Diffusion model for genotype-dependent migration

(population genetics/evolution/geographical variation/polymorphism/habitat choice)

THOMAS NAGYLAKI AND MICHAEL MOODY†

Department of Biophysics and Theoretical Biology, The University of Chicago, 920 East 58th Street, Chicago, Illinois 60637

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ABSTRACT A diffusion model for the joint action of genotype-dependent migration and genotype-independent population regulation is derived and investigated. The diploid, monoecious population occupies a finite chain of equally spaced colonies; generations are discrete and nonoverlapping; mating is random in each colony. A boundary-value problem is deduced for the gene frequencies at a multiallelic locus in the absence of mutation, selection, and random drift. This problem is studied for two alleles and constant and uniform population density and drift and diffusion coefficients. All equilibria are shown to be monotone, and explicit conditions for a protected polymorphism are established. Two examples of asymptotically stable clines are presented. It is demonstrated that genotype dependence of the mean displacements is necessary to produce or maintain spatial differentiation of gene frequencies.

It has been thoroughly demonstrated that the simultaneous action of genotype-independent migration and location-dependent selection can create and preserve stable, stationary, deterministic patterns of geographical differentiation. (The literature is reviewed in ref. 1; see also refs. 2 and 3.) Here we shall show that genotype-dependent migration and genotype-independent population regulation together can have qualitatively similar evolutionary consequences.

Edwards (4) and Parsons (5) studied special cases of genotype-dependent dispersion with two niches. Moody (6) formulated the recursion relations for a general migration pattern and arbitrary population subdivision. He obtained sufficient conditions for the maintenance of genetic variability and examined analytically and numerically several particular schemes of migration and subdivision. His examples of the global loss of an allele and stable polymorphisms with local differentiation of gene frequencies are especially significant. Consult ref. 6 for details and discussion.

In *Section 1* we shall derive the diffusion approximation for the gene frequencies at a multiallelic locus under genotype-dependent migration. The remainder of the paper is devoted to the analysis of the diallelic case. In *Section 2* we shall prove that the solution of our boundary-value problem is biologically acceptable and all equilibria are monotone. We shall also obtain explicit conditions, depending only on the expected displacements, for the protection of rare alleles. In *Section 3* we shall demonstrate that the production or maintenance of geographical differentiation of gene frequencies requires genotype dependence of the average displacements. We shall present two examples of asymptotically stable clines in the last section.

1. Formulation

The diploid, monoecious population occupies $N + 1$ equally spaced colonies in a line. Generations are discrete and nonoverlapping, and mating is random in each colony. The number of zygotes in deme i ($i = 0, 1, \dots, N$) in generation t ($t =$

$0, 1, \dots$), $n_i(t)$, is determined by genotype-independent population regulation. We consider a single locus with alleles A_j and denote the frequency of A_j in zygotes in colony i by $p_{i,j}$. Let $\tilde{m}_{i,j,kl}(t)$ designate the probability that an $A_k A_l$ individual migrates from niche i to niche j in generation t . We neglect mutation, selection, and random drift. Following the numbers (not frequencies) of migrating individuals with various genotypes and noting that regulation and reproduction do not alter the allelic frequencies immediately reveals that (6)

$$p_{i,j}(t+1) = \frac{\sum_{kl} n_k p_{k,j} p_{k,l} \tilde{m}_{ki,jl}}{\sum_{kl} n_k p_{k,n} p_{k,l} \tilde{m}_{ki,nl}}, \quad [1]$$

in which we have suppressed the argument t on the right-hand side.

We assume that the number of colonies is large ($N \rightarrow \infty$), the separation ϵ of adjacent colonies is small ($\epsilon \rightarrow 0$), and seek to approximate [1]. Let one generation correspond to δ units of time and posit that $\delta \rightarrow 0$ as $\epsilon \rightarrow 0$, with ϵ^2/δ tending to a positive constant. In terms of our new space and time variables $x = i\epsilon$ and $\tau = t\delta$, the gene frequencies read $u_j(x, \tau) = p_{i,j}(t)$. We suppose that the habitat length $L = N\epsilon$ is fixed and the population density $\rho(x, \tau)$ is proportional to $n_i(t)$ as $\epsilon \rightarrow 0$.

