Dynamical correlations in the escape strategy of Influenza A virus

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received 12 October 2012; accepted in final form 6 March 2013
published online 2 April 2013

PACS 87.23.Kg – Dynamics of evolution
PACS 87.23.Cc – Population dynamics and ecological pattern formation
PACS 87.19.xd – Viral diseases

Abstract – The evolutionary dynamics of human Influenza A virus presents a challenging theoretical problem. An extremely high mutation rate allows the virus to escape, at each epidemic season, the host immune protection elicited by previous infections. At the same time, at each given epidemic season a single quasi-species, that is a set of closely related strains, is observed. A non-trivial relation between the genetic (i.e., at the sequence level) and the antigenic (i.e., related to the host immune response) distances can shed light into this puzzle. In this paper we introduce a model in which, in accordance with experimental observations, a simple interaction rule based on spatial correlations among point mutations dynamically defines an immunity space in the space of sequences. We investigate the static and dynamic structure of this space and we discuss how it affects the dynamics of the virus-host interaction. Interestingly we observe a staggered time structure in the virus evolution as in the real Influenza evolutionary dynamics.

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Introduction. – The interest of the scientific community in the Influenza A virus evolution has been continuously increasing in the last years [1–3]. Understanding the mechanisms driving the continuous change of the antigenic determinants is crucial in order to implement effective prevention strategies. Major efforts have been devoted to explain apparently contradictory features. On the one hand, the virus mutates fast enough so that the same host can be infected several times in the course of its life; on the other hand a viral quasi-species can be sufficiently well defined in any given epidemic season, so that a temporarily effective vaccine can be developed. The peculiar evolutionary dynamics of the Influenza A virus is revealed by the comb-like shape of its phylogenetic tree [4–6], as reconstructed from haemagglutinin (HA) coding sequences. It has been contrasted with phylogenetic trees of other viruses [7,8], as measles virus and HIV virus at the population level, which show more ramified patterns\textsuperscript{1}.

A crucial mechanism driving the interaction between the virus and the host immune system is cross-immunity: after being infected by a strain, the host acquires partial or total immunity to a set of other strains antigenically similar to the infecting one [9]. However it is not yet clear what determines the similarity relation in terms of genetic distance. A first attempt to reproduce in a modelling framework the complex balance between strains proliferation induced by antigenic drift, and strains selection, induced by the increasing acquired immunity of the hosts, is due to Ferguson et al. [1]. In that work, a mechanism of broad spectrum cross-immunity, lasting for a period of several weeks after infection, in addition to the life-long cross-immunity, is claimed to be crucial in order to recover the observed evolutionary dynamics of the Influenza A virus. Although this idea seems to be confirmed in the framework of simple evolutionary models [10,11], clear evidence of the existence of such a mechanism has not been provided so far.

A common trait of the above-mentioned and previous models [12] is the assumed equivalence between genetic and antigenic distance: mutations in the HA protein accumulate in time until eventually the mutated strain becomes enough antigenically distant to escape host immunity. In this case the degree of cross-immunity between the two strains is measured in terms of the

\textsuperscript{1}The phylogenetic tree of HIV virus inside a single host, where selective pressure plays a crucial role, presents instead features similar to those of the Influenza A virus tree.
Hamming distance between their sequences. Recent studies, however, highlight how that assumption is not completely correct [13]: high genetic differences can be irrelevant from the antigenic point of view and, vice versa, few nucleotidic mutations can elicit a large antigenic effect [13,14], indicating that the accumulation of genetic distance is not a necessary (and sometimes not sufficient) condition for the emergence of antigenically novel strains.

Further, it has been pointed out that amino acid changes which seem to be relevant in differentiating two specific antigenic clusters, can exhibit a null antigenic effect when appearing in different sequences [13], suggesting that antigenic clusters cannot simply be associated with key influential sites [15].

