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Out-of-equilibrium competitive dynamics of quasispecies

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Abstract – The composition of a quasispecies is completely characterized, in the large population and long time limit, by the matrix yielding the transition probabilities between different types in the population. Further, its asymptotic growth rate —*i.e.* the largest eigenvalue of the transition matrix— completely determines the winning population in an equilibrium competition. However, due to the intrinsically heterogeneous nature of quasispecies, out-of-equilibrium fluctuations in population size might change the expected fate of competition experiments. Using a simple model for a heterogeneous population we quantify the probability that, after a population bottleneck, the *a priori* weaker competitor wins in a competition with a population characterized by a larger asymptotic growth rate. We analyse the role played by different degrees of neutrality in the outcome of the process, and demonstrate that lower neutrality favours the weaker competitor in out-of-equilibrium situations. Our results might shed light on empirical observations in competition experiments with RNA viruses.

The rate at which mutants appear in a population determines the amount of diversity that it can maintain. If the appearance of novelty is frequent enough, coexistence of different types is the rule, and the selection-mutation equilibrium population is necessarily heterogeneous. Such ensembles exist in nature, the most notable example being RNA viruses. Experimental analysis at the level of sequence composition [1] and at the level of function [2] reveal the natural heterogeneity of those organisms. Mutations affect the genotype and may or may not change the phenotype of an individual. This dependence is quantified through the neutrality of a population, which measures the relation between the microscopic mutation rate and the effect of those mutations on fitness. Several theoretical and experimental studies demonstrate that an increase in mutational robustness might be advantageous, implying that evolution would favor populations with higher neutrality [3–7]. In the long evolutionary run, an optimized population results from a trade-off between growth rate and robustness to mutations, a property that is however embedded in the specific form of the transition matrix, that is, in the probability that one type in the population produces another one under replication.

In a population holding $f=0,\ldots,F$ different types, with transition rates $M_{ff'}$ between types under replication dynamics, the asymptotic equilibrium frequency of each type corresponds to the normalized components of the right eigenvector of the matrix $M_{ff'}$. The largest eigenvalue λ yields the asymptotic growth rate of either type, thus of the population [8,9]. Although there has been some discussion recently on the relative roles played by replication ability, mutation rate, and neutrality when two heterogeneous populations compete, the fate of two (infinitely large) competing heterogeneous populations is deterministically set by the asymptotic growth rate. This property of the ensemble already takes into account, in an implicit manner, all the relevant properties of the population. The winner in the contest is that bearing the largest dominant eigenvalue λ.

This scenario changes, however, if fluctuations are taken into account. They might arise from different sources, but usually translate into varying population sizes. An often encountered situation is that of population bottlenecks, where the size of an ensemble is drastically reduced [10,11]. This might be the case in infection transmission, where one or a few viral particles out of a highly diverse population infect a new host. In coinfection of cells by a few viral particles of different origins, competition might as well take place inside the cell. During the transient time required to recover the original population from a few individuals, the interaction between the growing populations might induce the extinction of the better competitor —*i.e.* of the population with the largest λ. In another context, it has been shown that demographic fluctuations in heterogeneous populations might indeed drive them out of equilibrium and cause extinction despite the stability of the infinite system [12].

In this letter, we explore the competitive dynamics of heterogeneous populations of replicators. To this end we use a phenomenological model devised to mimic the dynamics of RNA virus populations subjected to exponential growth and stochastic bottleneck events [13,14]. Our goal is to quantify the relative role played by the asymptotic growth rates and the degree of neutrality in the out-of-equilibrium competition between two populations after they have been subjected to a population bottleneck. While the degree of neutrality of the best competitor affects only very slightly its probability to win in the competition, we observe that it pays to *decrease* neutrality in the population with the smaller growth rate: a rapid generation of diversity at the initial steps of the competition increases the probability to cause extinction of the *a priori* stronger competitor.

