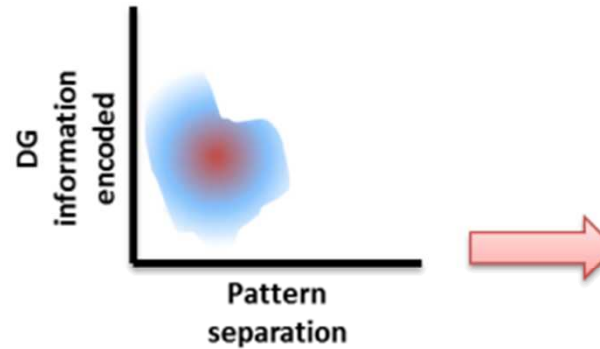
name	count	modcount/vt	vr	C	k	a	b	c	d	kmult	lrho	lfmax	area	globmult	gridmult	objmult	tau_n	tau_p	
IEC	55000	55	-40.6	-72.38	116.9	0.08	0.02894	0.4152	-57.96	95.58	10	100	100	100	2.18	0	3.08	0	0
mEC	55000	55	-37.88	-72.52	94.99	0.06212	0.05364	1.2234	-36.54	243.6	10	100	100	100	7.68	0.87	0	0	0
MOPP	5000	5	-43.55	-47.48	48.82	0.05384	0.01166	0.4821	-50.44	112.66	10	100	100	100	0	0	0	0	0
GC	1000000	10000	-45.43	-67.56	119.68	0.0838	0.00944	1.7782	-45.03	123.49	10	100	100	100	0	0	0	10.02	10.31
PV-BC	12500	1.25E+01	-51.27	-57.39	68.6	0.04043	0.02801	1.921	-47.58	170.37	10	100	100	100	0	0	0	0	0
CCK-BC	7500	7.50E+00	-45.7	-64.12	96.09	0.08019	0.01048	1.2236	-30.73	82.97	10	100	100	100	0	0	0	0	0
MC	30000	30	-42.35	-62.79	58.51	0.02483	0.02191	2.271	-49.19	242.66	10	100	100	100	0	0	0	7.91	10.46
HIPP	15000	15	-39.51	-69.56	70.77	0.07711	0.01671	2.1874	-40.34	161.93	10	100	100	100	0	0	0	0	0
HICAP	5000	5	-40.97	-67.64	69.61	0.04846	0.00417	0.528	-62.31	77.41	10	100	100	100	0	0	0	0	0
MSACh	1	1	-40	-60	50	0.1	0.02	10	-30	75	10	130	0	1000	0	0	0	30	20
DA	1	1	-35	-70	100	0.4	0.04	0.2	-65	20	10	123	0	1000	0	0	0	30	20
NE	1	1	-35	-70	100	0.4	0.04	0.2	-65	20	10	123	0	1000	0	0	0	30	20
DR-SHT	1	1	-35	-70	100	0.4	0.04	0.2	-65	20	10	410	0	1000	0	0	0	30	20
MR-SHT	1	1	-35	-70	100	0.4	0.04	0.2	-65	20	10	410	0	1000	0	0	0	30	20
MSGABA	1	1	-40	-60	50	0.1	0.015	10	-30	40	10	120	0	1000	0	0	0	30	20

