Bio-PEPAd: Integrating exponential and deterministic delays

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Joint work with Giulio Caravagna

Outline

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- 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) ;
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Actions with delays in biochemistry

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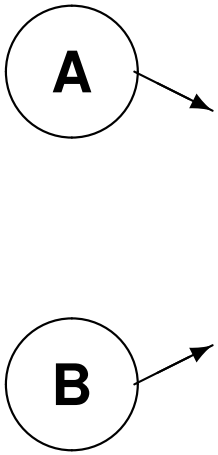

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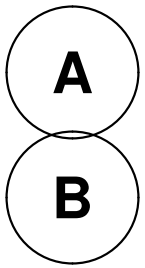

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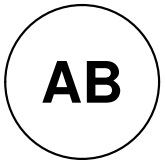

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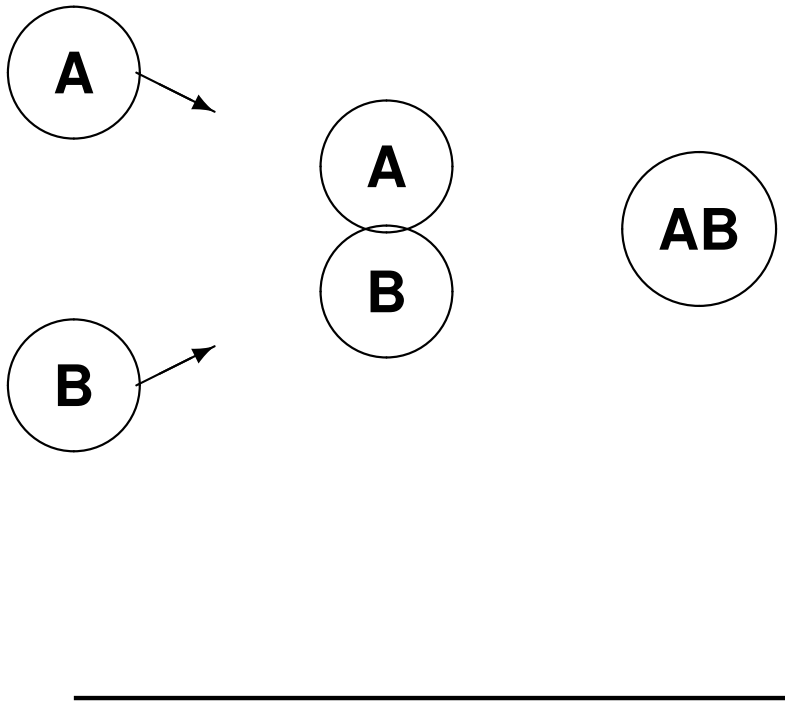

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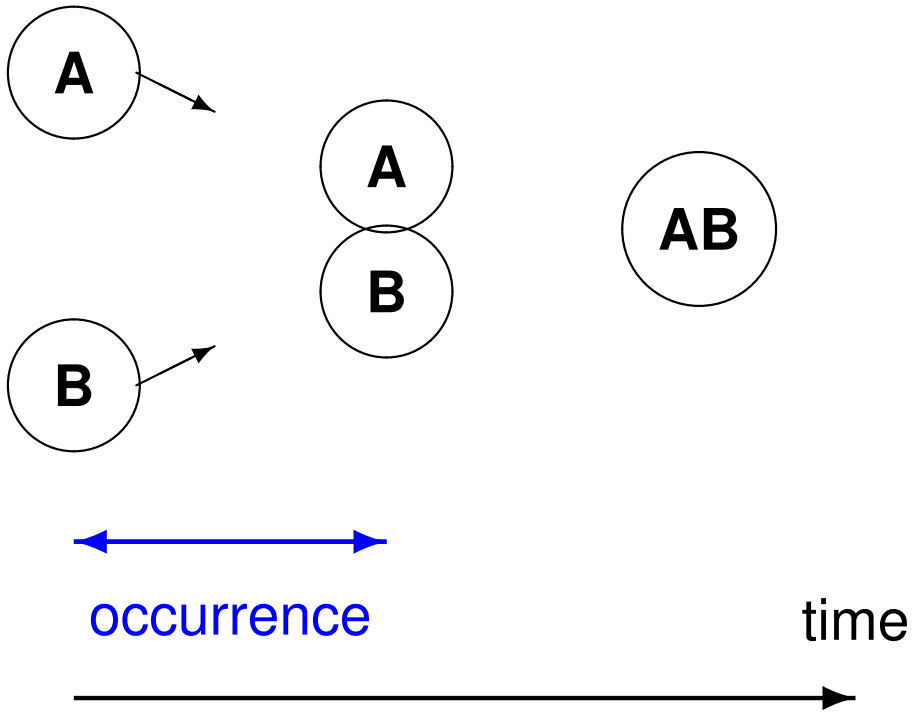

