Antique SEMINAR

Conservative approximation of models of polymers

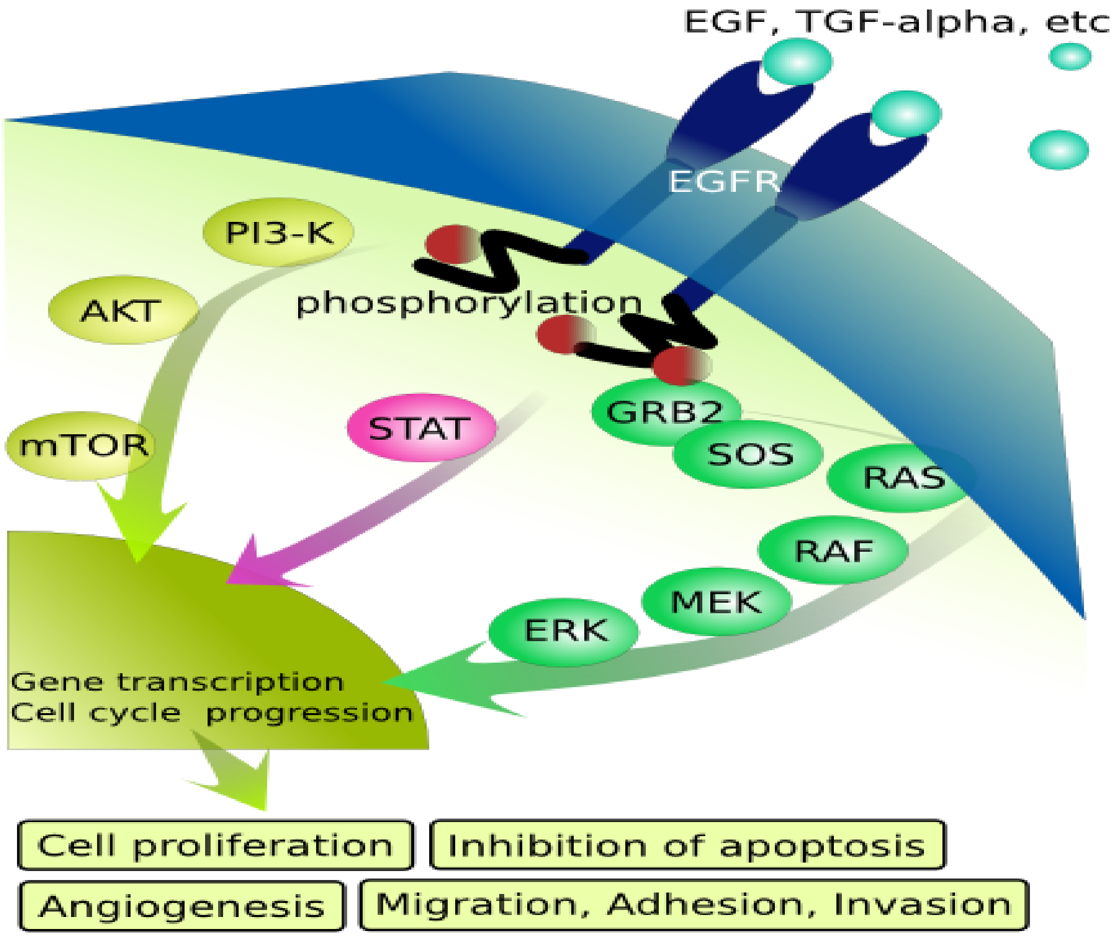
Jérôme Feret

Antique, Inria Paris

http://www.di.ens.fr/~feret

Monday, the 13th of January, 2025

Signaling Pathways



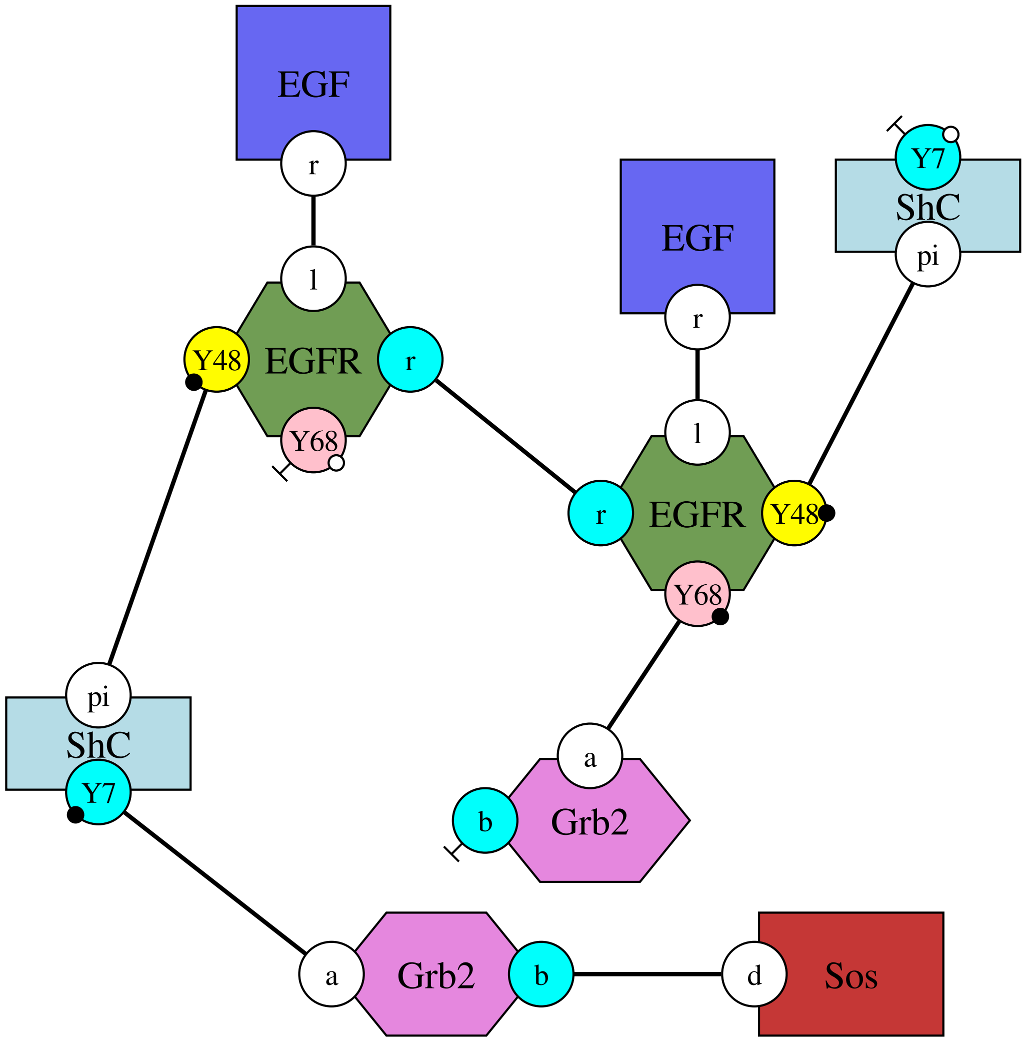
Eikuch, 2007

Challenges for computer science

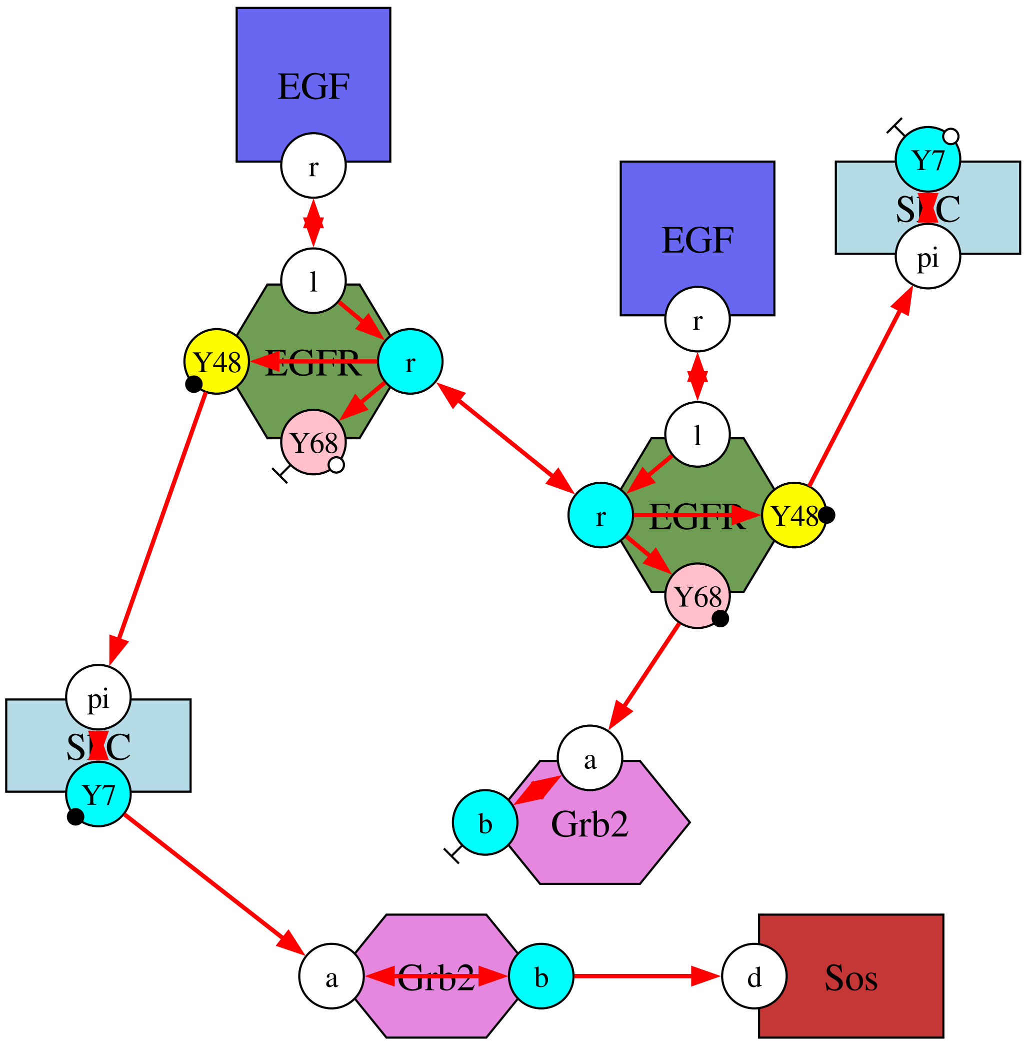
1. Break down combinatorial complexity
   - Occurrences of proteins can form huge instances of chemical species;
   - There may be many (or even infinitely many) different kinds of chemical species.

