Applying bisimulation and invariants to alternate pathways in a signalling cascade

Vashti Galpin

LFCS, School of Informatics, University of Edinburgh

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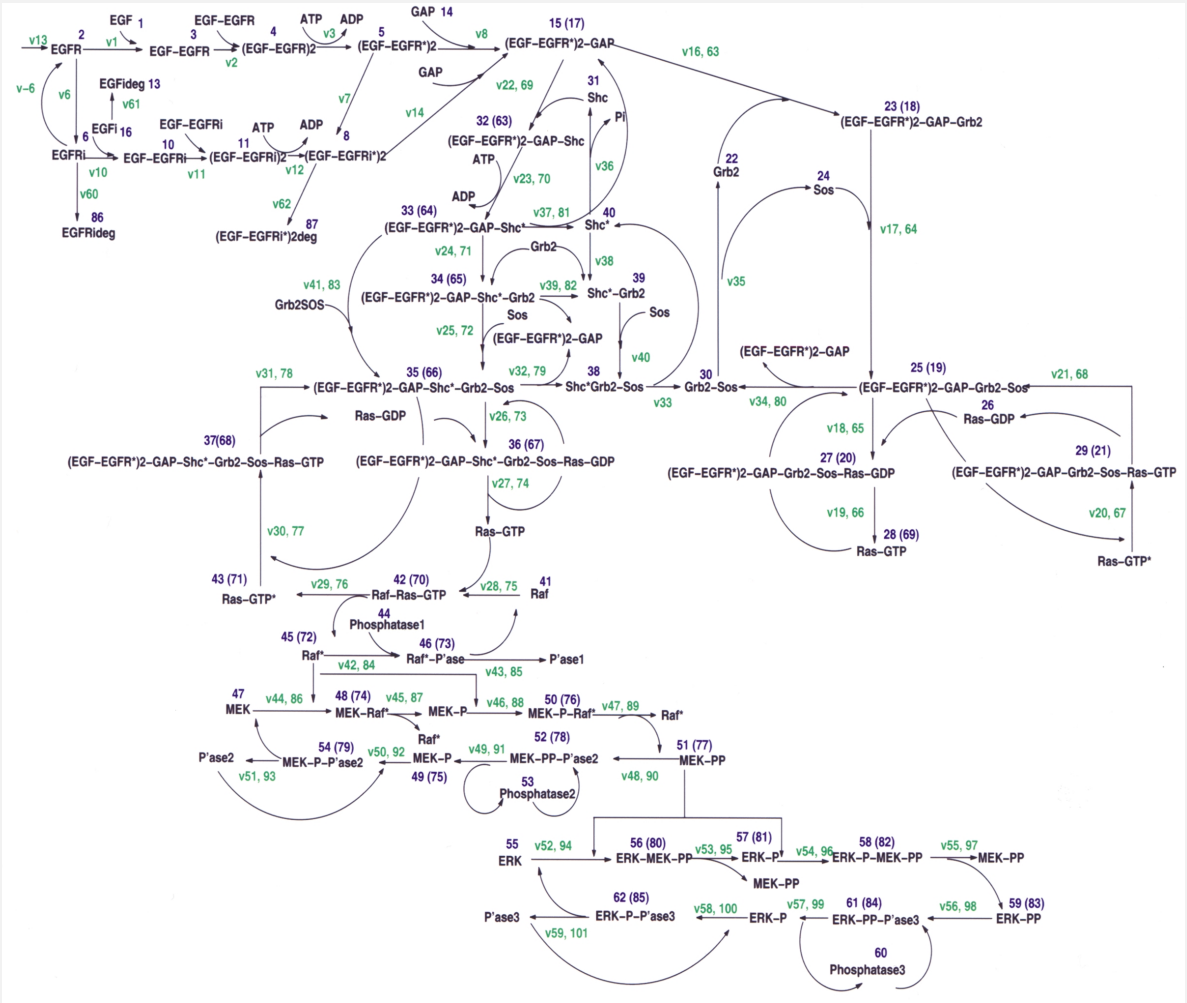
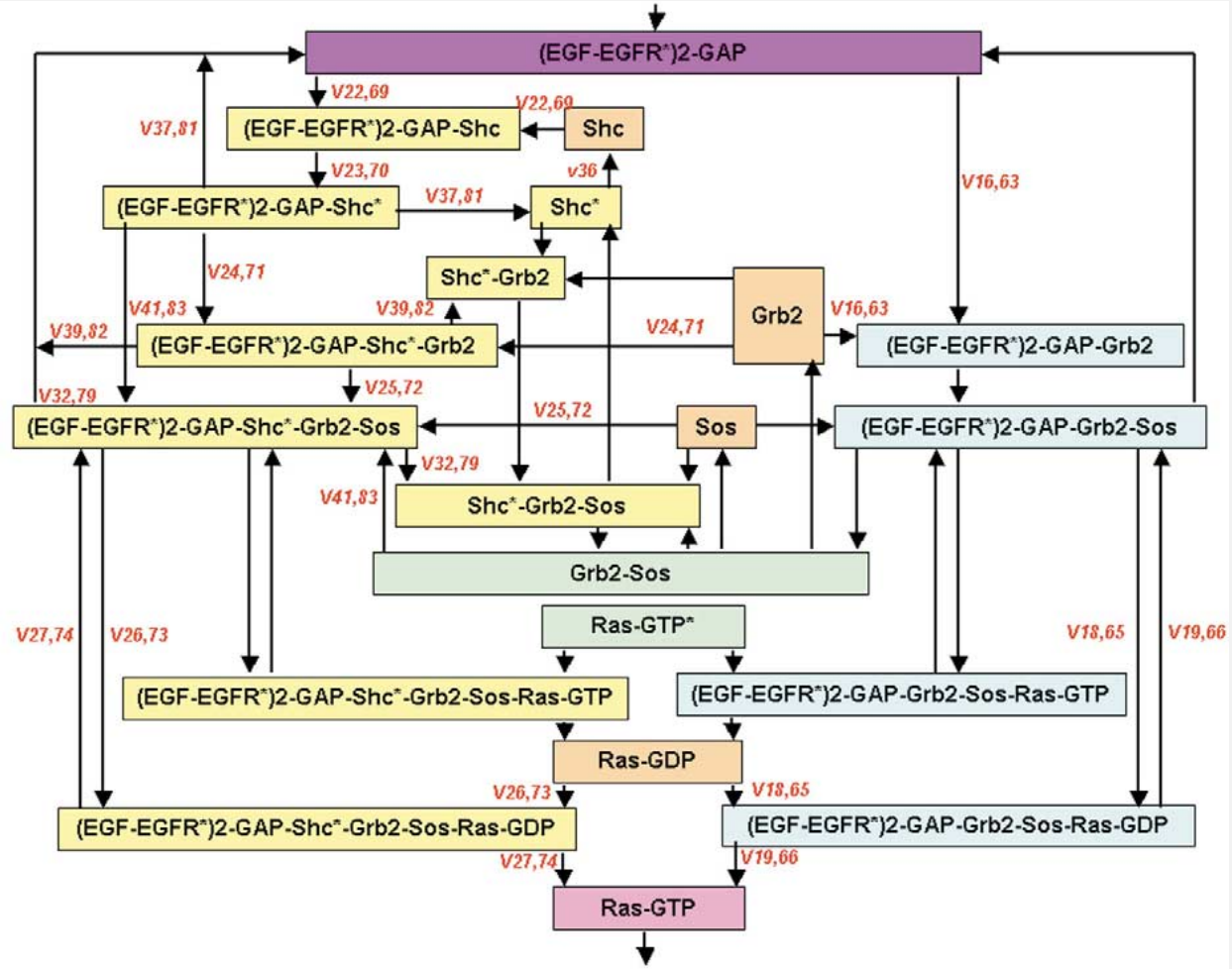
Outline

