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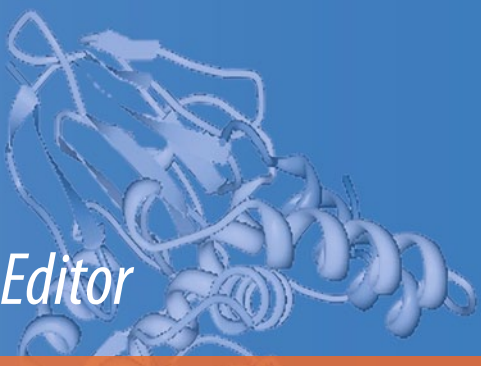

Mauricio G. Mateu *Editor*

Structure and Physics of Viruses

An Integrated Textbook

Springer

Structure and Physics of Viruses

SUBCELLULAR BIOCHEMISTRY

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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
November 2012

David Reguera

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
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Mauricio G. Mateu

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Part I
The Viral Machine

Chapter 1
Introduction: The Structural Basis of Virus Function

Mauricio G. Mateu

Abstract Viruses may be regarded as dynamic nucleoprotein assemblies capable of assisted multiplication within cells, and of propagation between cells and organisms. Infectious virus particles (virions) assembled in a host cell are dynamic, generally metastable particles: They are robust enough to protect the viral genome outside the cell, but are also poised to undergo structural changes and execute mechanochemical actions required for infection of other cells. This chapter provides an introduction to the structural and physical biology of viruses by including: (i) an elementary overview on virions and the structural basis of virus function; (ii) a concise summary on basic techniques used in structural or physical virology; (iii) brief structure-based general descriptions of the different stages in the virus cycle, especially those in which virions and/or their components are involved. These contents may facilitate a better understanding of the specialized subjects treated in the rest of the book. This chapter is also intended as a "road map" to help interconnect and integrate in a single picture the different topics described in depth in the 21 monographic chapters in this book.

Keywords Virus • Virus cycle • Infection • Capsid • Viral genome • Capsid subunits • Capsid building blocks • Oligomerization • Self-assembly • Assisted assembly • Assembly intermediates • Scaffolding proteins • Conformational stability • Conformational dynamics • Nucleic acid packaging • Capsid-nucleic acid condensation • Virus maturation • Virus stability and dynamics • Virus-antibody recognition • Virus-receptor recognition • Virus entry • Fusion • Uncoating • Antivirals • Vaccines • Biotechnology • Nanotechnology

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AAV	Adeno-associated virus
AFM	Atomic force microscopy
CBB	Capsid building block
CP	Capsid protein
cryo-EM	Cryo-electron microscopy
DNA	Deoxyribonucleic acid
ds	Double-stranded
EMDB	Electron Microscopy Data Bank
Fab	Antigen-binding antibody fragment
FMDV	Foot-and-mouth disease virus
HIV-1	Human immunodeficiency virus type 1
HRV	Human rhinovirus
HSV-1	Herpes simplex virus type 1
ICTV	International Committee on Taxonomy of Viruses
MD	Molecular dynamics
mRNA	Messenger RNA
MS	Mass spectrometry
MVM	Minute virus of mice
NMR	Nuclear magnetic resonance
PDB	Protein Data Bank
PV	Poliovirus
RNA	Ribonucleic acid
RT	Reverse transcriptase
SAXS	Small-angle X-ray scattering
ss	Single-stranded
TMV	Tobacco mosaic virus
VLP	Virus-like particle

1.1 The Structure and Physics of Viruses

Viruses are biological entities capable of assisted multiplication within cells and of propagation between cells and organisms. Virus multiplication and propagation is generally a cyclic process: An infectious viral particle (*virion*) introduces its genome into a host cell, new virions are formed in the cell and released, and these in turn may infect other host cells. This cycle of infection is often called the *virus* "*life*" *cycle*. There has been a largely philosophical debate on whether viruses are alive or not. We use the term *virus life cycle* as a synonym of *infectious cycle*; we are not making the statement that viruses are "living" organisms. In this book viruses are contemplated as macromolecular complexes that, through biological evolution, came into existence and were endowed with the capacity to make copies of themselves by using the genetic instructions they enclose and the host cell machinery.

Because of the effects many viral infections cause on living beings, viruses are frequently considered only as pathogens causing disease and human suffering, economic losses and social problems. However, since the times of the "Phage Group" and the advent of molecular virology more than half a century ago, scientists coming from different areas have become increasingly aware that viruses also provide outstanding, relatively simple models to explore biomolecular structure-function relationships using a combination of physical, chemical and biological approaches. The knowledge thus acquired has been decisive not only to combat viral disease, but also in the quest to understand in physico-chemical terms the molecular machinery of life.

