6-network-analysis

Thursday, February 19, 2026 9:38 AM

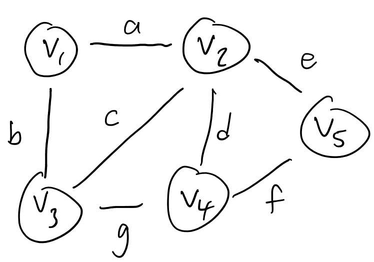
Protein Interactome

Proteins don't act in isolation. Instead, they work together in conjunction with each other. We can experimentally detect pairwise interactions using techniques such as Yeast-2-Hybrid, co-immuno-precipitation, proximity ligation, etc.

Can we go from pairwise interactions to understand complex systems of proteins?

Def. An (undirected) graph is a pair $G=(V,E)$ where $V=\{v_1,\dots,v_m\}$ is a set of vertices/nodes and E is a set of 2-element subsets of V called edges/links. Let $|E|=m'$.

Ex.



Def. The degree $d(v)=\left|\{u\in V \mid \{u,v\}\in E\}\right|$.

The diagonal degree matrix $D=D(G)=\begin{bmatrix} d(v_1) & & & 0 \\ & d(v_2) & & \\ & & \ddots & \\ 0 & & & d(v_m)\end{bmatrix}$.

Def. Given a graph $G=(V,E)$, $\forall$ two nodes $u,v\in V$, a path from $u\to v$ is a sequence of nodes $(v_0,\dots,v_k)$ s.t. $u=v_0$, $v=v_k$ and $\{v_i,v_{i+1}\}\in E$ for $0\le i\le k-1$. k is the length.

A path is closed if $u=v$. G is connected if $\forall u\neq v$, $\exists$ a path $u\to v$.

Connected components are equivalence classes of related nodes, where nodes are related if $\exists$ a path b/t them.

Def. The incidence matrix $B=B(G)\in\mathbb{R}^{m\times m'}$ is

$$b_{ij}=\begin{cases}1 & \text{if } e_j=\{v_i,v_k\} \text{ for some } k\\ 0 & \text{otherwise.}\end{cases}$$

Ex

$$\begin{array}{c} \\ 1\\2\\3\\4\\5\end{array}\begin{array}{c} \begin{array}{cccccc} a & b & c & d & e & f\end{array}\\ \begin{bmatrix}1&1&0&0&0&0\\1&0&1&1&1&0\\0&1&1&0&0&0\\0&0&0&1&0&1\\0&0&0&0&1&1\end{bmatrix}\end{array}$$

Def. The oriented incidence matrix B^σ is given by assigning an arbitrary orientation to every edge

each col has one positive & one negative

Def. The oriented incidence matrix B is given by assigning an arbitrary orientation to every edge

$$e = \{u,v\} = \{v,u\} \longrightarrow e = \underbrace{(u,v)}_{} \text{ or } e = \underbrace{(v,u)}_{}$$

we pretend the edges are directed $\Rightarrow$ ordered pair

Then
$$b_{ij} = \begin{cases} -1 & \text{if } e_j = (v_k, v_i) \text{ for some } k \\ 1 & \text{if } e_j = (v_i, v_k) \text{ for some } k \\ 0 & \text{otherwise.} \end{cases}$$

each col has one positive & one negative

Ex
$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array} \begin{array}{c} \begin{array}{cccccc} a & b & c & d & e & f \end{array} \\ \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & -1 & 1 & 0 \\ 0 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 0 & -1 & -1 \end{bmatrix} \end{array}$$

Note: If we were working with directed graphs, this orientation comes for free.

Def. If exists edge $\{u,v\}$, then v is adjacent to u, denoted $u \sim v$.

Def. The adjacency matrix $A = A(G)$ is the symmetric matrix with

$$a_{ij} = \begin{cases} 1 & \text{if } u \sim v \\ 0 & \text{otherwise} \end{cases}$$

Ex.
$$\begin{bmatrix} 0 & 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 1 & 1 \\ 1 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \end{bmatrix}$$

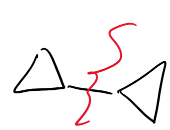
Aside: This is a diffusion operator as the value of Ax at v_i is the sum of the values of x at nodes v_j adjacent to v_i.

This gives a geometric interpretation of the eigenvalues of A, because

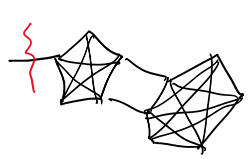
if $Ax = \lambda x$, then $\lambda x_i = \sum_{j \sim i} x_j$, so the sum of the values of x at nodes adjacent to i must be equal to λ times value at v_i.

Back to clustering

Idea 1: Minimize cut.



