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Toward a Systems Biology of the Neuron

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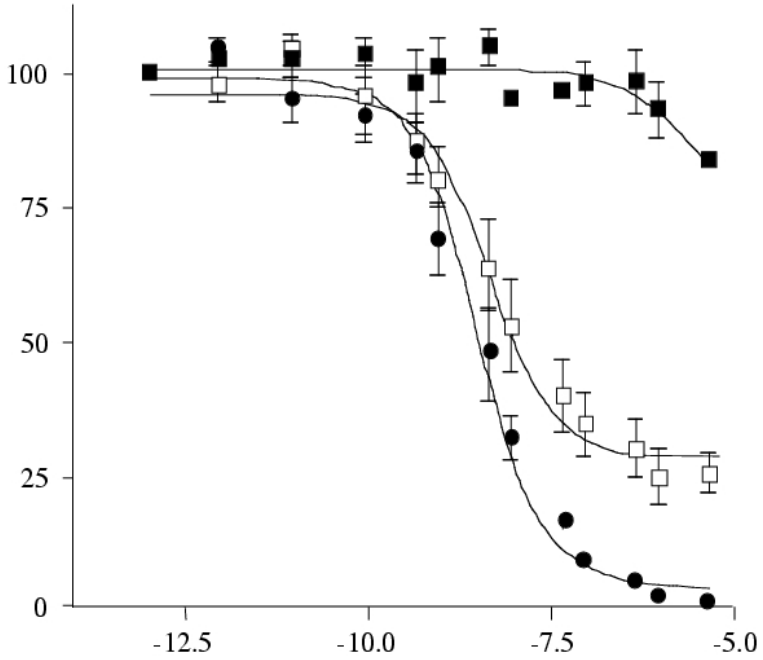
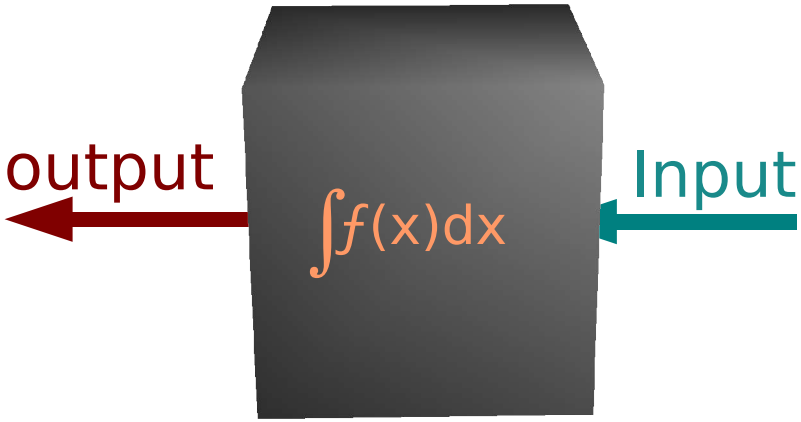
Classical modelling technics

(1)-The phenomenology

Snapshot of the system ⇒ Abstraction





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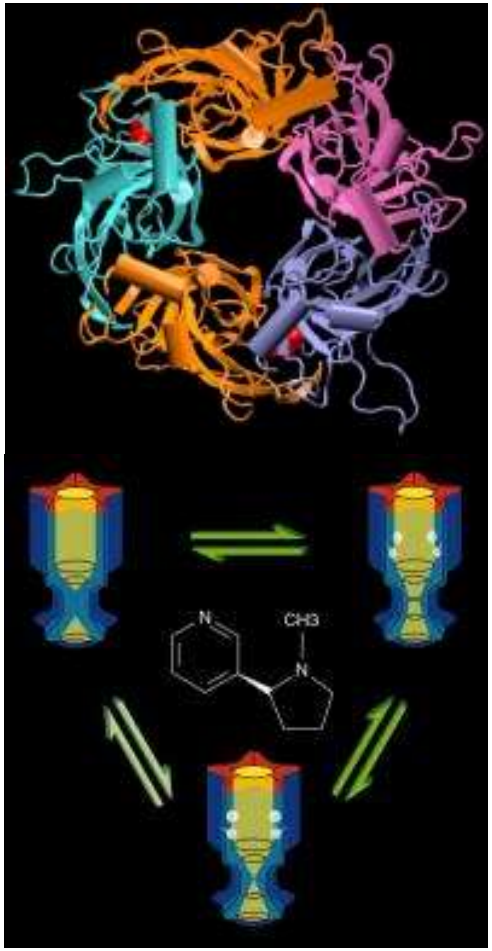
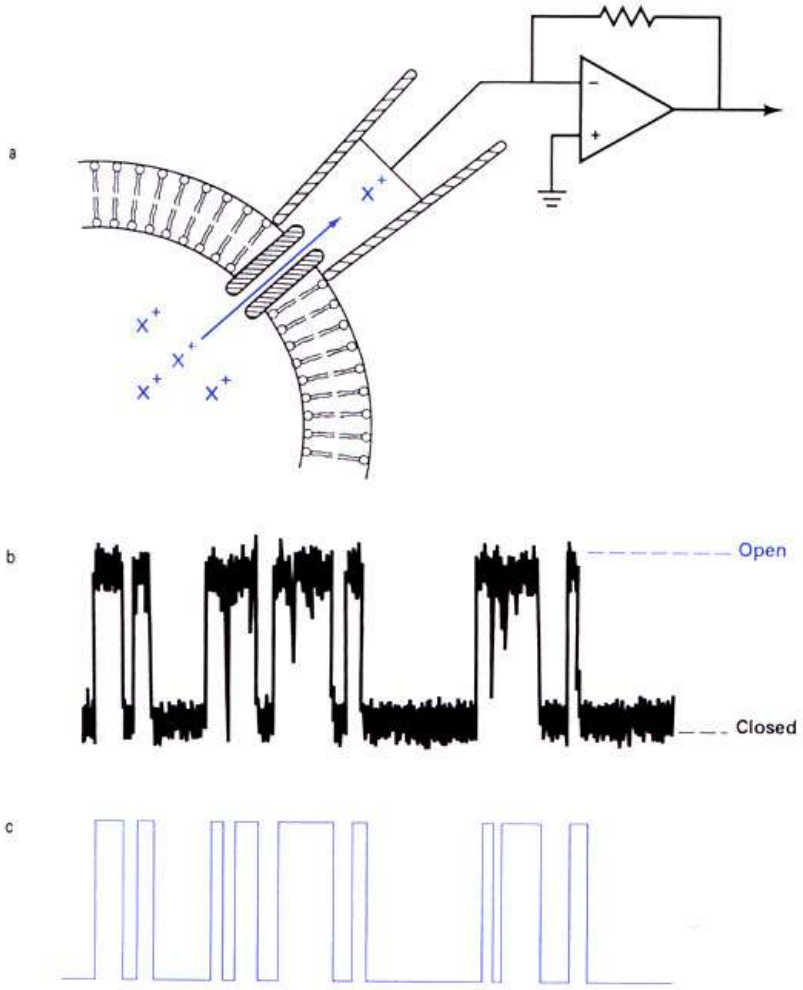
Classical modelling technics

