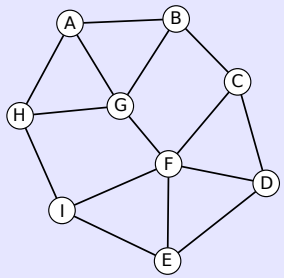
Protein Hypernetworks

Johannes Köster, Eli Zamir, Sven Rahmann

August 20, 2012

Protein Network Modelling

Interaction maps (undirected graphs)



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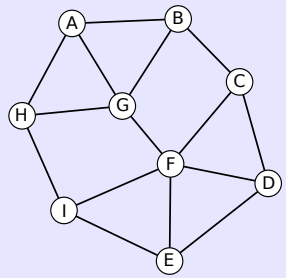

Differential equations (Law of Mass Action), Bayesian Networks, ...

$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = k_{\mathrm{on}}[A][B] - k_{\mathrm{off}}[C]$$

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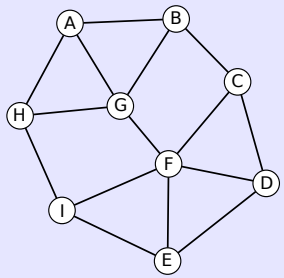

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accuracy ↓

scalability ↑

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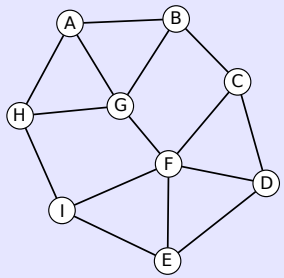

Protein Hypernetworks ?

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Structure

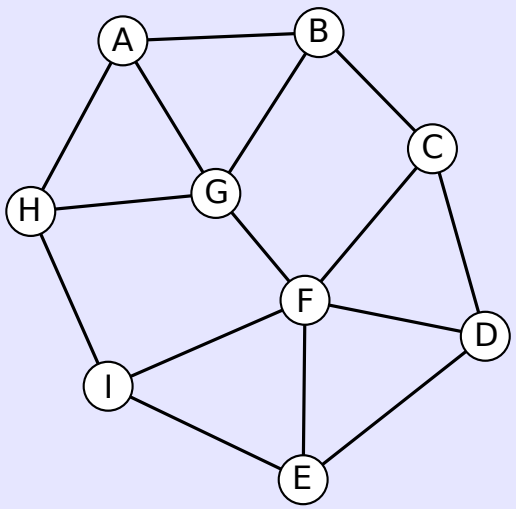
1 Protein Hypernetworks

2 Mining Protein Hypernetworks

3 Data Aquisition

Idea

Protein Network (P, I)



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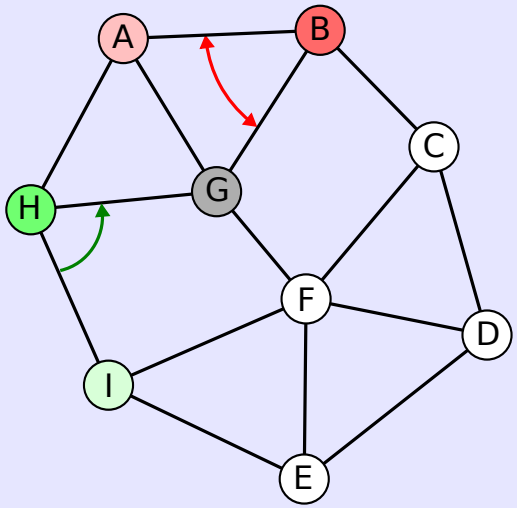
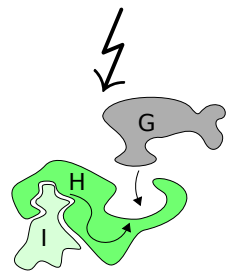
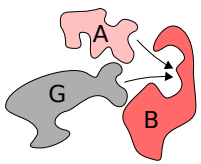


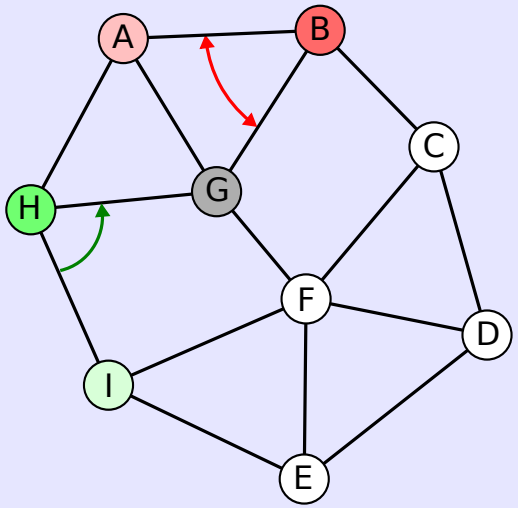


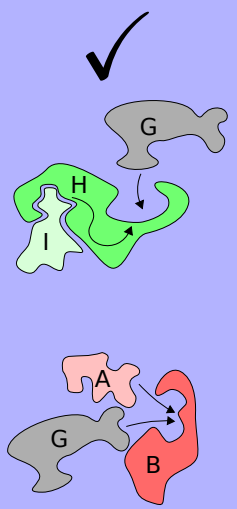


Idea

Protein Hypernetwork (P, I, C)

Protein Network (P, I)





Boolean Logic Constraints C

$$\{G, H\} \Rightarrow \{I, H\}$$

$$\{A, B\} \Rightarrow \neg\{G, B\}$$
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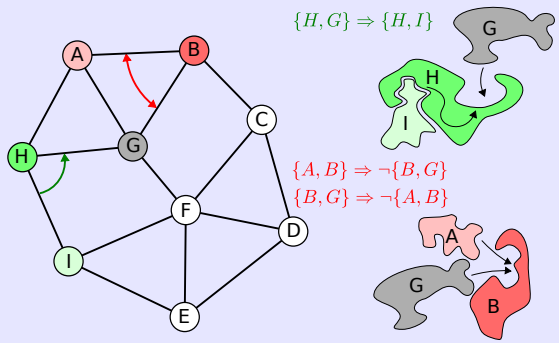
Mining Protein Hypernetworks

