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The adaptive filter of the yeast galactose pathway

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Abstract

In the yeast *Saccharomyces cerevisiae*, the interplay between galactose, Gal3p, Gal80p and Gal4p determines the transcriptional status of the genes required for galactose utilization. After an increase in galactose concentration, galactose molecules bind onto Gal3p. This event leads via Gal80p to the activation of Gal4p, which then induces *GAL3* and *GAL80* gene transcription. Here we propose a qualitative dynamical model, whereby these molecular interaction events represent the first two stages of a functional feedback loop that closes with the capture of activated Gal4p by newly synthesized Gal3p and Gal80p, decreasing transcriptional activation and creating again the protein complex that can bind incoming galactose molecules. Based on the differential time-scales of faster protein interactions versus slower biosynthetic steps, this feedback loop functions as a derivative filter where galactose is the input step signal, and released Gal4p is the output derivative signal. One advantage of such a derivative filter is that *GAL* genes are expressed in proportion to cellular requirements. Furthermore, this filter adaptively protects the cellular receptors from saturation by galactose, allowing cells to remain sensitive to variations in galactose concentrations rather than to absolute concentrations. Finally, this feedback loop, by allowing phosphorylation of some active Gal4p, may be essential to initiate the subsequent long-term response.

Keywords: Galactose switch; Yeast; Adaptive filter; Feedback loop; Qualitative modeling; Interaction networks

1. Background

Living organisms constantly adapt to fluctuations in their intra- and extra-cellular environments, in part by regulating the expression of their genes. Gene expression can be controlled at many levels that involve protein–DNA (transcriptional), protein–protein and protein–small molecule interactions. The process of galactose (GAL) utilization in the common yeast *Saccharomyces cerevisiae* has been thoroughly studied; yeast is known to exhibit sophisticated responses to the presence of different types of sugar in its environment. The GAL pathway is a classical example of a genetic regulatory switch, in which enzymes specifically required for the transport and catabolism of galactose are expressed only when galactose is present and repressing sugars such as glucose are absent in the cellular environment (Biggar and Crabtree, 2001).

The permease encoded by the *GAL2* gene, and possibly other hexose transporters (HXTs) transport galactose across the cell membrane. Other genes encode the enzymes required for conversion of intracellular galactose, including galactokinase (*GAL1*), uridyltransferase (*GAL7*), epimerase (*GAL10*), and phosphoglucomutase (*GAL5*/*PGM2*). Galactose activates the transcription of *GAL* genes from undetectable or low basal levels to high levels. The activated genes include *GAL1*, *GAL2*, *GAL3*, *GAL5*, *GAL7* and *GAL80* (Sakurai et al., 1994), but not *GAL4* (Ren et al., 2000; Ideker et al., 2001). The complex interplay of Gal4p, Gal80p, and Gal3p determines the transcriptional status of these *GAL* genes (Platt and Reece, 1998). Gal4p is a DNA-binding transcriptional activator that can bind to upstream activating sequences in the promoter regions of target *GAL* genes, thereby strongly activating their transcription. However, in the absence of galactose, Gal4p is sequestered by Gal80p and is unable to

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activate transcription of the *GAL* genes, although this Gal4p/80p complex appears to bind DNA (Parthun and Jaehning, 1992). The interaction between Gal4p and Gal80p is weaker in the presence of galactose (Sil et al., 1999). Gal80p and Gal3p may also form a complex, which in contrast is stabilized in the presence of galactose (Yano and Fukasawa, 1997). Gal3p overproduction, presumably by sequestering Gal80p away from Gal4p, causes galactose-independent activation of the GAL pathway (Bhat and Hopper, 1992; Peng and Hopper, 2000).

Gal3 mutant cells are still able to activate the GAL pathway in response to galactose. However, induction requires several days rather than a few minutes in wild-type yeast, a phenomenon called long-term adaptation (LTA) (Winge and Roberts, 1948; Bhat and Murthy, 2001). It was proposed (Rohde et al., 2000) that the LTA of the GAL pathway is mediated by Gal4p phosphorylation. Indeed, when Gal4p is bound to DNA and interacts with the RNA-polymerase II holoenzyme, its serine at position 699 (S699) becomes phosphorylated by Srb10p/Cdk8p, a component of the 'Mediator' subcomplex of the holoenzyme (Hirst et al., 1999; Bhaumik and Green, 2001; Larschan and Winston, 2001). Gal4p S699 phosphorylation is necessary to amplify and maintain full *GAL* gene induction (Sadowski et al., 1996; Yano and Fukasawa, 1997; Rohde et al., 2000).