We confine ourselves to nearest-neighbor migration. By dint of the local nature of the diffusion approximation, we expect the limiting boundary-value problem to be unaffected by this restriction. Define

$$a_{i,jk}(t) = \tilde{m}_{i,i+1,jk}(t), \quad 0 \leq i \leq N-1, \quad [2a]$$

$$b_{i,jk}(t) = \tilde{m}_{i,i-1,jk}(t), \quad 1 \leq i \leq N, \quad [2b]$$

and assume that as $\epsilon \rightarrow 0$

$$\epsilon \delta^{-1} [a_{i,jk}(t) - b_{i,jk}(t)] = M_{jk}(x, \tau) + o(\epsilon), \quad 0 \leq i \leq N, \quad [2c]$$

$$\epsilon^2 \delta^{-1} [a_{i,jk}(t) + b_{i,jk}(t)] = V_{jk}(x, \tau) + o(\epsilon^2), \quad 0 \leq i \leq N. \quad [2d]$$

We choose $b_{0,jk}$ and $a_{N,jk}$ so that [2c] and [2d] hold with smooth drift and diffusion coefficients, M_{jk} and V_{jk} , for the migration of $A_j A_k$. Thus, migration must be slow in the sense that the mean-square displacements per generation, δV_{jk} , are of order ϵ^2 . The mean displacements per generation, δM_{jk} , are measures of the amount of asymmetry in dispersion.

Expanding [1] for $0 < i < N$ as $\epsilon \rightarrow 0$ in terms of our new variables and substituting [2] leads to the partial differential equation [3a]. Keeping in mind that no individuals leave the population ($\tilde{m}_{0,-1,jk} = \tilde{m}_{N,N+1,jk} = 0$) and requiring finiteness of $\partial u_j / \partial \tau$ at the boundaries leads for $i = 0, N$ to the

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† Present address: Department of Genetics, The University of Wisconsin, Madison, WI 53706.

boundary conditions [3b]. Thus, we find the boundary-value problem

$$\rho(u_i)_\tau = - \sum_j (J_{ij})_x + u_i \sum_{jk} (J_{jk})_x, \quad \tau > 0, \quad 0 < x < L, \quad [3a]$$

$$\sum_j J_{ij} - u_i \sum_{jk} J_{jk} = 0, \quad \tau > 0, \quad x = 0, L, \quad [3b]$$

where the flux of $A_i A_j$ individuals is given by

$$J_{ij} = M_{ij} \rho u_i u_j - \frac{1}{2} (V_{ij} \rho u_i u_j)_x, \quad [3c]$$

and subscripts with respect to spatial and temporal variables always signify partial differentiation. We suppose that all partial derivatives in [3] are continuous, and the initial allelic frequencies $u_i(x, 0)$ have a continuous derivative in x and satisfy [3b].

Without genotype dependence, [3a] agrees with previous work (7). Consult Fleming and Su (8) for a somewhat similar treatment of boundary conditions for a different migration problem.

We specialize [3] to homogeneous migration, uniform population density, and two alleles. Then $u(x, \tau) = u_1(x, \tau)$ satisfies

$$u_\tau = \frac{1}{2} f_V(u) u_{xx} - f_M(u) u_x - g_V(u) u_x^2, \quad \tau > 0, \quad 0 < x < L, \quad [4a]$$

$$f_V(u) u_x = 2h_M(u), \quad \tau > 0, \quad x = 0, L, \quad [4b]$$

$$f_V(u) = V_{12} + 2(V_{11} - 2V_{12} + V_{22})u(1 - u), \quad [4c]$$

$$g_V(u) = V_{12} - V_{11} + (V_{11} - 2V_{12} + V_{22})u, \quad [4d]$$

$$h_M(u) = u(1 - u)[M_{12} - M_{22} + (M_{11} - 2M_{12} + M_{22})u]; \quad [4e]$$

f_M is obtained by replacing V_{ij} by M_{ij} in f_V . We shall investigate [4] for constant M_{ij} and V_{ij} . We posit throughout that $V_{12} > 0$ and $V_{11} + V_{22} > 0$ (i.e., the heterozygote and at least one homozygote must disperse with positive probability). Then $f_V(u) > 0$ for $0 \leq u \leq 1$, and hence the nonlinear parabolic partial differential equation is nonsingular.

2. General properties

2.1. Acceptability. Our first task is to demonstrate that the model [4] is biologically sensible: $0 \leq u(x, 0) \leq 1$ should imply $0 \leq u(x, \tau) \leq 1$ for all $\tau \geq 0$. To prove this, we shall be compelled to suppose that $u_x(x, \tau)$ is uniformly bounded, an assumption that ought to follow from [4].