Mean field model for the evolution of a single quasispecies. – Each individual in a population is characterized by a value f which determines the average number of offspring per generation for that individual. The new copies belong to the replicative class $f-1$ with probability p and to class $f+1$ with probability q. The replicative ability cannot grow beyond a maximal value $f=F$. The parameters p and q modify the phenotypic properties of the individual, and are interpreted as the visible part of a microscopic mutation rate. The neutrality of the genomes in a population is thus defined as

$$\mathcal{N} = 1 - q - p, \tag{1}$$

which exactly corresponds to the fraction of mutations that do not affect the replication rate. At each discrete generation g, the population is described by a vector $n_f(g)$ whose components correspond to the number of individuals in each replicative class $f = 0, 1, \dots F$. The evolution of the population obeys $n_f(g+1) = \sum_{f'=f-1}^{f+1} M_{ff'} n_{f'}(g)$, where the non-zero elements of the mean matrix $M_{ff'}$ are

$$M_{ff'} = \begin{cases} f(1-p-q)+1 & \text{for } f=f'<F, \\ (f+1)p & \text{for } f'=f+1, \\ (f-1)q & \text{for } f'=f-1 \end{cases} \tag{2}$$

with the boundary condition $M_{FF} = F(1-p)+1$. The class $f=0$ is introduced only to simplify the equations, and does not play any relevant role in the dynamics of the growth process. Given the population size at generation g, $N(g) = \sum^F n_f(g)$, and the average replicative ability at that time, $\bar{f}(g) = N^{-1}(g) \sum^F f n_f(g)$, the total population evolves according to

$$N(g+1) = (1+\bar{f}(g))N(g) \tag{3}$$

for any generation g. The average replicative ability results from a complex interplay between the composition of the population in different classes at generation g and the mutation parameters p and q. Thus, it is strongly dependent on the initial conditions. Only in the limit $g \to \infty$ do the relative fraction of individuals at each replicative class attain fixed values, $n_f(g+1)/n_f(g) \to \lambda$ [14], and $\bar{f}(g) \to \lambda - 1$.

Competition among Γ quasispecies. – As in the general quasispecies model, competition is introduced by fixing the maximum number $N_{\max}$ of individuals that the system can sustain. It is possible that populations start with low numbers and do not fill the system initially. If this happens, the different populations grow unrestrictedly for a (usually short) time. Afterwards, a flux E proportional to the population of each type is introduced. The equations for the evolution of $\gamma = 1, \dots, \Gamma$ different populations in this context are

$$n_f^\gamma(g+1) = (1-E) \sum_{f'=f-1}^{f+1} M_{ff'}^\gamma n_{f'}^\gamma(g) \ . \tag{4}$$

The total population is $N^{\text{tot}}(g) = \sum^\Gamma N^\gamma(g) = \sum^\Gamma \sum^F n_f^\gamma(g)$, and E is calculated by imposing the condition $N^{\text{tot}}(g) = N_{\max}$, once saturation is reached. Following a derivation analogous to that carried out for an isolated species, and considering now competition for space as represented by E, the dynamical equations for the total number of individuals in each population can be written as

$$N^\gamma(g+1) = \frac{[\bar{f}^\gamma(g)+1]N^\gamma(g)}{\sum_{\zeta=1}^{\Gamma}[\bar{f}^\zeta(g)+1]N^\zeta(g)} N_{\max}. \tag{5}$$

Note, however, that this equation does not independently yield the evolution of the total population, since $\bar{f}^\gamma(g)$ depends on the momentaneous composition of the population. The precise way in which $\bar{f}^\gamma(g)$ evolves is however independent of the rest of the populations. Only once the equilibrium distribution of each population is reached is the dynamics fully described by the set of asymptotic growth rates λ^γ. Thus, at equilibrium, the eventual winner in the competition is the population with the highest value of λ^γ, the only one that grows at a rate proportional to the growth of the whole population $N^{\text{tot}}(g)$. The density of any other population decreases to zero. Starting from an arbitrary initial condition, however, might imply a complex transient where independent populations do not change monotonically. This dynamics becomes relevant when finite populations are considered.

