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A SIMPLE MODEL FOR THE BALANCE BETWEEN SELECTION AND MUTATION

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Abstract

A model for the variation in time of the fitness distribution in a large haploid population is shown to have simple limiting properties which can be elucidated in fairly explicit terms. The novel feature is that mutation is not assumed to cause a small perturbation in fitness but to bring down the evolutionary 'house of cards'. A threshold phenomenon appears: if a certain inequality holds the limiting distribution is a skewed version of the mutant fitness distribution, but otherwise an atom of probability builds up at the upper limit of fitness.

SELECTION-MUTATION BALANCE; FITNESS DISTRIBUTION; BILINEAR RECURRENCE; HOUSE OF CARDS

1. Introduction

A mathematical model which aspired to represent in detail the evolution of a particular biological population would necessarily involve a large number of different mechanisms interacting in a complex manner. In the context of population genetics, for example, it should include selection acting on many loci with linkage and dominance, together with mutation, non-random mating, variation in time and space, and so on. If the population is to be in equilibrium, all these factors should contribute to a stable balance.

In practice, of course, such a model would be far too complex to be useful, and the more usual practice is to regard an equilibrium as existing because of a balance between two preponderant factors, other phenomena causing perturbations of the equilibrium. Thus it becomes necessary to analyse models for possible balances between the different pairs of factors likely to dominate particular situations.

The pair of factors to be considered here, selection and mutation, will therefore be supposed to act on gametes in a randomly mating population, so that the problem is effectively a haploid one. The population is supposed to be so large that genetic drift can be ignored. This situation has recently been the subject of study by Moran (whose papers [7], [8] and [9] contain references to earlier work).

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The usual picture of mutation (when a large or infinite number of alleles is allowed) is a 'random walk' model, in which the possible alleles at a locus are identified with points on a line, and mutation causes a small jump to the right or left. It has however been suggested [6] that the tendency for most mutations to be deleterious might be reflected in a model in which the gene after mutation is independent of that before, the mutation having destroyed the biochemical 'house of cards' built up by evolution. Such a model might be regarded as a selective analogue to the 'infinite alleles' neutral model of Ohta and Kimura ([10], [1], [12], [5]).

Thus suppose that, in the nth generation of a large population, the distribution of fitness is a probability measure p_n on a finite interval which (since fitness ratios only are relevant) will be taken as the unit interval $I = [0, 1]$. If selection were operating alone, we would expect the distribution in the next generation to be skewed by the higher fitnesses reproducing in greater numbers:

$$p_{n+1}(dx) = xp_n(dx) \Big/ \int yp_n(dy). \tag{1.1†}$$

Suppose however that a proportion β of the population is subject to mutation between one generation and the next, and that new mutants have a fitness distribution described by a probability measure q on I. Then (if mutation acts after selection), (1.1) must be modified to

$$p_{n+1}(dx) = (1-\beta)w_n^{-1}xp_n(dx) + \beta q(dx), \tag{1.2}$$

where

$$w_n = \int xp_n(dx) \tag{1.3}$$

is the viability or mean fitness of the nth generation.

The recurrence relation (1.2) will be the main concern of this paper, and it will be shown that in many cases p_n converges to a distribution independent of the initial fitness distribution p_0. It is possible to imagine non-genetical contexts in which (1.1) could occur, at least as a very simple model for a balance between an effect distorting a distribution in accordance with (1.1) and introduction of fresh material at a rate β.

2. Properties of the recurrence relation

Like the recurrence relations of Moran [7], the bilinear recurrence defined by (1.2) and (1.3) is effectively linear. If the w_n are regarded as known, (1.2) has the solution

† Where the range of integration with respect to a measure is not specified, it is to be taken as the whole support of the measure.

$$W_n p_n(dx) = \sum_{r=0}^{n-1} W_{n-r}(1-\beta)^r \beta x^r q(dx) + (1-\beta)^n x^n p_0(dx), \tag{2.1}$$

for $n \geqq 1$, where

$$W_n = w_0 w_1 \cdots w_{n-1}. \tag{2.2}$$

Integrating over I, (2.1) gives

$$W_n = \sum_{r=0}^{n-1} W_{n-r}(1-\beta)^r \beta \mu_r + (1-\beta)^n m_n,$$

or

$$W_n = \sum_{r=1}^{n-1} W_{n-r}(1-\beta)^{r-1} \beta \mu_r + (1-\beta)^{n-1} m_n, \tag{2.3}$$

where

$$\mu_n = \int x^n q(dx), \quad m_n = \int x^n p_0(dx). \tag{2.4}$$

If q and p_0 are given, (2.3) determines W_n by linear recursion starting from $W_0 = 1$, and (2.1) then determines p_n.

