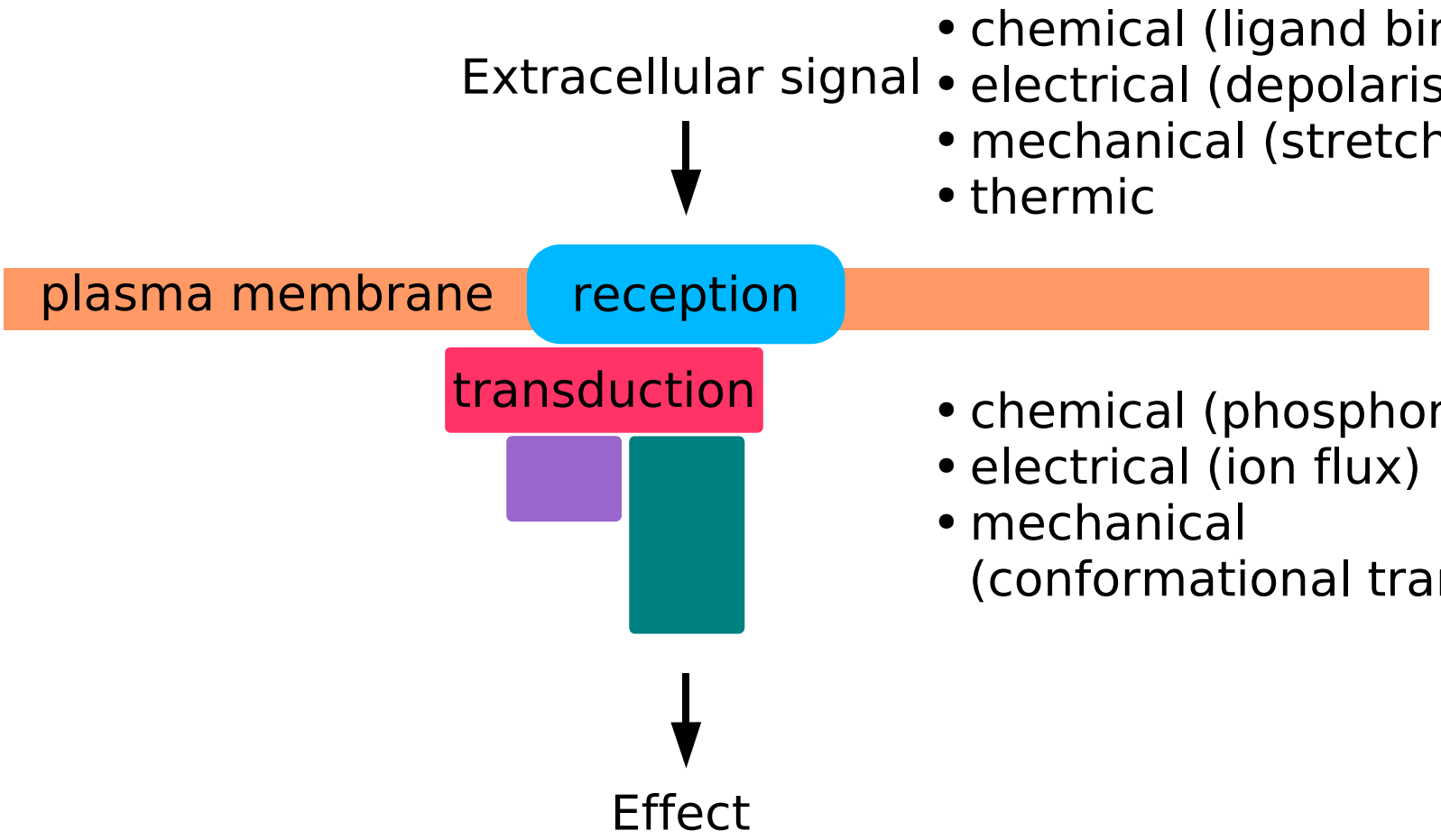
Apports de la simulation stochastique des particules en « Systems Biology »

Exemple de la transduction des signaux transmembranaires

Nicolas Le Novère, EBI

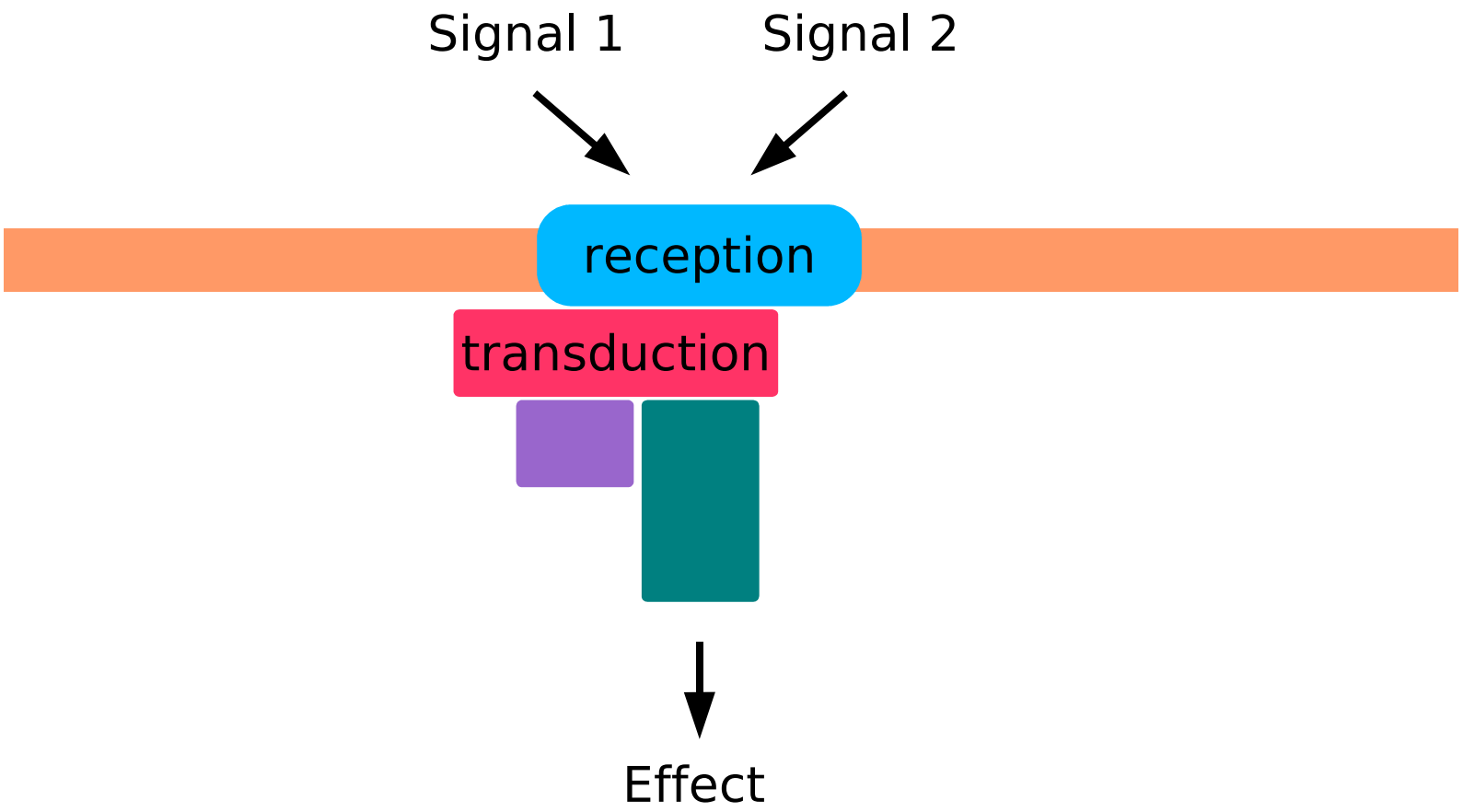
Signal transduction



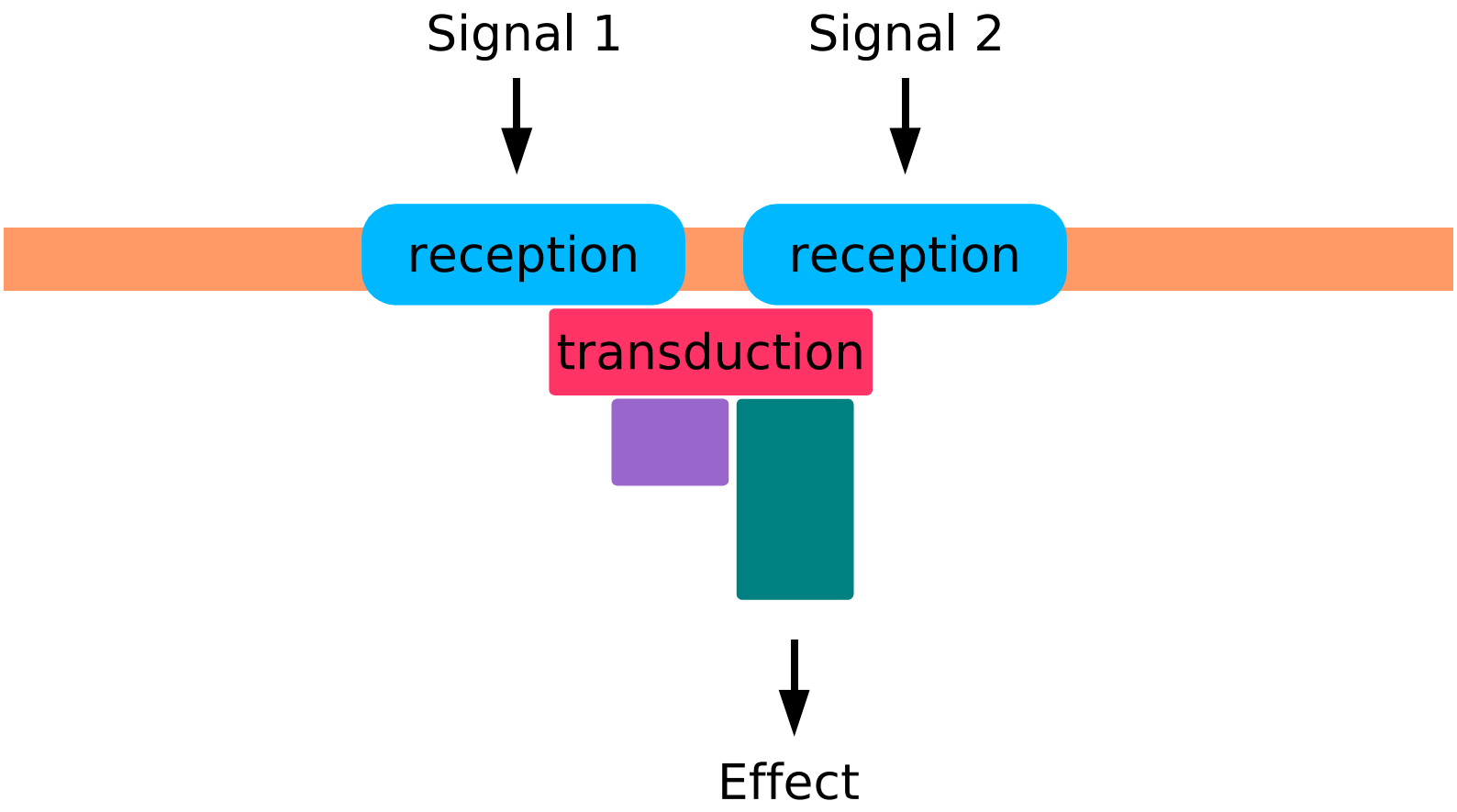
- chemical (ligand binding)
- electrical (depolarisation)
- mechanical (stretching)
- thermic

- chemical (phosphorylation)
- electrical (ion flux)
- mechanical (conformational transition

