Modélisation systémique de la transduction du signal dans les neurones. Changements d'échelles et niveaux d'analyse

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http://www.ebi.ac.uk/compneur/

Neurobiologie != Neuroscience (s)

- Neurosciences computationnelles
  - Modélisation et simulation des phénomènes liés au système nerveux (*neural*)
    i.e. : réseaux de neurones formels, modèles comportementaux, sciences cognitives etc.
- Neurobiologie computationnelle
  - Modélisation et simulation des phénomènes liés au fonctionnement du neuron (*neuronal*)
    i.e. : Modélisation des réseaux de signalisation, des fonctions synaptique, du remodelage dendritique etc.

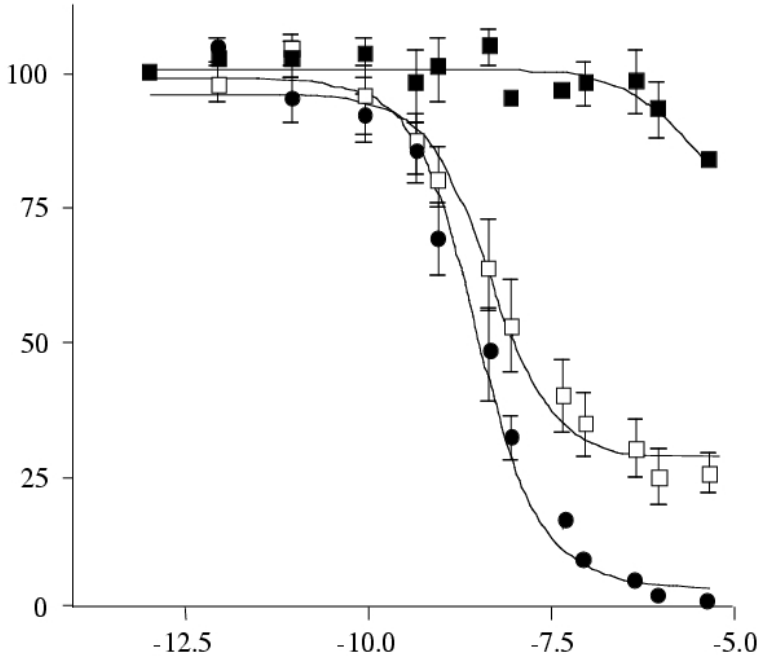
Simulation en neurobiologie

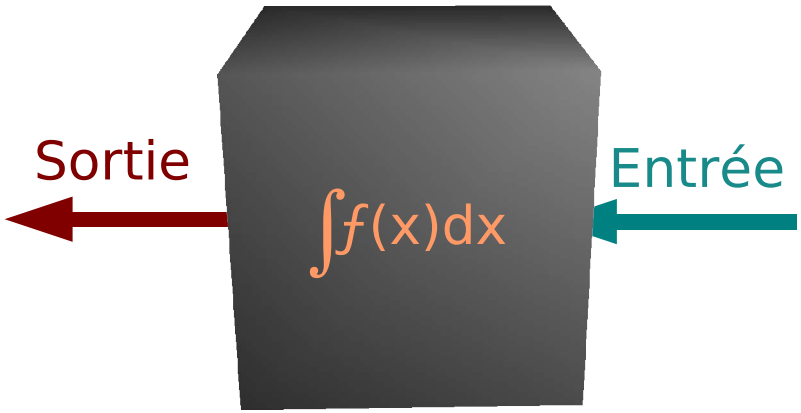
- Hodgkin and Huxley
  - "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve". J Physiol 1952, 117: 500-544
- Rall
  - "Branching dendritic trees and motoneuron membrane resistivity". Exp Neurol 1959, 1: 491-527
- [NEURON] Hines
  - "A program for simulation of nerve equations with branching geometries". Int J Biomed Comput 1989, 24:55-68
- 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
- Land, Salpeter, Salpeter
  - "Kinetic parameters for acetylcholine interaction in intact neuromuscular junction". Proc Natl Acad Sci USA 1981, 78:7200-4
- [MCell] Bartol, Land, Salpeter, Salpeter
  - "Monte-carlo simulation of miniature end-plate current generation in the vertebrate neuromuscular-junction". Biophys J 1991, 59: 1290-1307

Approches classique de modélisation

(1)- L'approche phénoménologique

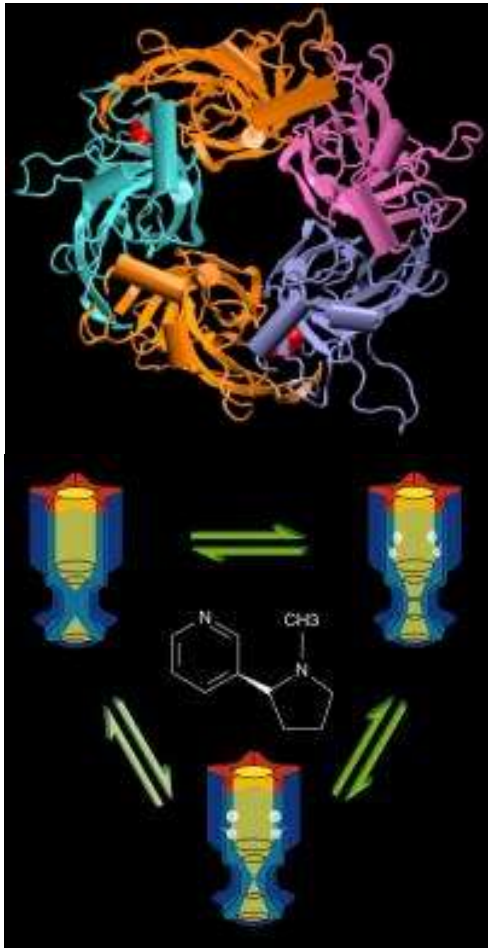
Enregistrements d'états du système ⇒ Abstraction

