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Theoretical analysis of divergence in mean fitness between initially identical populations

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SUMMARY

Initially identical populations in identical environments may subsequently diverge from one another not only via the effects of genetic drift on neutral alleles, but also by selection on beneficial alleles that arise stochastically by mutation. In the simple case of one locus with two alleles in a haploid organism, a full range of combinations of population sizes, selection pressures, mutation rates and fixation probabilities reveals two qualitatively distinct dynamics of divergence among such initially identical populations. We define a non-dimensional parameter k that describes conditions for the occurrence of these different dynamics. One dynamic ($k > 1$) occurs when beneficial mutations are sufficiently common that substitutions within the populations are essentially simultaneous; the other dynamic ($k < 1$) occurs when beneficial mutations are so rare that substitutions are likely to occur as isolated events. If there are more than two alleles, or multiple loci, divergence among the populations can be sustained indefinitely if $k < 1$. The parameter k pertains to the nature of biological evolution and its tendency to be gradual or punctuated.

1. INTRODUCTION

How reproducible is evolution, and in particular adaptive evolution? Gould (1989) proposed a thought experiment of 'replaying life's tape' to address this question. He suggested that:

any replay of the tape would lead evolution down a pathway radically different from the road actually taken ... Each step proceeds for cause, but no finale can be specified at the start, and none can ever occur a second time in the same way, because any pathway proceeds through thousands of improbable steps.

Rigorous experiments on the predictability of evolution using organisms with short generations, such as fruit flies and bacteria, demonstrate that: (i) the random origin of mutations, either alone or in concert with genetic drift, can cause unpredictability; and (ii) substantial divergence of (initially identical) replicate populations in identical environments can occur even for traits that are subject to strong selection (Cohan & Hoffmann 1986, 1989; Lenski *et al.* 1991; Bull & Molineux 1992; Bennett & Lenski 1993; Yin 1993; Korona *et al.* 1994; Lenski & Travisano 1994; Vasi *et al.* 1994; Travisano *et al.* 1995). We wish to complement these experimental studies of adaptation and divergence with theoretical analyses of their dynamics, beginning with the very simple case that we have analysed here.

To explore effects of random and non-random factors on the dynamics of adaptation and divergence,

we model the collective replacement process of one allele by another across a set of populations in a metapopulation, as opposed to the more familiar replacement process within a single population. The non-random factors in the model include population size and the strength of natural selection; the random factors include genetic drift and the spontaneous appearance of mutations. To describe the nature of collective replacement, we analyse the general features of the model.

2. THE MODEL

We consider a haploid organism having two alleles and hence two genotypes, A and B , at a single locus. A metapopulation of these organisms consists of initially identical and genetically homogeneous populations. The populations evolve independently in separate but identical environments (without migration). The size N of each population is constant and selection is soft (Wallace 1968), with relative fitness values of 1 and $1+S$ assigned to genotypes A and B , respectively, where $S > 0$ is a constant selection coefficient. Because the relative fitnesses are constant, selection is neither density- nor frequency-dependent. The rate of forward mutation is μ_{AB} (from genotypes A to B), and the rate of backward mutation is zero. Because genotype B has a higher fitness value than genotype A , back mutation, even at reasonably high rates, is an insignificant factor with respect to the processes of adaptation and divergence considered here.

In each population the number N_A of individuals having genotype A and the number N_B having genotype B change through time as follows. Initially each population contains only individuals of genotype A . Genotype B arises in each population by mutation, but due to genetic drift, a population may lose a particular mutation to genotype B before it becomes common. If a mutation to genotype B occurs in a population and is 'successful' (not lost while still rare), natural selection acts to replace genotype A with B . Thus, by means of mutation and natural selection, allele B , although initially absent, eventually becomes fixed in each population and therefore in the meta-population.

Until a successful mutation (genotype B) appears in a population, its mean fitness \bar{w} remains at 1, which is the relative fitness of genotype A . After the population receives a successful mutation, \bar{w} increases monotonically if the size of the population is large enough that drift is not a significant factor. The waiting time for a 'successful' mutation to appear in a given population includes two random components: the timing of mutations and random genetic drift. The latter determines whether a mutation succeeds or is eliminated: if a mutation is eliminated, then a wait for another ensues.

