THE recent technical advances of molecular biology have revealed many new and unanticipated features of both prokaryotic and eukaryotic genome structure. These include discoveries we will call "latent genes": phenotypically silent DNA sequences that are usually not expressed during the life cycle of an individual, but can be selected for and have the capacity to be activated by some genetic event, such as mutation, recombination or insertion of a transposable element. Latent genes are distinguished from other pseudogenes by this potential for expression; in fact, these genes were first detected by the altered phenotypes resulting from reactivation of the latent sequences. We can thus consider so-called "cryptic" genes (HALL, YOKOYAMA and CALHOUN 1983) and "silent" genes (BEACHAM 1987) as particular types of latent genes. Cryptic genes are defined by HALL, YOKOYAMA and CALHOUN (1983) as "... phenotypically silent DNA sequences not normally expressed during the life cycle of an individual but capable of activation as a rare event ..." whereas silent genes are defined by BEACHAM (1987) as unexpressed genes originating as duplications that do not confer a phenotype and are thus not subject to selection pressure.

Although there are many genetic systems that involve selection for specific functions or alteration of function, it is less common that selection favors the absence of function, such as with cryptic and silent genes. Two particularly well characterized cryptic genes (HALL, YOKOYAMA and CALHOUN 1983), are the ilvG sequence and the bgIBSRC operon of E. coli K-12. In the former system, ilvG is activated by naturally occurring frame-shift mutations, producing the ilvG isozyme II which confers a "mutant" valine-resistant growth phenotype. The cryptic bgI operon can be activated by mutations at a variety of sites or insertions of IS elements. The functional bgI operon expresses several genes responsible for the metabolism of β-glucosides (HALL, YOKOYAMA and CALHOUN 1983; HALL and BETTS 1987; KRICKER and HALL 1987).

There is substantial evidence that the presence or absence of pili can significantly affect the selective response of bacteria to the various physiological environments within the host. Phase variation of pilus formation in Neisseria gonorrhoeae has been shown to occur by chromosomal rearrangements and gene conversion (MEYER, MLAWER and SO 1982; SEGAL et al. 1985; HAAS and MEYER 1986; SWANSON et al. 1986; MEYER 1987). HAAS and MEYER (1986) describe six tandem pilus gene copies, most of which are silent (in the sense of BEACHAM, 1987), but have the capacity to function as "cassettes" for insertion into expressible genes. The pili promote colonization and infection of mucosal surfaces in humans by mediating adherence to epithelial cells (SWANSON et al. 1986), and it has been suggested that they might be disadvantageous in subsequent stages of infection (SEGAL et al. 1985).

LEUNK and MOON (1982) report that piliated Salmonella typhimurium are more easily trapped and cleared by the liver. Although pili are important for Proteus mirabilis to invade the kidney across the pelvic mucosa, they are detrimental in the renal parenchyma (SILVERBLATT and OFER 1978). It has also been shown that Neisseria meningitidis isolates from the throats of patients are generally more piliated than isolates from
Several problems of evolutionary interest are suggested by these examples. In particular, it is important to understand how latent genes can be maintained in a population in the face of the accumulation of (unselected) mutations, and why the functional forms of these sequences are sometimes also retained. This issue is essentially that of the evolution of non-expression, especially when the latent gene is found at high frequency. For cryptic genes, HALL, YOKOYAMA and CALHOUN (1983) proposed qualitative mechanisms which would operate to maintain the sequences. These mechanisms will preserve the cryptic gene if "under one set of conditions members of the population with the cryptic gene are more fit than those members who express the gene ... while under some alternative set of conditions those members who express the gene are at a strong selective advantage" (HALL, YOKOYAMA and CALHOUN 1983).

This selection argument was supported by a simple one-locus, three-allele population genetics model incorporating the effects of selection and mutation. The model revealed that polymorphism for cryptic genes and its functional form could be maintained even when the functional state enjoys a selective advantage over the cryptic and nonfunctional alleles. With but slight selective advantage over its functional and nonfunctional alternatives, cryptic genes can be maintained at quite high frequency. The authors also conjectured that cryptic genes could be maintained at high frequency by temporally-varying fitness that alternately favors the cryptic and functional alleles. These ideas were extended and validated by Li (1984), who analyzed the population genetics of cryptic genes in cyclically variable environments. He also predicted that geographic variation in fitnesses could contribute to the maintenance of polymorphism in these populations.

This last suggestion invites further consideration. Since the biological paradigm for latent genes is based on microorganisms, principally enteric bacteria, it seems reasonable to consider the effects of geographic heterogeneity on the evolution of latent gene systems. We propose a model for the evolution of latent genes through the interaction of migration and selection in a population composed of two subpopulations or demes; since there is substantial evidence for gene flow in microbial populations (WHITTAM, OCHMAN and SELANDER 1983; HARTL and DYKHUIZEN 1984), the structure of our model is consistent with observation. The model supposes that the functional form of the gene is favored in one environment and the latent gene in the other; gene flow occurs between the two populations. We derive conditions which will guarantee that polymorphism for all forms is maintained, and the global dynamics of the system is studied by numerical methods. Lastly, the temporal behavior of the allele frequencies is examined under conditions of interrupted gene flow.

