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Essays in Biochemistry

Systems Biology

Edited by O. Wolkenhauer,
P. Wellstead and K.-H. Cho

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Preface

There are many definitions available for systems biology; these range from the overly ambitious to the opportunist. The latter category is frequently associated with scientists working in genomics and bioinformatics, who seek to re-label their work as systems biology. Such scientific opportunism is open to criticism that their research areas have been unsuccessful. This is excessively harsh–genomics and bioinformatics are certainly not systems biology, they are in fact complementary to it. For example, omics research has provided important insights into the components of the cell, their molecular characterization and possible interactions that are typically formulated in network or pathway diagrams. The systems biology view, on the other hand, addresses the overall function of components, as they interact and are interconnected with a cell. More specifically, the common ground for most perspectives of systems biology is the need to understand the dynamic function of cells as integrated objects, rather than the static properties of their components.

In building a systems understanding of cellular function, there are two key requirements: the generation of quantitative experimental data and mathematical modelling. Central to this is the fact that cell functions are determined by non-linear spatio-temporal processes, such that there is no alternative to a dynamical systems approach. However, the generation of sufficiently informative data from quantitative, time-course, stimulus–response experiments remains the main bottleneck. The generation of such data is time-consuming, expensive, often unreliable and, in many cases, not yet possible. It will therefore be necessary to consider a range of cell systems, different technologies and a combination of various methodologies to generate the information about cell function needed to characterize the dynamics. The definition or working practice of systems biology will therefore inevitably be 'integrative', combining various approaches. For this reason, students and researchers will never find a single comprehensive book on systems biology (which is both affordable and does not require a backpack to carry it around). The present volume is an attempt to pick and mix key topics in systems biology, allowing for different perspectives, while keeping a common goal–the understanding of the principles (mechanisms, laws) by which molecules and cells interact in order to realize their function.

The structure of the book is as follows. Sreenath et al. give an overview of methodologies for the modelling of signal transduction pathways and show that in modelling we are spoilt for choice. Among the choices available for differential equation models, power-law formalism and S-systems provide a conceptual framework that is introduced by Eberhard Voit. Grima and Schnell

complement the discussion for differential equations by introducing stochastic models and simulations. Jan-Hendrik Hofmeyr looks at the cell as a whole and argues that there is nothing more practical than a good theory: experiments should be guided by hypotheses, which in turn require conceptual tools. Gene expression, cell signalling and metabolism are three important functional levels in the cell. For each level there exist different technologies to generate data and subsequently different methodologies to interpret them. Practical aspects of metabolonomics and fluxomics are covered by Cascante et al.

Moving on to signalling, Rangamani and Iyengar have given an overview of basic ideas in modelling as applied to cellular signalling systems. MAPK (mitogen-activated protein kinase) cell signalling cascades have been investigated through mathematical modelling for some time. They are of course of biological significance as well, but the fact that there exists already a solid body of work means that this topic is well-suited for a text like this. The team of young authors like Blüthgen and Legewie is an example of a new generation of true 'hybrids' in the area of systems biology; reading their words, you cannot tell whether their background is in biology or the physical and engineering sciences; they are well versed in both domains and thus act as prototypes for future generations of researchers.

Pfeifer et al. focus on the JAK (Janus kinase)/STAT (signal transducer and activator of transcription) signalling pathway, developing a mathematical model from biological considerations and using quantitative time-course data for parameter estimation. In this work microscopy plays a role and although this book cannot possibly cover all technologies, live-cell imaging has emerged as a promising source of data suitable for systems biology. For this reason it is discussed by Mullassery et al. in their contribution. With Ericsson et al. we continue with case studies, now looking at yeast. They show how diagrams of biological pathways can be converted into dynamical models. This is followed by Schaber and Klipp's contribution and their description of how changes in yeast cell volume can be modelled mathematically.

