

# SASB 2018

## Proving the absence of unbounded polymers in rule-based models

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DI - ÉNS



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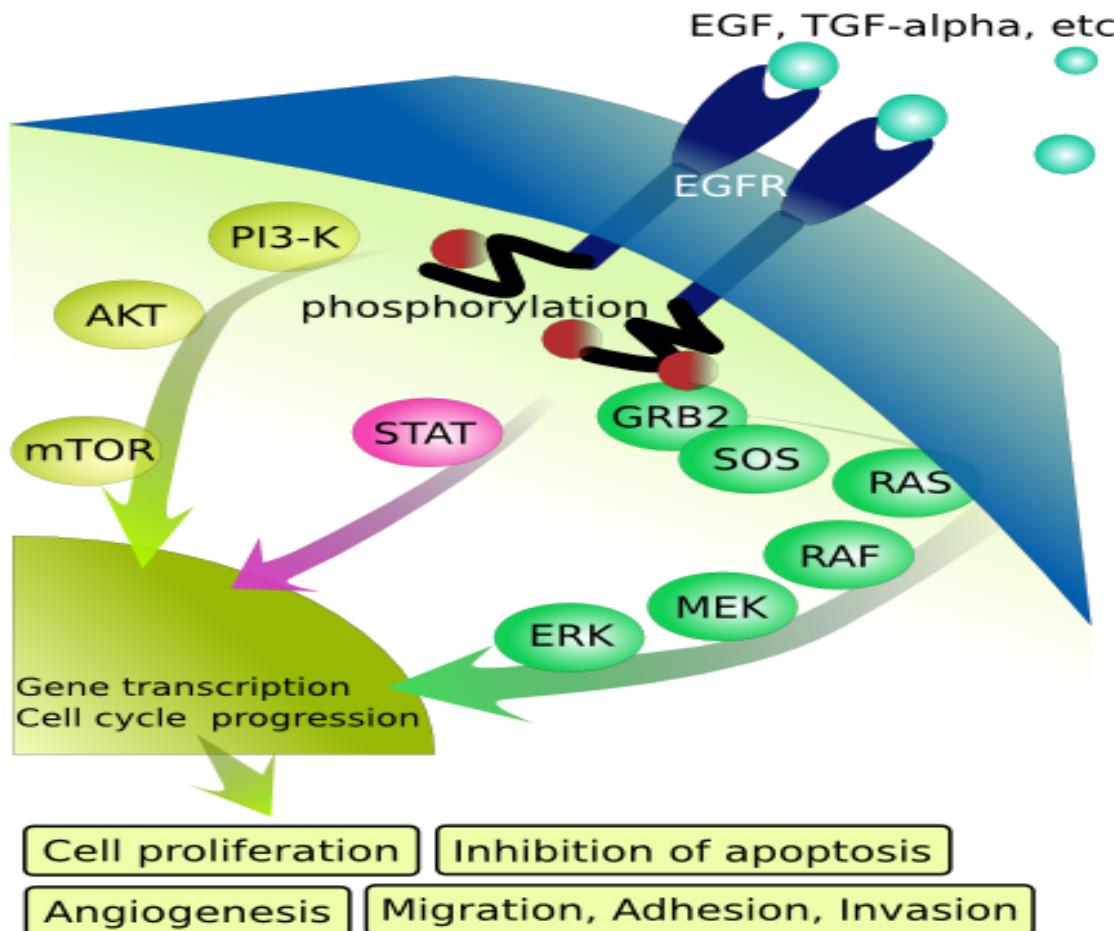
Joint work with Pierre Boutillier and Aurelie Faure de Pebeyre

Freiburg im Breisgau, August 28 2018

# On the menu today

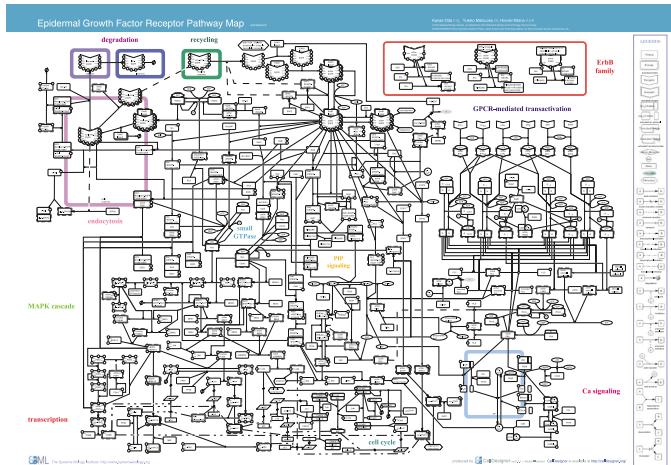
1. Rule-based modelling
2. Kappa
3. Unbounded bio-molecular compounds
4. The graph of the sites
5. The graph of the edges
6. Refinement
7. Conclusion