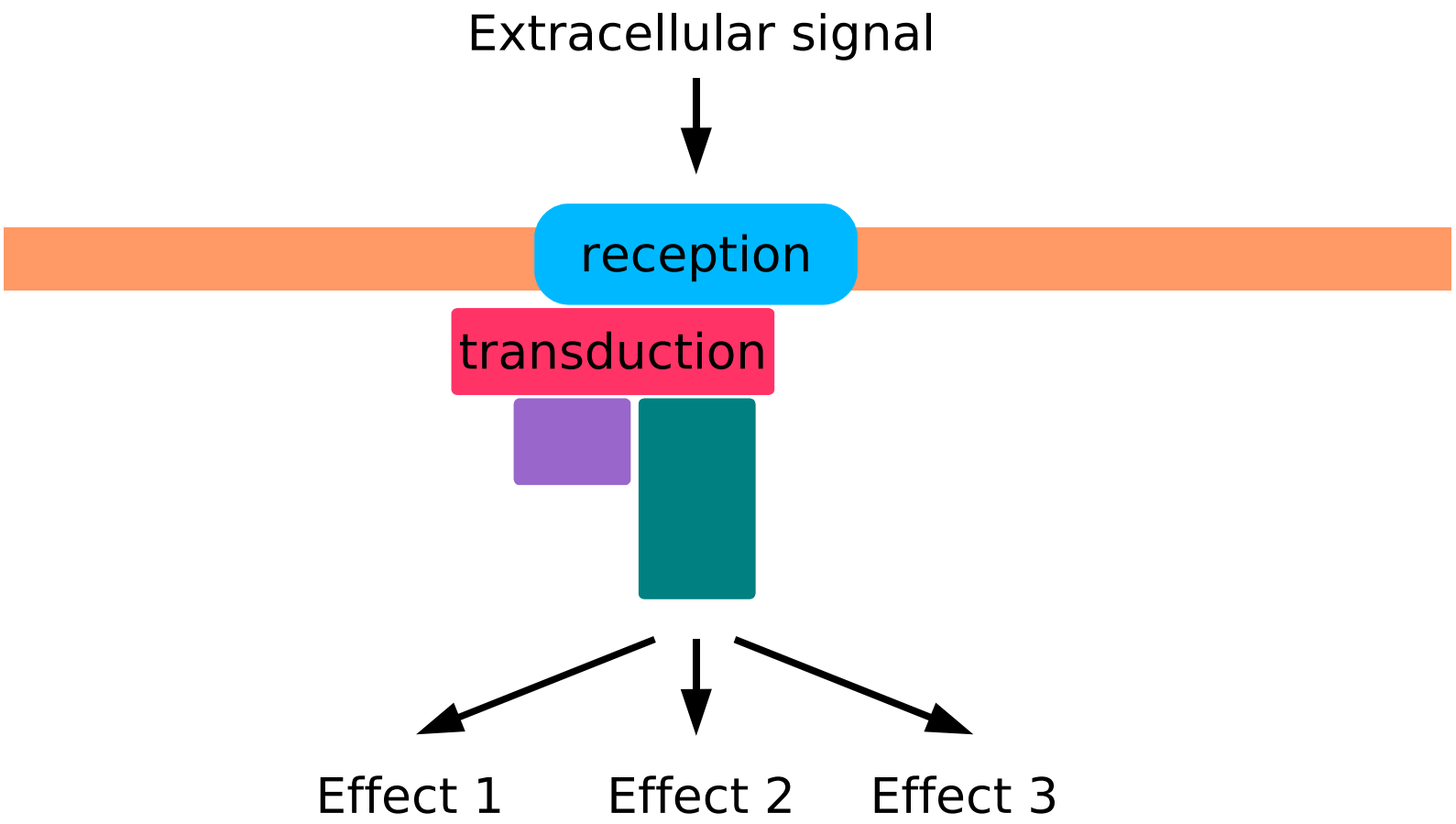
Signal convergence



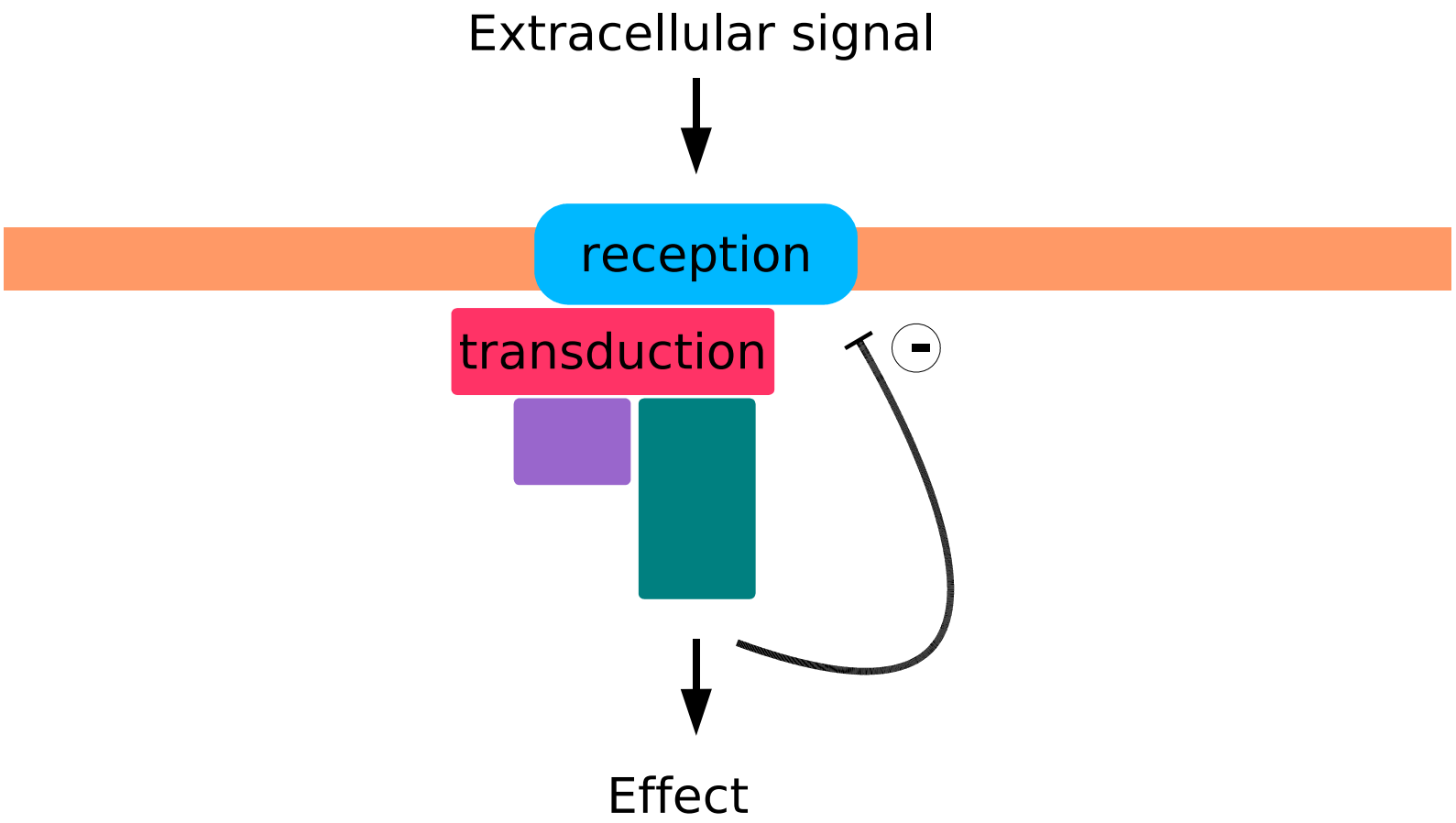
Signal convergence



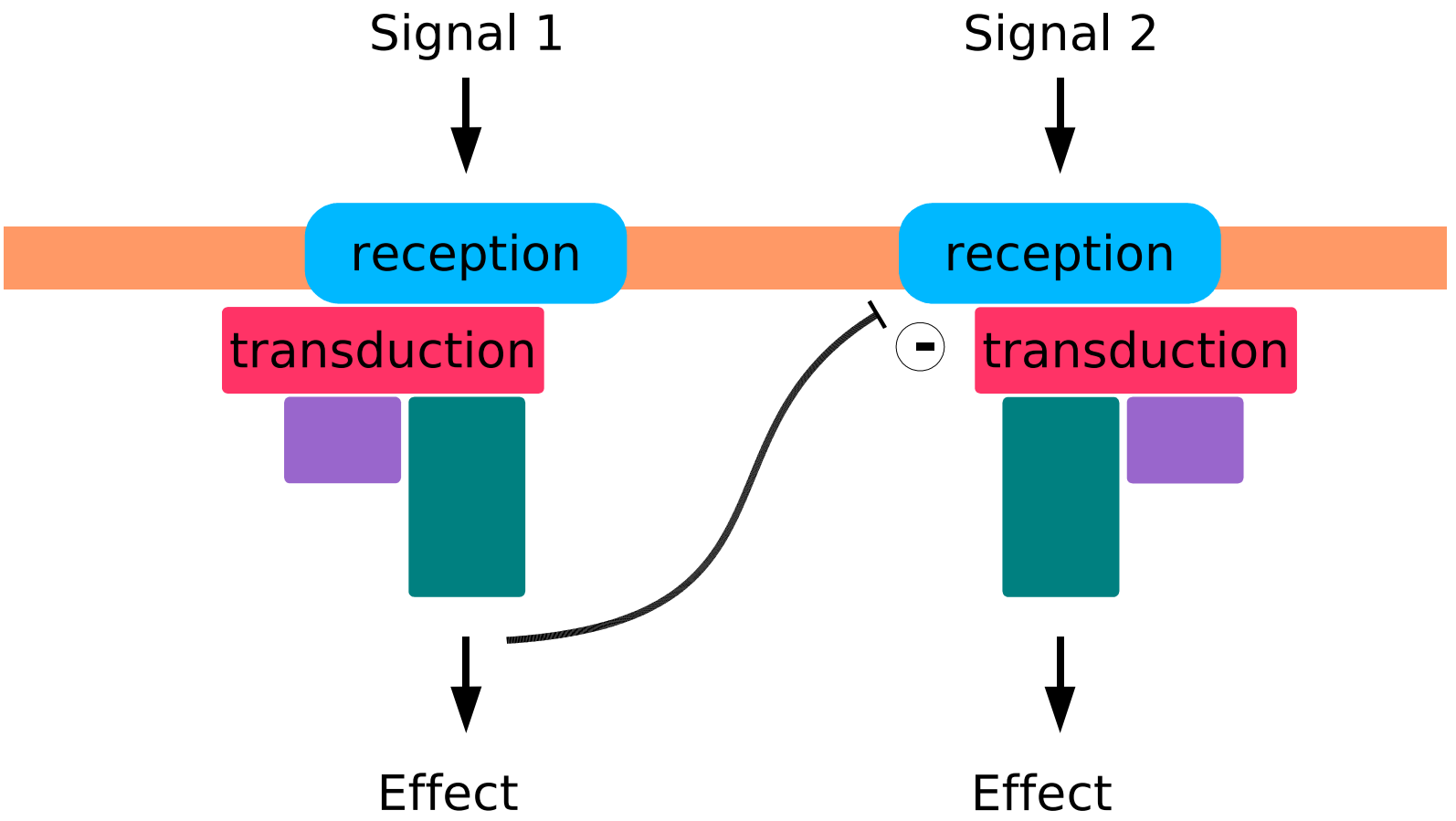
Signal divergence



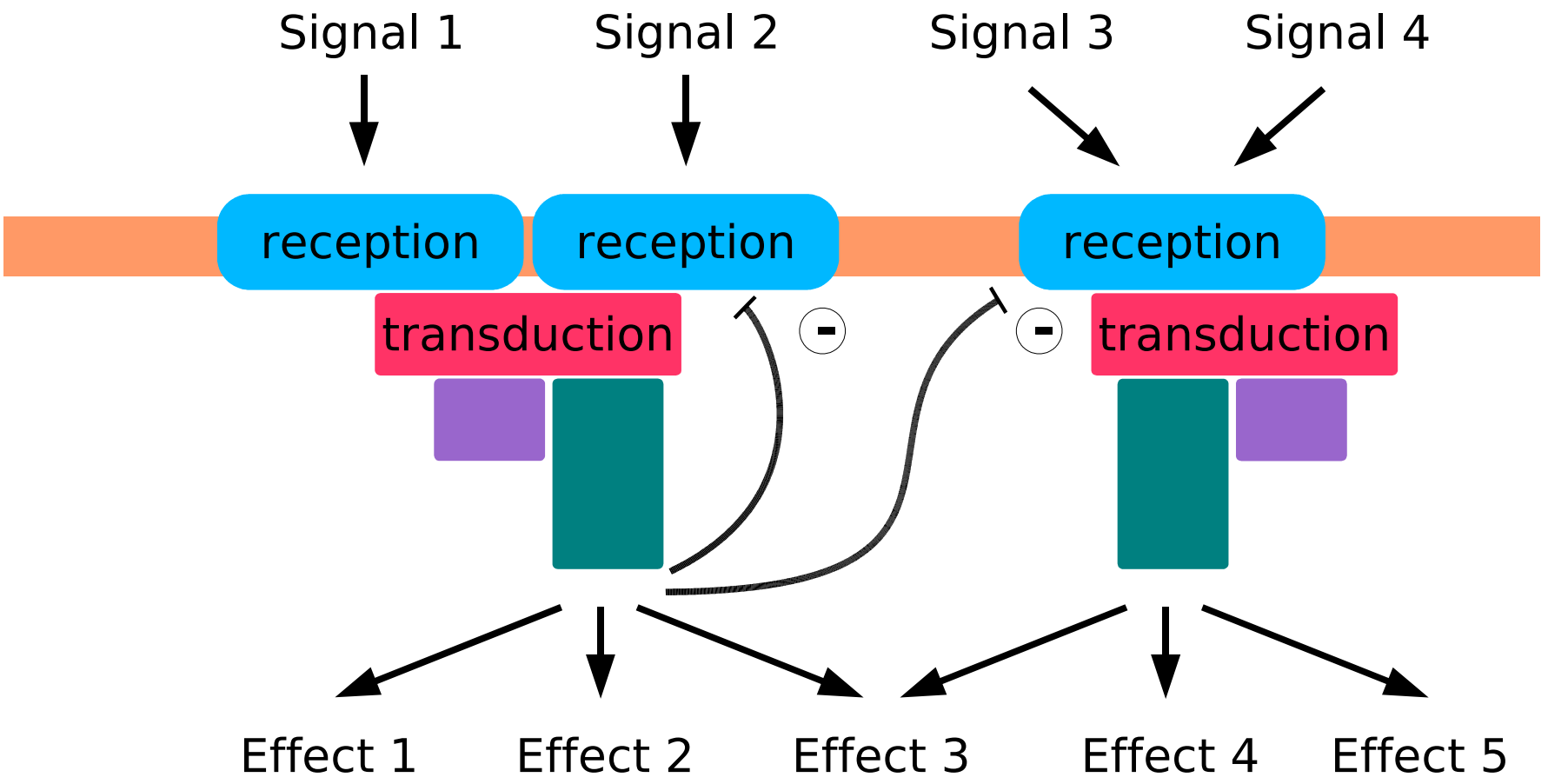
Signal adaptation



Cross-adaptation



The full monthy



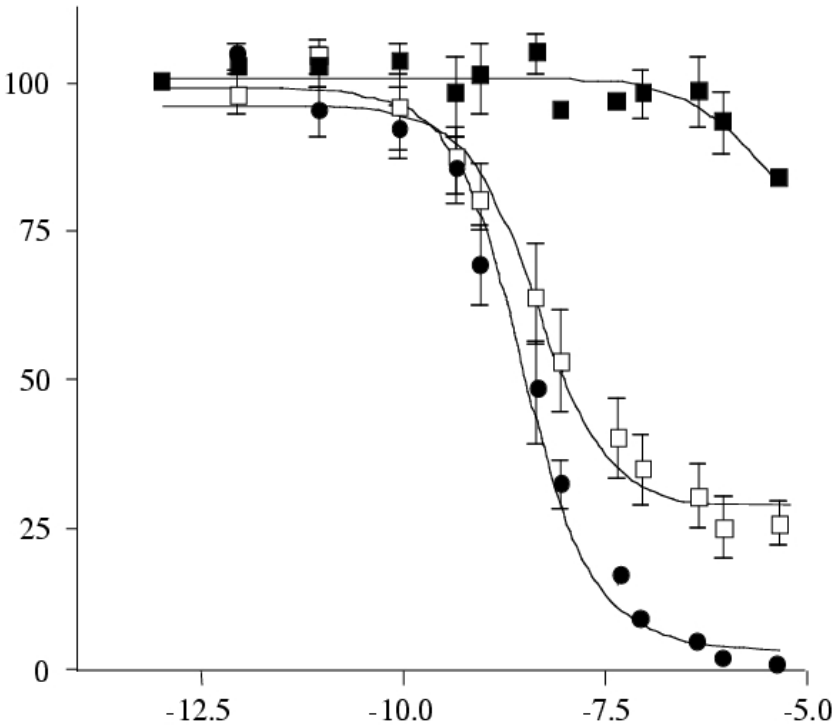
Specificities of signal transduction

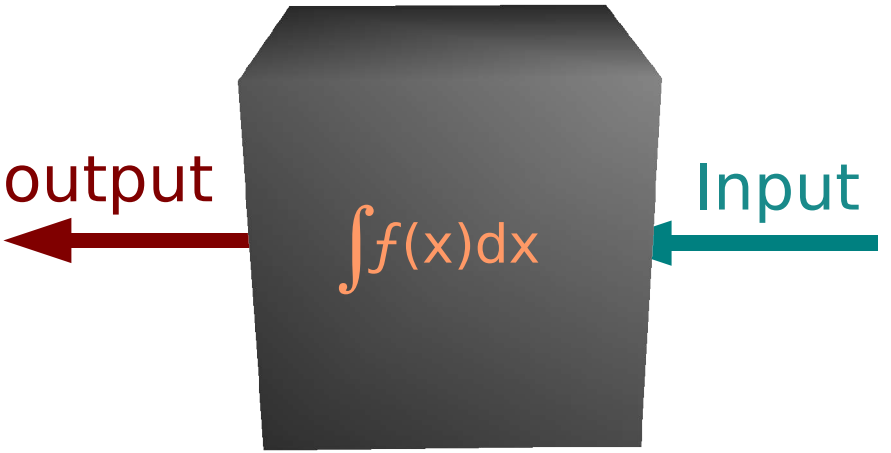
- Low number of partners (x10 to x1000)
- High sensitivity (often due to allosteric factors)
- Robustness (affinity unimportant, role of transduction)
- Gain (multiple steps of enhancement)
- Adaptation (stay sensitive to various intensity;
  decrease response to continuous signals)
- Relative location of partners is crucial

Classical approaches in theoretical biology

(1)-The phenomenology

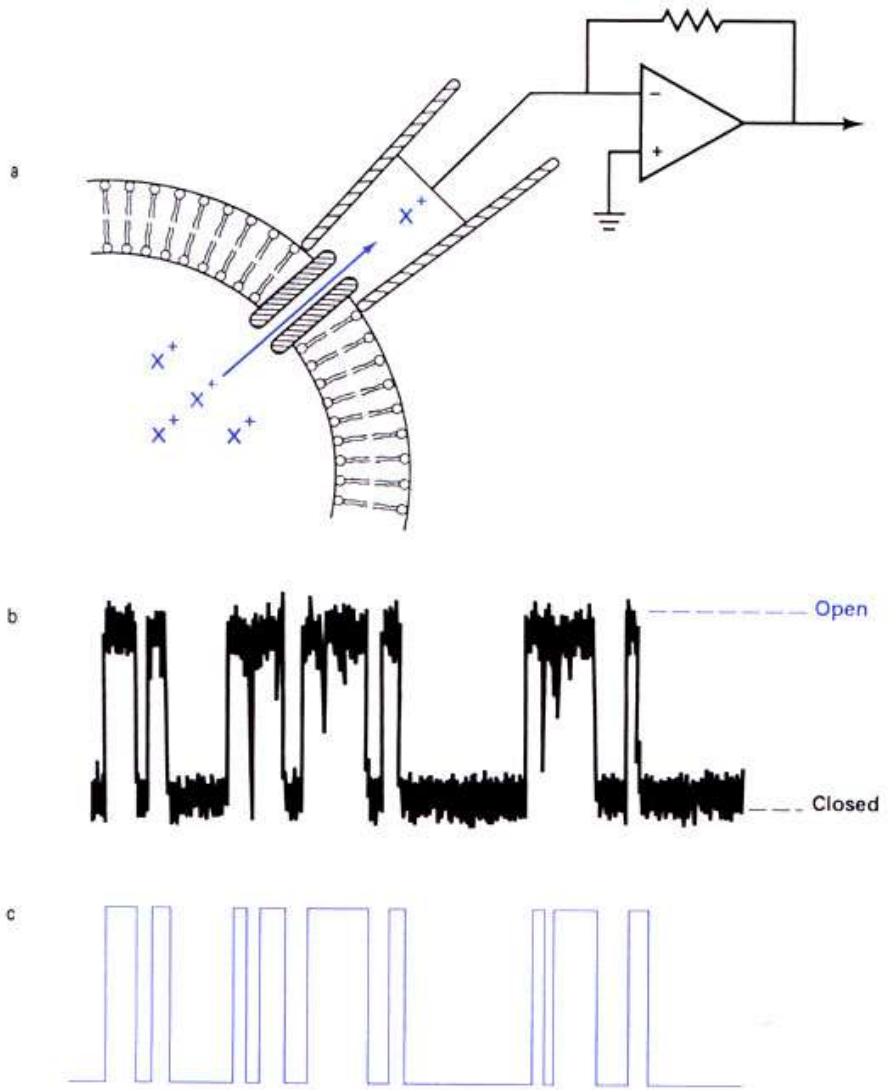
Snapshot of the system ⇒ Abstraction



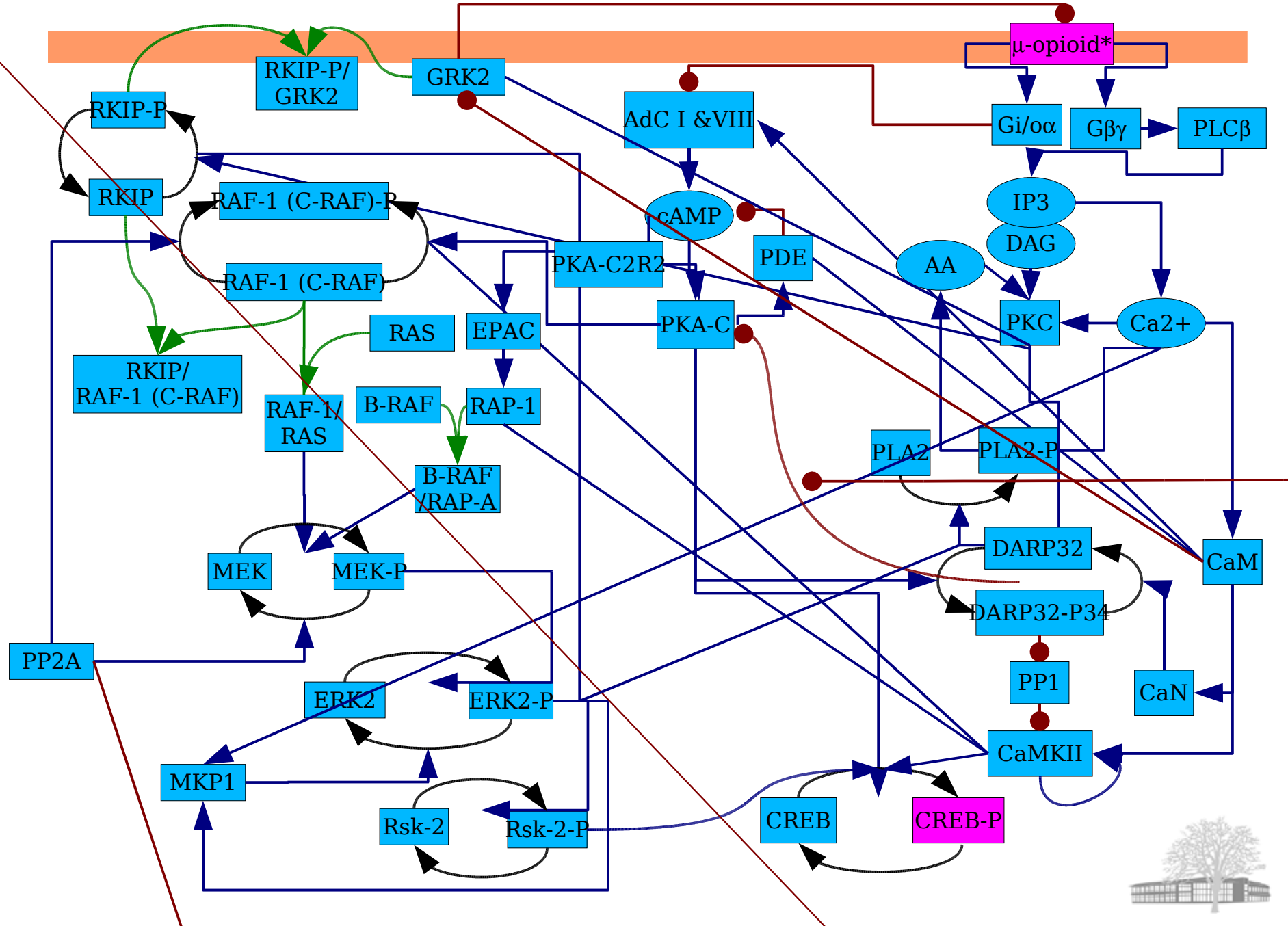


Classical approaches in theoretical biology

(2)-The reductionism



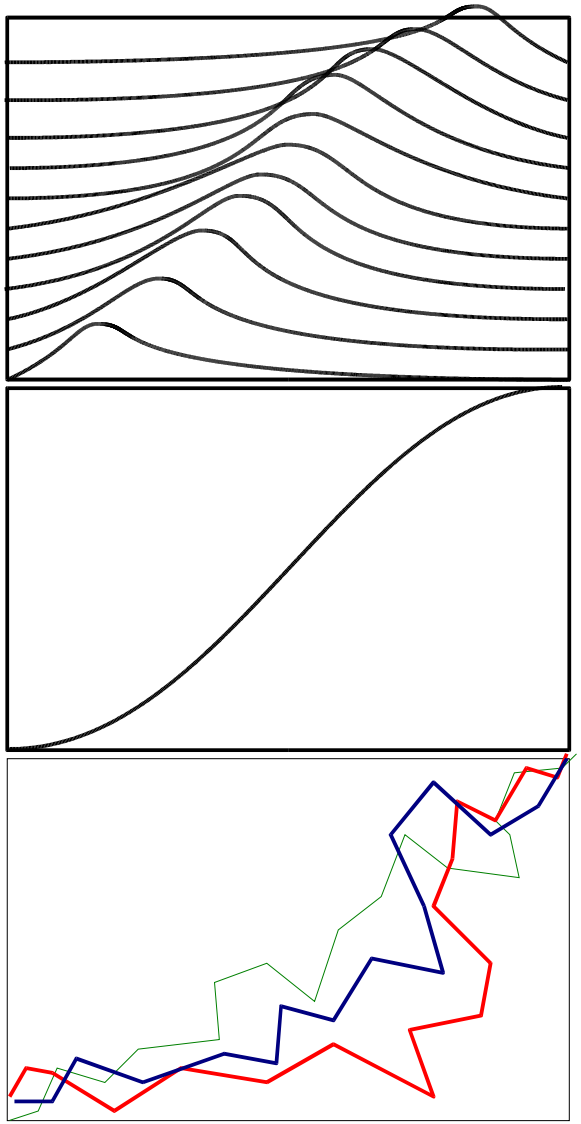
Complex signalling pathways



Systems Biology

- Reconstruction of dynamic systems from the properties of their elementary building blocks
- Made possible by large-scale data production & improvements of computing power and technics
- Cybernetics properties are conserved across systems (control theory: feedback, feedforward, robustness...)
  Relationships between building blocks are more important than their elementary properties.
  The theoretical treatment is already available.
- A New Era:
  Pre-molecular Biology was descriptive
  Molecular Biology made Biology explicative
  Systems Biology makes Biology predictive

Different approaches



Grand Probability function: P(X,t)

