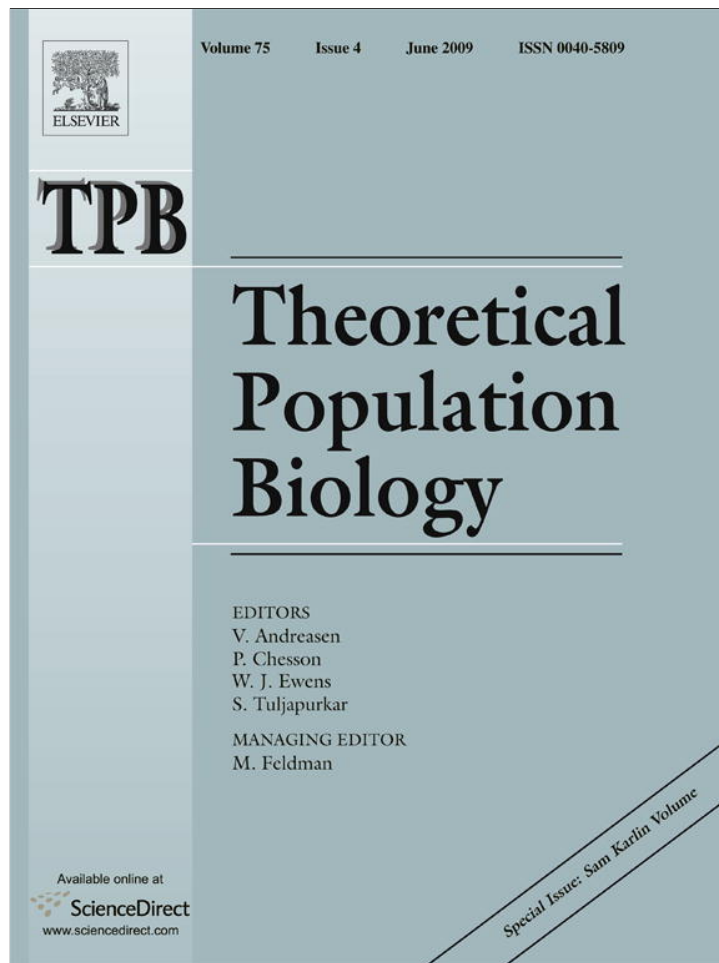


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Fixation probability with multiple alleles and projected average allelic effect on selection

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ABSTRACT

The first-order effect of selection on the probability of fixation of an allele, with respect to an intensity of selection $s > 0$ in a diploid population of fixed finite size N , undergoing discrete, non-overlapping generations, is shown to be given by the sum of the average effects of that allele on the coefficient of selection in the current generation and all future generations, given the population state in the current generation. This projected average allelic effect is a weighted sum of average allelic effects in allozygous and autozygous offspring in the initial generation, with weights given in terms of expected coalescence times, under neutrality, for the lineages of two or three gametes chosen at random in the same generation. This is shown in the framework of multiple alleles at one locus, with genotypic values determining either viability or fertility differences, and with either multinomial or exchangeable reproduction schemes. In the limit of weak selection in a large population such that Ns tends to zero, the initial average allelic effects in allozygous offspring and autozygous offspring have the same weight on the fixation probability only in the domain of application of the Kingman coalescent. With frequency-dependent selection in a linear-game-theoretic context with two phenotypes determined by additive gene action, the first-order effect on the fixation probability is a combination of two effects of frequency-independent selection, one in a haploid population, the other in a diploid population. In the domain of application of the Kingman coalescent as the population size goes to infinity and Ns to zero, the first effect is three times more important than the second effect. This explains the one-third law of evolutionary dynamics in this domain, and shows how this law can be extended beyond this domain.

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1. Introduction

The probability of eventual fixation of an allele has a long history in population genetics theory. Very early, Fisher (1922) raised the question of survival of a new mutant in a large, monomorphic, diploid population in relation with the evolution of dominance and used a branching process approach to estimate the survival probability at twice the selective advantage of the heterozygote over the prevailing homozygote when this advantage is small enough (Fisher, 1930; see, e.g., Ewens, 2004). Much later, Kimura (1962) deduced a formula for the probability of ultimate fixation of a mutant allele in the limit of a large population size based on the Kolmogorov backward equation applied to diffusion approximations for discrete-time population genetics models with an appropriate choice of time unit and scaled selection parameters (see, e.g., Crow and Kimura (1970)). Note that an exact formula is available in the case of a fixed finite population size when the transition matrix for the frequency of the mutant allele is a

continuant (see, e.g., Ewens (2004, p. 90)), as occurs in the case of the discrete-time version of the Moran model for a haploid population (Moran, 1958).

The study of the fixation probability has recently regained interest in relation with evolutionary stability concepts in a game-theoretic perspective (see, e.g., Rousset and Billiard (2000), Proulx and Day (2001), Nowak et al. (2004) and Wild and Taylor (2004)). Let us mention in particular evolutionarily stable strategy (ESS; Maynard Smith and Price, 1973), continuously stable strategy (Eshel and Motro, 1981), which adds m -stability or convergence stability (Taylor, 1989; Christiansen, 1991) to the ESS condition, or otherwise, anti-evolutionarily stable strategy or polymorphic evolutionarily attainable stable trait or evolutionary branching singular point (Uyenoyama and Bengtsson, 1982; Christiansen, 1991; Metz et al., 1996), and neighbourhood invader strategy (Apaloo, 1997). Such concepts can be considered with a payoff function defined as the growth rate of a mutant introduced in small frequency into a monomorphic population (see, e.g., Bulmer and Taylor (1980), Eshel and Feldman (1982), Lessard (1990, 2002), and references therein). This can be viewed as an initial invasion fitness or initial reproductive fitness, and this is the prevailing approach for a population so large that it is assumed to be of infinite size.

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The dynamics of the population following the initial invasion of a mutant has been the subject of numerous studies (Taylor and Jonker, 1978; Hofbauer et al., 1979; Zeeman, 1980; Karlin and Lessard, 1983; Lessard, 1984, 1989; Cressman, 1988; Hofbauer and Sigmund, 1998, 2003, and references therein).

Considering the population size to be finite and mutation non-recurrent, any mutant will go eventually to fixation or extinction. In such a case, the payment function can alternatively be defined as the probability of ultimate fixation of the mutant given that it is represented once initially. This corresponds to an initial replacement fitness or initial fixation fitness. Wild and Taylor (2004) showed the equivalence of the current evolutionary concepts for a continuous trait with both definitions of fitness at least in a Moran population, when they apply at any level of the mutant frequency for a small enough deviation of the mutant trait. This includes the case of mixed strategies in linear games.

Studying the emergence of cooperation in the framework of the repeated Prisoner's dilemma (Trivers, 1971; Axelrod and Hamilton, 1981) with two pure strategies, A (TFT for tit-for-tat) and B (AID for always defecting), and assuming random pairwise interactions in a finite population with a Moran reproduction scheme, Nowak et al. (2004) showed that a single A introduced into an all- B population becomes fixed with a selective advantage, in the limit of weak selection in a large population such that the intensity of selection times the population size goes to zero, if the reproductive payoff to A is greater than the reproductive payoff to B when A has frequency $1/3$. This has been called the one-third law of evolutionary dynamics. It is valid for any pair of pure strategies in a linear game that are the best replies to themselves, namely, strict Nash strategies, and therefore strategies that can resist initial invasion of the other, actually, initial invasion of any combination of the two, in an infinite population. Moreover, it holds in the case of a Wright–Fisher model of reproduction as well (Fisher, 1930; Wright, 1931), under the same assumptions on the population size and selection intensity (Lessard, 2005; Imhof and Nowak, 2006).

The following explanation for the one-third law has been proposed (Ohtsuki et al., 2007a): in one invasion attempt up to extinction or fixation in a neutral model, a single A -player effectively interacts on average with B -players twice as often as with A -players. The argument is based on the mean effective sojourn times in the different population states. In the case of the Moran model, the mean effective sojourn times correspond to the mean numbers of visits, and they can be obtained exactly from the mean sojourn times. In the case of the haploid Wright–Fisher model, the argument relies on an analogy with the Moran model and an approximation of the mean sojourn times in a large population (Fisher, 1930, p. 90).

The one-third law also comes up in the case of pairwise comparison updating (Traulsen et al., 2006) and with games on cycles or graphs (Ohtsuki and Nowak, 2006; Ohtsuki et al., 2006, 2007b). Population subdivision, however, can weaken the one-third law in cases of low migration rates or asymmetric population structures (Ladret and Lessard, 2007, 2008).