name	source	target	N_syn	E_rev	strength	strength_ix_var	y_var	spread_ty	distance_tau(ms)	p_release	transmitt	facil_dep	ionotropic	release_s	receptor	age_u	age_s	A_LTD	A_LTP	tau_pre	target_cor		
IECtoMOP	0	2	1805	0	0.03668	0.97	0.09	Inf	1	11	3	0.857	1	0.1	1	1	0	18	7	0	0	0	
IECtoGC	0	3	1911	0	0.02649	1.05	0.05	Inf	1	11	3	0.89	1	0.09	1	1	0	22	9	0.000029	0.000011	5	0
IECtoBC	0	4	2141	0	0.08343	1.13	0.11	Inf	1	18	2	0.893	1	0.13	1	1	0	19	7	0	0	11	0
IECtoC	0	5	1840	0	0.07019	0.68	0.12	Inf	1	18	4	0.901	1	0.1	1	1	0	24	7	0	0	10	0
mECtoMC	1	2	1955	0	0.03118	1.06	0.09	Inf	1	11	2	0.896	1	0.11	1	1	0	19	7	0	0	12	0
mECtoC	1	3	1603	0	0.02813	1.26	0.1	Inf	1	13	4	0.941	1	0.11	1	1	0	30	6	0.000042	0.00001	5	0
mECtoBC	1	4	2353	0	0.03334	1.14	0.1	Inf	1	12	2	0.888	1	0.06	1	1	0	24	10	0	0	7	0
mECtoC	1	5	2411	0	0.05002	0.99	0.09	Inf	1	15	3	0.943	1	0.09	1	2	0	22	8	0	0	11	0
MOPPtoG	2	3	110	-78.31	0.14088	0.37	0.12	0.37	1	3	5	1	2	-0.11	1	1	0	22	5	0	0	13	0
GCtoBC	3	4	12647	0	0.07653	1.06	0.06	0.11	2	3	3	0.255	1	0.38	1	1	0	14	10	0	0	12	0
GCtoC	3	5	3085	0	0.16955	0.53	0.05	0.12	2	4	2	0.309	1	0.55	1	4	0	22	5	0	0	15	0
GCtoMCP	3	6	102	0	0.7387	0.52	0.05	0.1	2	4	3	0.525	1	0.57	1	3	0	28	7	0	0	9	0
GCtoMCD	3	6	1092	0	0.06473	0.79	0.04	0.1	2	4	4	0.34	1	0.55	1	5	0	24	6	0.000008	0.000013	21	0
GCtoHIPP	3	7	3568	0	0.26227	0.39	0.04	0.08	2	5	2	0.41	1	0.31	1	4	0	23	9	0	0	9	0
GCtoHCA	3	8	3628	0	0.28235	0.54	0.04	0.05	2	4	2	0.492	1	0.58	1	3	0	7	8	0	0	6	0
pBCtoGC	4	3	304	-88.87	0.3538	0.22	0.18	0.21	1	2	5	0.949	2	-0.68	1	1	0	16	10	0	0	16	0
pBCtoBC	4	4	145	-75.38	0.37262	0.3	0.13	0.34	1	2	7	1	2	-0.1	1	1	0	17	7	0	0	3	0
cBCtoGC	5	3	201	-82.89	0.29812	0.42	0.15	0.37	1	2	6	0.951	2	-0.1	1	2	0	17	8	0	0	12	0
cBCtoBC	5	5	145	-79.46	0.35868	0.27	0.19	0.29	1	3	4	1	2	-0.09	1	2	0	14	6	0	0	14	0
MCToGC	6	3	983	0	0.02854	1.16	0.34	0.2	3	9	2	0.878	1	0.08	1	2	0	19	9	0.000009	0.000006	6	0
MCToBC	6	4	1298	0	0.06312	0.96	0.12	0.29	3	10	3	0.894	1	0.12	1	2	0	14	9	0	0	6	0
MCToC	6	5	1659	0	0.05258	0.98	0.18	0.24	3	10	1	0.85	1	0.05	1	2	0	26	6	0	0	8	0
HIPPtoGC	7	3	537	-78	0.15351	0.22	0.12	0.19	1	3	4	1	2	-0.13	1	1	0	17	7	0	0	8	0
HICAPtoG	8	3	517	-79.43	0.08075	0.23	0.09	0.12	1	3	4	1	2	-0.11	1	1	0	18	5	0	0	6	0
pBCtoMC	4	6	267	-83.71	0.24645	0.36	0.15	0.3	1	2	3	0.96	2	-0.09	1	2	0	20	8	0	0	11	0
cBCtoMC	5	6	318	-79.95	0.19568	0.35	0.12	0.29	1	3	5	0.954	2	-0.07	1	1	0	21	7	0	0	14	0
HIPPtoMC	7	6	504	-75.8	0.02565	0.36	0.09	0.17	1	2	4	1	2	-0.1	1	2	0	16	8	0	0	15	0
HICAPtoM	8	6	459	-82.16	0.0522	0.4	0.08	0.22	1	2	4	1	2	-0.09	1	1	0	22	6	0	0	13	0
MCToHIPP	6	7	1577	0	0.03521	0.96	0.13	0.41	3	3	3	0.327	1	0.1	1	3	0	13	6	0	0	7	0
MCToHIC	6	8	1400	0	0.02583	1.04	0.1	0.36	3	2	3	0.225	1	0.11	1	3	0	26	9	0	0	9	0
nAChtoM	9	2	1	0	2.06754	0	1	Inf	0	2	26	1	3	0	1	2	2	28	6	0	0	9	0
nAChtoC	9	5	1	0	2.4439	0	1	Inf	0	3	36	1	3	0	1	1	2	19	8	0	0	13	0
nAChtoM	9	6	1	0	0.87769	0	1	Inf	0	3	22	1	3	0	1	2	2	20	11	0	0	12	0
nAChtoH	9	7	1	0	0.83901	0	1	Inf	0	3	28	1	3	0	1	1	2	22	9	0	0	8	0
nAChtoH	9	8	1	0	0.9349	0	1	Inf	0	3	29	1	3	0	1	1	2	15	7	0	0	8	0
Sh3toBC	13	5	1	0	1.3393	0	1	Inf	0	2	1	1	6	0	1	2	11	18	10	0	0	17	0
MS-GABA	14	0	1	-84.63	9.99862	0	1	Inf	0	14	5	0.795	2	0	1	4	0	20	7	0	0	12	0
MS-GABA	14	1	1	-81	8.01003	0	1	Inf	0	15	3	0.791	2	0	1	6	0	21	10	0	0	8	0
MS-GABA	14	4	1	-81.04	1.36129	0	1	Inf	0	3	6	0.813	2	0	1	2	0	26	4	0	0	4	0
MS-GABA	14	5	1	-76.49	2.58296	0	1	Inf	0	3	6	0.749	2	0	1	2	0	17	5	0	0	10	0
MS-GABA	14	6	1	-75.53	3.32025	0	1	Inf	0	2	4	0.785	2	0	1	2	0	25	8	0	0	12	0
MS-GABA	14	7	1	-82.74	2.72738	0	1	Inf	0	3	4	0.703	2	0	1	2	0	28	8	0	0	8	0
MS-GABA	14	8	1	-74.42	3.86491	0	1	Inf	0	2	6	0.824	2	0	1	1	0	13	8	0	0	9	0
MS-GABA	14	9	1	-76.81	12.4504	0	1	Inf	0	2	6	1	2	0	1	3	0	24	6	0	0	12	0

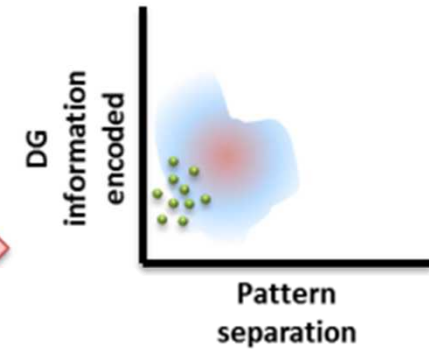
Systematically explore parameter space



Vary input parameters by reasonable uncertainty distributions



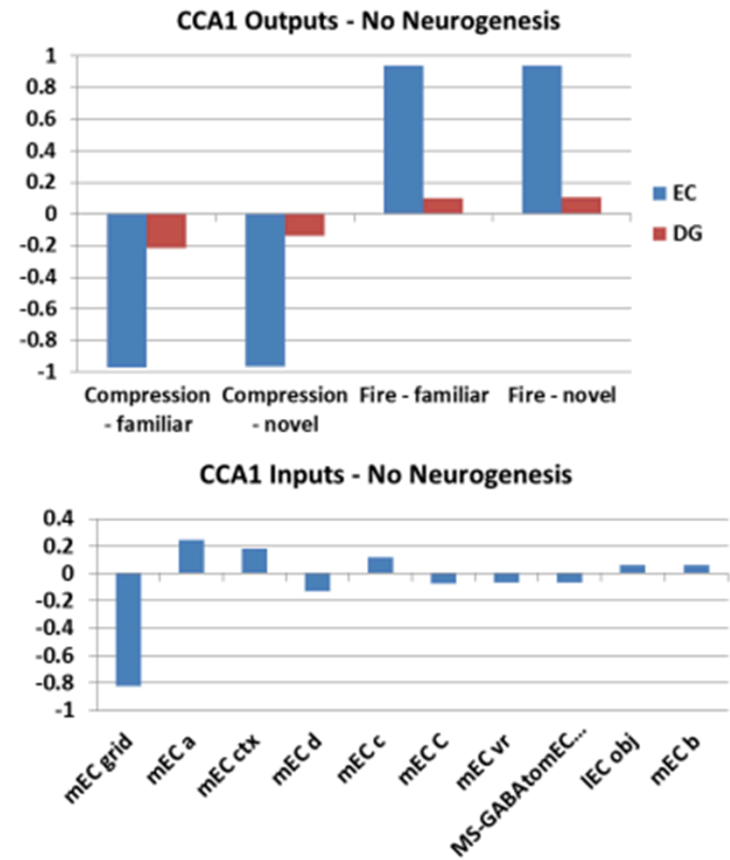
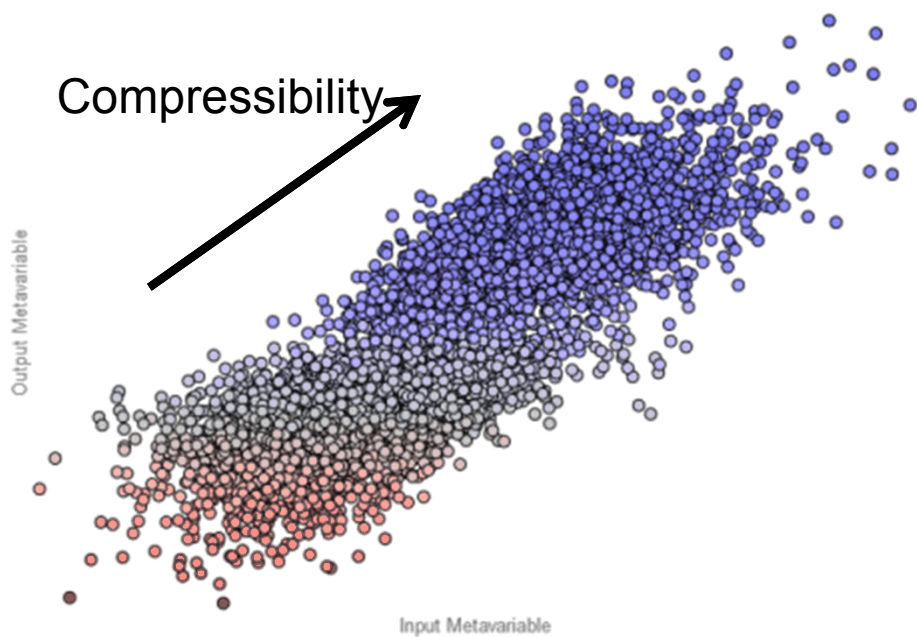
Obtain probability distribution of model outputs given explored parameter space



