Lively Networks!

From Graph Theory To Biological Systems

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  - It's likely that there's more than one way to affect a system
- Spectral graph theory is beautiful and useful :)
  - How will a change in the network structure affect the overall properties of the network?
  - Can the network adapt/compensate for changes in one area with changes in another?
  - Can we infer something about the dynamics of the network, even if all we have is its topology?

Spectral Graph Theory

Graphs

Consider a graph $G = (V, E)$:

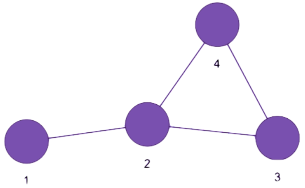
- V = set of vertices / nodes
  - Vectors $\mathbf{x} : V \to \mathbb{R}$; x_i is the value at node i

- E = set of edges
  - An edge is a pair of nodes (i, j)
  - Edges may be weighted ("strength" of the connection between i and j)
  - Graph may be directed or undirected:
    - directed: edge (i, j) goes *from* i *to* j, but not vice-versa
    - undirected: edge (i, j) is equivalent to edge (j, i)
    - (today we will only consider undirected graphs)

Adjacency Matrix

G can be uniquely described by its adjacency matrix $\boldsymbol{A}$:

- $A_{ij} = 1$ if $(i, j) \in E$
- For weighted graphs, $A_{ij} =$ weight for the (i, j)-th edge
- If G is undirected, $\boldsymbol{A}^\intercal = \boldsymbol{A}$
- Example:



$$\boldsymbol{A} = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{pmatrix}$$

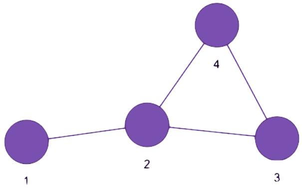
A Matter of Degrees

Degree d_i of vertex i = number of edges connecting to it:

$$d_i = \sum_{j=1}^{|V|} A_{ij}$$

- For weighted graphs, d_i is the sum of the edge weights connecting to node i.
- (For directed graphs, can consider the *in*-degree or *out* degree.)

$\boldsymbol{D}$ denotes a diagonal matrix such that $D_{ii} = d_i$:



$$\boldsymbol{D} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 3 & 0 & 0 \\ 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 2 \end{pmatrix}$$

Other Graph Matrices . . .

In general, we can think a matrix M in several ways:

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Other Graph Matrices ...

In general, we can think a matrix $\boldsymbol{M}$ in several ways:

- As a "table" (e.g., describing the connectivity);
- As an operator, ie, a function that maps a vector $\boldsymbol{x}$ to the vector $\boldsymbol{M}\boldsymbol{x}$;
- As uniquely defining a quadratic form, ie, providing a function that maps a vector $\boldsymbol{x}$ to a number $\boldsymbol{x}^\intercal \boldsymbol{M}\boldsymbol{x}$

I want to talk about the graph Laplacian, $\boldsymbol{L}$, by way of its quadratic form ...

Laplacian Quadratic Form

The Laplacian quadratic form:

$$\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x} = \sum_{(i,j) \in E} a_{ij} (x_i - x_j)^2 \,,$$

where

- a_{ij} is a (positive) edge weight for edge (i, j) if the graph is weighted;
- $a_{ij} = 1$ for edges in unweighted graphs; and
- $\boldsymbol{x}$ is a vector across the vertices V.

Consider the simpler unweighted case,

$$\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x} = \sum_{(i,j) \in E} (x_i - x_j)^2 \,.$$

Sum over edges

$$\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x} = \sum_{(i,j)\in E} (x_i - x_j)^2$$

can be thought of as the sum of per-edge Laplacians,

$$\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x} = \sum_{(i,j)\in E} x^\intercal L^{(i,j)} x \,,$$

(or, for weighted graphs, the weighted sum $\sum_{(i,j)\in E} a_{ij} x^\intercal L^{(i,j)} x$),

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It is easy to see that $L^{(i,j)} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}$, i.e.:

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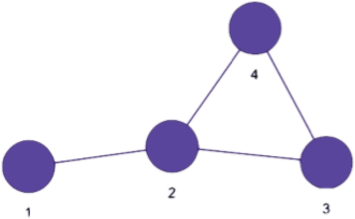
Thus, each "mini" Laplacian $L^{(i,j)}$ contributes 1 to the i-th and j-th diagonal entries of $\boldsymbol{L}$, and -1 to the entries corresponding to edge (i,j).