Introduce the continuous functions

$$F_V(u) = \begin{cases} f_V(0), & u < 0, \\ f_V(u), & 0 \leq u \leq 1, \\ f_V(1), & u > 1, \end{cases} \quad [5a]$$

$$H_M(u) = \begin{cases} h_M(u), & 0 \leq u \leq 1, \\ 0, & \text{otherwise,} \end{cases} \quad [5b]$$

and define F_M and G_V in terms of f_M and g_V , respectively, as in [5a]. We consider $u(x, \tau)$ as known and examine the uniformly parabolic problem

$$v_\tau = \frac{1}{2} F_V(u) v_{xx} - [F_M(u) + G_V(u) u_x] v_x, \quad \tau > 0, \quad 0 < x < L, \quad [6a]$$

$$F_V(u) v_x = 2H_M(v), \quad \tau > 0, \quad x = 0, L \quad [6b]$$

for $v(x, \tau)$. In view of [5] and our assumption on u_x , the coefficients in the linear equation [6a] are uniformly bounded and F_V is uniformly bounded above zero. Furthermore, [4], [5], and [6] inform us that u satisfies [6] as long as $0 \leq u \leq 1$. Therefore, it suffices to show that $0 \leq v(x, 0) \leq 1$ implies $0 \leq v(x, \tau) \leq 1$.

Consider [6] for $0 \leq x \leq L$ and $0 \leq \tau \leq \tau_1$ for some fixed, arbitrary τ_1 . According to the maximum principle for linear parabolic equations (ref. 9, p. 168), the maximum of $v(x, \tau)$ must occur on $\tau = 0$, $x = 0$, or $x = L$. By hypothesis, $v(x, 0) \leq 1$. If the maximum value of v on $x = 0$ or $x = L$ exceeds one, [5b] and [6b] tell us that $v_x = 0$ at the maximum, contradicting the positivity of the outward derivative at a maximum (ref. 9, p. 170). We conclude that $v \leq 1$. The same argument applied to $-v$ establishes that $v \geq 0$. Therefore, $0 \leq v(x, \tau) \leq 1$ for $\tau \geq 0$.

2.2. Protection of Rare Alleles. We turn to the investigation of the local stability of the trivial equilibria, $u = 0$ and $u = 1$. The behavior near $u = 0$ is governed by the linearization of [4]:

$$u_\tau = \frac{1}{2} V_{12} u_{xx} - M_{12} u_x, \quad \tau > 0, \quad 0 < x < L, \quad [7a]$$

$$V_{12} u_x = 2(M_{12} - M_{22})u, \quad \tau > 0, \quad x = 0, L. \quad [7b]$$

We separate the cases $M_{12} \neq 0$ and $M_{12} = 0$.

(i) $M_{12} \neq 0$: By appropriate choice of the x -direction we take $M_{12} > 0$, and introduce the constants $k = 2M_{12}/V_{12} > 0$, $l = kL$, and $\gamma = (M_{12} - M_{22})/M_{12}$. In terms of the new variables $y = kx$, $T = kM_{12}\tau$, and $w(y, T) = u(x, \tau)$, [7] becomes

$$w_T = w_{yy} - w_y, \quad T > 0, \quad 0 < y < l, \quad [8a]$$

$$w_y = \gamma w, \quad T > 0, \quad y = 0, l. \quad [8b]$$

Substituting $w(y, T) = \phi(y) \exp(-\lambda T)$ into [8] yields the eigenvalue problem

$$\phi'' - \phi' + \lambda \phi = 0, \quad 0 < y < l, \quad [9a]$$

$$\phi'(0) = \gamma \phi(0), \quad \phi'(l) = \gamma \phi(l), \quad [9b]$$

the primes indicating differentiation. The solution of [9a] reads

$$\phi(y) = e^{y/2} (A e^{\mu y/2} + B e^{-\mu y/2}), \quad [10a]$$

$$\mu = (1 - 4\lambda)^{1/2}, \quad \lambda = \frac{1}{4} (1 - \mu^2). \quad [10b]$$

Inserting [10a] into [9b] and requiring a nonzero solution determines the principal root μ as $\mu = |2\gamma - 1|$ or $\mu = 2\pi j i / l$, $j = 0, 1, 2, \dots$, $i = \sqrt{-1}$. By dint of [10b], only the first root, corresponding to $\lambda = \gamma(1 - \gamma)$, can yield $\lambda \leq 0$. Hence, $u = 0$ is asymptotically stable ($\lambda > 0$) if $0 < \gamma < 1$ (i.e., $0 < M_{22} < M_{12}$) and is unstable ($\lambda < 0$) if $\gamma < 0$ or $\gamma > 1$ (i.e., $M_{22} < 0$ or $M_{22} > M_{12}$).

