Integrated Analysis from Abstract Stochastic Process Algebra Models

Jane Hillston.
LFCS and CSBE, University of Edinburgh

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Joint work with Federica Ciocchetta, Adam Duguid, Stephen Gilmore and Maria Luisa Guerriero

Outline

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Introduction

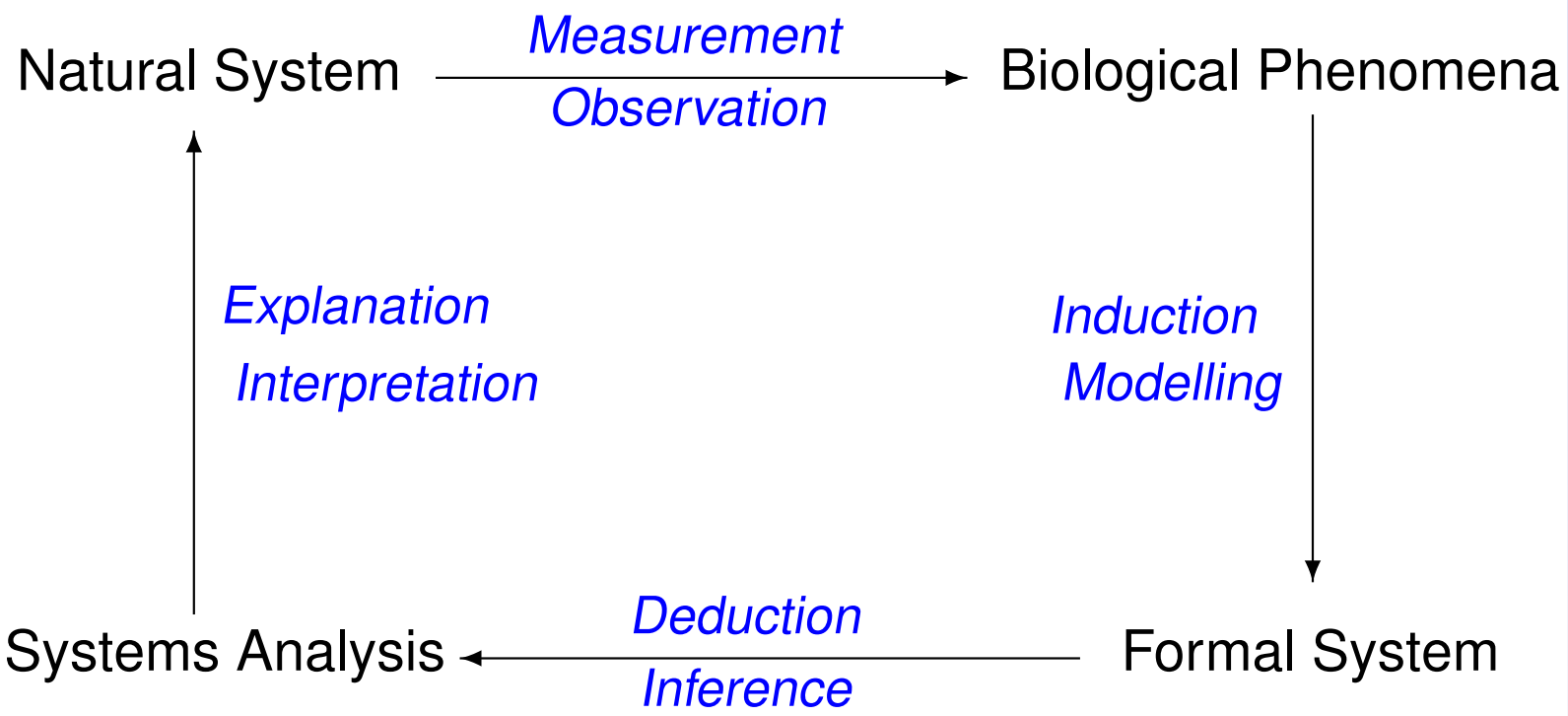
Bio-PEPA
Stochastic Process Algebra
Reagent-centric modelling
Syntax and semantics

Model Analysis
Mappings to analysis tools
Multiple analyses

Example
Goldbeter's model

Closing remarks
On-going work
Conclusions

Systems Biology Methodology



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- Ordinary Differential Equations:
  - continuous time,
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- Ordinary Differential Equations:
  - continuous time,
  - continuous behaviour (concentrations),
  - deterministic.
- Stochastic Simulation:
  - continuous time,
  - discrete behaviour (no. of molecules),
  - stochastic.

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- Previous experience in computer performance modelling has shown us that there can be benefits to interposing a formal model between the system and the underlying mathematical model.
- Moreover taking this "high-level programming" style approach offers the possibility of different "compilations" to different mathematical models: integrative modelling.

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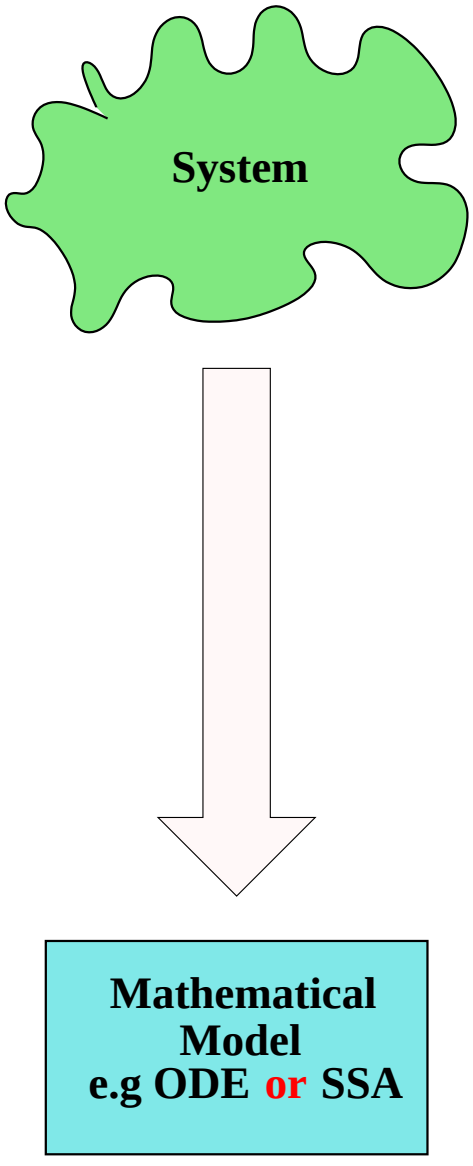

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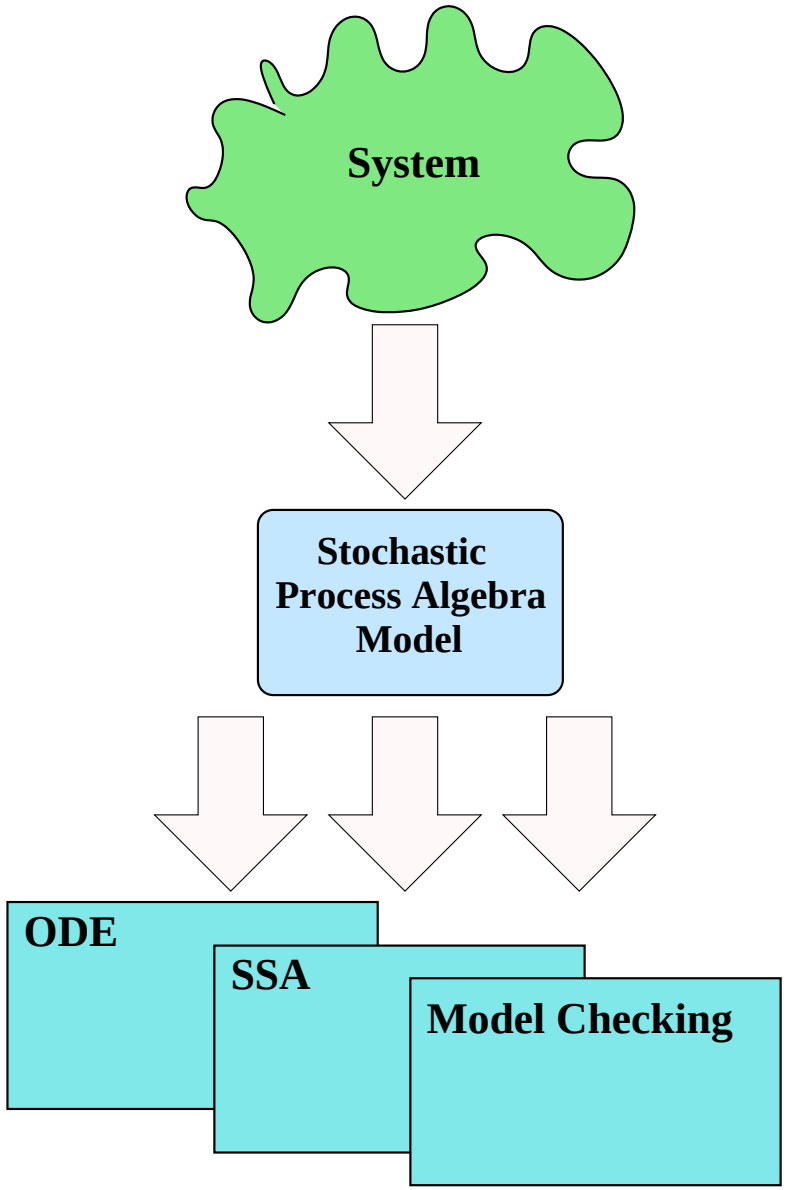

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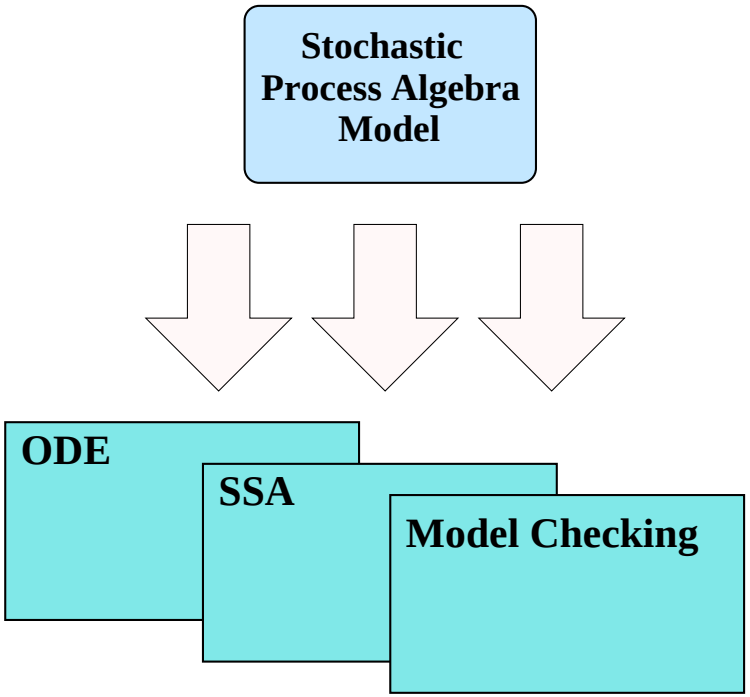

