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Clone Selection and the Evolution of Modifying Features

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A statistical mechanism of long-run selection is formulated in order to explain the evolution of modifying features governing mutation, recombination, sexual behavior, demographic mobility, and other factors that do not directly increase the individual fitness of their carrier but which are, supposedly, essential for future evolution of a population. Survival probability of a clone, rather than that of the individual, is shown to play the main role in this mechanism. Changing environment proves to be the main factor affecting it.

A theoretical possibility of a long-run adaptation to the dynamics of an environmental change—rather than to a static situation resulting from it—is demonstrated.

1. MODIFYING FEATURES AND SECOND ORDER SELECTION

The motivation for this work stems from studies concerning the evolution of a variety of traits or features which are commonly labeled as *modifying features* (see, for example, Karlin and McGregor (1972, 1972a) and references therein). When speaking of modifying features we mean inherited features with the following characteristics:

(i) Their main biological function does not involve a direct contribution to the Fisherian fitness of either their carrier or its neighboring individuals. This requirement distinguishes a modifying feature from an altruistic trait (see, for comparison, Haldane (1932), Hamilton (1964), Maynard-Smith (1964), and Eshel (1972)).

(ii) In affecting the process of reproduction within a population, modifying features determine further evolution (or preservation) of other features. These, in turn, may be directly advantageous for the survival of the future population.

Prevalant examples of modifying features are patterns governing sexual reproduction, mating systems, rates of mutation and recombination, and, possibly, also diploidy and polyploidy. In recent years, the long-run evolutionary function of sex and recombination has been extensively studied (e.g., see Crow and Kimura (1965), Bodmer (1970), Eshel and Feldman (1970), Mynard-Smith (1968) and references therein; see also Muller (1932)). Similar effects have

also been studied in connection with sex and diploidy (Eshel, 1970, 1972a), various mating systems (Karlin, 1968) and optimal mutation rates (Kimura, 1960, 1967). All these features appear to serve long run survival of a population, usually through maintaining a polymorphism at a minimal cost. Yet, in terms of individual fitness, modifying features often prove to be immediately costly for their carrier. Exceptions such as sexual coupling serving as an efficient regulator of team activities among higher vertebrates are from an apparently late, secondary path of adaptation. (For a different view see Scudo 1972.) Consequently it is often difficult to explain many phenomena in the evolution of modifying features based upon a strict analysis of fitness selection within a population.

Thus, for a fairly general condition it can be shown that in the long run, fitness-selection always operates to decrease nonzero rates of mutation (Karlin and McGregor, 1972) or recombination (Nei, 1967; Feldman, 1972). Furthermore, a maximum equilibrium-fitness is obtained in the case of a zero rate of either mutation or recombination (Karlin and McGregor, 1972, 1972a). The readers might note that these results are proved only asymptotically for the duration of the process. In fact, some simple models analysing fitness selection in a changing environment seem to reveal a temporal increase in the rate of mutation (or, with certain prerequisites, also in the rate of recombination). This is the case, for example, when, for mathematical convenience, only one mutant form is allowed which is advantageous in comparison with the conservative type. The situation is completely different, however, if irreversibly deleterious and lethal mutations are incorporated into the model in a higher frequency than the advantageous one is. In this case, despite the necessity of the rare advantageous mutation for future survival of the population, a strict analysis of fitness-selection paradoxically demonstrates a *monotone* decrease of the mutation rate up to a zero level.

Similar phenomena are manifested by applying fitness-selection to problems involving the evolution of intrinsic population controls (Wynne-Edwards, 1962; Lloyd and Christian, 1969), patterns of altruistic behaviour (Haldane, 1932) or tendencies to a negative assortment in mating (Karlin, 1968). Thus, unless a population is very sparce, fitness-selection is shown to favor tendencies to positive assortment while intrinsic tendencies to a negative assortment as well as to self incompatibility are always selected against, their existence being explained on the basis of their advantage in maintenance of polymorphism.

Complementary to the Fisherian approach, there is a natural tendency to explain the evolution of a modifying feature on the basis of some benefit with which it supposedly endows the future population. Yet, if unsupported by analysis of selection forces operating within a population, such a tendency devolves to an explanation of interpopulation selection. This type of selection now faces substantial theoretical objection as being a major force in evolution (see, for

example, Williams (1965)). Actually, it is hard to see how biological complexes, like those governing sexual systems, recombination, or even optimal mutation rates, will be spontaneously established in any population without (or even against) selection forces operating within that population. Indeed, without the establishment of a feature, at least within a few populations, interpopulation selection for this feature cannot occur.

