

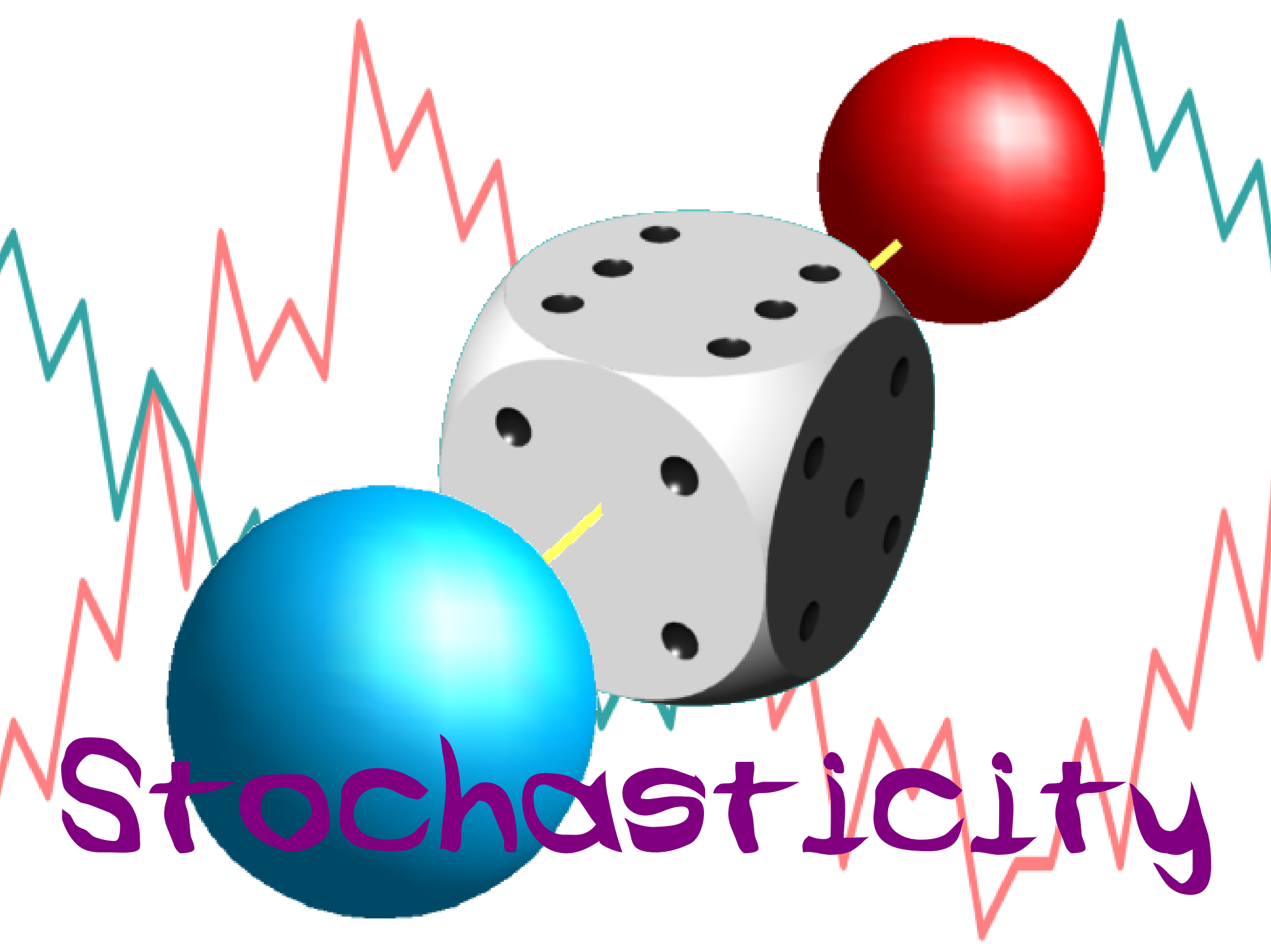
Mesoscopic simulations of receptive lattices



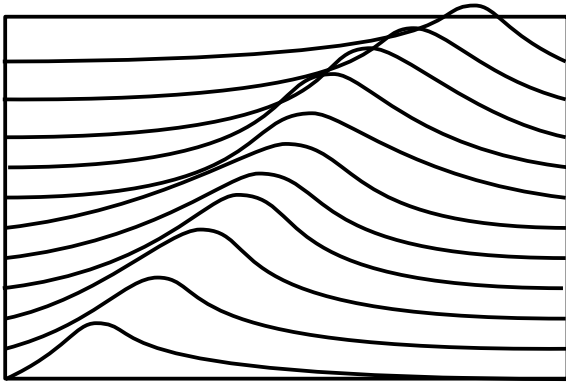
Continuous, deterministic models can't cope with:

1. Sensitivity to a very small number of molecules
2. Protein complexes with many states
3. Spatial heterogeneity



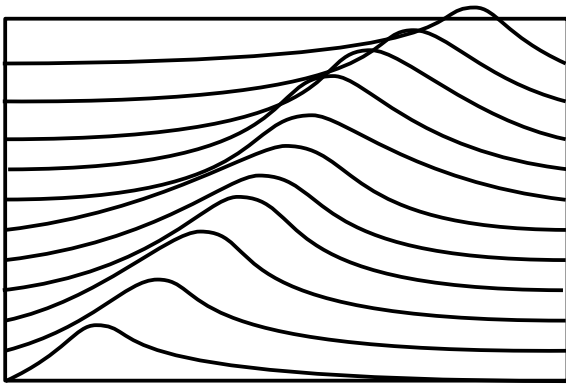


Stochasticity

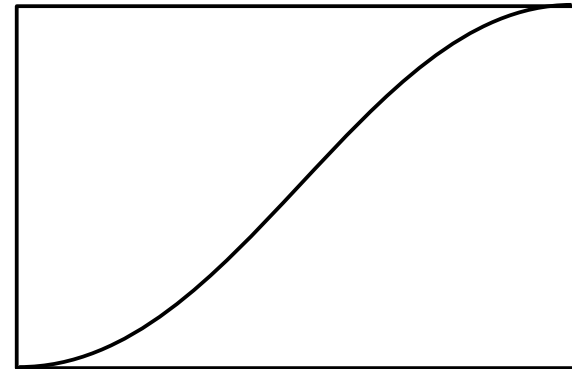


Grand Probability function: $P(X,t)$



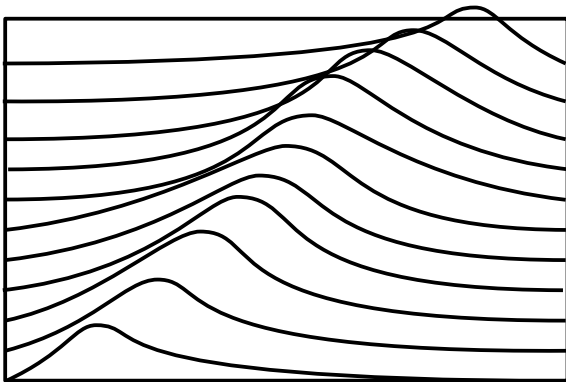


Grand Probability function: $P(X,t)$

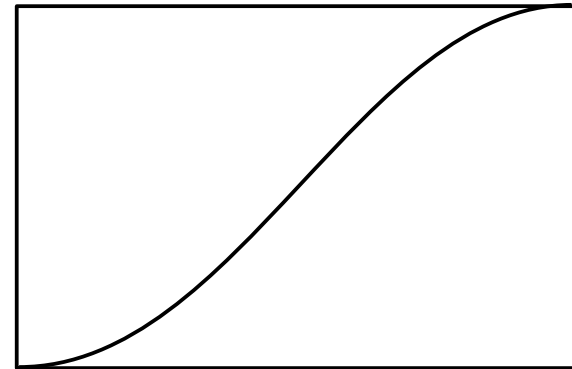


typologic view of the world: $(X)=f(t)$

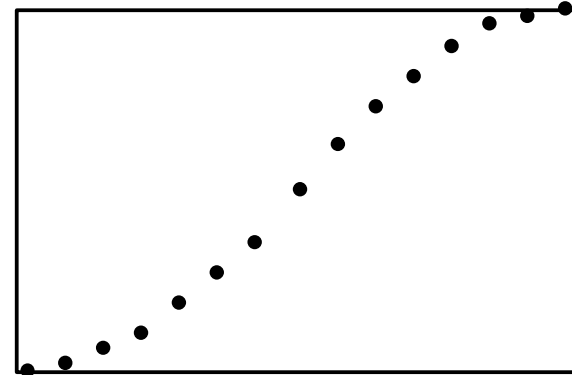




Grand Probability function: $P(X,t)$

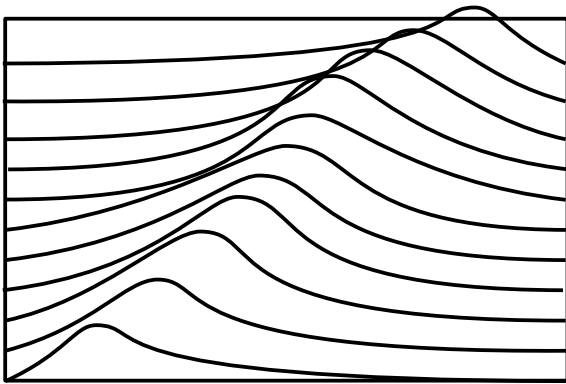


typologic view of the world: $(X)=f(t)$

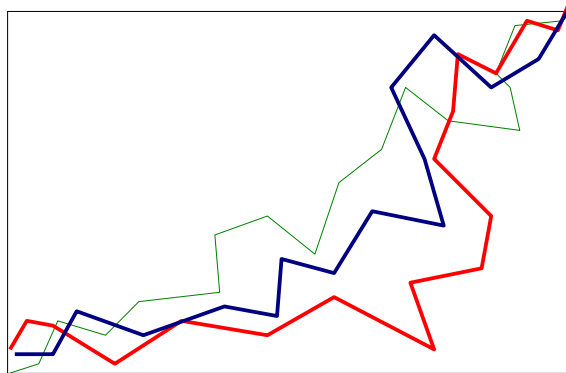


deterministic approach: $(X,t)=f(X',t-1)$

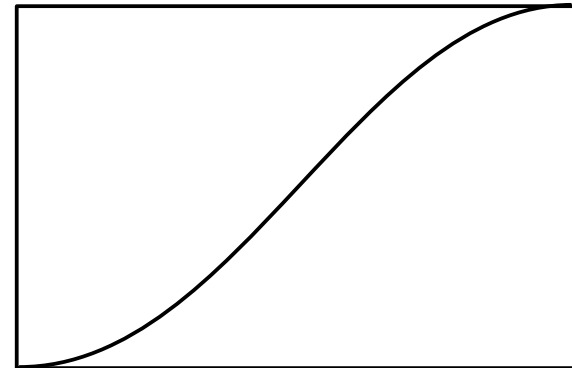




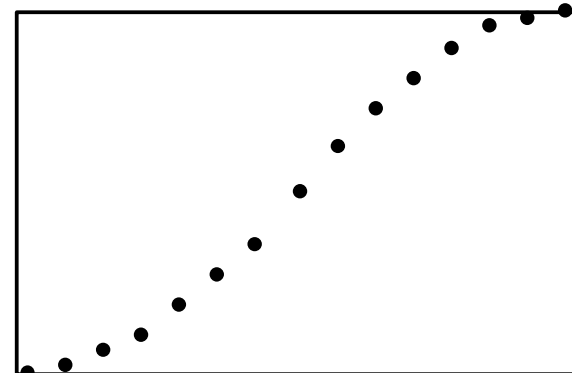
Grand Probability function: $P(X,t)$



stochastic approach: $P(X,t)/(X',t-1)$



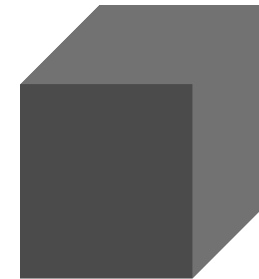
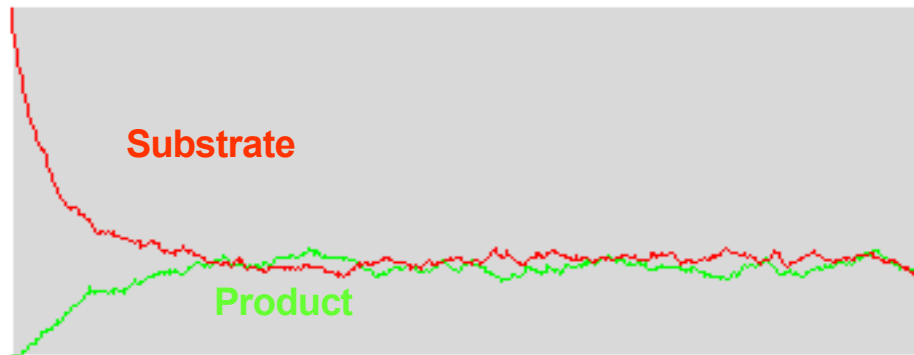
typologic view of the world: $(X)=f(t)$



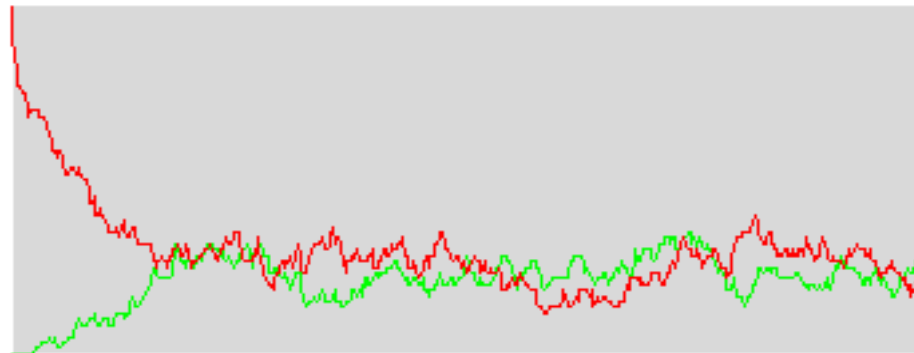
deterministic approach: $(X,t)=f(X',t-1)$



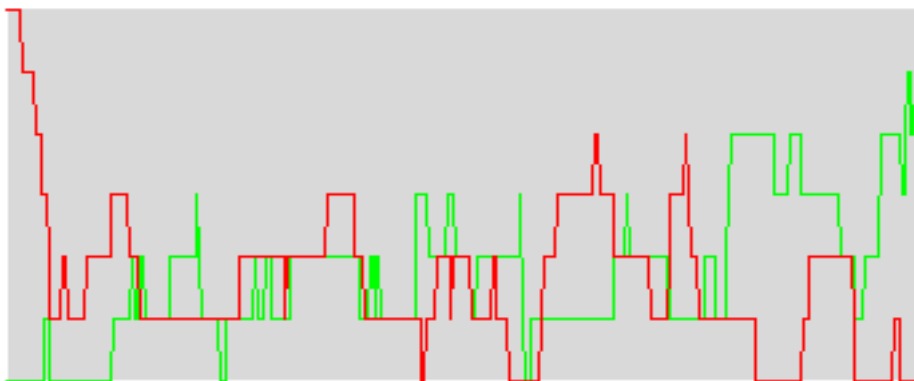
Concentration (μM)



