EVOLUTION AND EXTINCTION OF TRANSPOSABLE ELEMENTS IN MENDELIAN POPULATIONS

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ABSTRACT

A model of the evolution of a transposable element family in a Mendelian host population is proposed that incorporates heritable phenotypic mutations in the elements. The temporal behavior of the numbers of mutant and wild-type elements is studied, and the expected extinction time of the transposable element family is examined. Our results indicate that, if the mutant can be transposed equally well in the presence of the wild type, then it can be expected to be found in preponderance, whereas elements, such as retroviruses, where the transposing genome and its phenotypic expression are coupled, may be characterized by a low mutant frequency.

GENETIC variation among members of a transposable element family in metazooans is common (see SPRADLING and RUBIN 1981; Jelinek and SCHMIDT 1982 for reviews). In Drosophila, P, FB and 101F elements are examples in which copies are typically structurally heterogeneous (RUBIN KIDWELL and BINGHAM 1982; BINGHAM, KIDWELL and RUBIN 1982; ENGELS 1983; TRUETT, JONES and POTTER 1981; LEVIS, COLLINS and RUBIN 1982; PARDOE and DAWID 1981; DAWID et al. 1981). The copia-like elements, in contrast, are considerably more homogeneous but still frequently show size variation due to insertions or deletions (SPRADLING and RUBIN 1981; SCHERER et al. 1982). In vertebrates the Alu and Kpn families, which may be transposable elements, are quite variable in size (DEININGER et al. 1981; ADAMS et al. 1980). The retroviruses, which are similar to copia-like elements in that their genome is more conserved in size and structure, also have insertion-deletion variation (CHATTOPADHYAY et al. 1982; KHAN, ROWE and MARTIN 1982; RAPASKE et al. 1983). Some evidence is now available to suggest that the variants in several of these families may be functionally different (SPRADLING and RUBIN 1982; O'HARE and RUBIN 1983; Weinberg 1980; KHAN, ROWE and MARTIN 1982; RAPASKE et al. 1983). Thus, the genetic variation within families of elements may be an important consideration in understanding the evolution of transposable elements and their effect on the host.

In this paper a model describing the evolution of a family of transposable elements is proposed which allows mutation to functionally distinct mutant elements. This model is a modification of the one proposed by LANGLEY,
BROOKFIELD and KAPLAN (1983). It is assumed that the host population is a finite, randomly mating Mendelian population of size N. Within the genome of each host there are presumably a large number of locations at which new copies of the element can be inserted, so that when transposition occurs (replicatively) it is to a previously unoccupied site. Transposition is considered to be copy number dependent, i.e., in hosts with few copies transposition is more likely than in hosts with many copies. Also, the population dynamics of a newly occupied site are assumed to be independent of the dynamics of all other existing sites. This assumption is reasonable if occupied sites in the population are loosely linked.

The new aspect of the model is that there are two possible types of elements at any particular site, the wild type and the mutant. Each generation the wild type can delete or mutate, whereas the mutant can only delete. Two differences between the wild type and the mutant are accounted for in the model. First, the mutant may have a different deletion rate and, second, the mutant may not be able to transpose as efficiently as the wild type.

Unlike other models describing the evolution of transposable elements (LANGLEY, BROOKFIELD and KAPLAN 1983; CHARLESWORTH and CHARLESWORTH 1983), the proposed model predicts that the element will go extinct. In this paper we study the behavior of the time until extinction and the dynamics of the process until extinction occurs.

THE MODEL

A family of transposable elements will consist of two types of elements, the wild type and the mutant. A location in the genome at which either a wild type or mutant is found in at least one of the N genomes in the population is called a site. The first assumption of the model is that the frequency process of a site has the same stochastic structure as a three-allele Wright-Fisher process with deletion and mutation, i.e., if in generation t the population frequencies of the wild type and the mutant at a particular site are \( f_t(1) \) and \( f_t(2) \), respectively, then the joint distribution of \( f_{t+1}(1) \) and \( f_{t+1}(2) \) conditioned on \( f_t(1) \) and \( f_t(2) \) is

\[
P \left( f_{t+1}(1) = \frac{j_1}{N}, f_{t+1}(2) = \frac{j_2}{N} \right) = \frac{N!}{j_1!j_2!(N-j_1-j_2)!} q_1^{j_1} q_2^{j_2} q_3^{N-j_1-j_2}
\]

where

\[
q_1 = (1 - \delta_1 - \mu)f_t(1),
q_2 = (1 - \delta_2)f_t(2) + \mu f_t(1),
\]

and

\[
q_3 = 1 - (1 - \delta_1)f_t(1) - (1 - \delta_2)f_t(2).
\]

The parameters \( \delta_1 \) and \( \delta_2 \) which may be different are the probabilities each generation that a wild type and a mutant delete, and \( \mu \) is the probability that a wild type mutates. Thus, a wild type can delete or mutate, but a mutant can only delete.
The second assumption of the model is about the transpositional mechanism for introducing new sites into the population. Since there are a large number of possible locations in the genome at which new copies can be placed, it is assumed that each new copy is inserted at a location that is currently unoccupied in the population. Two essential features are incorporated in the stochastic structure governing the numbers of new sites introduced by transposition. First, the transposition process is assumed to be copy number dependent, i.e., when there are few copies (mutant and/or wild type) in the genome, the conditions are more favorable for the creation of new copies than if there are many copies in the genome. Second, a mutant cannot transpose as efficiently as a wild type. In particular, it will be assumed that a wild type must be present in the genome for the mutant to transpose.

A general way to model this process is the following. Each generation random numbers of wild type and mutant are created in each of the $N$ host daughters. Let $\mathbf{J}(1), \ldots, \mathbf{J}(N)$ denote these random quantities, where $\mathbf{J}(i) = (J(1, i), J(2, i))$ and $J(1, i)$ and $J(2, i)$ are the numbers of wild type and mutant created in the $i$th daughter. It is assumed that the $\mathbf{J}$'s are independent, identically distributed random vectors and that their common distribution depends only on the random quantities $\{p(i, j), i, j \geq 0\}$, where $p(i, j)$ is the fraction of the parent population having $i$ wild type and $j$ mutant copies. Since the $p(i, j)$ change from generation to generation, they will be written as $p(t, i, j)$ to denote the generation. Similarly, the $\mathbf{J}$'s are written as $\mathbf{J}(t, 1), \ldots, \mathbf{J}(t, N)$. To simplify notation $\mathbf{J}_t$ will denote any of the $\mathbf{J}(\cdot)$.

The following assumptions will be made about the distribution of $\mathbf{J}_t$. The daughters of each generation are formed by randomly choosing either $N$ or $2N$ gametes, depending on whether the population is haploid or diploid. In either case the number of copies created by transposition in each daughter is assumed to have a Poisson distribution with mean $r(g + b)w(g/(g + b))$, where $g$ and $b$ denote the numbers of existing wild-type and mutant copies in the daughter. If the population is diploid, $g$ and $b$ are the sums of the numbers of wild type and mutant in the two gametes making up the zygote. The function $r$ is 0 if $g + b$ equals 0, positive if $g + b$ is positive and decreases as $g + b$ increases. It should be interpreted as the average amount of transposition that can take place each generation in a randomly chosen daughter whose genome contains only wild type. The function $w$ is a positively increasing function with the properties that $w(0) = 0$ and $w(1) = 1$. This function is a measure of how essential the presence of the wild type is for transposition to take place. One should note that, since $w(0) = 0$, no transposition occurs if $g = 0$. Either the wild type or mutant may have a selective advantage in the transpositional process. Thus, it is assumed that the probability that a new copy is a wild type is $\beta g/(\beta g + b)$, and the probability that a new copy is a mutant is $b/(\beta g + b)$, where $\beta > 0$. It follows from the assumptions that, if mutation, deletion and transposition occur simultaneously, then the numbers of wild-type and mutant copies in a randomly chosen daughter having $g$ wild-type and $b$ mutant copies are independent Poisson variables with means

