# Why I'm always late!

***Dagstuhl Seminar***

Jeremy Bradley

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Department of Computing, Imperial College London

Produced with prosper and LaTeX

# With thanks to...

- Stephen Gilmore, Edinburgh
- Jane Hillston, Edinburgh
- Nigel Thomas, Newcastle
- Tom Thorne, Imperial College
- Helen Wilson, University College London


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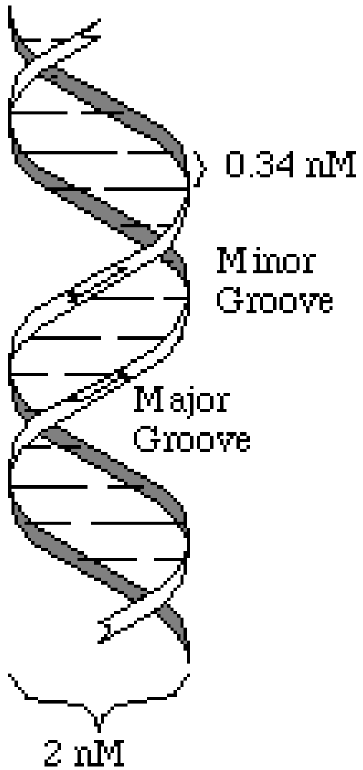
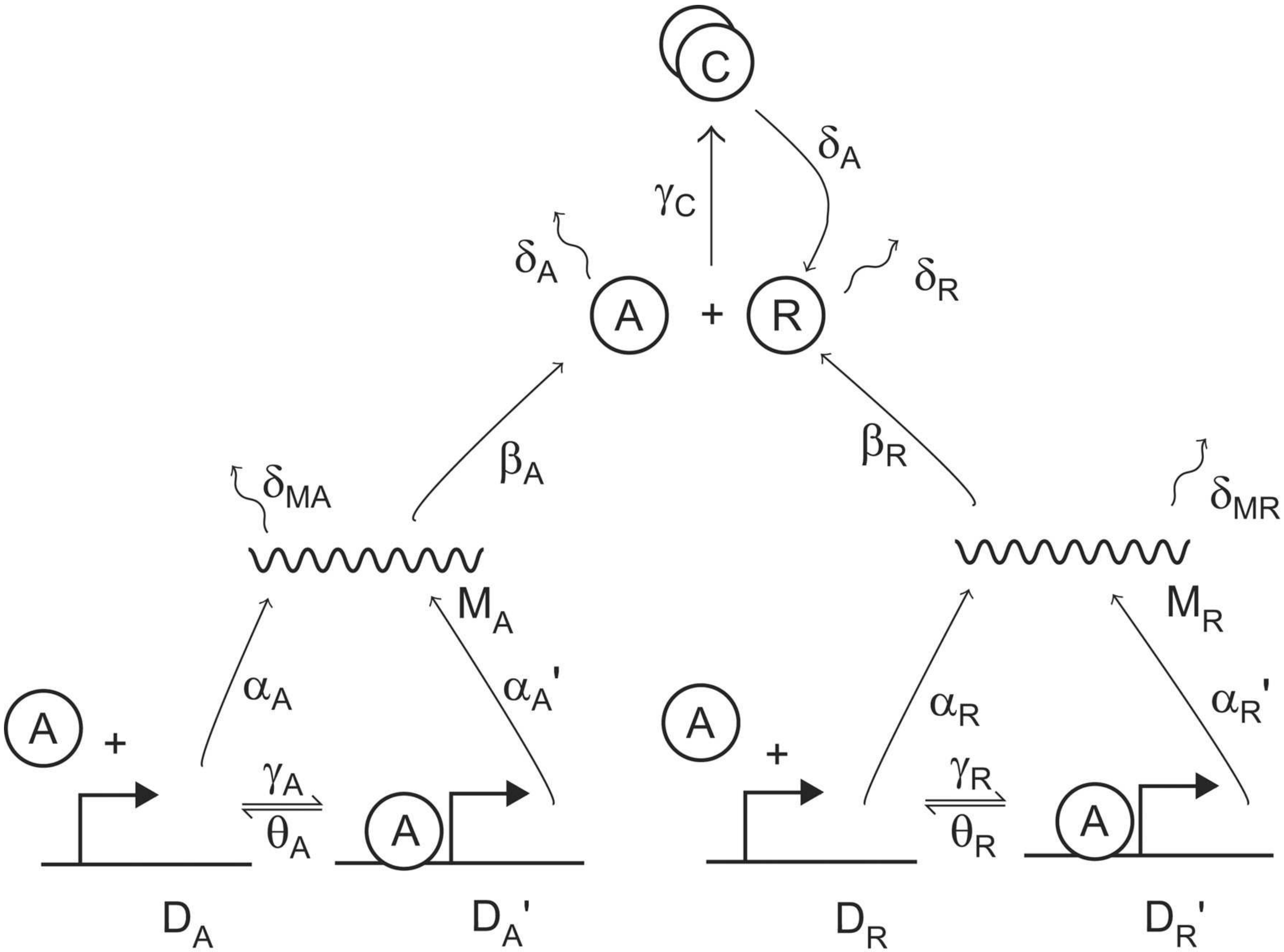
QUARTZ

# Something about genes...

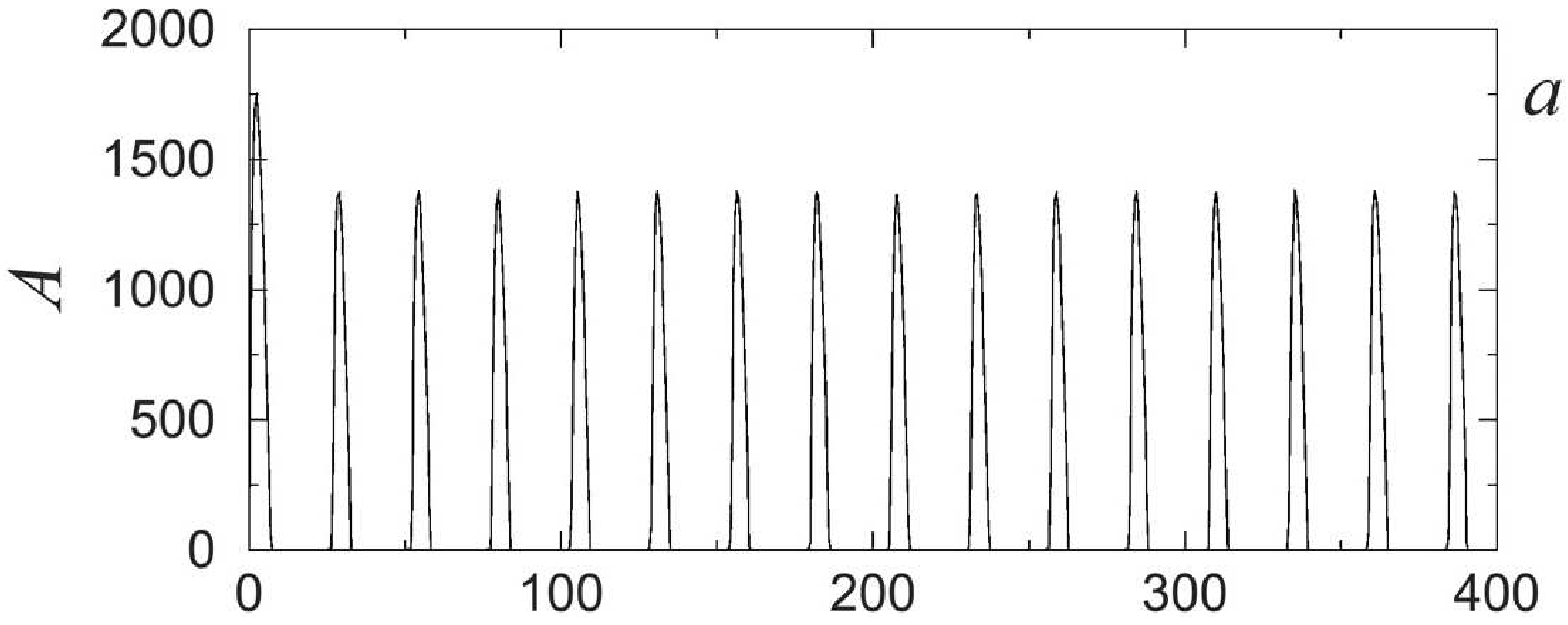
DNA $\longrightarrow$ RNA $\longrightarrow$ Protein



# Biological Circadian Clock Model



# Vilar oscillations of $A$



# Stochastic Process Algebra: PEPA

PEPA syntax:

$$P ::= (a, \lambda).P \;\Big|\; P + P \;\Big|\; P \bowtie_{L} P \;\Big|\; P/L \;\Big|\; A$$

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# PEPA: Example

$$\mathrm{Sys} \stackrel{\mathrm{def}}{=} (\mathrm{AA} \underset{\{\mathrm{run}\}}{\bowtie} \mathrm{A1}) \underset{\{\mathrm{alert}\}}{\bowtie} (\mathrm{BB} \underset{\{\mathrm{run}\}}{\bowtie} \mathrm{B1})$$

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# Types of Analysis

Steady-state and transient analysis in PEPA:

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Sys &\stackrel{\text{def}}{=} AA \underset{\{run\}}{\bowtie} A1
\end{aligned}
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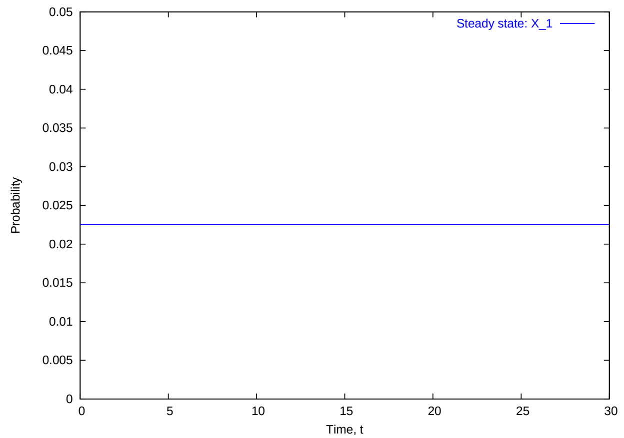
$\Rightarrow$



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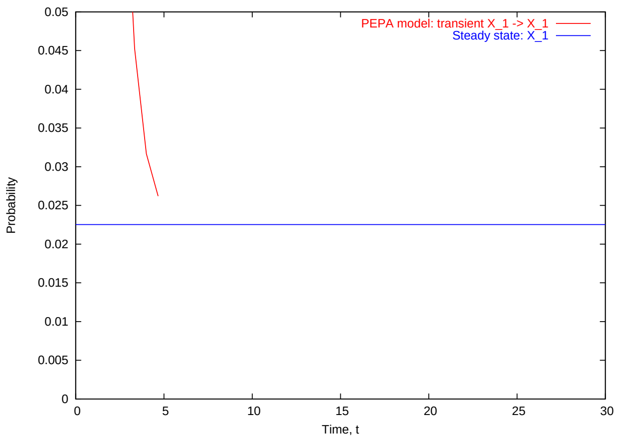

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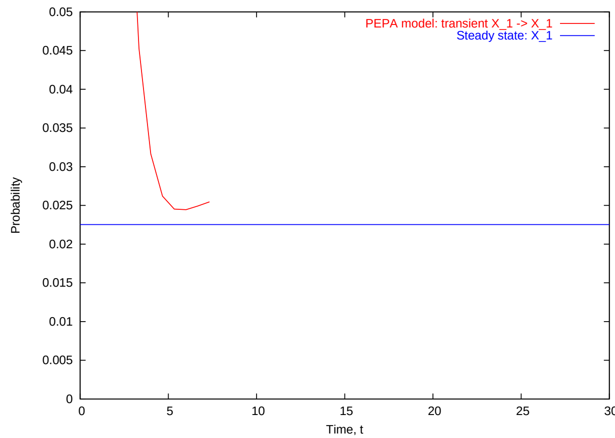

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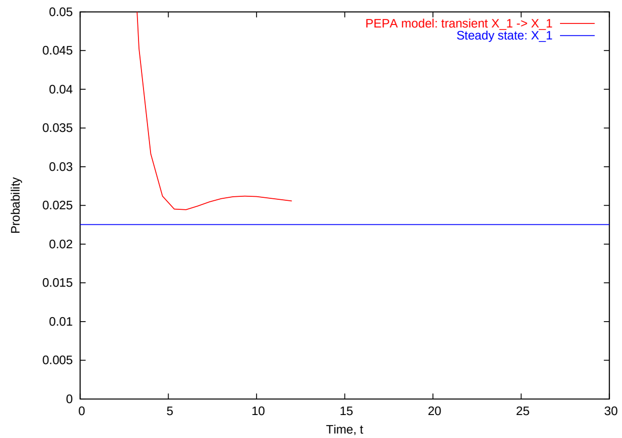

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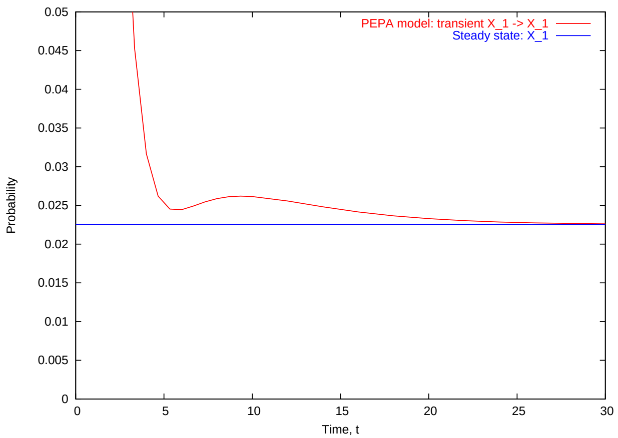

# Passage-time Quantiles

Extract a passage-time density from a PEPA model:

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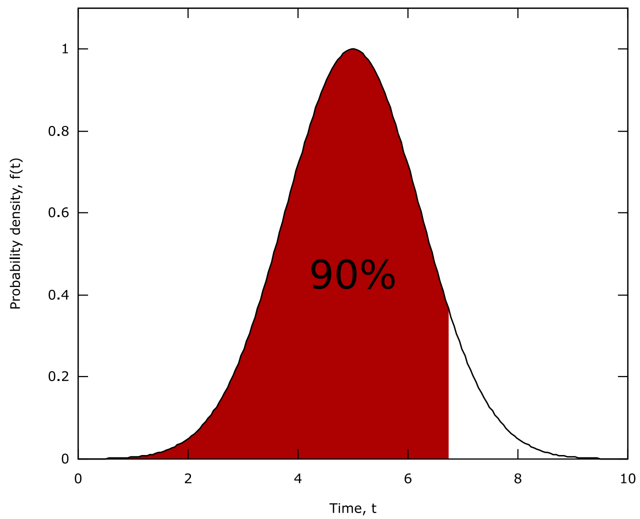
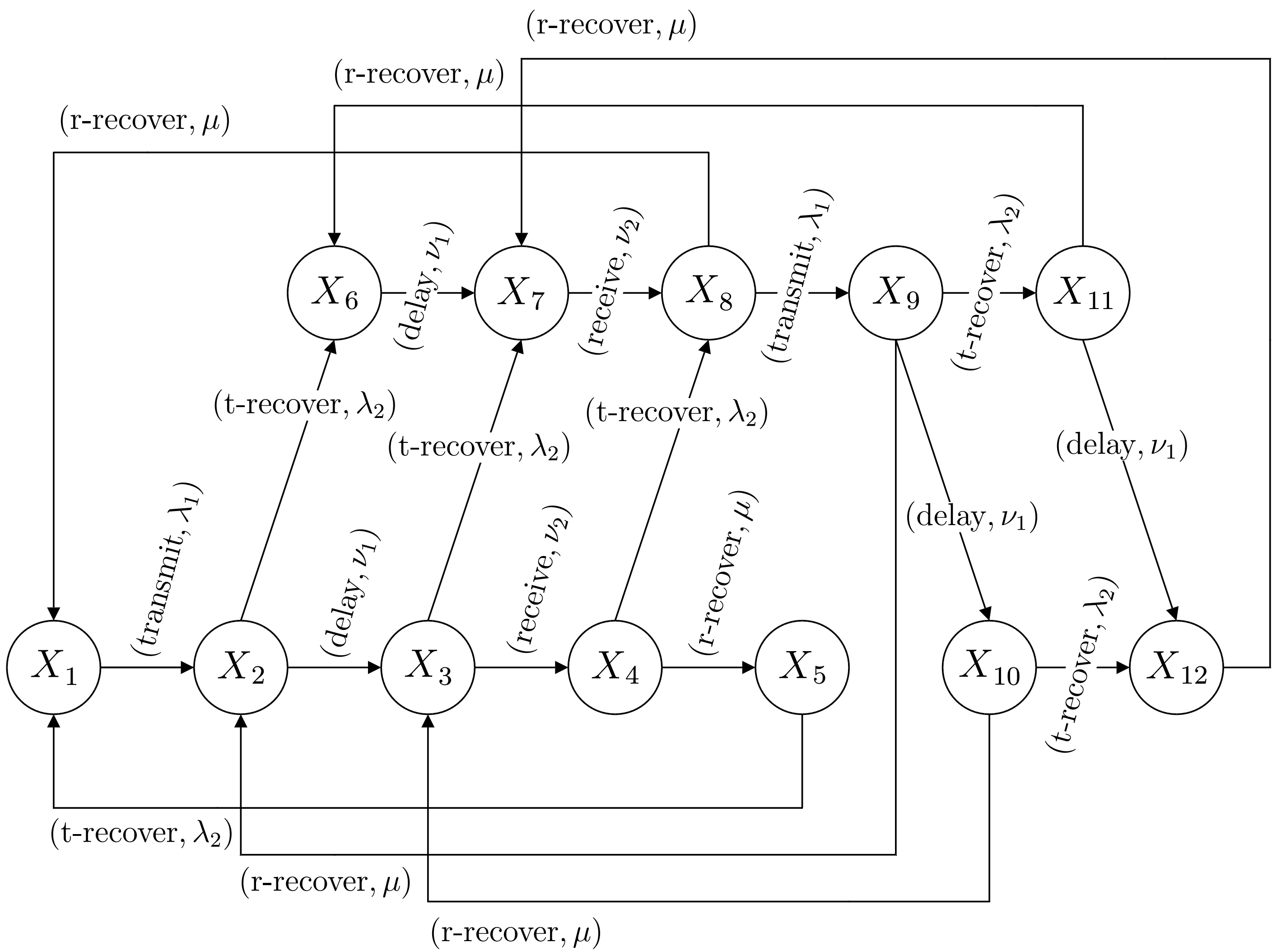
\end{aligned}
\quad \Longrightarrow
$$



# Need for explicit global state space



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- In PEPA, start with a system description:

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- What if we just count the number of components in state $A$ and $B$ (and derivatives):

$$(N_A(t), N_{A'}(t), \ldots)_{\emptyset} \underset{L}{\bowtie} (N_B(t), N_{B'}(t), \ldots)_M$$

# Continuous state space approximation

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  - For $X \xrightarrow{(a,\lambda)} X'$ in $(X \parallel \cdots \parallel X)$:

$$\frac{\mathrm{d}N_X(t)}{\mathrm{d}t} = -\lambda N_X(t)$$

# Models based on...

J. Vilar, H.Y. Kueh, N. Barkai and S. Leibler.
“Mechanisms of noise-resistance in genetic oscillators“,
PNAS, vol. 90, pp. 5988–5992. April, 2002.

