Bio-PEPAd: Integrating exponential and deterministic delays

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Joint work with Giulio Caravagna

Outline

Introduction

Bio-PEPA

Bio-PEPAd

Analysis of Bio-PEPAd

Bio-PEPAd vs. Bio-PEPA

Conclusions

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- Different styles of SPA have been defined (integrated time and orthogonal time) but in each case there is a single delay associated with an action.
- The usual interpretation of this delay the duration of the action or event.

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- There may be a delay from the time when an event becomes possible (enabled) ;
- When an event occurs there may be a delay until the effects of the event become apparent.

Actions with delays in biochemistry

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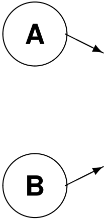

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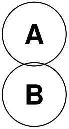

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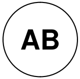

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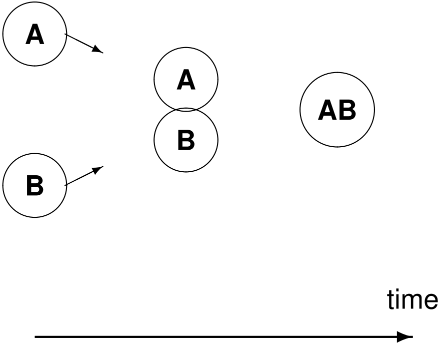

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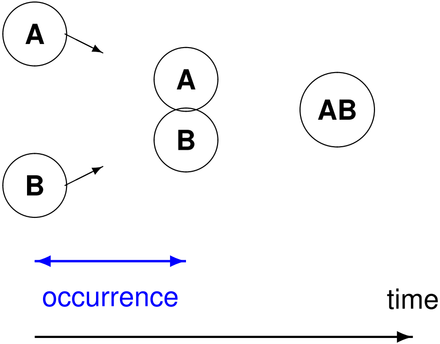

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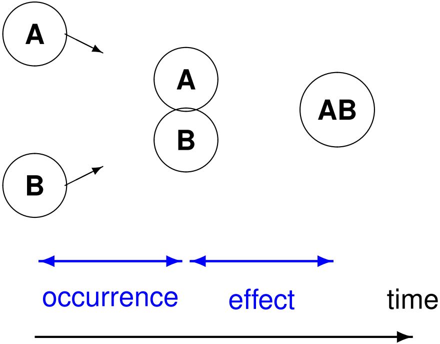

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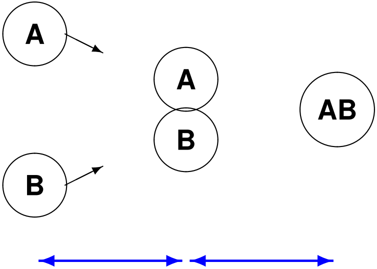

occurrence

effect

exponential

instantaneous

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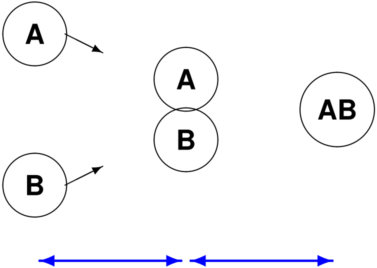

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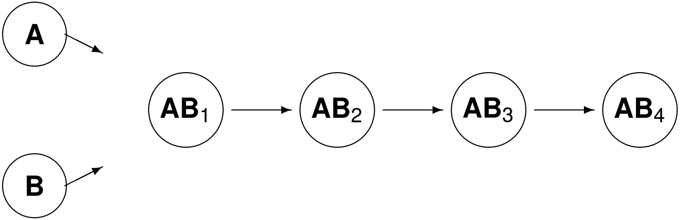
exponential deterministic

Delays as abstraction



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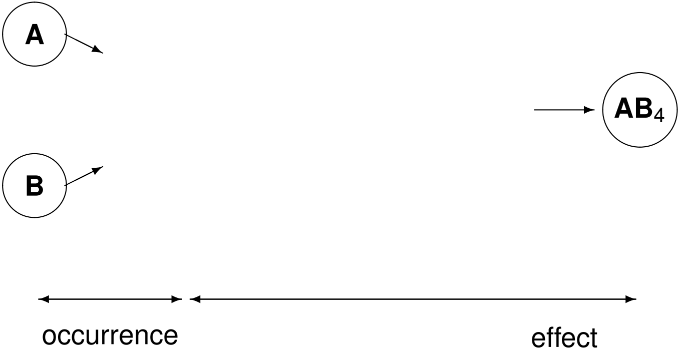

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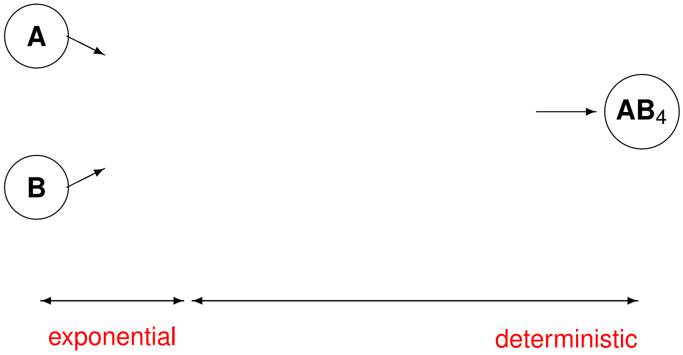

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Bio-PEPA is a recently defined stochastic process algebra for modelling biochemical processes.