$$H(g, b) = r(g + b)w(g/(g + b))(\beta g/(\beta g + b))$$
and

$$K(g, b) = r(g + b)w(g/(g + b))(b/(bg + b)).$$

The distribution \( J_t \) can be obtained by summing over all possible choices of \( g \) and \( b \). Indeed,

$$P(J_t = (j_1, j_2)) = \sum_{i_1} \sum_{i_2} d(i_1, i_2) e^{-H(i_1, i_2)} \frac{[H(i_1, i_2)]^{j_1}}{j_1!} e^{-K(i_1, i_2)} \frac{[K(i_1, i_2)]^{j_2}}{j_2!}.$$

where

$$d(i_1, i_2) = \begin{cases} E[p(i_1, i_2)] & \text{if the population is haploid} \\ \sum_{l_1+k_1=i_1} \sum_{l_2+k_2=i_2} E[p(l_1, l_2)p(k_1, k_2)] & \text{if the population is diploid} \end{cases}$$

The final assumption of the model is that the frequency process of a given site evolves in a random way independent of the dynamics of all other existing sites. Strictly speaking, this assumption requires free recombination between sites. It is conjectured that this assumption is reasonable when there is a moderate amount of recombination. Simulation results in Langley, Brookfield and Kaplan (1983) and Charlesworth and Charlesworth (1983) support this conjecture.

The description of the model is now complete except for the initial conditions. For simplicity, it is assumed that the process is started with one wild type which is randomly located in one of the \( N \) genomes.

The process that has just been described can be formulated as a countable state Markov chain (see appendix 1 in Langley, Brookfield and Kaplan 1983). Also, since no immigration is allowed, this process will go extinct with probability one; that is, the transposable element will eventually be lost from the population. Let \( \tau \) denote the time to extinction. A new element will usually either go extinct in a few generations or will establish itself in the population and then go extinct after a large number of generations. The probability that extinction occurs in a few generations can easily be estimated (see Appendix 1). The behavior of the expectation of \( \tau \), given that the element does establish itself in the population, is more complex and will be studied in the next section.

**THE EXTINCTION TIME**

It is shown in Appendix 2 that, if the population frequencies of wild type and mutant at individual sites are low, then the numbers of wild type and mutant in a randomly chosen gamete are approximately independent Poisson variables whose means are

$$\Lambda(1) = \frac{1}{N} \text{(total number of wild type in the population)}$$
and

\[ \Lambda(2) = \frac{1}{N} \] (total number of mutant in the population).

The recent data of Montgomer{}y and Langley (1983) suggest that in Drosophila melanogaster this condition holds for the three elements they examined: copia, 297 and 412. The sample distributions of the number of copies of copia and 412 in the 20 X chromosomes surveyed by Montgomer{}y and Langley are consistent with the Poisson approximation, whereas that for 297 is not.

The variables \( \Lambda(1) \) and \( \Lambda(2) \) change each generation and so they will be written as \( \Lambda_1(1) \) and \( \Lambda_1(2) \). Since the process \( \Lambda_r = (\Lambda_r(1), \Lambda_r(2)) \) is more convenient for studying the extinction time, its behavior will be considered. If the numbers of wild type and mutant in a randomly chosen daughter are taken to be independent Poisson variables, then the conditional means and variances of \( \Delta \Lambda_r(1) = \Lambda_{r+1}(1) - \Lambda_r(1) \) and \( \Delta \Lambda_r(2) = \Lambda_{r+1}(2) - \Lambda_r(2) \) can be expressed as

\[
E[\Delta \Lambda_r(1) | \Lambda_r(1), \Lambda_r(2)] = -(\delta_1 + \mu)\Lambda_r(1) + H^*(\Lambda_r(1), \Lambda_r(2)),
\]

\[
E[\Delta \Lambda_r(2) | \Lambda_r(1), \Lambda_r(2)] = -\delta_2\Lambda_r(2) + \mu\Lambda_r(1) + K^*(\Lambda_r(1), \Lambda_r(2)),
\]

\[
\sigma^2[\Delta \Lambda_r(1) | \Lambda_r(1), \Lambda_r(2)] \approx \frac{1}{N} [(1 - \delta_1 - \mu)\Lambda_r(1) + H^*(\Lambda_r(1), \Lambda_r(2))]
\]

and

\[
\sigma^2[\Delta \Lambda_r(2) | \Lambda_r(1), \Lambda_r(2)] \approx \frac{1}{N} [(1 - \delta_2)\Lambda_r(2) + \mu\Lambda_r(1) + K^*(\Lambda_r(1), \Lambda_r(2))],
\]

where

\[
H^*(\Lambda_r(1), \Lambda_r(2)) = \sum_i \sum_j e^{-\Lambda_r(1)-\Lambda_r(2)} \frac{\Lambda_r(1)}{i!} \frac{\Lambda_r(2)}{j!} H(i, j)
\]

and

\[
K^*(\Lambda_r(1), \Lambda_r(2)) = \sum_i \sum_j e^{-\Lambda_r(1)-\Lambda_r(2)} \frac{\Lambda_r(1)}{i!} \frac{\Lambda_r(2)}{j!} K(i, j).
\]

Equations (1)–(4) are consistent with the assumption that mutation deletion and transposition all occur simultaneously. If mutation and deletion occur before transposition, then \( \Lambda_r(1) \) and \( \Lambda_r(2) \) in equations (1)–(4) need to be replaced by \( \Lambda_r(1)(1 - \mu - \delta_1) \) and \( \Lambda_r(2)(1 - \delta_2) + \Lambda_r(1)\mu \), respectively. If \( \mu, \delta_1, \delta_2 \) are small, then the quantitative, as well as the qualitative, results in both cases are essentially the same.

The important observation is that for large \( N \), the conditional variances of \( \Delta \Lambda_r(1) \) and \( \Delta \Lambda_r(2) \) given in (3) and (4) are small compared to their conditional means given in (1) and (2). Markov processes with negligible conditional variances have been studied by many authors (Kurtz 1971; Norman 1975; Barbour 1974; Ludwig 1975, 1980). Their results show that for large \( N \) the
trajectories of the \( \Lambda_t \) process are with high probability very close to the solution of the following system of difference equations:

\[
\begin{align*}
    x_{k+1} - x_k &= -(\delta_1 + \mu)x_k + H^*(x_k, y_k) \\
    y_{k+1} - y_k &= -\delta_2 y_k + \mu x_k + K^*(x_k, y_k)
\end{align*}
\]

for \( k \geq 0 \)

\[
(x_0, y_0) = \left( \frac{1}{N}, 0 \right).
\]

If the system of difference equations in (5) has a globally attracting fixed point, \((x_\omega, y_\omega)\), then for all values of \( N \) the solution of this system of difference equations will converge to this point. Thus, when \( N \) is large, the expected value of \( \tau_1 \), the time that it takes the \( \Lambda_t \) process to first enter a small neighborhood of \((x_\omega, y_\omega)\), can be approximated by \( \tilde{\tau}_1 \), the time it takes for the solution of the system of difference equations in (5) to first enter this neighborhood.

