CLONE-SELECTION AND OPTIMAL RATES OF MUTATION

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CLONE-SELECTION AND OPTIMAL RATES OF MUTATION

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Abstract

The paper employs methods of multitype branching processes to evaluate the probability of survival of mutable clones under environmental conditions which are unfavorable to the original parent of the clone. When other factors are taken to be constant, the long-term survival probability of a clone is implicitly demonstrated as a function of the intrinsic rate of mutation carried by this clone. The existence of a mutation rate which maximizes clone survival probability is shown and the effects of environmental deterioration on this optimal rate are studied. Finally, rigorous quantitative results are obtained for the classical situation of a Poisson distribution of offspring numbers. These results are then applied to the biological problem of indirect selection (Eshel (1972)).

CLONE-SELECTION; RATE OF MUTATION; OPTIMAL RATE OF MUTATION; MODIFIER GENES; OPTIMAL MODIFIER GENES; MULTITYPE BRANCHING PROCESSES; ADAPTATION; INDIRECT ADAPTATION; EXTINCTION OF A POPULATION

1. Introduction

Quantitative problems involving the evolution of modifier traits in natural populations have recently attracted the attention of many population biologists (e.g., Nei [1], [2], Feldman [3], Karlin and McGregor [4], [5]). The term, *modifier* trait connotes an inherited feature whose main function is not in contributing to the *fitness* of the carrier or to the expected number of viable offspring, but which may be essential for further evolution of the species (Fisher [6]). Sex, recombination and mutation are a few examples of modifiers.

In a separate paper [7], a quantitative theory is suggested for the evolution of modifiers based on differences in survival probabilities of entire clones, rather than on viabilities of individuals in the population. Thus, while classically short-term selection is known to favor biological features which maximize the individual fitness of their carrier in a given environment, a long-term selection force has been shown to operate in favor of modifiers which maximize clone-survival probabilities, possibly in a changing environment. Such modifiers are labelled as *optimal*.

In most cases, however, the evaluation of an optimal modifying factor turns out to be a rather complicated analytic problem. A useful tool for such an evaluation in an *asexual* population is the model of a multitype branching process. It

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further appears that part of the results obtained for this model may be qualitatively extended to a sexual population (see [7]).

The purpose of the present work is to analyse the problem of the optimal modifier for the simplest case of an intrinsic mutation rate in an asexual population. The problem of an optimal mutation rate has been treated, from a different viewpoint, by Kimura ([8], [9]). However, employing the criterion of a maximal clone-survival-probability rather than Kimura's principle of a minimum genetic load, parts of the results achieved here are quite different from those of Kimura. Note, that these different results correspond to different connotations of the concept *optimal mutation rate*. Yet, manifestable selection mechanisms seem to operate in favor of that mutation rate which maximizes clone-survival-probabilities [7].

Finally, parts of the results in this work are obtained under the assumption of Poisson distributions of offspring numbers. For a validation of this postulate in a large variety of situations in population biology, refer to Karlin and McGregor [10].

2. The model and some general properties

Let each individual in a given asexual population be labelled according to two distinct parameters.

(i) A qualitative parameter A_i $(i = 1, \cdots, n)$, namely *the primary parameter*, reflects biological features which are due to immediate selection forces. More specifically it is assumed that the number of viable offspring born to any individual parent in the population is a random variable which depends only on the primary feature A_i of the parent in question. By $\phi_i(u)$ $(i = 1, \cdots, n)$ we denote the probability generating function of this r.v.

(ii) The primary feature is assumed to be biologically inherited except for a (usually small) probability ω, that an offspring will be mutated. This probability, namely the *mutation rate*, is again inherited and may be varied from one individual to another independent of the primary feature of this individual. Thus, it determines the *secondary parameter* of any individual in the population.

Let θ_{ij} $(i,j = 1, \cdots, n)$ be the probability of an offspring of an A_i parent altering its primary feature to A_j, provided it has been mutated; $\theta_{ij} \geqq 0$, $\sum_{j=1}^{n} \theta_{ij} = 1$ and, from the definition, $\theta_{ii} = 0$ for all $i = 1, \cdots, n$.

Denote the multitype offspring-generating-function of an $A_i\omega$-type parent by $\Phi_i^{(\omega)}(u_1, \cdots, u_n)$. Then clearly

$$\Phi_i^{(\omega)}(\boldsymbol{u}) = \phi_i((1-\omega)u_i + \omega \sum_j \theta_{ij} u_j), \qquad i = 1, 2, \cdots, n. \tag{2.1}$$

Let $\hat{\boldsymbol{u}} = \hat{\boldsymbol{u}}(\omega)$ be the smallest positive vector-solution of the system

$$\Phi_i^{(\omega)}(\boldsymbol{u}) = u_i, \qquad i = 1, 2, \cdots, n. \tag{2.2}$$

$\hat{u}_i(\omega)$ is the extinction-probability of a clone, starting from an $A_i\omega$-type parent (e.g., Harris [11], p. 41).

Set $\alpha_i = \phi_i'(1)$ for the *fitness* or expected offspring number of the type A_i. If a sequence $i_1, \cdots, i_r$ exists such that $\theta_{i,i_1}\theta_{i_1,i_2}\cdots\theta_{i_r,j} > 0$, then we say that A_i is mutable to A_j, notation $A_i \to A_j$. For convenience we also set $A_i \to A_i (i = 1, \cdots, n)$. Denote

$$I^0 = \{A_i \,|\, \alpha_j \leqq 1 \text{ for all } j \text{ with } A_i \to A_j\},$$

$$I^1 = \{A_i \,|\, \alpha_j > 1 \text{ for some } j \text{ with } A_i \to A_j\}.$$

Clearly $\hat{u}_i = 1$ for all $A_i \in I^0$. To avoid triviality we postulate $I^1 \neq \varnothing$ and thus, without loss of generality, assume $I^1 = \{A_1, \cdots, A_m\}$.