# Stochastic $\pi$-Calculus model

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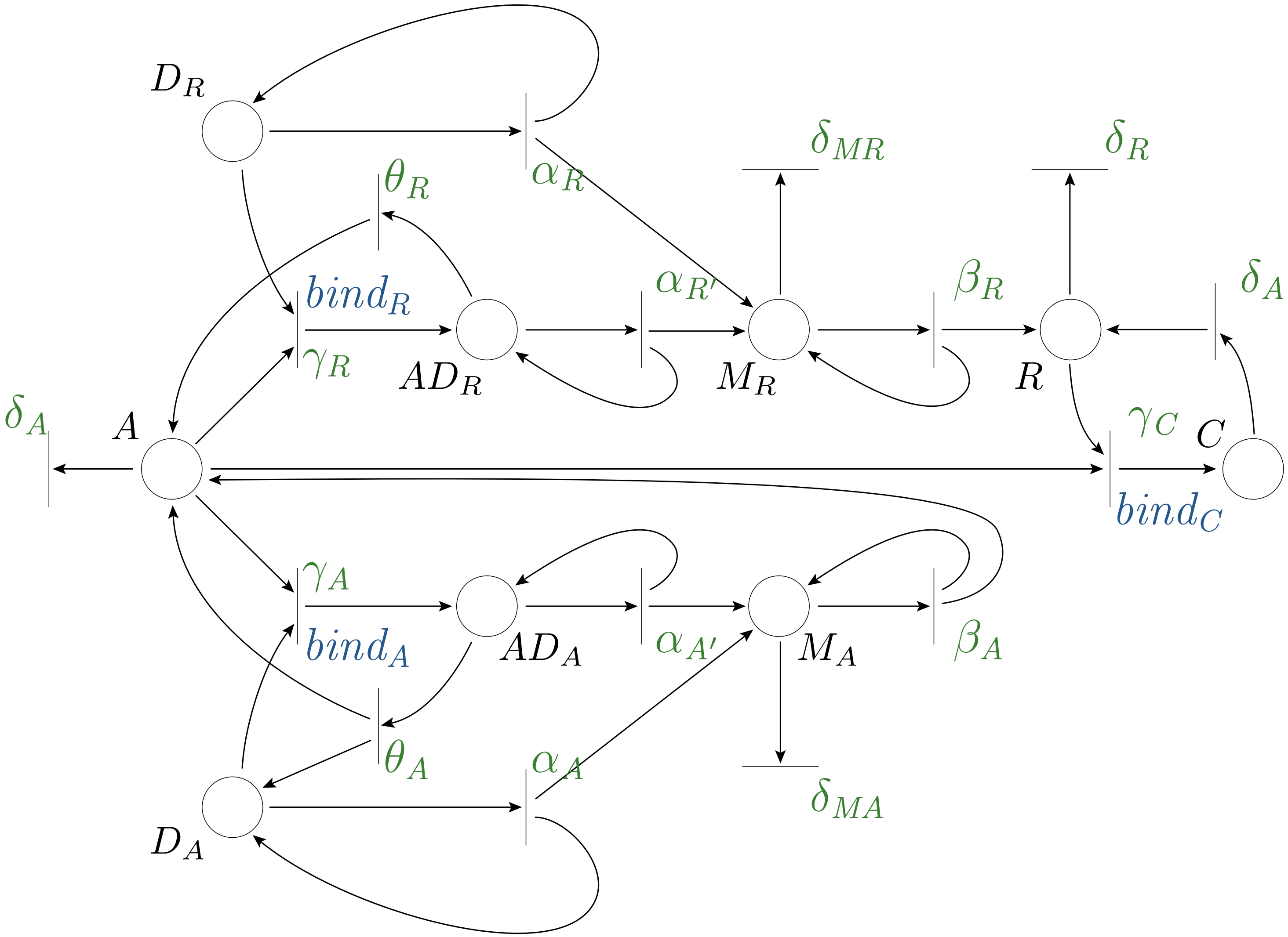
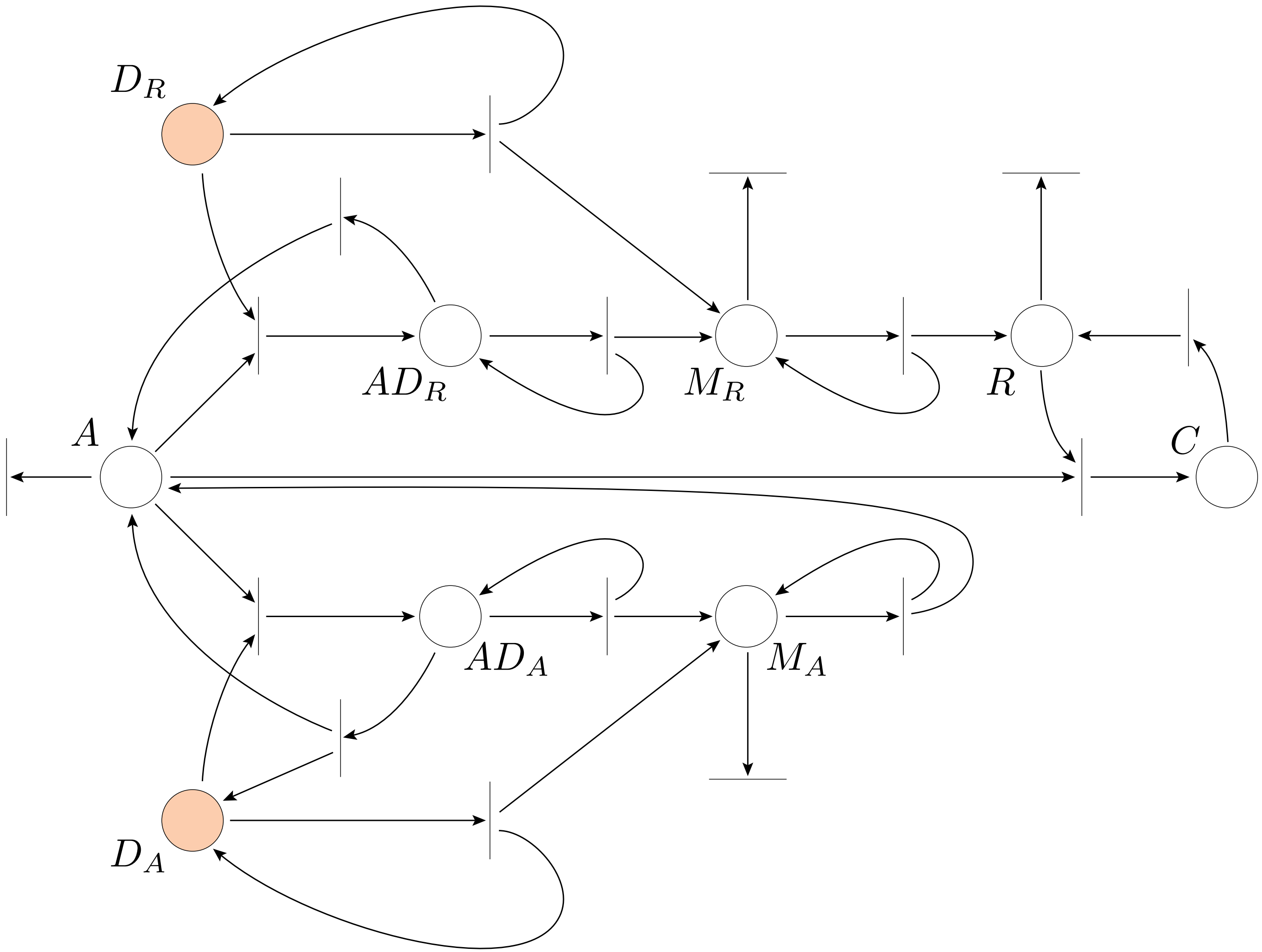
M_A &\stackrel{\text{def}}{=} \tau_{\delta_{MA}}.\emptyset + \tau_{\beta_A}.(M_A \mid A) \\
M_R &\stackrel{\text{def}}{=} \tau_{\delta_{MR}}.\emptyset + \tau_{\beta_R}.(M_R \mid R) \\
A &\stackrel{\text{def}}{=} \overline{bind_{A_{\gamma_A}}}.\emptyset + \overline{bind_{R_{\gamma_R}}}.\emptyset + \overline{bind_{C_{\gamma_C}}}.\emptyset + \tau_{\delta_A}.\emptyset \\
R &\stackrel{\text{def}}{=} bind_{C_{\gamma_C}}.C + \tau_{\delta_R}. \\
C &\stackrel{\text{def}}{=} \tau_{\delta_A}.R
\end{aligned}
$$

# Circadian clock: as a Petri net!



# Circadian clock: an explanation



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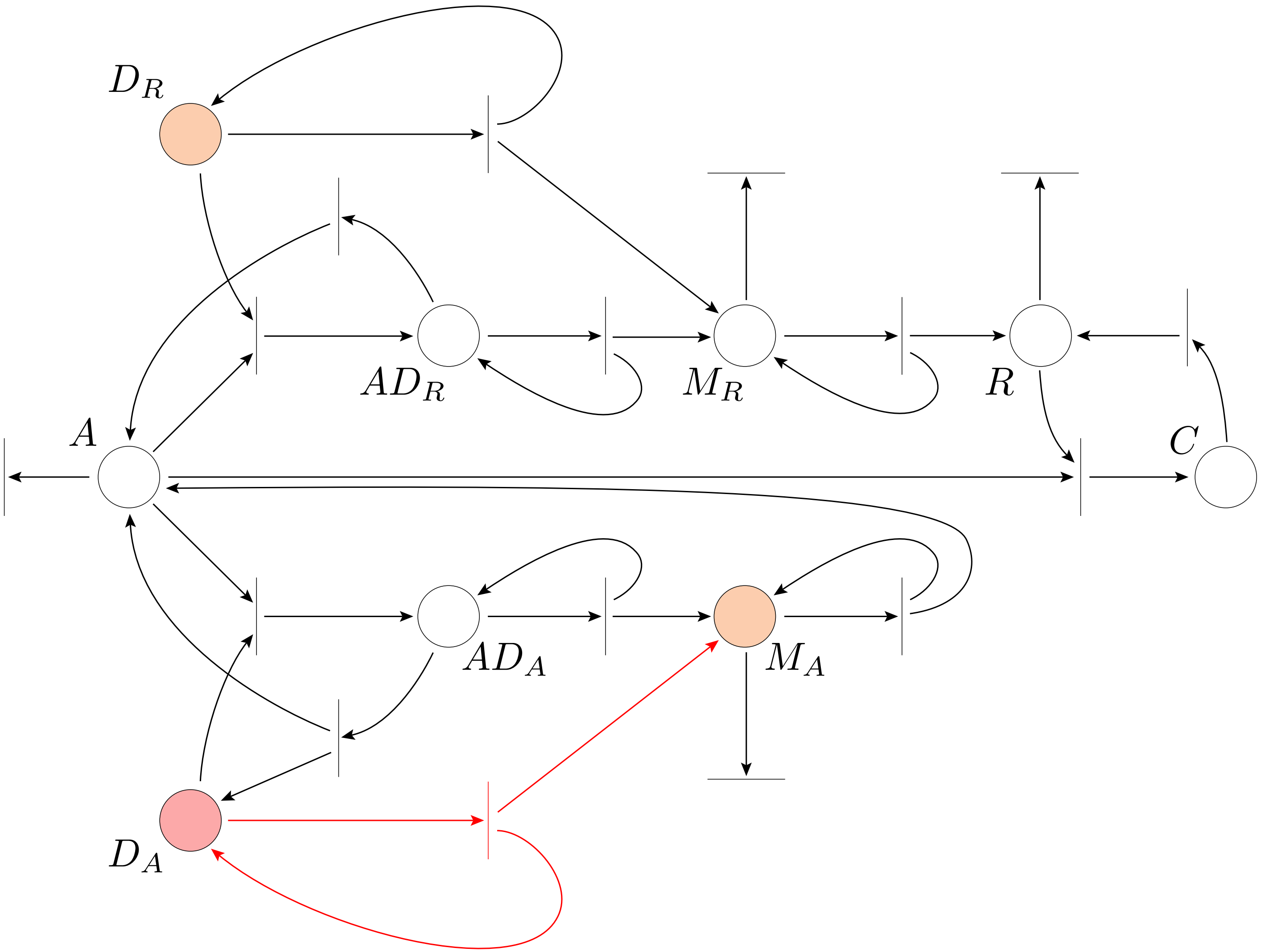

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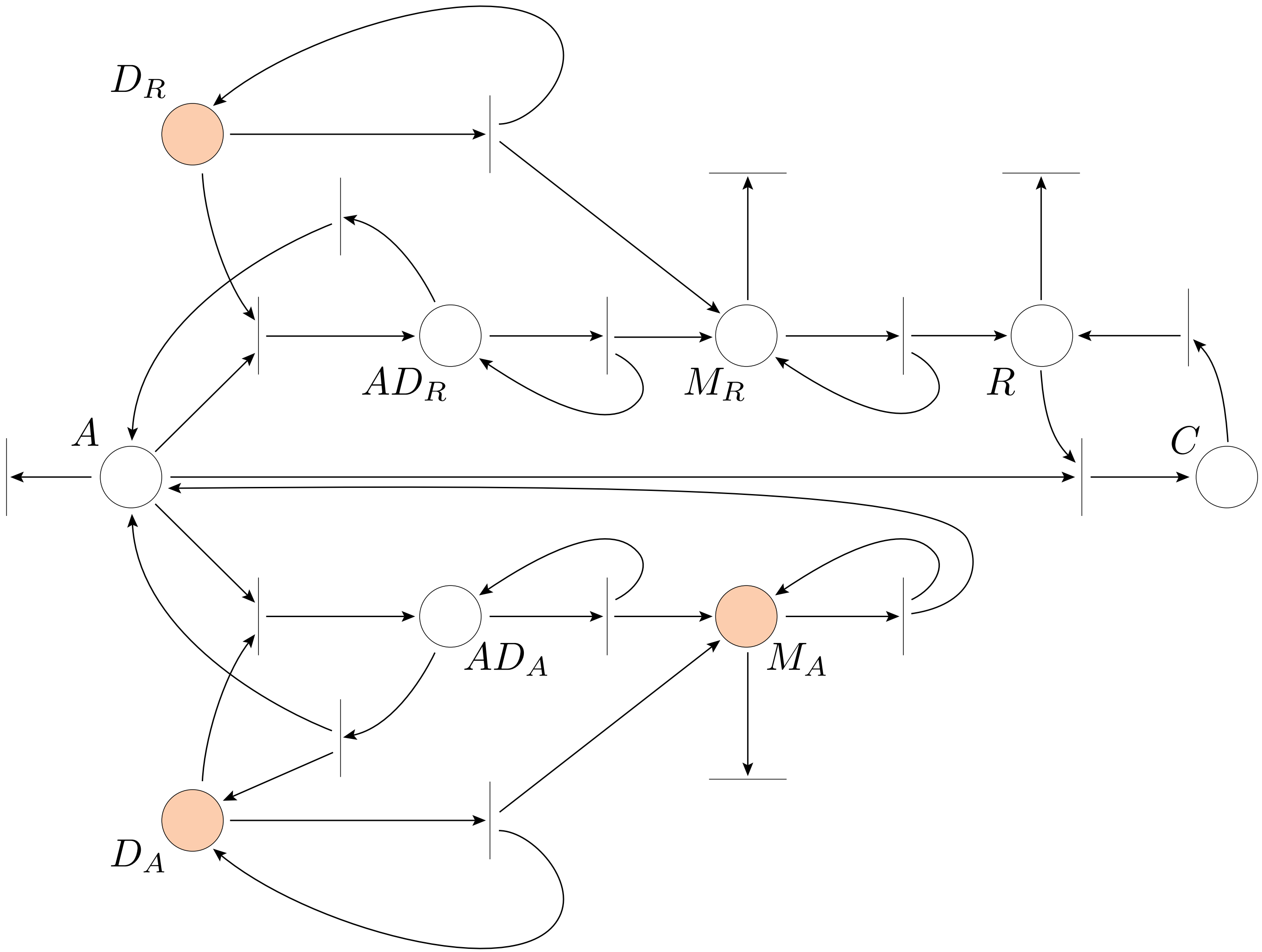

