A Graph Modification Approach for Finding Core–Periphery Structures in Protein Interaction Networks

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Protein Complex Identification

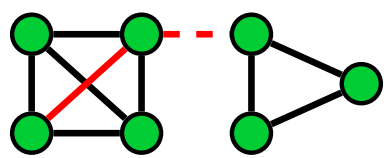
Task: Given a protein interaction network, identify its protein complexes and functional modules

Common assumptions:

- Complexes and functional modules are dense subnetworks
- Functional modules have no or only small overlap

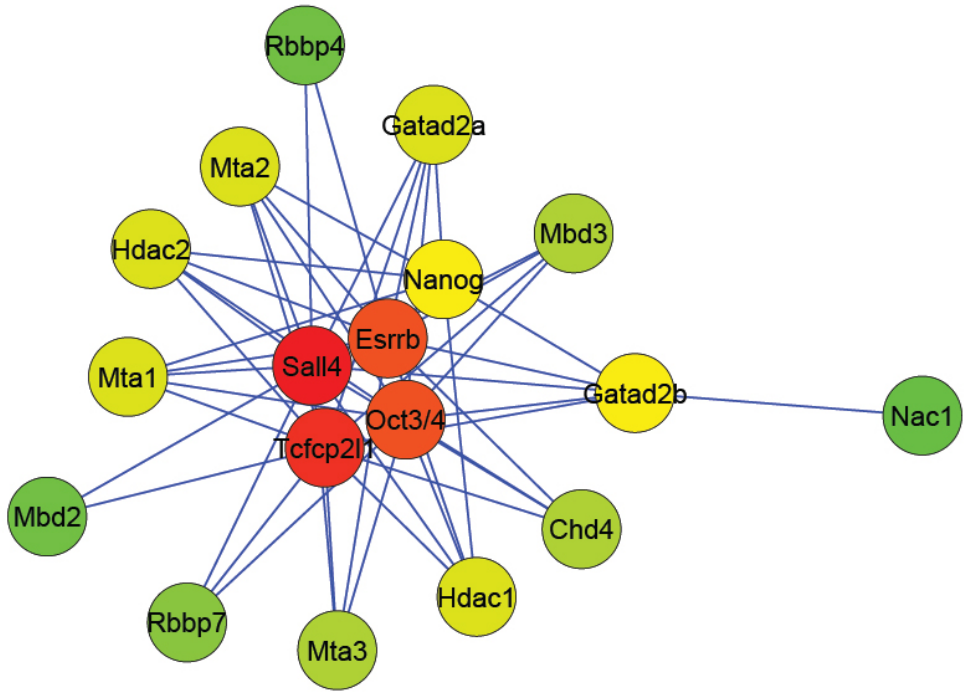
$\rightsquigarrow$ Formulation as graph clustering problem

Cluster Editing
Input: An undirected graph $G = (V, E)$.
Task: Find a minimum-size set of edge deletions and edge insertions that converts the graph into a **cluster graph**, that is, a graph where each connected component is a clique.



Denseness of Complexes and Functional Units

Problem: Functional units are not necessarily dense



Nucleosome remodeling deacetylase (NuRD) complex of *M. musculus* and its interactions with transcription factors

$\rightsquigarrow$

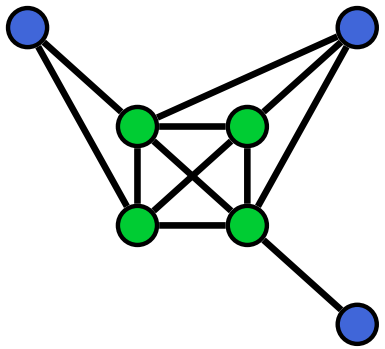
Core–periphery model of protein complexes
[Gavin et al., Nature '06]

Core–Periphery Model

Aim: Uncover global **core–periphery** structure of given PPI network with dense cores and sparse peripheries.