Example: MAPK cascade activated by EGF receptors



B. Schoeberl, C. Eichler-Jonsson, E.D. Gilles, G. Müller, Nature Biotechnology, 2002

Alternate subpathways in cascade



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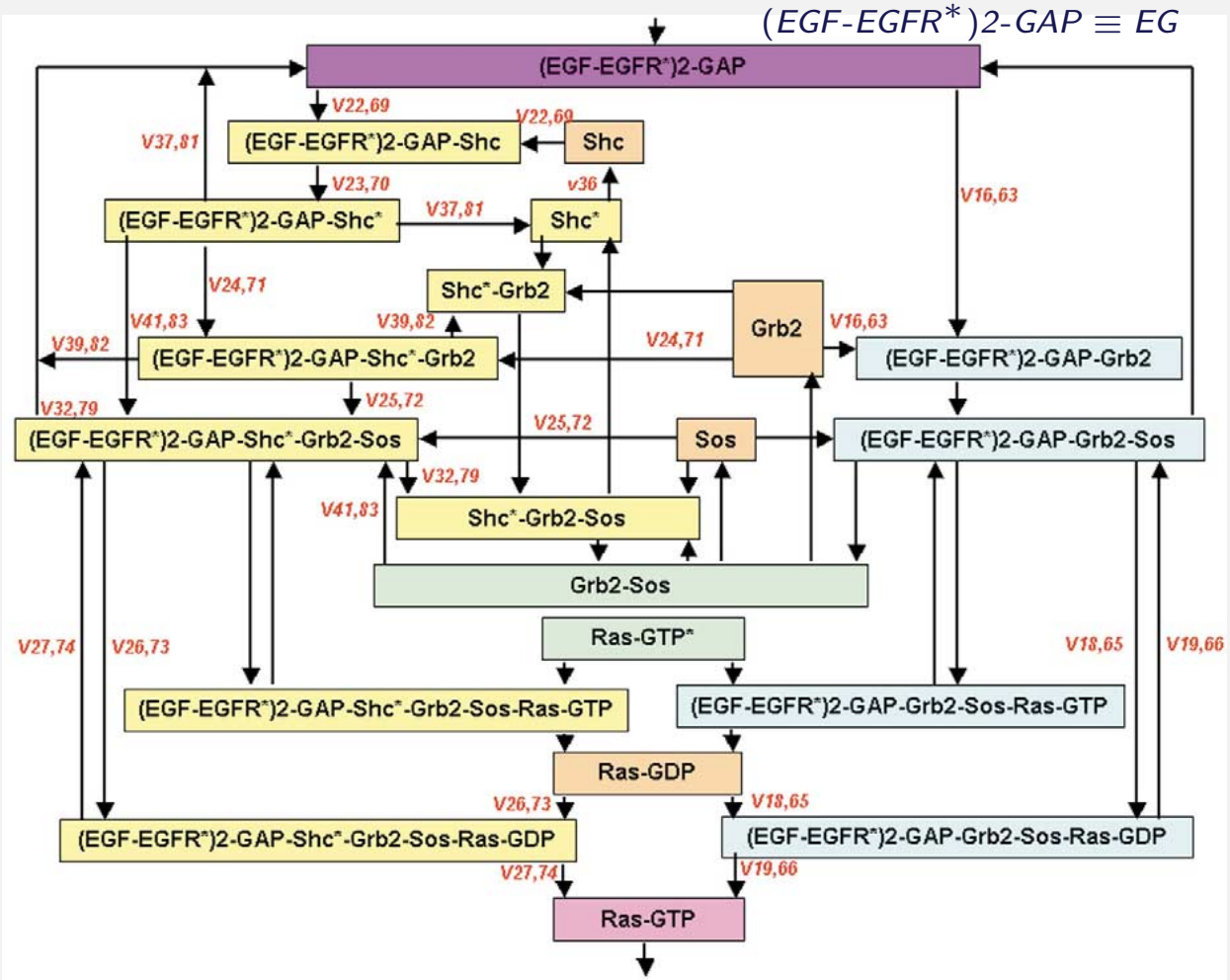

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- *Shc*-dependent pathway is redundant but dominant (Gong and Zhao, 2003)
- how can this be shown in Bio-PEPA with bisimulation?
  - consider it qualitatively
  - construct two Bio-PEPA models
  - compare with weak g-bisimulation

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- operational semantics for capability relation $\rightarrow_c$

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Bio-PEPA semantics (continued)

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- can define stochastic relation which is quantitative
- work with capability relation and context, well-defined

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$$P \xRightarrow{\phi_1 \ldots \phi_n}_g P' \text{ for } \phi_i \in X \cup \{\tau\} \text{ represents}$$
$$P \left(\xrightarrow{\tau}_g\right)^* \xrightarrow{\phi_1}_g \left(\xrightarrow{\tau}_g\right)^* \cdots \left(\xrightarrow{\tau}_g\right)^* \xrightarrow{\phi_n}_g \left(\xrightarrow{\tau}_g\right)^* P'$$

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and for all $\phi \neq \tau$

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- based on Milner's weak bisimilarity
- allows for abstraction from some details of reactions

Congruence of weak g-bisimilarity

- congruence for cooperation if g set-stable and species-blind

$$P_1 \approx_g P_2 \Rightarrow P_1 \underset{L}{\bowtie} Q \approx_g P_2 \underset{L}{\bowtie} Q \text{ and } Q \underset{L}{\bowtie} P_1 \approx_g Q \underset{L}{\bowtie} P_2$$

