SASB 2018

Proving the absence of unbounded polymers in rule-based models

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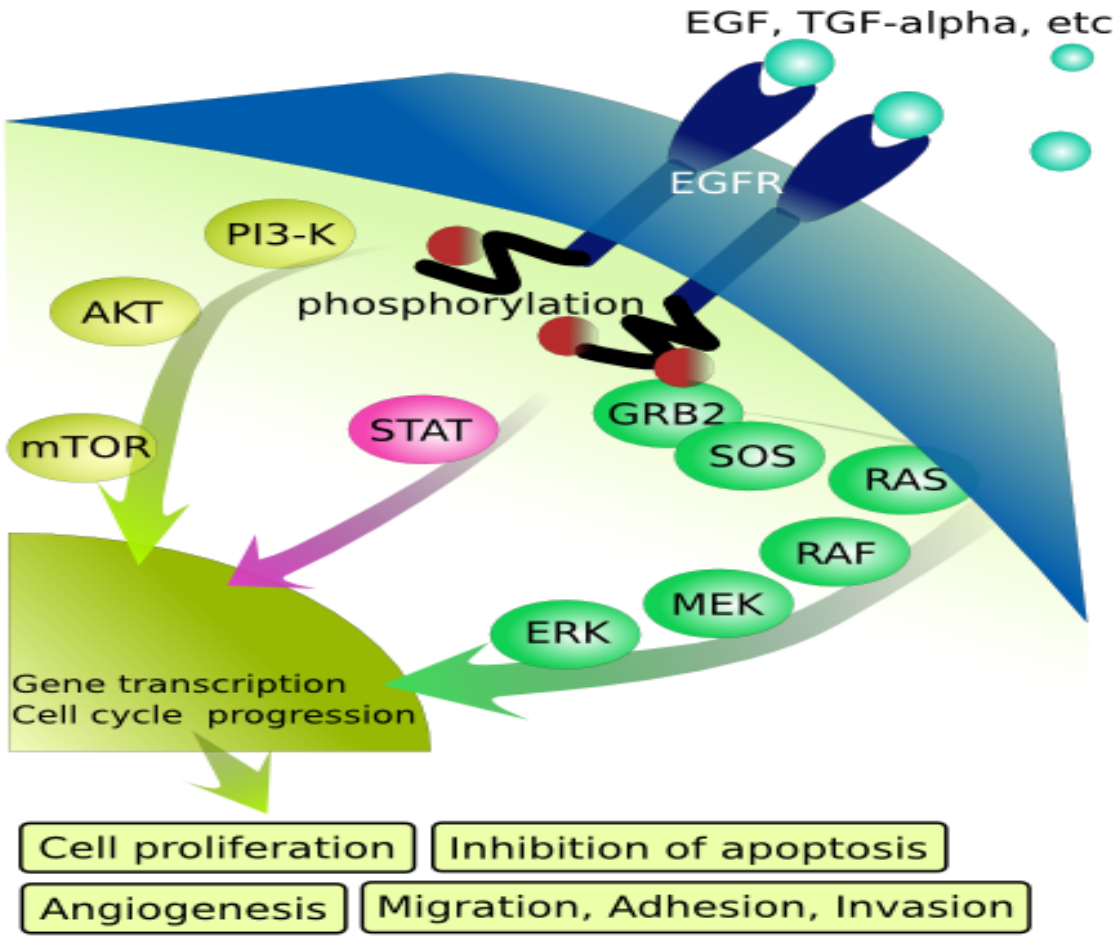
Joint work with Pierre Boutillier and Aurelie Faure de Pebeyre

Freiburg im Breisgau, August 28 2018

On the menu today

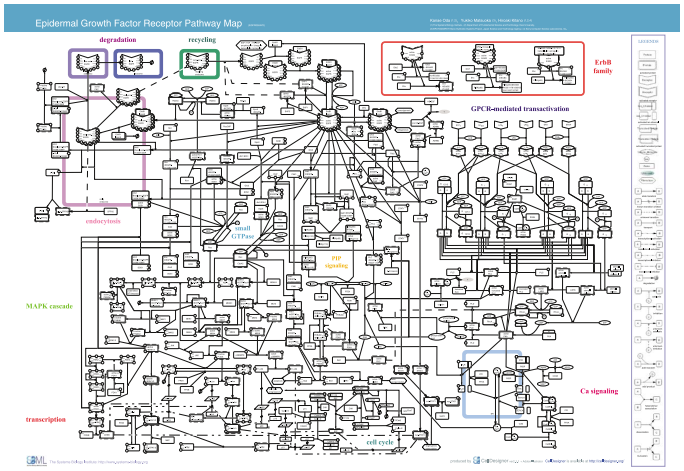
1. Rule-based modelling
2. Kappa
3. Unbounded bio-molecular compounds
4. The graph of the sites
5. The graph of the edges
6. Refinement
7. Conclusion

Signalling Pathways



Eikuch, 2007

Bridging the gap between...



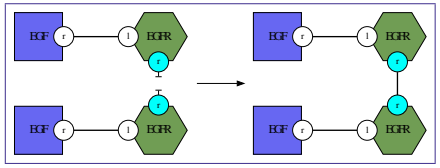
$$
\begin{cases}
\frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\
\frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\
\frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

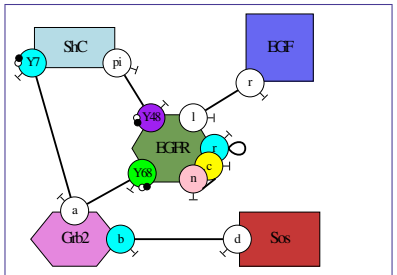
knowledge representation

and

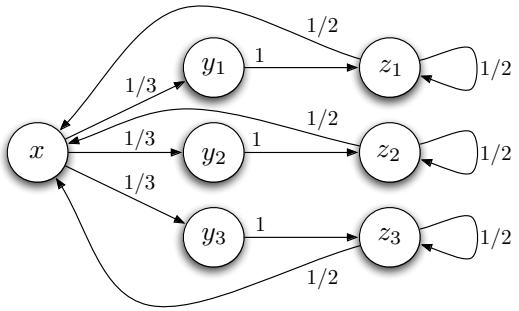
models of the behaviour of systems

Choices of semantics





interaction map

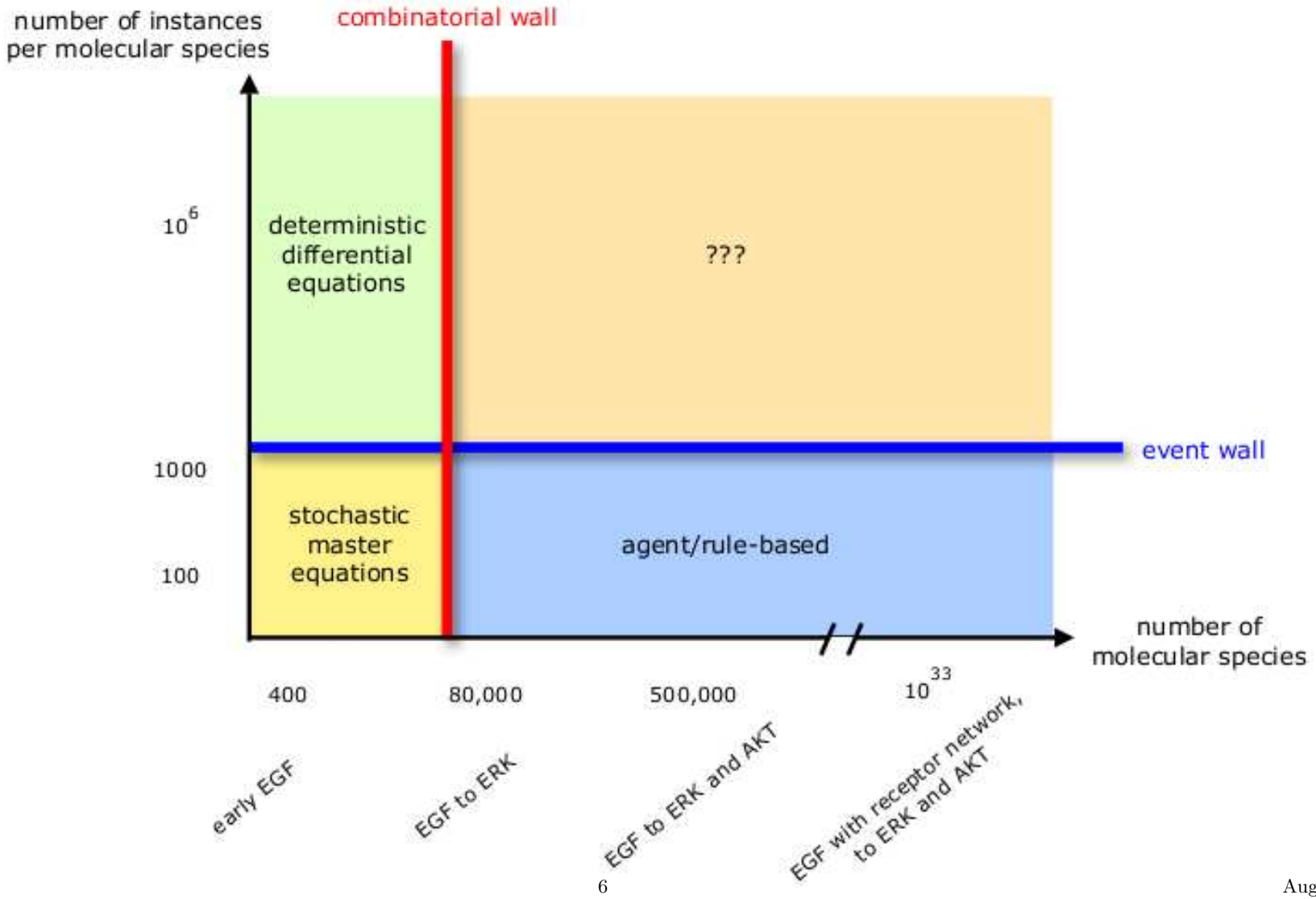


Markov chain

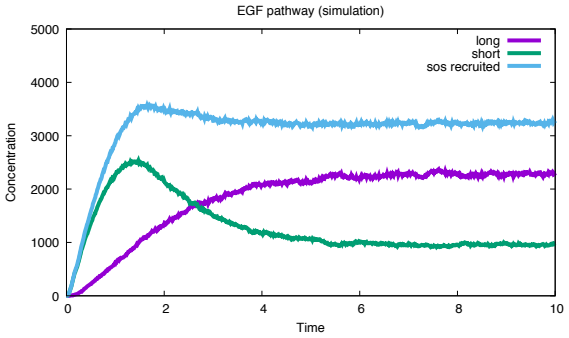
$$\begin{cases} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot x_3^2 - k_2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