From the aspect of clone survival probability, one may ignore all offspring of the class I^0. Thus, set

$$\hat{\Phi}_i^{(\omega)}(u_1, \cdots, u_m) = \Phi_i^{(\omega)}(u_1, \cdots, u_m, 1, \cdots, 1), \; i = 1, 2, \cdots, m. \tag{2.3}$$

$\hat{\Phi}_i^{(\omega)}(u_1, \cdots, u_m)$ are called the reduced offspring g.f's of the process. Clearly

$$\hat{\Phi}_i^{(\omega)}(u_1, \cdots, u_m) = \phi_i\left\{(1-\omega)u_i + \omega \sum_{j=1}^{m} \theta_{ij}u_j + (1-\theta_i)\omega\right\},$$

where

$$\theta_i = \sum_{j=1}^{m} \theta_{ij}$$

is the probability that a mutation occurring in an A_i type will not be irreversibly deleterious. The system

$$\hat{\Phi}_i(u_1, \cdots, u_m) = u_i, \qquad i = 1, \cdots, m, \tag{2.2a}$$

is the reduced form of (2.2), with a smallest vector solution coinciding with the due m-dimensional projection of the smallest vector solution $\hat{u}$ of (2.2).

Being interested in the effect of the mutation rate on a survival probability of a clone, we compare clones starting with parents of the same primary feature A_1 (henceforth, the *conservative primary feature*) but carrying different values of the mutation rate ω. Clone survival probability is then expressed by

$$\chi(\omega) = 1 - u_1(\omega).$$

From the theorem of the implicit functions it follows that $\chi(\omega)$ is a continuous function over $[0, 1]$ and, thus, assumes a maximum over this interval. We call a value $\omega^* \in [0, 1]$ which maximizes $\chi(\omega)$, *an optimal mutation-rate*. It appears that clones, carrying mutation rates close to ω^* are statistically selected in the long run (see [7]).

As a special case of (2.1) we have

$$\Phi_i^{(0)}(u) = \phi_i(u_i)$$

and (assuming $\phi_i(u)$ is not trivially u) $\hat{u}_i(0) < 1$ iff $\alpha_i > 1$. Thus, when $\alpha_1 \leqq 1$ (i.e., when the environmental condition is unfavorable for the conservative type) then $\chi(0) = 0$.

On the other hand, (with $\alpha_1 \leqq 1$) assuming $A_1 \in I^1 \neq \varnothing$ (otherwise the clone is bounded for extinction with any mutation rate) it is not difficult to show $\chi(\omega) > 0$ for ω in some small interval $(0, \varepsilon)$, hence $\omega^* > 0$.

3. Optimal mutation rate for a one-step gene substitution and the effect of environmental deterioration

In this section we treat some relatively simple cases of special biological interest. We will prove uniqueness of ω^*, estimate it and specifically study its change under the effect of environmental deterioration, as measured by the parameter

$$d = 1 - \alpha_1 \geqq 0.$$

Let us postulate the simplest biological case when there is a disadvantageous conservative type (i.e., when $d = 1 - \alpha_1 \geqq 0$), a single, adaptable type A_2 (i.e., $\alpha_2 > 1$), and many irreversibly deleterious mutations; $I^1 = \{A_1, A_2\}$, $I^0 = \{A_3, \cdots, A_n\}$. Let us further assume irreversibility of mutation ($\theta_{21} = 0$) and denote $\theta_1 = \theta_{12} = \theta$ (clearly $\theta_2 = \theta_{21} = 0$). The system of extinction-equations then becomes

$$\phi_1((1-\omega)u_1 + \theta\omega u_2 + (1-\theta)\omega) = u_1, \tag{3.1}$$

$$\phi_2((1-\omega)u_2 + \omega) = u_2. \tag{3.2}$$

We call a process, determined by (3.1) and (3.2) a process of a one-step gene-substitution. In such a system, it is readily shown that $u_2(\omega) < 1$ iff $\omega < (\alpha_2 - 1)/\alpha_2$ and $u_1(\omega) < 1$ iff both $\omega > 0$ and $u_2(\omega) < 1$. Hence $\chi(\omega) > 0$ iff $0 < \omega < (\alpha_2 - 1)/\alpha_2$ and thus $\omega^* \in (0, (\alpha_2 - 1)/\alpha_2)$.

We now assume that the effect of environmental deterioration on the conservative type is a changeable parameter. More specifically, instead of a fixed g.f. $\phi_1(u)$, we assume a parametric family

$$\phi_\alpha(u) = \phi_1(\alpha u)/\phi_1(\alpha) \tag{3.3}$$

with $0 < \alpha \leqq 1$ and $\phi_1'(1) = 1$ (see Dwass [12] for a comparison).

We know that $\phi_\alpha'(1) = \alpha\phi_1'(\alpha)/\phi_1(\alpha)$ is an increasing function of α, hence the environmental deterioration, measured by

$$d = d(\alpha) = 1 - \phi_\alpha'(1),$$

is a decreasing function of α. By $\hat{u}_\alpha(\omega)$, $\hat{u}_2(\omega)$ denote the smallest pair-solution of

the system (3.1)–(3.2) when we insert ϕ_α instead of ϕ_1. For a fixed g.f $\phi_2(u)$ we will first show that the optimal mutation rate is uniquely determined by the environmental deterioration. (Here we assume that environmental deterioration for the conservative type, does not affect the adaptable one.)

Let

$$R = R(\theta, \phi_1, \phi_2) = \{\omega^* \mid \hat{u}_\alpha(\omega^*) = \max_\omega \hat{u}_\alpha(\omega) \text{ for some } 0 < \alpha \leqq 1\}.$$

R is the set of all values which are relevant as optimal mutation rates. We know $R \subseteq (0, (\alpha_2 - 1)/\alpha_2)$.

