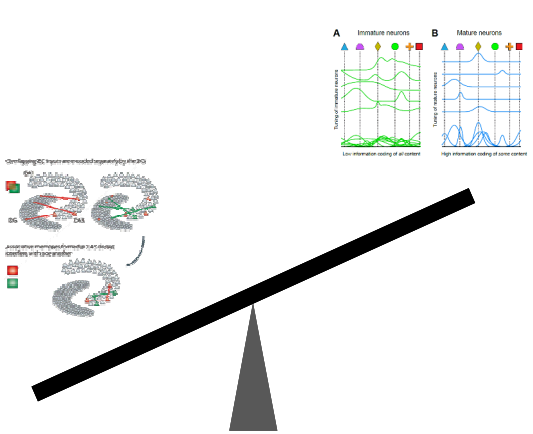
SAND2014-1866P

Validation of biologically realistic modeling

Should seeing be believing?

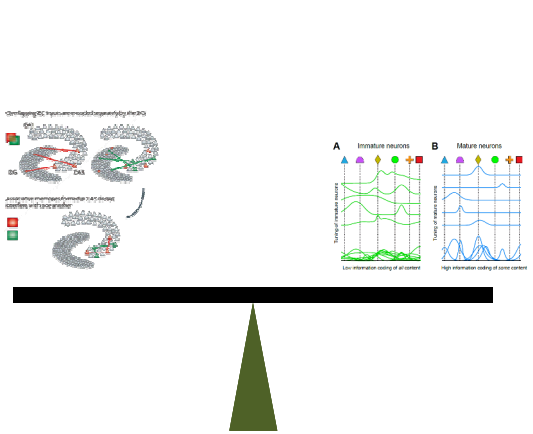
Brad Aimone

Neurogenesis strikes a balance between pattern separation and memory information content



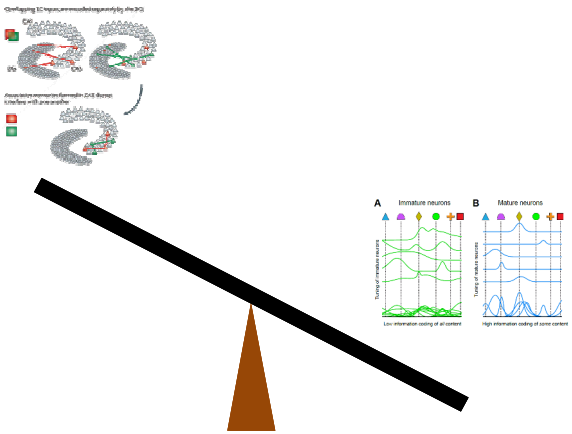
No neurogenesis yields very little activity

DG representations are separate but very sparse



Neurogenesis increases activity while preserving separation

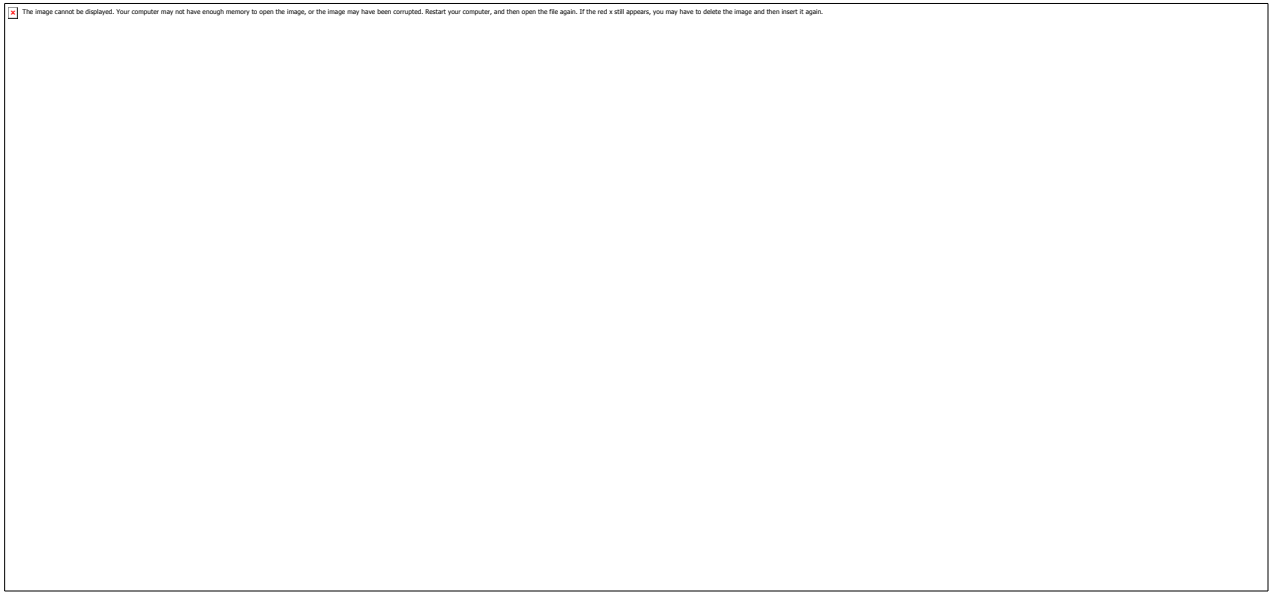
DG representations increase their resolution but avoid interference



Increasing activity directly ruins pattern separation

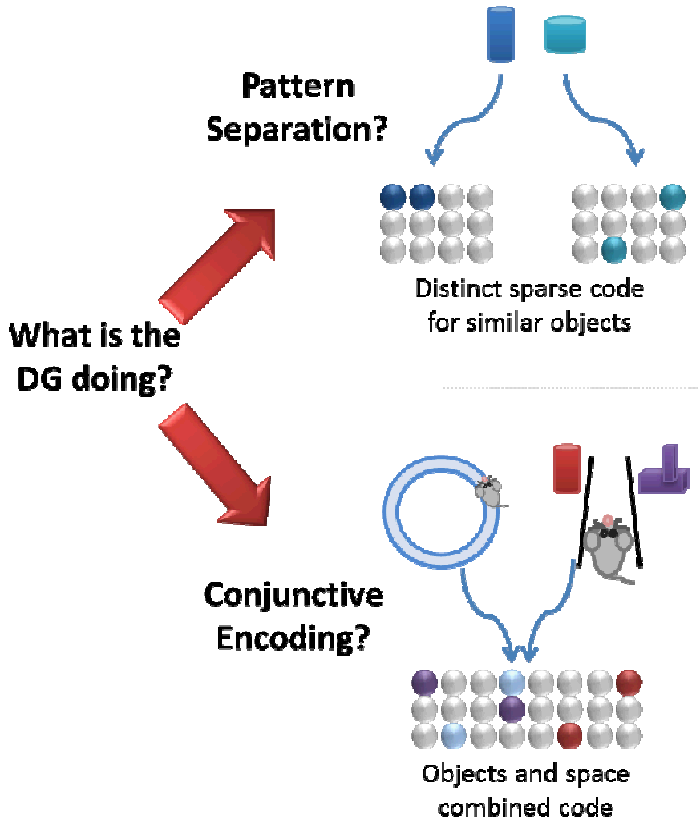
DG representations are dense and informative but potentially interfere with each other

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

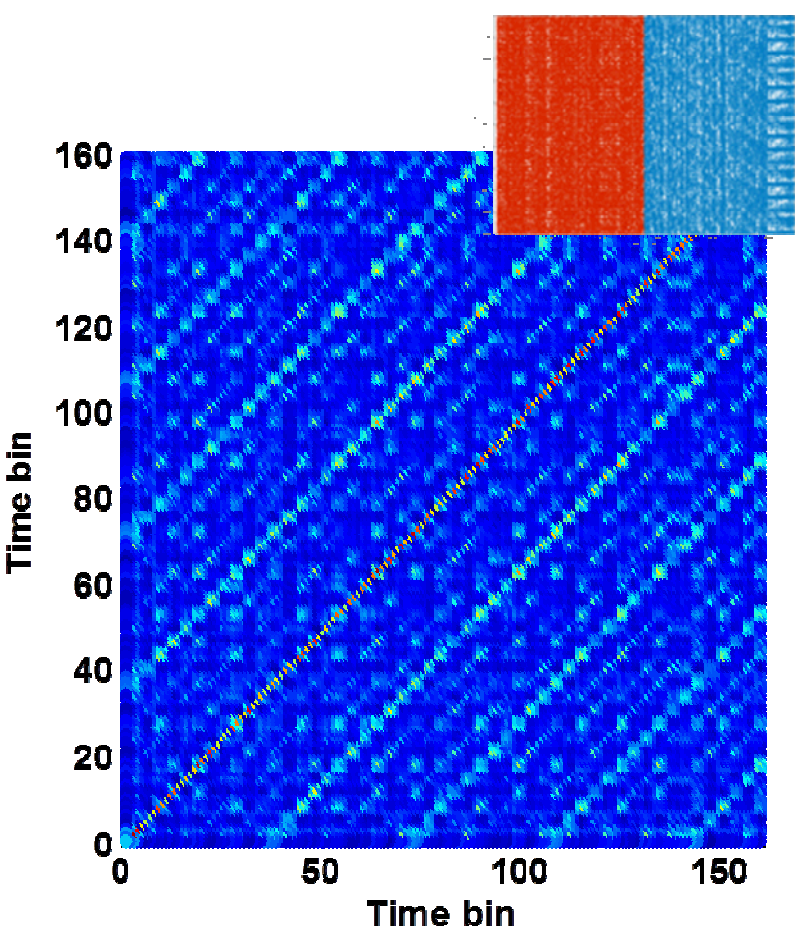
$$I = \sum_{ctx} {}^{p_{ctx}}/_{t} \log_2 {}^{f}/_{f}$$