10^{-15} litres



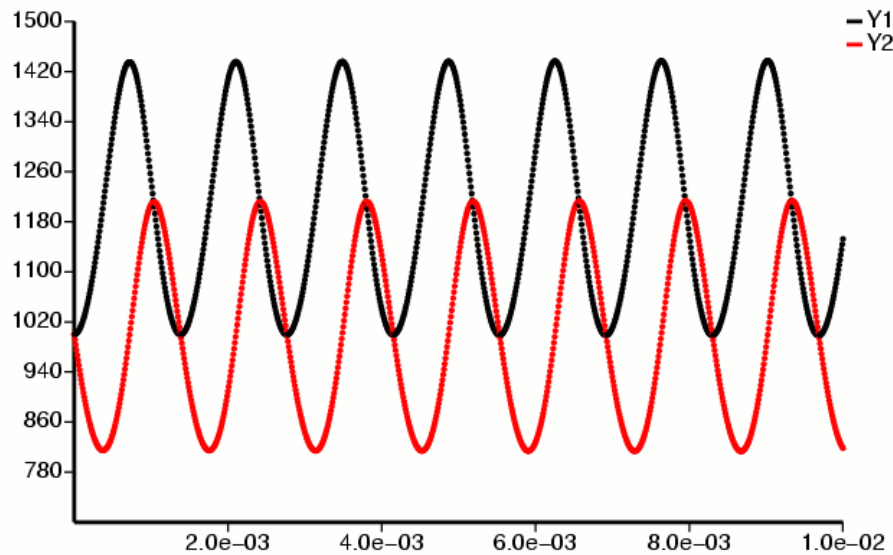
10^{-16} litres



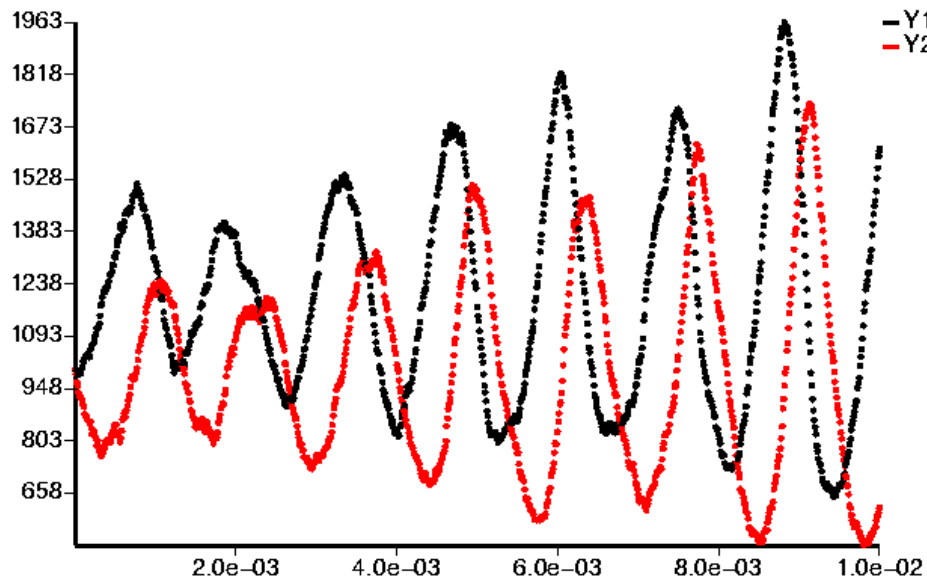
10^{-17} litres

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



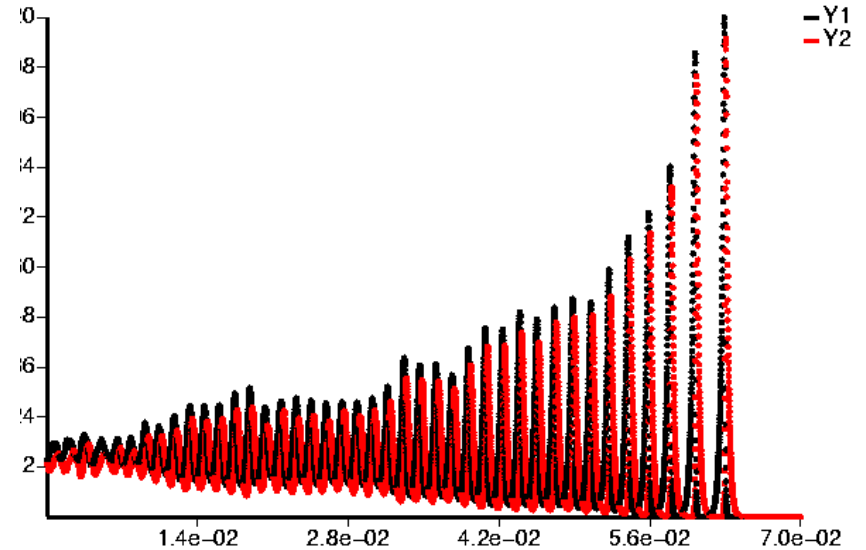
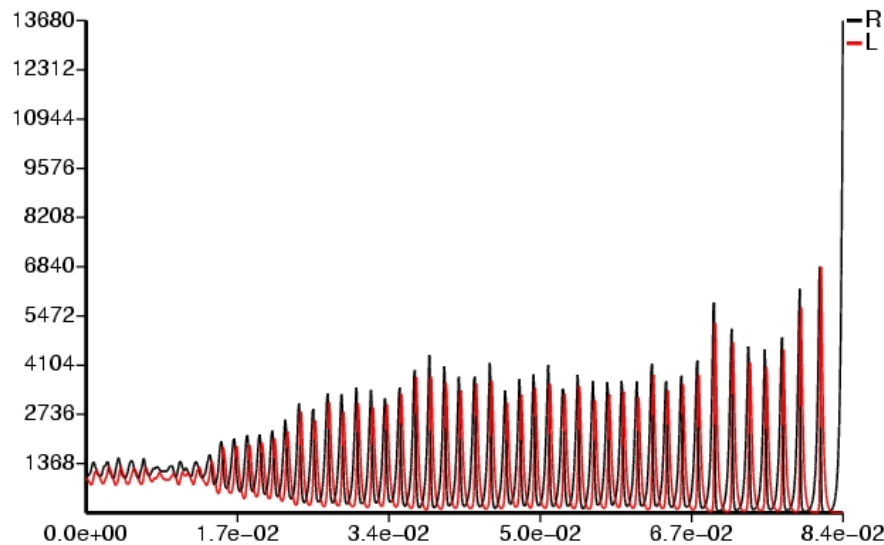
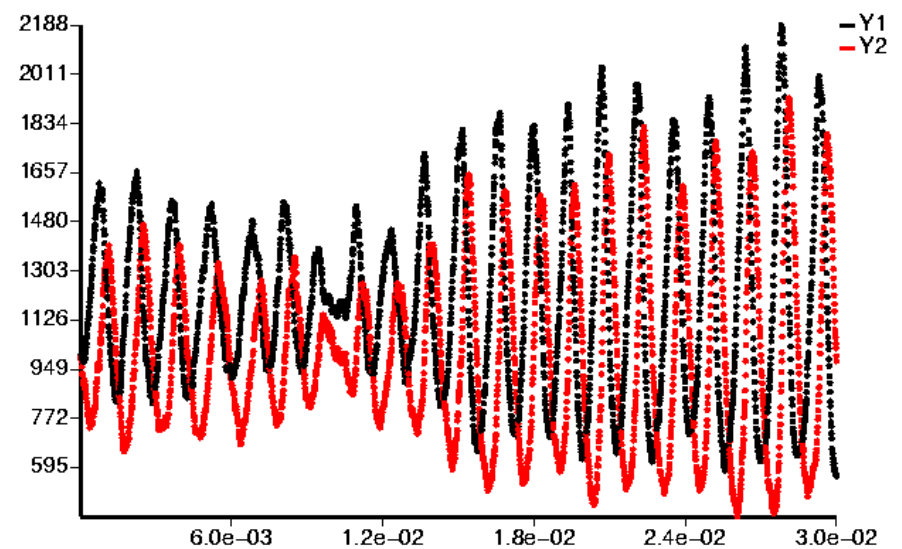
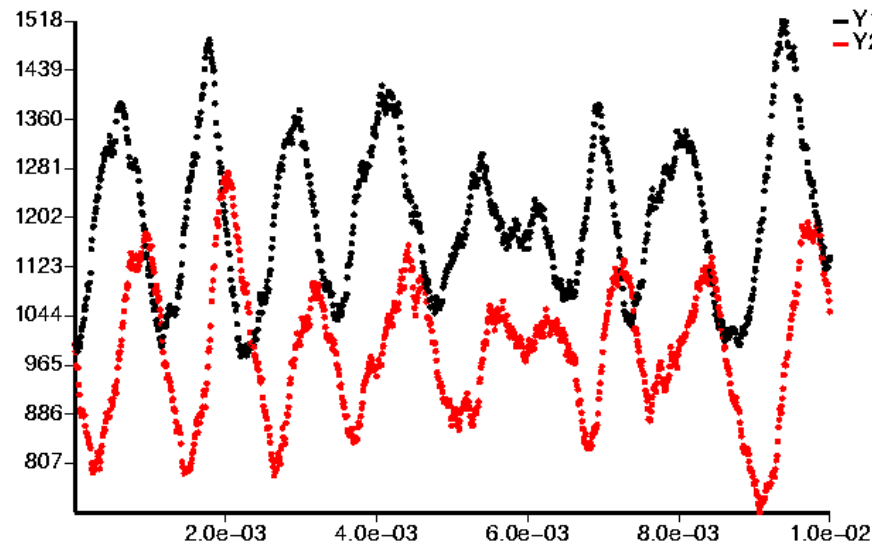


deterministic result



stochastic result





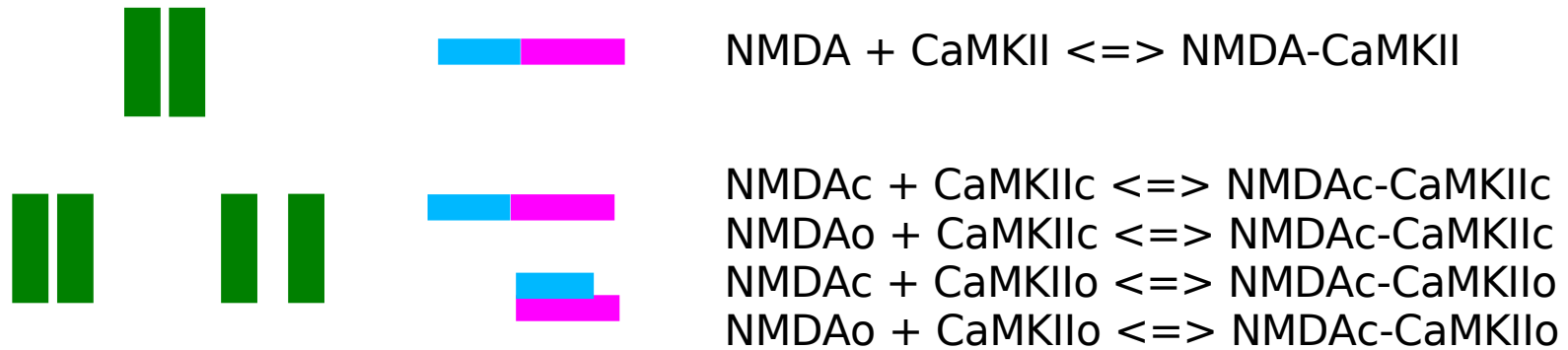


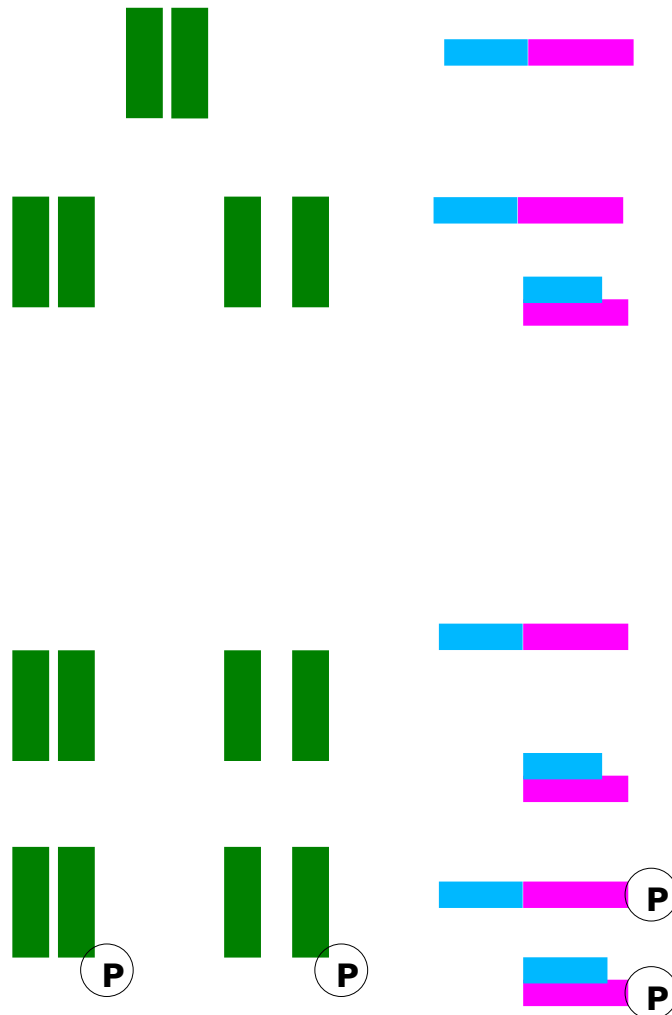
Combinatorial Explosion



NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII







NMDA + CaMKII $\rightleftharpoons$ NMDA-CaMKII

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAo + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAc + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAo + CaMKIIc $\rightleftharpoons$ NMDAc-CaMKIIc

NMDAc + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

NMDAo + CaMKIIo $\rightleftharpoons$ NMDAc-CaMKIIo

pNMDAc + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAo + CaMKIIc $\rightleftharpoons$ pNMDAc-CaMKIIc

pNMDAc + CaMKIIo $\rightleftharpoons$ pNMDAc-CaMKIIo

pNMDAo + CaMKIIo $\rightleftharpoons$ pNMDAc-CaMKIIo

NMDAc + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAo + pCaMKIIc $\rightleftharpoons$ NMDAc-pCaMKIIc

NMDAc + pCaMKIIo $\rightleftharpoons$ NMDAc-pCaMKIIo

NMDAo + pCaMKIIo $\rightleftharpoons$ NMDAc-pCaMKIIo

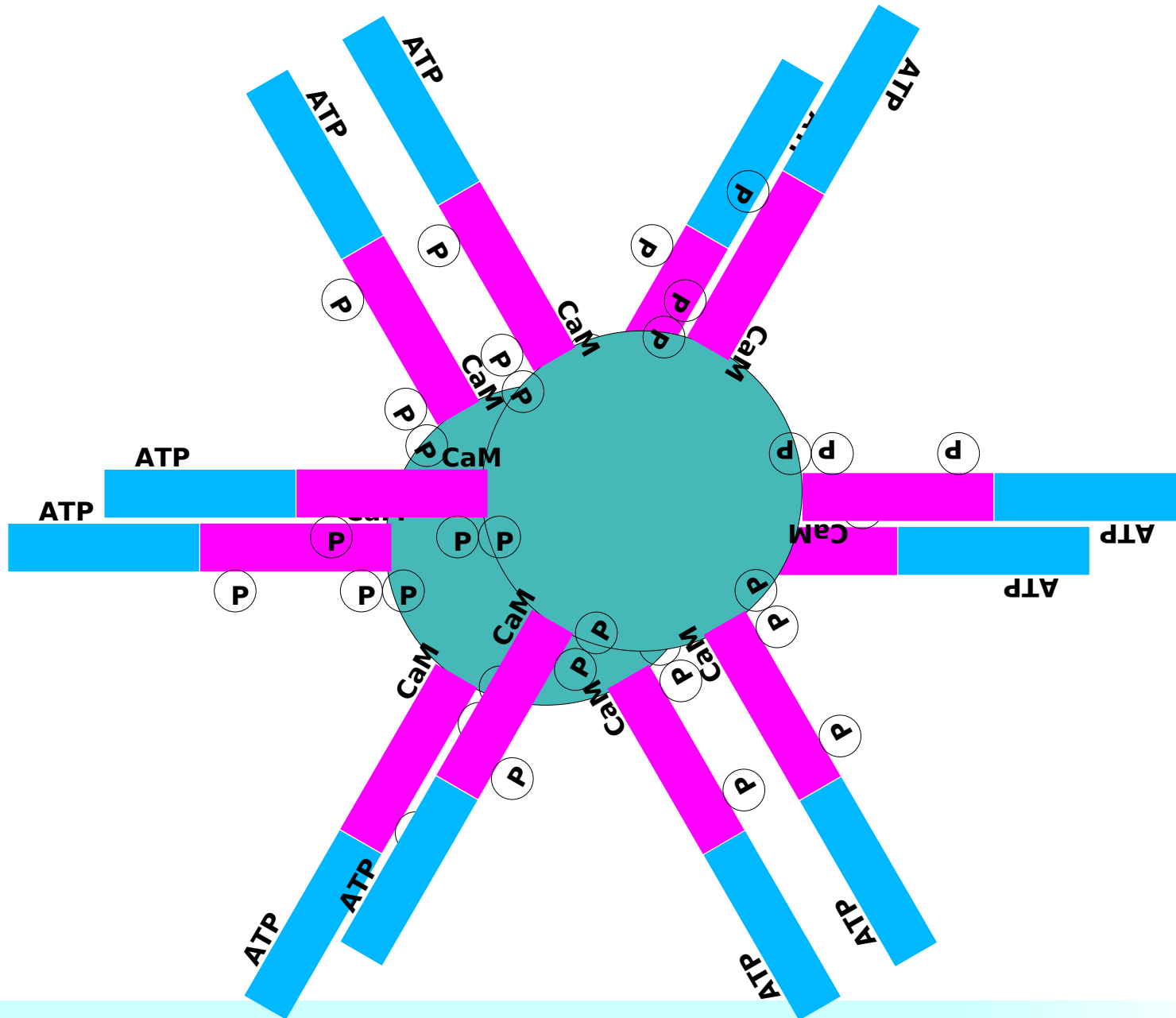
pNMDAc + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

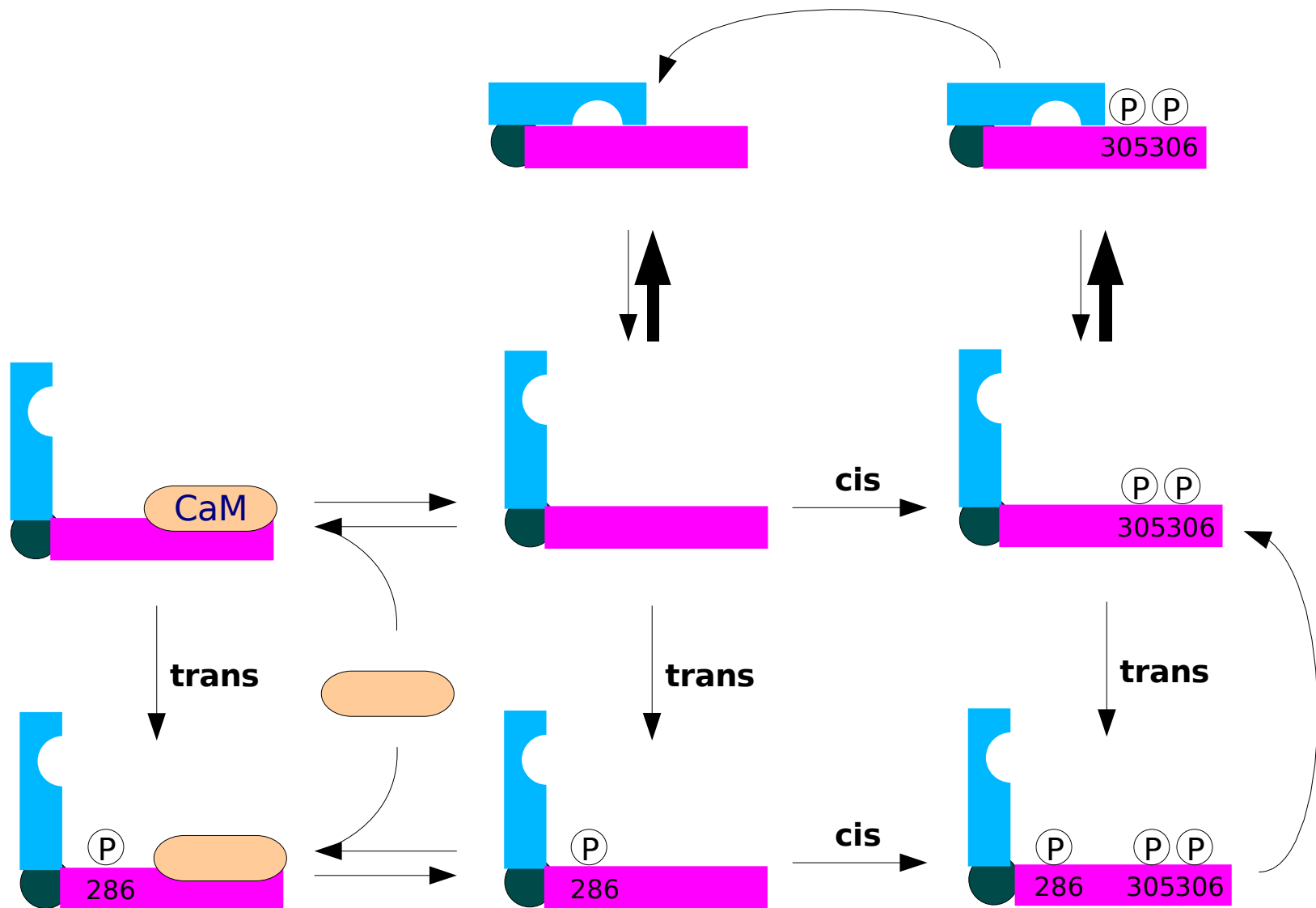
pNMDAo + pCaMKIIc $\rightleftharpoons$ pNMDAc-pCaMKIIc