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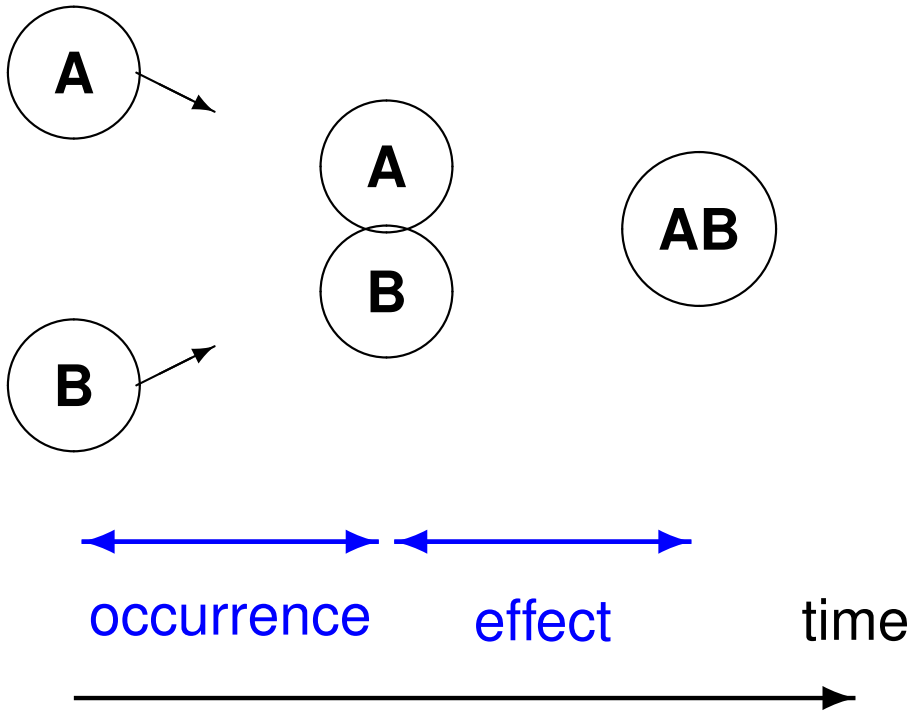

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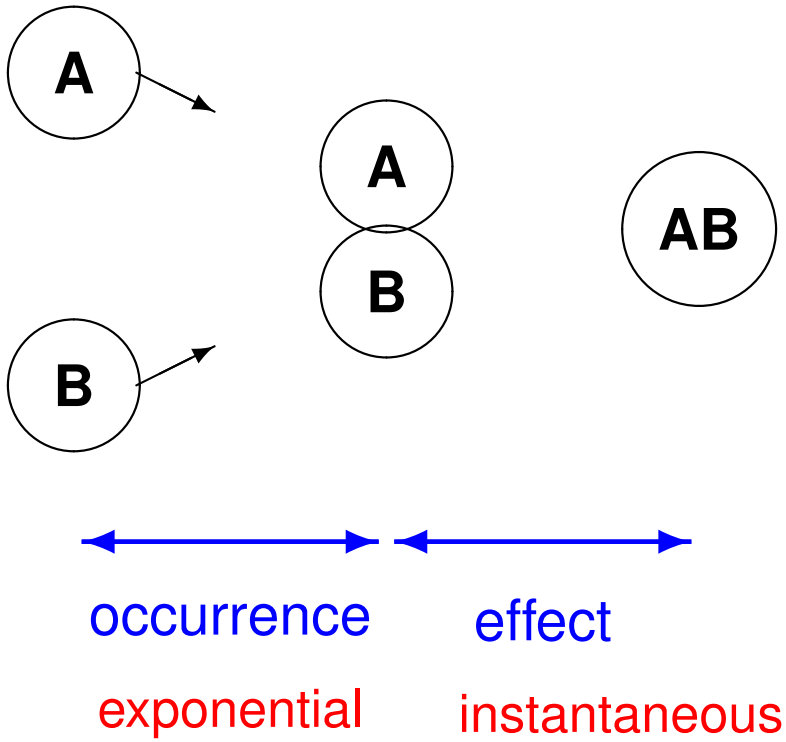

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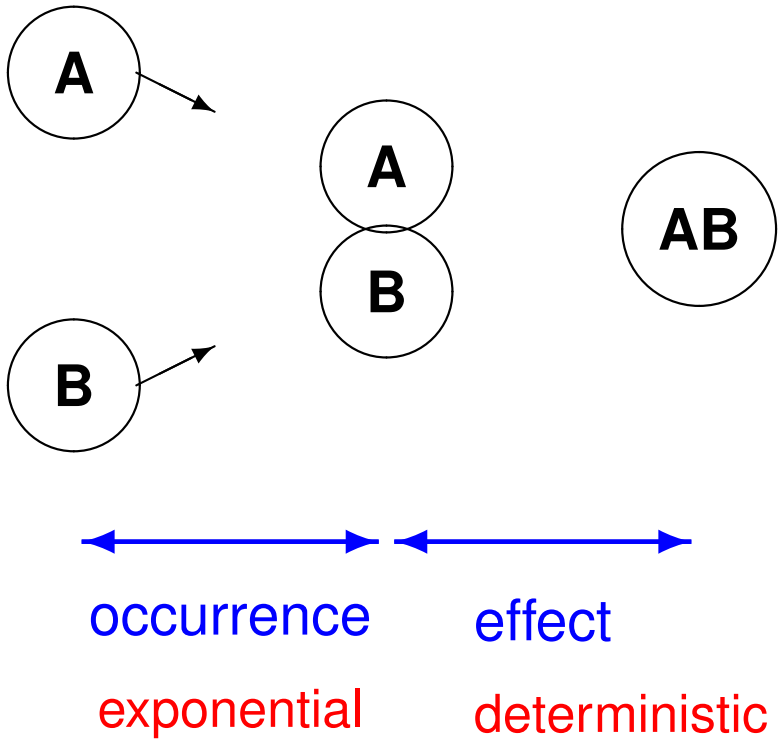

