A semi-quantitative equivalence for abstracting from fast reactions

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Outline

Example: competitive inhibition, bimolecular

$$S + E + I$$

- initially substrate, enzyme, inhibitor

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$$S + EI \rightleftarrows S + E + I \rightleftarrows SE + I \longrightarrow P + E + I$$

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$$\frac{dS}{dt} = \cdots \qquad \frac{dEI}{dt} = \cdots$$
$$\frac{dE}{dt} = \cdots \qquad \frac{dSE}{dt} = \cdots$$
$$\frac{dI}{dt} = \cdots \qquad \frac{dP}{dt} = \cdots$$

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- example: Michaelis-Menten kinetics for substrate and enzyme
- need to understand limitations of abstracted version

Example: competitive inhibition, abstract

$$S \xrightarrow{E,I} P$$

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- results in fewer ODEs
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How can these ideas be used to develop a behavioural equivalence for a biological process algebra?

Bio-PEPA: competitive inhibition, bimolecular

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Bio-PEPA: competitive inhibition, bimolecular

$$S + EI \underset{\alpha_{-1}}{\overset{\alpha_1}{\rightleftarrows}} S + E + I \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} SE + I \xrightarrow{\gamma} P + E + I$$

- name each reaction

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- well-defined Bio-PEPA species/sequential components

$$S \stackrel{def}{=} (\beta_1, 1) \downarrow S \quad + \quad (\beta_{-1}, 1) \uparrow S$$

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Prefix notation: (α, κ) op

α reaction name

κ stoichiometry for reaction

op role of species in reaction

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$$\begin{aligned} S &\stackrel{def}{=} (\beta_1, 1) \downarrow S + (\beta_{-1}, 1) \uparrow S \\ E &\stackrel{def}{=} (\alpha_1, 1) \downarrow E + (\alpha_{-1}, 1) \uparrow E + \\ &\quad (\beta_1, 1) \downarrow E + (\beta_{-1}, 1) \uparrow E + (\gamma, 1) \uparrow E \end{aligned}$$

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 & & (\beta_1, 1) \downarrow E & + & (\beta_{-1}, 1) \uparrow E & + \quad (\gamma, 1) \uparrow E \\
I & \stackrel{def}{=} & (\alpha_1, 1) \downarrow I & + & (\alpha_{-1}, 1) \uparrow I & \\
P & \stackrel{def}{=} & (\gamma, 1) \uparrow P & & & \\
EI & \stackrel{def}{=} & (\alpha_1, 1) \uparrow EI & + & (\alpha_{-1}, 1) \downarrow EI & \\
SE & \stackrel{def}{=} & (\beta_1, 1) \uparrow SE & + & (\beta_{-1}, 1) \downarrow SE & + \quad (\gamma, 1) \downarrow SE
\end{array}$$

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- well-defined Bio-PEPA model component, includes quantities/levels for each species

$$M \overset{\mathit{def}}{=} S(\ell_S) \underset{*}{\bowtie} E(\ell_E) \underset{*}{\bowtie} I(\ell_I) \underset{*}{\bowtie} P(\ell_P) \underset{*}{\bowtie} EI(\ell_{EI}) \underset{*}{\bowtie} SE(\ell_{SE})$$

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- well-defined Bio-PEPA system, defines context for model

$$\mathcal{P} = \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, Comp, M \rangle$$

$\mathcal{V}$	volume and location information for model
$\mathcal{N}$	quantitative information for each species
$\mathcal{K}$	constant definitions
$\mathcal{F}$	rate equations for each reaction
$Comp$	Bio-PEPA definition for each species

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- Bio-PEPA model in vector form

$$(\ell_{S'}, \ell_{E'}, \ell_{I'}, \ell_{P'}) \quad \text{and} \quad (\ell_S, \ell_E, \ell_I, \ell_P, \ell_{EI}, \ell_{SE})$$

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$$((\alpha,\kappa)\downarrow S)(\ell) \xrightarrow{(\alpha,[S:\downarrow(\ell,\kappa)])}_c S(\ell-\kappa) \quad \kappa \leq \ell \leq N_S$$

$$((\alpha,\kappa)\uparrow S)(\ell) \xrightarrow{(\alpha,[S:\uparrow(\ell,\kappa)])}_c S(\ell+\kappa) \quad 0 \leq \ell \leq N_S - \kappa$$

$$((\alpha,\kappa)\oplus S)(\ell) \xrightarrow{(\alpha,[S:\oplus(\ell,\kappa)])}_c S(\ell) \quad \kappa \leq \ell \leq N_S$$

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Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

$$\frac{P \xrightarrow{(\alpha,v)}_c P' \quad Q \xrightarrow{(\alpha,u)}_c Q'}{P \underset{L}{\bowtie} Q \xrightarrow{(\alpha,v::u)}_c P' \underset{L}{\bowtie} Q'} \quad \alpha \in L$$

