Effects of cell cycle noise on excitable circuits

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***Short Abstract* — We assess the impact of cell cycle noise on gene circuit dynamics. For bistable genetic switches and excitable circuits, we find that transitions between metastable states most likely occur just after cell division and that this concentration effect intensifies in the presence of transcriptional delay. We explain this concentration effect with a 3-states stochastic model. For genetic oscillators, we quantify the temporal correlations between daughter cells induced by cell division. Temporal correlations must be captured properly in order to accurately quantify noise sources within gene networks.**

***Keywords* — Bistable switch, cell cycle noise, excitable system, metastability, synthetic genetic oscillator, transcriptional delay**

I. Background

CELLULAR noise and transcriptional delay shape the dynamics of genetic regulatory circuits. Stochasticity in cellular processes has a variety of sources, ranging from low molecule numbers, to variability in the environment, metabolic processes, and available energy. Such fluctuations can drive a variety of dynamical phenomena, including oscillations, stochastic state-switching, and pulsing. Microbial and eukaryotic cells make use of such dynamics in probabilistic differentiation strategies to stochastically switch between gene expression states, and for transient cellular differentiation.

How cell cycle noise shapes dynamics is only partially understood. The cycle of cell growth and division results in a distinct noise pattern: Intrinsic chemical reaction noise decreases as cells grow before abruptly jumping following cell division. The partitioning of proteins and cellular machinery at division also induces a temporally localized, random perturbation in the two daughter cells. These perturbations are correlated, as a finite amount of cellular material is divided between the two descendant cells. Such correlations can propagate across multiple generations within a lineage.

II. Results

We find that cell cycle noise can strongly impact the dynamics of bistable and excitable systems. In both cases, transitions out of metastable states are concentrated within a short time interval just after cell division. Interestingly, this effect intensifies as transcriptional delay (the time required for a regulator protein to form and signal its target promoter) increases. We show that this concentration effect results primarily from the random partitioning of cellular material upon cell division, and explain the underlying mechanisms via a 3-states reduced model.

For genetic oscillators, we find that cell cycle noise plays an important role in shaping temporal correlations along descendant lineages. In particular, for a dual feedback genetic oscillator, we show that temporal correlations between daughter cells decay significantly faster when the cell cycle is modeled explicitly.

In models of genetic networks the effects of cell growth are frequently described by a simple dilution term, which does not capture the distinct temporal characteristics of cell cycle noise. We conclude that in order to accurately describe gene circuit dynamics, such models should include both cell cycle noise and transcriptional delay.

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