pNMDAc + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo

pNMDAo + pCaMKIIo $\rightleftharpoons$ pNMDAc-pCaMKIIo







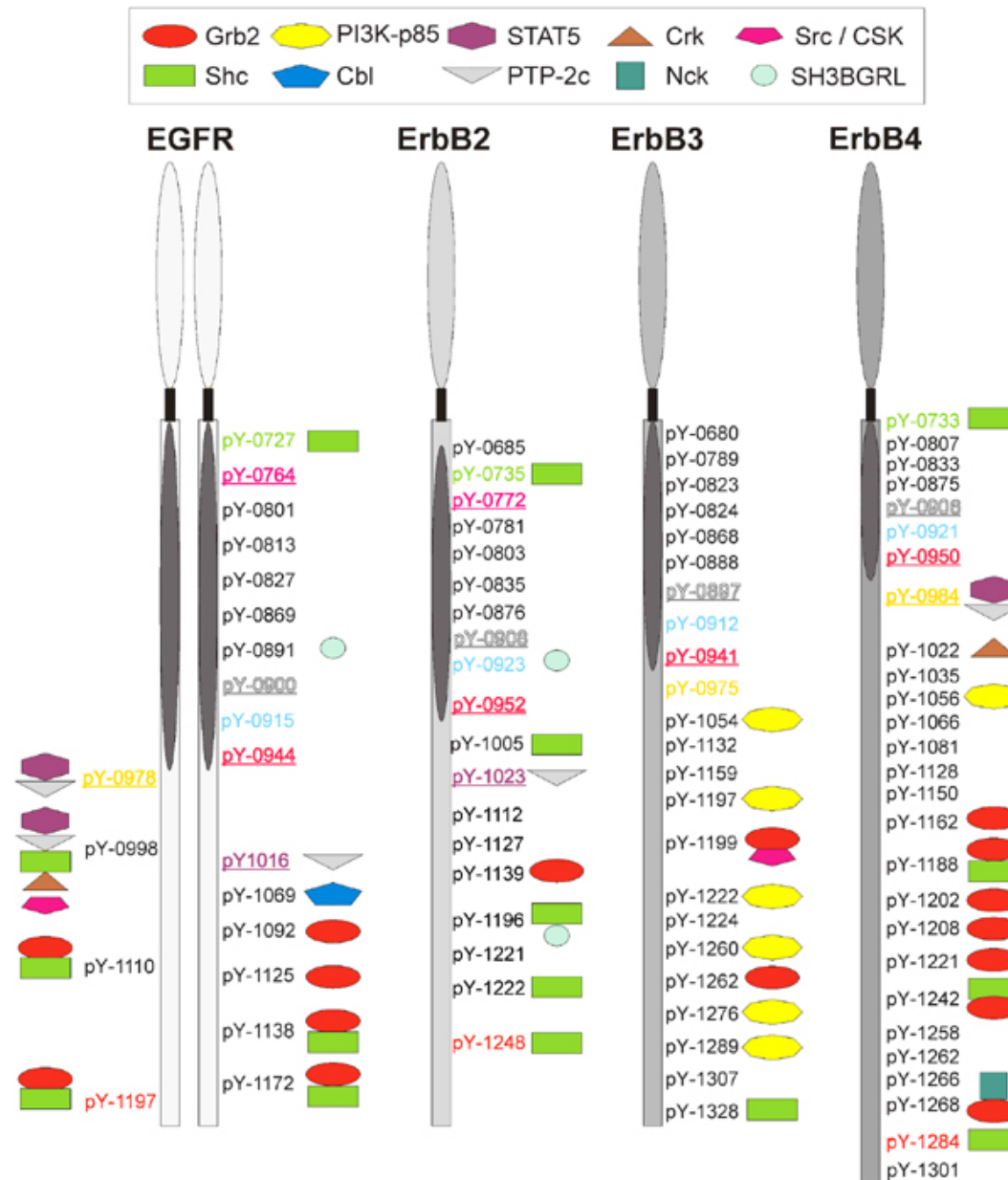
- number of states = 2^n
- A molecule with 10 features = $2^{10} = 1024$ states, that is 1024 pools. But most signalling molecules are present a few hundred times ...
- number of state conversions = $n \times 2^{n-1}$
- A molecule with 10 features reacting with a molecule with 10 features =

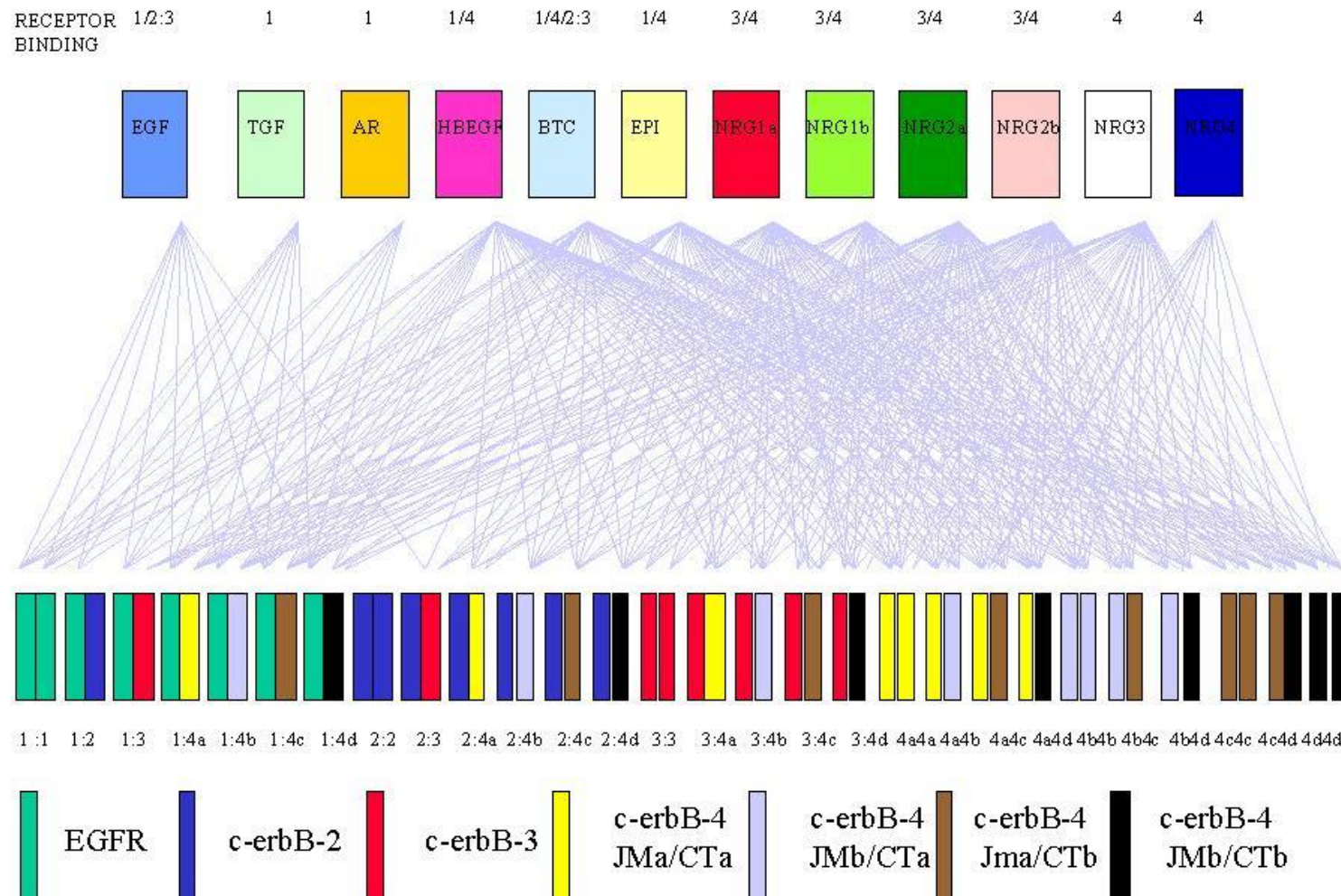


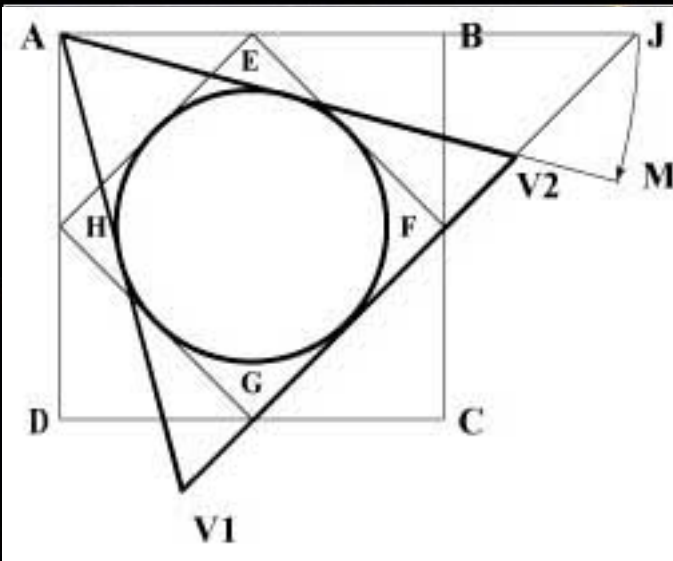
- number of states = 2^n
- A molecule with 10 features = $2^{10} = 1024$ states, that is 1024 pools. But most signalling molecules are present a few hundred times ...
- number of state conversions = $n \times 2^{n-1}$
- A molecule with 10 features reacting with a molecule with 10 features = 1058816 possible reactions!



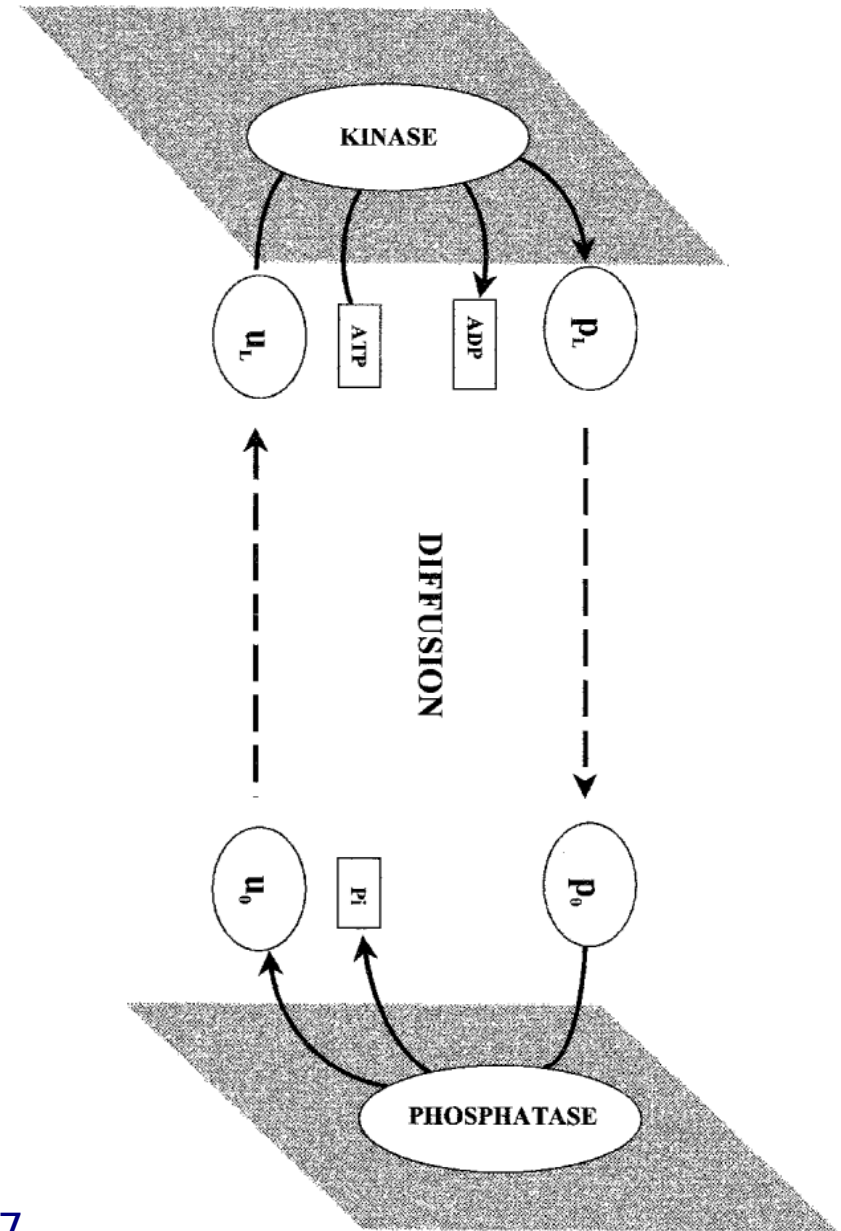
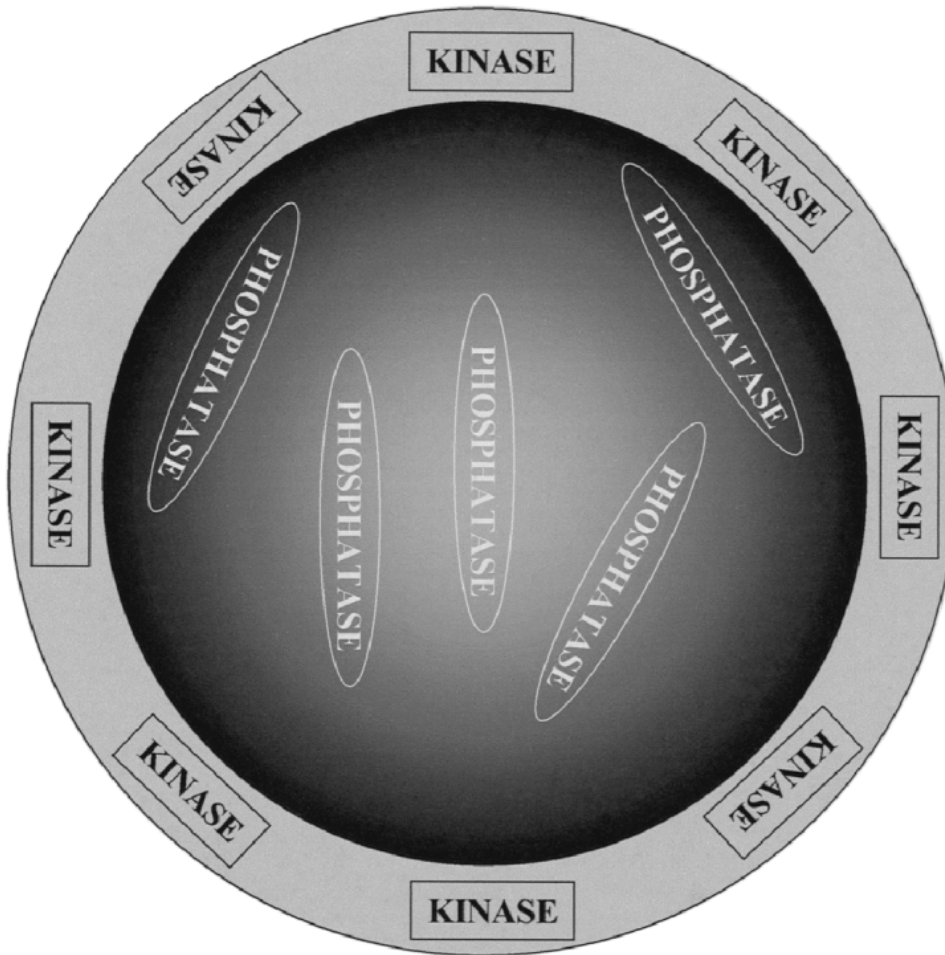
Schulze et al. (2005)
Mol Sys Bio,
 doi: 10.1038/msb4100012