Map experimental data onto distribution to further constrain studies

Model Sensitivity to different parameters

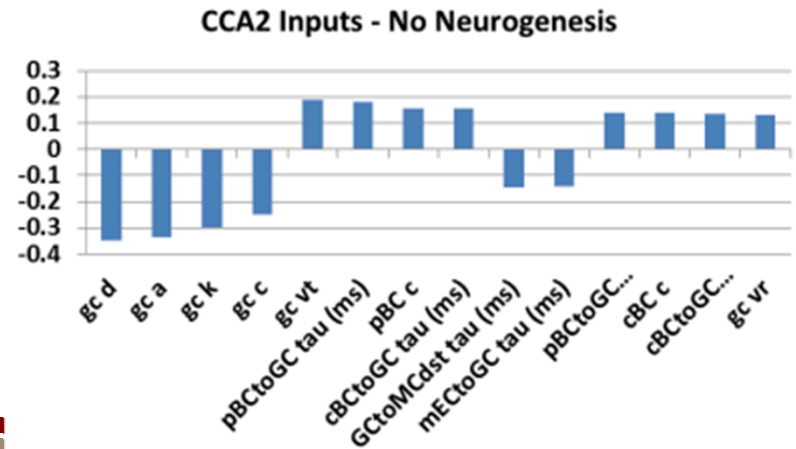
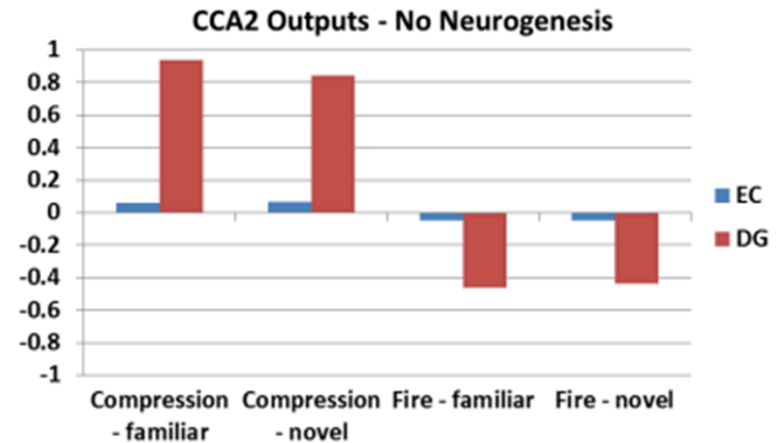
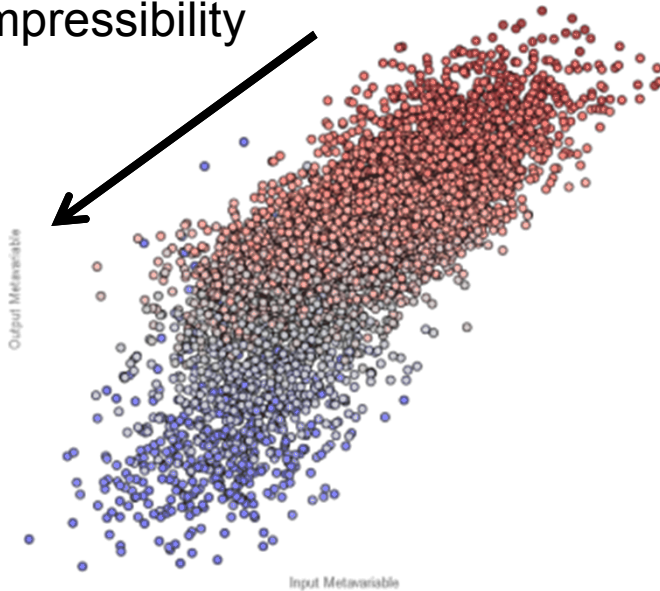
1st Canonical Component
Parameters driving EC inputs



Model Sensitivity to different parameters

2nd Canonical Component
Parameters driving GC activity
Most runs were highly separated

