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Commentary

Evolutionary Comparison of Predicting Gene Expression Levels in the Presence of Infinitesimal Delay

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ABOUT THE STUDY

Individual molecules are synthesized in bursts of multiple copies during gene expression. The frequency and size of these bursts can be affected by gene regulatory feedback. Whereas frequency regulation has traditionally received more attention, we concentrate specifically on burst size regulation. It turns out that there are (at least) two alternative formulations of feedback in burst size. In the first, newly produced molecules immediately participate in feedback, even within the same burst. Due to infinitesimal delay, there is no within-burst regulation in the second. We describe both alternatives using a minimalistic Markovian drift-jump framework that combines discrete and continuous dynamics. We provide thorough analytical findings and effective simulation methods for positive non-cooperative auto regulation (whether infinitesimally delayed or not). We demonstrate that at steady state, both options result in a protein level distribution with a gamma shape. It takes passing a trans-crucial bifurcation point before the steady-state distribution is accessible. It's interesting to note that the insertion of an infinitesimal delay delays the commencement of the bifurcation.

Individual gene expression is stochastically varying, which causes random variations in protein concentration in individual cells as well as in homogeneity of protein concentration across cell populations. Gene expression variability has been found to be mostly derived by the creation of protein molecules in bursts, or batches of many molecules during short periods of time. It is commonplace in biological circuits for proteins to provide feedback on the expression of their own genes. Regulatory feedback can have two fundamentally distinct effects if protein is made in bursts it can either change how frequently bursts happen over time or it can change how big they are. Both positive and negative feedback is possible, however in this case we'll concentrate on the positive input about burst size. The effect of negative feedback on burst size and frequency has been studied in stochastic gene expression models, which are frequently based on the random telegraph framework. A gene can be either on or off in a random telegraph model, switching randomly between the two states over time. Another time-dependent numerical variable that represents the amount of protein in the cell is present in addition to the binary variable indicating whether the gene is on or off. Many models regard the amount of protein to be a discrete variable, but in this case we employ a hybrid discrete-continuous formalism and treat the protein level as a continuous variable; we also refer to it as concentration. When the gene is active, the protein concentration rises, and when the gene is inactive, it falls. In various circumstances, the biological meanings of the abstraction of on and off states can vary. They can stand in for the promoter region of the gene's active and inactive stages. If a messenger transcript molecule is present or absent, they can serve as a substitute.

In summary, we investigated two versions of a stochastic model for pulsatile protein dynamics with burst size feedback. Differential and integral equations were combined with stochastic simulations in our methods. While we applied these methodologies to the specific example at hand, we anticipate that combinations of such approaches will be useful in the broader context of gene-expression and biological modeling.

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