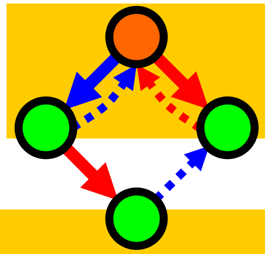
A useful theory is a compression of the data.
Leibniz, Discourse de métaphysique. Paraphrased by G.Chaitin.



Artificial Biochemistry

University of Trento – Information and Communication Technology
International Doctorate School – ICT Doctorate Course 21414
http://dit.unitn.it/edu/ict/courseinfo.xml?courseid=21414&year=2006

Luca Cardelli

Microsoft Research

The Microsoft Research - University of Trento
Centre for Computational and Systems Biology

Trento, 2006-05-22..26

www.luca.demon.co.uk/ArtificialBiochemistry.htm

Course Outline

One: Biology

0:15-1:45

- Course Intro
- Abstract Machines of Systems Biology

2:15-3:45

- Model Construction and Validation
- Probability Distributions (and SPiM intro)

Two: Stochastics

0:15-1:45

- Stochastic Communicating Automata
  - Case Studies: Epidemics
  - Case Studies: MHC Class I Flytrap

2:15-3:45

- Stochastic Collectives
  - Case Studies: Repressilator
- Varieties of Stochastic Calculi

Three: Chemistry

0:15-1:45

- Chemistry and Processes
  - Case Studies: Scaling Reactions
  - Case Studies: ERK Pathway

2:15-3:45

- From Processes to ODEs
  - Case Studies: Epidemics ODE
  - Case Studies: Groupies ODE
  - Case Studies: Tyson Cell Cycle

Aim: Modeling biological systems.

Four: Biochemistry

0:15-1:45

- Complexation
- PolyAutomata
  - Case Studies: MAPK Cascade

2:15-3:45

- Monopolin Circuits
  - Case Studies: Inverter ODE
- Dipolin and Thomas Circuits
  - Case Studies: François and Hakim

Five: Networks and Transport

0:15-1:45

- Gene Networks
  - Including: Guet & al.
- Bitonal Membrane Systems

2:15-3:15

- Brane Calculi
- Conclusions

Presentations available online as **PDF**:

www.luca.demon.co.uk/ArtificialBiochemistry.htm

Select text on PDF, e.g., to copy example code and URLs.
Zoom PDF, e.g., to see tiny example code.

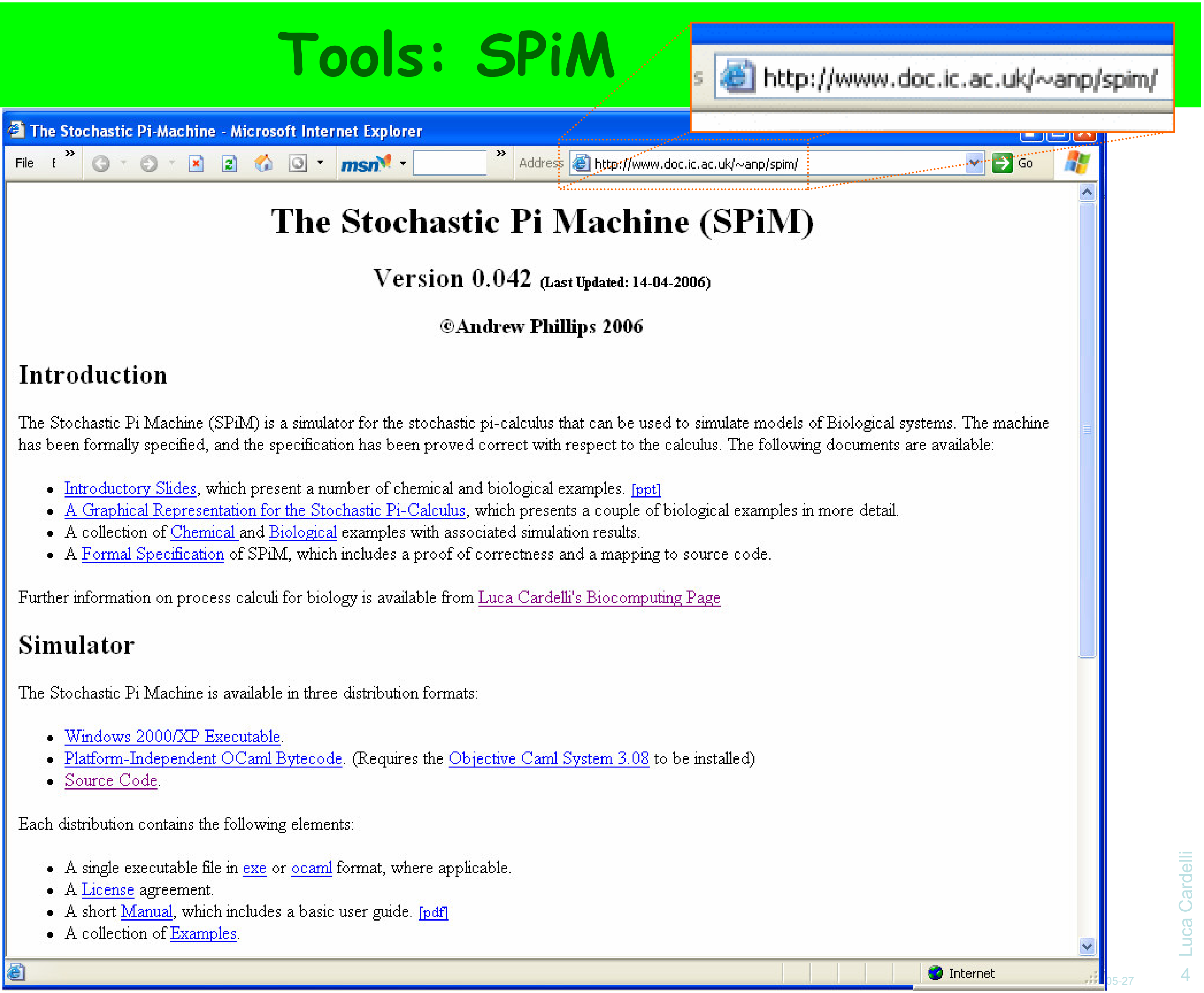
Online Sources

- General Background
  - Statistics
    - http://en.wikipedia.org/wiki/{Random_variable, Stochastic_process, Exponential_distribution}
    - Queueing Theory http://mia.ece.uic.edu/~papers/WWW/Flexi-Tunes/tarballs/queue.pdf
  - Chemistry
    - ChemGuide http://www.chemguide.co.uk/physmenu.html