Compressibility



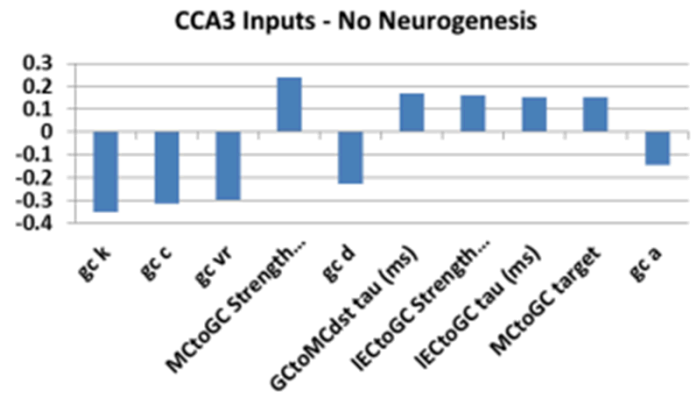
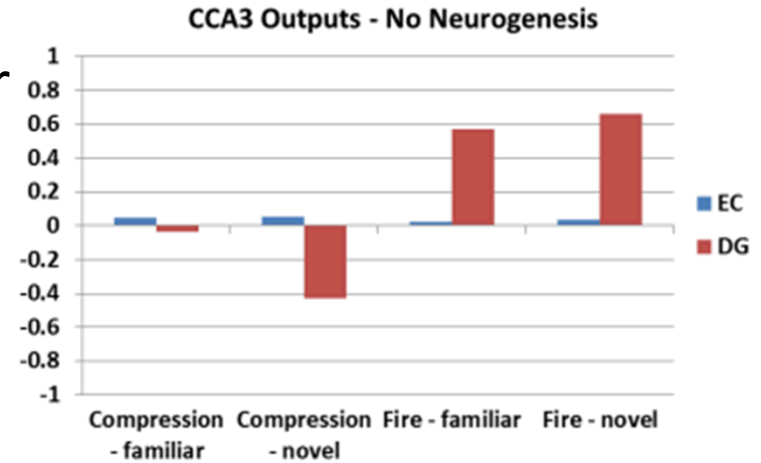
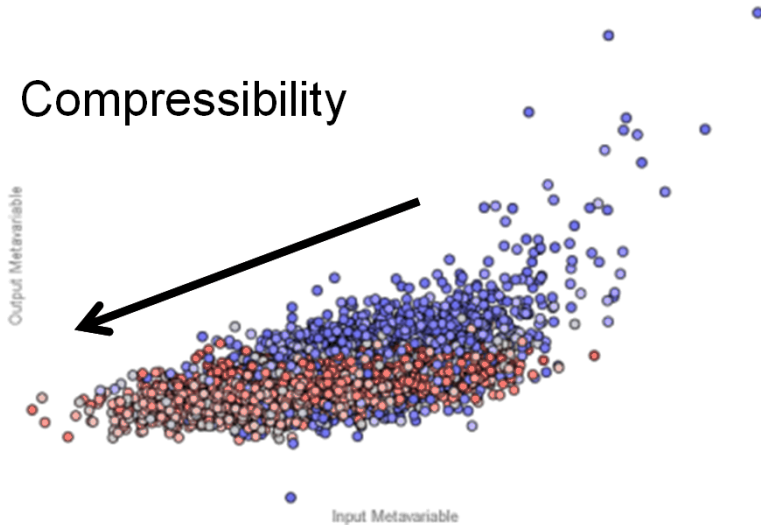
Model Sensitivity to different parameters

3rd Canonical Component

Parameters driving novel vs familiar difference

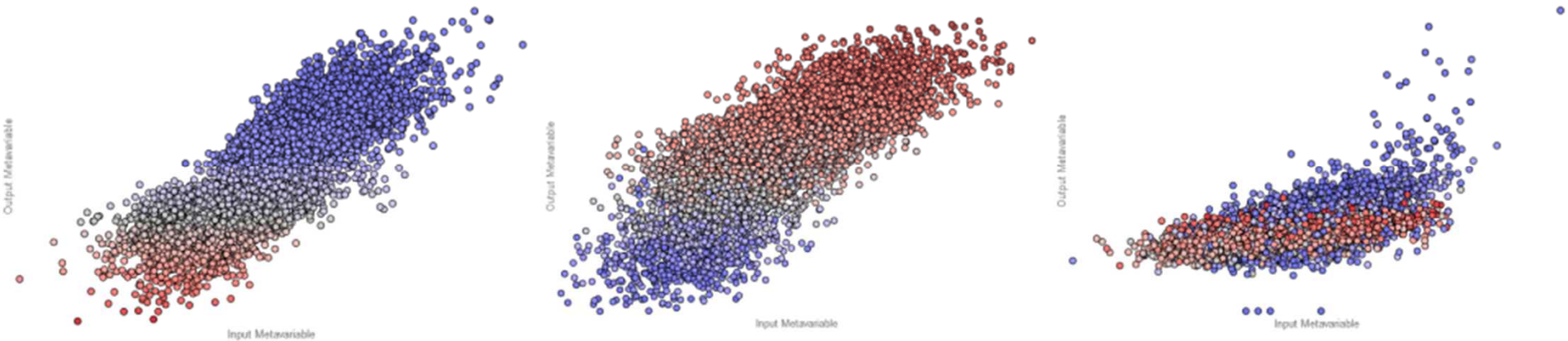
Quite a bit messier

Compressibility



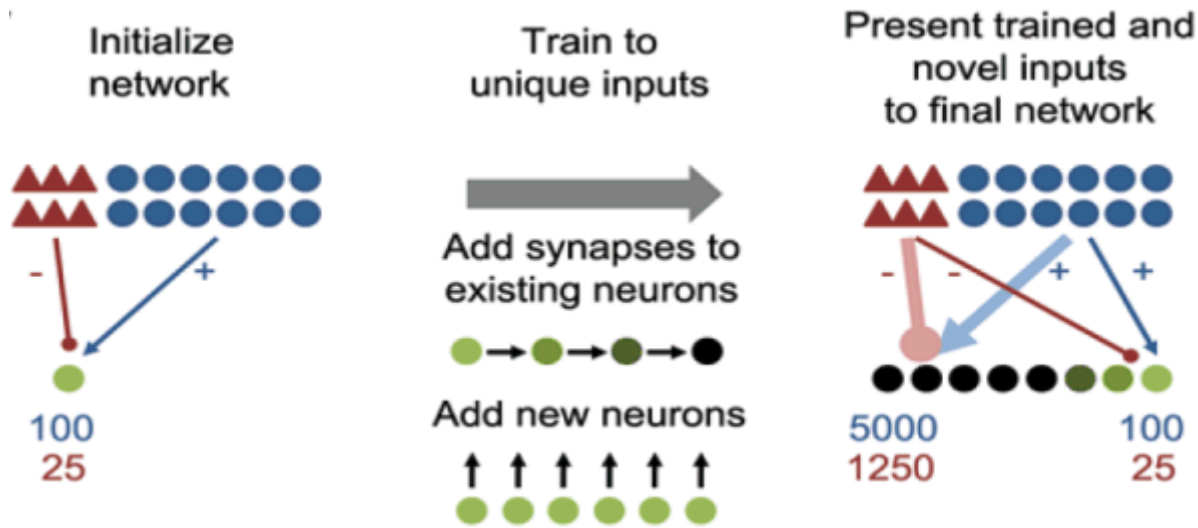
Neurogenesis simulations are similar

CCA 1 – EC Compressibility CCA 2 – DG Compressibility CCA 3 – DG Compressibility



- Overall simulation runs are located in high density of parameter search region
 - More confidence about inferences from primary results
- Inputs are driven by relative activity of grid cells in model
- Granule cell parameters (not surprisingly) are most influential in dictating GC activity and separation

