Calculi for Biological Systems Part 2

Jane Hillston and Federica Ciocchetta.
LFCS,
University of Edinburgh

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Outline

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Particular problems are encountered with:

- stoichiometry — the multiplicity in which an entity participates in a reaction;
- general kinetic laws — while mass action is widely used other kinetics are also commonly employed.
- multiway reactions — although thermodynamics 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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- Different possible decompositions.
- Rates must be found for all the intermediate steps.

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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.
- Multi-way reactions are possible in Bio-PEPA since it has CSP-style synchronisation rather than CCS-style synchronisation. Thus a multi-way reaction is abstracted as a multi-syncronisation.

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- We define the same step size h for all the species, with few exceptions. This follows from the law of conservation of mass.
- If l_i is the concentration level for the species i, the concentration is taken to be $x_i = l_i \times h$.

Reagent-centric modelling (2)

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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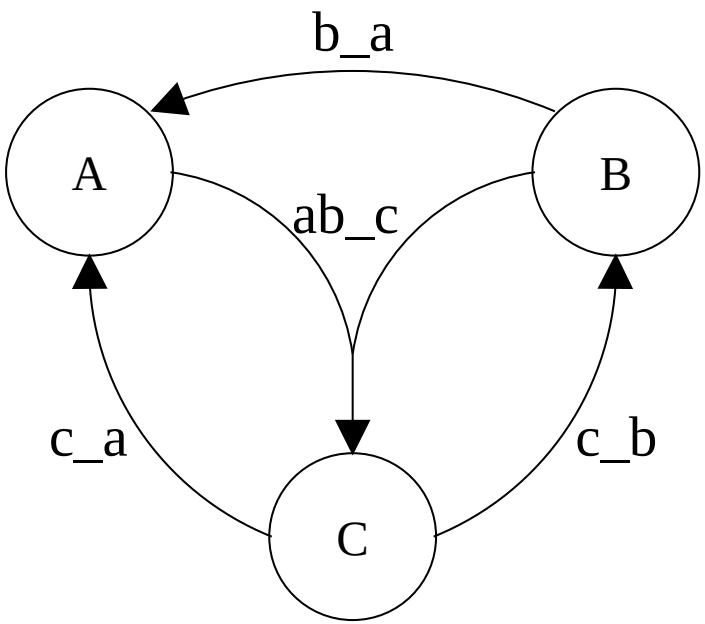
- The form of the CTMC derived from Bio-PEPA, which we term the CTMC with levels, will depend on the granularity of the model.
- As the granularity tends to zero the behaviour of this CTMC with levels tends to the behaviour of the ODEs [CDHC08].

Bio-PEPA reagent-centric example



$$A \stackrel{def}{=} (ab\_c, 1)\downarrow A + (b\_a, 1)\uparrow A + (c\_a, 1)\uparrow A$$

$$B \stackrel{def}{=} (ab\_c, 1)\downarrow B + (b\_a, 1)\downarrow B + (c\_b, 1)\uparrow B$$

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

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

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- A component varying its state corresponds to it varying its concentration level.
- This is captured by an integer parameter associated with the species and the effect of a reaction is to vary that parameter by a number of levels corresponding to the stoichiometry of this species in the reaction.

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The syntax

Sequential (species) component

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Model component

$$P \stackrel{def}{=} P \underset{\mathcal{L}}{\bowtie} P \mid S(l)$$

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

Semantics: prefix rules

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

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

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

Semantics: rates and transition system

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

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

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r_{α_j} represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition.
The rate r_{α_j} is defined as $f_{\alpha_j}(v, \mathcal{N})/h$.

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The species components are then composed together to describe the behaviour of the system.

Example: Michaelis-Menten

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(S(l_{S0}) \underset{\{\alpha\}}{\bowtie} E(l_{E0})) \underset{\{\alpha\}}{\bowtie} P(l_{P0})
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Example: Competitive Inhibition

Binding of the inhibitor to the enzyme prevents binding of the substrate and vice versa.

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Under QSSA (the intermediate species SE and EI are constant) we can approximate the reactions above by a unique reaction

$$S \xrightarrow{E,I:f_I} P \qquad \text{with rate } f_I = \frac{w \times S \times E}{S + K_M(1 + \frac{I}{K_I})}$$

where w: turnover number (catalytic constant),
K_M: Michaelis constant and K_I: inhibition constant.

Example: Competitive Inhibition (2)

The specification in Bio-PEPA is:

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with functional rate

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From the biological perspective. we are investigating the situations in which biologists regard models or elements of models to be equivalent, particularly when this is employed for model simplification.

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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.

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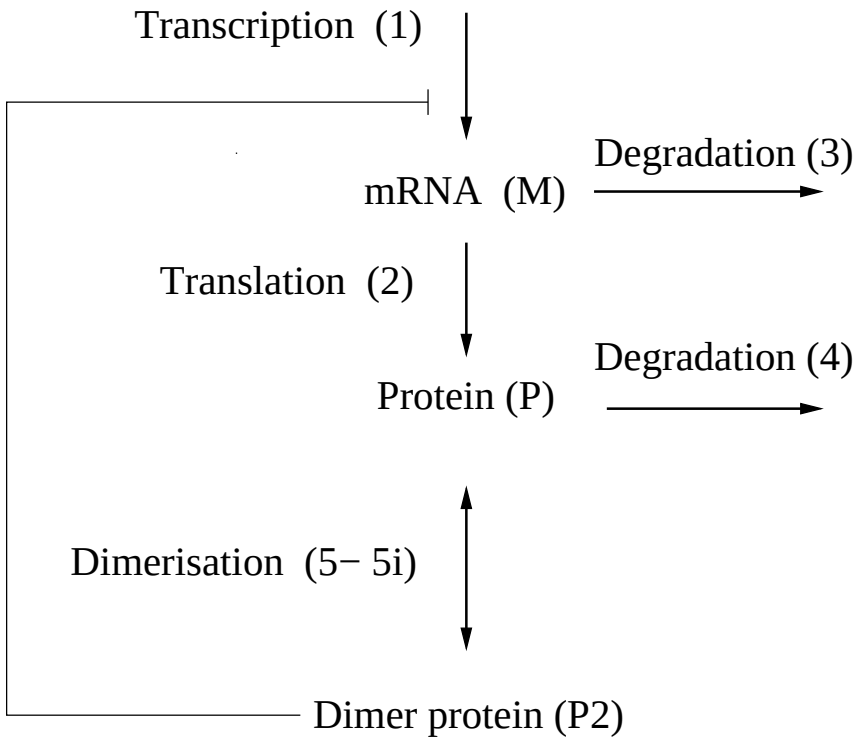
The biological model

Consider a genetic network with negative feedback through dimers.



Species and reactions

The biological entities are:

- the *mRNA molecule* (*M*),
- the protein in monomer form (*P*) and
- the protein in dimeric form (*P2*).

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- the *mRNA molecule* (*M*),
- the protein in monomer form (*P*) and
- the protein in dimeric form (*P2*).

All the reactions are described by mass action kinetics with the exception of the first reaction, that has an inhibition kinetics.

