Predictive models and simulations for the evolution of parasitic viral strains

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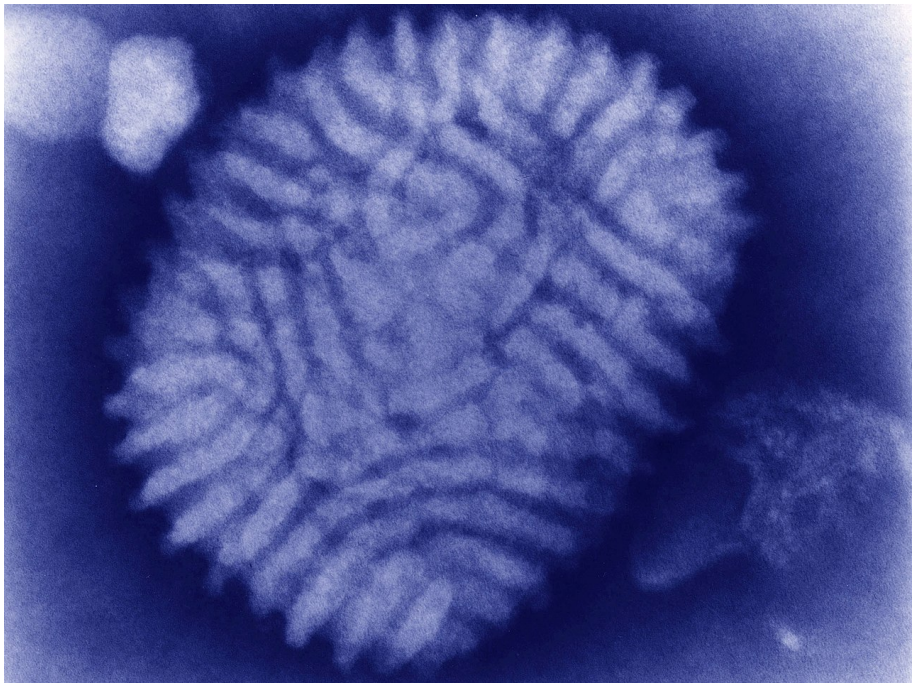
English Tiny Thesis



Myxoma virus (transmission electron microscope)

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1. WELL-DOCUMENTED PARASITE EVOLUTIONS

1.1 Why do parasites harm their hosts?

A parasite is a creature that lives inside a host, tries to spread at maximum and often harms it. It is generally agreed that parasites are as old as life. Malaria for example has been infectious since the beginning of humanity, and unfortunately still prevails nowadays. Similarly, the SIV, the simian version of AIDS, has evolved with apes for eons, but is yet perfectly benign. Why are some parasites so deadly, contrary to others?

According to the natural selection, the fittest strain is always favored. We should yet define what being *fit* means for a parasite. Over the generations, virulence, the parasite ability to kill, is rarely directly selected but rather the highest reproductive ratio (R_0), the expected number of infections for one case.

On the contrary, virulence seems at first glance detrimental to the parasite, as dead hosts scarcely spread the pathogen.

From these two remarks, the ideal parasitic strain should be avirulent, perfectly harmless, and highly transmittable, with an infinite R_0. This idea is empirically false, and that is what is shown by the analysis of the myxoma virus.

All in all, for a parasite, one should keep in mind that harming the host is a by-product of being the fittest to survive.

1.2 Myxomatosis and Australian rabbits

1.2.1 Presentation

A parasite exists in several versions but only a few will survive. That can be seen with the myxoma virus. This virus was studied by Ferner and Ratcliffe in the 1960s [4] who showed that neither the most avirulent strain, nor the deadliest was naturally selected.

The myxomatosis (spread by the myxoma virus) is a disease that had been intentionally introduced in Australia since the 1950s to control rabbit populations. It causes death within a few days due to skin lesions and high fever.

The data set is of primary importance: it was one of the first to show how a novel parasite evolves when first introduced in a new environment. Researchers are still trying to understand this example, adding to the initial epidemiological studies molecular and genetic analyses [6].

1.2.2 The experiment of Ferner and Ratckiffe [4]

Six viral strains were under study. At the very beginning of the experiment, the most virulent strain dominated. Ten years later, so in the late 1950s, the proportions changed: the strain of virulence III (third level of virulence over six) predominated and its relative abundance was quite stable for the following years. Put it another way, the myxoma had evolved into less virulence, to be less deadly.

1.2.3 Explanation [1]

The final victory of intermediate virulent strain seems to have a simple explanation. When the virulence is too high, the host dies too early to spread the disease. At the opposite, when the virulence is too low, the disease is cleared off before sufficient transmission. Nevertheless, this was not exactly true with the myxoma.