The question remains how to specify the neighborhood of the fixed point. The method by which this is done uses a conditional limit theorem of T. DARDEN and T. G. KURTZ (personal communication). This result states that, for large \( N \) and large \( t \), the distribution of \( \Lambda_t(1) \), given that \( \Lambda_0(1) > 0 \), is approximately bivariate normal with mean vector \( m = (x_\omega, y_\omega) \) and covariance matrix \( Q_N \), where \( Q_N = (1/N)Q \) and \( Q \) is the solution of the matrix equation

\[
RQ + QR^T + A = 0
\]

where

\[
A = \begin{pmatrix} x_\omega & 0 \\ 0 & y_\omega \end{pmatrix},
\]

\[
R = \begin{pmatrix}
\frac{\partial F_1}{\partial x}(x_\omega, y_\omega) & \frac{\partial F_1}{\partial y}(x_\omega, y_\omega) \\
\frac{\partial F_2}{\partial x}(x_\omega, y_\omega) & \frac{\partial F_2}{\partial y}(x_\omega, y_\omega)
\end{pmatrix},
\]

\( R^T \) is the transpose of \( R \) and

\[
\begin{align*}
    F_1(x, y) &= -(\delta_1 + \mu)x + H^*(x, y) \\
    F_2(x, y) &= -\delta_2 y + \mu x + K^*(x, y).
\end{align*}
\]

It is well known that there exists a matrix \( P_N \) such that \( P_N^TQ_NP_N \) is the identity matrix and that, assuming normality, \( P_N^T(A_t - m)(A_t - m)^T \) has an exponential distribution with mean 1. We now define the neighborhood of \((x_\omega, y_\omega)\) as

\[
I_N = \{ z = (x, y) : P_N^T(z - m)(z - m)^T P_N \leq \epsilon(0.99) \}\]
where

$$\int_0^{0.99} e^{-x} dx = 0.99.$$ 

It is of interest to determine the effect of $N$ on $\hat{p}_1$. One can show by linearizing the system of equations in (5) in the neighborhood of the fixed point and the origin that $\hat{p}_1$ is approximately a linear function of $\log N$. Possible exceptions can occur when $x_\infty$ is near 0. (See discussion of examples later.)

The behavior of the $\Delta_i$ process after it enters a small neighborhood of the fixed point has also been studied (LUDWIG 1975; BARBOUR 1976; SHUSS 1980). It is possible to show that the expected value of $\tau_2$, the time until all wild type are lost from the population (the first time $\Delta_i(1) = 0$), grows exponentially with $N$. That is, there exists a constant $\gamma$, not depending on $N$, such that

$$\lim_{N \to \infty} \frac{\log E(\tau_2)}{N} = \gamma.$$  

(7)

The implication of (7) is that, when $N\gamma$ is large, it takes an enormous amount of time for all of the wild type to be lost from the population. In general it is difficult to compute $\gamma$ (LUDWIG 1975, 1980). One would expect, however, that $x_\infty$ and $\gamma$ are positively correlated so long as $x_\infty + y_\infty$ remains constant. Although we cannot prove this in general, the examples of the next section support this conjecture.

If $x_\infty$ is close to 0, then $\gamma$ may be so small that $e^{N\gamma}$ may not be large. In this case, $\tau_3$, the time until the extinction of the mutant, may be relevant. Upon extinction of the wild type, the $\Delta_i$ process is one-dimensional and can be approximated by a diffusion with drift $-\delta_2 y$ and variance $y/N$. For a diffusion with these parameters, the expected absorption time at 0 can be computed explicitly (KARLIN and TAYLOR 1981). If $y^*$ is the average number of mutant copies per genome when all wild type delete, then

$$E(\tau_3 | y^*) \approx \frac{1}{\delta_2} \left[ \int_0^{2\delta_2 N y^*} \left( \frac{1 - e^{-z}}{z} \right) dz + (e^{2\delta_2 N y^*} - 1) \int_{2\delta_2 N y^*}^{\infty} \frac{e^{-z}}{z} dz \right].$$  

(8)

It follows from equation (8) that, when $\delta_2 N y^*$ is large,

$$E(\tau_3 | y^*) \approx \frac{1}{\delta_2} \log(2\delta_2 N y^*).$$

Thus, $E(\tau_3 | y^*)$ is large if $\delta_2$ is small. It is also clear that $E(\tau_3 | y^*)$ grows like $\log N$.

The analysis just presented can be summarized in the following way. If the process does not go extinct in a few generations, then $\tau$ is the sum of three components. The first component, $\tau_1$, is the time needed for the process to enter a small neighborhood of the fixed point, $(x_\infty, y_\infty)$. The second component, $\tau_2$, is the additional time necessary for the wild type to go extinct and the final component, $\tau_3$, is the ensuing time required for the mutant to go extinct. If
If \( N \gamma \) is large, then \( \tau_2 \) is very large, and for most of this time the process is in a neighborhood of the point \((x_\infty, y_\infty)\). If, on the other hand, \( N \gamma \) is small, then the loss of all wild type from the population can occur in a reasonable number of generations and so the deletion rate of the mutant can have a substantial effect on the expected extinction time.

**EXAMPLES**

The analysis of the behavior of the extinction time requires that the system of difference equations in (5) have a globally attracting fixed point. Although we have not been able to prove that a fixed point exists for all choices of \( r, w \) and \( \beta \), we have been able to prove its existence for all \( r \) as defined before, \( \beta = 0, \beta = \infty \) and for the following two choices of \( w \):

(a) \[
    w_1(x) = \begin{cases} 
    0 & x = 0 \\
    1 & x > 0 
    \end{cases}
\]

(b) \[
    w_2(x) = x
\]

If \( \beta = 1 \), then the expected proportion of newly transposed copies that are wild type is equal to the proportion of copies in the daughter that are wild type, i.e., the wild type has no selective advantage over the mutant in the transpositional process. On the other hand, if \( \beta = \infty \), then all transposed copies are wild type. The function \( w_1 \) is appropriate when it is envisioned that one wild type generates sufficient gene product for maximal transposition of both the wild type and mutant. The function \( w_2 \) corresponds to the case in which each wild type produces a small amount of gene product and so the total level of transposition is proportional to the number of wild type in the genome. Even for these special cases we are only able to establish that the fixed point is locally stable. All of the computer results, however, support the conjecture that the fixed point is globally stable. The detailed proofs of the existence and uniqueness of the fixed point, and of its local stability for the cases cited, are given in Appendix 3.

It is of interest to examine for these cases the behavior of the fixed point and the expected extinction time as \( \delta_1, \delta_2 \) and \( \mu \) vary. To do this \( r \) must be specified. For the rest of this section it will be assumed that \( r(x) = 1/x \) if \( x > 0 \) and \( r(0) = 0 \).

The values of \( x_\infty \) and \( y_\infty \) were found by solving the following equations for appropriate choices of \( \beta, w, \delta_1, \delta_2 \) and \( \mu \):

\[
-(\delta_1 + \mu)x_\infty + E \left[ r(X + Y)w \left( \frac{X}{X + Y} \right) \frac{\beta X}{\beta X + Y} \right] = 0 \tag{9}
\]

and

\[
-\delta_2y_\infty + \mu x_\infty + E \left[ r(X + Y)w \left( \frac{X}{X + Y} \right) \frac{Y}{\beta X + Y} \right] = 0, \tag{10}
\]

where \( X \) and \( Y \) are independent Poisson variables with means \( x_\infty \) and \( y_\infty \), respectively. For \( \beta = 1 \), the solution of (9) and (10) for both \( w_1 \) and \( w_2 \) cannot
be obtained analytically, and so a computer is needed to find it. For $\beta = \infty$, some simplification occurs since the expectation in (10) disappears. Thus, $y_\infty = (\mu/\delta_2)x_\infty$. Equation (9) is still intractable. One should note that (9) is the same for the two cases: $w = w_1$, $\beta = 1$ and $w = w_2$ and $\beta = \infty$.