2. Understand how collective behaviors emerge from individual interactions.
   - races for shared-ressources;
   - sequestration effects;
   - separation of time- and concentration- scales;
   - non-linear feedback loops.

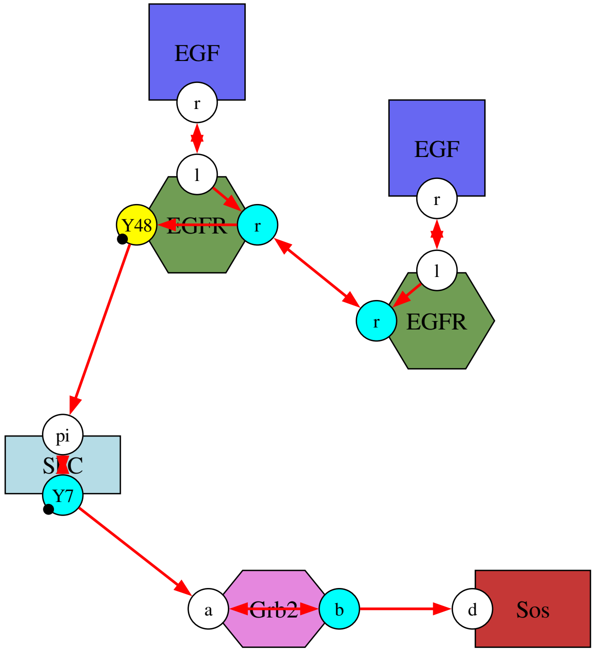
Model reduction

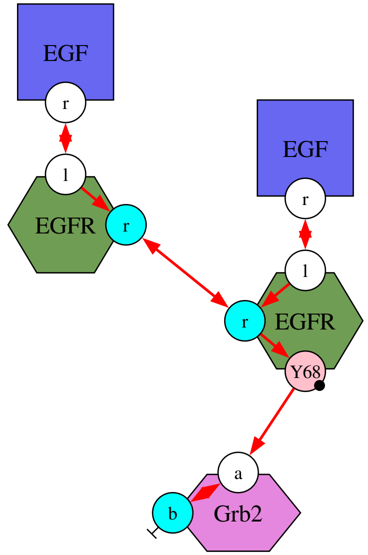


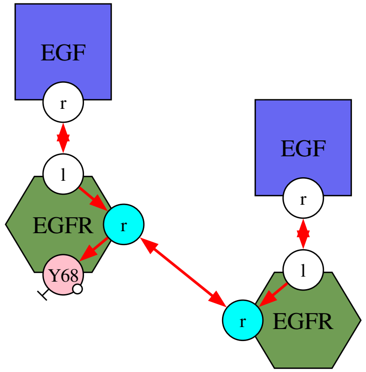
Model reduction

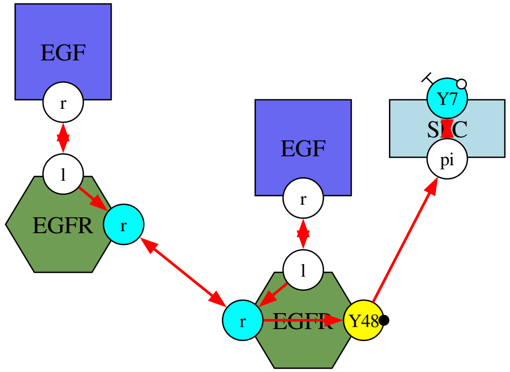


Model reduction









Exact model reduction

- We can derive an ode to describe the exact evolution of the concentration of patterns of interest.

- The choice of patterns is fixed by the analysis.

The trade-off between complexity and accuracy is imposed by the framework.

On the menu today
Conservative model reduction

1. Motivating example
2. Evolution systems
3. Box approximation
4. Symbolic reasoning
5. Conclusion

An example with polymers

We denote by A_n a chain of n proteins.

We consider the following reactions (for $i, j \geq 1$):

1. $A_i + A_j \rightarrow A_{i+j} \quad @ \, k$
2. $A_{i+j} \rightarrow A_i + A_j \quad @ \begin{cases} k_d & \text{when } \; i = 1 \\ k_d + k'_d & \text{when } \; i > 1. \end{cases}$

Principle of mass action

The following reaction:

$$A_1 + A_2 \to A_3 \qquad @\, k$$

has the following contribution:

$$\begin{cases} \frac{\mathrm{d}[A_1]}{\mathrm{d}t} = -k \cdot [A_1] \cdot [A_2] \\ \frac{\mathrm{d}[A_2]}{\mathrm{d}t} = -k \cdot [A_1] \cdot [A_2] \\ \frac{\mathrm{d}[A_3]}{\mathrm{d}t} = k \cdot [A_1] \cdot [A_2]. \end{cases}$$

(Infinite) system of odes

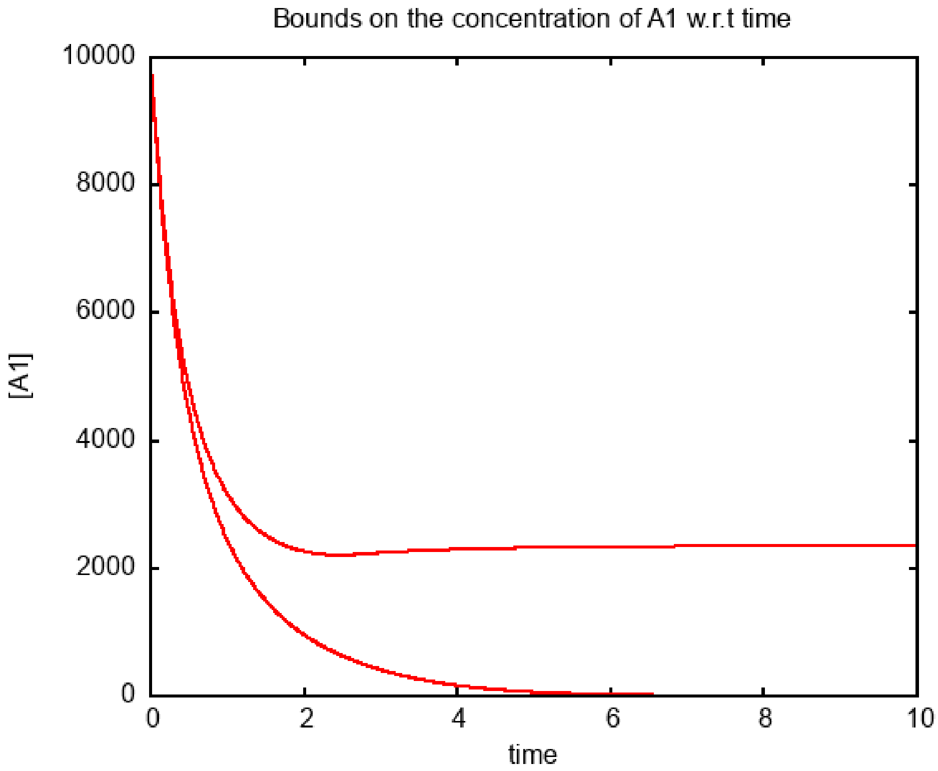
$$\frac{\mathrm{d}[A_n]}{\mathrm{d}t} = t_1^+(n) + t_2^+(n) + t_3^+(n) - t_1^-(n) - t_2^-(n) - t_3^-(n)$$

where:

$$\begin{aligned}
t_1^+(n) &\triangleq k \cdot \sum\nolimits_{i+j=n} [A_i] \cdot [A_j]; \\
t_2^+(n) &\triangleq 2 \cdot k_d \cdot \sum\nolimits_{i=n+1}^{+\infty} [A_i]; \\
t_3^+(n) &\triangleq \begin{cases} k'_d \cdot \sum\nolimits_{i=3}^{+\infty} [A_i] & \text{if } n = 1, \\ k'_d \cdot \sum\nolimits_{i=n}^{+\infty} ([A_{i+1}] + [A_{i+2}]) & \text{if } n \geq 2; \end{cases} \\
t_1^-(n) &\triangleq 2 \cdot k \cdot [A_n] \cdot \sum\nolimits_{i=1}^{+\infty} [A_i]; \\
t_2^-(n) &\triangleq k_d \cdot (n-1) \cdot [A_n]; \\
t_3^-(n) &\triangleq \begin{cases} k'_d \cdot (n-2) \cdot [A_n] & \text{if } n \geq 3, \\ 0 & \textit{otherwise.} \end{cases}
\end{aligned}$$

