AN EXTENSION OF FISHER'S FUNDAMENTAL THEOREM OF NATURAL SELECTION

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ABSTRACT

The notion of Darwinian selection naturally implies the question of if there exists any biological quantity that increases during the evolution of a population, indicating the "progress" of evolution. The first classical answer to this question was the Fundamental Theorem of Natural Selection (Fisher 1930, 1958) which in its mathematical form states that the rate of increase in mean fitness of a population is proportional to the variance of the potential fitness of an allele chosen randomly, implying that the mean fitness increases during the selection. Later on, different variants of this result were formulated. In this paper the possibility of an extension of the Fundamental Theorem is considered under the hypothesis that mutation is also present.

Keywords: natural selection, Fisher's Fundamental Theorem mean fitness, mutation.
Classification AMS: 92-D15.

1 Introduction

Setting up mathematical models of selection and mutation processes was iniciated in the works of the founding fathers of classical population genetics, Fisher (1930), Haldane (1937) and Wright (1968-69). The Fisher model of natural selection (see also Fisher 1958) in mathematical form was the first synthesis of Darwinism with Mendelian genetics. Despite the continuous criticism of this Fundamental Theorem of Natural Selection, this model became a reference point in the research of mathematical modelling of evolutionary processes The Fundamental Theorem in its first verbal form says that "the increasing rate of the fitness of any organism at any moment is equal to the variance of the fitness at the same moment". Although this formulation was followed by several corrections, criticisms and modifications (see e.g. Ewens (1992) and Lessard (1997)), Fundamental Theorem stimulated many important works in the field of selection processes, even the extension of the classical differential equation model of Fisher to the case of the presence of other evolutionary factors such as the mutation and recombination, see Akin (1979), Hofbauer and Sigmund (1988, 1998) and their references. Other basic papers concerning the selection-mutation model, considered in the present paper, are Crow and Kimura (1970), Moran (1976, 1977) and Hadeler (1981). A survey of selection-mutation models can be found in Bürger (1998). In mathematical terms, a consequence of Fisher's Fundamental Theorem is that in the course of selection the mean fitness of the population increases. For more recent results related this statement see Garay and Varga (1999), Garay (2003) and (2007). In this work it will be studied whether it is possible to extend the Fundamental Theorem to selection-mutation processes in a modified form. A literal generalization of it, as it will be seen, would not be valid. The basic continuous-time model and the problem of equilibrium are considered in Section 2. Section 3 is devoted to the formulation of a "Fundamental Theorem" in terms of the "velocity of the evolution" and the "balance of the potential fitness", that corresponds to the case of the simultaneous presence of selection and mutation. In Section 4 an approximate form of Fisher's statement on the rate of change in mean fitness is derived, which is valid for selection-mutation type evolutionary processes. Finally, in Section 5 the obtained results are illustrated presenting an analysis of the effect of mutation on the evolutionary process in the case of two- and three-allele models.

2 Dynamic selection-mutation model

A panmitic diploid population is considered with alleles $A_1, .., A_n$ at an autosomal locus. It is supposed that at zygote level selection takes place, which is described by a nonnegative symmetric fitness matrix $W \in \mathbb{R}^{n\times n}$, and for each $i, j \in \{1, \ldots, n\}$, w_{ij} is the fitness of a zygote A_iA_j. Then according to Fisher's classical model of natural selection, for frequency x_i of allele A_i the following dynamics holds:

$$\dot{x}_i = x_i\,[(Wx)_i - < x, Wx >] \qquad i \in \{1, \ldots, n\}, \tag{1}$$

where $x = [x_1, x_2, \ldots, x_n]^T$ denotes the population state, $(Wx)_i = \sum_{j=1}^{n} w_{ij}x_j$ is the potential (or marginal) fitness of allele A_i, and $< x, Wx >$ is the mean fitness of the population. The biological interpretation of dynamics (1) is the following: if the potential fitness of allele A_i is greater than the mean fitness of the whole population, then the frequency of A_i is increasing, whereas in the contrary case this frequency is decreasing.

