

# The SBML ODE Solver Library

past, present, future

`http://www.tbi.univie.ac.at/~raim/odeSolver/`

**Rainer Machné, Stefanie Widder, Christoph Flamm**

Theoretical Biochemistry Group, University of Vienna, Austria

**James Lu, Stefan Müller, Heinz Engl**

Inverse Methods Group, RICAM Linz, Austria

**Andrew Finney**

SBML Team, Oxford

2<sup>nd</sup> BioModels.net Training Camp, Manchester 2007

# Outline

- ▶ the past

- ▶ CVODE for RNA evolution, gene regulatory networks

- ▶ + libSBML = **SOSlib** and some MAPK models

- reactions*  $\Rightarrow$  *ODE*  $\Rightarrow$   $x(t), s(t)$

- ▶ the present

- ▶ Inverse Analysis:

- reactions*  $\Leftarrow$  *ODE*  $\Leftarrow$   $x(t)$

- ▶ Inverse Dynamical Analysis:

- evolution of the bifurcation phenotype*

- ▶ the future

- ▶ limitations and outlook

also see:

<http://www.tbi.univie.ac.at/~raim/talks/icsb06.pdf>

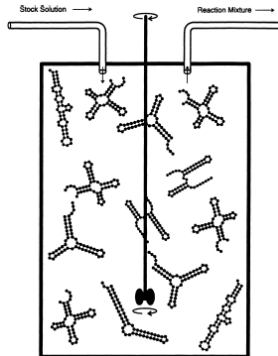
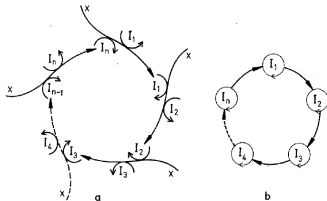
# Outline

- ▶ the past
  - ▶ CVODE for RNA evolution, gene regulatory networks
  - ▶ + libSBML = **SOSlib** and some MAPK models  
*reactions*  $\Rightarrow$  *ODE*  $\Rightarrow$   *$x(t), s(t)$*
- ▶ the present
  - ▶ Inverse Analysis:  
*reactions*  $\Leftarrow$  *ODE*  $\Leftarrow$   *$x(t)$*
  - ▶ Inverse Dynamical Analysis:  
*evolution of the bifurcation phenotype*
- ▶ the future
  - ▶ limitations and outlook

also see:

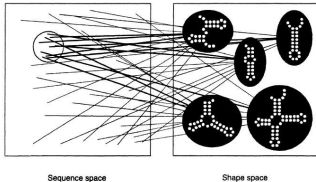
<http://www.tbi.univie.ac.at/~raim/talks/icsb06.pdf>

# In the beginning there was ...



... *in silico* evolution

... the RNA hypercycle



... a genotype-phenotype map

Manfred Eigen and Peter Schuster: *The hypercycle. A principle of natural self-organization. Part A: Emergence of the hypercycle.* Naturwissenschaften 1977

P. Schuster and W. Fontana: *Chance and Necessity in Evolution: Lessons from RNA.* Physica D: Nonlin. Phen. 1999

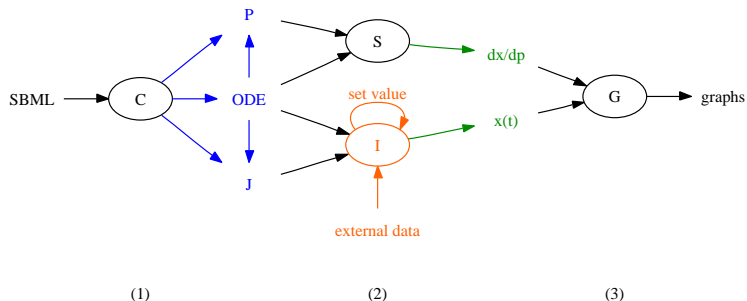
B.M.R. Stadler, P.F. Stadler, G. Wagner and W. Fontana: *The topology of the possible: Formal spaces underlying patterns of evolutionary change.* J. theor. Biol., 2001

Washietl S, Hofacker IL, Lukasser M, Huttenhofer A, Stadler PF. *Mapping of conserved RNA secondary structures predicts thousands of functional noncoding RNAs in the human genome.* Nat Biotechnol. 2005

S Widder J Schicho P Schuster: *Dynamic patterns of gene regulation I: simple two gene systems.*

