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Red Queen Dynamics, Competition and Critical Points in a Model of RNA Virus Quasispecies

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Abstract

Recent experiments involving competition of clonal populations of RNA viruses have shown that competition among virus strains of approximately equal relative fitness can result in the eventual competitive exclusion of one of the species. As competition proceeds in time, both the winners and the losers exhibited absolute gains in fitness, consistent with the “Red Queen” hypothesis of evolution. Further experiments involving closely related evolving quasispecies revealed a highly predictable nonlinear behavior suggesting a deterministic component in the underlying quasispecies dynamics. In this paper we present a simple model of RNA virus populations which allows previous hypothesis to be tested and provides an interpretation for the observed experimental results.

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1 Introduction

RNA viruses, because of their intrinsic simplicity and adaptability offer a unique opportunity for exploring long term evolution under controlled conditions (Domingo and Holland, 1994). They are by far the most important group of intracellular parasites. RNA viruses are successful because they are simple, small-sized, fast replicating but specially because of their enormous plasticity and adaptability to changing environments. Such plasticity stems from the high mutation rates operating during RNA genome synthesis and rapid replication. These two influences lead to an extremely heterogeneous population structure termed quasispecies (see below).

The dynamics of the viral population can be visualized as a dynamical process of growth, competition and selection which takes place in the sequence space. Although the sequence space is comprised of an astronomically large, multidimensional set of points, we can use a simple three-dimensional surface to illustrate the ideas developed below (figure 1). The fitness landscape (an idea first introduced by Sewall Wright and later extended by several authors, see Kauffman, 1990; Perelson and Kauffman, 1991, and references therein) is defined in terms of some particular traits which are implicit in the virus particle phenotype and are usually described in terms of replication rate or infectivity. The landscape appears as a multipeaked surface. Local maxima represents optimal fitness values which can be reached through mutation. Given an initial condition defined by a quasispecies distribution localized somewhere in the sequence space, the population will evolve by exploring nearest positions through mutation.

In a recent series of experiments with RNA viruses Holland and co-workers (Clarke et al, 1994) showed that the evolution of fitness of marked monoclonal antibody-resistant (MARM) clones of vesicular stomatitis virus (VSV) exhibit steady gains in fitness during repeated transfers of large virus populations in cell culture (Novella et al. 1995). The increase did not reveal sudden jumps in fitness and further theoretical analysis (Tsimring et al, 1996) concluded that the observations can be fairly well explained as hill climbing of the population towards higher replication values on a smooth landscape. In this paper the smoothness of the landscape will be assumed as an intrinsic property of the system.
Figure 1: The fitness landscape of a population defined by a given number of traits. Here we simplify the underlying multidimensional sequence space in order to provide some intuitive insight to the problem under consideration. The peaks are local optima which can be reached through mutation (which allows diffusion over sequence space) and selection pressures. Under specific conditions, the virus population starts at some point moving towards local maxima. Large jumps from one peak to another are unlikely to occur unless other phenomena—like recombination—take place.

2 Overview of experimental results

Two different, but closely related, sets of experiments will be analysed. Both of them lead to the formulation of some theoretical arguments that we will discuss here. The first experiment involved the mixing of two clonal populations of VSV of approximately equal fitness (Clarke et al., 1994). These populations were allowed to grow and compete by means of standard virus plaque assays (Holland et al., 1991). Genetically marked monoclonal antibody-resistant mutant clones of fitness nearly equal to the wild-type (wt) VSV were used and their relative fitness measured at each passage (figure 2). The results of these experiments, involving a large number of passages, was very interesting in evolutionary and ecological terms. Both competing populations grew up showing steadily increases in fitness. At some point, however, one of the populations suddenly dominates excluding the second one. The winner of this competition process was not always the same. Sometimes one of the populations dominated, sometimes the other one.
Figure 2: Passage experiments: starting from a given MARM clone of VSV virus mixed at 1:1 ratio with wt. Then $2 \times 10^5$ plaque forming units (pfu) of the initial mixture were used to infect a BHK21 monolayer ($2 \times 10^6$ cells). After cytopathic effect, around $2 \times 10^2$ pfu (out of total $10^{10}$ viral yield) were used for the next passage. In mathematical terms, we could interpret the passages as continuous evolutions with given mean parameter values followed by discontinuous sampling procedures which somehow alter the parameter values.