FORMULATION OF THE MODEL

We will construct a model for the maintenance of latent genes in a haploid population partitioned into two subpopulations (demes). Consider a gene which can have three allelic forms: functional ($A_f$), latent ($A_l$), or nonfunctional ($A_n$). The frequency of these alleles in deme $j (j = 1, 2)$ at the beginning of generation $t (t = 0, 1, 2, \ldots)$ will be written as $p_{f,j}$, $p_{l,j}$, and $p_{n,j}$, respectively; unless otherwise required for clarity, we will suppress the explicit dependence of our variables on $t$. Generations are discrete and nonoverlapping, and random genetic drift will be ignored. The order of biological effects will be selection, mutation and migration as indicated in the following schematic ($\alpha = f, l, \text{or} n$):

$$\begin{align*}
\frac{p_{\alpha,j}}{p_{\alpha,j}} & \xrightarrow{\text{selection}} \frac{p_{\alpha,j}}{p_{\alpha,j}} & \xrightarrow{\text{mutation}} \frac{p_{\alpha,j}}{p_{\alpha,j}} & \xrightarrow{\text{migration}} \frac{p_{\alpha,j}}{p_{\alpha,j}}.
\end{align*}$$

To derive the recursion relations for the allele frequencies, we define the fitnesses of alleles $A_f$, $A_l$, and $A_n$ in deme $j$ as, respectively, $w_{f,j}$, $w_{l,j}$, and $w_{n,j}$. If $p_{\alpha,j}$ represents the frequency of allele $A_{\alpha}$ in deme $j$ after selection, then

$$p_{\alpha,j} = \frac{w_{\alpha,j} p_{\alpha,j}}{\bar{w}_j},$$

where

$$\bar{w}_j = \sum_{\alpha} w_{\alpha,j} p_{\alpha,j}$$

is the mean fitness of deme $j$. After selection has acted we suppose that mutation occurs, with rates defined by the following diagram:

```
A_f  u  A_l
   \downarrow v
  \mu   \downarrow
       \nu
A_n
```

Mutation can thus reversibly convert functional alleles to latent alleles, and both functional and latent alleles mutate irreversibly to the nonfunctional variant. If $p_{f,j}^{**}$ is the frequency of allele $A_n$ in deme $j$ after mutation, then

$$\begin{align*}
p_{f,j}^{**} &= u p_{f,j}^* + (1 - u - \mu) p_{f,j}^*, \\
p_{l,j}^{**} &= u p_{l,j}^* + (1 - v - \nu) p_{l,j}^*, \\
p_{n,j}^{**} &= p_{n,j}^* + \mu p_{f,j}^* + \nu p_{l,j}^*.
\end{align*}$$

Finally, we introduce the constant 2 × 2 backward
migration matrix $M$ to describe migration between the two demes,

$$M = \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix};$$

$m_{12}$ is the proportion of postmigration individuals of deme 1 that originated in deme 2, while $m_{21}$ is the proportion in deme 2 that migrated from deme 1. Nagylaki (1977) describes the conditions for which it is reasonable to assume that $M$ is constant. If adults reproduce without differences in fertility, we easily infer that

$$p'_{\alpha j} = \sum_{i=1}^{2} p_{i\alpha}^{*} m_{ji}, \quad j = 1, 2, \quad \alpha = f, l, \text{ or } d, \quad (4)$$

where the prime (‘) denotes the next generation (Nagylaki 1977). Since each row sum of $M$ equals 1 there are only two independent migration parameters, and we define them as $m_1 = m_{12}$ and $m_2 = m_{21}$, so that $m_{11} = 1 - m_1$, $m_{22} = 1 - m_2$. This notation will be employed subsequently.

Upon specification of the selection, mutation, and migration parameters, Equations 1–4 constitute a complete set of recursion relations for the allele frequencies.

We note that the various descriptions of the genetics of the model (cryptic, silent, or latent alleles) are all essentially equivalent to a three allele system with mutation as schematically depicted above. In our terminology, allele $A_i$ is latent whatever its frequency—latency is defined in relation to its capacity to regain functionality by an appropriate mutation, not by its frequency in a population. If alleles $A_i$ and $A_\alpha$ are rare in a population, it would be conventional to refer to them merely as rare mutants of allele $A_f$. On the other hand, a much more interesting situation presents itself if $A_i$ happens to be common and the functional allele rare; this is essentially the situation with cryptic genes. In this circumstance it is conceptually convenient to distinguish the latent allele from its functional counterpart, which in a sense treats latency as a trait.

**ANALYSIS**

**Protection of latent alleles:** Functional genes are unlikely to have evolved from evolutionarily activated ancestral latent genes; it is much more plausible to suppose that latent genes evolve from deactivation of their functional precursors. Consequently, a necessary precondition for latent genes to evolve to high frequency, such as observed with cryptic genes, is that they be protected from loss at the early stages of their evolution. It is therefore important to analyze the dynamics of rare latent genes and evaluate conditions for their retention in populations.