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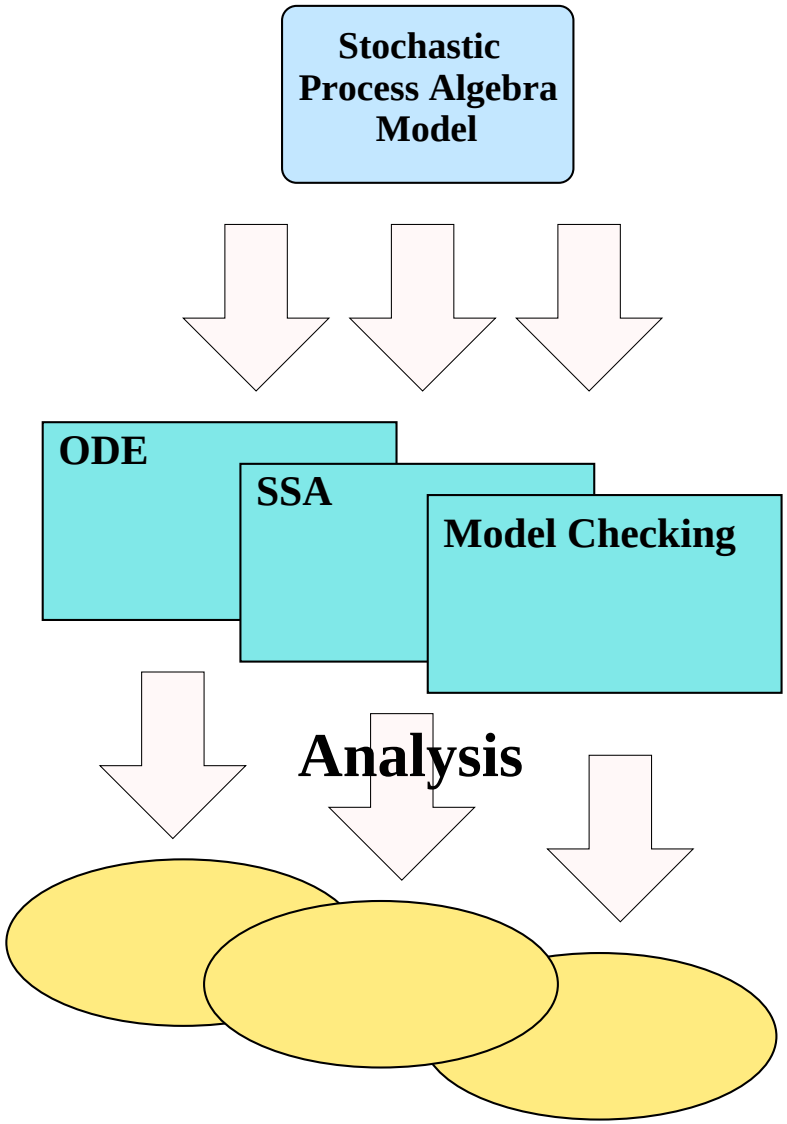

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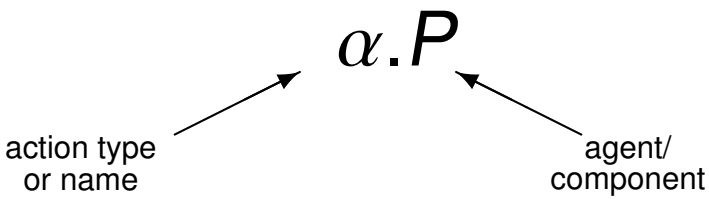

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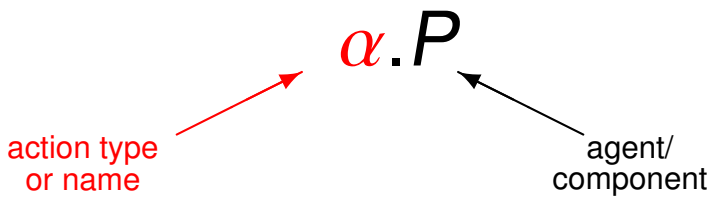

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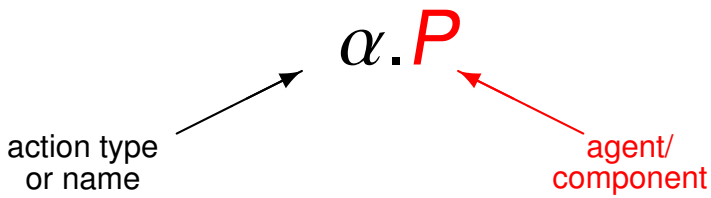

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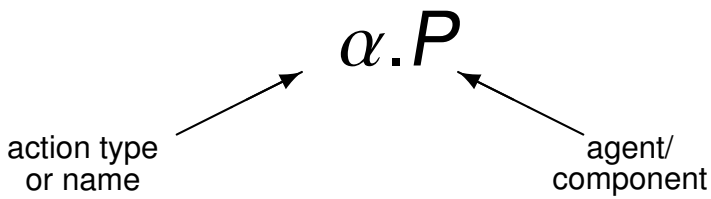

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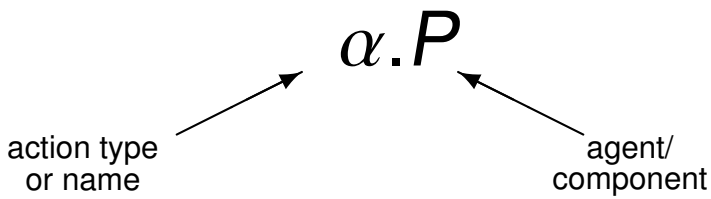

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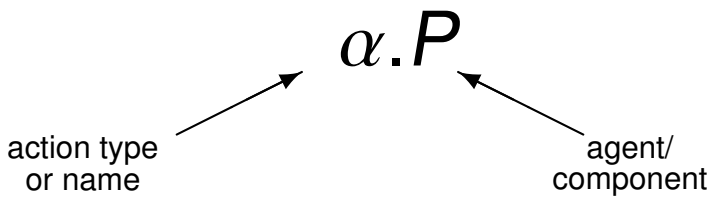

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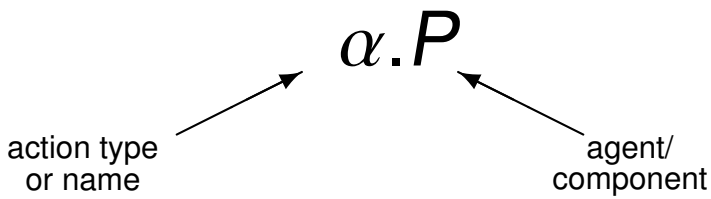

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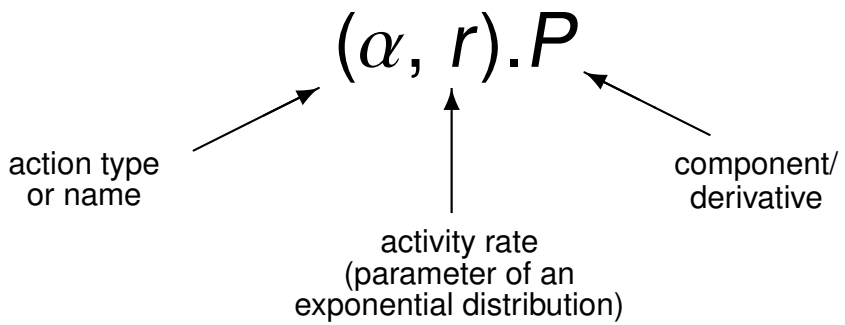

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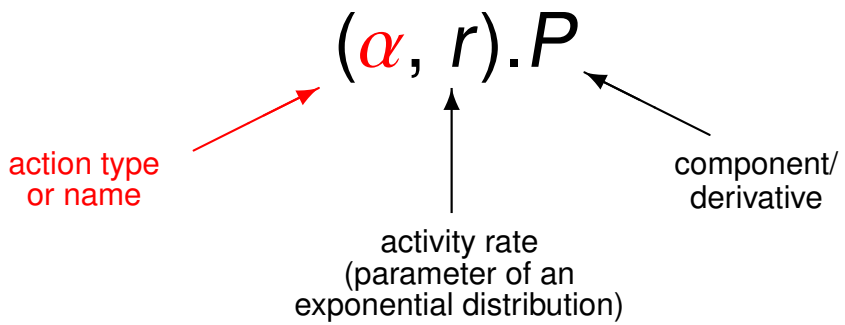

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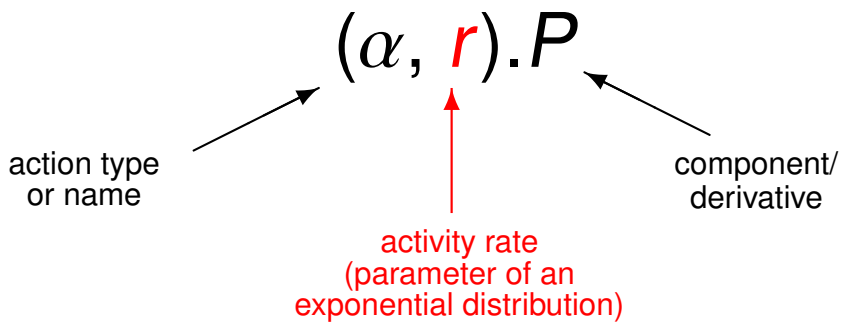

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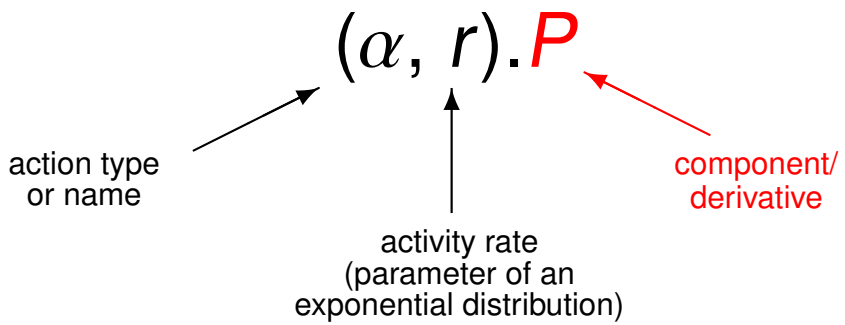

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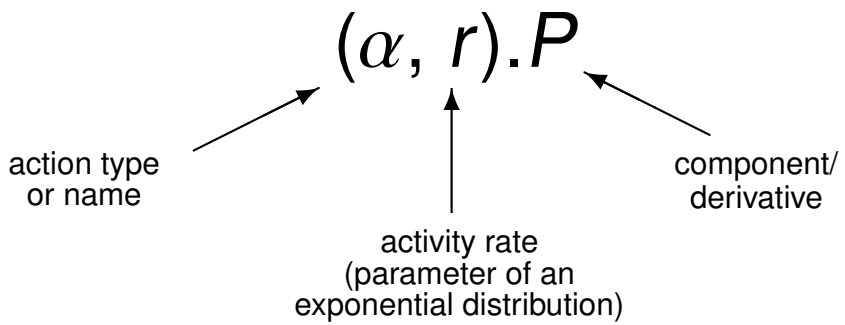

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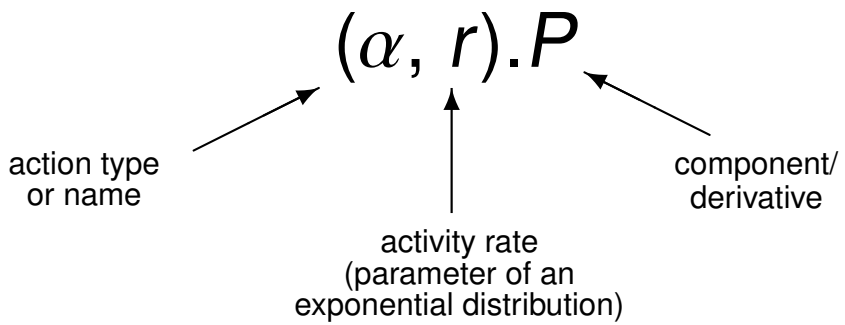

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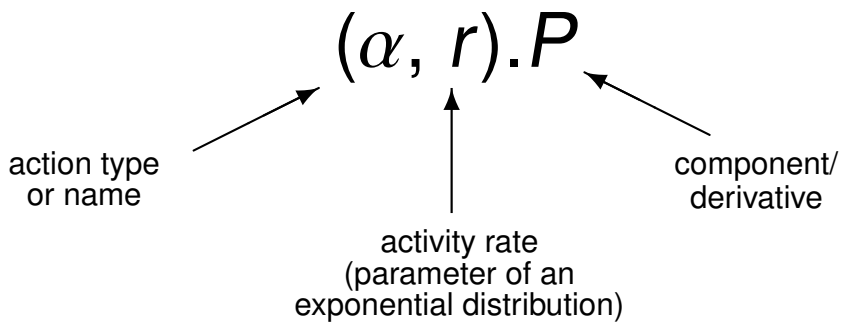