# Signalling Pathways



Eikuch, 2007

# Bridging the gap between...

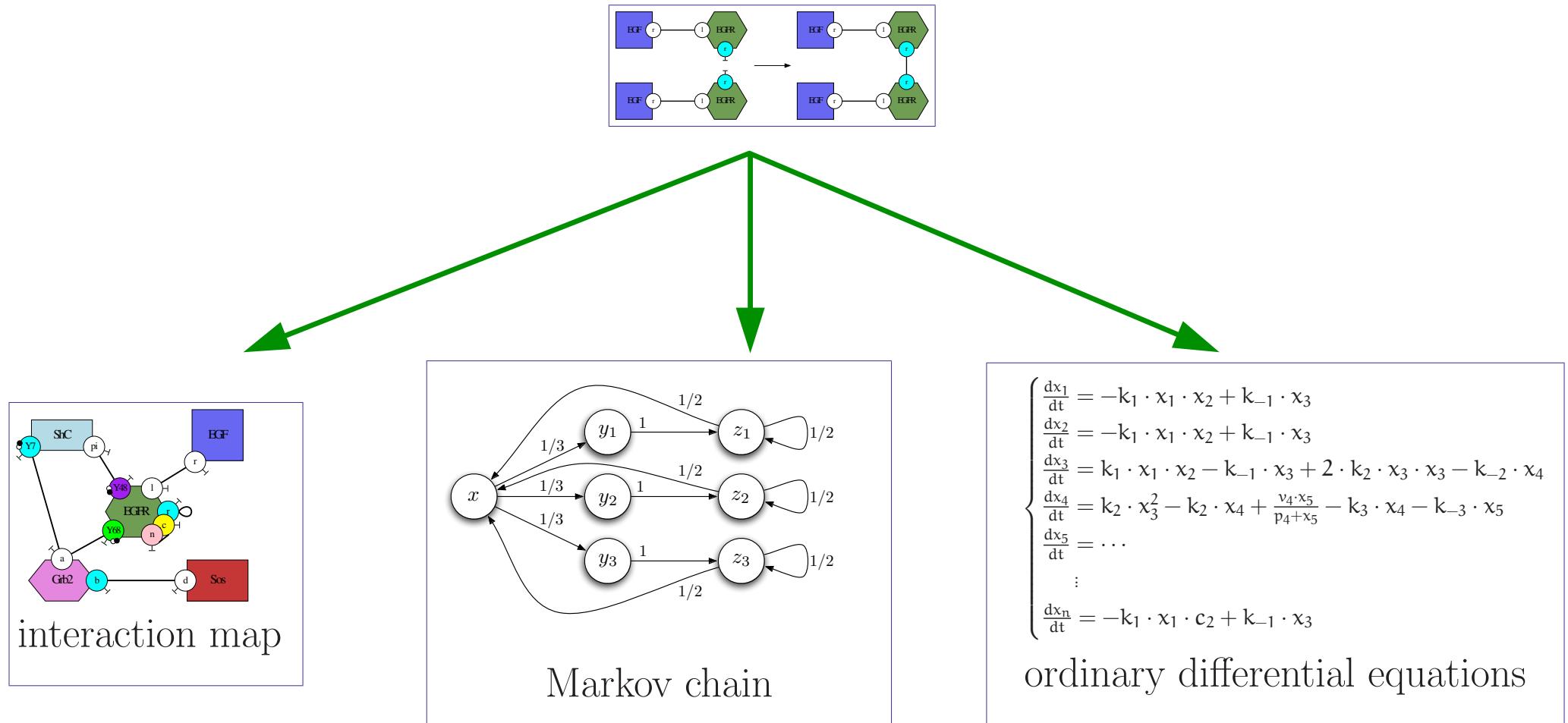


knowledge  
representation  
and

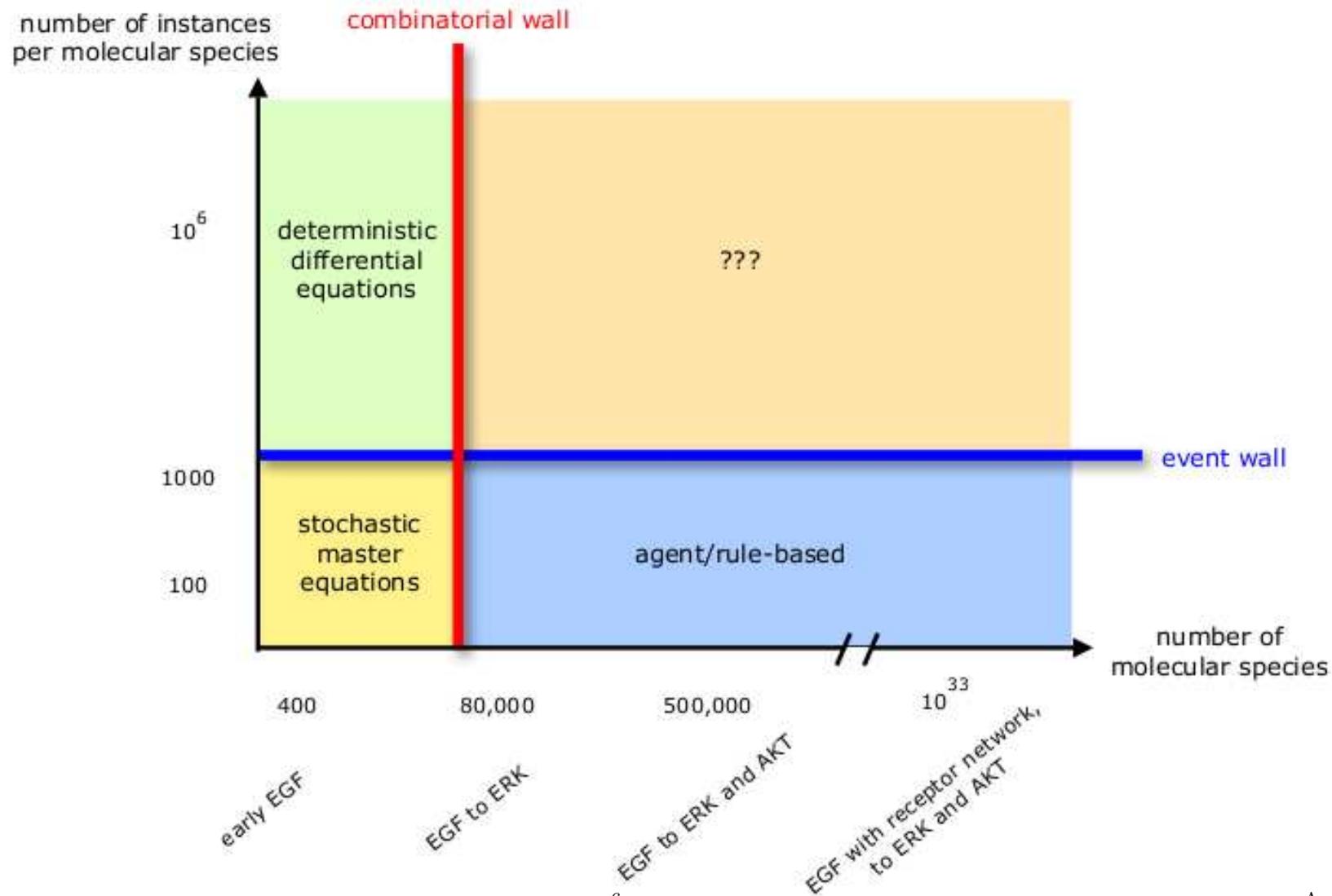
$$\left\{ \begin{array}{l} \frac{dx_1}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_2}{dt} = -k_1 \cdot x_1 \cdot x_2 + k_{-1} \cdot x_3 \\ \frac{dx_3}{dt} = k_1 \cdot x_1 \cdot x_2 - k_{-1} \cdot x_3 + 2 \cdot k_2 \cdot x_3 \cdot x_3 - k_{-2} \cdot x_4 \\ \frac{dx_4}{dt} = k_2 \cdot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

models of the  
behaviour of  
systems

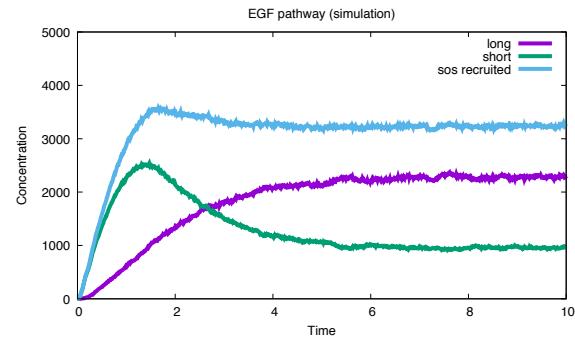
# Choices of semantics



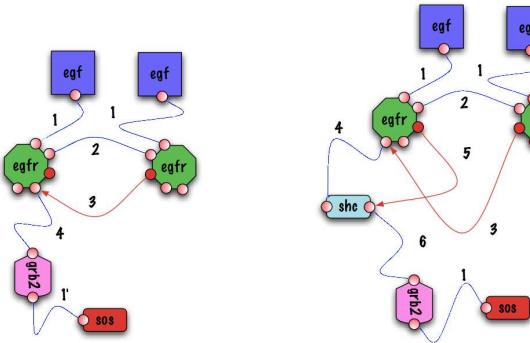
# Complexity walls



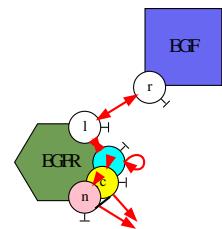
# Abstractions offer different perspectives on models