To this end, we present a local linear analysis about the fixation equilibrium to determine conditions for maintenance of the latent allele. First, observe that as long as $w_0 \neq 0$, extinction of the latent allele is possible if, and only if, the functional allele is also absent from the population. Thus, as long as mutation converts functional alleles to latent and vice versa, the latent form of the gene (as well as the functional) will be protected from extinction if the equilibrium monomorphic for the nonfunctional allele is unstable. To determine conditions for this, we choose the four variables $p_{\alpha j}(\alpha = f, l; j = 1, 2)$ as our independent allele frequencies and linearize the recursion system for small values of these frequencies.

Since the $p_{\alpha j}^{*}$ are unaffected by uniform scaling of the fitnesses by a constant, we define the selection intensities $s_j, j = 1, 2$ by

$$\frac{w_{\alpha j}}{w_{n j}} = 1 + s_j, \quad s_j \geqslant -1, \quad (5)$$

where we assume that $w_{n j} \neq 0$, i.e., the nonfunctional allele is viable in both environments. The diagonal matrix of fitness ratios $S$ will be defined by

$$S = \begin{pmatrix} 1 + s_1 & 0 \\ 0 & 1 + s_2 \end{pmatrix}.$$

We hereafter assume that the latent and nonfunctional alleles have the same fitness: $w_{f j}/w_{n j} = 1$ in each deme. This seems to be a reasonable assumption since phenotypically neither latent nor nonfunctional alleles are expressed, and is consistent with the empirical evidence (Hall, Betts and Kricker 1986). Figure 1 shows schematically the migration and selection pattern for the model. With these assumptions we readily find that

$$p_{f j} = (1 + s) p_{f j} + O(\|p\|^2), \quad (6)$$

$$p_{l j} = p_{l j} + O(\|p\|^2), \quad (7)$$

where $p = (p_{f1}, p_{f2}, p_{l1}, p_{l2})^T$ and the superscript $T$ denotes the matrix transpose. Since mutation and migration are linear we easily infer from (3), (4), (6), and (7) that

$$p' = Q p + O(\|p\|^2) \quad (8)$$

as $\|p\| \to 0$, where $Q = (q_{ij})$ is the following $4 \times 4$ matrix composed of the indicated $2 \times 2$ blocks:

$$Q = \begin{pmatrix} (1 - u - \nu)M & uMS \\ vM & (1 - u - \mu)MS \end{pmatrix}. \quad (9)$$
The conditions under which the latent and functional alleles are protected from loss are derived in the Appendix. Therein we deduce that

$$\gamma_1 \gamma_3 + \gamma_2 \gamma_4 > \gamma_4$$

(10) suffices for protection of the latent and functional alleles, where the constants $\gamma_1$ through $\gamma_4$ are defined as follows:

$$\gamma_1 = (1 - u - \mu)(1 - m_2) + \gamma_3$$
$$\gamma_2 = (1 - u - \mu)(1 - m_2) + \gamma_3$$
$$\gamma_3 = (1 - u - \mu)^2(1 + m_2 - 1)$$
$$\gamma_4 = 1 + \gamma_3 - \gamma_1 - \gamma_2$$

the approximations apply for weak mutation and migration.

The region of nonprotection is shaded in Figure 2a; Figure 2a is drawn with migration more or less symmetrical ($m_1 = m_2$). Notice that the functional and latent alleles are not protected if $s_1, s_2 < 0$, which confirms our intuition that the functional allele must have an advantage in at least one deme in order to avoid extinction. It is easily shown that the $s_1$ and $s_2$-intercepts (respectively $\gamma_4/\gamma_1$ and $\gamma_4/\gamma_2$) of the hyperbola defined by Equation 11 are positive. This implies that the functional and latent alleles are not always protected even if the functional allele is more fit in both subpopulations: if $s_1, s_2 > 0$, and $(s_1, s_2)$ lies beneath the hyperbola of Equation 10, then these alleles will not be protected. Protection therefore requires sufficiently great advantage to the functional allele, even if it has higher fitness in both demes; this minimal advantage does not have to be very great. As $u, \mu \to 0$ for fixed migration rates, we infer that $\gamma_4/\gamma_1 = (u + \mu)(1 + m_2/m_2)$ and $\gamma_4/\gamma_2 = (u + \mu)(1 + m_2/m_1)$; the “dimensions” of the region of nonprotection in the first quadrant are of the order of the mutation rate for sufficiently weak mutation.

As Figure 2b indicates for fixed mutation rates, altering the bias in the migration rates changes the shape of the region substantially: one intercept moves toward $u + \mu$ while the other moves toward infinity. Therefore, fixed, strong selection in only one deme will not guarantee protection—if selection is sufficiently weak in the other deme and migration between the demes is sufficiently asymmetrical in the appropriate direction, the latent and functional alleles can be lost. It would seem from these qualitative observations that protection will usually be guaranteed if

![Figure 2a](image)

![Figure 2b](image)
the functional allele is more fit in both demes, at least for biologically reasonable selection intensities, mutation and migration rates.