- Stochastic Process Algebra
  - A Compositional Approach to Performance Modelling. Jane Hillston.
    http://www.dcs.ed.ac.uk/pepa/book.pdf
  - Interactive Markov Chains. Holger Hermanns. Springer Lecture Notes in Computer Science, vol 2428 (2002)
    http://link.springer.de/link/service/series/0558/tocs/t2428.htm
  - Markovian Process Algebra: Composition and Equivalence. Peter Buchholz. 2nd Workshop on Process Algebra and Performance Modelling, Erlangen, Germany, July 21-22 1994.
    http:/citeseer.ist.psu.edu/cache/papers/cs/5748/http:zSzzSzwww7.informatik.uni-erlangen.dezSzpapmzSzproceedingszSzBuc.pdf/buchholz94markovian.pdf

- Biological Modeling
  - The Barrier of Objects: From Dynamic Systems to Bounded Organizations. Walter Fontana, Leo W. Buss. In J. Casti and A. Karlqvist, editors, Barriers and Boundaries, p. 56-116, 1996.
    http://www.santafe.edu/~walter/Papers/barrier.pdf
  - Biomolecular Processes as Concurrent Computation. Ehud Shapiro. An interdisciplinary course at Feinberg Graduate School of the Weizmann Institute of Science, Israel, 2001.
    http://www.wisdom.weizmann.ac.il/~biopsi/bpcc2001/

Tools: SPiM


http://www.doc.ic.ac.uk/~anp/spim/
The Stochastic Pi-Machine - Microsoft Internet Explorer
File
Address
http://www.doc.ic.ac.uk/~anp/spim/
Go
Internet

The Stochastic Pi Machine (SPiM)

Version 0.042 (Last Updated: 14-04-2006)

©Andrew Phillips 2006

Introduction

The Stochastic Pi Machine (SPiM) is a simulator for the stochastic pi-calculus that can be used to simulate models of Biological systems. The machine has been formally specified, and the specification has been proved correct with respect to the calculus. The following documents are available:

- Introductory Slides, which present a number of chemical and biological examples. [ppt]
- A Graphical Representation for the Stochastic Pi-Calculus, which presents a couple of biological examples in more detail.
- A collection of Chemical and Biological examples with associated simulation results.
- A Formal Specification of SPiM, which includes a proof of correctness and a mapping to source code.

Further information on process calculi for biology is available from Luca Cardelli's Biocomputing Page

Simulator

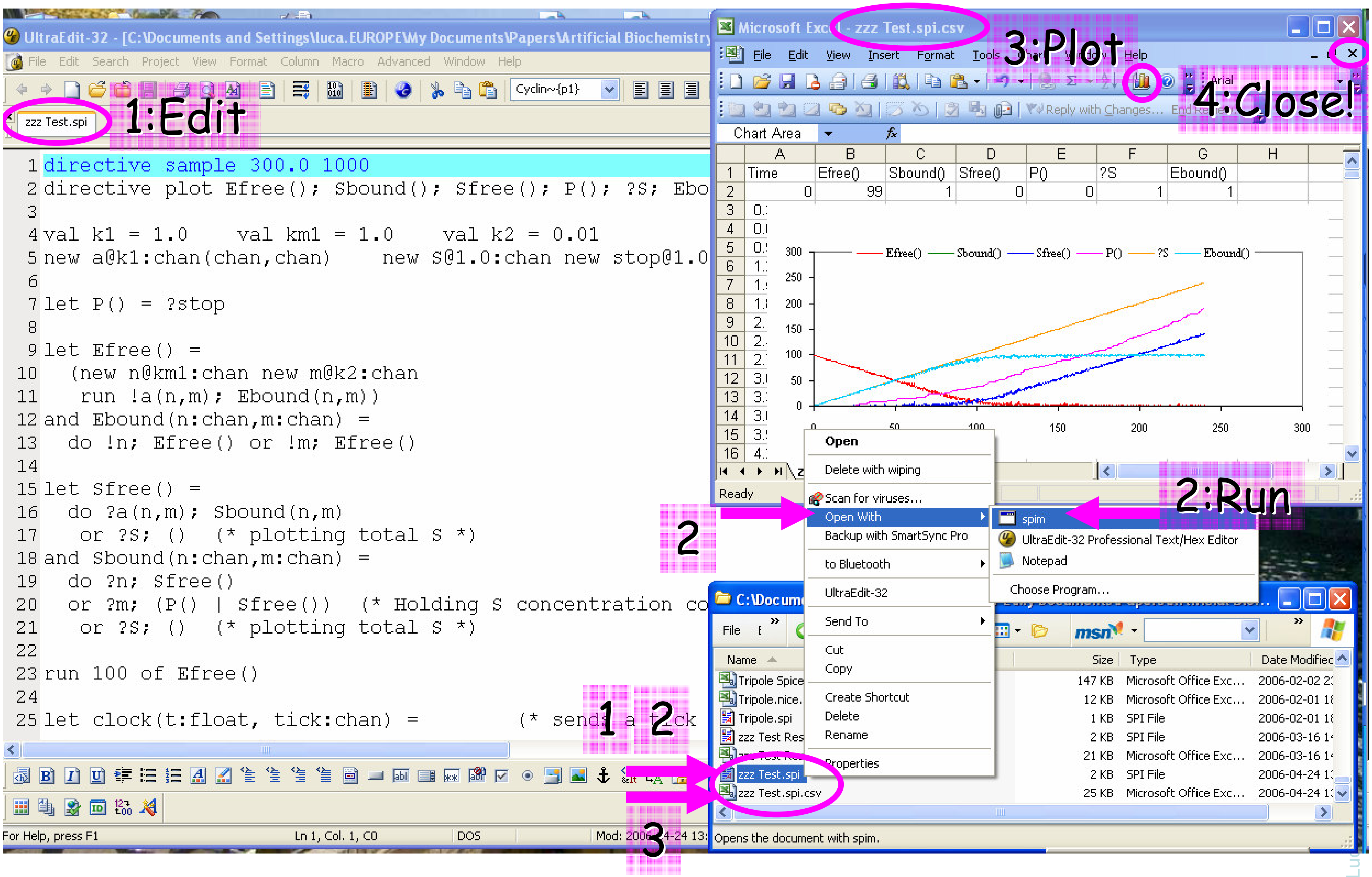
The Stochastic Pi Machine is available in three distribution formats:

