Bisimulations for biology

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Outline

Bio-PEPA

Syntax and semantics

Discretisation-based

Biologically-based

Existing equivalences

Bio-PEPA

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

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  3. existing equivalences – PEPA, bisimulation-based
- mostly qualitative – consider action, not rate

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- need a more constrained form

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- well-defined Bio-PEPA species

$$C \stackrel{\mathit{def}}{=} (\alpha_1, \kappa_1)\,\mathtt{op}_1\, C + \ldots + (\alpha_n, \kappa_n)\,\mathtt{op}_n\, C \text{ with all } \alpha_i\text{'s distinct}$$

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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

Example: reaction with enzyme

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Bio-PEPA semantics (continued)

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- Bio-PEPA system: $\mathcal{P} = \langle \mathcal{T}, P \rangle$

Example: reaction with enzyme, max level 3

- state vector (S, E, SE, P) and $N_S = N_E = N_{SE} = N_P = 3$

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- state vector (S, E, SE, P) and $N_S = N_E = N_{SE} = N_P = 3$

$$\begin{tikzcd}
(3,3,0,0) \arrow[r, shift left, "\alpha"] & (2,2,1,0) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (1,1,2,0) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (0,0,3,0) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] \\
& (2,3,0,1) \arrow[r, shift left, "\alpha"] & (1,2,1,1) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (0,1,2,1) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] \\
& & (1,3,0,2) \arrow[r, shift left, "\alpha"] & (0,2,1,2) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] \\
& & & (0,3,0,3)
\end{tikzcd}$$

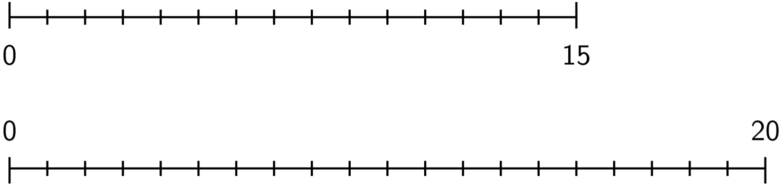
Example: reaction with enzyme, max level 7

- state vector $S\ E\ SE\ P$ and $N_S = N_E = N_{SE} = N_P = 7$

$$
\begin{tikzcd}
7700 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 6610 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 5520 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 4430 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 3340 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 2250 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 1160 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0070 \arrow[d, "\gamma"] \\
& 6701 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 5611 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 4521 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 3431 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 2341 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 1251 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0161 \arrow[d, "\gamma"] \\
& & 5702 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 4612 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 3522 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 2432 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 1342 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0252 \arrow[d, "\gamma"] \\
& & & 4703 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 3613 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 2523 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 1433 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0342 \arrow[d, "\gamma"] \\
& & & & 3704 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 2614 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 1524 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0614 \arrow[d, "\gamma"] \\
& & & & & 2705 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 1615 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & 0525 \arrow[d, "\gamma"] \\
& & & & & & 1706 \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & 0616 \arrow[d, "\gamma"] \\
& & & & & & & 0707
\end{tikzcd}
$$

Discretisation-based – motivating example

- $B \stackrel{\mathit{def}}{=} (\alpha, 3) \downarrow B \; + \; (\beta, 4) \uparrow B \; + \; (\gamma, 1) \uparrow B$



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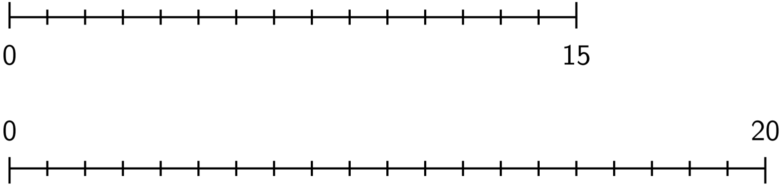

