

# Systems Microbiology

Current Topics and Applications

Edited by

Brian D. Robertson

Centre for Integrated Systems Biology and Bioinformatics  
Imperial College  
London

and

Brendan W. Wren

London School of Hygiene and Tropical Medicine  
London  
UK



Copyright © 2012

Caister Academic Press  
Norfolk, UK

[www.caister.com](http://www.caister.com)

British Library Cataloguing-in-Publication Data  
A catalogue record for this book is available from the British Library

ISBN: 978-1-908230-02-7

Description or mention of instrumentation, software, or other products in this book does not imply endorsement by the author or publisher. The author and publisher do not assume responsibility for the validity of any products or procedures mentioned or described in this book or for the consequences of their use.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publisher. No claim to original U.S. Government works.

Cover design adapted from Figures 3.2 and 6.3.

Printed and bound in Great Britain

# Contents

	Contributors	v
	Preface	ix
1	<b>Mathematical Models for Systems Biology and How to Construct Them</b>	1
	Chris P. Barnes, Maxime Huvet, Nathan Harmston and Michael P.H. Stumpf	
2	<b>Dynamics and Robustness of Metabolic Networks: A Systems Biology Review of <i>Escherichia coli</i> Metabolism</b>	17
	Eivind Almaas, Per Bruheim, Rahmi Lale and Svein Valla	
3	<b>Bacterial Chemotaxis: Rising Complexity</b>	47
	Diana Clausznitzer, Judith P. Armitage and Robert G. Endres	
4	<b>Systems Biology of Infection: The Pathogen Perspective</b>	69
	Dirk Bumann	
5	<b>Manipulating the Fight Between Human Host Cells and Intracellular Pathogens</b>	77
	Rico Barsacchi, Varadharajan Sundaramurthy, Kees Korbee, Jacques Neefjes, Tom H.M. Ottenhoff, Tiziana Scanu and Marino Zerial	
6	<b>How One Cell Eats Another: Principles of Phagocytosis</b>	95
	Sylvain Tollis, Navin Gopaldass, Thierry Soldati and Robert G. Endres	
7	<b>System-level Strategies for Studying the Metabolism of <i>Mycobacterium tuberculosis</i></b>	127
	Dany J.V. Beste and Johnjoe McFadden	

8	<b><i>Sulfolobus</i> Systems Biology: Cool Hot Design for Metabolic Pathways</b>	151
	Theresa Kouril, Alexey Kolodkin, Melanie Zaparty, Ralf Steuer, Peter Ruoff, Hans V. Westerhoff, Jacky Snoep, Bettina Siebers and the SulfoSYS consortium	
	<b>Index</b>	169

Dedicated to our deceased colleagues, Jaroslav Stark and Emmanuelle Caron,  
pioneers in systems biology.

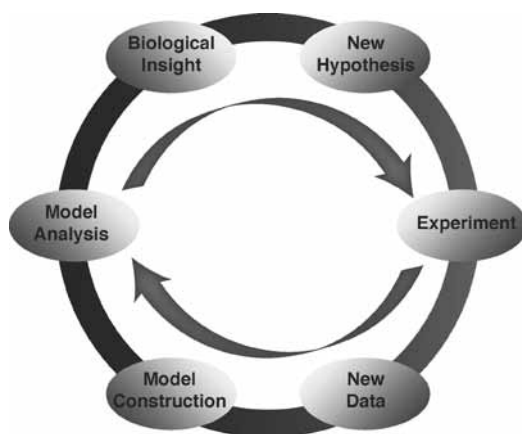
# Preface

Systems biology aims to study the dynamic interactions of more than one component in a biological system in order to understand and predict the behaviour of the system as a whole. Typical approaches involve an iterative cycle of ‘dry lab’ modelling and ‘wet lab’ verification.

Bringing order to biological data that inherently have noise due to a multitude of variables has previously been considered too challenging. However, systems biology is now a rapidly expanding discipline fuelled by the ‘omics’ era that is coupled to several new technological advances that have increased the precision of data obtainable. This has provided the bit parts of complex living cells. New challenges arise to put these levels of information together including finding a common language of the difference omics data sets (e.g. genomics, transcriptomics, proteomics, metabolomics).

The sheer complexity of biological systems means that systems biology is a fledgling science. However, a focus on simple single cell organisms such as bacteria aids tractability and means that systems microbiology is a rapidly maturing science.

This book will include case studies on single microbial species (e.g. bacteria and archaea), systems analysis of microbial phenomena (e.g. chemotaxis and phagocytosis) and this is complemented with theoretical approaches and mathematical modelling.



**Figure 0.1** Systems biology illustrating the iterative cycle of ‘dry lab’ modelling and ‘wet lab’ verification. Concept and design by Jaroslav Stark.

