A SYSTEMS APPROACH TO DISSECTING THE TISSUE-SPECIFIC ARCHITECTURE OF CELLULAR NETWORKS

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Outline

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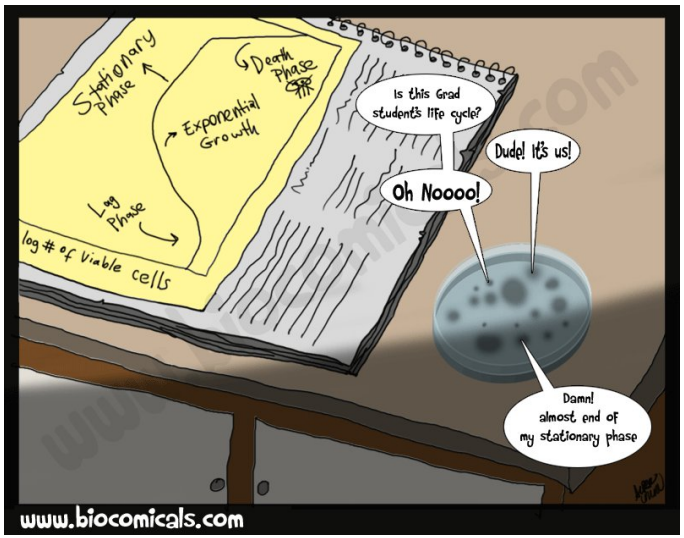
Yeast Aging



Courtesy of Alper Uzan, PhD.

- Yeast as a model organism for aging research:
  - ✓ Rapid growth
  - ✓ Ease of manipulation
- Replicative life-span (RLS): the number of buds a mother cell can produce before senescence occurs
- Chronological life-span (CLS): duration of viability after entering the stationary-phase

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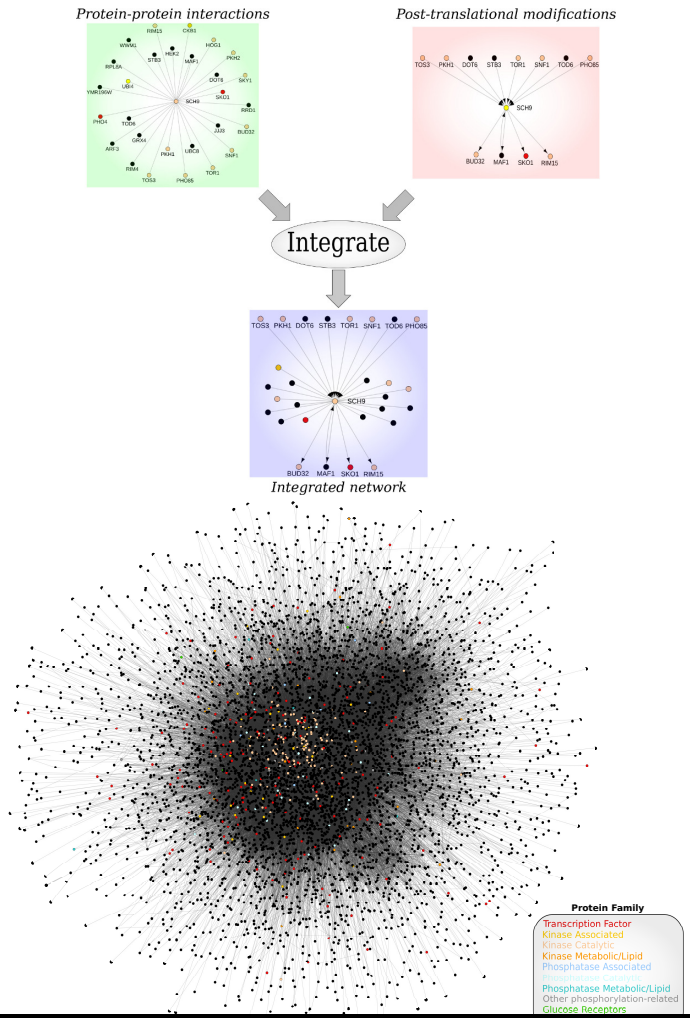
YEAST INTERACTOME



- *Mixed network:* Contains both directed (biochemical activities) and undirected (protein-protein interactions) edges
- 103,619 (63,395 non-redundant) physical interactions among 5,691 proteins.
- 5,791 (5,443 non-redundant) biochemical activities (mostly phosphorylation events) among 2,002 kinase-substrate pairs.

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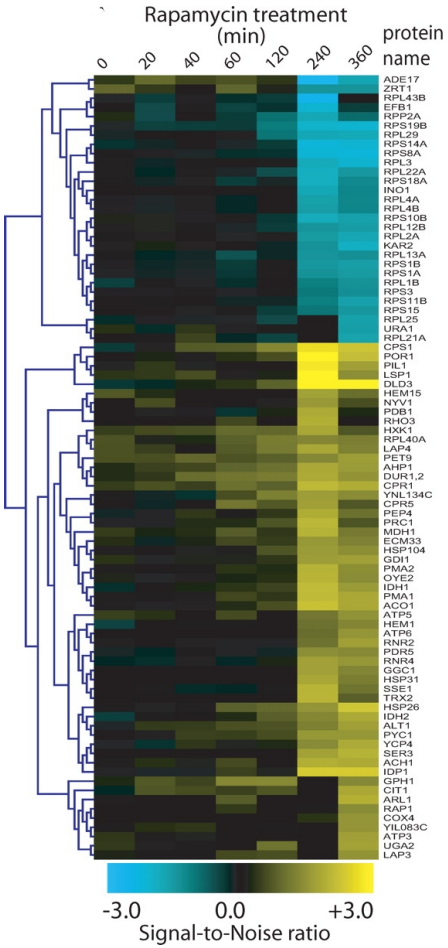
Transcriptional regulatory network (TRN) of yeast

- Directed graph
- Downloaded from the Yeast Search for Transcriptional Regulators And Consensus Tracking (YEASTRACT)
- Consists of 48,082 interactions between 183 transcription factors (TF) and 6,403 target genes (TG).

RAPAMYCIN-TREATMENT DATASET



Adopted from Fournier et al., 2010

- **Rapamycin**: A lipophilic macrolide that directly binds to and inhibits TOR *in vivo*
- Temporal analysis of gene expression changes for 6,000 ORFs in Baker's yeast, *Saccharomyces cerevisiae*, over 6h of rapamycin treatment.
- 366 repressed and 291 induced genes at a minimum threshold of 2-fold change.

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Directional information flow

Random walk

Definition

Random walk on a graph G, initiated from vertex v, is the sequence of transitions among vertices, starting from v. At each step, the random walker randomly chooses the next vertex from among the neighbors of the current node.

It is a Markov chain with the transition matrix P, where $p_{ij} = Prob(S_{n+1} = v_i | S_n = v_j)$ and random variable S_n represents the state of the random walk at the time step n.

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Directional information flow

Random walk with restart

Definition

Random walk with restart (RWR) is a modified Markov chain in which, at each step, a random walker has the choice of either continuing along its path, with probability α, or jump (teleport) back to the initial vertex, with probability $1 - \alpha$.

The transition matrix of the modified chain, M, can be computed as $M = \alpha P + (1 - \alpha)\boldsymbol{e}_v \mathbf{1}^T$, where $\boldsymbol{e}_v$ is a stochastic vector of size n having zeros everywhere, except at index v, and $\mathbf{1}$ is a vector of all ones.

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Directional information flow

Stationary distribution

The portion of time spent on each node in an infinite random walk with restart initiated at node v, with parameter α.

Definition

Stationary distribution of the modified chain

$$\begin{aligned} \pi_v(\alpha) &= M\pi_v(\alpha) \\ &= (\alpha P + (1-\alpha)\mathbf{e}_v\mathbf{1}^T)\pi_v(\alpha) \end{aligned}$$

Enforcing a unit norm on the dominant eigenvector to ensure its stochastic property, $\| \pi_v(\alpha) \|_1 = \mathbf{1}^T\pi_v = 1$, we will have:

Directional information flow

Stationary distribution–continue

Definition

Iterative form of the information flow process:

$$\pi_v(\alpha) = \alpha P \pi_v(\alpha) + (1-\alpha)\boldsymbol{e}_v,$$

Definition

Explicit (direct) formulation of the information flow process:

$$\pi_v(\alpha) = \underbrace{(1-\alpha)(I-\alpha P)^{-1}}_{Q}\boldsymbol{e}_v,$$

Directional information flow
Interpretation

Definition

Expansion using the Neumann series:

$$\pi_v(\alpha) = (1-\alpha)\sum_{i=0}^{\infty}(\alpha P)^i \boldsymbol{e}_v$$

Thus, $\pi_v(\alpha)$ is a function of:

- Distance to source node (v)
- Multiplicity of paths

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Sidebar: Functional PageRank (PR)

Computing PageRank (PR)

- PageRank as a *random surfer process*: Start surfing from a random node and keep following links with probability μ restarting with probability $1 - \mu$; the node for restarting will be selected based on a personalization vector v. The ranking value x_i of a node i is the probability of visiting this node during surfing.
- PR can also be cast in power series representation as $x = (1 - \mu) \sum_{j=0}^{k} \mu^j S^j v$; S encodes column-stochastic adjacencies.

