Subcellular Biochemistry 68

Mauricio G. Mateu *Editor*

Structure and Physics of Viruses

An Integrated Textbook

Springer

Structure and Physics of Viruses

SUBCELLULAR BIOCHEMISTRY

For further volumes:
http://www.springer.com/series/6515

Mauricio G. Mateu
Editor

Structure and Physics of Viruses

An Integrated Textbook

Springer

Editor
Mauricio G. Mateu
Centro de Biología Molecular
"Severo Ochoa" (CSIC-UAM)
and Department of Molecular Biology
of the Universidad Autónoma de Madrid
Madrid, Spain

ISSN 0306-0225
ISBN 978-94-007-6551-1 ISBN 978-94-007-6552-8 (eBook)
DOI 10.1007/978-94-007-6552-8
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2013939581

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

The great challenges of modern science are increasingly requiring the combined efforts of different branches of knowledge. A remarkable example is our long-standing battle to fight and understand viruses, these tiny pathogens that are a permanent companion and threat for living beings and humankind. Viruses have been traditionally a subject of study for biologists, but are increasingly fascinating physicists and chemists alike, dazzled by their clever operation and their outstanding potential for promising applications. What makes viruses special is that they are comparatively simple in the biological context, yet extremely effective in replicating themselves in all kinds of hosts. Viruses have found optimal solutions to survive in very harsh conditions and are teaching us important lessons on how to work efficiently at the nanoscale, making the most of their very limited resources.

A large part of our present knowledge of viruses has been facilitated by techniques, theories, and methods developed in physics and chemistry. In biology, structure is the key to understand function and physical techniques like X-ray diffraction or cryo-electron microscopy have opened the door to unveil structural details of viruses with nearly atomic resolution. In addition, function ultimately involves a set of processes that cannot escape physical laws and that, in fact, very often make a profitable use of them. In recent years, physics and chemistry are not only helping in providing new experimental tools to investigate viruses but are also increasingly contributing to achieve a qualitative and quantitative comprehension of the processes involved. This close collaboration between physics, chemistry, and biology has led to great advances and has boosted our present understanding of viruses.

But interdisciplinarity has its toll. It is often very hard for a scientist trained in one of the traditional sciences to navigate between two worlds, overcoming the different points of view and the methodological and terminological barriers between disciplines. In this context, a book like this constitutes an invaluable resource to cover this gap for students and scientists entering the fascinating world of viruses. The book gathers a complete selection of chapters written by leading experts in the field. It has been written primarily with a nonexpert audience of students and researchers in mind; however, it has been aimed also at providing practitioners in one area of structural or physical virology with updated overviews of most other areas of these broad scientific disciplines. It covers distinct but complementary aspects of the study of viruses that go from techniques required for their characterization to their potential applications, including its structure and functioning.

This effort has been partially possible thanks to the *Spanish Network on the Biophysics of Viruses* (BioFiViNet), supported by the Spanish Ministry of Science. This novel initiative is aiming at coordinating the efforts of the Spanish physicists, chemists, and biologists interested in the interdisciplinary study of viruses and has been the initial spark to agglutinate most of the experts that ended up being authors of this book. It has also promoted the added value of collaborative work between apparently widely different disciplines, thanks to the support and enthusiasm of all its members.

But, without doubt, the real artificer of this great work is its editor Mauricio G. Mateu, who has meticulously planned, coordinated, and assisted the efforts of all authors to accomplish this interdisciplinary and formative spirit. In the name of all authors, I would like to thank Mauricio for his relentless effort and countless hours of dedication to this book. I am sure that future physical and structural virologists will also appreciate his efforts, and that this book will help them to prepare for the myriad wonderful lessons that viruses still have to teach us.

Barcelona, Spain David Reguera
November 2012

Preface

Structural Virology is today an all-important discipline that permeates most other virological disciplines. The application of physical and physicochemical techniques has led to the determination of the high-resolution molecular structures of many viruses. The interplay of this approach with (bio)chemical and biological approaches has allowed in many cases the elucidation of the structural basis of viral function in unprecedented detail. In addition, in the last years, theoretical and experimental physicists have begun to tackle a fundamental physics-based approach to study different aspects of the architecture, self-assembly, and material properties of virus particles. A new term, *Physical Virology*, has recently been coined to encompass these and related studies. This approach is slowly beginning to merge with long-standing structural virology approaches to provide a renewed and richer view on viruses.