Figure 2 also reveals that selection against the functional allele in some deme can be offset by sufficiently strong selection in the other deme; this is not surprising. Similarly, if the functional allele is more fit in one of the demes, and less fit in the other, then protection can be assured if migration has a sufficiently high bias “in favor” of $A_f$ as long as this advantage is not too slight; qualitatively, it should be of larger order than the mutation rate. This is because the intersection points of the hyperbola with the lines $s_1 = -1$ and $s_2 = -1$ are, respectively, $m_2/(1 - m_2) + O(u + \mu)$ and $m_1/(1 - m_1) + O(u + \mu)$, so that reduction of the migration rate will expand the region of protection to include most of the available selection parameters. In sum, polymorphism for the three alleles can easily be maintained for a wide range of biologically meaningful parameter values.

**Numerical results:** Whereas linear analysis defines conditions for the protection of the latent and functional alleles, it fails to assert any importance of the allele in general. Furthermore, cryptic genes in particular are characterized by their relatively high frequency and local analysis is insufficient for understanding this aspect of cryptic gene evolution. A global analysis is therefore needed in order to understand the dynamics of the system when the allele frequencies are not small. Because of the aforementioned difficulty in analyzing the non-linear system, numerical simulations were employed to gain a qualitative understanding of the dynamics. We examined the polymorphic equilibrium states of the system for a wide range of migration and selection values, and also examined the transient behavior of the allele frequencies.

The system specified by Equations 1–4 (using Equation 5 to define the selection intensities) was iterated for various choices of the parameters. As a check on the accuracy of our simulations, the table of equilibrium frequencies in Hall, Yokoyama and Calhoun (1983) was exactly reproduced (except for two minor misprints in the original) in the special case of $m_1 = m_2 = 0$, i.e., two uncoupled and isolated demes. For any given choice of parameter values, iteration of the coupled system for many different initial allele-frequency conditions resulted in convergence to the same equilibrium point. Though not proven analytically, it appears as though the system either possesses a unique, globally stable polymorphic equilibrium or the non-functional allele is fixed.

According to Li (1984) for cryptic genes, reasonable “forward” mutation rates are given by $u = \mu = \nu = 10^{-5}$, while an agreeable value of the “reverse” mutation rate from the latent state to the functional would be $v = 10^{-7}$. It seems biologically sensible that the rate of mutation from latent to functional alleles should be significantly lower than the reverse rate. The selection intensities employed in the simulations were never larger than 0.01, and chosen to be consistent with those of Hall, Yokoyama and Calhoun (1983) and Li (1984). Since the literature provides little guidance vis-à-vis the migration rates, we analyzed the system under a variety of intuitively reasonable values. It was generally observed that migration rates of the order of $10^{-2}$ or higher effectively coupled the two demes into a “single” population: each deme equilibrated at essentially the same values of the allele frequencies. Decreasing the migration rate progressively decouples the subpopulations, and they eventually become independent in the limit $m_1, m_2 \rightarrow 0$.

Our prevailing interest in the simulations was to assess the qualitative behavior of the system when there is geographic heterogeneity in the direction of natural selection, i.e., when functional alleles are favored in one deme and latent alleles are favored in the other. We examined the relationships between selection and migration that would establish a significant polymorphism for the latent and functional alleles and assessed the general character of the approach to equilibrium. The results for the equilibria are summarized in the Tables 1–3. For each row of the tables, the initial conditions were chosen to be $(p_{f1}, p_{l1}, p_{n1}) = (p_{f2}, p_{l2}, p_{n2}) = (0.45, 0.45, 0.1)$ at $t = 0$; as mentioned earlier, extensive checks were performed which strongly suggest global asymptotic convergence. For the stated parameter values the equilibrium allele frequencies $\hat{p}_{fj}, \hat{p}_{lj}$ and the ratio $\hat{p}_{fj}/\hat{p}_{nj}$, $j = 1, 2$, are recorded. Tables 1–4 report the effects of changing the selection intensities with various fixed migration and mutation rates.

Selection intensities were chosen so that in the absence of migration the functional allele would be nearly fixed in the first deme and the nonfunctional allele fixed in the other. The tables clearly show that migration and selection can interact to maintain the functional and latent alleles in locales where they would otherwise be eliminated. The numerical results also indicate that polymorphism is not guaranteed—rows 5–8 of Table 1 and rows 5 and 6 of Table 2 correspond to global loss of both the functional and latent alleles. It is interesting to note that the protection condition fails for these cases, even though protection is a local result.