Translation into Bio-PEPA

Definition of the list $\mathcal{N}$

$$[M : N_M, h_M; \quad P : N_P, h_P; \quad P2 : N_{P2}, h_{P2}]$$

Translation into Bio-PEPA

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$$[M : N_M, h_M; \quad P : N_P, h_P; \quad P2 : N_{P2}, h_{P2}]$$

Definition of functional rates

$$f_{\alpha_1} = \frac{v}{K_M + P2}$$

$$f_{\alpha_2} = fMA(k_2) \qquad f_{\alpha_3} = fMA(k_3) \qquad f_{\alpha_4} = fMA(k_4)$$

$$f_{\alpha_5} = fMA(k_5) \qquad f_{\alpha_{5\_Inv}} = fMA(k_{5\_Inv})$$

Translation into Bio-PEPA (cont.)

Definition of the system components

$$
\begin{array}{lcl}
\mathrm{M} & = & (\alpha_1,1) \uparrow \mathrm{M} + (\alpha_2,1) \oplus \mathrm{M} + (\alpha_3,1) \downarrow \mathrm{M}; \\
\mathrm{P} & = & (\alpha_2,2) \uparrow \mathrm{P} + (\alpha_4,1) \downarrow \mathrm{P} + (\alpha_5,2) \downarrow \mathrm{P} + (\alpha_{5\_Inv},2) \uparrow \mathrm{P}); \\
\mathrm{P2} & = & (\alpha_1,1) \ominus \mathrm{P2} + (\alpha_{5\_Inv},1) \downarrow \mathrm{P2} + (\alpha_5,1) \uparrow \mathrm{P2}; \\
\mathrm{Res} & = & (\alpha_3,1) \odot \mathrm{Res} + (\alpha_4,1) \odot \mathrm{Res}; \\
\mathrm{CF} & = & (\alpha_1,1) \odot \mathrm{CF};
\end{array}
$$

Translation into Bio-PEPA (cont.)

Definition of the system components

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\mathrm{M} & = & (\alpha_1,1) \uparrow \mathrm{M} + (\alpha_2,1) \oplus \mathrm{M} + (\alpha_3,1) \downarrow \mathrm{M}; \\
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\mathrm{Res} & = & (\alpha_3,1) \odot \mathrm{Res} + (\alpha_4,1) \odot \mathrm{Res}; \\
\mathrm{CF} & = & (\alpha_1,1) \odot \mathrm{CF};
\end{array}
$$

Definitions of the system

$$((((CF(1) \underset{\{\alpha_1\}}{\bowtie} M(0)) \underset{\{\alpha_2\}}{\bowtie} P(0)) \underset{\{\alpha_5,\alpha_{5\_Inv}\}}{\bowtie} P2(0)) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} Res(0)$$

Analysis: the CTMC with levels

For **2 levels**, the CTMC consists of **8 states** and **18 transitions**.

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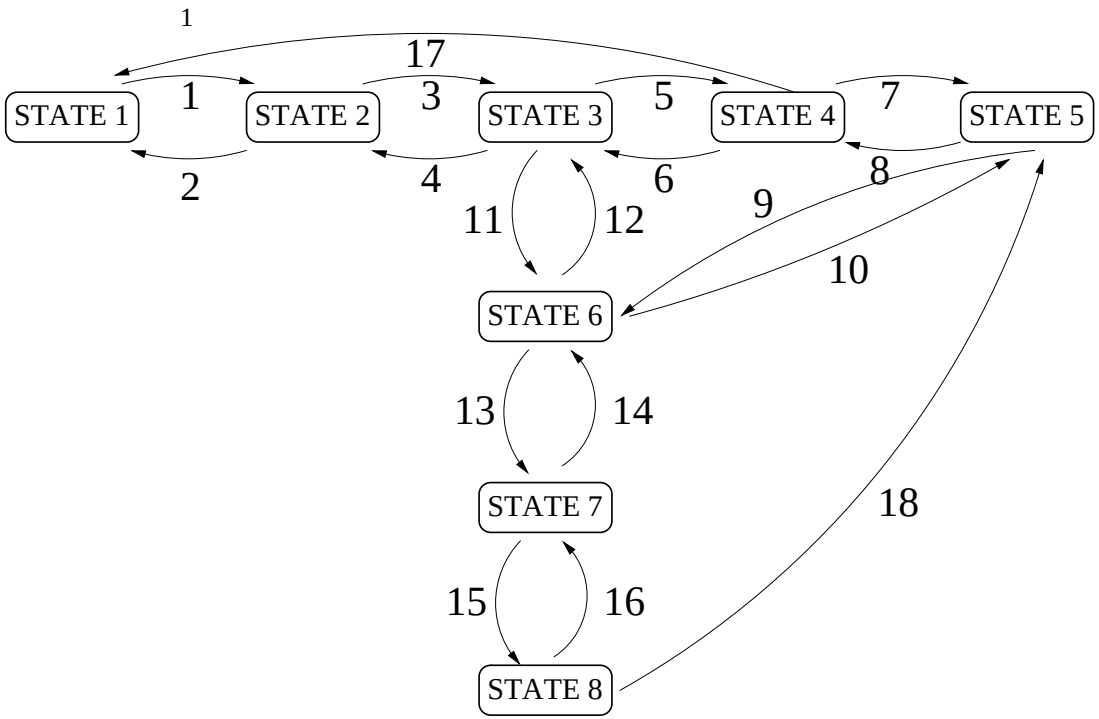

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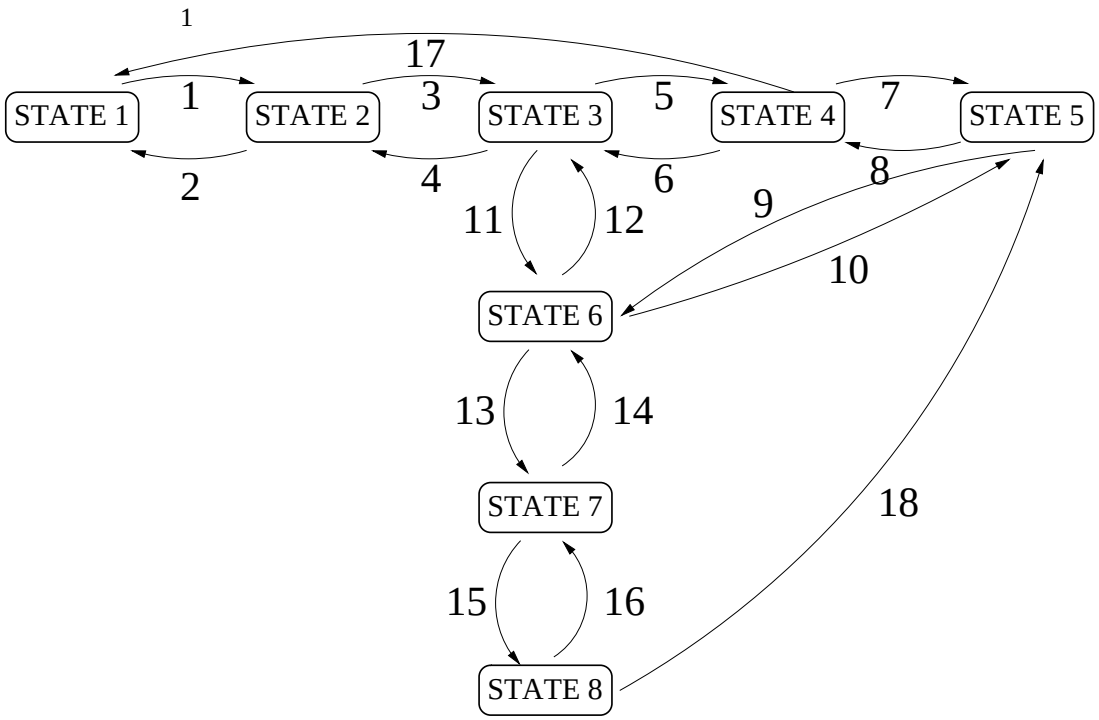

States are $(CF(l_1), M(l_2), P(l_3), P2(l_4), RES(l_5))$, with levels $l_1 \ldots l_5$.

