the promoter regions control the sensitivity of transcriptional induction as a function of NF-kB concentration.

By using a combination of quantitative biochemical measurements, we show that the NF-kB nuclear concentration is always lower than the dissociation constant for NF-kB binding to specific sites on DNA. We integrate these measurements in a minimal model of a promoter containing multiple sites, based on the thermodynamics of the one-dimensional Ising model. We demonstrate that in the measured NF-kB concentration range the model accounts for the observed analogical transcriptional response under the assumptions that NF-kB binding to adjacent sites is not cooperative, and that bound NF-kB molecules recruit the transcriptional machinery in an additive fashion, each NF-kB interacting weakly but additively with the Pol II complex.

1553-Pos   Board B397
Information Processing In Single Yeast Cells: Homogeneous Signal Transduction Result In Heterogeneous Gene Expression

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How cells sense their environment using signal transduction pathways and respond to environmental changes by regulating gene expression is a key problem in systems biology. The mitogen-activated protein kinase (MAPK) pathways, which are evolutionarily conserved from yeast to mammals, provide an excellent model to study how signal transduction is coupled to gene expression. Our research focus on the high-osmolarity glycerol (HOG) MAPK pathway in single, Saccharomyces cerevisiae yeast cells. During the last few decades, the components and regulatory network of this pathway have been elucidated via genetic and biochemical assays performed on large populations of yeast cells. However, surprisingly little is known about the detailed coupling dynamics of signal transduction and gene expression in individual cells. After osmotic shock, homogeneous Hog1 kinase dynamics were measured in all cells. In the subsequent gene expression of STL1, a gene that encodes for a glycerol proton symporter of the plasma membrane, we observed that one subpopulation of cells exhibits no gene expression at all (OFF-population), whereas another subpopulation of cells show gene expression over a wide range of expression levels (ON-population). Further, the ratio of the two subpopulations of cells remained constant despite changes in osmolyte concentration from 0.3 M to 0.6 M NaCl. To identify the origin of the bi-modality in gene expression, we over expressed specific transcription factors that regulate STL1 - gene expression. After over expression of one specific transcription factor, we observed a mono modal gene expression distribution for STL1. Furthermore, single cell time-lapse experiments, indicate that switching between gene expression levels after subsequent osmotic shocks was random and uncorrelated. These results indicate, that at least one transcription factor is responsible for the bi-modality and stochasticity in gene expression.

1554-Pos   Board B398
Negative Feedback Speeds Transcriptional Response-Time In Human Cytomegalovirus

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Upon infection of a cell, viruses initiate a complex gene-expression cascade that may result in productive/lytic infection, abortive infection, persistence, or latency depending on the state, cell-type, and environment of that particular cell. However, the regulatory networks underlying these diverse viral lifecycle fates are typically studied using experiments that are averaged over cell populations, potentially masking the dynamic behavior in individual cells. To understand how these diverse viral lifecycle fates are regulated at the single-cell level, we present a framework for quantitatively determining viral expression dynamics and regulatory circuit architectures in individual living cells using a simplified model of a herpesvirus signal transduction module: the human cytomegalovirus (HCMV) Major Immediate Early (MIE) circuit. The system utilizes time-lapse fluorescence video-microscopy of cells infected with recombinant viruses expressing fluorescent gene-products and quantitative modeling to analyze the resulting single-cell data. The combined computational-experimental approach revealed two previously unseen transient signal-processing characteristics of the MIE circuit: (i) negative feedback within the MIE circuit, counter-intuitively, speeds the gene-expression response-time of the essential viral transactivator gene-product IE2-86 (ii) transcriptional activators implicated in reactivation from latency (e.g. trichostatin A) generate a pulse in IE2-86 gene-expression in single-cells. As predicted by the model, mutational deletion of the MIE negative-feedback loop eliminated both the IE2-86 pulse and the accelerated response-time during viral infection. We propose that the negative-feedback architecture of the HCMV MIE circuit may allow the virus to respond quickly to external signals and outpace cellular innate defenses at the single-cell level.

1555-Pos   Board B399
Pitchfork And Hopf Bifurcations In Stochastic Regulatory Networks With Delayed Feedback

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The bifurcation diagram of a model nonlinear Langevin equation appropriate for delayed feedback loops in regulatory networks is obtained. We show that under parametric fluctuation the bifurcation remains sharp, both in the ranges of direct and oscillatory bifurcation. At threshold, the stationary distribution function becomes a power law in the dynamical variable. The combined effect of delay and stochasticity leads to a shift in the location of the bifurcation threshold relative to the deterministic limit of no fluctuation. The shift scales linearly with the noise intensity.

1556-Pos   Board B400
Power-Law Scaling in Protein Synthesis of a Stochastic Regulon-An Experimental Study

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We investigate the protein expression pattern of the lamB gene in Escherichia coli bacterium. The gene product LamB is an important membrane protein for maltose transport into cells but it is also exploited by bacteriophage lambda for infection. Using a dual-colored phage labeling technique, we find that the LamB receptor distribution p(n) has a majority population with average receptor number n~500 and a minority population at small n. This small-n distribution is scale invariant with $p(n) \sim n^{-\alpha}$. A power law is also observed when LamB expression is chemically repressed by growing the bacteria in a glucose medium. We propose a heuristic model which can account qualitatively for our observations.

1557-Pos   Board B401
Exploiting stochastic gene expression to infer promoter regulatory mechanisms: The Moment Analysis Method

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We introduce the moment analysis method for single cell gene expression data. This method exploits higher order moments (greater than two) of steady state fluorescence distributions from genetically identical cells expressing fluorescent proteins to make inferences about the regulatory mechanism of expression at the promoter level. We show that moment analysis can discriminate between mechanisms with a different number of kinetically relevant promoter states, characterized by the transcriptional rate at each state. For instance, we can distinguish between promoters that transcribe genes at a constant rate and those that switch between active and inactive states of transcription. We can also estimate values for the parameters that define the mechanism, such as the transcription rate, the translation efficiency, and the rates at which the promoter switches between different states. We apply this method to analyze gene expression data from the Ptet07 promoter in yeast. In our experiments this promoter is placed at different genomic locations within the yeast chromosome, some of them in silenced and others in open chromatin regions. Our analysis indicates that when we place the promoter-gene system at an open chromatin location, the promoter is well modeled by a single state mechanism, in which the gene is transcribed at a constant rate. Analysis of silenced regions indicates a more complex regulatory mechanism, involving transitions between active and inactive states of the promoter.

1558-Pos   Board B402
Feedback Control Of Fluctuations In Gene Expression And Epigenetic Memory

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Genes and proteins are organized into extensive networks that allow cells to respond and adapt to their environment. These networks are regulated through feedback loops. The dynamic behavior of a genetic network with a given architecture depends on stochastic fluctuations of the agents involved. However, it's still undetermined how the feedback strength and the noise levels couple to determine cellular behavior and its variability. In the present work, we analyze the stochastic dynamic behavior of the galactose uptake network of S. cerevisiae. We focus on how changing the strength of the positive and negative feedback loops influences circuit dynamics and adaptability, and how feedback controls