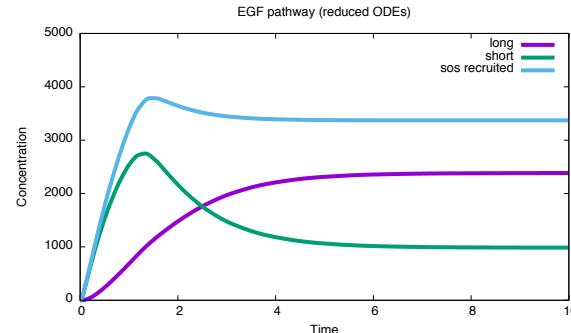
concrete semantics



causal traces



information flow

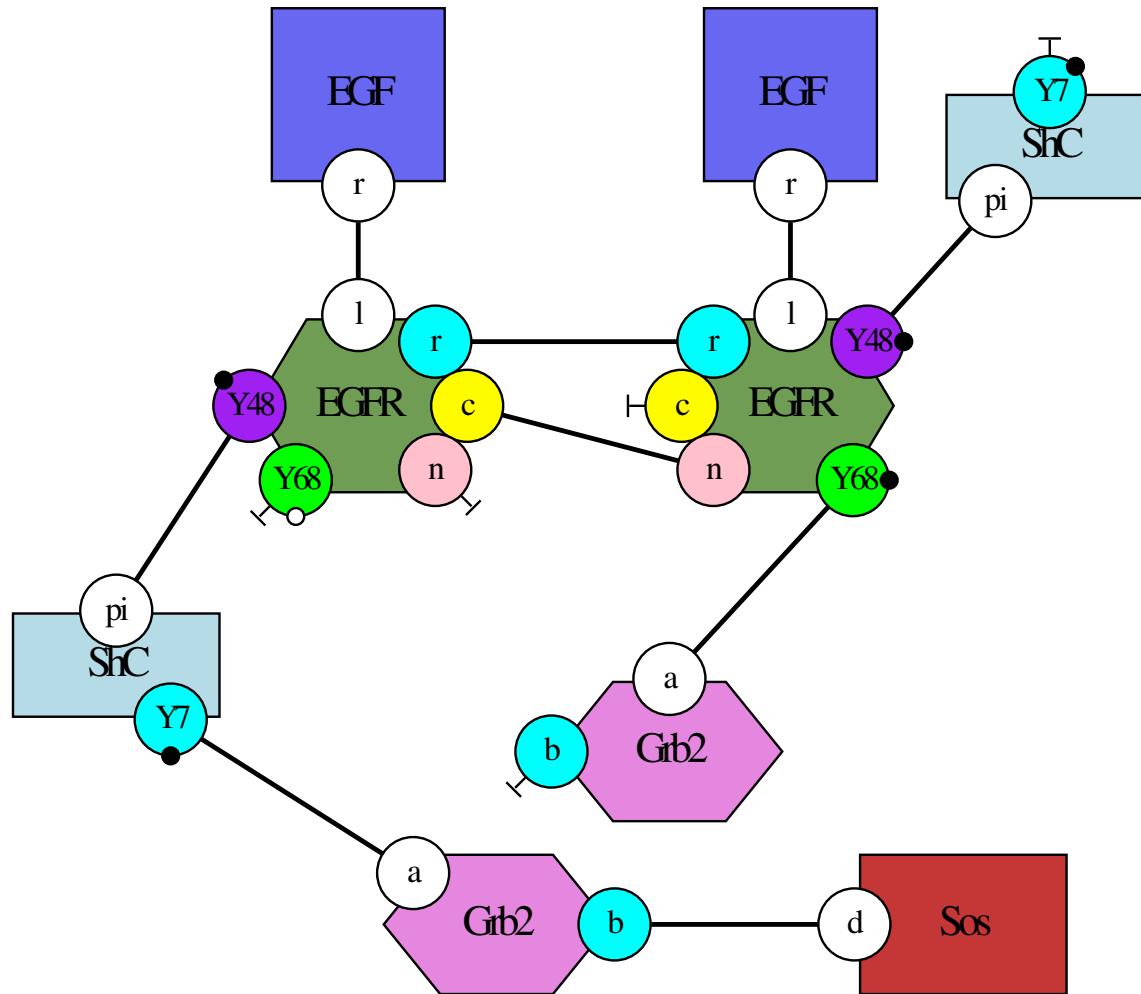


exact projection  
of the ODE semantics

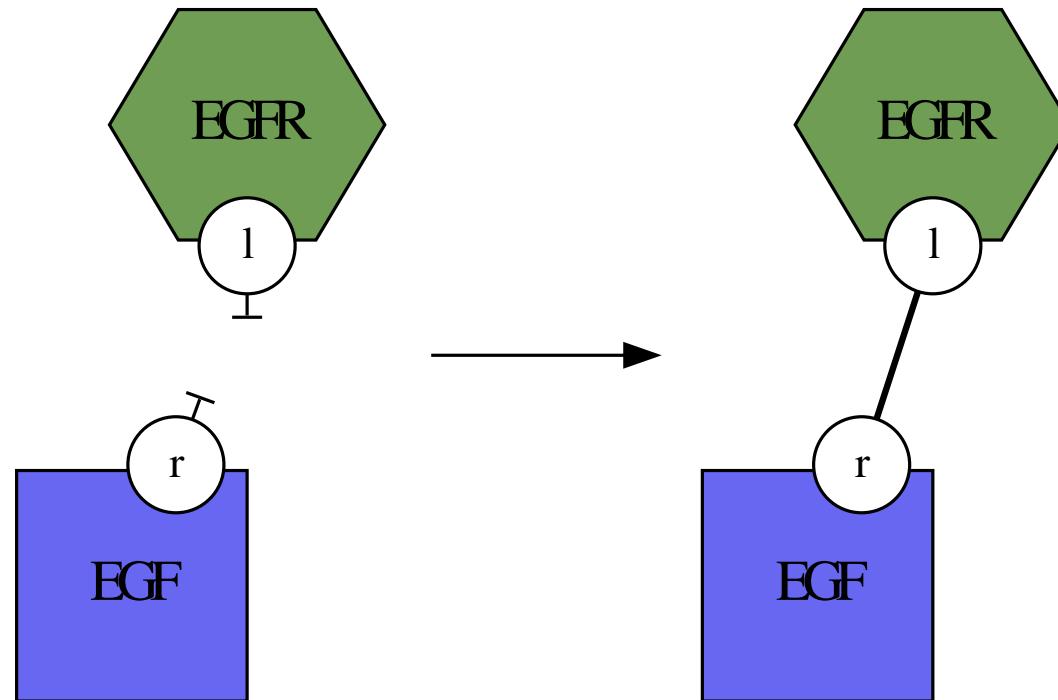
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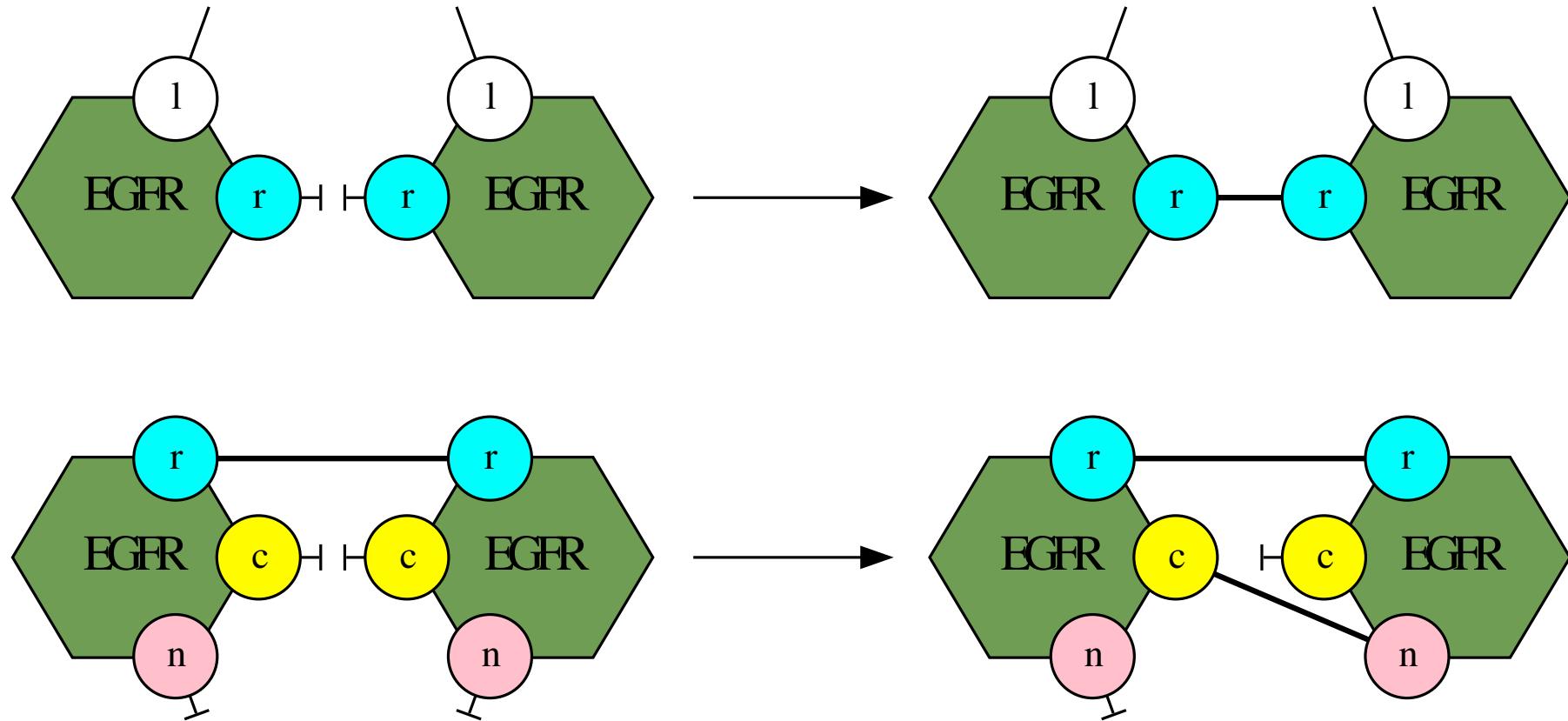
# Bio-molecular compound



