Using stochastic process algebra to model biochemical pathways

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Joint work with Federica Ciocchetta, Adam Duguid, Vashti Galpin, Stephen Gilmore, Maria Luisa Guerriero and Laurence Loewe

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Goldbeter's model

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Current Hypothesis

Some of the techniques we have developed over the last thirty years for modelling complex software systems can be beneficially applied to the modelling aspects of systems biology.

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In particular formalisms which encompass support for

- Abstraction
- Modularity and
- Reasoning

have a key role to play.

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have a key role to play.

Process algebras have mechanisms for each of these, and stochastic extensions which allow dynamic properties to be analysed.

Outline

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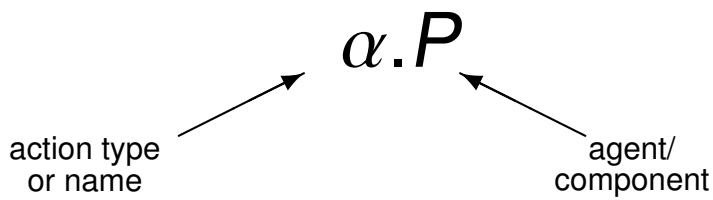
Process Algebra

- Models consist of agents which engage in actions.



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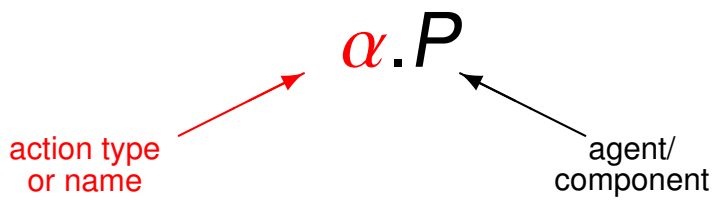

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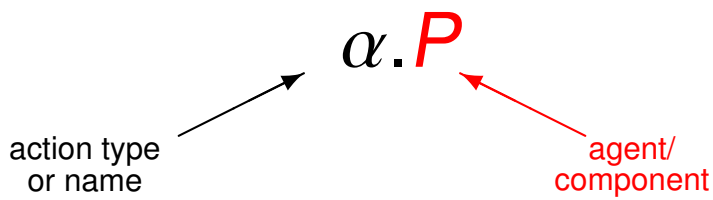

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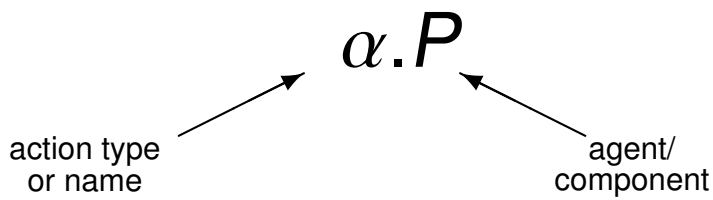

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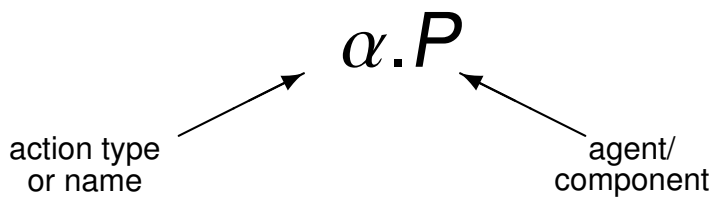

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Process algebra model $\xrightarrow{\text{SOS rules}}$ Labelled transition system

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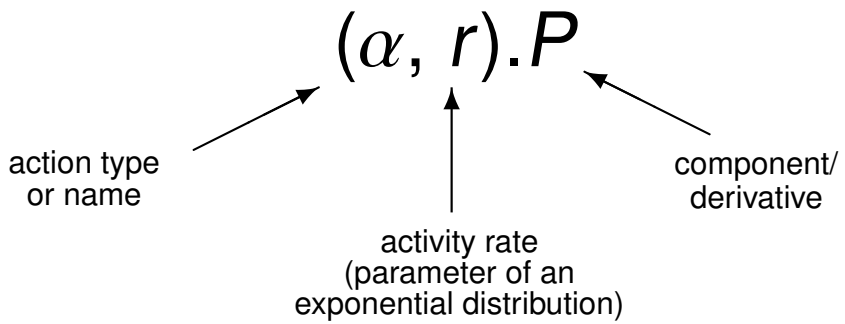
Stochastic Process Algebra (SPA)

- Models are constructed from components which engage in activities.



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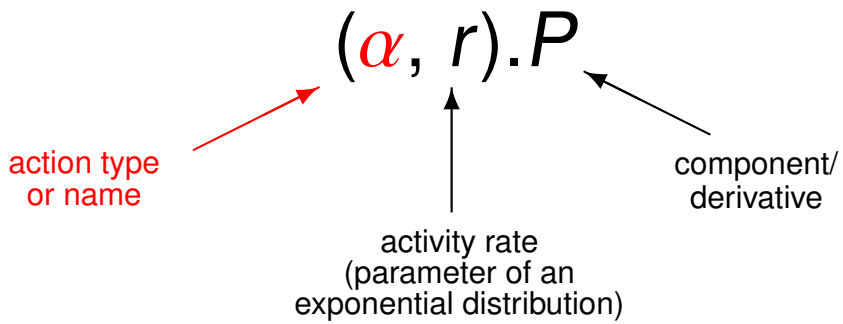

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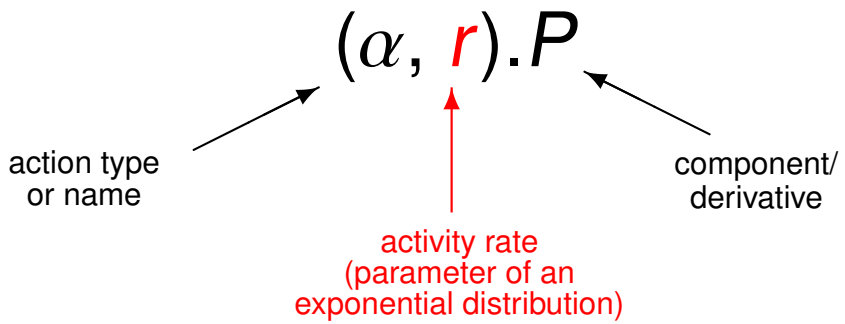

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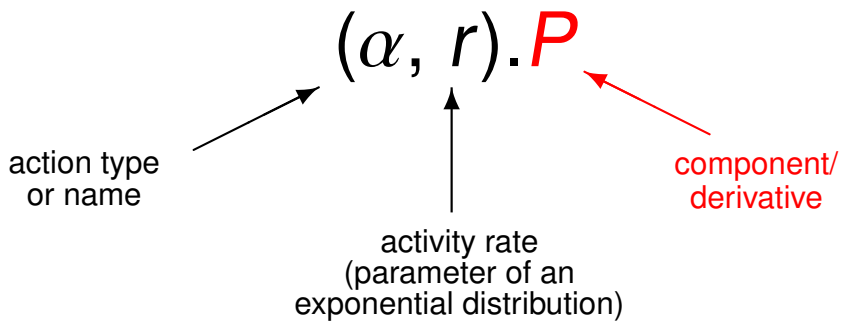

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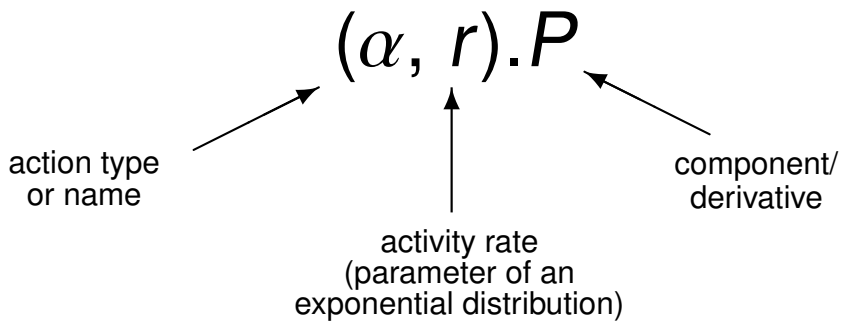

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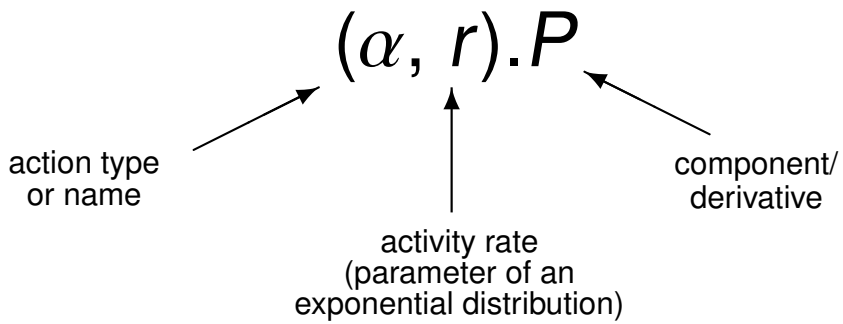

In addition to functional verification (ensuring the system does the "right" thing) we can now do quantitative analysis (timeliness and resource usage) using an underlying mathematical model.

Deriving quantitative data

SPA models can be analysed for quantified dynamic behaviour in a number of different ways.

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The language may be used to generate a Markov Process (CTMC).

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The language also may be used to generate a stochastic simulation.

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The language may be used to generate a system of ordinary differential equations (ODEs).

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The language may be used to generate a system of ordinary differential equations (ODEs).

Each of these has tool support so that the underlying model is derived automatically according to the predefined rules.

Process Algebras for Systems Biology

- Process algebraic formulations are compositional and make interactions/constraints explicit — not the case with classical ordinary differential equation models.

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- Abstraction can be used to mask complexity or incomplete knowledge.

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- Equivalence relations allow formal comparison of high-level descriptions.

