BioSimWare: A P Systems-based Simulation Environment for Biological Systems

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Outline

1 BioSimWare

- Stochastic Simulations Algorithms for Single and Multi-Volume Systems
 - Tools for The Analysis of Stochastic Simulations
 - Parameter Estimation (PE)
 - Parameter sweep applications (PSA)



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Applications

- The Schlögl System
- The Brussellator
- Stiff Systems
- Bacterial Chemotaxis
- Simulation of Fredkin Circuits by Chemical Reaction Systems



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5 Conclusion

Introduction

BioSimWare is a simulation environment based on P systems, that provides a user-friendly framework for the modeling of biological systems ranging from cellular processes to population phenomena.



User Interface: rules specification

| * | BioSimWare: Ras-cAMP-PKA pathway | |
|---|----------------------------------|----------------------|
| le Simulation Help | | |
| | | |
| | | |
| Rules Conditions Output | | |
| | | |
| | Ras-cAMP-PKA | pathway |
| 39 Reactions | Constants | 33 Molecular Species |
| 55 Reactions | constants | b a see |
| 1 Ras2_GDP+Cdc25->Ras2_GDP_Cdc25 | 1.000E00 | 1 Rasz GDP |
| 2 Ras2 GDP Cdc25-9Ras2 GDP+Cdc25 | 1.500500 | 2 Par2 GDB Cdc25 |
| 4 Ras2 Cdc25+ GDR >Ras2 GDR Cdc25 | 1.000500 | 4 Bas2 Cdc25 |
| 5 Bas2 Cdc25+GTP->Bas2 GTP Cdc25 | 1.000E00 | 5 GDP |
| 6 Ras2 GTP Cdc25->Ras2 Cdc25+GTP | 1,000E00 | 6 GTP |
| 7 Ras2 GTP Cdc25->Cdc25+Ras2 GTP | 1,000E00 | 7 Ras2 GTP Cdc25 |
| 8 Cdc25+Ras2 GTP+>Ras2 GTP Cdc25 | 1.000E00 | 8 Ras2_GTP |
| 9 Ras2_GTP+Ira2->Ras2_GTP_Ira2 | 3.000E-02 | 9 Ira2 |
| 10 Ras2 GTP_Ira2->Ras2 GDP+Ira2 | 7.000E-01 | 10 Ras2_GTP_Ira2 |
| 11 Ras2_GTP+CYR1->Ras2_GTP_CYR1 | 1.000E-03 | 11 CYR1 |
| 12 Ras2_GTP_CYR1+ATP->Ras2_GTP_CYR1+cAMP | 2.100E-06 | 12 Ras2_GTP_CYRL |
| 13 Ira2+Ras2_GTP_CYR1->Ras2_GDP+Ira2+CYR1 | 1.000E-03 | 13 ATP |
| 14 CAMP+PKA->CAMP_PKA | 1.0000-05 | 14 Guille |
| 15 CAMP+CAMP_PKA->2CAMP_PKA | 1.000E-05 | 16 CAMP DVA |
| 17 CAMP+2CAMP_PAA->3CAMP_PAA | 1.0005-05 | 17 2camp pka |
| 18 dramp PKA-SCAMP+ 3CAMP PKA | 1.000E+01 | 18 3CAMP PKA |
| 19 3CAMP PKA->CAMP+2CAMP PKA | 1.000E-01 | 19 4CAMP PKA |
| 20 2CAMP PKA->CAMP+CAMP PKA | 1.000E-01 | 20 C |
| 21 CAMP PKA->CAMP+PKA | 1.000E-01 | 21 R_2cAMP |
| 22 4cAMP_PKA->2*C+2*R_2cAMP | 1.000E00 | 22 R |
| 23 R_2cAMP+>2*cAMP+R | 1.000E00 | 23 R_C |
| 24 C+R->R_C | 7.500E-01 | 24 Pde1 |
| 25 2'R_C->PKA | 1.000E00 | 2 Pdelt |
| 26 C+Pde1->C+Pde1t | 1.000E-06 | 26 GAMP Pdelf |
| 27 CAMP+PGell->CAMP_PGell | 1.000E-01 | 28 0042 |
| 20 cAMD_Ddolf >Ddolf AMD | 7.500600 | 29 Pde2 |
| 30 Ddo1f+DDA2->Ddo1+DDA2 | 1.000E+04 | 30 cAMP Pde2 |
| 31 cAMP+Pde2->cAMP Pde2 | 1.000E-04 | 31. Cdc25f |
| 32 cAMP Pde2->cAMP+Pde2 | 1.000E00 | 32 Ira2P |
| 33 cAMP_Pde2->AMP+Pde2 | 1.700E00 | 33 Ras2_GTP_Ira2P |
| 34 Cdc25+C+>C+Cdc25f | 1.000E00 | |
| 35 PPA2+Cdc25f->Cdc25+PPA2 | 1.000E-02 | |
| 36 lra2+C->C+Ira2P | 0.000E00 | |
| 37 Ras2_GTP+Ira2P->Ras2_GTP_Ira2P | ■ 0.000E00 | |
| 0 | | |
| Insert | Delete | |
| | | |