The remaining part of the book returns to the model-building process. While the chapter by Eduardo Sontag focuses on network reconstruction based on steady-state data, Brian Ingalls introduces sensitivity analysis as an important analytical tool to study the consequence of changes in parameters. Parameter estimation and optimal experimental design form a key step in the model-building process, and an important message from the chapter by Banga and Balsa-Canto is that the design of an experiment should take account of the requirements in modelling. Gone are the times in which the modeller/control analyst was asked to help with the analysis of data after they were generated; they must be an intimate part of the experiment design process. The volume is completed by a discussion on SBML (Systems Biology Mark-Up Language) by Sauro and Bergmann and simulation tools by van Gend and Snoep.

Finally we thank Portland Press staff, in particular Clare Curtis and Michael Cunningham, for their efficient work in producing this book.

Olaf Wolkenhauer, Peter Wellstead and Kwang-Hyun Cho
June 2008

Authors

Olaf Wolkenhauer received his first degree in control engineering from the University of Applied Sciences in Hamburg, Germany, and the University of Portsmouth, Portsmouth, U.K., in 1994. His Ph.D. from UMIST (University of Manchester Institute of Science and Technology) in Manchester (1997) was on the application of possibility theory to data analysis. Following a research lectureship at the Control Systems Centre at UMIST, he held a joint senior lectureship with the Department of Biomolecular Sciences and the Department of Electrical Engineering and Electronics, at UMIST. In 2003 he moved to the University of Rostock in Germany, where he holds the Chair in Systems Biology and Bioinformatics. Olaf Wolkenhauer's research interest is mathematical modelling and data analysis, focusing on non-linear dynamical systems in molecular and cell biology.

Sree N. Sreenath is the Director of the Complex Systems Biology Center, and an Associate Professor at Electrical Engineering and Computer Science Department, Case Western Reserve University (Cleveland, OH, U.S.A.). His interests are in applying multilevel hierarchical systems approaches to the understanding of biological problems with particular focus on diseases and mammalian systems. His laboratory studies cell signalling and cell-cycle processes in leukaemic stem cells and prostate cancer to identify molecular drug targets and discover biomarkers. Another interest is the heart–brain interaction associated with stroke and hydrocephalus. He is the recipient of the U.S. NIH (National Institutes of Health) Career Development Award (2004–2009).
Peter Wellstead obtained a degree in Electrical Engineering from Hatfield College of Technology (later Hertfordshire University). After postgraduate study at Warwick University, he worked at CERN (European Organization for Nuclear Research), Geneva, before joining the Control Systems Centre at UMIST (University of Manchester Institute of Science and Technology). He stayed for 30 years at Manchester, teaching and researching the modelling, identification and control of dynamical systems, while also collaborating extensively with industry. In 2003 he moved to Ireland, where he is currently the Science Foundation Ireland Research Professor of Systems Biology at the Hamilton Institute, National University of Ireland Maynooth, in County Kildare. **Kwang-Hyun Cho** is currently a tenured Associate Professor in the Department of Bio and Brain Engineering at KAIST (Korea Advanced Institute of Science and Technology) and a director of the Laboratory for Systems Biology and Bio-Inspired Engineering (http://sbie.kaist.ac.kr). He is a founding Editor-in-Chief of *Systems Biology* (IEE, changed to IET in 2007)

and an Editorial Board Member of *Systems and Synthetic Biology* (Springer), *BMC Systems Biology*, *Gene Regulation and Systems Biology* (Libertas) and *Molecular BioSystems* (RSC). His research interests cover systems biology and the development of a new kind of engineering inspired by molecular systems biology.

Eberhard Voit is Professor and Georgia Research Alliance Eminent Scholar and holds the David D. Flanagan chair in biological systems at Georgia Tech (Georgia Institute of Technology, Atlanta, GA, U.S.A.). He is also the founding director of Georgia Tech's Integrative BioSystem Institute. Voit is a leading expert in Biochemical Systems Theory. He edited *Nonlinear Canonical Modeling*, a reference book on S-system modelling, authored the textbook *Computational Analysis of Biochemical Systems: a Practical Guide for Biochemists and Molecular Biologists*, and co-authored *Pathway Analysis and Optimization in Metabolic Engineering*; the latter two are also available in Chinese. Voit has been an invited speaker for technical presentations and tutorials on biomathematics around the world. He is the Editor-in-Chief of *Mathematical Biosciences*.

