Dear Editors,

In Systems Biology, ordinary differential equation models are often used to analyze signal transduction pathways, gene regulation or cellular decisions. One of the most critical steps in this approach is to construct models based on large sets of data generated under complex experimental conditions and to perform efficient and reliable parameter estimation for model fitting. We present the **Data2Dynamics** software environment that was tailored to solve these challenges.

The software is freely available, open source and developed in a community effort using a web-based code hosting service and a revision control system. It has been applied in several projects that led to publications, see below. Some of those applications are provided as benchmark examples within the software for further methods development and as guideline for novel applications. The software was awarded twice as best performer in the Dialogue for Reverse Engineering Assessments and Methods (DREAM, 2011 and 2012).

Beyond modeling of biological systems the software can be applied to any comparable problem in other fields of research.

We would be more than happy if you would consider our **Application Note** for publication in Bioinformatics.

Best wishes, Andreas Raue and colleagues

Biology publications making use of the Data2Dynamics software

- D'Alessandro LA, Samaga R, Maiwald T, Rho SH, Bonefas S, Raue A, Iwamoto N, Kienast A, Waldow K, Meyer R, Schilling M, Timmer J, Klamt S, and Klingmüller U. Disentangling the complexity of HGF signaling by combining qualitative and quantitative modeling. *PLOS Comput Biol*, in press
- Klett H, Rodriguez-Fernandez M, Rodriguez-Fernandez M, Dineen S, Leon LR, Timmer J, and Doyle III FJ. Modeling the inflammatory response in the hypothalamus ensuing heat stroke: Iterative cycle of model calibration, identifiability analy-

- sis, experimental design and data collection. *Mathematical Biosciences* **260**, 35–46, 2015
- Verbruggen P, Heinemann T, Manders E, von Bornstaedt G, van Driel R, and Höfer T. Robustness of DNA repair through collective rate control. *PLOS Computational Biology* 10(1), e1003438, January 2014
- Müller K, Engesser R, Timmer J, Zurbriggen MD, and Weber W. Orthogonal optogenetic triple-gene control in Mammalian cells. *ACS synthetic biology* **3**(11), 796–801, November 2014
- Kanodia J, Chai D, Vollmer J, Kim J, Raue A, Finn G, and Schoeberl B. Deciphering the mechanism behind fibroblast growth factor (FGF) induced biphasic signal-response profiles. *Cell Communication and Signaling* **12**, 34, 2014
- Beer R, Herbst K, Ignatiadis N, Kats I, Adlung L, Meyer H, Niopek D, Christiansen T, Georgi F, Kurzawa N, Meichsner J, Rabe S, Riedel A, Sachs J, Schessner J, Schmidt F, Walch P, Niopek K, Heinemann T, Eils R, and Di Ventura B. Creating functional engineered variants of the single-module non-ribosomal peptide synthetase IndC by T domain exchange. *Molecular bioSystems* **10**(7), 1709–18, July 2014
- Gin E, Diernfellner ACR, Brunner M, and Höfer T. The Neurospora photoreceptor VIVID exerts negative and positive control on light sensing to achieve adaptation. *Molecular Systems Biology* **9**(667), 667, 2013
- Müller K, Engesser R, Metzger S, Schulz S, Kämpf MM, Busacker M, Steinberg T, Tomakidi P, Ehrbar M, Nagy F, Timmer J, Zubriggen MD, and Weber W. A red/far-red light-responsive bi-stable toggle switch to control gene expression in mammalian cells. *Nucleic Acids Research* **41**(7), e77, April 2013a
- Müller K, Engesser R, Schulz S, Steinberg T, Tomakidi P, Weber CC, Ulm R, Timmer J, Zurbriggen MD, and Weber W. Multi-chromatic control of mammalian gene expression and signaling. *Nucleic Acids Research* **41**(12), e124, July 2013b
- Müller K, Engesser R, Timmer J, Nagy F, Zurbriggen MD, and Weber W. Synthesis of phycocyanobilin in mammalian cells. *Chemical Communications (Cambridge, England)* **49**(79), 8970–8972, October 2013c
- Boehm ME, Adlung L, Schilling M, Roth S, Klingmüller U, and Lehmann WD. Identification of Isoform-Specific Dynamics in Phosphorylation-Dependent STAT5 Dimerization by Quantitative Mass Spectrometry and Mathematical Modeling. *Journal of proteome research* 13(12), 5685–94, October 2014
- Bachmann J, Raue A, Schilling M, Böhm M, Kreutz C, Kaschek D, Busch H, Gretz N, Lehmann W, Timmer J, and Klingmüller U. Division of labor by dual feedback regulators controls JAK2/STAT5 signaling over broad ligand range. *Molecular*