For a fixed $0 < \alpha \leqq 1$, consider the equation

$$\hat{u}_\alpha(\omega) = \phi_\alpha((1-\omega)\hat{u}_\alpha(\omega) + \theta\omega\hat{u}_2(\omega) + (1-\theta)\omega). \tag{3.1a}$$

Differentiating with respect to ω (again using the implicit function theorem) and inserting $\omega = \omega^*(\alpha)$ (note that $\hat{u}'_\alpha(\omega^*(\alpha)) = 0$), we obtain

$$\{1 - \hat{u}_\alpha(\omega^*) - \theta[1 - \omega^*\hat{u}'_2(\omega^*) - \hat{u}_2(\omega^*)]\}\,\phi'_\alpha((1-\omega^*)\hat{u}_\alpha(\omega^*) + \theta\omega^*\hat{u}_2(\omega^*) + (1-\theta)\omega^*) = 0.$$

Since $\phi'_\alpha(u) > 0$ for all $0 < u \leqq 1$, this implies

$$\chi_\alpha(\omega^*) = \theta[1 - h'(\omega^*)] \tag{3.4}$$

where we set

$$h(\omega) = \omega\hat{u}_2(\omega). \tag{3.5}$$

For this function (which is independent of both α and θ), we first prove two lemmas.

Lemma 1. $h'(\omega) < 1$ for all $\omega \in R$.

Proof. If $\omega \in R$, then there is a value $0 \leqq \alpha < 1$ such that ω is optimal for a process with a deterioration parameter α, and

$$\chi_\alpha(\omega) = \theta[1 - h'(\omega)] > 0.$$

Lemma 2. $h(\omega)$ is an increasing convex function of ω over R.

Proof. Inserting (3.5) into (3.2) it may written in the form

$$h(\omega) = \omega\phi_2(\eta(\omega)) \tag{3.6}$$

where

$$\eta(\omega) = \omega^{-1}(1-\omega)\,h(\omega) + \omega = (1-\omega)\hat{u}_2(\omega) + \omega,$$

$$\eta' = 1 - \omega^{-2}h + \omega^{-1}(1-\omega)h' = 1 - \hat{u}_2 + (1-\omega)\hat{u}'_2 > 0.$$

By a differentiation of (3.6) and simple algebraic manipulation, we get

$$[1-(1-\omega)\phi_2'(\eta)]h' = \phi_2(\eta) + (\omega - \hat{u}_2)\phi_2'(\eta). \tag{3.7}$$

It is easy to see that $\hat{u}_2$ is an increasing function of ω, and $\omega\hat{u}_2$ is more so; therefore, $h' > 0$. As for the right-hand side of (3.7)

$$\begin{aligned}
&\phi_2(\eta) + (\omega - \hat{u}_2)\phi_2'(\eta) \\
&\quad > \phi_2(\eta) - \hat{u}_2(1-\omega)\phi_2'(\eta) \\
&\quad = \phi_2((1-\omega)\hat{u}_2 + \omega) + \hat{u}_2 \frac{d}{du_2}[\phi_2((1-\omega)u_2 + \omega)]_{u_2=\hat{u}_2}.
\end{aligned}$$

For all $0 \leqq \omega < (\alpha_2 - 1)/\alpha_2$, denote $\phi_2((1-\omega)u + \omega) = f_\omega(u)$. $f_\omega(u)$ is a supercritical g.f. with a variable u, $\hat{u}_2$ is the minimal solution of the equation $\hat{u}_2 = f_\omega(\hat{u}_2)$. Hence $f_\omega'(\hat{u}_2) < 1$ and $f_\omega(\hat{u}_2) > u_2 f_\omega'(\hat{u}_2)$. Thus we conclude

$$\phi_2(\eta) + (\omega - \hat{u}_2)\phi_2'(\eta) > f_\omega(\hat{u}_2) - \hat{u}_2 f_\omega'(\hat{u}_2) > 0. \tag{3.8}$$

From (3.7) and (3.8) it follows that

$$1 - (1-\omega)\phi_2'(\eta) > 0. \tag{3.9}$$

Now, by a further differentiation of (3.7) with respect to ω, collecting all terms without h'' on the right-hand side we get

$$\begin{aligned}
&[1-(1-\omega)\phi_2'(\eta)]h'' \\
&\quad = [\eta' + 1 - \hat{u}_2' - h']\phi_2'(\eta) + [(1-\omega)h' + \omega - \hat{u}_2]\eta'\phi''(\eta) \\
&\quad = 2(1-\hat{u}_2)\phi_2'(\eta) + \omega\eta'[1 - h' + \hat{u}_2']\phi_2''(\eta).
\end{aligned}$$

But we know $1 - \hat{u}_2 > 0$, $\phi_2''(\eta) > 0$. It has already been shown that $\eta' > 0$, and from Lemma 1, $1 - h' + \hat{u}_2' > 1 - h' > 0$ for all $\omega \in R$. Hence $h''(\omega) > 0$ and this completes the proof of Lemma 2.

As an immediate result we have the following theorem.

Theorem 3.1. In a one-step gene substitution, the optimal mutation rate is uniquely determined by the environmental deterioration, i.e., $\omega^* = \omega^*(\alpha)$.

Proof. Let both ω_1, ω_2 be optimal mutation rates for the parameter α, and let $\omega_1 > \omega_2$. From Lemma 2 we know $h'(\omega_1) > h'(\omega_2)$ and then, from (3.4), $\chi_\alpha(\omega_1) < \chi_\alpha(\omega_2)$ in contradiction to the choice of ω_1 as an optimal value.

Theorem 3.2. The optimal mutation rate $\omega^*(\alpha)$ is a monotone decreasing function of α, and, hence, a monotone increasing function of the environmental deterioration.

Proof. From (3.1a) it follows immediately that for a fixed ω, $\hat{u}_\alpha(\omega)$ is a decreasing, and thus $\chi_\alpha(\omega)$ is an increasing, function of α. Hence, so is

$$\chi_\alpha(\omega^*(\alpha)) = \max_{0 \leqq \omega \leqq 1} \chi_\alpha(\omega).$$

From this and (3.4) we infer that $h'(\omega^*(\alpha))$ is a decreasing function of α. Employing this and the lemma it follows that $\omega^*(\alpha)$ is a decreasing function of α.

