# HDR defense

# Static analysis and model reduction for site-graph rewriting


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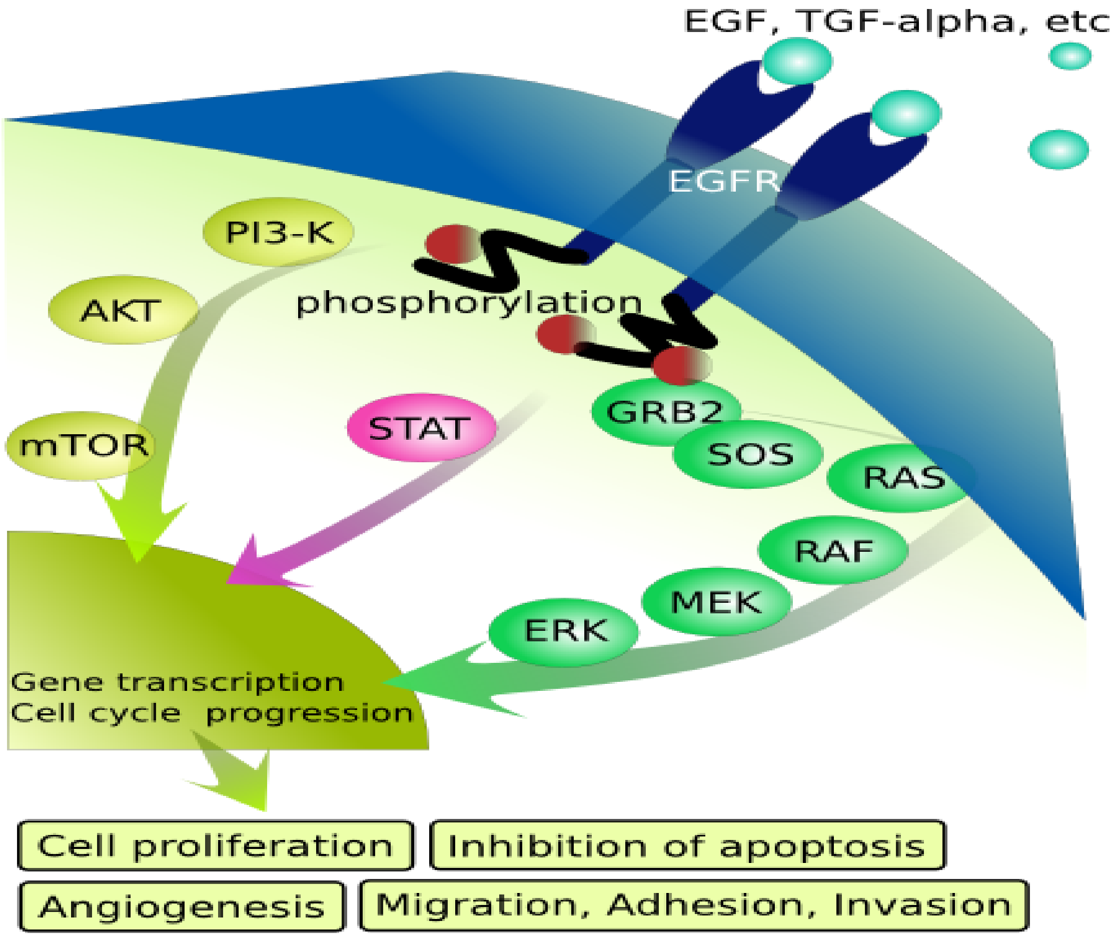
Tuesday, the 12th of December, 2023

# Outline

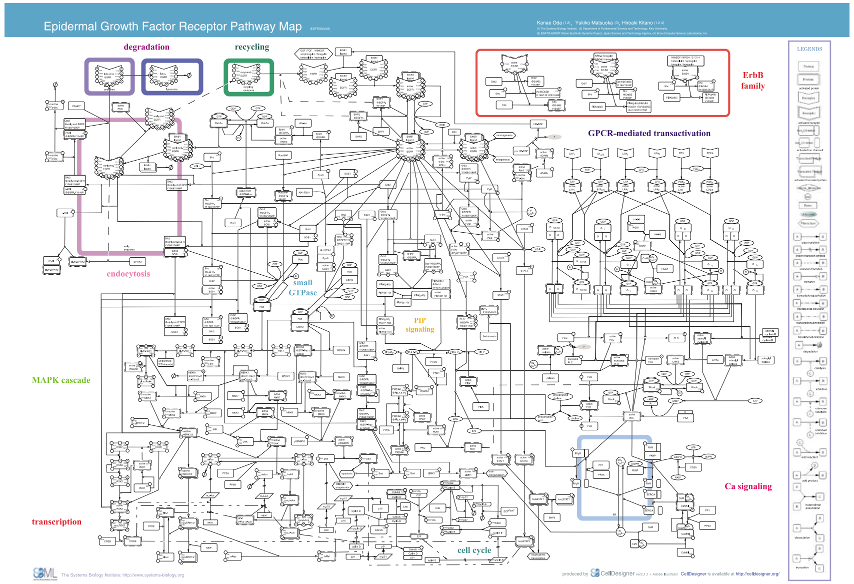
1. Context and motivations
2. Static analysis
3. Flow-based model reduction (differential)
4. Flow-based model reduction (stochastic)
5. Symmetries
6. Conclusion and perspectives

# Intra-cellular signalling pathways




Eikuch, 2007

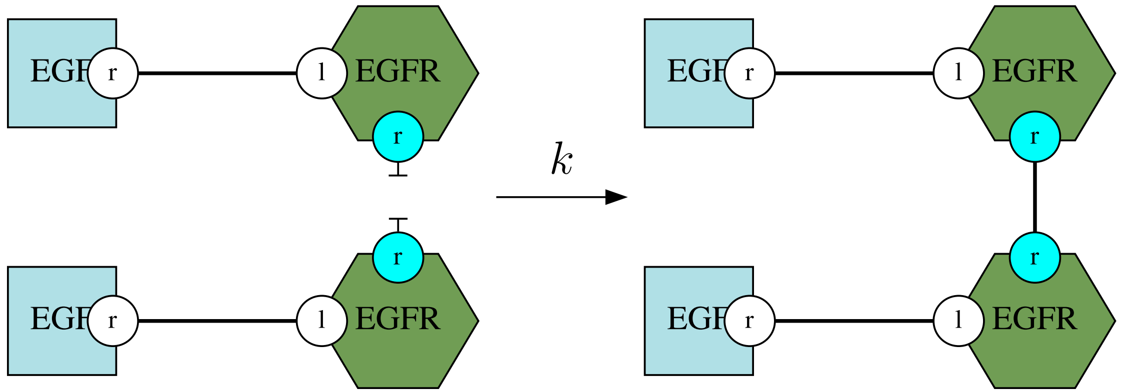
# Bridge the gap between...




$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2 \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - k_3 \cdot x_4 - k_{-3} \cdot x_5 \\
\frac{dx_5}{dt} = \cdots \\
\vdots \\
\frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3
\end{cases}
$$

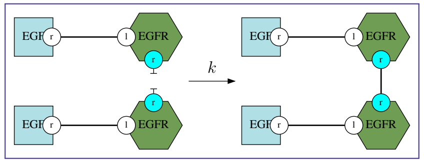
**knowledge representation** and **models of the behaviour of systems**

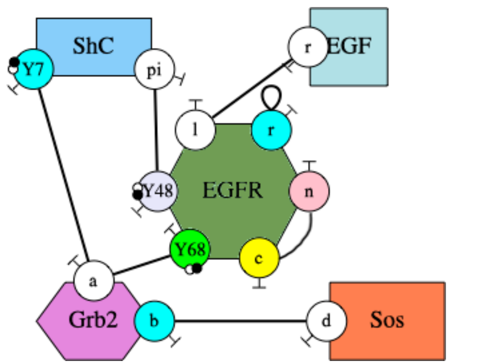
# Site-graph rewriting



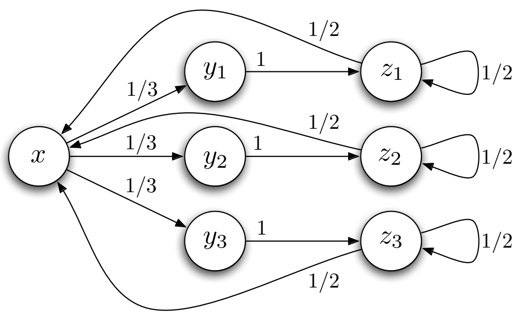

- a language close to knowledge representation;
- rules are easy to update;
- a compact description of models.

# Choices of semantics




interaction map

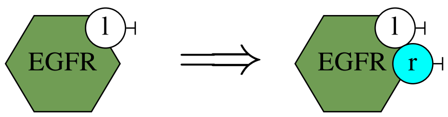



Markov chain

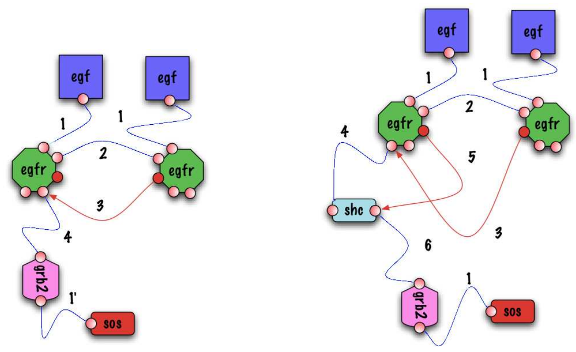
$$\begin{cases} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2 \cdot x_4 + \frac{v_4 \cdot x_5}{p_4 + x_5} - k_3 \cdot x_4 - k_{-3} \cdot x_5 \\ \frac{dx_5}{dt} = \cdots \\ \vdots \\ \frac{dx_n}{dt} = -k_1 \cdot x_1 \cdot c_2 + k_{-1} \cdot x_3 \end{cases}$$

ordinary differential equations

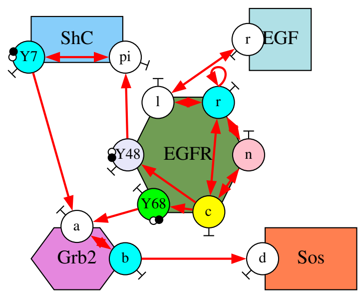
# Abstractions offer different perspectives



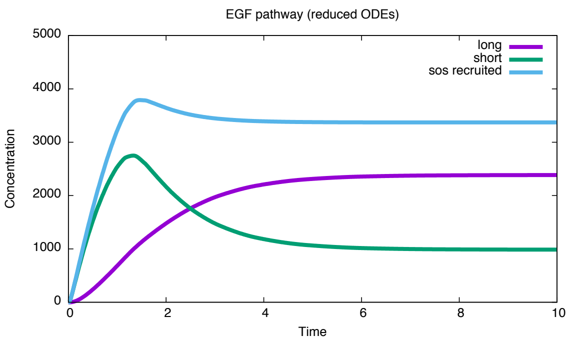

static analysis




causal traces




information flow




exact projection
of the ODE semantics

# Bottom up approach in modeling

1. Reaction-based modeling: Reactions are enumerated explicitly.
   - Reaction-networks [Feinberf, 1979]
   - Petri-nets [Heiner, 2003]
   - BIOCHAM [Fages *et al.* 2004]
2. Agent-based modeling: Each agent describes its potential behaviors.
   - $\pi$-calculus [Cardelli *et al.*, 2009]
   - communicating automata [Cardelli, 2007]
   - BlenX [Priami *et al.*, 2008]
3. Rule-base modeling: The behaviors of agents emerge from the rules
   - $\pi$-calculus [Regev *et al.*, 2001, 2004]
   - Kappa [Danos *et al.*, 2003-], BNGL [Faeder *et al.*, 2005-], Mød [Andersen etal, 2014-]
   - ML-Space: with spatial diffusion [Uhrmacher *et al.*, 2008-]

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# Motivations

**Main goal** : Increase confidence in models

- Summarize structural properties :
  - Relationships between the states of sites in biochemical complexes;
  - Prove the absence of polymers.

- Detect dead rules :
  - due to typos;
  - due to complex causal properties ;
  - due to parts that may be missing.

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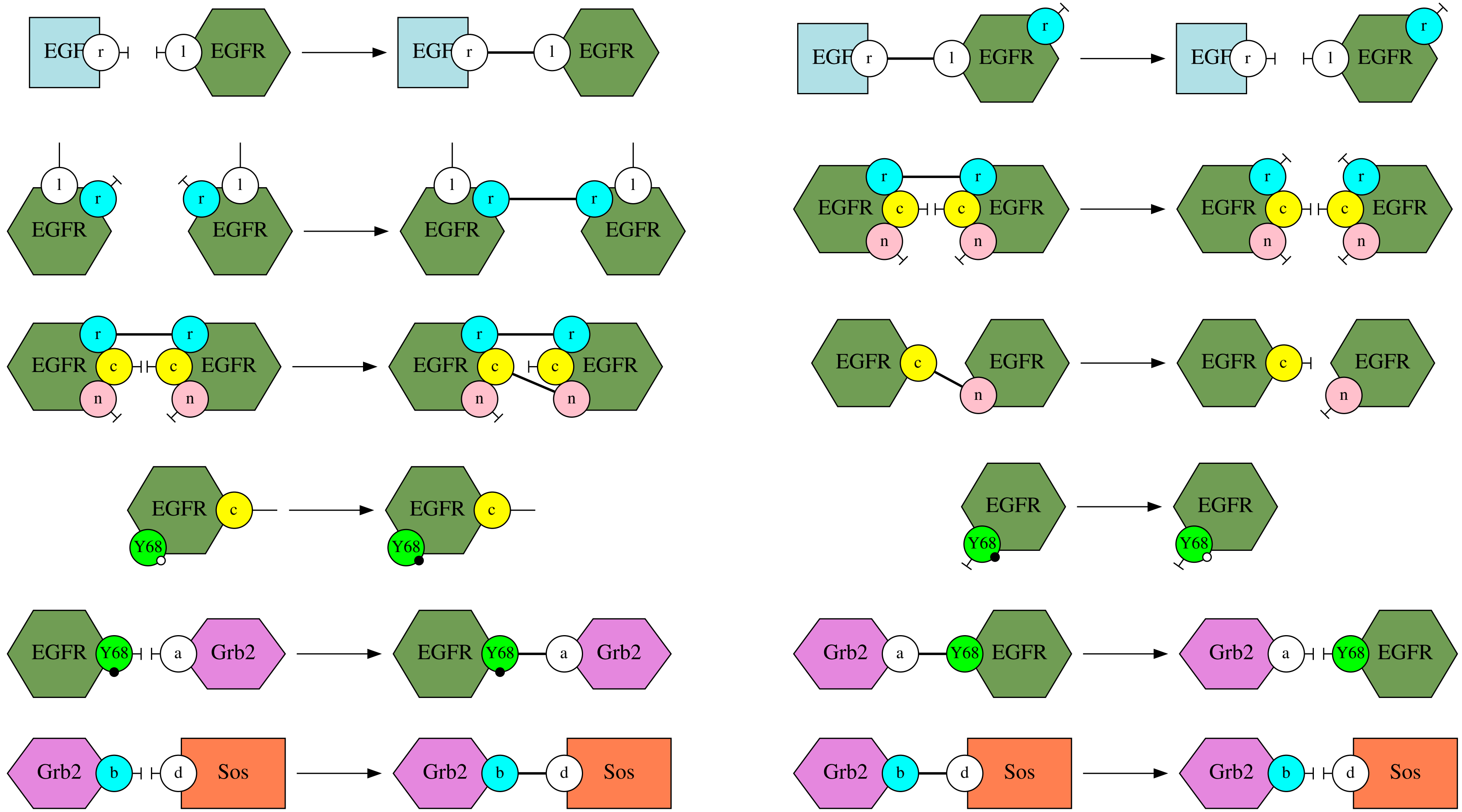
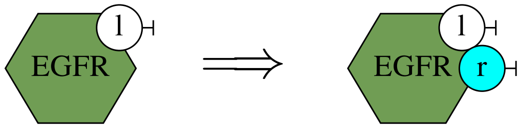
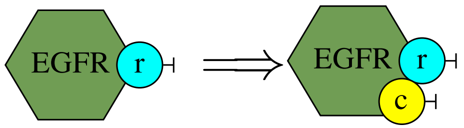
# Some rules



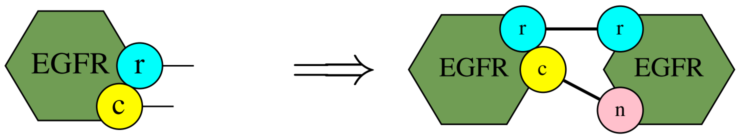
# Some invariants

- 

whenever the site *l* is free, the site *r* is free as well.

- 

whenever the site *r* is free, the site *c* is free as well.

- 

whenever the sites *c* and *r* are both bound, they are bound to a single occurrence of an occurrence of the protein *EGFR*.

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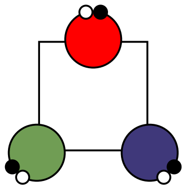
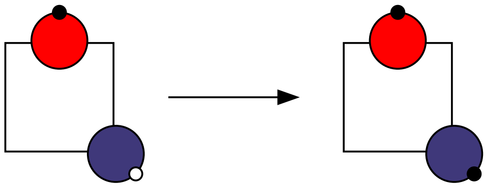
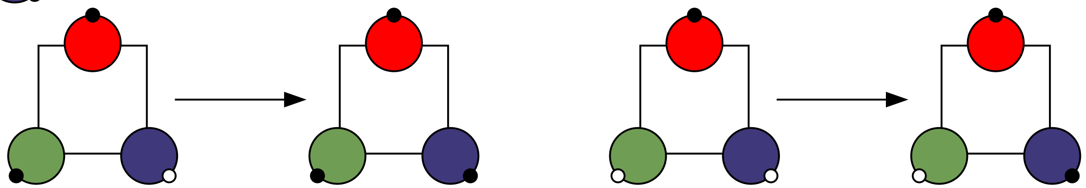
# Reachability semantics

A rule stands for a multi-set of reactions.

For instance, considering the protein: 

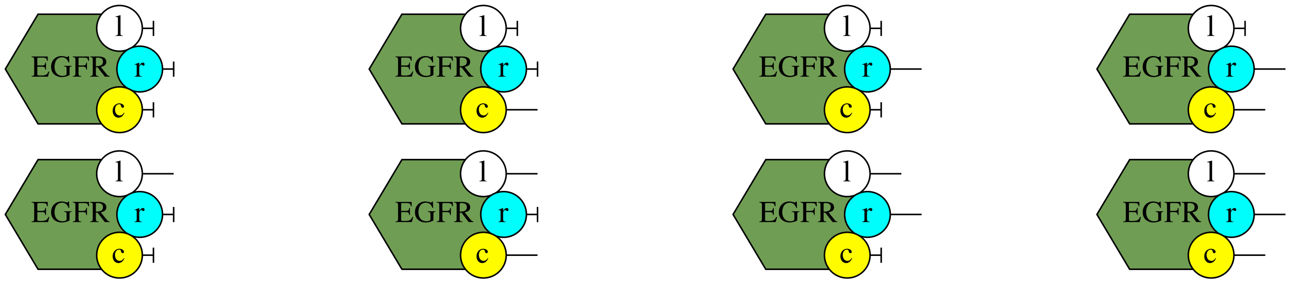
the rule 

stands for both reactions: 

We are interested in the set of states that are reachable after applying an arbitrary number of reactions (starting from an initial state).

