Universität Basel

Research Project

ANALYSIS OF RNA AND PROTEIN TURNOVER TO PREDICT STOCHASTIC NETWORK BEHAVIOR

Third-party funded project

Project title ANALYSIS OF RNA AND PROTEIN TURNOVER TO PREDICT STOCHASTIC NETWORK BEHAVIOR
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Understanding and prediction of the behavior of cellular networks is a major goal of systems biology. Nonlinearities and stochasticity in networks make this prediction difficult but they also promote the emergence of complex behaviors ranging from oscillations, adaptation in chemotaxis to cellular differentiation. Substantial efforts have been invested into deciphering how nonlinearity and noise are influenced by transcription and translation. On the other hand, little is known about how they are affected by decay processes. Our project proposal aims at uncovering how RNA and protein turnover rates determine fluctuations and precision in cellular functions.

Our first subproject aims at studying how RNA production and degradation jointly determines fluctuation in gene expression. Recent studies have revealed that decay processes can feedback on biosynthetic processes, which compounds the problem of distinguishing the stochastic effects of RNA degradation. Special attention will be paid to histone gene expression which is very tightly regulated since alterations in the histone gene dosage can lead to changes in the stoichiometry in the histone octamer with pleiotropic effects on the expression of the entire genome. The promoter of the histone gene is regulated by a cooperatively binding transcriptional activator and the decay of histone mRNAs is time dependent, linked to the cell cycle.

In the second subproject, we examine how protein decay shapes non-linear responses and how these - in conjunction with fluctuations - determine the stochastic transitions in positive feedback loops. The results will help to design measurements to explain the kinetic mechanisms of cellular memory and the stability of cellular differentiation states.

To realize these subprojects, we will use cutting edge techniques involving single molecule RNA detection and quantitative proteomics in yeast cells in combination with mathematical modeling of stochastic processes. Our results will advance the interpretation of non-invasive methods and will help to define the extent to which fluctuations have to be taken into account to efficiently model and understand nonlinear network dynamics. This in turn will be helpful to measure the most relevant biochemical reaction rates in genetically heterogeneous cell populations and to engineer cells with precise functioning. We expect applications in tissue engineering in the future.

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