4. Optimal mutation rate for a Poisson distribution of offspring numbers

The assumption of a Poisson distribution of the number of surviving offspring, or its mathematical equivalent, is employed in most classical stochastic models in population biology (Karlin and McGregor [10]; see also Moran [15]).

This assumption appears especially to fit natural situations of a large surplus in the average fecundity of the population. As regards the present model it may be written as

$$\phi_i(u) = \phi_{\alpha_i}(u), \qquad i = 1, 2, \cdots, n, \tag{4.1}$$

with $\phi_\alpha(u) = e^{\alpha(u-1)}$ for all $\alpha > 0$. Here the fitness coefficient is $\alpha = \phi'_\alpha(1)$.

Note that for a Poisson g.f $\phi_\alpha(u)$ and for any vector $(p_1, \cdots, p_n)$ in the n-dimensional simplex

$$\begin{aligned} \phi_\alpha\left(\sum_{i=1}^{n} p_i u_i\right) &= \prod_{i=1}^{n} \phi_\alpha(p_i u_i + 1 - p_i) \\ &= \prod_{i=1}^{n} \phi_{\alpha p_i}(u_i). \end{aligned} \tag{4.2}$$

Thus, (2.1) becomes

$$\Phi_i^{(\omega)}(\boldsymbol{u}) = \phi_{(1-\omega)\alpha_i}(u_i) \prod_j \phi_{\omega\alpha_i\theta_{ij}}(u_j), \qquad i = 1, 2, \cdots, n. \tag{4.3}$$

Especially in the case of a one-step gene-substitution, Equation (2.2) may be written as

$$\hat{\Phi}_1(\hat{u}_1, \hat{u}_2) = \phi_{(1-\omega)\alpha}(\hat{u}_1)\phi_{\alpha 0\omega}(\hat{u}_2) = \hat{u}_1, \tag{4.4a}$$

$$\hat{\Phi}_2(\hat{u}_1, \hat{u}_2) = \phi_{(1-\omega)\alpha_2}(\hat{u}_2) = \hat{u}_2. \tag{4.4b}$$

Note that in this case there is a possibility of mutation from A_2 to deleterious genes (rate ω) but such lines become extinct.

As before, set $d = 1 - \alpha$ for the rate of environmental deterioration (we assume $d \geqq 0$), and let us have also $s = \alpha_2 - 1$ for the selection coefficient in favor of the adaptable type A_2. For biological application s is assumed to be small. (Fisher [6], Crow and Kimura [14]). In this section we evaluate the optimal mutation

rate $\omega^* = \omega^*(d, s)$ and the optimal clone survival probability $\chi(\omega^*)$, the evaluation being asymptotically valid for small values of s. The method employed is valid only for a Poisson distribution of offspring and, presumably, cannot be generalized to other cases.

Let y be a random variable, standing for the number of all A_1-type descendents of a single A_1-type parent, including itself. From (4.4a) it follows that y may be represented as the total number of individuals being created throughout a subcritical one-dimensional branching process with a progeny g.f $\phi_{\alpha(1-\omega)}(u)$.

Let $F_\lambda(u)$ be the probability g.f of the total number of individuals coming into existence throughout a one-dimensional branching process with a progeny g.f $\phi_\lambda(u)$ $(\lambda < 1)$.

We know (e.g., see Harris [11]) that

$$F_\lambda(u) = u\phi_\lambda(F_\lambda(u)) = ue^{\lambda(F_\lambda(u)-1)}. \tag{4.5}$$

Furthermore, since the equation $x = ue^{\lambda(x-1)}$ has a single positive solution x for all u in the interval $(0, \lambda^{-1}e^{\lambda-1})$, we also know that the g.f $F_\lambda(u)$ converges on this interval and is analytic there. Having $\lambda^{-1}e^{\lambda-1} > 1$ for all $\lambda < 1$, we conclude analyticity at the point $u = 1$. From (4.5) one readily obtains

$$F'_\lambda(1) = 1/(1-\lambda), \tag{4.6}$$

$$F''_\lambda(1) = \lambda(1-\lambda)^{-3}. \tag{4.7}$$

Now it is also implied from (4.4a) that any A_1-type individual existing in the process produces offspring of type A_2 according to the probability g.f $\phi_{\alpha\theta\omega}(u)$, independent of the number of A_1-type offspring and deleterious mutants it produces. Hence, the number of first-generation A_2-type mutants to appear in the process is determined by its g.f $F_{\alpha(1-\omega)}(\phi_{\alpha\theta\omega}(u))$. Each of these original A_2-type mutants has a clone-extinction probability $\hat{u}_2(\omega)$. Hence, the total extinction probability of a clone, starting from a parent of the conservative type A_1, is

$$\begin{aligned} \hat{u}_1(\omega) &= F_{\alpha(1-\omega)}\{\phi_{\alpha\theta\omega}(\hat{u}_2(\omega)\} \\ &= F_{\alpha(1-\omega)}\exp\{\alpha\theta\omega(\hat{u}_2(\omega)-1)\}. \end{aligned} \tag{4.8}$$

To estimate $\hat{u}_2(\omega)$, note that when $\lambda - 1 > 0$ is a small number then the smallest solution $v = v(\lambda)$ of the equation $v = e^{\lambda(v-1)}$ may readily be represented in the form

$$v(\lambda) = 1 - 2(\lambda - 1) + O(\lambda - 1)^2.$$

From (4.4b) we thus obtain

$$1 - \hat{u}_2(\omega) = 2\{\alpha_2(1-\omega) - 1\} + O[\alpha_2(1-\omega) - 1]^2.$$