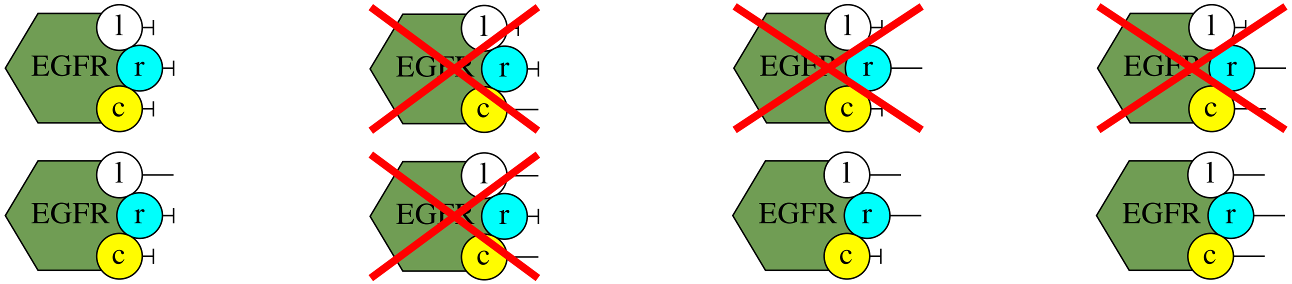
# Abstract domain

Among a set of patterns,



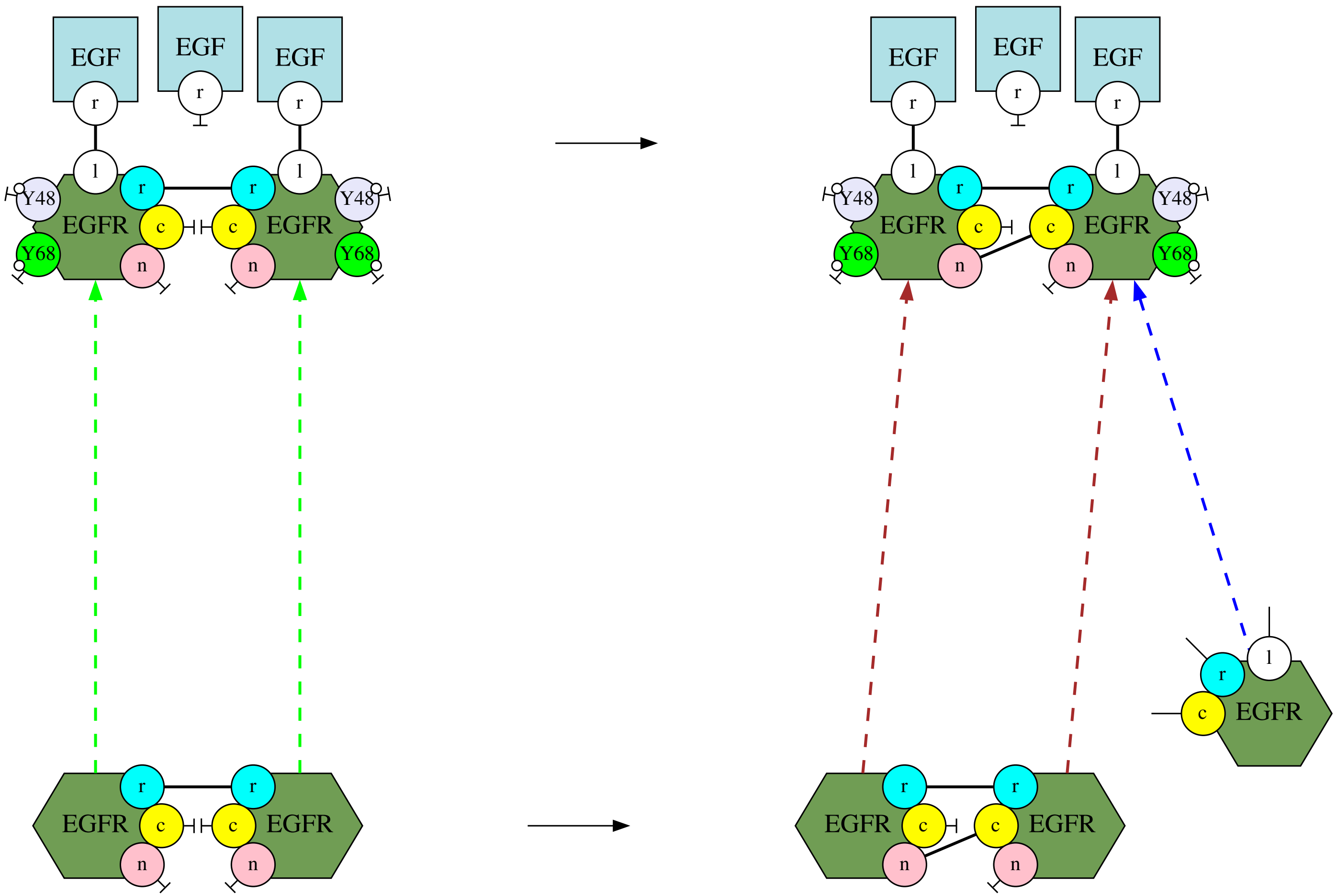
# Abstract domain

Among a set of patterns,

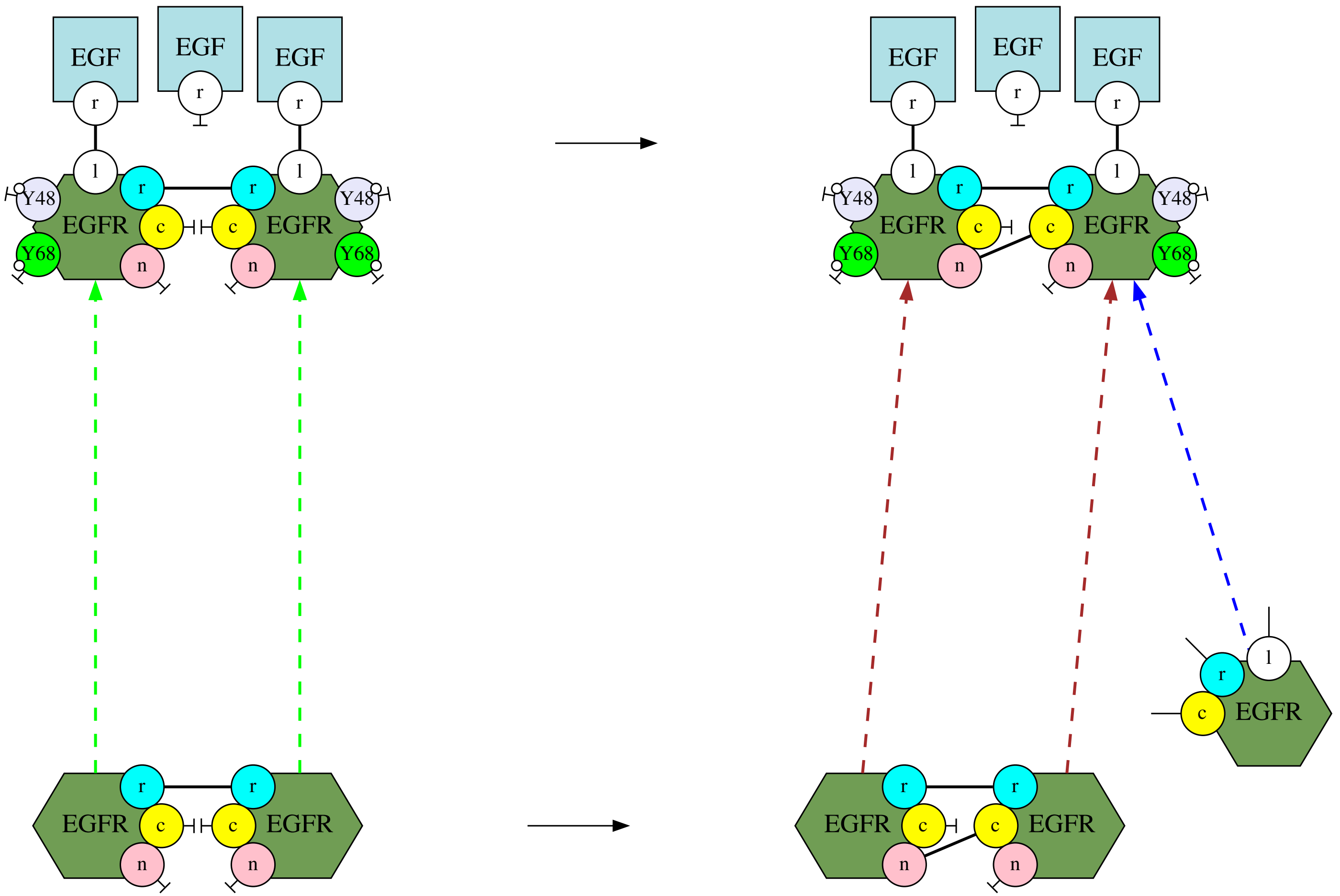



we would like to compute which ones may occur in a reachable state.
(*the initial state is given in the specification.*)

# Most precise abstract transition

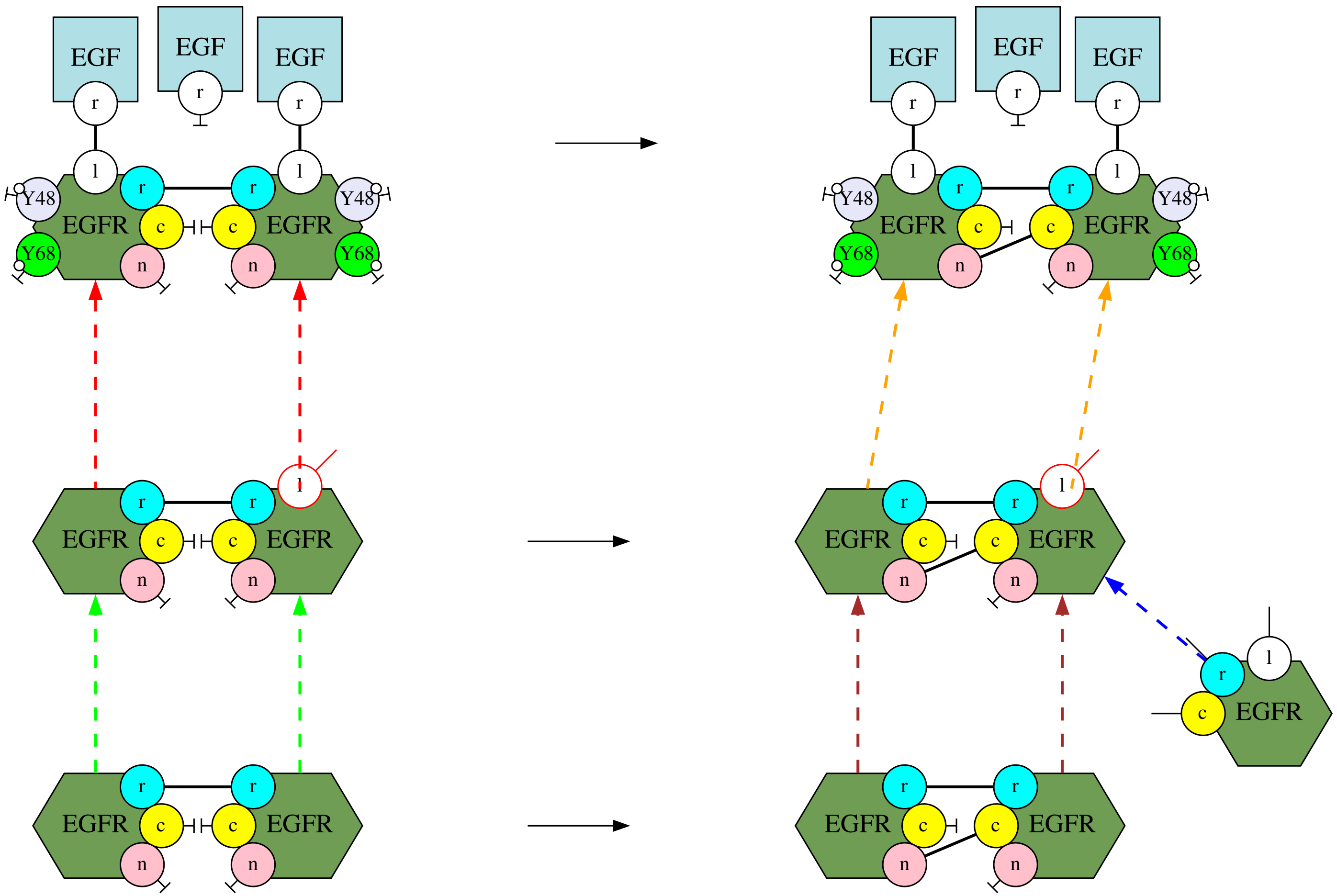


# Most precise abstract transition

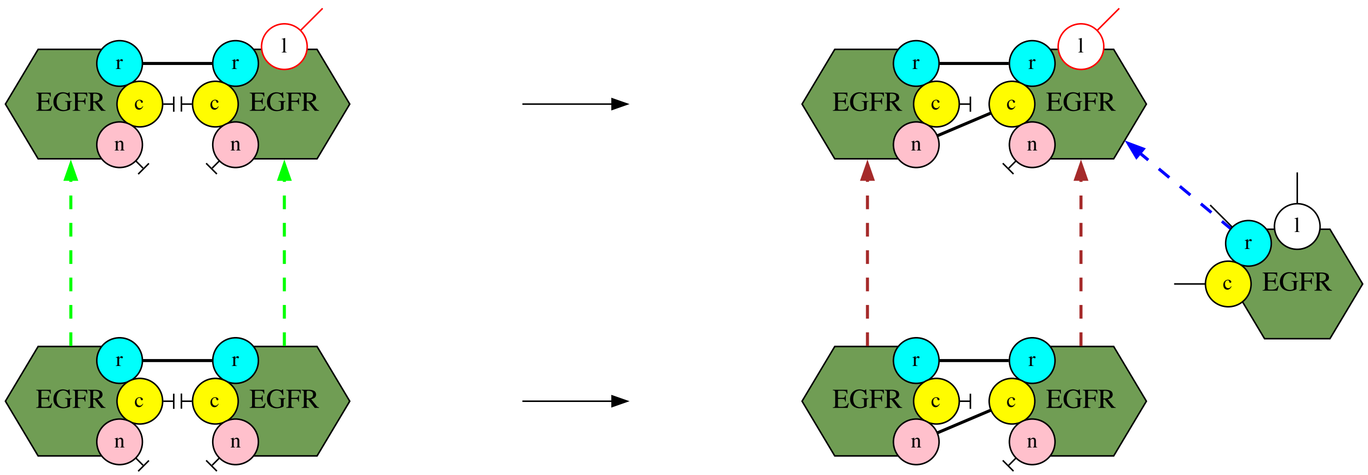



when the left hand side of the transition (top) contains no forbidden pattern.

# Simplified abstract transition



# Simplified abstract transition




We are left to check whether the left hand side of the refined rule is reachable given the forbidden patterns.

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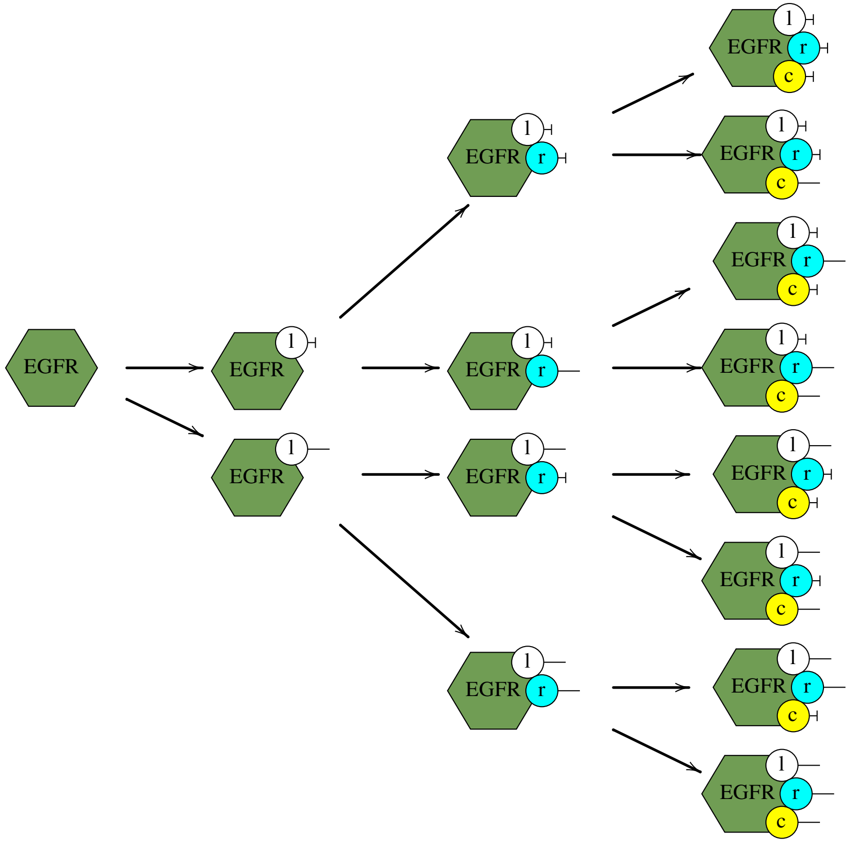
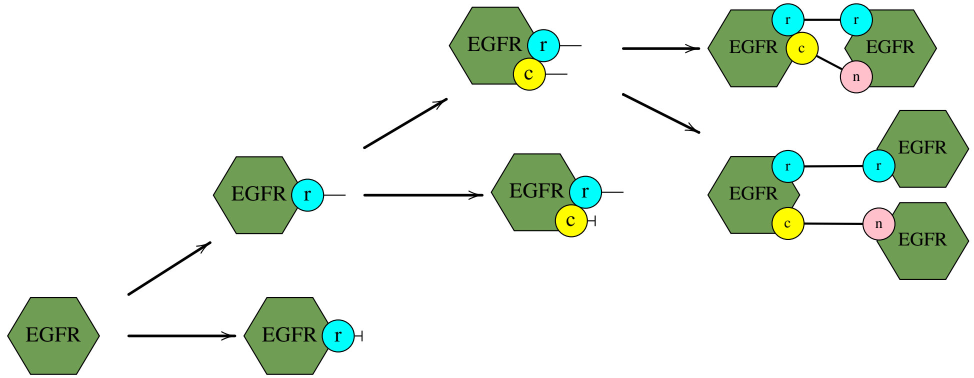
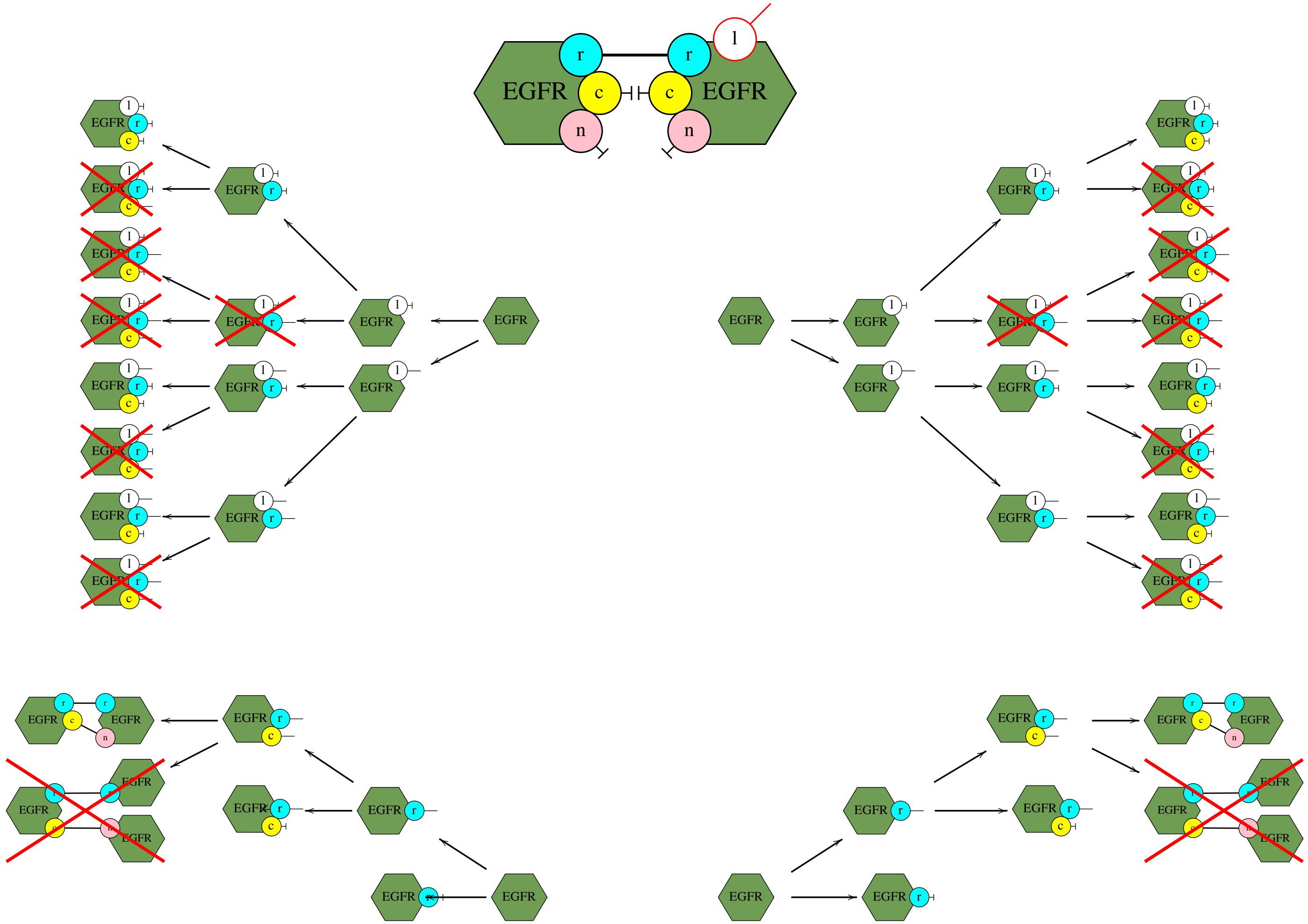
# Orthogonal sets of patterns