A comparison of Tables 1 and 2 shows that as the selective advantage enjoyed by the functional allele in deme 1 increases relative to its disadvantage in deme 2 (i.e., as $s_1$ increases relative to $-s_2$), the equilibrium representation of the functional gene generally increases in both demes, as expected. However, the responses of the latent and nonfunctional alleles to
TABLE 1
Equilibrium frequencies with biased migration

<table>
<thead>
<tr>
<th>( s_1 )</th>
<th>(-s_2)</th>
<th>( \hat{p}_{11} )</th>
<th>( \hat{p}_{12} )</th>
<th>( \hat{p}<em>{21}/\hat{p}</em>{22} )</th>
<th>( \hat{p}_{12} )</th>
<th>( \hat{p}_{22} )</th>
<th>( \hat{p}<em>{12}/\hat{p}</em>{22} )</th>
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Note: \( m_1 = 2 \times 10^{-4}, m_2 = 10^{-3} (u = \mu = \nu = 10^{-4}, v = 10^{-3}) \). In rows 5–7, the nonfunctional allele is fixed.

TABLE 2
Equilibrium frequencies with unbiased migration

<table>
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<th>( s_1 )</th>
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<th>( \hat{p}_{12} )</th>
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Note: \( m_1 = m_2 = 10^{-4}, (u = \mu = \nu = 10^{-5}, v = 10^{-3}) \). In rows 5 and 6, the nonfunctional allele is fixed.

TABLE 3
Equilibrium frequencies with biased migration

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<td>0.5212</td>
</tr>
</tbody>
</table>

Note: \( m_1 = 5 \times 10^{-5}, m_2 = 10^{-3} (u = \mu = \nu = 10^{-5}, v = 10^{-3}) \).

such changes in fitness are different. As \( s_1 \) increases relative to \(-s_2\), the frequency of the nonfunctional allele decreases in each deme, whereas the latent allele initially increases and thereafter decreases. Since \( p_{11} + p_{12} + p_{21} = 1, i = 1, 2, \) this is not surprising. We will note, though, that even as the equilibrium frequency of the latent allele decreases, the ratio of this frequency to the equilibrium frequency of the nonfunctional allele is increasing as we move down a table for fixed \( s_1 \). Thus, as the equilibrium frequency of the functional allele increases due to more favorable selective conditions, the relative frequency of the latent allele also increases as compared to the nonfunctional genotype.

Another important aspect of the model, revealed by comparing Tables 1–3, is the effect of bias in the migration rate. In Table 1, \( m_1/m_2 = 2 \), and migration is biased "toward" deme 1: more individuals arrive in deme 1 from deme 2 than arrive in deme 2 from deme 1. Table 3 reverses this situation and in Table 2 there is no bias to the migration rates. Whenever the equilibrium is polymorphic, we observe that for fixed selection coefficients \( s_1 \) and \(-s_2\) the equilibrium frequency of the functional allele generally increases in both demes as the ratio \( m_1/m_2 \) decreases. The Tables also reveal that the equilibrium frequency of the nonfunctional allele generally decreases in both demes as this ratio decreases, while the frequency of the latent allele increases in deme 2 and decreases in deme 1. We cast this behavior in the following terms: a higher rate of "invasion" of the deme where the latent and nonfunctional alleles are favored by indi-
becomes more intense (corresponding, say, to activation of the immune system acting on the pili), the attain a much higher frequency at equilibrium. If we inside the host. well over 90% for reasonable values of selection and advantage will usually increase the frequency of the nonfunctional. Table 4 shows that if the bias is high set equilibrium latent gene frequencies can reach substantial frequency (line 1), whereas now the latent and functional genes are maintained at high frequency in the favored deme if mutation rates are low. Li (1984) constructed examples involving temporal variation in selection intensities that maintain the latent allele at high frequency for long periods of time. We will demonstrate that an interruption of gene flow between two different subpopulations favoring alternative versions of the gene can accomplish the same quantitative result, and that the approach to equilibrium can entail sustained high frequency of the latent allele.

Consider the situation as presented in Figure 3. Initially the subpopulations are uncoupled (isolated), in the first of which the functional allele is favored and is at high frequency ($p_{f1} \approx 1$) and in the second

**TABLE 4**

<table>
<thead>
<tr>
<th>$s_1$</th>
<th>$-s_2$</th>
<th>$p_{f1}$</th>
<th>$p_{f2}$</th>
<th>$p_{l1}$</th>
<th>$p_{l2}$</th>
<th>$p_{l1}/p_{f1}$</th>
<th>$p_{l2}/p_{f2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>0.0100</td>
<td>0.7011</td>
<td>0.1075</td>
<td>0.5617</td>
<td>0.0670</td>
<td>0.2687</td>
<td>0.5710</td>
</tr>
<tr>
<td>0.0001</td>
<td>0.0100</td>
<td>0.7096</td>
<td>0.1074</td>
<td>0.5869</td>
<td>0.0674</td>
<td>0.2677</td>
<td>0.6027</td>
</tr>
<tr>
<td>0.0001</td>
<td>0.0010</td>
<td>0.7565</td>
<td>0.1014</td>
<td>0.7136</td>
<td>0.4268</td>
<td>0.2138</td>
<td>0.5947</td>
</tr>
<tr>
<td>0.0001</td>
<td>0.00001</td>
<td>0.7899</td>
<td>0.0951</td>
<td>0.7669</td>
<td>0.6314</td>
<td>0.1325</td>
<td>0.7367</td>
</tr>
</tbody>
</table>