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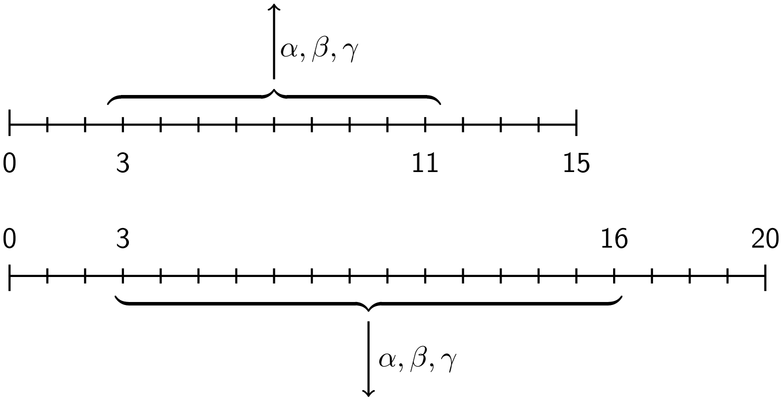

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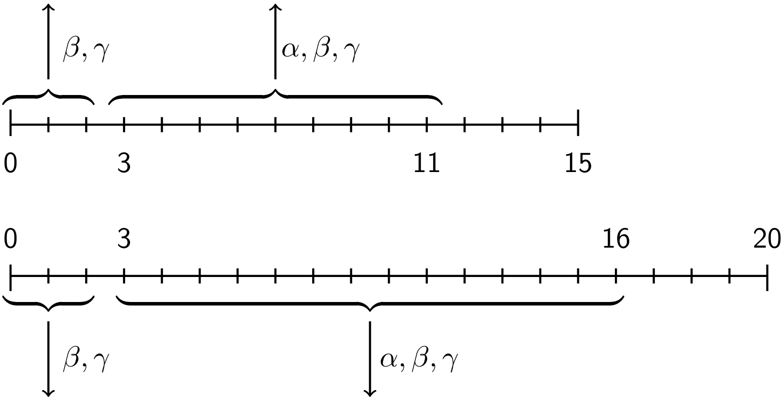

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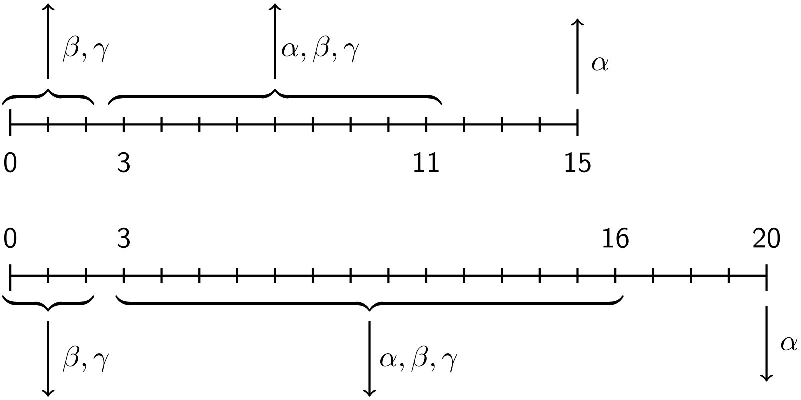

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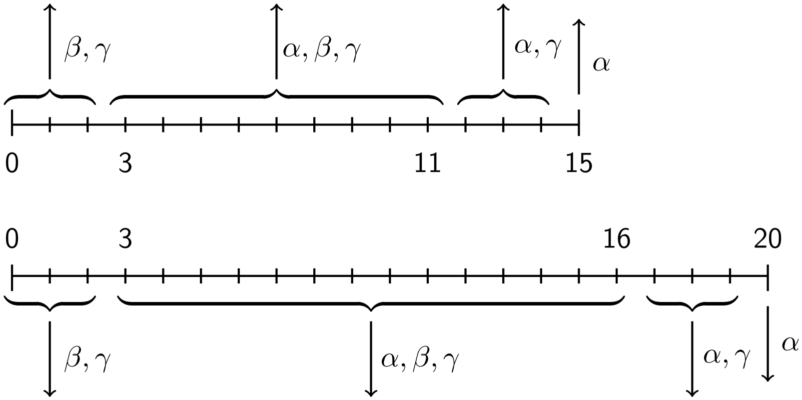