Functional rankings

- A general method to assign ranking values to graph nodes as $x = \sum_{j=0}^{k} \zeta_j S^j v$. PR is a functional ranking, $\zeta_j = (1 - \mu)\mu^j$.
- Terms attenuated by outdegrees in S *and* damping coefficients ζ_j.

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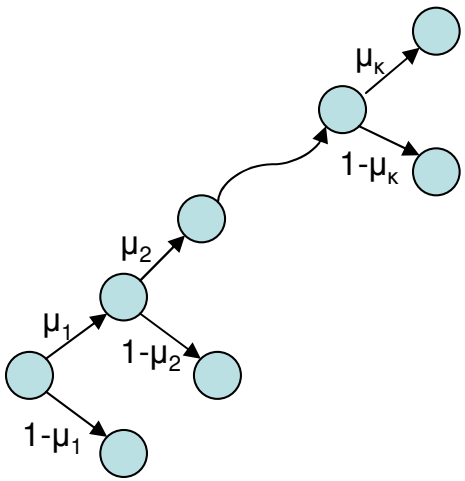
Functional Rankings Through Multidamping [Kollias, Gallopoulos, AG, TKDE'13]



Computing μ_j in Multidamping

Simulate a functional ranking by random surfers following emanating links with probability μ_j at step j given by :

$$\mu_j = 1 - \frac{1}{1+\frac{\rho_{k-j+1}}{1-\mu_{j-1}}}, j = 1, ..., k,$$

where $\mu_0 = 0$ and $\rho_{k-j+1} = \frac{\zeta_{k-j+1}}{\zeta_{k-j}}$

Examples

LinearRank (LR) $x^{\mathrm{LR}} = \sum_{j=0}^{k} \frac{2(k+1-j)}{(k+1)(k+2)} S^j v : \mu_j = \frac{j}{j+2}, j = 1, ..., k.$

TotalRank (TR) $x^{\mathrm{TR}} = \sum_{j=0}^{\infty} \frac{1}{(j+1)(j+2)} S^j v : \mu_j = \frac{k-j+1}{k-j+2}, j = 1, ..., k.$

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Multidamping and Computational Cost

Advantages of multidamping

- Interpretability and Design!
- Reduced computational cost in *approximating* functional rankings using the Monte Carlo approach. A random surfer terminates with probability $1 - \mu_j$ at step j.
- Inherently parallel and synchronization free computation.

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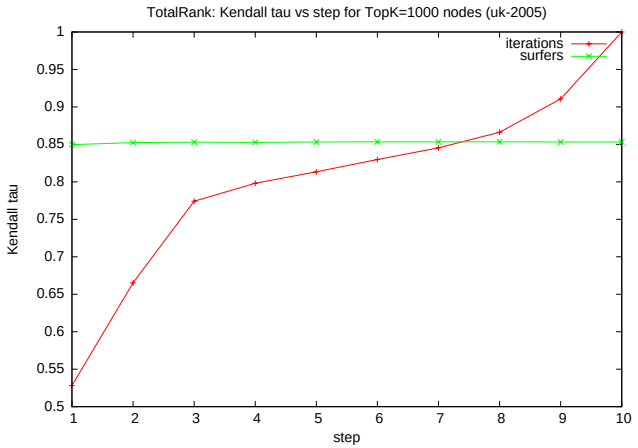
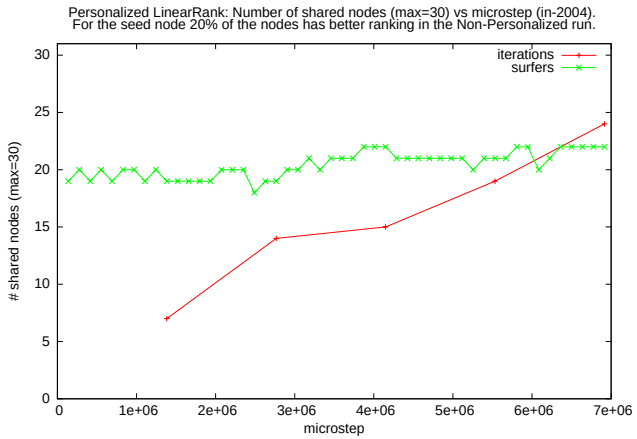
MULTIDAMPING PERFORMANCE





Approximate ranking: Run n surfers to completion for graph size n. How well does the computed ranking capture the "reference" ordering for `top`$-k$ nodes, compared to standard iterations of equivalent computational cost/number of operations? *[Left]*

Approximate personalized ranking: Run less than n surfers to completion (each called a microstep, x-axis), from a selected node (personalized). How well can we capture the "reference" `top`$-k$ nodes, i.e., how many of them are shared (y-axis), compared to the

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Experimental settings

We set the preference vector as:

$$e_{\mathcal{S}}(i) = \begin{cases} \frac{1}{|\mathcal{S}|} & \text{if } v_i \in \mathcal{S}, \\ 0 & \text{O.W.} \end{cases}$$

for $\mathcal{S}$ being the subset of vertices in the yeast interactome corresponding to members of the TORC1 protein complex. The diameter of the network is computed to be 6 and α parameter is set to $\frac{d}{d+1} = \frac{6}{7} \sim 0.85$ accordingly to give all nodes a fair chance of being visited.

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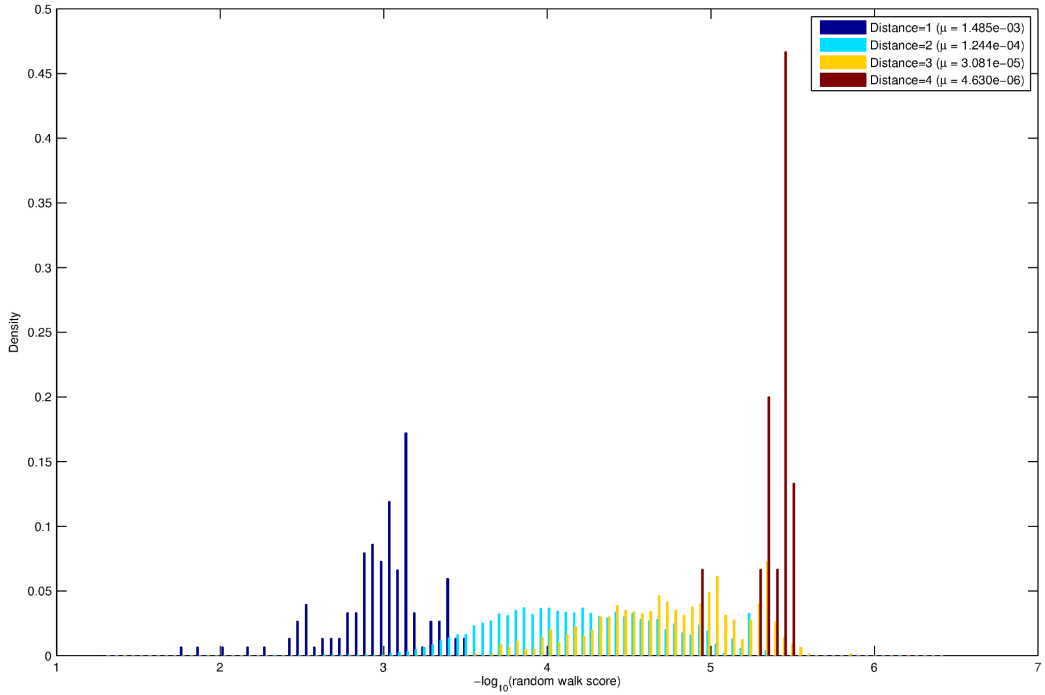
DISTRIBUTION OF INFORMATION FLOW SCORES

Distribution of information flow scores across nodes with similar distance from members of TORC1 are color coded accordingly. The μ parameter is the average of information flow scores for nodes under each distribution.