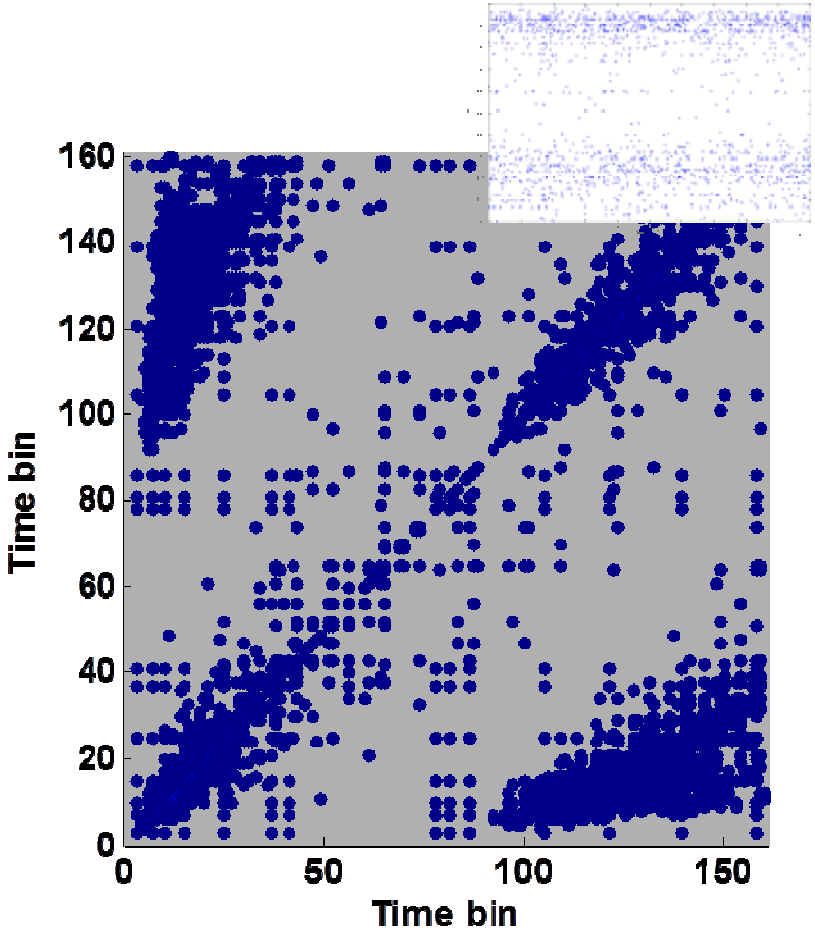
How to combine over neurons?

- **Independent variance**

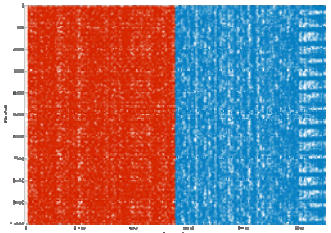
$$\varphi_{GC} = \sigma_{GC} \times \kappa_{\lambda}$$

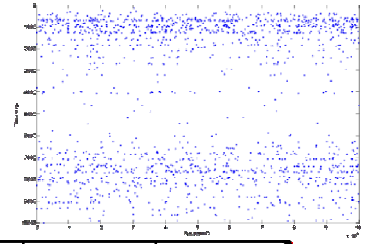
Information processing in large networks