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

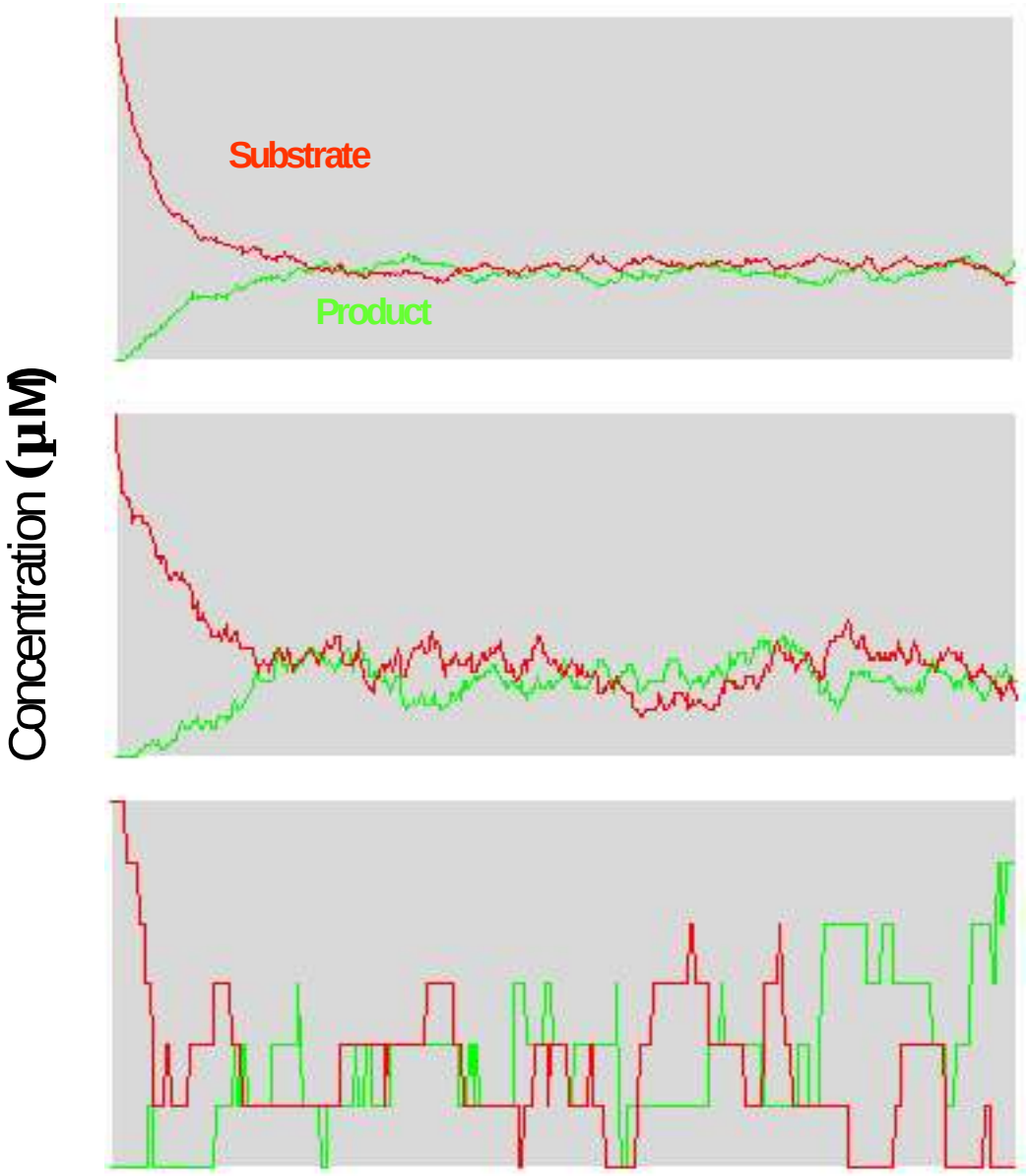
stochastic approach: P(X,t)/(X',t-1)

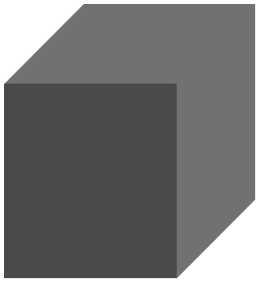
Limitation of deterministic approaches

Continuous, deterministic models can’t cope with:

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

On small numbers





10^{-15} litres

10^{-16} litres

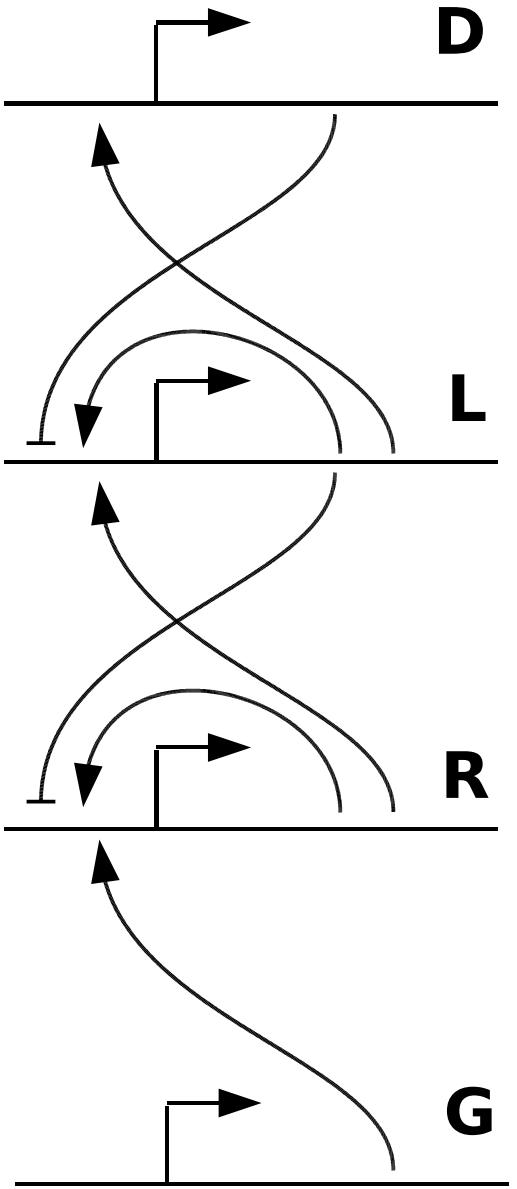
10^{-17} litres

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

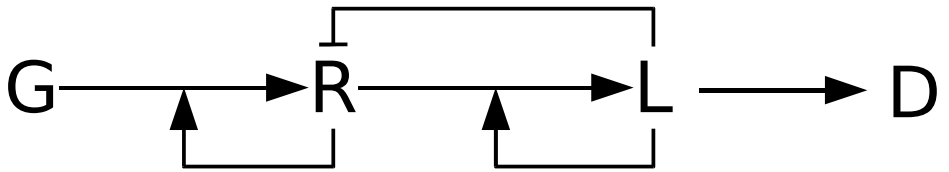
Stochastic approaches

- Stochastic master equation (McQuarrie 1964)
  - ~ grand probability function. Generally intractable
- Gillespie method (Gillespie 1976)
  - Reaction-based stochastic algorithm. No representation of individual particles. « Fast »
- particle-based methods. E.g. StochSim (Morton-Firth *et al*. 1998)
  - Molecule-based stochastic algorithm. individual particles are represented. Slow ...

A simple oscillating system



A simple oscillating system



Lotka, A.J. 1925. Elements of physical biology.
Williams and Wilkins, Baltimore, M.D.

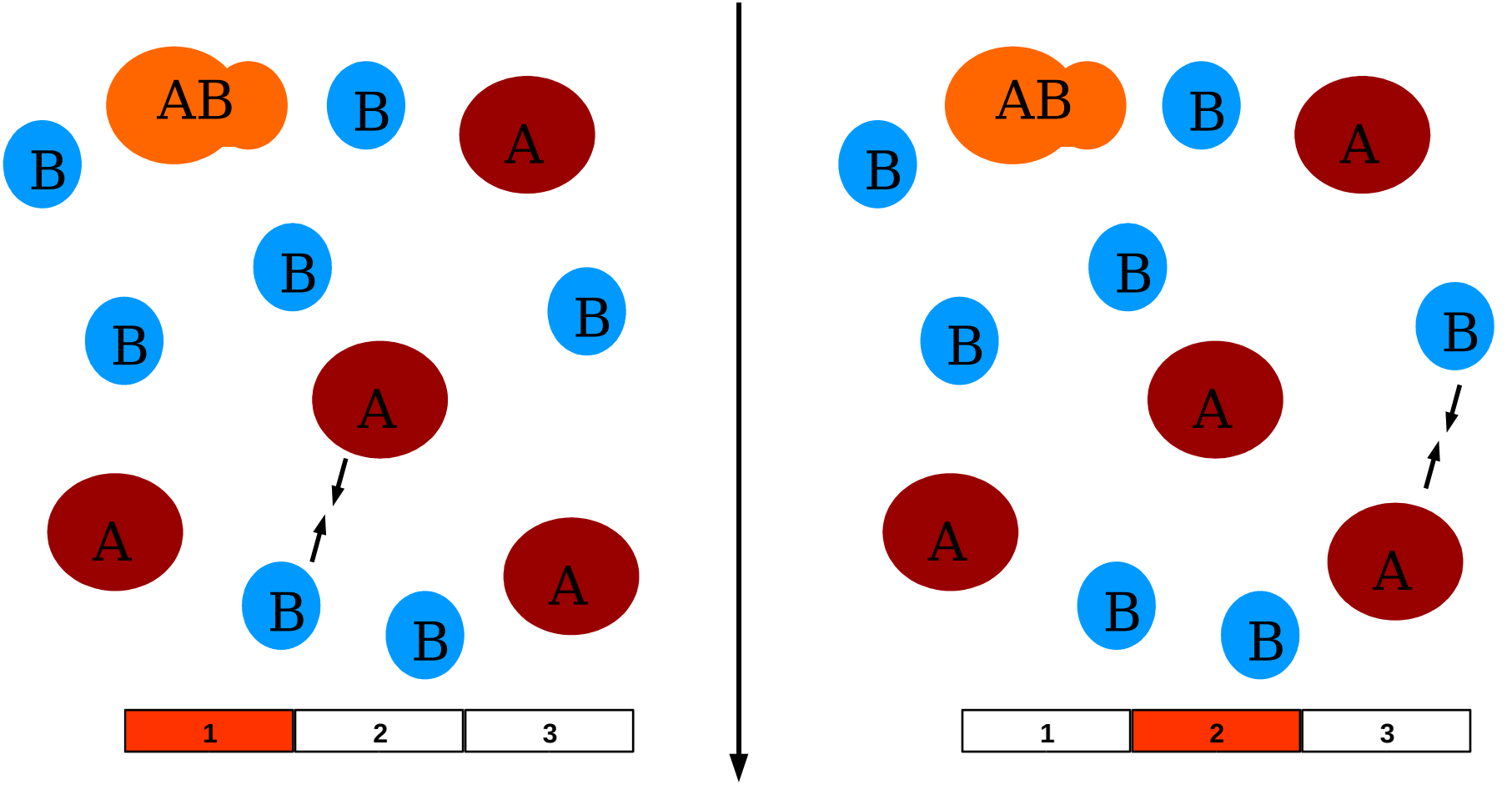
Volterra, V. 1926. "Fluctuations in the Abundance of a Species Considered Mathematically," Nature 118, 558-560.

Predator-Prey model:
G = Grass
R = Rabbit (Snowshoe Hare)
L = Lynx
D = Death

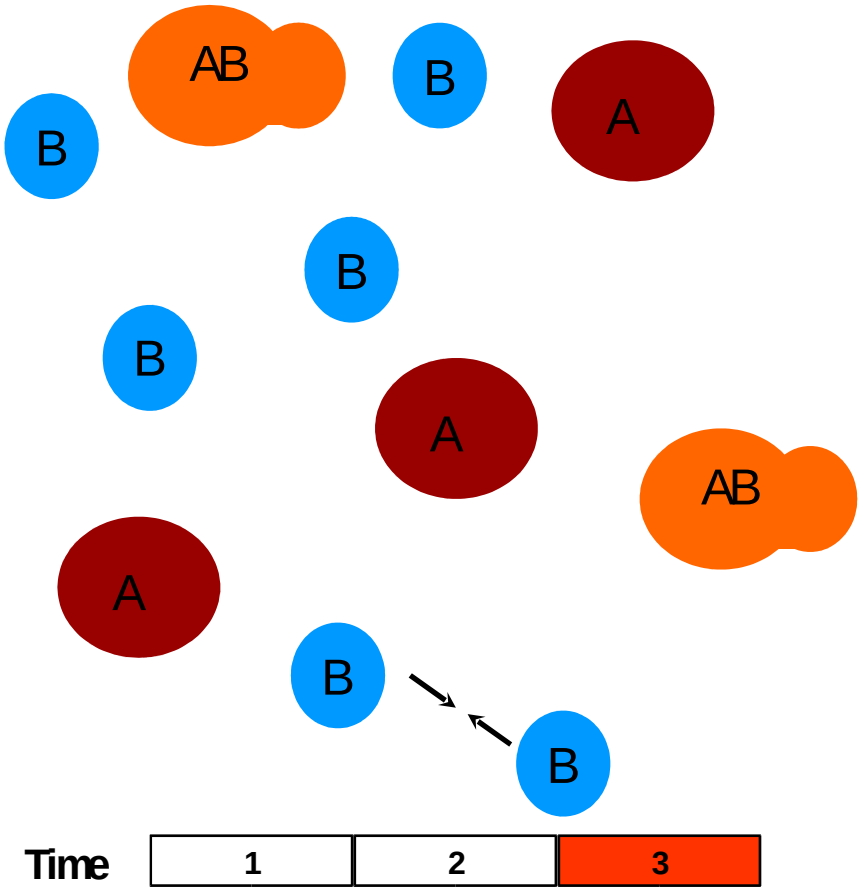
Carl Firth, Tom Shimizu,
Nicolas Le Novère, Dennis Bray

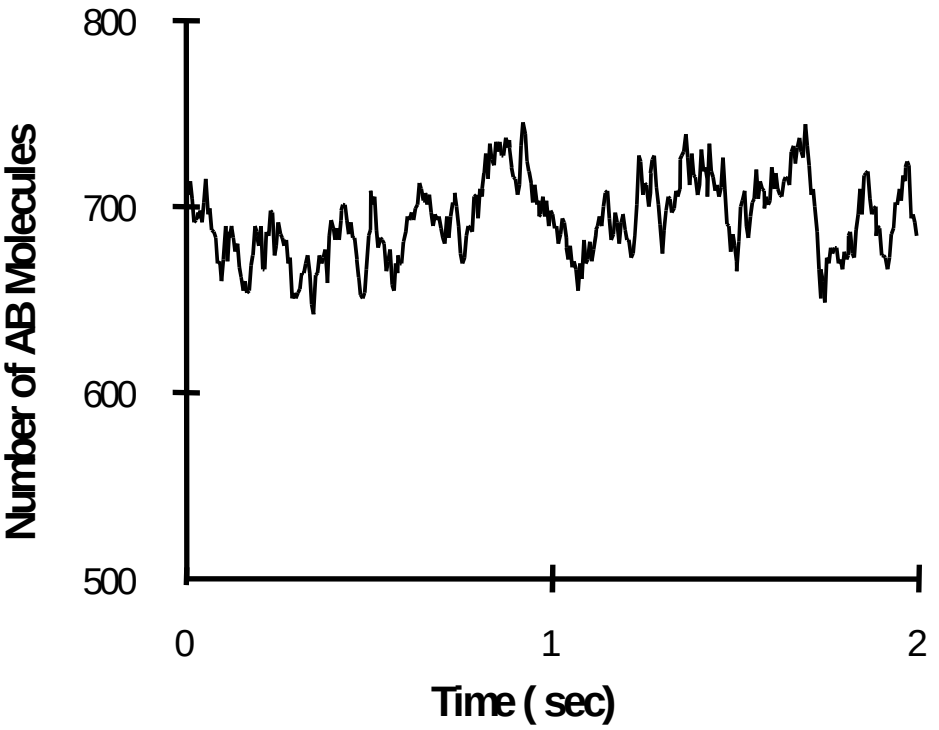
http://www.anat.cam.ac.uk/
~comp-cell/StochSim.html

StochSim algorithm



StochSim algorithm





Kinetic constant to probability

$$d[R]/dt = k1[G][R]$$

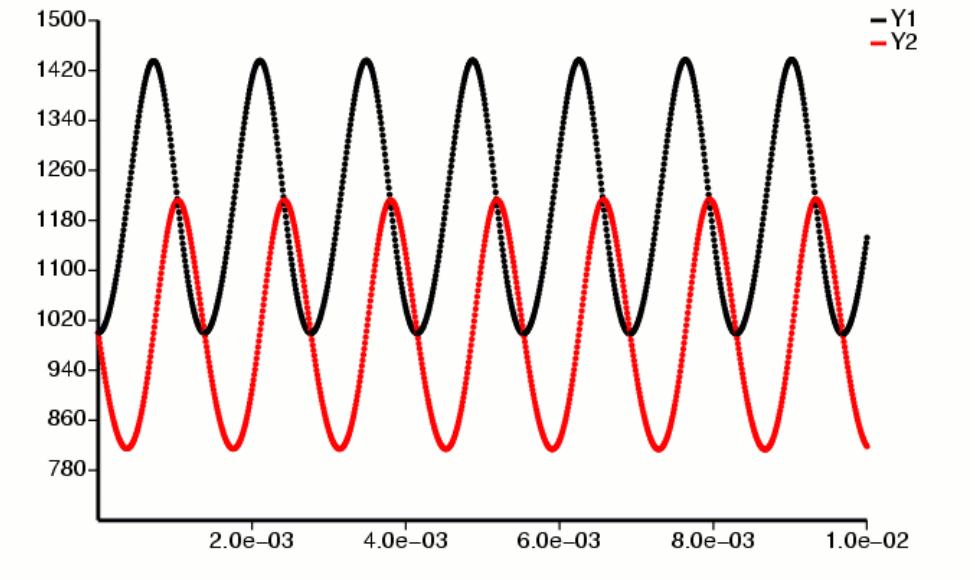
$$P1 = \frac{k1\ n(n+n_0)\Delta t}{2VN_A}$$

$$d[L]/dt = -k3[L]$$

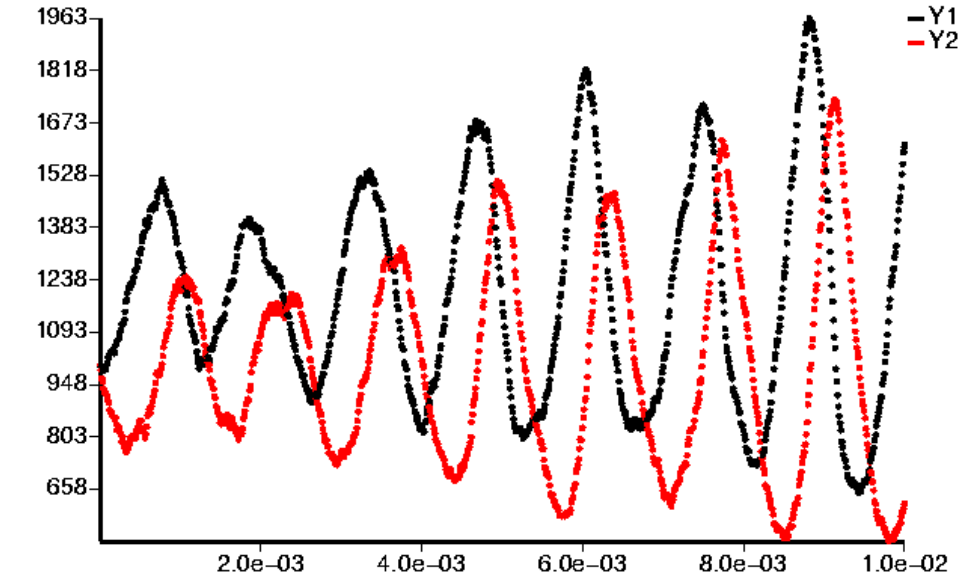
$$P3 = \frac{k3\ n(n+n_0)\Delta t}{n_0}$$