The simultaneous increase of fitness exhibited by both competing populations was suggested to be a neat illustration of what is known in evolutionary ecology as the “Red Queen” effect (Van Valen, 1973): in a complex ecosystem, species are imagined to be under constant pressure of change, both because of environmental changes but also because constant modifications in their biotic environment. Just like the Red Queen in Lewis Carroll’s *Through the Looking Glass*, each species is forced to keep running just to stay in the same place, i.e. to keep changing to adjust to the ever changing conditions of existence. In the context of quasispecies, newly arising mutants with higher fitness can outcompete lower-fitness mutants eventually leading to a shift in the quasispecies structure. The final outcome of these experiments (the exclusion of one strain) is consistent with the principle of competitive exclusion (Gause, 1971). This principle can be formulated in mathematical terms for a two-species model, the so-called Lotka-Volterra model (Lotka, 1925) which describes the time evolution of two populations $N_1, N_2$ of competing species:

\[
\frac{dN_1}{dt} = \mu_1 N_1 (1 - N_1 - \beta_{12} N_2) \\
\frac{dN_2}{dt} = \mu_2 N_1 (1 - N_1 - \beta_{21} N_1)
\]

(see e.g. Murray, 1988). Here $\mu_i$ and $\beta_{ij}$ are the growth and interspecific competition rates of each species, respectively. A mathematical analysis of this model shows
that it involves four relevant steady states. The first is the trivial \((0, 0)\) points. The second and third are the exclusion points: \((1, 0), (0, 1)\) and the fourth one is the coexistence point, \((N^c_1, N^c_2)\) where \(N^c_i\) will depend on the parameters under consideration. For simplicity (and because it will be relevant in our analysis) let us consider the symmetric case where \(\mu_i = \mu\) and \(\beta_{ij} = \beta\) for \(i, j = 1, 2\).

![Graph showing competition rate vs. time for two species competition model]

Figure 3: Symmetry-breaking in the two-species competition model, described by equations (1-2). Here \(\mu = 6\) and different values of the competition rate \(\beta\) are used. We can see that the difference \(N_1 - N_2\) remains zero (i.e., both populations have the same size) until the critical point \(\beta_c = 1\) is reached. Inset: we can mimic the dynamics of two evolving populations with changing rates by artificially increasing \(\beta\) with time. By iterating the previous equations (1-2) with \(\beta(t) = et\) (see also appendix)

The stability analysis of the previous system shows that coexistence is possible only if the competition coefficient is below a critical value, i.e. \(\beta < \beta_c = 1\). Otherwise, one of the species will exclude the second one. The process of competitive exclusion is highly sensitive to fluctuations: if we are at the point \((N^c_1, N^c_2)\) for \(\beta > \beta_c\) any small fluctuation (one of the populations becomes slightly larger than the other) will be amplified by the system. This type of process is known as a symmetry-
breaking phenomenon (solé et al., 1996). It is well known to be widespread in nature, from cosmology to the economy (Nicolis and Prigogine, 1988).

This phenomenon is illustrated in figure 3, where we plot the steady state points of the previous system of equations for different competition rates and for two different initial conditions: \( N_1(0) > N_2(0) \) (white circles) and \( N_2(0) > N_1(0) \) (white diamonds) being the difference only of \( |N_1 - N_2| = 0.01 \). The difference \( N_1(10^3) - N_2(10^3) \) between the two populations after \( 10^3 \) steps is plotted. We can see that it goes to zero for subcritical values of \( \beta \) but it suddenly changes to a situation where one of the populations excludes the other. Two possible branches are observed. A toy model of evolution can also be used to see how this bifurcation takes place (figure 3, inset). By allowing \( \beta \) to vary with time, we mimic the evolution of the two competitors towards higher interaction strength. Once \( \beta_c \) is reached, one of the competitors is excluded. The final winner is highly dependent on the random fluctuations occurring close to the critical value (see appendix).

