Calculi for Biological Systems
Part 2

Jane Hillston and Federica Ciocchetta.
LFCS,
University of Edinburgh

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Outline

Introduction and motivation

Bio-PEPA
- The syntax and semantics
- Some simple examples
- Equivalences
- Analysis

Examples
- Genetic network with negative feedback loop
- Goldbeter’s model

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

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The problems with this are various:

- The number of “states” of the system is significantly increased which has implications for computational efficiency/tractability.
- Different possible decompositions.
- Rates must be found for all the intermediate steps.
Motivation

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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.
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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.

▶ 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.
Reagent-centric view [CGH04]

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- The granularity of the system is defined in terms of the step size $h$ of the concentration intervals.
- 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)

<table>
<thead>
<tr>
<th>Role</th>
<th>Impact on reaction rate</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Reactant</td>
<td>positive impact, e.g. proportional to current concentration</td>
<td>decreases level</td>
</tr>
<tr>
<td>Product</td>
<td>no impact, except at saturation</td>
<td>increases level</td>
</tr>
<tr>
<td>Enzyme</td>
<td>positive impact, e.g. proportional to current concentration</td>
<td>level unchanged</td>
</tr>
<tr>
<td>Inhibitor</td>
<td>negative impact, e.g. inversely proportional to current concentration</td>
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</table>
Reagent-centric view (3)

- The rate of a transition is consistent with the granularity.
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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

\[ A \overset{\text{def}}{=} (ab\_c, 1)\downarrow A + (b\_a, 1)\uparrow A + (c\_a, 1)\uparrow A \]
\[ B \overset{\text{def}}{=} (ab\_c, 1)\downarrow B + (b\_a, 1)\downarrow B + (c\_b, 1)\uparrow B \]
\[ C \overset{\text{def}}{=} (c\_a, 1)\downarrow C + (c\_b, 1)\downarrow C + (ab\_c, 1)\uparrow C \]

\[
\left( A(l_{A0}) \boxplus_{\{ab\_c,b\_a\}} B(l_{B0}) \right) \boxplus_{\{ab\_c,c\_a,c\_b\}} C(l_{C0})
\]
State representation

- The state of the system at any time consists of the local states of each of its sequential/species components.
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- A component varying its state corresponds to it varying its concentration level.
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- The state of the system at any time consists of the local states of each of its sequential/species components.

- 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.

- 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
The syntax and semantics

The syntax

Sequential (species) component

\[ S \overset{def}{=} (\alpha, \kappa) \text{ op } S | S + S | C \quad \text{where op} = \downarrow | \uparrow | \oplus | \ominus | \odot \]
The syntax and semantics

The syntax

Sequential (species) component

\[ S \overset{\text{def}}{=} (\alpha, \kappa) \op S \mid S + S \mid C \quad \text{where } \op = \downarrow | \uparrow | \oplus | \ominus | \odot \]

Model component
The syntax

Sequential (species) component

\[ S \overset{\text{def}}{=} (\alpha, \kappa) \text{ op } S \mid S + S \mid C \quad \text{where op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot \]

Model component

\[ P \overset{\text{def}}{=} P \uplus L P \mid S(l) \]
The Bio-PEPA system

A Bio-PEPA system $\mathcal{P}$ is a 6-tuple $\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P \rangle$, 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;
- $\text{Comp}$ is the set of definitions of sequential components;
- $P$ is the model component describing the system.
Semantics

The semantics of Bio-PEPA is defined in terms of an operational semantics. We define two relations over the processes:

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

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Calculi for Biological Systems, Part 2
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## The syntax and semantics

### Semantics: prefix rules

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<th>Prefix Rule</th>
<th>Description</th>
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<td><code>prefixReac</code></td>
<td>$(\alpha, \kappa) \downarrow S(l) (\alpha, \left[S:\downarrow (l, \kappa)]) \rightarrow c S(l - \kappa)$ $\kappa \leq l \leq N$</td>
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<td><code>prefixProd</code></td>
<td>$(\alpha, \kappa) \uparrow S(l) (\alpha, \left[S:\uparrow (l, \kappa)]) \rightarrow c S(l + \kappa)$ $\kappa \leq l \leq N - \kappa$</td>
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<tr>
<td><code>prefixMod</code></td>
<td>$(\alpha, \kappa) op S(l) (\alpha, \left[S:op (l, \kappa)]) \rightarrow c S(l)$ $0 \leq l \leq N$</td>
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</table>

Where $op$ can be $\otimes$, $\oplus$, or $\ominus$. 