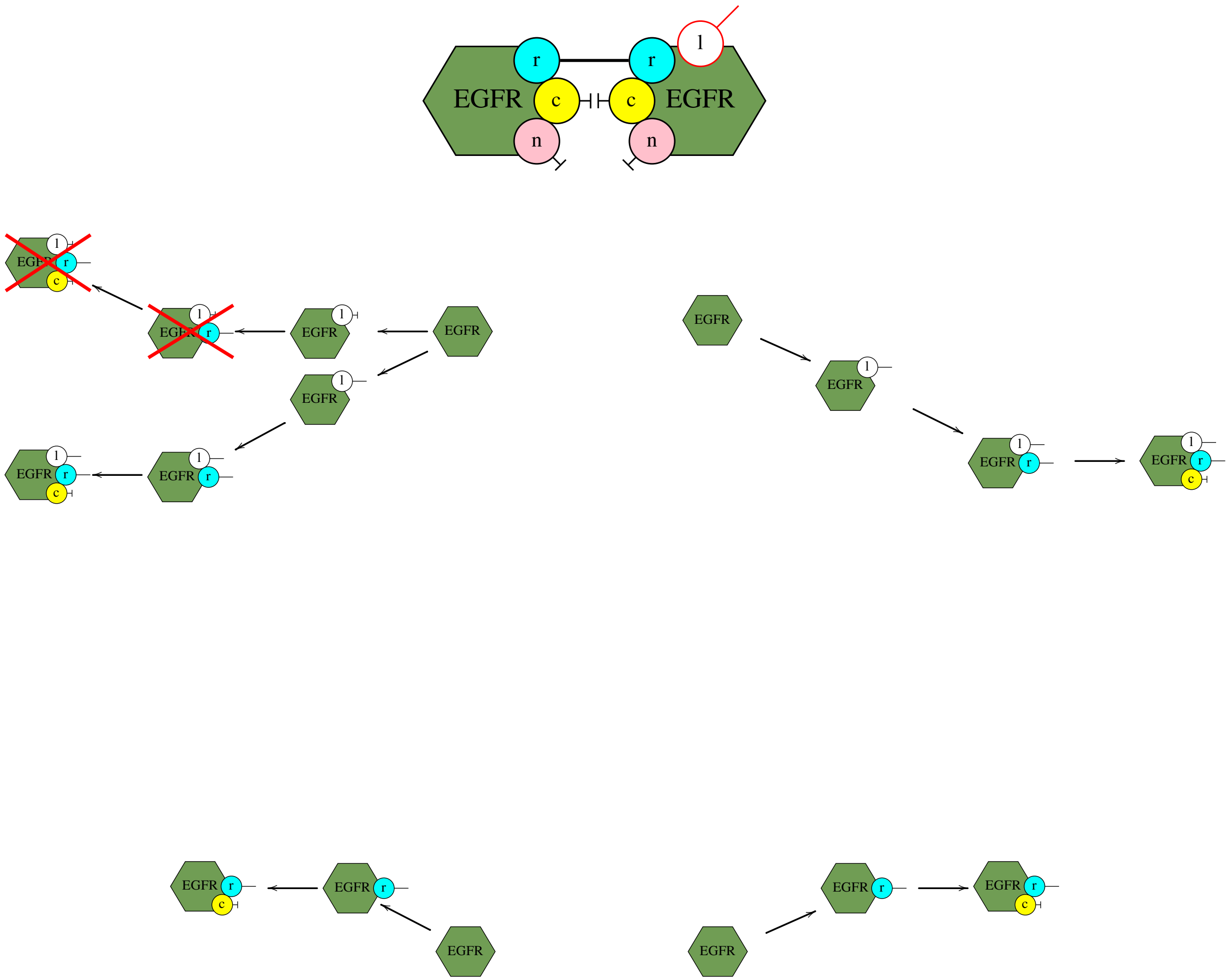


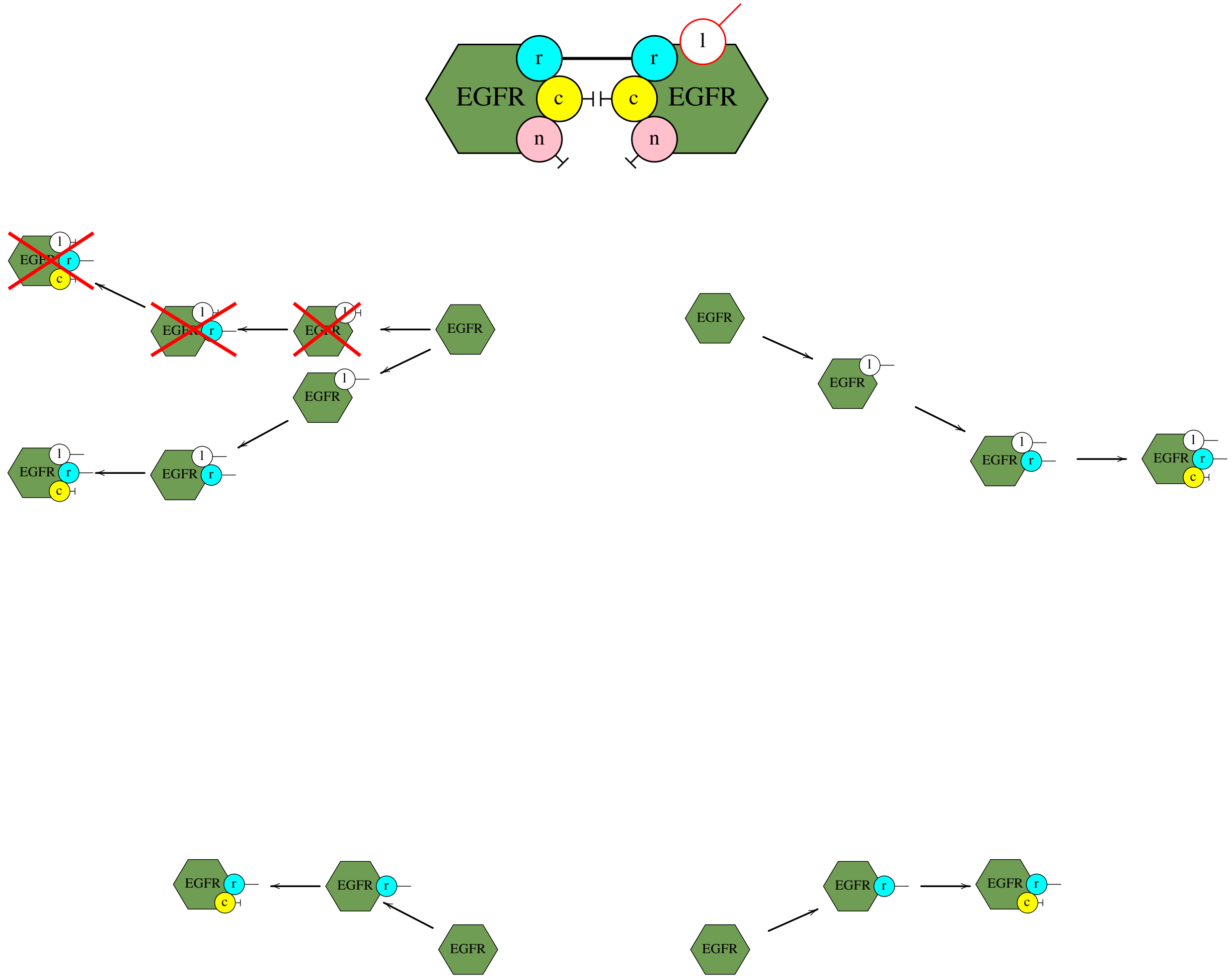
# Compatibility checking procedure



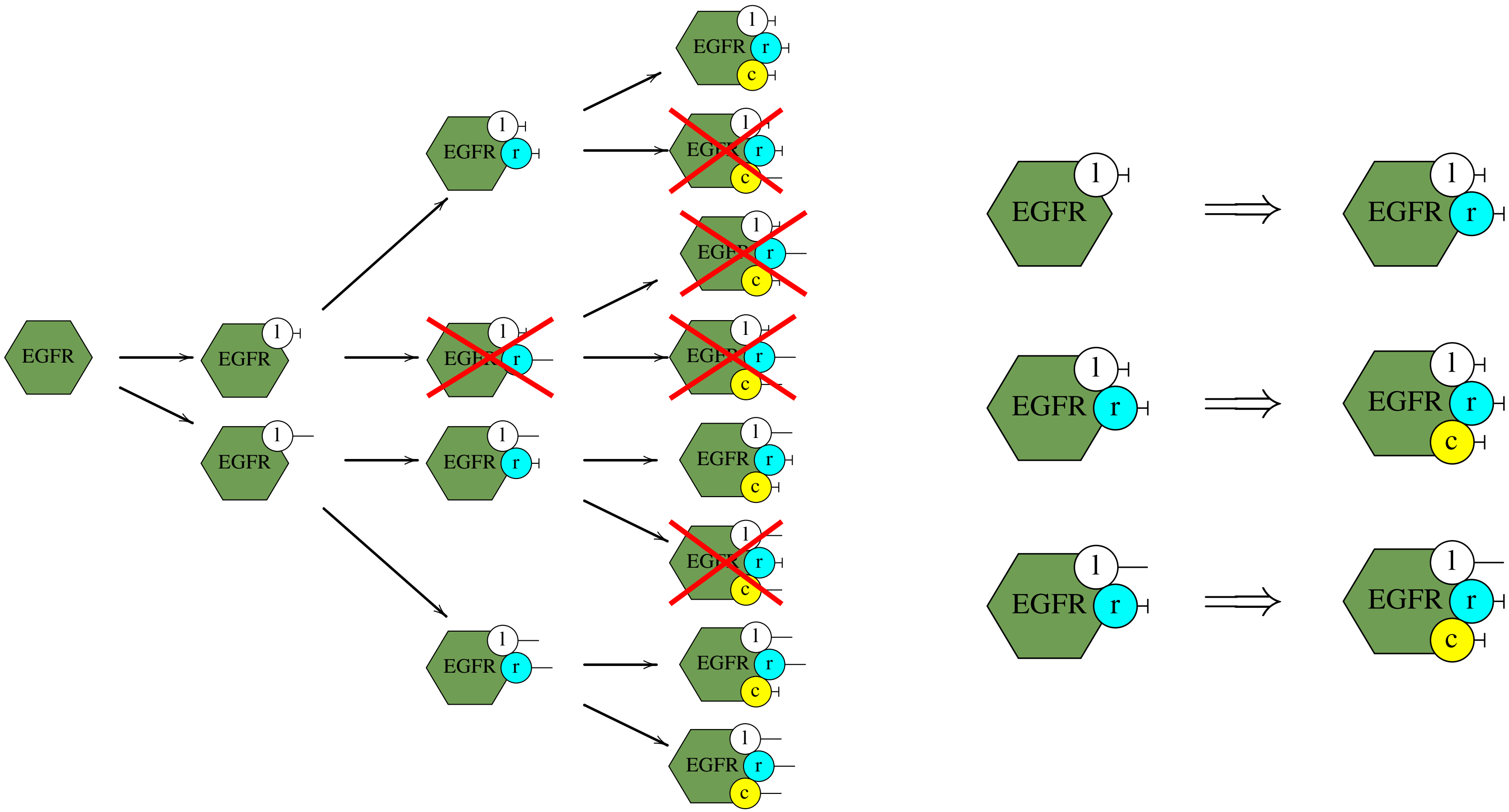
# Compatibility checking procedure



# Compatibility checking procedure



# Visualization



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# Benchmarks

| model | rules | inferred constraints | detected dead rules | analysis time (seconds) |
|---|---|---|---|---|
| repressilator | 42 | 0 | 0 | 0.005 |
| fceri_fyn_trimer | 362 | 4 | 36 | 0.301 |
| fceri_fyn_lyn_745 | 40 | 4 | 2 | 0.021 |
| egfr | 20 | 9 | 0 | 0.010 |
| egfr, erk, mapk, ras | 69 | 7 | 0 | 0.046 |
| machine | 220 | 13 | 7 | 0.405 |
| ensemble | 233 | 26 | 0 | 0.364 |
| korkut (2017/01/17) | 12896 | 0 | 874 | 24 |
| korkut (2017/02/06) | 5750 | 0 | 884 | 57 |
| TGF (2018/04/19) | 292 | 13 | 0 | 0.625 |
| BigWnt (2017/03/22) | 1486 | 14 | 12 | 8.74 |

on a MacBook Pro - Intel Core i7-6567U (3.3 GHz)

# Conclusion

- Mutual induction between several orthogonal sets;
- Automatic parameterization (by one-pass inspection of the rules);
- Accurate analysis (on the models we were given);
- Efficient analysis
  *but not enough to analyse big models in a text editor*.

# Perspectives

- Analysis of families of models;
- Incremental analysis.

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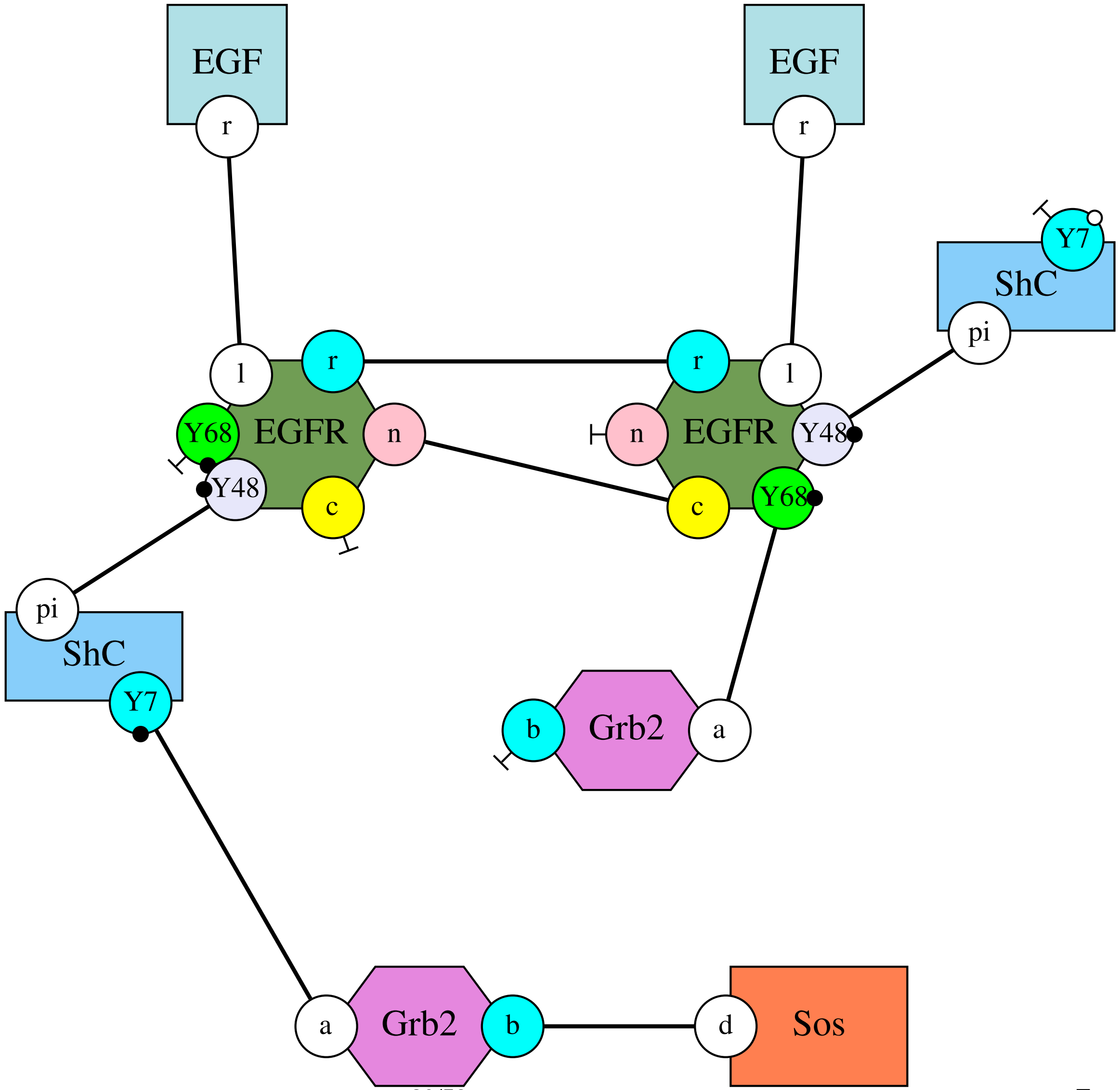
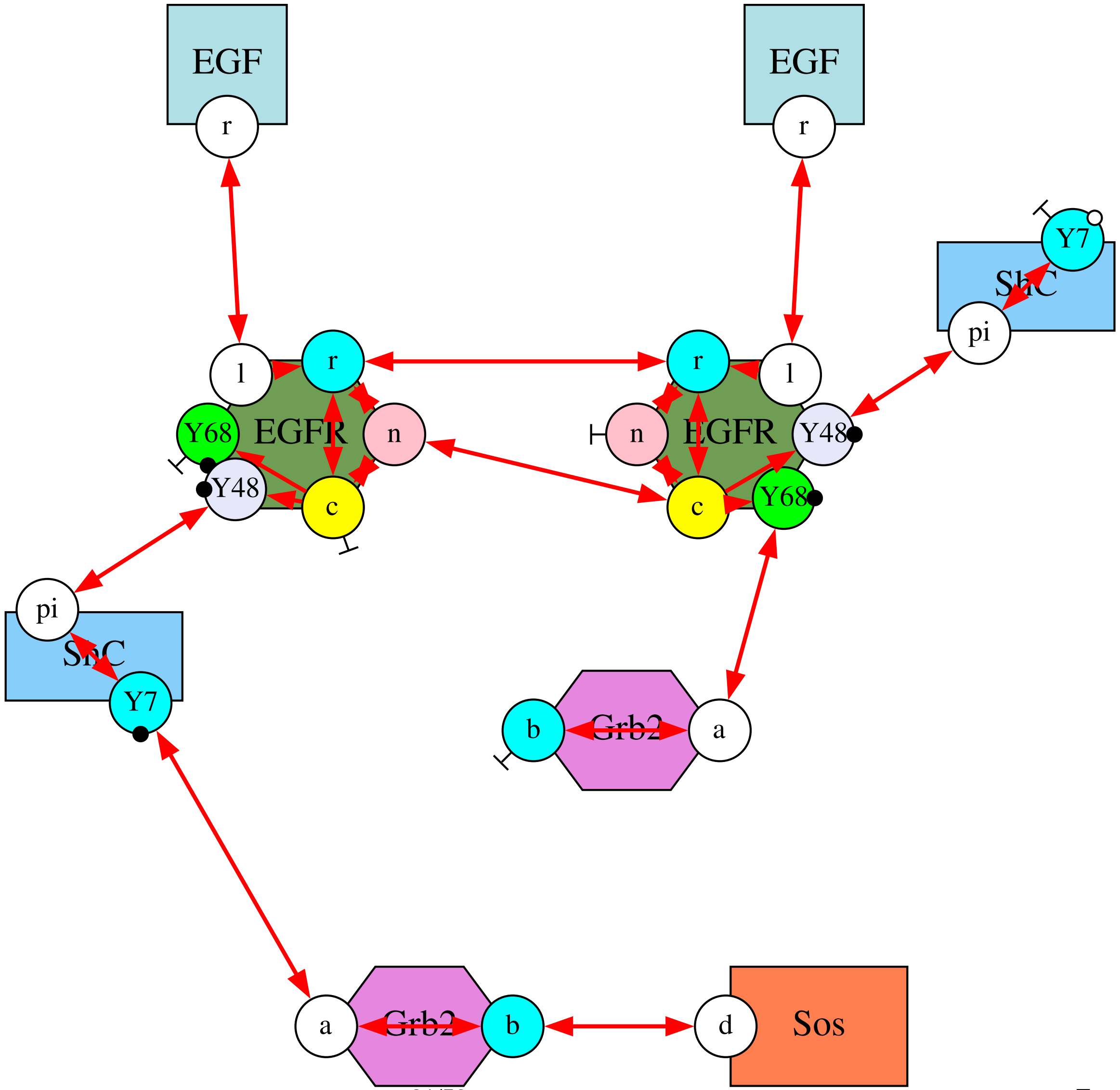
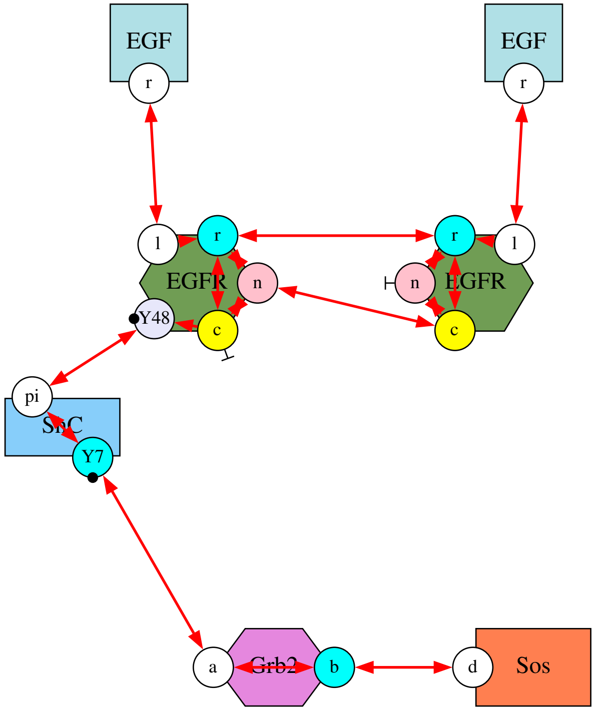
# Combinatorial wall