User Interface: system conditions specification

| Å | BioSimWare: Ras-cAMP-Pi | KA pathway | - <u> </u> |
|-------------------------|-------------------------|------------|------------|
| File Simulation Help | | | |
| 🗅 🚅 🖩 🕨 | | | |
| Rules Conditions Output | t | | |
| | Ras-cAMP-PKA | A pathway | |
| select all | | | |
| Output Ind | Molecular Species | Amounts | Feed |
| | Ras2_GDP | 1.932E04 | - |
| | Cdc25 | 0.000E00 | |
| | Ras2_GDP_Cdc25 | 1.760E02 | |
| | Ras2_Cdc25 | 0.000E00 | |
| | GDP | 1.500E06 | × |
| | GTP | 4.784E06 | |
| | Ras2_GTP_Cdc25 | 1.230E02 | |
| | Ras2_GTP | 2.000E01 | |
| | Ira2 | 0.000E00 | |
| | Ras2_GTP_Ira2 | 0.000E00 | |
| | CYRL | 1.000E00 | |
| | Ras2_GTP_CYR1 | 1.990E02 | |
| | ATP | 2.400E07 | × |
| × | cAMP | 3.962E04 | |
| | PKA | 5.450E02 | |
| | cAMP_PKA | 5.140E92 | |
| | 2cAMP_PKA | 5.910E02 | |
| | 3cAMP_PKA | 4.950E02 | |
| | 4cAMP_PKA | 1.650E02 | |
| | c | 3.540E02 | |
| | R_2cAMP | 3.520E02 | |
| | R | 2.000E00 | |
| | R_C | 2.600E01 | |
| | Pdel | 9.380202 | |
| | Pdelf | 2.000E00 | |
| | cAMP_Pde1f | 4.600E02 | |

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User Interface: plot of the dynamics



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5 Conclusion

Available simualtion algorithm

Single Volume

- SSA
- tau leaping
- adaptive tau leaping
- average tau leaping dynamics

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ODE integrator

Multi Volume

- DPP
- tau-DPP
- Stau-DPP

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5 Conclusion

PE: the goal

We would like to reproduce the target dynamics via stochastic simulations:



not necessarily using the same set of constants.

