Stochastic Process Algebras and Ordinary Differential Equations Salad

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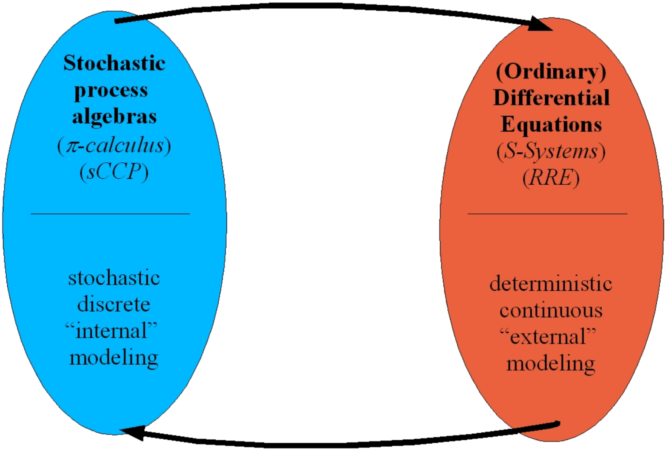
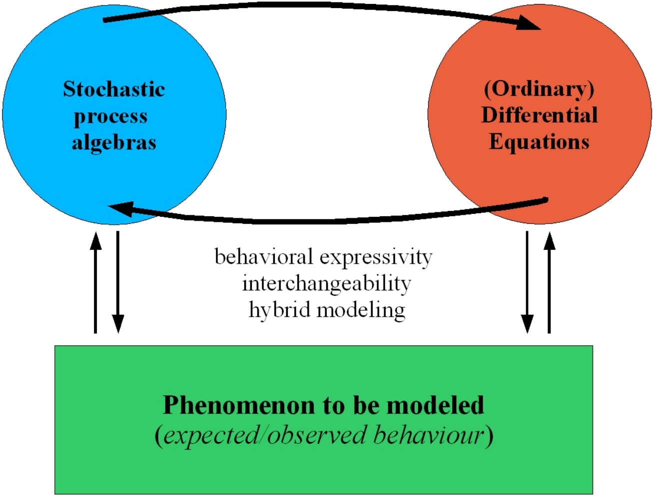
The picture


Stochastic process algebras
(π-calculus)
(sCCP)
stochastic discrete "internal" modeling
(Ordinary) Differential Equations
(S-Systems)
(RRE)
deterministic continuous "external" modeling

A more detailed picture



Outline

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Mass Action Equations

Chemical Equations

Chemical reactions can be represented by a set of chemical equations of the form:

$$R_1 + \ldots + R_n \to_k P_1 + \ldots + P_m,$$

where

- R_i's are the reactants;
- P_j's are the products;
- k is the basic rate (speed).

Mass Action Equations

Chemical equations can be converted into a set of differential equations with the format
$\dot{X}_i = \sum_{j=1}^{n_i} k_j X_{j_1} \cdots X_{j_{h_j}} - \sum_{l=1}^{m_i} k_j X_{l_1} \cdots X_{l_{h_l}}$.

Example

$$A + B \to_k 2C$$

$$\dot{[A]} = \dot{[B]} = -k[A][B]$$
$$\dot{[C]} = 2k[A][B]$$

S-Systems

S-systems describe the dynamical behavior of a biological system by a set of differential equations over reactants

- non-linear, time-invariant, DAE systems;
- biologically plausible and expressive;
- analytical approximation power.

Definition

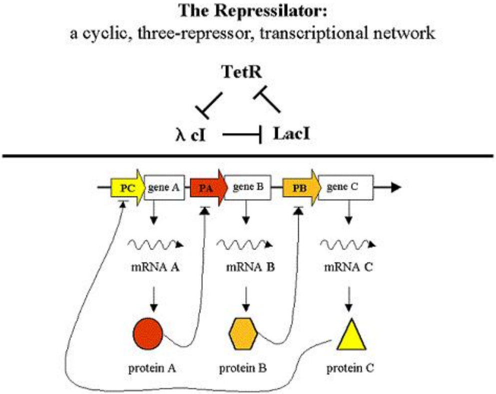
An S-system's equation has the form:

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}$$

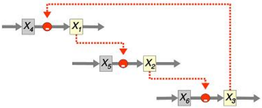
with $\alpha_i, \beta_i \geq 0$ called *rate constants* and g_{ij}, h_{ij} called *kinetic orders*.