From the foregoing it, thus, appears that some mechanism of selection operating in favor of advantageous modifying features at the *population* level is still to be studied. It also appears that this mechanism is not likely to be thoroughly explained by Fisherian methods based on the repeated effect of a direct fitness selection in a completely mixed, normalized-size population. Moreover, if we are not to regard the apparent, long-run biological function of a modifying feature as an evolutionary coincidence, this function should be incoporated into the selection mechanism of the modifying feature in question. To this end we are interested in the long-run survival probabilities of whole, evolving lines of descendents carrying a given modifying feature, rather than in the short term success of individuals in the population.

In an asexual population, such lines are naturally represented by clones. In a sexual population we speak about lines of identity by descent in a given locus ω as *generalized clones* with respect to this locus (see Kempthorn (1960), Karlin (1968a)). More specifically, a generalized clone consists of all individuals descending from a single parent, that carry duplications of a single allele in their ω-locus regardless of their genetic inheritance in other loci. Indeed, all individuals of the generalized clone are offsprings of the original parent but not all offspring of this parent belong to the generalized clone. In a diploid population we respectively speak about generalized clones of haplo-gametes.

Like individuals in an asexual population, all haplo-gametes of a sexual population are divided into mutually exclusive (generalized) clones each carrying a specific ω-gene. Unlike the asexual case, this division is not uniquely determined by the original parents but also depends on the choice of the specific locus in question. Generalized clones are, therefore, difficult to trace empirically. On a theoretical probabilistic level, however, it can be readily shown that clones characterized by different modifying features are likely to become linked with different *primary features* (i.e., genes which determine the fitness of their carrier) or, in a recombinant population, with different combinations of primary genes (see, for comparison, the deterministic analysis of Karlin and McGregor (1972) or Feldman (1972)). Thus, differences in exposure to direct selection forces result in differences in the long-run survival probabilities of these clones. Moreover, under certain conditions, and taking into consideration the pressures of environmental change, it can be shown that modifying features which maximize the survival probability of a clone also maximize the long-run survival probability of the entire population. We call these features *favorable in the broad sense* and speak

about *second order selection* in their favor. For example, clones characterized by a too low rate of mutation are likely to become extinct when environmental conditions become unfavorable to the conservative primary features. On the other hand, a too high mutation rate is likely to cause extinction of a clone even after the establishment of a new, adaptable, mutation. This fact introduces into the model a probabilistic equivalence of fitness selection operating for a favorable modifying feature. Hence, it can be shown that most surviving clones are characterized by a mutation rate which cannot be far away from some optimal value which is small but not zero. A similar process may be responsible for a second order selection for an optimal rate of recombination. In this case, the modifying feature is determined by the geometrical location of genes on the chromosome as well as, possibly, by a specific modifying locus (Simchen, 1967).

In a sexual population, possible recombination between the modifying and the primary genes makes quantitative analysis of second order selection very complicated to carry out. In an asexual population, however, a useful tool for such analysis is offered by the theory of multitype branching processes (with some qualitative results hopefully extended to the sexual case).

Since modifications of primary features in an asexual population can occur only through mutation, the most natural modifying feature to be studied in such a population is the intrinsic mutation rate itself. Yet, assuming a given (nonzero) mutation rate, other features affecting the spread and establishment of a new mutant in a clone may also be regarded as modifying—for example, an intrinsic tendency for migration. Furthermore, in the connotation of a biological type it is sometimes convenient to consider spatial as well as genetic factors. In this case, from the analytic viewpoint, mutation rate may be replaced by the tendency to migrate (Crow and Kimura, 1970).

Note that a crucial prerequisite for application of the theory of branching processes to second order selection is that the success of an individual in the population (measured in terms of progeny size) is independent of the size of its clone. This postulate proves quite acceptable for a large population consisting of many intermingled, small-sized clones, with relatively weak interactions between individuals of the same clone (for a more detailed argument see Mode (1971)). The situation becomes completely different when the size of a surviving clone approaches the capacity of a natural niche or habitat. However, it may be assumed that the clone-size behaves like a respectable branching process up to some critical, not too small size. In this case we know that the more conveniently calculated survival probability of the branching process is quite close to the probability of a clone to approach this critical size and, thus, to become established in some habitat (see Karlin (1966)).

