Why I'm always late!

PASTA 2005

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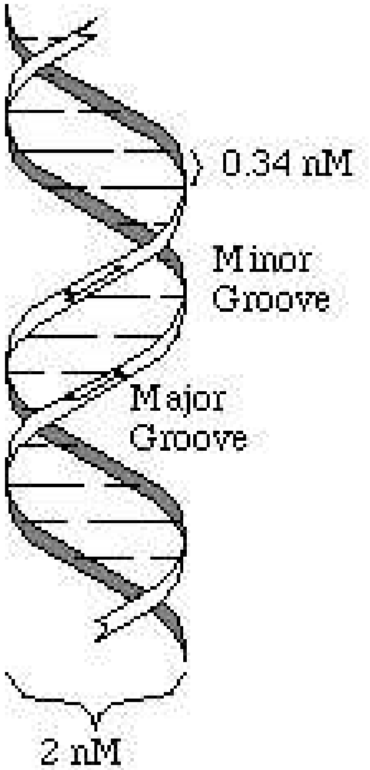
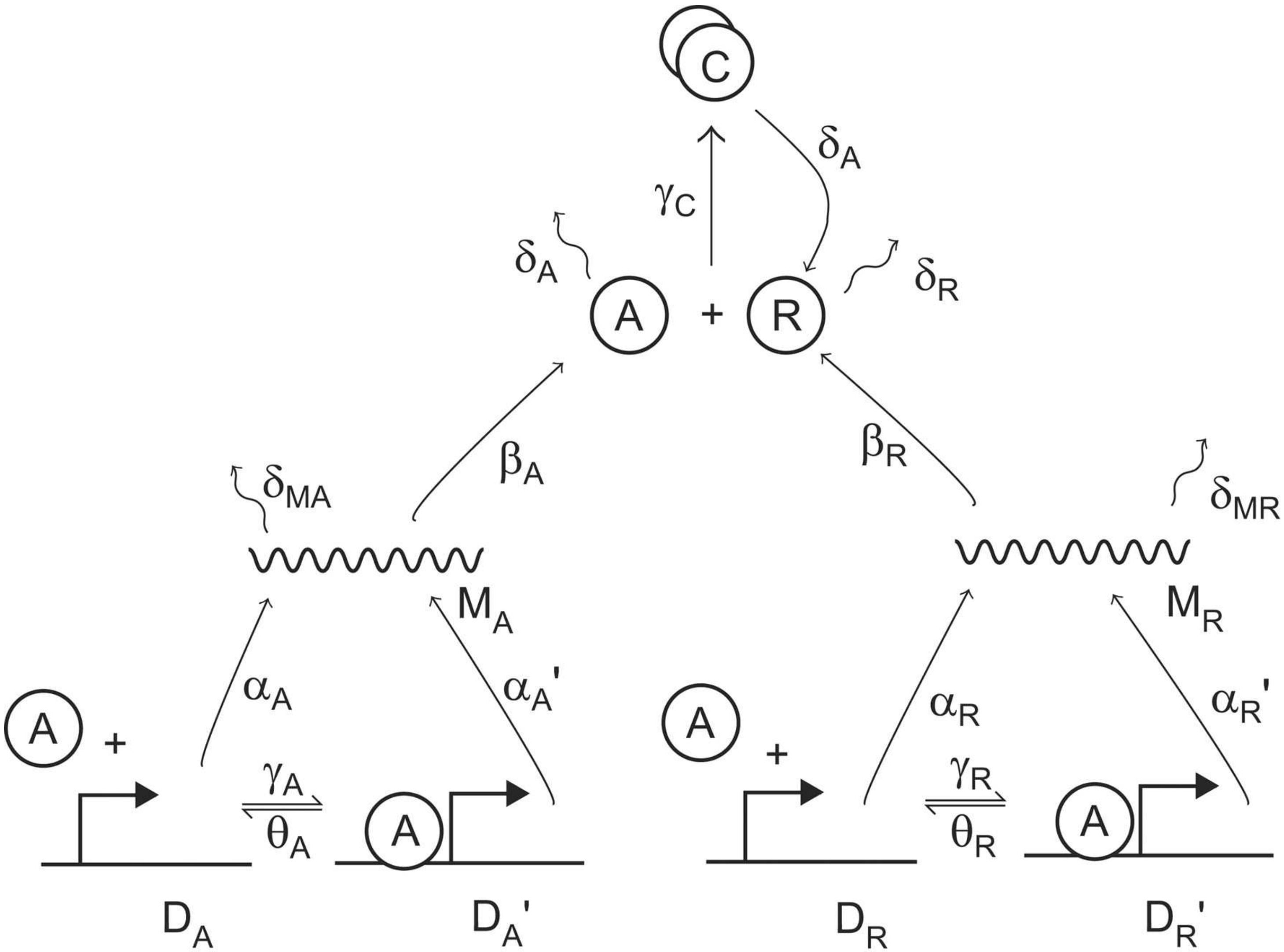
Produced with prosper and LaTeX

Something about genes...

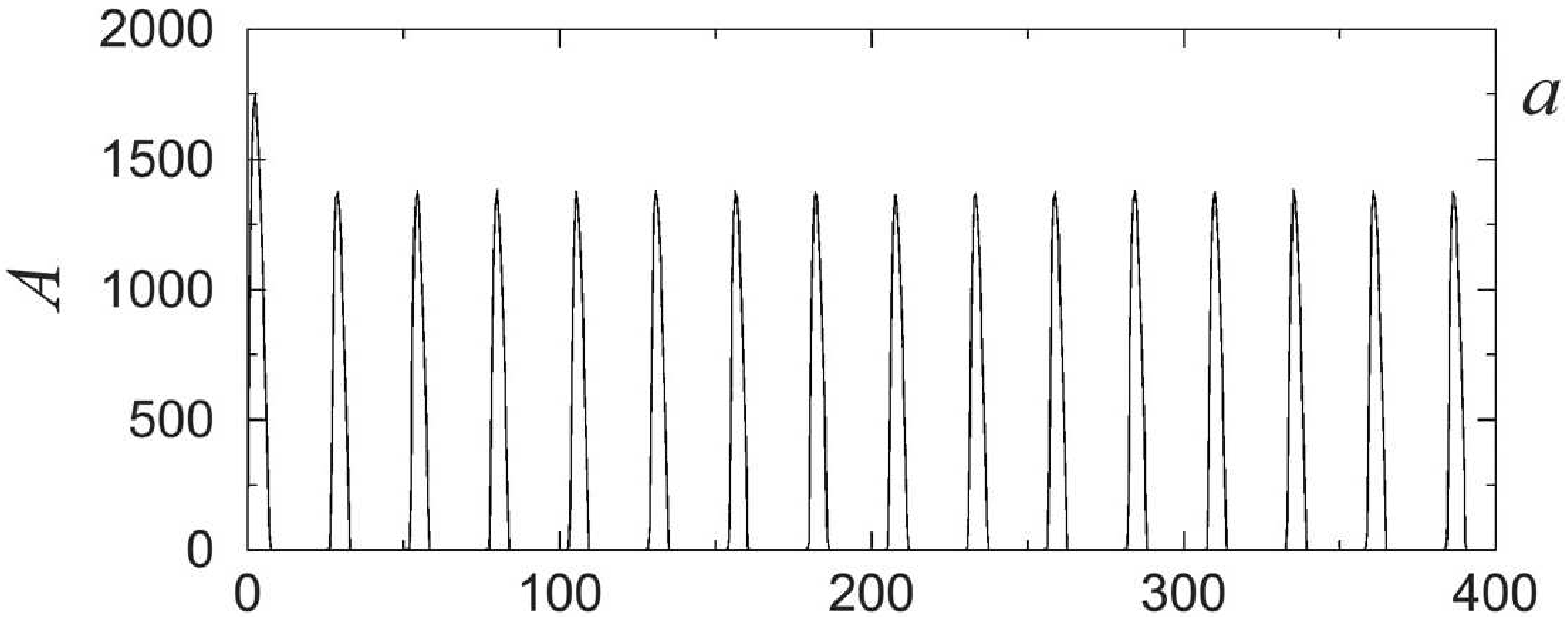
- DNA $\longrightarrow$ RNA $\longrightarrow$ protein



Biological Circadian Clock Model



Vilar oscillations of A



Stochastic π-Calculus model

$$D_A \stackrel{\text{def}}{=} bind_{A_{\gamma_A}}.AD_A + \tau_{\alpha_A}.(D_A \mid M_A)$$

$$AD_A \stackrel{\text{def}}{=} \tau_{\theta_A}.(D_A \mid A) + \tau_{\alpha_{A'}}.(AD_A \mid M_A)$$

$$D_R \stackrel{\text{def}}{=} bind_{R_{\gamma_R}}.AD_R + \tau_{\alpha_R}.(D_R \mid M_R)$$

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$$M_A \stackrel{\text{def}}{=} \tau_{\delta_{MA}}.\emptyset + \tau_{\beta_A}.(M_A \mid A)$$

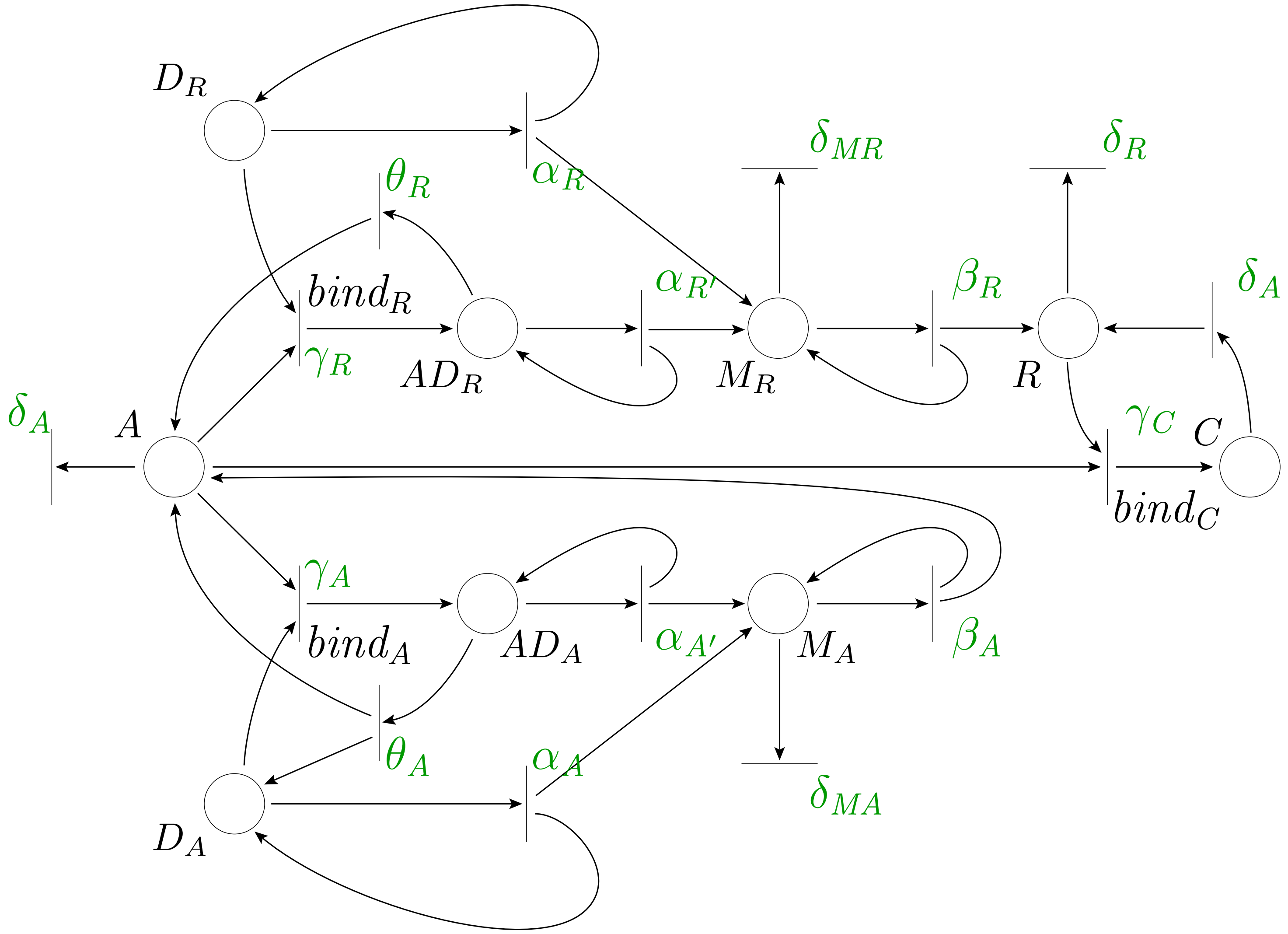
$$M_R \stackrel{\text{def}}{=} \tau_{\delta_{MR}}.\emptyset + \tau_{\beta_R}.(M_R \mid R)$$

$$A \stackrel{\text{def}}{=} \overline{bind_{A_{\gamma_A}}}.\emptyset + \overline{bind_{R_{\gamma_R}}}.\emptyset + \overline{bind_{C_{\gamma_C}}}.\emptyset + \tau_{\delta_A}.\emptyset$$

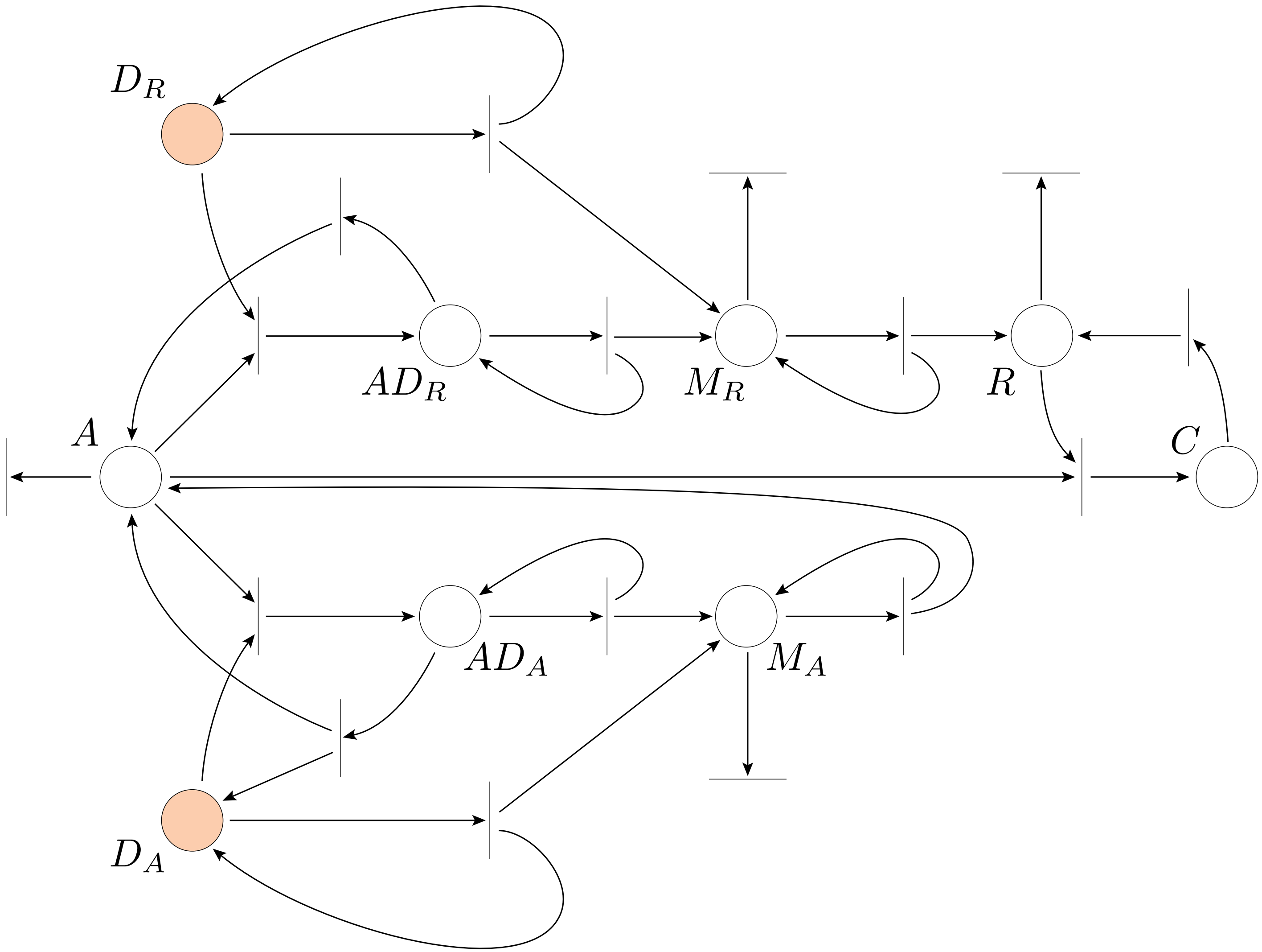
$$R \stackrel{\text{def}}{=} bind_{C_{\gamma_C}}.C + \tau_{\delta_R}.$$

$$C \stackrel{\text{def}}{=} \tau_{\delta_A}.R$$

Circadian clock: as a Petri net!



