ICNAAM 2010

Automatic reduction of stochastic rules-based models in a nutshell

Ferdinanda Camporesi
LIENS (INRIA, ENS, CNRS
University of Bologna

Jérôme Feret
LIENS (INRIA, ENS, CNRS)
Paris, France

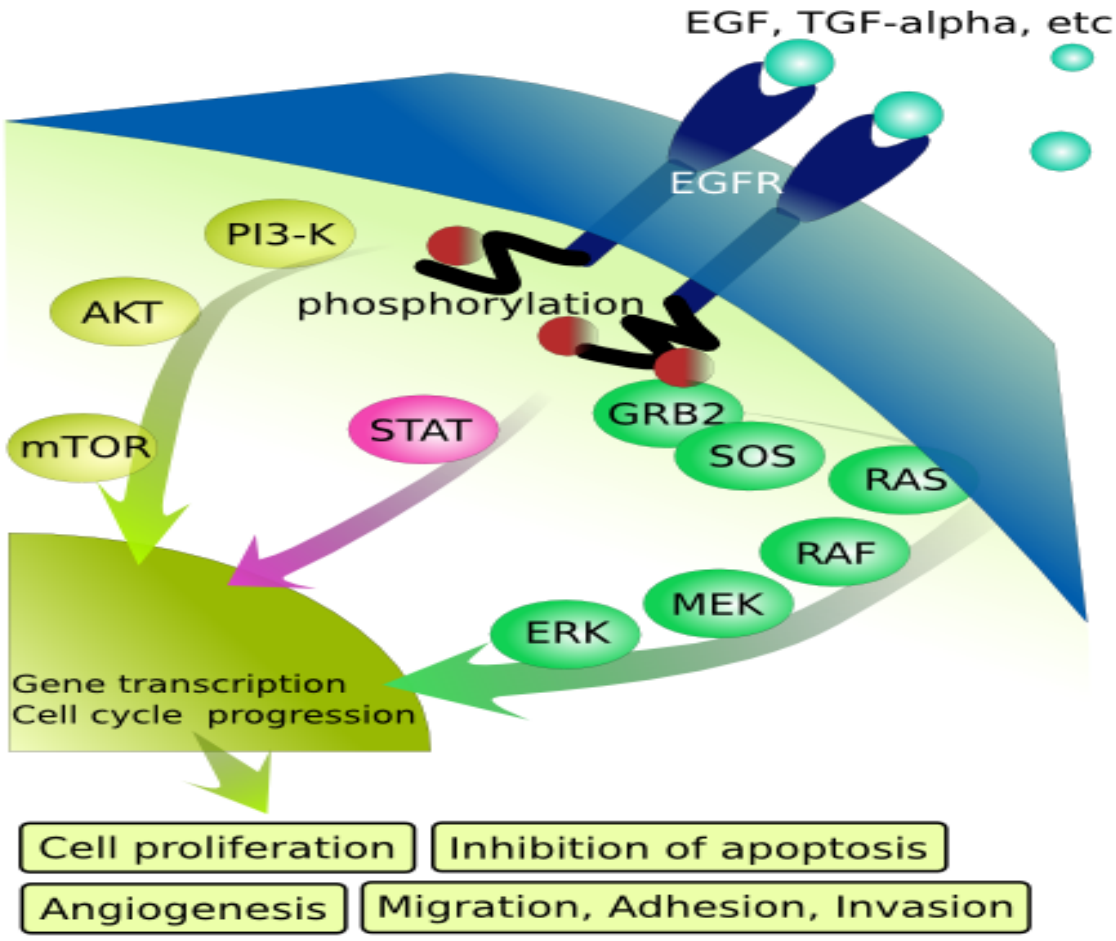
Heinz Koeppl
Ecole Polytechnique Federale de Lausanne
Lausanne, Switzerland

Tatjana Petrov
Ecole Polytechnique Federale de Lausanne
Lausanne, Switzerland

Overview

1. Context and motivations
2. Information flow
3. Symmetric sites
4. Generic framework
5. Conclusion

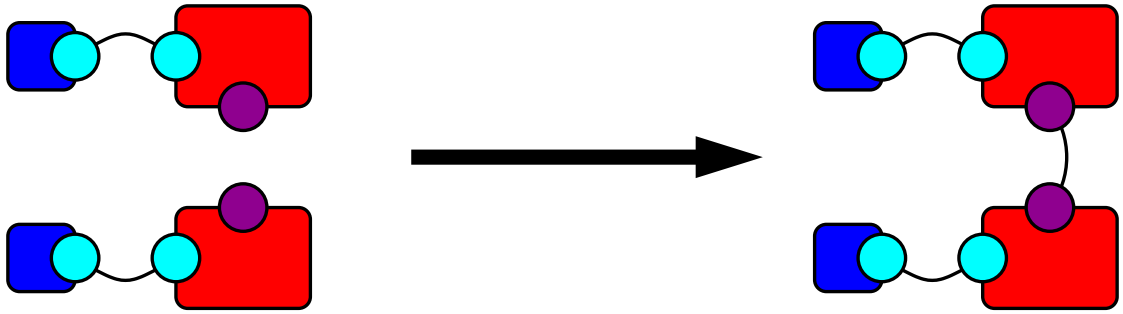
Signalling Pathways



Eikuch, 2007

Rule-based approach

We use site graph rewrite systems

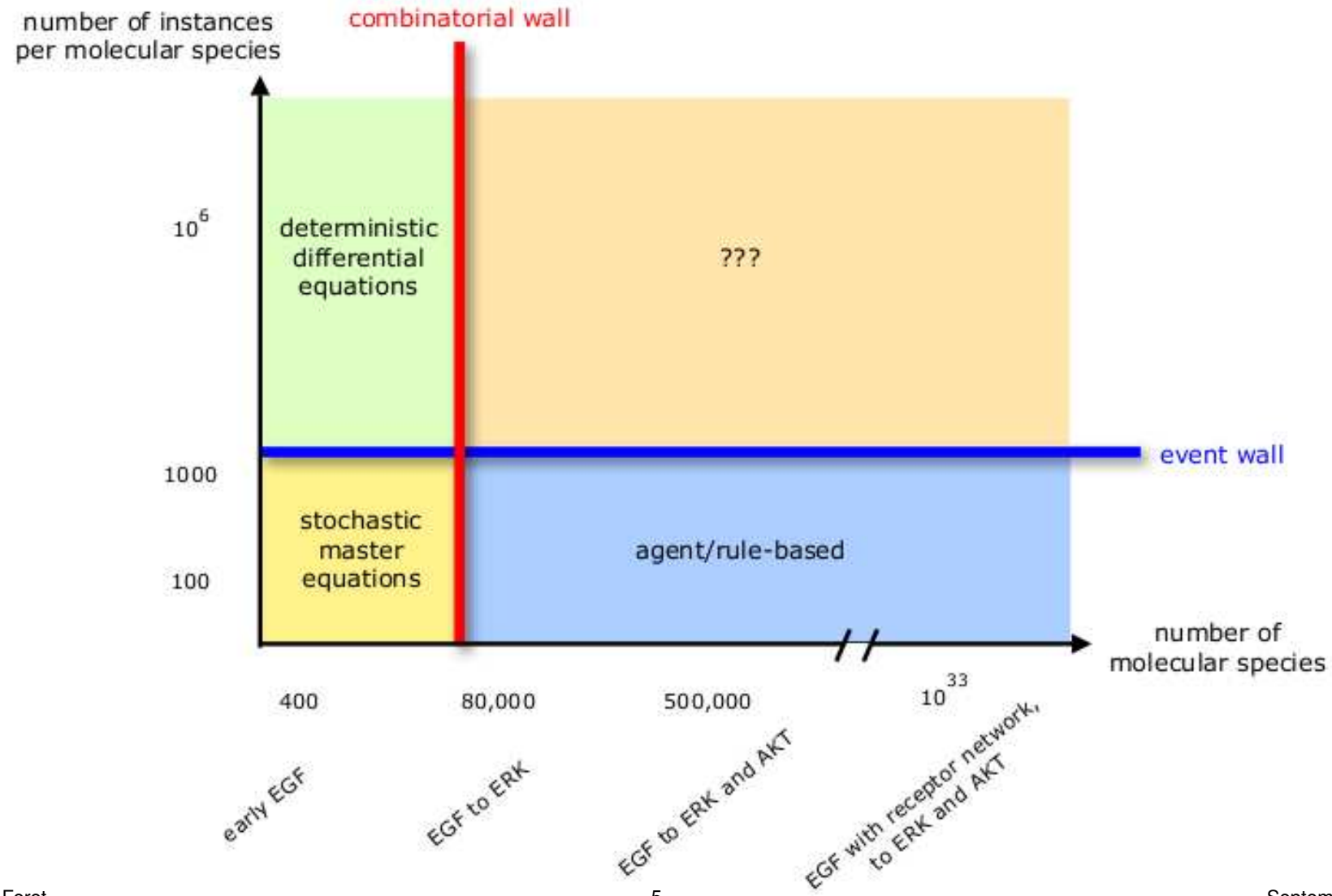


1. The description level matches with both
   - the observation level
   - and the intervention level

   of the biologist.

