

## Evolutionary games and quasispecies

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**Abstract.** – We discuss a population of sequences subject to mutations and frequency-dependent selection, where the fitness of a sequence depends on the composition of the entire population. This type of dynamics is crucial to understand, for example, the *coupled* evolution of different strands in a viral population. Mathematically, it takes the form of a reaction-diffusion problem that is nonlinear in the population state. In our model system, the fitness is determined by a simple mathematical game, the hawk-dove game. The stationary population distribution is found to be a quasispecies with properties different from those which hold in fixed fitness landscapes.

*Introduction.* – The roles of chance and determinism are a central theme in evolutionary biology. Eigen’s *quasispecies theory* [1] has been pivotal as a simple quantitative model for the intertwined effects of random mutations and Darwinian selection. These forces act on individuals with a *genotype* defined by an  $L$ -letter sequence  $\sigma = (\sigma_1, \dots, \sigma_L)$ . The individuals reproduce at a rate  $f(\sigma)$  called the *fitness* of the genotype  $\sigma$ , and are subject to random mutations of the sequence elements at a rate  $\mu$ . The population is described by a time-dependent frequency distribution  $P(\sigma)$ . The evolution of  $P(\sigma)$  is described by a deterministic equation in the limit of large population size, when sampling errors in the reproduction-mutation process become negligible. For small  $\mu$ , the evolution is dominated by reproductive success and produces a *quasispecies*, that is, a stationary population distribution  $p_s(\sigma)$  peaked around the genotype  $\sigma^*$  of maximal fitness. Large mutation rates, on the other hand, wipe out fitness differences and lead to a broad distribution. These two regimes are linked by a crossover which, depending on the fitness “landscape”  $f(\sigma)$ , may become a phase transition in the limit of infinite sequence length. The transition point is called the *error threshold*.

Quasispecies evolution can be seen as a reaction-diffusion problem in sequence space that is conceptually related to problems in statistical physics. It takes the form of an (imaginary-time) Schrödinger equation for the population state,  $\partial_t P = HP$ , with  $f(\sigma)$  as scalar potential and the kinetic term describing mutations [2]. This type of problem is mathematically tractable since  $H$  is a linear operator, and has been studied for many different fitness landscapes. In particular, there can be extended subsets of sequence space —called *neutral networks*  $\Gamma_{\mathbf{x}}$ —

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where the sequences encode the same *phenotype*  $\mathbf{x}$  and, therefore, the fitness is constant. The evolution of the phenotype population  $p(\mathbf{x}) = \sum_{\sigma \in \Gamma_{\mathbf{x}}} P(\sigma)$  can often be described by a projected equation,  $\partial_t p = H_{\mathbf{x}} p$ , taking into account the varying number of genotypes coding for the same phenotype. This means that the selection among different neutral networks is not only determined by their “fitness” (the reproduction rate) but also by their “robustness”, *i.e.*, to the probability that a random mutation leaves a genotype on the same neutral network [3]. In some cases, this effect can be described by a suitably defined “mutational entropy” [4].

The stationary distribution  $p_s(\mathbf{x})$  may again be a quasispecies around the phenotype  $\mathbf{x}^*$  of maximal fitness, while the sequence population within each neutral network  $\Gamma_{\mathbf{x}}$  remains broad. Examples are RNA sequences  $\sigma$  with only the folding configuration  $\mathbf{x}(\sigma)$  determining the fitness. In this case, the neutral networks  $\Gamma_{\mathbf{x}}$  consist of all sequences with the same fold  $\mathbf{x}$  [5]. A step towards a more realistic theory of mutation-selection processes is to take into account the dependence of the fitness on the population state. This is particularly apparent, for example, in viral evolution. The reproductive success of one viral strand will depend on the other strands that coexist in the same population. At the level of phenotypes, a well-known way to describe such coupled systems is *evolutionary game theory* [6–9]. Here we limit ourselves to the simplest form of a mathematical game, which is described by a set of basic *strategies*  $i = 1, \dots, s$  and a matrix  $\mathbf{A} = (A_{ij})$  which specifies the relative fitness or *payoff* of strategy  $i$  played against strategy  $j$ . Then the phenotype  $\mathbf{x}$  is a mixed strategy  $(x_1, \dots, x_s)$ , where  $0 \leq x_i \leq 1$  is the probability that the individual plays basic strategy  $i$ . One can then define the average strategy  $\bar{\mathbf{x}} = (\bar{x}_1, \dots, \bar{x}_s)$  by averaging the phenotype over the whole population. A (simplified) model of the evolutionary process is called *adaptive dynamics* (chapt. 9 in [8]). The time-dependent population state is approximated by a sequence of phenotypically homogeneous states, each evolving from the previous one by invasion of the neighboring mutant with the highest relative payoff. It can be shown that adaptive dynamics leads to strategic optimization: every stable fixed point  $\mathbf{x}^*$  of the population average is a *Nash equilibrium* [10], that is, a mixed strategy that maximizes the payoff against itself (see the more precise definition below).