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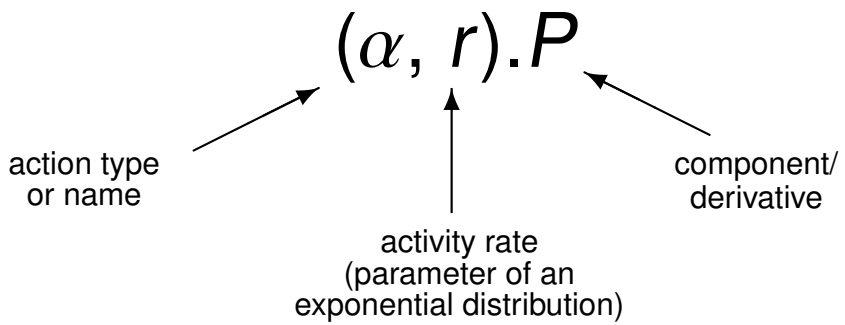

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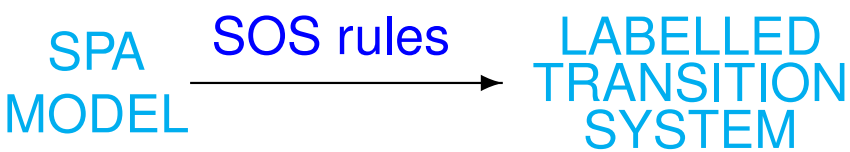

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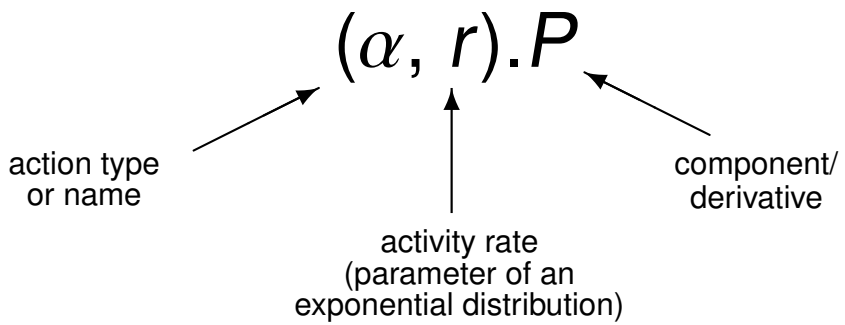

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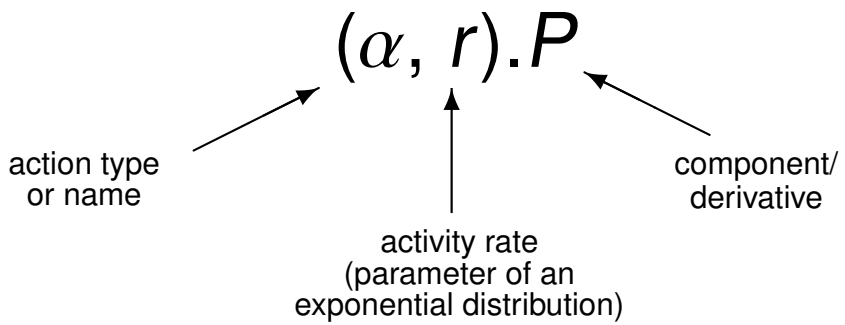

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Molecular processes as concurrent computations

Concurrency	**Molecular Biology**	**Signal Transduction**
Concurrent computational processes	Molecules	Interacting proteins
Synchronous communication	Molecular interaction	Binding and catalysis
Transition or mobility	Biochemical modification or relocation	Protein binding, modification or sequestration

[Regev *et al* 2000]

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We also wanted to be able to capture more of the biological features expressed in the models such as those found in the BioModels database.

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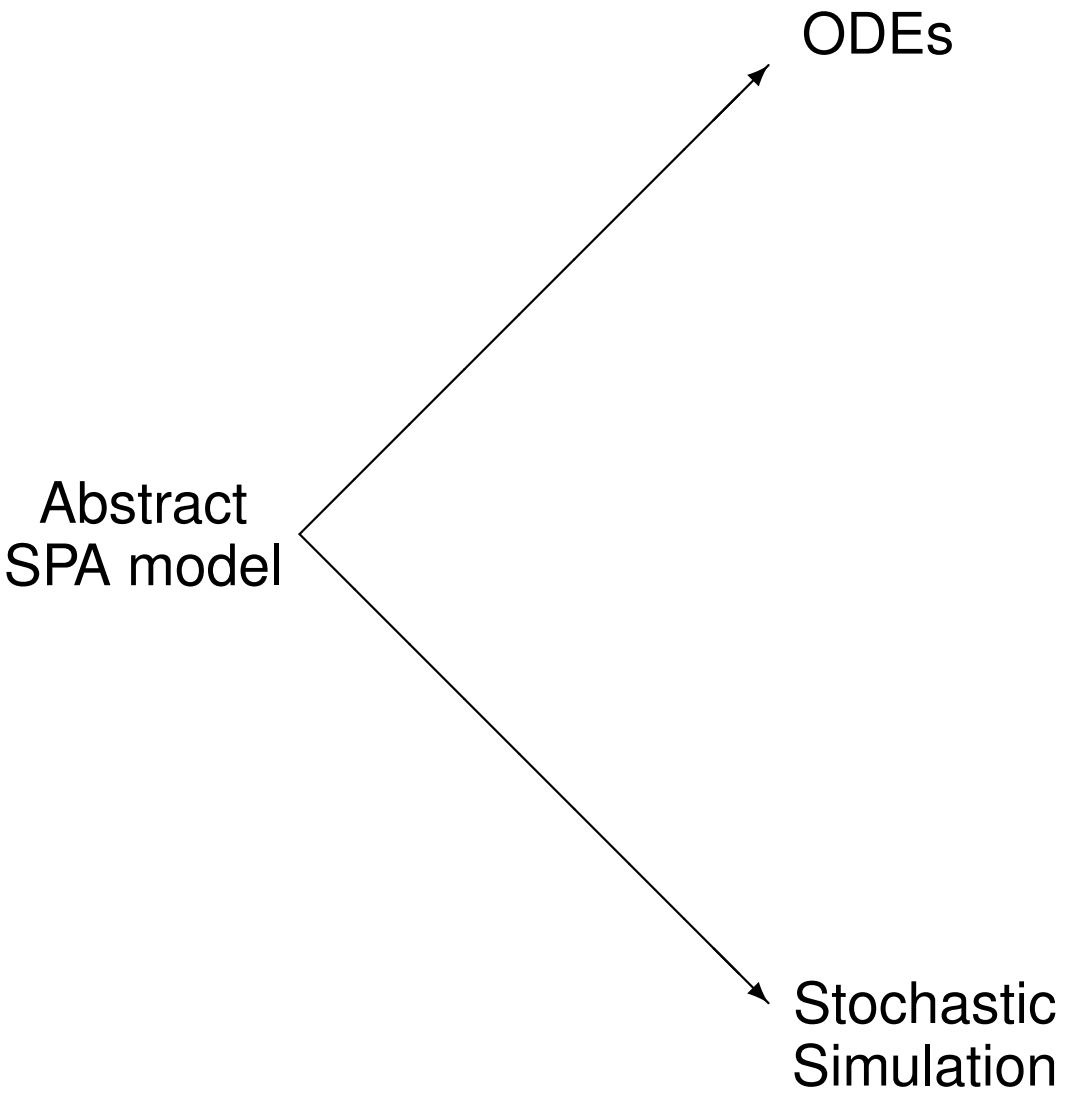
  This suggests that it can be useful to use semi-quantitative models rather than quantitative ones.

Alternative Representations



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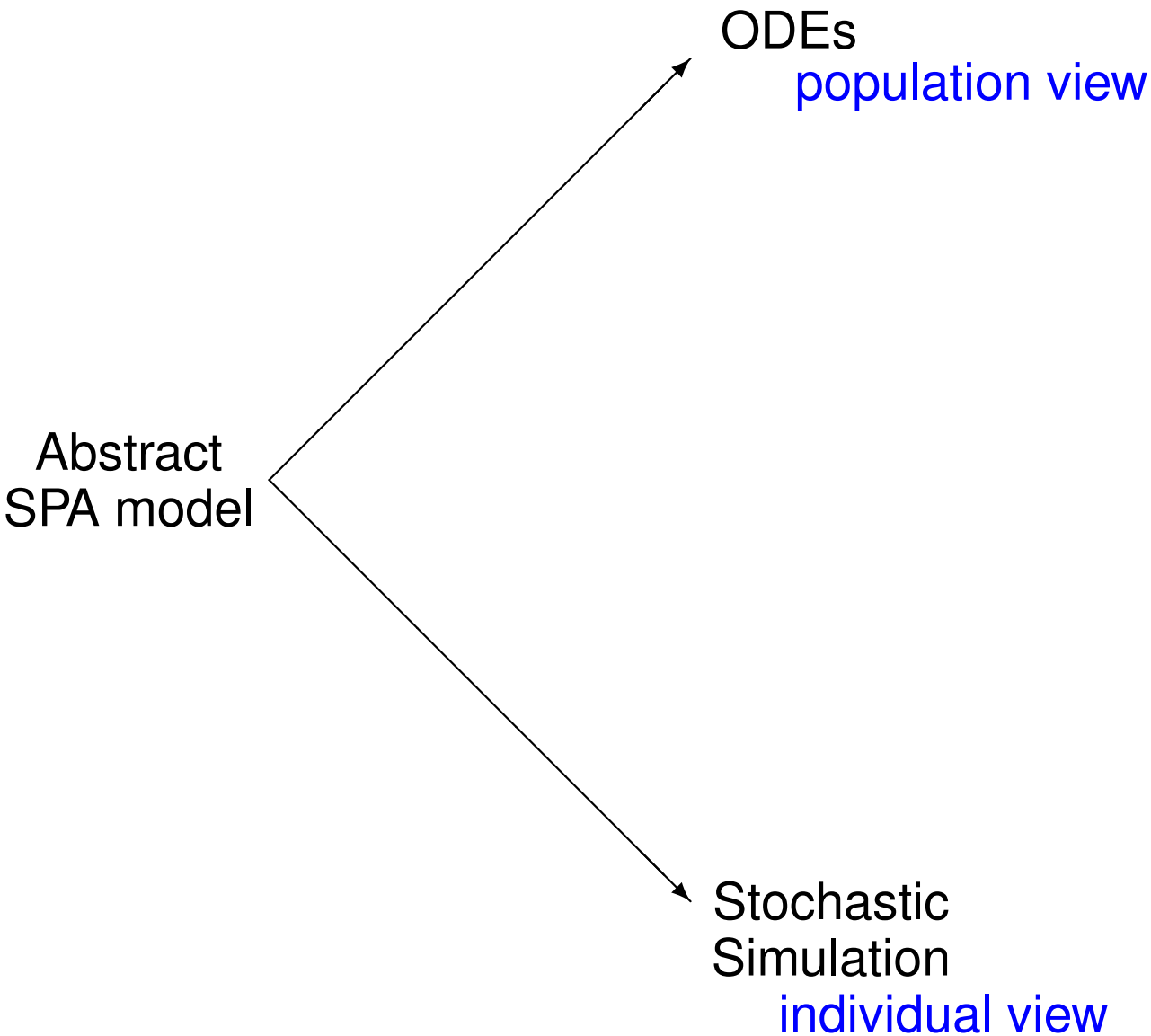

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Discretising the population view