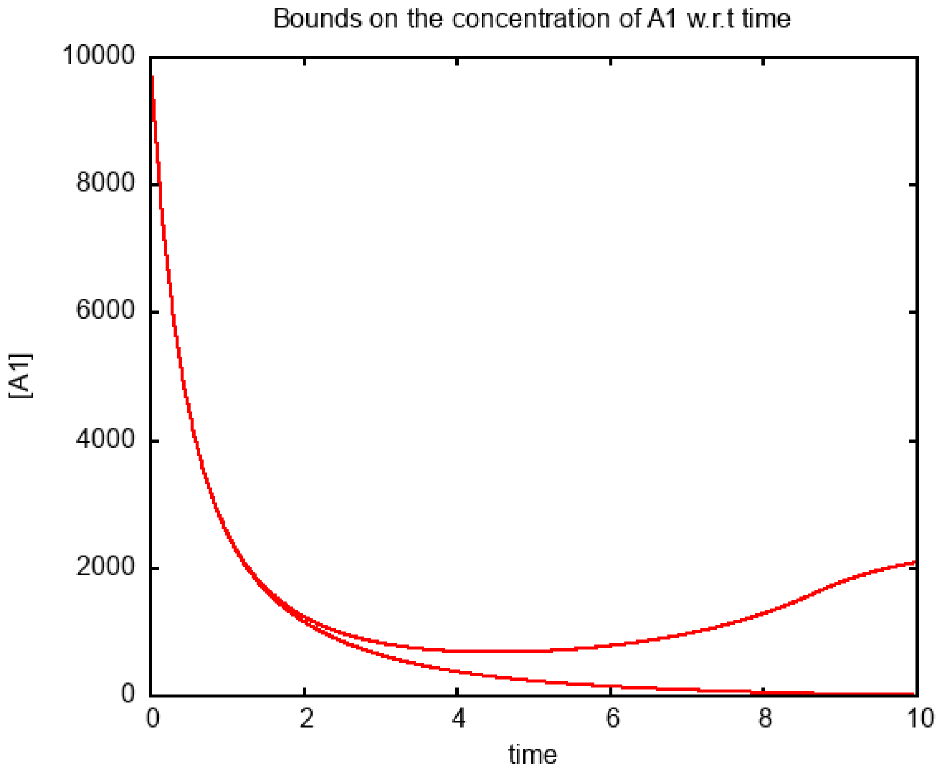
with the side condition: $\sum_{n \in \mathbb{N}} n \cdot [A_n] < +\infty$.

Our goal:
Bounding the concentration of A_1



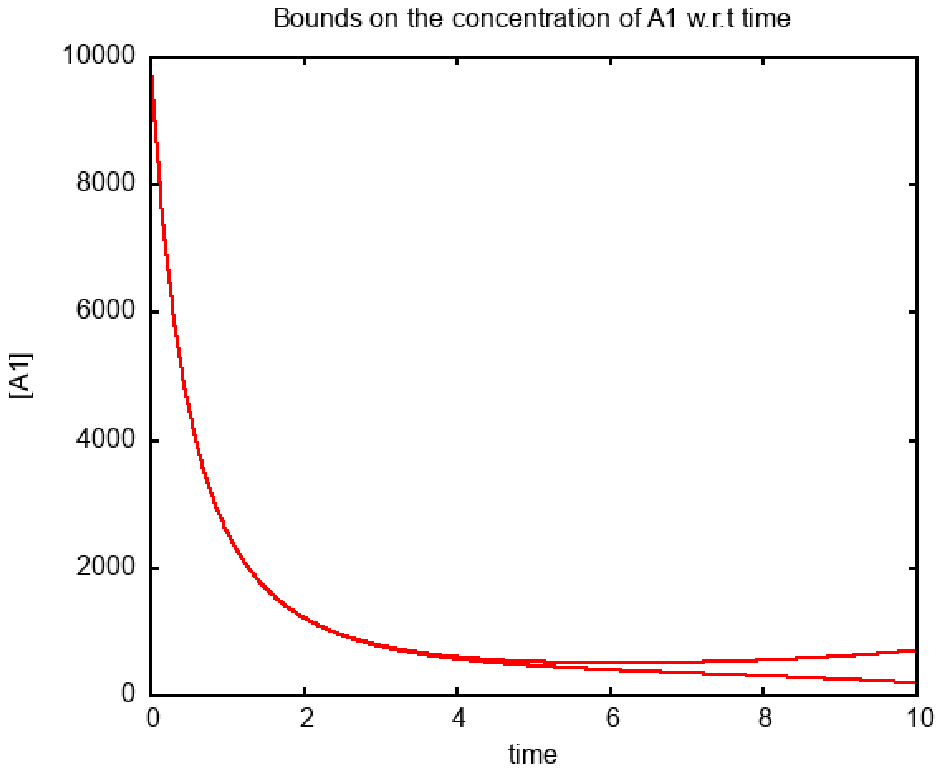
Obtained thanks to an odes of 18 variables.
(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Our goal:
Bounding the concentration of A_1



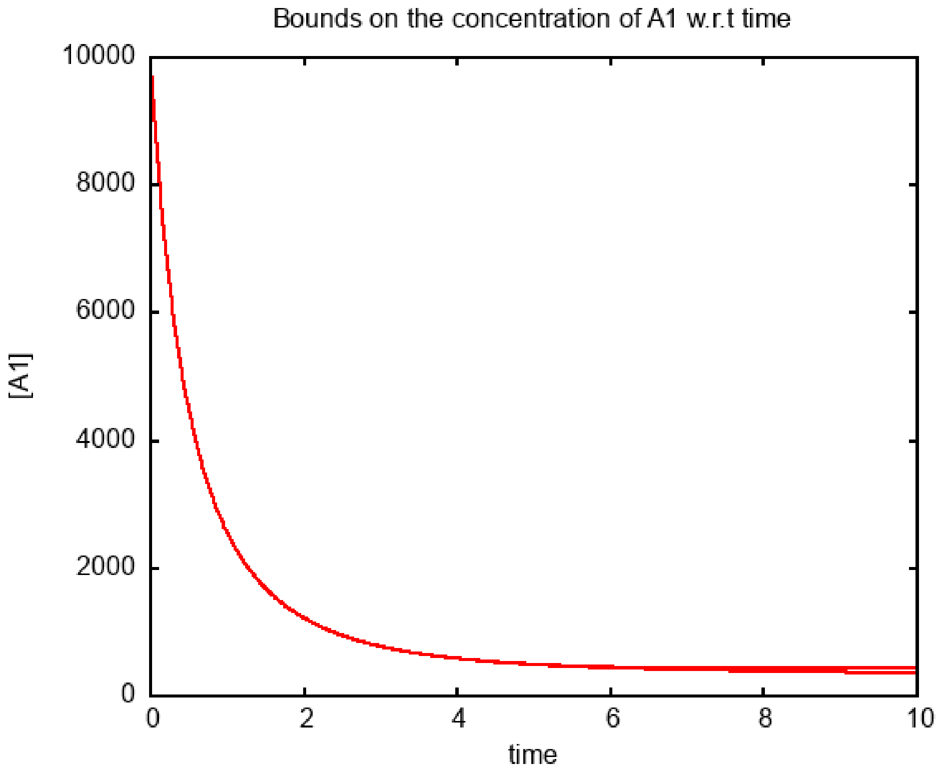
Obtained thanks to an odes of 36 variables.
(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Our goal:
Bounding the concentration of A_1