Let the random variable T denote the time when the first successful mutation appears in a population. Before time T (i.e. $t < T$), $N_A(t) = N$ and $N_B(t) = 0$, and at the instant of T (i.e. $t = T$), $N_A(T) = N - 1$ and $N_B(T) = 1$. Because T is a waiting time, we take it to be a non-negative, continuous random variable with standard exponential probability distribution

$$f(T) = \mu_{AB} \omega N e^{-\mu_{AB} \omega N T}, \quad (1)$$

where the product $\mu_{AB} \omega N$ is the effective rate of mutation from genotype A to B . The expected waiting time T is $1/(\mu_{AB} \omega N)$. The parameter ω is the probability of a mutation to genotype B becoming fixed, which is typically proportional to its selection coefficient (Haldane 1927; Moran 1962). If the number of populations in the metapopulation is sufficiently large, then regardless of how small the population size N happens to be, the random variation between populations in waiting time due to the random effects of drift, apart from that which is accounted for by ω , can be ignored with regard to the dynamics of the metapopulations. All of our simulations include 10000 populations in the metapopulation.

The product $U = \mu_{AB} \omega$ is the per capita rate of successful mutations, which represents the contribution of random factors (mutation and genetic drift) to the among-population variance for mean fitness $v(\bar{w})$ and to the grand mean fitness $\bar{\bar{w}}$, which is the mean of the mean fitnesses (\bar{w} 's) across populations. Because the size of each population is regulated to the same constant equilibrium value N , the mean fitness for the metapopulation is $\bar{\bar{w}}$.

3. ANALYSIS AND RESULTS

To analyse the model, we use a quasi-Monte Carlo method for obtaining $\bar{\bar{w}}$ and $v(\bar{w})$. To illustrate, suppose there are 10000 populations in a metapopulation. For

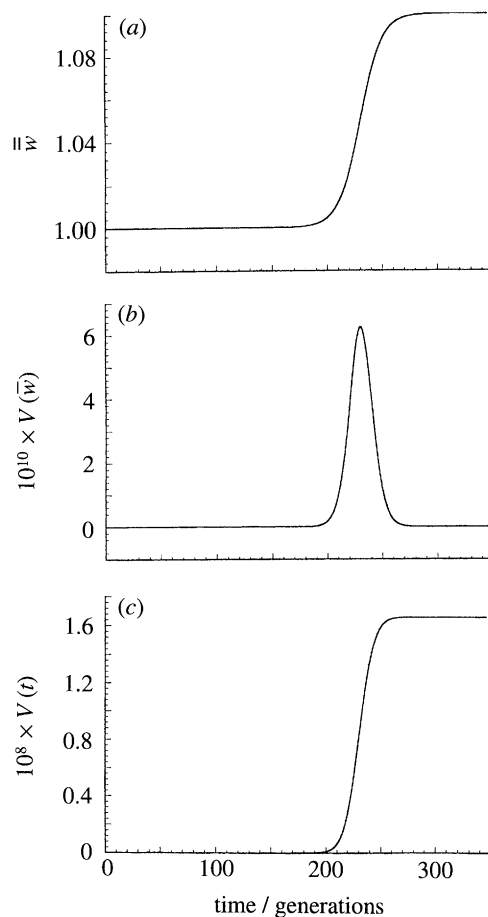


Figure 1. Trajectories describing the evolution of a meta-population containing ten thousand populations. The selection differential $S = 0.1$, population size $N = 10^{10}$, and average rate of successful mutations $U = 10^{-8}$ per generation. The rate of effective mutation UN is 100 mutations per population per generation. (a) The trajectory for the grand mean fitness $\bar{\bar{w}}$ ascends exponentially; (b) the trajectory for the slight among-population variance in mean fitness $v(\bar{w})$ is transient and resembles a spike; and (c) the trajectory of the cumulative among-population variance in mean fitness $V(t)$ is similar to that of $\bar{\bar{w}}$.

each population we draw a waiting time T from the probability distribution described by equation (1). Then, for each time t in a sample of times, we compute the mean fitness $\bar{w}(t, T)$ for each population, using equation (10) in Appendix 1.

From these mean fitnesses, the trajectories (see figure 1) for $\bar{\bar{w}}$, $v(\bar{w})$ and

$$V(t) = \int_0^t v[\bar{w}(z)] dz$$

are easily calculated. The accumulation $V(t)$ of among-population variance for mean fitness to time t reflects a potential for divergence within the metapopulation. As discussed later, this potential can include sustained divergence if other collective replacements (involving other pairs of alleles) are in process.