This last equality stands for a situation wherein $\alpha_2(1-\omega) = (1+s)(1-\omega) \downarrow 1$ as a result of a change either in the parameter s or in ω. Being interested in $\omega < (\alpha_2 - 1)/\alpha_2 = s/(1+s)$ (otherwise $\hat{u}_2(\omega) \equiv 1$), we conclude

$$1 - \hat{u}_2(\omega) = 2(s - \omega) + O(s^2). \tag{4.9}$$

From (4.6), (4.7) and (4.8) we now obtain

$$\begin{aligned} \hat{u}_1(\omega) &= F_{\alpha(1-\omega)} \exp\{\alpha\theta\omega(\hat{u}_2(\omega) - 1)\} \\ &= F_{\alpha(1-\omega)}(1) + \alpha\theta\omega(\hat{u}_2(\omega) - 1)F'_{\alpha(1-\omega)}(1) \\ &\quad + O[\theta^2\omega^2(\hat{u}_2(\omega) - 1)^2][F'_{\alpha(1-\omega)}(1) + 1] \\ &= 1 + \frac{\alpha\theta\omega(\hat{u}_2(\omega) - 1)}{1 - (1-\omega)\alpha} + O\left(\frac{\theta^2\omega^2[\hat{u}_2(\omega) - 1]^2}{1 - (1-\omega)\alpha}\right). \end{aligned} \tag{4.10}$$

Now, inserting (4.9) into (4.10), and having $\alpha = 1 - d$, (4.10) becomes

$$\begin{aligned} \chi(\omega) &= 1 - \hat{u}_1(\omega) \\ &= \frac{2\alpha\theta\omega(s - \omega)}{d + (1-d)\omega} + O\left[\theta\omega s^2\left(1 + \frac{\theta\omega}{\omega + d}\right)\right] \\ &= 2\alpha\theta f(\omega) + O(\theta\omega s^2), \end{aligned} \tag{4.11}$$

where we define

$$f(\omega) = \omega(s - \omega)/\{d + (1-d)\omega\}. \tag{4.12}$$

By a maximization of $f(\omega)$ we get, as a first approximation of the optimal value ω^*:

$$\omega^* \approx \frac{(d^2 + (1-d)sd)^{\frac{1}{2}} - d}{1-d} = \omega^{**}, \text{ say.} \tag{4.13}$$

And by a simple algebraic manipulation:

$$\chi(\omega^{**}) = 2\alpha\theta(\omega^{**})^2/d. \tag{4.14}$$

Note that for small values of s:

$$\omega^{**} = \begin{cases} \sqrt{ds} + o(ds) & \text{as } d \ll s, \\ (\sqrt{2} - 1)s + o(s) & \text{as } d = s, \\ \frac{1}{2}s + o(s) & \text{as } d \gg s, \end{cases} \tag{4.13a}$$

$$\chi(\omega^{**}) = \begin{cases} 2\theta s + o(\theta s) & \text{as } d \ll s, \\ (\sqrt{2} - 1)^2 2\theta s + o(\theta s) & \text{as } d = s, \\ \frac{1}{4}(1-d)sd^{-1}2\theta s + o(\theta s) & \text{as } d \gg s. \end{cases} \tag{4.14a}$$

These findings indicate the following phenomenon (see [7]): that while for an insubstantial environmental deterioration (say $d \ll s$), ω^{**} increases like $\sqrt{d}$, it almost approaches its maximum for $d \approx s$ and stays practically intact under a further, substantial, environmental deterioration ($d \gg s$). $\chi(\omega^{**})$, on the other hand, is affected practically only by values of d which are larger than s.

Since ω^* maximizes $\chi(\omega)$ and ω^{**} maximizes $f(\omega)$, we get from (4.11)

$$\begin{aligned}\chi(\omega^{**}) < \chi(\omega^*) &= 2\alpha\theta f(\omega^*) + O(\theta\omega^* s^2)\\ &< 2\alpha\theta f(\omega^{**}) + O(\theta\omega^* s^2)\\ &= \chi(\omega^{**}) + O(\theta s^2(\omega^* + \omega^{**}))\\ &= \chi(\omega^{**}) + O(\theta s^3).\end{aligned} \tag{4.15}$$

Employing (4.13a) we have,

$$\begin{aligned}\chi(\omega^*)/\chi(\omega^{**}) &= 1 + O(s^3 d(\omega^{**})^{-2})\\ &= 1 + O(\max\{s^2, sd\}).\end{aligned} \tag{4.16}$$

This justifies inserting $\chi(\omega^*)$ instead of $\chi(\omega^{**})$ in (4.14a). In the sense of maximizing $\chi(\omega)$, (4.16) also indicates that the value ω^{**} is quite "close" to the optimal value ω^*.

We now prove that for environmental deterioration which is not extremely small, say, for $d \gg s^3$

$$|\omega^* - \omega^{**}| = o(s). \tag{4.17}$$

From (4.12) it is shown that for $n \geqq 2$, $0 < \omega < s/(1+s)$,

$$f^{(n)}(\omega) = -\frac{d(d+s-ds)}{(1-d)^2}\, n!\, \frac{(-1)^n(1-d)^n}{[d+(1-d)\omega]^{n+1}}. \tag{4.18}$$

For $0 < \omega_1, \omega_2 < s/(1+s)$, it is thus not difficult to show:

$$\begin{aligned}f(\omega_1) - f(\omega_2) &= (\omega_1 - \omega_2) f'(\omega_2)\\ &\quad - \frac{d(d+s-ds)}{d+(1-d)\omega_2} \cdot \frac{(\omega_1-\omega_2)^2}{d+(1-d)\omega_1}.\end{aligned}$$

Knowing $f'(\omega^{**}) = 0$ and (from 4.13)

$$d + (1-d)\omega^{**} = (d^2 + (1-d)ds)^{\frac{1}{2}},$$

we get

$$f(\omega^{**}) - f(\omega^*) = \frac{d+(1-d)\omega^{**}}{d+(1-d)\omega^*}(\omega^* - \omega^{**})^2. \tag{4.19}$$

