Computational Systems Neurobiology

Nicolas Le Novère, EMBL-EBI

European Bioinformatics Institute

British outstation of the European Molecular Biology Laboratory

- Databases
  - Sequences, structures
  - Transcriptomics, Proteomics
  - Controlled vocabularies and dictionaries

- Research groups
  - Comparative genomics (Ouzounis)
    Structural Genomics (Thornton)
    Molecular Evolution (Goldman)
  - Text-Mining (Rebholz-Schumman)
    Computational Systems Biology (Le Novère)
    Statistical array analysis (Huber)
    Genomic analysis of regulatory systems (Luscombe)

Marie Curie Training site Fellowships: 3-6 months. Fully funded.

Computational Neurobiology

Computer simulation Vs. mathematical models

One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory *of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.*

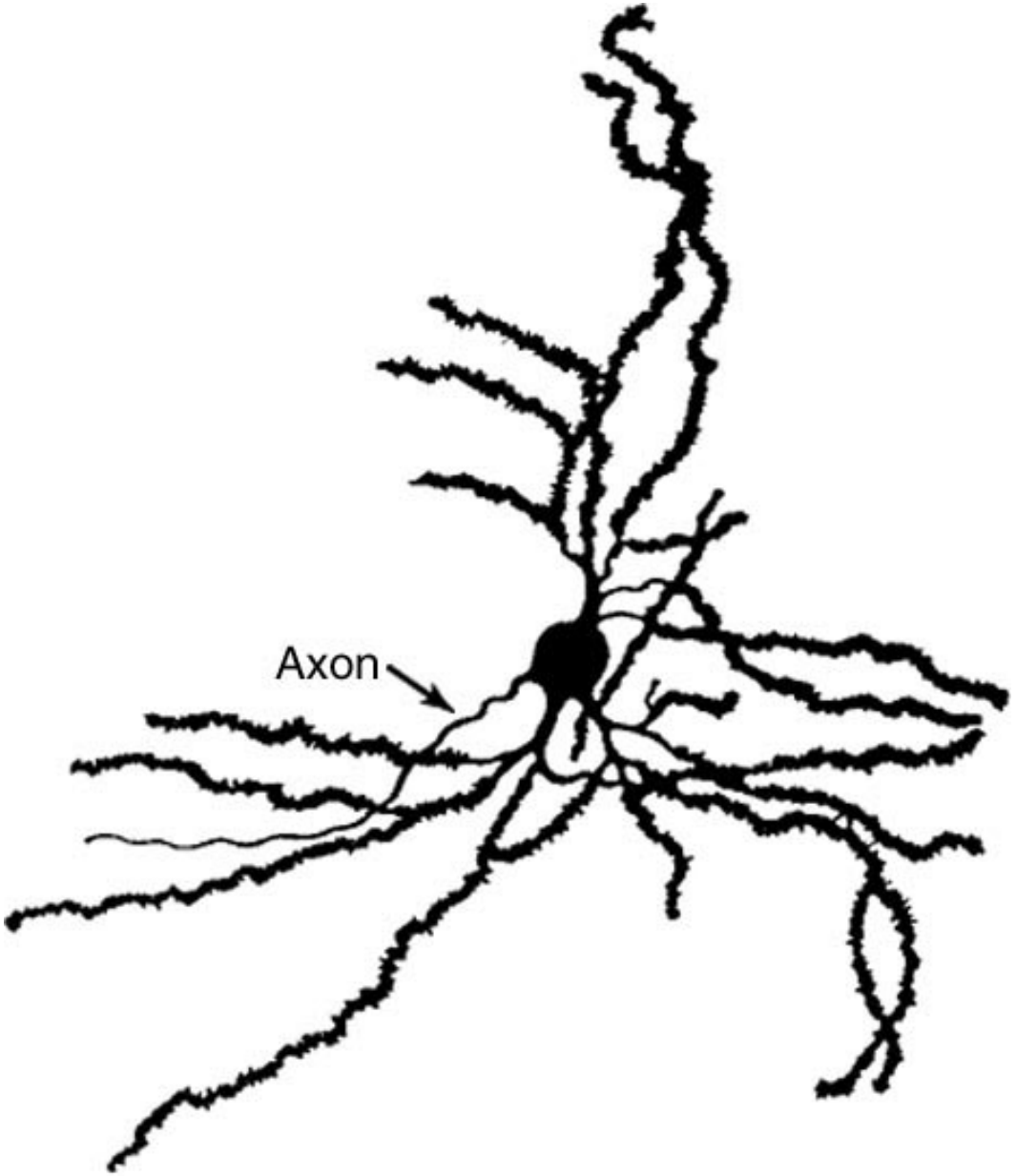
A.M. Turing (1952). The chemical basis of morphogenesis. *Phyl Trans Roy Soc Lond* B237: 37-72

[About the development from one developmental pattern to another, a non-linear process]

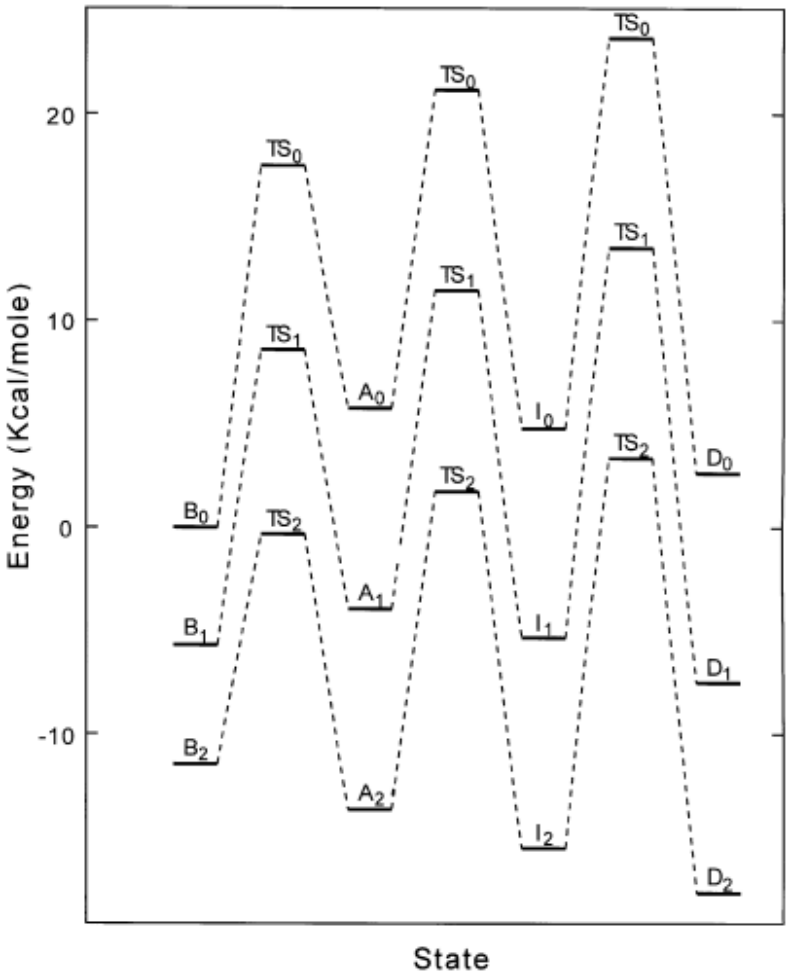
Simulation in Neurobiology

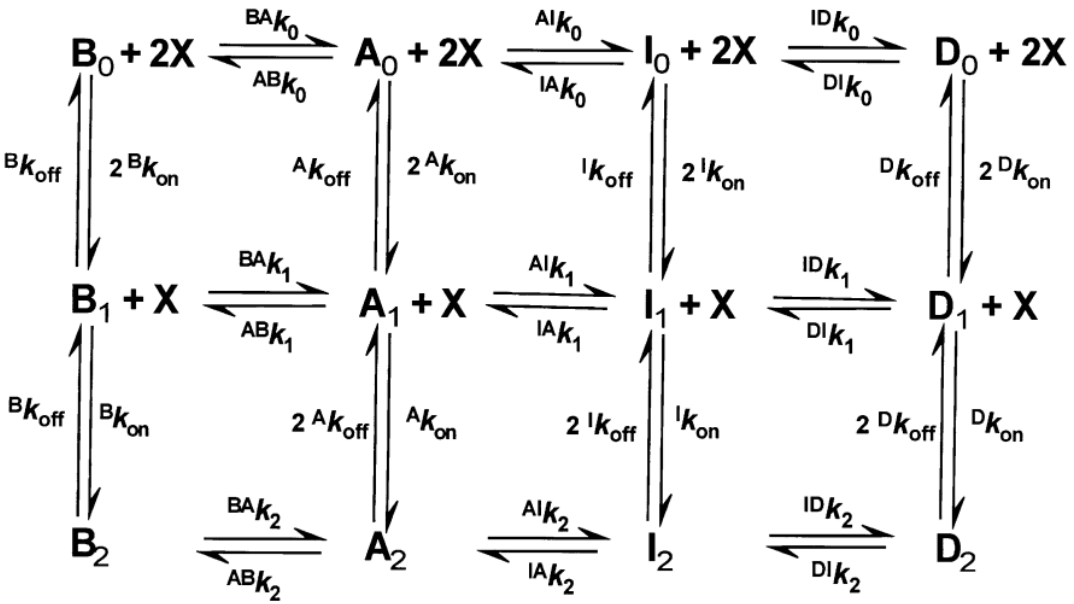
- Hodgkin and Huxley
  "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve". *J Physiol* 1952, 117: 500-544
- Rall
  “Branching dendritic trees and motoneuron membrane resistivity". Exp Neurol 1959, 1: 491-527
- [NEURON] Hines
  "A program for simulation of nerve equations with branching geometries". Int J Biomed Comput 1989, 24:55-68
- [GENESIS] Wilson, Bhalla, Uhley, Bower
  “GENESIS : A system for simulating neural networks.” Advances in neural information processing systems. Touretzky, D. ed, 1989, pp. 485-492
- Land, Salpeter, Salpeter
  "Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". Proc Natl Acad Sci USA 1981, 78:7200-7204
- [MCell] Bartol, Land, Salpeter, Salpeter
  “Monte Carlo simulation of miniature endplate current generation in the vertebrate neuromuscular junction”. Biophy J 1991, 59: 1290-1307
- Changeux, Courrège, Danchin
  "A theory of the epigenesis of neural networks by selective stabilization of synapses". Proc Natl Acad Sci USA 1973, 70: 2974-2978
- Tsodyks and Markram
  “The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability”. Proc Natl Acad Sci USA 1997, 94: 719-723

