

A Graphical Method For Reducing and Relating Models in Systems Biology

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From Models to Metamodels

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In Systems Biology, models are built with two contradictory perspectives:

- ▶ models for representing knowledge:
the more concrete the better
- ▶ models for making predictions:
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These two perspectives can be reconciled by organizing models in a **hierarchy of models** related by **reduction/refinement relations**.

To understand a system is not to know everything about it, but to know different abstraction levels that are sufficient for answering different questions about it.

State of the Art: Model Repositories

biomodels.net: **plain list of** 241 curated models in SBML format

- ▶ MAPK signaling cascade

009_Huan: three-level cascade of double phosphorylations

010_Khol: *reduced model without dephosphorylation catalysts*

011_Levc: *same model as 009_Huan with different parameter values and molecule names*

027_Mark, 028_Mark, 029_Mark, 030_Mark, 031_Mark:
reduced one-level models with different levels of details

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 - 027_Mark, 028_Mark, 029_Mark, 030_Mark, 031_Mark: *reduced one-level models with different levels of details*
- ▶ Circadian clock:
 - 074_Lelo, 021_Lelo, 170_Weim, 171_Lelo, ...
- ▶ Calcium oscillation: 122_Fish, 044_Borg, 117_Dupo,...
- ▶ Cell cycle: 056_Chen, 144_Calz, 007_Nova, 169_Agud,...

Our Contribution

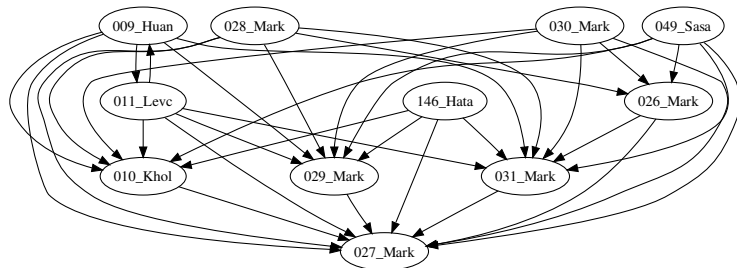
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A graphical method for **inferring model reduction relationships** between SBML models, automatically from the **structure of the reactions**, abstracting from names, kinetics and stoichiometry.

State-of-the-art mathematical methods for model reductions based on kinetics (time/phase decompositions with slow/fast reactions) are far too restrictive to be applicable on a large scale

Example (Hierarchy of MAPK models in biomodels.net computed from the structure of their reactions)

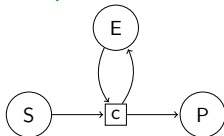


Reaction Graphs

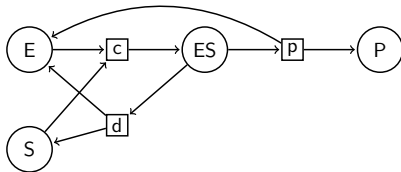
Definition

A *reaction graph* is a bipartite graph (S, R, A) where S is a set of *species*, R is a set of *reactions* and $A \subseteq S \times R \cup R \times S$.

Example $(E + S \rightarrow E + P)$



Example $(E + S \rightleftharpoons ES \rightarrow E + P)$



Model Reductions as Graph Operations

In our setting, a model reduction is a **finite sequence** of four graph reduction operations:

1. **Species deletion**

deletion of one species vertex
with all its incoming/outgoing arcs

2. **Reaction deletion**

idem

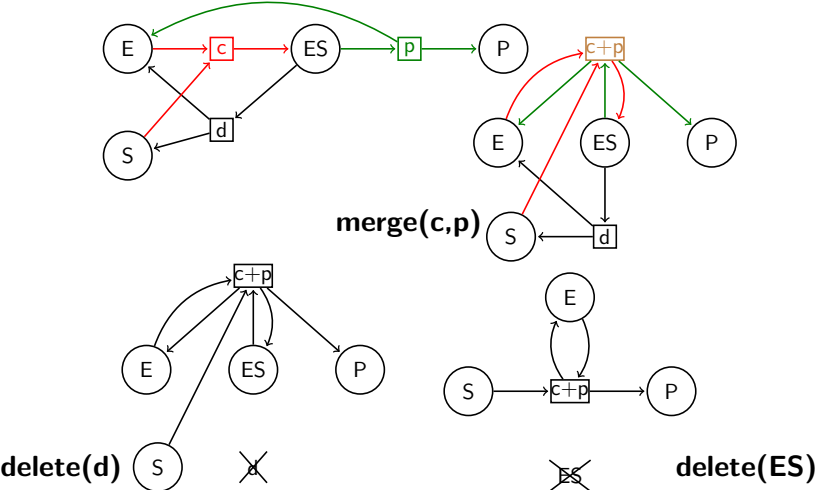
3. **Species merging**

replacement of two species vertices by one species vertex
with all their incoming/outgoing arcs

