Lecture 1

Introduction to virology and Virus architecture

INSTRUCTOR
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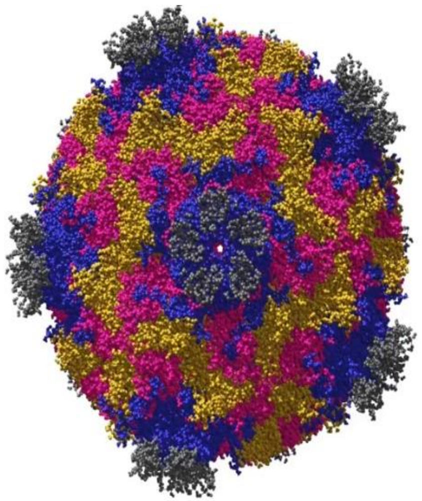
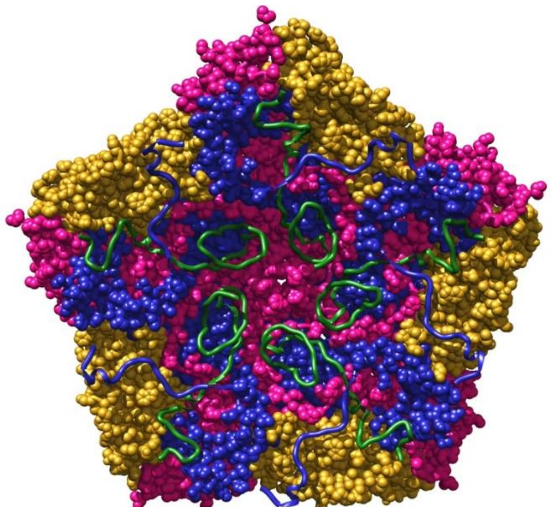
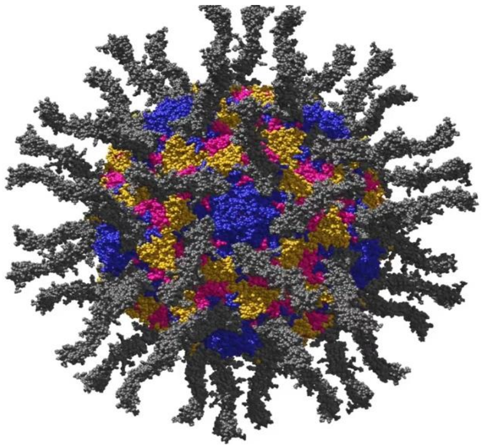
This lecture deals with
General Properties of Viruses: History, Structure, Symmetries of Viruses



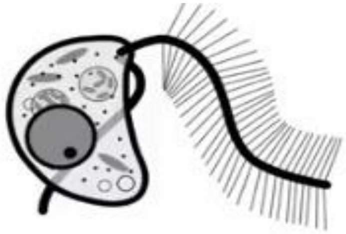




We live and prosper in a cloud of viruses

- We live and prosper in a cloud of viruses
- Viruses infect all living things
- We regularly eat and breathe billions of virus particles
- We carry viral genomes as part of our own genetic material
- Genomes are actually also the most widespread everywhere

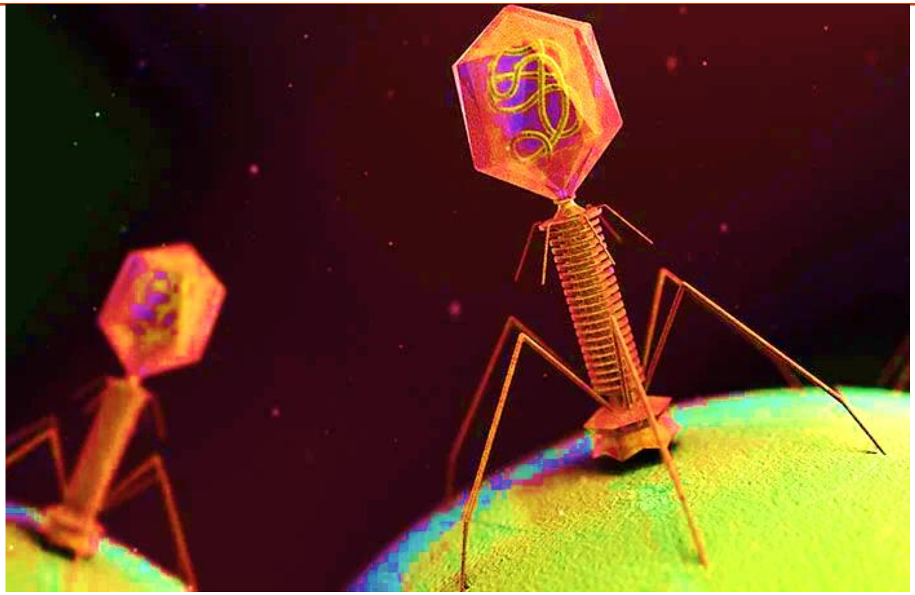


1. **Viruses are all around us, comprising an enormous proportion of our environment, in both number and total mass**
2. **All living things encounter billions of virus particles every day. For example, they enter our lungs in the 6 liters of air each of us inhales every minute;**
3. **Human and animals bodies are reservoirs for viruses that reside in respiratory, gastrointestinal, and urogenital tracts they enter digestive systems with the food ; and they are transferred to eyes, mouths, and other points of entry from the surfaces that touched.**

❑ Viruses are all around us

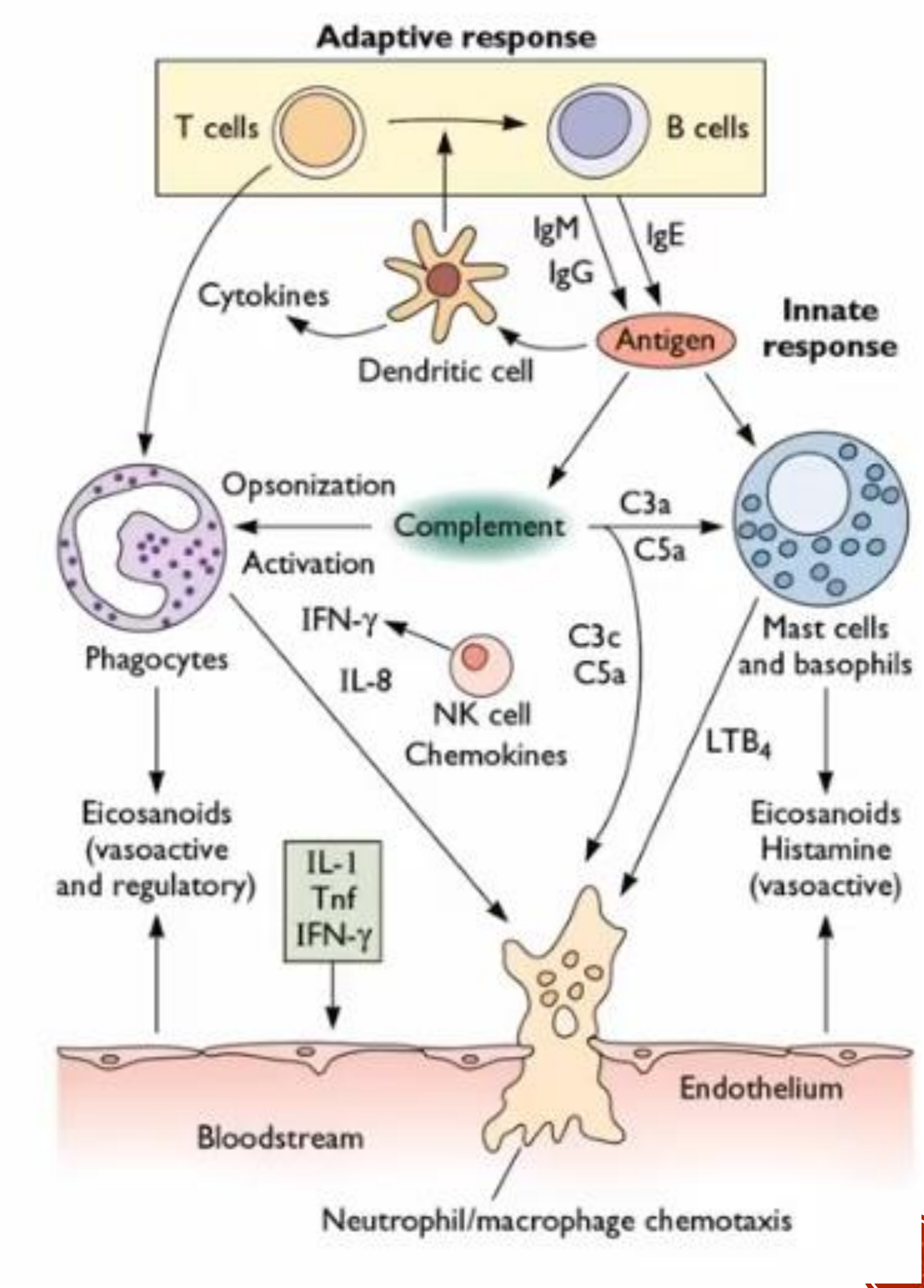
- **The number of viruses on Earth is staggering and amazing**
- **More than 10^{30} bacteriophage particles in the world's waters!**
- **A bacteriophage particle weighs about a femtogram (10^{-15}grams)**
- **10^{30}X 10^{-15}= the biomass on the planet of BACTERIAL VIRUSES ALONE exceeds the biomass of elephants by more than 1000-fold!**
- **The length of a head to tail line 10^{30}phages is 100 million light years!**
- **Viruses are catalysts for biogeochemical cycling**
- **More viruses in a liter of coastal seawater than people on Earth**



