Particle-based stochastic simulations

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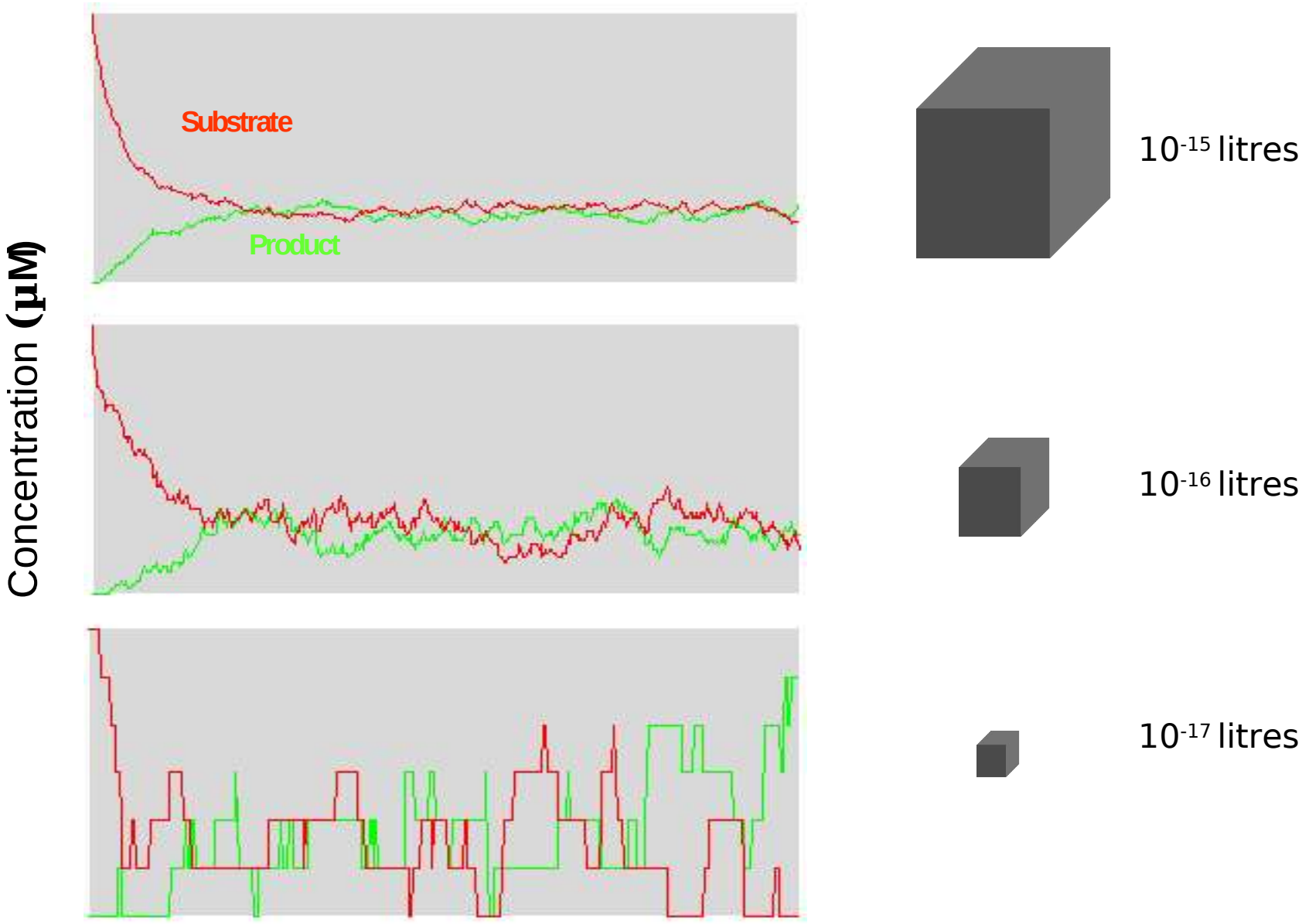
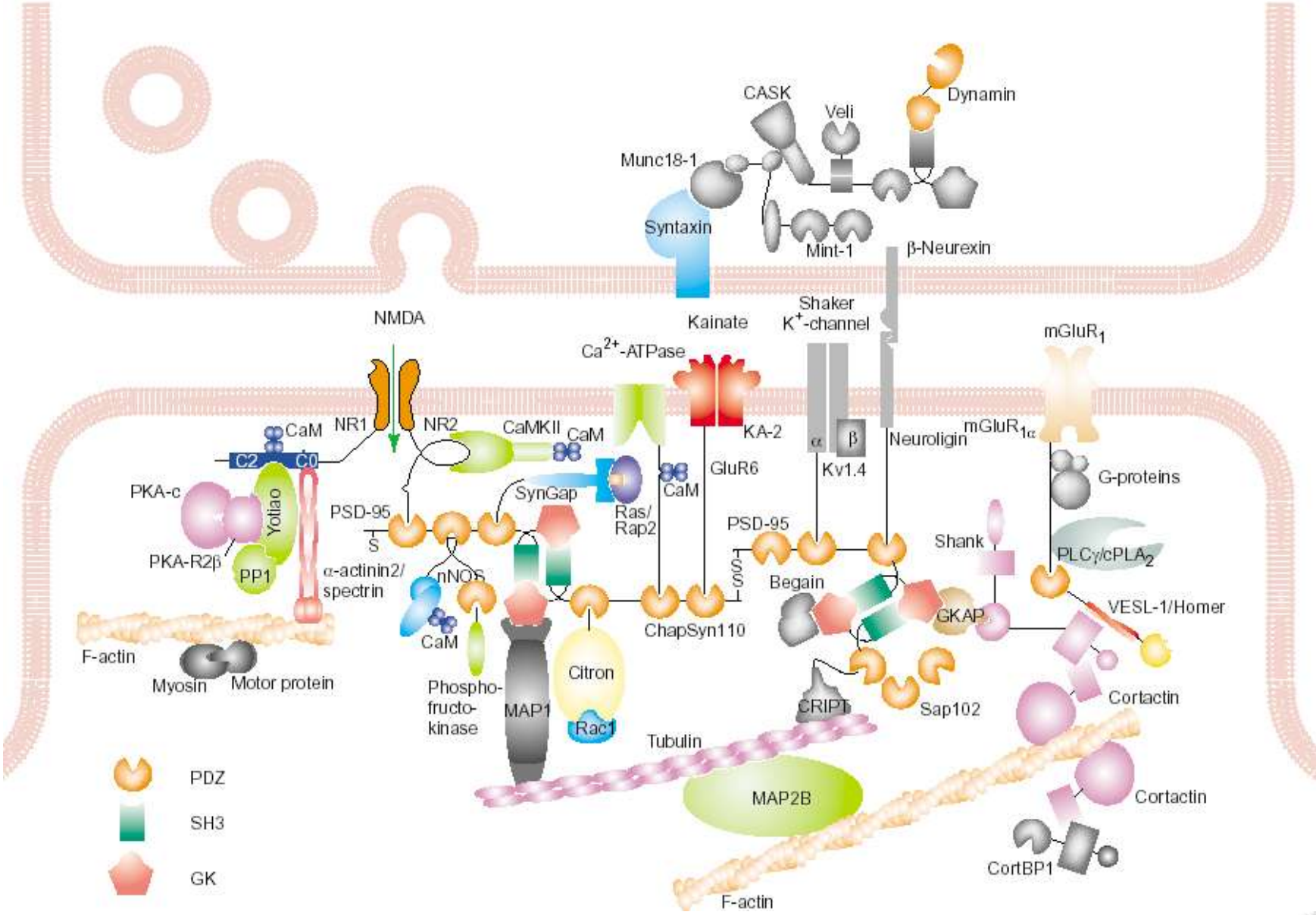
On small numbers



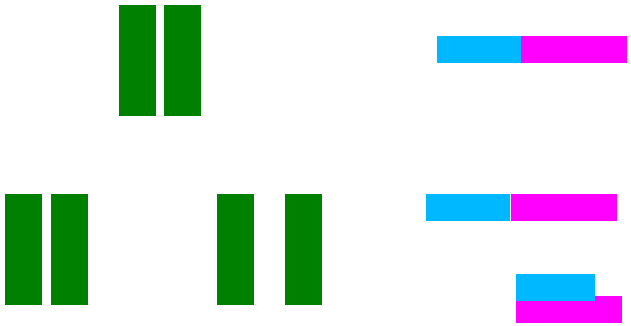
Number of calcium ions in a dendritic spine = 3-5 ...