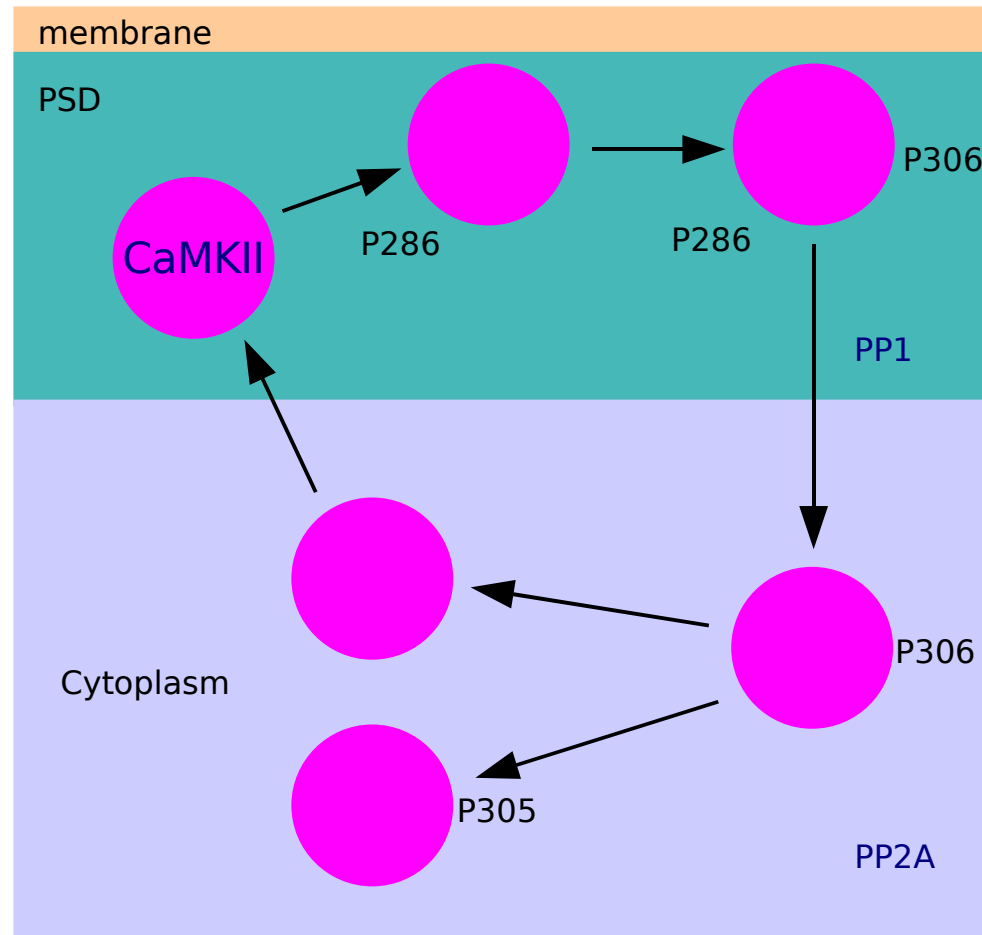


Space and
geometry

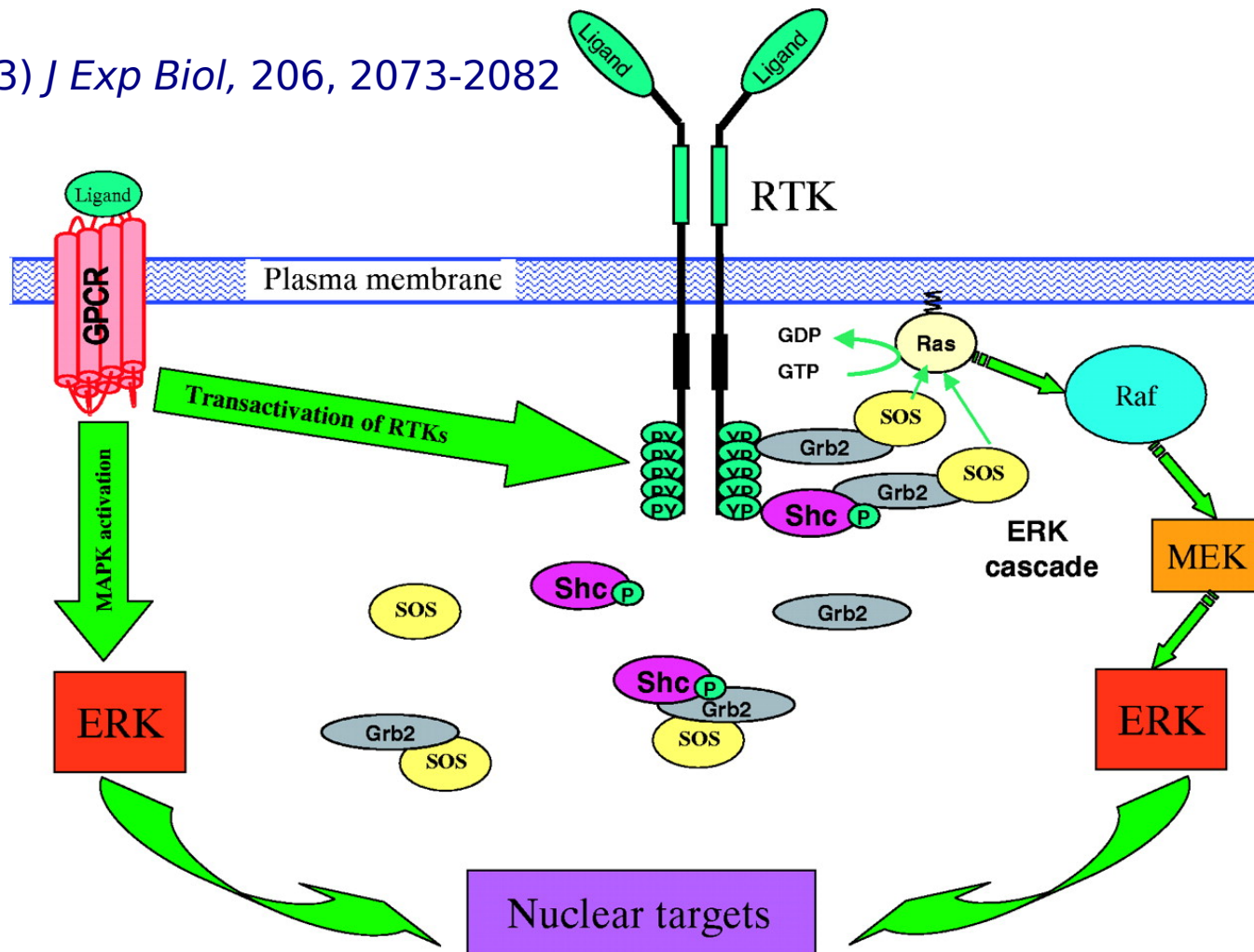


Kholodenko et al. *Biochem. J.* (2000) 350: 901–907





Kholodenko (2003) *J Exp Biol*, 206, 2073-2082



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-diffusion)
- Molecules under different states are represented by different pools

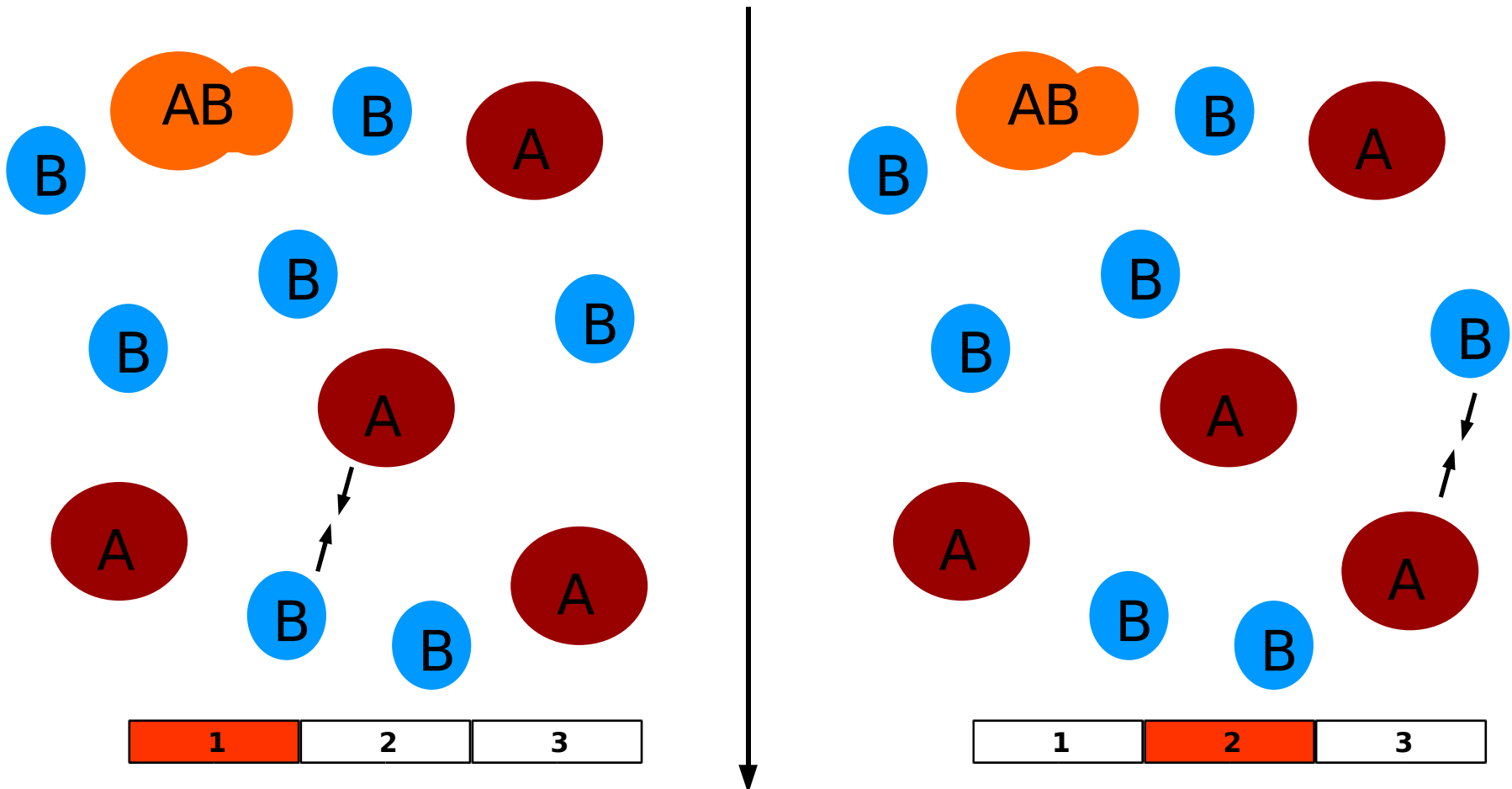
Particle-based simulation

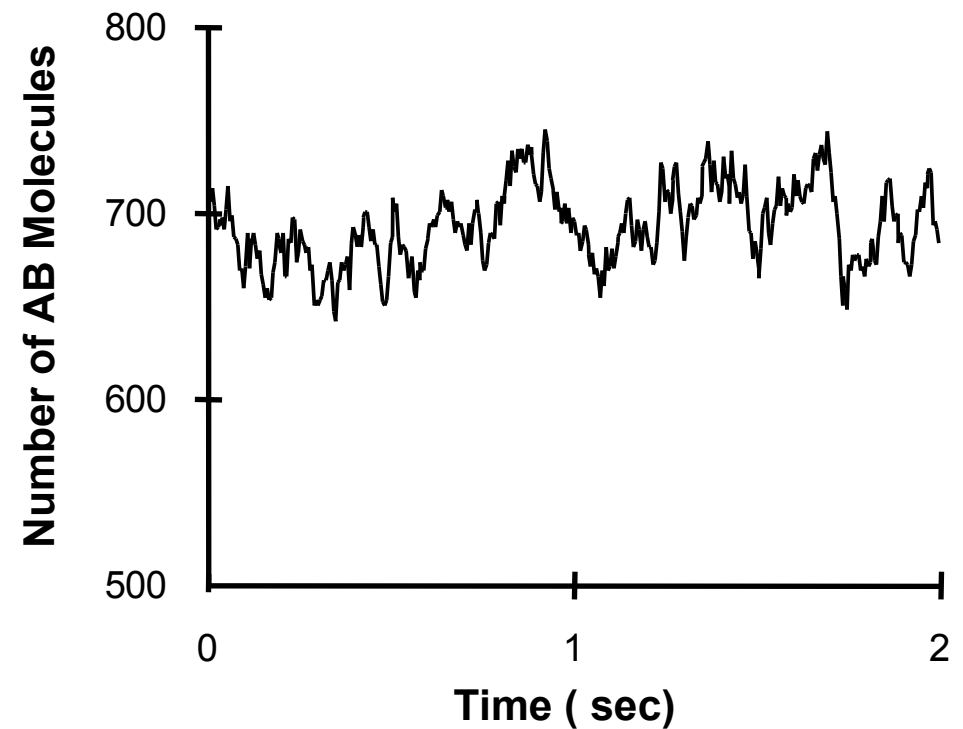
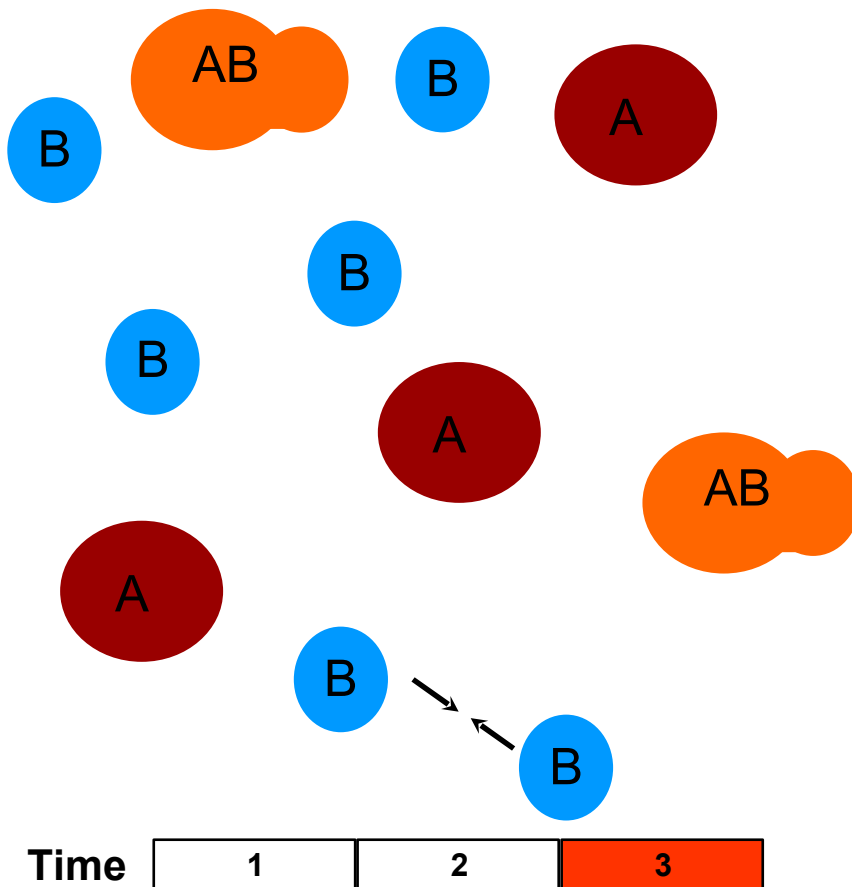
- Discrete representation of molecules
- Generally stochastic algorithms (but not always: deterministic automata)
- Generally location of molecules (but not always: StochSim v1)
- Representation of the movements of (some) molecules
- Possibility of multistates molecules



- 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







$$\Delta n_A = P(\text{pick A}) * P(\text{pick pseudo-mol}) * P1 * \Delta t \\ + P(\text{pick pseudo-molecule}) * P(\text{pick A}) * P1 * \Delta t$$

$$\Delta n_A = k_{on} * [A] * \Delta t$$

$$k_{on} * n_A / (V * N_A) = 2 * n_A / n * n_0 / (n + n_0) * P1 * \Delta t$$

n : # molecules in the system

n_0 : # pseudomolecules in the system

V : volume of the system

N_A : Avogadro constant



$$d[A]/dt = -k[A]$$

$$P1 = \frac{k n(n+n_0)\Delta t}{n_0}$$

$$d[A]/dt = -k[A][B]$$

$$P2 = \frac{k n(n+n_0)\Delta t}{2VN_A}$$

n : # molecules in the system

n_0 : # pseudomolecules in the system

V : volume of the system

N_A : Avogadro constant



$$d[A]/dt = -k[A] \qquad P1 = \frac{k n(n+n_0)\Delta t}{n_0}$$

$$d[A]/dt = -k[A][B] \qquad P2 = \frac{k n(n+n_0)\Delta t}{2VN_A}$$

n_0 optimized to limit the stiffness between unimolecular and bimolecular reactions

n : # molecules in the system

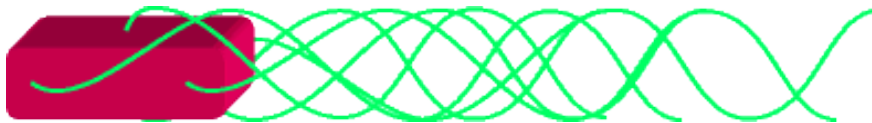
n_0 : # pseudomolecules in the system

V : volume of the system

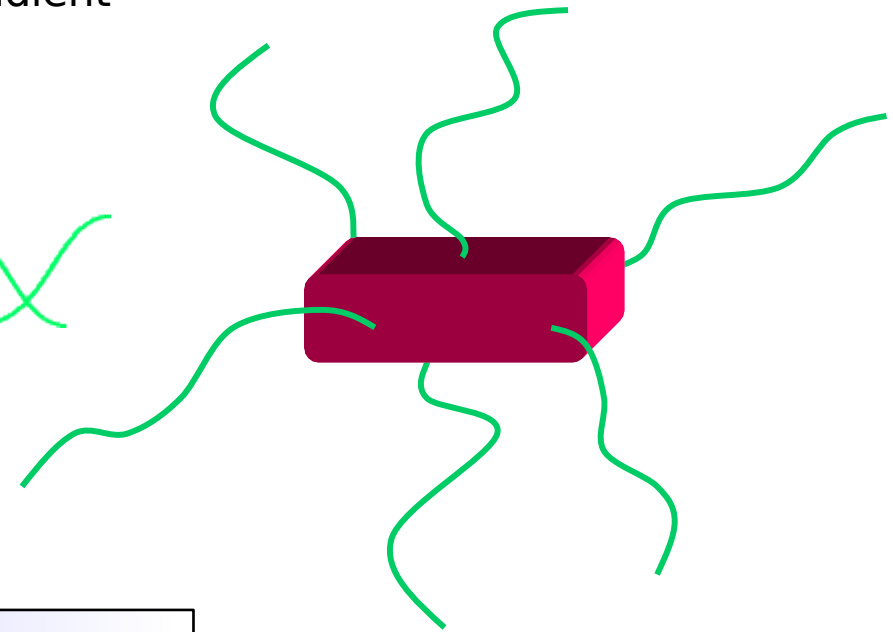
N_A : Avogadro constant



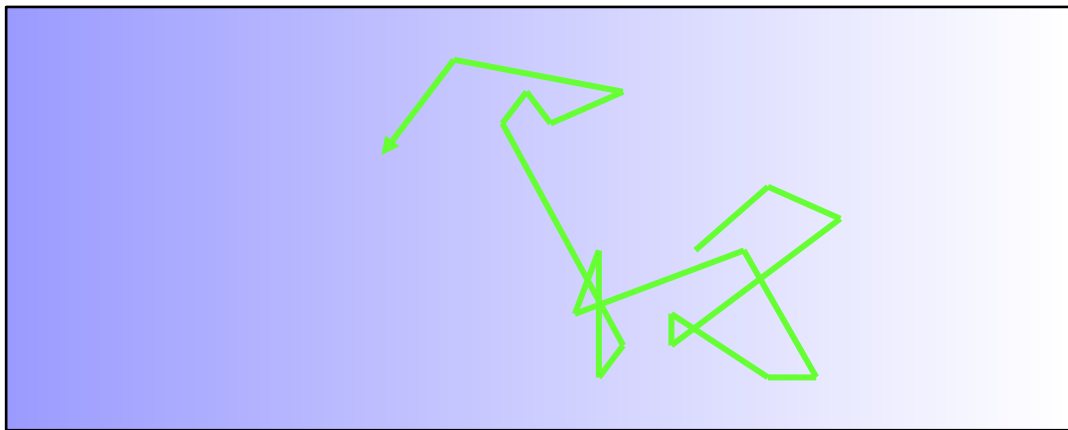
- small size $\Rightarrow$ unable to read gradient
- small weight $\Rightarrow$ no inertia

