A semi-quantitative equivalence for abstracting from fast reactions

Vashti Galpin Jane Hillston Federica Ciocchetta

LFCS and CSBE, University of Edinburgh

10 September 2011
Outline

Competitive inhibition

Bio-PEPA

Fast-slow bisimilarity

Slow bisimilarity

Conclusions
Example: competitive inhibition, bimolecular

\[ S + E + I \]

- initially substrate, enzyme, inhibitor
Example: competitive inhibition, bimolecular

\[ S + EI \xleftrightarrow{} S + E + I \xleftrightarrow{} SE + I \rightarrow P + E + I \]

- initially substrate, enzyme, inhibitor
- reactions produce two intermediate species and product
Example: competitive inhibition, bimolecular

\[ S + EI \xleftrightarrow{\text{fast}} S + E + I \xleftrightarrow{\text{slow}} SE + I \rightarrow P + E + I \]

- initially substrate, enzyme, inhibitor
- reactions produce two intermediate species and product
- using mass action, can obtain continuous ODE-based model
Example: competitive inhibition, bimolecular

\[ S + EI \xleftrightarrow{\text{fast}} S + E + I \xleftrightarrow{\text{slow}} SE + I \rightarrow P + E + I \]

- Initially substrate, enzyme, inhibitor
- Reactions produce two intermediate species and product
- Using mass action, can obtain continuous ODE-based model

\[
\begin{align*}
\frac{dS}{dt} &= \cdots \\
\frac{dEI}{dt} &= \cdots \\
\frac{dE}{dt} &= \cdots \\
\frac{dSE}{dt} &= \cdots \\
\frac{dI}{dt} &= \cdots \\
\frac{dP}{dt} &= \cdots 
\end{align*}
\]
Abstraction from fast reactions

- is it possible to construct model without intermediate species?
Abstraction from fast reactions

- is it possible to construct model without intermediate species?
- smaller model easier to analyse, fitting of fewer parameters
Abstraction from fast reactions

- is it possible to construct model without intermediate species?
- smaller model easier to analyse, fitting of fewer parameters
- quasi-steady state assumption (QSSA)
  - possible to partition reactions into fast and slow
  - intermediate species produced by fast reactions
  - quickly reach steady state, concentration shows little change
  - derive new model with new rates by setting some ODEs to zero
Abstraction from fast reactions

- is it possible to construct model without intermediate species?
- smaller model easier to analyse, fitting of fewer parameters
- quasi-steady state assumption (QSSA)
  - possible to partition reactions into fast and slow
  - intermediate species produced by fast reactions
  - quickly reach steady state, concentration shows little change
  - derive new model with new rates by setting some ODEs to zero
- example: Michaelis-Menten kinetics for substrate and enzyme
Abstraction from fast reactions

- is it possible to construct model without intermediate species?
- smaller model easier to analyse, fitting of fewer parameters
- quasi-steady state assumption (QSSA)
  - possible to partition reactions into fast and slow
  - intermediate species produced by fast reactions
  - quickly reach steady state, concentration shows little change
  - derive new model with new rates by setting some ODEs to zero
- example: Michaelis-Menten kinetics for substrate and enzyme
- need to understand limitations of abstracted version
Example: competitive inhibition, abstract

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

- using QSSA, express competitive inhibition as a single reaction
- results in fewer ODEs
- reaction rate depends on \( S \), \( E \) and \( I \)
Example: competitive inhibition, abstract

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

- using QSSA, express competitive inhibition as a single reaction
- results in fewer ODEs
- reaction rate depends on \( S, E \) and \( I \)

How can these ideas be used to develop a behavioural equivalence for a biological process algebra?
Bio-PEPA: competitive inhibition, bimolecular

\[
S + EI \leftrightarrow S + E + I \leftrightarrow SE + I \rightarrow P + E + I
\]
Bio-PEPA: competitive inhibition, bimolecular

\[ S + EI \xrightleftharpoons[\alpha_{-1}]{\alpha_1} S + E + I \quad \xrightleftharpoons[\beta_{-1}]{\beta_1} SE + I \xrightarrow{\gamma} P + E + I \]

- name each reaction
Bio-PEPA: competitive inhibition, bimolecular

\[
S + EI \xrightleftharpoons{\alpha_1}{\alpha_{-1}} S + E + I \xrightleftharpoons{\beta_1}{\beta_{-1}} SE + I \xrightarrow{\gamma} P + E + I
\]

- name each reaction
- well-defined Bio-PEPA species/sequential components

\[
S \overset{\text{def}}{=} (\beta_1, 1) \downarrow S + (\beta_{-1}, 1) \uparrow S
\]
Bio-PEPA: competitive inhibition, bimolecular

\[
S + EI \xrightarrow{\alpha_1} S + E + I \xleftarrow{\beta_1} SE + I \xrightarrow{\gamma} P + E + I
\]

- name each reaction
- well-defined Bio-PEPA species/sequential components

\[
S \overset{\text{def}}{=} (\beta_1, 1) \downarrow S + (\beta_{-1}, 1) \uparrow S
\]

Prefix notation: \((\alpha, \kappa)\) op

- \(\alpha\) reaction name
- \(\kappa\) stoichiometry for reaction
- op role of species in reaction
Bio-PEPA: competitive inhibition, bimolecular

\[
S + EI \xrightarrow{\alpha_1} S + E + I \xleftarrow{\alpha_1} \quad S + E + I \xrightarrow{\beta_1} SE + I \xleftarrow{\beta_1} P + E + I
\]

▶ name each reaction
▶ well-defined Bio-PEPA species/sequential components

\[
S \overset{\text{def}}{=} (\beta_1, 1) \downarrow S + (\beta_1, 1) \uparrow S \\
E \overset{\text{def}}{=} (\alpha_1, 1) \downarrow E + (\alpha_1, 1) \uparrow E + (\beta_1, 1) \downarrow E + (\beta_1, 1) \uparrow E + (\gamma, 1) \uparrow E
\]
Bio-PEPA: competitive inhibition, bimolecular

\[
\begin{align*}
S + EI & \xrightarrow{\alpha_1} S + E + I \xrightarrow{\beta_1} SE + I \xrightarrow{\gamma} P + E + I \\
\end{align*}
\]

- name each reaction
- well-defined Bio-PEPA species/sequential components

\[
\begin{align*}
S & \overset{\text{def}}{=} (\beta_1, 1) \downarrow S + (\beta_{-1}, 1) \uparrow S \\
E & \overset{\text{def}}{=} (\alpha_1, 1) \downarrow E + (\alpha_{-1}, 1) \uparrow E + (\beta_1, 1) \downarrow E + (\beta_{-1}, 1) \uparrow E \\
I & \overset{\text{def}}{=} (\alpha_1, 1) \downarrow I + (\alpha_{-1}, 1) \uparrow I \\
P & \overset{\text{def}}{=} (\gamma, 1) \uparrow P \\
EI & \overset{\text{def}}{=} (\alpha_1, 1) \uparrow EI + (\alpha_{-1}, 1) \downarrow EI \\
SE & \overset{\text{def}}{=} (\beta_1, 1) \uparrow SE + (\beta_{-1}, 1) \downarrow SE + (\gamma, 1) \downarrow SE
\end{align*}
\]
Bio-PEPA: competitive inhibition, bimolecular

\[ S + EI \xrightarrow{\alpha_1} S + E + I \xleftarrow{\alpha_{-1}} \quad SE + I \xrightarrow{\beta_1} \beta_{-1} \xrightarrow{\gamma} P + E + I \]