Since, by (1.3) and (2.2), $W_n \leqq 1$, (2.3) can be thrown into the generating function identity

$$\sum_{n=1}^{\infty} W_n z^n = \sum_{n=1}^{\infty} (1-\beta)^{n-1} m_n z^n \left\{1 - \sum_{n=1}^{\infty} (1-\beta)^{n-1} \beta \mu_n z^n\right\}^{-1}, \tag{2.5}$$

valid at least in $|z| < 1$.

It is sometimes useful to have information about the higher moments of p_n. Multiplying (1.2) by x^k and integrating, we have

$$\int x^k p_{n+1}(dx) = (1-\beta) w_n^{-1} \int x^{k+1} p_n(dx) + \beta \mu_k. \tag{2.6}$$

For example, with $k = 1$,

$$w_{n+1} = (1-\beta) w_n^{-1} \int x^2 p_n(dx) + \beta \mu_1,$$

so that

$$\int x^2 p_n(dx) = (1-\beta)^{-1} w_n (w_{n+1} - \beta \mu_1). \tag{2.7}$$

In order to examine the behaviour of w_n and p_n as n increases, it is necessary to distinguish three cases, to which for mnemonic purposes rather arbitrary labels will be attached.

3. Democracy

If (2.5) is written in the form

$$\sum_{n=1}^{\infty} W_n z^n = \int \frac{zxp_0(dx)}{1-(1-\beta)zx}\left\{1 - \int \frac{\beta zxq(dx)}{1-(1-\beta)zx}\right\}^{-1}, \tag{3.1}$$

it will be noted that the right-hand side is analytic in the disc

$$D = \{z\,; (1-\beta)\,|\,z\,| < 1\}$$

of the complex plane, except for singularities at the roots of the equation

$$\int \frac{\beta zxq\,(dx)}{1-(1-\beta)\,zx} = 1\,. \tag{3.2}$$

The imaginary part of (3.2) can be written

$$\beta \,\mathrm{Im}\,(z)\int \frac{xq\,(dx)}{|1-(1-\beta)\,zx\,|^2} = 0\,,$$

which can only be satisfied if $\mathrm{Im}(z) = 0$. When z is real (and in D), the left-hand side of (3.2) increases with z, so that (3.2) can have at most one root in D, and it has one if and only if

$$\int \frac{\beta xq(dx)}{(1-\beta)(1-x)} > 1\,,$$

or equivalently

$$\int \frac{q(dx)}{1-x} > \beta^{-1}\,. \tag{3.3}$$

When (3.3) holds, and including the case in which the integral diverges, we shall say that *democracy* obtains. Then (3.2) has exactly one root in D, necessarily real, which it is convenient to write as $z = s^{-1}$; s is determined by

$$\int \frac{\beta xq\,(dx)}{s-(1-\beta)x} = 1\,, \tag{3.4}$$

and

$$1-\beta < s \leqq 1\,. \tag{3.5}$$

It is easy to check that s^{-1} is a simple zero of the denominator of (3.1), so that $\Sigma W_n z^n$ has a continuation which is analytic in D except for a simple pole at s^{-1}. Hence, for some $a > 0$,

$$W_n = as^n + o\{(1-\beta)^n\theta^n\} \tag{3.6}$$

for any $\theta > 1$, and from (2.2),

$$w_n = s + o\{\delta^n\theta^n\} \tag{3.7}$$

with

(3.8) $$\delta = (1-\beta)s^{-1} < 1,$$

so that s is the limiting viability of the population. It now follows from (2.1) that, whatever the initial distribution p_0, p_n converges to the probability measure

$$p(dx) = \sum_{r=0}^{\infty} s^{-r}(1-\beta)^r \beta x^r q(dx),$$

that is,

(3.9) $$p(dx) = \frac{\beta s q(dx)}{s-(1-\beta)x}.$$

The convergence takes place in the strong sense that the total variation of $p_n - p$ is $o\{\delta^n \theta^n\}$ for any $\theta > 1$.

The name 'democracy' is intended to suggest the fact that the limit distribution p is absolutely continuous with respect to the mutant fitness distribution q. The effect of selection has simply been to skew this distribution to the right. In the next section it will be seen that a quite different phenomenon presents itself when (3.3) does not hold.

Although the exponentially fast convergence is encouraging, it should be noted that the convergence parameter δ can be very near unity when β is small. If for instance q has an atom at 1, then (3.3) holds and

$$\delta \doteqdot 1 - \beta q\{1\}$$

when β is small. If $q\{1\} = 0$ but q has a density with limit $d > 0$ at 1, there again (3.3) holds, and

$$\delta \doteqdot 1 - \exp(-1/\beta d)$$

for small β. Even for moderate β the convergence is not too fast: if for example q is uniform on I and $\beta = \frac{1}{2}$, then $\delta \doteqdot 0.80$.

