Adaptation and irreversibility in microevolution

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Abstract – Within the framework of population genetics we consider the evolution of an asexual haploid population under the effect of a rapidly varying natural selection (microevolution). We focus on the case in which the environment exerting selection changes stochastically. We derive the effective genotype and fitness dynamics on the slower timescales at which the relevant genetic modifications take place. We find that, despite the fast environmental switches, the population manages to adapt on the fast timescales yielding a finite positive contribution to the fitness. However, such contribution is balanced by the continuous loss in fitness due to the varying selection so that the statistics of the global fitness can be described neglecting the details of the fast environmental process. The occurrence of adaptation on fast timescales would be undetectable if one were to consider only the effective genotype and fitness dynamics on the slow timescales. We therefore propose an experimental observable to detect it.

Introduction. – Population genetics studies the evolutionary process of a population under forces such as mutations, Darwinian selection and the random genetic drift (see [1–3] for a general exposition). A key intuition for modeling the effects of natural selection is the concept of fitness of a population in a certain environment which describes the global ability of the population to reproduce and survive [4]. The different fitness of various genotypes can be effectively visualized in terms of a fitness landscape [5] which is usually “climbed” during the course of evolution. Such climbing is referred to as adaptation. Fisher’s fundamental theorem of natural selection [6] states that when evolution is subject only to natural selection in a constant environment, the fitness of a population increases at a positive rate equal to the variance of the population. Indeed, natural selection, by its very definition, is the force that favors fitter individuals, pushing towards the genotype configuration which maximizes the global fitness. When mutations and random drift are relevant, the stochastic nature of evolution emerges and adaptation becomes a more complex phenomenon. One of the most widely accepted models for the stochastic description of the evolutionary process is the Kimura-Ohta equation [7] that we will describe in detail in eq. (2) below. In most natural cases the environment in which the population evolves changes in time (see, for example, refs. [8–15]) and genotypes that were fit under the initial condition may successively be unfavored by selection. Consider for instance the case of a population of bacteria shaped by natural selection to metabolize a certain nutrient. If such nutrient is gradually replaced by a different one the metabolism of the bacteria (optimized for the first one) will now be less efficient and the global fitness of the bacterial population will decrease. At the same time adaptation to this new environment will start taking place providing a fitness increase. We can then represent the fitness dynamics as the result of two effects: adaptation driven by natural selection (analogous to the term appearing in Fisher’s theorem [16]) and fitness changes due to environmental variations:

\[
\frac{d}{dt}\text{Fitness} = \text{Adaptation} + \text{Environmental changes.} \tag{1}
\]

We will consider the explicit expression for the fitness variation and its quantitative interpretation below (see eq. (4)).

The changes brought about by the variability of the environment give a negative contribution countered by adaptation, which is, in general, positive. In the present work we consider the case in which the timescales of the environmental changes are much faster than the typical time of evolution of genotype frequencies due to
Fig. 1: (Colour on-line) Simulation of the two genotypes dynamics obeying eq. (2) coupled with an environment following an Ornstein-Uhlenbeck process, (11). The left panels refer to environment changes with a correlation time: $T_e = 1000$ gen, which is of the same order of the typical time of genotype variation. The right panels describe the microevolutionary regime with environmental time correlations of $T_e = 5$ gen. For the chosen parameters significant changes in the genotype frequency occur after typical times of 100–1000 generations.

evolutionary forces. Such scenario is referred to as the microevolutionary limit (see fig. 1). For the example of the bacteria culture in different growth media, microevolution corresponds to replacing the nutrients at a much faster rate than the changes in the genetic structure of the population of bacteria driven by evolution. In particular we focus on the case in which the dynamics of the environment is a stochastic process itself (as done also in refs. [9,12]). We are then considering a population in a rapidly fluctuating environment thereby subject to erratic selection. In order to understand our main result let us notice that if one studies the evolution of the population on long timescales it may seem neutral because the random contributions of the selection exerted by the succession of environments tend to cancel off\footnote{In the discussion we consider the general case in which the stochastic selection may have a non-zero average.}. However, this apparent neutrality does not mean that the population has not been subject to selection and that it has not adapted to the environments it has encountered. In the following we show how to detect and account for this hidden adaptation.