Out-of-equilibrium competition between two populations. – Once having derived exact results for the competition among an arbitrary number of infinite, heterogeneous populations in the asymptotic limit, we study here the particular case of two finite populations of composition n_f^α and n_f^β. Since we are interested in evaluating the dynamical effects of strong fluctuations in the population size, we consider from now on the initial condition $n_f^\alpha(0)=1$ for $f=f_0^\alpha$, $n_f^\alpha(0)=0$ for $f\neq f_0^\alpha$, and similarly for the population β. That is to say, we start with a single particle of each population with replicative ability chosen at random among the classes present in each population. The effective mutation rates for each population are (p^γ, q^γ), their degrees of neutrality are $\mathcal{N}^\gamma = 1-p^\gamma-q^\gamma$, and their asymptotic growth rates are λ^γ, with $\gamma=\{\alpha,\beta\}$. The populations grow in an independent fashion until the time when the sum of their populations equals $N_{\max}$. Then competition is turned on and eq. (4) applies. The total population reaches $N_{\max}$ usually before the independent distributions have attained their asymptotic profiles, so complex interactions between both might take place. The first population with total size $N^\gamma<1$ gets extinct, and the other is by definition the winner in that particular run.

In order to better analyse the effects of fluctuations in the dynamics, we have devised a stochastic model (DI) thas uses a discrete number of particles, and whose dynamics will be compared with the mean field model above (MF). In this discrete version of the problem, a particle with a replicative ability f gives rise to a progeny of size k, this value being drawn from a Poisson distribution of average f. With the corresponding probability p or q the new individual changes to class $f-1$ or $f+1$, respectively. Figure 1 represents two time series for the evolution of the total number of particles in each population as obtained from models DI and MF in two different situations. In fig. 1a, the two initial particles have a relatively low replication ability, and initial advantage is given to the asymptotically better competitor, who wins in this particular run after a short number of generations. In the MF model this occurs with probability one, while in the DI model there is a 0.138 probability that population β wins. In fig. 1b, however, and starting with a high replicative ability, the winner is the population with lower λ and lower neutrality. The probability to win is 1 for the MF model and 0.994 for the DI model. Indeed, after a transient time where population numbers are relatively constant, advantageous mutants are generated and become dominant in population β. The remarkable result is that the ability to generate diversity at the initial steps of evolution, together with a favourable initial condition, are essential to reverse the fate predicted by the asymptotic theory. Both models yield qualitatively equivalent results, and though the specific time series for each run differ due to discreteness in the DI model, the average behaviour is also quantitatively comparable.