Protein Hypernetwork (P, I, C)



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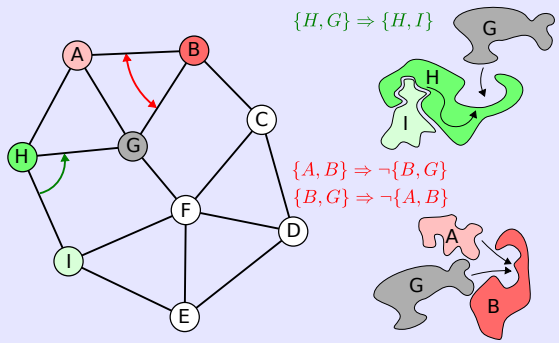
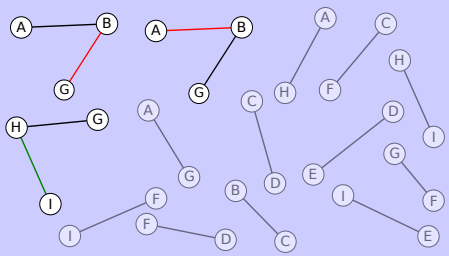


Minimal network states (Nec, Imp) for $q \in P \cup I$

$$q \wedge \bigwedge_{c \in C} c$$



- Satisfying model $\alpha : P \cup I \to \{0, 1\}$ by tableau algorithm

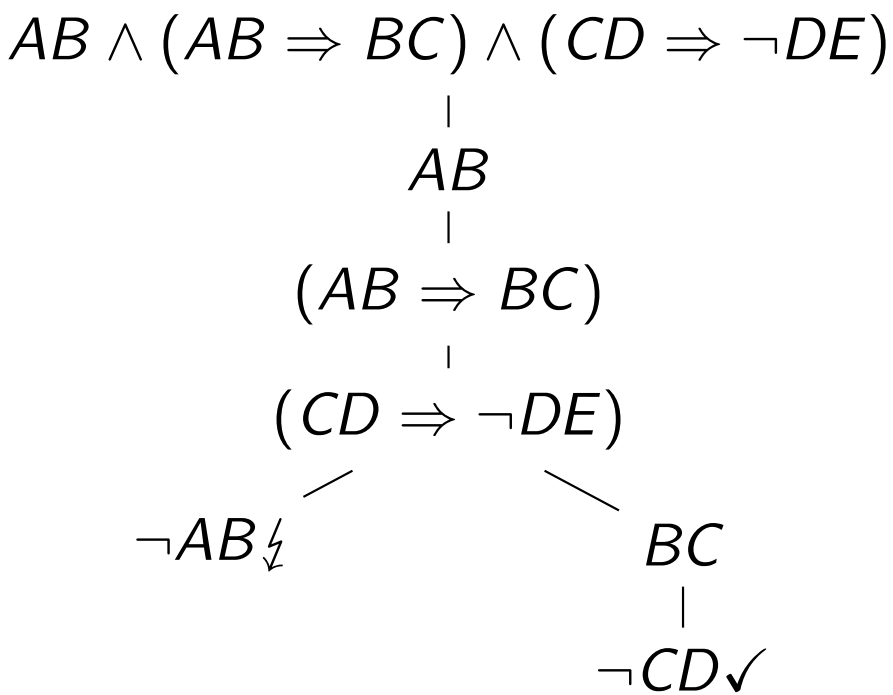
$$Nec := \{q' \in P \cup I \mid \alpha(q') = 1\}$$
$$Imp := \{q' \in P \cup I \mid \alpha(q') = 0 \text{ due to active } c \in C\}$$

Tableau Algorithm

Propositional Logic Tableau Algorithm

for a given formula f

- explore depth-first the tree of deductions from root f
- each root-leaf-path without contradiction is a satisfying model



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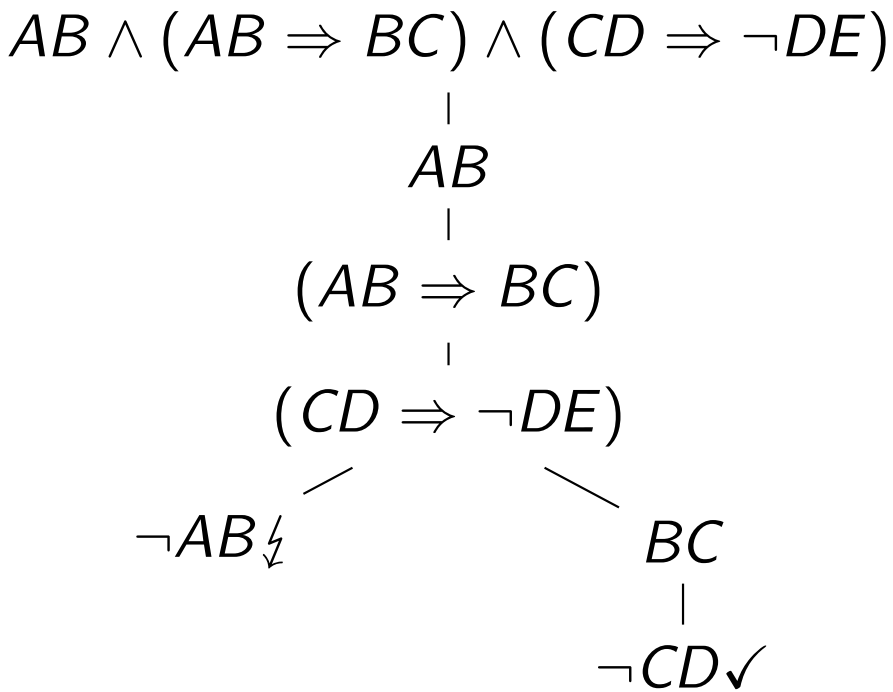
Modifications