the Medium Spiny Neuron of the striatum



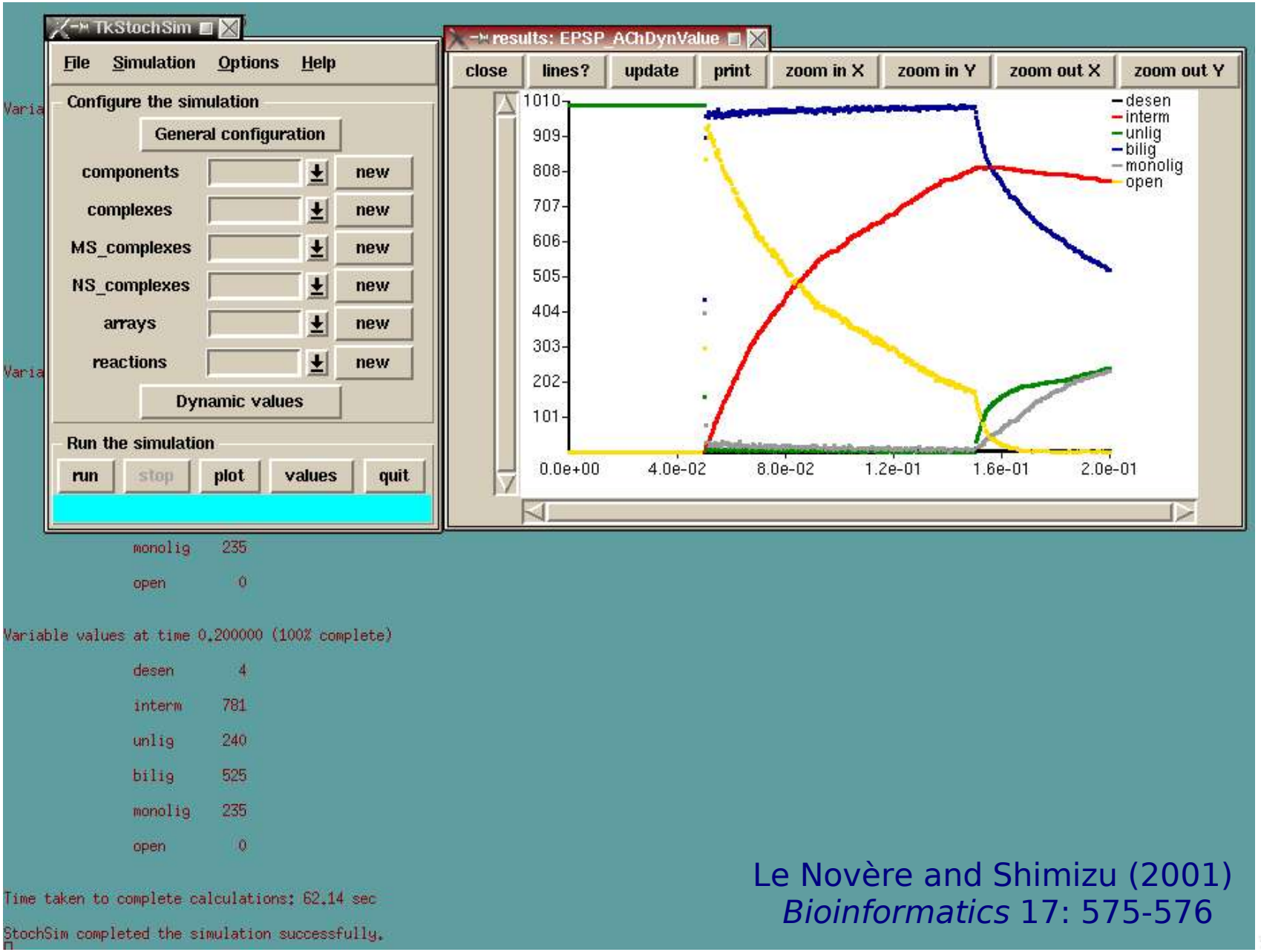
Kinetic model of receptor function





Edelstein et al. (1996) *Biol Cybern*, 75: 361-379

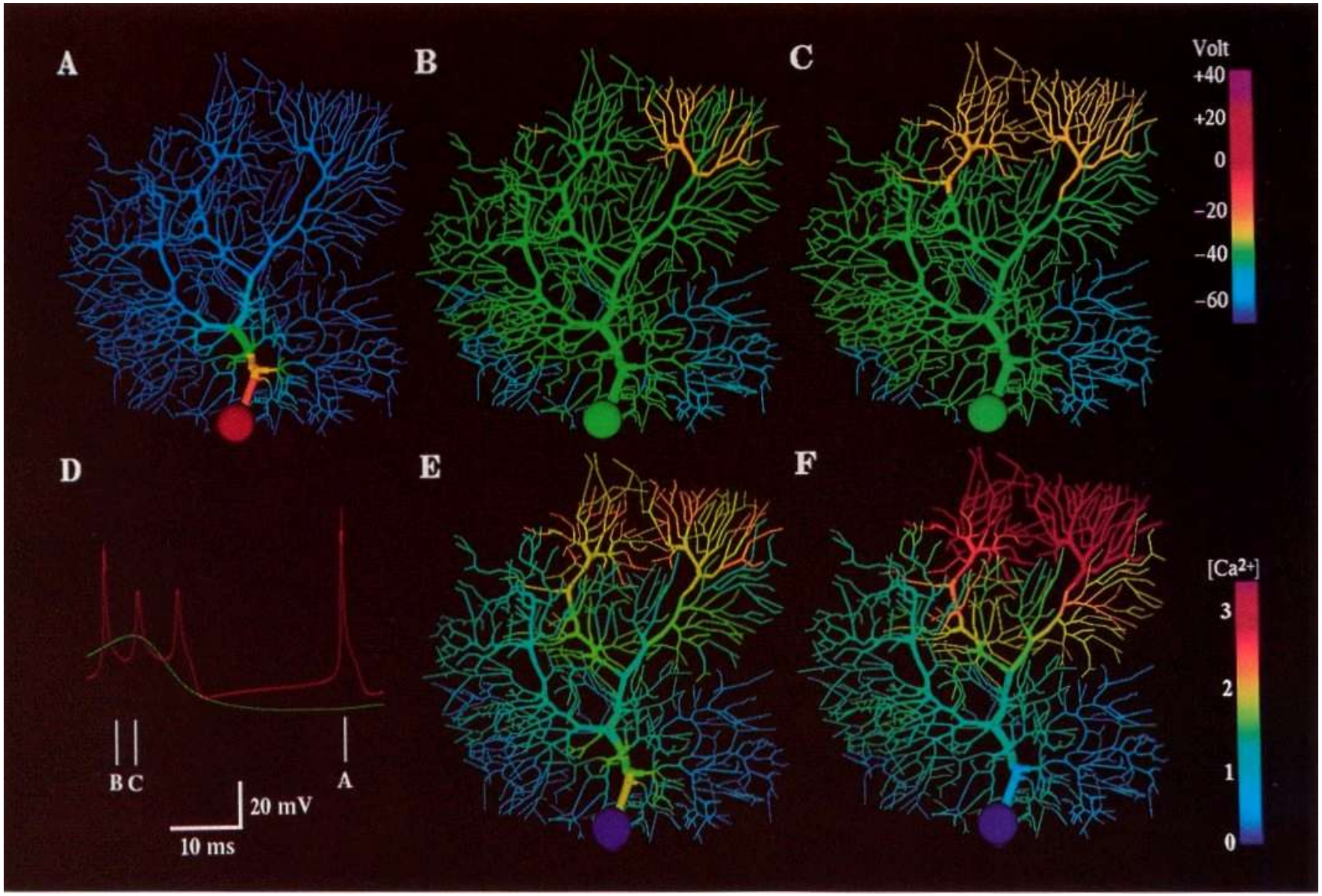
Excitatory post-synaptic potential



Le Novère and Shimizu (2001)
Bioinformatics 17: 575-576

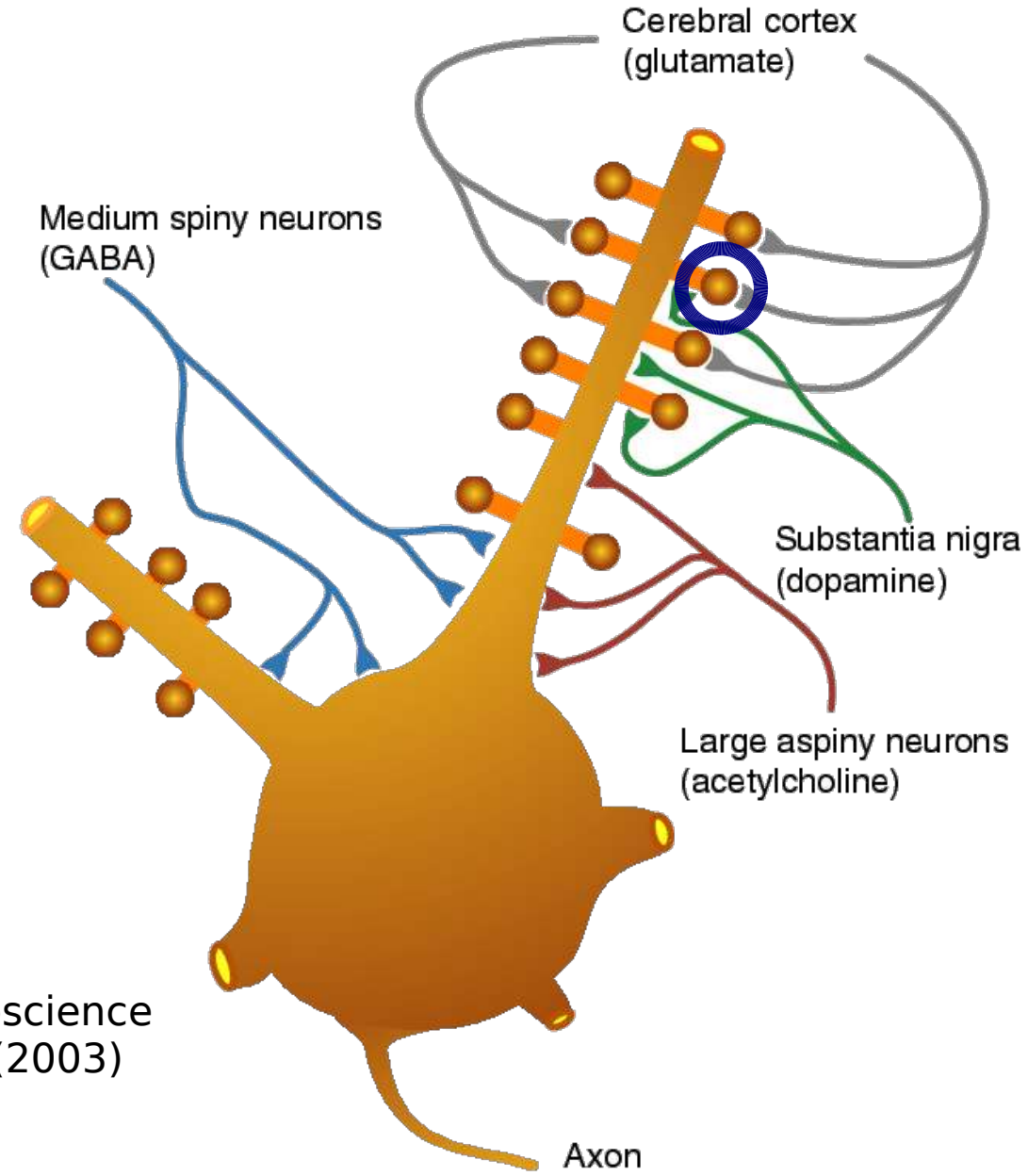
Movie Purkinge

Compartmental models



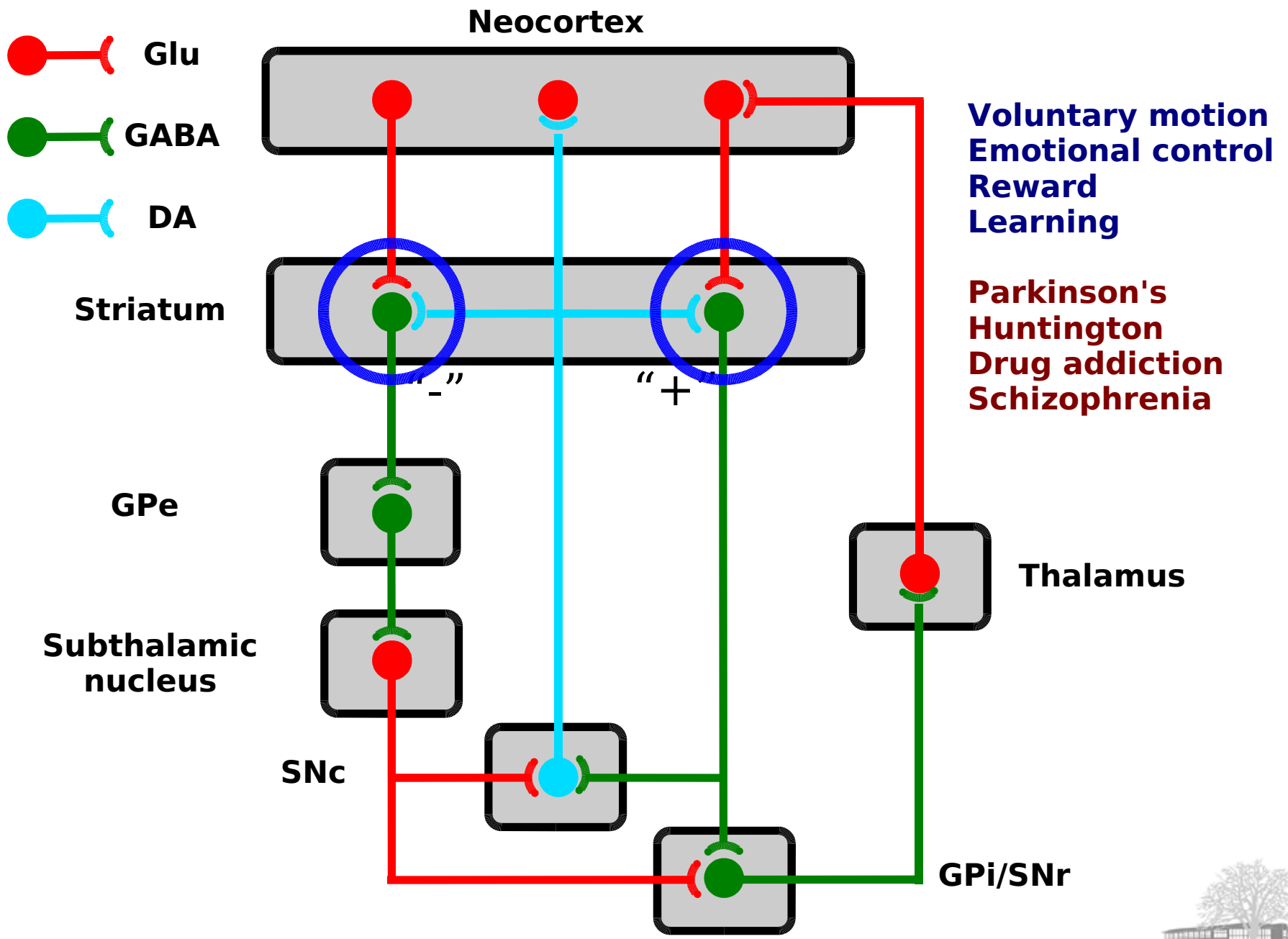
De Schuter and Bower (1994) *J Neurophysio*, 71: 375-419

Multiple afferent signals

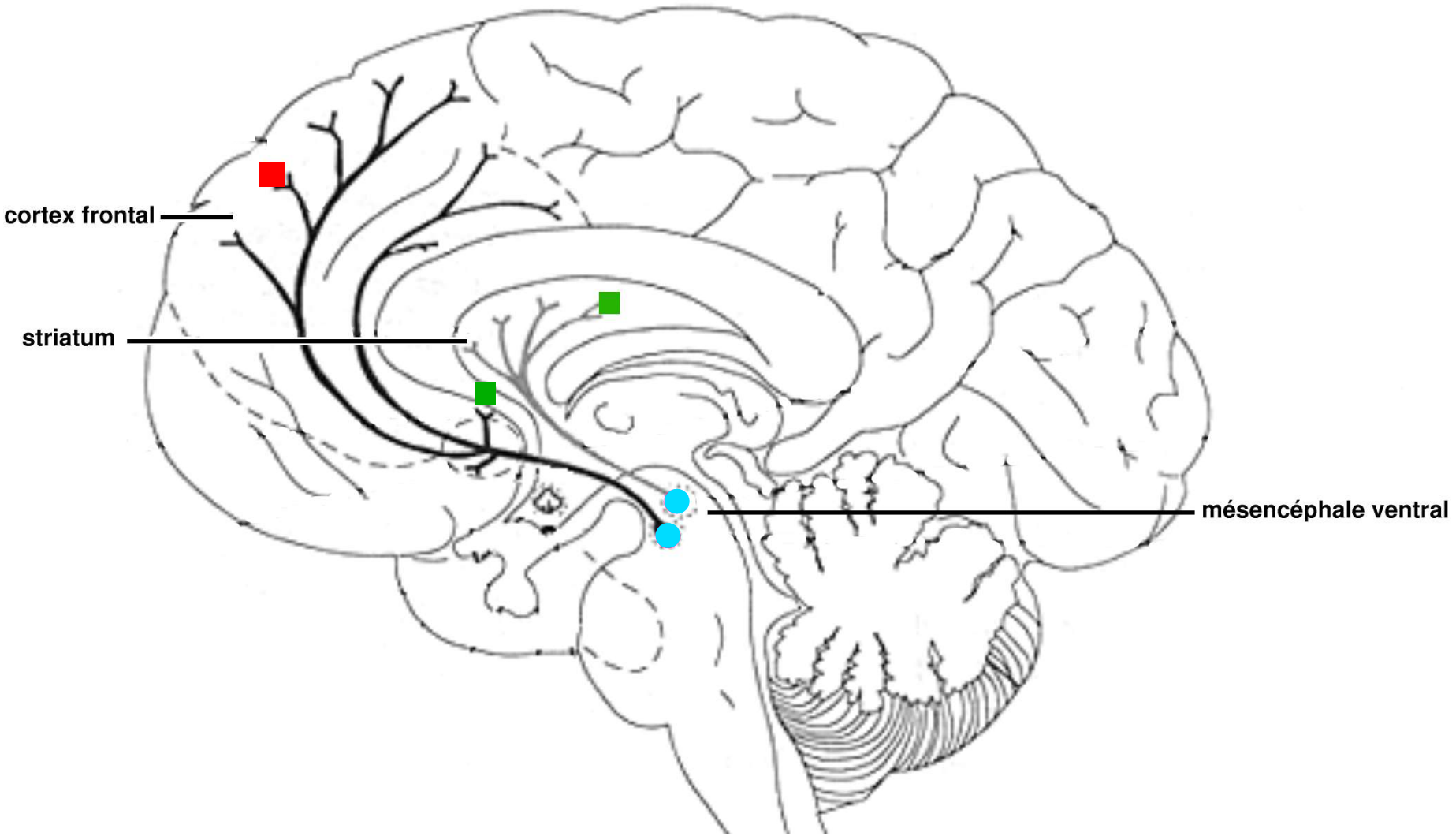


Fundamental Neuroscience
Squire et al. 2nd ed(2003)