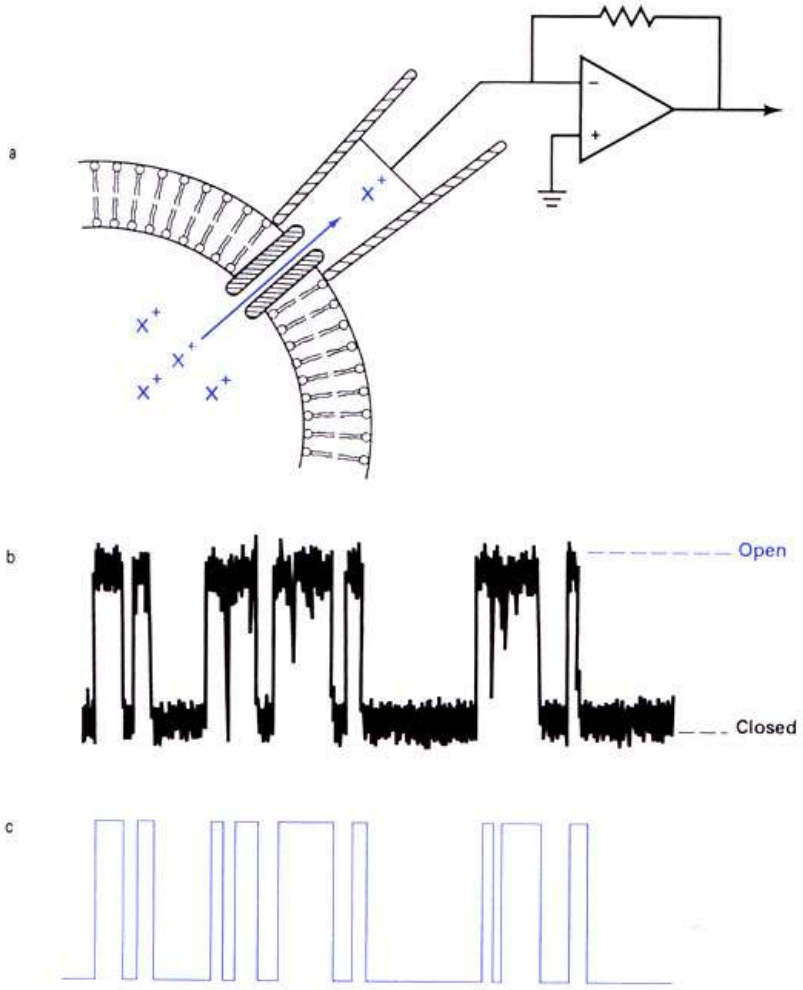


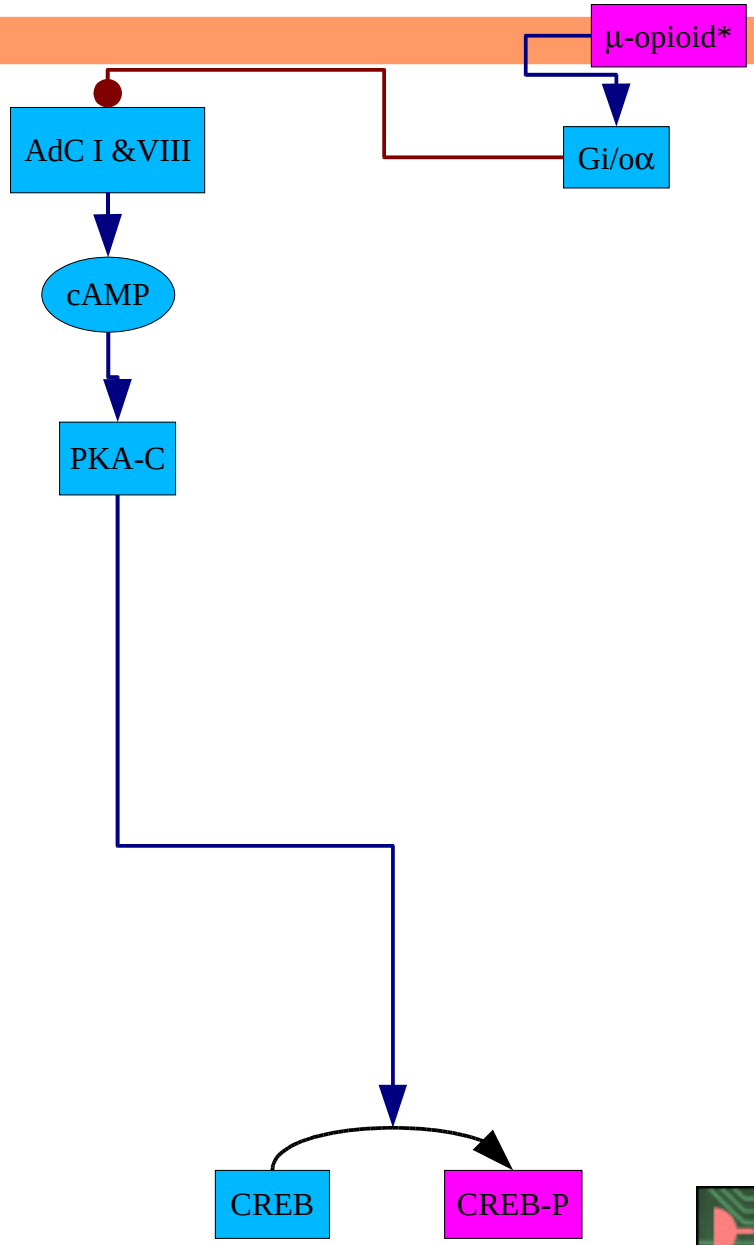


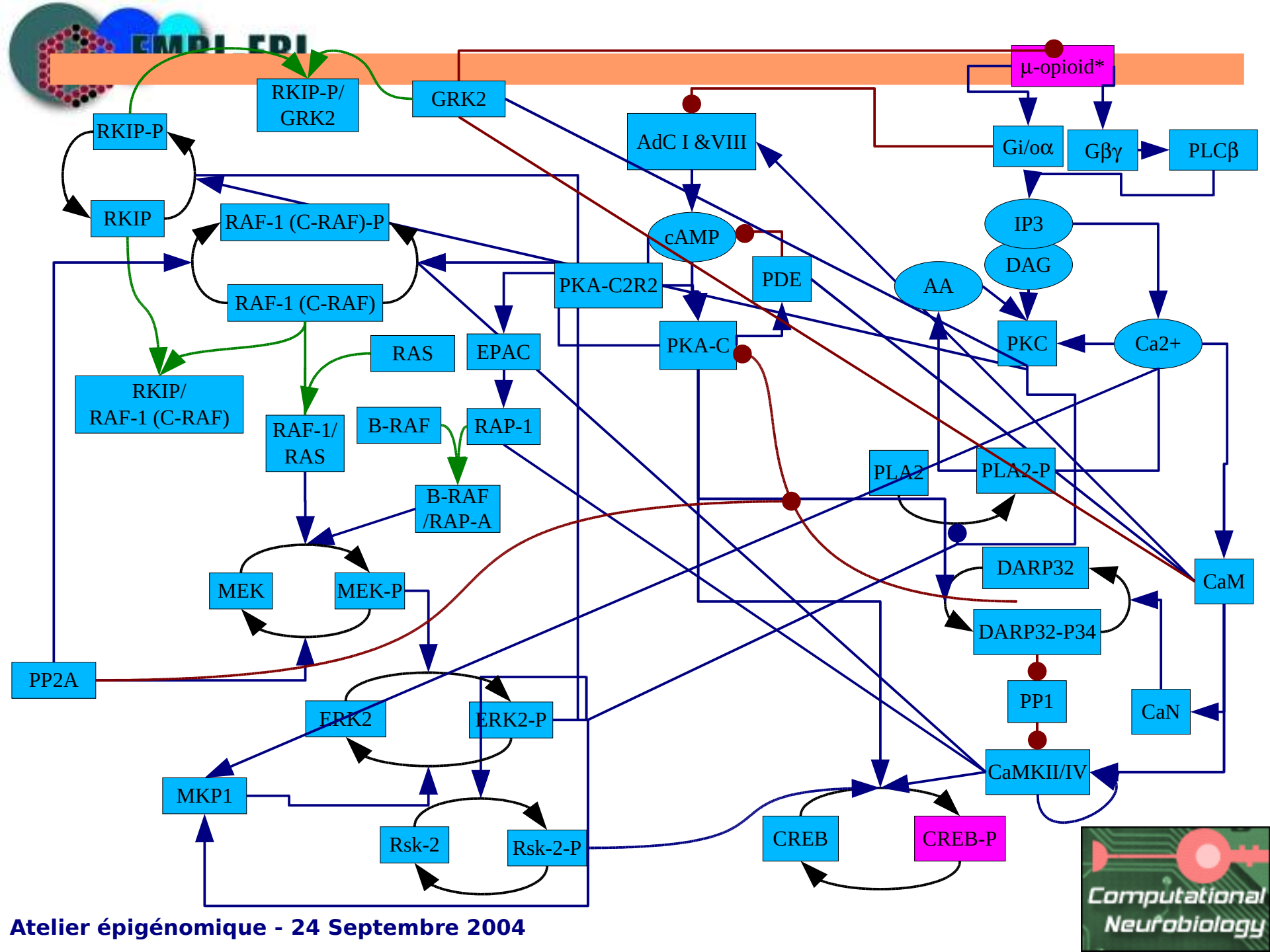
Approches classique de modélisation

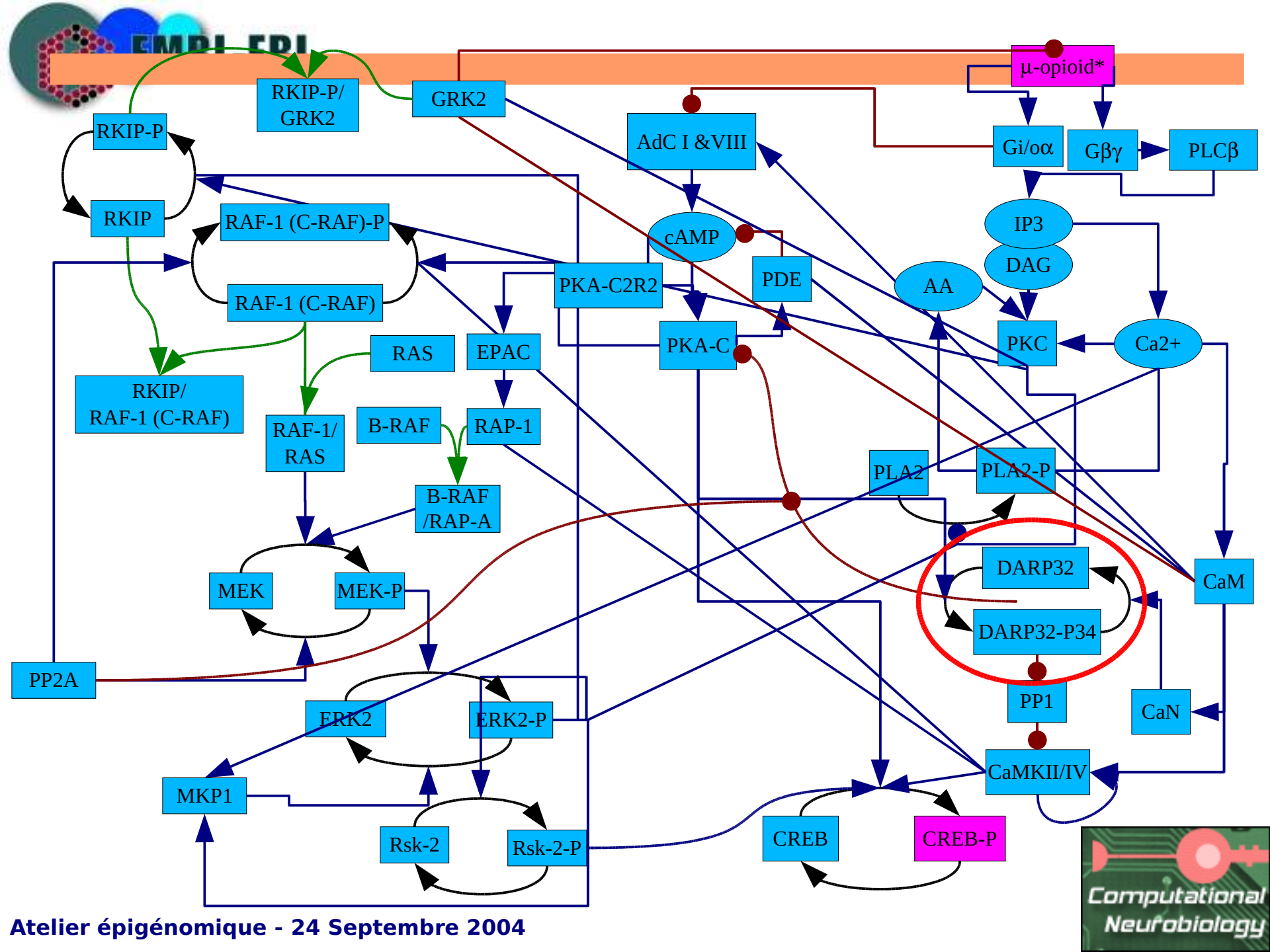
(2)-Le réductionisme






μ-opioid*
AdC I &VIII
Gi/oα
cAMP
PKA-C
CREB
CREB-P


RKIP-P/
GRK2
GRK2
μ-opioid*
RKIP-P
AdC I &VIII
Gi/oα
Gβγ
PLCβ
RKIP
RAF-1 (C-RAF)-P
cAMP
IP3
DAG
RAF-1 (C-RAF)
PKA-C2R2
PDE
AA
PKA-C
PKC
Ca2+
RAS
EPAC
RKIP/
RAF-1 (C-RAF)
RAF-1/
RAS
B-RAF
RAP-1
PLA2
PLA2-P
B-RAF
/RAP-A
DARP32
CaM
MEK
MEK-P
DARP32-P34
PP2A
PP1
CaN
ERK2
ERK2-P
CaMKII/IV
MKP1
Rsk-2
Rsk-2-P
CREB
CREB-P
Computational
Neurobiology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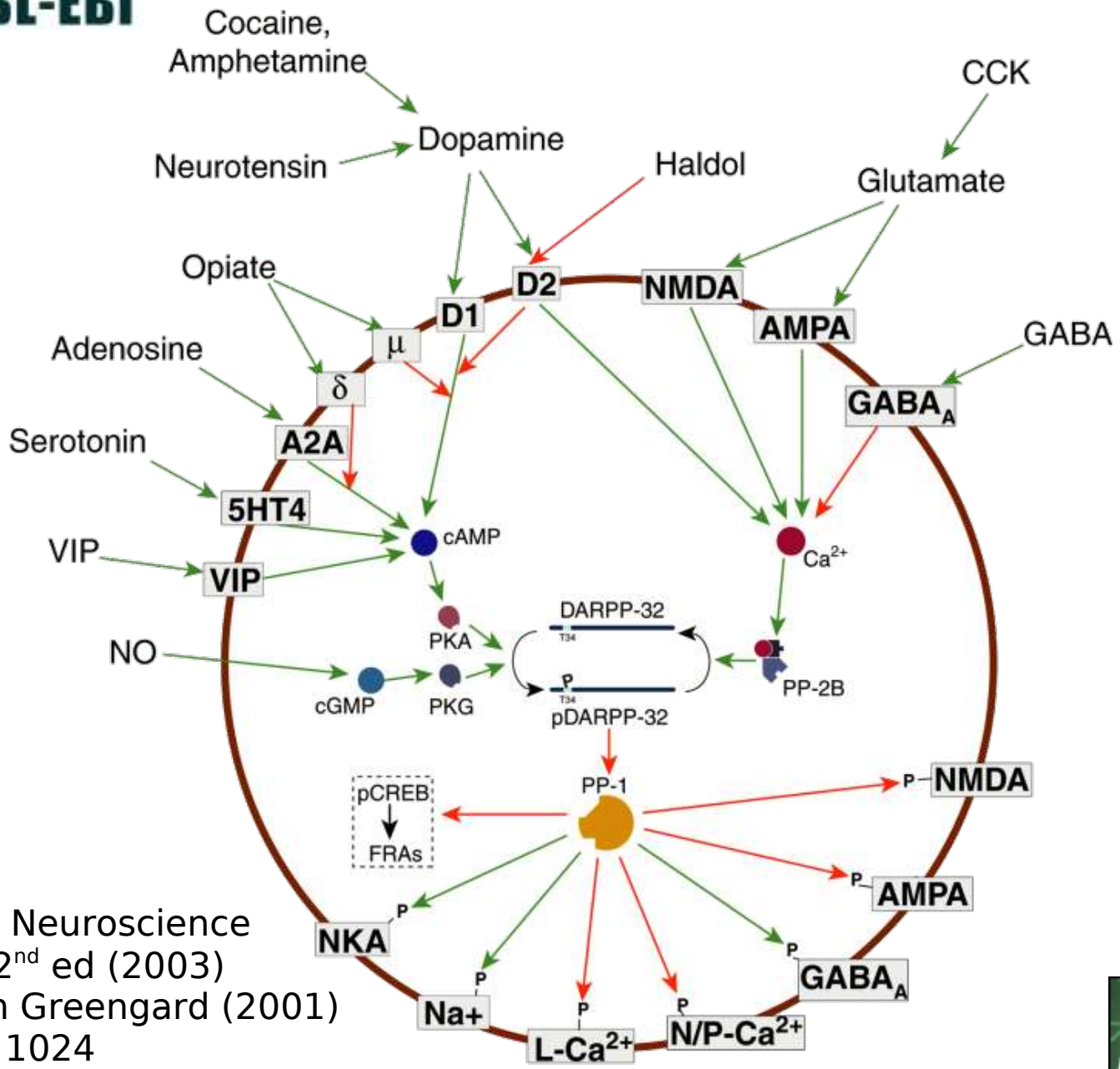
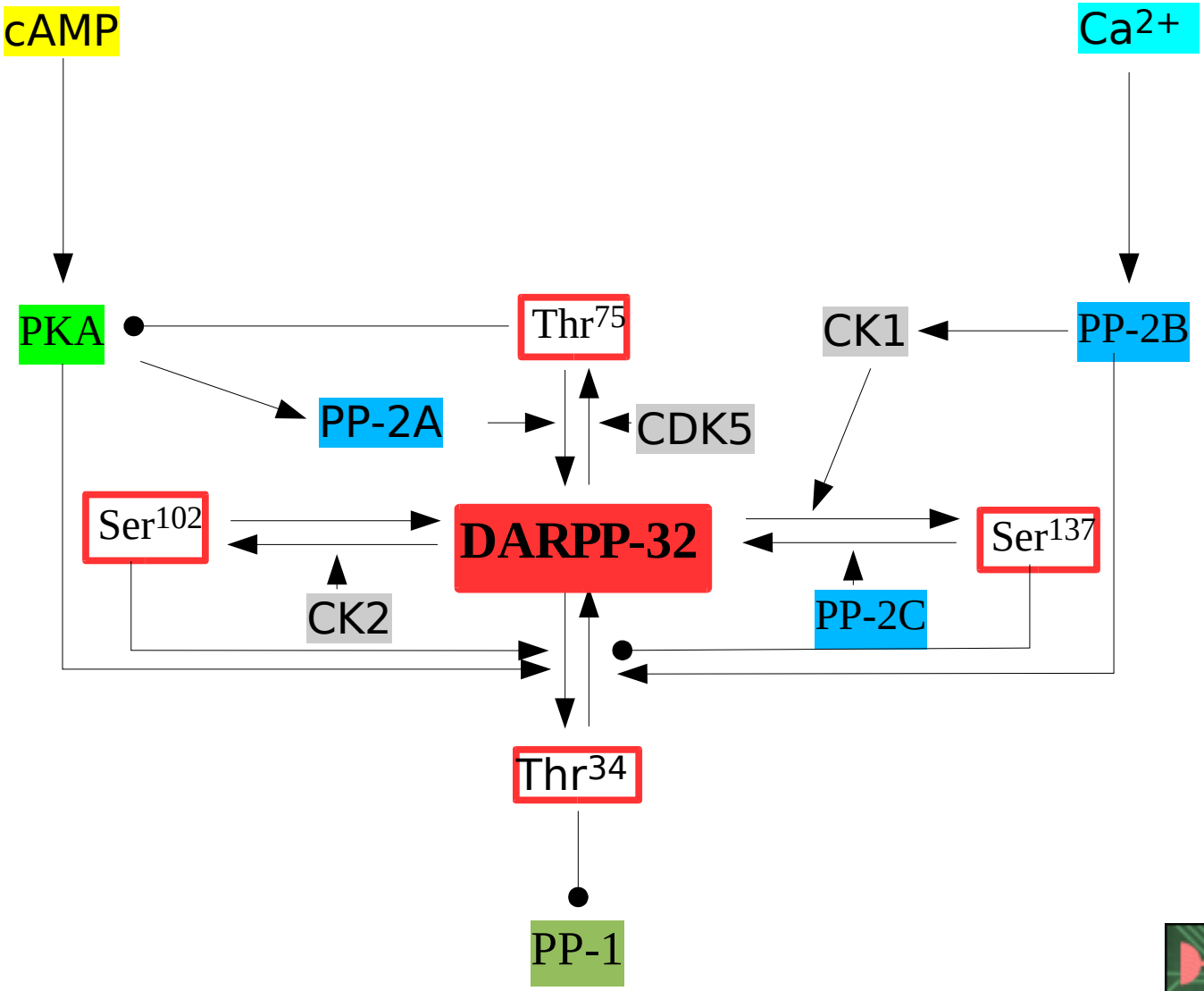
GRK2
GRK2
μ-opioid*
RKIP-P
AdC I &VIII
Gi/oα
Gβγ
PLCβ
RKIP
RAF-1 (C-RAF)-P
cAMP
IP3
DAG
RAF-1 (C-RAF)
PKA-C2R2
PDE
AA
PKA-C
PKC
Ca2+
RAS
EPAC
RKIP/
RAF-1 (C-RAF)
RAF-1/
RAS
B-RAF
RAP-1
PLA2
PLA2-P
B-RAF
/RAP-A
DARP32
CaM
MEK
MEK-P
DARP32-P34
PP2A
PP1
CaN
ERK2
ERK2-P
CaMKII/IV
MKP1
Rsk-2
Rsk-2-P
CREB
CREB-P
Computational
Neurobiology



Fundamental Neuroscience
Squire et al. 2nd ed (2003)
Adapted from Greengard (2001)
Science 294: 1024

Computational Neurobiology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Ca2+
PKA
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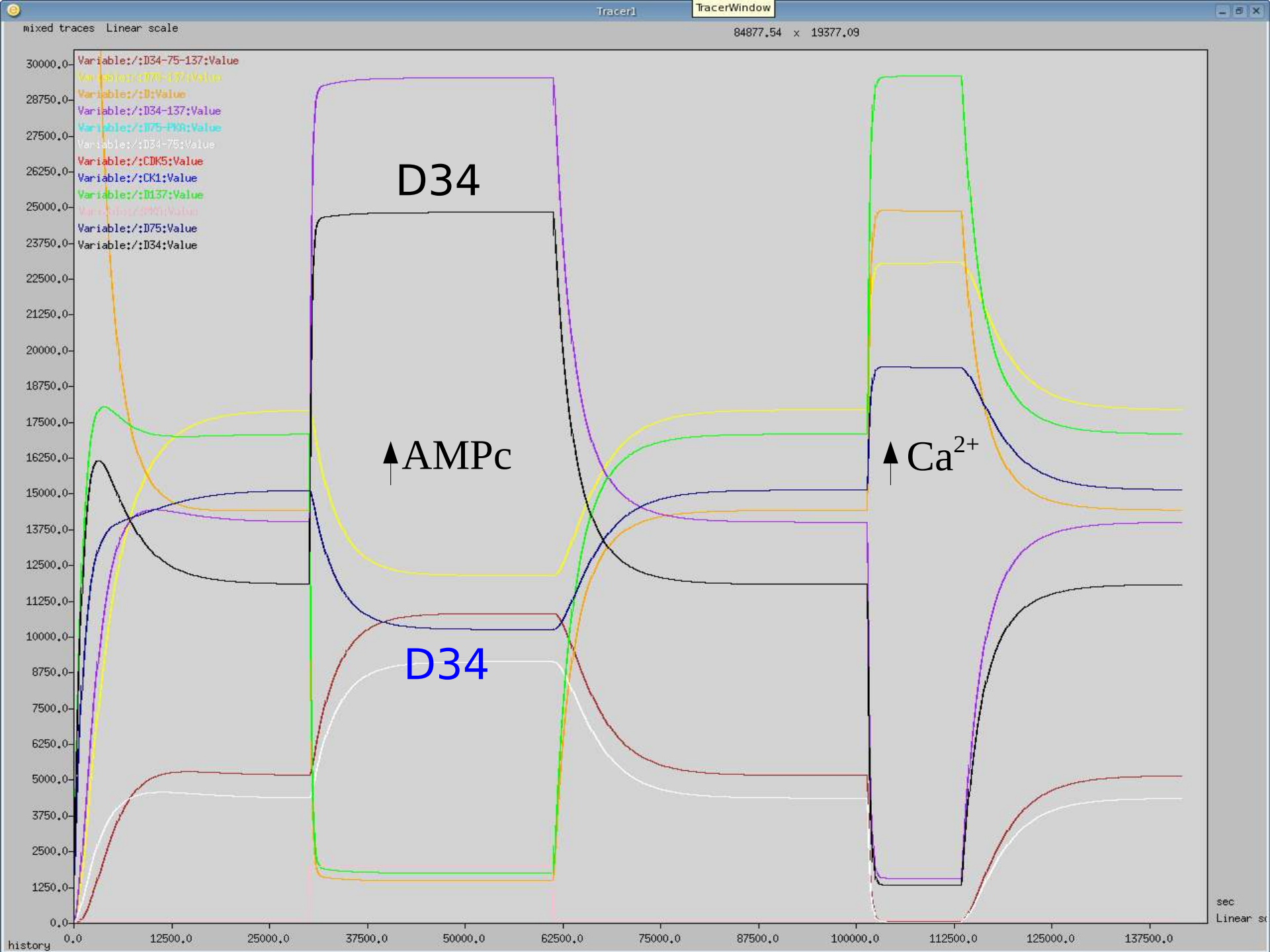
PP-2A
CDK5
Ser102
DARPP-32
Ser137
CK2
PP-2C
Thr34
PP-1