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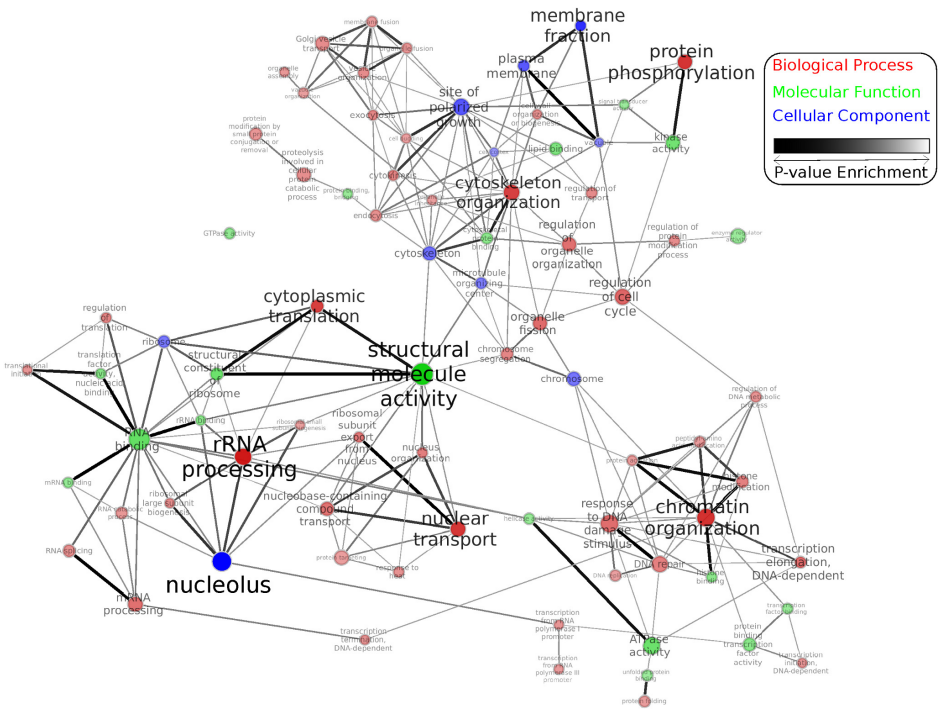
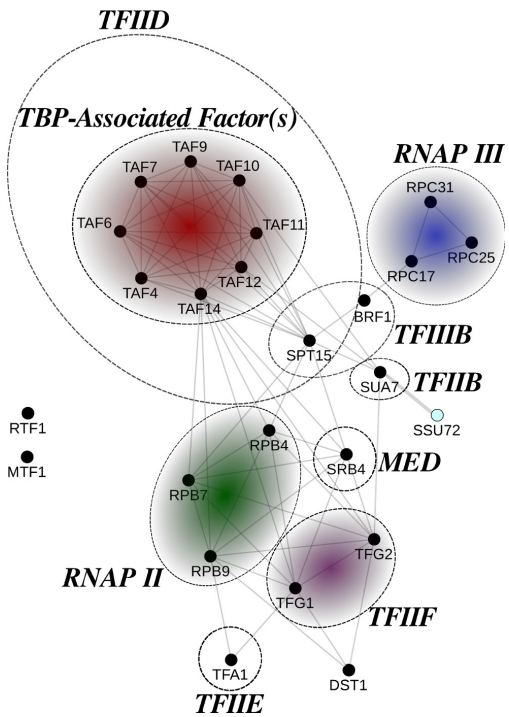
Enrichment map of yeast GOslim terms

Enriched terms are identified by mHG p-value, computed for the ranked-list of genes based on their information flow scores. Each node represents a significant GO term and edges represent the overlap between genesets of GO terms. Terms in different branches of GO are color-coded with red, green, and blue. Color intensity of each node represents the significance of its p-value, while the node size illustrates the size of its geneset. Thickness of edges is related to the extent of overlap among genesets.



TOR-DEPENDENT CONTROL OF TRANSCRIPTION INITIATION

Induced subgraph in the yeast interactome, constructed from the top-ranked genes in the information flow analysis that are annotated with the transcription initiation GO term. Different functional subunits are marked and color-coded appropriately.



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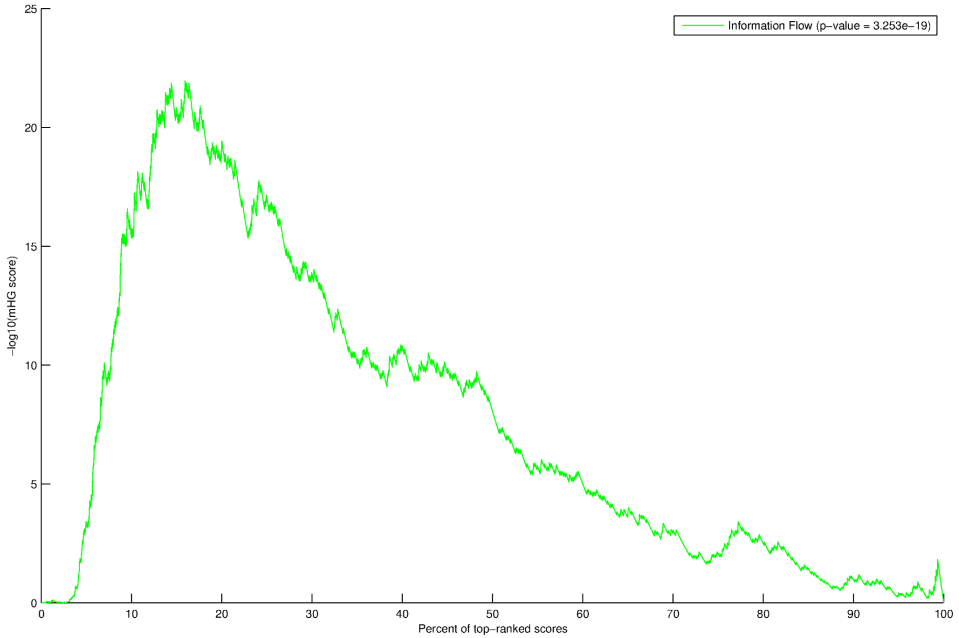
Enrichment plot for Rapamycin-treatment dataset

Enrichment score as a function of the score percentage. Computations are based on the set of differentially expressed genes in response to Rapamycin treatment. The peak of plot occurs at around top 15% of scores, resulting in the minimum hypergeometric (mHG) score of $\sim 1e-22$. The exact p-value for this score is computed, using dynamic programing, to be $3.3e-19$.



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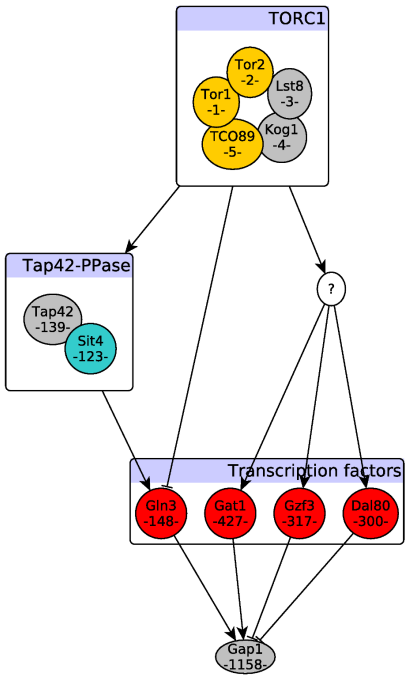
TORC1-DEPENDENT REGULATION OF GAP1

The schematic diagram is based on literature evidence for the interactions. Each node in the signaling pathway is annotated with the rank of its information flow score from TORC1. Ranking of nodes based on their information flow scores respect our prior knowledge on the structure of this pathway.



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Outline

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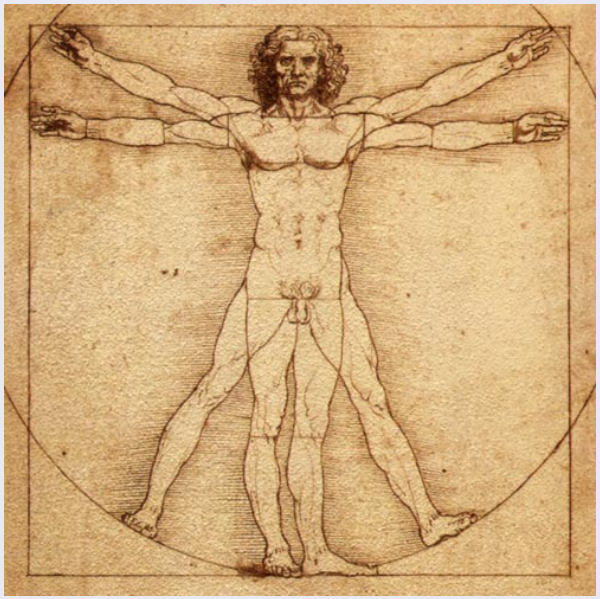
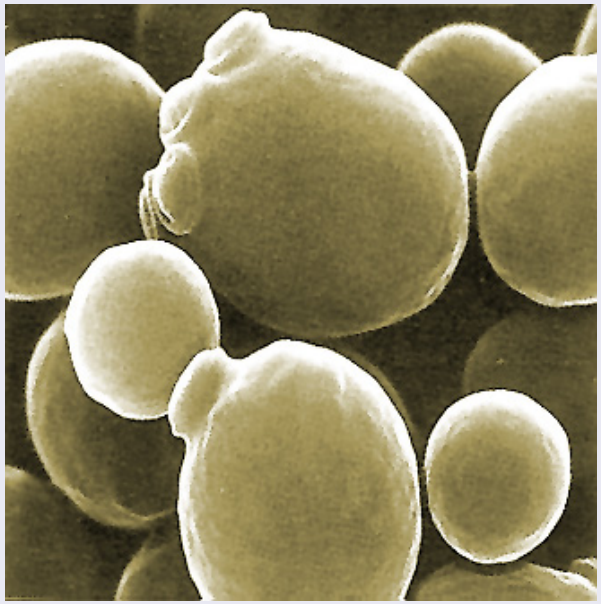
Comparative Network Analysis

Traditional approach

Key Challenge



$\Longleftrightarrow$



To project functional pathways from a well-studied organism, such as yeast, back to a higher-order organism, such as humans.