Complex post-synaptic machinery



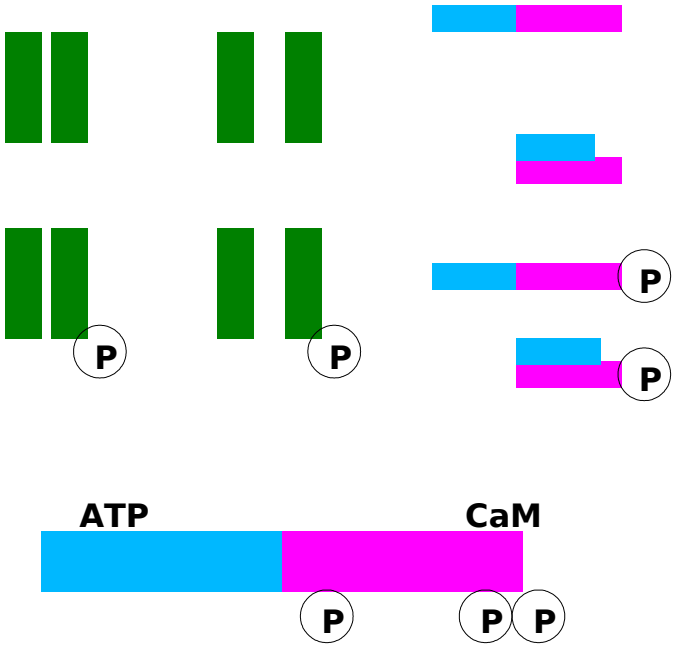
Husi & Grant (2001) *TINS, 24*: 259-266

Combinatorial explosion



NMDA + CaMKII <=> NMDA-CaMKII

NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo



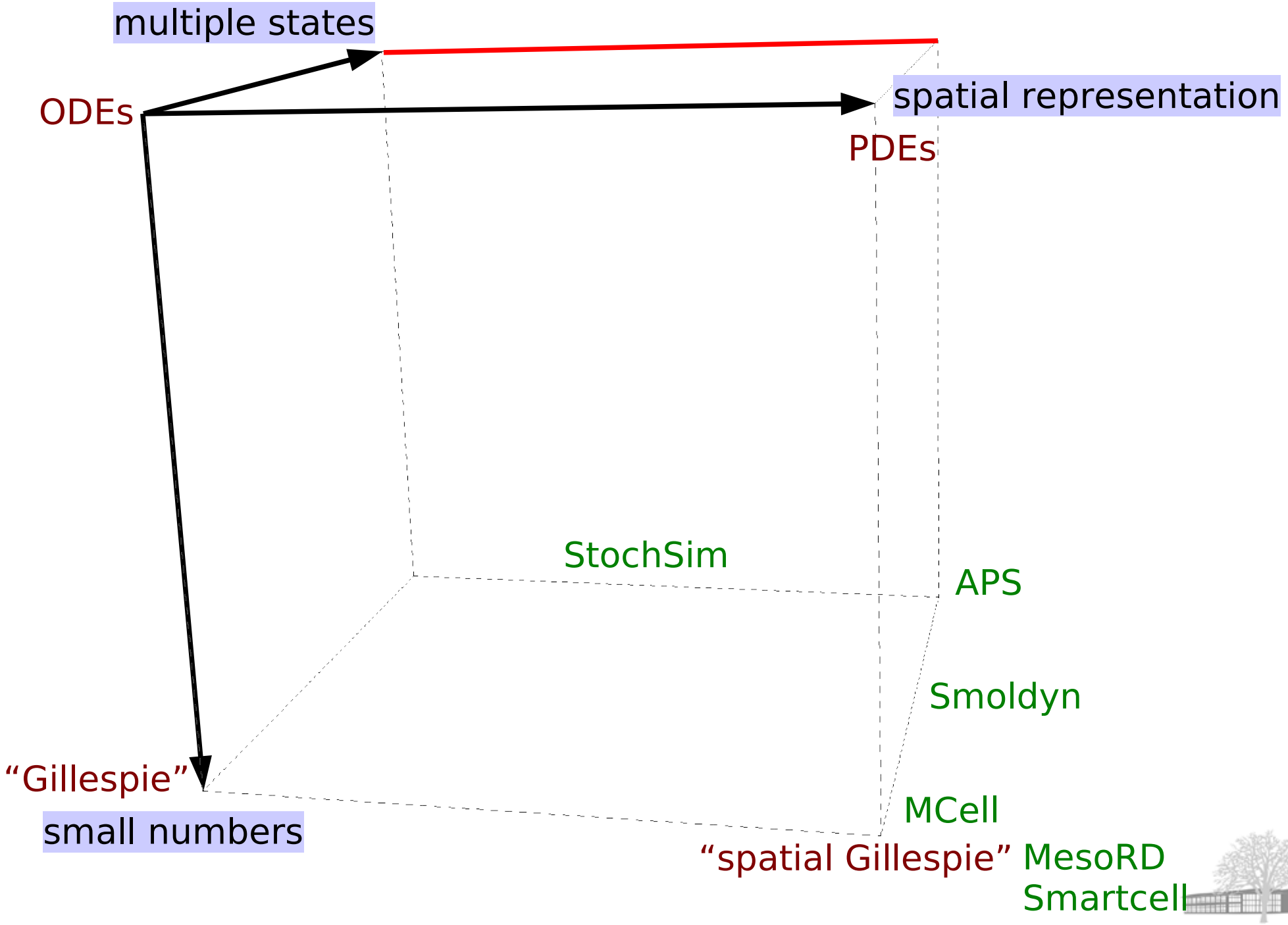
NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo
pNMDAc + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAo + CaMKIIc <=> pNMDAc-CaMKIIc
pNMDAc + CaMKIIo <=> pNMDAc-CaMKIIo
pNMDAo + CaMKIIo <=> pNMDAc-CaMKIIo
NMDAc + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAo + pCaMKIIc <=> NMDAc-pCaMKIIc
NMDAc + pCaMKIIo <=> NMDAc-pCaMKIIo
NMDAo + pCaMKIIo <=> NMDAc-pCaMKIIo
pNMDAc + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAo + pCaMKIIc <=> pNMDAc-pCaMKIIc
pNMDAc + pCaMKIIo <=> pNMDAc-pCaMKIIo
pNMDAo + pCaMKIIo <=> pNMDAc-pCaMKIIo

Combinatorial explosion

- 10 states reacting with 10 states = 262144 reactions combinations. However, all the states do not affect all the reactions:
  - ☛ Useless computation

- 10 states reacting with 10 states = 1536 pools.
  One glutamatergique synapse ~ 60-100 receptors
  Often more pools than molecules
  - ☛ Useless computation

The method space



Need another paradigm of simulation

Population-based simulation

- Continuous representation of populations
- Generally deterministic algorithms to simulate the evolution of populations (but not always: Gillespie)
- Generally no representation of space (but not always: finite elements)
- No movements (but not always: PDE or reaction-diffussion)
- Molecules under different states are represented by different pools