(2)-The reductionism





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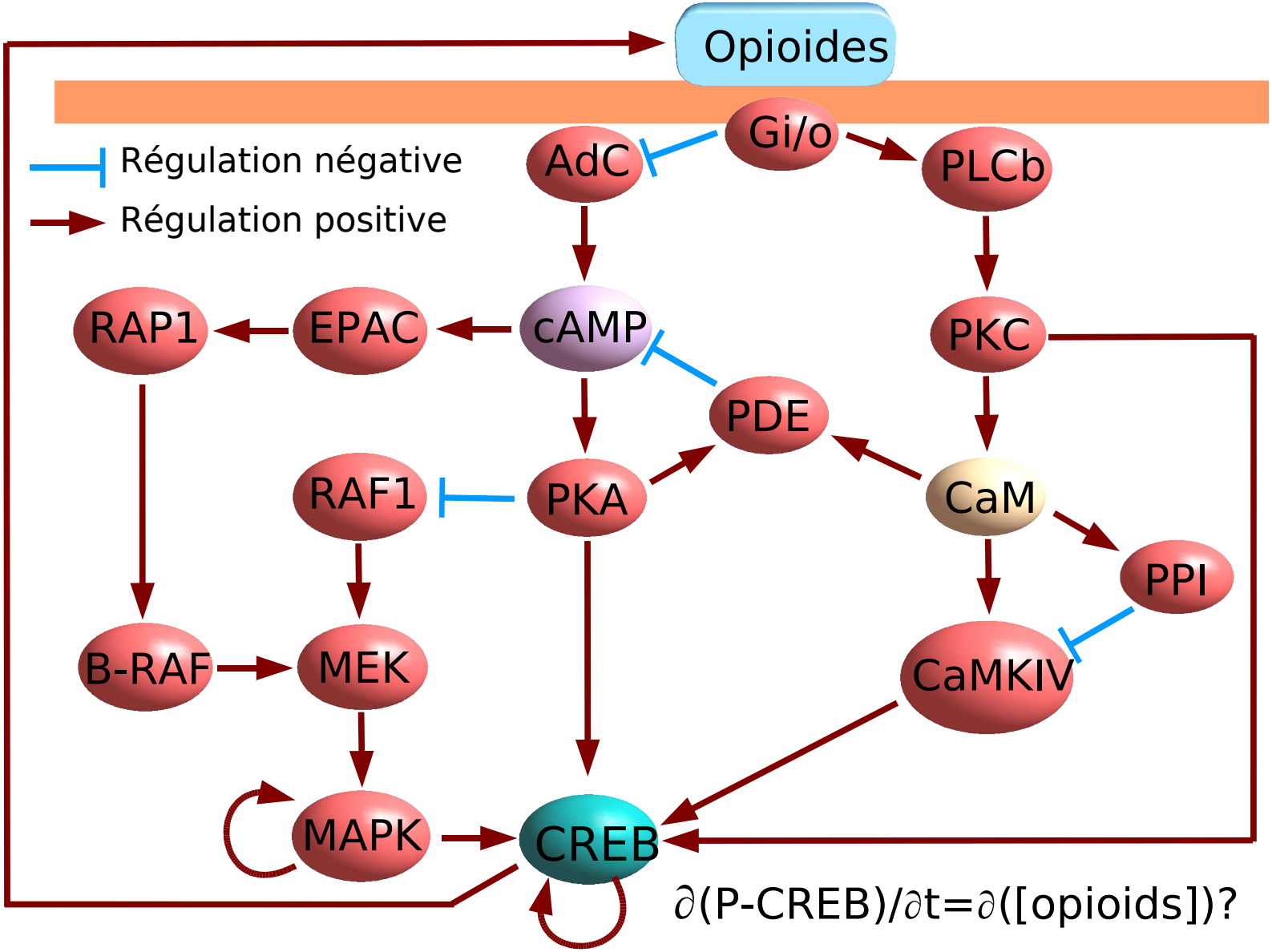
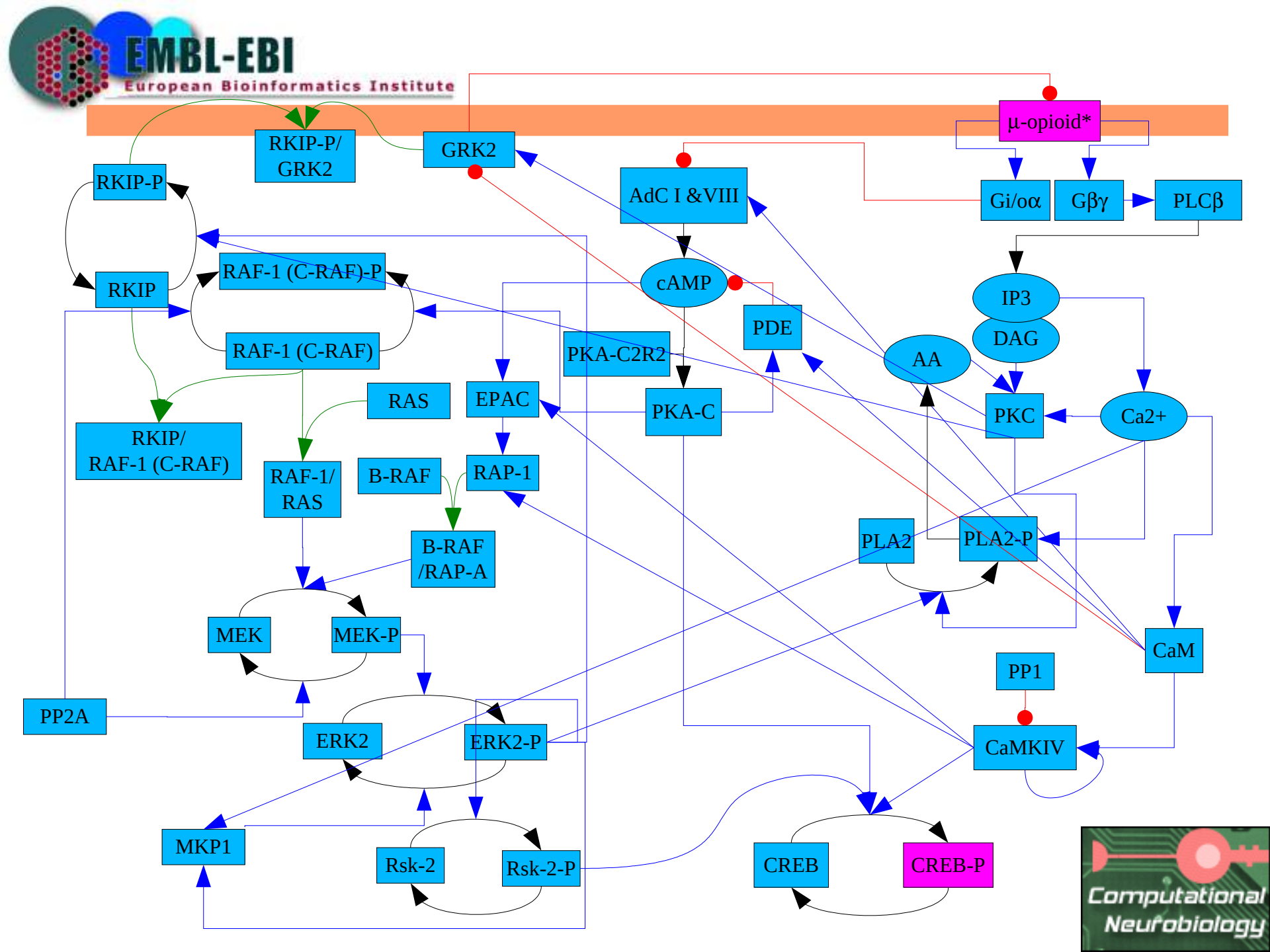
Emergent properties