   We can tune the model easily.
2. Model description is very compact.
3. Quantitative semantics can be defined.

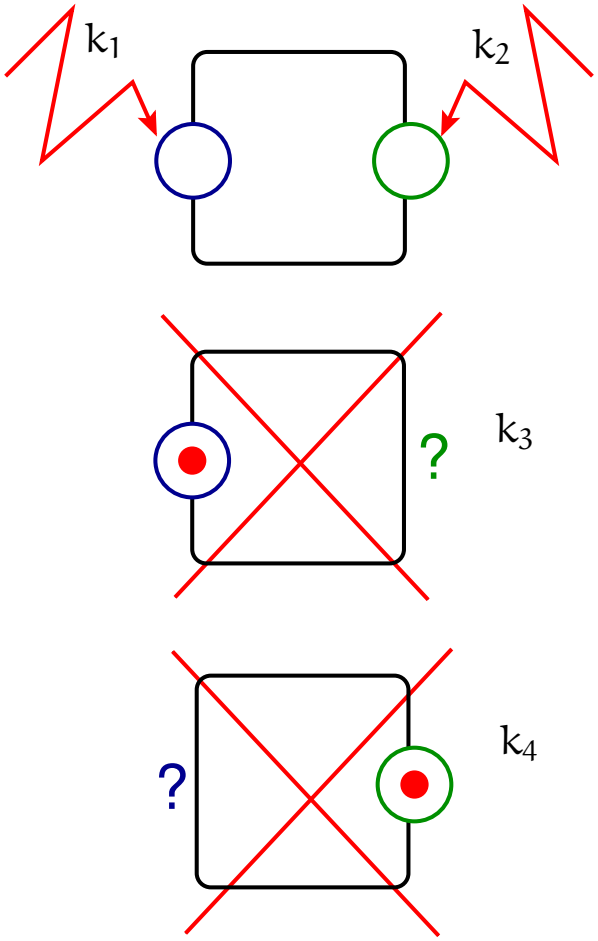
Complexity walls



Overview

1. Context and motivations
2. Information flow
3. Symmetric sites
4. Generic framework
5. Conclusion

A model with ubiquitination



$$P \xrightarrow{k_1} {}^{\star}P \qquad P^{\star} \xrightarrow{k_1} {}^{\star}P^{\star}$$

$$P \xrightarrow{k_2} P^{\star} \qquad {}^{\star}P \xrightarrow{k_2} {}^{\star}P^{\star}$$

$${}^{\star}P \xrightarrow{k_3} \emptyset$$

$${}^{\star}P^{\star} \xrightarrow{k_3} \emptyset$$

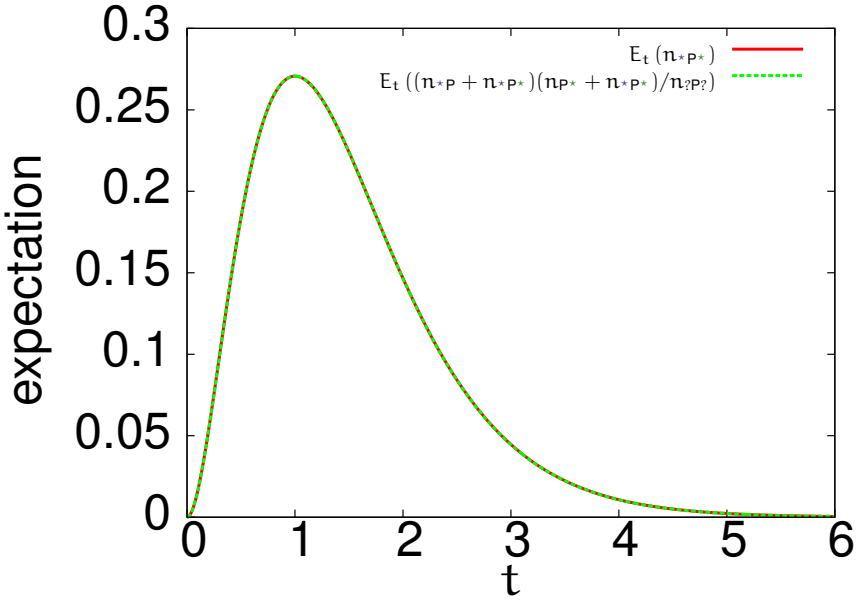
$$P^{\star} \xrightarrow{k_4} \emptyset$$

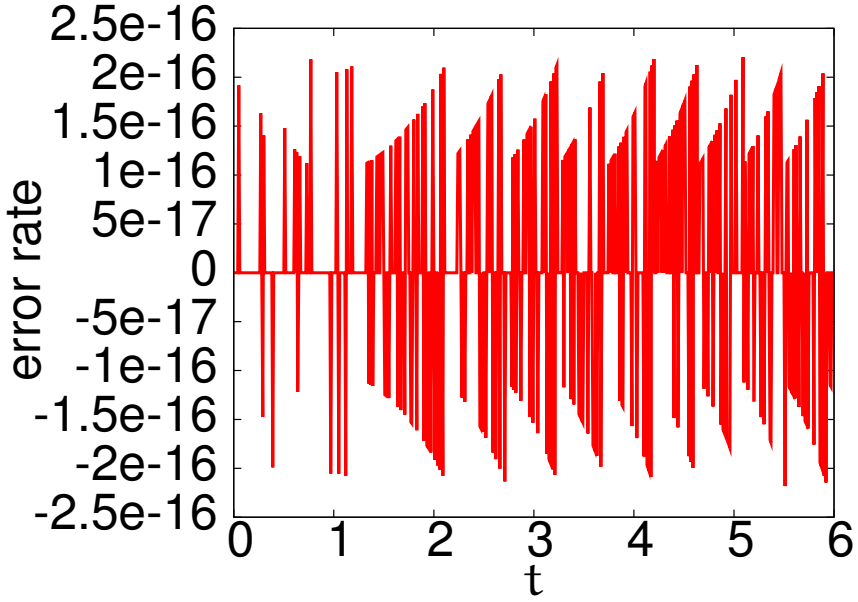
$${}^{\star}P^{\star} \xrightarrow{k_4} \emptyset$$

Statistical independence

We check numerically that:

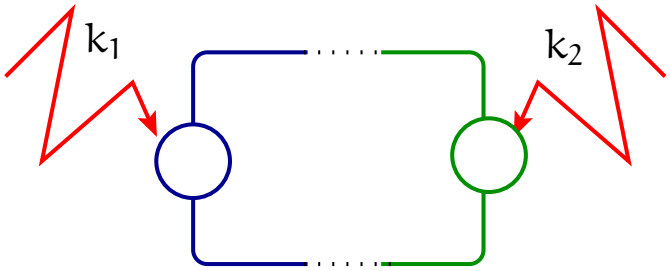
$$\mathrm{E_t}\left(n_{\star P\star}\right) = \mathrm{E_t}\left(\frac{(n_{\star P} + n_{\star P\star})(n_{P\star} + n_{\star P\star})}{n_P + n_{P\star} + n_{\star P} + n_{\star P\star}}\right).$$





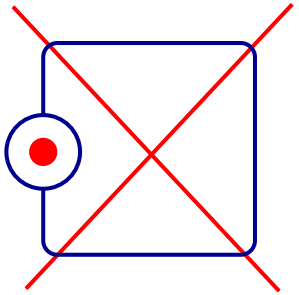
with $k_1 = k_2 = k_3 = k_4 = 1$
and two instances of P at time $t = 0$.

