# Systematic Identification of TOR Downstream Effectors Using Random-Walks on the Yeast Interactome

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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].
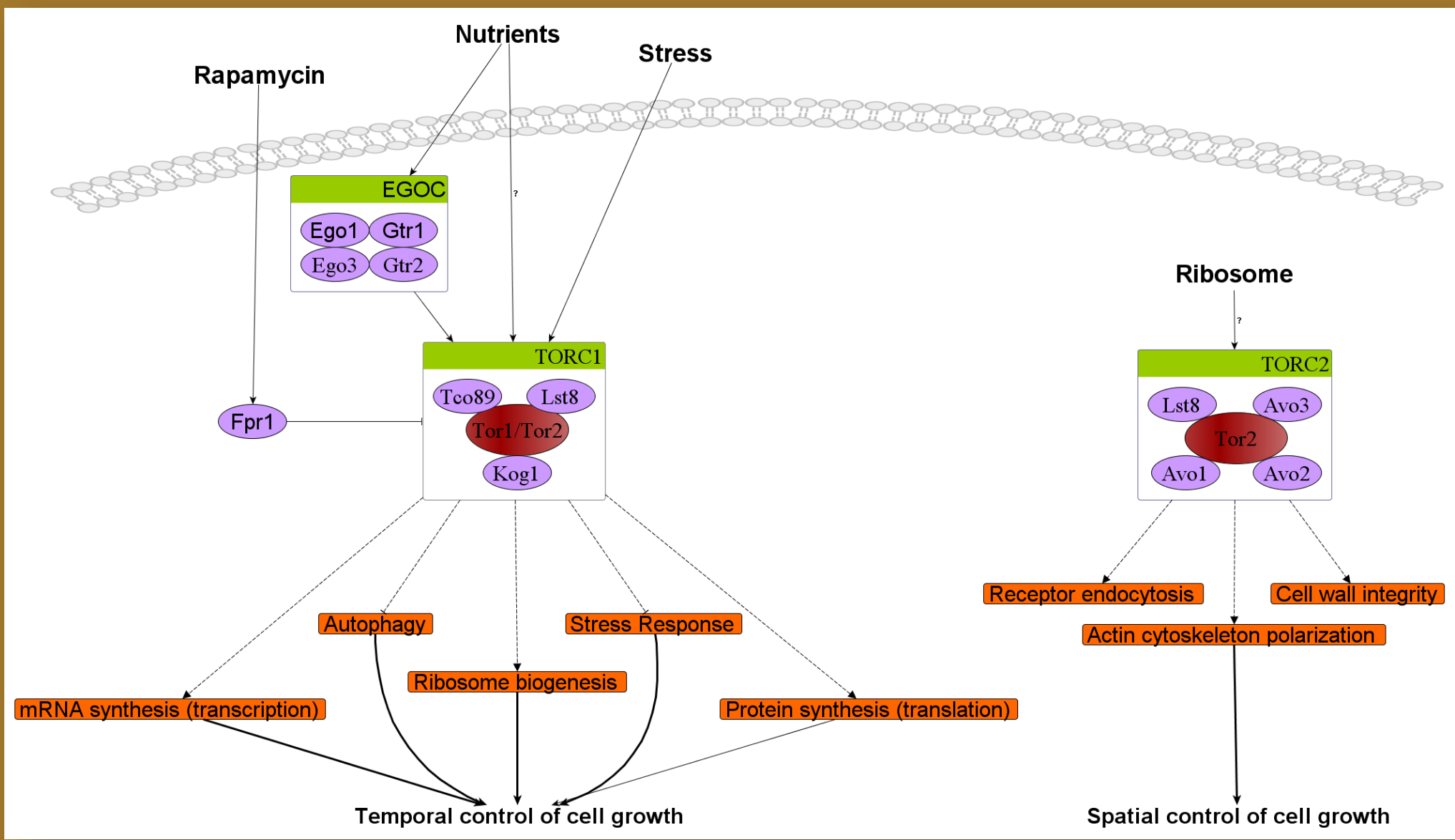

References

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[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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Acknowledgements