Thus, $u = 0$ is asymptotically stable if $A_1 A_2$ and $A_2 A_2$ have mean displacements in the same direction, that of the former exceeding that of the latter in absolute value. It is unstable if they have mean displacements in opposite directions. Instability also occurs if they have mean displacements in the same direction, that of the latter exceeding that of the former in modulus. Observe that (at least if $M_{22} \neq 0$ and $M_{22} \neq M_{12}$) the stability of $u = 0$ is independent of the diffusion coefficients.

If $u = 0$ is asymptotically stable and A_1 is initially sufficiently rare, A_1 will be ultimately lost. This occurs solely due to the interplay of genotype-dependent migration and genotype-independent population regulation, neither of which alone can change the gene frequencies in the entire population.

Since [9] is a Sturm–Liouville problem, the leading eigenfunction may be chosen as (strictly) positive, and all others have at least one zero (ref. 10, p. 212). We have just seen that here only the leading eigenvalue can lead to instability. But asymptotically a single eigenfunction must dominate (ref. 10, p. 212), and by the proof in Section 2.1, $u(x, \tau) \geq 0$. We infer that in case of instability A_1 is preserved for all initial configurations $u(x, 0)$.

By symmetry, $u = 1$ is asymptotically stable with $M_{12} > 0$ if $0 < M_{11} < M_{12}$ and is unstable if $M_{11} < 0$ or $M_{11} > M_{12}$.

We expect at least one unstable polymorphic equilibrium if both fixation states are asymptotically stable. If $u = 0$ and $u = 1$ are both unstable, there is a protected polymorphism (ref. 11, p. 68), and at least one asymptotically stable polymorphic equilibrium is likely to exist. If one fixation state is stable and the other unstable, global loss of an allele may occur.

(ii) $M_{12} = 0$: Set $z = x/L$, $T = V_{12}\tau/(2L^2)$, and $c = -2M_{22}L/V_{12}$ to obtain a simple boundary-value problem from [7]. By the method applied to [8], we see easily that the eigenvalues are $\lambda = -c^2$ and $\lambda = j^2\pi^2$, $j = 0, 1, 2, \dots$. Consequently, $c \neq 0$ (i.e., $M_{22} \neq 0$) guarantees instability of $u = 0$. This conclusion is hardly surprising: with $M_{22} \neq 0$, $M_{12} \rightarrow 0$ in case (i) means $\gamma \rightarrow \infty$ or $\gamma \rightarrow -\infty$, and we had found instability for $\gamma < 0$ and $\gamma > 1$.

Obviously, $u = 1$ is unstable if $M_{11} \neq 0$.

2.3. Equilibria. We consider the possible nontrivial equilibria $\hat{u}(x)$. By virtue of [4], these satisfy

$$\frac{1}{2}f_V(\hat{u})\hat{u}'' - f_M(\hat{u})\hat{u}' - g_V(\hat{u})(\hat{u}')^2 = 0, \quad 0 < x < L, \quad [11a]$$

$$f_V(\hat{u})\hat{u}' = 2h_M(\hat{u}), \quad x = 0, L. \quad [11b]$$

We assume that the drift coefficients are not all the same, postponing the case $M_{ij} = M$ until Section 3.

We prove first that all equilibria are monotone. Suppose there exists x_0 , $0 \leq x_0 \leq L$, such that $\hat{u}'(x_0) = 0$. Then $\hat{u}(x_0)$ is the unique solution of the spatial initial-value problem [11a] on $0 \leq x \leq L$ with $\hat{u}(x) = \hat{u}(x_0)$ and $\hat{u}'(x) = 0$ at $x = x_0$. But $\hat{u}(x_0)$ cannot satisfy [11b] because [4e] shows that with genotype-dependent mean displacements $h_M(u)$ has at most one zero for $0 < u < 1$. We conclude that $\hat{u}'(x) \neq 0$ for $0 \leq x \leq L$.