- E. O. Voit. Computational Analysis of Biochemical Systems A Practical Guide for Biochemists and Molecular Biologists. Cambridge University Press, 2000.

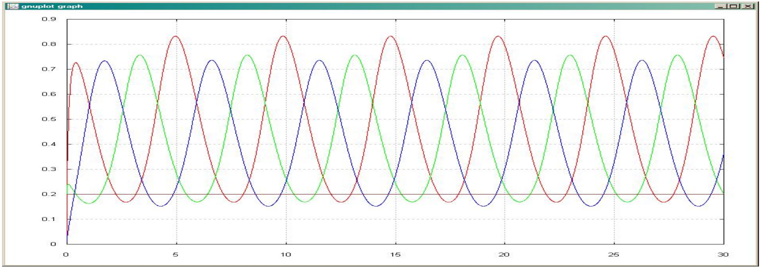
A paradigmatic example — the Repressilator



S-Systems — the Repressilator equations



$$
\begin{aligned}
\dot{X}_1 &= \alpha_1 X_3^{-1} - X_1^{0.5}, & \alpha_1 &= 0.2,\\
\dot{X}_2 &= \alpha_2 X_1^{-1} - X_2^{0.578151}, & \alpha_2 &= 0.2,\\
\dot{X}_3 &= \alpha_3 X_2^{-1} - X_3^{0.5}, & \alpha_3 &= 0.2.
\end{aligned}
$$



Biology and π-calculus

A (restricted) syntax of π-calculus

$$
\begin{array}{llll}
P, Q ::= & \Sigma & \text{Summation} & \Sigma ::= \mathbf{0} & \text{Null} \\
& \mid P|Q & \text{Parallel} & \quad \mid \pi.P + \Sigma & \text{Action} \\
& \mid !\pi.P & \text{Repication} & \pi ::= x\langle n\rangle & \text{Output} \\
& & & \quad \mid x(m) & \text{Input}, x \neq m
\end{array}
$$

Quantitative aspect: interaction "*rates*" assigned to channels.

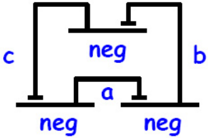
C.Priami. *The stochastic pi-calculus.* The Computer Journal 38: 578-589, 1995.

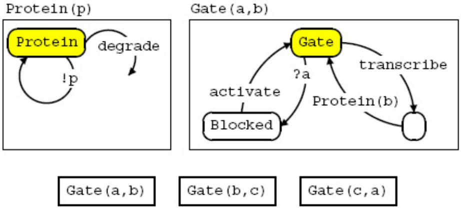
Can we use π-calculus for (biological) simulation?

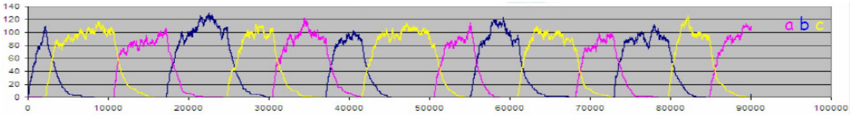
Molecule	Process
Interaction capability	Channel
Interaction	Communication
Modification (of cellular components)	State change (state transition systems)

A. Regev and E. Shapiro *Cellular Abstractions: Cells as Computation.* **Nature**, vol. 429 (2002)

Repressilator in π







L. Cardelli - Sept. 2005

Concurrent Constraint Programming

Constraint Store

- In this process algebra, the main object are **constraints**, which are *formulae over an interpreted first order language* (i.e. $X = 10$, $Y > X - 3$).
- Constraints can be added to a "container", the constraint store, but can never be removed.

Agents

Agents can perform two basic operations on this store (asynchronously):

- Add a constraint (**tell** ask)
- Ask if a certain relation is entailed by the current configuration (**ask** instruction)

V. Saraswat, *Concurrent Constraint Programming*, MIT press, 1993

Syntax of CCP

$$Program = Decl.A$$

$$D = \varepsilon \mid Decl.Decl \mid p(x) : -A$$

$$\begin{array}{ll} A = & \mathbf{0} \\ \mid & \mathrm{tell(c).A} \\ \mid & \mathrm{ask(c_1).A_1} + \mathrm{ask(c_2).A_2} \\ \mid & A_1 \parallel A_2 \mid \exists_x A \mid p(x) \end{array}$$

Stochastic CCP

Syntax of Stochastic CCP

$$Program = D.A$$

$$D = \varepsilon \mid D.D \mid p(\mathbf{x}) :- A$$

$$\pi = \mathrm{tell}_\lambda(c) \mid \mathrm{ask}_\lambda(c)$$
$$M = \pi.A \mid M + M'$$
$$A = \mathbf{0} \mid [p(\mathbf{x})]_\lambda \mid M \mid \exists_x A \mid (A_1 \parallel A_2)$$

L.Bortolussi. *Stochastic CCP.* QAPL, 2006.

