Evolution of viruses

Virus evolution and genetic variation. Drug-resistant HIV. Re-assortment of flu viruses.

Key points:

Viruses undergo evolution and natural selection, just like cell-based life, and most of them evolve rapidly.

When two viruses infect a cell at the same time, they may swap genetic material to make new, "mixed" viruses with unique properties. For example, flu strains can arise this way.

RNA viruses have high mutation rates that allow especially fast evolution. An example is the evolution of drug resistance in HIV.

Introduction

Have you ever wondered why a different strain of flu virus comes around every year? Or how HIV, the virus that causes AIDS, can become drug-resistant?

The short answer to these questions is that viruses evolve. That is, the "gene pool" of a virus population can change over time. In some cases, the viruses in a population—such as all the flu viruses in a geographical region, or all the different HIV particles in a patient's body—may evolve by natural selection. Heritable traits that help a virus reproduce (such as high infectivity for influenza, or drug resistance for HIV) will tend to get more and more common in the virus population over time.

Not only do viruses evolve, but they also tend to evolve faster than their hosts, such as humans. That

makes virus evolution an important topic—not just for biologists who study viruses, but also for doctors nurses, and public health workers, as well as anyone who might be exposed to a virus. (Hint: that means all of us!)

Variation in virus's

Natural selection can only happen when it has the right starting material: genetic variation. Genetic variation means there are some genetic (heritable) differences in a population. In viruses, variation comes from two main sources:

Recombination: viruses swap chunks of genetic material (DNA or RNA).

Random mutation: a change occurs in the DNA or RNA sequence of a virus.

We can see variation and evolution of viruses all around us if we know where to look—for instance, in the new flu strains that appear each year.

Mixing it up: Recombination

Before we looks specifically at the flu, let's examine how viruses swap DNA and RNA in a process called recombination.

Recombination usually happens when two viruses have infected the same cell at the same time. Since both viruses are using the cell to crank out more virus particles, there will be lots of virus parts – including newly made genomes – floating around in the cell at once.