Analysis: derivation of the ODE system

The stoichiometry matrix D associated with the system is

	α_1	α_2	α_3	α_4	α_5	α_{5_Inv}	
CF	0	0	0	0	0	0	x_{CF}
Res	0	0	0	0	0	0	x_{Res}
M	+1	0	-1	0	0	0	x_1
P	0	+1	0	-1	-2	+2	x_2
P2	0	0	0	0	+1	-1	x_3

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P	0	+1	0	-1	-2	+2	x_2
P2	0	0	0	0	+1	-1	x_3

The kinetic law vector is

$$w^T = (\frac{v \times x_{CF}}{K_M + x_3};\quad k_2 \times x_1; k3 \times x_1;\quad k4 \times x_2;\quad k5 \times {x_2}^2;\quad k5\_Inv \times x_3)$$

Analysis: derivation of ODEs (cont.)

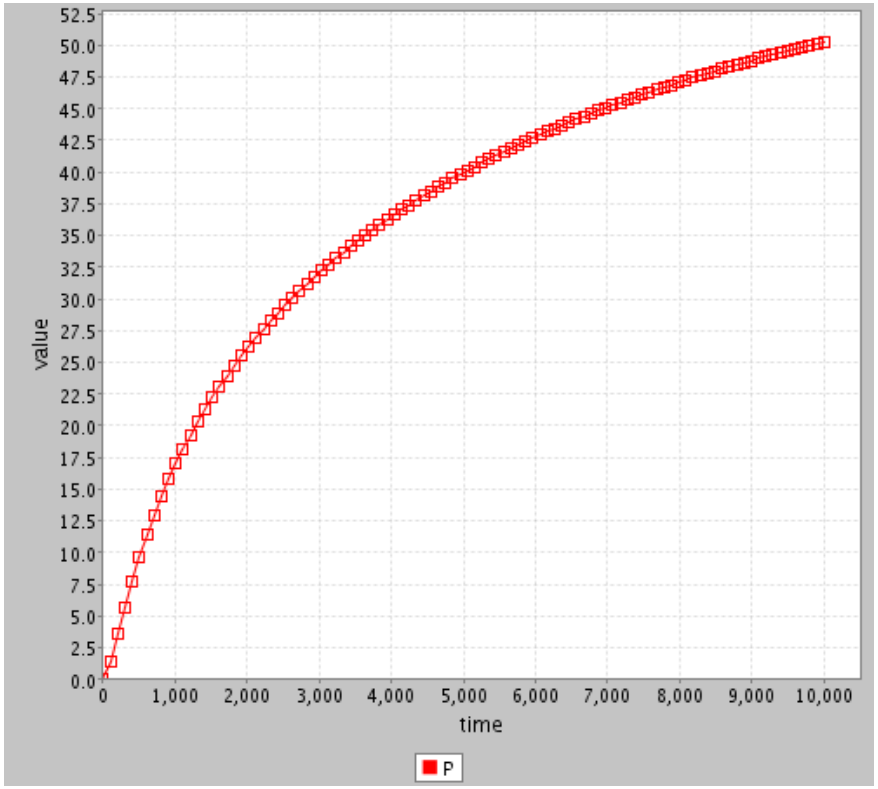
The system of ODEs is obtained as $\frac{d\bar{x}}{dt} = D \times w$:

$$\begin{aligned}
\frac{dx_1}{dt} &= \frac{v \times 1}{K_M + x_3} - k3 \times x_1 \\
\frac{dx_2}{dt} &= k2 \times x_1 - k4 \times x_2 - 2 \times k5 \times {x_2}^2 + 2 \times k5_Inv \times x_3 \\
\frac{dx_2}{dt} &= k5 \times {x_2}^2 - k5_Inv \times x_3
\end{aligned}$$

Analysis: stochastic simulation

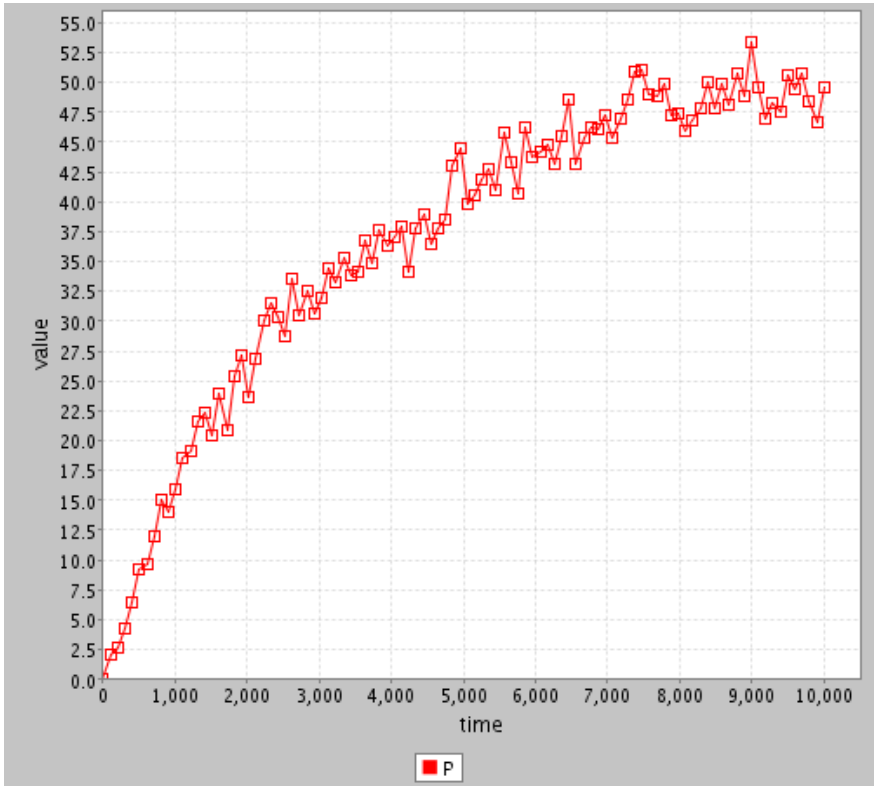
The derivation of the Gillespie model is made by creating molecules corresponding to each species and defining the possible reactions with appropriate adjustment of kinetic rates.

Simulation results



ODE results

Simulation results



Stochastic simulation results (10 runs)

PRISM model

Each species is represented as a PRISM module.

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For example, the protein is represented as:

module p
p: [0..Np] init 0;
$[Translation]\ p < Np \rightarrow (p' = p + 1);$
$[DegradationP]\ p > 0 \rightarrow (p' = p - 1);$
$[Dimerization]\ p > 1 \rightarrow (p' = p - 2);$
$[DimerizationInv]\ p < (Np - 1) \rightarrow (p' = p + 2);$
endmodule

PRISM model (cont.)