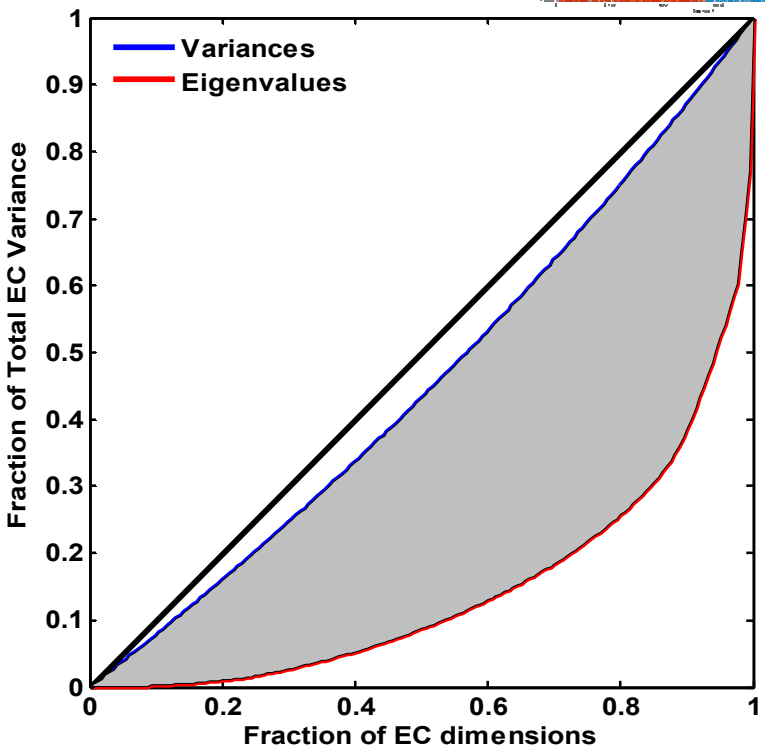


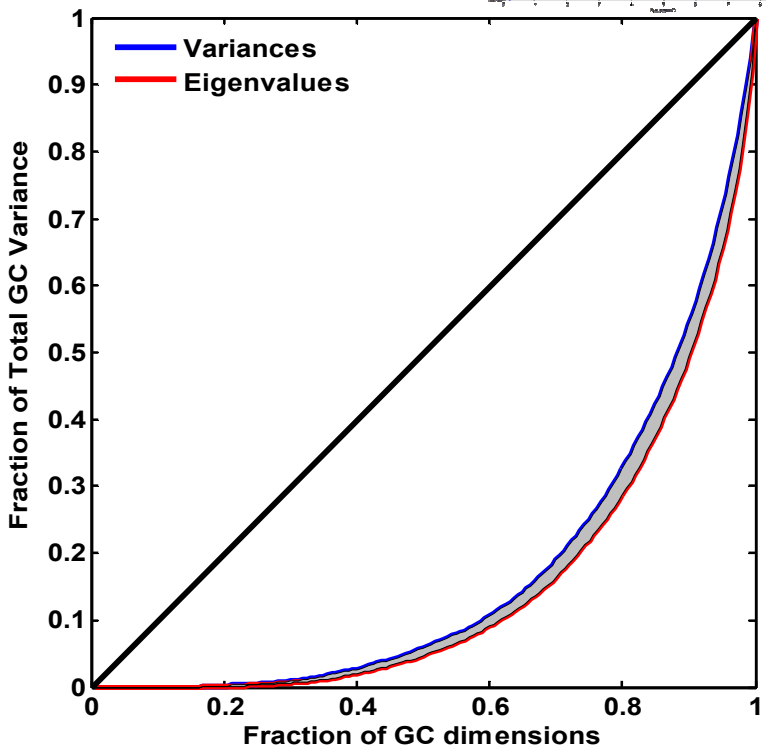


Information processing in large networks

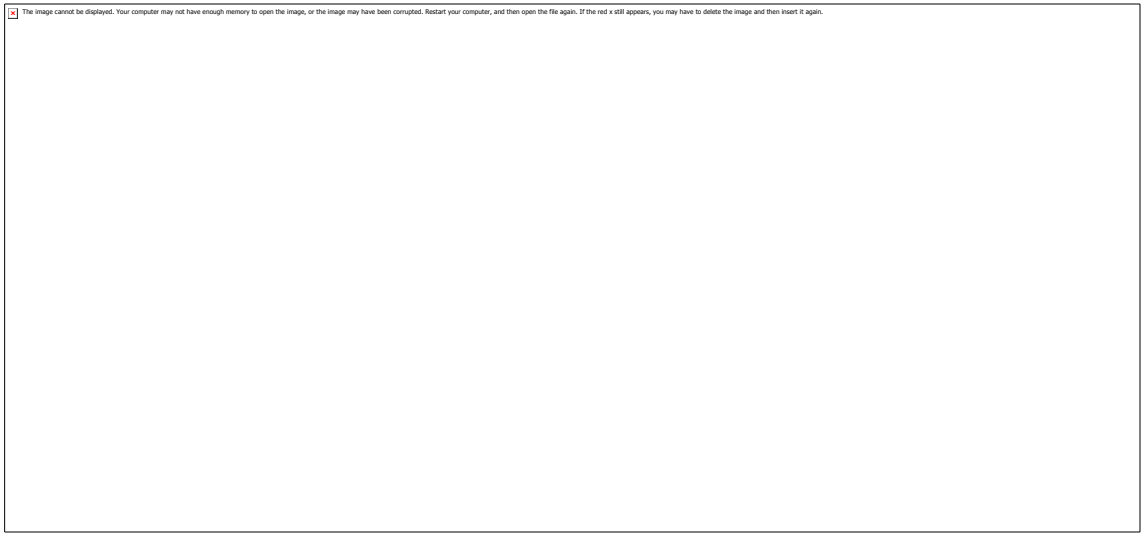




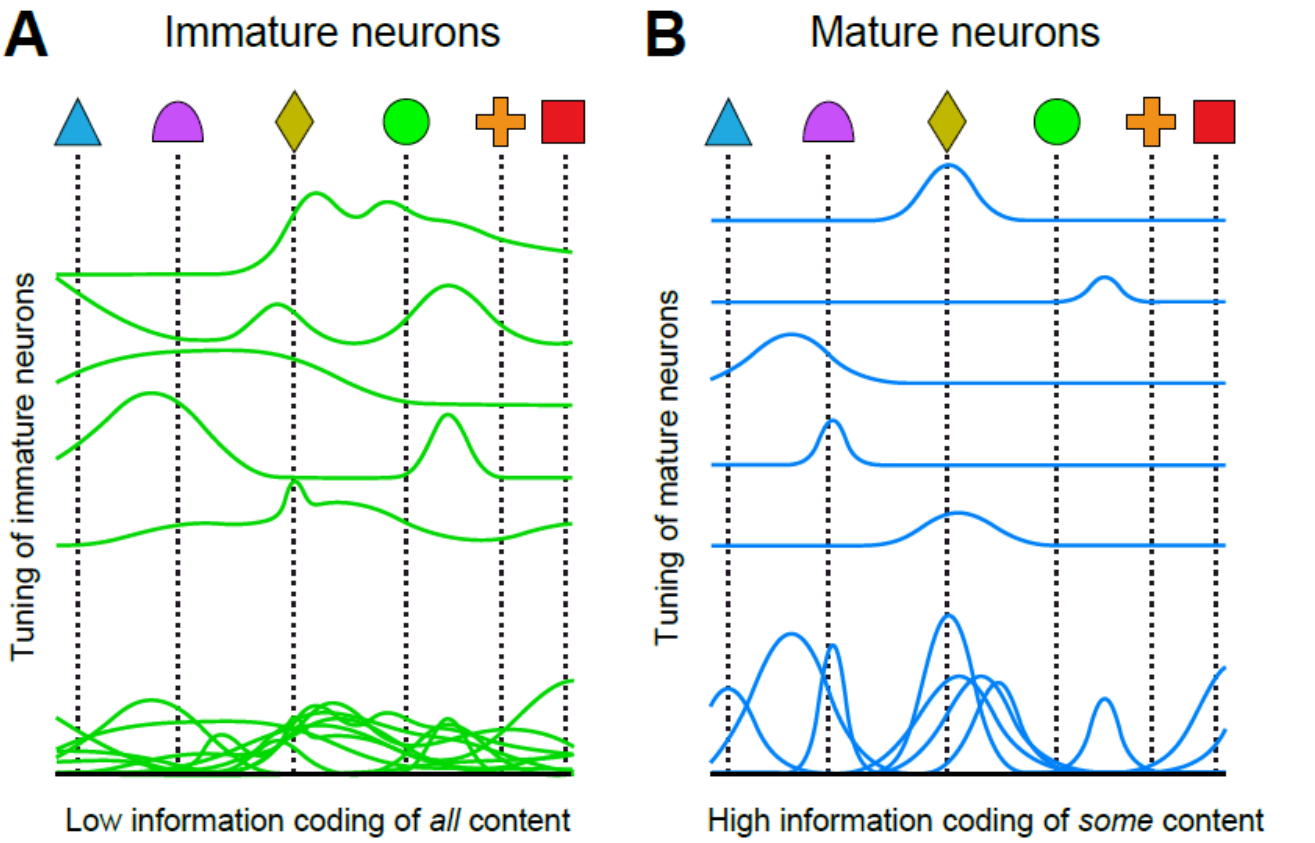




Neurogenesis maintains compressibility and increases total representation

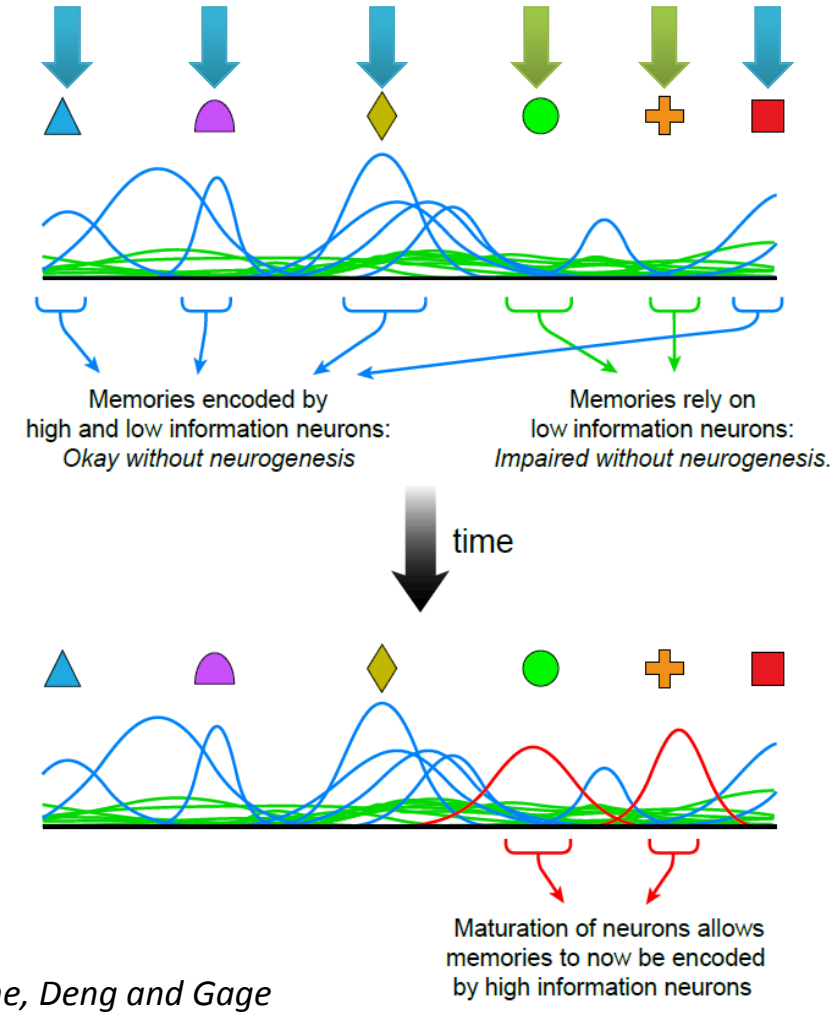


Immature and mature neurons encode information differently



Aimone, Deng and Gage
Neuron; 2011

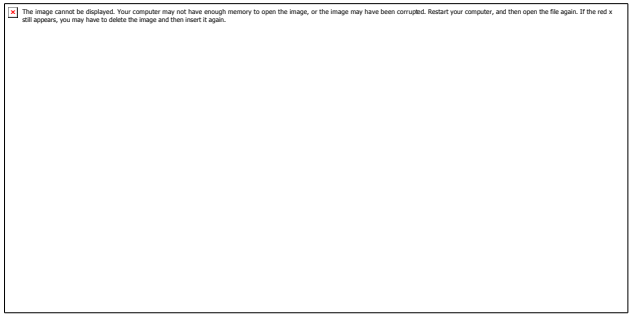
Mixed coding scheme in DG is potentially very powerful