Specific reasons for studying the structure, dynamics and physical and (bio) chemical properties of virus particles include the following:

(i) Virus particles constitute excellent models to understand and learn to manipulate molecular self-assembly.
(ii) Virus particles are paradigms to understand structure-function relationships in biomacromolecular assemblies and biological machines.
(iii) A profound knowledge of virus structure, dynamics and properties is essential to understand the life cycles of viruses.
(iv) Virus particles, their components and the processes in which they participate provide novel targets for the design of antiviral agents.
(v) Understanding the structural determinants of virus stability, dynamics and function may facilitate the rational manipulation of virus particles to develop new or improved vaccines, gene therapy vectors, and nanoparticles for drug delivery or other biomedical or bio/nanotechnological uses.

This chapter provides an introduction to structural and physical virology and is intended mainly for M.Sc. students, Ph.D. students and postdoctoral researchers in physics, chemistry, biology or related areas who are interested in viruses, but who may be relatively unfamiliar with the subject. It intends also to provide a "road map" to help the reader integrate in a general picture the topics treated in depth in the other chapters in this book. To achieve these aims, the present chapter includes:

(i) Brief explanations on some elementary concepts and terms in molecular, structural and physical virology; a detailed description of the basic architecture of viruses will follow in the accompanying Chap. 2 in Part I of this book.
(ii) Some broad guidelines on the applicability of most of the different techniques described in Part II, Chaps. 3, 4, 5, 6, 7, 8 and 9, and Chaps. 14, 19, to characterize the structure, dynamics and physical properties of virus particles.
(iii) A brief overview of a generic virus cycle and of the major roles in the cycle of virions and their components.
(iv) Brief accounts of general structural concepts and descriptions regarding each of the different stages of the viral cycle in which virions or their components are involved, and of relevant properties of virus particles. These short, elementary accounts may facilitate those readers with little background in molecular and structural virology a fullest and better integrated understanding of the

contents of Part III, Chaps. 10, 11, 12, 13, 14, 15, 16 and 17; each of these chapters deals in detail with structural aspects of one of those stages of the virus cycle.

(v) A schematic overview of novel, physics-based approaches to study virus structure, dynamics and properties, as a brief introduction to detailed accounts of some physical virology methods (Part II, Chaps. 8, 9), studies (Part III, Chaps. 18, 19) and applications (Part IV, Chap. 22).

(vi) A very brief overview of applied studies in structural virology, to put into a general context the particular applications described in detail in Part IV, Chaps. 20, 21 and 22.

1.1.1 Structural Virology

Our knowledge of the molecular structure and function of viruses has grown spectacularly in the last decades, largely because these entities have uniquely and increasingly attracted the interest of biologists, (bio)chemists and physicists alike. Viruses have, thus, been rediscovered as organized complexes of biomolecules that act as minute machines. These nanomachines are continuously being modified and diversified through mutation and biological adaptation. However, they are invariably determined by the laws of physics and chemistry to blindly perform sophisticated mechanochemical actions, including penetration into host cells and self-assembly from their molecular components after these have been replicated in the cell. 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 have allowed in many cases the elucidation of the structural basis of viral function in unprecedented detail. *Structural Virology* has permeated other virological disciplines to provide a molecular view of viruses and their biology. The detailed structural knowledge on viruses and their components has made, and will surely continue to make, decisive contributions in the fight against viral disease.

1.1.2 Physical Virology

In the last years, the advent of nanoscience and nanotechnology, and the increasing awareness on the outstanding features of virus particles as solid-state nanodevices are leading to a renewed look at viruses from the physicist's point of view. Theoretical physicists have begun to tackle at the most fundamental level different aspects of the architecture, self-assembly and physical properties of virus particles. Also, the development of atomic force microscopy (AFM), optical tweezers and other techniques to study individual molecules have opened up new possibilities for the experimental study of the structure, properties and mechanochemical actions of

viruses and their components. A new term, *Physical Virology*, has recently been coined to encompass theoretical and experimental physics-oriented studies of viruses. This novel approach is slowly beginning to merge with long-standing structural virology approaches based on other physical or physico-chemical techniques such as electron microscopy, X-ray crystallography and many others. As a consequence, viruses are currently being investigated for new developments not only in biomedicine and biotechnology but also in nanotechnology, including nanomaterials and nanoelectronics.