Laplacian matrix



$$L^{(i,j)} = \begin{pmatrix} \mathbf{1} & \mathbf{-1} \\ \mathbf{-1} & \mathbf{1} \end{pmatrix}$$

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 \\ -1 & 3 & -1 & -1 \\ 0 & -1 & 2 & -1 \\ 0 & -1 & -1 & 2 \end{pmatrix}$$

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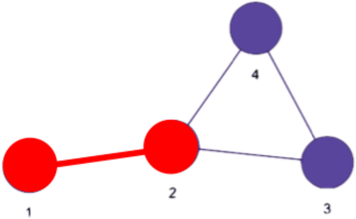

$$L^{(1,2)} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}$$

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 \\ -1 & 3 & -1 & -1 \\ 0 & -1 & 2 & -1 \\ 0 & -1 & -1 & 2 \end{pmatrix}$$

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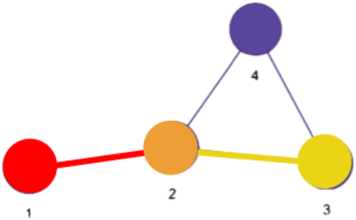
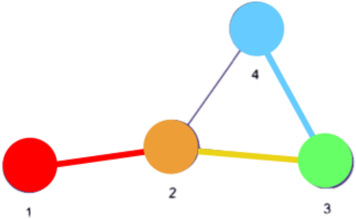


$$L^{(2,3)} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}$$

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 \\ -1 & 3 & -1 & -1 \\ 0 & -1 & 2 & -1 \\ 0 & -1 & -1 & 2 \end{pmatrix}$$

Laplacian matrix



$$L^{(3,4)} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}$$

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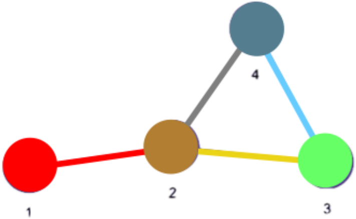
Laplacian matrix



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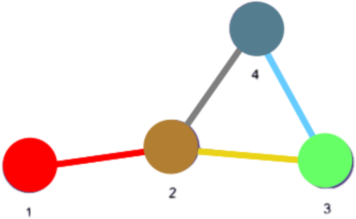
Laplacian matrix



$$L^{(i,j)} = \begin{pmatrix} 1 & -1 \\ -1 & 1 \end{pmatrix}$$

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 \\ -1 & 3 & -1 & -1 \\ 0 & -1 & 2 & -1 \\ 0 & -1 & -1 & 2 \end{pmatrix} = D - A$$

Properties of $\boldsymbol{L}$

$\boldsymbol{L} = \boldsymbol{D} - \boldsymbol{A}$

- For an *undirected* graph, $\boldsymbol{L}$ is symmetric.
- Diagonal entries are all positive.
- Off-diagonal entries are all non-positive.
- $\boldsymbol{L}$ is weakly diagonally dominant; row sums are 0.
- $\boldsymbol{L}$ is positive semidefinite.

"Laplacian"?

- Easy to show that $\boldsymbol{Lx}$ is the discrete form of the Laplace operator on a function $\boldsymbol{x_i} = f(\boldsymbol{v_i})$ of the vertices v_i.

  (Write the sum of unmixed partial 2nd derivatives as finite differences & set the spacing $h = 1$, i.e., one network "hop" away from the vertex v_i at which the Laplacian is being evaluated.)

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Interpretation?

$\boldsymbol{L}$ interpretation

- Vectors $\boldsymbol{x}$ that minimize $\boldsymbol{x}^\intercal \boldsymbol{L}\boldsymbol{x} = \sum_E (x_i - x_j)^2$ are trying to make the value at each node as similar to its neighbors as possible.
- Minimizing $\sum (x_i - x_j)^2$ represents minimizing the energy for many physical systems:
  - If the edges represent resistors and x_i measures the voltage at node i, current will flow such that $\sum_E (x_i - x_j)^2$ is minimized.
  - If the edges represent springs and x_i the displacement of a mass at node i, the nodes will move such that $\sum_E (x_i - x_j)^2$ is minimized.