We also study the dynamics of the global fitness of the population in the case in which the stochastic dynamics of the environment reaches a statistically steady state\footnote{A statistical steady state of the environment implies that the state of the environment is not fixed but continually changes in a stochastic manner. However, the probability distribution of the environment is constant.}. We expect that, given the statistical stationarity of the environment, after an initial adaptation, the average of the global fitness is constant in time. To check this intuition and to investigate in depth the issue, we make use of asymptotics techniques [17] to derive the effective evolution taking place at the relevant slow timescales (much longer than the correlation time of the environment). We find that the genotype dynamics becomes independent of the specific environmental state and is governed by the average of the selection coefficient. As expected, the global fitness is constant but not in a “static” way. It is rather the sum of two opposite finite terms that compensate each other: positive adaptation and the change of fitness due to the variability of the environment which gives negative contributions. The positive term accounts for the adaptation that has taken place on the fast timescales. It can be traced back to the fact that, even when the typical fluctuation time during which the environment favors a specific genotype tends to zero, the population undergoes an infinitesimal adaptation, which is of the order of the fluctuation time. The number of such infinitesimal positive contributions in a unit of time increases proportionally to the inverse of the typical time of fluctuations, so that they constitute a finite additional term. Such mechanism is analogous to the one recently found for entropy production in stochastic systems with fast and slow timescales [18,19]. We can give an intuitive picture for the balance of contributions leading to a constant fitness by considering a runner on a treadmill. The speed of the treadmill represents the loss in fitness due to the fast environmental changes.
In order to maintain a fixed position (i.e., constant fitness) the runner has to run (i.e., adaptation to the environment) at the same and opposite speed of the treadmill.

In the following sections we will detail the formalism underlying our discussion. We will present our results using the mathematical model of Kimura-Ohta and give a general example. To conclude we will suggest an observable which can provide experimental measures of the found adaptive behavior.

**Fitness and adaptation in a fluctuating environment.** – For the sake of clarity we illustrate the simplest situation considering a haploid population which can switch between two genotypes: A and B. We denote the frequency of A as x so that the Kimura-Ohta equation reads

\[ \frac{\partial P}{\partial t} = -\frac{\partial}{\partial x} [(m + gs)P] + \frac{1}{2N} \frac{\partial^2}{\partial x^2} [gP], \] (2)

where time is expressed in generation units. \( P(x, t) \) is the probability distribution that, at time \( t \), the frequency of genotype A is x. \( m(x) = -\mu x + \nu(1-x) \) is the mutation coefficient, \( \mu \) and \( \nu \) are the mutation rates. \( s(x, y) = f_A(x, y) - f_B(x, y) \) is the selection coefficient, which describes the effect of natural selection and depends on the environmental state. \( f_A/B(x, y) \) is the fitness of the genotype A/B. Note that we are considering the fitness to depend on the environmental state which we denote as y. \( N \) is the effective population size and \( g(x) = x(1-x) \). The global fitness of the population, \( F(x, y) \), is defined by the following relation:

\[ s(x, y) = \frac{\partial F(x, y)}{\partial x} \] (3)