Considering an exchangeable selection model for a haploid population extending the Moran and Wright–Fisher selection models and the Cannings neutral model (Cannings, 1974), it has been shown that the one-third law holds in the domain of application of the Kingman coalescent (Kingman, 1982) in the corresponding neutral model in the limit of a large population size (Lessard and Ladret, 2007). Outside this domain, in the case of a linear game with two strict Nash strategies, A and B , the reproductive payoff to A must be greater than the reproductive payoff to B when A has a frequency equal to some threshold value smaller than $1/3$ for a single A to get fixed with a selective advantage in the limit of weak selection, which is a more stringent condition than the one-third law. This makes cooperation less

likely to evolve in a finite population with a highly skewed distribution of family size, for instance (Lessard, 2007).

In this paper, we will first recall the classical Wright–Fisher multiallele viability model for a finite diploid population (Section 2). We will use a direct Markov chain approach as proposed by Rousset (2003) and ascertained by Lessard and Ladret (2007) in the case of two alleles to get the first-order effect of selection on the probability of fixation in a population of a fixed finite size (Section 3). This effect will be expressed in terms of expected values of products of allelic frequencies under neutrality (Section 4), and then in terms of expected coalescence times and initial allelic frequencies (Section 5). We will consider next the first-order effect of a two-phenotype linear game on the probability of fixation in the case of additive gene action on the phenotypic determination, which makes the model formally equivalent to a linearly frequency-dependent haploid model (Section 6). We will also consider the effect of fertility differences instead of viability differences (Section 7) and relax the assumption of a multinomial distribution for the contributions of the parents of any given generation (Section 8). Then, we will show that, in general, the first-order effect of selection on the probability of fixation is given by an average allelic excess in the coefficient of selection, or equivalently an average allelic effect on the coefficient of selection, understood in the classical sense (Fisher, 1930), but taking into account not only the population structure in the current generation but also in all future generations under neutrality (Section 9). This interpretation provides a theoretical framework for studying the fixation probability in a small population under weak selection, and explains the one-third law in the domain of application of the Kingman coalescent as the population size goes to infinity and its extension for more general situations (Section 10). A rigorous justification of the approach in the case of multiple alleles is included for completeness (Appendix).

2. Wright–Fisher multiallele viability model

We consider n alleles, A_1, A_2, \dots, A_n , at a single autosomal locus in a diploid population of N monoecious individuals ($2N$ genes) undergoing discrete, non-overlapping generations. Every generation starts with male and female gametes in large numbers, and female gametes are united at random with male gametes to form a virtually infinite number of offspring. Then, viability differences from conception to maturity depending on the genotype at the considered locus take place among the offspring. This is followed by population size regulation: N mature offspring are chosen at random to be the parents of the next generation. These N parents produce large numbers of gametes of each sex in equal proportions to start the next generation. Mendelian segregation of gametes is assumed. This is the Wright–Fisher multiallele viability model for a diploid monoecious population (Fisher, 1930; Wright, 1931; see, e.g., Ewens, 2004, Chap. 3, Nagylaki, 1992, pp. 248–253). See the next sections for other models.

Let $x_i(t)$ be the frequency of A_i and $x_{ij}(t) = x_{ji}(t)$ the frequency of the ordered genotype $A_i A_j$ at the beginning of generation $t \geq 0$, for $i, j = 1, \dots, n$. Random union of gametes implies

$$x_{ij}(t) = x_i(t)x_j(t) = x_{ji}(t), \quad (1)$$

for $i, j = 1, \dots, n$.

Let the viability of $A_i A_j$, which is proportional to the probability of survival from conception to maturity, be expressed in the form

$$w_{ij} = 1 + su_{ij}, \quad (2)$$

for $i, j = 1, \dots, n$, where $s \geq 0$ represents the intensity of selection and $u_{ij} = u_{ji}$ a coefficient of selection. Then, the frequency of the ordered genotype $A_i A_j$ after selection becomes

$$\tilde{x}_{ij}(t) = \frac{x_{ij}(t)(1 + su_{ij})}{1 + \bar{s}u(t)}, \quad (3)$$

for $i, j = 1, \dots, n$, where

$$\bar{u}(t) = \sum_{i=1}^n \sum_{j=1}^n x_{ij}(t) u_{ij} \quad (4)$$

is the mean coefficient of selection in generation $t \geq 0$. Note that $\tilde{x}_{ij}(t) = \tilde{x}_{ji}(t)$, for $i, j = 1, \dots, n$. This leads to

$$\tilde{x}_i(t) = \sum_{j=1}^n \tilde{x}_{ij}(t) = \frac{x_i(t)(1 + s\bar{u}_i)}{1 + s\bar{u}(t)}, \quad (5)$$

for the frequency of allele A_i after selection, where

$$\bar{u}_i(t) = \sum_{j=1}^n x_j(t) u_{ij} \quad (6)$$

is the marginal coefficient of selection of A_i , for $i = 1, \dots, n$. Note that this frequency will be the conditional expected value of $x_i(t + 1)$, the frequency of A_i at the beginning of generation $t + 1$, given $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$.

Actually, in the Wright–Fisher model, the random variable $2Nx_i(t + 1)$ will follow a conditional binomial distribution of parameters $2N$ and $\tilde{x}_i(t)$. More generally, in this case, the conditional distribution of the random vector $2N\mathbf{x}(t + 1) = (2Nx_1(t + 1), \dots, 2Nx_n(t + 1))$ will be multinomial with parameters $2N$ and $\tilde{x}_1(t), \dots, \tilde{x}_n(t)$, respectively.

3. Fixation probability under weak selection

For any fixed population size N , the frequency of allele A_i will converge, in probability owing to the ergodic theorem and therefore in mean by dominated convergence (see, e.g., Karlin and Taylor (1975)), to the random variable

$$x_i(\infty) = x_i(0) + \sum_{t \geq 0} \Delta x_i(t), \quad (7)$$

where $\Delta x_i(t) = x_i(t + 1) - x_i(t)$ is the change in the frequency of allele A_i from generation t to generation $t + 1$, for $i = 1, \dots, n$ and $t \geq 0$. The variable $x_i(\infty)$ takes the value 1 if allele A_i becomes ultimately fixed in the population, and 0 otherwise. Actually, the probability of ultimate fixation of A_i can be expressed as

$$P_s(A_i) = E_s[x_i(\infty)] = x_i(0) + \sum_{t \geq 0} E_s[\Delta x_i(t)], \quad (8)$$

where $x_i(0)$ represents the given initial frequency of A_i , while P_s and E_s denote probability and expectation, respectively, when the intensity of selection is $s \geq 0$. Conditioning on the allelic state of the population in the previous generation to get the expected change in the frequency of A_i in the current generation and using the tower property of conditional expectation, this probability can be written as

$$P_s(A_i) = x_i(0) + \sum_{t \geq 0} E_s[E_s[\Delta x_i(t)|\mathbf{x}(t)]], \quad (9)$$

where $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$ for $t \geq 0$, and

$$E_s[\Delta x_i(t)|\mathbf{x}(t)] = \tilde{x}_i(t) - x_i(t). \quad (10)$$

Owing to (5), this conditional expected change in the frequency of A_i takes the form

$$E_s[\Delta x_i(t)|\mathbf{x}(t)] = \frac{s x_i(t) (\bar{u}_i(t) - \bar{u}(t))}{1 + s \bar{u}(t)}, \quad (11)$$

which is such that

$$E_0[\Delta x_i(t)|\mathbf{x}(t)] = 0. \quad (12)$$

This reduces to the approximation

$$E_s[\Delta x_i(t)|\mathbf{x}(t)] \approx s x_i(t) (\bar{u}_i(t) - \bar{u}(t)), \quad (13)$$

when selection is weak, that is, $s \geq 0$ is small enough. Note that $\bar{u}_i(t) - \bar{u}(t)$ represents the average excess of A_i in the coefficient of selection in generation $t \geq 0$, which is the same in the model considered as the average effect, on the total measurement in the population in generation $t \geq 0$, of substituting a gamete of type A_i in place of a gamete chosen at random (Fisher, 1930). Inserting this expression into (9) yields

$$P_s(A_i) \approx x_i(0) + \sum_{t \geq 0} E_s[s x_i(t) (\bar{u}_i(t) - \bar{u}(t))], \quad (14)$$

for the probability of ultimate fixation of A_i , which in turn can be approximated as

$$P_s(A_i) \approx x_i(0) + s \sum_{t \geq 0} E_0[x_i(t) (\bar{u}_i(t) - \bar{u}(t))], \quad (15)$$

where E_0 designates expectation under neutrality, that is, when $s = 0$.