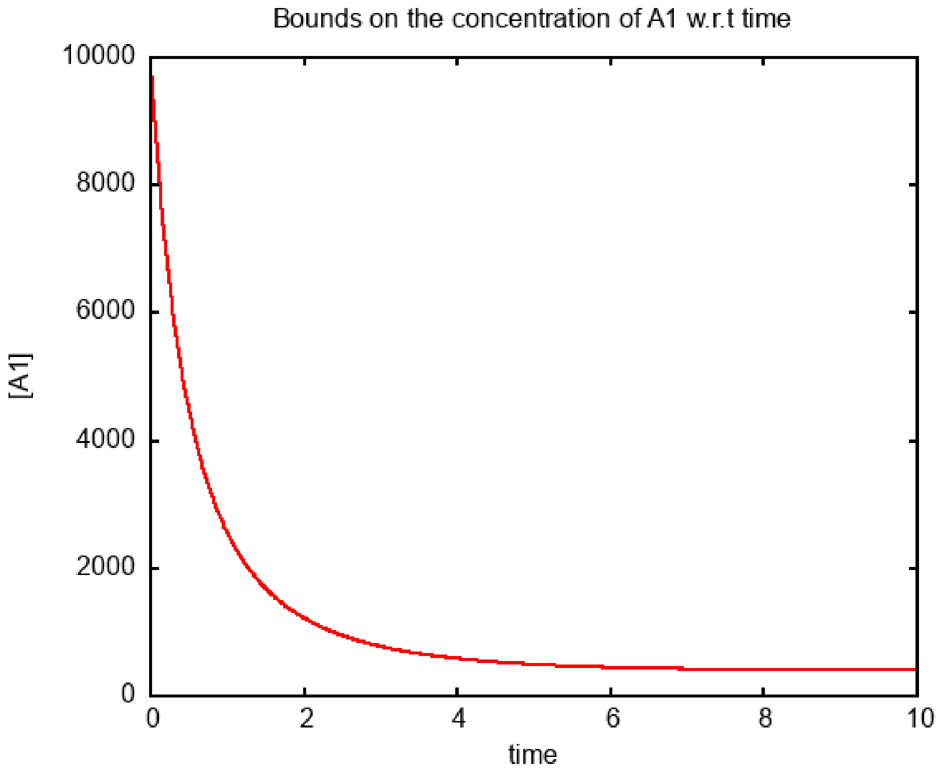
Obtained thanks to an odes of 54 variables.
(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Our goal:
Bounding the concentration of A_1



Obtained thanks to an odes of 72 variables.
(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Our goal:
Bounding the concentration of A_1



Obtained thanks to an odes of 90 variables.
(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Approach

1. Use a high level language to:
   (a) describe the model;
   (b) show the existence and uniqueness of the solution;
   (c) reason symbolically about some differentiable auxiliary variables:
      - express their derivatives,
      - infer inequalities among these derivatives.

2. Use box approximation to define a system of odes with two variables per auxiliary variable (one for the lower bound, one for the upper bound)
   (error bounds are computed *a posteriori*).

Main avantages

- Numerical approximations relax constraints on the choice of auxiliary variables.

- The choice of auxiliary variables can be driven by various methods:
  - truncation (this talk);
  - tropicalization (see Andreea Beica's PhD);
  - flow of information

  (a unifying framework to combine these methods)

- The approach provides error bounds.

On the menu today
Conservative model reduction

1. Motivating example
2. Evolution systems
3. Box approximation
4. Symbolic reasoning
5. Conclusion

Definition

In a Banach space, a system defined as:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X,t) + G(X,t)$$

where:

1. F is linear and triangular;
2. G is Lipschitz on every bounded set;

is called an evolution system.

Case study

- Define the norm of a state as $\sum n \cdot |A_n|$.
- Define F as the contribution of the unbinding reactions:

$$A_{i+j} \rightarrow A_i + A_j \quad @ \begin{cases} k_d & \text{when} \quad i = 1 \\ k_d + k'_d & \text{when} \quad i > 1 \end{cases} \qquad (\text{for } i, j \geq 1).$$

- Define G as the contribution of the binding reactions:

$$A_i + A_j \rightarrow A_{i+j} \quad @\, k \qquad (\text{for } i, j \geq 1).$$

Properties

Evolutions systems:

- they have unique maximal solutions;
- their maximal solutions are locally Lipschitz.
- whenever a maximal solution is not defined over $\mathbb{R}^+$, the norm diverges;
- whenever G is $\mathcal{C}_1$ and its derivative is bounded on bounded sets, maximal solutions are also $\mathcal{C}_1$.

[Hundertmark et al., Operator Semigroups and Dispersive Equations, 16th Internet Seminar on Evolution Equations 2013]

On the menu today
Conservative model reduction

1. Motivating example
2. Evolution systems
3. Box approximation
4. Symbolic reasoning
5. Conclusion

Principle

Given a finite system of odes:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X, t).$$

Box approximation:

1. approximate the state of the system by a (hyper)-box
   (twice many variables as in the initial system)
2. associate to each (hyper)-face an expression that bounds conservatively the partial derivative of the system with respect to the corresponding variable over this (hyper)-face.

Sound whenever F is locally Lipschitz w.r.t to the state and continuous w.r.t time.

[M. Kirkilionis and S. Walcher, On comparison systems for ordinary differential equations, J. Math. Anal. Appl. 299 (2004)]

Example: odes

Consider the following system of odes:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = y \cdot (2 - \cos(y)) - x \cdot (2 - \sin(y)) \\ \frac{\mathrm{d}y}{\mathrm{d}t} = x \cdot (2 - \cos(y)) - y \cdot (2 - \sin(y)) \\ x(0) = y(0) = 1 \end{cases}$$

Example: Invariants

Consider the following system of odes:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = y \cdot (2 - \cos(y)) - x \cdot (2 - \sin(y)) \\ \frac{\mathrm{d}y}{\mathrm{d}t} = x \cdot (2 - \cos(y)) - y \cdot (2 - \sin(y)) \\ x(0) = y(0) = 1 \end{cases}$$

We have:

$$\begin{cases} y - 3 \cdot x \leq \frac{\mathrm{d}x}{\mathrm{d}t} \leq 3 \cdot y - x \\ x - 3 \cdot y \leq \frac{\mathrm{d}y}{\mathrm{d}t} \leq 3 \cdot x - y. \end{cases}$$

Example: Box approximation

Thus, the following system of odes:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = y \cdot (2 - \cos(y)) - x \cdot (2 - \sin(y)) \\ \frac{\mathrm{d}y}{\mathrm{d}t} = x \cdot (2 - \cos(y)) - y \cdot (2 - \sin(y)) \\ x(0) = y(0) = 1 \end{cases}$$

can be safely approximated by the following one:

$$\begin{cases} \frac{\mathrm{d}\underline{x}}{\mathrm{d}t} = \underline{y} - 3 \cdot \underline{x} \\ \frac{\mathrm{d}\overline{x}}{\mathrm{d}t} = 3 \cdot \overline{y} - \overline{x} \\ \frac{\mathrm{d}\underline{y}}{\mathrm{d}t} = \underline{x} - 3 \cdot \underline{y} \\ \frac{\mathrm{d}\overline{y}}{\mathrm{d}t} = 3 \cdot \overline{x} - \overline{y} \\ \underline{x}(0) = \overline{x}(0) = \underline{y}(0) = \overline{y}(0) = 1 \end{cases}$$

Example:
Box approximation

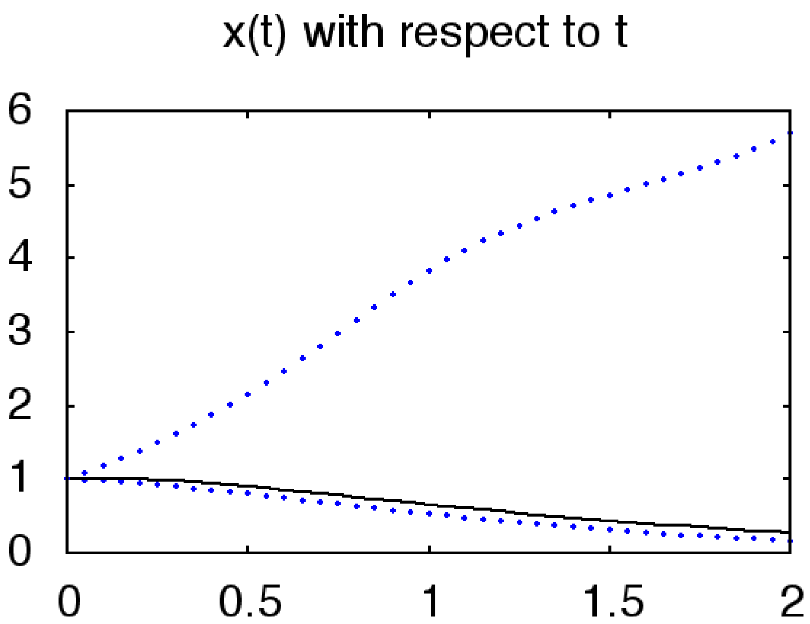
Thus, the following system of odes:

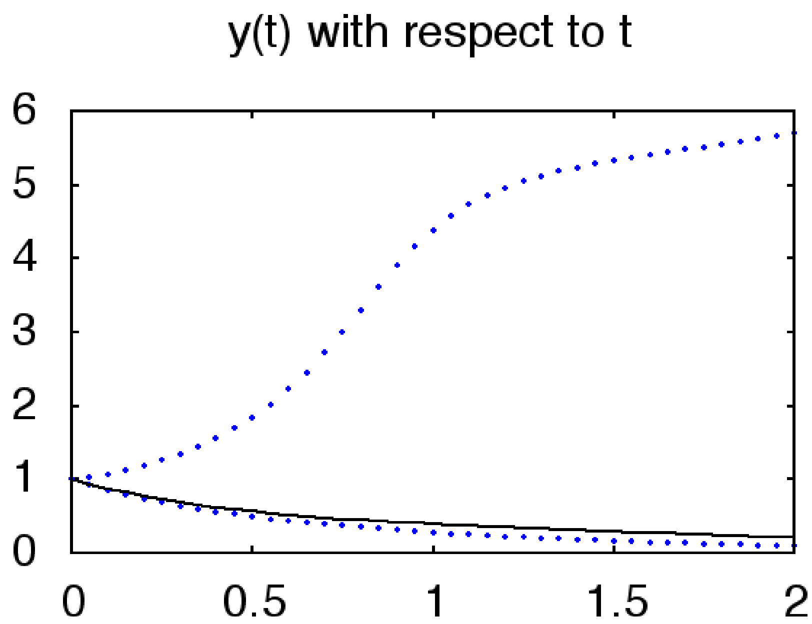
$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = y \cdot (2 - \cos(y)) - x \cdot (2 - \sin(y)) \\ \frac{\mathrm{d}y}{\mathrm{d}t} = x \cdot (2 - \cos(y)) - y \cdot (2 - \sin(y)) \\ x(0) = y(0) = 1 \end{cases}$$

can be safely approximated by the following one:

$$\begin{cases} \frac{\mathrm{d}\underline{x}}{\mathrm{d}t} = \underline{y} - 3 \cdot \underline{x} & \text{(lower bound on } y - 3 \cdot x \text{ for } x = \underline{x} \text{ and } \underline{y} \leq y \leq \overline{y}\text{)} \\ \frac{\mathrm{d}\overline{x}}{\mathrm{d}t} = 3 \cdot \overline{y} - \overline{x} & \text{(upper bound on } 3 \cdot y - x \text{ for } x = \overline{x} \text{ and } \underline{y} \leq y \leq \overline{y}\text{)} \\ \frac{\mathrm{d}\underline{y}}{\mathrm{d}t} = \underline{x} - 3 \cdot \underline{y} & \text{(lower bound on } x - 3 \cdot y \text{ for } \underline{x} \leq x \leq \overline{x} \text{ and } y = \underline{y}\text{)} \\ \frac{\mathrm{d}\overline{y}}{\mathrm{d}t} = 3 \cdot \overline{x} - \overline{y} & \text{(upper bound on } 3 \cdot x - y \text{ for } \underline{x} \leq x \leq \overline{x} \text{ and } y = \overline{y}\text{)} \\ \underline{x}(0) = \overline{x}(0) = \underline{y}(0) = \overline{y}(0) = 1 \end{cases}$$

Example:
Numerical results

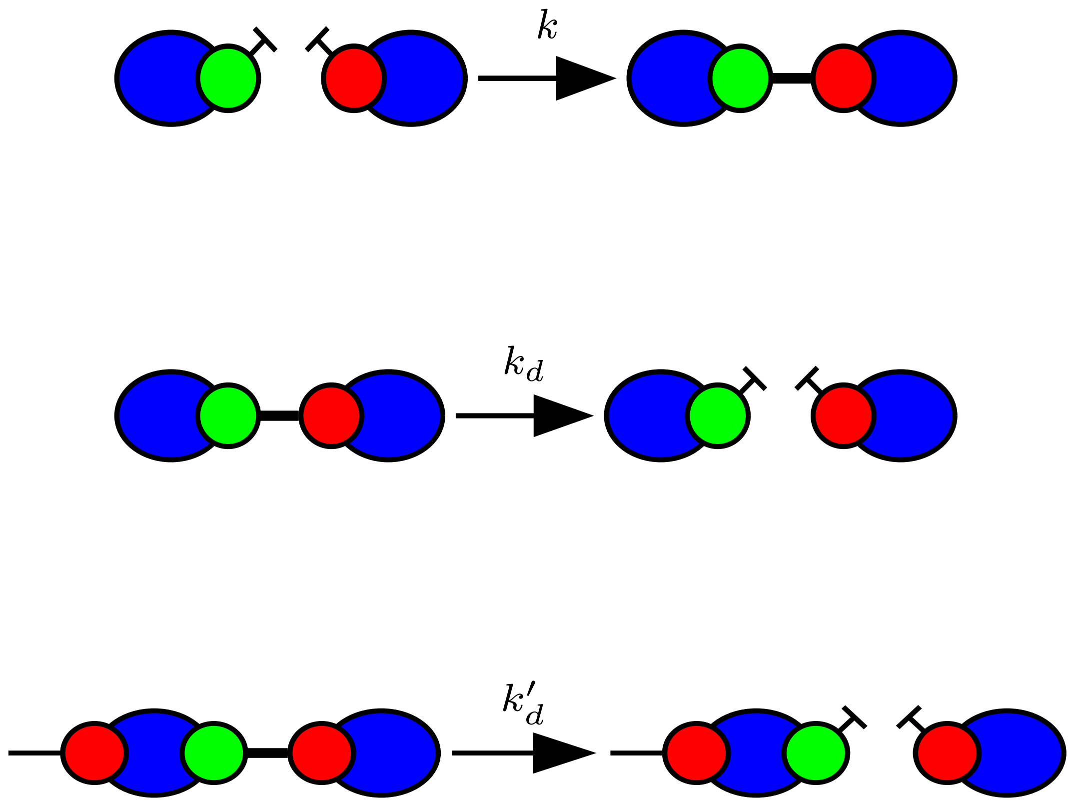




On the menu today
Conservative model reduction

1. Motivating example
2. Evolution systems
3. Box approximation
4. Symbolic reasoning
5. Conclusion

Our model of polymers in Kappa



Back to evolution systems

Let us consider both following definitions:

1. A rule is dispersive if it is unary and it splits its pattern into smaller ones.
2. A rule is locally Lipschitz if for every pattern P the number of embedding from the patterns in the lhs of the rules and the pattern P is uniformly bounded.

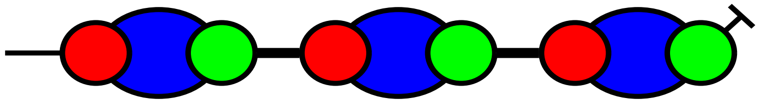
Then: A finite set of Kappa rules such that every rule is either dispersive, or locally Lipschitz (or both) induces an evolution system, for the norm defined as the overall concentration of proteins.

Auxiliary variables

Connected patterns have both an intensional and an extensional meaning.

A connected pattern may be seen:

1. as a connected graph:



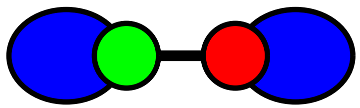
2. as a multi-set (potentially infinite) of fully specified connected graphs:

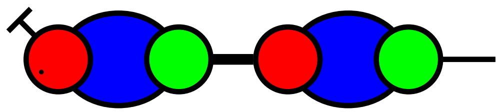
$$[-A_3\dashv] = \sum_{n\geq 4} [\vdash A_n \dashv]$$

List of connected patterns

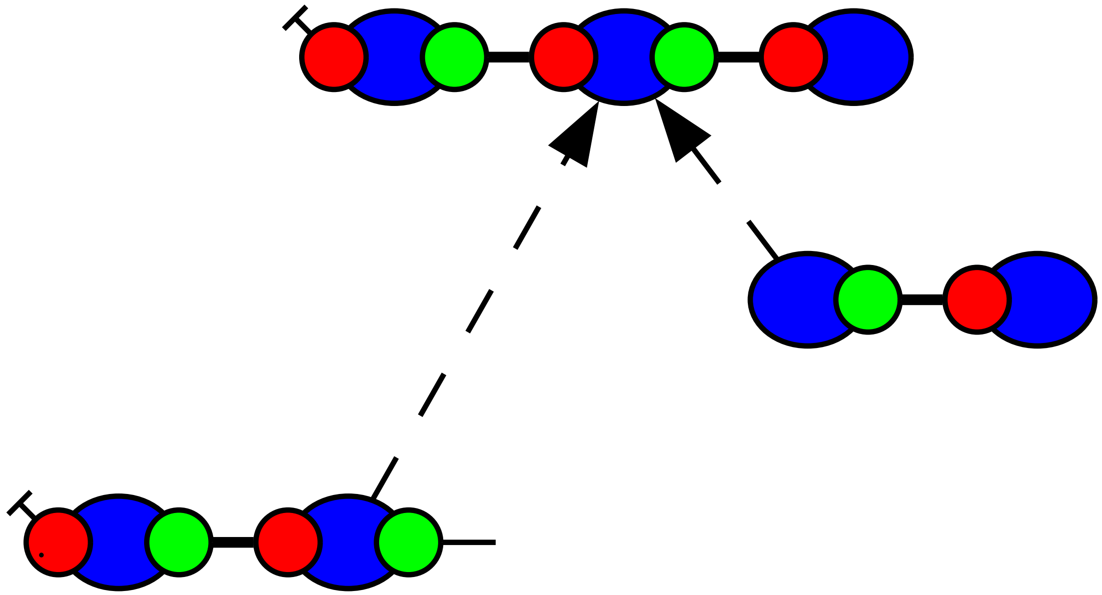
- $[\vdash A_n \dashv]$: concentration of polymer of length n;
- $[\vdash A_n]$: concentration of polymer of length at least n;
- $[A_n \dashv]$: concentration of polymer of length at least n;
- $[\vdash A_n -]$: concentration of polymer of length at least $n+1$;
- $[- A_n \dashv]$: concentration of polymer of length at least $n+1$;
- $[A_n] = \sum_{i \in \mathbb{N}} (i+1) \cdot [\vdash A_{n+i} \dashv]$;
- $[A_n -] = [A_{n+1}]$;
- $[- A_n] = [A_{n+1}]$;
- $[- A_n -] = [A_{n+2}]$.

