# Modelling Viral Evolution and Adaptation

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## 1 Introduction

Viral populations are extremely plastic [5]. They maintain and steadily generate high levels of genotypic and phenotypic diversity that result in the coexistence of several different viral types in quasi-species, and eventually constitute a powerful tool to deploy different adaptive strategies. The interest in understanding and formally describing viral populations has steadily increased. At present, there are major unknown factors that difficult the construction of realistic models of viral evolution, as the way in which mutations affect fitness [19] or, in a broader scenario, which is the statistical nature of viral fitness landscapes. Our understanding of viral complexity is however improving thanks to new techniques as deep sequencing [17] or massive computation, and to systematic laboratory assays that reveal that, as other complex biological systems (e.g., cancer or ecosystems) the term *virus* embraces a dissimilar collection of populations with a remarkable ensemble of evolutionary strategies. New empirical data and improved models of viral dynamics are clearing up the role played by neutral networks of genotypes [21], by defective and cooperative interactions among viral mutants [13], by co-evolution with immune systems [22], or by changes in host populations [10], to cite but a few examples. Models of viral evolution are steadily improving their accuracy and becoming more competent from a conceptual and a predictive viewpoint [11, 12]. Here, we review some examples were well-motivated models of viral evolution succeed at capturing experimentally described features of those populations. Such are the relationship between intra-species competition and the geometry of the propagating substrate of a viral infection [3], the origin of bipartite viral genomes [8], and the adaptation to multi-drug therapies [9, 16].

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## 2 Infection Propagation in Space

The geometry of the physical space where the propagation of viral infections occurs affects quantities such as the probability of transmission from an infected to a susceptible host, the pace of accumulation of mutations, or the diversity that a viral population can sustain [1], but also to design effective contention strategies. There are two other features of infection propagation often disregarded in quasi-species models. First, the appearance of compensatory or beneficial mutations is non-negligible, especially for sub-optimally adapted viruses; second, viruses often encounter host resistance to infection. These two features were implemented in a model that studied the propagation of a viral population in 2D space, and showed that the dynamical behaviour and fate of those populations qualitatively differs from their mean-field counterpart. A first important difference between spatial and mean-field models with otherwise identical rules for viral dynamics is the appearance of clustering (of similar viral types) induced by spatial proximity, which fades as mobility increases [1] or as mutations rates augment [2]. This clustering causes a local advantage of less fit viral types, and hinders the advantage of high-fitness types, which are locally forced to compete with their equals. A second important fact regards the effect of host resistance. When spatial restrictions are absent, viruses can overcome host resistance by increasing its progeny production; however, if the number of available hosts is limited, augmenting progeny does not confer any additional advantage beyond a certain limit threshold. As a result, infection clearance may occur at a finite value of host resistance, a situation that maps the spatial model to a multi-component generalization of the Domany–Kinzel probabilistic cellular automaton [4], and thus classifies viral extinction within the directed percolation (DP) universality class.

## 3 On the Origin of Multipartite Viral Genomes

Multipartite viruses, characterized by fragmented genomes encapsidated in different virions (from two to eight fragments), represent about 50 % of all viruses infecting plants. Infection by such viruses is successful if at least one representative of each fragment is present in the cell—usually requiring a high multiplicity of infection (MOI). For viral multi-partition to be an evolutionary stable strategy, those viruses must compensate the cost of high MOI with an advantage originating from their fragmented nature. It was experimentally shown that such an advantage may arise from the higher stability of particles enclosing smaller genomes [14]. Inspired by those observations, a simple model of competition between a complete, wild-type virus encapsidated in a single particle and its bipartite counterpart was developed [8]. The model was successful at recovering the observations cited, assuming that bipartition appeared, as in the experiment, through segment deletion of the wild-type genome followed by competition between the two strategies. The