The monotonicity of the polymorphic equilibria enables us to change uniquely on $0 \leq x \leq L$ independent and dependent variables in [11] from x and $\hat{u}(x)$ to $\hat{u}$ and $U(\hat{u}) = \hat{u}'(x)$, respectively. Defining $\alpha = \hat{u}(0)$, $\beta = \hat{u}(L)$, and dividing [11a] by $U(\hat{u}) \neq 0$ leads to

$$\frac{1}{2}f_V(\hat{u})U' - f_M(\hat{u}) - g_V(\hat{u})U = 0, \quad [12a]$$

$$f_V(\hat{u})U = 2h_M(\hat{u}), \quad \hat{u} = \alpha, \beta, \quad [12b]$$

where [12a] holds for $\min(\alpha, \beta) < \hat{u} < \max(\alpha, \beta)$. Since $\hat{u}'(x) \neq 0$ for $0 \leq x \leq L$, therefore $\alpha \neq \beta$. The solution of the linear, first-order equation [12a] satisfying [12b] at $\hat{u} = \alpha$ reads

$$U(\hat{u}) = \frac{2}{\psi(\hat{u})} \left[\frac{h_M(\alpha)}{f_V(\alpha)} + \int_{\alpha}^{\hat{u}} \frac{f_M(u)}{f_V(u)} \psi(u) du \right], \quad [13a]$$

where

$$\psi(\hat{u}) = \exp \left[-2 \int_{\alpha}^{\hat{u}} \frac{g_V(u)}{f_V(u)} du \right]. \quad [13b]$$

Then $\hat{u}(x)$ is implicitly given by

$$x = \int_{\alpha}^{\hat{u}} \frac{du}{U(u)}. \quad [13c]$$

The unknowns α and β are determined by [12b] at $\hat{u} = \beta$ and the length of the spatial interval:

$$f_V(\beta)U(\beta) = 2h_M(\beta), \quad [14a]$$

$$\hat{u}(L) = \beta, \quad [14b]$$

in which we always substitute from [13a] and [13c] for U and $\hat{u}$.

By monotonicity, each solution (α, β) of [14] such that $0 < \alpha, \beta < 1$ determines an acceptable equilibrium—i.e., one with $0 < \hat{u}(x) < 1$. There are no other biologically meaningful polymorphic equilibria.

We shall apply the above results to two examples in Section 4.

3. Genotype-independent mean displacements

The analyses of Sections 2.2 and 2.3 do not apply if all the drift coefficients are the same. We shall demonstrate in this section that if only the diffusion coefficients are genotype dependent, then the population evolves qualitatively as it would in the total absence of genotype dependence.

With $M_{ij} = M$, [4] reduces to

$$u_{\tau} = \frac{1}{2}f_V(u)u_{xx} - Mu_x - g_V(u)u_x^2,$$

$$\tau > 0, \quad 0 < x < L, \quad [15a]$$

$$u_x = 0, \quad \tau > 0, \quad x = 0, L. \quad [15b]$$

3.1. Equilibria. It is evident that all constants are equilibria of [15]. In fact, there are no other equilibria. For if $\hat{u}(x)$ is an equilibrium with $u_0 = \hat{u}(0)$, $\hat{u}(x)$ and u_0 both satisfy the initial-value problem

$$\frac{1}{2}f_V(\hat{u})\hat{u}'' - M\hat{u}' - g_V(\hat{u})(\hat{u}')^2 = 0, \quad 0 < x < L, \quad [16a]$$

$$\hat{u}(0) = u_0, \quad \hat{u}'(0) = 0. \quad [16b]$$

By uniqueness for [16], $\hat{u}(x) = u_0$.

3.2. Evolution. We first show that the gene frequency remains forever between its initial minimum and maximum values: $0 \leq u_- \leq u(x, 0) \leq u_+ \leq 1$ implies $u_- \leq u(x, \tau) \leq u_+$ for $\tau \geq 0$. Therefore (choose u_- and u_+ sufficiently close), all constants are stable equilibria. The stability is not asymptotic, however, because if u_0 is an equilibrium, so is u_1 , arbitrarily close to u_0 , and hence there is no convergence from u_1 to u_0 .

Substitute $v^{\pm}(x, \tau) = \pm u(x, \tau) \mp u_{\pm}$ into [15]:

$$v_{\tau}^{\pm} = \frac{1}{2}f_V(u)v_{xx}^{\pm} - Mv_x^{\pm} \mp g_V(u)(v_x^{\pm})^2,$$

$$\tau > 0, \quad 0 < x < L, \quad [17a]$$

$$v_x^{\pm} = 0, \quad \tau > 0, \quad x = 0, L. \quad [17b]$$

We have already established that $0 < u(x, \tau) < 1$. As in the last paragraph of Section 2.1, we prove easily that the maximum of $v^{\pm}(x, \tau)$ occurs at $\tau = 0$. Therefore, $v^{\pm}(x, 0) \leq 0$ implies $v^{\pm}(x, \tau) \leq 0$, as asserted.