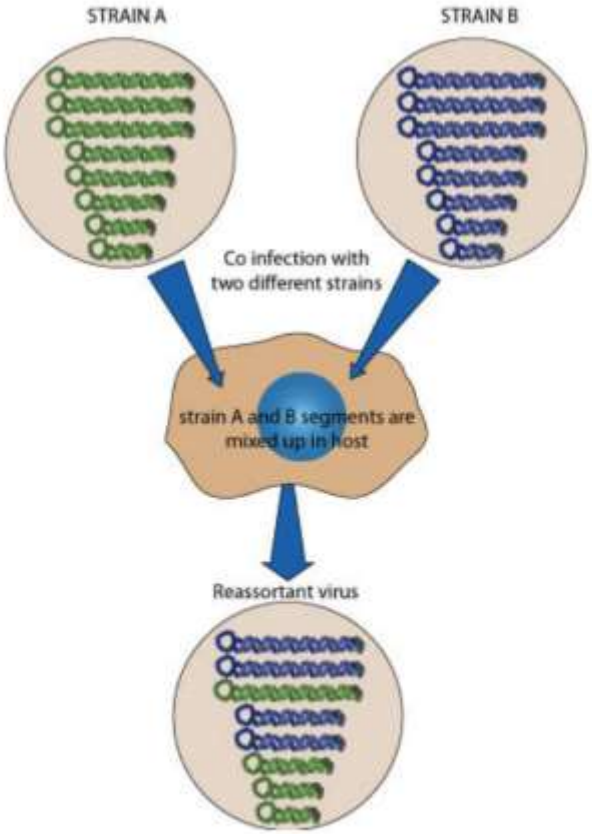


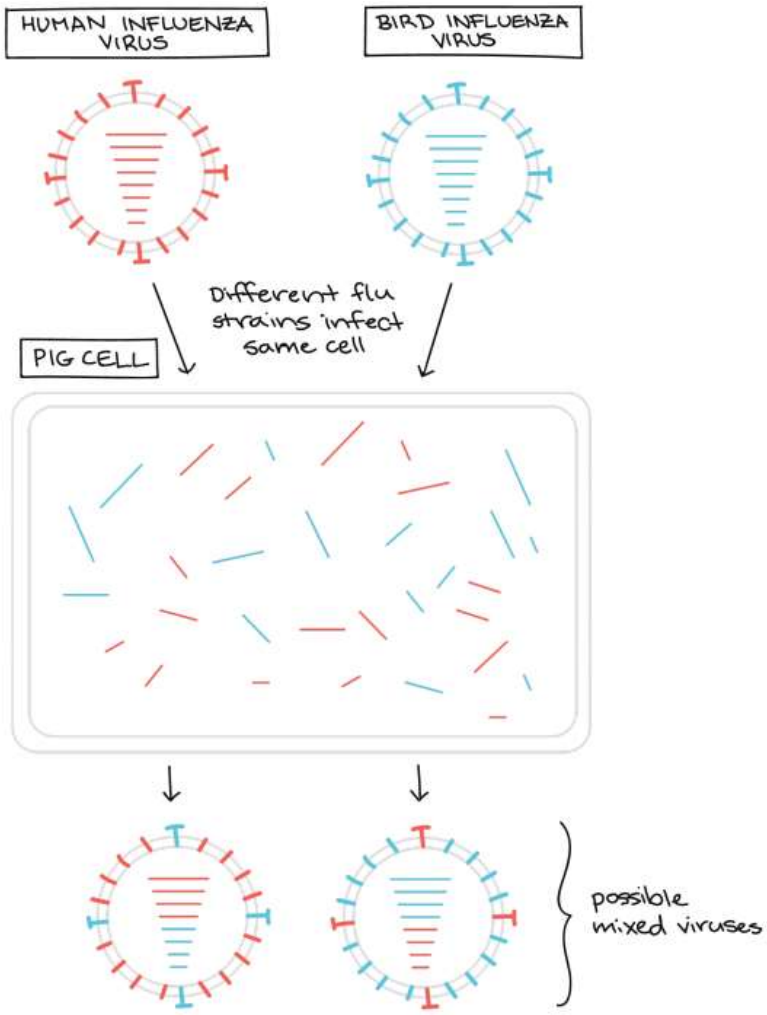
Image credit: "Segment reassortment," by ViralZone/Swiss Institute of Bioinformatics, CC BY-NC 4.0.

Under these circumstances, recombination can happen in two different ways. First, similar regions of viral genomes can pair up and exchange pieces physically breaking and re-connecting the DNA or RNA. Second, viruses with different segments (kind of like tiny chromosomes) can swap some of those segments, a process called re-assortment.

Recombination and influenza ("the flu")

Influenza ("flu") viruses are masters of re-assortment. They have eight RNA segments, each carrying one or a few genes.

When two influenza viruses infect the same cell at the same time, some of the new viruses made inside of the cell may have a mix of segments (e.g., segments 1-4 from strain A and segments 5-8 from strain B).



Pigs in particular are well-known "mixing vessels" for influenza viruses. Pig cells can be recognized, and thus infected, by both human and bird influenza viruses (as well as pig viruses). If a cell in the pig is infected with two types of virus at the same time, it may release new viruses may be made that contain a mixture of genetic material from the human and bird viruses.

This kind of swap is common for influenza viruses in nature. For example, remember the H1N1 influenza strain ("swine flu") that caused a pandemic in 2009? H1N1 had RNA segment from human and bird viruses as well as pig viruses from both North America and

Asia. This combo reflects a series of re-assortments that occurred step by step over many years to produce this H1N1 strain.

Viral mutations

We have seen how recombination can affect virus evolution, but what about mutation? A mutation is a permanent change in the genetic material (DNA or RNA) of a virus. A mutation can happen if there is a mistake during copying of the DNA or RNA of the virus.

Some viruses have very high mutation rates, but this is not universally the case. In general, RNA viruses tend to have high mutation rates, while DNA viruses tend to have low mutation rates.

Why is this the case? The key difference lies in the copying machinery. Most DNA viruses copy their genetic material using enzymes from the host cell called DNA polymerases, which “proofread" (catch and fix mistakes as they go). RNA viruses instead use enzymes called RNA polymerases, which don't proofread and thus make many more mistakes.

Case study: HIV drug resistance

Human immunodeficiency virus (HIV) is the virus that causes acquired immune deficiency syndrome (AIDS). HIV is an RNA virus with a high mutation rate and evolves rapidly, leading to the emergence of drug resistant strains.

HIV's high mutation rate

Because RNA viruses like HIV have a high mutation rate, there will be lots of genetic variation in the population of HIV viruses in a patient's body. Many of the mutations will be harmful, and the mutant viruses will simply "die" (fail to reproduce). However, some

mutations help viruses reproduce under specific conditions. For instance, a mutation may provide resistance to a drug.