Circadian clock: an explanation



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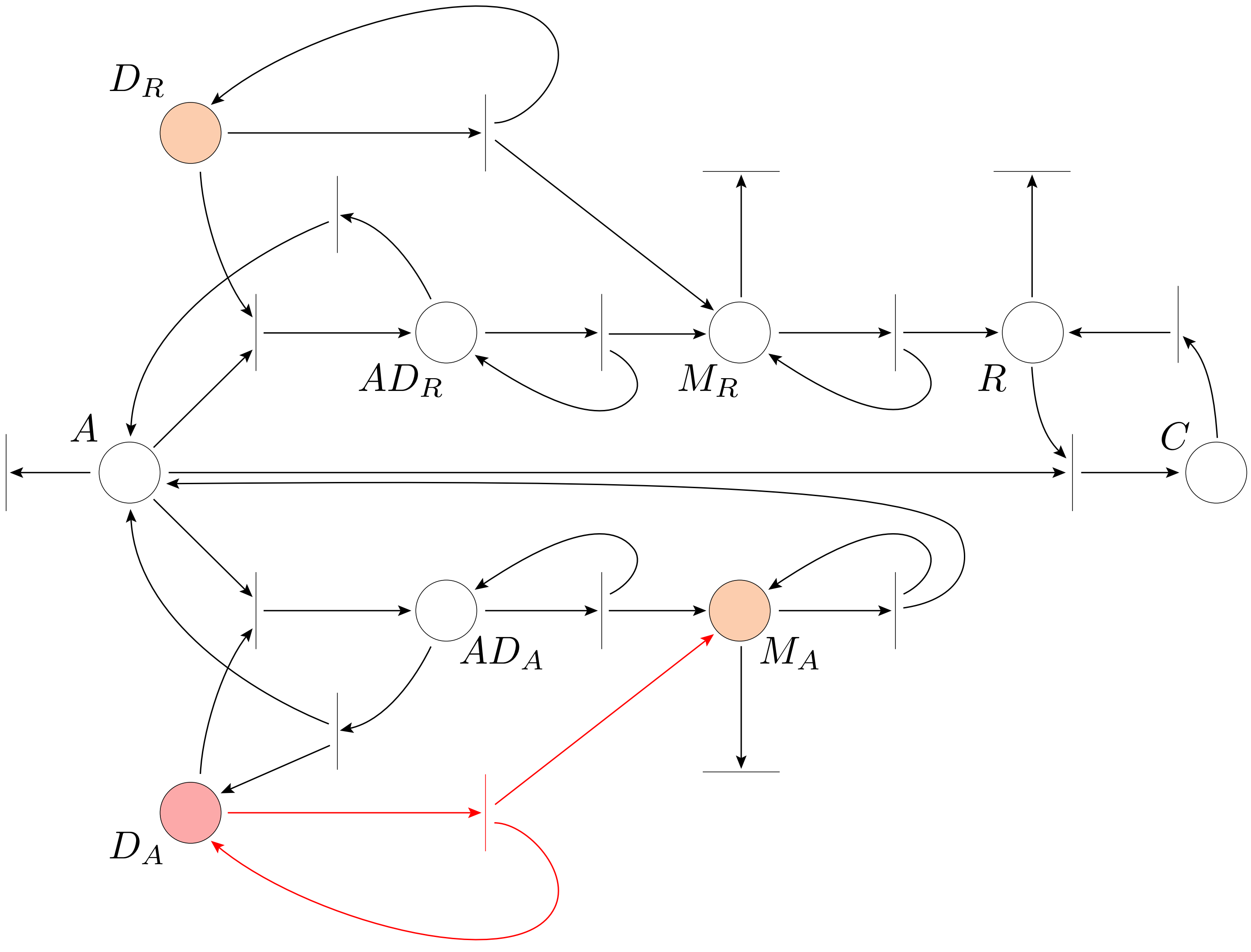

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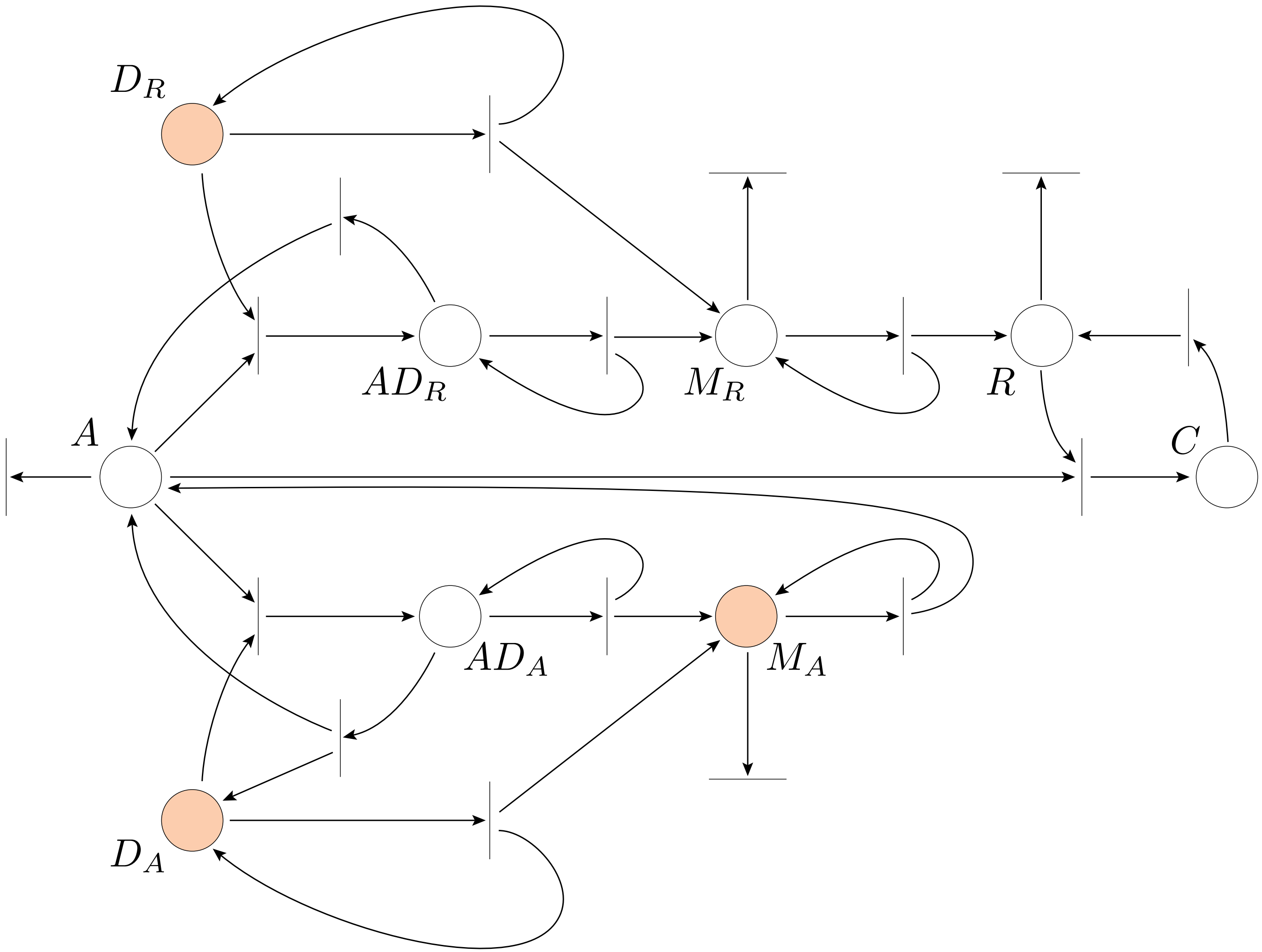

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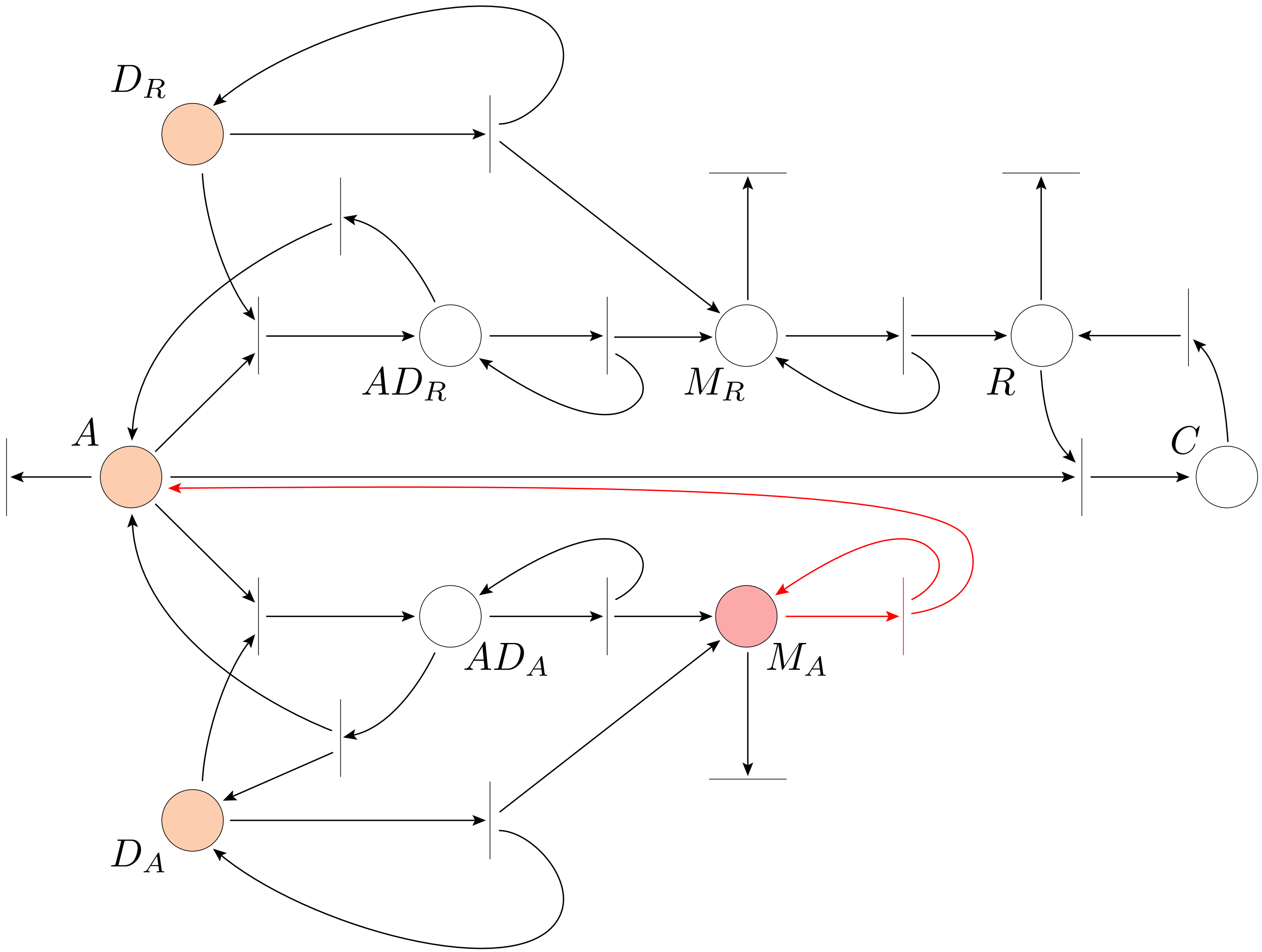

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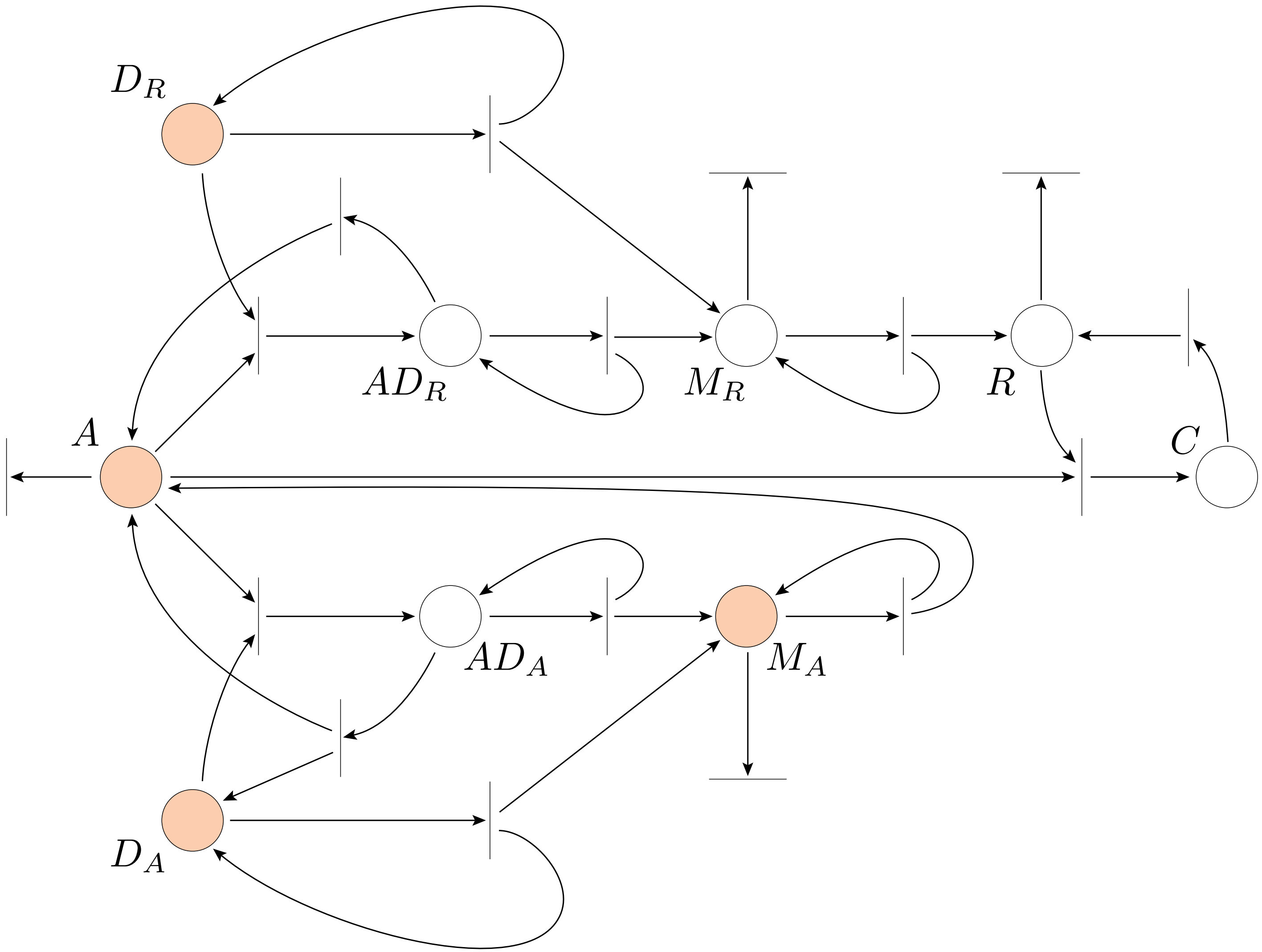