The reason why we mention symmetry breaking and critical points in deterministic systems with random fluctuations is that the second set of experiments revealed a deterministic phenomenon linked with some kind of critical point behavior (Quer et al, 1996). Specifically, these authors followed a similar protocol of competitive replication in a constant cell culture environment of two closely related evolving quasispecies of VSV. They determined the relative concentration of a wild-type clone and a surrogate marked virus subclone (MARM-C) at each daily passage. By repeating the same competition, a highly predictable nonlinear behavior was observed: a tendency of the MARM-C to gain less fitness than the wild-type. In addition, they reported the existence of critical points, defined as points from which viral competition (may) follow different trajectories. However, the exact interpretation of such critical points was not provided, although the deterministic nature of their results strongly pointed towards a scenario consistent with symmetry-breaking.

In this paper we will explore this idea by means of a simple model of competition in a quasispecies population of bit strings, together with some simple theoretical arguments. The model is able to account for both sets of experiments, showing already that Red Queen dynamics takes place in the first phase of the numerical experiments, followed by competitive exclusion of one of the strains. The reported critical points observed in the experimental study would be true critical points as defined in the previous context.
3 Competition within quasispecies

The standard approach to the quasispecies dynamics is based on the Eigen’s model of molecular quasispecies (Eigen, 1971; Eigen, MacCaskill and Schuster, 1987; 1988). It involves a set of molecules (sequences, strings) which can replicate and mutate. The basic equations are:

$$\frac{dx_i}{dt} = (A_i Q_i - D_i - \Phi)x_i + \sum_{j \neq i} \Psi_{ij} x_j$$

whith $i = 1, 2, ..., n$ accounting for the population size of each string. The parameters $A_i$ and $Q_i$ are the replication rate and the quality factor, respectively. $Q_i \in [0, 1]$ is a measure of the correctness of the replication process, and it is maximum ($Q_i = 1$) if no mutations occur. $D_i$ stands for spontaneous degradation of molecules (assumed to be linear) and $\Psi_{ij}$ are the mutation rates which can lead to transitions $j \rightarrow i$. Finally, the term $\Phi$ is an outflow term which take into account the removal of molecules from the system. If we introduce the constraint of constant population size (CP), the previous equations are:

$$\frac{dx_i}{dt} = (A_i Q_i - D_i - \bar{E})x_i + \sum_{j \neq i} \Psi_{ij} x_j$$

where the mean value of the so-called excess productivity $E_i = A_i - Q_i$ is given by:

$$\bar{E} = \frac{\sum_i (A_i - D_i)x_i}{\sum_i x_i}$$

Under the CP constraint, a simple selection process takes place. When mutation rates are very small, the fastest replicating sequence increases until $x_n$ gets the maximum population size. However, if mutation is present, no single-species population structure is found, but a quasispecies.

Using this approach, we can now explore the behavior of a set of competing quasispecies. In the general case, when $m$ different populations are be considered, $\{x_i^k\}$ (with $i = 1, ..., n$ ; $k = 1, ..., m$) which compete for a given set or resources. We can write down the following system of equations:

$$\frac{dx_i^k}{dt} = (A_i^k Q_i^k - D_i^k - \bar{E})x_i^k + \sum_{j \neq i} \Psi_{ij}^k x_j^k$$

($i = 1, ..., n; k = 1, ..., m$) where we are considering that different sets of populations (localized at different regions of the sequence space) compete for available resources.
In the context of the experiments with VSV, we are considering two clonal populations competing for the cells in the cell culture.