The fact that antigenic distances could depend on the presence of correlations among genetic mutations (epistasis)\(^2\) might explain why phenotypic changes do not necessarily appear as a consequence of accumulated mutations. Correlation between mutations have indeed been observed [16] and the existence of epistasis in neuraminidase (NA) and haemagglutinin (HA) proteins is supported by phylogenetic and sequence analysis [17–19]. The effect on the evolutionary dynamics of Influenza virus of a non-trivial relation between genotypic and phenotypic (antigenic) space has been investigated introducing the neutral network topology in the space of sequences [20,21]. Neutral networks are clusters of sequences connected by point-mutations which are associated to the same phenotype, i.e., each sequence is antigenically similar to the ones belonging to the same cluster and antigenically different from the ones belonging to other clusters. In the model proposed in [21], as a consequence of this specific choice of genotypic-phenotypic mapping, Influenza evolution occurs by “episodic selective sweeps”. When a mutated strain from a new cluster appears, it has a small probability of being highly advantageous. In that case, it fixes rapidly in the population. Selective sweeps are thus triggered by rare events, and followed by periods of neutral evolution during which all the genomes observed in the population have the same fitness. However, recent genomic analysis of Influenza data presented in [22] supports a different evolutionary process of Influenza, not compatible with the one described in [21]. In this scenario Influenza evolution is driven by a high supply of beneficial mutations that triggers “clonal interference”. Clones are sets of strains with similar sequences and a common ancestor. Due to competition, typically only lineages descending from a single high-fitness clone will survive, while the others eventually will become extinct. The expansion of a successful clone is driven by strongly beneficial mutations which rapidly fix in the population. Such selective sweeps reduce the diversity, though they never completely remove it, i.e., thanks to the high mutational rate, the population always remains multiclonal.

In this paper we introduce a simple epistatic rule which defines a genotypic-(antigenic) phenotypic mapping “dynamically” dependent on spatial correlations among point mutations. Here correlations are “dynamical”: neutral mutations at a certain point of the evolution are not established a priori as in [21], rather they depend on all the past infections up to that moment. Carved out by our epistatic rule, one can then identify a cluster of sequences respect to which the host is equally immune, that we call epistatic immunity space. Thus, on the contrary of the mentioned above neutral networks, our immunity space is not a static structure in the space of sequences, rather it evolves dynamically self-consistently with the virus-host interactions. This picture is compatible with the results presented in [22], considering a high rate of potentially beneficial mutations. We investigate the static and dynamical properties of such an immunity space and then we point out how they could affect the real virus dynamics. We first describe the non-trivial geometric and topological properties of the immunity space. Then we consider a simple greedy dynamics that mimics the escape strategies of a virus in an host population, relating in this way the emerging structure of the immunity space to the viral evolutionary dynamics. One striking consequence of the introduction of dynamically correlated point mutations is the existence of a staggered time structure in the virus evolution, characterised by an alternation of periods where a high number of relatively low fitness strains are able to spread the infection, followed by periods where a single highly fit strain is the favoured escape mutant. The fitness is here defined as proportional to the number of individuals not yet immune to that strain. Interestingly, this behaviour is absent when the antigenic distance is taken as directly proportional to the genetic distance.

Modelling cross-immunity with an epistatic immunity space. – We represent viral strains by binary sequences \(\vec{v}\) of fixed length \(n\) (see footnote\(^3\)). We define the immunity set \(I_n(\vec{v})\) of a strain \(\vec{v}\) as the set of viruses antigenically similar to it: those viruses that cannot infect a host that has been already infected by \(\vec{v}\). We can further consider the immunity elicited by more than one strain, for instance by all the strains produced by successive mutations and spread during an infection history. We call the immunity space, \(I_n(A)\), of the infection set \(A\) the union of all the immunity sets \(I_n(\vec{v})\) of the strains in \(A\):

\[
I_n(A) = \bigcup_{\vec{v} \in A} I_n(\vec{v}). \tag{1}
\]

\(^3\)We identify the viral strain with its epitope sites by representing them consecutively in a unique connected sequence. The generalisation to a four-letters alphabet will of course modify the quantitative results reported here, but should not affect our qualitative conclusions.
well-defined function \( j(n) = \frac{1}{\sqrt{n}} \), where \( i \) is the Hamming distance. As \( n \) increases, the epistatic density function converges to the well-defined function \( \rho_{\infty}(j) = \exp(-j^2) \).

