

Colloquium

Monday, November 27, 2006 4:10 pm 428 Pupin Hall

“Data-Driven Biophysical Modeling of Gene Expression Regulation”

It is the dynamic balance between transcription from DNA to messenger RNA and subsequent mRNA degradation that determines the steady-state mRNA abundance for each gene in a genome. However, while regulation of transcription rate by DNA binding transcription factors has been intensively studied, both experimentally and computationally, regulation of the transcript turnover rate by RNA binding factors has received far less attention. We took advantage of the fact that information about the condition-specific activity and sequence-specific affinity of RNA binding regulatory factors is implicitly represented in the steady-state mRNA abundances measured using DNA microarrays. Thus, by fitting a model based on a physical description of molecular interactions, we were able to gain quantitative insight into the mechanisms that underlie genome-wide regulatory networks. We developed a novel algorithm, MatrixREDUCE, that predicted the sequence-specific binding affinity of several known and unknown RNA-binding factors and their condition-specific activity, using only genomic sequence data and steady-state mRNA expression data as input.

We identified and computationally characterized the binding sites for six mRNA stability regulators in the yeast *S. cerevisiae*, which include two known RNA-binding proteins, Puf3p and Puf4p. We provide computational and experimental evidence that regulation of mRNA stability by the discovered factors is dynamic and responds to a variety of environmental stimuli. For example, little was previously known about the functional role of Puf3p, but our computational results suggest that Puf3p functions to destabilize mitochondrion-related transcripts when metabolite repressing sugars are present and in response to the drug rapamycin. We were able to experimentally confirm these predictions by growing a transformed strain expressing a hybrid mRNA designed to contain a functional Puf3p binding site in different culture conditions and measuring its half-life after a transcriptional shut-off.

Our work suggests that regulation of mRNA stability is not a special case phenomenon, but rather a pervasive regulatory mechanism that rapidly adapts cellular processes to a changing environment.



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