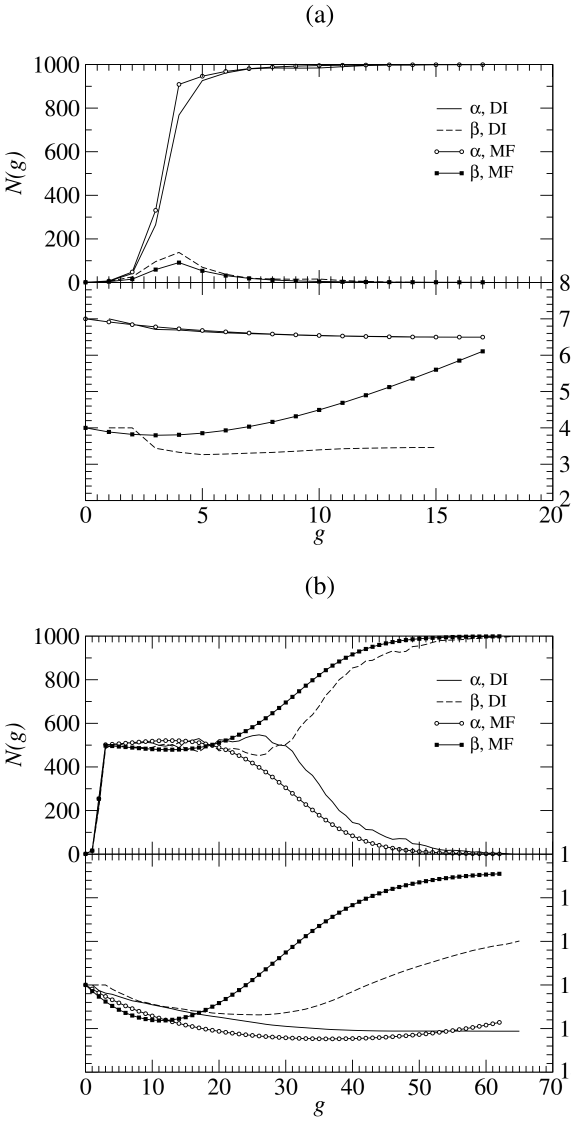

Fig. 1: Evolution of the total number of individuals (above) and of the time-dependent growth rate ($\bar{f}+1$, below) in two competing populations that start with a single particle each. Two models are used, a discrete (DI) and a mean field one (MF). Parameters are $N_{\max}=10^3$, $p^\alpha=0.1$, $q^\alpha=0.001$, $p^\beta=0.2$, $q^\beta=0.05$, and $F=20$, which yield asymptotic growth rates $\lambda^\alpha=19.04\ldots$ and $\lambda^\beta=18.61\ldots$. Hence, population α wins in all equilibrium competitions. (a) The replicative ability of the two initial particles is $f_0^\alpha=6$, $f_0^\beta=3$. In the MF model, population α wins; in the DI model, the probability that β wins is of 13.8%. (b) The initial replicative ability is $f_0^\alpha=15$, $f_0^\beta=15$. Contrary to the asymptotic expectations, population β wins in the MF model, and in the 99.4% of runs with DI.

In a competition experiment with the initial conditions described, it is important to know what is the probability w_β that the weaker competitor, that is population β, eliminates the superior population α. To estimate this quantity we first run all pairs of initial conditions (f_0^α, f_0^β), and evaluate for each pair the probability $[1-P_\alpha(f_0^\alpha, f_0^\beta)]$