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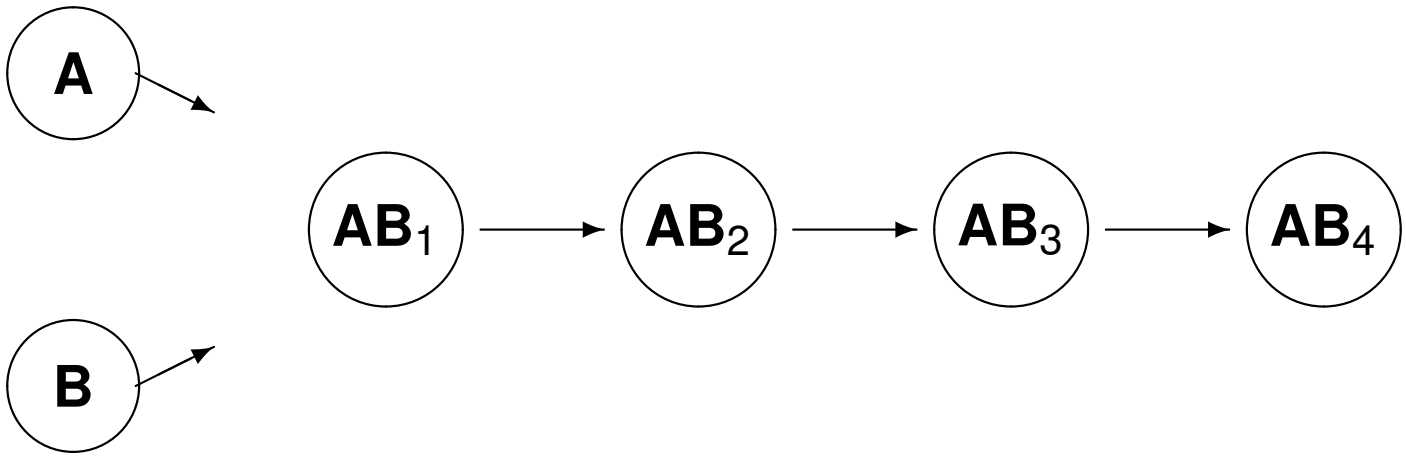

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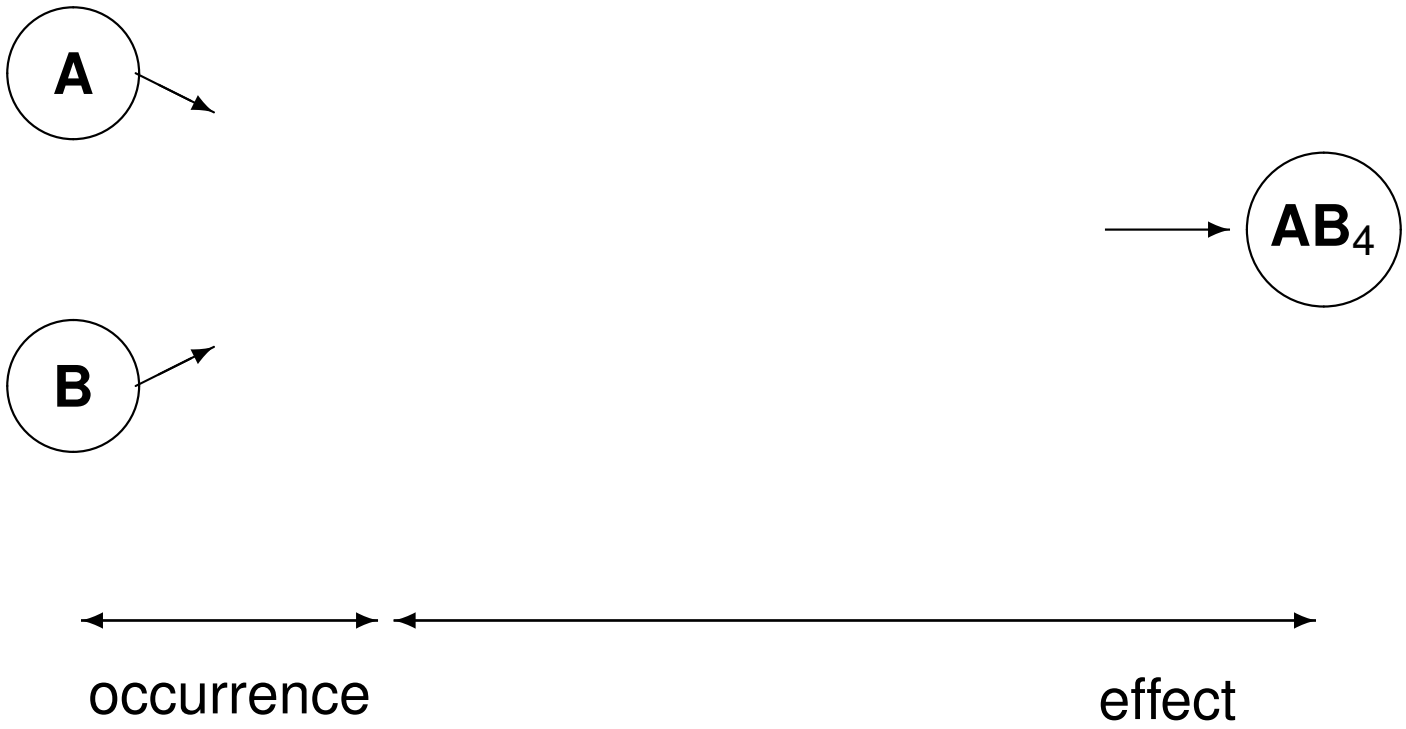