- Windows 2000/XP Executable.
- Platform-Independent OCaml Bytecode. (Requires the Objective Caml System 3.08 to be installed)
- Source Code.

Each distribution contains the following elements:

- A single executable file in exe or ocaml format, where applicable.
- A License agreement.
- A short Manual, which includes a basic user guide. [pdf]
- A collection of Examples.

Tools: SPiM Development Cycle



UltraEdit-32 - [C:\Documents and Settings\luca.EUROPE\My Documents\Papers\Artificial Biochemistry
File Edit Search Project View Format Column Macro Advanced Window Help
Cyclin~{p1}
zzz Test.spi
1:Edit

```
directive sample 300.0 1000
directive plot Efree(); Sbound(); Sfree(); P(); ?S; Ebo

val k1 = 1.0    val km1 = 1.0    val k2 = 0.01
new a@k1:chan(chan,chan)    new S@1.0:chan new stop@1.0

let P() = ?stop

let Efree() =
  (new n@km1:chan new m@k2:chan
   run !a(n,m); Ebound(n,m))
and Ebound(n:chan,m:chan) =
  do !n; Efree() or !m; Efree()

let Sfree() =
  do ?a(n,m); Sbound(n,m)
   or ?S; ()  (* plotting total S *)
and Sbound(n:chan,m:chan) =
  do ?n; Sfree()
  or ?m; (P() | Sfree())  (* Holding S concentration co
   or ?S; ()  (* plotting total S *)

run 100 of Efree()

let clock(t:float, tick:chan) =         (* sends a tick
```

For Help, press F1
Ln 1, Col. 1, C0
DOS
Mod: 2006-04-24 13:
Microsoft Excel - zzz Test.spi.csv
File Edit View Insert Format Tools Chart Window Help
3:Plot
4:Close!
Arial
Reply with Changes... End Review...
Chart Area

	A	B	C	D	E	F	G	H
1	Time	Efree()	Sbound()	Sfree()	P()	?S	Ebound()	
2	0	99	1	0	0	1	1	
3	0.:							
4	0.(							
5	0.!							
6	1.:							
7	1.!							
8	1.!							
9	2.							
10	2..							
11	2.'							
12	3.(							
13	3.:							
14	3.(							
15	3.!							
16	4.:							

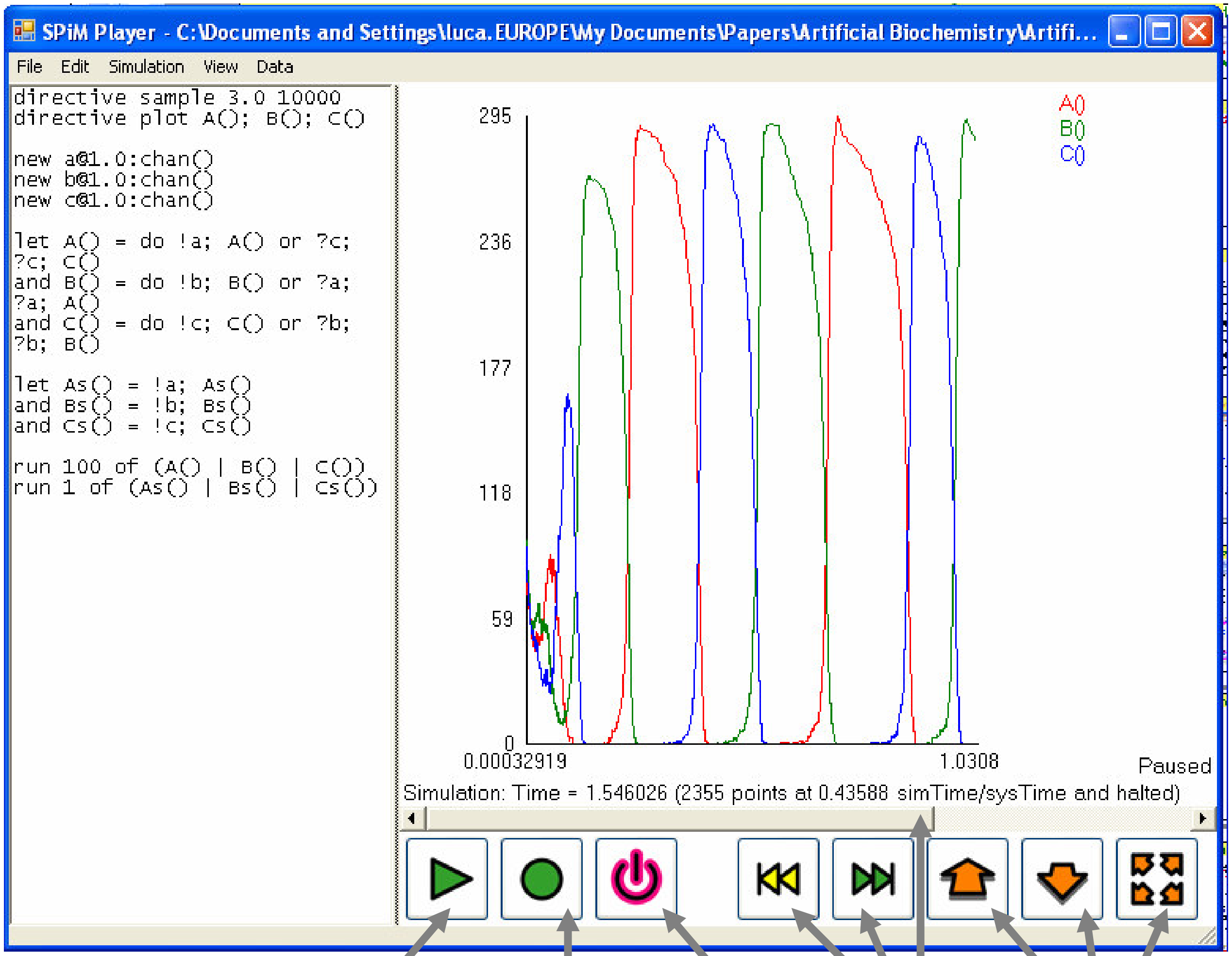
Name	Size	Type	Date Modified
Tripole Spice	147 KB	Microsoft Office Exc...	2006-02-02 2:
Tripole.nice.	12 KB	Microsoft Office Exc...	2006-02-01 1:
Tripole.spi	1 KB	SPI File	2006-02-01 1:
zzz Test Res	2 KB	SPI File	2006-03-16 1:
zzz Test Res	21 KB	Microsoft Office Exc...	2006-03-16 1:
zzz Test.spi	2 KB	SPI File	2006-04-24 1:
zzz Test.spi.csv	25 KB	Microsoft Office Exc...	2006-04-24 1:

Opens the document with spim.

Tools: SPiM Player

Windows binary available on USB stick (ask me).

Requires The 2.0 .NET runtime:
http://msdn.microsoft.com/netframework/downloads/updates/default.aspx


SPiM Player - C:\Documents and Settings\luca.EUROPE\My Documents\Papers\Artificial Biochemistry\Artifi...
File
Edit
Simulation
View
Data
295
236
177
118
59
0
0.00032919
1.0308
A()
B()
C()
Paused

```
directive sample 3.0 10000
directive plot A(); B(); C()

new a@1.0:chan()
new b@1.0:chan()
new c@1.0:chan()

let A() = do !a; A() or ?c;
?c; C()
and B() = do !b; B() or ?a;
?a; A()
and C() = do !c; C() or ?b;
?b; B()

let As() = !a; As()
and Bs() = !b; Bs()
and Cs() = !c; Cs()

run 100 of (A() | B() | C())
run 1 of (As() | Bs() | Cs())
```

Simulation: Time = 1.546026 (2355 points at 0.43588 simTime/sysTime and halted)

Play/ Pause plotting

Stop/ Continue simulation

Restart simulation

Scroll

Zoom

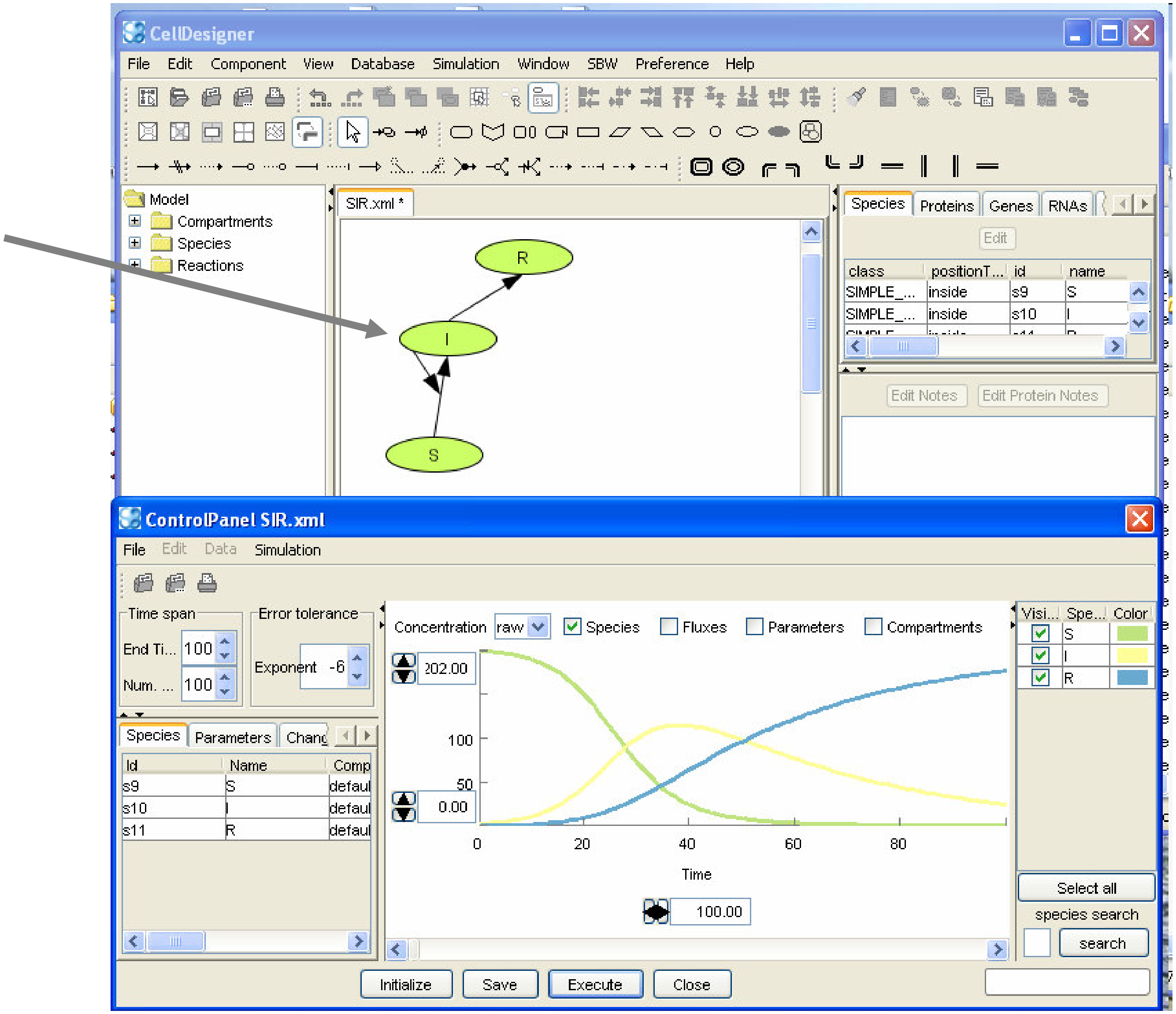
SPiM interactive GUI

```
directive sample 3.0 10000
directive plot A(); B(); C()

new a@1.0:chan()
new b@1.0:chan()
new c@1.0:chan()

let A() = do !a; A() or ?c; ?c; C()
and B() = do !b; B() or ?a; ?a; A()
and C() = do !c; C() or ?b; ?b; B()

let As() = !a; As()
and Bs() = !b; Bs()
and Cs() = !c; Cs()

run 100 of (A() | B() | C())
run 1 of (As() | Bs() | Cs())
```