$\boldsymbol{L}$ Eigendecomposition

- Minimize $\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x}$ subject to the constraint $\boldsymbol{x}^\intercal \boldsymbol{x} = 1 \ldots$
- Solution: eigenvectors/eigenvalues,

$$v_k = \operatorname*{argmin}_{x \perp v_0, \ldots, v_{k-1}} \frac{\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x}}{\boldsymbol{x}^\intercal \boldsymbol{x}}$$

$$\lambda_k = \min_{x \perp v_0, \ldots, v_{k-1}} \frac{\boldsymbol{x}^\intercal \boldsymbol{L} \boldsymbol{x}}{\boldsymbol{x}^\intercal \boldsymbol{x}}$$

  with $v_0 = \mathbf{1}/\sqrt{|V|}$, $\lambda_0 = 0$.
- $\lambda_1 =$ algebraic connectivity; indicates how easily the graph is partitioned (relaxation of min-cut), or, conversely, how readily the network will synchronize.
- Physical intuition for λ_k and v_k: frequencies and normal modes.

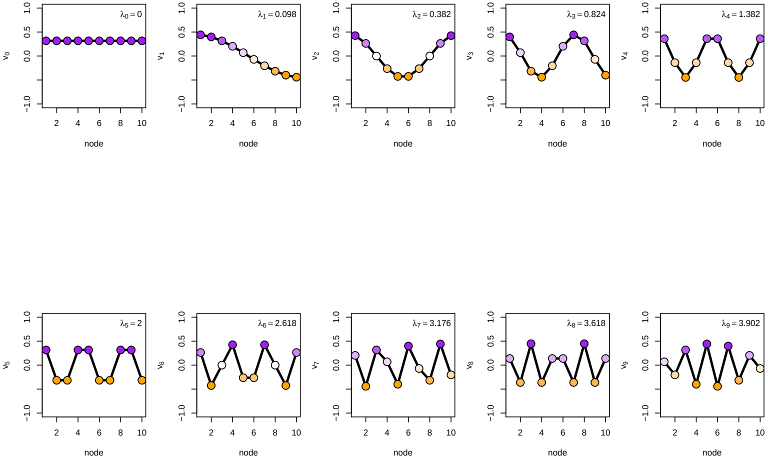
String

Consider a path graph; beads on a string:

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & \dots \\ -1 & 2 & -1 & 0 & 0 & \dots \\ 0 & -1 & 2 & -1 & 0 & \dots \\ 0 & 0 & -1 & 2 & -1 & \dots \\ 0 & 0 & 0 & -1 & 2 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

- Eigenvector v_k gives displacements of the beads that minimizes the nearest-neighbor distances, and is orthogonal to $v_0 \dots v_{k-1}$.
- Eigenvalues $\lambda_0 = 0 \leq \lambda_1 \leq \lambda_2 \leq \dots \leq \lambda_k$ give the associated pitch.

String


$\lambda_0 = 0$
$\lambda_1 = 0.098$
$\lambda_2 = 0.382$
$\lambda_3 = 0.824$
$\lambda_4 = 1.382$
$\lambda_5 = 2$
$\lambda_6 = 2.618$
$\lambda_7 = 3.176$
$\lambda_8 = 3.618$
$\lambda_9 = 3.902$
v_0
v_1
v_2
v_3
v_4
v_5
v_6
v_7
v_8
v_9
node
-1.0 0.0 0.5 1.0
2 4 6 8 10

Another string

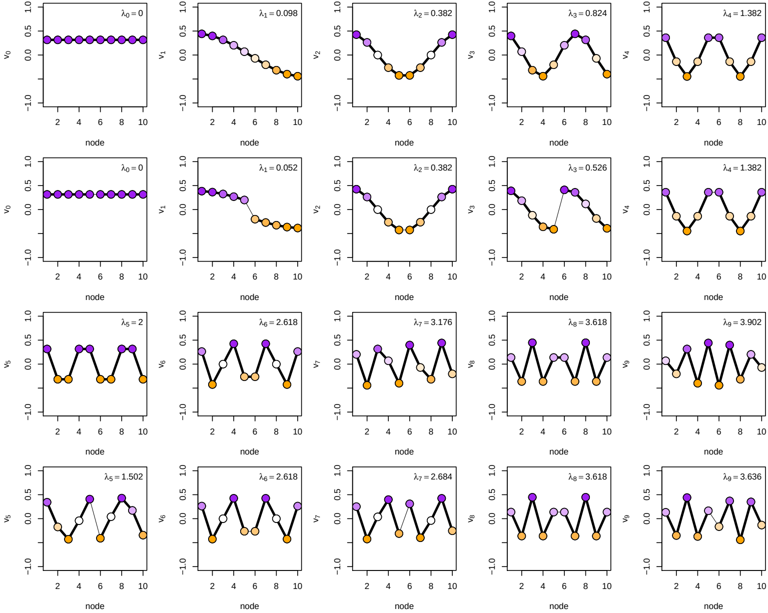
What if I reduce the weight of an edge?