We now examine the behavior of the fixed point. It is convenient for this purpose to define the ratio $p_\infty = x_\infty/(x_\infty + y_\infty)$. It is shown in Appendix 3 that, if $w = w_1$, and $r(x) \sim 1/x$ as $x \to \infty$, then $x_\infty + y_\infty \sim 1/(\sqrt{\delta_1} + \mu)$. Thus, in this case the values of $x_\infty$ and $y_\infty$ can be approximated if $p_\infty$ is known. In Figure 1 $p_\infty$ is plotted as a function of log $\mu$, assuming that $\beta = 1$, $w = w_1$ and $\delta_1 = \delta_2$. The cases in which $\delta_1 = \delta_2$ are in some sense the simplest since it is assumed that the mutant differs from the wild type only in that it cannot produce the necessary gene products for transposition. For most values of $\mu$ and $\delta_1 = \delta_2$, $p_\infty$ is close to 0, and only when $\mu$ is unrealistically small can $p_\infty$ come close to 1. Thus, wild type that mutate in this fashion should be rare during most of the evolution of the element. Selective differences between the mutant and the wild type can modify this conclusion. If $\delta_1 < \delta_2$, then the wild type deletes slower than the mutant, and so $p_\infty$ is closer to 1 for larger values of $\mu$. This behavior is demonstrated in Figure 1. It is also clear from Figure 1 that, when $\delta_1 < \delta_2$, $p_\infty$ can be close to 1 for values of $\mu$ comparable to $\delta_1$ and $\delta_2$. On the other hand, if $\delta_2 < \delta_1$, then the wild type deletes faster than the mutant, and so the associated $p_\infty$ values should be small, and indeed they are. For example, if $\delta_1 = 0.001$, $\delta_2 = 0.0001$ and $\mu = 10^{-3}$, then the value of $p_\infty$ is only 0.0035.

The effect of $\beta$ on $p_\infty$ is also of interest. One would expect on intuitive grounds that increasing $\beta$ should favor the wild type during transposition and, hence, increase $p_\infty$. Unfortunately, we cannot easily compute $p_\infty$ for any finite $\beta$ other than $\beta = 1$. However, for the limiting case, $\beta = \infty$, $p_\infty = \delta_2/(\mu + \delta_2)$. It is not difficult to check that in Figure 1 the value of $p_\infty$ for $\beta = 1$ lies below the value of $p_\infty$ for $\beta = \infty$ for any choice of $\mu$, $\delta_1$ and $\delta_2$. Furthermore, it is reasonable to expect that the value of $p_\infty$ for any $\beta < 1$ lies below the value for $\beta = 1$ and that the value of $p_\infty$ for any $\beta > 1$ lies above the value for $\beta = 1$ and below the value for $\beta = \infty$.

The functional form of $w$ can also affect $p_\infty$. The function $w$ measures the dependence of overall transposition on wild-type copy number. In particular, the closer $w$ is to 1 the more advantageous it is for the mutant during transposition. Thus, one would expect smaller values of $p_\infty$ for $w_1$ than for $w_2$. Calculations not given here show this to be the case. Indeed, if $\delta_1 = \delta_2$, $\beta = 1$ and $w = w_2$, then $p_\infty$ is close to 1 for values of $\mu$ comparable to $\delta_1$.

We next consider the behavior of the expected extinction time. Since the qualitative conclusions depend primarily on the location of the fixed point and not on the specific choices of $r$, $w$ and $\beta$, we will assume for definiteness that $r(x) = 1/x$, $x > 0$, $r(0) = 0$, $w = w_1$ and $\beta = 1$. The values of $\delta_1$, $\delta_2$ and $\mu$ for the three examples studied are $(10^{-5}, 10^{-4}, 10^{-3})$, $(10^{-5}, 10^{-3}, 10^{-5})$ and $(10^{-5}, 10^{-3}, 10^{-3})$, respectively. The value of $x_\infty + y_\infty$ is 32.0 in each case, but the values of $x_\infty$ are 0.1, 2.5 and 4.8, respectively.

In Figure 2 the trajectories of the system of difference equations in (5) are plotted for the three examples. Also indicated are the asymptotic 99% confidence ellipsoids around the fixed point for populations of sizes 100, 1000 and
1.0

0.8

0.6

0.4

0.2

0.0

Figure 1.—The graph of $p_\alpha = x_\alpha/(x_\alpha + y_\alpha)$ as a function of $\log \mu$. In all cases $\beta = 1$ and $w = w_1$.

The trajectories of the three examples have essentially the same shape. They appear to have three components. The first part of the trajectory is a rapid buildup of wild type. When the total copy number is sufficiently large, transposition slows down and mutation manifests itself. Finally, as the trajectory nears the fixed point, there may or may not be a spiral effect caused by the competing forces of deletion, mutation and transposition. In Table 1 the values of $\tau_1$ (measured in generations) are given for the various examples and values of $N$. Recall that $\tau_1$ is the time until the trajectory first enters the 99% confidence ellipsoid. It is clear from Table 1 that for examples 2 and 3 $\tau_1$ is approximately a linear function of $\log N$. The nonlinear behavior of $\tau_1$ for example 1 is due to the unusual shape of the trajectory (Figure 2a).

The values of $\gamma$ for the three examples are $4.0 \times 10^{-5}$, $2.7 \times 10^{-3}$ and $3.5 \times 10^{-3}$, respectively. A sketch of how $\gamma$ is computed is given in Appendix 4. The value of $\gamma$ increases as $x_\alpha$ increases, supporting the conjecture that $\gamma$ and $x_\alpha$ are positively correlated so long as $x_\alpha + y_\alpha$ remains constant. More detailed information regarding the relation between $\gamma$ and $x_\alpha$ is given in Figure 3. Here, $\gamma$ is plotted against $x_\alpha$, assuming that $\delta_1 = \delta_2$ and $x_\alpha + y_\alpha = 32$. Calculations not given here show that the curve in Figure 3 is essentially the same even if $\delta_1$ does not equal $\delta_2$ so long as $x_\alpha + y_\alpha = 32$. On the other hand, the
Figure 2.—The trajectories of the two difference equations in (5) and the associated 99% confidence ellipsoids. For all examples $x_0 = 0.01, \beta = 1$ and $w = w_i$. For example 1, $\delta_1 = 0.00001, \delta_2 = 0.0001$ and $\mu = 0.001$; for example 2, $\delta_1 = 0.00001, \delta_2 = 0.001$ and $\mu = 0.001$; for example 3, $\delta_1 = 0.001, \delta_2 = 0.001$ and $\mu = 0.00001$. The 99% confidence ellipsoids are indicated for $N = 100$ (---), $N = 1000$ (---) and $N = 10,000$ (. . .).
TABLE 1

The values of the time, $\tilde{t}$, for the trajectories and confidence ellipsoids in Figure 2

<table>
<thead>
<tr>
<th>Example</th>
<th>$N = 100$</th>
<th>$N = 1000$</th>
<th>$N = 10000$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>44</td>
<td>110</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>63</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
<td>915</td>
<td>1450</td>
</tr>
</tbody>
</table>

![Figure 3](image)

Figure 3.—The graph of $\gamma$ as a function $x_\infty$. In both cases $x_\infty + y_\infty = 32$, $\beta = 1$ and $\delta_1 = \delta_2$. The upper curve was computed with $w = w_1$ and the lower curve with $w = w_2$.

The curve does vary if $x_\infty + y_\infty$ is changed. It appears that multiplying $x_\infty + y_\infty$ by any constant $C$ changes $\gamma$ by approximately a factor of $C^{-2}$. The functional form of $w$ can affect these conclusions. In Figure 3 the $\gamma$ values are also plotted for $w = w_2$. The curve in this case does not rise as quickly, but as before the curve is essentially the same for $\delta_1$ not equal to $\delta_2$ so long as $x_\infty + y_\infty$ remains constant. Also, multiplying $x_\infty + y_\infty$ by any constant $C$ now changes $\gamma$ by approximately a factor of $C^{-3}$.

