Computational Systems Biology

Nicolas Le Novère

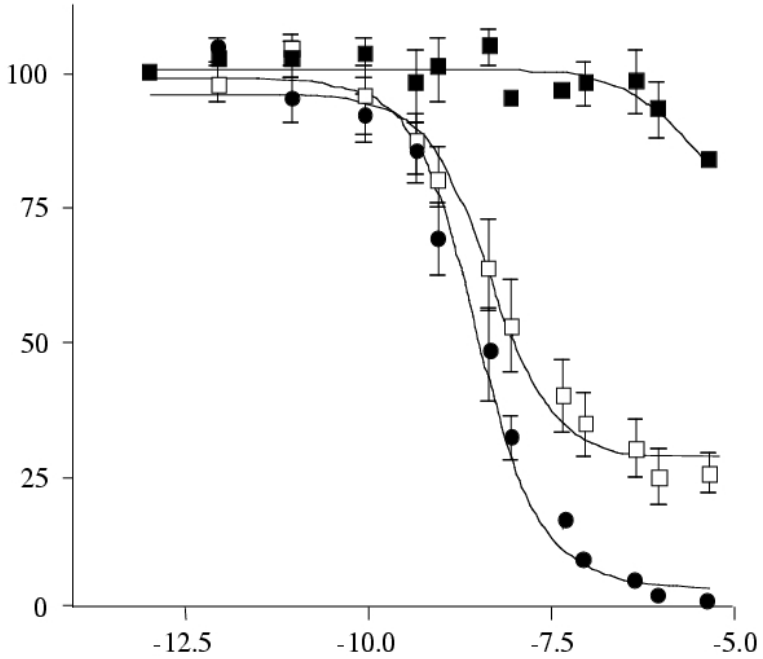
Computational Neurobiology group

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

Classical approaches in theoretical biology

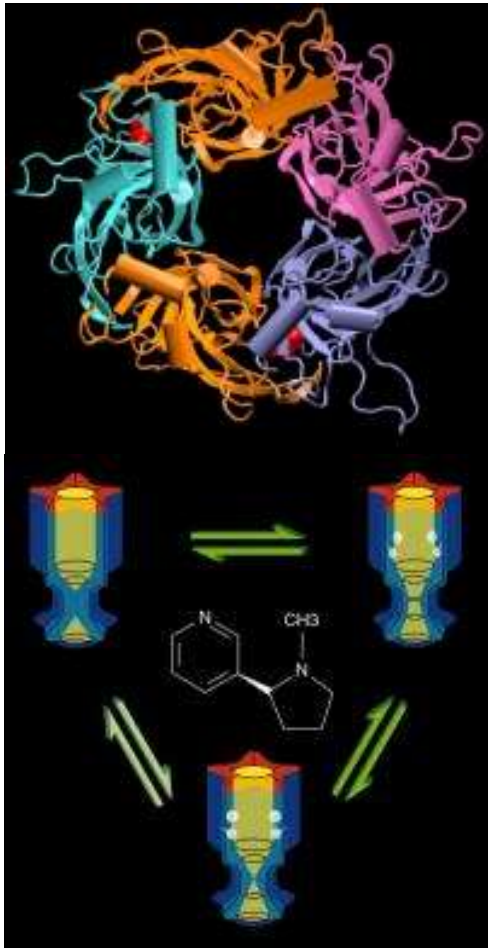
(1)-The phenomenology

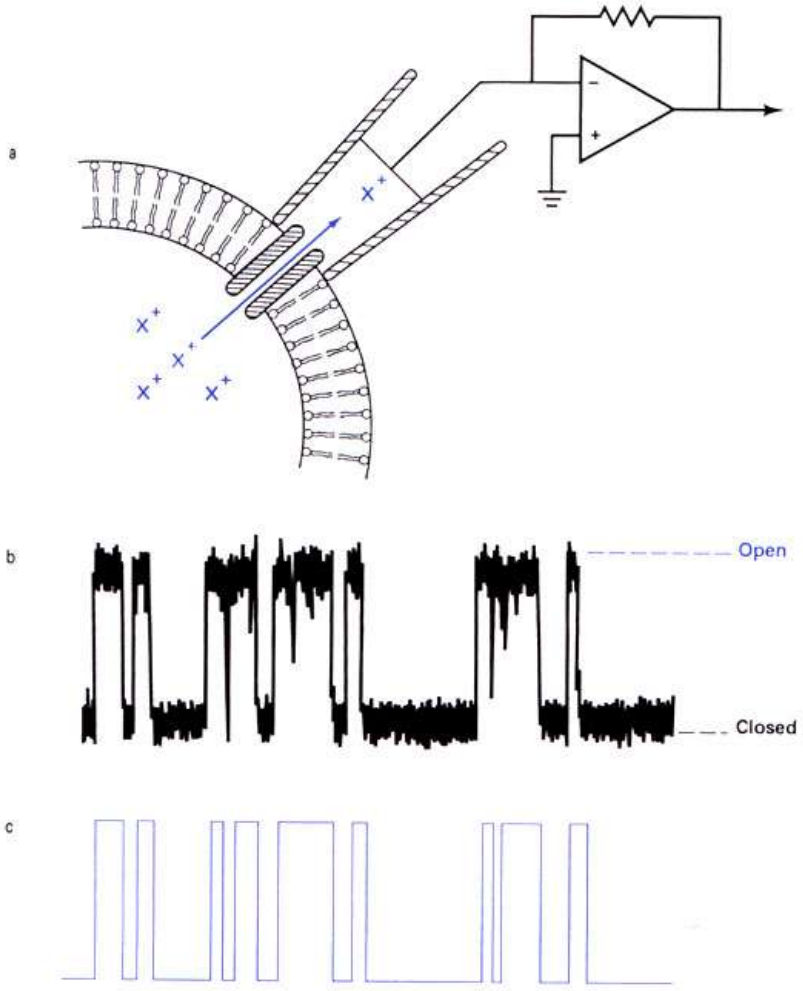
Snapshot of the system ⇒ Abstraction



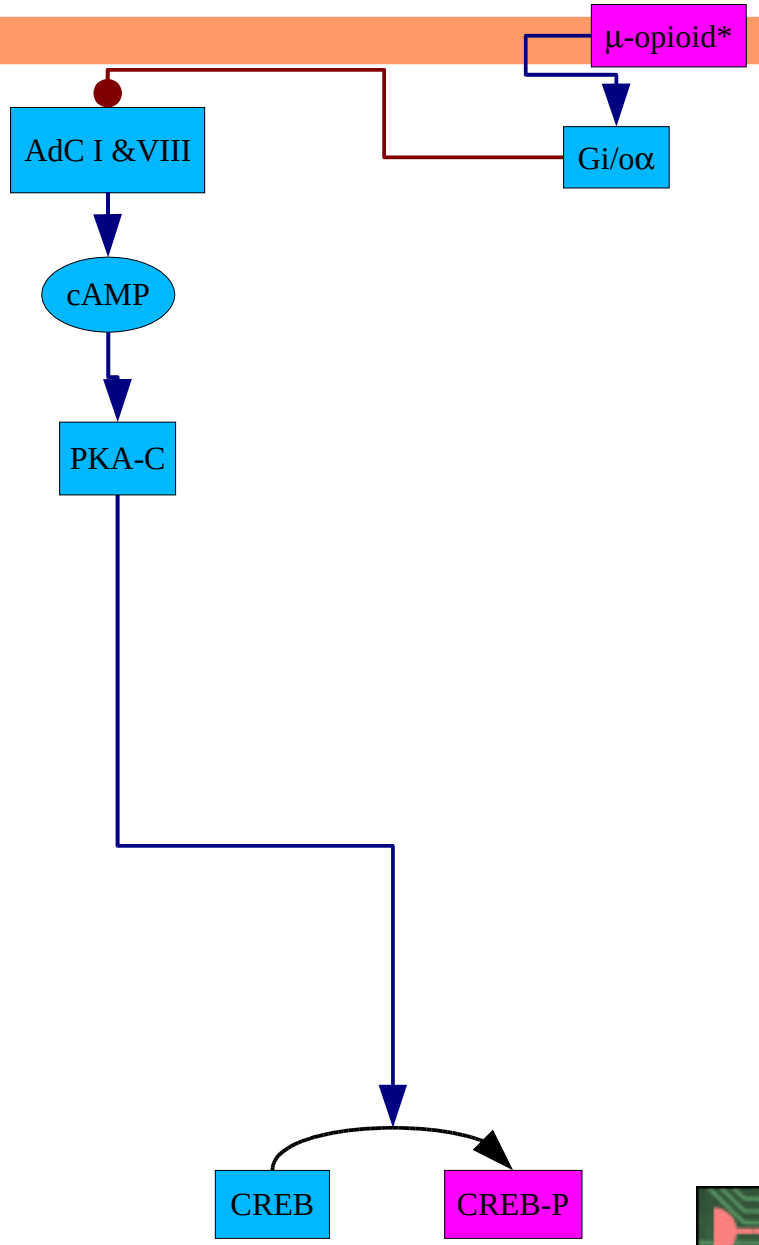
Classical approaches in theoretical biology

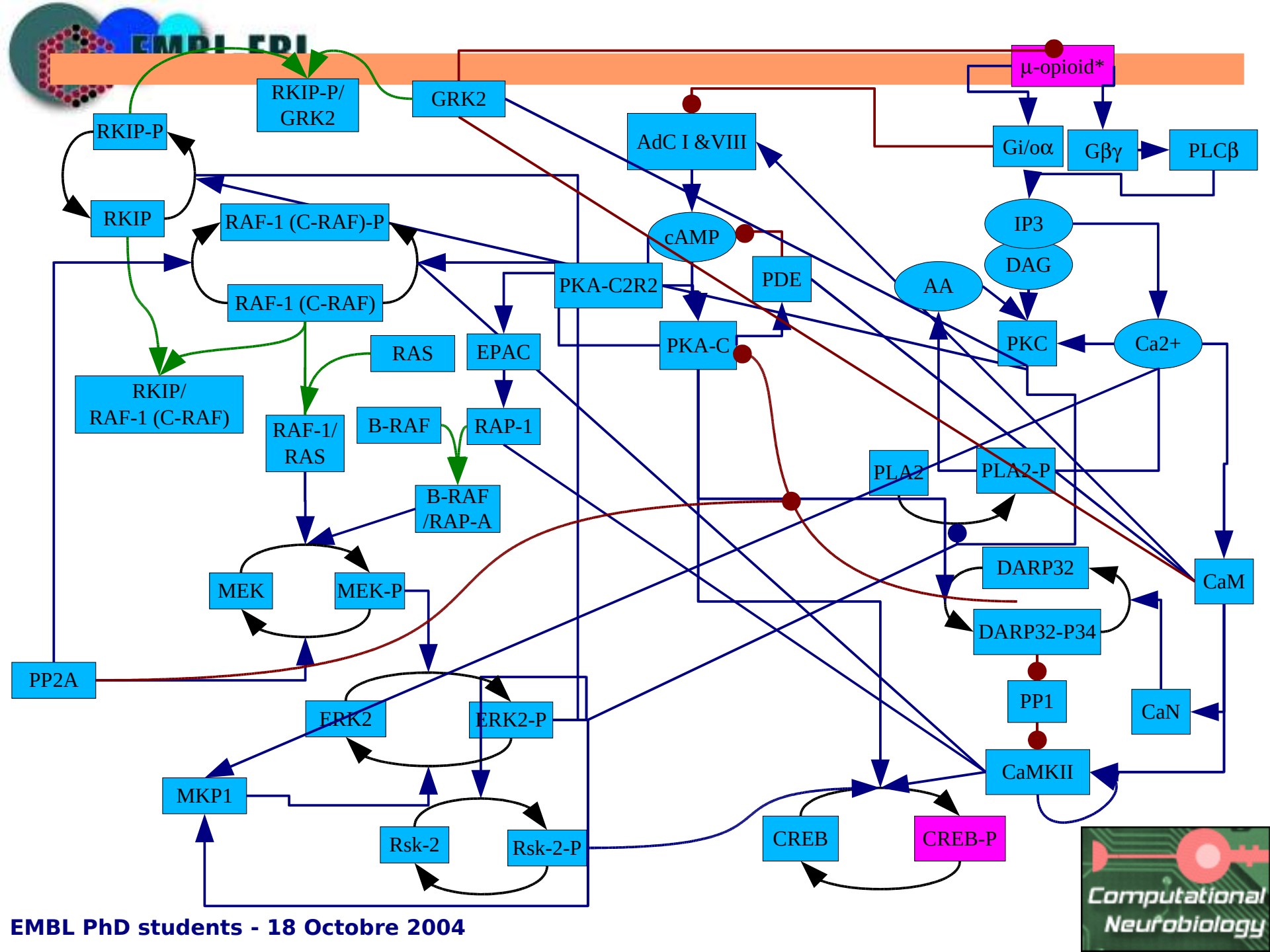
(2)-The reductionism





Computational Neurobiology


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

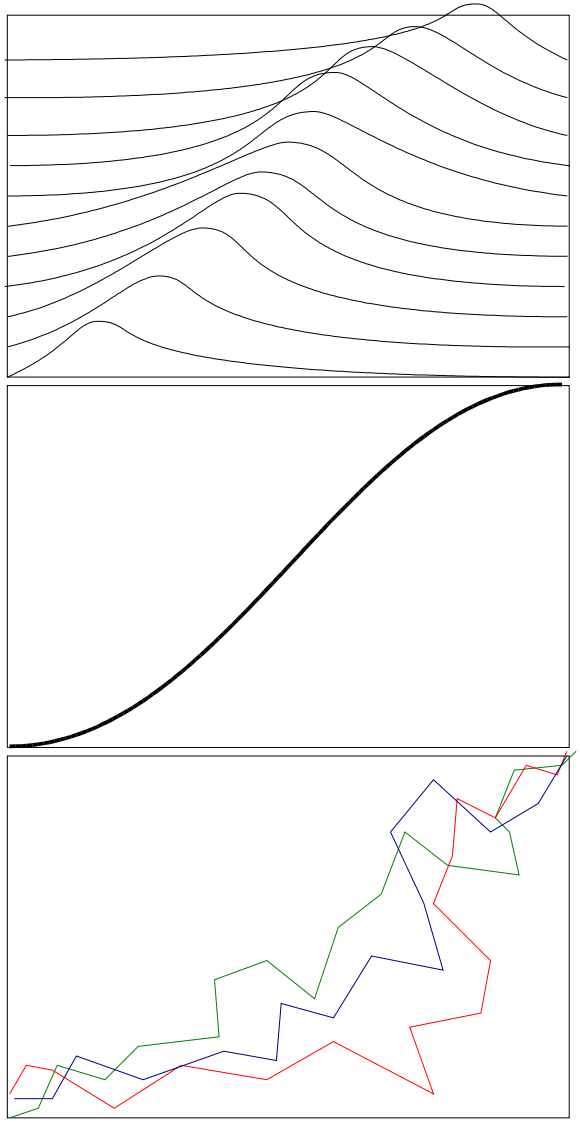

μ-opioid*
GRK2
RKIP-P/
GRK2
RKIP-P
RKIP
AdC I &VIII
Gi/oα
Gβγ
PLCβ
IP3
DAG
cAMP
PDE
AA
RAF-1 (C-RAF)-P
RAF-1 (C-RAF)
PKA-C2R2
PKA-C
PKC
Ca2+
RAS
EPAC
RKIP/
RAF-1 (C-RAF)
RAF-1/
RAS
B-RAF
RAP-1
B-RAF
/RAP-A
PLA2
PLA2-P
DARP32
CaM
DARP32-P34
MEK
MEK-P
PP2A
PP1
CaN
ERK2
ERK2-P
CaMKII
MKP1
Rsk-2
Rsk-2-P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