Upon receiving its first successful mutation, each population in the metapopulation then contributes to a monotonic increase in $\bar{\bar{w}}$, which eventually approaches and sustains indefinitely the maximum fitness of $1 + S$ (see figure 1a). However, $v(\bar{w})$, which is by definition zero at $t = 0$, cannot be sustained

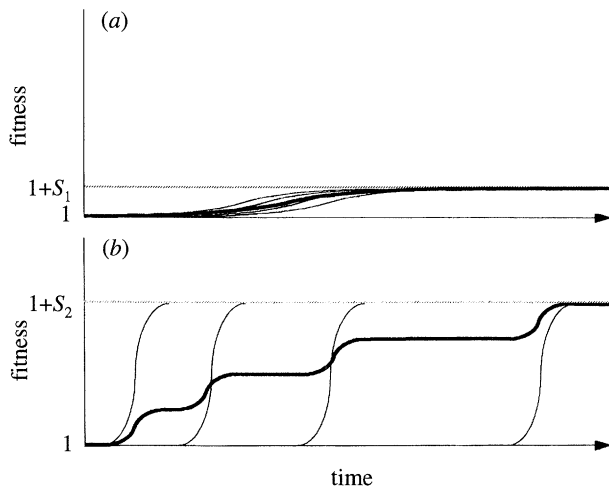


Figure 2. A depiction of (a) coincident-event and (b) isolated-event collective replacement when there are just four populations in a metapopulation: (a) The rate of recruitment UN is high and the selection coefficient S_1 small (slow within-population replacement); k is about ten. Conversely, in (b) the rate of recruitment is low and S_2 is large (rapid within-population replacement); k is about 0.5. Graphs show grand mean fitness for the metapopulation (thick lines) and mean fibres for a single population (thin lines).

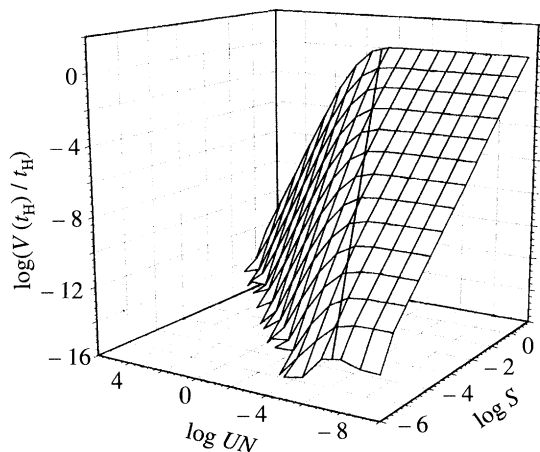


Figure 3. The effects of S and UN on a mean rate $V(t_H)/t_H$ of increase in $V(t)$ to time t_H . The ridge on the graph corresponds to cases when $k = 1$, as shown by the line, and separates the regions of coincident-event (left, $k > 1$) and isolated-event (right, $k < 1$) collective replacement. The metapopulation contains 10000 populations of size $N = 10^8$. The graph is truncated at the bottom because computations below those points involve small values that result in substantial computer rounding errors. We assume that the graph continues down so that $V(t_H)/t_H$ approaches zero as UN continues to increase and S to decrease.

indefinitely. The height of its trajectory increases for a time, and then returns to zero (see figure 1b) as B replaces A in all populations. That is, with only two genotypes, there is but one evolutionary route for every population, namely, replacement of genotype A by genotype B .

The selection differential S is the principal determinant of the duration of within-population replacement once a successful mutation from genotype A to B has occurred for a population. The recruitment rate

for a collective replacement process across populations is the rate at which the populations in a meta-population obtain a first successful mutation, and therefore proceed to carry out within-population replacement. In our model, the rate of effective mutation, that is, the product UN , reflects the rate of recruitment. Together, the rate of recruitment and the duration of within-population replacement define two distinct forms of collective replacement: coincident-event and isolated-event.