cooperating, smaller and fragmented solution, was able to displace the wild-type if MOI was above a threshold that could be analytically calculated. Since both fragments are symmetrically treated in the model (there were no experimental evidences indicating that they were different in any way), the stable solutions corresponded to equal amounts of each of the fragmented forms present in the population. In this scenario, the model made two predictions regarding the emergence and fixation of multipartite viruses with any number of fragments. First, it turned out that the values of MOI needed to compensate for the disadvantage of fragmentation appeared unrealistically high for viruses with four and more fragments; second, all stable solutions should present an equal amount of each of the fragmented types, any deviation from equal abundances resulting in even higher MOI values. However, it is known that the MOI of multipartite viruses is not as high as predicted by this simple model, and recent observations have come to challenge the second prediction, identifying significant imbalances in the frequencies of genomic fragments of two common plant viruses [18, 20]. The nature of the adaptive advantages enjoyed by these and likely many other multipartite viruses, and their evolutionary origin, are at this moment unsolved questions worth pursuing.

## 4 Viral Escape from Multidrug Therapies

Designers of antiviral therapies have to cope with the astonishing ability of viruses to escape medical treatments. The question is not whether a virus will develop resistance to an antiviral drug, but when will it occur. The simultaneous administration of two or more drugs has been used to delay the appearance of resistant mutants [6]. Searching for efficient therapeutic protocols, modelling may aid in three aspects: to characterize the response of viral populations to antiviral drugs through a more realistic implementation of their evolutionary strategies, to optimize drug administration protocols such that viral load is minimized, and to identify strategies that delay as much as possible the appearance of resistant forms [11]. A key issue to consider in multi-drug treatments is the possible interaction between the drugs involved. Combination therapies, where the drugs are simultaneously administered, are in general more efficient if the two drugs have a similar behaviour (e.g., both act as inhibitors of viral replication). However, in cases where a non-linear interaction between the effects caused by the two drugs is possible, a sequential administration might be preferred.

In experiments with foot-and-mouth disease virus, it was demonstrated that for a wide range of doses of an inhibitor of the viral replication and a mutagenic drug, their sequential administration ushered in a lower viral yield compared to their simultaneous use [15]. This fact motivated the design of a mathematical model that described viral dynamics and the response of the population to both drugs subjected to different modes of administration [9]. The model considered two types of viruses in the population, one susceptible to the inhibitor and another resistant. As indicated by experimental results, it was assumed that no resistance to the mutagen

could emerge. Viral properties (type of genome, replication mechanism, and basal mutation rate) were translated into model parameters, yielding a phase diagram where the preference of a sequential or combined administration of the drugs was quantified by means of the administered doses. The sequential treatment is preferred at high doses of both drugs, while for low doses a combination treatment is better suited. The precise dose value can be analytically calculated with the model. Further, it was also predicted that an intermediate region, where the combination treatment caused a lower viral load, but an increased likelihood of appearance of resistant forms (and vice versa for the sequential treatment), separated both phases at low doses of the inhibitor [16]. The disadvantage of a combination therapy at high doses of the mutagen (in particular) is due to the twofold effect of a mutagenic drug. On the one hand, it properly acts as an antiviral agent by augmenting the number of lethal and deleterious mutations in the population, increasing the number of defective (occasionally interfering) viral mutants. The latter are known to affect quasi-species fitness and may even cause the complete extinction of the population at doses below the error threshold [7]. On the other hand, it has been demonstrated that increases in the mutation rate may improve adaptation of suboptimal populations [12], since it produces higher diversity within the quasi-species and promotes the appearance of rare beneficial mutations. In the case of combination therapy, possible resistant forms that may get lost in absence of the inhibitor rapidly come to fixation due to the selection pressure it exerts.

## 5 Prospects

There are many unknowns regarding the adaptive potential of RNA viruses and their adaptive strategies. Current efforts are devoted to better understand and quantify the effect of mutational mechanisms, interactions within the mutant spectrum, and the role of the selective pressures at play. The fast increase in empirical knowledge and steady improvements in quasi-species models, together with technologies that are becoming easily accessible (as next generation sequencing or super-computation) are essential to acquire a better understanding of the general features involved in viral evolution and adaptation. Our hope for a meaningful theory of viral quasi-species depends on the existence of a reduced set of universal mechanisms, which should make possible the development of evolutionary theories of broad applicability. Advances in that direction are highly encouraging.

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