# Stochastic Concurrent Constraint Programming and Differential Equations

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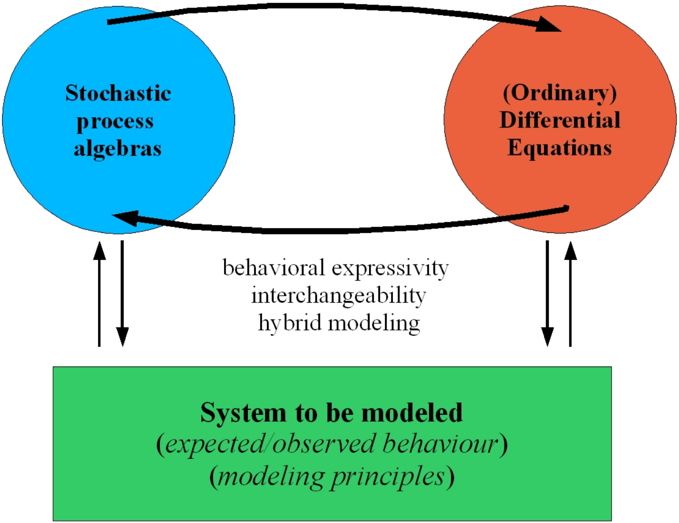
# The picture


Stochastic process algebras
(Ordinary) Differential Equations
behavioral expressivity
interchangeability
hybrid modeling
System to be modeled
(expected/observed behaviour)
(modeling principles)

# Outline

# Outline

# 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

$$Program = Decl.A$$

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

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

# Syntax of sCCP

## Syntax of Stochastic CCP

$$
\begin{array}{c}
Program = D.A \\
D = \varepsilon \mid D.D \mid p : -A \\
\pi = \mathrm{tell}_{\lambda}(c) \mid \mathrm{ask}_{\lambda}(c) \qquad M = \pi.G \mid M + M \\
G = \mathbf{0} \mid \mathrm{tell}_{\infty}(c).G \mid p \mid M \qquad A = \mathbf{0} \mid M \\
N = A \mid A \parallel N
\end{array}
$$

L. Bortolussi, *Stochastic Concurrent Constraint Programming*, QAPL, 2006

## Stochastic Rates

Rates are functions from the constraint store $\mathcal{C}$ to positive reals:

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

*Rates* can be thought as speed or duration of communications.

# Biochemical Arrows to sCCP processes

| | |
|---|---|
| $R_1 + \ldots + R_n \to_k P_1 + \ldots + P_m$ | reaction$(k, [R_1, \ldots, R_n], [P_1, \ldots, P_m]) :-$ ask$_{r_{MA}(k, R_1, \ldots, R_n)}\left(\bigwedge_{i=1}^{n}(R_i > 0)\right)$. $\left( \parallel_{i=i}^{n} \text{tell}_\infty(R_i = R_i - 1) \parallel_{j=1}^{m} \text{tell}_\infty(P_j = P_j + 1)\right)$. reaction$(k, [R_1, \ldots, R_n], [P_1, \ldots, P_m])$ |
| $R_1 + \ldots + R_n \rightleftharpoons_{k_2}^{k_1} P_1 + \ldots + P_m$ | reaction$(k_1, [R_1, \ldots, R_n], [P_1, \ldots, P_m]) \parallel$ reaction$(k_2, [P_1, \ldots, P_m], [R_1, \ldots, R_n])$ |
| $S \mapsto_{K, V_0}^{E} P$ | mm_reaction$(K, V_0, S, P) :-$ ask$_{r_{MM}(K, V_0, S)}(S > 0)$. $(\text{tell}_\infty(S = S - 1) \parallel tell_\infty(P = P + 1))$ . mm_reaction$(K, V_0, S, P)$ |
| $S \mapsto_{K, V_0, h}^{E} P$ | hill_reaction$(K, V_0, h, S, P) :-$ ask$_{r_{Hill}(K, V_0, h, S)}(S > 0)$. $(\text{tell}_\infty(S = S - h) \parallel tell_\infty(P = P + h))$ . Hill_reaction$(K, V_0, h, S, P)$ |

where $r_{MA}(k, X_1, \ldots, X_n) = k \cdot X_1 \cdots X_n$; $\quad r_{MM}(K, V_0, S) = \dfrac{V_0 S}{S + K}$; $\quad r_{Hill}(k, V_0, h, S) = \dfrac{V_0 S^h}{S^h + K^h}$