Overlap between connected patterns



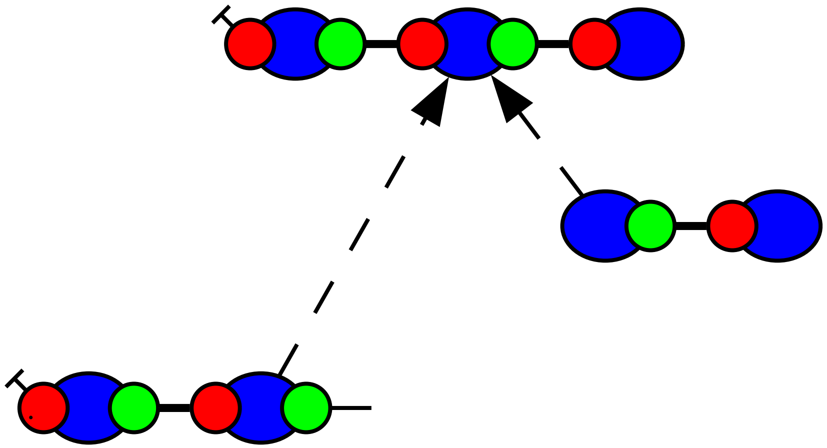


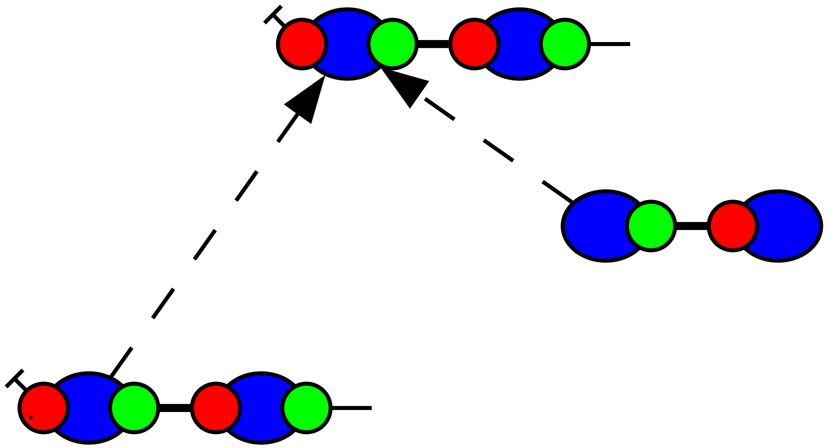
Overlap between connected patterns



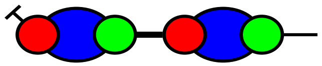
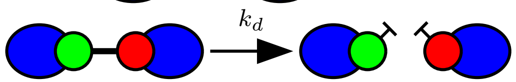
Overlap between connected patterns

There may be several overlaps between two patterns.



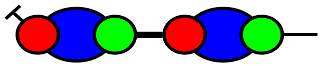
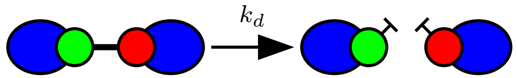


Consumption

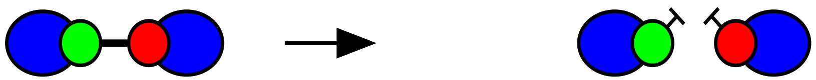
Which quantity of the pattern 
is consumed due to the rule 

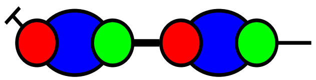
?

Consumption

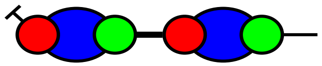
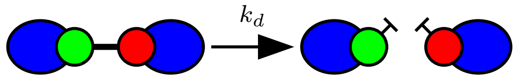
Which quantity of the pattern 
is consumed due to the rule 

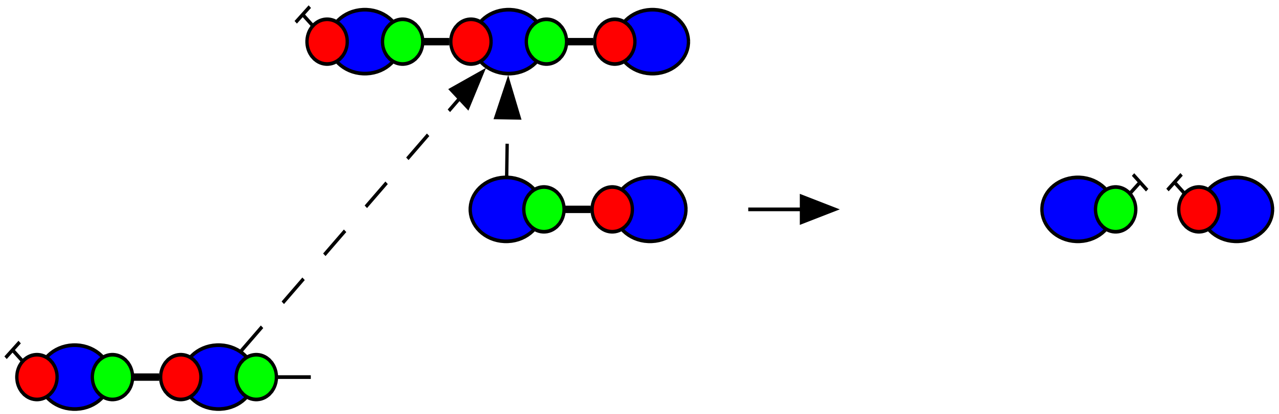
?



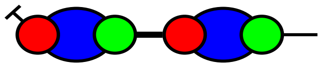
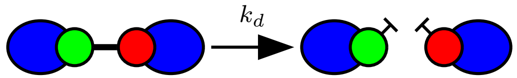


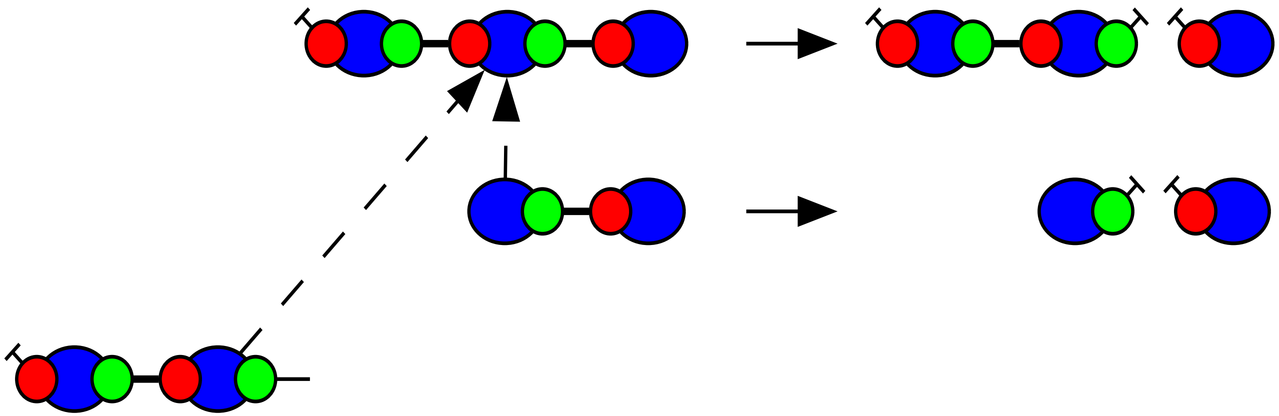
Consumption

Which quantity of the pattern 
is consumed due to the rule ?



