Toward a Computational Systems Neurobiology

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Scope

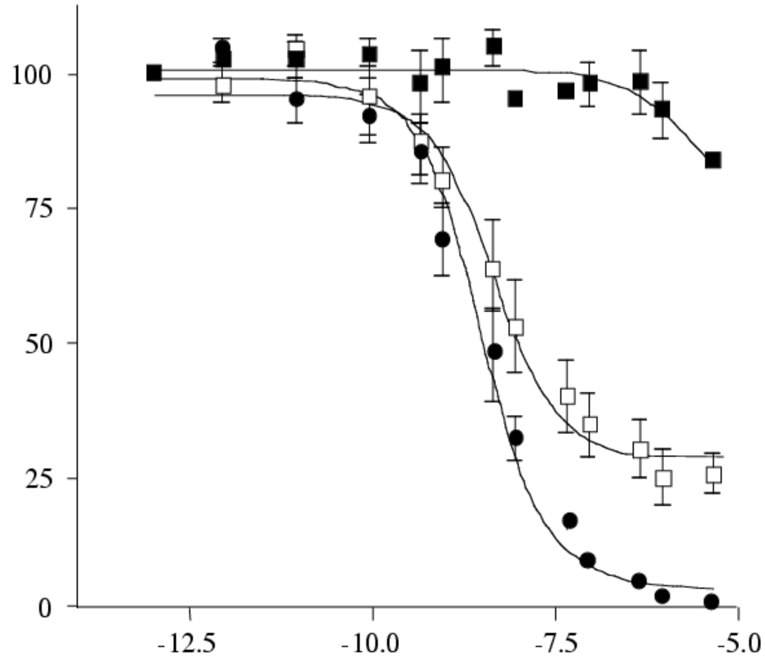
- Biology => alive objects
- typical timescale is second
- billion of billions atoms

- MD power equivalent x 10^{24}
- Our "multiscale" does not even overlap your "multiscale"

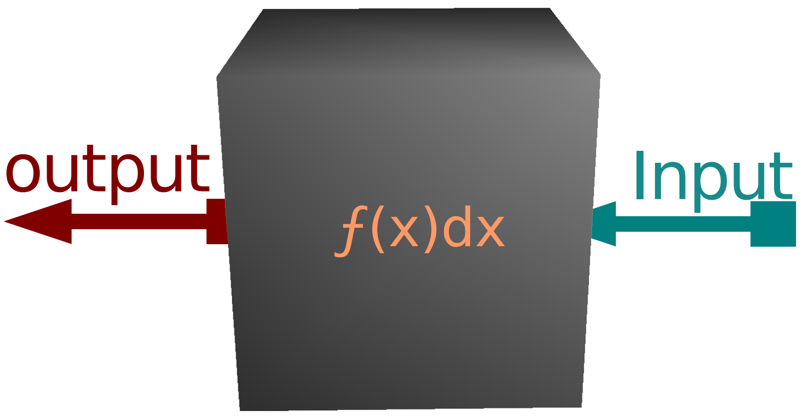
Classical modelling approaches in theoretical biology