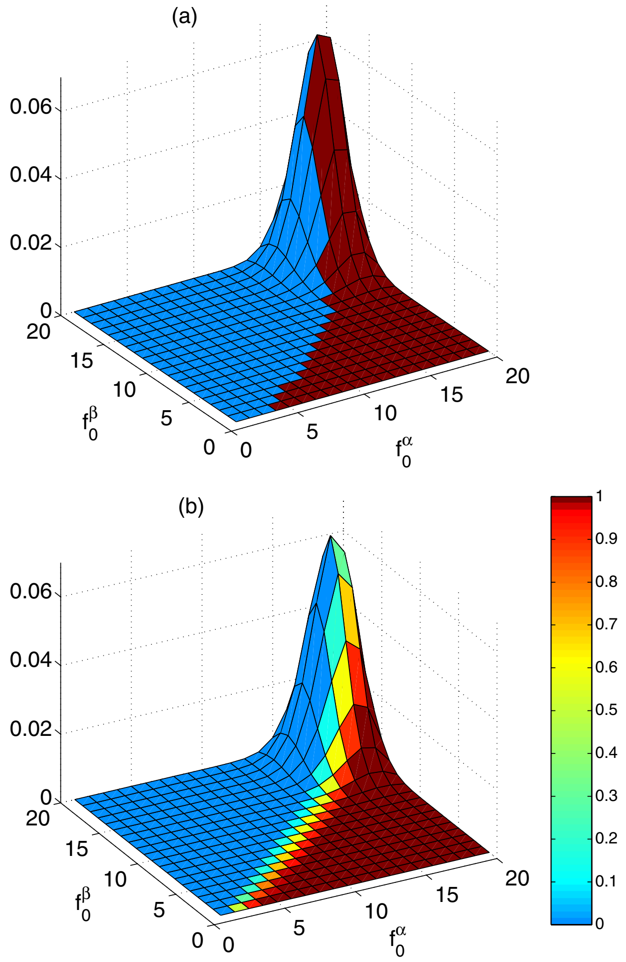

Fig. 2: Probability to choose the pair (f_0^α, f_0^β) as initial condition when the values are drawn from the equilibrium distribution $n_f^\gamma(g \to \infty)$, $\gamma = \alpha, \beta$. Since $\lambda^\alpha > \lambda^\beta$, population α is the winner in any equilibrium competition. The color code indicates, for all possible combinations of initial conditions, the probability $P_\alpha(f_0^\alpha, f_0^\beta)$ that the *a priori* stronger competitor wins. (a) MF model. Given a combination of initial conditions, α either wins with probability one or loses with certainty. (b) DI model. There is a smooth transition between the domains where either α or β win. Averages over 10^3 independent runs have been performed. For both models, and due to the finite size of the population, the probability that β wins reaches one even in a domain where $f_0^\alpha \geqslant f_0^\beta$. The strength of β relies on its ability to generate diversity faster than its competitor.

that β wins. Now, the likelihood that a particular pair of initial conditions is chosen depends on the fraction $n^\gamma(g)$ of individuals of each type in each population $\gamma = \alpha, \beta$, right before the bottleneck occurs. These distributions depend on the characteristics of the environment, and in particular on the number of generations allowed for independent evolution before the bottleneck takes place and competition is thus turned on. In general, the weighted fraction w_β of winning runs for β can be written as

$$w_\beta = \sum_{(f_0^\alpha, f_0^\beta)} \left[1 - P_\alpha(f_0^\alpha, f_0^\beta)\right] n_{f_0^\alpha}^\alpha(g)\, n_{f_0^\beta}^\beta(g)\,, \qquad (6)$$