Tracer1
TracerWindow
mixed traces Linear scale
84877.54 x 19377.09
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Variable:/:D34-137:Value
Variable:/:D75-PKA:Value
Variable:/:D34-75:Value
Variable:/:CDK5:Value
Variable:/:CK1:Value
Variable:/:D137:Value
Variable:/:D75:Value
Variable:/:D34:Value
D34
AMPc
Ca2+
D34
30000.0
28750.0
27500.0
26250.0
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20000.0
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12500.0
11250.0
10000.0
8750.0
7500.0
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2500.0
1250.0
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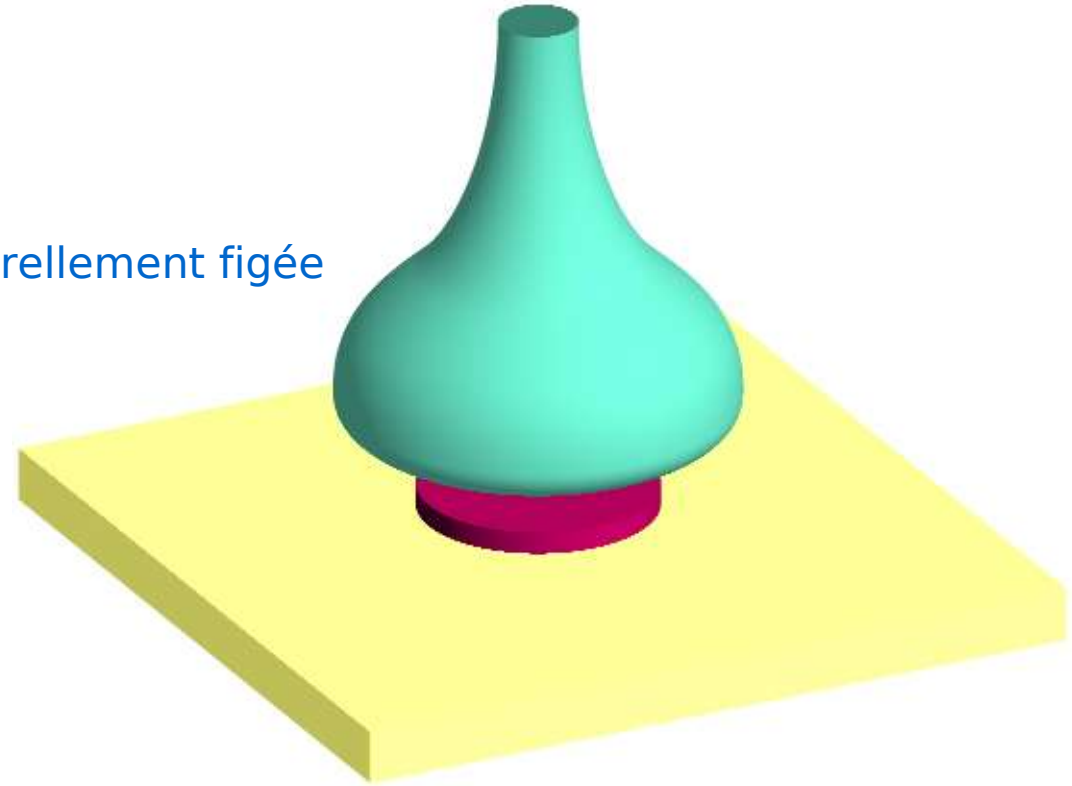
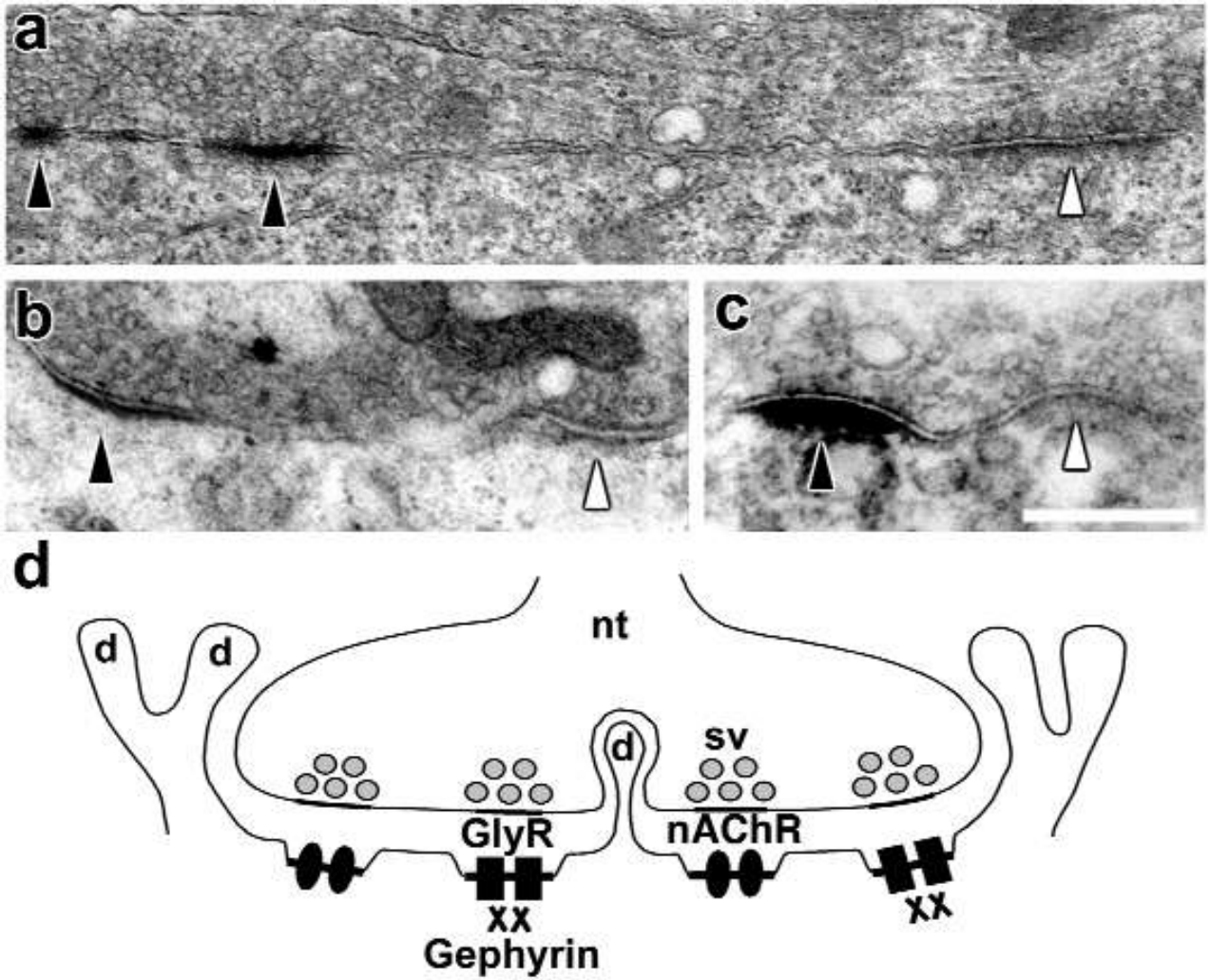
37500.0
50000.0
62500.0
75000.0
87500.0
100000.0
112500.0
125000.0
137500.0
sec
Linear sc
history

(Mis)conception commune de la synapse

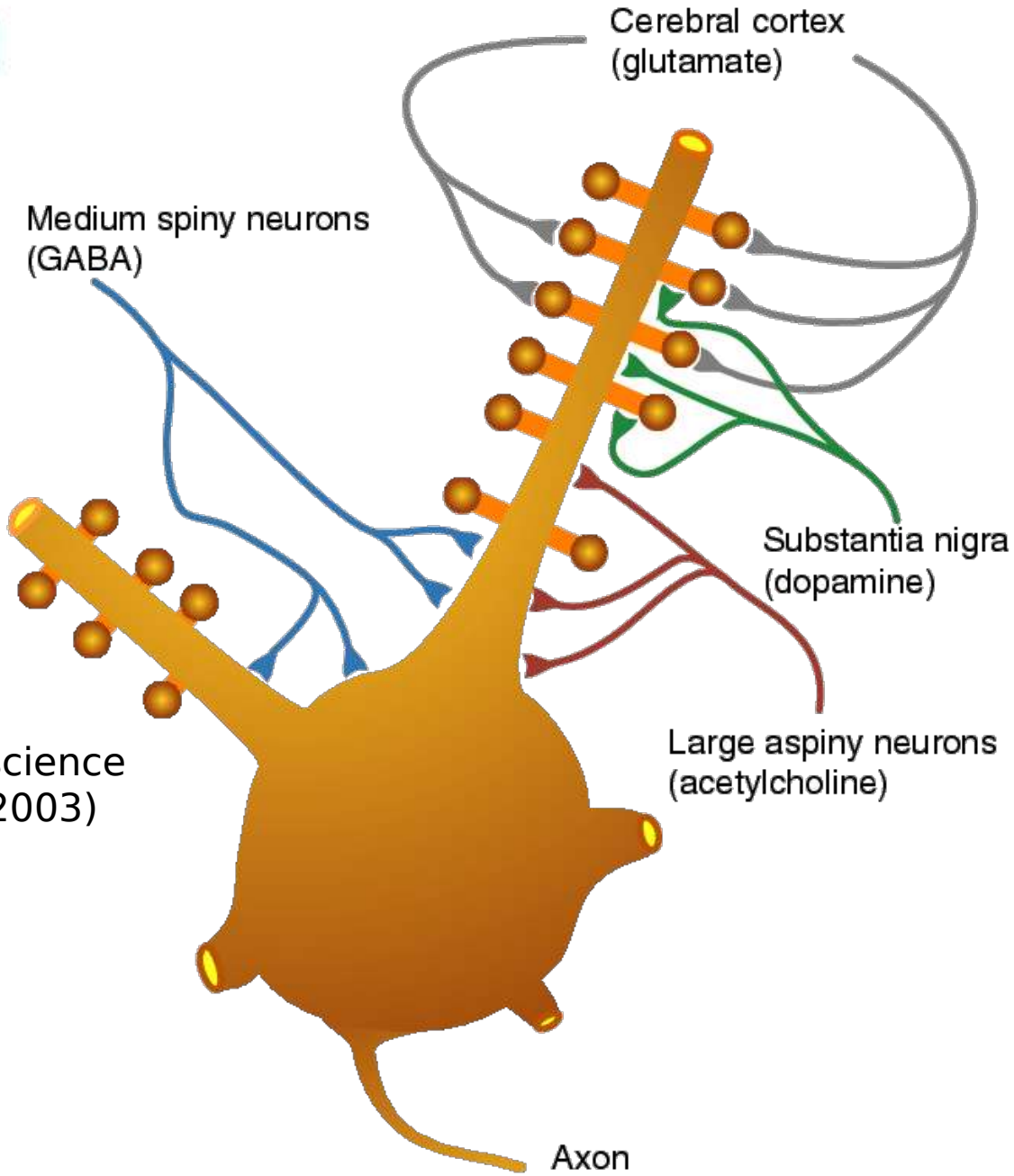
- Un neurotransmetteur
- Un récepteur
- Distribution homogène
- Spatialement et temporellement figée



Complexité pharmacologique



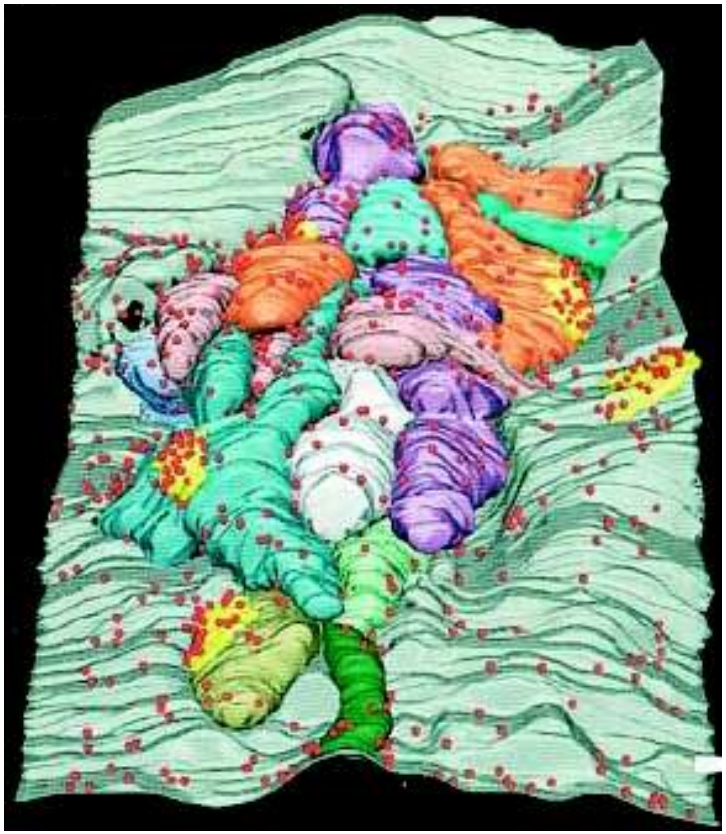
Tsen et al. (2000) *Nat Neurosci*, 3: 126-132



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

Complexité structurale (1)