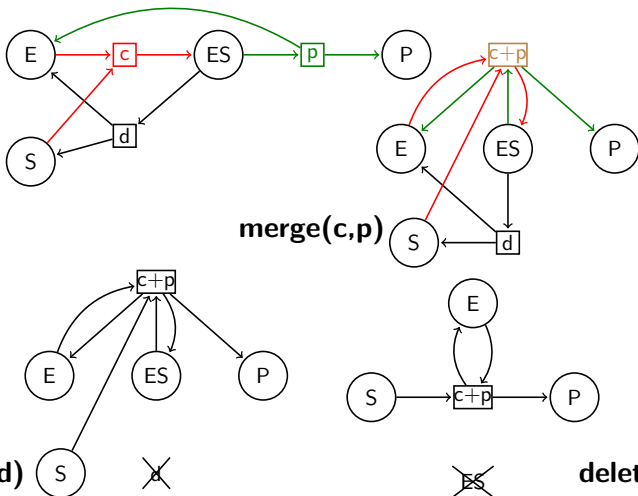
4. **Reactions merging**

idem

Example of the Michaelis-Menten Reduction



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Commutation properties studied in the paper [Bioinformatics 2010]

Subgraph Epimorphisms

Definition

A **subgraph morphism** μ from $G = (S, A)$ to $G' = (S', A')$ is a function $\mu : S_0 \rightarrow S'$, with $S_0 \subseteq S$ such that

- ▶ $\forall (x, y) \in A \cap (S_0 \times S_0), (\mu(x), \mu(y)) \in A'$.

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A **subgraph epimorphism** is a subgraph morphism that is surjective

$$\blacktriangleright \forall x' \in A' \exists x \in A \mu(x) = x',$$

$$\blacktriangleright \forall (x', y') \in A' \exists (x, y) \in A \mu(x) = x' \mu(y) = y'.$$

Theorem

There exists a subgraph epimorphism from G to G' if and only if

there exists a graphical reduction from G to G' (by species/reactions deletions and mergings)

Model Reductions as Subgraph Epimorphisms

Example (Michaelis-Menten reduction)

Subgraph epimorphism:

$$E \rightarrow C$$

$$S \rightarrow A$$

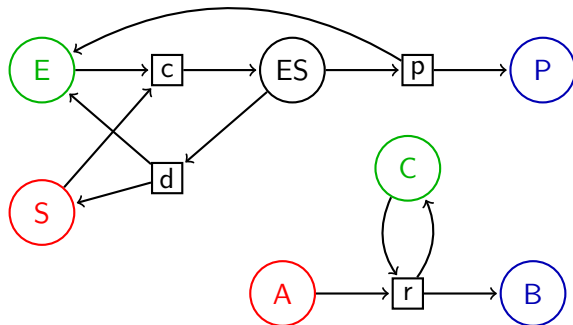
$$P \rightarrow B$$

$$c \rightarrow r$$

$$p \rightarrow r$$

$$d \rightarrow \perp$$

$$ES \rightarrow \perp$$



Equivalent to the graphical reduction:

merge(c,p), delete(d), delete(ES)

Implementation in Constraint Logic Programming

Constraint model:

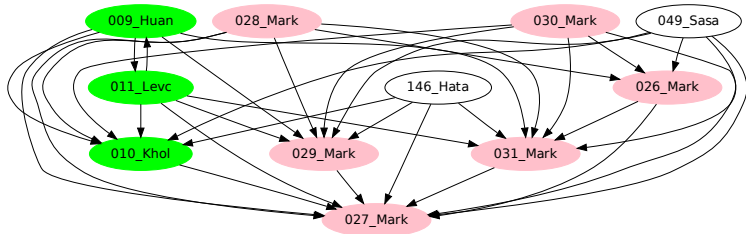
- ▶ variable X_u for each vertex $u \in V$ with domain $V' \cup \{\perp\}$
- ▶ morphism requirement (arc preservation) implemented with **relation** constraint $(X_u, X_v) \in A'$ for $(u, v) \in A$
- ▶ the surjectivity constraint is implemented with antecedent variables $\mathbf{A}_v = \mathbf{u} \Leftrightarrow \mathbf{X}_u = \mathbf{v}$
- ▶ Redundant constraint **all_different**($\{A_i\}$)

Enumeration strategy:

- ▶ on antecedent variables $\{A_i\}$
- ▶ before vertex variables $\{X_j\}$
- ▶ variables with least domain size first

Implemented in GNU-Prolog <http://gprolog.inria.fr>

MAPK Hierarchy

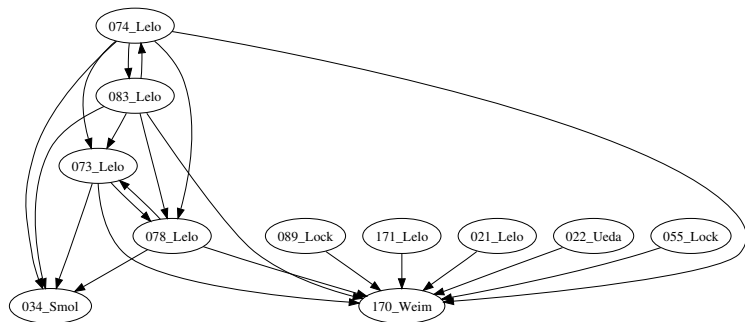


Models 009 (Huang 1996), 010 (Kholodenko 2000) and 011 (Levchenko 2000) are **three-level cascade models**.

Models 026 to 031 (Markevitch 2004) are **one-level**.

Model 049 (Sasagawa 2005) is a larger model (216 reactions), some computations timed out.

Circadian Clock Models Hierarchy

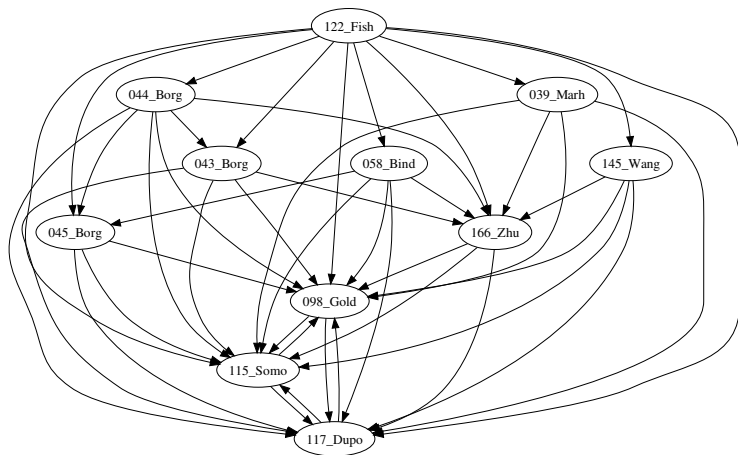


Models 073, 078 isomorphic [Leloup et al. 03) different parameter values.

Models 074, 083 isomorphic, refinement with ErvErb_α

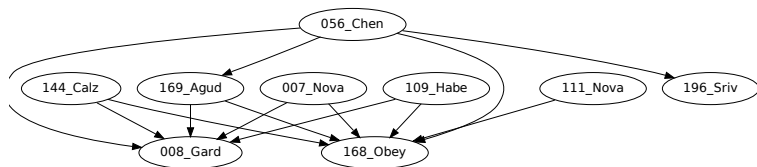
Models 021, 171 same but different encodings in SBML (functions vs species)

Calcium Oscillation Models Hierarchy



Models 098, 115, 117 are very small two-species oscillators.
Model 122 (Fisher et al. 2006) NFAT, NF κ B and side calcium oscillation.

Cell Cycle Models Hierarchy



Not satisfactory: these ODE models have been transcribed in SBML without writing all reactants in the reaction rules

Species eliminated by conservation laws are encoded in the kinetics and not visible in the rules

Events (cell division) are not reflected in the reaction graph.

Conclusion

Purely structural model reduction method that correctly identifies model reduction relationships in `biomodels.net` (as long as the SBML rules do not omit species hidden in the kinetic expressions)

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- ▶ NP-complete problem but efficient constraint logic program to solve it on real-size models
- ▶ Implemented in Biocham 3.0
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- ▶ New method for **querying model repositories** by the structure of the models

On-going work

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- ▶ Rewriting of cell cycle models in SBML to better reflect their dynamics in the structure of the rules.
- ▶ Evaluation of the subgraph epimorphism concept to compare other networks
- ▶ Maximum common epimorphic subgraph (model intersection)
Minimum common epimorphic supergraph (model union)
- ▶ Finding mathematical conditions on the kinetics for the graph reduction operations:
 - ▶ species deletions for species in excess
 - ▶ reaction deletions for slow reverse reactions
 - ▶ species mergings for fast equilibria (QSSA)
 - ▶ reaction mergings for limiting reactions