Stochastic information

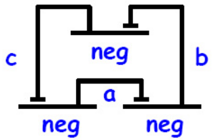
Each basic instruction (tell, ask, procedure call) has a rate attached to it.
Rates are functions from the constraint store $\mathcal{C}$ to positive reals:

$$\lambda : \mathcal{C} \longrightarrow \mathbb{R}^+.$$

Why another Process Algebra?

- Constraints are powerful and easy to program.
- Variables allow to store numerical information..
- We can use “clever” stochastic rates.

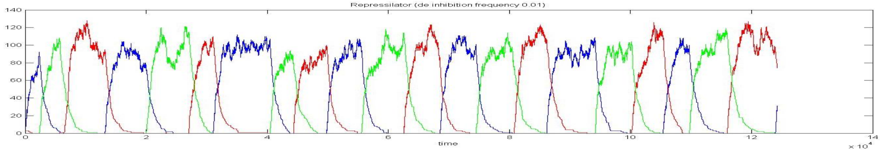
Repressilator in sCCP



degradator(X) :- $\mathrm{tell}_{[\lambda_D \cdot X]}(X = X - 1)$.degradator($X$)

neg(X, Y) :- ($\mathrm{tell}_{[\lambda_P]}(X = X + 1)$
+ $\mathrm{ask}_{[\lambda_I \cdot Y]}(Y > 0)$.$\mathrm{ask}_{[\lambda_U]}$(true)).neg($X$, Y)
).neg(X, Y)

neg_gate(X, Y) :- neg(X, Y) || degradator(X)



Using different kinetic laws: enzymatic reaction

Non-constant rates allow to describe more complicated kinetic dynamics than Mass Action's one.

Mass Action dynamics

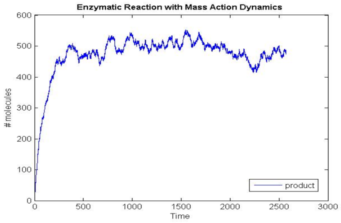
$$S + E \rightleftharpoons^{k_1}_{k_2} ES \rightarrow_{k_3} P + E$$
$$P \rightarrow_{k_4} \quad \rightarrow_{k_5} S$$

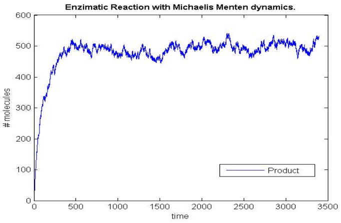
The rate of $S + E \rightarrow_{k_1} ES$ is $k_1[S][E]$.

Michaelis-Menten dynamics

$$S \mapsto^{E}_{K,V_0} P$$
$$P \rightarrow_{k_4} \quad \rightarrow_{k_5} S$$

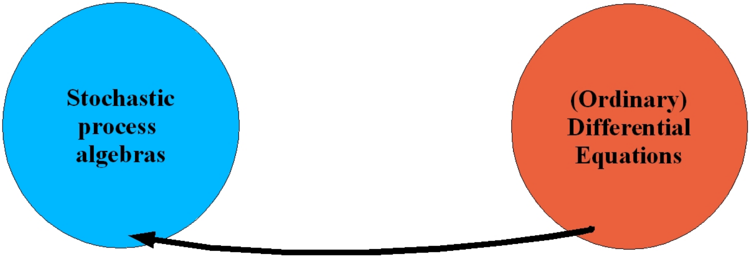
The rate of $S \mapsto^{E}_{K,V_0} P$ is $\frac{V_0[S]}{[S]+K}$





Outline

Simulating ODEs with SPAs



Motivations

- Study expressivity in terms of representable behaviors of SPA
- From “external” to “internal” descriptions: identify logical patterns of interactions.

Using S-Systems to determine rate functions

A generic form for S-System equations is

$$\dot{X}_i = \underbrace{V^+(X_1,\ldots,X_{m+n})}_{\text{production speed}} - \underbrace{V^-(X_1,\ldots,X_{m+n})}_{\text{degradation speed}}.$$

A generic S-System equation has *non-linear dependencies* on variables.

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}$$

We can use these expression as rates.

