Crucial Experimental Aspects for Designing Optimal Experiments in Systems Biology

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Abstract: The complexity of systems and models regarded by systems biology is rapidly increasing and with it the effort for obtaining reliable model parameter values from experimental data. Hence the strategy of *optimal experiment design* (OED) is becoming more and more interesting for systems biology. However, the transfer of this technique to this field forms some obstacles: both biological systems and applied measurement methods are often subject to poorly understood statistical fluctuations, making reliable parameter estimation challenging.

We want to apply OED to systems biology using a circadian clock model of *Neurospora* based on ordinary differential equations. The molecular clock consists of three central components: the *frequency* gene (*frq*), responsible for the expression of *frq* mRNA and FRQ protein, and WCC, a transcription activator of the *frq* gene. Phosphorylation of WCC—taking place at high FRQ levels—inhibits the transcription factor and therewith establishes a negative feedback loop for the *frq*'s gene expression. In order to measure oscillation of *frq* mRNA, FRQ protein and WCC phosphorylation, the fungus is first grown at constant light (day conditions) leading to the maintenance of a high expression level of *frq*, thus calibrating the clock. A transition into darkness (night conditions) removes this constitutive stimulus and triggers the running of the clock. Measurement of *frq* and FRQ abundance levels as well as WCC phosphorylation degrees provides experimental data used for estimating the model parameter values.

The resulting estimates—and therefore also results from OED—are only reliable if both measurement values *and* their standard deviations are known. In biology, the latter are usually intricate quantities depending on complex measurement procedures. This talk concentrates on the analysis of the *frq* mRNA transcription and its measurement error in the calibrated state of the *Neurospora* clock. In this context it emphasizes why system-intrinsic fluctuations—repetitively observed in the quantitative analysis of biological systems—are crucial to be considered for the success of parameter estimation and hence for OED.

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