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

\[ M \overset{\text{def}}{=} S(\ell_S) \otimes E(\ell_E) \otimes I(\ell_I) \otimes P(\ell_P) \otimes EI(\ell_{EI}) \otimes SE(\ell_{SE}) \]
**Bio-PEPA: competitive inhibition, bimolecular**

\[
\begin{align*}
S + EI & \xleftrightarrow{\alpha_1} S + E + I & \xleftrightarrow{\beta_1} SE + I & \xrightarrow{\gamma} P + E + I \\
\end{align*}
\]

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

\[
M \overset{\text{def}}{=} \mathcal{S}(\ell_S) \otimes \mathcal{E}(\ell_E) \otimes \mathcal{I}(\ell_I) \otimes \mathcal{P}(\ell_P) \otimes \mathcal{EI}(\ell_{EI}) \otimes \mathcal{SE}(\ell_{SE})
\]

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

\[
P = \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, M \rangle
\]

- \(\mathcal{V}\) volume and location information for model
- \(\mathcal{N}\) quantitative information for each species
- \(\mathcal{K}\) constant definitions
- \(\mathcal{F}\) rate equations for each reaction
- \(\text{Comp}\) Bio-PEPA definition for each species
Bio-PEPA: competitive inhibition, abstract

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

- well-defined Bio-PEPA species/sequential components

\[ S' \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \quad P' \overset{\text{def}}{=} (\gamma, 1) \uparrow P' \]
Bio-PEPA: competitive inhibition, abstract

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

- well-defined Bio-PEPA species/sequential components

\[
\begin{align*}
S' & \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \\
P' & \overset{\text{def}}{=} (\gamma, 1) \uparrow P' \\
E' & \overset{\text{def}}{=} (\gamma, 1) \oplus E' \\
I' & \overset{\text{def}}{=} (\gamma, 1) \ominus I'
\end{align*}
\]
Bio-PEPA: competitive inhibition, abstract

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

- well-defined Bio-PEPA species/sequential components
  \[ S' \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \quad P' \overset{\text{def}}{=} (\gamma, 1) \uparrow P' \]
  \[ E' \overset{\text{def}}{=} (\gamma, 1) \oplus E' \quad I' \overset{\text{def}}{=} (\gamma, 1) \ominus I' \]

- well-defined Bio-PEPA model
  \[ M' \overset{\text{def}}{=} S'(\ell_{S'}) \bowtie E' (\ell_{E'}) \bowtie I'(\ell_{I'}) \bowtie P'(\ell_{P'}) \]
Bio-PEPA: competitive inhibition, abstract

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

- well-defined Bio-PEPA species/sequential components

\[
S' \overset{\text{def}}{=} (\gamma, 1) \downarrow S' \\
E' \overset{\text{def}}{=} (\gamma, 1) \oplus E' \\
P' \overset{\text{def}}{=} (\gamma, 1) \uparrow P'
\]

- well-defined Bio-PEPA model

\[
M' \overset{\text{def}}{=} S'(\ell_{S'}) \otimes E'(\ell_{E'}) \otimes l'(\ell_{l'}) \otimes P'(\ell_{P'})
\]

- Bio-PEPA model in vector form

\[
(\ell_{S'}, \ell_{E'}, \ell_{l'}, \ell_{P'})
\]
Bio-PEPA: competitive inhibition, abstract

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

- well-defined Bio-PEPA species/sequential components

\[
\begin{align*}
S' & \stackrel{\text{def}}{=} (\gamma, 1) \downarrow S' \\
E' & \stackrel{\text{def}}{=} (\gamma, 1) \oplus E' \\
I' & \stackrel{\text{def}}{=} (\gamma, 1) \ominus I'
\end{align*}
\]

- well-defined Bio-PEPA model

\[
M' \stackrel{\text{def}}{=} S'(\ell_{S'}) \otimes E'(\ell_{E'}) \otimes I'(\ell_{I'}) \otimes P'(\ell_{P'})
\]

- Bio-PEPA model in vector form

\[
(\ell_{S'}, \ell_{E'}, \ell_{I'}, \ell_{P'}) \quad \text{and} \quad (\ell_{S}, \ell_{E}, \ell_{I}, \ell_{P}, \ell_{EI}, \ell_{SE})
\]
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$
- Choice, Cooperation for $\alpha \not\in L$, Constant as expected
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$
- Choice, Cooperation for $\alpha \not\in L$, Constant as expected
- Prefix rules
**Bio-PEPA semantics**

- Operational semantics for capability relation $\rightarrow_c$
- Choice, Cooperation for $\alpha \notin L$, Constant as expected
- Prefix rules

\[
\begin{align*}
((\alpha, \kappa) \downarrow S)(\ell) & \xrightarrow{(\alpha, [S:\downarrow(\ell,\kappa)])} c \ S(\ell - \kappa) \quad \kappa \leq \ell \leq N_S \\
((\alpha, \kappa) \uparrow S)(\ell) & \xrightarrow{(\alpha, [S:\uparrow(\ell,\kappa)])} c \ S(\ell + \kappa) \quad 0 \leq \ell \leq N_S - \kappa \\
((\alpha, \kappa) \oplus S)(\ell) & \xrightarrow{(\alpha, [S:\oplus(\ell,\kappa)])} c \ S(\ell) \quad \kappa \leq \ell \leq N_S \\
((\alpha, \kappa) \ominus S)(\ell) & \xrightarrow{(\alpha, [S:\ominus(\ell,\kappa)])} c \ S(\ell) \quad 0 \leq \ell \leq N_S \\
((\alpha, \kappa) \odot S)(\ell) & \xrightarrow{(\alpha, [S:\odot(\ell,\kappa)])} c \ S(\ell) \quad 0 \leq \ell \leq N_S
\end{align*}
\]
Bio-PEPA semantics

- operational semantics for capability relation $\rightarrow_c$
- Choice, Cooperation for $\alpha \not\in L$, Constant as expected
- Prefix rules

\[
\begin{align*}
((\alpha, \kappa) \downarrow S)(\ell) &\xrightarrow{(\alpha, [S: \downarrow(\ell, \kappa)])} c \ S(\ell - \kappa) \quad \kappa \leq \ell \leq N_S \\
((\alpha, \kappa) \uparrow S)(\ell) &\xrightarrow{(\alpha, [S: \uparrow(\ell, \kappa)])} c \ S(\ell + \kappa) \quad 0 \leq \ell \leq N_S - \kappa \\
((\alpha, \kappa) \oplus S)(\ell) &\xrightarrow{(\alpha, [S: \oplus(\ell, \kappa)])} c \ S(\ell) \quad \kappa \leq \ell \leq N_S \\
((\alpha, \kappa) \ominus S)(\ell) &\xrightarrow{(\alpha, [S: \ominus(\ell, \kappa)])} c \ S(\ell) \quad 0 \leq \ell \leq N_S \\
((\alpha, \kappa) \odot S)(\ell) &\xrightarrow{(\alpha, [S: \odot(\ell, \kappa)])} c \ S(\ell) \quad 0 \leq \ell \leq N_S
\end{align*}
\]
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

\[
\begin{array}{c}
    P \xrightarrow{(\alpha, v)}_c P' \\
    Q \xrightarrow{(\alpha, u)}_c Q' \\
    P \blacktriangledown L Q \xrightarrow{(\alpha, v::u)}_c P' \blacktriangledown L Q'
\end{array}
\]

