Reduction of a stochastic model of gene expression: Lagrangian dynamics gives access to basins of attraction as cell types and metastability

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Differentiation is the process whereby a cell acquires a specific phenotype, by differential gene expression as a function of time. This is thought to result from the dynamical functioning of an underlying Gene Regulatory Network (GRN). The precise path from the stochastic GRN behavior to the resulting cell state is still an open question. In this work we propose to reduce a stochastic model of gene expression, where a cell is represented by a vector in a continuous space of gene expression, to a discrete coarse-grained model on a limited number of cell types. We develop analytical results and numerical tools to perform this reduction for a specific model characterizing the evolution of a cell by a system of piecewise deterministic Markov processes (PDMP). Solving a spectral problem, we find the explicit variational form of the rate function associated to a Large deviations principle, for any number of genes. The resulting Lagrangian dynamics allows us to define a deterministic limit of which the basins of attraction can be identified to cellular types. In this context the quasipotential, describing the transitions between these basins in the weak noise limit, can be defined as the unique solution of an Hamilton-Jacobi equation under a particular constraint. We develop a numerical method for approximating the coarse-grained model parameters, and show its accuracy for a symmetric toggle-switch network. We deduce from the reduced model an approximation of the stationary distribution of the PDMP system, which appears as a Beta mixture. Altogether those results establish a rigorous frame for connecting GRN behavior to the resulting cellular behavior, including the calculation of the probability of jumps between cell types.

This work is the object of a paper which is under revision in J. Math. Biol [1].

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