Network topology as a source of information

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November 6, 2012
Vision

- Network topology - contains currently hidden biological information
- Need new computational tools to mine network data → biology
- “Network biology:”
  - In its infancy & rich in open research problems
  - Many unforeseen problems likely to emerge
  - Promising to remain at the top of scientific endeavour
  - Proposed research is well timed
    → Highly likely to make an impact

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Overview

Network Topology - new source of biological information

1. Data, Problems, Introduction, Background

2. New computational techniques
   - Network Alignment → function and phylogeny
   - How to measure topology? → Link it with function
   - Modeling networks and why to model them
   - GraphCrunch 2 software for network analysis
Data

Advances in biotechnology

Networks can model:
- gene interactions
- protein structure
- protein-protein interactions
- metabolism
- ...

X → Y represents transcription network

gene x gene y

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Advances in biotechnology

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➢ ...

Network structure ↔ function
Problems

- Making sense of these data
- Graph theory-based methods
  - Not statistical (inductive), but
  - Theory-based (mechanistic)

Why? ➔ Understanding

- Prediction / reproduction:
  - Biological function
  - Disease genes/proteins
  - Reconstruct phylogeny...
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Why? ➞ Understanding

• Prediction / reproduction:
  • Biological function
  • Disease genes/proteins
  • Reconstruct phylogeny...
Problems

• **Why analyze network data?**
  - Network topology: new source of biological information, not mere statistics
  - Complementary to sequence data
  - Need tools to mine networks: topology ↔ biology
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Problems

Why analyze network data?

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- Complementary to sequence data
- Need tools to mine networks: topology ↔ biology
  - Why?
    - Computational intractability (NP-hardness) of many problems dealing with large networks
1. Computational “hardness” (intractability) of graph theoretic problems
   E.g., NP-completeness of subgraph isomorphism
   ➔ Cannot exactly compare/align networks
      ➔ heuristics (approximate solutions)
   ➔ Exact comparison inappropriate in biology
      ➔ due to biological variation
2. Data noise ➔ robust tools
   ➔ revise models as data sets evolve
Introduction and Background

Properties of Large Networks (heuristic comparisons)

- **Global**
  - Degree distribution
  - Diameter
  - Clustering coefficient/spectrum

- **Local:**
  - network “motifs” and subgraphs (U. Alon’s group, ’02-’04)
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![Degree Distribution of D. Melanogaster PPI Network](image1)

![Induced vs. Partial Subgraphs](image2)
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Induced vs. **Partial** Subgraphs

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First 3-node path

Induced vs. Partial Subgraphs

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[Diagrams showing degree distribution and examples of subgraphs]
Introduction and Background

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---

**Induced vs. Partial Subgraphs**

Third 3-node path

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Properties of Large Networks (heuristic comparisons)

**Global**
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**Local:**
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The only triangle

**Induced vs. Partial Subgraphs**
Introduction and Background

Examples of different model networks:

- Erdös-Rényi (ER)
- Small-World
- Scale-Free (SF)
- Hierarchical
- Geometric (GEO)
Introduction and Background

Examples of different model networks:

Erdös-Rényi (ER)  Small-World  Scale-Free (SF)

Hierarchical

Geometric (GEO)
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All robust to noise
2. Network Analysis and Modeling

New measures of network local structure

**Definition 3** Graphlets are small connected non-isomorphic subgraphs of a graph $G$ induced on $n \geq 3$ nodes of $G$.

For $n = 3, 4, 5, \ldots, 10$, there are $2, 6, 21, \ldots, 11716571$ graphlets!