$\alpha \in L$
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

\[
P \xrightarrow{(\alpha,v)} P' \quad Q \xrightarrow{(\alpha,u)} Q' \quad \alpha \in L
\]

\[
P \nL L Q \xrightarrow{(\alpha,v::u)} P' \nL L Q'
\]
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

\[
\begin{align*}
\begin{array}{c}
P \xrightarrow{(\alpha,v)} P' \\
Q \xrightarrow{(\alpha,u)} Q'
\end{array}
\end{align*}
\]

\[
\begin{align*}
P \otimes_Q Q' \xrightarrow{(\alpha,v::u)} P' \otimes_Q Q'
\end{align*}
\]

- can define stochastic relation which is quantitative
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

\[
\frac{P \xrightarrow{(\alpha, v)}_c P'}{\nabla_L Q \xrightarrow{(\alpha, v :: u)}_c P' \nabla_L Q'}\]

- can define stochastic relation which is quantitative

- we work **semi-quantitatively** with capability relation

Vashti Galpin

A semi-quantitative equivalence for abstracting from fast reactions
Bio-PEPA semantics (continued)

- Cooperation for $\alpha \in L$

$$
P \xrightarrow{c} P' \quad Q \xrightarrow{c} Q' \quad \alpha \in L$$

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

$A_f$ : fast reactions
$A_s$ : slow reactions
Fast-slow bisimilarity

- identify initial reactants and products
- compounds formed during reactions are intermediate species
- $\Delta$: species in the reactions that are not intermediate
Fast-slow bisimilarity

- identify initial reactants and products
- compounds formed during reactions are intermediate species
- $\Delta$: species in the reactions that are not intermediate
- define new transitions

$$w_\Delta = \{ C : \text{op} (l, \kappa) \in w \mid C \in \Delta \}$$

If $P \xrightarrow{(\alpha,w)}_{c} P'$ and $\alpha \in A_f$ then $P \rightarrow P'$

If $P \xrightarrow{(\alpha,w)}_{c} P'$ and $\alpha \in A_s$ then $P \xrightarrow{\alpha,w_\Delta} P'$
Fast-slow bisimilarity

- identify initial reactants and products
- compounds formed during reactions are intermediate species
- $\Delta$: species in the reactions that are not intermediate
- define new transitions

$w_\Delta = \{ C : \text{op} (l, \kappa) \in w \mid C \in \Delta \}$

If $P \overset{\alpha, w}{\rightarrow}_c P'$ and $\alpha \in A_f$ then $P \rightarrow P'$

If $P \overset{\alpha, w}{\rightarrow}_c P'$ and $\alpha \in A_s$ then $P \overset{\alpha, w_\Delta}{\rightarrow} P'$
Fast-slow bisimilarity

- identify initial reactants and products
- compounds formed during reactions are intermediate species
- $\Delta$: species in the reactions that are not intermediate
- define new transitions

$$w_\Delta = \{ C : \text{op} ( l, \kappa) \in w \mid C \in \Delta \}$$

If $P \xrightarrow{\alpha,w_{c}} P'$ and $\alpha \in A_f$ then $P \rightarrow P'$

If $P \xrightarrow{\alpha,w_{c}} P'$ and $\alpha \in A_s$ then $P \xrightarrow{\alpha,w_{\Delta}} P'$
Fast-slow bisimilarity

- fast-slow bisimilarity, \( P \approx_{\mathcal{A}_f} Q \) if whenever

1. \( P \rightarrow P' \) then \( Q (\rightarrow)^* Q' \) and \( P' \approx_{\mathcal{A}_f} Q' \)
2. \( Q \rightarrow Q' \) then \( P (\rightarrow)^* P' \) and \( P' \approx_{\mathcal{A}_f} Q' \)
Fast-slow bisimilarity

- fast-slow bisimilarity, $P \approx_{A_f} Q$ if whenever

1. $P \xrightarrow{} P'$ then $Q (\xrightarrow{})^* Q'$ and $P' \approx_{A_f} Q'$
2. $Q \xrightarrow{} Q'$ then $P (\xrightarrow{})^* P'$ and $P' \approx_{A_f} Q'$

and for all $\alpha \in A_s$

3. $P \xrightarrow{\alpha, w\Delta}_c P'$ then $Q (\xrightarrow{})^* \xrightarrow{\alpha, w\Delta}_c Q'$ and $P' \approx_{A_f} Q'$
4. $Q \xrightarrow{\alpha, w\Delta}_c Q'$ then $P (\xrightarrow{})^* \xrightarrow{\alpha, w\Delta}_c P'$ and $P' \approx_{A_f} Q'$
Fast-slow bisimilarity

- fast-slow bisimilarity, $P \approx_{Af} Q$ if whenever
  
  1. $P \rightarrow P'$ then $Q(\rightarrow)^* Q'$ and $P' \approx_{Af} Q'$
  2. $Q \rightarrow Q'$ then $P(\rightarrow)^* P'$ and $P' \approx_{Af} Q'$

  and for all $\alpha \in \mathcal{A}_s$

  3. $P \xrightarrow{\alpha, w, \Delta} c P'$ then $Q(\rightarrow)^* \xrightarrow{\alpha, w, \Delta} c (\rightarrow)^* Q'$ and $P' \approx_{Af} Q'$
  4. $Q \xrightarrow{\alpha, w, \Delta} c Q'$ then $P(\rightarrow)^* \xrightarrow{\alpha, w, \Delta} c (\rightarrow)^* P'$ and $P' \approx_{Af} Q'$

- similar definition to Milner’s weak bisimilarity

- fast reactions play same role as $\tau$ labelled transitions
Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

\[ P_1 \approx_{A_f} P_2 \Rightarrow P_1 \blacktriangleleft Q \approx_{A_f} P_2 \blacktriangleleft Q, \quad Q \blacktriangleright P_1 \approx_{A_f} Q \blacktriangleright P_2 \]
Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

\[ P_1 \approx_{A_f} P_2 \Rightarrow P_1 \cong_L Q \approx_{A_f} P_2 \cong_L Q, \quad Q \cong_L P_1 \approx_{A_f} Q \cong_L P_2 \]

- biological motivation, not identical to weak bisimilarity
Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

\[ P_1 \approx_{A_f} P_2 \Rightarrow P_1 \bowtie_L Q \approx_{A_f} P_2 \bowtie_L Q, \quad Q \bowtie_L P_1 \approx_{A_f} Q \bowtie_L P_2 \]

