Optimal Experimental Design in Computational Systems Biology

R. Eils[1], J. Keienburg[1], C. Hoffmann[2], J. P. Schlöder[2], and H. G. Bock[2]

Abstract: Systems Biology is a recently established yet rapidly emerging research area in the life sciences. Based on molecular and cellular data this discipline thrives at a systems based understanding of complex biological processes. Large-scale experimental collection of temporal and spatially resolved data still provides a major bottleneck in model generation in systems biology. A quantitative understanding of biological systems requires accurate knowledge about parameter values. For most models of such systems, however, kinetic parameters are poorly known. Controls are parameters or variables that can be externally manipulated to change the behavior of a system. Optimal Experiment Design (OED) uses this possibility and optimizes system dynamics to increase the yield of measurement information for efficient parameter estimation; in addition it also suggests optimal measurement time points. The concept of OED is implemented in the software package VPLAN, and it has proven very useful in process engineering and the chemical industry; however, the application in biological systems modeling is just starting.

As a case study we investigate the core network of the circadian clock in *Neurospora* to verify the experimental applicability of OED. The central module for circadian oscillation is the rhythmic expression of the *frq* gene via a negative feedback loop, which comprises three components: expression of the *frq* gene increases the abundances of *frq* mRNA and FRQ, which phosphorylates WCC - a protein dimer consisting of WC-1 and WC-2. WCC binds in the unphosphorylated state as transcription activator to the *frq* promoter. However, phosphorylation of WC-2 by FRQ prevents WCC from binding and thereby decreases *frq* expression. The Goodwin model quantitatively describes the core of this circadian clock network, and it has been shown that assignment of a temperature dependent term to each kinetic parameter provides the capability of temperature regulated clock adaptation. In measuring *frq* and FRQ abundances, as well as the phosphorylation degree of WC-2, we will show that temperature is a suitable control parameter to change the course of the circadian rhythm in *Neurospora*. Usage of this control in designing optimal experiments will finally lead to substantial savings in time and expenses, while at the same time improving the reliability of parameter estimations significantly.

---

[1] BioQuant, University of Heidelberg
Im Neuenheimer Feld 267, 69120 Heidelberg, Germany
r.eils@dkfz.de, j.keienburg@dkfz.de

[2] Interdisciplinary Center for Scientific Computing, University of Heidelberg
Im Neuenheimer Feld 368, 69120 Heidelberg, Germany
{*christian.hoffmann, j.schloeder, bock*}*@iwr.uni-heidelberg.de*