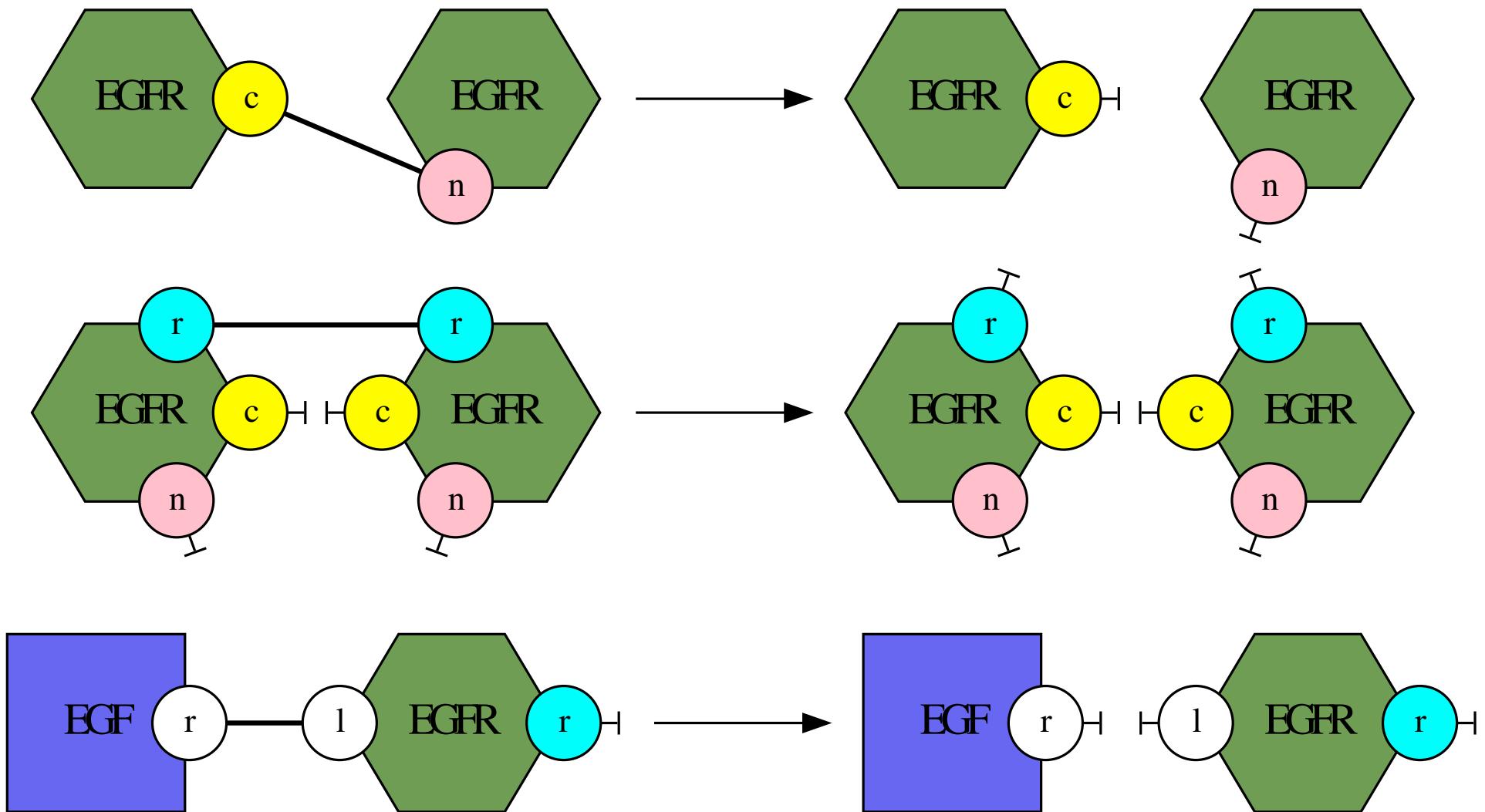
# Receptor activation



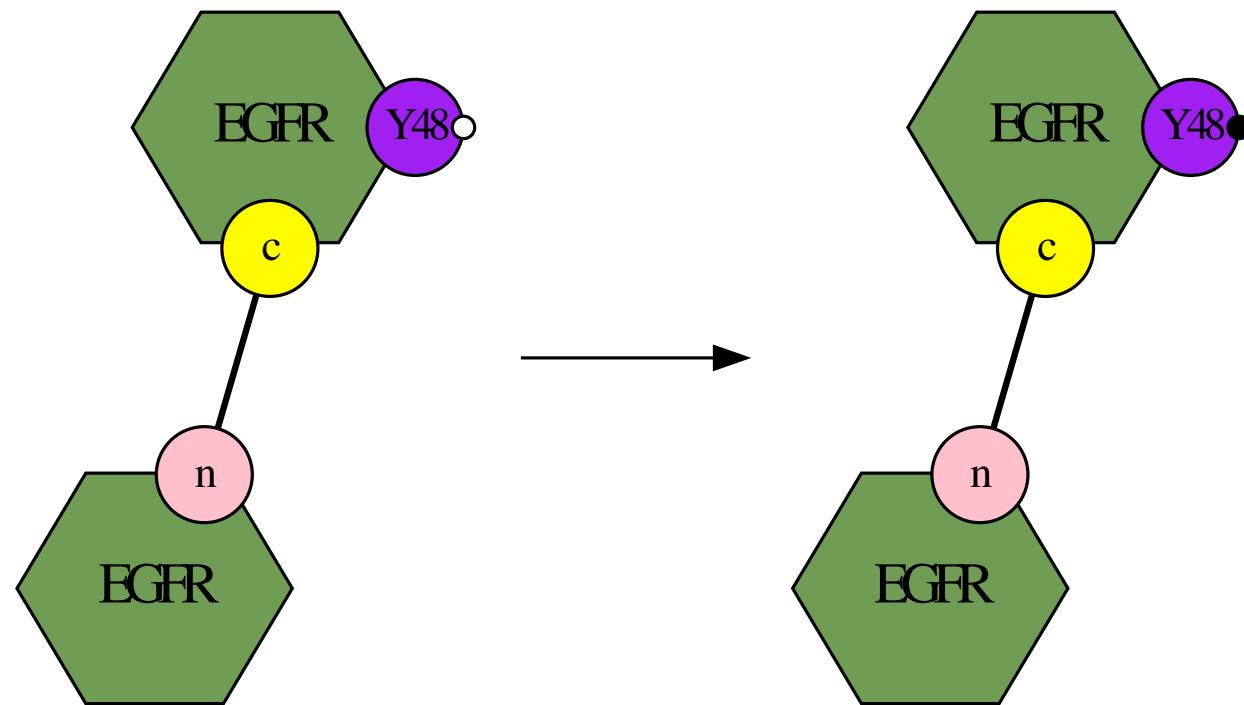
# Asymmetric dimerisation



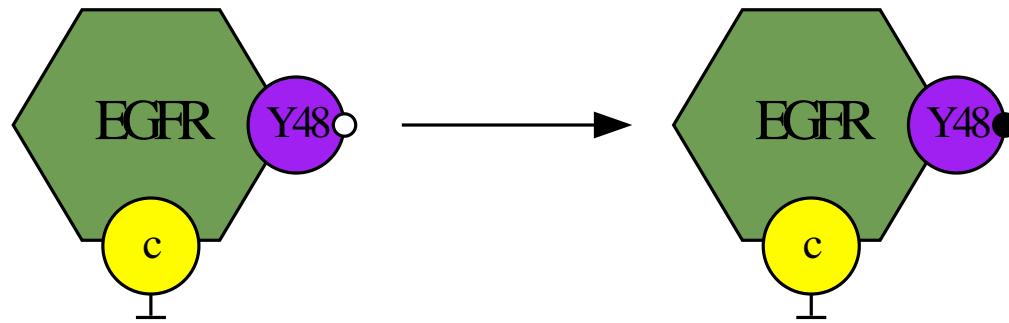
# Sequential unbinding



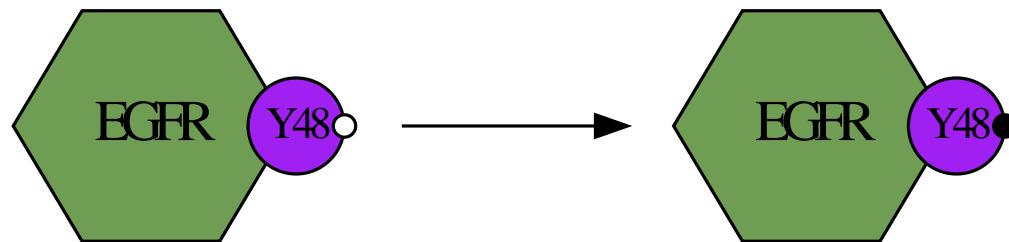
# Phosphorylation



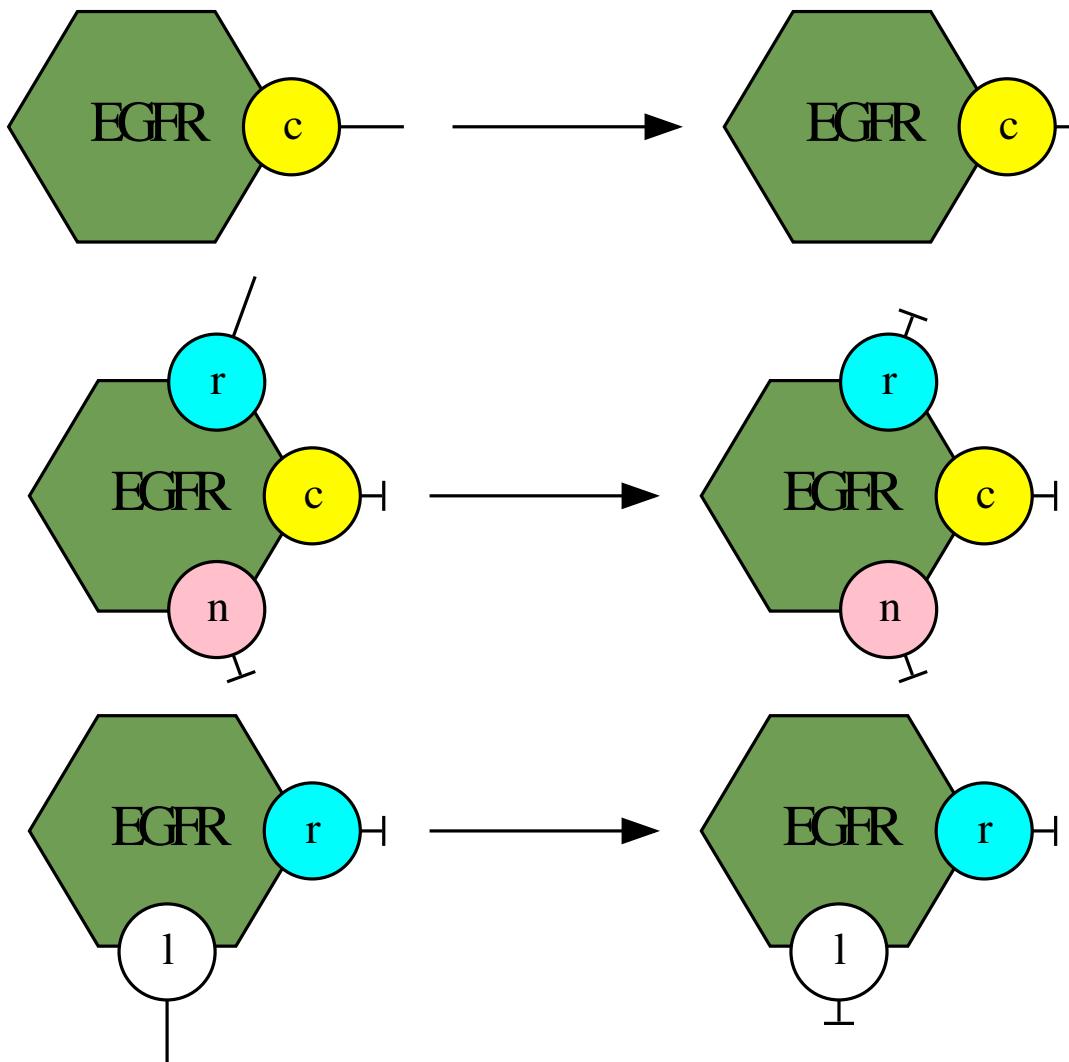
# Don't care, Don't write



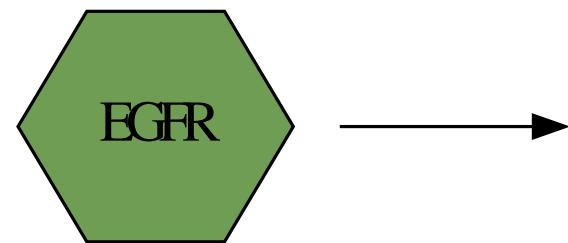
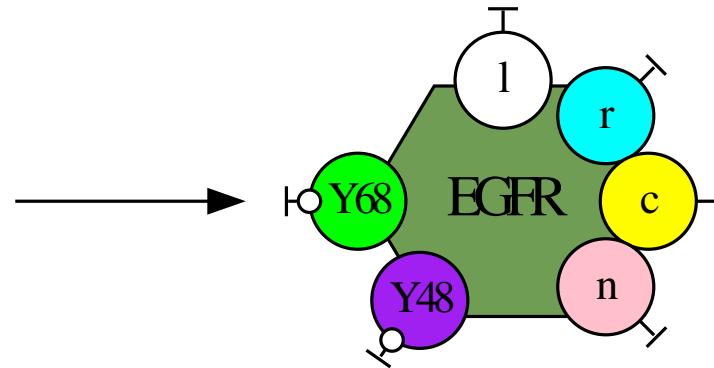
$\neq$