Formalization:

Split graph = can be partitioned into **clique** and **independent set**



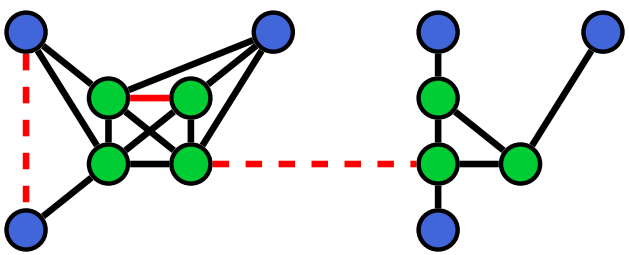
Split cluster graph = every connected component is a split graph

$\rightsquigarrow$

Split Cluster Editing

Input: An undirected graph $G = (V, E)$.

Task: Find a minimum-size set of edge deletions and edge insertions that converts the graph into a **split cluster** graph.



Shared Peripheries

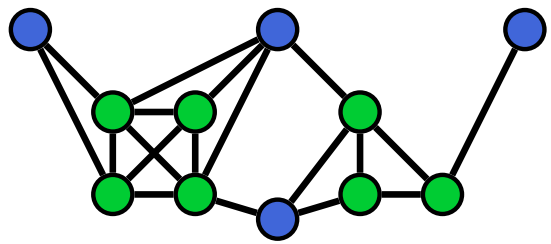
So far:

- Complexes and functional modules
  ~~are dense subnetworks~~ have core–periphery structure
- Functional modules have no or only small overlap

Now: allow overlap but only in peripheries $\rightsquigarrow$

Monopolar graph = can be partitioned into **cluster graph** and **independent set**

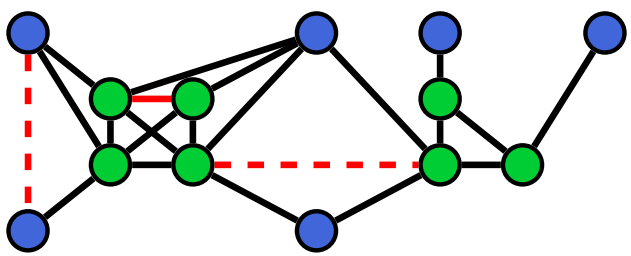
$\rightsquigarrow$



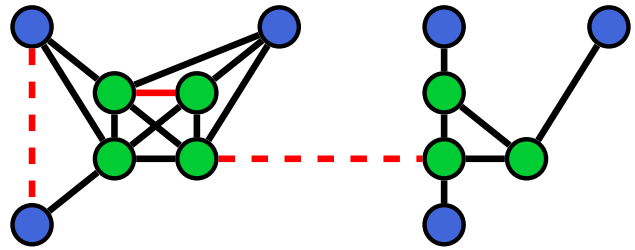
Monopolar Editing

Input: An undirected graph $G = (V, E)$.

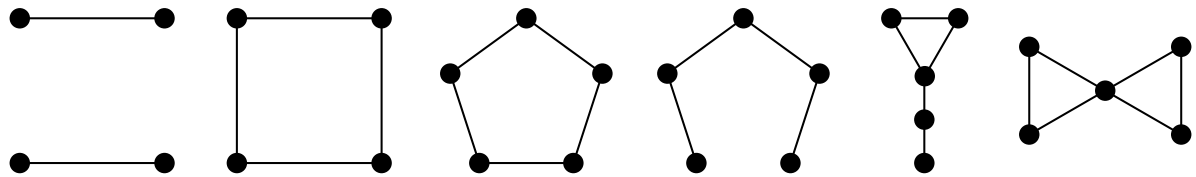
Task: Find a minimum-size set of edge deletions and edge insertions that converts the graph into a monopolar graph.



Problem Complexity—Split Cluster Editing



Theorem: (Foldes & Hammer '71) A graph is a split graph iff it does not contain an induced subgraph that is a $2K_2$, C_4, or C_5.



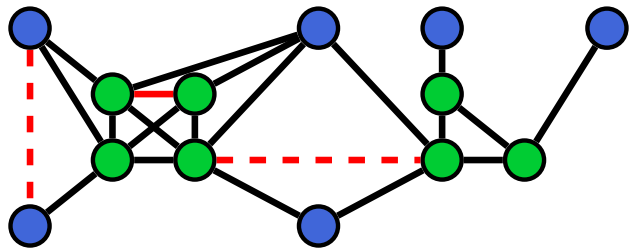
Main Results:

A graph is a split cluster graph iff it does not contain an induced subgraph that is a C_4, C_5, P_5, necktie, or bowtie.