The immunity set depends on the definition of antigenic similarity. We here investigate the simplest choice which includes correlations: we assume that two strains are cross-immune unless they differ in at least two consecutive bits. This choice is made for the sake of simplicity, but any pair of sites could be chosen without loss of generality and the present framework can be easily extended to more complex patterns of correlated mutations. We thus consider from now on

\[
I_n(\vec{v}) \equiv \{ \vec{z} \in H_n: z_i \neq v_i \Rightarrow z_{|i+1|} = v_{|i+1|}; \forall i \}, \tag{2}
\]

where \( H_n \) is the \( n \)-dimensional hypercube, composed of \( 2^n \) strings, with the metric given by the Hamming distance, and periodic boundary conditions. We will call \( I_n(\vec{v}) \) the epistatic immunity set generated by the strain \( \vec{v} \) and \( I_n(A) \) the epistatic immunity space (EIS) of the infection set \( A \).

**Static properties of the epistatic immunity space.** – The fraction \( \rho_n(i) \) of strains that belong to \( I_n(\vec{v}) \) and have Hamming distance \( i \) from \( \vec{v} \) can be computed and reads \( \rho_n(i) \approx \exp(-i^2/n) \) (see fig. 1 for the numerical plot and [23] for the analytical proof): on the one hand correlations introduce a non-trivial correspondence between genotypic and phenotypic space, on the other hand antigenic similarity is not completely uncorrelated from genetic distance [13]. The size \( S(n) \equiv |I_n(\vec{v})| \) of the immunity set generated by a strain, i.e., the number of strains cross-immune to it, satisfies a Fibonacci-like recursive relation: \( S(n) = S(n-1) + S(n-2) \) with initial condition \( S(2) = 3 \) and \( S(3) = 4 \). \( S(n) \) is known as Lucas sequence, and an explicit expression is known: \( S(n) = \phi^n + (1 - \phi)^n \approx \phi^n \), where \( \phi = (1 + \sqrt{5})/2 \approx 1.618 \) is the golden ratio, and the last asymptotic holds for large \( n \) (see also [23]). The size \( |I_n(A)| \) of the EIS generated by \( k \) different strains strongly depends on the actual form of the set \( A \). Two quantities are particularly relevant to provide bounds for every epidemic dynamics with the above-defined antigenic similarity measure: i) \( M(n) \), the maximum number of distinct strings that fit in the sequence space, and such that the next string would immunise the whole space (the strings are therefore chosen with the maximum overlap between their immunity sets); ii) \( m(n) \), the minimum number of strings needed to immunise the whole sequence space, and therefore chosen with the minimum overlap between their immunity sets. The computation of \( M(n) \) is straightforward: in order to have at least a string, say \( \vec{v} \), left out of the EIS, the infection set cannot contain any of the strings in \( I(\vec{v}) \). Therefore, the largest infection set that does not immunise the whole hypercube is \( A_D(n) = H_n / I(\vec{v}) \), which immunises the set \( H_n / \{ \vec{v} \} \), and \( M(n) = 2^n - S(n) \). We estimate \( m(n) \) by numerical simulations and we provide analytically an upper \( m_U(n) \) and a lower \( m_L(n) \) bound. A (trivial) lower bound is given by assuming totally disjoint immunity sets, and it is given by counting the total number of sequences divided by the size \( S(n) \) of a single immunity set: \( m_L(n) \approx 2^n / \phi^n = 2^m \), with \( \eta = 1 - \ln_2 \phi \approx 0.306 \). The fraction of strings contained in the immunity set of a single strain is therefore \( 2^{-m} \). An upper bound \( m_U(n) \) can be derived constructively by exhibiting a set of sequences whose immunity sets cover the sequence space. Such a set of sequences is obtained for example by combining in all possible ways \( n/2 \) pairs of identical bits, either \((0,0)\) or \((1,1)\) (for instance, for \( n = 4 \) such a coverage is realised by the four sequences \((0,0,0,0),(1,1,0,0),(0,0,1,1),(1,1,1,1)\)). The number of such sequences is \( m_U(n) = 2^n / n! \), where \( \lceil \cdot \rceil \) denotes the integer part. We estimate the asymptotic value of \( m(n) \) numerically by simulated annealing [24]. For any \( n \) we look for the set \( A \) composed of \( k \) sequences which minimises the cost function \( f_{n,k}(A) = 2^n - |I_n(A)| \). \( m(n) \) corresponds to the smallest \( k \) such that the minimum of the cost function \( f_{n,k}(A) \) is equal to 0 (see [23] for a more detailed analysis). Our estimation is \( m(n) \approx 2^n \) with \( v \approx 0.4 \), compatible with the analytical bounds (see fig. 2).