Reduced model



$$P \xrightarrow{k_1} {}^{\star}P$$

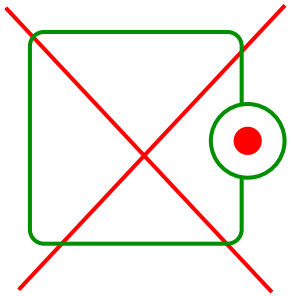
$$P \xrightarrow{k_2} P^{\star}$$



k_3

$${}^{\star}P \xrightarrow{k_3} \emptyset$$

+ side effect: remove one P

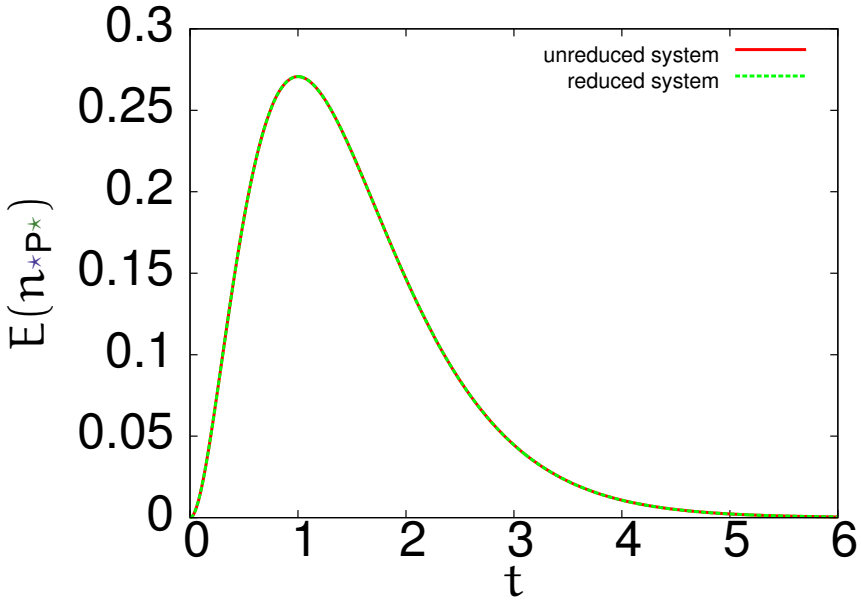


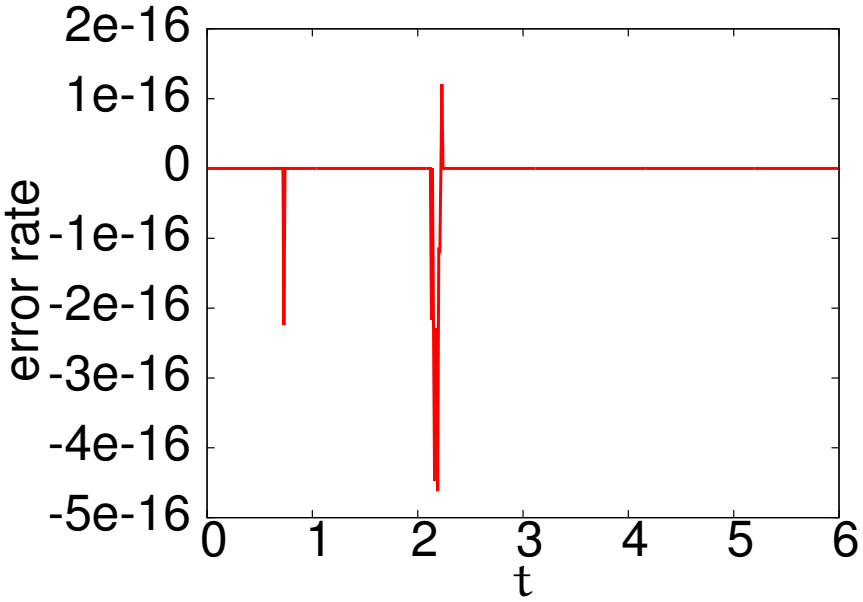
k_4

$$P^{\star} \xrightarrow{k_4} \emptyset$$

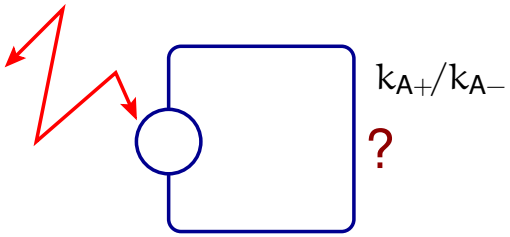
+ side effect: remove one P

Comparison between the two models

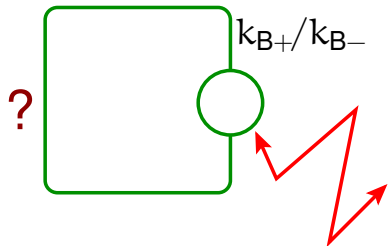




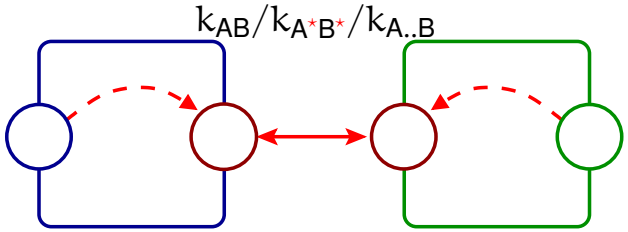
Coupled semi-reactions



$$A \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^\star, \quad AB \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^\star B, \quad AB^\star \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^\star B^\star$$



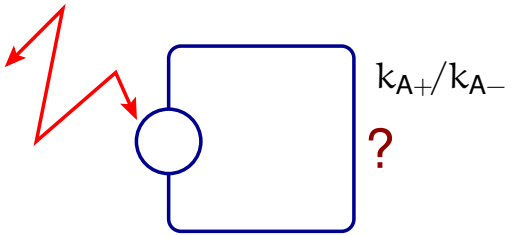
$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^\star, \quad AB \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} AB^\star, \quad A^\star B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^\star B^\star$$

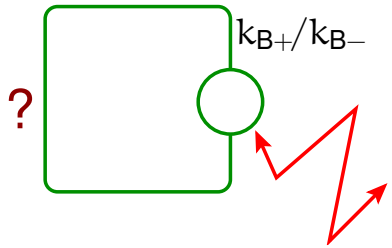


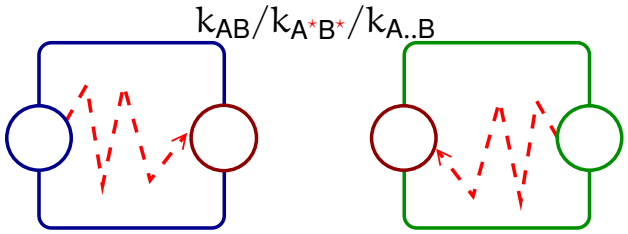
$$A + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB, \quad A^\star + B \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} A^\star B,$$

$$A + B^\star \underset{k_{A..B}}{\overset{k_{AB}}{\rightleftharpoons}} AB^\star, \quad A^\star + B^\star \underset{k_{A..B}}{\overset{k_{A^\star B^\star}}{\rightleftharpoons}} A^\star B^\star$$

Reduced model







$$A \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^\star, \quad AB^\diamond \underset{k_{A-}}{\overset{k_{A+}}{\rightleftharpoons}} A^\star B^\diamond,$$

$$B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} B^\star, \quad A^\diamond B \underset{k_{B-}}{\overset{k_{B+}}{\rightleftharpoons}} A^\diamond B^\star,$$

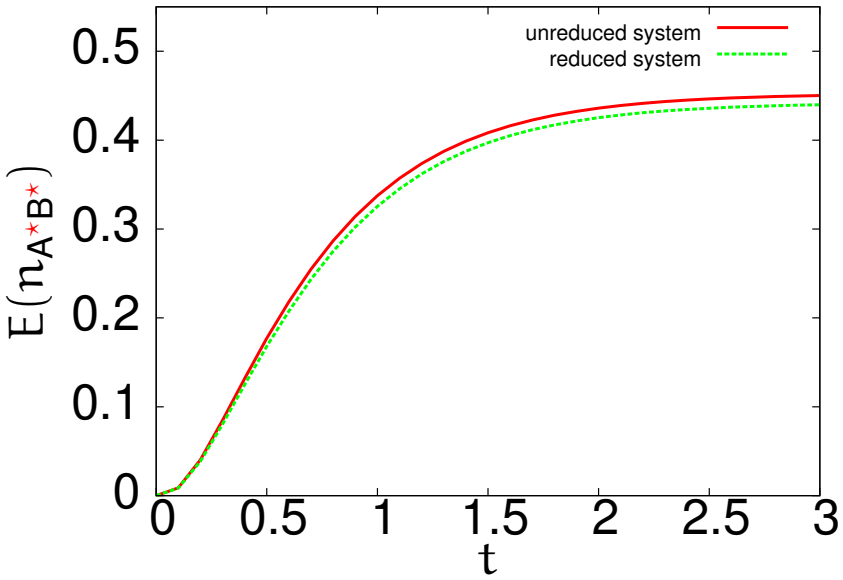
$$A + B \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{AB}}{\rightleftharpoons}} AB^\diamond + A^\diamond B,$$