All Graphlets on 3-5 nodes:

- 3-node graphlets
  - 1
  - 2
  - 3

- 4-node graphlets
  - 4
  - 5
  - 6
  - 7
  - 8

- 5-node graphlets
  - 9
  - 10
  - 11
  - 12
  - 13
  - 14
  - 15
  - 16
  - 17
  - 18
  - 19
  - 20
  - 21
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  - 26
  - 27
  - 28
  - 29

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All Graphlets on 3-5 nodes:

- **Induced**
- **Of any frequency**


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2. Network Analysis and **Modeling**

**Graphlet Frequencies: *S. cerevisiae* High-Confidence PPI Network**

(von Mering et al., *Nature* 417)

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**Graphlet Frequencies:** *D. melanogaster* **Noisy** PPI Network
(Giot et al., *Science* 302) (**77%** of edges are of **low confidence**)


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**Graphlet Frequencies:** *D. melanogaster* Higher-Confidence PPI Network

*(Giot *et al.*, *Science* 302)*

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2. Network Analysis and Modeling

How to measure topology around a node → graphlets

• Degree of a node

2. Network Analysis and Modeling

**Definitions:**

An *isomorphism* \( f \) from graph \( G \) to graph \( H \) is a bijection: \( f : V(G) \to V(H) \) such that \( xy \) is an edge of \( G \) iff \( f(x)f(y) \) is an edge of \( H \).

An *automorphism* is an isomorphism from a graph to itself.

The automorphisms of a graph \( G \) form a *group*, called the *automorphism group of \( G \)*, and commonly denoted by \( \text{Aut}(G) \).

For a node \( x \) of graph \( G \), the *automorphism orbit of \( x \)* is \( \text{Orb}(x) = \{y \in V(G') | y = f(x) \text{ for some } f \in \text{Aut}(G)\} \), where \( V(G') \) is the set of nodes of graph \( G \).

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How to measure topology around a node → graphlets

“Graphlet Degree Vector” (GDV) of a node $u$:

$$\text{GDV}(u) = (u_0, u_1, u_2, \ldots, u_{72})$$

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How to measure topology around a node → graphlets

Graphlet Degree (GD) vectors, or “node signatures”

\[ \text{GDV}(u) = (2, 1, 1, 0, 0, 1) \]

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How to measure topology around a node → graphlets

**Similarity measure** between nodes’ Graphlet Degree vectors

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**Signature Similarity Measure**

- \( o_i \) is number of orbits that affect orbit \( i \in \{0, \ldots, 72\} \)
- \( w_i = 1 - \frac{\log(o_i)}{\log(73)} \)
- Distance between the \( i^{th} \) orbits of nodes \( u \) and \( v \) is
  \[
  D_i(u, v) = w_i \times \frac{|\log(u_i+1) - \log(v_i+1)|}{\log(\max\{u_i, v_i\}+2)}
  \]
- The total distance between nodes \( u \) and \( v \) is
  \[
  D(u, v) = \frac{\sum_{i=0}^{72} D_i}{\sum_{i=0}^{72} w_i}
  \]
- The **signature similarity** between nodes \( u \) and \( v \) is
  \[
  S(u, v) = 1 - D(u, v)
  \]


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2. Network Analysis and Modeling

Network topology -> biological function & disease


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Network topology → biological function & disease

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Network topology $\rightarrow$ biological function & disease

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Network topology $\rightarrow$ biological function & disease

Significantly enriched:
- Biological function
- Protein complexes
- Sub-cellular localization
- Tissue expression
- Disease

2. Network **Analysis and Modeling**

Network topology → biological function & disease

⇒ Find new members of melanin production pathways

⇒ Same cancer type → more similar topology in PPI net

⇒ Could not have been identified by existing approaches


2. Network **Analysis** and **Modeling**

Network topology $\rightarrow$ biological function & disease

$\Rightarrow$ Find new members of yeast proteosome PPI network


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Generalize Degree Distribution

The degree distribution measures:
- the number of nodes “touching” \( k \) edges for each value of \( k \).