- expand disjunctions from left to right
- allow to pre-block subformulas to guide the algorithm to the right model



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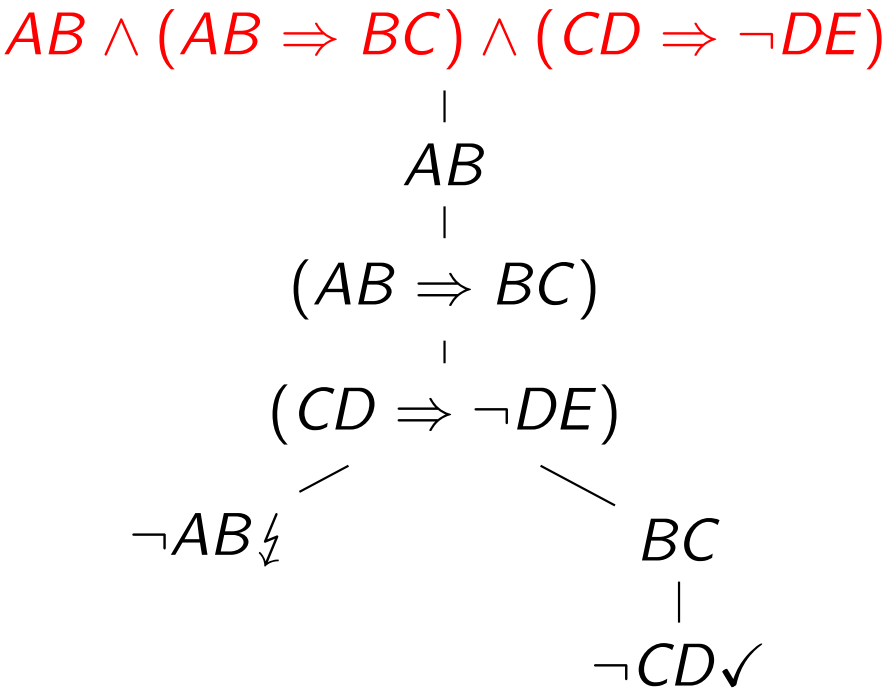

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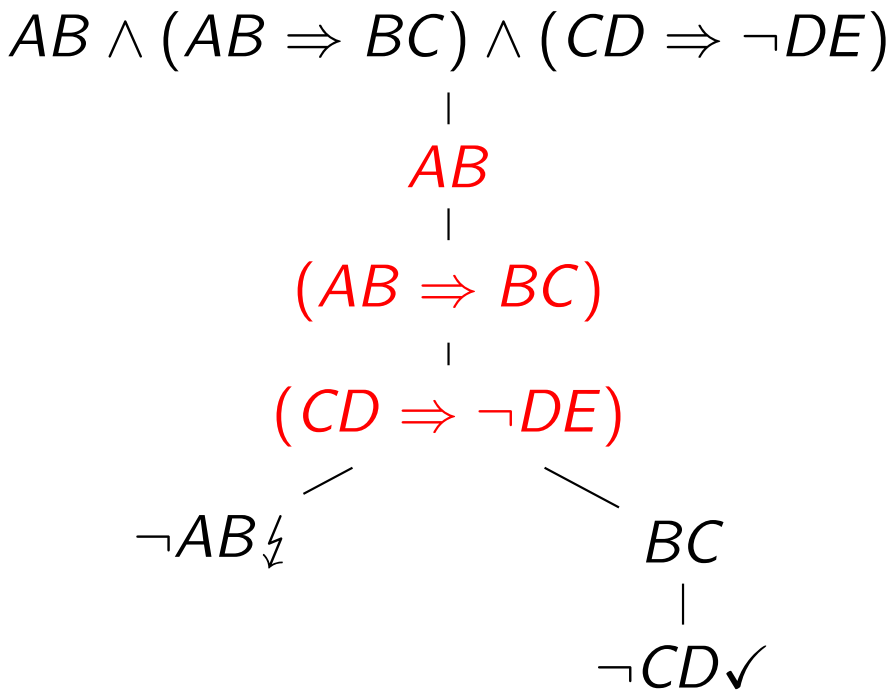

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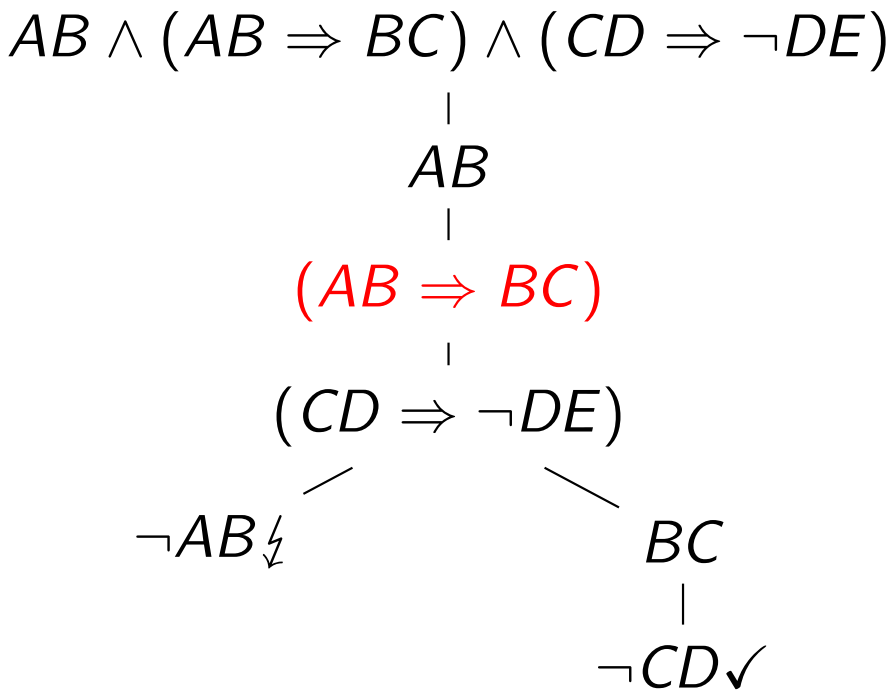