ordinary differential equations

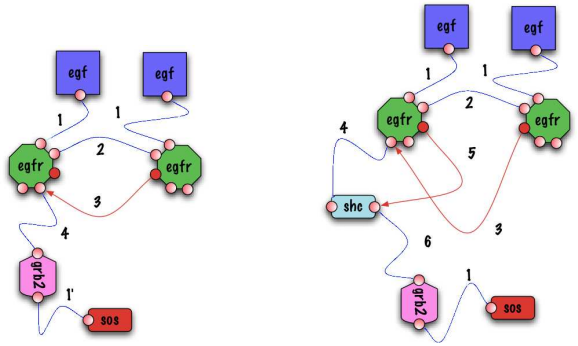
Complexity walls



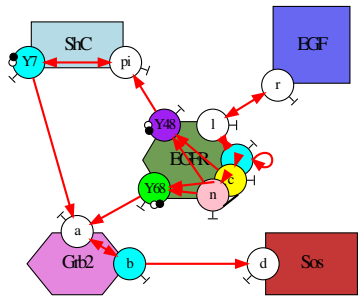
Abstractions offer different perspectives on models



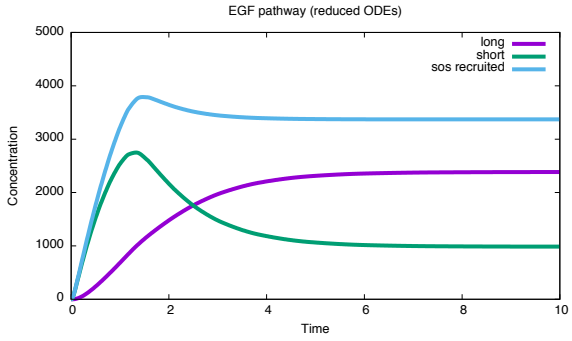
concrete semantics



causal traces



information flow



exact projection
of the ODE semantics

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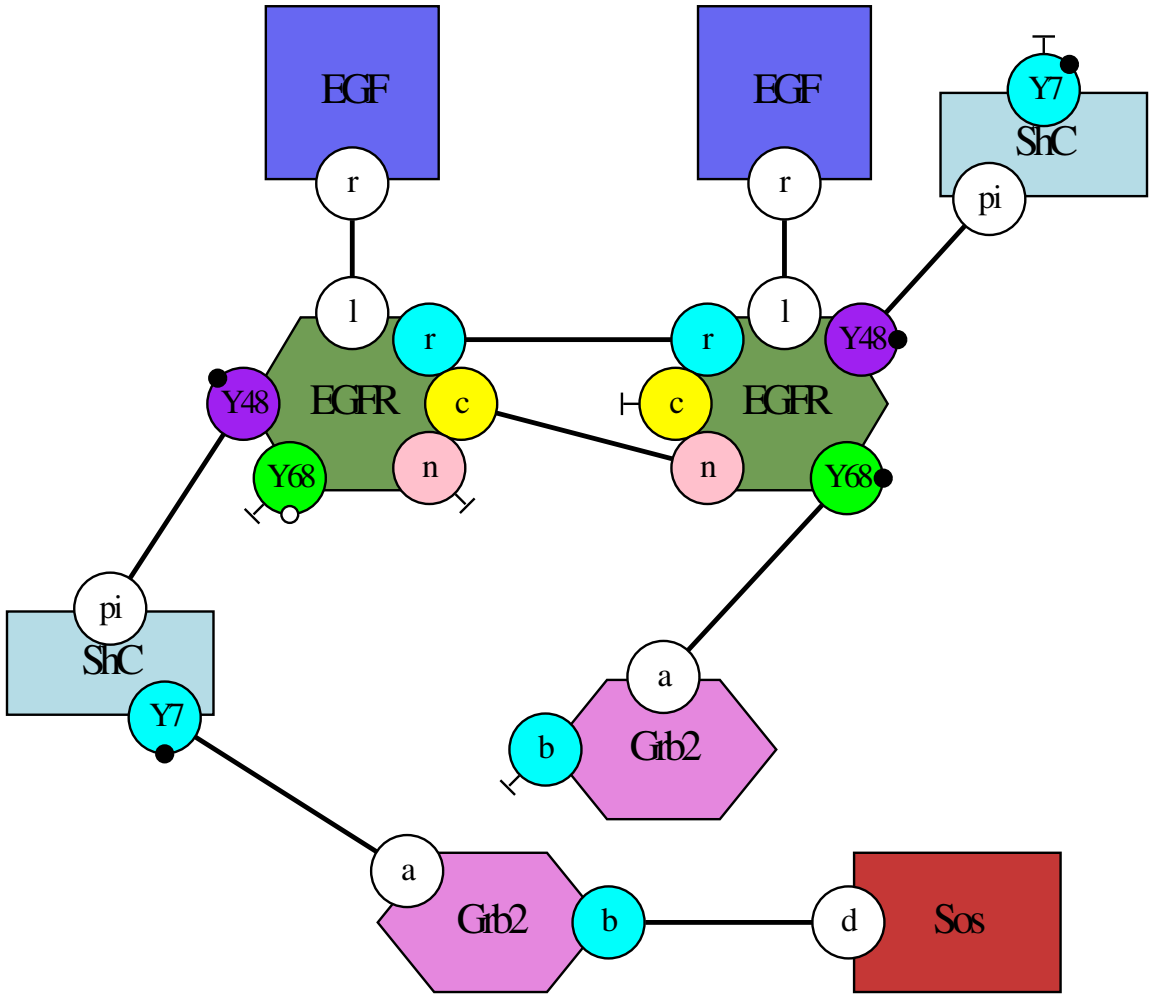
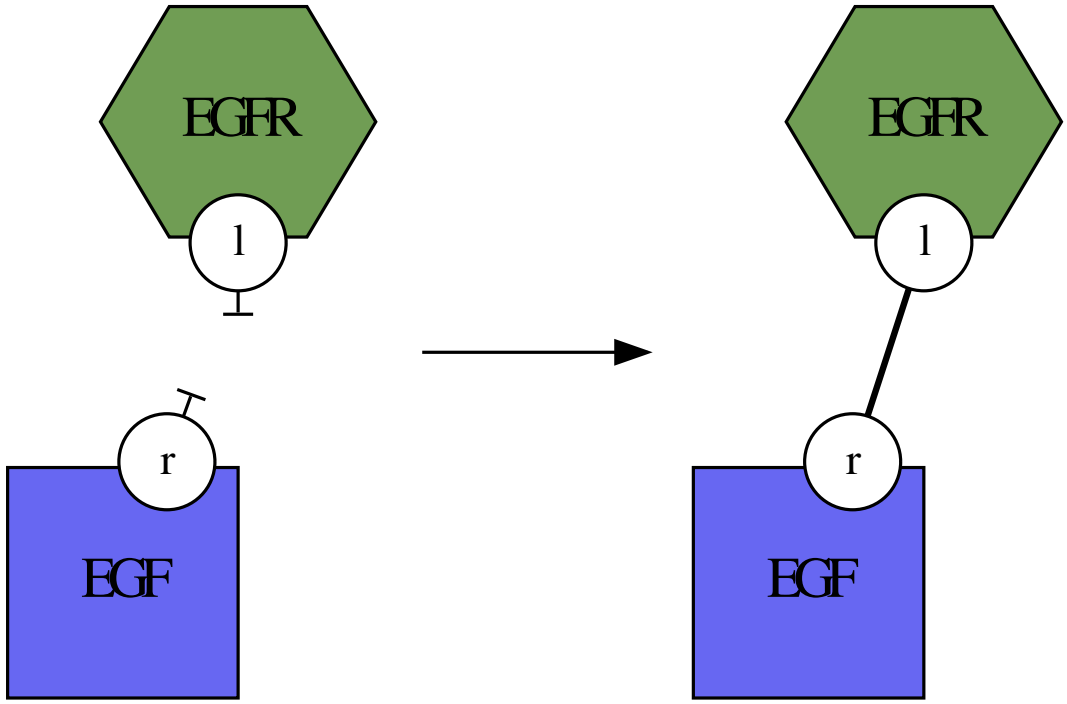
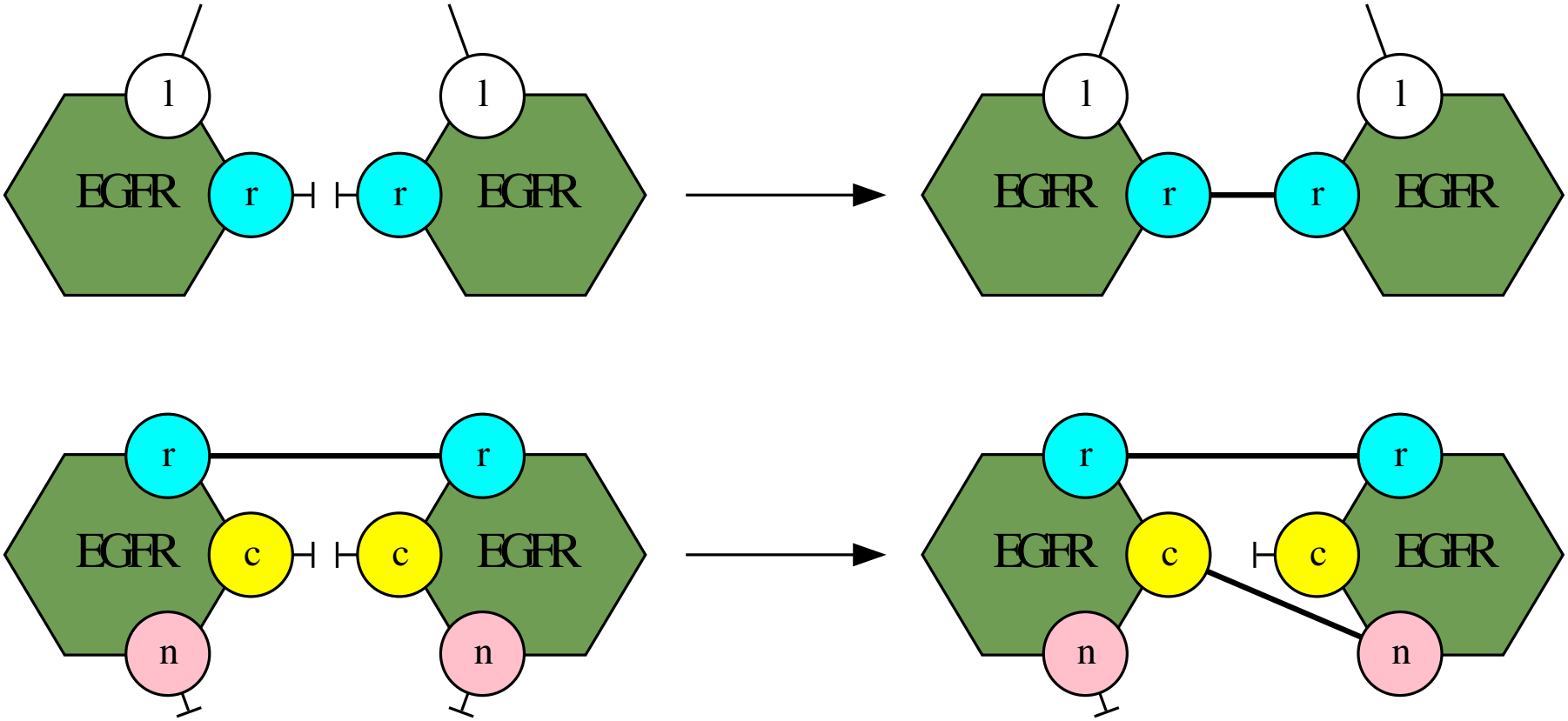
Bio-molecular compound