❑ Viruses Can Be Beneficial

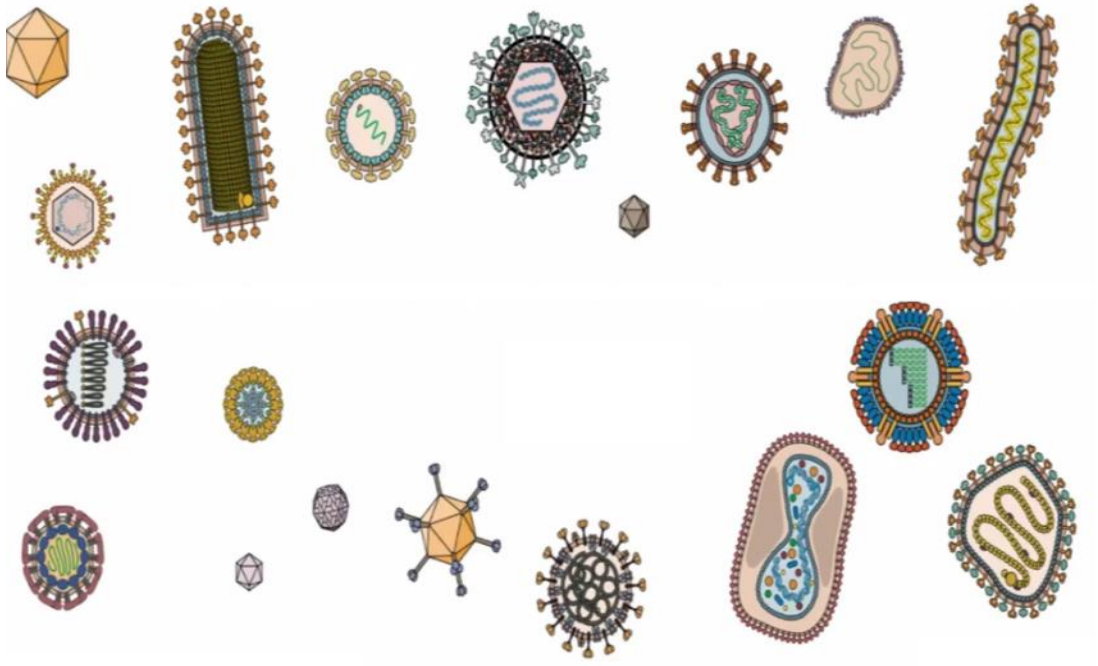
Viruses are not solely pathogenic nuisances; they can be beneficial., keep our immune responses activated and alert, and can be used as molecular flashlights to illuminate cellular processes.
Viruses contribute to ecological homeostasis
In marine ecology, where virus particles are the most abundant biological entities Viral infections in the ocean kill 20 to 40% of marine microbes daily, converting these living organisms into particulate matter, and in so doing release essential nutrients that supply phytoplankton at the bottom of the ocean's food chain, as well as carbon dioxide and other gases that affect the climate of the earth.

- Keep our immune responses activated and alert

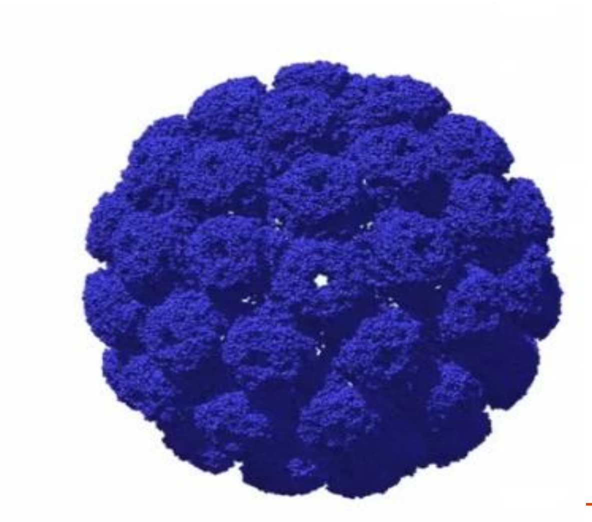


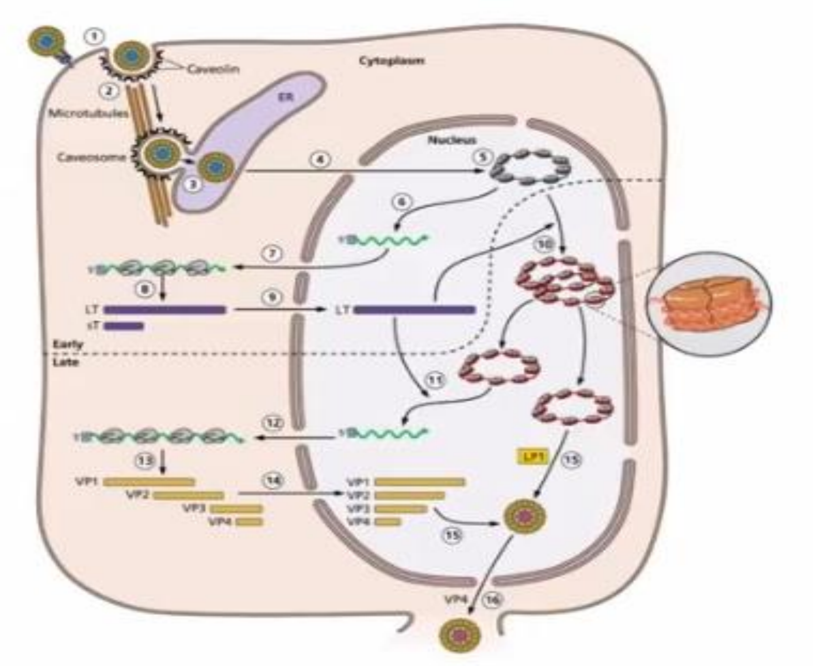
What is a virus?

An infectious, obligate intracellular parasite comprising genetic material (DNA or RNA), often surrounded by a protein coat, sometimes a membrane



Are viruses living entities





Virion (infectious particle) **infected cell**

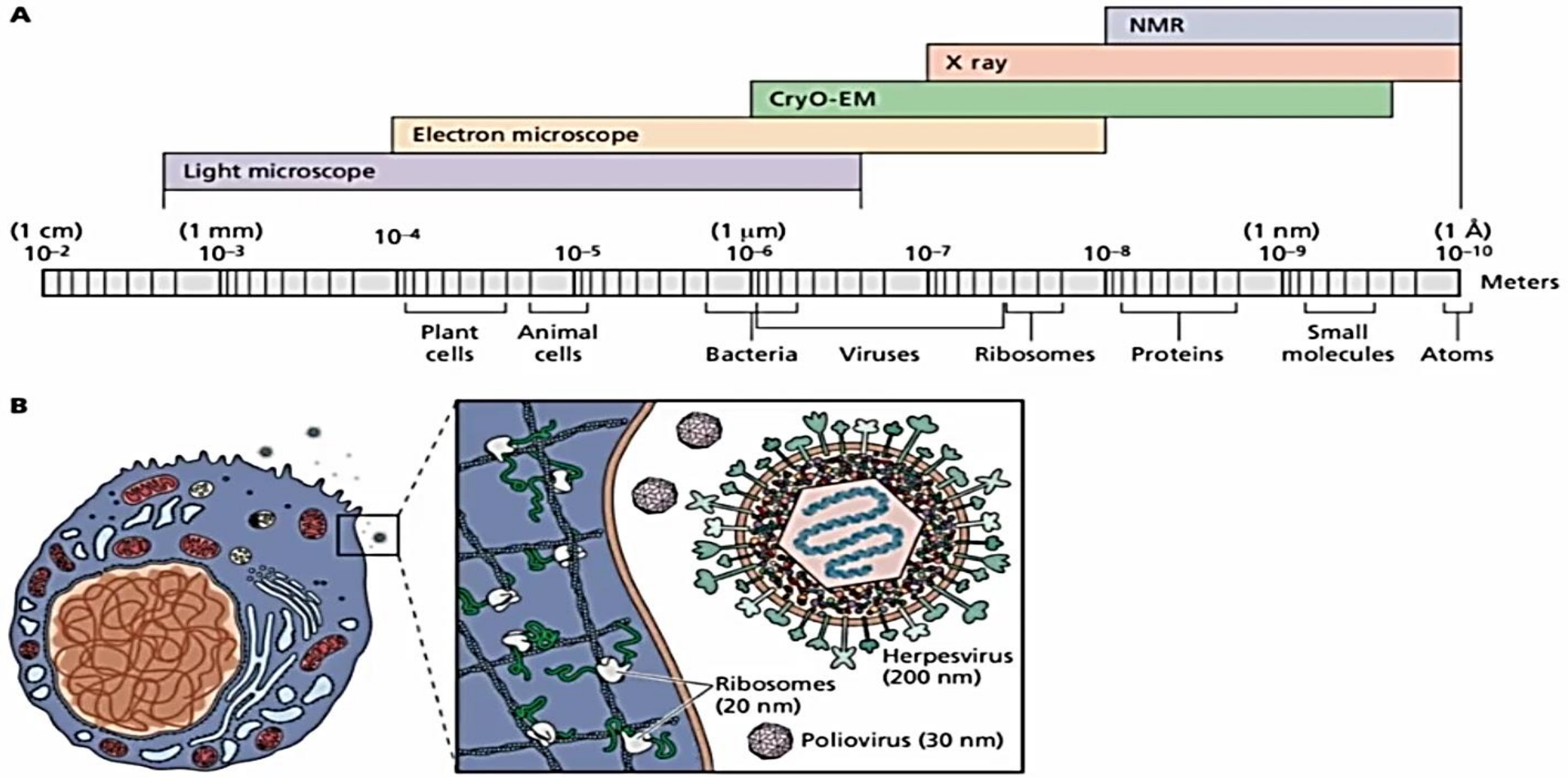
an inanimate(stationary) phase

a multiplying phase in an infected cell

Some researchers have promoted the idea that viruses are organisms and that the inanimate virions may be viewed as “spores” that come “alive” in cells, or in factories within cells

Viruses are very small

- The units commonly used in descriptions of virus particles or their components are the nanometer (nm 10^{-9} m]) and the angstrom A (10^{-10}]m])
- Viruses cannot be seen by ordinary microscope, but only by Electron Microscope (EM).