Systems Biology

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

Computational Neurobiology

Different approaches



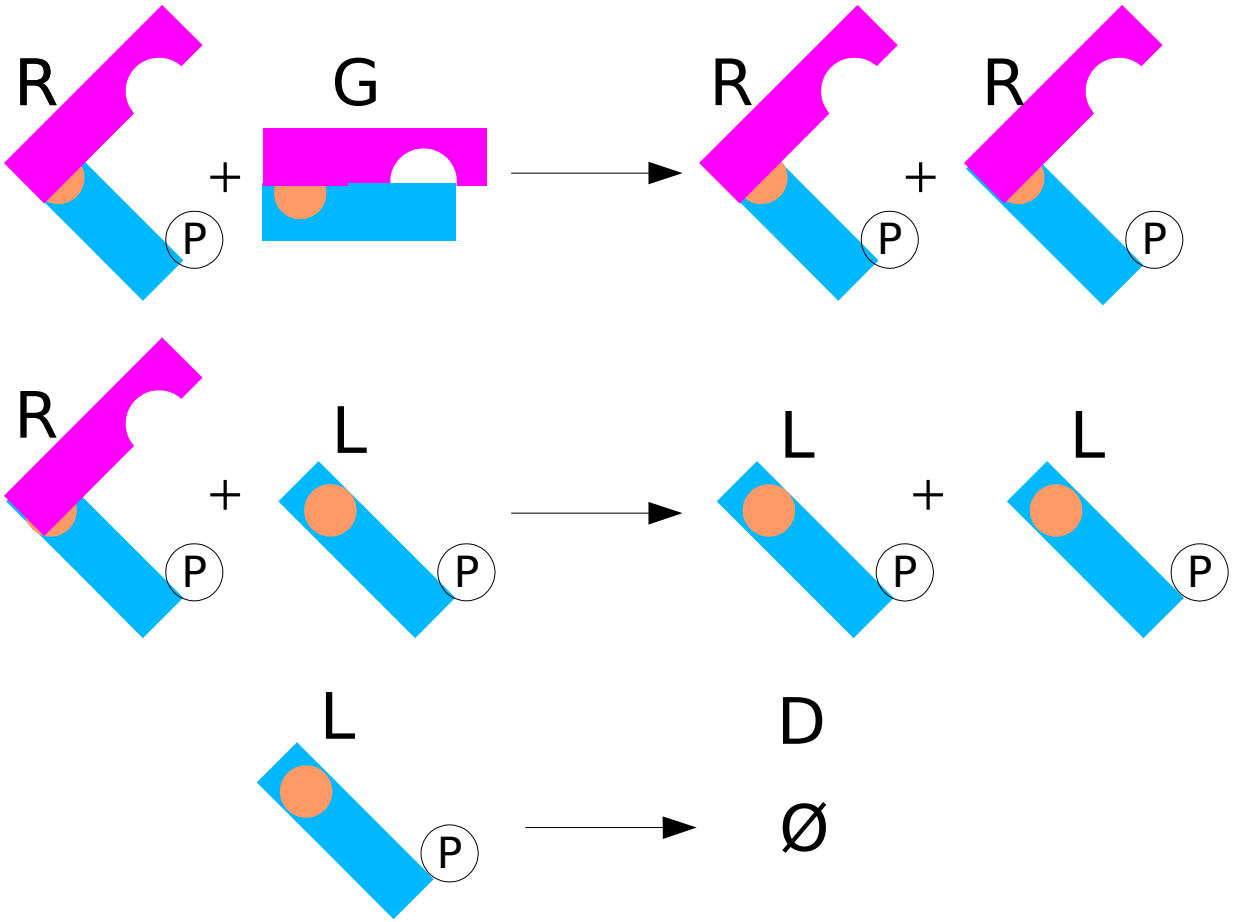
Grand Probability function: P(X,t)

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

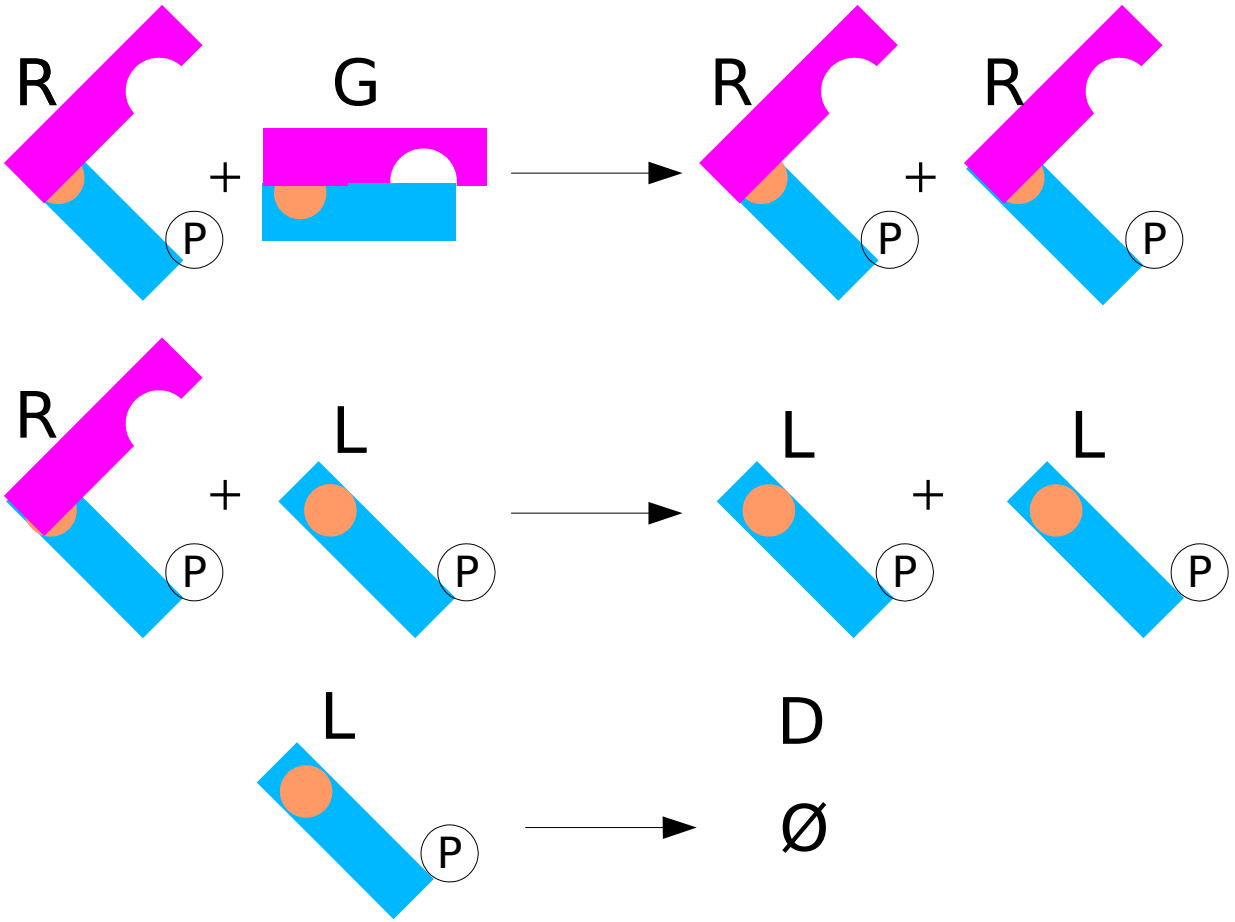
stochastic approach: P(X,t)/(X',t-1)

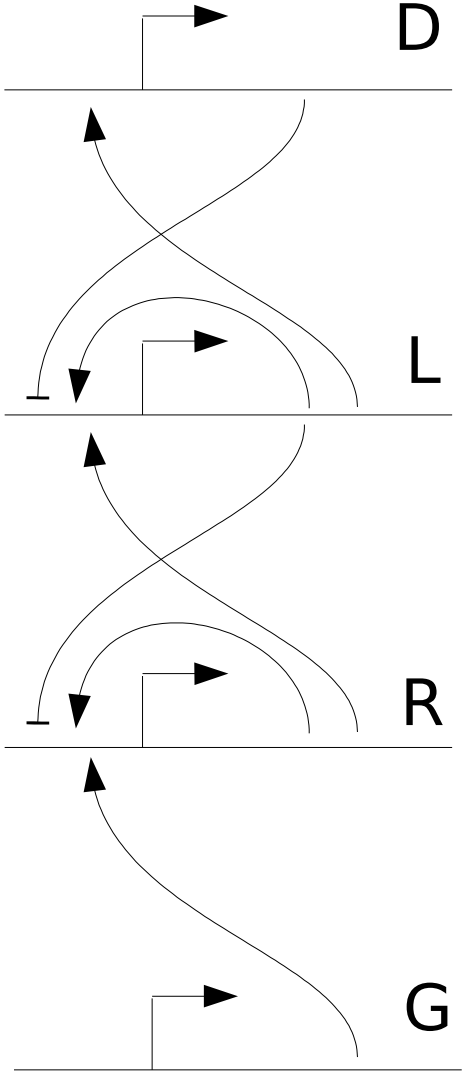
Computational Neurobiology

A simple oscillating system

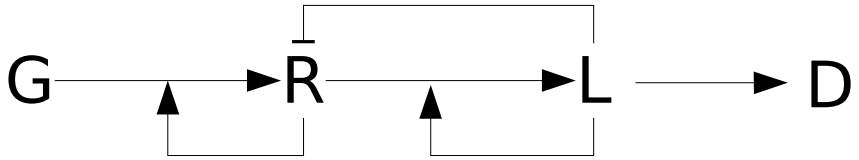


A simple oscillating system

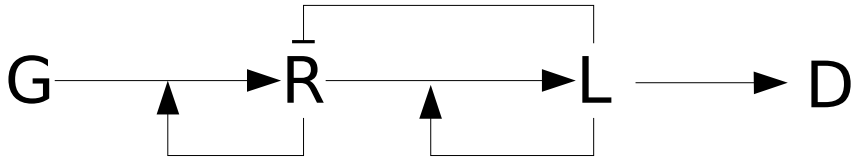




A simple oscillating system



A simple oscillating system

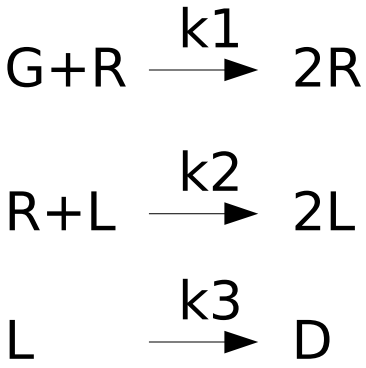


Lotka, A.J. 1925. Elements of physical biology.
Williams and Wilkins, Baltimore, M.D.