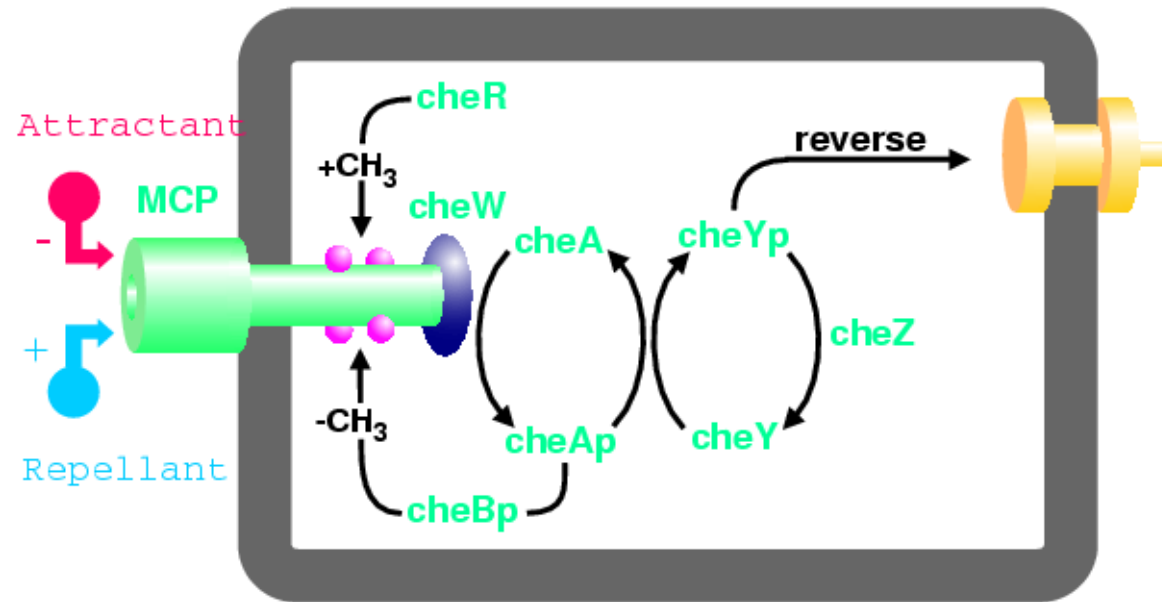


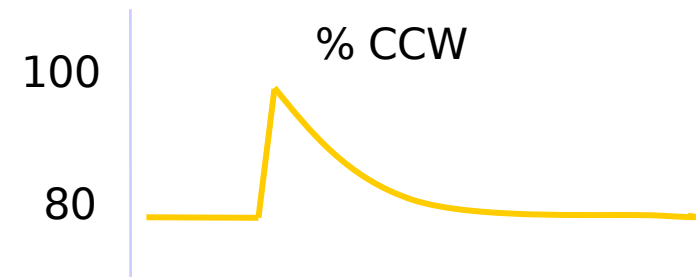
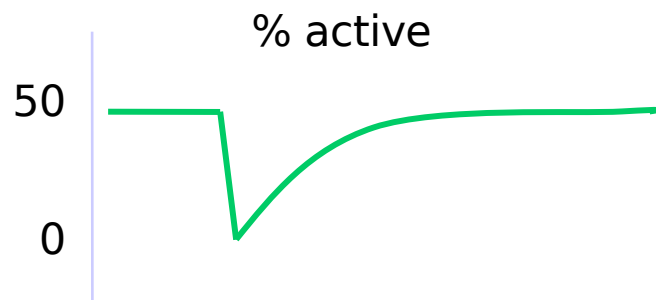
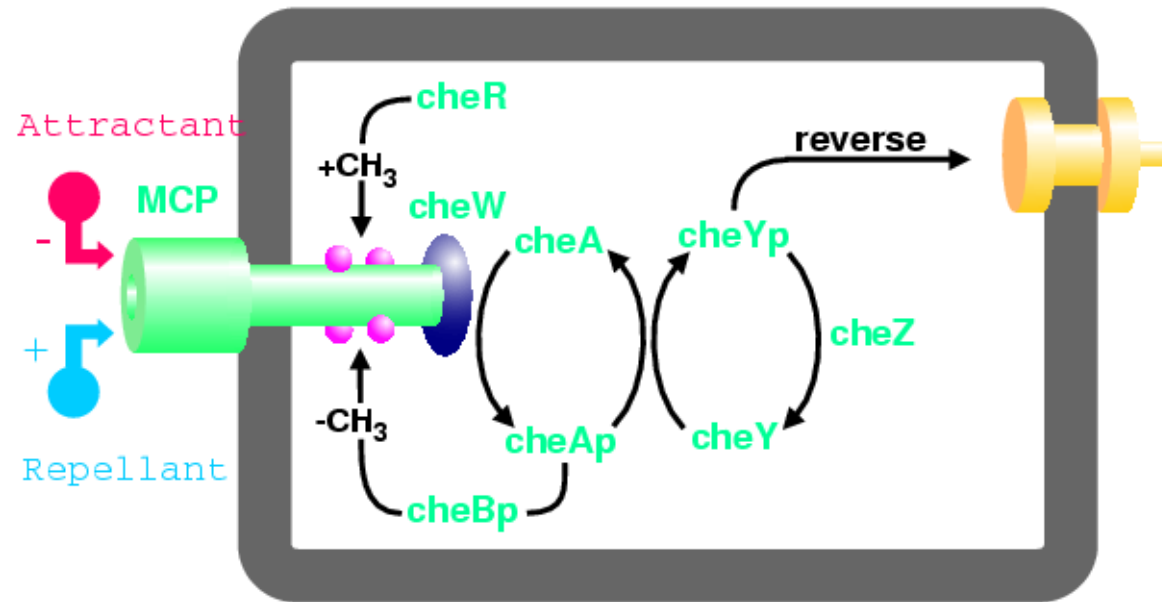
CCW = smooth



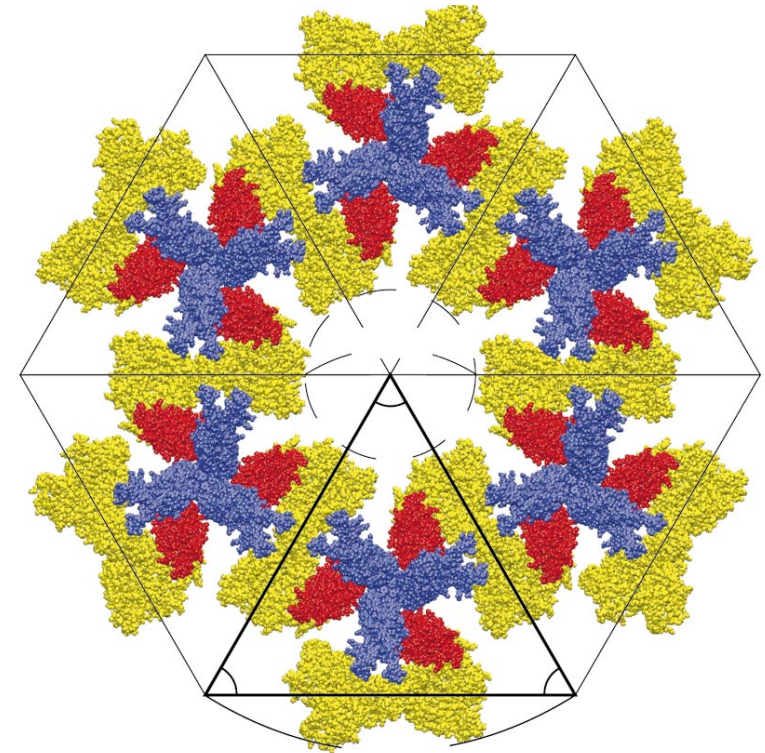
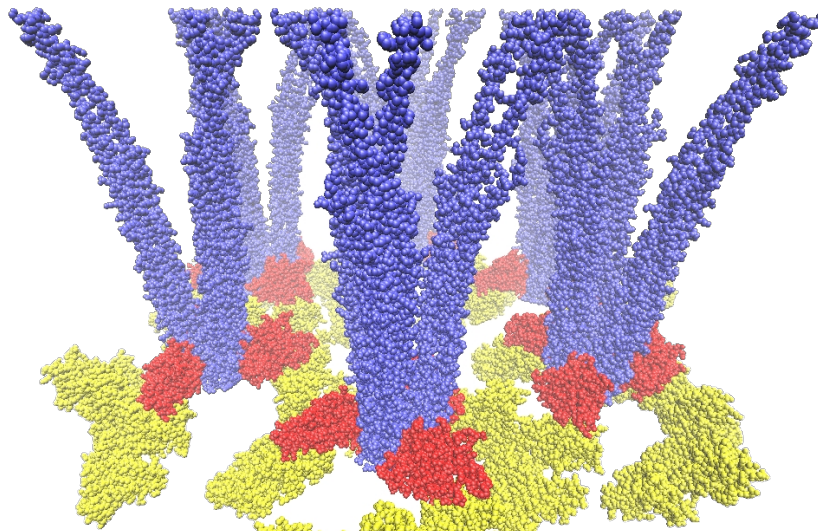
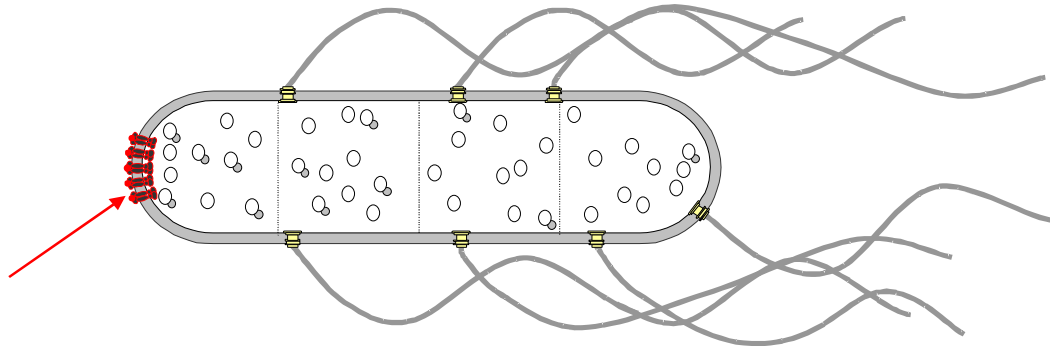
CW = tumble







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

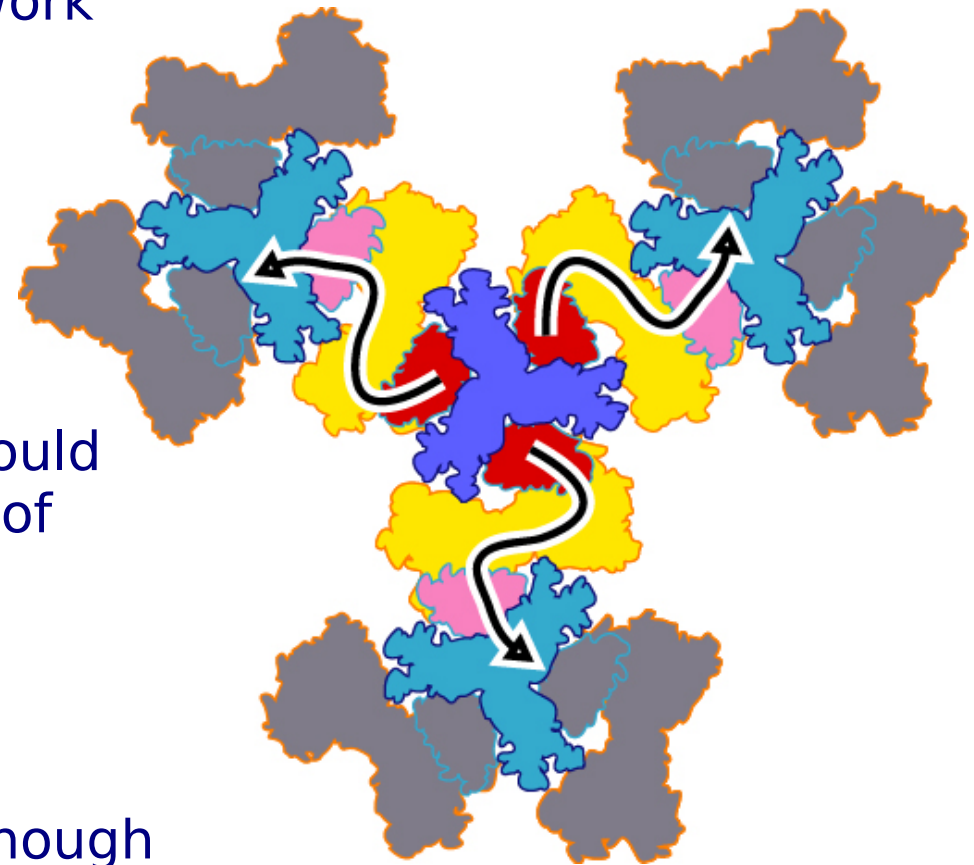


Clustered Receptors could enhance sensitivity (Changeux *et al.* 1967, Bray *et al.* 1998).

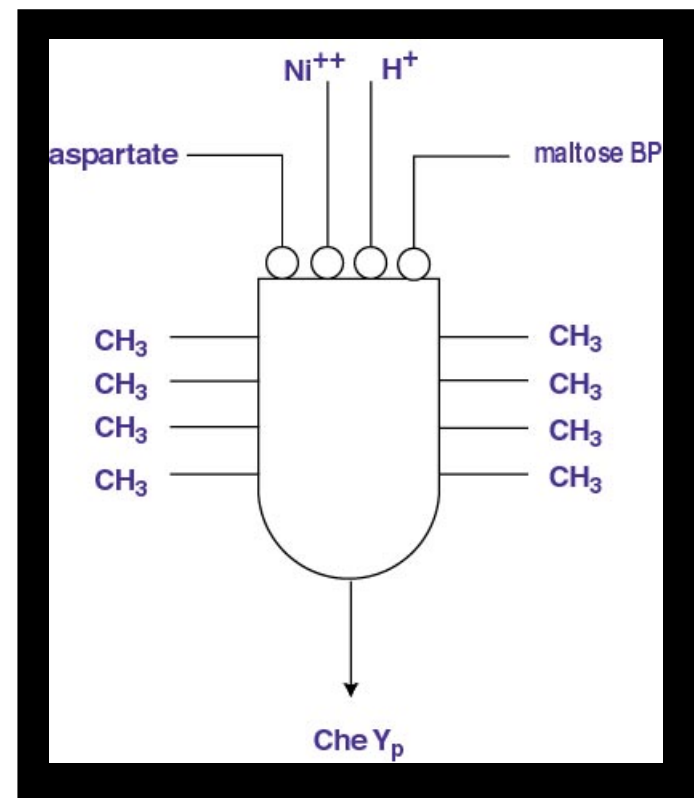
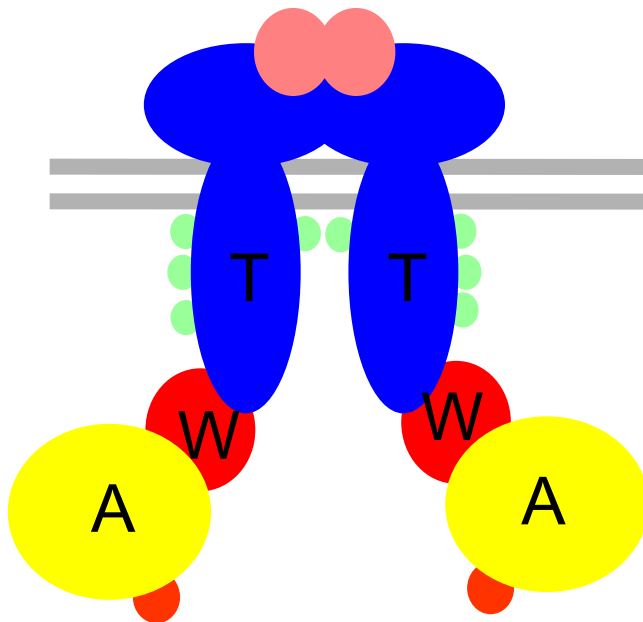
Integration of various signals (Hazelbauer *et al.* 1989).



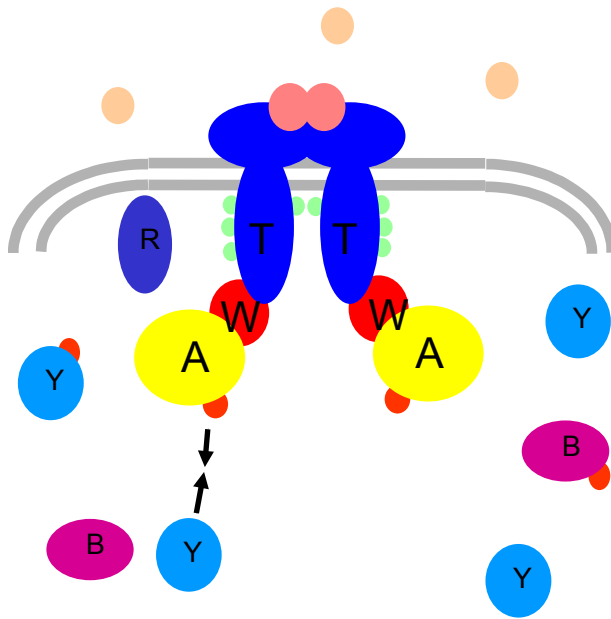
- Conformational changes could be propagated through the network via CheA/CheW
Enhanced gain;
- Hybrid networks containing multiple types of receptors could integrate signals at the level of CheA activity;
- Receptor dimers are close enough (6-10 nm) for adaptational cross-talk.



Internal features represented by binary flags. States are vectors of flags.