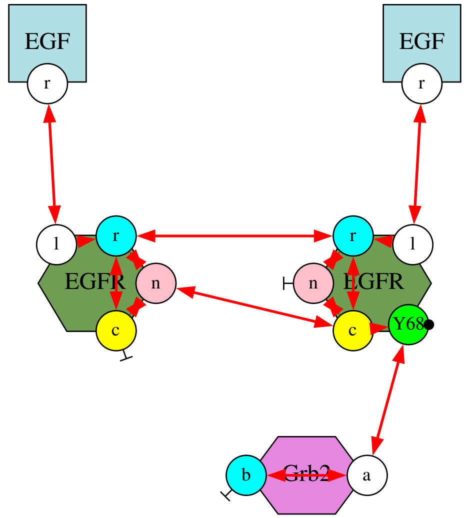


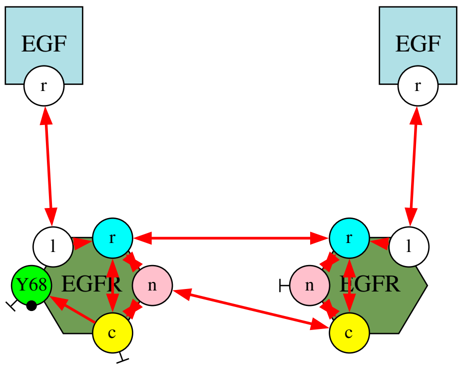
# Information flow

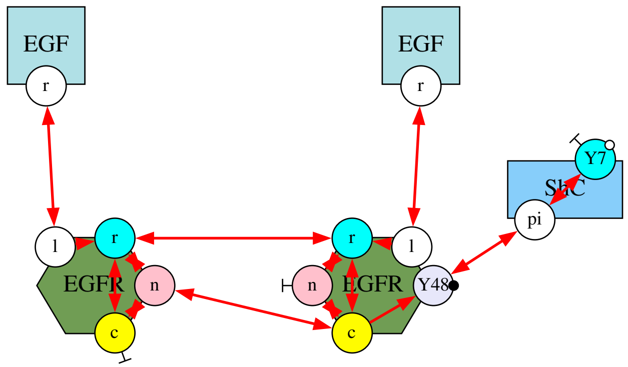


# A potential breach



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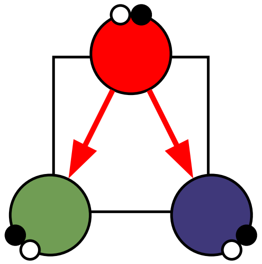
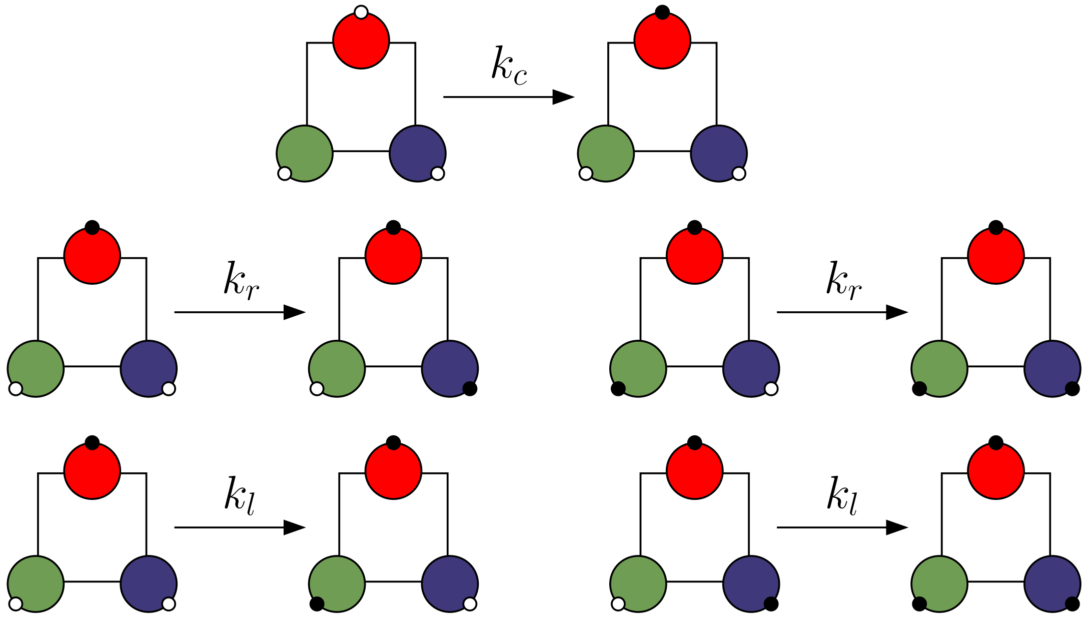
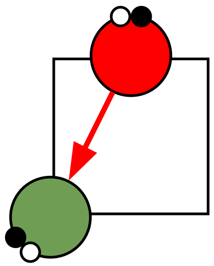
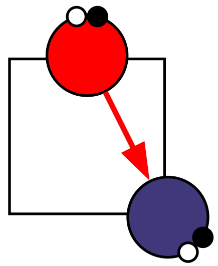
# Case study






$$
\begin{cases}
\frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\
\frac{d[(u,p,u)]}{dt} = -k_l \cdot [(u,p,u)] + k_c \cdot [(u,u,u)] - k_r \cdot [(u,p,u)] \\
\frac{d[(u,p,p)]}{dt} = -k_l \cdot [(u,p,p)] + k_r \cdot [(u,p,u)] \\
\frac{d[(p,p,u)]}{dt} = k_l \cdot [(u,p,u)] - k_r \cdot [(p,p,u)] \\
\frac{d[(p,p,p)]}{dt} = k_l \cdot [(u,p,p)] + k_r \cdot [(p,p,u)]
\end{cases}
$$

# Case study

$$[(u,u,u)] = [(u,u,u)]$$
$$[(u,p,?)] \triangleq [(u,p,u)] + [(u,p,p)]$$
$$[(p,p,?)] \triangleq [(p,p,u)] + [(p,p,p)]$$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(u,p,?)]}{dt} = -k_l \cdot [(u,p,?)] + k_c \cdot [(u,u,u)] \\ \frac{d[(p,p,?)]}{dt} = k_l \cdot [(u,p,?)] \end{cases}$$

$$[(u,u,u)] = [(u,u,u)]$$
$$[(?,p,u)] \triangleq [(u,p,u)] + [(p,p,u)]$$
$$[(?,p,p)] \triangleq [(u,p,p)] + [(p,p,p)]$$

$$\begin{cases} \frac{d[(u,u,u)]}{dt} = -k_c \cdot [(u,u,u)] \\ \frac{d[(?,p,u)]}{dt} = -k_r \cdot [(?,p,u)] + k_c \cdot [(u,u,u)] \\ \frac{d[(?,p,p)]}{dt} = k_r \cdot [(?,p,u)] \end{cases}$$

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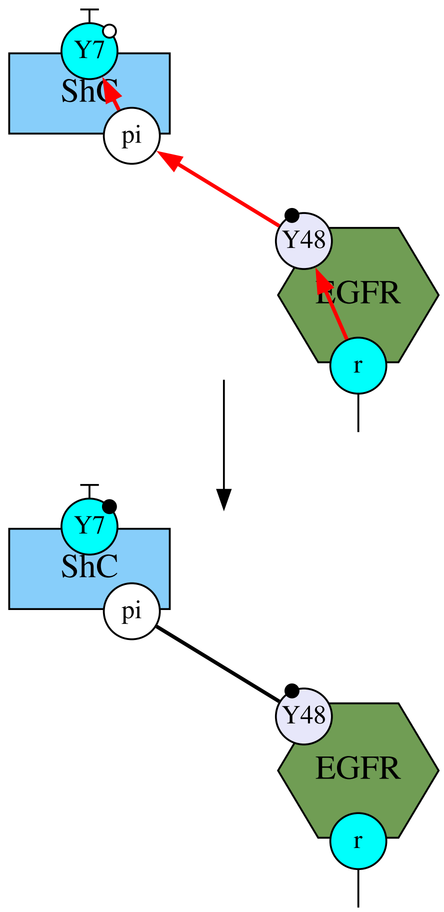
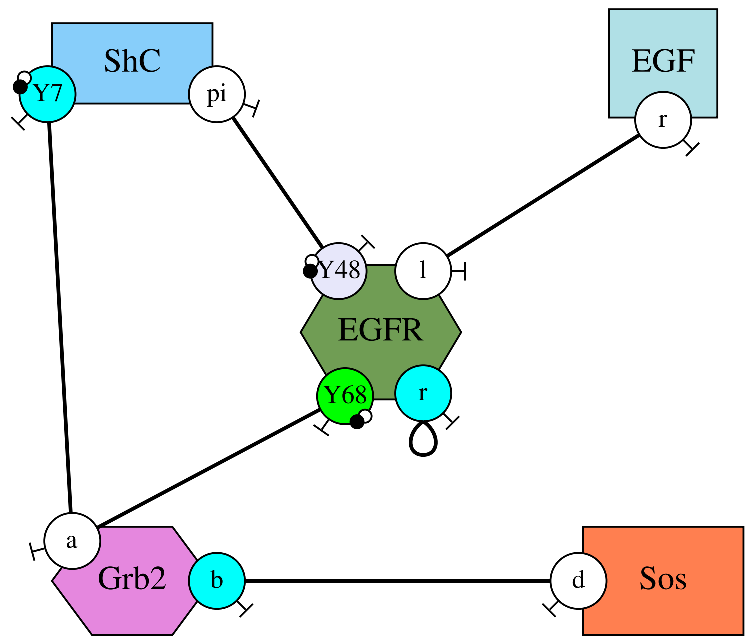
# Approximation of the flow of information



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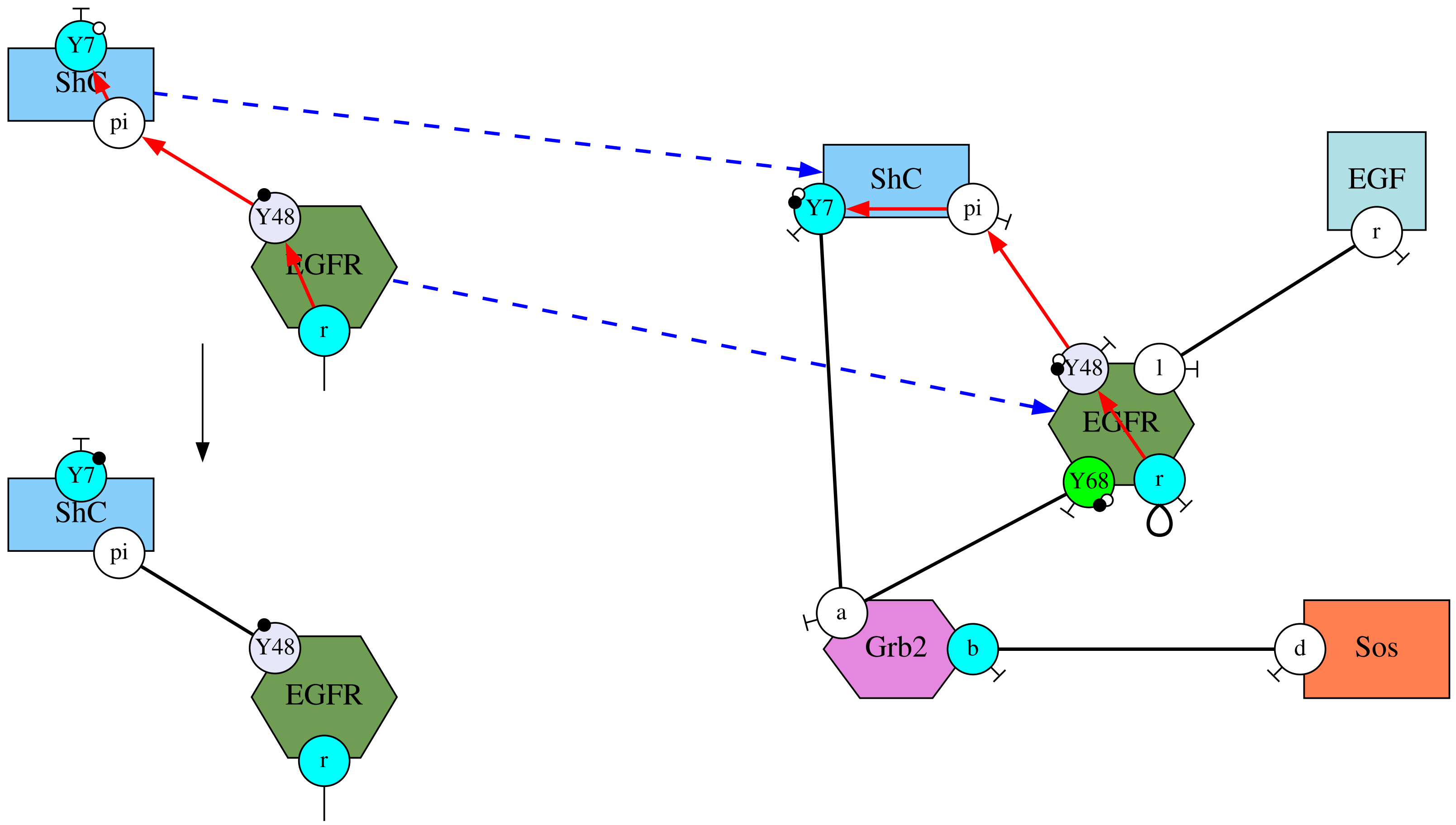
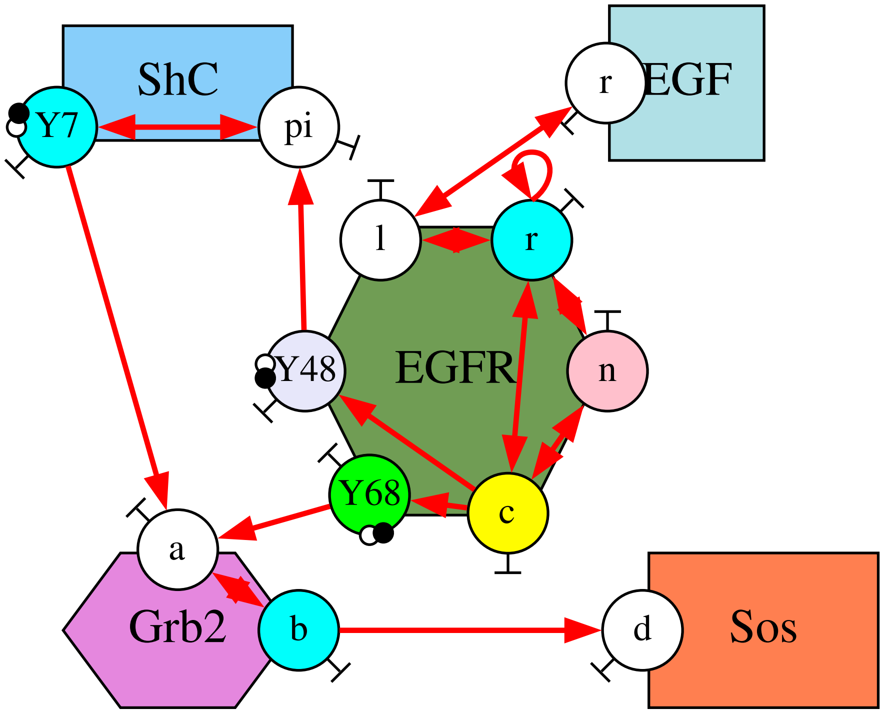


# Annotated interaction map



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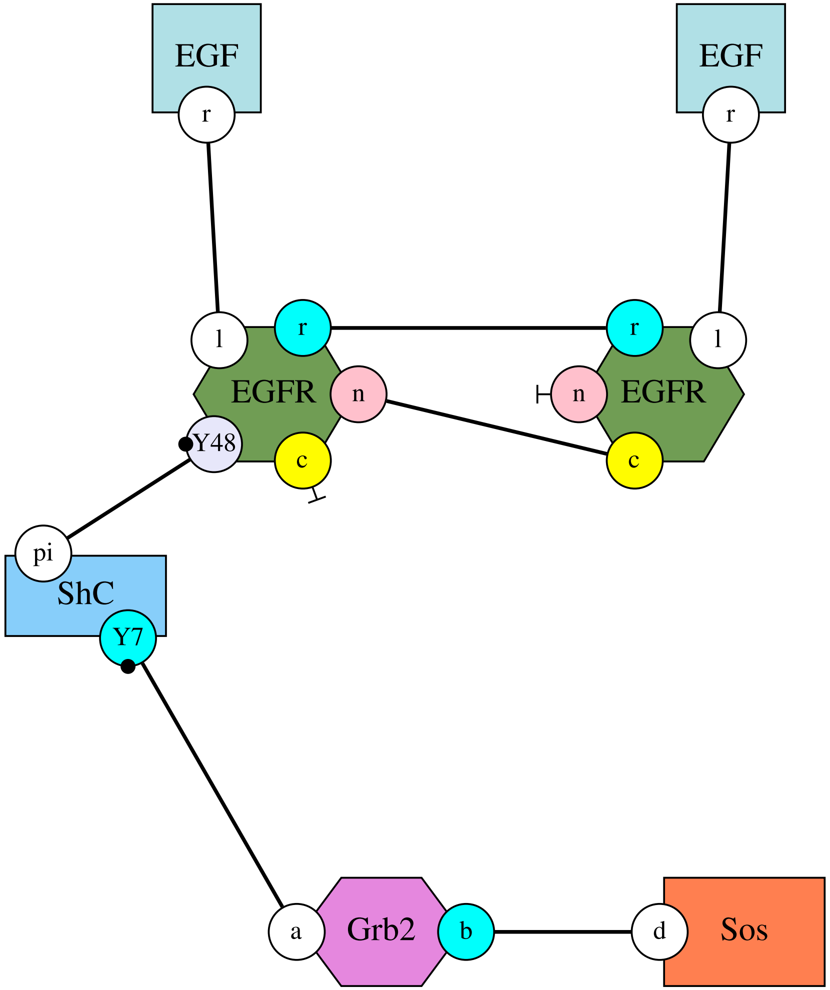
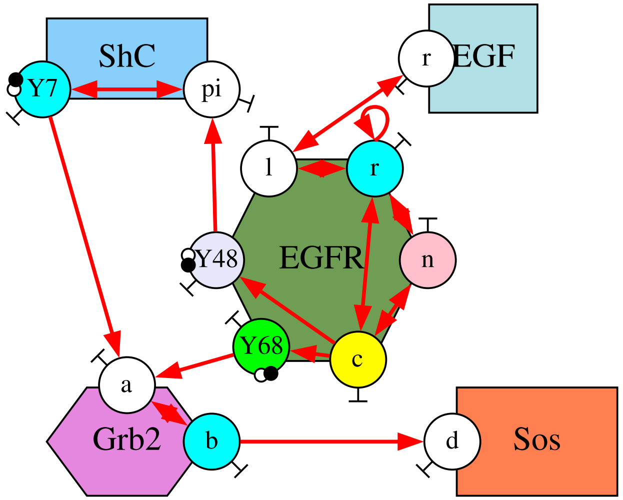
# Pattern annotation