But from (4.15) we know $0 < f(\omega^{**}) - f(\omega^*) = O(s^3)$, and (4.19) thus implies

$$\frac{d+\omega^{**}}{d+\omega^*}(\omega^* - \omega^{**})^2 = O(s^3).$$

Now, exploiting (4.13a), and knowing $0 < \omega^* < s$, we readily conclude

$$\begin{aligned} \frac{|\omega^* - \omega^{**}|}{s} &= \frac{d + \omega^*}{d + \omega^{**}} O(s^{\frac{1}{2}}) \\ &= O(s / \max\{d^{\frac{1}{2}}; s^{\frac{1}{2}} d^{\frac{1}{2}}\}) \\ &= \begin{cases} O(s^{\frac{1}{2}}) & \text{if } r \geqq s, \\ O(s^{\frac{1}{2}} d^{-\frac{1}{2}}) & \text{if } r < s, \end{cases} \end{aligned} \tag{4.20}$$

and for $d \gg s^3$ we proved (4.17).

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References

[1] Nei, M. (1967) Modification of linkage intensity by natural selection. *Genetics* **57**, 625–626.

[2] Nei, M. (1969) Linkage modification and sex difference in recombination. *Genetics* **63**, 681–699.

[3] Feldman, W. M. (1972) Selection for linkage modification I: random mating populations. *Theor. Pop. Biol.* **3**, 324–346.

[4] Karlin, S. and McGregor, J. (1973) Toward a theory of modifier genes. *Theor. Pop. Biol.* To appear.

[5] Karlin, S. and McGregor, J. (1972) The evolutionary development of modifier genes. *Proc. Nat. Acad. Sci.* U.S.A. **69**, 3611–3614.

[6] Fisher, R. A. (1958) *The Genetical Theory of Natural Selection.* Dover, New York.

[7] Eshel, I. (1973) Clone selection and the evolution of modifier genes. *Theor. Pop. Biol.* To appear.

[8] Kimura, M. (1960) Optimum mutation rate and degree of dominance as determined by the principle of minimum genetic load. *J. Genetics* **57**, 21–34.

[9] Kimura, M. (1967) On the evolutionary adjustment of spontaneous mutation rates. *Genet. Res.* **9**, 23–34.

[10] Karlin, S. and McGregor, J. (1968) The role of the Poisson progeny distribution in population genetics models. *Math. Biosci.* **2**, 11–17.

[11] Harris, T. (1963) *The Theory of Branching Processes.* Springer-Verlag, Berlin.

[12] Dwass, M. (1969) The total progeny in a branching process and a related random walk. *J. Appl. Prob.* **6**, 682–686.

[13] Karlin, S. (1966) *A First Course in Stochastic Processes.* Academic Press, New York.

[14] Crow, J. F. and Kimura, M. (1970) *An Introduction to Population Genetics Theory.* Harper and Row, New York.

[15] Moran, P. A. P. (1962) *The Statistical Processes of Evolutionary Theory.* Clarendon Press, Oxford.

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Altruism, Competition and Kin Selection in Populations

I. ESHEL and D. COHEN

INTRODUCTION

The concept of inclusive fitness introduced by Hamilton (1964) has provided a general basis for the understanding of selection in populations of genetically related individuals. As further developed (Hamilton, 1970), it could account for the evolution of both altruism and spite between individuals in a population. According to Hamilton, selection will favor a limited risk-taking by an individual in order to save the life of an identified relative, when the risk is less than the excess of genetical relatedness between them above the mean genetical relatedness in the population. Risk taking would be expected to be equal between individuals with equal genetic relatedness. It seems, however, that parental care and self sacrifice is much stronger and commoner than mutual help between sibs, inspite of the fact that the genetical relatedness is identical in both cases. In some extreme cases there may be spiteful relations between sibs. It is very likely that the difference in reproductive potential and in the expected competitivity may account for this difference.

This paper is a further development of the general approach

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of Hamilton, which takes into account, in addition to genetic relatedness, the inherent competitivity and the reproductive potential of the individuals concerned.

An important new contribution of our model is the consideration of high order reciprocal relationships between individuals with altruistic or spiteful interactions. These reciprocal relations may lead to altruism between unrelated individuals which have a common relative, and in an extreme case, to altruism between unrelated individuals without a common relative, provided that the mutual dependence is strong enough. Reciprocation may also amplify spiteful relations, and in general, allows two or more stable states at different levels of altruism or spite.

THE MODEL

Consider any two individuals $\underline{i}$ and $\underline{j}$ with a genetic relatedness a_{ij}, in a group of relatives, $1,\ldots,k,\ldots,n$. Define the competitive effect of $\underline{j}$ on $\underline{i}$,

$$C_{ij} = \frac{W_i - W_{i/j}}{W_{i/j}} \tag{1}$$

or:

$$W_i = W_{i/j}(1 - C_{ij}) \tag{2}$$

where W_i is the expected number of offspring of $\underline{i}$ in the presence of $\underline{j}$, and $W_{i/j}$ is the expected number in the absence of $\underline{j}$.

The inclusive fitness of the genes of $\underline{i}$ in the presence of a relative $\underline{j}$ and of other relatives is:

$$g_i = W_i + \sum_{k \neq i} a_{ik} W_k \quad .$$

With the death of $\underline{j}$, the inclusive fitness of $\underline{i}$ is:

$$g_{i/j} = W_{i/j} + \sum_{\substack{k\neq i \\ k\neq j}} a_{ik} W_{k/j} \quad .$$

Thus, the overall change in the inclusive fitness of i when j dies is:

$$\Delta g_{i/j} = W_i - W_{i/j} + a_{ij} W_j - \sum_{\substack{k\neq i \\ k\neq j}} a_{ik} (W_{k/j} - W_k) \qquad (3)$$

If an individual j is in danger of death, and it can be rescued by i with a risk r_{ij} that i itself will die, the loss in inclusive fitness of i because of the risk is:

$$L_{ij} = r_{ij} \left[W_i - a_{ij} (W_{j/i} - W_j) - \sum_{\substack{k\neq i \\ k\neq j}} a_{ik} (W_{k/i} - W_k) \right] . \qquad (4)$$

As long as the loss in inclusive fitness of i because of the risk is less than the gain in the inclusive fitness of i in the presence of j, there will be selective advantage for taking the risk. The maximal risk will be reached when the loss is equal to the gain.