In this letter, we extend the quasispecies approach to populations evolving according to evolutionary games. This is appropriate for the example of viral evolution, where the frequency-dependent fitness differences are balanced by mutations (occurring with a high rate of  $10^{-4}$  per nucleotide per generation). Unlike for standard quasispecies theory, the “Hamiltonian”  $H$  is now a nonlinear operator acting on the population state. Quite remarkably, the stationary population distributions  $p_s(\sigma)$  and  $p_s(\mathbf{x})$  can still be calculated exactly in some cases. We will demonstrate this for sequences playing the *hawk-dove game*, one of the simplest games with a nontrivial Nash equilibrium. An individual’s phenotype is associated with a mixed strategy  $\mathbf{x}$  uniquely determined by its genotype  $\sigma$ . There are extended neutral networks  $\Gamma_{\mathbf{x}}$  consisting of all sequences encoding the same strategy  $\mathbf{x}$ . The phenotype population  $p(\mathbf{x})$  is found to be a quasispecies. The population average  $\bar{\mathbf{x}}$  deviates from the Nash equilibrium by an amount depending on the mutation rate. The properties of the quasispecies are different from those in a fixed fitness landscape. This reflects the fact that the system exhibits a higher degree of near neutrality, as will be discussed in detail below.

*Phenotypes and evolutionary game theory.* – Consider a population whose phenotypes correspond to the mixed strategies  $\mathbf{x}$  of a game with payoff matrix  $\mathbf{A}$ . That is, an individual of phenotype  $\mathbf{x}$  plays the basic strategy  $i$  with probability  $x_i$  ( $i = 1, \dots, s$ ), and the payoff for a mixed strategy  $\mathbf{x}$  against a mixed strategy  $\mathbf{x}'$  is assumed to be bilinear:

$$\phi(\mathbf{x} | \mathbf{x}') = \sum_{i,j=1}^s A_{ij} x_i x'_j. \quad (1)$$

A Nash equilibrium is defined to be a strategy  $\mathbf{x}^*$  that is optimal against itself, *i.e.*,

$$\phi(\mathbf{x} | \mathbf{x}^*) \leq \phi(\mathbf{x}^* | \mathbf{x}^*) \quad \text{for all strategies } \mathbf{x}. \quad (2)$$

In evolutionary game theory, the game payoff determines the relative fitness of individuals. The population state is a time-dependent phenotype distribution  $p(\mathbf{x})$ ; we suppress the dependence on  $t$  in the notation here and below. Assuming random mixing of the population, the fitness of a phenotype  $\mathbf{x}$  is given by

$$\int d\mathbf{x}' \phi(\mathbf{x} | \mathbf{x}') p(\mathbf{x}') = \phi(\mathbf{x} | \bar{\mathbf{x}}), \quad (3)$$

where  $\bar{\mathbf{x}}$  denotes the average strategy. Hence, the population evolves according to

$$\partial_t p(\mathbf{x}) = [\phi(\mathbf{x} | \bar{\mathbf{x}}) - \phi(\bar{\mathbf{x}} | \bar{\mathbf{x}})] p(\mathbf{x}); \quad (4)$$