Tools: CellDesigner

http://celldesigner.org/

This took me 30m to input!



class	positionT...	id	name
SIMPLE_...	inside	s9	S
SIMPLE_...	inside	s10	I

Time span

End Ti... 100

Num. ... 100

Error tolerance

Exponent -6

Concentration raw

☑ Species ☐ Fluxes ☐ Parameters ☐ Compartments

Id	Name	Comp
s9	S	defaul
s10	I	defaul
s11	R	defaul

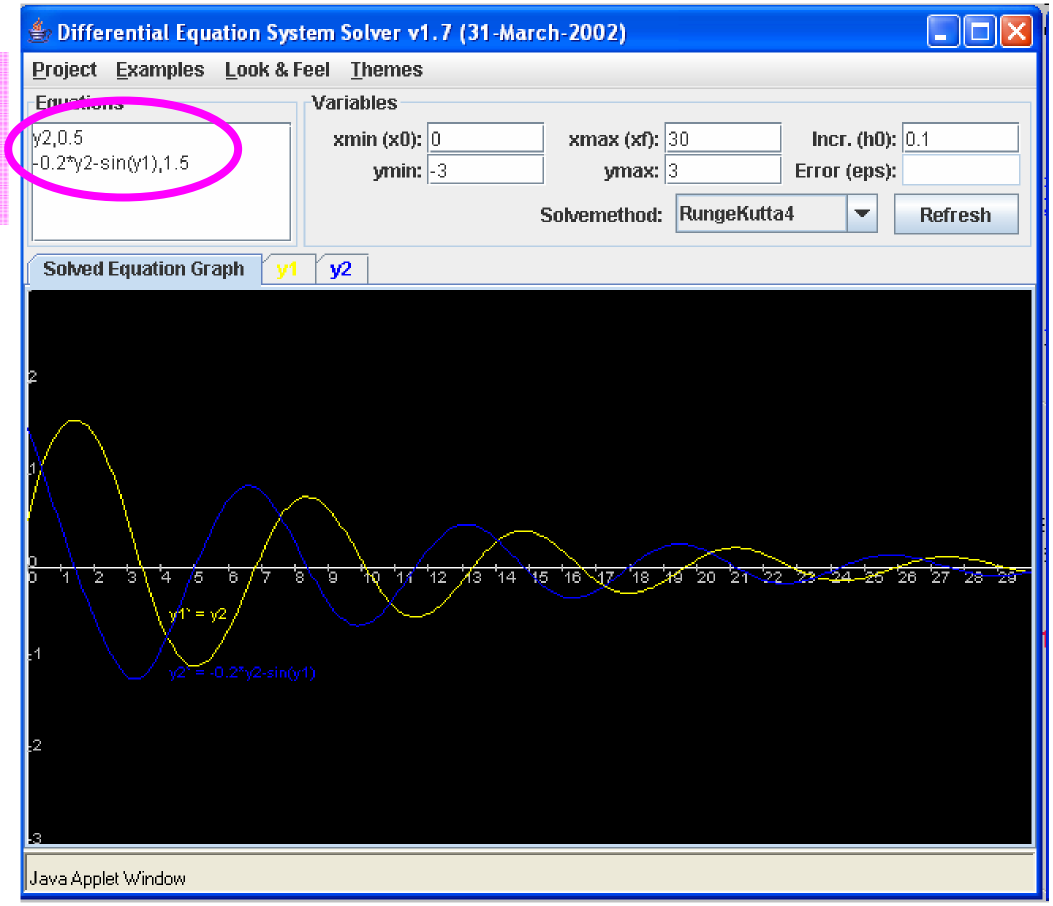
Visi...	Spe...	Color
☑	S	🟩
☑	I	🟨
☑	R	🟦

Tools: DESSolver ODE solver

- Applet or Download:
  - http://www.jens-langner.de/dessolver/
- Great when it works
  - Seems to have editing/refresh problems.