While fitness selection, at any given time, is determined by ecological factors which are prevailing at the moment, it appears that the indirectly selected optimal value of a modifying feature depends on the intensity of the environ-

mental change. The intensity of a change is measured in terms of a decrease in the fitness of the conservative type. This optimal value is shown to maximize the survival probability of the entire population when facing new environmental changes of the *same intensity*. In this sense, second order selection enables the adaptation of a population to the pace of the environmental change, rather then to a static ecological situation. This sort of an indirect adaptation is carried out through modifications in modifying features, which, though not likely to increase individual fitness in any specific environment, facilitate further adaptation to repeated environmental changes of the same intensity. It is speculatively suggested that this aspect of a second order adaptation may be responsible for the accelerating pace by which pest and bacterial populations adapt themselves to newly introduced pesticides and medicines (see Section 3).

Finally, the method of second order selection as well as the concept of biological favorability in the wide, are not restricted to features which are labelled as modifying. For example, when applied to primary features, it is shown that the eventual result of second order selection virtually agrees with classic predictions of fitness selection. In this sense, fitness selection may be interpreted as a case of a clone-selection.

In Sections 2 and 3 we describe the analytic model and basic results of clone-selection in an asexual population. The mathematical analysis of an optimal mutation rate is carried out in a different paper (Eshel, 1972b). A research dealing with some quantitative aspects of second order selection in a sexual population is now in development.

2. Direct Product-Branching-Process and Second-Order-Selection in an Asexual Population

Let ω represent any inherited feature in the population, either continuous or discrete. Ω is the set of all relevant values of ω. Let $A_1, \ldots, A_n$ be the collection of all possible types in respect to another feature in the population. For convenience, we shall call A_i the primary feature of the type A_i^{ω}. This feature generally represents a directly selected trait in the population. ω is called the secondary feature and generally represents a modifier.

An individual in the population may produce offspring of either his own primary feature or another one. The vector-distribution of progeny-sizes of an individual of type A_i^{ω} is given by the multidimensional probability-generating-function $\psi_i^{\omega}(\mathbf{u})$. This function depends both on the primary feature A_i and on the secondary one ω. More specifically, we denote by $p_i^{\omega}(k_1, \ldots, k_n)$ the probability that an individual of type A_i^{ω} produces exactly k_j offspring of the type $A_j (j = 1, \ldots, n)$; then

$$\psi_i^{\omega}(\mathbf{u}) = \psi_i^{\omega}(u_1, \ldots, u_n) = \sum_{k_1, \ldots, k_n = 0}^{\infty} p_i^{\omega}(k_1, \ldots, k_n)\, u_1^{k_1} \cdots u_n^{k_n}. \qquad (2.1)$$

The expected number of all viable offspring born to an A_i^{ω} parent is given by

$$\alpha_i(\omega) = [(\partial/\partial u)\,\psi_i^{\omega}(u,\ldots,u)]_{u=1}\,. \tag{2.2}$$

Employing the classic Fisherian terminology, this is the *individual fitness* of the type A_i^{ω}. If for all $i = 1,\ldots, n$ the functions $\alpha_i(\omega)$ are constants—say, $\alpha_i(\omega) = \alpha_i$ —then no fitness-selection operates on the secondary feature ω. If, on the other hand, the $\alpha_i(\omega)$ are all monotone increasing (decreasing) with ω, then we say that individual fitness-selection operates in favor of (against) high values of ω.

We will now see that long-run survival of a secondary feature in the population may not depend on short-term forces of fitness-selection operating directly on it.

Let $(u_1,\ldots, u_n) = \mathfrak{u}(\omega)$ be the smallest positive vectorial solution of the system of equations

$$\psi_i^{\omega}(u_1,\ldots, u_n) = u_i\,; \qquad i = 1,\ldots, n. \tag{2.3}$$

As a general result of the theory of branching processes (e.g., Mode (1971)), we know that the ith component $u_i(\omega)$ of the solution represents the extinction probability of a clone beginning with a single parent of type A_i^{ω}. As a special case, if the conservative primary feature is represented by A_1, then $\chi(\omega) = 1 - u_1(\omega)$ represents the survival probability of a clone carrying the secondary feature ω. The frequency of the ω-feature within the surviving population, if it exists, will, thus, be multiplied by a coefficient proportional to the clone-survival-probability $\chi(\omega)$.