*Note: $m_1 = 10^{-5}$, $m_2 = 10^{-4}$, $u = v = 10^{-5}$.*

**TABLE 5**

<table>
<thead>
<tr>
<th>$s_1$</th>
<th>$-s_2$</th>
<th>$m_1$</th>
<th>$m_2$</th>
<th>$p_{f1}$</th>
<th>$p_{f2}$</th>
<th>$p_{l1}$</th>
<th>$p_{l2}$</th>
<th>$p_{l1}/p_{f1}$</th>
<th>$p_{l2}/p_{f2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0020</td>
<td>0.0001</td>
<td>0.1477</td>
<td>0.8305</td>
<td>0.0506</td>
<td>0.9160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0010</td>
<td>0.0001</td>
<td>0.1698</td>
<td>0.8179</td>
<td>0.0528</td>
<td>0.9238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0010</td>
<td>0.0010</td>
<td>0.0005</td>
<td>0.0001</td>
<td>0.1833</td>
<td>0.8084</td>
<td>0.0541</td>
<td>0.9267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0010</td>
<td>0.0010</td>
<td>0.0005</td>
<td>0.0001</td>
<td>0.1953</td>
<td>0.7990</td>
<td>0.0552</td>
<td>0.9284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0100</td>
<td>0.0100</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0055</td>
<td>0.9105</td>
<td>0.0046</td>
<td>0.0994</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>0.0100</td>
<td>0.0100</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0140</td>
<td>0.8285</td>
<td>0.0123</td>
<td>0.2553</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

*Note: $u = 10^{-5}$, $v = 10^{-6}$, $v = 5 \times 10^{-5}$.*

viduals from a deme where functional alleles are at an advantage will usually increase the frequency of the latent allele at equilibrium, and always increases the relative frequency of the latent allele to that of the nonfunctional. Table 4 shows that if the bias is high ($m_1/m_2 = 0.1$) the latent allele can equilibrate at significantly higher frequency than with unbiased migration.

With relatively strong mutation the latent allele can attain a much higher frequency at equilibrium. If we use the silent genes of N. gonorrhoeae as an example, we take piliated $P^+$ bacteria to be the functional type, revertible nonpiliated $P^-$ as latent and non-revertible $P^-\alpha$ as the nonfunctional type in our model. We then set $u = 10^{-5}$, $v = 5 \times 10^{-5}$ (Segal et al. 1985) and $\mu = v = 10^{-6}$, and note that elimination of all the copies of the multi-gene unit is highly unlikely. Numerical simulation with these values of mutation rates reveals that equilibrium latent gene frequencies can reach well over 90% for reasonable values of selection and migration parameters. In biological terms, if the pili are strongly selected for on the epithelium (deme 1) but selection against them is much less intense within the body (deme 2; e.g., set $s_1 = 0.1$ and $-s_2 = 0.001$), low migration rates with a bias into the body can yield 99% $P^+$ on the epithelium with 20% revertible $P^-$ in the body at equilibrium. If selection in the body then becomes more intense (corresponding, say, to activation of the immune system acting on the pili), the revertible $P^-$, i.e., the latent gene, can reach over 90% inside the host.

Typical equilibria are displayed in Table 5; in the table we show only the frequencies of the functional and latent alleles, and use the mutation values suggested in Segal et al. (1985). In lines 1–4, we have used the migration and selection parameters from the third lines of Tables 1–4 along with the new mutation rates. Note that the frequency of the latent allele is in all cases much higher in response to the new mutation rates, as we intuitively expect. Lines 5 and 6 correspond to lines 7 and 8 of Table 1 but with the higher mutation values. Recall from Table 1 that the nonfunctional allele had virtually fixed in both populations, whereas now the latent and functional genes are present and have substantial frequency (line 6).

**Temporal behavior:** Latent genes can easily be maintained at high frequency in the favored deme if they are strictly more fit than the other alleles there; this is intuitively obvious. If we assume that $w_1 = w_2 > w_0$ in some deme, and $A_0$ and $A_0$ are unfavored in the other, it is possible to equilibrate the latent allele at substantial frequency ($\approx 25\%$ or so, viz. Table 4), but not at frequencies approaching fixation if mutation rates are low. Li (1984) constructed examples involving temporal variation in selection intensities that maintain the latent allele at high frequency for long periods of time. We will demonstrate that an interruption of gene flow between two different subpopulations favoring alternative versions of the gene can accomplish the same quantitative result, and that the approach to equilibrium can entail sustained high frequency of the latent allele.
the nonfunctional allele is fixed; this situation would prevail if the demes do not exchange migrants and if $w_{1,1} > w_{1,2}$, and $w_{2,2} > w_{2,1}$. If these two populations are then coupled via migration, the frequency of the latent allele will increase in the second deme within several hundred generations to a value on the order of several percent, the exact time and value depending upon the intensities of selection and migration. If the populations are reisolated ($M = I$), the frequency of the latent and nonfunctional alleles in deme 2 quickly rises nearly to 1 ($p_{1,2} + p_{2,2} \approx 1$) within a few hundred generations, whereafter $p_{1,2}$ slowly decreases towards 0, the equilibrium value without migration. We will note from the figure that the frequency of the latent allele can be quite high (>50%), and persists at or near its maximum frequency for many tens of thousands of generations, surely a biologically significant interval of time. If mutation rates are higher, such as in Figure 4, the latent allele can persist near fixation for extended periods. This is because the “time scale” for elimination of the effectively neutral latent allele by mutation is roughly $O(1/\nu)$, where $\nu = O(10^{-3} - 10^{-7})$.