Using sCCP, we can associate to each dependent variable an agent $\mathrm{subs}(X_i)$:

$$\left(\mathrm{tell}(X_i = X_i + \sigma)_{\left[\alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}}\right]} + \mathrm{tell}(X_i = X_i - \sigma)_{\left[\beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}\right]}\right).\mathrm{subs}(X_i).$$

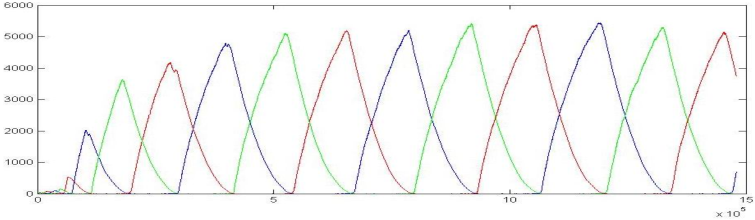
Encoding S-System's Repressilator

$$\begin{aligned}
\dot{X}_1 &= \alpha_1 X_3^{-1} - \beta_1 X_1^{0.5}, \\
\dot{X}_2 &= \alpha_2 X_1^{-1} - \beta_2 X_2^{0.5}, \\
\dot{X}_3 &= \alpha_3 X_2^{-1} - \beta_3 X_3^{0.5},
\end{aligned}$$

$$\alpha_i = 0.2, \quad \beta_i = 1.$$

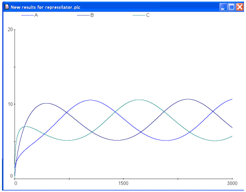
$$\begin{aligned}
\mathrm{subs}(X_1) \quad &::= (\mathrm{tell}(X_1 = X_1 + \sigma)_{[\alpha_1 X_3^{-1}]} \\
&+ \mathrm{tell}(X_1 = X_1 - \sigma)_{[\beta_1 X_1^{0.5}]}).\mathrm{subs}(X_1) \\
\mathrm{subs}(X_2) \quad &::= (\mathrm{tell}(X_2 = X_2 + \sigma)_{[\alpha_2 X_1^{-1}]} \\
&+ \mathrm{tell}(X_2 = X_2 - \sigma)_{[\beta_2 X_2^{0.5}]}).\mathrm{subs}(X_2) \\
\mathrm{subs}(X_3) \quad &::= (\mathrm{tell}(X_3 = X_3 + \sigma)_{[\alpha_3 X_2^{-1}]} \\
&+ \mathrm{tell}(X_3 = X_3 - \sigma)_{[\beta_3 X_3^{0.5}]}).\mathrm{subs}(X_3)
\end{aligned}$$

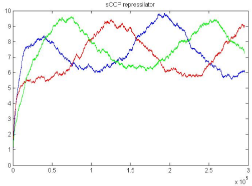
$$\sigma = 1$$



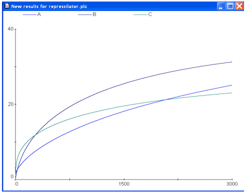
Repressilator gone wild

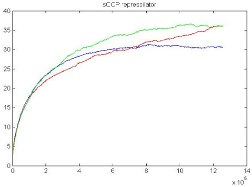
S-System's model of repressilator suffers from an high sensitivity from parameters, differently from the usual PA models. sCCP model with variable rates has the same "wild" behaviour!





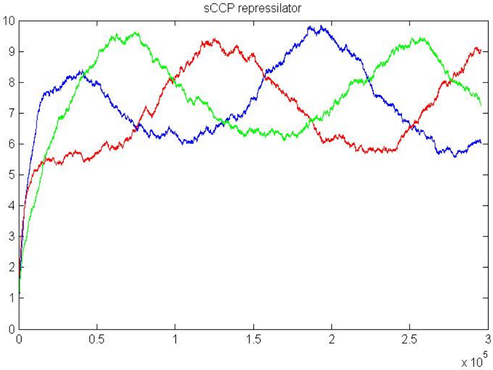
$\beta_i = 0.01$





$\beta_i = 0.001$

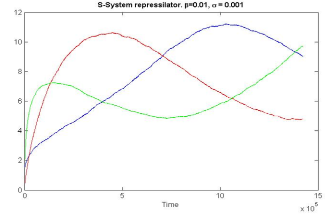
There's a trick...