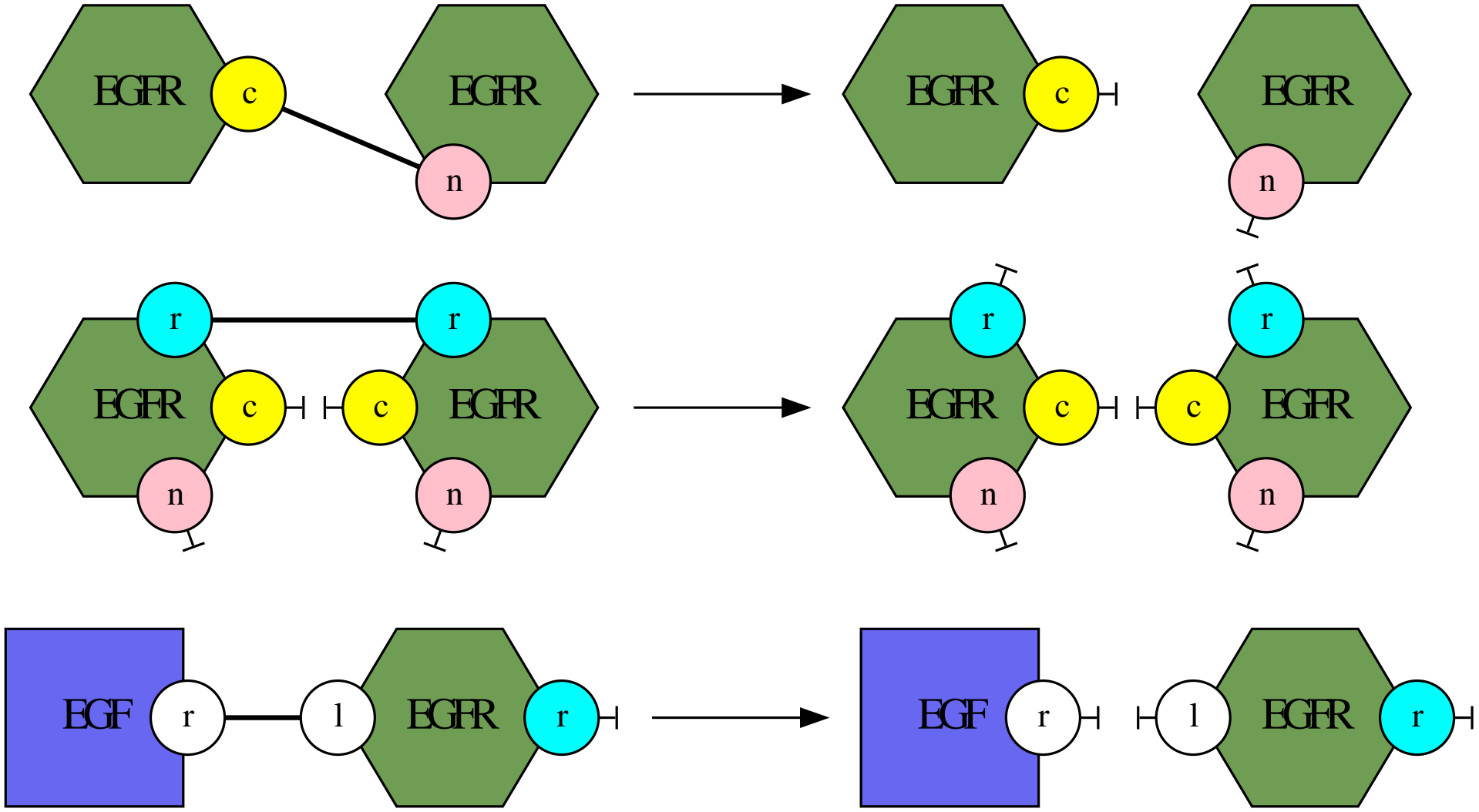
Receptor activation



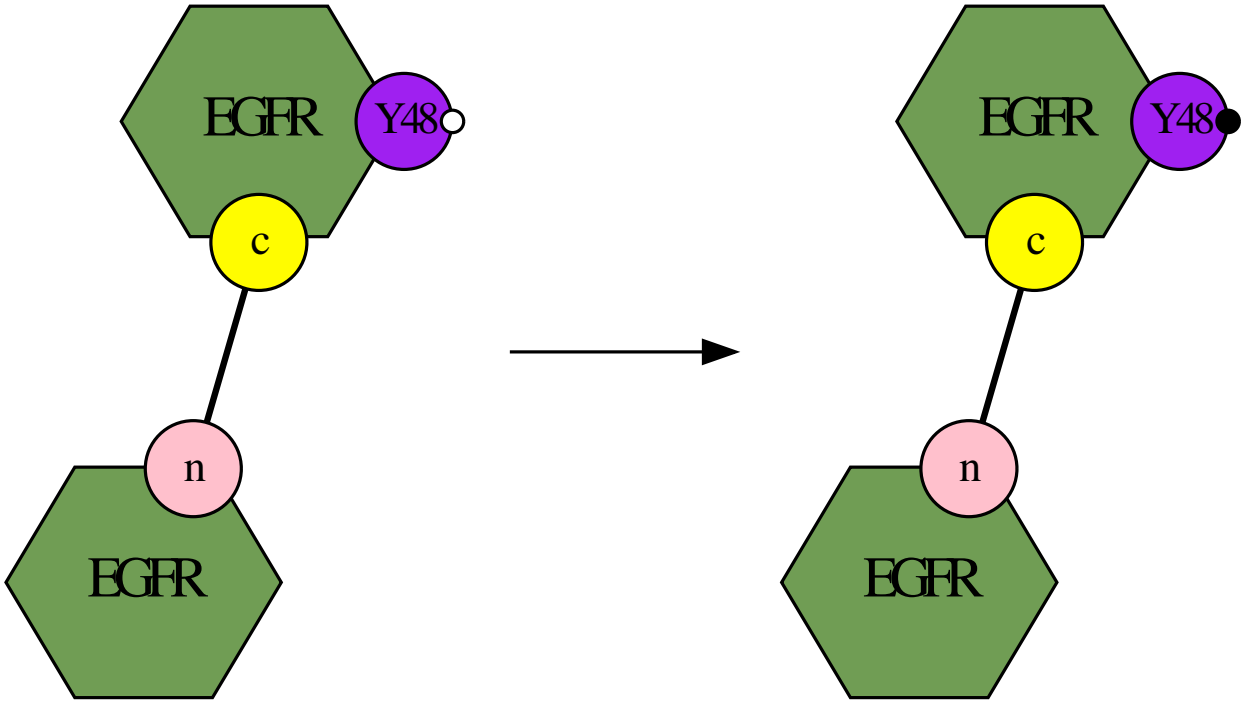
Asymmetric dimerisation



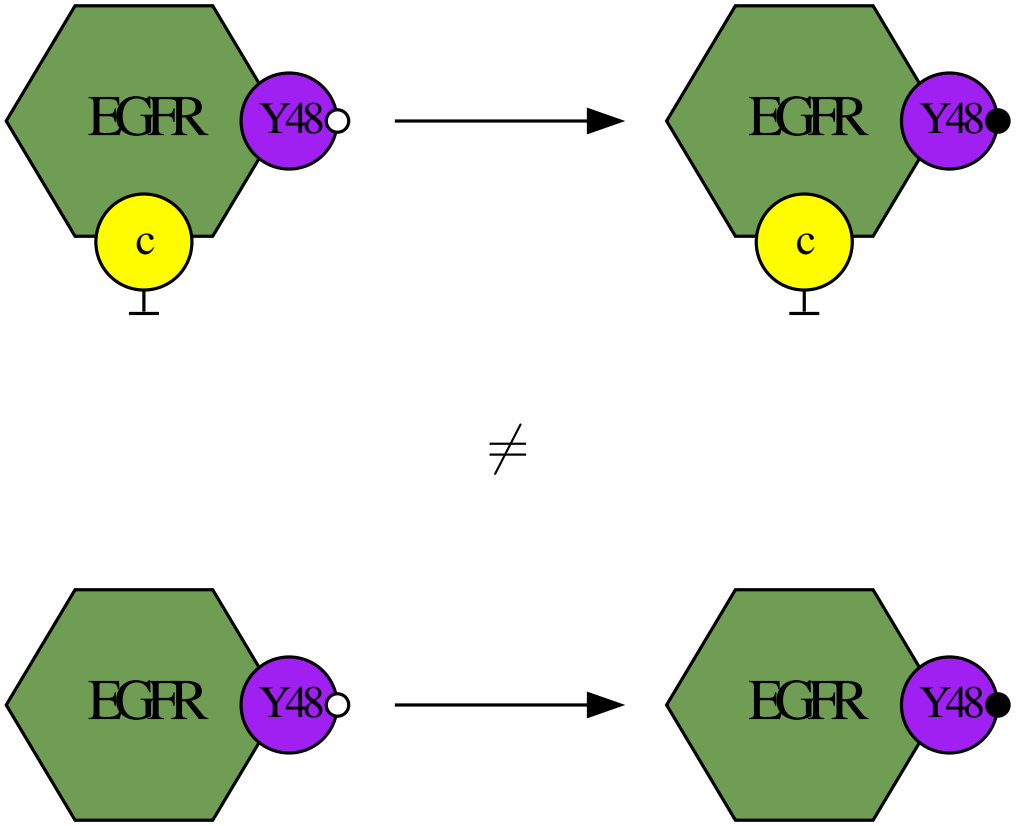
Sequential unbinding



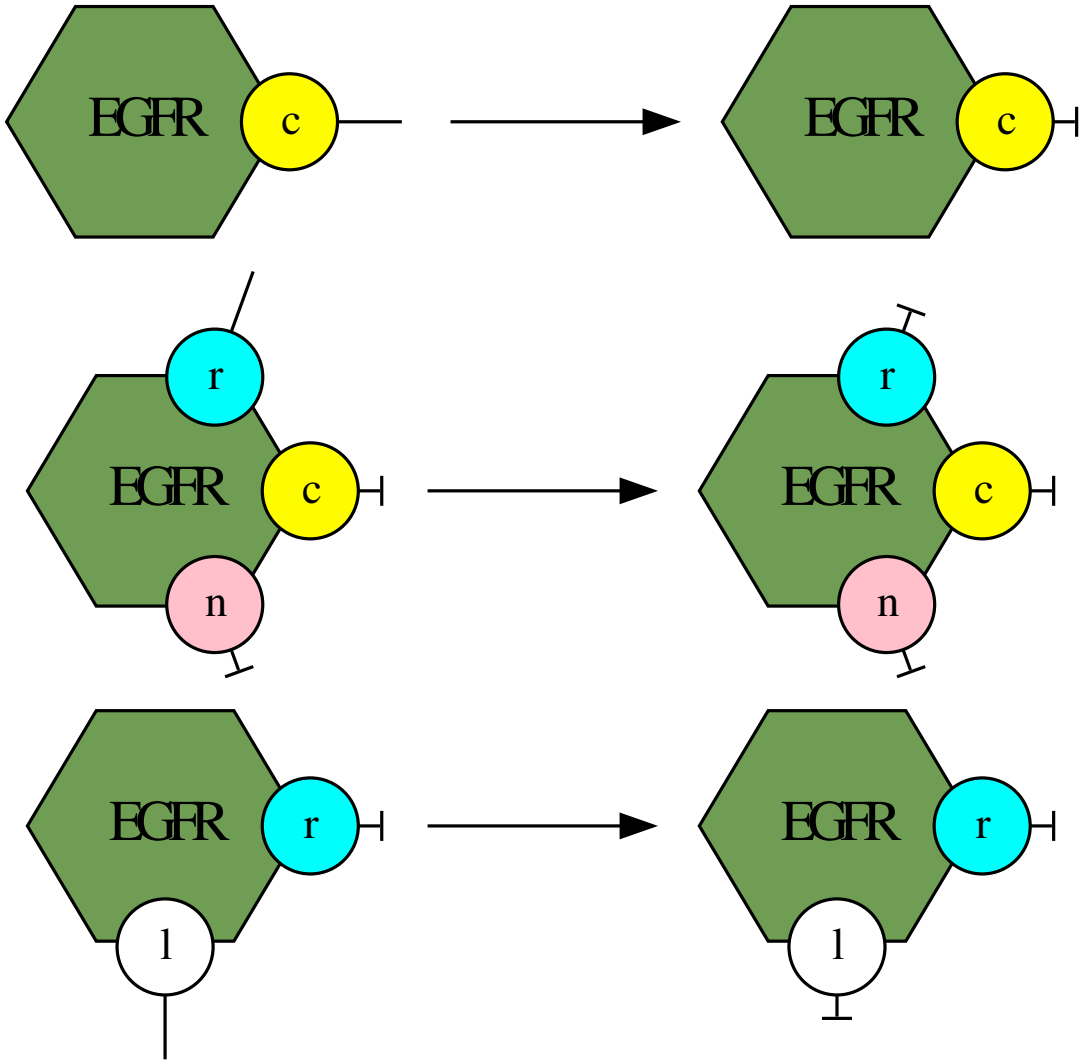
Phosphorylation



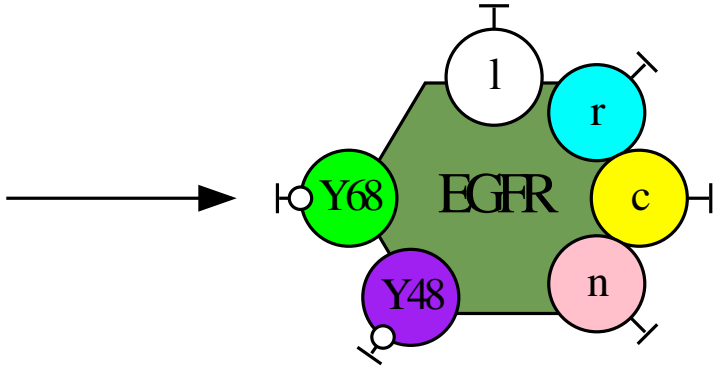