Our dynamical examples make clear that examination of the equilibrium of the system alone is insufficient, though useful. There can be significant long-term transient polymorphism for latent alleles.

Let us consider for a moment the selective scenario proposed by Li (1984). In that model, functional alleles were favored for about 200 generations, followed by about 25,000 generations wherein the cryptic and nonfunctional alleles enjoyed an advantage over the functional variety. By adjusting selection intensities and the periodicity accordingly, significant frequencies of the cryptic alleles were established. In some sense, this reflects the dynamics of the system as observed in Figure 4. However, if our paradigm is the microbial environment of the mammalian gut, and if we assume a generation time of about 1 h, this model corresponds to approximately 10 days out of every 3 yr for which the functional allele would be favored. Even if the environmental cycle favoring cryptic alleles lasts for only 10,000 generations, the functional allele would have to be favored for about 1.5 weeks out of every 13 months or so. Since many small mammals live for only a year or two, this would seem to constrain the range of systems to which the model applies.

It seems reasonable to suppose that variation in the environment of the gut would not be so “asymmetric,” but would tend to be correlated with seasonal variation in the food supply, or longer term variation due to ecological changes affecting the food supply. This supposition is consistent with the observation that most of the cryptic gene systems that have actually been studied involve genes for nutrient utilization. However, it is easy to imagine geographically coexisting species with different food resource specializations (possibly with different selective environments in their respective guts), that occasionally exchange intestinal
fauna and thereby induce the dynamical responses described above. An environmental situation that comes readily to mind is that of a common watering hole: many opportunities exist for the water to be contaminated with various bacteria from diverse intestinal environments, and then transmitted to other individuals by drinking.

**DISCUSSION**

Latent genes have been characterized best in microorganisms, principally enteric bacteria. For such systems one can consider an individual, or a closely-knit group of individuals, as corresponding to a subpopulation. Higher levels of gene flow between individuals of such subpopulations would tend to maintain a relatively homogeneous genetic structure, so that these groups of individuals could be viewed as comprising a separate niche. This group could then exchange enteric fauna with other groups (perhaps of different species) by the various means that are familiar. Since genetic exchanges between demes probably occur less frequently than exchanges between individuals within a deme, these demes may be regarded as separate environments.

If our environmental paradigm is the mammalian gut, variation in fitness between groups could be due to differences in diet or physiological variation which "selects" particular forms of the gene. Dispersal of microorganisms between two habitats favoring alternative versions of the gene can then lead to polymorphism, as our analytical and numerical results demonstrate. Furthermore, depending upon the species of individuals involved, dispersal might be expected to have an asymmetric character: humans are perhaps more apt to be infected with *E. coli* from the horse than vice versa, as anyone strolling inattentively across a pasture will no doubt soon realize. As we have noted, such asymmetries can greatly enhance (or hinder) the prospects for polymorphism. We remark that the populations exchanging migrants do not have to be different species; our model would apply as well to intra-specific gene flow between populations in different selective environments. In fact, these differing selective environments could be within one individual, as the example of Neisseria demonstrates.

In many circumstances, polymorphism maintained by migration and selection offers a reasonable alternative to maintenance by temporally varying environments. Temporal fluctuations in the fitness of particular forms of the latent gene would likely be correlated with environmental variation in components of the diet, or with evolutionary modification of the physiological functions of the organism or its host. The time scale over which these evolutionary events would occur seems somewhat incompatible for many species with the scale of temporal variation previously proposed to explain the retention of latent alleles. Our model suggests that geographical structure can play an important role in the evolution of latent genes: contemporaneous species or subpopulations differing in their selective regard for latent alleles can interact to preserve polymorphism. Shifts in the distribution of allele frequencies due to environmental perturbations or changes in migration rates can be followed by prolonged periods in which the latent allele is at high frequency and the functional allele is at low frequency. Certainly a more complete picture of latent gene evolution in natural populations will acknowledge both the selective heterogeneity and gene flow to be found in geographically structured populations, as well as whatever temporal variation in fitness occurs.

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**LITERATURE CITED**


Communicating editor: W.-H. Li

APPENDIX

If migration is bidirectional (m1,m2 ≠ 0) then M is irreducible and thus Q. The Frobenius theorem will then imply that Q has a real, positive, simple eigenvalue (say, p) that is larger in modulus than all other eigenvalues of Q. Standard theory informs us that the equilibrium p = 0 will be unstable if p > 1, thereby protecting the latent and functional alleles from loss.