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**Calculi for Biological Systems, Part 2**
Semantics: prefix rules

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\text{prefixReac} \quad ((\alpha, \kappa) \downarrow S)(l) \xrightarrow{(\alpha, [S: \downarrow (l, \kappa)])} c S(l - \kappa) \quad \kappa \leq l \leq N
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prefixMod \( ((\alpha, \kappa) \text{op} S)(l) \xrightarrow{(\alpha, [S: \text{op}(l, \kappa)])} c S(l) \quad 0 \leq l \leq N \)

with \( \text{op} = \odot, \oplus, \) or \( \ominus \)
Semantics: constant and choice rules
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\[ S_1(l) \xrightarrow{(\alpha, v)}^c S'_1(l') \]

\[ (S_1 + S_2)(l) \xrightarrow{(\alpha, v)}^c S'_1(l') \]
Semantics: constant and choice rules

Choice1

\[ S_1(l)^{(\alpha,\nu)} \rightarrow_c S'_1(l') \]

\[ (S_1 + S_2)(l)^{(\alpha,\nu)} \rightarrow_c S'_1(l') \]

Choice2

\[ S_2(l)^{(\alpha,\nu)} \rightarrow_c S'_2(l') \]

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The syntax and semantics

Semantics: constant and choice rules

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\[ (S_1 + S_2)(l)^{(\alpha, v)} \xrightarrow{c} S'_2(l') \]

Constant

\[ S(l)^{(\alpha, S: [op(l, \kappa)])} \xrightarrow{c} S'(l') \]

\[ C(l)^{(\alpha, C: [op(l, \kappa)])} \xrightarrow{c} S'(l') \]

with \( C \overset{\text{def}}{=} S \)

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Calculi for Biological Systems, Part 2
Semantics: cooperation rules
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\[ \text{coop1:} \quad \frac{P_1 \xrightarrow{c} P_1'}{P_1 \ominus P_2 \xrightarrow{c} P_1' \ominus P_2} \quad \text{with } \alpha \notin \mathcal{L} \]
Semantics: cooperation rules

coop1

\[
P_1 \xrightarrow{(\alpha, v)} cP_1 \quad \text{with } \alpha \notin L
\]

coop2

\[
P_2 \xrightarrow{(\alpha, v)} cP_2 \quad \text{with } \alpha \notin L
\]
Semantics: cooperation rules

coop1: $\frac{P_1^{(\alpha, v)} \xrightarrow{c} P_1'}{P_1 \triangleright P_2^{(\alpha, v)} \xrightarrow{c} P_1' \triangleright P_2'}$ with $\alpha \notin \mathcal{L}$

coop2: $\frac{P_2^{(\alpha, v)} \xrightarrow{c} P_2'}{P_1 \triangleright P_2^{(\alpha, v)} \xrightarrow{c} P_1' \triangleright P_2'}$ with $\alpha \notin \mathcal{L}$

coopFinal: $\frac{P_1^{(\alpha, v_1)} \xrightarrow{c} P_1' \quad P_2^{(\alpha, v_2)} \xrightarrow{c} P_2'}{P_1 \triangleright P_2^{(\alpha, v_1 :: v_2)} \xrightarrow{c} P_1' \triangleright P_2'}$ with $\alpha \in \mathcal{L}$
Semantics: rates and transition system