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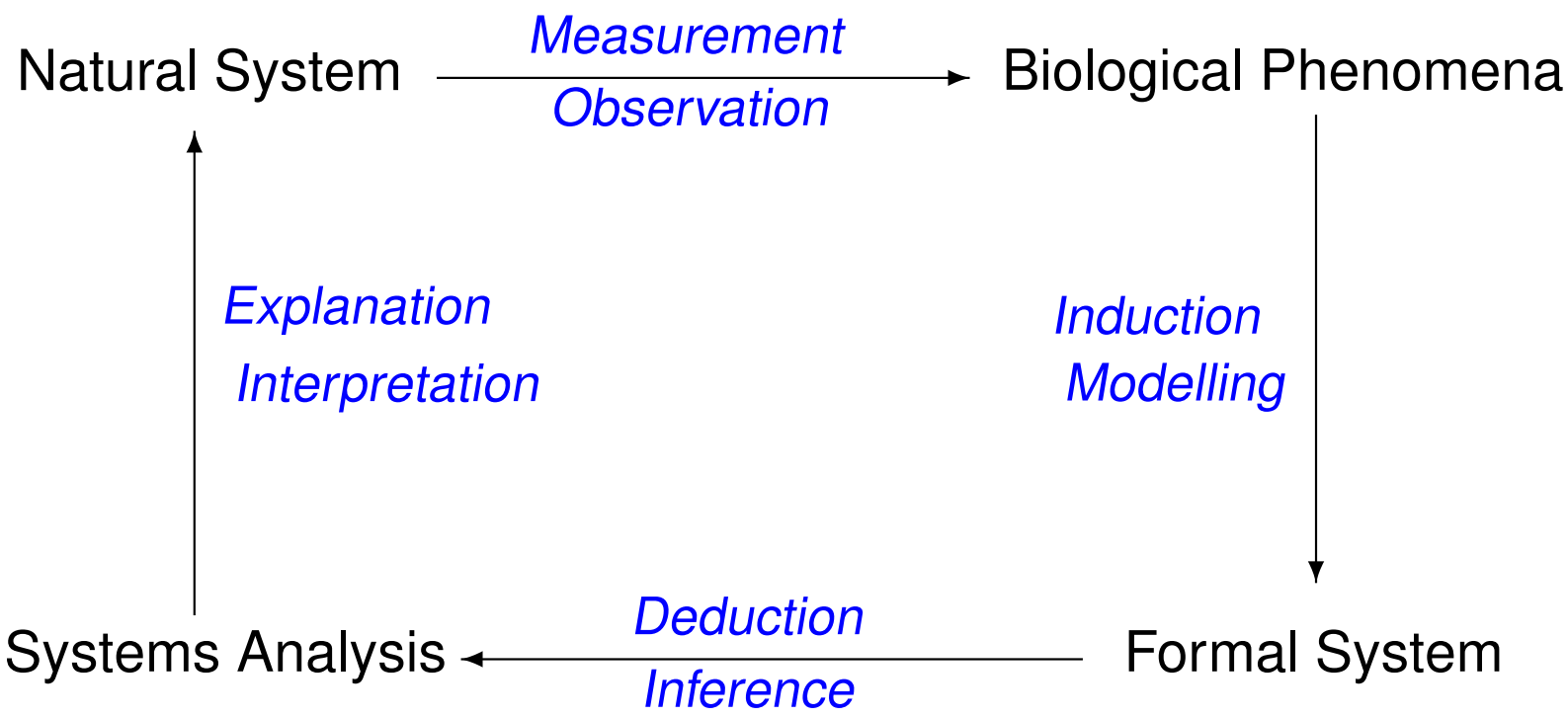
- Structure can also be apparent.
- Abstraction can be used to mask complexity or incomplete knowledge.
- Equivalence relations allow formal comparison of high-level descriptions.
- There are well-established techniques for reasoning about the behaviours and properties of models, supported by software.

Systems Biology Methodology



Formal Systems

There are two alternative approaches to constructing dynamic models of biochemical pathways commonly used by biologists:

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There are two alternative approaches to constructing dynamic models of biochemical pathways commonly used by biologists:

- Ordinary Differential Equations:
  - continuous time,
  - continuous behaviour (concentrations),
  - deterministic.

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There are two alternative approaches to constructing dynamic models of biochemical pathways commonly used by biologists:

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

Systems Biology Modelling

- In most current work mathematics is being used directly as the formal system.

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- Previous experience in computer performance modelling has shown us that there can be benefits to interposing a formal process algebra model between the system and the underlying mathematical model.

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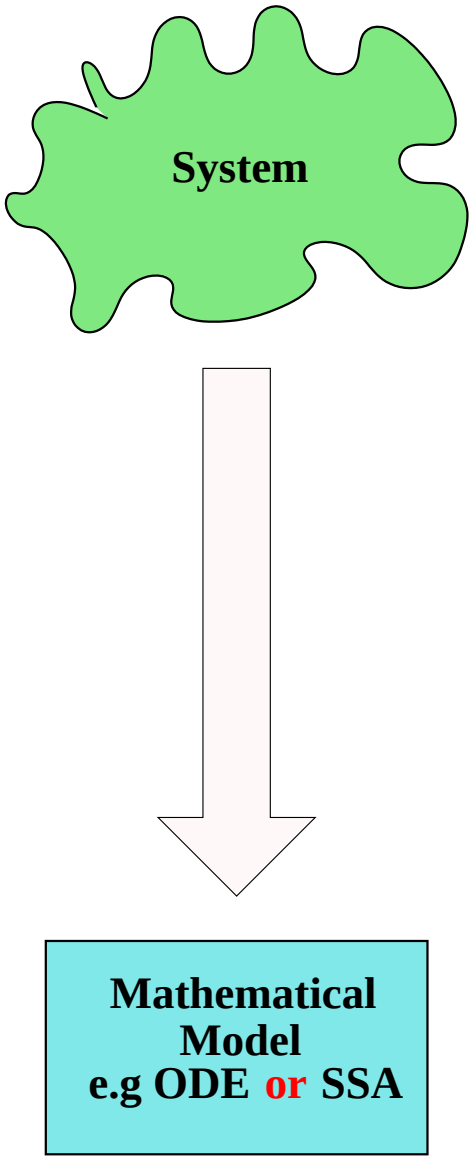
- In most current work mathematics is being used directly as the formal system.
- Previous experience in computer performance modelling has shown us that there can be benefits to interposing a formal process algebra model between the system and the underlying mathematical model.
- Moreover taking this "high-level programming" style approach offers the possibility of different "compilations" to different mathematical models: integrated modelling and analysis.

Integrated Analysis



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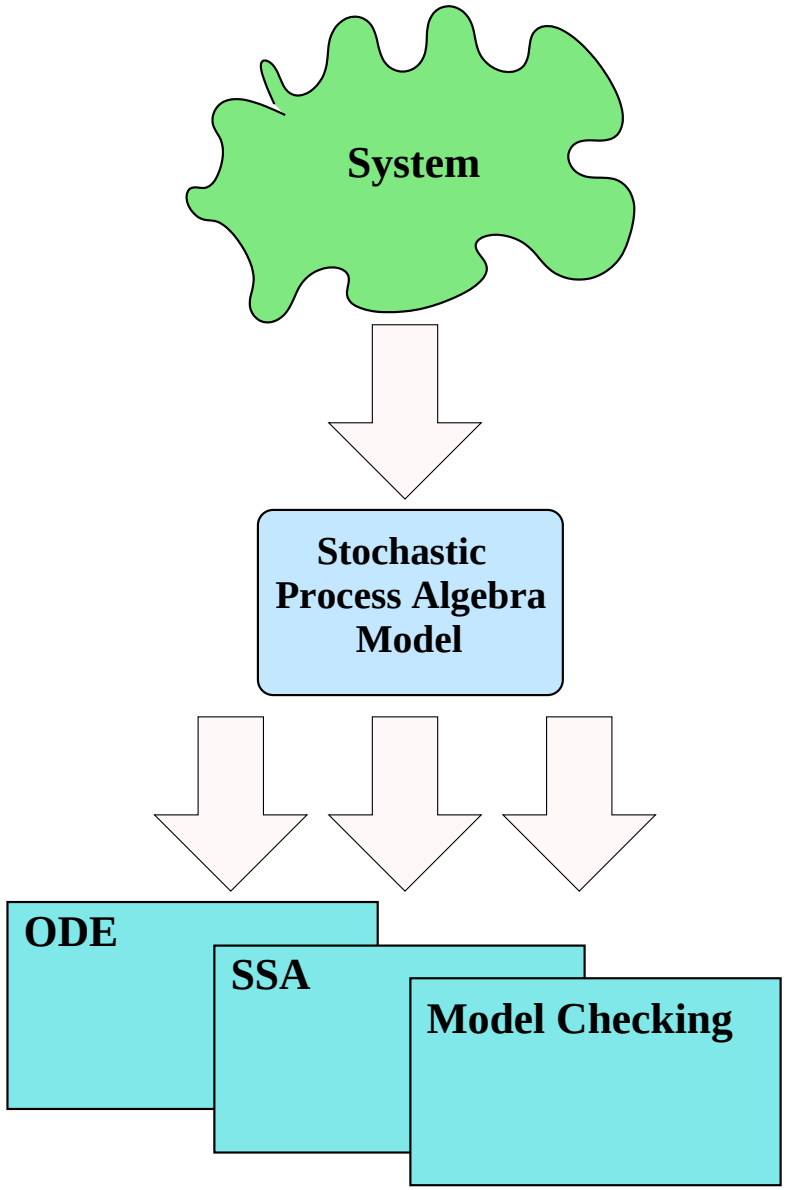