Now, for each $i, j \in \{1, \ldots, n\}$, $i \neq j$, the nonnegative number m_{ij} will denote the rate of mutation $A_j \to A_i$, and for all $i \in \{1, \ldots, n\}$ with the additional definition

$$m_{ii} := -\sum_{j\neq i} m_{ji}.$$

Let x be the vector of frequencies of alleles in function of time. Then in terms of fitness matrix W and the mutations matrix $M := [m_{ij}]_{n\times n}$, the selection-mutation process is described with the following system of differential equations:

$$\dot{x_i} = x_i[(Wx)_i - < x, Wx >] + (Mx)_i \quad (i \in \{1, \ldots, n\}). \tag{2}$$

This system defines a vector field in the simplex Δ_n of allelic frequencies, see for example Akin (1979).

In Varga and Zubiri (1993), using the Brower fixed point theorem, the existence of an equilibrium was proved for the case of weak selection and small mutation. For the relation between the equilibria of models (1) and (2), see Scarelli and Varga (2002). Introducing the notations $w_i(x) := (Wx)_i$ and $\overline{w}(x) :=< x, Wx >$, a state x^* in the interior $\overset{\circ}{\Delta}_n$ of simplex is called polymorphic equilibrium, if for all $i \in \{1, \ldots, n\}$ equality $w_i(x^*) = \overline{w}(x^*)$ holds. Concerning the existence and calculation of a polymorphic equilibrium , from Scarelli and Varga (2002) the following lemma is recalled.

Lemma 2.1 *Suppose that*

(i) *W is invertible,*

(ii) *for vector $\mathbf{1} := (1, \ldots, 1) \in \mathbb{R}^n$ relation $< W^{-1}\mathbf{1}, \mathbf{1} > \neq 0$ holds,*

(iii)

$$x^* := \frac{W^{-1}\mathbf{1}}{< W^{-1}\mathbf{1}, \mathbf{1} >} > 0, \tag{3}$$

(iv) *$W^{-1}\mathbf{1} \in KerM$.*

Then x^* is a polymorphic equilibrium of the selection-mutation dynamics (2)

Remark 2.2. If the first three conditions (i)-(iii) hold, then x^* is a polymorphic equilibrium of the pure selection model (with $M := 0$).

3 Extension of Fisher's Fundamental Theorem of Natural Selection

Let φ be a selection-mutation process, that is, a solution of system (2). Then the composition $\phi := \overline{w} \circ \varphi$ describes the evolution in terms of the mean fitness of the population. The velocity of the evolution in function of time is $\dot{\phi} = \overline{w}' \circ \varphi \cdot \dot{\varphi}$. In terms of the derivative $D\overline{w}$ of $\overline{w}$ with respect to system (2), the velocity of the evolution at moment t is

$$\dot{\phi}(t) = D\overline{w}(\varphi(t)) \qquad (t \in D_\varphi). \tag{4}$$

Denoting by f the right-hand side of system (2), $D\overline{w}(x)$ for an allelic state $x \in \Delta_n$can be calculated as follows:

$$\begin{aligned} D\overline{w}(x) &= \ <\overline{w}'(x), f(x)>= 2\textstyle\sum_{i=1}^n w_i(x)\{x_i[w_i(x) - \overline{w}(x)] + (Mx)_i\} \\ &= \ 2\{\textstyle\sum_{i=1}^n x_i w_i^2(x) - \overline{w}^2(x) + \sum_{i=1}^n w_i(x) \sum_{j=1}^n m_{ij}x_j\}. \end{aligned} \tag{5}$$

For an interpretation of the terms in (5) let x be a fixed state of the population. Let $w(x)$ be the random variable equal to the potential fitness of an allele chosen randomly from a population in state x. The value of $w(x)$ is $w_i(x)$ if the picked allele is A_i. Then a simple calculation shows that the variance of $w(x)$ is

$$Var[w(x)] = \sum_{i=1}^n x_i[w_i(x) - \overline{w}(x)]^2 = \sum_{i=1}^n x_i w_i^2(x) - \overline{w}^2(x).$$

Substituting the latter into (5), and transforming the term containing the mutation, the following equality is obtained:

$$D\overline{w}(x) = 2Var[w(x)] + 2\sum_{i=1}^n w_i(x) \left[\sum_{j\neq i} m_{ij}x_j - \left(\sum_{k\neq i} m_{ki}\right) x_i\right].$$

Here the term

$$B(x) := \sum_{i=1}^n w_i(x) \sum_{j\neq i} m_{ij}x_j - \sum_{i=1}^n w_i(x) \left(\sum_{k\neq i} m_{ki}\right) x_i \tag{6}$$

can be interpreted as the "balance of the potential fitness" due to the mutation process. The first term expresses the total gain in potential fitness due to mutation, whereas the second one is the total lost in potential fitness caused by mutation, being the population in state x. Combining formulas (4)-(6), the dynamics of the evolution is obtained in the following form:

$$\dot{\phi}(t) = 2Var[w(\varphi(t))] + 2B(\varphi(t)) \quad (t \in D_\varphi) \tag{7}$$

Therefore, the following extension of the Fisher theorem is proved.