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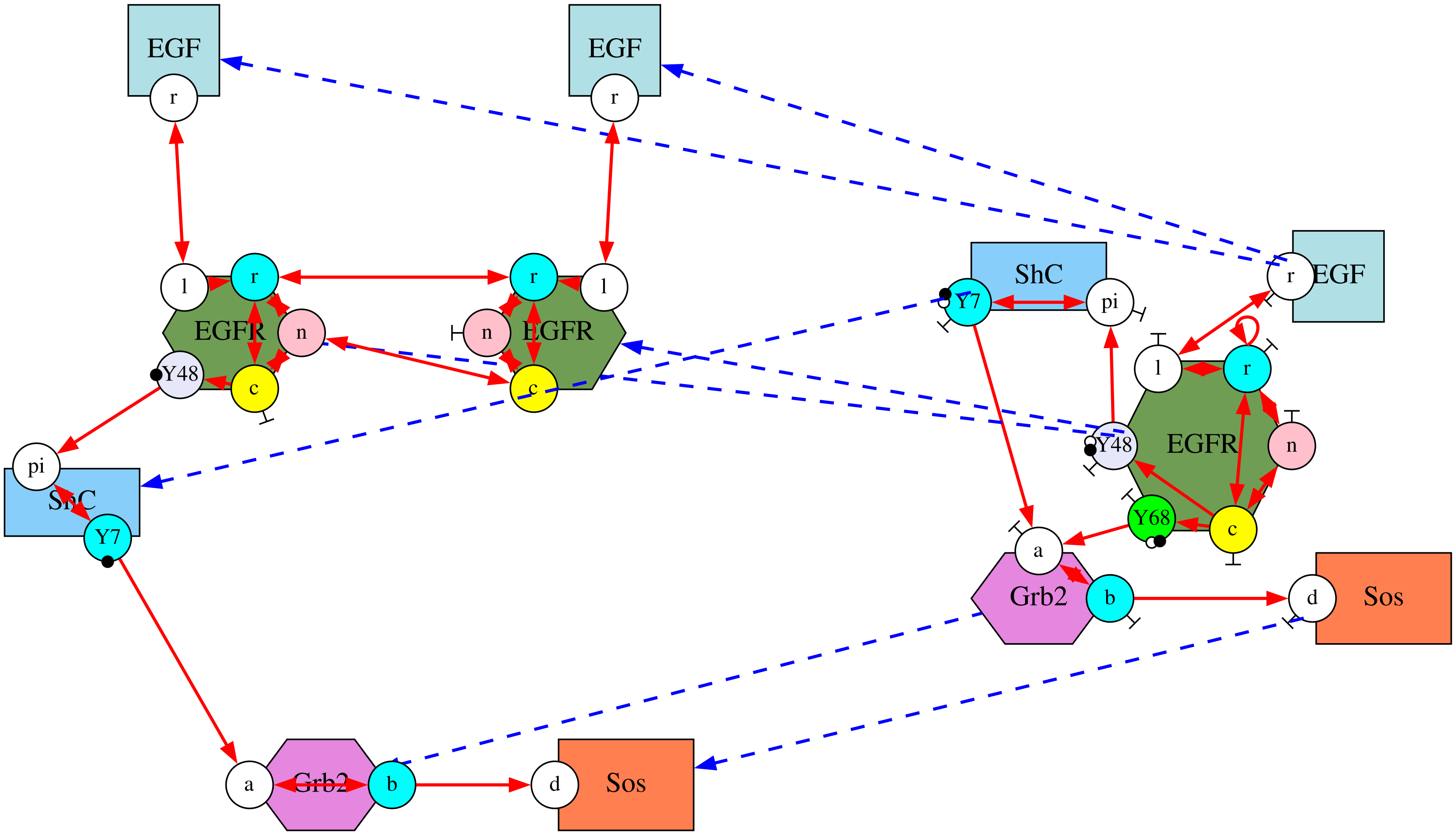
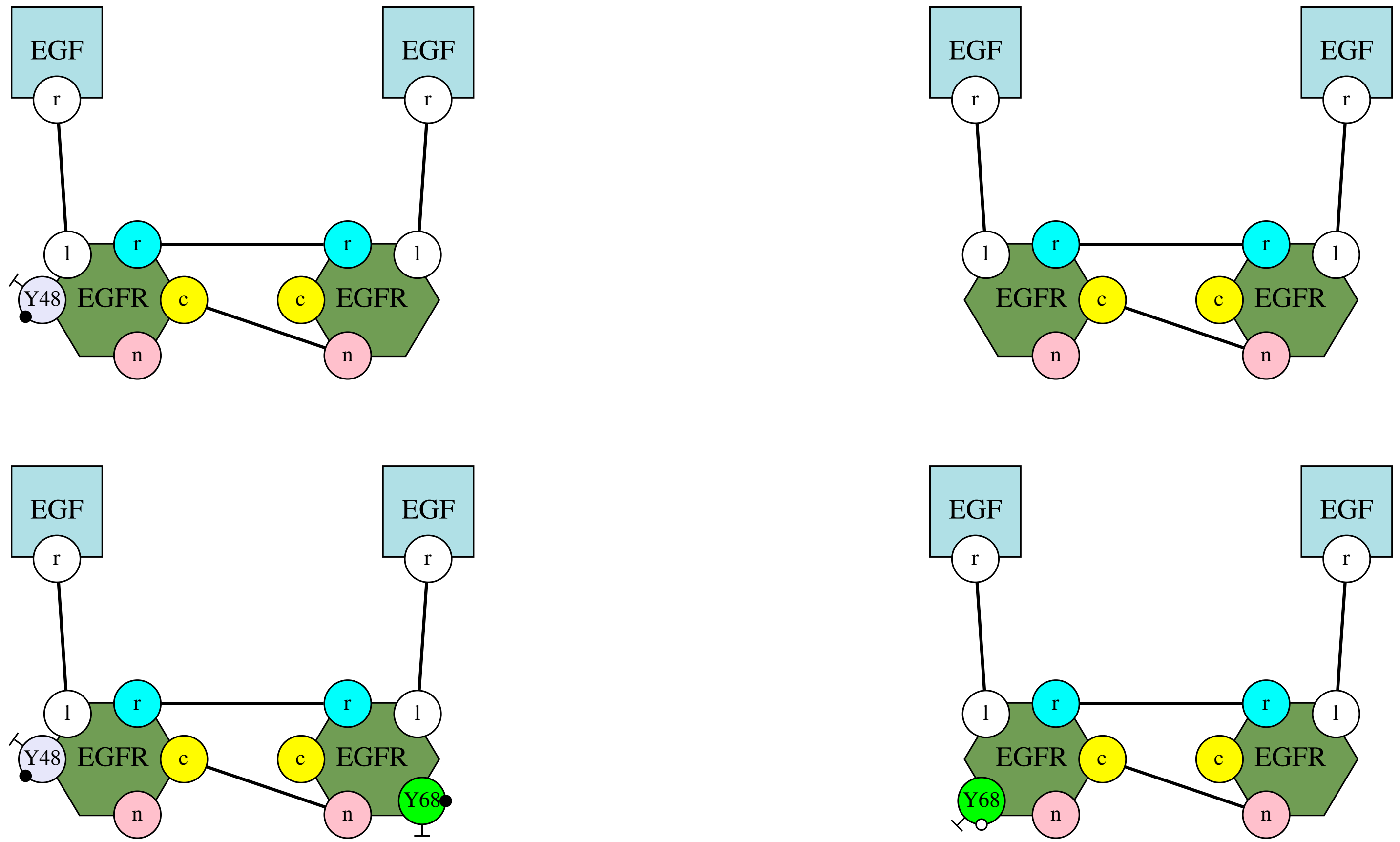
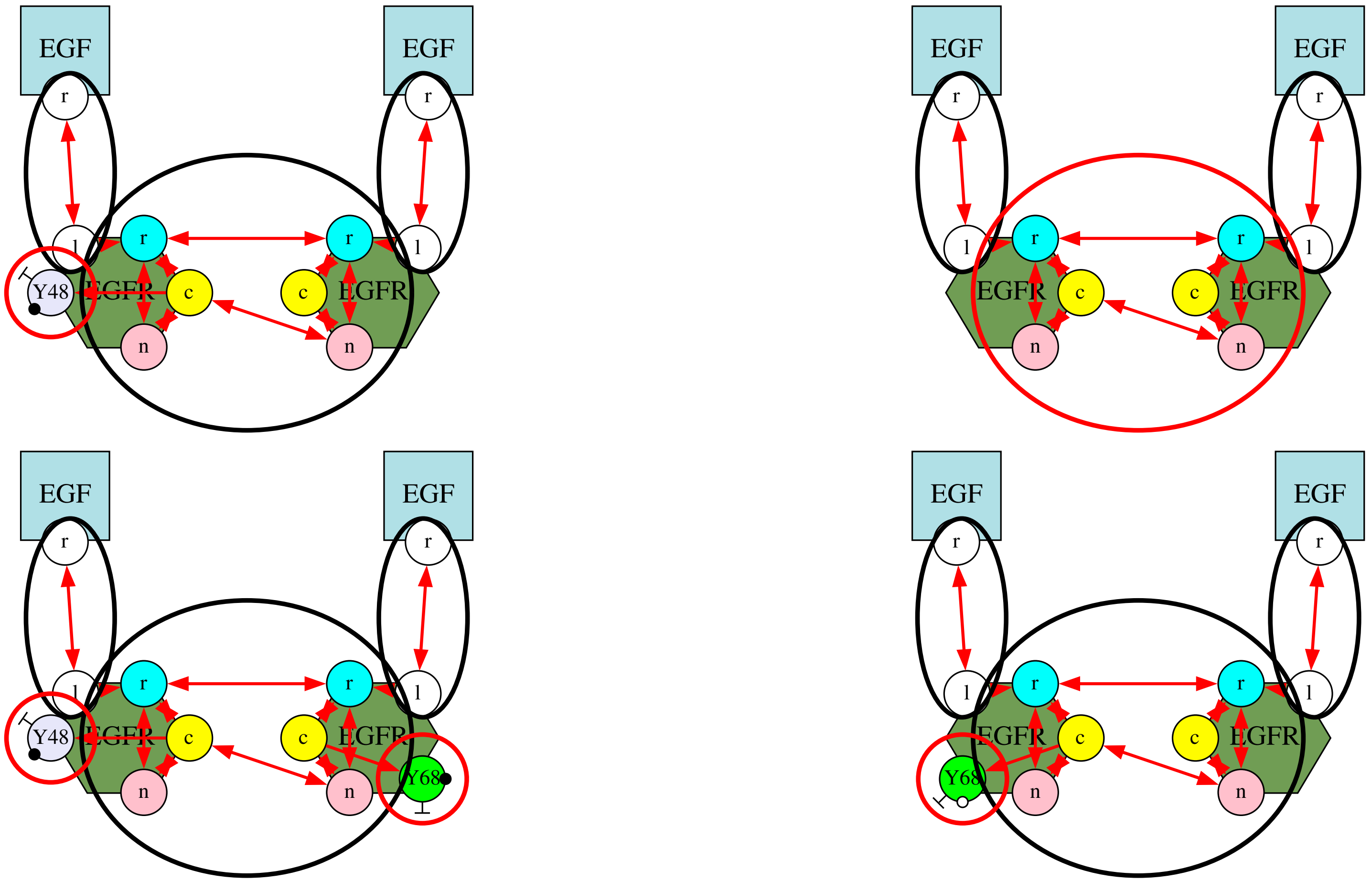


# Which patterns to keep as variables?

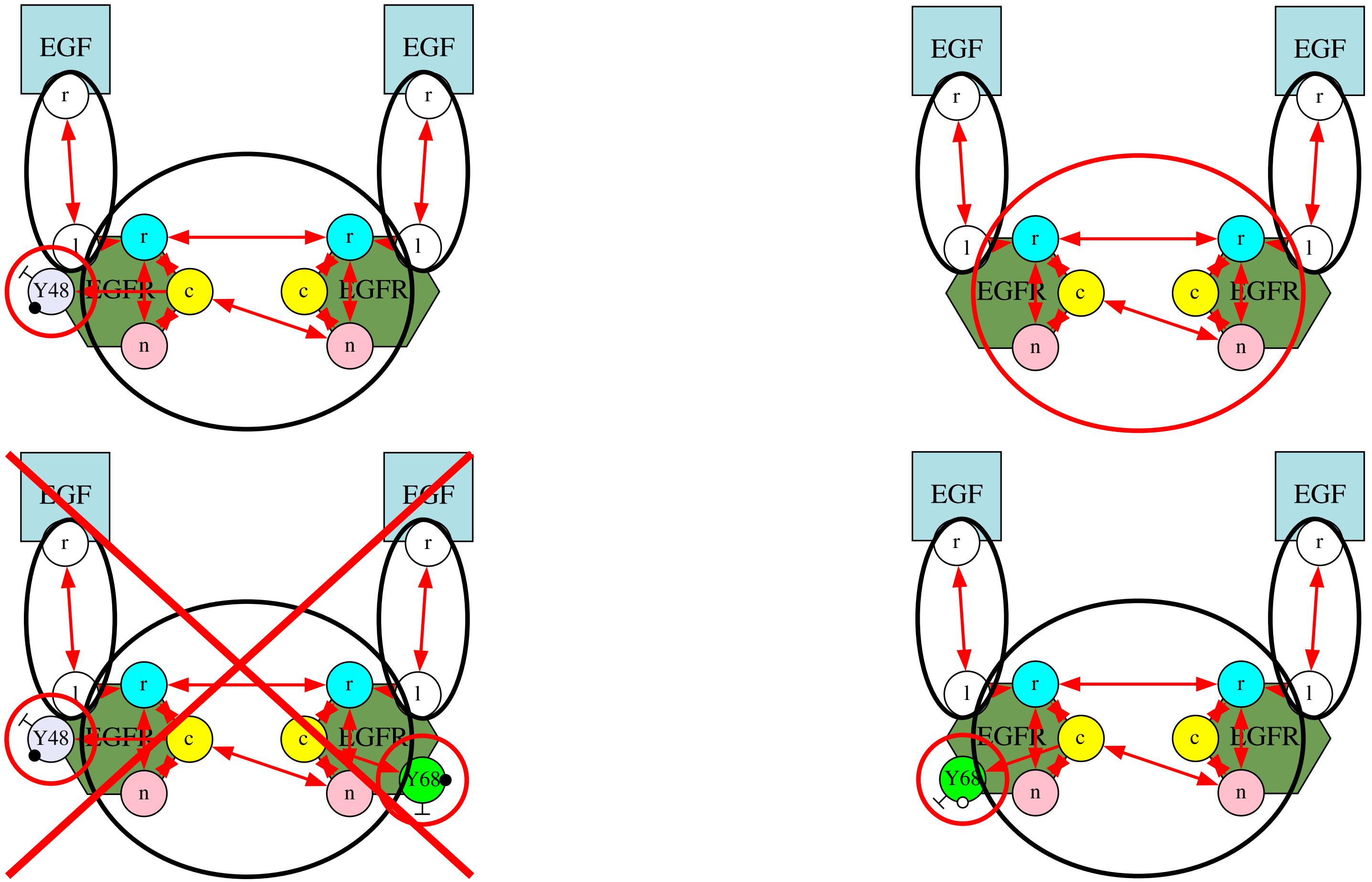


# Which patterns to keep as variables?



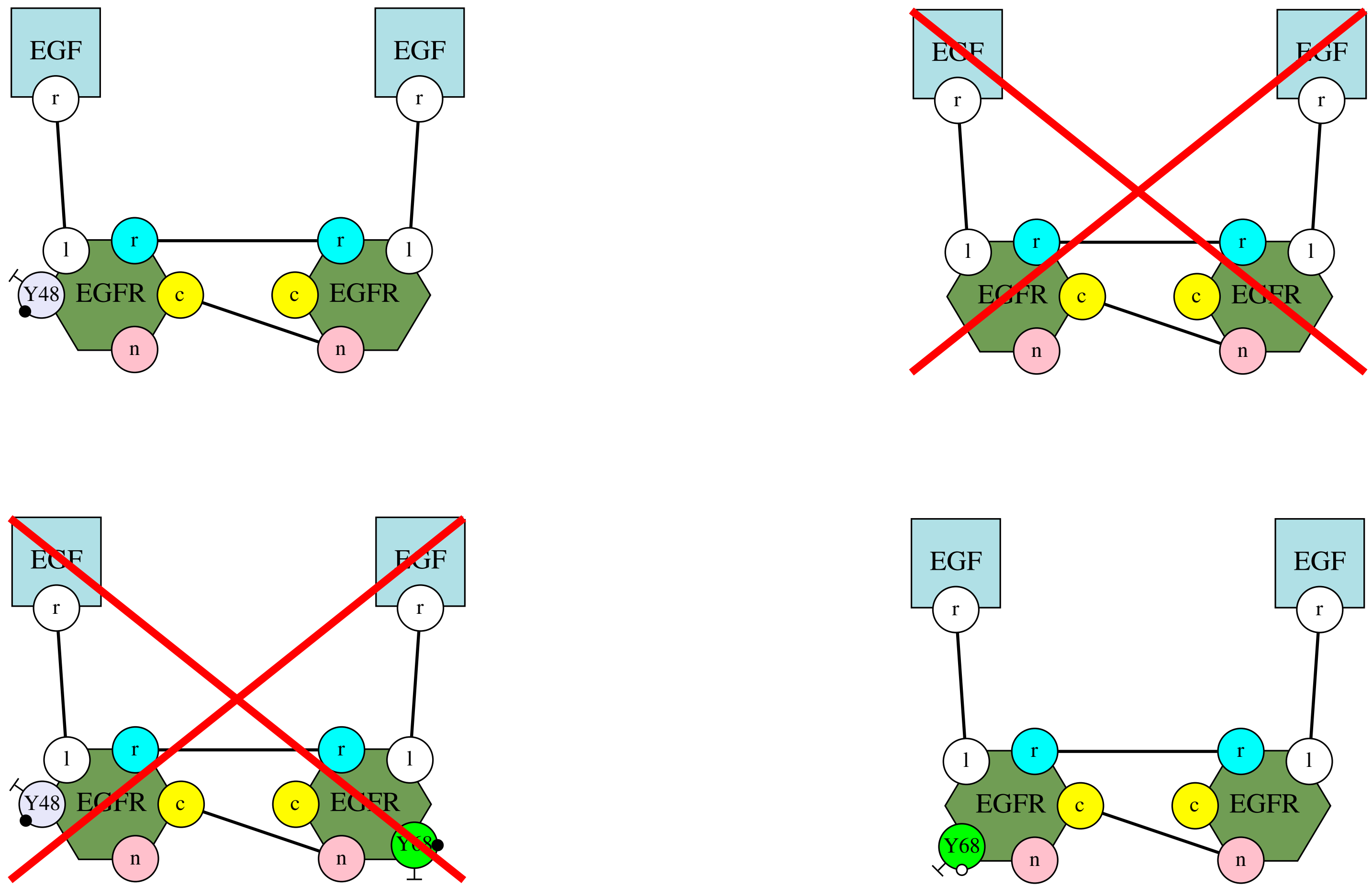
# Which patterns to keep as variables?

Prefragments: only one terminal strongly connected component

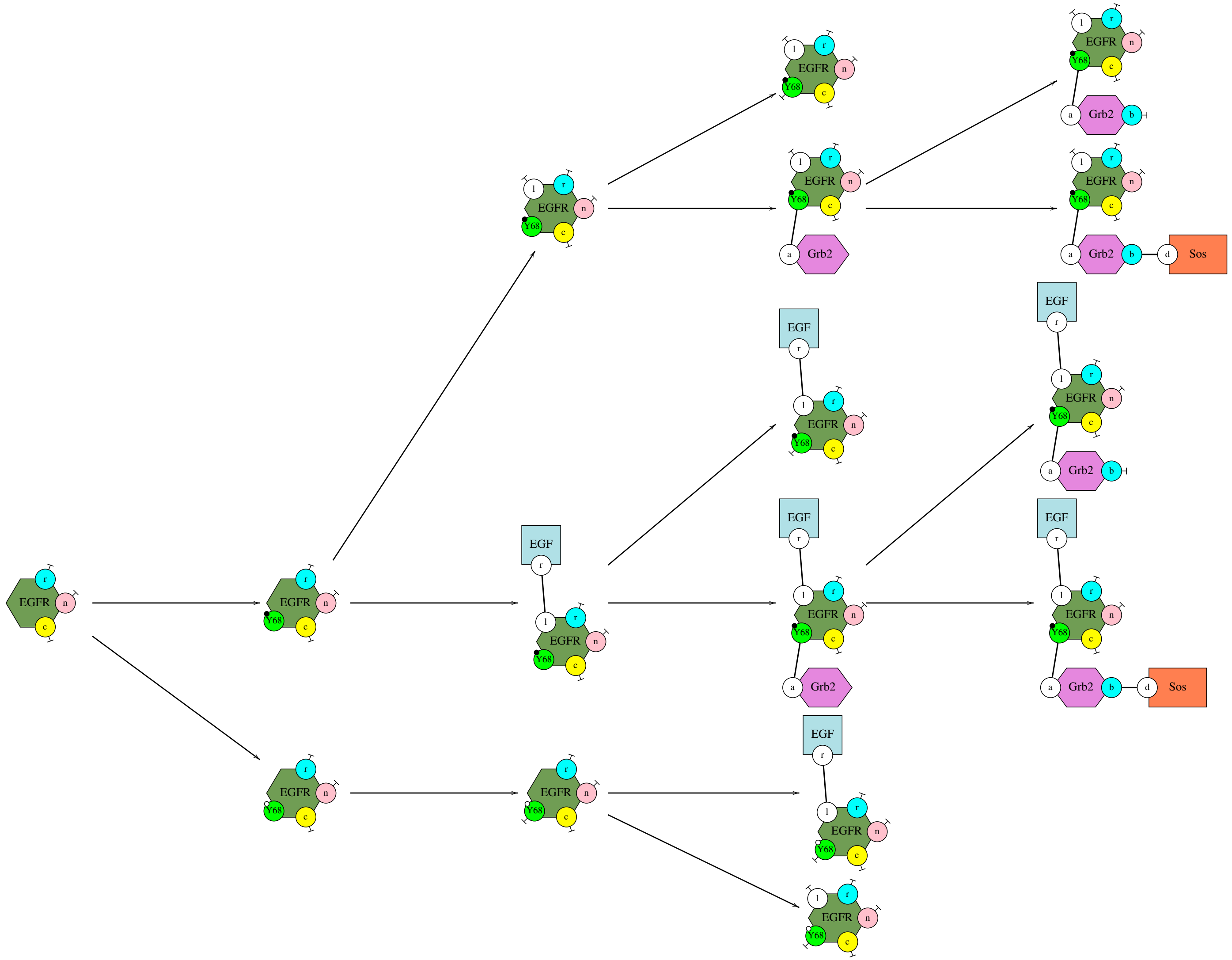


# Which patterns to keep as variables?

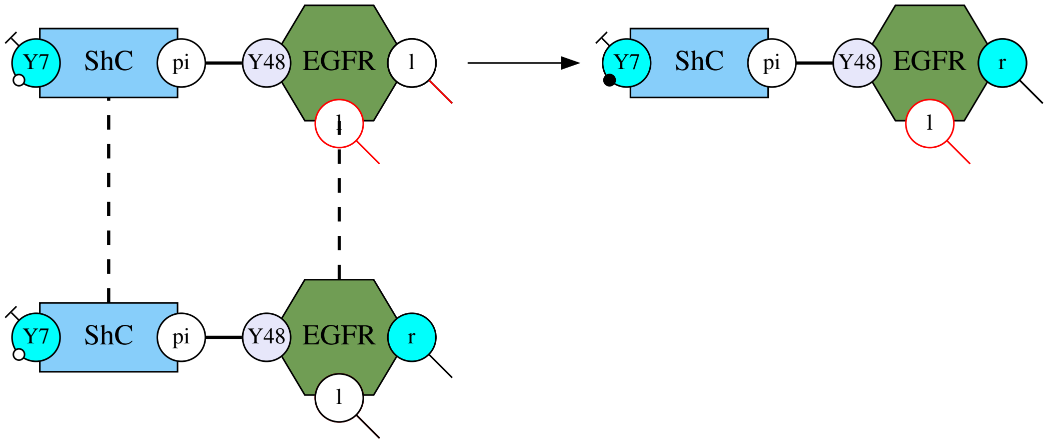
Fragments: maximal (embedding order) prefragments



