

# Robustness analysis of HOG pathway related genes in budding yeast

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## Extended abstract

Robustness is a fundamental and ubiquitous property of complex biological systems. By being robust the system maintains its function in the face of external and internal perturbations. During evolution internal parameters such as gene expression have been optimized to allow a precise and accurate function of the system. These parameters must have permissible ranges to account for fluctuations in environmental conditions (external perturbation) or internal conditions such as noise in gene expression (internal perturbation) [1, 2]. In this study we approached the problem of quantitatively measure these ranges by estimating upper limit gene copy number for 29 HOG pathway related genes in the yeast *Saccharomyces cerevisiae* [3]. This was done using a novel genetic screening method named “genetic tug-of-war” (gTOW). This method is based on the naturally occurring 2 micron plasmid of yeast with the inserted amplification marker *leu2d* and a gene of interest (together with its native regulatory DNA elements). In a selective condition the plasmid copy number will increase due to the need of leucine, while at the same time the plasmid copy number will decrease if the target gene has a toxic or inhibitory effect on the cell. The two biases give rise to the term “genetic tug-of-war” or gTOW [2]. In addition to estimating the plasmid copy number a phenotypic profiling of the 29 target genes was performed resulting in three different readouts: lag phase, rate of growth and efficiency of growth [4]. Among the 29 studied genes the MAPKK *PBS2* had the most severe growth inhibition which correlates well with previous studies on overexpression of *PBS2* [5]. The strain also had a low plasmid copy number (~30). This fact points toward the validity of the study and its extension to encompass the entire known signal transduction system in yeast. Especially interesting will be the most sensitive target genes which will be points of fragility in the network. The quantitative data provided could potentially also be used in existing computational models for the HOG pathway or other pathways in the signal transduction system to further deepen our knowledge about robust properties of the system.

## References

1. Kitano, H. (2004) Biological robustness. *Nat Rev Genet.* 5, 826-837
2. Moriya, H., Shimizu-Yoshida, Y., Kitano, H. (2006) In vivo robustness analysis of cell division cycle genes in *Saccharomyces cerevisiae*. *PLoS Genet* 2(7): e111, 1034-1045
3. Hohmann, S. (2002) Osmotic stress signaling and osmoadaptation in yeasts. *Microbiol. Mol. Biol. Rev.* 66, 300-372
4. Warringer, J., Ericson, E., Fernandez, L., Nerman, O., Blomberg, A. (2003) High-resolution yeast phenomics resolves different physiological features in the saline response. *PNAS.* 100, 15724-15729
5. Mapes, J., Ota, I. M. (2004) Nbp2 targets the Ptc1-type 2C Ser/Thr phosphatase to the HOG MAPK pathway. *EMBO J.* 23, 302-311