Particle-based simulation

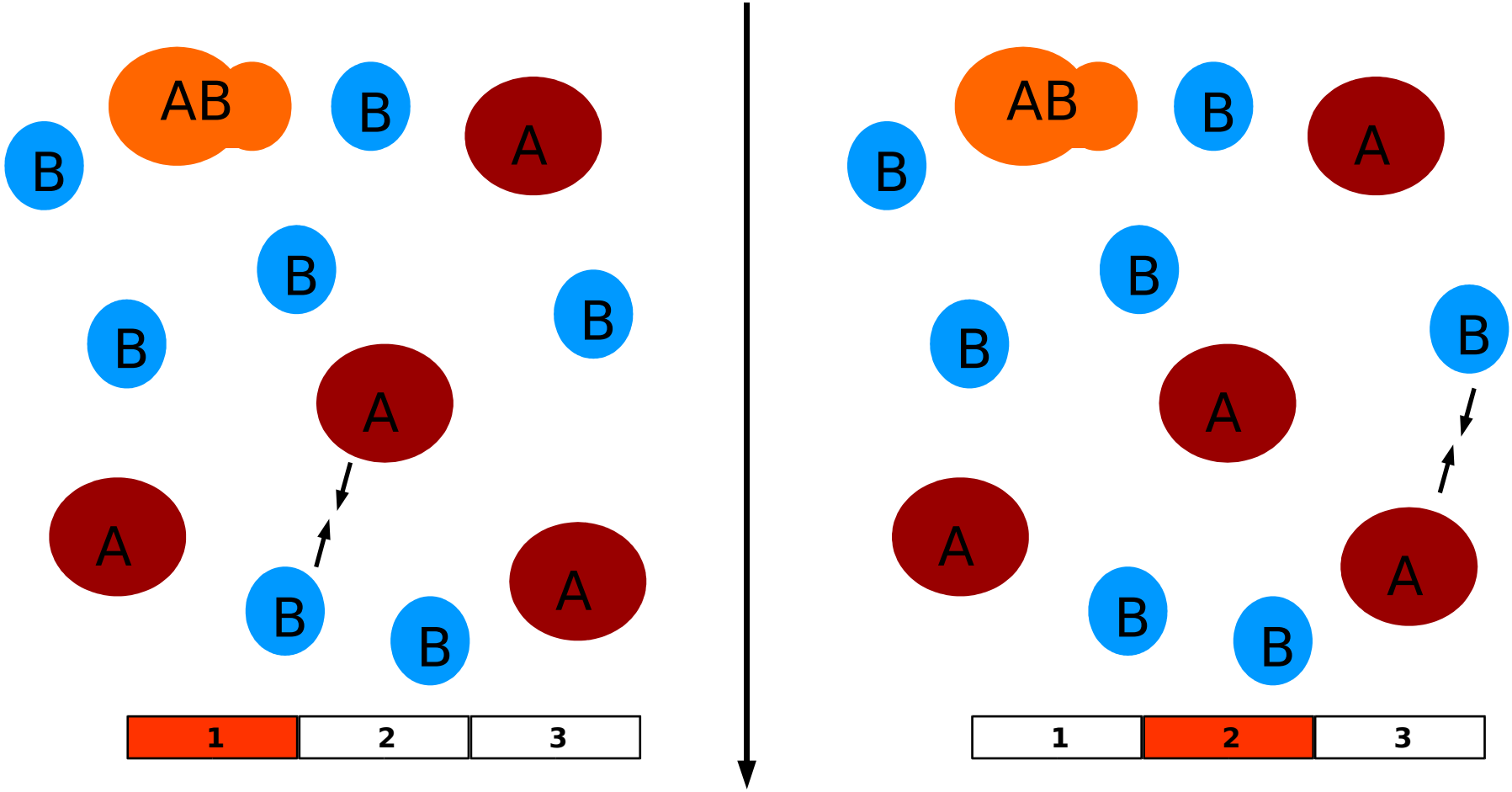
- Discrete representation of molecules
- Generally stochastic algorithms (but not always: deterministic automata)
- Generally location of molecules (but not always: StochSim v1)
- Representation of the movements of (some) molecules
- Possibility of multistates molecules

StochSim

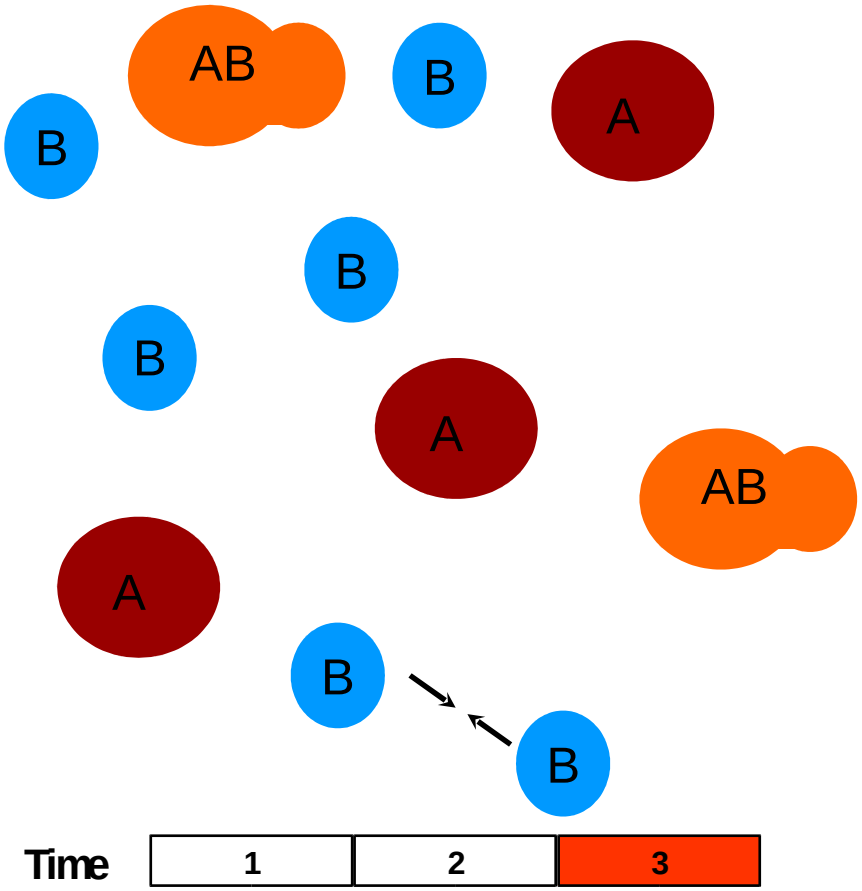
- Morton-Firth CJ, Bray D (1998) *J. Theor. Biol.* 192: 117–128.
- Le Novère N, Shimizu TS (2001) *Bioinformatics* 17: 575-576

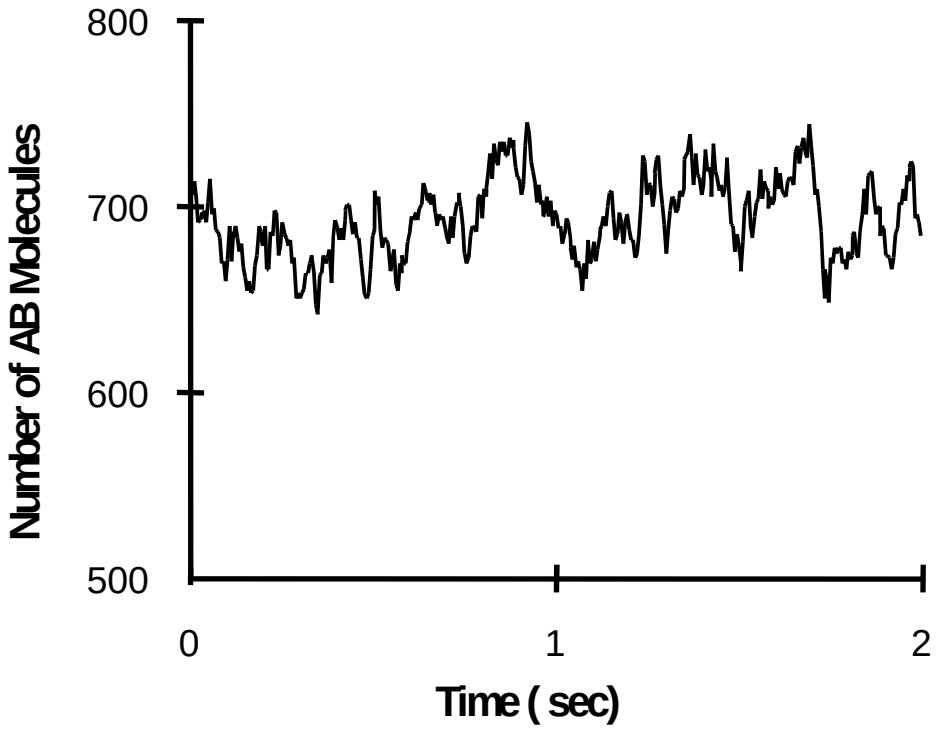
- Particle-based stochastic simulations
- Possibility of multistate complexes
- Rapid equilibria to reduce stiffness problems
- 2D lattices of various geometry