1.2 Virions and Their Structural Components

1.2.1 Molecular Composition of Viruses

From a structural point of view virions may be generally regarded as nucleoprotein assemblies. They all include a nucleic acid genome and many copies of one or more proteins. However, virions present remarkable differences in size, shape, molecular composition, structural organization and complexity (Fig. 1.1). Considering its molecular composition only, viruses are generally classified into two large groups, *non-enveloped viruses* and *enveloped viruses*, depending on the absence or presence of an outer lipid layer.

Non-enveloped Viruses

The simplest non-enveloped virions are composed just of a protein shell, or *capsid* (sometimes called *coat*) made of multiple copies of one or more proteins, that contains the viral nucleic acid (Fig. 1.1, left). In less simple non-enveloped virions, the capsid may contain not only the viral genome, but also other proteins and/or other macromolecules, which may be organized in subassemblies. These additional biomolecules or subassemblies can be enclosed in the capsid shell or externally attached to its surface (Fig. 1.1, center) (see Chaps. 2, 10, 11, 17).

Enveloped Viruses

In enveloped virions, the capsid and/or other internal structures are typically surrounded by a lipid bilayer, or *envelope*, in which some proteins are embedded (Fig. 1.1, right); some enveloped virions have a complex multi-layer structure made of organized lipid, protein and/or nucleoprotein layers (see Chaps. 2, 11).

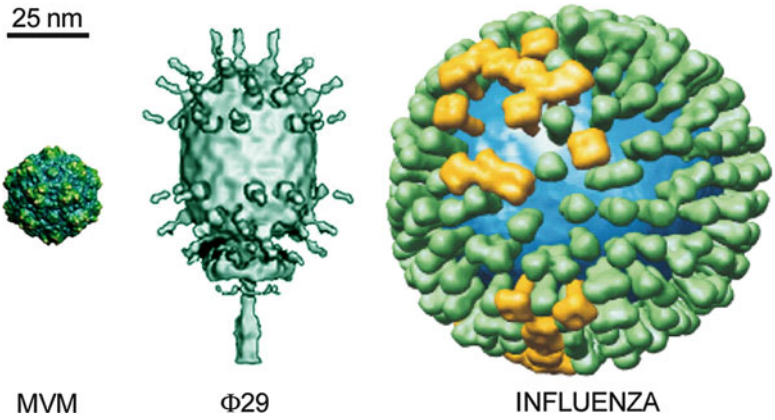

Fig. 1.1 Major types of viruses by molecular composition. *Left* and *center*, non-enveloped viruses; *left*, a very simple virus (the parvovirus MVM); *center*, a complex virus (the tailed bacteriophage ϕ29). *Right*, an enveloped virus (the orthomyxovirus influenza virus). They are reproduced at (approximately) the same scale, indicated by the *horizontal bar* (*top left*). The MVM structural model [Agbandje-McKenna M, Llamas-Saiz AL, Wang F, Tattersall P, Rossmann MG (1998) Structure 6:1369–1381] was obtained from VIPERdb [Carrillo-Tripp M, Sheperd CM, Borelli IA, Sangita V, Lander G, Natarajan P, Johnson JE, Brooks III CL, Reddy VS (2009) Nucleic Acids Res 37:D436–D442]. The models of ϕ29 and influenza virus are respectively reproduced from [Wikoff WR, Johnson JE (1999) Curr Biol 9:R296–R300] and [Harris A, Cardone C, Winkler DC, Heymann JB, Brecher M, White JM, Steven AC (2006) Proc Natl Acad Sci USA 103:19123–19127], with permission. (Figure kindly provided by M.A. Fuertes)

1.2.2 The Virus Capsid

The capsid plays a fundamental role in both the architecture and the biological function of a virus. A virus capsid can be generally described as a hollow symmetric protein oligomer or multimer made from several tens to many hundreds of copies of one or a few different types of folded polypeptides, the *capsid protein* (CP) subunits. Most CPs (or their individual structural domains if formed by more than one domain) can be ascribed to one of a very limited number of protein architectures or *folds* that can assemble into a limited number of quaternary structures (Chap. 2).

