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Intrinsic Noise in Nonlinear Gene Regulation Inference

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ABSTRACT

Cellular intrinsic noise plays an essential role in the complex regulatory interactions between genes, which, in turn, govern many fundamental cellular processes, such as cell differentiation and response to medication. Although a variety of quantitative methods are used to analyze gene expression data, the role of intrinsic noises in regulatory mechanisms has largely been overlooked. Using the Kolmogorov backward equation (master equation), we formulate a causal and mechanistic Markov point process model. While many existing quantitative models and inference approaches have no direct connection to the laws of physics, this framework recognizes the discrete, nonlinear and stochastic natures of gene regulation and therefore presents a more realistic description of the physical systems. Within this framework, we develop an associated moment-based statistical method, aiming for inferring the unknown regulatory relations. By analyzing the observed distributions of gene expression measurements from both unperturbed and perturbed steady-states of gene regulation systems, this method is able to learn valuable information concerning regulatory mechanisms. In spite of the complexity of our model, this design allows us to estimate the model parameters with a simple convex optimization algorithm. We apply this approach to a synthetic system that resembles a genetic toggle switch. We also demonstrate that this algorithm can recover the regulatory parameters efficiently and accurately.

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