MAR15-2014-020010

Abstract for an Invited Paper
for the MAR15 Meeting of
the American Physical Society

Integrating discrete stochastic models and single-cell experiments to infer predictive models of MAPK-induced transcription dynamics

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MAPK signal-activated transcription plays central roles in myriad biological processes including stress adaptation responses and cell fate decisions. Recent single-cell and single-molecule experiments have advanced our ability to quantify the spatial, temporal, and stochastic fluctuations for such signals and their downstream effects on transcription regulation. This talk explores how integrating such experiments with discrete stochastic computational analyses can yield quantitative and predictive understanding of transcription regulation in both space and time. We use single-molecule mRNA fluorescence in situ hybridization (smFISH) experiments to reveal locations and numbers of multiple endogenous mRNA species in 100,000's of individual cells, at different times and under different genetic and environmental perturbations. We use finite state projection methods to precisely and efficiently compute the full joint probability distributions of these mRNA, which capture measured spatial, temporal and correlative fluctuations. By combining these experimental and computational tools with uncertainty quantification, we systematically compare models of varying complexity and select those which give optimally precise and accurate predictions in new situations. We use these tools to explore two MAPK-activated gene regulation pathways. In yeast adaptation to osmotic shock, we analyze Hog1 kinase activation of transcription for three different genes STL1 (osmotic stress), CTT1 (oxidative stress) and HSP12 (heat shock). In human osteosarcoma cells under serum induction, we analyze ERK activation of c-Fos transcription.