$$L = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & \dots \\ -1 & 2 & -1 & 0 & 0 & \dots \\ 0 & -1 & 1.2 & -0.2 & 0 & \dots \\ 0 & 0 & -0.2 & 1.2 & -1 & \dots \\ 0 & 0 & 0 & -1 & 2 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

- Reducing the weight between the 5th & 6th vertex "decouples" the left and right portions of the string.
- Can minimize other nearest-neighbor distances at the expense of $x_5 - x_6$ to minimize $\sum a_{ij}(x_i - x_j)^2$.
- Odd modes (eigenvectors) with nodes 5 & 6 far apart are not as unfavorable; should have lower λ's.

NICO

Two strings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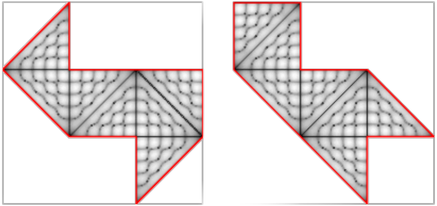
$\lambda_3 = 0.526$
$\lambda_4 = 1.382$
$\lambda_5 = 2$
$\lambda_6 = 2.618$
$\lambda_7 = 3.176$
$\lambda_8 = 3.618$
$\lambda_9 = 3.902$
$\lambda_5 = 1.502$
$\lambda_6 = 2.618$
$\lambda_7 = 2.684$
$\lambda_8 = 3.618$
$\lambda_9 = 3.636$
v_0
v_1
v_2
v_3
v_4
v_5
v_6
v_7
v_8
v_9
node

"Hearing the Shape" of a network

- The geometry of the network can tell us something about dynamics of processes on the network (e.g. displacements, flow of current).
- Changing the edge weights can result in changes to the spectrum λ.
- Atay &al 2006: a network's *spectral* properties, rather than other network statistics, determines the dynamics.
- Isospectral graphs exist! Much like isospectral drums:

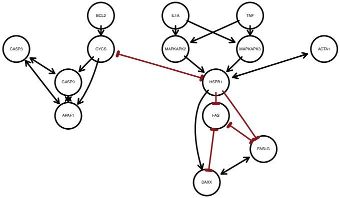


(Gordon, Webb, Wolpert 1992)

“Hearing the Shape” of Cancer

Spectral methods to infer aberrant network regulation

Pathway–level view



Idea: overlay experimental data onto a known interaction network and use the graph's spectral properties to say something about the behavior of the system as a whole.

Nodes in a network; the head of a drum.

- The graph Laplacian uniquely describes the geometry of a network (adjacency & degree of nodes, edge weights);
- Spectral decomposition of the graph Laplacian yields eigenvalue-eigenvector pairs that summarize the connectivity of the network and reveal its dynamical properties.

Lively Networks

R. Braun

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Graph Defns

Laplacian

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Application

Spectral Pathway Analysis

Inferring Dynamics

Conclusions

Open questions

Thanks!

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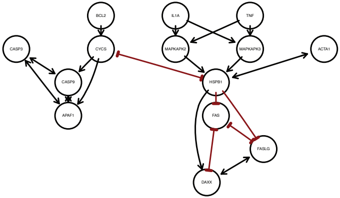
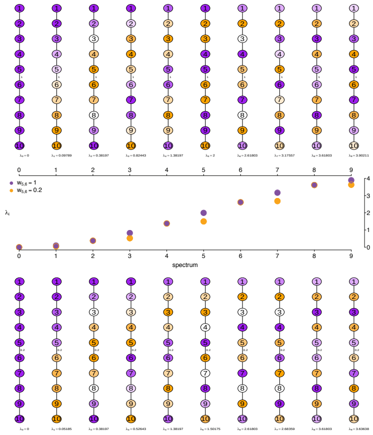


Idea: overlay experimental data onto a known interaction network and use the graph's spectral properties to say something about the behavior of the system as a whole.