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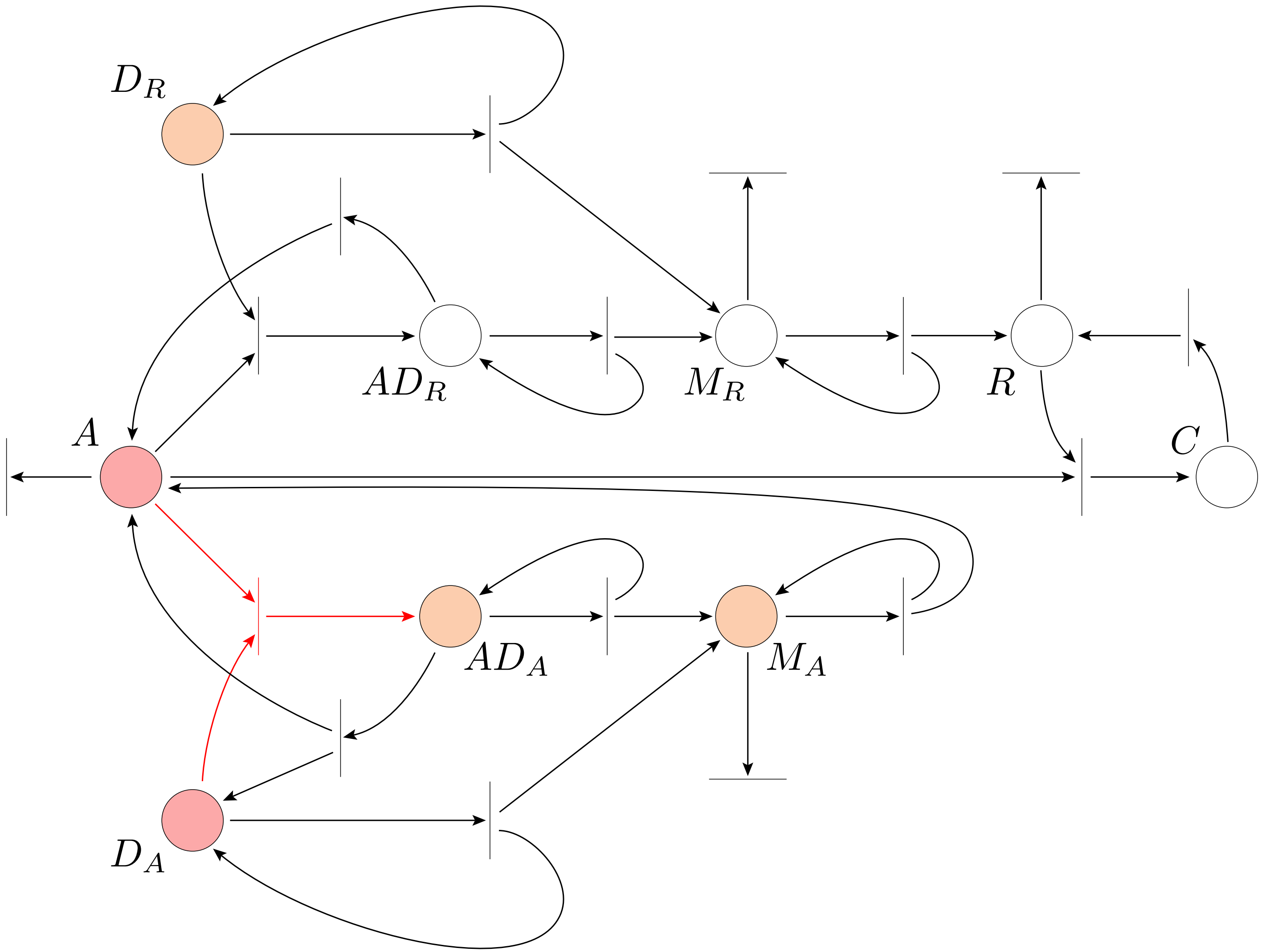

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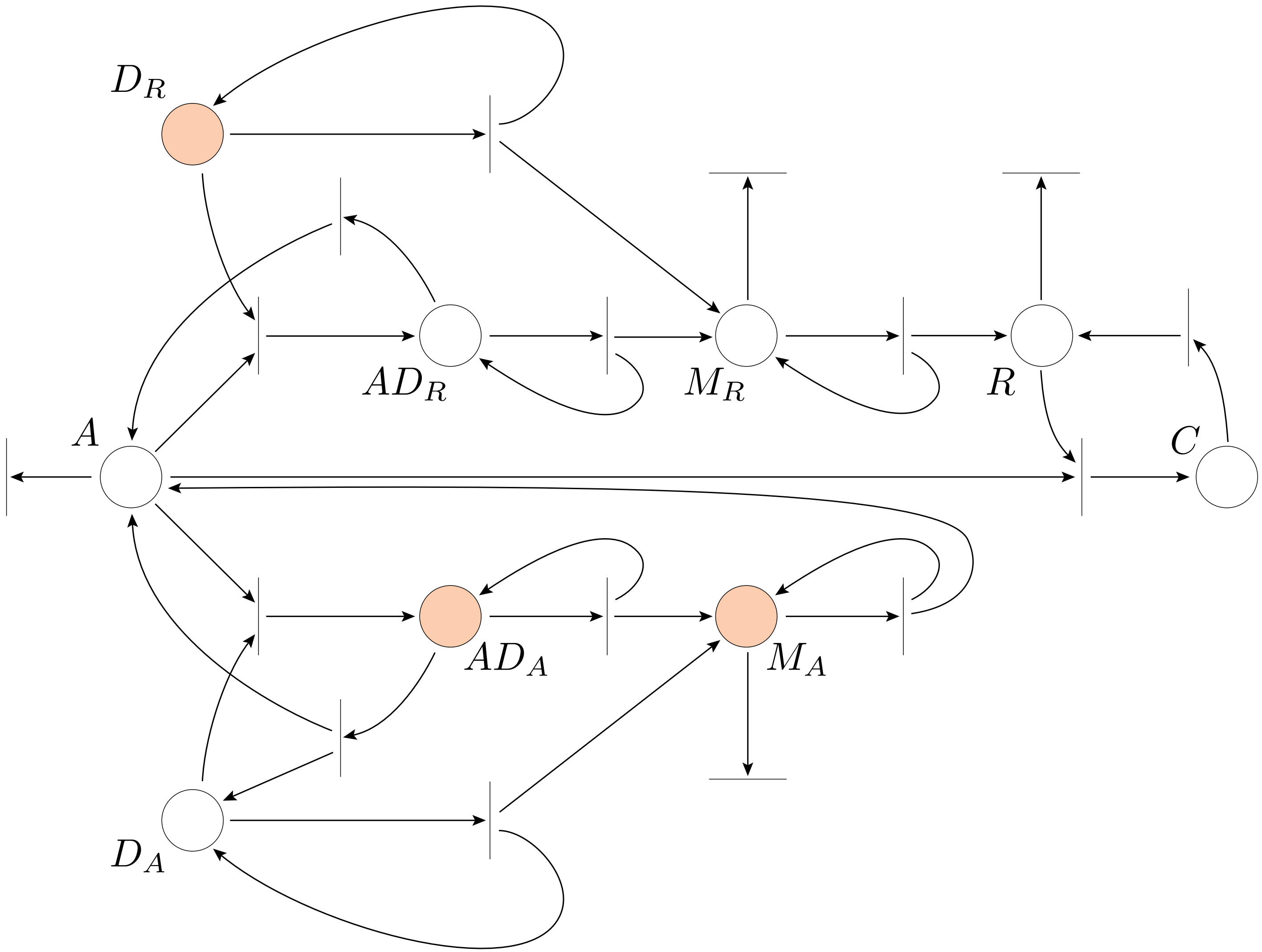

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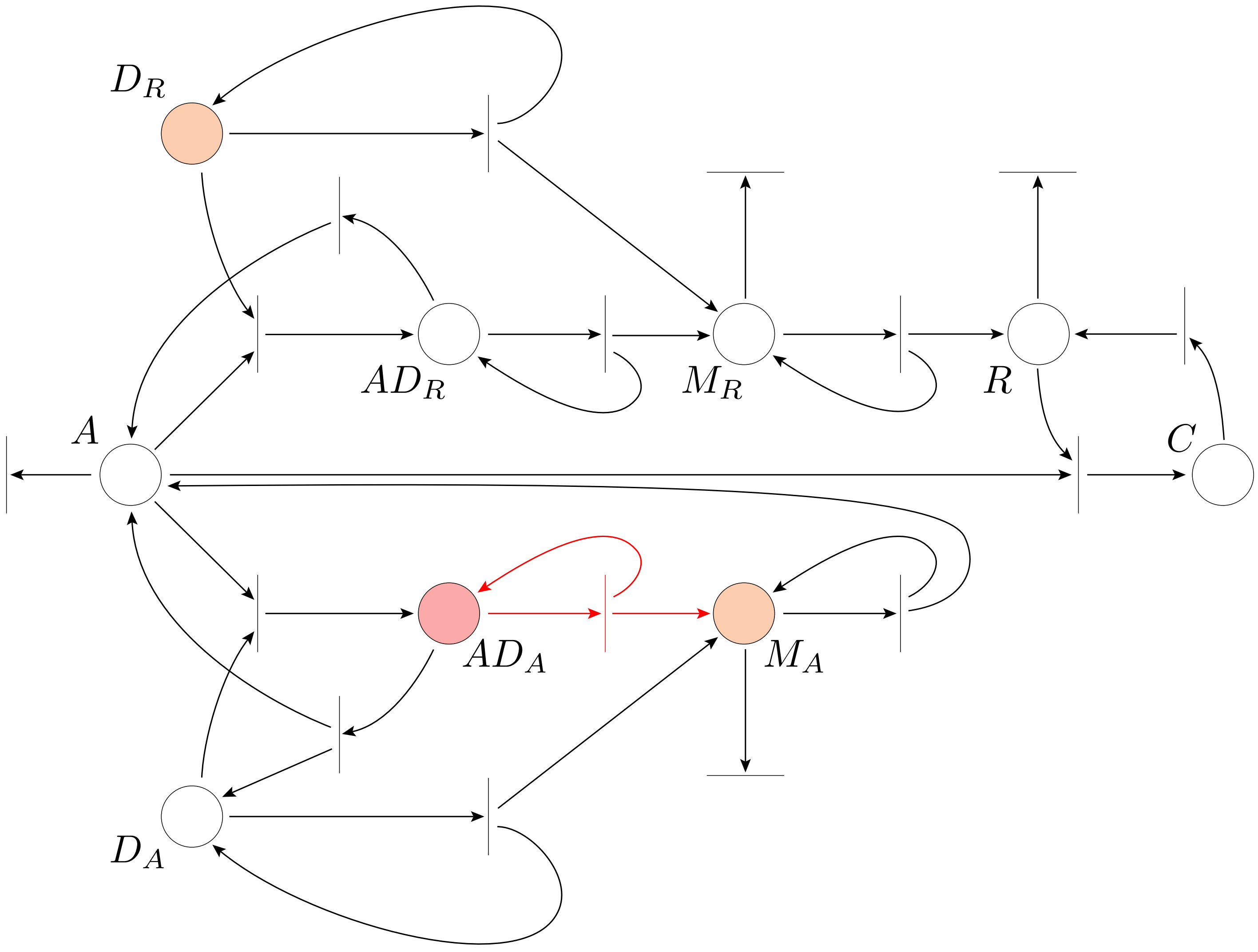

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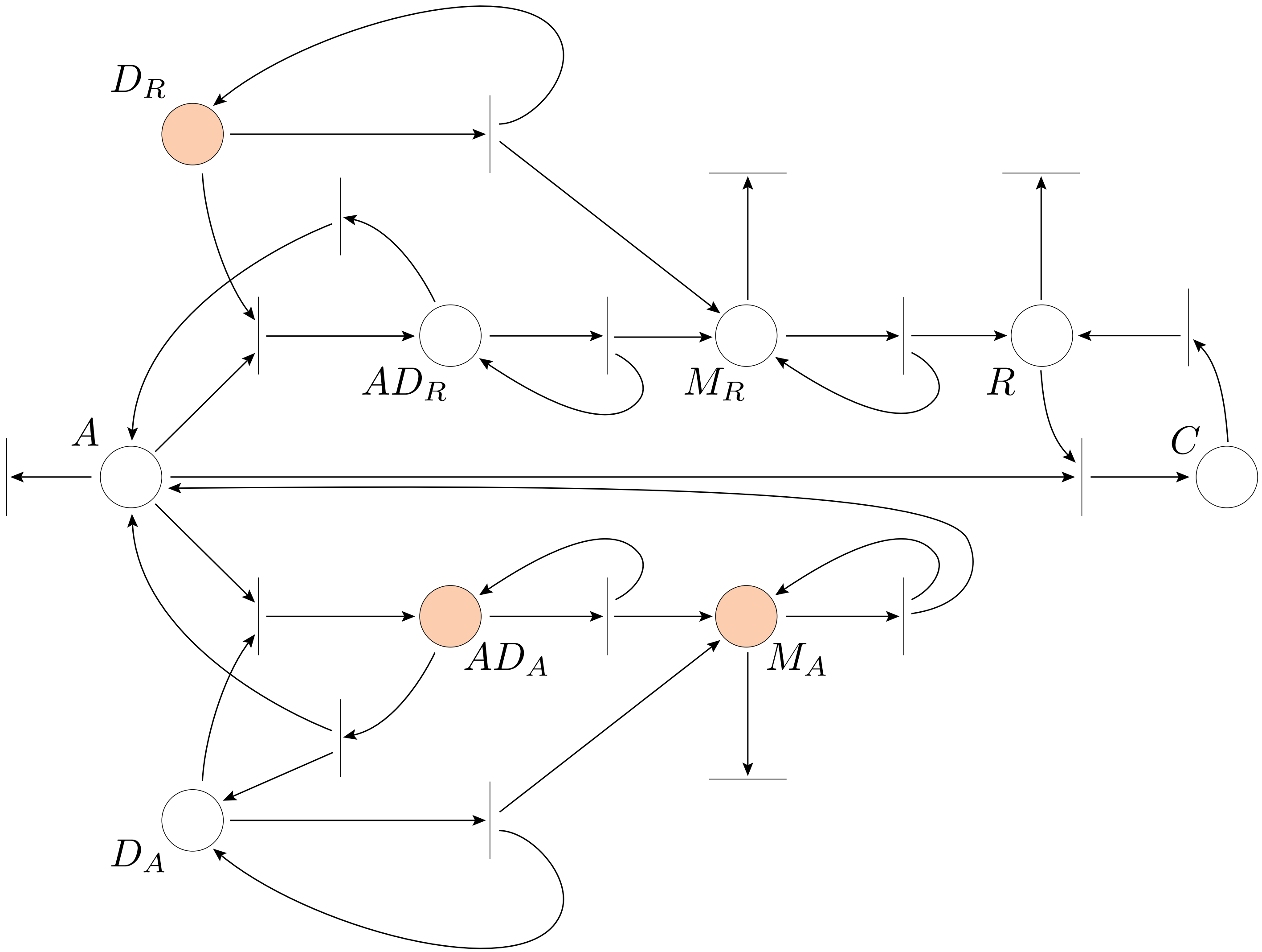

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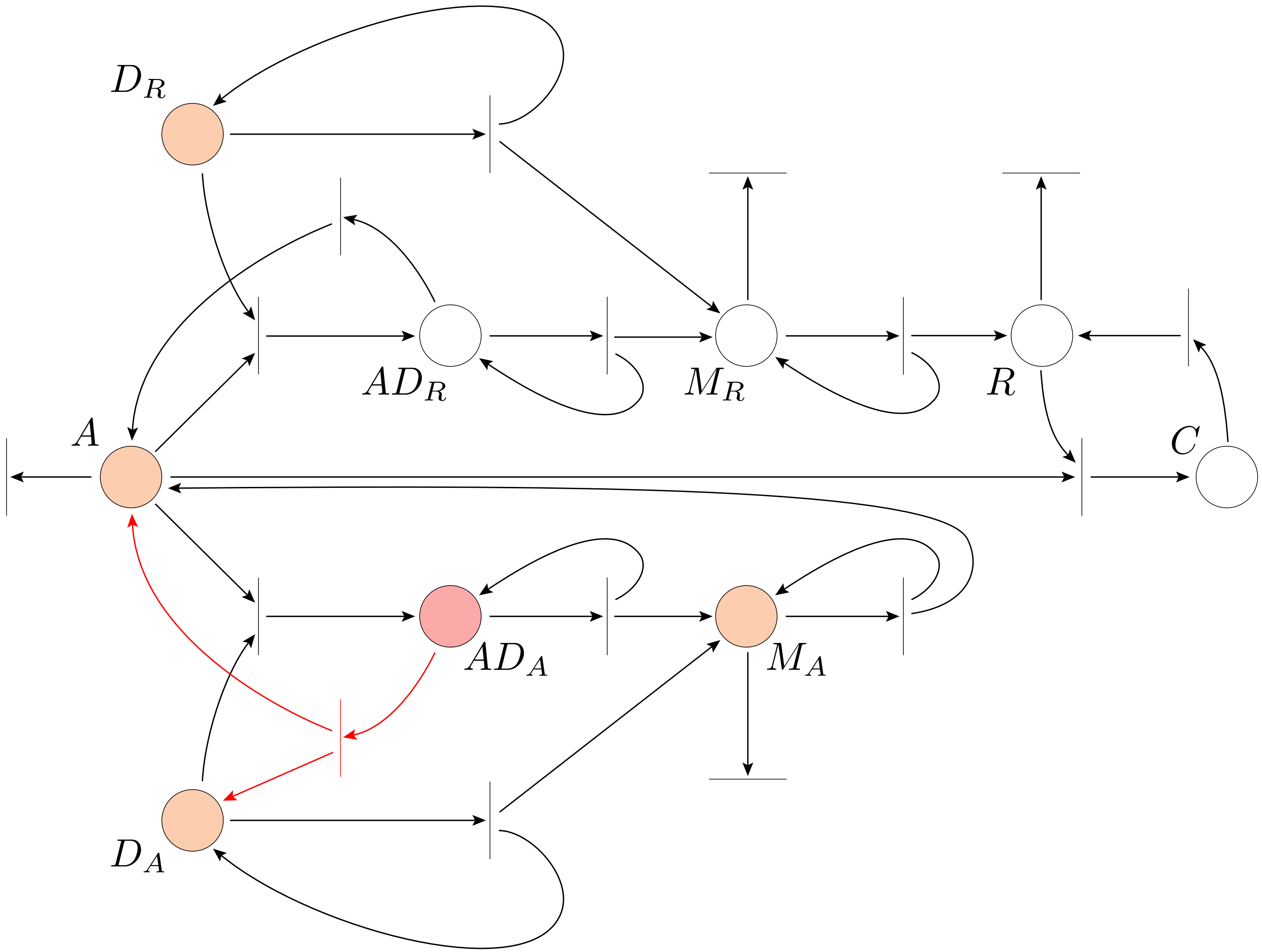