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

A simple oscillating system

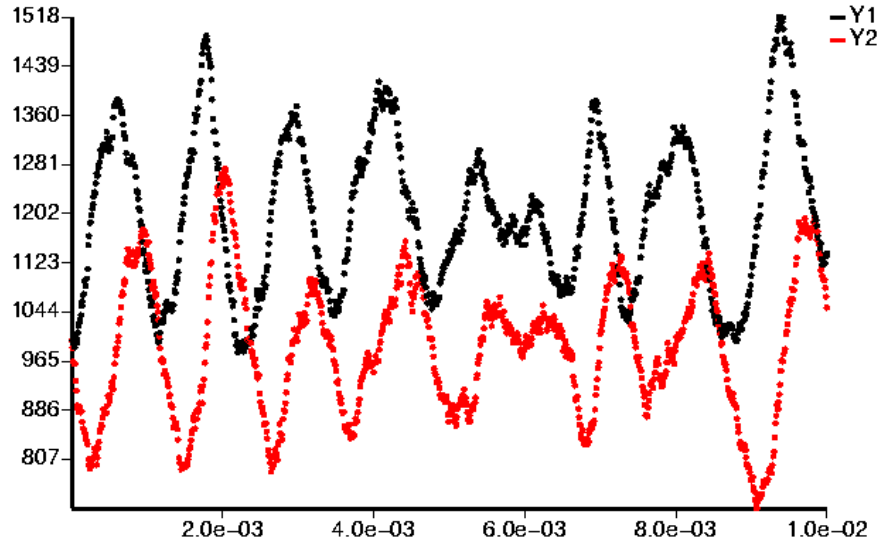


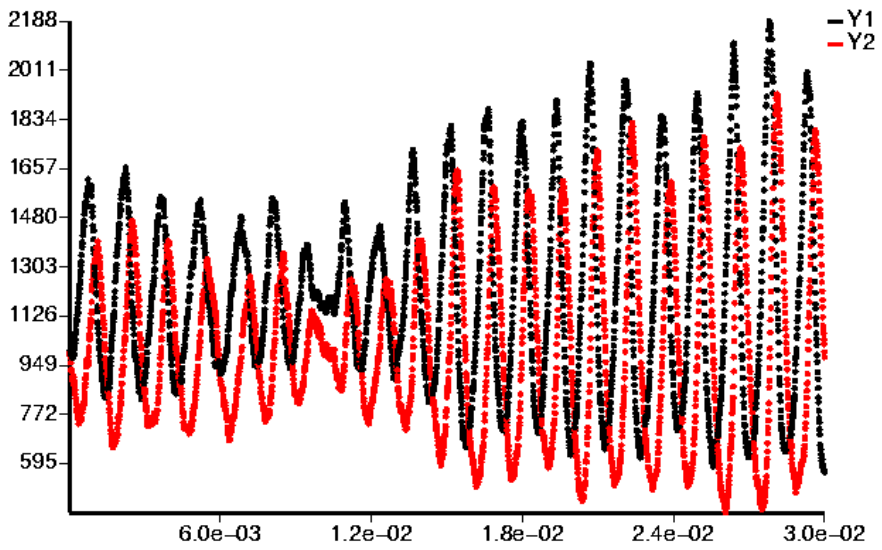
deterministic result

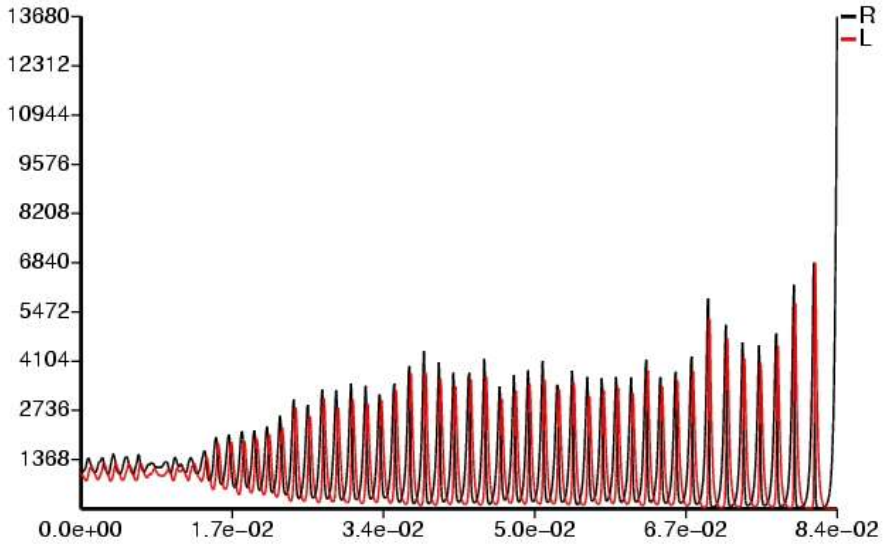


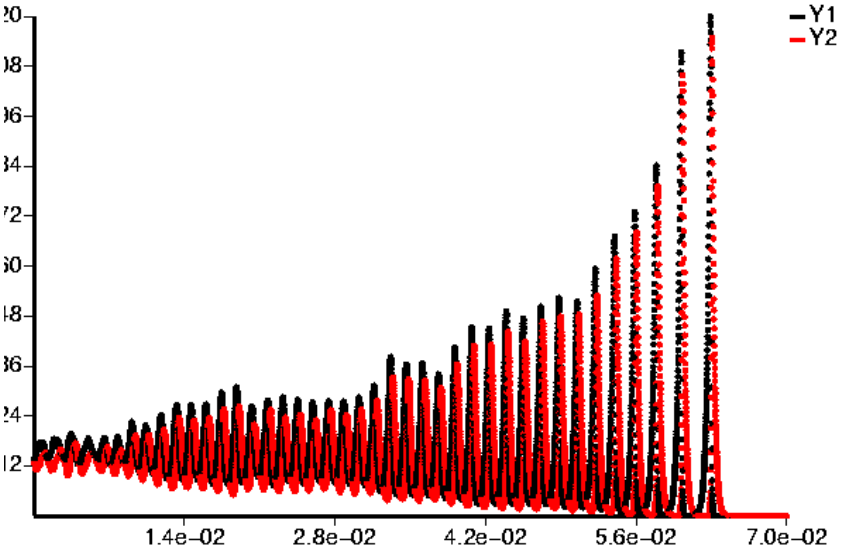
stochastic result

Pathological situations



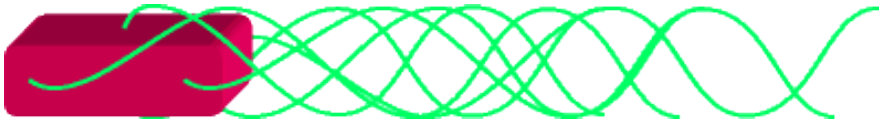




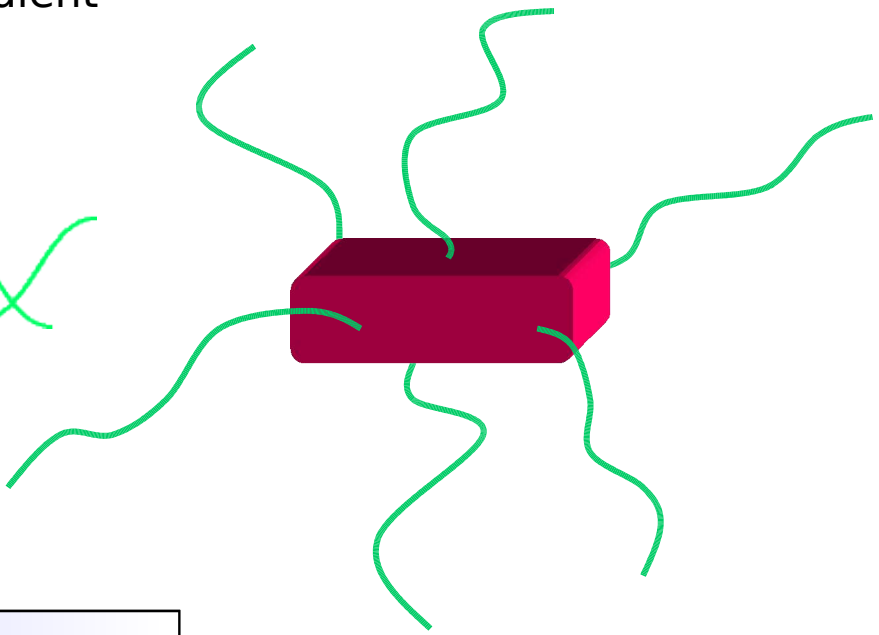


Mechanism of bacterial chemotaxis

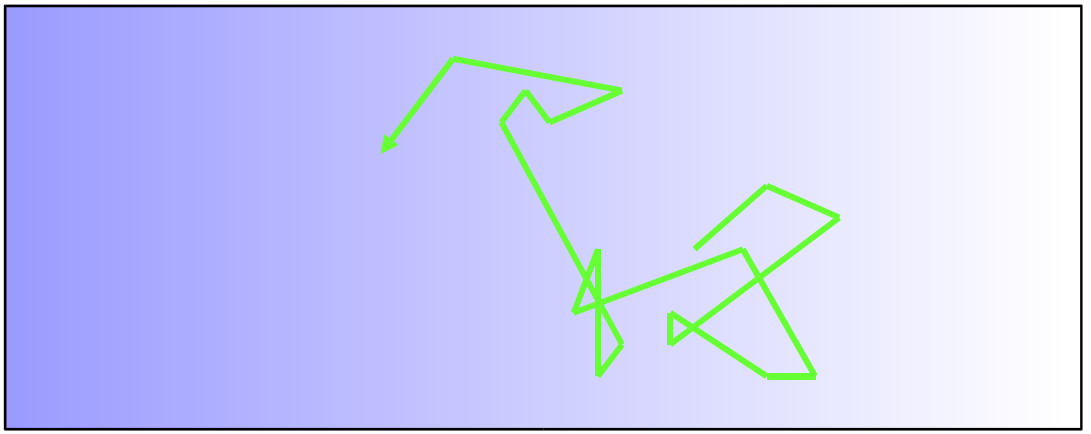
- small size ⇒ unable to read gradient
- small weight ⇒ no inertia



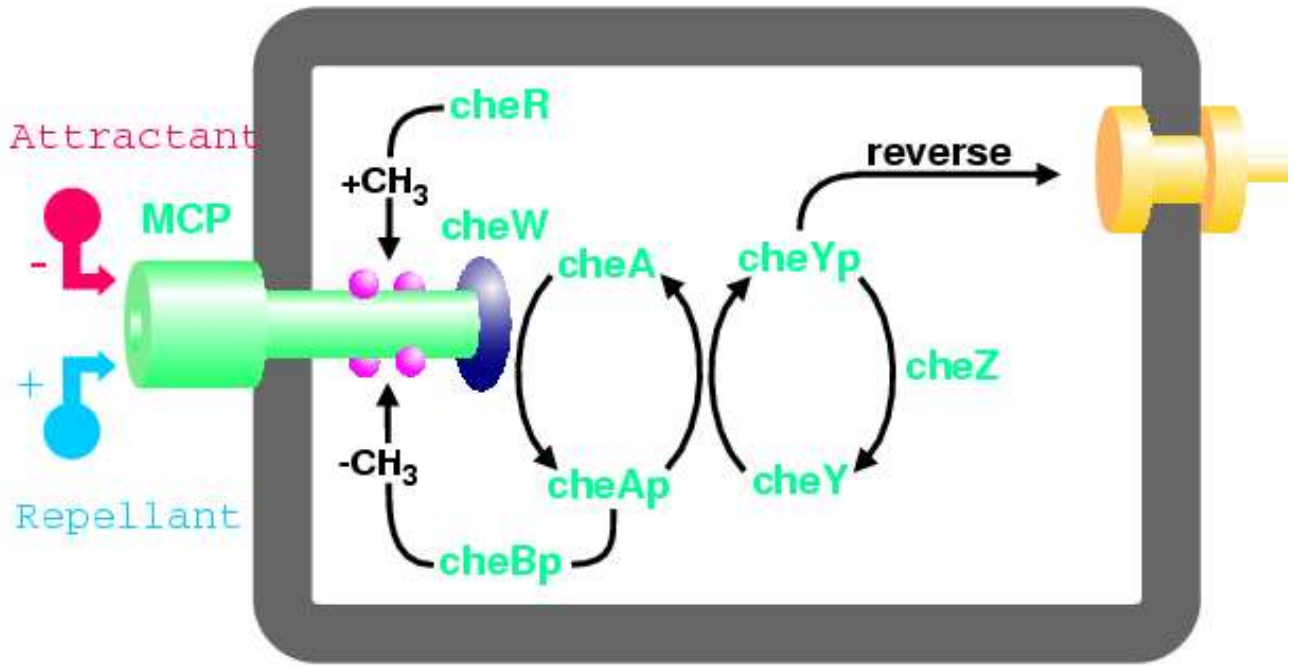
CCW = smooth

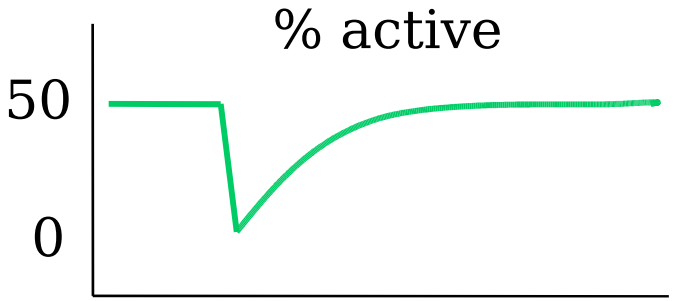


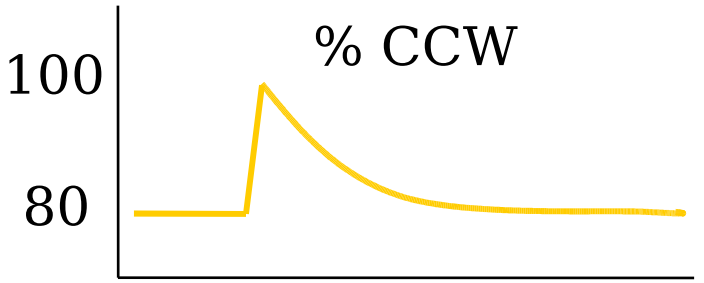
CW = tumble



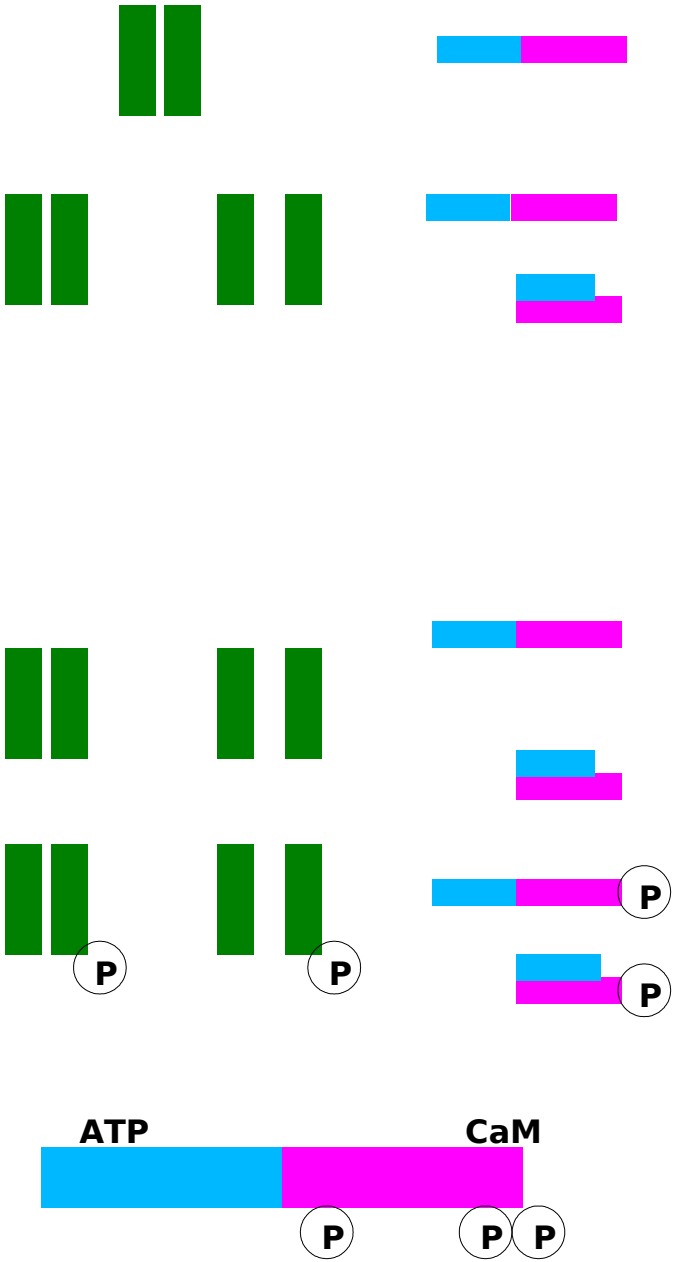
Mechanism of bacterial chemotaxis







Combinatorial explosion



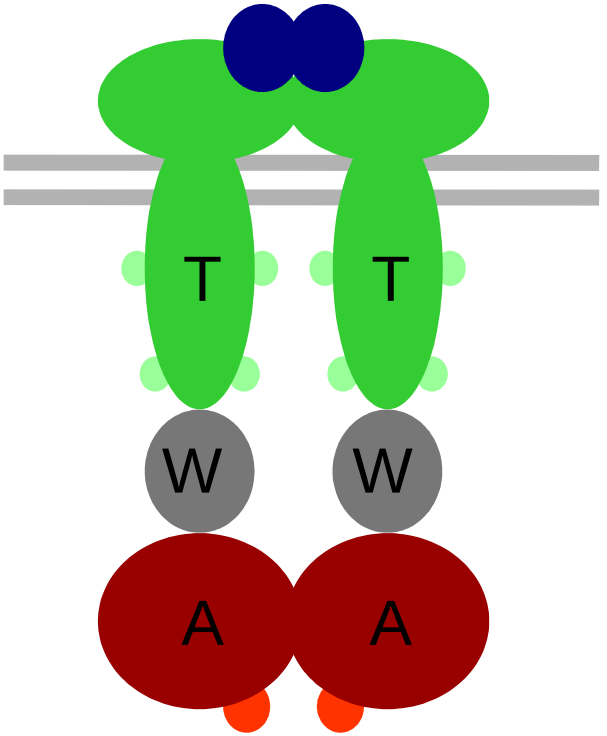
NMDA + CaMKII <=> NMDA-CaMKII

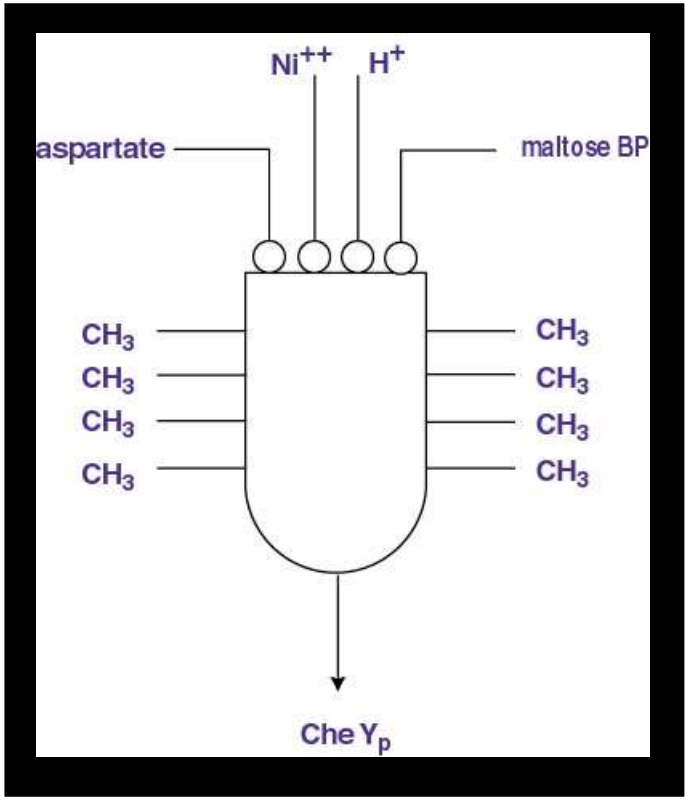
NMDAc + CaMKIIc <=> NMDAc-CaMKIIc
NMDAo + CaMKIIc <=> NMDAc-CaMKIIc
NMDAc + CaMKIIo <=> NMDAc-CaMKIIo
NMDAo + CaMKIIo <=> NMDAc-CaMKIIo

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

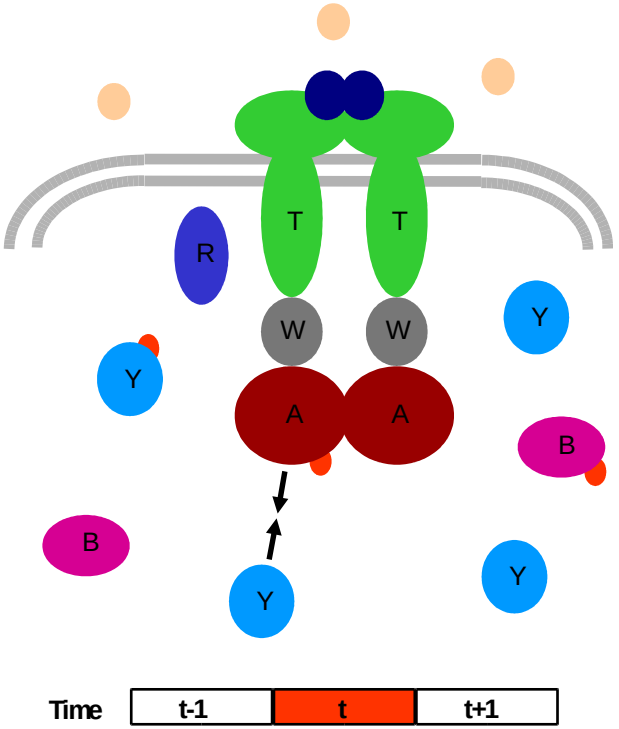
Internal states represented by binary flags





Multistate reactions

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



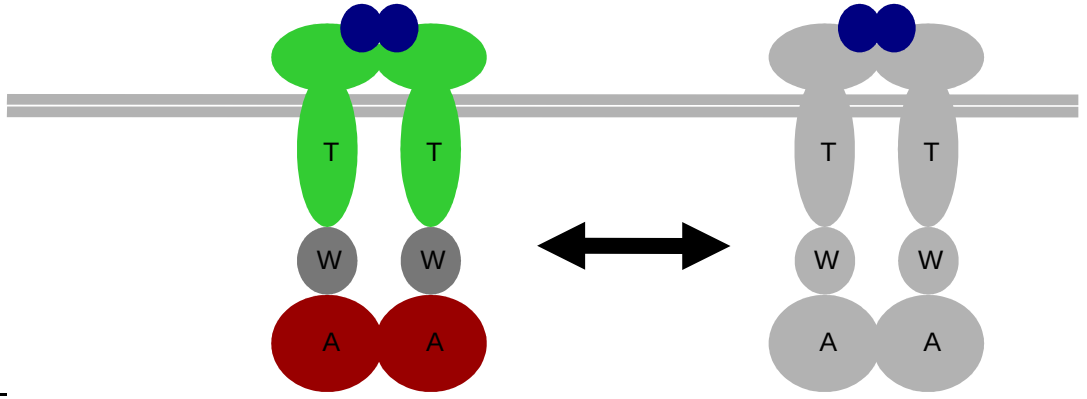
$$p_{MS} = p_{base} \times p_{rel}$$

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

Multistate 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'.

