The approximate controllability of a model for mutant selection

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to Walter Littman with best wishes upon his retirement

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Abstract

It is shown that the problem of eliminating a less-fit allele by allowing a mixture of genotypes whose densities satisfy a system of reaction-diffusion equations with population control to evolve in a reactor with impenetrable walls is approximately controllable.

1 Introduction.

We are concerned with the interaction between genotypes of a diploid species which only differ by the presence or absence of two possible alleles a and A

at a single genome site. We denote the populations of the genotypes aa, aA, and AA by ρ_{aa}, ρ_{aA}, and ρ_{AA} respectively. A classical model for the evolution of the population under the assumption of random mating is the system

$$\begin{aligned}
\frac{\partial \rho_{aa}}{\partial t} - D\Delta\rho_{aa} &= \frac{r[2\rho_{aa}+\rho_{aA}]^2}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{aa}\rho_{aa} \\
\frac{\partial \rho_{aA}}{\partial t} - D\Delta\rho_{aA} &= 2\frac{r[2\rho_{aa}+\rho_{aA}][2\rho_{AA}+\rho_{aA}]}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{aA}\rho_{aA} \qquad (1.1) \\
\frac{\partial \rho_{AA}}{\partial t} - D\Delta\rho_{AA} &= \frac{r[2\rho_{AA}+\rho_{aA}]^2}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{AA}\rho_{AA}.
\end{aligned}$$

Here the death rates τ_{aa}, τ_{aA}, and τ_{AA} depend on the genotype, while the per capita reproduction rate r does not. This model with no diffusion ($D = 0$) and all four parameters constant is just the system (5) in chapter XV of the book of Kostitzin [3] with $h = 0$.

We shall be concerned with the so-called **heterozygote intermediate** case, which is defined by the inequalities

$$0 < \tau_{AA} \leq \tau_{aA} \leq \tau_{aa} \text{ and } \tau_{AA} < \tau_{aa}. \qquad (1.2)$$

That is, the AA homozygotes are more fit than the aa homozygotes, and the fitness of the aA heterozygotes is intermediate between the two others.

It was recently shown by Souplet and Winkler [7, 8] that if all the parameters are constant, then any solution of this equation in a Euclidean space in which the allele A is initially present has the property that the fraction $v := [2\rho_{aa}+\rho_{aA}]/\{2[\rho_{aa}+\rho_{aA}+\rho_{AA}]\}$ of alleles a in the population converges to zero, uniformly on each bounded set. That is, the fitter allele drives the less fit one out of the population.

In the biologically interesting case, the proof in [7, 8] consists of showing that all the population densities approach infinity at exponential rates, and that the exponential growth rate of ρ_{AA} is greater than that of the other two genotypes. The authors of [7, 8] pointed out that the fact that the population densities approach infinity means that the model contains no population control, which makes it unrealistic. In fact it was shown by T. Malthus that faith in a model without a population control mechanism can lead to absurd predictions. We are interested in seeing what happens when the model is modified in such a way that the total population density remains bounded and uniformly positive. This is done by making the per capita reproduction rate be a suitable function of the total population density $\rho = \rho_{aa}+\rho_{aA}+\rho_{AA}$.

We shall show elsewhere [9] that such a model in all of a Euclidean space predicts not only that the fitter allele A drives the allele a out of the population, but also that the set where the populations of the two genotypes which contain a are small has growth properties similar to those predicted by the corresponding scalar Fisher-KPP equation. The process of obtaining such a result begins with showing that when the populations are confined to a smooth bounded set with impenetrable boundary, then the densities $\rho_{aa}(x,t)$ and ρ_{aA} approach zero and the density $\rho_{AA}(x,t)$ approaches a certain constant $m > 0$, uniformly in x. This result, which is our Theorem 2.1, can be interpreted as the statement that a suitable initial-boundary value problem is approximately controllable. This concept is, of course, weaker than that of exact controllabiliy, which occurs in the pioneering works of Walter Littman and Larry Markus [4, 5].

Our result can be applied to the problem of finding an optimal strategy for the common procedure of breeding a mutant which is resistant to certain adverse conditions by putting some of the species into a reactor in which these adverse conditions are enforced. For example, one can expect to produce a heat resistant mutant of a useful species by growing the species in a reactor whose temperature is so high that a certain mutant allele A confers death rate advantages to individuals which contain it. The cost depends on the heat supplied and the time in the reactor, while the income depends on the yield of biomass of the improved mutant homozygote.

