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DYNAMICAL MODELING OF BIOLOGICAL SYSTEMS

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Within this thesis, novel methods have been suggested covering all central steps in the process of mathematical modeling of signal transduction pathways, namely experimental planning, quantitative measurement of protein concentrations, creation and validation of differential equation based mathematical models, and calculation of characteristic system properties like control coefficients, half-lifes, and sojourn times. The findings are based on close collaborations with the group of PD Dr. Ursula Klingmüller from the German Cancer Research Center in Heidelberg, especially Dr. Marcel Schilling, Dr. Peter Nickel, and Dr. Sebastian Bohl, with Dr. Stefan Legewie from the Humboldt University, Berlin and Clemens Kreutz and Stefan Hengl in the group of Prof. Jens Timmer, University of Freiburg. The author implemented all concepts into the software PottersWheel and GelInspector, which are freely available for the research community at *www.potterswheel.de*.

(1) **GelInspector**: Quantitative Western blotting is a widespread approach to determine the relative amount of proteins in a solution. However, we identified systematic errors during the blotting process which significantly decrease the achieved data quality potentially leading to wrong conclusions about the measured biochemical system [1]. In the case of time-course experiments, the correlation structure of the error may lead to spurious dynamics of the investigated system. Therefore, a laboratory and statistical randomization and normalization procedure is suggested, which dramatically reduces the impact of the measurement error.

(2) **In Silico Labeling**: Mathematical models of dynamic systems facilitate the computation of characteristic properties which are not accessible experimentally. We developed a novel approach called In Silico Labeling to calculate the half-life and sojourn time of species in arbitrarily complex non-linear reaction networks. Application to a non-linear model of the STAT signaling pathway enabled the calculation of the time-dependent half-life of STAT cycling through the nucleus.

(3) The software **PottersWheel** has been developed to provide an intuitive and yet powerful framework for data-based modeling of dynamical systems which can be expressed as sets of ordinary differential equations [2, 3]. Its key functionality is multi-experiment fitting, where several experimental data sets from different laboratory conditions are fitted simultaneously in order to improve the estimation of unknown model parameters, to check the validity of a given model, and to discriminate competing model hypotheses.

(4) An **experimental design** approach is suggested in order to discriminate competing biological hypotheses taking into account given laboratory constraints like measurement noise or technically feasible stimulations [4]. A minimal but sufficient set of the most informative experiments is compiled to significantly distinguish the models under consideration.

(5) The **TGFbeta/SMAD signaling pathway** is an important functional unit in the context of mitosis and cellular differentiation. Based on mRNA and protein data of primary hepatocytes, a detailed mathematical model has been established and fitted to experimental data from 32 data sets simultaneously in order to successfully predict 14 independent measurements comprising 506 data points.

[1] M. Schilling*, T. Maiwald*, S. Bohl, M. Kollmann, C. Kreutz, J. Timmer, U. Klingmüller *Computational processing and error reduction strategies for standardized quantitative data in biological networks* FEBS Journal 272 , 2005, 6400-6411, *equal contribution

[2] T. Maiwald and J. Timmer, *Dynamical modeling and multi-experiment fitting with PottersWheel,* Bioinformatics 2008, 24:2037-2043

[3] S. Hengl, C. Kreutz, J. Timmer, T. Maiwald *Data-based identifiability analysis of nonlinear dynamical models,* Bioinformatics 2007, 23, 2612-2618

[4] T. Maiwald, C. Kreutz, A. Pfeifer, S. Bohl, U. Klingmüller, J. Timmer *Dynamic pathway modeling: Feasibility analysis and optimal experimental design* Annals New York Acad. Sci. 115, 2007, 212-220