StochSim algorithm



StochSim algorithm





Kinetic constant to probability

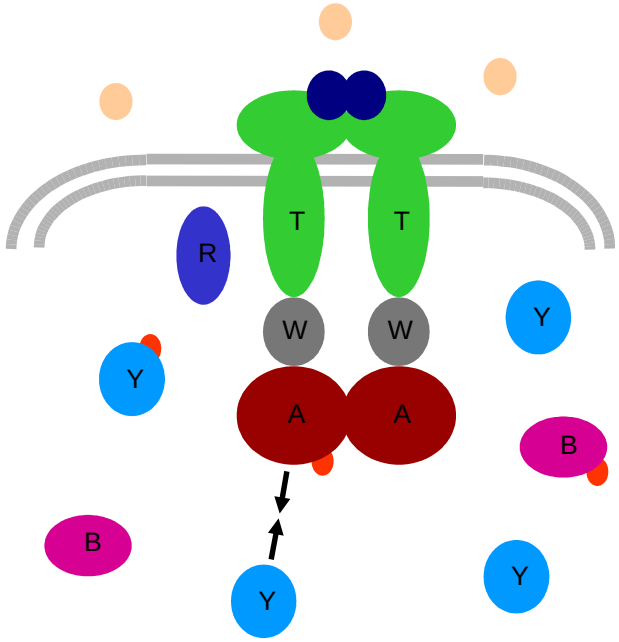
$$d[A]/dt = k[A][B] \qquad P = \frac{k\, n(n+n_0)\Delta t}{2VN_A}$$

$$d[A]/dt = -k[A] \qquad P = \frac{k\, n(n+n_0)\Delta t}{n_0}$$

n: # molecules in the system
n_0: # pseudomolecules in the system
V: volume of the system
N_A: Avogadro constant

Multistate reactions

Reaction probabilities can be modified by the state of a participating multistate complex



$$p_{MS} = p_{base} \times p_{rel}$$

Where p_{base} is the base probability, and is p_{rel} the state-dependent relative probability.

Multistate reactions

$$(???0???) \xrightarrow{p_{base}} (???1???)$$

$$(0??0???) \xrightarrow{p_{base} \times p_{rel(0,0)}} (0??1???)$$

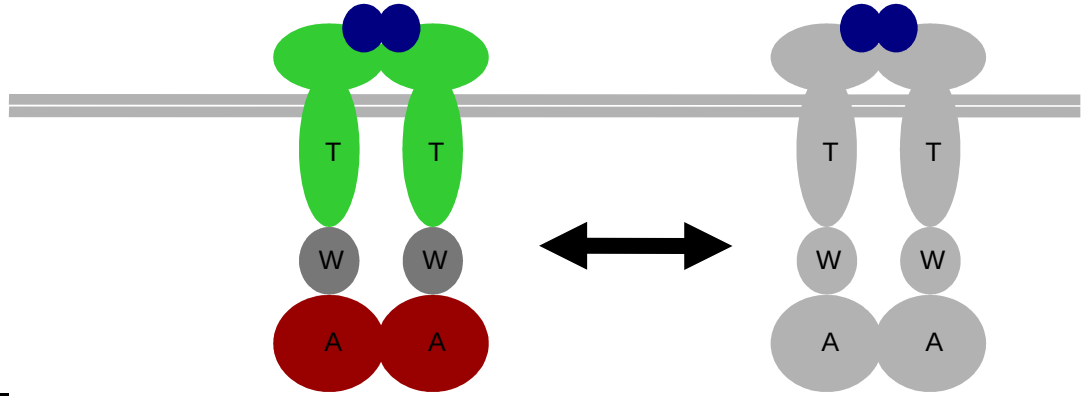
$$(1??0???) \xrightarrow{p_{base} \times p_{rel(0,1)}} (1??1???)$$

- '?' Flags do not affect the reaction
- only 4 species are needed instead of 128

Multistate rapid equilibria

- *Instantaneously* determines state of flag according to predefined probabilities.
- Probability can depend on the state of other flags.
- Primarily used to represent conformational 'flipping'.

$$\Delta G = -RT \ln \frac{p_{set}}{p_{clear}}$$



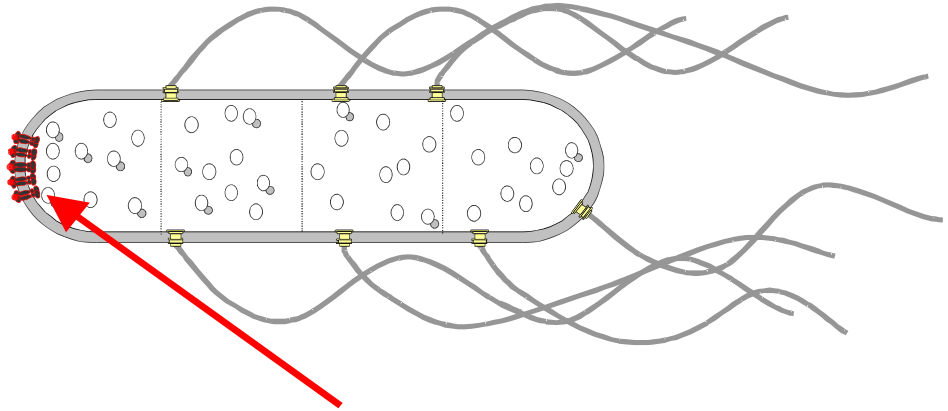
p_{set} p_{clr}

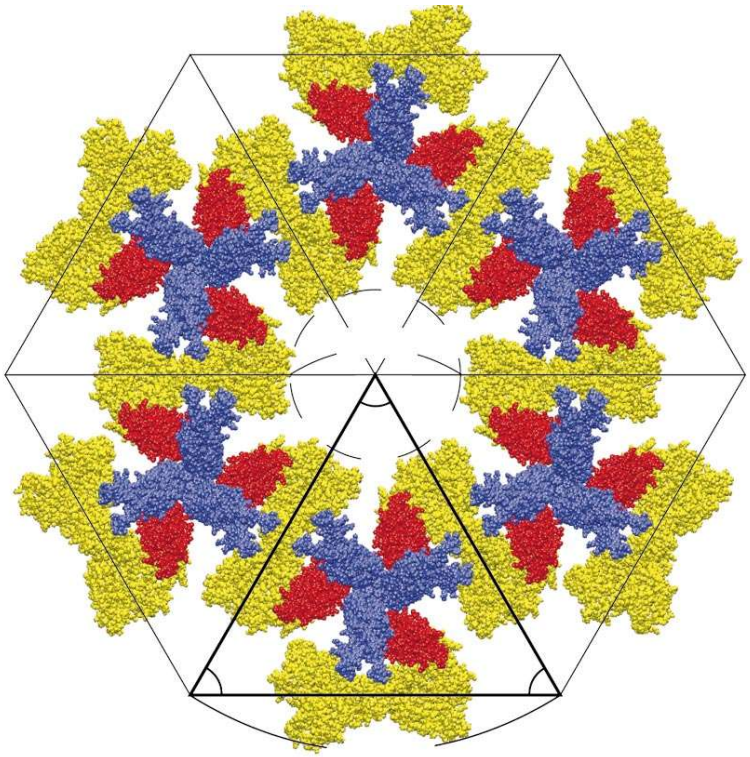
Free-energy based activation probabilities