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

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Systems Biology

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

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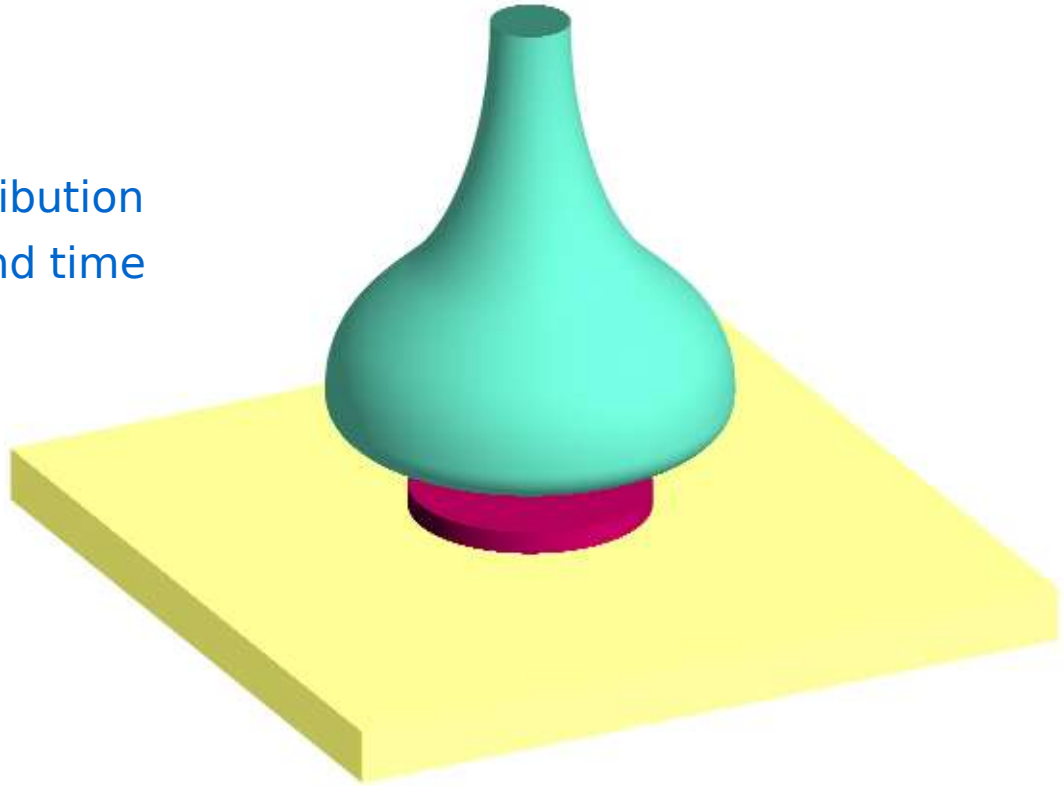
Common (mis)conception of the synapse

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



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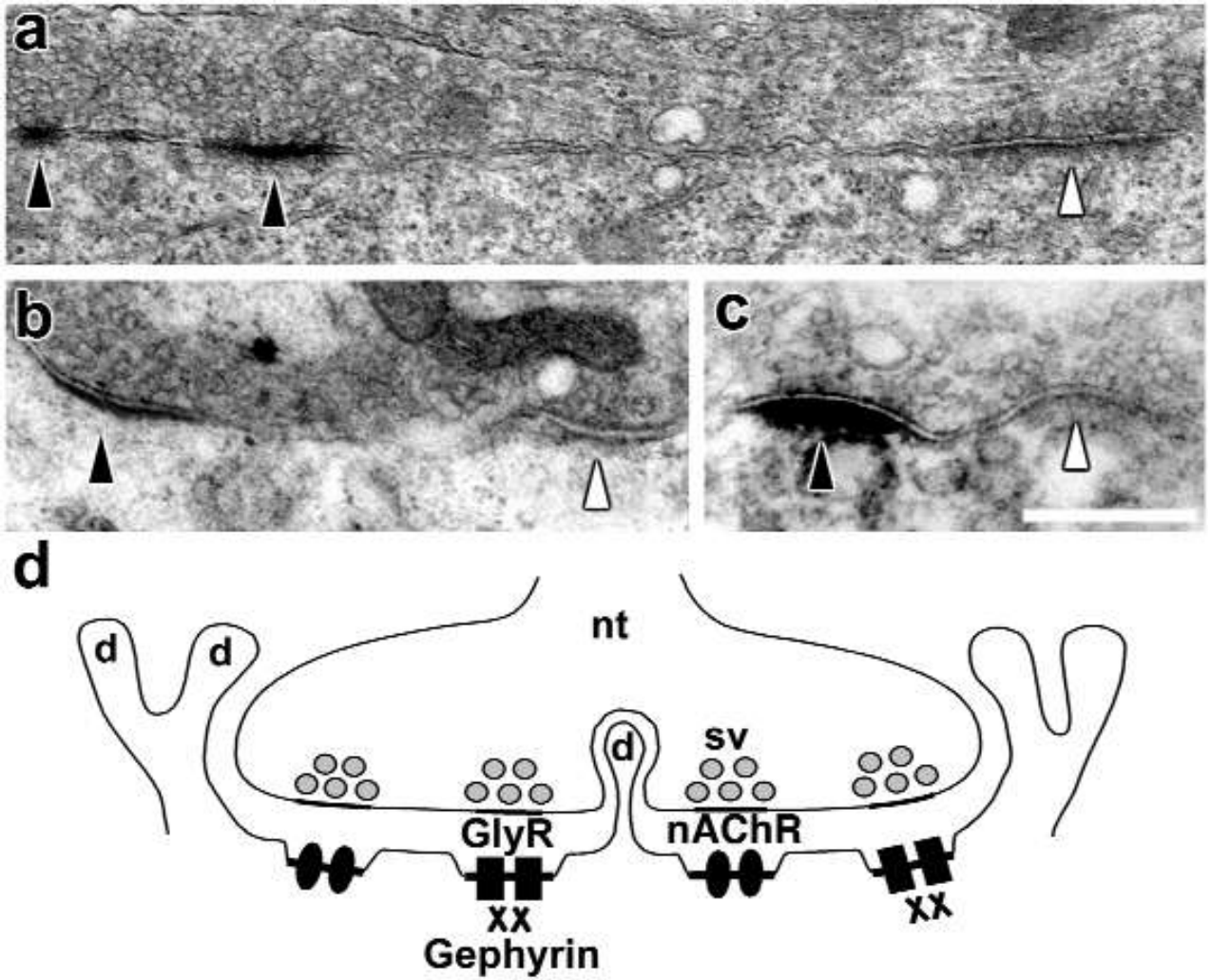
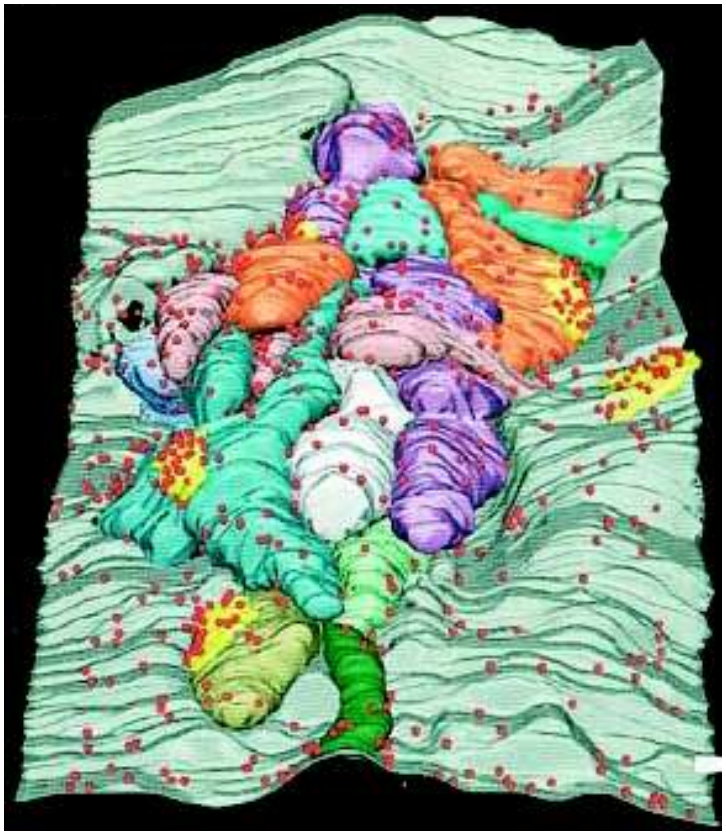
Pharmacological complexity