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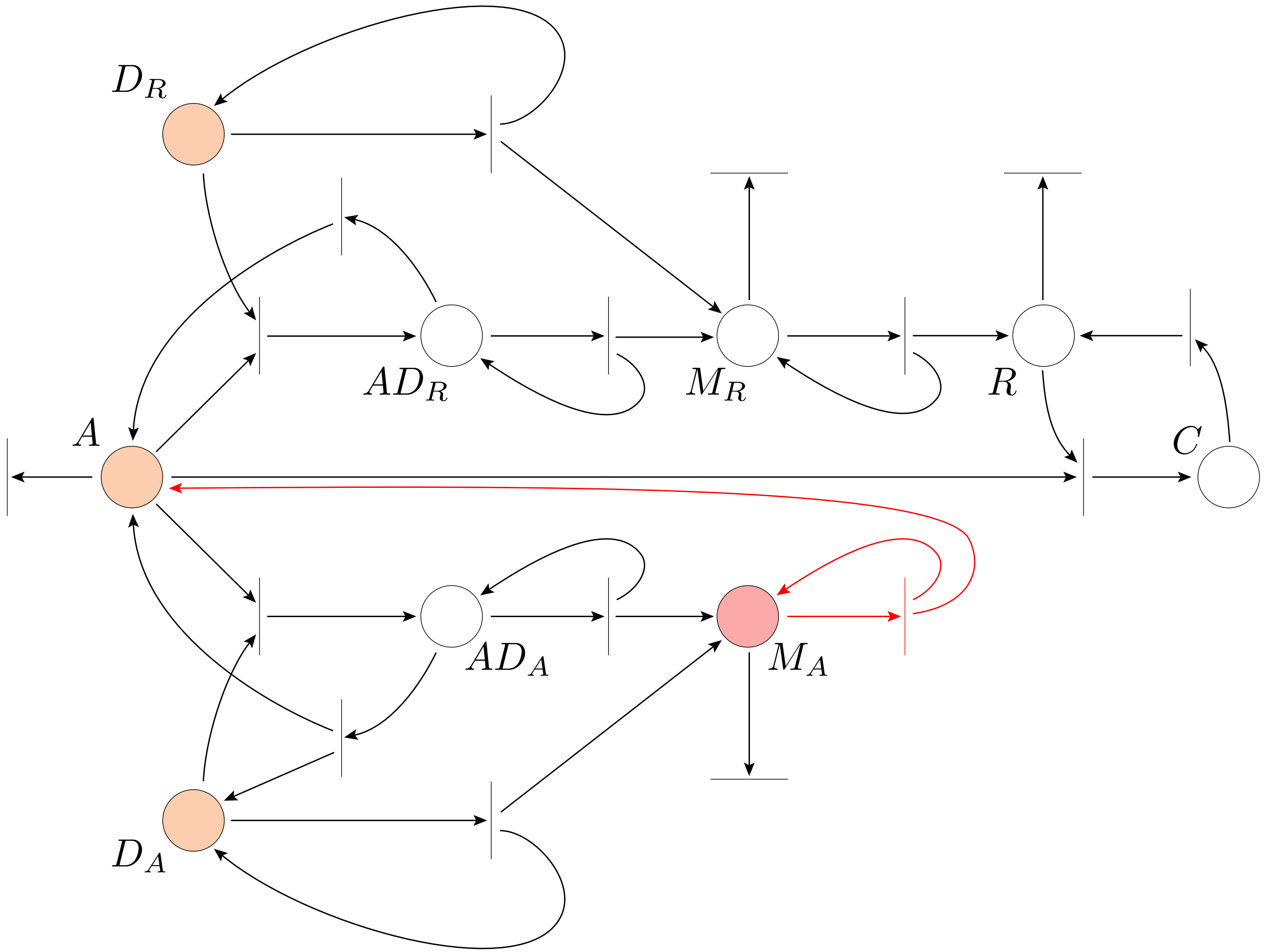

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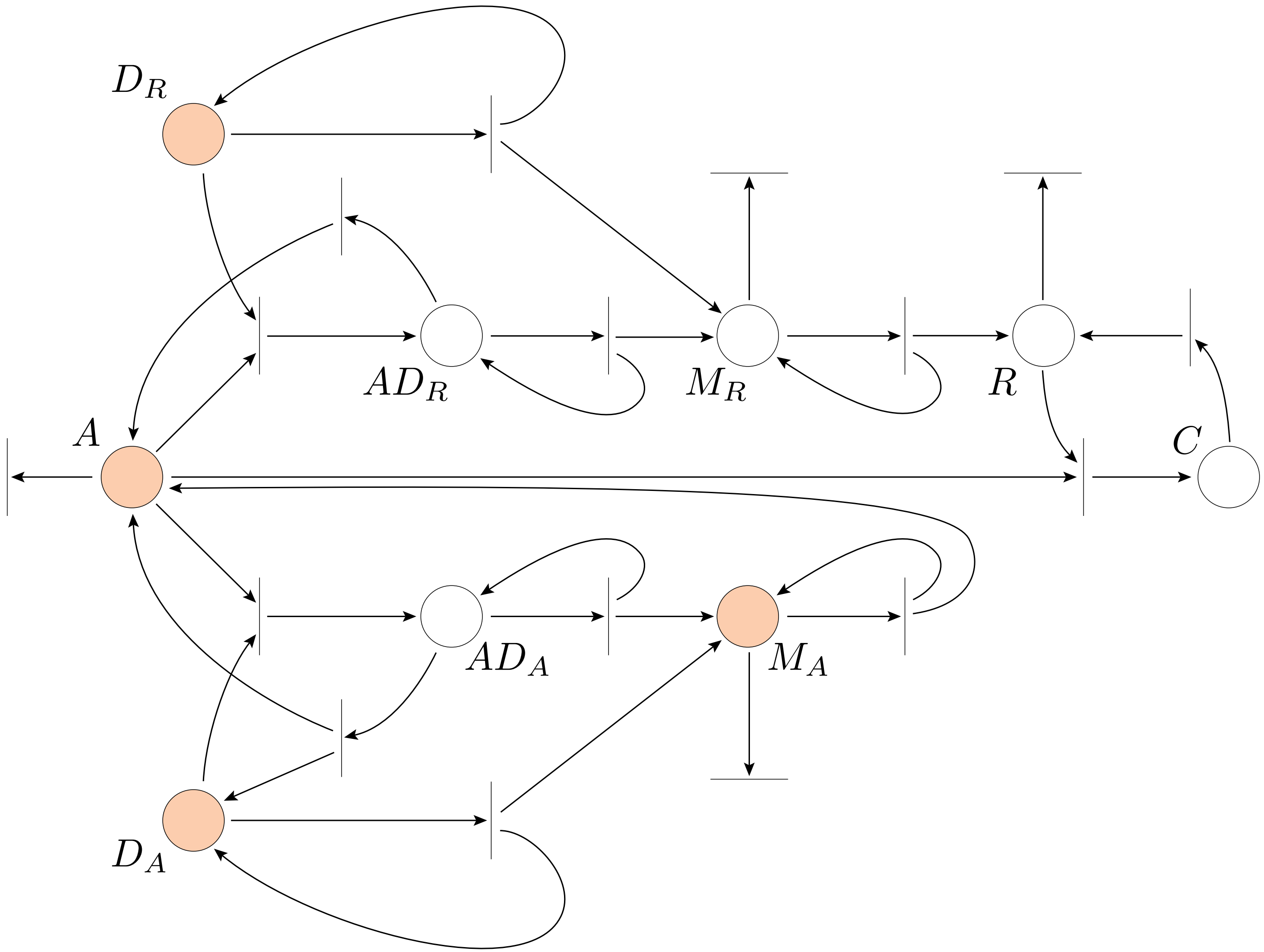

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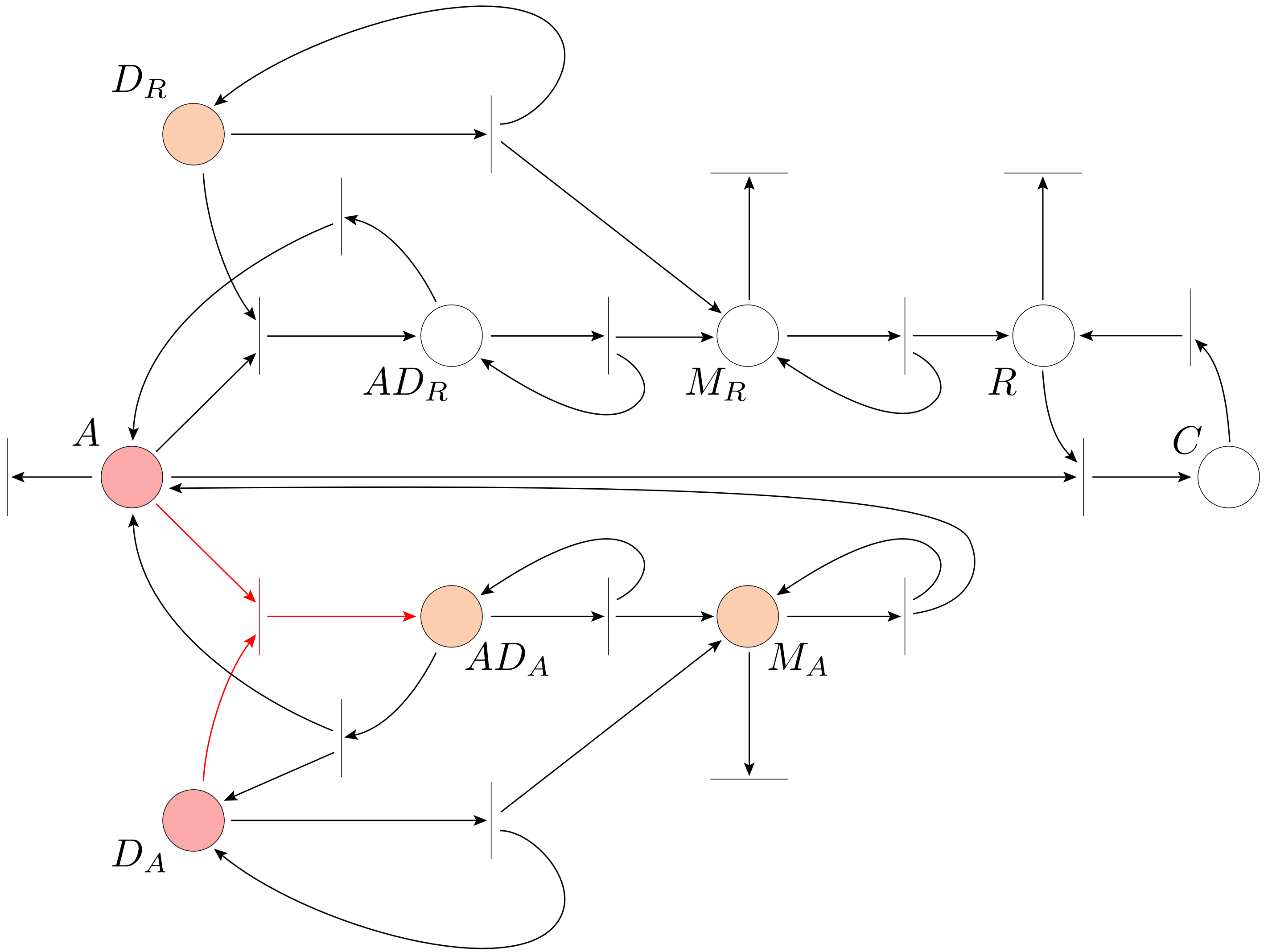

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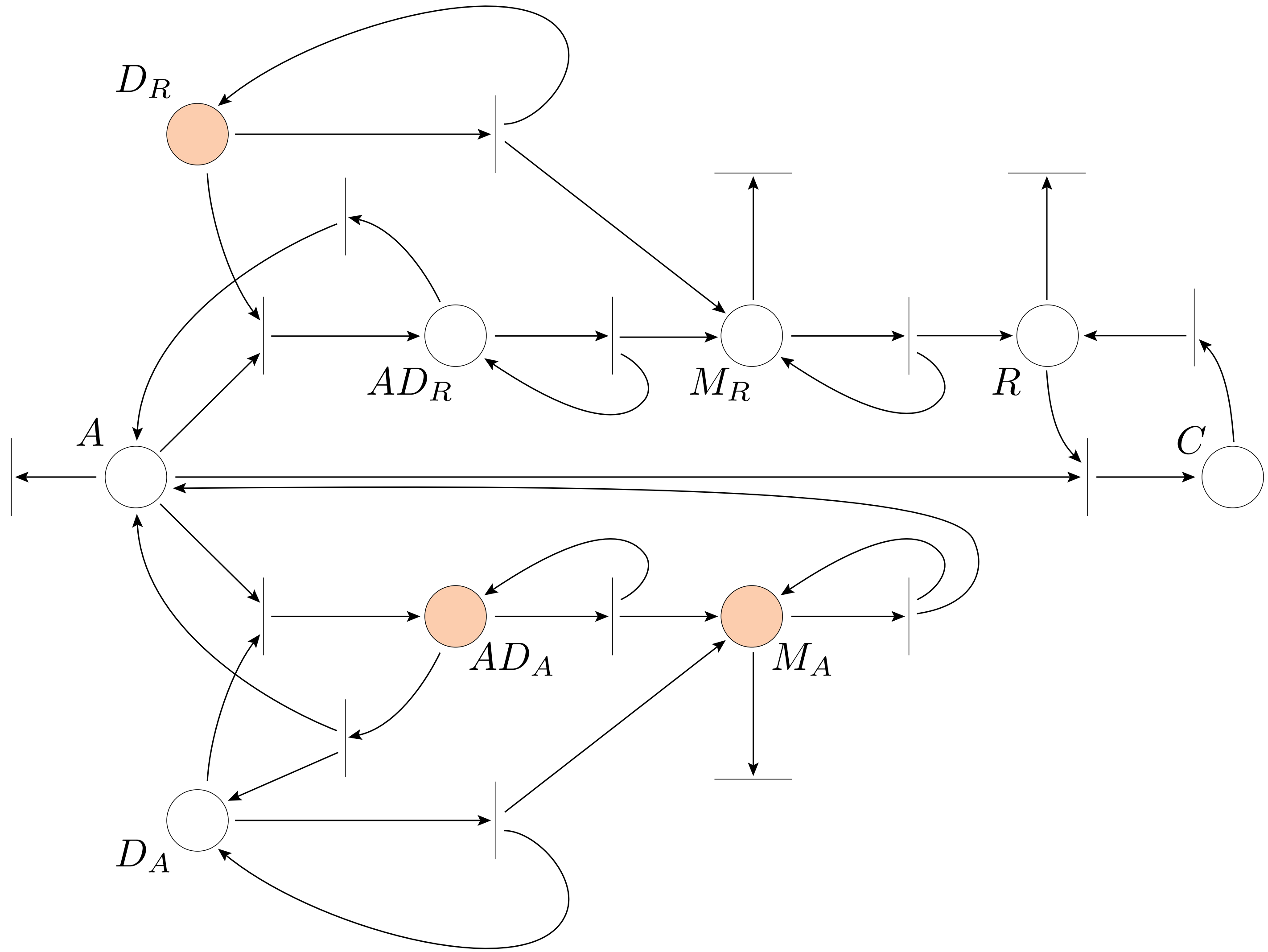

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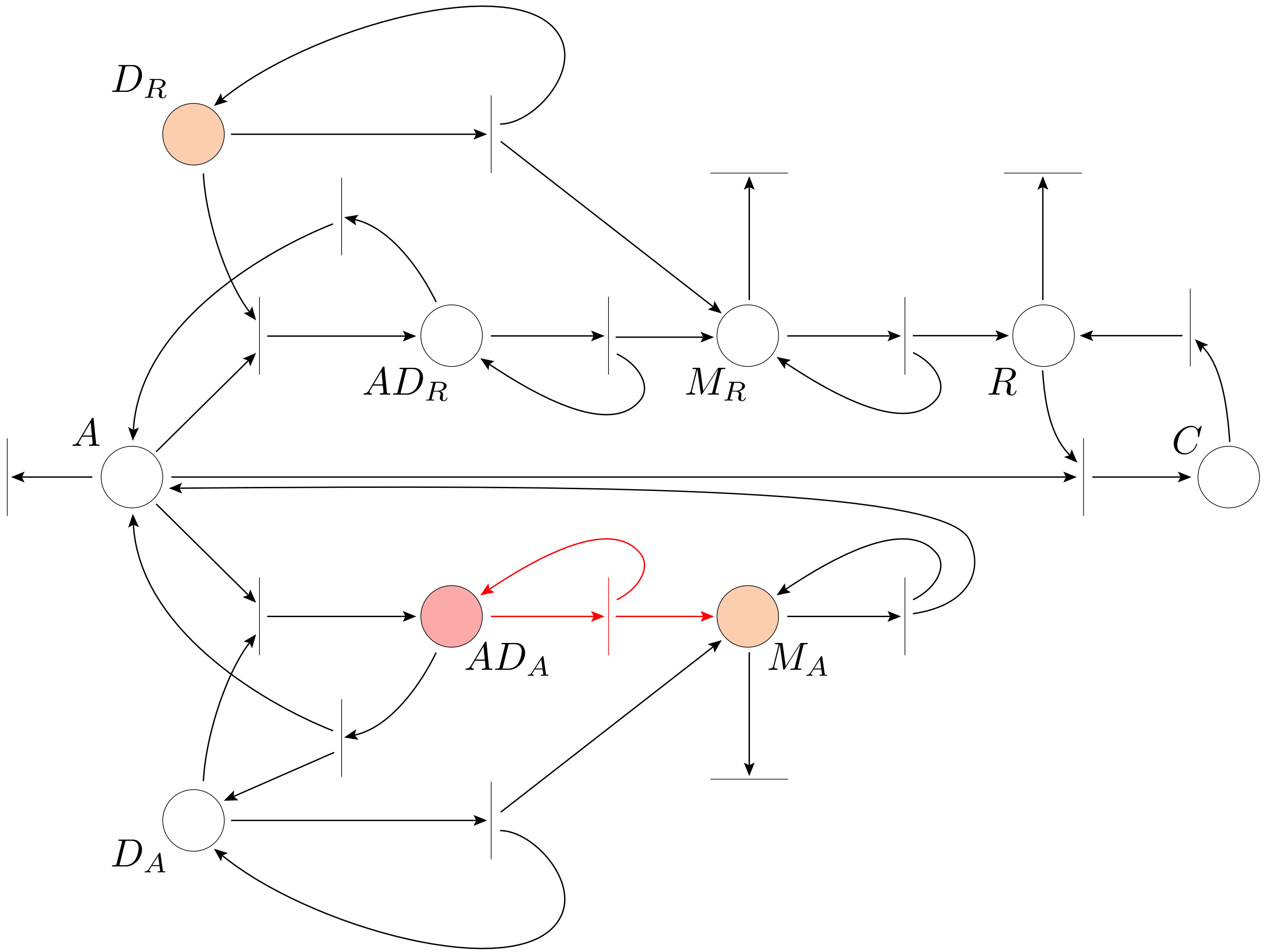