For each of the 73 orbits, count:
- the number of nodes “touching” a particular graphlet at a particular orbit

- 73 Graphlet Degree Distributions (GDDs)

We used GDDs to show that:
- PPI networks of eukaryotes are the best modeled by Geometric Graphs
2. Network Analysis and Modeling

Network Alignment

- Exact network comparisons are computationally intractable
  - Subgraph Isomorphism Problem is NP-C (Cook, 1971)
  - Rely on approximate or heuristic approaches
2. Network Analysis and Modeling

Network Alignment:

**GRAAL family of algorithms**

Global Network Alignment algorithms - topology-based:

1. **GRAAL**
   - seed-and-extend, finds *an alignment*
   

2. **H-GRAAL**
   - finds *an optimal* alignment
   

3. **MI-GRAAL**
   - combines the two + uses *any number and type of node similarity measures*
   
2. Network Analysis and Modeling

Network Alignment:

**GRAAL (GRAph ALigner)**

- Find **topology around nodes** across different networks
- Align “topologically-similar” nodes – “seed nodes” in each network
- Extend around seed nodes
- Break ties randomly; ~60% of alignment consistent across runs

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- Repeat seed-and-extend on 2\textsuperscript{nd} and 3\textsuperscript{rd} powers of the two graphs
- Power $p$ of $G$ is: $G^p(V,E^p)$, edge $(u,v) \in E^p$ iff $d_G(u,v) \leq p$
- This is to allow for “insertions” and “deletions”


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  - Align PPI networks of yeast and human
2. Network Analysis and Modeling

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**Predict function**

IsoRank:
116 nodes and 261 edges

GRAAL:
267 nodes and 900 edges

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All statistically significant


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2. Network Analysis and Modeling

**GRAAL family of algorithms**

- Align “topologically-similar” nodes
- BUT, not in a seed-and-extend greedy way
- Use the Hungarian Algorithm for minimum weight bipartite matching
  - Finds *an optimal alignment* with respect to the cost function
  - “Core (stable) alignment” - present in all optimal alignments
  - Problem: running time

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**Yeast - Human alignment:**

- Millions of optimal alignments
- 72% of yeast proteins have a unique human protein that they’re aligned to by *every* optimal alignment

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GRAAL family of algorithms

MI-GRAAL (Matching-based Integrative)

- Includes **any number and type of node similarity** measures:
  - e.g., network topology, sequence similarity...
- Each similarity measure votes as an independent agent → “seed nodes”
- Combines the two (GRAAL and H-GRAAL):
  - Seed-and-extend approach
  - Break the problem into several matching problems:
    - consider aligning nodes only if they have aligned neighbors, hence increase number of aligned edges (EC)
  - Fast enough for PPI networks

Isorank:
116 nodes and 261 edges

GRAAL:
267 nodes and 900 edges

MI-GRAAL:
1,858 nodes and 3,467 edges


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**GRAAL family of algorithms**

**MI-GRAAL (Matching-based Integrative)**

- 78% of yeast proteins are connected and contained in human PPI net (was about 11% in GRAAL and H-GRAAL)
- Produces stable alignments - don’t change over different runs
- Allows a user to experiment with combinations of similarity measures
- Aligned PPI networks of herpes viruses using only topology

---

Application: Track Network Dynamics


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Hypothesis:
Topologically central nodes are biologically important

Questions:
A. How to measure “topological centrality” in a network?
B. What genes are “biologically important”?
2. Network Analysis and Modeling

Centrality and domination → biological function & disease

A. How to measure “topological centrality” in a network?

1. Graphlet Degree Centrality (GDC)

\[ GDC(v) = \sum_{i=0}^{72} w_i \times \log(v_i + 1) \]

Dense neighborhoods

2. Dominating Set (DS)

- min. size: NP-hard

“Spine” - signal transduction?


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2. Network Analysis and Modeling

Centrality and domination $\rightarrow$ biological function & disease

Fig. 2. The overlap of BC genes from the four categories in the human PPI network [48].