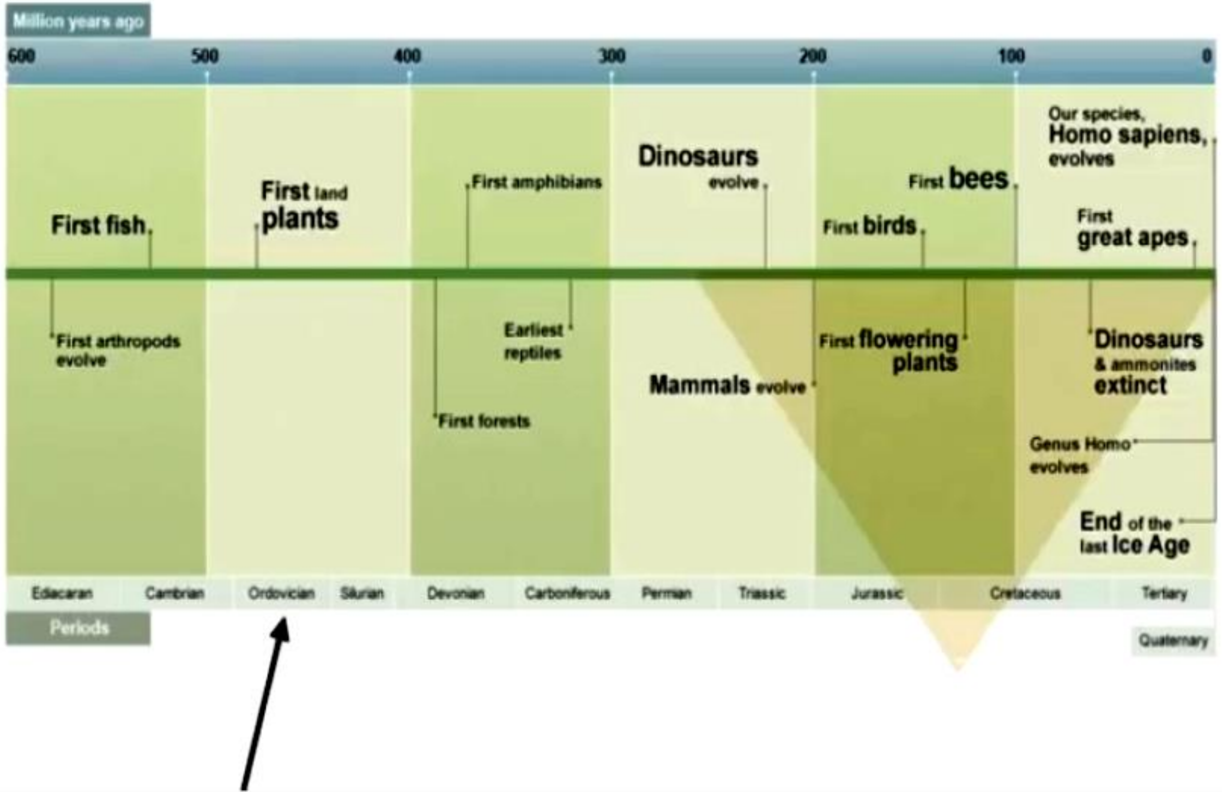


Cryogenic electron microscopy (cryo-EM) — Nuclear magnetic resonance (NMR) is Multi-dimensional NMR spectroscopy

How old are viruses?

Estimates of molecular evolution suggest marine origin of some retroviruses >450 Ma, Ordovician period
The Ordovician Period lasted almost 45 million years, beginning 488.3 million years ago and ending 443.7 million years ago.
Likely originated billions of years ago - before cells

Nobu Tamura (http://spinops.blogspot.com)



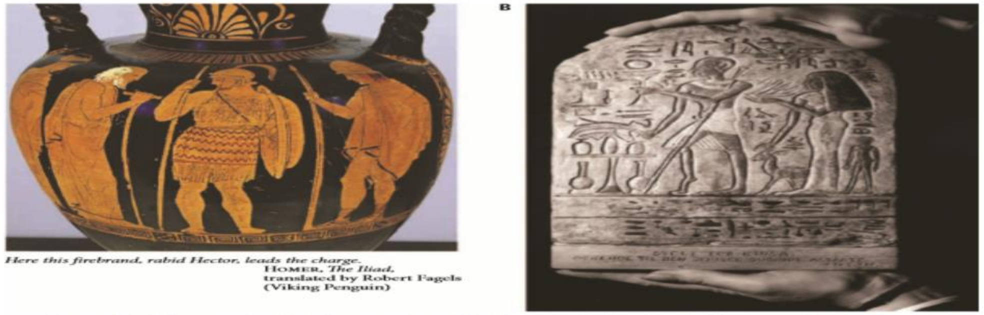
GENERAL PROPERTIES OF VIRUSES

HISTORY: Generally the information regarding viruses are only a century old. Most of the information regarding viruses were obtained after the development of electron microscope (EM) and the techniques of negative staining in EM and x-ray crystallography.

Ancient references to viral diseases

- **The Greek poet Homer characterizes one of his characters Hector as rabid in *The Iliad.***
- **The Mesopotamian law before 1000 B.C describes the dog owner's responsibility pertaining to rabid dogs.**
- **In Egyptian hieroglyphs, one of the characteristic squeal of polio virus infection – withered leg has been depicted.**
- **The spread of small pox, which was common in Ganges river basin into continental Europe has been mentioned in old records of 5 century B.C.**
- **Other common viral infections prevalent in those days include yellow fever, influenza and mumps.**
- **The control measures of small pox (variolation) that include irrational approaches of Indians and Chinese, which was fine tuned by Lady Mary Wortley Montague in Asia Minor during 18th century.**

A B



Here this firebrand, rabid Hector, leads the charge.
HOMER, *The Iliad*,
translated by Robert Fagels
(Viking Penguin)

Figure 1.1 References to viral diseases abound in the ancient literature. **(A)** An image of Hector from an ancient Greek vase. Courtesy of the University of Pennsylvania Museum (object 30-44-4). **(B)** An Egyptian stele, or stone tablet, from the 18th dynasty (1580–1350 B.C.) depicting a man with a withered leg and the "drop foot" syndrome characteristic of polio. Panel B is reprinted from W. Biddle, *A Field Guide to Germs* (Henry Holt and Co., LLC, New York, NY, 1995; © 1995 by Wayne Biddle), with permission from the publisher.

In 1790, Edward Jenner standardized the protection method against small pox using cowpox virus, which was termed as vaccination.
In 1885, Louis Pasteur developed an inactivated vaccine against rabies, which was found successful in post exposure treatment of rabies) “Every virus is a microbe

Virus discovery - filterable viruses

<u>First report of viruses: In 1892, Russian scientis Dimitrii Ivanowsky attributed the causative agent of tobacco mosaic disease to an agent that is filterable in porcelain filters.</u>

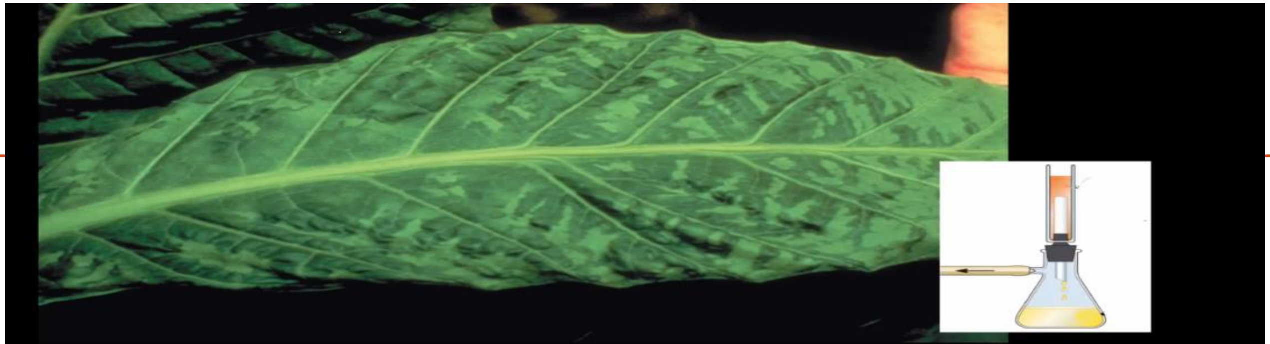
Martinus Beijerinck also made the same observation seven year later. He termed the causative agent of tobacco mosaic disease as C*ontagium vivium fluidum* with clear idea about its distinct physical properties. This term evolved to **virus,** which in Latin means poison.