Ramon Grima is a SULSA (Scottish Universities Life Science Alliance) Lecturer in Systems Biology at the University of Edinburgh (Edinburgh, U.K.). Previously he was a Mathematical Institute Fellow at Imperial College London (U.K.) and a postdoctoral fellow in the School of Informatics at Indiana University (Bloomington, IN, U.S.A.). He received his undergraduate degree in Physics and Pure Mathematics from the University of Malta (Msida, Malta) and his Ph.D. in Physics from Arizona State University (Tempe, AZ, U.S.A.). Dr Grima's primary research interests lie in the development of models which integrate dynamics over many scales (subcellular to multicellular) and using the models to enhance experimental data interpretation and testing of biological hypotheses. **Santiago Schnell** is Associate Professor of Integrative and Molecular Physiology, and faculty at the Center for Computational Medicine and Biology at the University of Michigan Medical School (Ann Arbor, MI, U.S.A.). He was previously Assistant Professor of Informatics and Associate Director of the Biocomplexity Institute at Indiana University (Bloomington, IN, U.S.A.). He received his Licence in Biology from Universidad Simón Bolívar (Venezuela) and then his D.Phil. in mathematical biology from the University of Oxford (Oxford, U.K.) respectively. At the University of Oxford, he was Junior Research Fellow at Christ Church and Senior Research Fellow of the Wellcome Trust at the Centre for Mathematical Biology within the Mathematical Institute. Dr Schnell's major research interest is in developing models to investigate phenomena in cell biochemistry and physiology, and to quantify experimental data.

Jan-Hendrik Hofmeyr is Professor in the Department of Biochemistry at the University of Stellenbosch, South Africa. He obtained his Ph.D. in 1986

at the University of Stellenbosch. His research focuses on the control and regulation of cellular processes. He has made fundamental contributions to metabolic control analysis and computational cell biology, and, with Athel Cornish-Bowden, developed supply–demand analysis as a basis for understanding metabolic regulation. A recent interest is understanding the functional organization of the cell in terms of a theory of molecular fabrication. He is a fellow of the Academy of Science of South Africa and of the Royal Society of South Africa. He won the Harry Oppenheimer Fellowship Award for 2002 and the Beckman Gold Medal of the South African Biochemical Society in 2003.

Marta Cascante is Professor of Biochemistry and Molecular Biology and a member of the Institute of Biomedicine (IBUB) at the University of Barcelona, Barcelona, Spain. She leads the research group devoted to 'Integrative Biochemistry and Cancer therapy' (http://www.bq.ub.es/bioqint/arecerca.html). Professor Cascante's research focuses on systems biology, particularly the study of metabolic adaptations that support distinct cell functions and their exploitation in drug discovery. Her current research interests centre on the development of new computational tools to integrate experimental data obtained from the diverse 'omics' and *in silico* models of altered cell metabolism. She is a member of the editorial board of *Metabolomics* and the *Biochemical Journal*, and belongs to the Scientific Board of the International Metabolomics Society. **Silvia Marin** obtained her Ph.D. from the University of Barcelona, Barcelona, Spain and currently works as a postdoctoral researcher with the 'Integrative Biochemistry and Cancer Therapy' research group at the same university. Current and previous research interests include the development of experimental and bioinformatic tools to perform fluxomics characterization of biological systems, mainly of central carbon metabolic network in hepatocytes. She has also developed GC/MS-based metabolomic approaches to study healthy and tumoral cell lines.

Padmini Rangamani is a graduate student in Professor Iyengar's (see below) laboratory. She completed her M.S. in Chemical Engineering from the Georgia Institute of Technology and is working towards her Ph.D. thesis on computational analysis of integrin-mediated signalling to the actin cytoskeleton. **Ravi Iyengar** is the Dorothy H. and Lewis Rosenstiel Professor and Chair of the Department of Pharmacology and Systems Therapeutics at Mount Sinai School of Medicine (New York, U.S.A.). He also heads the Systems Biology Center of New York (http://amp.pharm.mssm.edu/). His research interests include spatio-temporal organization of cellular networks, origins of microdomains of signalling components and graph-theory-based methods for network analysis. For more information, see http://www.mssm.edu/labs/iyengar/general_information.shtml