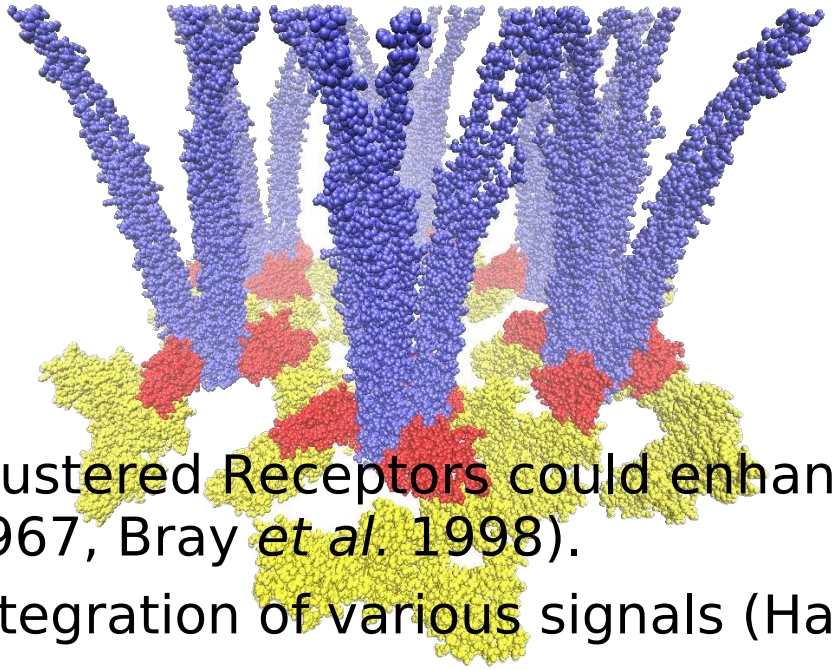
Non-ligand bound			Ligand bound		
Species	p	ΔG (kcal/mol)	Species	p	ΔG (kcal/mol)
	0.017	2.37		0.003	3.55
	0.125	1.18		0.017	2.37
	0.500	0.00		0.125	1.18
	0.874	1.18		0.500	0.00
	0.997	3.55		0.980	2.37

Receptor clustering and sensitivity

Chemotactic receptors form clusters at cell poles in E. coli (Shimizu, Le Novère et al. (2000) *Nat Cell Biol* 2: 792-796).







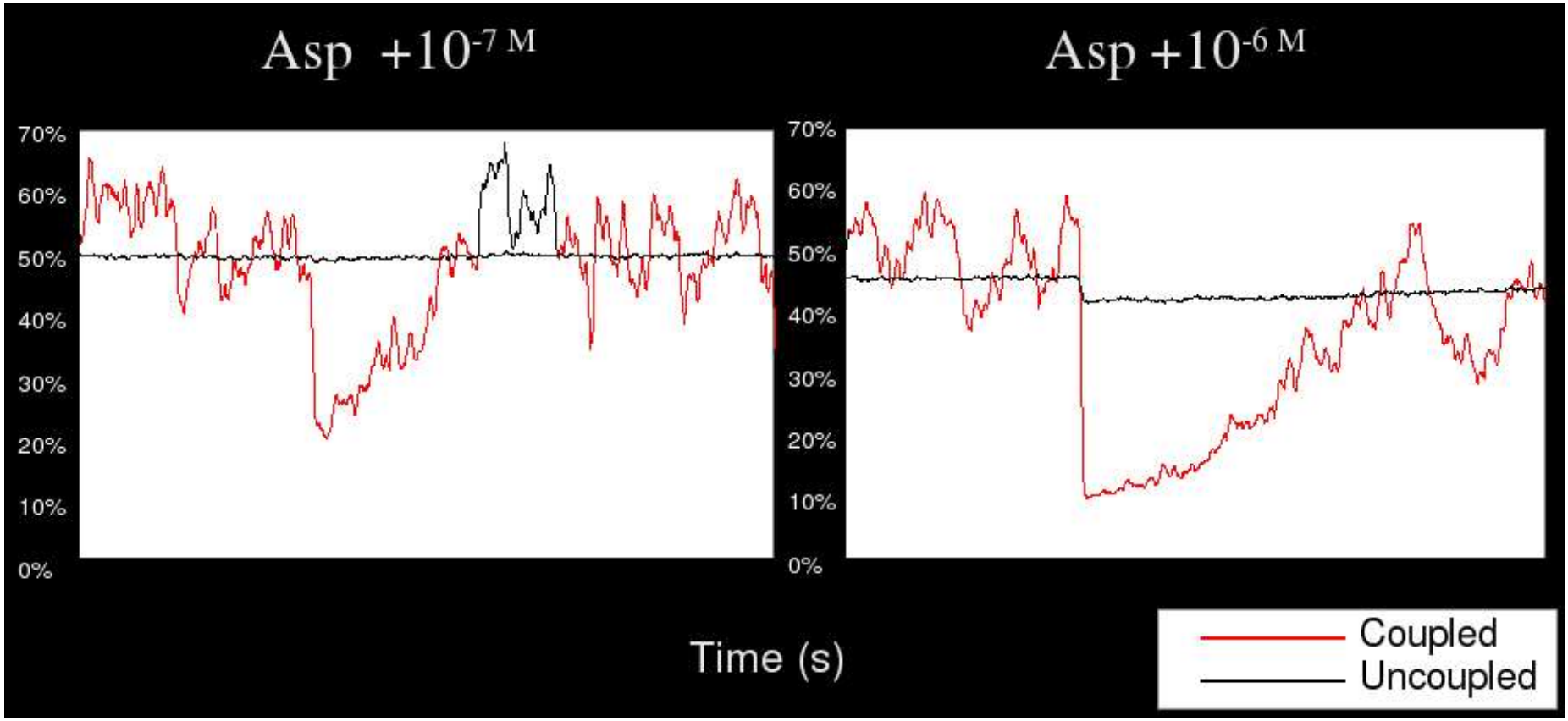
Clustered Receptors could enhance sensitivity (Changeux *et al.* 1967, Bray *et al.* 1998).

Integration of various signals (Hazelbauer et al. 1989).

Free-energy values for coupled receptors

	Ligand unbound						Ligand bound					
	Species	0	1	2	3	4	Species	0	1	2	3	4
p		0.00	0.00	0.02	0.08	0.30		0.00	0.00	0.00	0.01	0.07
ΔG		4.47	3.49	2.50	1.51	0.53		5.55	4.56	3.58	2.59	1.61
p		0.01	0.03	0.13	0.41	0.78		0.00	0.00	0.02	0.08	0.30
ΔG		3.17	2.18	1.20	0.21	-0.77		4.47	3.49	2.50	1.51	0.53
p		0.04	0.17	0.50	0.83	0.96		0.01	0.03	0.13	0.41	0.78
ΔG		1.97	0.99	0.00	-0.99	-1.97		3.17	2.18	1.20	0.21	-0.77
p		0.22	0.58	0.87	0.97	0.99		0.04	0.17	0.50	0.83	0.96
ΔG		0.78	-0.21	-1.19	-2.18	-3.16		1.97	0.99	0.00	-0.99	-1.97
p		0.93	0.99	1.00	1.00	1.00		0.67	0.91	0.98	1.00	1.00
ΔG		-1.61	-2.59	-3.58	-4.56	-5.55		0.43	-1.41	-2.40	-3.38	-4.37