Tobacco mosaic virus. Ivanoski reported in 1892 that extracts from infected leaves were still infectious after filtration through a Chamberland filter-candle

Beijerinck, in 1898, was the first to call 'virus',

Ivanovski and Beijerinck brought unequal but crucial and complementary contributions to the discovery of viruses

Discoveries made on Tobacco mosaic virus have stood **<u>out as milestones of virology history.</u>**



In 1898, Friedrich **Loeffler and Paul Frosch** attributed the causative agent of foot and mouth disease to an agent that is filterable

- **Key concept: agents not only small, but replicate only in the host, not in broth**
- **0.2 micron filters (µm, one millionth of a meter) nm 10^{-9} m**
- **Still thought to be liquids**

Filtration studies showed that virus particles (virions) range from about the size of the smallest unicellular microorganisms (300 nm) down to objects little bigger than the largest protein molecules (20 nm).

In 1901, the **Reeds Commission** gave details of yellow fever virus, which was the first human virus to be identified.

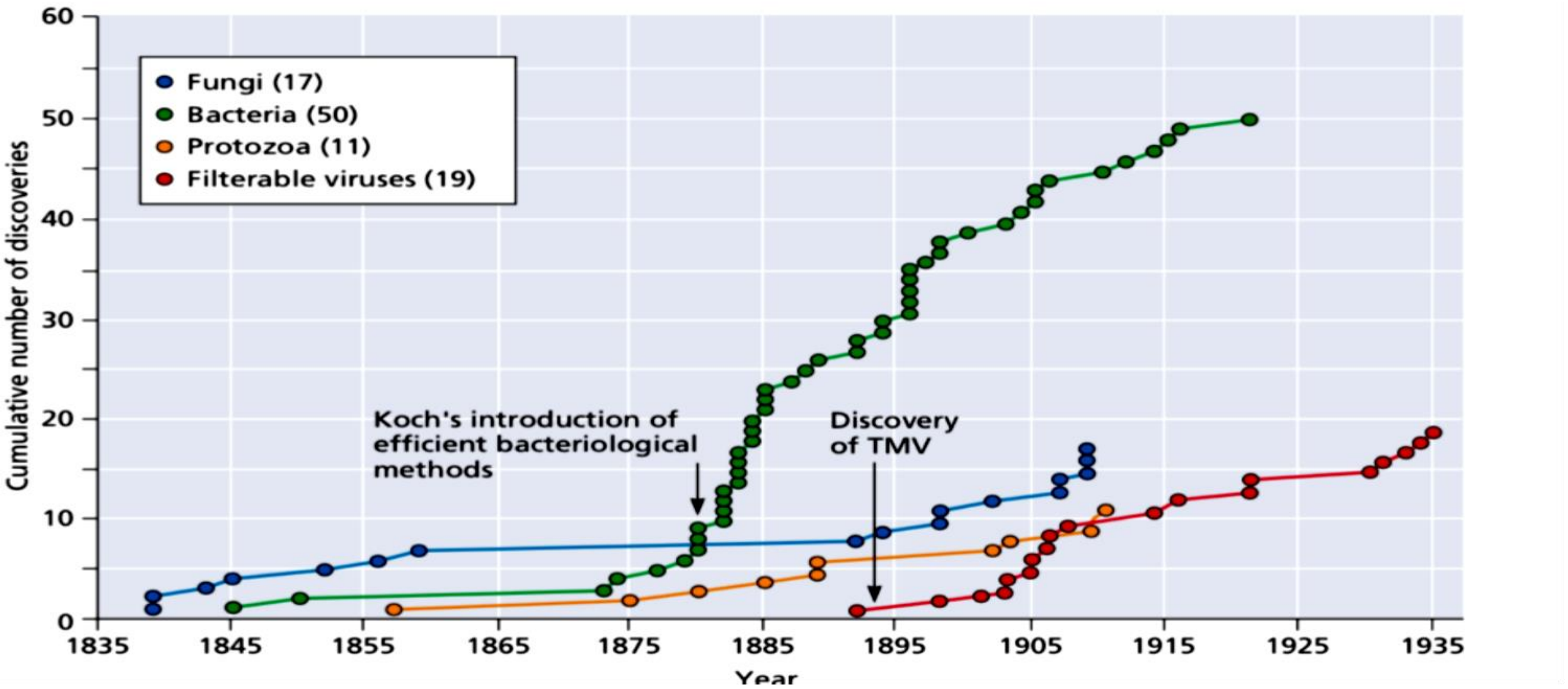
In 1915 and 1917 Frederick Twort and Felix d'Herelle respectively described viruses affecting bacteria, which were described as bacteriophages.

Filterable virus discovery

- **1901 - first human virus, yellow fever virus**
- **1903 - rabies virus**
- **1906 - variola virus**
- **1908 - chicken leukemia virus, poliovirus**
- **1911 - Rous sarcoma virus**
- **1915 – 1917 bacteriophages**
- **1933 - influenza virus**

1939 - Viruses are not liquids!

- Helmut Ruska built first electron microscope 1933
- First EM of bacteriophage, 1939



TMV (Tobacco Mosaic Virus) by Dmitry Ivanovsky, a Russian microbiologist 1887 and 1890

DEFINITION:

Viruses are defined as small ultra-microscopic obligate parasites, which have either DNA or RNA as genetic material. They replicate using host cell machinery and produce progeny virion by *de novo* synthesis. The spread of virus infection from one host to another is through progeny virions.

The term virion refers to whole acellular viral particles.

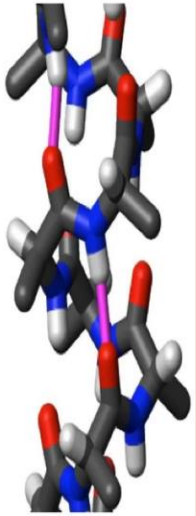
A virion possesses nucleic acid contained in protective coat called capsid. The complete infectious virus particle is also referred as virion.

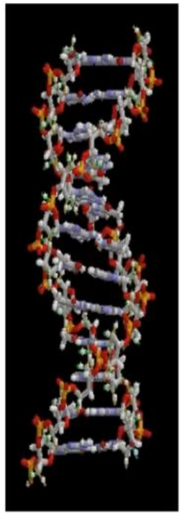
TYPES OF VIRUSES: The viruses known are broadly grouped under animal viruses, plant viruses, insect viruses and bacterial. The correct classification of viruses will be dealt separately.

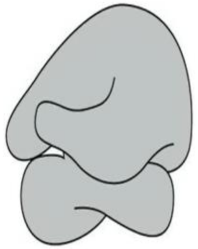
STRUCTURE OF VIRUSES: Viruses are extremely small particles comprises of just proteins and nucleic acid. The largest giant virus, named "mamavirus are about size (>0.7 micrometers) in size, whereas the smallest known viruses are about 30nm.

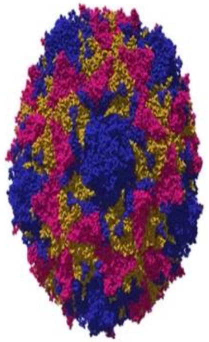
Putting virus particles into perspective

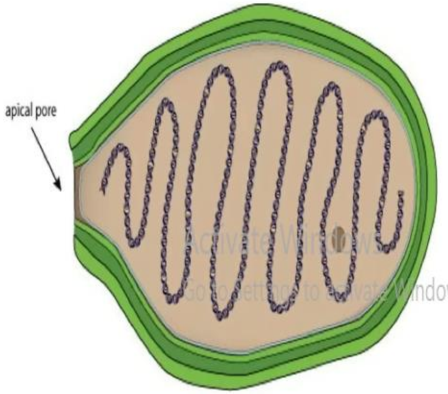
- Nanometer: 10^{-9} meters = 10 Å = 0.001 microns
- Alpha helix in protein: 1 nm diameter
- DNA: 2 nm diameter
- Ribosome: 20 nm diameter
- Poliovirus: 30 nm
- Pandoravirus: 1000 nm