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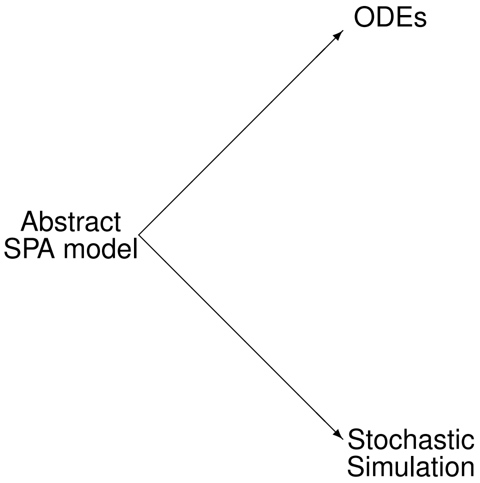
Unlike many of the other SPA in use in systems biology which derive from the stochastic π-calculus it is not based on the molecules as processes abstraction.

Instead it is based on the species as processes abstraction which means that it readily supports a number of different kinds of analysis.

Alternative Representations

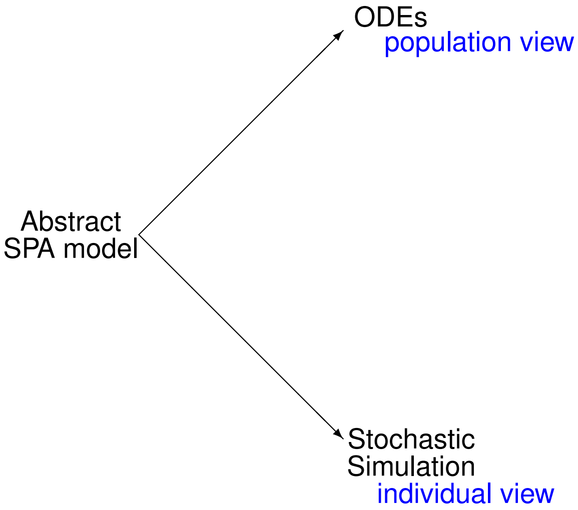


Abstract SPA model

ODEs

Stochastic Simulation

Alternative Representations

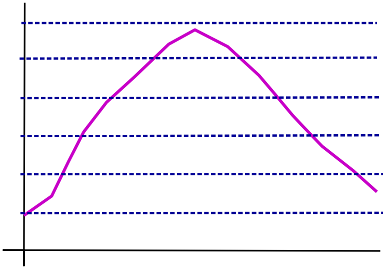


ODEs
population view

Abstract
SPA model

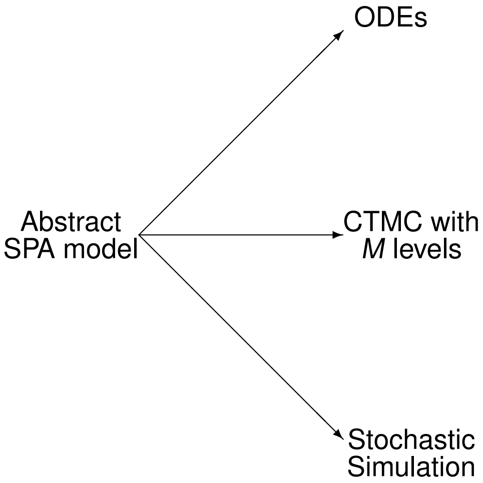
Stochastic
Simulation
individual view

Discretising the population view



We can discretise the continuous range of possible concentration values into a number of distinct states. These form the possible states of the component representing the reagent.