Abstract model: scaling neuron sizes yields neurogenesis effect

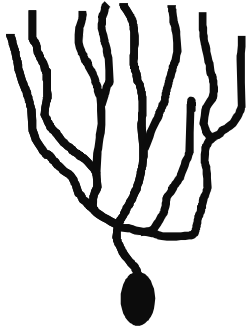


Li, Aimone et al., PNAS 2012

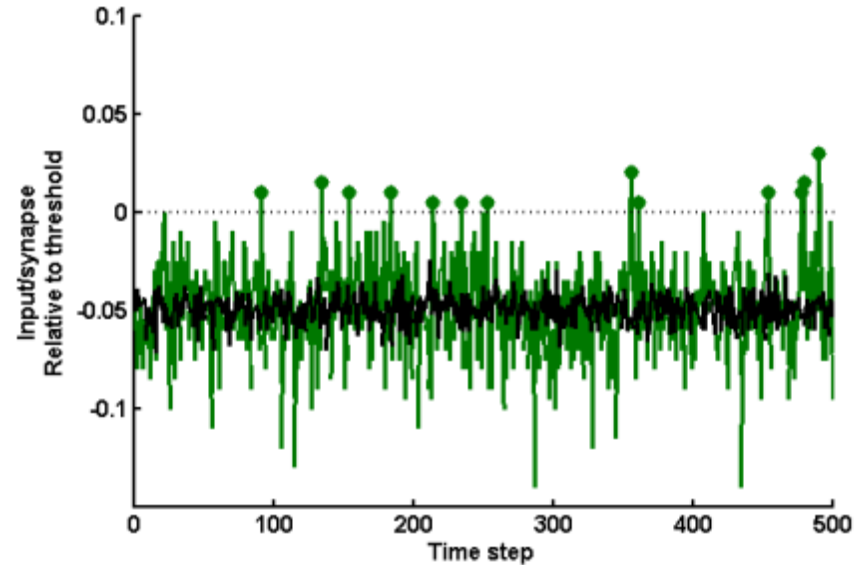
Noise affects lower dimensional neurons



200 synapses
25% (50) active
required to fire
20% (40) active on
average



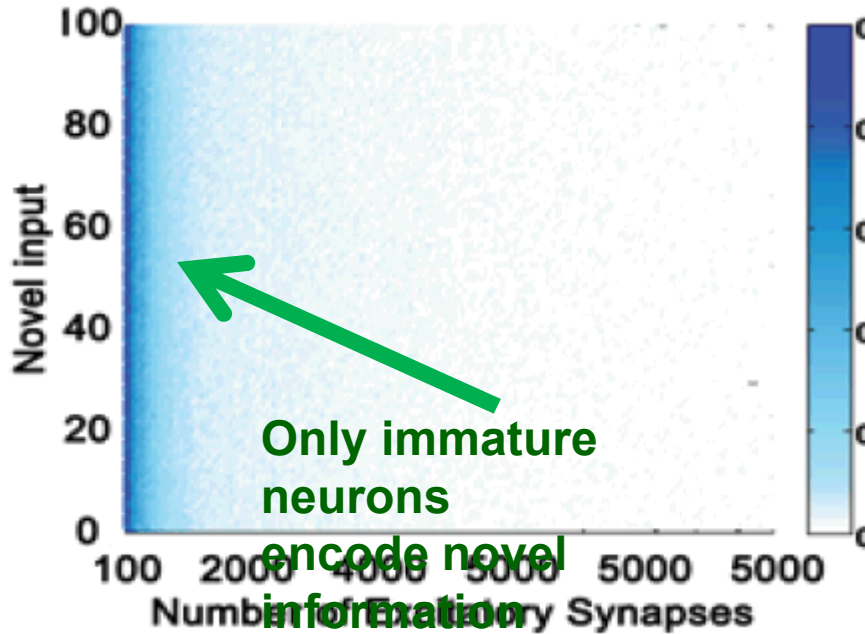
2000 synapses
25% (500) active
required to fire
20% (400) active on
average



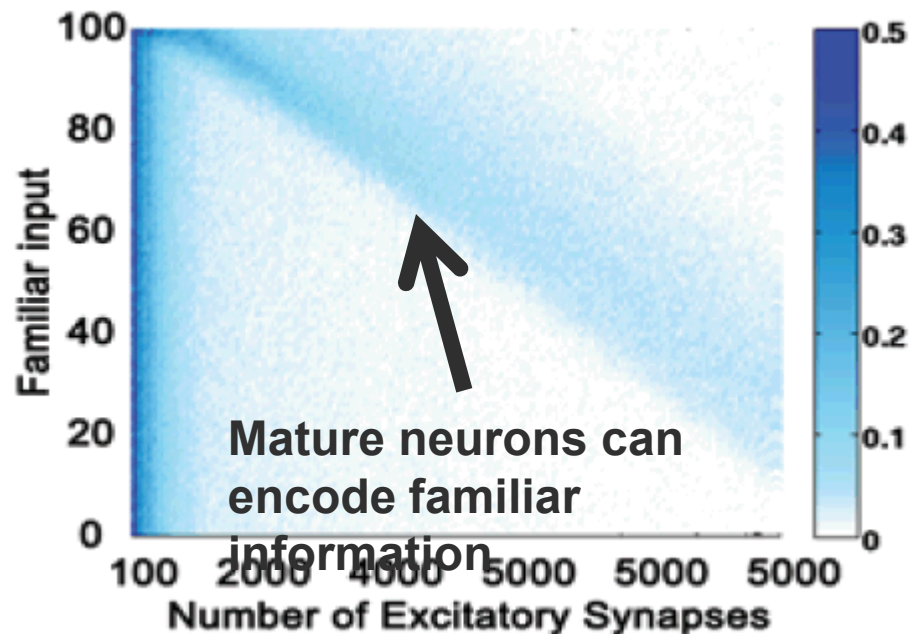
Li, Aimone, et al., PNAS 2012

Neurons maturing to large number of synapses contain high information about maturation cues