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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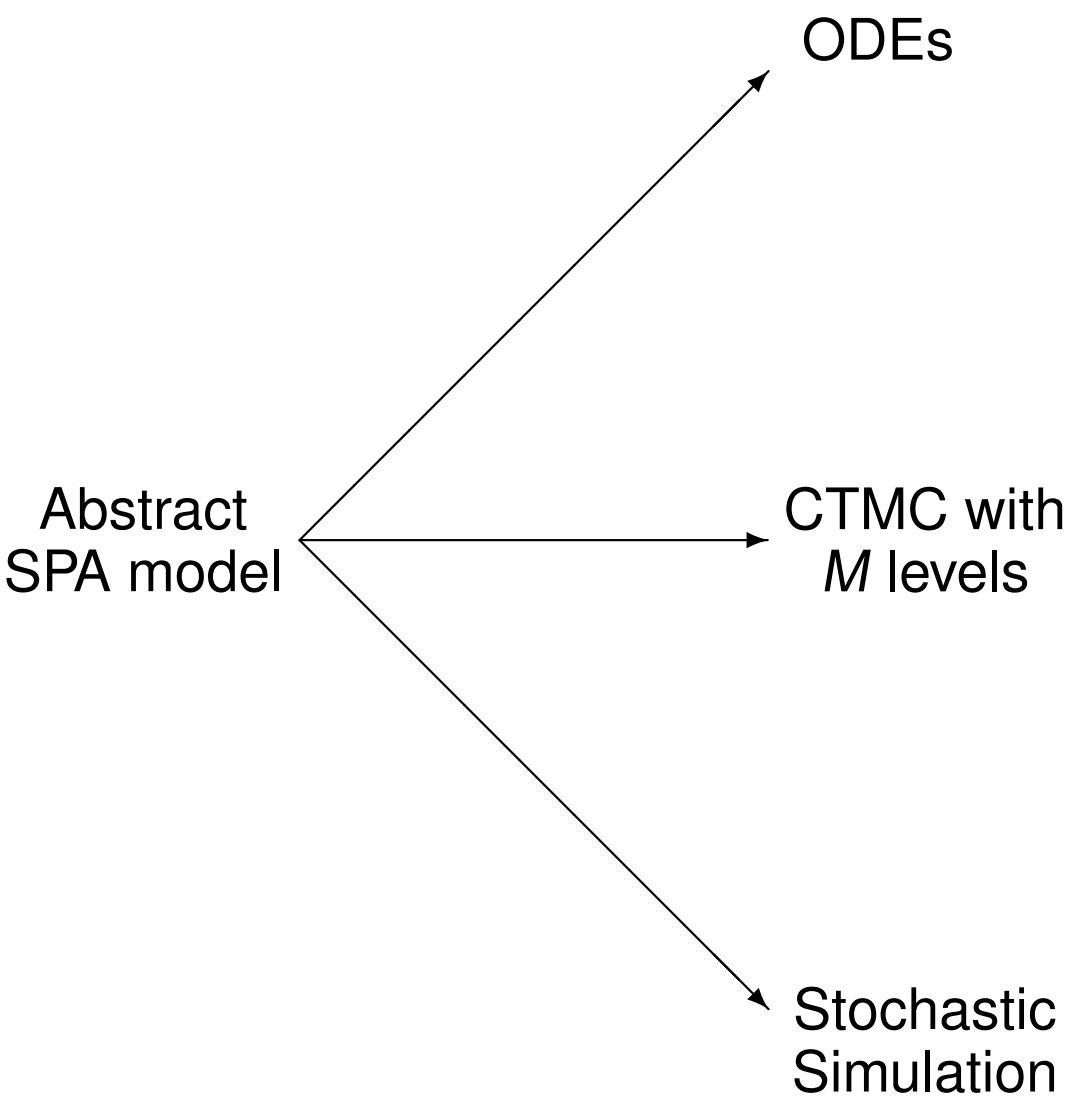

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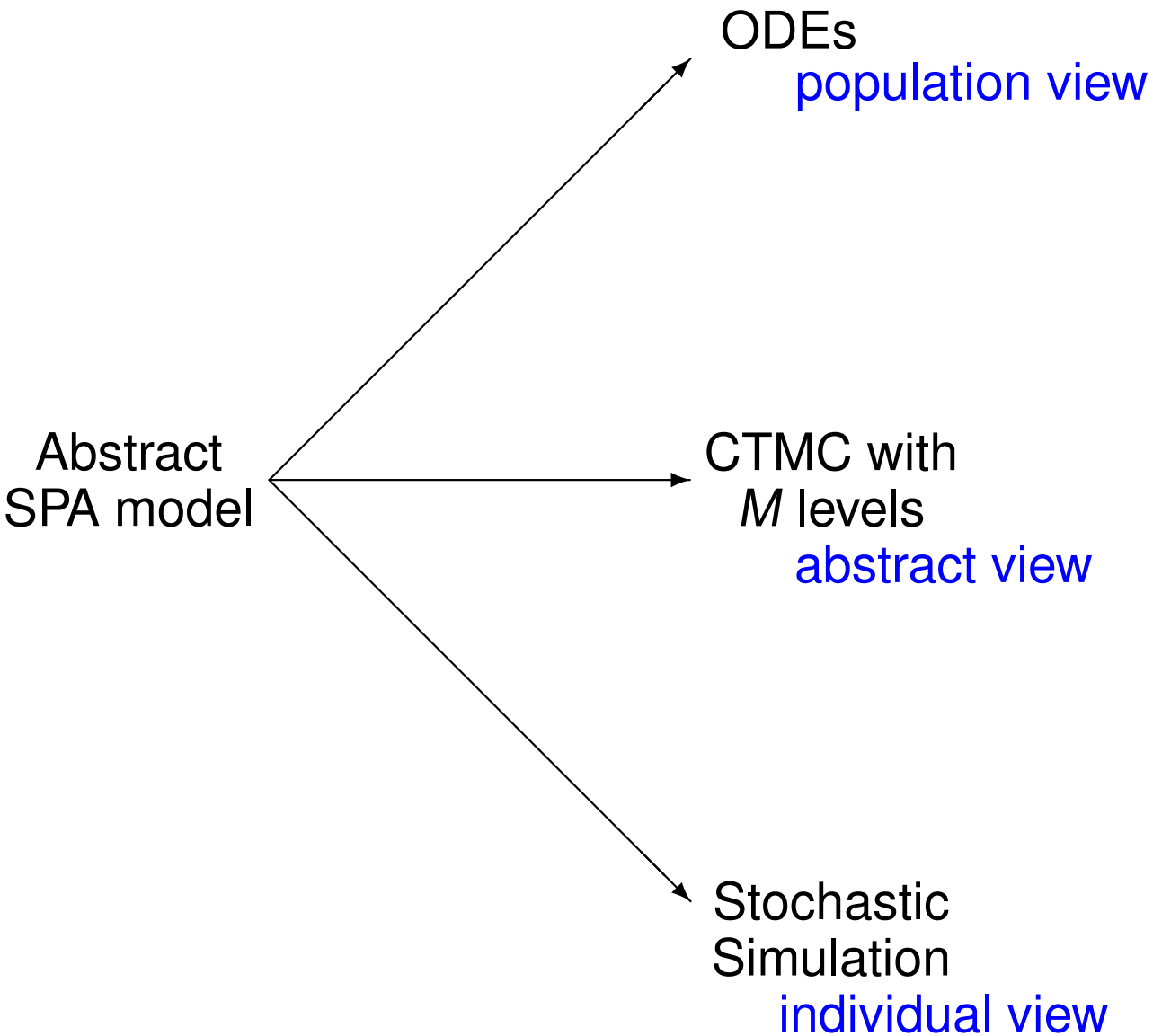

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- In models with levels, each level of granularity gives rise to a CTMC, and the behaviour of this sequence of Markov processes converges to the behaviour of the system of ODEs.
- Some analyses which can be carried out via numerical solution of the CTMC are not readily available from ODEs or stochastic simulation.

Modelling biological features

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Particular problems are encountered with:

- stoichiometry — the multiplicity in which an entity participates in a reaction;
- general kinetic laws — although mass action is widely used other kinetics are also commonly employed.
- multiway reactions — although thermodynamic arguments can be made that there are never more than two reagents involved in a reaction, in practice it is often useful to model at a more abstract level.

Illustration

Consider a conversion of a substrate S, with stoichiometry 2, to a product P, under the influence of an enzyme E, i.e.

$$2 \times S \xrightarrow{E} P$$

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In the stochastic π-calculus (for example) this must modelled as a sequence of unary and binary reactions:

- $S + S \longrightarrow 2S$
- $2S + E \longrightarrow 2S : E$
- $2S : E \longrightarrow P : E$
- $P : E \longrightarrow P + E$

Illustration cont.

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The use of multiway synchronisation, and the reagent-centric style of modelling, avoids these problems

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In Bio-PEPA this is described as:

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\begin{aligned}
S &\stackrel{def}{=} (\alpha, 2)\downarrow S \\
E &\stackrel{def}{=} (\alpha, 1) \oplus E \\
P &\stackrel{def}{=} (\alpha, 1)\uparrow P
\end{aligned}
$$

$$
(S(l_{S0}) \underset{\{\alpha\}}{\bowtie} E(l_{E0})) \underset{\{\alpha\}}{\bowtie} P(l_{P0})
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The dynamics is described by the law $f_\alpha = \frac{v \times E \times S^2}{(K + S^2)}$.

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- 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.

Reagent-centric view [CGH BioCONCUR04]

Role	*Impact on reaction rate*	*Impact on reagent*
Reactant	positive impact, e.g. proportional to current concentration	decreases level
Product	no impact, except at saturation	increases level
Enzyme	positive impact, e.g. proportional to current concentration	level unchanged
Inhibitor	negative impact, e.g. inversely proportional to current concentration	level unchanged

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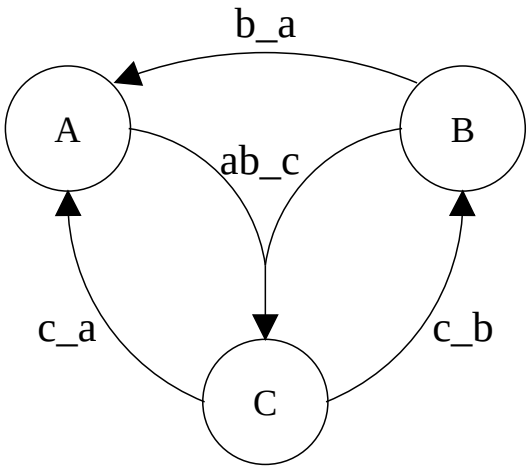
Bio-PEPA reagent-centric example



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&\quad + (c\_b, 1)\uparrow B \\
C &\stackrel{def}{=} (c\_a, 1)\downarrow C + (c\_b, 1)\downarrow C \\
&\quad + (ab\_c, 1)\uparrow C
\end{aligned}
$$

$$
\Big(A(l_{A0}) \underset{\{ab\_c, b\_a\}}{\bowtie} B(l_{B0})\Big) \underset{\{ab\_c, c\_a, c\_b\}}{\bowtie} C(l_{C0})
$$

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.

The system description records the impact of action on this quantity which 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.

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The semantics of Bio-PEPA is given as a small-step operational semantics.

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

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

Semantics: rates and transition system

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

Outline

Introduction

Bio-PEPA

Stochastic Process Algebra
Reagent-centric modelling
Syntax and semantics

Model Analysis

Mappings to analysis tools
Multiple analyses

Example

Goldbeter's model

Closing remarks

On-going work
Conclusions

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Each of these kinds of analysis can be of help for studying different aspects of the biological model. Moreover we are exploring how they can be used in conjunction.