An additional module is needed to capture the kinetic rates.

module Functional_rates
dummy: bool **init** true;
$[Transcription]\ m < Nm \rightarrow (v/(K + p2 * h_{p2}) * h_{p2}) : (dummy' = dummy);$
$[Translation]\ m > 0 \rightarrow (k2 * m * h_m/h_m) : (dummy' = dummy);$
$[DegradationmRNA]\ m > 0 \rightarrow (k3 * m * h_m/h_m) : (dummy' = dummy);$
$[DegradationP]\ p > 0 \rightarrow (k4 * p * h_p/h_p) : (dummy' = dummy);$
$[Dimerization]\ p > 1 \rightarrow (k5 * p * h_p * p * h_p/h_p)(dummy' = dummy);$
$[DimerizationInv]\ p2 > 0 \rightarrow (k5\_Inv * p2 * h_{p2}/h_{p2}) : (dummy' = dummy);$
endmodule

PRISM analysis

PRISM analysis

- **Proportion of monomer P in total P (in terms of levels).**

  We need to define a reward structure in the PRISM file as:

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$true : \frac{p}{(p+p2)};$
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  We can ask for the proportion of monomer P by using the query:

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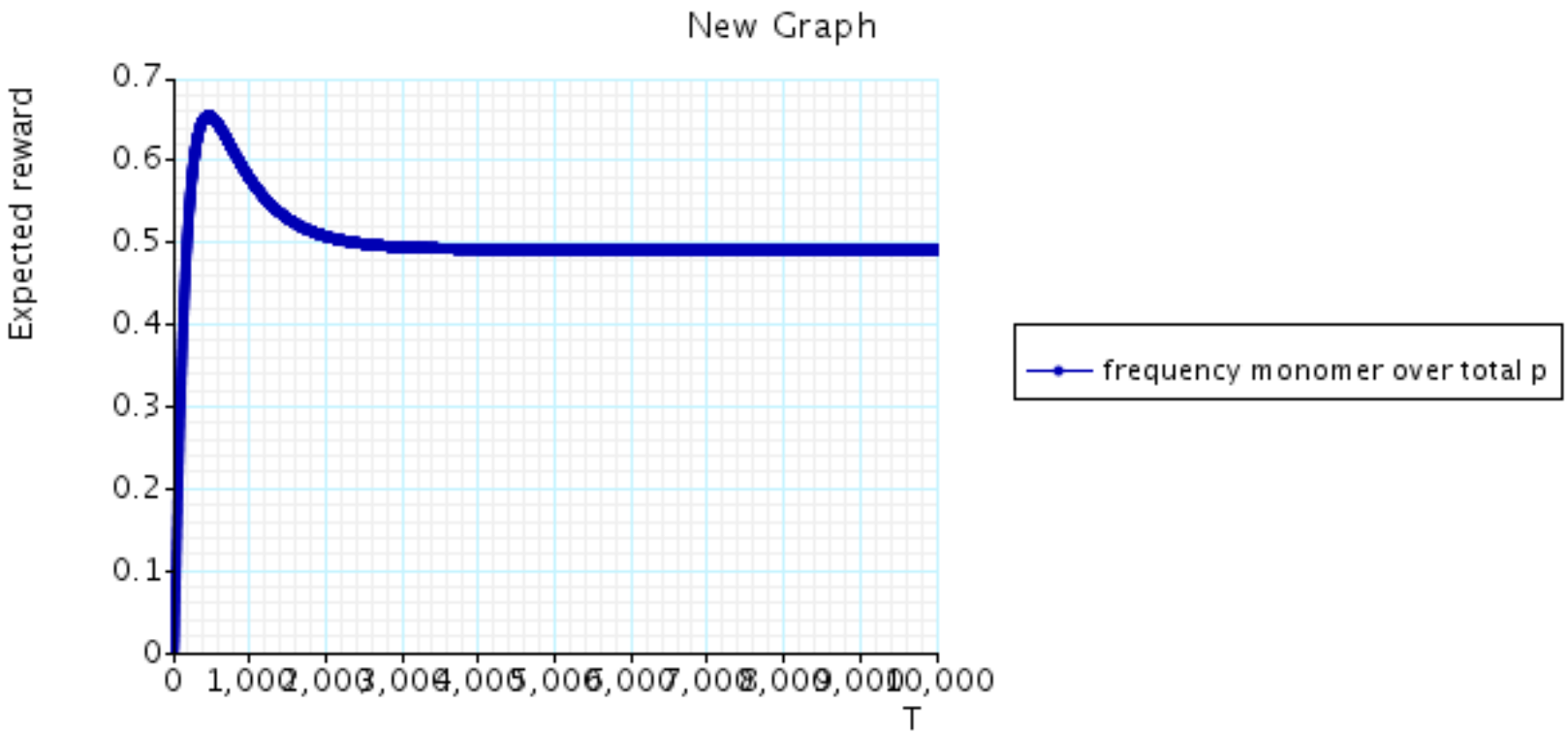
- **Probability that P is at level i at time T**

