SWEET-TALKING TO YEAST:

SYSTEMATIC IDENTIFICATION OF TOR DOWNSTREAM EFFECTORS UNDER GLUCOSE RESTRICTION

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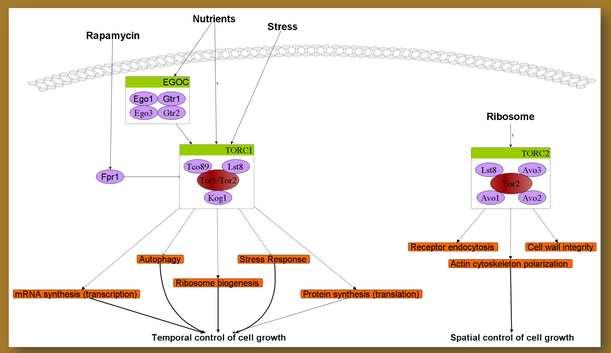
Reducing glucose concentration in yeast growth medium from 2% to 0.05%, known as severe dietary restriction (DR), had been shown recently to increase both RLS and CLS in a Sir2-independent manner*[1-2]*. The target of Rapamycin (TOR) signaling pathway plays a key role in fine-tuning cellular response to nutrient-availability by coordinately orchestrating various aspects of cellular machinery, including cell growth, translation initiation, ribosome biogenesis, and autophagy, among others*[3]*. Additionally, inhibition of the TOR signaling pathway by Rapamycin treatment exhibits similar phenotype and the lifespan can not be further extended by subjecting yeast to severe DR. These changes, as a whole, shift the energy allocation from growth and reproduction towards cell maintenance/repair. Regardless of the difference in the DR protocol, this mechanism is conserved in distant species, ranging from yeast to humans*[4]*.



REFERENCES

[1] M. Kaeberlein, et al., ***Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients***, Science (New York, N.Y.), 310(5751):1193-6, Nov. 2005
[2] N. A. Bishop and L. Guarente, ***Genetic links between diet and lifespan: shared mechanisms from yeast to humans***, Nature reviews, Genetics, 8(11):835-44, Nov. 2007
[3] Y. Wei and X. F. S. Zheng, ***Nutritional control of cell growth via TOR signaling in budding yeast***, Methods in molecular biology (Clifton, N.J.), 759:307-19, Jan. 2011
[4] L. Fontana, L. Partridge, and V. D. Longo, ***Extending healthy life span-from yeast to humans***, Science (New York, N.Y.), 328(5976):321-6, Apr. 2010
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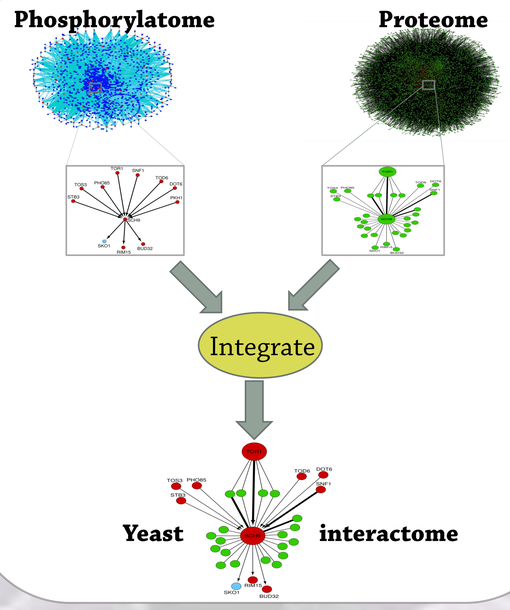
Network integration



Biasing the network

Key Idea:
To give relevant neighbors of each node, with respect to glucose signaling, a higher chance of selection by the random-walker.

Methods:
Transform the input network by assigning weight to the out-going edges of each node, encoding the relevance of each neighbor.