Note that the result $u_- \leq u(x, \tau) \leq u_+$ means that neither allele can be lost if the gene frequency is initially strictly between zero and one everywhere ($u_- > 0$ and $u_+ < 1$). Without genotype dependence, [15] is linear, and an eigenfunction expansion reveals that genetic variability is maintained if $0 < u(x, 0) < 1$ on any interval.

To show that geographical differentiation is neither created nor preserved, we must establish that convergence to a constant always occurs. To this end, define

$$\Lambda(\tau) = \int_0^L \Phi[u(x, \tau)][u_x(x, \tau)]^2 dx, \quad [18]$$

where we shall attempt to determine $\Phi(u) > 0$ such that $\Lambda(\tau)$ is a Lyapunov functional for [15]. Differentiating [18], inte-

grating by parts, and appealing to [15b], we find the time derivative

$$\Lambda'(\tau) = - \int_0^L u_\tau (2\Phi u_{xx} + \Phi' u_x^2) dx. \quad [19]$$

If we can cast [15a] into the form

$$u_\tau = \Psi(u)[2\Phi(u)u_{xx} + \Phi'(u)u_x^2] - Mu_x \quad [20]$$

with $\Psi(u) > 0$, then substituting [20] into [19], observing that the coefficient of M in the integrand is $-(\Phi u_x^2)_x$, and again invoking [15b] yields

$$\Lambda'(\tau) = - \int_0^L \Psi(2\Phi u_{xx} + \Phi' u_x^2) dx. \quad [21]$$

Since [18] and [21] inform us that $\Lambda \geq 0$ and $\Lambda' \leq 0$, we conclude that $\Lambda'(\tau) \rightarrow 0$ as $\tau \rightarrow \infty$. Hence, the expression in parentheses in [21] must tend to zero. But by the argument applied to [16], the solutions of

$$2\Phi(u)u_{xx} + \Phi'(u)u_x^2 = 0, \quad 0 < x < L, \quad [22a]$$

$$u_x = 0, \quad x = 0, L \quad [22b]$$

are independent of x : $u(x, \tau) = \bar{u}(\tau)$. Then by [15a], $\bar{u}_\tau = 0$, so that $u(x, \tau)$ indeed converges to a constant as $\tau \rightarrow \infty$.

It remains to determine Φ and Ψ . Comparing [15a] and [20] gives

$$2\Phi\Psi = \frac{1}{2}f_V, \quad \Phi'\Psi = -g_V,$$

whence

$$\Phi(u) = \exp \left[-4 \int_0^u \frac{g_V(v)}{f_V(v)} dv \right] > 0, \quad \Psi(u) = \frac{f_V(u)}{4\Phi(u)} > 0.$$

4. Examples of asymptotically stable clines

We simplify our problem now by positing genotype-independent diffusion coefficients, $V_{ij} = V$, and drift coefficients without "dominance," $2M_{12} = M_{11} + M_{12}$. Then [4] reduces to

$$u_\tau = \frac{1}{2}Vu_{xx} - M_{12}u_x, \quad \tau > 0, \quad 0 < x < L, \quad [23a]$$

$$Vu_x = 2(M_{12} - M_{22})u(1 - u), \quad \tau > 0, \quad x = 0, L. \quad [23b]$$

As in Section 2, we choose the x -direction so that $M_{12} \geq 0$. We name our alleles so as to arrange the ordering $M_{11} > M_{12} > M_{22}$, excluding the case $M_{11} = M_{12} = M_{22}$, which we investigated in Section 3.

At equilibrium, [13a] and [13b] yield

$$U(\hat{u}) = 2V^{-1}[(M_{12} - M_{22})\alpha(1 - \alpha) + M_{12}(\hat{u} - \alpha)]. \quad [24]$$

Inserting [24] into [14a], we find

$$\alpha + \beta = M_{22}/(M_{22} - M_{12}). \quad [25]$$

We separate the cases $M_{12} = 0$ and $M_{12} \neq 0$.