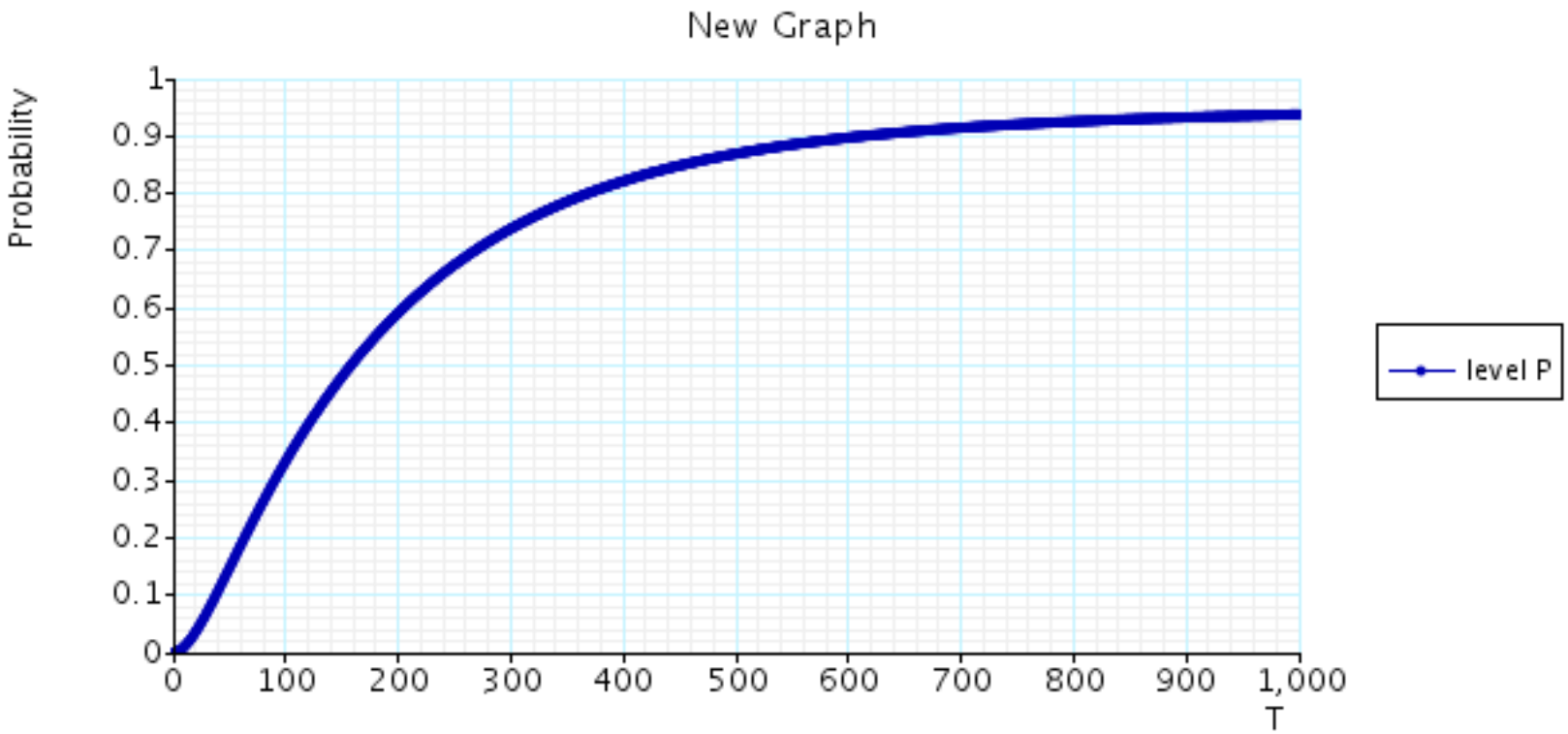
  $$P =?[trueU[T, T]p = i]$$

PRISM results



monomer frequency

PRISM results



Probability monomer protein is at high level over time

Goldbeter's model [Goldbeter 91]

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

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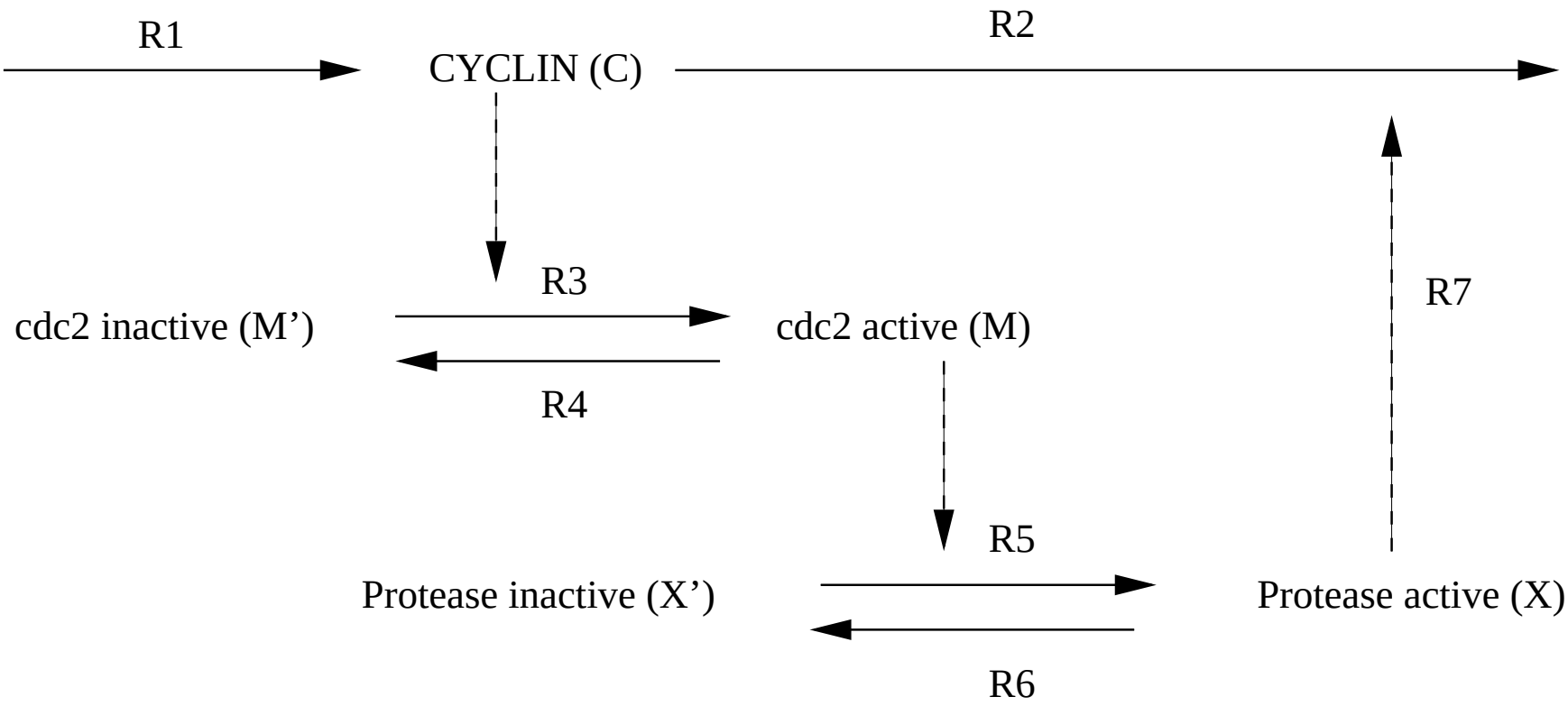
- This leads to a negative feedback loop.
- In the model most of the kinetic laws are of kind Michaelis-Menten and this can be reflected in the Bio-PEPA model.

The biological model



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- cyclin, the protein protagonist of the cycle, C;
- cdc2 kinase, in both active (i.e. dephosphorylated) and inactive form (i.e. phosphorylated). The variables used to represent them are M and M', respectively;
- cyclin protease, in both active (i.e. phosphorylated) and inactive form (i.e. dephosphorylated). The variable are X and X'.

Reactions

id	desc.	react.	prod.	mod.	kinetic laws
R1	creation of cyclin	-	C	-	vi
R2	degradation of cyclin	C	-	-	$kd \times C$
R3	activation of cdc2 kinase	M'	M	-	$\frac{C*V_{M1}}{(K_c+C)} \frac{M'}{(K_1+M')}$
R4	deactivation of cdc2 kinase	M	M'	-	$\frac{M \times V_2}{(K_2+M)}$
R5	activation of cyclin protease	X'	X	M	$\frac{X' \times M \times V_{M3}}{(K_3+X')}$
R6	deactivation of cyclin protease	X	X'	-	$\frac{X \times V_4}{K_4+X}$
R7	X triggered degradation of cyclin	C	-	X	$\frac{C \times v_d \times X}{C+K_d}$

R1 and R2 have Mass-Action kinetics, whereas all others are Michaelis-Menten.

Translation into Bio-PEPA

Definition of the set $\mathcal{N}$:

$$\mathcal{N} = [Res : 1, 1;\ CF : 1, 1;\ C : h_C, N_c;\ M : h_M, N_M;$$
$$M' : h_{M'}, N_{M'};\ X : h_X, N_X, ;\ X' : h_{X'}, N_{X'}]$$

Res and *CF* represent degradation and synthesis respectively.

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$$\mathcal{N} = [Res : 1, 1;\ CF : 1, 1;\ C : h_C, N_c;\ M : h_M, N_M;\ M' : h_{M'}, N_{M'};\ X : h_X, N_X, ;\ X' : h_{X'}, N_{X'}]$$

Res and *CF* represent degradation and synthesis respectively.