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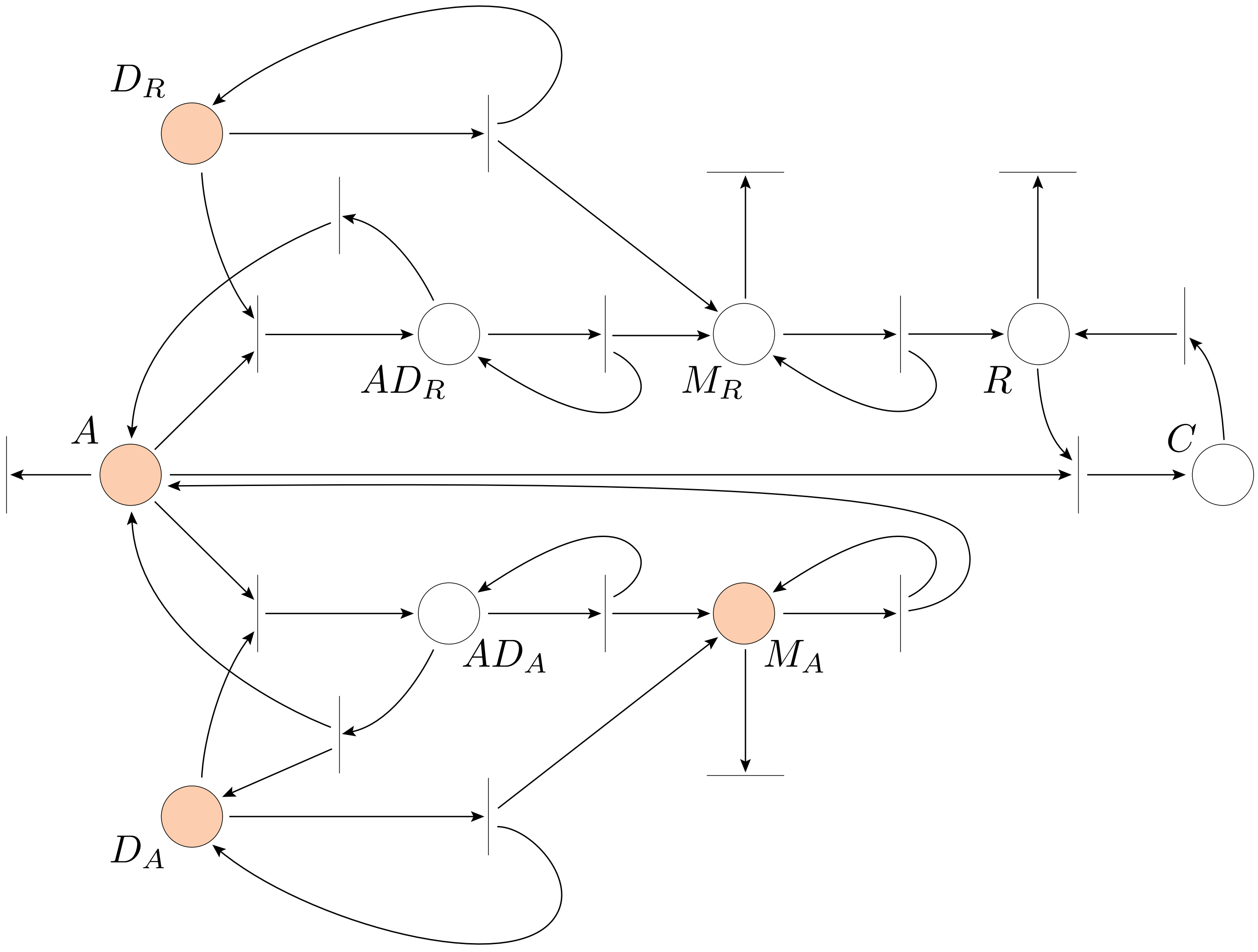

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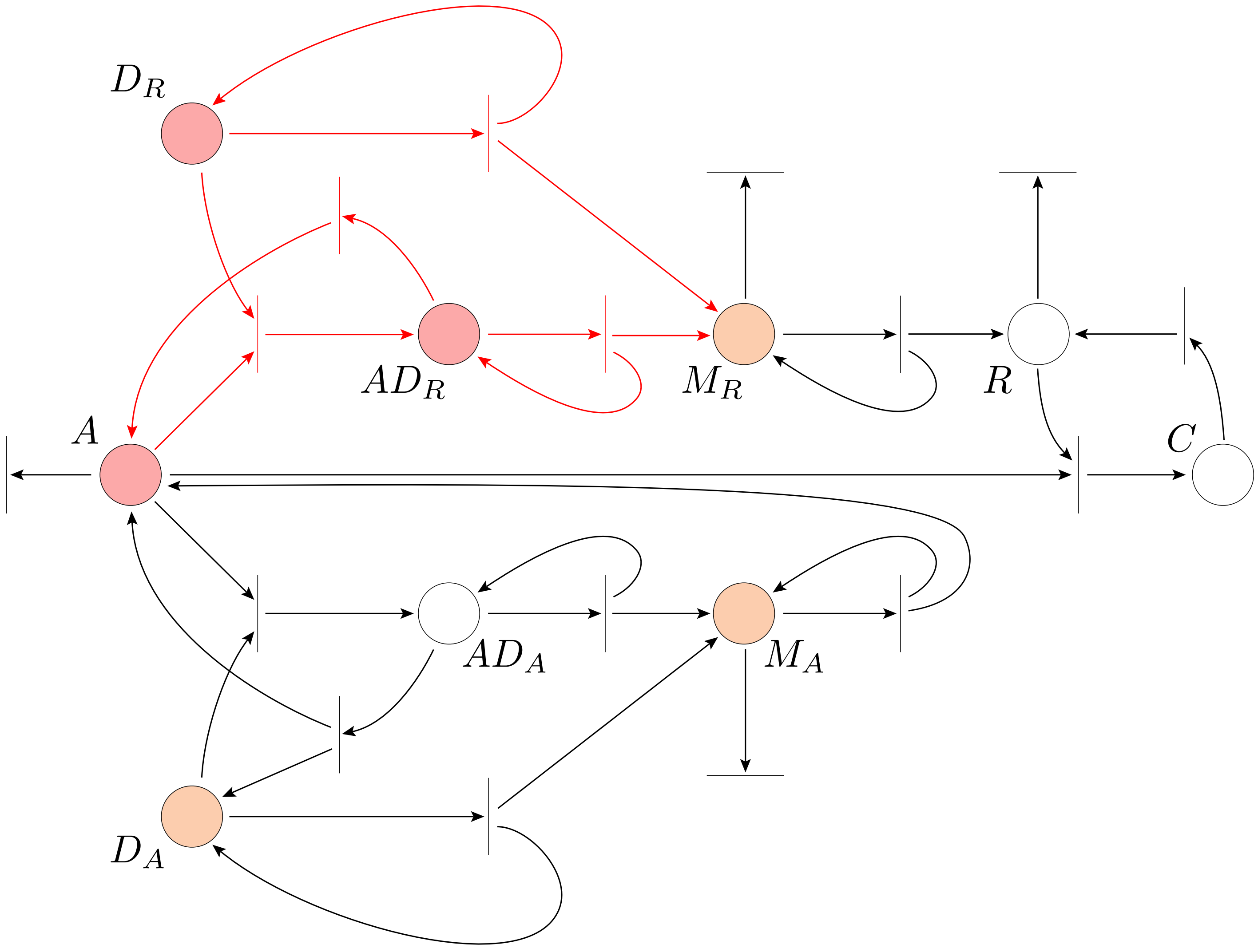

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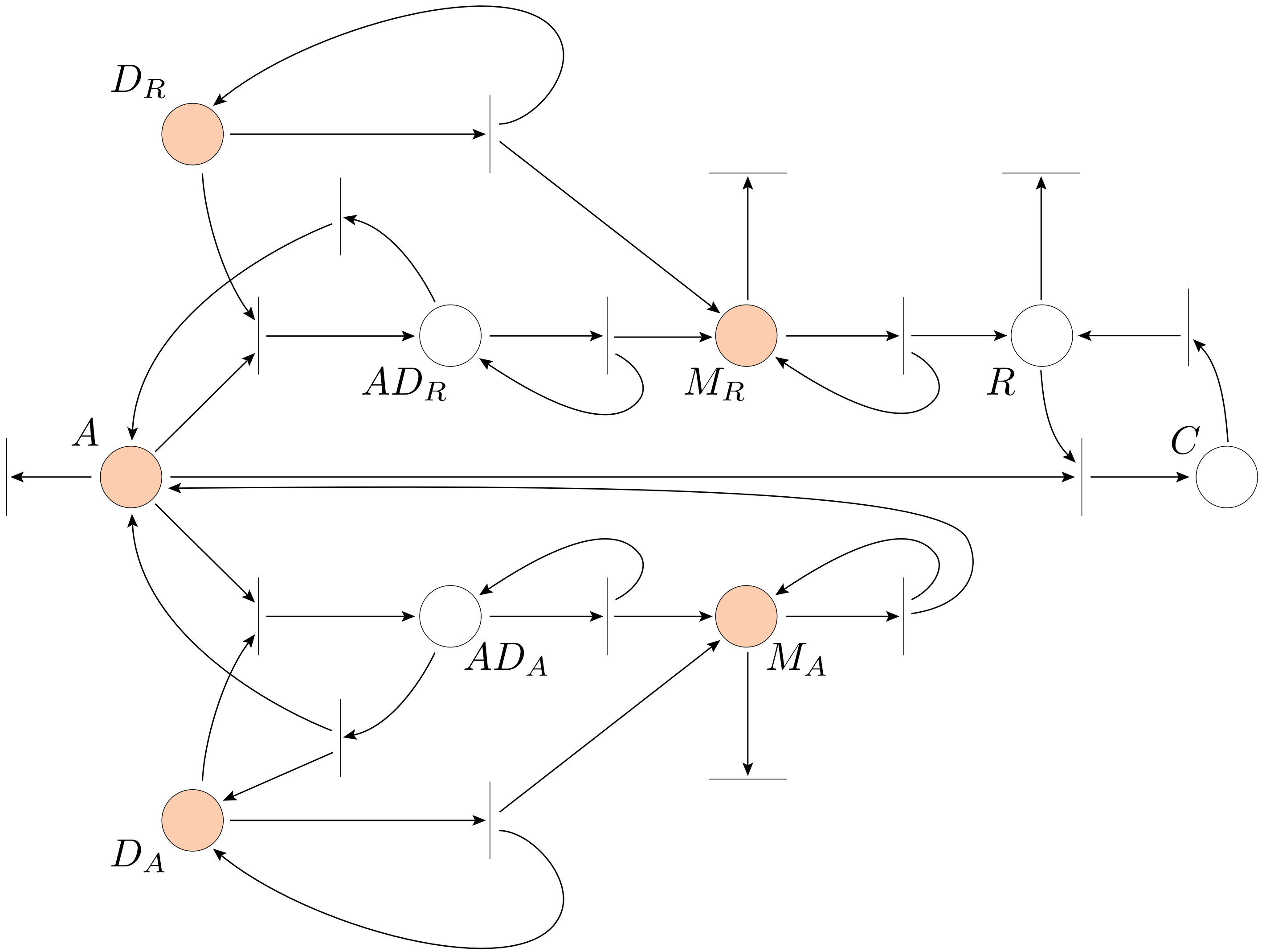

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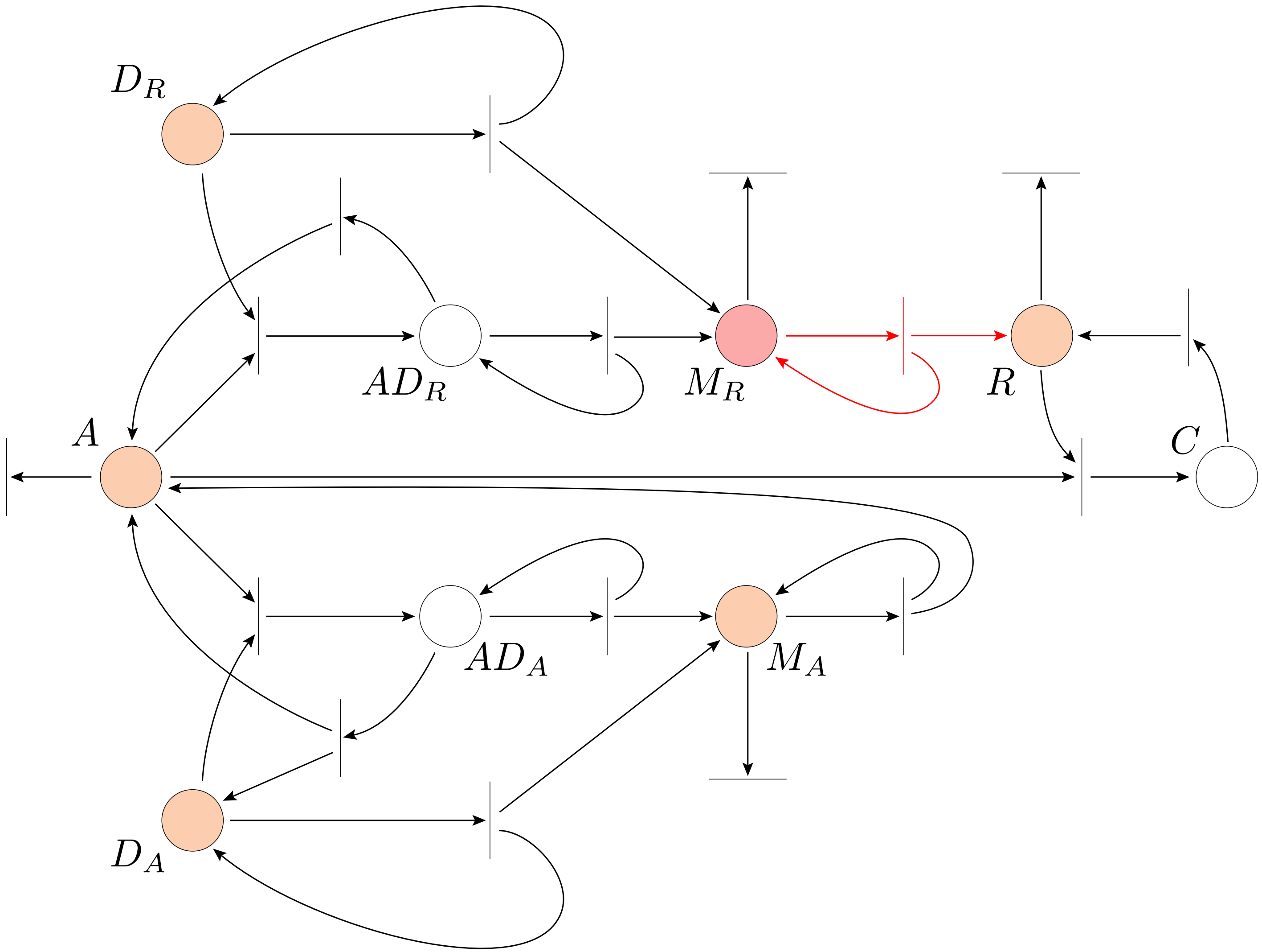