that is, the function that the natural selection tends to maximize. This identification is valid when the selective advantage can be expressed in terms of the gradient of a fitness landscape. We are therefore not taking into account the more involved settings of cyclic selective advantages discussed for example in refs. [20–22]. When the selection coefficient does not depend on the genotype frequencies (frequency-independent selection) the global fitness corresponds (up to an additive constant) to the average population fitness: \( f(x) = f_A(x, y)x + f_B(x, y)(1-x) \) (see ref. [8] for a detailed discussion). We will consider such instance in the example below. On the contrary, when selection depends on the genotype frequency the global fitness differs from the average population fitness. In general, \( F \) can be interpreted as the fitness landscape, i.e., the quantity that Darwinian selection tends to maximize. Indeed, its gradient is what sets the direction in which natural selection drives evolution (see eq. (3)). In other words, natural selection pushes towards a set of genotype frequencies with a higher \( F \). To appreciate this property let us consider an example involving a frequency-dependent selection highlighting the difference with the average fitness. Let us take the first genotype fitness to be \( f_A(x) = \alpha + 1 - x \), and the second one to be \( f_B(x) = 1 - x \) with \( 0 < \alpha < 1 \). In this case, the first genotype is favored by natural selection, \( s = f_A - f_B = \alpha > 0 \), and increases in number through generations. The global fitness \( F(x) = \alpha x \) consistently grows along this adaptive process in which x increases. On the contrary, the average fitness, \( \langle f \rangle = x f_A(x) + (1-x) f_B(x) = (\alpha - 1)x + 1 \), decreases with the increase of x and is therefore not suitable for characterizing the adaptation which is taking place.

Let us now study in detail the infinitesimal variation of the global fitness introduced in eq. (1). It can be written as

\[ dF(X_t, Y_t) = s(X_t, Y_t) \circ dX_t + \frac{\partial F}{\partial x} \circ dY_t \text{,} \] (4)

where \( X_t \) and \( Y_t \) are, respectively, the first genotype frequency and the environmental state at time \( t \), and “◦” is a Stratonovich product3. We remark that \( dX_t \) is given by the genotype evolution (following eq. (2)) and includes the effects of mutations and genetic drift. The first term on the right-hand side accounts for the changes in fitness caused by changes in the genotype frequencies. It coincides with the definition of the fitness flux at time \( t \) introduced in ref. [8]

\[ d\phi(t) = s(X_t, Y_t) \circ dX_t = \frac{\partial F}{\partial x} \circ dX_t \] (5)

which measures the adaptation driven by natural selection following the intuition used by Fisher in the derivation of his fundamental theorem [16]. To probe this interpretation consider the case in which the first genotype has a higher fitness so that the selection coefficient is positive. If the first genotype frequency grows, the population is adapting to the environment and we see that this corresponds to a positive fitness flux. A dis-adaptive behavior would imply a decrease in the first genotype frequency and consequently a negative fitness flux. The second term on the right-hand side of eq. (4) accounts for the variation of fitness at fixed genotype frequency due to changes in the environment. If the population is well adapted these changes usually reduce the global fitness. The adaptation of a population to an environment clearly shows a temporal direction and is therefore an irreversible process. For general stochastic dynamics irreversibility is measured in terms of entropy production [23,24]. The authors of ref. [8] highlighted the connection between population genetics and out-of-equilibrium stochastic systems by showing that the fitness flux corresponds to the entropy production in the environment of the stochastic dynamics describing the genotype evolution. We provide the details in the supplemental material [25]. Such analogy allowed the authors of ref. [8] to derive a sort of second law of thermodynamics.

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3For a generic function \( f(X_t) \) the Stratonovich product implies the midpoint discretization \( f(X_t) \circ dX_t \equiv \frac{f(X_{t+\tau}+f(X_{t+\tau})}{2}(X_{t+\tau} - X_t) \).
Fig. 2: (Colour on-line) Computer simulation of an evolutionary process in microevolution at the stationary state. The population evolves following the Kimura-Ohta equation (2) for two genotypes under a very fast fluctuating environment obeying eq. (11). The parameters of the process are $k = 1$, $D = 0.01$, $N = 10^4$, $\mu = \nu = 10^{-3}$, $\sigma = 0.1$. Panel (A) shows four trajectories of the cumulative fitness flux and its average value with a slope equal to the average fitness flux. Panel (B) depicts the dynamics of the fitness variation due to the environmental changes $R(t)$. The slope of the average is the opposite to the average of the fitness flux, but the statistic of this term is completely different from the statistic of $\Phi(t)$. The average fitness dynamics is shown in panel (C) and, following eq. (4), it shows the compensation of the terms in panel (A) and (B). Panel (D) shows the observable defined in eq. (9) computed for parameters: $k = 1$, $D = 1$, $N = 10^5$, $\mu = \nu = 5 \cdot 10^{-4}$, $\sigma = 0.02$, $T_e = k^{-1}$.

for population genetics which they dubbed fitness flux theorem. Just as entropy production, the fitness flux at the stationary state is, on average, always positive $\langle d\Phi(t) \rangle \geq 0$. This implies that the evolutionary process is adaptive and irreversible. The equality holds if and only if the system is at equilibrium. In this case the system is reversible and the population is not adapting.