Since I became interested in virus structure–function relationships over 25 years ago, I have had the privilege of collaborating not only with virologists but also with molecular and structural biologists, organic and physical chemists, and theoretical and condensed-matter physicists interested in viruses. Since 8 years ago, my group is involved in a multidisciplinary network of physicists, chemists, and biologists to study nano-objects, coordinated first by Prof. Fernando Flores and later by Prof. Julio Gómez-Herrero and funded by the Comunidad de Madrid regional government. As collaborations progressed, I became aware of the difficulties we sometimes faced in finding common scientific goals and interdigitating research pathways instead of merely crossing scientific trajectories. Like many others in similar situations I happily found that, once we began to understand each other's scientific language and aims, we were able to tackle together fruitful combined studies on viruses. This experience and talks with colleagues and students convinced me, about 3 years ago, on the usefulness of an interdisciplinary textbook in which the rapidly expanding fields of structural and physical virology were dealt with in an integrated way. The opportunity to realize such a project came from a kind invitation in early 2011 by Dr. Thijs van Vlijmen at Springer.

At about the same time Prof. David Reguera had the idea of creating in Spain a national network on the biophysics of viruses (*BioFiViNet*) to reinforce previous bonds and promote further interactions between physicists, chemists, and biologists doing research on virus biophysics. Also, a Master in Virology in which many structural virologists were invited to participate had recently been organized under the auspices of the Spanish Society for Virology presided by Prof. Esteban Domingo. I decided it was high time to try and convince some of my colleagues at BioFiViNet and the Spanish Society for Virology, particularly those who had been or are presently engaged in collaborative research among us, to jointly write an advanced textbook on the structure and physics of viruses. I contacted 20 close colleagues (including physicists, chemists, and biologists) from 12 Spanish institutes or university departments. All of them are active senior researchers and internationally recognized experts at the cutting edge of their research areas within structural or physical virology. They all accepted, and some recruited other close colleagues to coauthor their chapters. Such general closeness among book authors has allowed intense mutual feedback during the organization and writing of the book through frequent e-mails, phone calls, and meetings of the editor with the authors, and also between authors of different chapters. Every chapter has been critically read by the editor and (in nearly all cases) by at least one author of a different chapter as well. As a result, each chapter has been written and revised considering the detailed contents of the other chapters, and relating to them as much as possible and practical. However, some minor overlaps between chapters have been kept to facilitate the understanding of each chapter subject without a need to read other chapters in the book. We feel these minor overlaps may also help in connecting the different chapter's contents.

After an infectious virus particle (a virion) targets a host cell, it loses its integrity and releases its nucleic acid genome inside the cell. In the period of time that goes from that point until the progeny viruses are formed, the virus as a discrete physical entity ceases to exist, but the viral genetic instructions inside the infected cell may subvert the cell metabolism. Eventually, many copies of the viral genome and of the viral proteins required to form a new virus particle will be made in the cell, and a number of progeny virions will be assembled from them, closing an infectious cycle (or viral "life" cycle). The structural biology of viral metabolic processes such as replication, recombination, integration, transcription, or translation and their spatial and temporal regulation, and the virus-induced alteration of cellular components and reactions, are outside the scope of this book. Structure-based aspects regarding these processes are integrated in many excellent Molecular Virology books, a few of which are referred to at the end of the introductory chapter in this book (Chap. 1).

The present book has been focused instead on the "other half" of the viral cycle, which is generally less well known. Specifically, this book contemplates the structure, dynamics, and physics of virus particles: From the moment they come into existence by self-assembly from viral components produced in the infected cell, through their extracellular stage, until they recognize and infect a new host cell and cease to exist by losing their physical integrity to start a new infectious cycle. (Bio)physical techniques used to study the structure of virus particles and components and some applications of structure-based studies of viruses are also contemplated.