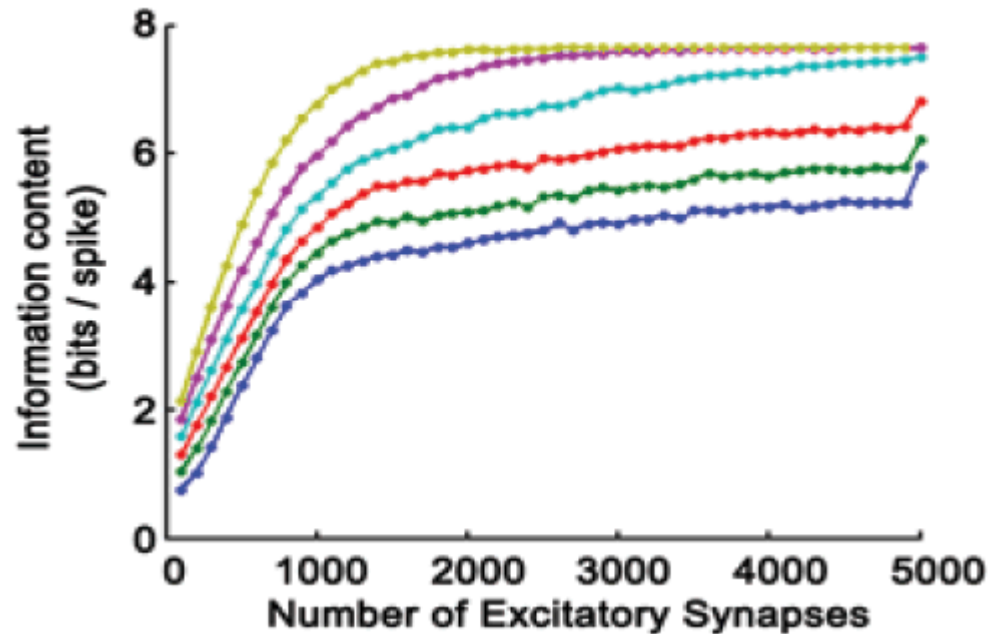
Novel Inputs



Trained Inputs



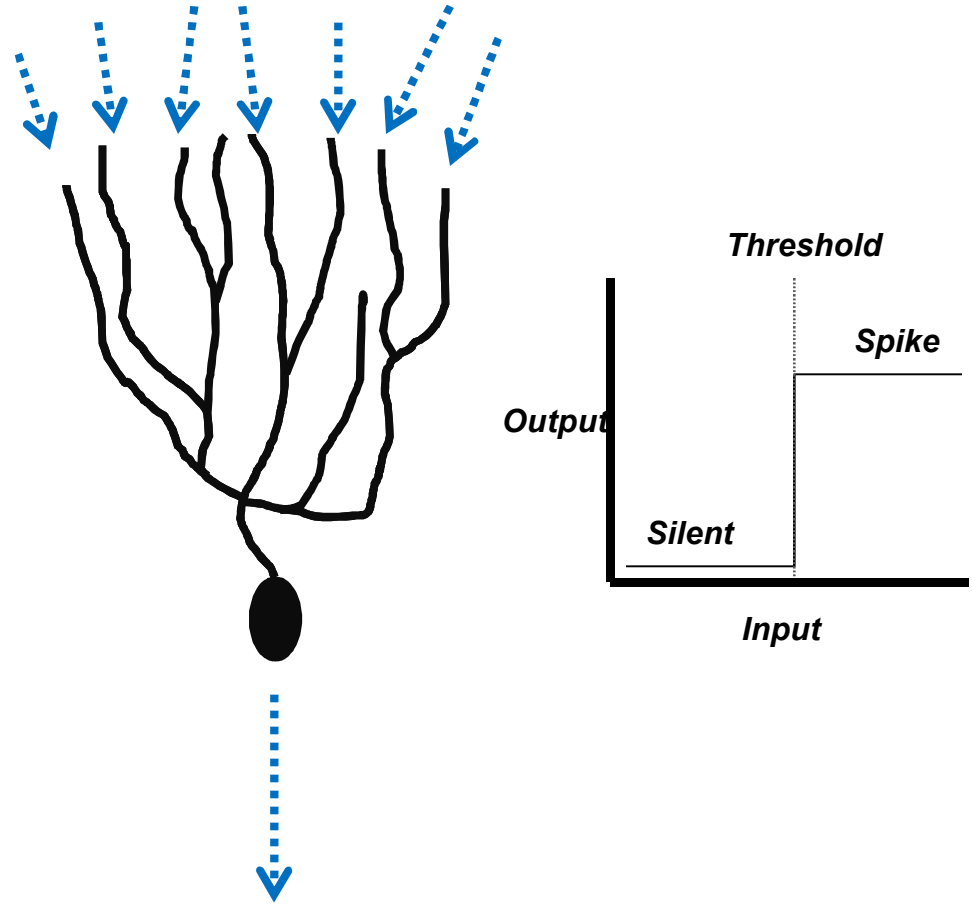
High synapse neurons have higher information content



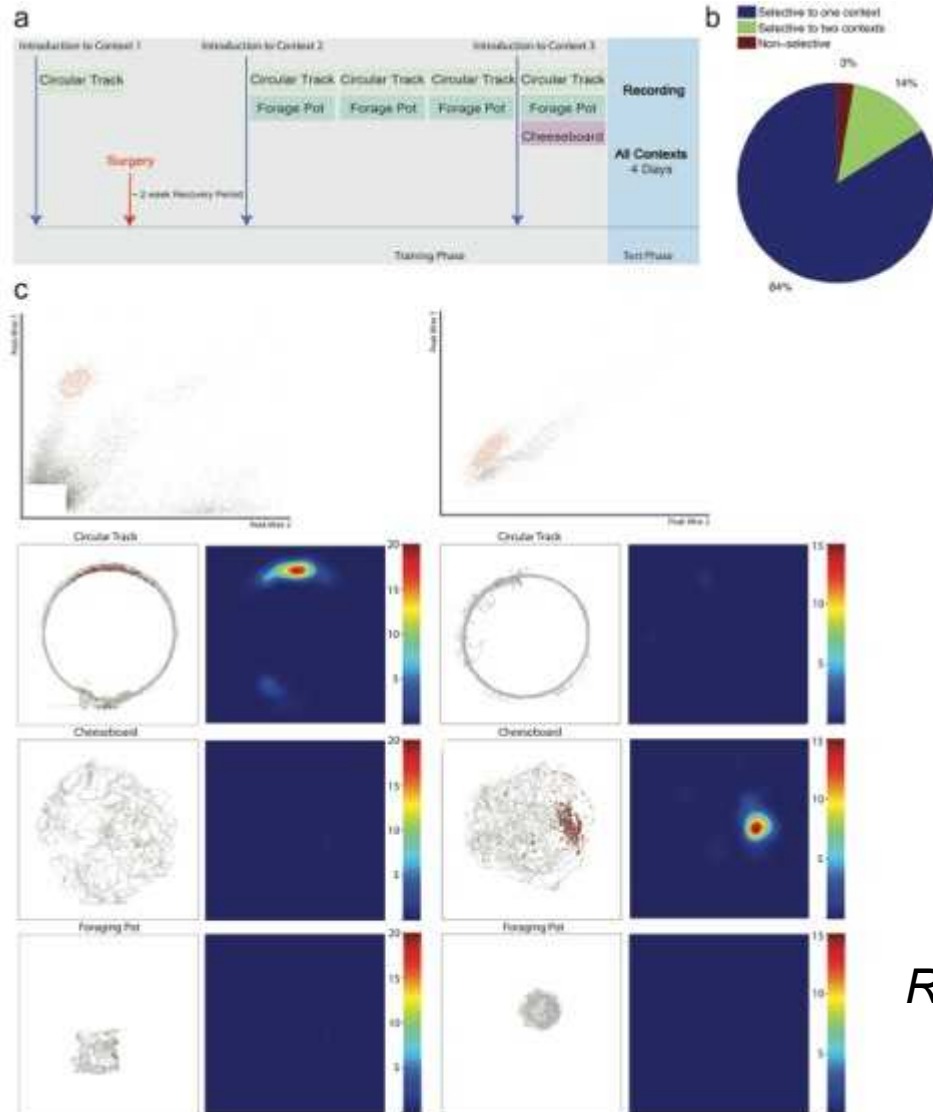
Li, Aimone et al., PNAS 2012

Simple example of scaling dimensionality

- Simple binary threshold neuron
- Input are many different synapses
- Cell “fires” if inputs surpass a threshold
 - Threshold is typically many inputs active at the same time