# Sequential unbinding (by side effects)



# Creation/Suppression

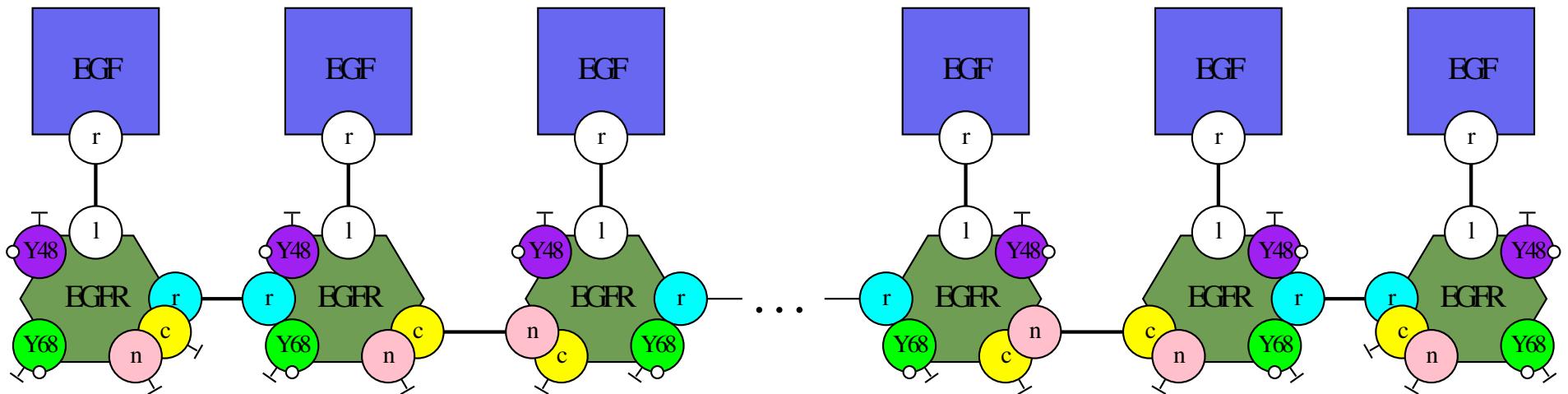


# On the menu today

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# Our goal

We want to prove the absence of unbounded polymers:



# Why?

1. Debugging:

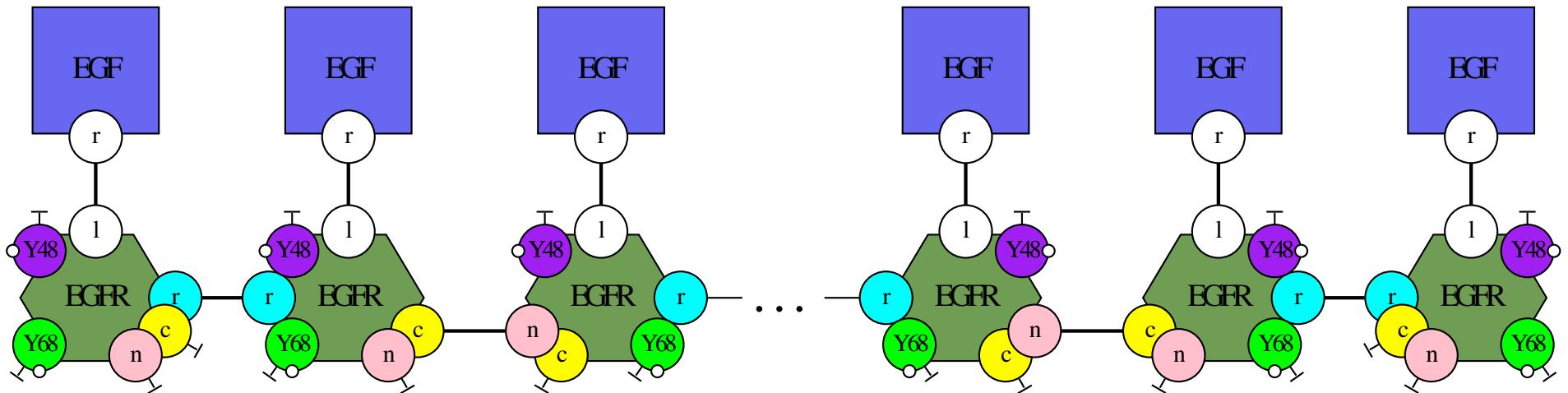
When models come from a more abstract specification language, some conflicts are often forgotten.

2. Understanding the model:

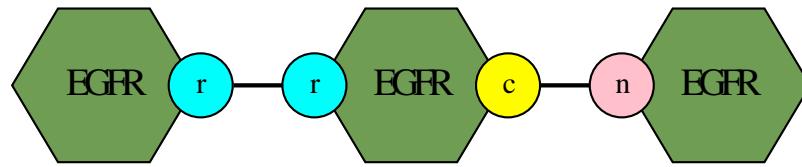
Self-assembling of geant macro-molecules.