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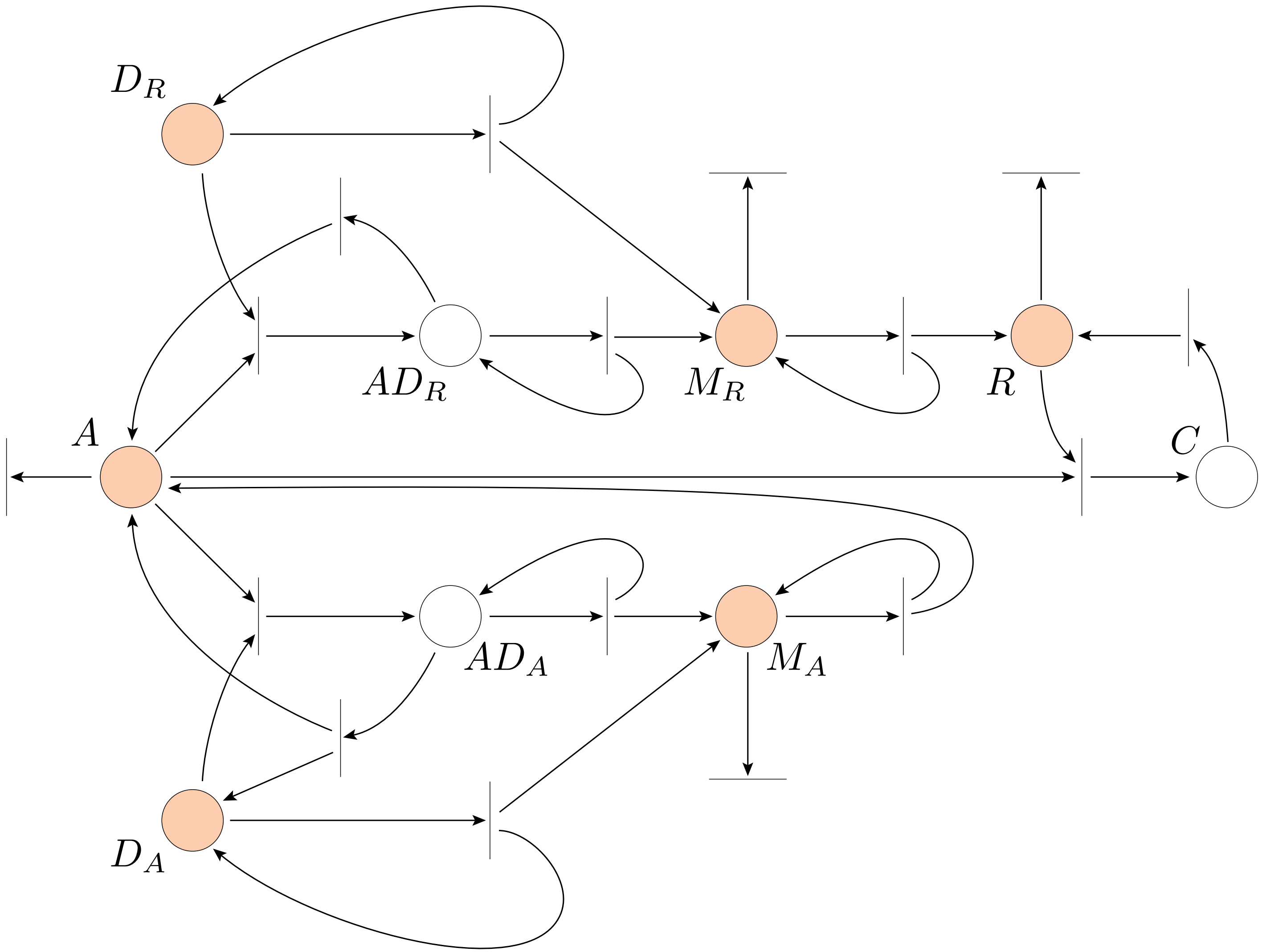

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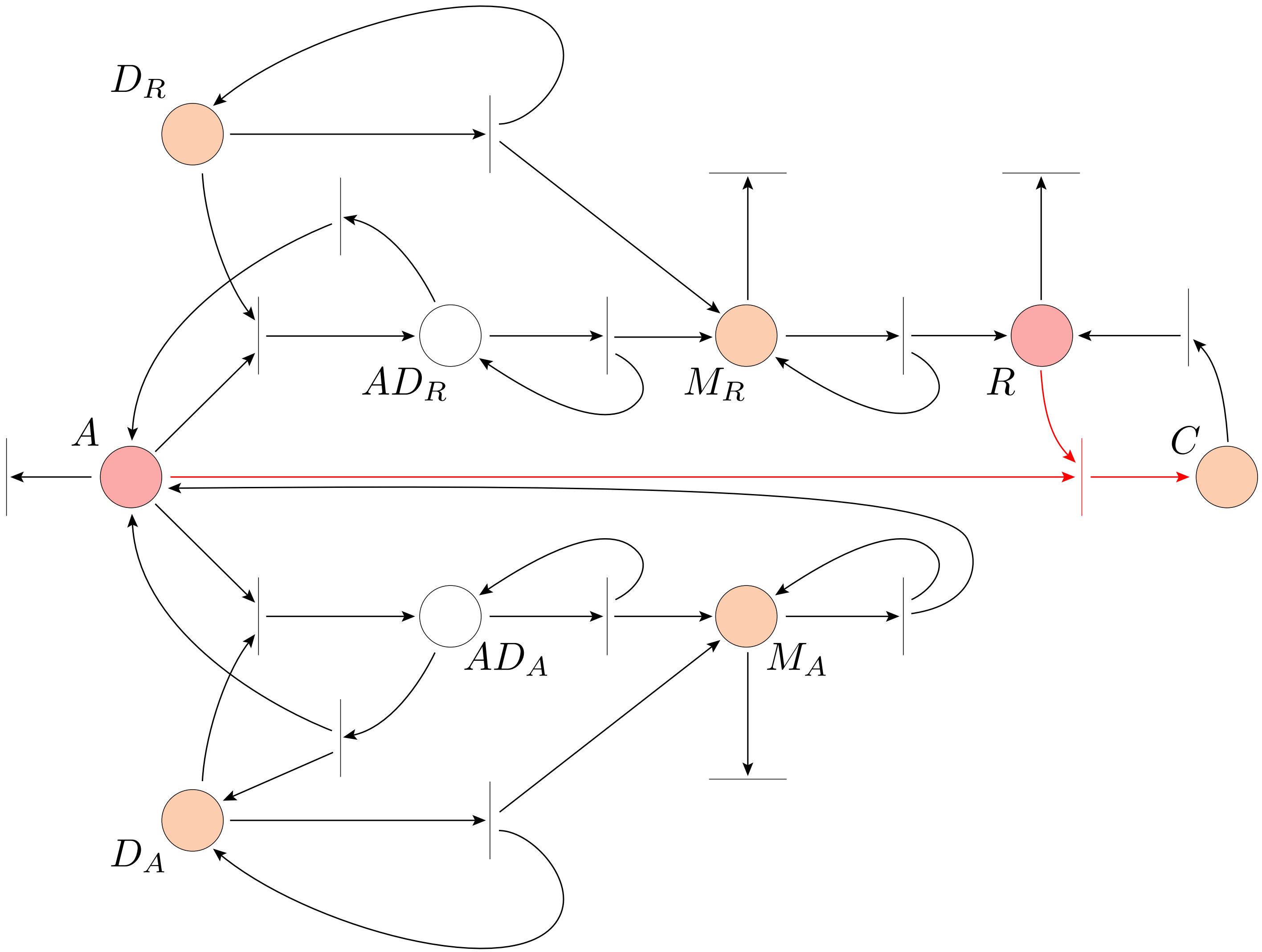

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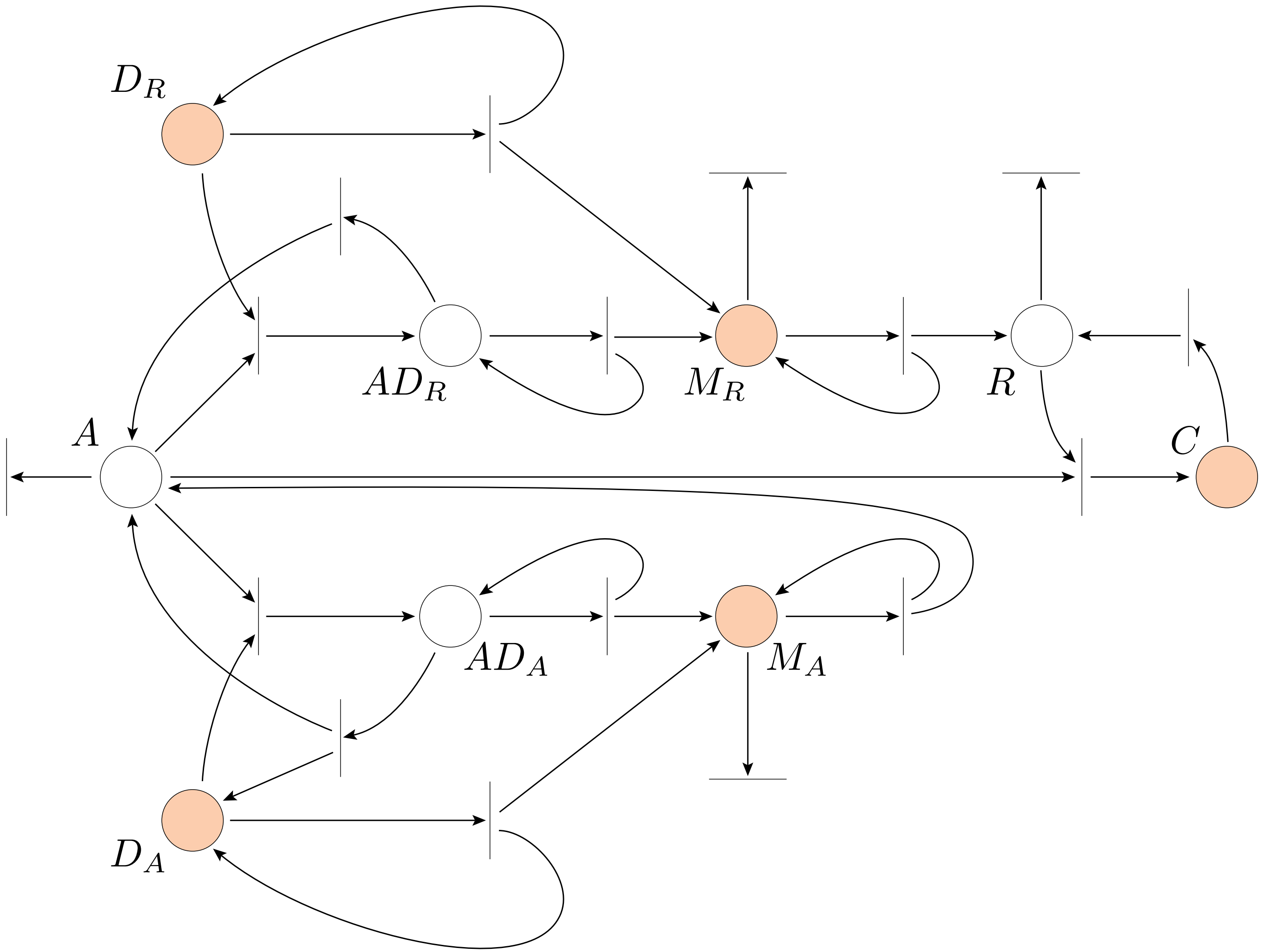

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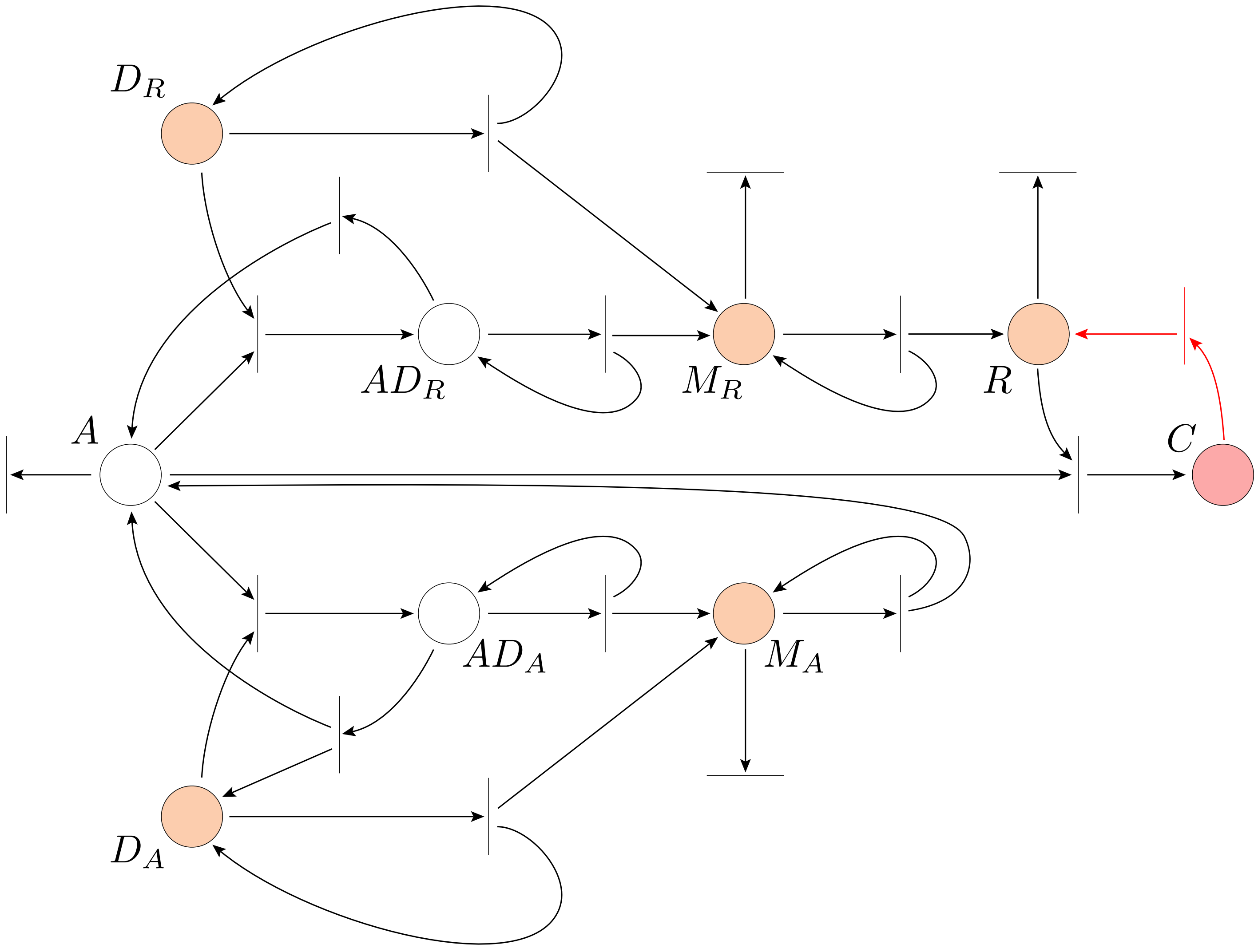