Definition of functional rates ($\mathcal{F}$):

$$f_{\alpha_1} = fMA(v_i); \qquad f_{\alpha_2} = fMA(k_d);$$
$$f_{\alpha_4} = fMM(V_2, K_2); \qquad f_{\alpha_5} = fMM(V_3, K_3);$$
$$f_{\alpha_6} = fMM(V_4, K_4); \qquad f_{\alpha_7} = fMM(V_d, K_d);$$

$$f_{\alpha_3} = \frac{v_1 \times C}{K_c + C} \frac{M'}{K1 + M'}$$

The Bio-PEPA system (2)

Definition of species components (*Comp*):

$$
\begin{array}{lcl}
C & = & (\alpha_1, 1)\uparrow C + (\alpha_2, 1)\downarrow C + (\alpha_3, 1) \oplus C + (\alpha_7, 1)\downarrow C; \\
M' & = & (\alpha_3, 1)\downarrow M' + (\alpha_4, 1)\uparrow M'; \\
M & = & (\alpha_3, 1)\uparrow M + (\alpha_4, 1)\downarrow M + (\alpha_5, 1) \oplus M; \\
X' & = & (\alpha_5, 1)\downarrow X' + (\alpha_6, 1)\uparrow X'; \\
X & = & (\alpha_5, 1)\uparrow X + (\alpha_6, 1)\downarrow X + (\alpha_7, 1) \oplus X; \\
Res & = & (\alpha_2, 1) \odot Res; \quad CF = (\alpha_1, 1) \odot CF;
\end{array}
$$

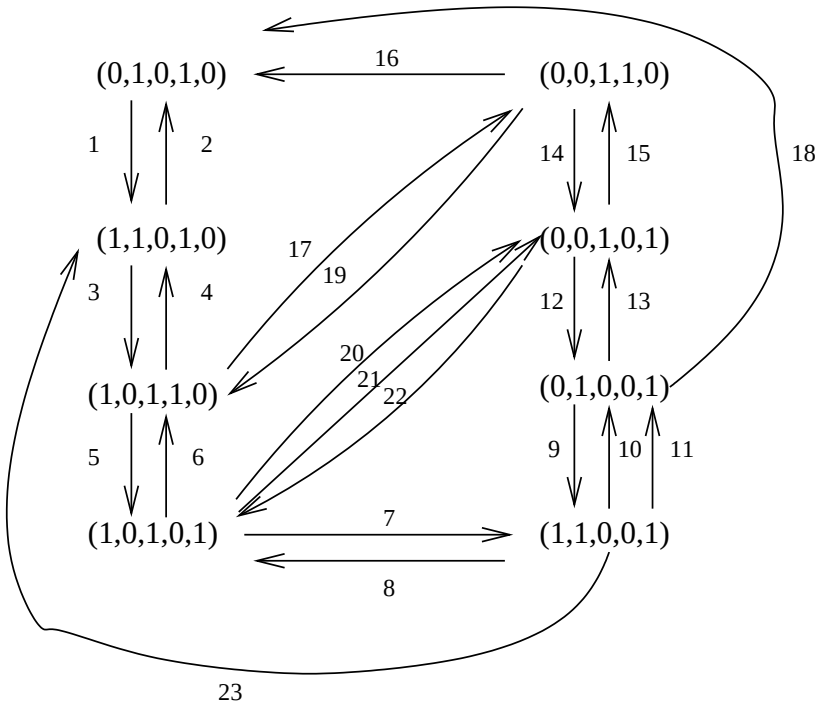
Definition of the model component (*P*):

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

$$
\underset{\{\alpha_2\}}{\bowtie} Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)
$$

Analysis: CTMC with 2 levels

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



Analysis: ODEs

The stoichiometry matrix D:

	R1	R2	R3	R4	R5	R6	R7	
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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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

The vector that contains the kinetic laws is:

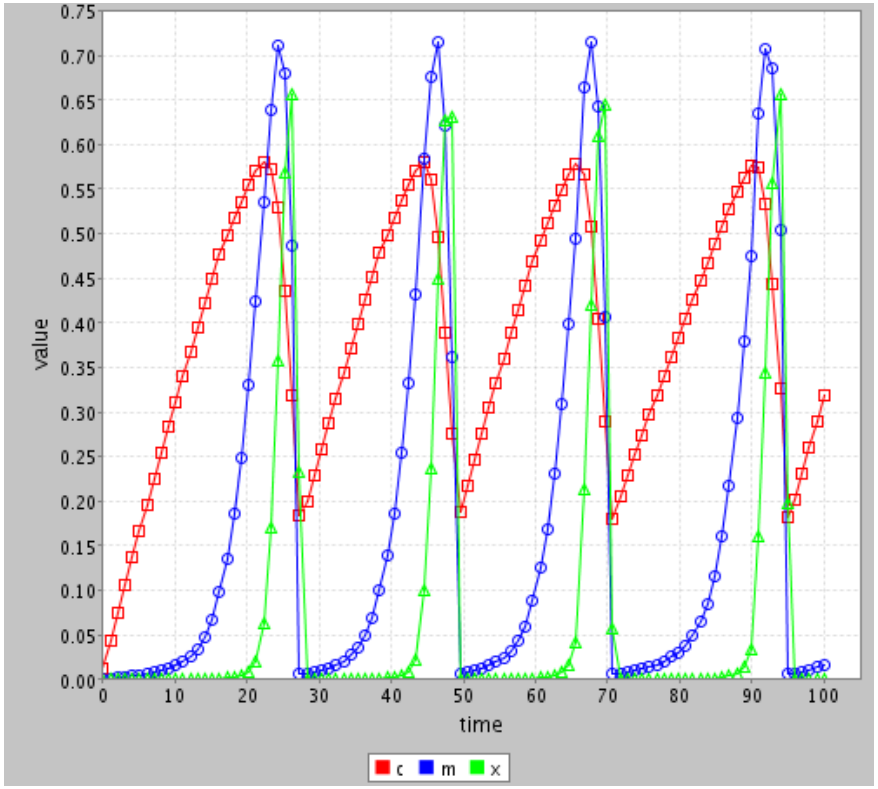
$$w = \Big(v_i \times 1, k_d \times x_C, \frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})}, \frac{V_2 \times x_M}{(K_2 + x_M)}, \frac{V_{M3} \times x_M \times x_{X'}}{(K_3 + x_{X'})}, \frac{V_4 \times x_X}{(K_4 + x_X)}, \frac{v_d \times x_C \times x_X}{(K_d + x_C)}\Big)$$

Analysis: 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:

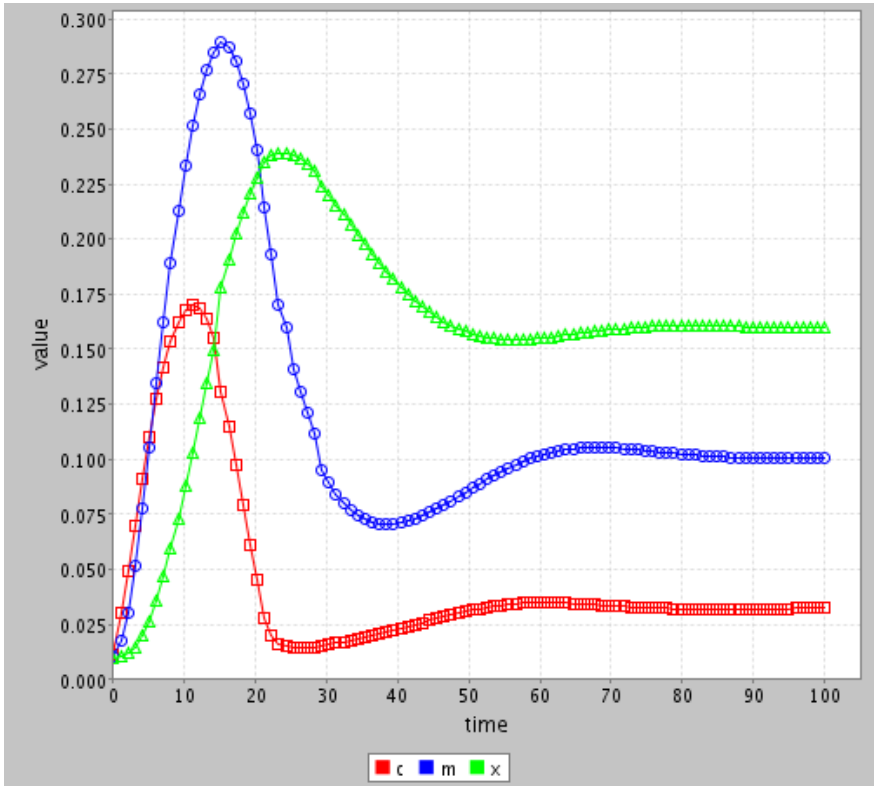
$$
\begin{aligned}
\frac{dx_C}{dt} &= v_i \times 1 - k_d \times x_C - \frac{v_d \times x_C \times x_X}{(K_d + x_C)} \\
\frac{dx_{M'}}{dt} &= -\frac{V_{M1} \times x_C}{K_c + x_C} \frac{x_{M'}}{(K_1 + x_{M'})} + \frac{V_2 \times x_M}{(K_2 + x_M)} \\
\frac{dx_M}{dt} &= +\frac{V_{M1} \times x_C}{K_c + x_C}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

ODE results



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

ODE results



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

Extension of the Goldbeter's model

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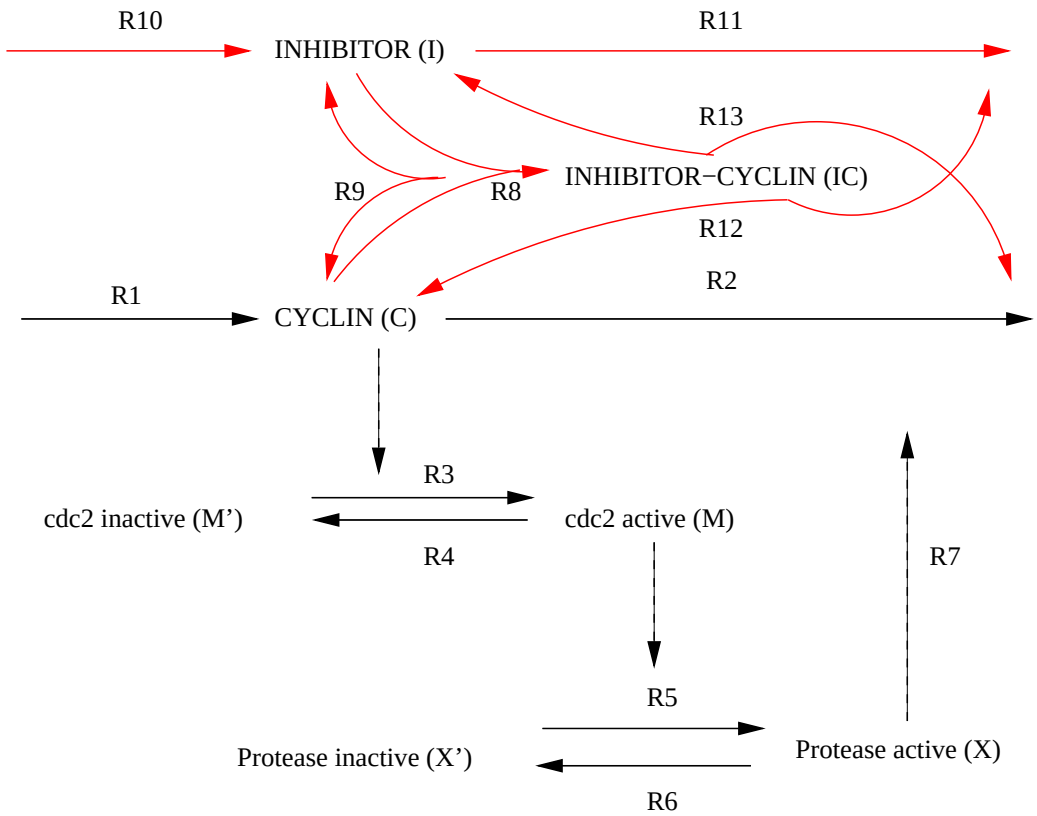
Several possible extensions were presented; we consider one of them.

Schema of the extended model



Extended Bio-PEPA system

$$C = \cdots + (\alpha_8, 1)\downarrow C + (\alpha_9, 1)\uparrow C + (\alpha_{12}, 1)\uparrow C;$$

$$\vdots \qquad \vdots$$

$$Res = \cdots + (\alpha_{11}, 1) \odot Res; \quad CF = \cdots + (\alpha_{10}, 1) \odot CF;$$

$$I = (\alpha_8, 1)\downarrow I + (\alpha_9, 1)\uparrow I + (\alpha_{10}, 1)\uparrow I + (\alpha_{11}, 1)\downarrow I + (\alpha_{13}, 1)\uparrow I;$$

$$IC = (\alpha_8, 1)\uparrow IC + (\alpha_9, 1)\downarrow IC + (\alpha_{12}, 1)\downarrow IC + (\alpha_{13}, 1)\downarrow IC;$$