Network integration

Phosphorylatome   Proteome

Integrate

Yeast   Interactome
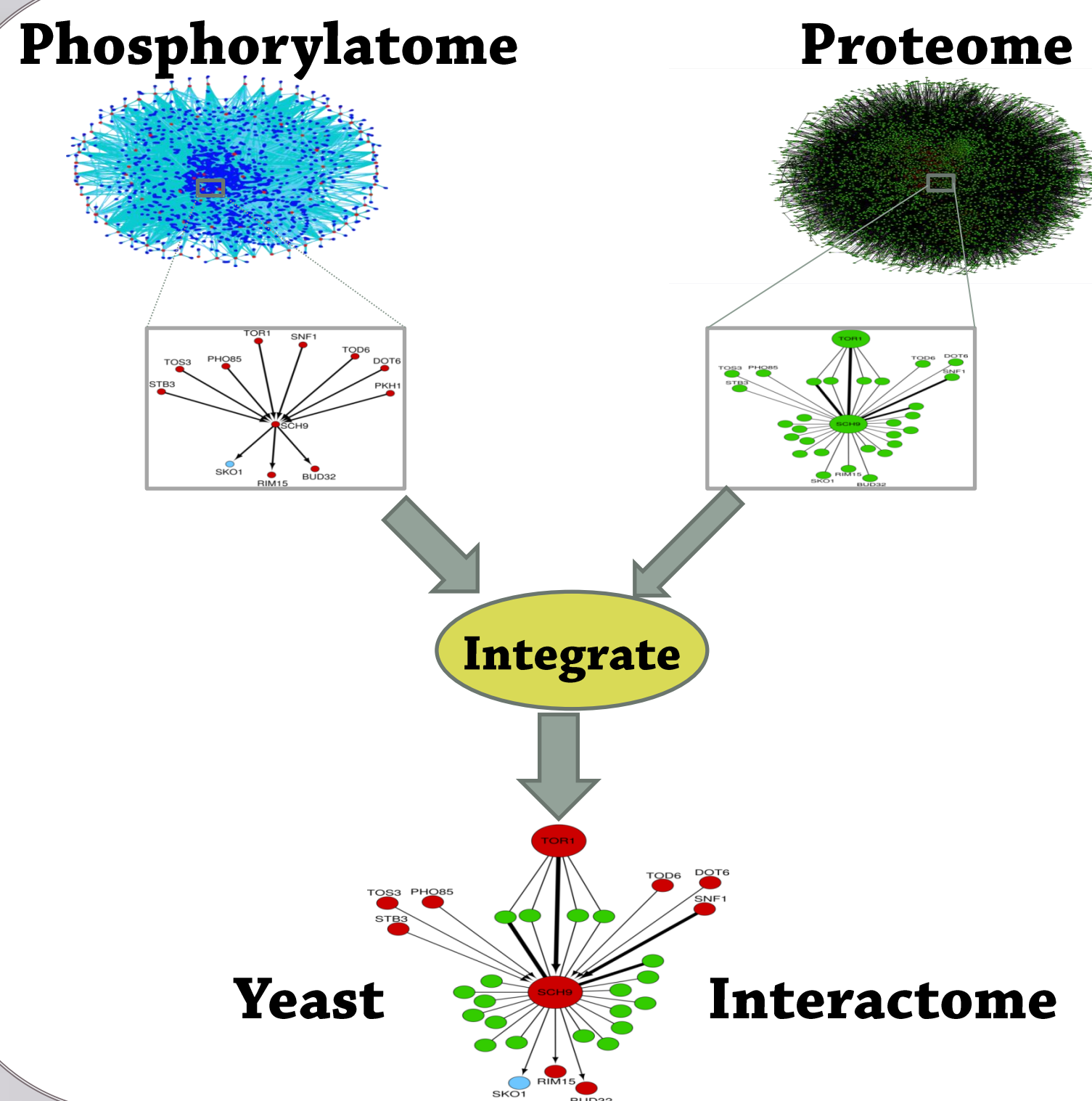
Tracing information flow