subtracting the average fitness  $\phi(\bar{\mathbf{x}} | \bar{\mathbf{x}})$  ensures that the normalization of the distribution  $p(\mathbf{x})$  is preserved. In general, this equation does not have a unique stationary solution. It is easy to see that  $p(\mathbf{x})$  is an attractive fixed point if and only if the population average  $\bar{\mathbf{x}}$  is a Nash equilibrium and all phenotypes  $\mathbf{x}$  in the support of  $p$  are degenerate in fitness, *i.e.*,  $\phi(\mathbf{x} | \mathbf{x}^*) = \phi(\mathbf{x}^* | \mathbf{x}^*)$ .

In this letter, we will focus on the classical hawk-dove game, which has the two basic strategies “hawk” ( $i = 1$ ) and “dove” ( $i = 2$ ); see, *e.g.*, chapt. 6 in [8]. Consider individuals of a population competing for resources of reproductive value  $\lambda$ . Doves avoid confrontation, while hawks escalate fights. Thus, on average, two doves will share the resources. A dove meeting a hawk will leave the entire resources to the hawk. Two hawks will also share the resources but have to pay a confrontation cost  $C\lambda$ . These payoffs can be written in matrix form,

$$\mathbf{A} = \lambda \begin{pmatrix} (1-C)/2 & 1 \\ 0 & 1/2 \end{pmatrix}. \quad (5)$$

An individual with strategy  $\mathbf{x}$  plays, by definition, hawk with probability  $x_1 \equiv x$  and dove with probability  $x_2 = 1 - x$ . The unique Nash equilibrium of the hawk-dove game is  $x^* = \min(1, 1/C)$ . In the following, we assume  $C > 1$  so that the Nash equilibrium is a mixed strategy. According to eqs. (3) and (5), the relative fitness of an arbitrary mixed strategy is given by

$$\phi(\mathbf{x} | \bar{\mathbf{x}}) - \phi(\bar{\mathbf{x}} | \bar{\mathbf{x}}) = \frac{\lambda}{2x^*} (x - \bar{x})(x^* - \bar{x}). \quad (6)$$

*Genotypes and mutations.* – The phenotype of an individual is assumed to be uniquely determined by its genotype. We consider here genotypes with  $L$  loci contributing additively to the phenotype. Each locus has  $c$  alleles, of which  $a$  encode the hawk strategy and  $c - a$  the dove strategy. We denote by  $q = a/c$  the relative fraction of hawk coding alleles. Such genotypes can be represented by sequences  $\sigma = (\sigma_1, \dots, \sigma_L)$  whose letters take the values 0 and 1 representing dove and hawk alleles, respectively. The corresponding phenotype is given by

$$x(\sigma) = \frac{1}{L} \sum_{\alpha=1}^L \sigma_{\alpha}, \quad (7)$$

and takes the discrete values  $x = k/L$ , where  $k = 1, \dots, L$  is the number of hawk alleles. During a time interval of duration  $dt$  any given locus in an individual’s genotype mutates with probability  $\mu dt$  into a randomly chosen allele. It is easy to see that in the absence of selection the mutations change the discrete population distribution,

$$\partial_t p(x) = -[J(x) - J(x - L^{-1})], \quad (8)$$

where  $J(x)$  is the net probability current between all genotypes with  $k = Lx$  and with  $k + 1$  hawk alleles:

$$J(x) = \frac{\mu c}{c-1} L [(1-x)qp(x) - (x+L^{-1})(1-q)p(x+L^{-1})]. \quad (9)$$

This neutral evolution leads to a stationary state  $p_0(x)$  where all alleles are equally probable:

$$p_0(x) = \binom{L}{Lx} q^{Lx} (1-q)^{L(1-x)}. \quad (10)$$

Hence the average phenotype in the population is  $\bar{x}_0 = q$ .

