The coarse-graining of biochemical fluctuations

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***Short Abstract* — Biochemical events are usually represented as memory-less single-molecule events. But creation and degradation can occur in bursts of many molecules, increasing variability. Conversely, each birth or death of a macromolecule could involve several small steps, creating a memory between individual events and reducing variances without changing average abundances, lifetimes, or any concentration-dependent control loops. Here we present generalized theory for stochastic gene expression, and discuss the effective coarse-graining of the molecular hardware. We thereby explain why previous simple models have been so successful, but also that they do not discriminate between qualitatively different types of coarse-graining, which requires time-series with single-molecule resolution.**

***Keywords* — Stochasticity, gene expression, noise.**

I. Purpose

In gene expression and many other biological processes, the inherent randomization of biochemical events is increased because events tend to come in 'bursts' of many molecules [1]. But macromolecules are complicated structures whose births and deaths may require numerous elementary reactions. Fluctuations could then be decreased by fine-graining the processes that generate the randomness in the first place, i.e., by taking sub-integer microscopic reaction steps rather than by tightening control. Is this extra complexity compatible with the simple cartoon networks that are used in most cases?

II. Methods and Results

Here we derive analytical expressions for the noise in gene expression that show that it is indeed possible. We show that the variance in the protein concentration depends only on the noise in the timing between events, regardless of their distribution, as well as the average and noise in the bursts of creation, not on their distribution. This means that events in different timescales are effectively coarse-grained into simpler systems, albeit with non-exponential distributions of times between events.

Based on these intuitive mathematical results and a wide range of biological examples, we explain how fine-graining or 'molecular memory' can act as the opposite of bursts or dampen the randomizing effect of bursting. These mechanisms modify noise levels without affecting average turnover rates or steady state signaling: a change in the rate constants for synthesis or degradation still has a proportional effect on the steady state averages, as opposed to positive or negative feedback control that similarly amplify or dampen noise but then also amplify or dampen external signals. We have previously shown that transmitted noise from other components in a genetic network can be the dominant source of noise [2], so we also show how the timing of events can affect noise transmission, including such counter-intuitive results as the fact that making protein decay more regular increases overall noise.

Most of the literature on stochastic gene expression can be captured by an expression analogous to the fluctuation dissipation theorem [3], with the focus on which component of the system the noise comes in. Here we show that current observations are consistent with almost any quantal size of the individual chemical events, making them unable to distinguish how the noise comes into each component. Even in the ideal case where simple models without tunable parameters provide predictions that later are tested experimentally [4], they cannot rule out most possible stochastic mechanisms. Conversely, this lack of sensitivity to the details of the stochastic process makes them more robust at identifying which molecular components introduce the noise. We explain how single molecule experiments [5,6] can determine the effective coarse-graining of the biochemical machinery of gene expression and the origin of its noise.

III. Conclusions

Our findings mathematically connect noise in the single-cell protein abundance to bursting, gestation and senescence in gene expression – describing how 10 molecules in some sense can statistically behave as if they were 5 or 20 molecules without control loops. We also show that standard single-cell measurements cannot detect or exclude these features: they only suggest which components contribute fluctuations, not how they contribute, and that this can be overcome only through single molecule experiments.

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