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- can define stochastic relation which is quantitative
- we work semi-quantitatively with capability relation
- reaction names are partitioned into two sets

$$\begin{array}{ll} \mathcal{A}_f : & \text{fast reactions} \\ \mathcal{A}_s : & \text{slow reactions} \end{array}$$

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- identify initial reactants and products
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- similar definition to Milner's weak bisimilarity
- fast reactions play same role as τ labelled transitions

Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

$$P_1 \approx_{\mathcal{A}_f} P_2 \Rightarrow P_1 \underset{L}{\bowtie} Q \approx_{\mathcal{A}_f} P_2 \underset{L}{\bowtie} Q, \quad Q \underset{L}{\bowtie} P_1 \approx_{\mathcal{A}_f} Q \underset{L}{\bowtie} P_2$$

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- species extension operator, A and B have no shared reactions

$$A \stackrel{def}{=} \sum_{i=1}^{n} (\alpha_i, \kappa_i)\text{op}_i A \text{ and } B \stackrel{def}{=} \sum_{j=1}^{m} (\beta_j, \lambda_j)\text{op}_j B$$

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$$A\{B\} \stackrel{def}{=} \sum_{i=1}^{n}(\alpha_i, \kappa_i)\mathrm{op}_i A\{B\} + \sum_{j=1}^{m}(\beta_j, \lambda_j)\mathrm{op}_j A\{B\}$$

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- congruence for extension operator if no shared reactions

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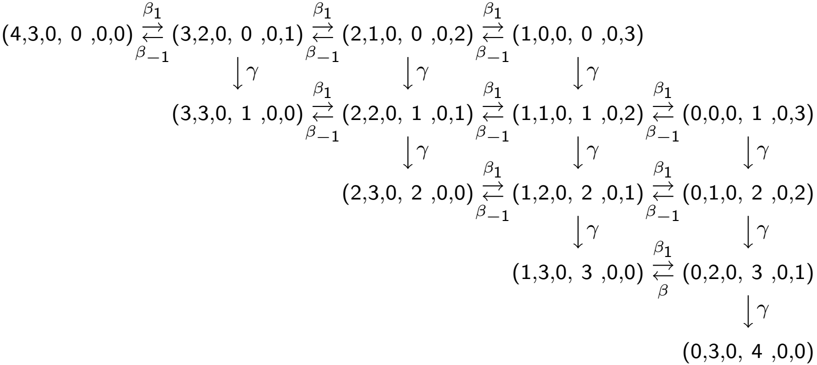
- can understand how L interacts with other systems
- use in model checking with appropriate logics

Applying bisimulation to competitive inhibition



bimolecular

Applying bisimulation to competitive inhibition

$$
\begin{array}{ccccccccccc}
(4,3,0,\ 0\ ,0,0) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (3,2,0,\ 0\ ,0,1) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (2,1,0,\ 0\ ,0,2) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (1,0,0,\ 0\ ,0,3) & & & & (4,3,0,\ 0\ ) \\
 & & \downarrow\gamma & & \downarrow\gamma & & \downarrow\gamma & & & & \downarrow\gamma \\
 & & (3,3,0,\ 1\ ,0,0) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (2,2,0,\ 1\ ,0,1) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (1,1,0,\ 1\ ,0,2) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (0,0,0,\ 1\ ,0,3) & & (3,3,0,\ 1\ ) \\
 & & & & \downarrow\gamma & & \downarrow\gamma & & \downarrow\gamma & & \downarrow\gamma \\
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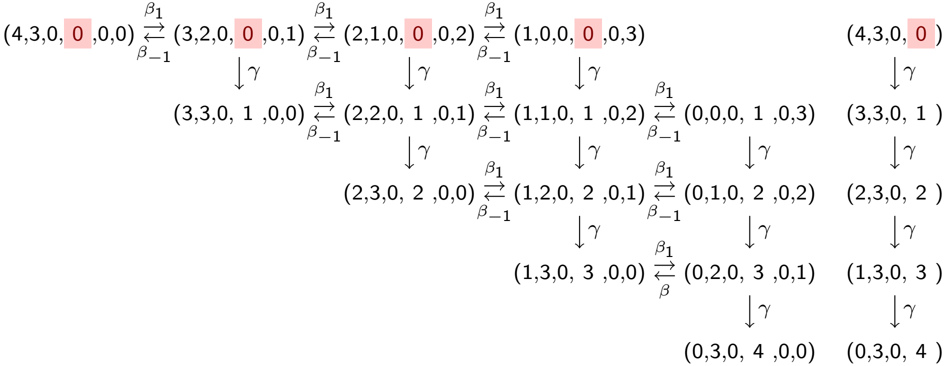
 & & & & & & \downarrow\gamma & & \downarrow\gamma & & \downarrow\gamma \\
 & & & & & & (1,3,0,\ 3\ ,0,0) & \underset{\beta}{\overset{\beta_1}{\rightleftarrows}} & (0,2,0,\ 3\ ,0,1) & & (1,3,0,\ 3\ ) \\
 & & & & & & & & \downarrow\gamma & & \downarrow\gamma \\
 & & & & & & & & (0,3,0,\ 4\ ,0,0) & & (0,3,0,\ 4\ )
\end{array}
$$