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

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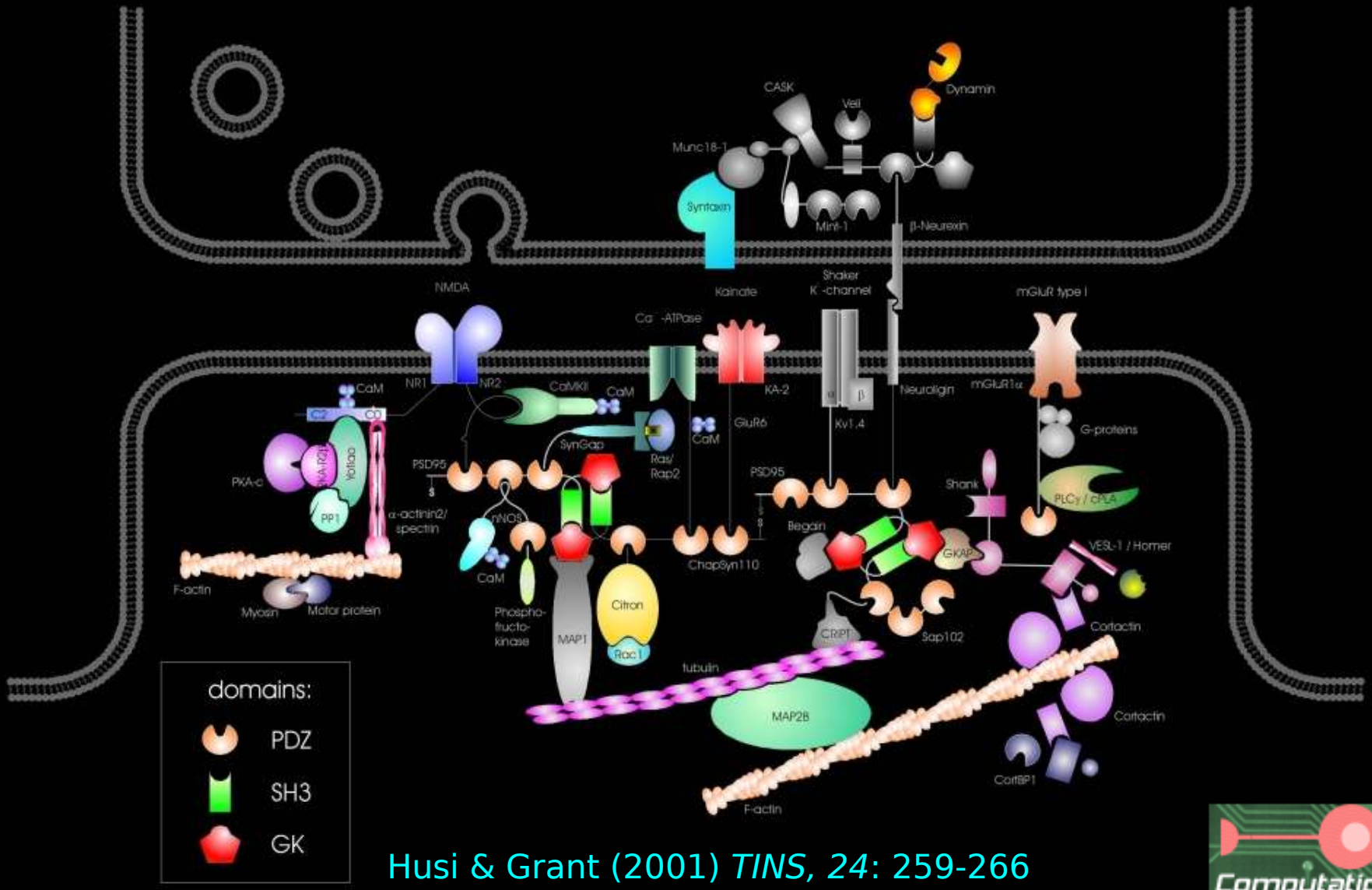
Structural complexity (2)



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

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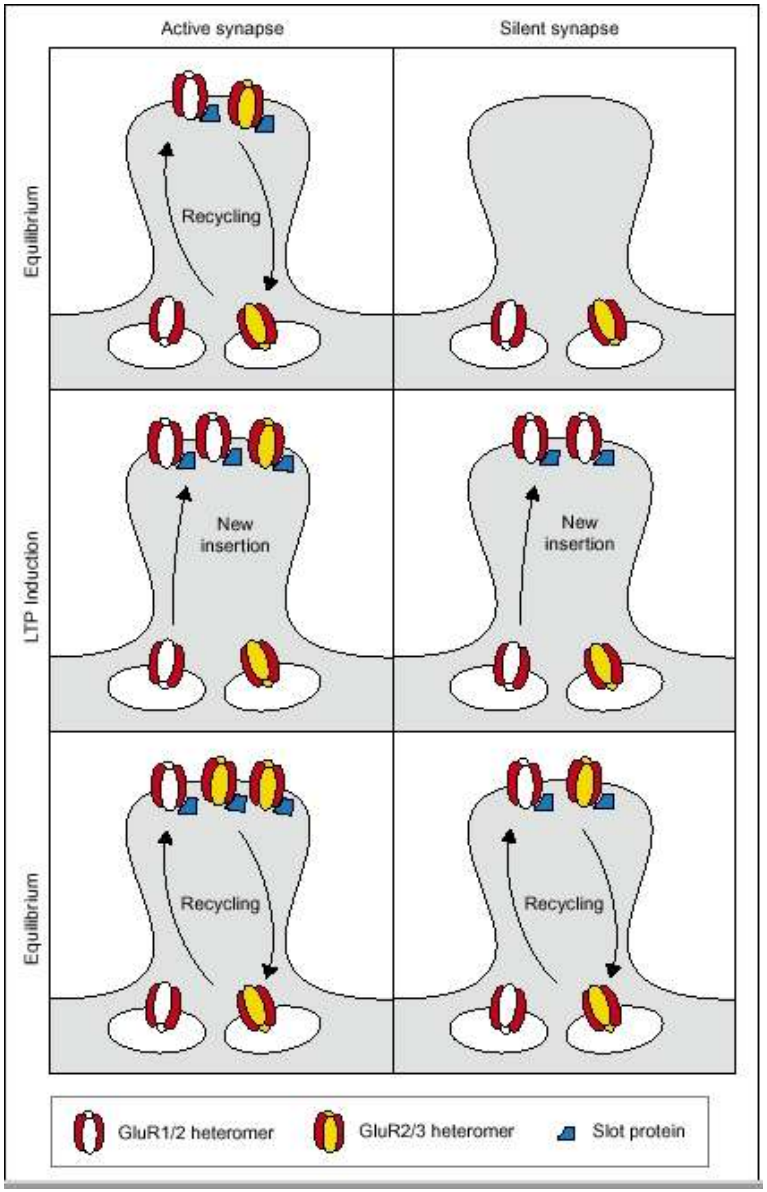
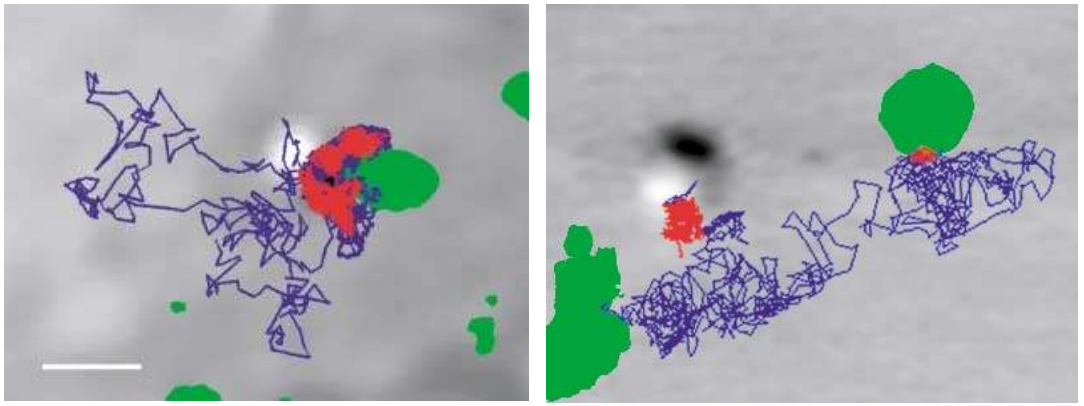
Temporal complexity