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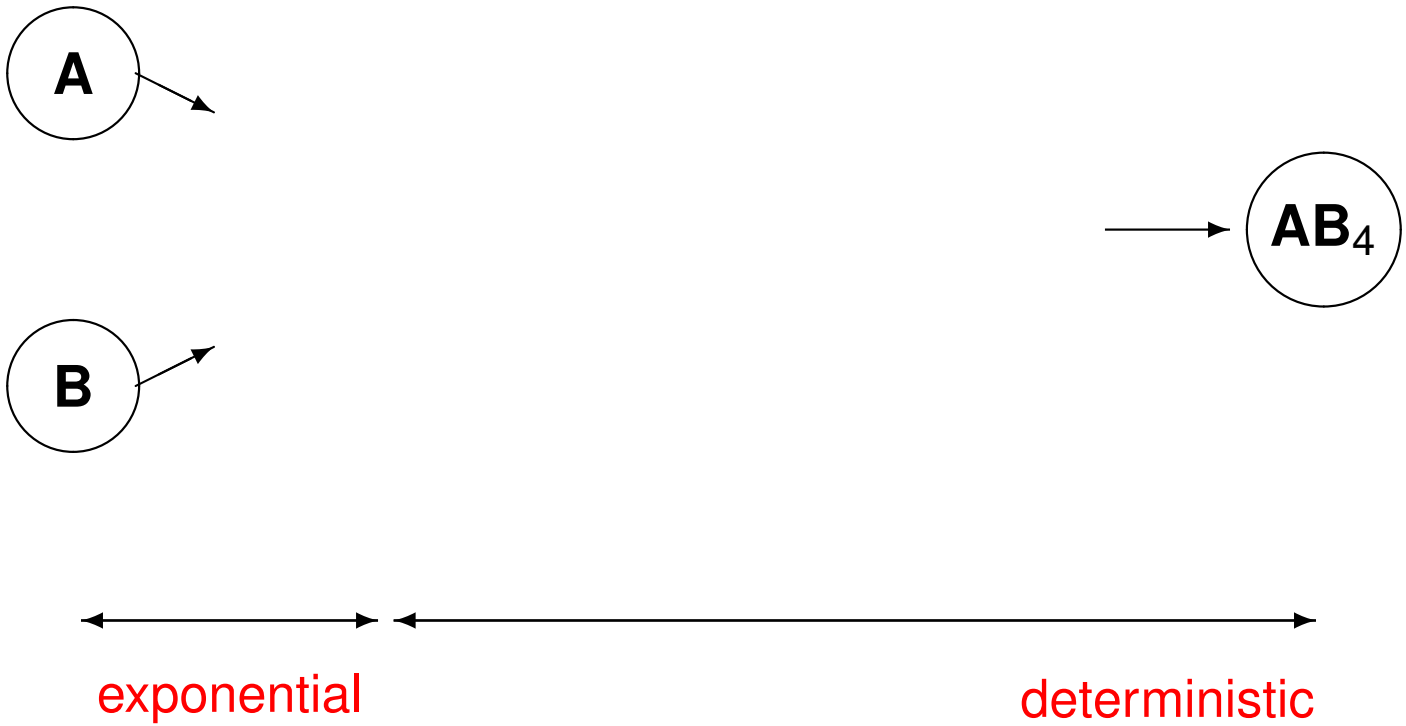

Outline

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

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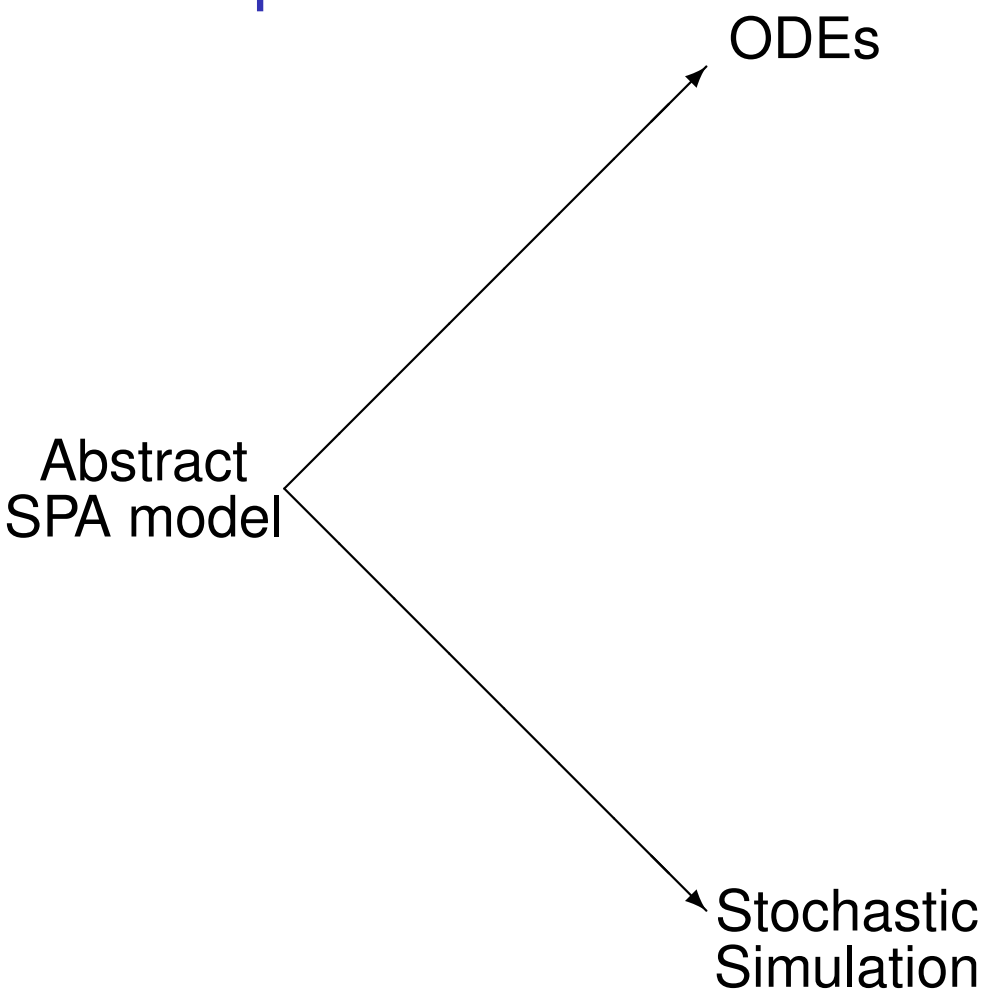
Instead it is based on the species as processes abstraction which means that it readily supports a number of different kinds of analysis.

