The Cell as A Machine

This unique introductory text explains cell functions using the engineering principles of robust devices. Adopting a process-based approach to understanding cell and tissue biology, it describes the molecular and mechanical features that enable the cell to be robust in operating its various components, and explores the ways in which molecular modules respond to environmental signals to execute complex functions. The design and operation of a variety of complex functions are covered, including engineering lipid bilayers to provide fluid boundaries and mechanical controls, adjusting cell shape and forces with dynamic filament networks, and DNA packaging for information retrieval and propagation. Numerous problems, case studies and application examples help readers connect theory with practice, and solutions for instructors and videos of lectures accompany the book online. Assuming only basic mathematical knowledge, this is an invaluable resource for graduate and senior undergraduate students taking single-semester courses in cell mechanics, biophysics and cell biology.

Michael Sheetz is the Founding Director of the Mechanobiology Institute and a distinguished professor in the Department of Biological Sciences both at the National University of Singapore.

Hanry Yu is a professor in both the Department of Physiology and the Mechanobiology Institute at the National University of Singapore. He is also the Director of the National University Health System's research facilities in microscopy and cytometry.

CAMBRIDGE TEXTS IN BIOMEDICAL ENGINEERING

Cambridge Texts in Biomedical Engineering provide a forum for high-quality textbooks targeted at undergraduate and graduate courses in biomedical engineering. They cover a broad range of biomedical engineering topics from introductory texts to advanced topics, including biomechanics, physiology, biomedical instrumentation, imaging, signals and systems, cell engineering and bioinformatics, as well as other relevant subjects, with a blending of theory and practice. While aiming primarily at biomedical engineering students, this series is also suitable for courses in broader disciplines in engineering, the life sciences and medicine.

The Cell as A Machine

Michael Sheetz
National University of Singapore

Hanry Yu
National University of Singapore

CAMBRIDGE UNIVERSITY PRESS

CAMBRIDGE
UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

314–321, 3rd Floor, Plot 3, Splendor Forum, Jasola District Centre, New Delhi – 110025, India

79 Anson Road, #06–04/06, Singapore 079906

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning, and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9781107052734
DOI: 10.1017/9781107280809

First published 2018

Printed in the United Kingdom by Clays, St Ives plc.

A catalogue record for this publication is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Names: Sheetz, Michael P., author. | Yu, Hanry, author.
Title: The cell as a machine / Michael Sheetz, Columbia University, New York, Hanry Yu, National University of Singapore.
Description: Cambridge, United Kingdom ; New York, NY : Cambridge University Press, 2018. | Series: Cambridge texts in biomedical engineering | Includes bibliographical references and index.
Identifiers: LCCN 2017046256 | ISBN 9781107052734 (hardback)
Subjects: LCSH: Cells–Mechanical properties. | Cell physiology.
Classification: LCC QH645.5 .S54 2018 | DDC 571.6–dc23 LC record available at https://lccn.loc.gov/2017046256

ISBN 978-1-107-05273-4 Hardback

Additional resources available at www.cambridge.org/sheetz

Contents

Preface and acknowledgments

The motivation for this book is to provide an approach for understanding and integrating the complex functions of cells that shape tissues and drive growth and differentiation. Correlative information in the catalogs of DNA sequences, mRNA levels, interactomes, and biochemical reactions involved in complex cellular functions provides an insufficient understanding. Having the parts list of a complex machine does not enable one to assemble that machine, much less to understand how it works. In contrast, a bioengineering approach that focuses on the physical aspects of cells and tissues provides only a part of the function. A detailed engineering diagram of the steps involved and how the physical parameters relate to the biochemical functions is needed to understand most cell functions. For example, the biochemical reactions involved in the uncontrolled cell proliferation of cancer cells are known, as are the physical behaviors of tumor cells, but how physical signals from the cell environment are integrated with the biochemistry of growth is not known. In normal cells, physical feedback from matrix rigidity and morphology controls normal cell growth, whereas in cancer cells, those same parameters are misread, resulting in uncontrolled growth. By considering the reverse engineering of complex cell functions as a problem similar to reverse engineering a complex automobile, it should be possible to understand cellular functions.

The premise of this book is that cells are small, self-replicating machines that exploit fundamental physical and physical–chemical principles of mesoscale objects to pass on the DNA of the organism that they form. From the revolution in molecular biology, we know the sequences of many genomes, as well as the sequences of the mRNAs in many specific cell types, which identify the proteins that are present. Further, we know many of the mutations that correlate with specific genetic diseases or altered phenotypes. Thus, we possess a cellular parts list. Fortunately, there are now ways to measure subcellular forces, protein positions at the nanometer level, and protein dynamics. By coupling those tools with real-time observations of cell functions, it will be possible to determine the steps in very complex functions.