- biological motivation, not identical to weak bisimilarity

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

\[
A \overset{\text{def}}{=} \sum_{i=1}^{n}(\alpha_i, \kappa_i)_{op_i}A \quad \text{and} \quad B \overset{\text{def}}{=} \sum_{j=1}^{m}(\beta_j, \lambda_j)_{op_j}B
\]
Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

\[ P_1 \approx_{Af} P_2 \Rightarrow P_1 \otimes_l Q \approx_{Af} P_2 \otimes_l Q, \quad Q \otimes_l P_1 \approx_{Af} Q \otimes_l P_2 \]

- biological motivation, not identical to weak bisimilarity

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

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

\[ A\{B\} \overset{\text{def}}{=} \sum_{i=1}^{n}(\alpha_i, \kappa_i)\text{op}_i A\{B\} + \sum_{j=1}^{m}(\beta_j, \lambda_j)\text{op}_j A\{B\} \]
Congruence of fast-slow bisimilarity

- congruence for cooperation if no shared fast reactions

\[ P_1 \approx_{Af} P_2 \Rightarrow P_1 \bowtie_l Q \approx_{Af} P_2 \bowtie_l Q, \quad Q \bowtie_l P_1 \approx_{Af} Q \bowtie_l P_2 \]

- biological motivation, not identical to weak bisimilarity

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

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

\[
A\{B\} \overset{\text{def}}{=} \sum_{i=1}^{n} (\alpha_i, \kappa_i) \text{op}_i A\{B\} + \sum_{j=1}^{m} (\beta_j, \lambda_j) \text{op}_j A\{B\}
\]

- congruence for extension operator if no shared reactions

\[ A_1 \approx_{Af} A_2 \Rightarrow A_1\{B\} \approx_{Af} A_2\{B\} \quad \text{and} \quad B\{A_1\} \approx_{Af} B\{A_2\} \]
Use of congruence in biological modelling

- $M$, detailed model, large state space
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
- $L$, another model of a related system or supersystem
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
- $L$, another model of a related system or supersystem
- then $L \bowtie M \equiv L \bowtie M'$ by congruence
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
- $L$, another model of a related system or supersystem
- then $L \uplus M \equiv L \uplus M'$ by congruence
- can reduce size of overall model by replacing $M$ with $M'$
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
- $L$, another model of a related system or supersystem
- then $L \bowtie M \equiv L \bowtie M'$ by congruence
- can reduce size of overall model by replacing $M$ with $M'$
- can understand how $L$ interacts with other systems
Use of congruence in biological modelling

- $M$, detailed model, large state space
- $M'$, reduced model, smaller state space
- $M \equiv M'$, capturing some notion of same behaviour
- $L$, another model of a related system or supersystem

then $L \otimes M \equiv L \otimes M'$ by congruence

- can reduce size of overall model by replacing $M$ with $M'$
- can understand how $L$ interacts with other systems
- use in model checking with appropriate logics
Applying bisimulation to competitive inhibition

\[
\begin{align*}
(4,3,0,0,0) & \xrightarrow{\beta_1} (3,2,0,0,0,1) & \xrightarrow{\beta_1} (2,1,0,0,0,2) & \xrightarrow{\beta_1} (1,0,0,0,0,3) \\
& \xrightarrow{\beta_1} (3,3,0,1,0,0) & \xrightarrow{\beta_1} (2,2,0,1,0,1) & \xrightarrow{\beta_1} (1,1,0,1,0,2) & \xrightarrow{\beta_1} (0,0,0,1,0,3) \\
& \xrightarrow{\beta_1} (2,3,0,2,0,0) & \xrightarrow{\beta_1} (1,2,0,2,0,1) & \xrightarrow{\beta_1} (0,1,0,2,0,2) & \xrightarrow{\beta_1} (1,3,0,3,0,0) & \xrightarrow{\beta_1} (0,2,0,3,0,1) & \xrightarrow{\beta_1} (0,3,0,4,0,0)
\end{align*}
\]

bimolecular
Applying bisimulation to competitive inhibition

\[
\begin{align*}
(4,3,0,0,0) & \xrightarrow{\beta_1} (3,2,0,0,1) \xrightarrow{\beta_1} (2,1,0,0,2) \xrightarrow{\beta_1} (1,0,0,0,3) \\
& \xrightarrow{\beta_1} (0,0,0,1,0,3) \\
& \xrightarrow{\beta_1} (0,0,0,2,0,2) \\
& \xrightarrow{\beta_1} (0,0,0,3,0,1) \\
& \xrightarrow{\beta_1} (0,0,0,4,0,0)
\end{align*}
\]

bimolecular abstract
Applying bisimulation to competitive inhibition

\[(4,3,0,0,0) \xleftrightarrow{\beta_1} (3,2,0,0,0) \xleftrightarrow{\beta_1} (2,1,0,0,0) \xleftrightarrow{\beta_1} (1,0,0,0,0) \xleftrightarrow{\beta_1} (0,0,0,0,0)\] (4,3,0,0)

\[(3,3,0,1,0,0) \xleftrightarrow{\beta_1} (2,2,0,1,0,0) \xleftrightarrow{\beta_1} (1,1,0,1,0,0) \xleftrightarrow{\beta_1} (0,0,0,1,0,0) \xleftrightarrow{\beta_1} (0,0,0,0,1,0)\] (3,3,0,1)

\[(2,3,0,2,0,0) \xleftrightarrow{\beta_1} (1,2,0,2,0,0) \xleftrightarrow{\beta_1} (0,1,0,2,0,0) \xleftrightarrow{\beta_1} (0,0,0,2,0,0) \xleftrightarrow{\beta_1} (0,0,0,0,2)\] (2,3,0,2)

\[(1,3,0,3,0,0) \xleftrightarrow{\beta_1} (0,2,0,3,0,0) \xleftrightarrow{\beta_1} (0,0,0,3,0,0) \xleftrightarrow{\beta_1} (0,0,0,0,3)\] (1,3,0,3)

\[(0,3,0,4,0,0) \xleftrightarrow{\beta_1} (0,0,0,4,0,0) \xleftrightarrow{\beta_1} (0,0,0,0,4)\] (0,3,0,4)

bimolecular abstract

Vashti Galpin
A semi-quantitative equivalence for abstracting from fast reactions

CompMod 2011
Applying bisimulation to competitive inhibition

\[
\begin{align*}
\beta_1 &\quad (4,3,0, 0,0,0) \xleftrightarrow{\beta_1} (3,2,0, 0,0,1) \xleftrightarrow{\beta_1} (2,1,0, 0,0,2) \xleftrightarrow{\beta_1} (1,0,0, 0,0,3) \\
\beta^{-1} &\quad (4,3,0, 0 ) \\
\gamma &\quad (3,3,0, 1,0,0) \xleftrightarrow{\beta_1} (2,2,0, 1,0,1) \xleftrightarrow{\beta_1} (1,1,0, 1,0,2) \xleftrightarrow{\beta_1} (0,0,0, 1,0,3) \\
\beta^{-1} &\quad (3,3,0, 1 ) \\
\gamma &\quad (2,3,0, 2,0,0) \xleftrightarrow{\beta_1} (1,2,0, 2,0,1) \xleftrightarrow{\beta_1} (0,1,0, 2,0,2) \\
\beta^{-1} &\quad (2,3,0, 2 ) \\
\gamma &\quad (1,3,0, 3,0,0) \xleftrightarrow{\beta} (0,2,0, 3,0,1) \\
\beta &\quad (1,3,0, 3 ) \\
\gamma &\quad (0,3,0, 4,0,0) \xrightarrow{\gamma} (0,3,0, 4 )
\end{align*}
\]