# Enzymatic reaction

$$S + E \rightleftharpoons^{k_1}_{k_{-1}} ES \rightarrow_{k_2} P + E$$

## Mass Action Kinetics

enz_reaction($k_1, k_{-1}, k_2, S, E, ES, P$) :-
reaction($k_1$, [$S$, $E$], [$ES$]) ||
reaction($k_{-1}$, [$ES$], [$E$, $S$]) ||
reaction($k_2$, [$ES$], [$E$, $P$])

## Mass Action Equations

$$\frac{d[ES]}{dt} = k_1[S][E] - k_2[ES] - k_{-1}[ES]$$
$$\frac{d[E]}{dt} = -k_1[S][E] + k_2[ES] + k_{-1}[ES]$$
$$\frac{d[S]}{dt} = -k_1[S][E]$$
$$\frac{d[P]}{dt} = k_2[ES]$$

## Michaelis-Menten Equations

$$\frac{d[P]}{dt} = \frac{V_0 S}{S+K}$$
$$V_0 = k_2[E_0]$$
$$K = \frac{k_2+k_{-1}}{k_1}$$

## Michaelis-Menten Kinetics

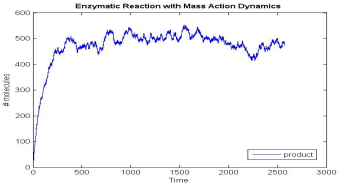
$$\text{mm\_reaction}\left(\frac{k_2 + k_{-1}}{k_1}, k_2 \cdot E, S, P\right)$$

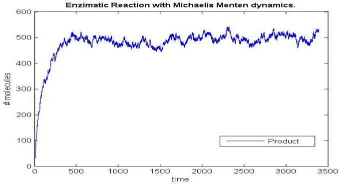
# Enzymatic reaction

$$S + E \rightleftharpoons_{k_{-1}}^{k_1} ES \rightarrow_{k_2} P + E$$

## Mass Action Kinetics

enz_reaction($k_1, k_{-1}, k_2, S, E, ES, P$) :-
 reaction($k_1$, [$S, E$], [$ES$]) ||
 reaction($k_{-1}$, [$ES$], [$E, S$]) ||
 reaction($k_2$, [$ES$], [$E, P$])

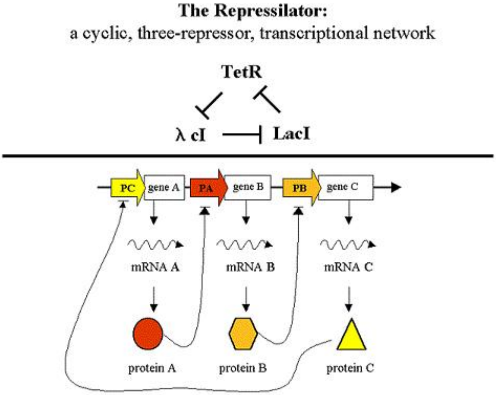


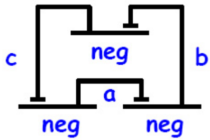

## Michaelis-Menten Kinetics

$$\text{mm\_reaction}\left(\frac{k_2 + k_{-1}}{k_1}, k_2 \cdot E, S, P\right)$$

# A paradigmatic example — the Repressilator



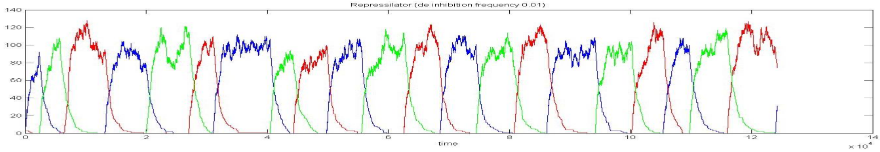
# Repressilator in sCCP




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

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

$\text{neg}(A, C) \parallel \text{neg}(B, A) \parallel \text{neg}(C, B) \parallel \text{degr}(A) \parallel \text{degr}(B) \parallel \text{degr}(C)$



# Outline

# From ODE to sCCP

## What?

We want to associate a set an sCCP program to a set of ODEs.