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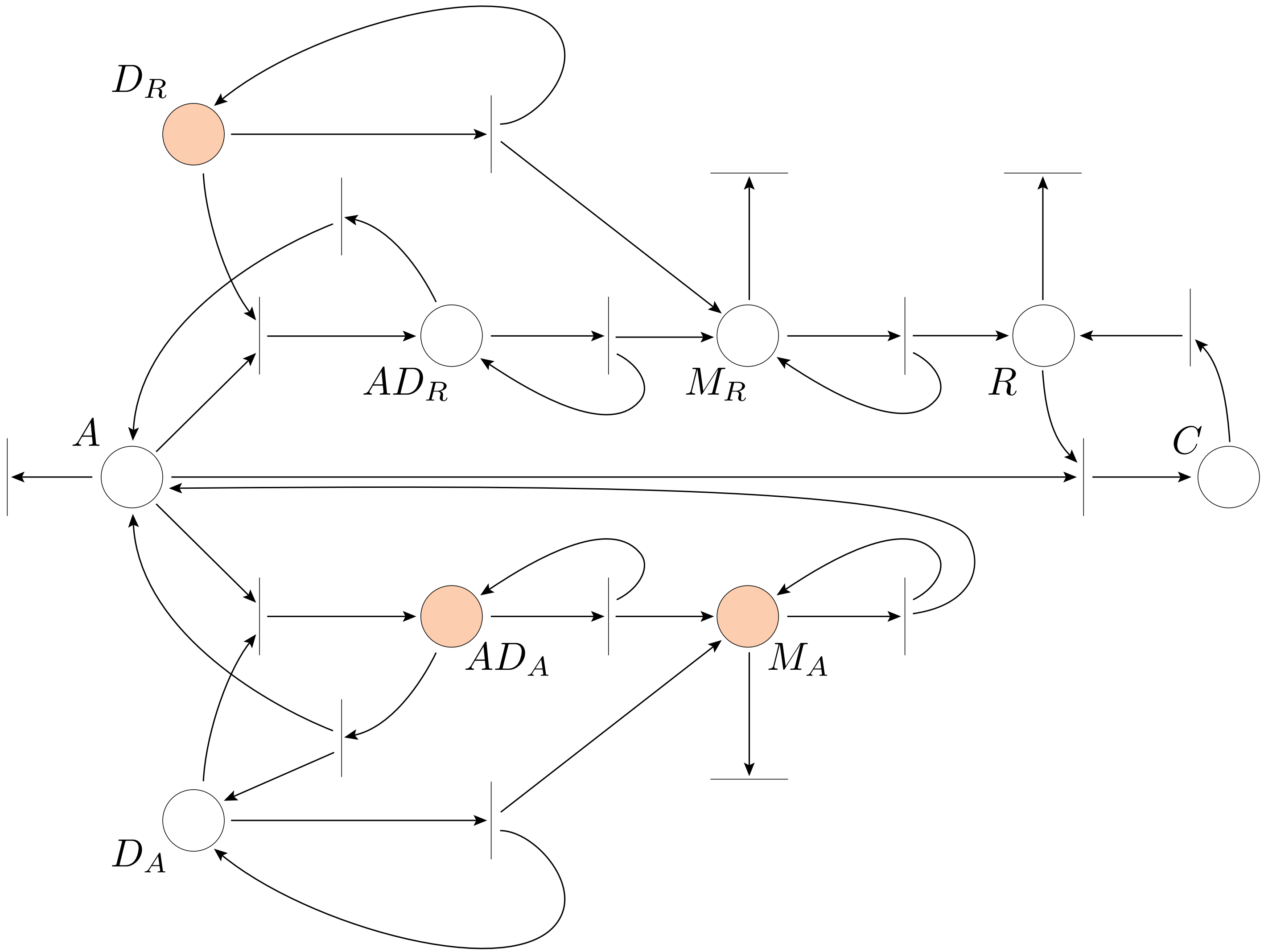

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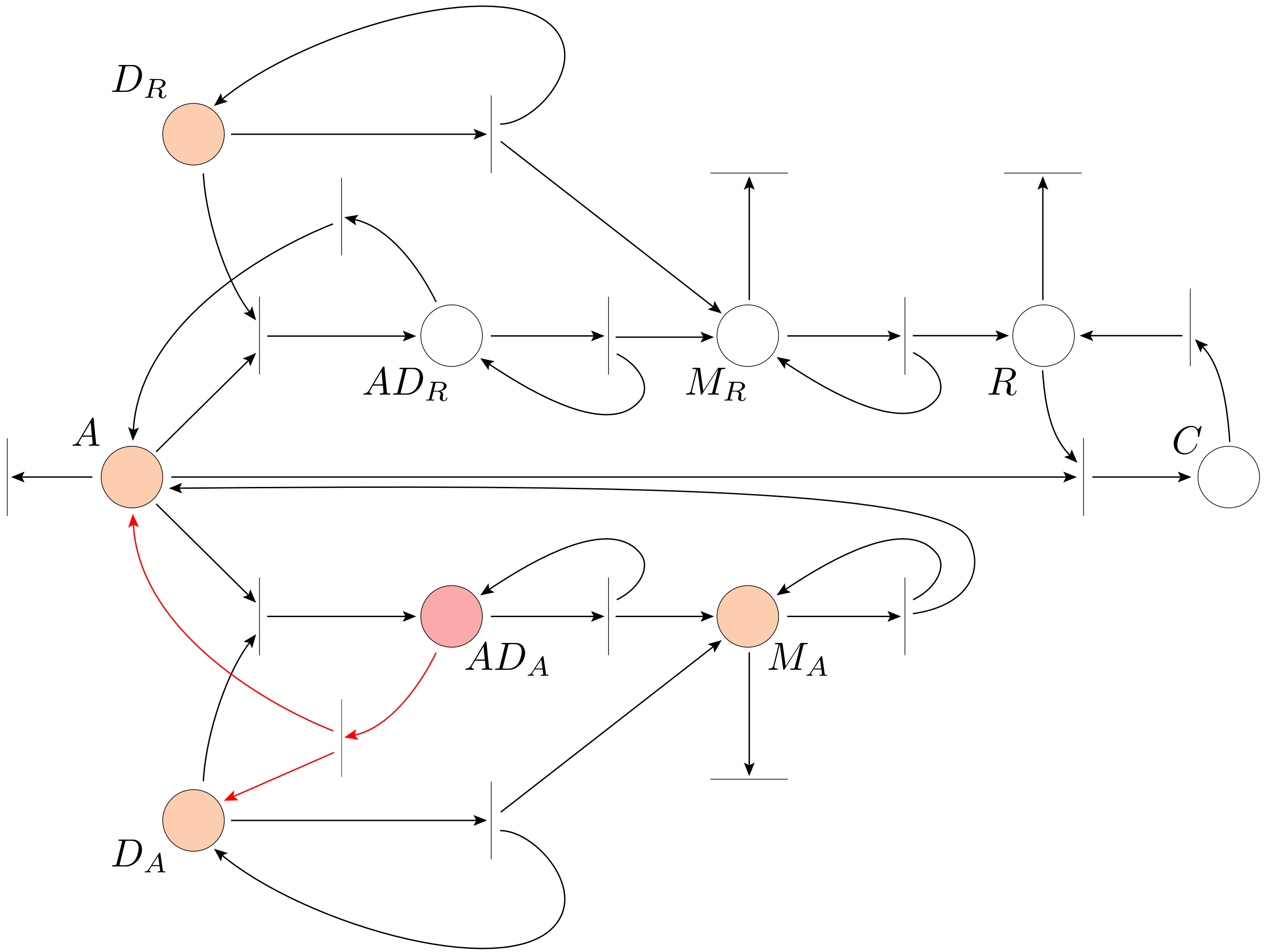

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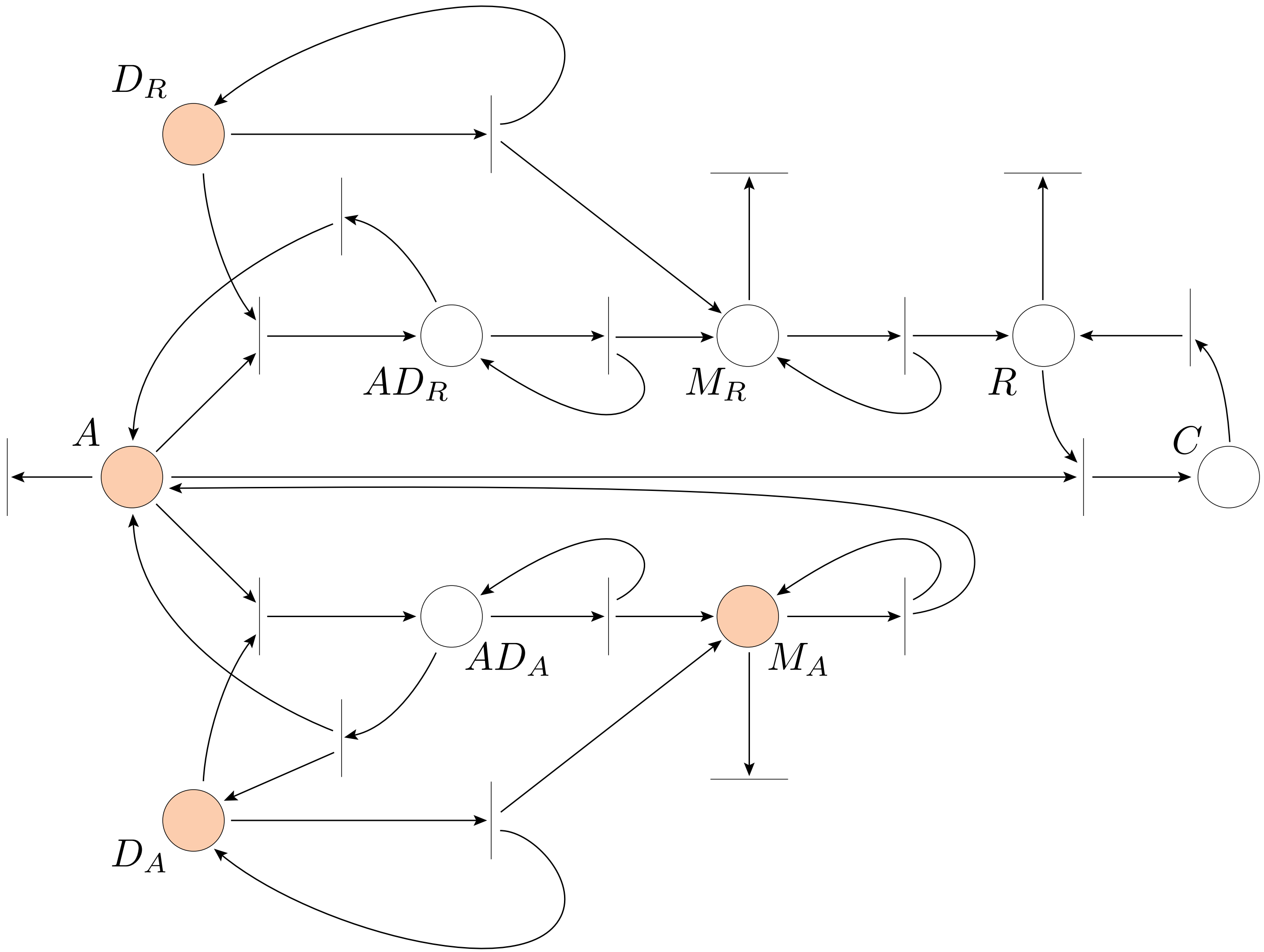

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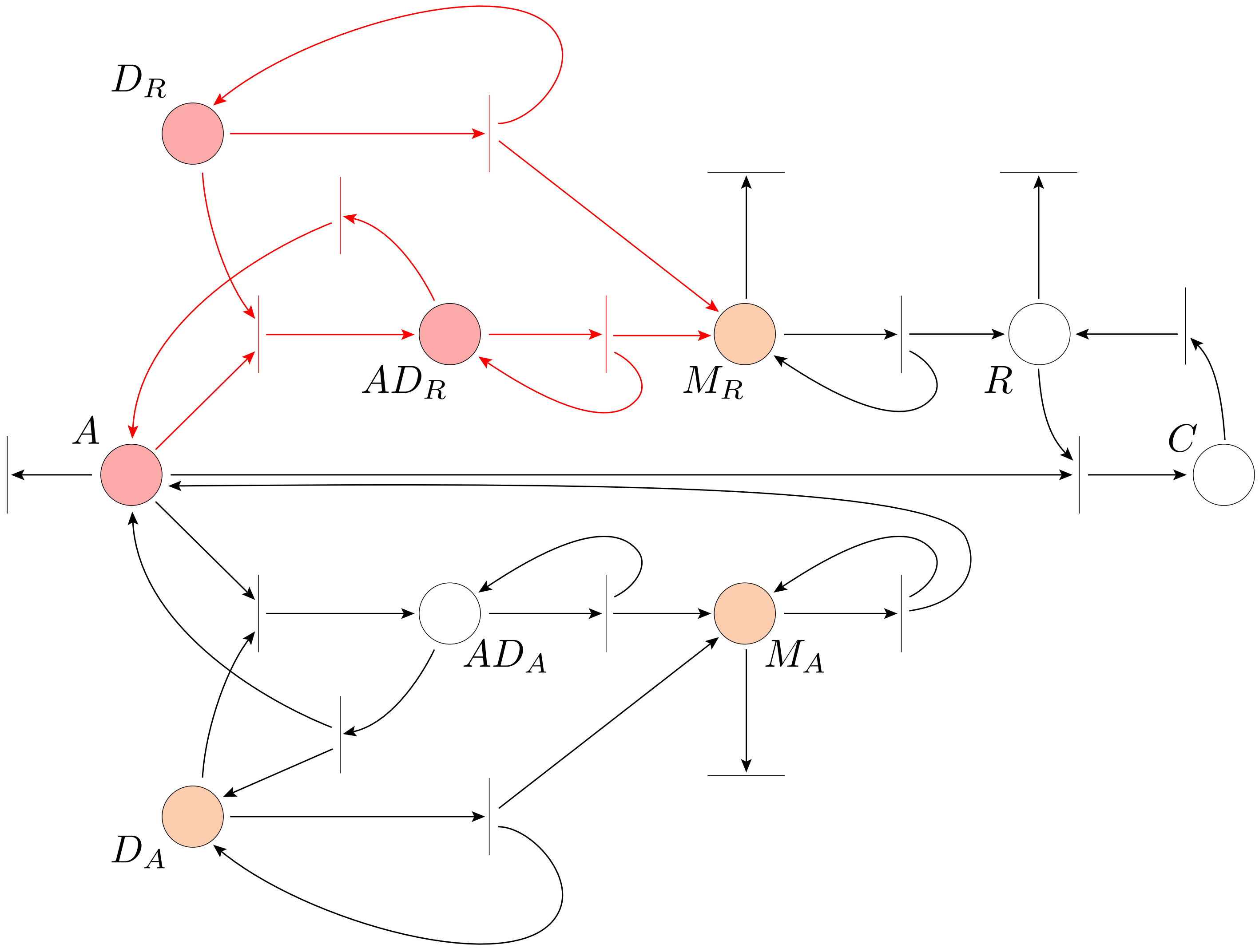

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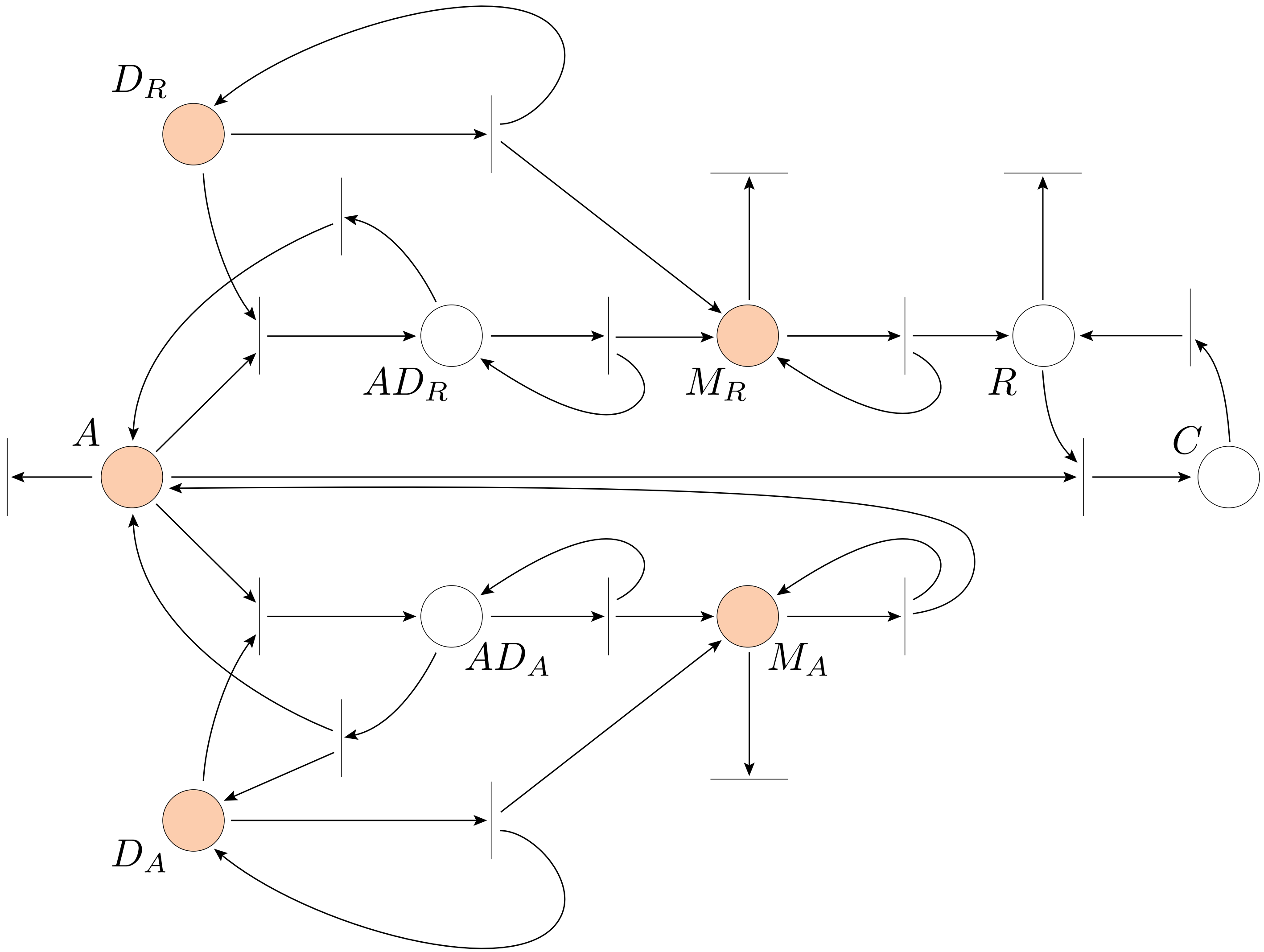