bimolecular

abstract

Applying bisimulation to competitive inhibition



bimolecular

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$$
\begin{array}{ccccccccccc}
(4,3,0,0,0,0) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (3,2,0,0,0,1) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (2,1,0,0,0,2) & \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftarrows}} & (1,0,0,0,0,3) & & & & (4,3,0,0) \\
& & \downarrow\gamma & & \downarrow\gamma & & \downarrow\gamma & & & & \downarrow\gamma \\
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& & & & & & & & (0,3,0,4,0,0) & & (0,3,0,4)
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can this be done more efficiently by just checking slow reactions?

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2. $Q \xrightarrow{\alpha, w_\Delta}_c Q'$ then $P \, (\twoheadrightarrow)^* \xrightarrow{\alpha, w_\Delta}_c (\twoheadrightarrow)^* \, P'$ and $P' \approx_{\mathcal{A}_s} Q'$

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- identify conserved, fast and slow variables by transforming stoichiometry matrix [Gómez-Uribe *et al*, 2008]
- result about relationship between bisimulations

M_1 has slow variables and fast variables
M_2 has same slow variables, no fast variable and $\Delta_2 = \Delta_1$
$\mathcal{R} = \{((s_1, \ldots, s_n, f_1, \ldots, f_m), (s_1, \ldots, s_n)) \mid \text{ranges for } s_i,\ f_j\}$
$\mathcal{R}$ slow bisimulation $\Rightarrow$ $\mathcal{R}$ fast-slow bisimulation.

Variable classification

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$$\mathbf{Q} = \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{Q}_{ss} & \mathbf{0} \\ \mathbf{Q}_{fs} & \mathbf{Q}_{ff} \end{bmatrix}$$

Columns: reactions
groups: slow, fast
Rows: variables
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- species values can be recovered from transformed matrix

Variable classification (cont.)

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- use Bio-PEPA Eclipse Plug-in to discover potential variables
- choose independent variables
- choose sufficient fast variables so that there are the same number of variables as species

Applying classification to competitive inhibition

$$S + EI \rightleftarrows S + E + I \rightleftarrows SE + I \longrightarrow P + E + I$$

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- bimolecular model

$$
\begin{array}{rclcl l}
X_{S_T} & = & S + SE + P & = & S_0 = n & \text{conserved} \\
X_{E_T} & = & E + EI + SE & = & E_0 = m & \text{conserved} \\
X_{I_T} & = & EI + I & = & I_0 = p & \text{conserved} \\
X_P & = & P & & = k & \text{slow} \\
X_{EI} & = & EI & & = l & \text{fast} \\
X_{SE} & = & SE & & = j & \text{fast}
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Applying classification to competitive inhibition (cont.)

$$S \xrightarrow[\gamma]{E,I} P$$

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- ignore conserved variables as they never change
- choose non-intermediate species

$$\Delta = \{P\}$$

Transformation of transition systems

- without loss of information, states can be transformed

bimolecular model: $(\ell_S, \ell_E, \ell_I, \ell_P, \ell_{EI}, \ell_{SE})$ to $(\ell_P, \ell_{EI}, \ell_{SE})$
abstract model: $(\ell_{S'}, \ell_{E'}, \ell_{I'}, \ell_{P'})$ to (ℓ_P)

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- $\mathcal{R}'$ is defined over the new transition system as

$$\Big\{\Big(\big(k, l, j\big), \big(k\big)\Big) \mid 0 \leq k \leq n, 0 \leq j \leq \min\{m, n-k\}, 0 \leq l \leq p, j+l \leq m\Big\}$$

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- hence M and M' are fast-slow bisimilar

Conclusions and further work

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- investigate application to other process algebras

Thank you

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- how to decide which behaviours are the same?
  1. different abstractions of the same model – discretisation
  2. ideas from biology – fast/slow reactions, grouping of species
  3. existing equivalences – PEPA, bisimulation-based

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- work with a more constrained form

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- well-defined Bio-PEPA model component with levels
  - minimum and maximum concentrations/number of molecules
  - fix step size, convert to minimum and maximum levels
  - species S: 0 to N_S levels