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

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

ODE approach



$$d[R]/dt = k1[G][R]-k2[R][L]$$

$$d[L]/dt = k2[R][L] - k3[L]$$

ODE approach

$$G+R \xrightarrow{k1} 2R$$

$$R+L \xrightarrow{k2} 2L$$

$$L \xrightarrow{k3} D$$

$$d[R]/dt = k1[G][R]-k2[R][L]$$

$$d[L]/dt = k2[R][L] - k3[L]$$

- Euler

$$d[L]/dt \sim ([L]_{t+Dt} - [L]_t) / \Delta t = f([L],t)$$

$$[L]_{t+Dt} = [L]_t + f([L],t) \times \Delta t$$

- 4th order Runge-kutta

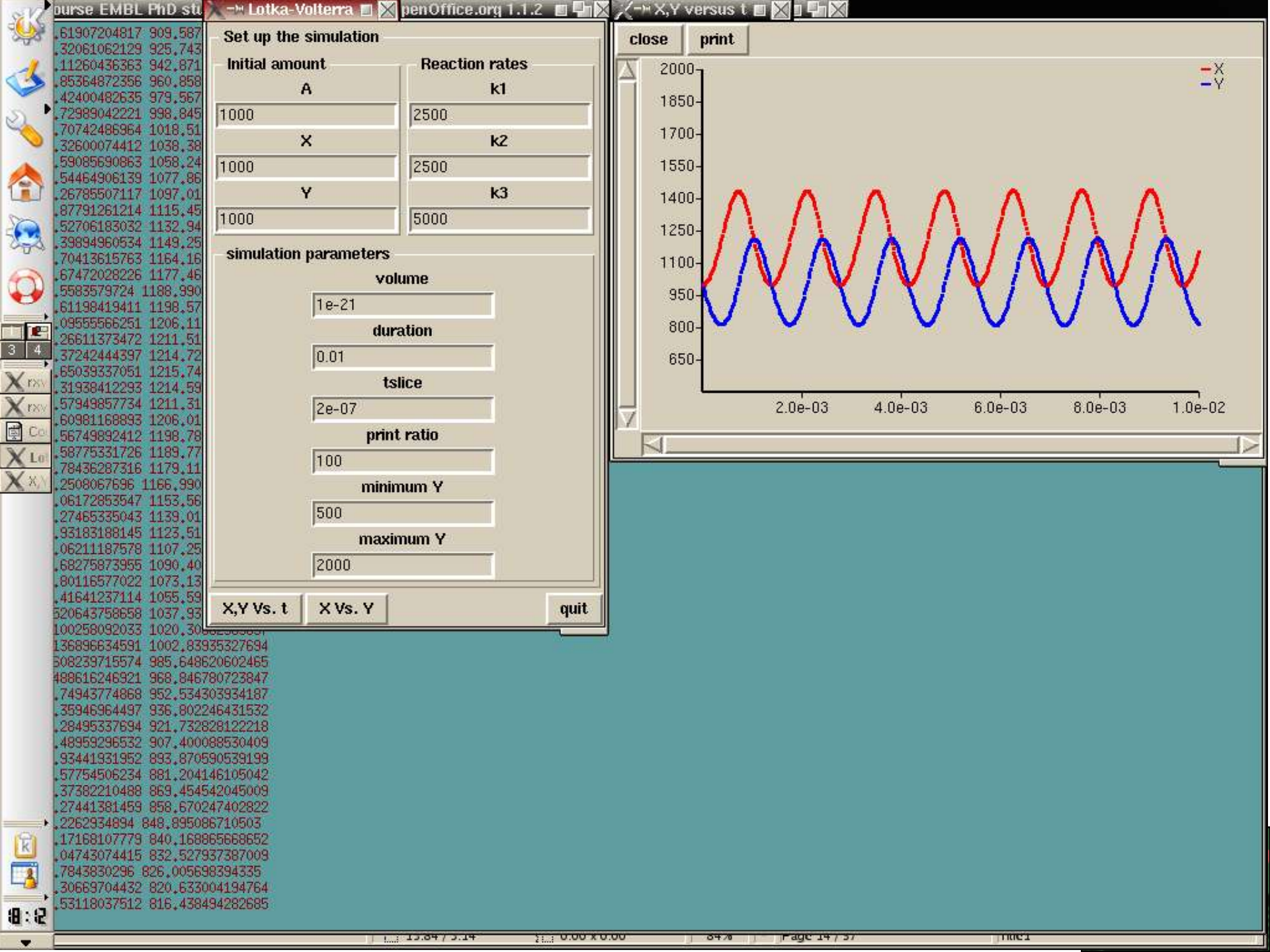
$$[L]_{t+Dt} = [L]_t + \Delta t \times (F_1+2F_2+2F_3+F_4) / 6$$

with $F_1 = f([L],t)$

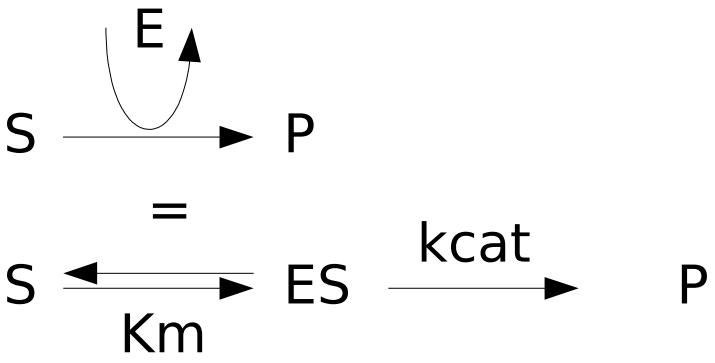
$$F_2 = f([L]_t + \Delta t/2 \times F_1, t+ \Delta t/2)$$

$$F_3 = f([L]_t + \Delta t/2 \times F_2, t+ \Delta t/2)$$

$$F_4 = f([L]_t + \Delta t \times F_3, t+ \Delta t)$$


Lotka-Volterra
penOffice.org 1.1.2
X,Y versus t
Set up the simulation
Initial amount
A
1000
X
1000
Y
1000
Reaction rates
k1
2500
k2
2500
k3
5000
simulation parameters
volume
1e-21
duration
0.01
tslice
2e-07
print ratio
100
minimum Y
500
maximum Y
2000
X,Y Vs. t
X Vs. Y
quit
close
print
X
Y
2000
1850
1700
1550
1400
1250
1100
950
800
650
2.0e-03
4.0e-03
6.0e-03
8.0e-03
1.0e-02

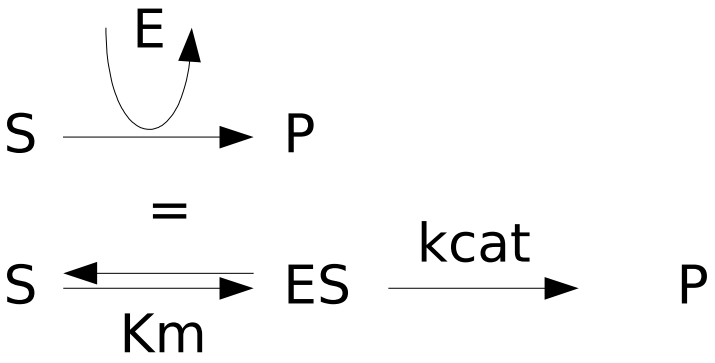
Beyond Mass Action Law



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

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

Beyond Mass Action Law



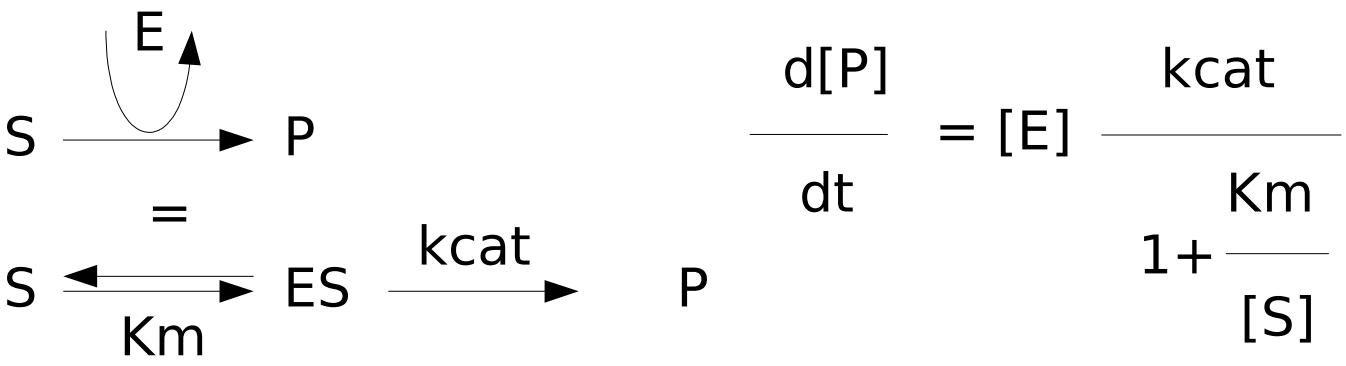
$$\frac{d[P]}{dt} = [E]\frac{kcat}{1+\frac{Km}{[S]}}$$

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

- Allosteric regulations (J Monod, J Wyman, JP Changeux 1965, DE Koshland, G Nemethy, D Filmer 1966)

Computational Neurobiology

Beyond Mass Action Law



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

- Allosteric regulations (J Monod, J Wyman, JP Changeux 1965, DE Koshland, G Nemethy, D Filmer 1966)

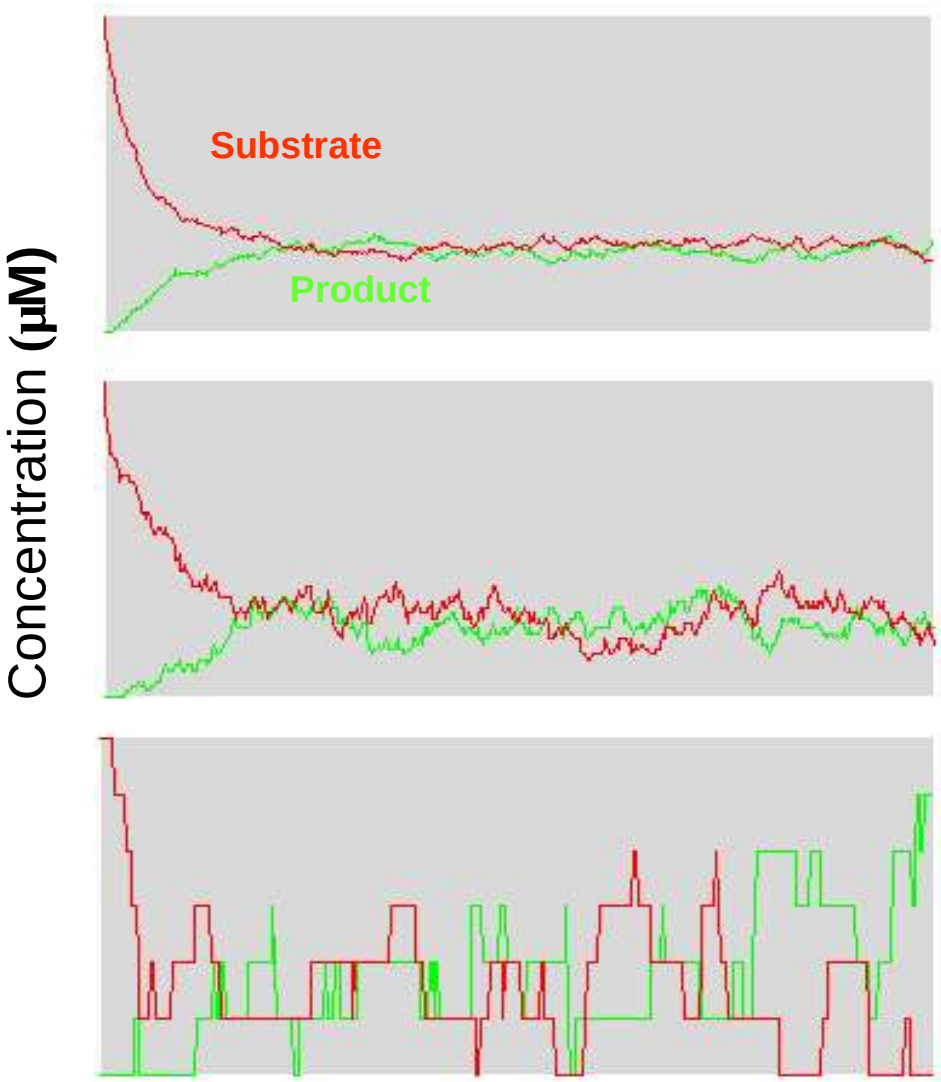
- Metabolic Control Analysis (H Kacser, JA Burns 1973)
- Biochemical Systems Theory (M Savageau 1969)
- Stoichiometric Network Analysis (R Heinrich, SM Rapoport, TA Rapoport 1997)
- Logical representations (R Thomas 1973)
- Petri Net (VN Reddy, ML Mavrovouniotis, MN Liebman)
- etc.

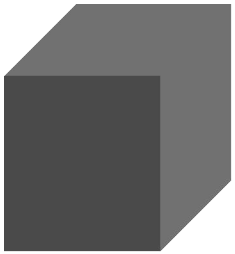
Limitation of deterministic approaches

Continuous, deterministic models can’t cope with:

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

On small numbers





10^{-15} litres

10^{-16} litres

10^{-17} litres

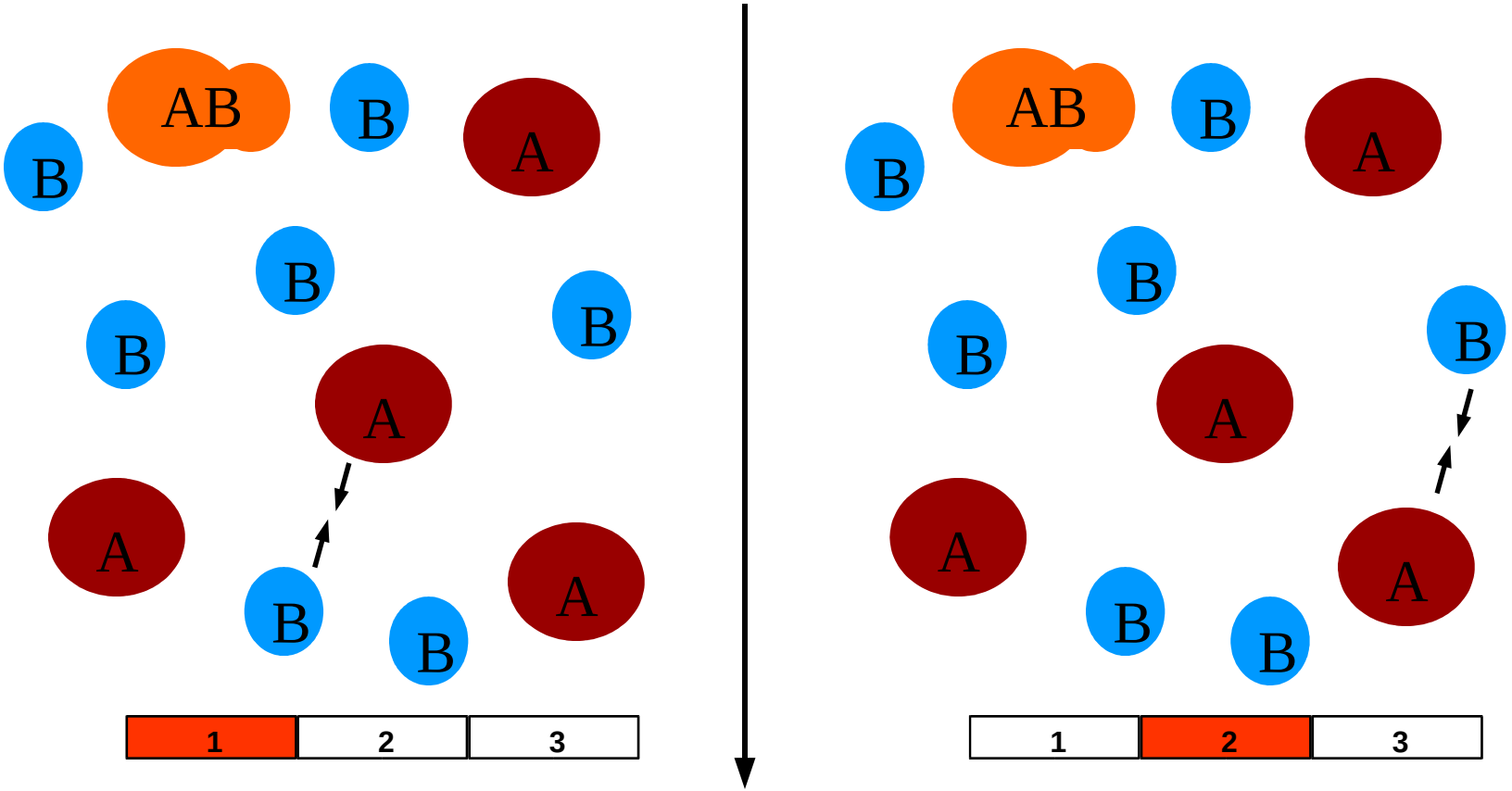
Number of calcium ions in a dendritic spine = 3-5