❑ **Meter**
10^{0} m
1 m

❑ **Centimeter**
10^{-2} m
0.01 m
1/100 m
hundreth of a meter

❑ **Millimeter**
10^{-3} m
0.001 m
1/1,000 m
thousandth of a meter

❑ **Micrometer**
10^{-6} m
0.000001 m
1/1,000,000 m
millionth of a meter

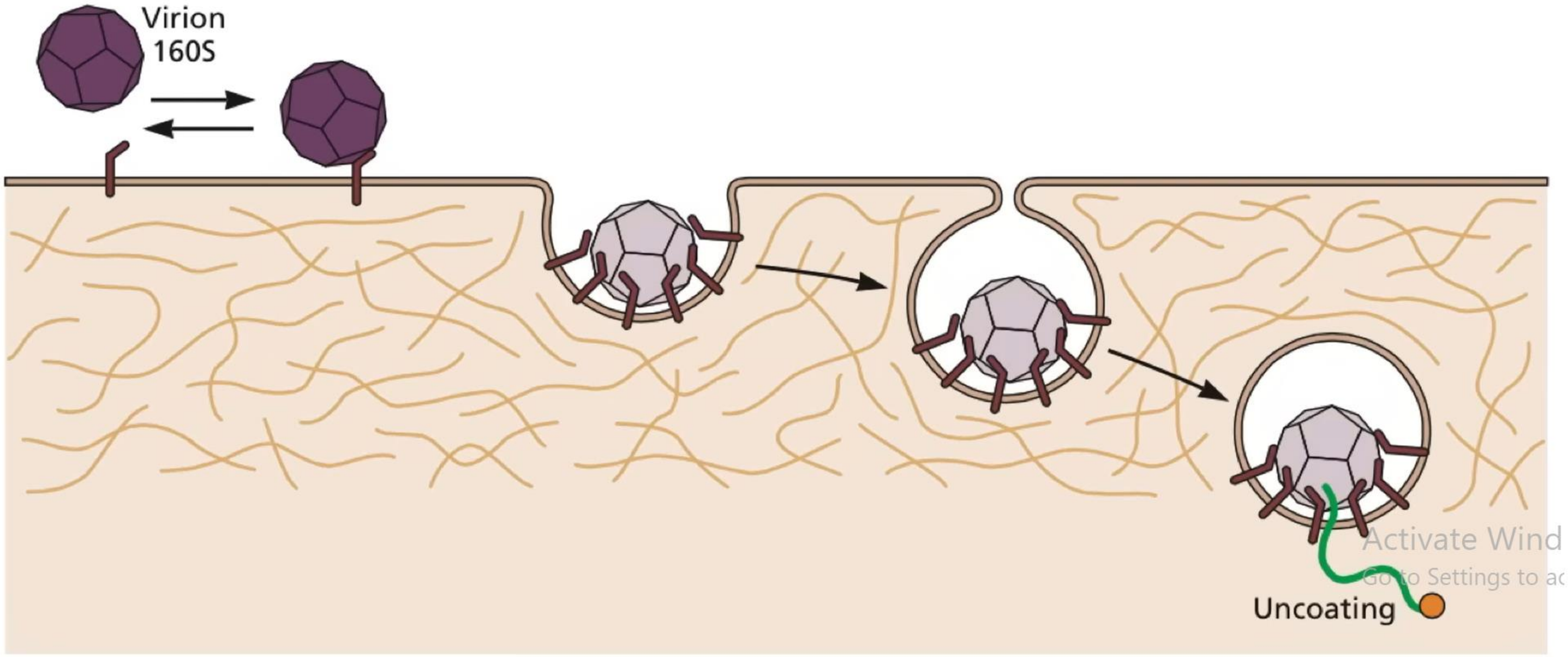
❑ **Nanometer**
10^{-9} m
0.000000001 m
1/1,000,000,000 m
billionth of a meter

❑ **Angstrom**
10^{-10} m
0.0000000001 m
1/10,000,000,000 m
ten billionth of a meter

❑ **Picometer**
10^{-12} m
0.000000000001 m
1/1,000,000,000,000 m

Virus particles are metastable

- Must protect the genome (stable)
- Must come apart on infection (unstable)



❑ STRUCTURE

- **The viral structures are studied by electron microscopic techniques like negative staining, freeze etching and shadowing. The method that is more commonly used in X ray crystallography, of late nuclear magnetic resonance (NMR) imaging is used to study structural details.**
- **Viruses are comprised of two important components a protein capsid covering the nucleic acid. Not all viruses have envelopes, some viruses possess a lipid envelope**
- **Design of structure :**
  - **To protect the viral NA from variety of agents and environmental conditions**
  - **Extreme temptur and pH**
  - **Chemical substances, detergents**
  - **Prevents entry of extraneous agents**

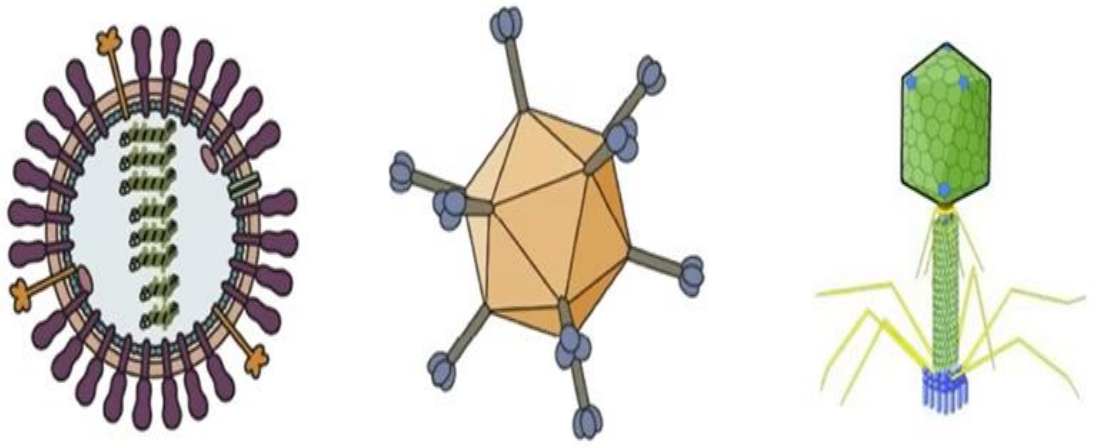
Functions of structural proteins of virus

Protection of the genome

1. Assembly of a stable protective protein shell
2. Specific recognition and packaging of the nucleic genome
3. Interaction with host cell membranes to form the envelope

Delivery of the genome

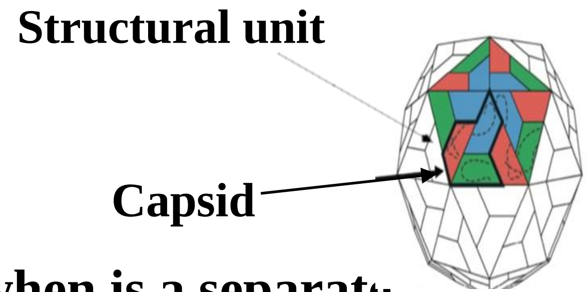
1. Bind host cell receptors
2. Uncoating of the genome
3. Transport of genome to the appropriate site



STRUCTURE COMPONENTS

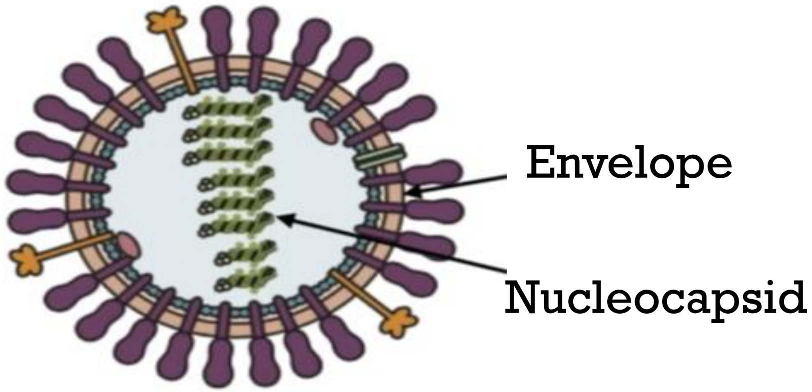
1. **Subunit –single folded polypeptides chain**

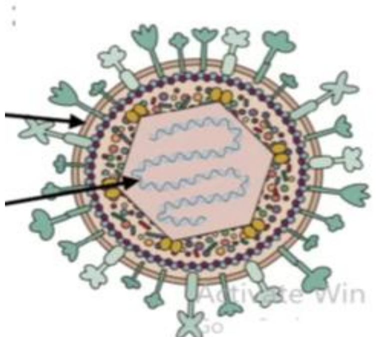
2. **Structural unit (protomer, asymmetric unit)-Unit from which capsids or nucleocapsides are built ; one or more subunits**
3. **Capsid (capsa =latin , box)-Protein shell surrounding genome**



4. **Envelope(viral memberane)-Host cell –derived lipid bilayer**

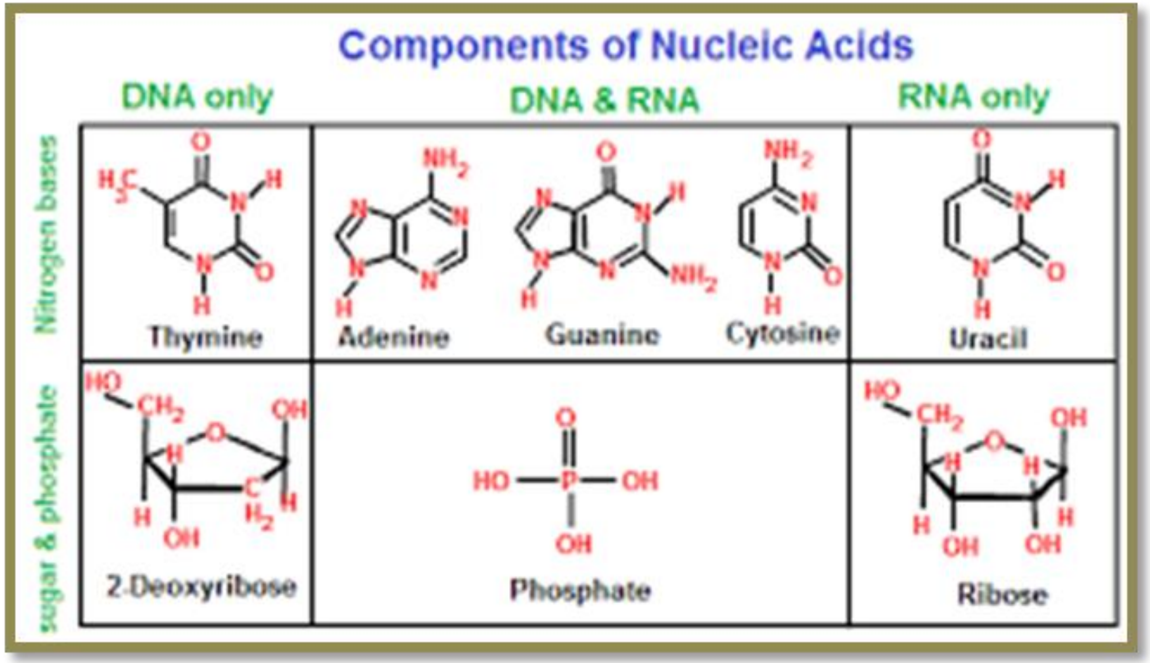
5. **Nucleocapsid (core)-Nucleic acid –protein assembly within particle ; used when is a separate substructure**