The form of collective replacement depends on the proportion of populations that are simultaneously in the process of replacement. Recruitment is rapid (high UN) and the within-population replacement process slow (low S) in coincident-event replacement, so that almost all of the populations in the metapopulation are in transition simultaneously (see figure 2a). By contrast, in the isolated-event form, only a tiny fraction of the populations undergo replacement at the same time (see figure 2b) because recruitment is slow (low UN) and selection, which drives replacement within a population, is fast (high S).

We approximate quantitatively the form of collective replacement as follows. From equation (10) in the Appendix 1, we obtain the time

$$\tau_H = \log_e [(N-1)/2] / r_{AB}. \quad (2)$$

that it takes for a population to reach halfway to the maximum mean fitness (i.e. $\bar{w} = 1 + S/2$). Here r_{AB} is the rate of selection ($r_{AB} = m_A S = m_B - m_A$), where m_A and m_B are the malthusian parameters for populations A and B , respectively. The product of the rate UN of successful mutations for a population and the time ($\approx 2\tau_H$) required for the replacement process, once initiated, is

$$k \cong UN 2\tau_H = \mu_{AB} \omega N \cdot 2 \log_e [(N-1)/2] / r_{AB} \quad (3)$$

which is non-dimensional. Stated differently, k is the time required for within-population replacement by a given genotype divided by the waiting time for a successful mutant of that genotype. If one assumes, as we have for our simulation models (see Appendix 1), that the time units are scaled such that the malthusian parameter $m_A = 1$, then $m_A S$ can be substituted for the denominator r_{AB} in equation (3).

Let t_H denote the time when genotype B has reached halfway to fixation in the metapopulation [i.e. when $\bar{w} = 1 + S/2$]. Then $[V(t_H)]/t_H$ is an average rate of increase in $V(t)$ to time t_H . Because the two forms of collective replacement represent distinctly different amounts of accumulation of among-population variance in mean fitness within the duration ($\approx 2t_H$) of the replacement process, $[V(t_H)]/t_H$ clearly distinguishes between the two forms, as shown in figure 3. A definite ridge at $k = 1$ separates the parameter space into two distinct regions.

In the coincident-event region, which is on the left side of the ridge, k becomes much greater than 1.0, and $\log [V(t_H)]/t_H$ decreases linearly as $\log S$ decreases and $\log UN$ increases. In the isolated-event region, which is on the right side of the ridge, k is much smaller than 1.0, and $\log [V(t_H)]/t_H$ increases linearly as $\log S$ increases, but remains constant for different values of $\log UN$.

During isolated-event collective replacement, most populations are either waiting for a successful mutation ($\bar{w} = 1$, the minimum) or have already completed the replacement process ($\bar{w} = 1 + S$, the maximum). Therefore, most pairs of populations either do not differ in mean fitness or differ maximally by the amount S . This means that throughout an isolated event collective replacement process ($k < 1$), variation between populations is virtually the maximum possible for the number of populations recruited. In contrast, throughout the process of coincident-event collective replacement ($k \gg 1$), variation in mean fitness among populations tends toward the minimum for the number of populations recruited. Hence, for a given value of S , values for $[V(t_H)]/t_H$ (figure 3) and $V(t_H)$ are highest when collective replacement is isolated-event.

4. DISCUSSION

The replacement in a single population of an inferior allele by a superior allele is a fundamental unit for organic evolution (Spiess 1977; Ewens 1979), and it has therefore been studied extensively. But collective replacement across a set of initially identical populations, which extends this fundamental unit to metapopulations, has not been previously studied. Yet such collective replacement provides an indication of the ‘reproducibility’ (and hence predictability) of the replacement process, and the dynamics of collective replacement may thereby encompass the contributions of natural selection, chance events, and historical constraints to the processes of adaptation and divergence.

For coincident-event collective replacement ($k \gg 1$), the non-random factor of natural selection is virtually the sole determinant for the trajectory of the genetic composition of any of the populations. When coincident-event collective replacement occurs, each population acquires its first successful beneficial allele almost immediately because the population size and mutation rate are large. Hence, predicting the genetic composition of a particular population in the metapopulation during the collective replacement process only requires knowledge of the selection coefficient, which determines the rate of replacement within a population.

In contrast, for isolated-event collective replacement ($k \ll 1$), random factors largely determine the gene frequencies for any given population. Timing of mutations and genetic drift determine when the first ‘successful’ beneficial mutation occurs in a particular population. This makes predicting the genetic composition of any given population difficult, and knowing the selection coefficient is of little help.