Dopamine mesotelencephalic pathway

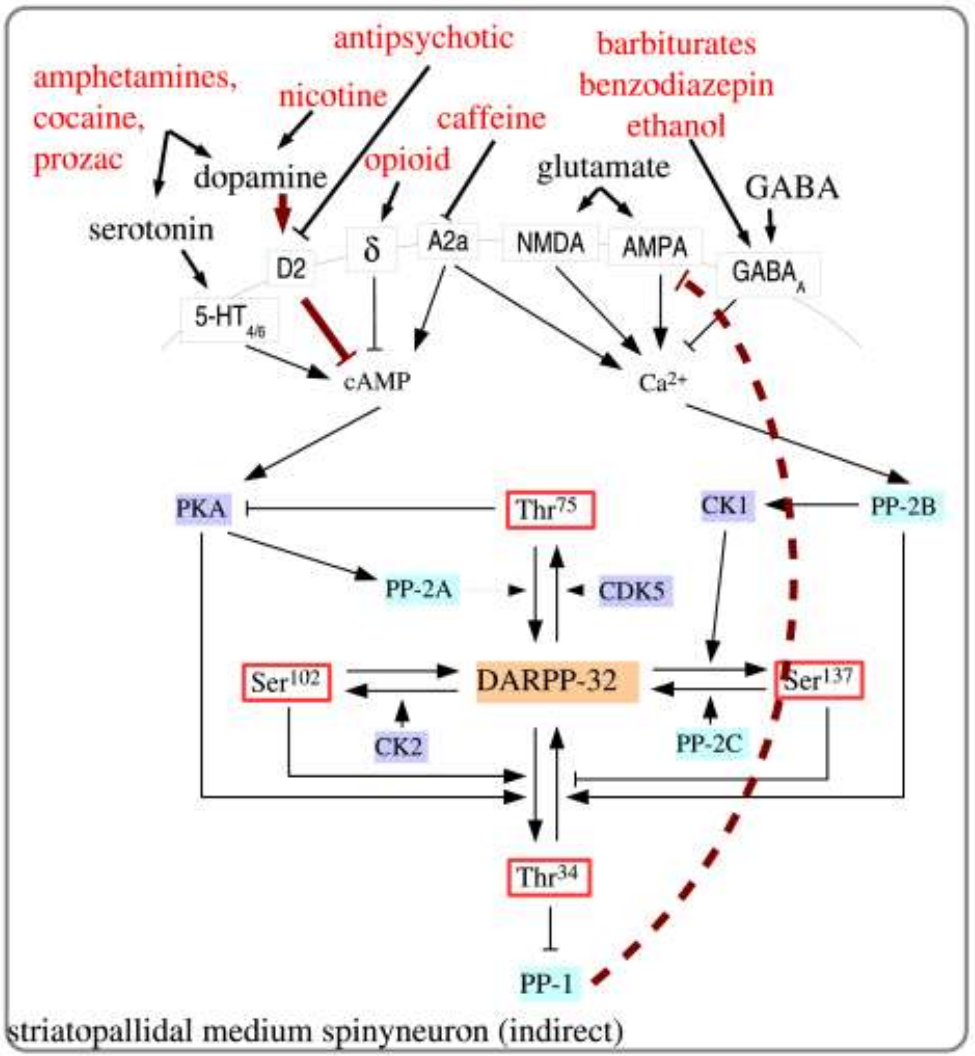


Dopamine mesotelencephalic pathway

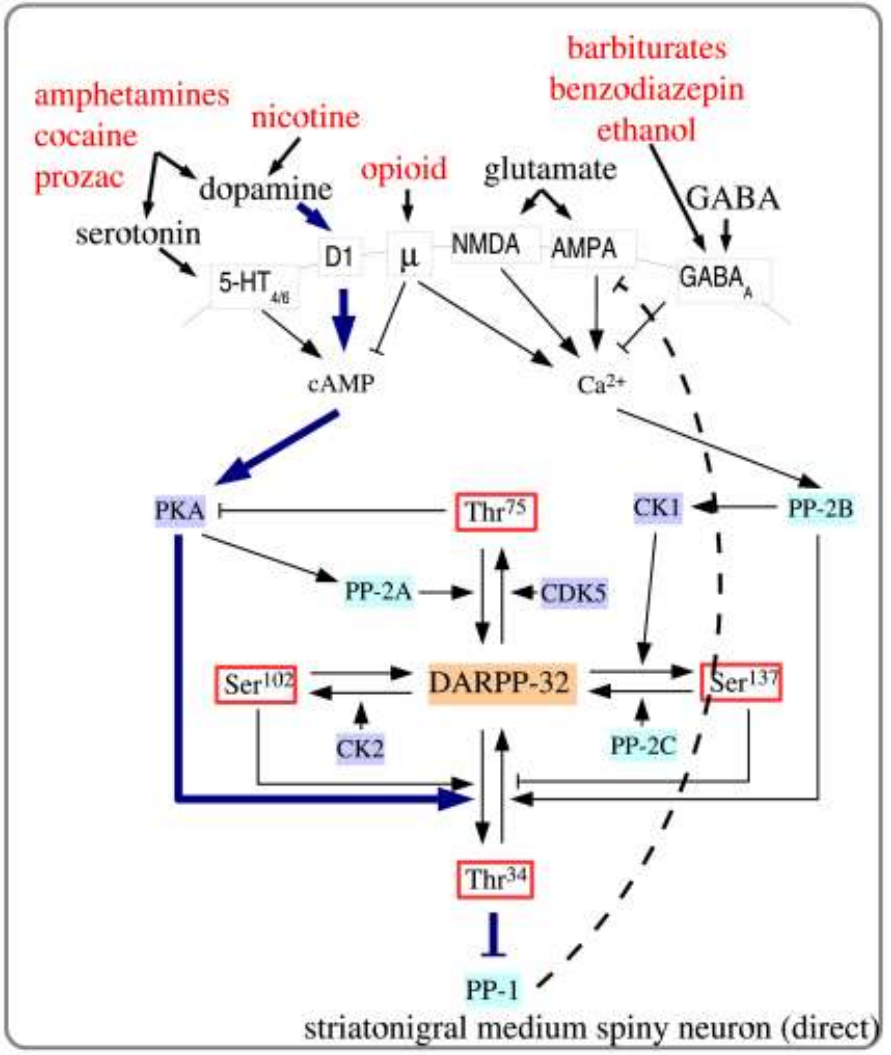


Computational Neurobiology

DARPP-32, a signal integrator



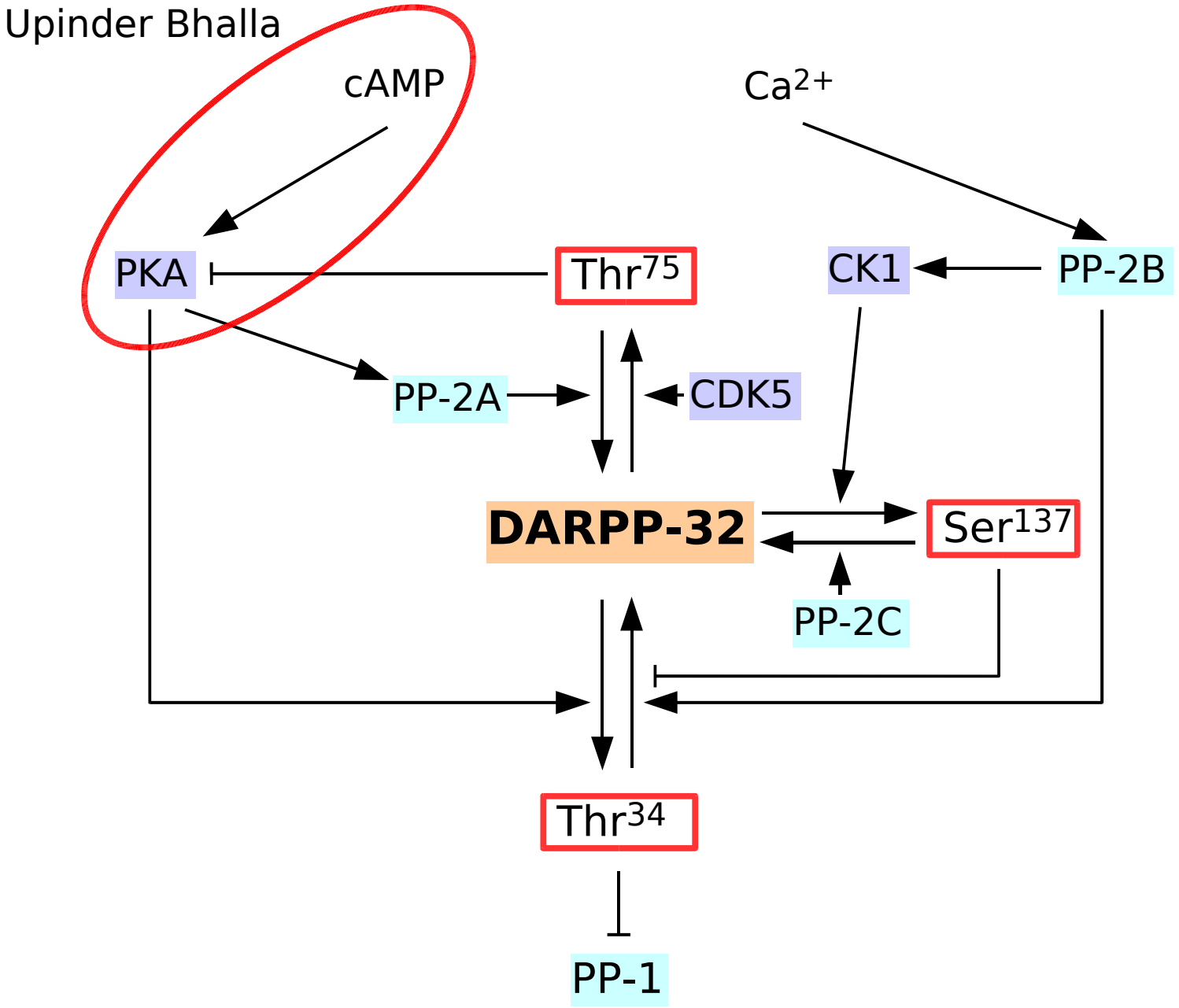
striatopallidal medium spinyneuron (indirect)



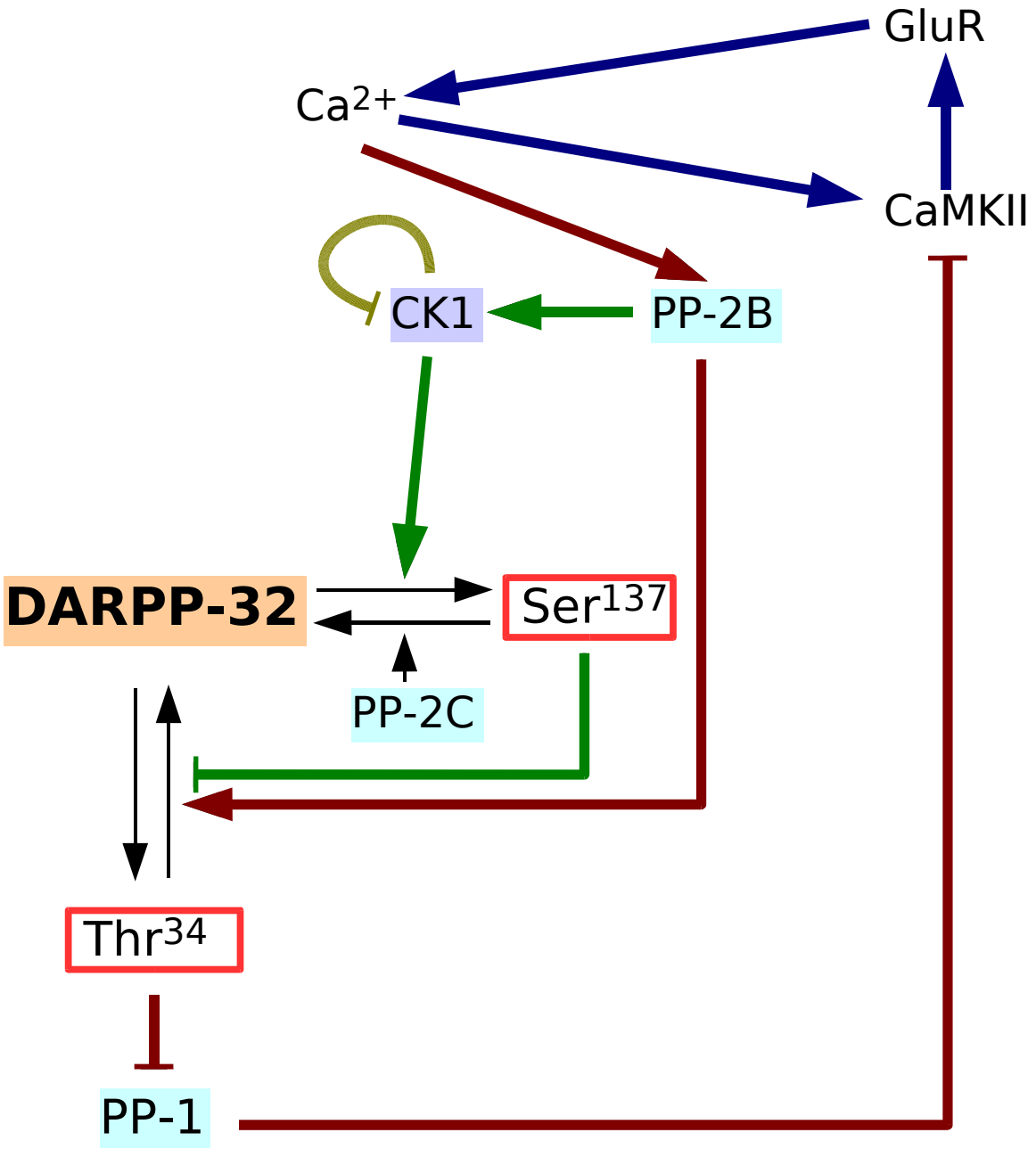
striatonigral medium spiny neuron (direct)

Computational Neurobiology

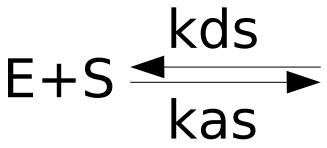
Model of DARPP-32 regulation

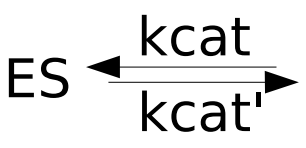


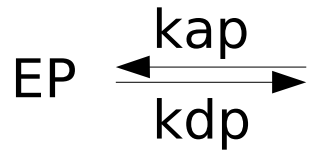
Negative loops: “russian dolls”



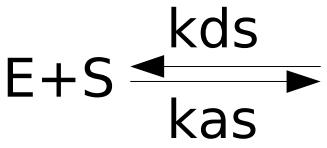
Choose the right formalism

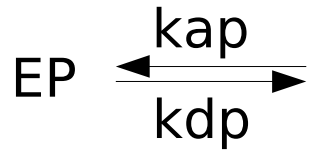




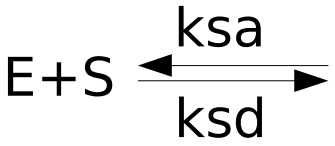


$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

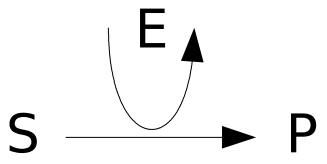




catalysis irreversible



product is consumed before rebinding



steady-state

$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

Leonor Michaelis, Maud Menten (**1913**).
Die Kinetik der Intertinwerkung, Biochem. Z. 49:333-369.

G. E. Briggs and J. B. S. Haldane (**1925**)
A note on the kinetics of enzyme action, Biochem. J., 19, 339-339.

Signal Transduction ≠ Metabolic Control

- Signal transduction and steady-state are contradictory.
- Enzyme, substrate, product are proteins:
  - [S] ~ [E]
  - Rebinding of product is not negligible.
- Approximations are context-dependant: Model composition becomes questionable (validity of the assumptions), or even impossible (no explicit representation of some species).
- Michaelis-Menten is an approximation meant to ease analytical work. In most case we don't need it anymore, and should use elementary steps, representing all molecular species.

  ⇒ computers do (part of) the job for you!

The complete model

57 species, 104 reactions

- D + CDK5 ⇔ D_CDK5 → D75 + CDK5
- D75 + PP2A ⇔ D75_PP2A → D + PP2A
- D75 + PP2AP ⇔ D75_PP2AP → D + PP2AP
- D137 + CDK5 ⇔ D137_CDK5 → D75-137 + CDK5
- D75-137 + PP2A ⇔ D75-137_PP2A → D137 + PP2A
- D75-137 + PP2AP ⇔ D75-137_PP2AP → D137 + PP2AP
- D34 + CDK5 ⇔ D34_CDK5 → D34-75 + CDK5
- D34-75 + PP2A ⇔ D34-75_PP2A → D34 + PP2A
- D34-75 + PP2AP ⇔ D34-75_PP2AP → D34 + PP2AP
- D34-137 + CDK5 ⇔ D34-137_CDK5 → D34-75_137 + CDK5
- D34-75-137 + PP2A ⇔ D34-75-137_PP2A → D34-137 + PP2A
- D34-75-137 + PP2AP ⇔ D34-75-137_PP2AP → D34-137 + PP2AP

- D + CK1 ⇔ D_CK1 → D137 + CK1
- D137 + PP2C ⇔ D137_PP2C → D + PP2C
- D75 + CK1 ⇔ D75_CK1 → D75-137 + CK1
- D75-137 + PP2C ⇔ D75-137_PP2C → D75 + PP2C
- D34 + CK1 ⇔ D34_CK1 → D34-137 + CK1
- D34-75 + PP2C ⇔ D34-75_PP2C → D75 + PP2C
- D34-75 + CK1 ⇔ D34-75_CK1 → D34-75-137 + CK1
- D34-75-137 + PP2C ⇔ D34-75-137_PP2C → D34-75 + PP2C

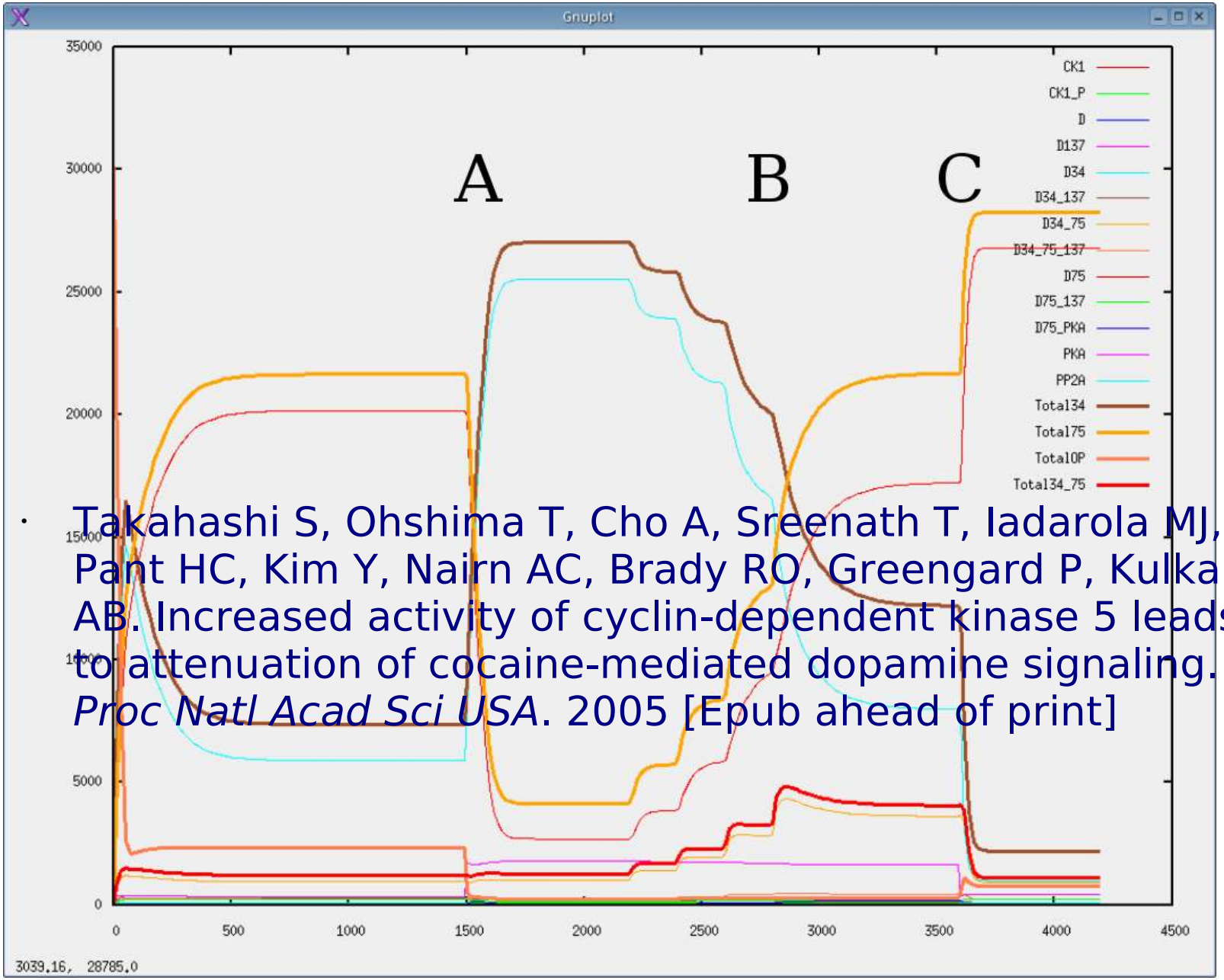
- D + PKA ⇔ D_PKA → D34 + PKA
- D34 + PP2B ⇔ D34_PP2B → D + PP2B
- D75 + PKA ⇔ D75_PKA → D34-75 + PKA
- D34-75 + PP2B ⇔ D34-75_PP2B → D75 + PP2B
- D137 + PKA ⇔ D137_PKA → D34-137 + PKA
- D75-137 + PKA ⇔ D75-137_PKA → D34-75-137 + PKA