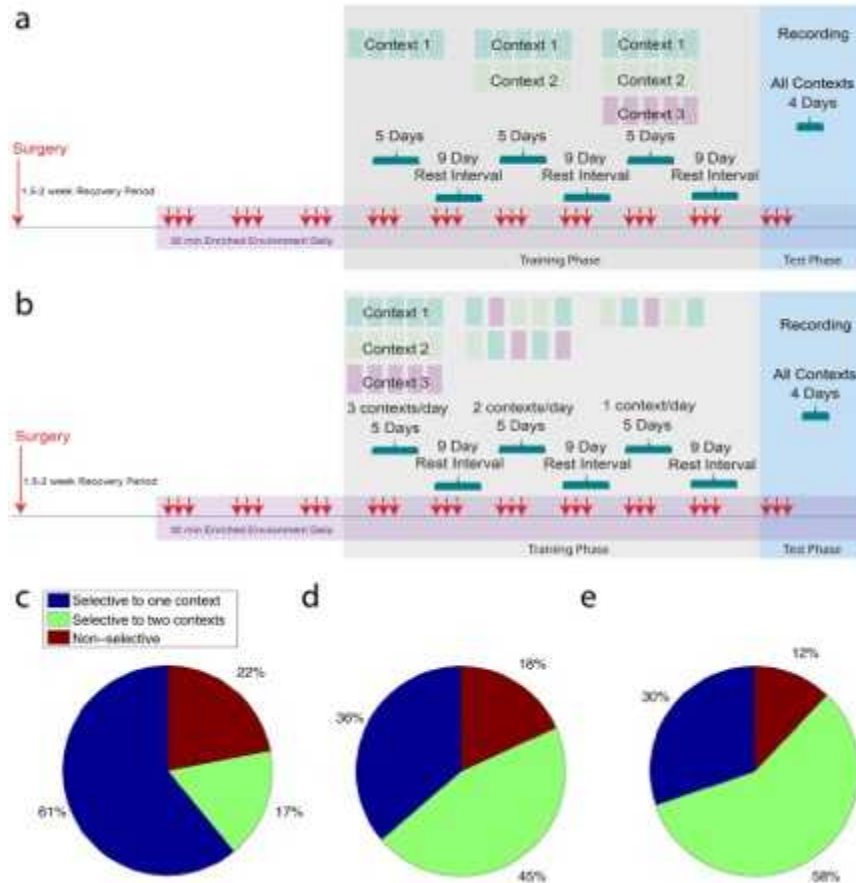


Some biological evidence



Rangel et al., submitted

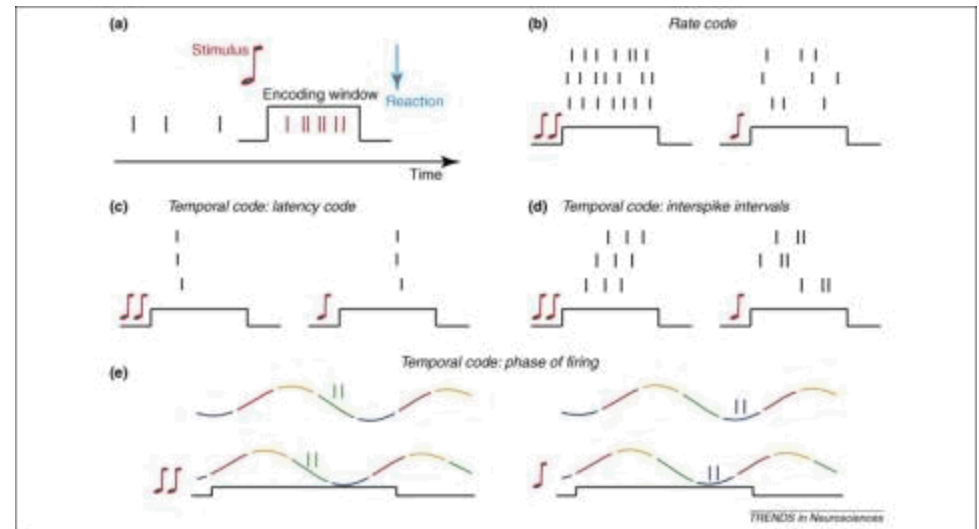
Non-neurogenesis animals have more selective neurons



Rangel et al., submitted

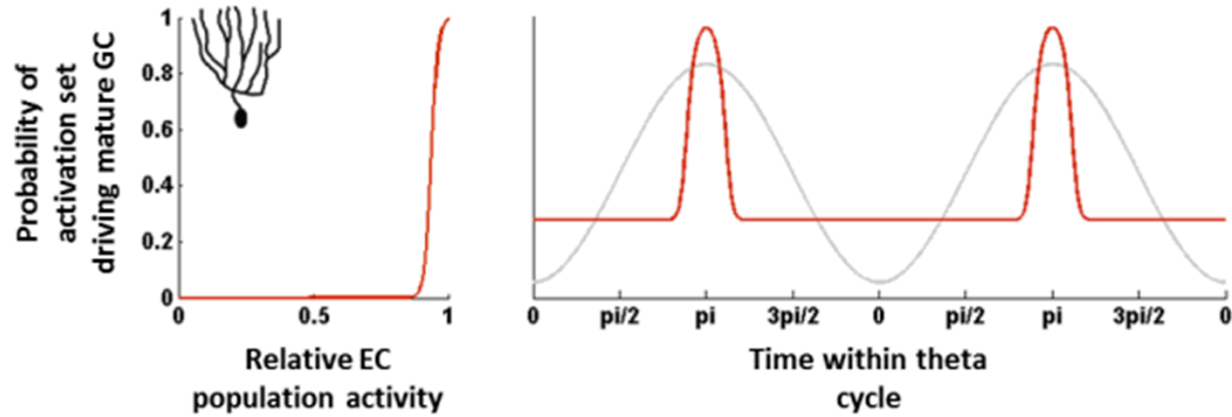
When neurons fire is often as important as how often they fire

- Sensory systems
 - Synchrony in responses
- Motor systems
 - Dynamical representation of cognitive state
- Hippocampal phase precession
 - “When” within an oscillation corresponds to “where” within the place field