Theorem 3.1 *In the selection-mutation process the velocity of the evolution is proportional to the sum of the variance of the potential fitness and the balance of the potential fitness due to mutation.*

Remark 3.2. In the case of pure selection ($M := 0$), the Theorem reduces to. Fisher's classical Fundamental Theorem of Natural Selection:

$$\dot{\phi}(t) = 2Var[w(\varphi(t))] \quad (t \in D_\varphi). \tag{8}$$

Due to the nonnegativity of the variance the mean fitness is increasing throughout the evolution.

4 Estimation of the velocity of evolution

Suppose now that in the case of pure selection there exists a unique polymorphic equilibrium x^* defined in (3) of Section 2. Then x^* is obviously the unique interior point of Δ_n such that

$$w_i(x^*) = \overline{w}(x^*) \quad (i \in \{1, \ldots, n\}).$$

This fact implies the positivity of the variance $Var[w(x)]$ for all $x \in \overset{\circ}{\Delta}_n \backslash \{x^*\}$. In this situation the mean fitness of the population strictly increases. In the presence of mutation, in general, a similar behaviour is not possible. Indeed, from Hofbauer and Sigmund (1989), Th. 24.6 it is known that selection and mutation matrices can be chosen such that system (2) has a periodic solution. This periodicity obviously excludes a strict increase of the mean fitness. Hence the question arise, to what extend mutation can change the velocity of the selection process. Let be

$$M^* := \max_i \sum_{k \neq i} m_{ki}.$$

Then for all $x \in \Delta_n$, by the nonnegativity of $w_i(x), \overline{w}(x)$ and $\sum_{j \neq i} m_{ij} x_j$, the following inequality holds:

$$B(x) \geq -M^* \sum_{i=1}^{n} x_i w_i(x) = -M^* \overline{w}(x).$$

Therefore, for any selection-mutation process φ, a lower estimate of the velocity of evolution is obtained:

$$\dot{\phi}(t) \geq 2Var[w(\varphi(t))] - 2M^* \overline{w}(\varphi(t)) \quad (t \in D_\varphi) \tag{9}$$

Now, defining $W^* := \max\limits_{i,j} w_{ij}$, for the mean fitness of the population, the following estimate holds:

$$\overline{w}(x) = \sum_{i,j=1}^{n} w_{ij} x_i x_j \leq W^* \quad (t \in D_\varphi).$$

The above reasoning can be summarized in the following theorem, which is considered an approximate form of Fisher's theorem, expressing the effect of small mutation on the velocity of selection.

Theorem 4.1 *Given a selection matrix W, for all $\epsilon > 0$ there exists $\delta > 0$, ($\delta := \frac{\epsilon}{2W^*}$) such that for any mutation matrix M with $M^* < \delta$,*

$$\dot{\phi}(t) > 2Var[w(\varphi(t))] - \epsilon \quad (t \in D_\varphi) \tag{10}$$

holds.

5 Analysis of the velocity of evolution in two- and three-allele models

In general, the mutation can essentially change the course of the evolution, even it can make decrease the mean fitness of the population.In this section the effect of mutation on the velocity of the selection process is analyzed in two examples, illustrating the application of the above results. In this section with the example of two alleles we shall see how the results of Section 3 can be used for an finer analysis of the effect that produces mutation in the evolution.

Example 5.1. Consider a two-allele model corresponding to the selection-mutation equation (2) with the following selection and mutation matrices,

$$W := \begin{bmatrix} p & q \\ q & r \end{bmatrix} \quad \text{and} \quad M := \begin{bmatrix} -a & b \\ a & -b \end{bmatrix}$$

with parameters $a, b, p, q, r > 0$, such that the fitness of the heterozygote is greater than those the homozygotes: $q > p, r$. Then,

$$W^{-1}\mathbf{1} = \frac{1}{pr - q^2} \begin{bmatrix} r & -q \\ -q & p \end{bmatrix} \begin{bmatrix} 1 \\ 1 \end{bmatrix} = \frac{1}{pr - q^2} \begin{bmatrix} r - q \\ p - q \end{bmatrix},$$

$$< W^{-1}\mathbf{1}, \mathbf{1} >= \frac{r-2q+p}{pr-q^2} > 0$$

and

$$x^* = \frac{W^{-1}\mathbf{1}}{< W^{-1}\mathbf{1}, \mathbf{1} >} = \frac{1}{r-2q+p}\begin{bmatrix} r-q \\ p-q \end{bmatrix} > 0.$$