In a formal way, let μ_1 be the frequency-measure of the value ω in the initial population as distributed over the set Ω of its relevant values. The expected survival probability of a random clone starting with a single parent in the initial A_1-population is

$$E^{(1)}\chi = \int_{\Omega} \chi(\omega)\,\mu_1(d\omega). \tag{2.4}$$

We assume that this value is positive (otherwise, the whole population is bound for extinction). The frequency-measure of the secondary feature among surviving clones becomes

$$\mu_2(d\omega) = \frac{\chi(\omega)\,\mu_1(d\omega)}{E^{(1)}\chi}\,. \tag{2.5}$$

We then say that *an indirect (or second order) process of natural selection* alternates the frequency-measure of ω from μ_1 in the initial population to μ_2 in the surviving one.

DEFINITION 1. A value ω_1 of the secondary feature is said to be *favorable* over a value ω_2 if it endows a clone carrying it with a higher probability of survival, i.e., if

$$\chi(\omega_1) > \chi(\omega_2).$$

DEFINITION 2. If the clone probability $\chi(\omega)$ assumes a maximum at a point $\omega = \omega^*$, then ω^* will be called an *optimal value of the secondary parameter*.

The value $\chi(\omega^*)$ is the survival probability of an optimal clone. From the definition of the optimal value ω^*, it immediately follows that $\chi(\omega^*) \geqslant E^{(1)}\chi$ with a strict inequality unless the frequency-measure of the optimal value in the initial population is already 1. We conclude that in the long run, indirect selection always increases the frequency of the optimal value in the population. A stronger statement will be proved in the next chapter.

In the general case an optimal value ω^* of the secondary feature ω may or may not maximize the individual fitness of its carrier.

EXAMPLE 1. Let

$$\psi_i^{\omega}(\mathbf{u}) = \frac{\psi_i(\omega u_1, \ldots, \omega u_n)}{\psi_i(\omega, \ldots, \omega)},$$

where $\psi_i(\mathbf{u})$ is a probability generating function determining some law of progeny distribution, and the right side of the equation converges. Biologically, this is the simplest case where ω represents a pure fertility parameter, increasing the number of viable offspring born to its carrier by a monotone likelihood ratio (see Karlin (1968a)).

Employing (2.2), the fitness of the A_i^{ω} type is readily given by

$$\alpha_i(\omega) = \omega(d/d\omega)\, l_n \psi_i(\omega, \ldots, \omega).$$

Owing to the logarithmic convexity of generating functions, this is, not surprisingly, a monotone-increasing function of ω. Classic fitness-selection is shown to always operate in favor of high ω values. But it is also not difficult to show that the smallest positive vectorial solution of the system

$$\frac{\psi_i(\omega u_1, \ldots, \omega u_n)}{\psi_i(\omega, \ldots, \omega)} = u_i, \qquad i = 1, \ldots, n,$$

is monotone decreasing with ω. We, thus, conclude that when a contribution in fertility (or viability) does not interfere with other aspects of the process, clone selection leads to the same end result as fitness selection.

EXAMPLE 2. ω is an intrinsic rate of mutation. In this example we assume that the total number of offsprings, either viable or lethal, born to a parent of a type A_i^{ω}, depends only on its primary feature and not on its rate of mutation ω. Thus, the generating function of its total progeny size is denoted by $\Phi_i(s)$. Now, once a primary feature A_i $(i = 1, \ldots, n)$ is mutated, assume a probability $\theta_i > 0$ that it will be mutated to a lethal form, and a probability p_{ij} that it will be mutated to the nonlethal form A_j, $j = 1, 2, \ldots, n$; $\theta_i + \sum_j p_{ij} = 1$.