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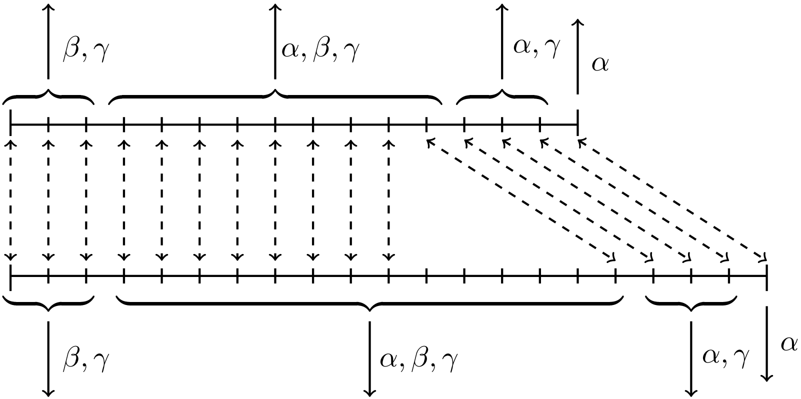

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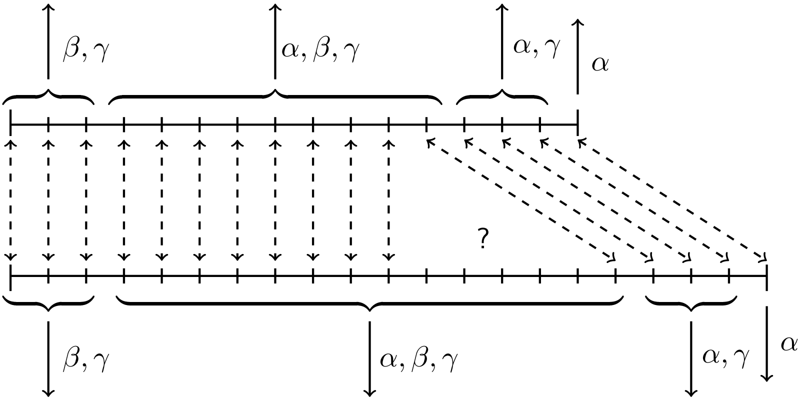

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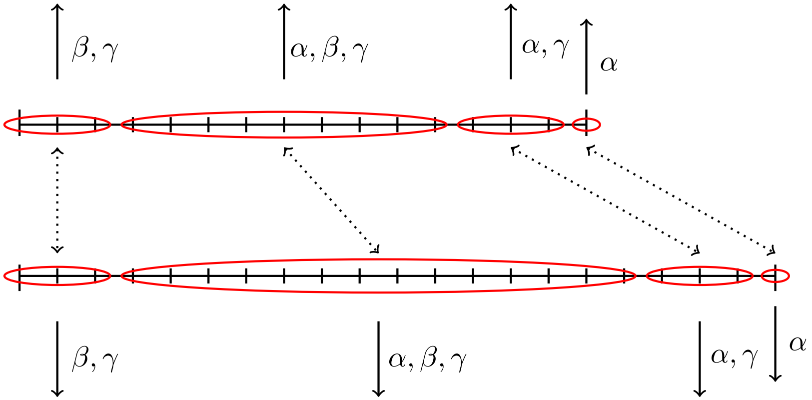

Compression bisimilarity

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- compression bisimilarity, $P \doteq Q$ if $[P] \sim [Q]$, namely whenever
  1. $[P] \xhookrightarrow{\alpha} [P']$, then $[Q] \xhookrightarrow{\alpha} [Q']$ and $[P'] \sim [Q']$
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- single species: $C^n \doteq C^m$, n and m large enough
- multiple species: $P^n \doteq P^m$, n and m large enough and a condition necessary for stoichiometry greater than one

