Statistical analysis of stochastic biochemical signaling: inference, information processing and experimental design

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Short Abstract — We present an integrated framework to statistically analyze stochastic dynamical models of biochemical reactions. Statistical tools are employed to take a comprehensive view at stochastic biochemical models. Cellular signal transduction can be seen as inference problem, therefore statistical methodology of estimation and experimental design can provide insight about information processing and design principles of biochemical circuits. Our approach is based on the likelihood function and Fisher Information. Having developed a method to calculate these two quantities efficiently we analyze a number of biochemical dynamical models. We show that statistical methodology can provide an unprecedented insight about consequences of stochasticity both for data analysis and cellular information processing.

Keywords **— stochastic chemical kinetics, inference, Fisher Information, information processing**

I. INTRODUCTION

IN the past decade, dynamic modeling of biochemical systems using stochastic approaches has gained substantial interest as the role of stochastic effects turned out to be significant in the functioning of living cells. The dynamical behaviors of such systems cannot be understood by intuition alone and require tools for their analysis. In the case of deterministic models parameter inference and sensitivity analysis greatly help to understand the dependence between parameter values, the dynamic output and experimental data. Due to the qualitative difference between deterministic and stochastic systems, the development of these methods in the latter regime is rather limited.

II. RESULTS

We have constructed an efficient framework to compute likelihood function and Fisher Information, which are the basic concepts of inference, sensitivity analysis and optimal experimental design. Our methodology breaks the barrier of computationally prohibitive Monte Carlo simulations. It allows applying classical statistical tools to analysis of stochastic biochemical models. We reduced the problem of calculating likelihood function and Fisher Information to solving a set of ordinary differential equations [1,3].

Primarily, we used our framework to extract information from experimental single cell data [1,2]. This approach allowed us to appreciate the reliability of parameter estimates and provided information regarding parameter sensitivity and model robustness. Overcoming the computational barrier also opened a way to apply experimental design approaches using stochastic modeling, which is essential for single cell experiments. It can be used to resolve problems arising in single cell experimentation such as choice between fluorescent microscopy and flow cytometry experiments [3,4].

Efficiency of our method allowed us to employ methodology of inference and optimal design of experiments to study cellular information processing. Living cells are forced to solve inference problems as they measure constantly changing parameters of their environment. Therefore, their biochemical machineries encode certain experimental procedures that, at least to some extent, must have been optimized. We used the theory of optimal experimental design to unravel design principles of nitrogen assimilation circuit in Escherichia coli.

III. CONCLUSIONS

Given the role of inference and Fisher Information in model analysis and increasing interest in stochastic models of biochemical reactions, our approach is widely applicable [3,4]. We demonstrate that it provides unprecedented insight about consequences of stochasticity for single cell gene expression data [4] as well as for biochemical signal transduction.

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