Genetic control mechanisms in fluctuating environments

Cells live in complex and fluctuating environments and bear intracellular stochastic components. Yet, they robustly maintain functionality either by suppressing the fluctuating stimuli or by adapting to them. Cells generally implement these responses by complex genetic control mechanisms. This thesis focuses on a couple of such mechanisms. One of them and a recurrent motif in human cells is an intronic microRNA-mediated self-loop. MicroRNAs are small non-coding RNAs that regulate the expression of protein-coding genes at the post-transcriptional level in both plants and animals. In this particular small control circuit the microRNA is located in the intronic region of a host gene and negatively regulates the expression of that gene. Despite its simple topology this circuitry can perform several regulatory tasks depending on the availability of the molecular species involved. We show mathematically and through simulations that this control mechanism can filter fluctuations from upstream transcription factors, alter the response times eventually locking the on-phase of the target product, and implement adaptation and fold-change detection. We provide a map of functions in terms of experimentally measurable variables for a possible application in synthetic biology. In the second part we present work from a research visit to the group of Peter Swain at the Centre for Systems Biology at Edinburgh, UK. The group's focus is on cellular decision-making and, in particular, on the galactose sensing network in Saccharomyces cervisiae. The network implements a switch-like response to the sugar and is controlled by two positive and one negative feedback loops. Here, we focus on parts of the model building process, specifically, on the data analysis and parameter estimation by means of Bayesian Monte Carlo methods. Interestingly, as a result of this analysis, we found that the growth rate of the population decreases with increasing concentrations of the sugar while the carrying capacity increases.

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