Let us now focus on the topological properties of the EIS. Noticeably, the EIS is always a connected set, for any infection history. To prove this we need to show that for any pair of sequences \( \vec{x}, \vec{y} \), there exists a path of cross-immune sequences joining them. Since every single immunity set is connected, it is thus enough to show that any pair of immunity sets overlaps, or is at most contiguous. Take \( \vec{x} = \vec{0} \) without loss of generality, and \( \vec{y} = (y_1, y_2, \ldots, y_n) \). For \( n \) even, the two immune sets always overlap at least in the sequence \((0, y_2, 0, y_4, 0, \ldots, 0, y_n)\). For \( n \) odd they are contiguous in the two points \((0, y_2, 0, y_4, 0, \ldots, 0, y_{n-1}, 0) \in I_n(\vec{0}) \) and \((0, y_2, 0, y_4, 0, \ldots, 0, y_{n-1}, y_n) \in I_n(\vec{y}) \) (actually they always overlap at some point unless \( y_1 = 1 \)).
Cardinality of the generating set

\[ M(n) \]

\[ m_N(n) \]

\[ m_L(n) \]

\[ m_U(n) \]

Fig. 2: (Colour on-line) Numerical estimate of \( m(n) \), \( m_N(n) \), along with its lower and upper bound, and the value of \( M(n) \) as a function of \( n \). The dotted line represents the function \( 2^{2^n} \), with \( \nu = 0.399 \pm 0.002 \), which has been used to fit the first 15 values of \( m_N(n) \).

Fig. 3: (Colour on-line) Sketch of the non-infectious (green) and infectious (blue) region of the sequence space. Left: for small \( k \) above threshold the infectious region features a large connected cluster, corresponding to a infectious region of the hypercube, along as many small connected clusters. Right: by increasing \( k \), only small holes in the EIS are left.

Simple dynamics on the epistatic immunity space. – We have so far examined general topological properties of the EIS from a static point of view. The non-trivial shape of the set of cross-immune sequences can be however better highlighted considering simple infectious dynamics. We then consider a local maximisation (LM) of the EIS: starting with a random strain, we choose at every step the next strain among those not already belonging to the EIS, and such that it maximises the size of the current EIS (and thus minimises the overlap with the existing EIS). In case that several strings satisfy this criterion we choose one at random among them. We iterate until the whole space \( H_n \) is non-infectious. Each step of the LM process corresponds to a new infection of the same host population from the virus. Although virus evolution happens by point mutations, when a virus infects again the same host it presents multiple mutations with respect to the genome of the previous infection. In fact the largest part of the population is typically infected once every one or more epidemic seasons, while the point mutation rate of the virus is much higher. This local maximisation dynamics represents an attempt to model an effective interaction between a population of viruses and a population of hosts who is more likely to get infected provided the mutated virus is more antigenically dissimilar from the previous successful one. From this perspective this LM process mimics a successful escape strategy of the virus in a host population in a coarse grained way in order to capture the implications of the adoption of the epistatic rule.