Don't care, Don't write

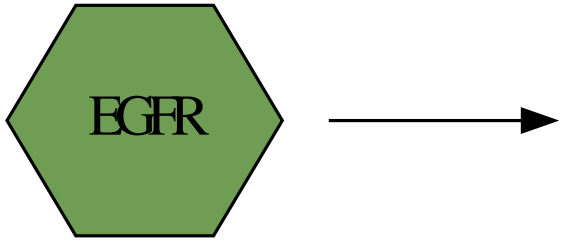


Sequential unbinding (by side effects)



Creation/Suppression





On the menu today

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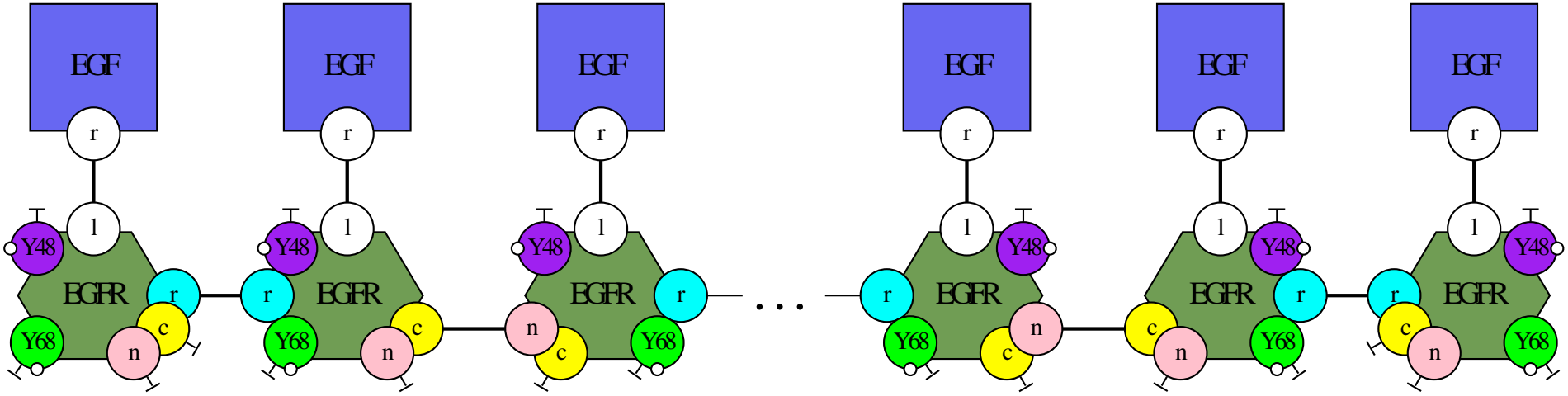
Our goal

We want to prove the absence of unbounded polymers:



Why?