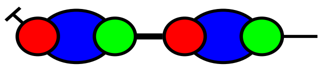
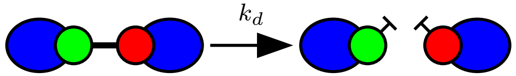
Consumption

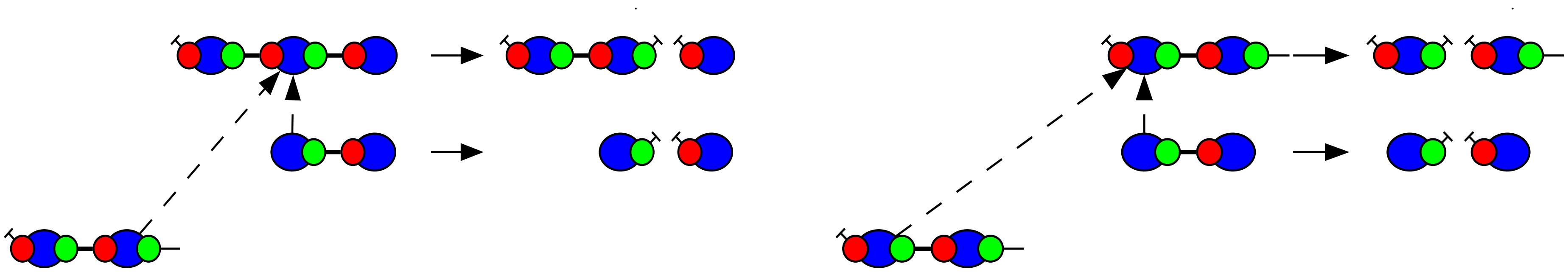
Which quantity of the pattern 
is consumed due to the rule ?



$$k_d{\cdot}[\vdash A_3]$$

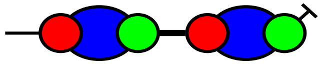
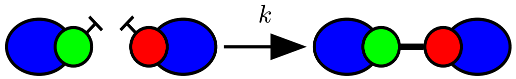
Consumption

Which quantity of the pattern 
is consumed due to the rule ?

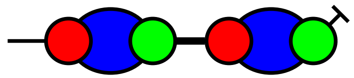


$$k_d \cdot ([\vdash A_3] + [\vdash A_2 -]).$$

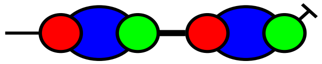
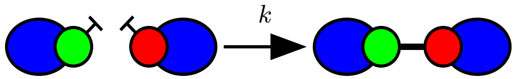
Production

Which quantity of the pattern 
is produced due to the rule 

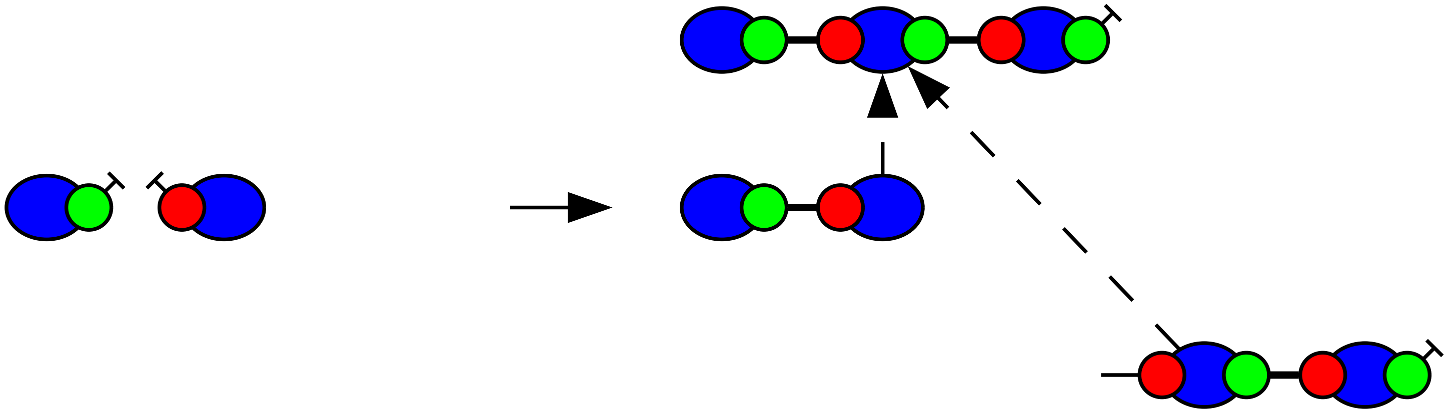
?



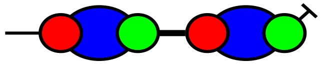
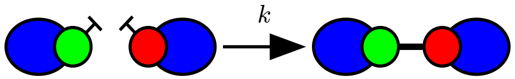
Production

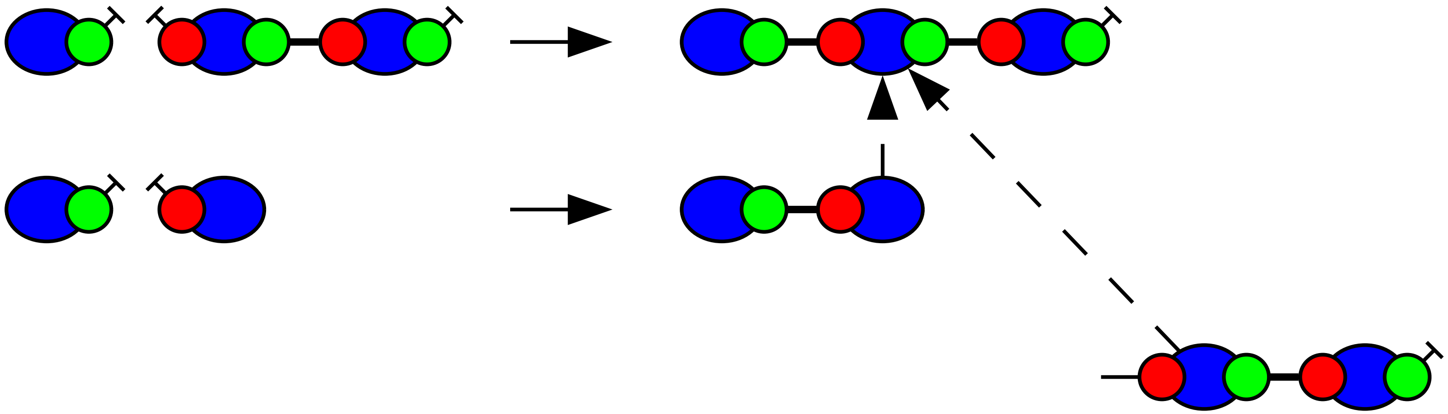
Which quantity of the pattern 
is produced due to the rule 

?



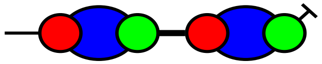
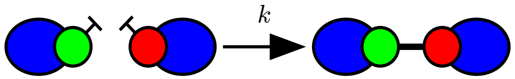
Production

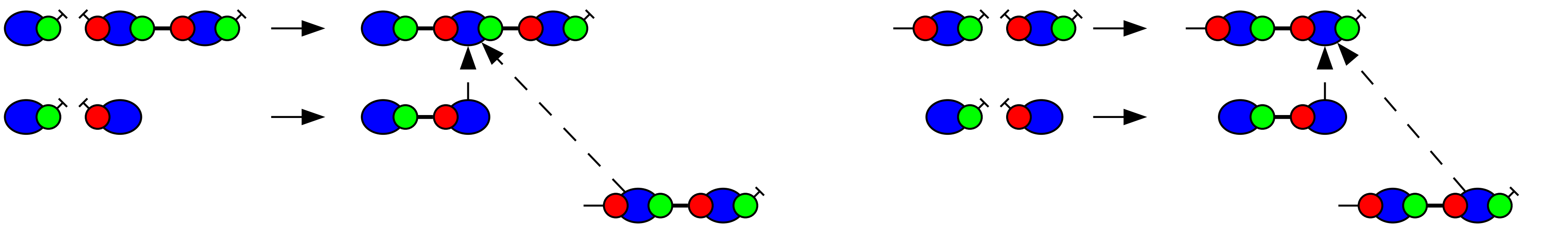
Which quantity of the pattern 
is produced due to the rule ?



$$k \cdot [A_1 \dashv] \cdot [\vdash A_2 \dashv].$$

Production

Which quantity of the pattern 
is produced due to the rule ?



$$k \cdot ([A_1\dashv] \cdot [\vdash A_2\dashv] + [-A_1\dashv] \cdot [\vdash A_1\dashv]).$$

Exact derivatives

$$\frac{\mathrm{d}[\vdash A_n \dashv]}{\mathrm{d}t} = \mathcal{T}^{+}_{1,1}(n) + \mathcal{T}^{+}_{1,2}(n) + \mathcal{T}^{+}_{1,3}(n) - \mathcal{T}^{-}_{1,1}(n) - \mathcal{T}^{-}_{1,2}(n) - \mathcal{T}^{-}_{1,3}(n)$$

where:

$$\mathcal{T}^{+}_{1,1}(n) \triangleq k \cdot \sum_{i+j=n} [\vdash A_i \dashv] \cdot [\vdash A_j \dashv];$$

$$\mathcal{T}^{+}_{1,2}(n) \triangleq k_d \cdot ([\vdash A_{n+1}] + [A_{n+1} \dashv]);$$