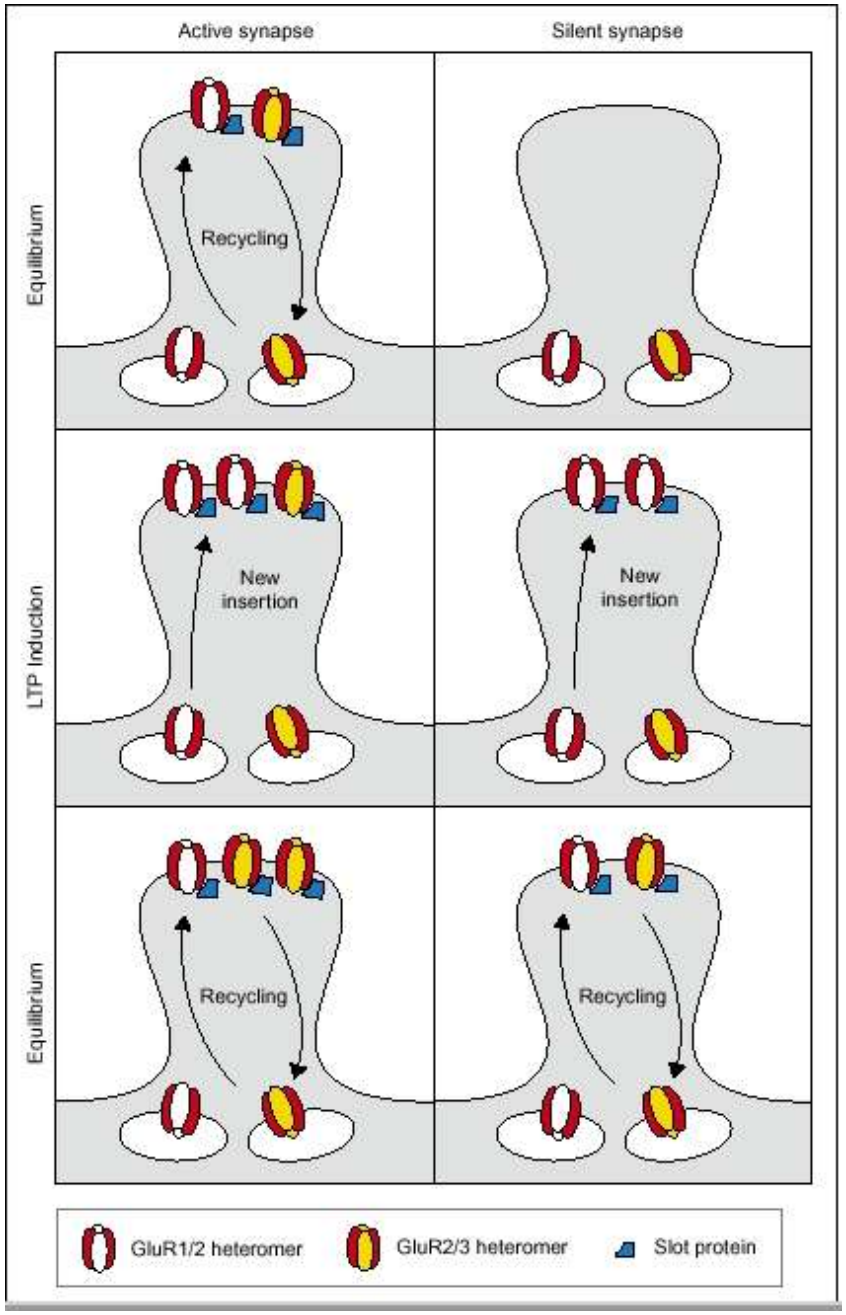
Gain



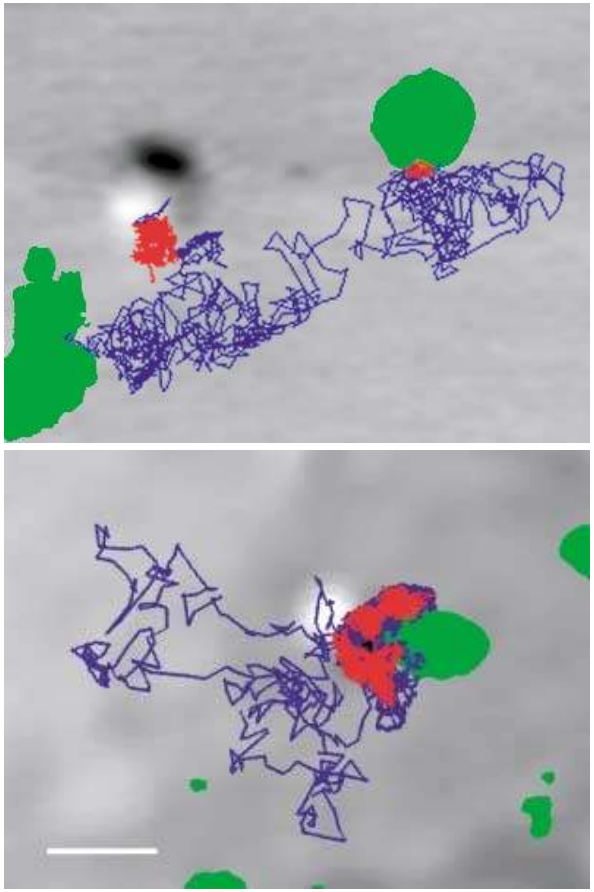
Change in signal

Shimizu et al. (2003) *J Mol Biol*

Receptors for neurotransmitters are moving



Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279-286

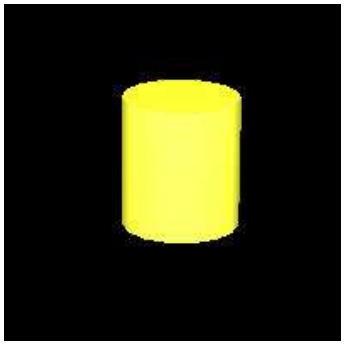


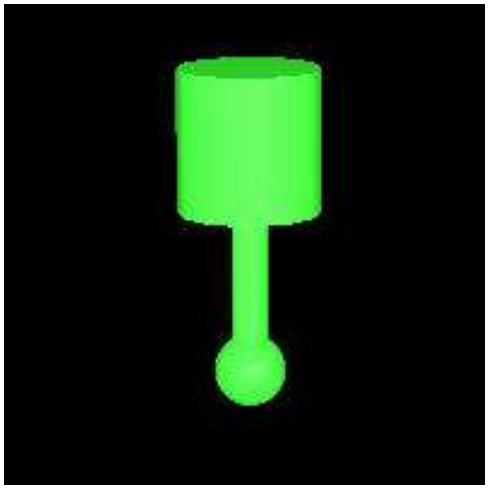
Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