1. Debugging:

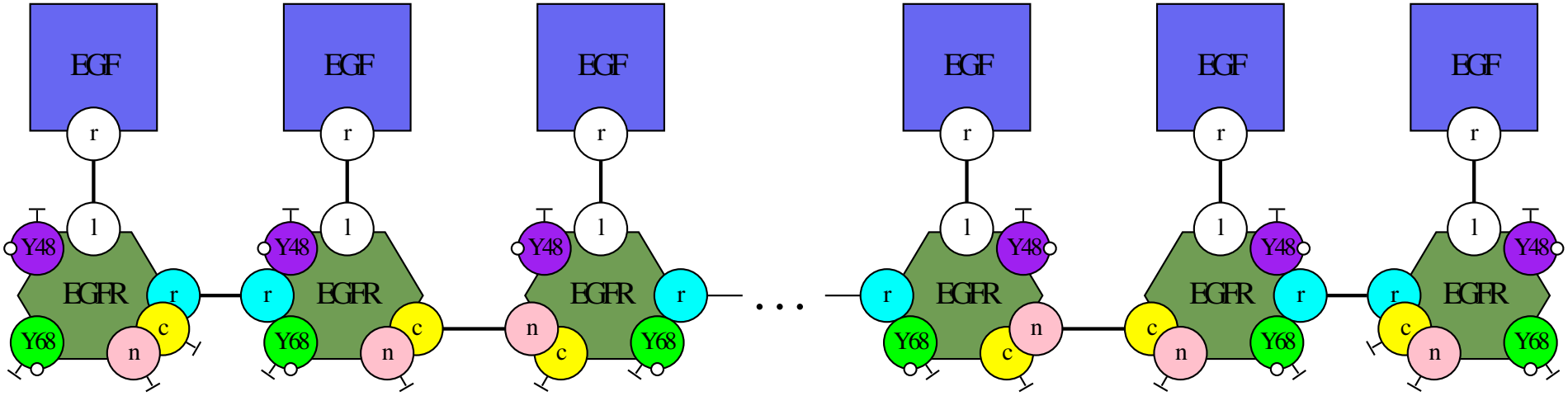
   When models come from a more abstract specification language, some conflicts are often forgotten.

2. Understanding the model:

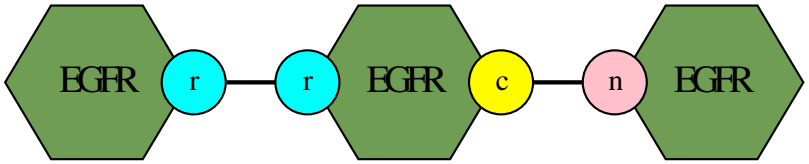
   Self-assembling of geant macro-molecules.

Strengthened goal

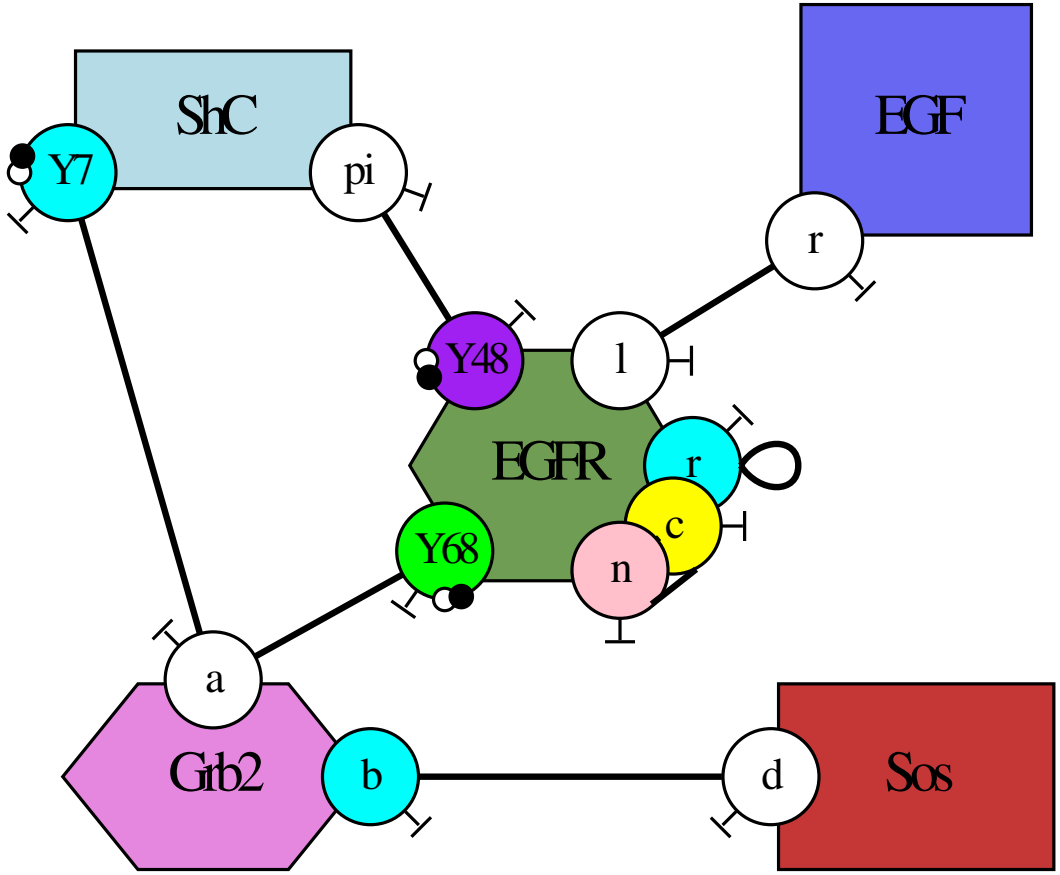
We want to prove the absence of unbounded polymers:



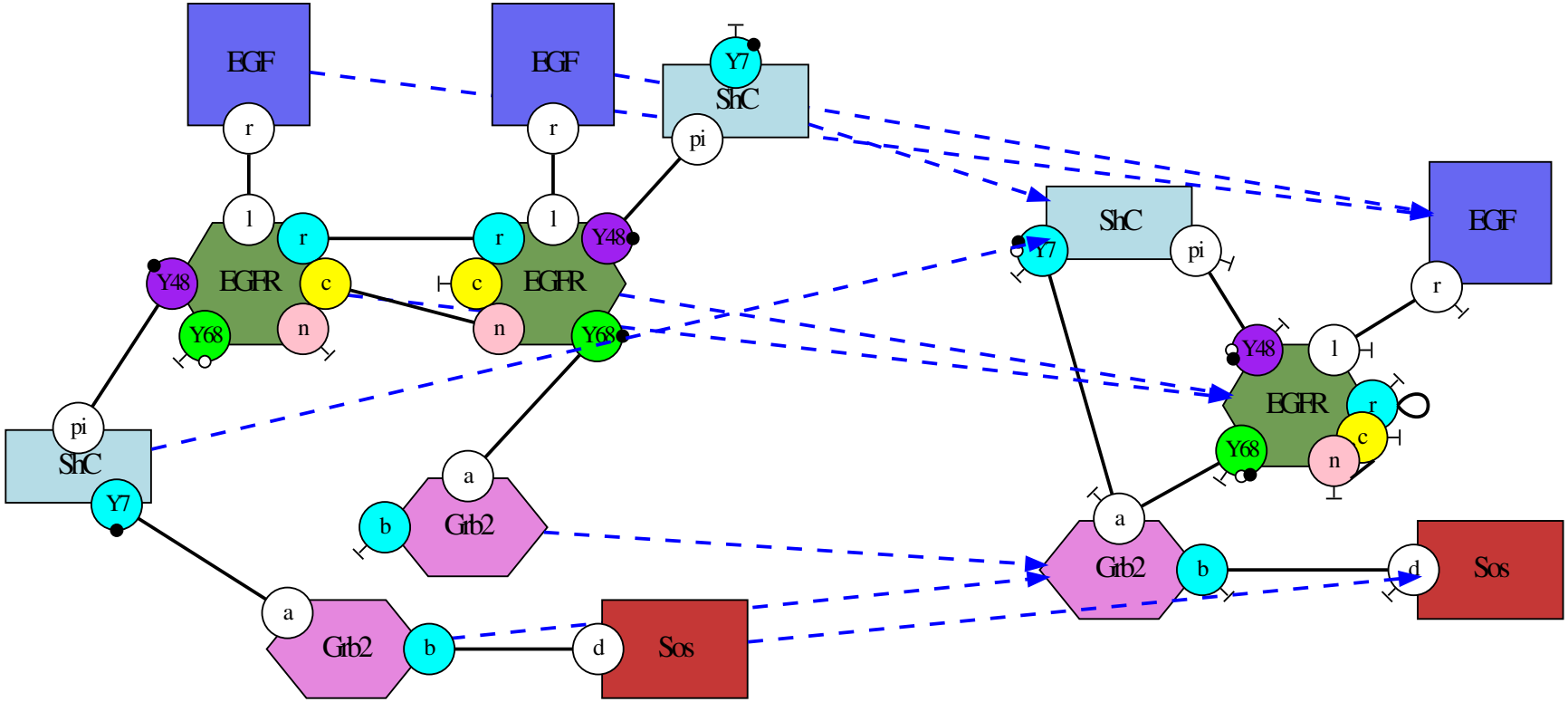
Instead, we will prove the absence of repeatable patterns:



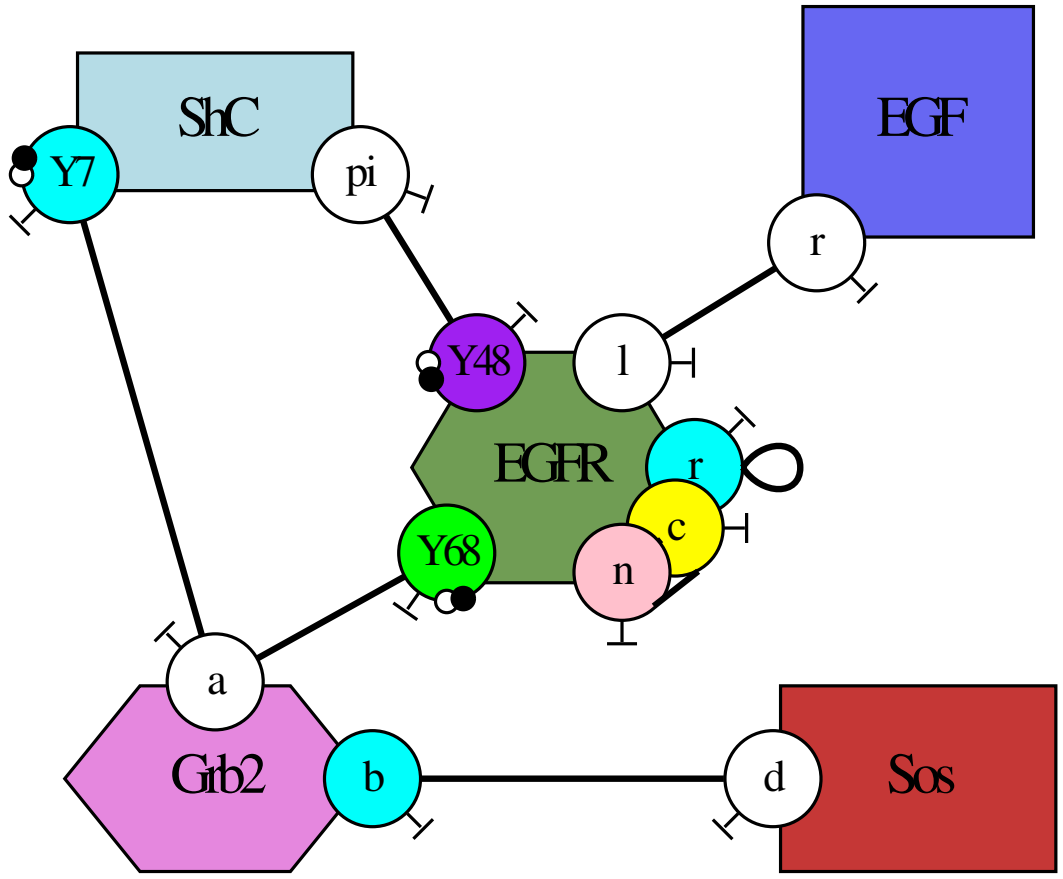
Interaction map



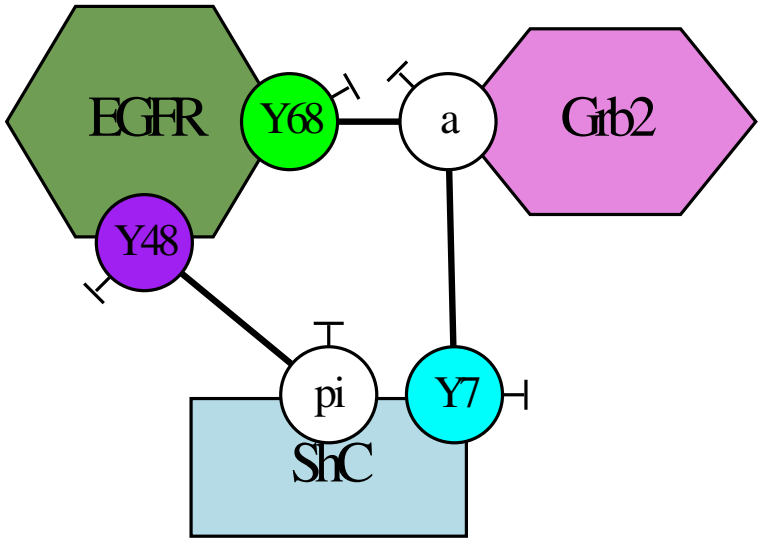
Interpretation



Interaction map

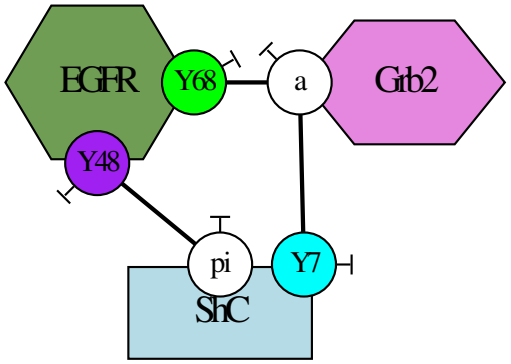


Conflicts

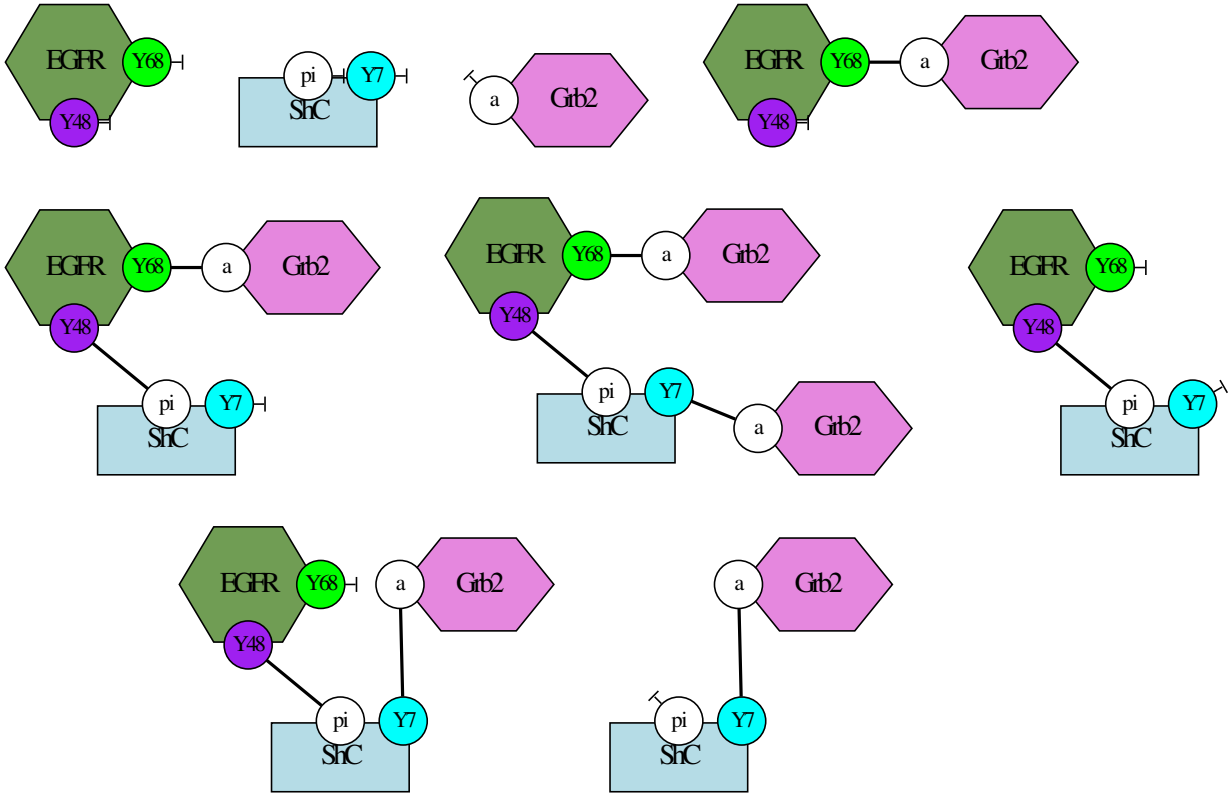


Interaction map.

Conflicts:



Interaction map.



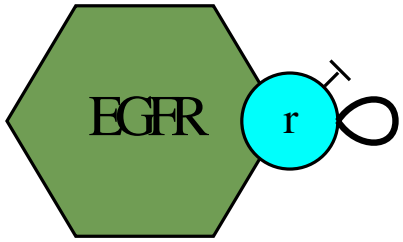
Bio-molecular compounds.

Alternative encoding

Alternative encoding

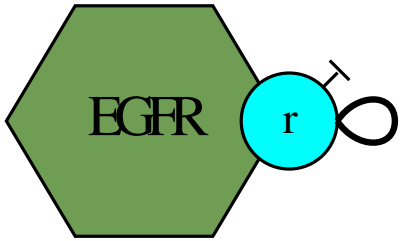
Alternative encoding

Self-loops

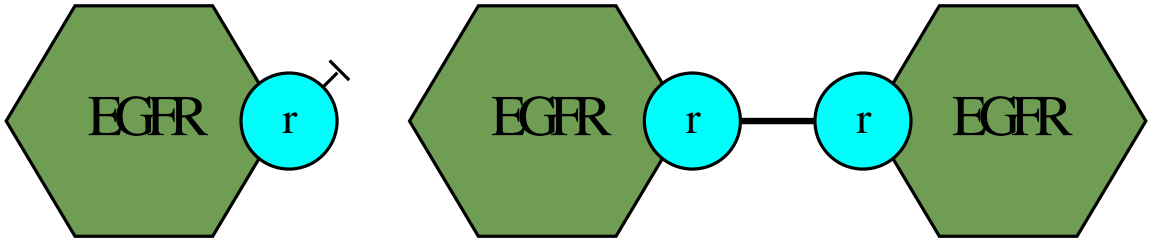


Interaction map.

Self-loops

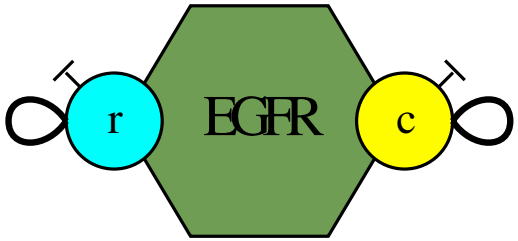


Interaction map.



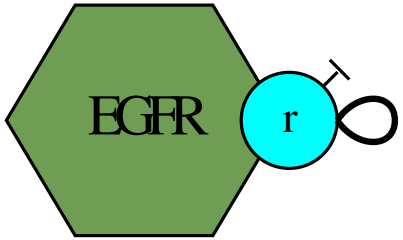
Bio-molecular compounds.