Problem:



Might just cut out dangling edge.

Idea 2: Cut edges with high betweenness

└ between every pair of nodes, find shortest path, ... based on number of

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└ between every pair of nodes, find shortest path, + each edge gets a score based on number of shortest paths going through it

[Girvan-Newman early 2000s]

We can keep iterating until we have disconnected the graph into however many chunks we want.

Problem: how many components is the right number?

Idea 3: "Modularity" quality function.

Clusters should

(1) have few edges crossing clusters

(2) have many edges within clusters

} problem: best solution is not to cut!

compared to a randomized version of "same" network / partitioning

Let A be adj matrix

d_i the degree of node i

c_i the community of node i, partition P

$\delta(c_i, c_j) = 1$ iff $c_i = c_j$ (0 otherwise)

Proportion of edges inside community: $\frac{1}{2m} \sum_{i,j \in V} A_{ij} \, \delta(c_i, c_j)$

In "random" configuration model, where degrees are kept the same but connections randomized:

$$\frac{1}{2m} \sum_{i,j \in V} \frac{d_i d_j}{2m} \, \delta(c_i, c_j)$$

Def. modularity

$$Q(P) = \frac{1}{2m} \sum_{i,j \in V} \left[A_{ij} - \frac{d_i d_j}{2m} \right] \delta(c_i, c_j)$$

$$= \frac{1}{2m} \sum_{C \in P} \left[e_C - \frac{\left(\sum_{i \in C} d_i\right)^2}{2m} \right]$$

} also due to Girvan-Newman

With a quality function, we can now separate out partitioning algorithms from measuring how good the partitions are.

Directly optimizing for Q is NP-hard, but we can now use other heuristics to approximately optimize it, like Louvain or Leiden.

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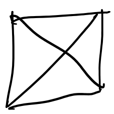
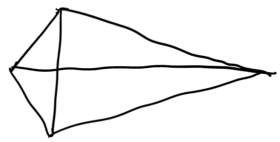
Graph Drawing (also sometimes called graph embedding or graph immersion)

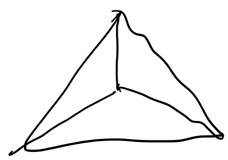


or



are the same graph.

or



How do we compute a "good" drawing?

Aside: maybe a good drawing will tell us something about clusters too.

Def. The matrix $L = B^\sigma (B^\sigma)^T$ is called the (unnormalized) graph Laplacian.

Exercise: Show that for any orientation σ, $L = D - A$.

Def. We can define a weighted graph by a weighted adjacency matrix W where $w_{ij} = w_{ji} > 0$ is the weight on edge $\{v_i, v_j\}$, and $w_{ij} = 0$ iff that edge does not exist.

Def. The degree $d(v_i) = \sum_{j \neq i} w_{ij}$ in a weighted graph.

We can thus define a diagonal matrix D.

Def. The Laplacian matrix is $L = D - W$.

Exercise: If we define the weighted oriented incidence matrix B^σ by

$$b_{ij} = \begin{cases} \sqrt{w_{ij}} & \text{if } v_i \text{ is the source of } e_j \\ -\sqrt{w_{ij}} & \text{if } v_i \text{ is the target of } e_j \\ 0 & \text{else} \end{cases}$$

where σ is an arbitrary orientation of the edges,

then $L = B^\sigma (B^\sigma)^T$.

Theorem L is positive semidefinite. (i.e. it has all nonnegative eigenvalues)

... equivalent statement is that the symmetric quadratic form

Theorem L is positive semidefinite.

proof. Recall that an equivalent statement is that the symmetric quadratic form given by L, $x^T L x$, is always nonnegative.

(Else, let x be an eigenvector with eigenvalue $\lambda < 0$. Then $x^T L x = \lambda x^T x = \lambda \|x\|^2 < 0$.)

For any $x \in \mathbb{R}^m$,

$$x^T L x = x^T D x - x^T W x$$

$$= \sum_{i=1}^{m} d_i x_i^2 - \sum_{i,j} w_{ij} x_i x_j$$

$\left(d_i = \sum_j w_{ij}\right)$

$$= \frac{1}{2}\left(\sum_{i=1}^{m} d_i x_i^2 - 2\sum_{i,j} w_{ij} x_i x_j + \sum_{j=1}^{m} d_j x_j^2 \right)$$

$$= \frac{1}{2}\left(\sum_{i=1}^{m}\sum_{j=1}^{m} \left[w_{ij} x_i^2 - 2 w_{ij} x_i x_j + w_{ij} x_j^2 \right] \right)$$

$$= \frac{1}{2} \sum_{i,j} w_{ij} (x_i - x_j)^2 \geq 0.$$

Exercise: Prove that the all 1's vector $\vec{1}$ is an eigenvector of L with eigenvalue 0.