## Why?

- To unveil the logical patterns of interactions hidden in the ODEs.
- To study expressivity in terms of representable behaviors of sCCP.

## How?

Using the functional form of rates of sCCP.

L. Bortolussi, A. Policriti. Stochastic Concurrent Constraint Programming and Differential Equations, 2007.

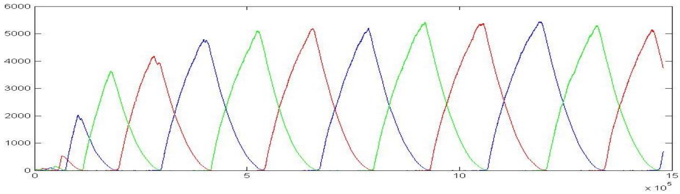
# Example: encoding S-System's Repressilator

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

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

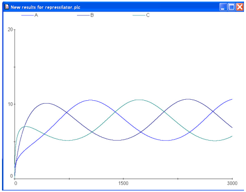
$$\begin{aligned}
\text{subs}(X_1) \quad &::= (\text{tell}(X_1 = X_1 + \sigma)_{[\alpha_1 X_3^{-1}]} \\
&+\text{tell}(X_1 = X_1 - \sigma)_{[\beta_1 X_1^{0.5}]}).\text{subs}(X_1) \\
\text{subs}(X_2) \quad &::= (\text{tell}(X_2 = X_2 + \sigma)_{[\alpha_2 X_1^{-1}]} \\
&+\text{tell}(X_2 = X_2 - \sigma)_{[\beta_2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

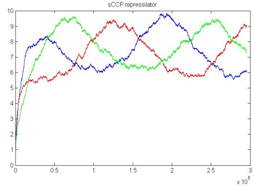
$$\sigma = 1$$



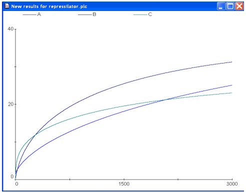
# Repressilator gone wild

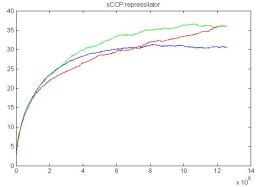
S-System's model of repressilator suffers from an high sensitivity from parameters, differently from the usual PA models. sCCP model with variable rates has the same "wild" behaviour!



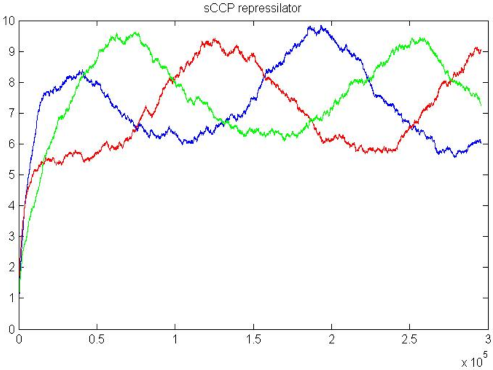

$\beta_i = 0.01$




$\beta_i = 0.001$

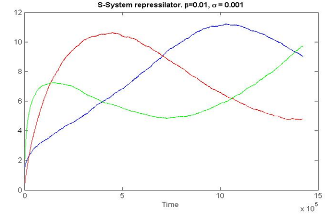
# There's a trick...



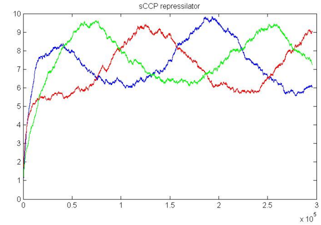

The magnitude of fluctuations is small.
We used $\sigma = 0.01$

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

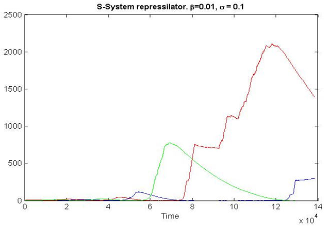
# Dependency on the step size $\sigma$



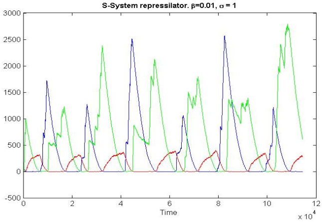

$\sigma = 0.001$




$\sigma = 0.01$




$\sigma = 0.1$




$\sigma = 1$

# Outline

# From sCCP to ODE

## What?

We want to associate a set of ODE to an sCCP program (written with a restricted syntax).