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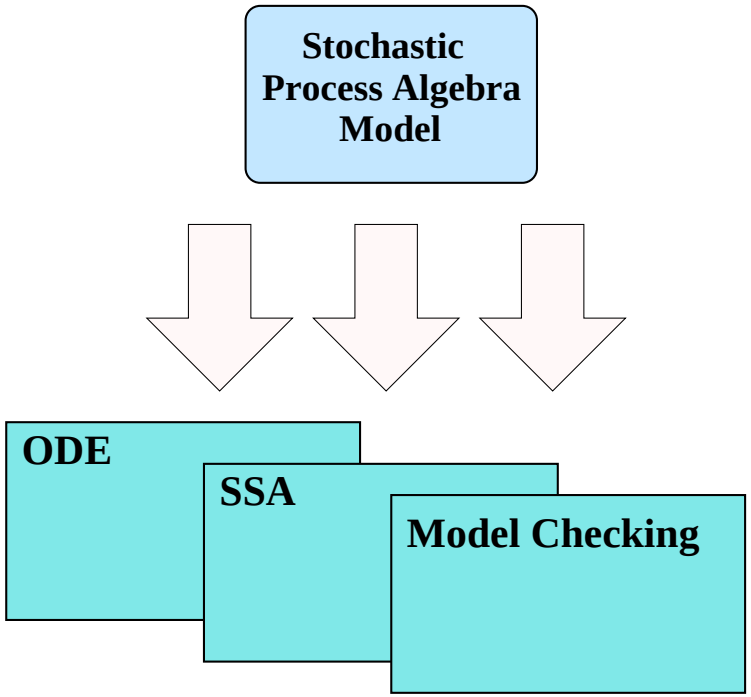

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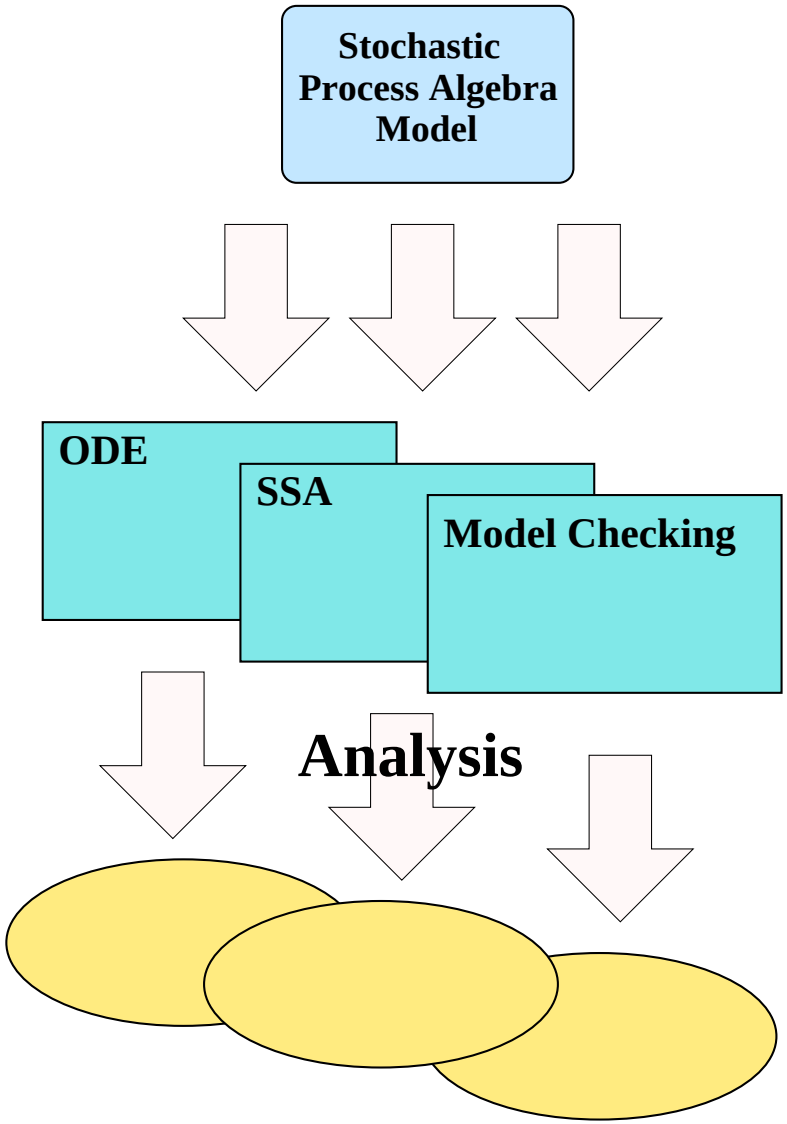

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Molecular processes as concurrent computations

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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Bio-PEPA: motivations

Work on the stochastic π-calculus and related calculi, is typically based on Regev's mapping, meaning that a molecule maps to a process.

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Abstract models are more amenable to integrated analysis.

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Abstract models are more amenable to integrated analysis.

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.

Motivations for Abstraction

Our motivations for seeking more abstraction in process algebra models for systems biology are:

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Our motivations for seeking more abstraction in process algebra models for systems biology are:

- Process algebra-based analyses such as comparing models (e.g. for equivalence or simulation) and model checking are only possible is the state space is not prohibitively large.

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- The data that we have available to parameterise models is sometimes speculative rather than precise.

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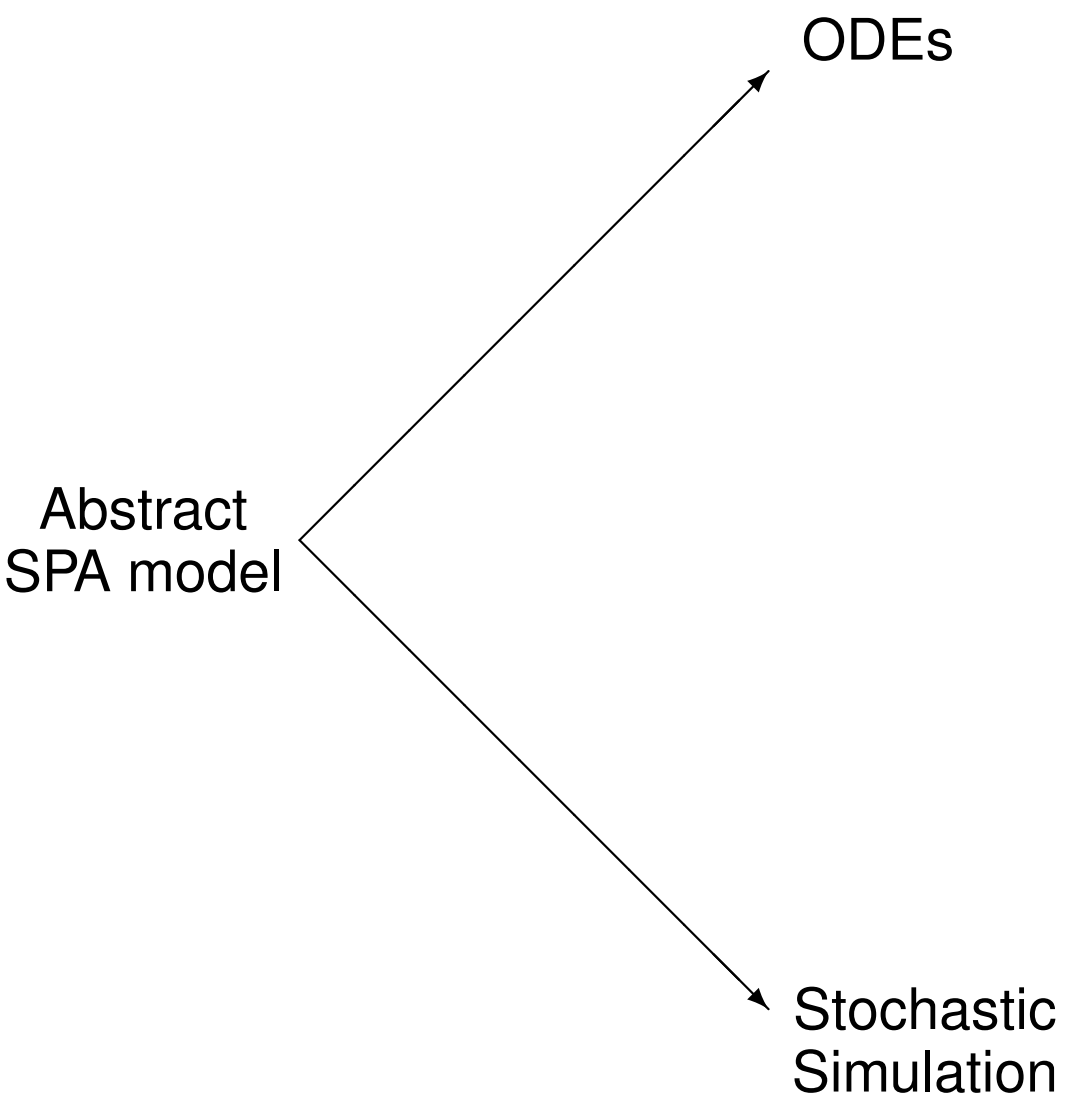
- The data that we have available to parameterise models is sometimes speculative rather than precise.