Computational Neurobiology

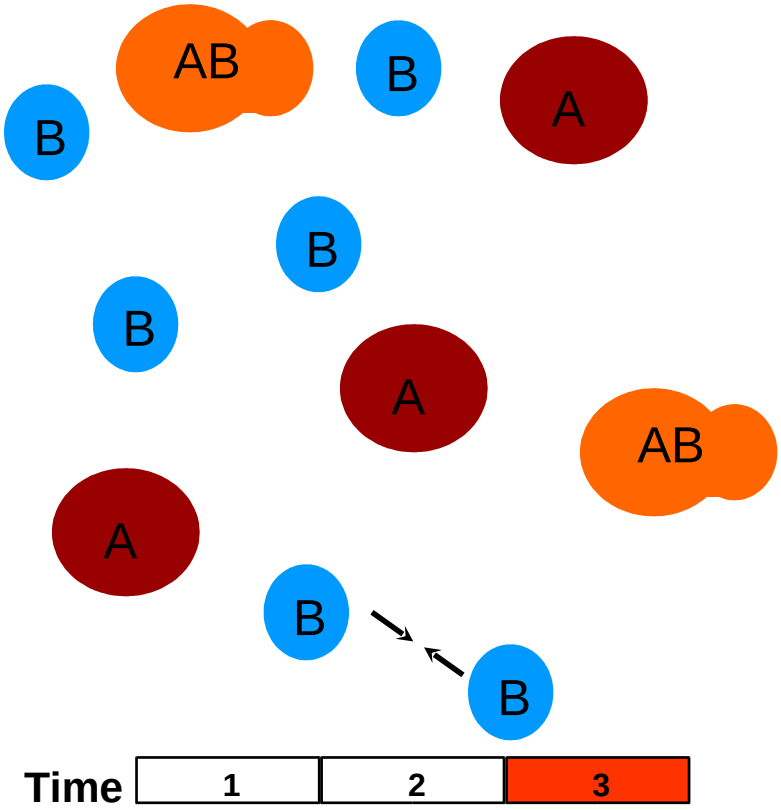
stochastic approach

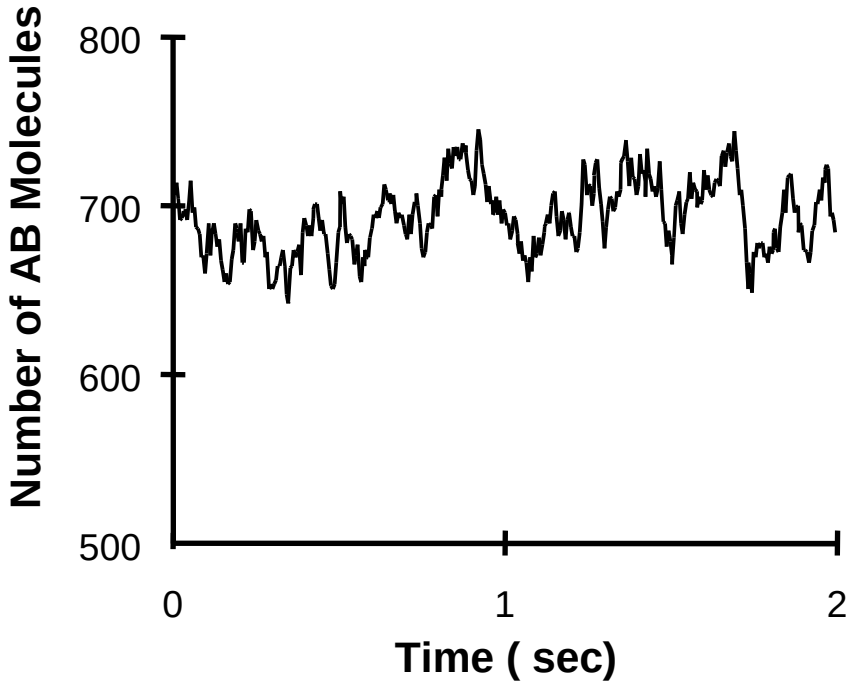
- Stochastic master equation (McQuarrie 1964)
  - ~ grand probability function. Generally intractable
- Gillespie method (Gillespie 1976)
  - Reaction-based stochastic algorithm. No representation of individual particles. Fast!
- StochSim (Morton-Firth *et al*. 1998) and other Monte-Carlo methods
  -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

StochSim algorithm



StochSim algorithm





Computational Neurobiology

Kinetic constant to probability

$$d[R]/dt = k1[G][R] \qquad P1 = \frac{k1\ n(n+n_0)\Delta t}{2VN_A}$$

$$d[L]/dt = -k3[L] \qquad P3 = \frac{k3\ n(n+n_0)\Delta t}{n_0}$$

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

rxvt

TkStochSim

File Simulation Options Help

Configure the simulation

General configuration

components new

complexes new

MS_complexes new

NS_complexes new

arrays new

reactions new

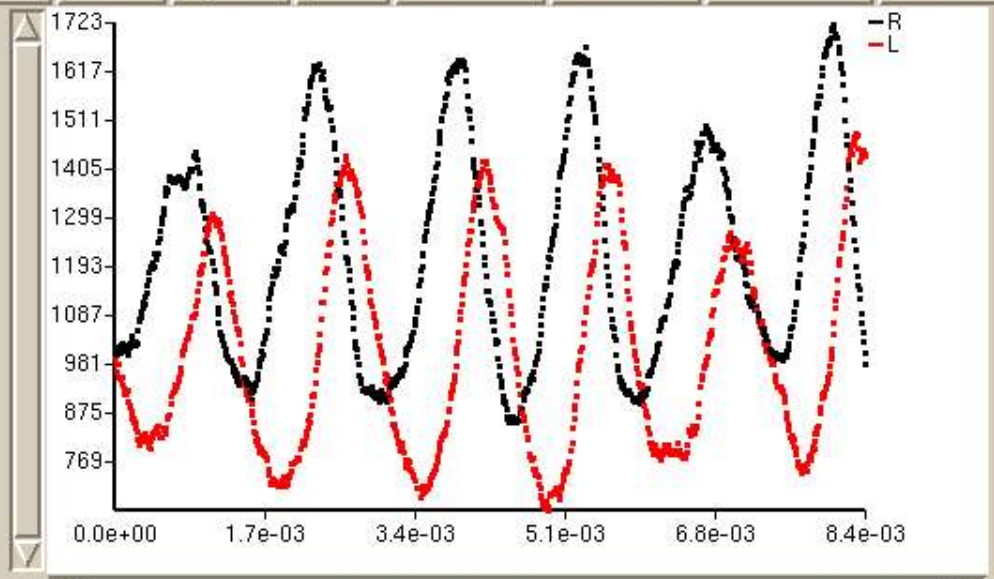
Dynamic values

Run the simulation

run stop plot values quit

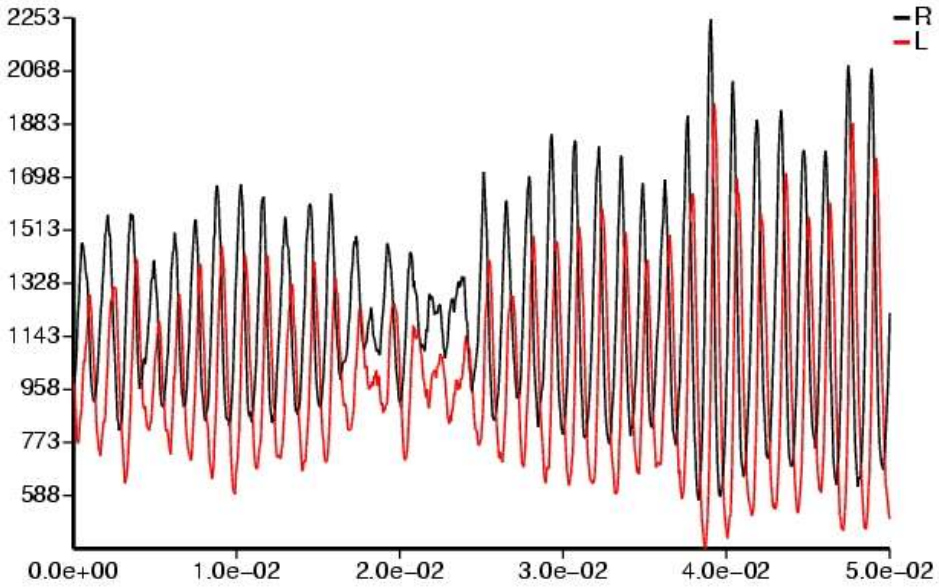
results: LotkaVolterra

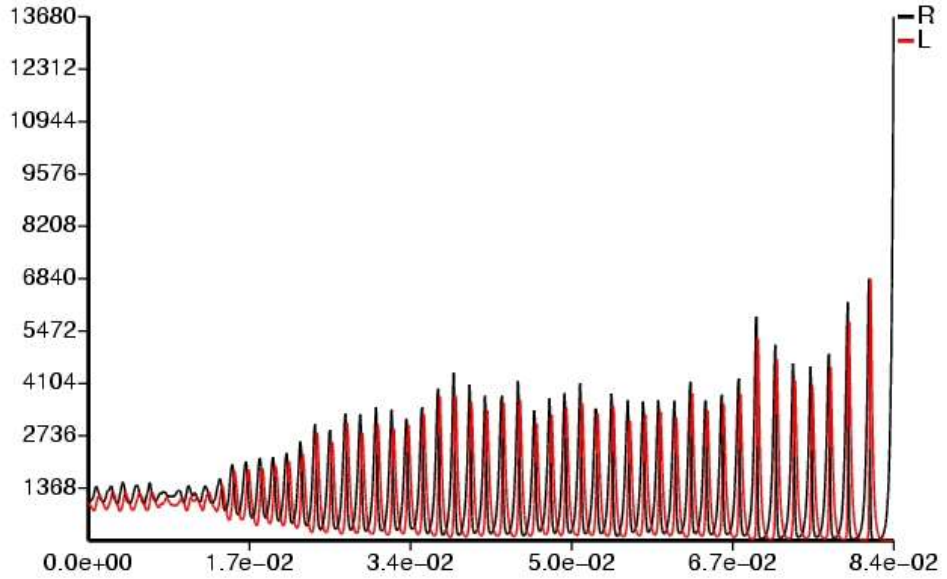
close lines? update print zoom in X zoom in Y zoom out X zoom out Y

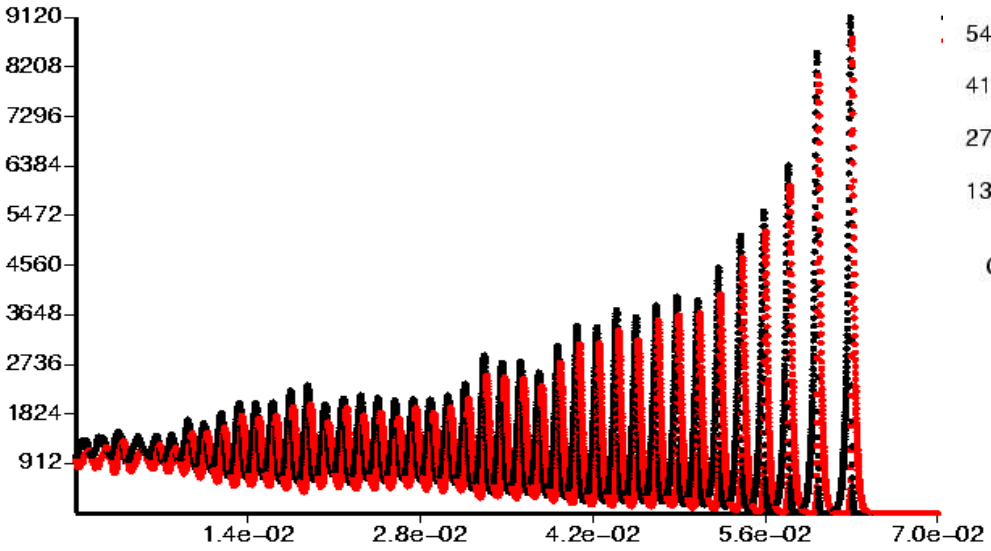



```
Variable values at time 0.008410 (84% complete)
              R   1049
              L   1446

Variable values at time 0.008420 (84% complete)
              R   1030
              L   1444

Variable values at time 0.008430 (84% complete)
              R   1007
              L   1439

Variable values at time 0.008440 (84% complete)
              R    982
              L   1433
```