Let us rewrite the previous equations to show that they are to a large extent equivalent to the Lotka-Volterra competition equations. Using the notation $E^k_i = A^k_i - D^k_i$ (the so called excess productivity) we get:

$$\frac{dx^k_i}{dt} = x^k_i \left( E^k_i - \frac{\sum_{r=1}^m \sum_{j=1}^n E^r_j x^r_j}{\sum_{r=1}^m \sum_{j=1}^n x^r_j} \right) + \sum_{j \neq i} \Psi^k_{ij} x^k_j$$

(7)

$$= \frac{E^k_i}{C} x^k_i \left( C - \sum_{r=1}^m \sum_{j=1}^n \Lambda^k_{ij} x^r_j \right) + \sum_{j \neq i} \Psi^k_{ij} x^k_j$$

(8)

$$= \mu^k_i x^k_i \left( C - x^k_i - \sum_{r \neq k} \sum_{j \neq i} \Lambda^k_{ij} x^r_j \right) + \sum_{j \neq i} \Psi^k_{ij} x^k_j$$

(9)

where we made use of the CP constraint and where $\mu^k_i = E^k_i / C$ and $\Lambda^k_{ij} = E^r_j / E^k_i$ gives us a measure of the competition among different strains and different sequences of each strain. Clearly, if the mutation term is ignored, a generalized Lotka-Volterra model of $m \times n$-species competition is obtained.

If no mutations are considered, for the $r = 2$ case, a couple of equations are obtained from (9), which are in fact the Lotka-Volterra equations (1-2):

$$\frac{dx^1_i}{dt} = x^1_i \left( E^1_i - \sum_{j=1}^n (E^1_j x^1_j + E^2_j x^2_j) \right)$$

(10)

$$\frac{dx^2_i}{dt} = x^2_i \left( E^2_i - \sum_{j=1}^n (E^1_j x^1_j + E^2_j x^2_j) \right)$$

(11)

Using the definition of the time-dependent average excess productivity,

$$< E_k(t) > = \frac{\sum_{i=1}^n E_k x^k_i(t)}{\sum_{i=1}^n x^k_i(t)}$$

an system of equations for the population size of each type, i. e. $x_k = \sum_j x^k_j$ can be derived:

$$\frac{dx_1}{dt} = < E_1(t) > x_1(1 - x_1 - \frac{< E_2(t) >}{< E_1(t) >} x_2)$$

(12)

$$\frac{dx_1}{dt} = < E_2(t) > x_2(1 - x_2 - \frac{< E_1(t) >}{< E_2(t) >} x_1)$$

(13)
which tells us that under the symmetry requirements of this model, the competition coefficients are such that an net increase in the replication rate of one of the clones will immediately generate a deviation from the symmetric case.

Comparing these equations with (1-2) we can see that the interspecific competition terms are such that \( \beta_{12} = 1/\beta_{21} \). This leads to an interesting situation: the set of possible steady states is reduced to three. The coexistence point is no longer a solution of the previous equations, and this leads to the conclusion that, under the present conditions exclusion must occur.

In this sense, if the mutation terms are considered as the source of change in \( < E_i(t) > \) two possible processes leading to competitive exclusion are allowed: (a) symmetry breaking, where \( < E_i(t) > \) is the same for both populations but one of them takes advantage by generating more individuals through random fluctuations and (b) changes in the mean parameters, allowing for an asymmetric set of equations and exclusion of the less fit population.