Alternative Representations



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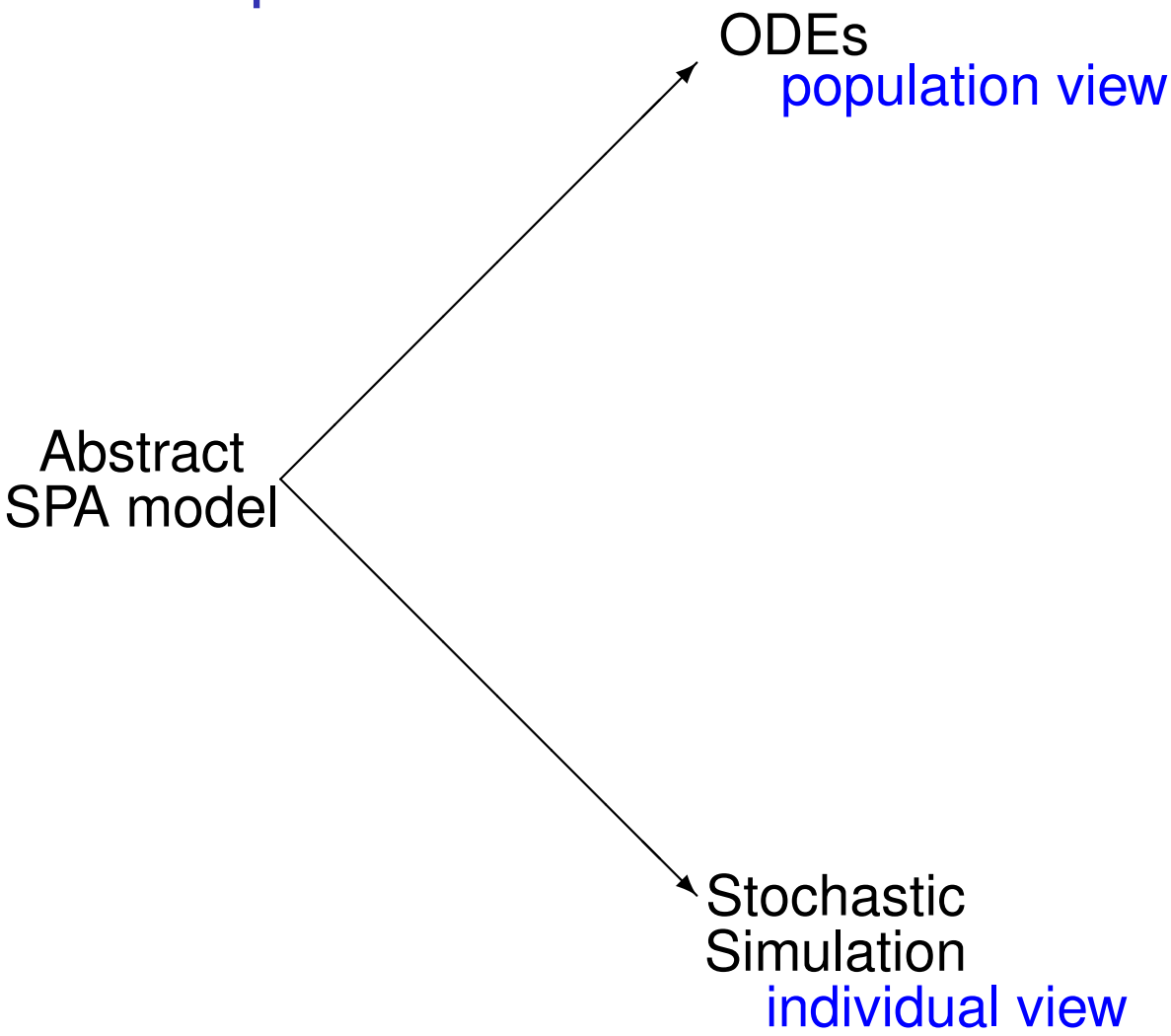

Discretising the population view

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.