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

Alternative Representations



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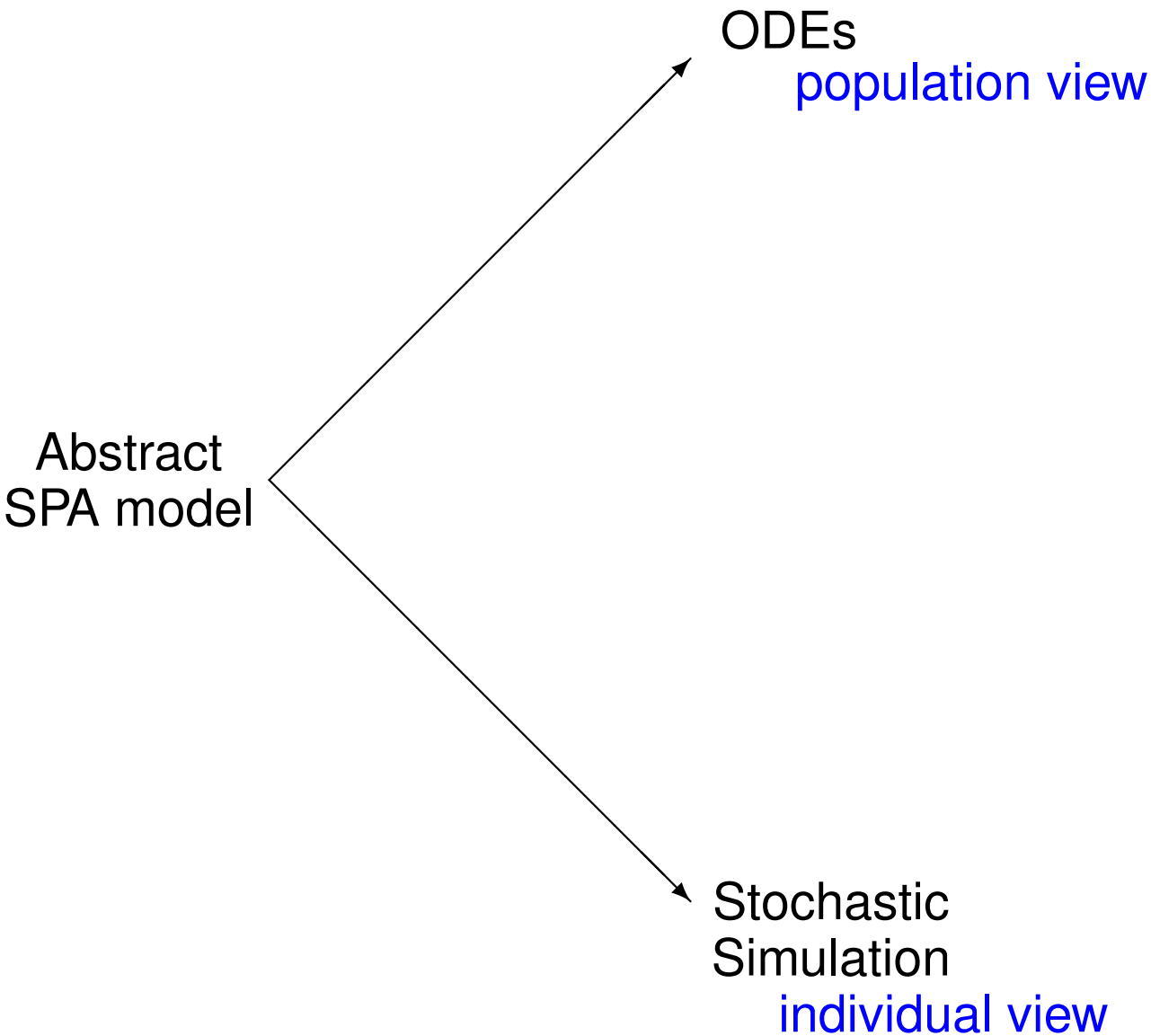

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Discretising the population view

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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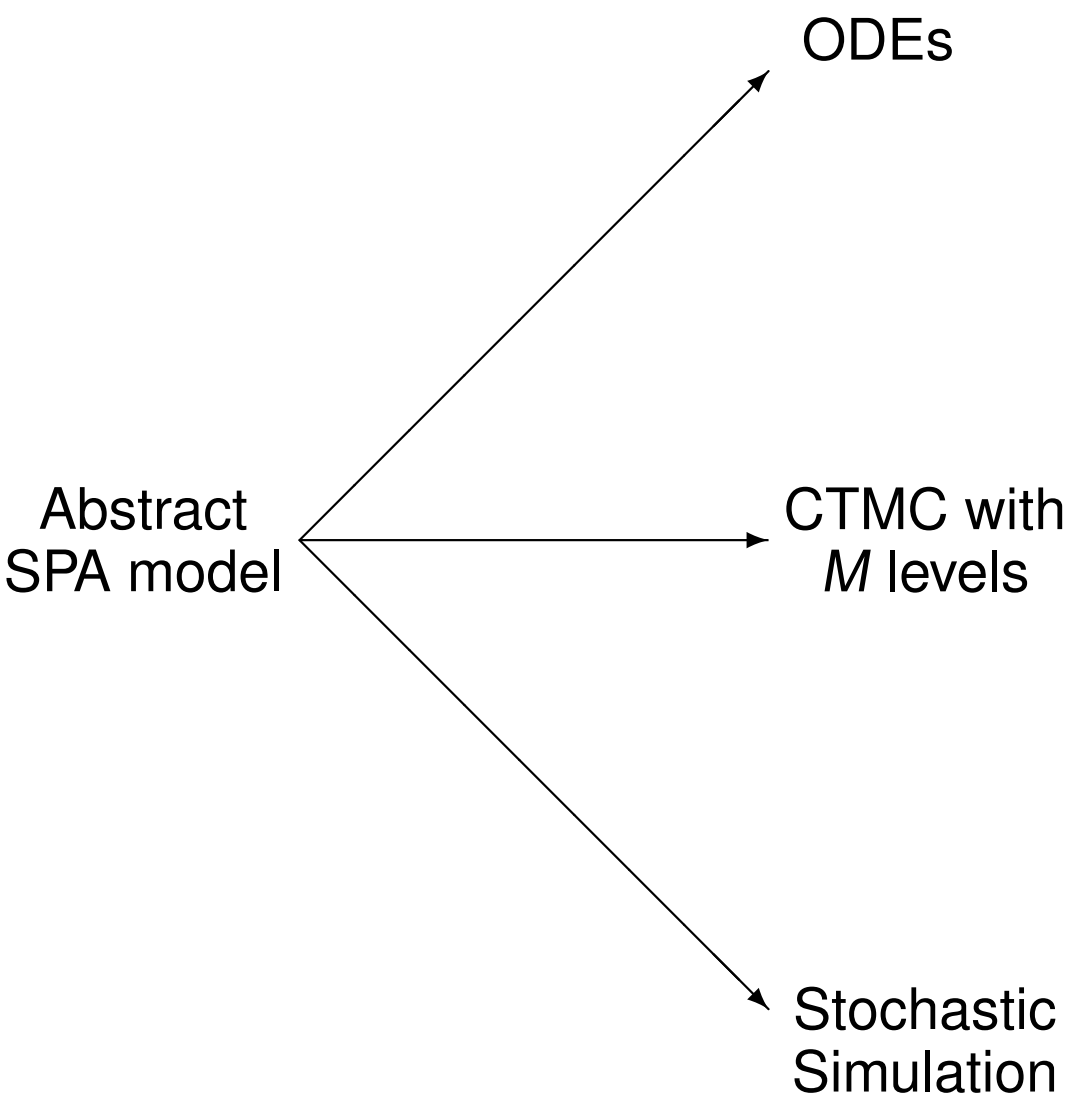

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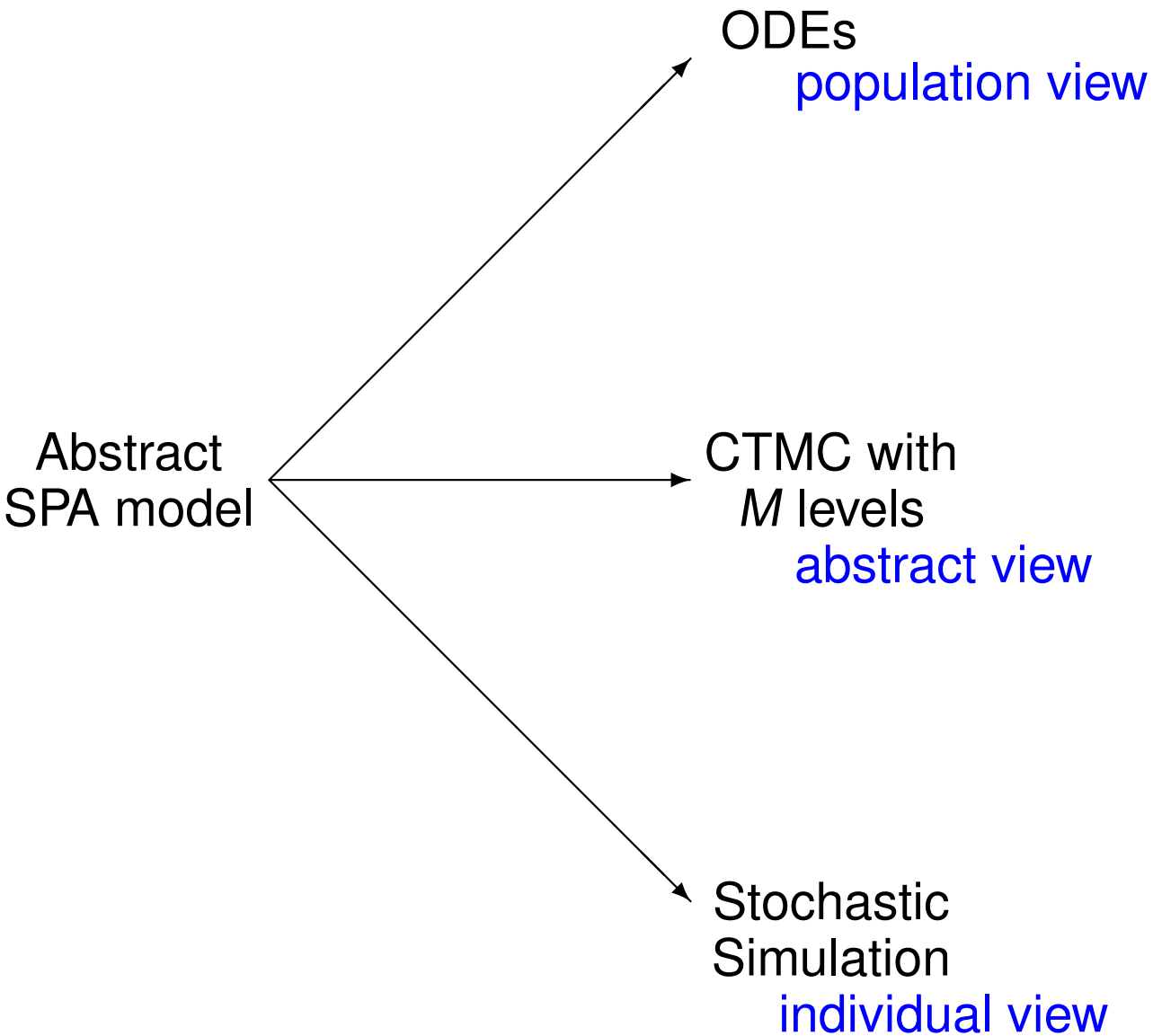

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- The ODE model can be regarded as an approximation of a CTMC in which the number of molecules is large enough that the randomness averages out and the system is essentially deterministic.

