Assigning function to natural allelic variation via dynamic modeling of a gene regulatory network

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Abstract

Optimizing growth and survival in face of an environmental signal is a major challenge for single-cell organisms. To adapt the new environment and respond to external stimuli, many cells operate a genetic switch, during which groups of genes are activated of repressed. This type of cellular response has been extensively studied at steady state but the dynamical behaviour of regulatory networks remains poorly understood. The yeast galactose regulatory network is a well-characterized standard model system which offers the possibility to investigate the dynamic regulation of the network at a very fine dynamic scale. Our work aimed to develop a dynamic modeling of network inducibility in order to better understand the nature of the galactose response and to explore how natural genetic variations affect the network inducibility. We addressed those questions by integrating both experimental and theoretical approaches, taking advantage of the well-defined galactose network. The high complexity of galactose network interactions makes systematic analysis of the effect of polygenic natural variations highly challenging. To bypass this issue, we decided to focus our work on natural variations present in the *GAL3* locus, which is the core component of the regulatory response. First, we experimentally characterized the dynamic activation of the network in isogenic cell population, except for *GAL3*. We observed that natural variation in GAL3 loci is sufficient to convert a dynamically graded response into a transient probabilistic bimodal response. Second, we used this time course experiments to develop a predictive quantitative model of the system inducibility. A comprehensive analysis of the model indicated that natural variations of *GAL3* play on two key parameters controlling the network dynamical behaviour: the association constant of galactose to Gal3p and the regulatory strength of Gal3p on Gal80. Finally, we demonstrated that our model is predictive of the effect of single genetic mutation at a broad range of galactose concentration. Together, these results provide a quantitative understanding of the galactose network dynamic response and allow us to better characterize the functional effect of genetic diversity on the system.

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