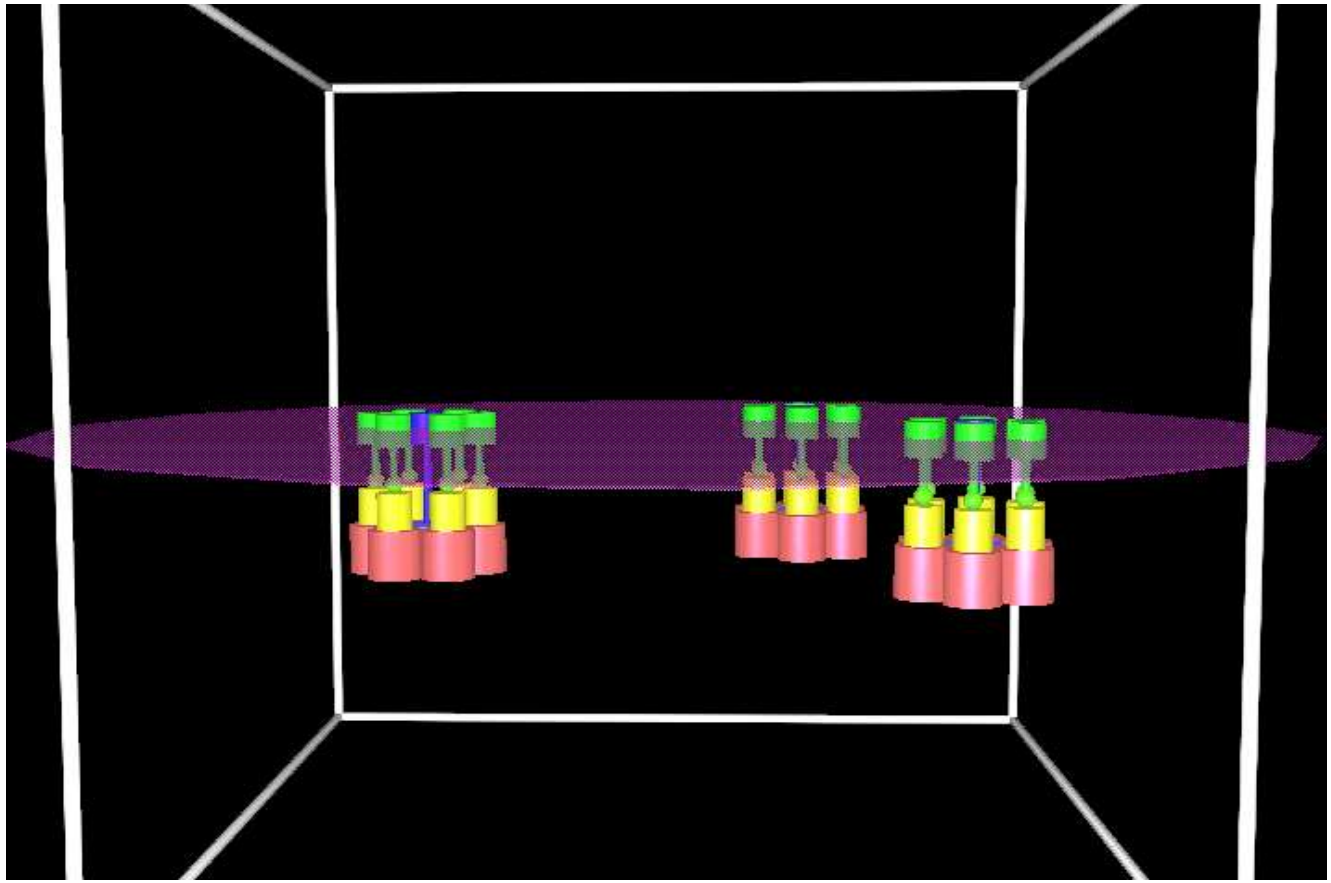
APS: the mesoscopic scale

- molecule abstracted ⇒ macroscopic scale
- atomic details ⇒ microscopic scale
- Abstracted but realistic geometry ⇒ mesoscopic scale
- Relative size of object respected
- Differential location of binding sites
- realistic movements (speed and topology)

Particles, Objects and Clusters







Particles carry binding sites

Cluster class allows recording of Center Of Mass, radius, RMS displacement;
possibility of cluster state

Clusters are dynamically created and destroyed – transient.

Molecule diffusion

- Different diffusion spaces:
  - Static; Free diffusion; Membrane diffusion; Above membrane; Below membrane
- Two types of motion:
  - Translational $\bar{r}^2 = 2D_T t = 2kb_T t$
  - Rotational $\bar{\theta}^2 = 2D_R t = 2kb_R t$
- random walk algorithm

$$p(x,t) = \frac{1}{\sqrt{4\pi Dt}} \exp - \frac{x^2}{4Dt}$$ gaussian with $\sigma^2 = 2Dt$

  - Translational $\Delta(x,y,z) = \sqrt{2D_T t} \times gaussRand$
  - Rotational $\Delta\theta = \frac{\sqrt{2D_R t}}{r} \times gaussRand$
- Two types of diffusion equations:
  - unrestricted brownian motion – Low Trans/Rot
  - intra-membrane diffusion (Saffman and Delbrück 1975) – High Trans/Rot

Molecule diffusion

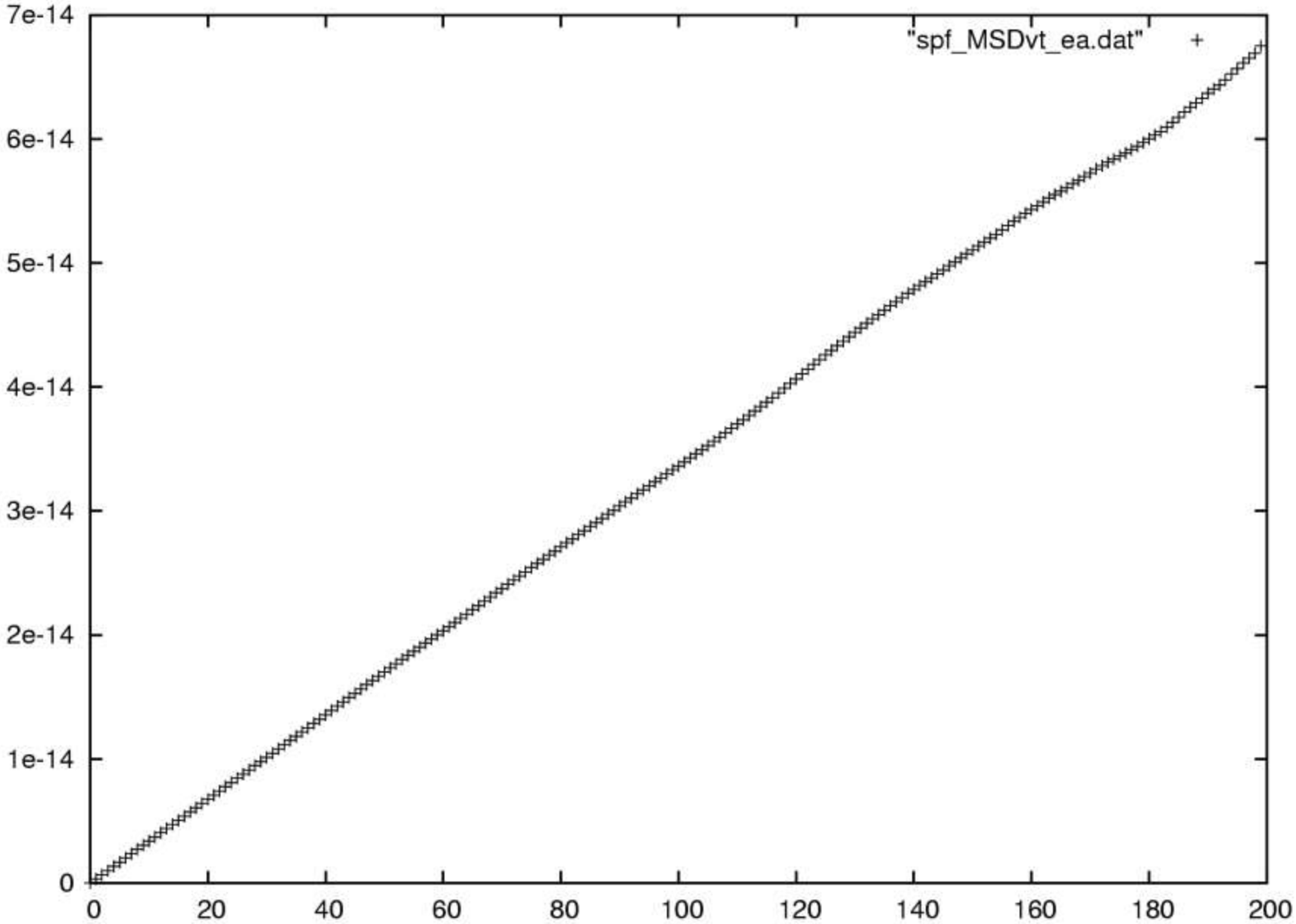
- Unrestricted brownian motion – Low Translation/Rotational

$$b_T = \frac{1}{6\pi\mu r} \qquad b_R = \frac{1}{8\pi\mu r^3} \qquad \frac{b_T}{b_R} = \frac{4}{3}r^2$$