# Quantity of a prefragement



# Fragments consumption



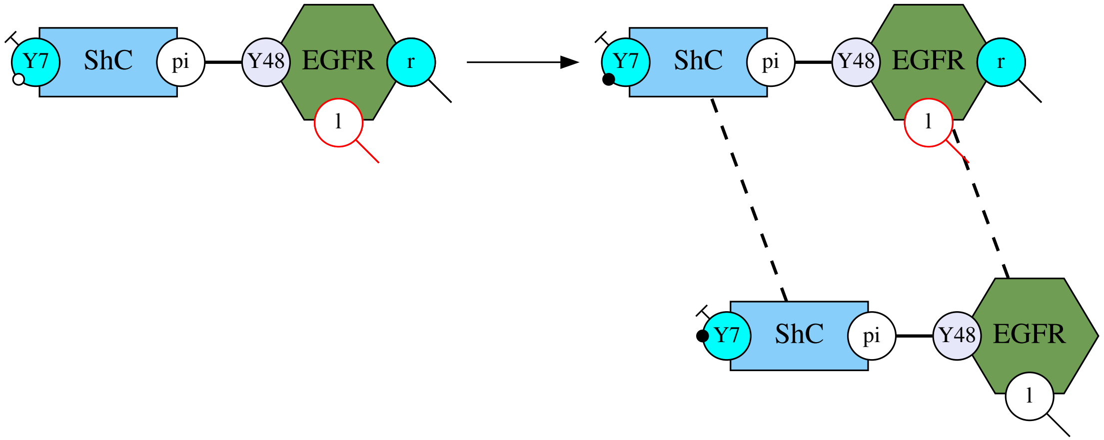

For each fragment $F$, for each rule:

$$\textit{r}: \; C_1, \ldots, C_n \to \textit{rhs} \quad\quad k$$

and for each occurrence of a connected component $C_j$ in the fragment $F$:

$$\frac{d[F]}{dt} \overset{-}{=} \frac{k \cdot [F] \cdot \prod_{i \neq j} [C_i]}{\mathsf{SYM}[C_1, \ldots, C_n] \cdot \mathsf{SYM}[F]}.$$

# Fragments production




For each overlap between a fragment and the right hand side of a rule:

$$r \quad : C_1, \ldots, C_m \rightarrow \textit{rigth hand side} \quad k,$$

we have the following contribution:

$$\frac{d[F]}{dt} \stackrel{+}{=} \frac{k \cdot \prod_i [C'_i]}{\mathsf{SYM}[C_1, \ldots, C_m] \cdot \mathsf{SYM}[F]}.$$

where $C'_1, \ldots, C'_n$ is the left hand side of the refined rule.

# Outline

1. Context and motivations
2. Static analysis
3. Flow-based model reduction (differential)
    - Intuitions
    - Case studies
    - Abstraction of the information flow
    - Model reduction
    - Conclusion and perspectives
4. Flow-based model reduction (stochastic)
5. Symmetries
6. Conclusion and perspectives

# Benchmarks

| model | number of variables | number of fragments | generation time |
|---|---|---|---|
| egfr (simplified) | $356$ | $38$ | $0.3$ s. |
| egfr | $1232$ | $238$ | $0.2$ s. |
| egfr, erk, mapk, ras | $\sim 2.10^{19}$ | $\sim 2.10^{5}$ | $180$ s. |

on a MacBook Pro Intel Core i7-6567U (3.3 GHz)).

# Conclusion

We propose an exact model reduction framework :

- relying on the structure of biological complexes;
- formally proven with respect to the concrete semantics
  as opposed to [Borisov *et al.* 2005, Conzelman (2006,2007)];
- no need to enumerate biological complexes, nor the reactions
  as opposed to [Tribastone *et al.* (2015-2023)];
- able to break the combinatorial complexity on large examples;
- context-sensitivity of the approximation of information flow can be tuned.
  [Ferdinanda Camporesi PhD (2017)].

# Perspectives

- How to tune context-sensitivity automatically?
- Approximate reduction.

# Outline

1. Context and motivations
2. Static analysis
3. Flow-based model reduction (differential)
4. Flow-based model reduction (stochastic)
    - Master equation
    - Case studies
    - Abstraction of the information flow
    - Bisimulations
    - Conclusion and perspectives
5. Symmetries
6. Conclusion and perspectives

# Master equation

$P_t(q^\star)$ denotes the probability that the system is in state $q^\star$ at time $t$.

It is defined by the following equation:

$$\frac{\mathsf{d}\,P_t(q^\star)}{\mathsf{d}t} = \left(\sum_{q \xrightarrow{\lambda} q^\star} \lambda \cdot P_t(q)\right) - \left(\sum_{q^\star \xrightarrow{\lambda} q'} \lambda \cdot P_t(q^\star)\right).$$

# Outline

1. Context and motivations
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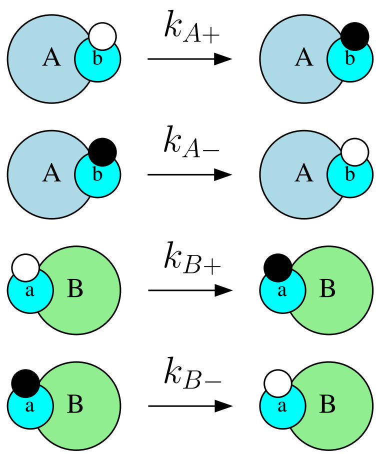
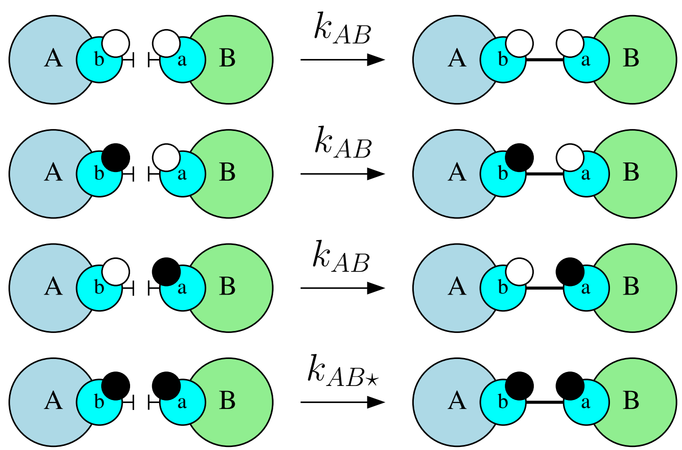
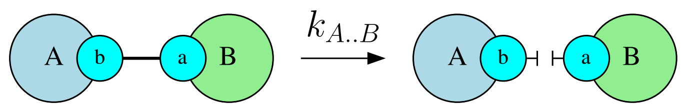
# First case study

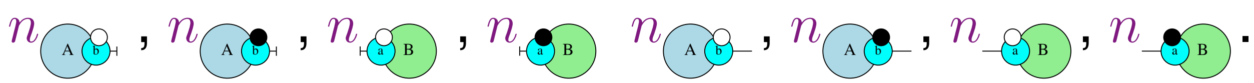


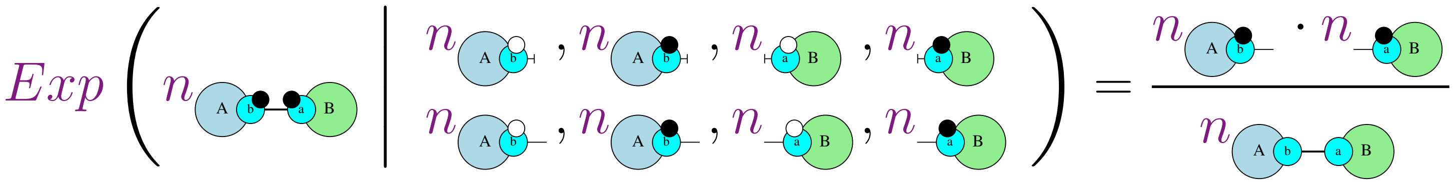
# First case study

We want to abstract a state by:

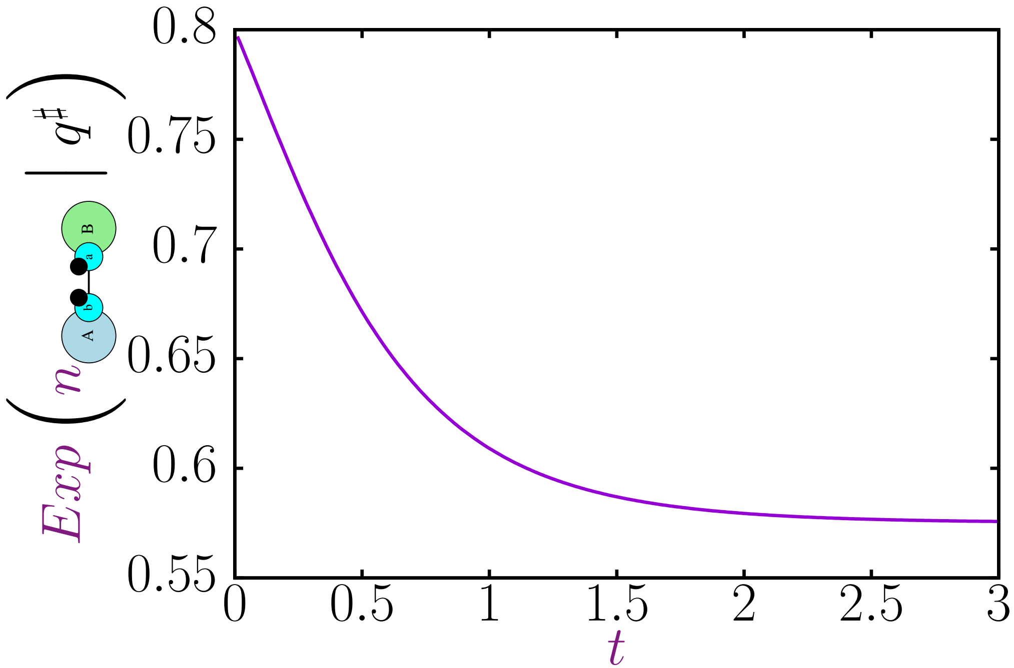


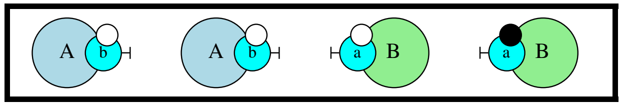
To simulate dissociation, we need to know the correlation between the states of both proteins in dimer occurrences.

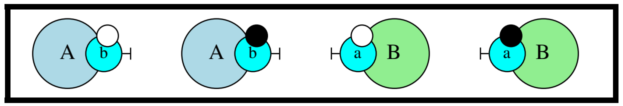
When $k_{AB} = k_{AB\star}$, we have (for well chosen initial distributions):



# First case study: correlation




- starting in the state: 

;
- with the rates $k_{A+} = k_{A-} = k_{B+} = k_{B-} = k_{AB} = k_{A..B} = 1$ and $k_{AB\star} = 10$;
- and with the abstract state $q^\sharp$ equal to: 

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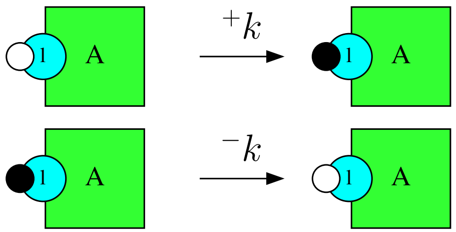
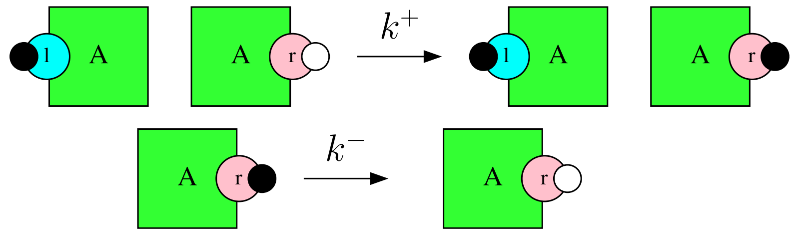
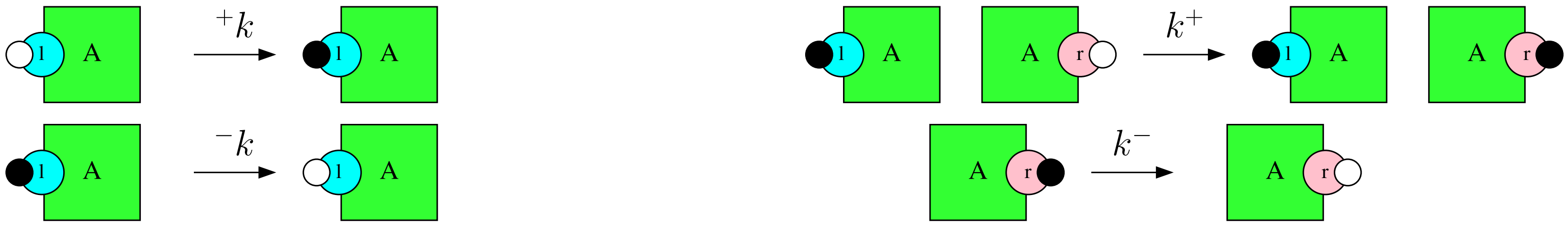
# Second case study



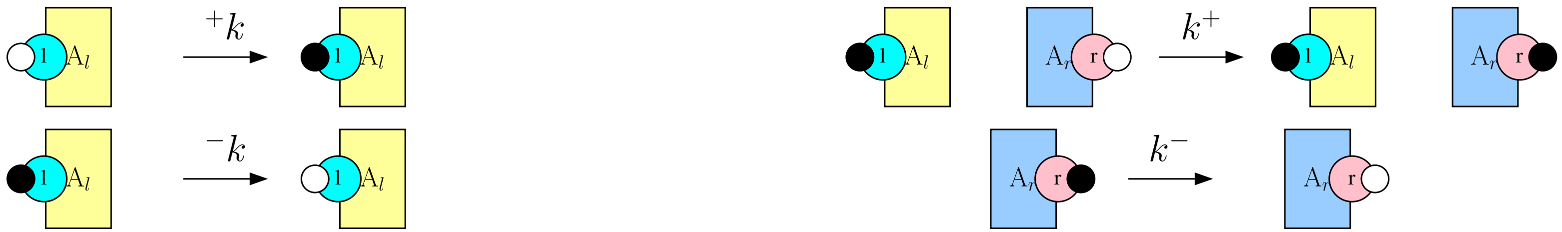



# Second case study

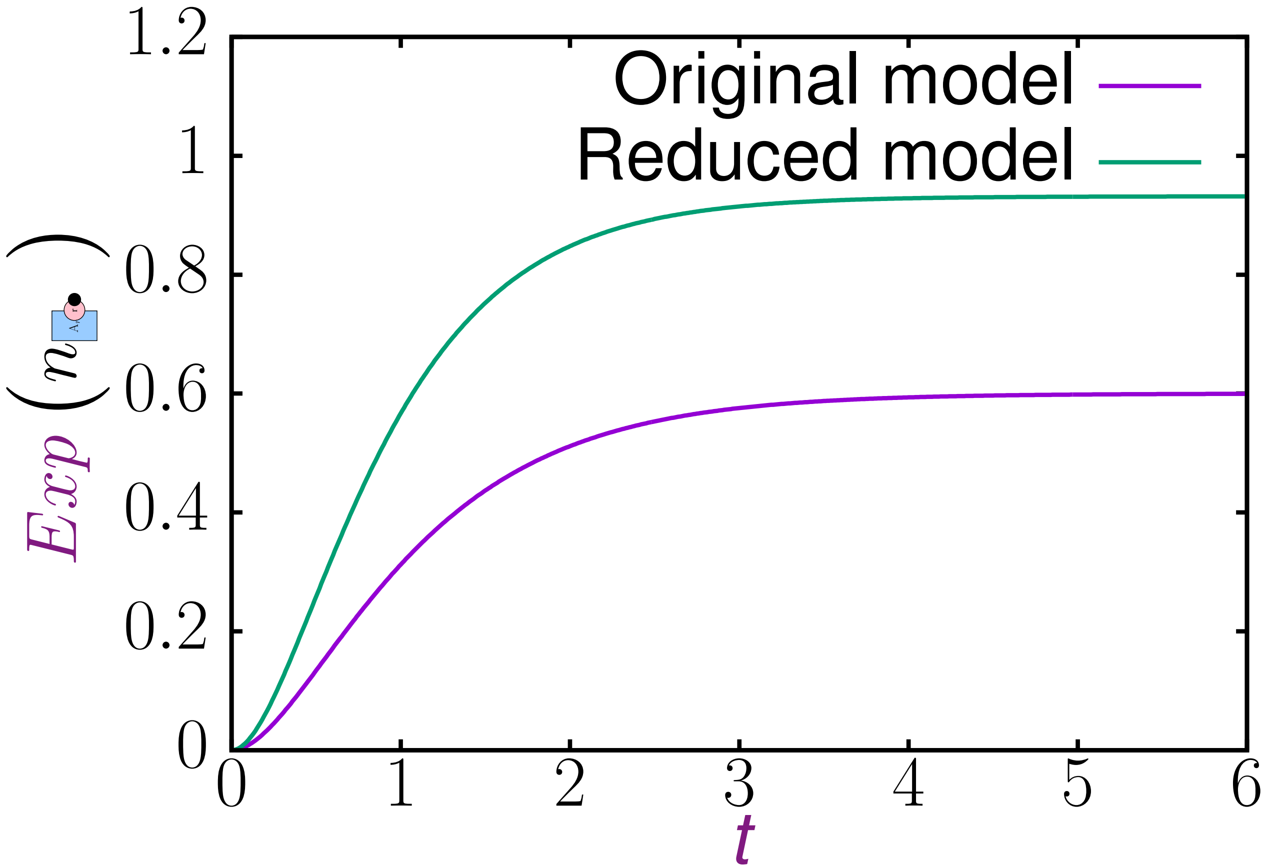
Initial model:




Reduced model:



# Second case study: distant control




with two occurrences of the protein, all rates equal to $1$.

# Outline

1. Context and motivations
2. Static analysis
3. Flow-based model reduction (differential)
4. Flow-based model reduction (stochastic)
    - Master equation
    - Case studies
    - Abstraction of the information flow
    - Bisimulations
    - Conclusion and perspectives
5. Symmetries
6. Conclusion and perspectives

# Stochastic fragments

- Issues:
  - correlations cannot be discarded
    when bonds are released,
    when modifying overlapping regions between fragments,
  - occurrences of proteins may affect each others even if not in the same rule connected component;

- What is left:
  - cut each occurrence of proteins into equivalence classes ;
  - two sites occurring in a same rule shall belong to the same equivalence class.

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# Properties

The reduction induces a back-and-forth bisimulation:

- Forward:

  The behaviors of two equivalent states are the same with respect to equivalence classes.

- Backward:

  If the probability of every two equivalent states is inversely proportional to their numbers of automorphisms, it remains this way all along the execution of the model.

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# Benchmarks

| Model | early EGF | EGF/Insulin | SFB |
|---|---|---|---|
| Number of mollecular species | $356$ | $2899$ | $\sim 2.10^{19}$ |
| Number of fragments<br>(ODEs semantics) | $38$ | $208$ | $\sim 2.10^{5}$ |
| Number of fragments<br>(CTMC semantics) | $356$ | $618$ | $\sim 2.10^{19}$ |

# Conclusion

- We use information flow to infer back-and-forth bisimulations ;
- Formally sound — but not very useful in practice ;
- Better understanding of the various semantics
  and why it is difficult to reduce them exactly.

# Perspectives

- Bisimulation metrics [Panagaden (1999-), Ferns (2011-2012)]
- Conservative approximate reductions.