The microevolutionary limit. — In this section we investigate what is the asymptotic behavior of the genotype and the global fitness dynamics in the limit of a very rapidly changing environment. In such microevolutionary settings the typical time of environmental changes ($\theta = \epsilon^{-1}t$) is much faster than the typical time of genotype frequencies changes due to evolutionary forces $t$ (see the right panels of fig. 1). We seek to determine what is the effective behavior of the system on the timescale of the genotype frequency change $t$. We obtain our results by means of multiple-scale methods (see ref. [17]) taking the limit $\epsilon \to 0$.

Effective genotype dynamics. We find that the evolution of the genetic structure of a population in the microevolutionary limit is described by an effective Kimura-Ohta equation (eq. (2)), where the selection coefficient is given by its average over the possible environments:

$$\overline{s(x)} = \int dy \ w(y) s(x,y)$$

and $w(y)$ is the equilibrium distribution of possible environments. The effective Kimura-Ohta equation is then independent of the environmental state. This can be intuitively understood by considering that when the environment changes very rapidly, the genotype dynamics does not manage to fully react to the natural selection exerted by the current environmental state before the environment changes again. The dynamics is rather affected by a smeared, net contribution of the succession of environments it encounters. When the environment is in a statistically stationary state such contribution corresponds to the average selection of the environments.

Fitness dynamics. At the steady state the average global fitness is constant in time. As mentioned in the introduction we find that in microevolution this stationarity is achieved by the compensation of two opposite finite
contributions:
\[
d\langle F(X_t, Y_t) \rangle = \frac{d\phi(t)}{\partial y} + \left. \frac{\partial F}{\partial y} \right|_{\langle \delta R \rangle < 0} dY_t = 0. \tag{7}
\]

Both terms can be shown to be constant at the steady state (see supplemental material [25]) so that their finite time contributions scale linearly in time as shown in fig. 2. The adaptive fitness flux term displays an anomalous behavior analogous to that of the entropy production in stochastic systems with slow and fast scales [18,19]. In the microevolutionary limit its average value is always greater than the value that one would obtain by simply using the definition (5) with the effective dynamics (6). Namely,
\[
\langle d\phi(t) \rangle = \left( s(X_t) \circ dX_t + g(X_t) \left( s(X_t)^2 - s(X_t)^2 \right) dt \right)_{d\phi_{\text{eff}}},
\]
where the additional contribution is clearly always positive. In order to understand the implications of this result, consider the case in which the average selection vanishes, i.e. no specific genotype is favored in the long term. In this case, the effective Kimura-Ohta equation is not subject to natural selection and we would expect no adaptation. However, if we compute the limiting value of fitness flux we obtain a finite positive value (see fig. 2) testifying that adaptation is continuously taking place contrasting the fitness loss due to the fluctuating environment.