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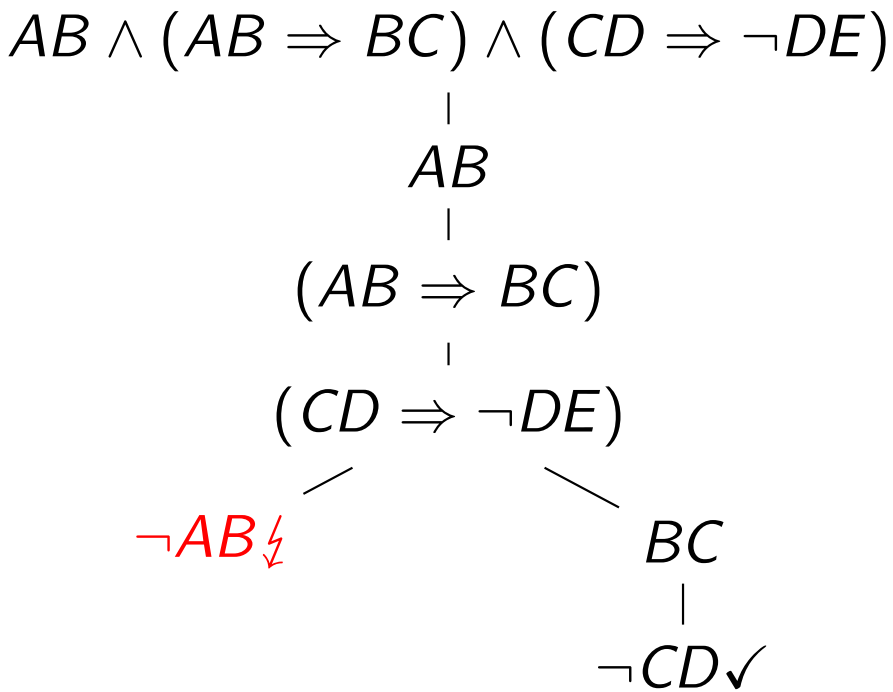

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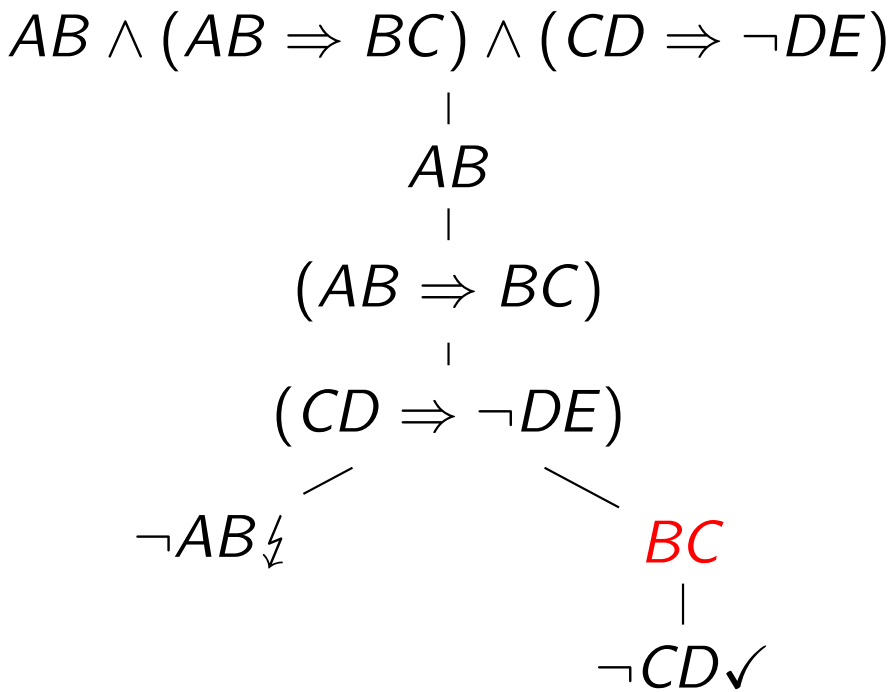

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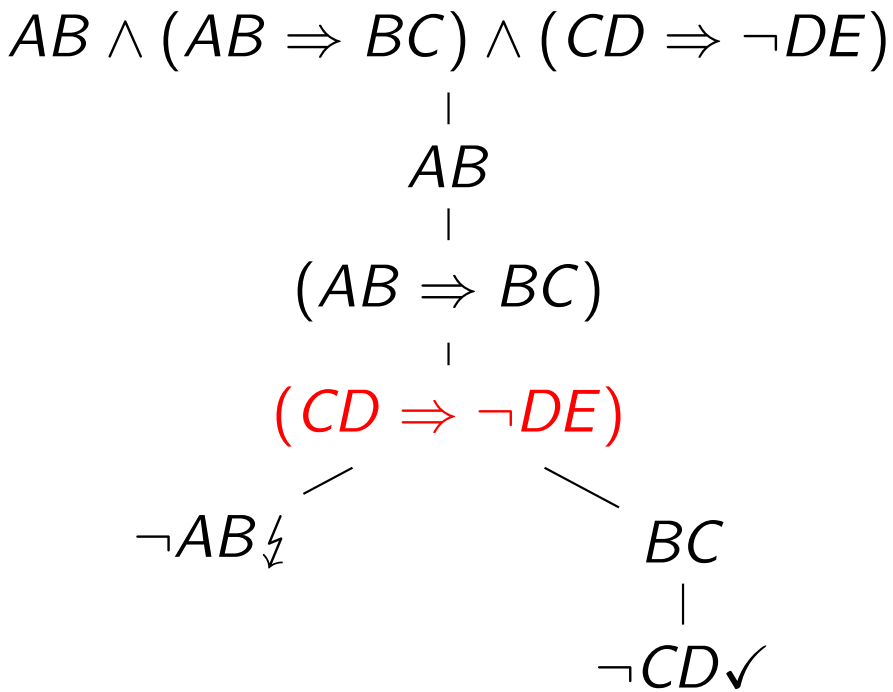