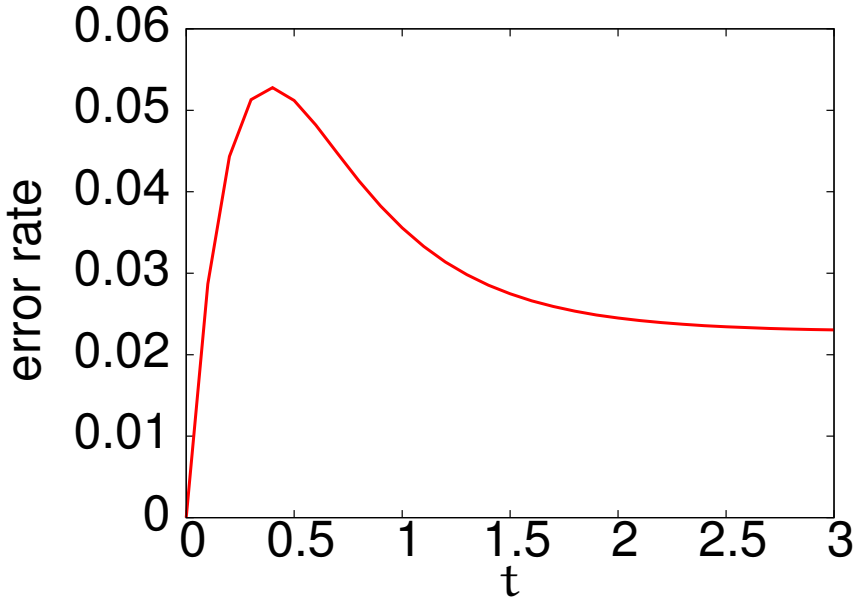
$$A^\star + B \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{AB}}{\rightleftharpoons}} A^\star B^\diamond + A^\diamond B,$$

$$A + B^\star \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{AB}}{\rightleftharpoons}} AB^\diamond + A^\diamond B^\star,$$

$$A^\star + B^\star \underset{k_{A..B}/(n_{A^\diamond B}+n_{A^\diamond B^\star})}{\overset{k_{A^\star B^\star}}{\rightleftharpoons}} A^\star B^\diamond + A^\diamond B^\star$$

Comparison between the two models

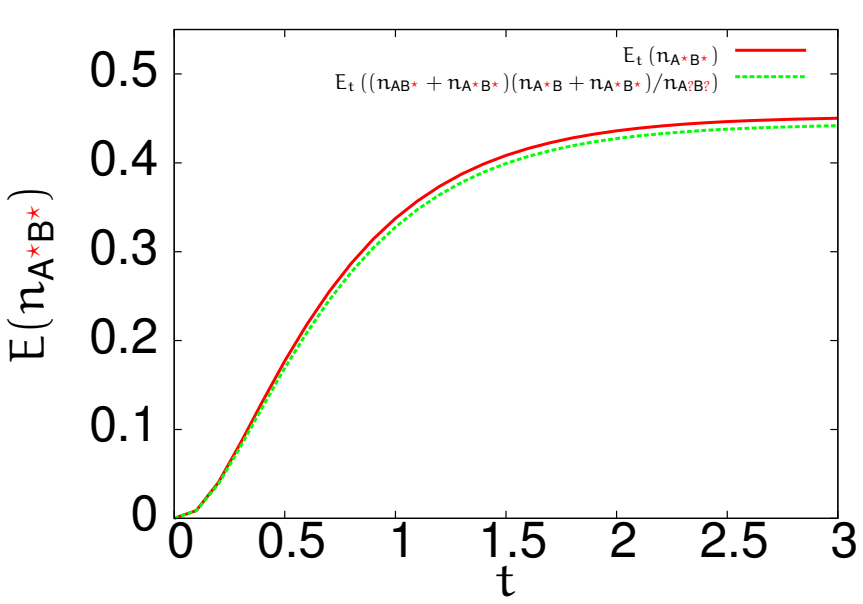


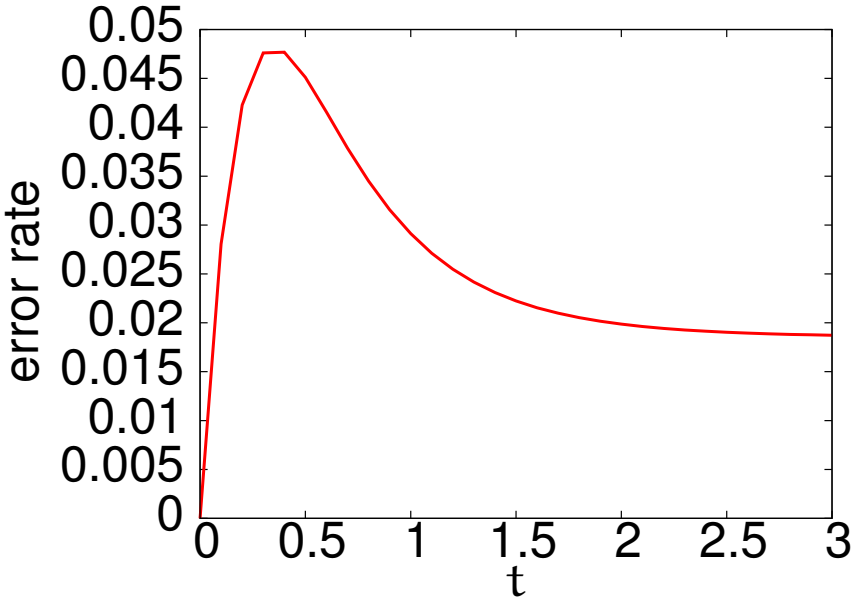


with $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$, $k_{A^\star B^\star} = 10$,
and two instances of A and B at time $t = 0$.

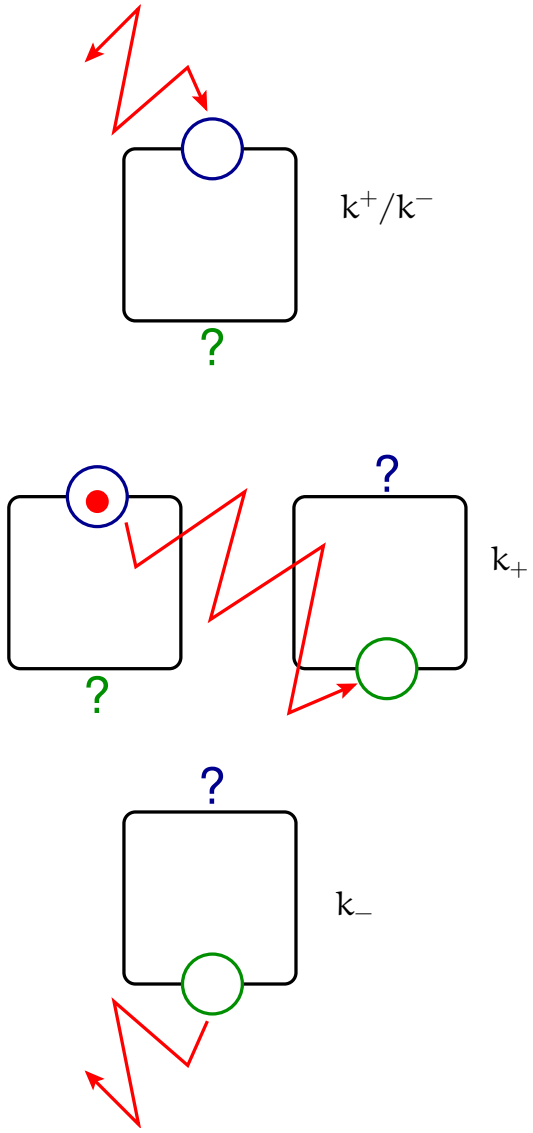
Although the reduction is correct in the ODE semantics.