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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

There are some features of biochemical reaction systems which are not readily captured by many of the stochastic process algebras that are currently in use.

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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.

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In Bio-PEPA:

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In Bio-PEPA:

- Unique rates are associated with each reaction (action) type, separately from the specification of the logical behaviour. These rates may be specified by functions.

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- 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.

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The Bio-PEPA Language

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 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).

Goldbeter's model [Goldbeter 91]

- Goldbeter's model describes the activity of the cyclin in the cell cycle.

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- 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

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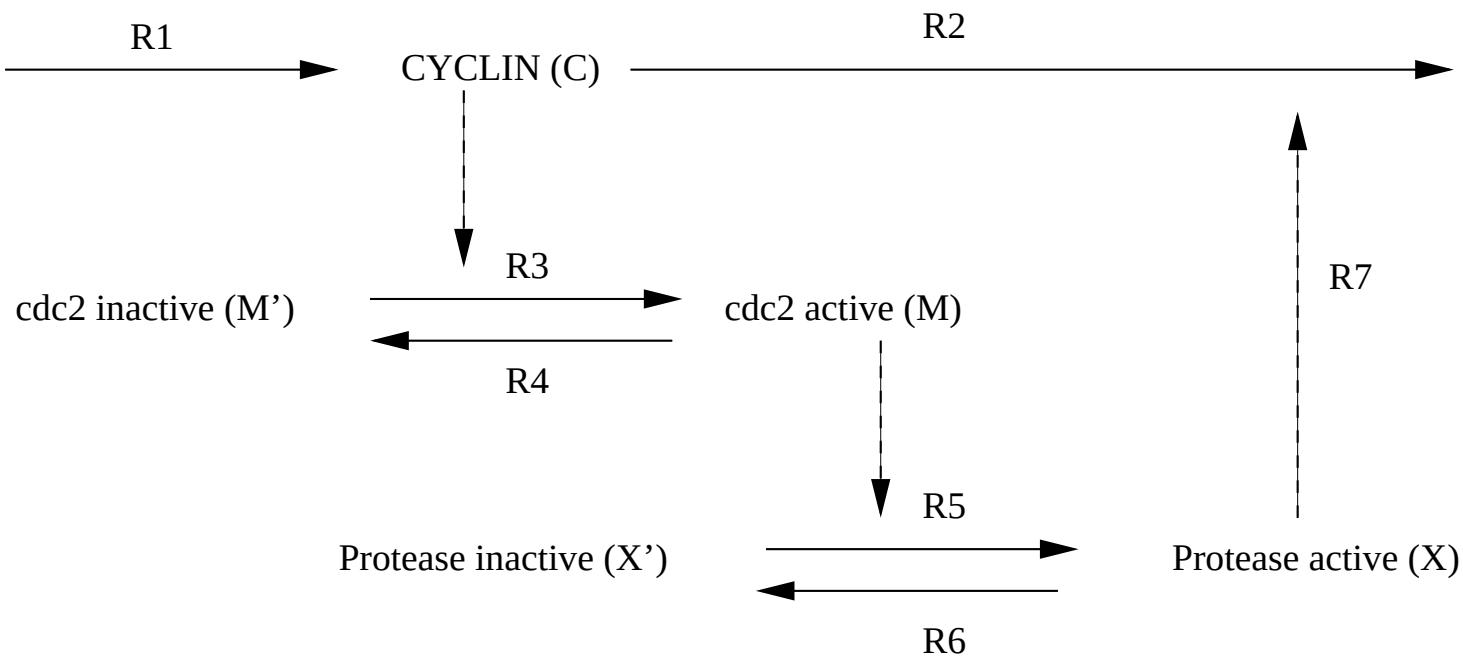
The biological model



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The biological model (2)

There are three different biological species involved:

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

These give rise to five species definitions in the Bio-PEPA model.

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.

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The Bio-PEPA model

Definition of species components (*Comp*):

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

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 with Bio-PEPA

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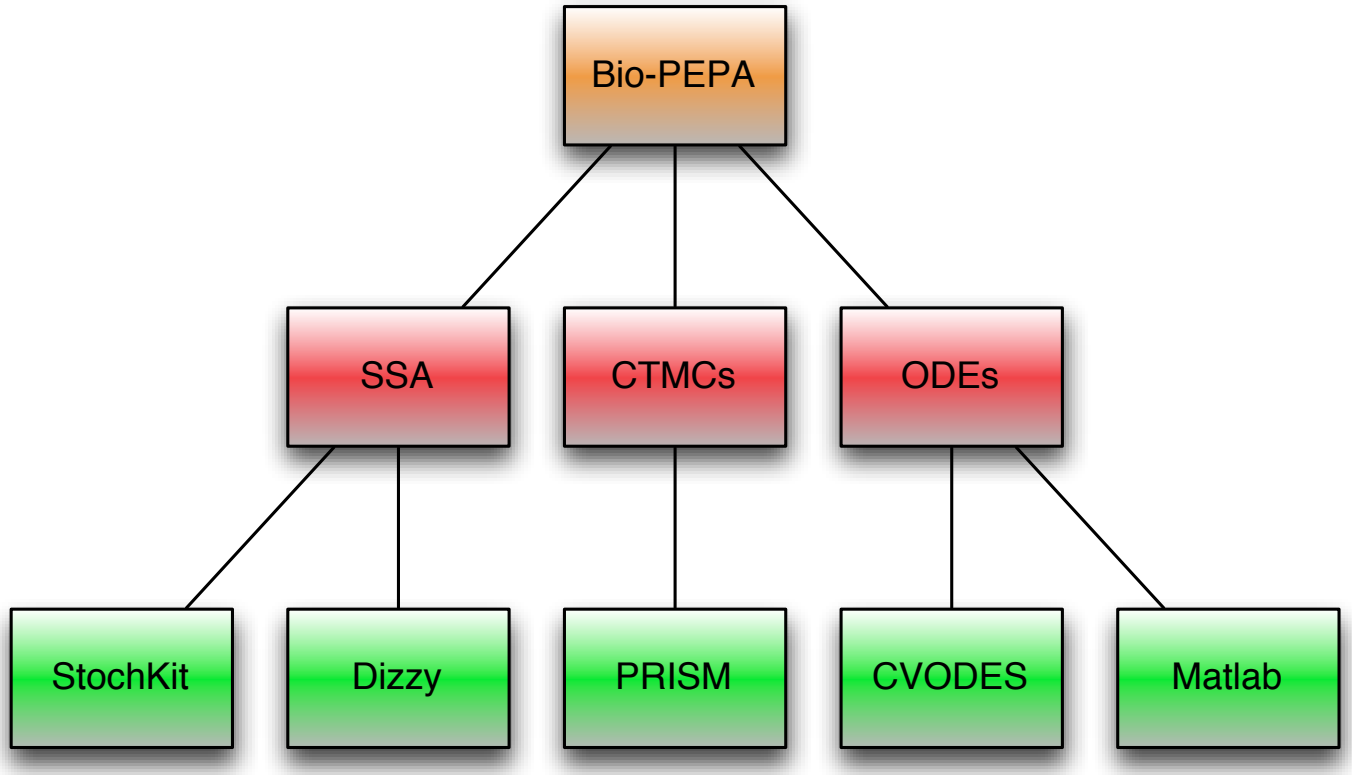

CTMC with levels

- Analysis of the Markov process can yield quite detailed information about the dynamic behaviour of the model.

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- A transient analysis provides statistics relating to the evolution of the model over a fixed period. This will be dependent on the starting state.

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- The rate of a transition is consistent with the granularity.
- The granularity must be specified by the modeller as the expected range of concentration values and the number of levels considered.
- 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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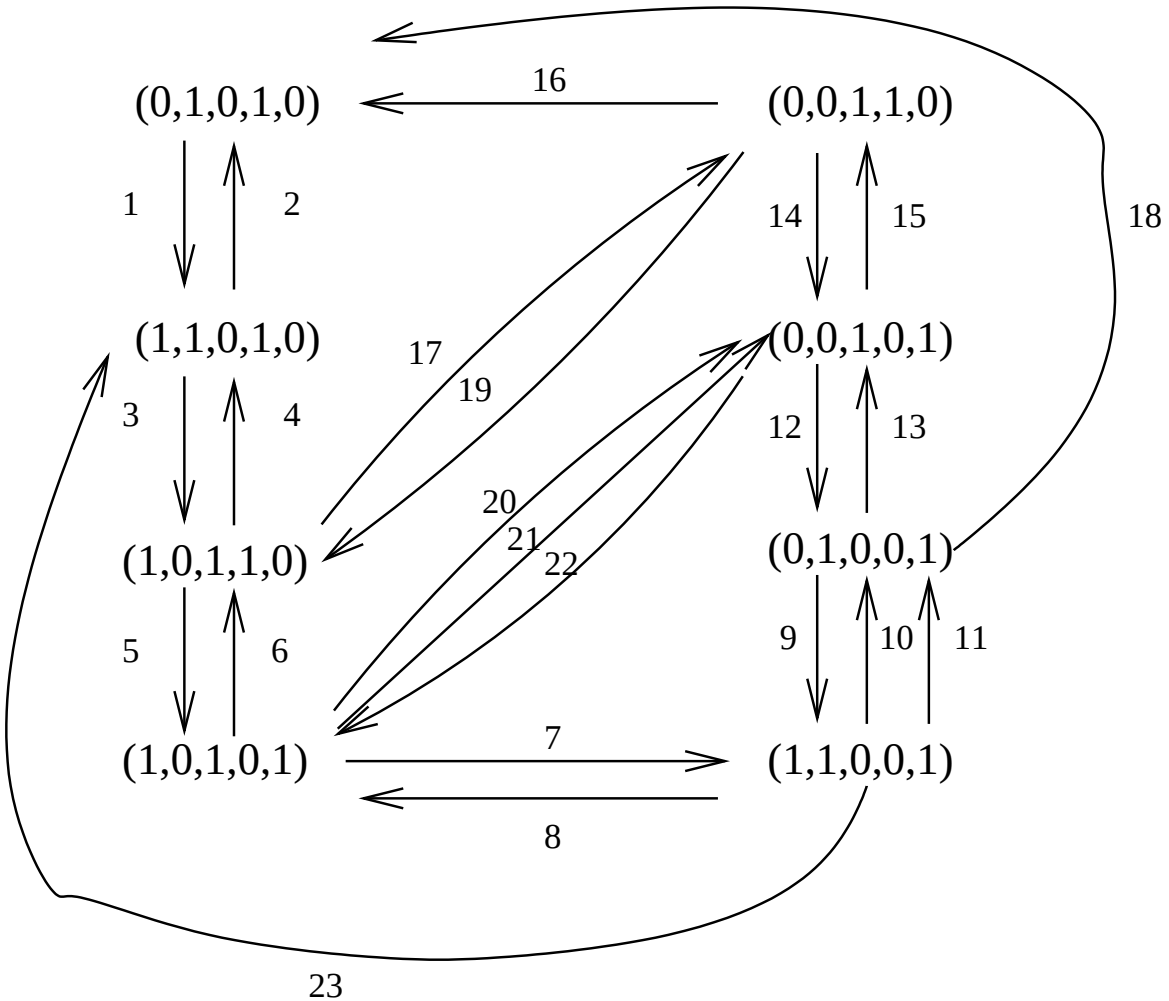
Goldbeter's model: explicit CTMC

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 $(l_C(1), l_{M'}(0), l_M(1), l_{X'}(0), l_X(1))$.