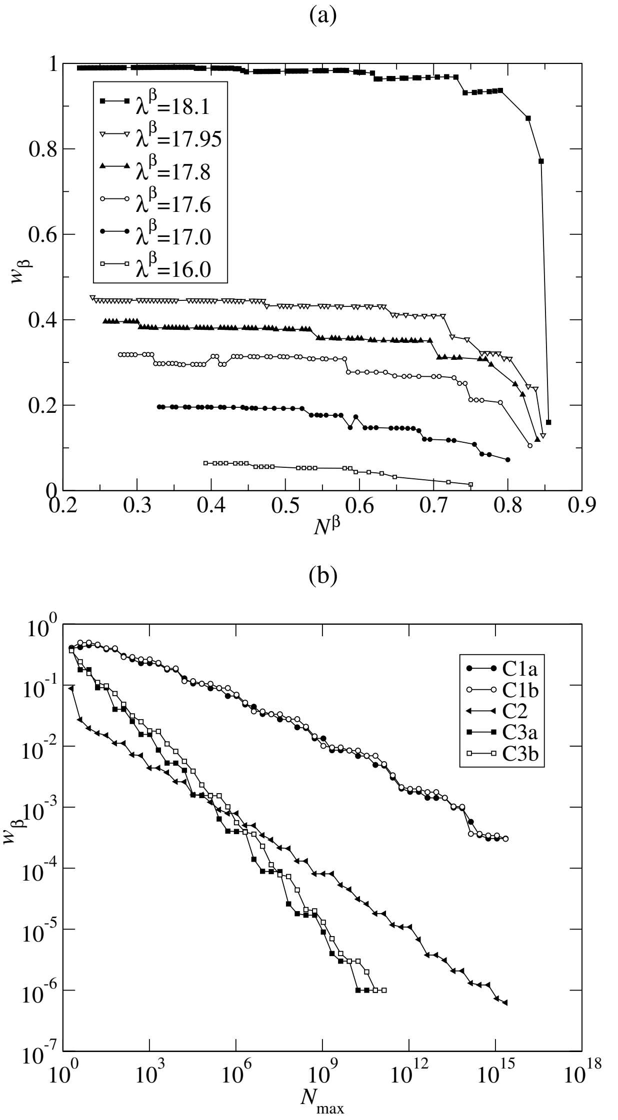

Fig. 3: Fraction of winning runs for the weaker competitor. (a) Variation of w_β with the degree of neutrality. The asymptotic growth rate of α is $\lambda^\alpha = 18.0$ with $p^\alpha = 0.1575$ and $q^\alpha = 0.0025$; λ^β is as shown in the legend. Each point in the curves corresponds to a combination of parameters (p^β, q^β) yielding the growth rate specified, with p^β, $q^\beta < 0.5$ and $p^\beta > q^\beta$. (b) Dependence of w_β with the system size. Numerical results indicate that $w_\beta \simeq N_{\max}^{-a}$, with a dependent on the values of λ^α and λ^β. Results are for the MF model. The curves shown correspond to $\lambda^\alpha = 19$, $p^\alpha = 0.1$, $q^\alpha = 0.001$ and two competitors, both with $\lambda^\beta = 18.6$, and parameters $p^\beta = 0.2$, $q^\beta = 0.05$ (C1a) and $p^\beta = 0.27$, $q^\beta = 0.11$ (C1b); same population α and a competitor with $\lambda^\beta = 16$ ($p^\beta = 0.405$, $q^\beta = 0.055$) (C2); $\lambda^\alpha = 18.6$, $p^\alpha = 0.2$, $q^\alpha = 0.05$ and two competitors, both with $\lambda^\beta = 18$, and $p^\beta = 0.1575$, $q^\beta = 0.0025$ (C3a) and $p^\beta = 0.315$, $q^\beta = 0.1$ (C3b).

and the precise form of $n^\gamma(g)$ needs to be estimated in each particular case.

Previous studies with single populations subjected to bottlenecks have addressed two particular situations where

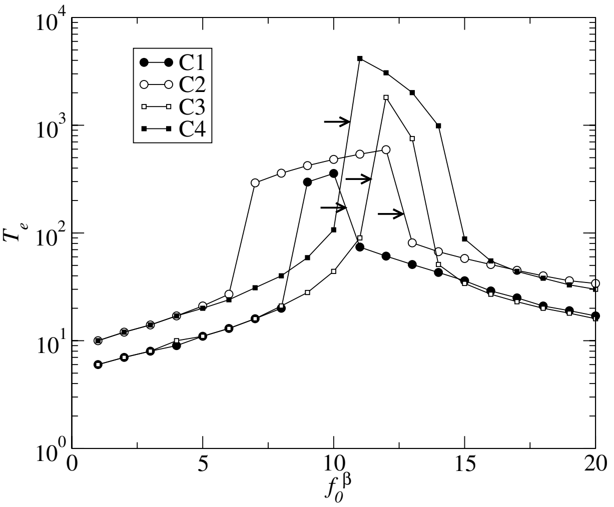

Fig. 4: Time to elimination (in number of generations) of one of the populations in competition experiments. The parameters for population α are fixed in all runs: $f_0^\alpha = 12, p^\alpha = 0.1575$, and $q^\alpha = 0.0025$, yielding $\lambda^\alpha = 18.0$. The four curves shown have parameters as follows: $N_{\max} = 10^3$, $p^\beta = 0.3$, $q^\beta = 0.04$, yielding $\lambda^\beta = 17.0$ (C1); $N_{\max} = 10^6$, same p^β and q^β as C1 (C2); $N_{\max} = 10^3$, $p^\beta = 0.15$, $q^\beta = 0.0017$, yielding $\lambda^\beta = 18.1$ (C3); and $N_{\max} = 10^6$, same p^β and q^β as C3 (C4). Arrows signal, for each case, the value of f_0^β where the winner changes from one population to the other. Population α wins in all positions at the left of the arrow. Results are for the MF model.

the distribution of replicative ability types can be analytically calculated: the case of small g and the asymptotic limit $g \to \infty$. In the former case, the time allowed for independent development between bottlenecks is short enough that only the types f_0, $f_0 + 1$, and $f_0 - 1$ are present before the population bottleneck takes place [14]. In the latter case, the population has evolved for a large enough number of generations such that the asymptotic distribution of replicative types has been achieved [14,15]. In the first case, average values of the replicative ability are low, and the population cannot be optimized, as it occurs in the asymptotic case. As an example, we show quantitative results corresponding to the limit $g \to \infty$ in figs. 2 and 3.

