

systemic effects of extracellular cues on cellular phenotypes, and generated comparable time-course predictions when contrasted with an equivalent kinetic model.

In this research, we applied this framework to the *Saccharomyces cerevisiae* high osmolarity glycerol (HOG) pathway, one of four principal MAP kinase cascades in *S. cerevisiae* (Hohmann 2002). Under hyperosmotic conditions, yeast cells accumulate glycerol to balance the intracellular osmotic pressure with the extracellular environment. Specifically, osmotic stress signals are communicated via the HOG pathway, leading to the activation of Hot1 and other HOG-mediated transcription factors. Hot1 promotes the expression of glycolytic enzymes, Gpd1 and Gpp2, thereby increasing glycerol production. The MAPK Hog1 is inhibited by phosphatases such as Ptp2, Ptp3, and Ptc1, allowing the cell to keep the HOG pathway in check and maintain healthy osmotic balance. The reconstruction of the integrated HOG module in yeast is comprised of 72 components spanning 68 reactions across signaling, metabolism, and regulation, including three regulated metabolic genes.

Analysis of the integrated yeast module yielded novel findings of HOG mechanisms and validated the **idFBA** approach for facilitating quantitative and dynamic analysis of systemic effects of extracellular cues on cellular phenotypes.

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