Analysis with Bio-PEPA

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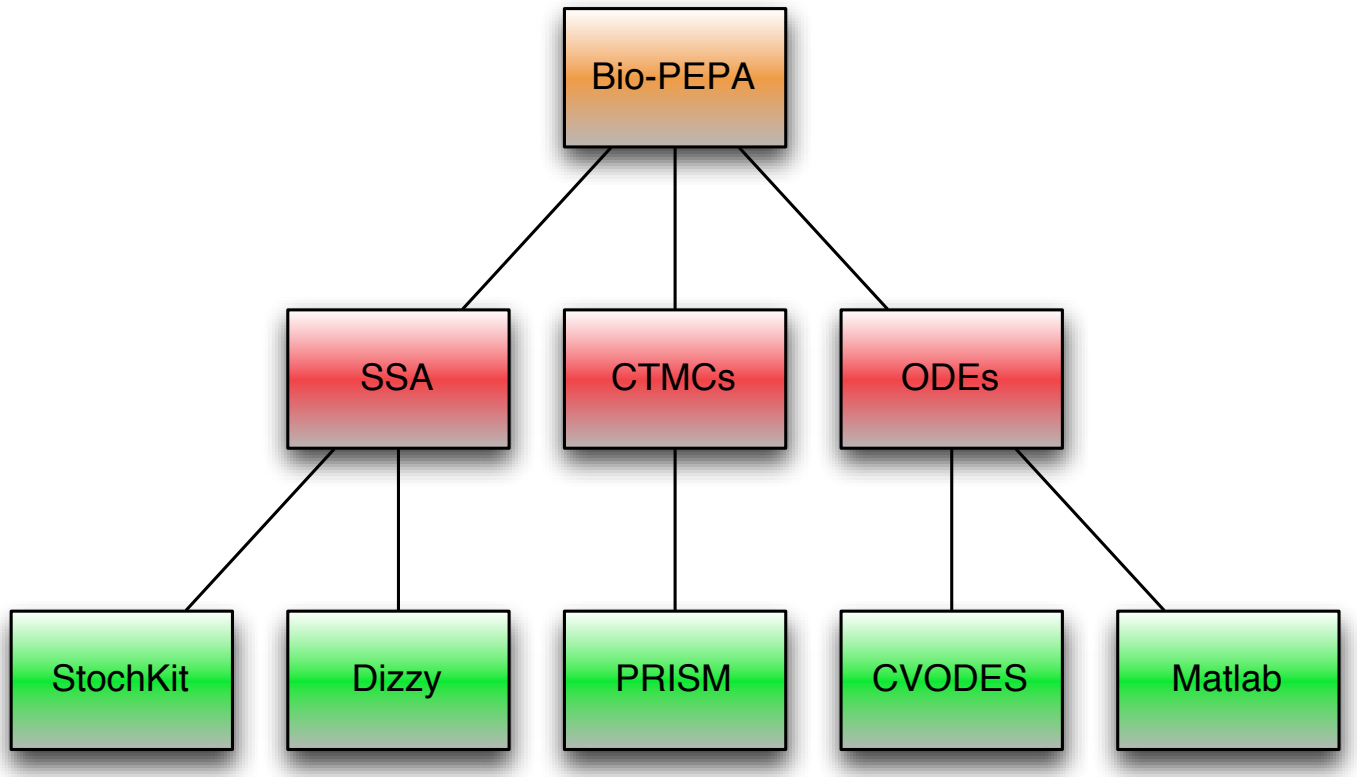

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SPA
MODEL

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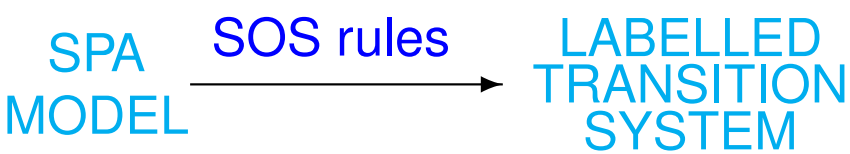

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- The structure of the CTMC derived from Bio-PEPA, which we term the CTMC with levels, will depend on the granularity of the model.
- As the granularity tends to zero the behaviour of this CTMC with levels tends to the behaviour of the ODEs [CDHC FBTC08].

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  - The process algebra model allow us to derive properties of the model, such as freedom from deadlock, before numerical analysis is carried out.
  - The algebraic formulation of the model emphasises interactions between the biochemical entities.

Analysing Bio-PEPA models with Matlab

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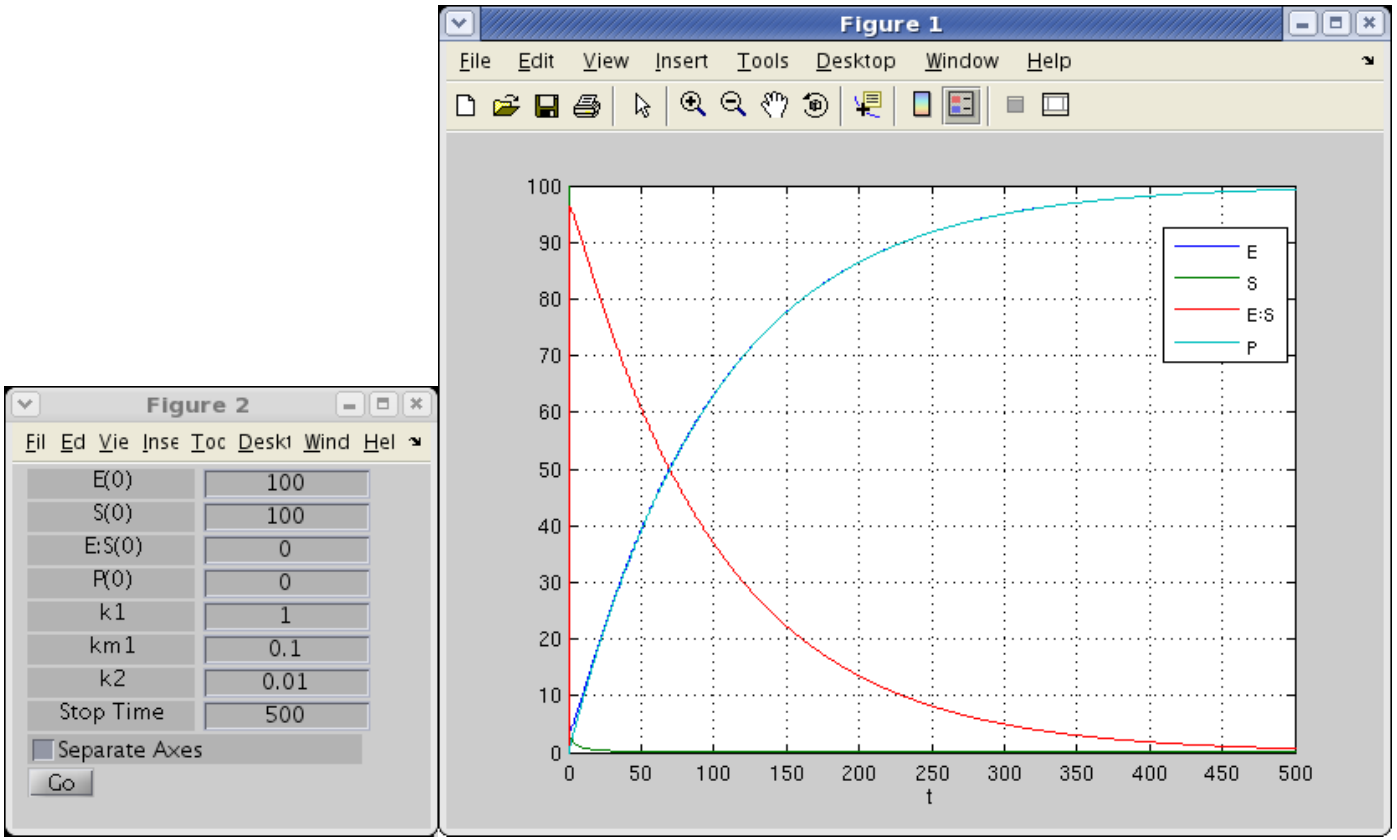

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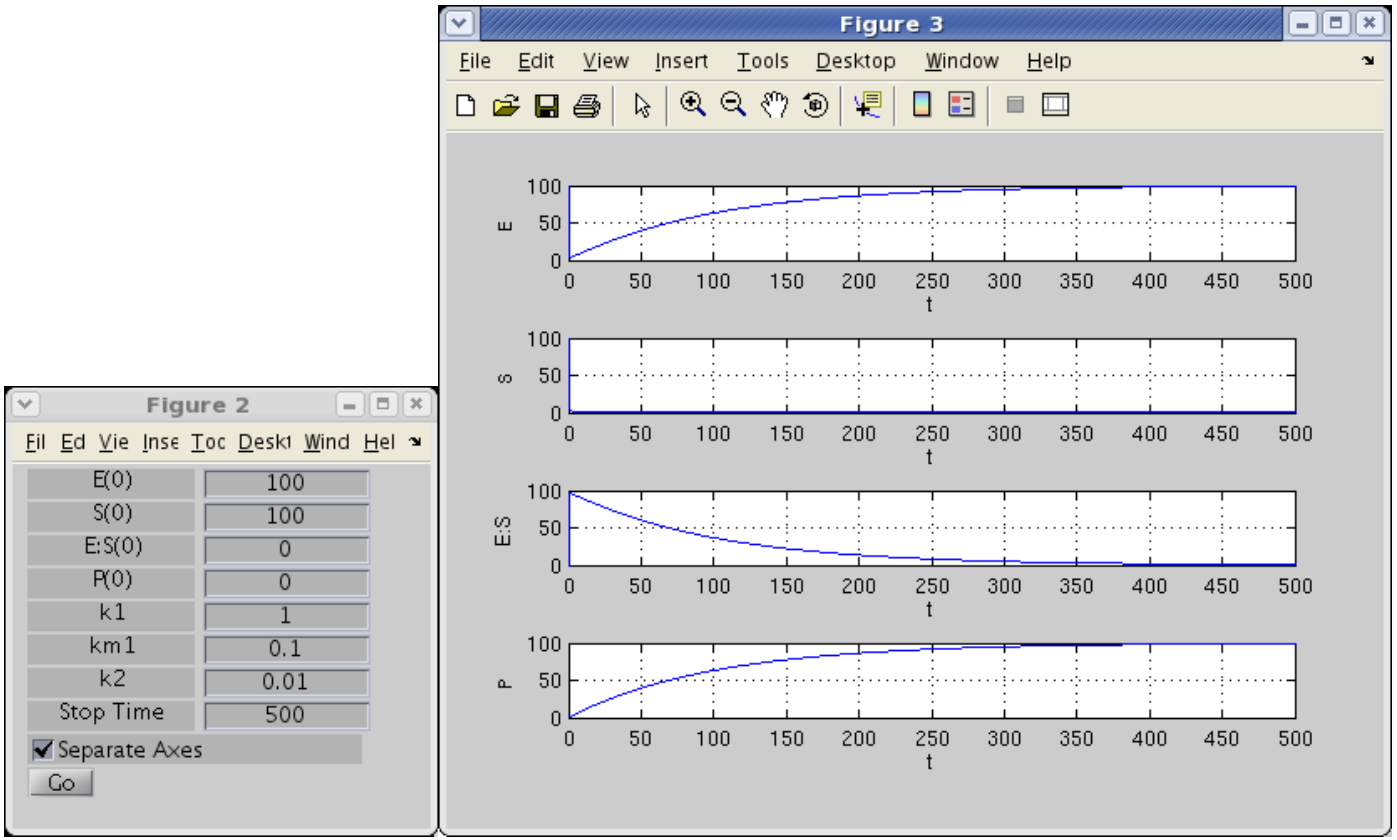

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In practice it is more efficient to map directly into the input lanugage of one of the many stochastic simulation tools which are readily available.

We currently generate models for Dizzy and Stochkit.

PRISM model and model checking

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- However, in contrast to a simulation run which generates just one trajectory, probabilistic model-checking gives a definitive answer so it is not necessary to re-run the analysis repeatedly and compute ensemble averages of the results.
- Building a reward structure over the model it is possible to express complex analysis questions.