PE: the problem

Quantify the "distance" among the dynamics and find the closest one



The fitness: Standard Distance



The fitness: tricks

Facts related to intrinsic noise that should not be neglected:

- each outcome *j* is quantitatively different $\{X(\tau_i)\}_i$
 - not evenly sampled $\{\tau_i\}_i$
 - not same number of points
 - $\{ \neq X(\tau_i) \}_j$
- in the thermodynamic limit $\{X(\tau_i)\} \rightarrow [X](t_i)$
 - exploit ensemble behavior (may flatten oscillations, not in phase outcome)

•
$$\langle F(X(\tau_i)) \rangle \stackrel{?}{=} F(\langle X(\tau_i) \rangle)$$

 same parameters, possibly (almost always), generate different values of the fitness function ("weak convergence")

The fitness: "Area" distance



Reconstructed dynamics



Parameter sweep applications (PSA)

A PSA consists in a repeated execution of an application (usually performed a large number of times), where each execution is achieved using a different parametrisation. In the context of biochemical stochastic models a PSA could be viewed as PSA = (P; D; M), where

- $P = (p_1; ...; p_n)$ is the set of parametrisations with $p_i = (x_0^i; c^i)$
- $D = (d_1; ...; d_n)$ $d_i = (x_i(0); ...; x_i(t))$ where t is the halting time of the simulation *i*
- *M* is the biochemical model that provides the map $p_i \rightarrow d_i$

PSA: EGEE Grid



EGEE project infrastructure, a wide area grid platform for scientific applications, composed of thousands of CPUs, which implements the Virtual Organisation (VO) paradigm.

- More than 90 partners in 32 countries, organised in 13 Federations
- A Grid infrastructure spanning almost 240 sites across 45 countries
- An infrastructure of 41,000 CPU available to users 24 hours a day, 7 days a week
- More than 5 Petabytes (5 million Gigabytes) of storage
- Sustained and regular workloads of 30K jobs/day, reaching up to 98K jobs/day

Perturbed parameters fitness







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The Schlögl System

$$r_{1}: A + 2X \xrightarrow{3 \cdot 10^{-7}} 3X$$

$$r_{2}: 3X \xrightarrow{10^{-4}} A + 2X$$

$$r_{3}: B \xrightarrow{10^{-3}} 3X$$

$$r_{4}: X \xrightarrow{3.5} B$$

$$A = 1 \cdot 10^5$$
 $B = 2 \cdot 10^5$ $X = 250$







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The Brusselator

$$r_{1} : A \xrightarrow{1} X$$

$$r_{2} : B + X \xrightarrow{5 \cdot 10^{-3}} Y$$

$$r_{3} : 2X + Y \xrightarrow{2 \cdot 5 \cdot 10^{-5}} 3X$$

$$r_{4} : X \xrightarrow{1 \cdot 5} \lambda$$

A = X = 200 B = 600 Y = 300







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Comparison GA & PSO: Oscillating Brusselator



Comparison GA & PSO: Damped Brusselator



Stiff systems: an example

A system is said to be stiff if is characterized by well-separeted fast and slow dynamical modes, the fastest of which is stable.

The decaying dimerization model:

$$r_{1}: S_{1} \xrightarrow{1} \lambda$$

$$r_{2}: S_{1} + S_{1} \xrightarrow{10} S_{2}$$

$$r_{3}: S_{2} \xrightarrow{10^{3}} S_{1} + S_{1}$$

$$r_{4}: S_{2} \xrightarrow{0.1} S_{3}$$

$$S_1 = 10^4 \, \, S_2 = S_3 = 0$$

| | SSA | tau leaping | adaptive tau leaping |
|-------------------------|------------------------|---------------------|----------------------|
| average number of steps | 2.46 · 10 ⁷ | 1 · 10 ⁶ | 945 |
| total execution time | 175h 1m | 11h 47m | 1m 51s |

Decaying dimerization: algorithms comparison



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Bacterial chemotaxis

Chemotaxis allows bacteria to respond to ligand concentration gradients in their surroundings:

- random walk through an homogeneous environment \rightarrow high switching frequency of flagellar rotation
- directional swimming in presence of ligand concentration gradient → reduced switching frequency of flagellar rotation
- adaptation: if ligand concentration remains constant → switching frequency is reset to random walk level





