

Phylogenetics for Predicting Virus Evolution

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1 Introduction

1.1 Problem at Hand

Viruses and the diseases they provoke put a large burden on human life. These comparably simple structures are capable of modifying and possibly destroying vital functions in the human body, by infiltrating their genetic material into the reproductive apparatus of cells.

All viruses that persist in the human population over longer times share some common features:

- They need some form of protection from their surroundings, a hull
- They need to find a way to get into human cells
- They aim at reproducing quickly
- If there is no constant infection source, they need to find a path to get from one individual to another
- They will have to deal with human immune system response
- They will underlie some kind of evolutionary pressure

(This rough characterisation is of course incomplete, and there may also be exceptions.)

To give another rough image of what makes up a virus, here are the essential constituents:

- A piece of genetic code (RNA or DNA, positive or negative sense, usually some few kilobase(pairs) long)
- A hull: either only a capsid (of proteins) or an additional envelope (bilipid layer) with surface proteins

For enveloped viruses such as in the *Orthomyxoviridae* family (including influenza) or *Coronaviridae* (e.g. SARS-CoV-2), there is usually a variety of different surface proteins that populate the bilipid layer.

These surface proteins take up functions such as binding to a cell to infiltrate the viruses genetic sequence into it, or releasing a freshly assembled virus from the host cell's surface into the surrounding body fluids. This is usually done via interactions with specific host cell receptors, therefore defining a *receptor binding domain (RBD)* as the part of the surface protein that fits onto the receptor as a key fits into a lock.

At the same time, the human immune system will also get in contact with mostly surface proteins. The immune system will eventually develop antibodies that are targeted to bind to a specific region of virus surface proteins, thereby rendering them innocuous. The surface protein region targeted by the immune system is called *epitope site* and may have a large overlap with the RBD.

These two mechanisms put an evolutionary pressure on the virus, especially on the surface proteins and its epitope sites. While having to maintain essential functions as binding to receptors, the virus will draw large advantage from an epitope site modified to such an extent that the antibodies cannot bind to it any longer. This way of disguising itself—by amino acid mutations in crucial places—will allow the virus to reinfect previously immune individuals.

An accelerated evolution can be very beneficial to the virus, *but*—since the capability to sequence and read out the viral genome—also provides a large record to trace a virus' history.

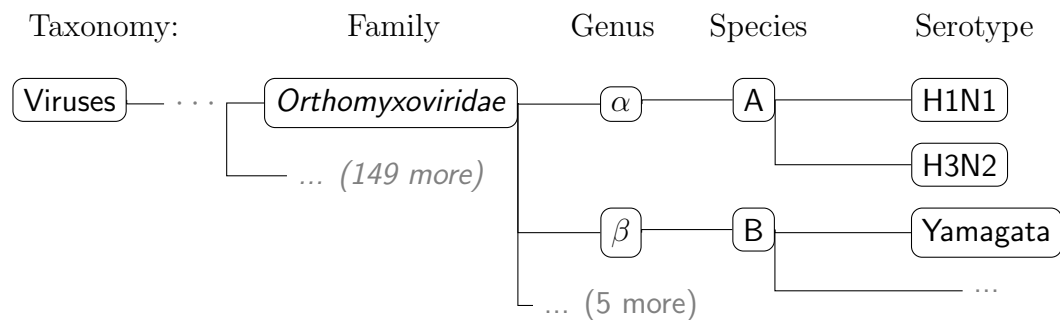
In this write-up, we will look at how the sequencing of the viral genome, along with phylogenetic tree inference, can provide useful insights on (i) the route that the virus takes to spread in the human population, (ii) the existence and prevalence of strains within a virus (sub)type, and (iii) the projected evasion of the virus from immune system response and vaccines.

1.2 Influenza

Influenza is one of the most common viral diseases [Duda and Menna, 2020] and puts a large burden on human health. The disease is estimated to cause symptomatic illness in about 3 – 11% of the human population (in the U.S.) [Tokars et al., 2018] every season. Globally, up to 650,000 individuals die from influenza illness every season [see Iuliano et al., 2018].

Influenza refers to a disease caused by a virus of the influenza family *Orthomyxoviridae*. All orthomyxo viruses have an envelope that carries surface proteins and their genome is a negative sense RNA.

Most relevant for human infectious diseases are the genera *Alpha-* and *Beta*influenzavirus that contain the species *Influenza A* and *Influenza B* respectively.



1.2.1 Basics

History diagram from [Alberts, 2015]

HA: epl

NA: expl

Phylo tree of A/H3N2 HA Volz+2013

1.2.2 Hemagglutination Inhibition Assay

Short description

Hirst 1943

mention cartography from Smith+2004 (?)

2 Phylodynamics

Essentially the Wikipedia Article + Volz 2013 (TODO read)

3 Nextstrain

3.1 Idea

3.2 Short Usage Instructions

3.3 Example

4 Mapping Influenza Evolution

4.1 Mapping Titer to Tree

Minimizing a Cost function

Tree model vs. substitution model

Proving Treelikeness

4.2 Results

Figure 6 Interpretation

5 Conclusion

Very interesting!

References

Alberts, B. (2015). *Molecular Biology of the Cell*.

Duda, K. and Menna, M. (2020). 7 Remarkably Common Viral Infections Explained. <https://www.verywellhealth.com/common-viral-infections-770660>.

- Iuliano, A. D., Roguski, K. M., Chang, H. H., Muscatello, D. J., Palekar, R., Tempia, S., Cohen, C., Gran, J. M., Schanzer, D., Cowling, B. J., Wu, P., Kyncl, J., Ang, L. W., Park, M., Redlberger-Fritz, M., Yu, H., Espenhain, L., Krishnan, A., Emukule, G., van Asten, L., Pereira da Silva, S., Aungku-lanon, S., Buchholz, U., Widdowson, M.-A., Bresee, J. S., and Global Seasonal Influenza-associated Mortality Collaborator Network (2018). Estimates of global seasonal influenza-associated respiratory mortality: A modelling study. *Lancet (London, England)*, 391(10127):1285–1300.
- Tokars, J. I., Olsen, S. J., and Reed, C. (2018). Seasonal Incidence of Symptomatic Influenza in the United States. *Clinical Infectious Diseases*, 66(10):1511–1518.