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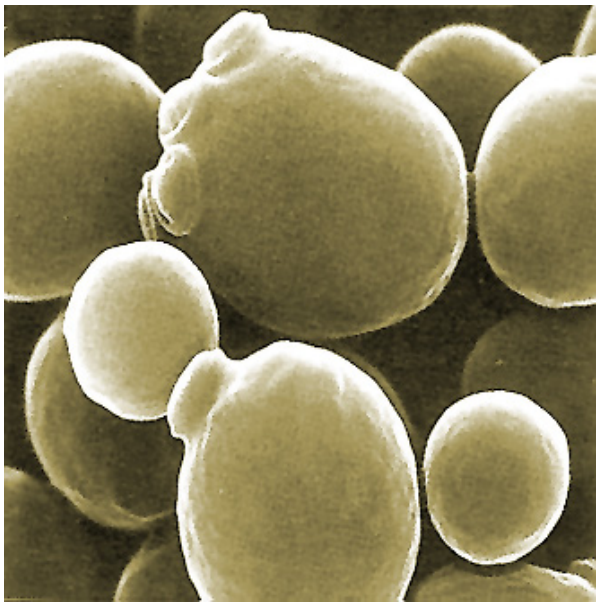
YEAST AS A KEY MODEL ORGANISM

SIMPLE YET POWERFUL



"... yeast has graduated from a position as the premier model for eukaryotic cell biology to become the pioneer organism that facilitated the establishment of entirely new fields of study called *functional genomics* and *systems biology*." – D. Botstein and G. Fink (2011).

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Yeast as a key model organism

Why yeast?

- Rapid growth and ease of manipulation
- Mature genetic and molecular toolbox, including deletion mutants, over-expression libraries, and green fluorescent protein (GFP)-tagged yeast strains
- Multitude of high-throughput datasets, ranging from genetic arrays, transcriptome, proteome, and metabolome profiles
- Saccharomyces Genome Database (SGD)

SGD Saccharomyces GENOME DATABASE

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Conserved pathways between yeast and higher-order organisms

Many of the underlying functionalities and associated machineries are shared with higher eukaryotes:

- Cell cycle
- Programmed cell death
- Protein folding, quality control, and degradation
- Signaling pathways, such as MAPK, TOR, and insulin/IGF-I
- Aging and CR-mediated pathways
  - **Chronological:** amount of time cells survive in post-mitotic state
  - **Replicative:** number of times a cell can divide before senescence occurs.

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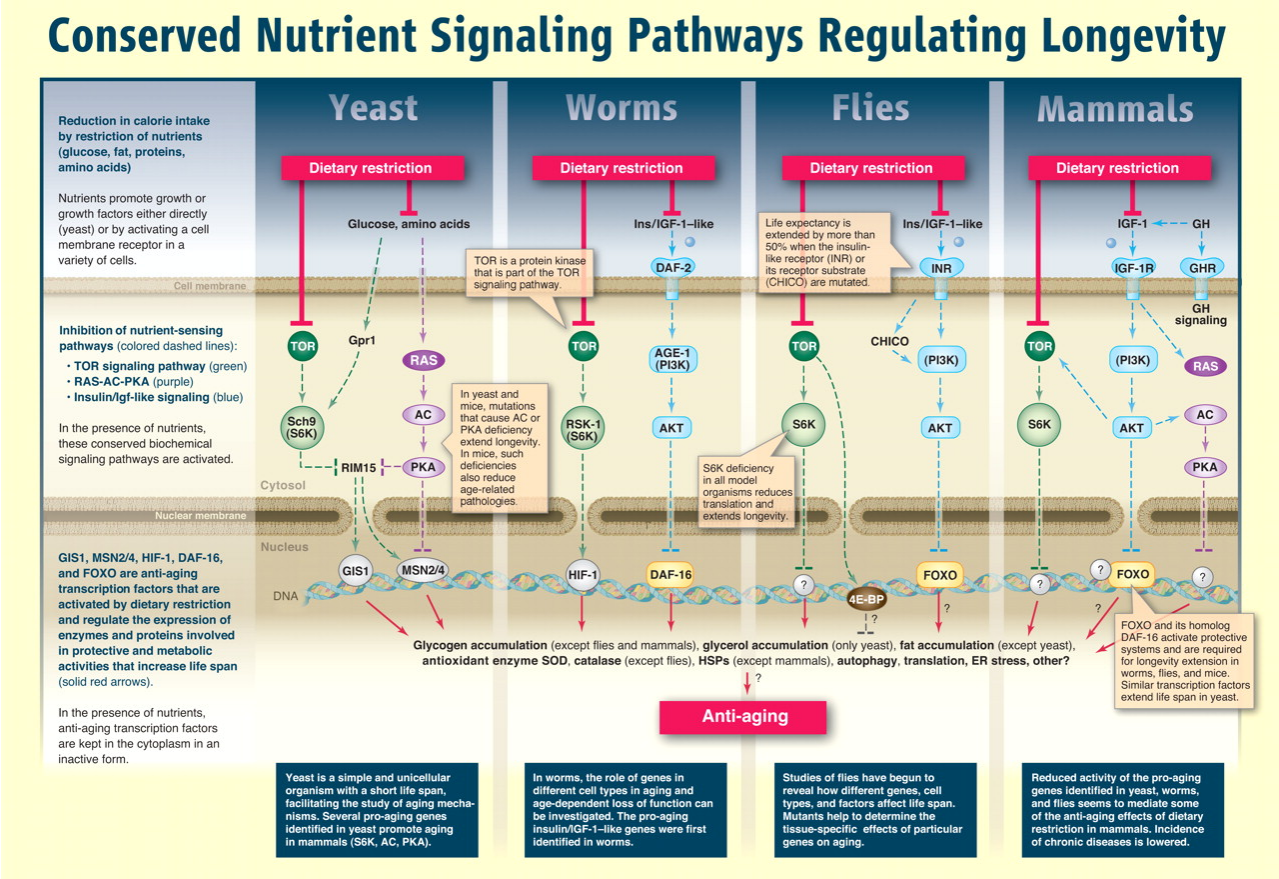
Conserved pathways
Continued



Fontana *et al*, Science (2010)

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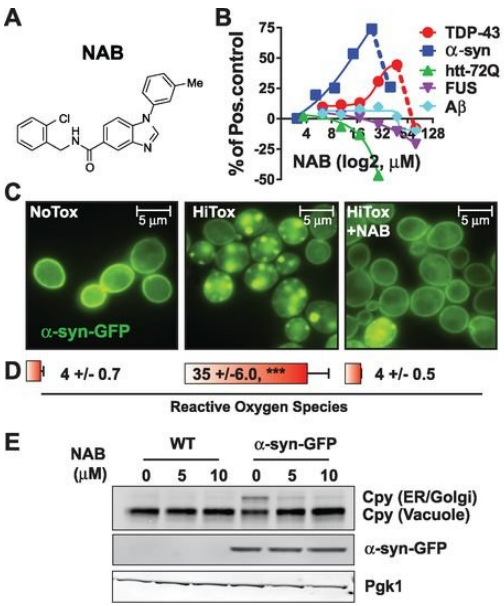
YEAST AS A MODEL ORGANISM FOR HUMAN DISEASE

RECENT SUCCESS STORIES



Adopted from D. Tardiff *et al.* (2013)

- Heterologous expression of disease gene(s)
- Yeast as an unbiased phenotypic screen
- N-aryl benzimidazole (NAB) strongly protects cells from α-synuclein toxicity in the humanized yeast model
- Validated this discovery using iPS cell from Parkinson's patients with α-Syn mutation

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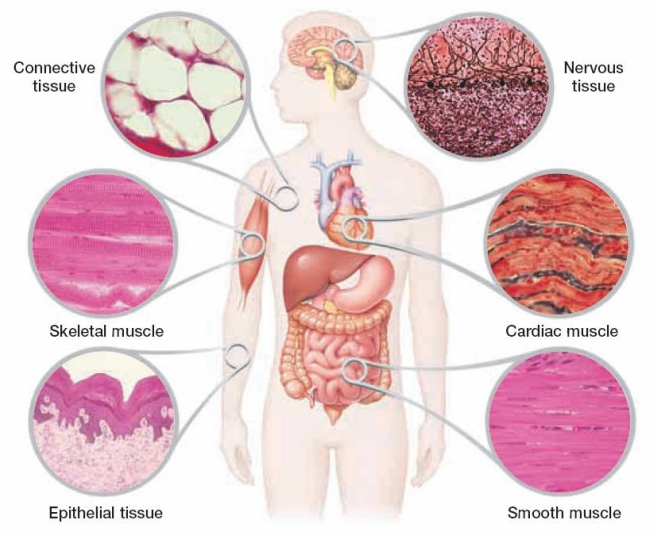
PROBLEM STATEMENT

For which tissues is yeast a good model organism?



