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A Box of Paradoxes: The Fascinating World of Viruses

Boriana Marintcheva

Tiny. Deadly. Fascinating. And useful. Viruses have been all around us for thousands of years and have had tremendous impacts on human society, regardless of how well we understood them. When the word virus is mentioned, it is hard for us to imagine anything positive. After all, viruses get their name from the Latin word for poison, which fits them perfectly when we picture the devastating diseases they cause in humans, animals and plants.

When the widespread use of computers came into being and self-replicating programs became a fact of our technological lives, the term virus gained a new meaning, and not a positive one. Not that long ago, the Internet brought to us the idea of viral videos. Today, we can describe as viral not only meningitis but also anything caught on video that is funny, crazy, amazing or spectacular. Now, thanks to *YouTube*, we are starting to believe that viruses can be associated with something other than poison or disaster. In truth, scientists have known that for a long time.

What are viruses?

Viruses are tiny non-living agents with very complicated lives. Sir Peter Medawar (1915–87), a Nobel laureate and the father of organ transplantation, once described viruses figuratively as “a piece of bad news wrapped in a protein.” Viruses are built from nucleic acid packed in protective protein coat (a capsid) and some are wrapped in an additional layer of lipids and proteins (an envelope). Viral capsids can be viewed as architectural masterpieces assembled with minimal numbers of building protein blocks. For example, the capsid of the Polio

virus (Figure 1) is built from only three types of proteins elegantly assembling a robust icosahedral structure.

A virus is a box of paradoxes. Viruses are considered non-living agents due to their complete dependence on a host cell, however being “dead” does not prevent them from causing disease or executing various life styles. Lytic viruses are direct killers. They infect their host, propagate and literally explode the cell allowing their

progeny to be released and infect again. Latent viruses tend to exist quietly in their hosts for a long time, occasionally producing bursts of new viruses. Herpes Simplex Virus Type 1 (HSV-1), the causative agent of cold sores, is a good example how lytic and latent life styles work together. Most people in the world are infected with HSV-1 early in life. The infection manifests itself as a cold sore, which is practically a bunch of blisters full with viruses. While the immune system is generally effective in taking care of the viruses circulating in the body, some viruses become permanent residents of the dorsal root ganglia (an anatomically distinct section of our spinal nerves) and establish dormancy or latent infection. When the body is experiencing high levels of stress (caused by a big deadline, intense UV exposure on the beach or a severe cold, for example) the virus reactivates and travels back to the lip, where it executes lytic infection resulting in a new cold sore. Science settles the “dead-or-alive” paradox by classifying viruses as infectious non-living agents and studies them in the context of the evolution and taxonomy principles applicable for living creatures.