Note that if the selection coefficient is held constant, population size largely determines the form of collective replacement for a pair of alleles in a metapopulation because the effective rate of mutation scales with population size. Thus population size plays a large role in determining the relative importance of random and non-random factors in the evolution of adaptive as well as neutral traits.

The form of collective replacement that underlies the development of variation among populations may also determine whether divergence will be transient or sustained. For the simple case that we have analysed (one locus with two alleles), from any starting point there is only one possible evolutionary path for each of the replicate populations. Although the populations in the metapopulation can differ in the time elapsed before the superior allele becomes fixed, their final state is identical, namely, genotype A replaced by genotype B . Consequently, among-population variance in mean fitness $v(\bar{w})$ is necessarily transient. However, when there are more than two alleles, either at one locus or several loci, more than one evolutionary path with distinct endpoints may be available to the replicate populations. In such cases, $v(\bar{w})$ can be sustained indefinitely because different populations can ascend and become stuck on different adaptive peaks (see also Mani & Clarke 1990), provided that collective replacement is isolated-event.

For example, consider a simple case in which there are three alleles A_1 , A_2 , and A_3 , with relative fitnesses 1, $1 + S$, and $1 + T$, respectively, where $T > S > 0$. Let μ_{ij} be the mutation rate from A_i to A_j , and suppose that $\mu_{12} = \mu_{13} = \mu$ and all other $\mu_{ij} = 0$. Thus there are two stable equilibria representing disconnected adaptive peaks of unequal height with no route between them. Letting the initial frequency of A_1 be 1 in all replicate populations, then $\bar{w} = 1$ and the $v(\bar{w}) = 0$ at the onset. If the effective mutation rates are sufficiently low (given the selection coefficients S and T) so that collective replacement occurs as isolated events, then a replicate population may become stuck at the sub-optimal peak ($1 + S$), if A_2 replaces A_1 before a successful mutation to A_3 has occurred.

Although $\mu_{12} = \mu_{13}$ in this simple hypothetical case, a population is more likely to end up at the higher peak ($1 + T$) due to the greater likelihood of fixation for a beneficial mutation with large effect than one with small effect (the one of smaller effect being more likely to be lost due to random drift). Given that the probability of fixation of a beneficial mutation is roughly proportional to its selective value (Haldane 1927; Moran 1962), then if collective replacement is isolated-event, fractions $p = T/(T + S)$ and $1 - p$ of the subpopulations are expected to end up at the higher and lower adaptive peaks, respectively. In this case, the asymptotic value of \bar{w} , namely

$$\lim_{t \rightarrow \infty} \bar{w}(t) = p(1 + T) + (1 - p)(1 + S) \quad (4)$$

lies between $1 + S$ and $1 + T$, and the asymptotic value of $v(\bar{w})$

$$\begin{aligned} \lim_{t \rightarrow \infty} [v(\bar{w}(t))] &= p(1 + T - \bar{w})^2 + (1 - p)(1 + S - \bar{w})^2 \quad (5) \\ &= p(1 - p)(T - S)^2 \\ &= TS[(T - S)/(T + S)]^2 \end{aligned}$$

lies between zero and the product TS .

Thus, when collective replacement is isolated-event, the random origin of mutations, either along or in concert with random genetic drift, can theoretically

lead to sustained divergence of formerly identical populations in identical environments, even for selectively important traits. In contrast, if collective replacement is coincident event, then the most fit allele will usually appear and win in every population, so that there is no opportunity for sustained divergence among the populations of the metapopulation.

In the above illustration of sustained divergence there are two elementary (i.e. two-allele) collective replacements taking place at the same time: allele A_2 replacing A_1 , and allele A_3 replacing A_1 . Suppose we consider all the possible elementary collective replacements that are in process at a given time within a metapopulation. Each such replacement contributes among-population variation within the metapopulation, and each can increase the probability that all or some of that variation is sustained indefinitely. The overall contribution of an elementary collective replacement process to sustained divergence among populations within a metapopulation is a monotonically increasing function of the integral $V(t)$, or of a similar integral for a trait other than mean fitness.