(1)-The phenomenology

Snapshot of the system

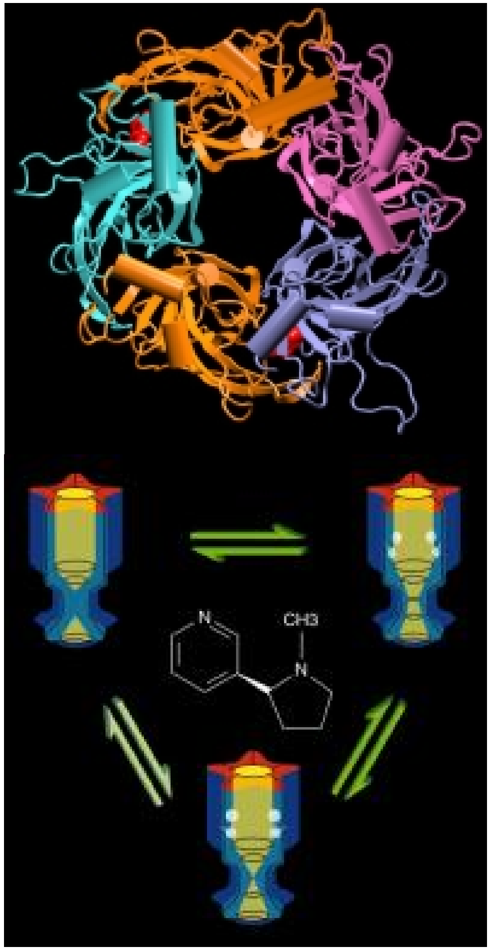


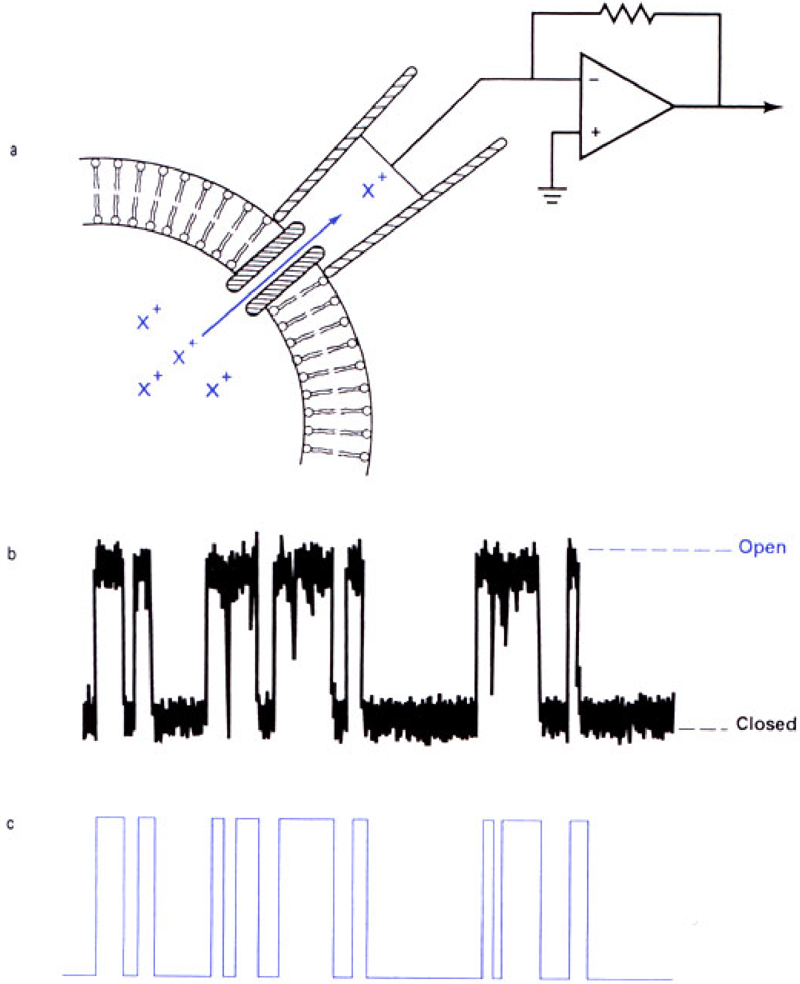
Abstraction

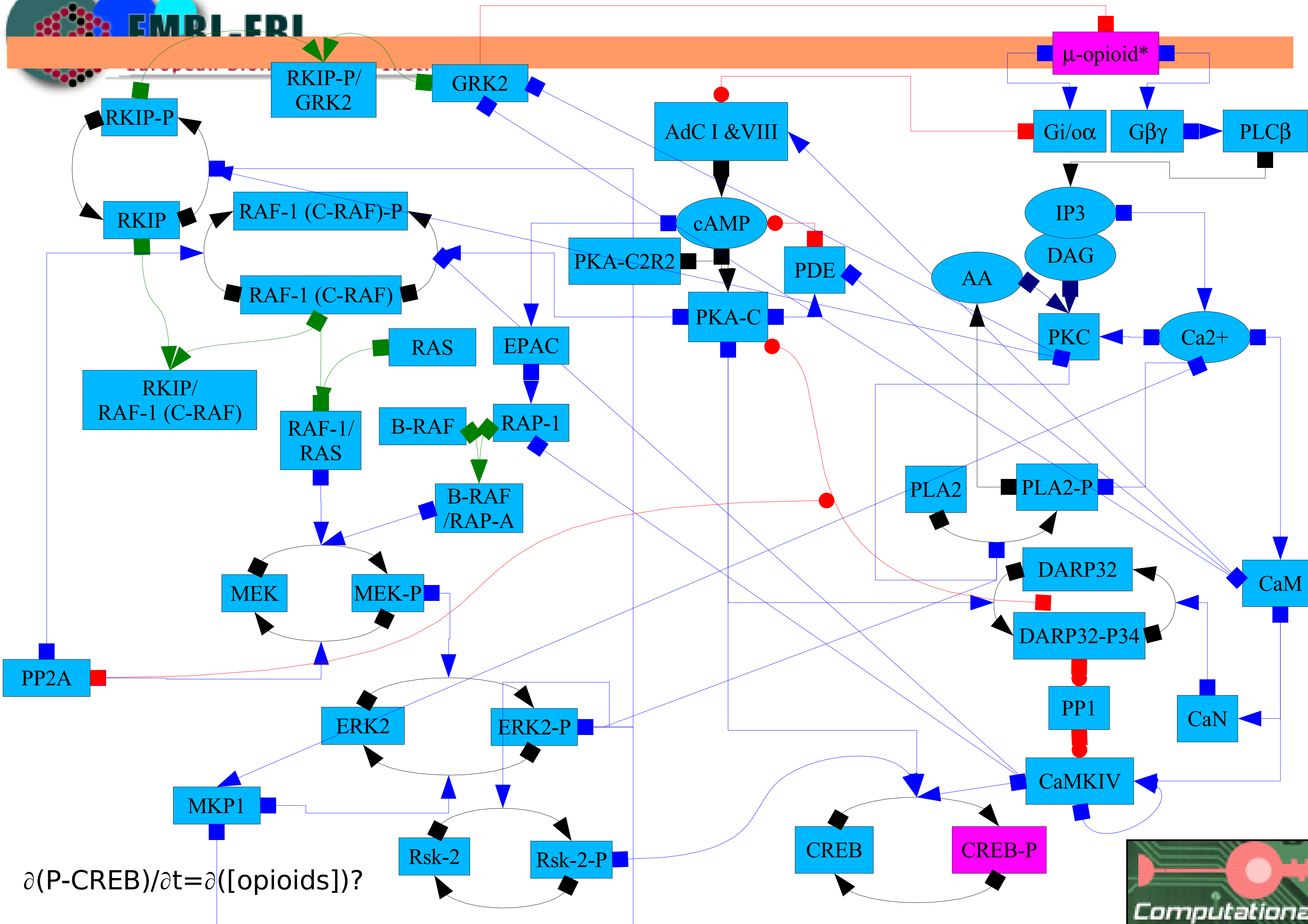


Classical modelling approaches in theoretical biology

(2)-The reductionism







$\partial(\text{P-CREB})/\partial t = \partial([\text{opioids}])$?

Systems Biology

- Reconstruction of the dynamic biological systems from the properties of their elementary building blocks

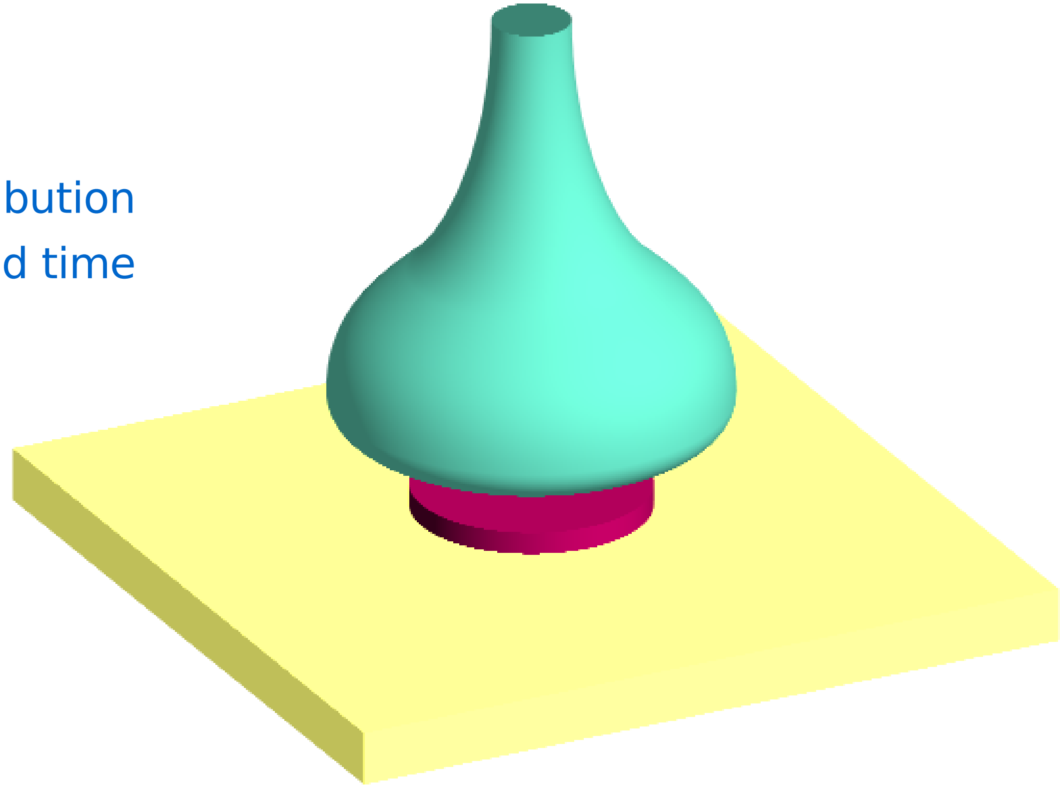
- Relationships between building blocks are more important than their elementary properties.
  Cybernetics properties are conserved across systems (control theory: feedback, feedforward, robustness)
  The theoretical treatment is already available

- Made possible by large-scale quantitative data production & improvements of computing power and technics

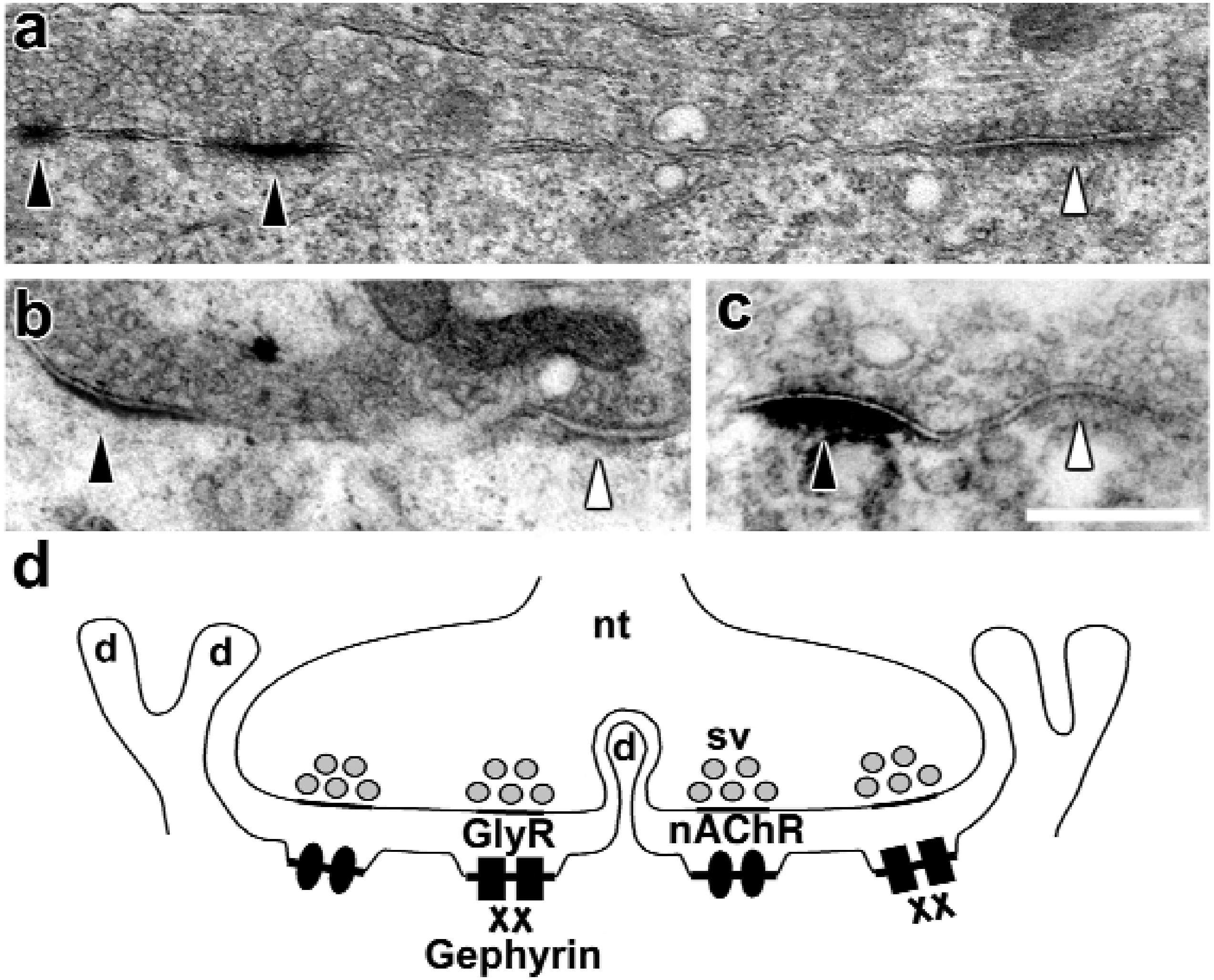
- A New Era:
  Molecular Biology made Biology understandable (sometimes)
  Systems Biology makes Biology predictive (we hope so)

