# Topology-Free Querying of Protein Interaction Networks

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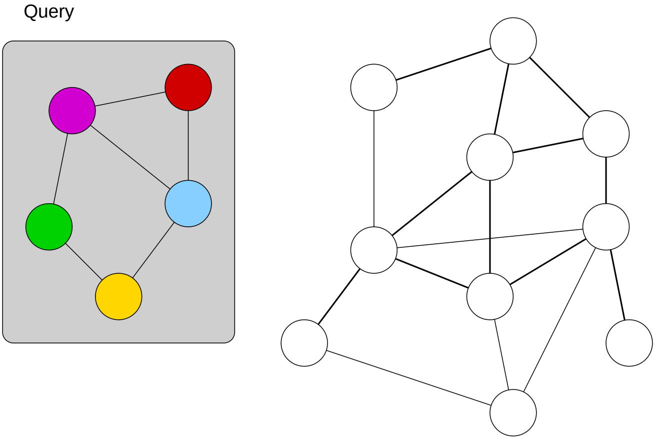
4 May 2009

# Protein complexes

- A protein complex is a group of proteins which interact with each other to perform some task.
- Many protein complexes are known, in particular for model organisms like yeast.
- Problem: does a known protein complex also exists in the protein interaction network of another species?

# Complex query as Constrained Subgraph Isomorphism



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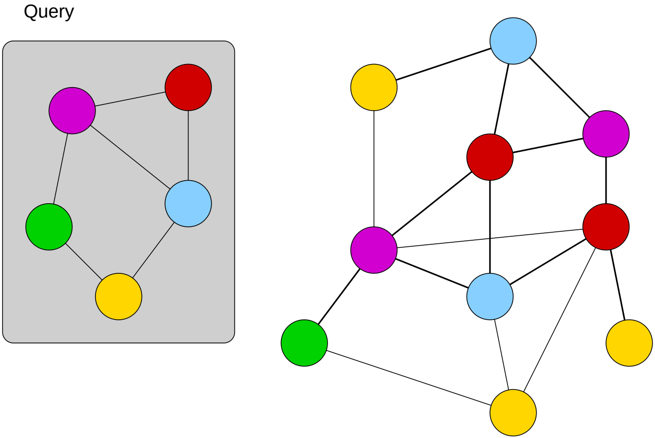

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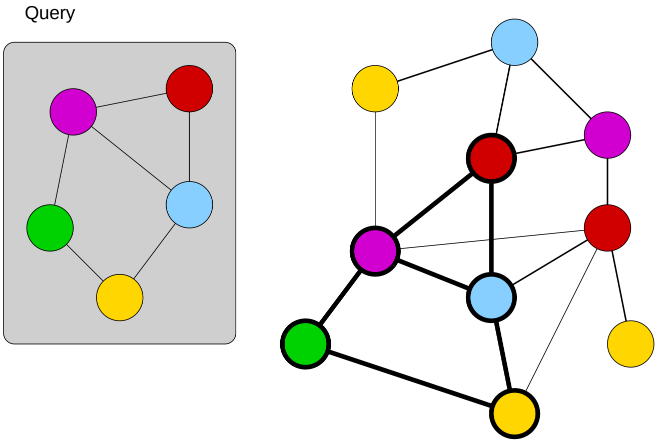
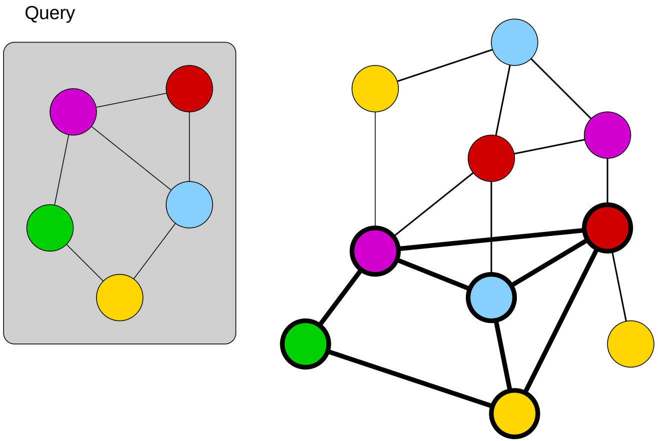