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- congruence for extension operator if g is species-blind

$$A_1 \approx_g A_2 \Rightarrow A_1\{B\} \approx_g A_2\{B\} \text{ and } B\{A_1\} \approx_g B\{A_2\}$$

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- analysis of models is required

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- new diagram to support reconceptualisation

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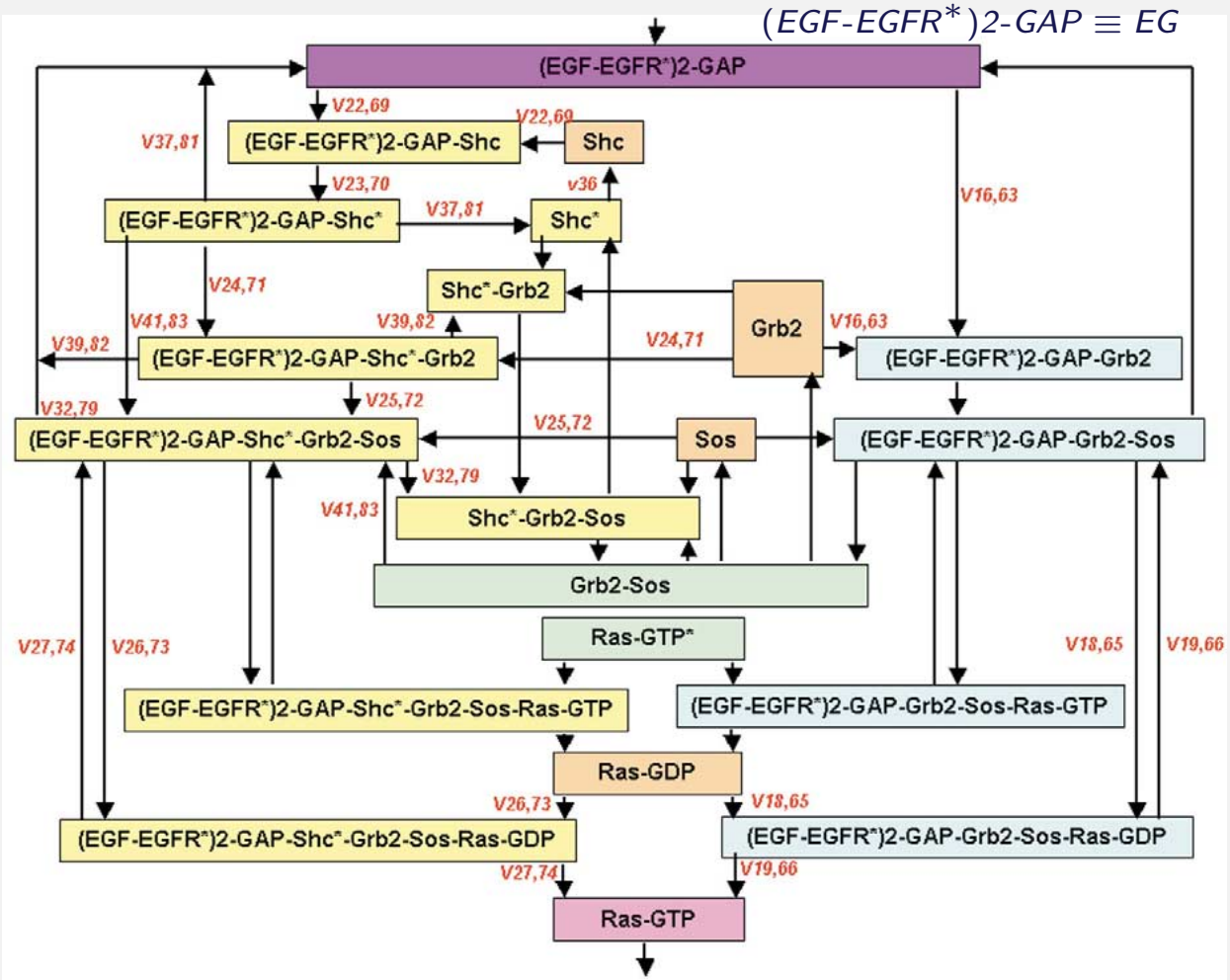