The maximal risk is:

$$r^*_{ij} = \frac{W_i - W_{i/j} + a_{ij} W_j - \sum_{\substack{k\neq i \\ k\neq j}} a_{ik} (W_{k/j} - W_k)}{W_i - a_{ij} W_{j/i} + a_{ij} W_j - \sum_{\substack{k\neq i \\ k\neq j}} a_{ik} (W_{k/j} - W_k)} \qquad (5)$$

r^*_{ij} is a decreasing function of $W_{i/j}$ and an increasing function of $W_{j/i}$ and a_{ij}. The quantity under the summation is the decrease in inclusive fitness contributed by i or j by the competitive effect they have on their relatives. When $r^*_{ij} < 0$, it means spite. It is the risk taken by i to decrease the survival of j. r^*_{ij} is infinitely high

when the loss function is negative, since its inclusive fitness will increase if it commits suicide.

Considering the simplest case of only two related individuals, $\underline{i}$ and $\underline{j}$, (5) reduces to:

$$r^*_{ij} = \frac{W_i + a_{ij}W_j - W_i}{W_i + a_{ij}W_j - a_{ij}W_{j/i}} \tag{5.1}$$

or, using the definition of C_{ij},

$$r^*_{ij} = \frac{W_i + a_{ij}W_j - \dfrac{W_i}{1 - C_{ij}}}{W_i + a_{ij}W_j - \dfrac{a_{ij}W_j}{1 - C_{ji}}} \quad . \tag{5.2}$$

r^*_{ij} is an increasing function of the reproductive potential of $\underline{j}$ and of the genetic relatedness between $\underline{i}$ and $\underline{j}$. It is a decreasing function of the reproduction potential of $\underline{i}$. r^*_{ij} is a decreasing function of C_{ij} and an increasing function of C_{ji}.

$r^*_{ij} > 0$ when:

$$a_{ij} > \frac{W_{i/j} - W_i}{W_j} \quad \text{or} \quad a_{ij} > \frac{W_i}{W_j}\,\frac{C_{ij}}{1 - C_{ij}} \tag{6}$$

when the loss function L_{ij} is positive; otherwise r^*_{ij} is infinitely high.

When possible altruistic or spiteful interaction is with a subset of n individuals out of the whole population, without discrimination of particular individuals, the loss in the expected reproduction of the genes of $\underline{i}$ through the death of all n individuals is:

$$\Delta g_{i/n} = W_i + \sum_{k \neq i} a_{ik}W_k - W_{i/n} \quad .$$

The loss in inclusive fitness because of the risk r_{in} is:

$$L_{in} = r_{in} \left[W_i - \sum_{k \neq i} a_{ik} (W_{k/i} - W_k) \right] .$$

In this case,

$$r^*_{in} = \frac{W_i + \sum_{k \neq i} a_{ik} W_k - W_{i/n}}{W_i + \sum_{k \neq i} a_{ik} W_k - \sum_{k \neq i} a_{ik} W_{k/i}} . \qquad (7)$$

The size of the subset may be determined by the range of a territorial predator, or by the mobility range of the individuals during their feeding and reproductive activities, or by the diffusion of the products of their metabolism.

We may note some special cases of inequality (6).

1. In the symmetrical case $W_i = W_j$, $r^*_{ij} > 0$ when $a_{ij} > \frac{C_{ij}}{1 - C_{ij}}$. In this case the interaction will be altruistic or spiteful, depending on whether the relatedness is higher or lower than the competitivity.

2. $r^*_{ij} > 0$ when W_i is small or when $C_{ij} = 0$ if all the other parameters are positive. $r^*_{ij} < 0$ when $W_j = 0$, or when $a_{ij} = 0$ when all the other parameters are positive. These extreme cases are quite obvious intuitively.

3. $a_{ij} = 1$ between members of a clone. Altruism between them is of course much more likely than between individuals of lower genetic relatedness. There is, however, the possibility of spite between members of a clone either in the very asymmetrical cases of $W_j \ll W_i$, or in the destructive case of $C_{ij} \sim 1$.

4. In extremely asymmetrical situations it is quite possible to have $r^*_{ij} > 0$ and $r^*_{ji} < 0$. Such, for example, would be the case when $W_i \gg W_j$ or when $C_{ij} \ll C_{ji}$. This would be a situation when one of the two individuals is

nearing the end of its reproductive period, but is still competing for limiting resources with a younger relative with a high reproductive potential. It should be noted, however, that this conclusion is reached without regard to the reciprocal relations of mutual altruism between such individuals, which is discussed below.

In a well mixed closed habitat with N individuals, $W_{i/j} = W_i \frac{N}{N-1}$.

Substituting in (5) and rearranging gives:

$$r^*_{ij} = \frac{a_{ij} - \bar{a}_i}{1 - \bar{a}_i}$$

where $\bar{a}_i = \frac{1}{N} \sum a_{ik}$, including $a_{ii} = 1$. $r^*_{ij} > 0$ when $a_{ij} > \bar{a}_i$; $r^*_{ij} < 0$ when the opposite is the case. This result is similar in principle to that reached by Hamilton (1970).

An interesting case of $r^*_{ij} > 0$ and $r^*_{ji} < 0$ can arise in such a situation when $\bar{a}_j < a_{ij} < \bar{a}_i$, i.e. when j is weakly related to i and is not related to other individuals, while i is strongly related to many other individuals.