# Complex query as CONSTRAINED SUBGRAPH ISOMORPHISM



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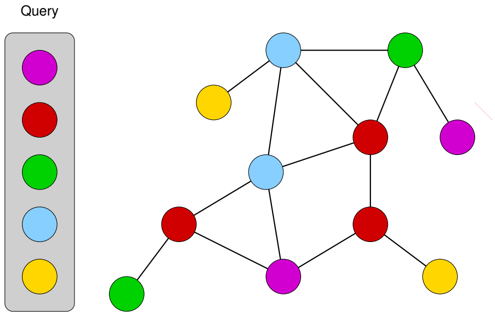
- Interactions between query proteins (*topology*) might not be available
- Computationally very hard

# Complex Query as Colorful Connected Subgraph



### Colorful Connected Subgraph

**Input:** An undirected, vertex colored graph $G$.
**Output:** Find a connected subgraph of $G$ whose vertices use each color exactly once (*colorful subgraph*).

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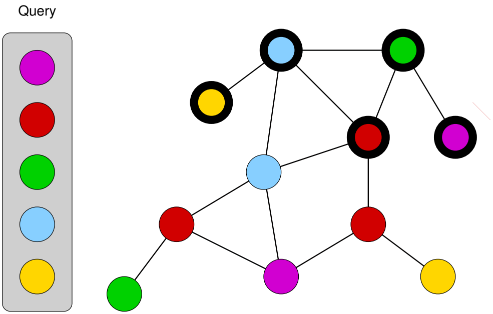

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$T[v, S]$ for $v \in V$ and $S$ a set of colors: true if there is a connected subgraph of $|S|$ vertices containing $v$ with exactly the colors in $S$

$$T[v, S] = \bigvee_{\substack{u \in N(v) \\ S_1 \uplus S_2 = S}} T[v, S_1] + T[u, S_2] + w(u, v)$$

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## Theorem

*Colorful Connected Subgraph with $k$ colors can be solved in $O(3^k|E|)$ time.*

# Fixed-parameter tractability

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### Corollary

Colorful Connected Subgraph *is fixed-parameter tractable with respect to $k$.*

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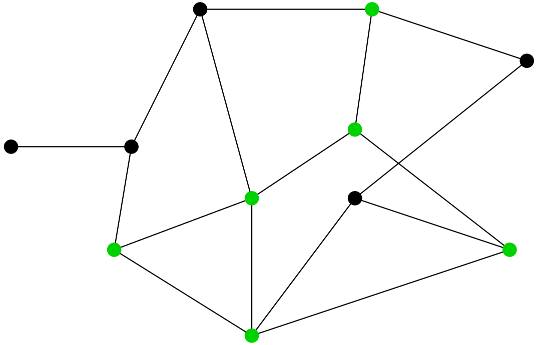
## Central problem

Given a graph $G = (V, E)$ and binary variables $c_v, v \in V$, find linear constraints such that $G[\{v \mid c_v = 1\}]$ is connected.

# Connected Subgraph als ILP

Sufficient: find a directed tree



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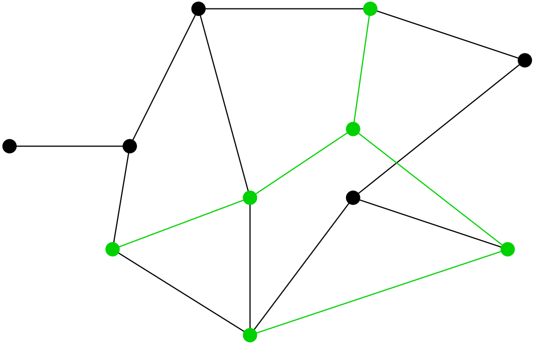

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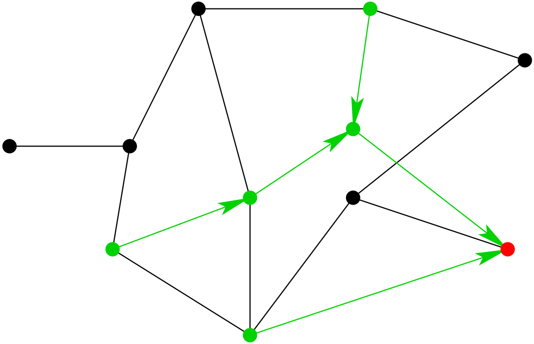