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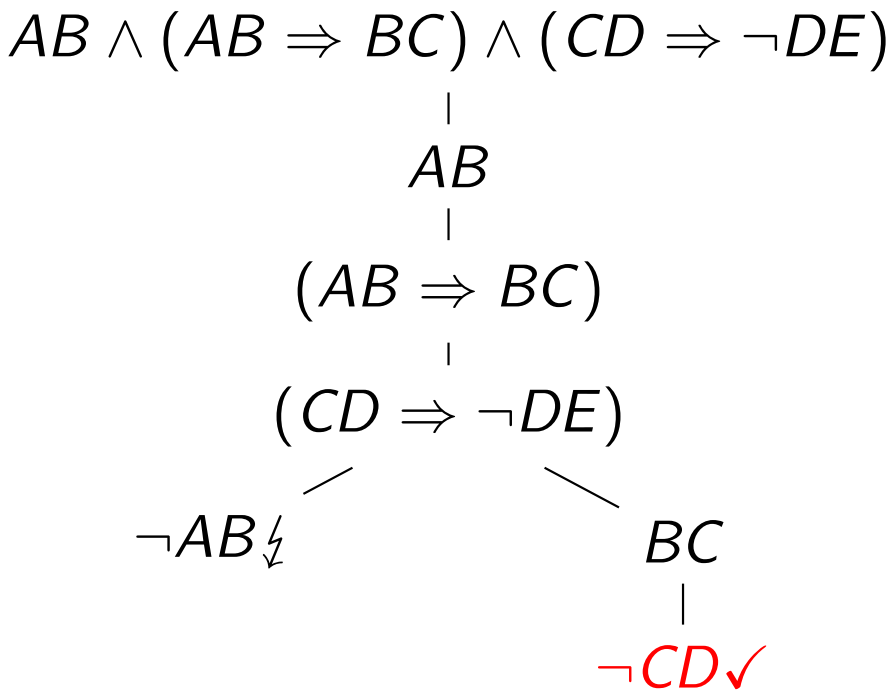

Minimal Network States

Clashes

Two minimal network states (Nec, Imp) and (Nec', Imp') are clashing iff

$$Nec \cap Imp' \neq \emptyset \text{ or } Nec' \cap Imp \neq \emptyset.$$

not clashing pair $\rightarrow$ interactions simultaneously possible

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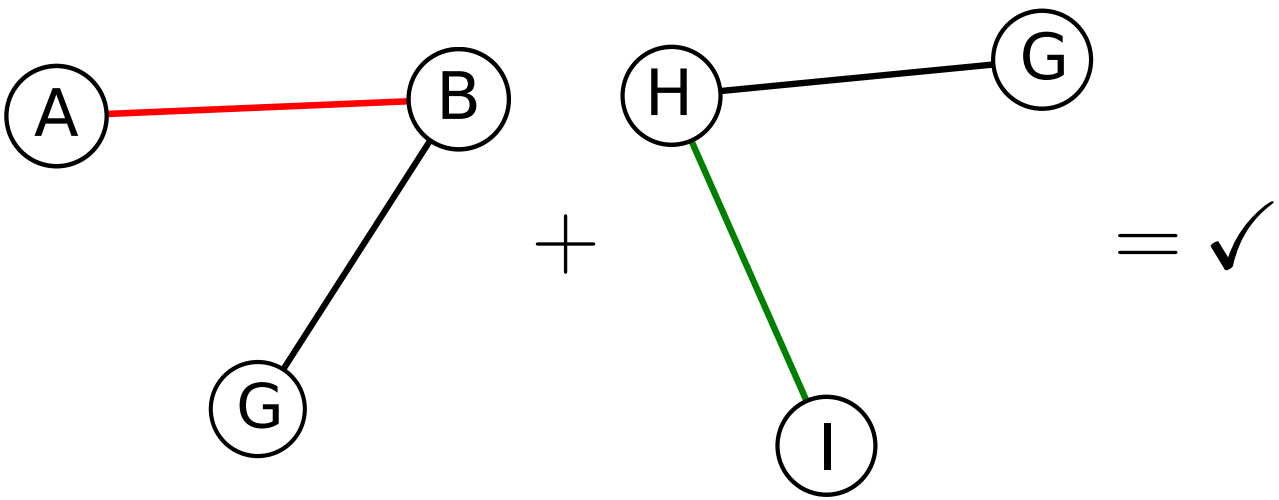

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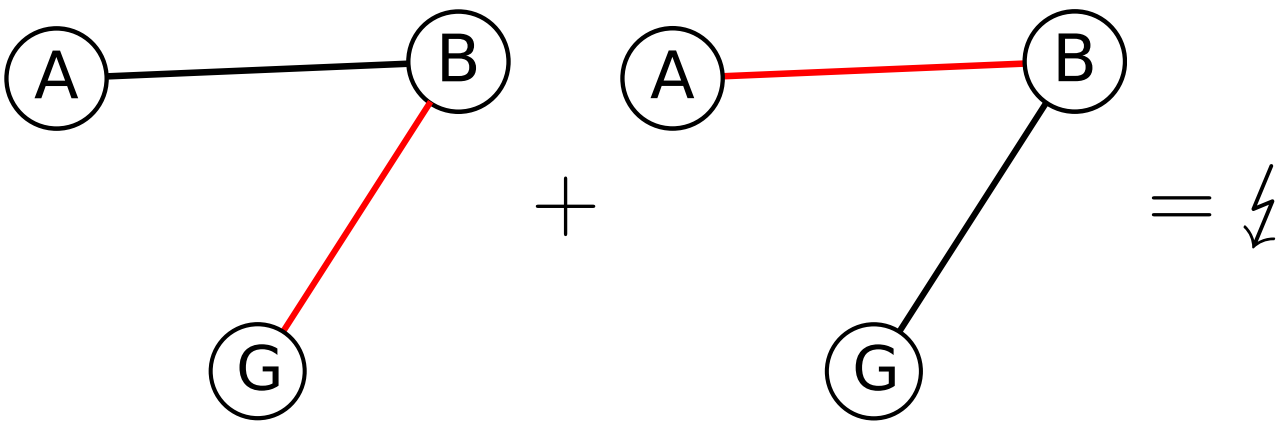
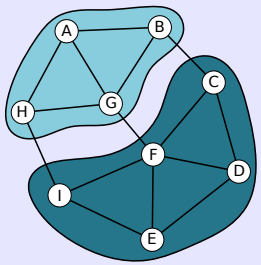