pathological situations







Computational Neurobiology

control

File | Units | Tools | Options | Graphs | Help

start (variable dt) | Start stimulus | Stop | Reset

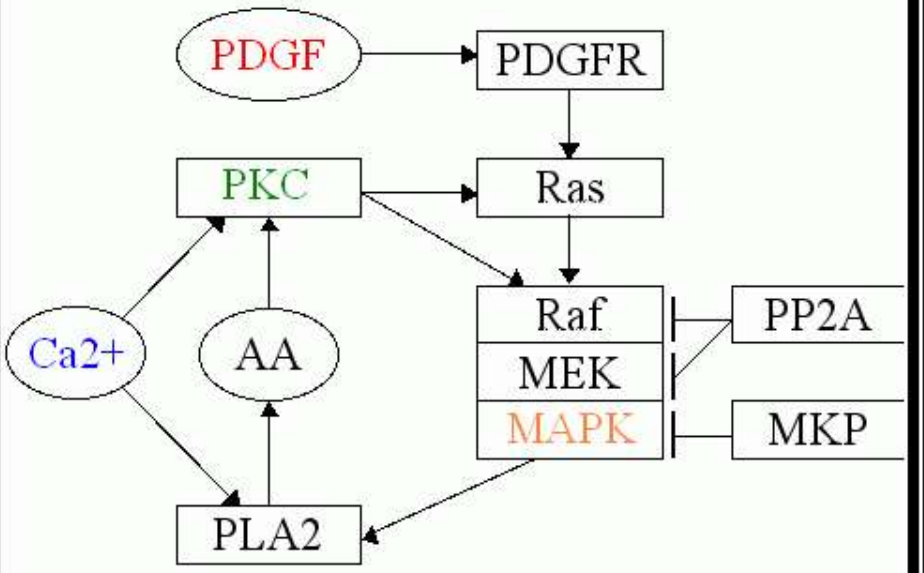
Runtime (sec) 10200 | dt = 0.005 | Current time 10196

kpool kreac kenz transport stim xtab group uplink unlink mirror Delete Duplicate

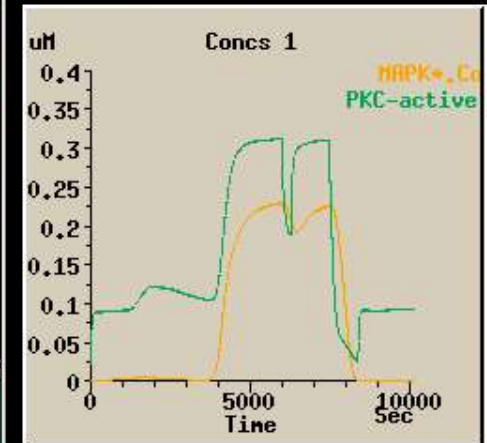
version = 0, fixcoords= 1

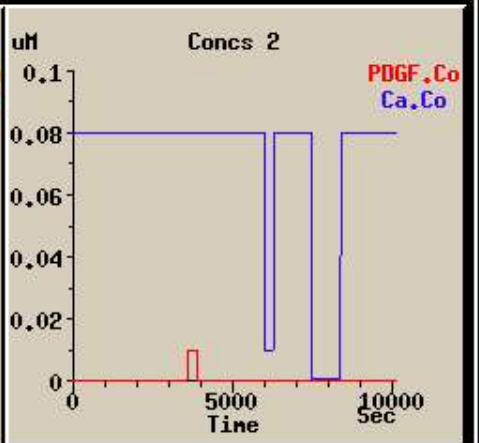
edit

Schematic | Reaction view | Entire model | Select demo...



graphs





comment

```
Selecting model: 03_MAPK_PKC_bistable_feedback
t=0 Starting simulation, stimulus is at baseline.
t=600 System settles to baseline.
t=900 Applying subthreshold stimulus of 0.12 nM PDGF.
t=1200 Terminating PDGF stimulus
t=1800 System returning to basal activity
t=3600 Applying strong stimulus of 0.01 uM PDGF.
t=3900 Terminating PDGF stimulus
t=4500 System settles to upper stable state
t=6000 Applying subthreshold inhib stimulus by reducing Ca to 10 nM
t=6300 Terminating inhib stimulus
t=6900 System recovers its activity
t=7500 Applying long, strong inhib stimulus by reducing Ca to 1 nM
t=8400 Terminating inhib stimulus
t=10200 System returns to lower stable state.
```

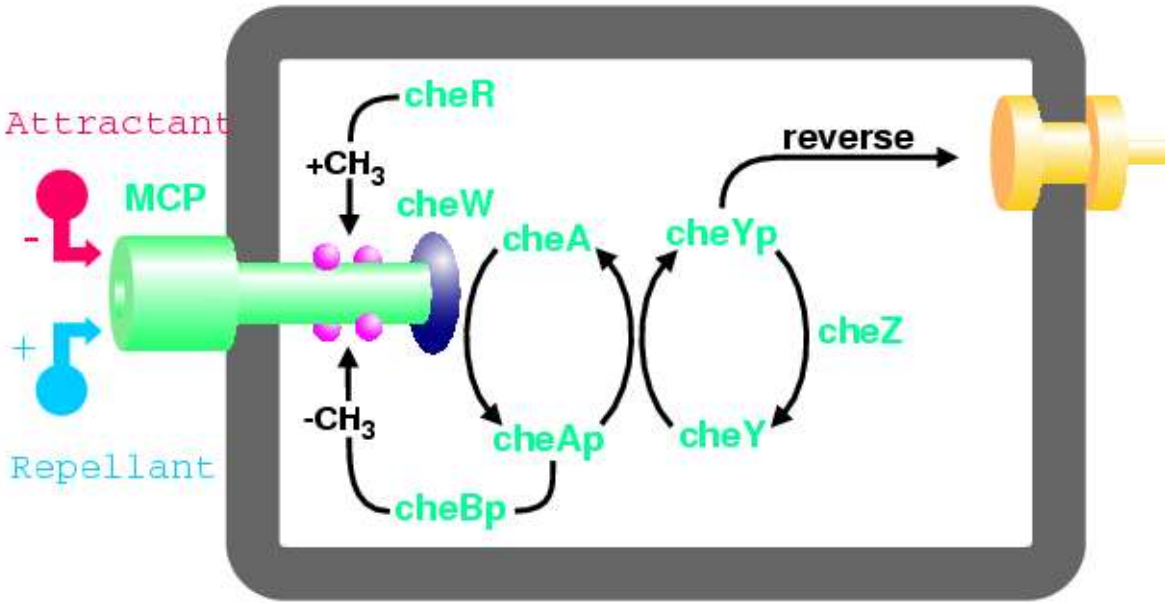
Parameter search

Very often, parameters are unknown or uncertain. If sets of input and output are known, one can launch an exploration of a whole range of parameter values by an iterative process. Many algorithms are available:

- evolutionary algorithms (e.g. Genetic Algorithms)
- stochastic algorithms (e.g. Simulated Annealing)
- gradient-descent methods (based on derivatives)
- direct search methods (e.g. amoeba algorithm)
- etc.

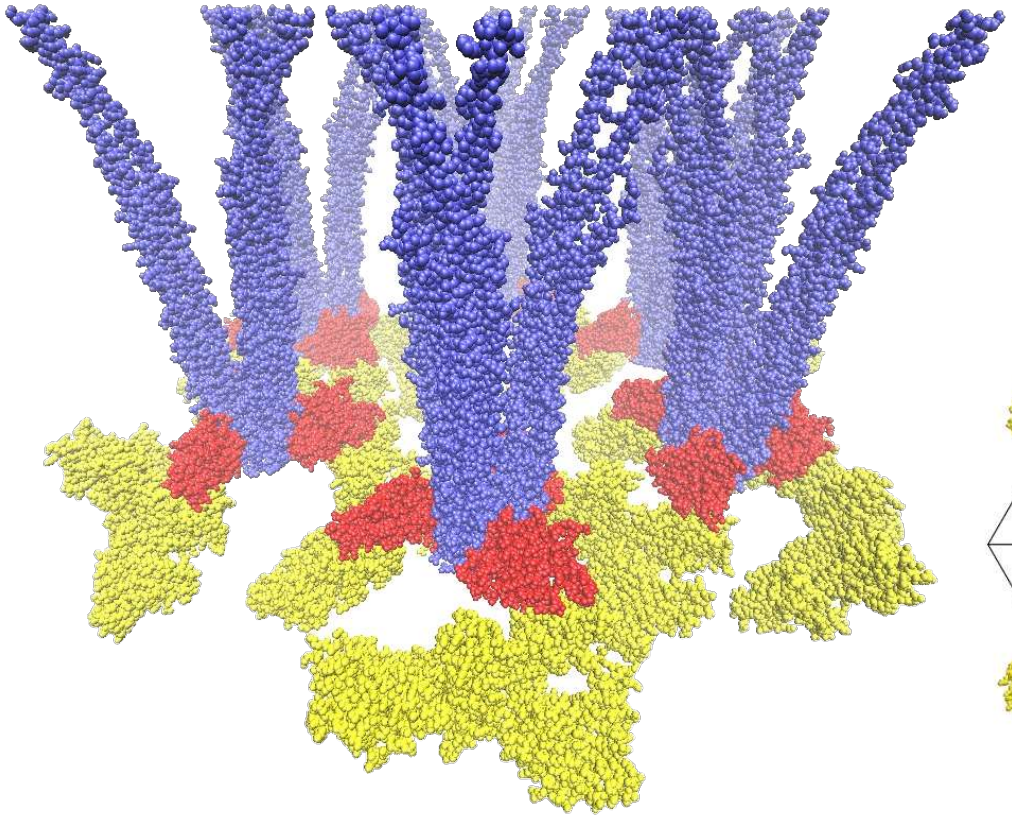
One possibly need thousands of iterations, that is a demanding computation, even for limited models. However, since the iterations are represent independent simulations, distributed or parallel computing are possible.

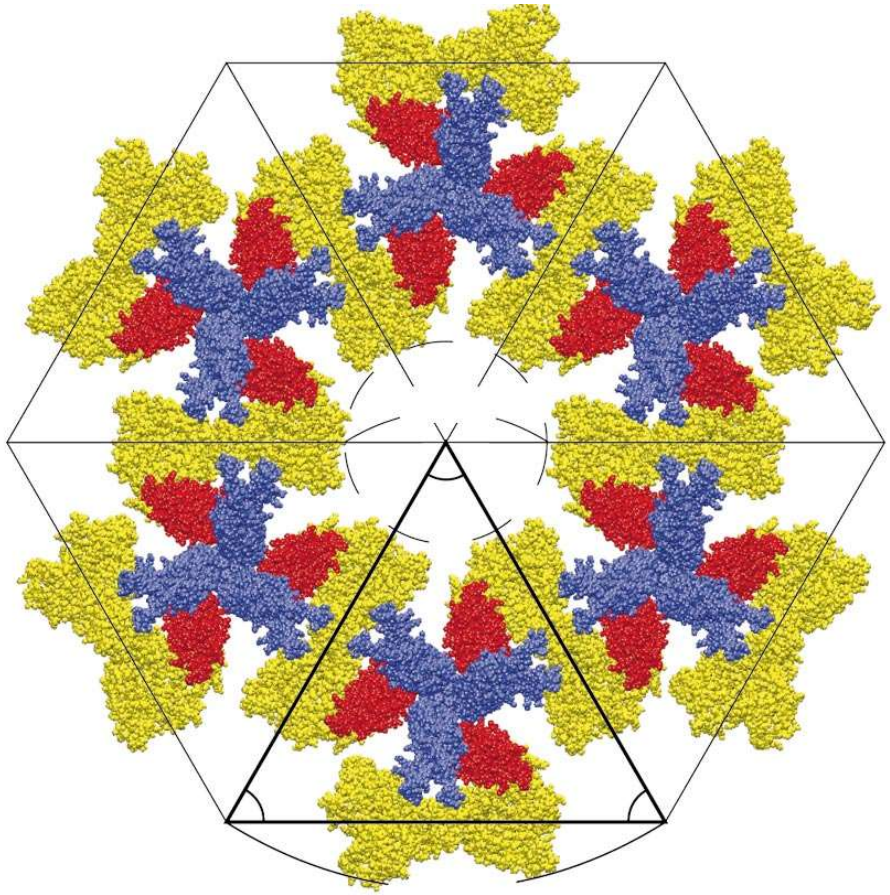
Bacterial chemotaxis



Computational Neurobiology

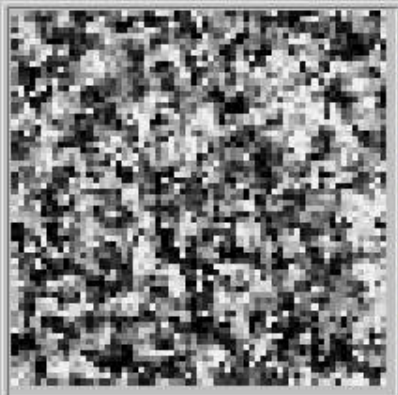
Bacterial chemotaxis



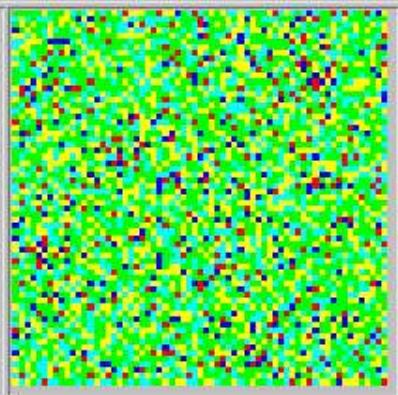


Computational Neurobiology

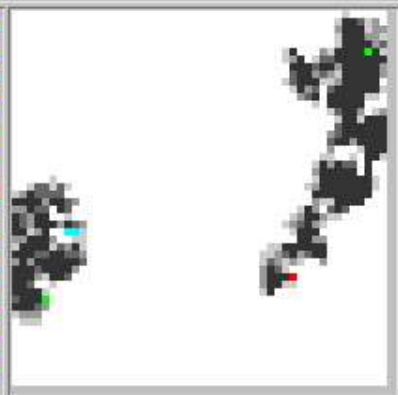
Modelisation of a lattice of chemotactic receptors