In each virus, oligomerization of the CPs during capsid assembly normally leads to a defined type of symmetric quaternary structure. Only very few types of capsid symmetry are frequent. The basic types are *helical* (Fig. 1.2, top) and *icosahedral* (Fig. 1.2, bottom left and right). In some viruses, capsids adopt an elongated (prolate) icosahedral architecture (Fig. 1.1, right). Other capsids, such as those of retroviruses or poxviruses, are made of less simple arrangements of CP subunits (see Chaps. 2, 10, 11). Structural models (density maps) of virions and other virus particles determined by electron microscopy (Chap. 3) are available at the Electron Microscopy Data Bank (EMDB) (http://www.ebi.ac.uk/pdbe/emdb). Atomic coordinates and high-resolution structural models of virions or other virus particles

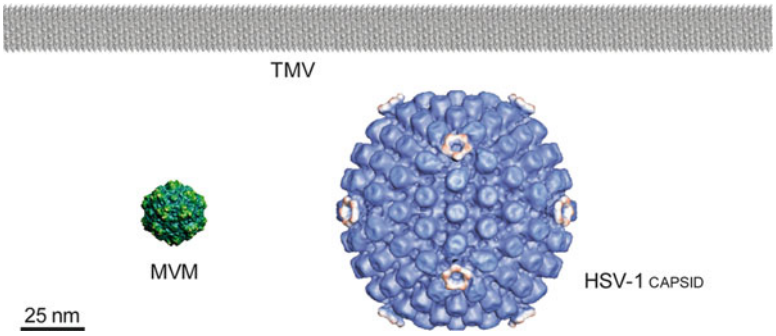

Fig. 1.2 Major types of viral capsid symmetry. *Top image*: helical; the capsid of TMV is shown. *Bottom images*: icosahedral; *left image*, the simple icosahedral capsid of the parvovirus MVM; *right image*, the complex icosahedral capsid of the herpesvirus HSV-1. Images of TMV, MVM and HSV-1 are respectively adapted or reproduced from [Clare DK, Orlova EV (2010) J Struct Biol 171:303–308], [Agbandje-McKenna M, Llamas-Saiz AL, Wang F, Tattersall P, Rossmann MG (1998) Structure 6:1369–1381], and [Grünewald K, Desai P, Winkler DC, Heymann JB, Belnap D, Baumeister W, Steven AC (2003) Science 302:1396–1398], with permission. (Figure kindly provided by M.A. Fuertes)

whose structures have been determined by X-ray crystallography (Chap. 4) are available at the Protein Data Bank (PDB) (http://www.rcsb.org).

Helical Capsids

Helical capsids (Fig. 1.2, top) are extremely simple, theoretically infinite multimers and (in principle) could be made as long as required to encapsidate a nucleic acid genome irrespective of its length; thus, there is no theoretical limitation on the amount of genetic information these capsids could store. However, physical and biological restrictions limit the length of helical capsids, which are much less frequent than icosahedral capsids; regular helical capsids are found in about 10 % of virus families. Chapter 2 provides a description of the architecture of helical capsids; examples of helical viruses can be found in other chapters of this book.

Icosahedral Capsids

In contrast to helical capsids, strictly icosahedral capsids (Fig. 1.2, bottom left) must be made of exactly 60 structurally identical components (CP monomers or oligomers) in order to fulfill intrinsic geometric constraints. This fact could severely limit the size of the nucleic acid genome and, hence, the amount of genetic information that could be enclosed (see Chap. 2). However, evolution has led to different structural solutions to make very large viral capsids with icosahedral symmetry, made of hundreds of chemically identical CP subunits, that can enclose

very large genomes (Fig. 1.2 bottom right). Many large capsids containing many subunits are made of only one type of CP that is capable to adopt different *quasi-equivalent* (similar) conformations (given by the *triangulation number* T); this feature allows the CP molecule to fit into T non-equivalent positions in the icosahedral capsid (see Chap. 2 for a detailed description). This evolutionary strategy minimizes the amount of genetic information required to encode the capsid. Icosahedral capsids are extremely frequent; they occur in about half the virus families. See Chap. 2 for an in-depth description of the architectures of icosahedral viral capsids; Chaps. 2, 10, 11 and others in this book provide many examples of icosahedral capsids and viruses. A database (VIPERdb) contains abundant structural information on viruses with icosahedral capsids whose structure has been determined to high resolution (http://viperdb.scripps.edu).

Virion Architecture

In non-enveloped viruses with a helical or icosahedral capsid, the basic architecture of the capsid determines also the basic architecture of the virion. In enveloped virions, the situation is more complex. Many enveloped virions containing icosahedral capsids and/or other types of compact (nucleo)protein complexes tend to adopt a relatively flexible, frequently spheroidal shape which may differ in size between individual particles.