<u>Random walk with restart (preferential PageRank)</u>

➤ **Constructing transition matrix**:
  ✓ Normalizing out-going edges:
  $$\bar{P}_{ji} = \begin{cases} 0 & \text{if } A_{ik} = 0; \forall 1 \le k \le n, \\ \frac{A_{ij}}{\sum_{k=1}^{n} A_{ik}} & \text{O.W.} \end{cases}$$
  ✓ Adding self-loop to dangling nodes:
  $$P = \bar{P} + diag(\mathbf{1}^T - \mathbf{1}^T \bar{P})$$
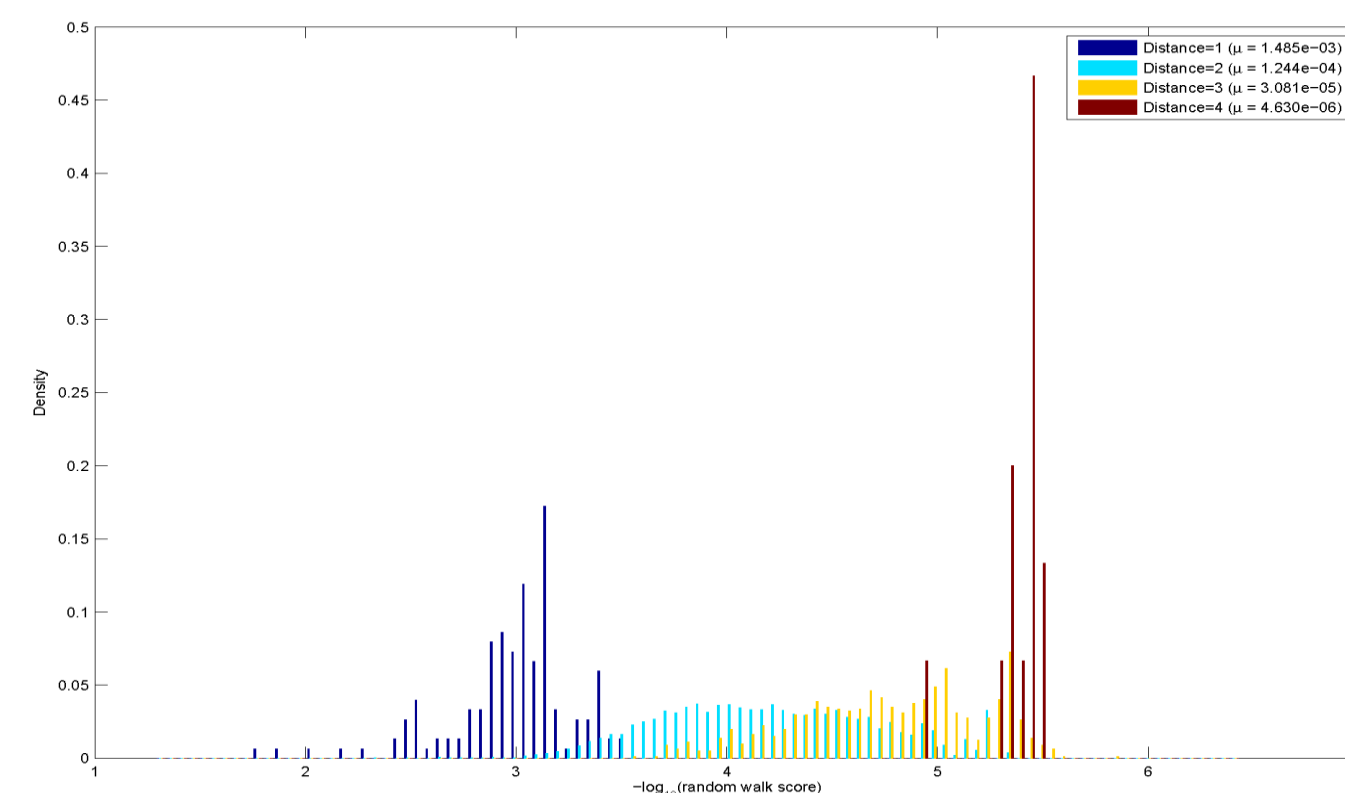
➤ **Computing stationary distribution**:
  ✓ <u>Iterative method:</u>
  $$\boldsymbol{\pi}_v(\alpha) = \alpha P \boldsymbol{\pi}_v(\alpha) + (1 - \alpha)\boldsymbol{e}_v$$
  ✓ <u>Direct method:</u>
  $$\boldsymbol{\pi}_v(\alpha) = \frac{(1 - \alpha)(I - \alpha P)^1 \quad \boldsymbol{e}_v}{Q}$$