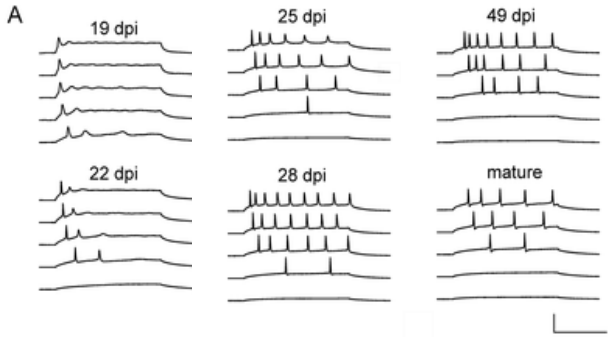
Aimone, Deng and Gage
Neuron; 2011

- 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*

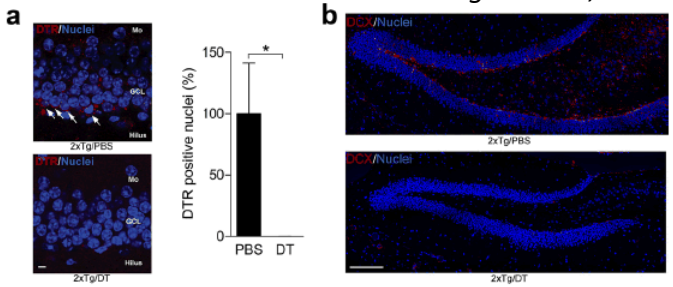
Modeling considerations



courtesy Chunmei Zhao



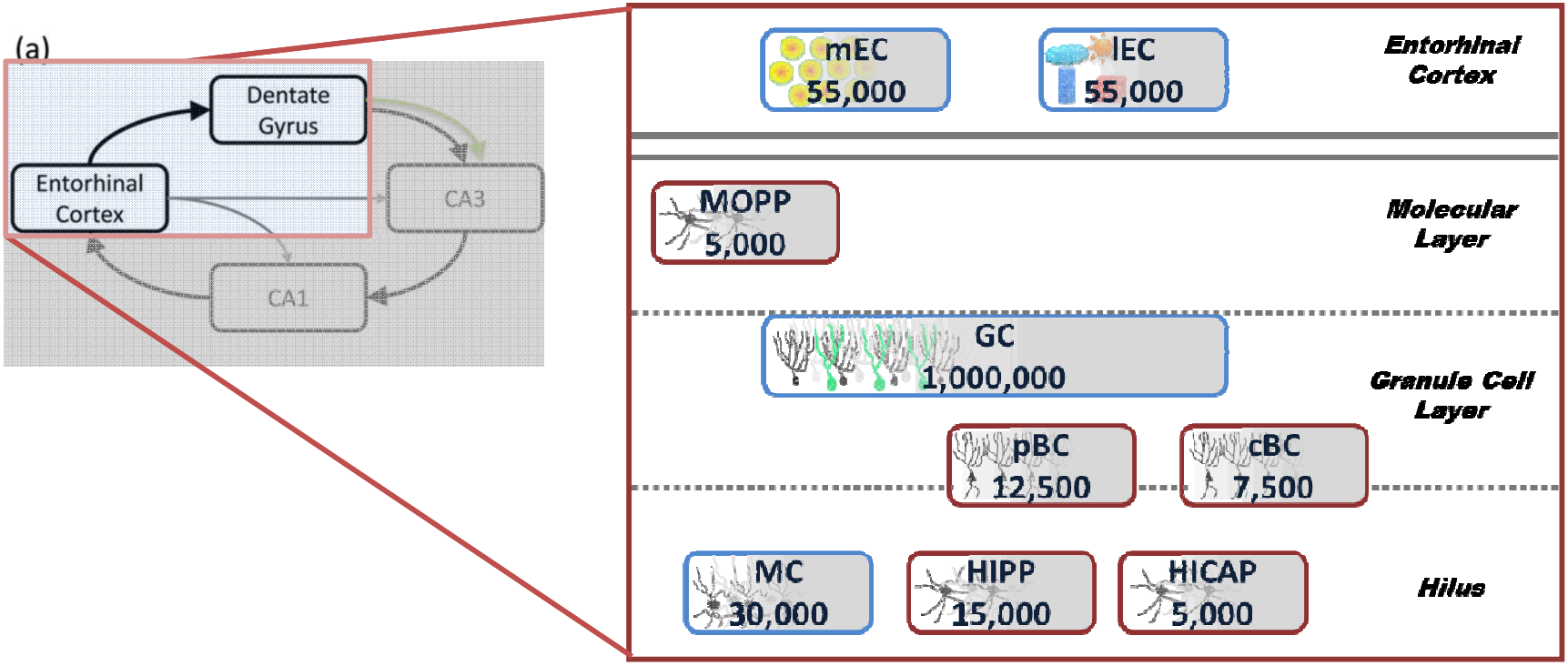
Mongiat et al., 2009



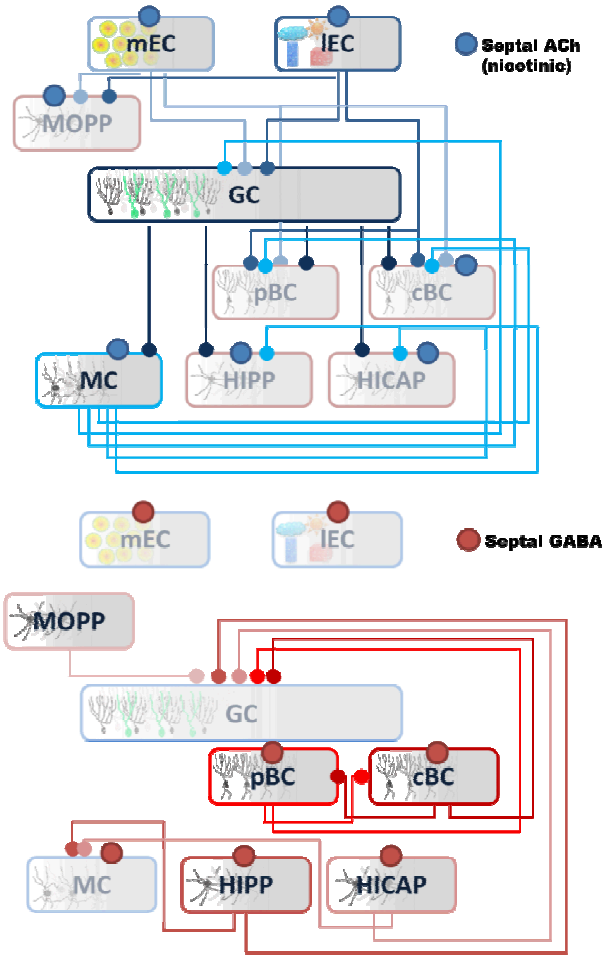
Arruda-Carvalho et al., 2011

- 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

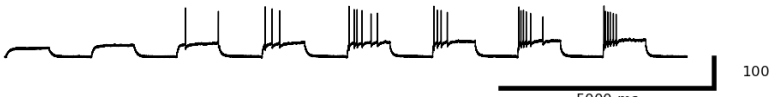
Realistic scale model



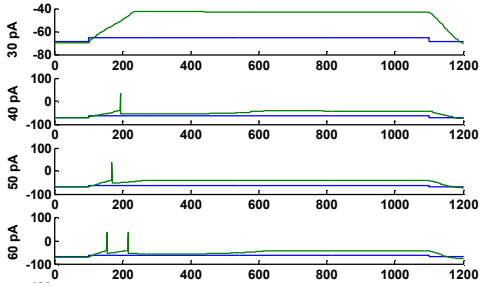
Realistic connectivity and dynamics

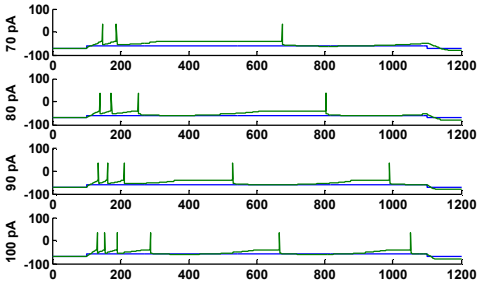


Physiology data

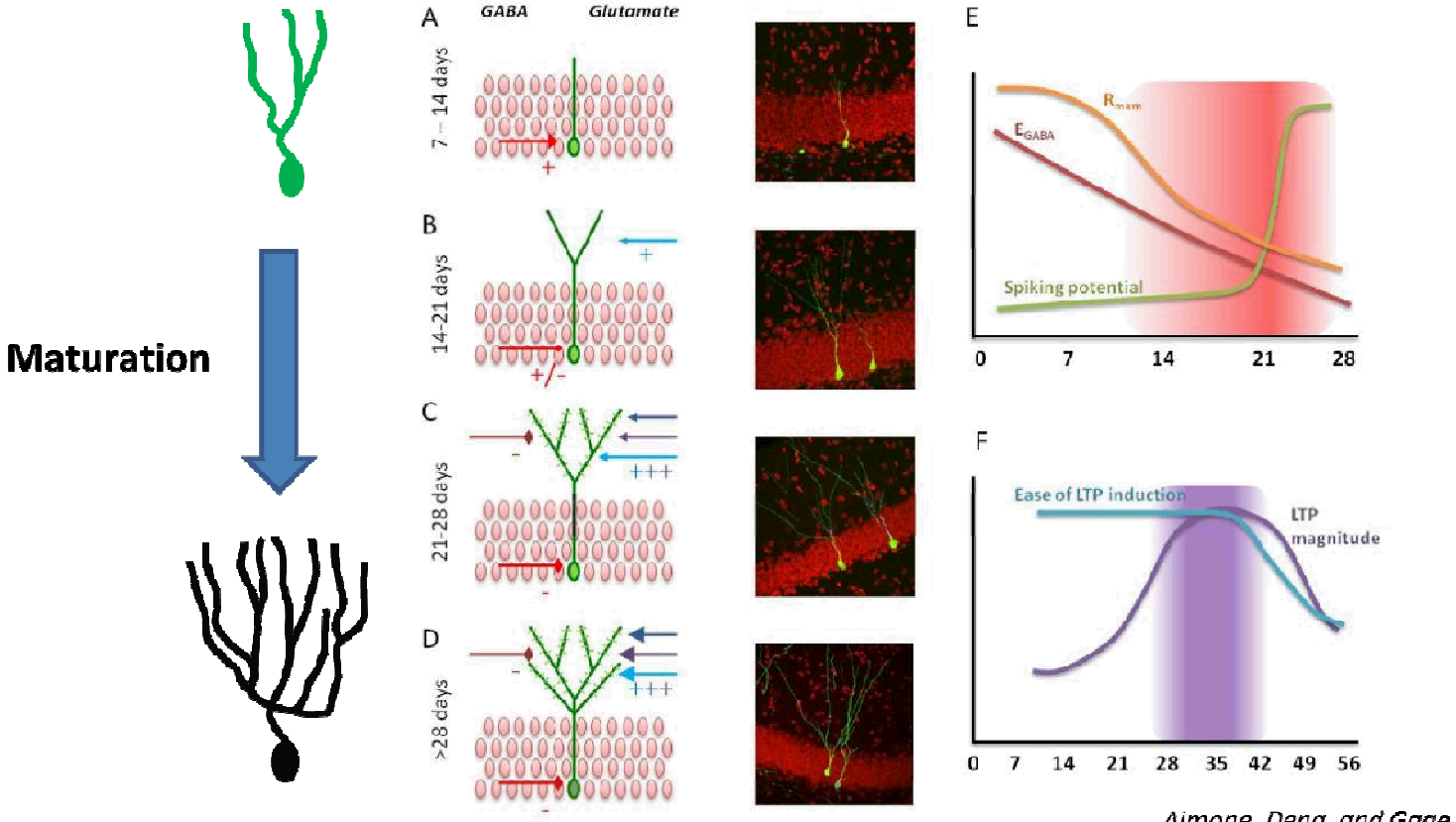


Modeled neuronal dynamics





Neurogenesis Process



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

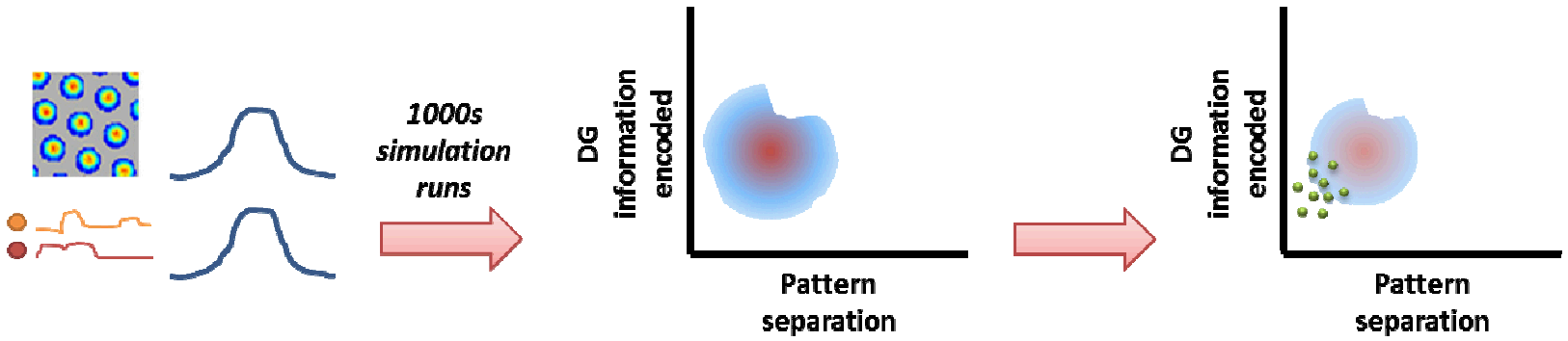
Sensitivity Analysis of Model

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

name	count	modcoun	vt	vr	C	k	a	b	c	d	kmult	lrheo	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	1000	-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-5HT	1	1	-35	-70	100	0.4	0.04	0.2	-65	20	10	410	0	1000	0	0	0	30	20
MR-5HT	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_	x_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
IEctoMOI	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	8	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
IEctopBC	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