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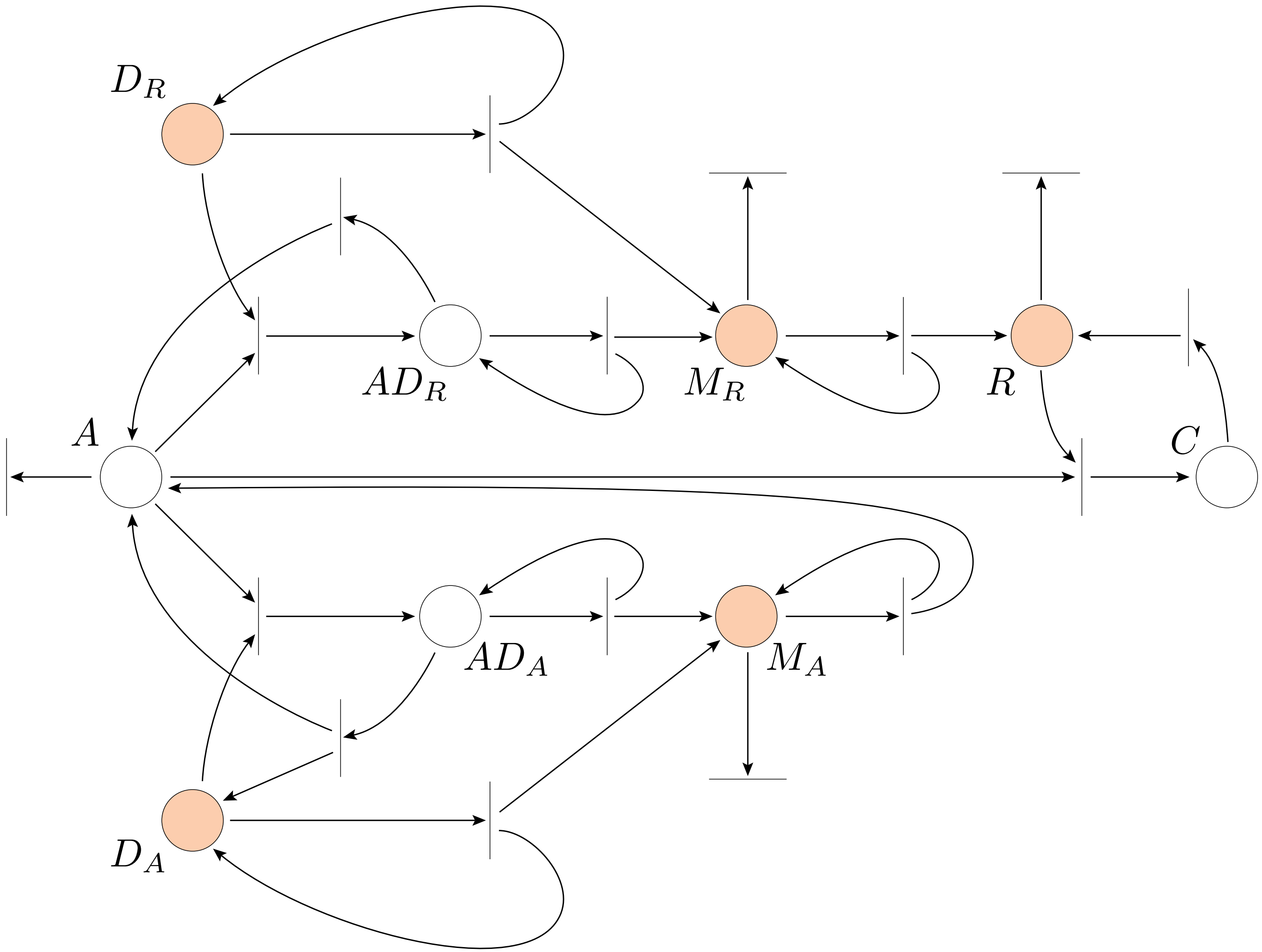

Modelling with π-Calculus

Stochastic π-Calculus model

$$D_A \stackrel{\text{def}}{=} bind_{A_{\gamma_A}}.AD_A + \tau_{\alpha_A}.(D_A \mid M_A)$$

$$AD_A \stackrel{\text{def}}{=} \tau_{\theta_A}.(D_A \mid A) + \tau_{\alpha_{A'}}.(AD_A \mid M_A)$$

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$$M_A \stackrel{\text{def}}{=} \tau_{\delta_{MA}}.\emptyset + \tau_{\beta_A}.(M_A \mid A)$$

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$$A \stackrel{\text{def}}{=} \overline{bind_{A_{\gamma_A}}}.\emptyset + \overline{bind_{R_{\gamma_R}}}.\emptyset + \overline{bind_{C_{\gamma_C}}}.\emptyset + \tau_{\delta_A}.\emptyset$$

$$R \stackrel{\text{def}}{=} bind_{C_{\gamma_C}}.C + \tau_{\delta_R}.$$

$$C \stackrel{\text{def}}{=} \tau_{\delta_A}.R$$

PEPA model: Circadian Clock

$$D_A \stackrel{\text{def}}{=} (bind_{AD_A}, \gamma_A).AD_A + (mk_{MA}, \alpha_A).D_A$$

$$AD_A \stackrel{\text{def}}{=} (unbind_{AD_A}, \theta_A).D_A + (mk_{MA}, \alpha_{A'}).AD_A$$

PEPA model: Circadian Clock

$$D_A \stackrel{\text{def}}{=} (bind_{AD_A}, \gamma_A).AD_A + (mk_{MA}, \alpha_A).D_A$$

$$AD_A \stackrel{\text{def}}{=} (unbind_{AD_A}, \theta_A).D_A + (mk_{MA}, \alpha_{A'}).AD_A$$

$$M'_A \stackrel{\text{def}}{=} (mk_{MA}, \top).M_A$$

$$M_A \stackrel{\text{def}}{=} (decay_{M_A}, \delta_{MA}).M'_A + (mk_A, \beta_A).M_A$$

PEPA model: Circadian Clock

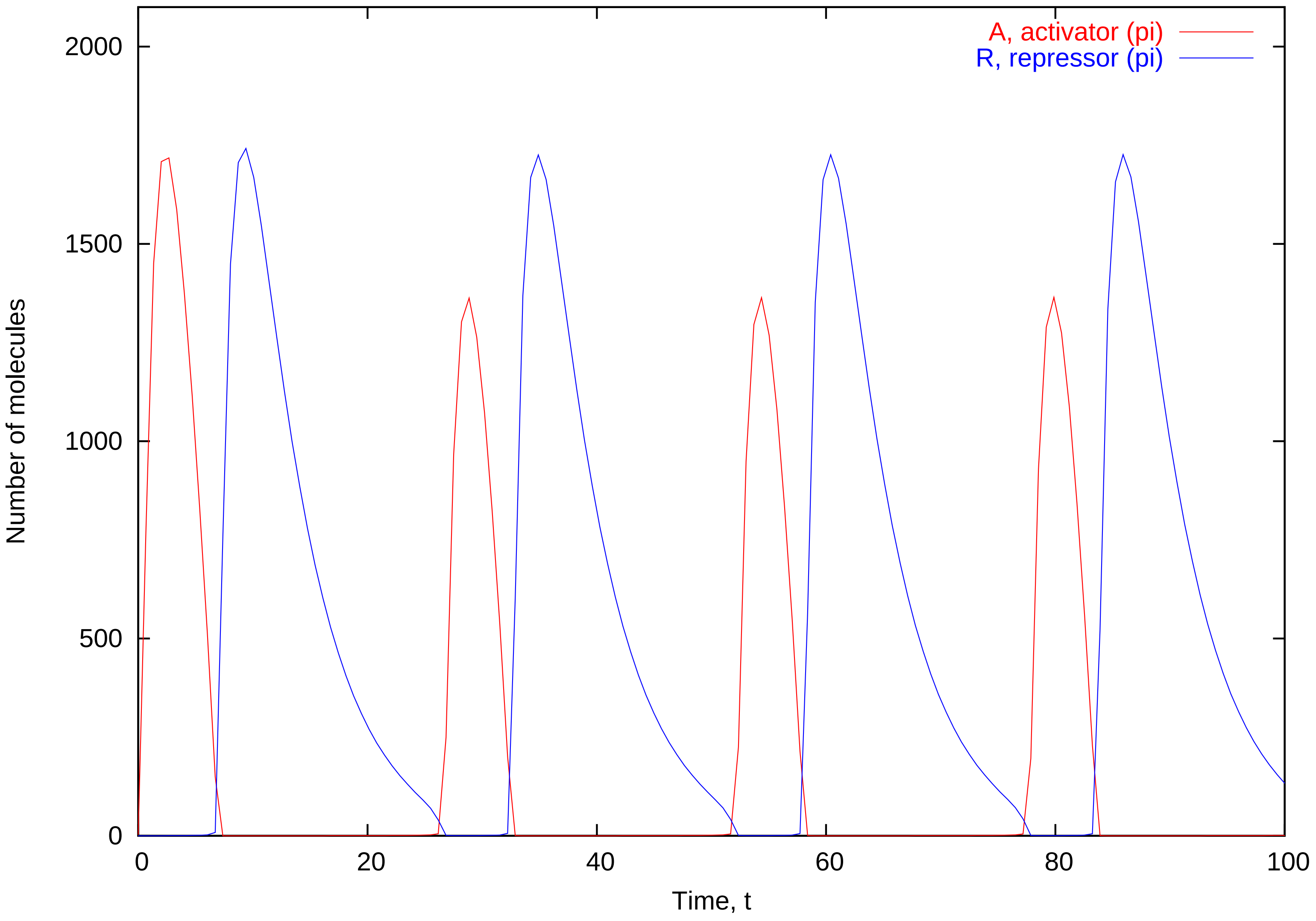
$$
\begin{aligned}
D_A &\stackrel{\text{def}}{=} (bind_{AD_A}, \gamma_A).AD_A + (mk_{MA}, \alpha_A).D_A \\
AD_A &\stackrel{\text{def}}{=} (unbind_{AD_A}, \theta_A).D_A + (mk_{MA}, \alpha_{A'}).AD_A
\end{aligned}
$$

$$
\begin{aligned}
M'_A &\stackrel{\text{def}}{=} (mk_{MA}, \top).M_A \\
M_A &\stackrel{\text{def}}{=} (decay_{M_A}, \delta_{MA}).M'_A + (mk_A, \beta_A).M_A
\end{aligned}
$$

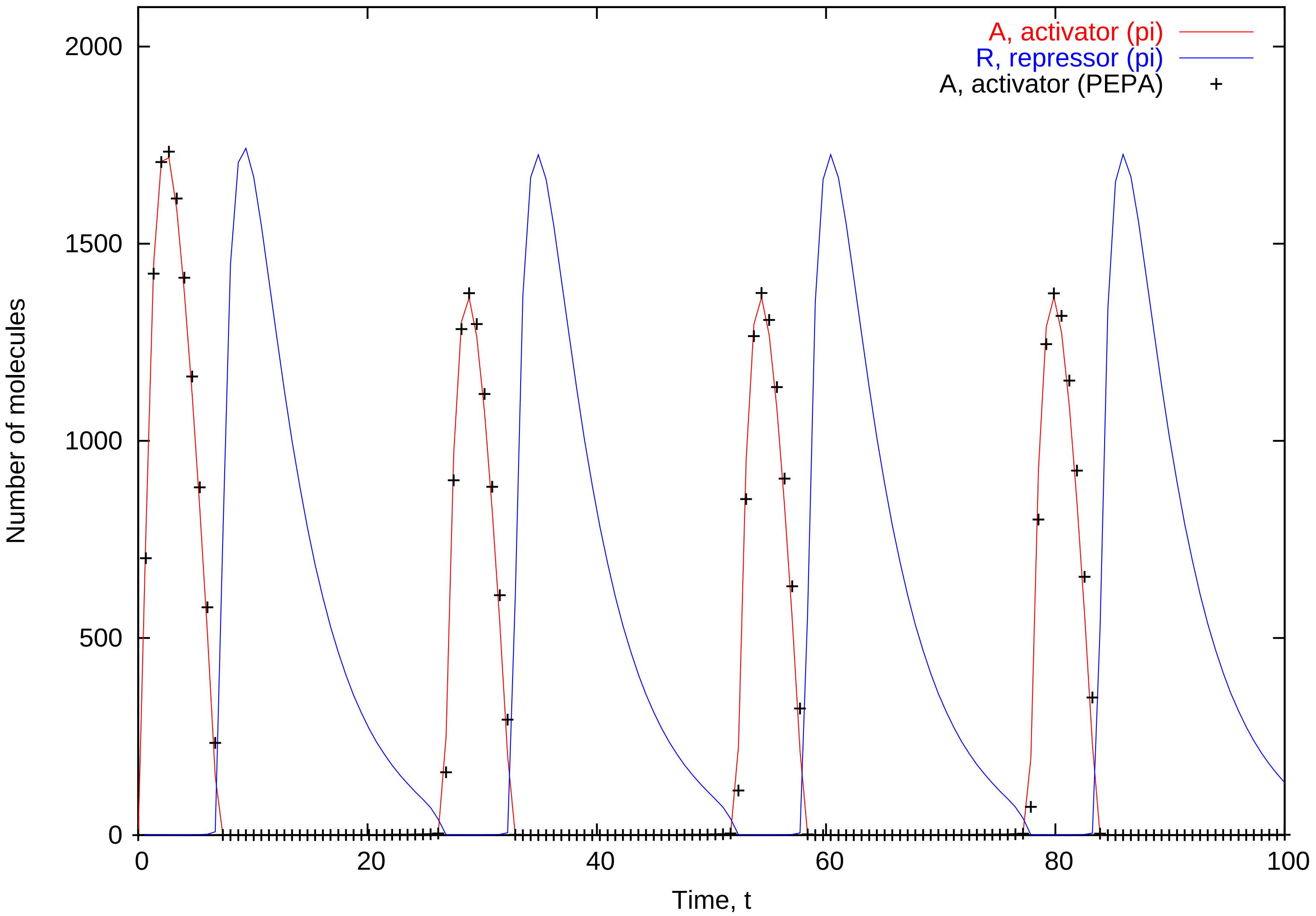
$$
\begin{aligned}
A' &\stackrel{\text{def}}{=} (mk_A, \top).A \\
A &\stackrel{\text{def}}{=} (bind_{AD_A}, \gamma_A).A_{D_A} + (bind_{AD_R}, \gamma_R).A_{D_R} \\
&\quad + (bind_{AR}, \gamma_C).A_C + (decay_A, \delta_A).A'
\end{aligned}
$$