THE SIMULATIONS

To examine the validity of the results for the expected extinction time, a simulation study was performed. The following procedure was used to obtain $\Lambda_{t+1}$ from $\Lambda_t$. First, the numbers of wild type and mutant in each of the $N$ haploid daughters are independent Poisson variables with means $\Lambda_t(1)$ and $\Lambda_t(2)$, respectively. Second, in each daughter each wild type deletes and (or) mutates with probabilities $\delta_1$ and $\mu$, respectively, and each mutant deletes with probability $\delta_2$. Finally, random numbers of new wild-type and mutant copies are created in each daughter. These numbers are independent Poisson variables with means $\Lambda_t(1)$ and $\Lambda_t(2)$, respectively, where $g$ and $b$ are the
Simulation results with sampling

<table>
<thead>
<tr>
<th>Example</th>
<th>N</th>
<th>( \hat{q} )</th>
<th>( \hat{\tau}_1 \times 10^{-2} )</th>
<th>( \hat{\tau}_2 \times 10^{-2} )</th>
<th>( \hat{\tau}_3 \times 10^{-2} )</th>
<th>( \hat{E}(\tau_y) \times 10^{-2} )</th>
<th>( \hat{y}^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>0.52</td>
<td>0.16 (0.04)</td>
<td>23 (14)</td>
<td>71 (101)</td>
<td>62 (24)</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.54</td>
<td>19 (12)</td>
<td>12 (15)</td>
<td>75 (57)</td>
<td>83 (28)</td>
<td>58.6</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.52</td>
<td>23 (12)</td>
<td>10 (8)</td>
<td>140 (77)</td>
<td>137 (31)</td>
<td>74.6</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>0.44</td>
<td>13 (8)</td>
<td>13 (21)</td>
<td>13 (18)</td>
<td>14 (4)</td>
<td>31.1</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.56</td>
<td>15 (8)</td>
<td>23 (31)</td>
<td>17 (13)</td>
<td>20 (4)</td>
<td>35.6</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.38</td>
<td>23 (13)</td>
<td>28 (34)</td>
<td>27 (14)</td>
<td>24 (2)</td>
<td>27.2</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>0.56</td>
<td>3 (2)</td>
<td>15 [9]</td>
<td>13 (12)</td>
<td>13 (3)</td>
<td>25.7</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.54</td>
<td>5 (3)</td>
<td>24 [9]</td>
<td>18 (15)</td>
<td>24 (3)</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>0.50</td>
<td>9 (5)</td>
<td>29 [9]</td>
<td>24 (20)</td>
<td>24 (3)</td>
<td>26.7</td>
</tr>
</tbody>
</table>

The numbers in parentheses are the sample standard deviations. The numbers in the brackets are the numbers of simulations that exceeded 100,000 generations before the wild type was lost from the population. In those cases \( \hat{\tau}_2 \) was not computed (see text).

* For each set of parameter values 50 replicates were performed.

The numbers of wild type and mutant in the daughter before deletion and mutation. Let \( g_i^t \) and \( b_i^t \) denote the number of wild type and mutant in the ith daughter after the processes of deletion, mutation and transposition have occurred. Then,

\[
\Delta_{t+1}(1) = \frac{1}{N} \sum_{i=1}^{N} g_i^t \quad \text{and} \quad \Delta_{t+1}(2) = \frac{1}{N} \sum_{i=1}^{N} b_i^t.
\]

It was assumed for all simulations that \( r(x) = 1/x, \ x > 0, \ r(0) = 0, \ \beta = 1 \) and \( w = w_1 \). Furthermore, the simulations were started with \( \Delta_0(1) = 1/N \) and \( \Delta_0(2) = 0 \) and were run for 100,000 generations or until extinction occurred. For each set of parameter values the simulation was repeated 50 times.

In Table 2, the results of the simulations for the three examples considered in the last section are tabulated for populations of size 25, 50, and 100. The predicted value of \( \hat{q} \), the probability that the element does not establish itself in the population is 0.497 (APPENDIX 1). The estimates of \( q \) in Table 2 are all within sampling error of this value. The estimates of \( E(\tau_1) \) in Table 2 are not very meaningful since the 99% confidence ellipsoids for \( N = 25, 50, \) and 100 are so large. The estimates of \( E(\tau_2) \) behave properly in that the estimates...
increase as $x_m$ increases. However, since $N\gamma$ is never large, the exponential character of $E(\gamma_2)$ (equation 6) predicted by the theory is not observed. The estimates of $E(\gamma_2)$ are consistent with the values obtained from (7). The simulation results also show that $y*$, the average number of mutant copies per daughter when the wild type goes extinct, can differ markedly from $y_m$ if $x_m$ is small (example 1). On the other hand, if $x_m$ is not near 0, then $y*$ is more centered around $y_m$ (examples 2 and 3). The behavior of $y*$ in example 1 is not surprising in view of the trajectory of the system of difference equations in (5) (Figure 2a). For several of the simulations of example 3, the wild type was still in the population after 100,000 generations (see Table 2). Since the simulation was stopped after 100,000 generations, the values of $\tau_2$ in these cases are not known, and so there is no way to compute $\hat{\tau}_2$.

It follows from the description of the simulation that each generation the numbers of wild type and mutant in the population after mutation and deletion, but before transposition, are independent Poisson variables with means $N\Delta_A(1)(1 - \delta_1 - \mu)$ and $N\Delta_A(1)\mu + N\Delta_A(2)(1 - \delta_2)$, respectively. Also the numbers of wild type and mutant created in the population each generation by transposition are independent Poisson variables with means $\sum_i H(g_i, b_i)$ and $\sum_i K(g_i, b_i)$, respectively. Since $H$ and $K$ are nonlinear functions, all of the $g_i$ and $b_i$ need to be simulated each generation, and so this approach is not feasible if $N$ is large. However, since the $(g_i, b_i)$ are independently identically distributed, it is reasonable to estimate $\sum_{i=1}^N H(g_i, b_i)$ and $\sum_{i=1}^N K(g_i, b_i)$ by 0 if $\sum_{i=1}^n g_i = 0$ and $NE(H(g_1, b_1))$ and $NE(K(g_1, b_1))$ if $\sum_{i=1}^n g_i > 0$. In the simulation it was more convenient to replace $\sum_{i=1}^N g_i$ by the number of wild type in the population after deletion and mutation have occurred. If $\delta_1$ and $\mu$ are small, this modification has little effect. Although these changes modify the process, the general qualitative features of the original process still remain. In Table 3 the results of the modified simulations are presented for population sizes of 100, 500, 1000, 2000 and 10,000. The results for $N = 100$ are very similar to the results in Table 2 for $N = 100$, suggesting that this pseudosampling scheme does not introduce significant error. The values of $\hat{\tau}_1$ in Table 3 for examples 1 and 2 agree quite well with the values of $\hat{\tau}_1$ in Table 1. The values of $\hat{\tau}_1$ could not be computed for example 3 since several of the simulations did not enter the 99% confidence ellipsoid before 100,000 generations. This behavior is not surprising in view of the low mutation rate for this example. The values of $\hat{\tau}_2$ for example 1 do not show exponential behavior because of the small value of $x_m$. The negative entry in the table indicates that the wild type went extinct on average 25 generations before the process entered the 99% confidence ellipsoid. The values of $\hat{\tau}_2$ for example 2 do suggest exponential behavior and, in fact, it is possible to estimate $\gamma$. Let $\hat{\tau}_2(N)$ denote the value of $\hat{\tau}_2$, when the population is of size $N$. Then (7) implies that, for $N_2 > N_1$, $\gamma(N_1, N_2) = (\log \hat{\tau}_2(N_2) - \log \hat{\tau}_2(N_1))/(N_2 - N_1)$ is an estimate of $\gamma$. For example 2 the three estimates of $\gamma$ are $\gamma(100, 500) = 0.0029$, $\gamma(100, 1000) = 0.0025$ and $\gamma(500, 1000) = 0.0022$. All of these values compare favorably with the computed values of $\gamma$, 0.0027. In example 3, for each value of $N$ there were several simulations that still had copies of the wild type in the population.
### TABLE 3