bimolecular abstract
Applying bisimulation to competitive inhibition

\[
\begin{align*}
(4,3,0,0,0) & \xrightarrow{\beta_1} (3,2,0,0,1) \xrightarrow{\beta_1} (2,1,0,0,2) \xrightarrow{\beta_1} (1,0,0,0,3) \\
& \quad \downarrow \gamma \quad \downarrow \gamma \quad \downarrow \gamma \quad \downarrow \gamma \\
(3,3,0,1,0,0) & \xrightarrow{\beta_1} (2,2,0,1,0,1) \xrightarrow{\beta_1} (1,1,0,1,0,2) \xrightarrow{\beta_1} (0,0,0,1,0,3) \\
& \quad \downarrow \gamma \quad \downarrow \gamma \quad \downarrow \gamma \\
(2,3,0,2,0,0) & \xrightarrow{\beta_1} (1,2,0,2,0,1) \xrightarrow{\beta_1} (0,1,0,2,0,2) \\
& \quad \downarrow \gamma \quad \downarrow \gamma \\
(1,3,0,3,0,0) & \xrightarrow{\beta} (0,2,0,3,0,1) \\
& \quad \downarrow \gamma \\
(0,3,0,4,0,0) & \xrightarrow{\beta} (0,3,0,4,0,0)
\end{align*}
\]

bimolecular abstract
Applying bisimulation to competitive inhibition

\[
\begin{align*}
(4,3,0,0,0) & \xrightarrow{\beta_1} (3,2,0,0,1) \xrightarrow{\beta_1} (2,1,0,0,2) \xrightarrow{\beta_1} (1,0,0,0,3) \\
& \xrightarrow{\beta_1} (4,3,0,0) \\
& \xrightarrow{\beta_1} (3,3,0,1,0) \xrightarrow{\beta_1} (2,2,0,1,0) \xrightarrow{\beta_1} (1,1,0,1,0) \xrightarrow{\beta_1} (0,0,0,1,0,3) \\
& \xrightarrow{\beta_1} (3,3,0,1) \\
& \xrightarrow{\beta_1} (2,3,0,2) \xrightarrow{\beta_1} (1,2,0,2) \xrightarrow{\beta_1} (0,1,0,2,0,2) \\
& \xrightarrow{\beta_1} (2,3,0,2) \\
& \xrightarrow{\beta_1} (1,3,0,3) \xrightarrow{\beta} (0,2,0,3) \xrightarrow{\beta} (0,3,0,1) \\
& \xrightarrow{\beta} (1,3,0,3) \\
& \xrightarrow{\beta} (0,3,0,4) \xrightarrow{\beta} (0,3,0,4)
\end{align*}
\]

bimolecular abstract

Vashti Galpin
A semi-quantitative equivalence for abstracting from fast reactions CompMod 2011
Collaborating with Simon Smith

Applying bisimulation to competitive inhibition

\[
\begin{align*}
(4,3,0,0,0) & \xrightarrow{\beta_1} (3,2,0,0,0,1) & \xrightarrow{\beta_1} (2,1,0,0,0,2) & \xrightarrow{\beta_1} (1,0,0,0,0,3) & \xrightarrow{\beta_1} (4,3,0,0,0) \\
\end{align*}
\]
\[
\begin{align*}
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\end{align*}
\]
\[
\begin{align*}
(3,3,0,0,0) & \xrightarrow{\beta_1} (2,2,0,0,0,1) & \xrightarrow{\beta_1} (1,1,0,0,0,2) & \xrightarrow{\beta_1} (0,0,0,0,0,3) & \xrightarrow{\beta_1} (3,3,0,0,0) \\
\end{align*}
\]
\[
\begin{align*}
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\end{align*}
\]
\[
\begin{align*}
(2,3,0,0,0) & \xrightarrow{\beta_1} (1,2,0,0,0,1) & \xrightarrow{\beta_1} (0,1,0,0,0,2) & \xrightarrow{\beta_1} (2,3,0,0,0) \\
\end{align*}
\]
\[
\begin{align*}
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\end{align*}
\]
\[
\begin{align*}
(1,3,0,0,0) & \xrightarrow{\beta_1} (0,2,0,0,0,1) & \xrightarrow{\beta_1} (1,3,0,0,0) \\
\end{align*}
\]
\[
\begin{align*}
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\end{align*}
\]
\[
\begin{align*}
(0,3,0,0,0) & \xrightarrow{\beta} (0,2,0,0,0,1) & \xrightarrow{\beta} (0,3,0,0,0) \\
\end{align*}
\]
\[
\begin{align*}
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\beta_1 & & \beta_1 & & \beta_1 \\
\end{align*}
\]

Vashti Galpin

A semi-quantitative equivalence for abstracting from fast reactions

CompMod 2011
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_1, \beta_1, \beta_1\}$
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_1, \beta_1, \beta_1\}$

- define $\mathcal{R}$ as

$$\left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \mid 0 \leq k \leq n, \ 0 \leq j \leq \min\{m, n-k\}, \ 0 \leq l \leq p, \ j+l \leq m \right\}$$
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_1, \beta_1, \beta_1\}$
- define $R$ as

$$\left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \mid 0 \leq k \leq n, 0 \leq j \leq \min\{m, n-k\}, 0 \leq l \leq p, j+l \leq m \right\}$$
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$
- define $R$ as

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

- check this is a fast-slow bisimulation
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$

- define $R$ as

  
  \[
  \left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \mid \right. \\
  0 \leq k \leq n, \ 0 \leq j \leq \min\{m, n-k\}, \ 0 \leq l \leq p, \ j+l \leq m \right\}
  
- check this is a fast-slow bisimulation
  - check each $\gamma$ transition
  - check each fast transition
Applying bisimulation to competitive inhibition (cont.)

- first let $\mathcal{A}_f = \{\alpha_1, \alpha_1, \beta_1, \beta_1\}$
- define $\mathcal{R}$ as

$$\left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \mid \begin{array}{c} 0 \leq k \leq n, \ 0 \leq j \leq \min\{m, n-k\}, \ 0 \leq l \leq p, \ j+l \leq m \end{array} \right\}$$

- check this is a fast-slow bisimulation
  - check each $\gamma$ transition
  - check each fast transition
- lots of regularity, exploit parametricity
Applying bisimulation to competitive inhibition (cont.)