Results

- equivalence classes: n levels, $E_1, \ldots, E_p$; m levels, $F_1, \ldots, F_q$

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  - if n, m large enough then $E_i \xrightarrow{\alpha} E_j$ if and only if $F_i \xrightarrow{\alpha} F_j$
  - transition-preserving isomorphism between equivalence classes hence bisimilar

Results (continued)

- if $P_1 \doteq P_2$, $Q_1 \doteq Q_2$ and then $P_1 \underset{L}{\bowtie} Q_1 \doteq P_2 \underset{L}{\bowtie} Q_2$ if technical conditions holds

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  - $(P_1, P_2) \in \mathcal{H}$ then $(P_1 \underset{L}{\bowtie} Q, P_2 \underset{L}{\bowtie} Q) \in \mathcal{H}$
  - construct a suitable bisimulation over equivalence classes

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- well-defined system, $P^n \doteq P^m$ if $n, m \geq k_\downarrow + \max\{k_\downarrow, k_\uparrow\} + k_\uparrow$ and technical condition
- hypothesis: if T is the lcm for all stoichiometric coefficients, $n = m + cT$ for $c \in \mathbb{N}$ and n, m large enough, then $P^n \doteq P^m$

Hypothesis: motivating example

$$\begin{aligned}
A &\stackrel{\mathit{def}}{=} (\alpha_1, 1) \downarrow A \\
&+ (\alpha_2, 1) \uparrow A \\
&+ (\alpha_3, 2) \downarrow A
\end{aligned}$$

$$B \stackrel{\mathit{def}}{=} (\alpha_3, 1) \uparrow B$$

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C &\stackrel{\mathit{def}}{=} (\alpha_1, 1) \uparrow C \\
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$$A(\ell_A) \underset{*}{\bowtie} B(\ell_B) \underset{*}{\bowtie} C(\ell_C)$$

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$$
\begin{tikzcd}
{\color{red}(5,0,0)} \arrow[r, shift left, "\alpha_1"] \arrow[d, "\alpha_3"'] & (4,0,1) \arrow[l, shift left, "\alpha_2"] \arrow[r, shift left, "\alpha_1"] \arrow[d, "\alpha_3"'] & (3,0,2) \arrow[l, shift left, "\alpha_2"] \arrow[r, shift left, "\alpha_1"] & \cdots \arrow[l, shift left, "\alpha_2"] \\
(3,1,0) \arrow[r, shift left, "\alpha_1"] \arrow[d, "\alpha_3"'] & (2,1,1) \arrow[l, shift left, "\alpha_2"] \arrow[r, shift left, "\alpha_1"] \arrow[d, "\alpha_3"'] & (1,1,2) \arrow[l, shift left, "\alpha_2"] \arrow[r, shift left, "\alpha_1"] & \cdots \arrow[l, shift left, "\alpha_2"] \\
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\begin{array}{ccccccc}
{\color{red}(6,0,0)} & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (5,0,1) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (4,0,2) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & \cdots \\
\alpha_3 \downarrow & & \alpha_3 \downarrow & & \alpha_3 \downarrow & & \\
(4,1,0) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (3,1,1) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (2,1,2) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & \cdots \\
\alpha_3 \downarrow & & \alpha_3 \downarrow & & \alpha_3 \downarrow & & \\
(2,2,0) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (1,2,1) & \underset{\alpha_2}{\overset{\alpha_1}{\rightleftarrows}} & (0,2,2) & & \\
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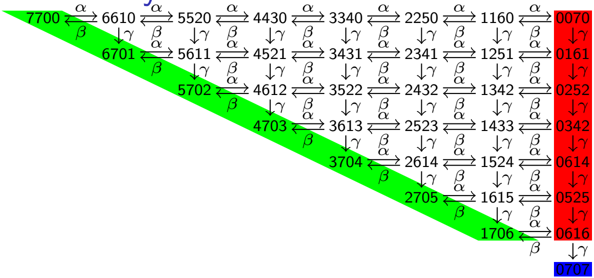
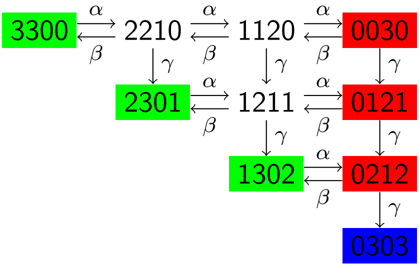
(1,3,0) \arrow[r, shift left, "\alpha_1"] & (0,3,1) \arrow[l, shift left, "\alpha_2"] & &
\end{tikzcd}
$$