# Strengthened goal

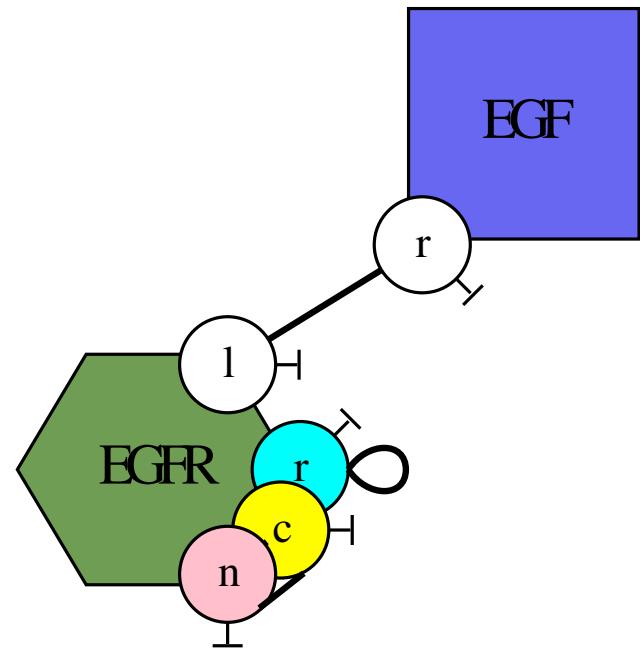
We want to prove the absence of unbounded polymers:



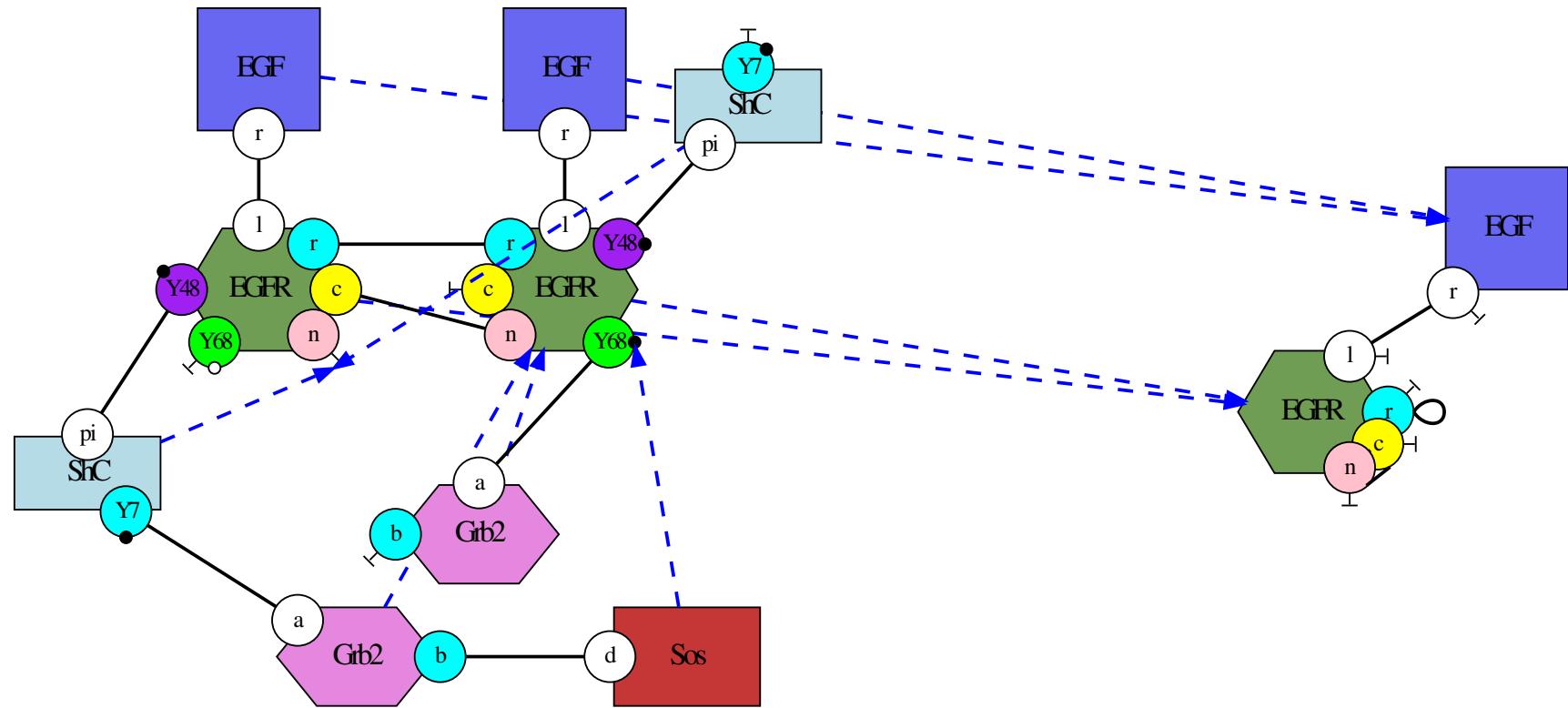
Instead, we will prove the absence of repeatable patterns:



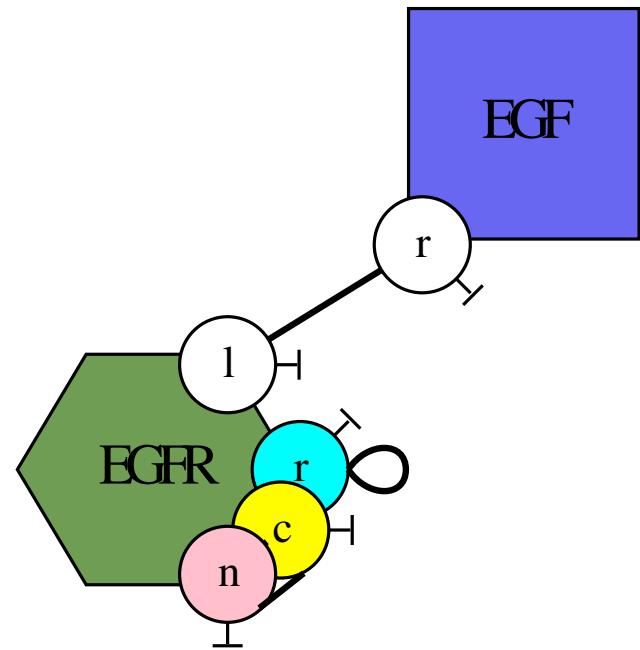
# Interaction map



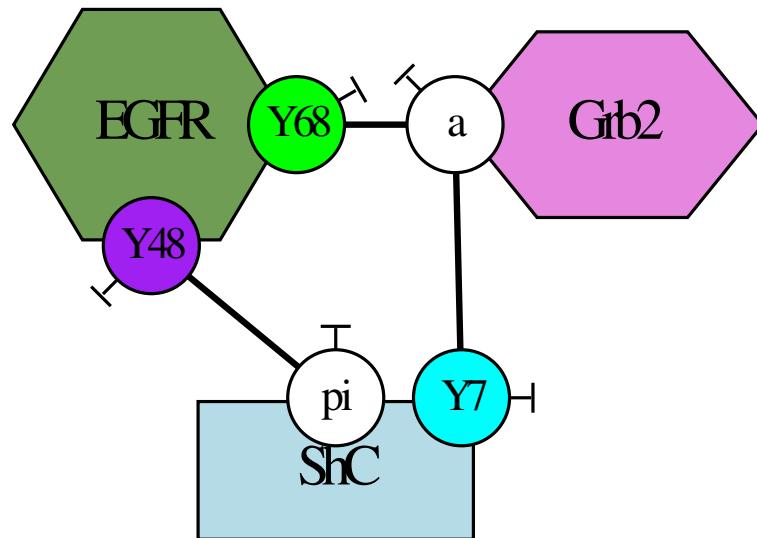
# Interpretation



# Interaction map

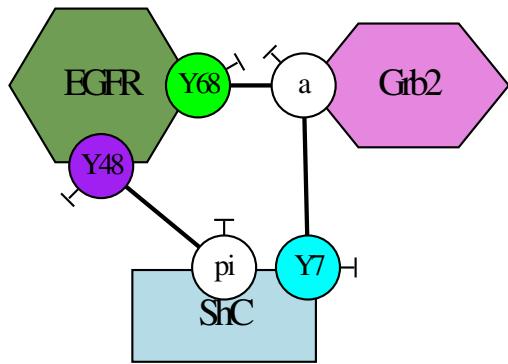


# Conflicts

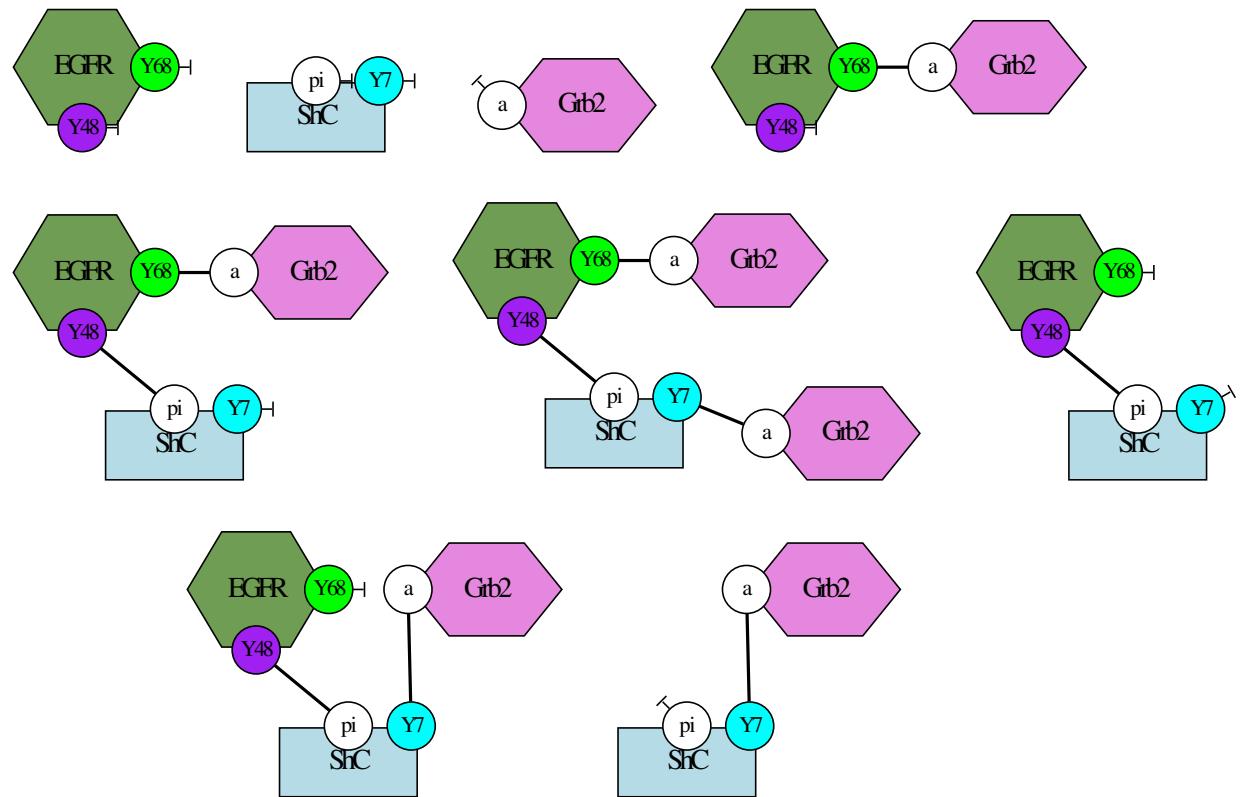


Interaction map.

# Conflicts:



Interaction map.



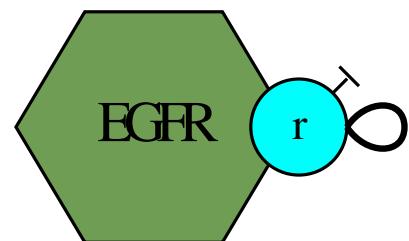
Bio-molecular compounds.

# Alternative encoding

# Alternative encoding

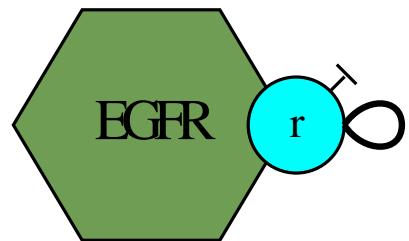
# Alternative encoding

# Self-loops

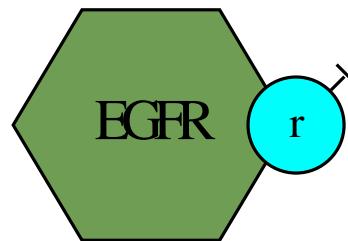


Interaction map.

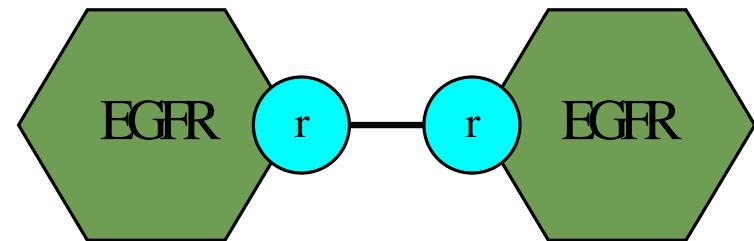
# Self-loops



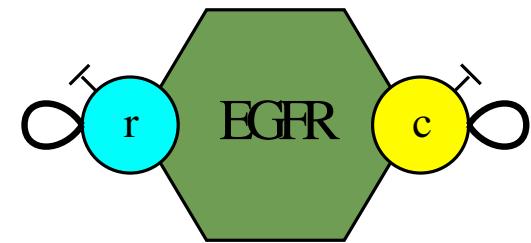
Interaction map.



Bio-molecular compounds.

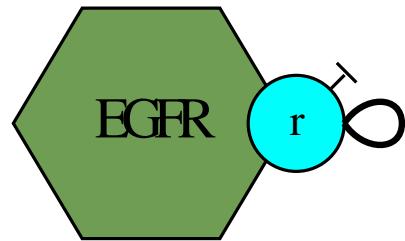


# Several self-loops

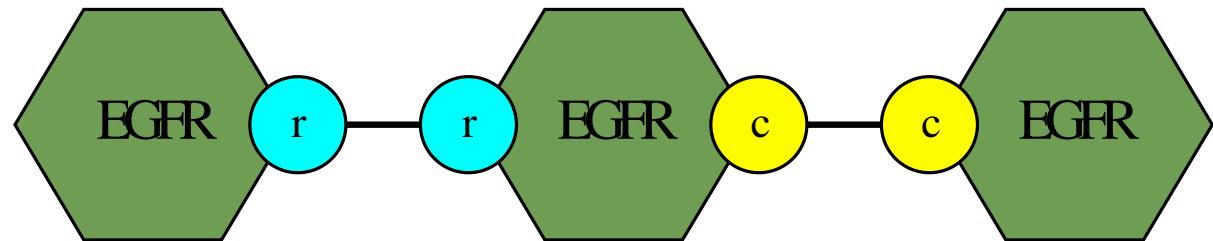


Interaction map.

# Several self-loops

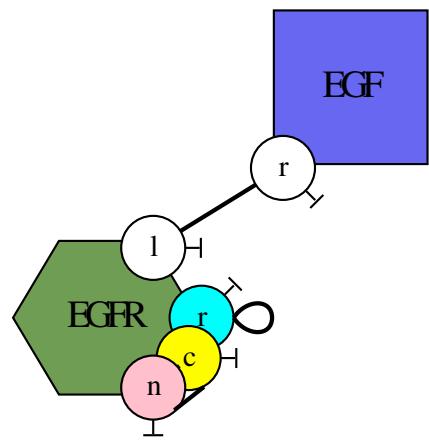


Interaction map.

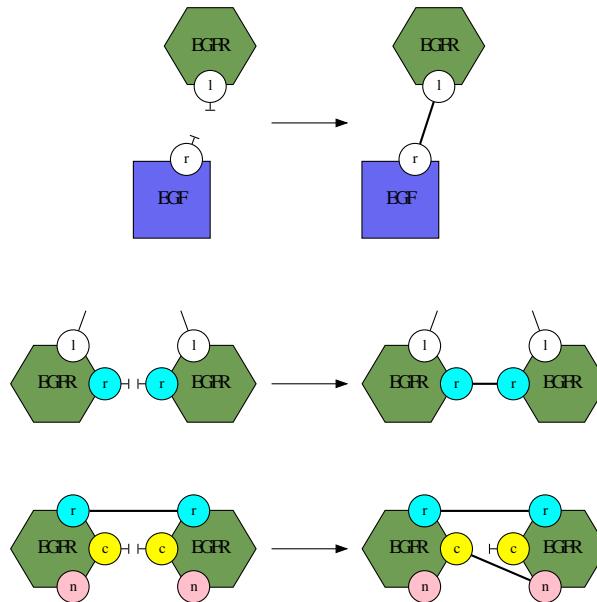


A repeatable pattern.