# Outline

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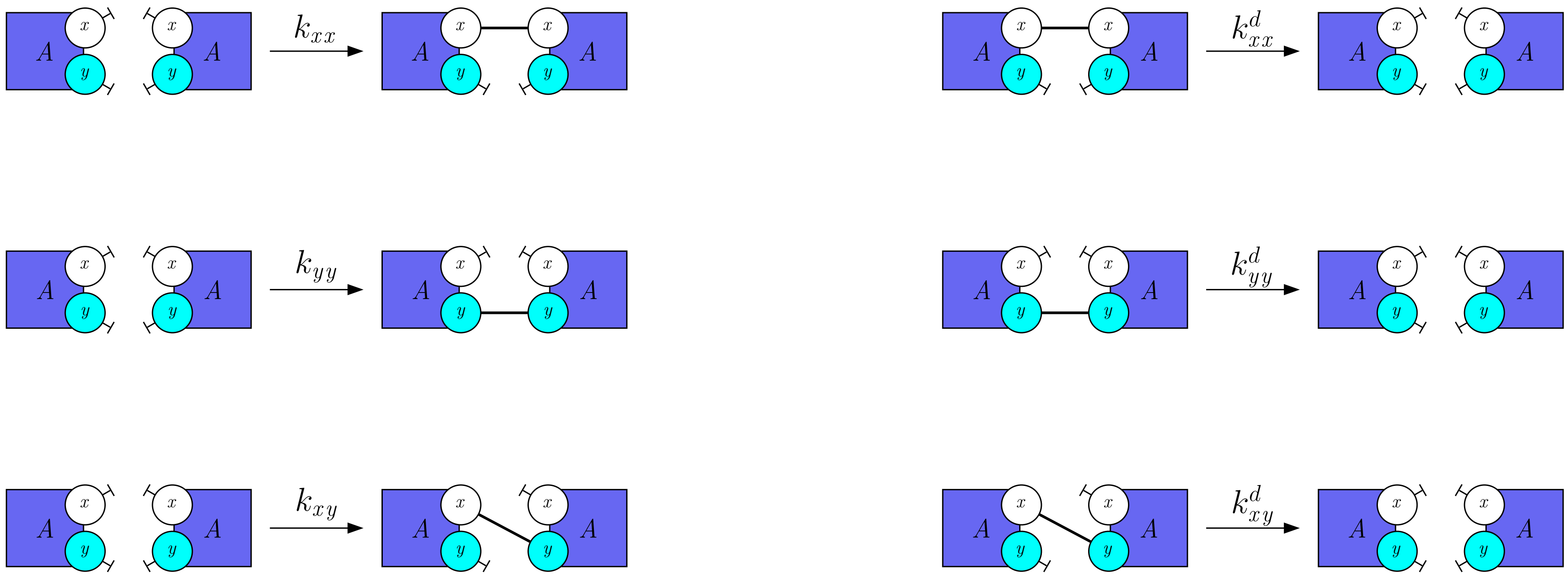
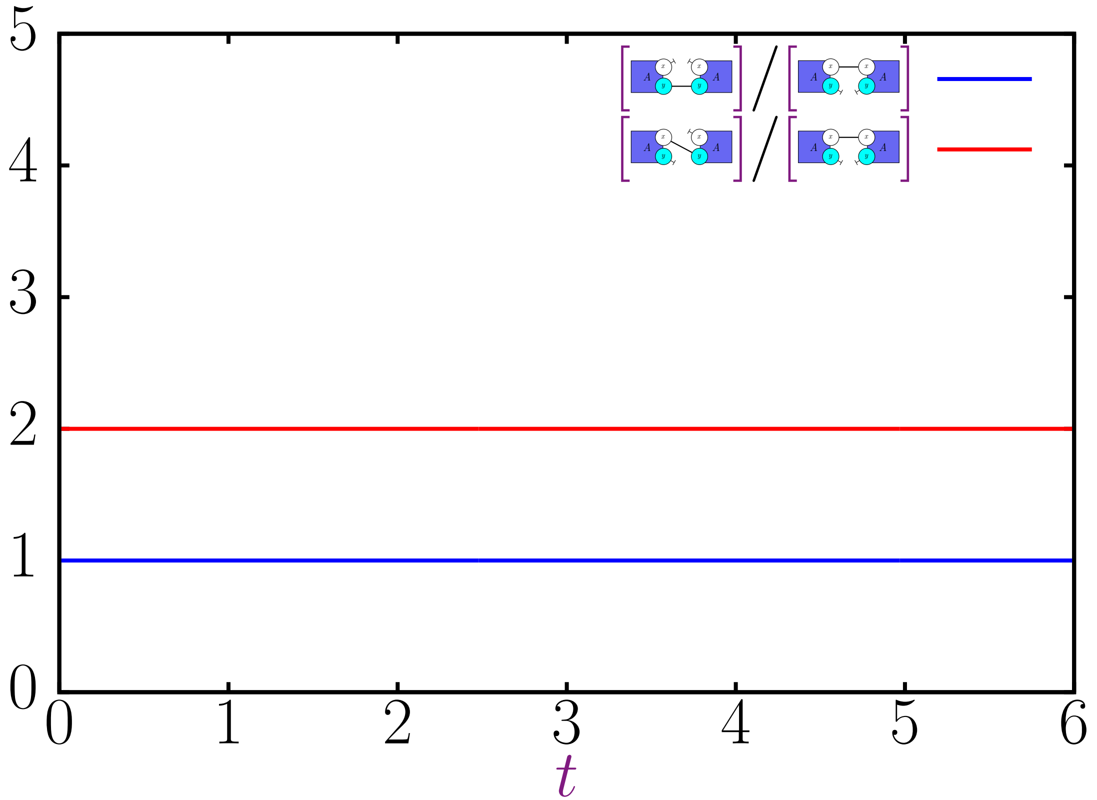
# Case study

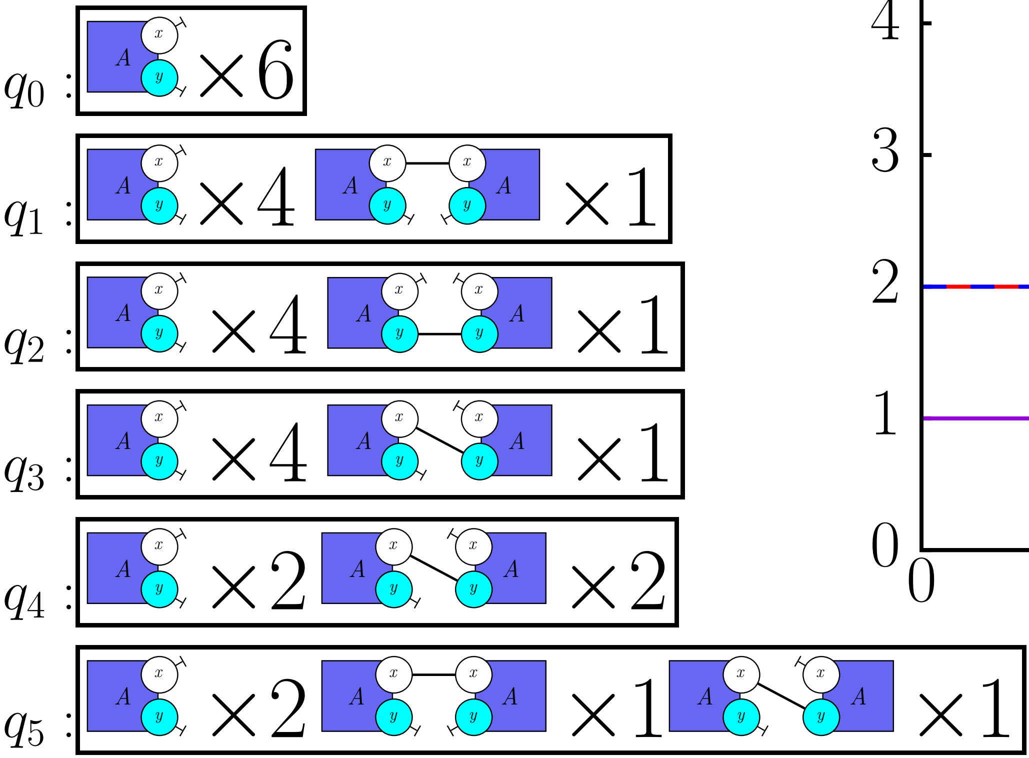


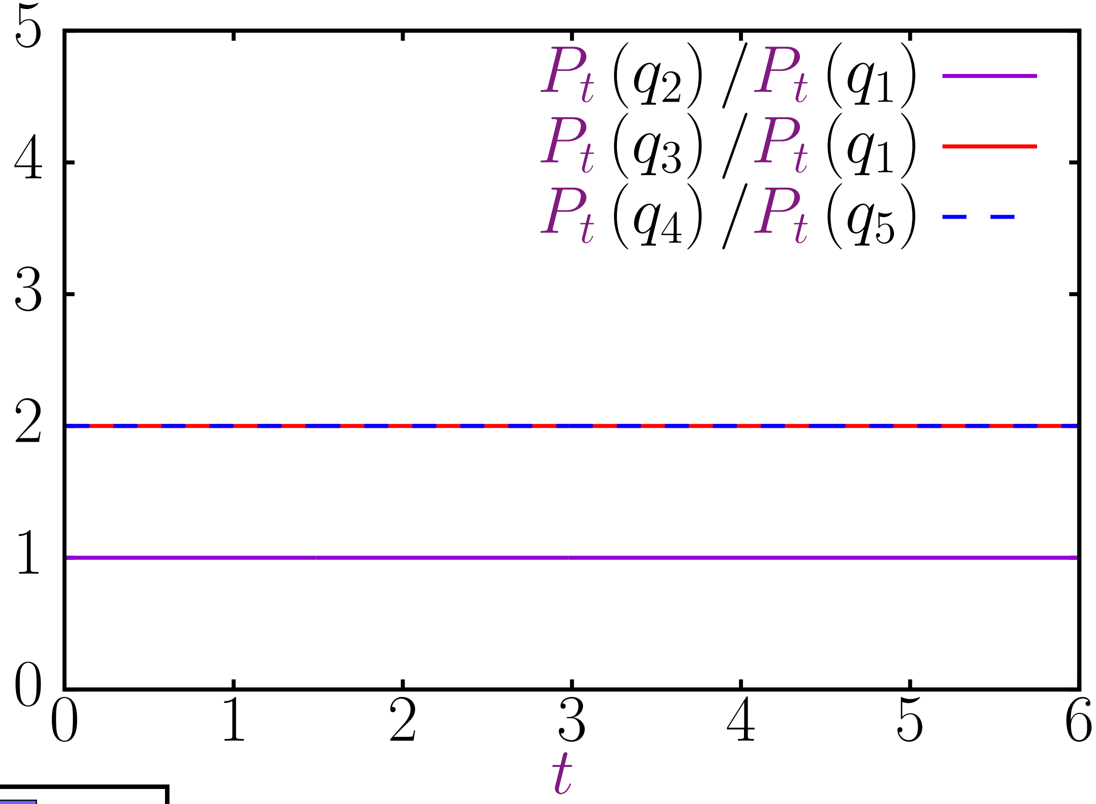
# Quotients between concentrations




with: $\begin{cases} k_{xx} = k_{yy} = 0.5,\ k^d_{xy} = 2,\ k_{xy} = k^d_{xx} = k^d_{yy} = 1 \\ [\ ]_0 = 6,\ [\ ]_0 = [\ ]_0 = [\ ]_0 = 0 \end{cases}$

# Quotients between state probabilities



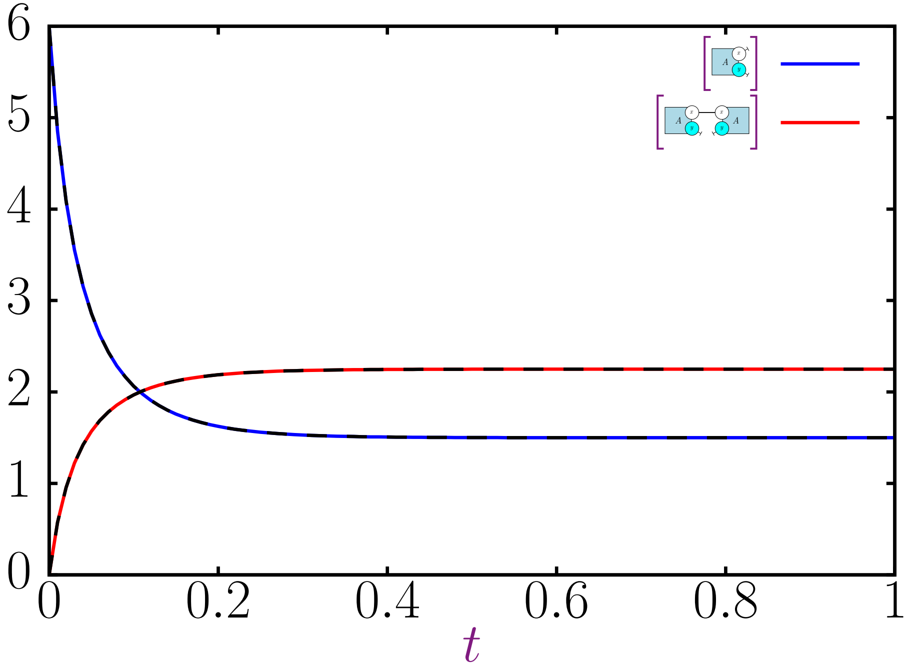

with: $$\begin{cases} k_{xx} = k_{yy} = 0.5,\ k^d_{xy} = 2 \\ k_{xy} = k^d_{xx} = k^d_{yy} = 1 \\ P_0(q_0) = 1 \end{cases}$$

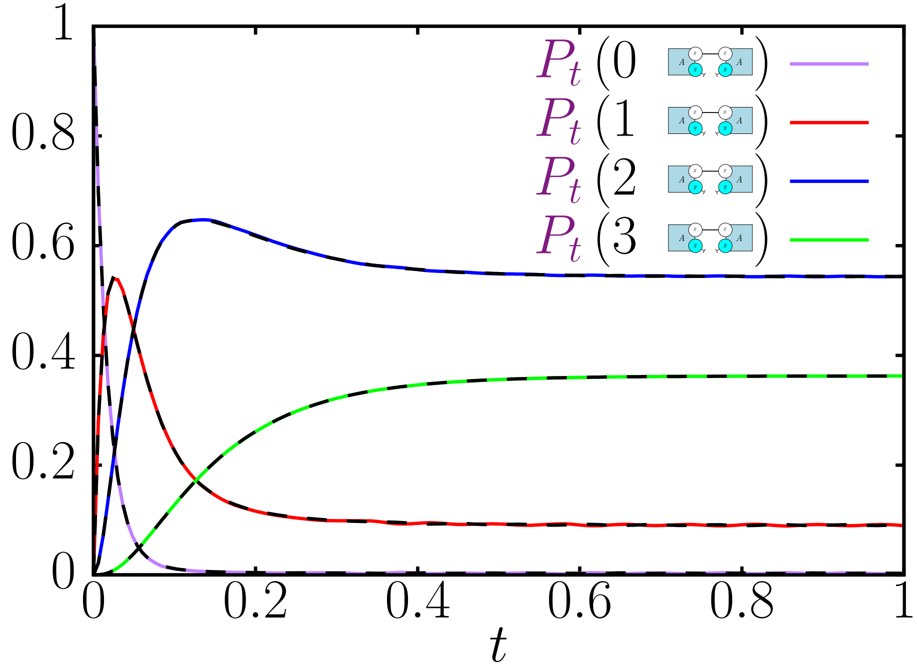
# Initial model

# Initial model


# Reduced model

# Macrostate distribution




with:

- $k_{xx} = k_{yy} = 0.5$, $k^d_{xy} = 2$, $k_{xy} = k^d_{xx} = k^d_{yy} = 1$ ;
- $K = 2$, $K^d = 1$,

(continuous lines: initial model; dashed lines: reduced model)

# Outline

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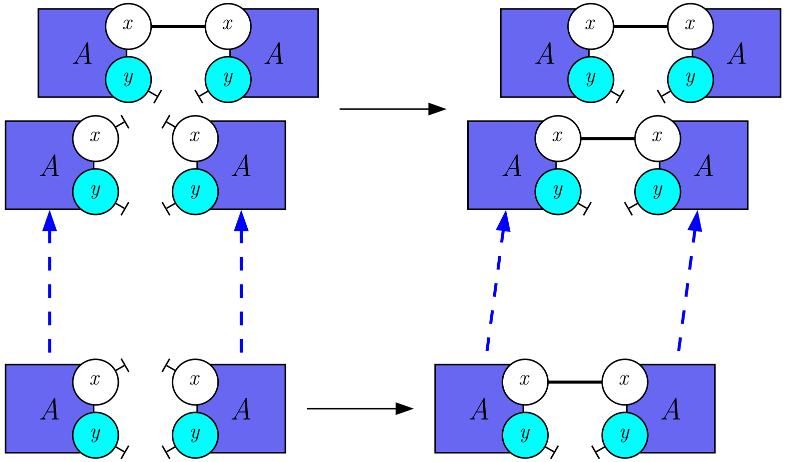
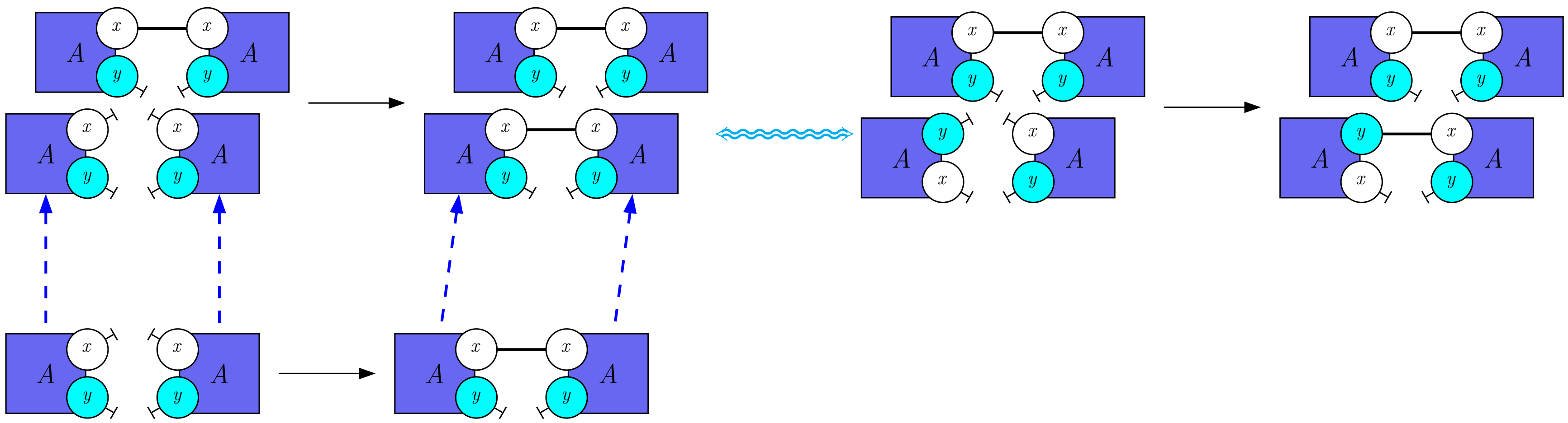
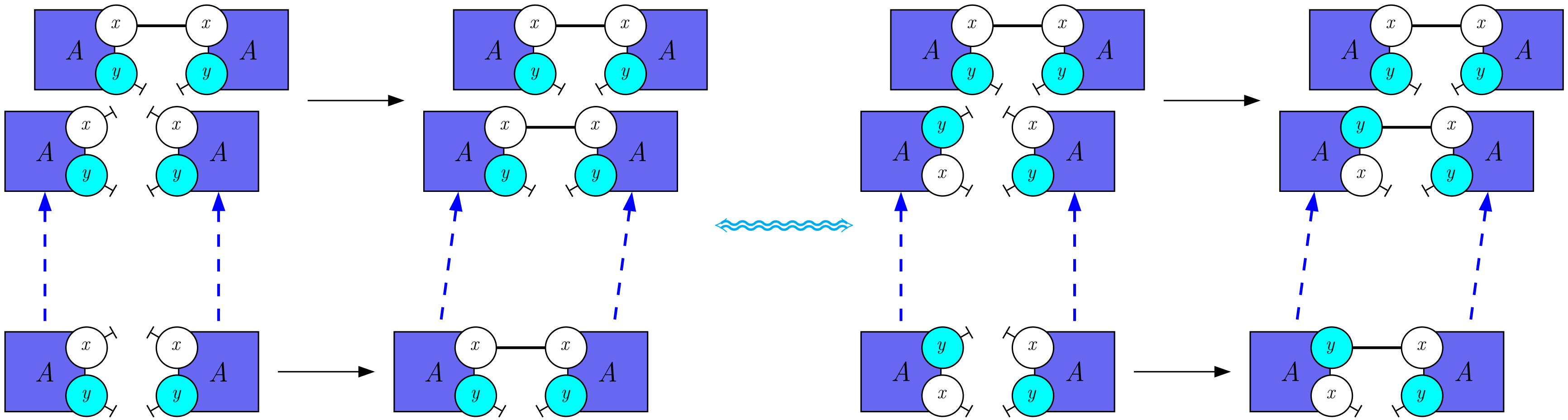
# Symmetric of a transition step



