

345e Extrinsic and Intrinsic Cell Population Heterogeneity in Genetic Networks with Positive Feedback Loop Architecture

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Systems biology approaches have provided significant insights into the complexity at the single-cell level. However, biological complexity is not only a result of interactions among the numerous components within individual cells; it also strongly depends on the various direct and indirect interactions among the cells of a population. These intra- and inter-cellular interactions lead to significant phenotypic cell-to-cell variability, or cell population heterogeneity. Due to the instrumental role that regulatory molecules play in the determination of single-cell phenotype, phenotypic variability among the cells of a population is tightly related to regulation of gene expression and, hence, the architecture and dynamics of single-cell regulatory networks. Therefore, quantitatively elucidating the link between single-cell genetic architecture and heterogeneous behavior at the cell population level is of fundamental importance in understanding biological behavior across the scales.

Heterogeneity in an isogenic cell population originates from two fundamentally different sources. First, due to the operation of the cell cycle and unequal partitioning of cellular material at cell division, cells of the population may have different cellular content at the same point in time. Since the phenotype of each individual cell is a strong function of its intracellular state, cells with different states will have different phenotypes (extrinsic heterogeneity). Second, regulatory molecules typically exist in small concentrations. Thus, inherently random fluctuations characterize the rates of reactions regulated by such molecules. Hence, at a given point in time even cells with equal numbers of regulatory molecules may behave differently (intrinsic heterogeneity). The lack of quantitative understanding of the relative contribution of each source of heterogeneity on the overall heterogeneous phenotype of cell populations still hinders the efficient and rigorous design of biological systems for various applications.

Motivated by these challenges, we developed a computational stochastic framework that can track both the intrinsic and extrinsic sources of cell population heterogeneity. The framework will be applied to a class of genetic networks characterized by the positive feedback regulatory architecture. Using this model system we will first illustrate the importance of accounting for cell population heterogeneity by comparing our results with a corresponding model that neglects cell population heterogeneity altogether. Moreover, we will quantitatively isolate the effects of extrinsic population heterogeneity and validate the results of our algorithm through comparison with a deterministic cell population balance model. We will also elucidate the key effects of the intrinsic source of cell population heterogeneity as a function of the molecular characteristics of the network. Conclusions on the quantitative contribution of each source of cell population heterogeneity on the distribution of phenotypes amongst the cells of the population in systems with positive feedback loop architectures will be presented and discussed.