Distribution of Scores

➤ **Interpretation:**
Expansion using Neumann series:
$$\boldsymbol{\pi}_v(\alpha) = (1 - \alpha)\sum_{i=0}^{\infty}(\alpha P)^i \boldsymbol{e}_v$$
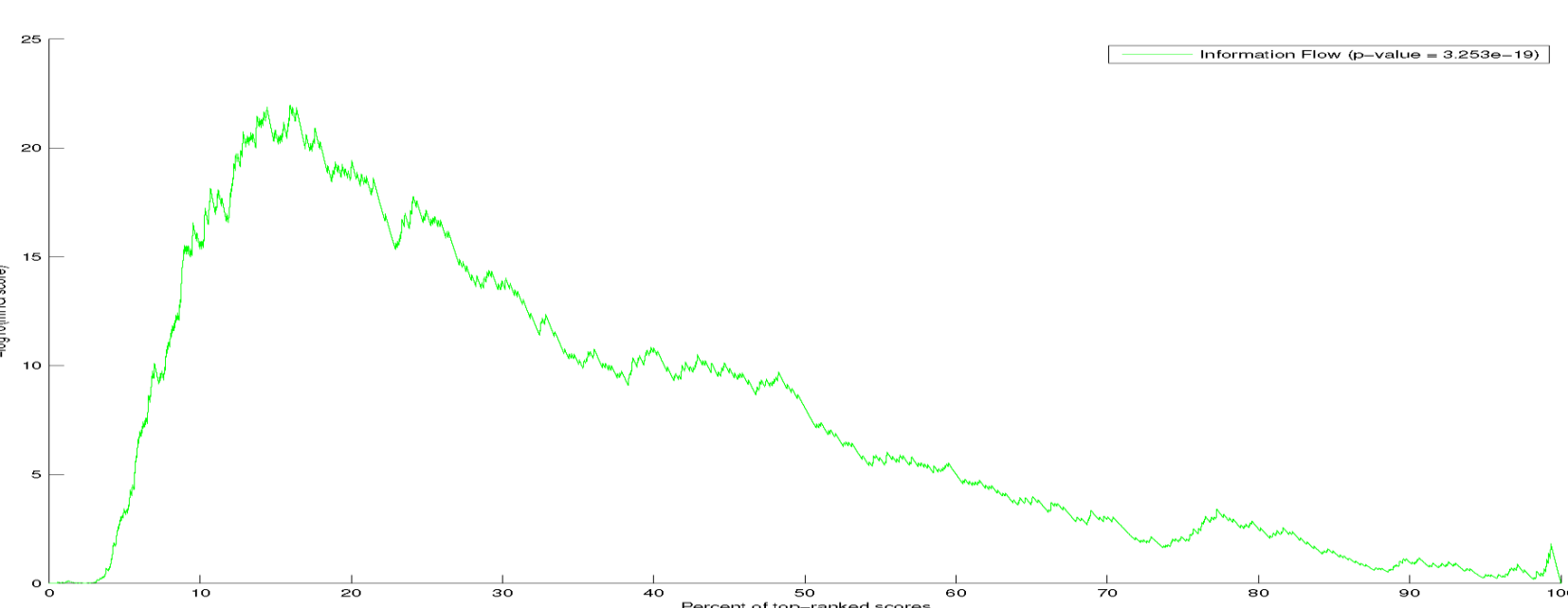Thus, $\boldsymbol{\pi}_v$ is a function of:
1. *Distance to source node*
2. *Multiplicity of paths*