J. theor. Bio. accepted

# The SBML ODE Solver Library: ISO-C90, LGPL



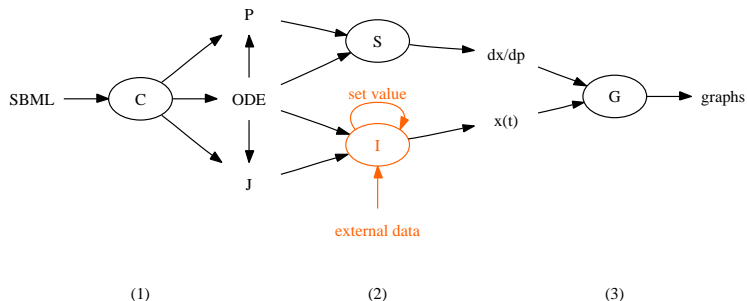
```
model      = SBMLDocument_getModel(d);
settings   = CvodeSettings_createWithTime(100, 50);
results    = Model_odeSolver(model, settings);
timecourse = SBMLResults_getTimeCourse(results, ``flux_G6PDH``);
value      = TimeCourse_getValue(timecourse, 3);
```

libSBML + SUNDIALS (+ graphviz, + xmgrace) = SOSlib

*A native API for symbolic and fast numerical analysis of reaction networks.*

Machné R, Finney A, Müller S, Lu J, Widder S, Flamm C. Bioinformatics 2006, 22(11):1406-7

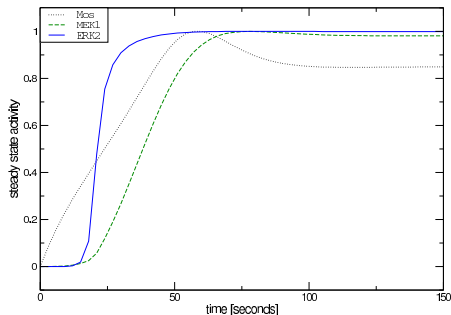
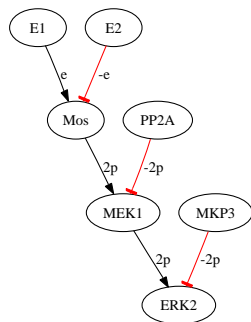
# Numerical Capabilities - via SUNDIALS/CVODES



```
ii = IntegratorInstance_create(odemodel, settings);  
while ( !IntegratorInstance_timeCourseCompleted(ii) ) {  
    IntegratorInstance_integrateOneStep(ii);  
    if ( IntegratorInstance_getTime(ii) > 30 )  
        IntegratorInstance_setVariableValue(variable, 300);  
}
```

- ▶ External data sets
- ▶ Multi-scale modeling
- ▶ Hybrid solvers

# the Mitogen-activated protein kinase cascade



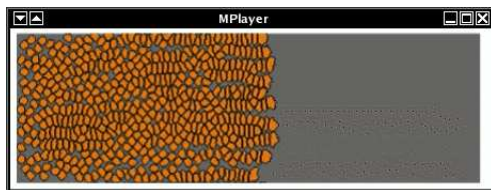
a cascade of dual protein phosphorylation

Ultrasensitivity: Huang CY, Ferrell JE Jr. PNAS 1996

Oscillation: Kholodenko BN. Eur J Biochem 2000

Bistability: Markevich NI, Hoek JB, Kholodenko BN. J Cell Biol. 2004

# Multi-scale modeling



a collaboration with Camille Stephan-Otto Attolini:  
**vertebrate somitogenesis: FGF/MAPK + Hes, Notch + Calcium**

- ▶ Cellular Potts model + one SBML model
- ▶ Multiple IntegratorInstances, communicating via IntegratorInstance\_g/setVariableValue