## Why?

ODE can be numerically simulated faster than stochastic processes.

## On the market...

There are (syntactic) methods to write set of ODEs for PEPA and stochastic $\pi$-calculus, looking at the speed of creation and destruction of terms. We did analogously for sCCP.
However, the ODE can show a behavior different from that of SPA models.

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

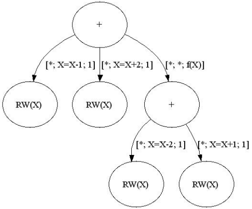
L. Cardelli, From Processes to ODEs by Chemistry, 2006.

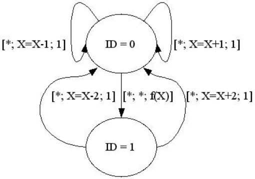
L. Bortolussi, A. Policriti. Connecting Process Algebras and Differential Equations for systems biology, 2006.

# From sCCP to ODE: example

$RW_X$ :-
  $tell_1(X = X - 1).RW_X$
  + $tell_1(X = X + 2).RW_X)$
  + $ask_{f(X)}(true).($ $tell_1(X = X - 2).RW_X$
    + $tell_1(X = X + 1).RW_X$ )

$f(X) = \frac{1}{X^2+1}$

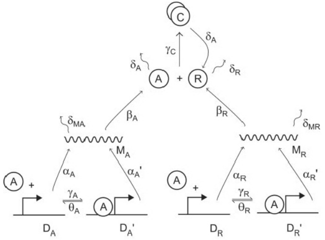


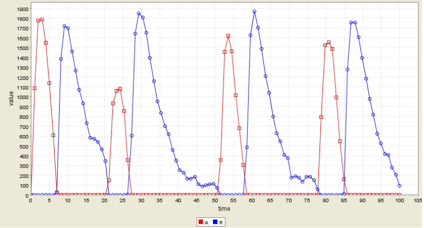



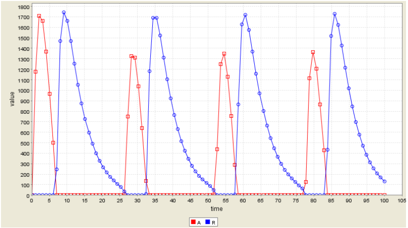

| $X$ | $-1$ | $+2$ | $0$ | $-2$ | $+1$ |
|---|---|---|---|---|---|
| $P_0$ | 0 | 0 | $-1$ | $+1$ | $+1$ |
| $P_1$ | 0 | 0 | $+1$ | $-1$ | $-1$ |

$$\begin{cases} \dot{X} = P_0 - P_1 \\ \dot{P}_0 = -\frac{1}{X^2+1}P_0 + 2P_1 \\ \dot{P}_1 = \frac{1}{X^2+1}P_0 - 2P_1 \end{cases}$$

# A “yes” case: the circadian clock



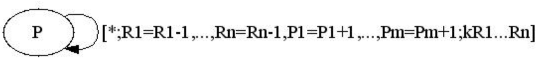
# Preservation of chemical kinetics

## Mass Action Kinetics

$$
\begin{array}{l}
\text{reaction}(k, [R_1, \ldots, R_n], [P_1, \ldots, P_m]) :- \\
\qquad \text{ask}_{r_{MA}(k, R_1, \ldots, R_n)} \left(\bigwedge_{i=1}^{n} (R_i > 0)\right) . \\
\qquad \left( \|_{j=i}^{n} \; \text{tell}_{\infty}(R_i = R_i - 1) \; \| \right. \\
\qquad \left. \|_{j=1}^{m} \; \text{tell}_{\infty}(P_j = P_j + 1)\right) . \\
\qquad \text{reaction}(k, [R_1, \ldots, R_n], [P_1, \ldots, P_m])
\end{array}
$$