ODE system

- The derivation of the ODEs from the Bio-PEPA is straightforward, based on the stoichiometry matrix which is readily derived from the definitions of the species components.

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  - The ODEs can be automatically generated from the descriptive process algebra model, thus reducing human error.
  - 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.

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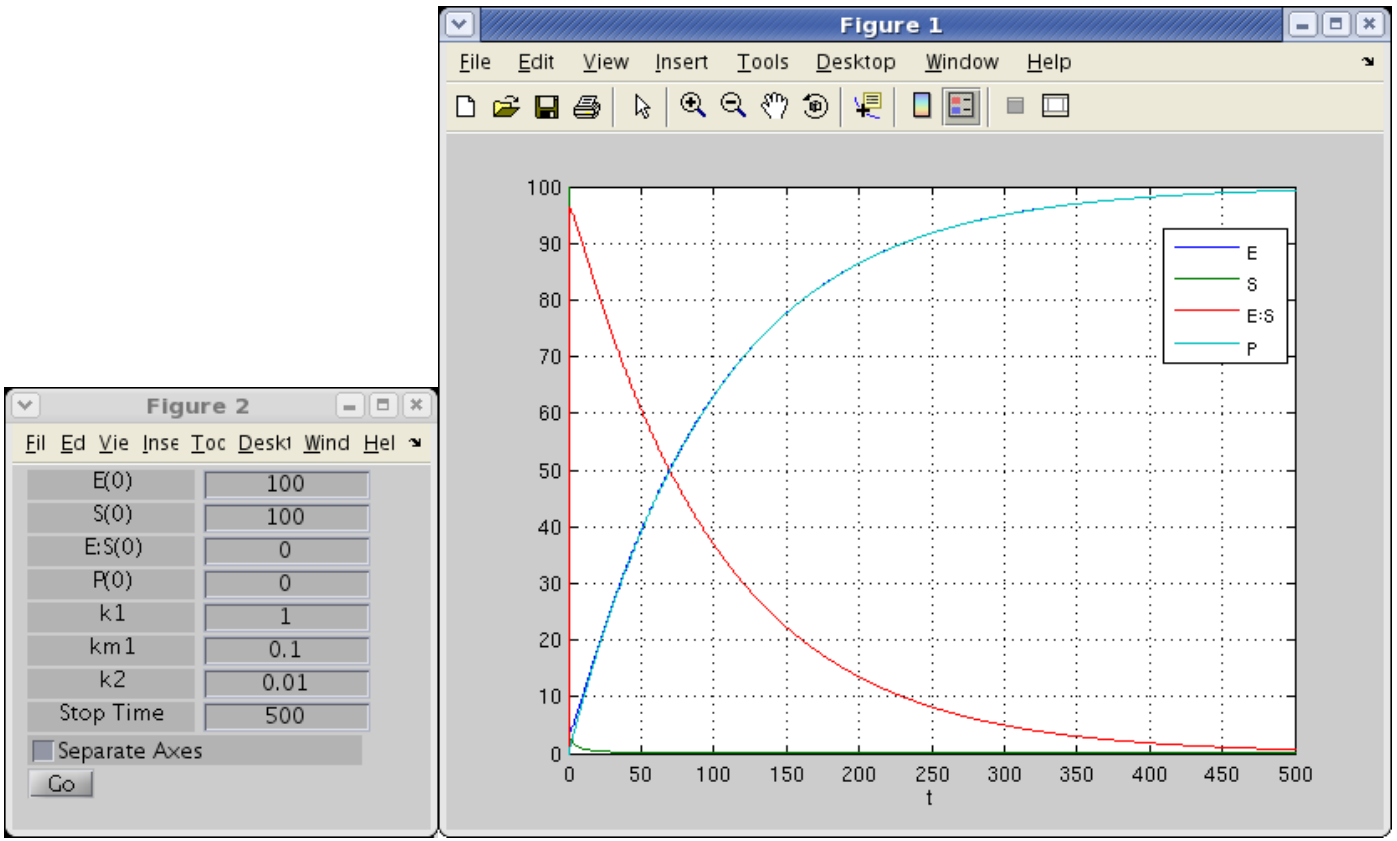
Analysing Bio-PEPA models with Matlab



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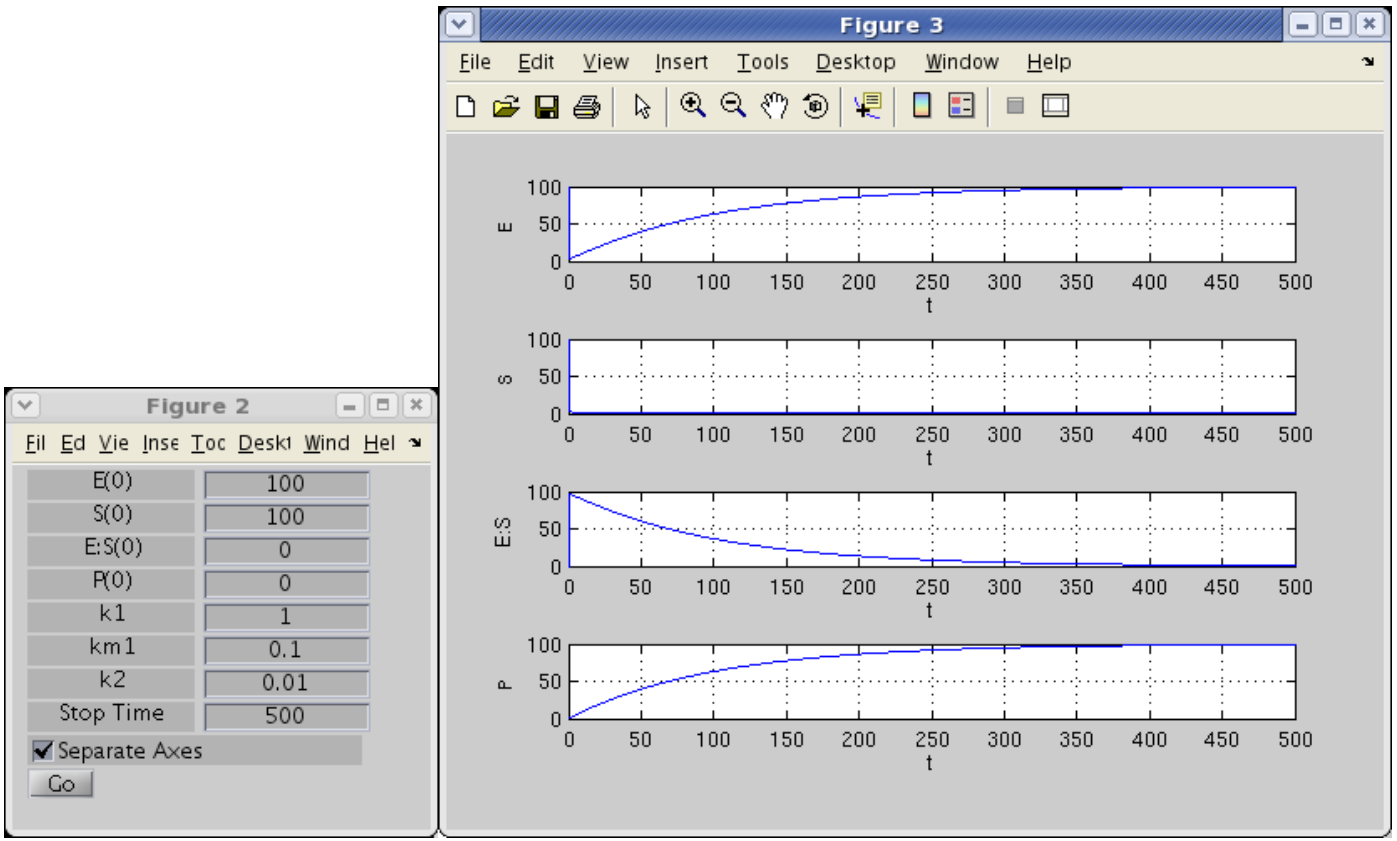

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Goldbeter's model

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:

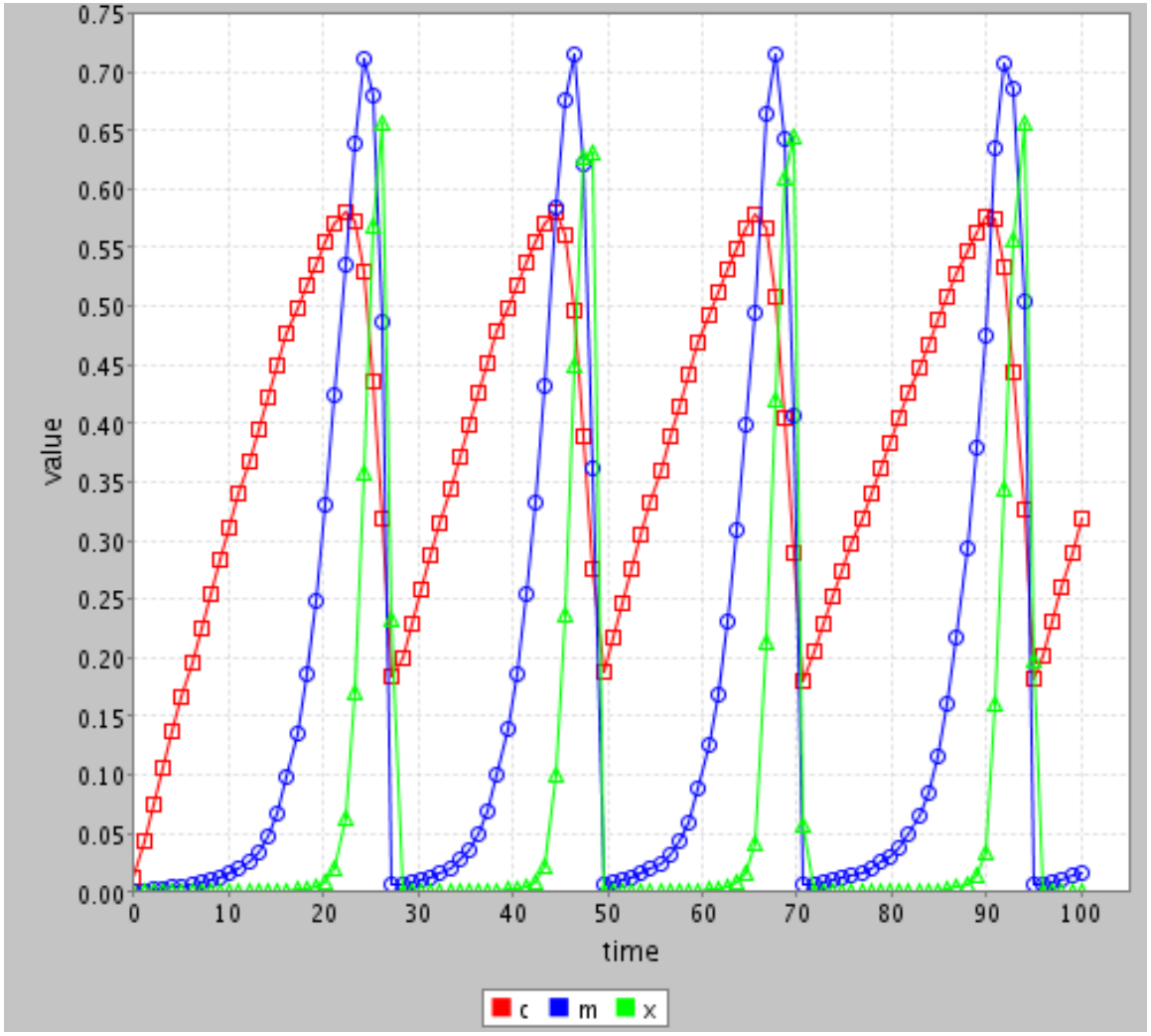
$$w = \left(v_i \times 1, k_d \times x_C, \frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 \times x_M}{(K_2 + x_M)}, \right.$$
$$\left. \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 \times x_X}{(K_4 + x_X)}, \frac{v_d \times x_C \times x_X}{(K_d + x_C)}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

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:

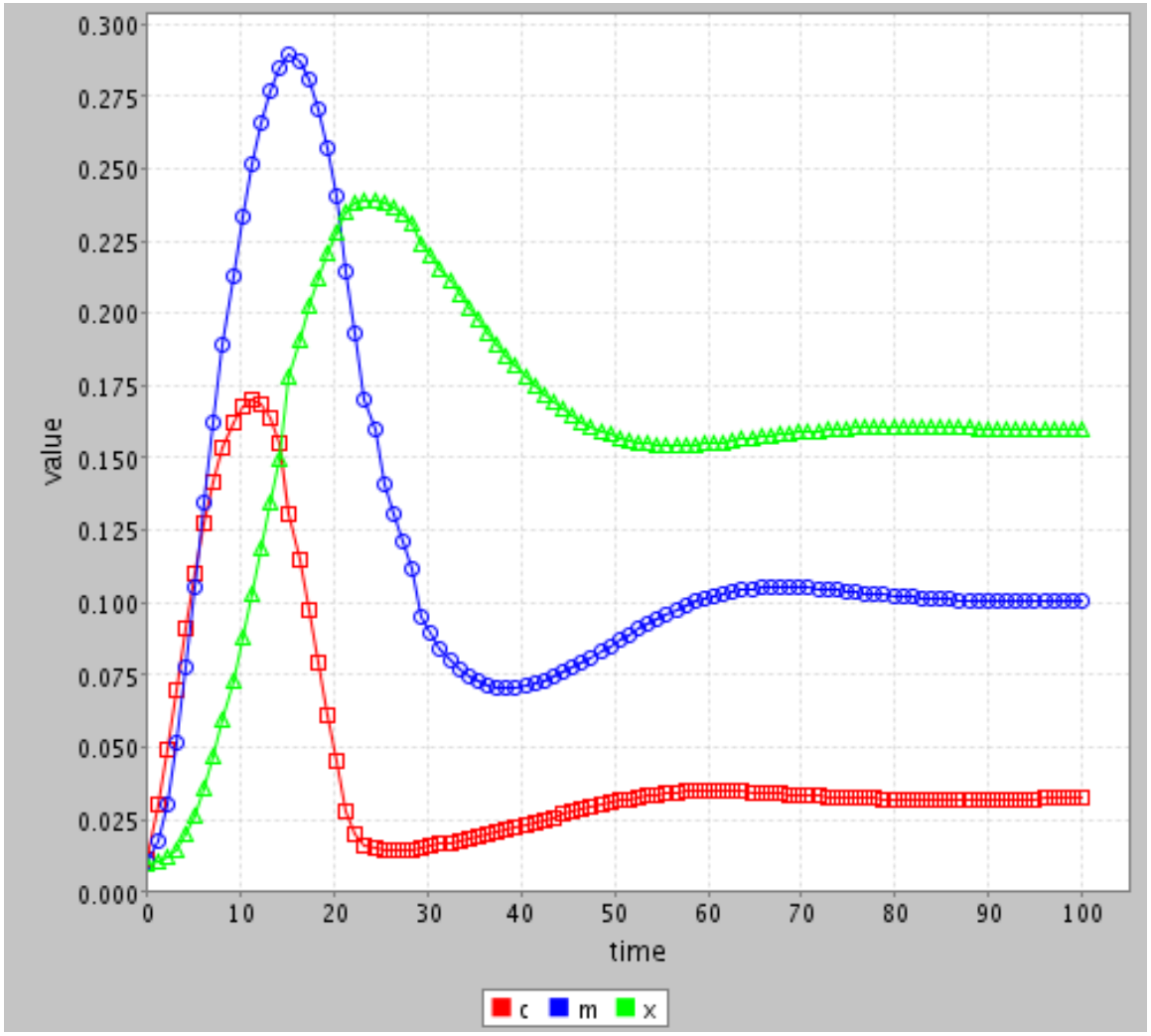
$$\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C}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

ODE results



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

ODE results



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

Stochastic Simulation

Stochastic Simulation based on Gillespie's algorithm and similar are simulations of a CTMC.

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Thus formally a stochastic simulation model is derived from a Bio-PEPA model by applying the structured operational semantics with parameters interpreted as molecule counts.

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We currently generate models for Dizzy and Stochkit.

PRISM model and model checking

- Analysing models of biological processes via probabilistic model-checking has considerable appeal.

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PRISM model and model checking

- Analysing models of biological processes via probabilistic model-checking has considerable appeal.
- As with stochastic simulation the answers which are returned from model-checking give a thorough stochastic treatment to the small-scale phenomena.

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- As with stochastic simulation the answers which are returned from model-checking give a thorough stochastic treatment to the small-scale phenomena.
- 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.

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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.

PRISM model and model checking

- Probabilistic model checking in PRISM is based on a CTMC and the logic CSL.

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- 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.