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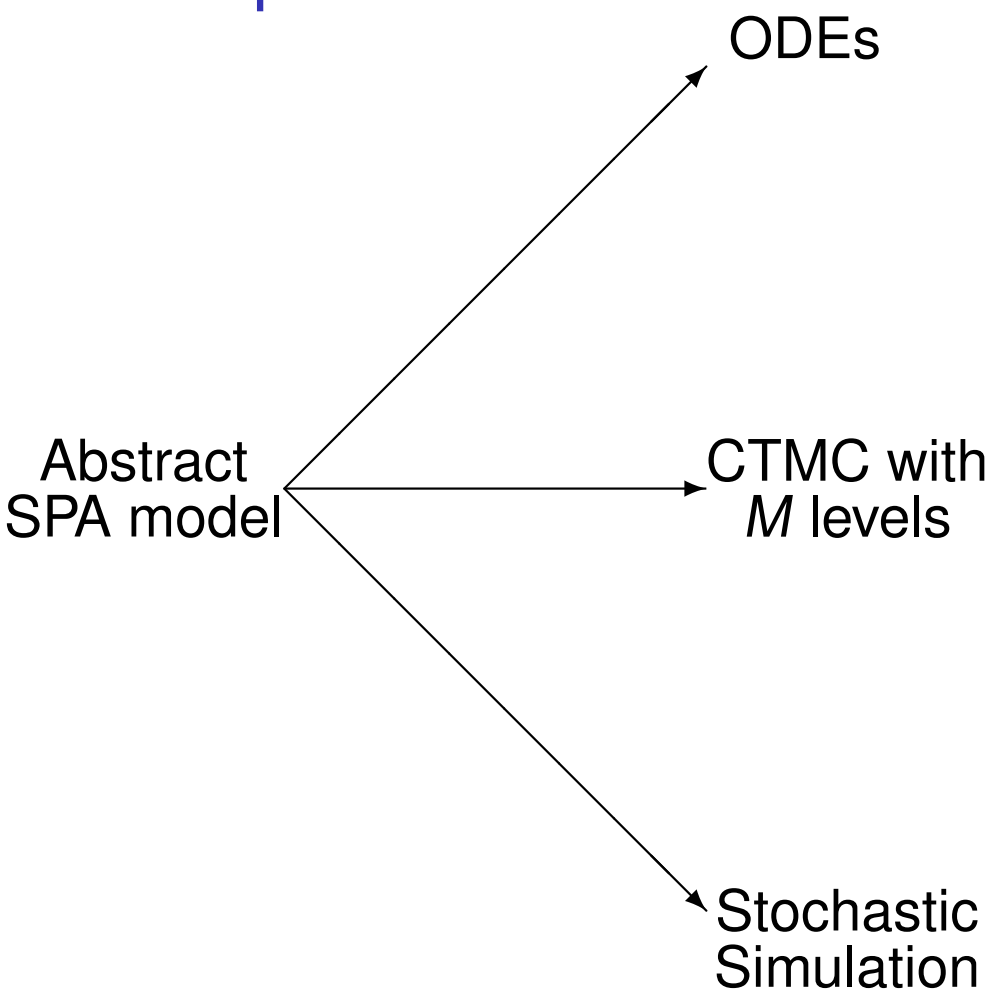

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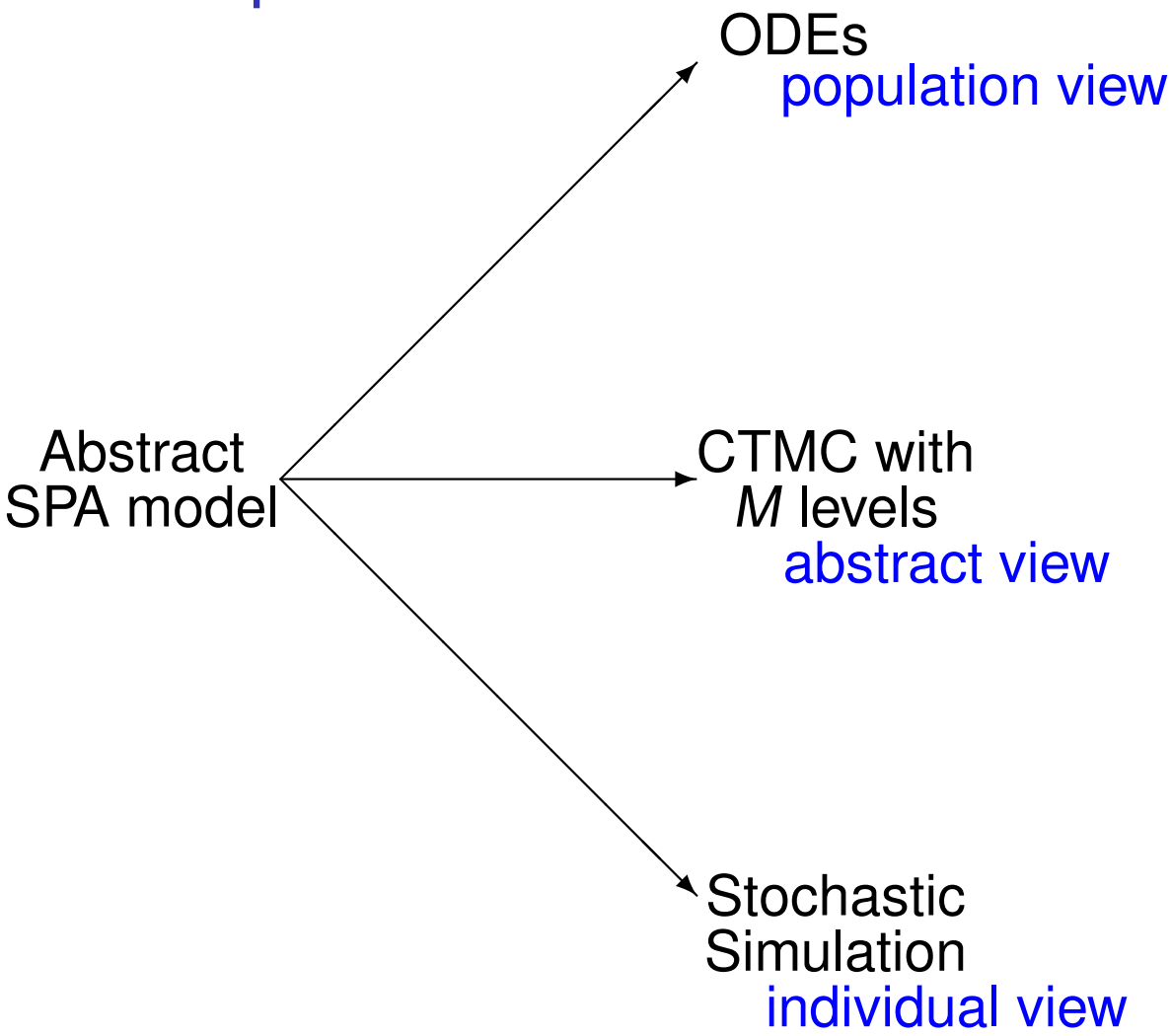