$$r_{MA}(k, X_1, \ldots, X_n) = k \cdot X_1 \cdots X_n$$

$$
\begin{array}{lcl}
\dot{R}_1 = -kR_1 \cdots R_n & & \dot{P}_1 = kR_1 \cdots R_n \\
\vdots & & \vdots \\
\dot{R}_n = -kR_1 \cdots R_n & & \dot{P}_m = kR_1 \cdots R_n \\
 & \dot{P} = 0 &
\end{array}
$$



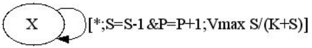
# Preservation of chemical kinetics

## Michaelis-Menten Kinetics

$$
\begin{array}{l}
\text{mm\_reaction}(K, V_0, S, P) :- \\
\quad \text{ask}_{r_{MM}(K, V_0, S)}(S > 0). \\
\quad (\text{tell}_\infty(S = S - 1) \parallel tell_\infty(P = P + 1)) . \\
\quad \text{mm\_reaction}(K, V_0, S, P)
\end{array}
$$

$$r_{MM}(K, V_0, S) = \frac{V_0 S}{S+K}$$

$$\dot{P} = \frac{Vmax\, S}{K+S} \qquad \dot{X} = 0 \qquad \dot{S} = -\frac{Vmax\, S}{K+S}$$



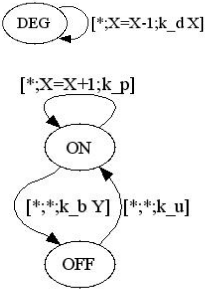
# Back on repressilator

degr(X) :- tell$_{[k_d \cdot X]}$($X = X - 1$).degr($X$)

neg($X$, $Y$) :- ( tell$_{[k_p]}$($X = X + 1$)
+ ask$_{[k_b \cdot Y]}$($Y \geq 1$).ask$_{[k_u]}$(true)
).neg($X$, $Y$)

neg($A$, $C$) $\|$ neg($B$, $A$) $\|$ neg($C$, $B$) $\|$

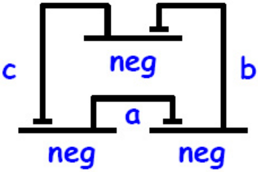
degr($A$) $\|$ degr($B$) $\|$ degr($C$)



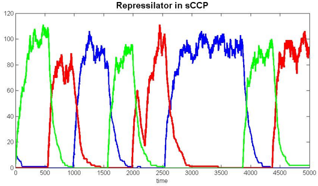

$$\dot{A} = k_p Y_1 - k_d X_1 \qquad \dot{Y}_1 = k_u Z_1 - k_b Y_1 C \qquad \dot{Z}_1 = k_b Y_1 C - k_u Z_1$$
$$\dot{B} = k_p Y_2 - k_d X_2 \qquad \dot{Y}_2 = k_u Z_2 - k_b Y_2 A \qquad \dot{Z}_2 = k_b Y_2 A - k_u Z_2$$
$$\dot{C} = k_p Y_3 - k_d X_3 \qquad \dot{Y}_3 = k_u Z_3 - k_b Y_3 B \qquad \dot{Z}_3 = k_b Y_3 B - k_u Z_3$$

# The strange beast of repressilator

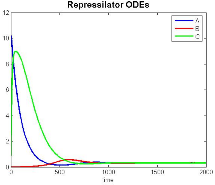
Repressilator with gene gates



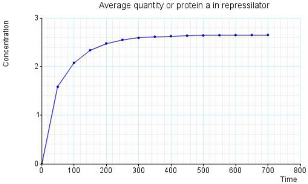

Repressilator in sCCP




Repressilator: ODE from sCCP




Repressilator: average of sCCP model



# Conclusions

- We defined transformations from sCCP to ODE and back, preserving rate semantics.
- Dynamic behavior is not always conserved, the quest for behaviorally invariant translations (for a wider class of models) is still open.
- The concept of “behavioral equivalence” needs to be treated more formally.