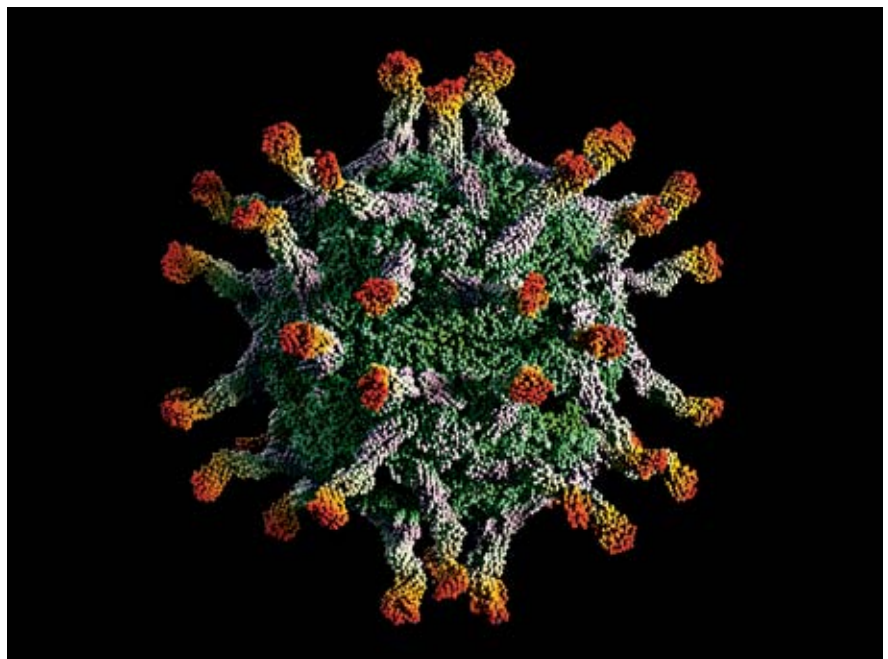


Figure 1. Model of a Polio Virus Capsid

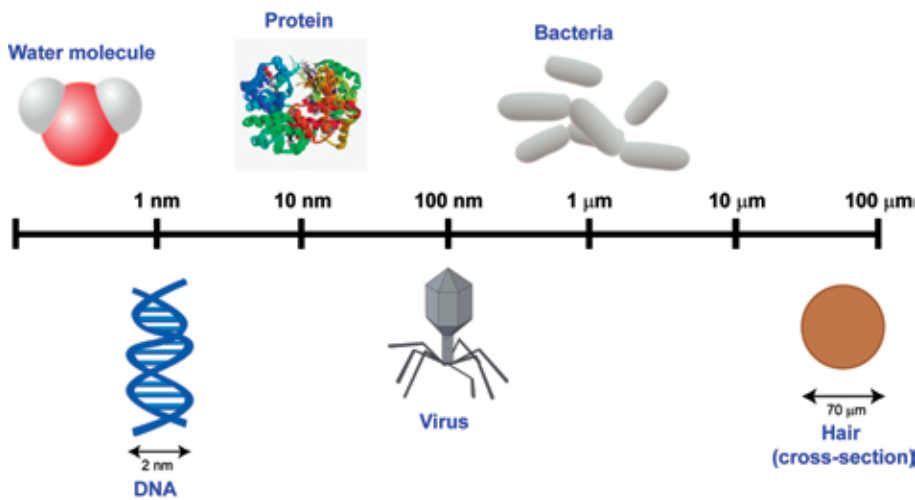


Figure 2. Virus Size in Comparative Scale

Another paradox is the huge disproportion between the amount of genetic information encoded by viruses and the magnitude of complexity viruses govern. Physically, viruses are very small, measurable on the nanometer (nm) scale. The Flu virus measures 80–120 nm in diameter; in other words, about 1,000 Flu viruses placed side-by-side would fit along the diameter of a single human hair (Figure 2). Most viral particles can be observed only with an electron microscope (though recently the conventional wisdom of all viruses being too small to be seen with a light microscope was “cracked” by the discovery of a novel class of giant viruses called Mimiviruses).

Amazingly, viruses are able to execute productive infection—and of course make us sick—with very limited genetic information. The Flu virus, for example, contains only 15,000 nucleotides (building blocks of nucleic acids carrying the genetic blueprint). By comparison, the human blueprint is 3,200,000,000 nucleotides or approximately 200,000 times longer. Needless to say, viruses have to be super-efficient in their quest to invade host cells and propagate. One can easily compare them to very creative and resourceful spies that manage to hijack cellular components, introduce switches in the cell physiology and force the host to

produce viral building blocks instead of normal cellular parts and molecules. Among their most fascinating tricks is their ability to have their genetic code read in multiple ways, thus increasing significantly the meanings of their limited-sized blueprint. One can think about this phenomenon as an exercise in generation—like counting how many three-digit numbers one can draw out of a phone number, for example BSU’s switchboard: 5085311000. One can start with the first digit and read 508 531 100, or one can start with the second digit and read 085 311 000, and so on. Similarly, one can begin to read viruses’ genetic information at different positions and derive multiple meanings of the limited size of their nucleic acid.

Scientists have the daunting task of studying and understanding how viruses work. Extensive knowledge

about pathogenic viruses offers better ideas about how to combat them and how to protect ourselves from viral infections. Surprisingly, despite the huge expansion of virology as a science, we have developed very few antiviral drugs and not many antiviral vaccines. One big reason for the apparent paradox is the constant tug of war virus versus host. Many clinically important viruses such as the Flu and HIV mutate very quickly, thus making therapeutics largely ineffective unless the infection is diagnosed early when the host and his or her drug team have a greater chance to win the tug of war. Cold viruses are tough to combat simply because they are very diverse group. It is simply not feasible to develop vaccines or drugs against each of the several hundred known viruses that cause the common cold. That said, science and medicine have triumphed against some of the world’s most deadly viruses, eradicating Smallpox and creating effective vaccines against Polio and Rabies.

Viruses as Scientific Tools

Scientists have taken advantage of the spying approaches of viruses to study the intricacies of cellular function. Since cellular structure and physiology are very complex, it is hard to understand how human cells are working. The presentation of viruses allows researchers to compare the differences between infected and uninfected cells and to eventually reconstitute cellular pathways. Viruses also have proved themselves as invaluable resources for

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tools to propel science. For example, major advancements are being made today in the area of personalized medicine due to the increasing capabilities for sequencing. Sequencing is nothing more than determining the specifics of one's genetic blueprint (or DNA), which allows for forecasting probabilities of certain diseases, and evaluating the probability that drugs will be effective. The sequencing of the

behind the rapid destruction of algae blooms known as red tides (Figure 3), which often disturb the ecological balance of the ocean and are harmful for marine life.