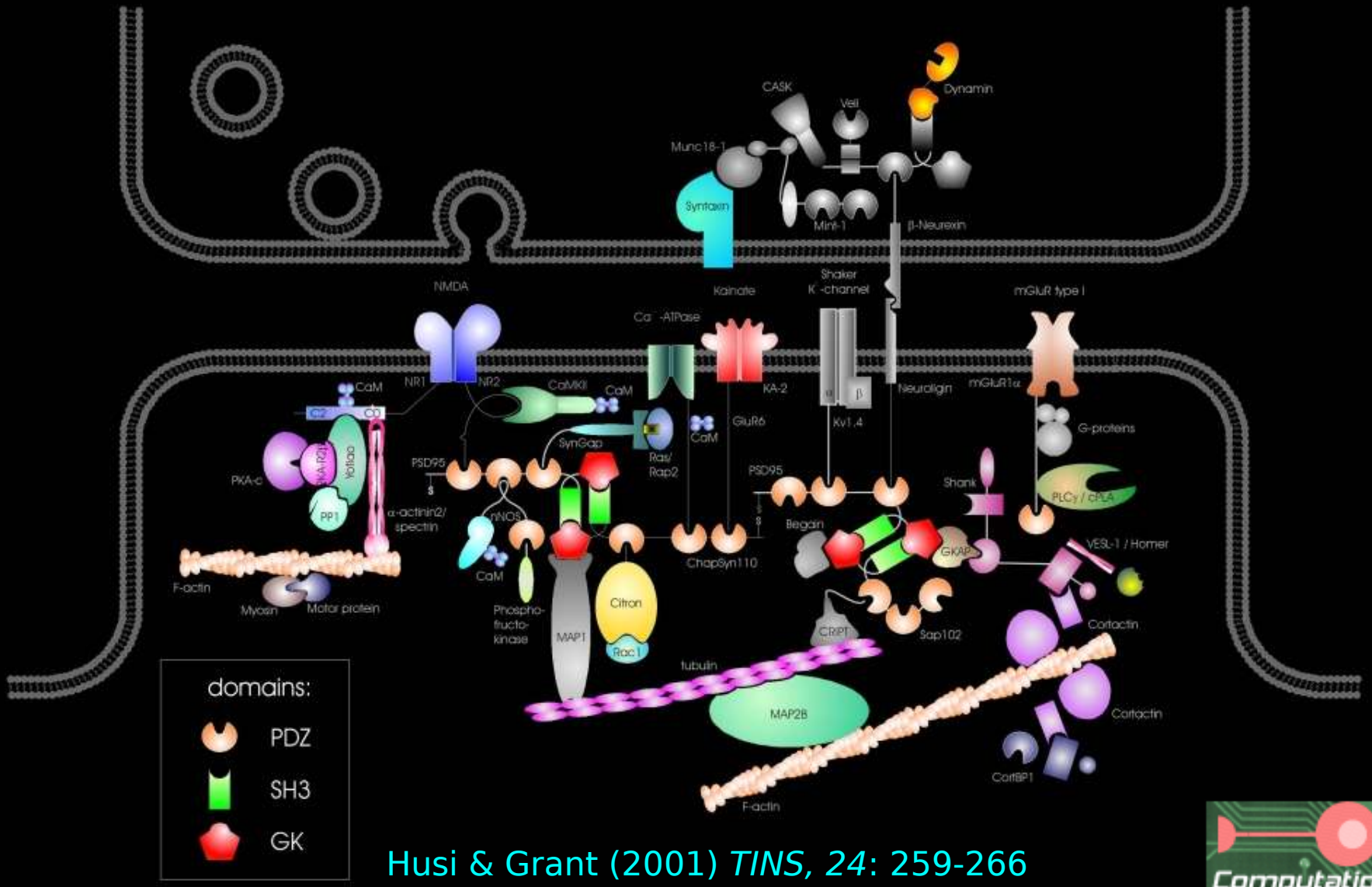
Atlas of Ultrastructural Neurocytology
http://synapses.mcg.edu/atlas/eurosci



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

EMBL-EBI
European Bioinformatics Institute

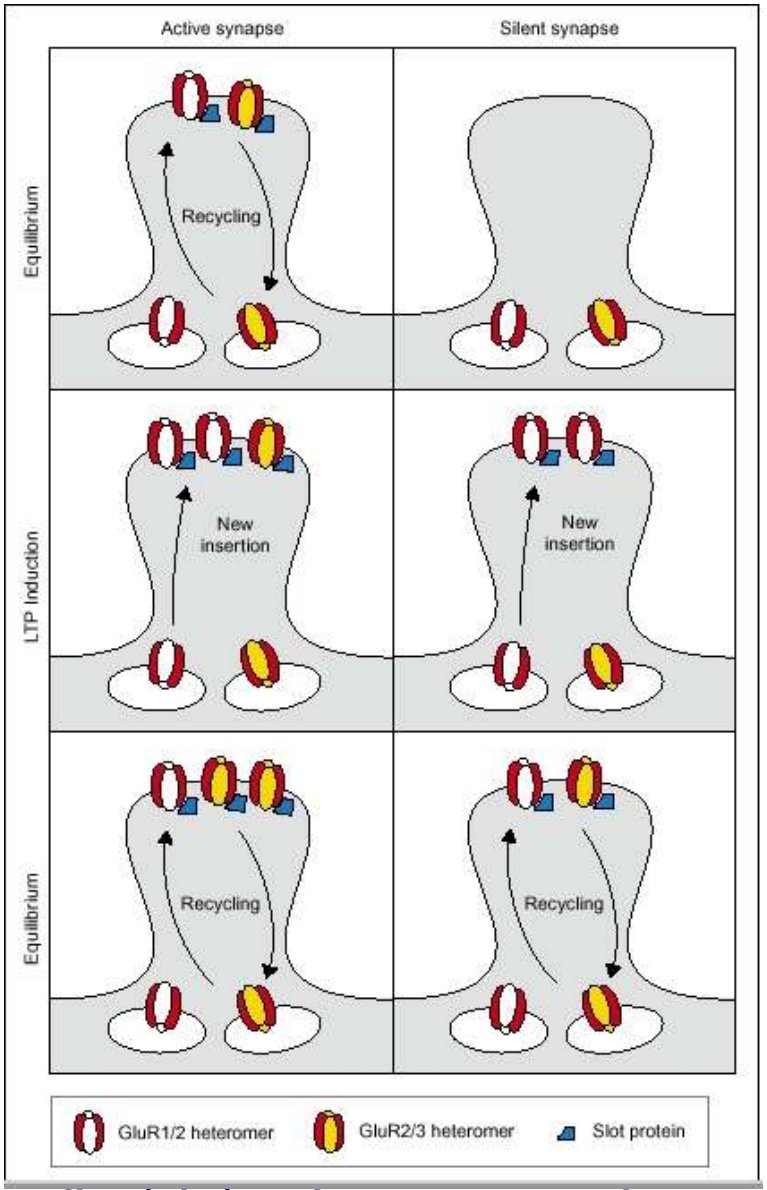
Complexité structurale (2)



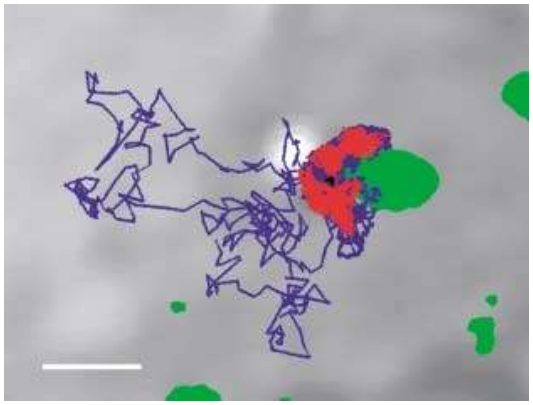
Husi & Grant (2001) *TINS, 24*: 259-266

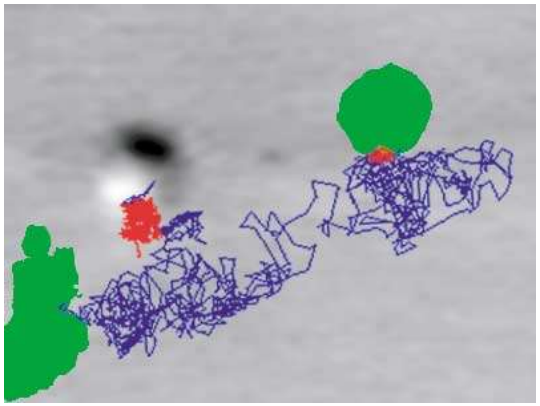
Computational Neurobiology

Complexité temporelle



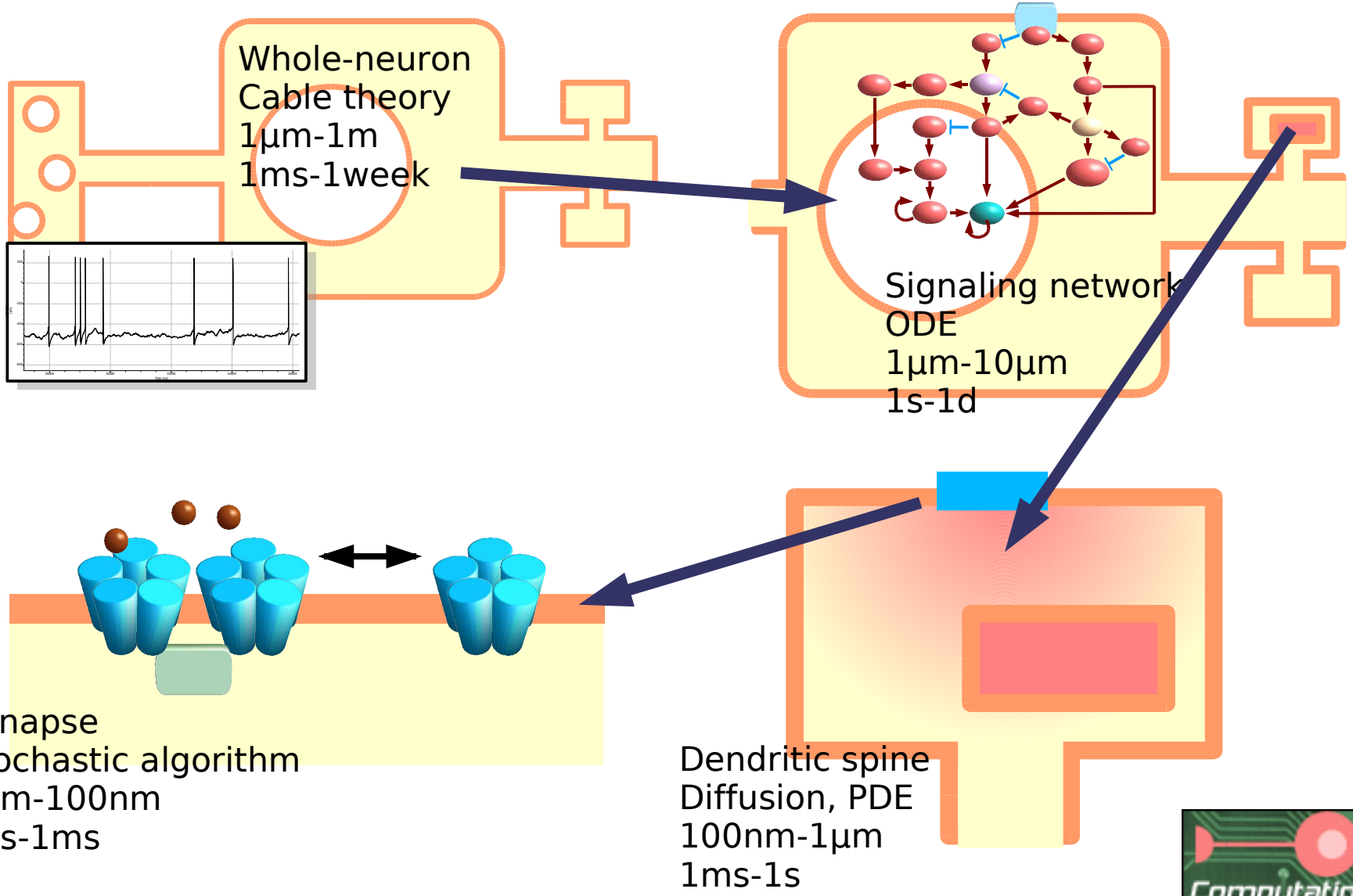
Barry and Ziff. (2002)
Curr Opin Neurobiol, 12: 279-286



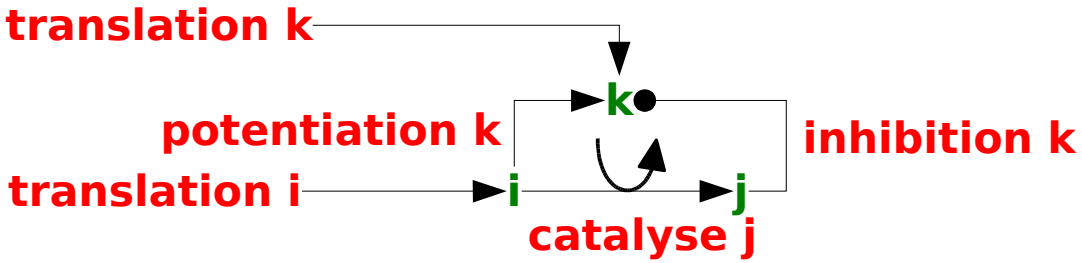


Choquet & Triller (2003)
Nat Rev Neurosci, 4: 251-265

multiples échelles
multiple algorithmes



E-Cell System 3 (Kouichi Takahashi)
mém partagée, hyper-threading



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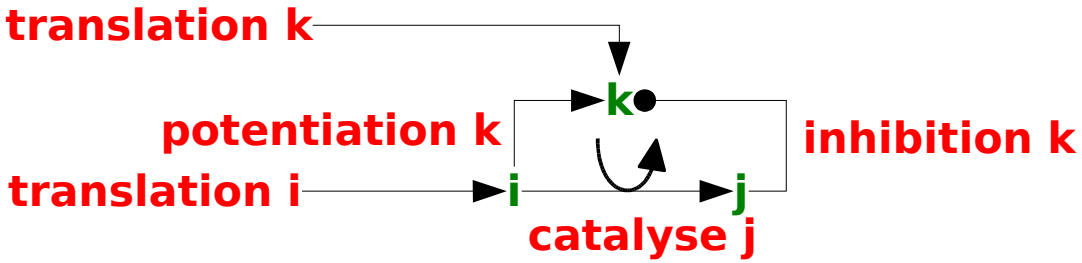
mém partagée, hyper-threading

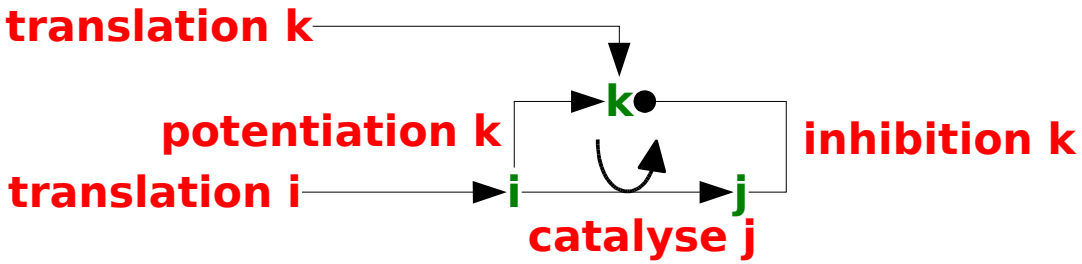


variable j

variable i

variable k

E-Cell System 3 (Kouichi Takahashi)
mém partagée, hyper-threading



catalyse j
(ExpressionFluxProcess)

inhibition k
(MassActionFluxProcess)

potentiation k
(MassActionFluxProcess)

translation i
(GillespieProcess)

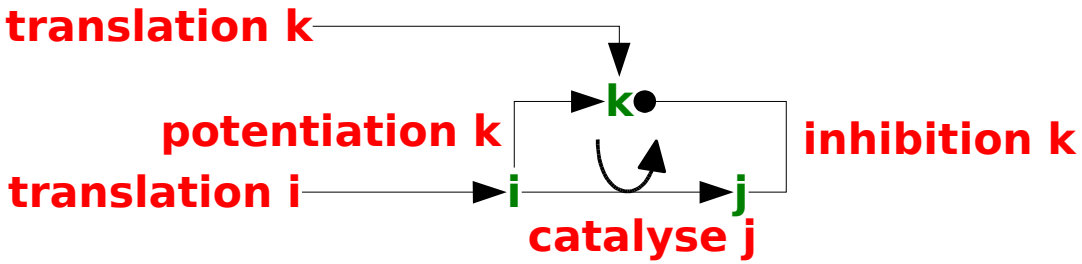
translation k
(GillespieProcess)