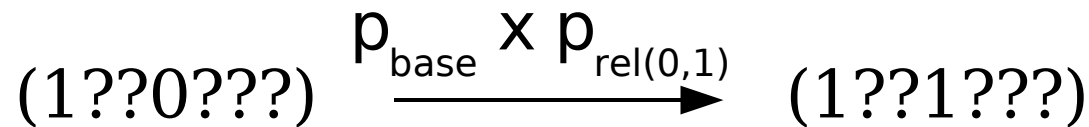
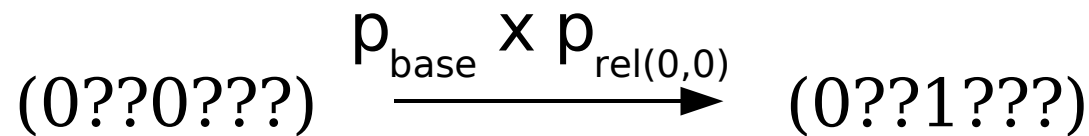
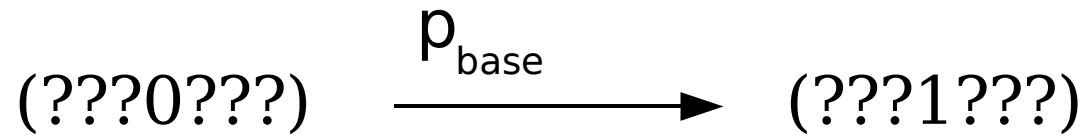
Reaction probabilities can be modified by the state of a participating multistate complex



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

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

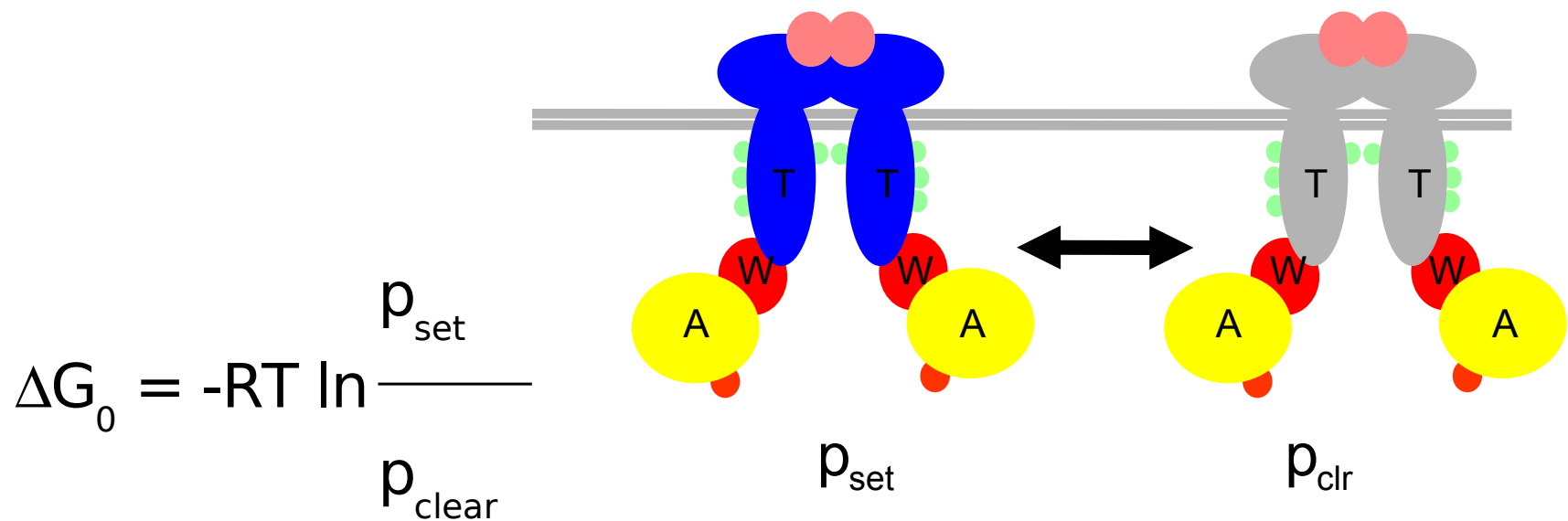




- '?' Flags do not affect the reaction
- only 4 species are needed instead of 128



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



no attractant bound			attractant 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

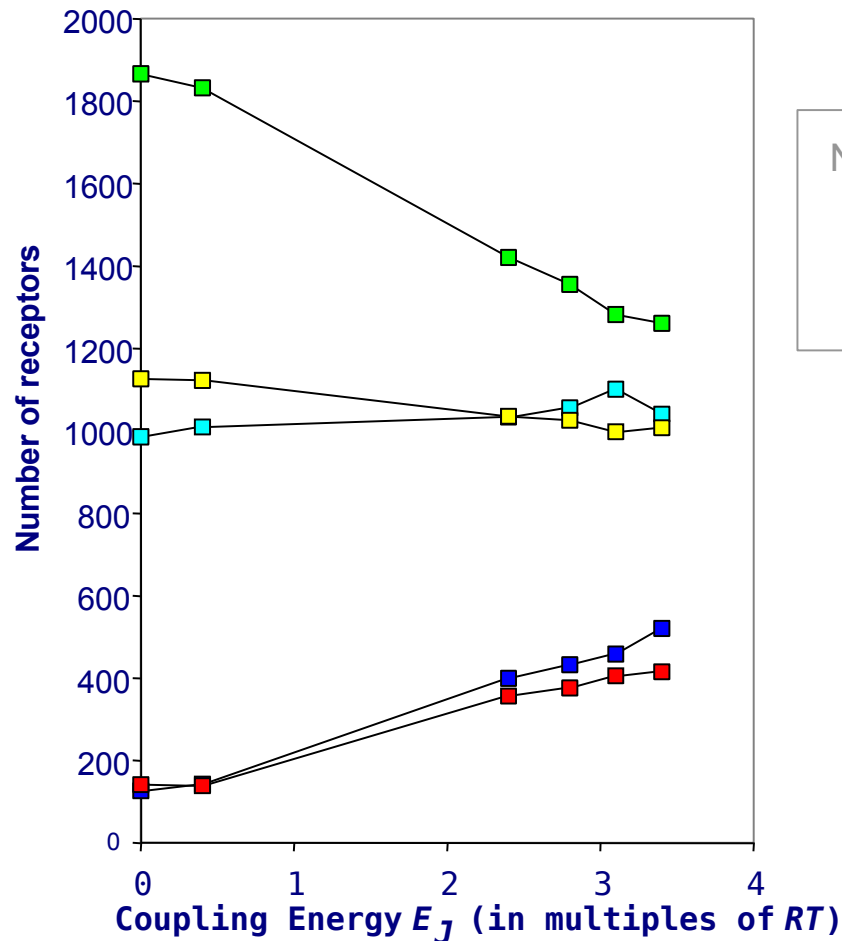


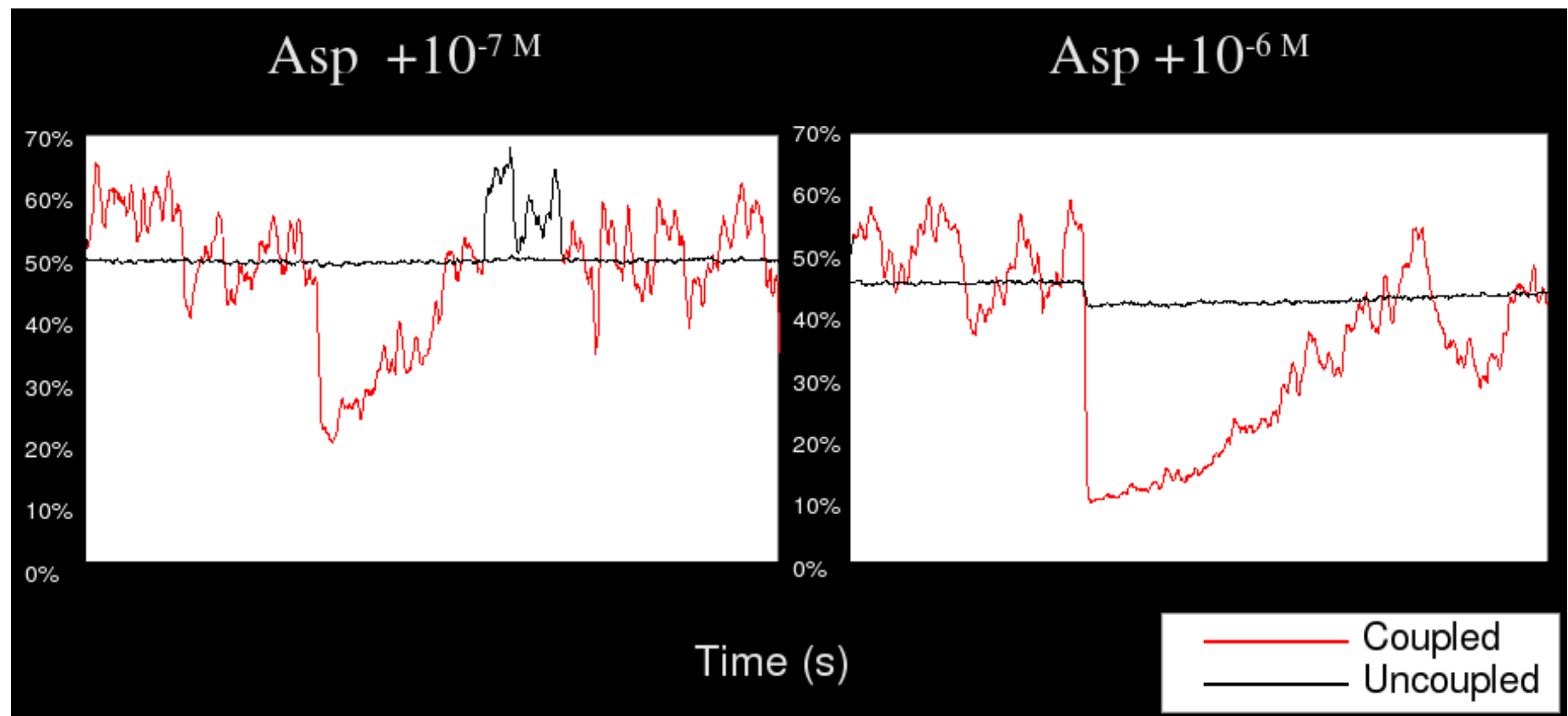
		no attractant bound						attractant bound				
	active neighbours	0	1	2	3	4	active neighbours	0	1	2	3	4
p		0.00	0.00	0.02	0.08	0.30		0.00	0.00	0.00	0.01	0.07
ΔG		4.47	3.49	2.50	1.51	0.53		5.55	4.56	3.58	2.59	1.61
p		0.01	0.03	0.13	0.41	0.78		0.00	0.00	0.02	0.08	0.30
ΔG		3.17	2.18	1.20	0.21	-0.77		4.47	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

Shimizu *et al.* (2003) J Mol Biol 329: 291-309.

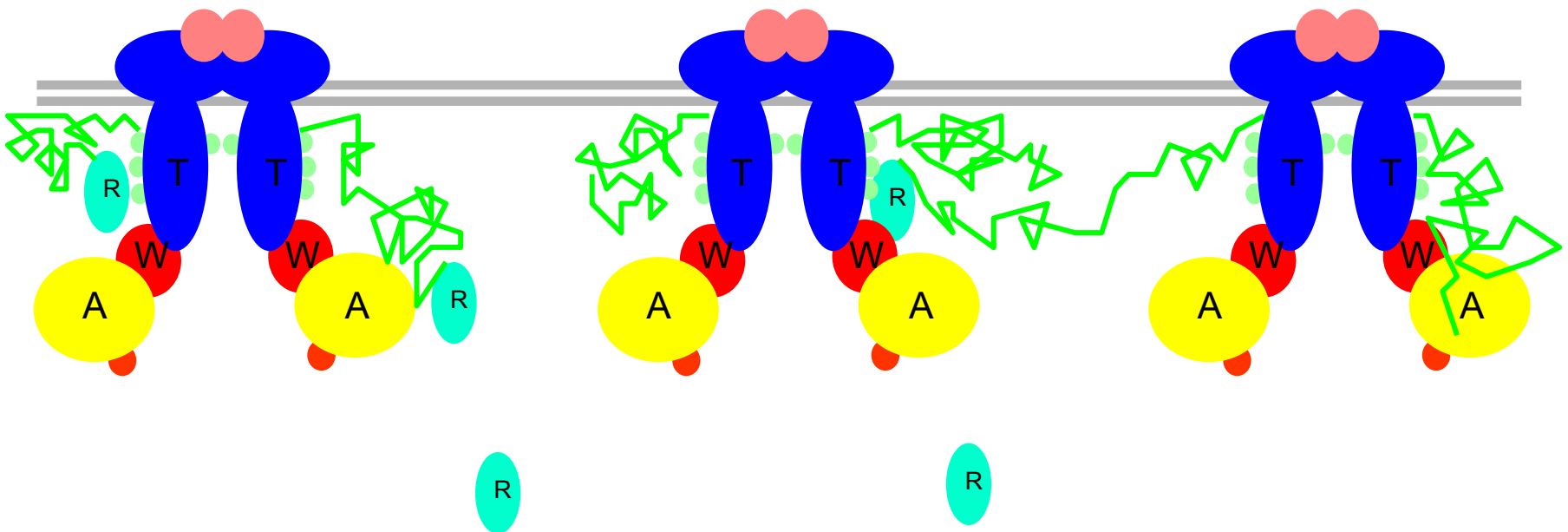


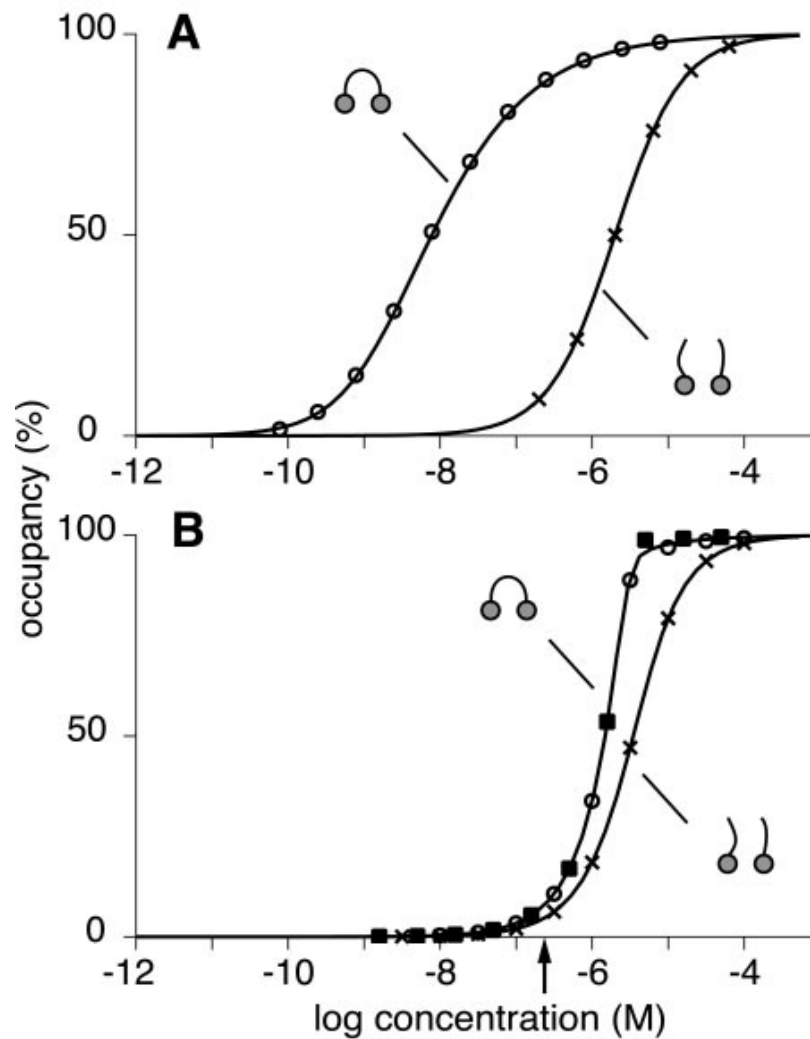
- Steady-state population profile of receptor methylation states changes with degree of coupling





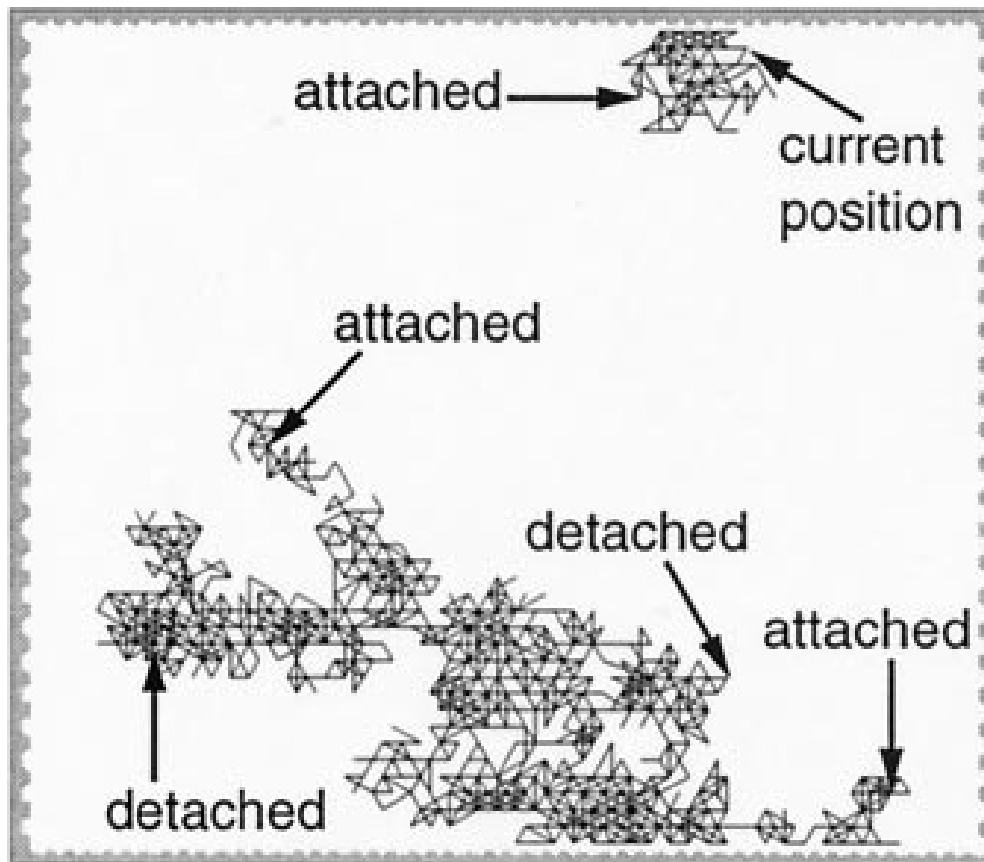
Interaction between receptors and CheR (methyltransferase)





Levin et al. (2002) *Biophys J* 82:1809-1817.





