

Viral Genomes

I. Genomes of DNA and RNA Viruses

DNA and RNA viruses differ profoundly in the nature of their genetic material, their replication sites, and their enzymatic strategies. However, they follow a common principle: producing the proteins required for replication and ensuring the transmission of their genome.

1. DNA Viruses: Nuclear replication and cellular dependence

Most DNA viruses replicate inside the nucleus of the host cell, where they use host enzymes, particularly DNA polymerases. This enzymatic dependence makes their replication cycle closely linked to the cellular cycle, especially the S phase, during which the cell replicates its own DNA. Therefore, when the host cell is not undergoing division, the virus may be unable to efficiently replicate its genome and may mainly produce viral proteins. Some viruses, such as adenoviruses and papillomaviruses, overcome this limitation by producing cell-cycle-inducing proteins capable of forcing the host cell to enter the S phase. This mechanism may contribute to cellular transformation and tumor development. Poxviruses, however, represent a remarkable exception: they replicate in the cytoplasm because they encode their own transcription and replication enzymes.

2. RNA Viruses:

RNA viruses are characterized by highly variable genomes and generally higher mutation rates compared with DNA viruses. Their genome size is often limited because their RNA-dependent RNA polymerases (RdRps) usually lack proofreading activity. This low replication fidelity explains their rapid evolution and high genetic variability. However, it also constrains genome size, resulting in compact genomes encoding a limited number of proteins. Most RNA viruses replicate in the cytoplasm because animal cells do not possess RNA-dependent RNA polymerases. Therefore, viral polymerases are essential for copying RNA genomes and producing viral messenger RNAs. However, some RNA viruses, particularly Orthomyxoviruses, replicate partly in the nucleus

Positive-sense and negative-sense RNA genomes

Positive-sense RNA viruses (+ssRNA): Positive-sense RNA genomes can directly function as messenger RNA molecules and are immediately translated after infection.

Negative-sense RNA viruses (–ssRNA): Negative-sense RNA genomes cannot be directly translated. They must first be converted into positive-sense RNA by the viral RNA-dependent RNA polymerase already packaged inside the virion.

This enzyme performs multiple functions:

- synthesis of complementary RNA strands for genome replication;
- transcription of viral mRNAs required for protein production.

Genome organization and expression strategies

- **Non-segmented RNA viruses:** Non-segmented RNA viruses generally produce a single polyprotein that is subsequently cleaved into several functional proteins. Example: Picornaviruses.
- **Segmented RNA viruses:** Segmented RNA viruses possess several independent RNA molecules, each encoding one or more viral proteins. Examples: Orthomyxoviruses and Reoviruses. Genome segmentation facilitates genetic diversity through reassortment, contributing to the emergence of new viral variants.

II. Virus–Host coevolution : Virus–host coevolution is a dynamic evolutionary process in which both partners develop strategies to gain an advantage over the other.

Host defenses

Infected organisms (animals, humans, and other hosts) have evolved antiviral proteins that limit viral multiplication. A key example is the tetherin protein (also called BST-2), which is produced by host cells in response to viral infection, particularly under the effect of interferons. This protein acts as a physical “tether”: it attaches to the cell membrane and retains newly formed enveloped viruses attempting to leave the cell. As a result, it prevents the release of viral particles and limits their ability to infect neighboring cells. Therefore, tetherin functions as a physical barrier against viral dissemination.

Viral counterattacks

Viruses, in turn, evolve mechanisms to overcome these host defenses. Many enveloped viruses have developed specific proteins capable of neutralizing tetherin activity. **Example: HIV** Human immunodeficiency virus (**HIV**) has acquired a viral protein called **Vpu**, which interacts with tetherin and prevents its antiviral activity. This allows newly produced viral particles to be released from infected cells and continue infecting other target cells.

This continuous process of adaptation and counter-adaptation represents a typical example of coevolution:

- Hosts modify their antiviral proteins to resist viral infection.
- Viruses modify their proteins to bypass host defense mechanisms and maintain transmission.

III. Mechanisms of viral variability

Viral genetic variability results from several mechanisms:

III.1. Mutations: A mutation is a genetic modification occurring within the viral nucleic acid sequence. A **point mutation** corresponds to a change affecting a single nucleotide. Different types of point mutations include:

- **Substitution mutation:** Replacement of one nucleotide base pair by another.
- **Insertion mutation:** Addition of one or more nucleotide bases into the genome.
- **Deletion mutation:** Loss of one or more nucleotide bases from the genome. These mutations can modify viral proteins and may influence viral properties such as replication efficiency, host range, antigenicity, or drug sensitivity.

III.2. Recombination: Viral recombination can occur when:

- Two different viruses infect the same host cell.
- Multiple viral genomes coexist within the same infected cell.

It results in the formation of recombinant viral genomes containing genetic material derived from parental viruses. The process involves:

1. Breakage of a nucleic acid strand.
2. Exchange of genetic material between viral genomes.
3. Rejoining (ligation) of the exchanged fragments.

Recombination plays an important role in viral evolution because it can:

- increase genetic diversity;
- facilitate adaptation to new environments;
- generate viral strains with altered characteristics;

- contribute to changes in pathogenicity or immune escape.