2 The takeover by the fitter allele of a system with population control.

We shall study the system

$$\begin{aligned}
\frac{\partial \rho_{aa}}{\partial t} - D\Delta\rho_{aa} &= \frac{R(\rho_{aa}+\rho_{aA}+\rho_{AA})[2\rho_{aa}+\rho_{aA}]^2}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{aa}\rho_{aa} \\
\frac{\partial \rho_{aA}}{\partial t} - D\Delta\rho_{aA} &= 2\frac{R(\rho_{aa}+\rho_{aA}+\rho_{AA})[2\rho_{aa}+\rho_{aA}][2\rho_{AA}+\rho_{aA}]}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{aA}\rho_{aA} \\
\frac{\partial}{\rho_{AA}}\partial t - D\Delta\rho_{AA} &= \frac{R(\rho_{aa}+\rho_{aA}+\rho_{AA})[2\rho_{AA}+\rho_{aA}]^2}{4[\rho_{aa}+\rho_{aA}+\rho_{AA}]} - \tau_{AA}\rho_{AA},
\end{aligned} \tag{2.1}$$

which is the system (1.1) with the constant per capita birth rate r replaced by a function $R(\rho)$ of the total population density

$$\rho := \rho_{aa} + \rho_{aA} + \rho_{AA}. \tag{2.2}$$

The following well-known proposition shows that very simple properties of the function $R(\rho)$ result in the boundedness and uniform positivity of the total population density ρ.

Proposition 2.1. *Suppose that $R(\rho)$ is smooth, that the inequalities (1.2) are satisfied, and that there are positive numbers $\ell < m$ such that*

$$R(\ell) = \tau_{aa} \text{ and } R(m) = \tau_{AA}. \tag{2.3}$$

Let $(\rho_{aa}, \rho_{aA}, \rho_{AA})$ be a nonnegative solution of (2.1) in a bounded domain Ω with smooth boundary $\partial\Omega$, and let the Neumann conditions

$$\frac{\partial \rho_{aa}}{\partial n} = \frac{\partial \rho_{aA}}{\partial n} = \frac{\partial \rho_{AA}}{\partial n} = 0 \text{ on } \partial\Omega \tag{2.4}$$

be satisfied.

If the initial value $\rho(x, 0)$ satisfies the inequalities $\ell \leq \rho(x, 0) \leq m$, then

$$\ell \leq \rho(x, t) \leq m \text{ for all } t \geq 0. \tag{2.5}$$

Proof. By adding the three equations of (2.1), we obtain the equation

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\}\rho = R(\rho)\rho - [\tau_{aa}\rho_{aa} + \tau_{aA}\rho_{aA} + \tau_{AA}\rho_{AA}]. \tag{2.6}$$

Because of the inequalities (1.2), the right-hand side is bounded below by $[R(\rho)-\tau_{aa}]\rho$. Since $\rho \equiv \ell$ satisfies the corresponding equality, the comparison theorem and the boundary point lemma for a parabolic equation (see, e.g., Theorems 5 and 6 of Chapter 3 of [6]) give the lower bound in (2.5). Since the right-hand side of (2.6) is bounded above by $[R(\rho) - \tau_{AA}]\rho$, the same argument gives the upper bound, so that the Proposition is established. □

Remark. It is easily verified that the constant states $(\ell, 0, 0)$ and $(0, 0, m)$ are equilibria of the system (2.1).

Our main result is the following theorem, which shows that if the function $R(\rho)$ has a few more properties, then the equilibrium $(0, 0, m)$ is a global attractor.

Theorem 2.1. *Let the death rates satisfy the inequalities*

$$0 < \tau_{AA} \leq \tau_{aA} \leq \tau_{aa} \text{ and } \tau_{AA} < \tau_{aa}. \tag{2.7}$$

Assume that the function $R(\rho)$ is smooth on an interval $[\ell, m]$, that

$$R(\ell) = \tau_{aa} \text{ and } R(m) = \tau_{AA},$$

and that

$$\tau_{AA} < R(\rho) \leq \tau_{aa} \text{ for } \ell \leq \rho < m. \tag{2.8}$$

(That is, $\tau_{AA} \leq R(\rho) \leq \tau_{aa}$ on $[\ell, m]$, and m is the smallest root above ℓ of the equation $R(\rho) = \tau_{AA}$.)

Let the domain Ω be bounded and let its boundary $\partial\Omega$ be smooth.