VIRAL NUCLEIC ACID:

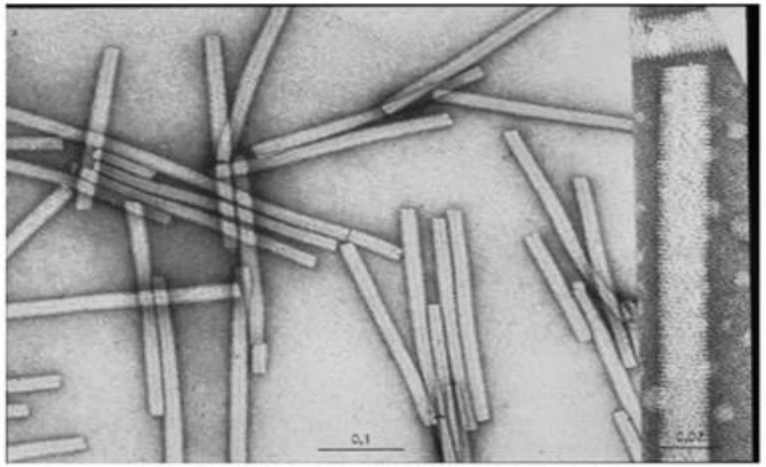
The genetic material of viruses are made up of only one type of nucleic acid ie. either DNA or RNA but never composed of both. The nucleic acid both DNA and RNA may be present either as single stranded or double stranded. The nucleic acid (RNA) may also present either as a single molecule or in segments.

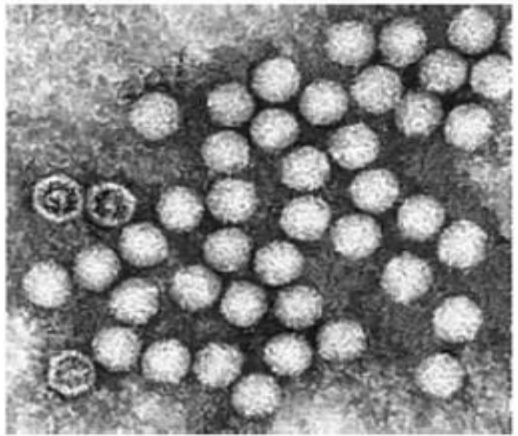


Forming viral particles: Symmetry is essential

Watson and Crick did more than discover DNA structure, their significant contribution to virology Distinguished that most virus particles were **<u>spherical or rod shaped.</u>** Virus genomes are small particles would be built with many copies of a few proteins

<u>Identical protein subunits of rod –shaped viruses has helical symmetry, while</u>
<u>Icosahedral symmetry for round viruses.</u>





The symmetry rules

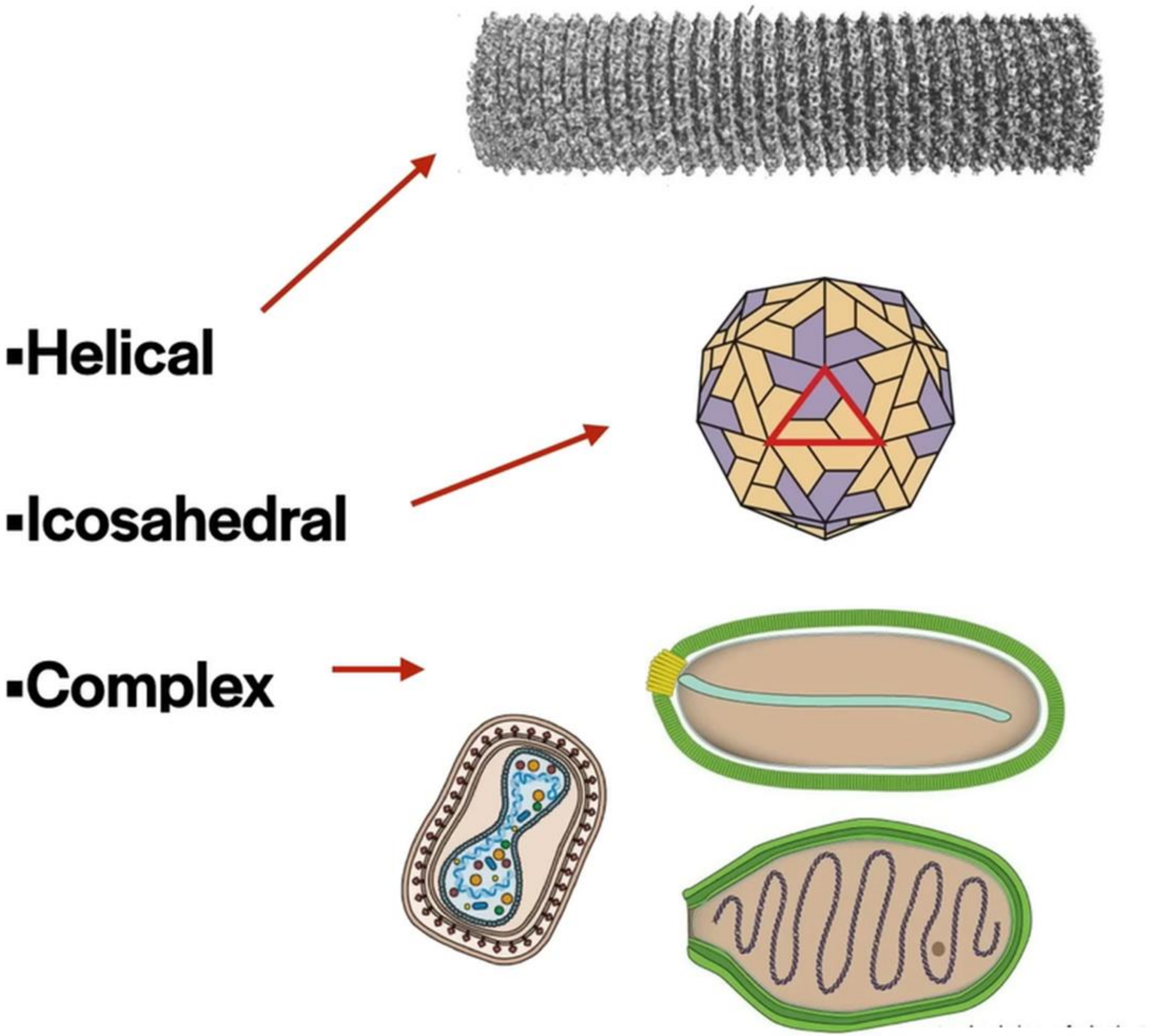
- ❑ Each subunit has identical bonding contacts with its neighbors

Repeated interaction of chemically complementary surfaces at the subunit interfaces naturally leads to a symmetric arrangement .

- ❑ These bonding contacts are usually non-covalent

Reversible ; error-free assembly

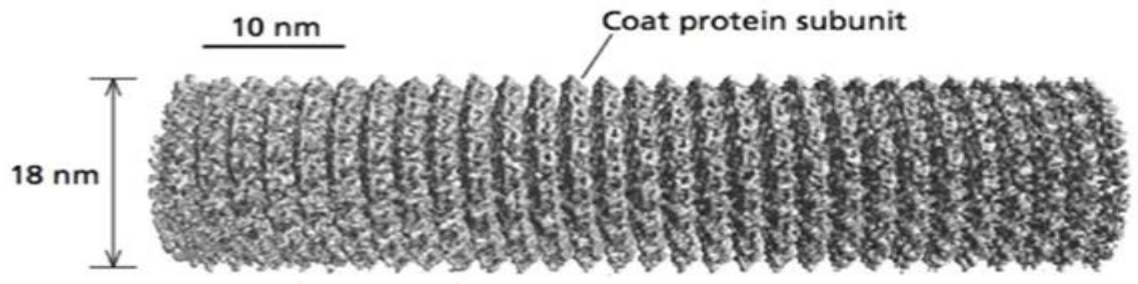
- **Three different forms (symmetries)**

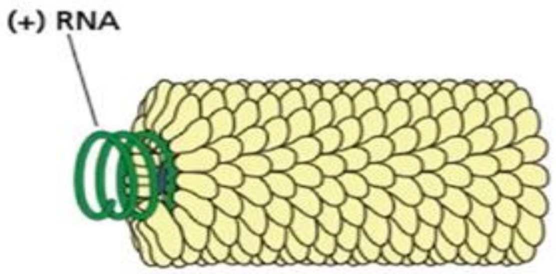


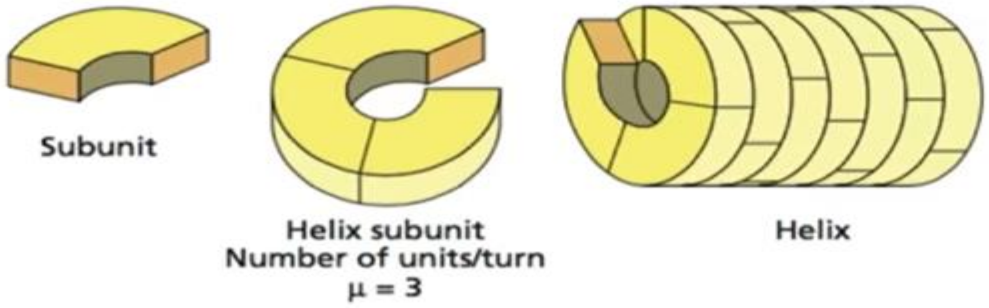
A. Helical symmetry:

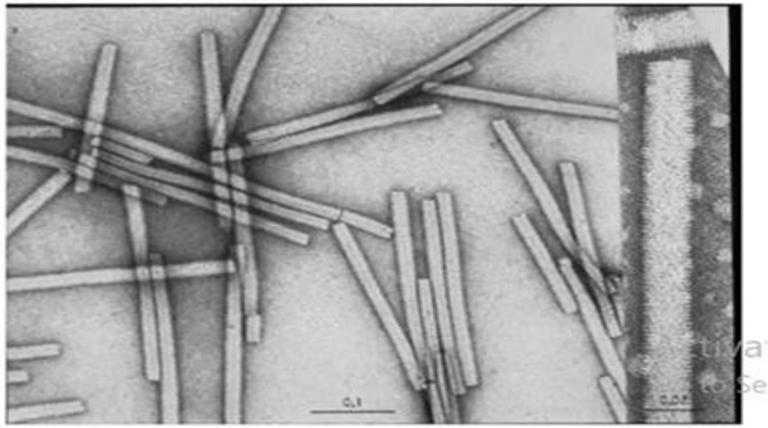
In this arrangement, coat protein molecules engage in identical , equivalent interactions with one another and with the viral genome to allow construction of a large , stable structure from a single protein

The cylinder or helical structure as stacking of multiple discs, with the virus genome coated by the protein shell or contained in the hollow center of the cylinder.



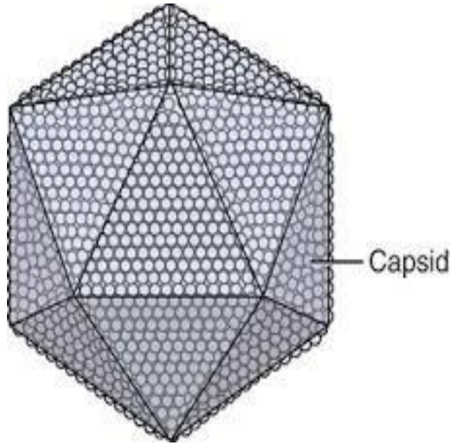


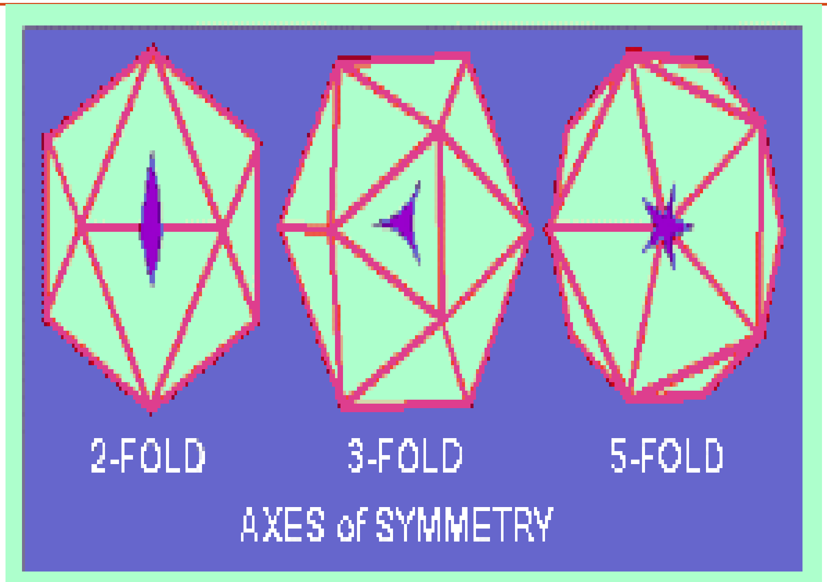


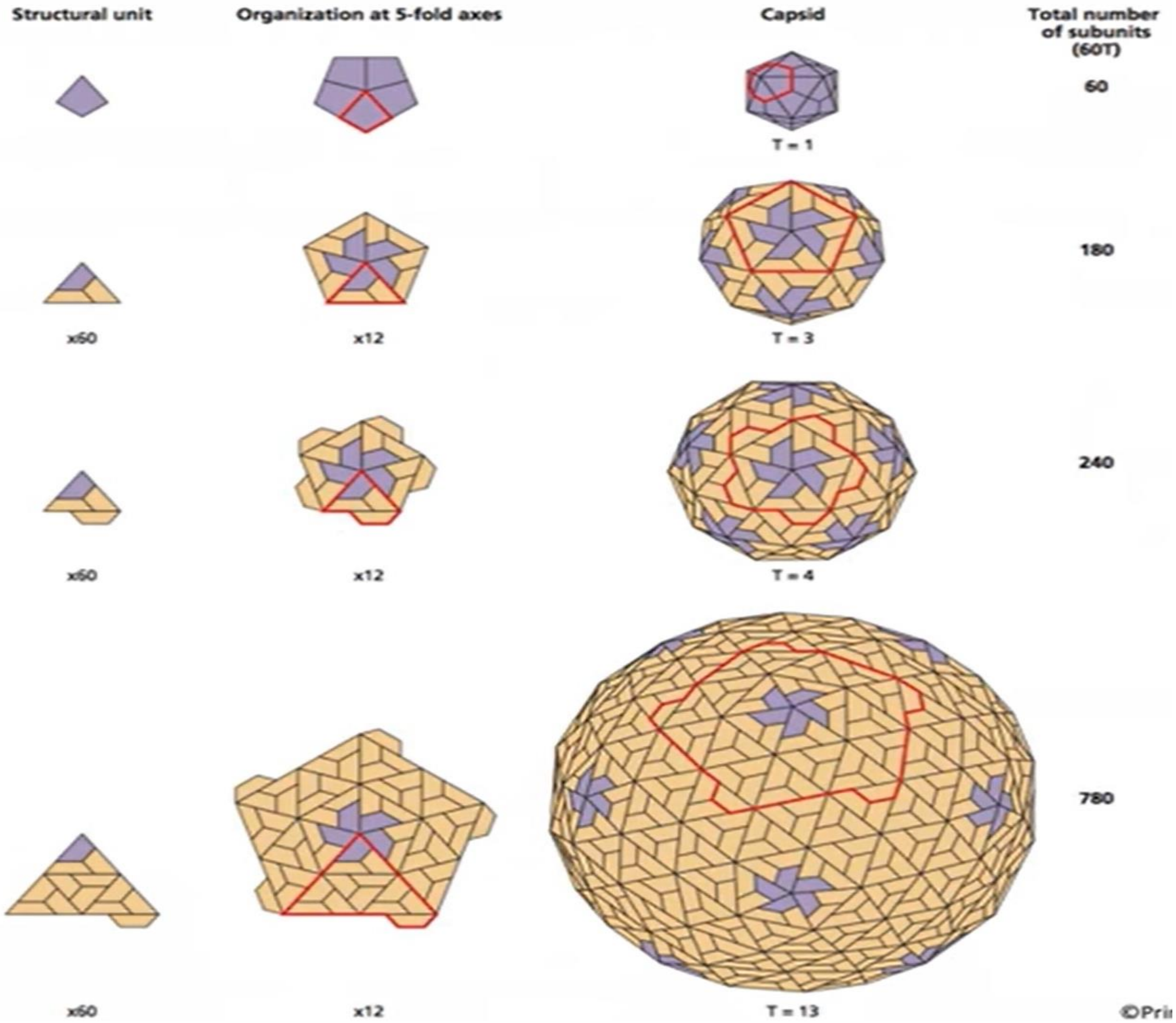


B. Cubical symmetry

- **It is also referred as icosahedral symmetry.**
- **In this arrangement, the nucleic acids are arranged inside a shell, which is in the shape of an icosahedran.**
- **Icosahedran is a geometrical figure with 12 vertices (corners) and 20 identical facets (faces). Each facet is an equilateral triangle. There are six 5-fold axes of symmetry passing through the vertices, ten 3-fold axes extending through each face and fifteen 2-fold axes passing through the edges of an icosahedron.**
- **Icosahedral symmetry requires definite numbers of structure units to complete a shell.**
- **A virus with icosahedral symmetry (5X12:3X20:2X30 symmetry) requires a multiple of 60 subunits to cover the surface completely.**