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



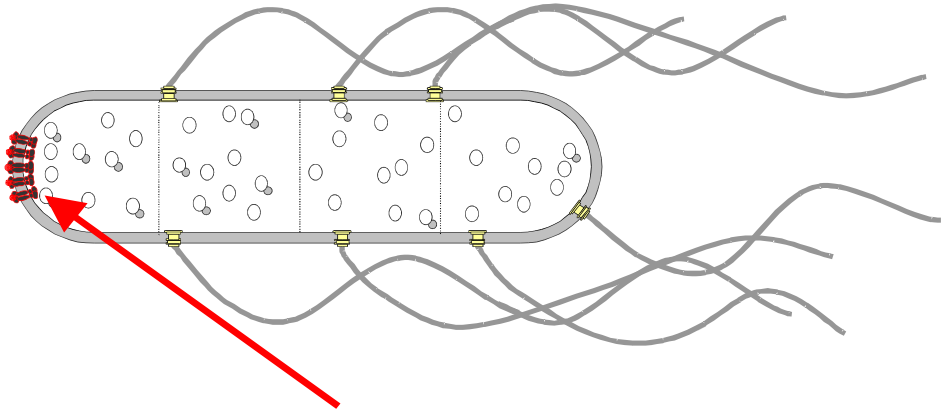
p_{set} p_{clr}

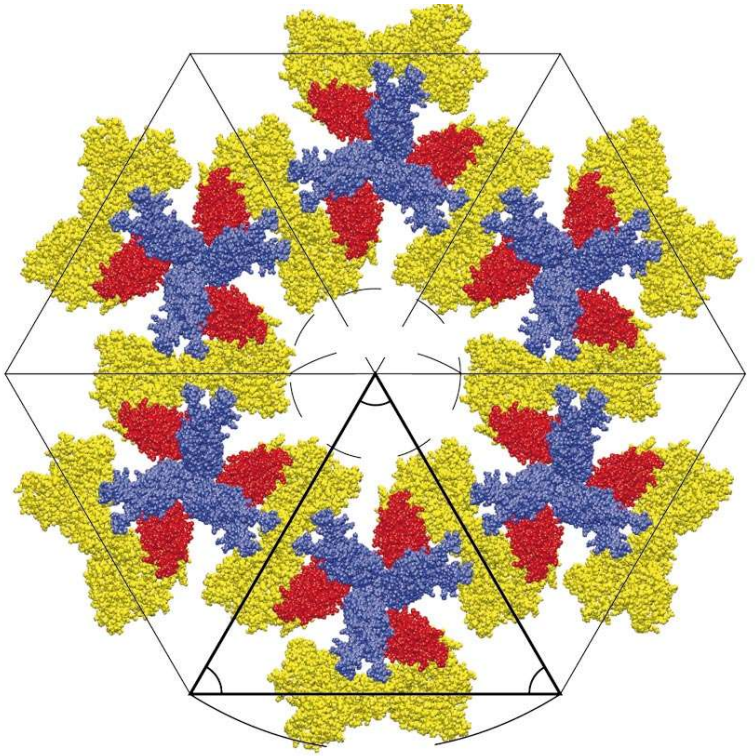
Free-energy based activation probabilities

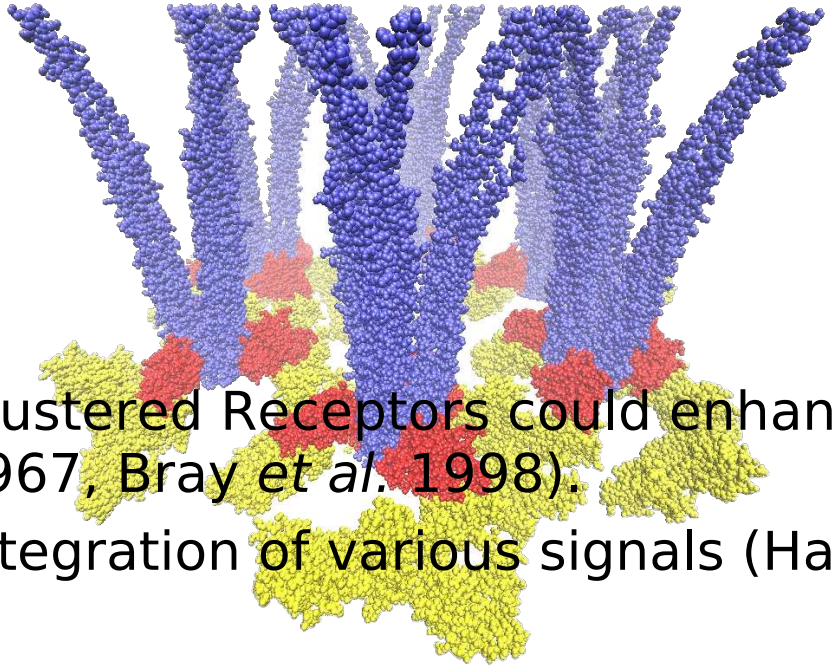
Non-ligand bound			Ligand bound		
Species	p	ΔG (kcal/mol)	Species	p	ΔG (kcal/mol)
	0.017	2.37		0.003	3.55
	0.125	1.18		0.017	2.37
	0.500	0.00		0.125	1.18
	0.874	1.18		0.500	0.00
	0.997	3.55		0.980	2.37

Receptor clustering and sensitivity

Chemotactic receptors form clusters at cell poles in E. coli. (Maddock and Shapiro 1993, Shimizu, Le Novère et al 2000).







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

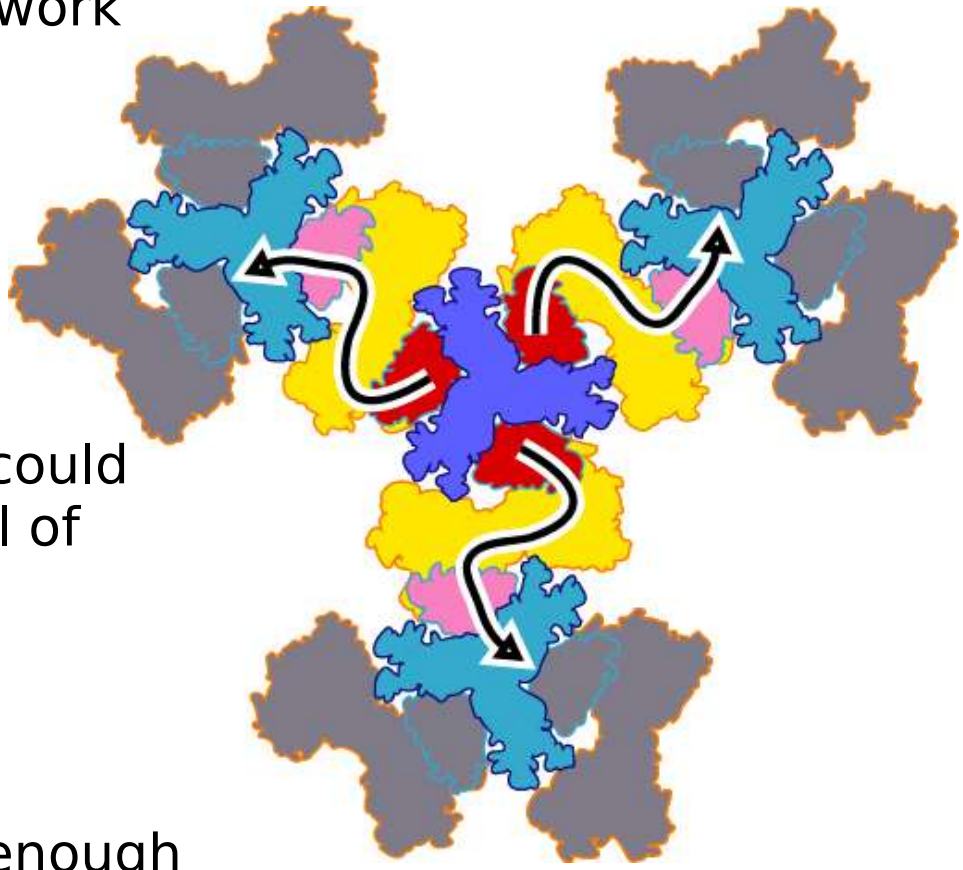
Integration of various signals (Hazelbauer et al. 1989).

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

Consequences for signalling

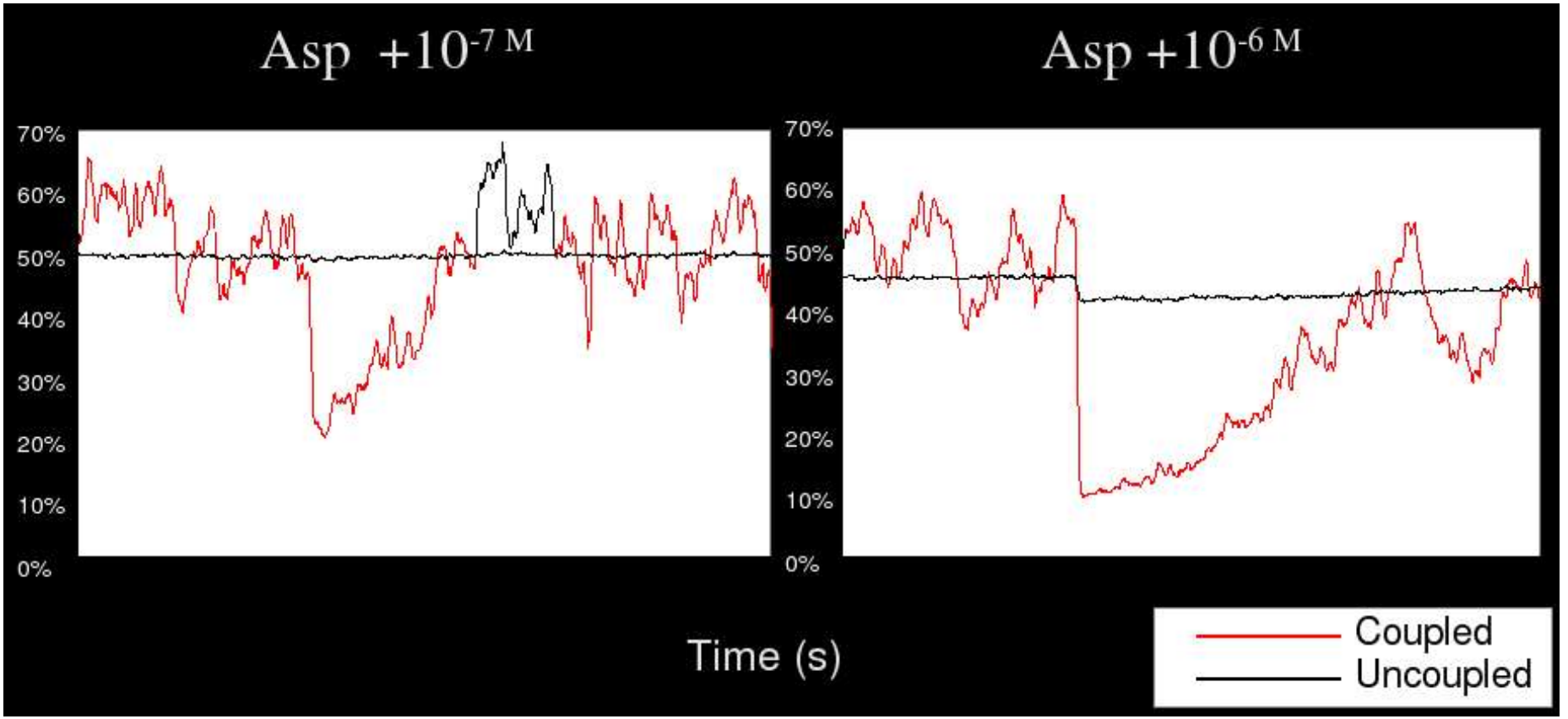
- Conformational changes could be propagated through the network via CheA/CheW
  ⇒Enhanced gain;



- Hybrid networks containing multiple types of receptors could integrate signals at the level of CheA activity;

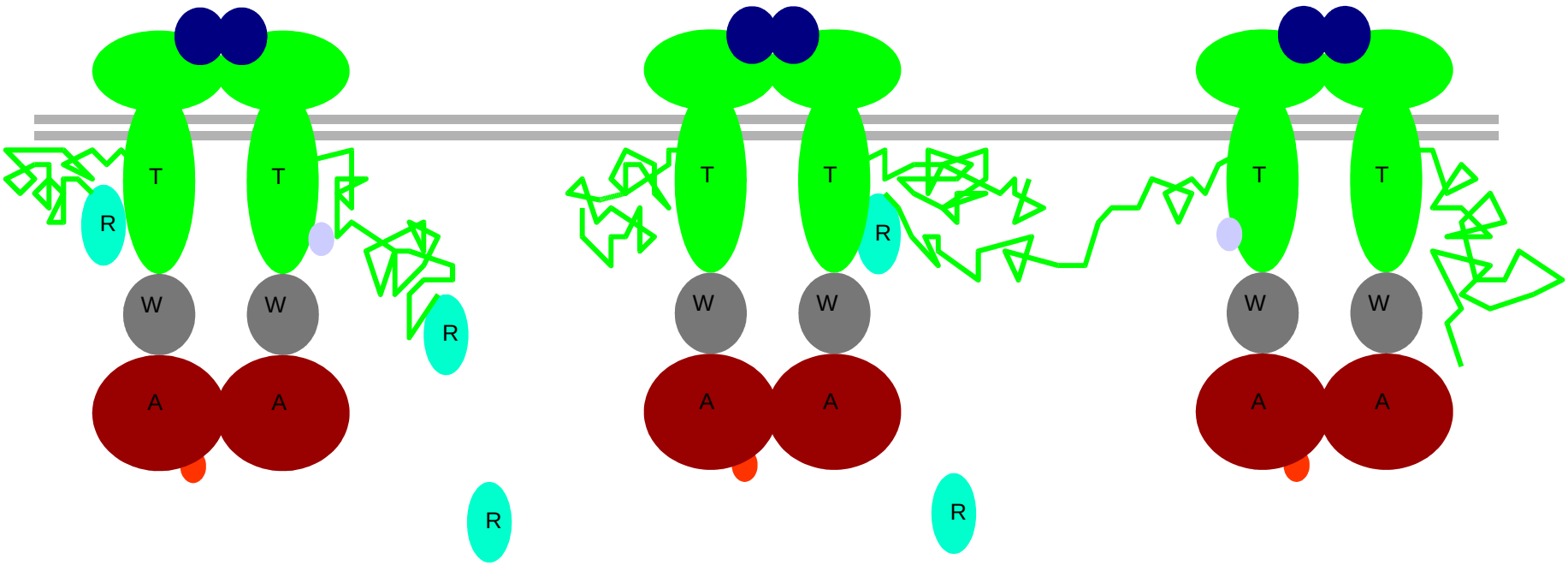
- Receptor dimers are close enough (6-10 nm) for adaptational cross-talk.

Gain

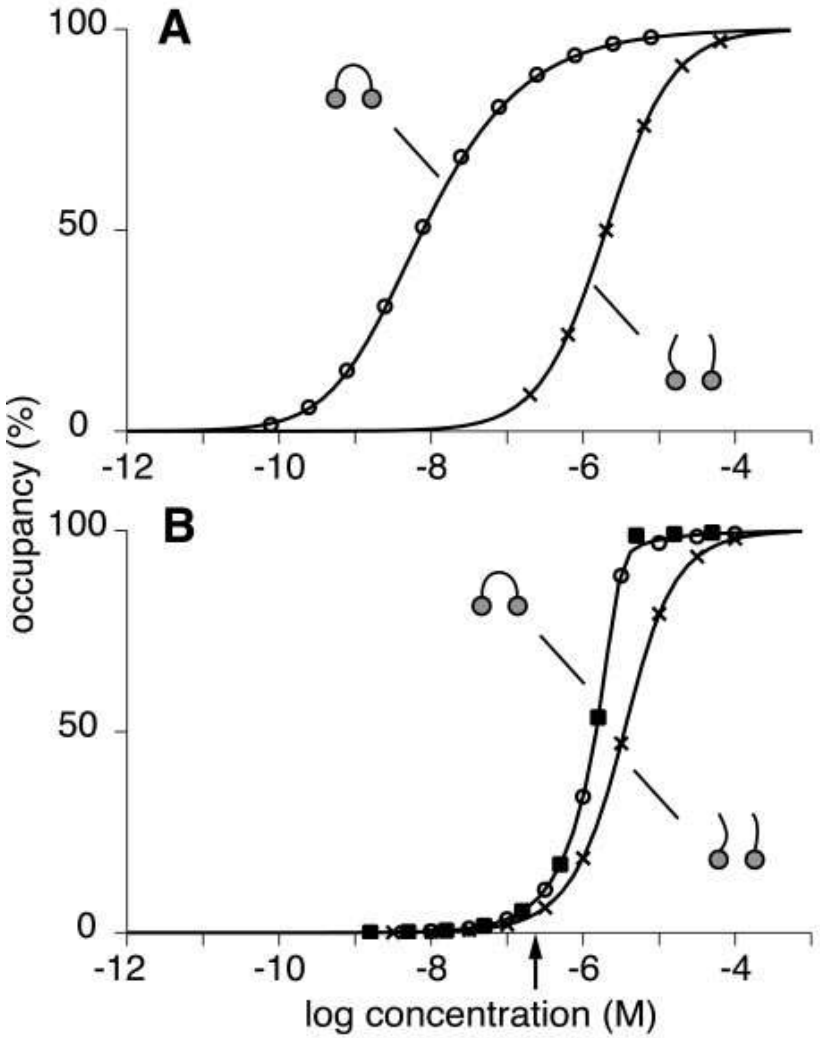

Asp +10-7 M
Asp +10-6 M
70%
60%
50%
40%
30%
20%
10%
0%
Change in signal
Time (s)
Coupled
Uncoupled

Molecular brachiation

Interaction between receptors and CheR (methyltransferase)



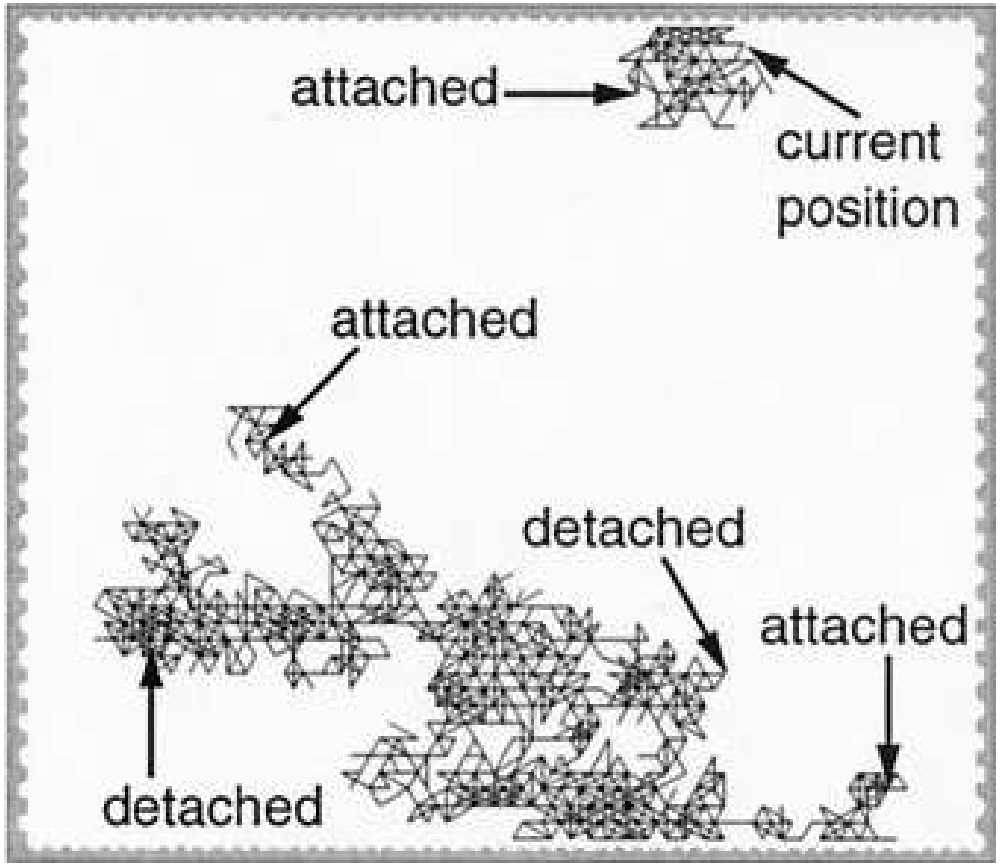
Effective Kd



Excess brachiating molecule

Limiting brachiating molecule

Segregation by affinity



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

CheR molecules are trapped into the receptor lattice.