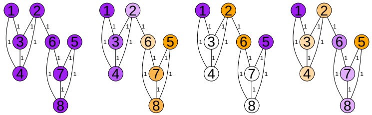
- Integrates both gene expression and gene *co*-expression (correlation, MI, etc) data;
- Incorporates the pathway network topology (not all edges/nodes are equally critical);
- Encapsulates the bulk variation in the data for genes on that pathway;
- Robust to noise in gene expression measurements;
- Permits inferences about gene expression dynamics.

Prioritizing interactions

Not all alterations are equally important; want to identify differences that significantly impact network dynamics.

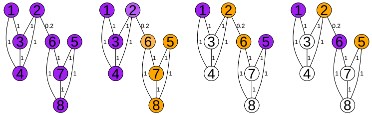


$a_{2,6} = 1,\ a_{2,4} = 1 \ \Rightarrow \lambda_1 = 0.29$:



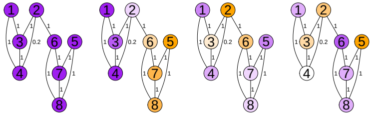
$\lambda_0 = 0$ $\lambda_1 = 0.29072$ $\lambda_2 = 2$ $\lambda_3 = 2.80606$

$a_{2,6} = 0.2,\ a_{2,4} = 1 \ \Rightarrow \lambda_1 = 0.08$:



$\lambda_0 = 0$ $\lambda_1 = 0.08848$ $\lambda_2 = 2$ $\lambda_3 = 2.19802$

$a_{2,6} = 1,\ a_{2,4} = 0.2 \ \Rightarrow \lambda_1 = 0.25$:



$\lambda_0 = 0$ $\lambda_1 = 0.2482$ $\lambda_2 = 1.6007$ $\lambda_3 = 2.76056$

Spectral Pathway Analysis

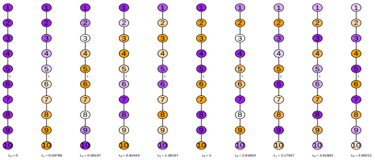
We can use these properties to:

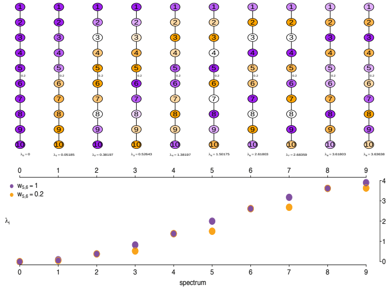
- Detect pathways (networks) that appear to be differentially connected in cases vs. controls;
- Identify elements that contribute to network-wide gene regulatory differences;
- Make inferences about the time evolution of the network (under certain assumptions of gene regulation);
- Identify new regulators of network dynamics.

Several appealing features:

- No reliance on single-gene association statistics – consider "bulk" pathway behavior;
- Natural way to prioritize critical interactions;
- Noise reduction/robustness via filtering high-eigenvalued eigenvectors.

Pathway-wide coexpression





Comparing spectra:

Identify coexpression changes that are likely to influence bulk pathway characteristics.

Starting with putative pathway topology:

1. Weight the edges based on class-conditional gene-gene coexpression data;
2. Calculate eigenvalues and take differences between phenotypes;
3. Permute phenotype labels to assess statistical significance and flag pathways with significant spectral differences.

Application

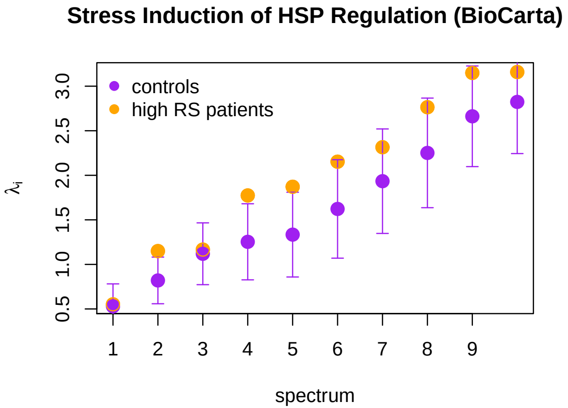
Radiation sensitivity study (public data, Reiger 2004, GEO accession GSE1725):