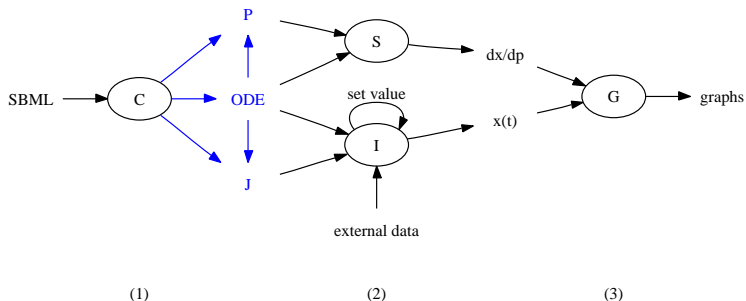
## The need for speed ©Andrew Finney

Biomodel DB Id	9	14	33	22	repress.
Type	stable	stable	stable	oscil.	oscil./stiff
NEQ/Time	22/150	86/300	28/60	10/2000	6/10,000
Dizzy 1.11.1	15,499	12,711	2,634	19,350	6,369
Jarnac 2.16n	344	14,531	1,157	5,843	4,516
SBMLToolbox	188	920	302	5,554	6,681
SOSlib 1.6	234	<b>515</b>	171	<b>562</b>	1,062
Copasi 4.0.b15	<b>156</b>	4,062	<b>109</b>	1,437	<b>500</b>

Preliminary benchmarking of *SBML* Solvers, in milliseconds CPU time (including model parsing, ODE construction and integration)

⇒ perfect for *in silico* evolution, multi-scale modeling, or optimization

# Analytic Capabilities - via libSBML

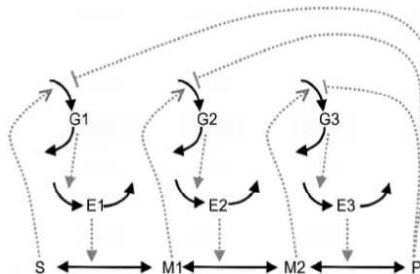


```
odeModel = ODEModel_create(model);  
if ( ODEModel_constructJacobian(odeModel) )  
    formula = ODEModel_getJacobianIJEntry(odeModel, i, j);
```

- ▶ **AST** evaluation, differentiation, simplification
- ▶ ODE model structure:  $dx/dt = f(x, t, p)$
- ▶ Jacobian and parametric matrices:  $J = df/dx$  and  $P = df/dp$

# Inverse Analysis: parameter identification

- ▶ SOSlib: forward and adjoint sensitivities
- ▶ + IpOpt: interior point optimization method
  - ▶ combining local + global optimization
- ▶ accounting for data noise by *regularization methods!!*



Moles, Mendes and Banga, Genome Research (2003)

```
IntegratorInstance_setObjFunction(ii,"gen.obj");  
IntegratorInstance_readTimeSeriesData(ii,"gen.dat");  
% Create nonlinear programming problem  
nlp = CreateIpoptProblem(..., ...);
```

⇒ upcoming C tool by James Lu, S. Müller, R. Machné, H. Engl

# Inverse Dynamical Analysis: *bifurcation phenotype*

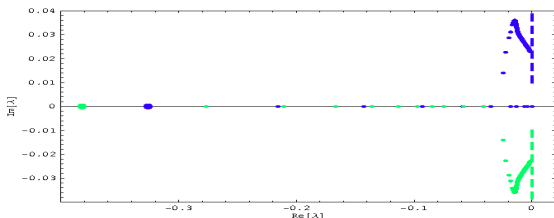
## 1. Inverse eigenvalue analysis

- ▶ Probe the possibility for multistability/oscillations
- ▶ Identify minimal dynamic-changing parameter combinations using sparsity-promoting regularization

## 2. Forward bifurcation analysis (w.r.t identified parameters)

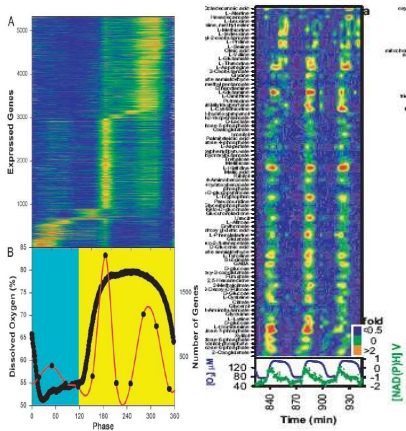
## 3. Inverse bifurcation analysis

- ▶ Design the system to obtain desired dynamical behavior
- ▶ Identify influential parameters: propose experiments for verification



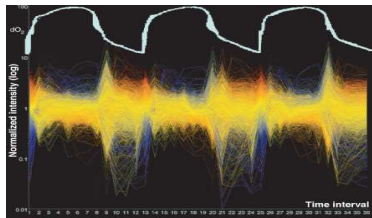
⇒ upcoming MathSBML extension by James Lu

# Respiratory oscillations in yeast

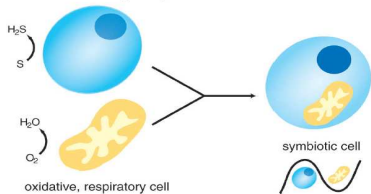


Short-period: 40 minutes, cell-cycle gating ?