**A**

Actin 80, 81, 85, 95–120  
Amoeba 95, 96, 102, 113–118  
Archaea 48, 151–163  
ATP 19, 25, 48, 56, 58, 109, 133, 134, 136,  
138, 153–156, 158, 159

**B**

Bayesian statistics 4, 8, 9–10  
Boolean networks 4, 7

**C**

<sup>13</sup>C-isotope  
labelling 32, 37, 38–39  
metabolic flux analysis 31, 37, 39, 144  
Carbohydrate metabolism 153  
Cell cycle 2, 48, 86  
Chemical genetics 88–90  
Chemotaxis  
*E. coli* 47, 51–58  
*R. sphaeroides* 48, 58–62  
robust adaptation 56–58  
signal amplification 51–54  
signal integration 54–56  
Comparative approaches 7, 10–12, 14  
Computational linguistics 13  
Conditional random fields 13  
Constraint-based modelling 20, 21–24, 131

**D**

Data analysis 7, 73–74  
Deterministic 4–6, 11, 13, 112  
*Dictyostelium* 95, 96, 98, 99, 106, 114–118,  
119  
Drug discovery 139–140, 146  
Dynamical 3, 4, 49

**E**

*Escherichia coli* *see E. coli*  
*E. coli* 17, 19, 20, 23–32, 37, 39  
chemotaxis 47, 49, 51–54, 63–65  
metabolic models 17–18, 24

Expression levels 17, 26, 31, 57, 60, 141  
Extremophiles 152–153

**F**

Flux–balance analysis *see* FBA  
FBA 17, 18–20, 22–24, 133–136, 139, 140,  
142, 144, 145

**G**

Gene  
essentiality 135, 138, 139, 141, 143  
expression profiling 71–72  
knock-out 21, 26–30, 143  
Genome annotation 132, 133, 138–139  
Genomics 31, 71, 90, 127, 140, 153  
Glycolysis 128, 132, 137, 142, 151, 156–159,  
163  
Graphical models 3–5

**H**

Host–pathogen 71, 77–83, 87, 88, 99, 119,  
120, 136, 140, 145  
Hypothesis testing 7–9

**I**

Influenza 77, 81–82, 84  
Information retrieval 13

**M**

*M. tuberculosis* 77–79, 85–89, 127  
Metabolite extraction 32–33  
metabolic models 132–136, 136–139  
metabolism 128–129  
Machine learning 2, 13  
Malaria 82–83, 87–88, 89–90, 119  
Mass spectrometry *see* MS 34–36, 38  
Mechanistic models 7, 8  
Metabolic 4, 12, 17, 18  
flux 17–21, 24, 31–32, 37–40, 141, 142, 144  
network 12, 17, 20–21, 25–26, 132, 133,  
135, 141, 145, 153–155  
Metabolite analysis 33–36

Metabolomics 31, 32–37, 72, 127  
 Minimization of metabolic adjustment *see*  
 MOMA  
 MOMA 18, 22, 23–24  
 Monod–Wyman–Changeux *see* MWC  
 MWC 51–56, 57, 63  
 Models  
 mechanistic 1, 2, 7, 8, 12, 15  
 stochastic 4, 5, 6, 10, 57, 72, 98, 102, 104,  
 107, 110, 112, 118  
 MS 32, 33, 34–37, 38, 39,  
*Mycobacterium tuberculosis see M. tuberculosis*  
 Myosin 95, 97, 109, 110, 116–118, 119

**N**

Named entity recognition 13  
 Natural language processing 13  
 NMR 32, 33, 34, 36, 38  
 Nucleic magnetic resonance *see* NMR

**P**

Parameter estimation 7, 8  
 Petri networks 4  
 Phagocytosis 80, 95–99  
 Bistability 99, 110–113, 119  
 cup closure 108, 109–110, 116, 118  
 zipper mechanism 98, 100–103, 104, 108,  
 109, 110, 111, 112, 118, 119  
 membrane availability 105–107  
 particle size 102, 103–105, 110

myosins 109–110  
 Phenotypes 3, 12, 18, 19, 21–26, 28, 30,  
 72–73, 87, 89, 91,  
 Probabilistic models 4, 5, 6  
 Promoters 31

**R**

Regulatory on/off minimization  
 (ROOM) 18, 22, 24  
 Repressilator 5, 6, 10, 11  
 Reverse engineering 7, 14

**S**

*S. solfataricus* 151  
 glycolysis 158–159  
*Salmonella* 28, 79–81, 85, 102  
 Signal amplification 51, 53, 64  
 Space–time coordination 113  
 Spatio-temporal dynamics 114  
 Statistical inference 7  
 Stochastic modelling 5, 6  
*Sulfolobus solfataricus see S. solfataricus*  
 Support vector machines 13

**T**

Text mining 7, 13–14  
 Transcriptome 38, 71, 141–144  
 Transposon 30–31, 72, 134, 135, 138, 141  
 Tuberculosis 77, 85–87, 119, 127