Sensing Responding Adapting

| | Reagents | Products | Methyl. state |
|-------|---|---|--------------------|
| 1 | 2MCP ^m + 2CheW | 2MCP ^m ::2CheW | <i>m</i> = 0 |
| 2 | 2MCP ^m ::2CheW | 2MCP ^m + 2CheW | <i>m</i> = 0 |
| 3 | 2MCP ^m ::2CheW + 2CheA | 2MCP ^m ::2CheW::2CheA | <i>m</i> = 0 |
| 4 | 2MCP ^m ::2CheW::2CheA | 2MCP ^m ::2CheW + 2CheA | <i>m</i> = 0 |
| 5-8 | 2MCP m ::2CheW::2CheA + CheR | 2MCP ^{m+1} ::2CheW::2CheA + CheR | $m = 0, \ldots, 3$ |
| 9-12 | 2MCP ^m ::2CheW::2CheA + CheBp | 2MCP ^{m-1} ::2CheW::2CheA + CheBp | m = 1,, 4 |
| 13-17 | 2MCP ^m ::2CheW::2CheA + ATP | 2MCP ^m ::2CheW::2CheAp | $m = 0, \ldots, 4$ |
| 18-22 | 2MCP ^m ::2CheW::2CheAp + CheY | 2MCP ^m ::2CheW::2CheA + CheYp | $m = 0, \ldots, 4$ |
| 23-27 | 2MCP ^m ::2CheW::2CheAp + CheB | 2MCP ^m ::2CheW::2CheA + CheBp | $m = 0, \ldots, 4$ |
| 28-32 | lig + 2MCP ^m ::2CheW::2CheA | lig::2MCP ^m ::2CheW::2CheA | $m = 0, \ldots, 4$ |
| 33-37 | lig::2MCP ^m ::2CheW::2CheA | lig + 2MCP ^m ::2CheW::2CheA | $m = 0, \ldots, 4$ |
| 38-41 | lig::2MCP ^m ::2CheW::2CheA + CheR | lig::2MCP ^{m+1} ::2CheW::2CheA + CheR | $m = 0, \ldots, 3$ |
| 42-45 | lig::2MCP ^m ::2CheW::2CheA + CheBp | lig::2MCP ^{m-1} ::2CheW::2CheA + CheBp | $m = 1, \ldots, 4$ |
| 46-50 | lig::2MCP ^m ::2CheW::2CheA + ATP | lig::2MCP ^m ::2CheW::2CheAp | $m = 0, \cdots, 4$ |
| 51-55 | lig::2MCP ^m ::2CheW::2CheAp + CheY | lig::2MCP ^m ::2CheW::2CheA + CheYp | $m = 0, \ldots, 4$ |
| 56-60 | lig::2MCP ^m ::2CheW::2CheAp + CheB | lig::2MCP ^m ::2CheW::2CheA + CheBp | $m = 0, \ldots, 4$ |
| 61 | CheYp + CheZ | CheY + CheZ | |
| 62 | CheBp | CheB | |

62 reactions, 32 molecular species

Sensing Responding Adapting



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CheYp and the flagellar rotation

Our assumptions:

- the flagellar motor switch is sensitive to a threshold level of CheYp, that is hereby evaluated as the mean value of CheYp at steady state
- we make a one-to-one correspondence between the behavior of a single flagellum and one temporal evolution of CheYp generated by one run of the tau leaping algorithm.

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Many flagella and running or tumbling

$$\mathcal{T}_{\mathsf{sync}}^{\mathsf{n}} = \{t \in \Delta t_{sim} \mid \mathsf{CCW}_{s_i}(t) = true \text{ for all } i = 1, \dots, n\}$$

 \mathcal{T}_{sync}^{n} is the set of all times during which *all* time series s_{i} are below the threshold μ



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That corresponds to the running motion of the bacterium