The above treatment suggests that the derivative of $P_s(A_i)$ with respect to s , evaluated at $s = 0$ is given by

$$P'_0(A_i) = \sum_{t \geq 0} E_0[x_i(t) (\bar{u}_i(t) - \bar{u}(t))]. \quad (16)$$

Actually, this is ascertained if the derivative of the sum in (8) is the sum of the derivatives in a neighborhood of $s = 0$. This will be the case if the derivatives converges uniformly in a neighborhood of $s = 0$. A proof is given in the Appendix under the condition that the one-step transition probabilities of the Markov chain $\mathbf{x}(t)$, for $t \geq 0$, and their derivatives with respect to $s \geq 0$ are continuous at $s = 0$.

Finally, expressing $\bar{u}_i(t)$ and $\bar{u}(t)$ in terms of the allelic frequencies, the first-order effect of selection on the probability of ultimate fixation of A_i can be written as

$$P'_0(A_i) = \sum_{t \geq 0} E_0 \left[x_i(t) \left(\sum_{j=1}^n x_j(t) u_{ij} - \sum_{j=1}^n \sum_{k=1}^n x_j(t) x_k(t) u_{jk} \right) \right], \quad (17)$$

which can be rearranged into the form

$$P'_0(A_i) = \sum_{t \geq 0} \left\{ E_0[x_i^2(t)(1 - x_i(t))u_{ii}] + \sum_{\substack{j=1 \\ j \neq i}}^n E_0[x_i(t)x_j(t)]u_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n E_0[x_i(t)x_j^2(t)]u_{jj} - 2 \sum_{\substack{j=1 \\ j \neq i}}^n E_0[x_i^2(t)x_j(t)]u_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n \sum_{\substack{k=1 \\ k \neq i, j}}^n E_0[x_i(t)x_j(t)x_k(t)]u_{jk} \right\}, \quad (18)$$

with indices i, j, k all different.

4. Expectation of products of allele frequencies

In order to express the expected value of a product of allele frequencies in generation $t \geq 0$ under neutrality with respect to the initial allelic frequencies, let us introduce the probability $p_{kl}^{(t)}$ that k gametes chosen at random in generation $t \geq 0$ descend from exactly l ancestral gametes in generation 0 under neutrality.

First, consider two gametes, labeled 1 and 2, chosen at random in generation $t \geq 0$. Then, the expected value of $x_i(t)x_j(t)$ gives the

probability that gametes 1 and 2 are of types A_i and A_j , respectively. This will be the case, for $i \neq j$, if and only if the corresponding ancestral gametes in generation 0 are distinct, which occurs with probability $p_{22}^{(t)}$, and these are of types A_i and A_j , respectively, which has probability $x_i(0)x_j(0)$ under neutrality. Therefore, we have

$$E_0[x_i(t)x_j(t)] = p_{22}^{(t)}x_i(0)x_j(0), \quad (19)$$

for $i \neq j$. Note that this entails

$$E_0[x_i(t)(1 - x_i(t))] = p_{22}^{(t)}x_i(0)(1 - x_i(0)), \quad (20)$$

since $1 - x_i(t) = \sum_{j \neq i} x_j(t)$, for $t \geq 0$.

Next, consider three gametes chosen at random in generation $t \geq 0$ and label them arbitrarily 1, 2 and 3. Then, the expected value of $x_i^2(t)(1 - x_i(t))$ gives the probability that gametes 1 and 2 are of type A_i and gamete 3 of any other type. Conditioning on the number of the ancestral gametes in generation 0 and noting that these are chosen at random under neutrality, we get

$$E_0[x_i^2(t)(1 - x_i(t))] = \left(\frac{x_i(0)(1 - x_i(0))}{2} \right) \times \left[2x_i(0)p_{33}^{(t)} + p_{22}^{(t)} - p_{33}^{(t)} \right]. \quad (21)$$

Indeed, with probability $p_{33}^{(t)}$, the ancestral gametes are all distinct and they are of the required types with probability $x_i^2(0)(1 - x_i(0))$. On the other hand, with probability $p_{22}^{(t)} - p_{33}^{(t)}$, the ancestral gametes of gametes 1 and 3 are distinct and one of them is ancestral also to gamete 2, the ancestral gametes being of the required types with probability $x_i(0)(1 - x_i(0))$ divided by 2.

Similarly, for three labeled gametes in generation $t \geq 0$ to be of two different types, one of type A_i and two of type A_j different from A_i , for instance, there must be either 2 or 3 ancestral gametes in generation 0 of the corresponding types and, in the case of 2 ancestral gametes, the two lineages that have coalesced must be associated to type A_j . This leads to

$$E_0[x_i(t)x_j^2(t)] = \left(\frac{x_i(0)x_j(0)}{2} \right) \left[2x_j(0)p_{33}^{(t)} + p_{22}^{(t)} - p_{33}^{(t)} \right], \quad (22)$$

for $i \neq j$. Symmetrically, we have

$$E_0[x_i^2(t)x_j(t)] = \left(\frac{x_i(0)x_j(0)}{2} \right) \left[2x_i(0)p_{33}^{(t)} + p_{22}^{(t)} - p_{33}^{(t)} \right], \quad (23)$$

for $i \neq j$.

Finally, the only way for three gametes in generation $t \geq 0$ to be of different types, say A_i , A_j and A_k , is that their ancestral gametes in generation 0 are all distinct and of the corresponding types. In other words, we have

$$E_0[x_i(t)x_j(t)x_k(t)] = p_{33}^{(t)}x_i(0)x_j(0)x_k(0), \quad (24)$$

for i, j, k all different.

5. Effect of selection on fixation probability

We are now prepared to express the first-order effect of selection on the probability of ultimate fixation in terms of the initial allelic frequencies and the mean coalescence times

$$\sum_{t \geq 0} p_{22}^{(t)} = E_0(T_2) \quad (25)$$

and

$$\sum_{t \geq 0} p_{33}^{(t)} = E_0(T_3). \quad (26)$$

The times T_2 and T_3 represent the numbers of generations backward in time, under neutrality, for the first coalescence of lineages starting from two and three gametes, respectively, to occur.

Plugging the expressions of the expected products of allele frequencies found in the previous section into Eq. (18) and summing over $t \geq 0$ yield

$$P'_0(A_i) = \left(\frac{x_i(0)(1 - x_i(0))}{2} \right) \left[2x_i(0)E_0(T_3) + E_0(T_2) - E_0(T_3) \right] u_{ii} + \sum_{\substack{j=1 \\ j \neq i}}^n x_i(0)x_j(0)E_0(T_2)u_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n x_i(0)x_j(0) \times \left[2x_i(0)E_0(T_3) + E_0(T_2) - E_0(T_3) \right] u_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n \left(\frac{x_i(0)x_j(0)}{2} \right) \left[2x_j(0)E_0(T_3) + E_0(T_2) - E_0(T_3) \right] u_{ij} - \sum_{\substack{j=1 \\ j \neq i}}^n \sum_{\substack{k=1 \\ k \neq i, j}}^n x_i(0)x_j(0)x_k(0)E_0(T_3)u_{jk}. \quad (27)$$

Some algebraic manipulations lead to

$$P'_0(A_i) = x_i(0) \left[E_0(T_3)(\bar{u}_i(0) - \bar{u}(0)) + \left(\frac{E_0(T_2) - E_0(T_3)}{2} \right) (u_{ii} - \bar{\bar{u}}(0)) \right], \quad (28)$$

where

$$\bar{u}_i(0) = \sum_{j=1}^n x_j(0)u_{ij} \quad (29)$$

is the initial marginal coefficient of selection of A_i in allozygous offspring,

$$\bar{u}(0) = \sum_{i=1}^n x_i(0)\bar{u}_i(0), \quad (30)$$

the initial mean coefficient of selection in allozygous offspring, and

$$\bar{\bar{u}}(0) = \sum_{i=1}^n x_i(0)u_{ii}, \quad (31)$$

the initial mean coefficient of selection in autozygous offspring.