The above set of experimental observations raises two main questions. Firstly, the system responds to galactose increases rather than to absolute galactose concentration: how is this achieved (Rohde et al., 2000)? Secondly, several authors have observed that Gal4p does not become phosphorylated unless it activates transcription, yet that it is not fully active unless it is phosphorylated (Sadowski et al., 1991; Sadowski et al., 1996; Hirst et al., 1999). A satisfactory explanation for this 'chicken and egg' enigma is lacking. In this paper we propose a mathematical model of the early response to galactose and we analyse its dependence upon time delays, protein degradation rate and initial conditions. The model accounts for the above-mentioned sensitivity to galactose fluctuations. It also proposes a solution to the apparent paradox described above by showing that a feedback loop brings active Gal4p onto gene promoters, thus allowing its phosphorylation and consequent maintenance of transcriptional activation.

2. Qualitative modeling of the galactose response

2.1. Assumptions

The present model deals with the early steps of galactose induction; it does not consider the events occurring after Gal4p phosphorylation. It does not emphasize the details of signal transmission from galactose to Gal4p (except in Appendix A). Thus, Gal4p appears in this model either bound to DNA, or bound to DNA and to Gal80p. Gal80p is either bound to DNA and to Gal4p, or bound to Gal3p, or unbound. An equilibrium between nuclear and cytoplasmic forms of Gal80p has been considered by other authors (Peng and Hopper, 2000, 2002; Verma et al., 2003), but is not relevant here given the scope of our model. The order in which galactose, ATP, Gal3p and Gal80p bind together is not fully known but should have no effect on the conclusions reached with our model, which simply considers Gal80p consumption upon galactose addition.

The *GAL1* gene is a paralogue of the *GAL3* gene (Wolfe and Shields, 1997) that encodes a galactokinase, while Gal3p does not have galactokinase activity (Platt et al., 2000). Galactokinase activity is irrelevant to the present model which does not address galactose catabolism. Therefore, Gal1p and Gal3p are taken to play a similar role in GAL pathway activation, averaged over their respective abundances and inducing properties. In the model, they will be lumped together under the name of Gal3p.

2.2. Dynamical description of the GAL system

Fig. 1 shows the different states of the system. Fig. 2A illustrates the core regulatory mechanism. In the absence of galactose, Gal4p can bind to Gal80p and has no transcriptional activity. Following a step increase in galactose, Gal3p rapidly binds galactose, and Gal80p is consumed by being recruited in a complex with Gal3p. As the concentration of unbound Gal80p decreases, the

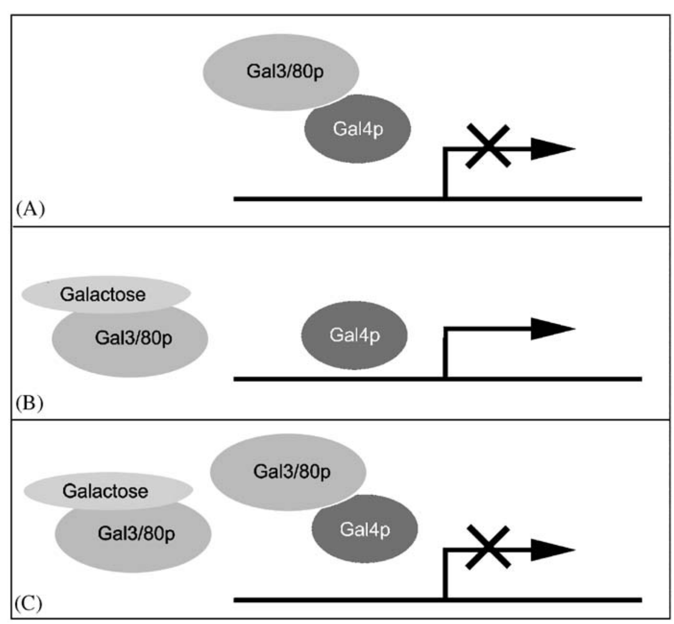

Fig. 1. Diagrammatic representation of the galactose induction loop. (A) In the absence of galactose, the transcriptional activity of Gal4p is inhibited by Gal3/80p. (B) The association of galactose with Gal3/80p allows Gal4p to be freed from Gal80p inhibition and to activate transcription of new Gal3/80p. (C) Newly synthesized Gal3/80p inhibits the transcriptional activity of Gal4p.