Alternative Representations



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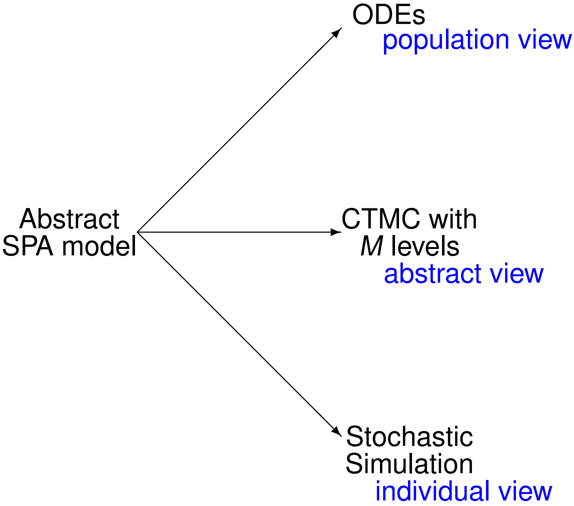

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- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour. These rates may be specified by functions.
- The representation of an action within a component (species) records the stoichiometry of that entity with respect to that reaction. The role of the entity is also distinguished.
- The local states of components are quantitative rather than functional, i.e. distinct states of the species are represented as distinct components, not derivatives of a single component.

The syntax

Sequential component (species component)

$$S ::= (\alpha, \kappa) \text{ op } S \mid S + S \mid C \qquad \text{where op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot$$

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The parameter l is abstract, recording quantitative information about the species.

Depending on the interpretation, this quantity may be:

- number of molecules (SSA),
- number of molecules (ODE) or
- a level within a semi-quantitative model (CTMC).

The Bio-PEPA system

A Bio-PEPA system $\mathcal{P}$ is a 6-tuple $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \mathit{Comp}, P \rangle$, where:

- $\mathcal{V}$ is the set of compartments;
- $\mathcal{N}$ is the set of quantities describing each species (step size, number of levels, location, ...);
- $\mathcal{K}$ is the set of parameter definitions;
- $\mathcal{F}_R$ is the set of functional rate definitions;
- *Comp* is the set of definitions of sequential components;
- P is the model component describing the system.

Semantics

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We define two relations over the processes:

1. capability relation, that supports the derivation of quantitative information;
2. stochastic relation, that gives the rates associated with each action.

Semantics: prefix rules

$$\texttt{prefixReac} \quad ((\alpha,\kappa){\downarrow}S)(l) \xrightarrow{(\alpha,[S:\downarrow(l,\kappa)])}_c S(l-\kappa) \qquad \kappa \le l \le N$$

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$$\texttt{prefixMod} \quad ((\alpha,\kappa)\ op\ S)(l) \xrightarrow{(\alpha,[S:op(l,\kappa)])}_c S(l) \qquad 0 \le l \le N$$

with $op = \odot, \oplus$, or $\ominus$

Semantics: constant and choice rules

$$\texttt{Choice1} \quad \frac{S_1(l) \xrightarrow{(\alpha,v)}_c S'_1(l')}{(S_1 + S_2)(l) \xrightarrow{(\alpha,v)}_c S'_1(l')}$$

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Constant
$$\frac{S(l)\xrightarrow{(\alpha,S:[op(l,\kappa))]}_c S'(l')}{C(l)\xrightarrow{(\alpha,C:[op(l,\kappa))]}_c S'(l')}$$
with $C \overset{def}{=} S$

Semantics: cooperation rules

$$\text{coop1} \qquad \frac{P_1 \xrightarrow{(\alpha,v)}_c P_1'}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha,v)}_c P_1' \underset{\mathcal{L}}{\bowtie} P_2} \qquad \text{with } \alpha \notin \mathcal{L}$$

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$$\texttt{coopFinal} \qquad \frac{P_1 \xrightarrow{(\alpha,v_1)}_c P_1' \qquad P_2 \xrightarrow{(\alpha,v_2)}_c P_2'}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha,v_1::v_2)}_c P_1' \underset{\mathcal{L}}{\bowtie} P_2'} \qquad \text{with } \alpha \in \mathcal{L}$$

Semantics: rates and transition system

In order to derive the rates we consider the stochastic relation $\longrightarrow_s \subseteq \mathcal{P} \times \Gamma \times \mathcal{P}$, with $\gamma \in \Gamma := (\alpha, r)$ and $r \in \mathbb{R}^+$.

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$$\frac{P \xrightarrow{(\alpha_j, v)}_c P'}{\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, Comp, P' \rangle}$$

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The rate r_{α_j} is defined as $f_{\alpha_j}(\mathcal{V}, \mathcal{N}, \mathcal{K})/h$.

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- Such a model is constituted by a single reaction channel of the form $A \xrightarrow{k} B$.
- We assume the initial state contains three elements of species A and no elements of species B;
- Formally it is described by the 2-dimensional vector $\mathbf{x}_0 = (3, 0)^T$.

Small example in Bio-PEPA

The Bio-PEPA processes modelling the species are

$$A \overset{def}{=} (\alpha, 1)\downarrow A \qquad B \overset{def}{=} (\alpha, 1)\uparrow B$$

where α is the action corresponding to the reaction and $f_\alpha = f_{MA}(k)$.