Classical view of the synapse

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



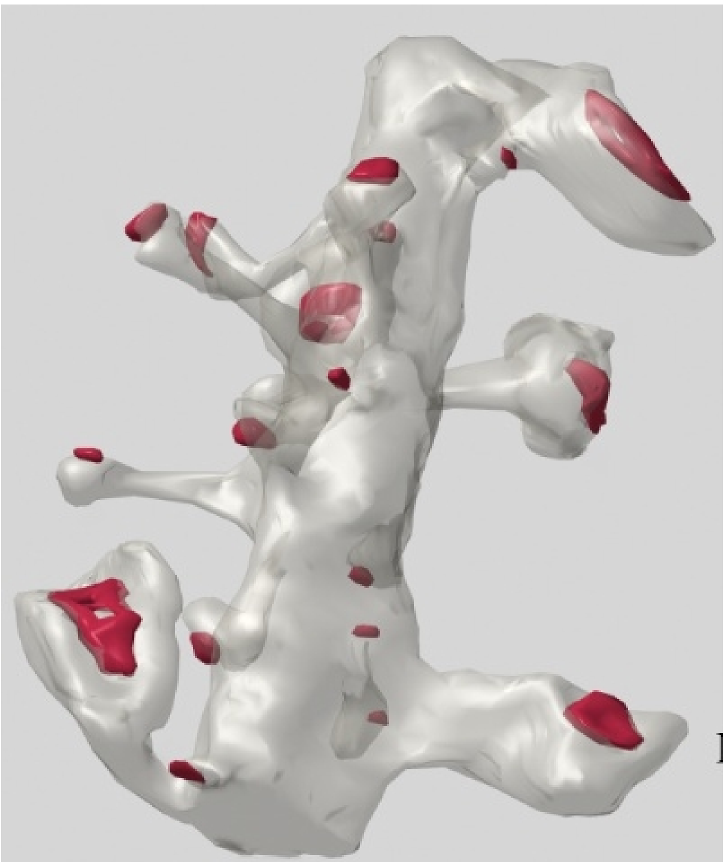
Pharmacological complexity

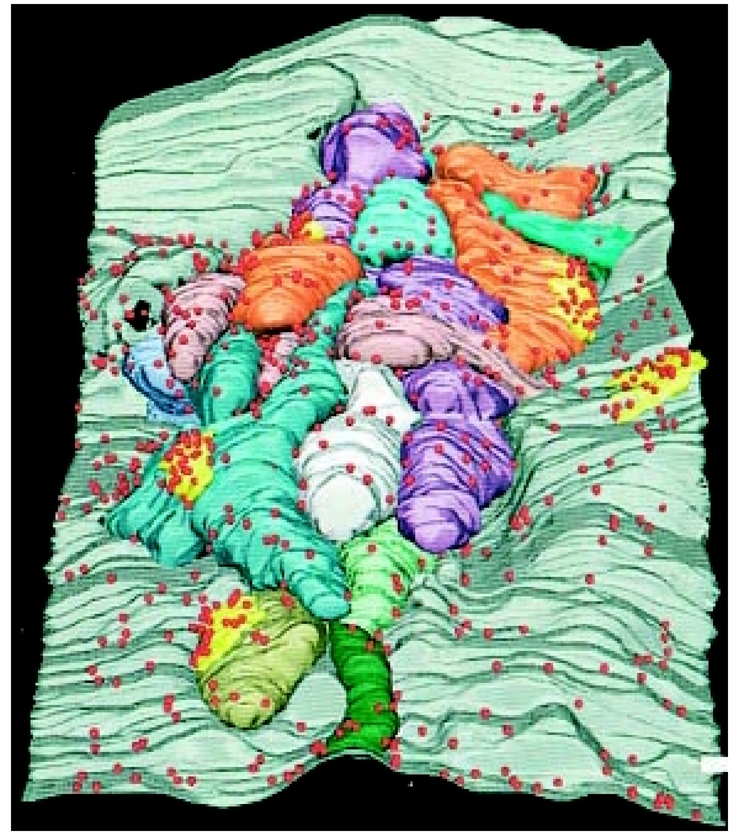


Tsen et al. (2000) *Nat Neurosci*, 3: 126-132

Structural complexity (1)

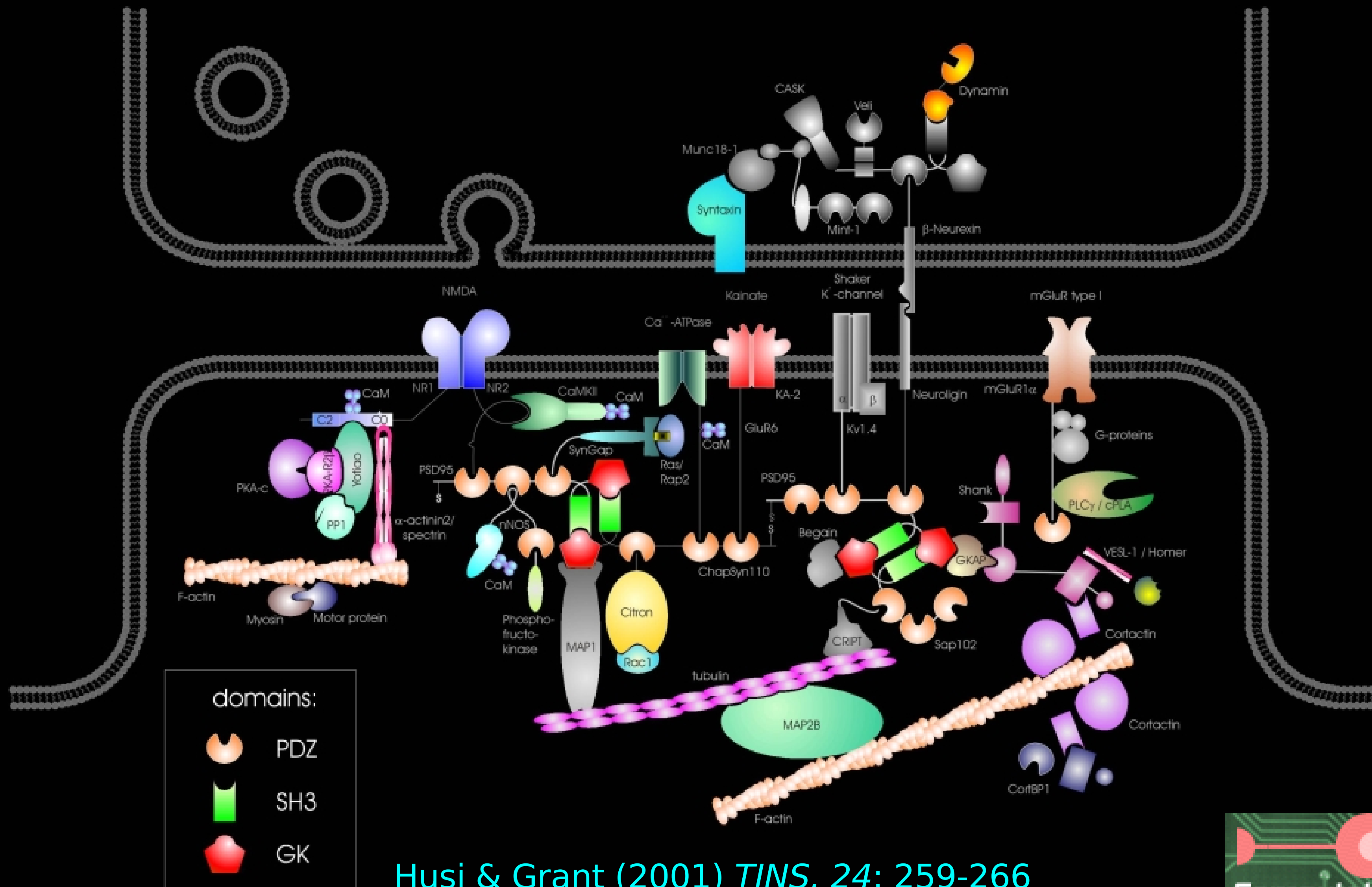
Atlas of Ultrastructural Neurocytology
http://synapses.mcg.edu/atlas/eurosci