IEctocBC	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	0.1	1	1	0	19	7	0	0	12	0
mEctoGC	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
mEctopBC	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
mEctocBC	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
GCtopBC	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
GCtocBC	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
GCtoHICA	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	0.2638	0.22	0.18	0.21	1	2	5	0.949	2	-0.08	1	1	0	16	10	0	0	16	0
pBCtopBC	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
cBCtocBC	5	5	145	-79.46	0.35868	0.27	0.19	0.29	1	3	4	1	2	-0.09	1	2	0	24	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
MCtopBC	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
MCtocBC	6	5	1659	0	0.05258	0.98	0.18	0.24	3	10	1	0.887	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	0.0622	0.4	0.08	0.22	1	2	4	1	2	-0.09	1	1	0	22	6	0	0	13	0
MCtoHIPF	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
MCtoHICA	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
nAChtocB	9	5	1	0	2.4439	0	1	Inf	0	3	36	1	3	0	1	1	2	19	8	0	0	13	0
nAChtoMI	9	6	1	0	0.87769	0	1	Inf	0	3	22	1	3	0	1	2	2	20	11	0	0	12	0
nAChtoHI	9	7	1	0	0.83901	0	1	Inf	0	3	28	1	3	0	1	1	2	22	9	0	0	8	0
nAChtoHI	9	8	1	0	0.5949	0	1	Inf	0	3	29	1	3	0	1	1	2	15	7	0	0	8	0
5ht3toBC	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	10	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	3.21025	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