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

$$\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P \rangle \xrightarrow{\langle \alpha_j, r_{\alpha} \rangle} \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P' \rangle$$
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\[ \text{Final} \quad \frac{P^{(\alpha_j,v)}}{\rightarrow_c P'} \]

\[ \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P \rangle \xrightarrow{(\alpha_j, r_{\alpha_j})} S \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P' \rangle \]

\( r_{\alpha_j} \) represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition.
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\[
\begin{array}{c}
\text{Final} \\
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\end{array}
\]

\[
\langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P \rangle^{(\alpha_j, r_{\alpha_j})} \xrightarrow{S} \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}_R, \text{Comp}, P' \rangle
\]

\(r_{\alpha_j}\) represents the parameter of an exponential distribution and the dynamic behaviour is determined by a race condition.

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

- Each species \( i \) is described by a Bio-PEPA component \( C_i \).
The syntax and semantics

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- Each species \( i \) is described by a Bio-PEPA component \( C_i \).
- Each reaction \( j \) is associated with an action type \( \alpha_j \) and its dynamics is described by a specific function \( f_{\alpha_j} \).
The abstraction

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Given a reaction $j$, all the species/components cooperate together along the action type $\alpha_j$ and consequently, reactants decrease their levels, while products increase them. All the reactions are abstracted by cooperation.
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- Compartments are static and represented by names indicating the location of species.

The species components are then composed together to describe the behaviour of the system.
Example: Michaelis-Menten

The reaction $S^E \rightarrow P$ represents the enzymatic reaction from the substrate $S$ to the product $P$ with enzyme $E$. 
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The dynamics is described by the law $\frac{v \times E \times S}{(K + S)}$. 
Some simple examples

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\[
\begin{align*}
S & \overset{\text{def}}{=} (\alpha, 1) \downarrow S \\
E & \overset{\text{def}}{=} (\alpha, 1) \oplus E \\
P & \overset{\text{def}}{=} (\alpha, 1) \uparrow P
\end{align*}
\]

\[
(S(l_{S0}) \boxdot_{\{\alpha\}} E(l_{E0})) \boxdot_{\{\alpha\}} P(l_{P0})
\]
Some simple examples

Example: Competitive Inhibition

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

\[ EI \leftrightarrow S + E + I \leftrightarrow SE \rightarrow P + E \]
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Binding of the inhibitor to the enzyme prevents binding of the substrate and vice versa.

\[ EI \leftrightarrow S + E + I \leftrightarrow SE \rightarrow P + E \]

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

\[ S \xrightarrow{E, I: f_I} P \]

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:

\[
S = (\alpha, 1) \downarrow S \quad P = (\alpha, 1) \uparrow P \quad E = (\alpha, 1) \oplus E \quad I = (\alpha, 1) \ominus I
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Example: Competitive Inhibition (2)

The specification in Bio-PEPA is:

\[ S = (\alpha, 1) \downarrow S \quad P = (\alpha, 1) \uparrow P \quad E = (\alpha, 1) \oplus E \quad I = (\alpha, 1) \ominus I \]

The system is described by

\[
\left( \left( S(l_{S0}) \boxplus E(l_{E0}) \right) \boxplus I(l_{I0}) \right) \boxplus P(l_{P0})
\]
Example: Competitive Inhibition (2)

The specification in Bio-PEPA is:

\[ S = (\alpha, 1) \downarrow S \quad P = (\alpha, 1) \uparrow P \quad E = (\alpha, 1) \oplus E \quad I = (\alpha, 1) \ominus I \]

The system is described by

\[
\left\langle \left( S(l_{S0}) \uplus E(l_{E0}) \right) \uplus I(l_{I0}) \right\rangle \uplus P(l_{P0})
\]

with functional rate

\[
f_\alpha = \frac{w \times S \times E}{S + K_M \left(1 + \frac{l}{K_I}\right)}
\]
Equivalence relations

We are seeking to define a number of equivalence relations for BioPEPA — both those that are expected from the computer science perspective and those that are useful from the biological perspective.
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Equivalence relations

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From the computer science perspective we have defined an isomorphism and a (strong) bisimulation.