Degree of correlation (in the unreduced model)





Distant control



$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^\star$$

$$A_\star \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^\star_\star$$

$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$

$$A^\star + A^\star \xrightarrow{k_+} A^\star_\star + A^\star$$

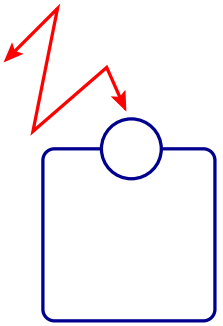
$$A + A^\star_\star \xrightarrow{k_+} A_\star + A^\star_\star$$

$$A^\star + A^\star_\star \xrightarrow{k_+} A^\star_\star + A^\star_\star$$

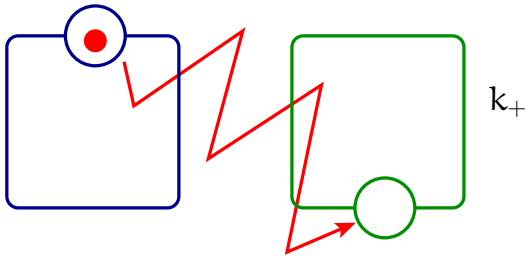
$$A^\star_\star \xrightarrow{k_-} A^\star$$

$$A_\star \xrightarrow{k_-} A$$

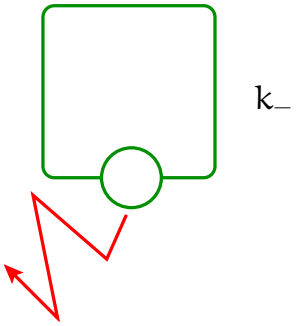
Reduced model



$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} A^\star$$

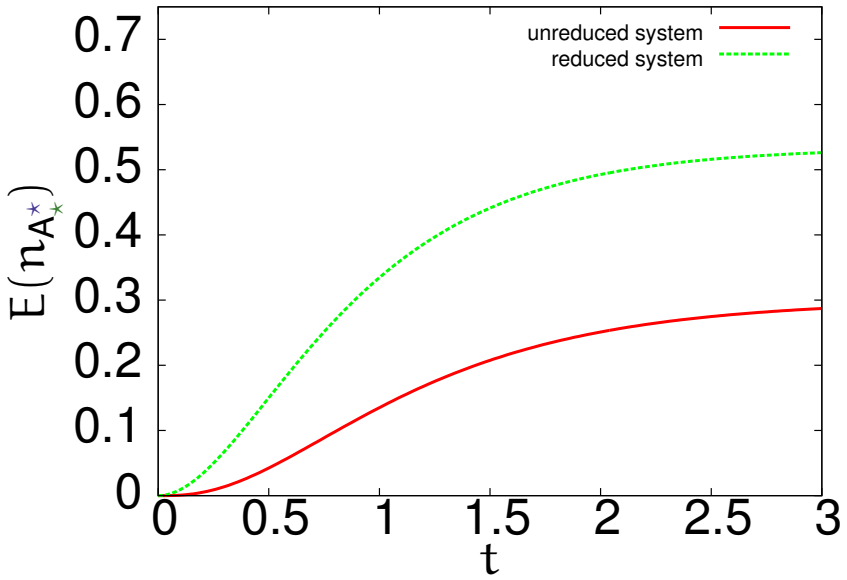


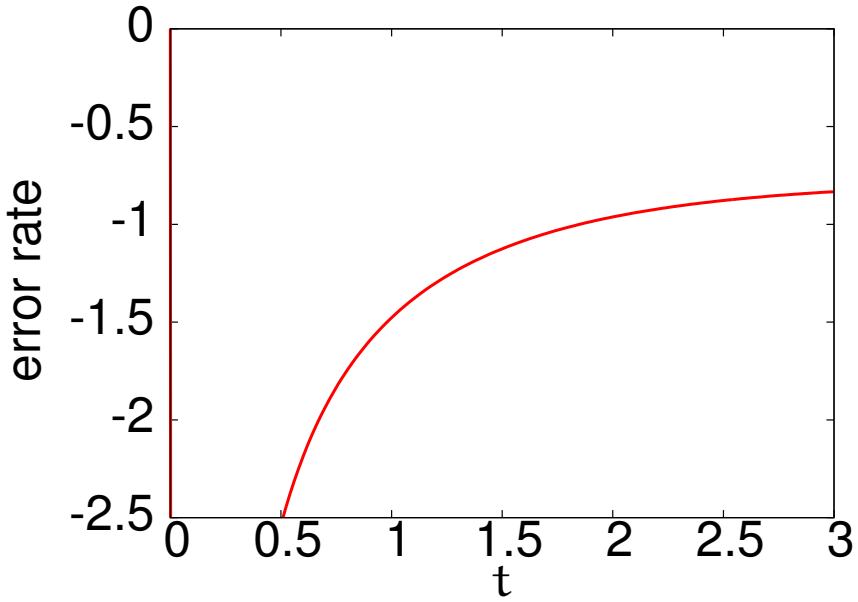
$$A + A^\star \xrightarrow{k_+} A_\star + A^\star$$



$$A_\star \xrightarrow{k_-} A$$

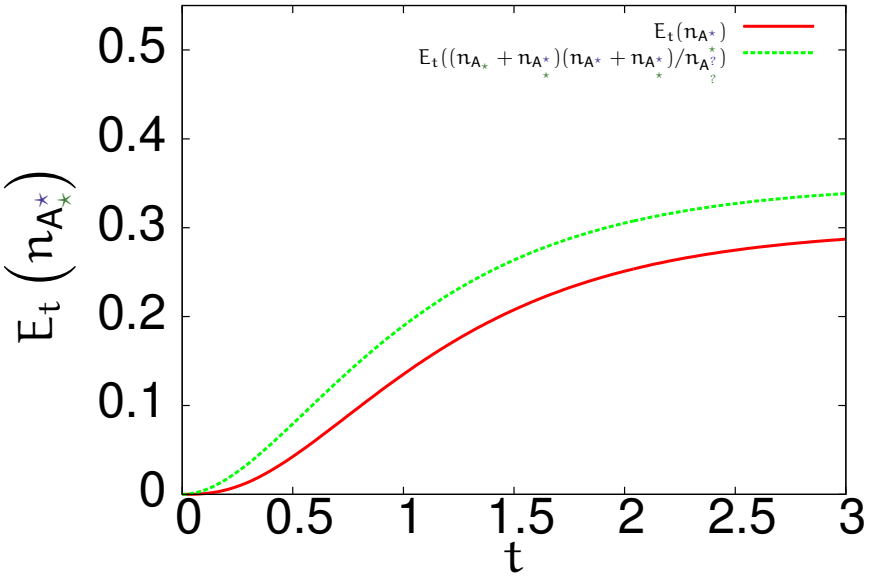
Comparison between the two models

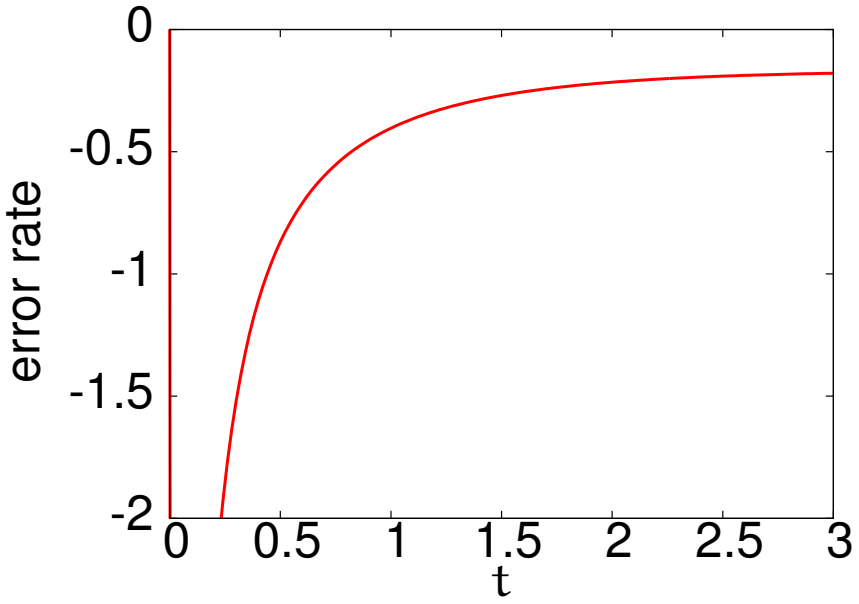




with $k^+ = k^- = k_+ = k_- = 1$,
and two instances of A at time $t = 0$.