Our approach is to model the cell as a complex machine that has been selected for robustness over many millions of years. Thus, the functions in cells follow the general rules for robust devices, and can be described by an engineering diagram

that details the steps in the function, the potential branch points, and the various outcomes. At this time, there is detailed knowledge of only a few functions that enable this approach, but the paradigm provides a path to a detailed understanding of how cells actually work. This book describes how such an approach can help with understanding the major functions of a typical mammalian cell such as a fibroblast.

There are a number of basic tools that one needs to understand how cell functions are performed. For example, all intracellular processes are diffusively driven and are therefore stochastic. In contrast, we are used to thinking about macroscopic machines that use momentum and are naturally deterministic. Noisy, stochastic processes can be averaged to give a deterministic outcome, but we don't understand how cells with the same genetic code can produce nearly identical twins using those noisy processes.

To replicate themselves, cells rely upon a number of basic functions that can be broken down into component functional steps. These steps, in turn, are typically driven by multi-protein complexes (cofactors and environmental factors such as lipid surfaces or membranes often play critical roles). Each of the functional processes will be considered as a system that is engineered for robustness and efficiency. From such a systems-engineering viewpoint, physical and physical–chemical parameters are critical in determining the throughput, efficiency, and fidelity of the product of a given function. Because we have an incomplete understanding of many cell functions, this description will also be incomplete. Our emphasis is on the principles that govern these functions and on providing senior undergraduate and beginning graduate students with the tools needed to address the general problem of understanding cellular functions in other systems.

For example, over 70+ known proteins participate in clathrin-dependent endocytosis. This process bends the plasma membrane inward, ultimately to form an intracellular vesicle. Knowing the parts involved, and roughly where they are in the complex, we can start to build a detailed description of the process at the nanometer level. It starts with simple steps from initial recruitment of the components to be taken into the vesicle, to the inward bending of the membrane, to forming a deep invagination of the membrane, and, finally, to pinching off a vesicle from the plasma membrane. The enzymatic activities of the proteins must then be linked with the specific sub-steps in these larger steps. In the extreme, the goal is to produce a detailed description of the steps and the roles of each of the 70+ proteins in those steps. The functions provide a simple way to organize our knowledge of cellular physiology. Further, the characterization of the links between the different functions will enable the control processes to be understood.

Although we are far from having an atlas that describes all cellular functions, we are at a point where we can imagine building such an atlas for all 300+ cell

types in the human body. We suggest that the vast amount of information of biological cells can be best linked with the functions that are involved and their regulatory pathways. In addition to knowing how to treat diseases and engineer organisms better, having a better understanding of subcellular functions will enable us to exploit nanodevices, such as computers and nanomachines. As they approach the scale of functional complexes in cells, they will also be governed by the principles that govern mesoscale processes. From a complete understanding of the several hundred major cellular functions that are commonly used by mammalian cells, it should be possible to develop a repair manual for the human organism. This would have many benefits for health and welfare.

For the past few years, both basic biology and translational biomedical engineering research communities have paid increasing attention to integrating biochemical reactions in relevant physical contexts, such as the hardened tissue in wound healing, to causally determine the cellular and tissue functions. Many of these are described with biochemical and physical terms in this book. This emerging research approach of understanding and controlling both the physical and biochemical aspects of cellular and tissue functions is what we called the mechanobiology approach, which systematically describes concepts, terminology, technologies, and methodology to develop detailed descriptions of biological functions.

Finally, I would like to acknowledge the support of the many people who made this book possible. First, there were many students and colleagues who helped to hone this message and provide relevant examples. Second, my wife, Dr. Linda Kenney, has patiently supported this effort, which has taken much longer than either of us had expected. My co-author, Hanry Yu, has provided a lot of encouragement and has really helped to make this more relevant to the engineering community. Our illustrator, Dr. Cindy Zhang, has done an excellent job in enlivening important concepts. Steven Wolf and Stuart McLaughlin have kindly proofread the book. This would not have been possible without the support of the Mechanobiology Institute at the National University of Singapore (supported by an RCE grant from the Singapore National Research Foundation and Ministry of Education). Early concepts for this book were formed in a Nanomedicine Center funded by National Institutes of Health, USA.

The full figure caption information can be found online here: www.cambridge.org/sheetz