For example, in herpesviruses (*e.g.*, herpes simplex virus type 1, HSV-1) a large icosahedral capsid (Fig. 1.2, bottom right) containing the viral genome is enclosed in an outer layer of proteins (*tegument*), surrounded in turn by a lipidic envelope; the virion that results is considerably larger than the capsid and spheroidal in shape. In influenza virus (Fig. 1.1, right), several roughly helical nucleocapsid complexes (ribonucleoprotein particles) are directly surrounded by a protein layer (the *matrix*) and the lipid envelope, and this virus is clearly pleomorphic. Many other variations in virion architecture, some of them very complex, do exist. In some cases, two concentric capsids are found; in others, internal lipidic envelopes are present. The structures of some complex viruses are described in detail in Chaps. 2, 11. Other examples of complex virion architectures can be found in several chapters in this book.

1.2.3 Types of Viral Nucleic Acid

The type of genomic nucleic acid used by different viruses is of prime importance to determine the mechanisms of genome replication and expression during the metabolically active phase of the viral cycle. From the perspective of this book the type of nucleic acid, especially whether it is single-stranded (ss) or double-stranded (ds), is extremely relevant for the assembly of many virus capsids (Chaps. 2, 10, 11, 19), the mechanism of nucleic acid packaging (Chap. 12), the organization of the nucleic acid inside the capsid (Chap. 12), virus particle maturation (Chap. 13), and some properties and functions of the virion (Chaps. 2, 10, 11, 12, 13 and 18).

RNA Viruses

Riboviruses (*RNA viruses*) use RNA as genetic material. Some of them use ssRNA (*ssRNA viruses*), others use dsRNA (*dsRNA viruses*). In turn, two types of ssRNA viruses can be distinguished depending on the polarity of their RNA genome strand (*ssRNA*(+) *viruses* and *ssRNA*(−) *viruses*). A genomic single-stranded nucleic acid is considered of positive (+) polarity if its sequence corresponds to that in the viral messenger RNAs (mRNA), and of negative (−) polarity if its sequence corresponds to the complementary of the mRNA sequences. In some viruses, the virion encloses more than one copy of the genome (*e.g.*, retroviruses), or the genome is *segmented*, split into several nucleic acid molecules (*e.g.*, influenza virus). Most of the virus species known are RNA viruses.

DNA Viruses

Deoxyviruses (*DNA viruses*) use DNA as their genetic material. Some of them use ssDNA (*ssDNA viruses*); others use dsDNA (*dsDNA viruses*).

1.2.4 Host Cells and Organisms

Viruses can be grouped also by the kind of cell they can infect (Table 1.1). Many known viruses infect eukaryotic cells (*eukaryotic viruses*). Of them, many infect animals such as vertebrates (including humans) or insects (*animal viruses*); others infect fungi (*fungal viruses* or *mycoviruses*), plants (*plant viruses*) or protista (*protist viruses*). Many other viruses infect prokaryotic cells such as bacteria (*prokaryotic viruses*). Bacterial viruses are usually called *bacteriophages* or, simply, *phages*. Archea are also infected by viruses (*archeal viruses*). Most viruses have evolved to infect one or a few species of organisms (limited *host range*) and one or a few cell types (specific *tropism*). The type of cell a virus can infect is, in part, the consequence of the structural and functional features the virus particle has evolved to enter a particular cell. In general, infection by an animal virus or bacteriophage depends largely on the receptor molecule(s) on the cell surface that the virion can specifically bind (see Sect. 1.4.5 and Chaps. 15, 16, 17). Although some archeal, protist and fungal viruses are providing fascinating cases for structural study (a few of which are mentioned in this book), the vast majority of viruses that have been the subject of structural and molecular virology studies infect animals, plants or bacteria (see Table 1.1). Detailed information on the molecular biology of animal viruses, plant viruses and/or phages can be found also in the books listed at the end of this chapter [1–10].

Table 1.1 Some virus families and species grouped according to type of host and viral genome