*Quasispecies equation.* – In the following, we describe systematically the interplay between mutations and selection, which leads to nontrivial stationary population states  $p_s(x)$ . Assuming that the two kinds of processes act in parallel, we obtain the mutation-selection equation

$$\partial_t p(x) = -[J(x) - J(x-1/L)] + \frac{\lambda L}{2x^*} (x - \bar{x})(x^* - \bar{x})p(x). \quad (11)$$

This type of dynamics is usually referred to as *paramuse* models [2]. The  $L$ -dependence in the fitness has been introduced in order to obtain a well-behaved large- $L$  limit, *i.e.*, a distribution of the form  $p(x) \propto \exp[-L\mathcal{F}(x)]$ , in analogy with the thermodynamic limit in statistical mechanics and with the standard quasispecies theory [1]. Since the phenotype average  $\bar{x}$  depends on  $p(x)$ , eq. (11) leads to a nonlinear equation for the stationary population state  $p_s(x)$ .

In the present case, the stationary solution can be obtained exactly. Indeed, one can argue that each different locus undergoes an independent mutation-selection process, where the only interaction is encoded in  $\bar{x}$ . Thus one may look for a probability distribution that factorizes into a product of single-locus probabilities (this is a general property when the fitness is a linear functional of the genome [11]). Since all loci are equal in the present model, the stationary distribution  $p_s(x)$  in the presence of selection is still a binomial, but with a different average  $\bar{x}$ :

$$p_s(x) = \binom{L}{Lx} \bar{x}^{Lx} (1-\bar{x})^{L(1-x)}. \quad (12)$$

The scaled variance of this distribution,  $\sigma^2 \equiv L \overline{(x - \bar{x})^2}$ , is linked to  $\bar{x}$  by

$$\sigma^2 = \bar{x}(1-\bar{x}). \quad (13)$$

On the other hand, the equation of motion (11) implies a hierarchy of evolution equations for the moments of  $p(x)$ . The leading equation of this hierarchy reads

$$\partial_t \bar{x} = \frac{\mu c}{c-1} (\bar{x} - q) + \frac{\lambda}{2x^*} \sigma^2 (\bar{x} - x^*). \quad (14)$$

Inserting eq. (13) we obtain a self-consistency equation for  $\bar{x}$ , which is of cubic order. The resulting values of  $\bar{x}$  and  $\sigma^2$  at stationarity are plotted in fig. 1 against the effective mutation rate  $\mu/\lambda$  together with the results from numerical simulations for  $L = 16$ . In accordance with the results obtained above, there is no  $L$ -dependence in these quantities (except for the effects of rounding errors).

Note that a straightforward application of the well-known  $\Omega$ -expansion (see, *e.g.*, chapt. IX in [12]) overestimates the variance of  $x$  and therefore does not give the correct result. This can be seen from the next-to-leading evolution equation for the moments of  $p(x)$ ,

$$\partial_t \sigma^2 = \frac{\mu c}{c-1} [-2\sigma^2 + \bar{x}(1-2q) + q] + \frac{\lambda}{2x^*} L^2 (x^* - \bar{x}) \overline{(x - \bar{x})^3}. \quad (15)$$

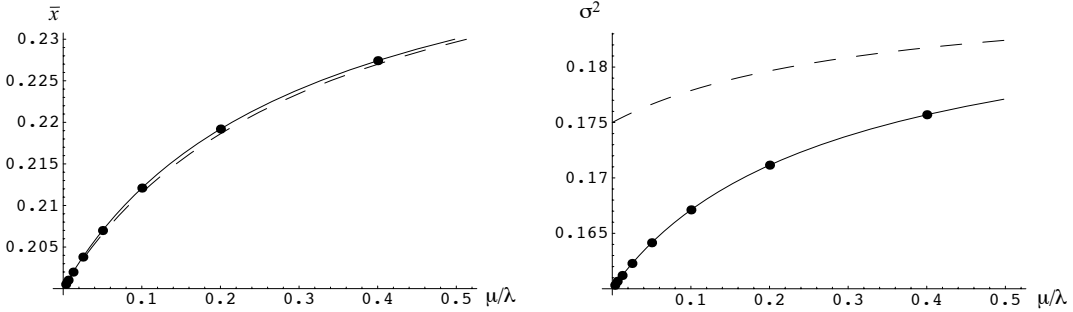


Fig. 1 – Average strategy  $\bar{x}$  (left) and strategy variance  $\sigma^2$  (right) of the phenotypic quasispecies as a function of the effective mutation rate  $\mu/\lambda$ . The points are simulation data for  $c = 4$ ,  $a = 1$ ,  $\lambda = 1$ ,  $x^* = 0.2$ ,  $L = 16$ . The continuous lines give the solutions of eqs. (13), (14). The dashed lines represent the solution obtained from the  $\Omega$ -expansion by neglecting the last term in eq. (15).