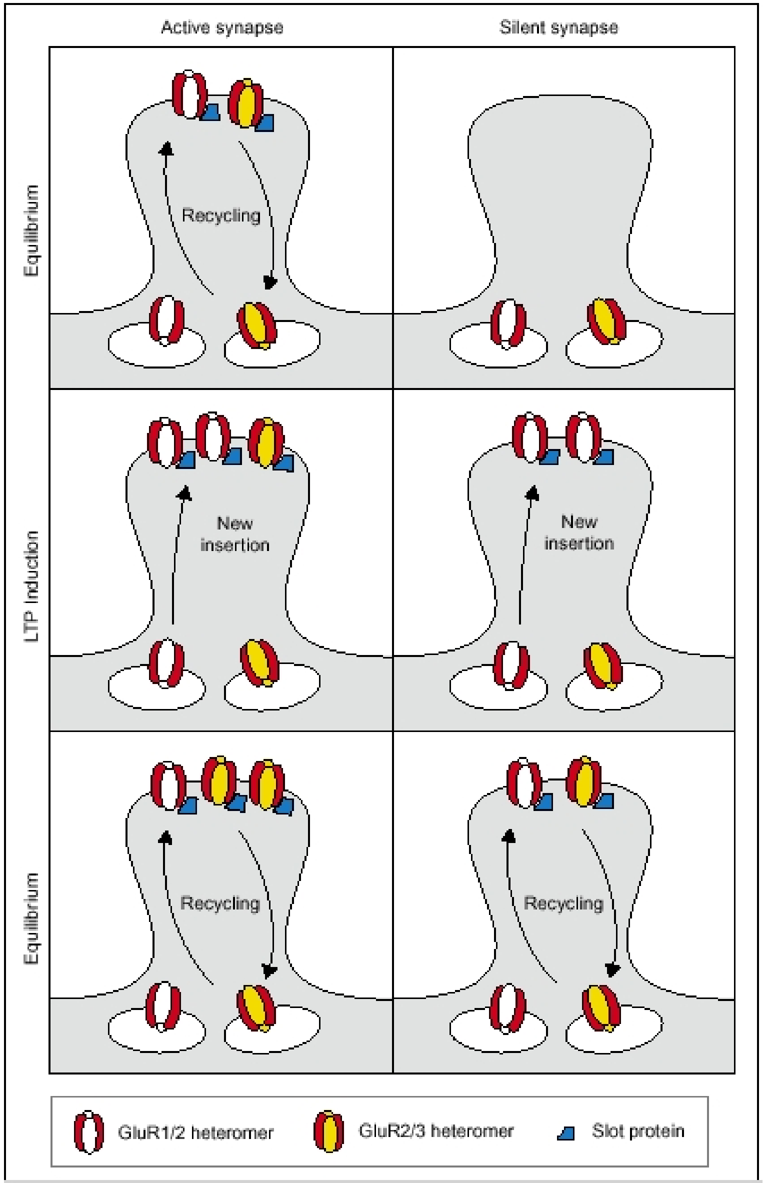
Shoop et al. (2002)
J Neurosci, 22: 748-756

Structural complexity (2)

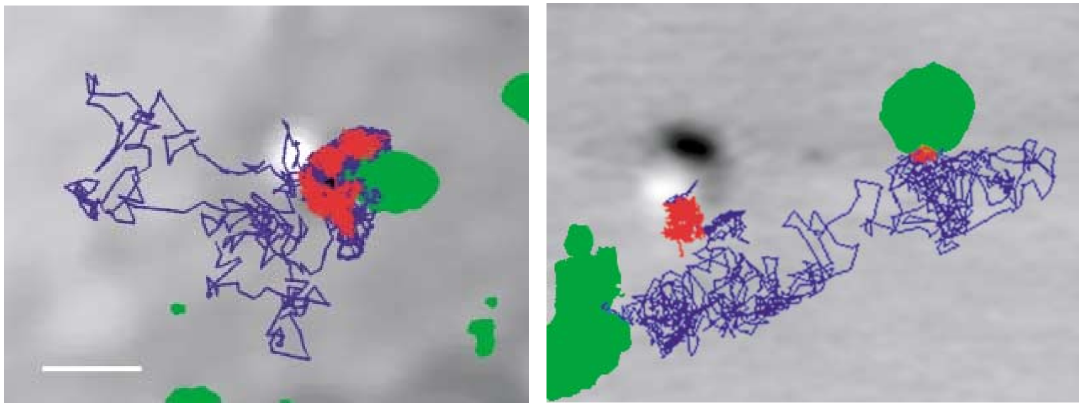


Husi & Grant (2001) *TINS, 24*: 259-266

Temporal complexity



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



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

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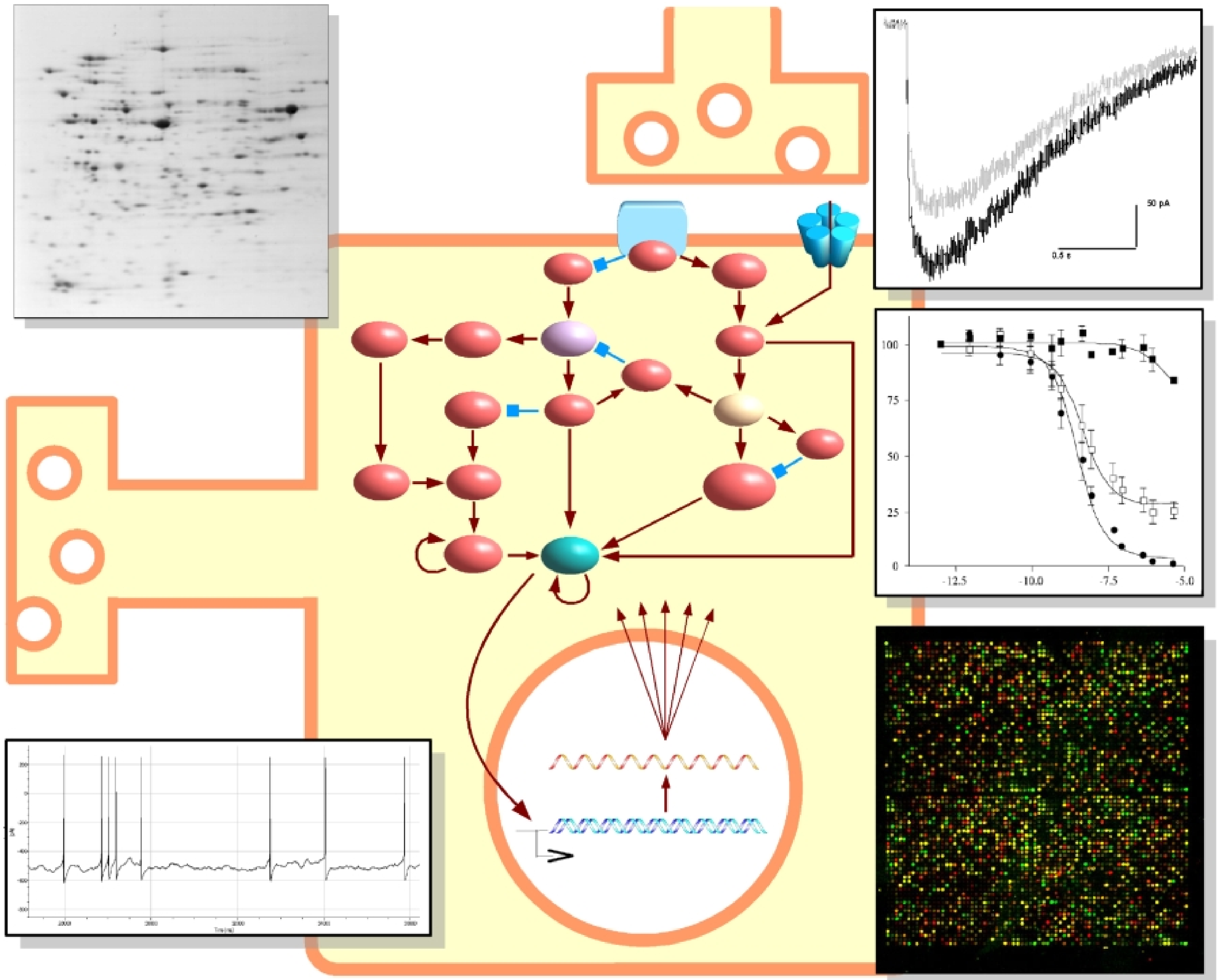
Heterogeneous quantitative data