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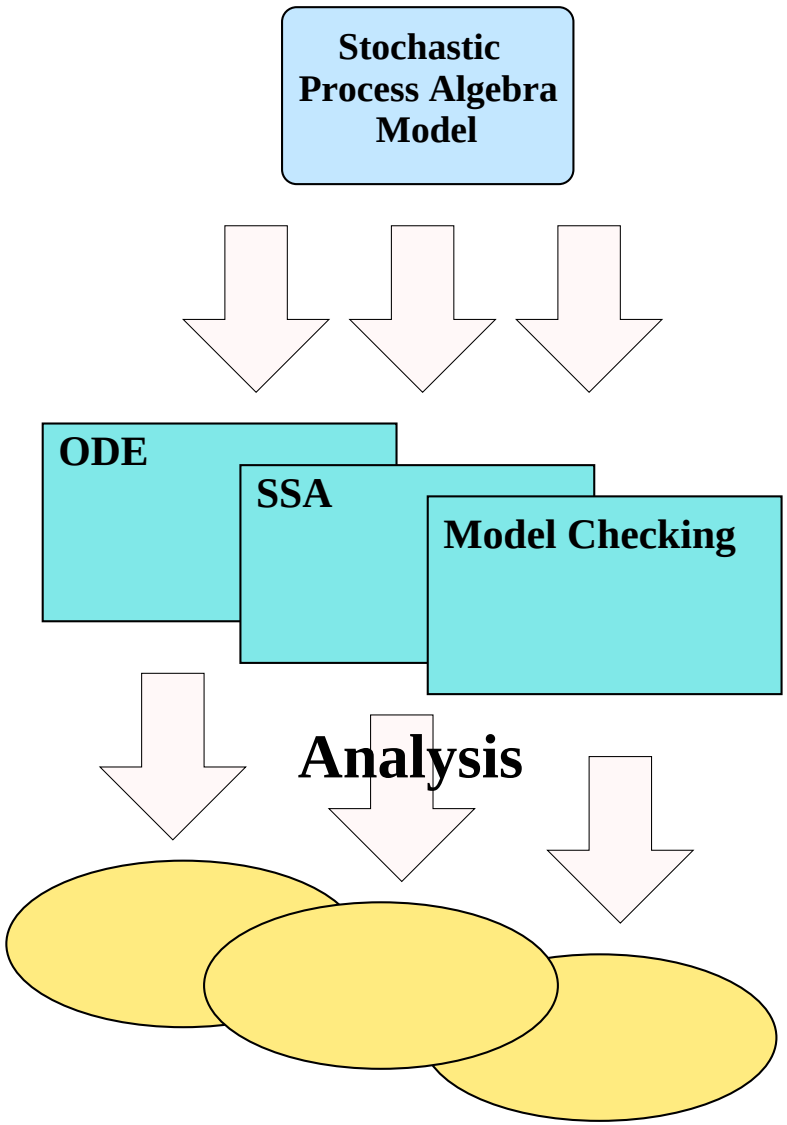
- Formally the mapping from Bio-PEPA is based on the structured operational semantics, generating the underlying CTMC in the usual way.
- As with SSA, in practice it is more straightforward to directly map to the input language of the tool.
- PRISM expresses systems as interacting, reactive modules. From a Bio-PEPA description one module is generated for each species component with an additional module to capture the functional rate information.

Multiple Analyses



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- This can increase our confidence in the analysis techniques, or highlight problems.
- In [CDHH CMSB06] we uncovered a problem with the published numerical solution of a set of ODEs using just this approach.

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- Moreover, the finite nature of the state representation used means that *a priori* bounds must be set (whether numbers of molecules or discrete levels for each species are used).
- We can use stochastic simulation and probabilistic model checking in tandem, running the simulation to establish appropriate bounds then used for the PRISM state space.

Outline

Goldbeter's model [Goldbeter 91]

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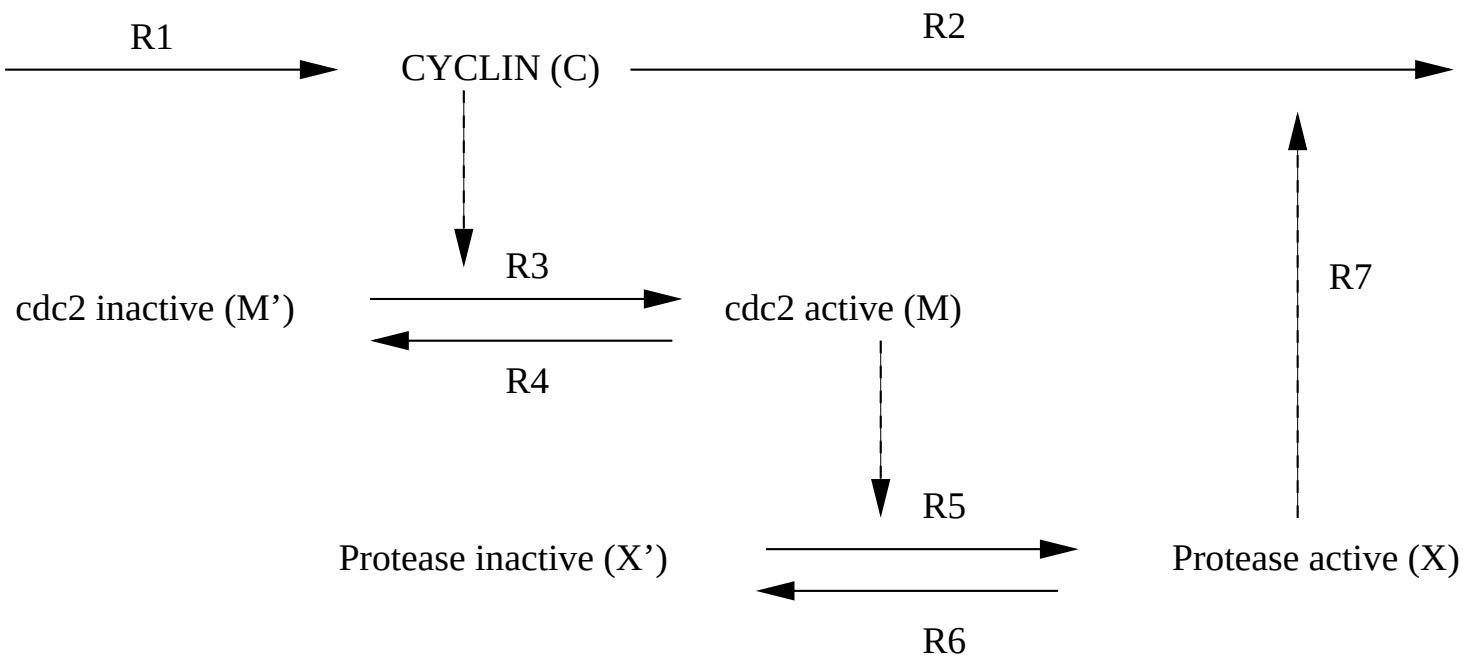
- The cyclin promotes the activation of a cdk (cdc2) which in turn activates a cyclin protease.
- This protease promotes cyclin degradation.
- This leads to a negative feedback loop.
- In the model most of the kinetic laws are of kind Michaelis-Menten and this can be reflected in the Bio-PEPA model

The biological model



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- cyclin protease, in both active (i.e. phosphorylated) and inactive form (i.e. phosphorylated). The variable are X and X'.

Reactions

id	reaction	react.	prod.	mod.	kinetic laws
α_1	creation of cyclin	-	C	-	v_i
α_2	degradation of cyclin	C	-	-	$kd \times C$
α_3	activation of *cdc*2 kinase	M'	M	C	$\frac{C \times V_{M1}}{(K_c + C)} \frac{M'}{(K_1 + M')}$
α_4	deactivation of *cdc*2 kinase	M	M'	-	$\frac{M \times V_2}{(K_2 + M)}$
α_5	activation of cyclin protease	X'	X	M	$\frac{X' \times M \times V_{M3}}{(K_3 + X')}$
α_6	deactivation of cyclin protease	X	X'	-	$\frac{X \times V_4}{K_4 + X}$
α_7	X triggered degradation of cyclin	C	-	X	$\frac{C \times v_d \times X}{C + K_d}$

α_1, α_2 have mass-action kinetics; others are Michaelis-Menten.

The Bio-PEPA model

Definition of species components (*Comp*):

$$
\begin{aligned}
C &\stackrel{def}{=} (\alpha_1, 1)\uparrow C + (\alpha_2, 1)\downarrow C + (\alpha_7, 1)\downarrow C + (\alpha_3, 1) \oplus C \\
M' &\stackrel{def}{=} (\alpha_4, 1)\uparrow M' + (\alpha_3, 1)\downarrow M' \\
M &\stackrel{def}{=} (\alpha_3, 1)\uparrow M + (\alpha_4, 1)\downarrow M + (\alpha_5, 1) \oplus M \\
X' &\stackrel{def}{=} (\alpha_6, 1)\uparrow X' + (\alpha_5, 1)\downarrow X' \\
X &\stackrel{def}{=} (\alpha_5, 1)\uparrow X + (\alpha_6, 1)\downarrow X + (\alpha_7, 1) \oplus X
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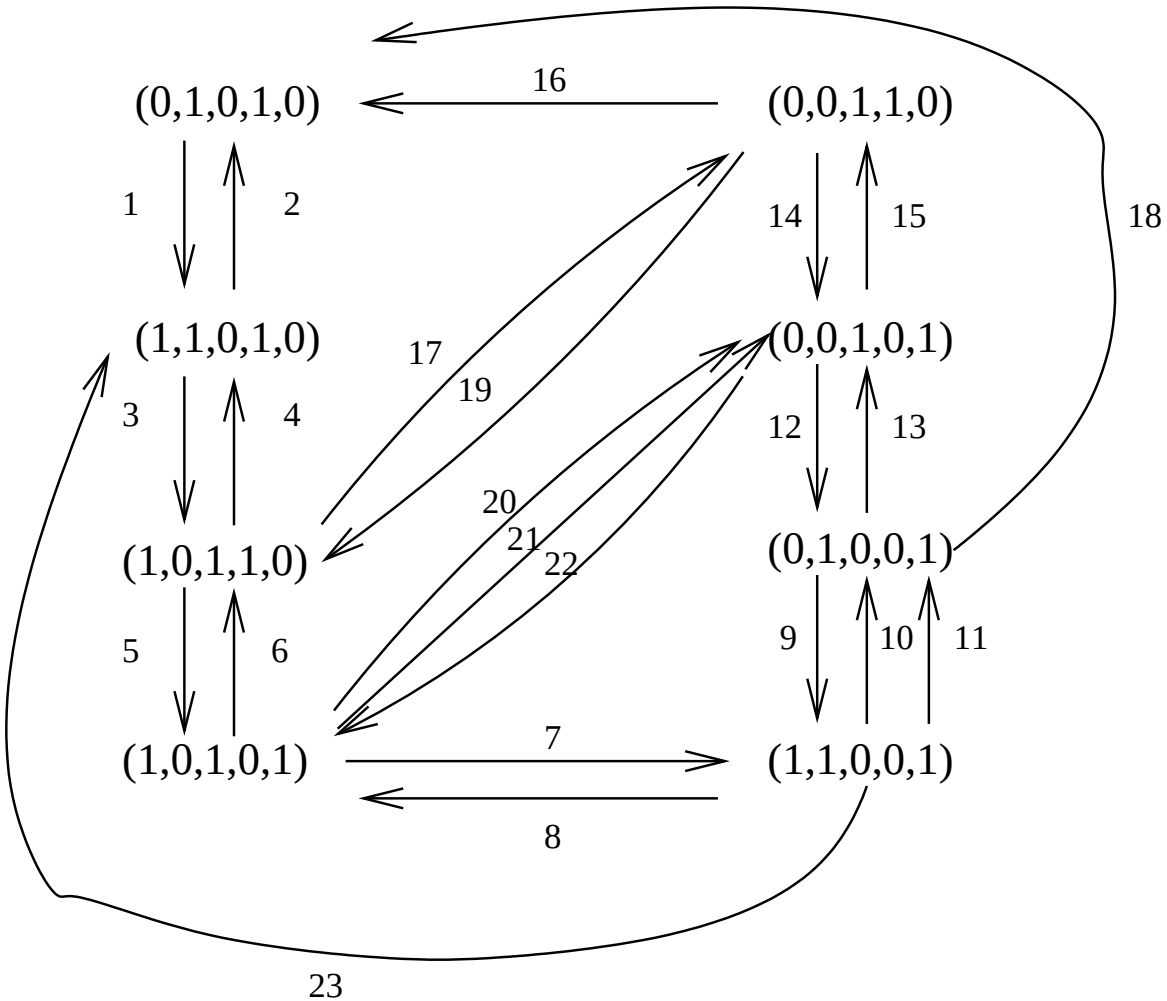
$$

Definition of the model component (*P*):

$$
C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'})
$$

Analysis

Assume two levels for each species and initially C, M and X present (level 1) and the other elements not present (level 0). The initial state is $(l_C(1), l_{M'}(0), l_M(1), l_{X'}(0), l_X(1))$.