- CK1 + CK1 ⇔ CK1_CK1 → CK1P + CK1
- CK1P + PP2B ⇔ CK1P_PP2B → CK1 + PP2B

- D75 + PKA ⇔ D75_PKA
- D34-75 + PKA ⇔ D34-75_PKA
- D34-75-137 + PKA ⇔ D34-75-137_PKA

- R2_PKA2 + cAMP ⇔ cAMP_R2_PKA2
- cAMP_R2_PKA2 + cAMP ⇔ cAMP2_R2_PKA2
- cAMP2_R2_PKA2 + cAMP ⇔ cAMP3_R2_PKA2
- cAMP3_R2_PKA2 + cAMP ⇔ cAMP4_R2_PKA2
- cAMP4_R2_PKA2 ⇔ cAMP4_R2_PKA + PKA
- cAMP4_R2_PKA ⇔ cAMP4_R2 + PKA

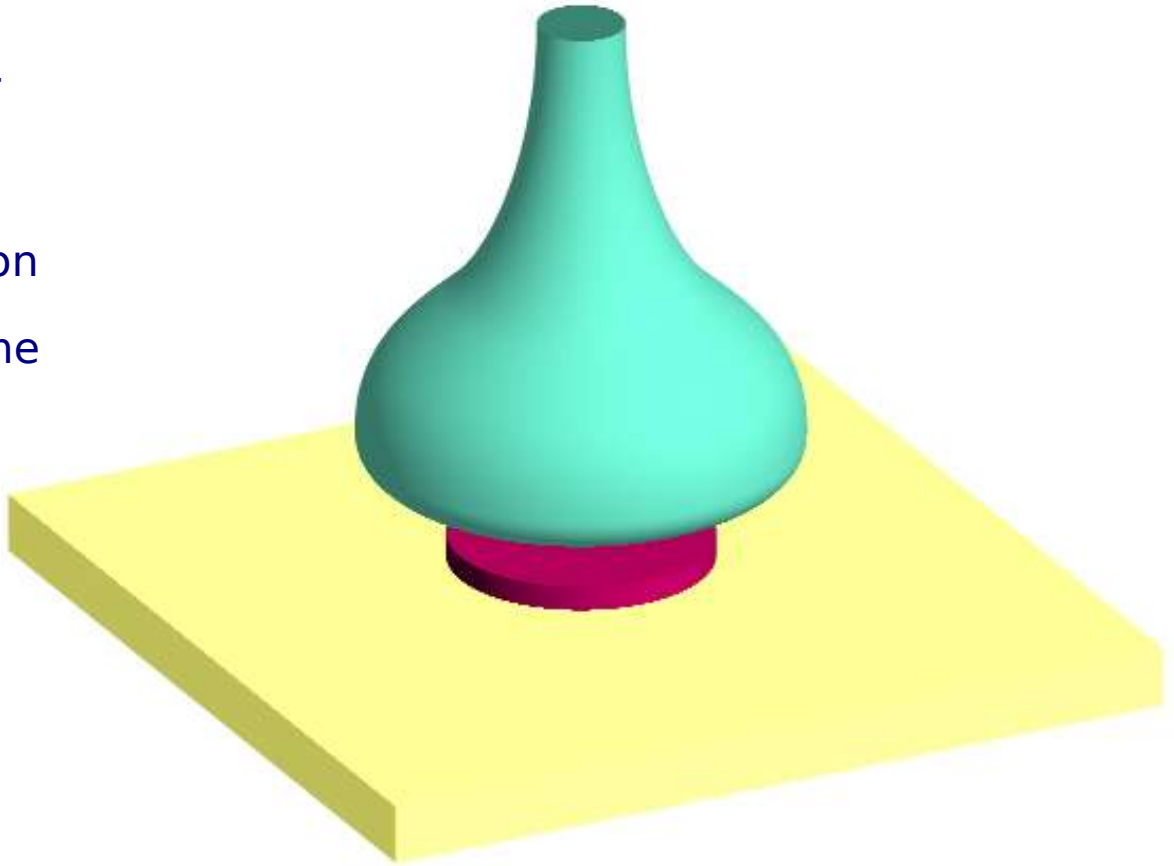
Effect of CDK5 activity



- Takahashi S, Ohshima T, Cho A, Sreenath T, Iadarola MJ, Pant HC, Kim Y, Nairn AC, Brady RO, Greengard P, Kulkarni AB. Increased activity of cyclin-dependent kinase 5 leads to attenuation of cocaine-mediated dopamine signaling. *Proc Natl Acad Sci USA*. 2005 [Epub ahead of print]

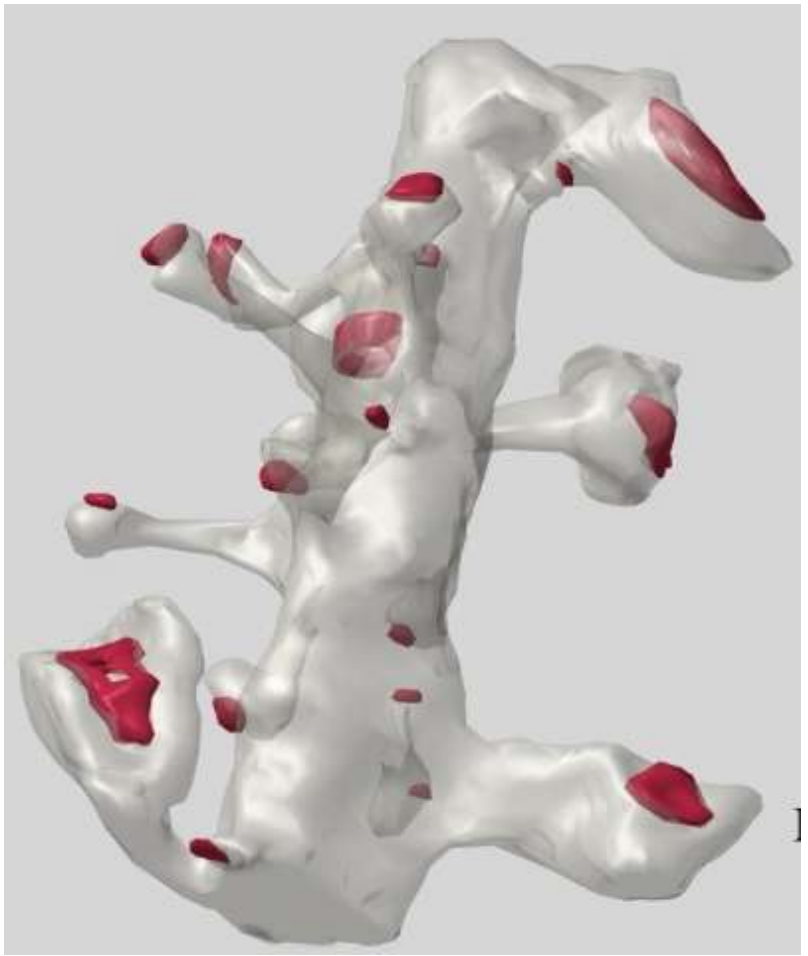
Classical view of the synapse

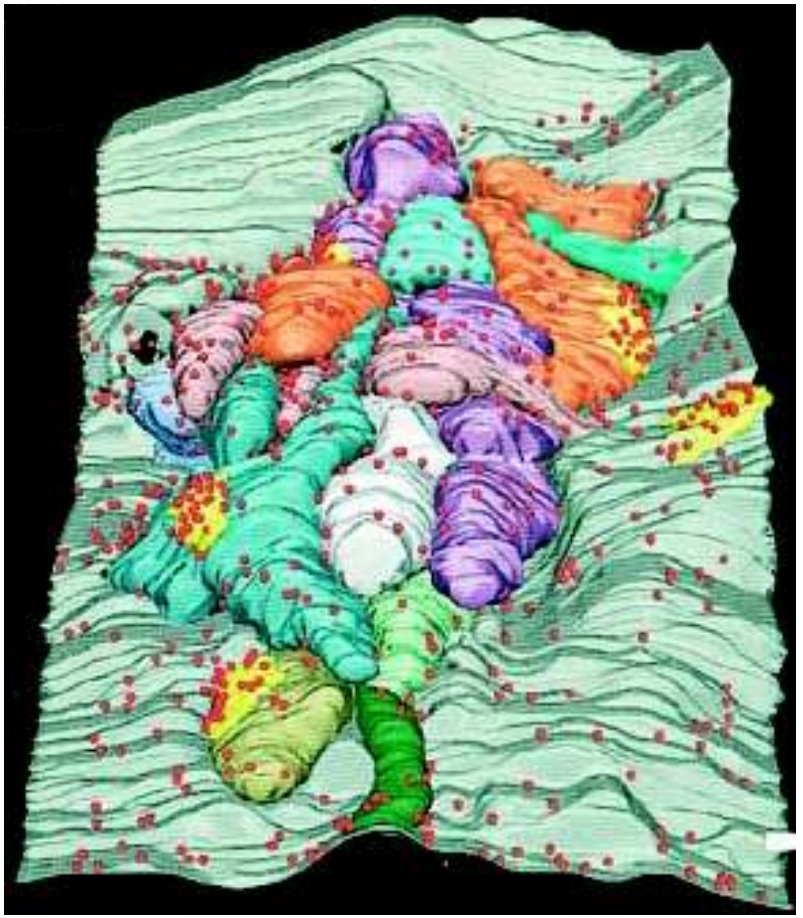
- One kind of transmitter
- One kind of receptor
- Homogenous distribution
- Frozen in space and time