If we look at the number of sequences that satisfy the local maximisation constraint at each time step, we find a peculiar behaviour that is not observed when the immunity sets are constructed by means of the bare Hamming distance from the generating strain. The time behaviour features a well-defined series of peaks corresponding to an alternation of periods with many equivalent options (i.e., possible strategies for the virus) and only one optimal option to maximise the immunity set (fig. 4). This gives a hint of how dynamical constraints arise from the presence of epistatic interactions with respect to the case in which antigenic distance is directly proportional to genetic distance.

To further characterise the epidemic dynamics we look at the normalised invasion rate, i.e., the fraction of strains becoming non-infectious at each step of the LM dynamics (fig. 5). This quantity also shows a non-trivial behaviour characterised by a series of hierarchically distributed jumps that occur always at the same time steps, independently of \( n \), and that are not present when the same dynamics is studied with a Hamming rule for cross-immunity (see fig. 5, right). This points again to a staggered time structure with an alternation of periods of highly effective immunisation, followed by periods with a relatively lower immunisation rate. This picture is also confirmed by the parametric plot in the bottom of fig. 5 where the degeneracy (the fraction of optimal strains) is plotted vs. the normalised invasion rate. The peculiar triangular structure, absent in the Hamming case, is the signature of an alternation of times with no
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Fig. 4: (Colour on-line) Left: degeneracy of strings allowed by the local optimisation dynamics (normalised with $2^n$) as a function of the iteration number $k$ (time) for the epistatic rule. The averages are taken over 1000 realisations. Right: for comparison: same dynamics, but with cross-immunity defined by the Hamming rule. In this case no jumps are observed. Bottom: parametric plot of the degeneracy vs. the normalised invasion rate for the epistatic rule with $n = 19$.

degeneracy (only one option) corresponding to a high invasion rate followed by times with a very high degeneracy and low invasion rate. This behaviour can be related to the comb-like shape of the Influenza A phylogenetic tree, where a single quasi-species is responsible for each annual epidemic and antigenic clusters follow one another each for a few years [14].

Conclusion and perspectives. – In this paper we focused on the long-standing puzzle behind the strategies of viruses trying to escape the immune system. We introduced in particular a model in which cross-immunity, i.e., the mechanism through which a host acquires partial or total immunity to a set of other strains antigenically similar to the infecting one, is defined in terms of dynamically correlated point mutations. We have investigated how this epistatic rule carves in a non-trivial way the immunity space of the host, i.e., the set of viruses to which a host is immune after infection by all the strains in his infection history. We quantified the geometrical and topological properties of this space, highlighting qualitative differences with respect to the case when a distance that disregards correlations among different sites (e.g., the Hamming distance) is considered. We have further studied a simple greedy virus dynamics, focusing on the important differences with respect to the case where the usual Hamming distance defines cross-immunity. Here we obtained the striking result that a simple escape virus dynamics on the epistatically carved immunity space, leads to a staggered time structure of the virus evolution. Times where one single choice exists that maximises the invasion rate are followed by times where many different options exist to immunise a relatively smaller set of sequences. This results contrasts with the corresponding result obtained without dynamical correlations in the definition of the cross-immunity. Although obtained in the framework of a toy model, it is quite tempting to identify our staggered time structure with the succession in time of different antigenic clusters and with the more violent epidemic outbreaks at each cluster change, as observed in real virus-host dynamics. The analysis presented here can help understand the effect of the conjectured epistatic interactions on the shape of immunity clusters as well as on the viral evolutionary dynamics at large. This in turn can trigger the investigation of more realistic virus-host interaction schemes incorporating the epistatic rule.

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