Prediction of Protein Complexes

Network based complex prediction

- e.g. dense regions



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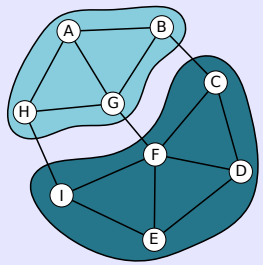
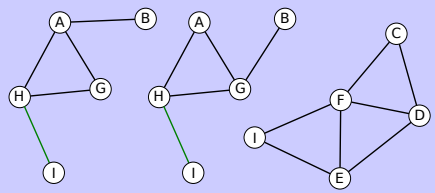


Maximal combinations of minimal network states



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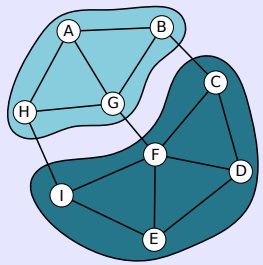

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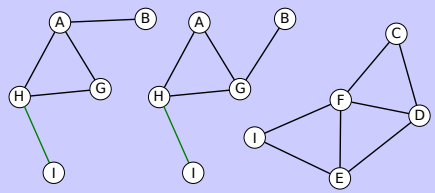
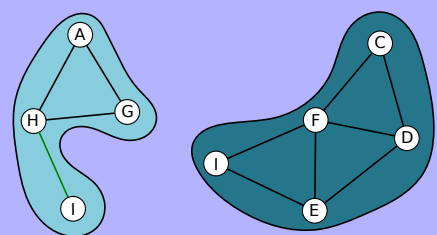


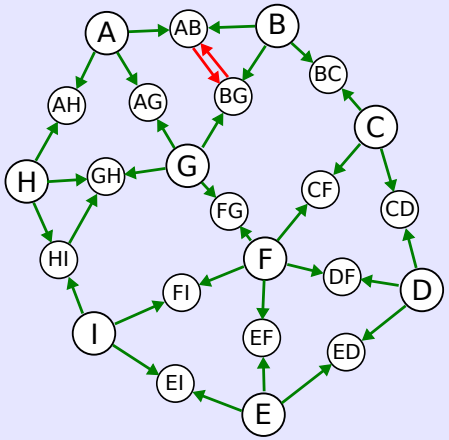
Refined complexes

- no violated constraints



Prediction of Functional Importance

Minimal network state graph



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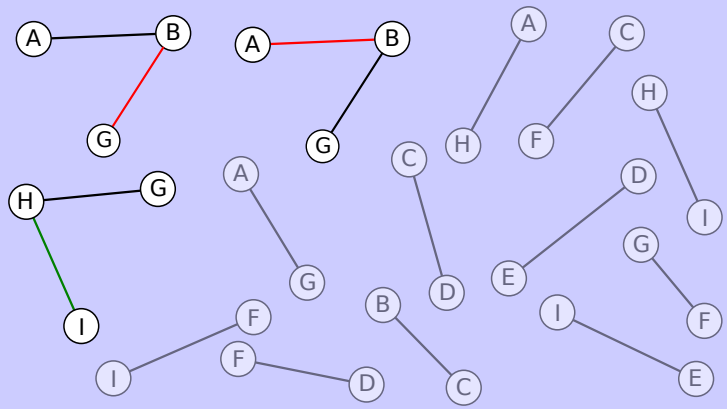

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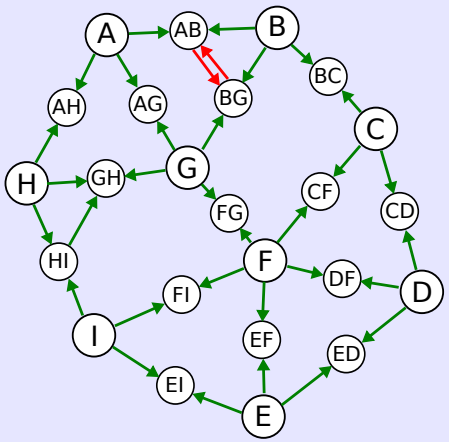
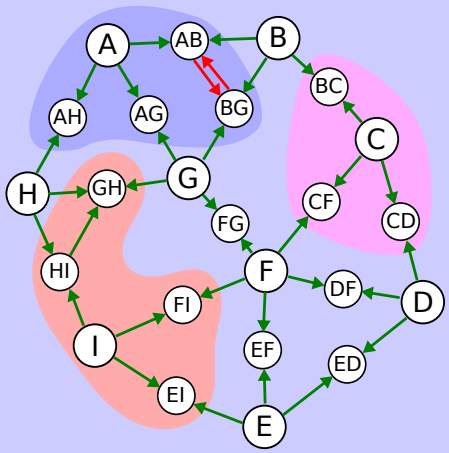