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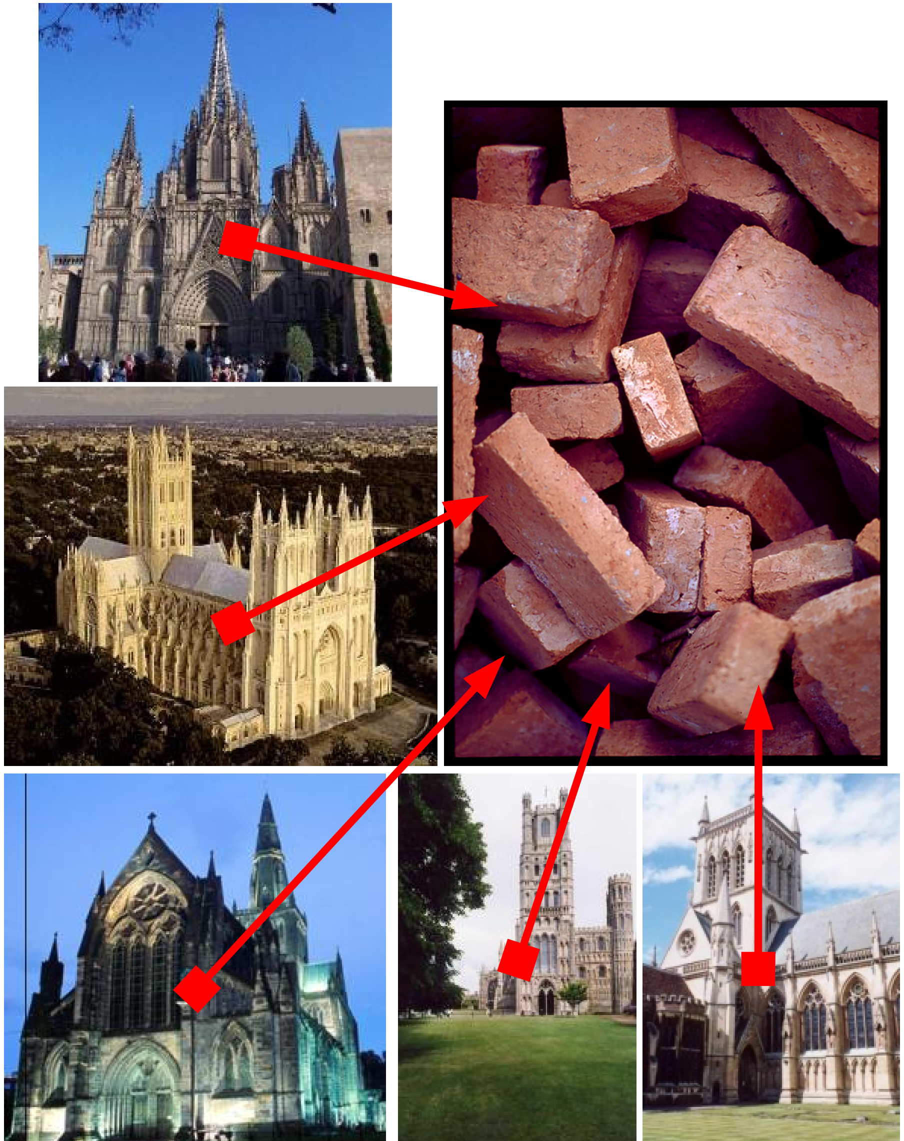
Cellular Neurobiology today



Computational Neurobiology

DopaNet: The Meso-Telencephalic Dopamine Consortium - Mozilla

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http://www.dopanet.org/index.html

Search

Issue list | DopaNet: The Meso-Telence...

DopaNet is supported by:

EMBL-EBI European Bioinformatics Institute

European Science Foundation

Institut Pasteur

Centre National de la Recherche Scientifique

DopaNet: The Meso-Telencephalic Dopamine Consortium

What is DopaNet?	DopaNet structure
DopaNet members	Open positions
Neuronal ontology	Molecule Pages
How can I help?	Contact

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

June 2003: The construction of an ontology of the neuronal cell has been 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 booklet)

Nicolas Le Novère
Last modified: Wed Mar 24 14:50:59 GMT 2004

EMBL-EBI European Bioinformatics Institute

DopaNet members

Heinrich Betz
Bertrand Bloch
Paul Bolam
Paolo Calabresi
Eero Castrén
Jean-Pierre Changeux
Daniel Choquet
Francesco Clementi
Graham Collindgridge
Pier De Benedetti
Alexander Dityatev
Stuart Edelstein
Piers Emson
Gilberto Fisone
GeneScore
Jean-Antoine Girault
Bruno Giros
Sten Grillner
Eckart Gundelfinger
Hybrigenics
Reinhard Jahn
Nicolas Le Novère
Marie-Claude Potier
Joche Roeper
Carlo Sala
Amelia Sánchez-Capelo
Marten Smidt
Serge Schiffmann
Torgny Svensson
Michele Zoli

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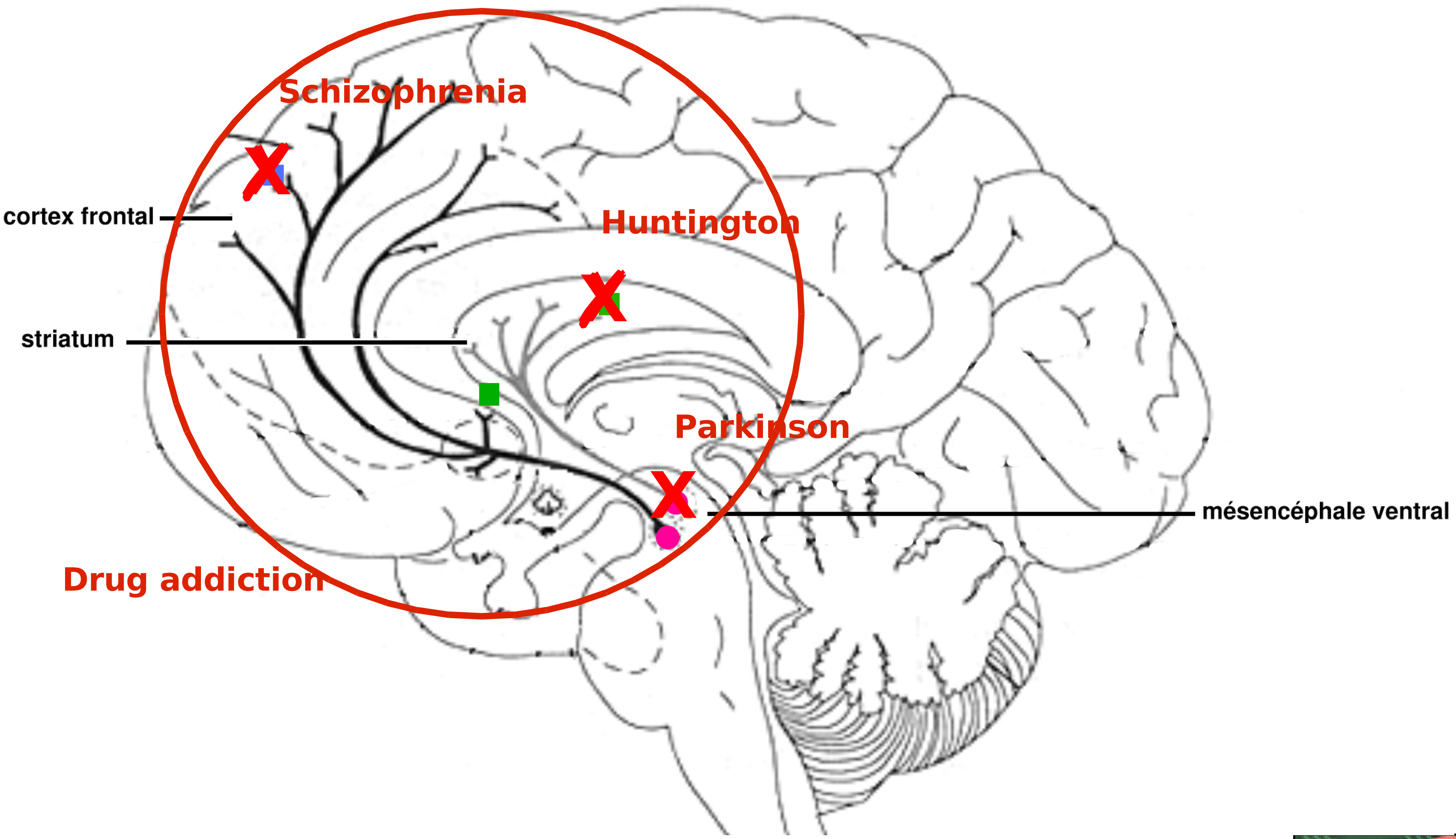
The mesotelencephalic DA system



DopaNet roadmap

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.

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.

Third level

Generalisation to all missing molecules:

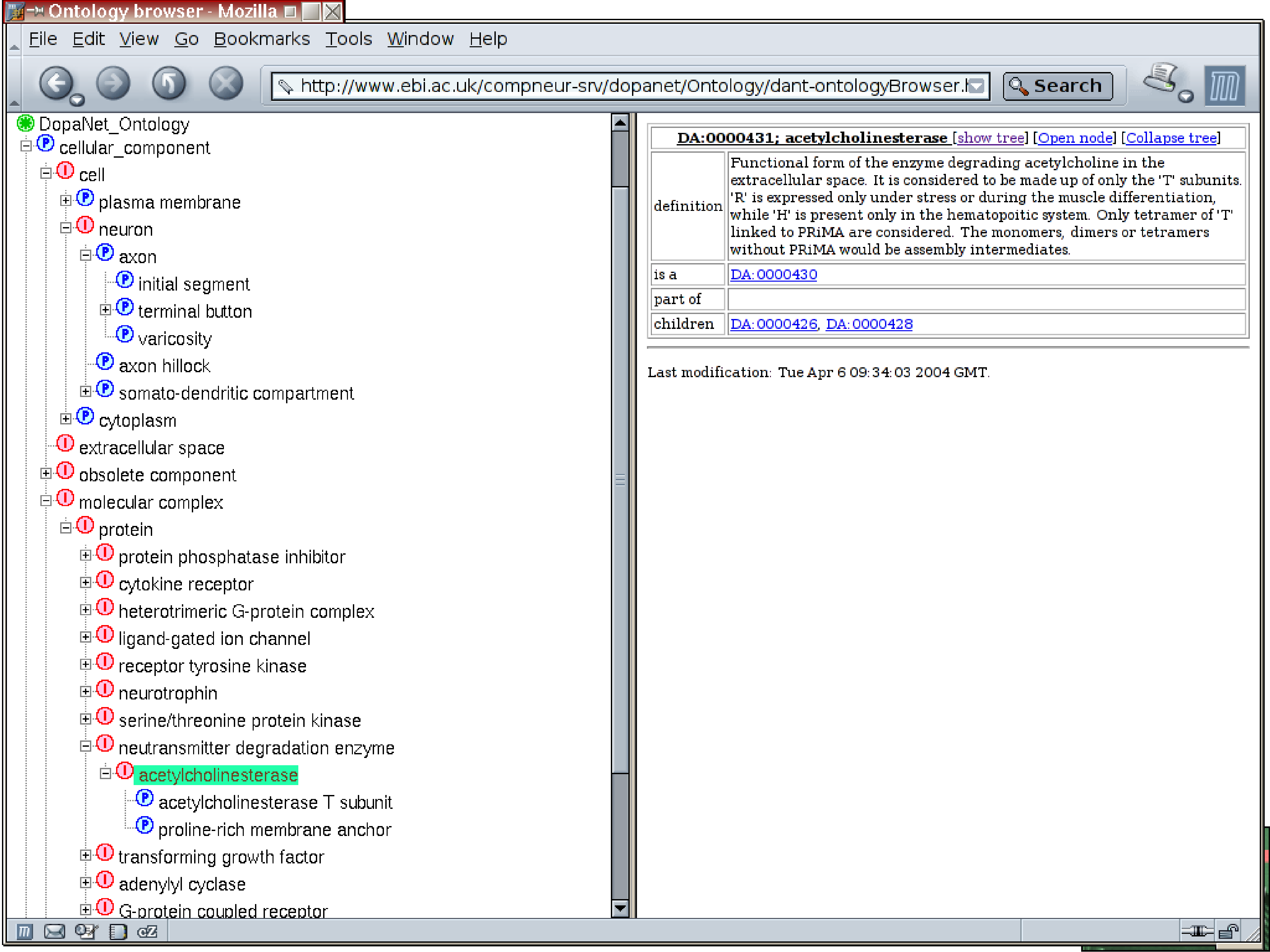
Not specific to the dopaminergic neuron, but crucial to its function.
- post-translational machinery
- intracellular targeting systems
- protein recycling etc.

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.


Ontology browser - Mozilla
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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
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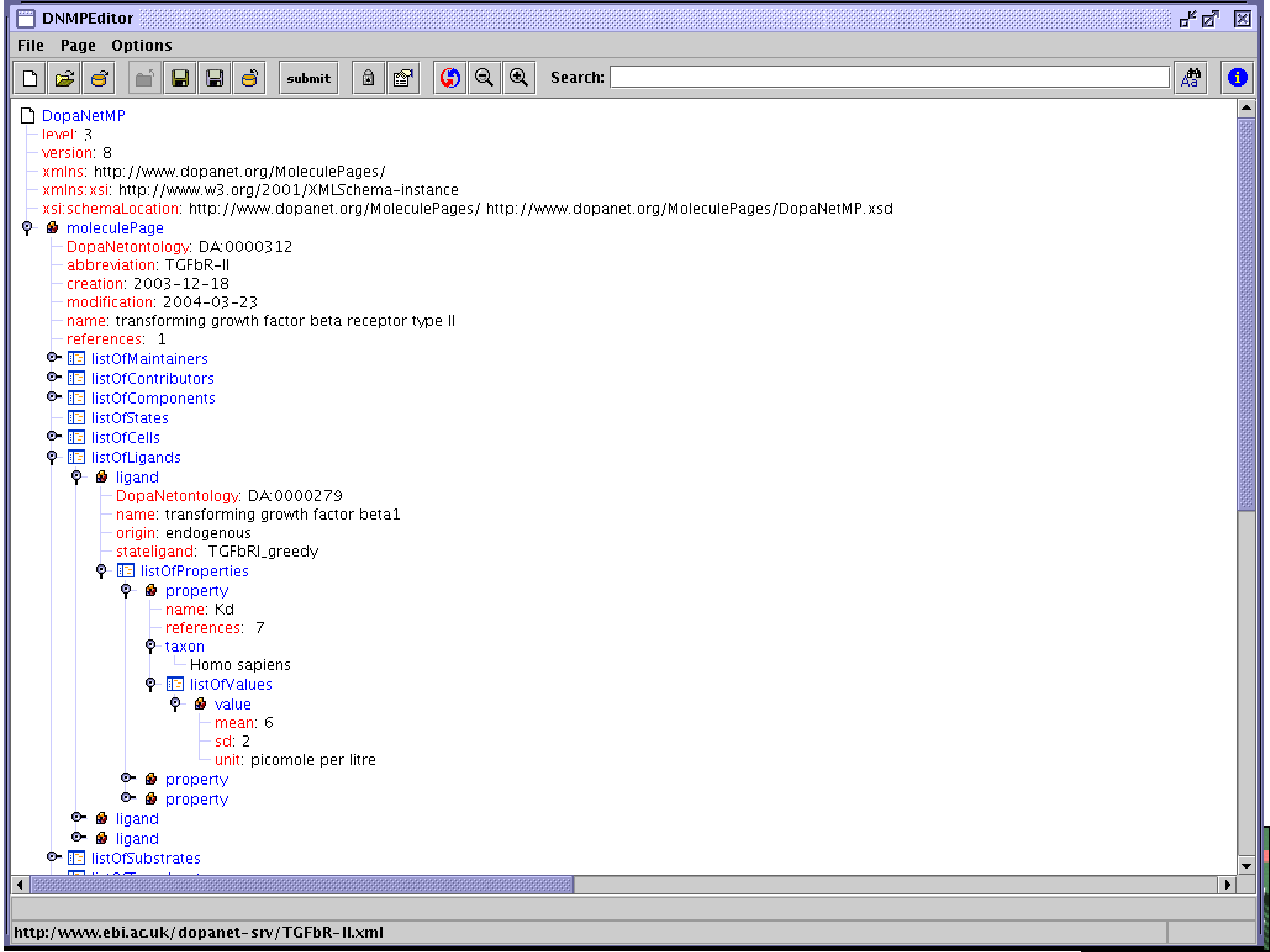
part of
children
DA:0000426, DA:0000428
Last modification: Tue Apr 6 09:34:03 2004 GMT.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File Page Options
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xsi:schemaLocation: http://www.dopanet.org/MoleculePages/ http://www.dopanet.org/MoleculePages/DopaNetMP.xsd
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modification: 2004-03-23
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listOfContributors
listOfComponents
listOfStates
listOfCells
listOfLigands
ligand
DopaNetontology: DA:0000279
name: transforming growth factor beta1
origin: endogenous
stateligand: TGFbRI_greedy
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property
name: Kd
references: 7
taxon
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mean: 6
sd: 2
unit: picomole per litre
property
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ligand
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http://www.ebi.ac.uk/dopanet-srv/TGFbR-II.xml