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The initial configuration of the process is

$$A(3) \underset{\{\alpha\}}{\bowtie} B(0)\,.$$

Small example in Bio-PEPA

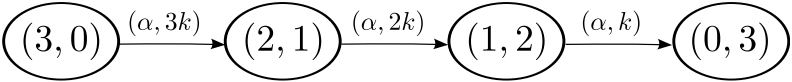
The components of the system in which this process is embedded are:

$$\mathcal{V} = \{\text{cell} : 1\} \qquad \mathcal{K} = \{k' = k\}$$

$$\mathcal{N} = \begin{array}{l}\{A \text{ in cell} : \mathrm{N_A} = 3, \mathrm{h_A} = 1; \\ \quad \mathrm{B} \text{ in cell} : \mathrm{N_B} = 3, \mathrm{h_A} = 1\}\end{array} \qquad \mathcal{F} = \{f_\alpha = f_{MA}(k')\}$$

$$Comp = \{A \overset{def}{=} (\alpha, 1)\downarrow A,\ B \overset{def}{=} (\alpha, 1)\uparrow B\} \qquad P = A(3) \underset{\{\alpha\}}{\bowtie} B(0)\,.$$

The SLTS for the Bio-PEPA example



Starting from the initial configuration $\mathbf{X}(t_0) = 0$ the process eventually reaches the final state $(0,3)$, which corresponds to the process $A(0) \underset{\{\alpha\}}{\bowtie} B(3)$.

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$$\left\{\sigma : \mathcal{A} \to \mathbb{R}^{+}\right\} \in \Delta$$

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Currently we assume all actions have a non-zero delay.

Bio-PEPAd system

A Bio-PEPAd system is a 7-tuple $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, P \rangle$ where:

- $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, P \rangle$ is a Bio-PEPA system;
- $\sigma \in \Delta$ is a function used to specify the delays of the actions.

Process configuration

Bio-PEPAd process configurations are defined by the following syntax:

$$\begin{array}{rcl} C_S & ::= & (\alpha,\kappa) op\ C_S \quad \Big| \quad C_S + C_S \quad \Big| \quad C \\ C_P & ::= & C_P \underset{\mathcal{L}}{\bowtie} C_P \quad \Big| \quad C_S(l, L) \end{array}$$

where L is a list of 4-tuples $(l', \kappa', \alpha', op')$ with $l, \kappa \in \mathbb{N}$, $\alpha \in \mathcal{A}$ and $op \in \{\downarrow, \uparrow, \odot, \oplus, \ominus\}$.

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For example, if $(l', \kappa, \alpha, op) \in L$ there are κ levels of concentration of species S involved in a currently running action α which fired when the level of S was l', and its role was op.

Bio-PEPAd semantics

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- In this case the end of the exponentially distributed event corresponds to the start of the action, denoted α^+.
- Whereas the end of the deterministically timed delay corresponds to terminating the action, denoted α^-.
- As usual for the ST style, we have two transition relations over process configurations.

Initial process configuration

From Bio-PEPAd process P we derive its corresponding process configuration P_C using a function $\mu : \mathcal{P} \rightarrow \mathcal{C}$ such that

$$\mu((\alpha,\kappa)op\ S) = (\alpha,\kappa)op\ S \qquad \mu(P_1 \underset{\mathcal{L}}{\bowtie} P_2) = \mu(P_1) \underset{\mathcal{L}}{\bowtie} \mu(P_2)$$

$$\mu(S_1 + S_2) = S_1 + S_2 \qquad \mu(S(l)) = S(l,[\,]).$$

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$$\mu(S_1 + S_2) = S_1 + S_2 \qquad \mu(S(l)) = S(l, [\,]).$$

For example, the process $S(l_1) \underset{\mathcal{L}_1}{\bowtie} S(l_2) \underset{\mathcal{L}_2}{\bowtie} S(l_3)$ is transformed into the configuration $S(l_1, [\,]) \underset{\mathcal{L}_1}{\bowtie} S(l_2, [\,]) \underset{\mathcal{L}_2}{\bowtie} S(l_3, [\,])$.

Auxiliary functions

We define four auxiliary functions to examine and manipulate the scheduling lists:

- *pick*: given α and a scheduling list, select the first α action entry in the list.
- *del*: given α and a scheduling list, remove the first α action entry in the list.
- *prod*: given a scheduling list for species *S*, select those entries in which *S* is involved as a product.
- *pend*: given a scheduling list find how many levels are involved.