It remains to calculate the expected values of the coalescence times T_2 and T_3 under neutrality. Note that $p_{22}^{(t)} = p_{22}^t$ and $p_{33}^{(t)} = p_{33}^t$, for $t \geq 0$, where p_{22} and p_{33} designate the probabilities for two and three gametes, respectively, to descend from two and three ancestral gametes, respectively, one generation back in the neutral model. Therefore, the coalescence times T_2 and T_3 under neutrality are geometric random variables with parameters p_{22} and p_{33} , respectively, whose expected values are

$$E_0(T_2) = \frac{1}{1 - p_{22}} \quad (32)$$

and

$$E_0(T_3) = \frac{1}{1 - p_{33}}. \quad (33)$$

Under the assumptions of the neutral Wright–Fisher model, we have

$$p_{22} = \frac{2N - 1}{2N} \quad (34)$$

and

$$p_{33} = \left(\frac{2N-1}{2N}\right) \left(\frac{2N-2}{2N}\right). \quad (35)$$

This leads to

$$E_0(T_2) = 2N \quad (36)$$

and

$$E_0(T_3) = \frac{2N^2}{3N-1}, \quad (37)$$

from which

$$\frac{E_0(T_2) - E_0(T_3)}{2} = \frac{N(2N-1)}{3N-1}. \quad (38)$$

Therefore, for the Wright–Fisher model, (28) translates into

$$P'_0(A_i) = \frac{2N^2 x_i(0)}{3N-1} \times \left[(\bar{u}_i(0) - \bar{u}(0)) + \left(1 - \frac{1}{2N}\right) (u_{ii} - \bar{u}(0)) \right]. \quad (39)$$

This result implies that the ultimate fixation of allele A_i , given the initial allelic state of the population, is favored by weak selection, that is, $P'_0(A_i) > 0$, which ensures that $P_s(A_i) > P_0(A_i)$ for $s > 0$ small enough, if and only if

$$(\bar{u}_i(0) - \bar{u}(0)) + \left(1 - \frac{1}{2N}\right) (u_{ii} - \bar{u}(0)) > 0. \quad (40)$$

Note that, for a large population, the factor $1/(2N)$ can be neglected. In this case, the initial average excess of A_i in autozygous offspring, $u_{ii} - \bar{u}(0)$, is as important as the initial average excess of A_i in allozygous offspring, $\bar{u}_i(0) - \bar{u}(0)$, for the occurrence of ultimate fixation of A_i to occur.

6. Frequency-dependent selection model

In this section, we will consider the case with additive allelic effects on the coefficient of selection that depend linearly on the allelic state of the current generation. Actually, we will consider a two-phenotype multiallele model in the context of evolutionary game theory (Maynard Smith and Price, 1973; Maynard Smith, 1974) as in Lessard (1984) for an infinite diploid population, but with semidominance for the phenotypic determination, weak selection and population size regulation.

Assume two phenotypes, 1 and 2, and suppose that an $A_i A_j$ offspring is of phenotype 1 with probability $v_{ij} = (h_i + h_j)/2$ and of phenotype 2 with the complementary probability $1 - v_{ij}$, for $i, j = 1, \dots, n$. Assume random pairwise interactions between the offspring in the same generation and let

$$M = \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix} \quad (41)$$

be the payoff matrix, with m_{kl} representing the selection coefficient of an offspring of phenotype k in interaction with an offspring of phenotype l , for $k, l = 1, 2$. Then, the coefficient of selection of genotype $A_i A_j$ in generation $t \geq 0$ is found to be

$$u_{ij}(t) = m_{22} + (m_{21} - m_{22})\bar{h}(t) + \left(\frac{h_i + h_j}{2}\right) [m_{12} - m_{22} + (m_{11} - m_{12} - m_{21} + m_{22})\bar{h}(t)], \quad (42)$$

where

$$\bar{h}(t) = \sum_{i=1}^n h_i x_i(t) \quad (43)$$

is the current frequency of phenotype 1. This gives

$$\bar{u}_i(t) = m_{22} + (m_{21} - m_{22})\bar{h}(t) + \left(\frac{h_i + \bar{h}(t)}{2}\right) [m_{12} - m_{22} + (m_{11} - m_{12} - m_{21} + m_{22})\bar{h}(t)], \quad (44)$$

for the marginal coefficient of selection of allele A_i , which leads to

$$\bar{u}_i(t) - \bar{u}(t) = (h_i - \bar{h}(t)) (-a + b\bar{h}(t)), \quad (45)$$

for the average excess of allele A_i in the coefficient of selection, where

$$a = \frac{m_{22} - m_{12}}{2},$$

and

$$b = \frac{m_{11} - m_{21} - m_{12} + m_{22}}{2}. \quad (46)$$

Note that this corresponds to the average excess in a haploid population with h_i and $1 - h_i$ being the probabilities for an A_i offspring to be of phenotypes 1 and 2, respectively, for $i = 1, \dots, n$, and $(m_{kl}/2)$ being the selection coefficient for an offspring of phenotype k in interaction with an offspring of phenotype l , and $k, l = 1, 2$.

Taking the expected value, under neutrality, of the average excess of A_i in generation $t \geq 0$ multiplied by $x_i(t)$ and regrouping the frequencies of the same alleles yield

$$\begin{aligned} E_0 [x_i(t) (\bar{u}_i(t) - \bar{u}(t))] &= -a h_i E_0 [x_i(t) (1 - x_i(t))] + b h_i^2 E_0 [x_i^2(t) (1 - x_i(t))] \\ &+ (b h_i + a) \sum_{\substack{j=1 \\ j \neq i}}^n h_j E_0 [x_i(t) x_j(t)] - b \sum_{\substack{j=1 \\ j \neq i}}^n h_j^2 E_0 [x_i(t) x_j^2(t)] \\ &- 2b h_i \sum_{\substack{j=1 \\ j \neq i}}^n h_j E_0 [x_i^2(t) x_j(t)] \\ &- b \sum_{\substack{j=1 \\ j \neq i}}^n \sum_{\substack{k=1 \\ k \neq i, j}}^n h_j h_k E_0 [x_i(t) x_j(t) x_k(t)]. \end{aligned} \quad (47)$$

Summing over $t \geq 0$ and using the results of Section 4 give

$$P'_0(A_i) = x_i(0) \left[(-a E_0(T_2) + b \bar{h}(0) E_0(T_3)) (h_i - \bar{h}(0)) + b \left(\frac{E_0(T_2) - E_0(T_3)}{2}\right) (h_i^2 - \bar{h}^2(0)) \right], \quad (48)$$

for the first-order effect of selection on the probability of ultimate fixation of allele A_i , where

$$\bar{h}(0) = \sum_{j=1}^n h_j x_j(0) \quad (49)$$

and

$$\bar{h}^2(0) = \sum_{j=1}^n h_j^2 x_j(0). \quad (50)$$

Under the assumptions of the Wright–Fisher model, this result reduces to

$$P'_0(A_i) = 2N x_i(0) \left[\left(-a + \frac{bN\bar{h}(0)}{3N-1}\right) (h_i - \bar{h}(0)) + b \left(\frac{N - \frac{1}{2}}{3N-1}\right) (h_i^2 - \bar{h}^2(0)) \right], \quad (51)$$

which gives the approximation

$$P'_{0}(A_i) \approx 2N x_i(0) \left[\left(-a + \frac{b \bar{h}(0)}{3} \right) (h_i - \bar{h}(0)) + \frac{b}{3} (h_i^2 - \bar{h}^2(0)) \right], \quad (52)$$

when N is large.

7. Multiallele fertility model

Consider the multiallele model of Section 2, but with fertility differences after population size regulation instead of viability differences before regulation. More precisely, let the parameter $w_{ij} = 1 + s u_{ij} = w_{ji}$ measure the relative quantity of gametes produced by a parent of genotype $A_i A_j$, for $i, j = 1, \dots, n$ (see, e.g., Moran (1962, pp. 144–152), for such a model). Note that this relative quantity is assumed to be the same for male gametes and female gametes so that the fertility of each parent as a male is the same as its fertility as a female. Moreover, the proportion of male and female gametes provided by each parent to start a new generation will depend not only on its own genotype, but also on the genotypes of the other parents contributing to the same generation. Mendelian segregation is assumed so that a gamete produced by an $A_i A_j$ parent is of type A_i with probability $1/2$ and of type A_j with probability $1/2$. As before, male and female gametes are united at random to form a large number of offspring, among which N are sampled at random to become the parents of the next generation.

Numbering the parents of generation $t + 1$ from 1 to N , each one will be of ordered genotype $A_i A_j$ with probability $x_i(t) x_j(t)$, for $i, j = 1, \dots, n$, independently of all the others. If $N_{ij}(t)$ designates the number of $A_i A_j$ parents of generation $t + 1$, then the random vector $\mathbf{N}(t) = (N_{ij}(t); i, j = 1, \dots, n)$ will have a conditional multinomial distribution with parameters N and $x_i(t) x_j(t)$, for $i, j = 1, \dots, n$, respectively, given $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$. Moreover, the frequency of A_i at the beginning of generation $t + 1$ will be

$$\tilde{x}_i(t + 1) = \frac{\sum_{j=1}^n \left(\frac{N_{ij}(t) + N_{ji}(t)}{2} \right) (1 + s u_{ij})}{N + s \sum_{k=1}^n \sum_{l=1}^n N_{kl}(t) u_{kl}}. \quad (53)$$

We find that, up to terms of order s ,

$$E_s [\Delta x_i(t) | \mathbf{x}(t)] \approx s x_i(t) \left(1 - \frac{1}{N} \right) \left\{ \sum_{j=1}^n x_j(t) u_{ij} - \sum_{k=1}^n \sum_{l=1}^n x_k(t) x_l(t) u_{kl} \right\}, \quad (54)$$

using the facts that

$$\begin{aligned} E_s [N_{ij}(t) | \mathbf{x}(t)] &= N x_i(t) x_j(t), \\ E_s [N_{ij}(t)^2 | \mathbf{x}(t)] &= N x_i(t) x_j(t) (1 - x_i(t) x_j(t)) + N^2 x_i(t)^2 x_j(t)^2, \\ E_s [N_{ij}(t) N_{kl}(t) | \mathbf{x}(t)] &= N(N - 1) x_i(t) x_j(t) x_k(t) x_l(t), \end{aligned} \quad (55)$$

for $i, j, k, l = 1, \dots, n$, $(i, j) \neq (k, l)$. The only difference with the viability model is that the intensity of selection is reduced by a factor $(1 - 1/N)$.