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- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour. These rates may be specified by functions.
- The representation of an action within a component (species) records the stoichiometry 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)

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

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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),
- concentration (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

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

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

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

Semantics: cooperation rules

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

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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

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

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

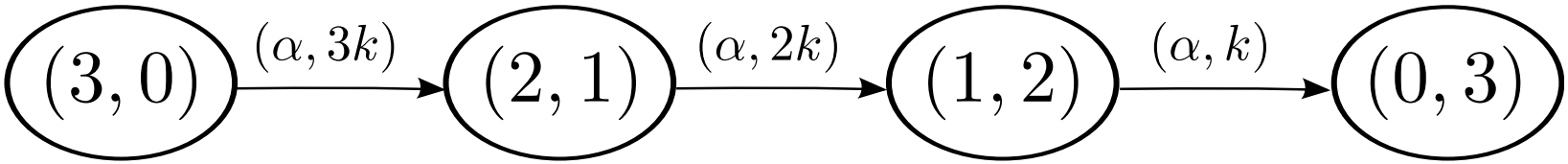
The components of the system in which this process is embedded are:

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

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

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

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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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:

$$C_S ::= (\alpha, \kappa)op\ C_S \mid C_S + C_S \mid C$$
$$C_P ::= C_P \underset{\mathcal{L}}{\bowtie} C_P \mid C_S(l, L)$$

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.

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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 $\mu : \mathcal{P} \rightarrow C$ such that

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

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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

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

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

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

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

The start relation

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

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

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

The start relation

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

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The completion relation

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

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

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The stochastic relation

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

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Timing aspects of Bio-PEPAd

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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:

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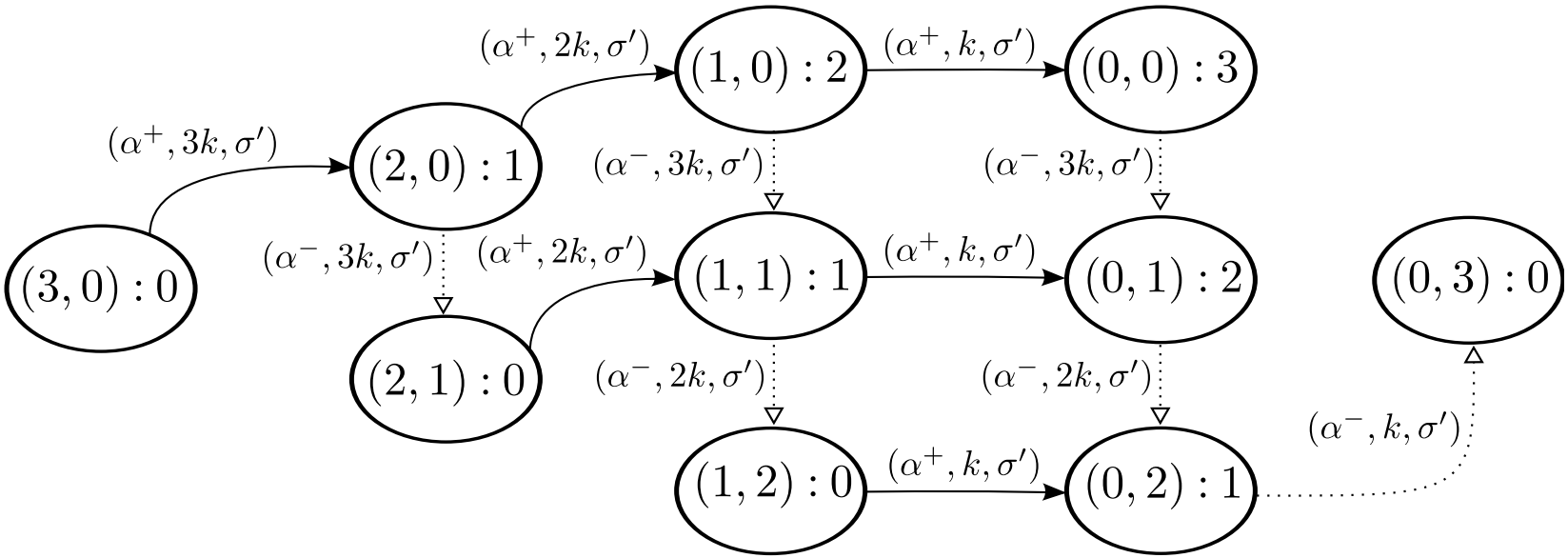
The initial configuration of the process, obtained by applying the function μ is

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

The SLTS for the Bio-PEPAd example



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

Outline

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:

Abstract 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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Only Step 2 differs from the Bio-PEPAd/DDE case.

Step 1

We enumerate the actions as $\alpha_1, \ldots, \alpha_m$ and the species in the system as $S_1, \ldots, S_n$.

The entry $d_{i,j}$, representing the change in the levels induced by performing action α_j with species S_i, is defined as follows:

$$d_{i,j} = \begin{cases} -\kappa_{i,j} & \text{if } (\alpha_j, \kappa_{i,j})\downarrow \text{ is an action for species } S_i \\ +\kappa_{i,j} & \text{if } (\alpha_j, \kappa_{i,j})\uparrow \text{ is an action for species } S_i \\ 0 & \text{otherwise.} \end{cases}$$

Step 2

Let x_i denote the deterministic variable representing species S_i, where mass action and Michaelis Menten reactions have two species S_1 and $S2$, whereas hill kinetic reactions have a single species S_1.