Split Cluster Editing is APX-hard and NP-hard even on graphs with maximum degree 11.

Split Cluster Editing can be solved in $O(10^k \cdot m)$ time, where k is the number of necessary edge modifications.

Problem Complexity—Monopolar Editing



Observation: Monopolar graphs have **infinitely** many forbidden subgraphs (smallest and only with 5 vertices is the wheel W_4 (⌘)).

Known: Vertex-partitioning into fixed additive induced-hereditary properties is NP-hard [Farrugia, Electron. J. Combin. '04].

$\rightsquigarrow$ **Deciding** whether a graph is monopolar is NP-hard.

ILP formulations

- Forbidden subgraph-based
- Partition variables
- Column generation

Forbidden subgraph-based ILP formulation for SCE

First try: use forbidden subgraph characterization

$\rightsquigarrow$

Binary variable $e_{uv} = 1$ if $\{u, v\}$ is in the solution graph
Define $\bar{e}_{uv} := 1 - e_{uv}$

$$\text{minimize} \sum_{\{u,v\} \in E} \bar{e}_{uv} + \sum_{\{u,v\} \notin E} e_{uv}$$

subject to

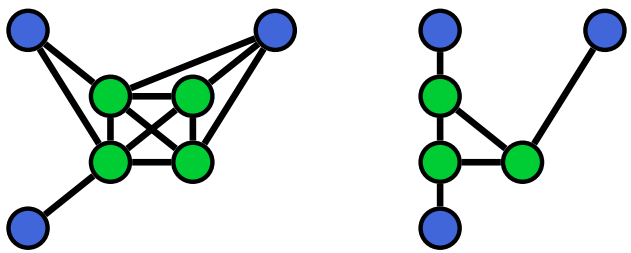
$$\forall \text{ forbidden subgraph } F : \sum_{\{u,v\} \in F} \bar{e}_{uv} + \sum_{\{u,v\} \notin F} e_{uv} \geq 1$$

$O(n^5)$ constraints $\rightsquigarrow$ use row generation (lazy constraints)

Partition variable ILP formulation for SCE

Idea: Fix the assignment to core and periphery before destroying the forbidden subgraphs

Lemma: Let $G = (V, E)$ be a graph and $C \dot{\cup} I = V$ a partition of the vertices. Then G is a split cluster graph with **core vertices** C and **independent set vertices** I iff it does not contain an edge with both endpoints in I, nor an induced P_3 with both endpoints in C.



Partition variable ILP formulation for SCE

Binary variable $e_{uv} = 1$ if $\{u, v\}$ is in the solution graph.
Define $\bar{e}_{uv} := 1 - e_{uv}$

Binary variable $c_u = 1$ if u is a core vertex.
Define $\bar{c}_u := 1 - c_u$.

$$\text{minimize} \sum_{\{u,v\} \in E} \bar{e}_{uv} + \sum_{\{u,v\} \notin E} e_{uv}$$

subject to

$$\forall u, v : c_u + c_v + \bar{e}_{uv} \geq 1$$

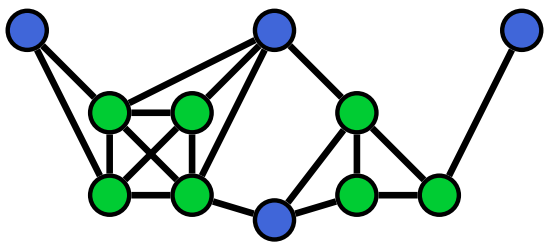
$$\forall u \neq v, v \neq w > u : \bar{e}_{uv} + \bar{e}_{vw} + e_{uw} + \bar{c}_u + \bar{c}_w \geq 1$$

$O(n^3)$ constraints $\rightsquigarrow$ still use row generation (lazy constraints)

Partition variable ILP formulation for Monopolar Editing

Idea (again): Fix the assignment to core and periphery before destroying the forbidden subgraphs

Lemma: Let $G = (V, E)$ be a graph and $C \dot{\cup} I = V$ a partition of the vertices. Then G is a split cluster graph with **core vertices** C and **independent set vertices** I iff it does not contain an edge with both endpoints in I, nor an induced P_3 consisting only of vertices in C.