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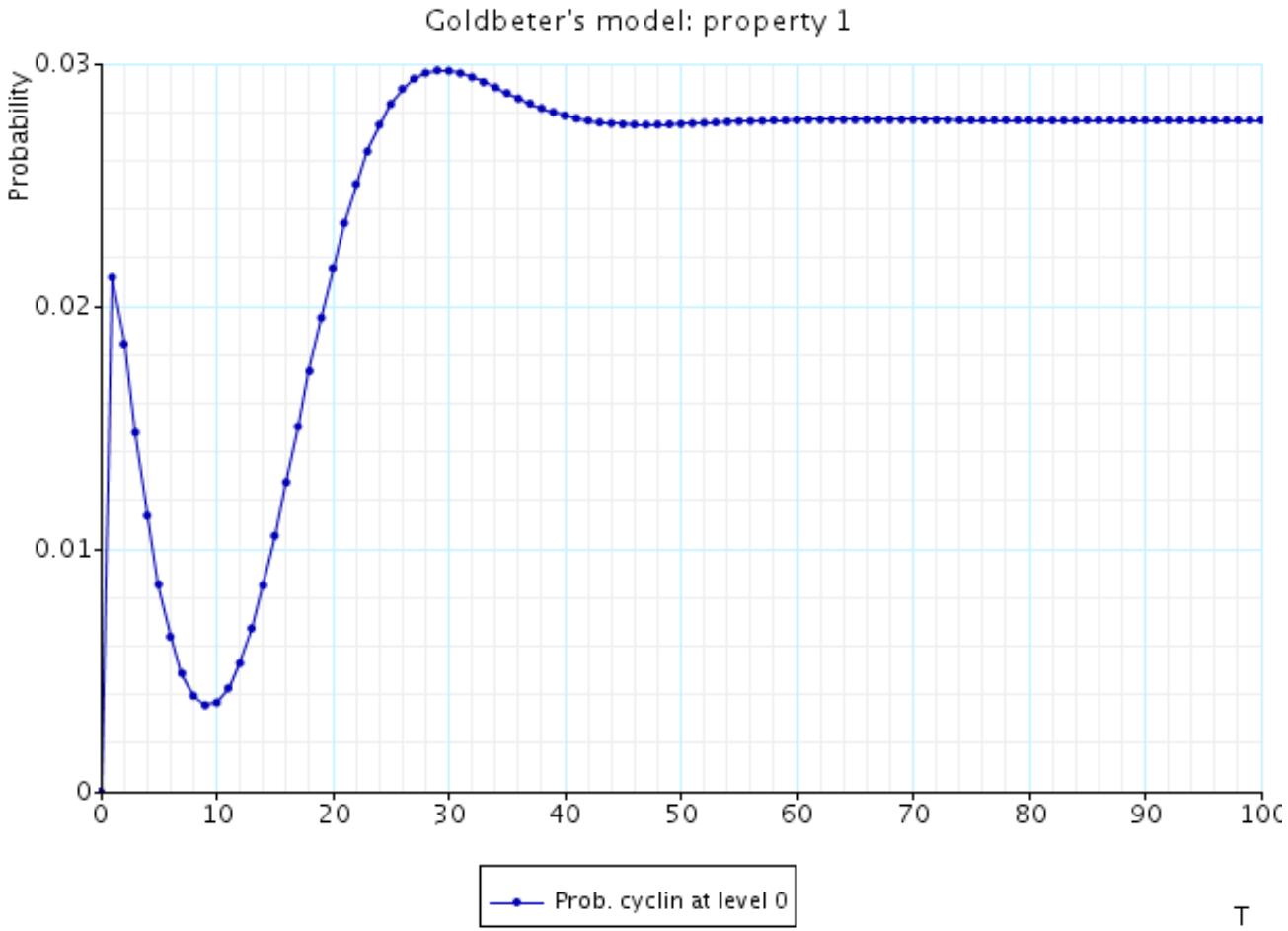
Goldbeter's model: PRISM results



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

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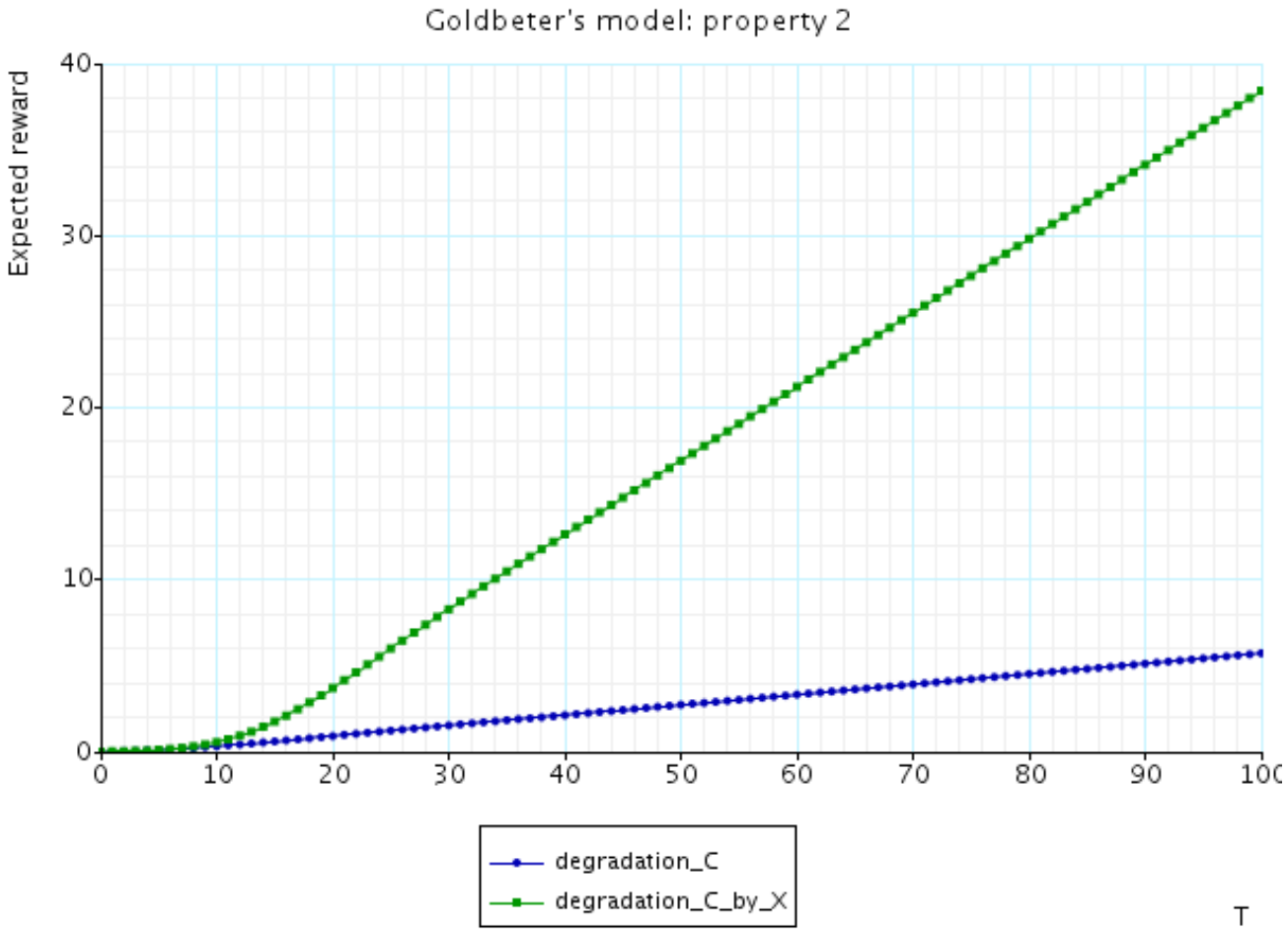
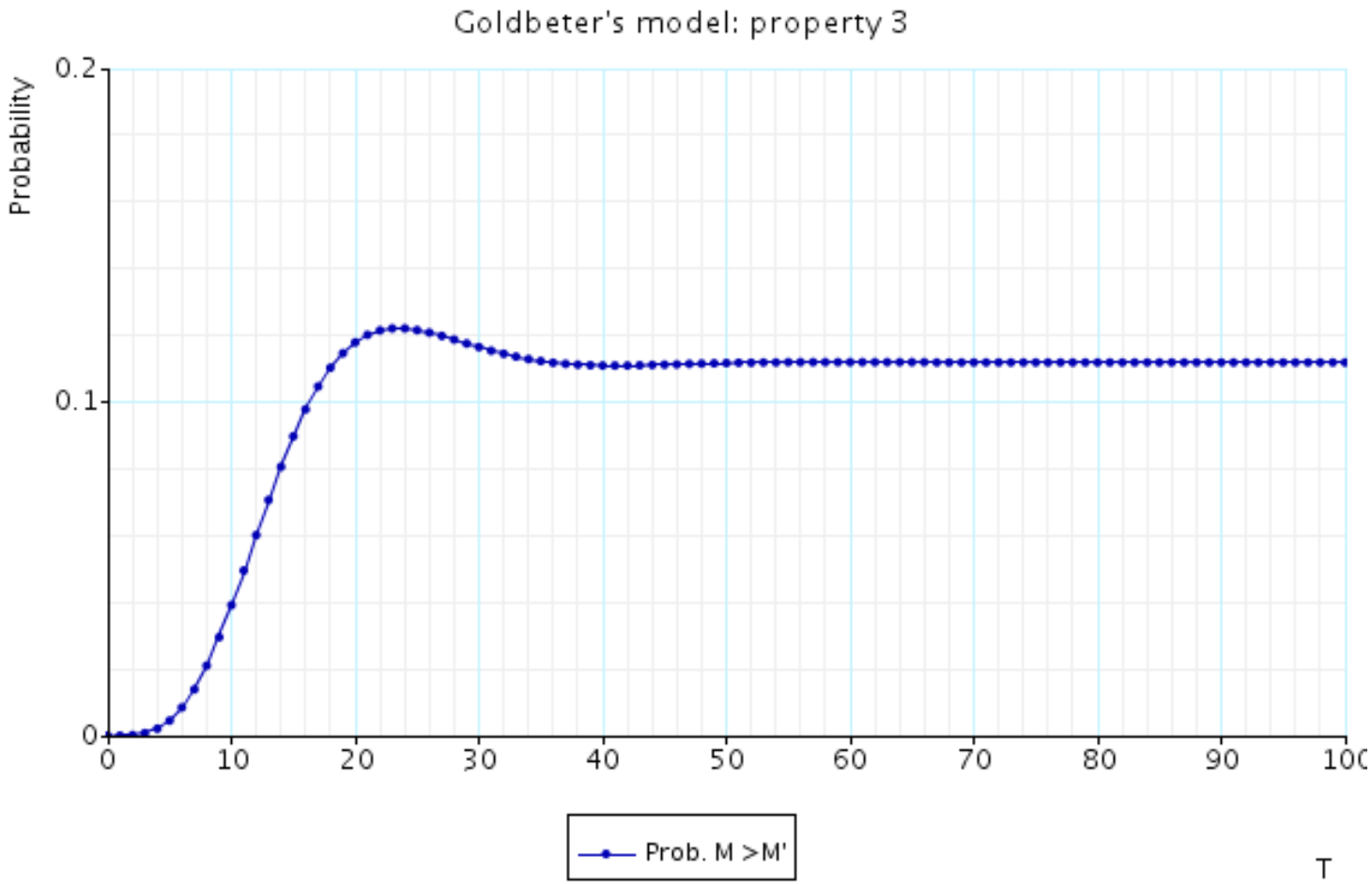


$R\alpha_2 =?[C <= T]$ and $R\alpha_7 =?[C <= T]$

Goldbeter's model: PRISM results



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

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.

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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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Conclusions (2)

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

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

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Conclusions (2)

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

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!

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