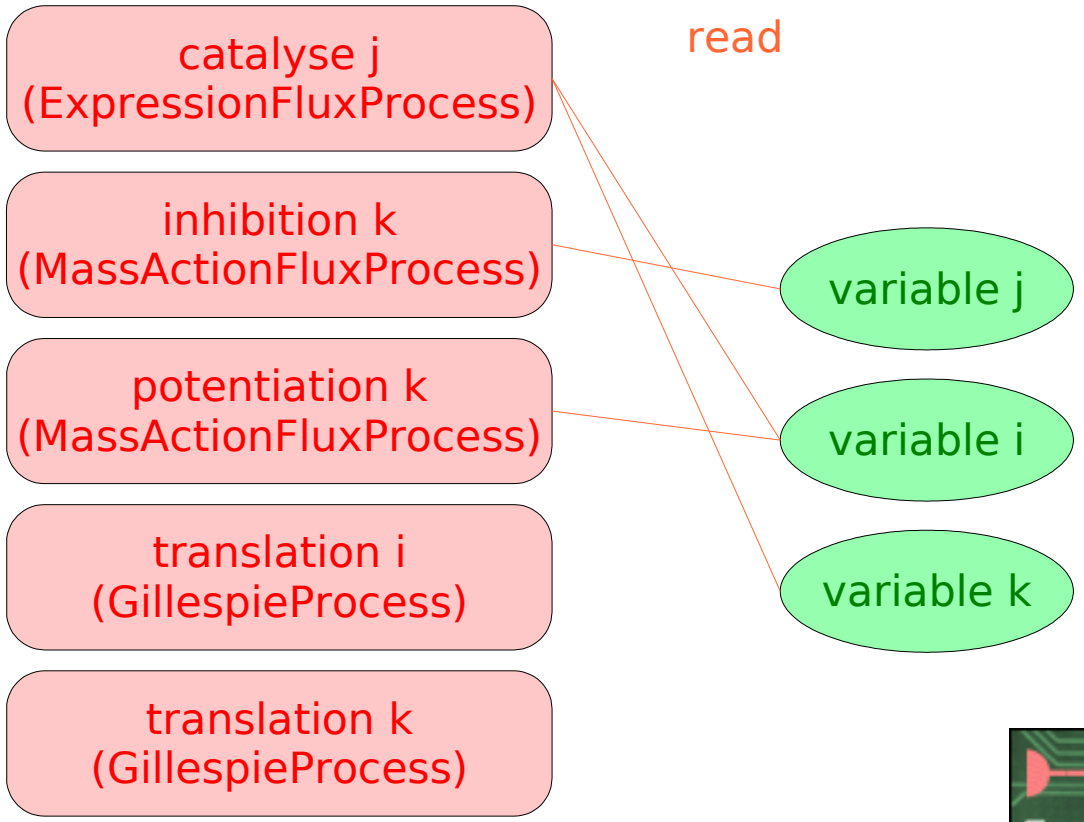
variable j

variable i

variable k

E-Cell System 3 (Kouichi Takahashi)
mém partagée, hyper-threading





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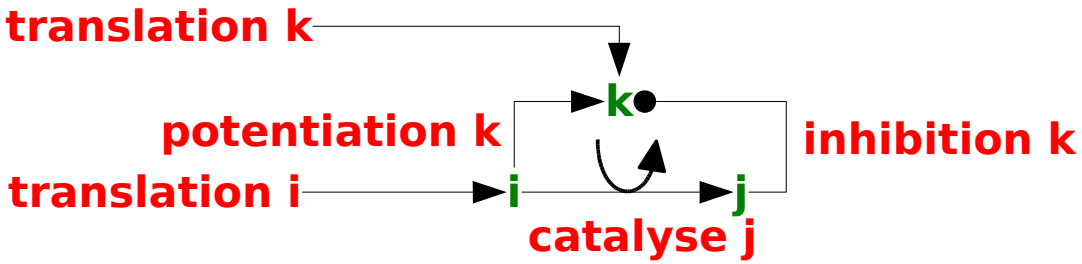
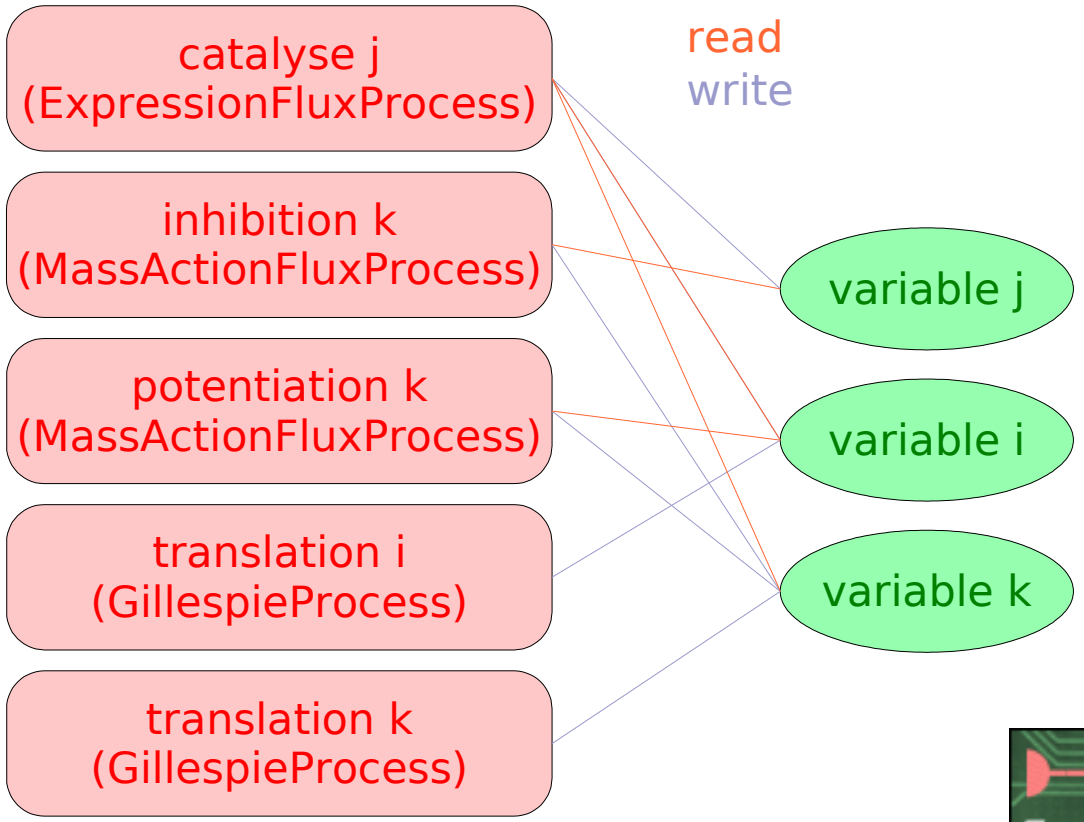
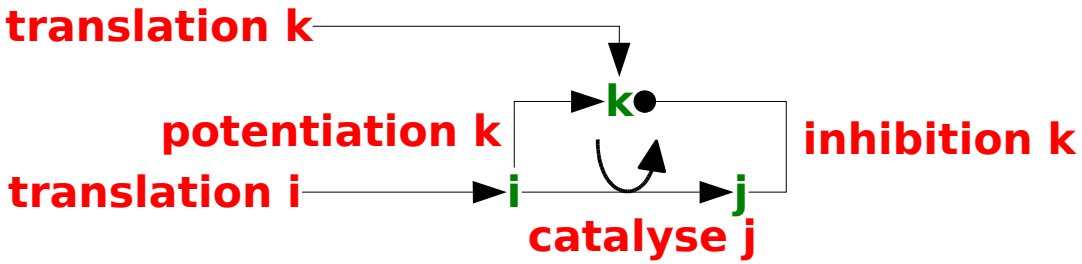
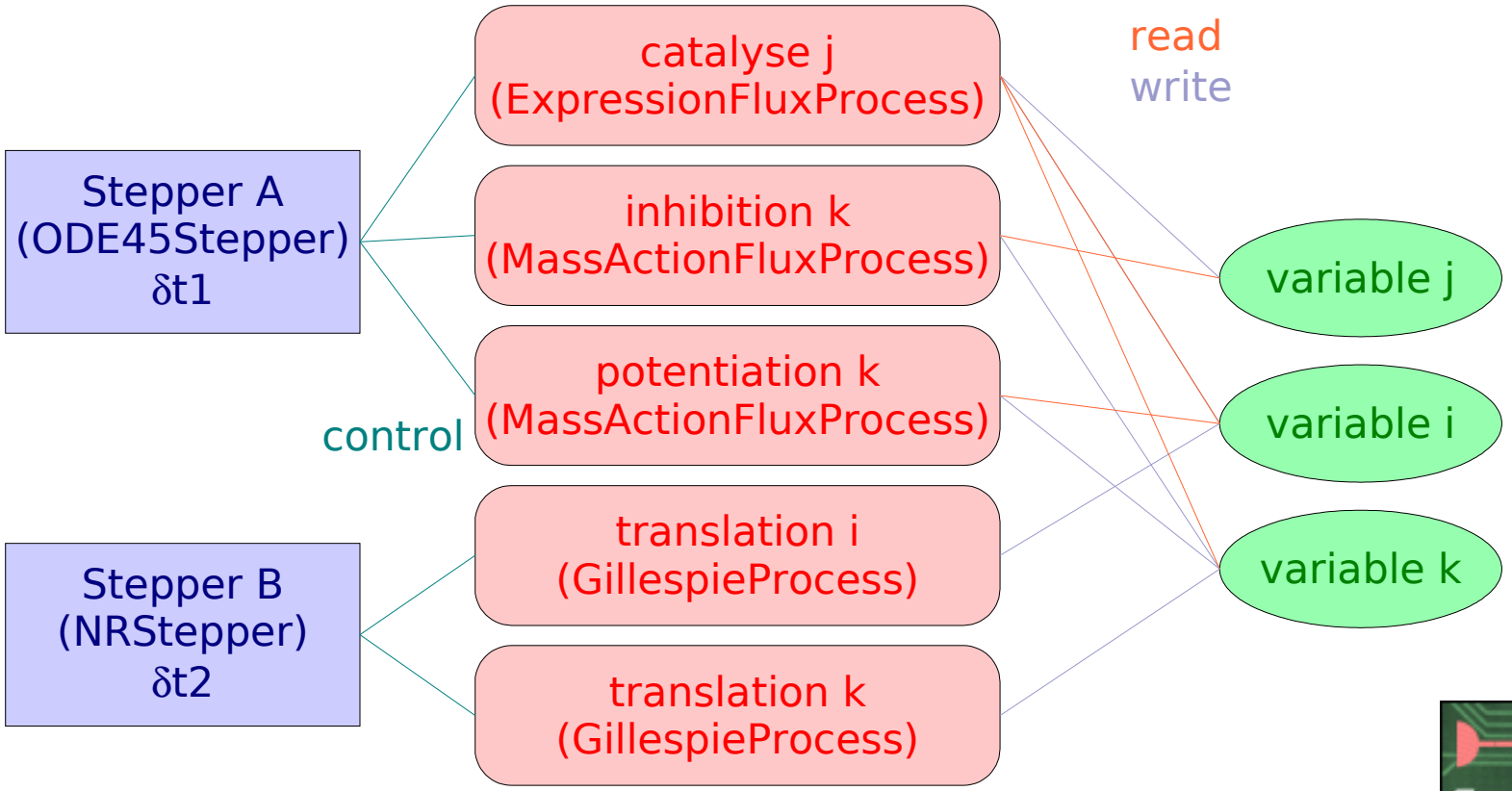
mém partagée, hyper-threading



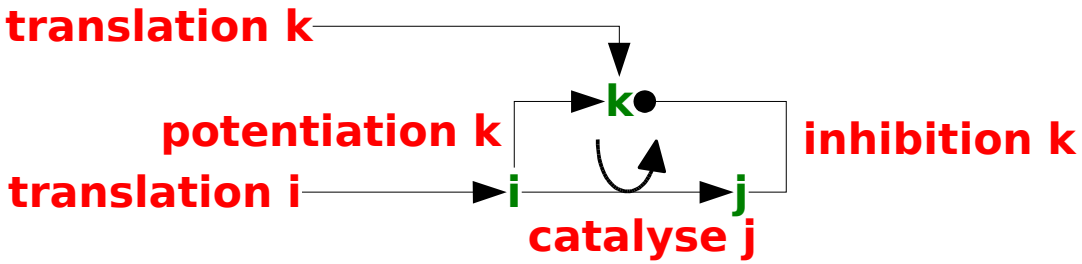


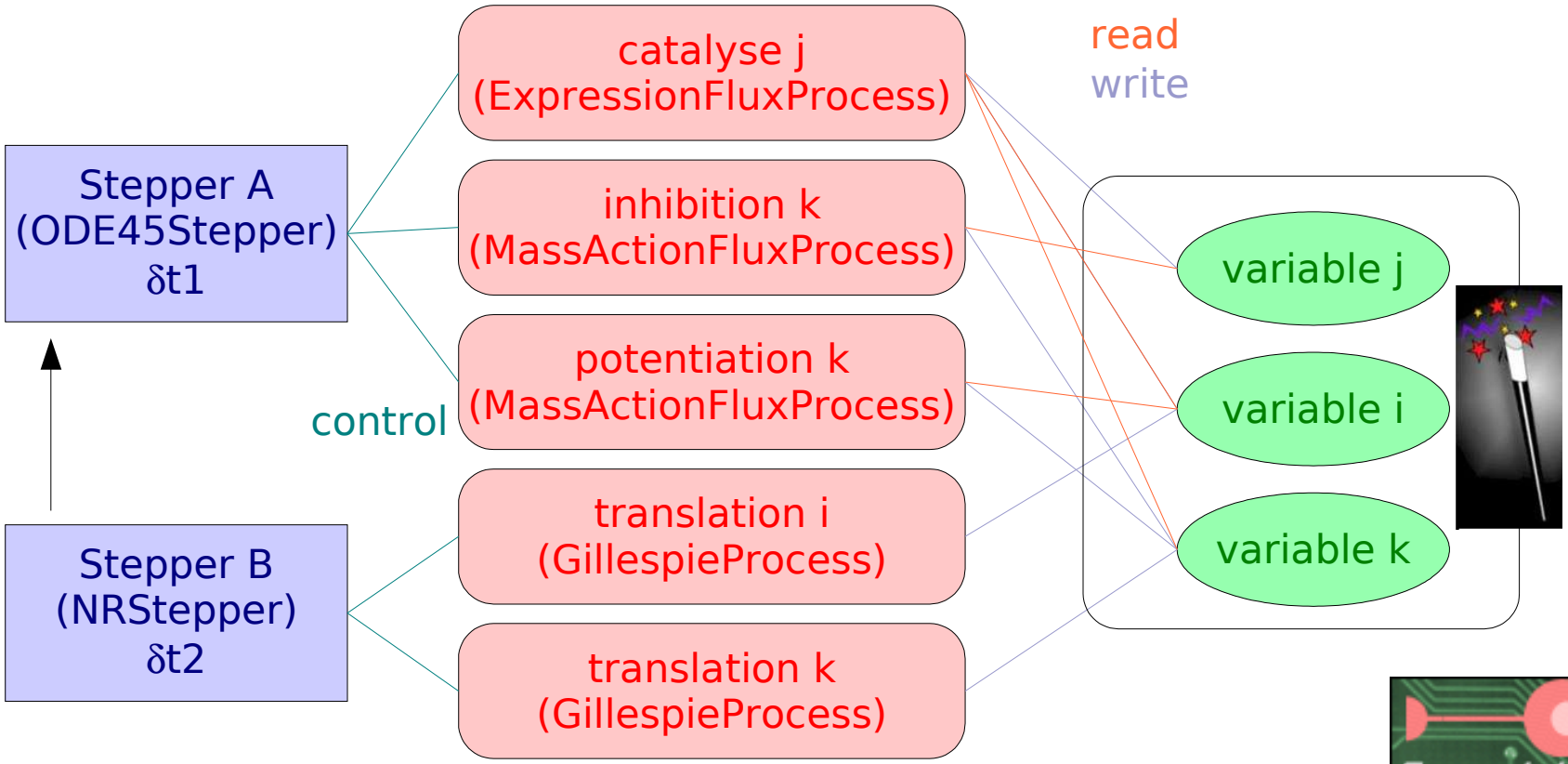
E-Cell System 3 (Kouichi Takahashi)
mém partagée, hyper-threading





