

Colored extrinsic fluctuations and stochastic gene expression

Vahid Shahrezaei¹, Julien F. Ollivier¹, and Peter S. Swain¹

Short Abstract — Stochasticity is both exploited and controlled by cells. Although the intrinsic stochasticity inherent in biochemistry is relatively well understood, cellular variation is predominantly generated by interactions of the system of interest with other stochastic systems in the cell or its environment. Such extrinsic fluctuations are non-specific, affecting many system components, and have a substantial lifetime comparable to the cell cycle (they are ‘colored’). Here we extend the standard stochastic simulation algorithm to include extrinsic fluctuations. Using our algorithm we demonstrate that both the timescales of extrinsic fluctuations and their non-specificity substantially affect the function and performance of biochemical networks.

Keywords — biochemical network; extrinsic noise; intrinsic noise; stochastic simulation algorithm.

I. INTRODUCTION

BIOCHEMICAL networks are stochastic: fluctuations in numbers of molecules are generated intrinsically by the dynamics of the network and extrinsically by interactions of the network with other stochastic systems [1, 2]. Stochastic effects in protein numbers can drive developmental decisions, be inherited for several generations, and have perhaps influenced the organization of the genome. Intrinsic fluctuations are generated by thermal fluctuations affecting the timing of individual reactions. Their magnitude is increased by low copy numbers. The source of extrinsic fluctuations, however, is mostly unknown [3], although cell cycle effects [4, 5] and upstream networks [5] contribute. Yet extrinsic fluctuations dominate cellular variation in both prokaryotes [1] and eukaryotes [6]. They are colored, having a lifetime that is not negligible but comparable to the cell cycle [4], and they are non-specific, potentially affecting equally all molecules in the system [7]. They are thus difficult to model and their effects hard to predict.

Here we consider the effects of extrinsic fluctuations on gene expression and gene regulatory networks. Extrinsic fluctuations typically cause fluctuations in the parameters of a network. For our simulations, we designed a novel extension of the standard algorithm [8] for simulating intrinsic fluctuations that includes discontinuous, time-varying parameters and therefore can simulate extrinsic fluctuations with any desired properties.

II. RESULTS AND CONCLUSION

Using our algorithm and analytical methods, we study the effect of extrinsic fluctuations in parameters of a simple

model of gene expressions. We show that both mean protein numbers and intrinsic noise can be increased or decreased by extrinsic fluctuations. These changes in mean protein numbers and intrinsic noise can explain discrepancies in recent high throughput measurements of noise. We demonstrate that to reduce fluctuations the strength of negative feedback has an optimum value because of competitive effects between intrinsic and extrinsic fluctuations. We show that extrinsic fluctuations can speed up typical response times in simple networks. Finally, we illustrate that extrinsic fluctuations in different components of a network can combine destructively to negate each other or constructively to significantly amplify fluctuations in the output of the network and these constructive and destructive effects are likely to be exploited by cells in feedforward loops, one of the most common motifs in genetic networks.

Extrinsic fluctuations, through their timescales and non-specificity, are thus an important component of the intracellular environment. To function in this environment, biochemical networks are likely to have evolved to control or exploit these fluctuations. Our stochastic simulation algorithm and mathematical analysis should therefore help to quantitatively understand endogenous networks and to design effective synthetic ones [9].

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