Example: reaction with enzyme





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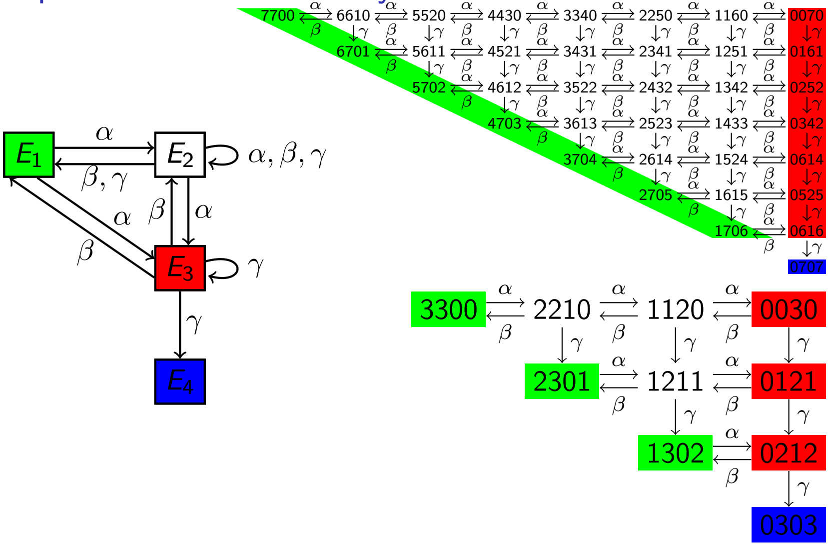

Biologically-based – motivating example

$S(5) \underset{*}{\bowtie} E(3) \underset{*}{\bowtie} SE(0) \underset{*}{\bowtie} P(0)$ $S'(5) \underset{*}{\bowtie} E'(3) \underset{*}{\bowtie} P'(0)$

$$
\begin{tikzcd}
(5,3,0,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (4,2,1,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (3,1,2,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (2,0,3,0) \arrow[d, "\gamma"] & & & (5,3,0) \arrow[d, "\gamma"] \\
& (4,3,0,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (3,2,1,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (2,1,2,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (1,0,3,1) \arrow[d, "\gamma"] & & (4,3,1) \arrow[d, "\gamma"] \\
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& & & & (1,3,0,4) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (0,2,1,4) \arrow[d, "\gamma"] & (1,3,4) \arrow[d, "\gamma"] \\
& & & & & (0,3,0,5) & (0,3,5)
\end{tikzcd}
$$

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  - $\mathcal{R} = \{(s_1, r, \ldots, s_n), (t_1, \ldots, r, t_m) \mid 1 \leq r \leq l, \ldots\}$
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- enzyme example, only slow actions modify match list

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

Motivating example revisited

$$S(5) \underset{*}{\bowtie} E(3) \underset{*}{\bowtie} SE(0) \underset{*}{\bowtie} P(0) \qquad\qquad S'(5) \underset{*}{\bowtie} E'(3) \underset{*}{\bowtie} P'(0)$$