Therefore, the application of Lemma 2.1 implies that x^* is the unique polymorphic equilibrium of the pure selection model.
Assume now that the respective rates of mutations $A_1 \to A_2$ and $A_2 \to A_1$ are proportional to the respective advantages of the heterozygote A_1A_2 over the homozygotes A_1A_1 and A_2A_2. In Scarelli and Varga (2002) it was proved that then x^* is also an equilibrium of the model with mutation. Now it will be seen which are the population states where mutation speeds up or slows down the evolutionary effect of selection. The definition (6) of function B now reads

$$\begin{aligned} B(x) &= (px_1 + qx_2)(bx_2 - ax_1) + (qx_1 + rx_2)(ax_1 - bx_2) \\ &= (w_2(x) - w_1(x))(ax_1 - bx_2). \end{aligned}$$

It is clear that the mutation effect depends of the sign of $B(x)$. Fix a state $x \in \overset{\circ}{\Delta}_n$ different from equilibrium x^*, and suppose that in this state x the potential fitness of A_2 is greater than that of A_1, Then the fact that in state x the velocity ax_1 of mutation $A_1 \to A_2$ is greater than the velocity bx_2 of mutation $A_2 \to A_1$, implies that the mutation speeds up the selection, in the opposite case the mutation slows down the selection process.

Example 5.2. Now a three-allele model is considered under the following conditions: All homozygotes have the same fitness $w_{ii} = 1$, and the fitness of each heterozygote is the same, $w_{ij} = p \in \mathbb{R}_+ \setminus \{1\}$ ($i \neq j$), furthermore, the sum of the rows of the mutation matrix is equal to zero, that is, the sum of the rates of mutation from any allele to the rest of the alleles coincides with the sum of the rates of mutation from the rest of alleles to this allele.
Now the corresponding dynamic selection-mutation model is

$$\dot{x}_i = x_i[(Wx)_i - \overline{W}(x)] + (Mx)_i \qquad i \in \{1, 2, \ldots, n, \tag{11}$$

where the selection and mutation matrices are

$$W := \begin{pmatrix} 1 & p & p \\ p & 1 & p \\ p & p & 1 \end{pmatrix} \quad \text{and} \quad M := \begin{pmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{pmatrix}$$

with $m_{ij} \in \mathbb{R}_+,$ con $m_{ii} = -\sum_{j \neq i} m_{ji}$ $i, j \in \{1, 2, 3\}$ and $\sum_{j=1}^{3} m_{ij} = 0$ for all $i \in \{1, 2, 3\}$.
Since $det\ W = (p-1)^2(2p+1) \neq 0$,the fitness matrix is invertible and

$$W^{-1} = \frac{1}{det\ W}\begin{pmatrix} 1-p^2 & p^2-p & p^2-p \\ p^2-p & 1-p^2 & p^2-p \\ p^2-p & p^2-p & 1-p^2 \end{pmatrix}.$$

Furthermore, $W^{-1}\mathbf{1} = 1/(2p+1)\mathbf{1}$ y $< W^{-1}\mathbf{1}, \mathbf{1} >= 3/(2p+1) \neq 0$. Now Lemma 2.1 implies that the only polymorphic state for the pure selection model is

$$x^* := \frac{W^{-1}\mathbf{1}}{< W^{-1}\mathbf{1}, \mathbf{1} >} = \frac{1}{3}\mathbf{1} > 0.$$

which by the "double symmetry" of W is no surprise.