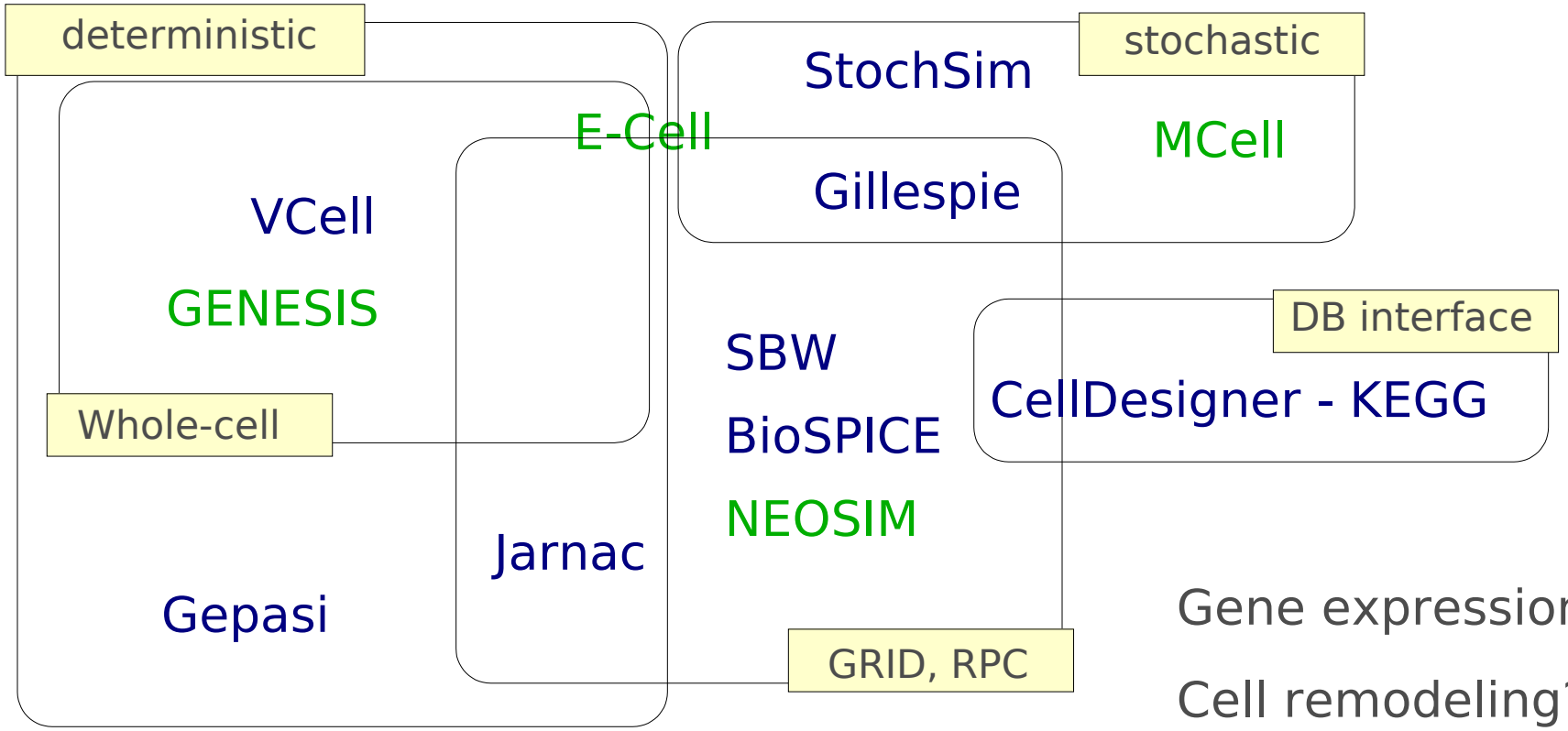
E-Cell System 3 (Kouichi Takahashi)
mém partagée, hyper-threading





Tentatives actuelles

used to model neurons



Gene expression?

Cell remodeling?

All these programs speak SBML
(Systems Biology Markup Language)

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, genomic regulatory networks, and many other areas in systems biology.

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 50 software systems**, including the following (where '*' indicates SBML support in development):

BALSA	CellDesigner	Gepasi	MathSBML	SCIpath
BASIS	Cellerator	Jarnac	Modesto	SigPath
BioCharon	Cellware	JDesigner	MOMA*	SigTran
biocyc2SBML	COPASI	JigCell	Monod	Simpathica
BioGrid	Cytoscape	JSIM	NetBuilder	StochSim
Bio Sketch Pad	DBsolve	JWS*	PathArt	STOCKS
BioSpreadsheet	Dizzy	Karyote*	PathScout	Trelis
BioUML	E-CELL	kegg2sbml	PathwayBuilder	Virtual Cell
BSTLab	ecellJ	Kinsolver*	ProcessDB*	VLX Suite
CADLIVE	ESS	libSBML	SBW	WinSCAMP

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

KEGG2SBML 1.0 Released!

(March 28, 2004) The first full version of KEGG2SBML, the KEGG-to-SBML converter, is now available. It supports SBML Level 2, KEGG release 29, LIGAND release 29 and KGML v0.3.

read more

MathSBML 2.3.0 Released!

(March 15, 2004) The latest version of MathSBML has just been released, and it's chock-full of features. MathSBML now supports virtually every aspect of SBML Level 2.

'sysbio' survey results are in

(February 28, 2004) The results are in, and people voted to expand the role of the 'sysbio' mailing list. The changes take effect immediately.

'sysbio' mailing list survey

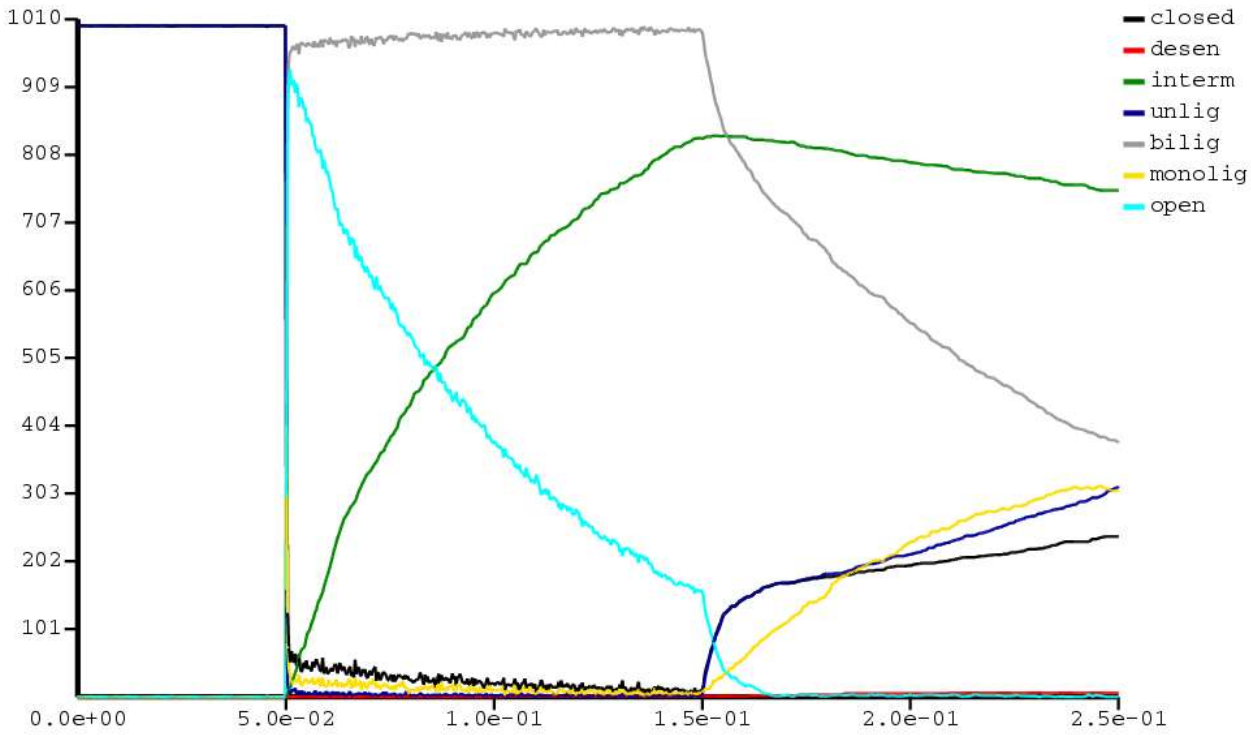
(February 10, 2004) We are running a survey to find out what to do with the 'sysbio@caltech.edu' mailing list. Please visit the survey page to cast your vote.

read more

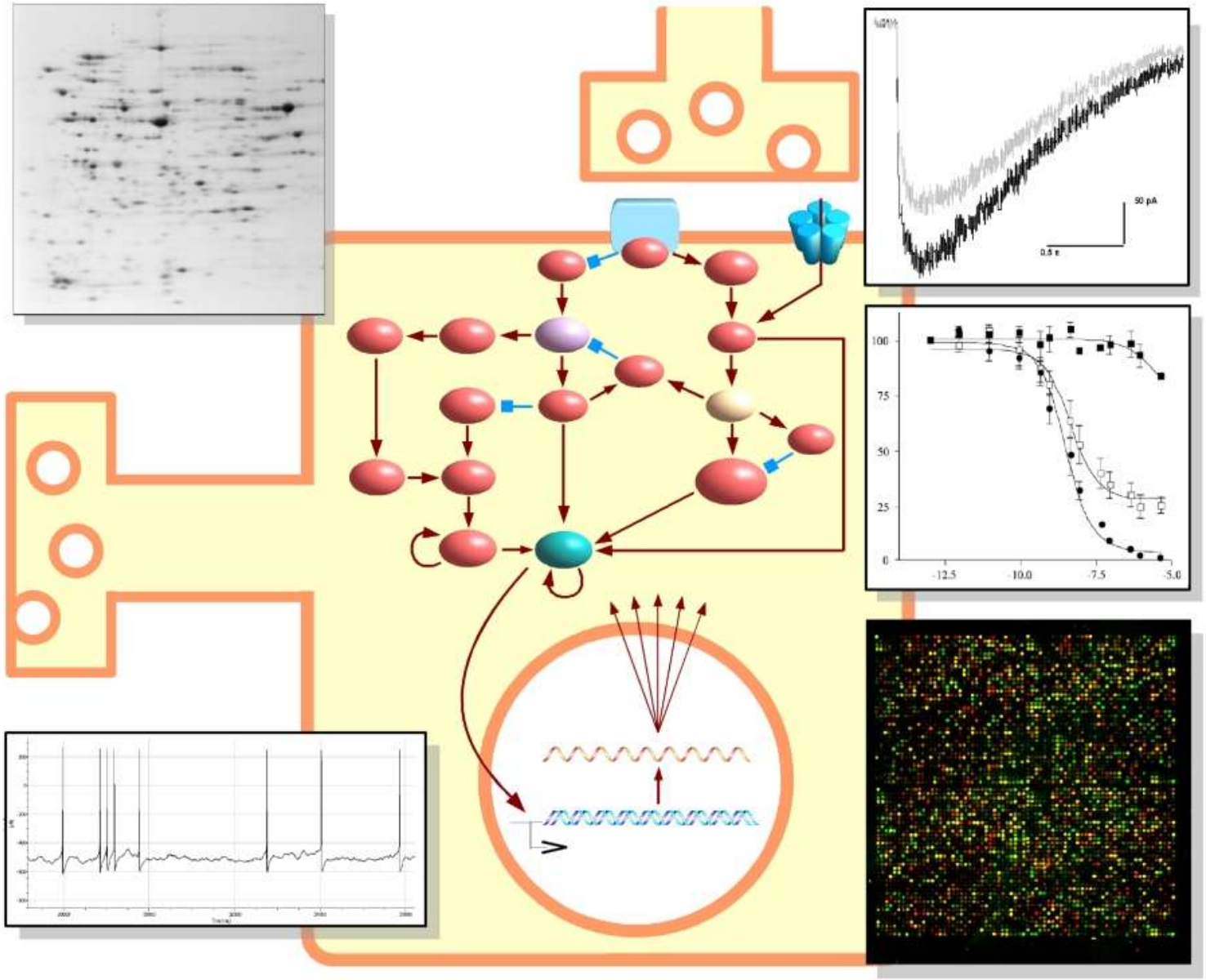
Exemple minimum: Simulation stochastique d'un EPSP nicotinique