$$\begin{tikzcd}
(5,3,0,0) \arrow[r, shift left, "\alpha"] & (4,2,1,0) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (3,1,2,0) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (2,0,3,0) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] & & \\
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& & & & (1,3,0,4) \arrow[r, shift left, "\alpha"] & (0,2,1,4) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] \\
& & & & & (0,3,0,5)
\end{tikzcd}
\qquad
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(5,3,0) \arrow[d, "\gamma"] \\
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$$\begin{tikzcd}
(5,3,0,{\color{red}0}) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (4,2,1,{\color{red}0}) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (3,1,2,{\color{red}0}) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (2,0,3,{\color{red}0}) \arrow[d, "\gamma"] & & & (5,3,{\color{red}0}) \arrow[d, "\gamma"] \\
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& & (3,3,0,\textcolor{red}{2}) \arrow[r, shift left, "\alpha"] & (2,2,1,\textcolor{red}{2}) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (1,1,2,\textcolor{red}{2}) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (0,0,3,\textcolor{red}{2}) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] & (3,3,\textcolor{red}{2}) \arrow[d, "\gamma"] \\
& & & (2,3,0,3) \arrow[r, shift left, "\alpha"] & (1,2,1,3) \arrow[l, shift left, "\beta"] \arrow[r, shift left, "\alpha"] \arrow[d, "\gamma"] & (0,1,2,3) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] & (2,3,3) \arrow[d, "\gamma"] \\
& & & & (1,3,0,4) \arrow[r, shift left, "\alpha"] & (0,2,1,4) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] & (1,3,4) \arrow[d, "\gamma"] \\
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Motivating example revisited

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& & & & (1,3,0,4) \arrow[r, shift left, "\alpha"] & (0,2,1,4) \arrow[l, shift left, "\beta"] \arrow[d, "\gamma"] & (1,3,4) \arrow[d, "\gamma"] \\
& & & & & (0,3,0,\textcolor{red}{5}) & (0,3,\textcolor{red}{5})
\end{tikzcd}$$

Motivating example revisited

$$S(5) \underset{*}{\bowtie} E(3) \underset{*}{\bowtie} SE(0) \underset{*}{\bowtie} P(0) \qquad \approx_{\{\alpha,\beta\}} \qquad S'(5) \underset{*}{\bowtie} E'(3) \underset{*}{\bowtie} P'(0)$$

$$\begin{tikzcd}
(5,3,0,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (4,2,1,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (3,1,2,0) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (2,0,3,0) \arrow[d, "\gamma"] & & & (5,3,0) \arrow[d, "\gamma"] \\
& (4,3,0,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] & (3,2,1,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (2,1,2,1) \arrow[r, shift left, "\alpha"] \arrow[r, leftarrow, shift right, "\beta"'] \arrow[d, "\gamma"] & (1,0,3,1) \arrow[d, "\gamma"] & & (4,3,1) \arrow[d, "\gamma"] \\
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Congruence of fast-slow bisimilarity

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

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- congruence with respect to new operator

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- consider general notion of bisimulation based on function

Parameterised bisimilarity

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- strong bisimilarity: $g_c((\alpha, w), P, P') = (\alpha, w)$

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- strong bisimilarity: $g_c((\alpha, w), P, P') = (\alpha, w)$
- congruence for all operators under certain conditions on g

Grouping of species

$$\begin{tikzcd} & J_1 \arrow[dr] & \\ A' \arrow[ur] \arrow[dr] & & B' \\ & J_2 \arrow[ur] & \end{tikzcd} \qquad \begin{tikzcd} A \arrow[r] & J \arrow[r] & B \end{tikzcd}$$

$$\begin{aligned}
A' &\overset{def}{=} (\alpha_1, 1)\downarrow A' + (\alpha_2, 1)\downarrow A' \\
J_1 &\overset{def}{=} (\alpha_1, 1)\uparrow J_1 + (\beta_1, 1)\downarrow J_1 \\
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Grouping of species

$$\begin{tikzcd} & J_1 \arrow[dr] & \\ A' \arrow[ur, red] \arrow[dr] & & B' \\ & J_2 \arrow[ur] & \end{tikzcd}$$

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$$\begin{aligned}
A' &\stackrel{\mathit{def}}{=} ({\color{red}\alpha_1}, 1)\!\downarrow\! A' + (\alpha_2, 1)\!\downarrow\! A' \\
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- seek more examples and more biological motivations