The start relation: Prefix

$$(\alpha,\kappa)\!\downarrow S(l,L) \xrightarrow{(\alpha^{+},[S:\downarrow(l,\kappa)])}_{st} S(l-\kappa, L@[(l,\kappa,\alpha,\downarrow)]) \qquad \kappa \leq l \leq N$$

$$(\alpha,\kappa)\!\uparrow S(l,L) \xrightarrow{(\alpha^{+},[S:\uparrow(l,\kappa)])}_{st} S(l, L@[(l,\kappa,\alpha,\uparrow)]) \qquad 0 \leq l + \mathit{pend\ prod}\ L \leq N$$

$$(\alpha,\kappa)\!\oplus S(l,L) \xrightarrow{(\alpha^{+},[S:\oplus(l,\kappa)])}_{st} S(l, L@[(l,\kappa,\alpha,\oplus)]) \qquad \kappa \leq l \leq N$$

$$(\alpha,\kappa)\mathit{op}\, S(l,L) \xrightarrow{(\alpha^{+},[S:\mathit{op}(l,\kappa)])}_{st} S(l, L@[(l,\kappa,\alpha,\mathit{op})]) \qquad 1 \leq l \leq N,\ \ \mathit{op} \in \{\odot,\ominus\}$$

The start relation: Choice and Constant

$$\frac{S_1(I, L) \xrightarrow{(\alpha^+, w)}_{st} S_1'(I', L')}{(S_1 + S_2)(I, L) \xrightarrow{(\alpha^+, w)}_{st} S_1'(I', L')}$$

$$\frac{S_2(I, L) \xrightarrow{(\alpha^+, w)}_{st} S_2'(I', L')}{(S_1 + S_2)(I, L) \xrightarrow{(\alpha^+, w)}_{st} S_2'(I', L')}$$

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$$\frac{S(l,L) \xrightarrow{(\alpha^+,w)}_{st} S'(l',L') \quad C \overset{def}{=} S(l,L)}{C \xrightarrow{(\alpha^+,w)}_{st} S'(l',L')}$$

The start relation: Cooperation

$$\frac{P_1 \xrightarrow{(\alpha^+,w)}_{st} P_1' \quad \alpha \notin \mathcal{L}}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha^+,w)}_{st} P_1' \underset{\mathcal{L}}{\bowtie} P_2}$$

$$\frac{P_2 \xrightarrow{(\alpha^+,w)}_{st} P_2' \quad \alpha \notin \mathcal{L}}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha^+,w)}_{st} P_1 \underset{\mathcal{L}}{\bowtie} P_2'}$$

$$\frac{P_1 \xrightarrow{(\alpha^+,w_1)}_{st} P_1' \quad P_2 \xrightarrow{(\alpha^+,w_2)}_{st} P_2' \quad \alpha \in \mathcal{L}}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{(\alpha^+,w_1 @ w_2)}_{st} P_1' \underset{\mathcal{L}}{\bowtie} P_2'}$$

The completion relation: Ongoing actions

$$\frac{\mathit{pick}\ \alpha\ L = (l, \kappa, \alpha, \uparrow)}{S(l', L) \xrightarrow{(\alpha^{-},[S:\uparrow(l,\kappa)])}_{co} S(l' + k, \mathit{del}\ \alpha\ L)}$$

$$\frac{\mathit{pick}\ \alpha\ L = (l, \kappa, \alpha, op)\ \ op \in \{\downarrow, \odot, \oplus, \ominus\}}{S(l', L) \xrightarrow{(\alpha^{-},[S:op(l,\kappa)])}_{co} S(l', \mathit{del}\ \alpha\ L)}$$

The completion relation: Choice and Constant

$$\frac{S_1(l, L) \xrightarrow{(\alpha^-, w)}_{co} S_1'(l', L')}{(S_1 + S_2)(l, L) \xrightarrow{(\alpha^-, w)}_{co} S_1'(l', L')} \qquad \frac{S_2(l, L) \xrightarrow{(\alpha^-, w)}_{co} S_2'(l', L')}{(S_1 + S_2)(l, L) \xrightarrow{(\alpha^-, w)}_{co} S_2'(l', L')}$$

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The stochastic relation

$$\frac{P \xrightarrow{(\alpha^+,w)}_{st} P' \qquad r_\alpha = f_\alpha[w,\mathcal{N},\mathcal{K}]h^{-1}}{\langle \mathcal{V},\mathcal{N},\mathcal{K},\mathcal{F},Comp,\sigma,P\rangle \xrightarrow{(\alpha^+,r_\alpha,\sigma(\alpha))}_{s} \langle \mathcal{V},\mathcal{N},\mathcal{K},\mathcal{F},Comp,\sigma,P'\rangle}$$

$$\frac{P \xrightarrow{(\alpha^-,w)}_{co} P' \qquad r_\alpha = f_\alpha[w,\mathcal{N},\mathcal{K}]h^{-1}}{\langle \mathcal{V},\mathcal{N},\mathcal{K},\mathcal{F},Comp,\sigma,P\rangle \xrightarrow{(\alpha^-,r_\alpha,\sigma(\alpha))}_{s} \langle \mathcal{V},\mathcal{N},\mathcal{K},\mathcal{F},Comp,\sigma,P'\rangle}$$

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- Moreover, by construction, instances of an action complete while respecting their starting order.