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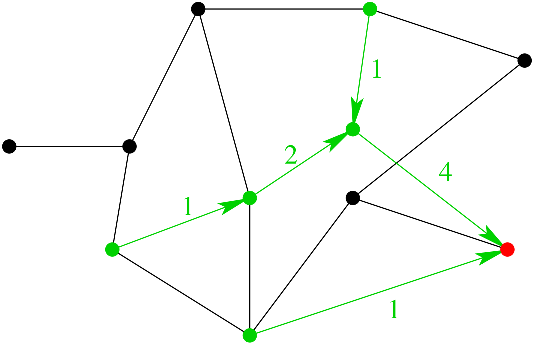

- An (arbitrary) selected vertex servers as sink
- Each other selected vertex is source of a flow of 1
- Only selected vertices take part in flow

# Model extensions

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- Maximize edge weight of complex

# Complete ILP

$$\text{maximize} \sum_{(v,w)\in E} \omega_{vw} e_{vw} \tag{1}$$

subject to

$$\sum_{v\in V} c_v = t \tag{2}$$

$$\sum_{v\in V} r_v = 1 \tag{3}$$

$$e_{vw} \leq c_v \wedge e_{vw} \leq c_w \qquad \forall (v,w) \in E \tag{4}$$

$$e_{vw} \geq 1/2 c_v + 1/2 c_w - 1/2 \qquad \forall (v,w) \in E \tag{5}$$

$$f_{vw} = -f_{wv} \qquad \forall (v,w) \in E \tag{6}$$

$$\sum_{w\in N(v)} f_{vw} = c_v - t r_v \qquad \forall v \in V \tag{7}$$

$$f_{vw}, f_{wv} \leq (t-1) e_{vw} \qquad \forall (v,w) \in E \tag{8}$$

$$\sum_{\gamma\in\Gamma(v)} g_{v\gamma} \leq 1 \qquad \forall v \in V \tag{9}$$

$$\sum_{v\in V} g_{v\gamma} \leq 1 \qquad \forall \gamma \in C \tag{10}$$

$$\sum_{v\in V} \sum_{\gamma\in\Gamma(v)} g_{v\gamma} = t - N_{\text{ins}} \tag{11}$$

$$g_{v\gamma} \leq c_v \qquad \forall v \in V, \gamma \in \Gamma(v) \tag{12}$$

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    - If few colors, but large instance, use dynamic programming
    - Otherwise, use ILP

# Data

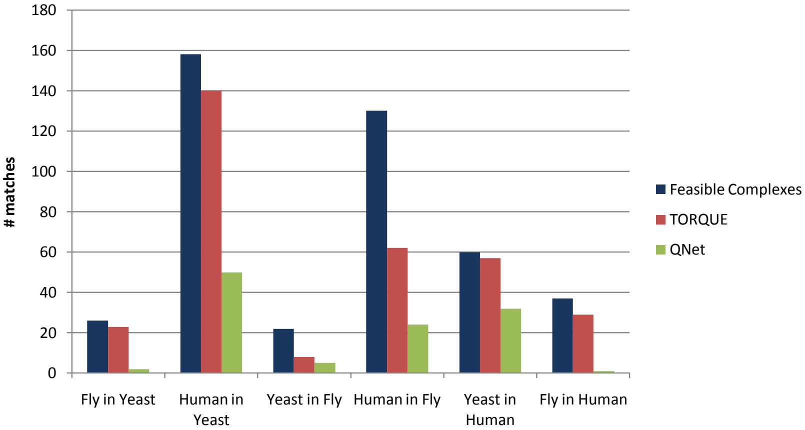
Protein–protein interaction networks:

- yeast (5 430 proteins, 39 936 interactions)
- fly (6 650 proteins, 21 275 interactions)
- human (7 915 proteins, 28 972 interactions)

Query several hundred complexes of size 4–25 from:

- yeast, fly, human (interaction information available)
- bovine, mouse, and rat (not enough interaction information available)