Breadth first search from each node



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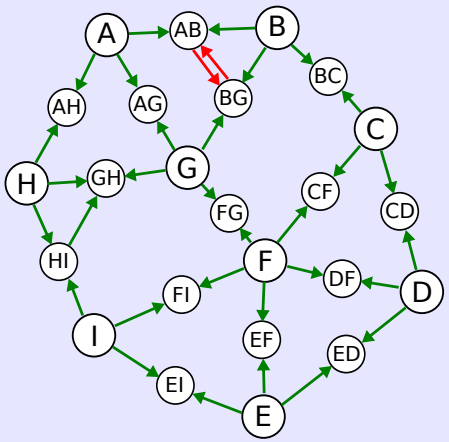

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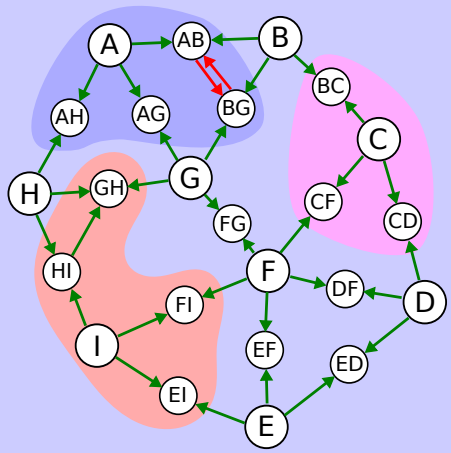


Perturbation Impact Score

$$PIS_{(P,I,C)}(Q_{\downarrow}) := |BFS(Q_{\downarrow})|$$

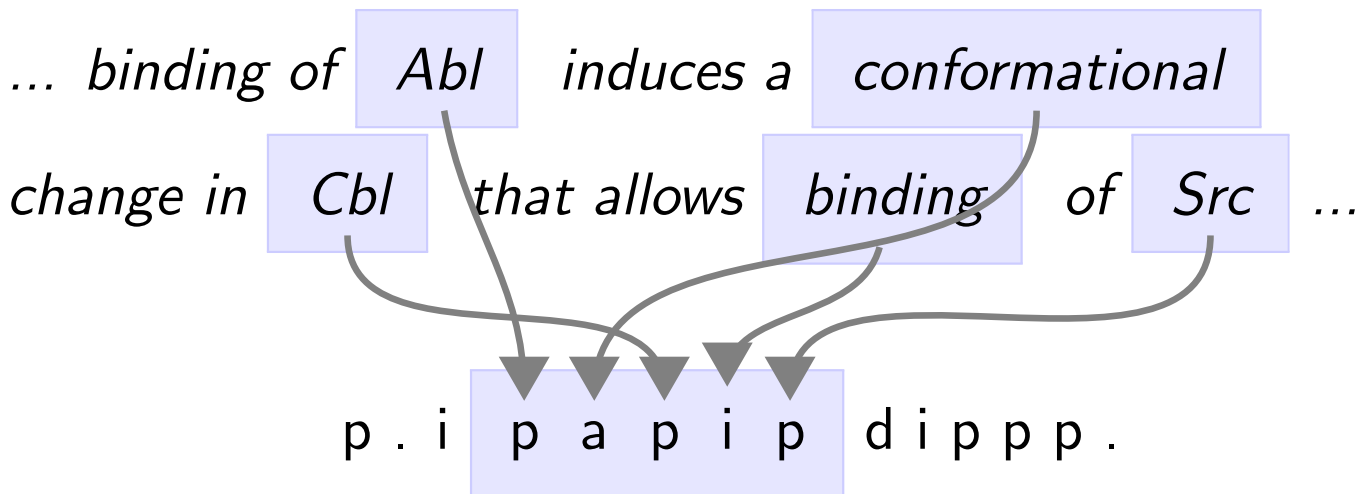
Harvesting Constraints

Text-Mining

- Observation: Interaction dependencies are reported as single sentence natural language statements in literature.
- Tokenize full-text papers into relevant words and search for simple regular expression patterns.

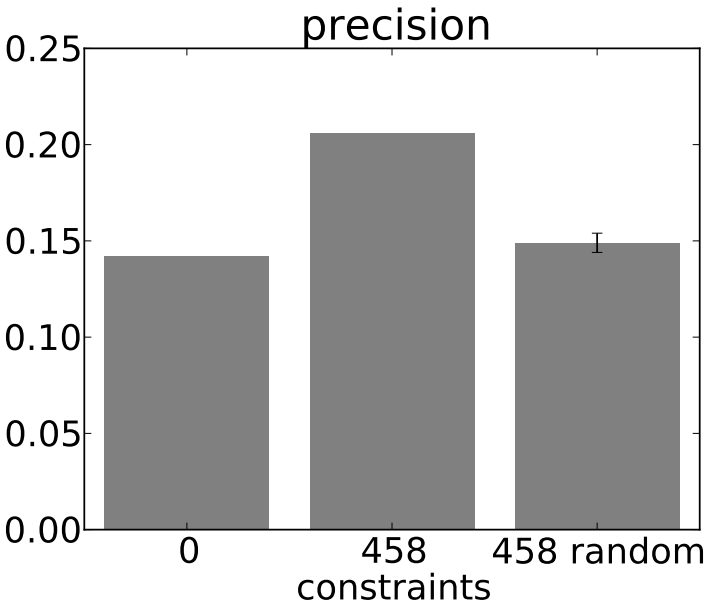
71 new interaction dependencies from 59 000 human adhesome related papers.