Degree of correlation (in the unreduced model)

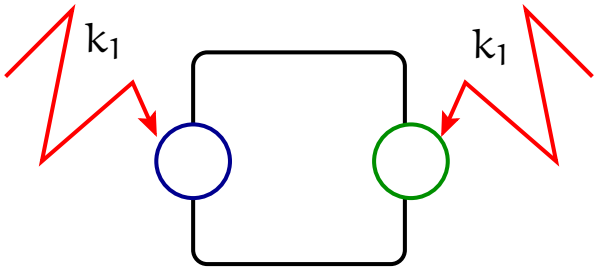




Overview

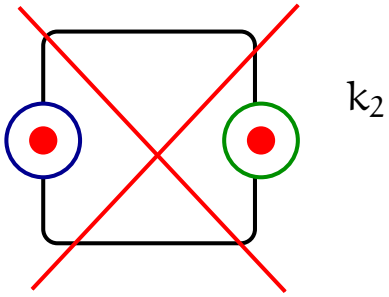
1. Context and motivations
2. Information flow
3. Symmetric sites
4. Generic framework
5. Conclusion

A model with symmetries



$$P \xrightarrow{k_1} {}^\star P \qquad P^\star \xrightarrow{k_1} {}^\star P^\star$$

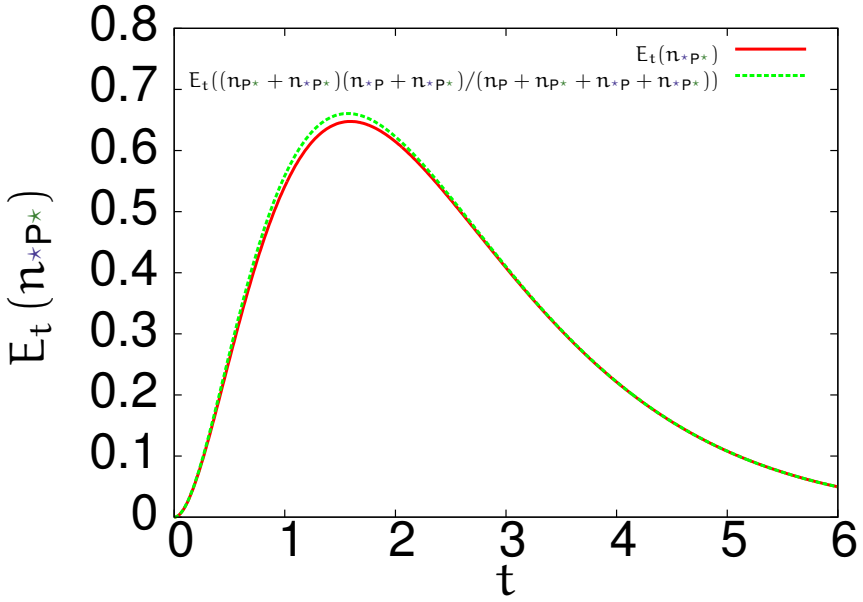
$$P \xrightarrow{k_1} P^\star \qquad {}^\star P \xrightarrow{k_1} {}^\star P^\star$$

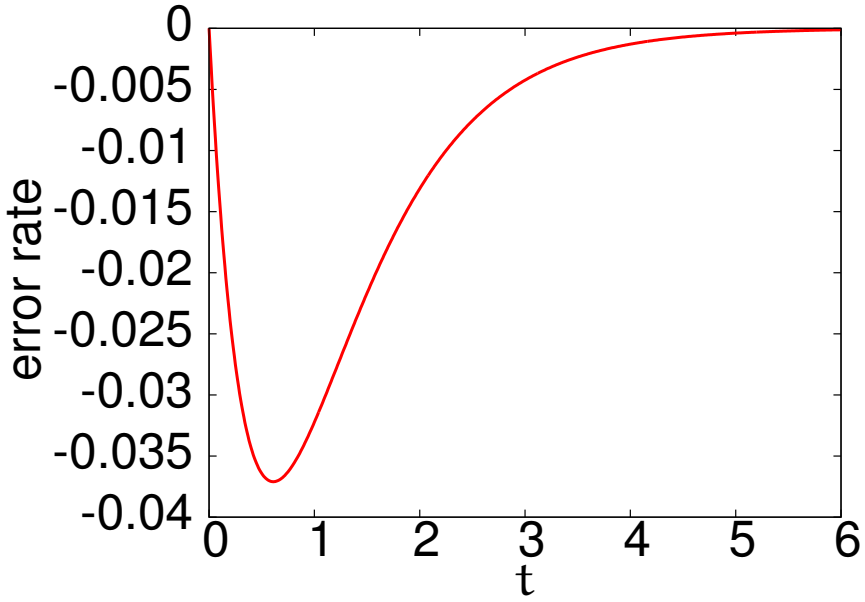


$${}^\star P^\star \xrightarrow{k_2} \emptyset$$

Degree of correlation (in the unreduced model)

$$E_t\left(n_{\star P^\star}\right) = E_t\left(\frac{(n_{\star P} + n_{\star P^\star})(n_{P^\star} + n_{\star P^\star})}{n_P + n_{P^\star} + n_{\star P} + n_{\star P^\star}}\right).$$



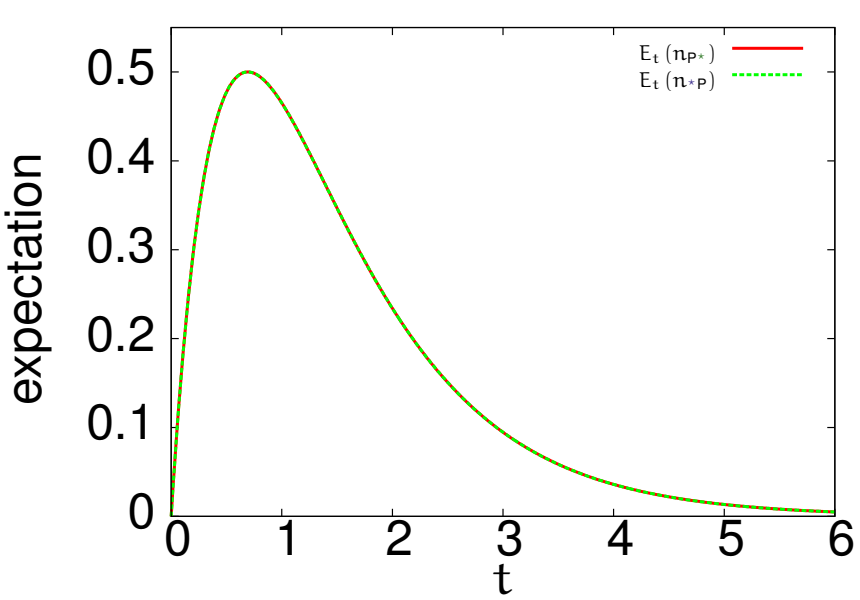


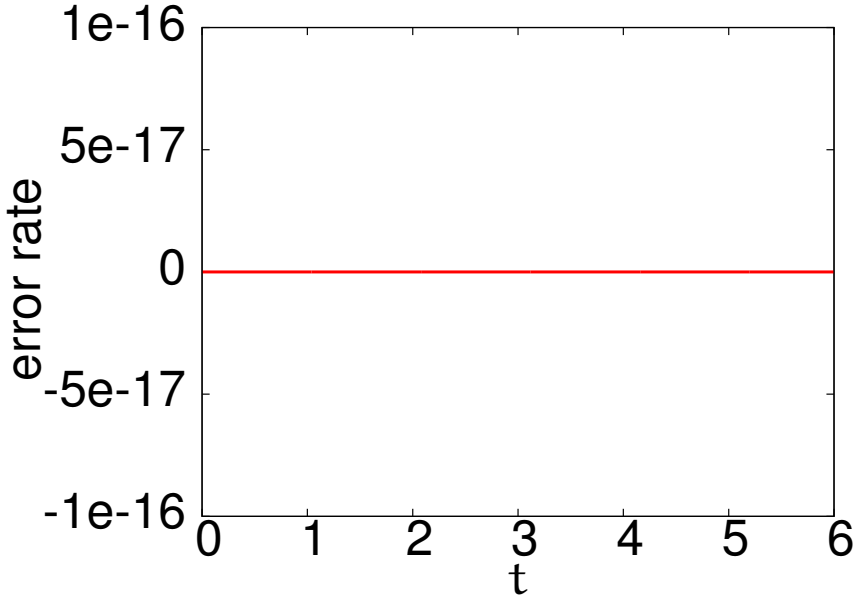
with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Equivalent chemical species