Host[a]	Viral genome[b]	Virus order[c]	Virus family[d]	Some virus species[e]
Bacteria	dsDNA		*Corticoviridae*	PM2
		C	*Myoviridae*	P1, P2, P4, SPO1, T4, μ, ϕ92, 8a, 44RR
		C	*Podoviridae*	BPP-1, K1F, P22, Sf6, T7, ε15, ϕ15, ϕ29
		C	*Siphoviridae*	HK97, p2, SF6, SPP1, TP901-1, T5, λ
			Tectiviridae	PRD1, P23-77
	ssDNA		*Microviridae*	ϕX174
			Inoviridae	fd, M13
	dsRNA		*Cystoviridae*	ϕ6, ϕ12
	ssRNA(+)		*Leviviridae*	MS2, Qβ
Archea	dsDNA		*Ampullaviridae*	ABV
			Guttaviridae	SNDV
			Lipothrixviridae	AFV-1
			Rudiviridae	SIRV-2
Protista	dsDNA		*Phycodnaviridae*	PBCV-1
Plant	ssDNA		*Geminiviridae*	BGYMV
	ssRNA(+)		*Bromoviridae*	AMV, BMV, CCMV, CMV
		T	*Flexiviridae* (*Alphaflexiviridae*)	PapMV
			Potyviridae	BYMV
		P	*Secoviridae*	BPMV
			Sobemovirus (*unassigned genus*)	RYMV, SBMV
			Tombusviridae	CPMV, RCNMV, STNV, TBSV, TNV A
		T	*Tymoviridae*	PhMV, TYMV
			Virgaviridae	TMV
	dsDNA-RT		*Caulimoviridae*	CaMV
Fungi	dsRNA		*Partitiviridae*	*Atkinsonella hypoxylon* virus
			Chrysoviridae	*Penicillium chrysogenum* virus
Animal	dsDNA		*Adenoviridae*	(h)Ad
			Asfarviridae	ASFV
			Baculoviridae	AcNPV, cytoplasmic polyhedrosis virus, WNPV
			Iridoviridae	Frog virus 3
		H	*Herpesviridae*	HCMV, HSV-1, VZV
			Mimiviridae	*Acanthamoeba polyphaga* mimivirus
			Papillomaviridae	BPV, HPV 1
			Polyomaviridae	SV40, (human) polyomavirus
			Poxviridae	Vaccinia virus, Variola virus
	ssDNA		*Circoviridae*	PCV2
			Parvoviridae	AAV-2, CPV, FHV, H1-PV, MEV, MVM, PPV

(continued)

Table 1.1 (continued)

Host[a]	Viral genome[b]	Virus order[c]	Virus family[d]	Some virus species[e]
	dsRNA		*Birnaviridae*	IBDV
			Reoviridae	BTV, Rotavirus (A)
	ssRNA(+)		*Astroviridae*	Mamastrovirus 1
			Caliciviridae	NV (Norovirus), RHDV
		N	*Coronaviridae*	SARS virus
			Flaviviridae	Dengue virus, HCV, TBEV, yellow fever virus
			Hepeviridae	HEV
			Nodaviridae	FHV, PaV
		P	*Picornaviridae*	Coxsackievirus, echovirus, FMDV, HAV, HRV, PV
			Tetraviridae (*Alphatetraviridae*)	NωV
			Togaviridae (*genus Alphavirus*)	Chikungunya virus, Semliki Forest virus, Sindbis virus
	ssRNA(−)		*Arenaviridae*	LCMV
			Bunyaviridae	Bunyamwera virus, Hantaan virus, RVFV
		M	*Filoviridae*	Ebola virus, Marburg virus
			Orthomyxoviridae	Influenza virus (A, B, C)
		M	*Paramyxoviridae*	HeV, hMPV, hPIV, measles virus, mumps virus, NDV, NiV, Sendai virus, RSV(Respiratory Syncytial virus)
		M	*Rhabdoviridae*	Rabies virus, VSV
	ssRNA(+)-RT		*Retroviridae*	BLV, EIAV, HIV-1, HIV-2, HTLV-I, MLV, MMTV, MoMuLV, MPMV; RSV(Rous sarcoma virus), SIV
	dsDNA-RT		*Hepadnaviridae*	HBV

[a]Classified according to kingdom. Different virus species of some families may infect organisms from different kingdoms. For example, some species of the *Reoviridae*, *Bunyaviridae*, *Rhabdoviridae* may infect animals and other species may infect plants

[b]*RT* indicates that virus replication involves a reverse transcriptase

[c]The six virus orders are: *C Caudovirales*, *H Herpesvirales*, *M Mononegavirales*, *N Nidovirales*, *P Picornavirales*, *T Tymovirales*. All other virus families listed have not been assigned to any order (see text)

[d]The virus families listed include nearly all of those mentioned in this book and a few others. The current ICTV virus classification includes 94 families, and several independent genera that have not been ascribed to families (see text). The families *Flexiviridae* and *Tetraviridae* have recently been split into several families each; according to the current ICTV classification, the virus species listed for those families belong to the *Alphaflexiviridae* and *Alphatetraviridae* families, respectively

[e]The virus species listed as examples include nearly all of those mentioned in this book and a few additional ones. Virus species abbreviations: *AAV* adeno-associated virus, *ABV Acidianus* bottle-shaped virus, *AcNPV Autographa californica* nuclear polyhedrosis virus, *AFV Acidianus* filamentous virus, *AMV* alfalfa mosaic virus, *ASFV* african swine fever virus, *BGYMV* bean gold yellow

(continued)