$dy1/dt = y2 \qquad y1_0 = 0.5$

$dy2/dt = -0.2*y2-\sin(y1) \qquad y2_0 = 1.5$



Differential Equation System Solver v1.7 (31-March-2002)

Equations

```
y2,0.5
-0.2*y2-sin(y1),1.5
```

Variables

xmin (x0): 0 xmax (xf): 30 Incr. (h0): 0.1

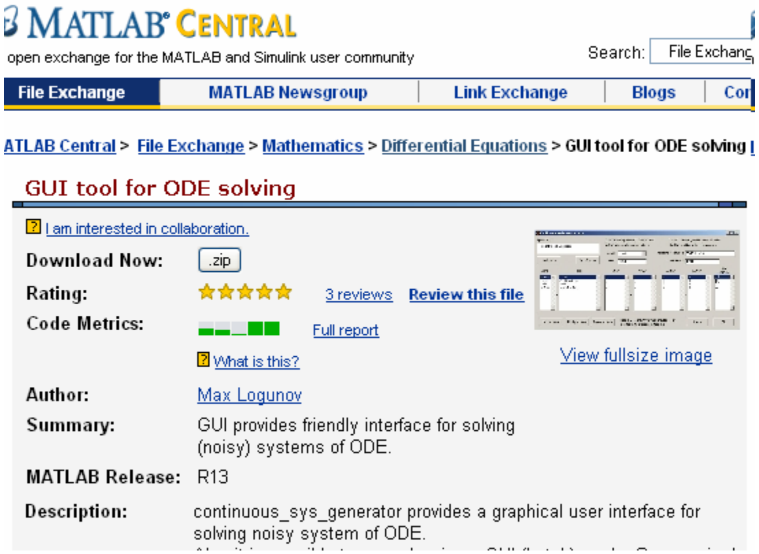
ymin: -3 ymax: 3 Error (eps):

Solvemethod: RungeKutta4

Java Applet Window

Tools: Matlab ODE solver (continuous_sys_generator)

Download: http://www.mathworks.com/matlabcentral/fileexchange/loadFile.do?objectId=6703&objectType=file



MATLAB® CENTRAL

open exchange for the MATLAB and Simulink user community

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ATLAB Central > File Exchange > Mathematics > Differential Equations > GUI tool for ODE solving

GUI tool for ODE solving

? I am interested in collaboration.

Download Now: .zip

Rating: ★★★★★ 3 reviews **Review this file**

Code Metrics: Full report

? What is this?

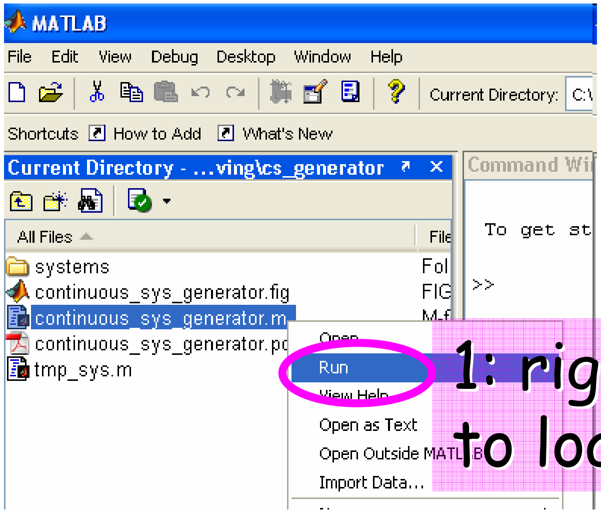
View fullsize image

Author: Max Logunov

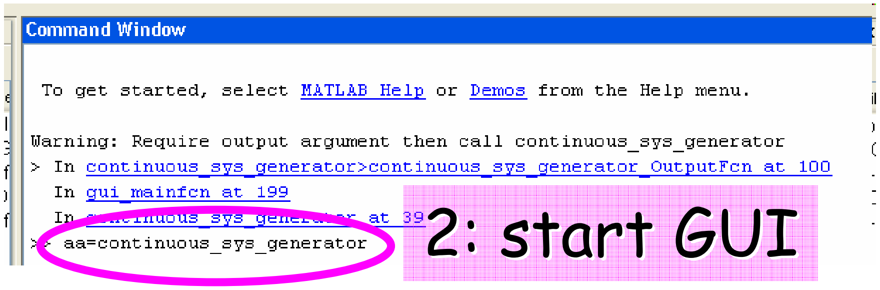
Summary: GUI provides friendly interface for solving (noisy) systems of ODE.

MATLAB Release: R13

Description: continuous_sys_generator provides a graphical user interface for solving noisy system of ODE.


MATLAB
File Edit View Debug Desktop Window Help
Current Directory: C:\
Shortcuts How to Add What's New
Current Directory - ...ving\cs_generator
Command Wi
All Files
File
systems
continuous_sys_generator.fig
continuous_sys_generator.m
continuous_sys_generator.pd
tmp_sys.m
Fol
FIG
M-f
Open
Run
View Help
Open as Text
Open Outside MATLAB
Import Data...
To get st
>>

1: right-click to load package

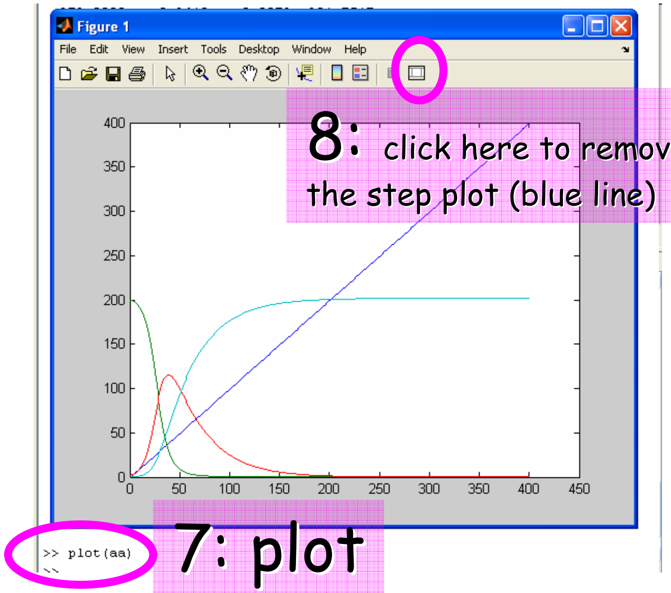


```
Command Window

 To get started, select MATLAB Help or Demos from the Help menu.

Warning: Require output argument then call continuous_sys_generator
> In continuous_sys_generator>continuous_sys_generator_OutputFcn at 100
  In gui_mainfcn at 199
  In continuous_sys_generator at 39
>> aa=continuous_sys_generator
```