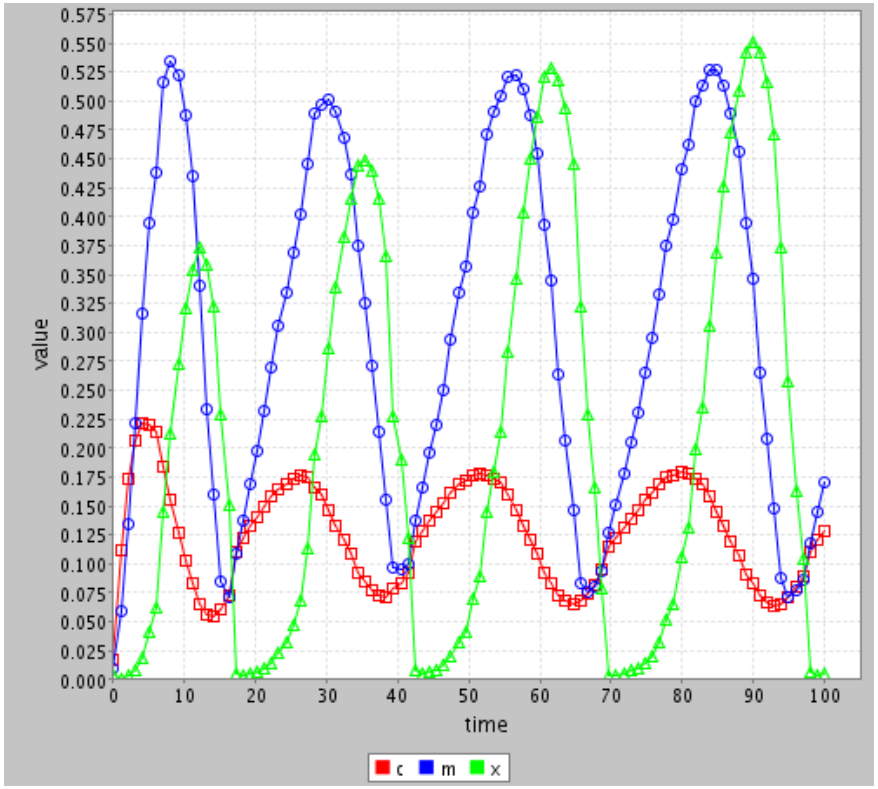
New functional rates

$$
\begin{aligned}
f_{\alpha_8} &= v_s; \\
f_{\alpha_9} &= fMA(d_1); \\
f_{\alpha_{10}} &= fMA(a_1); \\
f_{\alpha_{11}} &= fMA(a_2); \\
f_{\alpha_{12}} &= fMA(\theta \times d_1); \\
f_{\alpha_{13}} &= fMA(\theta \times k_d)
\end{aligned}
$$

Complete Bio-PEPA system

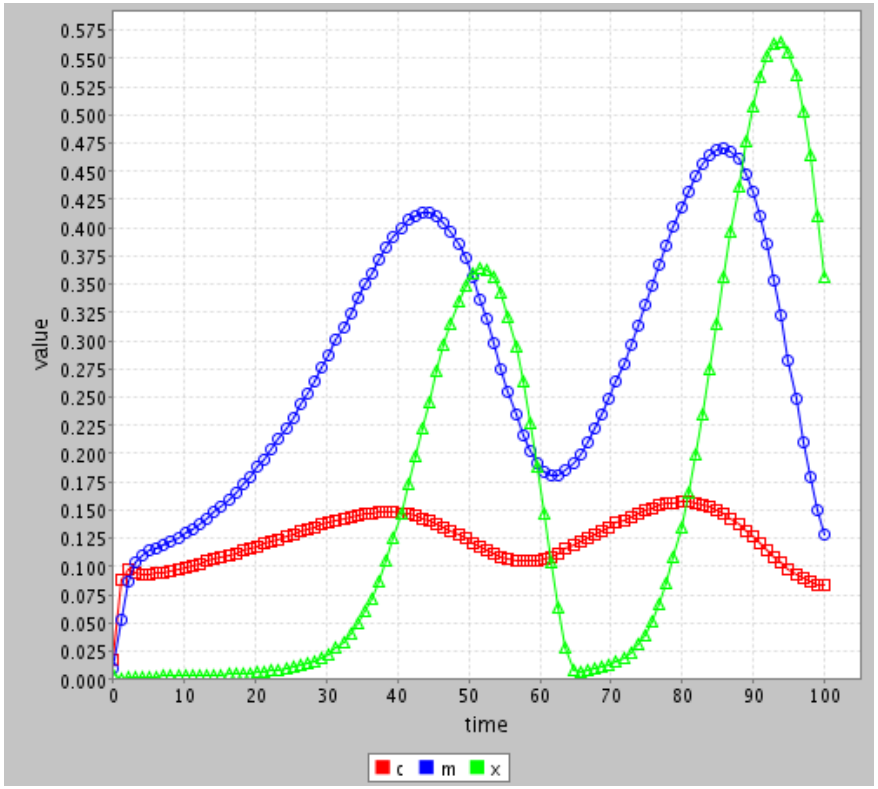
$$C(l_{0C}) \underset{\{\alpha_3\}}{\bowtie} M(l_{0M}) \underset{\{\alpha_3,\alpha_4\}}{\bowtie} M'(l_{0M'}) \underset{\{\alpha_5,\alpha_7\}}{\bowtie} X(l_{0X}) \underset{\{\alpha_5,\alpha_6\}}{\bowtie} X'(l_{0X'}) \underset{\{\alpha_2\}}{\bowtie}$$
$$Deg(0) \underset{\{\alpha_1\}}{\bowtie} CF(1)$$
$$\underset{\{\alpha_8,\alpha_9,\alpha_{10},\alpha_{11}\}}{\bowtie} I(l_{0I}) \underset{\{\alpha_8,\alpha_9,\alpha_{12},\alpha_{13}\}}{\bowtie} IC(l_{0IC})$$

New ODE results



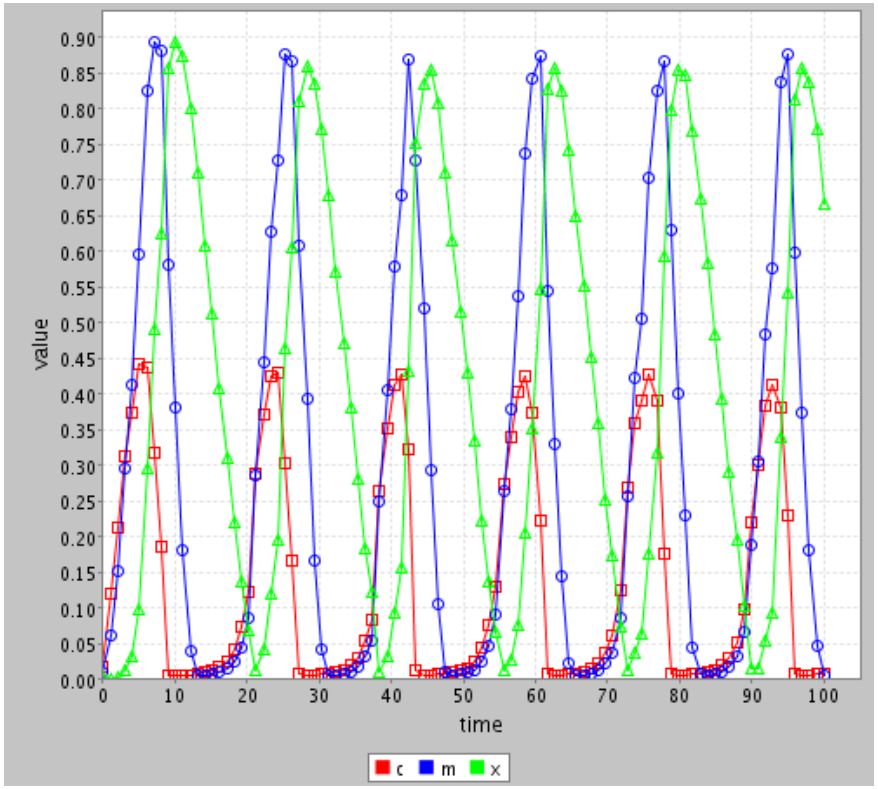
$a_1 = a_2 = 0.3$ and $v_s = 0.6$

New ODE results



$a_1 = a_2 = 0.7$ and $v_s = 1.4$

New ODE results



$a_1 = a_2 = 0.05$ and $v_s = 0.1$

Outline

Conclusion: SPA for Systems Biology

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However, such molecular mappings typically generate state spaces which are too large for other SPA analysis techniques.

Conclusions: Bio-PEPA

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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.

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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.

Future directions

There are number of areas for on-going and future work. For example:

- The definition of bisimulations and equivalences.
- The extent to which the process algebra compositional structure can be exploited during model analysis, particularly in conjunction with model checking techniques.
- The issue of coping with unknown and uncertain values in experimental data.
- *...and many more...*

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Thank you