The multitype generating function of the nonlethal progeny born to an individual of a type A_i^{ω} is then

$$\psi_i^{\omega}(\mathbf{u}) = \Phi_i\left\{(1-\omega)\,u_i + \omega\sum_j p_{ij}u_j + \omega\theta_i\right\}. \tag{2.6}$$

The Fisherian fitness of this type is given by

$$\alpha_i(\omega) = (1-\theta_i\omega)\,\Phi_i'(1) = (1-\theta_i\omega)\,\alpha_i(0),$$

which for all $i = 1,\ldots, n$ is a decreasing function of ω. This reflects the fact that a direct fitness selection always operates toward a zero rate of mutation (see Kimura (1967)). Yet, we know that neither a population nor a clone within it can survive in a changing environment unless it is subjected to some positive rate of mutation.

In terms of our model, let us start with a conservative primary feature A_1, and assume $\alpha_1(0) \leqslant 1$. In this situation, a clone with a zero mutation rate assumes a one dimensional subcritical branching process and, thus, is bound for extinction, i.e., $\chi(0) = 0$. For a general ω, $0 \leqslant \omega \leqslant 1$, it has further been shown (Eshel, 1972b) that the clone-survival-probability $\chi(\omega)$ is a continuous function of ω and is positive only within the open interval,

$$\left(0, \max_i\left\{\frac{\alpha_i(0)-1}{\theta_i\alpha_i(0)}\right\}\right).$$

An optimal rate of mutation is, thus, obtained for a positive value within this interval.

Assume, moreover, a Poisson distribution of the progeny size, i.e., $\Phi_i(s) = e^{\alpha_i(s-1)}$. (For a validation of this postulate, see Karlin and McGregor (1964, 1968).) Let $n = 2$, $\alpha_1 \leqslant 1$ and $\alpha_2 > 1$. (Here, A_2 may represent the class of all adaptable types.) Let the value $r = 1 - \alpha_1 \geqslant 0$ measure the intensity of environmental deterioration, while $s = \alpha_2 - 1 > 0$ is the Fisherian measure of the selection coefficient in favor of the adaptable type. When these two values are small, it may be shown that clone-survival-probability virtually behaves like

$$\hat{\chi}(\omega) = \begin{cases} 2\alpha_2(1-\theta)\dfrac{\omega(s-\omega)}{r+(1-r)\omega} & 0 < \omega < s, \\ 0 & \text{otherwise,} \end{cases}$$

and

$$\omega^* \approx r^{1/2}\frac{(r+(1-r)s)^{1/2} - r^{1/2}}{1-r}.$$

This last value, as readily established, is of the order of $\min\{s, (rs)^{1/2}\}$.

For the optimal clone survival probability, we get

$$\chi(\omega^*) \approx 2\alpha_2(1 - \theta)((\omega^*)^2/r)$$

which is of the order of $(1 - \theta)(s/r) \min(s, r)$.

More precisely, it may be shown that up to a multiplication coefficient of order $(1 + 0(s))$, we get the following values of ω^* and $\chi(\omega^*)$ as functions of r and s:

	Intensity of environmental deterioration	Optimal mutation rate	Optimal clone-survival-probability
Case I	$r \ll s$	$(rs)^{1/2}$	$2(1 - \theta)s$ virtually unchanged with r
Case II	$r \approx s$	$(2^{1/2} - 1)s$	$2(2^{1/2} - 1)(1 - \theta)s$
Case III	$r \gg s$	$s/2$ virtually unchanged with r	$[(1 - \theta)s^2]/2r$

Case I represents a situation with insubstantial environmental deterioration. Optimal clone survival probability is essentially not affected; whereas, optimal mutation rate increases as a square root of the intensity of the environmental deterioration.

Case III represents a situation with relatively intensive deterioration. Optimal mutation rate is no longer affected, while a further deterioration results in a substantial increase in the extinction probability of the optimal clones and, thus, of the entire population (see Eshel (1972b)).

3. Indirect Adaptation

We now take into consideration a succession of gene substitutions caused by repeated changes of the environment. We will see that while fitness selection operates anew each time toward an adaptation of the population to a given, static, environmental condition, indirect selection operates on a longer scale of time towards an adaptation to the dynamics of this repeated process. For this purpose, the dynamics of a change will be measured in terms of the intensities of the selection forces it imposes on primary features. We already know that the survival probability of a clone during gene-substitution depends both on the selection forces operating on the substituted primary features and on the secondary feature which is carried by this clone. Thus, if throughout successive gene-substitutions the dynamics of the process are kept approximately unchanged, then the probability $\chi(\omega)$ of a clone to survive a gene-substitution stays an invariant function of its intrinsic secondary feature ω.