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- Note that the underlying SLTS does not contain an explicit quantitative notion of time.
- By means of the ST semantics, in Bio-PEPAd a qualitative notion of time can be retrieved by observing state changes induced by either the start or the completion of an action.
- Moreover, by construction, instances of an action complete while respecting their starting order.
- However note that the SLTS contains all the potential behaviours for a process configuration but some of these may not be possible given the kinetic information of the system.

Small example revisited

To illustrate Bio-PEPAd we consider again the small example earlier modelled in Bio-PEPA:

$$A \xrightarrow{k} B$$

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We again assume the initial state described by the vector $\mathbf{x}_0 = (3, 0)^T$.

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We are able to fully reuse the Bio-PEPA specification for this model:

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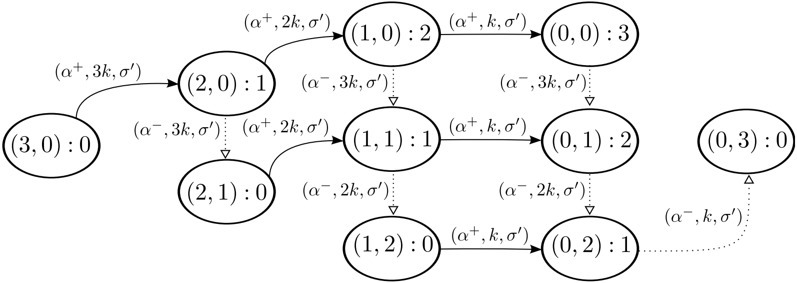
The initial configuration of the process, obtained by applying the function μ is

$$A(3, [\,]) \underset{\{\alpha\}}{\bowtie} B(0, [\,])\,.$$

The SLTS for the Bio-PEPAd example


$(3,0):0$
$(2,0):1$
$(2,1):0$
$(1,0):2$
$(1,1):1$
$(1,2):0$
$(0,0):3$
$(0,1):2$
$(0,2):1$
$(0,3):0$
$(\alpha^+, 3k, \sigma')$
$(\alpha^+, 2k, \sigma')$
(α^+, k, σ')
$(\alpha^-, 3k, \sigma')$
$(\alpha^-, 3k, \sigma')$
$(\alpha^-, 3k, \sigma')$
$(\alpha^+, 2k, \sigma')$
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(α^+, k, σ')
(α^-, k, σ')

Starting from the initial configuration $(3,0):0$, we eventually reach the final state $(0,3):0$, which corresponds to the final configuration $A(0,[\,])\underset{\{\alpha\}}{\bowtie}B(3,[\,])$.

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Analysis of Bio-PEPAd

Just as in Bio-PEPA, we can subject Bio-PEPAd models to different analyses based on the different views of the system:

Population view:

Individual view:

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The simplest form of DDE considers constant delays $\sigma_1 > \ldots > \sigma_n \geq 0$ and consists of an equation of the form

$$\frac{dX}{dt} = \varphi_X(t, \{X(t - \sigma_i) \mid i = 1, \ldots n\})$$

where $X(t - \sigma_i)$ denotes the state of the system at the past time $t - \sigma_i$.

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Moreover, the initial conditions must be defined in the interval $[t_0 - \sigma(\alpha); t_0]$ where α is the action with maximum delay.

This is left to the modeller.

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Luckily, based on DDEs, variants of SSA which incorporate deterministic delays have previously been defined [Barrio et al 2006; Barbuti et al 2009].

These algorithms work for the delay-as-duration abstraction (cf. the purely delayed abstraction), which is what we use for Bio-PEPAd.

Mapping Bio-PEPAd to DSSA

To prepare a Bio-PEPAd system for simulation using DSSA

1. Define the algebraic representation of the process:

$$\left\{ (\!|\_|\!)_n : \mathcal{C} \cup \mathcal{P} \rightarrow \mathbb{N}^n \mid n \in \mathbb{N} \right\}$$

encodes a Bio-PEPA process/Bio-PEPAd process configuration as a population vector:

$$(\!| S_1(l_1) \underset{\mathcal{L}_1}{\bowtie} \dots \underset{\mathcal{L}_m}{\bowtie} S_m(l_m) |\!)_m = (l_1, \dots, l_m)^T$$
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2. Create the reactions to simulate: The actual rates of the reactions have to be defined, case by case, using the parameters in $\mathcal{F}$ (as for Bio-PEPA).