In the  $\Omega$ -expansion it is assumed that the first two moments can be obtained self-consistently from the *truncated* system of eqs. (14) and (15), neglecting all higher cumulants as  $L \rightarrow \infty$ . Indeed, the  $m$ -th order cumulant of  $p_s(x)$  scales like  $L^{1-m}$  as required by the  $\Omega$ -expansion. However, in eq. (15) the skewness is multiplied by a factor  $L^2$ , so that its contribution to  $\sigma^2$  remains finite in the limit  $L \rightarrow \infty$  and the truncation fails.

As a function of  $\mu/\lambda$ , the solution  $p_s(x)$  describes a crossover between two dynamical regimes:

i) In the *fast-mutation* regime  $\mu/\lambda \gg 1$ , the evolution becomes effectively neutral. The phenotype distribution approaches the asymptotic form  $p_0(x)$  given by eq. (10); we have

$$\bar{x} = q + O\left(\frac{\lambda}{\mu}\right). \quad (16)$$

ii) In the *slow-mutation* regime  $\mu/\lambda \ll 1$ , the phenotype average approaches the Nash equilibrium but the variance remains finite,

$$\bar{x} = x^* + \frac{\mu c}{c-1} \frac{2x^*}{\lambda \sigma^2} (q - x^*) + o\left(\frac{\mu}{\lambda}\right), \quad \sigma^2 = x^*(1-x^*) + O\left(\frac{\mu}{\lambda}\right). \quad (17)$$

The salient feature of this crossover is that the phenotypic quasispecies is always broad, even in the limit  $\mu \rightarrow 0$ . (In contrast, the standard quasispecies in a fixed fitness landscape would be localized around a master phenotype with a variance  $\sigma^2 = O(\mu)$ .) This broadness reflects the fact that at a mixed Nash equilibrium, all participating basic strategies have the same fitness. Hence, as  $\bar{x}$  approaches  $x^*$ , the fitness differences between phenotypes become small.

*Discussion.* – A generic feature of this mutation-selection dynamics is broad equilibria around Nash points, with a larger degree of sequence divergence than in many fixed fitness landscapes. It is clear that this method can be applied without major changes to evolutionary games with unconditional strategies, in which the payoff  $\phi(\mathbf{x} | \mathbf{x}')$  is a linear function of  $\mathbf{x}'$ . The expression of the mutational entropy can be easily generalized to games with  $s$  pure strategies, encoded by  $a_i$  ( $i = 1, \dots, s$ ) alleles, respectively. Systems where different loci have a different weight in the genotype-phenotype mapping (7) can be treated along the lines of ref. [4]. In general, the stationary distribution of strategies will be close to an evolutionary stable strategy for small mutation rate, if there is one. The situation is different in games with conditional strategies, like the celebrated Prisoner's Dilemma game, see [13], and p. 101

in [8]. In this case, the payoff of a given strategy depends on more properties of the population than the average strategy alone. This case will be the subject of a separate publication [14]. It is also clear that the present approach can be generalized to the case of asymmetric games, which can be used to model the co-evolution of different (but interacting) populations.

The main limitation of the quasispecies approach is the assumption of large population sizes. In finite populations, there are sampling fluctuations, which lie at the heart of the Neutral Evolution approach [15,16]. Recently, these fluctuations have been incorporated into phenotypical evolutionary game theory, using a quantum-mechanical formalism [17]. Analogous finite-population effects in our co-evolutionary sequence dynamics lead to a quantum field theory, which will also be the subject of future work [14].

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