Fact: For any weighted symmetric graph $G = (V, W)$, the eigenvalues (with multiplicity) $0 = \lambda_1 \leq \lambda_2 \leq \cdots \leq \lambda_m$ of L are real and nonnegative, and there is an orthonormal basis of eigenvectors.

Exercise: Prove that if G is disconnected, $\lambda_2 = 0$.

Hint: Construct two independent eigenvectors for the eigenvalue 0.

Fact: $\dim(\operatorname{Ker} L) = \#$ connected components of G.

Exercise: Prove this fact using $L = B^\sigma (B^\sigma)^T$.

Corollary: If G is connected, $\lambda_2 > 0$.

λ_2 known as the **Fiedler number** of the graph.

Def. A **graph drawing** is a function $\rho : V \to \mathbb{R}^n$. The matrix of a graph drawing ρ is an $m \times n$ matrix R where the row $\rho(v_i)$ corresponds to the point representing v_i in $\mathbb{R}^n$.

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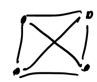
Ex.

$$R = \begin{bmatrix} 0 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 1 \end{bmatrix}$$



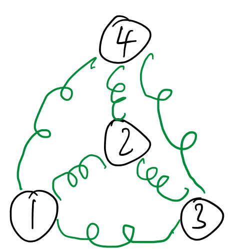
We let $\rho(v_i) = e_i R$ where $e_i = (0 \cdots 0 \, 1 \, 0 \cdots 0)$
↑ pos. i.

Def. A graph drawing is *balanced* iff the sum of the entries of every col of the matrix R is 0. i.e. $\mathbb{1}^T R = 0$.
(i.e. the graph drawing is centered at the origin)

Def. The *energy* of a drawing R is

$$\mathcal{E}(R) = \sum_{\{v_i, v_j\} \in E} \| \rho(v_i) - \rho(v_j) \|^2$$

Analogy:



Connect nodes by springs and minimize potential energy of the system.

"good" drawings are ones that minimize energy, but are not trivial.

Define: The energy of a drawing R of a weighted graph $G = (V, W)$ is

$$\mathcal{E}(R) = \sum_{\{v_i, v_j\} \in E} w_{ij} \| \rho(v_i) - \rho(v_j) \|^2.$$

(think of w_{ij} as spring stiffness)

Thm: $\mathcal{E}(R) = tr(R^T L R)$

proof.

$$\mathcal{E}(R) = \sum_{\{v_i, v_j\} \in E} w_{ij} \| \rho(v_i) - \rho(v_j) \|^2$$

$$= \sum_{k=1}^{n} \sum_{\{v_i, v_j\} \in E} w_{ij} (R_{ik} - R_{jk})^2$$

$$= \sum^{n} \ldots \sum^{m} \ldots (R \ldots - R \ldots)^2$$

$$k=1 \quad \{v_i,v_j\}\in E$$

$$= \sum_{k=1}^{n} \frac{1}{2} \sum_{i,j=1}^{m} w_{ij} \left(R_{ik} - R_{jk}\right)^2$$

$$= \sum_{k=1}^{n} (R^k)^T L R^k \qquad \text{(where } R^k \text{ is the } k\text{th col of } R\text{)}$$

$$= tr(R^T L R)$$

So the energy is the sum of the (nonnegative) eigenvalues of $R^T L R$.

Notice that for any invertible matrix M, $p(v_i)M$ is another graph drawing that conveys the same information as R, so we may as well choose R to have pairwise orthonormal unit length cols, $\underline{R^T R = I}$.

this gives us an orthonormal graph drawing, & rules out trivial drawings.

Notice: We can choose an orthonormal eigenbasis of L

$$u_1, u_2, \dots, u_m$$

$$0 = \lambda_1 < \lambda_2 \le \cdots \le \lambda_m$$

Let $R = \underbrace{\begin{bmatrix} u_2 & u_3 & \cdots & u_{n+1} \end{bmatrix}}_{\text{each } u_i \text{ is a column}}$. Then $R^T L R = \begin{bmatrix} \lambda_2 & & 0 \\ & \ddots & \\ 0 & & \lambda_{n+1} \end{bmatrix}$, so $Tr(R^T L R) = \sum_{k=2}^{n+1} \lambda_k$.

Fact: This choice minimizes the energy of a balanced orthonormal drawing.

Exercise: Explain why we don't want to use the 1st eigenvector associated with $\lambda_1 = 0$.

Notice: We can draw onto the 1D number line, and then divide the graph in half by positive & negative nodes. This corresponds to the Fiedler eigenvector, and is the idea behind spectral clustering.