- 12 reactants
- 17 reactions
- 36 parameters
- 2 events
- SBML2: 867 lines

=> Parsing
=> Storage

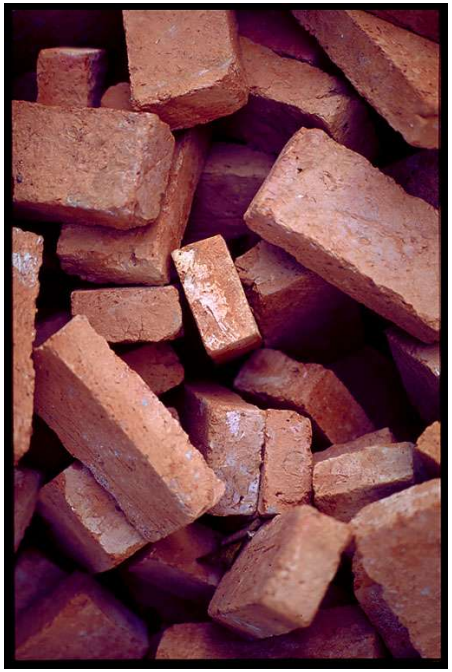


Données hétérogènes

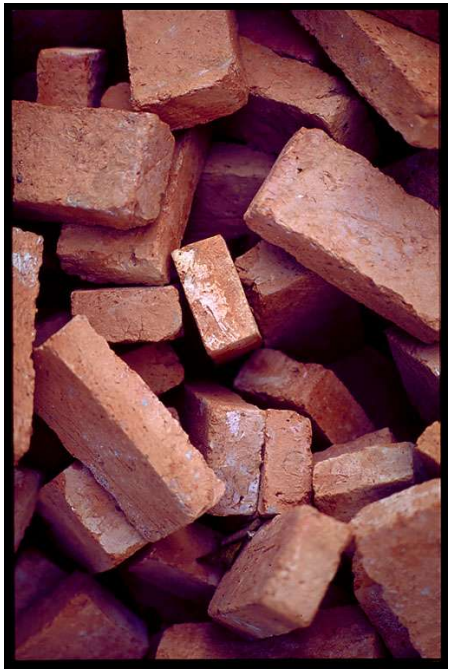


Computational Neurobiology

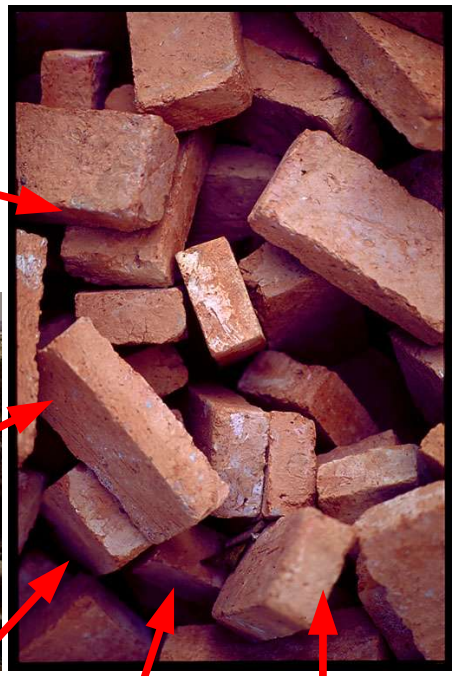
La neurobiologie cellulaire aujourd'hui

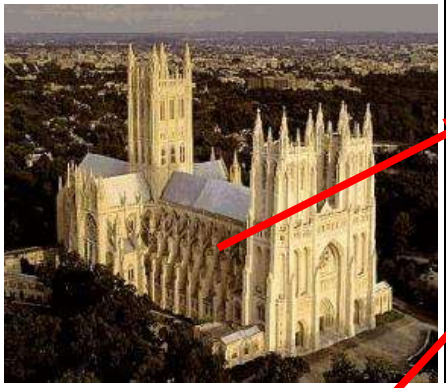


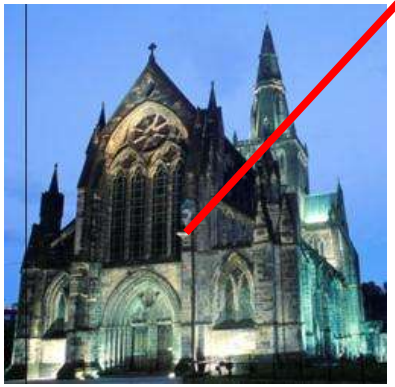
La neurobiologie cellulaire aujourd'hui

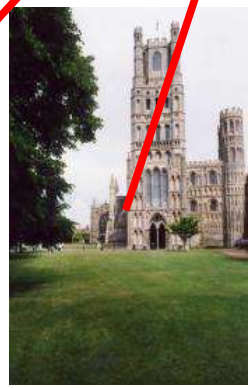


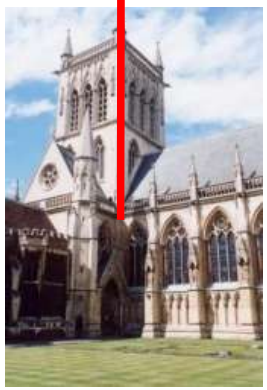
La neurobiologie cellulaire aujourd'hui











Atelier épigénomique - 24 Septembre 2004

Computational Neurobiology

EMBL-EBI

En neurobiologie systémique le facteur limitant est la donnée, et non l'outil de simulation

Computational Neurobiology

```
if (remaining_time < 15 min) {
      remerciements();
} else {
      DopaNet();
}
```

DopaNet is supported by:

DopaNet: The Meso-Telencephalic Dopamine Consortium

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

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.

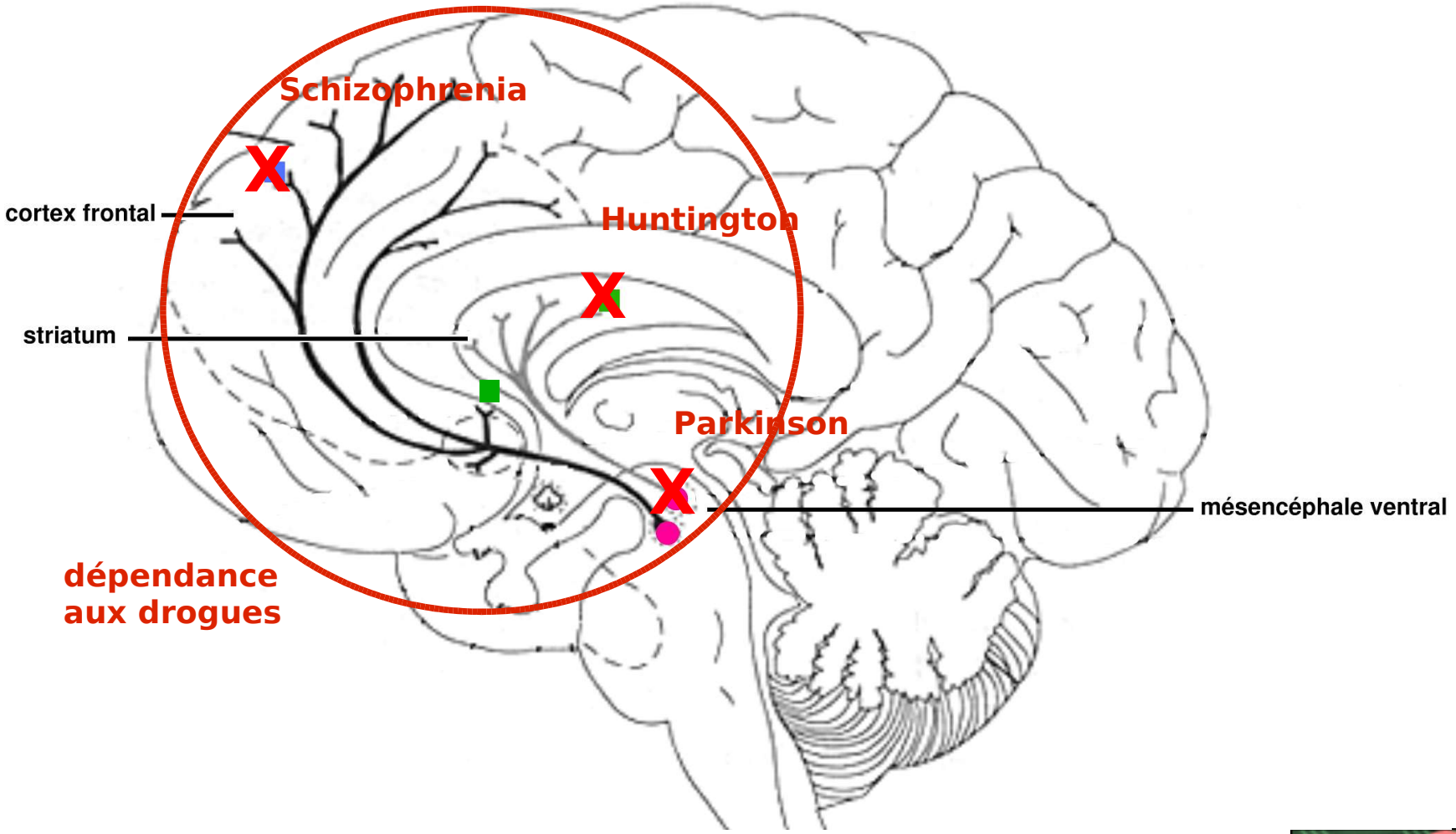
June 2003: The construction of an ontology of the neuronal cell has started. Everybody is invited to participate.

February 2003: The computing infrastructure of DopaNet will be hosted by the European Bioinformatic 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)

Nicolas Le Novère

Le système dopaminergique méso-télencephalique



Plan d'action

First level

Neuronal ontology:

Hierarchical vocabulary entirely describing the system.
⇒ Database structure
⇒ Simulation objects

Major neurotransmissions:

Literature mining for basic and quantifiable properties
- abundance of molecules
- subcellular location
- elementary properties

Modelling and simulation:

Evaluation of available simulation tools. Development of inovative tools launched.

Plan d'action

First level

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- abundance of molecules
- subcellular location
- elementary properties

Modelling and simulation:

Evaluation of available simulation tools. Development of inovative tools launched.

Second level

Major neurotransmissions:

Generation of missing or inaccurate data.

Extensions to other systems:

- neurotrophins
- adhesion molecules
- subsynaptic cytoskeleton
- second-messenger cascades
- transcription factors etc.

Modelling and simulation:

Realistic simulations of local processes, like synaptic function, and signal integration.

Plan d'action

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⇒ Database structure
⇒ Simulation objects

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- adhesion molecules
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Third level

Generalisation to all missing molecules:

Not specific to the dopaminergic neuron, but crucial to its function.
- post-translational machinery
- intracellular targeting systems
- protein recycling etc.

Experimental data at the level of circuits:

Long term changes of the neuron activity. Behavioural and clinical data.

Modelling and simulation:

Large-scale models and simulations. Normal and pathological situations.

Plan d'action

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Hierarchical vocabulary entirely describing the system.
⇒ Database structure
⇒ Simulation objects

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started

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- protein recycling etc.

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Modelling and simulation:

Large-scale models and simulations. Normal and pathological situations.

EBI group

Plan d'action

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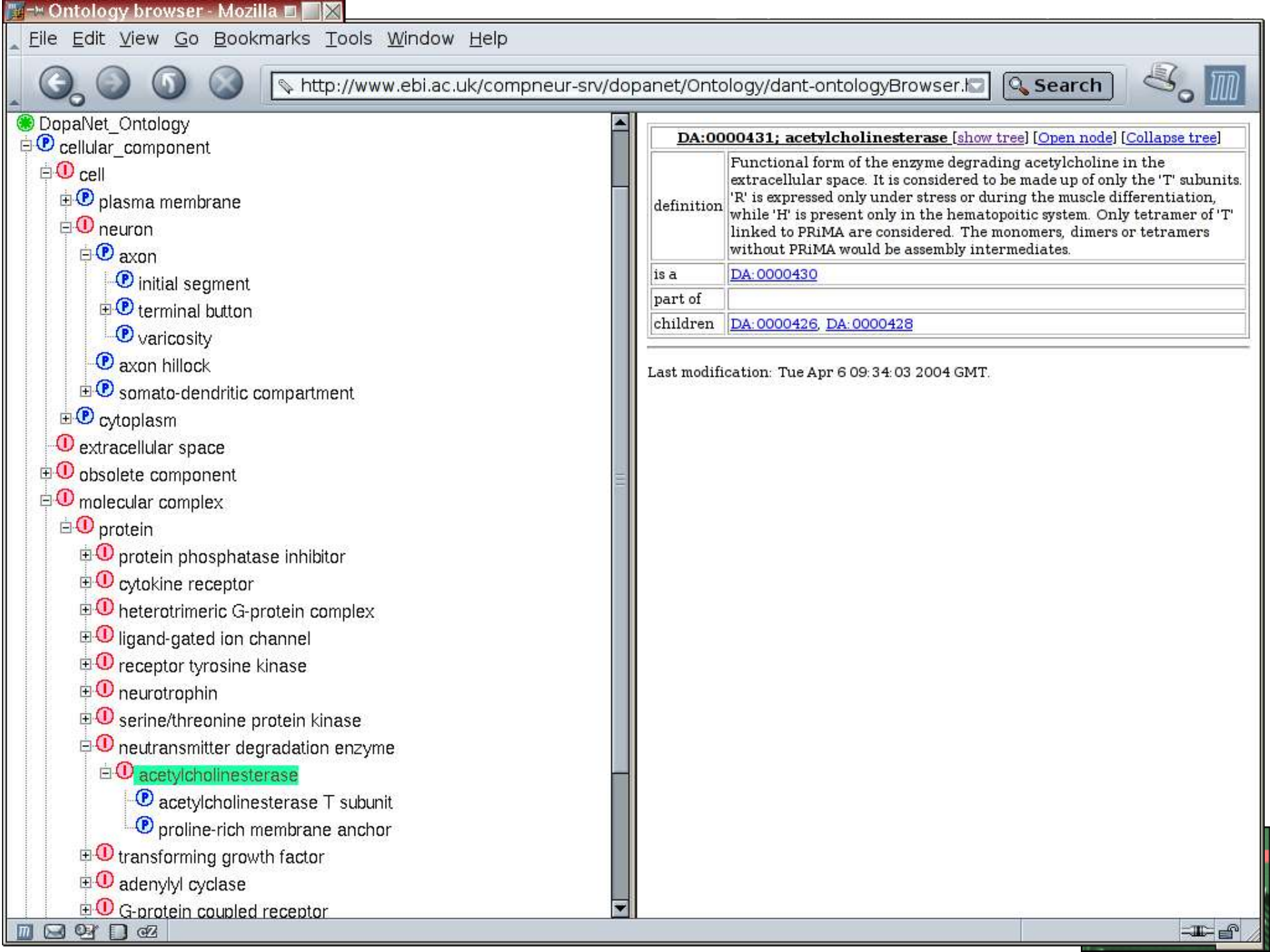
forthcoming european project


Ontology browser - Mozilla
File Edit View Go Bookmarks Tools Window Help
http://www.ebi.ac.uk/compneur-srv/dopanet/Ontology/dant-ontologyBrowser.h
Search
DopaNet_Ontology
cellular_component
cell
plasma membrane
neuron
axon
initial segment
terminal button
varicosity
axon hillock
somato-dendritic compartment
cytoplasm
extracellular space
obsolete component
molecular complex
protein
protein phosphatase inhibitor
cytokine receptor
heterotrimeric G-protein complex
ligand-gated ion channel
receptor tyrosine kinase
neurotrophin
serine/threonine protein kinase
neutransmitter degradation enzyme
acetylcholinesterase
acetylcholinesterase T subunit
proline-rich membrane anchor
transforming growth factor
adenylyl cyclase
G-protein coupled receptor
DA:0000431; acetylcholinesterase [show tree] [Open node] [Collapse tree]
definition
Functional form of the enzyme degrading acetylcholine in the extracellular space. It is considered to be made up of only the 'T' subunits. 'R' is expressed only under stress or during the muscle differentiation, while 'H' is present only in the hematopoitic system. Only tetramer of 'T' linked to PRiMA are considered. The monomers, dimers or tetramers without PRiMA would be assembly intermediates.
is a
DA:0000430
part of
children
DA:0000426, DA:0000428
Last modification: Tue Apr 6 09:34:03 2004 GMT.

Current Molecular Pages

- Main Page
- What Is DopaNet?
- DopaNet Structure
- DopaNet Members
- Open Positions
- How Can I Help?
- Neuronal Ontology
- Molecular Pages
- Mailing Lists
- Contact
- Sign In
- Current Molecular Pages
- Forthcoming Molecular Pages
- Adopted Molecular Pages
- Planned Molecular Pages
- Search Molecular Pages
- Create/Edit Molecular Pages
  - Run MPeditor (Java Plug-in)
  - Run MPeditor for Java 1.3 (Java Plug-in)
  - Run MPeditor (Java policy)
  - Run MPeditor for Java 1.3 (Java policy)
  - MPeditor User Guide

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 code of the second column should redirect to the relevant "leaf" of the DopaNet Neuronal Ontology. Please contact the Page maintainers (5th column) should you wish to correct or complete a Page.

