Telling time with an intrinsically noisy clock

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***Short Abstract* — We consider the ability of transcriptional regulatory networks to propagate information about the phase of intracellular oscillatory signals in the presence of intrinsic cellular noise. For a simple stochastic regulatory model, in which a chemical species driven by oscillatory production regulates via copy number a second species, we compute the mutual information between time and copy number for both the regulating and regulated species. The simplicity of the model permits analytic predictions, which we verify numerically, such as the scaling of information with driving frequency and copy number. We find that depending on the number of available protein molecules and the response time, different regulatory functions perform optimally. We show that there can exist an optimal driving frequency for threshold regulation, at which more information can be transmitted than by infinitely long integration of the signal.**

***Keywords* — stochastic gene regulation, oscillatory signals, information processing**

I. Purpose

As cells progress through the cell cycle [1], oscillatory signals regulate the expression levels of genes via temporal information encoded in regulatory protein concentrations [2]. Regulatory proteins in cells are often present in small copy numbers. Intracellular "clocks" are thus constrained by the fact that the molecules which oscillate in number also intrinsically fluctuate in number. A transcriptional regulatory network, whose function is to respond to such driving, must be able to distinguish oscillations from random fluctuations. Information theory provides natural measures of the reliability with which the oscillatory signal can be extracted from this intrinsic "noise" and propagated to other species in the cell.

To study the optimal transmission of temporal information, we consider the mutual information between the phase of an input oscillation and the concentration of either of two species in a simple model of transcriptional regulation in the presence of oscillations [3]. We explicitly discuss the optimal regulatory functions and frequencies that enable the downstream proteins to "tell time."

II. The Model

We consider a-two gene stochastic transcriptional model in which an external oscillatory signal directly regulates the first gene (the parent), the product protein of which regulates a downstream gene (the child). Within the model, we use a birth-death process to describe protein synthesis and degradation. Regulation is modeled as a dependence of the synthesis rate on the number of regulatory proteins. We compare the information transmitted over a period of the oscillation of the initial signal for a linear, activating threshold, and repressing threshold regulation function.

Evaluating the mutual information between the phase and the output number of proteins requires probability distributions over the number of proteins of each species at a given time. In order to calculate these probability distributions efficiently we extend the spectral method, previously proposed for steady state solutions [4], to the post-transient regime. The efficiency of the computation permits numerical optimization of information over model parameters.

III. Results

We find that the optimal regulatory strategy depends on the biophysical constraints, i.e. the total number of proteins that can be produced and the driving period. For systems with large total protein numbers and long periods, linear regulation is optimal as threshold regulation is observed to be unable to transduce more than ~1 bit of information. However, for small numbers of total proteins and small periods threshold regulation is optimal. Threshold repression requires more proteins than activation, hence at small total protein numbers activation is most informative. We find that for threshold regulation, in the limit of relatively large total protein concentrations, there exists an optimal frequency of the oscillation of the input signal, at which the downstream protein has the largest amount of information about the input phase. In this case, the regulatory system is able to transmit more information than in the case of an infinite period, due to a larger number of distinguishable states. The scaling of information with the frequency shows that the child acts as a stronger low pass filter than the parent. We also show that the child may transmit more information than the parent.

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