2: start GUI

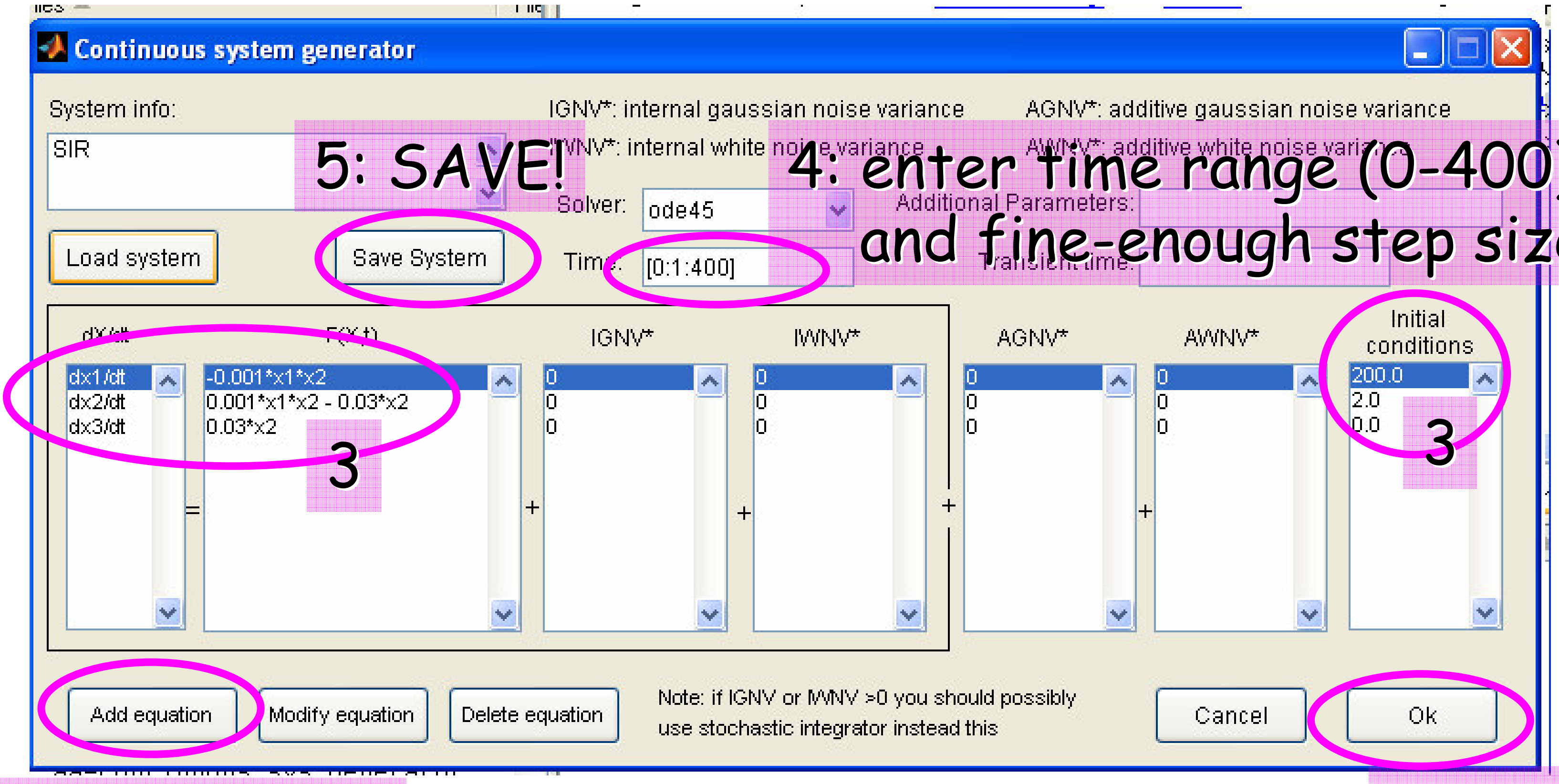


```
>> plot(aa)
>>
```

8: click here to remove the step plot (blue line)

7: plot

Tools: Matlab ODE solver (continuous_sys_generator)



Continuous system generator

System info: SIR

IGNV*: internal gaussian noise variance
IWNV*: internal white noise variance
AGNV*: additive gaussian noise variance
AWNV*: additive white noise variance

Solver: ode45

Additional Parameters:

Time: [0:1:400]

Transient time:

dX/dt	F(X,t)	IGNV*	IWNV*	AGNV*	AWNV*	Initial conditions
dx1/dt	-0.001*x1*x2	0	0	0	0	200.0
dx2/dt	0.001*x1*x2 - 0.03*x2	0	0	0	0	2.0
dx3/dt	0.03*x2	0	0	0	0	0.0

Note: if IGNV or IWNV >0 you should possibly use stochastic integrator instead this

5: SAVE!

4: enter time range (0-400) and fine-enough step size (1)

3: enter ODEs

6: run

Methods: Reactive Systems

- Reactive Systems. A generic term for the mathematical study of:

  Entities that react to their environment and to each other.

- Particularly as distinguished from mathematical (I/O) functions

  A reactive system "computes", but does not compute a function:
  it computes reactions to stimuli,
  and produces stimuli for further reactions.

- And as distinguished from mathematical (passive) objects

  A reactive system is normally the composition of subsystems
  each reactive and each forming the other subsystem's environment.

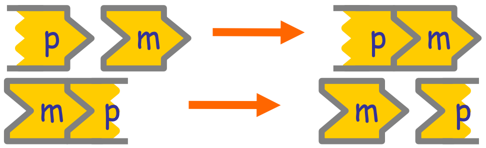
- A (still mathematical) answer to questions like:
  - What does the internet compute?
  - What does a bacterium compute?