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.
A Bio-PEPA system is a formal, intermediate and compositional representation of the system.
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From it we can obtain

- a CTMC (with and without levels)
- an ODE system for simulation and other kinds of analysis
- a Gillespie model for stochastic simulation
- a PRISM model for model checking

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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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.
Outline

Introduction and motivation

Bio-PEPA
- The syntax and semantics
- Some simple examples
- Equivalences
- Analysis

Examples
- Genetic network with negative feedback loop
- Goldbeter’s model

Conclusions
The biological model

Consider a genetic network with negative feedback through dimers.
The biological model

Consider a genetic network with negative feedback through dimers.

Transcription (1)  \[\text{mRNA (M)}\]  Degradation (3)

Translation (2)  \[\text{Protein (P)}\]  Degradation (4)

Dimerisation (5–5i)  \[\text{Dimer protein (P2)}\]
Species and reactions

The biological entities are:

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

The biological entities are:

- the \textit{mRNA molecule} $(M)$,
- the protein in monomer form $(P)$ and
- the protein in dimeric form $(P2)$.

All the reactions are described by \textit{mass action kinetics} with the exception of the first reaction, that has an \textit{inhibition kinetics}.
Translation into Bio-PEPA

Definition of the list $\mathcal{N}$

$[M : N_M, h_M; \ P : N_P, h_P; \ P2 : N_{P2}, h_{P2}]$
Translation into Bio-PEPA

Definition of the list $\mathcal{N}$

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

Definition of functional rates

$$f_{\alpha_1} = \frac{v}{K_M + P2}$$
$$f_{\alpha_2} = f_{MA}(k_2) \quad f_{\alpha_3} = f_{MA}(k_3) \quad f_{\alpha_4} = f_{MA}(k_4)$$
$$f_{\alpha_5} = f_{MA}(k_5) \quad f_{\alpha_{5_{inv}}} = f_{MA}(k_{5_{inv}})$$
Translation into Bio-PEPA (cont.)

Definition of the system components

\[
\begin{align*}
M &= (\alpha_1,1) \uparrow M + (\alpha_2,1) \oplus M + (\alpha_3,1) \downarrow M; \\
P &= (\alpha_2,2) \uparrow P + (\alpha_4,1) \downarrow P + (\alpha_5,2) \downarrow P + (\alpha_{5_{\text{Inv}}},2) \uparrow P; \\
P_2 &= (\alpha_1,1) \ominus P_2 + (\alpha_{5_{\text{Inv}}},1) \downarrow P_2 + (\alpha_5,1) \uparrow P_2; \\
Res &= (\alpha_3,1) \odot Res + (\alpha_4,1) \odot Res; \\
CF &= (\alpha_1,1) \odot CF;
\end{align*}
\]
Translation into Bio-PEPA (cont.)

Definition of the system components

\[
\begin{align*}
M &= (\alpha_1, 1)^\uparrow M + (\alpha_2, 1) \oplus M + (\alpha_3, 1)^\downarrow M; \\
P &= (\alpha_2, 2)^\uparrow P + (\alpha_4, 1)^\downarrow P + (\alpha_5, 2)^\downarrow P + (\alpha_5_{\text{inv}}, 2)^\uparrow P; \\
P_2 &= (\alpha_1, 1)^\ominus P_2 + (\alpha_5_{\text{inv}}, 1)^\downarrow P_2 + (\alpha_5, 1)^\uparrow P_2; \\
Res &= (\alpha_3, 1) \circ Res + (\alpha_4, 1) \circ Res; \\
CF &= (\alpha_1, 1) \circ CF;
\end{align*}
\]

Definitions of the system

\[
(((\text{CF}(1) \diamond M(0)) \diamond P(0)) \diamond P_2(0)) \diamond Res(0)
\]
Analysis: the CTMC with levels

For 2 levels, the CTMC consists of 8 states and 18 transitions.
Analysis: the CTMC with levels

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

For the genetic network with negative feedback loop, the CTMC with levels is illustrated with a state transition diagram. The states are denoted as follows:

- STATE 1
- STATE 2
- STATE 3
- STATE 4
- STATE 5
- STATE 6
- STATE 7
- STATE 8

There are 18 transitions labeled as 1 to 18, connecting these states. The states are defined as:

- STATE 1
- STATE 2
- STATE 3
- STATE 4
- STATE 5
- STATE 6
- STATE 7
- STATE 8

The levels are labeled as follows:

1. STATE 1
2. STATE 2
3. STATE 3
4. STATE 4
5. STATE 5
6. STATE 6
7. STATE 7
8. STATE 8

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Calculi for Biological Systems, Part 2
Analysis: the CTMC with levels

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

States are \((CF(l_1), M(l_2), P(l_3), P2(l_4), RES(l_5))\), with levels \(l_1 \ldots l_5\).
Genetic network with negative feedback loop

Analysis: derivation of the ODE system

The stoichiometry matrix $D$ associated with the system is

$$
\begin{array}{cccccc}
  & \alpha_1 & \alpha_2 & \alpha_3 & \alpha_4 & \alpha_5 & \alpha_{5,\text{Inv}} \\
\hline
\text{CF} & 0 & 0 & 0 & 0 & 0 & 0 \\
\text{Res} & 0 & 0 & 0 & 0 & 0 & 0 \\
\text{M} & +1 & 0 & -1 & 0 & 0 & 0 \\
\text{P} & 0 & +1 & 0 & -1 & -2 & +2 \\
\text{P2} & 0 & 0 & 0 & +1 & -1 & 0 \\
\end{array}
$$

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Calculi for Biological Systems, Part 2
**Analysis: derivation of the ODE system**

The stoichiometry matrix $D$ associated with the system is

<table>
<thead>
<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\alpha_3$</th>
<th>$\alpha_4$</th>
<th>$\alpha_5$</th>
<th>$\alpha_{5_{-inv}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Res</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P</td>
<td>0</td>
<td>+1</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>+2</td>
</tr>
<tr>
<td>P2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
</tr>
</tbody>
</table>

The kinetic law vector is

$$ w^T = \left( \frac{v \times x_{CF}}{K_M + x_3}; \ k_2 \times x_1; \ k_3 \times x_1; \ k_4 \times x_2; \ k_5 \times x_2^2; \ k_{5_{-inv}} \times x_3 \right) $$
Analysis: derivation of ODEs (cont.)

The system of ODEs is obtained as \( \frac{d\vec{x}}{dt} = D \times w \):

\[
\begin{align*}
\frac{dx_1}{dt} &= \frac{v \times 1}{K_M + x_3} - k3 \times x_1 \\
\frac{dx_2}{dt} &= k2 \times x_1 - k4 \times x_2 - 2 \times k5 \times x_2^2 + 2 \times k5_{Inv} \times x_3 \\
\frac{dx_2}{dt} &= k5 \times x_2^2 - k5_{Inv} \times x_3
\end{align*}
\]
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.
PRISM model