8. Exchangeable multiallele viability model

Let us make the assumptions of the multiallele viability model of Section 2, except that the N mature offspring chosen at random in any given generation to be the parents of the next generation, arbitrarily numbered $1, \dots, N$, produce gametes in proportions v_1, \dots, v_N , respectively. These proportions are only supposed to be exchangeable random variables, satisfying $0 \leq v_l \leq 1$, for $l = 1, \dots, N$, and $\sum_{l=1}^N v_l = 1$, which entails an expected value equal to $1/N$ for each proportion. Moreover, their joint distribution is the same in every generation, independently of everything else. The Wright–Fisher multiallele viability model (Fisher, 1930; Wright, 1931; see, e.g., Ewens, 2004) corresponds to the particular case $v_l = 1/N$, for $l = 1, \dots, N$. The more general exchangeable model is an extension of the Cannings neutral model (Cannings, 1974) to incorporate selection.

In the general exchangeable model, the vector of allele frequencies at the beginning of generation $t \geq 1$, that is, $\mathbf{x}(t + 1) = (x_1(t + 1), \dots, x_n(t + 1))$, can be expressed as

$$\mathbf{x}(t + 1) = \sum_{l=1}^N v_l(t) \mathbf{z}_l(t), \quad (56)$$

where $v_l(t)$ is the proportion of gametes produced by parent l of generation $t + 1$ and $\mathbf{z}_l(t) = (z_{l,1}(t), \dots, z_{l,n}(t))$ with $z_{l,i}(t)$ representing the frequency of A_i in this parent, for $i = 1, \dots, n$ and $l = 1, \dots, N$. These random variables take the values $1, 1/2$ and 0 with probabilities $\tilde{x}_{ii}(t)$, $2\tilde{x}_i(t) - 2\tilde{x}_{ii}(t)$ and $1 - 2\tilde{x}_i(t) + \tilde{x}_{ii}(t)$, respectively, and independently for $l = 1, \dots, N$. This gives $\tilde{\mathbf{x}}(t) = (\tilde{x}_1(t), \dots, \tilde{x}_n(t))$ as the conditional expected value of $\mathbf{x}(t + 1)$, given $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$, which does not depend on the joint distribution of v_1, \dots, v_N .

On the other hand, the probability that two gametes descend from two ancestral gametes one generation back in the neutral model is

$$p_{22} = \sum_{k=1}^N \sum_{\substack{l=1 \\ l \neq k}}^N E_0 [v_k v_l] + \frac{1}{2} \sum_{k=1}^N E_0 [v_k^2]. \quad (57)$$

Using the fact that v_1, \dots, v_N are exchangeable and sum up to 1, we find that

$$p_{22} = 1 - \frac{N}{2} E_0 [v_1^2]. \quad (58)$$

Similarly, three gametes will descend from three ancestral gametes one generation back with probability

$$p_{33} = \sum_{k=1}^N \sum_{\substack{l=1 \\ l \neq k}}^N \sum_{\substack{m=1 \\ m \neq k, l}}^N E_0 [v_k v_l v_m] + \frac{3}{2} \sum_{k=1}^N \sum_{\substack{l=1 \\ l \neq k}}^N E_0 [v_k^2 v_l], \quad (59)$$

which yields, after some algebraic manipulations,

$$p_{33} = 1 - \left(\frac{3N}{2} \right) E_0 [v_1^2] + \left(\frac{N}{2} \right) E_0 [v_1^3]. \quad (60)$$

Note that

$$\frac{1 - p_{33}}{3(1 - p_{22})} = 1 - \frac{E_0 [v_1^3]}{3E_0 [v_1^2]}, \quad (61)$$

while

$$\frac{E_0(T_2) - E_0(T_3)}{2E_0(T_3)} = \frac{1 - p_{33}}{2(1 - p_{22})} - \frac{1}{2}, \quad (62)$$

where T_2 and T_3 designate the numbers of generations back for the first coalescence of lineages starting from two and three gametes,

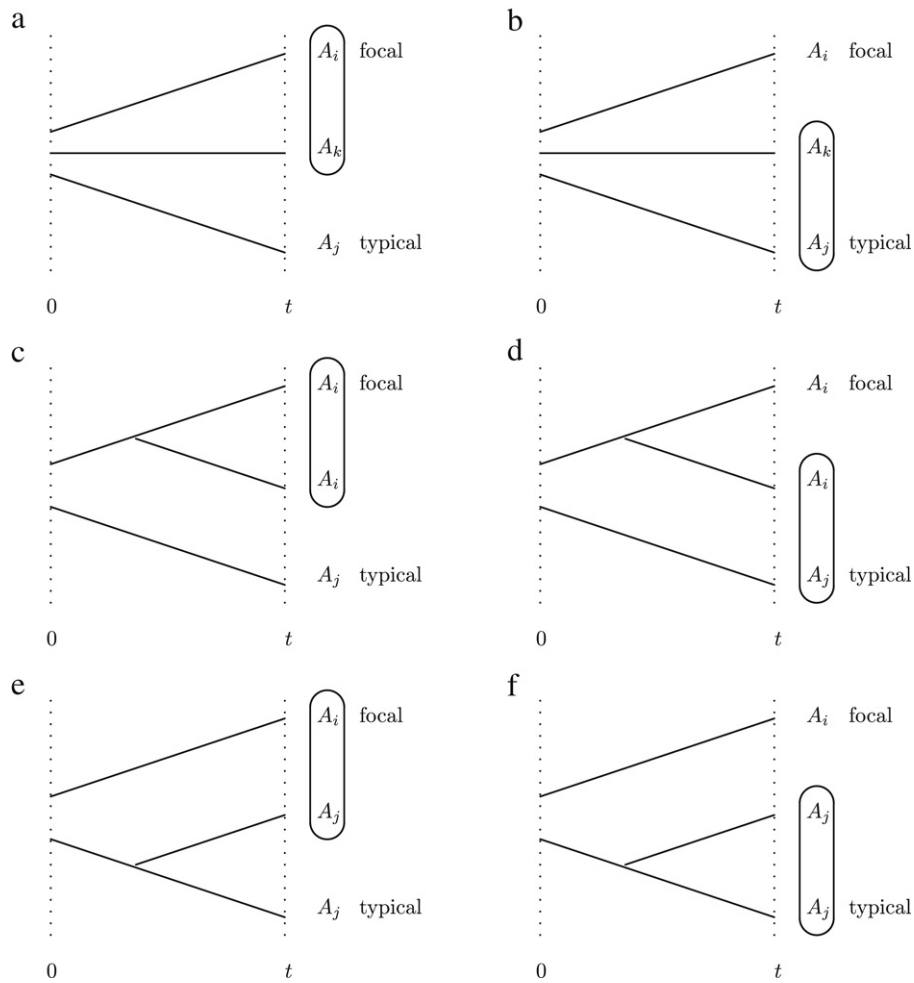


Fig. 1. Possible genealogical structures for three gametes in generation $t \geq 0$, a focal gamete A_i and a typical gamete A_j originating from distinct ancestral gametes in generation 0, and a third gamete (A_i, A_j or A_k) united with either the focal gamete (a, c, e) or the typical gamete (b, d, f) to form an offspring. The structures (a, b), (c, d) and (e, f) have probabilities $p_{33}^{(t)}$, $(p_{22}^{(t)} - p_{33}^{(t)})/2$ and $(p_{22}^{(t)} - p_{33}^{(t)})/2$, respectively.

respectively. Therefore, we have

$$\frac{E_0(T_2) - E_0(T_3)}{2E_0(T_3)} \approx 1, \tag{63}$$

if and only if

$$\frac{1 - p_{33}}{3(1 - p_{22})} \approx 1, \tag{64}$$

which holds if and only if

$$\frac{E_0[v_1^3]}{E_0[v_1^2]} \approx 0. \tag{65}$$

This means that the initial average excesses in the selection coefficient in autozygous and allozygous offspring will have approximately the same weight for the fixation probability whenever the probability of coalescence of three lineages can be neglected compared to the probability of coalescence of any two out of three. This condition corresponds to the domain of application of the Kingman coalescent in the limit of a large population size (Kingman, 1982; Möhle, 2000).

