

Modeling the dynamic behavior of an oleate-responsive gene regulatory network in *Saccharomyces cerevisiae*

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Motivation

Peroxisomes are essential eukaryotic organelles responsible for various metabolic functions, most notably beta-oxidation of fatty acids. Peroxisomal functions are linked to several important human health concerns including aging, developmental neuropathologies, and heart disease. Although peroxisome biogenesis is affected by a variety of environmental factors, peroxisomes are dramatically induced by fatty acids (e.g. oleic acid, a monounsaturated omega-9 fatty acid) in yeast. Although several key molecules of the oleate-responsive yeast transcriptional network and their core interactions are known, a systems-level understanding of how this network controls dynamic oleate-induced gene expression is lacking. Understanding the regulatory networks of oleate-induced biogenesis of peroxisomes in a comprehensive manner demands an iterative cycle of experimentation, model development, and simulation-based prediction of dynamic behavior.

Results

Here we present a kinetic model of the core oleate-responsive gene regulatory network in *Saccharomyces cerevisiae*. The model describes the transport of extracellular oleate into the cell, which activates a molecular network governing peroxisome protein production and organelle proliferation. The model describes the oleate-dependent expression and function of four transcription factor genes (*ADR1*, *PIP2*, *OAF1* and *OAF3*), as well as the expression of two reporter genes (*POT1* and *CTA1*). A cartoon of oleate-responsive gene regulatory network architecture is presented in Figure 1.

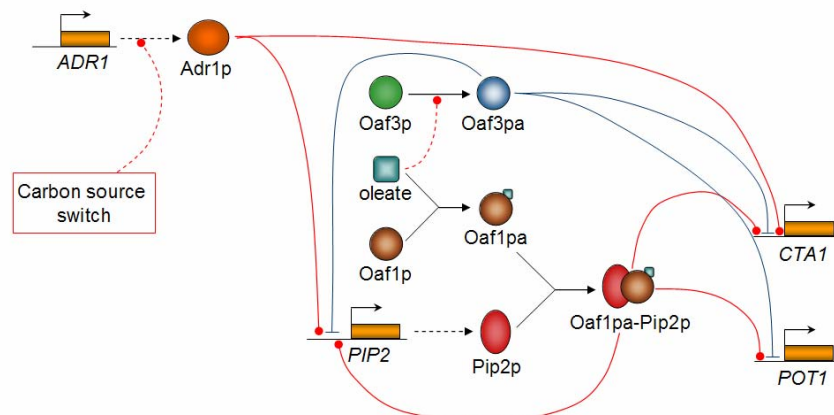


Figure 1. Cartoon of oleate-responsive gene regulatory network architecture. Arrows designate molecular processes (transcription, translation, activation, dimerization); oval and blunted lines are up- and down regulatory events, respectively. Solid and dashed lines indicate direct and indirect effects, respectively.

For each gene in the model, both the gene-specific mRNA and protein are accounted for separately as dynamical variables in a set of delay differential equations. Kinetic parameters of the model are estimated from steady-state and time-course expression data (Smith *et al.*, 2002; Smith *et al.*, 2007) or taken from the literature. Simulated and measured time-course gene expression ratios under a carbon source switch from glycerol to oleic acid are shown in Figure 2(a). Unknown kinetic parameters of the model were varied (within a biochemically plausible range) to obtain an acceptable agreement with published steady-state dose-response data for oleate induction of *POT1* (Phelps *et al.*, 2006). The dose-response of the kinetic model to extracellular oleate, and the measured *POT1* expression, are shown in Figure 2(b).

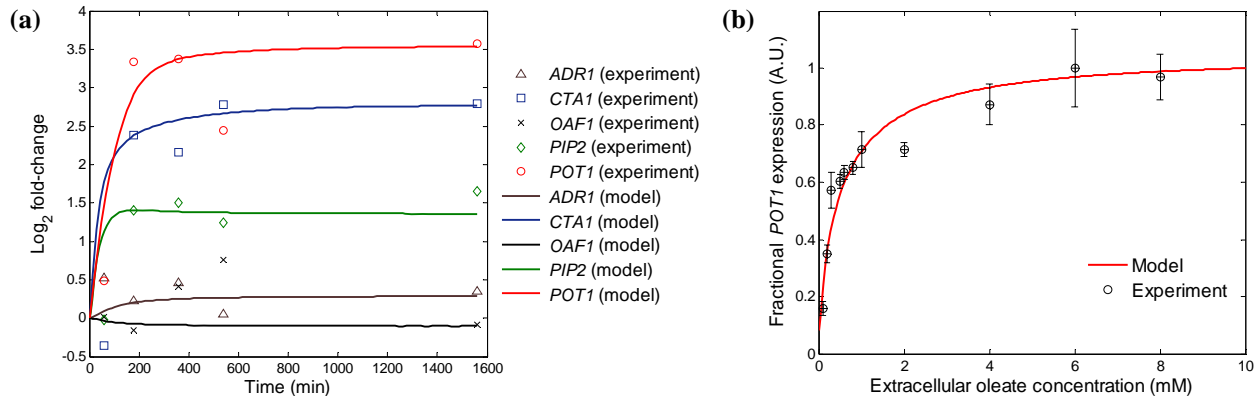


Figure 2. Comparison of model simulations with experimental data. (a) Time-course expression ratios for *ADR1*, *CTA1*, *OAF1*, *PIP2*, and *POT1* under a carbon source switch from 3% glycerol to 0.12% oleate. Data points indicate experimental measurements (Smith *et al.*, 2002); lines indicate the expression ratios from a simulation of the kinetic model. (b) The effect of oleate on steady-state *POT1* expression. Data points indicate experimental data (Phelps *et al.*, 2006) normalized relative to the maximum level; the line plot shows the model prediction.

In order to understand their function in controlling the dynamics of the oleate response, we mathematically simulated several reduced models representing “network motifs” of the oleate-responsive network (Fig. 1). The motif simulations give the following insights into their functions:

- **Heterodimerization of Oaf1p/Pip2p.** The gene circuit in which the target gene is activated by the Oaf1p-Pip2p heterodimer is significantly less “noisy” than the gene circuit driven directly by a hypothetical autoregulated monomeric transcription factor. This suggests that heterodimerization of Oaf1p with Pip2p provides a selective advantage by suppressing large fluctuations in target gene expression.
- **Nonlinear autoregulation of *PIP2*.** The sensitivity of oleate response strongly depends on the degree of nonlinearity of transcriptional activation of *PIP2*. The system without autoregulation of *PIP2* is exquisitely sensitive to low concentrations of oleate, whereas the autoregulated system is insensitive up to a transition point.
- **Oaf3p-mediated incoherent feed-forward network motif.** The late-activation of the transcriptional repressor, Oaf3p suggests that repression modulates the late-time response of many oleate-inducible genes. Furthermore, simulations suggest that the modulation of the Oaf1p-Pip2p feed-forward loop by Oaf3p prevents transient de-induction of target genes in response to fluctuations in the concentration of intracellular oleate.

Acknowledgements

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References

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