After bacteriophages were discovered by British bacteriologist Frederick Twort in 1915, they were soon considered a possible means to combat bacterial infections, especially ones associated with hard-to-heal wounds

were discovered and as a result the phage therapy idea was overtaken by the promise of these wonder drugs. But phage therapy was never completely forgotten. Ironically, today we live in the era of antibiotic resistant bacteria and phage therapy strategy is gaining new ground. Currently, there are U.S. Food and Drug Administration-approved protocols to treat meat and produce with phage in order to eliminate food spoilage and poisoning mediated by bacteria. Phage sprays are considered as a possible approach to control unwanted infections in hospital settings, and viral lytic enzymes are patented as components of toothpaste fighting plaque. Scientists are using viruses to deliver molecules in cells and starting to understand oncolytic viruses that selectively attack and kill cancer cells. The application of knowledge about viruses is far-reaching and often surprising. For example, the production of cheese and other dairy products has been revolutionized by understanding which viruses infect the bacteria carrying out the fermentation processes that convert milk into cheese. This knowledge allows scientists to genetically engineer bacterial strains no longer prone to viral infection, thus ensuring highly controllable and efficient fermentation processes.

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human genome was done with the help of a highly specialized enzyme found in bacteriophage T7. Bacteriophages are bacterial viruses that are widely spread in nature and contribute to our quality of life on daily basis. The term bacteriophage literally means bacteria eater and presents an accurate description of most bacterial viruses in nature which simply explode bacteria day and night. Bacteriophages are calculated to be the most abundant entity on Earth, accounting for most of the roughly 10^{31} or 100 billion trillion viruses on Earth. Bacteriophages are most abundant in the ocean, marine sediments, soils and sewage and play a critical role for the recycling of the biomass on the planet. Viruses are responsible for exploding approximately 20 per cent of the ocean biomass on daily basis, thus ensuring sufficient material to support the growth of bacteria, archaea and algae, many of which are needed for oxygen production and thus life on the planet. Viruses are the main force

or burns. Scientists envisioned that bacteriophage stocks would be grown in a laboratory and applied to wounds as a wash. The viruses would attack the wound resident bacteria and explode them, thus breaking the course of the stubborn infection. The approach is known as bacteriophage therapy or phage therapy. In 1928, antibiotics



Figure 3. Red Tide

Tulipomania

The “tulipomania” story is a favorite tale that reveals the unexpected connections of viruses to everyday life. In the early seventeenth century, Dutch gardeners developed spectacular bicolor tulips called “breaking tulips” whose flowers appeared as flares of red and white in patterns that hardly ever repeated themselves. Society was so mesmerized by the beautiful flowers that artists were including them in still life paintings (Figure 4) or as decoration on music instruments. These tulips became so popular in the Netherlands that the prices of their bulbs skyrocketed. Between 1634 and 1637, wealthy Dutch gardeners were reportedly willing to spend up to 10,000 florins—the price of a house with a garden in a good location in Amsterdam—to acquire just



Figure 4. *Tulipomania*. Ambrosius Bosschaert (1573-1621), *Still Life with Flowers in a Wan-Li vase* (1619). Rijksmuseum Amsterdam.

Most scientific discoveries start with a simple observation followed by a bumpy journey of inquiry and experimentation which years later could bring some understanding of the original observation and propel science and technology forward.

a single bulb. To their great dismay, the admired tulips became sick only a few years after planting and eventually died. Not much later, gardeners experimenting with tulips found out that when a breaking tulip bulb is grafted onto a bulb of unicolor tulip, the flare-like appearance of the flowers could be “transferred.” But the discovery came too late. In 1637, sellers of the precious bulbs greatly outnumbered interested

buyers and the market “bubble” collapsed. More than 300 years later, a virus called the Tulip Breaking Virus (TBV) was isolated and the scientific explanation of the phenomenon became apparent. The uniquely flared tulip patterns were actually a product of a viral infection that resulted in the loss of color (i.e. appearance of white stripes) in the infected parts of the plant. As larger and larger proportions of the plant became affected, the plants

started getting sick and eventually died. If you happen to have striped bicolor tulips in your garden for many years in a row and they never get sick, you are probably not buying the sick-tulip story above. And you should not, because it is not applicable to your plants. Years later, long after tulipomania was over, scientists discovered a genetic mutation that produces healthy, truly bicolor tulips that display the same pattern of stripes generation after generation. Today, commercially available tulip bulbs are screened to be virus-free and molecular biology approaches are used to engineer plants resistant to viral infection. Interestingly, a similar story is currently unfolding among orchid breeders and collectors.

The tulipomania story is fascinating, and not only to biologists. Depending on one’s inclinations, it can be read as telling tale about history, art, economics or human nature. For me, it is a great example how science works. Most scientific discoveries start with a simple observation followed by a bumpy journey of inquiry and experimentation which years later could bring some understanding of the original observation and propel science and technology forward. As with many things in life, so it goes with our quest to understand the nature and uses of viruses: both the journey and final destination are invaluable.



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