Nils Blüthgen is a Research Fellow at the Manchester Interdisciplinary Biocentre (Manchester, U.K.). His research focuses on the analysis of

mammalian signalling networks, the interaction between signalling and gene-regulatory networks. He studied physics in Heidelberg and at the Technical University Berlin, and obtained a Ph.D. in biophysics from Humboldt University Berlin for a systems analysis of Ras-mediated signal transduction at the Institute for Theoretical Biology. His postdoctoral work was at the Institute for Molecular Neuroscience at the Free University in Berlin on activity-regulated gene expression (2005–2006). **Stefan Legewie** is currently finishing his Ph.D. on modelling signal transduction at the Institute for Theoretical Biology in Berlin (his supervisor is Hanspeter Herzel). He studied Biochemistry at the University of Witten/Herdecke (Witten, Germany). He was working on insulin signalling at the Max–Planck Institute for Dynamics of Complex Technical Systems in Magdeburg (with Birgit Schoeberl), and on purine metabolism at the Max–Delbrueck Centre in Berlin (with Stefan Schuster). His research interests include modelling cell-fate decisions via transforming growth factor β, apoptosis and MAPK (mitogen-activated protein kinase) signalling networks.

Andrea Pfeifer studied biochemistry in Tübingen and Witten/Herdecke, Germany. For her Ph.D. thesis she joined the group of Jennifer Lippincott-Schwartz at the NIH (National Institutes of Health, Bethesda, MD, U.S.A.) to study the dynamics of GBF1 by live-cell imaging. As a postdoctoral fellow, she works with Ursula Klingmüller at the German Cancer Research Center (DKFZ) in Heidelberg, Germany, investigating the dynamic behaviour of STAT5 (signal transducer and activator of transcription 5). **Jens Timmer** studied Physics in Oldenburg and Freiburg, Germany. He holds a Chair for Theoretical Physics and its Applications in the Life Sciences at the University of Freiburg (Freiburg, Germany). His research interests are the development and interdisciplinary application of mathematical methods to analyse and model data from dynamic complex systems in the Life Sciences. The applications range from basic research in cell biology to clinical applications in neurology. He is the speaker of the German Systems Biology competence network HepatoSys. **Ursula Klingmüller** completed her Ph.D. thesis at the ZMBH (Zentrum für Molekulaire Biologie Heidelberg), University of Heidelberg, Heidelberg, Germany. As a postdoctoral fellow she joined the group of Professor Lewis Cantley at Harvard Medical School (Boston, MA, U.S.A.) and the group of Professor Harvey Lodish at the Whitehead Institute for Biomedical Research (Boston, U.S.A.) studying signalling through the erythropoietin receptor. As a junior group leader at the Max–Planck Institute for Immunobiology (Freiburg) and at DKFZ (German Cancer Research Centre, Heidelberg, Germany) she focused on combining quantitative data generation with mathematical modelling. Since 2007 she has headed the division 'Systems Biology of Signal Transduction' at the DKFZ. She is co-coordinator and experimental partner in multiple systems biology initiatives.