Figure 2 represents the winning population as a function of the replicative ability of the initial particles. In the MF model, there is a sudden transition from initial conditions where α wins to a domain where β wins. Stochastic fluctuations in the population sizes and in their compositions smoothen the transition in the DI model. This transition corresponds to the values codified in the color scale. Keeping the characteristics of population α fixed, the probability w_β that β wins increases when the population size decreases, when the difference between the asymptotic growth rates decreases (maintaining the same degree of neutrality) and when the degree of neutrality decreases (maintaining the same λ^β). These cases are shown in fig. 3, which summarizes the response of the system of two populations to changes in the model parameters. Finally, let us remark that the qualitative behavior described is independent of the precise form of the density functions $n^\gamma(g)$, though as a way of example we have used the asymptotic distribution to yield the quantitative results represented in figs. 2 and 3.

A relevant quantity in the competition process is the time T_e elapsed until the eventual winner eliminates its competitor. Different representative parameters have been used to analyse how T_e behaves, as represented in fig. 4. In all cases, the time to elimination attains maximal values at the transition where the winner shifts, and takes higher values the smaller the difference between the asymptotic growth rates. Lower neutrality favors the weaker competitor for other conditions fixed, as already observed. As the population size increases, the time to elimination grows as well. Not only the absolute value of T_e depends on the parameters, but also the precise position of the transition threshold.

Discussion. – The outcome of a competition between two infinite populations of quasispecies is completely determined by the relative asymptotic growth rates. However, the combination of out-of-equilibrium situations with finite populations might induce extinction of the asymptotically better competitor. Natural heterogeneous populations, as RNA viruses, rarely evolve under equilibrium situations. Actually, the high mutation rate of those organisms is an adaptive response to highly fluctuating environments. The scenario tackled in this letter should thus be applicable to real world situations, where two or more viral strains, each structured in a number of fitness classes, infect and compete for the resources of the host. In certain cases, extinction of the supposedly fitter population might occur simply due to unfavourable initial conditions or to an exceedingly high neutrality in comparison to the competing population, as described. Though other more complex interactions, as viral interference, might be at play, we have shown that the faster appearance of advantageous mutants in a population with a smaller asymptotic growth rate can cause the extinction of the superior population, even in extremely large populations. The finite size effect studied becomes less probable as $N_{\max}$ increases, and eventually disappears in the limit of infinitely large populations. However, biological populations have sizes in a range where elimination of the stronger competitor might occur with relatively high probability. For example, the number of viral particles inside a cell rarely exceeds 10^3, and competition between strains and even different fitness classes within a population might be determinant to settle the characteristics of an infectious process [16].

There is experimental evidence supporting the kind of mechanism here described. In several experiments with different strains of vesicular stomatitis virus (VSV), it was observed that one of the strains could occasionally displace the other [17] (as it happens close to our transition boundary, see fig. 2b) or with probability one [18] (before or after the transition in our case). Those experiments inspired theoretical approaches able to qualitatively explain an observed increase of replicative ability during competition and the eventual exclusion of one of the populations [19]. More recently, other experiments suggest that an exceedingly high degree of neutrality can be deleterious under environmental stress, since beneficial mutations of a supposedly superior strain are not generated rapidly enough to displace the competitor [20]. Finally, in another experiment of coinfection with two strains of VSV, it was shown that a superior mutant could be suppressed by a population that replicated at a lower rate if the size of the first population did not exceed a critical threshold level [21]. Theoretical and experimental analyses demonstrate that finite size effects are important in non-equilibrium competition and in co-evolution situations, and can act as a relevant selective pressure towards different evolutionary strategies, among others a decrease of neutrality to mutations.

* * *

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