- Four phenotypes:
  - high radiation sensitivity cases (n=14)
  - low radiation sensitivity controls (n=13)
  - healthy controls (n=15)
  - skin cancer patients (n=15);
- Three radiation exposures: UV, ionizing radiation, mock;
- RNA from 171 samples hybridized to Affy HGU95Av2 chips (12625 probes);
- Intensities normalized using RMA [Bolstad 2003];
- Pathways retrieved from the NCI-PID database (663 pathways, 1195 connected components).

Systematically search all connected components for significant spectral differences in cases vs. controls.

Results: HSP pathway

An illustrative example (13th most significant):



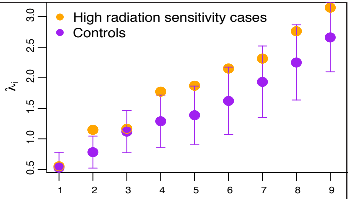
High λ_2 in the high radiation-sensitivity patients corresponds to increased coupling across the pathway. . .

HSP pathway

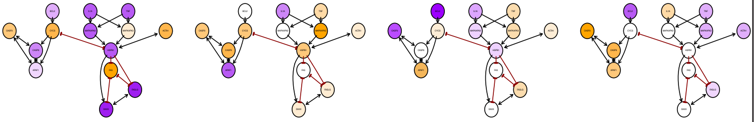
Example pathway: Stress Induction of HSP [BioCarta]

Inset right: spectrum of the pathway in cases vs. controls for first 9 eigenvalues. Errorbars indicate difference between case and control spectra under random label permutations, centered about true control values.

Below: network colored by eigenvectors values for the first four mode in cases vs. controls. Intensity of color indicates magnitude; purple and orange are of opposite sign.

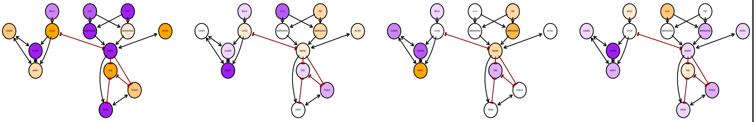


High radiation sensitivity cases:



λ_1=0.55211 λ_2=1.14978 λ_3=1.16619 λ_4=1.77413

Controls:



λ_1=0.52951 λ_2=0.82013 λ_3=1.1192 λ_4=1.25352

NORTHWESTERN UNIVERSITY

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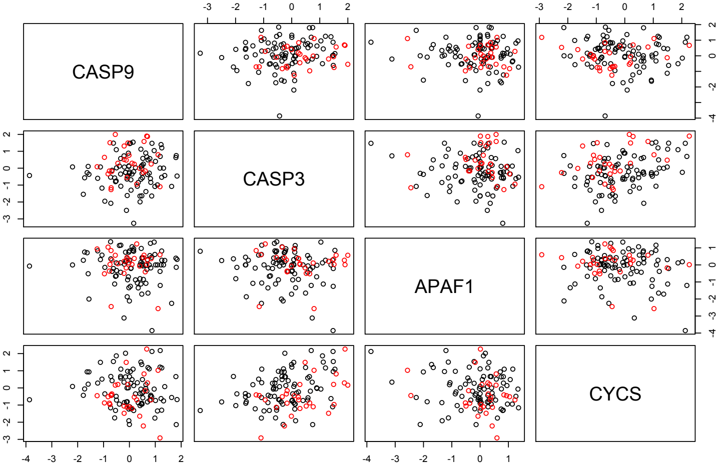
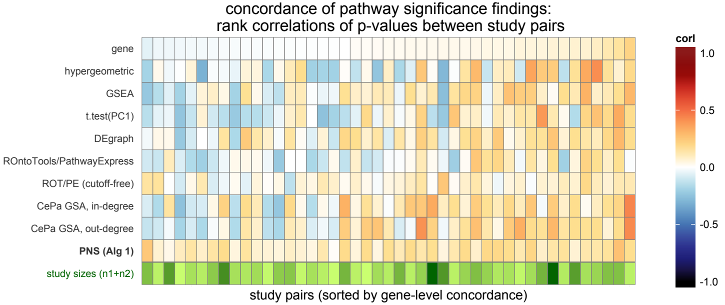
Thanks!