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2. Network Analysis and Modeling

Centrality and domination \(\rightarrow\) biological function & disease

- Enrichment in DS of “biologically central” and signaling pathway (SP) genes, \(p\)-values \(\leq 10^{-11}\)
- Non-DS: no significant enrichment

- GO terms: 153 MF, 574 BP, 44 CC significantly enriched in DS
  7 MF, 7 BP, 0 CC significantly enriched in non-DS

\{ \text{No overlap} \}


Drug targets:
- In DS U GDC-central: 11\%, \(p\)-value=\(10^{-4}\)
- In DS \(\cap\) GDC-central: 32\%, \(p\)-value=0

Central/DS and non-central/DS genes group by different functions

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Machine Learning on network properties

• Different models best-fitting w.r.t. different network properties
• Integrate many network properties into “network fingerprint” vector
• Apply a series of machine learning classifiers to network fingerprints:
  1. Backpropagation method (BP)
  2. Probabilistic neural networks (PNN)
  3. Decision tree (DT)
  4. Multinomial naive Bayes classifier (MNB)
  5. Support vector machine (SVM)

➢ PPI networks are geometric

2. Network Analysis and **Modeling**

**Network Embedding into Space**

- MDS-based embedding of PPI nets into low dimensional space
- Shortest paths play a role of distances

2. Network Analysis and Modeling

Network Embedding into Space

- MDS-based embedding of PPI nets into low dimensional space
- Shortest paths play a role of distances

```
D. J. Higham, M. Rasajski, N. Przulj, “Fitting a Geometric Graph to a Protein-Protein Interaction Network”, Bioinformatics, 24(8), 1093-1099, 2008.
```
2. Network Analysis and Modeling

PPI Network are GEOMETRIC

- Erdős-Rényi (ER)
- Small-World
- Scale-Free (SF)
- Hierarchical
- Geometric (GEO)

- De-noise PPI networks
- Network evolution
- Fast algorithms

---


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2. Network Analysis and Modeling

Application: de-noising PPI networks

- Embed a PPI network into space
- Learn from coordinates of node embedding points probability densities \( p(\text{dist} \mid \text{edge}) \) and \( p(\text{dist} \mid \text{non-edge}) \)
- Choose a threshold \( \delta \)
- For each pair of nodes at distance \( \leq \delta \), compute its Confidence Score:

\[
CS(i,j) = \frac{p(\text{edge}(i,j) \mid \text{dist}(i,j))}{p(\text{edge}(i,j) \mid \text{dist}(i,j)) + p(\text{nonedge}(i,j) \mid \text{dist}(i,j))}
\]

⇒ Predict new PPIs

Why PPI networks might be geometric?

- Intuitive “geometricity” of PPI networks:
  - Genes exist in some bio-chemical space
  - Gene duplications and mutations
  - Natural selection = “evolutionary optimization”
GraphCrunch 2 software

- 1,663 downloads
- 2nd most accessed article in all of BMC journals in February 2011
- For biologists: Select Data, Select Analysis → Run, View Results
- Open-source

GraphCrunch 2 demo
Other Research Projects


2) Protein Structure Graphs:
   - New null model:

3) Brain functional networks:

4) Economic networks

Etc.
Acknowledgements

➢ Funding: ERC Starting Grant, €1.6M (2012-2017)
   NSF CDI: $2M (2010 — 2014)
   GlaxoSmithKline: £80K (2010-2014)

➢ Alumni:

1. Tijana Milenković, Ph.D.
   Assistant Prof., U. of Notre Dame
2. Oleksii Kuchaiev, Ph.D.
   Microsoft, Redmond
3. Vesna Memišević, Ph.D.
   US Army, Bioinformatics Res.
Acknowledgements

➢ **Funding:** ERC Starting Grant, €1.6M (2012-2017)
  - GlaxoSmithKline: £80K (2010-2014)

➢ **Post-docs:**
  - Noel Malod-Dognin
  - Joana Goncalves

➢ **PhD students:**
  - Vuk Janjic, Anida Sarajlic, Omer Yaveroglu and Kai Sun

Looking for post-docs & new Ph.D. students (ERC, NSF)