Before proceeding with the analysis, observe that for meaningful values of the mutation rates (0 < u, v, μ, ν < 1), loss of both the latent and functional alleles when sufficiently rare is guaranteed if s1 and s2 are both negative: since max(2, q3) < 1 if s1, s2 < 0, we must have p < 1 (GANTMACHER 1959, Vol. II). As expected, if the nonfunctional allele is favored every-

where, functional and latent alleles are lost when initially sufficiently rare. Additionally, if neutrality prevails, s1 = s2 = 0, then the functional (and hence the latent) allele will not be protected from loss when rare due to the irreversibility of mutation to the nonfunctional form. Thus, long-term maintenance of these alleles requires selection in favor of the functional allele at least one deme.

Determining the spectrum of Q for arbitrary values of the parameters is quite complicated and algebraically involved; the characteristic polynomial is of fourth degree. To simplify matters we impose the biologically reasonable assumption that u, v < 1, and neglect terms on the order of the mutation rate squared. This assumption is reasonable for the case of cryptic genes in which the mutation rates are generally < 10^-2 (HALL, YOKOYAMA and CALHOUN 1983; LI 1984). For the case of Neisseria, this assumption is somewhat less reasonable though still tenable. However, since selection is generally quite strong for the functional allele, the question of its loss is not as important as in the case of cryptic systems. We also suppose that migration does not occur at very high rates, i.e. m1 + m2 < 1, which is not a severe biological constraint, even in the case of the Neisseria.

We apply CHRISTIANSEN’s (1974) criterion to determine when (to this order) ρ > 1. For ease of expression, rewrite Q as

\[ Q = \begin{bmatrix} A & B \\ C & D \end{bmatrix} \]

where the 2 × 2 block matrices A, B, C and D are defined in Equation 9. Let (Q^n), 1 ≤ n ≤ 4 be the submatrix of Q composed of the intersection of the first n rows and columns of Q, and Q₀ the n × n identity matrix. If det[(Q^n) - Q₀] < 0 for some n = 1, 2, 3, 4 then ρ > 1 (CHRISTIANSEN 1974). For n = 1, 2, it is simple to show det[(Q^n) - Q₀] > 0. For n = 3, a cofactor expansion along the third column (or row) yields (1 - u - μ)(1 - m1)(1 + s1) det[(Q^n) - A] for det[(Q^n) - Q₀], ignoring terms of order mutation rate squared. Since det[(Q^n) - A] > 0, we immediately have that (1 - u - μ)(1 - m1)(1 + s1) < 0 assures protection. Simple algebraic manipulation leads to our first protection condition,

\[ s_1 > \frac{\gamma_2 + \gamma_3}{\gamma_1 - \gamma_3} \quad (A1) \]

For n = 4, notice that [I^2 - (1 - u - μ)M] and [(1 - u - μ)M] (that is I^2 - A) commute; thus from GANTMACHER (1959, Vol. II, p. 46) we infer that det[(Q^n) - A] = det[(Q^n) - A] = det[(Q^n) - A] = det[(Q^n) - A] = det[(Q^n) - A]. Setting det[(Q^n) - (1 - μ)M] < 0 yields our second sufficient condition for protection, namely

\[ \gamma_1 s_1 + \gamma_2 s_2 + \gamma_3 s_1 s_2 > \gamma_4, \quad s_1, s_2 ≥ 1. \quad (A2) \]

Algebraic manipulations reveal that condition (A1) is more stringent than (A2), so that satisfying (A2) suffices for protection, as claimed in Equation 10.

Observe that a protected polymorphism always exists if either

\[ s_2 > \frac{\gamma_2 + \gamma_3}{\gamma_2 - \gamma_3} \quad or \quad s_1 > \frac{\gamma_4 + \gamma_3}{\gamma_1 - \gamma_3} \]

otherwise, we find that

\[ s_1 > \frac{\gamma_2 - \gamma_3 s_2}{\gamma_2 + \gamma_3 s_2} \]

suffices to ensure protection of the latent and functional alleles. If selection is sufficiently weak in both demes, then for fixed selection intensity s_2, mutation and migration rates, this last inequality gives the minimum value of s_1 sufficient to guarantee polymorphism.
If the protection condition is linearized in \( s_1 \) and \( s_2 \) (and the mutation rates) we obtain the sufficient condition

\[
\frac{m_2}{m_1 + m_2} s_1 + \frac{m_1}{m_1 + m_2} s_2 > \mu + \mu
\]  

(A3)

for polymorphism, provided migration is not too weak compared to selection: \( m_1 + m_2 \gg s_1 + s_2 \). Thus, the functional allele (and hence the cryptic allele) will be maintained in the population if the average fitness in the two demes, when weighted by the relative migration rate, exceeds the rate of mutation of \( A_f \) to other alleles. We can interpret the weighted average of Equation A3 as the effective selective advantage of the functional allele in the population.