If $(\rho_{aa}(x,t), \rho_{aA}(x,t), \rho_{AA}(x,t))$ is a nonnegative solution of the system (2.1) which satisfies the Neumann conditions (2.4) and has continuous initial data, if

$$\ell \leq \rho_{aa}(x,0) + \rho_{aA}(x,0) + \rho_{AA}(x,0) \leq m,$$

and if

$$2\rho_{AA}(x,0) + \rho_{aA}(x,0) \not\equiv 0, \tag{2.9}$$

then

$$\begin{aligned} &\lim_{t\to\infty}[\max_x \rho_{aa}(x,t)] = 0, \\ &\lim_{t\to\infty}[\max_x \rho_{aA}(x,t)] = 0, \text{ and} \\ &\lim_{t\to\infty}[\max_x |m - \rho_{AA}(x,t))|] = 0. \end{aligned} \tag{2.10}$$

We shall prove this result by means of a series of lemmas. Because the right-hand side of the system (2.1) is not quasi-monotone, we cannot expect to find vector comparison theorems for its solutions. We are thus confined to the hammer-and-tongs method of applying comparison theorems to sufficiently many scalar-valued functions of the unknowns.

The following lemma serves to show that the function

$$q(x,t) := 2\rho_{AA}(x,t) + \rho_{aA}(x,t), \tag{2.11}$$

which is the density of the allele A, is uniformly positive for all $t \geq 1$. We shall use the usual notation $\overline{\Omega} := \Omega \cup \partial\Omega$ for the closure of Ω.

Lemma 2.1. *Let the conditions of Theorem 2.1 be satisfied. Then there exists a positive constant α such that*

$$q(x,t) \geq 2\alpha\rho(x,t) \text{ for all } x \in \overline{\Omega} \text{ and } t \geq 1.$$

Proof. We see from the system (2.1 that

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\} q = [R(\rho) - \tau_{aA}]q + 2[\tau_{aA} - \tau_{AA}]\rho_{AA}.$$

The inequalities $\tau_{AA} \leq R(\rho) \leq \tau_{aa}$ and (2.7) give a lower bound for the right-hand side. In particular,

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\} q \geq -[\tau_{aA} - \tau_{AA}]q.$$

Since q also satisfies the Neumann boundary conditions, and since (2.9) shows that $q(x,0) \not\equiv 0$, the strong maximum principle and the boundary point lemma (Theorems 5 and 6 of chapter 3 of [6]) applied to the function

$e^{[\tau_{aA}-\tau_{AA}]t}q$ show that $q(x,t) > 0$ for $x \in \overline{\Omega}$ and $t > 0$. Since $R(\rho) \geq \ell$, the function $q(x,1)/\rho(x,1)$ is positive and continuous in $\overline{\Omega}$. Because $\overline{\Omega}$ is closed and bounded, there is an $\alpha > 0$ such that

$$q(x,1) \geq 2\alpha\rho(x,1). \tag{2.12}$$

We now see from (2.1) that

$$\begin{aligned}\left\{\frac{\partial}{\partial t} - D\Delta\right\}[q - 2\alpha\rho] = [R(\rho) - \tau_{aA}][q - 2\alpha\rho] \\ + 2\alpha[\tau_{aa} - \tau_{aA}]\rho_{aa} + 2[1-\alpha][\tau_{aA} - \tau_{AA}]\rho_{AA}.\end{aligned} \tag{2.13}$$

It is clear from (2.12) that

$$0 < \alpha \leq 1.$$

Therefore, the last two terms on the right are nonnegative, so that the left-hand side is at least as large as the first term on the right. The maximum principle with $R(\rho)$ regarded as a fixed function of x and t then shows that

$$q(x,t) - 2\alpha\rho(x,t) \geq 0 \text{ for } t \geq 1. \tag{2.14}$$

This is the statement of Lemma 2.1. □

Lemma 2.2. *Let the conditions of Theorem 2.1 be satisfied. Then there is a constant β such that*

$$\rho_{AA}(x,t) \geq \beta > 0 \textit{ for } x \in \overline{\Omega} \textit{ and } t \geq 2.$$

Proof. By Proposition 2.1, Lemma 2.1, and the inequality $R(\rho \geq \tau_{AA}$, the function $R(\rho)[2\rho_{AA} + \rho_{aA}]^2/\rho$, which is the first term of the right-hand side of the last equation of (2.1), is bounded below by the positive number $\gamma := \tau_{AA}\ell\alpha^2$ on the set $\overline{\Omega}\times[1,\infty)$. Therefore, ρ_{AA} satifies the differential inequality

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\}\rho_{AA} \geq \gamma - \tau_{AA}\rho_{AA} \text{ for } t \geq 1.$$