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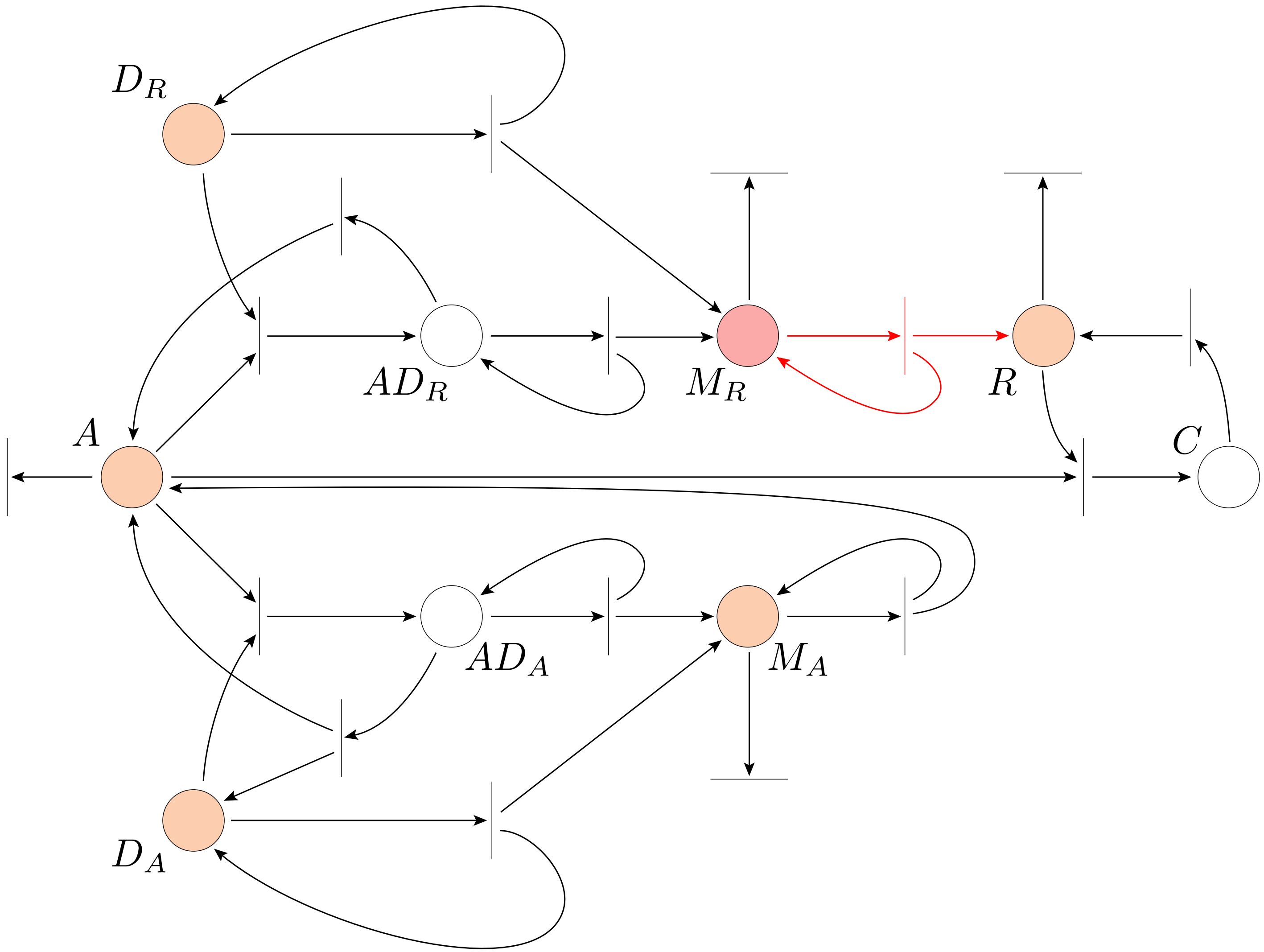

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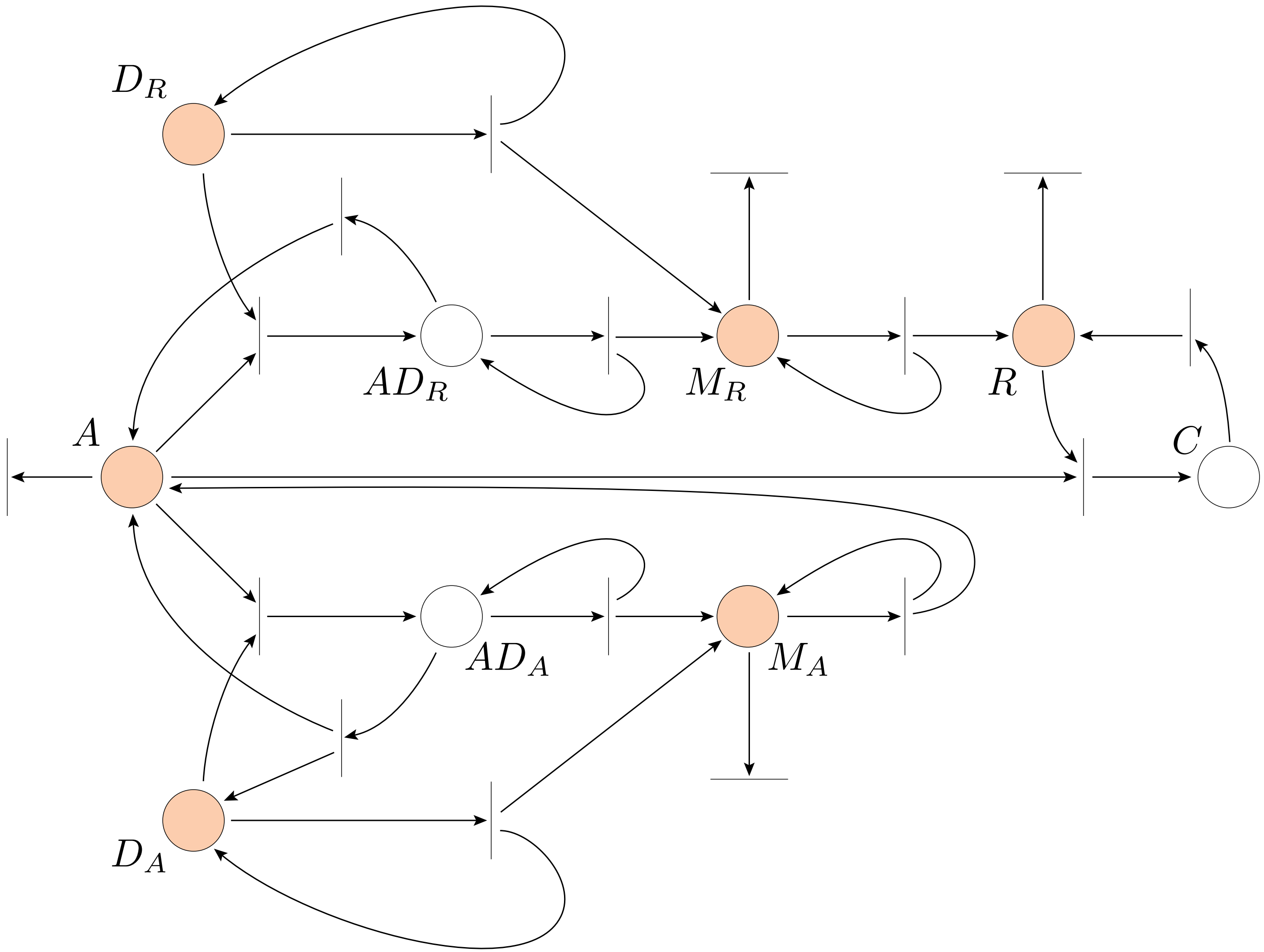

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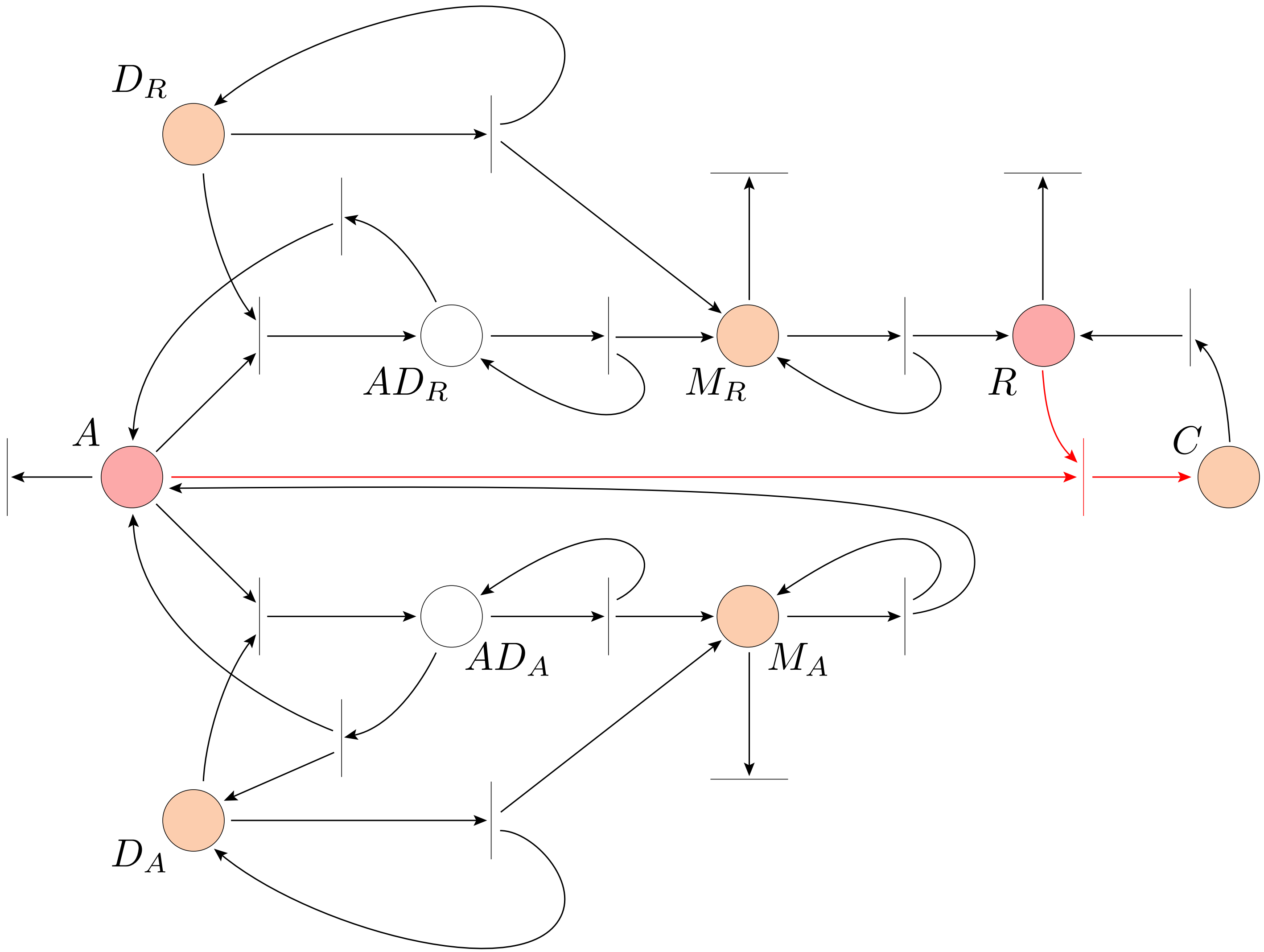

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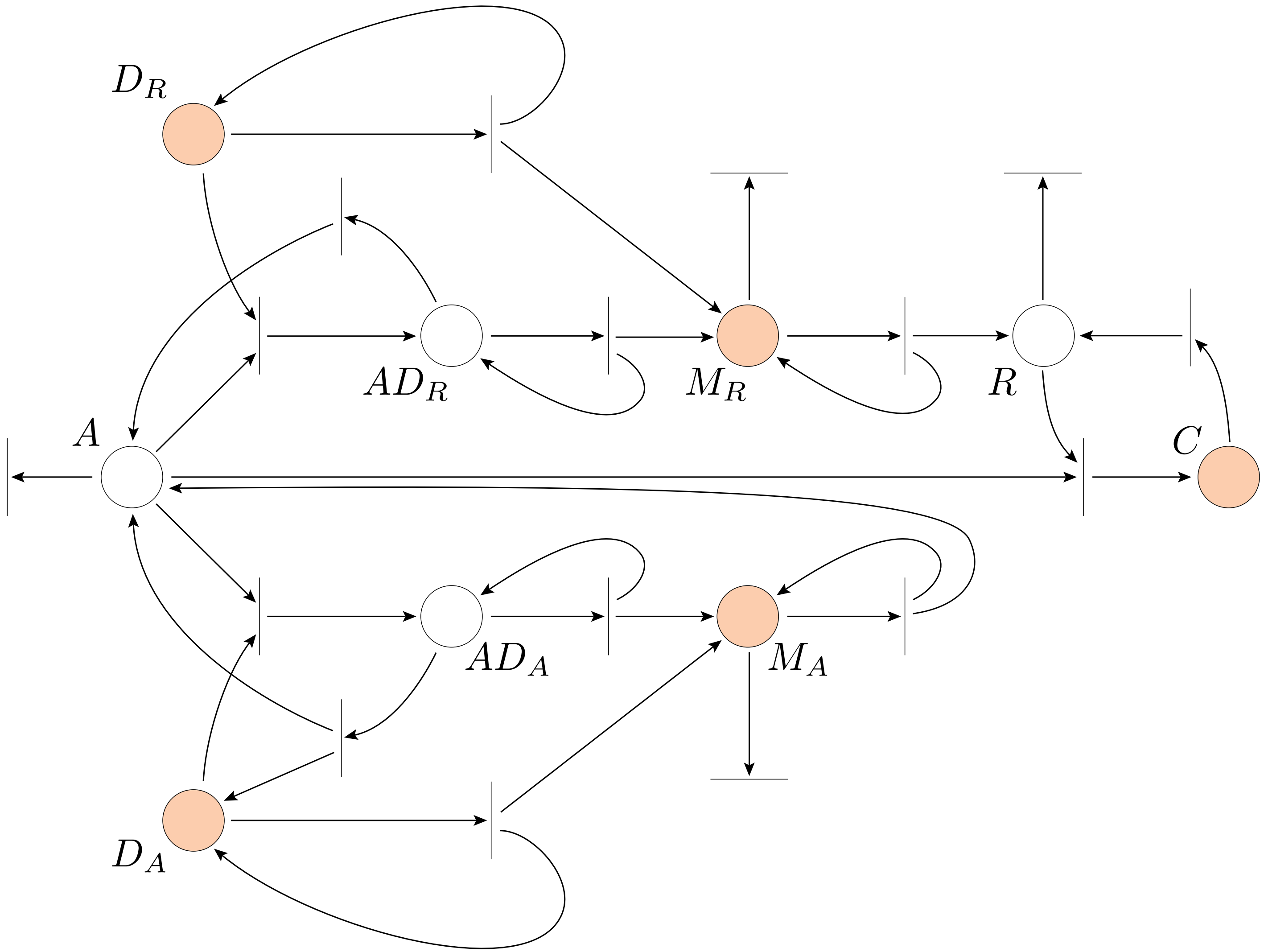

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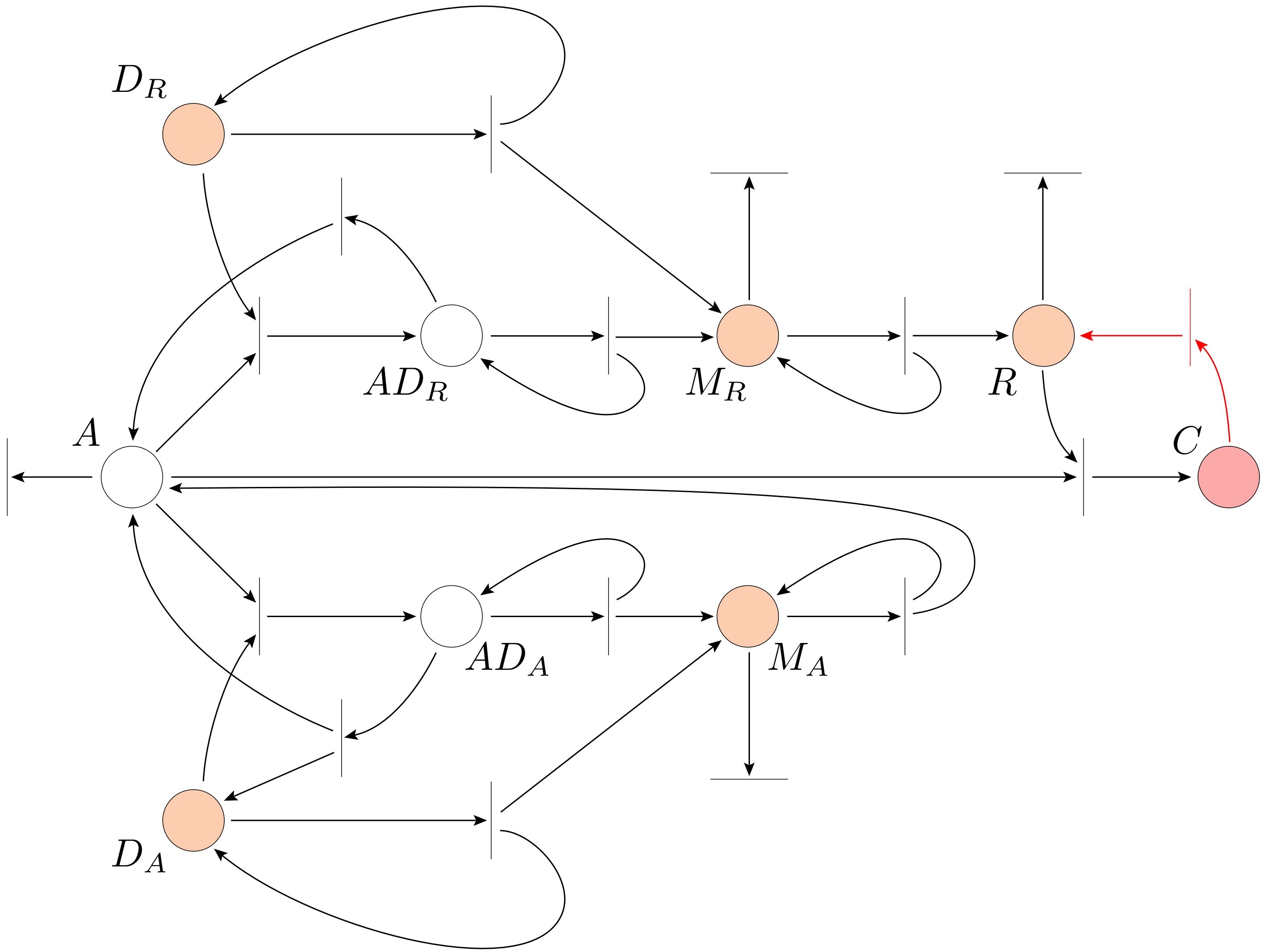