Dhanya Mullassery is a trainee paediatric surgeon who is currently undertaking a Ph.D. on an MRC (Medical Research Council)-funded clinical research training fellowship at the Centre for Cell Imaging, University of Liverpool (Liverpool, U.K.). Following her undergraduate medical training from the University of Calicut (Kerala, India), Dhanya completed her basic surgical training in Liverpool and gained membership of the Royal College of Surgeons of England. The main focus of her current research project is investigating the role and potential for manipulation of the transcription factor NF-κB (nuclear factor κB) in the childhood tumour neuroblastoma to develop novel therapeutic strategies for this disease. **Caroline Horton** is a postdoctoral researcher at the Centre for Cell Imaging. Following a Bachelors degree in Computer Science, her Ph.D. at the Centre for Cell Imaging (Liverpool, U.K.) involved the introduction of computational and mathematical modelling as new tools in the laboratory to aid understanding of cell-signalling dynamics. The main focus of her research has involved the development and analysis of models of the NF-κB system, based on quantitative time-series data extracted from live-cell imaging experiments. This has also involved the design and analysis of experiments to investigate important features of NF-κB signalling, measure system parameters and validate model predictions. **Chris Wood**'s core interest lies in the application of microscopic techniques to the study of biological events in single cells in real time. He currently applies such methods to determine the role of Ca^{2+} signalling in the earliest stages of neurogenesis using a transplant-explant model based around a mouse embryonic midbrain culture system. Prior achievements in Mexico include measuring millisecond Ca^{2+} transients in beating flagella of swimming sperm using a stroboscopic LED (light-emitting diode)-based fluorescent-imaging technique. Before migrating to Latin America, his work included developing a single-cell luciferase assay for real-time measurement of promoter activity, and measurements of phospholipid turnover during sperm–egg fusion and the early stages of fertilization using GFP (green fluorescent protein)–PH (pleckstrin homology) domain fusion proteins. **Mike White** pioneered the application of the firefly luciferase reporter for gene expression imaging in mammalian cells while working at Amersham International. Following a move to Liverpool in 1995, he founded the Centre for Cell Imaging for non-invasive multi-parameter imaging of cellular processes. He was appointed Professor in 2004. His recent work has concentrated on the dynamics and function of NF-κB signalling. He has demonstrated that NF-κB oscillations between the nucleus and cytoplasm maintain persistent NF-κB-dependent transcription. This combination of cell imaging and mathematical modelling has developed a new systems biology programme to investigate dynamic cell signalling, transcription and cell fate.

Abraham Ericsson received an M.Sc. in Computing Science from the University of Gothenburg (Gothenburg, Sweden) in 2004. Currently, he

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Jörg Schaber has been a postdoctoral researcher in the group of Edda Klipp at the Max–Planck Institute for Molecular Genetics since 2002. **Edda Klipp** has been group leader of the Computational Systems Biology group at the Max–Planck Institute for Molecular Genetics since 2000. Since 2005 she has also been Professor for Theoretical Biophysics at Humboldt University (Berlin, Germany).

Eduardo Sontag received his Ph.D. in Florida in 1977. He is a Professor of Mathematics at Rutgers University (The State University of New Jersey, Piscataway, NJ, U.S.A.), where he is also in the Steering Committee of the BioMapS Institute for Quantitative Biology, and in the Graduate Faculties of Computer Science and of Electrical and Computer Engineering. He directs the Rutgers Center for Systems and Control and the Biomathematics undergraduate program. His research in control theory and systems biology has been documented in over 400 peer-reviewed journal and conference papers and book chapters, as well as several books. Sontag's awards include the 2001 Reid Prize in Mathematics, the 2002 Bode Prize and the 2002 Board of Trustees Award for Excellence in Research and the 2005 Teacher/Scholar Award from Rutgers University. Sontag is on the Editorial Boards of *IET Proceedings Systems Biology*, *SIAM Review*, *Synthetic and Systems Biology*, *International Journal of Biological Sciences*, *Nonlinear Analysis*, *Nonlinear Dynamics and*

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Brian Ingalls received his Ph.D. in Mathematics from Rutgers University in New Jersey, U.S.A. He is currently an Associate Professor in the Department of Applied Mathematics at the University of Waterloo in Ontario, Canada. His research interests are in the application of methods from control and systems theory to systems biology. He currently serves on the editorial board of *IET Systems Biology* and recently received an Early Researcher Award from the Government of Ontario.