# Invariants

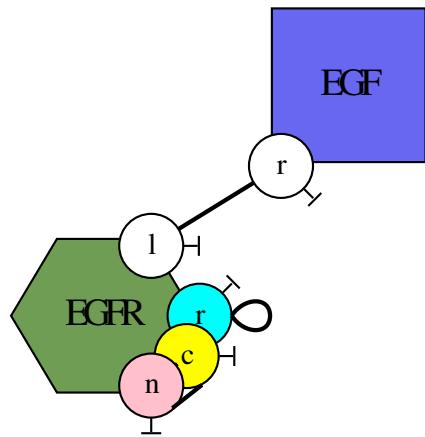


Interaction map.

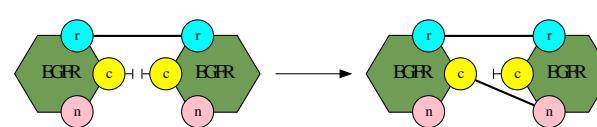
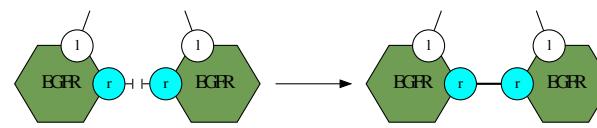
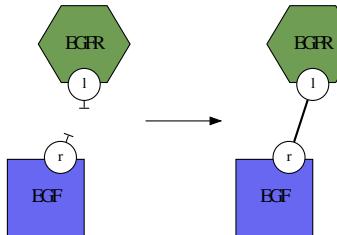


Rules.

# Invariants



Interaction map.



Rules.

The repeatable pattern:



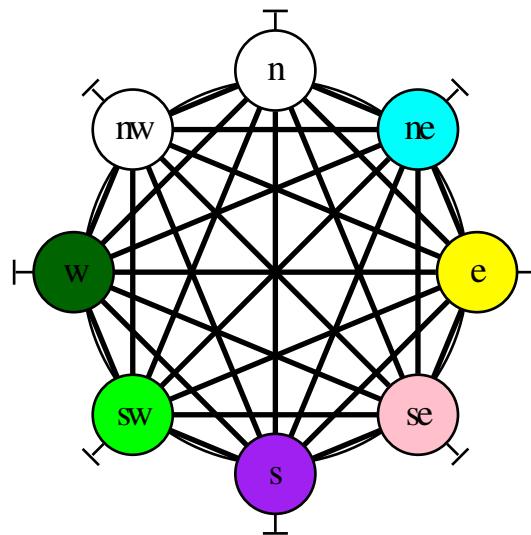
is not reachable.

# Breaking invariants

# Triangle

# Triangle

# Combinatorial complexity



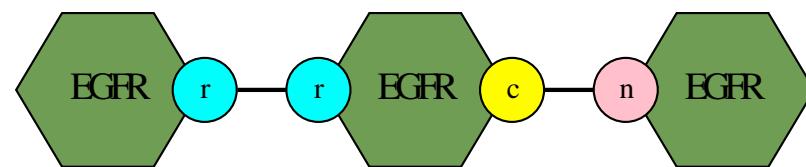
On many model, elementary cycles are too numerous to enumerate them.

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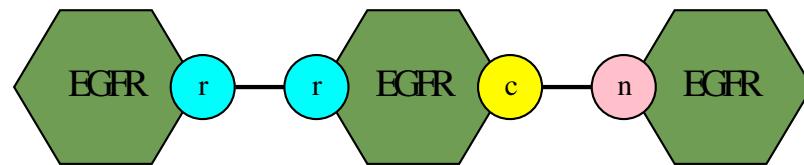
# Repeatable pattern

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

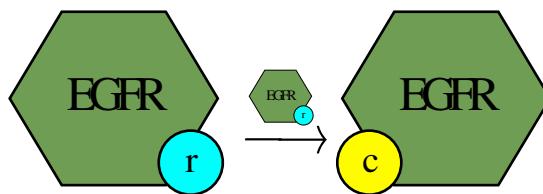


# Transitions between sites

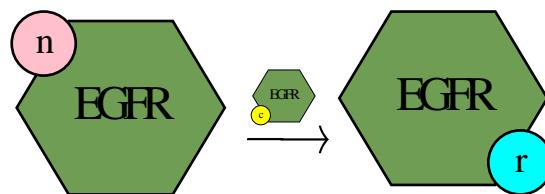
We convert patterns into sequence of transitions, by taking each other site:



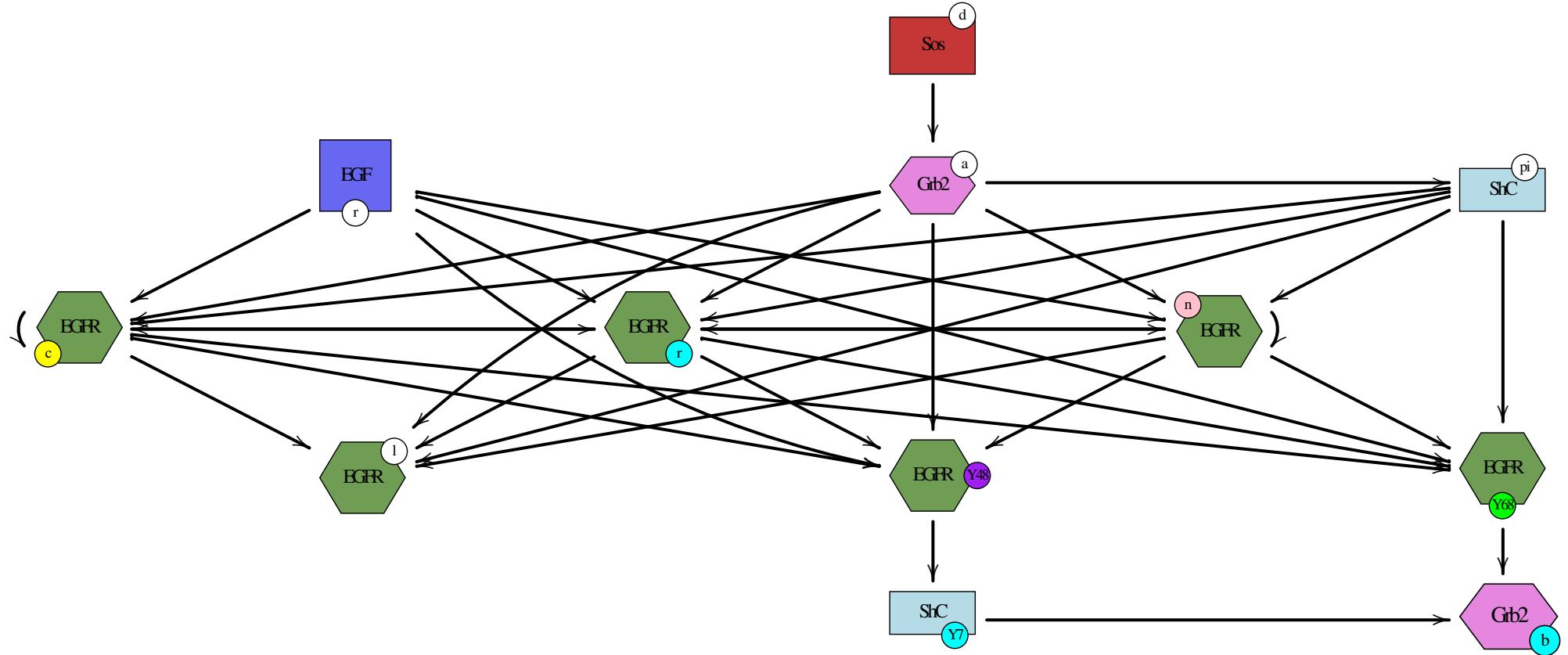
1. From left to right:



2. From right to left



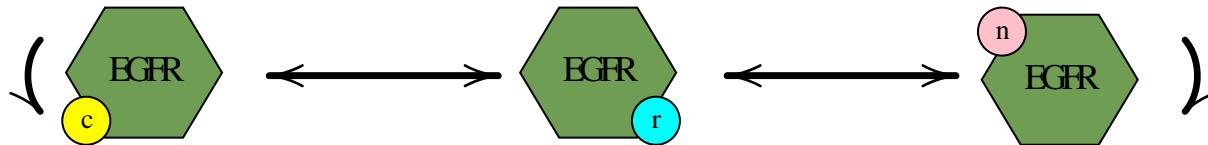
# The graph of the sites



# 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.

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# Repeatable pattern

# Transitions between the edges

# The graph of the links

# Detection of unbounded polymers

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# Issues

# The graph of the links

# Labelled transitions

# Refinement

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