## 4 A bit string model for VSV dynamics

The model that we will use in this paper is a discrete model where each RNA virus is represented by a string of \( \nu \) bits. Instead of four different units we only consider (as usual in many theoretical studies with quasispecies) two different types of monomers, which will be indicated as zero and one. So our population is formed by \( N \) bit strings (BS) each one indicated by \( S_i \) and their sequence can be written as:

\[
S_i = S_i^1 S_i^0 ... S_i^\nu ; \quad i = 1, 2, ..., N
\]

with \( S^j_i \in \{0, 1\} \). Each time step (generation, passage) we repeat \( N \) times the following set of rules:

- We take a BS at random from the population, say \( S_i \) and replicate it. The replication probability \( r_i \) is, in principle, string-dependent, i.e.

  \[
  r_i = \phi(S_i^1 S_i^0 ... S_i^\nu)
  \]

  although (see below) a simple choice of the replication rate in relation with string structure can be made allowing to simplify the problem.

- Replication takes place by replacing one of the strings in the population (also chosen at random) say \( S_j \) by a copy of \( S_i \). The copy mechanisms presents error, at a rate (per bit and replication cycle) \( \mu \). So we have: \( S_j^k = S_i^k \) with probability \( 1 - \mu \) and \( S_j^k = 1 - S_i^k \) with probability \( \mu \).
Figure 4: Evolution of fitness in a single-strain bit string model, with $N = 1000$ bit strings, $\nu = 15$ bits and a mutation rate $\mu = 10^{-3}$. The fitness is defined as the mean replication rate $< r >$, i.e. $< r(t) > = \int p(r,t) r dr / \int p(r,t) dr$, where $p(r,t)$ is the frequency of strings with $r$-replication rate. As reported from experiment with VSV (Novella et al., 1995) two well-defined phases are observed. Inset: evolution of mutant populations. After a first short phase, where a fast-replicating string is selected, afterwards new, faster mutants replace the previous ones.

There are many ways of describing the mapping between replication rate and string sequence. In this paper we consider a simple mapping, which involves a linear relation:

$$r(S_i) = r(S_i^1, \ldots, S_i^\nu) = \sum_{j=1}^{\nu} S_i^j$$

(15)

which means that the landscape of our problem is smooth (we can increase fitness, starting from a given sequence, by consecutive single-bit jumps in the sequence space) and single-peaked (there is a maximum replication rate $r = 1$ for $S_i = 1111\ldots11$. These choice has been used by other authors (Tsimring et al. 1996) and is consistent with the experimental observations: in the experiments by Holland and co-workers with VSV revealed a continuous growth of fitness from day to day. Fitness
was measured by mixing a sample of the virus population with a sample of wild-type (wt), taken from a frozen, nonevolving stock. By doing a small number of passages of this mixed population, the ratio between both populations was measured and the relative fitness estimated from the logarithm of the ratio $r(\text{mutant})/r(\text{wt})$ versus $n$, the $n$-th passage in the experiment.

The Novella et al. experiments revealed two phases in the dynamics of fitness growth: a first phase where a rapid growth takes place and a second phase with a slower rate of increase. A first test for our model, before the competition experiment, should be to check whether or not such two phases are observed in our model. In figure (4) we show an example of the dynamics of a $N = 1000$ string system with $\nu = 15$ units per string. We can see that two phases are effectively present. The initial condition is a random population with equally distributed 1’s and 0’s, and so $< r(0) > = 0.5$. Although a more complex landscape can be used, this choice seems particularly appropriate. If we use a random replication rate $r(S) = \xi$ with $xi$ randomly distributed over the interval $(0, 1)$ a monotonous increase in fitness is also observed, but not such two phases are found.

The origin of this two-phase behavior has been explained by Tsimring et al by means of a simple mean-field approach (Tsimring et al. 1996). Their work is in fact an extension of previous studies on reaction-diffusion models of molecular evolution (ebling et al, 1984). If we assume that we can lump together all sequences which share the same replication rate, a diffusion equation for the population density can be derived. Let us assume that the fitness is defined over a given interval and let $p(r, t)$ be the fraction of strings with a replication rate $r$. The simplest mathematical model for this process will be:

$$\frac{\partial p(r, t)}{\partial t} = (r - < r(t) >)p(r, t)$$

which trivially leads to a monotonous increase eventually reaching $r_{\text{max}}$. This equation should be completed by adding a diffusion term and a drift term, i.e.