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



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

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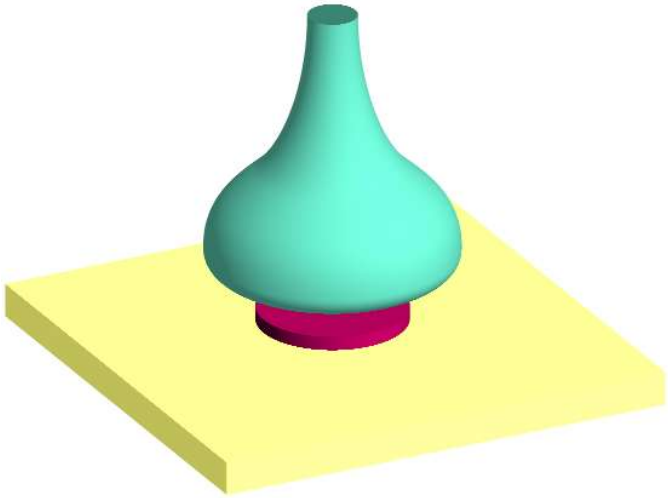
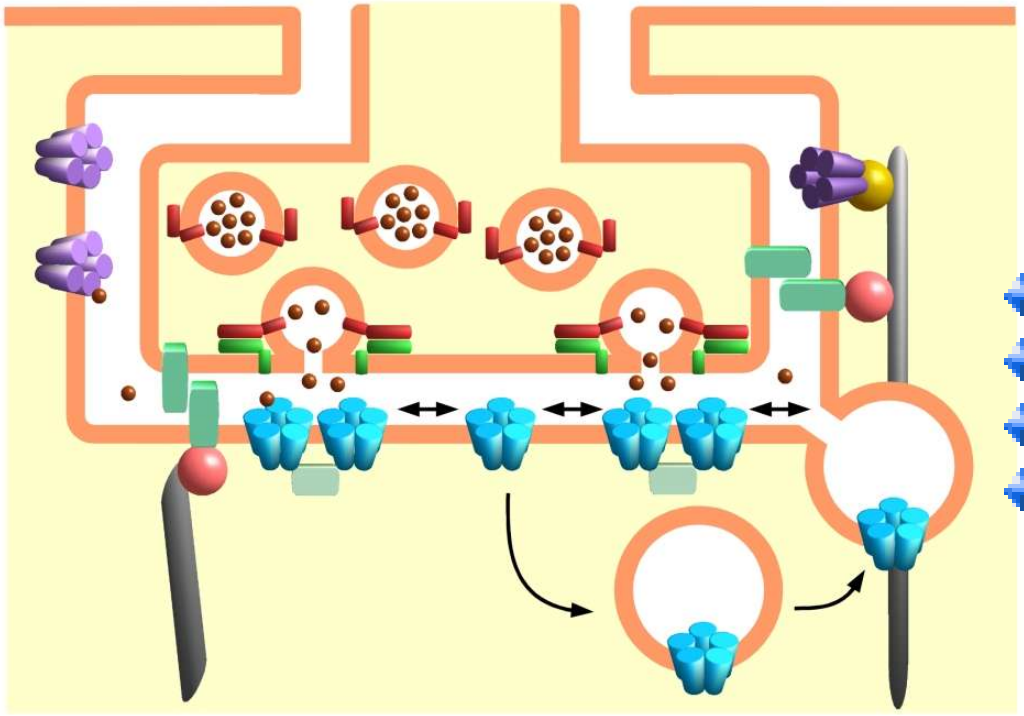
Classical and current views of the synapse

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





- Several receptors
- Heterogous distribution
- Horizontal and vertical movements
- Supra-macromolecular assembly

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Need a System view?

- Signalling pathways exhibits non-linear features
  - Interplay between different signalling pathways
  - Presence of feedback and feedforward controls
  - Sensitivity to cell environment

  ⇒ Numerical simulations are mandatory
- The synaptic millenium revolution
  - The synapses can contain several (interacting) types of receptors
  - The spatial organisation of subcellular compartments is important
  - Partners move across the membrane, are inserted and removed

  ⇒ Present models of synaptic transmission are no longer in phase with the current biological knowledge
- In silico cell pathology
  - Realistic modelling of molecular diseases
  - Identification of bottlenecks, robust modules, sensitive steps etc.
  - Analysis of the effect of pharmacological agents

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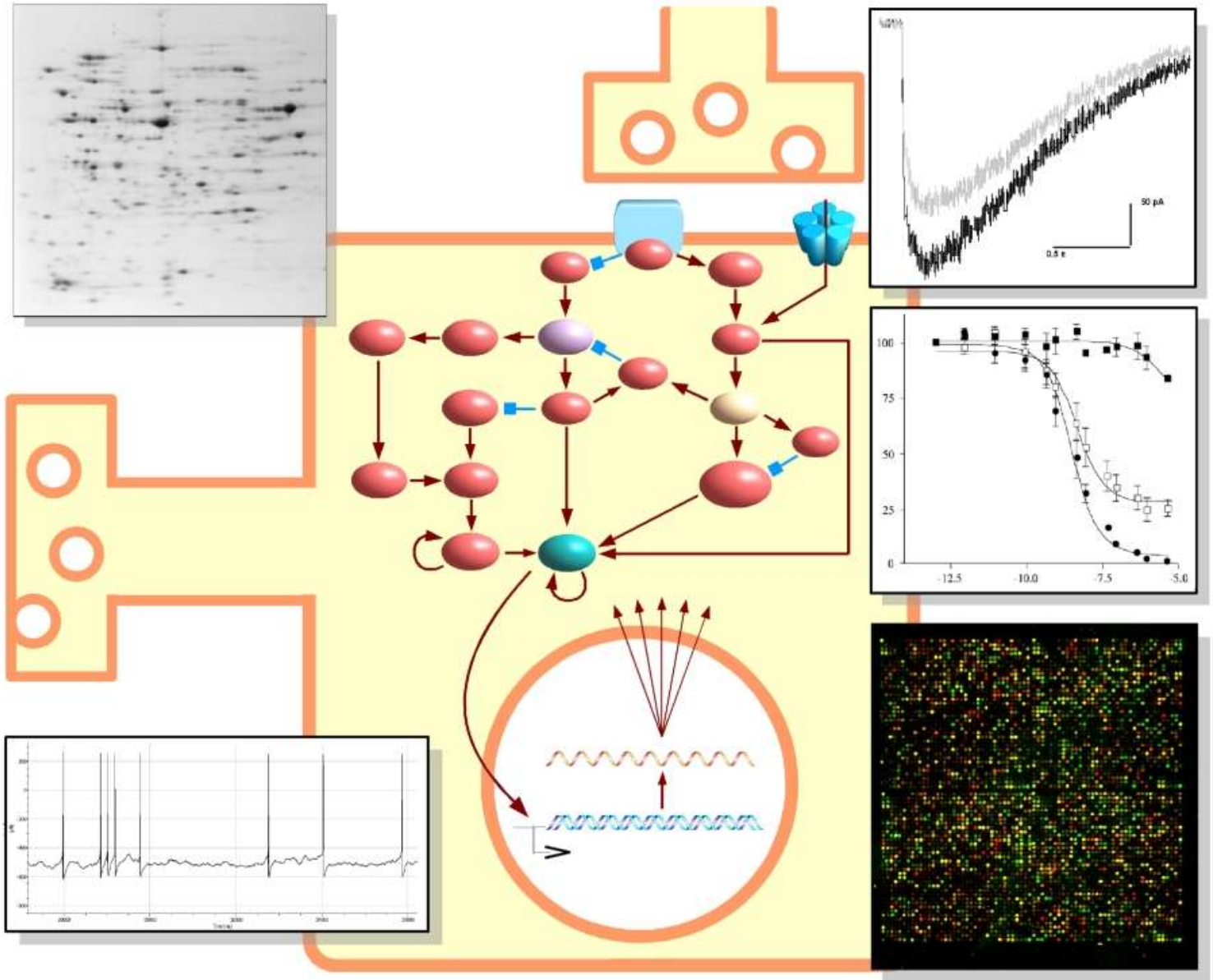
Heterogeneous quantitative data