Netscape: Lattice of chemotactic receptors

rxvt <2>

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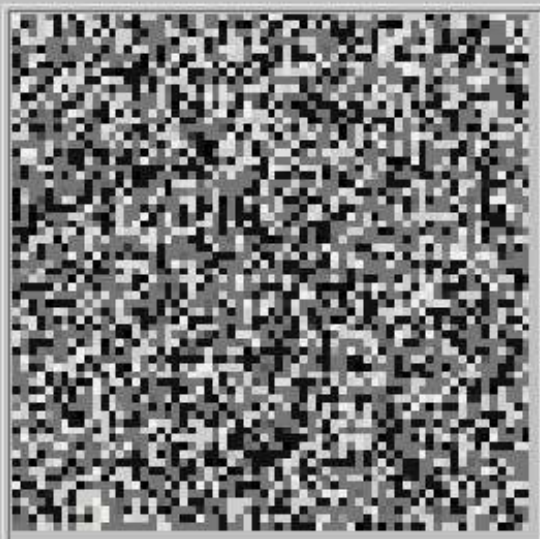
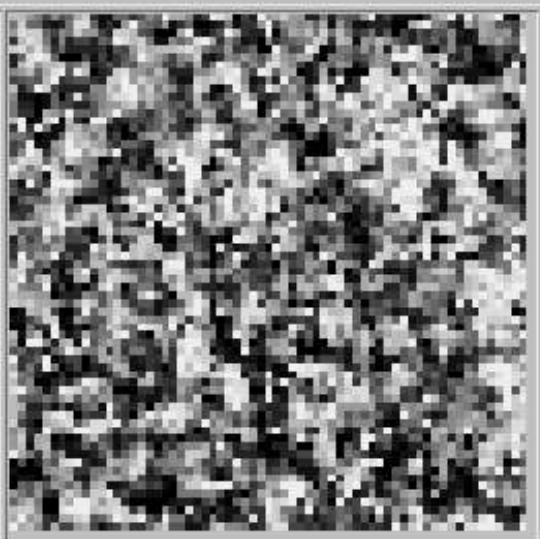
Bookmarks Location: file:/home/lenov/MEETINGS/VicAnne/chemotaxis/chemotaxis.html What's Related

Modelisation of a lattice of chemotactic receptors



Non coupled receptors



Coupled receptors

Next

Nicolas Le Novère

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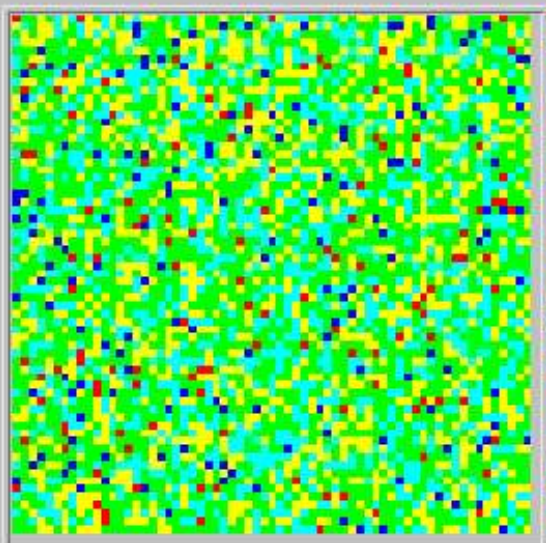
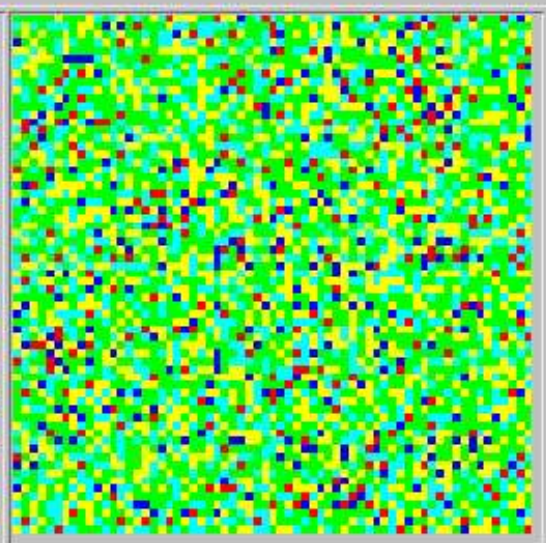
Modelisation of a lattice of chemotactic receptors



Non coupled receptors



Coupled receptors

Next

Nicolas Le Novère
Last modified: Wed Jan 19 16:00:01 GMT 2005

Netscape: Lattice of chemotactic receptors

rxvt <2>

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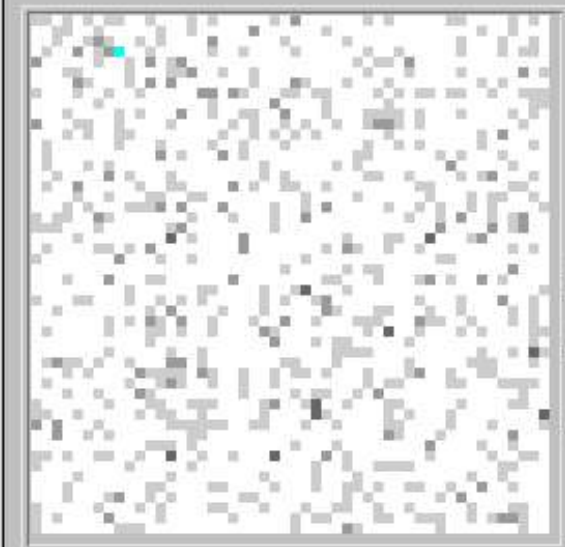
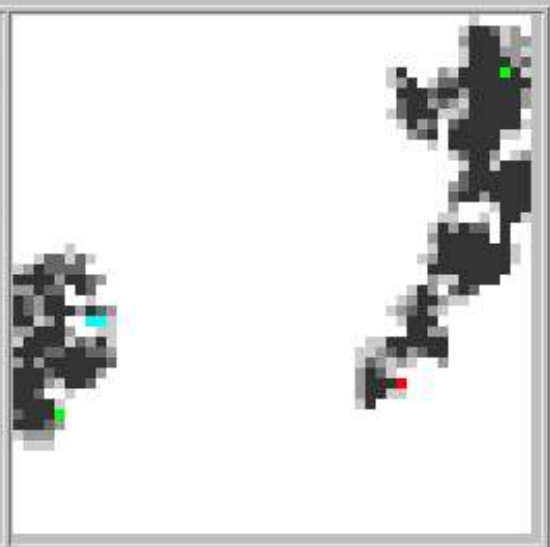
Bookmarks Location: file:/home/lenov/MEETINGS/VicAnne/chemotaxis/chemotaxis3.html What's Related

Modelisation of a lattice of chemotactic receptors



Single site



Twin sites

Nicolas Le Novère

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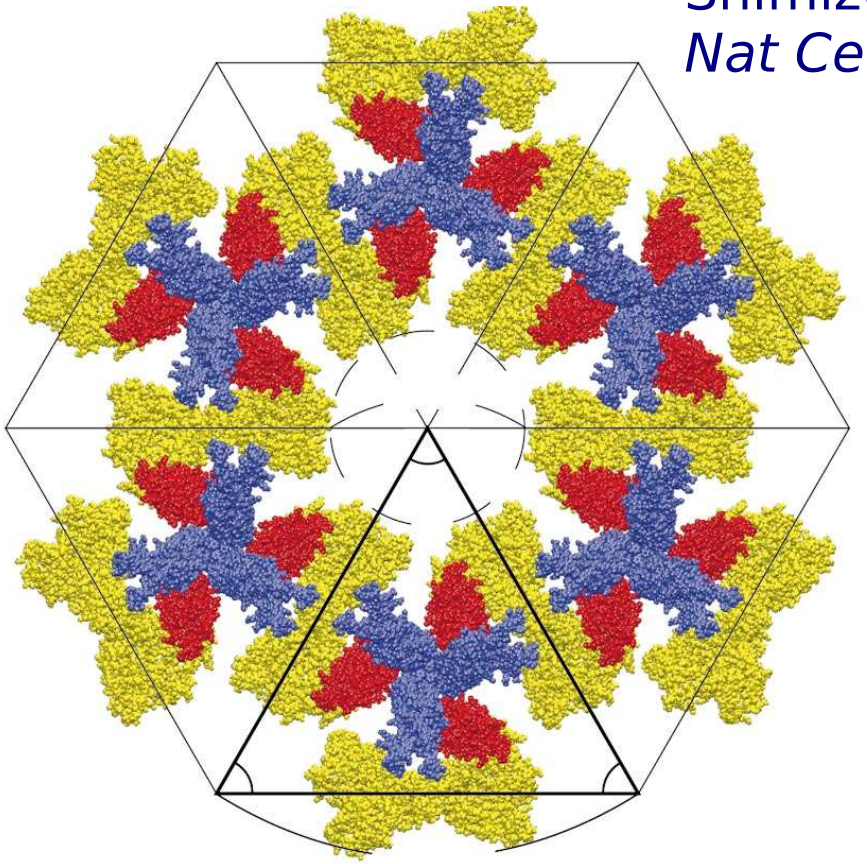
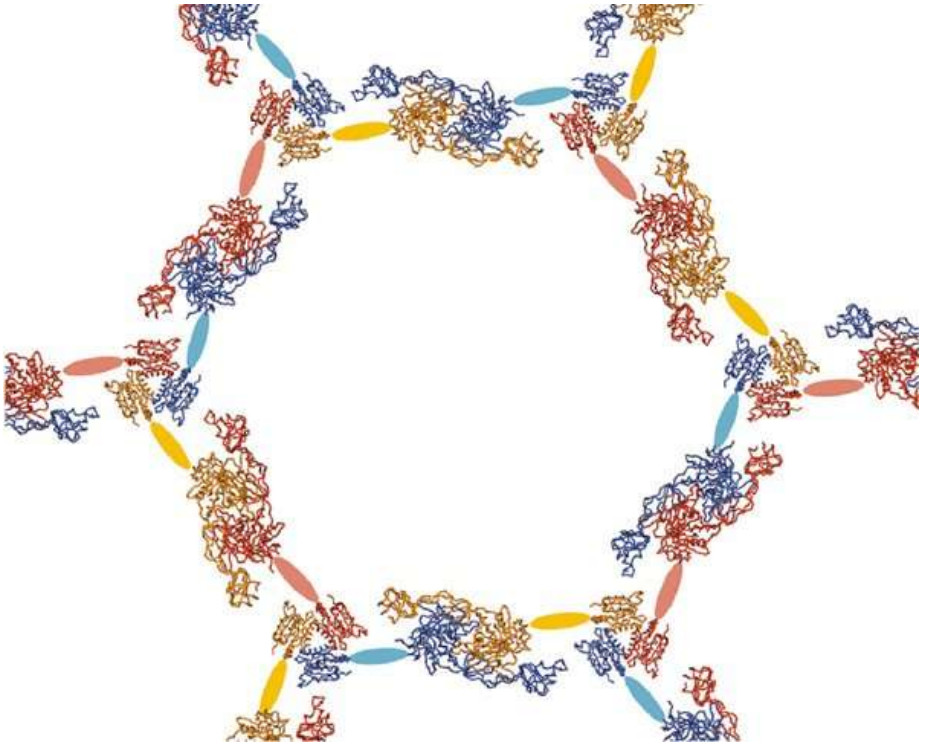
Document: Done.

Alright, but what about Neurobiology

Shimizu, Le Novère et al (2000)
Nat Cell Biol, 2:792-796



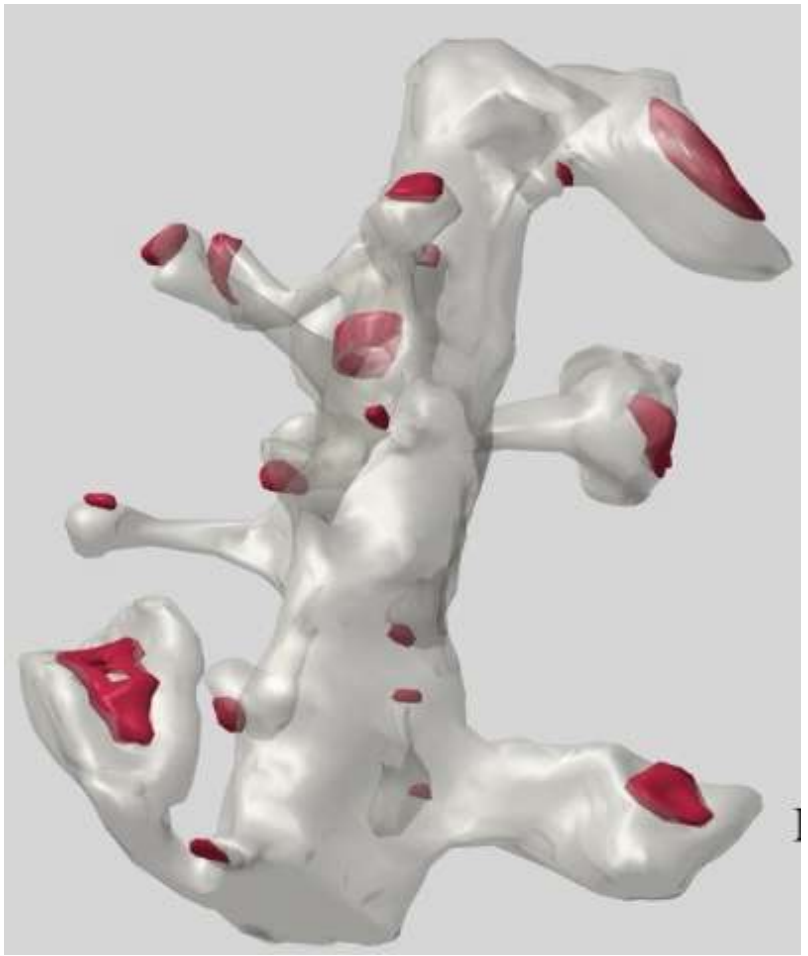


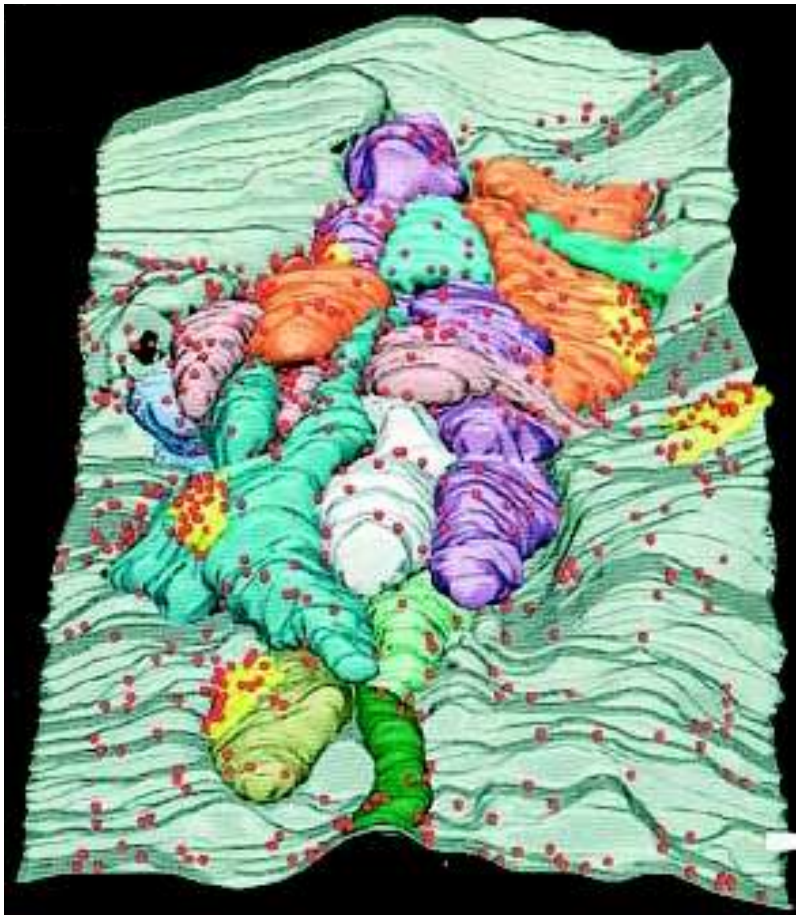
Kneussel & Betz (2000) *Trends Neurosci*, 9: 429-435

Sol et al (2004) *EMBO J*, 23: 2510-2519

Complexité structurale

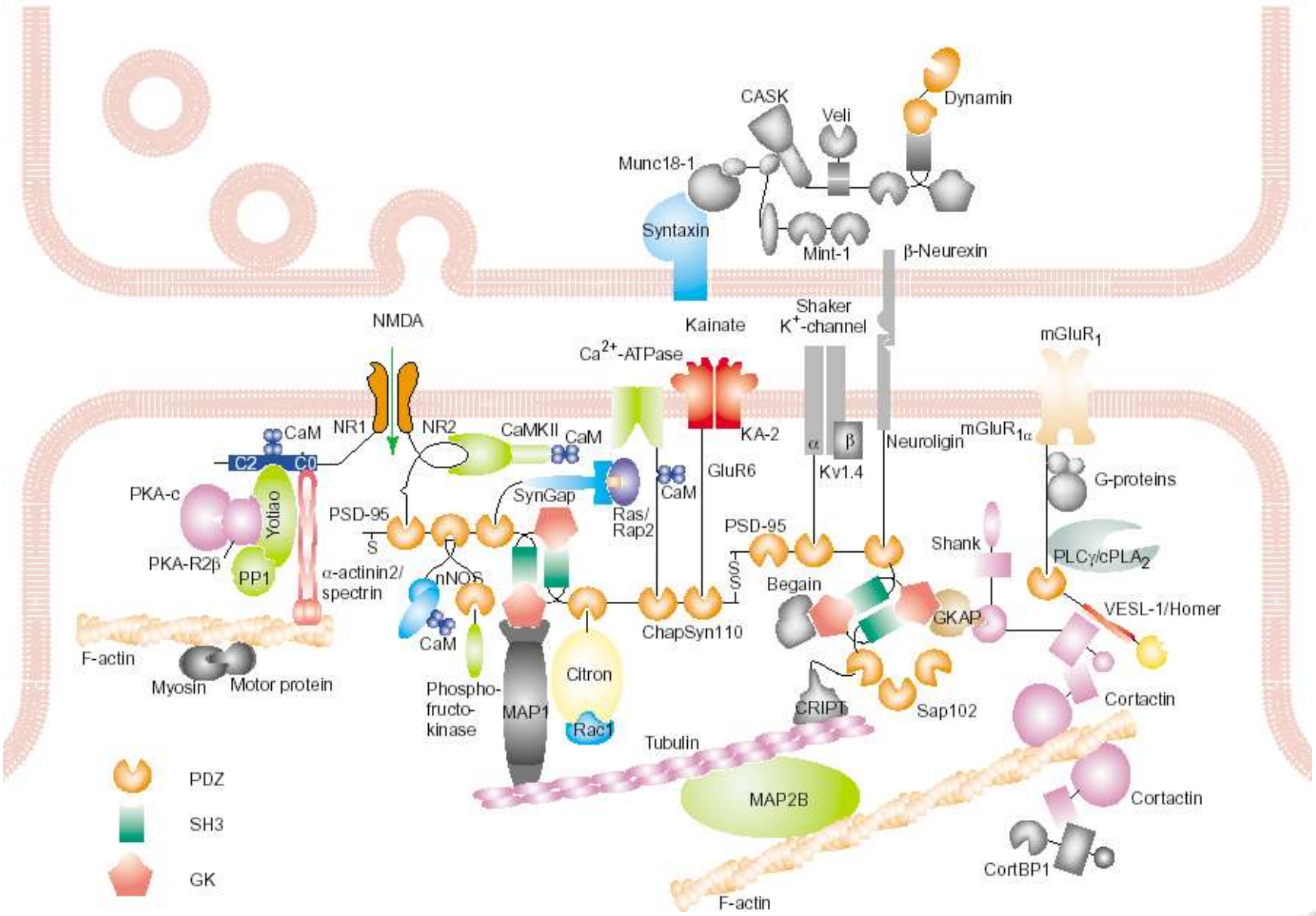
Atlas of Ultrastructural Neurocytology
http://synapses.mcg.edu/atlas/eurosci