Because the function

$$\hat{v} := [1 - e^{-\tau_{AA}(t-1)}]\gamma/\tau_{AA}.$$

satisfies the corresponding equation and the Neumann boundary condition, and because $\hat{v}(x,1) \equiv 0 \leq \rho_{AA}(x,1)$, $\rho_{AA}(x,t) \geq \hat{v}(x,t)$ for $t \geq 1$. Therefore,

$$\rho_{AA}(x,t) \geq \hat{v}(x,t) \geq [1 - e^{-\tau_{AA}}]\gamma/\tau_{AA} \text{ for } t \geq 2.$$

This is the statement of Lemma 2.2 with $\beta = [1 - e^{-\tau_{AA}}]\gamma/\tau_{AA}$. □

Lemma 2.3. *Let the conditions of Theorem 2.1 be satisfied. Then*

$$\lim_{t\to\infty}[\max_x \rho_{aa}(x,t)] = 0. \textit{ and } \lim_{t\to\infty}[\max_x |m - \rho_{AA}(x,y)|] = 0.$$

Proof. Subtract the first equation of (2.1) from the third to find that

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\}[\rho_{AA} - \rho_{aa}] = [R(\rho) - \tau_{AA}]\rho_{AA} + [\tau_{aa} - R(\rho)]\rho_{aa}.$$

We integrate both sides of this equation over the cylinder $\overline{\Omega} \times [0,T]$. The integral of the Laplacian vanishes because of the Neumann boundary conditions. Because $|\rho_{AA} - \rho_{aa}| \leq m$, the integral of the t derivative is bounded uniformly in T. Because $\tau_{AA} \leq R(\rho) \leq \tau_{aa}$, the two terms on the right are nonnegative. Hence, their integrals must converge as $t\to\infty$. That is,

$$\int_0^\infty \int_{\overline{\Omega}} [R(\rho) - \tau_{AA}]\rho_{AA} dxdt < \infty \tag{2.15}$$

and

$$\int_0^\infty \int_{\overline{\Omega}} [\tau_{aa} - R(\rho)]\rho_{aa} dxdt < \infty \tag{2.16}$$

Because Lemma 2.2 shows that ρ_{AA} is uniformly positive for $t \geq 2$, (2.15) shows that the integral of $R(\rho) - \tau_{AA}$ is finite. Standard parabolic estimates show that the the integrand $R(\rho) - \tau_{AA}$ is uniformly continuous for $t \geq 1$. Therefore, if this integrand takes on a positive value i_0 at a point Q, then it is at least $i_0/2$ on a disc centered at Q whose radius does not depend on Q. The integral over this disc is thus a fixed multiple of i_0. Therefore, the convergence of the integral and the Cauchy criterion imply that $R(\rho) - \tau_{AA} < i_0$ for all sufficiently large t. Since i_0 is an arbitrary positive number, we have shown that

$$\lim_{t\to\infty} \max_x [R(\rho) - \tau_{AA}] = 0.$$

Since $\rho_{AA} \leq \rho \leq m$, and (2.8) shows that $R(\rho) > \tau_{AA}$, for $\rho < m$, we conclude that

$$\lim_{t\to\infty}[|m - \max_x \rho(x,t)|] = 0,$$

which is one of the statements of Lemma 2.3.

This statement implies that $\tau_{aa} - R(\rho)$ converges uniformly to $\tau_{aa} - \tau_{AA} > 0$. Therefore, (2.16) shows that

$$\int_0^\infty \int_\Omega \rho_{aa}(x,t) dxdt < \infty. \tag{2.17}$$

As before, parabolic estimates show that the integrand is uniformly continuous for $t \geq 1$, and this fact and (2.17) imply that

$$\lim_{t\to\infty}[\max_x \rho_{aa}(x,t)] = 0.$$

We have proved both statements of Lemma 2.3. □

The following lemma yields the remaining statement of Theorem 2.1.

Lemma 2.4.

$$\lim_{l\to\infty}[\max_x \rho_{aA}(x,t)] = 0.$$

Proof. We consider the first equation of (2.1). As in the proof of Lemma 2.3, we integrate both sides of the equation over the cylinder $\overline{\Omega}\times[0,T]$, and let T approach infinity. As before, we find that the integral of the left-hand side is bounded, uniformly in T. the formula (2.17) shows that the integral of the second term $-\tau_{aa}\rho_{aa}$ on the right also remains bounded. We conclude that the integral of the other term on the right is also finite. That is,

$$\int_0^\infty \int_{\overline{\Omega}} R(\rho)[2\rho_{aa}+\rho_{aA}]^2/[4\rho]dxdt < \infty.$$

Since the integrand is bounded below by $\tau_{AA}\rho_{aA}^2/[4m]$, this implies that

$$\int_0^\infty \int_{\overline{\Omega}} \rho_{aA}^2 dxdt < \infty.$$

As in the proof of Lemma 2.3, this implies that as t goes to infinity, ρ_{aA} goes to 0 uniformly in x. This is the statement of Lemma 2.4. □

Lemmas 2.3 and 2.4 prove the three parts of the statement (2.10) of Theorem 2.1.