Many flagella and running or tumbling



Running

 $<\Delta t_{run}>$

all flagella rotate CCW

Tumbling

 $<\Delta t_{\textit{tumb}}>$ some flagella rotate CW

Adapting

$$<\Delta t_{a dapt}>$$

length of the negative peak

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Fredkin Gate: definition





| Reacti | on | Constant |
|-------------------------|---------------------------------------|----------------------------|
| <i>r</i> ₁ : | a + b ightarrow a + d | $c_1 = 1 \cdot 10^{-3}$ |
| r ₂ : | $a + c \rightarrow a + e$ | $c_2 = 1 \cdot 10^{-3}$ |
| <i>r</i> 3 : | $a + B \rightarrow a + D$ | $c_3 = 1 \cdot 10^{-3}$ |
| <i>r</i> ₄ : | $a + C \rightarrow a + E$ | $c_4 = 1 \cdot 10^{-3}$ |
| <i>r</i> ₅ : | A+b ightarrow A' | $c_5 = 1 \cdot 10^{-3}$ |
| r ₆ : | A' + c ightarrow A + d + e | $c_6 = 1 \cdot 10^{-1}$ |
| r ₇ : | A'+C ightarrow A+D+e | $c_7 = 1 \cdot 10^{-1}$ |
| r ₈ : | $A + B \rightarrow A^{\prime\prime}$ | $c_8 = 1 \cdot 10^{-3}$ |
| r ₉ : | $A^{\prime\prime}+c ightarrow A+d+E$ | $c_9 = 1 \cdot 10^{-1}$ |
| r ₁₀ : | $A^{\prime\prime}+C ightarrow A+D+E$ | $c_{10} = 1 \cdot 10^{-1}$ |

| $\alpha_i \beta_i \gamma_i$ | \mapsto | $\alpha_o \beta_o \gamma_o$ |
|-----------------------------|-----------|-----------------------------|
| 000 | | 000 |
| 001 | | 001 |
| 010 | | 010 |
| 011 | | 011 |
| 100 | | 100 |
| 101 | | 110 |
| 110 | | 101 |
| 111 | | 111 |

| React | ion | Constant |
|-------------------|-----------------------------|---------------------------------|
| r ₁₁ : | $a + A ightarrow \lambda$ | $c_{11} = 1 \cdot 10^{-1}$ |
| r ₁₂ : | $b + B ightarrow \lambda$ | $c_{12} = 1 \cdot 10^{-1}$ |
| r ₁₃ : | $c+C ightarrow \lambda$ | $c_{13} = 1 \cdot 10^{-1}$ |
| r ₁₄ : | $d + D \rightarrow \lambda$ | $c_{14} = 1 \cdot 10^{-1}$ |
| r ₁₅ : | $e + E ightarrow \lambda$ | $c_{15} = 1 \cdot 10^{-1}$ |
| r ₁₆ : | $\lambda \rightarrow a$ | $c_{16} \in \{0, 1\}$ |
| r ₁₇ : | $\lambda \rightarrow A$ | $c_{17} \in \{0, 1\}$ |
| r ₁₈ : | $\lambda \rightarrow b$ | <i>c</i> ₁₈ ∈ {0, 1} |
| r ₁₉ : | $\lambda \rightarrow B$ | <i>c</i> ₁₉ ∈ {0, 1} |
| r ₂₀ : | $\lambda \rightarrow c$ | $c_{20} \in \{0,1\}$ |
| r ₂₁ : | $\lambda \rightarrow C$ | $c_{21} \in \{0, 1\}$ |

Fredkin Gate: definition





| Reacti | on | Constant |
|-------------------------|---------------------------------------|----------------------------|
| <i>r</i> ₁ : | a + b ightarrow a + d | $c_1 = 1 \cdot 10^{-3}$ |
| r ₂ : | a + c ightarrow a + e | $c_2 = 1 \cdot 10^{-3}$ |
| r3 : | $a + B \rightarrow a + D$ | $c_3 = 1 \cdot 10^{-3}$ |
| <i>r</i> ₄ : | $a + C \rightarrow a + E$ | $c_4 = 1 \cdot 10^{-3}$ |
| <i>r</i> ₅ : | A+b ightarrow A' | $c_5 = 1 \cdot 10^{-3}$ |
| r ₆ : | A' + c ightarrow A + d + e | $c_6 = 1 \cdot 10^{-1}$ |
| r ₇ : | A'+C ightarrow A+D+e | $c_7 = 1 \cdot 10^{-1}$ |
| r ₈ : | $A + B \rightarrow A^{\prime\prime}$ | $c_8 = 1 \cdot 10^{-3}$ |
| r ₉ : | $A^{\prime\prime}+c ightarrow A+d+E$ | $c_9 = 1 \cdot 10^{-1}$ |
| r ₁₀ : | $A^{\prime\prime}+C ightarrow A+D+E$ | $c_{10} = 1 \cdot 10^{-1}$ |