Klavec et al., PNAS 2004  
Murray, Beckmann, Kitano, PNAS accepted



reductive, non-respiratory cell

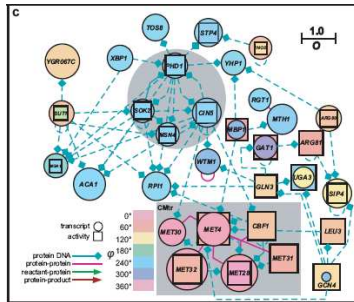
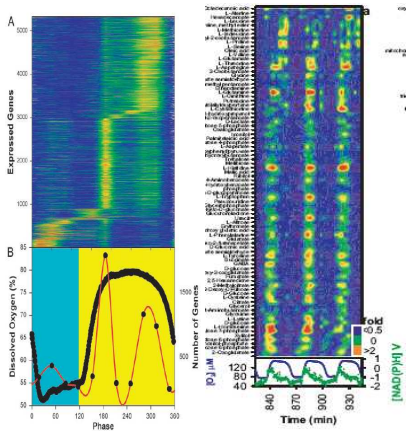


Long-period: 300 minutes, cell-cycle synchrony ?

Tu et al. Science 2005

Murray et al. 1999 Microbiology, Lloyd et al. 2002 Microbiology  
Murray 2004 Current Genomics, Lloyd and Murray 2005 Trends Biochem Sci

# Respiratory oscillations in yeast

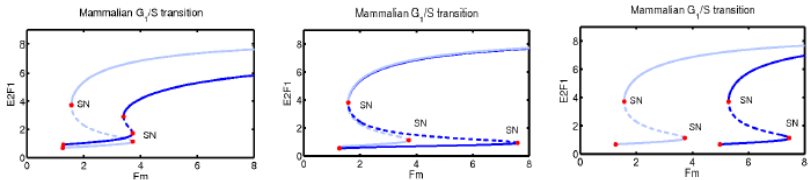


Short-period: 40 minutes, cell-cycle gating ?

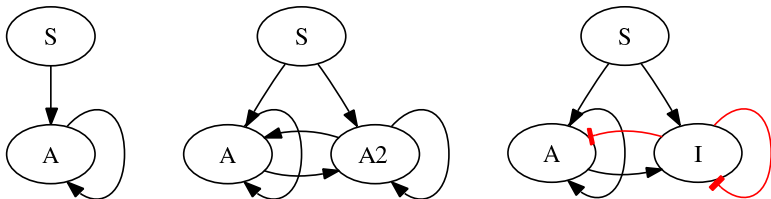
Klavec et al., PNAS 2004  
Murray, Beckmann, Kitano, PNAS accepted

Murray et al. 1999 Microbiology, Lloyd et al. 2002 Microbiology  
Murray 2004 Current Genomics, Lloyd and Murray 2005 Trends Biochem Sci

# Evolution of the *bifurcation phenotype*

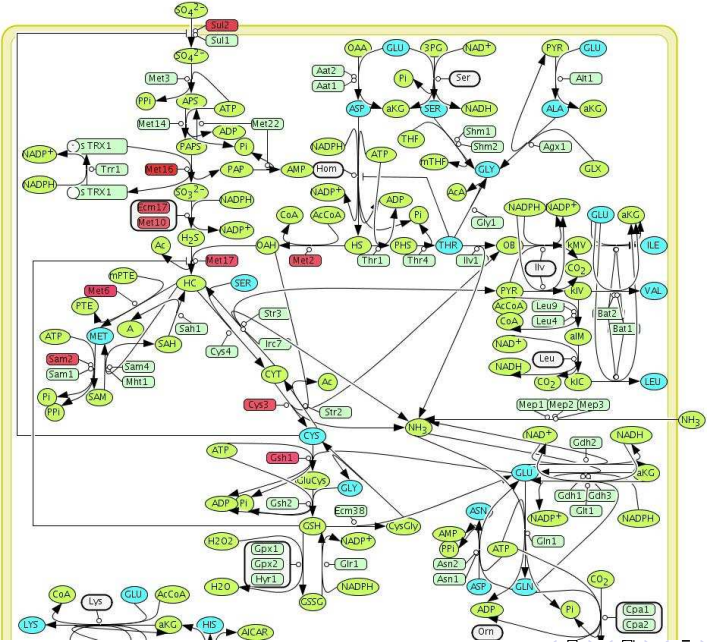


transitions of the *bifurcation phenotype*



duplication of an auto-activating transcription factor

# Metabolic models II - amino acid synthesis





# Limitations - in order of ToDo list

Current framework:

- ▶ Online compilation via TCC (Andrew Finney's code)
- ▶ Variable compartments: ODEs in substance/time
- ▶ Exact event handling (Sundials *root finder*)
- ▶ SWIG-based interfaces
- ▶ Differential Algebraic Equations (Sundials IDA)
- ▶ Delay Differential Equations (e.g. XPP)

Do you have preferences? Want to join?

Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# Limitations - in order of ToDo list

Current framework:

- ▶ Online compilation via TCC (Andrew Finney's code)
- ▶ Variable compartments: ODEs in substance/time
- ▶ Exact event handling (Sundials *root finder*)
- ▶ SWIG-based interfaces
- ▶ Differential Algebraic Equations (Sundials IDA)
- ▶ Delay Differential Equations (e.g. XPP)

Do you have preferences? Want to join?

Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# Limitations - in order of ToDo list

Current framework:

- ▶ Online compilation via TCC (Andrew Finney's code)
- ▶ Variable compartments: ODEs in substance/time
- ▶ Exact event handling (Sundials *root finder*)
- ▶ SWIG-based interfaces
- ▶ Differential Algebraic Equations (Sundials IDA)
- ▶ Delay Differential Equations (e.g. XPP)

Do you have preferences? Want to join?

Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# Outlook

- ▶ SOSlib: new release around march/april
- ▶ Inverse methods:  $reactions \Leftarrow ODE \Leftarrow x(t)$ 
  - ▶ Separate package, GPL or other license
- ▶ Inverse Dynamical Analysis
  - ▶ Mathematica package, MathSBML extension

Do you have preferences? Want to join?  
Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# Outlook

- ▶ SOSlib: new release around march/april
- ▶ Inverse methods:  $reactions \Leftarrow ODE \Leftarrow x(t)$ 
  - ▶ Separate package, GPL or other license
- ▶ Inverse Dynamical Analysis
  - ▶ Mathematica package, MathSBML extension

Do you have preferences? Want to join?  
Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# Outlook

- ▶ SOSlib: new release around march/april
- ▶ Inverse methods:  $reactions \Leftarrow ODE \Leftarrow x(t)$ 
  - ▶ Separate package, GPL or other license
- ▶ Inverse Dynamical Analysis
  - ▶ Mathematica package, MathSBML extension

Do you have preferences? Want to join?

Contact us at [sbmlsolver-discuss@lists.sourceforge.net](mailto:sbmlsolver-discuss@lists.sourceforge.net)

# SOSlib - an open source project

- ▶ TBI Vienna, Peter Schuster's group
  - ▶ Christoph Flamm, Stefanie Widder, Rainer Machné
- ▶ RICAM Linz, Heinz Engl's group
  - ▶ Stefan Müller, James Lu, Philipp Kügler
- ▶ SBML core team
  - ▶ Andrew Finney
  
- ▶ Akira Funahashi (CellDesigner team)
- ▶ Nicolas Le Novère (BioModels DB team)
- ▶ Eryk Wolski (SBML\_odeSolveR)



Wiener Wissenschafts-, Forschungs- und Technologiefonds

**Project Nr. MA05**

# SOSlib - an open source project

- ▶ TBI Vienna, Peter Schuster's group
  - ▶ Christoph Flamm, Stefanie Widder, Rainer Machné
- ▶ RICAM Linz, Heinz Engl's group
  - ▶ Stefan Müller, James Lu, Philipp Kügler
- ▶ SBML core team
  - ▶ Andrew Finney
  
- ▶ Akira Funahashi (CellDesigner team)
- ▶ Nicolas Le Novère (BioModels DB team)
- ▶ Eryk Wolski (SBML\_odeSolve**R**)



Wiener Wissenschafts-, Forschungs- und Technologiefonds

Project Nr. MA05