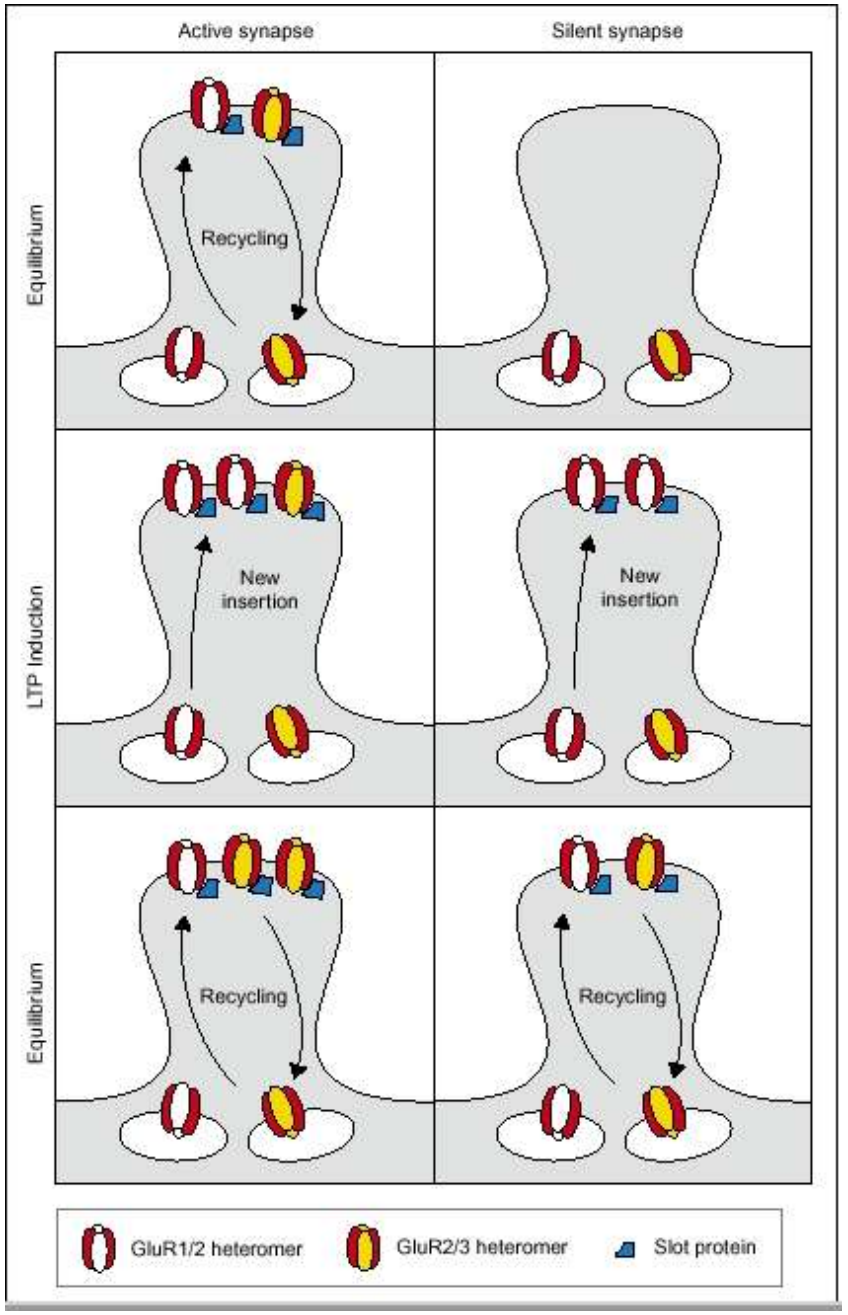


Shoop et al. (2002)
J Neurosci, 22: 748-756

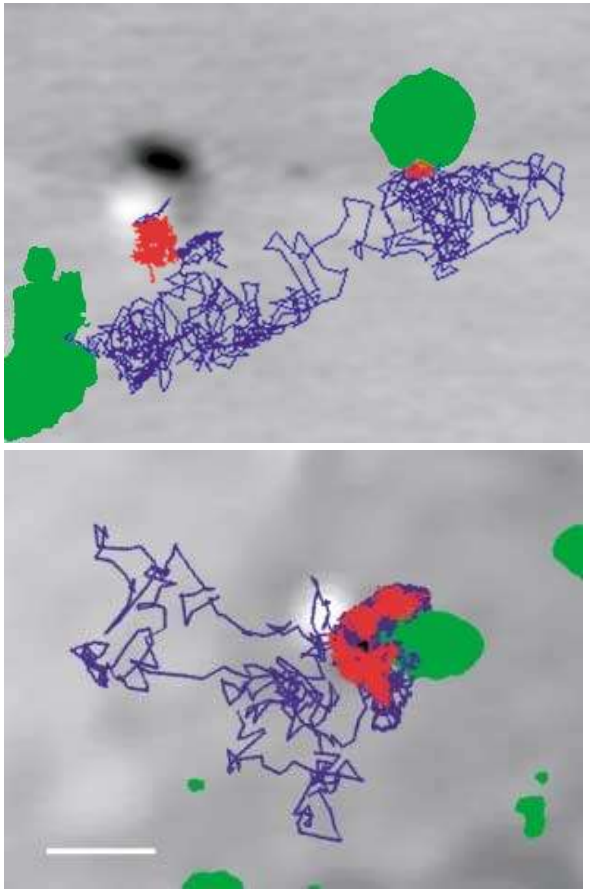
Complex post-synaptic machinery



Complexité temporelle



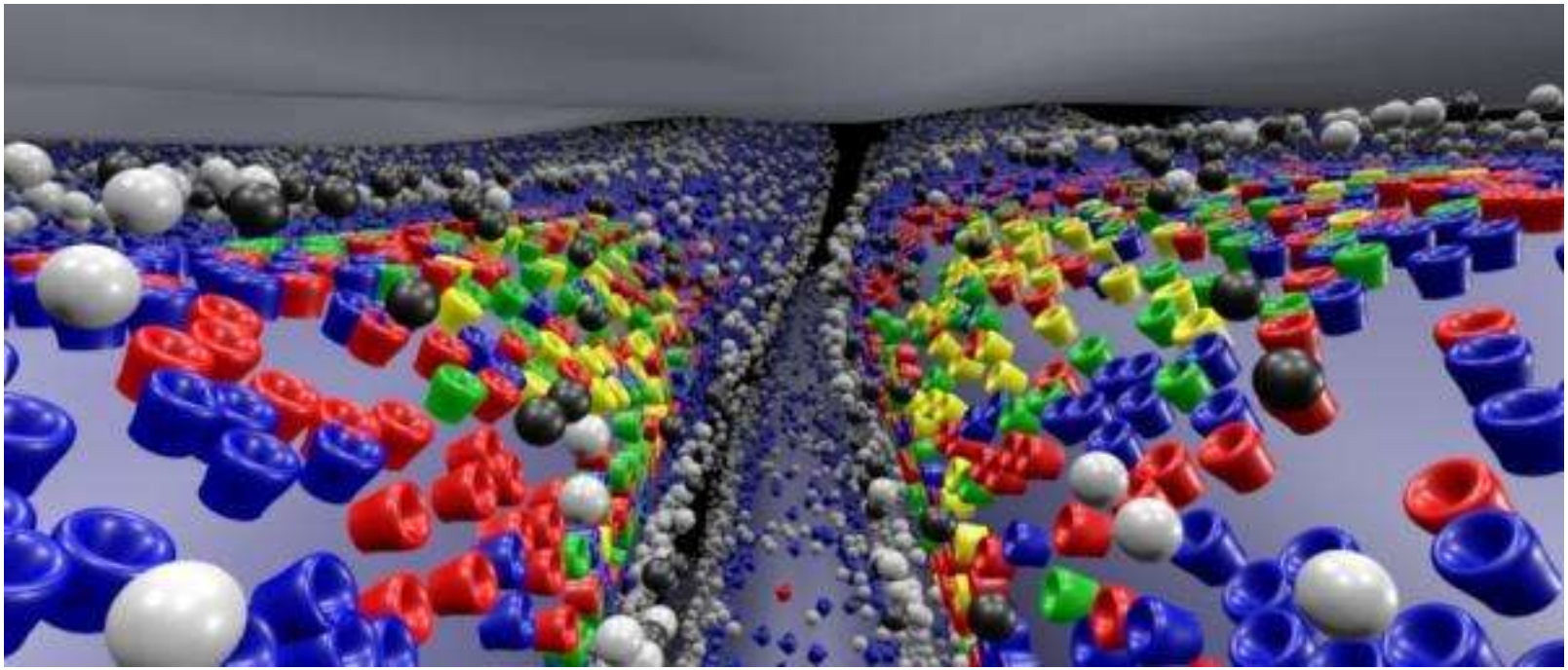
Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279-286



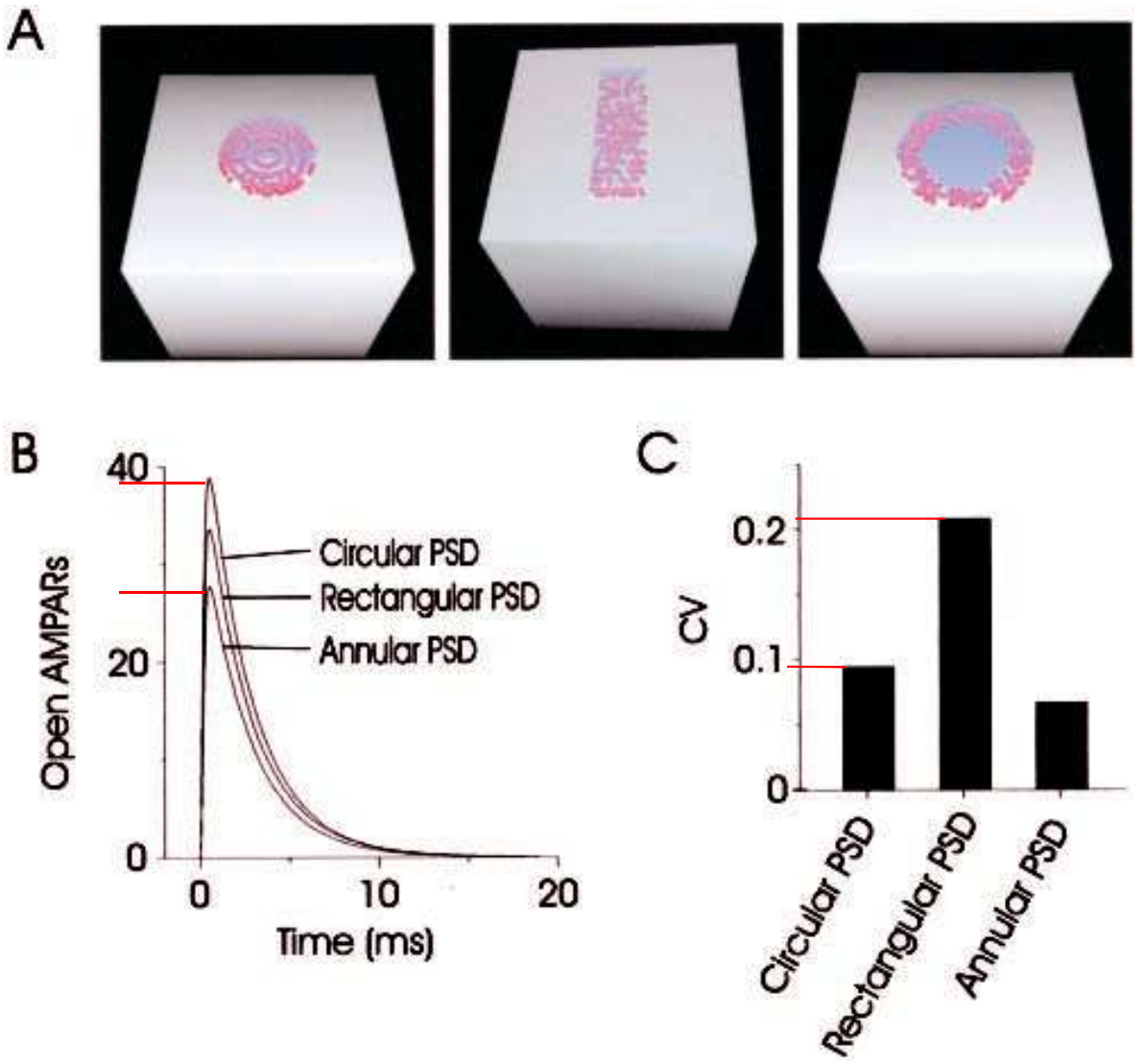
Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

Thomas Bartol, Joel Stiles

http://www.mcell2.cnl.salk.edu/

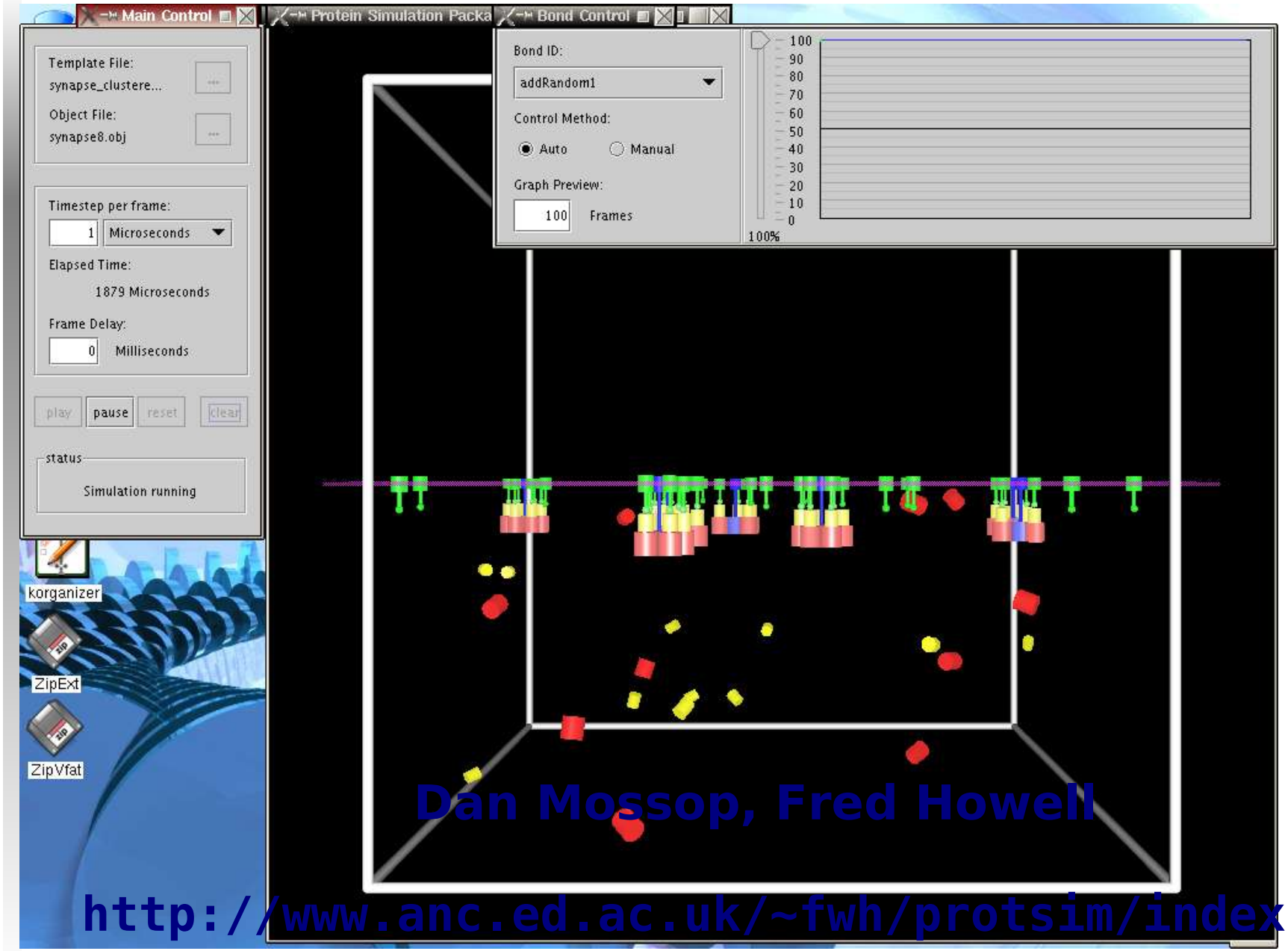


Position of receptors affects the signal



Franks et al. (2003) *J Neurosci*, 23: 3186-3195

Abstracted Protein Simulator

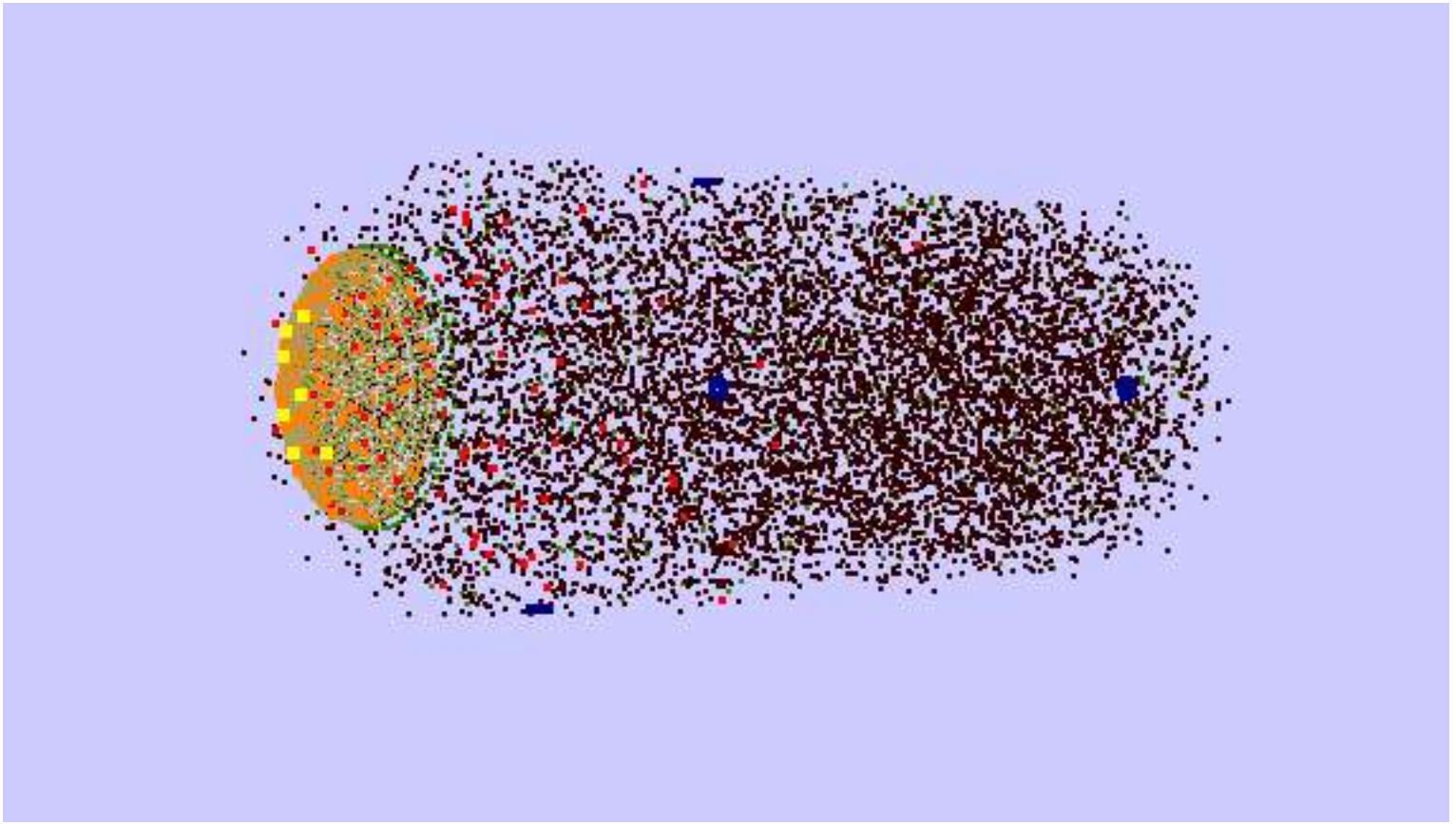


Dan Mossop, Fred Howell

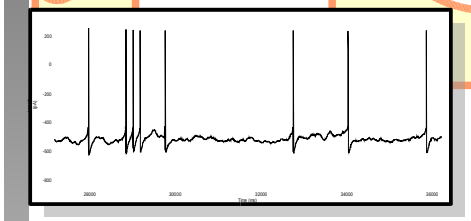
http://www.anc.ed.ac.uk/~fwh/protsim/index.php/