**Simulation results with pseudosampling**

<table>
<thead>
<tr>
<th>Example</th>
<th>$N$</th>
<th>$\hat{q}$</th>
<th>$\hat{r}_1$ ($\times 10^{-2}$)</th>
<th>$\hat{r}_2$ ($\times 10^{-2}$)</th>
<th>$\hat{r}_3$ ($\times 10^{-2}$)</th>
<th>$\hat{E}_{\psi}(\sigma^*)$ ($\times 10^{-2}$)</th>
<th>$\gamma^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0.54</td>
<td>22 (8)</td>
<td>15 (17)</td>
<td>164 (134)</td>
<td>137 (28)</td>
<td>(33.0)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>0.58</td>
<td>37 (11)</td>
<td>14 (8)</td>
<td>267 (117)</td>
<td>273 (21)</td>
<td>(18.8)</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>0.46</td>
<td>43 (9)</td>
<td>20 (10)</td>
<td>372 (117)</td>
<td>331 (16)</td>
<td>(12.3)</td>
</tr>
<tr>
<td></td>
<td>2,000</td>
<td>0.44</td>
<td>52 (16)</td>
<td>17 (16)</td>
<td>367 (117)</td>
<td>391 (18)</td>
<td>(12.7)</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>0.56</td>
<td>113 (11)</td>
<td>-25 (19)</td>
<td>574 (118)</td>
<td>541 (13)</td>
<td>(8.2)</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>0.46</td>
<td>23 (11)</td>
<td>33 (25)</td>
<td>26 (15)</td>
<td>25 (2)</td>
<td>(8.2)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>0.46</td>
<td>34 (10)</td>
<td>104 (56)</td>
<td>36 (16)</td>
<td>37 (2)</td>
<td>(4.6)</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>0.52</td>
<td>47 (18)</td>
<td>517 (193)</td>
<td>41 (13)</td>
<td>42 (2)</td>
<td>(4.3)</td>
</tr>
<tr>
<td></td>
<td>2,000</td>
<td>0.46</td>
<td>50 (16)</td>
<td>[19]</td>
<td>50 (18)</td>
<td>47 (2)</td>
<td>(2.8)</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>0.54</td>
<td>81 (18)</td>
<td>[23]</td>
<td>[81]</td>
<td>[18]</td>
<td>[23]</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.62</td>
<td>7 (4)</td>
<td>23 (10)</td>
<td>23 (12)</td>
<td>23 (3)</td>
<td>(7.8)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>0.40</td>
<td>[2]</td>
<td>[17]</td>
<td>41 (13)</td>
<td>38 (2)</td>
<td>(4.4)</td>
</tr>
<tr>
<td></td>
<td>1,000</td>
<td>0.54</td>
<td>[6]</td>
<td>[18]</td>
<td>32 (8)</td>
<td>40 (3)</td>
<td>(3.8)</td>
</tr>
<tr>
<td></td>
<td>2,000</td>
<td>0.46</td>
<td>[5]</td>
<td>[27]</td>
<td>[5]</td>
<td>[12]</td>
<td>[22]</td>
</tr>
</tbody>
</table>

The numbers in the parentheses are the sample standard deviations. The numbers in the brackets are the numbers of simulations that exceeded 100,000 generations before either the process entered the 99% confidence ellipsoid or the wild type was lost from the population. In these cases $\hat{r}_1$ or $\hat{r}_2$ were not computed (see text).

* For each set of parameter values 50 replicates were performed.

The wild type was lost from the population on average 25 generations before the process entered the 99% confidence ellipsoid.

This value could not be computed since the wild type was still in the population after 100,000 generations for all the simulations.

after 100,000 generations and so $\hat{r}_2$ was not computable in these cases. Another interesting feature of Table 3 is the decreasing behavior of $\gamma^*$ as $N$ increases; see examples 2 and 3. This phenomenon is predicted by the theory, and in fact, as $N$ increases $\gamma^*$ would be expected to continue to decrease (VENTZEL and FRIEDLIN 1970).
DISCUSSION

The analysis suggests that, if an element does not go extinct in the first few generations, then the average copy number per host genome of the wild type increases quickly in the early stages of the element's evolution and then decreases slowly as the average copy number of the mutant starts to grow. The average copy numbers in the population of the wild type and mutant then appear to stabilize, but ultimately the wild type disappears from the population leaving only the mutant. At this point transposition stops, and the mutant eventually goes extinct due to the forces of deletion and drift. The values around which the average copy number of the wild type and mutant stabilize effectively determine the time to extinction. For any reasonable population size, the extinction time is moderate if the average copy number of the wild type stabilizes around a value near 0 and quickly becomes enormous as this value increases.

A distinguishing feature of copia-like elements in Drosophila is that most copies are complete. In light of this observation, the behavior of the model suggests that either copia-like elements have recently invaded and are in the early stages of their evolution or copia-like elements are ancient, having long and stable evolutionary histories. The latter appears more probable since copia-like elements in D. melanogaster are found in related species and are distributed in a phylogenetic rather than an ecological or geographical pattern (MARTIN, WEIRNASZ and SCHEDL 1983; BROOKFIELD, MONTGOMERY and LANGLEY 1984). In contrast to copia-like elements, copies of P, FB and 101F elements in Drosophila are typically variant. In addition the P element is found in natural populations of D. melanogaster but is absent from older laboratory strains and strains of related species (BINGHAM, KIDWELL and RUBIN 1982; BROOKFIELD, MONTGOMERY and LANGLEY 1984). The prediction of the model consistent with these observations is that these elements have recently invaded the population and will have a short, less stable evolutionary history (KIDWELL 1979).

The mode of transposition of retroviruses and probably copia-like elements provides a plausible explanation of the high frequencies of wild type and their evolutionary stability (WEINBERG 1980; FLAVELL and ISH-HOROWICZ 1981; SCHERER et al. 1982; SHIBA and SAIGO 1983). If most transposition is via an RNA intermediate genome copy, then mutation might be expected to be greater than if transposition depended solely on DNA replication since RNA transcription is generally more error prone. However, the critical relationship between the phenotypic expression of a copy (i.e., the function of the translation products of the RNA transcript) and the actual transposing genome (the same RNA transcript) links defective mutant expression with the mutant genome. Thus, one would expect that in this case selection against defective genomes should be severe, i.e., \( \beta \gg 1 \). Indeed, the analysis of the model indicates that, if the mutant is equally well transposed in the presence of the wild type (\( \beta = 1 \)) and is not otherwise selected against (\( \delta_1 = \delta_2 \)), then the average copy number of the wild type will be low during most of the evolution of the element. Therefore, it seems likely that defective copies will be the rule in higher organisms for those elements without an RNA and/or viral inter-
mediate form (e.g., P element), since little selection can act on the individual element. Conversely, those elements that transpose via an RNA intermediate or transfect via a viral intermediate will be represented more often by functional copies.

LITERATURE CITED


LEVIS, R., COLLINS and G. M. RUBIN, 1982 FB elements are the common basis for the instability of the \( w^{\text{DZL}} \) and \( w^{\text{D}} \) Drosophila mutations. Cell 30: 551–565.