The entry $\overline{\nu_{KL}}_i$ of the vector is defined as follows:

$$\overline{\nu_{KL}}_i = \begin{cases} kx_1(t-\sigma(\alpha_i))x_2(t-\sigma(\alpha_i)) & \text{if } f_{\alpha_i} = f_{MA}(k) \\ \dfrac{vx_1(t-\sigma(\alpha_i))x_2(t-\sigma(\alpha_i))}{K + x_2(t-\sigma(\alpha_i))} & \text{if } f_{\alpha_i} = f_{MM}(v,K) \\ \dfrac{vx_1(t-\sigma(\alpha_i))^p}{K + x_1(t-\sigma(\alpha_i))^p} & \text{if } f_{\alpha_i} = f_H(v,K,p) \end{cases}$$

Step 3 and Initialization

As in Bio-PEPA, now we associate the variable x_i with each species component S_i and so define the n-dimensional vector $\overline{x}$.

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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

In order to prepare a Bio-PEPAd system for simulation using DSSA we need to

1. Define the algebraic representation of the process;
2. Create the reactions to simulate.

Encoding the process

We introduce a family of functions

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

to encode a Bio-PEPA process/Bio-PEPAd process configuration in an n-dimensional vector such that:

$$(\!|S_1(l_1) \underset{\mathcal{L}_1}{\bowtie} \ldots \underset{\mathcal{L}_m}{\bowtie} S_m(l_m)|\!)_m = (l_1, \ldots, l_m)^T$$

$$(\!|S_1(l_1, L_1) \underset{\mathcal{L}_1}{\bowtie} \ldots \underset{\mathcal{L}_n}{\bowtie} S_n(l_n, L_n)|\!)_n = (l_1, \ldots, l_n)^T .$$

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Given $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, \sigma, P \rangle$ and $\mathbf{x}'_0 = (\!|P|\!)$, a vector $\mathbf{x}_0$ of the initial number of molecules is $\mathbf{x}_0[i] = \mathbf{x}'_0[i] \times h \times N_A \times v$ where h is the step size, v is the volume and N_A is the Avogadro number.

Creating the reactions

The actual rates of the reactions have to be defined, case by case, using the parameters in $\mathcal{F}$.

This is done in the same way for Bio-PEPAd as it is for Bio-PEPA.

DSS Algorithm

1: $t \leftarrow t_0$; $\mathbf{x} \leftarrow \mathbf{x}_0$; $S \leftarrow \emptyset$;
2: **while** $t < T$ **do**
3: $\quad a_0(\mathbf{x}) \leftarrow \sum_{j=1}^{M} a_j(\mathbf{x})$;
4: $\quad$ let $r_1, r_2 \sim U[0,1]$;
5: $\quad \tau \leftarrow a_0(\mathbf{x})^{-1} \ln({r_1}^{-1})$;
6: $\quad$ let $S_{t,\tau} = \{(t'', \nu'') \in S \mid t'' \in (t, t+\tau]\}$;
7: $\quad$ **if** $S_{t,\tau} \neq \emptyset$ **then**
8: $\quad\quad (t', \nu') \leftarrow \min\{S_{t,\tau}\}$;
9: $\quad\quad \mathbf{x} \leftarrow \mathbf{x} + \nu'$; $t \leftarrow t'$; $S \leftarrow S \backslash \{(t', \nu')\}$;
10: $\quad$ **else**
11: $\quad\quad$ let j such that $\sum_{i=1}^{j-1} a_i(\mathbf{x}) < r_2 \cdot a_0(\mathbf{x}) \leq \sum_{i=1}^{j} a_i(\mathbf{x})$;
12: $\quad\quad \mathbf{x} \leftarrow \mathbf{x} + \nu_j^r$; $t \leftarrow t + \tau$; $S \leftarrow S \cup \{(t + \tau + \sigma_j, \nu_j^p)\}$;
13: $\quad$ **end if**
14: **end while**

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- 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.

Outline

Relating Bio-PEPAd and Bio-PEPA

In order to relate Bio-PEPAd and Bio-PEPA we start by defining the inverse of function μ.

$$\mu^{-1}((\alpha,\kappa)op\ S) = (\alpha,\kappa)op\ S$$
$$\mu^{-1}(P_1 \underset{\mathcal{L}}{\bowtie} P_2) = \mu^{-1}(P_1) \underset{\mathcal{L}}{\bowtie} \mu^{-1}(P_2)$$
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$$\mu^{-1}(S(l, L)) = S(l)\,.$$

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

$$\forall (P, P_C) \in \mathcal{I}.\ \forall P' \in \mathcal{P}.P \xrightarrow{(\alpha,w)}_c P' \implies$$

$$\exists P'_C, P''_C \in \mathcal{C}.P_C \xrightarrow{(\alpha^+,w)}_{st} P'_C \xrightarrow{(\alpha^-,w)}_{co} P''_C \ \wedge\ (P', P''_C) \in \mathcal{I}$$

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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

$$\forall P' \in \mathcal{P}.\ \langle \mathcal{T}, P \rangle \xrightarrow{(\alpha, r)}_s \langle \mathcal{T}, P' \rangle$$

$$\Longrightarrow\ \forall \sigma \in \Delta.\langle \mathcal{T}, \sigma, P_C \rangle \xrightarrow{(\alpha^+, r, \sigma(\alpha))}_s \langle \mathcal{T}, \sigma, P'_C \rangle$$

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where $\langle \mathcal{T}, P \rangle$ denotes $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \mathit{Comp}, P \rangle$ 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

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

where σ is a generic function from Δ.

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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 $\exp(-a_0(\mathbf{x} + \nu_\alpha^r)\sigma_\alpha)$.

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-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!