Different human tissues, while inheriting a similar genetic code, exhibit unique anatomical and physiological properties.

What are the shared/ missing functional components in yeast, compared to human tissues?

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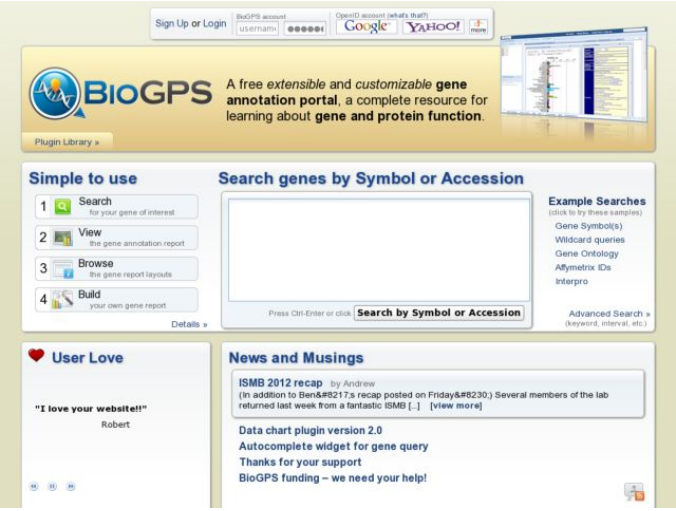
TISSUE-SPECIFIC GENE EXPRESSION

The GNF Gene Atlas dataset:



- 79 different tissues
- 44,775 human transcripts
- Platforms:
  1. Affymetrix HG-U133A.
  2. Custom GNF1H array.

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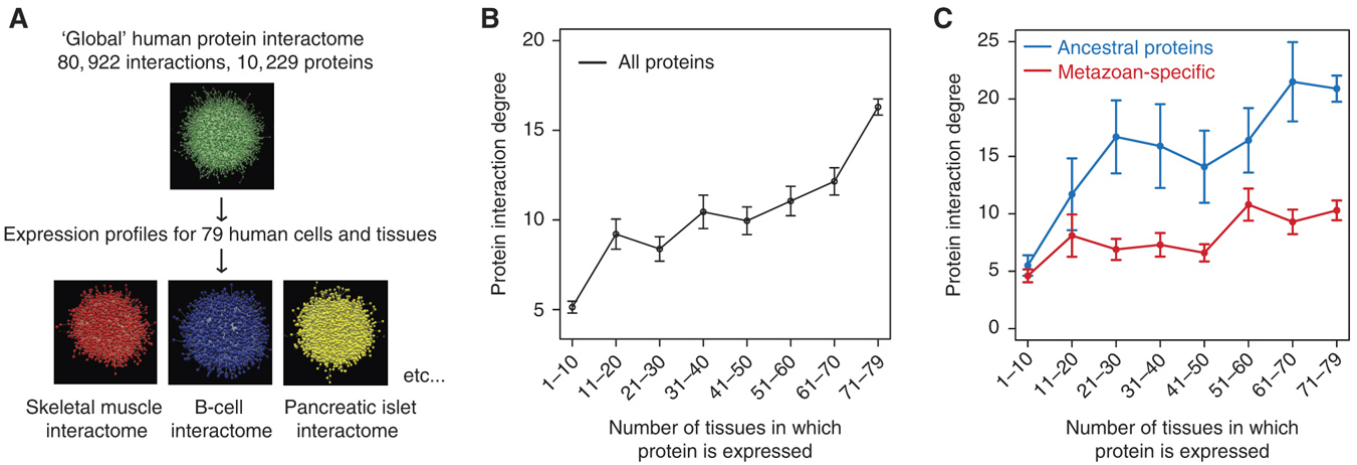
TISSUE-SPECIFIC INTERACTOMES

- Vertex-induced subgraphs of the global human interactome
- Based on the GNF Gene Atlas dataset

  $\Rightarrow$ A gene is considered as present in a tissue, if its normalized expression level is $>$ 200 (average difference between match-mismatch pairs).



Adopted from Bossi et al., 2009

SEQUENCE SIMILARITY OF PROTEIN PAIRS

- Protein sequences are downloaded from Ensembl database, release 69.
- Reference genomes:
  - **Human**: GRCh37
  - **Yeast**: EF4
- Number of protein sequences:
  - **Human**: 101,075
  - **Yeast**: 6,692
- Low-complexity regions are masked using **pseg**
- Smith-Waterman algorithm is used to compute local sequence alignments.

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SPARSE NETWORK ALIGNMENT

Integer Quadratic Program– Approximated using Belief Propagation:

$$\max_{\boldsymbol{x}} \quad (\alpha \boldsymbol{w}^T \boldsymbol{x} + \frac{\beta}{2} \boldsymbol{x}^{\mathsf{T}} \mathcal{S} \boldsymbol{x})$$

$$\text{Subject to:} \quad \begin{cases} \mathcal{C}\boldsymbol{x} \leq \mathbf{1}_{n_G * n_H} & \text{Matching constraints;} \\ x_{ii'} \in \{0,1\}, & \text{Integer constraint.} \end{cases}$$

- $\boldsymbol{x}$: Matching vector
- L: Bipartite graph of similarities between pair of proteins in input networks
- $\boldsymbol{w}$: Edge-weights in the graph L (based on sequence similarities)
- $\mathcal{S}$: Matrix encoding conserved edges in the product graph ($G \otimes H$)
- $\mathcal{C}$: Incidence matrix of graph L

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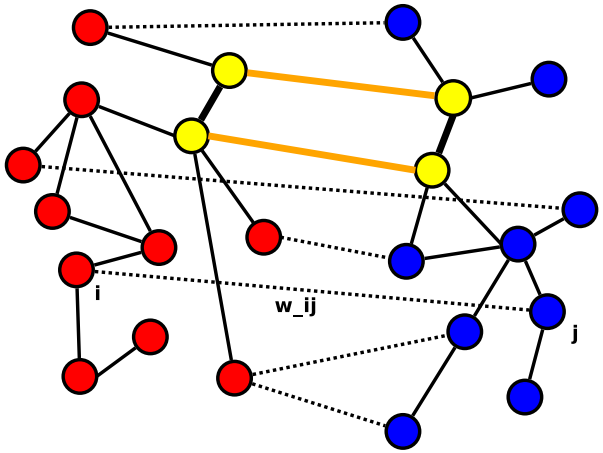
Sidebar: Network Alignment



- **Node similarity:** Two nodes are similar if they are linked by other similar node pairs. By pairing similar nodes, the two graphs become *aligned*.

- Let $\tilde{A}$ and $\tilde{B}$ be the normalized adjacency matrices of the graphs (normalized by columns), H_{ij} be the independently known similarity scores (preferences matrix) of nodes $i \in V_B$ and $j \in V_A$, and μ be the fractional contribution of topological similarity.
- To compute X, IsoRank iterates:

$$X \leftarrow \mu \tilde{B} X \tilde{A}^T + (1 - \mu) H$$

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Network Similarity Decomposition (NSD) [Kollias, Mohammadi, AG, TKDE'12]

Network Similarity Decomposition (NSD)

- In n steps of we reach
  $X^{(n)} = (1-\mu)\sum_{k=0}^{n-1} \mu^k \tilde{B}^k H(\tilde{A}^T)^k + \mu^n \tilde{B}^n H(\tilde{A}^T)^n$
- Assume that $H = uv^T$ (1 component). Two phases for X:
  1. $u^{(k)} = \tilde{B}^k u$ and $v^{(k)} = \tilde{A}^k v$ *(preprocess/compute iterates)*
  2. $X^{(n)} = (1-\mu)\sum_{k=0}^{n-1} \mu^k u^{(k)} {v^{(k)}}^T + \mu^n u^{(n)} {v^{(n)}}^T$ *(construct X)*

  This idea extends to s components, $H \sim \sum_{i=1}^{s} w_i z_i^T$.
- NSD computes matrix-vector iterates and builds X as a sum of outer products; these are much cheaper than triple matrix products.

We can then apply Primal-Dual or Greedy Matching (1/2 approximation) to extract the actual node pairs.