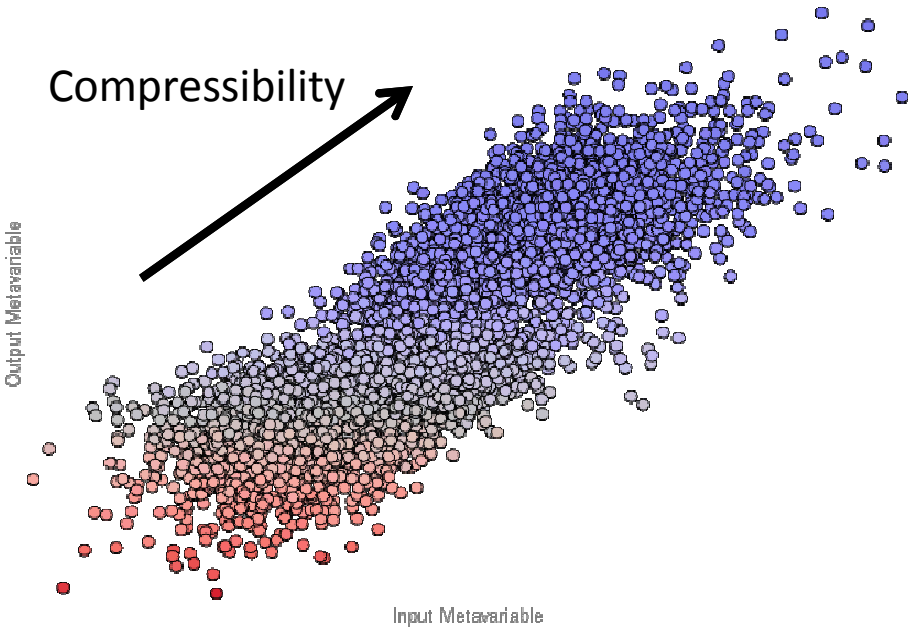
Obtain probability distribution of model outputs given explored parameter space

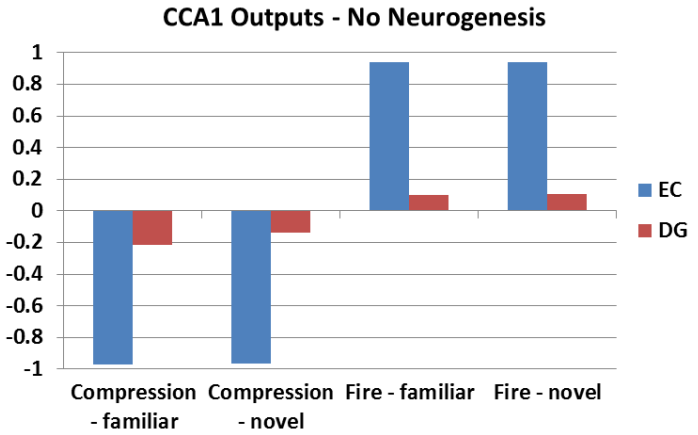
Map experimental data onto distribution to further constrain studies

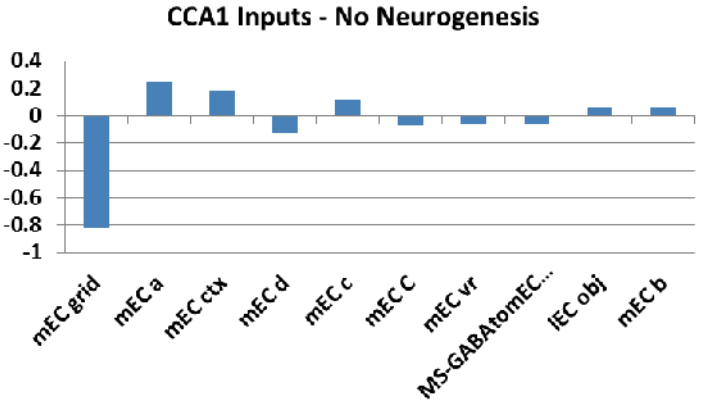
Model Sensitivity to different parameters

1st Canonical Component

Parameters driving EC inputs





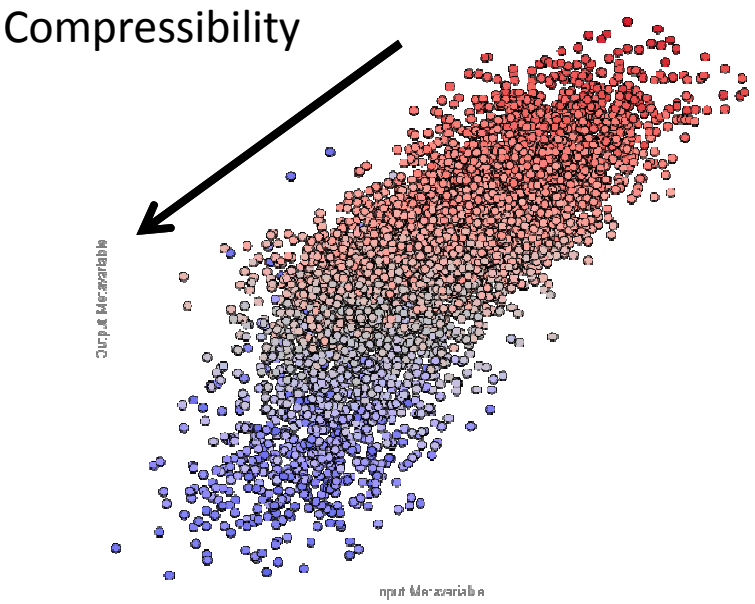


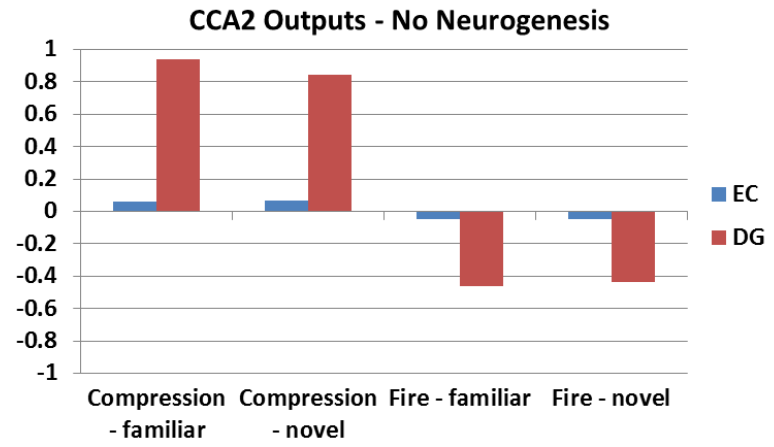
Model Sensitivity to different parameters