4.1. Symmetric Heterozygote Dispersion. With $M_{12} = 0$, we have $M_{11} = -M_{22} = M > 0$, and from [13c], [14b], and [25] we obtain the equilibrium gene frequency

$$\hat{u}(x) = \alpha + L^{-1}(1 - 2\alpha)x, \quad [26a]$$

$$\alpha = (2c)^{-1}[2 + c - (4 + c^2)^{1/2}], \quad [26b]$$

where $c = 2ML/V$. (The root with a plus sign in front of the radical exceeds one.) From [26b] we see that $0 < \alpha < 1/2$; since $\beta = 1 - \alpha$, this means that $1/2 < \beta < 1$. Thus, the cline [26] is acceptable and unique. Biologically, $\hat{u}(x)$ is monotone increasing because A_1A_1 migrates preferentially to the right, A_2A_2 preferentially to the left, and A_1A_2 symmetrically.

The gene-frequency difference $D(c) = 1 - 2\alpha$ between the two ends of the habitat measures geographical differentiation. From [26b] we easily verify that $D'(c) > 0$. It follows that, as is intuitive, genetic differentiation increases as the asymmetry of migration or the habitat length increases or as the amount of migration decreases. As $c \rightarrow \infty$, $D(c) \rightarrow 1$.

We saw in Section 2.2 case *ii* that the fixation states are unstable for our parameters. Therefore, we expect our equilibrium to be asymptotically stable. To prove this (locally), we substitute $u(x, \tau) = \hat{u}(x) + \eta(x, \tau)$ into [23] and linearize:

$$\eta_\tau = \frac{1}{2}V\eta_{xx}, \quad \tau > 0, \quad 0 < x < L, \quad [27a]$$

$$\eta_x(0, \tau) = b\eta(0, \tau), \quad \eta_x(L, \tau) = -b\eta(L, \tau), \quad \tau > 0, \quad [27b]$$

where $b = 2MV^{-1}(1 - 2\alpha) > 0$. From theorem 4 of Friedman (ref. 12, p. 167) we infer that $\eta(x, \tau) \rightarrow 0$ as $\tau \rightarrow \infty$.

4.2. Asymmetric Heterozygote Dispersion. For $M_{12} > 0$, we derive from [13c], [14b], and [25]

$$\hat{u}(x) = \alpha + \gamma\alpha(1 - \alpha)(e^{kx} - 1), \quad [28a]$$

$$\alpha = (2\gamma\kappa)^{-1}[2 + \gamma\kappa - (4 + 4\kappa + \gamma^2\kappa^2)^{1/2}], \quad [28b]$$

where $k = 2M_{12}/V$, $\gamma = (M_{12} - M_{22})/M_{12}$, and $\kappa = e^{kL} - 1$ are positive constants. (The root with a plus before the radical exceeds one.) Now, $\alpha > 0$ if and only if $\gamma > 1$, in which case $0 < \alpha < (\gamma - 1)/(2\gamma) < 1/2$, whence $\beta = 1 - \alpha - \gamma^{-1}$ satisfies $1/2 < \beta < 1 - \gamma^{-1}$. We conclude that for $\gamma \leq 1$ ($M_{22} \geq 0$) there is no equilibrium with $0 < \hat{u}(x) < 1$, while for $\gamma > 1$ ($M_{22} < 0$) there exists a unique acceptable equilibrium, given by [28]. This result is consistent with Section 2.2 case *i*, where we found that $u = 0$ is stable and $u = 1$ is unstable for $\gamma < 1$, and both trivial equilibria are unstable for $\gamma > 1$. The existence of a monotone cline if and only if A_2A_2 migrates preferentially in the direction opposite to the preferred direction of A_1A_1 and A_1A_2 is biologically quite reasonable.

The gene-frequency difference $D = 1 - \gamma^{-1} - 2\alpha$ has the property $\partial D/\partial \kappa > 0$, from which exactly the same biological conclusions follow as in Section 4.1. As $\kappa \rightarrow \infty$, $D \rightarrow 1 - \gamma^{-1}$.