- first let $A_f = \{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$
- define $R$ as

\[
\left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \mid 0 \leq k \leq n, \ 0 \leq j \leq \min\{m, n-k\}, \ 0 \leq l \leq p, \ j+l \leq m \right\}
\]

- check this is a fast-slow bisimulation
  - check each $\gamma$ transition
  - check each fast transition
- lots of regularity, exploit parametricity
  
  can this be done more efficiently by just checking slow reactions?
Slow bisimilarity

- slow bisimilarity, $P \approx_{A_s} Q$ if for all $\alpha \in A_s$ whenever
Slow bisimilarity

- slow bisimilarity, $P \approx_{A_s} Q$ if for all $\alpha \in A_s$ whenever

1. $P \xrightarrow{\alpha, w, \Delta} P'$ then $Q (\rightarrow)^* \xrightarrow{\alpha, w, \Delta} Q'$ and $P' \approx_{A_s} Q'$
2. $Q \xrightarrow{\alpha, w, \Delta} Q'$ then $P (\rightarrow)^* \xrightarrow{\alpha, w, \Delta} P'$ and $P' \approx_{A_s} Q'$

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 $\Delta_2 = \Delta_1$ $R = \{ ((s_1, ..., s_n, f_1, ..., f_m), (s_1, ..., s_n)) \mid$ ranges for $s_i, f_j \}$ $R_{\text{slow bisimulation}} \Rightarrow R_{\text{fast-slow bisimulation}}$
Slow bisimilarity

- slow bisimilarity, $P \approx_{A_s} Q$ if for all $\alpha \in A_s$ whenever

1. $P \xrightarrow{\alpha, w\Delta}_c P'$ then $Q \xrightarrow{\alpha, w\Delta}_c (\xrightarrow{\bullet})* \xrightarrow{\alpha, w\Delta}_c (\xrightarrow{\bullet})* Q'$ and $P' \approx_{A_s} Q'$
2. $Q \xrightarrow{\alpha, w\Delta}_c Q'$ then $P \xrightarrow{\alpha, w\Delta}_c (\xrightarrow{\bullet})* \xrightarrow{\alpha, w\Delta}_c (\xrightarrow{\bullet})* P'$ and $P' \approx_{A_s} Q'$

- identify conserved, fast and slow variables by transforming stoichiometry matrix [Gómez-Uribe et al, 2008]
Slow bisimilarity

- slow bisimilarity, \( P \approx_{A_s} Q \) if for all \( \alpha \in A_s \) whenever
  
  1. \( P \xrightarrow{\alpha,w,\Delta} c P' \) then \( Q \xrightarrow{\alpha,w,\Delta} c (\rightarrow)^* Q' \) and \( P' \approx_{A_s} Q' \)
  2. \( Q \xrightarrow{\alpha,w,\Delta} c Q' \) then \( P \xrightarrow{\alpha,w,\Delta} c (\rightarrow)^* P' \) and \( P' \approx_{A_s} Q' \)

- identify conserved, fast and slow variables by transforming stoichiometry matrix [Gómez-Uribe et al, 2008]

- result about relationship between bisimulations

\[ R_{\text{slow bisimulation}} \Rightarrow R_{\text{fast-slow bisimulation}}. \]

\( M_1 \) 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

- variables are pairwise independent linear combinations of species

\[
Q = \begin{pmatrix}
0 & 0 \\
Q_{ss} & 0 \\
Q_{fs} & Q_{ff}
\end{pmatrix}
\]

- Columns: reactions
- Groups: slow, fast
- Rows: variables
- Groups: conserved, slow, fast

- Species values can be recovered from transformed matrix
Variable classification

- variables are pairwise independent linear combinations of species
- conserved variables are unchanged by reactions
Variable classification

- variables are pairwise independent linear combinations of species
- conserved variables are unchanged by reactions
- slow variables are only modified by slow reactions

\[
\begin{pmatrix}
0 & 0 \\
Q_{ss} & 0 \\
Q_{fs} & Q_{ff}
\end{pmatrix}
\]

Columns: reactions
Groups: slow, fast
Rows: variables
Groups: conserved, slow, fast

species values can be recovered from transformed matrix
Variable classification

- variables are pairwise independent linear combinations of species
- conserved variables are unchanged by reactions
- slow variables are only modified by slow reactions
- fast variables are modified by fast and slow reactions

\[ Q = \begin{bmatrix} 0 & 0 \\ Q_{ss} & 0 \\ Q_{fs} & Q_{ff} \end{bmatrix} \]

Columns: reactions
Groups: slow, fast
Rows: variables
Groups: conserved, slow, fast

Species values can be recovered from transformed matrix
Variable classification

- variables are pairwise independent linear combinations of species
- conserved variables are unchanged by reactions
- slow variables are only modified by slow reactions
- fast variables are modified by fast and slow reactions
- transform stoichiometry matrix to this form

\[ Q = \begin{bmatrix} 0 & 0 \\ Q_{ss} & 0 \\ Q_{fs} & Q_{ff} \end{bmatrix} \]

Columns: reactions
Groups: slow, fast
Rows: variables
Groups: conserved, slow, fast
Variable classification

- Variables are pairwise independent linear combinations of species.
- Conserved variables are unchanged by reactions.
- Slow variables are only modified by slow reactions.
- Fast variables are modified by fast and slow reactions.
- Transform stoichiometry matrix to this form:

\[
Q = \begin{bmatrix}
0 & 0 \\
Q_{ss} & 0 \\
Q_{fs} & Q_{ff}
\end{bmatrix}
\]

Columns: reactions
- Groups: slow, fast

Rows: variables
- Groups: conserved, slow, fast

- Species values can be recovered from transformed matrix.
Variable classification (cont.)

- how to determine classification
Variable classification (cont.)

- how to determine classification

conserved variables are simply species invariants
Variable classification (cont.)

▶ how to determine classification

conserved variables are simply species invariants

slow variables are species invariants after fast reactions are removed
Variable classification (cont.)

- how to determine classification
  - conserved variables are simply species invariants
  - slow variables are species invariants after fast reactions are removed
- use Bio-PEPA Eclipse Plug-in to discover potential variables
Variable classification (cont.)

- how to determine classification
  - conserved variables are simply species invariants
  - slow variables are species invariants after fast reactions are removed
- use Bio-PEPA Eclipse Plug-in to discover potential variables
- choose independent variables
Variable classification (cont.)

- how to determine classification
  
  conserved variables are simply species invariants

  slow variables are species invariants after fast reactions are removed

- 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

\[
S + EI \leftrightarrow S + E + I \leftrightarrow SE + I \rightarrow P + E + I
\]
Applying classification to competitive inhibition

\[ S + EI \quad \overset{\text{bimolecular model}}{\rightleftharpoons} \quad S + E + I \quad \overset{\rightleftharpoons}{\text{SE} + I} \quad \rightarrow \quad P + E + I \]

- \( X_{ST} = S + SE + P = S_0 = n \) conserved
- \( X_{ET} = E + EI + SE = E_0 = m \) conserved
- \( X_{IT} = EI + I = I_0 = p \) conserved
- \( X_P = P = k \) slow
- \( X_{EI} = EI = l \) fast
- \( X_{SE} = SE = j \) fast

Vashti Galpin
A semi-quantitative equivalence for abstracting from fast reactions
CompMod 2011
Applying classification to competitive inhibition (cont.)

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

- abstract model
Applying classification to competitive inhibition (cont.)

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

- Abstract model

\[
\begin{align*}
X_{S'} & = S' + P' = S_0 = n \text{ conserved} \\
X_{E'} & = E_0' = m \text{ conserved} \\
X_{I'} & = I_0' = p \text{ conserved} \\
X_{P'} & = P' = k \text{ slow}
\end{align*}
\]
Applying classification to competitive inhibition (cont.)