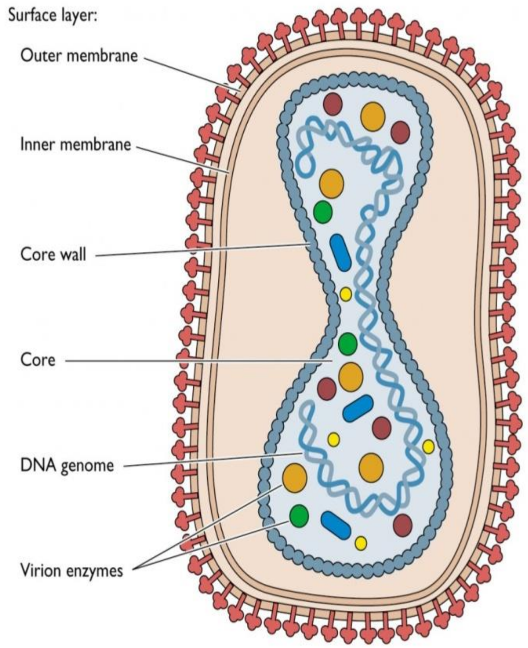


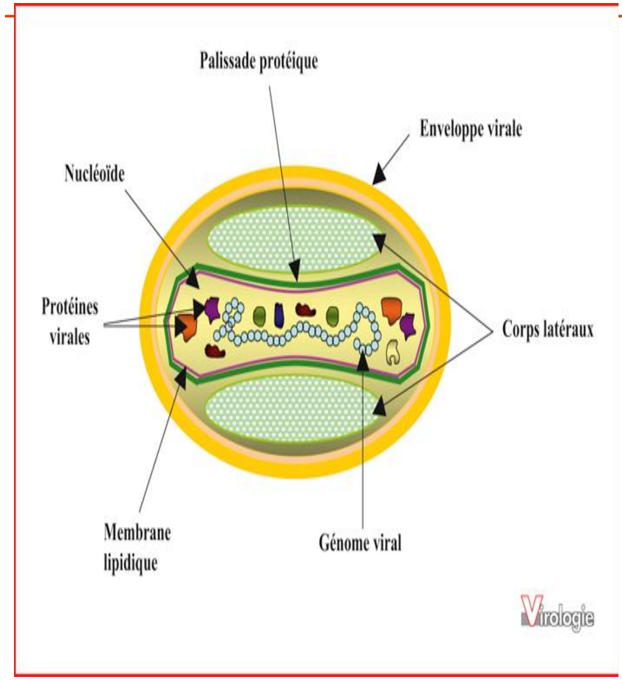



Structural unit
Organization at 5-fold axes
Capsid
Total number of subunits (60T)
T = 1
60
x60
x12
T = 3
180
x60
x12
T = 4
240
x60
x12
T = 13
780
©Pri

C. Complex symmetry:

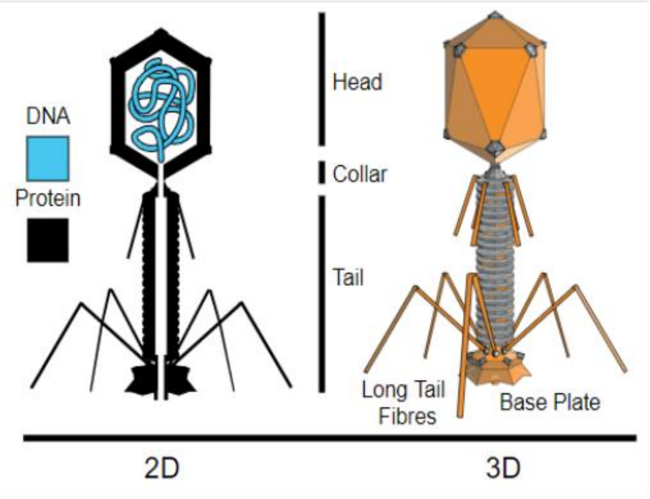
Viruses have many structural shapes, often falling into certain categories. While some have symmetrical shapes, viruses with asymmetrical structures are referred to as "complex. " These viruses possess a capsid that is neither purely helical nor purely icosahedral, and may possess extra structures such as protein tails or a complex outer walls.
pox viruses have exceptional and their ultra structure appears to be complex. Some pox viruses are brick- shaped, while others are ovoid and the DNA is contained in nucleoid, shaped like a biconcave disc and surrounded by one or more membranes.





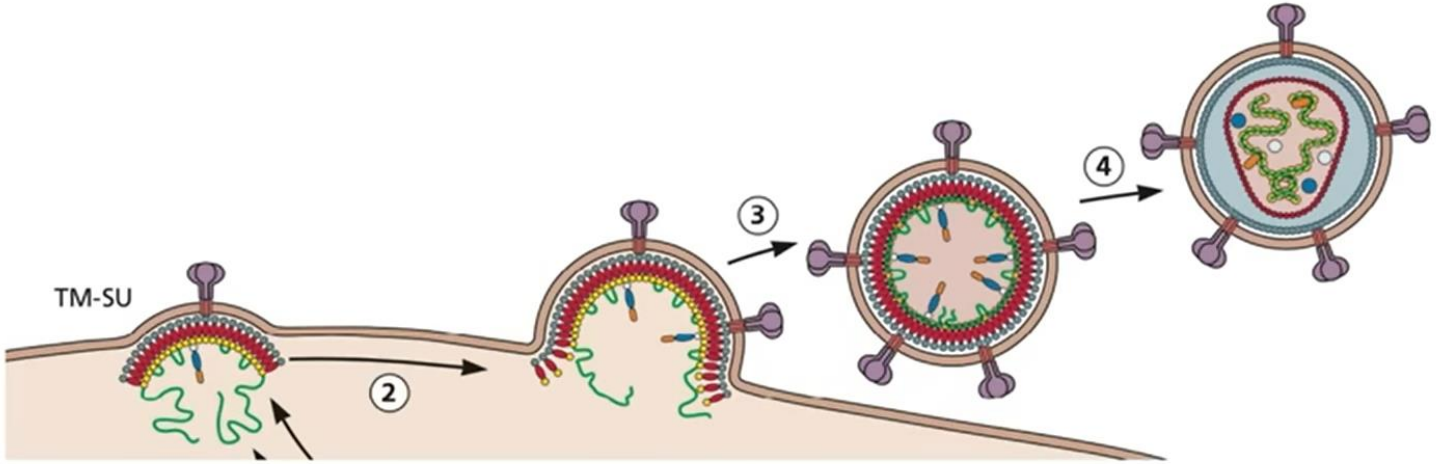
Complex symmetry:

Some bacteriophages, such as Enterobacteria phage T4, have a complex structure consisting of an icosahedral head bound to a helical tail, which may have a hexagonal base plate with protruding protein tail fibers. This tail structure acts like a molecular syringe, attaching to the bacterial host and then injecting the viral genome into the cell.



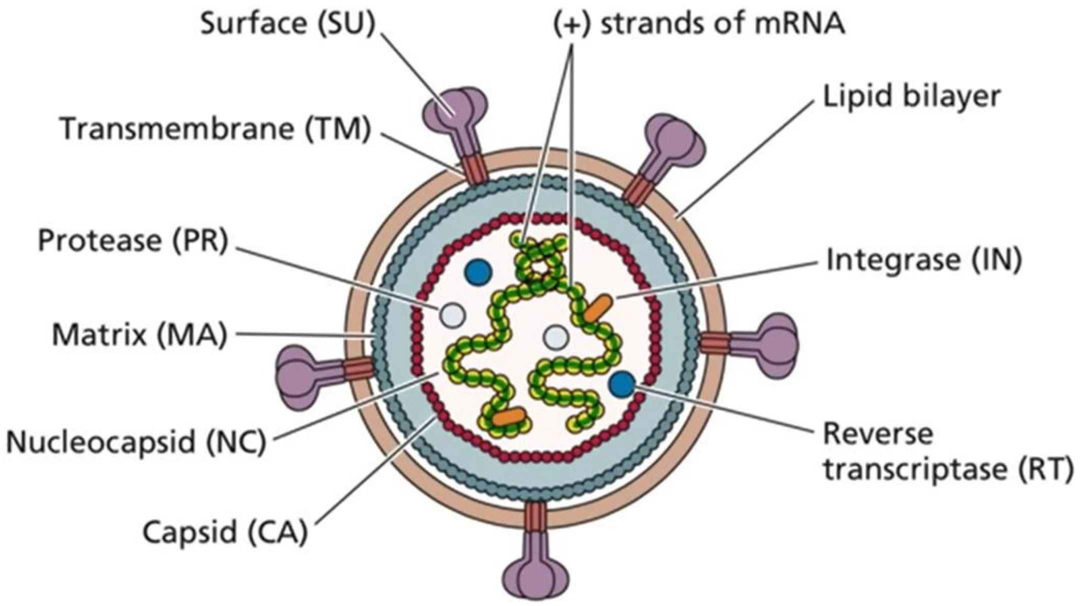
Capsids can be covered by host membranes: enveloped virions

- Envelope is a lipid bilayer derived from host cell
  - Viral genome does not encode lipid synthetic machinery
- Envelope acquired by budding of nucleocapsid through a cellular membrane
  - Can be any cell membrane, but is virus-specific
- Nucleocapsids inside the envelope may have helical or icosahedral symmetry



Other components of the virus particle

- Enzymes
  - polymerases, integrases, associated proteins
  - proteases
  - poly(A) polymerase
  - capping enzymes
  - topoisomerase



- Activators, mRNA degradation, required for efficient infection, mRNAs
- Cellular components - histones, tRNAs, myristate, lipid, cyclophilin A, and many more

The definitive properties of viruses are summarized as follows:

- **A virus is an infectious, obligate intracellular parasite.**
- **The viral genome comprises DNA or RNA.**
- **The viral genome directs the synthesis of viral components by cellular systems within an appropriate host cell.**
- **Infectious progeny virus particles, called virions , are formed by *de novo* self-assembly from newly synthesized components.**
- **A progeny virion assembled during the infectious cycle is the vehicle for transmission of the viral genome to the next host cell or organism, where its disassembly initiates the next infectious cycle**