Structural complexity

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

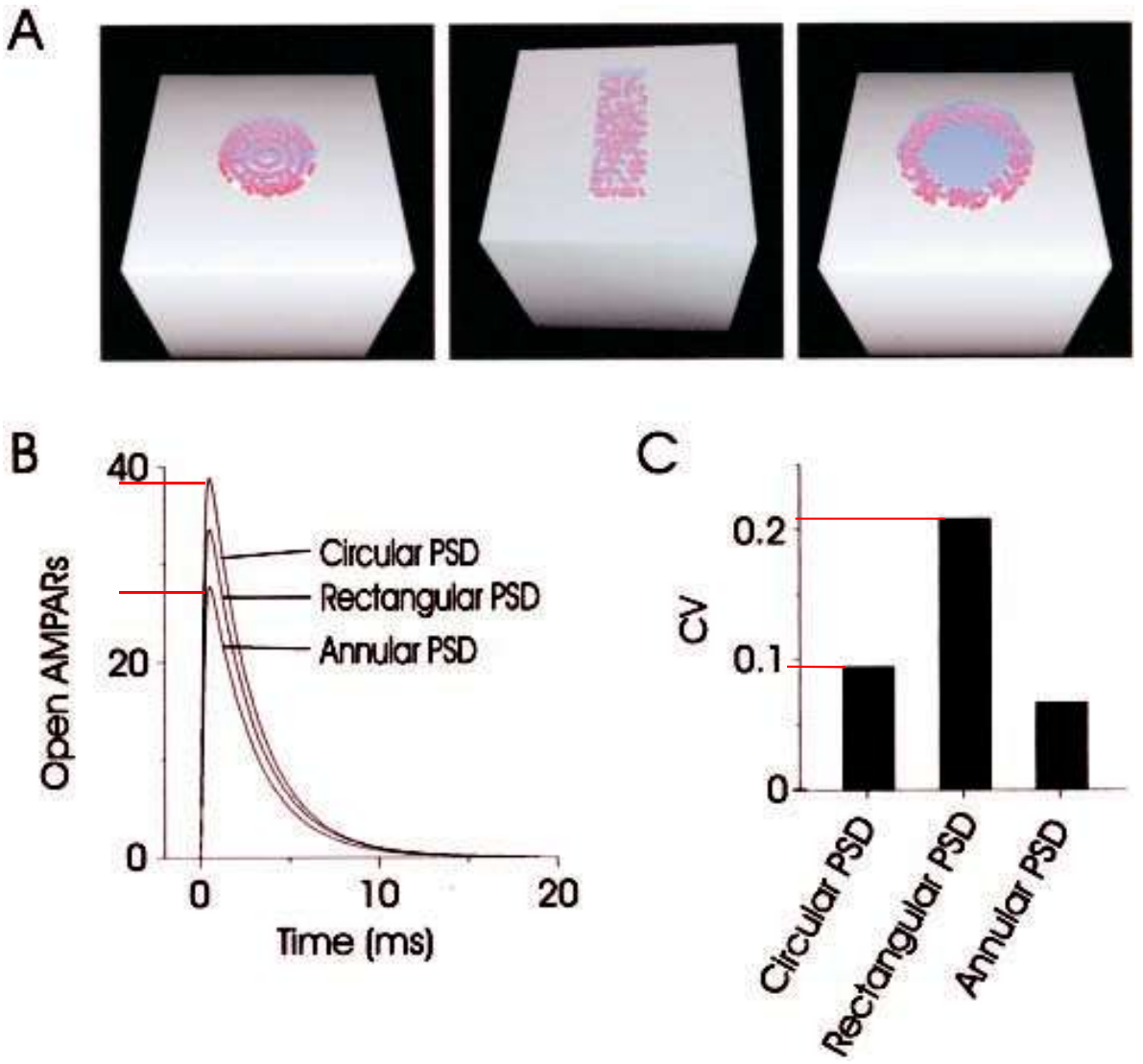




Shoop et al. (2002)
J Neurosci, 22: 748-756

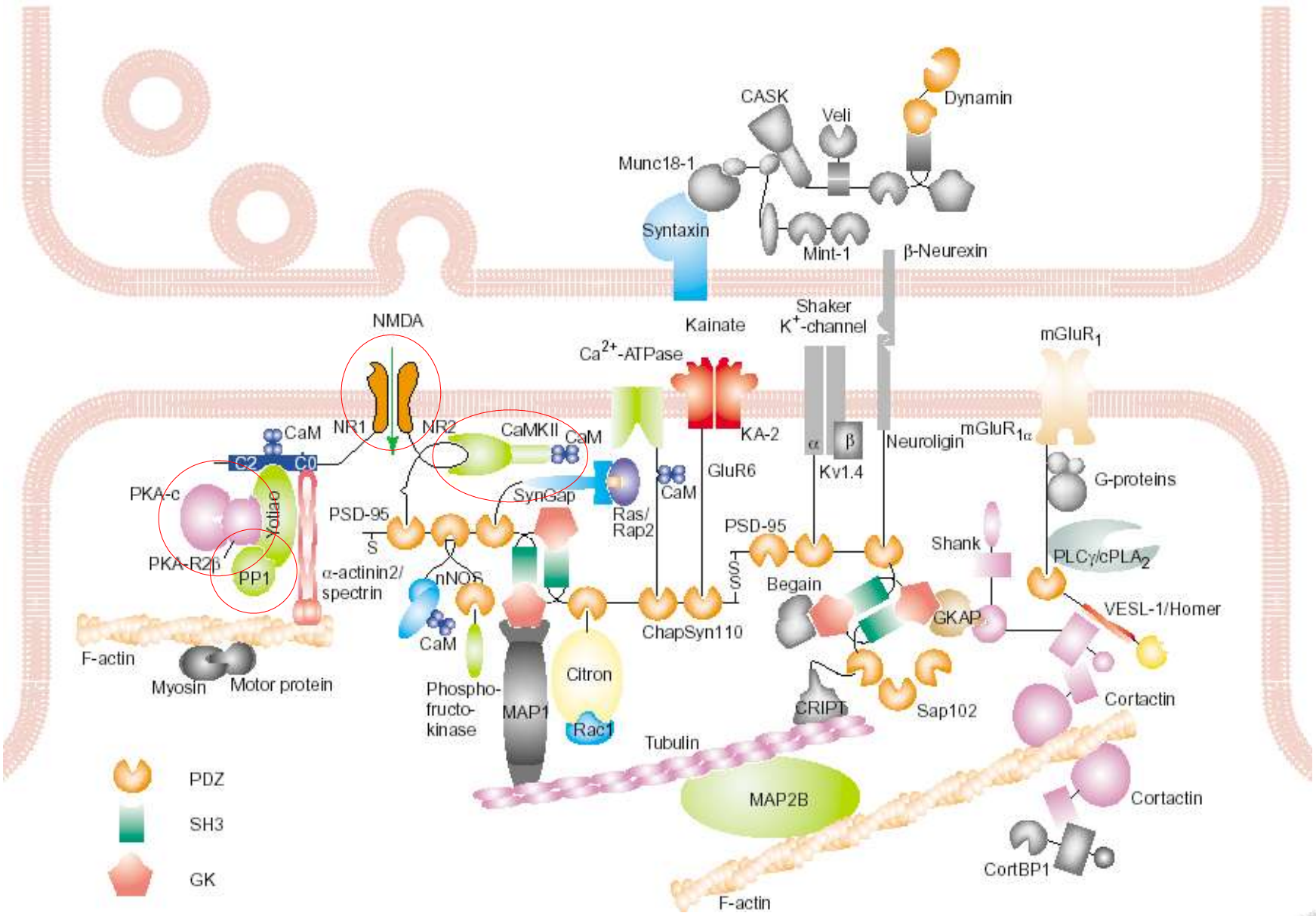
Movie NMJ

The position of receptors affects the signal



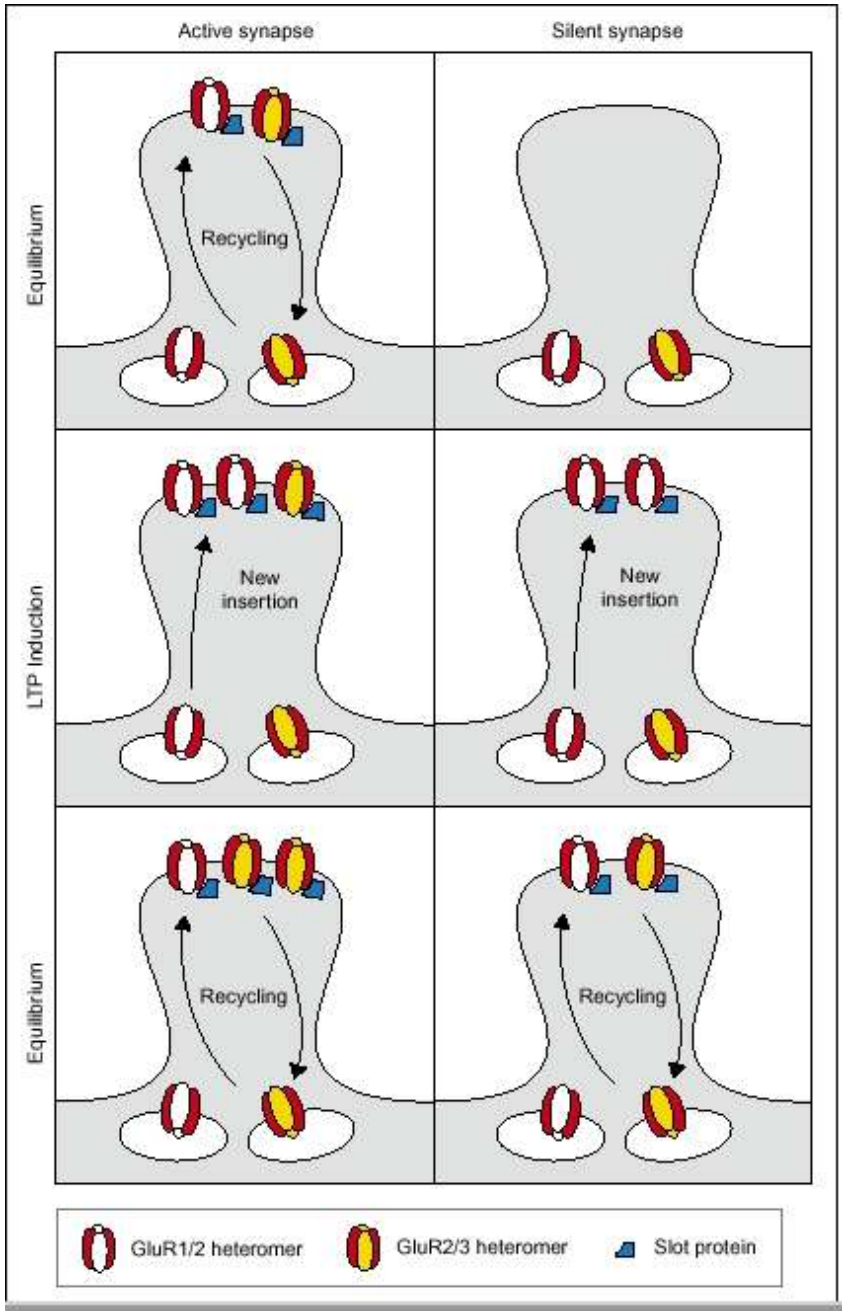
Franks et al. (2003) *J Neurosci*, 23: 3186-3195

Complex post-synaptic machinery

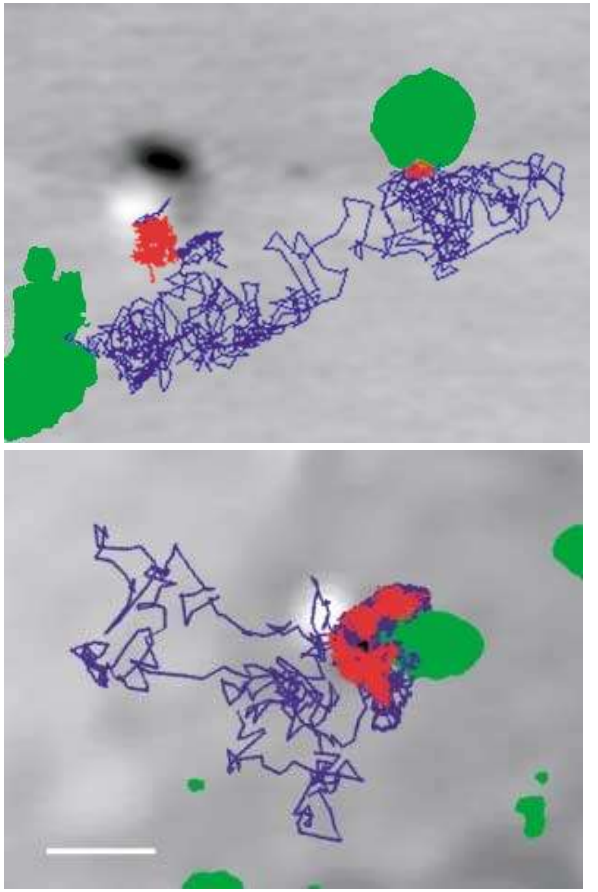


Husi & Grant (2001) *TINS, 24*: 259-266

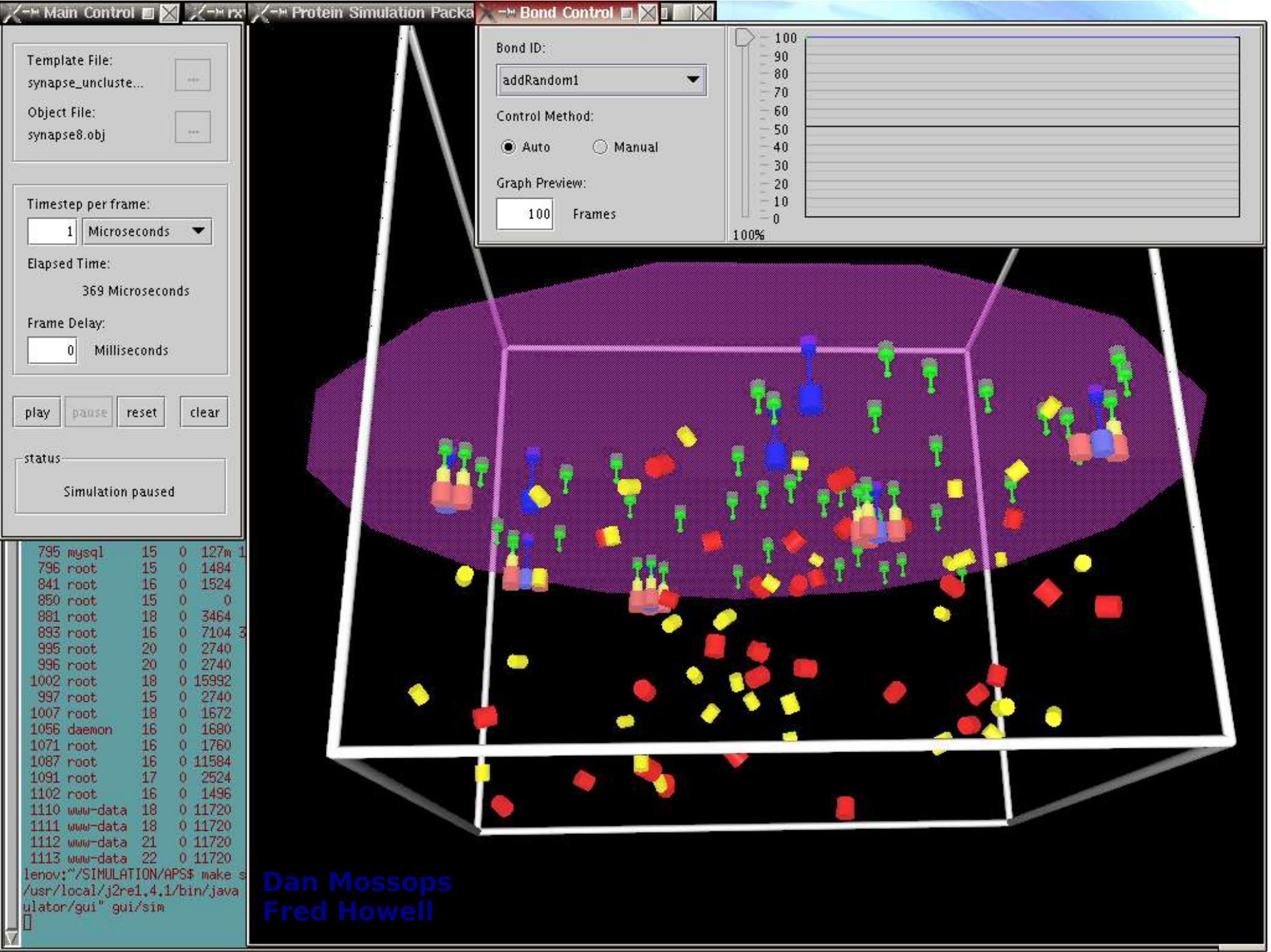
Receptors for neurotransmitters are moving



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



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


Main Control
Protein Simulation Packa
Bond Control
Template File:
synapse_uncluste...
Object File:
synapse8.obj
Timestep per frame:
1
Microseconds
Elapsed Time:
369 Microseconds
Frame Delay:
0
Milliseconds
play
pause
reset
clear
status
Simulation paused
Bond ID:
addRandom1
Control Method:
Auto
Manual
Graph Preview:
100
Frames
100%
795 mysql 15 0 127m 1
796 root 15 0 1484
841 root 16 0 1524
850 root 15 0 0
881 root 18 0 3464
893 root 16 0 7104 3
935 root 20 0 2740
936 root 20 0 2740
1002 root 18 0 15992
937 root 15 0 2740
1007 root 18 0 1672
1056 daemon 16 0 1680
1071 root 16 0 1760
1087 root 16 0 11584
1091 root 17 0 2524
1102 root 16 0 1496
1110 www-data 18 0 11720
1111 www-data 18 0 11720
1112 www-data 21 0 11720
1113 www-data 22 0 11720
lenov:~/SIMULATION/APS$ make s
/usr/local/j2re1.4.1/bin/java
ulator/gui" gui/sim
Dan Mossops
Fred Howell

G2C: Home - Mozilla

http://www.genes2cognition.org

Search

Genes to Cognition

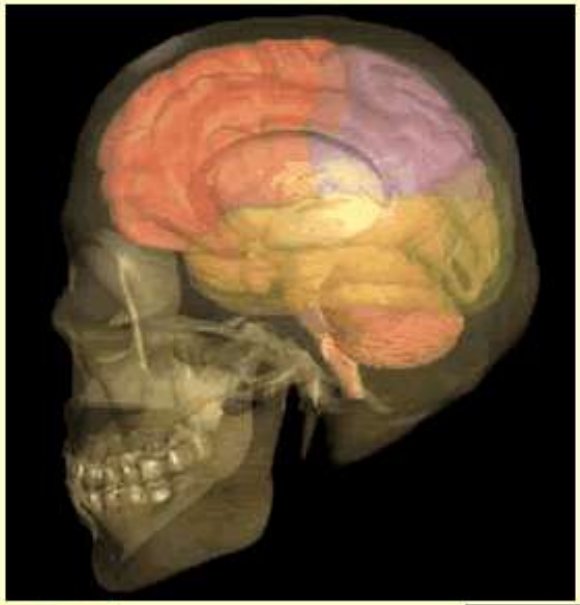
research consortium

a neuroscience research program supported by The Wellcome Trust

HOME | ABOUT | SCIENCE | PEOPLE | JOBS | LINKS | CONTACT | SITE MAP

Genes to Cognition

a neuroscience research programme



Select a picture for information..

Done

EMBL-EBI

DopaNet

Home
What Is DopaNet?
DopaNet Day
Molecular Pages
Neuronal Ontology
DopaNet Members
DopaNet Structure
Open Positions
How Can I Help?
Mailing Lists
Contact
Sign In

DopaNet:
The Meso-Telencephalic Dopamine Consortium

DopaNet aim is to investigate precisely and quantitatively all the aspects of neurotransmission - at the levels of the molecule, the supra-molecular assembly, the neuronal cell and the neuronal network - in a specific neuronal system, involved in many neuropathologies, such as Parkinson's disease, schizophrenia and drug abuse. The resulting integrated knowledge will not only provide relevant up-to-date information, methods and tools for the diagnosis and treatment of such pathologies, but will also form a firm substrate to link the function of the neurobiological structures with the implementation of cognitive and mental abilities.

News

NEW July 2004: The DopaNet Day will take place at Lille on Tuesday May 17th, as a satellite of the 7th Congress of the French Society for Neurosciences. The meeting is open to everyone.

March 2004: The construction of the Molecular Pages, aimed to store detailed functional information about molecules present in DopaNet target cells, has started. Everybody is invited to participate.

June 2003: The construction of an ontology of the neuronal cell has started. Everybody is invited to participate.

February 2003: The computing infrastructure of DopaNet will be hosted by the European Bioinformatics Institute (EBI), outstation of the European Molecular Biology Laboratory (EMBL).

December 2002: DopaNet is accepted as a Network of the European Science Foundation. A grant of 80 000 € is attributed for the period 2003-2005. (ESF Leaflet)

Search DopaNet

Google Google Search

DopaNet is supported by:

EMBL-EBI

EUROPEAN SCIENCE FOUNDATION ESF

INSTITUT PASTEUR

CNRS CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

EMBL-EBI

DopaNet

Current Molecular Pages

The following Molecular Pages have already been released.

To view a Molecular Page as a web-page, complete with hyperlinks to the various relevant resources, click on the Page molecule name (first column). A click on the ontology identifier of the second column should redirect to the relevant "leaf" of the DopaNet Neuronal Ontology.

If you wish to correct or complete a Page, please contact the Page maintainers (5th column).

Molecule Name	Ontology	Abbreviation	Last Modified	Maintainers
(alpha)_12 CaMKII	DA:0000561	CaMKIIa_12	2004-09-23	Nicolas Le Novère
(alpha4)_2(beta2)_2alpha5 nAChR	DA:0000421	nAChRa4_2b2_2a5	2004-09-09	Nicolas Le Novère
(alpha4)_2(beta2)_3 nAChR	DA:0000027	nAChRa4_2b2_3	2004-09-02	Nicolas Le Novère
(alpha6)_2(beta2)_3 nAChR	DA:0000031	nAChRa6_2b2_3	2004-09-09	Nicolas Le Novère
A1 adenosine receptor	DA:0000047	A1R	2004-06-22	Serge Schiffmann
A2a adenosine receptor	DA:0000048	A2aR	2004-12-14	Serge Schiffmann
alpha olf G-protein subunit	DA:0000218	Gaolf	2004-06-22	Denis Hervé
alpha7 homomeric nAChR	DA:0000023	nAChRa7_5	2004-09-09	Nicolas Le Novère
calcium/calmodulin-dependant protein kinase type IV	DA:0000562	CaMKIV	2004-09-09	Nicolas Le Novère
calmodulin	DA:0000565	CaM	2004-09-09	Nicolas Le Novère
DARPP32 dopamine- and cAMP-regulated phosphoprotein	DA:0000381	DARPP32	2004-11-29	Eric Fernandez
dopamine transporter	DA:0000092	DAT	2004-06-22	Bruno Giros
M1 muscarinic acetylcholine receptor	DA:0000040	M1R	2004-06-22	Véronique Bernard
M2 muscarinic acetylcholine receptor	DA:0000041	M2R	2004-06-22	Véronique Bernard
M3 muscarinic acetylcholine receptor	DA:0000042	M3R	2004-06-22	Véronique Bernard
M4 muscarinic acetylcholine receptor	DA:0000043	M4R	2004-06-22	Véronique Bernard
M5 muscarinic acetylcholine receptor	DA:0000044	M5R	2004-06-22	Véronique Bernard
transforming growth factor beta receptor type I	DA:0000311	TGFbR-I	2004-06-22	Amelia Sánchez Capelo
transforming growth factor beta receptor type II	DA:0000312	TGFbR-II	2004-06-22	Amelia Sánchez Capelo

					release); no proof at the molecular level
striatal enkephalinergic/GABAergic medium spiny neuron					
cell soma [DA:0000137]					
in situ hybridisation	All striatopallidal neurons expressing D2R and enkephalin		*Rattus norvegicus*	(3, 5, 6)	
in situ hybridisation			*Mus musculus*	(2)	
immunocytochemistry optical	Strong labelling.		*Rattus norvegicus*	(4)	
terminal button [DA:0000006]					
immunocytochemistry optical	Medium to strong labelling.		*Rattus norvegicus*	(4)	
cortical glutamatergic pyramidal neuron					
cell soma [DA:0000137]					
immunocytochemistry optical	very few cells in layer VI in cingulate cortex (as in other cortical areas) with a very weak expression, not qualified as pyramidal neurons		*Rattus norvegicus*	(4)	
terminal button [DA:0000006]					Available functionnal data arguing for the presence of A2A receptor in cortical neurons/terminals (facilitation of glutamate release); no proof at the molecular level
Function					
Binding					
adenosine [DA:0000195]					
	EC50	150 ± 17.3 nanomole per litre	*Rattus norvegicus*	(7)	EC50 in a adenylyl cyclase assay in rat PC12 cell membranes. No available data for the affinity properties (Kd,Ki, IC50) of this endonenous ligand to the receptor since all binding experiments are carried out in the presence of adenosine deaminase.
CGS21680					
A2aR active	Kd	13.1 ± 4.7 nanomole per litre	*Rattus norvegicus*	(8, 9, 10)	rat striatum, mean +/- SD of data from three articles giving values in the same range
A2aR active	Kd	31.4 ± 9.3 nanomole per litre	*Homo sapiens*	(11, 12)	human striatum, mean +/- SD of data from two articles giving about the same value
caffeine					
	IC50_CGS21680	47.8 ± 6.93 micromole per litre	*Homo sapiens*	(8)	
SCH58261					
A2aR inactive	Kd	1.4 ± 0.08 nanomole per litre	*Rattus norvegicus*	(13, 14)	rat striatum, mean +/- SD of data from two articles giving about the same value
A2aR inactive	Kd	1.1 ± 0.13 nanomole per litre	*Homo sapiens*	(15)	
Enzymatic function					