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

- abstract model

\[
\begin{align*}
X_{S'} & = S' + P' = S_0 = n \text{ conserved} \\
X_{E'} & = E_0' = m \text{ conserved} \\
X_{I'} & = I_0' = p \text{ conserved} \\
X_{P'} & = P' = k \text{ slow}
\end{align*}
\]

- ignore conserved variables as they never change
Applying classification to competitive inhibition (cont.)

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

- abstract model

\[
\begin{align*}
X_{S'} &= S' + P' = S_0 = n \text{ conserved} \\
X_{E'} &= E_0' = m \text{ conserved} \\
X_{I'} &= I_0' = p \text{ conserved} \\
X_{P'} &= P' = k \text{ slow}
\end{align*}
\]

- 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 \((\ell_P)\)
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 \((\ell_P)\)

- relation \(\mathcal{R}\) was defined as

\[
\left\{ \left( (n-(k+j), m-(j+l), p-l, \quad k, \quad l, j), \quad (n-k, m, p, \quad k) \right) \right. \\
\left. \quad \mid 0 \leq k \leq n, \quad 0 \leq j \leq \min\{m, n-k\}, \quad 0 \leq l \leq p, \quad j+l \leq m \right\}
\]
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 $(\ell_P)$

- relation $\mathcal{R}$ was defined as

$$\left\{ \left( (n-(k+j), m-(j+l), p-l, k, l, j), (n-k, m, p, k) \right) \right\} | 0 \leq k \leq n, 0 \leq j \leq \min\{m, n-k\}, 0 \leq l \leq p, j+l \leq m \}$$

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

$$\left\{ \left( (k, l, j), (k) \right) \right\} | 0 \leq k \leq n, 0 \leq j \leq \min\{m, n-k\}, 0 \leq l \leq p, j+l \leq m \}$$
Proof that $\mathcal{R}'$ is a slow bisimulation

- let $(P)_i = \{ P:↑(1, i) \}$
Proof that $\mathcal{R}'$ is a slow bisimulation

- let $(P)_i = \{P: \uparrow(1, i)\}$
- $((k, l, j), (k)) \in \mathcal{R}'$ for $0 \leq k < n$, $0 \leq l \leq p$, $0 < j \leq \min\{m, n-k\}

$(k) \xrightarrow{\gamma_i(P)_k} (k+1)$ matches $(k, l, j) \xrightarrow{\gamma_i(P)_k} (k+1, l, j-1)$ and v.v.
Proof that $\mathcal{R}'$ is a slow bisimulation

- let $(P)_i = \{P: \uparrow (1, i)\}$
- $((k, l, j), (k)) \in \mathcal{R}'$ for $0 \leq k < n$, $0 \leq l \leq p$, $0 < j \leq \min\{m, n-k\}$

\[(k) \xrightarrow{\gamma_i(P)_k} (k+1) \text{ matches } (k, l, j) \xrightarrow{\gamma_i(P)_k} (k+1, l, j-1) \text{ and v.v.}\]

- $((k, l, 0), (k)) \in \mathcal{R}'$ for $0 \leq k < n$, $0 \leq l \leq p$
Proof that $R'$ is a slow bisimulation

- let $(P)_i = \{P : \uparrow (1, i)\}$
- $((k, l, j), (k)) \in R'$ for $0 \leq k < n$, $0 \leq l \leq p$, $0 < j \leq \min\{m, n-k\}$

\[
(k) \xrightarrow{\gamma, (P)_k} (k+1) \text{ matches } (k, l, j) \xrightarrow{\gamma, (P)_k} (k+1, l, j-1) \text{ and v.v.}
\]

- $((k, l, 0), (k)) \in R'$ for $0 \leq k < n$, $0 \leq l \leq p$
  - if $m > p$ and $0 \leq l \leq p$, or if $m \leq p$ and $0 \leq l \leq m-1$

\[
(k) \xrightarrow{\gamma, (P)_k} (k+1) \text{ is matched by } (k, l, 0) \rightarrow (k, l, 1) \xrightarrow{\gamma, (P)_k} (k+1, l, 0)
\]
Proof that $\mathcal{R}'$ is a slow bisimulation

- let $(P)_i = \{ P: \uparrow(1, i) \}$
- $((k, l, j), (k)) \in \mathcal{R}'$ for $0 \leq k < n$, $0 \leq l \leq p$, $0 < j \leq \min\{m, n-k\}$
  
  $$(k) \xrightarrow{\gamma,(P)_{k}} (k+1) \text{ matches } (k, l, j) \xrightarrow{\gamma,(P)_{k}} (k+1, l, j-1) \text{ and v.v.}$$

- $((k, l, 0), (k)) \in \mathcal{R}'$ for $0 \leq k < n$, $0 \leq l \leq p$
  - if $m > p$ and $0 \leq l \leq p$, or if $m \leq p$ and $0 \leq l \leq m-1$
    
    $$(k) \xrightarrow{\gamma,(P)_{k}} (k+1) \text{ is matched by}$$
    $$(k, l, 0) \rightarrow (k, l, 1) \xrightarrow{\gamma,(P)_{k}} (k+1, l, 0)$$
  - if $m \leq p$ and $l = m$
    
    $$(k) \xrightarrow{\gamma,(P)_{k}} (k+1) \text{ is matched by}$$
    $$(k, 0, m) \rightarrow (k, 0, m+1) \rightarrow (k, 1, m+1) \xrightarrow{\gamma,(P)_{k}} (k+1, 0, m-1)$$
Equivalence between competitive inhibition models

- result holds
Equivalence between competitive inhibition models

- result holds
- in $\mathcal{R}'$ states match for slow variables: $\{(k, l, j), (k)\} \mid \ldots\}$
- $\Delta_1 = \Delta_2 = \Delta$
- $\mathcal{R}'$ is a slow bisimulation for $\{\gamma\}$

Vashti Galpin
A semi-quantitative equivalence for abstracting from fast reactions
CompMod 2011
Equivalence between competitive inhibition models

- result holds
- in $\mathcal{R}'$ states match for slow variables: $\{(k, l, j), (k)\} | \ldots$
- $\Delta_1 = \Delta_2 = \Delta$
- $\mathcal{R}'$ is a slow bisimulation for $\{\gamma\}$
- hence $\mathcal{R}'$ is a fast-slow bisimulation for $\{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$

Vashti Galpin

A semi-quantitative equivalence for abstracting from fast reactions

CompMod 2011
Equivalence between competitive inhibition models

- result holds
- in $\mathcal{R}'$ states match for slow variables: $\{(k, l, j), (k)\} | \ldots$
- $\Delta_1 = \Delta_2 = \Delta$
- $\mathcal{R}'$ is a slow bisimulation for $\{\gamma\}$
- hence $\mathcal{R}'$ is a fast-slow bisimulation for $\{\alpha_1, \alpha_1, \beta_1, \beta_1\}$
- transformed transition system is isomorphic to the original transition system
- hence $\mathcal{R}$ is a fast-slow bisimulation for $\{\alpha_1, \alpha_1, \beta_1, \beta_1\}$
Equivalence between competitive inhibition models

▶ result holds

▶ in $\mathcal{R}'$ states match for slow variables: $\{(k, l, j), (k)\} | \ldots \}$