When relatedness in the population cannot be identified, and it has some average value $a_{ij} < 1$, or when all individuals are equally related,

$$\bar{a}_i = \frac{1 + (N-1)\, a_{ij}}{N} ,$$

and we get that $r^*_{ij} = \frac{-1}{N-1}$, which is always negative, i.e. spite, irrespective of the average relatedness. The absolute value of this spite decreases as N increases, becoming negligible at large N .

Real habitats are never perfectly closed. If we assume that there is an average probability ϵ for each individual

to send an offspring to other habitats, then $r^*_{ij} > 0$ if $(N-1) \in a_{ij} > 1 - a_{ij}$.

THE EFFECT OF RECIPROCATION ON THE SELECTIVE ADVANTAGE OF ALTRUISM AND SPITE

It is intuitively clear that altruism increases and spite decreases the contribution which one individual has on the inclusive fitness of another individual and thus increase or decrease the optimal risk. We call these mutual effects between interacting individuals reciprocation. We do not consider reciprocation in the sense of Trivers (1971) in which reciprocal altruism is the result of a binding contract between individuals to repay in kind for help received.

Considering the simpler case of only two related individuals, we introduce an increasing function $f_{ji}(r_{ji})$ which is the factor by which W_i is multiplied when a risk r_{ji} is taken by j ; $f(0) = 1$. So in this case,

$$r^*_{ij} = \frac{W_i f_{ji}(r^*_{ji}) + a_{ij} W_j f_{ij}(r^*_{ij}) - W_{i/j}}{W_1 f_{ji}(r^*_{ji}) + a_{ij} W_j f_{ij}(r^*_{ij}) - a_{ij} W_{j/i}} \quad . \tag{8}$$

In the simplest symmetrical case of two individuals with $W_i = W_j$, $C_{ij} = C_{ji} = C$, $r^*_{ij} = r^*_{ji} = r$, $a_{ij} = a$, and $f_{ij} = f_{ji} = 1 + \alpha r$, we get from (8),

$$r = \frac{(1-C)(1+\alpha r)(1+a)-1}{(1-C)(1+\alpha r)(1+a)-a} \quad . \tag{9}$$

For small values of α the effect of reciprocation is to increase the level of r when it is positive, and to decrease it when it is negative. Reciprocation in this case amplifies the altruistic or spiteful relations expected without it.

From (9) we get the quadratic form

$$\alpha(1-c)(1+a)r^2+[(1-\alpha)(1-C)(1+a)-a]r+1-(1-C)(1+a) = 0 \quad . \tag{10}$$

As long as $(1-C)(1+a) > 1$, there are one positive and one negative roots to equation (10). This is the case when competitivity is greater than the genetic relatedness.

When $(1-C)(1+a) < 1$, there are two positive roots when $a > (1-\alpha)(1-C)(1+a)$, which is always true when $\alpha > 1$, and there are two negative roots when $a < (1-\alpha)(1-C)(1+a)$ provided that the discriminant of equation (10) is positive.

A specially interesting case is of two unrelated individuals, i.e. $a = 0$. In this case the discriminant is positive when $\frac{C}{1-C} < \frac{(1-\alpha)^2}{4\alpha}$, which holds when α is very small or quite large. When this is the case, the two roots are positive when $\alpha > 1$, and negative when $\alpha < 1$.

Since genetic relatedness is not required when this condition holds, altruistic relations may become possible between individuals of different species, i.e. symbiosis. It is important to note that no binding contract or gratitude are assumed. The advantage for the helper is that it helps to maintain alive an individual which helps it to survive.

In any of the above cases it seems that any one solution is probably stable over some local neighborhood. Thus, it seems likely that the actual behavior will depend on the initial conditions in the relationship. Very likely, an initially high level of altruism in one individual may select for an increase in altruism in the second individual until a high stable level is reached. Conversely, an initially low level of altruism or a high level of spite may select for further decrease of altruism or for increased spite. This is very likely the explanation for the extremely high aggressiveness found between some insects' larvae (quoted in Hamilton, 1970). It could also explain the great differences in the social cooperation between individuals in some fairly closely

related species. Cases of cooperative association between unrelated individuals are known in slime molds, in algal zoospores, and in queen ants (Hamilton, 1964).

DISCUSSION

Slatkin: One thing which bothers me about such reciprocation models is that although the model may explain the social behavior in a given population, I do not see how it can explain the evolution of such a situation.

Eshel: Our model, unlike that of Trivers, has to be understood in genetic terms. Specifically, once a direct kin selection results in fixation of genes which determine a certain optimal level of mutual help among individuals of a given relatedness, then the mutual importance of such relatives in increasing each others' inclusive fitness is also increased. This in turn increases the optimal selected level of mutual help among individuals of the same relatedness and so on. In this case, the limit of the process is given by the smallest positive solution nearest to the Hamilton solution.

Cohen: In general, there will be several solutions to r_{ij} under reciprocation. Selection will increase or decrease the frequencies of altruistic genes according to their frequencies in the population. The final stable level will depend on the initial frequencies. These may depend on some slight differences in the environment, and in small populations may sometimes result from random fluctuations. Thus, the degree of altruism or spite is expected to vary enormously between species with fairly similar ecologies.

Cockerham: What degree of intelligence is required for the evolution of altruism?

Cohen: Fairly complex patterns of behavior are known in organisms with little or no intelligence. It is sufficient that such behavioral patterns are genetically determined. Cooperative interactions are found in very primitive organisms. I am experimenting now with selection in bacterial populations for and against the "altruistic" character of secretion of extracellular enzymes which digest polymeric substances and convert them into soluble substrates for the whole population.

REFERENCES

Hamilton, W.D. (1964). J. Theor. Biol. 7: 1-52.

Hamilton, W.D. (1970). Nature 228: 1218-1220.

Trivers, R.L. (1971). Quart. Rev. Biol. 46: 35-57.