The reason is that highly virulent strain were also highly transmittable. When the rabbits were infected by a highly virulent strain, they developed open lesions that would be easily bitten by mosquitoes, thus transmitting the disease more easily to other rabbits. This is why the high virulent strain won at the very beginning, but it still does not explain why they lost at the end.

1.2.4 Limits

The main factor is that the rabbits progressively became resistant to high levels of virulence. Therefore, when the evolution of a virus is studied during a long time span, it is important to model it as a coevolution with the host.

On a different ground, the myxomatosis introduction shows us the need for predictive models for practical applications. In this case, the extinction of the high virulent strains, that could have killed a lot of hosts, was a major failure to control the rabbits populations [6]. Maybe with well-chosen initial quantities of viral strains, would it have been otherwise?

1.2.5 How to use the data set?

For building predictive models and simulations, we will keep some of the features of this data.

We will first consider virulence as the determinant parameter in the evolution of the virus. Therefore we will focus on the evolution of virulence: at the end, does the most deadly or benign strain dominate? A parameter like the transmissibility, the rate at which the hosts become infected, will be a function of it.

Whereas the notion of coevolution between host and parasite seem to be important, we will not retain it. It seems indeed that focusing on genetic resistance will make us study the direct interaction between the virus and the rabbits, which is difficult to generalize. The hosts do not resist in the same fashion with two different parasites.

2. CHOOSING THE RIGHT MATHEMATICAL MODEL ACCORDING TO REAL-LIFE EXAMPLES

2.1 Presentation

In this section, we will consider a big picture of existing models that are used to describe the evolution of a parasitic strain.

The myxoma will serve us to derive useful parameters.

First of all, contrary to the conclusion of the myxoma case, we will not keep any dynamic of the host immune response, with memory phases for instance. Nor will the host evolve, as virus generally mutates much faster.

As the evolution of a virus cannot be thought outside an epidemic, epidemiological equations will serve as the environment in which the different viral strains will struggle.

2.2 A Susceptible-Infected-Removed model (Kermack and McKendrick, 1927 [5])

A very first model for epidemics was proposed by Kermack and McKendrick.

It assumes that an infected person is introduced in a country where some people are susceptible to the disease.

The model only focuses on the host population and divides it into several classes:

1. The susceptible population (S), who are not yet infected but could be.
2. The infected population (I).
3. The removed population (R), who are both the recovered and life-immune and the deceased .

It considers the following parameters:

1. The removal rate (α), that is the rate at which the infected are removed in a fixed period of time. In the case of the myxoma virus that confers few immunity, it will be a death rate.
2. The transmission rate (β), the rate at which the susceptible become infected.

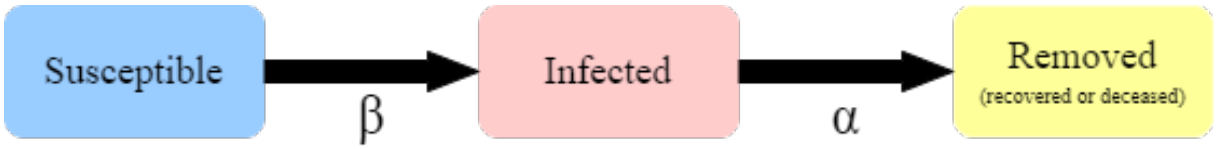

Fig. 2.1: The model of Kermack and McKendrick (1927). The susceptible population becomes infected at rate β. The infected are either recovered or deceased at rate α

Here is the corresponding system of equations:

$$\begin{cases} \frac{dS}{dt} = -\beta SI \\ \frac{dI}{dt} = \beta SI - \alpha I \\ \frac{dR}{dt} = \alpha I \end{cases}$$

2.3 The basic reproductive ratio

A fundamental quantity in this model is $R_0 = \frac{\beta}{\alpha}$. This is called the *basic reproductive ratio*. It corresponds to the number of infected people due to one person introduced in an uninfected host community.

For example for the measles that has a basic reproductive ratio of about 15, when 10 infected people are introduced in a new population, they will directly cause 150 cases, which is a lot. On the contrary, with COVID-19 these 10 infected people will cause less cases because COVID has a reproductive ratio of about 2.87 [3].

This ratio gives information on how emerging epidemics propagate. If $R_0 > 1$, the disease will spread, else if $R_0 < 1$, it is not viable.

Let us come back to our subject, that is the evolution of parasitic strains. We will see that, very often, natural selection maximizes this quantity.

2.4 A model with two strains

The idea would be to consider two strains of the same parasite instead of one. As a scenario, we could suppose that one strain is a mutation of another, meaning that it spreads differently and has another virulence. The two strains come into a novel country at the same time.

We can show that necessarily the strain with the lower reproductive ratio goes extinct. A proof is to be found in the book *The Equations of Life* [8] at the chapter *Evolution of Virulence*.