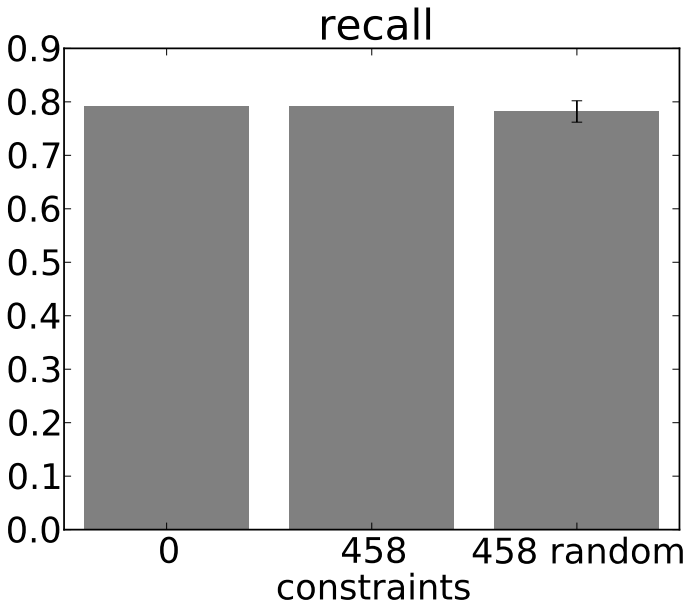
Köster, Zamir, Rahmann. 2012



Results for Complex Predicton

- Network: CYGD (4579 proteins, 12576 interactions)
- Constraints: Competition on binding sites *(Jung et al. 2010)*
- Complexes: CYGD (55 connected complexes)
- Network based complex prediction: LCMA *(Li et al. 2005)*





Results for Perturbation Impact Score

- Network: CYGD (4579 proteins, 12576 interactions)
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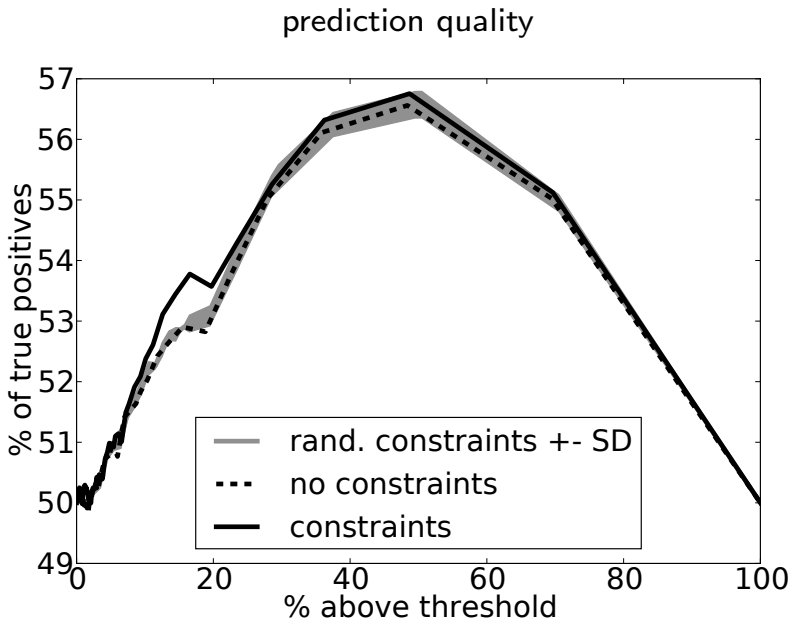
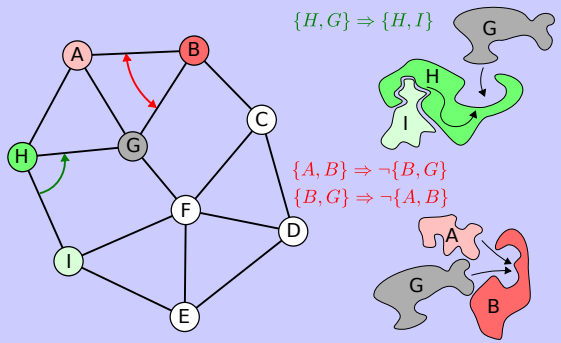
- Perturbations classified as lethal/sick and viable: SGD



TP: lethal/sick and $PIS \geq t$, viable and $PIS < t$

Conclusion

Protein Hypernetworks



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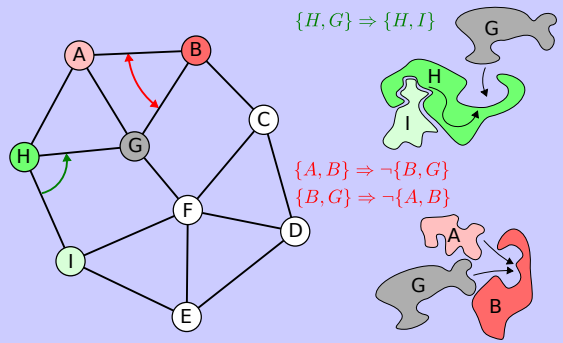


more precise protein complexes

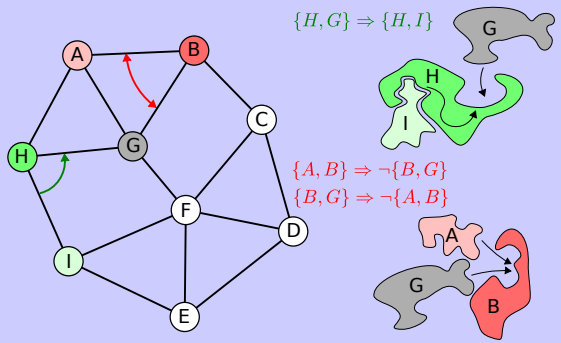
perturbation effects

Conclusion

text-mining

logic inference from real measurements

Protein Hypernetworks



more precise protein complexes

perturbation effects

Harvesting Constraints

Using the Quine-McCluskey-Algorithm

- Given a truth table with interactions in columns and simultaneous observations in rows.
- Infer logic relationships using the Quine-McCluskey-Algorithm.

AB	BC	observed
0	0	1
0	1	1
1	0	1
1	1	0

Inferred constraints:
$AB \Rightarrow \neg BC$

Harvesting Constraints

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derive rows from

- simultaneous interaction measurements (e.g. future variants of FCS)
- combination of protein complex measurements (e.g. MS) with binary protein interactions

AB	BC	observed
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0	1	1
1	0	1
1	1	0

Inferred constraints:
$AB \Rightarrow \neg BC$