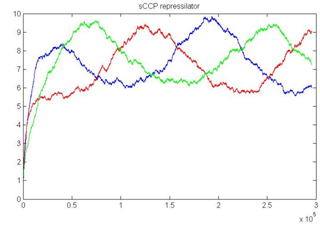
The magnitude of fluctuations is small.
We used
$\sigma = 0.01$

In this way we can reduce the perturbation effect effect of stochastic fluctuations.

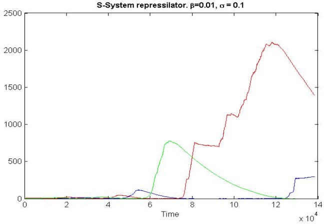
Dependency on the step size σ



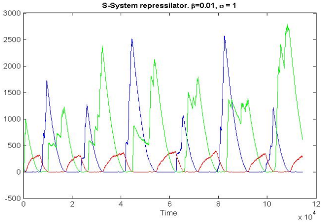
$\sigma = 0.001$



$\sigma = 0.01$



$\sigma = 0.1$



$\sigma = 1$

Outline

Hillston's method

Jane has developed a method to associate a set of ODEs to a SPA (precisely PEPA) program.

The method can be easily adapted to the (restricted version of) stochastic π-calculus

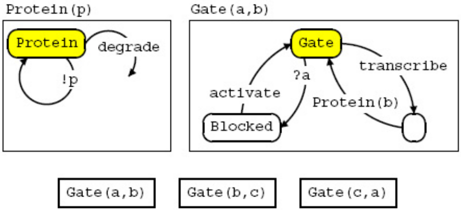
The translation produces always a set of Mass Action Equations, due to the definition of the SOS.

Question

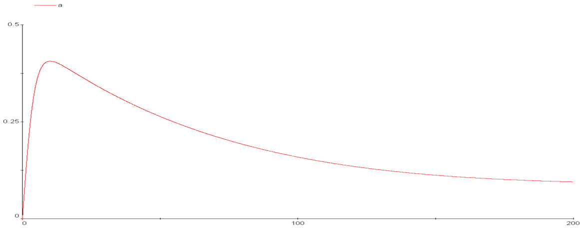
What does these ODEs tell us? Something about the average behavior?

J. Hillston, Fluid Flow Approximation of PEPA models, *QEST*, 2005.

ODEs for the repressilator in π-calculus

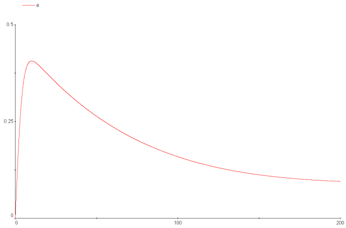


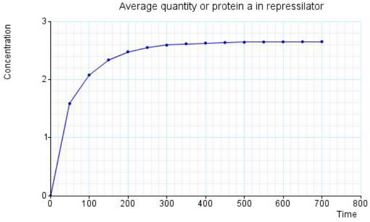
$$
\begin{aligned}
\dot{X}_1 &= \lambda_P Y_1 - \lambda_D X_1\\
\dot{X}_2 &= \lambda_P Y_2 - \lambda_D X_2\\
\dot{X}_3 &= \lambda_P Y_3 - \lambda_D X_3\\
\dot{Y}_1 &= \lambda_U Z_1 - \lambda_I Y_1 X_3\\
\dot{Y}_2 &= \lambda_U Z_2 - \lambda_I Y_2 X_1\\
\dot{Y}_3 &= \lambda_U Z_3 - \lambda_I Y_3 X_2\\
\dot{Z}_1 &= \lambda_I Y_1 X_3 - \lambda_U Z_1\\
\dot{Z}_2 &= \lambda_I Y_2 X_1 - \lambda_U Z_2\\
\dot{Z}_3 &= \lambda_I Y_3 X_2 - \lambda_U Z_3
\end{aligned}
$$



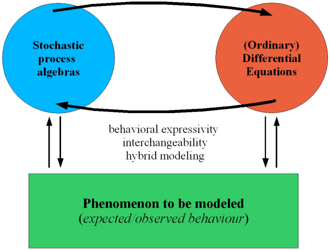
What's the average?

What's the relationship between the solution of the ODEs and the average value of proteins in the π-repressilator?
Neither the ODEs nor the average oscillates, but they stabilize at values different two orders of magnitude.





Conclusions



- "non-constant rates" are a powerful addition to SPAs (simulating ODEs, complex kinetic laws, etc.)
- stochastic fluctuations sometimes dominate, and they cannot be safely neglected in a translation process.
- Can we find translation techniques invariant w.r.t. the observed behaviour of the "real" system?