$$\frac{\partial p(r, t)}{\partial t} = (r - < r(t) >)p(r, t) + D\frac{\partial^2 p(r, t)}{\partial r^2} + \frac{\partial}{\partial r}[G(r)p(r, t)]$$

Tsimring et al., showed that the constant fitness growth in the experiments allows to ignore the drift term. Starting from a random distribution of fitness within $(r_{\text{min}}, r_{\text{max}})$, they show that, at the first phase, a pulse-like distribution is formed and localized around $r_{\text{max}}$. This phase is followed by a slow drift towards higher values while keeping the stationary pulse-like form. This behavior is also observed in our model.
Figure 5: Dynamics of the bit string ecosystem (see text) for a population of $N = 2500$ strings of length $\nu = 20$. The initial condition corresponds to two equal fit populations with random structure. The top figures show the evolution of the total population size for each clone (string population) and their corresponding mean fitness (insets). We can see that a SB bifurcation takes place at $t \approx 25$. Up to this point both populations share similar sizes and their replication rates raises (right inset). A RedQueen dynamics is observed with successive replacements of the population structure by higher-fitness mutants (bottom).

The next step is to simulate the competition between two different clones. The experimental results revealed again a smooth-fitness landscape behavior with a highly predictable outcome when the same clones where used in repeated experiments (Quer et al, 1996). It was shown that both losers and winers exhibited absolute gains in fitness. Using the Red Queen metaphor, both populations keep changing in order to remain in the play. Now using our model we can explore how this Red Queen dynamics takes place and why it is interrupted by competitive exclusion.

In figure 5 we show typical outcomes of our model for a $N = 2500$ strings of length $\nu = 20$. The initial condition is defined by two populations with $S_i^k = 0$ for $k > 2$ and
the first two bits randomly generated. In this way their initial fitness are low enough
and their mean replication rates will be the same. Now each time step (generation)
consist in repeating $N$ times the previous rules. Clearly our strings are competing
for the available space (i. e. $N$ available sites) and relevant biological processes
such efficiency of infection, presence of defective interfering particles, intracellular
competition when two viruses from each competing population infect some cell or
random sampling are not taken into account nor the specific procedure of the passage
experiment. However, we have explored a much more detailed model involving most
of these aspects and an equivalent set of results has been obtained.

A Red Queen dynamical pattern is immediately observable in these simulations.
Instead of following the population numbers of specific strings, and given the way in
which we assign the fitness, we follow the time evolution of the populations sharing
the same replication rate (the replication classes) i. e. the numbers

$$n(r,t) = \sum_{i=1}^{N} \delta(\sum_{t=1}^{\nu} S_{t}, r)$$

(18)

where $\delta(x,y) = 1$ when $x = y$ and zero otherwise. In figure 5 we show the total
population size of each quasispecies together with the corresponding evolution of the
population sizes of different replication classes. We can see how the total population
size of both strains is maintained roughly constant over some period of time (about
t $\approx 20$ generations). The left column in figure (5) corresponds to the typical outcome
of our simulations. From time to time, however, a much more fluctuating pattern is
observed, with a longer period of time until exclusion. This occurs when, after a first
divergence in the population size of each clone, a random fluctuation enables the
lower population to get higher replication rates. Some plateaus are then observed,
followed by further fluctuations before exclusion takes place. This type of fluctuation
was also reported to occur in one of the MARM-C clones studied by Quer et al.

Over the transient time, both populations win fitness, as their spread over the
sequence space towards the maximum fitness peak. But their replication rates re-
main the same over the whole process. Following our previous arguments, if the
replication rates are barely the same, the symmetry of the dynamical process is
preserved. In this sense, the Red Queen dynamics takes place on the critical point
and the constantly changing fitness keeps the system at such a critical point. As a
consequence both total populations are basically equal.