3 Discussion.

The system (2.1) is a greatly simplified model for evolution. In general, one can expect the birth rates to depend on the genotypes, and they may depend on the three population densities in a more complicated way than being functions of their sum. Moreover, the death rates my also depend upon the population densities. More generally, the genotypes may also involve more than one gene locus, as well as more alleles per site. A special case of such a generalization in the absence of diffusion is found in equation (4) of chapter XV of the book of Kostitzin [3]. The present paper is intended to be a first step toward results on these more realistic models.

R. A. Fisher [2] derived his scalar equation by a assuming that the ratio

$$u := [2\rho_{AA}+\rho_{aA}]/\{2[\rho_{aa}+\rho_{aA}+\rho_{AA}]\}$$

diffuses. This is physically incorrect because, while densities can diffuse, ratios can not. The mathematical counterpart of this statement is the fact that when the Laplace operator is applied to any nonlinear function of the densities, the chain rule leads not only to a linear combination of Laplacians of the denities, but also to a quadratic form in their gradients. This quadratic form can be called the cross-diffentiation form. For example, the equation for u is

$$\left\{\frac{\partial}{\partial t} - D\Delta\right\} u = -[\nabla[2\rho_{AA} + \rho_{aA}] \cdot \nabla\rho]/\rho^2 \\ + \{2[\tau_{aa} - \tau_{AA}]\rho_{aa}\rho_{AA} + [\tau_{aA} - \tau_{AA}]\rho_{aA}\rho_{AA} + [\tau_{aa} - \tau_{aA}]\rho_{aa}\rho_{aA}\}/[2\rho^2]. \tag{3.1}$$

The first term on the right is the cross-differentiation form, about which not much can be said, and which is missing from [2] and from many works since then.

When the parameter $\epsilon := [\tau_{aa} - \tau_{AA}]/\tau_{AA}$ is very small, it is tempting to approximate the equation (3.1) by dropping terms of higher order in ϵ, and to predict the large-time asymptotic behavior of u from that of the solution of the approximating equation with the same initial values. However, as pointed out in the appendix of [1], the solution of the approximate equation is close to the value of u only for a limited time $T(\epsilon)$, which is large when ϵ is small. Because large-time asymptotics involve times which are much larger than $T(\epsilon)$, this approach does not yield the asymptotic form of u. That is, one cannot interchange the order of the iterated limit as $t \to \infty$ and $\epsilon \to 0$.

References

[1] D. G. Aronson and H. F. Weinberger, Nonlinear diffusion in population genetics, combustion, and nerve propagation. in Partial Differential Equations and Related Topics, Lecture Notes in Mathematics 446, Springer, New York, 1975, pp' 5-49.

[2] R. A. Fisher, The advance of advantageous genes. *Ann. of Eugen.* **7** (1937), pp. 355-369.

[3] V. A. Kostitzin, Mathematical Biology. G.G. Harrap & Co., London, Toronto, 1939.

[4] W. Littman and L. Markus, Exact boundary controllability of a hybrid system of elasticity. *Arch. Rational Mech. Anal.* **103** (1988) pp. 193-236.

[5] W. Littman and L. Markus, Remarks on exact controllability and stabilization of a hybrid system in elasticity through boundary damping. Control of partial differential equations (Santiago de Compostela, 1987),

Lecture Notes in Control and Inform. Sci., 114, Springer, Berlin, 1989, pp. 202-207.

[6] M. H. Protter and H. F. Weinberger, Maximum Principles in Differential Equations. Springer Verlag, New York, Berlin, 1984.

[7] P. Souplet and M. Winkler, The influence of space dimension on the large-time behavior in a reaction-diffusion system modeling diallelic selection. *J. Math.Biol.* **62** (2011), pp. 391-421.

[8] P. Souplet and M. Winkler, Classification of large-time behaviors in a rection-diffusion system modeling diallelic selection. preprint, 2012.

[9] H. F. Weinberger, The retreat of the less fit allele in a population-controlled model for population genetics. Submitted to the Journal of Mathematical Biology, 8-28-2012.