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NSD: Performance [Kollias, Madan, Mohammadi, AG, BMC RN'12]

Species	Nodes	Edges
celeg (worm)	2805	4572
dmela (fly)	7518	25830
ecoli (bacterium)	1821	6849
hpylo (bacterium)	706	1414
hsapi (human)	9633	36386
mmusc (mouse)	290	254
scere (yeast)	5499	31898

Species pair	NSD (secs)	PDM (secs)	GM (secs)	IsoRank (secs)
celeg-dmela	**3.15**	152.12	7.29	783.48
celeg-hsapi	**3.28**	163.05	9.54	1209.28
celeg-scere	**1.97**	127.70	4.16	949.58
dmela-ecoli	**1.86**	86.80	4.78	807.93
dmela-hsapi	**8.61**	590.16	28.10	7840.00
dmela-scere	**4.79**	182.91	12.97	4905.00
ecoli-hsapi	**2.41**	79.23	4.76	2029.56
ecoli-scere	**1.49**	69.88	2.60	1264.24
hsapi-scere	**6.09**	181.17	15.56	6714.00

- We compute similarity matrices X for various pairs of species using Protein-Protein Interaction (PPI) networks. $\mu = 0.80$, uniform initial conditions (outer product of suitably normalized 1's for each pair), 20 iterations, one component.
- We then extract node matches using PDM and GM.
- *Three orders of magnitude speedup* from NSD-based approaches compared to IsoRank.

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NSD: Parallelization [KKG JPDC'14 (to appear)]

Parallelization: NSD has been ported to parallel and distributed platforms.

- We have aligned up to million-node graph instances using over 3K cores.
- We process graph pairs of over a billion nodes and twenty billion edges each (!), on MapReduce-based distributed platforms.

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Random model for tissue-specific networks

Definition

- Global human interactome: All potential interactions between human proteins, represented by graph $G = (V_G, E_G)$
- Tissue-specific network(s): Vertex-induced subgraph(s) of the Global human interactome, represented by $G_T = (V_T, E_T)$ with $n_T = |V_T|$, $V_T \subset V_G$, and $E_T \subset E_G$
- Universal genes: Ubiquitously expressed subset of human genes corresponding to houskeeping functions, represented by $V_U \subset V_G$, and $n_U = |V_U|$
- Random tissue-specific network(s): Vertex-induced subgraphs of G, constructed from $V_{\mathcal{R}} = V_U \cup V_S$, with V_S being random set of vertices of size $n_T - n_U$ selected from $V_G \setminus V_U$

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Significance of network alignment(s)

Definition

- Original alignment: $\mathcal{W} = \boldsymbol{w}^T \boldsymbol{x}$, $\mathcal{O} = \frac{1}{2} \boldsymbol{x}^T \mathcal{S} \boldsymbol{x}$
- Monte-Carlo simulation: Let $\mathcal{W}_{\mathcal{R}}$ and $\mathcal{O}_{\mathcal{R}}$ be the random vectors representing the weight and overlap of aligning $k_{\mathcal{R}}$ random tissue-specific networks with yeast
- Positive/Negative cases: k_P is the number of random cases with both $\mathcal{W}_{\mathcal{R}} \leq \mathcal{W}$ and . $\mathcal{O}_{\mathcal{R}} \leq \mathcal{O}$. k_N is defined as the size of complement set.
- p-value bounds:

$$\delta_{\mathcal{R}} = \frac{k_P}{k_{\mathcal{R}}} \leq \text{alignment p-value} \leq 1 - \frac{k_N}{k_{\mathcal{R}}} = \Delta_{\mathcal{R}}$$

- Alignment p-value:

$$p - value = Prob(\alpha * \mathcal{O} + \beta * \mathcal{W} \leq \mathcal{O}\mathcal{W}_{\mathcal{R}})$$

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Partitioning human genes based on their expression selectivity

Definition

Selectivity *p*-value– Given a cluster of homogenous tissues:

$$\begin{aligned} p\text{-value}(X = c_n) &= Prob(c_n \leq X) \\ &= HGT(c_n|N, n, c_N) \\ &= \sum_{x=c_n}^{min(c_N,n)} \frac{C(c_N, x)C(N - c_N, n - x)}{C(N, n)} \end{aligned}$$

N: total number of tissues, n: number of tissues in the cluster, c_N: number of tissues in which a given gene is expressed, c_n: number of tissue in the cluster that the given gene is expressed.

HUMAN-SPECIFIC OR CONSERVED?

DEFINITION

Classification of human tissue-selective genes:

- Conserved: Subset of tissue-selective genes that are consistently aligned in the "majority" of aligned tissues in the given group
- Human-specific: Subset of tissue-selective genes that are consistently unaligned in the "majority" of tissues in the given group
- Unclassified: None of the above

DEFINITION

Majority voting:

- Alignment consistency table: Yeast partner of each tissue-selective gene in the given cluster of tissues
- Consensus rate: Minimum percentage of tissues (columns) in each row of the alignment consistency table that have to agree to make a decision about conserved/human-specificity

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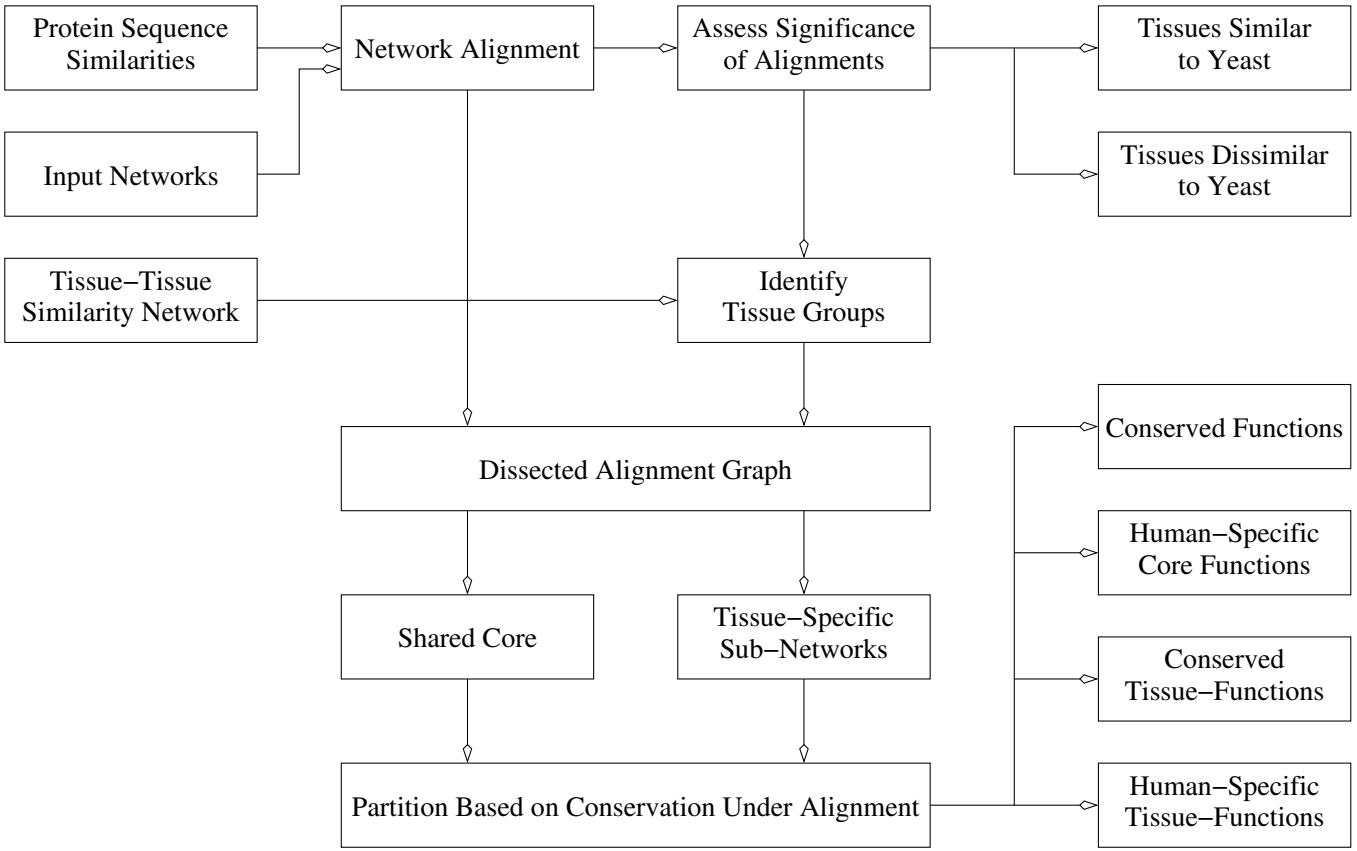
SUMMARY


Protein Sequence Similarities
Input Networks
Tissue–Tissue Similarity Network
Network Alignment
Assess Significance of Alignments
Identify Tissue Groups
Tissues Similar to Yeast
Tissues Dissimilar to Yeast
Dissected Alignment Graph
Shared Core
Tissue–Specific Sub–Networks
Partition Based on Conservation Under Alignment
Conserved Functions
Human–Specific Core Functions
Conserved Tissue–Functions
Human–Specific Tissue–Functions
Input
Processing
Output