Each species is represented as a PRISM module. For example, the protein is represented as:

```plaintext
module p
p: [0..Np] init 0;
[Translation] p < Np → (p' = p + 1);
[DegradationP] p > 0 → (p' = p - 1);
[Dimerization] p > 1 → (p' = p - 2);
[DimerizationInv] p < (Np - 1) → (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 \times h_{p2}) \times h_{p2}) : (dummy' = dummy);
[Translation] m > 0 \rightarrow (k2 \times m \times h_m/h_m) : (dummy' = dummy);
[DegradationmRNA] m > 0 \rightarrow (k3 \times m \times h_m/h_m) : (dummy' = dummy);
[DegradationP] p > 0 \rightarrow (k4 \times p \times h_p/h_p) : (dummy' = dummy);
[Dimerization] p > 1 \rightarrow (k5 \times p \times h_p \times p \times h_p/h_p)(dummy' = dummy);
[DimerizationInv] p2 > 0 \rightarrow (k5_{Inv} \times p2 \times 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:

\[
\text{rewards} \\
\text{true} : \frac{p}{(p+p_2)}; \\
\text{endrewards}
\]
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:

  \[
  \text{rewards} \\
  \text{true : } \frac{p}{(p+p^2)}; \\
  \text{endrewards}
  \]

  We can ask for the proportion of monomer P by using the query:

  \[R = \mathbb{E}[I = T]\]
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:

  \[
  \text{rewards} \\
  \text{true : } \frac{p}{(p+p_2)}; \\
  \text{endrewards}
  \]

  We can ask for the proportion of monomer $P$ by using the query:

  \[R = \mathbb{P}[I = T]\]

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

  \[P = \mathbb{P}[trueU[T, T]p = i]\]
Genetic network with negative feedback loop

PRISM results

expected reward

monomer frequency

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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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- Goldbeter’s model describes the activity of the cyclin in the cell cycle.
- The cyclin promotes the activation of a cdk (cdc2) which in turn activates a cyclin protease.
Goldbeter’s model [Goldbeter 91]

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- This protease promotes cyclin degradation.
Goldbeter’s model [Goldbeter 91]

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- This leads to a negative feedback loop.
Goldbeter’s model [Goldbeter 91]

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

- R1: CYCLIN (C)
- R2: cdc2 active (M)
- R3: cdc2 inactive (M')
- R4: Protease inactive (X')
- R5: Protease active (X)
- R6: Protease inactive (X')
- R7: Protease active (X)
The biological model (2)

There are three different biological species involved:

- Cyclin, the protein protagonist of the cycle, denoted as $C$.
- Cdc2 kinase, in both active (dephosphorylated) and inactive (phosphorylated) forms, denoted as $M$ and $M'$, respectively.
- Cyclin protease, in both active (phosphorylated) and inactive (dephosphorylated) forms, denoted as $X$ and $X'$.
The biological model (2)

There are three different biological species involved:

- **cyclin**, the protein protagonist of the cycle, $C$;
The biological model (2)

There are three different biological species involved:

- cyclin, the protein protagonist of the cycle, \( C \);
- \textit{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;
The biological model (2)

There are three different biological species involved:

- **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 $X'$. 

Goldbeter's model

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Calculi for Biological Systems, Part 2
## Reactions

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

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

Definition of the set $N$:

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

Res and CF represent degradation and synthesis respectively.
Translation into Bio-PEPA

Definition of the set \( \mathcal{N} \):

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

\( \text{Res} \) and \( \text{CF} \) represent degradation and synthesis respectively.

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

\[
f_{\alpha_1} = f_{\text{MA}}(v_i); \\
f_{\alpha_4} = f_{\text{MM}}(V_2, K_2); \\
f_{\alpha_6} = f_{\text{MM}}(V_4, K_4); \\
f_{\alpha_2} = f_{\text{MA}}(k_d); \\
f_{\alpha_5} = f_{\text{MM}}(V_3, K_3); \\
f_{\alpha_7} = f_{\text{MM}}(V_d, K_d); \\
f_{\alpha_3} = \frac{v_1 \times C}{K_C + C} \frac{M'}{K1 + M'}
\]
Goldbeter’s model

The Bio-PEPA system (2)

Definition of species components (Comp):

\[
\begin{align*}