We check numerically that:

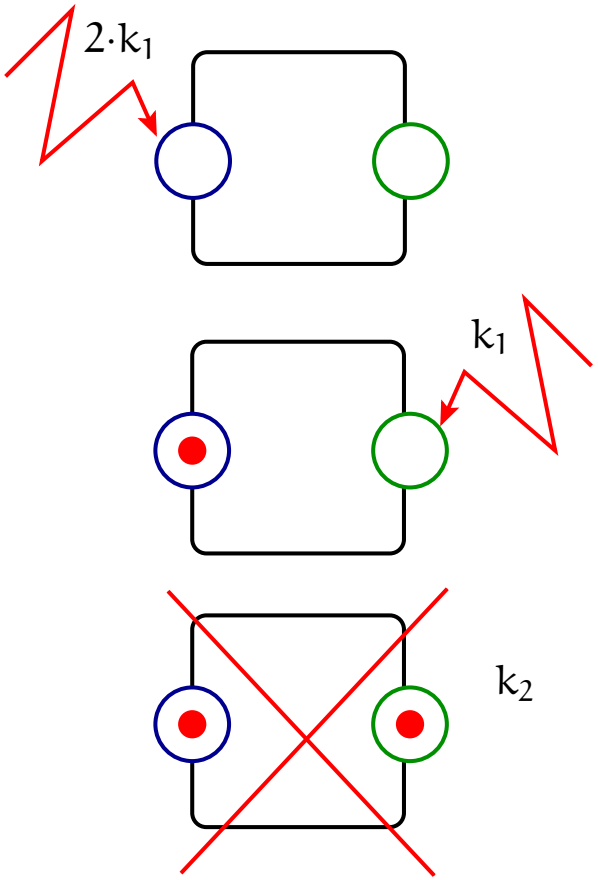
$$E_t\left(n_{P\star}\right) = E_t\left(n_{\star P}\right).$$





with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Reduced model



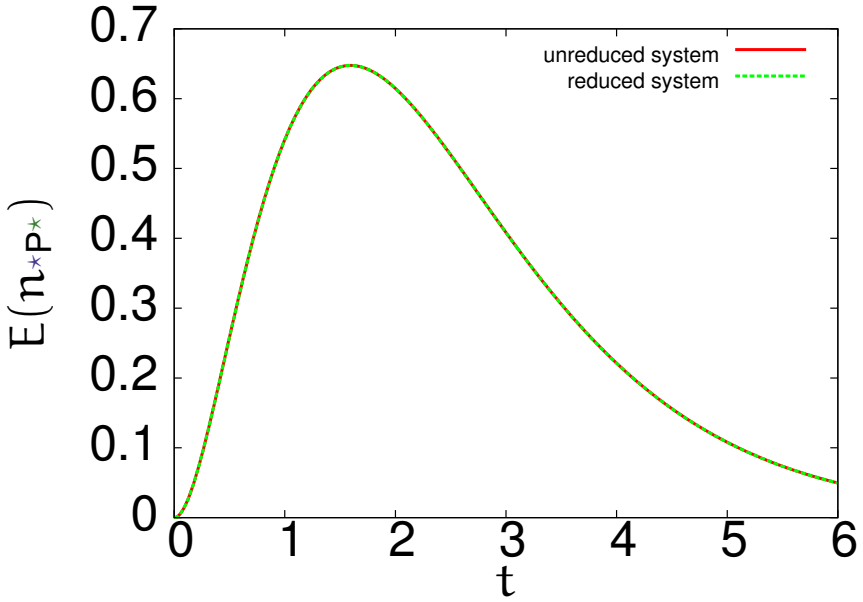
$$P \xrightarrow{2 \cdot k_1} {}^{\star}P$$

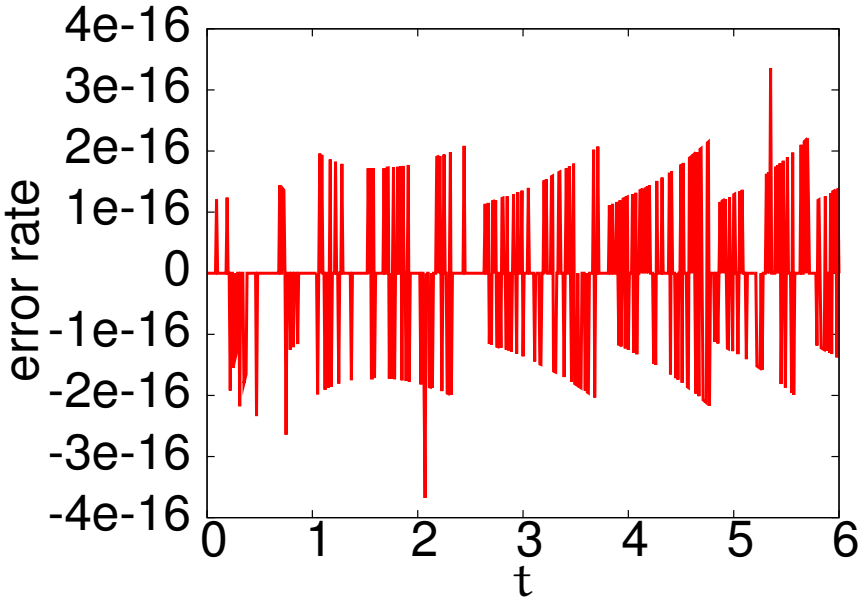
$${}^{\star}P \xrightarrow{k_1} {}^{\star}P^{\star}$$

$${}^{\star}P^{\star} \xrightarrow{k_2} \emptyset$$

Exponential reduction!!!

Comparison between the two models





with $k_1 = k_2 = 1$
and two instances of P at time $t = 0$.

Overview

1. Context and motivations
2. Information flow
3. Symmetric sites
4. Generic framework
5. Conclusion

Weighted Labelled Transition Systems

A weighted-labelled transition system $\mathcal{W}$ is given by:

- $\mathcal{Q}$, a countable set of states;
- $\mathcal{L}$, a set of labels;
- $w : \mathcal{Q} \times \mathcal{L} \times \mathcal{Q} \to \mathbb{R}_0^+$, a weight function;
- $\pi_0 : \mathcal{Q} \to [0, 1]$, an initial probability distribution.

We also assume that:

- the system is finitely branching, i.e.:
  - the set $\{q \in \mathcal{Q} \mid \pi_0(q) > 0\}$ is finite
  - and, for any $q \in \mathcal{Q}$, the set $\{l, q' \in \mathcal{L} \times \mathcal{Q} \mid w(q, l, q') > 0\}$ is finite.
- the system is deterministic:
  if $w(q, \lambda, q_1) > 0$ and $w(q, \lambda, q_2) > 0$, then: $q_1 = q_2$.