In an nutshell, we first find the equilibria of the system, where the three populations (susceptible, infected and removed) stop to grow. As the two strains have different R_0, the only equilibrium forces a strain to disappear. Looking at the stability, the strain with the higher reproductive ratio wins.

If we suppose that mutated strains appear with R_0 between 0 and infinity, evolution will tend to make R_0 infinity. That means that the ideal strain is avirulent ($\alpha = 0$) and highly transmittable ($\beta = +\infty$), what was stated in the introduction. This idea is of course false when β and α are linked, like for the myxomatosis.

2.5 Adding superinfection (Levin and Pimentel, 1981) [7]

The rule of the greater R_0 is false when we consider *superinfection*. It means that the infected people with a less virulent strain can become infected with a more virulent strain. However there is no multiple infection, that means that one can only be infected by one strain. A parameter s for superinfection is introduced. It yields the following system:

$$\begin{cases} \frac{dS}{dt} = -\beta_1 S I_1 - \beta_2 S I_2 \\ \frac{dI_1}{dt} = \beta_1 S I_1 + s\beta_1 I_1 I_2 - \alpha_1 I_1 \\ \frac{dI_2}{dt} = \beta_2 S I_2 - s\beta_1 I_1 I_2 - \alpha_2 I_2 \\ \frac{dR}{dt} = \alpha_1 I_1 + \alpha_1 I_2 \end{cases}$$

Here strain 1 takes over individual infected by strain 2 at rate $s\beta_1$.

2.6 Choosing a model despite alternatives

One other interesting model would have been the one of Antia, Levin and May (1994) [2]. The host-parasite dynamic is boiled down to the quantities of parasite and immune cells inside the host.

The goal for the parasite would be to maximize its total transmission but without ever reaching the *lethal density* which would imply the death of the host. There would as a consequence an optimal growth rate for the parasite above which the hosts would die too early, and below which the transmission would not be sufficient.

For the simulations, we will however use the model with superinfection.

3. SIMULATING THE EVOLUTION OF A HYPOTHETICAL STRAIN AND ITS IMPACT ON POPULATIONS

3.1 Presentation

Here will be simulated a hypothetical virus invading a country. Scientists would like to measure its impact in the long run: will the virus dangerously evolve?

My frame of work will be a population that is suddenly invaded by virus. A certain ratio of this population is susceptible to the virus, i.e can be infected. This virus exists in different strains that have each a different virulence (α) and different transmissibility (β).

As a generalization of the superinfection model, there will be a good number of strains. A given strain will be outcompeted by more virulent strains, but will win against less virulent strains.

Strains will go extinct when their infected population is either took-over or dead from the disease. A low virulent strain will have to fight the other strains who want to take its infected. Conversely, the arch enemy of a high virulent strain is itself: its own virality which wipes out so many infected. A trade-off has to be found.

3.2 Parameters

Inspired by the analysis of Martin Nowak in *The Equations of Life* [8], the following parameters will be kept:

- We consider 100 strains, with virulence drawn randomly between 0 and 5 (arbitrary units).
- Transmissibility grows proportionally to virulence, but reaches a limit for high virulence
- The take-over between strains occurs at rate s times transmissibility of the more virulent strain.

3.3 Results

In the figures, we can see different bars, each corresponding to a parasitic viral strain. Its virulence is on the x-axis and its relative abundance is on the y-axis. For example, a strain at x = 1 and y = 0.5 has a virulence of 0.1 and makes up 50% of the strains.

In black is plotted the basic reproductive ratio as a function of virulence. It is maximal for a virulence of about 1.