C &= (\alpha_1, 1)\uparrow C + (\alpha_2, 1)\downarrow C + (\alpha_3, 1) \oplus C + (\alpha_7, 1)\downarrow C; \\
M' &= (\alpha_3, 1)\downarrow M' + (\alpha_4, 1)\uparrow M'; \\
M &= (\alpha_3, 1)\uparrow M + (\alpha_4, 1)\downarrow M + (\alpha_5, 1) \oplus M; \\
X' &= (\alpha_5, 1)\downarrow X' + (\alpha_6, 1)\uparrow X'; \\
X &= (\alpha_5, 1)\uparrow X + (\alpha_6, 1)\downarrow X + (\alpha_7, 1) \oplus X; \\
Res &= (\alpha_2, 1) \odot Res; \\
CF &= (\alpha_1, 1) \odot CF;
\end{align*}
\]

Definition of the model component (P):

\[
\begin{align*}
C(l_{0C}) \bowtie M(l_{0M}) \bowtie M'(l_{0M'}) \bowtie X(l_{0X}) \bowtie X'(l_{0X'}) \\
\bowtie Deg(0) \bowtie CF(1)
\end{align*}
\]
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 $(l_C(1), l_M'(0), l_M(1), l_X'(0), l_X(1))$. 

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Calculi for Biological Systems, Part 2
**Goldbeter’s model**

**Analysis: ODEs**

The stoichiometry matrix $D$:

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>R7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>$M'$</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>X'</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
</tr>
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*Calculi for Biological Systems, Part 2*
Analysis: ODEs

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<th>R6</th>
<th>R7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
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<td>$M'$</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$X'$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

$x_C$
$x_{M'}$
$x_M$
$x_{X'}$
$x_X$

The vector that contains the kinetic laws is:

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

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:

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

ODE results

\[ K_1 = K_2 = K_3 = K_4 = 0.02 \mu M \]
Goldbeter’s model

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.
Goldbeter’s model

Schema of the extended model

- $R1$: $\text{CYCLIN (C)}$ to INHIBITOR (I)
- $R2$: INHIBITOR (I) to INHIBITOR–CYCLIN (IC)
- $R3$: cdc2 inactive (M') to INHIBITOR–CYCLIN (IC)
- $R4$: INHIBITOR–CYCLIN (IC) to cdc2 active (M)
- $R5$: cdc2 active (M) to Protease inactive (X')
- $R6$: Protease inactive (X') to Protease active (X)
- $R7$: Protease active (X) to Protease inactive (X')
- $R8$: INHIBITOR–CYCLIN (IC) to INHIBITOR (I)
- $R9$: INHIBITOR (I) to INHIBITOR–CYCLIN (IC)
- $R10$: $\text{CYCLIN (C)}$ to INHIBITOR (I)
- $R11$: INHIBITOR (I) to INHIBITOR–CYCLIN (IC)
- $R12$: INHIBITOR–CYCLIN (IC) to cdc2 active (M)
- $R13$: cdc2 active (M) to INHIBITOR–CYCLIN (IC)
Extended Bio-PEPA system

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

\[ \vdots \]

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

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

\[ IC = (\alpha_8, 1) \uparrow IC + (\alpha_9, 1) \downarrow IC + (\alpha_{12}, 1) \downarrow IC + (\alpha_{13}, 1) \downarrow IC; \]
Goldbeter’s model

New functional rates

\[ f_{\alpha_8} = v_s; \]
\[ f_{\alpha_9} = fMA(d_1); \]
\[ f_{\alpha_{10}} = fMA(a_1); \]
\[ f_{\alpha_{11}} = fMA(a_2); \]
\[ f_{\alpha_{12}} = fMA(\theta \times d_1); \]
\[ f_{\alpha_{13}} = fMA(\theta \times k_d) \]
Complete Bio-PEPA system
Goldbeter’s model

New ODE results

\[ a_1 = a_2 = 0.3 \text{ and } v_s = 0.6 \]
Goldbeter’s model

New ODE results

\[ a_1 = a_2 = 0.7 \text{ and } \nu_S = 1.4 \]
New ODE results

\[ a_1 = a_2 = 0.05 \text{ and } v_s = 0.1 \]
Outline

Introduction and motivation

Bio-PEPA
  The syntax and semantics
  Some simple examples
  Equivalences
  Analysis

Examples
  Genetic network with negative feedback loop
  Goldbeter’s model

Conclusions
Conclusion: SPA for Systems Biology

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The inclusion of stochastic information about the duration of actions/reactions creates a very natural mapping from SPA models to stochastic simulations at the molecular models.

However, such molecular mappings typically generate state spaces which are too large for other SPA analysis techniques.
Conclusions: Bio-PEPA

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: Abstract Modelling

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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.
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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