DopaNet

The Meso-Telencephalic Dopamine Consortium

EMBL-EBI

European Bioinformatics Institute

Systems Biology of Neuroadaptation in Mesotelencephalic Dopamine Pathways

Speakers

Keynote Speaker

Professor J. Paul Bolam, MRC Anatomical Pharmacology Unit, Oxford, UK

Synaptic plasticity and diversity of electrophysiological responses

Stephen Fitzjohn, MRC Center for Synaptic Plasticity, UK
Mark Ungless, University of Oxford, UK
Stephane Charpier, College de France, France
Kevin Gurney, University of Sheffield, UK

From the receptors to the molecular targets

Éric Fernandez, EMBL-EBI, UK
Kerstin Håkansson, Karolinska Institute, Sweden
Emmanuel Valjent, INSERM, France

Genetics of cellular plasticity

Peter Vanhoutte, Université Pierre et Marie Curie, France
Birgit Liss, Philipps University Marburg, Germany
Sabine Spijker, Free University of Amsterdam, Netherlands

Venue Information

Lille Grand Palais
1, Bd des Cités Unies
59777 Euralille,
Lille, FRANCE

On 17 May 2005, From 08:45-17:30

Organisers

Nicolas Le Novère
Jean-Antoine Girault
Marie-Claude Potier

The meeting is open to everyone. Students of DopaNet teams are eligible for a refunding of their travel and accomodation expenses.

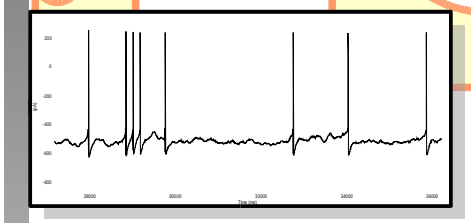
The Webpage

http://www.ebi.ac.uk/compneur-srv/dopanet/dopanetDay.php

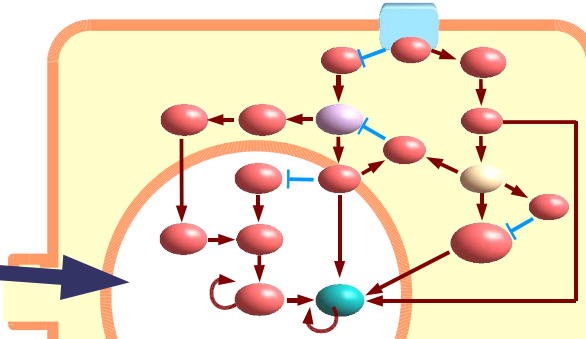
Sponsored by

EUROPEAN SCIENCE FOUNDATION

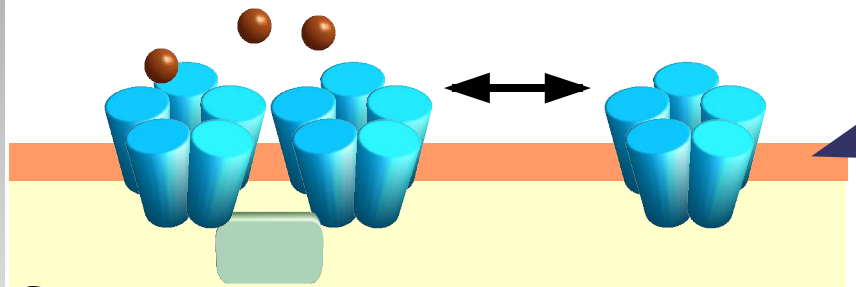
Multi-scale multi-algorithm problem



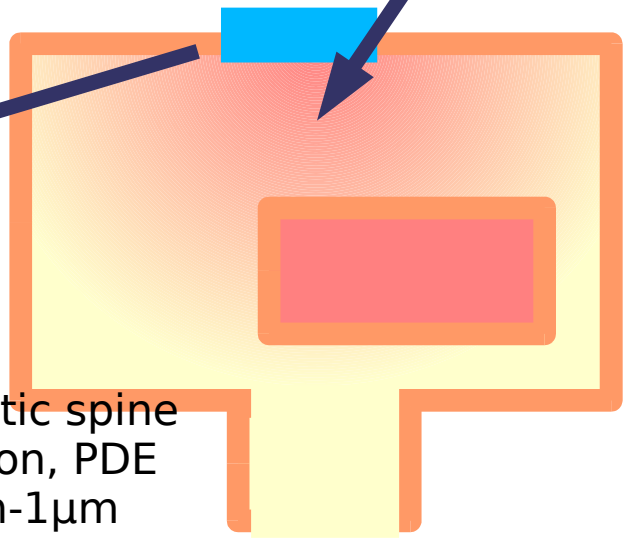
Whole-neuron
Cable theory
1µm-1m
1ms-1week



Signaling network
ODE
1µm-10µm
1s-1d

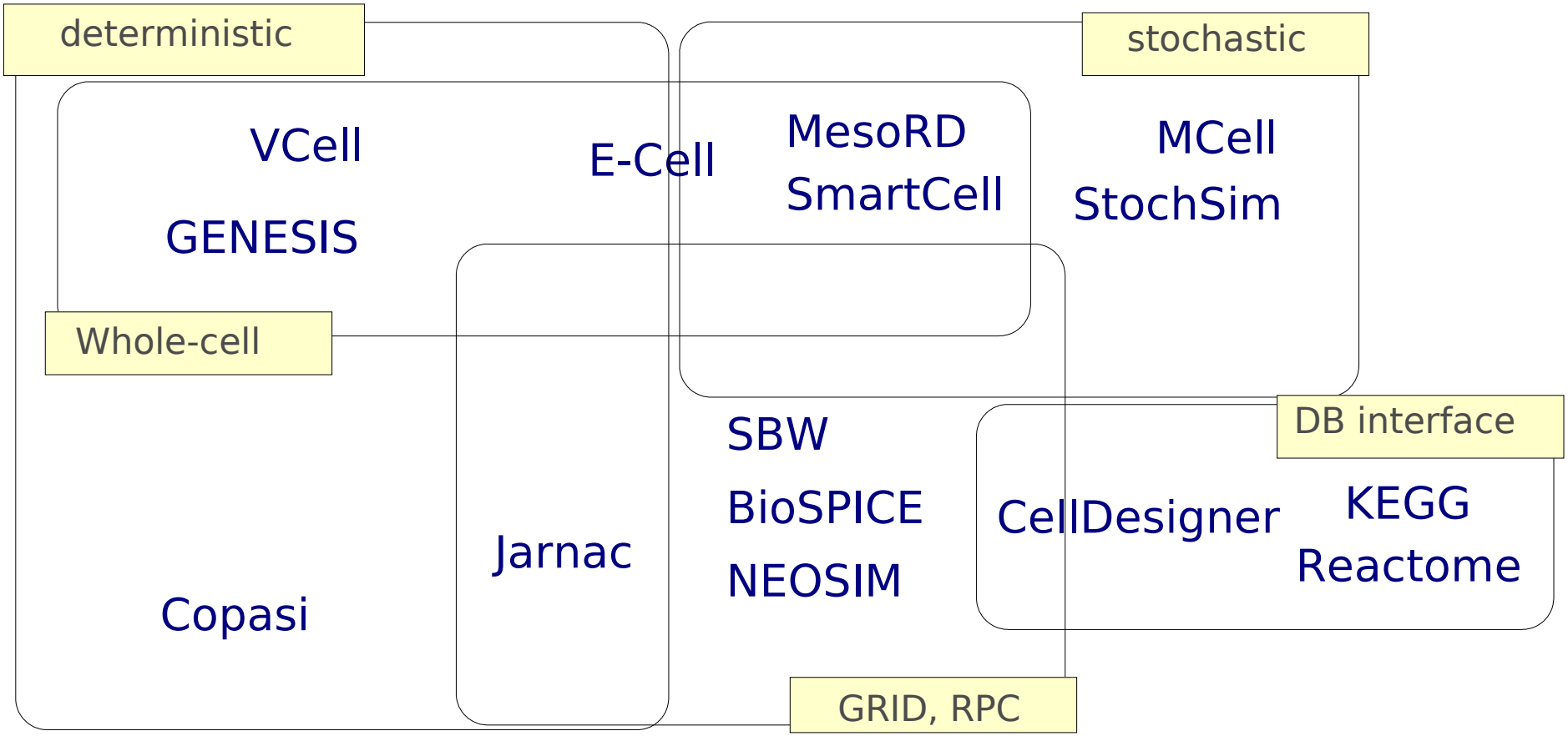


Synapse
Stochastic algorithm
1nm-100nm
1µs-1ms



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

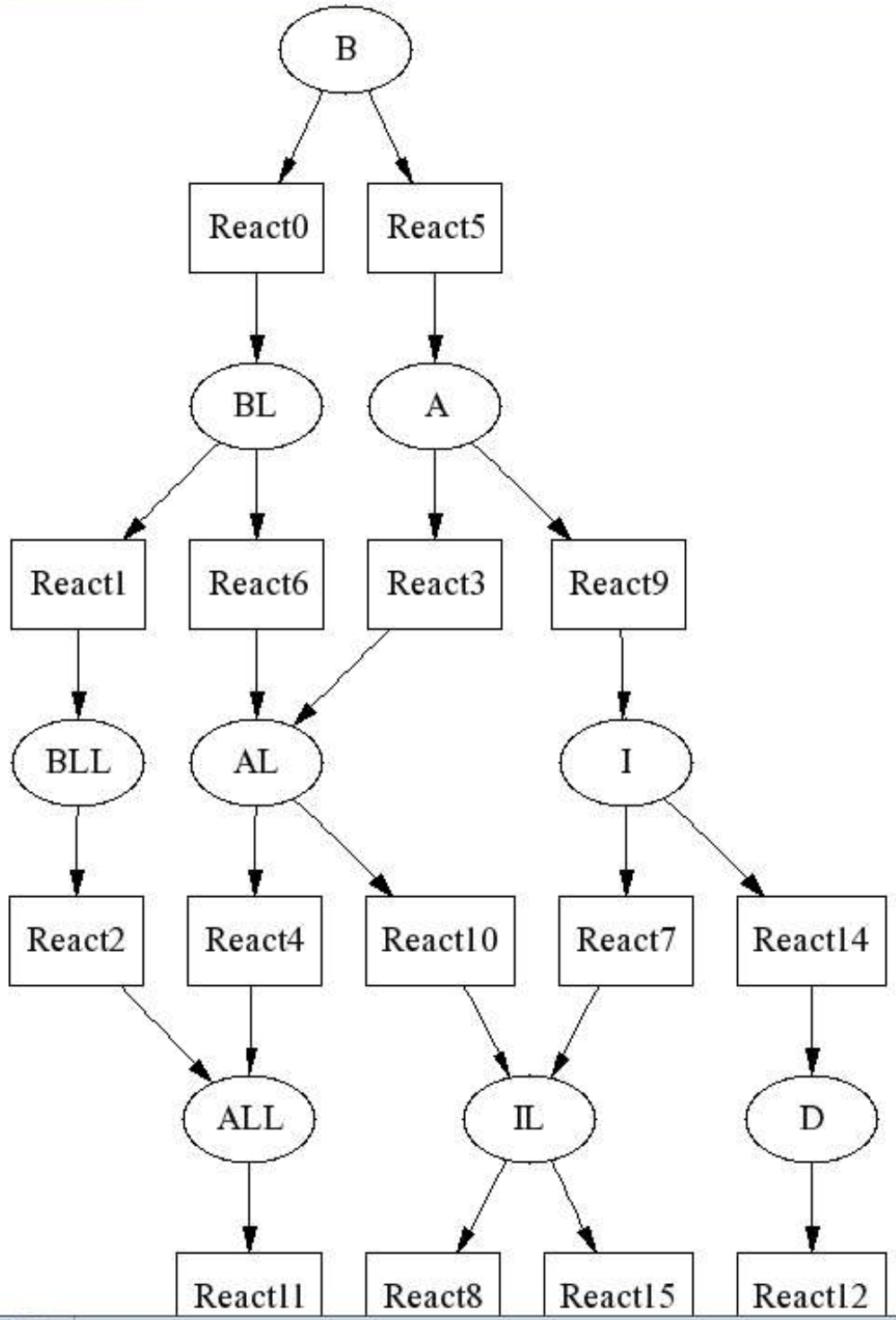
Forum meeting in October!

(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.


B
React0
React5
BL
A
React1
React6
React3
React9
BLL
AL
I
React2
React4
React10
React7
React14
ALL
IL
D
React11
React8
React15
React12

Requirements for mathematical models

- Bench biologists need to find models relevant for their research.
- Modellers need to reuse existing models, or portions of models, rather than rewrite them from scratch. Model composition on a large scale will be possible only if we have such a model “shopping cart”.
- But ...
  - No true database of models, only repositories, sometimes with side information.
  - few quality control on the models available online (JWS excepted).
  - No annotation of models: reactants are A,B,C, reactions 1, 2, 3 etc.
  - Lack of standards on production, curation and annotation of models.
- ⇒ Biomodels.net: collaboration between Caltech, EMBL-EBI, SBI, JWS etc. etc.
  - SBML: Systems Biology Markup Language
  - MIRIAM:
    Minimum Information Requested In the Annotation of Models
  - Controlled vocabularies:
    - Parameters: Kd, Ka, Kp, IC50 ARE DIFFERENT!
    - “Michaelis-Menten”, “Mass Action Law” etc.
  - Biomodels database, a database of “Systems Biology Models”

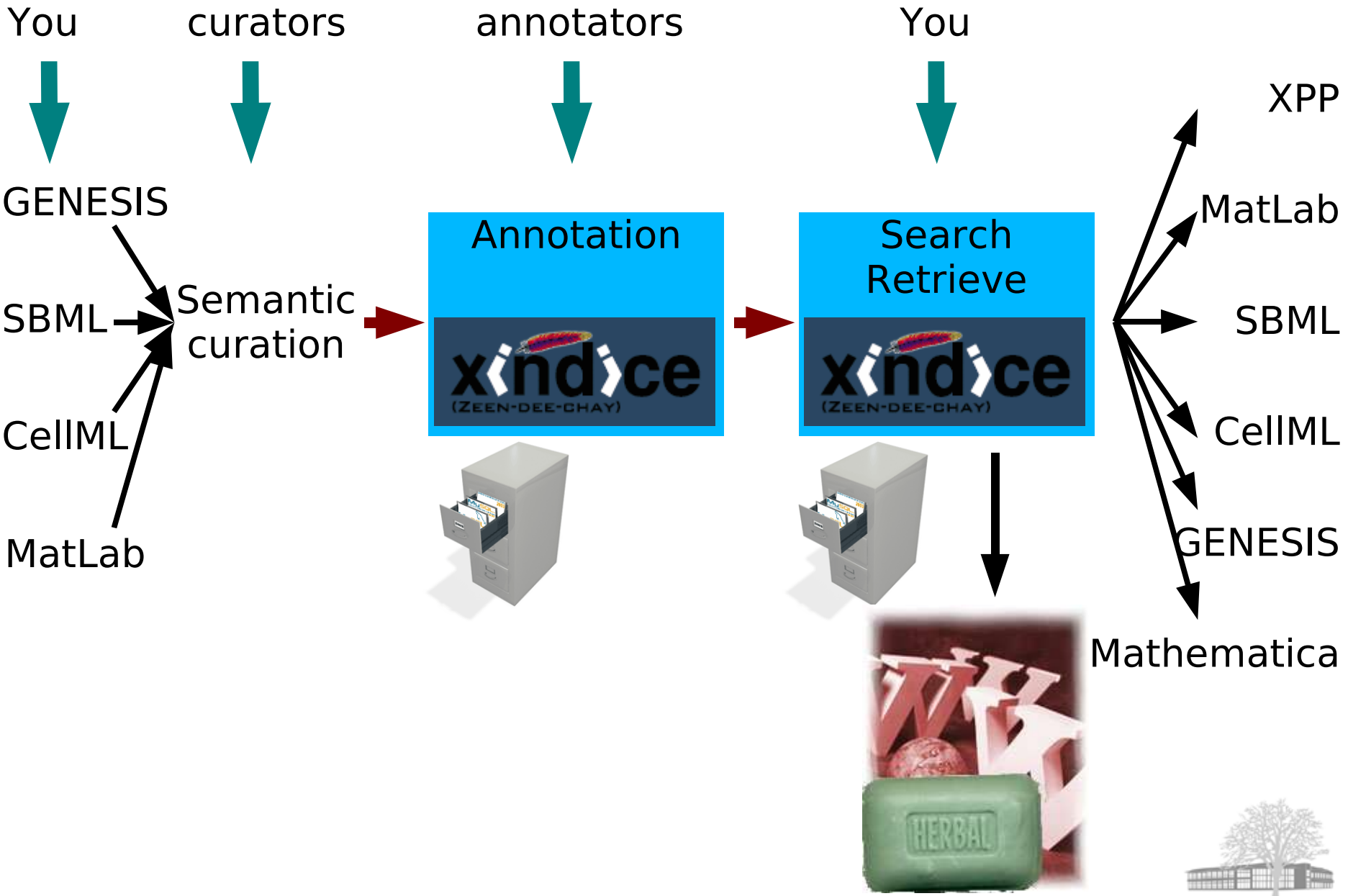
Models repositories already exist

- SBML model repository [SBML]
- CellML models repository [CellML][curation][search]
- JWS online [SBML, Pysces][curation]
- E-Cell Developer Network [E-Cell, SBML]
- DOQCS [GENESIS][curation][search]
- SenseLab ModelDB [NEURON, GENESIS]
- ...