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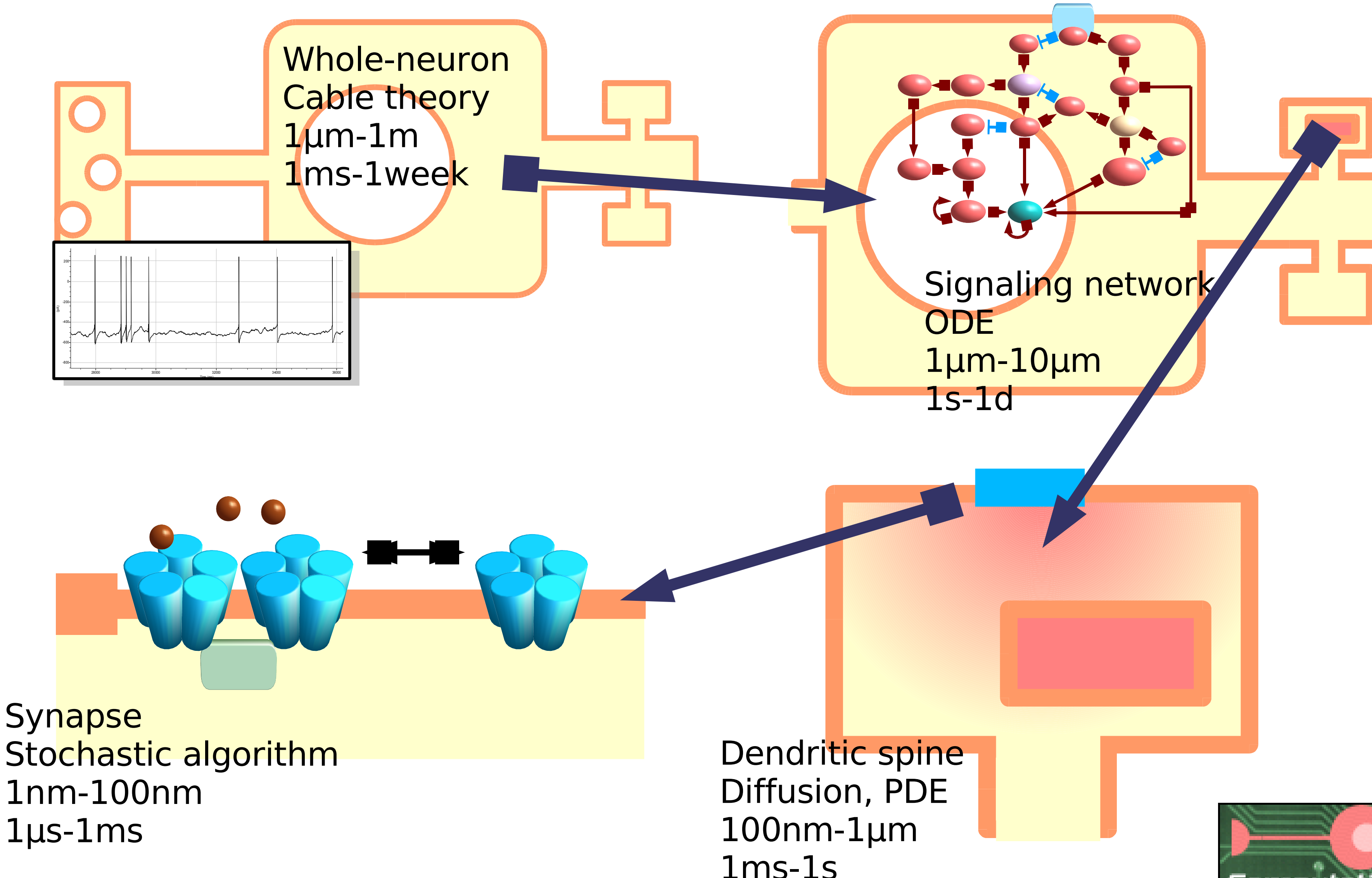
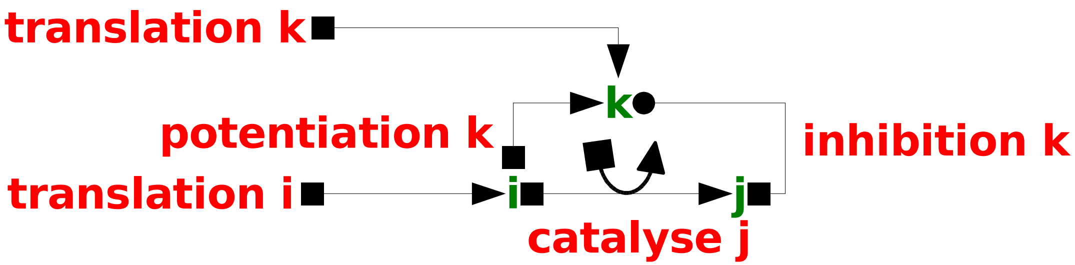
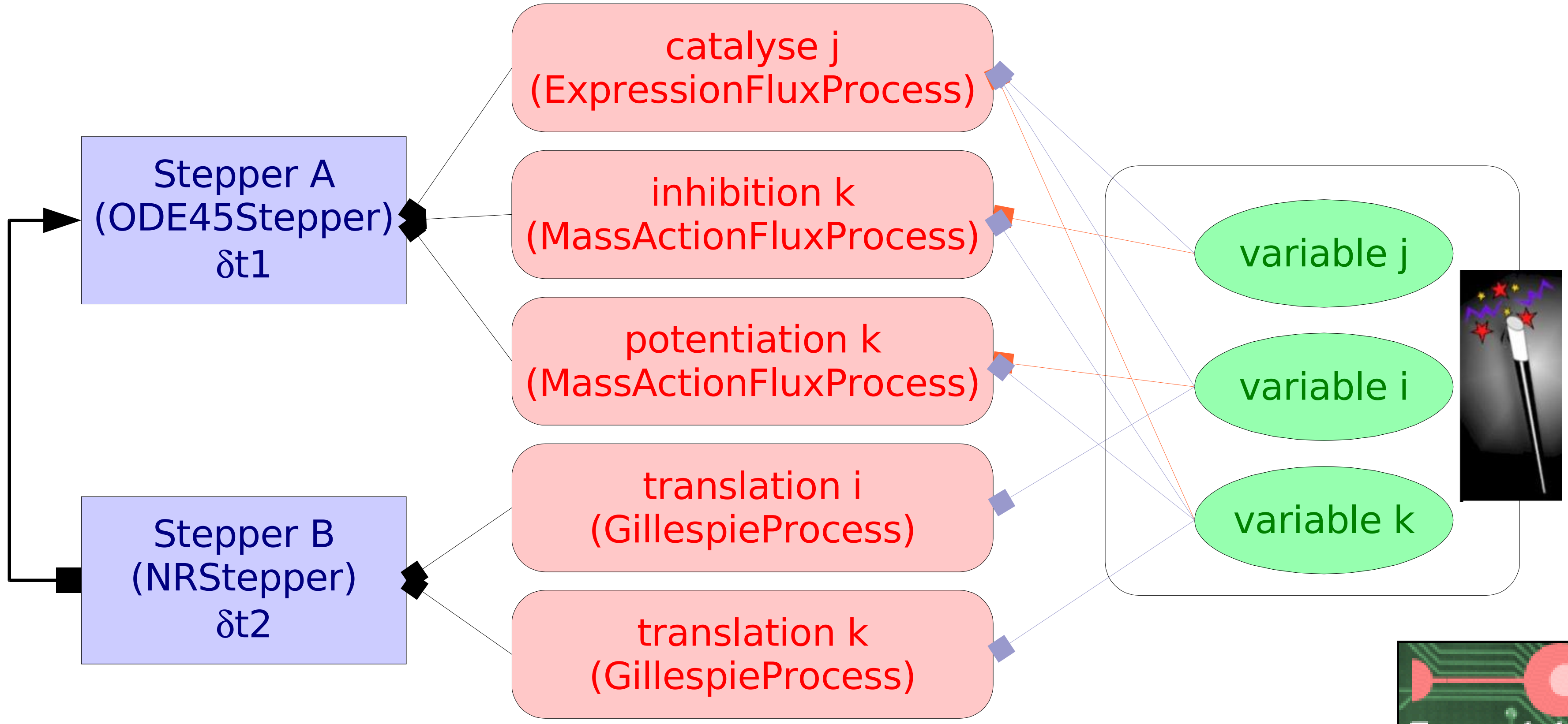
Computational Neurobiology

multi-scale multi-algorithm models are required



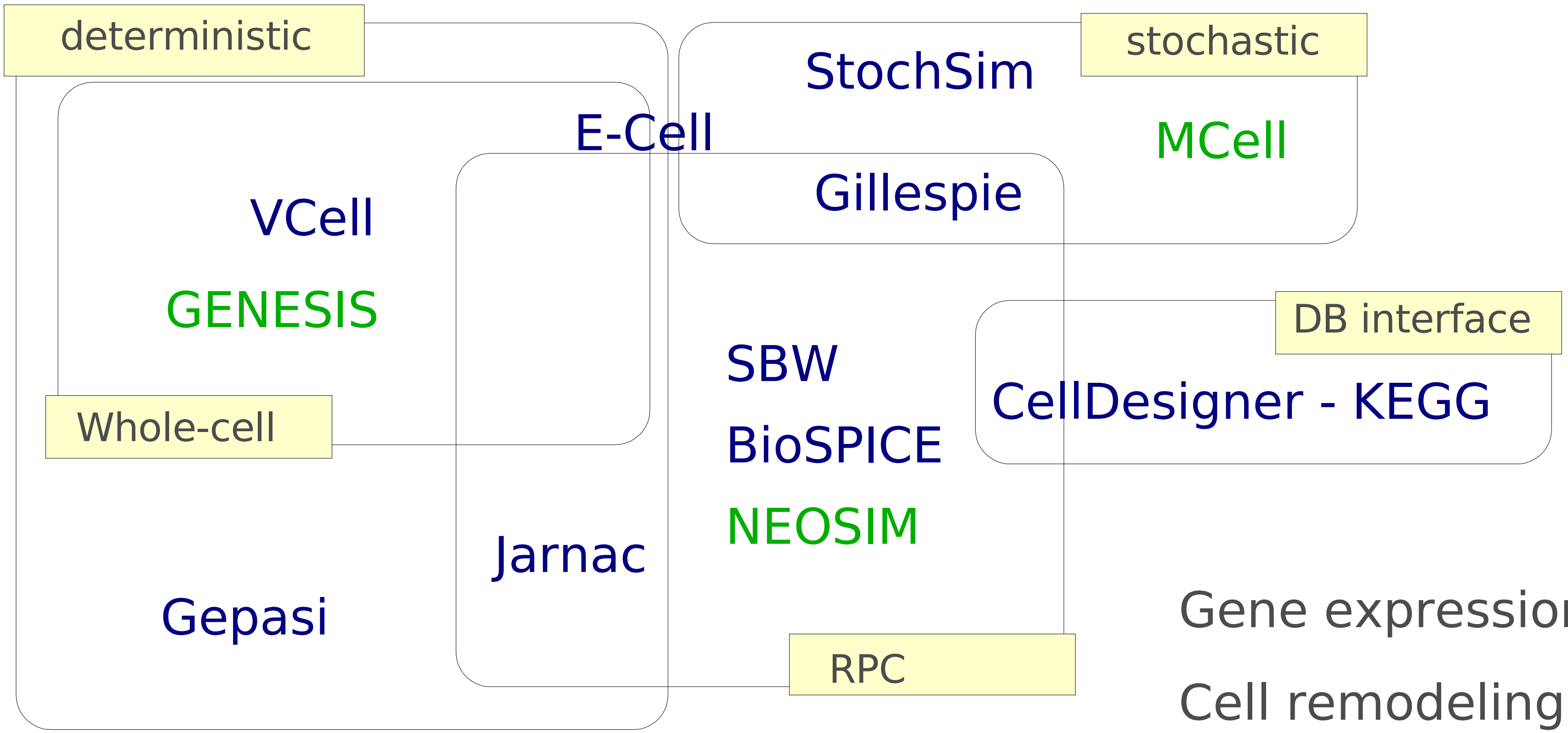
E-Cell System 3 (Kouichi Takahashi) shared mem, hyper-threading