But there is a maximum fitness value which is reached after the transient and
where no further rapid changes in mean replication rates are allowed to occur. Then
Figure 6: Predictable nonlinear behavior: several runs of the BS model are plotted (only one of the populations is shown). The initial condition is defined as $S^k_i = 0$ for $k > 2$ and the first two bits randomly generated. This provides a population with equal, low fitness for both clones. We can see that the Red Queen dynamics keeps both populations with similar values over the first $t \approx 20$ generations. This is the time needed to reach a situation where strings with the high fitness appear. Until then, the constantly changing replication rates grow together at the same rhythm fluctuations take over and one of the populations increases, and symmetry breaking takes place. Such process can of course at low $r$-values but for large populations high fitness values needs to be reached before competition ends.

5 Discussion

In this paper we have explored the dynamics of a simple bit string ecosystem with two competing populations involving error-prone replication. The goal of our study was to test the hypothesis suggested by the experiments on competition with MARM clones of VSV (Clarke et al, 1994; Quer et al. 1996). Specifically, two types of phenomena, consistent with two major theories of classical population biology, where
observed: a phase of absolute gains of fitness in both populations followed by a phase where competitive exclusion take place. The starting situations i.e. clonal populations of VSV virus with approximately equal relative fitness, implies that some symmetry between the populations is present, somehow maintained through the selection process as both quasiespecies perform their uphill climb towards higher fitness values. In terms of our analysis, we can interpret this dynamics as a Red Queen race close to a critical point. Although the symmetry of the competition process should break because of fluctuations, the constant change in the fitness allows the system to avoid the breaking of the symmetry. This is an interesting result in terms of the standard assumptions of the Red Queen theory. The Red Queen dynamics poises the system into the critical state and keeps it at such point. Because the landscape is smooth and the evolution of both strains takes place in a similar way, some transient time is required before the maximum fitness is reached or, more precisely, before the first highest fit strings appear.

Once strings with high replication rates take advantage in one of the clones, amplification processes are at work and random fluctuations in the population size can eventually break the symmetry. In most of our numerical experiments we observe the two phases followed by a such breaking of symmetry. So the model shows that deterministic dynamics is present as far as both populations are likely to simultaneously increase their fitness in a predictable way. But there is also a very important role for the random events: at some point a small deviation in the relative abundances of the competing quasiespecies will by amplified in a highly nonlinear way.

The results reported by Quer et al. are also easily interpreted under our theoretical framework. Again, two clones with similar replication rates are mixed and the same experiment is repeated several times. A highly predictable outcome is reported: concomitant with expected fitness gain of both competing viral populations, a tendency of the MARM-C clone to gain less fitness than the wild type was observed. Although this tendency was noisy, it was reported in all evolutionary replicas. This shows us that, despite the underlying stochastic dynamics, a strong deterministic component was present. It is not difficult to interpret these results in our present framework. Even if symmetric populations are used, the smoothness of the landscape allows for a well defined transient phase which is rarely violated by random fluctuations (see appendix).

However, if a slight change into the landscape structure of both populations is included (like an increase in the replication rate of one of the populations for some strings) then the Red Queen scenario is followed by a deterministic change in a well defined direction. The parameters in the system are no longer symmetric, and so a
selection process always happens favouring the same MARM clone.

Further studies should explore how the properties of the fitness landscape and other biologically sensible factors can modify our results. Such studies can also be useful in exploring the nature of the real landscapes of RNA viruses and the possible relevance of nonlinear phenomena in the evolution of real populations. The use of nonlinear models of population dynamics incorporating random fluctuations can be of great help in understanding the outcome of evolutionary processes from both experimental and field populations.