Finally, we desire to establish that [28] is locally asymptotically stable. We put $y = kx$, $T = kM_{12}\tau$, $l = kL$, and $d = \gamma(1 - 2\alpha)$, and linearize [23]:

$$\eta_T = \eta_{yy} - \eta_y, \quad T > 0, \quad 0 < y < l, \quad [29a]$$

$$\eta_y(0, T) = d\eta(0, T), \quad \eta_y(l, T) = (2 - d)\eta(l, T), \quad [29b]$$

in which $1 < d < \gamma$. The method applied to [8] now leads to the eigenvalue equation

$$\mu^2 + 4(d - 1)^2 - 1 = -4(d - 1)\mu \coth(l\mu/2), \quad [30]$$

μ and λ being related by [10b]. Because the Sturm-Liouville eigenvalue λ is real, the principal root μ is either real and non-negative, or pure imaginary with non-negative imaginary part. Instability can occur only if μ is real and $\mu \geq 1$. But then the right-hand side of [30] is negative while the left-hand side is positive, so no such roots exist. Hence, [28] is asymptotically stable, as expected from the simultaneous instability of the trivial equilibria for $\gamma > 1$.

5. Discussion

We derived and investigated a diffusion model for the joint action of genotype-dependent dispersion and genotype-independent population regulation. Although the model was deduced for a one-dimensional habitat (e.g., organisms in or along a river, along a sea shore, or in a narrow valley), it applies also in two dimensions if migration is genotype independent in one

of the directions. Then we may suppose that the gene frequency is a function only of the genetically pertinent coordinate (e.g., latitude, distance from a river or sea shore, or altitude on a mountain range).

We examined in detail the case of two alleles at a single locus, establishing that genotype-dependent migration and genotype-independent population regulation together can create and preserve stable, stationary, deterministic patterns of geographical differentiation. Therefore, detailed measurements are required to distinguish genotype-dependent habitat choice from position-dependent selection. In this connection, it may be useful to note that in the first instance all equilibria are monotone, while in the second (because the slope of the gene frequency is zero at both ends of the habitat) there is at least one point of inflection.

Two examples of asymptotically stable clines were presented. In both cases, genetic differentiation increases as the asymmetry of migration or the habitat length increases, or the amount of migration decreases.

Let $M_{jk}^* = \delta M_{jk}$ and $V_{jk}^* = \delta V_{jk}$ represent the mean displacement and mean-square displacement per generation of genotype $A_j A_k$; choose $M_{12}^* \geq 0$. If $0 < M_{22}^* < M_{12}^*$ and A_1 is sufficiently rare initially, then it will be lost; if $M_{22}^* < 0$ or $M_{22}^* > M_{12}^*$, then A_1 cannot be lost for any initial condition. The ultimate rate of loss of A_1 in the first case is $\exp[-2M_{22}^*(M_{12}^* - M_{22}^*)t/V_{12}^*]$, t being the time in generations.

If only the diffusion coefficients, V_{jk} , are genotype dependent, then the population evolves qualitatively as it would in the complete absence of genotype dependence. In particular, all constants are equilibria, there are no other equilibria, convergence to a constant always occurs, and the gene frequency remains between its initial minimum and maximum values. The

last result implies that genetic variability is maintained if the gene frequency is initially strictly between zero and one everywhere.

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1. Nagylaki, T. (1978) *Genetics* 88, 813-827.
2. Peletier, L. A. (1976) in *Proceedings of the Fourth Conference on Ordinary and Partial Differential Equations*, eds. Everitt, W. N. & Sleeman, B. D., Lecture Notes in Mathematics No. 564 (Springer, Berlin), pp. 365-371.
3. Peletier, L. A. (1978) in *Journées d'Analyse Non Linéaire*, eds. Bénéilan, P. & Robert, J., Lecture Notes in Mathematics No. 665 (Springer, Berlin), pp. 170-187.
4. Edwards, A. W. F. (1963) *Heredity* 16, 101-106.
5. Parsons, P. A. (1963) *Genetica* 33, 184-206.
6. Moody, M. (1979) Dissertation (The University of Chicago, Chicago, IL).
7. Nagylaki, T. (1975) *Genetics* 80, 595-605.
8. Fleming, W. H. & Su, C.-H. (1974) *Theor. Popul. Biol.* 5, 431-449.
9. Protter, M. H. & Weinberger, H. F. (1967) *Maximum Principles in Differential Equations* (Prentice-Hall, Englewood Cliffs, NJ).
10. Coddington, E. A. & Levinson, N. (1955) *Theory of Ordinary Differential Equations* (McGraw-Hill, New York).
11. Nagylaki, T. (1977) *Selection in One- and Two-Locus Systems* (Springer, Berlin).
12. Friedman, A. (1964) *Partial Differential Equations of Parabolic Type* (Prentice-Hall, Englewood Cliffs, NJ).