An experimental observable to probe adaptation in microevolution. As we have shown, in microevolution the trajectories of the genotype frequency follow an effective dynamics which is independent of the environmental state. Therefore, if we want to determine whether the population evolves in a microevolutionary regime presenting an anomalous adaptation or in a scenario with a fixed environmental state and a selection coefficient equal to the effective coefficient, it is not sufficient to consider only the trajectories on the slow timescale. In this section we suggest an experimental observable that captures the trace of the anomalous behavior of the fitness flux in the microevolutionary limit. When the additional adaptation is taking place, the following observable:
\[
A_t(\tau) = \frac{1}{|\tau|} \left( g_t^{-1} (X_{t+\tau} - X_t)^2 \right) = \frac{1}{|\tau|} \left( X_{t+\tau} - X_t \right)^2 \left( X_t (1 - X_t) \right)^2 \tag{9}
\]
presents a linear growth for short times (as shown in fig. 2). This follows form the fact that such quantity is closely related to the fitness flux. Indeed, when mutations are negligible compared with the selection and the population is large, the slope of \( A(\tau) \) is equal to the fitness flux rate (see the supplemental material in ref. [25]). Therefore computing such observable allows to discriminate the dynamic balance of adaptation and fitness loss from the static, non-adapting case. Note that, as for the fitness flux, once the separation of timescale is large enough to allow the asymptotic expansion the additional contribution is independent of the specific environmental correlation time.

Example. – To illustrate our findings let us now consider a frequency-independent selection with \( s(Y_t) = \sigma Y_t \) so that the global fitness coincides with the average fitness (up to a constant). When \( Y_t > 0 \) genotype \( A \) is favored whereas \( Y_t < 0 \) favors genotype \( B \). The fitness of the population then reads
\[
F(x, y) = \sigma xy = f_A(y)x + f_B(y)(1 - x) + C_0 = \langle f \rangle + C_0, \tag{10}
\]
where \( C_0 = -f_B \) is a term constant in \( x \).

For example we take an environment dynamics described by an Ornstein-Uhlenbeck process with constant diffusion \( D \) and spring constant \( K \) (of order 1)
\[
dY_t = -\epsilon^{-1}KY_t dt + \epsilon^{-1/2} \sqrt{2D} \cdot dB_t, \tag{11}
\]
where \( dB_t \) is a Wiener process and \( \epsilon \ll 1 \) is the parameter accounting for the timescale separation between the environment and the genotype evolution. At the steady state \( \overline{y} = 0 \) and \( \overline{y}^2 = D/K \). This implies that \( \overline{y} = 0 \) and that, consequently, the effective evolution on the slow timescales seems neutral. Indeed, the regular term of the fitness flux \( \langle \phi_{\text{eff}} \rangle \) is equal to zero. However, on the timescale of the environmental variation, adaptation is taking place and this is accounted for by the additional contribution we have derived which in the present case gives
\[
d\langle F(X_t, Y_t) \rangle = \frac{D}{K} \sigma^2(y) - \frac{D}{K} \sigma^2(y) = 0 \tag{12}
\]
showing that the constant fitness average arises from the balance of two finite terms.

Conclusions and discussion. – Population genetics under varying or fluctuating selection has been considered in a number of studies (see for instance refs. [8–15]). In particular, the case when the selection that acts on a population changes on timescales different from the ones of the evolutionary process was also considered in ref. [11]. There, the authors analyzed a scenario specular to the one we have studied. They focused on a very slowly changing environment and found that such slow variation impacts on the fitness of the population providing a correction term of the order of the environment change rate. Conversely, we have dealt with the opposite limit and shown that when a population evolves in a rapidly changing environment its dynamics is governed by the average of the selection coefficients experienced across the various conditions. If the environment reaches an equilibrium the global fitness of the population is then stationary. Such stationarity emerges from a tug of war between the loss of
fitness due to the fast environmental changes and a continuous adaptation taking place at the fast timescales of the environmental variations. On average the two contributions scale linearly in time but they exactly compensate yielding a constant global fitness. They do not depend on the magnitude of timescale separation (provided it is large enough to allow the asymptotic expansion). Our findings support the idea that in varying environments a constant population fitness does not imply that no adaptation is taking place. To further investigate the issue we have suggested an experimental observable based on genotypic frequencies alone that is able to discriminate the case of adaptive behavior at constant fitness from the static non-adaptive one. In closing, we note that similar reasonings have been adopted in more complex and exhaustive studies attempting to reconcile the data about the rapid speciation episodes (which is not present in our analysis) and to extend the formalism adopted in this paper to account for the influence of geographical effects on evolution.

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