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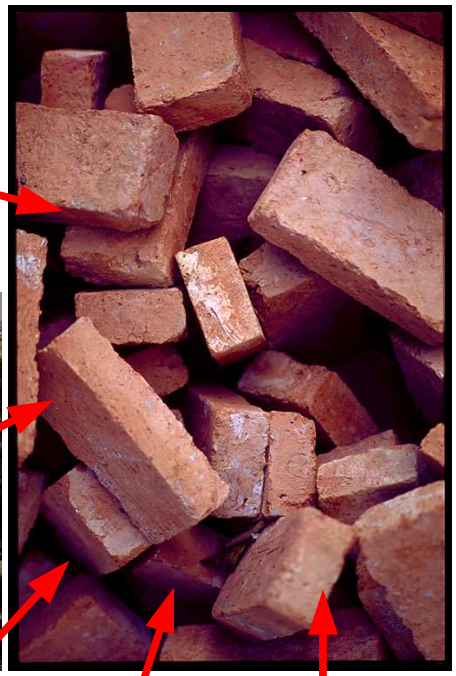
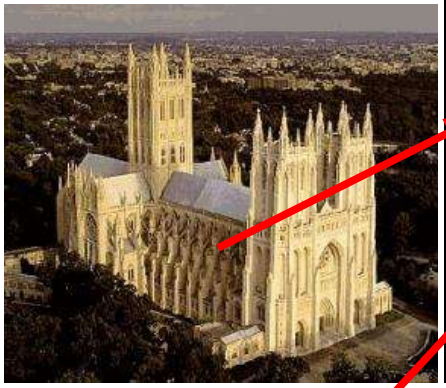
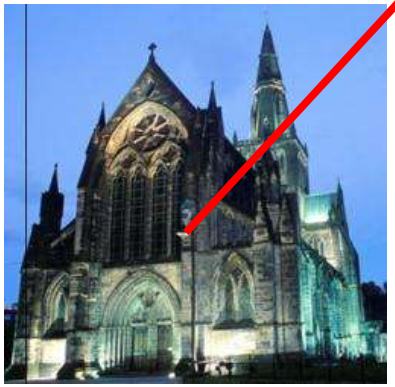
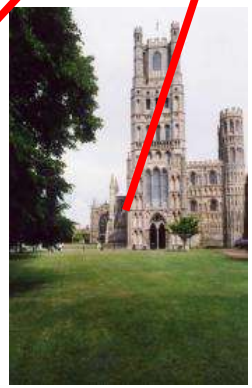
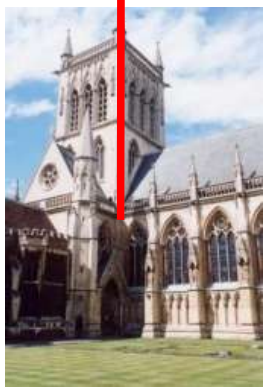
Cellular Neurobiology today











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DopaNet is supported by:

EMBL-EBI European Bioinformatics Institute

EUROPEAN SCIENCE FOUNDATION E·S·F

INSTITUT PASTEUR

CNRS 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

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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.

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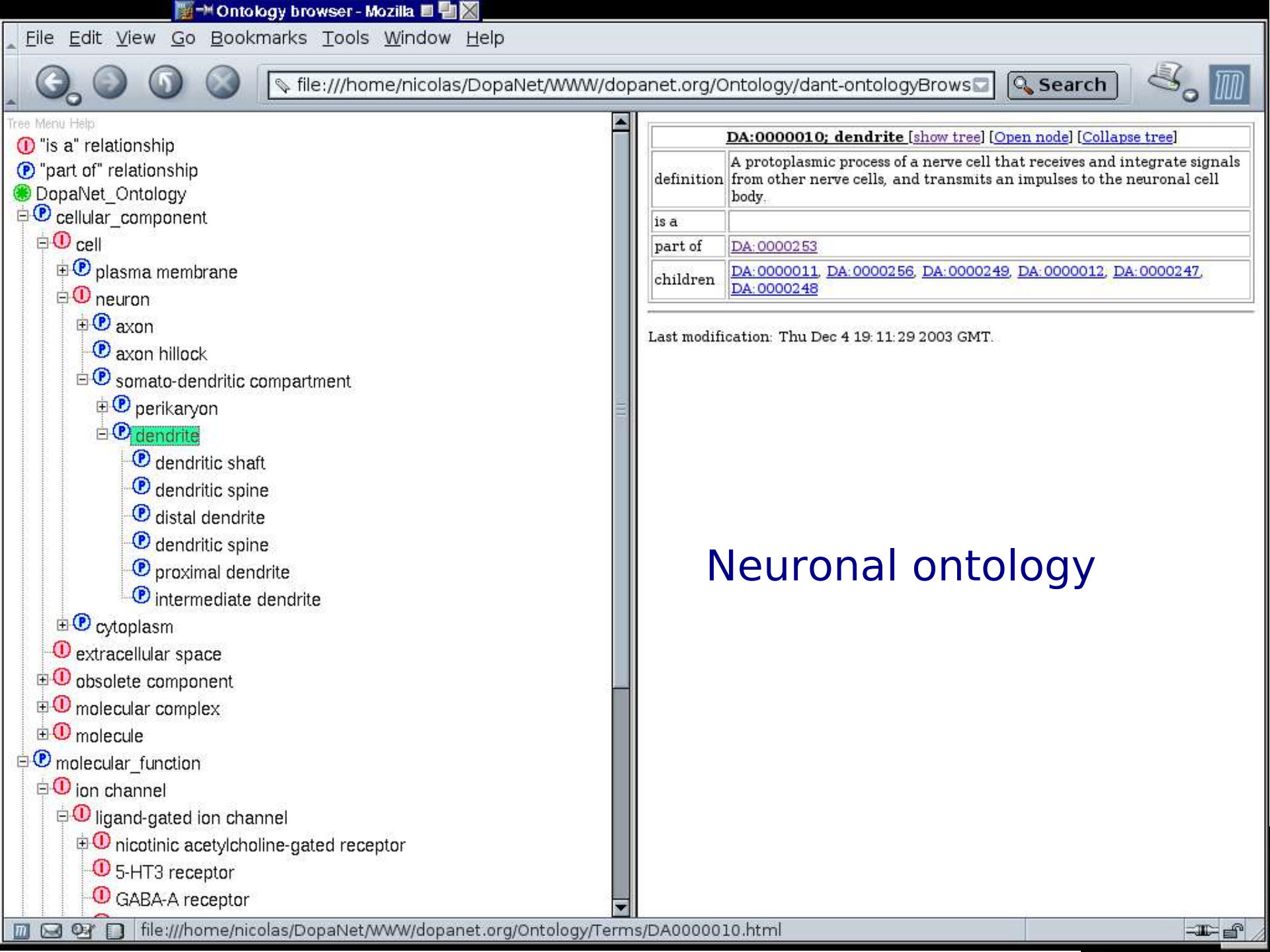
Ontology browser - Mozilla
File Edit View Go Bookmarks Tools Window Help
file:///home/nicolas/DopaNet/WWW/dopanet.org/Ontology/dant-ontologyBrows
Search
Tree Menu Help
"is a" relationship
"part of" relationship
DopaNet_Ontology
cellular_component
cell
plasma membrane
neuron
axon
axon hillock
somato-dendritic compartment
perikaryon
dendrite
dendritic shaft
dendritic spine
distal dendrite
dendritic spine
proximal dendrite
intermediate dendrite
cytoplasm
extracellular space
obsolete component
molecular complex
molecule
molecular_function
ion channel
ligand-gated ion channel
nicotinic acetylcholine-gated receptor
5-HT3 receptor
GABA-A receptor
DA:0000010; dendrite [show tree] [Open node] [Collapse tree]
definition
A protoplasmic process of a nerve cell that receives and integrate signals from other nerve cells, and transmits an impulses to the neuronal cell body.
is a
part of
DA:0000253
children
DA:0000011, DA:0000256, DA:0000249, DA:0000012, DA:0000247, DA:0000248
Last modification: Thu Dec 4 19:11:29 2003 GMT.
Neuronal ontology
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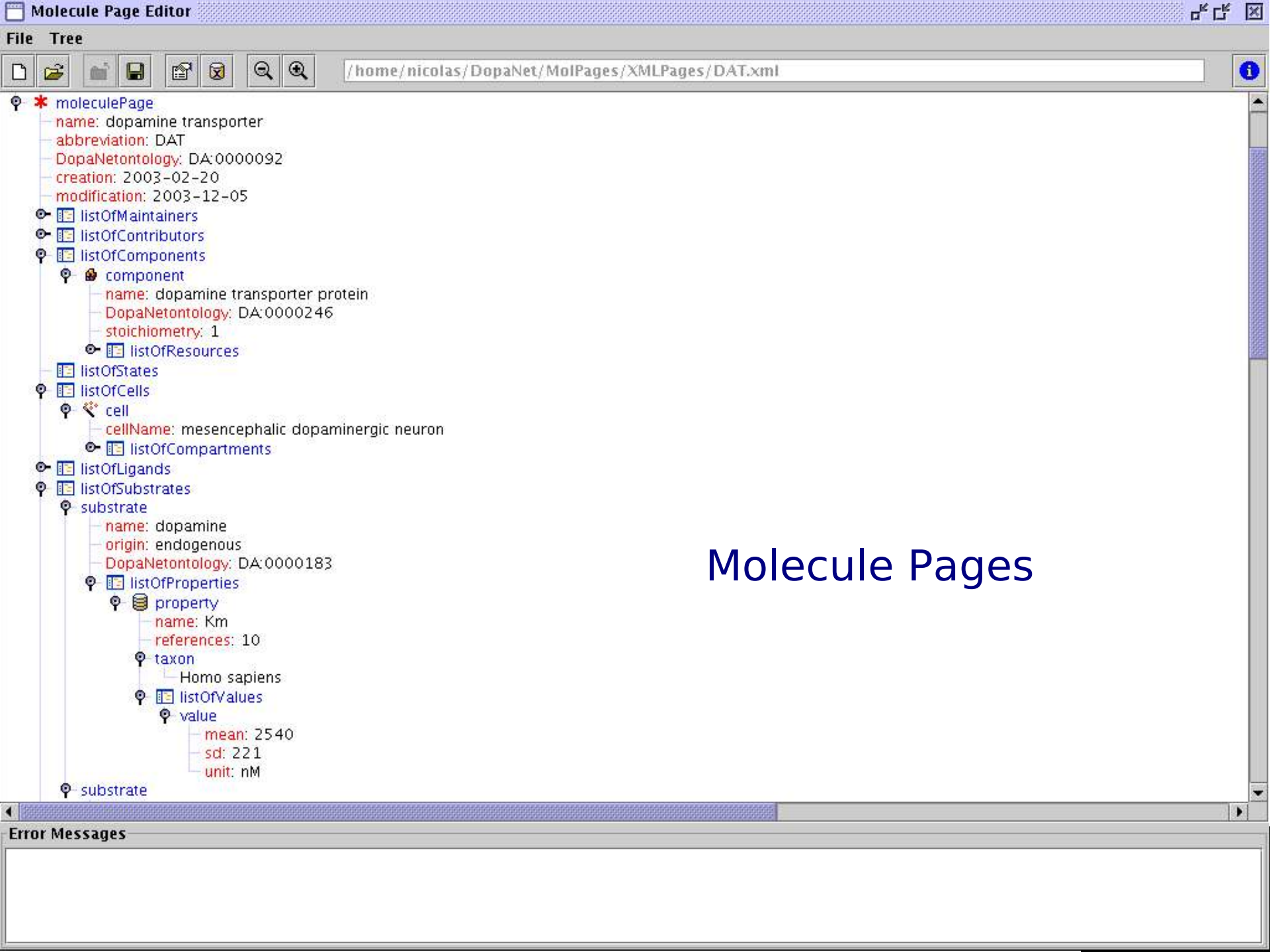
Molecule Page Editor
File Tree
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abbreviation: DAT
DopaNetontology: DA:0000092
creation: 2003-02-20
modification: 2003-12-05
listOfMaintainers
listOfContributors
listOfComponents
component
name: dopamine transporter protein
DopaNetontology: DA:0000246
stoichiometry: 1
listOfResources
listOfStates
listOfCells
cell
cellName: mesencephalic dopaminergic neuron
listOfCompartments
listOfLigands
listOfSubstrates
substrate
name: dopamine
origin: endogenous
DopaNetontology: DA:0000183
listOfProperties
property
name: Km
references: 10
taxon
Homo sapiens
listOfValues
value
mean: 2540
sd: 221
unit: nM
substrate
Error Messages
Molecule Pages