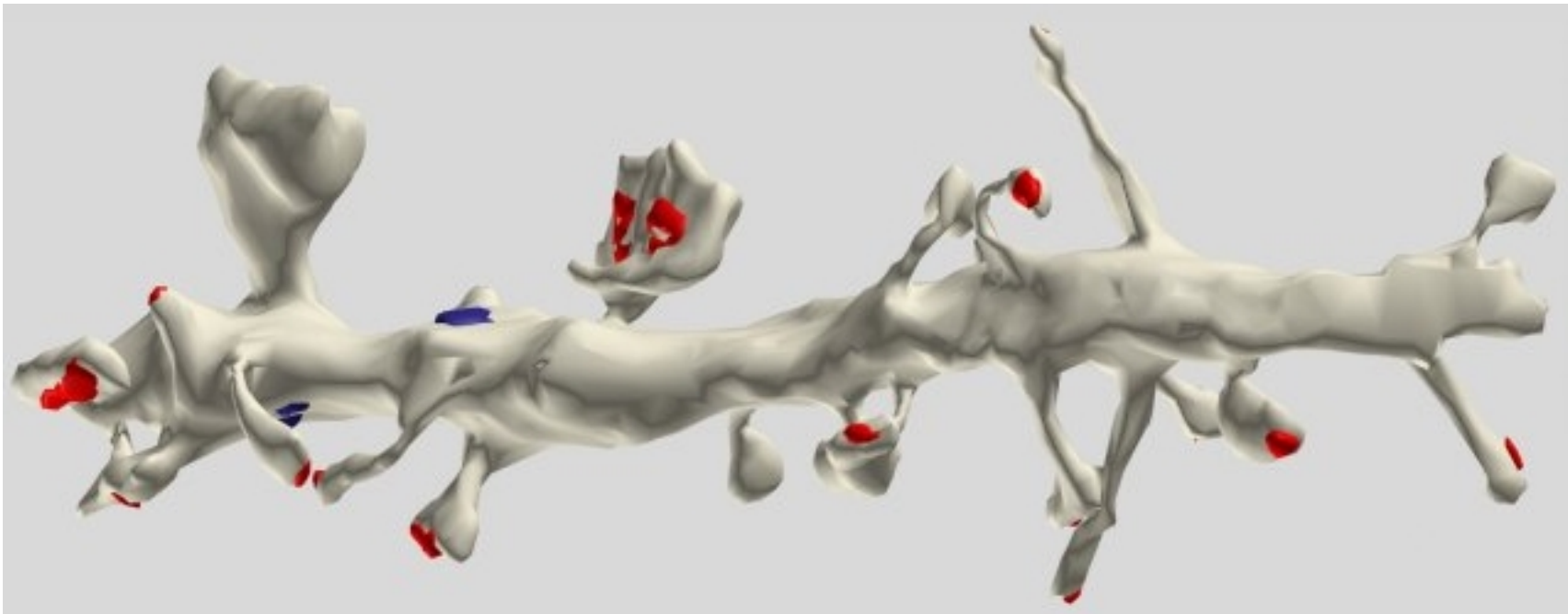
Each CheR molecule visits more receptors, some of them repetitively;

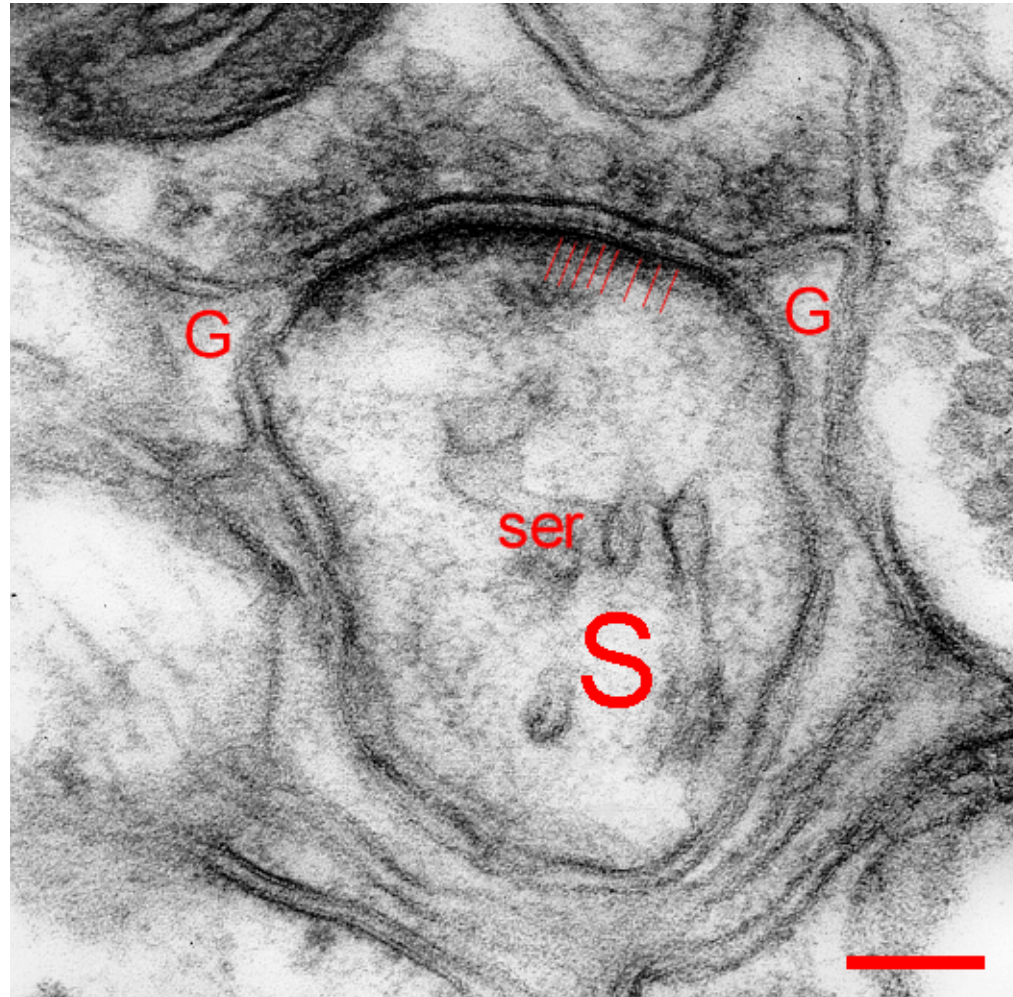
CheR molecules are trapped into the receptor lattice.

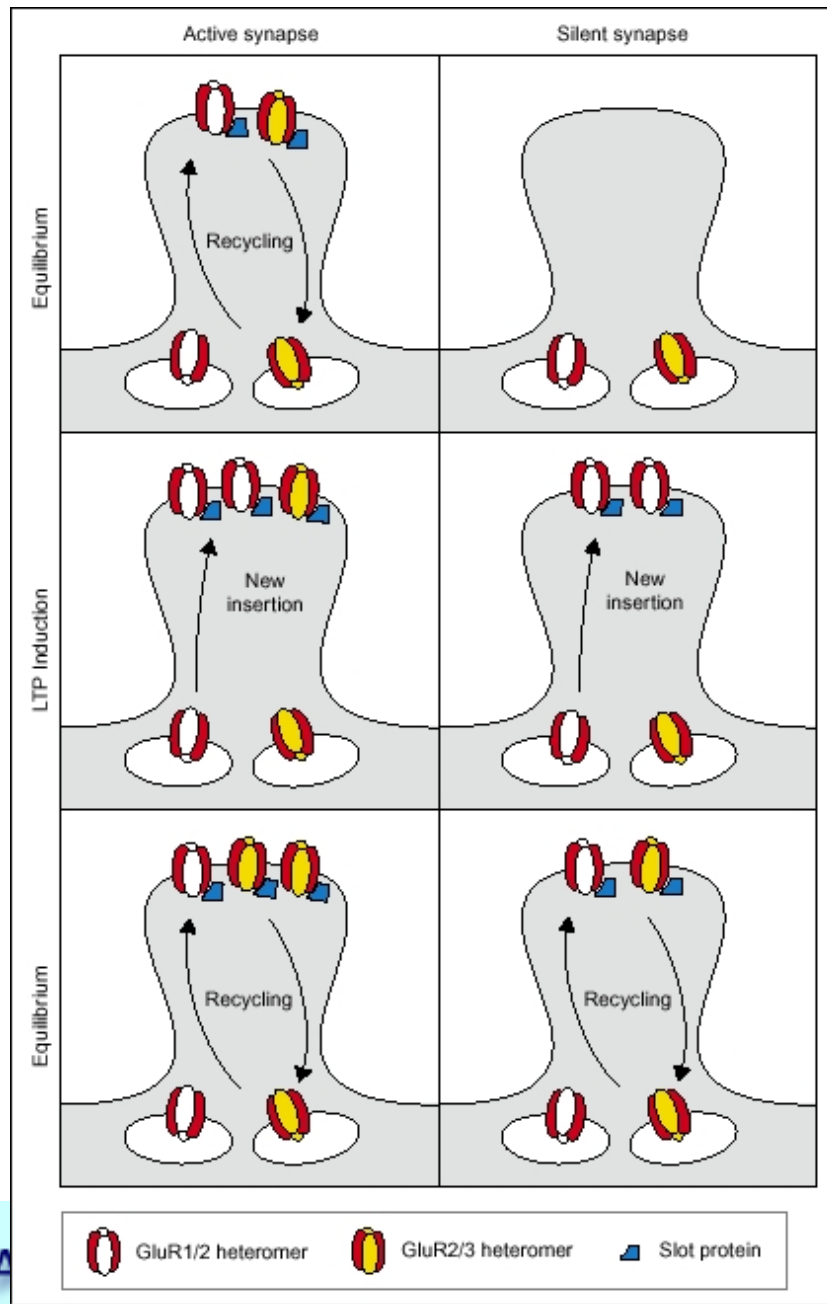


- 3D lattice
- Reactions between different multistate molecules
- New native format based on XML (extension of SBML)
- New GUI

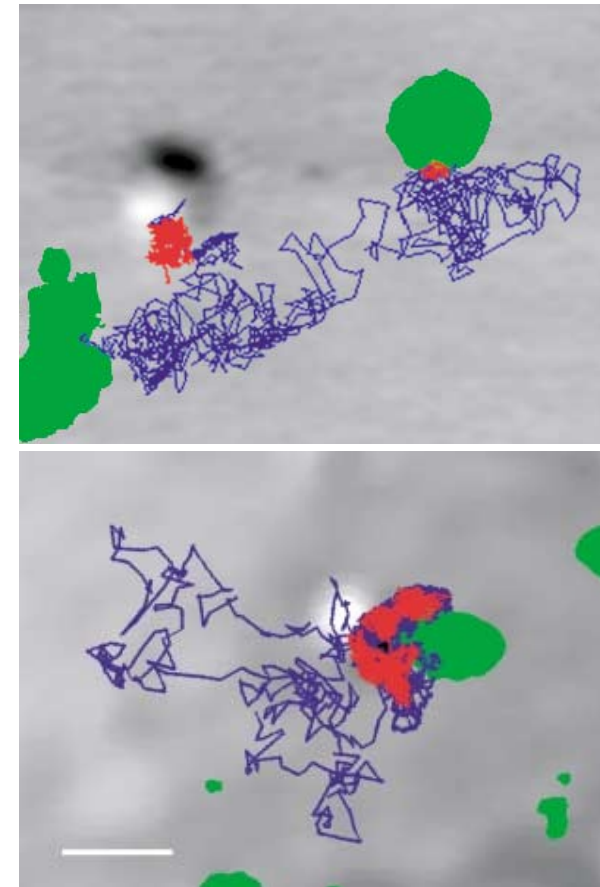








Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279-286



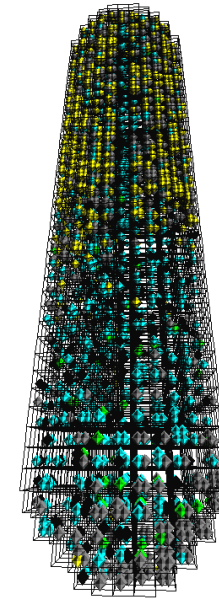
Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265



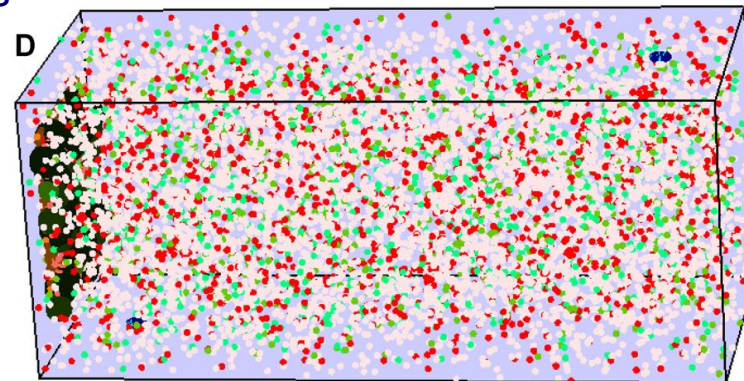
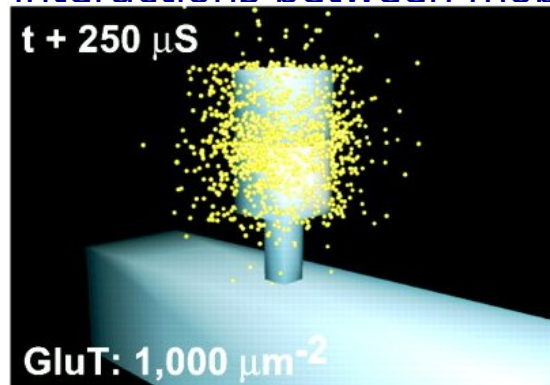
- molecule abstracted $\Rightarrow$ macroscopic scale
- atomic details $\Rightarrow$ microscopic scale
- Abstracted but realistic geometry $\Rightarrow$ mesoscopic scale
- Relative size of object respected
- Differential location of binding sites
- realistic movements (speed and topology)



- Population based (“spatial Gillespie”)
 - SmartCell, Mesord
 - finite elements (voxels), no individual molecules

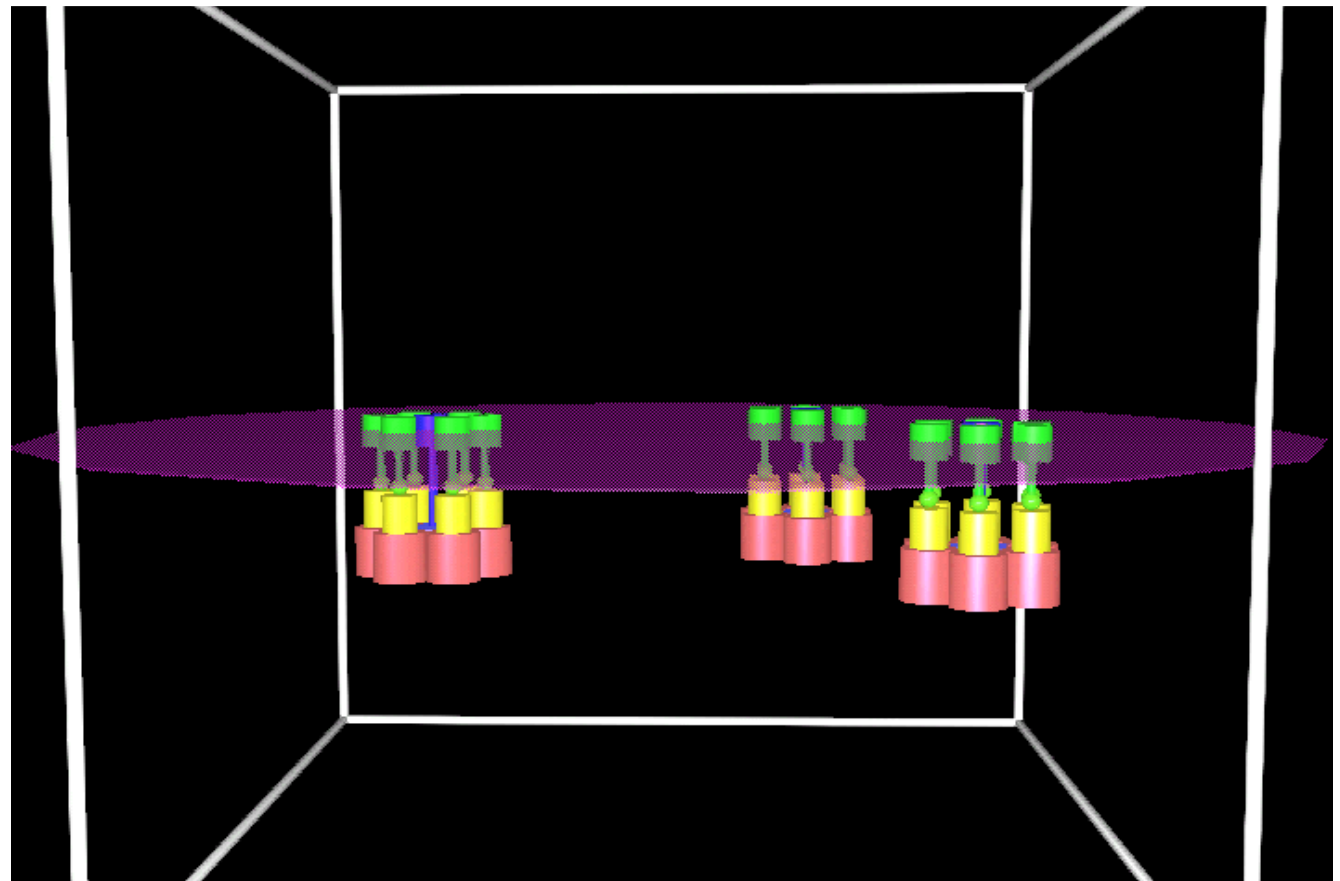
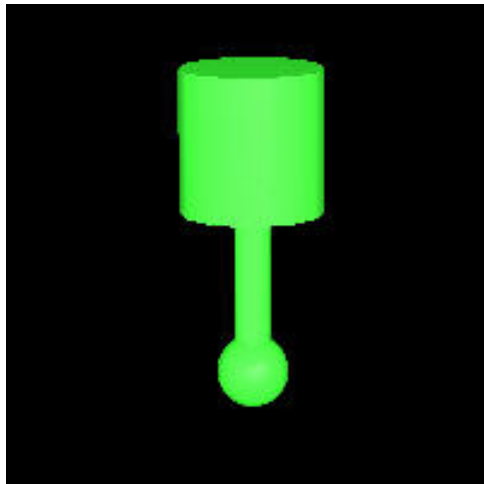
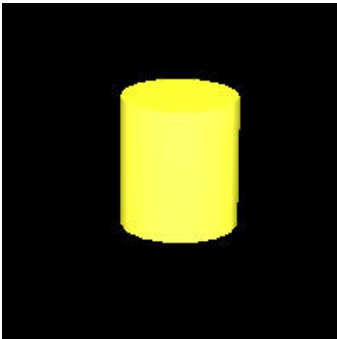


- Single-particle based
 - MCell: individual small molecules, ray-tracing. Immobile reactive surfaces. no interactions between mobile molecules



- Smoldyn: individual small molecules, reactions between them
- Meredys: Everything plus topology of molecules





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.