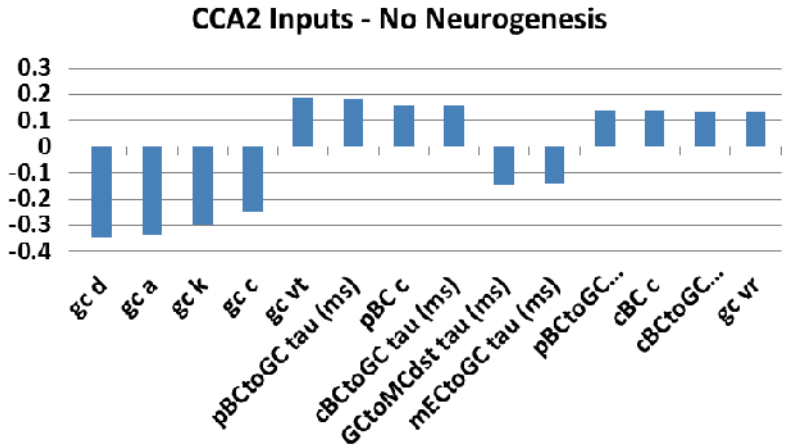
2nd Canonical Component

Parameters driving GC activity

Most runs were highly separated





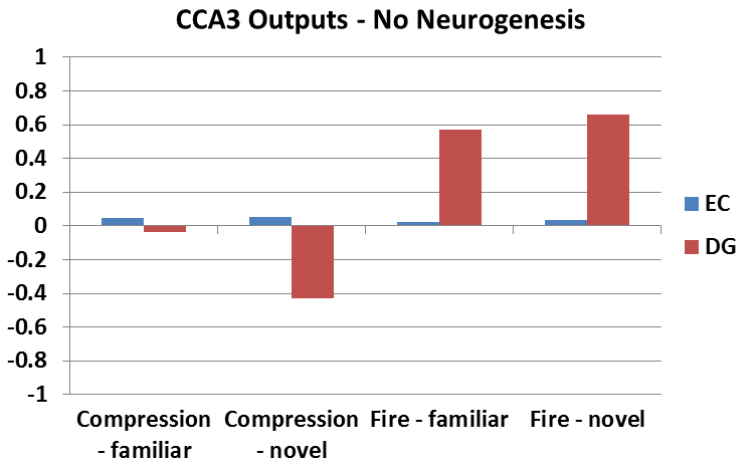


Model Sensitivity to different parameters

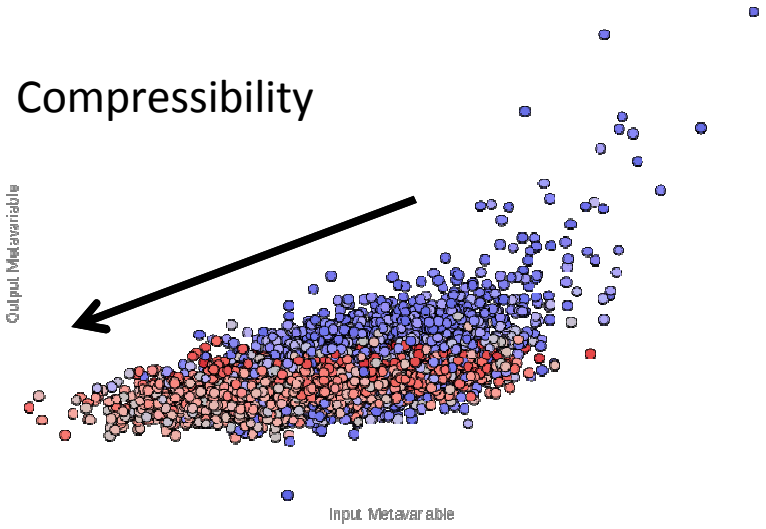
3rd Canonical Component

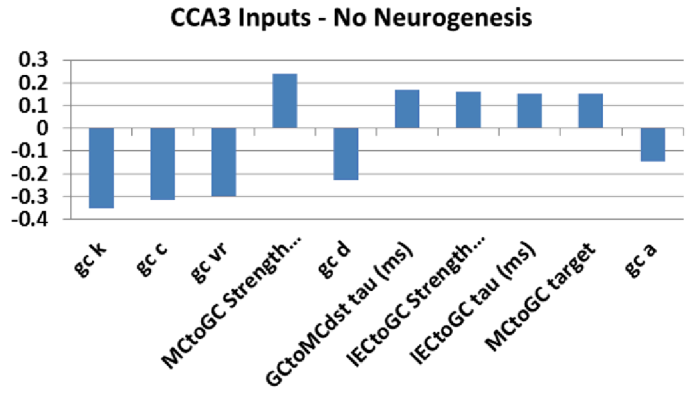
Parameters driving novel vs familiar difference