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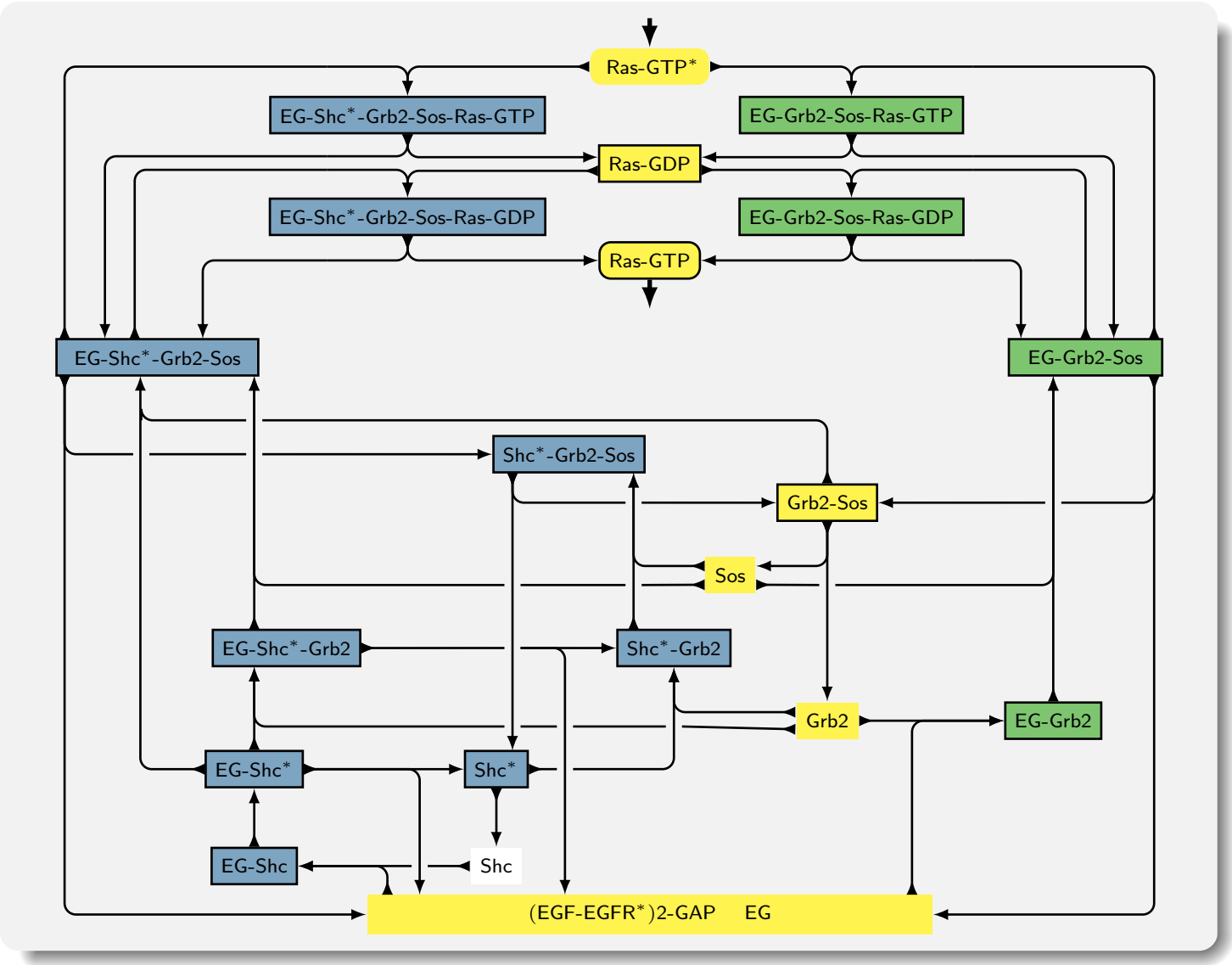
Alternate subpathways, reconceptualised



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- vector notation for well-defined Bio-PEPA models

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- equivalence relation over vectors, $\mathcal{R}$

$$\left\{\left((k_1, k_2, k_3, k_4, k_5, x_6, \ldots, x_{17}), (k_1, k_2, k_3, k_4, k_5, y_6, \ldots, y_{11})\right)\right\}$$

how to choose g?

Construction of bisimulation (cont.)

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- function to capture changes for a set of species

$$g_{\{A_1,\ldots,A_m\}}((\alpha, w), P, P') = \begin{cases} (\Delta(A_1, w), \ldots, \Delta(A_m, w)) \\ \qquad \text{if any } A_i \text{ appears in } w \\ \tau \quad \text{otherwise} \end{cases}$$

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is matched by

$$\begin{aligned}
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&\vdots \qquad\qquad \vdots \\
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- quantitative aspects as further work
- 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

Alternate subpathways, reconceptualised