Trace distribution

A cylinder set of traces is defined as:

$$\tau \stackrel{\Delta}{=} q_0 \stackrel{\lambda_1, I_1}{\rightarrow} q_1 \ldots q_{k-1} \stackrel{\lambda_k, I_k}{\rightarrow} q_k$$

where:

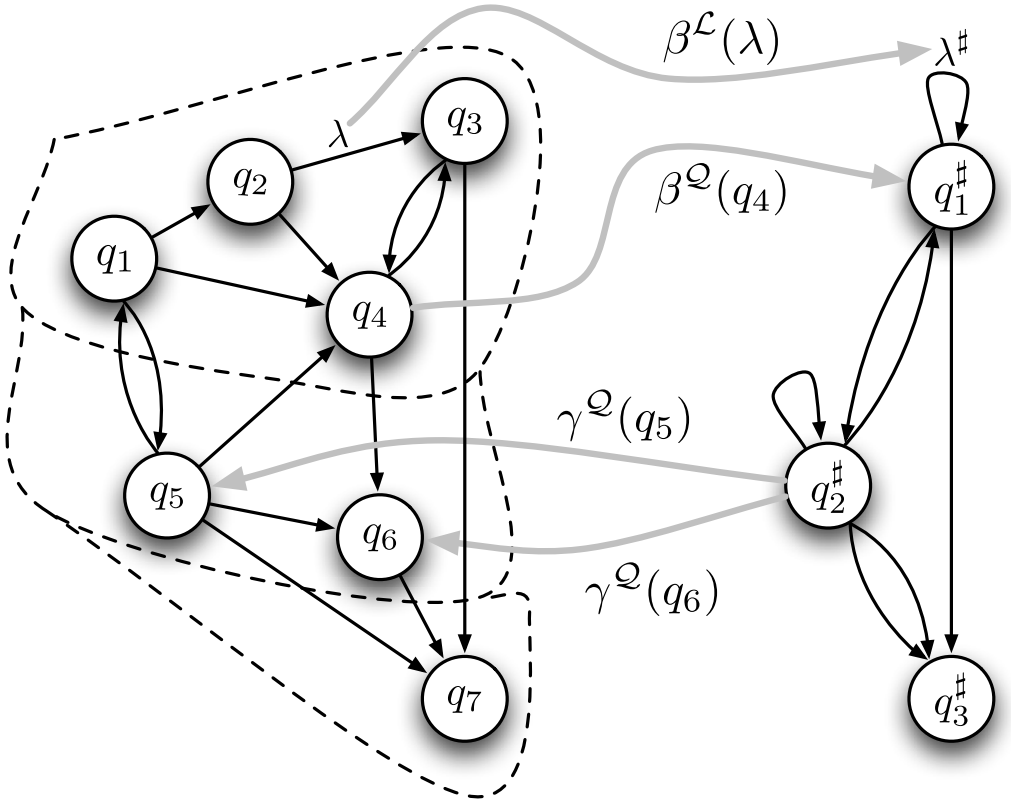
- $(q_i)_{0 \leq i \leq k} \in \mathcal{Q}^{k+1}$ and $(\lambda_i)_{1 \leq i \leq k} \in \mathcal{L}^k$,
- $(I_i)_{1 \leq i \leq k}$ is a family of open intervals in $\mathbb{R}_0^+$.

The probability of a cylinder set of traces is defined as follows:

$$\mathcal{P}r(\tau) \stackrel{\Delta}{=} \pi_0(q_0) \prod_{i=1}^{k} \frac{w(q_{i-1}, l_i, q_i)}{a(q_{i-1})} \left(e^{-a(q_{i-1}) \cdot \inf(I_i)} - e^{-a(q_{i-1}) \cdot \sup(I_i)} \right),$$

where $a(q) \stackrel{\Delta}{=} \sum_{\lambda, q'} w(q, \lambda, q')$.

Abstraction between WLTS



Soundness

Given:

- two WLTS $\mathcal{S} \triangleq (\mathcal{Q}, \mathcal{L}, \rightarrow, w, \mathcal{I}, \pi_0)$ and $\mathcal{S}^\sharp \triangleq (\mathcal{Q}^\sharp, \mathcal{L}^\sharp, \rightsquigarrow, w^\sharp, \mathcal{I}^\sharp, \pi_0^\sharp)$,
- two abstraction functions $\beta^{\mathcal{Q}} : \mathcal{Q} \rightarrow \mathcal{Q}^\sharp$ and $\beta^{\mathcal{L}} : \mathcal{L} \rightarrow \mathcal{L}^\sharp$,

$\mathcal{S}^\sharp$ is a sound abstraction of $\mathcal{S}$, if and only if, for any cylinder set τ of traces of $\mathcal{S}$, we have:

$$\mathcal{P}r(\beta^{\mathbb{T}}(\tau)) = \sum\nolimits_{\tau'} (\mathcal{P}r(\tau') \mid \beta^{\mathbb{T}}(\tau) = \beta^{\mathbb{T}}(\tau')),$$

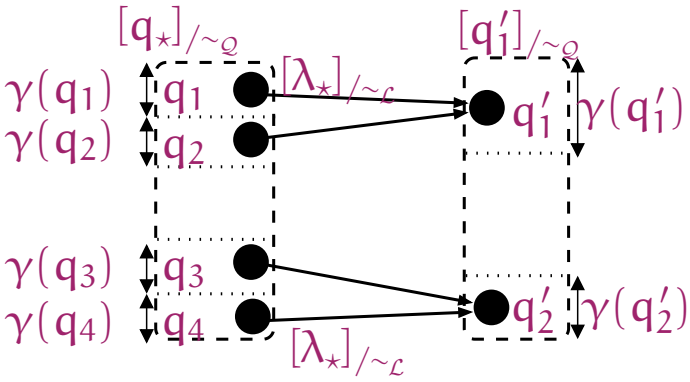
where,

$$\beta^{\mathbb{T}}(q_0 \overset{\lambda_1, I_1}{\rightarrow} q_1 \dots q_{k-1} \overset{\lambda_k, I_k}{\rightarrow} q_k) \triangleq \beta^{\mathcal{Q}}(q_0) \overset{\beta^{\mathcal{L}}(\lambda_1), I_1}{\rightarrow} \beta^{\mathcal{Q}}(q_1) \dots \beta^{\mathcal{Q}}(q_{k-1}) \overset{\beta^{\mathcal{L}}(\lambda_k), I_k}{\rightarrow} \beta^{\mathcal{Q}}(q_k).$$

Backward bisimulation

Let $\sim_{\mathcal{Q}}$ be an equivalence relation over $\mathcal{Q}$ and $\sim_{\mathcal{L}}$ be an equivalence relation over $\mathcal{L}$.

We say that $(\sim_{\mathcal{Q}}, \sim_{\mathcal{L}})$ is a backward bisimulation, if and only if, there exists $\gamma : \mathcal{Q} \to \mathbb{R}^+$, such that: for any $q'_1, q'_2 \in \mathcal{Q}$ which satisfies $q'_1 \sim_{\mathcal{Q}} q'_2$:



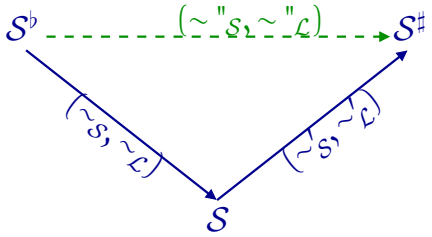
- $a(q'_1) = a(q'_2)$;
- and for any $\lambda_\star \in \mathcal{L}$, $q_\star \in \mathcal{Q}$,
  $\mathrm{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q'_1) = \mathrm{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q'_2)$

where: $\mathrm{bwd}([q_\star]_{/\sim_{\mathcal{Q}}}, [\lambda_\star]_{\sim_{/\mathcal{L}}}, q') = \sum_{q,\lambda'} \left(\frac{\gamma(q)}{\gamma(q')} w(q, \lambda', q') \,|\, q \sim_{\mathcal{Q}} q_\star, \lambda' \sim_{\mathcal{L}} \lambda_\star \right)$.

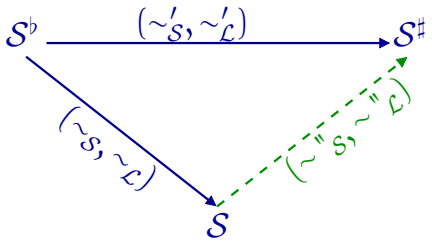
Bisimulation algebra

Backward bisimulations can be:

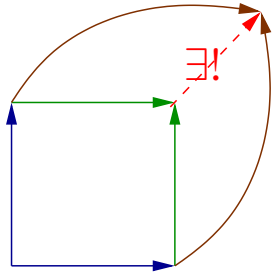
- composed:



- factored:



- combined with a symmetric product (c.f. lub or pushout):



Overview

1. Context and motivations
2. Information flow
3. Symmetric sites
4. Generic framework
5. Conclusion

Conclusion

- A framework for reducing stochastic rule-based models.
  - We use:
    - the sites the state of which are uncorrelated;
    - the sites having the same capabilities of interactions.
  - Algebraic operators combine these abstractions.

- We use backward bisimulations in order to prove statistical invariants, we use them to reduce the dimension of the continuous-time Markov chains.

Future works

- Forward bisimulations are very convenient to abstract ODE semantics.
  $\Rightarrow$investigate the use of hybrid bisimulation.

- Propose approximated simulation algorithms to approximate different scale rate reactions.
  - hybrid systems,
  - tau-leaping,
  - ...