Biomodels database

- Originally a collaboration between the EMBL-EBI, and SBML core team. Forthcoming collaborations: Keck Graduate Institute, EML, JWS plus X plus Y plus you.
- Each model served by the database will be published (submitted or in the press will be processed but kept private).
- To be accepted in biomodels, a model has to be semantically correct, i.e. when instanciated, provides values corresponding “well” to the results described in the publication.
- Model components are annotated: creator, publication, Gene Ontology, Taxonomy, Reactome, UniProt, KEGG, OMIM, ChEBI etc.
  ⇒ search for all models related to “synaptic plasticity”, “Hodgkin” or “CALM_HUMAN”

Structure of Biomodels



BIOMODELS.NET

BioModels Demo

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

Search Models

You can search for models using one or more of the following criteria:

- *BioModels ID* → Allows to retrieve only the models whose BioModels identifier contains the entered string. For instance, if you enter *3*, only the models with BioModels identifier *BIOMD0000000003*, *BIOMD0000000013*, *BIOMD0000000033*, etc., are returned.
- *Person* → Permits to retrieve only the models where the full name of the submitter, and/or of the creators, contains the entered string. For instance, if you enter *Nicolas*, only the models submitted by *Nicolas Le Novère* are returned; if you enter *Shapiro*, only the models created by *Bruce Shapiro* are returned.
- *SBML Elements* → Allows to retrieve only the models whose names of various SBML elements (such as model, compartments, species, reactions, etc.) contain the entered string, for example *ach* or *mapk*.
- *Publication* → Permits to retrieve only the models whose publication PubMed ID, title and/or abstract contain the entered string, for example *9256450* or *cyclin*.
- *Resource ID* → Permits to retrieve only the models whose SBML element annotations contain the entered identifier for the selected resource, for example *CHEBI:15422* or *15422* for ChEBI, *GO:0007049* or *7049* for Gene Ontology, *69278* for Reactome, or *6616* for Taxonomy.

For each criteria, the search operates on a *contains the entered string basis*, case-insensitive. That is, searching *Person* for *Nico* or *nico* will return the same results as searching for *Nicolas* or *nicolas*. In addition, since search strings are treated as words, do not enter regular expressions.

Multiple criteria can be combined with either *and* or *or*. If *and* is selected, only those models satisfying all the criteria will be returned. If instead *or* is selected, all the models satisfying at least one of the criteria will be returned.

BioModels ID:

Person:

SBML Elements:

Publication:

Resource ID: BIND

Resource ID: BIND

Resource ID: BIND

Compose by: and or

Search Reset

BIOMODELS.NET

BioModels Demo

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

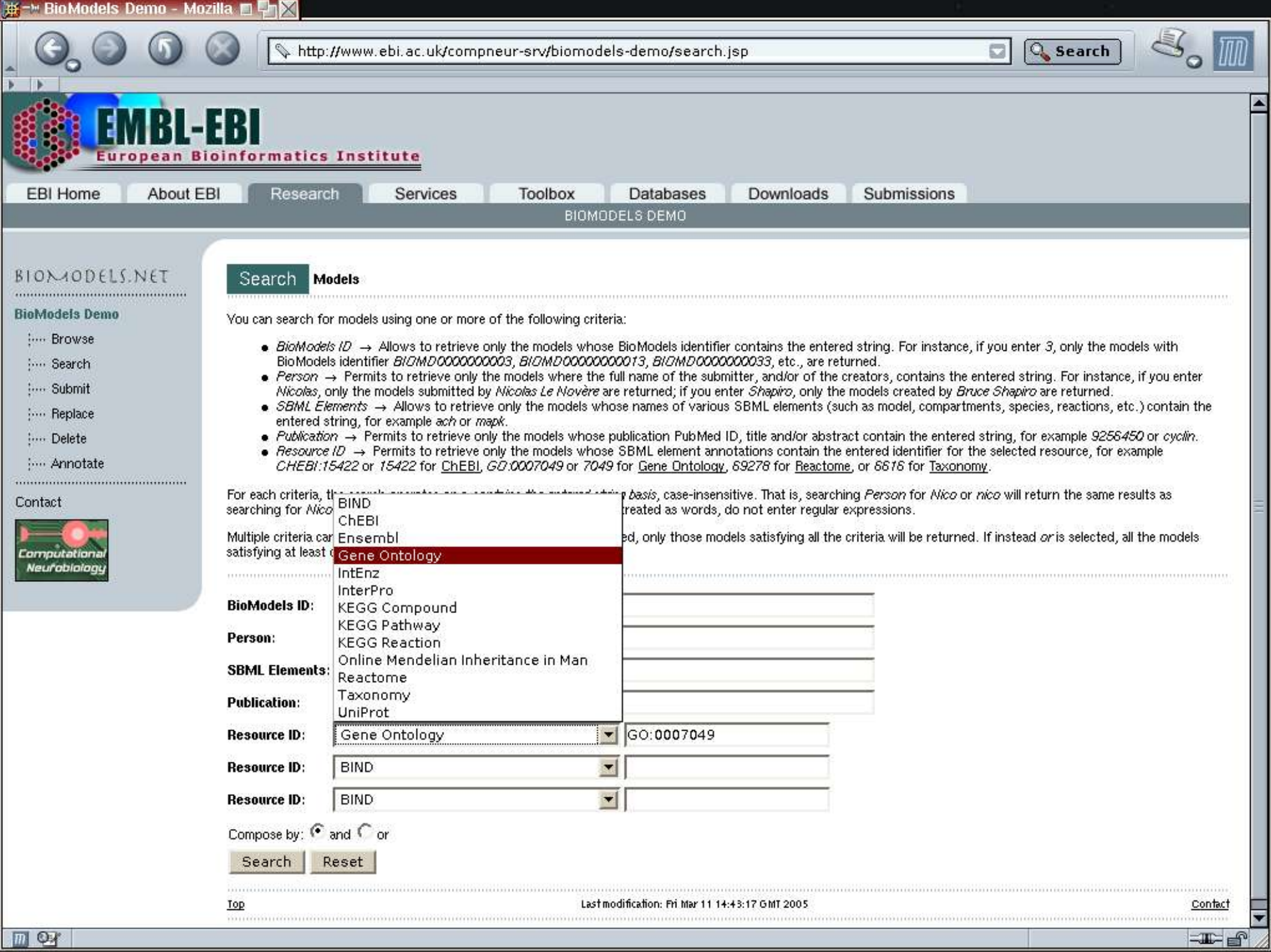
Search Models

The search returned **3** models.

New Search

BioModels ID	Name	Submitter	Last Modified	PubMed Id	
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	Nicolas Le Novère	2005-02-11T22:35:24	9826676	SBML
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	Nicolas Le Novère	2005-03-07T23:42:13	10823939	SBML
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	Nicolas Le Novère	2005-03-08T00:11:41	10823939	SBML

New Search


BioModels Demo - Mozilla
http://www.ebi.ac.uk/compneur-srv/biomodels-demo/search.jsp
Search
EMBL-EBI
European Bioinformatics Institute
EBI Home
About EBI
Research
Services
Toolbox
Databases
Downloads
Submissions
BIOMODELS DEMO
BIOMODELS.NET
BioModels Demo
Browse
Search
Submit
Replace
Delete
Annotate
Contact
Computational Neurobiology
Search Models
You can search for models using one or more of the following criteria:
BioModels ID → Allows to retrieve only the models whose BioModels identifier contains the entered string. For instance, if you enter 3, only the models with BioModels identifier BIOMD0000000003, BIOMD0000000013, BIOMD0000000033, etc., are returned.
Person → Permits to retrieve only the models where the full name of the submitter, and/or of the creators, contains the entered string. For instance, if you enter Nicolas, only the models submitted by Nicolas Le Novère are returned; if you enter Shapiro, only the models created by Bruce Shapiro are returned.
SBML Elements → Allows to retrieve only the models whose names of various SBML elements (such as model, compartments, species, reactions, etc.) contain the entered string, for example ach or mapk.
Publication → Permits to retrieve only the models whose publication PubMed ID, title and/or abstract contain the entered string, for example 9258450 or cyclin.
Resource ID → Permits to retrieve only the models whose SBML element annotations contain the entered identifier for the selected resource, for example CHEBI:15422 or 15422 for ChEBI, GO:0007049 or 7049 for Gene Ontology, 69278 for Reactome, or 6616 for Taxonomy.
basis, case-insensitive. That is, searching Person for Nico or nico will return the same results as
treated as words, do not enter regular expressions.
ed, only those models satisfying all the criteria will be returned. If instead or is selected, all the models
BIND
ChEBI
Ensembl
Gene Ontology
IntEnz
InterPro
KEGG Compound
KEGG Pathway
KEGG Reaction
Online Mendelian Inheritance in Man
Reactome
Taxonomy
UniProt
BioModels ID:
Person:
SBML Elements:
Publication:
Resource ID:
Gene Ontology
GO:0007049
Resource ID:
BIND
Resource ID:
BIND
Compose by: and or
Search
Reset
Top
Last modification: Fri Mar 11 14:43:17 GMT 2005
Contact

BIOMODELS.NET

BioModels Demo

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

Search Models

The search returned **6** models.

New Search

BioModels ID	Name	Submitter	Last Modified	PubMed Id	
BIOMD0000000003	Goldbeter1991_MinMitOscil	Nicolas Le Novère	2005-02-10T14:33:09	1833774	SBML
BIOMD0000000004	Goldbeter1991_MinMitOscil_ExplInact	Nicolas Le Novère	2005-02-10T14:33:43	1833774	SBML
BIOMD0000000005	Tyson1991_CellCycle_6var	Nicolas Le Novère	2005-03-08T00:21:09	1831270	SBML
BIOMD0000000006	Tyson1991_CellCycle_2var	Nicolas Le Novère	2005-02-08T18:37:08	1831270	SBML
BIOMD0000000007	Novak1997_CellCycle_13var	Nicolas Le Novère	2005-02-10T14:28:48	9256450	SBML
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	Nicolas Le Novère	2005-02-11T22:35:24	9826676	SBML

New Search

Top

Last modification: Fri Mar 11 14:43:17 GMT 2005

Contact

BIOMODELS.NET

BioModels Demo

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

Search Models

The search returned **6** models.

New Search

BioModels ID	Name	Submitter	Last Modified	PubMed Id	
BIOMD0000000003	Goldbeter1991_MinMitOscil	Nicolas Le Novère	2005-02-10T14:33:09	1833774	SBML
BIOMD0000000004	Goldbeter1991_MinMitOscil_ExplInact	Nicolas Le Novère	2005-02-10T14:33:43	1833774	SBML
BIOMD0000000005	Tyson1991_CellCycle_6var	Nicolas Le Novère	2005-03-08T00:21:09	1831270	SBML
BIOMD0000000006	Tyson1991_CellCycle_2var	Nicolas Le Novère	2005-02-08T18:37:08	1831270	SBML
BIOMD0000000007	Novak1997_CellCycle_13var	Nicolas Le Novère	2005-02-10T14:28:48	9256450	SBML
BIOMD0000000008	Gardner1998_CellCycle_Goldbeter	Nicolas Le Novère	2005-02-11T22:35:24	9826676	SBML

New Search

Top

Last modification: Fri Mar 11 14:43:17 GMT 2005

Contact

Contact

Reference Publication: 9256450

Creators: Bruce Shapiro

Compartments

Species

Reactions

Reaction1
Reactants: Empty Set
Products: mass
Modifiers:

Reaction2
Reactants: Empty Set
Products: G2K
Modifiers:

Reactome	68910 69282

Reaction3
Reactants: G2K
Products: Empty Set
Modifiers: UbE

Gene Ontology	GO:0008054
Reactome	69271 69766

Reaction4
Reactants: Empty Set
Products: R
Modifiers:

Reaction5
Reactants: R
Products: Empty Set
Modifiers:

Reaction6
Reactants: G2K
Products: PG2
Modifiers: Wee1

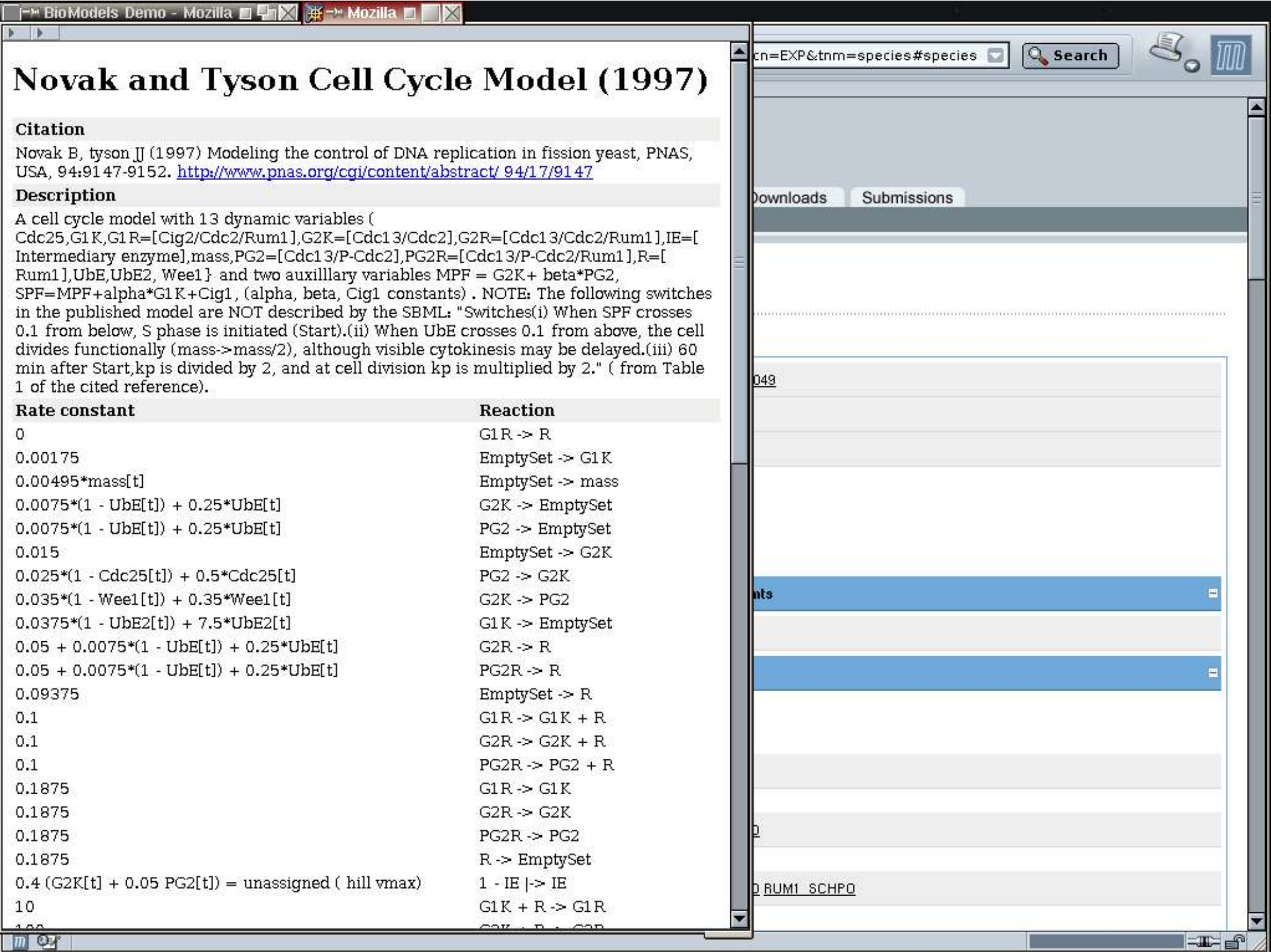
Gene Ontology	GO:0045736
Reactome	69260

Reaction7
Reactants: PG2
Products: G2K
Modifiers: Cdc25

Gene Ontology	GO:0045737
Reactome	69263

Reaction8
Reactants: G2K R
Products: G2R
Modifiers:

Reaction9



Novak and Tyson Cell Cycle Model (1997)

Citation

Novak B, tyson JJ (1997) Modeling the control of DNA replication in fission yeast, PNAS, USA, 94:9147-9152. http://www.pnas.org/cgi/content/abstract/ 94/17/9147

Description

A cell cycle model with 13 dynamic variables (Cdc25,G1K,G1R=[Cig2/Cdc2/Rum1],G2K=[Cdc13/Cdc2],G2R=[Cdc13/Cdc2/Rum1],IE=[Intermediary enzyme],mass,PG2=[Cdc13/P-Cdc2],PG2R=[Cdc13/P-Cdc2/Rum1],R=[Rum1],UbE,UbE2, Wee1} and two auxilllary variables MPF = G2K+ beta*PG2, SPF=MPF+alpha*G1K+Cig1, (alpha, beta, Cig1 constants) . NOTE: The following switches in the published model are NOT described by the SBML: "Switches(i) When SPF crosses 0.1 from below, S phase is initiated (Start).(ii) When UbE crosses 0.1 from above, the cell divides functionally (mass->mass/2), although visible cytokinesis may be delayed.(iii) 60 min after Start,kp is divided by 2, and at cell division kp is multiplied by 2." (from Table 1 of the cited reference).