Outline

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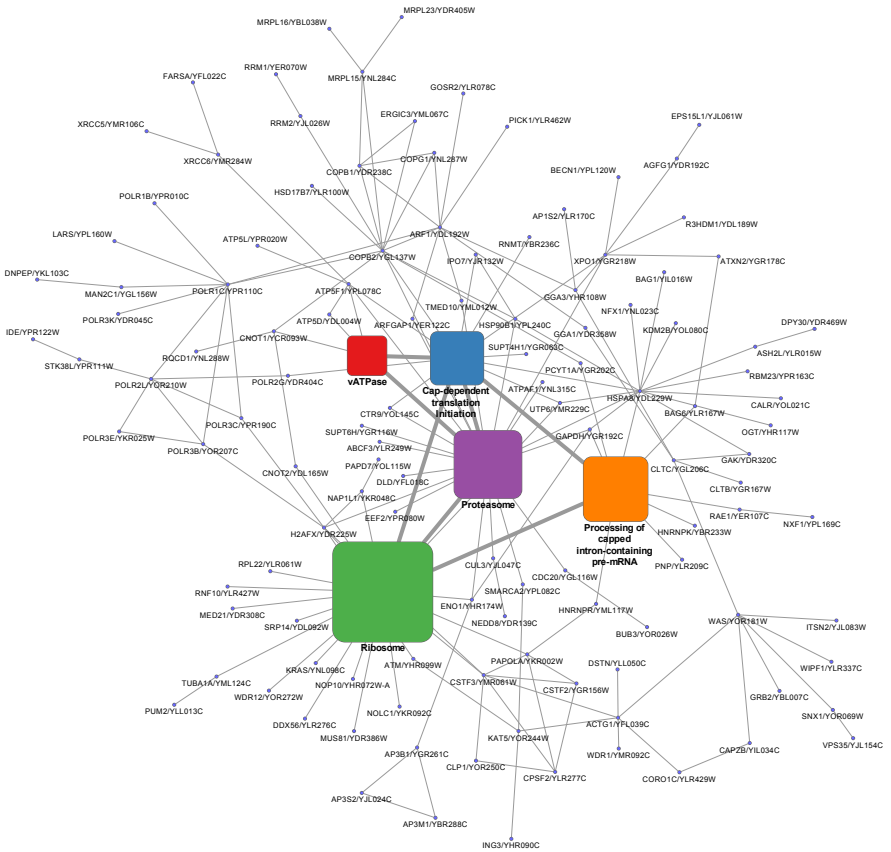
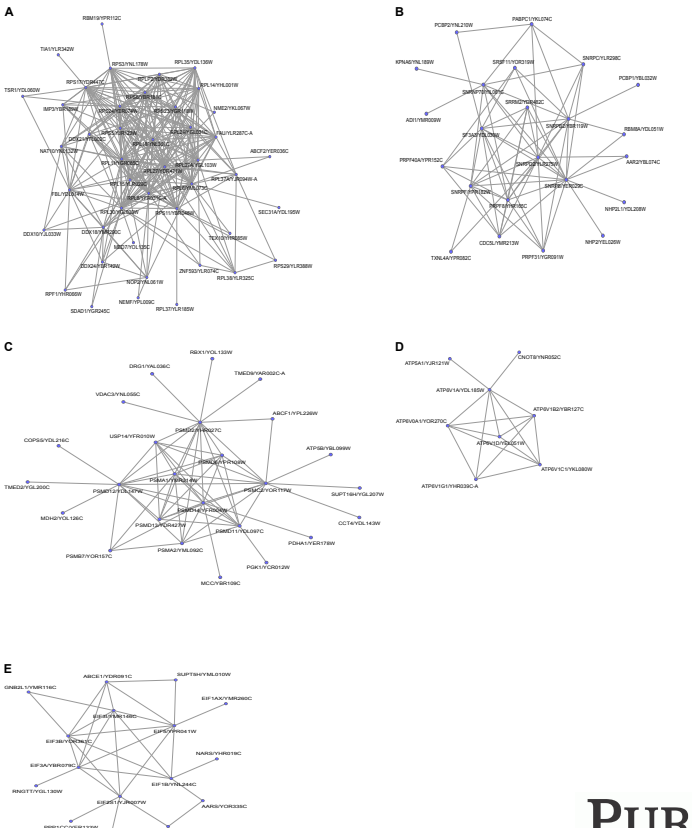
CORE GENES– THE MOST CONSERVED SUBSET OF HOUSEKEEPING GENES





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Functional enrichment of HK genes

Core subset

- Ribosome biogenesis
- Translation
- Protein targeting
- RNA splicing
- mRNA surveillance

Functional enrichment of HK genes

Human-specific subset

- Anatomical structure development
- Paracrine signaling
- NADH dehydrogenase (mitochondrial Complex I)

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THE MOST SIMILAR TISSUES TO YEAST

Name	pval lower bound	overall pval	pval upper bound	confidence
Myeloid Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Monocytes	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Dentritic Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
NK Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
T-Helper Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Cytotoxic T-Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
B-Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Endothelial	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Hematopoietic Stem Cells	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
MOLT-4	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
B Lymphoblasts	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
HL-60	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
K-562	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Early Erythroid	< 1.00e-04	< 1.00e-04	< 1.00e-04	1
Bronchial Epithelial Cells	< 1.00e-04	< 1.00e-04	0.0002	0.9998
Colorectal Adenocarcinoma	< 1.00e-04	< 1.00e-04	0.0004	0.9996
Daudi	< 1.00e-04	< 1.00e-04	0.0009	0.9991
Testis Seminiferous Tubule	< 1.00e-04	< 1.00e-04	0.0012	0.9988
Smooth Muscle	< 1.00e-04	< 1.00e-04	0.0016	0.9984
Blood (Whole)	< 1.00e-04	< 1.00e-04	0.0053	0.9947
Thymus	< 1.00e-04	0.0001	0.0062	0.9938
Testis Interstitial	< 1.00e-04	0.0004	0.0086	0.9914

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THE LEAST SIMILAR TISSUES TO YEAST

Name	pval lower bound	overall pval	pval upper bound	confidence
Trigeminal Ganglion	0.9947	0.9994	1	0.9947
Superior Cervical Ganglion	0.9847	0.9991	1	0.9847
Ciliary Ganglion	0.9407	0.9813	0.9964	0.9443
Atrioventricular Node	0.8746	0.9792	0.9921	0.8825
Skin	0.8355	0.9297	0.9809	0.8546
Heart	0.7934	0.9585	0.9815	0.8119
Appendix	0.7596	0.9371	0.973	0.7866
Dorsal Root Ganglion	0.7065	0.933	0.9717	0.7348
Skeletal Muscle	0.3994	0.5902	0.7866	0.6128
Uterus Corpus	0.233	0.7736	0.8769	0.3561
Lung	0.0771	0.3853	0.5544	0.5227
Pons	0.0674	0.5201	0.6983	0.3691
Salivary Gland	0.0639	0.3449	0.5173	0.5466
Liver	0.0600	0.6857	0.8519	0.2081
Ovary	0.0388	0.2735	0.4481	0.5907
Trachea	0.0259	0.2376	0.4146	0.6113
Globus Pallidus	0.0206	0.2471	0.4336	0.587
Cerebellum	0.0127	0.1950	0.3783	0.6344