Subtle differences



Cross-study concordance

Exceptional cross-study concordance compared with other methods:



From Network Structure to Network Function

Inferring differences in pathway dynamics from analysis of "snapshot" data.

From structure to function

Projection onto the network eigenvectors:

- Analogous to using PCA for dimension reduction, but "topology–aware;"
- Assess which modes are being hit in the phenotype of interest, *without* requiring that all samples do so in the same way.

  E.g., the same mode may be excited by down regulating one subnetwork or upregulating another, admitting molecular heterogeneity of complex diseases.
- In principle, these may be predictive of the pathway's dynamical response to the perturbation of a gene.

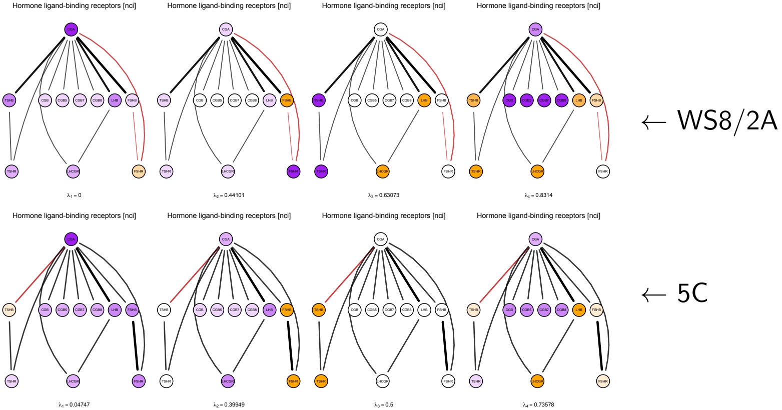
Spectral differences ⇒ dynamical differences

Projection onto the network eigenvectors:

- ER+ breast cancer study using MCF-7 cells:
  - WS8 estrogen-dependent growth (typical ER+: deprive estrogen);
  - 2A non-responsive to estrogen deprivation;
  - 5C apoptoses in reponse to estrogen (after long-term estrogen deprivation).
- Edge weights assigned from a static "snapshot" study of cells under normal growth conditions;
- Pathway with significantly different spectra are flagged;
- Data from a separate time-course study following estrogen exposure is projected onto the eigenspace of those networks weighted by the WS8 data.

Differential connectivity

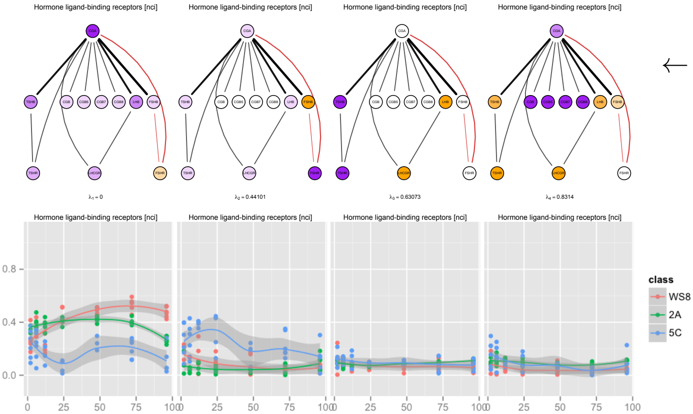
Hormone ligand binding receptors: first 4 "modes"



(Recall: WS8 requires estrogen; 2A does not; 5C dies.)

Differential dynamics

Projection of gene expression onto pathway eigenvectors:



← WS8/2A

time→

Significantly different projections over time. Notably, the WS8 cells all tend toward the first (lowest eigenvalued) mode over time, while 2A cells do not sustain the response and 5C move away from it.

Open questions

We assumed:

- undirected graphs;
- positive edge weights;
- no self links.

However, real biological networks:

- are directed (i may control j but not vice-versa);
- have both activating ($+$) and inhibiting (–) interactions;
- have autoregulating nodes (self loops).

Issues:

- If $L \nsucceq 0$, how should we interpret the complex spectrum or non-orthogonal eigenvectors?
- Is there a way to formulate the analysis to ensure $L \succeq 0$?
- What is the minimal number of edge-weight changes required to recover the spectral properties of a graph?

Thanks!

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$fin.$