Table 1.1 (continued)

mosaic virus, *BLV* bovine leukemia virus, *BMV* brome mosaic virus, *BPMV* bean pod mottle virus, *BPV* bovine papillomavirus, *BTV* bluetongue virus, *BYMV* barley yellow mosaic virus, *CaMV* cauliflower mosaic virus, *CCMV* cowpea chlorotic mosaic virus, *CMV* cucumber mosaic virus, *CPMV* cowpea mosaic virus, *CPV* canine parvovirus, *EIAV* equine infectious anemia virus, *FHV* flock house virus, *FMDV* foot-and-mouth disease virus, *FPV* feline parvovirus, *H1-PV* parvovirus H1, *(h)Ad* (human) adenovirus, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCMV* human cytomegalovirus, *HCV* hepatitis C virus, *HeV* Hendra virus, *HEV* hepatitis E virus, *HIV* human immunodeficiency virus, *hMPV* human metapneumovirus, *HPV* human papillomavirus, *hPIV* human parainfluenza virus, *HRV* human rhinovirus, *HSV* human herpesvirus, *HTLV* human T-lymphotropic virus, *IBDV* infectious bursal disease virus, *LCMV* lymphochoriomeningitis virus, *MEV* mink enteritis virus, *MLV* murine leukemia virus, *MMTV* mouse mammary tumor virus, *MPMV* Mason-Pfizer monkey virus, *MVM* minute virus of mice, *NDV* Newcastle disease virus, *NiV* Nipah virus, *NV* Norwalk virus, *NωV Nudaurelia capensis* ω virus, *PapMV* papaya mosaic virus, *PaV* Pariacoto virus, *PBCV Paramecium bursaria Chlorella* virus, *PCV* porcine circovirus, *PhMV Physalis* mottle virus, *PPV* porcine parvovirus, *PV* polio virus, *RCNMV* red clover necrosis mosaic virus, *RHDV* rabbit haemorrhagic disease virus, *RSV* respiratory syncytial virus, *RSV* Rous sarcoma virus, *RVFV* Rift Valley fever virus, *RYMV* rice yellow mottle virus, *SARS* virus, severe acute respiratory syndrome virus, *SBMV* southern bean mosaic virus, *SIRV Sulfolobus islandicus* rod-shaped virus, *SIV* simian immunodeficiency virus, *SNDV Sulfolobus neozelandicus* droplet-shaped virus, *STMV* satellite tobacco mosaic virus, *STNV* satellite tobacco necrosis virus, *SV40* simian virus 40, *TBEV* tick-borne encephalitis virus, *TBSV* tomato bushy stunt virus, *TMV* tobacco mosaic virus, *TNV* tobacco necrosis virus, *TYMV* turnip yellow mosaic virus, *VSV* vesicular stomatitis virus, *VZV* varicella-zoster virus, *WNPV Wiseana* nuclear polyhedrosis virus

Animal Viruses

Animal viruses are extremely diverse in terms of size, shape, presence or absence of envelope, capsid architecture, type of nucleic acid genome, and specific mechanisms employed to complete the different stages of the viral cycle as required for infection, multiplication and propagation. Some animal viruses are among the structurally simplest viruses known. These include the parvoviruses (*e.g.*, the minute virus of mice, MVM (Fig. 1.1, left) or the adeno-associated viruses, AAV; see Chap. 10). Others are structurally much more complex, such as the adenoviruses, herpesviruses (*e.g.*, HSV-1), retroviruses (*e.g.*, the human immunodeficiency virus type 1 (HIV-1) or the giant mimivirus (see Chap. 11)). The study of the structure, function, biology and pathogenicity of many animal viruses has been or is still hampered by a number of difficulties, including their structural and/or functional complexity, technical problems to grow and/or manipulate them and/or safety issues. However, despite all the difficulties, and mainly because of the biomedical or socioeconomic importance of a large number of animal viruses that are pathogenic for humans or livestock, many of these are among the most intensively studied viruses of all. This is reflected also in the many human and animal viruses used as examples and case studies in most chapters of this book. Many particular aspects related to the molecular biology and structure of many different animal viruses can be found also in the books listed at the end of this chapter [1–6, 9–16].