This book is aimed first at M.Sc. students, Ph.D. students, and postdoctoral researchers with a university degree in biology, chemistry or physics or related sciences who share an interest or are actually working on viruses. We have aimed also at providing an updated account of many important concepts, techniques, studies, and applications in structural and physical virology for established scientists working on viruses, irrespective of their physical, chemical, or biological background and their field of expertise. We have *not* attempted to provide a collection of *for-experts-only* reviews focused mainly on the latest research in specific topics; we have *not* generally assumed that the reader knows all of the jargon and all but the most recent and advanced results in each topic dealt with in this book. In short, we have attempted to write a book basic enough to be useful to M.Sc. and Ph.D. students, as well as advanced and current enough to be useful to senior scientists.

Inevitably, some compromises had to be made. Because of space limitations, not every possible topic has been contemplated; however, we believe most of the important general aspects of the structure and physics of virus particles as they are known have been covered. Space limitations have also prevented the authors of the different chapters to include explanations of some elementary or general concepts or terms. However, we believe the most important aspects in each chapter will be clearly understandable by those with a B.Sc.-level knowledge of physics, chemistry, biology or related scientific areas. Quick consultation to *Wikipedia* or other general sources may solve an occasional doubt on a specific term by a reader coming from a different area of knowledge. In any case, several teaching aids have been implemented in the book to facilitate the reading and understanding of each chapter by a newcomer to the field; these aids include:

An introductory chapter. Chapter 1 includes a brief general introduction to viruses and their structure, some basic concepts and terms in molecular and structural virology, and general descriptions of different steps in the virus cycle. The chapter is also intended as a guide to help the reader integrate in a general picture the topics treated in each monographic chapter (Chaps. 2–22).

A similar outline in different chapters in each part of the book. Each Part II chapter dealing with a specific technique includes sections on the principles of the technique, on relevant examples of contributions of the technique for understanding viruses, and on technical perspectives. Each Part III chapter dealing with a stage in the viral cycle includes sections that connect the stage described with stages described in other chapters.

Frequent cross-references between chapters. They may be useful to find in other chapters additional information on certain subjects and/or to connect particular aspects treated in different chapters.

Basic systematic information on viruses species and families mentioned in the book. This information is intended mainly to help the reader navigate among the multitude of virus names that will inevitably appear in the different chapters of this book (or of any other virology book). Table 1.1 includes (nearly) all virus species, families, and orders mentioned in this book, with indication of host and viral genome types. Figure. 1.3 gives a scheme of the general virion structure for some of the most important families of animal viruses. *Specific indexes* at the end of the book include (nearly) all virus species and families mentioned, each with reference to pages where some information regarding the species or family is mentioned.

A list of references focused largely on review articles. The list of references at the end of each chapter has purposefully been kept relatively short in order not to overwhelm the nonexpert reader; reviews have been included wherever possible, and the advanced reader is referred in many cases to those reviews for the original references that have not been included in the book. We apologize to the many authors whose work, however important, could not be directly cited.

A section on further reading. In each chapter, a short list under the subheading *further reading* includes references to a few books and/or reviews. These may be particularly useful either for learning or refreshing basic principles, or for more detailed/advanced information on the subject.

This book is organized into four parts. Although the chapters are self-contained and may be understood individually, all chapters, especially those in each part (I–IV), are inter-related and they have been designed with the input of the editor and every author to tell a complete story.

Part I, *The viral machine*, includes an introductory chapter to the rest of the book (Chap. 1) and another chapter on the fundamental composition and basic architecture of virus particles (Chap. 2). This knowledge is essential for understanding many subjects treated in the following chapters.

Part II, *Determination of the structure and physical properties of viruses*, contemplates most of the major experimental techniques in structural and physical virology. These include different electron microscopy techniques, with emphasis in cryo-electron microscopy and tomography (Chap. 3); X-ray crystallography (Chap. 4); nuclear magnetic resonance spectroscopy (Chap. 5); other spectroscopic techniques (circular dichroism and fluorescence) and mass spectrometry (Chap. 6); the combination of the above and other structural biology methods (Chap. 7); and single-molecule techniques, including atomic force microscopy (Chap. 8) and optical tweezers (Chap. 9). In all cases, the techniques are described not in broad, general terms (as can be found in general technical books) but in the ways they are specifically applied to study virus particles and their components.