# Symmetric of a transition step

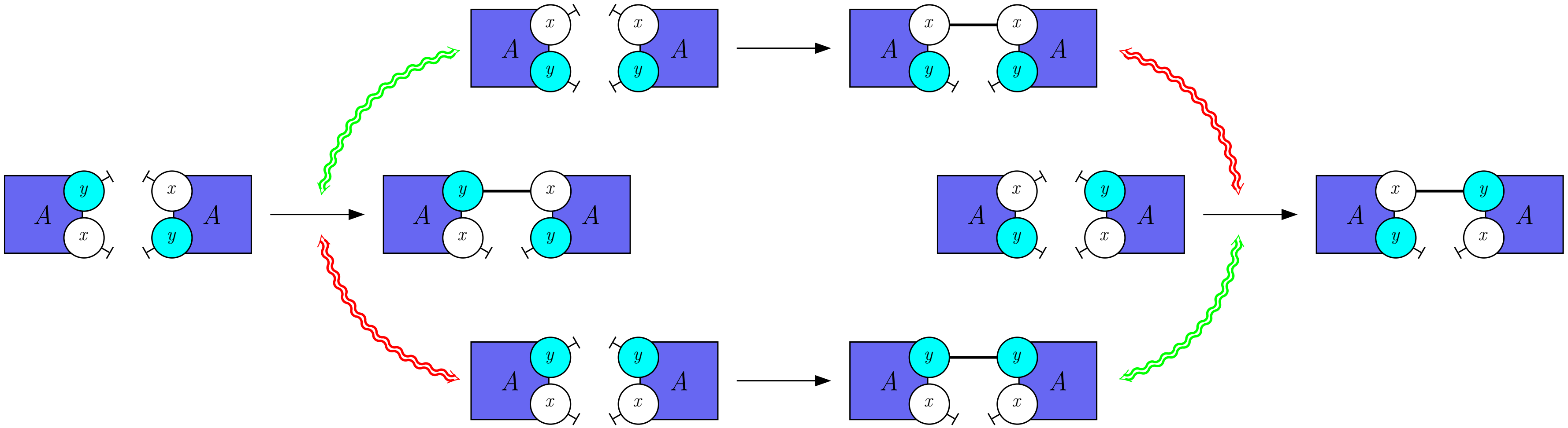


# Symmetric of a transition step



# Outline

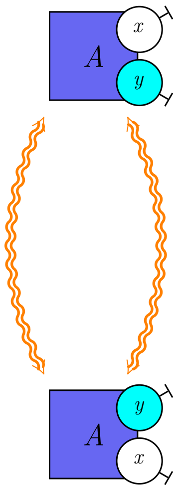
# Symmetric sets of rules

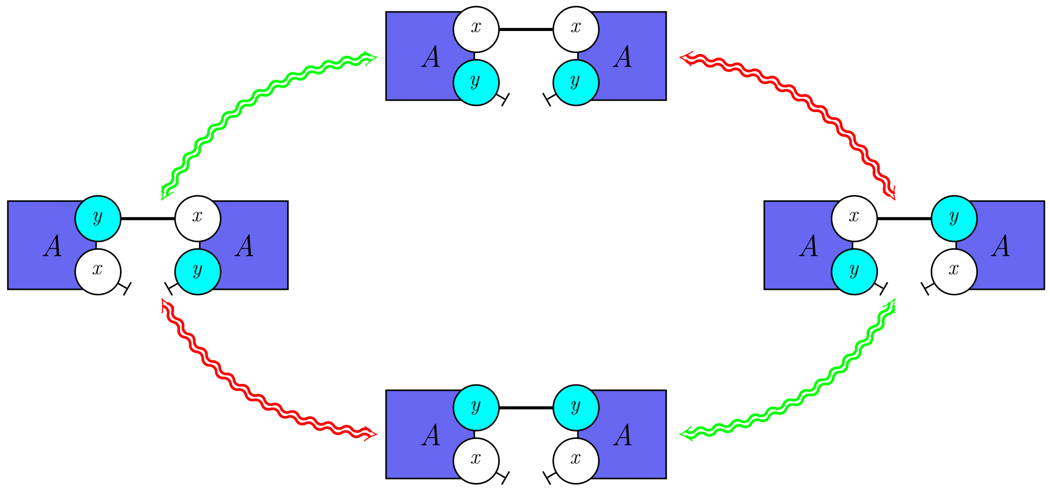



A set of rules is symmetric if the rates of two symmetric rules are proportional to their numbers of occurrences in the corresponding orbit.

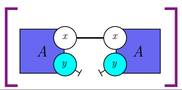
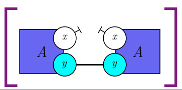
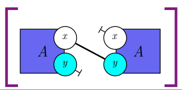
Here: $\frac{k_{xx}}{1} = \frac{k_{yy}}{1} = \frac{k_{xy}}{2}$.

# Symmetric continuous states

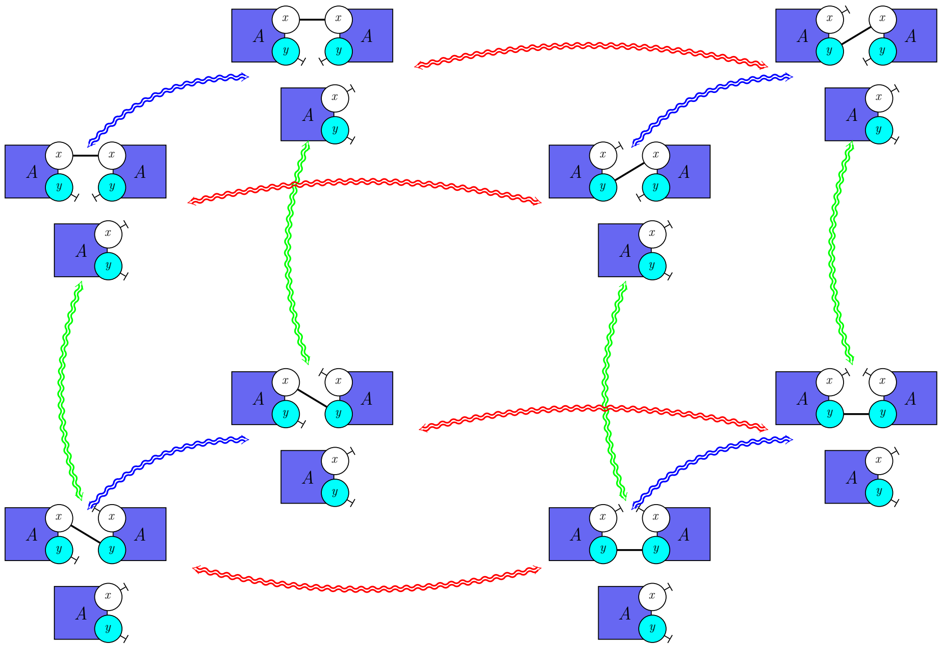



A continuous state is symmetric if the quantity of two symmetric biological complexes are proportional to their numbers of occurrences in the corresponding orbit.

Here:  / 1 =  / 1 =  / 2.

# Symmetric distributions of states



A continuous state is symmetric if the quantity of two symmetric biological complexes are proportional to their numbers of occurrences in the corresponding orbit.

Here proportional to their numbers of occurrences of asymmetric dimers.

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    - Conclusion and perspectives
6. Conclusion and perspectives

# Properties

Permutations of sites induce back-and-forth bisimulations:

- Forward:

  The semantics can be computed directly on symmetric classes of states (resp. distributions of states).

- Backward:

  Starting in a symmetric state (resp. distribution of states), the state (resp. distribution of states) is symmetric at any time.

# Outline

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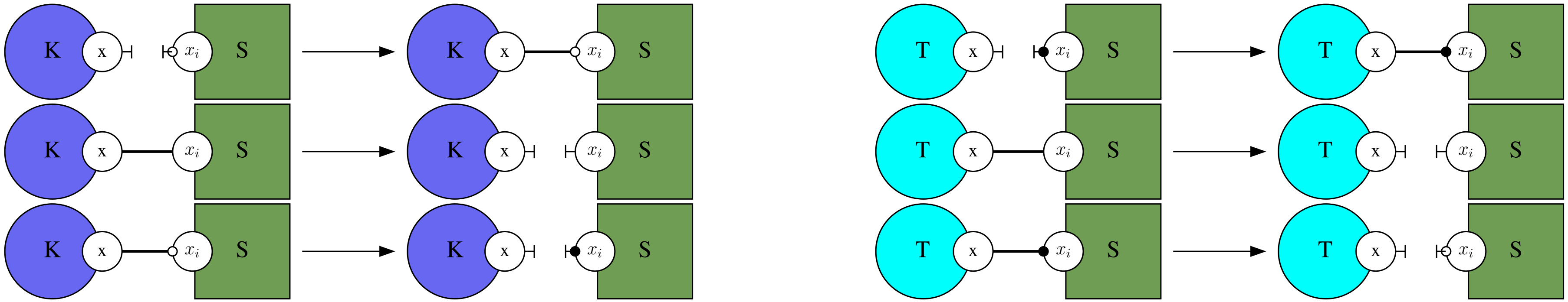
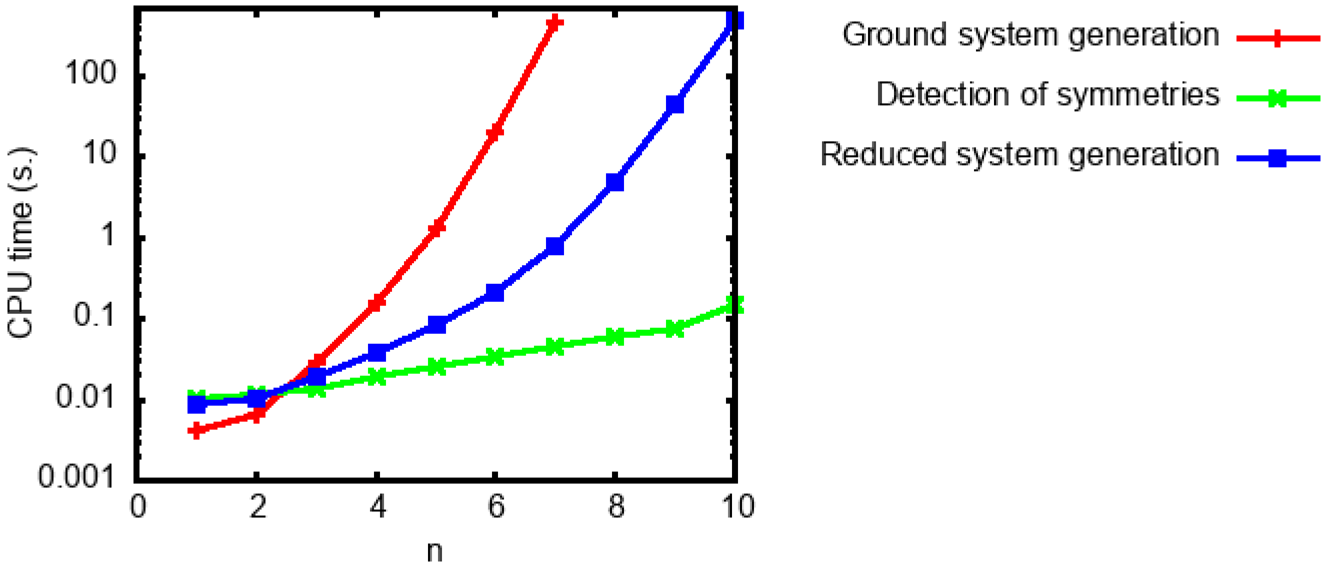
# Performance: parametric example




- Number of sites in $S$: $n$
- Number of reactions (initial model): $6 \cdot n \cdot 4^{n-1}$
- Number of reactions (reduced model): $n \cdot (n+1) \cdot (n+2)$

# Performance: computation time




on a MacBook Pro - Intel Core i7-6567U (3.3 GHz)

# Conclusion

- Model reduction based on site permutations
  - it scales on large models
- Categorical framework
  - subgroups of symmetries;
  - necessary conditions to induce (forward and/or backward) bisimulations

# Perspectives

- Investigate specific subgroups of symmetries
  (Chemistry, contextual symmetries)
- Automatic parameterization of context-sensitivity.

# Outline

1. Context and motivations
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# Conclusion

- An efficient and precise static analysis.
  - To improve the confidence in models.
  - Based on the detection of structural properties of reachable states.

- Exact model reductions
  - No need to generate the set of biological complexes;
    1. Relying on the topology of information flow;
       Differential case: efficient on models of signaling pathways;
       Stochastic case: no reduction in most of the cases.
    2. Relying on groups of symmetries
       One-to-one relations between reactions and transitions.

# Perspectives on static analysis

- Analyze families of models (meta-languages, scripts);
- Incremental analysis.

# Perspectives on exact model reduction

- Provide heuristic for tuning context sensitivity automatically;
- Investigate more (sub)groups of symmetries.

# Perspectives on approximate model reduction

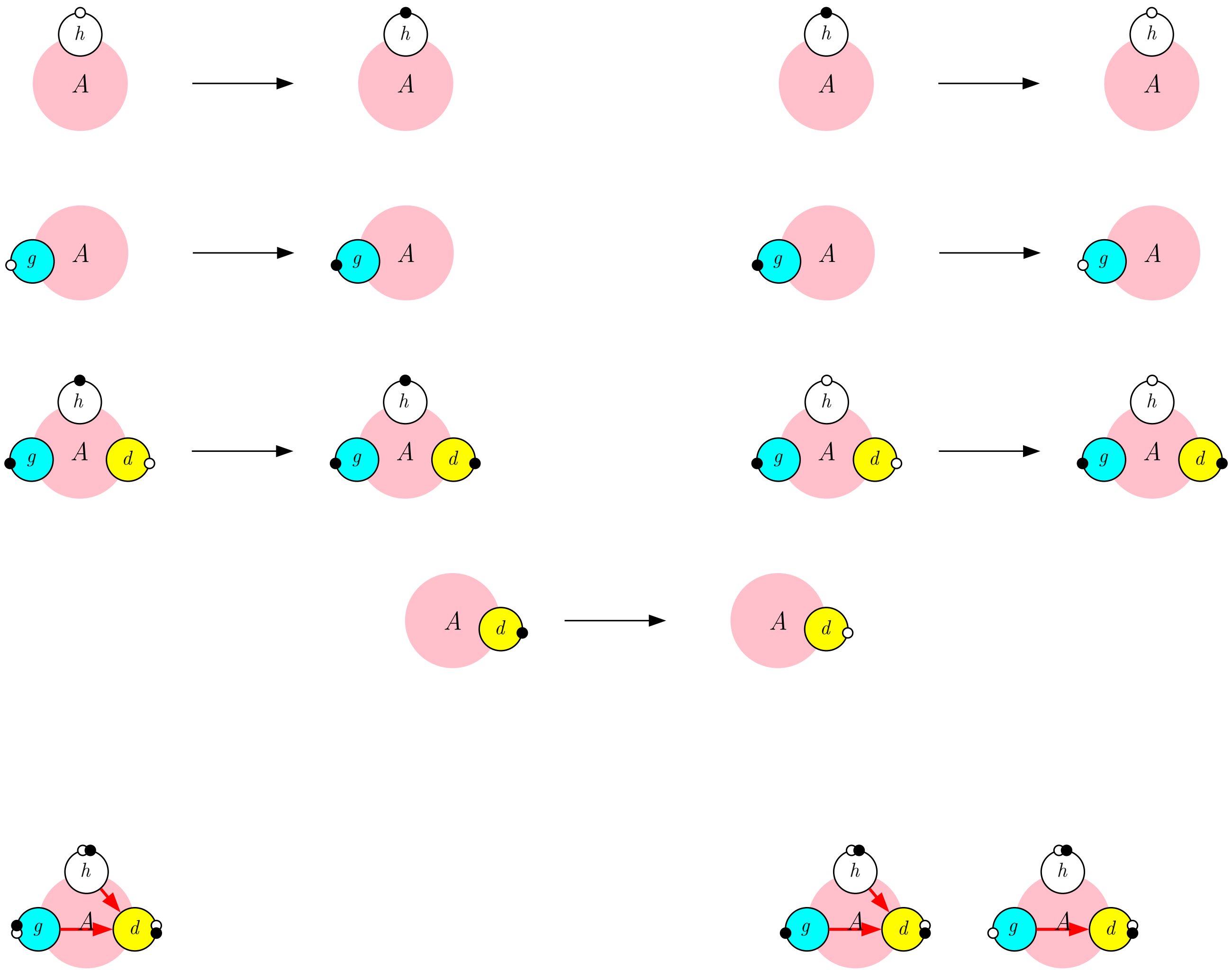
Design conservative numerical methods for approximate model reduction

- the choice of fragments is not imposed by the analysis;
- with interval bounds computed *a posteriori*;
- to be declined for differential, stochastic, hybrid semantics.

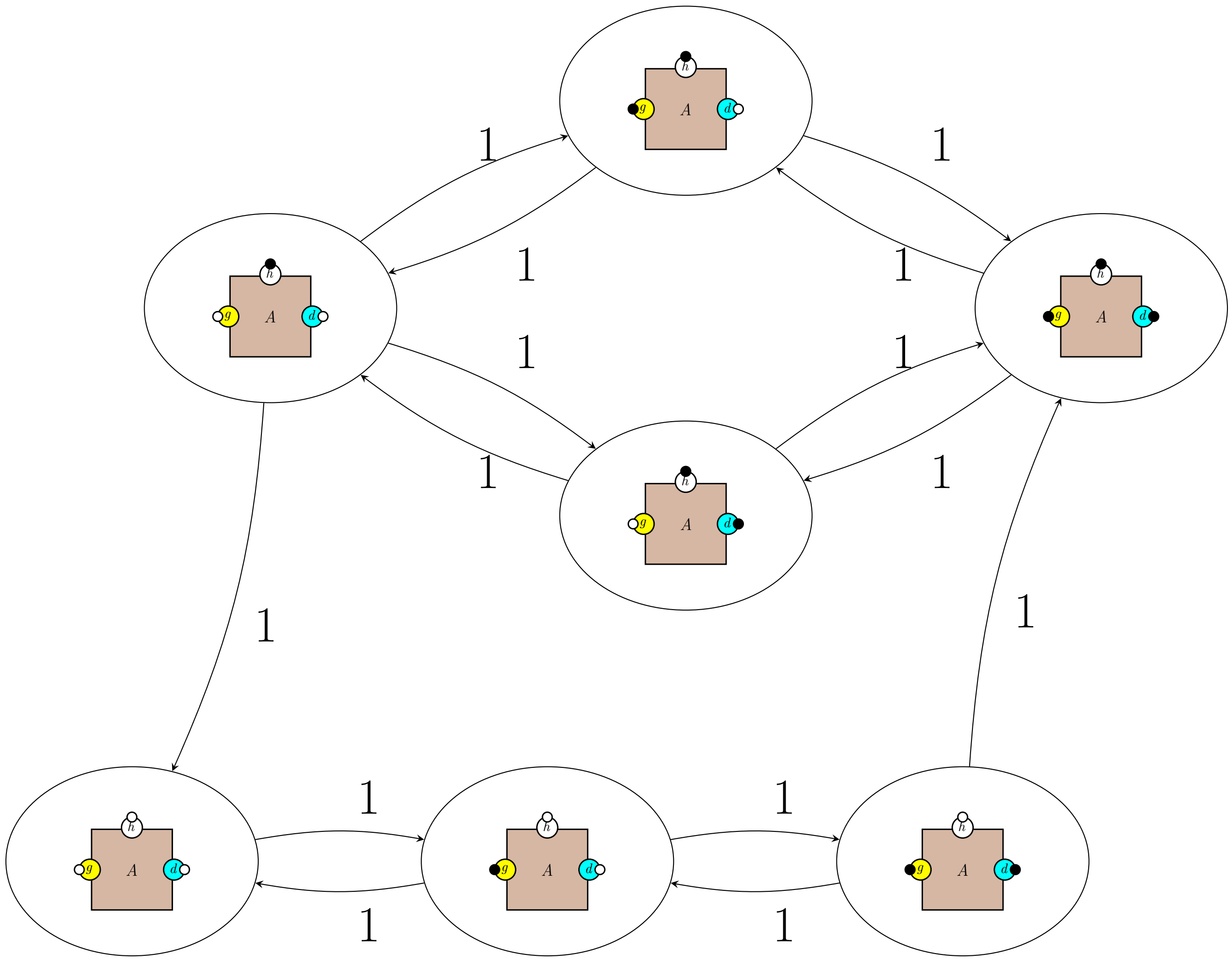
A toolkit to recast and unify existing approaches and propose new ones:

- early results on tropicalization [Beica *et al.* 2020];
- early results on finite expansions (models of polymers);
- tropical equilibration;
- flow of information;
- ...

# Contextual flow



# Contextual symmetries



# Homogeneous permutations