Deterministic Characterization of Phase Diffusion in Biochemical Oscillators

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***Short Abstract* — Evaluating the effect of molecular noise in biochemical oscillators is necessary to fit data coming from single-cell experiments. Unfortunately such tasks need extensive computational resources. In this work, we propose a semi-analytical method that efficiently approximates the diffusion of the phase of uncoupled noisy oscillators. We test the approach on the 1-loop model of the Drosophila circadian clock. Our results are consistent with those obtained through stochastic simulations. The computed analytic measure correlates well with the half-life of the autocorrelation function, which is widely used to evaluate the effect of molecular noise to biochemical oscillations.**

***Keywords* — biochemical oscillations, molecular noise, phase diffusion.**

I. Introduction

IN this work, we study the effect of molecular noise on the phase of biochemical cycle. More specifically, we would like to understand how identical systems, such as cells under the control of internal oscillations, experience desynchronization when isolated. In recent literature, the evaluation of the effect of noise in such systems is based on the autocorrelation function [1] or other statistical analyses [2]. These methods are computationally expensive as many long stochastic simulations are necessary to obtain a statistically relevant result.

Different means, such as the linear noise approximation (LNA) [3] or tau-leaping algorithms [4] have been proposed to circumvent the problem of computational time. However, they may not properly approximate the molecular noise in an oscillatory system. Moreover, methods such as tau-leaping speed-up simulations, but they return a single stochastic sample path and scale badly when used to characterize phase diffusion with high statistical accuracy.

Here, we propose a semi-analytical method that can be used for systems where the perturbations due to the noise are small, i.e. where a Langevin approximation is justified. We approximate the diffusion rate of the phase of individual oscillators by integrating a specific function along the deterministic limit cycle. Even if simulation is still necessary, it is based on the integration of the governing ordinary differential equation, which is computationally much cheaper than ensemble stochastic simulations.

II. Results

We apply the approach to the 1-loop model of the Drosophila circadian clock proposed in [5]. The results from the semi-analytical method and from the simulation show good agreement with a small constant difference. As expected the measure correctly captures the scaling of the phase diffusion with the inverse of the reaction volume. A comparison of our semi-analytical measure with the half-life of the autocorrelation function shows that both measures of molecular noise are highly correlated. This new method can therefore properly substitute for the evaluation of the autocorrelation function. Furthermore, we calculate this phase diffusion coefficient along a general nonlinear path in 15-dimensional parameter space and find good agreement with the results obtained from ensemble stochastic simulations.

III. Conclusion

Based on the discussed case study, the proposed method appears to be an accurate means to estimate the phase diffusion due to molecular noise in biochemical oscillators. Being efficient to compute, it allows the test and comparison of multiple models and can help to parameterize them with respect to molecular noise. For instance, it may be used to test multiple architectures and different parameter sets of a specific system and fit the data available from single cell analysis. Moreover, the mathematical analysis resolves the long-standing discrepancy that LNA-based approaches yield inconsistent results for oscillatory systems.

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