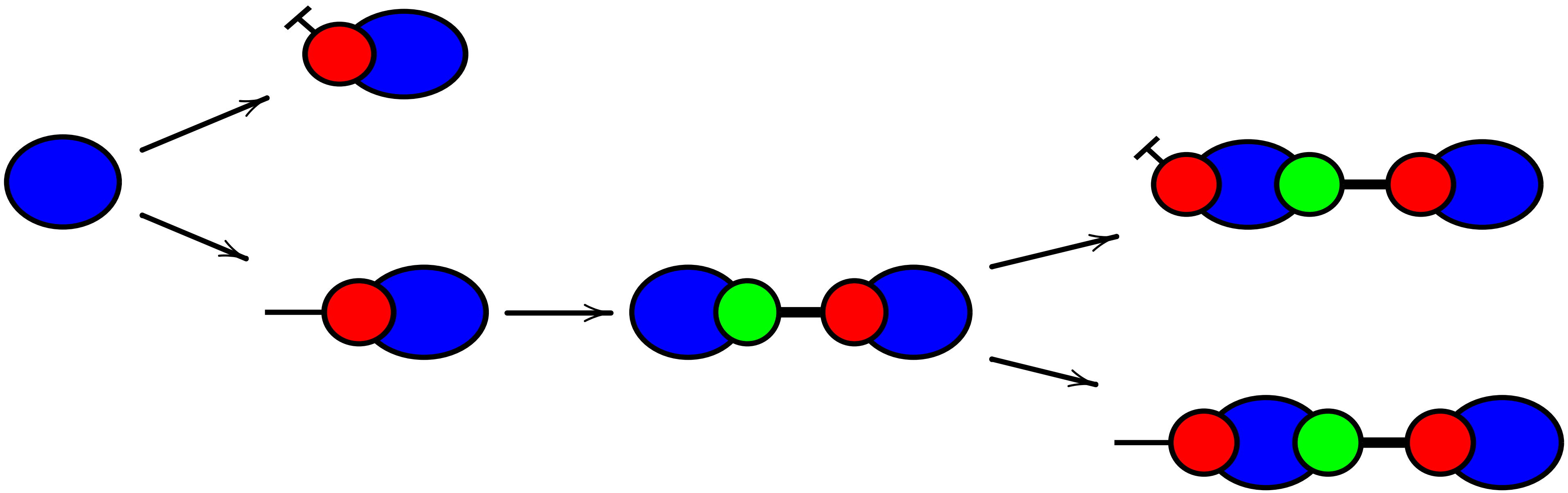
$$\mathcal{T}^{+}_{1,3}(n) \triangleq \begin{cases} k'_d \cdot [-A_{n+1} \dashv] & \text{if } n = 1 \\ k'_d \cdot ([-A_{n+1} \dashv] + [\vdash A_{n+1}]) & \text{if } n \geq 2; \end{cases}$$

$$\mathcal{T}^{-}_{1,1}(n) \triangleq k \cdot [\vdash A_n \dashv] \cdot ([\vdash A_1] + [A_1 \dashv]);$$

$$\mathcal{T}^{-}_{1,2}(n) \triangleq k_d \cdot (n-1) \cdot [\vdash A_n \dashv];$$

$$\mathcal{T}^{-}_{1,3}(n) \triangleq \begin{cases} k'_d \cdot (n-2) \cdot [\vdash A_n \dashv] & \text{if } n \geq 3 \\ 0 & \text{otherwise.} \end{cases}$$

Linear equalities among auxiliary variables



Inequalities

1. $[\vdash A_n \dashv] \leq \dfrac{[A_1] - \sum_{k=1,k\neq n}^{N} k\cdot[\vdash A_k \dashv]}{n}$;
2. $[A_n] \leq [A_1] - \sum_{k=1}^{n-1} k\cdot[\vdash A_k \dashv]$;
3. $[A_n \dashv] \leq \dfrac{[A_1] - \sum_{k=1}^{n-1} k\cdot[\vdash A_k \dashv]}{n}$;
4. $[\vdash A_n] \leq \dfrac{[A_1] - \sum_{k=1}^{n-1} k\cdot[\vdash A_k \dashv]}{n}$.
5. $[-A_n\diamond] = [A_{n+1}\diamond] \qquad \forall\diamond \in \{\dashv, -, \varepsilon\}$;
6. $[\diamond A_n -] = [\diamond A_{n+1}] \qquad \forall\diamond \in \{\dashv, -, \varepsilon\}$.

The odes

$$\frac{\mathrm{d}\underline{[\vdash A_1 -]}}{\mathrm{d}t} = \underline{t^+_{2,1}} + \underline{t^+_{2,2}} + \underline{t^+_{2,3}} - \overline{t^-_{2,1}} - \overline{t^-_{2,2}} - \overline{t^-_{2,3}},$$

where:

$$\underline{t^+_{2,1}} \triangleq k \cdot \underline{[\vdash A_1 \dashv]} \cdot (\underline{[\vdash A_1 \dashv]} + \underline{[\vdash A_1 -]});$$

$$\underline{t^+_{2,2}} \triangleq k_d \cdot \underline{[- A_1 -]};$$

$$\underline{t^+_{2,3}} \triangleq k'_d \cdot \underline{[- A_2 -]};$$

$$\overline{t^-_{2,1}} \triangleq k \cdot \underline{[\vdash A_1 -]} \cdot \left(min \left(\underline{[\vdash A_1 -]}, \overline{[A_1]} - \sum_{n=2}^{N} n \cdot \underline{[\vdash A_n \dashv]} \right) + min \left(\overline{[- A_1 \dashv]}, \overline{[A_1]} - \sum_{n=2}^{N} n \cdot \underline{[\vdash A_n \dashv]} \right) \right);$$

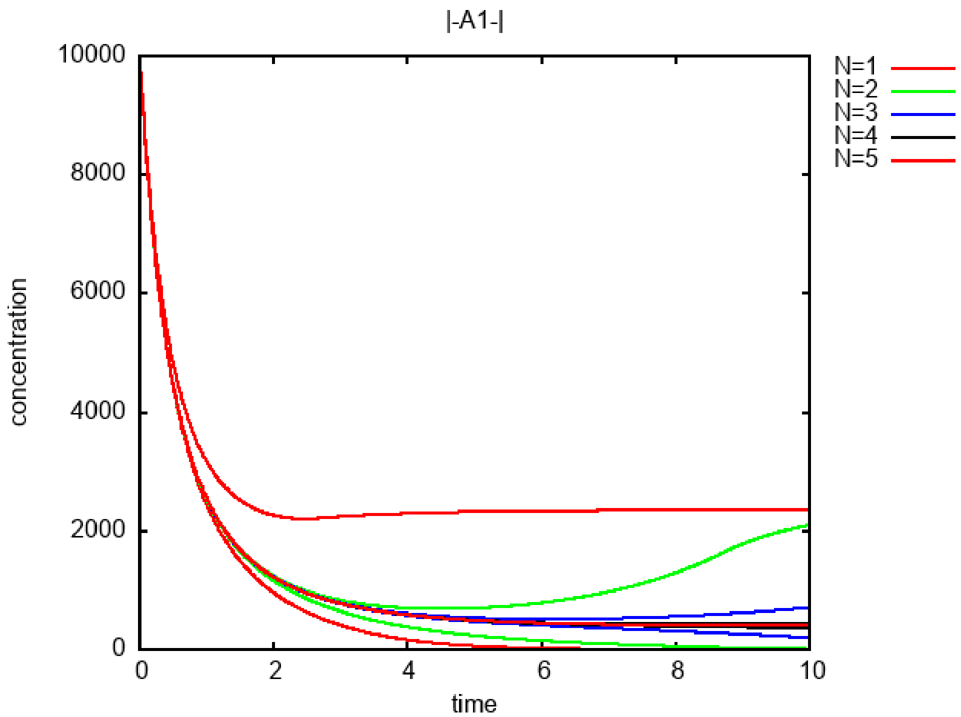
$$\overline{t^-_{2,2}} \triangleq k_d \cdot \underline{[\vdash A_1 -]};$$

$$\overline{t^-_{2,3}} \triangleq 0.$$

On the menu today
Conservative model reduction

1. Motivating example
2. Evolution systems
3. Box approximation
4. Symbolic reasoning
5. Conclusion

Numerical results



(with parameters $[A_1]_0 = 10000$, $k = 10^{-4}$, $k_d = 10^{-2}$, and $k'_d = 10^{-1}$).

Conclusion

- We can deal models of polymers that:
  1. are finitely branching;
  2. and locally defined.

- High-level languages enable to denote some infinite sums of variables and to handle them symbolically

  (Prove that they are differentiable, express their derivative, compare them).

- Box approximation can be used to derive time-dependent bounds on the values of some observables

  (Safe numerical bounds are computed *a posteriori*)
  (Approximation locally adapts to the state of the system)
  (Partial derivatives are considered only on the corresponding (hyper)-faces).

Perspectives

1. Conservative approximation of the differential semantics
   - Provide a toolkit
     (box approximation, symbolic reasoning, partitioning, ...)
     to design and compose conservative approximations.
   - Recast existing methods in the light of this framework.
   - Automate the process and the choice of auxiliairy variables.
2. Conservative approximation of the stochastic semantics
   - Provide analogous abstractions for stochastic simulation.
   - Design a stochastic simulator for abstract states
     (with an abstract notion of time).
3. Conservative approximation of hybrid semantics