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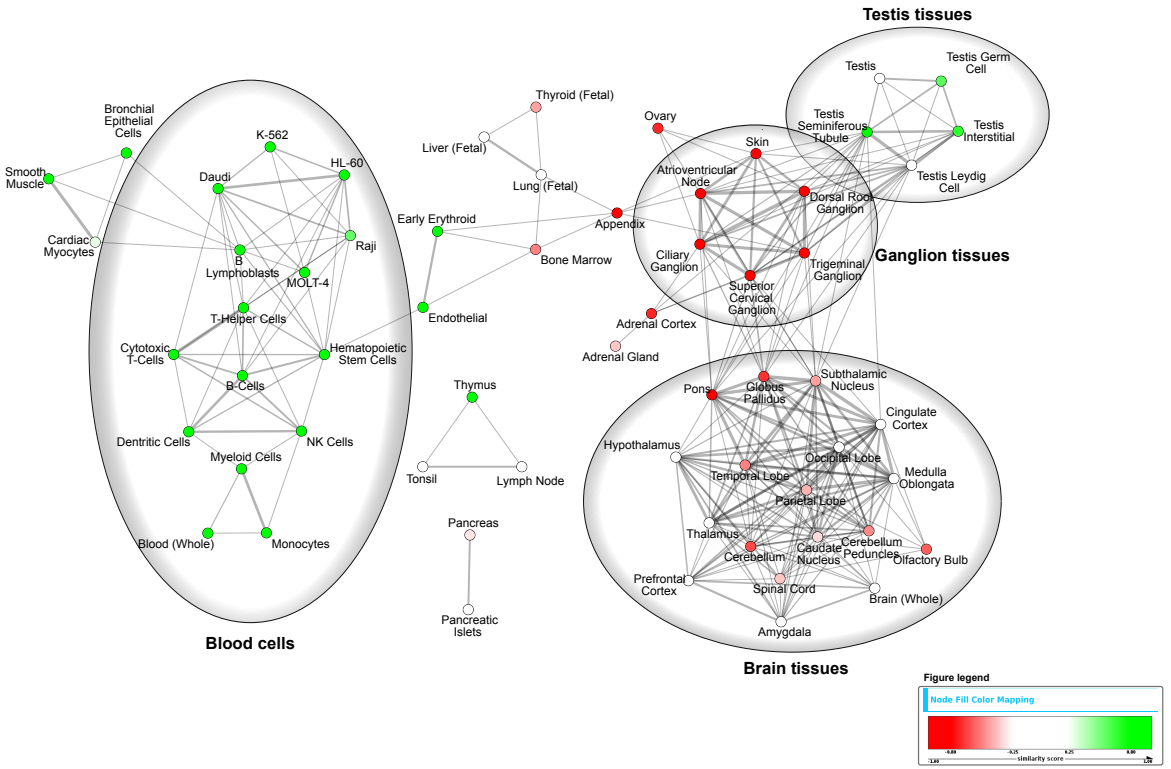
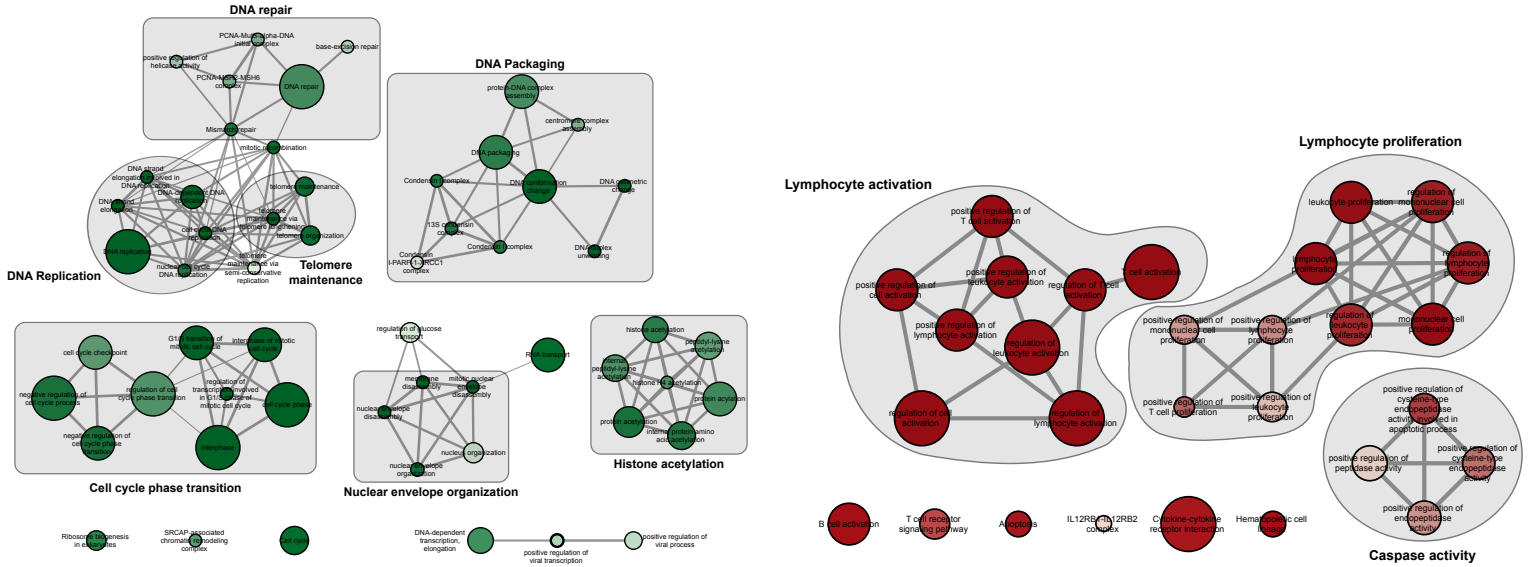
TISSUE-TISSUE SIMILARITY NETWORK



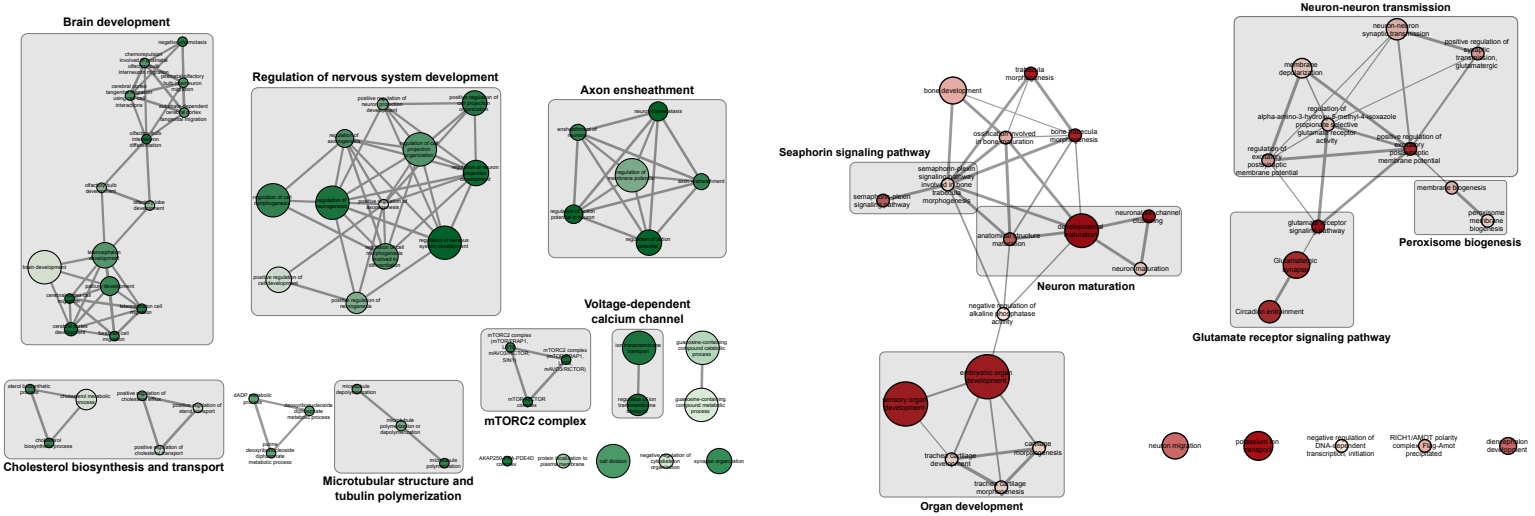
BLOOD CELLS



(a) Conserved (b) Human-specific

FIGURE : **Enrichment map of unique blood-selective functions.**

BRAIN TISSUES



(a) Conserved (b) Human-specific

FIGURE : **Enrichment map of unique brain-selective functions.**

Enriched disease classes

	Conserved genes Disease class	*p*-value	Human-specific genes Disease class	*p*-value
Blood cells	Cancer	$2.85 * 10^{-3}$	Immune	$1.88 * 10^{-9}$
			Infection	$1.00 * 10^{-2}$
Brain tissues	Psych	$3.59 * 10^{-4}$	Psych	$5.70 * 10^{-8}$
	Chemdependency	$2.60 * 10^{-3}$	Neurological	$2.97 * 10^{-2}$
	Pharmacogenomic	$9.74 * 10^{-2}$		

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COMPARATIVE ANALYSIS OF BRAIN-SPECIFIC PATHOLOGIES

Disorder	Conserved genes	Human-specific genes
schizophrenia	0.008573	8.4905E-06
autism	0.048288	0.00077448
dementia	0.0014356	-
schizophrenia; schizoaffective disorder; bipolar disorder	-	0.0021433
myocardial infarct; cholesterol, HDL; triglycerides; atherosclerosis, coronary; macular degeneration; colorectal cancer	0.0051617	-
epilepsy	0.071562	0.0064716
seizures	-	0.020381
bipolar disorder	0.048288	0.022016
attention deficit disorder conduct disorder oppositional defiant disorder	0.032444	0.023865

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Concluding Remarks

- Tissue-specific networks and interactions emerging as important datasets for understanding and mitigating pathologies.
- This work represents among the first computational investigations into tissue-specific networks.
- Our results reveal a significantly refined understanding of tissue-specific processes and their functions.
- Tissue-specific networks show significant enrichment of a number of important diseases, identifying a number of drug targets.
- Comparative analysis with yeast sheds light on humanized yeast models and their use in identifying targets.

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