Let μ_n be the frequency measure of ω in the population after n gene-substitutions. Then the survival probability of a typical clone throughout the $n+1$-th gene-substitution will be

$$E^{(n)}\chi = \int_\Omega \chi(\omega)\, \mu_n(d\omega).$$

Knowing (see 2.5)

$$\mu_n(d\omega) = \frac{\chi(\omega)\, \mu_{n-1}(d\omega)}{E^{(n-1)}\chi}, \tag{3.1}$$

we readily obtain

$$E^{(n)}\chi = \frac{\int_\Omega [\chi(\omega)]^2\, \mu_{n-1}(d\omega)}{\int_\Omega \chi(\omega)\, \mu_{n-1}(d\omega)} = \frac{\mathrm{Var}^{(n-1)}\,\chi}{E^{(n-1)}\chi} + E^{(n-1)}\chi \geqslant E^{(n-1)}\chi, \tag{3.2}$$

where for all $n = 0, 1, 2, \ldots$

$$\begin{aligned} \mathrm{Var}^{(n)}\,\chi &= \int [\chi(\omega) - E^{(n)}\chi]^2\, \mu_n(d\omega) \\ &= \int_\Omega [\chi(\omega)]^2\, \mu_n(d\omega) - [E^{(n)}\chi]^2 \geqslant 0 \end{aligned} \tag{3.3}$$

is the variance in survival probabilities of clones throughout the $n+1$-th gene-substitution.

Whenever $\chi(\omega)$ assumes any variation in the initial population (i.e., whenever indirect selection is operating on the ω feature), then inequalities (3.1) and (3.2) become strict.

As a corollary, we get the following.

THE FIRST LAW OF INDIRECT SELECTION. *When type-substitutions occur successively with similar intensities of direct selection, an indirect selection of secondary features (if it occurs) always increases the expected clone-survival-probability in the population.*

Furthermore, the increase in average probability of clone survival being achieved during a single type-substitution in the primary feature is proportional to the standard deviation of clone-survival probabilities in the population.

On a longer scale of time, though not in terms of change through successive generations, this stands in virtual agreement with Fisher's fundamental law of natural selection. (For comparison, see Cavalli-Sforza and Bodmer (1971)).

Furthermore, by an iteration of (3.1), we readily get

$$\mu_n(d\omega) = \frac{[\chi(\omega)]^{n-1}\, \mu_1(d\omega)}{\prod_{k=1}^{n-1} E^{(k)}\chi}. \tag{3.4}$$

Hence, if $\mu_1(\omega^*) > 0$ (i.e., if secondary features of the optimal value are in existence in the initial population), then, since $\chi(\omega)/\chi(\omega^*) < 1$ for all non-optimal values of ω, we get

$$\frac{\mu_n(d\omega)}{\mu_n(d\omega^*)} = \left[\frac{\chi(\omega)}{\chi(\omega^*)}\right]^{n-1} \frac{\mu_1(d\omega)}{\mu_1(d\omega^*)} \to 0 \quad \text{as} \quad n \to \infty. \tag{3.5}$$

Together with (3.2), this becomes

$$E^{(n)}\chi = \int \chi(\omega)\, \mu_n(d\omega) \uparrow \chi(\omega^*) \quad \text{as} \quad n \to \infty. \tag{3.6}$$

As a corollary, we now get the following.

THE SECOND LAW OF INDIRECT SELECTION. *When type-substitutions of the primary feature occur successively with similar intensities of direct selection, an optimal value of the secondary feature tends to become fixed in the population.*

Here again, indirect selection reveals a strong similarity to the classic fitness-selection.

An example of the effect of indirect selection may be the accelerating pace by which pest populations become adapted to the use of new pesticides. Keeping in mind the theoretical possibility of a second-order adaptation of pest populations towards the dynamic process of pesticide introduction, it is suggested that possible changes in the secondary feature of pest populations subjected to repeated use of pesticides be experimentally studied. This includes sexual behavior, demographic mobility, and intrinsic rates of mutation and recombination.

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