Evolution of drug resistance in HIV

Certain drugs can block the replication of HIV by inhibiting key viral enzymes. Taking one of these drugs will at first reduce a patient's viral levels. After awhile, however, the HIV viruses typically "bounce back" and return to high levels, even though the drug is still present. In other words, a drug-resistant form of the virus emerges.

To see why this took place, let's use the example of a specific type of antiviral drug, a reverse transcriptase inhibitor. Reverse transcriptase inhibitors, like the nevirapine molecule shown in the diagram below, bind to a viral enzyme called reverse transcriptase (the red and-brown structure). The drug keeps the enzyme from doing its job of copying the RNA genome of HIV into DNA. If this enzyme is inactive, an HIV virus can't permanently infect a cell.

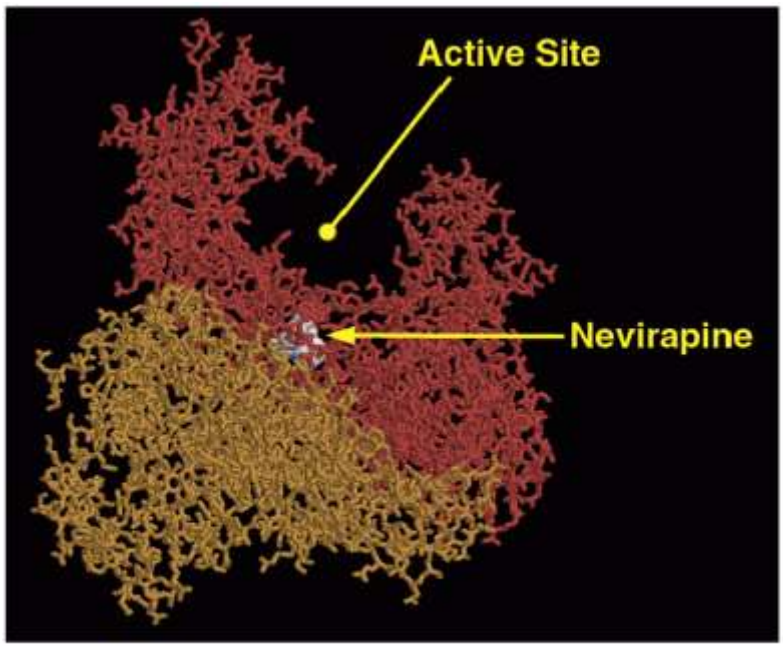


Image modified from "Exploring the structure," by David S. Goodsell, RCSB PDB Molecule of the Month, CC BY 4.0.

Most HIV viruses are stopped by nevirapine. However, a very small fraction of the viruses in the HIV population will (by random chance) have a mutation in the gene for reverse transcriptase that makes them resistant to the drug. For instance, they might have a genetic change that alters the drug's binding site on the enzyme, so that the drug is no longer able to latch on and inhibit enzyme activity.

The viruses with this resistance mutation will reproduce despite the presence of the drug and, over generations, can re-establish the viral levels present before the drug was administered. Not only that, but the entire virus population will now be resistant to the drug!

HAART drug resistance

If HIV can evolve its way around a drug, how can the virus be stopped? What seems to work best is a combination approach, with three or more drugs taken at the same time. This approach to treatment is called

highly active antiretroviral therapy, or HAART for short. The drugs given in a HAART "cocktail" typically target different parts of the HIV lifecycle.

The HAART approach works because it's relatively unlikely that any one HIV virus in a population will happen to have three mutations that give resistance to all three drugs at the same time. Although multi-drug resistant forms of the virus do eventually evolve, multi-drug combinations considerably slow the evolution of resistance.

Why do viruses evolve so fast?

Viruses evolve faster than humans. Why is this the case?

As we saw in the case of HIV, some viruses have a high mutation rate, which helps them evolve quickly by providing more variation as starting material. Two other factors that contribute to the fast evolution of viruses are large population size and rapid lifecycle. The bigger the population, the higher the odds that it'll have a virus with a particular random mutation (e.g. one for drug resistance or high infectivity) on which natural selection can act. Also, viruses reproduce quickly, so their populations evolve on shorter timescales than those of their hosts. For instance, the HIV virus goes through its lifecycle in just 52 hours, as compared to roughly 20 years for the human lifecycle!

What tools do we have to combat fast-evolving viruses? Taking steps to prevent transmission identifying new drugs for treatment, and developing and using vaccines are all important strategies.