III.3. Reassortment: Reassortment occurs exclusively in viruses possessing segmented genomes, such as influenza viruses (Orthomyxoviruses). It corresponds to the exchange of complete genome segments between two viruses co-infecting the same host cell.

Steps of reassortment:

1. Co-infection: Two different viral strains simultaneously infect the same host cell.
2. Independent replication: Each genome segment replicates independently within the infected cell.
3. Reassortment: During the assembly of new viral particles, genome segments from the parental viruses are randomly mixed. This produces reassortant viruses containing genome segments derived from both parental strains.

IV. Consequences of Viral Genetic Variation

1. **Genotype modification:** Modification of the viral genome sequence (DNA or RNA).
2. **Phenotype modification:** Modification of observable viral characteristics, including: host range; antiviral resistance; temperature adaptation; replication efficiency; pathogenic properties.

Thermosensitive mutant viruses: Thermosensitive mutant viruses are able to replicate efficiently in cells maintained at lower temperatures but show reduced or absent replication at higher temperatures compared with the wild-type strain.

Temperature-adapted (“cold-adapted” or heat-resistant) mutants: Some viral mutants may display improved replication efficiency under specific temperature conditions compared with the parental strain.

Modification of host range: A viral mutant may acquire the ability to replicate:

- only in a specific cell type;
- in a new cell population;
- or in a new host species after overcoming species barriers.

Modification of pathogenicity: Mutations may alter viral pathogenicity. For example:

- mutant viruses may produce larger or smaller plaques in cell culture compared with wild-type viruses;
- attenuated mutants may induce milder symptoms or asymptomatic infections.

Resistance to antiviral drugs: A mutant virus may acquire genetic changes allowing replication despite antiviral treatment.

IV. Virus–Virus Interactions

Viruses do not always interact independently. When different viruses infect the same cell or host, several types of interactions may occur.

IV.1. Viral Interference

Viral interference occurs when one virus inhibits the replication of another virus within the same cell through:

- **Competition for cellular resources:** ribosomes; cellular enzymes; energy resources.
- **Blocking cellular receptors :** The first virus may modify or occupy cellular receptors, reducing entry of a second virus.
- **Induction of interferon responses:** The first virus may stimulate antiviral interferon pathways that inhibit subsequent viral infections.

Example: Rhinovirus infection may reduce influenza virus replication in respiratory epithelial cells through induction of antiviral responses.

IV.2. Viral Synergy: Viral synergy occurs when two viruses facilitate each other's replication. Possible mechanisms include:

- one virus providing enzymes or envelope proteins required by another virus;
- one virus suppressing host immune responses, thereby facilitating replication of the second virus.

Example: Hepatitis D virus (HDV) depends on hepatitis B virus (HBV) envelope proteins to form infectious particles.

IV.3. Complementation: Complementation is a mechanism in which a defective virus lacking an essential gene product benefits from the presence of another virus that provides the missing function. This interaction allows replication of viral variants that would otherwise be unable to complete their life cycle.

IV.4. Recombination and reassortment: When two related viruses infect the same cell:

V. Segmented and multipartite viral genomes

Segmented Genome: A segmented viral genome is composed of several independent nucleic acid molecules rather than a single continuous molecule. Each segment may encode one or several viral proteins. All genome segments are packaged together within the same viral particle. Example: Orthomyxoviridae.

Multipartite Genome: Multipartite genomes represent a special form of segmented genomes. In these viruses, genomic segments are not only physically separated but are also packaged into different viral particles. Each viral particle contains only one or a few genome segments. Therefore, successful infection requires that all necessary particles carrying complementary genome segments infect the same host cell.

Examples: Many plant viruses, including members of: Nanoviridae; Bromoviridae possess multipartite genomes. This organization creates transmission constraints because all required genome components must reach the same host cell for productive infection.

VI. Reverse transcription

Reverse transcription is a fundamental mechanism in the replication cycle of certain viruses, particularly **retroviruses**. In these viruses, the viral genome is composed of RNA and is converted into DNA through the action of a specific enzyme called reverse transcriptase. This conversion is essential because it allows the viral genetic material to integrate into the host cell genome, forming a proviral DNA molecule. Once integrated, the viral genome can be transcribed by the host cellular machinery, leading to the production of viral proteins and the formation of new virions. Reverse transcription is not restricted to retroviruses. It is also a central mechanism in the biology of retrotransposons, mobile genetic elements derived from ancient retroviral sequences. These elements use reverse transcriptase to convert RNA intermediates into DNA copies that can integrate into new genomic locations.

VII. Transposition

Transposition refers to the movement of mobile genetic elements, known as transposable elements (transposons), within a genome. There are two major classes of transposable elements:

1. DNA transposons: DNA transposons move through a mechanism often described as “cut-and-paste”.

This process is mediated by an enzyme called transposase, which recognizes the transposon ends, excises the element from its original location, and inserts it into another genomic site.