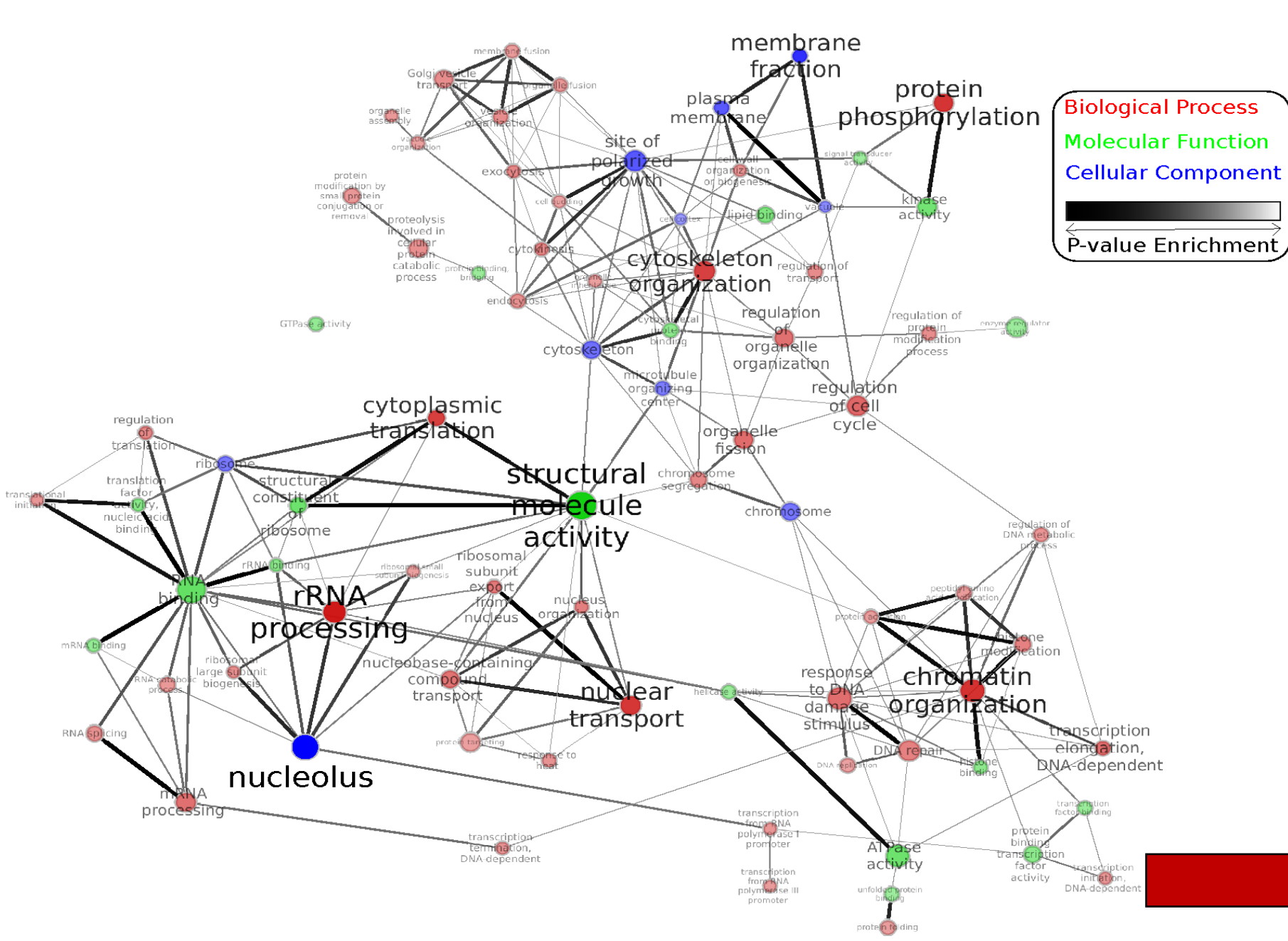## Experimental Validation
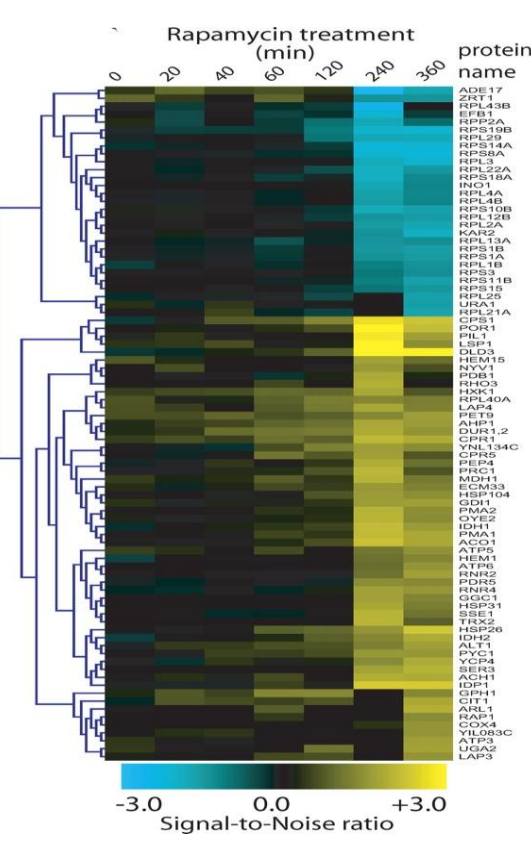
- Dataset: Transcriptional changes in response to Rapamycin treatment
- Tail of hypergeometric distribution as a function of cut-off
- Exact p-value is computed using dynamic programming

Enrichment Analysis

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 of GO Slim terms

✓ Each node represents a GO term
✓ Edges represent the overlap between genesets of GO terms.
✓ Color intensity of nodes encodes the mHG p-value enrichment
✓ Node size represents the number of enriched genes

Transcription initiation

Daily dose of humor (courtesy of www.biocomicals.com, Alper Uzun, PhD.)