Transcription Factor Binding Site Organization Influences Regulatory Logic in Yeast

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1 Introduction.

Transcription processes in eukaryotes are often controlled in response to the combined activity of several transcription factors (TFs). In the simplest models, TFs bind upstream in controlling regions of DNA, and promote or repress the transcriptional behavior of their targeted genes. Thus, activity states of different TFs combined with the effects these states exert on different targets define a type of logic that makes up larger gene regulatory networks. Results of previous computational models have suggested that regulatory binding site organization may play a role in determining the logical control of genes[1]. Here, we analyze generally how the organization of two transcription factor binding sites (TFBS) upstream of genes influences the logic programs implemented by their combinatorial activity. We discuss evidence for such effects in light of physical models of how TFBS organization may constrain the logic in gene regulation.

2 Methods and Results.

Integrating information from expression data with systematic TFBS identification in *Saccharomyces cerevisiae*, we find a pattern whereby inferred binding site positioning significantly distinguishes instances of *AND*-like and *OR*-like regulatory circuits in yeast. We begin by assuming that two-transcription-factor control can be broadly classified according to the cases shown in Figure 1. These cases have three distinct types: 1) *AND*-like, where the expression of a gene depends on both of the regulators, 2) *OR*-like, where the expression depends on either of the regulators and 3) *EQ*-like, where the activity of one of the regulators is sufficient to predict the expression state of the target gene.

We tested the hypothesis that the relative positions of transcription factor binding sites would affect preference of gene regulation towards particular types of logic. To do this, we used published methods for screening transcription factor binding sites with reported position-weight-matrices of TFs in yeast[2]. We then applied a probabilistic screening method to identify cases of ON/OFF regulation of genes from 550 compiled experiments measuring whole-genome expression[3-5]. Having identified regulation cases where two transcription factors with sites upstream of a gene exhibited significant control over the gene, we then grouped these cases by the type of input-output behavior (i.e. logic) they exhibited. We tested (χ^2) the association between AND-like and OR-like behavior with whether or not the inferred biding sites of the genes were overlapping, and found that this was a significant relationship ($p < 0.0001$) between these two variables. From this we conclude that binding site organization has a significant effect on the type of regulatory logic enacted by two transcription factors which control the same genes. We anticipate that this effect can be examined in cases of control by larger numbers of regulators.

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3 Figures.

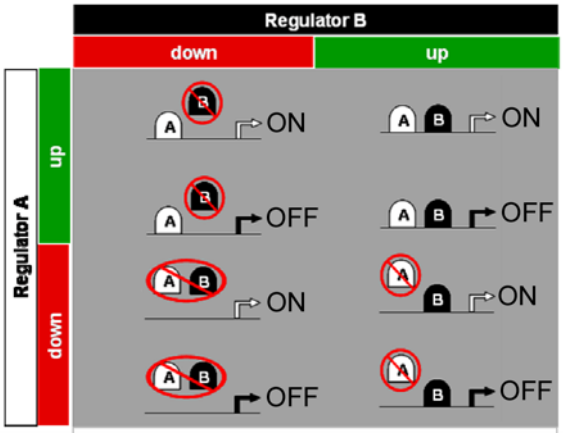

Figure 1: Possible types of control of a gene by two regulators (*A* and *B*). Regulatory logic is determined by the types of these control that actually occur. For example *A AND B* only allows expression of the gene when both A and B are present and active (upper right).

4 References.

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