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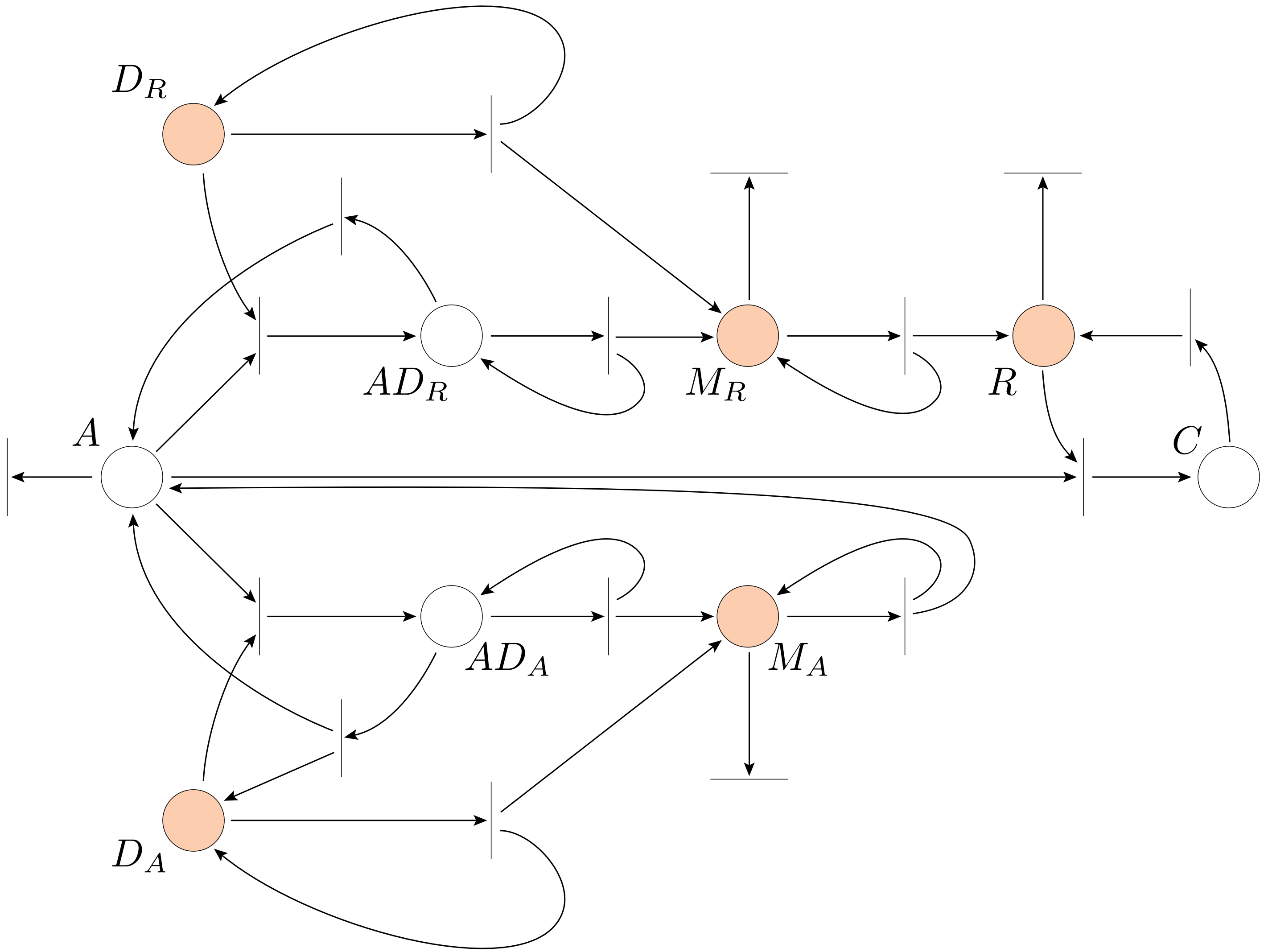

# Modelling Styles

Note the different modelling styles in the use of *stochastic* $\pi$ and *PEPA*

# Modelling with $\pi$-Calculus

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

# Stochastic $\pi$-Calculus model

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

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

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

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

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

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

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

$$AD_R \stackrel{\text{def}}{=} \tau_{\theta_R}.(D_R \mid A) + \tau_{\alpha_{R'}}.(AD_R \mid M_R)$$

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

# PEPA model: Circadian Clock

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

# PEPA model: Circadian Clock

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

# PEPA model: Circadian Clock

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

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

# 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

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

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

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

$$A' \stackrel{\text{def}}{=} (mk_A, \top).A$$

# PEPA model: Circadian Clock

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

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

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

# PEPA model: Circadian Clock

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

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

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

# PEPA Combination

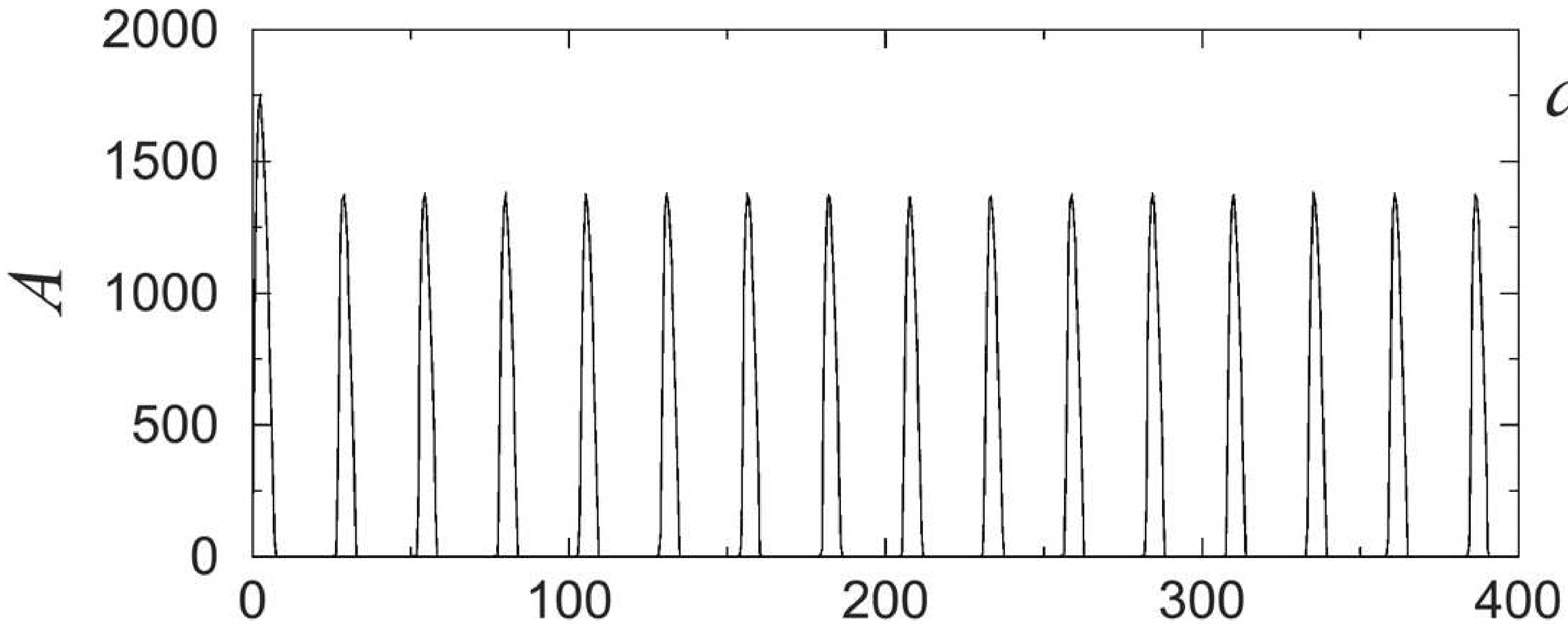
Part of PEPA system combination looks like:

$$((D_A \bowtie_{L} M'_A[500]) \bowtie_{M} A'[2500]) \bowtie_{N} \cdots$$

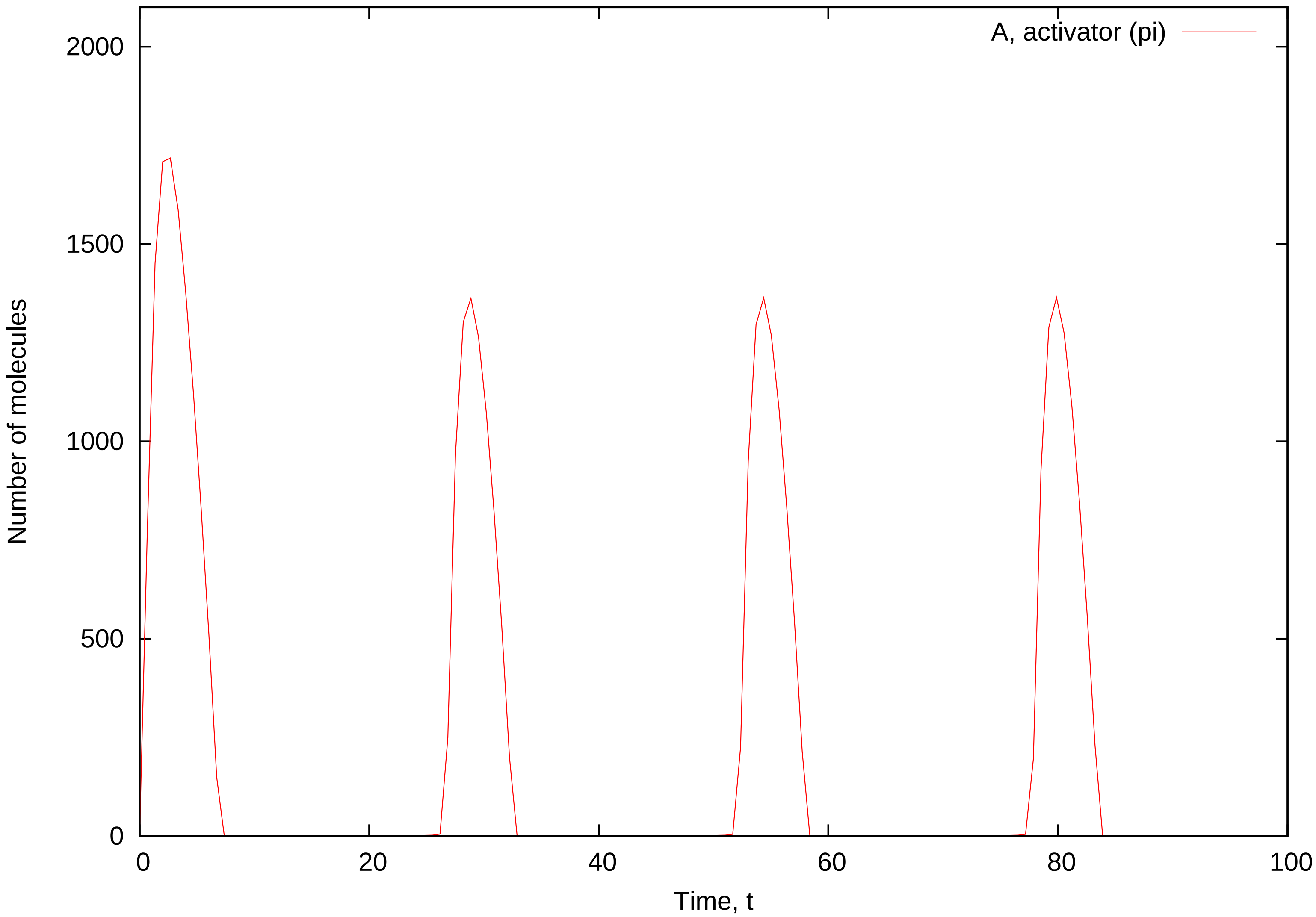
where:

- $L = \{mk_{MA}\}$
- $M = \{mk_A, bind_{AD_A}\}$

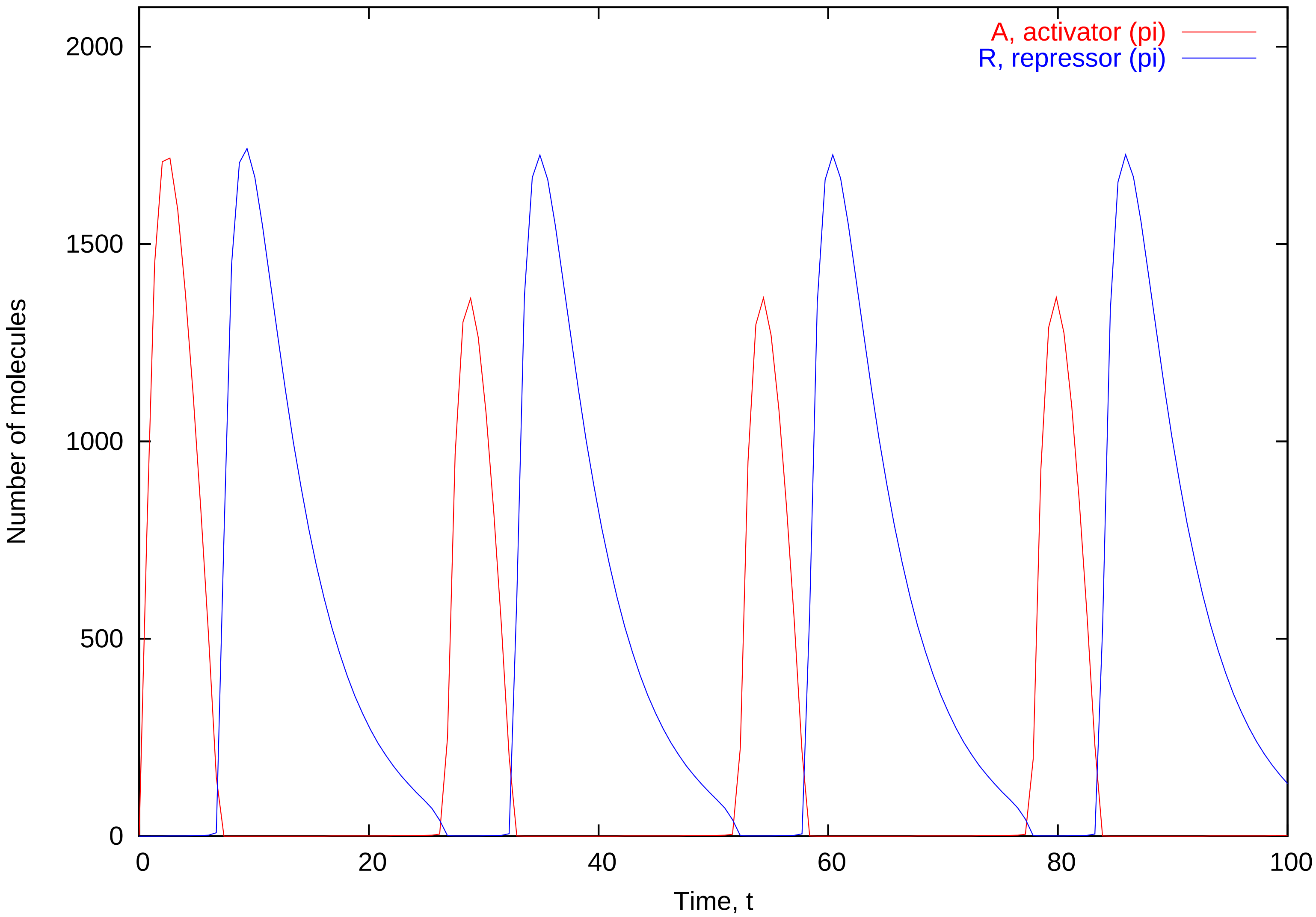
# Vilar oscillations of $A$: reminder



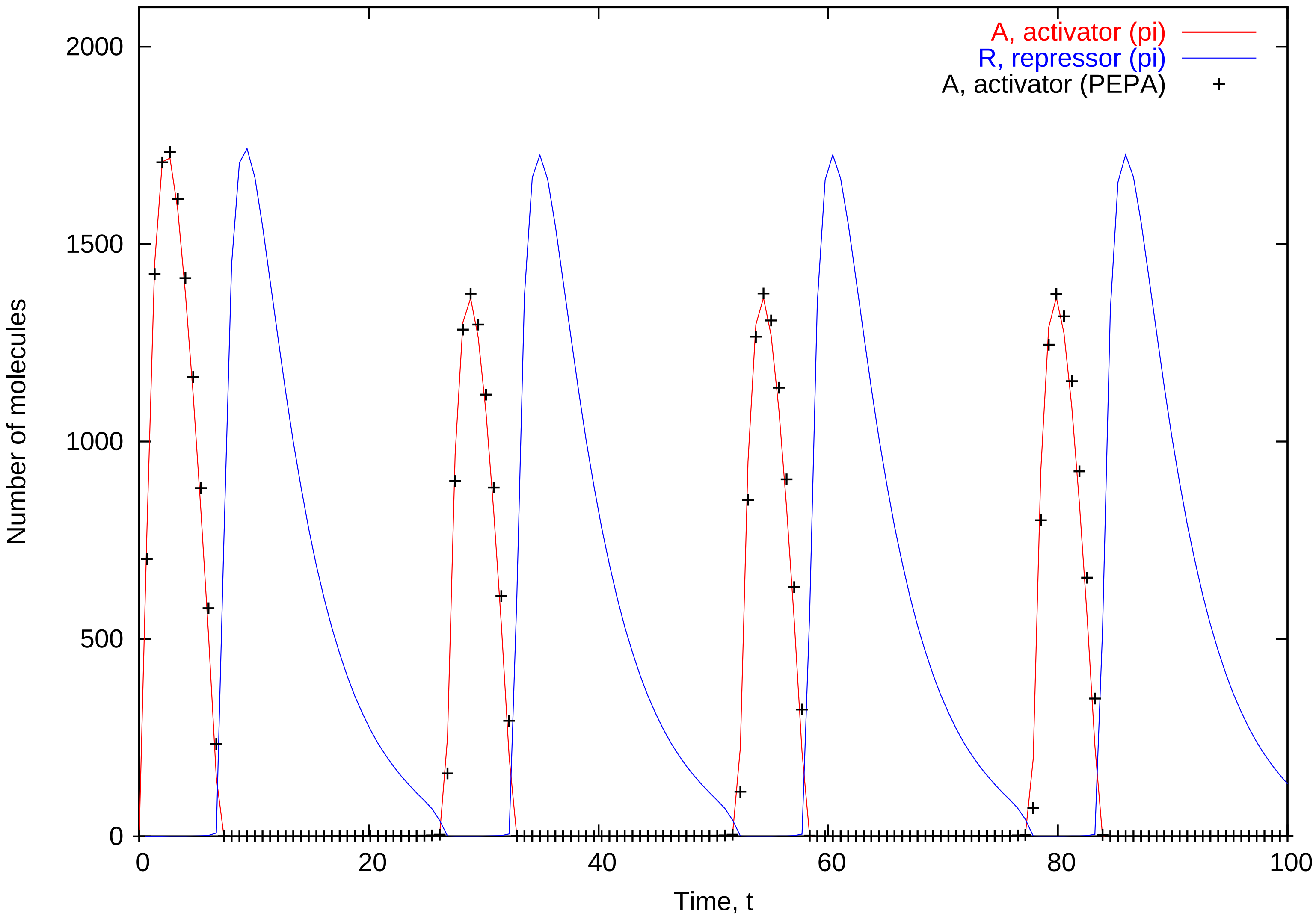
# Stochastic $\pi$ model results



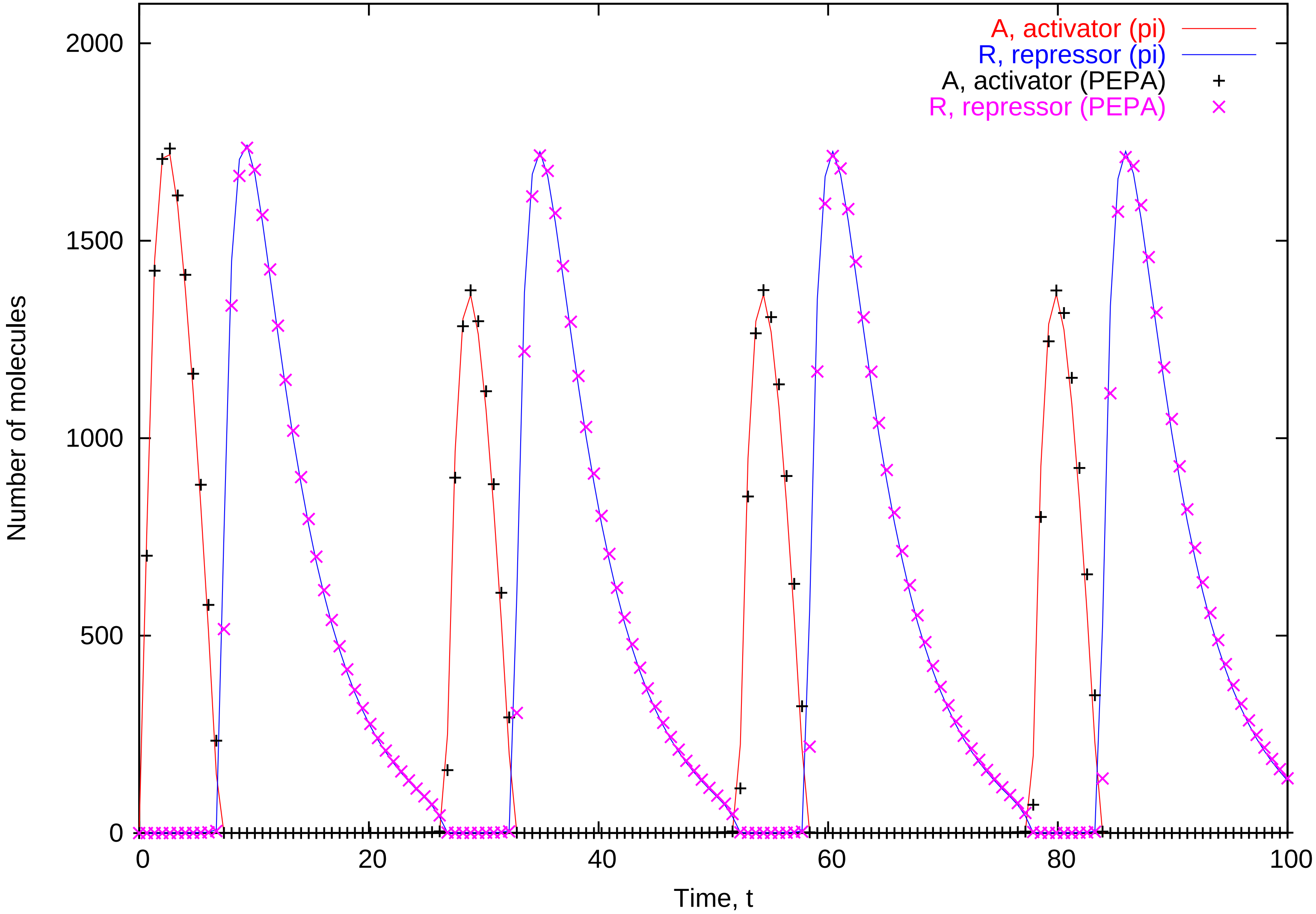
# Results: $\pi$ v PEPA



# Results: $\pi$ v PEPA



# Results: $\pi$ v PEPA



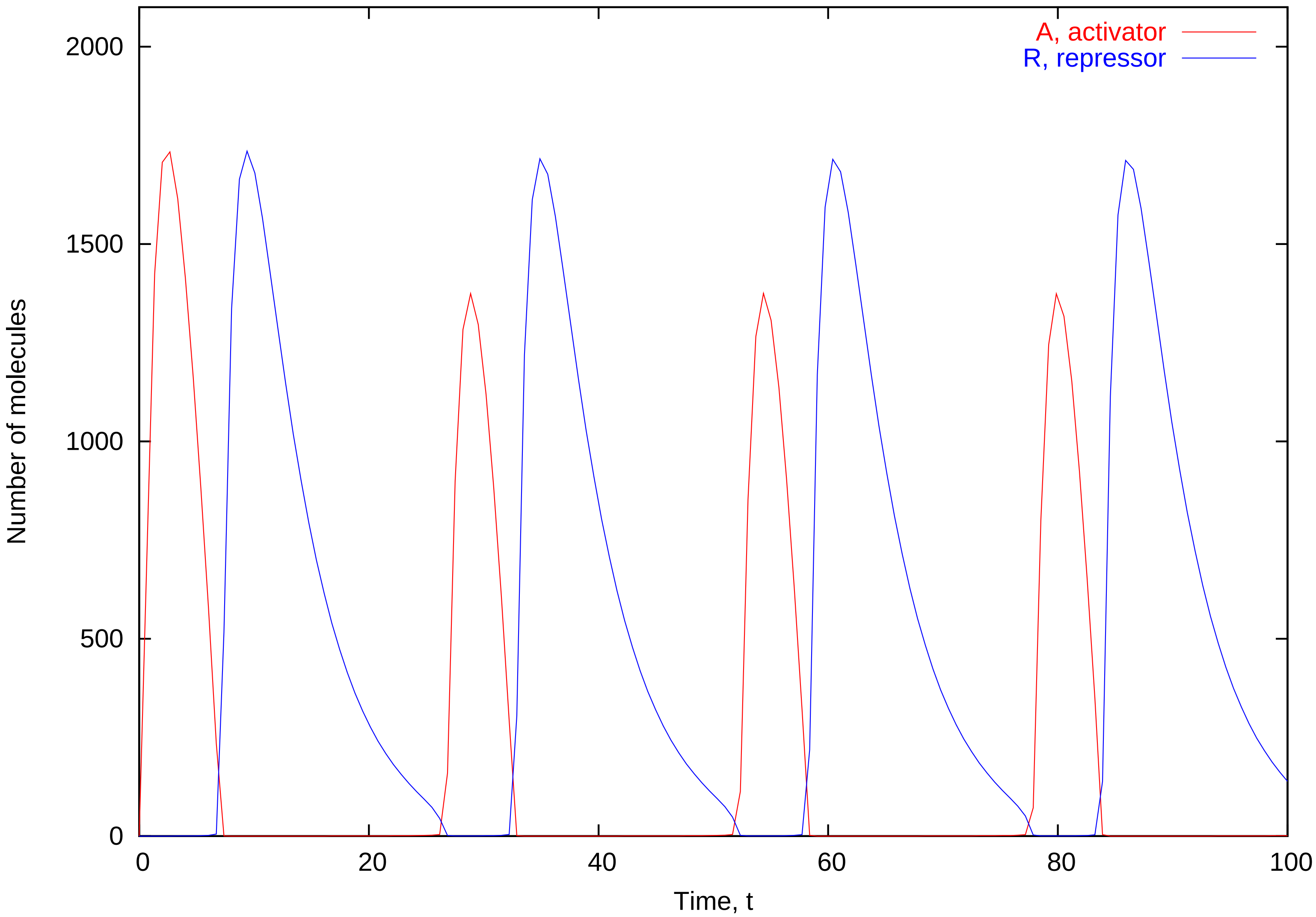
# Resource restriction

PEPA model explcitly represents the available resources:

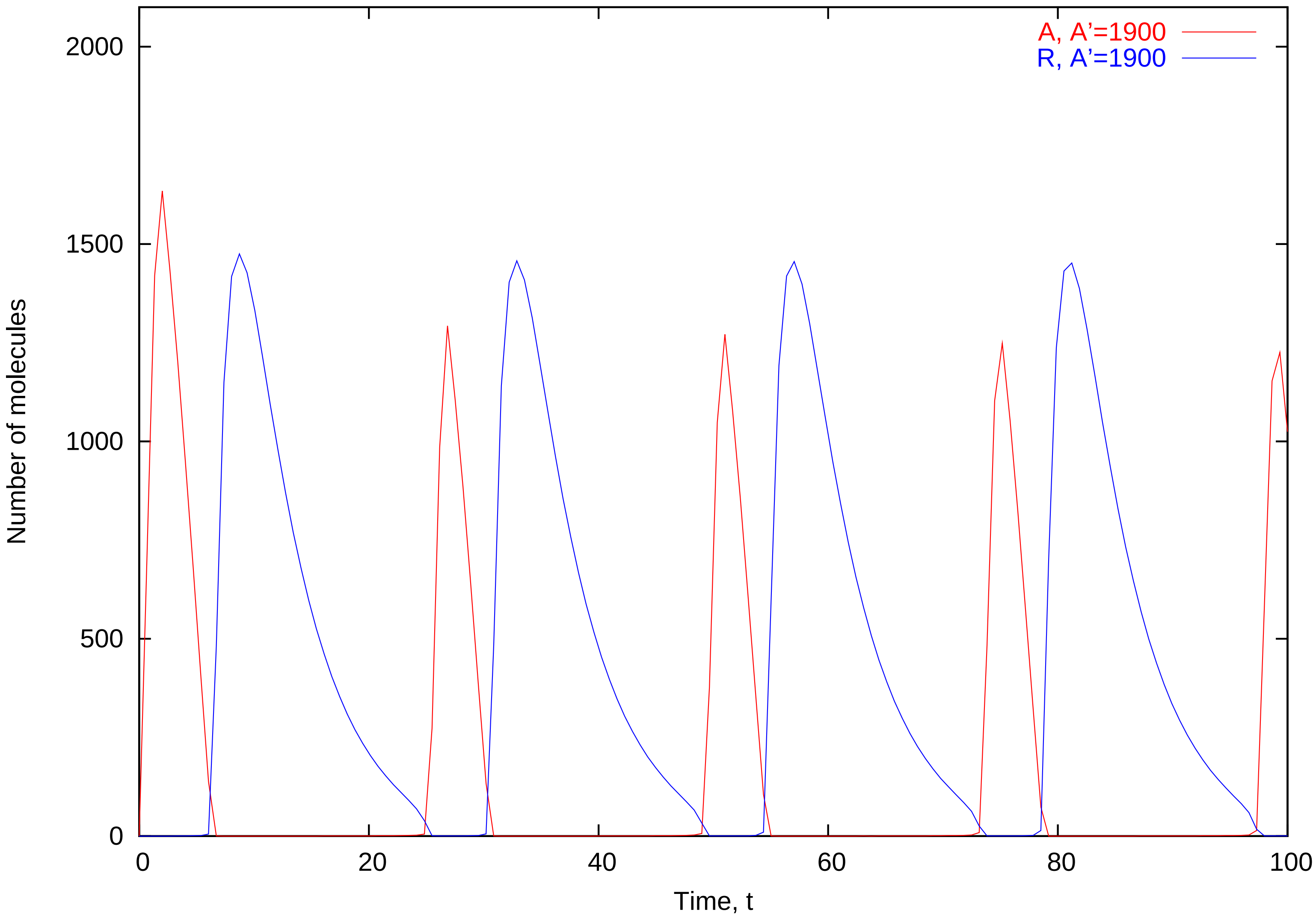
$$((D_A \underset{L}{\bowtie} M'_A[500]) \underset{M}{\bowtie} A'[2500]) \underset{N}{\bowtie} \cdots$$