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      Crescenzo et al.
    </bibitem>
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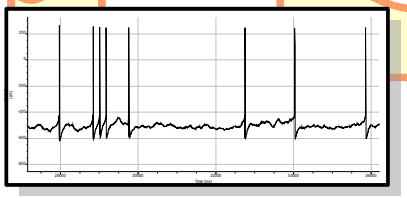
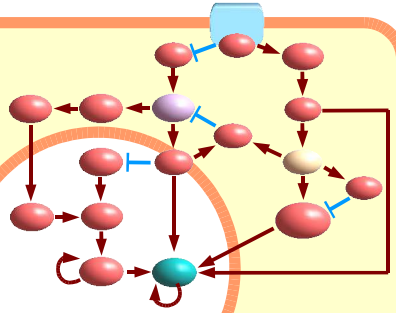
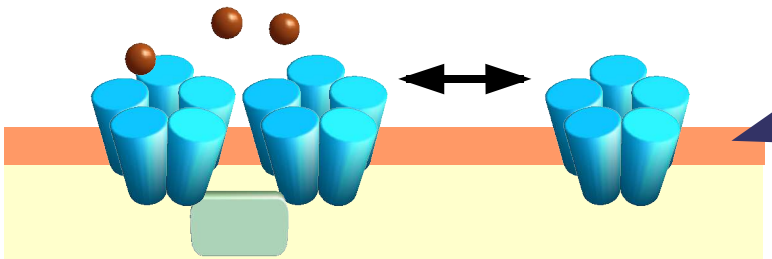
Modular multi-scales multi-algorithms program



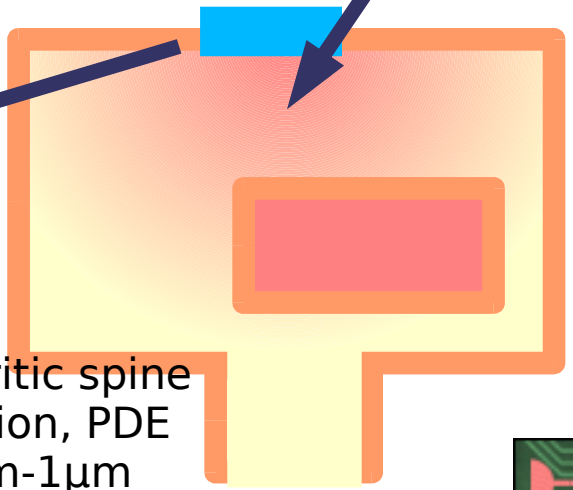
Whole-neuron
Cable theory
1µm-1m
1ms-1week