DSS Algorithm

```
$t \leftarrow t_0$; $\mathbf{x} \leftarrow \mathbf{x}_0$; $S \leftarrow \emptyset$;
while $t < T$ do
    $a_0(\mathbf{x}) \leftarrow \sum_{j=1}^{M} a_j(\mathbf{x})$;
    let $r_1, r_2 \sim U[0,1]$;
    $\tau \leftarrow a_0(\mathbf{x})^{-1} \ln({r_1}^{-1})$;
    let $S_{t,\tau} = \{(t'', \nu'') \in S \mid t'' \in (t, t+\tau]\}$;
    if $S_{t,\tau} \neq \emptyset$ then
        $(t', \nu') \leftarrow \min\{S_{t,\tau}\}$;
        $\mathbf{x} \leftarrow \mathbf{x} + \nu'$; $t \leftarrow t'$; $S \leftarrow S \backslash \{(t', \nu')\}$;
    else
        let $j$ such that $\sum_{i=1}^{j-1} a_i(\mathbf{x}) < r_2 \cdot a_0(\mathbf{x}) \leq \sum_{i=1}^{j} a_i(\mathbf{x})$;
        $\mathbf{x} \leftarrow \mathbf{x} + \nu_j^r$; $t \leftarrow t + \tau$; $S \leftarrow S \cup \{(t + \tau + \sigma_j, \nu_j^p)\}$;
    end if
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```

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- Clocks may decay at state- and event-dependent rates, but for our purposes we assume that all clocks decay at rate 1.
- When a clock expires the state is updated according to an event-dependent probability distribution.
- For all other events it is known whether the completion of this event cancels, creates or maintains the event.

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- Each completion action α^- in the SLTS corresponds to a deterministically timed clock in the corresponding GSMP state.
- When an exponentially timed clock expires the state is updated according to the probability distribution given by the relative rates of all the possible start actions in that state.
- When a deterministically timed clock expires there is only one possible next state.

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Note that function μ is not a bijection.
Specifically $\forall L \in \mathcal{L}_{\mathcal{D}} \,.\, \mu^{-1}(S(l, L)) = S(l)$,
i.e. we lose information about the structure of L, namely the actions started and not yet completed in $S(l, L)$.

Interchangeability

A Bio-PEPA process $P \in \mathcal{P}$ and a Bio-PEPAd process configuration $P_C \in \mathcal{C}$ are said to be interchangeable if and only if

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If P and P_C are interchangeable, then by definition $\mu(P) = P_C$ and all the lists appearing in P_C must be empty, i.e. there must be no uncompleted actions running.

Theorem: Relating processes and configurations

If P and P_C are interchangeable, then for any possible action derivable from P and leading to a state P', there exists a sequence of start and completion transitions, from P_C through P'_C to P''_C, such that P' and P''_C are interchangeable.

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Let $\mathcal{I} = \{(P, P_C) \mid P \in \mathcal{P}, P_C \in \mathcal{C}, \mu(P) = P_C, \mu^{-1}(P_C) = P\}$, then

$$\forall (P, P_C) \in \mathcal{I}.\ \forall P' \in \mathcal{P}.P \xrightarrow{(\alpha,w)}_c P' \implies$$
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Thus we can think of interchangeability as a simulation.

Theorem: Relating Bio-PEPA and Bio-PEPAd Systems

For any Bio-PEPA system $\langle \mathcal{T}, P \rangle$ there exists $P_C \in \mathcal{C}.(P, P_C) \in \mathcal{I}$ such that

$$
\begin{aligned}
&\forall P' \in \mathcal{P}.\ \langle \mathcal{T}, P \rangle \xrightarrow{(\alpha,r)}_s \langle \mathcal{T}, P' \rangle \\
&\qquad \Longrightarrow\ \forall \sigma \in \Delta. \langle \mathcal{T}, \sigma, P_C \rangle \xrightarrow{(\alpha^+, r, \sigma(\alpha))}_s \langle \mathcal{T}, \sigma, P'_C \rangle \\
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where $\langle \mathcal{T}, P \rangle$ denotes $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, Comp, P \rangle$ whenever we are not concerned with the elements of the system specifically, and similarly for $\langle \mathcal{T}, \sigma, P \rangle$.

Implications of Interchangeability

If a process and process configuration are interchangeable, then any of the possible Bio-PEPA systems is interchangeable to an infinity of different Bio-PEPAd systems.

This happens because any Bio-PEPAd system with the same $\mathcal{T}$ simulates the Bio-PEPA system, independently of the delays.

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The Bio-PEPA stochastic semantics are embedded in the Bio-PEPAd stochastic semantics.

Relating the stochastic semantics

The Bio-PEPA stochastic relation $\rightarrow_s$ is equivalently defined by the following inference rule