Part III, *Structural foundations of virus properties and functions*, deals with the different stages in the viral cycle in which virus particles and/or their structural components are involved. Confronting the *chicken and egg* problem, we decided to start the endless viral cycle when a viral particle comes into existence by self-assembly and proceed until the viral particle ceases to exist by losing its integrity and releasing its nucleic acid in a host cell. As previously noted, the metabolism of the viral nucleic acid and other viral components until new viral particles are formed (thus closing the viral cycle) does not involve virus particles and is, thus, out of the scope of this book. Chapters 10–17 consider each viral cycle stage in which virus particles are involved. In most of these chapters, the authors have focused in studies on some model viruses that constitute paradigms to understand the structural bases of virus function at that stage in the cycle. In addition, some general conclusions are extracted from the cases described and other studies.

Chapter 10 deals with experimental studies on the basic assembly of structurally simple viruses; both structural aspects and the cellular environment where assembly occurs are contemplated. Chapter 11 builds on what has been described in Chaps. 2 and 10 on relatively simple viruses, to describe important specific aspects of the structure and assembly of more complex viruses, including their scaffold-mediated assembly. Chapter 12 focuses on the different ways in which the viral nucleic acid is packaged inside the virus particle. Chapter 13 deals with the process of maturation of viral particles to become infectious virions. Self-assembly or assisted assembly of a virus shell (capsid), packaging of the nucleic acid, and virus particle maturation are not clear-cut steps and they frequently overlap in space and time; thus, particularly frequent cross-references between Chaps. 10–13 have been included. Chapter 14 recollects a wide range of structural, molecular, and cell biology techniques as they are applied to understand the complete virus morphogenetic process as it occurs *in vivo*; this chapter also describes several important observations obtained on this still little-known process.

No specific chapter in Part III is devoted to the properties of the extracellular mature virions because they are sufficiently covered in Chap. 1 and/or in other chapters dealing with processes in which those properties come into play. Virion conformational stability and dynamics are revised in Chap. 1 in the context of the complete viral cycle and are dealt with also in other chapters as related with some particular stages in the infectious cycle. Several aspects of the recognition of extracellular virus particles by the immune system, mechanisms of virus recognition and neutralization by antibodies and virus escape from antibody recognition are briefly revised in Chaps. 21 and 1, respectively.

Chapters 15–17 describe the complex process of virus entry into cells and viral nucleic acid transfer. Chapters 15 and 16 deal with the specific recognition of host cells by animal viruses through interaction with receptor molecules, the entry of nonenveloped or enveloped viruses into these cells by different mechanisms, and the release (uncoating) of the viral genome inside the cell. Chapter 17 describes the mechanisms bacteriophage viruses follow for bacterial cell recognition and transfer into the cell of their genome.

The last chapters in Part III (Chaps. 18 and 19) deal with salient studies on the fundamental physics of viruses. Chapter 18 describes recent experimental studies on the mechanical properties of virus particles and their possible impact on virus biology. Chapter 19 contemplates theoretical physics-based studies on the more fundamental aspects of virus architecture, material properties, assembly and entry into host cells, all of them highly relevant subjects about which some experimental studies have been described in previous chapters (Chaps. 2 and 10–18). Readers of any of those chapters are strongly encouraged to read also Chap. 19 to acquire a more complete understanding of the structure and properties and functions of virions, and the synergy between experimental and theoretical, structural and physical virology studies.

Part IV, *Applied structural and physical virology*, includes some important current or potential developments and applications of the structural and physical knowledge being acquired on viral particles. We chose three major applied areas.

Chapter 20 contemplates the general design and structural basis of action of antivirals. In this chapter, antivirals against molecules other than virus particles or their components are contemplated first, because the design principles and structural basis of action do not largely depend on the target, and some of those antivirals have been well-studied and proved remarkably successful; the chapter then continues by considering novel approaches based on the inhibition or misdirection of virus entry or morphogenesis. Chapter 21 describes novel approaches to vaccines based on virus-like particles or chimeric virions. Chapter 22 contemplates the chemical and genetic manipulation and the use of viral particles for applications in the rapidly expanding nanotechnology field, from biomedicine to electronics.

I would like to gratefully acknowledge the authors of this book for their enthusiasm, time, effort, and patience devoted not only to write their chapters but to meet and discuss contents, presentation, and improvements; Prof. David Reguera for writing the foreword and for critically reading many book chapters; Miguel Angel Fuertes for most helpful assistance with a number of tasks; and José A. Pérez for formatting some figures. The authors of this book wish to collectively express here our gratitude to those other book authors who critically read our chapter's manuscripts. We are indebted to Dr. Thijs van Vlijmen at Springer for his support and interest in this book project, and to him, Ms. Sara Germans at Springer and Mr. Ibrahim Mohamed Asif at SPi Technologies for their invaluable help and patience during the writing, edition and production of this book.