Condition $x^* \in KerM$ is easily checked:

$$Mx^* = \frac{1}{3}M\mathbf{1} = \frac{1}{3}\begin{pmatrix} m_{11}+m_{12}+m_{13} \\ m_{21}+m_{22}+m_{23} \\ m_{31}+m_{32}+m_{33} \end{pmatrix} = \mathbf{0},$$

because by condition $\sum_{j=1}^{3} m_{ij} = 0$ for all $i \in \{1,2,3\}$.
Therefore, the conditions of Lemma 2.1 are fulfilled, implying x^* is a polymorphic equilibrium of dynamics (11). Now the value of the "balance of potential fitness" can be calculated from the definition (6) of function B :

$$\begin{aligned} B(x) &= \sum_{i=1}^{3} w_i(x) \sum_{j \neq i} m_{ij} x_j - \sum_{i=1}^{3} w_i(x) (\sum_{k \neq i} m_{ki}) x_i \\ &= w_1(x)(m_{12}x_2 + m_{13}x_3) + w_2(x)(m_{21}x_1 + m_{23}x_3) + w_3(x)(m_{31}x_1 + m_{32}x_2) \\ &\quad -w_1(m_{21}+m_{31})x_1 - w_2(m_{12}+m_{32})x_2 - w_3(m_{13}+m_{23})x_3 \\ &= (m_{21}x_1 - m_{12}x_2)(w_2(x) - w_1(x)) + (m_{31}x_1 - m_{13}x_3)(w_3(x) - w_1(x)) \\ &\quad +(m_{32}x_2 - m_{23}x_3)(w_3(x) - w_2(x)). \end{aligned}$$

Again, the mutation effect depends of the sign of the balance $B(x)$. For a state $x \in \overset{\circ}{\Delta}_N$, different from the equilibrium x^* suppose that, for all $i,j \in \{1,2,3\}$, $i > j$, the potential fitness of A_i is higher that the potential fitness of A_j, and the velocity $m_{ij}x_j$ of mutation $A_j \to A_i$ is higher than the velocity $m_{ji}x_i$ of mutation $A_i \to A_j$. Then in state x mutation speeds up the selection process. In a similar way, simple biological conditions can be obtained for the mutation to slow down the selection process.
In the particular case when mutation matrix has the form

$$M = \begin{pmatrix} -a & 0 & a \\ a & -b & b-a \\ 0 & b & -b \end{pmatrix} \quad a,b \in \mathbb{R}_+, \quad b \geq a,$$

the balance of the potential fitness simplifies to

$$\begin{aligned} B(x) &= ax_1(w_2(x) - w_1(x)) - ax_3(w_3(x) - w_1(x)) + [bx_2 - (b-a)x_3](w_3(x) - w_2(x)) \\ &= ax_1(w_2(x) - w_1(x)) + b(x_2 - x_3)(w_3(x) - w_2(x)) + ax_3(w_3(x) - w_2(x) - w_3(x) + w_1(x)) \\ &= a(x_1 - x_3)(w_2(x) - w_1(x)) + b(x_2 - x_3)(w_3(x) - w_2(x)). \end{aligned}$$

Then, for instance in state $x \in \overset{\circ}{\Delta}_N$, different to equilibrium x^*, for the mutation to accelerate the selection process the following biological conditions are sufficient: $x_1 > x_3, x_2 > x_3, w_2(x) > w_1(x), w_3(x) > w_2(x)$; while conditions $x_1 > x_3, x_2 > x_3, w_2(x) < w_1(x), w_3(x) < w_2(x)$ imply that mutation will slow down the selection process.

6 Conclusion

Fisher's classical model of natural selection is a mathematical synthesis of the basic principles of the Darwinian theory of evolution and the Mendelian genetics. The resulting Fundamental Theorem guarantees that the mean fitness of population increases in the course of the selection. The Fundamental Theorem can not be extended to selection-mutation processes just by adding a mutation term to the dynamic selection model. In fact, the mean fitness of the population will not necessarily increase. However, introducing the concept of balance of the potential fitness due to mutation, as an extension of Fisher's Fundamental Theorem, it can be shown that in the selection-mutation process the velocity of the evolution is proportional to the sum of the variance of the potential fitness and the balance of potential fitness. In terms of the model parameters, the discrepancy from the classical Fisher theorem is also estimated. Moreover, for an outlook it is worth to mention that a similar analysis of the effect of mutation could be carried out to the Fundamental Theorem formulated in terms of the so-called relative advantage, that similarly to the the classical case, increases in the course of a pure selection process, see Garay and Varga (1999).

7 Acknowledgements

This publication has been realized with the support of the Hungarian Scientific Research Fund (OTKA 62000 and 68187). The authors wish to thank the Ministry of Education and Science of Spain for the project TIN2007-67418-C03-02, which has partially supported this work.

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