- Systems Biology 7, 516, 2011
- Raia V, Schilling M, Böhm M, Hahn B, Kowarsch A, Raue A, Sticht C, Bohl S, Saile M, Möller P, Gretz N, Timmer J, Theis F, Lehmann W, Lichter P, and Klingmüller U. Dynamic mathematical modeling of IL13-induced signaling in Hodgkin and primary mediastinal B-cell lymphoma allows prediction of therapeutic targets. *Cancer Research* 71, 693–704, 2011
- Becker V, Schilling M, Bachmann J, Baumann U, Raue A, Maiwald T, Timmer J, and Klingmueller U. Covering a broad dynamic range: information processing at the erythropoietin receptor. *Science* **328**(5984), 1404–1408, 2010

Methodology publications making use of the Data2Dynamics software

- Meyer P, Cokelaer T, Chandran D, Kim KH, Loh PR, Tucker G, Lipson M, Berger B, Kreutz C, Raue A, et al. Network topology and parameter estimation: from experimental design methods to gene regulatory network kinetics using a community based approach. *BMC Systems Biology* **8**(1), 13, 2014
- Toensing C, Timmer J, and Kreutz C. Cause and cure of sloppiness in ordinary differential equation models. *Phys. Rev. E* **90**, 023303, 2014
- Raue A, Karlsson J, Saccomani M, Jirstrand M, and Timmer J. Comparison of approaches for parameter identifiability analysis of biological systems. *Bioinformatics* 30(10), 1440–1448, 2014
- Kreutz C, Raue A, Kaschek D, and Timmer J. Profile likelihood in systems biology. *FEBS Journal* **280**(11), 2564–2571, 2013
- Raue A, Kreutz C, Theis F, and Timmer J. Joining forces of Bayesian and frequentist methodology: A study for inference in the presence of non-identifiability. *Phil. Trans. Roy. Soc. A* **371**, 20110544, 2013a
- Schelker M, Raue A, Timmer J, and Kreutz C. Comprehensive estimation of input signals and dynamical parameters in biochemical reaction networks. *Bioinformatics* **28**(18), i522–i528, 2012
- Hug S, Raue A, Hasenauer J, Bachmann J, Klingmüller U, Timmer J, and Theis F. High-dimensional Bayesian parameter estimation: Case study for a model of JAK2/-STAT5 signaling. *Mathematical Biosciences* **246**(2), 293–304, 2013
- Vehlow C, Hasenauer J, Kramer A, Raue A, Hug S, Timmer J, Radde N, Theis F, and Weiskopf D. iVUN: interactive visualization of uncertain biochemical reaction networks. *BMC Bioinformatics* **14**(Suppl 19), S2, 2013
- Steiert B, Raue A, Timmer J, and Kreutz C. Experimental design for parameter

- estimation of gene regulatory networks. PLOS ONE 7(7), e40052, 2012
- Raue A, Schilling M, Bachmann J, Matteson A, Schelker M, Kaschek D, Hug S, Kreutz C, Harms B, Theis F, Klingmüller U, and Timmer J. Lessons learned from quantitative dynamical modeling in systems biology. *PLOS ONE* **8**(9), e74335, 2013b
- Kreutz C, Raue A, and Timmer J. Likelihood based observability analysis and confidence intervals for predictions of dynamic models. *BMC Systems Biology* **6**, 120, 2012
- Raue A, Becker V, Klingmüller U, and Timmer J. Identifiability and observability analysis for experimental design in non-linear dynamical models. *Chaos* 20(4), 045105, 2010
- Raue A, Kreutz C, Maiwald T, Klingmüller U, and Timmer J. Addressing parameter identifiability by model-based experimentation. *IET Systems Biology* 5(2), 120– 130, 2011
- Raue A, Kreutz C, Maiwald T, Bachmann J, Schilling M, Klingmüller U, and Timmer J. Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics* **25**(15), 1923–1929, 2009

Benchmark applications distributed with the Data2Dynamics software

- Raia V, Schilling M, Böhm M, Hahn B, Kowarsch A, Raue A, Sticht C, Bohl S, Saile M, Möller P, Gretz N, Timmer J, Theis F, Lehmann W, Lichter P, and Klingmüller U. Dynamic mathematical modeling of IL13-induced signaling in Hodgkin and primary mediastinal B-cell lymphoma allows prediction of therapeutic targets. *Cancer Research* 71, 693–704, 2011
- Bachmann J, Raue A, Schilling M, Böhm M, Kreutz C, Kaschek D, Busch H, Gretz N, Lehmann W, Timmer J, and Klingmüller U. Division of labor by dual feedback regulators controls JAK2/STAT5 signaling over broad ligand range. *Molecular Systems Biology* 7, 516, 2011
- Becker V, Schilling M, Bachmann J, Baumann U, Raue A, Maiwald T, Timmer J, and Klingmueller U. Covering a broad dynamic range: information processing at the erythropoietin receptor. *Science* **328**(5984), 1404–1408, 2010
- Swameye I, Müller T, Timmer J, Sandra O, and Klingmüller U. Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by databased modeling. *PNAS* **100**(3), 1028–1033, 2003