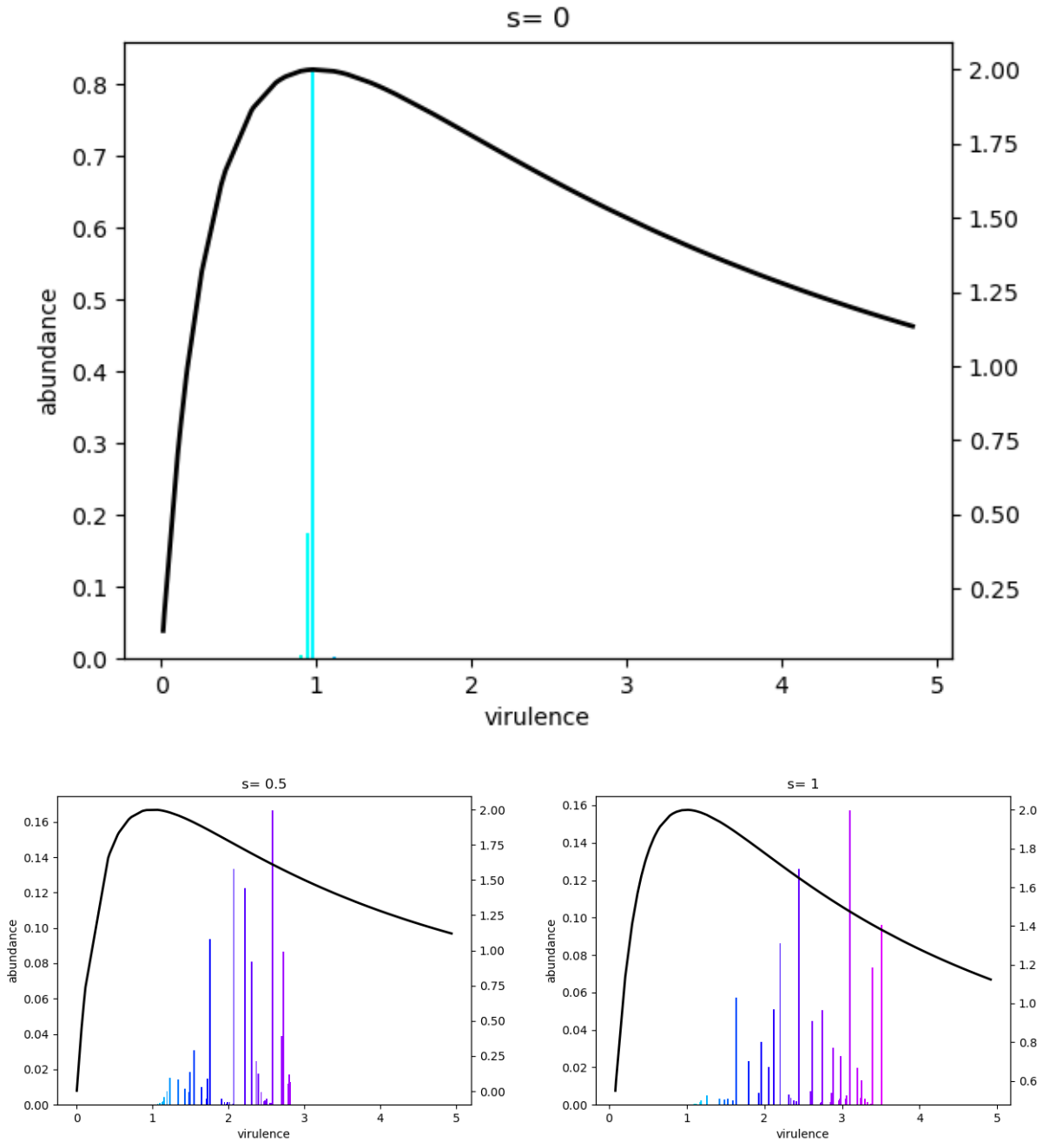

Fig. 3.1: Simulation with no superinfection (s = 0) then with different levels of competition (s = 0.5 , 1)

Without competition between strains (first graph), the last strain to survive is the one with the higher R_0. An idea of an analytical proof was discussed in part 2.

The graphs 2 and 3 shows that introducing superinfection yields complex final situations.

We observe that no strain seems to dominate, contrary to s = 0. In addition, the greater the superinfection factor, the greater the virulence in the end.

3.4 Conclusion

If we suppose that strains do not interact together, the course of the disease is easy to predict: one intermediate virulent strain wins.

However, the more the strains interact, the more both chaotic and virulent the disease. Should the virus reinfect a new population, the disease would be more dangerous than ever.

To answer why parasite harm their hosts, a first explanation is the link between transmission and virulence, a second comes from the simulations: death rates are stimulated by competition between strains.

BIBLIOGRAPHY

[1] R.M Anderson and R.M. May. “Coevolution of hosts and parasites”. In: *Parasitology* (1982).

[2] B. R. Levin Antia R. and R.M. May. “Within-host population dynamics and the evolution and maintenance of microparasite virulence”. In: *The American Naturalist* (1994).

[3] Khan MN Billah MA Miah MM. “Reproductive number of coronavirus: A systematic review and meta-analysis based on global level evidence”. In: *Plos ONE* (2020).

[4] F.N. Ratcliffe Frank Fenner. *Myxomatosis*. Cambridge University Press, 1965.

[5] W. O. Kermack and A. G. McKendrick. “A contribution to the mathematical theory of epidemics”. In: *Proceedings of the Royal Society of London* (1927).

[6] Peter J. Kerr. “Myxomatosis in Australia and Europe: A model for emerging infectious diseases”. In: *Ecosystem Sciences* (2012).

[7] Pimentel D. Levin S. “Selection of intermediate rates of increase in parasite-host systems”. In: *American Naturalist* (1981).

[8] Martin A. Nowak. *Evolutionary dynamics: exploring the equations of life*. Harvard University Press, 2006.