- 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

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

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



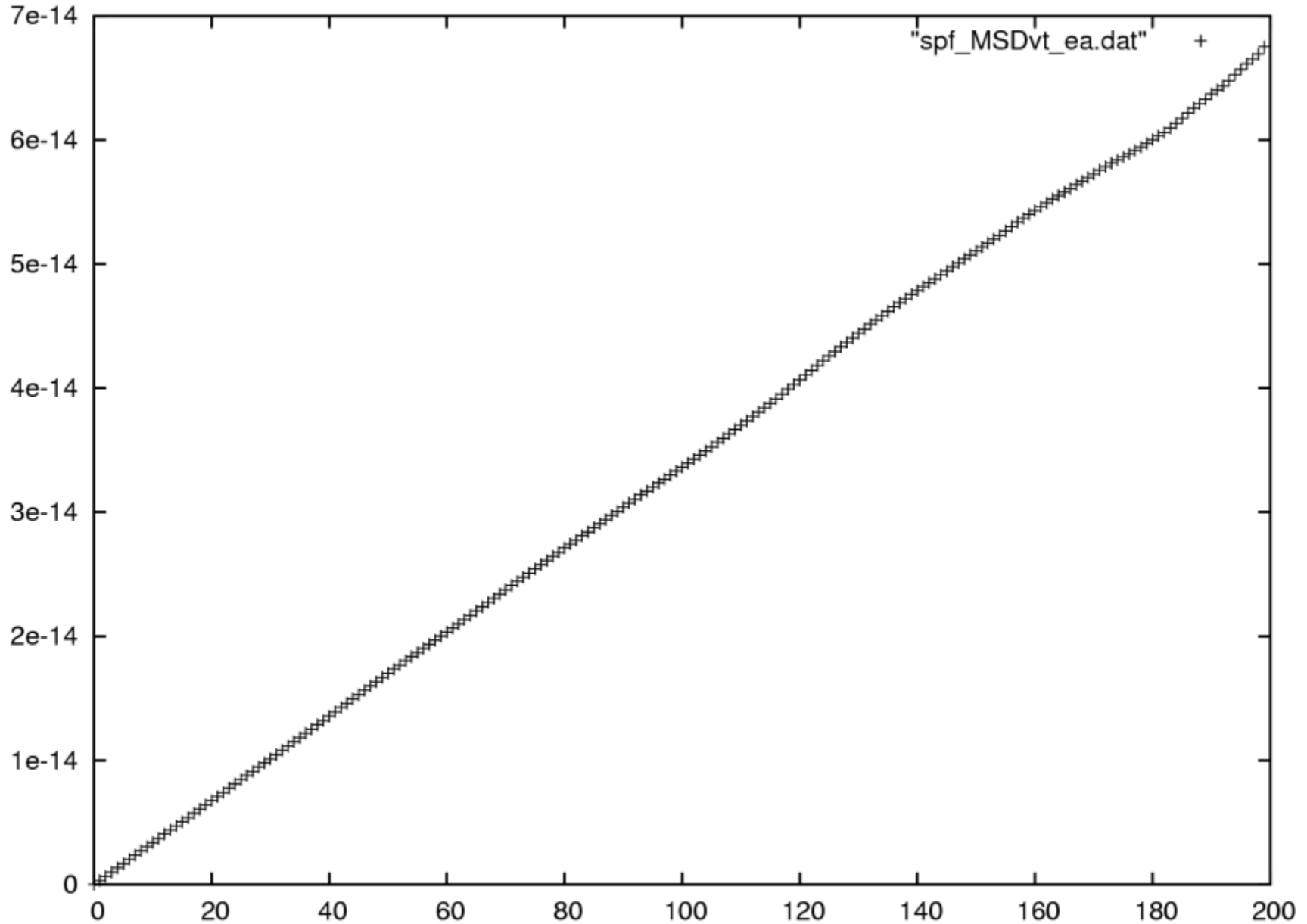
- Unrestricted brownian motion – Low Translation/Rotational

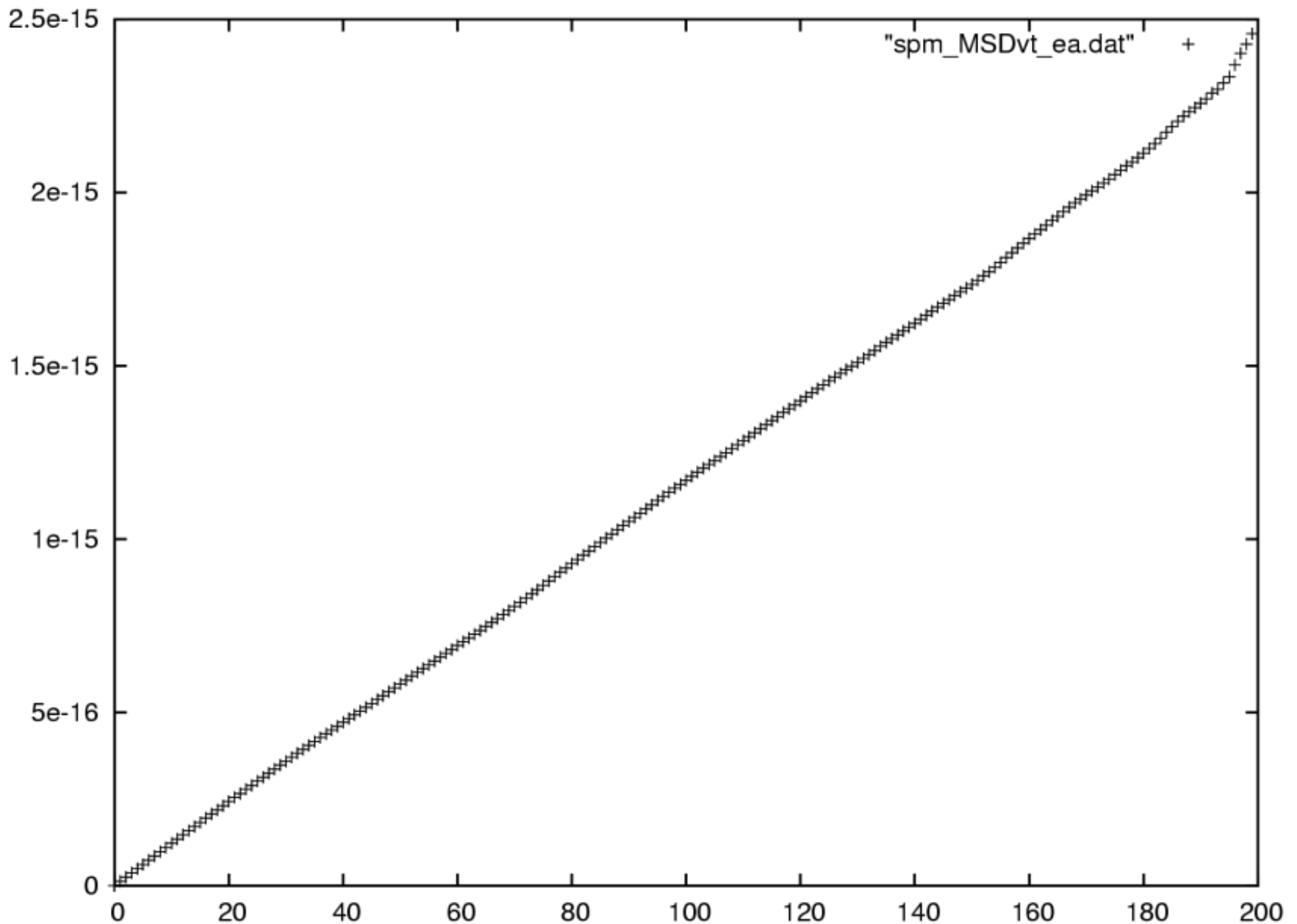
$$b_T = \frac{1}{6\pi\mu r} \quad b_R = \frac{1}{8\pi\mu r^3} \quad \frac{b_T}{b_R} = \frac{4}{3}r^2$$

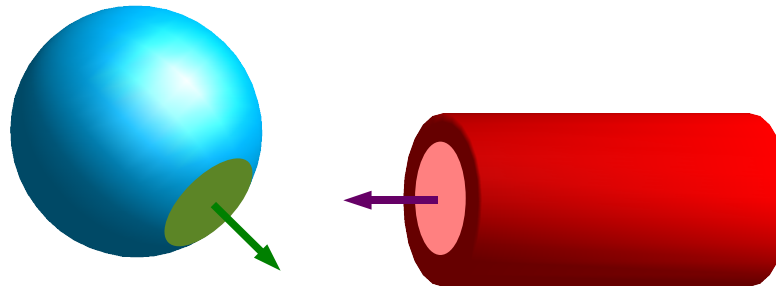
- Intra-membrane diffusion (Saffman and Delbrück 1975)
High Translational/Rotational

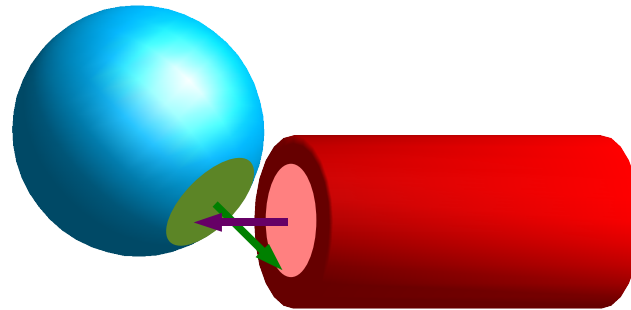
$$b_T = \frac{1}{4\pi\mu h} \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma \right) \quad b_R = \frac{1}{4\pi\mu r^2 h} \quad \frac{b_T}{b_R} = \left(\log\left(\frac{\mu h}{\mu' r}\right) - \gamma \right) \times r^2$$

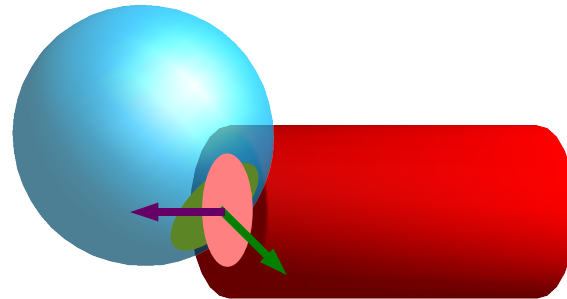


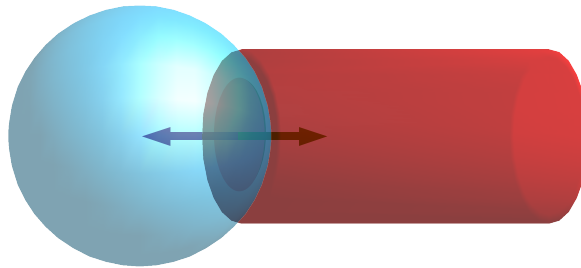


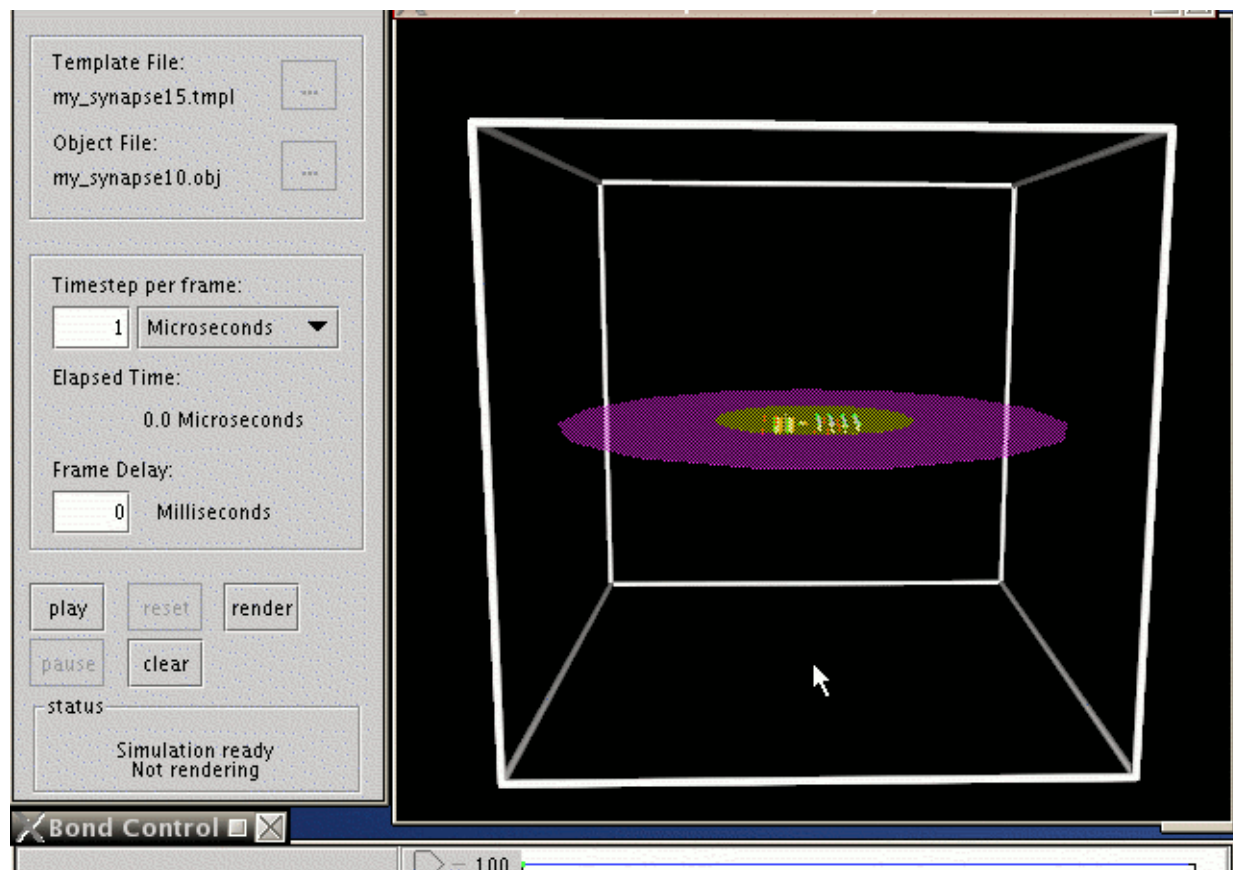












- Probabilities of reactions are hard-coded
- Molecules can have several states, but a state does not affect the reactions
- Shape of molecules does not affect diffusion
- ...

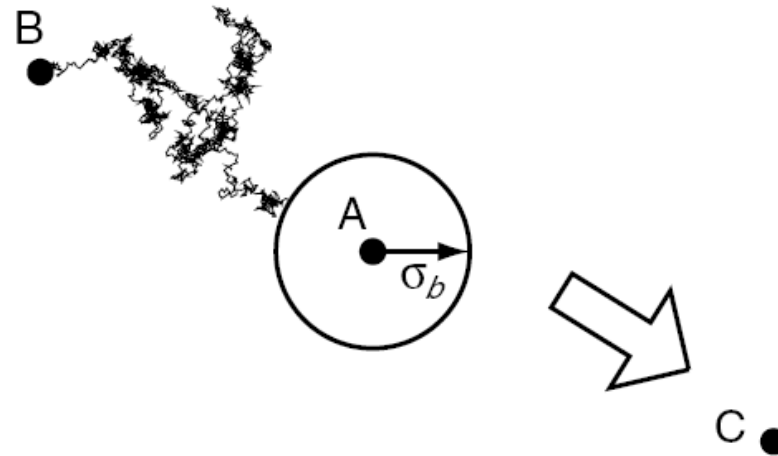


- Smoldyn

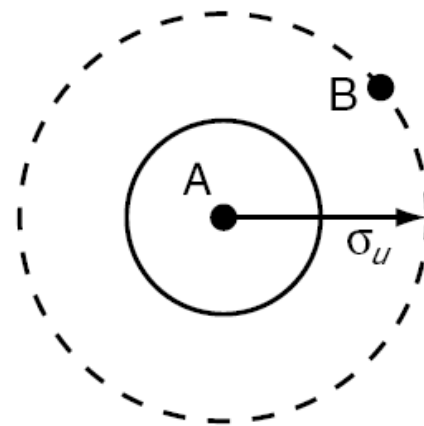
(Andrews and Bray (2004) *Phys Biol* 1: 137-151)

- + single-particle
- + binding radius (probability of reaction) related to kinetics
- - no volume, shape, mass,
- - No complexes
- - No multistate molecules

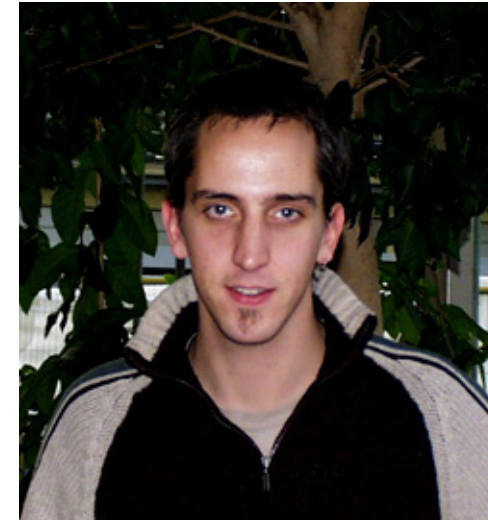
Forward reaction: $A + B \rightarrow C$



Back reaction: $C \rightarrow A + B$



- Dennis Bray
 - Matthew Levin
 - Carl Morton-Firth
 - Thomas Simon Shimizu
-
- Fred Howell
 - Dan Mossop



Dominic Tolle

