Mathematical and experimental characterization of feed-forward circuits in gene regulation

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***Short Abstract* —The feed-forward motifs have been found to exhibit unique functions. The coherent type-1 feed-forward loop (C1-FFL) generates sign sensitive delay, the incoherent type-1 feed-forward loop (I1-FFL) accelerates the response time and performs fold change detection (FCD). An open question is how much they differ among systems in terms of their dynamics and biochemical parameters. We solve the dynamic model analytically, finding these functions to be least sensitive when the second activator/repressor has low cooperativity. We also find the response of the I1-FFL in the FCD regime to be in agreement with Weber's law and Stevens' power law for different levels of cooperativity.**

Keywords* — feed-forward loop, fold change detection, *E.coli

TRANSCRIPTION networks are built of a small set of recurring circuit patterns called network motifs [1, 2]. Two of the most common circuits are the coherent and incoherent type-1 feed-forward loops (C1-FFL and I1-FFL), in which an activator controls a second activator or a repressor, and both jointly regulate an output gene [3].

These circuits have been found to exhibit unique functions. The C1-FFL can generate delay of the output gene, and in this way to filter out brief pulses of input signal [4]. The I1-FFL can accelerate the response time of the output gene, generate pulses and perform fold change detection (FCD) where the response depends only on the fold change of the input signal and no on the absolute change [5-7]. An open question is how much the C1-FFL and the I1-FFLs differ among different systems in terms of their dynamics and biochemical parameters.

Here we built a theoretical framework to address this question. We used dimensional analysis to reduce C1-FFL and I1-FFL models to three dimensionless parameters, related to the steepness n, the halfway activation/repression point γ of the output gene and the ratio ρ of the removal rates of the second activator/repressor and output gene of the regulation. We solved the dynamics analytically and found that a delay in the C1-FFL and an acceleration in the response of the I1-FFL occur for all parameters. Moreover, these functions are least sensitive to parameters when activators/repressors have low cooperativity.

We experimentally compared three C1-FFLs in the arabinose system of *E. coli*, using fluorescent reporter strains [8]. All showed a delay, had low cooperativity n and their halfway activation point γ was close to one.

We also found that within the regime of strong repression the I1-FFL exhibit FCD. By changing only one parameter, the cooperativity of the repressor, the amplitude of the response exhibits two different dependences in the fold change of the input signal. For a Michaelis-Menten input function the response depends logarithmically on the fold consistent with Weber's law. For higher levels of cooperativity the response increases in a power law of the fold. Thus the I1-FFL can explains the origin of two empirical laws in physiology.

This study thus demonstrates how theoretical analysis and dynamical measurements can be used to understand and parameterize the different occurrences of the C1-FFL and I1-FFL in biological systems in a concise way.

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