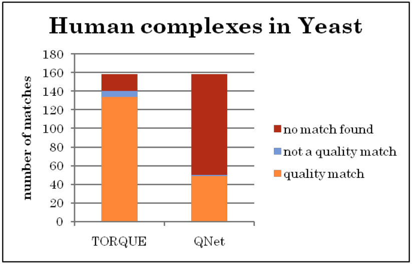
# Number of complexes found

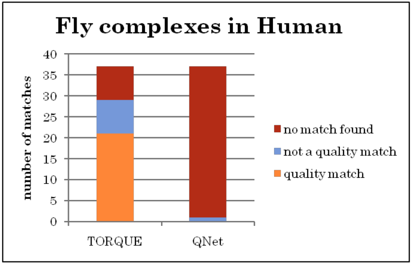


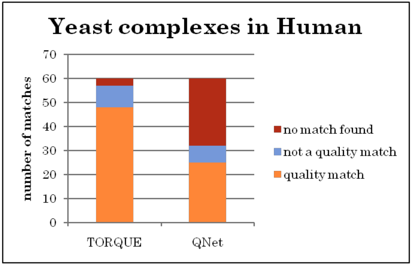
# Evaluation of results

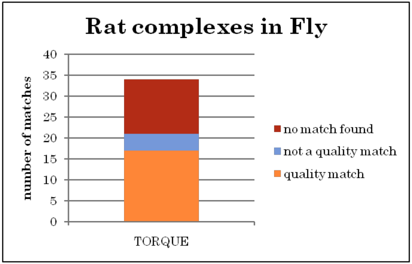
- Functional coherence: Percentage of proposed complexes that are significantly enriched with “GO-Terms”
- Specificity: Percentage of proposed complexes that overlap significantly with known complexes

# Quality of matches

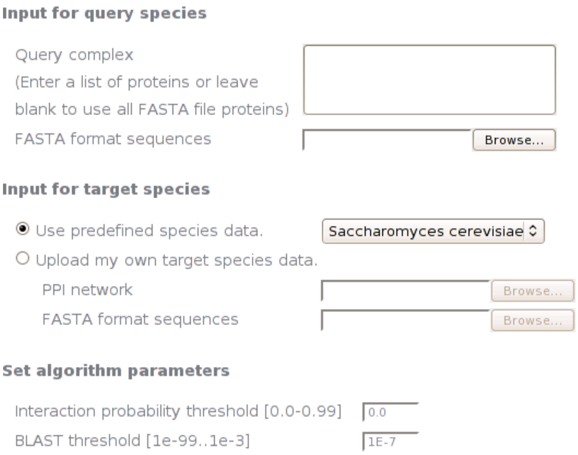








# Torque Web-Server



**Input for query species**

Query complex
(Enter a list of proteins or leave
blank to use all FASTA file proteins)

FASTA format sequences

**Input for target species**

● Use predefined species data. Saccharomyces cerevisiae

○ Upload my own target species data.

PPI network

FASTA format sequences

**Set algorithm parameters**

Interaction probability threshold [0.0-0.99] 0.0

BLAST threshold [1e-99..1e-3] 1E-7

http://www.cs.tau.ac.il/˜bnet/torque.html

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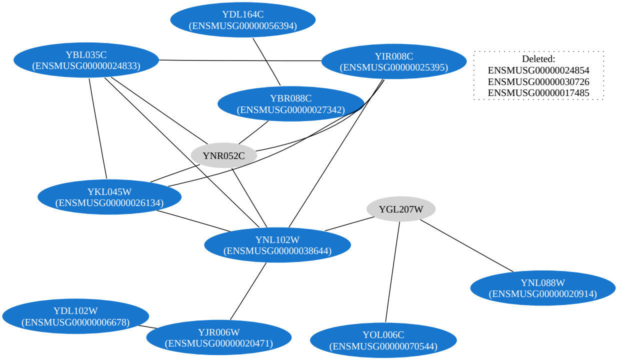

Blue: matched nodes in the target species. Within each node, top: target protein, bottom: the matching query protein.
Grey: insertions of target proteins. The box lists the deleted query proteins, if any.

Best match for the DNA synthesome complex of the mouse in the network of yeast

# Summary

- A topology-free querying model yields significant complex query results.
- With a combination of dynamic programming and ILP, even difficult instances can be solved optimally.