Several self-loops

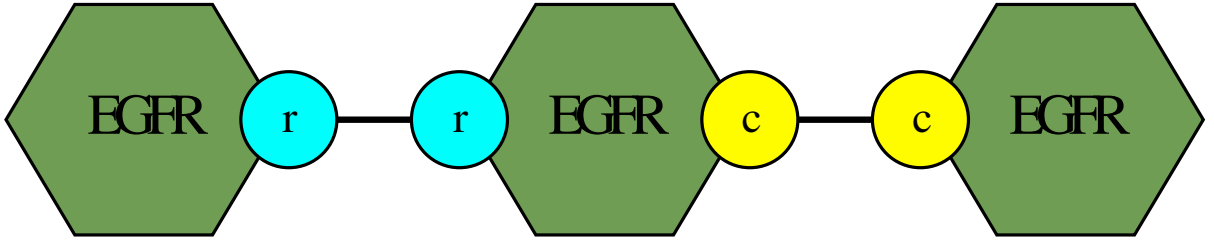


Interaction map.

Several self-loops

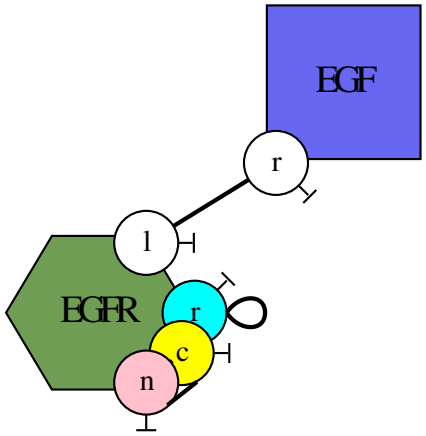


Interaction map.

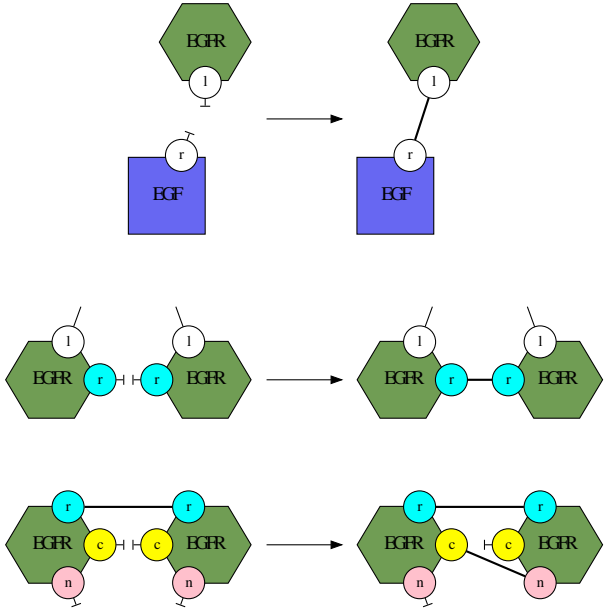


A repeatable pattern.

Invariants

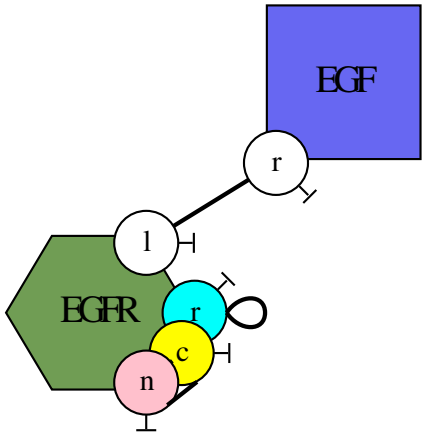


Interaction map.

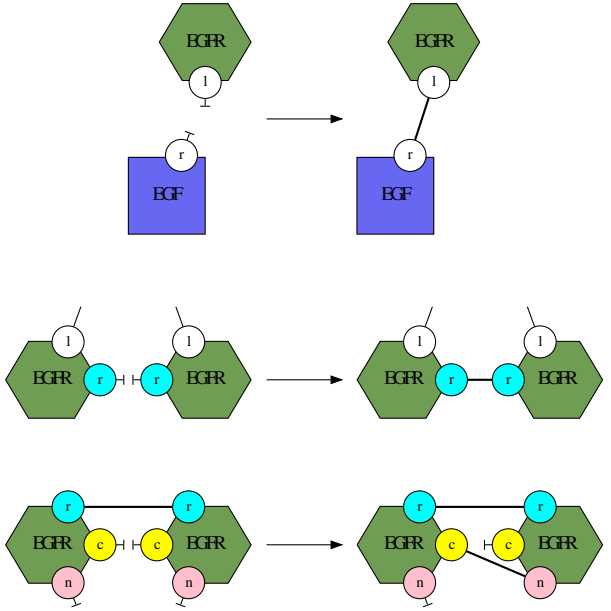


Rules.

Invariants

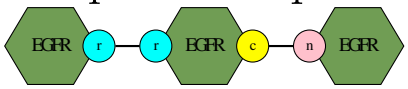


Interaction map.



Rules.

The repeatable pattern:



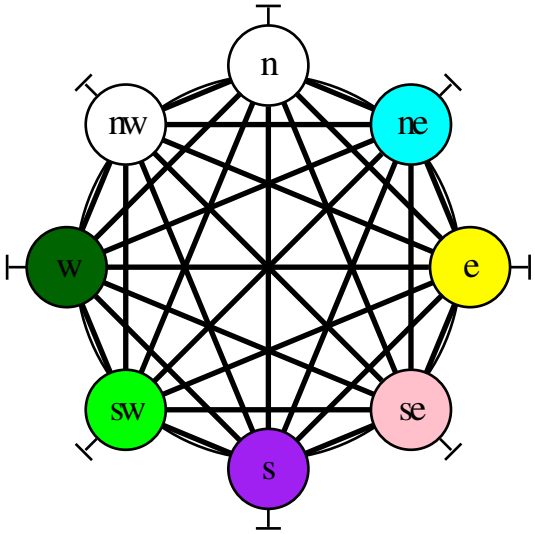
is not reachable.

Breaking invariants

Triangle

Triangle

Combinatorial complexity



On many model, elementary cycles are too numerous to enumerate them.

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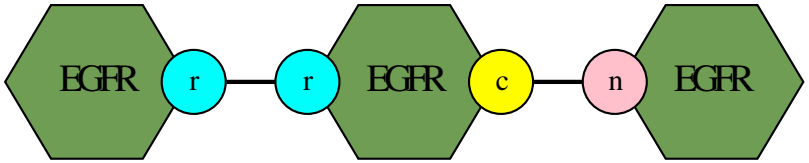
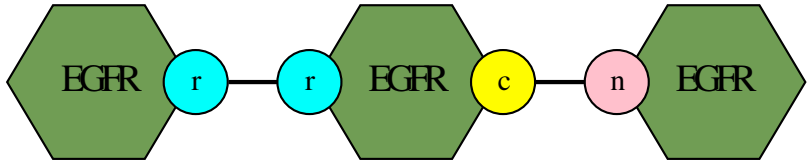
Repeatable patterns

We want to prove the abscence of repeatable of the form:

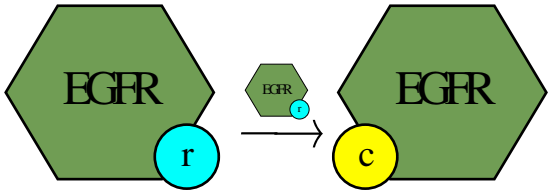


Transitions between sites

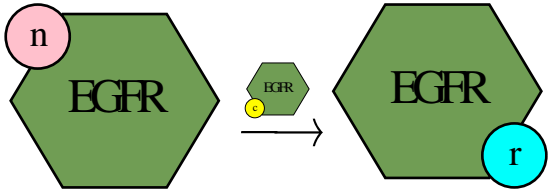
We convert repeatable patterns into sequences of sites, by taking each other one:



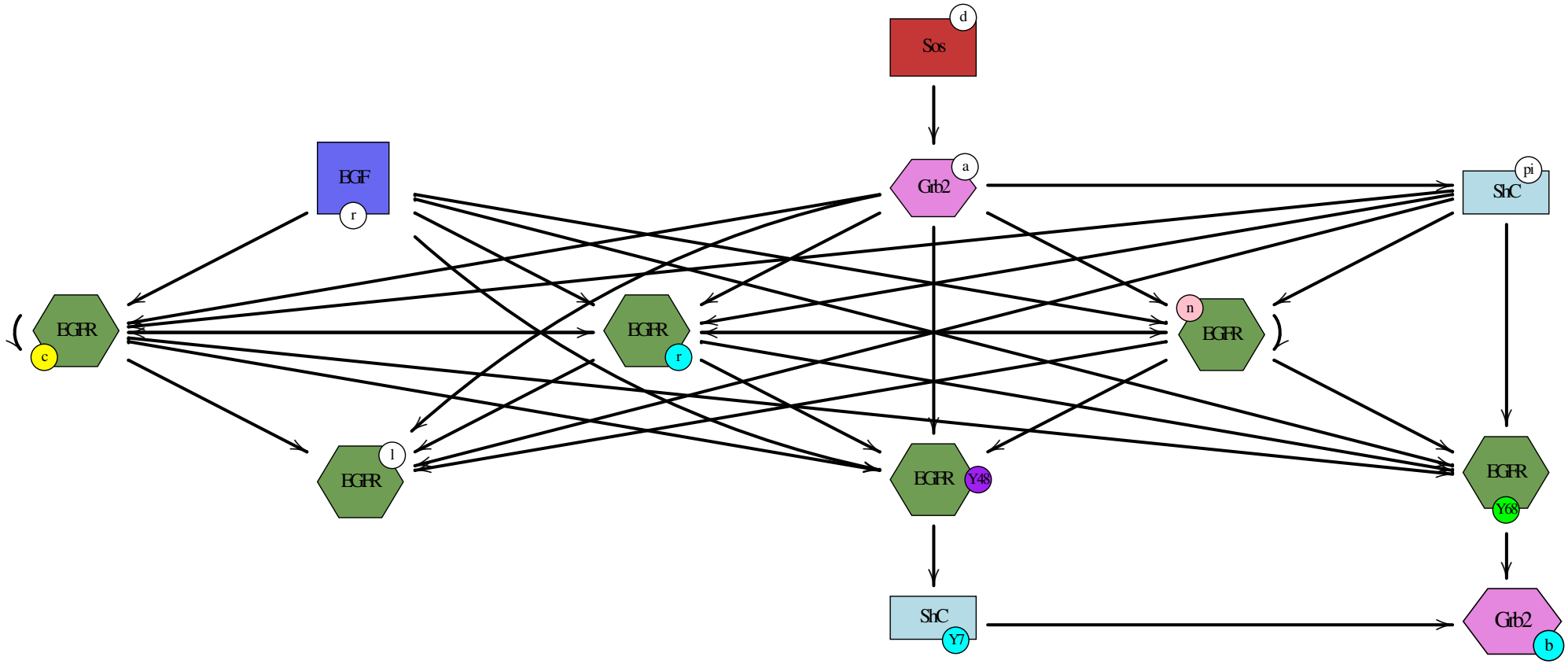
1. From left to right:



2. From right to left:



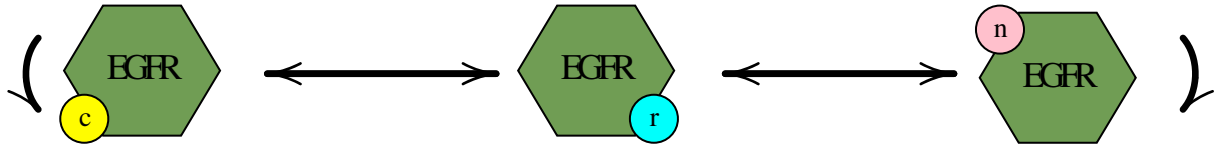
The graph of the sites



Detection of unbounded polymers

We use Tarjan's algorithm to extract non trivial strongly connected components.

Here there is only one:



This is a false alarm and we do not know how to do better with this data-structure.

Pros / Cons

1. Pros:
    - Can deal with self-bonds;
    - Can deal with conflicting sites;
    - Avoid combinatorial blow up.

2. Cons:
    - Cannot deal with structural invariants.

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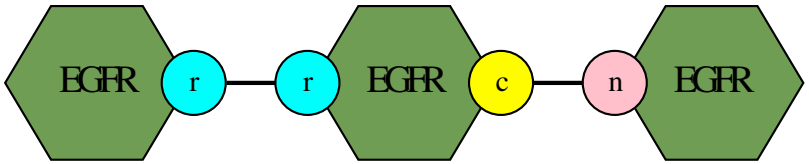
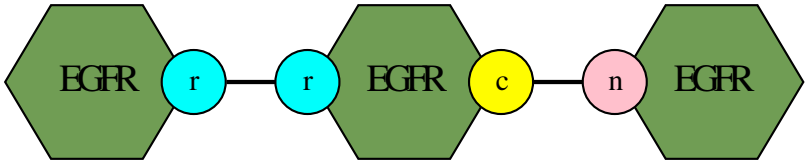
Repeatable patterns

Coming back to repeatable patterns:

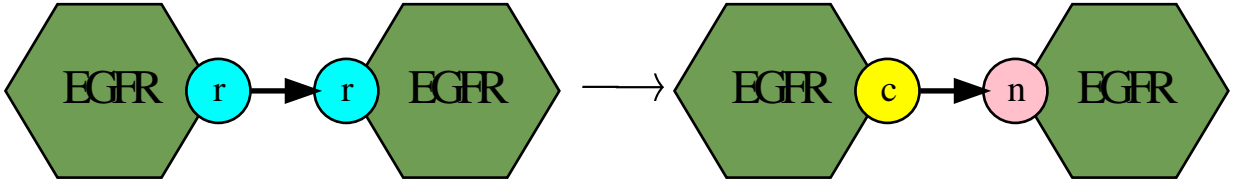


Transitions between the edges

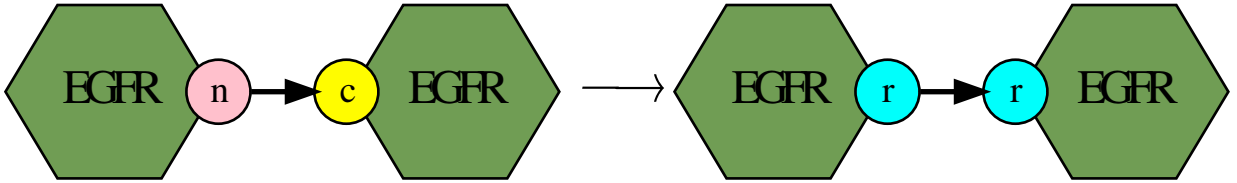
We interpret repeatable patterns as sequences of oriented links:



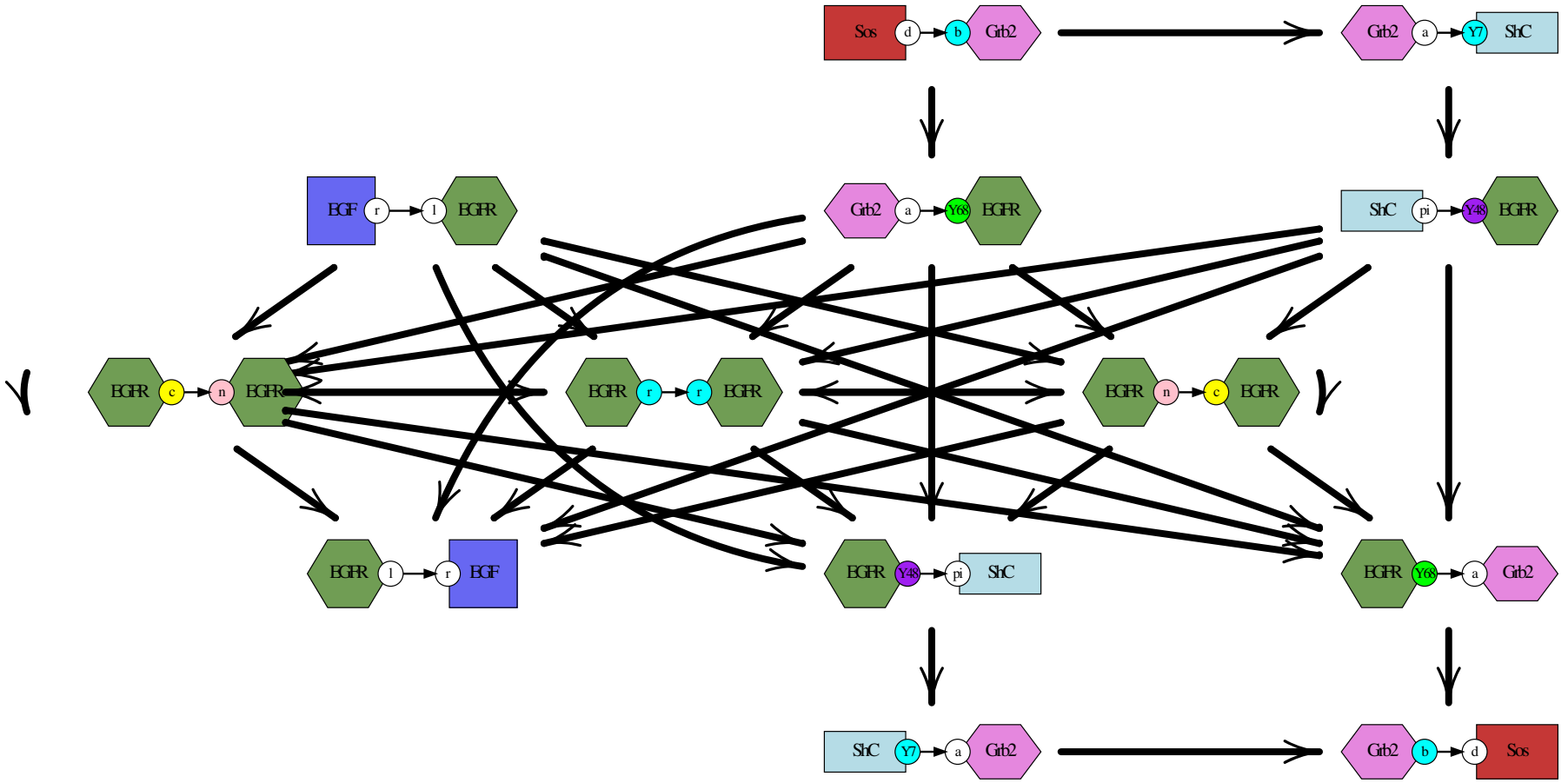
1. From left to right:



2. From right to left:



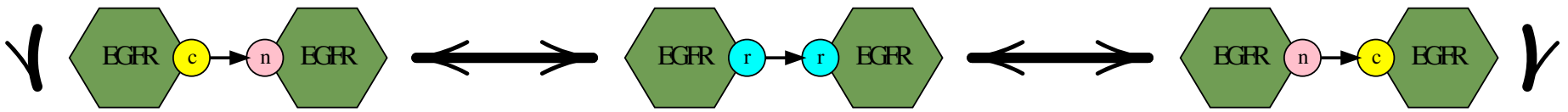
The graph of the links



Detection of unbounded polymers

We use Tarjan's algorithm to extract non trivial strongly connected components.

Here there is only one:



This is a false alarm and we do not know how to do better with this data-structure.

Pros / Cons

1. Pros:
   - Can deal with self-bonds;
   - Can deal with conflicting sites;
   - Avoid combinatorial blow up.

2. Cons:
   - Cannot deal with structural invariants.

On the menu today

1. Rule-based modelling
2. Kappa
3. Unbounded bio-molecular compounds
4. The graph of the sites
5. The graph of the edges
6. Refinement
7. Conclusion

Issues

The graph of the links

Labelled transitions

Refinement

On the menu today

1. Rule-based modelling
2. Kappa
3. Unbounded bio-molecular compounds
4. The graph of the sites
5. The graph of the edges
6. Refinement
7. Conclusion