ODEs

The stoichiometry matrix D:

	α_1	α_2	α_3	α_4	α_5	α_6	α_7	
C	$+1$	0	0	0	0	0	-1	x_C
M'	0	0	-1	$+1$	0	0	0	$x_{M'}$
M	0	0	$+1$	-1	0	0	0	x_M
X'	0	0	0	0	-1	$+1$	0	$x_{X'}$
X	0	0	0	0	$+1$	-1	0	x_X

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X'	0	0	0	0	-1	$+1$	0	$x_{X'}$
X	0	0	0	0	$+1$	-1	0	x_X

The vector that contains the kinetic laws is:

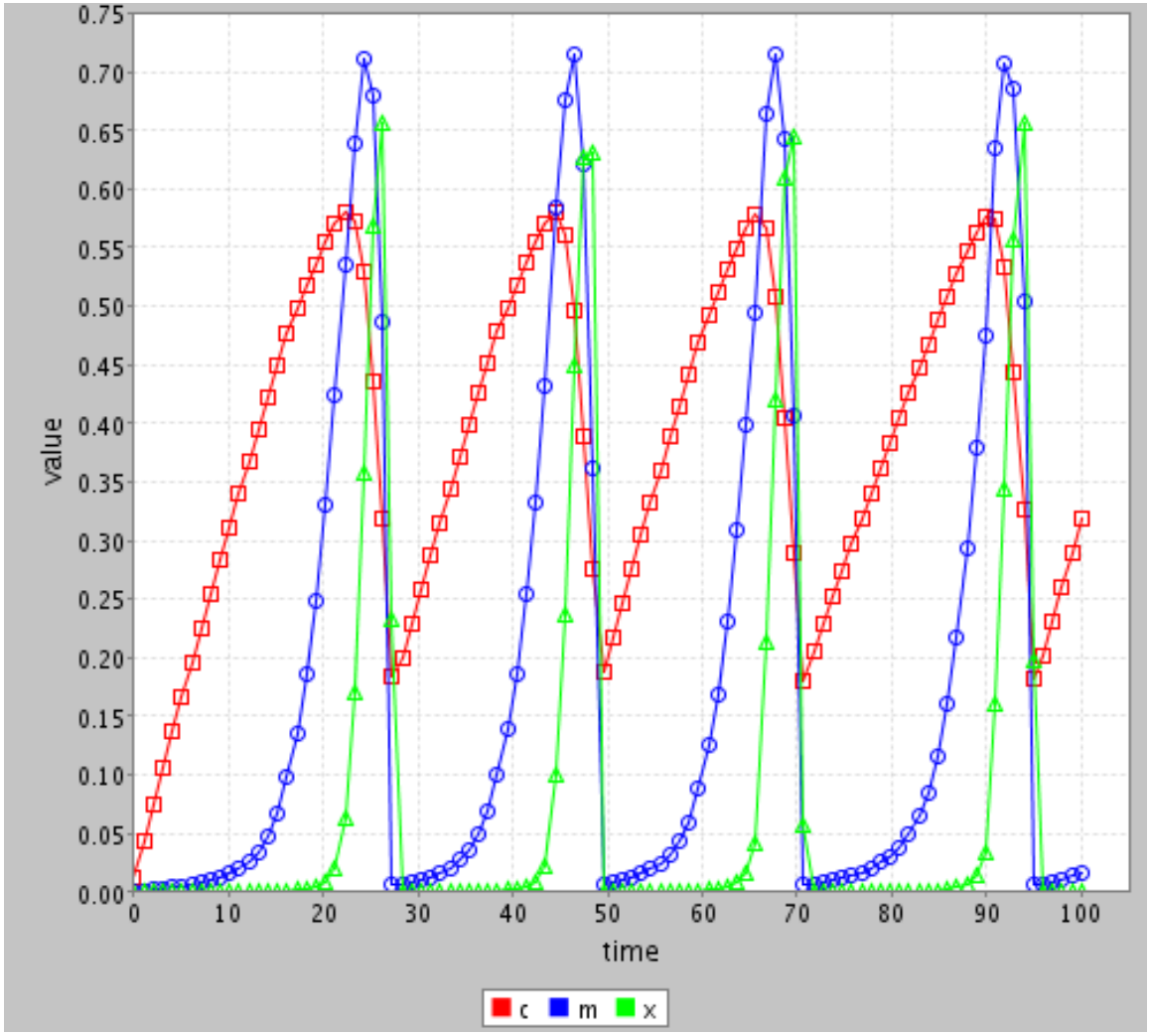
$$w = \left(v_i \times 1, k_d \times x_C, \frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 \times x_M}{(K_2 + x_M)}, \right.$$
$$\left. \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 \times x_X}{(K_4 + x_X)}, \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \right)$$

ODEs (2)

The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$, where $\bar{x}^T =: (x_C, x_{M'}, x_M, x_{X'}, x_X)$ is the vector of the species variables:

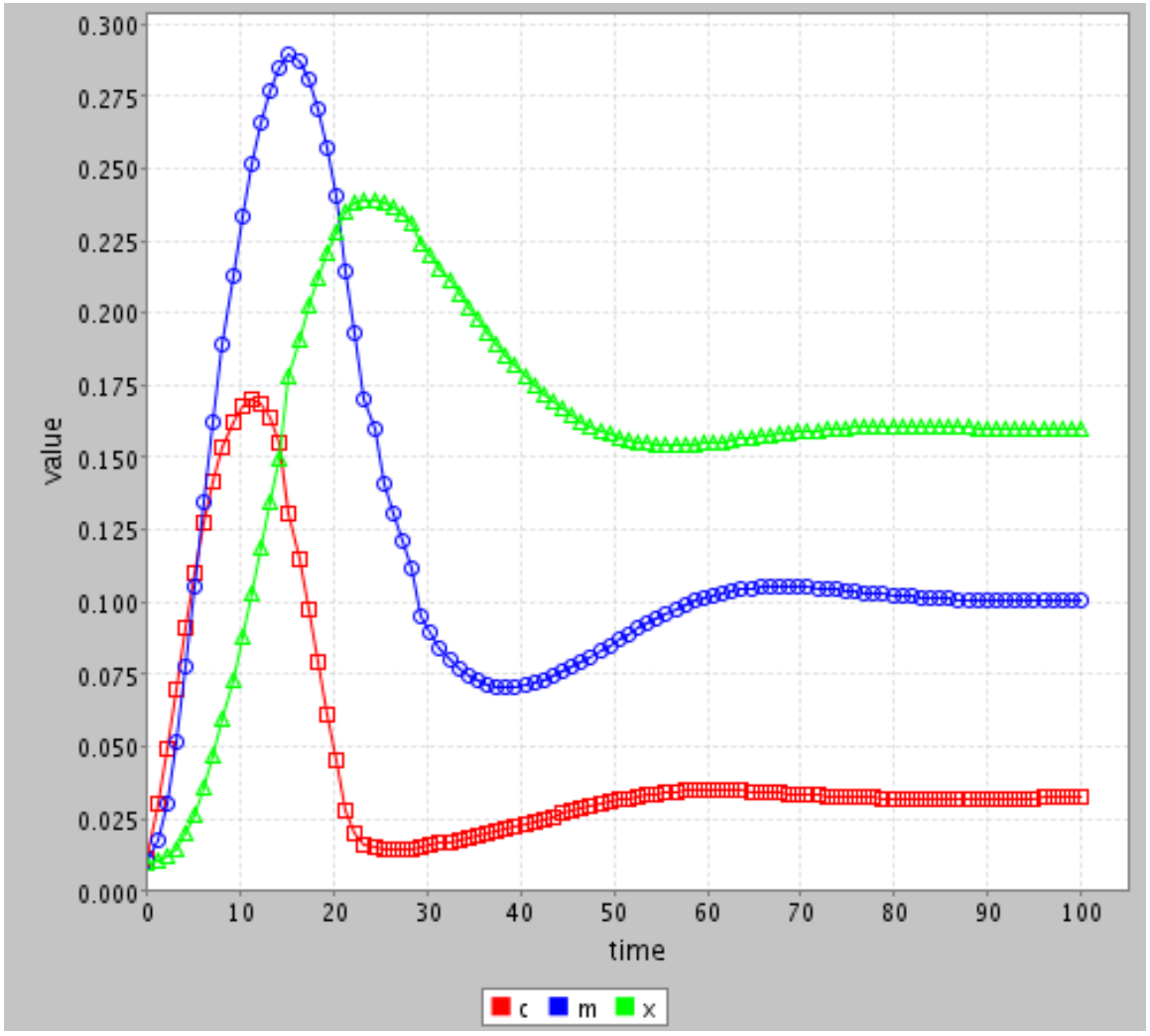
$$
\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} - \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_{X'}}{dt} &= -\frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})} + \frac{V_4 \times x_X}{(K_4 + x_X)} \\
\frac{dx_X}{dt} &= \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})} - \frac{V_4 \times x_X}{(K_4 + x_X)}
\end{aligned}
$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 0.02\mu M$$