Molecule Name	Ontology	Abbreviation	Last Modified	Maintainers
(alpha) 12 calcium/calmodulin-dependant protein kinase type II	DA:0000561	CaMKIIa_12	2004-08-03	Nicolas Le Novère
(alpha4) 2(beta2) 2alpha5 nAChR	DA:0000421	nAChRa4_2b2_2a5	2004-08-03	Nicolas Le Novère
(alpha4) 2(beta2) 3 nAChR	DA:0000027	nAChRa4_2b2_3	2004-07-05	Nicolas Le Novère
(alpha6) 2(beta2) 3 nAChR	DA:0000031	nAChRa6_2b2_3	2004-07-06	Nicolas Le Novère
A1 adenosine receptor	DA:0000047	A1R	2004-06-22	Serge Schiffmann
A2a adenosine receptor	DA:0000048	A2aR	2004-06-22	Serge Schiffmann
alpha olf G-protein subunit	DA:0000218	Gaolf	2004-06-22	Denis Hervé
alpha7 homomeric nAChR	DA:0000023	nAChRa7_5	2004-07-06	Nicolas Le Novère
calcium/calmodulin-dependant protein kinase type IV	DA:0000562	CaMKIV	2004-08-03	Nicolas Le Novère
calmodulin	DA:0000565	CaM	2004-08-03	Nicolas Le Novère
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
transforming growth factor beta1	DA:0000279	TGFb1	2004-06-22	Amelia Sánchez Capelo
transforming growth factor beta2	DA:0000280	TGFb2	2004-06-22	Amelia Sánchez Capelo
transforming growth factor beta3	DA:0000281	TGFb3	2004-06-22	Amelia Sánchez Capelo

A2a adenosine receptor [DA:0000048]

Structure | Distribution | Function | Maintainers | Contributors | References

Creation of the page:2003-01-05, Last modification of the page:2004-05-17

Structure

Components

1 X A2a adenosine receptor subunit [DA:0000224]

Genbank	*Homo sapiens*	(1)
Genbank	*Mus musculus*	(2)
Genbank	*Rattus rattus*	(3)

States Comment: Those states were not provided by the maintainer. They were created in order to differenciate between binding of agonists and antagonists. Of course, some ligands bind to several states. In a first approximation, the binding constants reflect the binding to the state of highest affinity. Nicolas Le Novere.

active

inactive

Distribution

mesencephalic dopaminergic neuron

cell soma [DA:0000137]

immunocytochemistry optical	very few cells in the SN with a very weak expression, not qualified as DA neurons.	*Rattus norvegicus*	(4)

terminal button [DA:0000006]

Comment: Available functionnal data arguing for the presence of A2A receptor in dopaminergic neurons/terminals (facilitation of dopamine 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]

Comment: 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 nanomole per litre ± 17.3	*Rattus norvegicus*	(7)	Comment: 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

EMBL-EBI

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  abbreviation="TGFbR-I" />
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    <state name="inactive">
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      Crescenzo et al.
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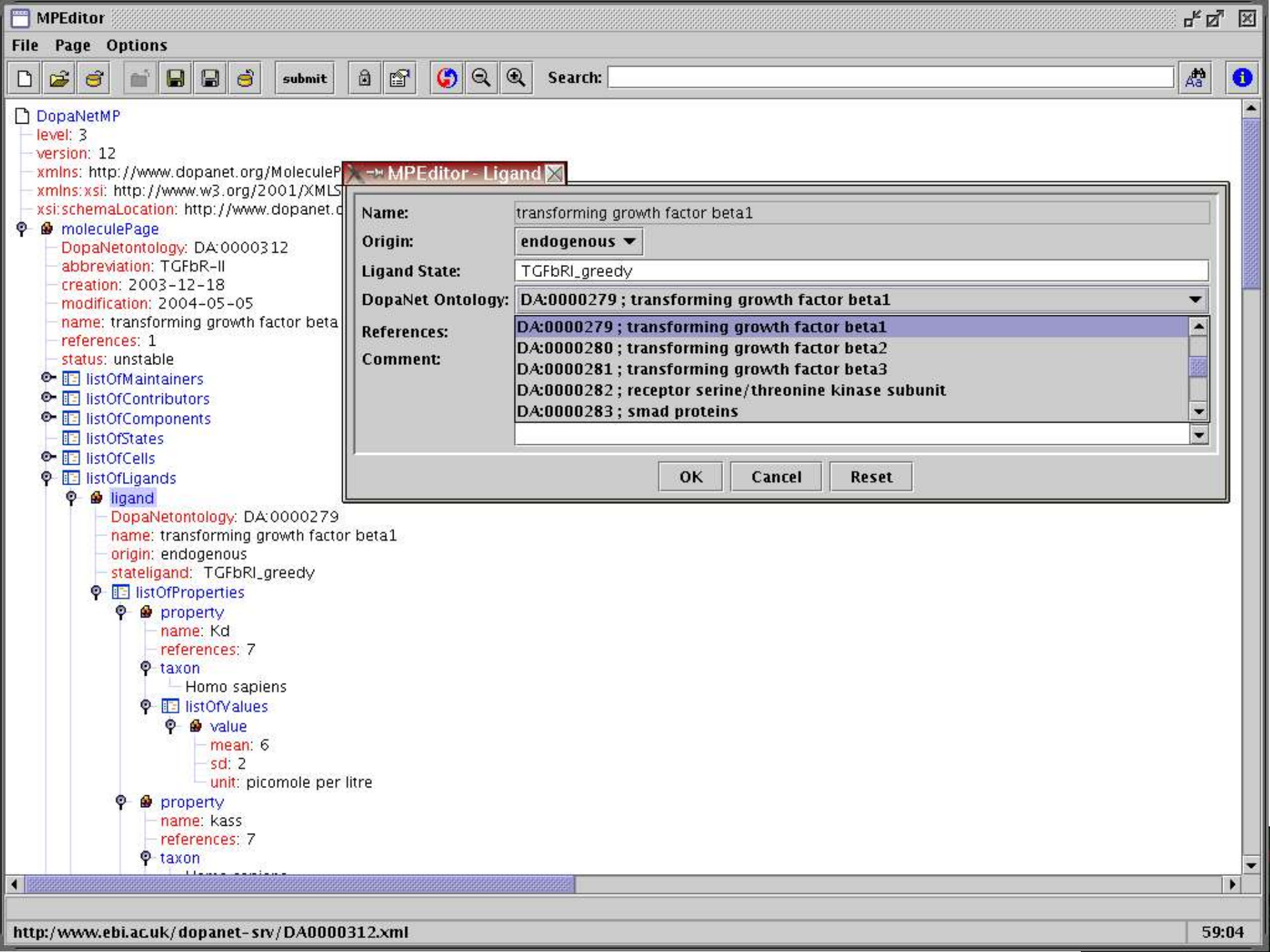
Computational Neurobiology


MPEditor
File Page Options
submit
Search:
DopaNetMP
level: 3
version: 12
xmlns: http://www.dopanet.org/MoleculeP
xmlns:xsi: http://www.w3.org/2001/XMLS
xsi:schemaLocation: http://www.dopanet.c
moleculePage
DopaNetontology: DA:0000312
abbreviation: TGFbR-II
creation: 2003-12-18
modification: 2004-05-05
name: transforming growth factor beta
references: 1
status: unstable
listOfMaintainers
listOfContributors
listOfComponents
listOfStates
listOfCells
listOfLigands
ligand
DopaNetontology: DA:0000279
name: transforming growth factor beta1
origin: endogenous
stateligand: TGFbRI_greedy
listOfProperties
property
name: Kd
references: 7
taxon
Homo sapiens
listOfValues
value
mean: 6
sd: 2
unit: picomole per litre
property
name: kass
references: 7
taxon
MPEditor - Ligand
Name:
transforming growth factor beta1
Origin:
endogenous
Ligand State:
TGFbRI_greedy
DopaNet Ontology:
DA:0000279 ; transforming growth factor beta1
References:
Comment:
DA:0000279 ; transforming growth factor beta1
DA:0000280 ; transforming growth factor beta2
DA:0000281 ; transforming growth factor beta3
DA:0000282 ; receptor serine/threonine kinase subunit
DA:0000283 ; smad proteins
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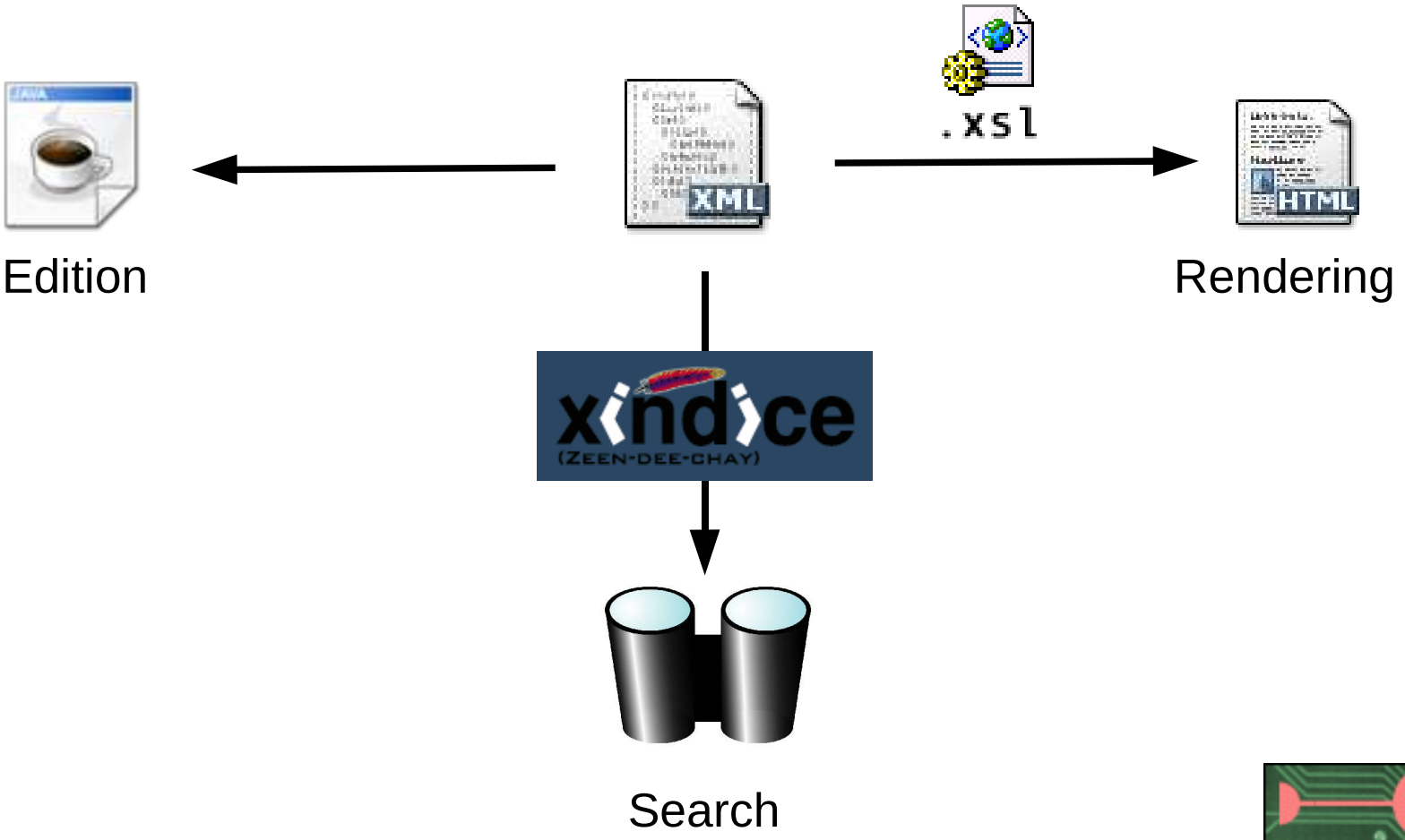
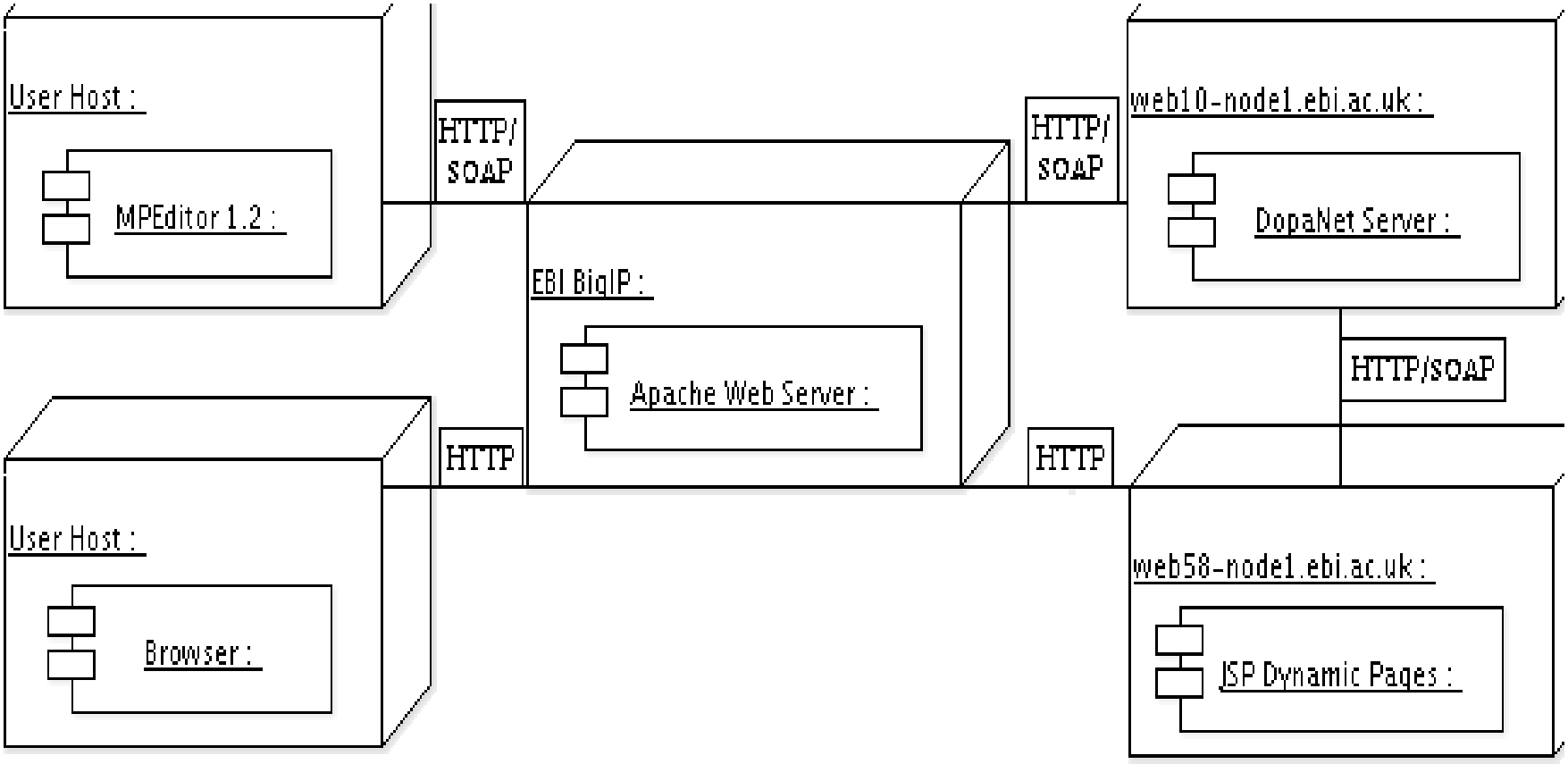
Construction de la resource



Structure de la resource



L'équipe





- Alexander Broicher (étudiant)
- Mélanie Courtot (ingénieure banques de données)
- Marie-Ange Djibe (étudiante)
- Marco Donizelli (ingénieur dévelopement logiciel)
- Éric Fernandez (stagiaire post-doctoral)