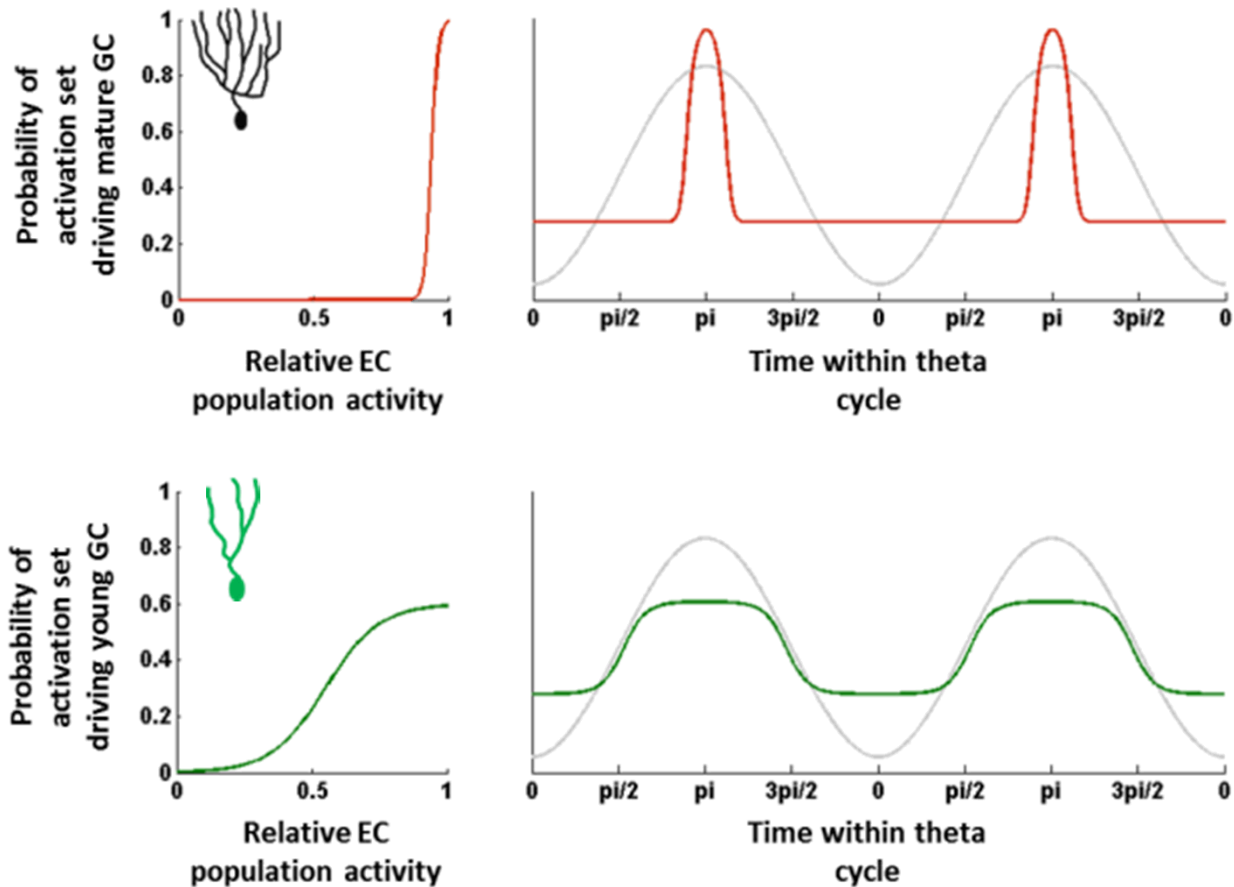


Panzeri et al., TINS, 2010

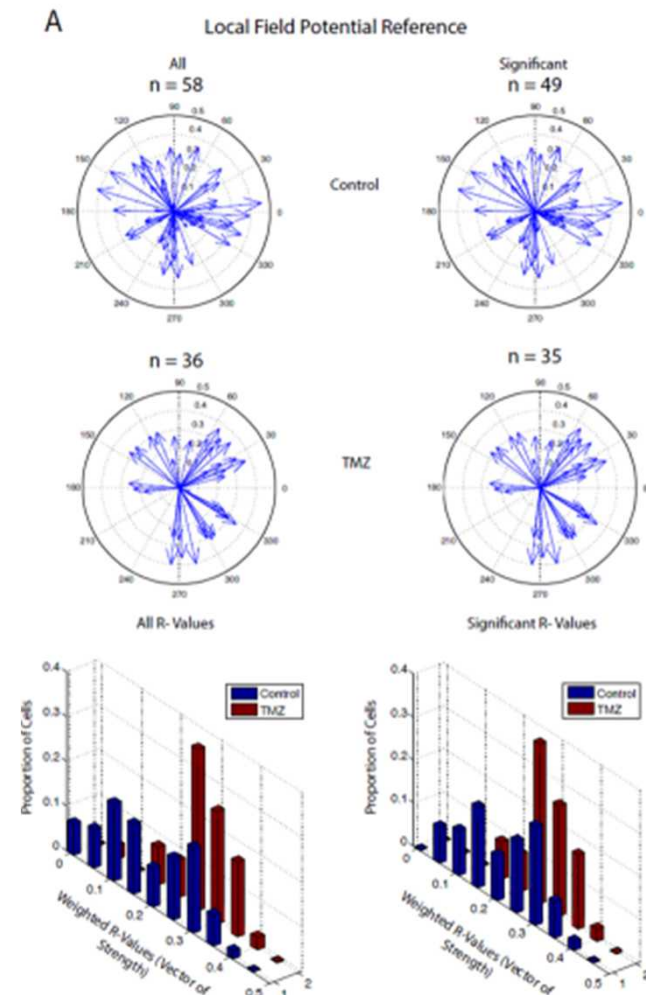
Tight tuning of GCs yields tight temporal tuning?



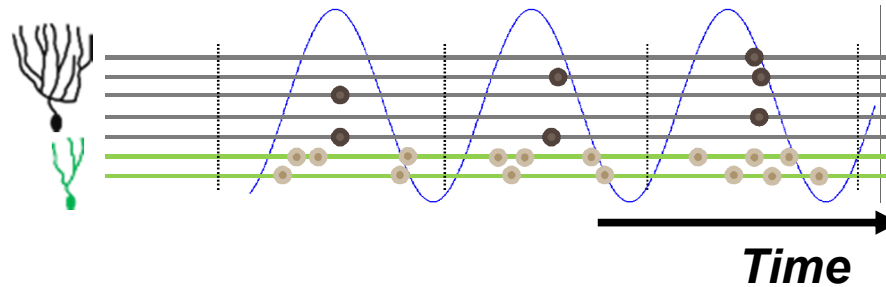
Broad tuning of GCs yields broad temporal tuning?



- TMZ and control rats with in vivo DG recordings
- Compare spikes of isolated GCs to local theta rhythm
 - *Prediction: young GCs would be phase incoherent; mature GCs would be phase coherent*
- TMZ animals show higher density of phase coherent (putative mature) neurons
- Control animals show mix of phase coherent (putative mature) and incoherent (putative young) neurons.



What temporal new neuron coding could mean



Potential Impacts

- Young neurons “prime” subset of CA3 population to entrain to inputs
- Synchronization of mature neurons to improve CA3 attractor formation
- Young neurons increase separation by activating feed-forward (in CA3) and feedback inhibition (in DG)