ODE results



$$K_1 = K_2 = K_3 = K_4 = 40\mu M$$

PRISM results

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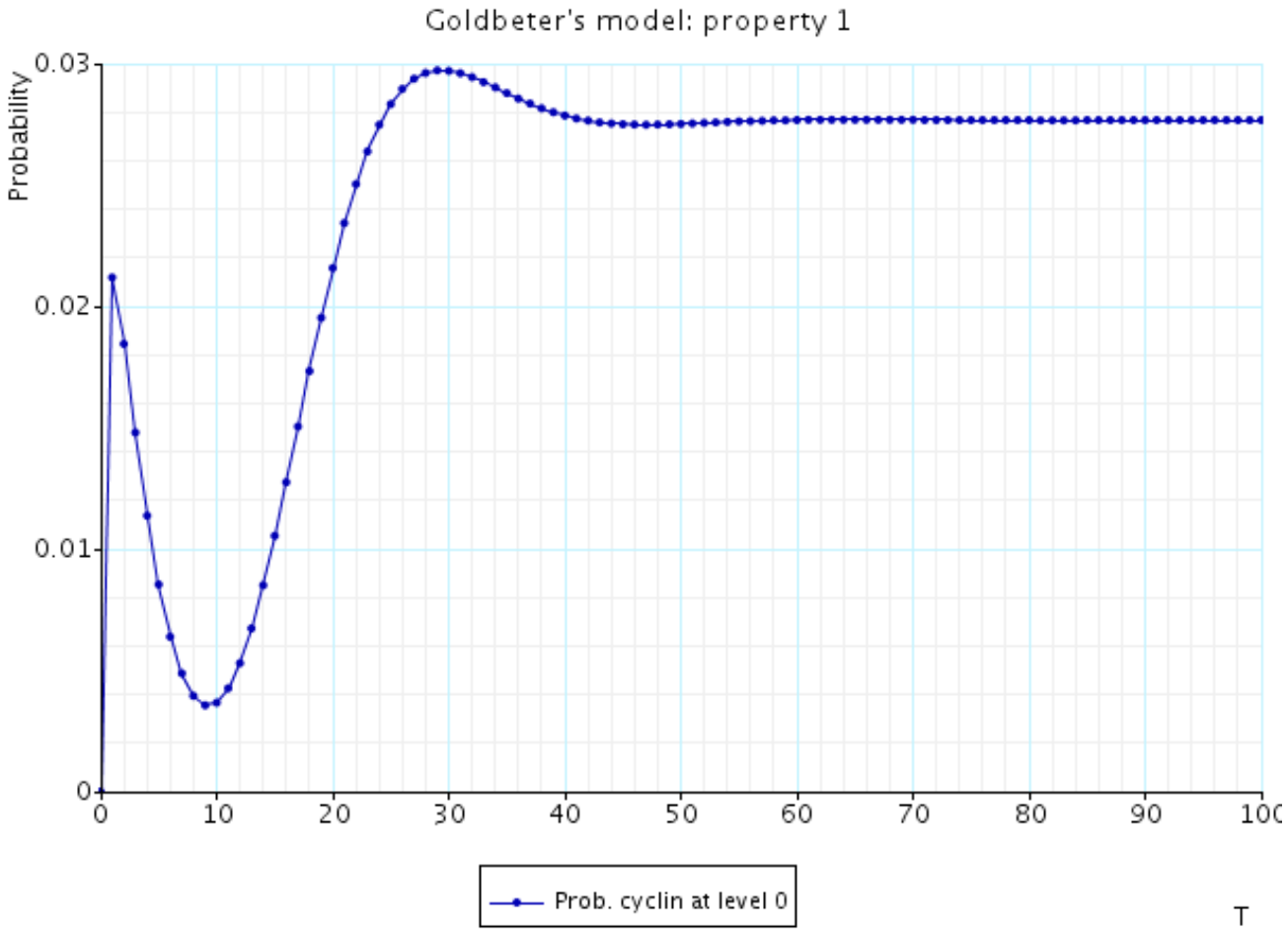
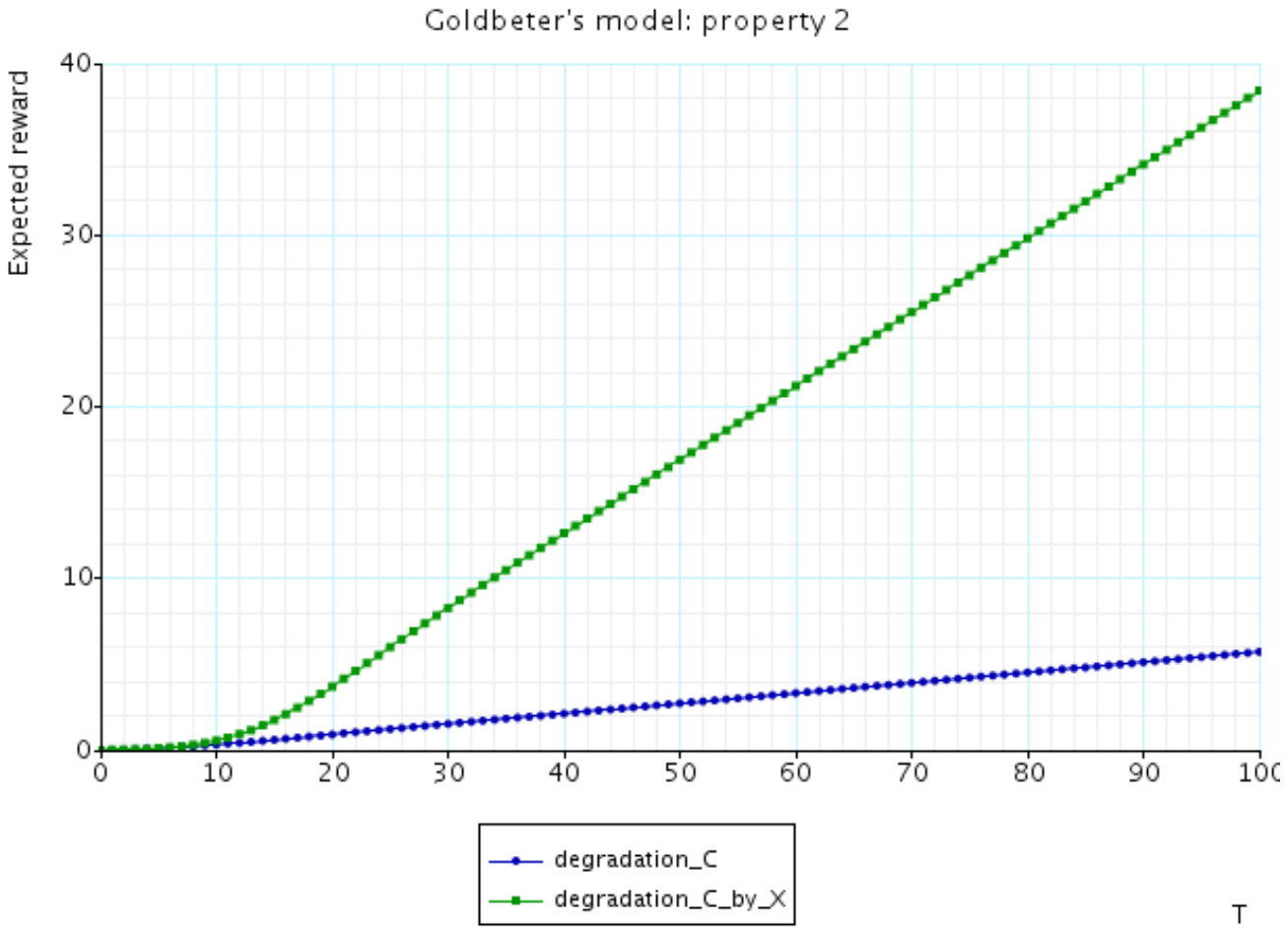


$$P =?[trueU[T, T]cyclin = 0]$$

PRISM results



$R\alpha_2 =?[C <= T]$ and $R\alpha_7 =?[C <= T]$

PRISM results

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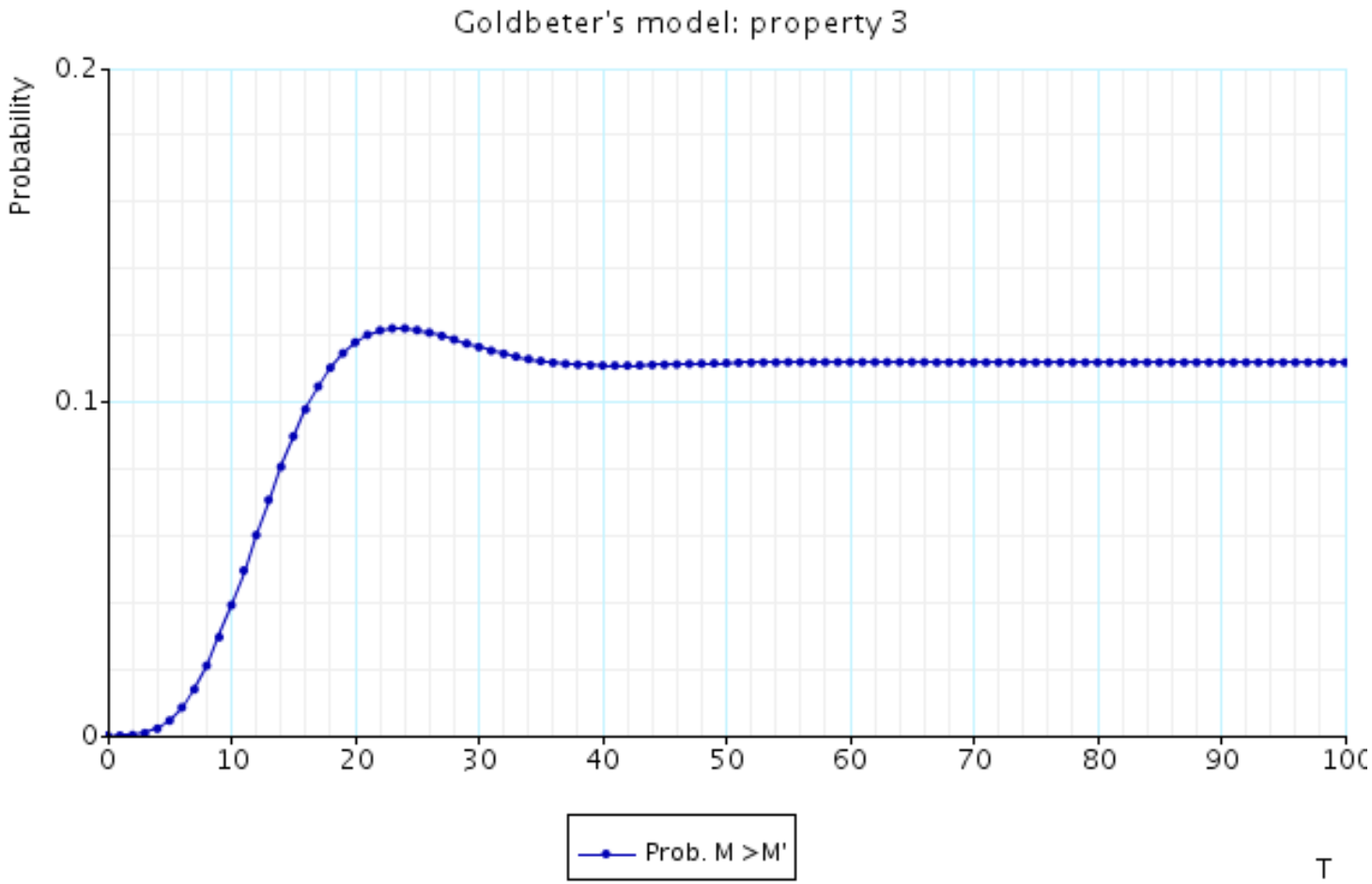

$$P =?[trueU[T, T]M > M']$$

Outline

Bio-PEPA with Events [Cioc ProcMod08]

In a recent extension we consider events to be constructs that change the state of the system due to some trigger conditions.

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- When modelling *in vitro* systems it can be the case that the system is deliberated perturbed in a controlled way at a specific time.
- There may be discrete changes in systems, such as gene activation and deactivation.

Such an extension of Bio-PEPA has been defined consisting of a separate specification of the events and their effects, and mappings to hybrid automata and stochastic simulation models.

Improved Compartments [CG MeCBiC08]

In the current version of Bio-PEPA compartments are simply containers for species, only the size of the compartment being used to calculate concentrations when necessary.

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Recent work by Ciocchetta and Guerriero has extended this view of compartments, allowing the relative positioning of compartments and membranes to be captured.

Additionally species and reactions may be specified to have a particular location relative to this structure, for example on a membrane or within a compartment.

Equivalence relations

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We are now seeking to define equivalence and simulation relations for Bio-PEPA which might be more useful from the biological perspective.

In particular we are investigating the situations in which biologists regard models or elements of models to be equivalent, especially when this is employed for model simplification.

Conclusions

Bio-PEPA is a modification of the process algebra PEPA for the *modelling* and *analysis* of biochemical networks.

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Bio-PEPA allows us to represent explicitly features of biological networks, such as stoichiometry and general kinetic laws.

Moreover the reagent-centric, abstract style of modelling supports an integrative approach in which several different approaches to analysis may be applied to the same model.

Conclusions (2)

Abstract modelling offers a compromise between the individual-based and population-based views of systems which biologists commonly take.

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Moveover we can undertake additional analysis based on the discretised population view.

The abstract Markovian models allow quantities of interest such as "response times" to be expressed as probability distributions rather than single estimates. This may allow better reflection of wet lab data which also shows variability.

Thank You!

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Thank You!

Collaborators: Muffy Calder, Federica Ciocchetta, Andrea Degasperi, Adam Duguid, Stephen Gilmore and Maria Luisa Guerriero.

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