receptor kinase activity



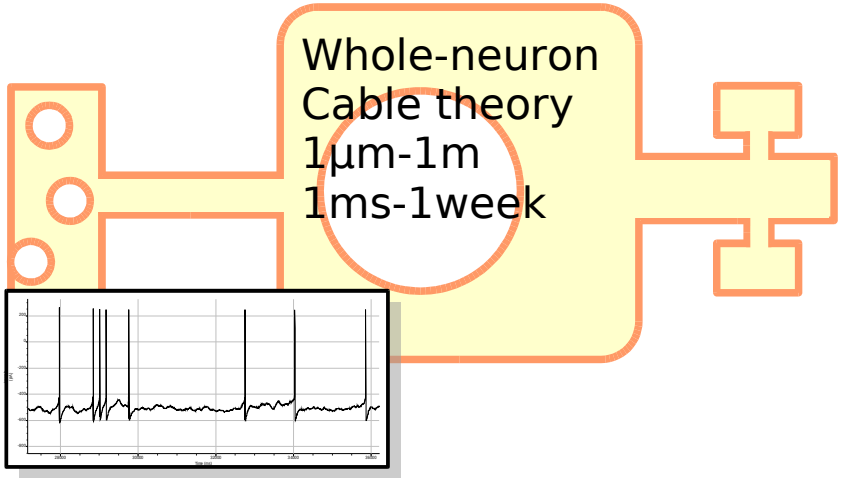
receptor methylation state



methylase trajectory

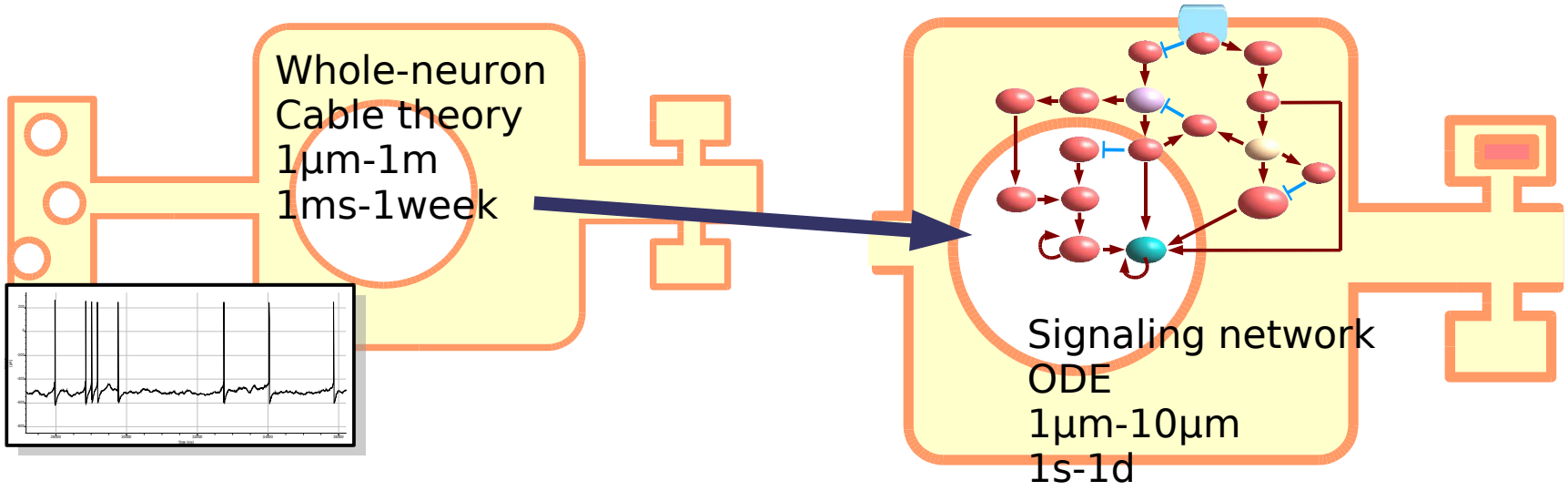
Nicolas Le Novère
Last modified: Fri Oct 15 20:56:17 BST 2004

Modular multi-scales multi-algorithms program



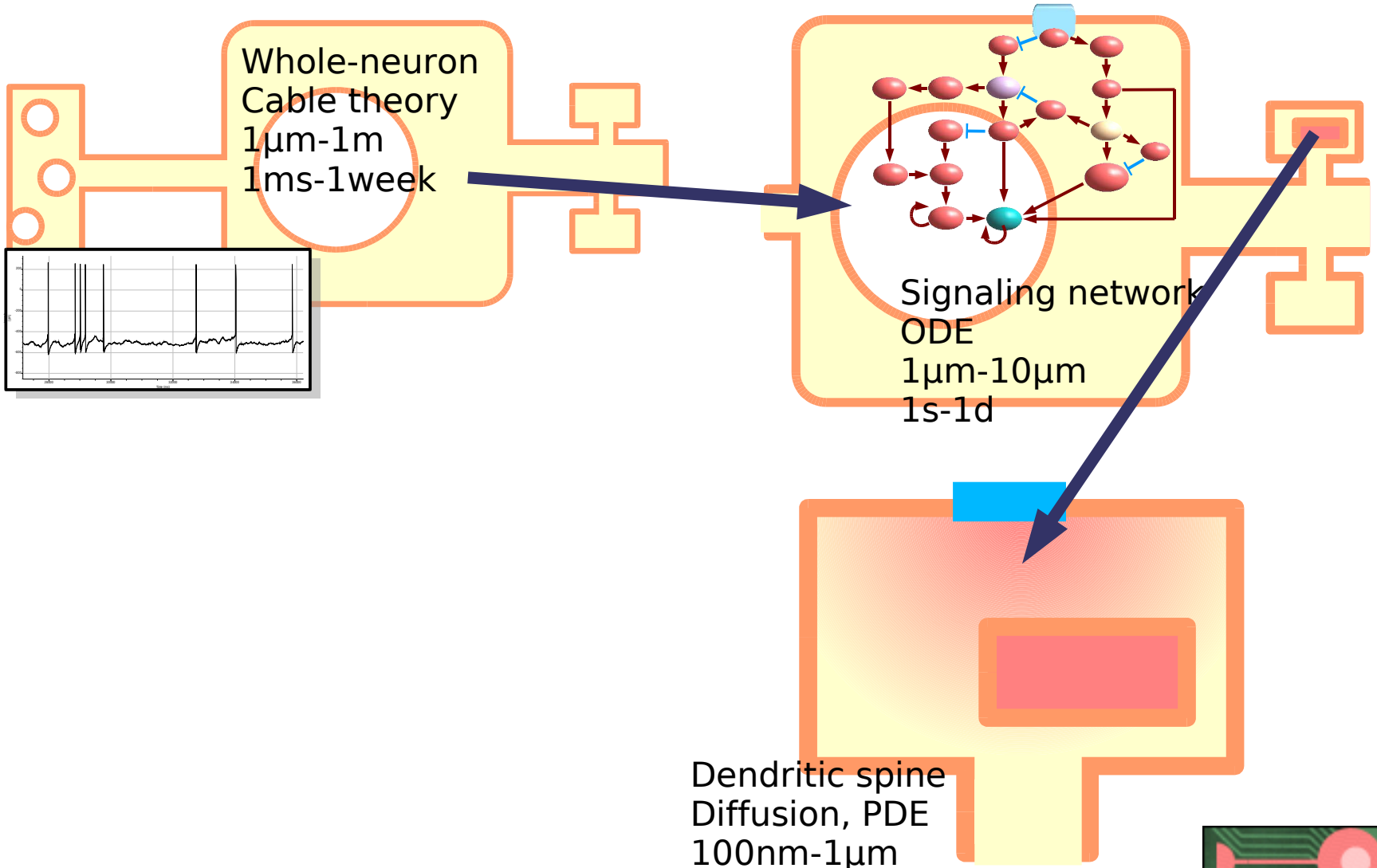
Computational Neurobiology

Modular multi-scales multi-algorithms program

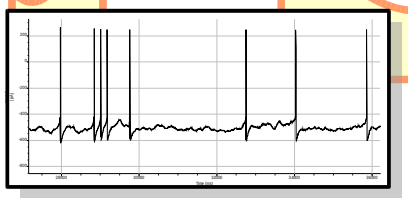


Computational Neurobiology

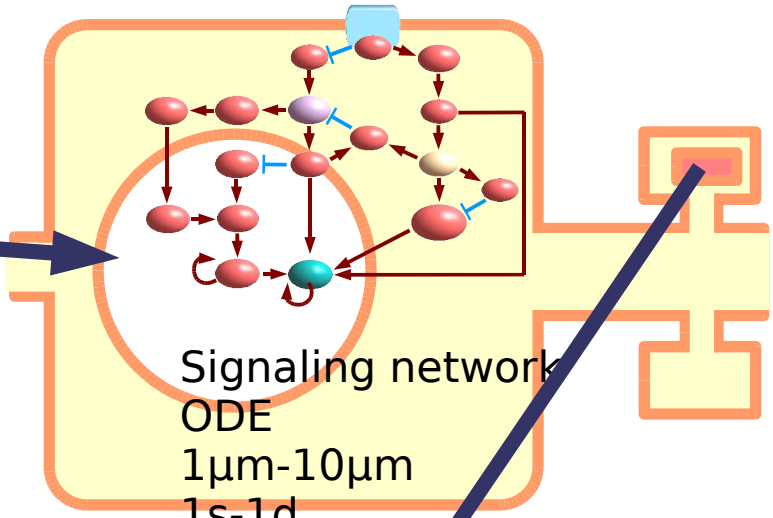
Modular multi-scales multi-algorithms program



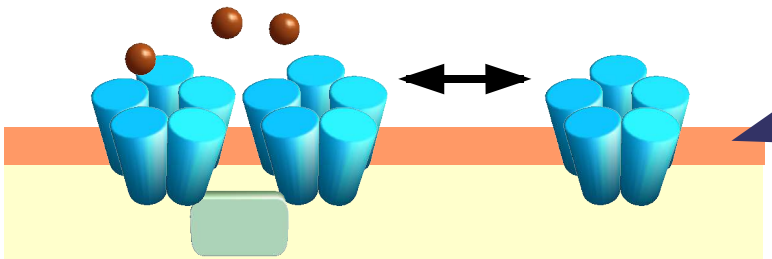
Modular multi-scales multi-algorithms program



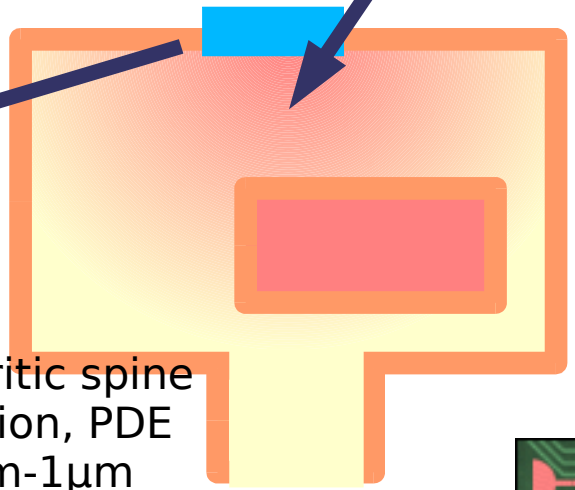
Whole-neuron
Cable theory
1µm-1m
1ms-1week



Signaling network
ODE
1µm-10µm
1s-1d



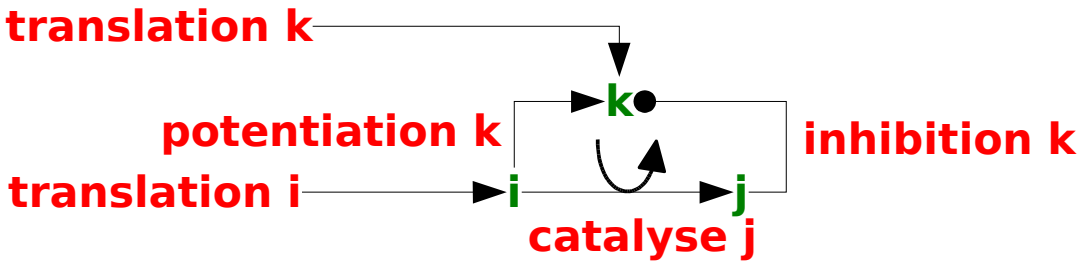
Synapse
Stochastic algorithm
1nm-100nm
1µs-1ms



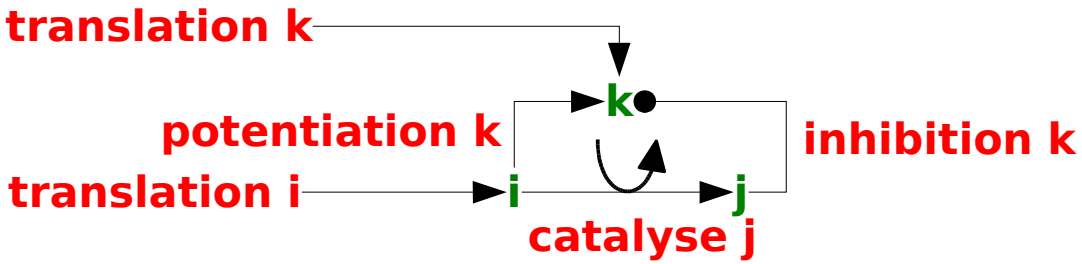
Dendritic spine
Diffusion, PDE
100nm-1µm
1ms-1s

Computational Neurobiology

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



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

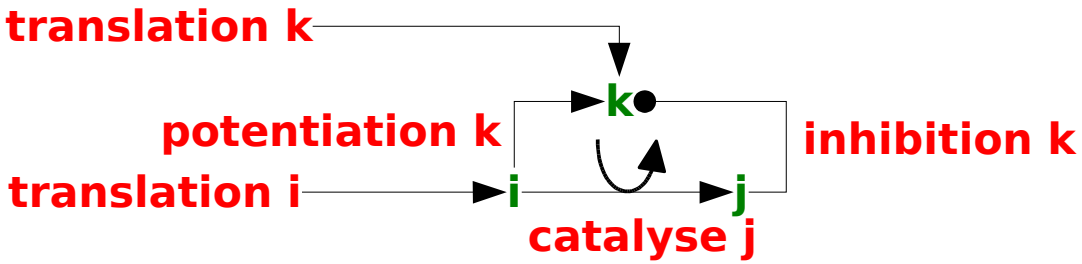


variable j

variable i

variable k

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



catalyse j
(ExpressionFluxProcess)

inhibition k
(MassActionFluxProcess)

potentiation k
(MassActionFluxProcess)

translation i
(GillespieProcess)