Julio R. Banga was born in Spain in 1964. He obtained an M.Sc. in Industrial Chemistry from the University of Santiago de Compostela (Santiago de Compostela, Spain) in 1988, and a Ph.D. in Chemical Engineering from the same University in 1991. During 1992, he was a postdoctoral researcher at the University of California, Davis (CA, U.S.A.), and then spent 3 years as Assistant Professor of Chemical Engineering at the University of Vigo (Vigo, Spain). During those years, he also spent periods as visiting researcher at the University of Pennsylvania and at MIT (Massachusets Institute of Technology, U.S.A.). Since 1996, he has been a tenured Scientific Researcher at the Process Engineering Group, IIM-CSIC (Spanish Council for Scientific Research) in Vigo, Spain. His main research topic is computational optimization, with emphasis on global optimization using deterministic, stochastic and hybrid methods. These methods are used to solve important classes of problems arising from the domain of non-linear dynamic processes, with applications targeting the areas of bioprocess engineering and systems biology. **Eva Balsa-Canto** was born in A Coruña, Spain in 1974. She received a B.S. degree in Physics from the University of Santiago de Compostela (Santiago de Compostela, Spain) in 1996 and obtained her Ph.D. in Chemical Engineering from the University of Vigo (Vigo, Spain) in 2001. She joined, as a postdoctoral researcher, the International Center for Numerical Methods in Engineering (CIMNE, Barcelona Spain) for 2 years and the Department of Applied Mathematics at the University of Vigo for 1.5 years where she was also teaching mathematics courses to engineering students. Currently she is a tenured researcher at the Process Engineering Group at the IIM-CSIC (Spanish Council for Scientific Research, Vigo, Spain). Her major research interests include modelling, simulation and optimization of distributed and lumped parameter bioprocesses and biosystems. Current efforts are devoted to devise new theoretical and numerical techniques for large-scale model identification with applications in the modelling of biological networks.

Herbert Sauro was originally educated as a biochemist/microbiologist but became interested in the use of simulation and theory to understand cellular networks after accidentally coming across a paper by David Garkfinkel on the simulation of glycolysis. He wrote one of the first biochemical simulators

for the PC (SCAMP) in the 1980s to assist work on extending metabolic control analysis (a theory closely related to biochemical systems theory) with David Fell. He also did postdoctoral work with Henrik Kacser in Edinburgh. However, with the lack of community interest in systems biology during the late 1980s and early 1990s, he left science to start a successful software company and offer consultancy work to finance firms in the U.K. With the surge in interest in systems biology in the U.S.A. in the late 1990s, he returned to science by securing a position at Caltech (The California Institute of Technology, Pasadena, CA, U.S.A.) to assist in the development of the Systems Biology Markup Language. He now works as an Associate Professor in the Department of Bioengineering at the University of Washington, Seattle, where his interests focus on software, cellular control systems and synthetic biology. **Frank Bergmann** is currently a Ph.D. student under the supervision of Herbert Sauro at the Keck Graduate Institute/University of Washington. He received his first degree in computer science from the Johann Wolfgang Goethe University, Frankfurt, Germany. For his diploma he specialized in computer graphics and carried out his senior thesis on visualization of reaction-diffusion systems in biology. He is the lead developer for the Systems Biology Workbench and his Ph.D. is concerned with the development of tools and applications of computer science to Systems Biology. His web page is http://public.kgi.edu/~fbergman.

Carel van Gend completed a Ph.D. in particle physics at the University of Cape Town (Cape Town, South Africa) in 1998. He has worked as a mathematical modeller in the fields of mobile telecommunications, immunology and biochemistry, and has had research positions at the European Media Laboratory in Heidelberg, Germany, and at Vecien Technologies and the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. He is currently employed as a postdoctoral fellow at the University of Stellenbosch, South Africa, where he works on the development of the JWS Online modelling system. **Jacky Snoep** completed his Ph.D. in 1992 at the University of Amsterdam (Amsterdam, The Netherlands) in the fields of Microbiology and Biochemistry. As a postdoctoral fellow he worked on a quantitative analyses of biological systems, at the University of Florida (Gainesville, FL, U.S.A.) and at the Netherlands Cancer Institute (Amsterdam, The Netherlands). Currently Jacky has appointments at three universities: the University of Stellenbosch, in the Biochemistry department, with his fellow Triple-J members, Jannie Hofmeyr and Johan Rohwer; at Manchester University where he works on implementations of webservices and the integration of experimental data with modelling studies; and at the Vrije Universiteit in Amsterdam, in the Molecular Cell Physiology group, in close collaboration with Hans Westerhoff.