Bacteriophages

Bacteriophages show widely diverse structures and types of nucleic acid genomes; they have helical or icosahedral capsids, and may or may not include a lipid envelope. Phages range from very small and simple non-enveloped icosahedral viruses (*e.g.*, ϕX174) and long but simple helical viruses (filamentous phages), to large and complex viruses (*e.g.*, tailed DNA phages such as ϕ29; Fig. 1.1, center). Since the origins of Molecular Biology over half a century ago, and continuing through several decades, some bacteriophages were found to present important advantages as model systems for molecular and genetic studies compared to most animal and/or plant viruses. Their advantages include the facility to grow phages and their bacterial hosts in large amounts; the relative structural and functional simplicity and ease of handling of bacterial cells compared to eukaryotic cells; and the possibility to readily obtain certain types of mutant viruses to investigate virus structure and function. These and other reasons led to the intensive use of phages as paradigms for many molecular biology studies on nucleic acid replication, gene expression and their regulation. Several bacteriophages have also provided and continue to provide model systems for studying molecular recognition and self-assembly during the morphogenesis of biomolecular complexes. As a consequence, the structure and function of some bacteriophages, and most stages in their life cycles, are known in great detail (see Chaps. 11, 17). Many particular aspects of the molecular biology of different bacteriophages can be found in several books listed at the end of this chapter. For a book on bacteriophage molecular biology see [7].

Plant Viruses

Most of the very abundant plant viruses are non-enveloped ssRNA(+) viruses with a slender helical capsid or a relatively small icosahedral capsid. The structure and/or function of a few plant viruses, such as the tobacco mosaic virus (TMV; Fig. 1.2 top) have been intensively studied for many decades, in many cases because of some advantages of those viruses as model systems; for example, the facility to grow plant viruses in very large quantities by simply infecting host plants. In addition, studies on many plant viruses have been greatly stimulated because of the economically important diseases they cause in crop plants. Recently, some of the advantages of phages and plant viruses referred to above have led to their preferential use as platforms for many bio/nanotechnological developments (see Chap. 22). However, generally speaking plant viruses have been the subject of fewer studies than animal viruses or bacteriophages, and many stages of the life cycles of the former remain less well known than those of the latter. For a book on plant virus molecular biology and structure see [8].

1.2.5 Classification of Viruses

Comparisons of the sequences of viral genes and genomes have led to the establishment of phylogenetic relationships between many viruses. In addition, comparison of the tertiary structure of viral proteins, especially CPs, has allowed the tentative proposal of distant evolutionary relationships among different viruses, or at least between some of their genes (see a brief description in Chap. 7). It must be noted here that genetic recombination and horizontal gene transfer between even very different, unrelated viruses are frequent. Thus, viruses of widely different origins could share some evolutionarily closely related genes, and of course the proteins these genes encode. It is not yet possible to solidly establish a general phylogenetic-based classification of viruses. In 1973 the International Committee on Taxonomy of Viruses (ICTV) was established, and a general database on viruses was created later (http://www.ncbi.nlm.nih.gov/ICTVdb).

Known viruses have been classified into seven major groups based on the type of nucleic acid genome (*Baltimore classification*). These groups are: I: dsDNA viruses; II: ssDNA viruses; III: dsRNA viruses; IV: ssRNA(+) viruses; V: ssRNA (−) viruses; VI: ssRNA(+) virus whose replication involves the action of a reverse transcriptase (RT) that synthesize DNA from a RNA template; VII: dsDNA viruses whose replication involves the action of an RT (see Table 1.1).

In addition to their classification according to type of nucleic acid genome, viruses have been classified by ICTV in a number of taxonomic groups (*taxons*): viral *order*, *family*, *subfamily*, *genus*, and *species*. The most useful taxon in virus classification is the *family* (see Table 1.1). Viruses in a same family probably share a not too distant evolutionary relationship, as established mainly by comparative sequence analysis. There are currently 94 recognized virus families; only 22 of these families have been grouped in 6 orders (*Caudovirales*, *Herpesvirales*, *Mononegavirales*, *Nidovirales*, *Picornavirales*, *Tymovirales*; see Table 1.1); the remaining families have not been assigned to any order yet. Also, several virus genera have not been assigned to any family yet.

Virus family latin names (italicized) include the suffix –*viridae*. Very frequently, the family english name (non-italicized), which include the suffix –virus (plural - viruses) is used instead of the latin name. However, this may occasionally cause confusion on whether one is referring to a viral family or genus, unless this point is specified. Virus species are usually referred to by their english names, and most have been given standard abbreviations. Most bacteriophages are named according to a code of latin letters, greek letters and/or numbers.

In this book, viruses will be generally identified by type of nucleic acid, by family (latin or english name) and/or by species. For example, in different chapters repeated mention is made to the human immunodeficiency virus type 1 (HIV-1). HIV-1 is a virus species of the *Retroviridae* (retrovirus family), which belongs to a group of ssRNA(+) viruses whose replication involves a RT (group VI). A list of