9. Interpretation in term of projected average allelic effect

The term in brackets in (28) is the average excess of A_i in the coefficient of selection in all generations $t \geq 0$ for the multiallele

viability model of Section 2. This can be better understood with the help of Fig. 1. Consider a focal gamete of type A_i in generation $t \geq 0$. We want to compare its marginal coefficient of selection with the mean coefficient of selection in the same generation. This mean will be the expected value of the marginal coefficient for a typical gamete chosen at random in the same generation. If this gamete has the same ancestral gamete in generation 0 as the focal gamete, then its marginal coefficient will also be the same. Therefore, it suffices to consider the case of distinct ancestral gametes, whose probability is $p_{22}^{(t)}$. Note that the typical gamete will be of type A_j with probability $x_j(0)$. Then, a third gamete is chosen at random in the same generation and united with either the focal gamete or the typical gamete to form an offspring. With probability $p_{33}^{(t)}$, the three ancestral gametes in generation 0 are all distinct and the genotype of the offspring is A_iA_k with probability $x_k(0)$ in the former case and A_jA_k with probability $x_j(0)x_k(0)$ in the latter. On the other hand, with probability $(p_{22}^{(t)} - p_{33}^{(t)})/2$, the third gamete has the same ancestral gamete in generation 0 as the focal gamete, and the genotype of the offspring is A_iA_i with probability one in the former case and A_iA_j with probability $x_j(0)$ in the latter. Finally, with probability $(p_{22}^{(t)} - p_{33}^{(t)})/2$, the third gamete has the same ancestral gamete in generation 0 as the typical gamete, and then the genotype of the offspring is A_iA_j in the former case and A_jA_j in the latter, with probability $x_j(0)$ in both cases. Then, the difference between the expected coefficient of selection of the offspring formed in generation $t \geq 0$ with the focal gamete and

the one of the offspring formed in the same generation with the typical gamete is

$$a_i^{(t)}(0) = p_{33}^{(t)} \left[\sum_{k=1}^n u_{ik}x_k(0) - \sum_{j=1}^n \sum_{k=1}^n u_{jk}x_j(0)x_k(0) \right] + \left(\frac{p_{22}^{(t)} - p_{33}^{(t)}}{2} \right) \left[u_{ii} - \sum_{j=1}^n u_{ji}x_j(0) + \sum_{j=1}^n u_{ij}x_j(0) - \sum_{j=1}^n u_{jj}x_j(0) \right]. \quad (66)$$

Summing over $t \geq 0$ and using the symmetry condition $u_{ij} = u_{ji}$, for $i, j = 1, \dots, n$, yield

$$a_i(0) = E_0(T_3)(\bar{u}_i(0) - \bar{u}(0)) + \left(\frac{E_0(T_2) - E_0(T_3)}{2} \right) (u_{ii} - \bar{u}(0)) \quad (67)$$

as the total average excess of A_i in the coefficient of selection. Note that this can also be interpreted as the projected average effect, on the coefficient of selection in all generations $t \geq 0$, of substituting a gamete of type A_i in place of a gamete chosen at random in generation 0. This holds not only for the Wright–Fisher multiallele viability model, but also the corresponding fertility model and the more general exchangeable model.

In the case of additive gene action on viability differences, namely, a coefficient of selection in the form

$$u_{ij} = v_i + v_j, \quad (68)$$

for $i, j = 1, \dots, n$, the total average excess of A_i reduces to

$$a_i(0) = E_0(T_2)(v_i - \bar{v}(0)), \quad (69)$$

where

$$\bar{v}(0) = \sum_{j=1}^n v_j x_j(0). \quad (70)$$

Note that this corresponds to the total average excess of A_i in a haploid population with v_j being the coefficient of selection of A_j , for $j = 1, \dots, n$.

On the other hand, the two-phenotype linear game model of Section 6 with additive gene action on the phenotypic determination is formally equivalent to a selection coefficient of A_i in interaction with A_j given by

$$u_{ij} = \frac{m_{22}}{2} - ah_i - ch_j + bh_i h_j, \quad (71)$$

for $i, j = 1, \dots, n$, where $c = (m_{22} - m_{21})/2$. In general, $u_{ij} \neq u_{ji}$ as soon as $h_i \neq h_j$ if $a \neq c$, that is, $m_{12} \neq m_{21}$, and then the symmetry condition does not hold. Nevertheless, the average excess of A_i in generation $t \geq 0$ is still given by (66) and leads to

$$a_i(0) = -a [E_0(T_2)(h_i - \bar{h}(0))] + b \left[\bar{h}(0)E_0(T_3)(h_i - \bar{h}(0)) + \left(\frac{E_0(T_2) - E_0(T_3)}{2} \right) (h_i^2 - \bar{h}^2(0)) \right], \quad (72)$$

for the projected average effect of A_i , in agreement with (48). Note that this is a combination of a projected average effect in a haploid population with $-ah_i$ as selection coefficient of A_i , for $i = 1, \dots, n$, and a projected average effect in a diploid population with $bh_i h_j$ as selection coefficient of $A_i A_j$, for $i, j = 1, \dots, n$.

10. Discussion

It has been shown that the first-order effect of viability or fertility selection on the probability of ultimate fixation of an allele in a diploid population of a fixed finite size, undergoing discrete, non-overlapping generations is given by the average effect of such an allele in the current generation on the coefficient of selection in the present generation and all future generations. This projected average allelic effect is the sum of the average allelic excesses in the coefficient of selection in the initial generation and all future generations, given the population state in the initial generation. It is calculated over all possible histories of the population forward in time in the absence of selection.

The projected average allelic effect is a weighted sum of average allelic effects in allozygous and autozygous offspring in the initial generation, with weights given by $E_0(T_3)$ and $(E_0(T_2) - E_0(T_3))/2$, respectively, where $E_0(T_2)$ and $E_0(T_3)$ are the expected times for the lineages of two and three gametes, respectively, to coalesce for the first time. These are calculated under neutrality, using the property that gametes chosen at random in a given generation have ancestral gametes in any generation backward in time that are exchangeable, which means that, given their number, the ancestral gametes are chosen at random. Such conditions hold for exchangeable selection models extending the neutral Cannings model (1974) that are more general than the Wright–Fisher viability model as shown in Section 8.

Note that $(E_0(T_2) - E_0(T_3))/2$ is the expected time that the lineage of a focal gamete will spend being non-ancestral to a typical gamete chosen at random in the same generation, but ancestral to another gamete chosen at random in the same generation. In the case of a neutral Wright–Fisher model in the limit of a large population size, and more generally in the domain of application of the Kingman coalescent (Kingman, 1982), this is asymptotic to $E_0(T_3)$, which is asymptotic to $(1/3)E_0(T_2)$. In such a case, the average allelic effect in autozygous offspring in the initial generation will be as important as the average allelic effect in allozygous offspring for the probability of fixation under weak selection.

The fertility model considered in Section 7 corresponds to what is known as a multiplicative fertility scheme, with the relative quantity of offspring produced by any pair of parents, one as a male and the other as a female, given by the product of the relative quantities of gametes produced by both parents. Moreover, we have assumed a monoecious diploid population in which the relative quantity of gametes produced by a parent as a male is the same as the one produced by a parent as a female, and depends only on the genotype of the parent at a single locus. In an infinite population, such a model is equivalent to a two-sex viability model with equal viability parameters for males and females (see, e.g., Karlin (1978) and Ewens (2004, p. 54–57)), which is like a one-sex viability model. In a finite population, the first-order effect of selection on the expected change in the frequency of an allele differs only by a positive multiplicative factor. Therefore, this is also the case for the first-order effect on the probability of fixation of that allele.

A linearly frequency-dependent selection model in a diploid population with additive gene action is formally equivalent to a similar model in a haploid population, which is itself equivalent to a frequency-independent selection model in a diploid population, but with genotypic selection parameters that are not necessarily symmetric. In the case considered, this model is equivalent to a combination of two frequency-independent symmetric selection models, one in a haploid population and the other in a diploid population. In the domain of application of the Kingman coalescent as the population size goes to infinity, the first model has a first-order effect on the fixation probability three times more important than the second model.