▶ $\Delta_1 = \Delta_2 = \Delta$

▶ $\mathcal{R}'$ is a slow bisimulation for $\{\gamma\}$

▶ hence $\mathcal{R}'$ is a fast-slow bisimulation for $\{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$

▶ transformed transition system is isomorphic to the original transition system

▶ hence $\mathcal{R}$ is a fast-slow bisimulation for $\{\alpha_1, \alpha_{-1}, \beta_1, \beta_{-1}\}$

▶ hence $M$ and $M'$ are fast-slow bisimilar
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
- abstraction from fast reactions, time-scale difference
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
- abstraction from fast reactions, time-scale difference
- simpler equivalence can be used on certain models
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
- abstraction from fast reactions, time-scale difference
- simpler equivalence can be used on certain models
- use of invariants for variable classification
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
- abstraction from fast reactions, time-scale difference
- simpler equivalence can be used on certain models
- use of invariants for variable classification
- currently semi-quantitative, quantitative as further work
Conclusions and further work

- equivalence motivated by quasi-steady-state assumption
- abstraction from fast reactions, time-scale difference
- simpler equivalence can be used on certain models
- use of invariants for variable classification
- currently semi-quantitative, quantitative as further work
- investigate application to other process algebras
Thank you
Bio-PEPA

- stochastic process algebra for modelling biological systems
  [Ciocchetta and Hillston 2008]
Bio-PEPA

- stochastic process algebra for modelling biological systems
  [Ciocchetta and Hillston 2008]

- different analyses: ODEs, CTMCs, stochastic simulation
Bio-PEPA

- stochastic process algebra for modelling biological systems [Ciocchetta and Hillston 2008]
- different analyses: ODEs, CTMCs, stochastic simulation
- semantic equivalences – capture notion of same behaviour
Bio-PEPA

- stochastic process algebra for modelling biological systems [Ciocchetta and Hillston 2008]
- different analyses: ODEs, CTMCs, stochastic simulation
- semantic equivalences – capture notion of same behaviour
- can base on ideas from biology
Bio-PEPA

- stochastic process algebra for modelling biological systems
  [Ciocchetta and Hillston 2008]
- different analyses: ODEs, CTMCs, stochastic simulation
- semantic equivalences – capture notion of same behaviour
- can base on ideas from biology
- 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
Bio-PEPA syntax

- two-level syntax
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[
S ::= (\alpha, \kappa) \ op \ S \mid S + S \quad \text{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\}
\]
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \text{ op } S \mid S + S \quad \text{op } \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]

- \(\alpha\) action, reaction name, \(\kappa\) stoichiometric coefficient
- \(\uparrow\) product, \(\downarrow\) reactant
- \(\oplus\) activator, \(\ominus\) inhibitor, \(\odot\) generic modifier
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \text{ op } S \mid S + S \quad \text{ op } \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]

- \(\alpha\) action, reaction name, \(\kappa\) stoichiometric coefficient
- \(\uparrow\) product, \(\downarrow\) reactant
- \(\oplus\) activator, \(\ominus\) inhibitor, \(\odot\) generic modifier
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \text{ op } S | S + S \quad \text{op } \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]

- \alpha action, reaction name, \kappa stoichiometric coefficient
- \uparrow product, \downarrow reactant
- \oplus activator, \ominus inhibitor, \odot generic modifier

- model component, system

\[ P ::= S(\ell) | P \boxtimes L P \]
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \op S \mid S + S \quad \op \in \{↑, ↓, ⊕, ⊖, ⊙\} \]

  - \(\alpha\) action, reaction name, \(\kappa\) stoichiometric coefficient
  - ↑ product, ↓ reactant
  - ⊕ activator, ⊖ inhibitor, ⊙ generic modifier

- model component, system

\[ P ::= S(\ell) \mid P \bowtie_{\ell} P \]
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \text{ op } S \mid S + S \quad \text{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \oslash\} \]

  - \(\alpha\) action, reaction name, \(\kappa\) stoichiometric coefficient
  - \(\uparrow\) product, \(\downarrow\) reactant
  - \(\oplus\) activator, \(\ominus\) inhibitor, \(\oslash\) generic modifier

- model component, system

\[ P ::= S(\ell) \mid P \bowtie_{\ell} P \]
Bio-PEPA syntax

- two-level syntax

- sequential component, species

\[ S ::= (\alpha, \kappa) \text{ op } S \mid S + S \quad \text{op} \in \{\uparrow, \downarrow, \oplus, \ominus, \odot\} \]

  - \( \alpha \) action, reaction name, \( \kappa \) stoichiometric coefficient
  - \( \uparrow \) product, \( \downarrow \) reactant
  - \( \oplus \) activator, \( \ominus \) inhibitor, \( \odot \) generic modifier

- model component, system

\[ P ::= S(\ell) \mid P \boxtimes P \]

  - work with a more constrained form
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ \rho_1 C + \ldots + (\alpha_n, \kappa_n) \circ \rho_n C \text{ with all } \alpha_i \text{'s distinct} \]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ \rho_1 C + \ldots + (\alpha_n, \kappa_n) \circ \rho_n C \text{ with all } \alpha_i \text{'s distinct} \]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[
C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ \mathcal{P}_1 C + \ldots + (\alpha_n, \kappa_n) \circ \mathcal{P}_n C \quad \text{with all } \alpha_i \text{'s distinct}
\]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} \sum_{i=1}^{n} (\alpha_i, \kappa_i) \circ \mu_i C + \ldots + (\alpha_n, \kappa_n) \circ \mu_n C \] with all \( \alpha_i \)'s distinct

- well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \circ \mu_1 \ldots \circ \mu_{m-1} C_m(\ell_m) \] with all \( C_i \)'s distinct
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ p_1 C + \ldots + (\alpha_n, \kappa_n) \circ p_n C \] with all \( \alpha_i \)'s distinct

- well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \otimes \ldots \otimes C_m(\ell_m) \] with all \( C_i \)'s distinct
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species
  \[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1)op_1 C + \ldots + (\alpha_n, \kappa_n)op_n C \text{ with all } \alpha_i \text{'s distinct} \]

- well-defined Bio-PEPA model
  \[ P \overset{\text{def}}{=} C_1(\ell_1) \otimes \ldots \otimes C_m(\ell_m) \text{ with all } C_i \text{'s distinct} \]

- well-defined Bio-PEPA system
  \[ \mathcal{P} = \langle \mathcal{V}, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P \rangle \]
Well-defined Bio-PEPA systems

- well-defined Bio-PEPA species

\[ C \overset{\text{def}}{=} (\alpha_1, \kappa_1) \circ p_1 C + \ldots + (\alpha_n, \kappa_n) \circ p_n C \text{ with all } \alpha_i \text{'s distinct} \]

- well-defined Bio-PEPA model

\[ P \overset{\text{def}}{=} C_1(\ell_1) \triangleright \ldots \triangleright C_m(\ell_m) \text{ with all } C_i \text{'s distinct} \]

- well-defined Bio-PEPA system

\[ \mathcal{P} = \langle V, \mathcal{N}, \mathcal{K}, \mathcal{F}, \text{Comp}, P \rangle \]

- 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