Steven Andrews, Dennis Bray

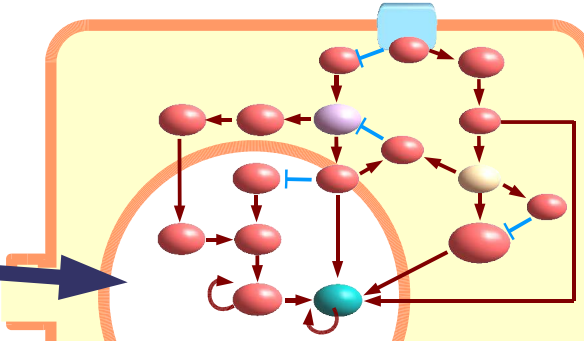
http://sahara.lbl.gov/~sandrews/software.html



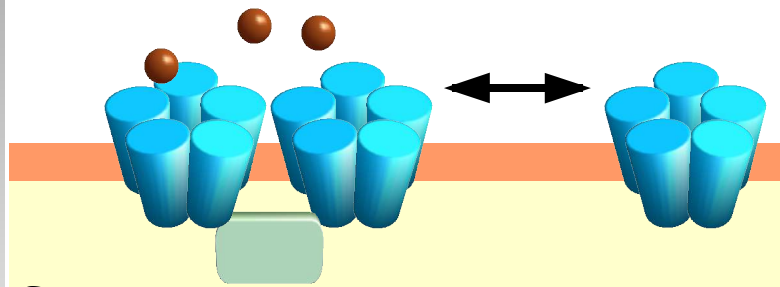
Need for modular multi-scale hyrid program



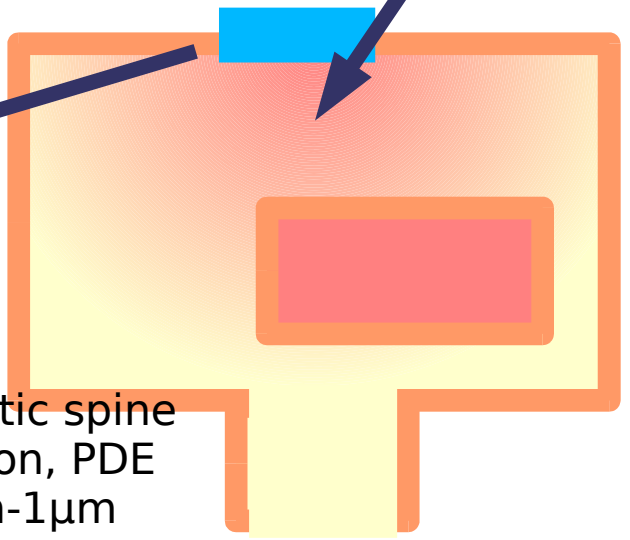
Whole-neuron
Cable theory
1µm-1m
1ms-1week



Signaling network
ODE
1µm-10µm
1s-1d

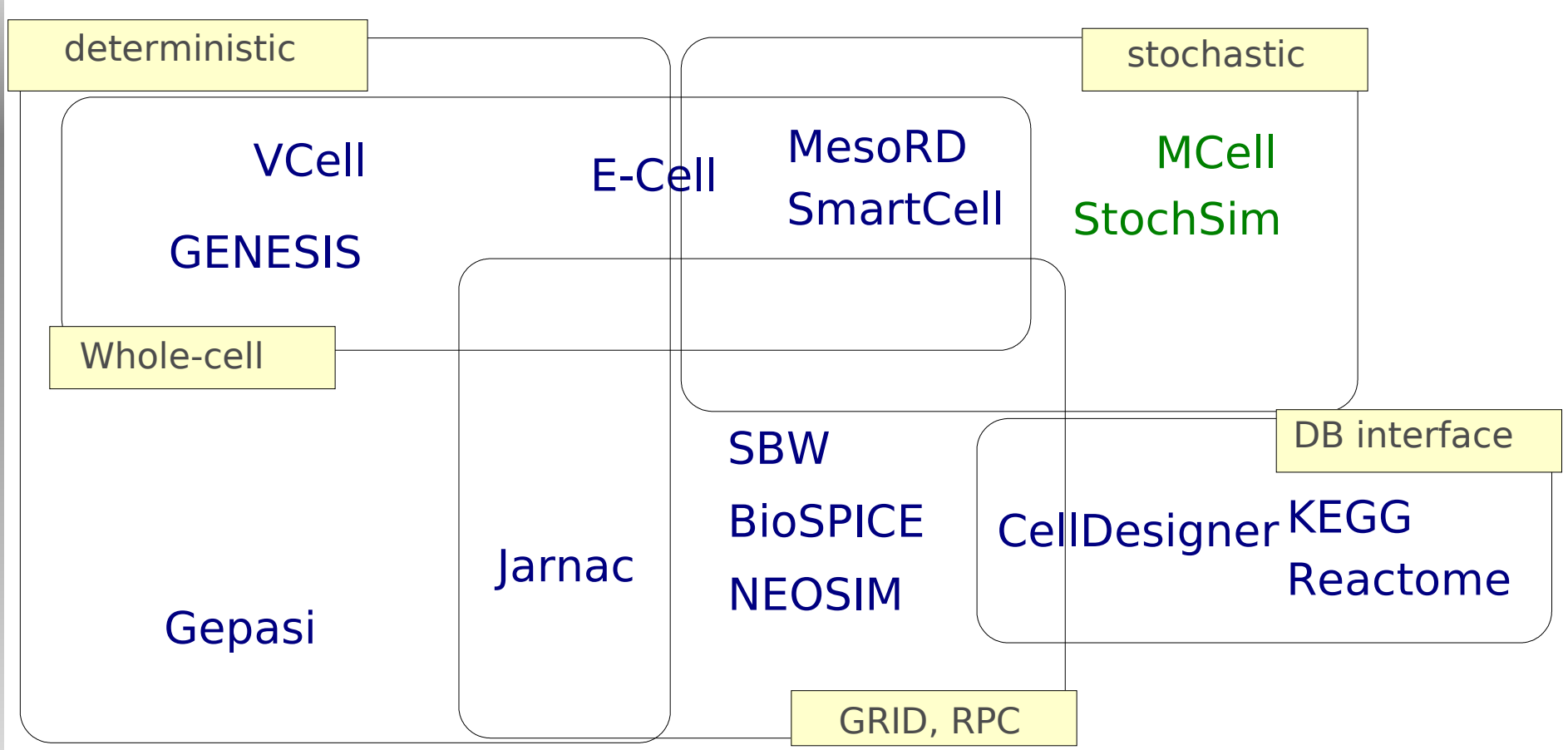


Synapse
Stochastic algorithm
1nm-100nm
1µs-1ms



Dendritic spine
Diffusion, PDE
100nm-1µm
1ms-1s

Modelisation: the collaborative approach



All these programs speak SBML
(Systems Biology Markup Language)

SBML

Computational Neurobiology

SBML Systems Biology Markup Language

A Tool-Neutral Exchange Format

The Systems Biology Markup Language (SBML) is a computer-readable format for representing **models of biochemical reaction networks**. SBML is applicable to metabolic networks, cell-signaling pathways, regulatory networks, and many others.

Internationally Supported and Widely Used

SBML has been evolving since mid-2000 through the efforts of an international group of software developers and users. Today, SBML is **supported by over 60 software systems**, including the following (where '*' indicates SBML support in development):

BALSA	Cellerator	JDesigner	Modesto	SCIpath
BASIS	Cellware	JigCell	Moleculizer	Sigmoid*
BioCharon	COPASI	JSIM	MOMA*	SigPath
biocyc2SBML	Cytoscape	JWS*	Monod	SigTran
BioGrid	DBsolve	Karyote*	NetBuilder	Simpathica
BioNetGen	Dizzy	KEGG2SBML	PathArt	SimWiz
Bio Sketch Pad	E-CELL	Kinsolver*	PathScout	StochSim
Dashboard	ecellJ	libSBML	PaVESy	STOCKS
BioSpreadsheet	ESS	LION Target Engine	PathwayBuilder	Trelis
BioUML	FluxAnalyzer	MathSBML	ProcessDB*	Virtual Cell
BSTLab	Gepasi	MesoRD	PySCeS*	VLX Suite
CADLIVE	INSILICO discovery	MetaboLogica	SBMLToolbox	WinSCAMP
CellDesigner	Jarnac	MMT2	SBW	

A Free and Open Language

Advances in biotechnology are leading to larger, more complex models. The systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. SBML's widespread adoption **offers many benefits**:

- Enabling the use of multiple tools without rewriting models for each tool
- Enabling models to be shared and published in a form other researchers can use even in a different software environment
- Ensuring the survival of models (and the intellectual effort put into them) beyond the lifetime of the software used to create them

Does Your Software Support SBML?

LibSBML 2.2.0 Released!

(October 6, 2004) A new version of libSBML is now available. It's full of new features, including support for Lisp and Perl.
read more

MathSBML 2.4.0 Released!

(September 24, 2004) A new version of MathSBML is now available. It adds new features and support for even more SBML and MathML constructs.
read more

SBMLToolbox 1.0 Released!

(September 21, 2004) SBMLToolbox lets you work with SBML models in MATLAB. It provides functions for reading and writing SBML, converting and manipulating models, and more.
read more

Forum meeting in October!

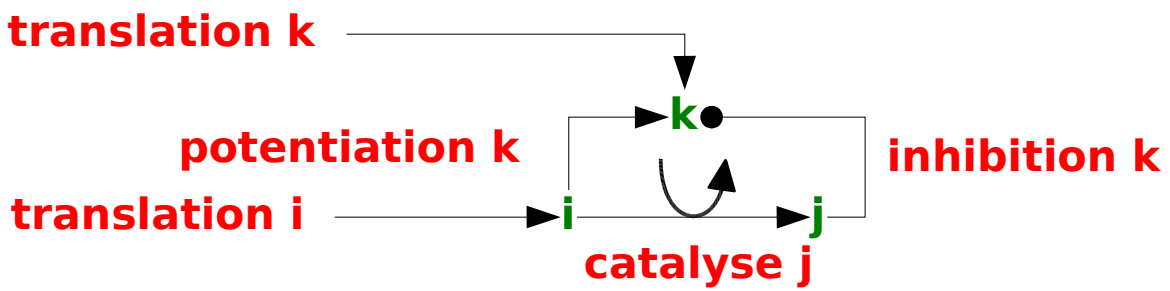
(September 10, 2004) The next **SBML Forum** meeeting will be October 14-15, right after ICSB 2004 in Heidelberg, Germany.
read more

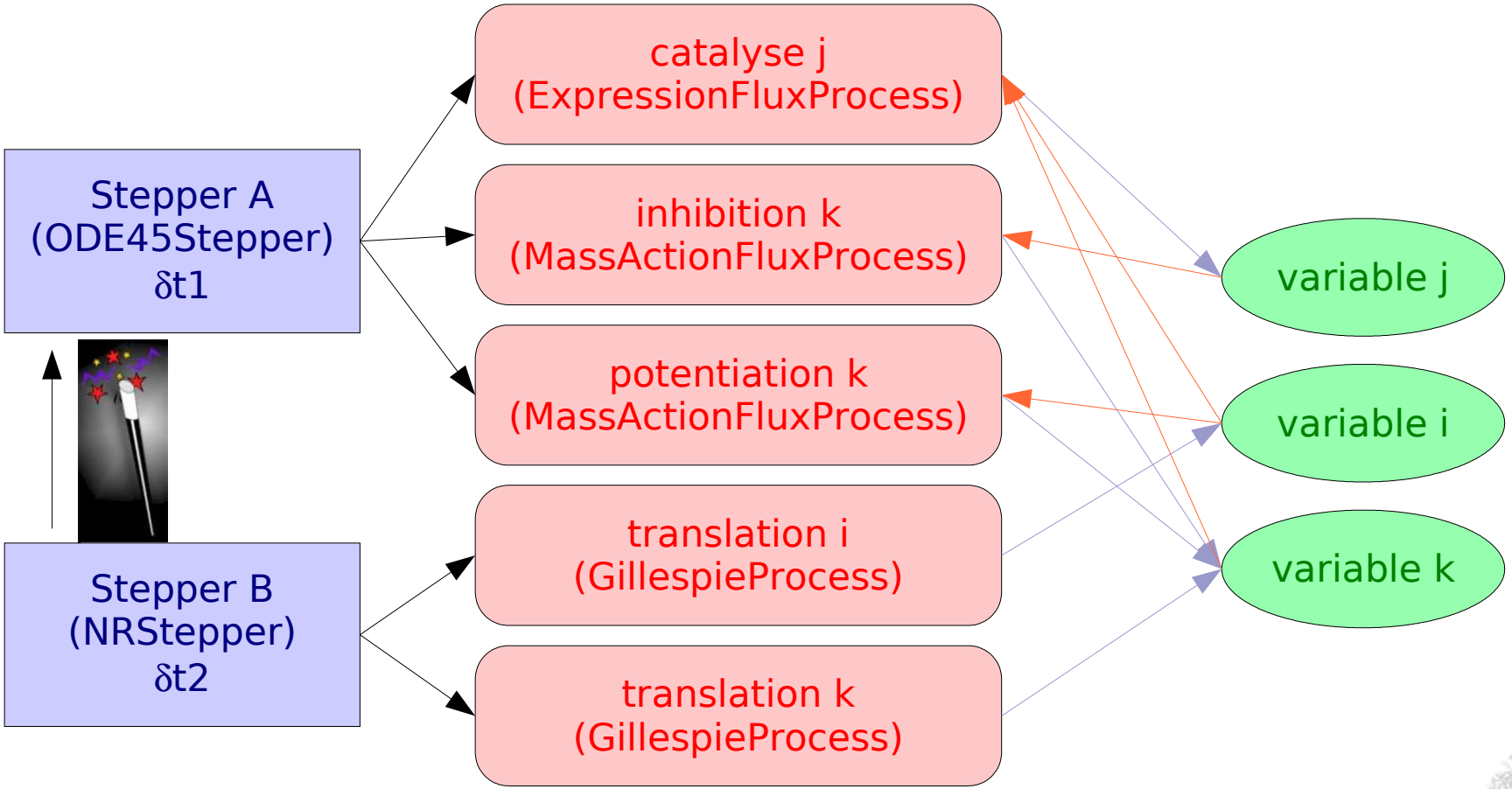
Announcement: MesoRD

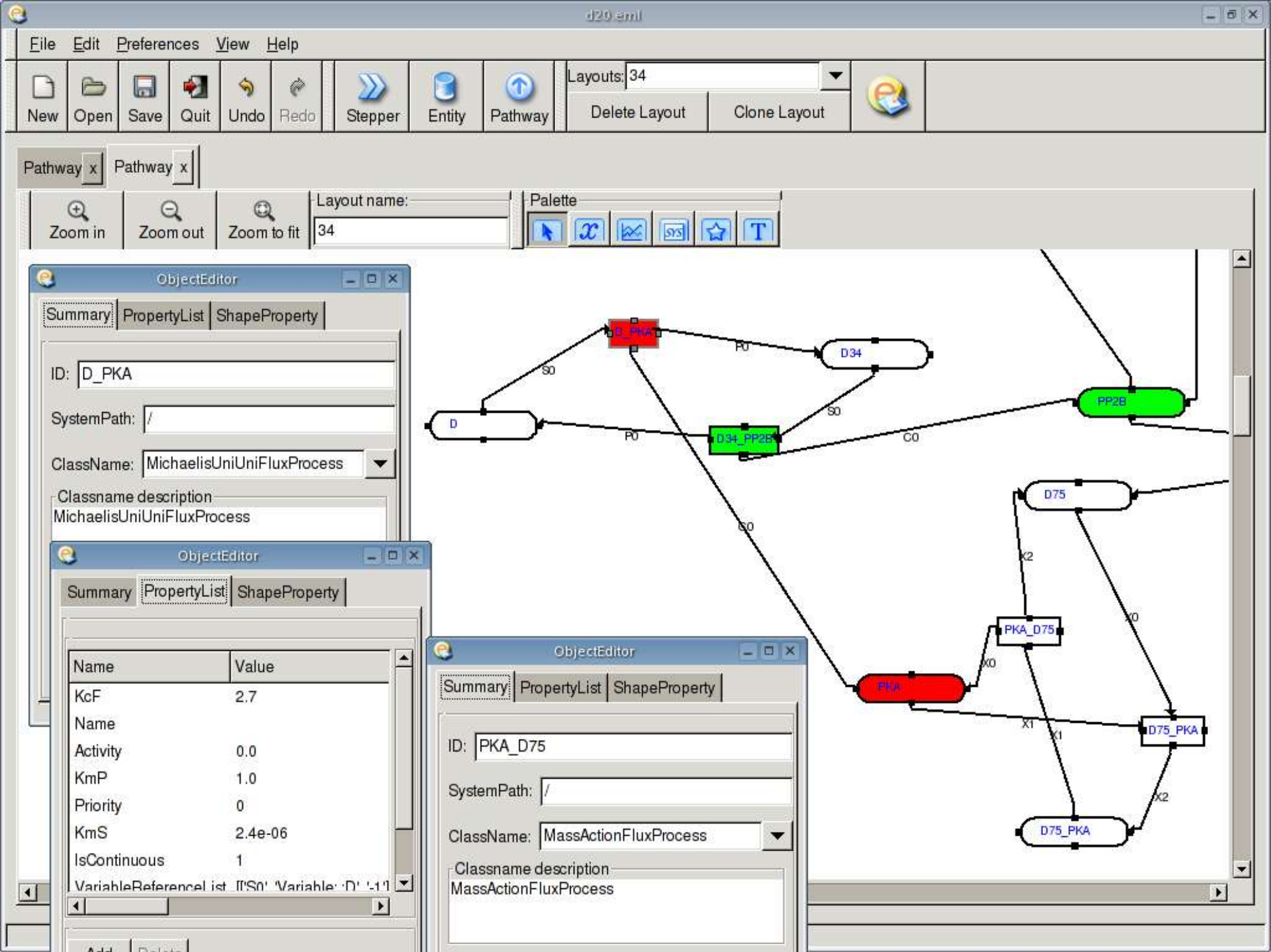
(September 9, 2004) MesoRD is a stochastic simulator of reactions and diffusions in space. It implements a new simulation method and supports SBML.
read more

See older news items.

E-Cell System 3 (Kouichi Takahashi) shared memory, hyper-threading



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New Open Save Quit Undo Redo Stepper Entity Pathway
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Delete Layout Clone Layout
Pathway x Pathway x
Zoom in Zoom out Zoom to fit
Layout name: 34
Palette
ObjectEditor
Summary PropertyList ShapeProperty
ID: D_PKA
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Classname description
MichaelisUniUniFluxProcess
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KmP 1.0
Priority 0
KmS 2.4e-06
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Classname description
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PKA
D75_PKA
D75_PKA
P0
S0
P0
S0
C0
S0
X2
X0
X0
X1
X1
X2

Useful quantitative models

- Systems Biologists need:
  - to retrieve easely existing relevant models
- Computational Systems Biologists need:
  - reuse existing models rather than reimplement them
  - construct models from building blocks
- No true database of models, only repositories
- No quality control on the models available online
- No annotation of models: reactants are A,B,C etc
- MIRIAM:
  Minimum Information Requested In the Annotation of Models
- Controlled vocabularies:
  - Parameters: Kd, Ka, Kp, IC50 ARE DIFFERENT!
  - “Michaelis-Menten”, “Hopf bifurcation” etc.
- Biomodels, a database of “Systems Biology Models”

Biomodels database

- Collaboration between SBML teams of Caltech and University of Herdfordshire (curation) and EBI (DB)
- Each model served will be published or in the press (submitted will be processed but kept private)
- To be accepted in biomodels, a model will have to be semantically sound: simulation should correspond to results described in the referenced paper
- Models will be annotated: GO, NCBI Taxonomy, UniProt, ChEBI, Reactome etc.
  => search for all models related to “synaptic plasticity”, or “CALM_HUMAN”
- Possibility of online simulation

Acknowledgments

University of Cambridge (UK)

- Dennis Bray
- Tom Shimizu
- Matthew Levin

EMBL-European Bioinformatics Institute

- Alexander Broicher
- Marco Donizelli
- Éric Fernandez
- Dominic Tölle