In the case of two alleles A_1 and A_2 coding for two pure strategies, (1, 0) and (0, 1), in a 2×2 matrix game determining the selection coefficient, the projected average effect of A_1 is given by (72) for $i = 1$ with $h_1 = 1, h_2 = 0, \bar{h}(0) = \bar{h}^2(0) = x_1(0)$, that is,

$$a_1(0) = (1 - x_1(0)) \left[-aE_0(T_2) + bx_1(0)E_0(T_3) + b \left(\frac{E_0(T_2) - E_0(T_3)}{2} \right) \right], \quad (73)$$

where $a = (m_{22} - m_{12})/2$ is the advantage of A_2 against itself and $b = (m_{11} - m_{21} - m_{12} + m_{22})/2$ the sum of the advantages of A_1 and A_2 against themselves. If the initial frequency of A_1 is small, then this effect reduces to the approximation

$$a_1(0) \approx -aE_0(T_2) + b \left(\frac{E_0(T_2) - E_0(T_3)}{2} \right). \quad (74)$$

In the case $b > 0$, which occurs when both pure strategies are the best replies to themselves, weak selection favors a rare A_1 replacing A_2 , in the sense that its fixation probability exceeds its initial frequency, if

$$\frac{a}{b} < \frac{E_0(T_2) - E_0(T_3)}{2E_0(T_2)}. \quad (75)$$

The left-side member of this inequality is the unstable equilibrium frequency of A_1 in an infinite population, while the right-side member reduces to $1/3$ in the limit of a large population size in the domain of application of the Kingman coalescent. In general, in this domain and for any initial frequency of A_1 , we have

$$a_1(0) \approx (1 - x_1(0))E_0(T_2) \left[-a + \frac{b}{3} (1 + x_1(0)) \right]. \quad (76)$$

This explains and extends the one-third law of evolutionary dynamics (Nowak et al., 2004).

Note that the one-third law is meaningful for long-term evolution only in a context of pure strategies. If all mixed strategies $0 \leq h_1, h_2 \leq 1$ are allowed, then it is easy to check that weak selection favors A_1 replacing A_2 in a finite population whenever $h_2 < h_1 < a/b$ or $a/b < h_1 < h_2$ in the case where $a, b < 0$, and this means that $h_1 = a/b$ is convergence stable in this case (see, Christiansen (1991), and references therein) with the fixation probability as measure of fitness, in agreement with Wild and Taylor (2004). Similarly, if $a, b > 0$, then the pure strategies 0 and 1 are convergence stable.

Note that frequency-dependent selection in a diploid population without additive gene action would lead to consider the lineages of more than three gametes, actually of at least five. The same principles would apply, but the formulas would be more recondite.

Finally, let us stress that the present method is valid for any finite number of alleles and any initial population state. It supposes, however, that selection is much weaker than random drift. Actually, it gives an approximation for the fixation probability in a population of fixed finite size as the selection intensity goes to zero. When the intensity of selection is of the same order of magnitude as the inverse of the population size, the probability of fixation of an allele given any initial allelic population state satisfies a diffusion equation in the limit of a large population size (Kimura, 1964), but this equation is difficult to solve. The present direct method offers an alternative tractable approach when the intensity of selection is of order smaller than the inverse of the population size.

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Appendix

We show that

$$\sum_{t=0}^{T-1} \frac{d}{ds} E_s [\Delta x_i(t)] = \frac{d}{ds} E_s [x_i(T) - x_i(0)] \quad (77)$$

converges uniformly in a neighborhood of the intensity of selection $s \geq 0$, as T tends to infinity, where $x_i(t)$ represents the frequency of allele A_i in generation $t \geq 0$ with possible values $k/(2N)$ for $k = 0, 1, \dots, 2N$ and $i = 1, \dots, n$, and $\Delta x_i(t) = x_i(t+1) - x_i(t)$. Since $E_s [x_i(T) - x_i(0)]$ is a weighted sum of the T -step transition probabilities of the Markov chain $\mathbf{x}(t) = (x_1(t), \dots, x_n(t))$, for $t \geq 0$, on a finite state space, with constant weights, it suffices to show that the derivatives of these probabilities converge uniformly. This will be shown under the assumption that the one-step transition probabilities and their derivatives with respect to s are continuous at $s = 0$. This is an extension of the proof given in Lessard and Ladret (2007) for the case of two alleles segregating in the population, that is, $n = 2$.

With n alleles, there are

$$\binom{2N + n - 1}{n - 1} \quad (78)$$

possible allelic states for the population. This is the number of ways that $2N$ indistinguishable balls can be placed into n distinguishable cells. The chain has n absorbing states corresponding to the allele fixation states; all other states are transient. Let

$$m = \binom{2N + n - 1}{n - 1} - n \quad (79)$$

be the number of transient states. Ordering the states such that the transient states come first, and the absorbing states last, the one-step transition matrix takes the form

$$\mathbf{P}_s = \begin{bmatrix} Q_s & R_s \\ O_{n \times m} & I \end{bmatrix}, \quad (80)$$

where Q_s is the $m \times m$ matrix that contains the probabilities of transition between the transient states, R_s the $m \times n$ matrix that contains the probabilities of transition from the transient states to the absorbing states, I the $n \times n$ identity matrix associated to the absorbing states, and $O_{n \times m}$ a null matrix of size $n \times m$. The T -step transition matrix can be expressed as

$$\mathbf{P}_s^{(T)} = \mathbf{P}_s^T = \begin{bmatrix} Q_s^T & \sum_{i=0}^{T-1} Q_s^i R_s \\ O_{n \times m} & I \end{bmatrix}. \quad (81)$$

The derivation rule for a matrix product tells us that

$$\frac{d\mathbf{P}_s^{(T)}}{ds} = \frac{d\mathbf{P}_s^T}{ds} = \sum_{t=0}^{T-1} \mathbf{P}_s^t \frac{d\mathbf{P}_s}{ds} \mathbf{P}_s^{T-t-1}. \quad (82)$$

This leads to

$$\frac{d\mathbf{P}_s^{(T)}}{ds} = \begin{bmatrix} B_s^{(T)} & C_s^{(T)}R_s + A_s^{(T)}\frac{dR_s}{ds} \\ O_{n \times m} & O_{n \times n} \end{bmatrix}, \quad (83)$$

where

$$A_s^{(T)} = \sum_{t=0}^{T-1} Q_s^t, \quad (84)$$

$$B_s^{(T)} = \sum_{t=0}^{T-1} Q_s^t \frac{dQ_s}{ds} Q_s^{T-t-1}, \quad (85)$$

$$C_s^{(T)} = \sum_{t=0}^{T-1} Q_s^t \frac{dQ_s}{ds} \sum_{i=0}^{T-t-1} Q_s^i. \quad (86)$$

We will show uniform convergence to the matrix

$$\frac{d\mathbf{P}_s^{(\infty)}}{ds} = \begin{bmatrix} O_{m \times m} & (I - Q_s)^{-1} \frac{dQ_s}{ds} (I - Q_s)^{-1} R_s + (I - Q_s)^{-1} \frac{dR_s}{ds} \\ O_{n \times m} & O_{n \times n} \end{bmatrix}, \quad (87)$$

in some neighborhood of $s \geq 0$.

Note that $(I - Q_s)$ is invertible, since 1 is not an eigenvalue of Q_s . Otherwise, there would exist an associated right eigenvector $\mathbf{v} = (v_1, \dots, v_m) \neq (0, \dots, 0) = \mathbf{0}$, so that

$$Q_s^T \mathbf{v} = \mathbf{v}, \quad (88)$$

for all $T \geq 1$. This would contradict the ergodic theorem for discrete-time Markov chains (see, e.g., Karlin and Taylor (1975)) which stipulates that the T -step transition probabilities to transient states tend to 0 as T goes to infinity and, therefore, that $\lim_{T \rightarrow \infty} Q_s^T \mathbf{v} = \mathbf{0}$.