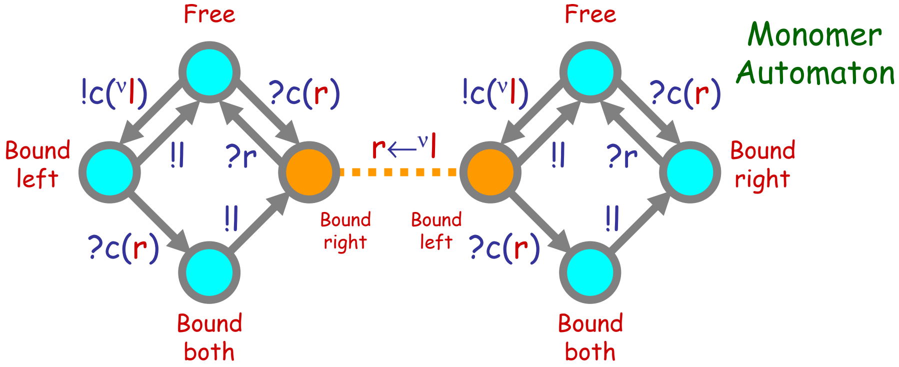
N.B.: "reactive system" is a popular term, and sometimes defined more narrowly.

Methods: Why π-calculus, in particular

- Well studied, compact, precise, and general
  - A “programming language” first, a mathematical model second
  - Syntax (configurations): $P ::= 0 \mid P+P \mid P|P \mid ?n(n).P \mid !n(n).P \mid (\nu n)P \mid *P$
  - Semantics (reactions): $(P' + !n(m).P) \mid (Q' + ?n(m').Q) \rightarrow P \mid Q\{m' \leftarrow m\}$
- Binary interactions
  - Chemistry is based on binary “collisions”.
- Reactive and compositional
  - Each subsystem is a separate (composition of) automata interacting with the environment (more automata)
- Dynamic network evolution and species evolution
  - Each subsystem can create fresh connections or spawn new subsystems
- Compact description of combinatorics (like any programming language)
  - $(\mathrm{Bit}_1 \mid \mathrm{Bit}_2 \mid \ldots \mid \mathrm{Bit}_n)$ where Bit is a 2-state subsystem
    - A system with 2^n configurations (i.e. “different chemical species”)
- Complexation/polymerization
  - The most characteristic feature of π-calculus (fresh names) models “sticking”

Actin-like
Poly/depolymerization





Basic References

Biology

[MCB] Molecular Cell Biology, Freeman.

[MBC] Molecular Biology of the Cell, Garland.

[Ptashne] A Genetic Switch.

[Davidson] Genomic Regulatory Systems.

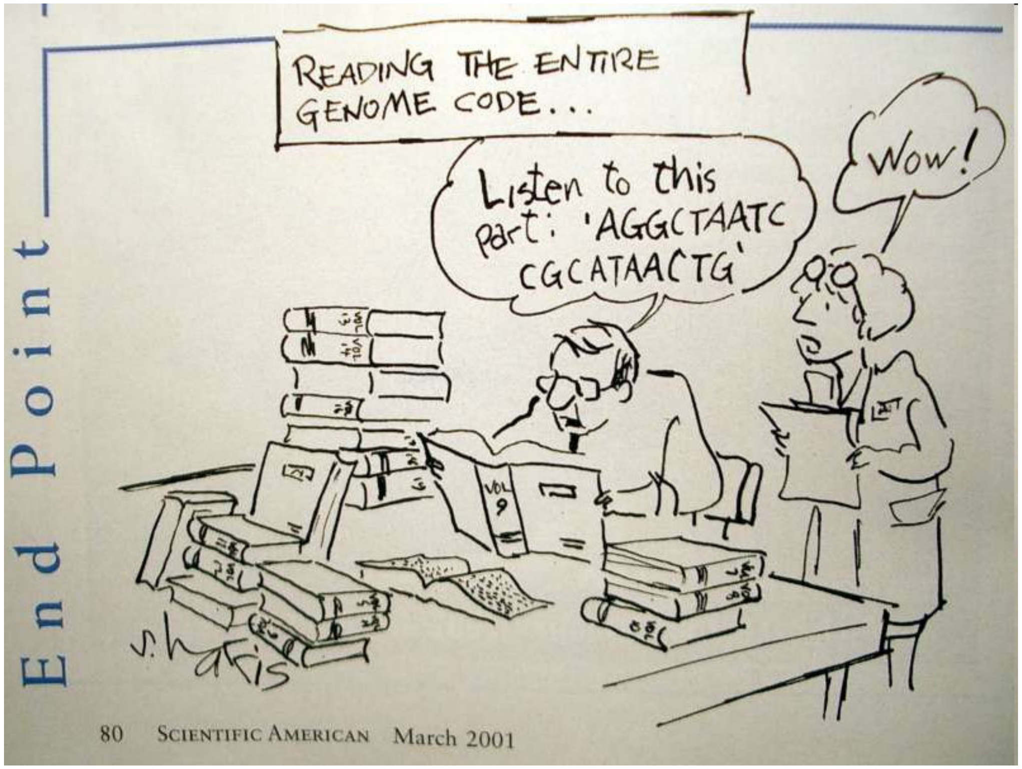
Computing

[Milner] Communicating and Mobile Systems: the Pi-Calculus.

[Regev] Computational Systems Biology: A Calculus for Biomolecular Knowledge (Ph.D. Thesis).

www.luca.demon.co.uk/BioComputing.htm

End Point


End Point
READING THE ENTIRE GENOME CODE...
Listen to this part: 'AGGCTAATC CGCATAACTG'
Wow!
VOL 9
S. Harris
80 SCIENTIFIC AMERICAN March 2001

Q: "The data are accumulating and the computers are humming, what we are lacking are the words, the grammar and the syntax of a new language..."

D. Bray (TIBS 22(9):325-326, 1997)

A: "The most advanced tools for computer process description seem to be also the best tools for the description of biomolecular systems."

E.Shapiro (Lecture Notes)

Q?