Madrid, Spain
November 2012

Mauricio G. Mateu

Contents

Contributors

Nicola G.A. Abrescia Structural Biology Unit, CICbioGUNE, CIBERehd, Derio, Spain

Ikerbasque, Basque Foundation for Science, Bilbao, Spain

José M. Almendral Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), and Department of Molecular Biology, Universidad Autónoma de Madrid, Madrid, Spain

José María Alonso CIC nanoGUNE, San Sebastián, Spain

J. Ricardo Arias-Gonzalez Instituto Madrileño de Estudios Avanzados en Nanociencia (IMDEA Nanociencia), Madrid, Spain

Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

CNB-CSIC-IMDEA Nanociencia associated unit "Unidad de Nanobiotecnología", Madrid, Spain

Daniel Badía-Martínez Structural Biology Unit, CICbioGUNE, CIBERehd, Derio, Spain

Juan Bárcena Centro de Investigación en Sanidad Animal (INIA), Madrid, Spain

Alexander M. Bittner CIC nanoGUNE, San Sebastián, Spain

Ikerbasque, Basque Foundation for Science, Bilbao, Spain

Esther Blanco Centro de Investigación en Sanidad Animal (INIA), Madrid, Spain

José L. Carrascosa Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

José M. Casasnovas Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

José R. Castón Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Ana Cuervo Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

María I. Daudén Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Laura R. Delgui Laboratorio de Biología Celular y Molecular, Instituto de Histología y Embriología Mendoza (IHEM), Facultad de Ciencias Médicas, Universidad Nacional de Cuyo-CONICET, Mendoza, Argentina

Instituto de Ciencias Básicas, Universidad Nacional de Cuyo, Mendoza, Argentina

Isabel Fernández de Castro Cell Structure Laboratory, Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Pedro J. de Pablo Department of Physics of the Condensed Matter, C-III, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain

Ignacio Fita Institut de Biología Molecular de Barcelona (CSIC), and IRB Barcelona, Parc Científic de Barcelona, Barcelona, Spain

Federico Gago Department of Pharmacology, Universidad de Alcalá, Madrid, Spain

Carmela Garcia-Doval Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Damià Garriga Department of Molecular and Cell Biology, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Marcin Ł. Górzny CIC nanoGUNE, San Sebastián, Spain

Antoni Luque Department of Fundamental Physics, Universitat de Barcelona, Barcelona, Spain

Department of Chemistry, New York University, New York, NY, USA

Vicente Más Biología Viral, Centro Nacional de Microbiología and CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III Majadahonda, Madrid, Spain

Mauricio G. Mateu Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), and Department of Molecular Biology, Universidad Autónoma de Madrid, Madrid, Spain

José A. Melero Biología Viral, Centro Nacional de Microbiología and CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III Majadahonda, Madrid, Spain

Luis Menéndez-Arias Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), Madrid, Spain

José L. Neira Instituto de Biología Molecular y Celular, Universidad Miguel Hernández, Alicante, Spain

Instituto de Biocomputación y Física de Sistemas Complejos, Zaragoza, Spain

Hanna M. Oksanen Institute of Biotechnology and Department of Biosciences, Viikki Biocenter, University of Helsinki, Helsinki, Finland

David Reguera Department of Fundamental Physics, Universitat de Barcelona, Barcelona, Spain

Cristina Risco Cell Structure Laboratory, Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

José F. Rodríguez Department of Molecular and Cell Biology, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Carmen San Martín Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

David I. Stuart Division of Structural Biology, The Wellcome Trust Centre for Human Genetics, University of Oxford, Headington, UK

Diamond Light Source Ltd, Diamond House, Didcot, UK

Mark J. van Raaij Department of Macromolecular Structure, Centro Nacional de Biotecnología (CSIC), Madrid, Spain

Nuria Verdaguer Institut de Biología Molecular de Barcelona (CSIC), Parc Científic de Barcelona, Barcelona, Spain

Christina Wege Institute of Biology, University of Stuttgart, Stuttgart, Germany