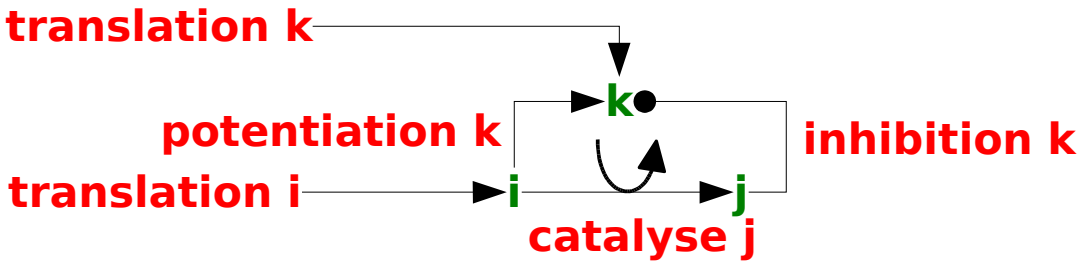
translation k
(GillespieProcess)

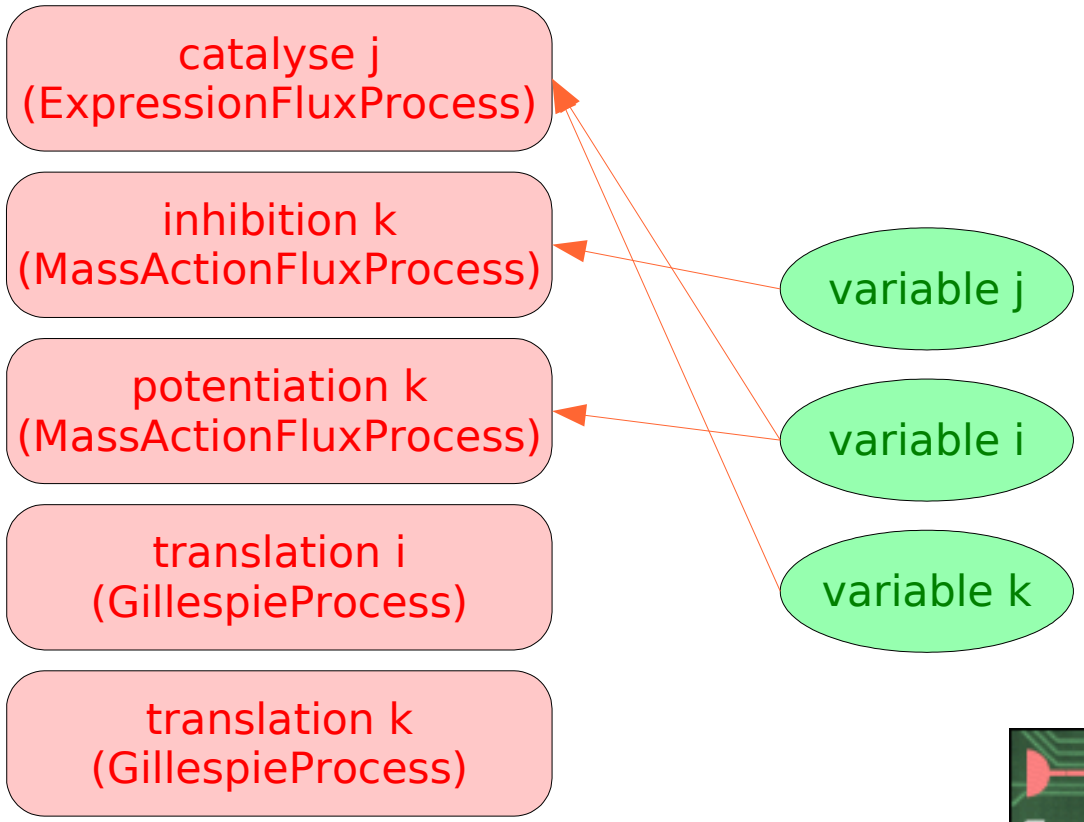
variable j

variable i

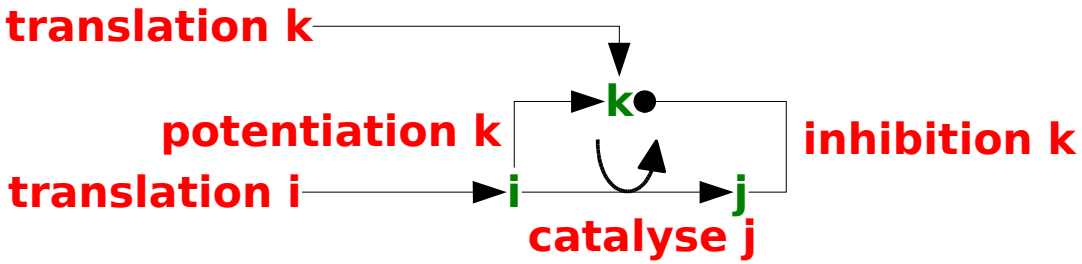
variable k

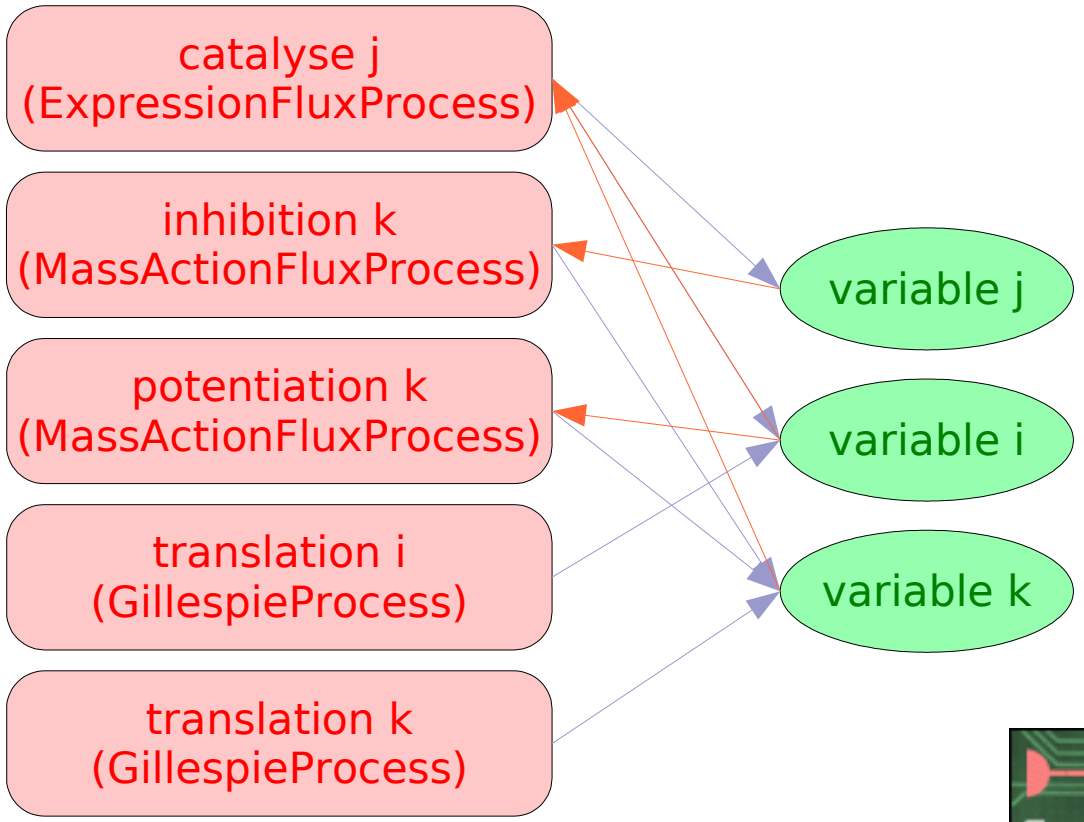
E-Cell System 3 (Kouichi Takahashi)
shared mem, hyper-threading



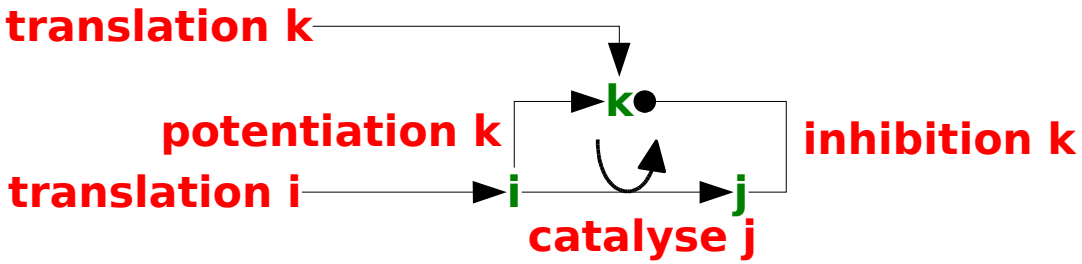


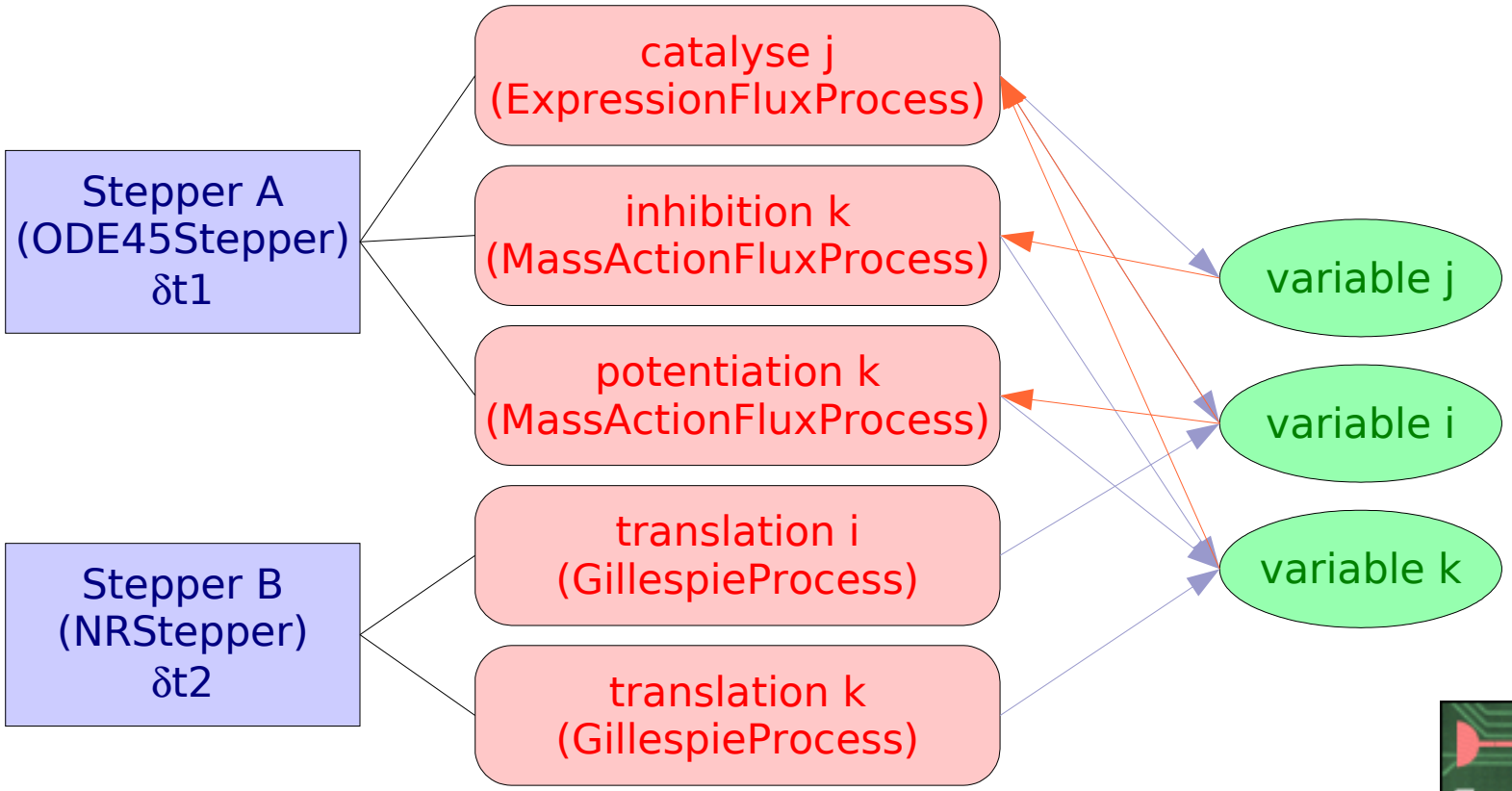
E-Cell System 3 (Kouichi Takahashi)
shared mem, hyper-threading