Signaling network
ODE
1µm-10µm
1s-1d



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



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

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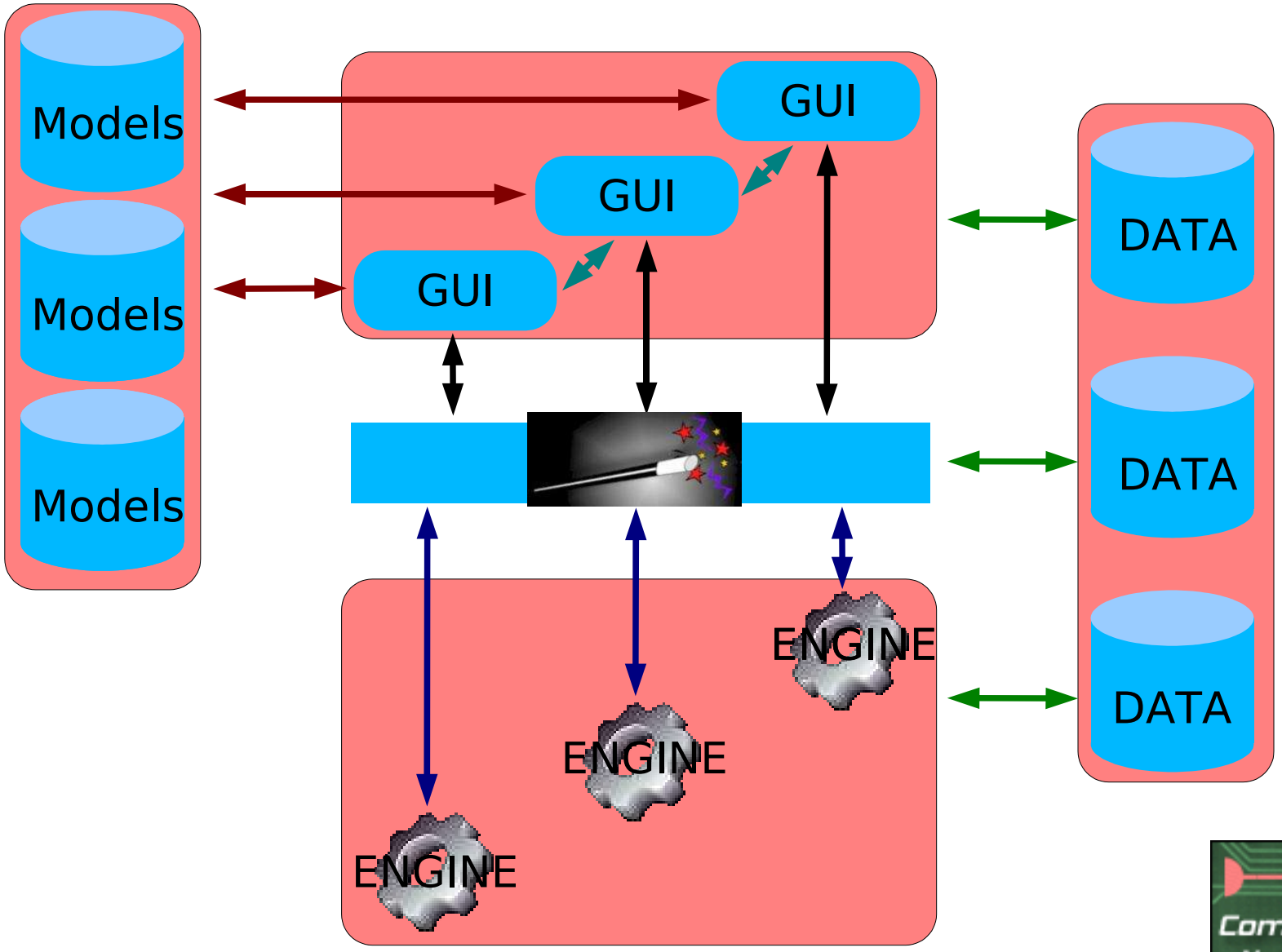
Modular multi-scales multi-algorithms program



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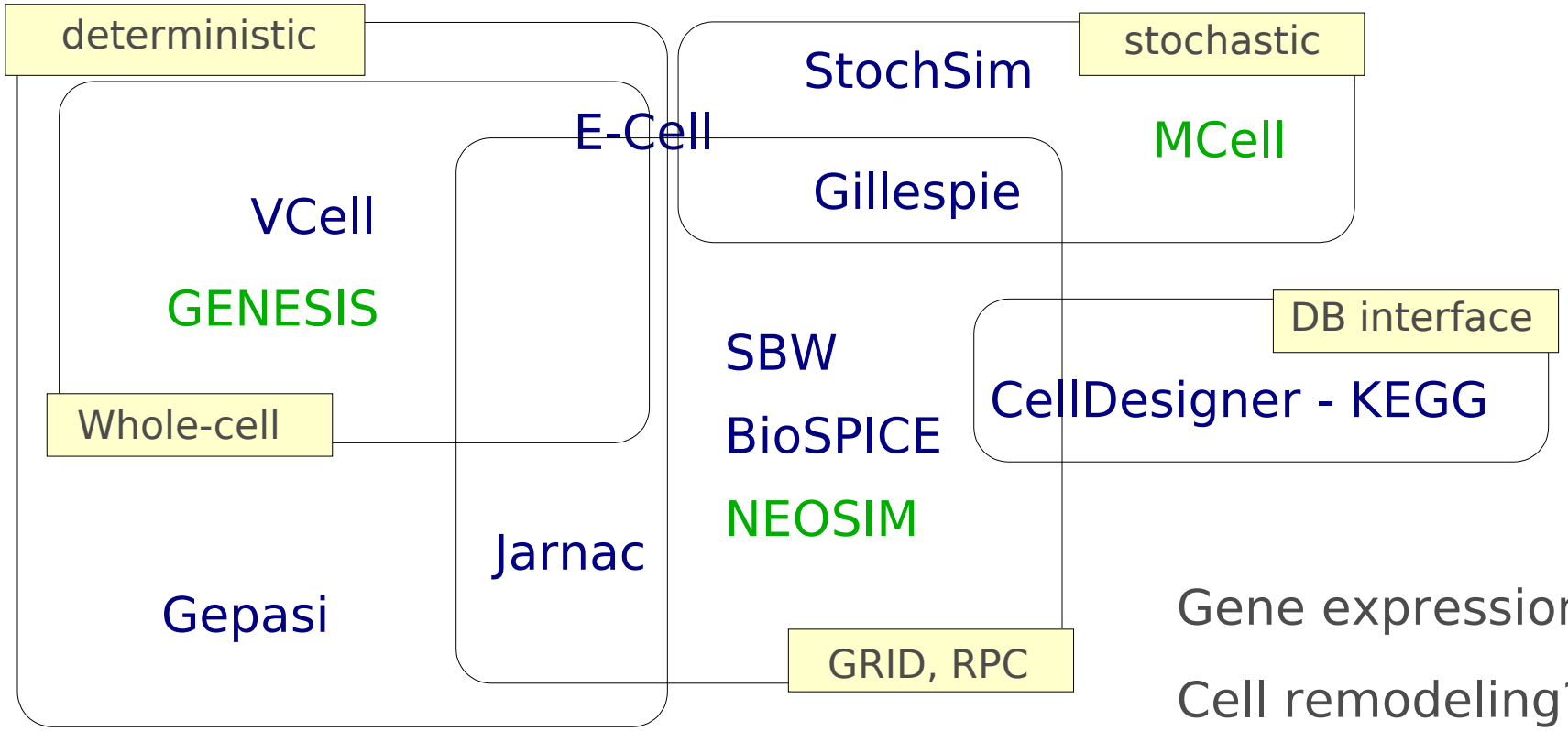
Existing efforts

used to model neurons



Gene expression?

Cell remodeling?

All these programs speak SBML
(Systems Biology Markup Language)

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Systems Biology Markup Language

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        </listOfReactants>
        <listOfProducts>
          <speciesReference species="Y" />
        </listOfProducts>
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          </body>
        </notes>
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    </listOfReactions>
    <listOfSpecies>
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          </body>
        </notes>
      </species>
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        </notes>
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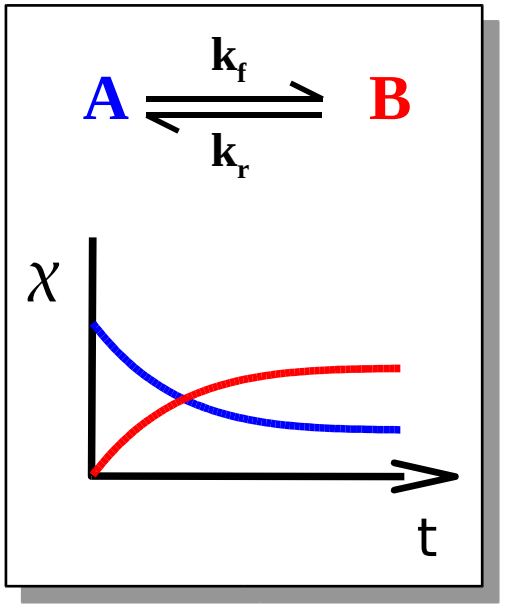

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A real situation: Stochastic simulation of a nicotinic EPSP

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