We shall use the maximum absolute row sum norm defined as

$$\|X\| = \max_{1 \leq i \leq l} \sum_{j=1}^l |X_{ij}|, \quad (89)$$

for a square matrix X of size l with entries X_{ij} for $i, j = 1, \dots, l$. This norm is subadditive and submultiplicative, which means that, for any two square matrices of the same size X and Y , we have

$$\|X + Y\| \leq \|X\| + \|Y\| \quad (90)$$

and

$$\|XY\| \leq \|X\| \|Y\|. \quad (91)$$

Applying these properties to the difference between the matrices given in (83) and (87), we get the inequality

$$\begin{aligned} \left\| \frac{d\mathbf{P}_s^{(T)}}{ds} - \frac{d\mathbf{P}_s^{(\infty)}}{ds} \right\| &\leq \|B_s^{(T)}\| \\ &+ \left\| C_s^{(T)} - (I - Q_s)^{-1} \frac{dQ_s}{ds} (I - Q_s)^{-1} \right\| \left\| \begin{matrix} O_{m \times m} & R_s \\ O_{n \times m} & O_{n \times n} \end{matrix} \right\| \\ &+ \|A_s^{(T)} - (I - Q_s)^{-1}\| \left\| \begin{matrix} O_{m \times m} & \frac{dR_s}{ds} \\ O_{n \times m} & O_{n \times n} \end{matrix} \right\|. \end{aligned} \quad (92)$$

Under the assumption that \mathbf{P}_s and $d\mathbf{P}_s/ds$ are continuous at $s = 0$, this is also the case for the submatrices R_s and dR_s/ds . Therefore, there exists a neighborhood V_1 of $s = 0$, in which

$$\left\| \begin{matrix} O_{m \times m} & R_s \\ O_{n \times m} & O_{n \times n} \end{matrix} \right\| \leq \alpha \quad (93)$$

and

$$\left\| \begin{matrix} O_{m \times m} & \frac{dR_s}{ds} \\ O_{n \times m} & O_{n \times n} \end{matrix} \right\| \leq \alpha, \quad (94)$$

for some constant $0 < \alpha < \infty$. In this neighborhood, we have

$$\begin{aligned} \left\| \frac{d\mathbf{P}_s^{(T)}}{ds} - \frac{d\mathbf{P}_s^{(\infty)}}{ds} \right\| &\leq \|B_s^{(T)}\| + \left\| C_s^{(T)} - (I - Q_s)^{-1} \frac{dQ_s}{ds} (I - Q_s)^{-1} \right\| \alpha \\ &+ \|A_s^{(T)} - (I - Q_s)^{-1}\| \alpha. \end{aligned} \quad (95)$$

From (84)–(86) and the fact that

$$\sum_{i=0}^{T-t-1} Q_s^i = (1 - Q_s^{T-t})(1 - Q_s)^{-1}, \quad (96)$$

we deduce that

$$C_s^{(T)} = A_s^{(T)} \frac{dQ_s}{ds} (1 - Q_s)^{-1} - B_s^{(T)} Q_s (I - Q_s)^{-1}, \quad (97)$$

from which we get

$$\begin{aligned} \left\| C_s^{(T)} - (I - Q_s)^{-1} \frac{dQ_s}{ds} (I - Q_s)^{-1} \right\| &\leq \|A_s^{(T)} - (I - Q_s)^{-1}\| \left\| \frac{dQ_s}{ds} \right\| \|(1 - Q_s)^{-1}\| \\ &+ \|B_s^{(T)}\| \|Q_s\| \|(I - Q_s)^{-1}\|. \end{aligned} \quad (98)$$

Using this bound in (95), we find that

$$\begin{aligned} \left\| \frac{d\mathbf{P}_s^{(T)}}{ds} - \frac{d\mathbf{P}_s^{(\infty)}}{ds} \right\| &\leq \|B_s^{(T)}\| (1 + \|Q_s\| \|(I - Q_s)^{-1}\| \alpha) \\ &+ \alpha \|A_s^{(T)} - (I - Q_s)^{-1}\| \left(\left\| \frac{dQ_s}{ds} \right\| \|(1 - Q_s)^{-1}\| + 1 \right). \end{aligned} \quad (99)$$

Under the assumption that \mathbf{P}_s and $d\mathbf{P}_s/ds$ are continuous at $s = 0$, this is also the case for $Q_s, dQ_s/ds$ and $(I - Q_s)^{-1}$. Therefore, there exists a neighborhood $V_2 \subseteq V_1$ of $s = 0$ where $\|dQ_s/ds\|$ and $\|(I - Q_s)^{-1}\|$ are bounded by some constant $0 < \beta < \infty$. Note that $\|Q_s\| \leq 1$, since Q_s is a submatrix of a transition matrix. Then, in the neighborhood V_2 , we have

$$\begin{aligned} \left\| \frac{d\mathbf{P}_s^{(T)}}{ds} - \frac{d\mathbf{P}_s^{(\infty)}}{ds} \right\| &\leq \|B_s^{(T)}\| (1 + \beta\alpha) + \alpha \|A_s^{(T)} - (I - Q_s)^{-1}\| (\beta^2 + 1). \end{aligned} \quad (100)$$

Since

$$A_s^{(T)} = \sum_{t=0}^{T-1} Q_s^t = (I - Q_s)^{-1} (I - Q_s^T), \quad (101)$$

we find that

$$\|A_s^{(T)} - (I - Q_s)^{-1}\| \leq \|(I - Q_s)^{-1}\| \|Q_s^T\| \leq \beta \|Q_s^T\|, \quad (102)$$

in the neighborhood V_2 . On the other hand, the decomposition

$$\begin{aligned} B_s^{(T)} &= \sum_{t=0}^{\lfloor T/2 \rfloor - 1} Q_s^t \frac{dQ_s}{ds} Q_s^{T-t-1} + \sum_{t=\lfloor T/2 \rfloor}^{T-1} Q_s^t \frac{dQ_s}{ds} Q_s^{T-t-1} \\ &= \sum_{t=0}^{\lfloor T/2 \rfloor - 1} Q_s^t \frac{dQ_s}{ds} Q_s^{\lfloor T/2 \rfloor} Q_s^{T-t-1-\lfloor T/2 \rfloor} \\ &+ \sum_{t=\lfloor T/2 \rfloor}^{T-1} Q_s^{\lfloor T/2 \rfloor} Q_s^{t-\lfloor T/2 \rfloor} \frac{dQ_s}{ds} Q_s^{T-t-1}, \end{aligned} \quad (103)$$

for $T \geq 2$, where $\lfloor T/2 \rfloor$ is the integer part of $T/2$, and the fact that $\|Q_s\| \leq 1$, lead to

$$\begin{aligned} \|B_s^{(T)}\| &\leq \left\| \frac{dQ_s}{ds} \right\| \|Q_s^{\lfloor T/2 \rfloor}\| \left(\sum_{t=0}^{\lfloor T/2 \rfloor - 1} \|Q_s^t\| + \sum_{t=\lfloor T/2 \rfloor}^{T-1} \|Q_s^{T-t-1}\| \right) \\ &\leq 2\beta \|Q_s^{\lfloor T/2 \rfloor}\| \sum_{t \geq 0} \|Q_s^t\|, \end{aligned} \quad (104)$$

in the neighborhood V_2 . Combining these two results yields

$$\begin{aligned} \left\| \frac{dP_s^{(T)}}{ds} - \frac{dP_s^{(\infty)}}{ds} \right\| &\leq 2\beta (1 + \alpha\beta) \|Q_s^{\lfloor T/2 \rfloor}\| \sum_{t \geq 0} \|Q_s^t\| \\ &\quad + \alpha\beta (\beta^2 + 1) \|Q_s^T\|, \end{aligned} \quad (105)$$

for $T \geq 2$ in the neighborhood V_2 .

The next step is to find a bound for $\|Q_s^t\|$. The ergodic theorem tells us that Q_0^t tends to $O_{m \times m}$, and consequently $\|Q_0^t\|$ tends to 0, as t tends to infinity. Therefore, there exists an integer T_0 for which

$$\|Q_0^{T_0}\| < 1. \quad (106)$$

Since the transition matrix P_s is continuous at $s = 0$, so is $\|Q_s^{T_0}\|$, and it is possible to find a neighborhood $V_3 \subseteq V_2$ of $s = 0$ in which

$$\|Q_s^{T_0}\| < \gamma, \quad (107)$$

for some constant $0 < \gamma < 1$.

Note that, for every integer $k \geq 0$, there exists a unique positive integer $r(k)$ for which $k = \lfloor k/T_0 \rfloor T_0 + r(k)$. Writing $\lfloor T/2 \rfloor$, t and T in this form in (105) and using again the fact that $\|Q_s\| \leq 1$ result in the inequality

$$\begin{aligned} \left\| \frac{dP_s^{(T)}}{ds} - \frac{dP_s^{(\infty)}}{ds} \right\| &\leq 2\beta (1 + \beta\alpha) \|Q_s^{T_0}\|^{\lfloor \lfloor T/2 \rfloor / T_0 \rfloor} \sum_{t \geq 0} \|Q_s^{T_0}\|^{\lfloor t/T_0 \rfloor} \\ &\quad + \alpha\beta (\beta^2 + 1) \|Q_s^{T_0}\|^{\lfloor T/T_0 \rfloor}. \end{aligned} \quad (108)$$

Finally, in the neighborhood V_3 , we find the bound

$$\begin{aligned} \left\| \frac{dP_s^{(T)}}{ds} - \frac{dP_s^{(\infty)}}{ds} \right\| &\leq \frac{2\beta (1 + \beta\alpha) T_0}{1 - \gamma} \gamma^{\lfloor \lfloor T/2 \rfloor / T_0 \rfloor} \\ &\quad + \alpha\beta (\beta^2 + 1) \gamma^{\lfloor T/T_0 \rfloor}. \end{aligned} \quad (109)$$

This is valid for $T \geq 2$. Moreover, since $0 < \gamma < 1$, the bound tends to 0 as T tends to infinity.

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