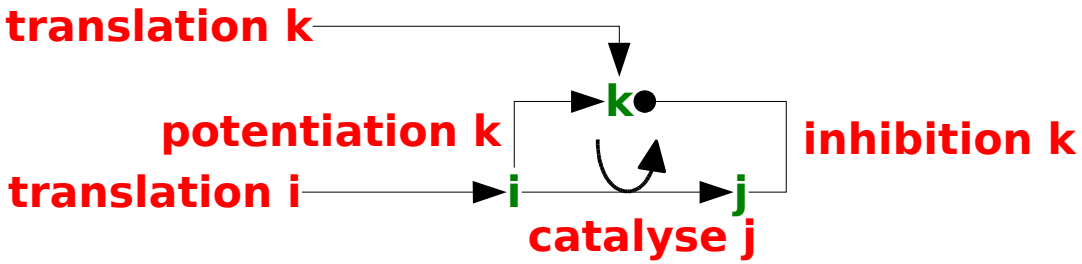


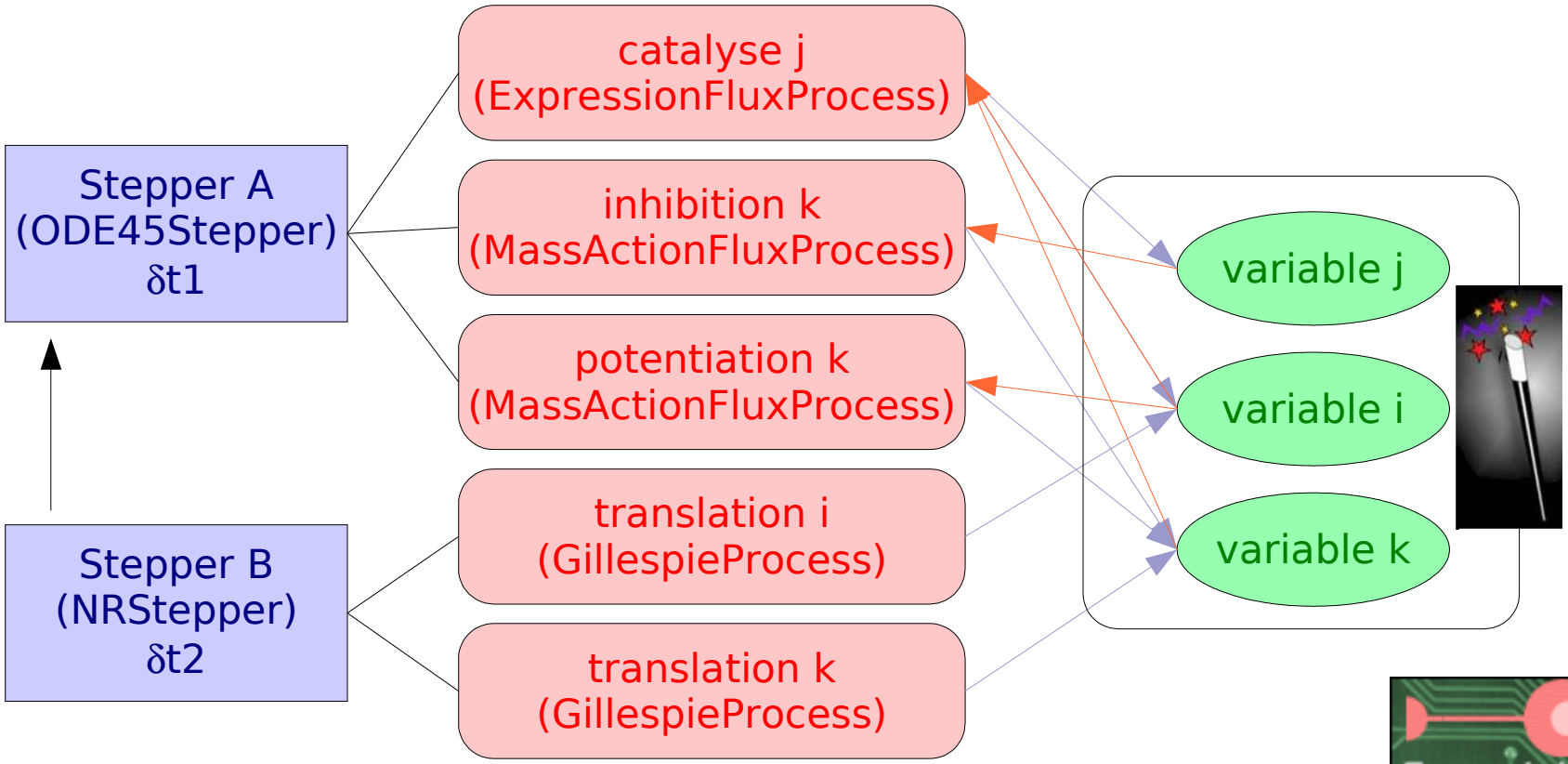
E-Cell System 3 (Kouichi Takahashi) shared mem, hyper-threading



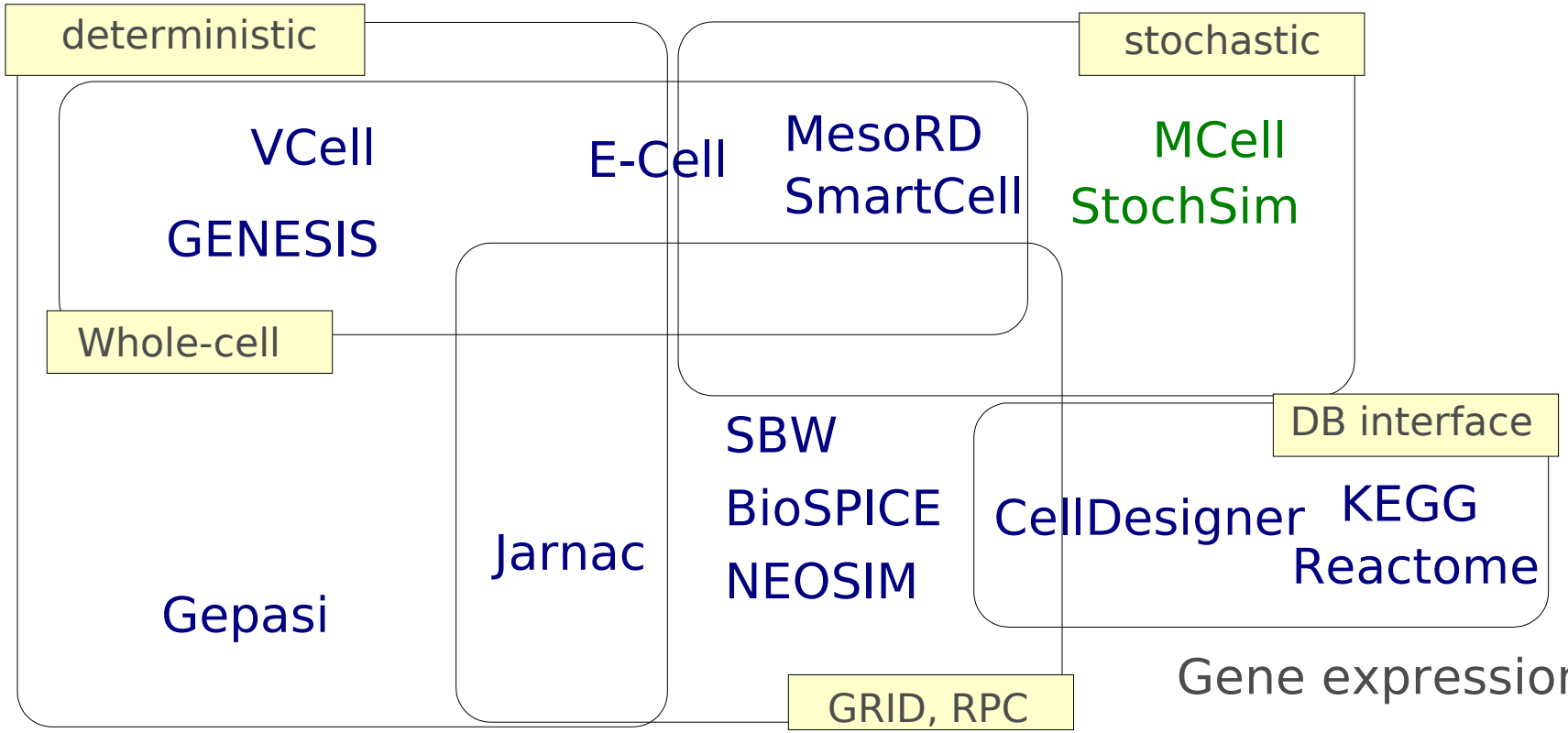


E-Cell System 3 (Kouichi Takahashi)
shared mem, hyper-threading





The collaborative approach



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, 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.

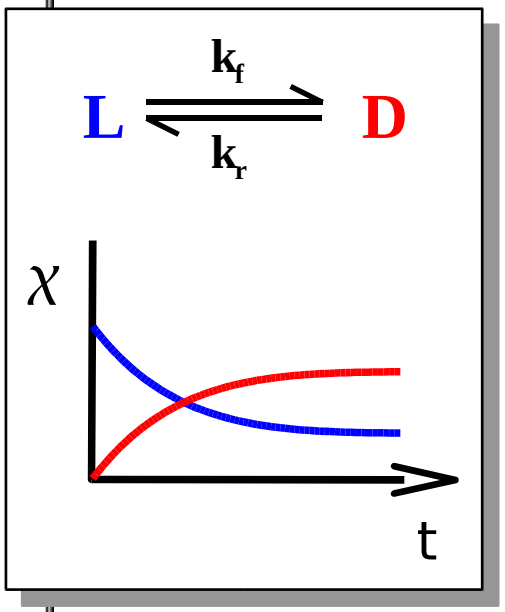
EMBL-EBI

SBML Systems Biology Markup Language

Source of: file:///home/lenov/MEETINGS/CourseEMBL/LynDies.xml - Mozilla

File Edit View Help

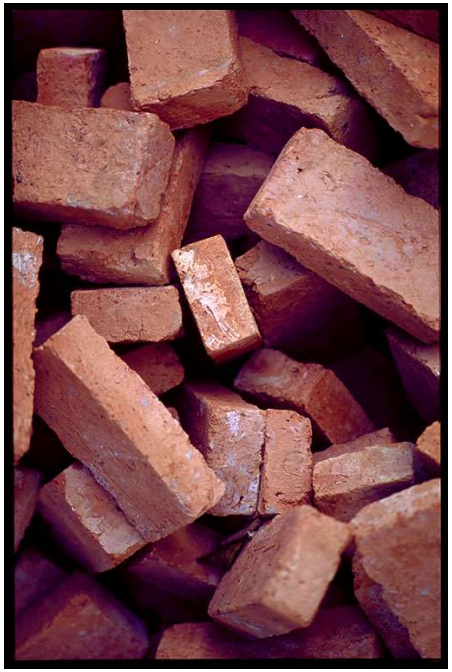
```
<?xml version="1.0" encoding="ISO-8859-1"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2">
  <model name="LotkaVolterra">
    <listOfCompartments>
      <compartment volume="1e-021" name="compl" />
    </listOfCompartments>
    <listOfSpecies>
      <species compartment="compl" initialAmount="0" name="D" units="mole" />
      <species compartment="compl" initialAmount="1.7e-21" name="L" units="mole" />
    </listOfSpecies>
    <listOfReactions>
      <reaction name="_2">
        <listOfReactants>
          <speciesReference species="L" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="D" />
        </listOfProducts>
        <kineticLaw formula="(kf * L - kr * D) * compl">
          <listOfParameters>
            <parameter value="5000" name="kf" />
            <parameter value="0" name="kr" />
          </listOfParameters>
        </kineticLaw>
        <notes>
          <body xmlns="http://www.w3.org/1999/xhtml">
            <p>Lynx dies</p>
          </body>
        </notes>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```



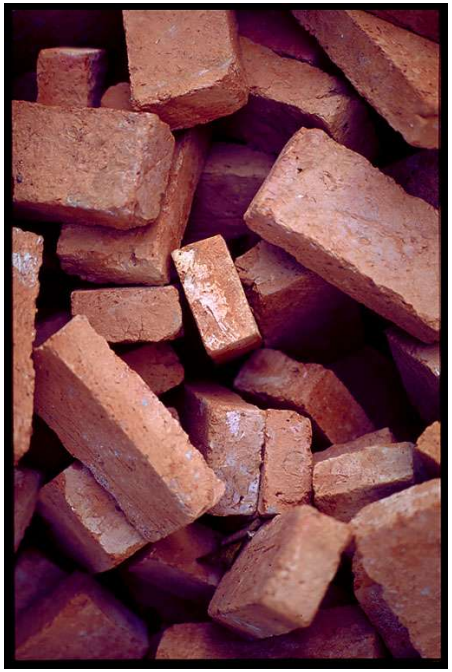
IETF mime-type: application/sbml+xml

Computational Neurobiology

Cellular Neurobiology today

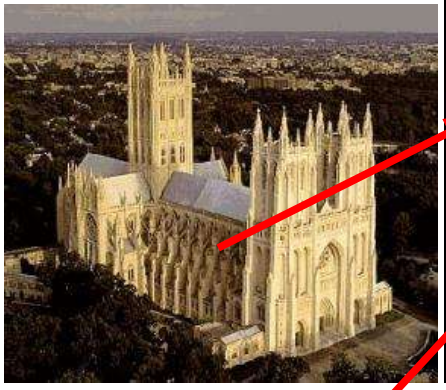


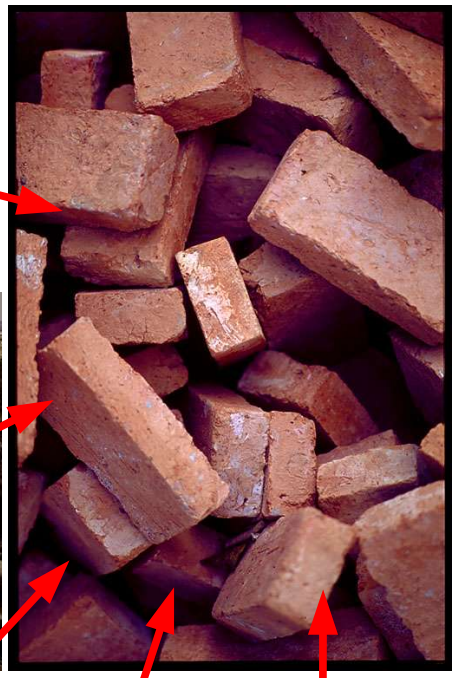
Cellular Neurobiology today

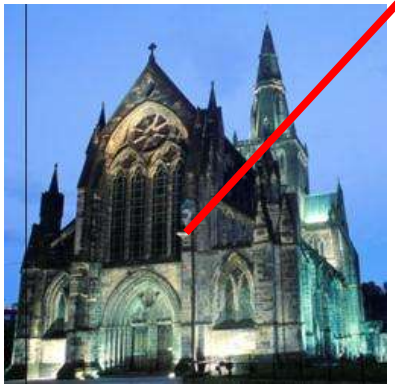


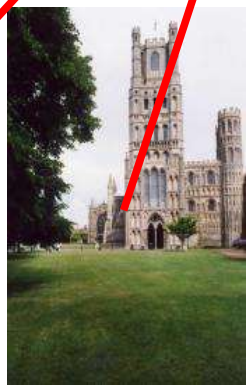
Computational Neurobiology

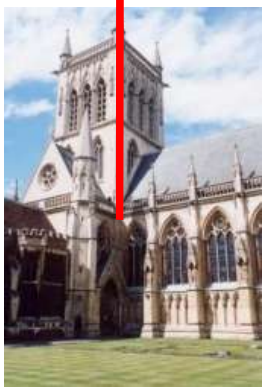
Cellular Neurobiology today











Computational Neurobiology

In Computational Systems Biology the bottleneck is often the data, not the tool