Communicating editor: W. J. EWENS

APPENDIX 1

If \( \delta_1 \) and \( \mu \) are small, then deletion and mutation play little or no role in the first few generations, and so only sampling and transposition need to be considered. Let \( Z_n \) denote the total number of copies in the adult population in generation \( n \). The distribution of \( Z_{n+1} \) conditioned on \( Z_n \) can be represented as the sum of two variables. The first component of the sum \( Y_{n+1} \) represents the number of copies in the \( n+1 \) generation resulting from sampling. It follows from the Poisson assumptions that \( Y_{n+1} \) has a Poisson distribution with mean \( Z_n \). The second variable of the sum \( W_{n+1} \) represents the number of copies created by transposition. If \( Y_{n+1}/N \) is small, then \( W_{n+1} \) is
approximately Poisson with mean \( r(1)Y_{n+1} \). Thus, the conditional generating function of \( Z_{n+1} \) can be approximated by

\[
E(s^{Z_{n+1}} \mid E_n) \approx E(s^{Z_n} e^{-Y_{n+1}(1-s)Y_n}) \approx e^{-Z_n(1-s)(1-r(1))},
\]
and so \( Z_n \) is essentially a branching process whose offspring distribution has generating function

\[
f(s) = e^{-(1-s)(1-r(1))}.
\]

It follows from standard theory (HARRIS 1963) that the probability of extinction \( q \) for the branching process is the smallest solution of the equation

\[
q = f(q) = e^{-(1-r(1)-1)(1-s)}.
\]

A straightforward calculation shows that, if \( r(1) = 1 \), then \( q = 0.497 \).

**APPENDIX 2**

Suppose in generation \( t \) there are \( I(t) \) sites in the population and for the \( i \)th site (\( 1 \leq i \leq I(t) \)) let \( g_i(t) \) and \( b_i(t) \) denote the frequencies of wild type and mutant in generation \( t \). Let \( G(t+1) \) and \( B(t+1) \) denote the numbers of wild type and mutant in a randomly chosen gamete. Then \( G(t+1) \) and \( B(t+1) \) can be represented as

\[
G(t+1) = \sum_{i=1}^{I(t)} \eta_i(t) \quad \text{and} \quad B(t+1) = \sum_{i=1}^{I(t)} \delta_i(t)
\]

where

\[
\eta_i(t) = \begin{cases} 1 & \text{if at site } i \text{ there is a wild type} \\ 0 & \text{otherwise} \end{cases}
\]

\[
\delta_i(t) = \begin{cases} 1 & \text{if at site } i \text{ there is a mutant} \\ 0 & \text{otherwise} \end{cases}
\]

Furthermore,

\[
P((\eta_i(t), \delta_i(t)) = (1, 0) \mid \mathcal{F}_t) = g_i(t)
\]

\[
P((\eta_i(t), \delta_i(t)) = (0, 1) \mid \mathcal{F}_t) = b_i(t)
\]

and

\[
P((\eta_i(t), \delta_i(t)) = (0, 0) \mid \mathcal{F}_t) = 1 - g_i(t) - b_i(t).
\]

where \( \mathcal{F}_t \) represents the history of the process up to time \( t \). If the sites are loosely linked, then the conditional joint generating function of \( G(t+1) \) and \( B(t+1) \), \( E(s^{G(t+1)} e^{B(t+1)} \mid \mathcal{F}_t) \) can be approximated by

\[
\prod_{i=1}^{I(t)} (1 - g_i(t)(1-s) - b_i(t)(1-r)).
\]

Furthermore, if for all \( i \) \( g_i(t) + b_i(t) \) is small, then

\[
\prod_{i=1}^{I(t)} (1 - g_i(t)(1-s) - b_i(t)(1-r)) \approx \exp[- (1-s) \sum_i g_i(t) - (1-r) \sum_i b_i(t)]
\]

\[
= \exp[- (1-s) \Lambda(1) - (1-r) \Lambda(2)],
\]

since \( \Lambda(1) = \sum_i g_i(t) \) and \( \Lambda(2) = \sum_i b_i(t) \). If \( N \) is large, the approximation is not unreasonable since the frequency process of wild type plus mutant at any site is stochastically bounded by a random deletion process with deletion parameter \( \min(\delta_1, \delta_2) \).
In this section we prove the existence and local stability of the fixed point for the system of difference equations in (5). We will always assume that $\beta = 1$. The case $\beta = \infty$, which is easier, is handled in the same way.

**Theorem 1:** Let $r(x)$ be a bounded, decreasing function for $x > 0$. Furthermore, let $r(0) = 0$ and $r(1) > \delta_1 + \mu$. Then for $w$ equal to either $w_1$ or $w_2$, there exist unique positive values of $x_w$ and $y_w$ such that

$$-(\delta_1 + \mu)x_w + E \left[ r(X + Y)w_1 \left( \frac{X}{X + Y} \right) \frac{X}{X + Y} \right] = 0 \quad (A1)$$

and

$$-\delta_2 y_w + \mu x_w + E \left[ r(X + Y)w_2 \left( \frac{X}{X + Y} \right) \frac{Y}{X + Y} \right] = 0 \quad (A2)$$

where $X$ and $Y$ are Poisson variables with means $x_w$ and $y_w$, respectively.

**Proof Case 1:** $w = w_1$. The key observation is that, if $X$ and $Y$ are independent Poisson variables with means $x$ and $y$, respectively, then the distribution of $X$ given $X + Y$ is binomial with parameters $X + Y$ and $x/(x + y)$. Using this observation we have

$$E \left[ r(X + Y)w_1 \left( \frac{X}{X + Y} \right) \frac{X}{X + Y} \right] = E \left[ r(X + Y)E \left[ \frac{X}{X + Y} \right] \frac{X}{X + Y} \right] = \frac{x}{x + y} E[r(X + Y)].$$

Also,

$$E \left[ r(X + Y)w_1 \left( \frac{X}{X + Y} \right) \frac{Y}{X + Y} \right] = E \left[ r(X + Y) \frac{Y}{X + Y} (1 - \chi_{X=0}) \right]$$

$$= \frac{y}{x + y} E[r(X + Y)] - e^{-y} E[r(Y)],$$

where $\chi_{X=0} = 1$ if $X = 0$ and is zero otherwise.

Let $H(x) = e^{-x} \sum_{j=0}^x r(j) x^{-1} j!$. To prove the theorem we need to show there exists unique values of $x_w$ and $y_w$ such that

$$-(\delta_1 + \mu)x_w + x_w H(x_w + y_w) = 0 \quad (A3)$$

and

$$-\delta_2 y_w + \mu x_w + y_w H(x_w + y_w) - y_w e^{-y} H(y_w) = 0. \quad (A4)$$

It is straightforward to show that $H$ is decreasing, if $r$ is decreasing. Since $H(0) = r(1) > \delta_1 + \mu$, there exists a unique value of $x_w + y_w$ such that $H(x_w + y_w) = \delta_1 + \mu$. Let $z_w = x_w + y_w$. (A4) can then be written as

$$(-\delta_2 + \delta_1)y_w + \mu z_w = y_w e^{-y} \sum_{j=0}^y r(j) \frac{y_w^{-1}}{j!}. \quad (A5)$$

It remains to show that for $z_w$ fixed, there exists a unique value of $y_w$ between 0 and $z_w$ satisfying (A5). Let $H_1$ denote the lefthand side of (A5) and $H_2$ the right. As a function of $y_w$, $H_1$ is linear with $H_1(0) = \mu z_w$ and $H_1(z_w) = (-\delta_2 + \delta_1 + \mu)z_w$. Also, $H_2$ is convex, increasing with $H_2(0) = 0$ and $H_2(z_w) = z_w H(z_w) = z_w (\delta_1 + \mu)$. Thus, there must exist a unique value of $y_w$, $0 < y_w < z_w$, such that $H_1(y_w) = H_2(y_w)$.