Quite a bit messier



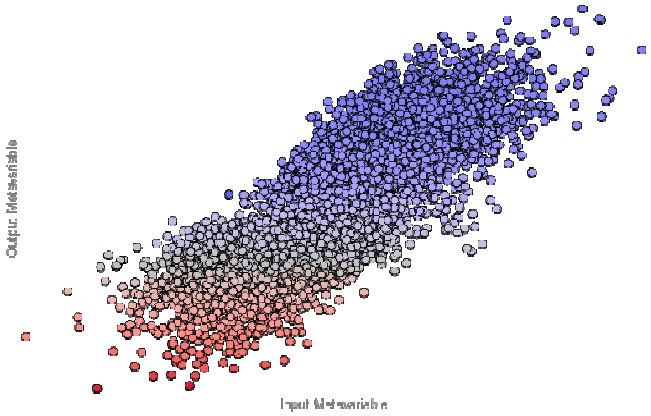
Compressibility



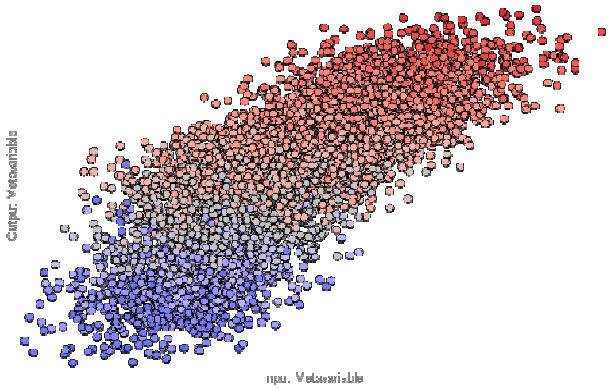


Neurogenesis simulations are similar

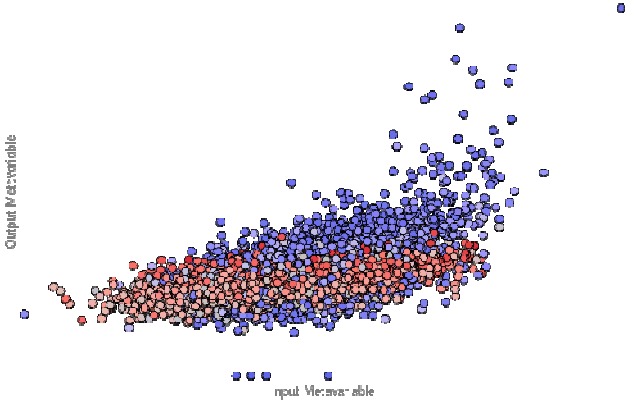
CCA 1 – EC Compressibility



CCA 2 – DG Compressibility



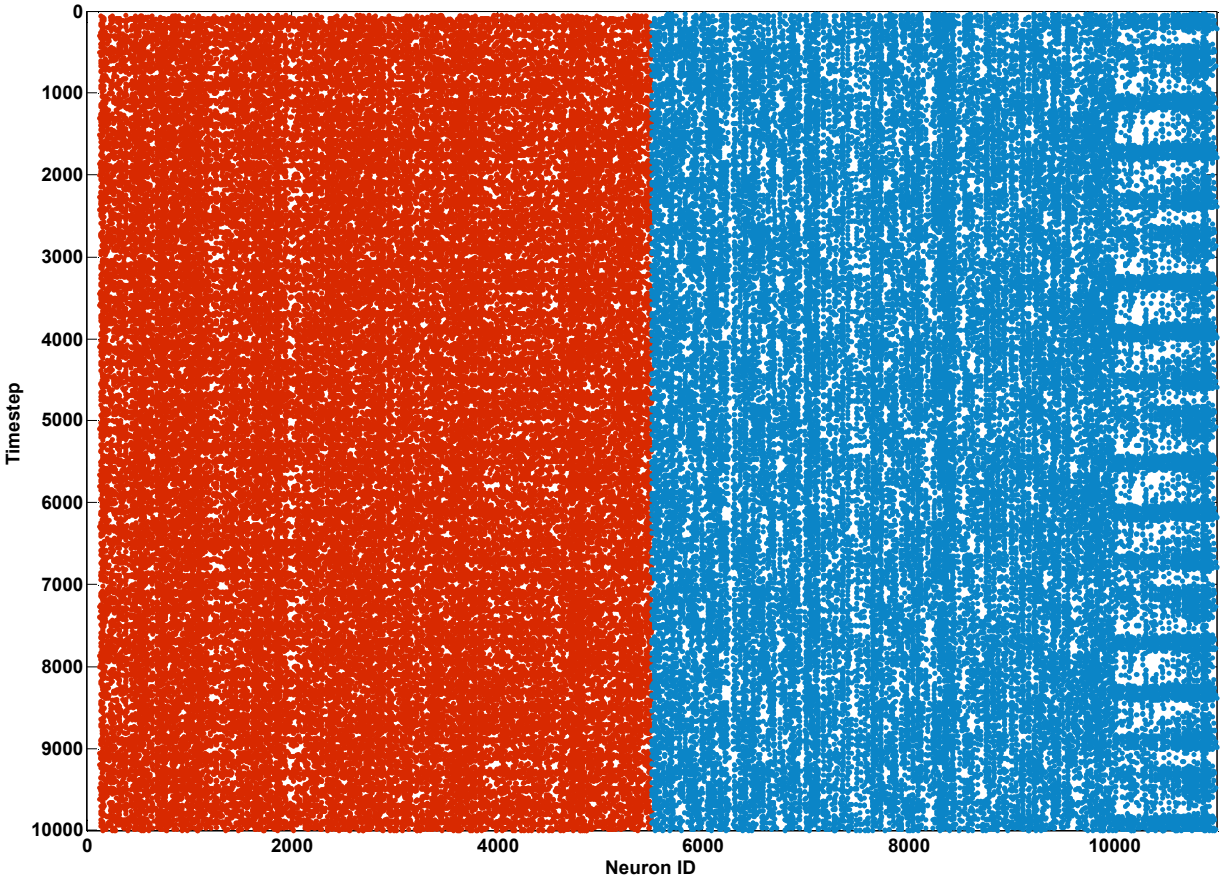
CCA 3 – DG Compressibility



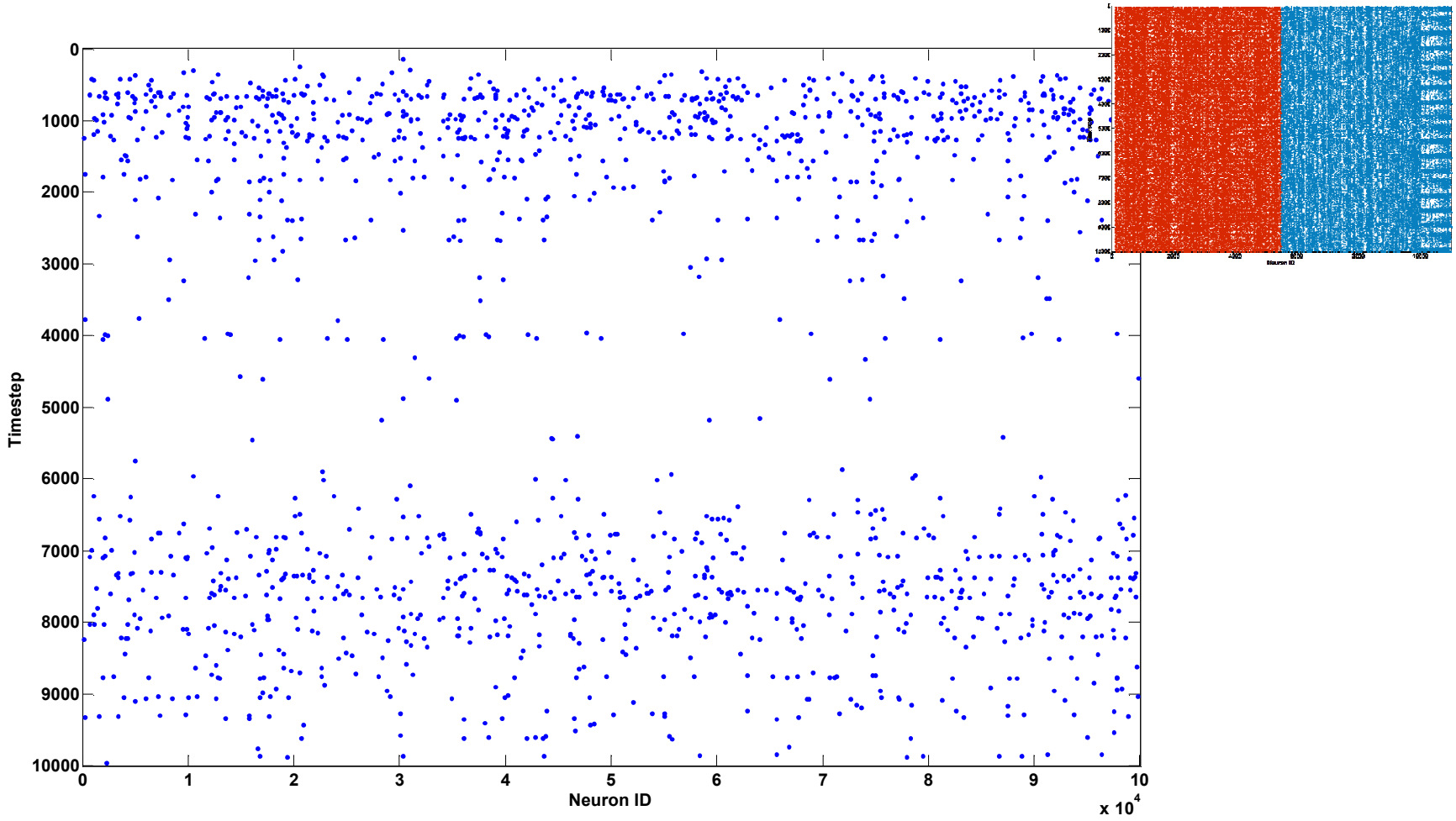
Sensitivity Conclusions

- 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

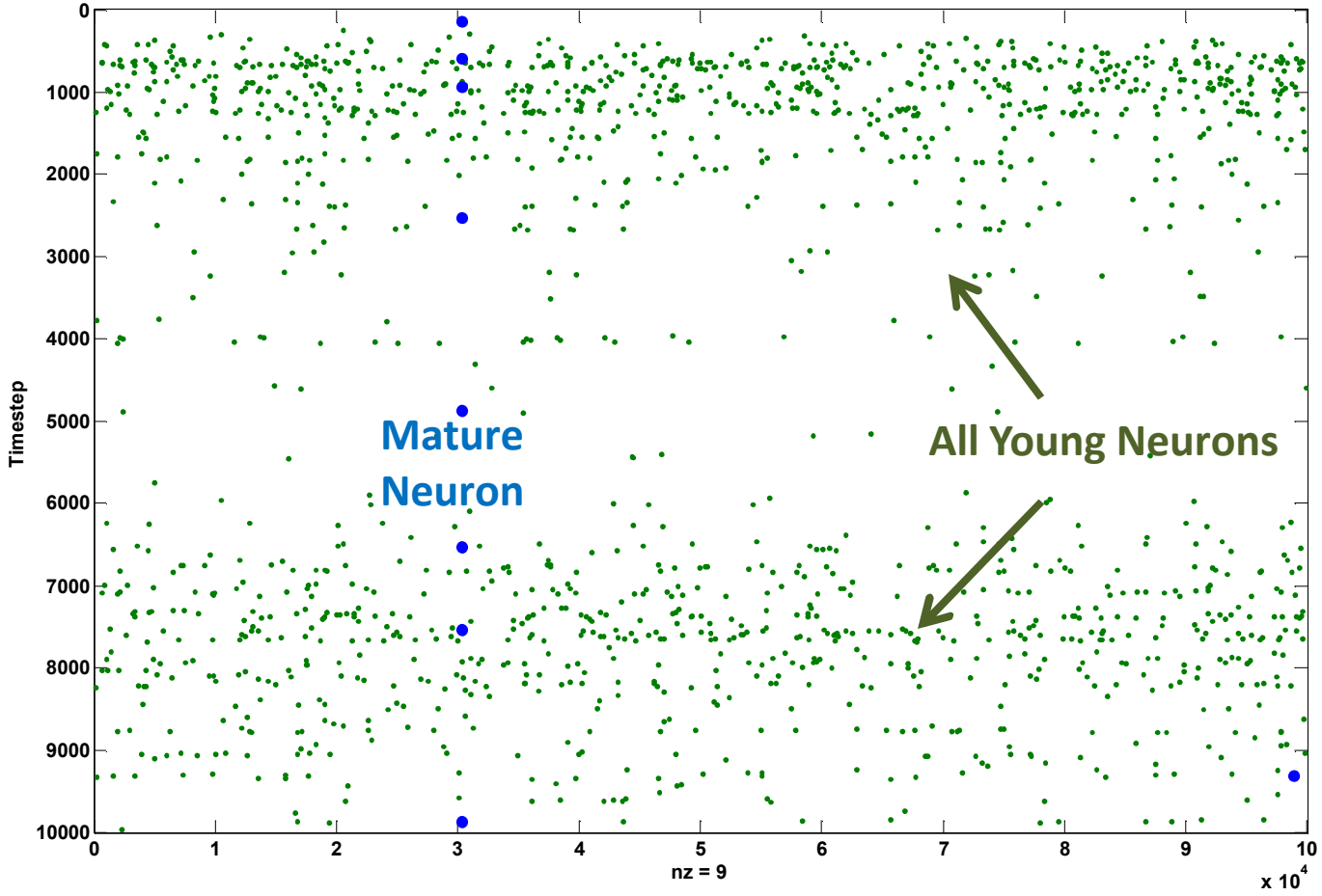
Activity of network – EC Inputs



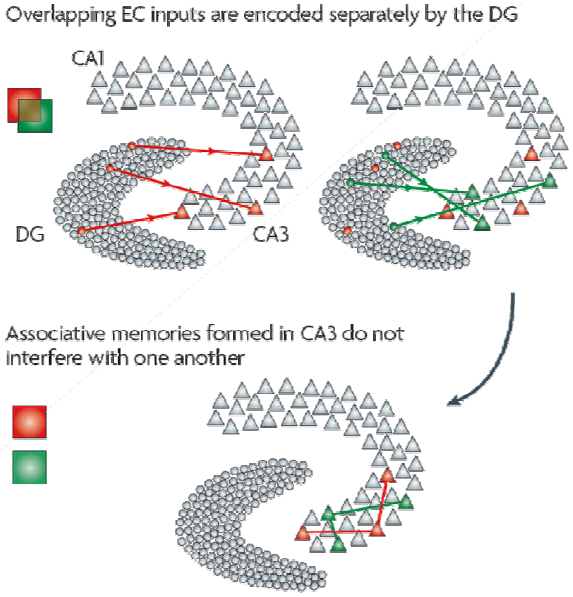
Activity of network – GC Outputs



Young GCs dominate



So which is right?



Pattern separation?

Or memory resolution?