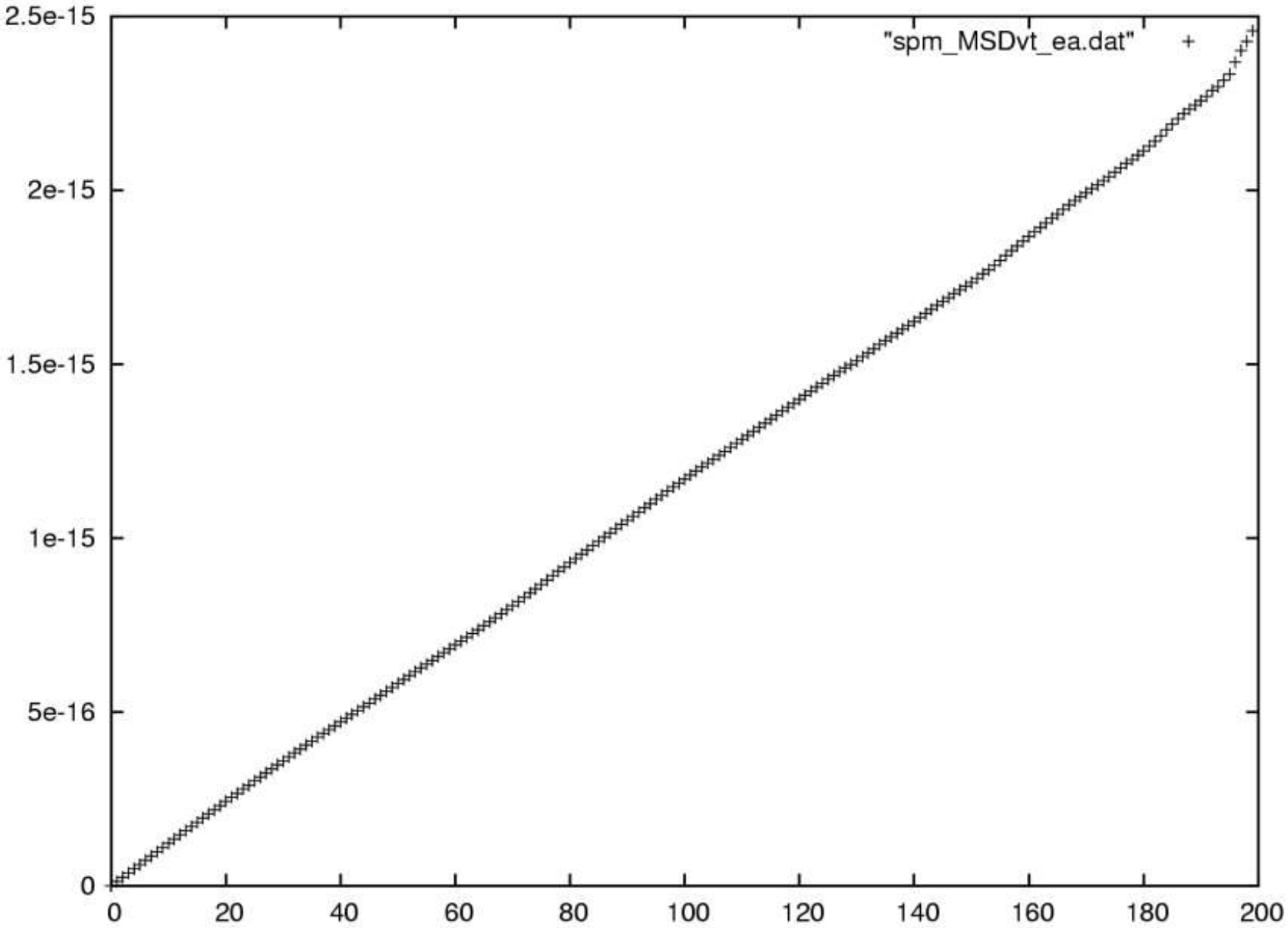
- Intra-membrane diffusion (Saffman and Delbrück 1975)
  High Translational/Rotational

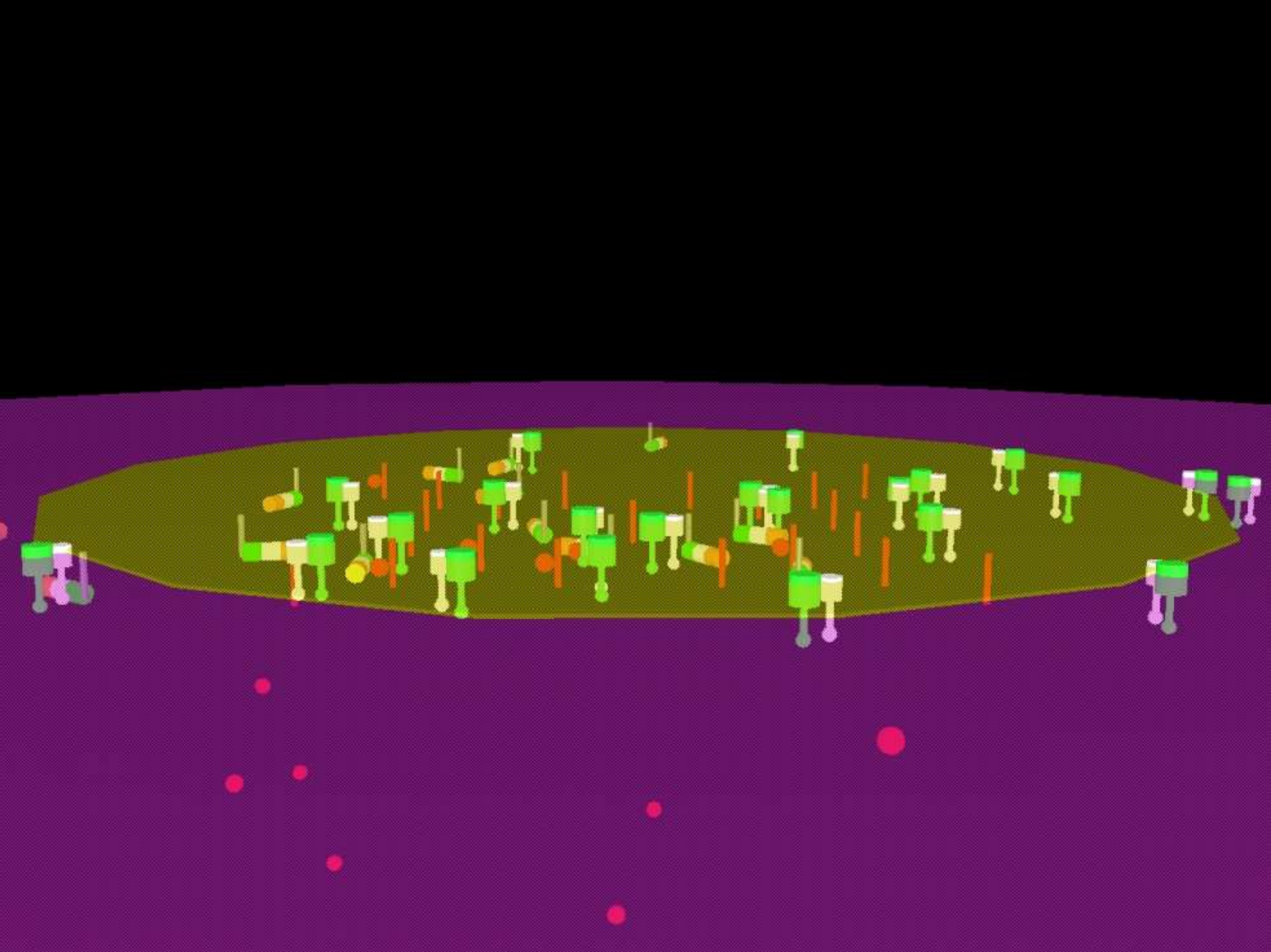
$$b_T = \frac{1}{4\pi\mu h}\left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \qquad b_R = \frac{1}{4\pi\mu r^2 h} \qquad \frac{b_T}{b_R} = \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma\right) \times r^2$$

RMS displacement for free diffusion



RMS displacement for membrane diffusion





Acknowledgements

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  - Dennis Bray
  - Carl Morton-Firth
  - Thomas Simon Shimizu
- APS
  - Fred Howell
  - Dan Mossop
  - Dominic Tölle