**Case 2:** $w = w_2$. Arguing just as in Case 1, we can show that

$$E \left[ r(X + Y)w_2 \left( \frac{X}{X + Y} \right) \frac{X}{X + Y} \right] = \frac{xy}{(x + y)^2} E \left[ r(X + Y) \left( \frac{X}{X + Y} \right) + \left( \frac{x}{x + y} \right)^2 \right] E[r(X + Y)]$$

and
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\[ E \left[ r(X + Y)w_2 \left( \frac{X}{X + Y} \right) \left( 1 - \frac{X}{X + Y} \right) \right] = \frac{x}{x + y} E[r(X + Y)] - \frac{xy}{(x + y)^2} E \left[ \frac{r(X + Y)}{X + Y} \right] + \left( \frac{x}{x + y} \right)^2 E[r(X + Y)]. \]

(A1) and (A2) can now be written as

\[-(\delta_1 + \mu)p_m + H_3(z_m)(p_m(1 - p_m)) + p_m^2 H_4(z_m) = 0 \quad (A6)\]

and

\[-\delta_2(1 - p_m) + p_m \mu + p_m H_4(z_m) - (\mu + \delta_1)p_m = 0, \quad (A7)\]

where

\[ p_m = \frac{x_m}{x_m + y_m}, \quad H_3(z_m) = \frac{E[r(X + Y)/(X + Y)]}{z_m} \quad \text{and} \quad H_4(z_m) = \frac{E[r(X + Y)]}{z_m}. \]

A rearrangement of (A6) and (A7) leads to

\[ p_m = \frac{\delta_2}{H_4(z_m) + \delta_2 - \delta_1} = G_1(z_m) \]

and

\[ p_m = 1 - \frac{\mu}{H_3(z_m) + \delta_2 - \delta_1} = G_2(z_m). \]

We need to show that there is a unique \( z_m \) such that \( 0 < G_1(z_m) = G_2(z_m) < 1 \). Since \( G_1 \) increases, \( G_2 \) decreases and \( 0 < G_1(0) < G_2(0) < 1 \), the existence and uniqueness of \( z_m \) is guaranteed regardless of the values of \( \mu, \delta_1 \) and \( \delta_2 \). This completes the proof of the theorem.

It follows from the properties of the Poisson distribution that \( H(x) \sim r(x)/x \) as \( x \to \infty \). We thus have the following corollary.

**Corollary:** Suppose \( r(x) \sim x^{-\nu} \) as \( x \to \infty \). Then, for \( w = w_1, x_m + y_m \sim [1/(\delta_1 + \mu)]^{\nu/(\nu + 1)} \).

We now turn to local stability.

**Theorem 2:** The fixed point \((x_-, y_-)\) is locally stable for both the case 1 and case 2.

**Proof:** We will only consider case 1 since case 2 is proved in a similar way. The functions \( F_1 \) and \( F_2 \) in (6) can be written as

\[ F_1(x, y) = -(\delta_1 + \mu)x + xH(x + y) \quad \text{(A8)} \]

\[ F_2(x, y) = -\delta_2 y + \mu x + yH(x + y) - ye^{-H(y)}. \]

Let

\[ M = \begin{pmatrix} \frac{\partial F_1}{\partial x} & \frac{\partial F_1}{\partial y} \\ \frac{\partial F_2}{\partial x} & \frac{\partial F_2}{\partial y} \end{pmatrix}. \]

To prove local stability it suffices to show that the real parts of the eigenvalues of the matrix \( M \) are negative at \((x_m, y_m)\). To do this it suffices to show that at \((x_m, y_m)\) the trace of \( M \) is negative and that the determinant of \( M \) is positive.

It follows from (A8) that \( H(x_m + y_m) = \mu + \delta_1 \) and \( xe^{-\nu}H(y_m) = \mu(x_m + y_m) + (\delta_1 - \delta_2)y_m \). Thus,

\[ \text{trace } M = -\frac{x_m \mu}{y_m} + (x_m + y_m)H'(x_m + y_m) - ye^{-H'(y_m)}. \]

Also,

\[ (x_m + y_m)H'(x_m + y_m) - ye^{-H'(y_m)} = e^{-(x_m + y_m)} \sum_{l=0}^\infty (x_m + y_m)^l \frac{(-1)^l}{l!} \left( \frac{r(l + 2)}{l + 2} - \frac{r(l + 1)}{l + 1} \right) < 0 \]
since \([r(l + 2)/(l + 2)] - [r(l + 1)/(l + 1)] < 0\) for all \(l > 0\). Thus, trace \(M < 0\). We next show that the determinant of \(M\) is positive. We first note that at \((x_\omega, y_\omega)\), \(\partial F_1/\partial x = \partial F_1/\partial y\). Thus, the determinant of \(M\) is equal to \((\partial F_1/\partial x)(\partial F_2/\partial y - \partial F_2/\partial x)\). Since the \(\partial F_1/\partial x < 0\), it suffices to show that \(\partial F_2/\partial y < \partial F_2/\partial x\). A straightforward calculation shows that

\[
\frac{\partial F_2}{\partial y} - \frac{\partial F_2}{\partial x} = (-\delta_2 + y_\omega H'(x_\omega + y_\omega) + H(x_\omega + y_\omega) - \varepsilon^{-\omega}H(y_\omega) - y_\omega e^{-\omega}H'(y_\omega))
\]

\[
- (\mu + y_\omega H'(x_\omega + y_\omega) + y_\omega e^{-\omega}H(y_\omega))
\]

\[
= \delta_1 - \delta_2 - y_\omega e^{-\omega}(H(y_\omega) + H'(y_\omega)) - \varepsilon^{-\omega}H(y_\omega)
\]

\[
= -\mu \left(1 + \frac{x_\omega}{y_\omega}\right) - y_\omega e^{-\omega}(H(y_\omega) + H'(y_\omega)) < 0
\]

since \(H(y_\omega) + H'(y_\omega) > 0\). This completes the proof of the result.

APPENDIX 4

The proof of the exponential behavior of \(E(\tau_2)\), which is patterned after the arguments in VENTZEL and FRIEDLIN (1970), is too complicated to present. One consequence of the proof is the following formula for \(\gamma\). Let \(\Gamma(t) = (\theta_1(t), \theta_2(t))\) denote any continuously differentiable curve from \((x_\omega, y_\omega)\) to some point on the positive \(y\) axis, and define

\[
l(\Gamma) = \int \left[ \left( \frac{d\theta_1(t)}{dt} - \frac{F_1(\theta_1(t), \theta_2(t))}{2\theta_1(t)} \right)^2 + \left( \frac{d\theta_2(t)}{dt} - \frac{F_2(\theta_1(t), \theta_2(t))}{2\theta_2(t)} \right)^2 \right] dt.
\]

\([F_1 \text{ and } F_2 \text{ are given in (6)]}\). Then \(\gamma\) equals the infimum of all possible values of \(l(\Gamma)\). To actually compute \(\gamma\), one uses a result from the calculus of variation which asserts that \(\gamma = u(0, 0)\) where \(u(x, y)\) satisfies the Hamilton-Jacobi equation

\[
\frac{1}{2} x \left( \frac{\partial u}{\partial x} \right)^2 + \frac{1}{2} y \left( \frac{\partial u}{\partial y} \right)^2 + F_1(x, y) \frac{\partial u}{\partial x} + F_2(x, y) \frac{\partial u}{\partial y} = 0.
\]

For additional details one should consult LUDWIG (1975, 1980). Due to the singular behavior of \(u(x, y)\) near the boundary, a continuation method was used to numerically obtain \(\gamma\).