$$\ldots$$

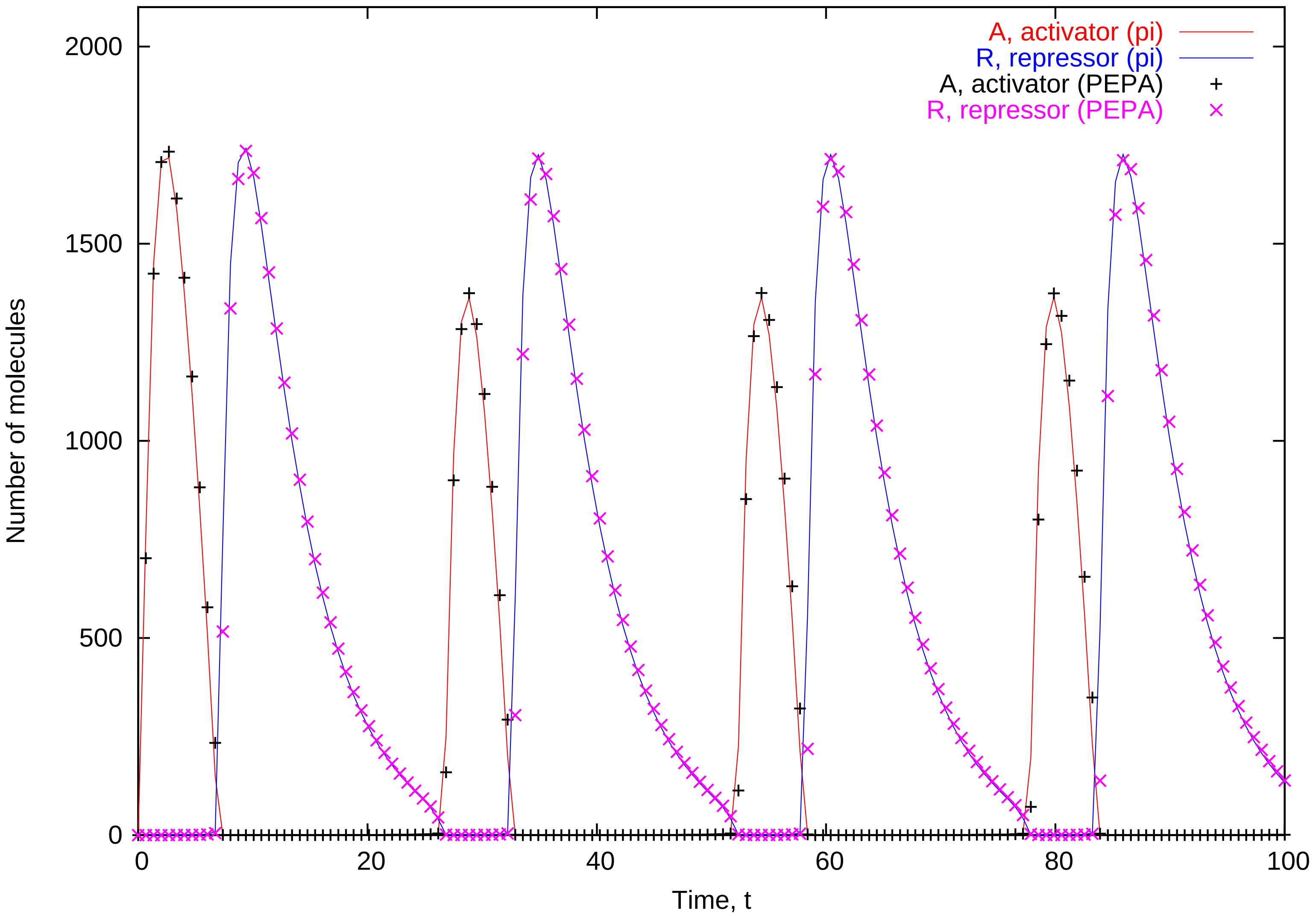
Results: π v PEPA



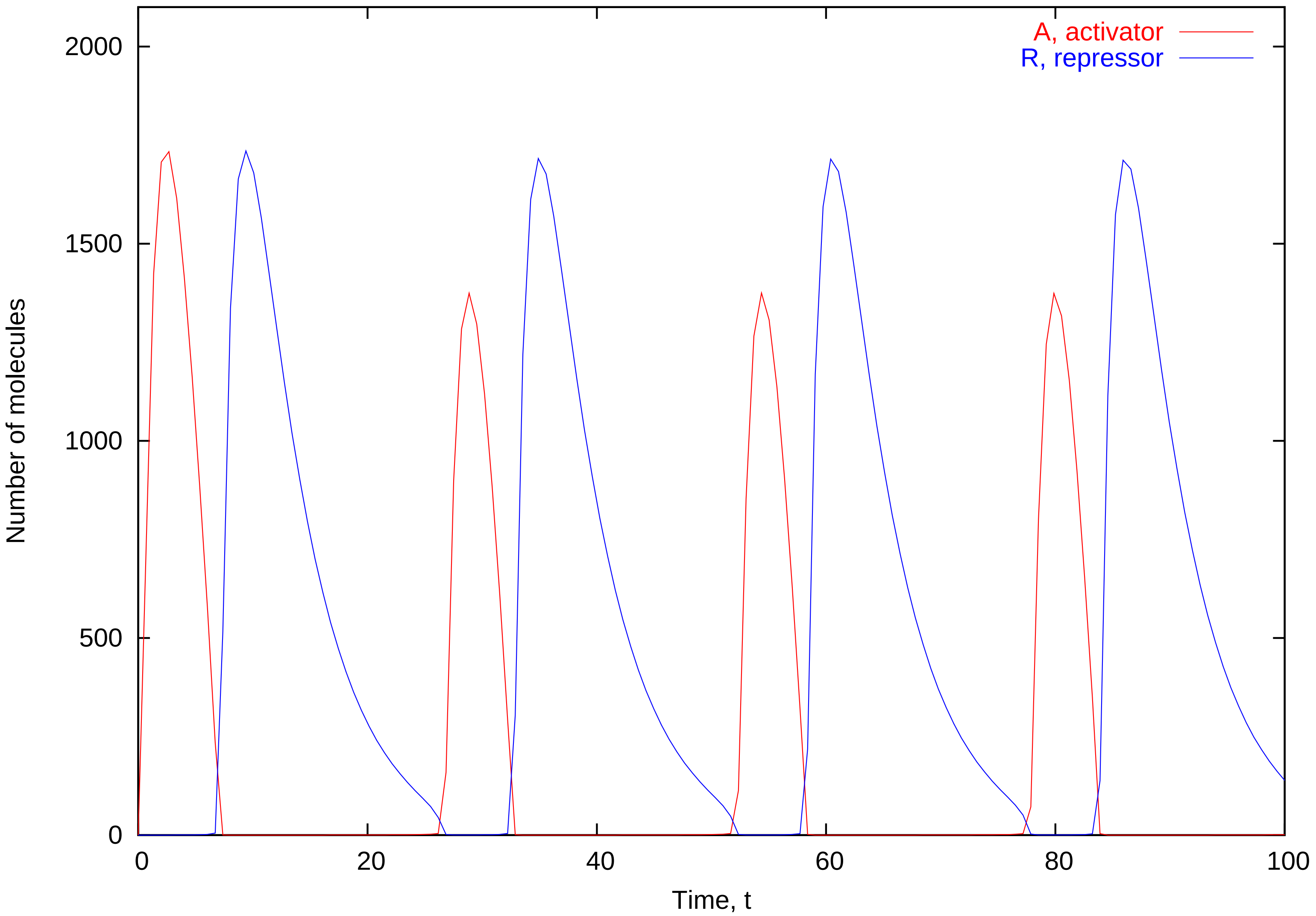
Results: π v PEPA



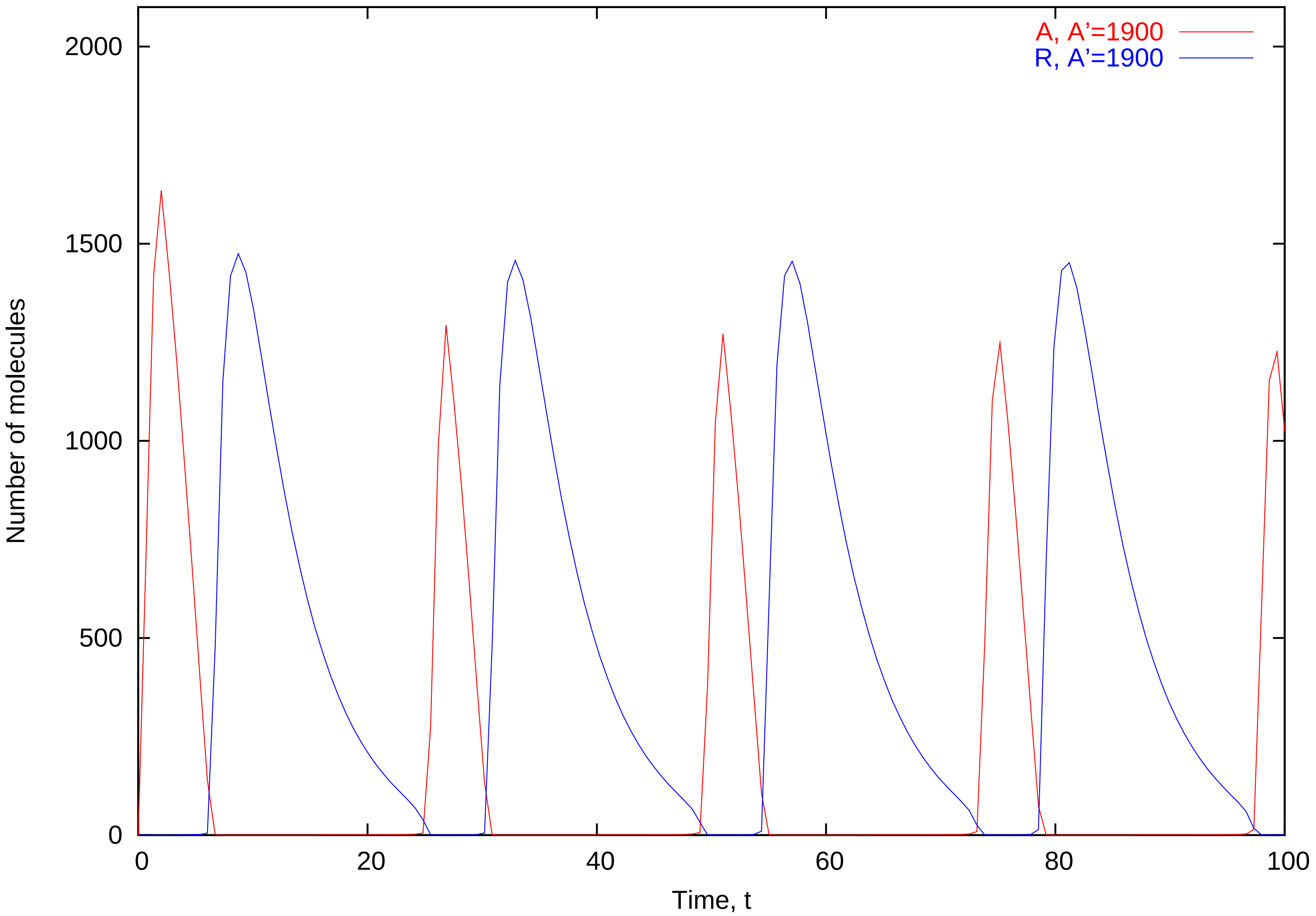
Results: π v PEPA



Limiting protein A: PEPA



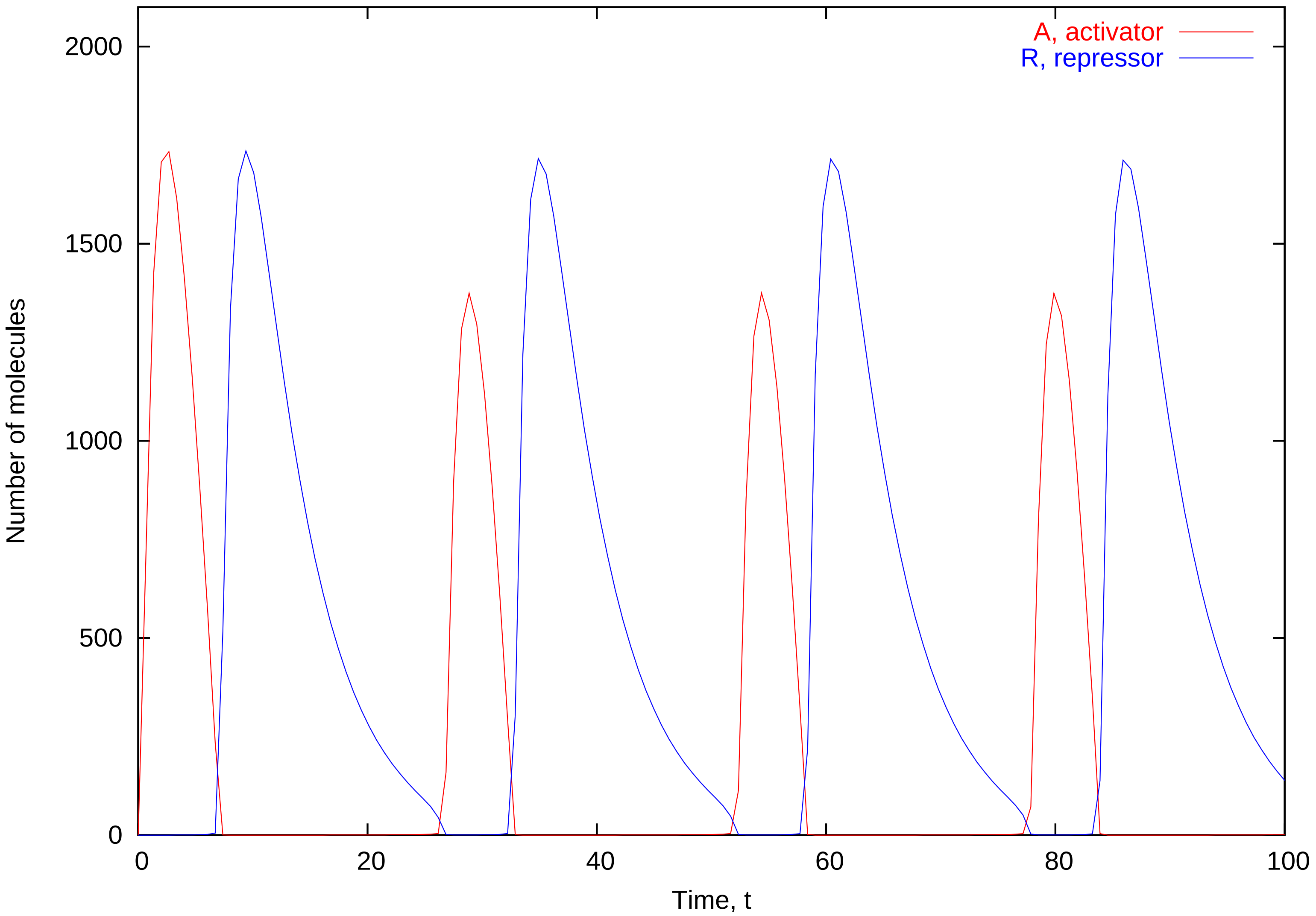
Limiting protein A: PEPA



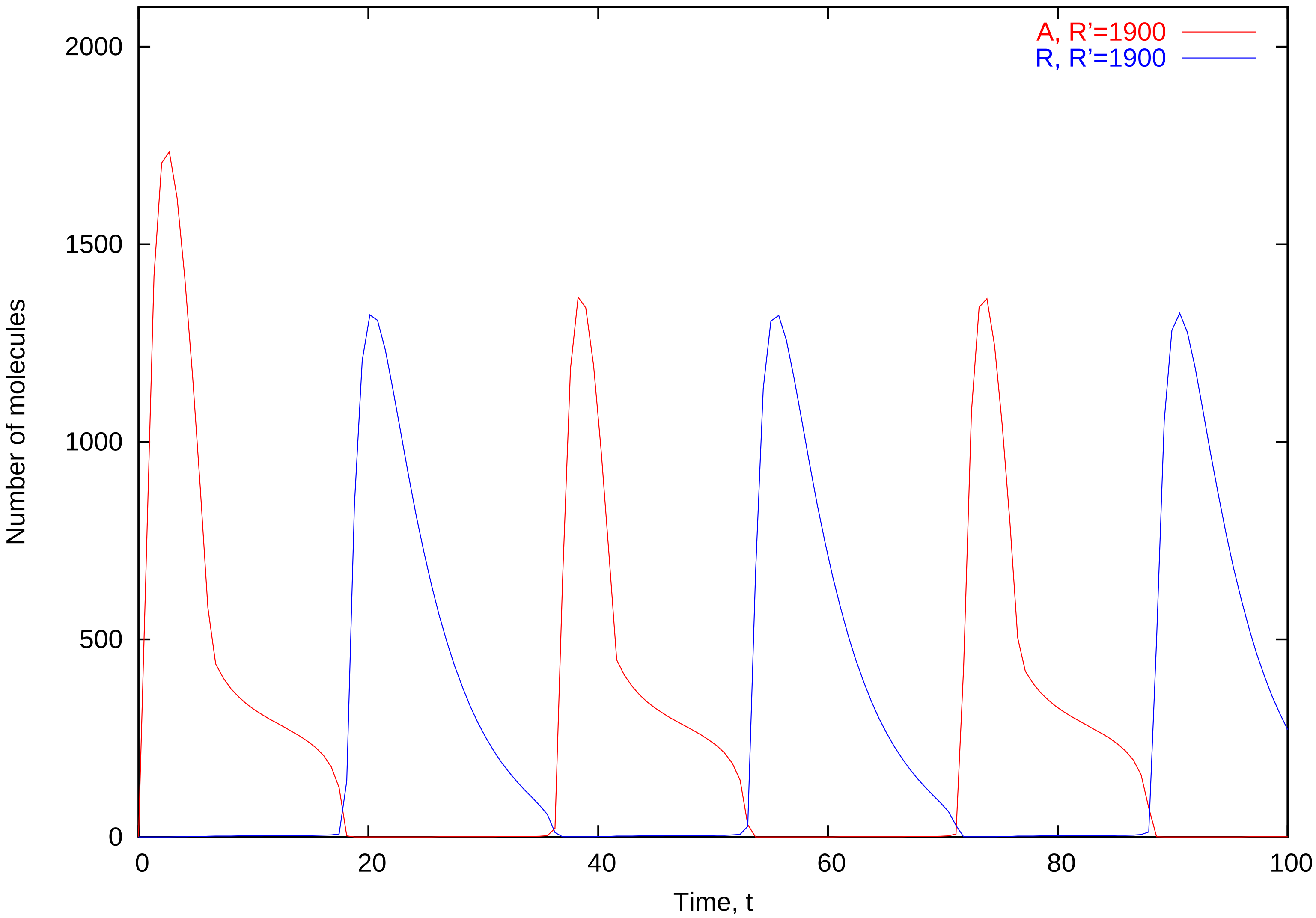
Question...

- If A restriction makes the clock fire early:
- ...Why am I late...?
- ...not enough R perhaps?