Measure of relevance:
Existence of parallel, alternative, pathways starting from glucose receptors and ending at each node, computed using max-flow algorithm.

Motivation:
Robustness of DR ⟷ Existence of parallel pathways

Tracing information flow

Random walk with restart (preferential PageRank)

- **Constructing transition matrix**:
  - ✓ Normalizing out-going edges:

$$\tilde{P}_{ji} = \begin{cases} 0 & \text{if } A_{ik} = 0; \forall 1 \le k \le n, \\ \frac{A_{ij}}{\sum_{k=1}^{n} A_{ik}} & \text{O.W.} \end{cases}$$

  - ✓ Adding self-loop to dangling nodes:

$$P = \tilde{P} + diag(\mathbf{1}^T - \mathbf{1}^T \tilde{P})$$

- **Computing stationary distribution:**
  - ✓ Iterative method:

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

  - ✓ Direct method:

$$\boldsymbol{\pi}_v(\alpha) = \frac{(1-\alpha)(I-\alpha P)^1}{Q} \quad \boldsymbol{e}_v$$

- **Interpretation:**
  Expansion using Neumann series:

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

  Thus, $\boldsymbol{\pi}_v$ is a function of:
  1. *Distance to source node*
  2. *Multiplicity of paths*

GO Enrichment

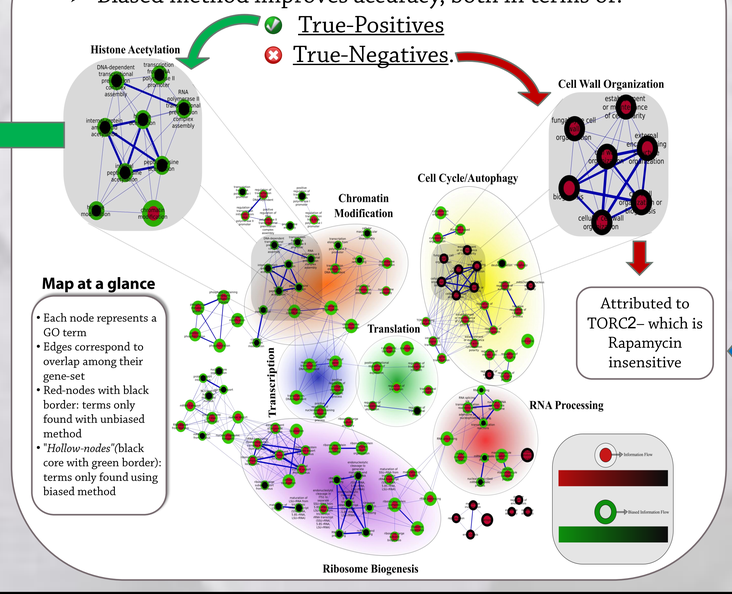
1. We sort all nodes in the interactome (N nodes) based on their random walk distance to TORC1
2. For each functional term, we encode all annotated nodes (n true-positives) using binary vector λ
3. For each binary vector λ, we compute the enrichment score as:

$$mHG(\lambda) = min_{1 \le l \le N} \text{HGT}(b_l(\lambda); N, n, l)$$

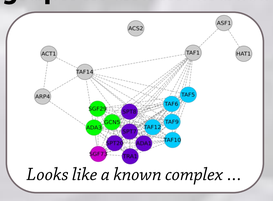
where $b_l(\lambda) = \sum_{i=1}^{l} \lambda_i$

Enrichment map

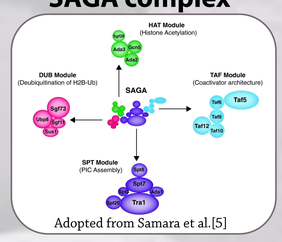
- Both methods are able to identify previously known downstream effectors of the TOR pathway
- Biased method improves accuracy, both in terms of:
  - ✓ True-Positives
  - ✗ True-Negatives.



Subgraph in the interactome



SAGA complex



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