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6 Appendix: Predictability, noise and symmetry breaking

The passage experiments with MARM clones suggest that both random fluctuations and deterministic components play an important role in the final outcome of the RNA competition dynamics. But how much can be predicted from a nonlinear dynamical system involving symmetry breaking and stochastic fluctuations? To analyse this problem within the context of the critical points, let us consider a simple, very well known model of nonlinear dynamics (Haken, 1988) described by:

$$\frac{dx}{dt} = (\beta - \beta_c)x - \gamma x^3 + \eta(t)$$

where $x$ can be understood, in our case, as the difference $x = x_1 - x_2$ between population sizes of each type. Here $\eta(t)$ is a noise term with mean zero $< \eta(t) > = 0$ and $< \eta(t)\eta(t') > = 2Q\delta(t - t')$. This one of the simplest models of symmetry-breaking dynamics and all the properties derived from it are shared by the symmetric Lotka-Volterra model. This model has three solutions $x^* = 0$ and $x_\pm = \sqrt{\beta - \beta_c/}\gamma$

We take $\beta_c = 1$, like in the competition model. For $\beta < \beta_c$, only $x^*$ is stable (equivalent to the coexistence state). Once $\beta > \beta_c$, the two alternative states $x_\pm$ are available. Any small fluctuation will drive the system to one of the two attractors.

We can calculate the (stationary) probability distribution $P_s(x)$ of finding the system near a given value $x$ by using the Fokker-Planck equation corresponding to (19). It reads (Haken, 1988):

$$\frac{\partial P(x,t)}{\partial t} = \frac{\partial}{\partial x} [(\beta - \beta_c)x - \gamma x^3]P(x,t) + \frac{Q}{2} \frac{\partial^2 P(x,t)}{\partial^2 x}$$

A stationary solution can be derived, leading to:

$$P_s(x) = \mathcal{N} \exp \left[ \frac{2}{Q} \int ((\beta - \beta_c)x - \gamma x^3) dx \right]$$

where $\mathcal{N}$ is a normalization constant. This distribution is shown in figure (7) for different values of $\beta$. We can clearly see that this distribution splits into two peaks (centered around the points $x_\pm$) corresponding to the two available branches. A large number of competition experiments with MARM clones should provide a similar picture.
Figure 7: Probability distribution for model (20). As the competition rate increases, we move from a unimodal distribution towards a bimodal one. The peaks correspond to the maxima of the distribution, centered around the corresponding deterministic steady states.

Now the question is: if we start from a parameter range where two available states are present and the initial condition is \( x = 0 \), how predictable is the system’s evolution as defined by the stochastic model (19)? This question arises from the previous discussion concerning deterministic dynamics in the MARM-clone experiments with VSV. In their paper, Quer et al. measure the variance MARM-C:wt ratios for several competition sets in order to characterize their critical points. It was observed that this measure remain low before the critical point is reached and it raises up afterwards.

Using \( \beta = 2 \) and \( \gamma = 1 \), and starting from \( x(0) = 0 \), we can follow the evolution of model (18) and explore the onset of symmetry breaking through time. We will also measure (as in Quer et al. 1996) the variance of the system in terms of the average
Figure 8: Predictable nonlinear behavior in a simple model with symmetry breaking and stochastic dynamics. A transient with no divergence is observed (a predictable phase) followed by a symmetry breaking phenomenon leading to one of the two available states with the same probability.

fluctuation $\sigma(t) = \langle x^2(t) \rangle - \langle x(t) \rangle^2$, with $Q = 10^{-5}$. Using standard Monte Carlo techniques (Hammersley and Handscomb, 1979) the previous equation can be approached by a discrete analog $x_n = x_{n-1} + x_n(1 - x_n^2)\Delta t + \eta_{n-1}\Delta t$ where $\Delta t$ and $\eta_{n-1}\Delta t$ are sampled from a Gaussian distribution. By averaging over $10^3$ samples, the variance at each step can be calculated and it is shown in figure (8). We can clearly appreciate that a predictable transient time is present, with $x(t) \approx 0$ and with no divergence in the system’s state. Later on, fluctuations are amplified through the deterministic nonlinear dynamics and symmetry breaking will be observable. This seems quite consistent with the experimental results with MARM clones.
7 References