...so what happens if we limit the number of molecules in the system

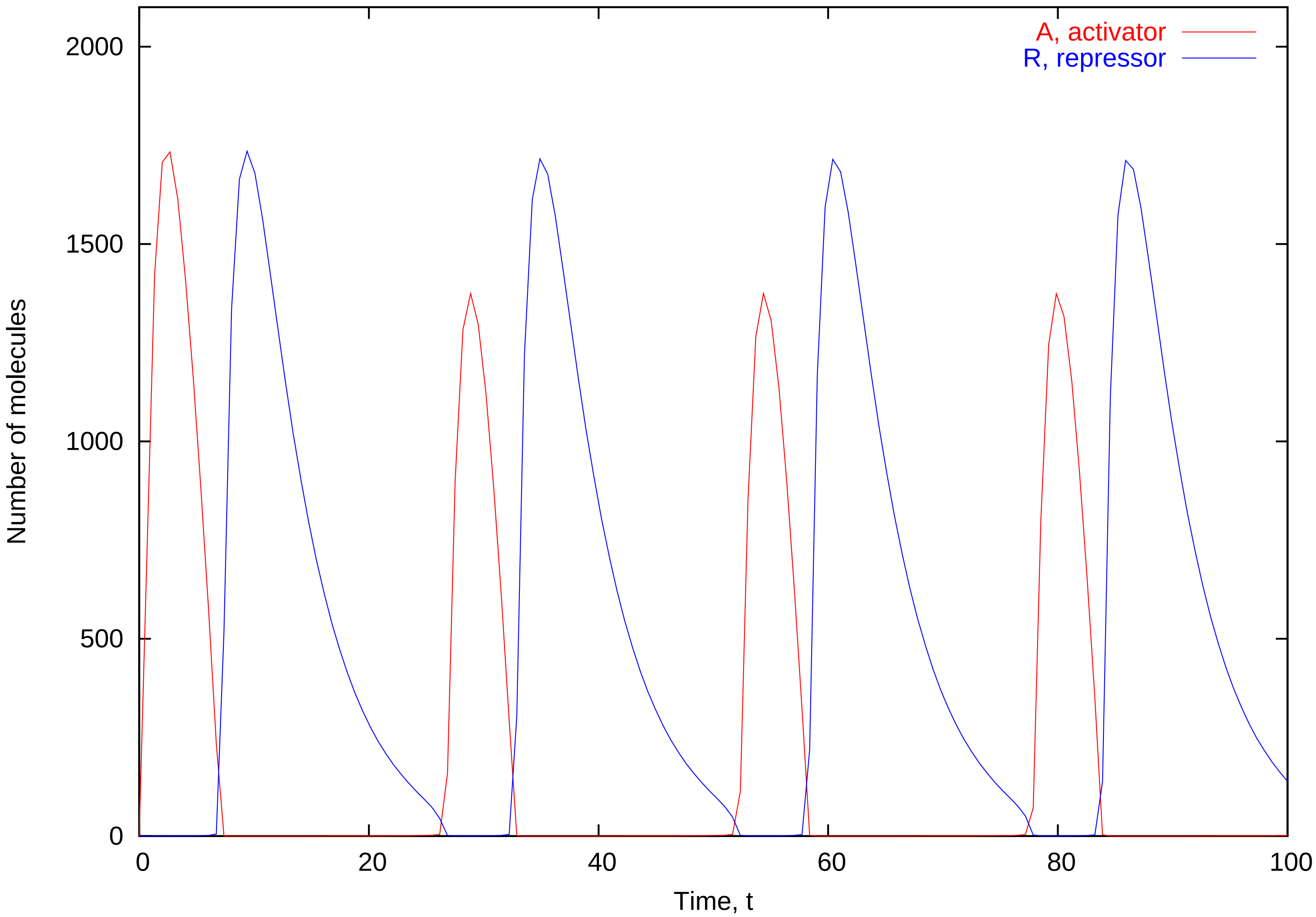
# Limiting protein A: PEPA



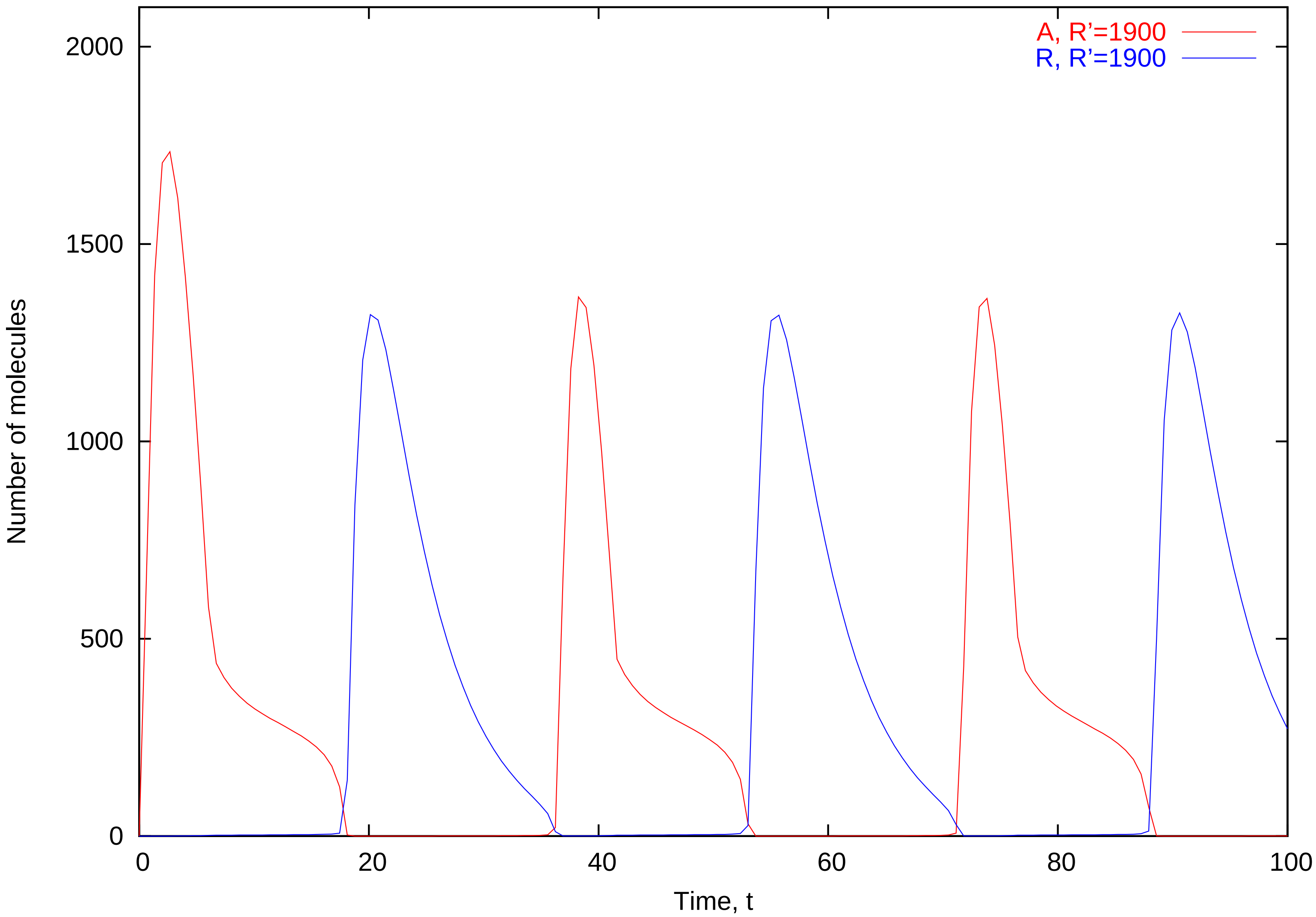
# Limiting protein A: PEPA



# Limiting protein R: PEPA



# Limiting protein R: PEPA



# Why am I late?

# Why am I late?

Obviously not enough $R$ repressor!

# 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

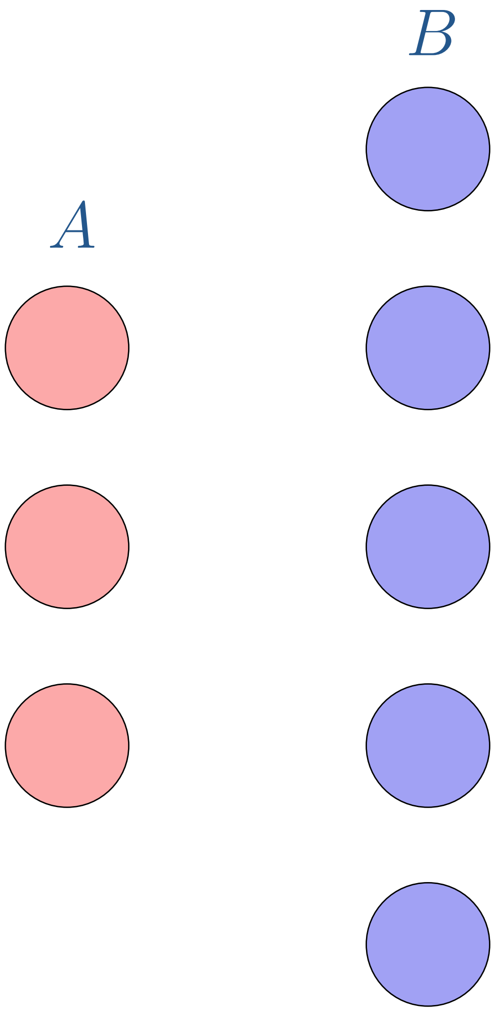
# Synchronisation: Mass action

- 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:

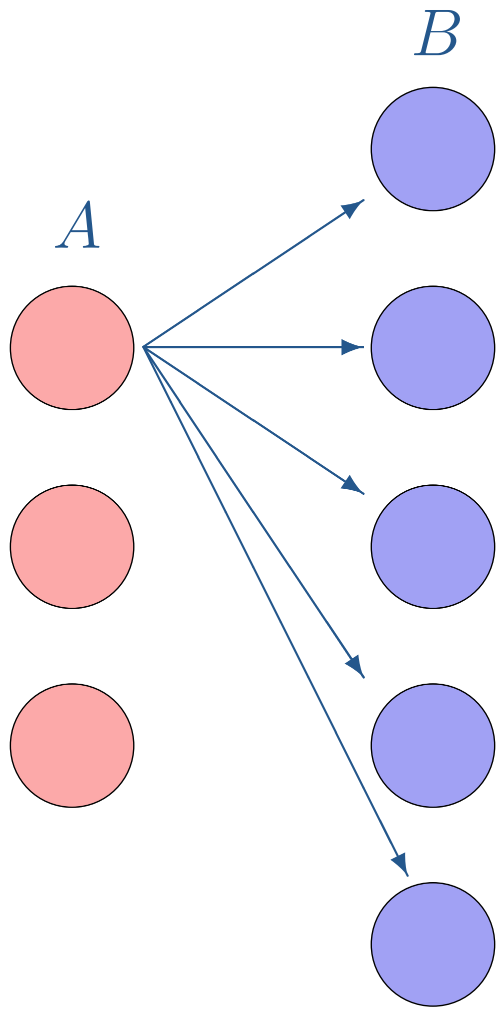
$$A + B \xrightarrow{\lambda} AB$$

- Initially $m$ $A$ molecules, $n$ $B$ molecules

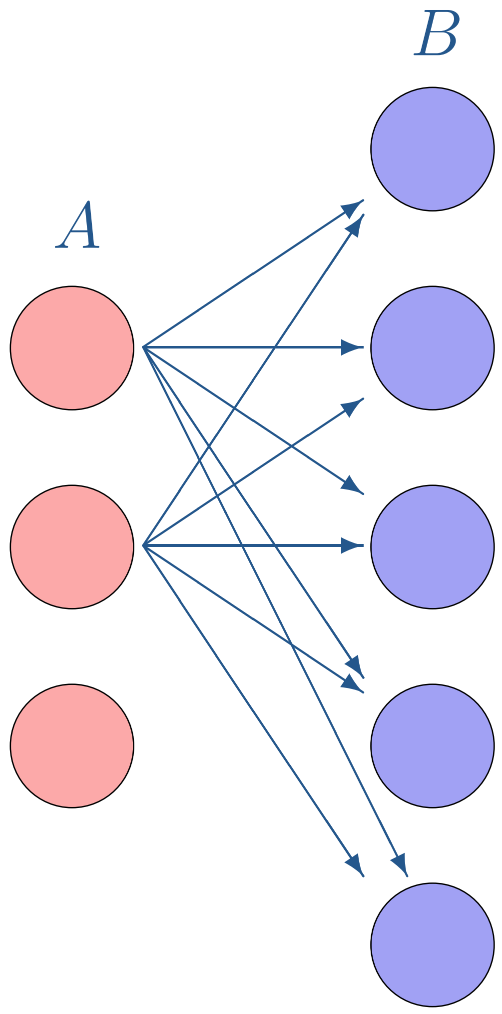
# Synchronisation: Mass action



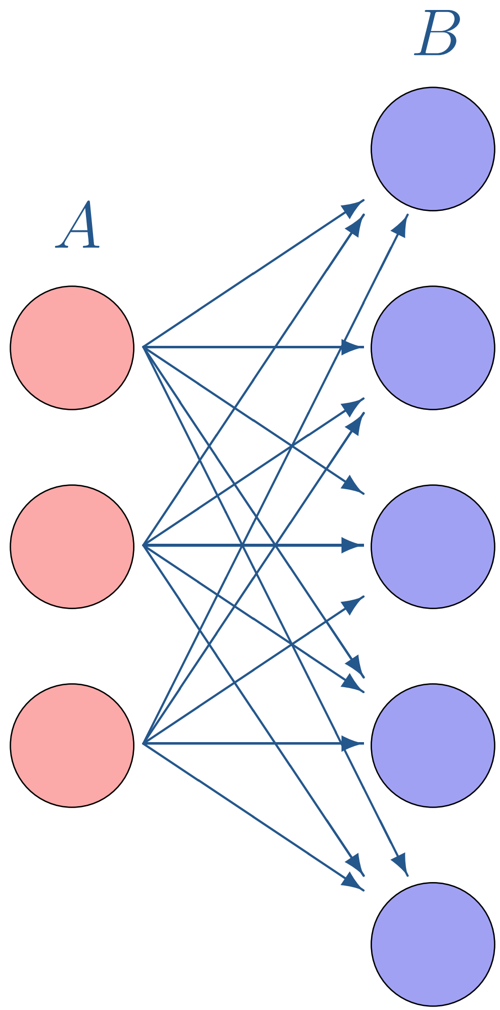
# Synchronisation: Mass action



# Synchronisation: Mass action

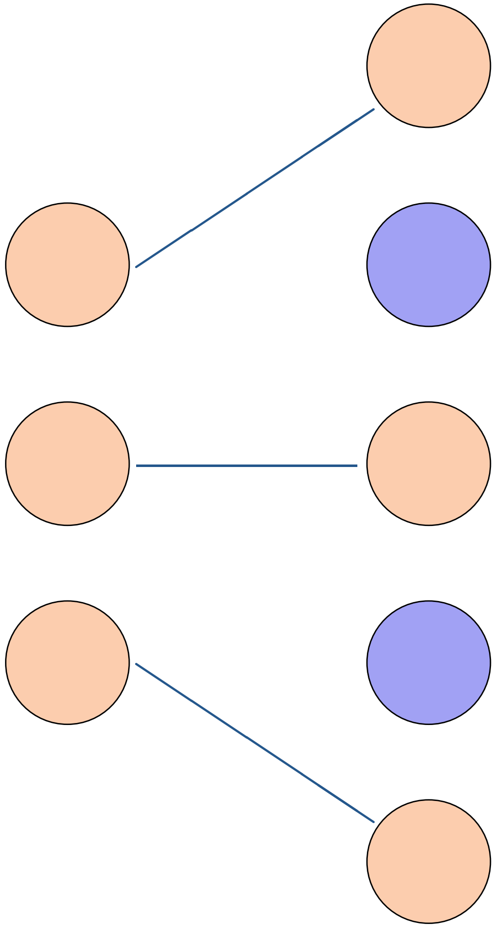


# Synchronisation: Mass action




- Total number of possible interactions: $mn$

# Synchronisation: Mass action



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

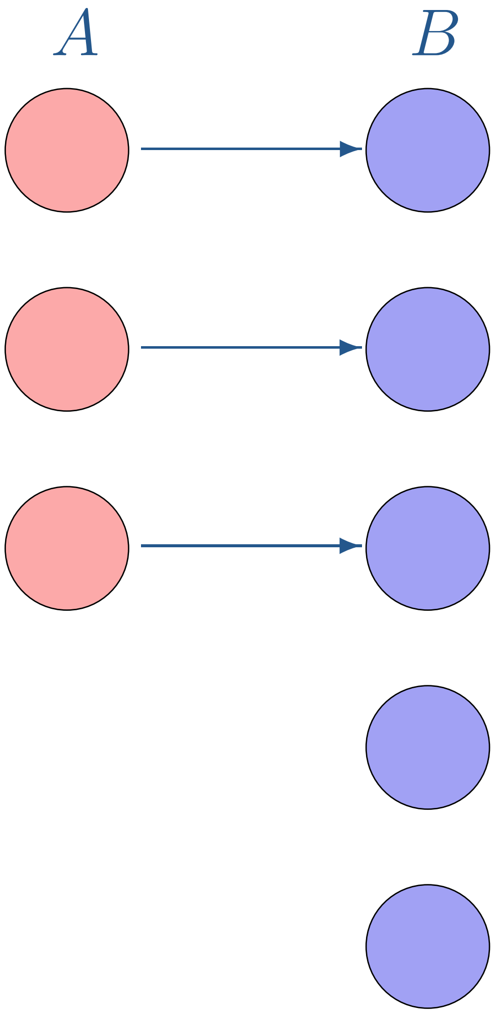
# Synchronisation: Local action

- 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:

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

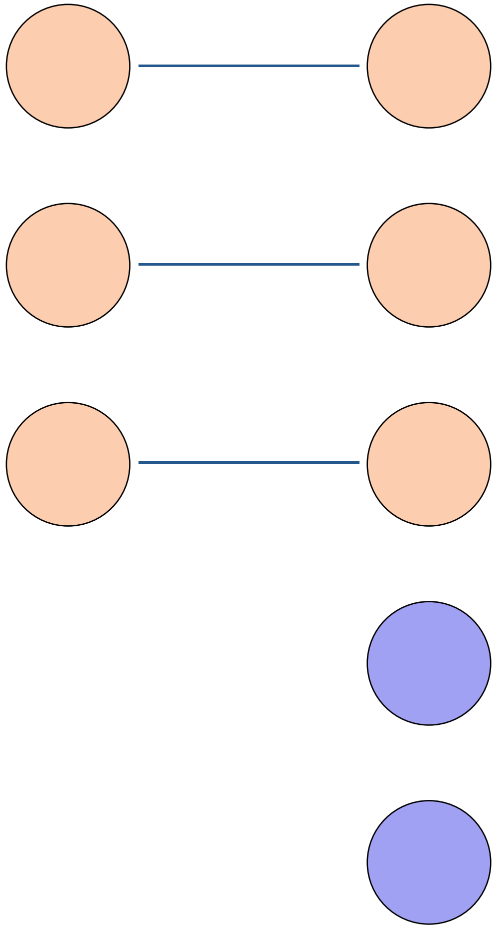
- Initially $m$ $A$ molecules, $n$ $B$ molecules

# Synchronisation: Local action




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

# Synchronisation: Local action



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

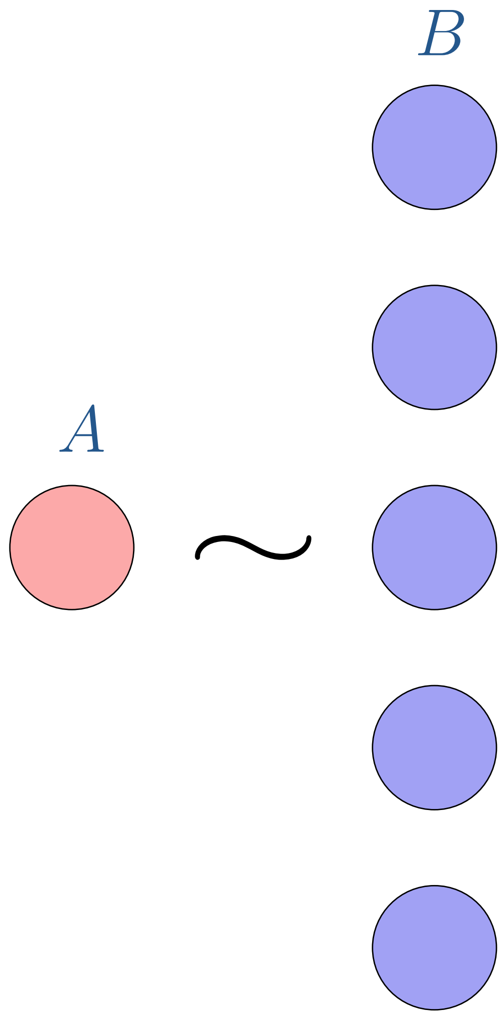
# Synchronisation: Passive action

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

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

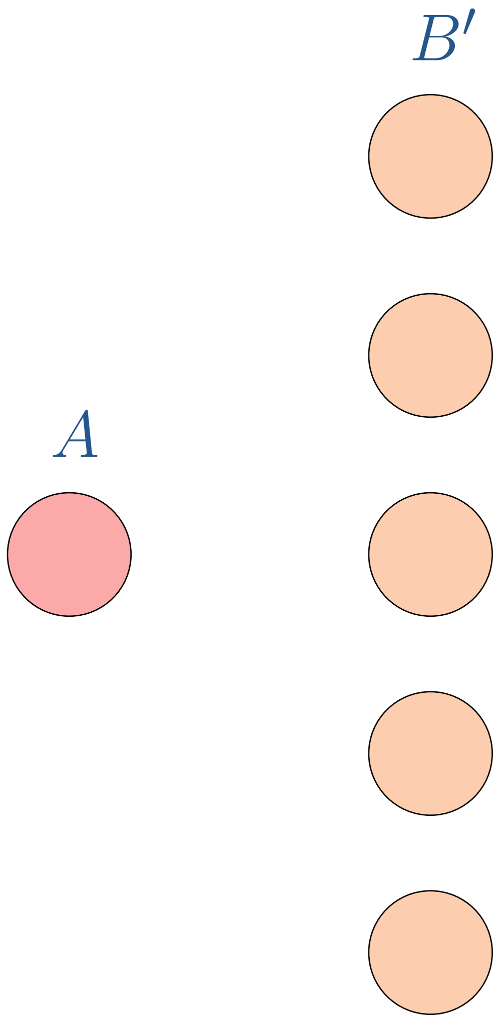
- Initially 1 $A$ molecule, $n$ $B$ molecules

# 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!)