Limiting protein R: PEPA



Limiting protein R: PEPA



The Nature of Synchronisation (in Nature)

- The type of synchronisation/reaction between sets of molecules determines:
  - ODE translation
  - stochastic simulaton
- Synchronisation/reaction rate is affected by:
  - Location of molecules
  - Shape of molecules
  - How molecules are moving during reaction phase

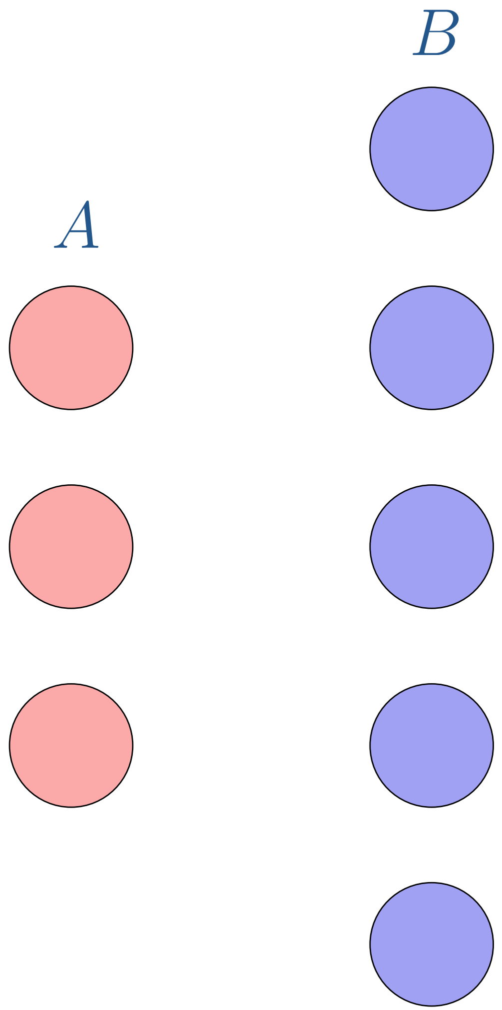
Synchronisation: Mass action

- Reaction between e.g. well-mixed fluids and gases
- Molecules diffuse (Brownian motion)
- Molecules can potentially react with any other co-reagant molecule
- Example reaction:

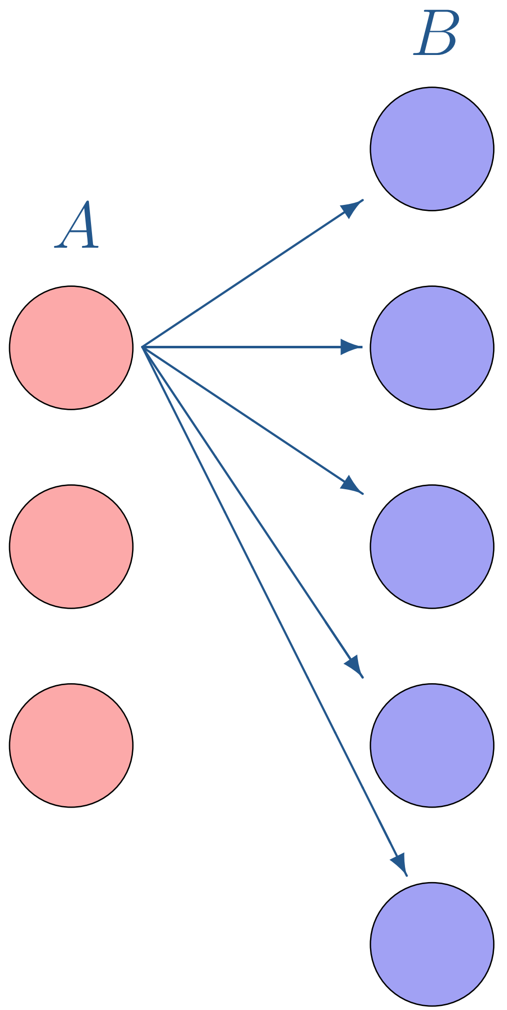
$$A + B \xrightarrow{\lambda} AB$$

- Initially m A molecules, n B molecules

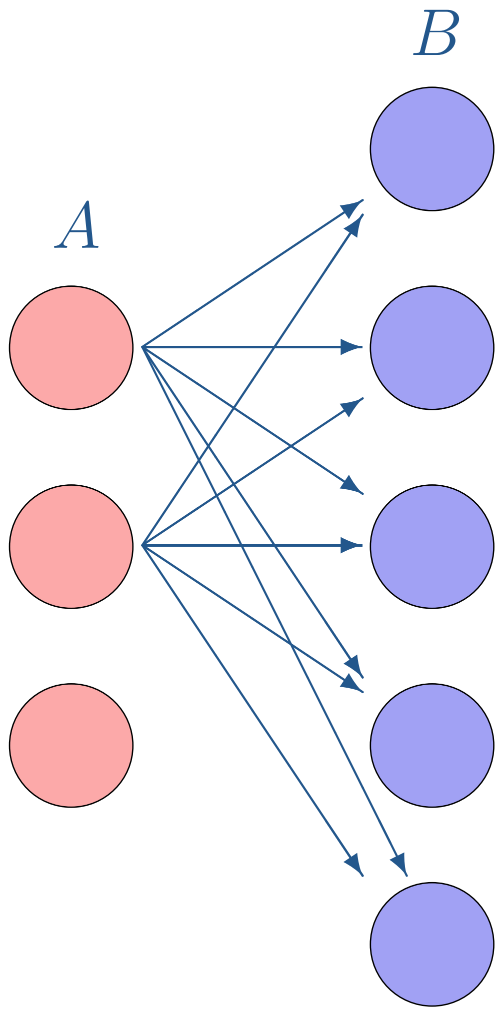
Synchronisation: Mass action



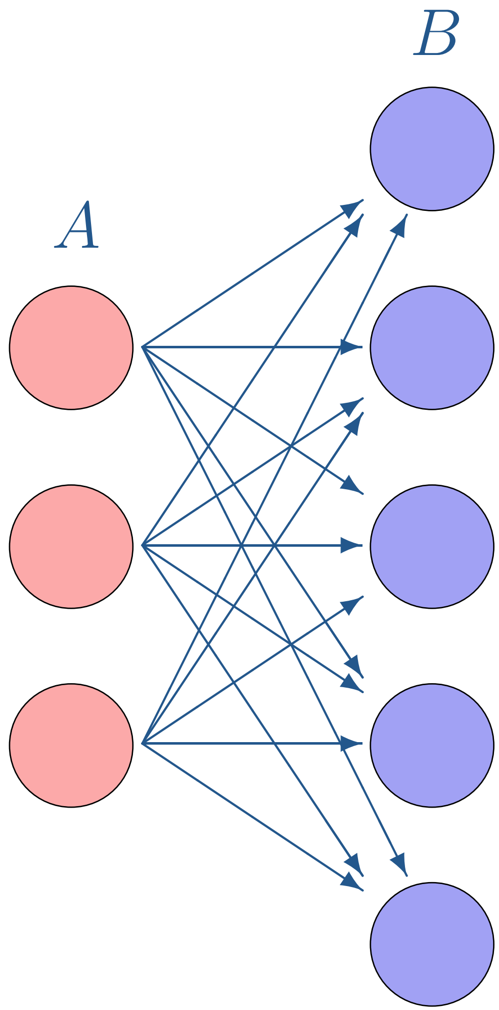
Synchronisation: Mass action



Synchronisation: Mass action

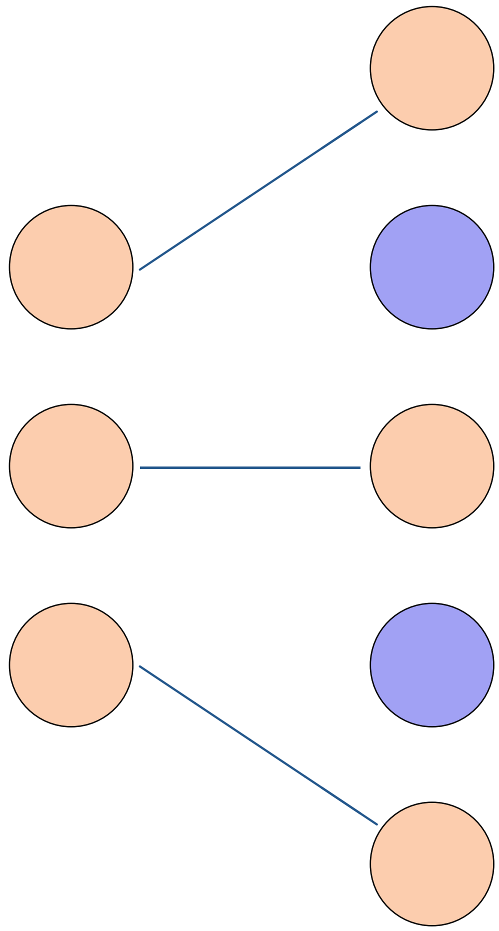


Synchronisation: Mass action



- Total number of possible interactions: mn

Synchronisation: Mass action



- Total number of actual AB products: $\min(m, n)$

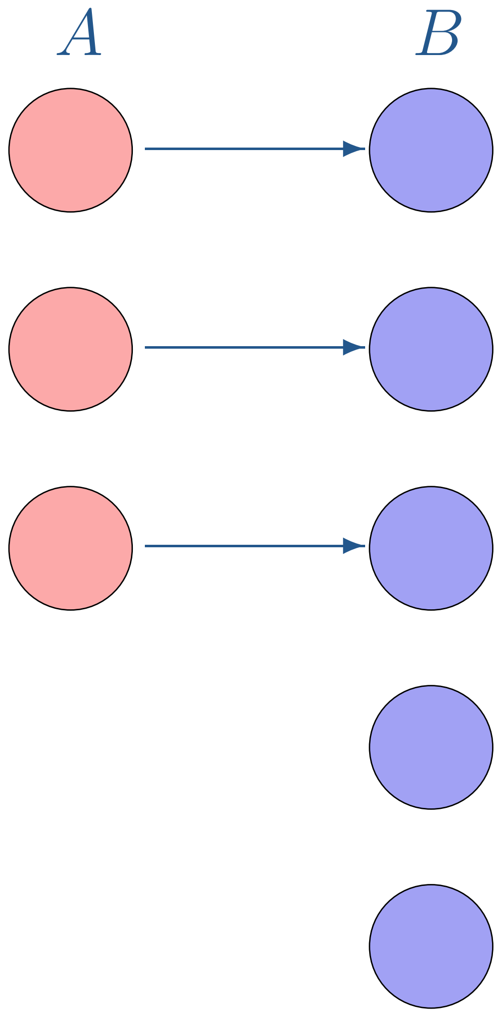
Synchronisation: Local action

- Reaction between e.g. surface of two solids, two jellies, two very viscous fluids
- No molecule diffusion
- Molecules react with closest local neighbour
- No reaction competition
- Example reaction:

$$A + B \xrightarrow{\lambda} AB$$

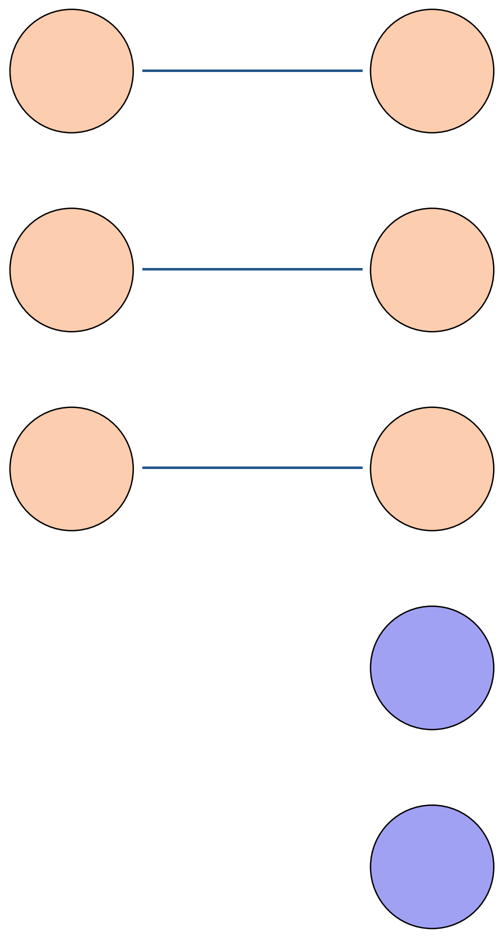
- Initially m A molecules, n B molecules

Synchronisation: Local action



- Total number of possible reactions: $\min(m, n)$

Synchronisation: Local action



- Total number of AB products: $\min(m, n)$

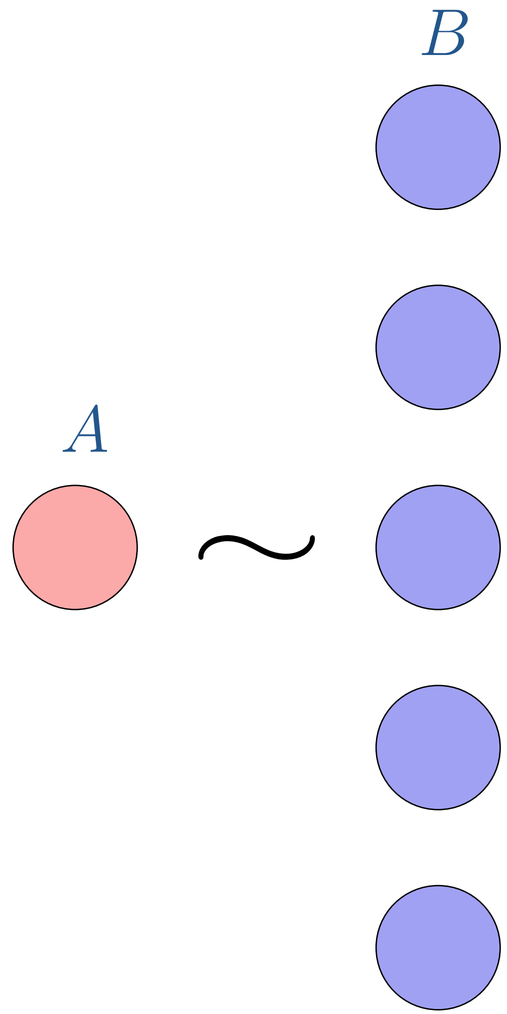
Synchronisation: Passive action

- Reaction catalysed by one or more passive molecules
- Heavily spatially dependent on catalyst shape/configuration
- Example reaction:

$$A + B \xrightarrow{\lambda} A + B'$$

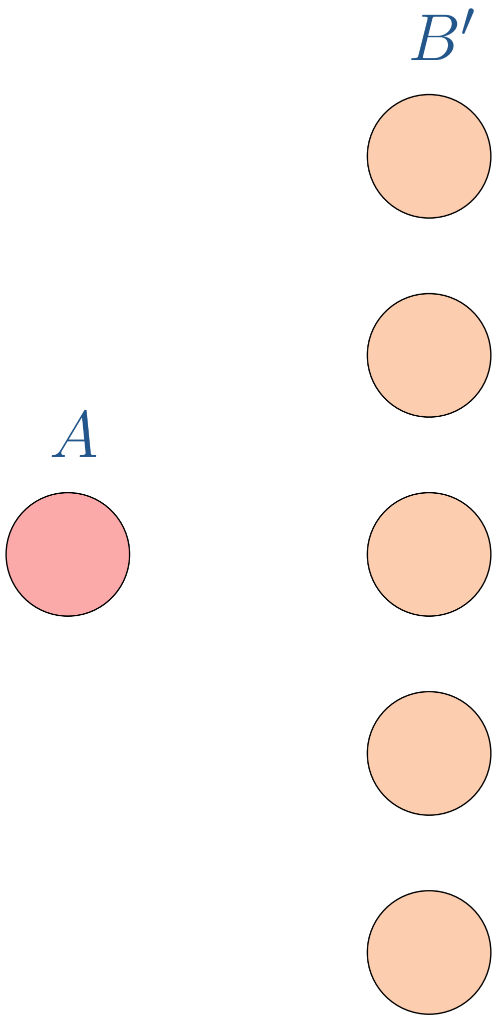
- Initially 1 A molecule, n B molecules

Synchronisation: Passive action



- Total number of possible reactions: $I(m > 0)\, n$

Synchronisation: Catalyst



- Total number of B' products: $I(m > 0)\, n$

Synchronisation and ODEs

- For a reaction, starting: $A + B \xrightarrow{\lambda}$
  - Mass action leads to ODEs of form:

$$\frac{\mathrm{d}}{\mathrm{d}t}[A] = -\lambda[A][B]$$

  - Local action leads to ODEs of form:

$$\frac{\mathrm{d}}{\mathrm{d}t}[A] = -\lambda \min([A], [B])$$

  - Passive action leads to ODEs of form:

$$\frac{\mathrm{d}}{\mathrm{d}t}[A] = -\lambda I([A] > 0)\,[B]$$

Synchronisation and SPA

- Local action maps well onto *active synchronisation* in PEPA

$$
\begin{aligned}
Sys &\stackrel{\text{def}}{=} A[m] \underset{\{a\}}{\bowtie} B[n] \\
A &\stackrel{\text{def}}{=} (a, \lambda).A' \\
B &\stackrel{\text{def}}{=} (a, \lambda).B'
\end{aligned}
$$

Synchronisation and SPA

- Passive action maps well onto *passive synchronisation* in PEPA

$$
\begin{aligned}
Sys &\stackrel{\text{def}}{=} A[m] \underset{\{a\}}{\bowtie} B[n] \\
A &\stackrel{\text{def}}{=} (a, \lambda).A' \\
B &\stackrel{\text{def}}{=} (a, \top).B'
\end{aligned}
$$

- Mass action, until now, has not been used in SPA world (not TIPP!)