The divergence of initially identical populations subject to identical environments can be examined by rigorous experiments using fruit flies, bacteria and other organisms with suitably rapid generations. Several such experiments have shown that random mutation and drift can cause substantial divergence among replicate populations in important traits, even including mean fitness (Cohan & Hoffmann 1986, 1989; Lenski 1988; Korona *et al.* 1994; Lenski & Travisano 1994; Travisano *et al.* 1995). In nature, there is usually some migration between populations and we therefore expect that many local adaptations would have been wiped out in competition with better solutions that were independently derived in other populations (Crow *et al.* 1990; Wade & Goodnight 1991). Even with this bias against detection of this phenomenon in nature, many different populations of the same species appear to have independently evolved somewhat different adaptive solutions to the same selective challenge (Gould & Lewontin 1979; Cohan 1984).

Collective replacement addresses questions of global evolutionary change. The non-dimensional parameter k may be useful in describing when evolution tends to be gradual ($k > 1$) or punctuated ($k < 1$), and in assessing what proportion of genetic variation among populations is sustainable, and therefore can contribute to phylogenetic divergence. This theoretical study and that of Mani & Clarke (1990) are first steps towards formalizing the dynamics of collective replacement. By extending this theoretical framework to more complex situations involving multiple alleles and loci, we hope to complement on-going experimental studies of the long-term evolutionary dynamics of initially identical populations of bacteria (Lenski *et al.* 1991; Korona *et al.* 1994; Lenski & Travisano 1994; Vasi *et al.* 1994; Travisano *et al.* 1994).

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APPENDIX 1

Here we consider a single population. Let m_A and m_B be the malthusian parameters for genotypes A and B , respectively. The mean malthusian fitness is $\bar{m} = (m_A N_A + m_B N_B)/N$. Multiplying $\bar{m}(t)$ by the constant $1/m_A$, we obtain a corresponding mean relative fitness $\bar{w} = \bar{m}/m_A = 1 + S(N_B/N)$ for the population. The malthusian fitnesses m_A and m_B and also the rate of selection ($r_{AB} = m_B - m_A$) have units of inverse time, whereas relative fitness is non-dimensional. Because the selection coefficient $S = (m_B - m_A)/m_A = r_{AB}/m_A$ is also non-dimensional (and constant), we assume that the time units are scaled such that $m_A = 1$ and $\bar{w} = \bar{m}/m_A$.

We denote by $N_B(t; T)$ the number of individuals in genotype B for the population at time t , given that a value for time T has been drawn from its probability distribution. Before a successful mutation occurs ($t < T$), several unsuccessful mutations may appear and then disappear due to genetic drift. For practical purposes, $N_B(t; T) = 0$ when $t < T$. Once a successful mutation occurs ($t \geq T$), the expected change in $N_B(t; T)$ is described by the equation of genotype dynamics for soft selection:

$$d/dt N_B(t; T) = r_{AB} N_B(t; T) [1 - N_B(t; T)/N]. \quad (\text{A } 1)$$

Integration of equation (6) gives the expected number of individuals of genotype B at time t , that is

$$N_B(t; T) = [N \cdot N_B(T^2 T) e^{r_{AB}(t-T)}] / [N - N_B(T; T) + N_B(T; T) e^{r_{AB}(t-T)}], \quad (\text{A } 2)$$

where $N_B(T; T)$ denotes the number of individuals of genotype B when $t = T$; namely, $N_B(T; T) = 1$. Consequently, we may rewrite the equation as

$$N_B(t; T) = N / [1 + (N-1) e^{-r_{AB}(t-T)}]. \quad (\text{A } 3)$$

This is a strictly deterministic model of the expected increase in $N_B(t; T)$ when a mutant is destined to become fixed. Actually, the expected increase in $N_B(t; T)$ tends to be slightly faster in models that are not strictly deterministic, but in this paper we forego the complicated mathematics for the distribution of the required acceleration factor. With regard to our results, the inclusion of such a factor would cause a slight shift toward isolated-event collective replacement.

The mean relative fitness for a population can now be expressed as

$$\bar{w}(t; T) = 1 + (S/N) N_B(t; T). \quad (\text{A } 4)$$

When $t < T$, $N_B(t; T) = 0$ and $\bar{w}(t; T) = 1$; and when $t \geq T$, we use equations (8) and (9) to obtain the equation

$$\bar{w}(t; T) = 1 + S / [1 + (N-1) e^{r_{AB}(T-t)}] \quad (\text{A } 5)$$

for computing the mean fitnesses of a population that has obtained a successful mutation at time T .