$$\frac{\begin{array}{c}\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, \mu(P) \rangle \xrightarrow{(\alpha^+, r_\alpha, \sigma(\alpha))}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, P'_C \rangle \\ \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, P'_C \rangle \xrightarrow{(\alpha^-, r_\alpha, \sigma(\alpha))}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, \mu(P') \rangle\end{array}}{\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, P \rangle \xrightarrow{(\alpha, r_\alpha)}_s \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, P' \rangle}$$

where σ is a generic function from Δ.

Relating trajectories

There are trajectories in the DSSA which are close to the SSA trajectory in the sense that no more than one delay is running at a time.

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The likelihood of following such a path depends on the probability of the stochastic derivations

$$\forall \alpha \in \mathcal{A}.\ \langle \sigma, \mu(P) \rangle \xrightarrow{(\alpha^{+}, r_{\alpha}, \sigma(\alpha))}_{s} \langle \sigma, P'_{C} \rangle \xrightarrow{(\alpha^{-}, r_{\alpha}, \sigma(\alpha))}_{s} \langle \sigma, \mu(P') \rangle\,.$$

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Let $(\!|\mu(P)|\!) = \mathbf{x}$, $(\!|P'_C|\!) = \mathbf{x} + \nu^r_\alpha$, $(\!|\mu(P')|\!) = \mathbf{x} + \nu^r_\alpha + \nu^p_\alpha = \mathbf{x} + \nu_\alpha$ where ν^r_α and ν^p_α denote the stoichiometry vector for the reactants and the products and are such that $\nu_\alpha = \nu^r_\alpha + \nu^p_\alpha$.

Relating trajectories

- In state $\mathbf{x}$, the next value for $\tau \sim Exp(a_0(\mathbf{x}))$ is sampled and reaction R_j is chosen to fire with probability $a_j(\mathbf{x})/a_0(\mathbf{x})$; (the scheduling list is empty since $P_C \equiv \mu(P)$.)

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- If $\tau' > \sigma_\alpha$ then the state changes to $\mathbf{x} + \nu_\alpha$ and time to $t + \sigma_\alpha$, otherwise a new reaction is scheduled.
- The case $\tau' > \sigma_\alpha$ has probability $\exp(-a_0(\mathbf{x} + \nu^r_\alpha)\sigma_\alpha)$.

Relating trajectories

Since events are independent, if we generalize among all possible reactions we get equation

$$p(\mathbf{x}) = \sum_{i=1}^{m} \frac{a_i(\mathbf{x})}{a_0(\mathbf{x})} e^{-a_0(\mathbf{x}+\nu_i^r)\sigma_i}.$$

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In systems where $\forall R_i.\ f_{\alpha_i}[w, \mathcal{N}, \mathcal{K}] = a_i(\mathbf{x}) = r_{\alpha_i}$, we can write a probability which is logically equivalent to $p(\mathbf{x})$ for $\mu(P)$ as

$$\mathbb{P}(\mu(P)) = \sum_{i=1}^{m} \frac{f_{\alpha_i}[w, \mathcal{N}, \mathcal{K}]}{ExitRate(\mu(P))} e^{-ExitRate(\mu(P))\sigma(\alpha_i)}.$$

Relating trajectories

Note that

$$\lim_{\sigma \to \infty} \mathbb{P}(\mu(P)) = 0 \qquad \lim_{\sigma \to 0} \mathbb{P}(\mu(P)) = \sum_{i=1}^{m} \frac{f_{\alpha_i}[w, \mathcal{N}, \mathcal{K}]}{ExitRate(\mu(P))}$$

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In particular, in the limit $\sigma \to 0$ the probability of making the stochastic transition reduces to the probability of leaving P, in its associated CTMC.

Thus the probability of observing, during a simulation of a Bio-PEPAd model, a series of steps which correspond to the interchangeable Bio-PEPA process is the closure of $\mathbb{P}(\mu(P))$.

Outline

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Bio-PEPA

Bio-PEPAd

Analysis of Bio-PEPAd

Bio-PEPAd vs. Bio-PEPA

Conclusions

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- Bio-PEPAd is a conservative extension of Bio-PEPA.
- The firing of actions with delays is assumed to follow the delay-as-duration abstraction.

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- Based on the semantics, the encoding of Bio-PEPAd systems in GSMP has been given and mapping to other analysis frameworks have been demonstrated.
- The expressiveness of Bio-PEPA and Bio-PEPAd have been compared at a semantic level, and results proved about the probabilities of performing actions in the two algebras.

On-going work

There are several strands of possible further development of Bio-PEPAd:

- It could be interesting to consider the alternative interpretation of delays, the so-called purely delayed abstraction, rather than the delay as duration abstraction.
- We could consider the combination of delayed and non-delayed actions.
- Based on the developed semantics we could equip Bio-PEPAd with equivalence relations, perhaps based on the previously defined relations for Bio-PEPA.
- And course there is always more work to do on case studies and tool development!

Thank you!