| $\alpha_i \beta_i \gamma_i$ | \mapsto | $\alpha_o \beta_o \gamma_o$ |
|-----------------------------|-----------|-----------------------------|
| abc | | ade |
| abC | | a d E |
| aBc | | аDе |
| a B C | | a D E |
| Abc | | Ade |
| AbC | | A D e |
| ABC | | AdE |
| ABC | | ADE |

| Reacti | on | Constant |
|-------------------|----------------------------|---------------------------------|
| r ₁₁ : | $a + A ightarrow \lambda$ | $c_{11} = 1 \cdot 10^{-1}$ |
| r ₁₂ : | $b + B ightarrow \lambda$ | $c_{12} = 1 \cdot 10^{-1}$ |
| r ₁₃ : | $c+C ightarrow \lambda$ | $c_{13} = 1 \cdot 10^{-1}$ |
| r ₁₄ : | $d + D ightarrow \lambda$ | $c_{14} = 1 \cdot 10^{-1}$ |
| r ₁₅ : | $e + E ightarrow \lambda$ | $c_{15} = 1 \cdot 10^{-1}$ |
| r ₁₆ : | $\lambda \rightarrow a$ | <i>c</i> ₁₆ ∈ {0, 1} |
| r ₁₇ : | $\lambda \rightarrow A$ | $c_{17} \in \{0, 1\}$ |
| r ₁₈ : | $\lambda \rightarrow b$ | <i>c</i> ₁₈ ∈ {0, 1} |
| r ₁₉ : | $\lambda \rightarrow B$ | $c_{19} \in \{0,1\}$ |
| r ₂₀ : | $\lambda \rightarrow c$ | $c_{20} \in \{0, 1\}$ |
| r ₂₁ : | $\lambda \rightarrow C$ | $c_{21} \in \{0, 1\}$ |

Fredkin Gate: simulations



First input $(\alpha_i, \beta_i, \gamma_i) = (0, 0, 1)$ at t = 0Second input $(\alpha_i, \beta_i, \gamma_i) = (0, 1, 1)$ at t = 500

 $\begin{array}{c} a \ b \ C \rightarrow a \ d \ E \\ a \ B \ C \rightarrow a \ D \ E \end{array}$

First input $(\alpha_i, \beta_i, \gamma_i) = (0, 0, 1)$ at t = 0Second input $(\alpha_i, \beta_i, \gamma_i) = (1, 0, 1)$ at t = 400

 $a b C \rightarrow a d E$ $A b C \rightarrow A D e$

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Fredkin Circuits







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Outline

BioSimWare

- 2 Stochastic Simulations Algorithms for Single and Multi-Volume Systems
- 3 Tools for The Analysis of Stochastic Simulations
 - Parameter Estimation (PE)
 - Parameter sweep applications (PSA)

Applications

- The Schlögl System
- The Brussellator
- Stiff Systems
- Bacterial Chemotaxis
- Simulation of Fredkin Circuits by Chemical Reaction Systems



Summary

BioSimWare is a simulation environments for the investigation of various biological systems that can range from cellular processes to population phenomena and to ecological systems.

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Features

- Single/Multi volume simulations (stochastic and deterministic)
- Parameter Estimation (HC, GA, PSO)
- Parameter Sweep
- Analysis of the dynamics

Implementations

- Linux, Windows, Mac OS
- Single Processor, MPI, GRID
- SBML