2. Retrotransposons: Retrotransposons move through a copy-and-paste mechanism involving an RNA intermediate. The process includes:

1. Transcription of the retrotransposon DNA into RNA.
2. Reverse transcription of this RNA intermediate into DNA.
3. Integration of the newly synthesized DNA copy into another genomic location.

Because retrotransposons can generate multiple copies of themselves, they represent a major component of eukaryotic genomes. In humans, transposable elements account for approximately 45–50% of the genome, contributing to genetic variation, mutations, genomic rearrangements, and evolutionary innovation.

VIII. Viral epidemiology

The evolutionary dynamics of viruses have major consequences for epidemiology. A virus that is well adapted to its host may cause limited disease, whereas host jumps and genetic changes may generate variants with altered biological properties. Genetic variability mechanisms, including:

- mutation;
- recombination;
- reassortment in segmented viruses;

facilitate the emergence of new viral variants, some of which may contribute to outbreaks or epidemics. The rate of viral evolution depends on several factors, including:

- adaptation to new hosts;
- immune selection pressure;
- antiviral treatment pressure;
- replication characteristics of the virus.

For example, nucleotide substitution rates can increase during adaptation to a new ecological environment.

Viral Emergence

Viral emergence refers to the appearance or reappearance of a virus within a specific host population, creating a new host–pathogen interaction.

In some situations, viral emergence may lead to:

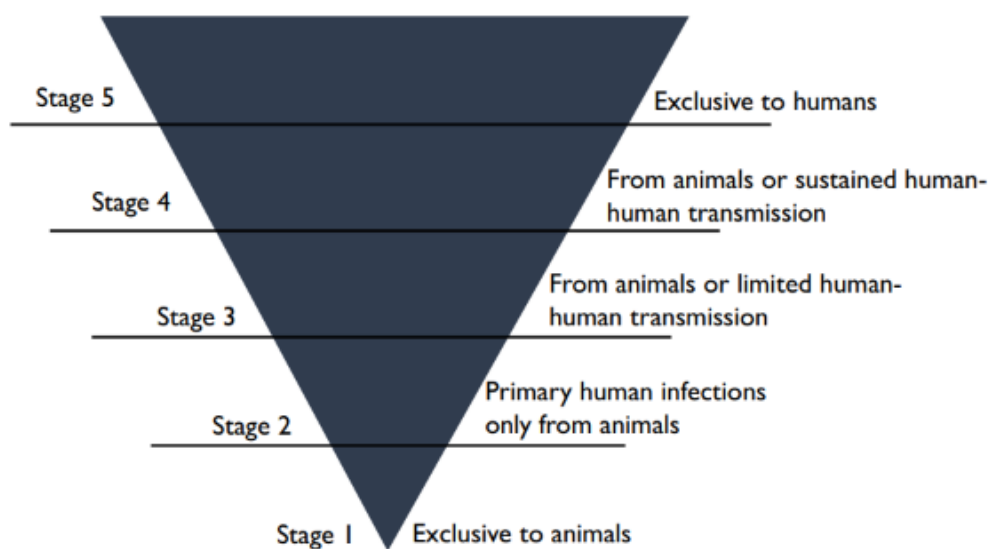
- epidemics;
- pandemics.

A large proportion of emerging human viruses have a **zoonotic origin**, meaning that they initially circulate in animal reservoirs before infecting humans. Interactions between humans and animals, as well as the crossing of species barriers, play a critical role in the emergence of these viruses.

Major steps involved in zoonotic viral emergence

When zoonotic viruses from an animal reservoir come into contact with humans, they encounter the species barrier, which consists of cellular factors that restrict viral replication, known as restriction factors. The ability of a virus to replicate in a new host may vary:

- 1. Inefficient replication:** viruses replicate poorly in the new host because they are not adapted to human cellular conditions.
- 2. Viral adaptation:** Through mutation and selection, some viral variants may acquire improved replication efficiency in the new host.
- 3. Emergence in humans:** Viruses capable of efficient replication may become established in human populations.
- 4. Human-to-human transmission:** Some emerging viruses acquire efficient transmission between humans, allowing sustained circulation. Other viruses with suboptimal adaptation may fail to spread effectively. During replication in animal or human reservoirs, viral mutations continuously generate genetic variants that are selected according to their ability to replicate successfully in the host.



Zoonotic disease emergence model outlining the 5 stages of pathogen emergence from animals to humans.

Adapted from Pike et al. (2010), Wolfe et al. (2007)

Mahanti, R. (2022). *How Data Can Manage Global Health Pandemics: Analyzing and Understanding COVID-19*. CRC Press.

This figure illustrates the five stages through which an animal pathogen may become adapted to humans, potentially leading to the emergence of new infectious diseases.

- Stage 1: The pathogen infects animals exclusively and does not naturally infect humans.
- Stage 2: The pathogen can cross the species barrier and infect humans, but human-to-human transmission does not occur.
- Stage 3: The pathogen can spread between humans, but transmission remains limited to a few secondary cases.
- Stage 4: The pathogen can be transmitted from animals to humans and can also sustain prolonged human-to-human transmission.
- Stage 5: The pathogen is maintained exclusively in human populations, without requiring an animal reservoir.