Modularity efforts

used to model neurons



Gene expression?

Cell remodeling?

All these programs speak SBML
(Systems Biology Markup Language)

SBML.org - The home site for the Systems Biology Markup Language - Mozilla

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http://sbml.org/index.psp

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Systems Biology Markup Language

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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.

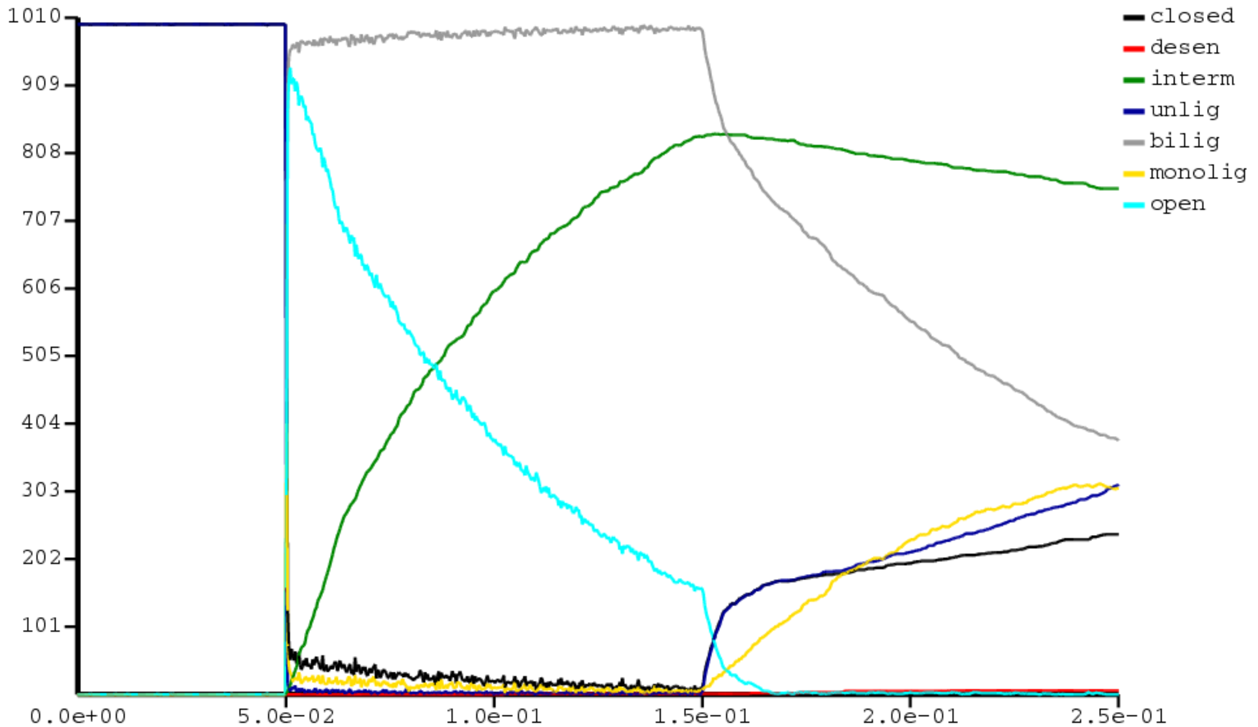
'sysbio' mailing list survey

(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

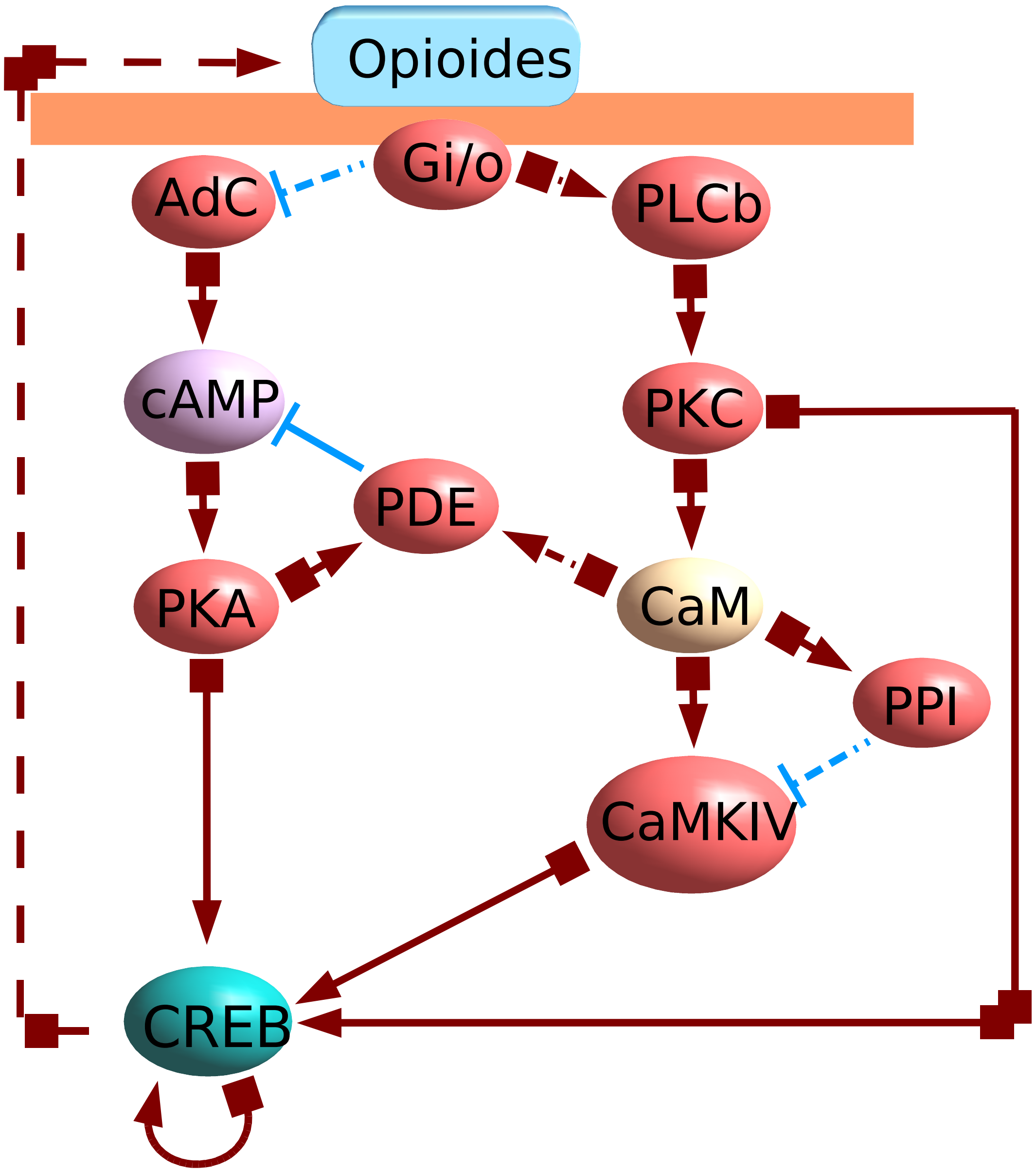
A minimal example: Stochastic simulation of a nicotinic EPSP

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



Parsing can be an HPC problem ;-)

Parameter search



Unknown or uncertain parameters
⇒Iterative determination

- evolutionary algorithms (GA)
- stochastic algorithms (SA)
- gradient-descent
- direct search

Thousands of iterations, i.e. demanding computation, whatever the simulation. However, independent simulations, allowing for distributed computing

The team ...

- Marco Donizelli (software engineer)
- Éric Fernandez (post-doc, start in may)
- Mélanie Courtot (database engineer, start in july)
- Dominic Tölle (PhD student, start in september)