Abbreviations

BiGG	biochemically, genetically and genomically structured
BioNetGen	Biological Network Generator
BioPAX	Biological Pathway Exchange
BST	Biochemical Systems Theory
BTK	BioThermoKinetics
CCD	charge-coupled-device
CCDB	Cell Cycle Database
CE	capillary electrophoresis
CIS	cytokine-inducible Src homology 2-domain-containing protein
CME	chemical master equation
CML	chronic myelogenous leukaemia
CSV	comma separated variable
DAE	differential algebraic equation
DCMI	Dublin Core Metadata Initiative
DDE	delay differential equation
DOQCS	Database of Quantitative Cellular Signalling
ECFP	enhanced cyan fluorescent protein
EGF	epidermal growth factor
EGFP	enhanced green fluorescent protein
EGFR	epidermal growth factor receptor
EMBL-EBI	European Molecular Biology Laboratory/European Bioinformatics Institute
EpoR	erythropoietin receptor
ER	endoplasmic reticulum
ERK	extracellular-signal-regulated kinase
EYFP	enhanced yellow fluorescent protein
FCFM	fibred confocal fluorescence microscopy
FCS	fluorescence correlation spectroscopy
FIM	Fisher information matrix
FLIP	fluorescence loss in photobleaching
FRAP	fluorescence recovery after photobleaching
FRET	Förster (or fluorescence) resonance energy transfer
FRS	fibroblast growth factor receptor substrate
FT-IR	Fourier transform IR spectroscopy
GAP	GTPase-activating protein

GC	gas chromatography
GFP	green fluorescent protein
GUI	graphical user interface
HEK	human embryonic kidney
HMDB	human metabolome database
HMP	4-amino-5-hydroxymethyl-2-methylpyrimidine
IFNγ	interferon-γ
i-FRAP	inverse-FRAP
IκB	inhibitor of nuclear factor κB
IKK	inhibitor of nuclear factor κB kinase
IL-1	interleukin-1
IRAK	IL-1-receptor-associated kinase
JAK	Janus kinase
KAIST	Korea Advanced Institute of Science and Technology
KEGG	Kyoto Encyclopedia of Genes and Genomes
KiSAP	Kinetic Algorithm Ontology
LC	liquid chromatography
LMB	leptomycin B
ma	mass-action
MAPK	mitogen-activated protein kinase
MCA	Metabolic Control Analysis
MEK	MAPK/ERK kinase
MIASE	Minimum Information About a Simulation Experiment
MIDA	mass isotopomer distribution analysis
MIRIAM	Minimum Information Requested In the Annotation of biochemical Models
MKP	MAPK phosphatase
MM	Michaelis–Menten
MML	Mathematical Modelling Language
MRA	Modular Response Analysis
NF-κB	nuclear factor κB
NGF	nerve growth factor
NLP	non-linear programming
ODE	ordinary differential equation
PDE	partial differential equation
PDGF	platelet-derived growth factor
PIAS	protein inhibitor of activated signal transducer and activator of transcription
PKC	protein kinase C
PLA_2	phospholipase A_2

POSIX	Portable Operating System Interface
PTP-STEP	protein tyrosine phosphatase, non-receptor type 5 (striatum-enriched)
PySCeS	Python Simulator for Cellular Systems
RDE	reaction-diffusion equation
RDF	Resource Description Framework
RDME	reaction-diffusion master equation
RE	rate equation
RNAi	RNA interference
SBGN	Systems Biology Graphical Notation
SBML	Systems Biology Markup Language
SBO	Systems Biology Ontology
SBW	Systems Biology Workbench
SH2	Src homology 2
Shc	Src homology and collagen homology
SHP2	SH2-domain-containing tyrosine phosphatase
SiC	Silicon Cell project
SMI	single-molecule imaging
SOCS	suppressor of cytokine signalling
SSA	stochastic simulation algorithm
SSm	Scatter Search metaheuristic
SSR	sum of squared residuals
STAT	signal transducer and activator of transcription
SVD	singular value decomposition
TAB2	TAK1-binding subunit 2
TAK1	transforming growth factor β-activated kinase 1
TCA	tricarboxylic acid
TCR	T-cell receptor
TEDDY	Terminology for the Description of Dynamics
TGF-β	transforming growth factor β
ThDP	thiamine diphosphate
Thi80	thiamine pyrophosphokinase
ThMP	thiamine monophosphate
TNFα	tumour necrosis factor α
TRAF-6	tumour-necrosis-factor-receptor-associated factor 6
WSDL	Web Service Description Language