Rate constant	Reaction
0	G1R -> R
0.00175	EmptySet -> G1K
0.00495*mass[t]	EmptySet -> mass
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2K -> EmptySet
0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2 -> EmptySet
0.015	EmptySet -> G2K
0.025*(1 - Cdc25[t]) + 0.5*Cdc25[t]	PG2 -> G2K
0.035*(1 - Wee1[t]) + 0.35*Wee1[t]	G2K -> PG2
0.0375*(1 - UbE2[t]) + 7.5*UbE2[t]	G1K -> EmptySet
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	G2R -> R
0.05 + 0.0075*(1 - UbE[t]) + 0.25*UbE[t]	PG2R -> R
0.09375	EmptySet -> R
0.1	G1R -> G1K + R
0.1	G2R -> G2K + R
0.1	PG2R -> PG2 + R
0.1875	G1R -> G1K
0.1875	G2R -> G2K
0.1875	PG2R -> PG2
0.1875	R -> EmptySet
0.4 (G2K[t] + 0.05 PG2[t]) = unassigned (hill vmax)	1 - IE |-> IE
10	G1K + R -> G1R

Reactome: Formation of CyclinA/B:Cdc2 complexes - Mozilla

File Edit View Go Bookmarks Tools Window Help

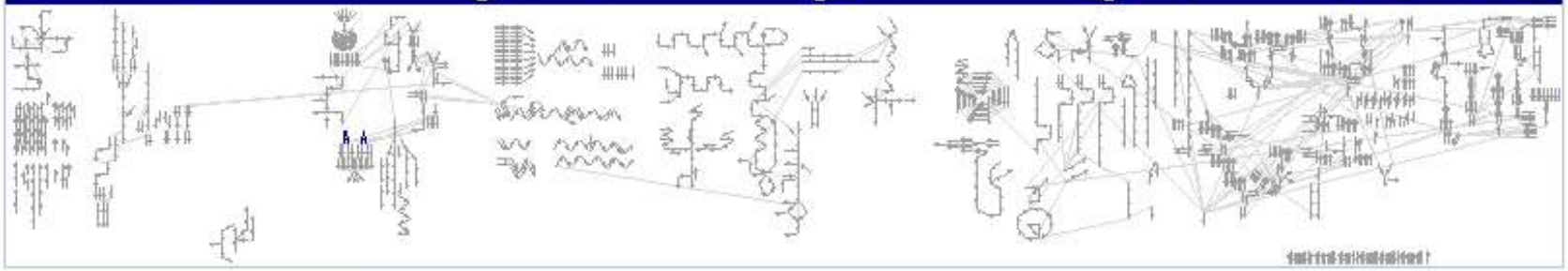
http://www.reactome.org/cgi-bin/eventbrowser?DB=gk_current&ID=68910

Search

About | TOC | User Guide | Data Model | Schema | Extended search | PathFinder | SkyPainter | Download | Linking | Citing

Find everything with ALL of the words in Homo sapiens Go!

Click on the map: shifts focus zooms in zooms out



[Reactome Home]

+ Cell Cycle, Mitotic

+ G2/M Transition

+ Cyclin A/B associated events during G2/M transition

- **Formation of CyclinA/B:Cdc2 complexes [Homo sapiens]**

Formation of Cyclin B2:Cdc2 complexes

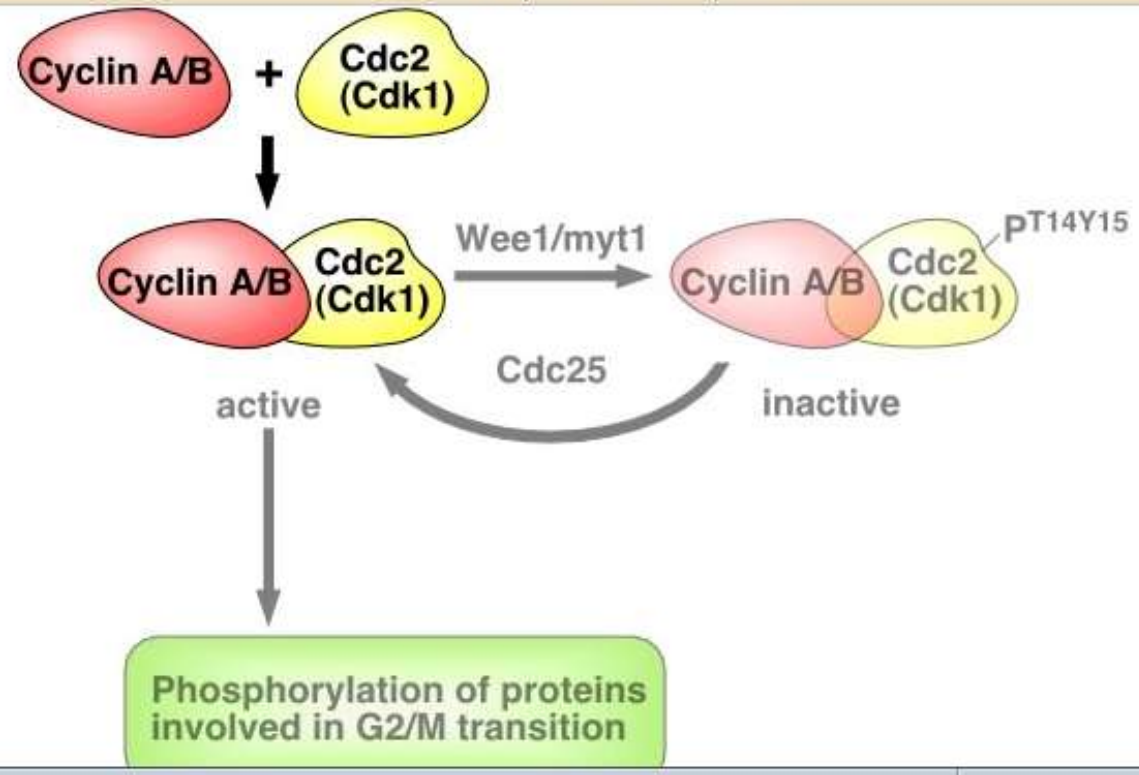
Formation of Cyclin B1:Cdc2 complexes

Formation of Cyclin A2:Cdc2 complexes

Formation of Cyclin A1:Cdc2 complexes

Show hierarchy types

Formation of CyclinA/B:Cdc2 complexes



Done

BIOMODELS.NET

BioModels Demo

- Browse
- Search
- Submit
- Replace
- Delete
- Annotate

Contact

Computational Neurobiology

Search Models

The search returned **4** models.

New Search

BioModels ID	Name	Submitter	Last Modified	PubMed Id	
BIOMD0000000009	Huang1996_MAPK_ultrasens	Nicolas Le Novère	2005-03-06T23:15:46	8816754	SBML
BIOMD0000000010	Kholodenko2000_MAPK_feedback	Nicolas Le Novère	2005-02-12T17:31:53	10712587	SBML
BIOMD0000000011	Levchenko2000_MAPK_noScaffold	Nicolas Le Novère	2005-03-07T23:42:13	10823939	SBML
BIOMD0000000014	Levchenko2000_MAPK_Scaffold	Nicolas Le Novère	2005-03-08T00:11:41	10823939	SBML

New Search

Top

Last modification: Fri Mar 11 14:43:17 GMT 2005

Contact

BIOMD0000000010 Kholodenko2000_MAPK_feedback

Download SBML

Submitter: Nicolas Le Novère

Submission Date: 2005-02-12T00:18:12

Last Modification Date: 2005-02-12T17:31:53

Reference Publication: 10712587

Creators: Herbert Sauro

Gene Ontology	GO:0000165
Taxonomy	8355

Compartments

uVol

Species

MAPKKK Compartment: uVol Initial Amount: 90	UniProt RAF1_XENLA
MAPKKK-P Compartment: uVol Initial Amount: 10	UniProt RAF1_XENLA
MAPKK Compartment: uVol Initial Amount: 280	UniProt MP2K1_XENLA
MAPKK-P Compartment: uVol Initial Amount: 10	UniProt MP2K1_XENLA
MAPKK-PP Compartment: uVol Initial Amount: 10	UniProt MP2K1_XENLA
MAPK Compartment: uVol Initial Amount: 280	UniProt MK01_XENLA
MAPK-P Compartment: uVol Initial Amount: 10	UniProt MK01_XENLA
MAPK-PP Compartment: uVol	UniProt MK01_XENLA

Display Abstract Show: 20 Sort Send to Text

All: 1 Review: 0

1: Eur J Biochem. 2000 Mar;267(6):1583-8.

Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades.

Kholodenko BN.

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA 19107, USA. Boris.Kholodenko@mail.tju.edu

Functional organization of signal transduction into protein phosphorylation cascades, such as the mitogen-activated protein kinase (MAPK) cascades, greatly enhances the sensitivity of cellular targets to external stimuli. The sensitivity increases multiplicatively with the number of cascade levels, so that a tiny change in a stimulus results in a large change in the response, the phenomenon referred to as ultrasensitivity. In a variety of cell types, the MAPK cascades are imbedded in long feedback loops, positive or negative, depending on whether the terminal kinase stimulates or inhibits the activation of the initial level. Here we demonstrate that a negative feedback loop combined with intrinsic ultrasensitivity of the MAPK cascade can bring about sustained oscillations in MAPK phosphorylation. Based on recent kinetic data on the MAPK cascades, we predict that the period of oscillations can range from minutes to hours. The phosphorylation level can vary between the base level and almost 100% of the total protein. The oscillations of the phosphorylation cascades and slow protein diffusion in the cytoplasm can lead to intracellular waves of phospho-proteins.

PMID: 10712587 [PubMed - indexed for MEDLINE]

Display Abstract Show: 20 Sort Send to Text

Species

Reactions

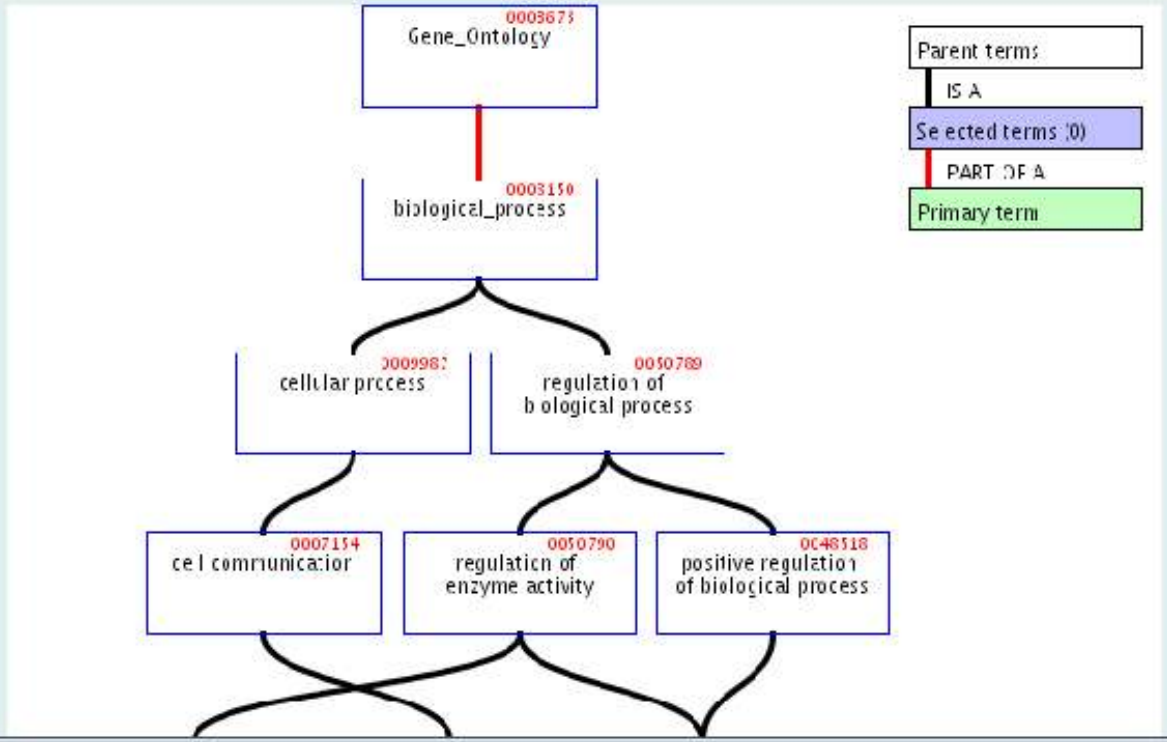
MAPKKK activation Reactants: MAPKKK Products: MAPKKK-P Modifiers: MAPK-PP	**Gene Ontology** GO:0000185 GO:0008349
MAPKKK inactivation Reactants: MAPKKK-P Products: MAPKKK Modifiers:	
phosphorylation of MAPKK Reactants: MAPKK Products: MAPKK-P Modifiers: MAPKKK-P	**Gene Ontology** GO:0004709
phosphorylation of MAPKK-P Reactants: MAPKK-P Products: MAPKK-PP Modifiers: MAPKKK-P	**Gene Ontology** GO:0000186 GO:0004709
dephosphorylation of MAPKK-PP Reactants: MAPKK-PP Products: MAPKK-P Modifiers:	
dephosphorylation of MAPKK-P Reactants: MAPKK-P Products: MAPKK Modifiers:	
phosphorylation of MAPK Reactants: MAPK Products: MAPK-P Modifiers: MAPKK-PP	**Gene Ontology** GO:0004708
phosphorylation of MAPK-P Reactants: MAPK-P Products: MAPK-PP Modifiers: MAPKK-PP	**Gene Ontology** GO:0000187 GO:0004708
dephosphorylation of MAPK-PP Reactants: MAPK-PP Products: MAPK-P Modifiers:	**Gene Ontology** GO:0000188
dephosphorylation of MAPK-P Reactants: MAPK-P Products: MAPK Modifiers:	

Download SBML

QuickGO GO Term GO:0000185

[?] = help

Term ID [?]	GO:0000185
Name [?]	activation of MAPKKK
Last updated [?]	2001-03-30 04:29:44.0
Definition [?]	Upregulation of MAPKKK activity in response to a signal.
Synonyms [?]	activation of MAP kinase kinase kinase positive regulation of MAP kinase kinase kinase activity positive regulation of MAPKKK activity
Hierarchy [?]	• View this term's parents in a denormalised tree. • View with neither graph nor tree. • Hide all selected terms except the primary one • Add more terms to the selection with a search



```
<reaction id="React13" metaid="000029" name="React13">
    <annotation>
        <rdf:RDF xmlns:dc="http://purl.org/dc/elements/1.1/" xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.or
            <rdf:Description rdf:about="#000029">
                <rdf:Bag>
                    <rdf:li>
                        <dc:relation rdf:resource="http://www.geneontology.org/">
                            GO:0042166
                        </dc:relation>
                    </rdf:li>
                </rdf:Bag>
            </rdf:Description>
        </rdf:RDF>
    </annotation>
    <notes>
        <body xmlns="http://www.w3.org/1999/xhtml">
            <p>second ligand on desensitised</p>
        </body>
    </notes>
    <listOfReactants>
        <speciesReference species="DL" />
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="DLL" />
    </listOfProducts>
    <kineticLaw>
        <notes>
            <body xmlns="http://www.w3.org/1999/xhtml">
                <p>(kf_13 * DL - kr_13 * DLL) * compl</p>
            </body>
        </notes>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <minus />
                <apply>
                    <times />
                    <ci>kf_13</ci>
                    <ci>DL</ci>
                </apply>
                <apply>
                    <times />
                    <ci>kr_13</ci>
                    <ci>DLL</ci>
                </apply>
            </apply>
        </math>
```

The team







- Nicolas Le Novère
- Alexander Broicher
- Mélanie Courtot
- Marco Donizelli
- Éric Fernandez
- Nicolas Rodriguez
- Dominic Tölle