Partition variable ILP formulation for Monopolar Editing

Binary variable $e_{uv} = 1$ if $\{u, v\}$ is in the solution graph.
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$$\text{minimize} \sum_{\{u,v\} \in E} \bar{e}_{uv} + \sum_{\{u,v\} \notin E} e_{uv}$$

subject to

$$\forall u, v : c_u + c_v + \bar{e}_{uv} \geq 1$$

$$\forall u \neq v, v \neq w > u : \bar{e}_{uv} + \bar{e}_{vw} + e_{uw} + \bar{c}_u + \bar{c}_v + \bar{c}_w \geq 1$$

$O(n^3)$ constraints $\rightsquigarrow$ still use row generation (lazy constraints)

Column generation for Split Cluster Editing

Binary variables $z_C = 1$ if cluster $C \in 2^V$ is part of the solution.

$$\begin{aligned} \text{maximize} \quad & \sum_{C \in 2^V} c_C z_C, \\ \text{s.t.} \quad & \sum_{C \in 2^V \mid u \in C} z_C = 1 \quad \forall u \in V, \end{aligned}$$

where c_C is the "value" of the cluster (number of edges of $G[C]$ minus the *splittance* of $G[C]$, that is, the number of edge insertions and deletions to make it a split graph).

Problem: Exponentially many variables.

Idea: Successively add only those variables ("columns") that are "needed", that is, their introduction improves the objective.

Column Generation: Auxiliary problem

Lemma: For the relaxation of the ILP, the objective function change from adding a cluster C is

$$c_C - \sum_{u \in C} \lambda_u,$$

where λ_u is the shadow price associated with the constraint of vertex u.

$\rightsquigarrow$ need to find a cluster that maximizes cluster value minus vertex weights.

Idea: Use an ILP.

ILP tuning tricks

- Warm start with heuristic solution
- MIP emphasis: balance between proving optimality and finding better solutions
- Cutting planes for P_5: for all distinct $u, v, w, x, y \in V$:

$$\bar{e}_{uv} + \bar{e}_{vw} + \bar{e}_{wx} + \bar{e}_{xy} + \frac{1}{2}e_{uw} + e_{vx} + \frac{1}{2}e_{wy} + \frac{1}{2}e_{xu} + \frac{1}{2}e_{yv} \geq 1.$$

(for monopolar, W_4)

Heuristics

- Forbidden subgraph-based
- Simulated annealing

Forbidden subgraph heuristic for Split Cluster Editing

Idea

Edit an edge that destroys many forbidden subgraphs.

Problems

- Slow
- Can get caught in loops
- Not very good results

Simulated Annealing heuristic for Split Cluster Editing

Simulated Annealing

- Start with a clustering where each vertex is a singleton.
- Randomly move a vertex to a cluster that contains one of its neighbors.
- Accept if this improves the objective k; otherwise, accept with small probability that decreases over time.

To evaluate the objective, we can use the following theorem:

Theorem (Hammer & Simeone '81)

The minimum number of edits to make a graph a split graph can be found in linear time.

Data reduction

We didn't find any useful data reduction rules. However, we have two rules that allow to fix the value of variables in the ILP:

Rule 1

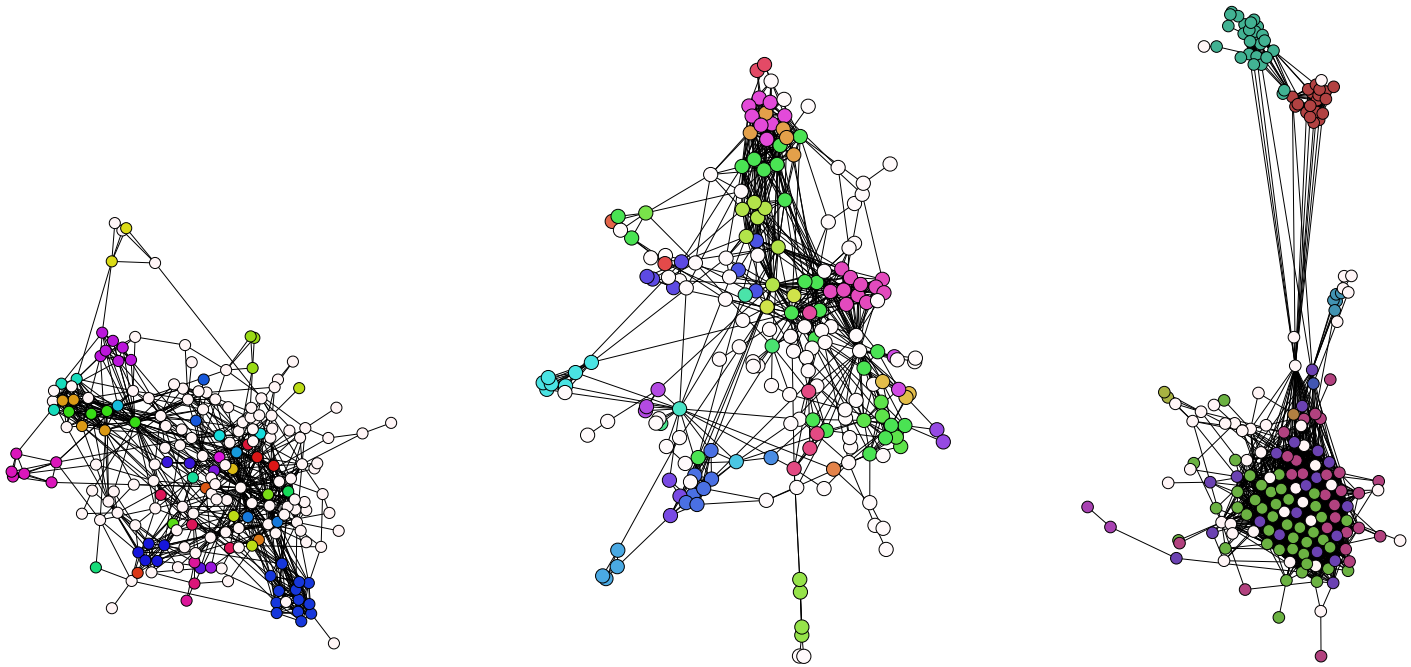
If there is a degree-one vertex u whose neighbor has degree larger than one, then label u as periphery ($c_u = 0$).

Rule 2

If there is an edge $\{u, v\}$ between two vertices labeled as periphery, then this edge cannot be present in the solution ($e_{uv} = 0$).

Experimental Setup

Data: three yeast protein interaction subnetworks



cell cycle transcription translation

Comparison with:

- Core–periphery enumeration algorithm [Luo et al., BMC Bioinformatics '09]
- **SCAN** clustering algorithm [Xu et al., KDD '07]

Experimental Results (I)

Objective value:

	n	m	k_{SCE}	k_{ME}
cell cycle	196	797	321	126
transcription	215	786	273	106
translation	188	2352	308	240

Results for Simulated Annealing; confirmed as optimal by ILP in green.

Experimental Results (II)

GO-term coherence & cluster number:

	transcription					
	K	p	k	c_t	c_c	c_p
SCE	13	112	273	0.54	0.54	0.57
ME	26	78	106	0.55	0.61	0.54
SCAN	26	58	—	0.53	0.51	0.47
Luo	12	125	—	0.40	0.52	0.38

K = number of clusters
p = size of periphery
c_t = average cluster coherence
c_c = average core coherence
c_p = average periphery coherence

Experimental Results (III)

Overlap test with known protein complexes (CYC2008):

Hypothesis for perfect recovery:

- Core contains only complex proteins
- Complex is contained completely in cluster

	transcription		
	D	$\text{core}_{\%}$	$\text{comp}_{\%}$
SCE	7 / 11	89	100
ME	11 / 11	100	100
SCAN	8 / 11	84	100
Luo	6 / 11	87	100

D : number of detected clusters

$\text{core}_{\%}$: median percentage of core proteins in complex

$\text{comp}_{\%}$: median percentage of complex proteins in cluster

Conclusion

Results:

- Two new concrete graph-theoretic models for uncovering global core–periphery structure of PPI networks
- Useful ILP formulations based on core/periphery-assignment
- Simulated Annealing heuristic performs well
- **Monopolar Editing** gives best biological results

Outlook:

- Algorithmic improvements
  (goal: good results for complete interactome)
- Incorporate interaction confidence scores
- Further combinatorial core–periphery models
- Find further approaches to exploit/evaluate predictions by **Monopolar Editing**