4. Meritocracy

Having analysed the case in which (3.3) holds, we now turn to the contrary, and suppose that

(4.1) $$\int \frac{q(dx)}{1-x} \leqq \beta^{-1}.$$

Then the numbers

(4.2) $$f_n = \beta(1-\beta)^{-1}\mu_n$$

satisfy

$$f_n \geqq 0, \quad \sum_{n=1}^{\infty} f_n \leqq 1, \tag{4.3}$$

and determine a renewal sequence (u_n) by the Feller recurrence relation [3]

$$u_0 = 1, \quad u_n = \sum_{r=1}^{n} f_r u_{n-r} \qquad (n \geqq 1). \tag{4.4}$$

Then induction on n, using (2.3), shows that for $n \geqq 1$,

$$W_n = (1-\beta)^{n-1} \sum_{r=1}^{n} m_r u_{n-r}. \tag{4.5}$$

From (4.2) and (2.4), (f_n) is a completely monotone sequence, and it follows by an argument set out in Section 7 that (u_n) is also completely monotone. Hence u_n/u_{n-1} increases to a limit as $n \to \infty$. We shall say that *meritocracy* obtains if (4.1) and

$$u_n/u_{n-1} \to 1 \qquad (n \to \infty) \tag{4.6}$$

both hold, and these will be assumed for the rest of this section.

Under these conditions, the constants

$$v_n = \sum_{r=1}^{n} m_r u_{n-r} \tag{4.7}$$

necessarily satisfy

$$v_n/v_{n-1} \to 1 \qquad (n \to \infty). \tag{4.8}$$

To see this, note that, since (u_n) is completely monotone and $u_0 = 1$, u_n is the nth moment of some probability measure on I. If λ (a probability measure on the unit square I^2) is the product of this measure with p_0, then

$$m_r u_{n-r} = \int x^{n-r} y^r \lambda(dx\, dy),$$

so that

$$v_n = \int g_n(x, y) \lambda(dx\, dy), \tag{4.9}$$

with

$$g_n(x, y) = \frac{x^n - y^n}{x - y} y \quad (x \neq y), \quad g_n(x, x) = n x^n.$$

Since $(n-1) g_n \leqq n g_{n-1}$, we have $(n-1) v_n \leqq n v_{n-1}$, so that

$$\limsup (v_n/v_{n-1}) \leqq 1. \tag{4.10}$$

To prove an inequality in the reverse direction, let $0 < \alpha < 1$ and note that $g_n(x, y) \geqq \alpha g_{n-1}(x, y)$ if $\max(x, y) \geqq \alpha$. Hence

$$\begin{aligned}v_n &\geqq \int_{\max(x,y)\geqq\alpha} g_n(x,y)\lambda(dx\,dy) \geqq \alpha \int_{\max(x,y)\geqq\alpha} g_{n-1}(x,y)\lambda(dx\,dy)\\ &= \alpha v_{n-1} - \alpha \int_{x<\alpha, y<\alpha} g_{n-1}(x,y)\lambda(dx\,dy)\\ &\geqq \alpha v_{n-1} - n\alpha^n.\end{aligned}$$

Thus

$$\frac{v_n}{v_{n-1}} \geqq \alpha - \frac{n\alpha^n}{v_{n-1}} \geqq \alpha - \frac{n\alpha^n}{m_1 u_{n-2}} \to \alpha$$

as $n \to \infty$ because of (4.6). Combining this with (4.10) establishes (4.8).

From (2.2) and (4.5) it now follows that

$$w_n \to 1-\beta \qquad (n\to\infty) \tag{4.11}$$

in contradistinction to (3.7). (In this case the convergence is never exponentially fast.) Moreover, from (2.1), we see that p_n converges in norm on any interval $[0,\xi]$ $(\xi<1)$ to the measure

$$\tilde{p}(dx) = \sum_{r=0}^{\infty} \beta x^r q(dx) = \frac{\beta q(dx)}{1-x},$$

regardless of the original distribution p_0. If there is strict inequality in (4.1), p_n does not converge in norm on I. However, in the sense of weak convergence, (p_n) must have convergent subsequences since I is compact, and the limit of any such subsequence must coincide with $\tilde{p}$ on $[0,1)$. Hence the only limit point of (p_n) is the probability measure

$$p(dx) = \frac{\beta q(dx)}{1-x} + \left(1 - \int \frac{\beta q(dy)}{1-y}\right)\varepsilon_1(dx), \tag{4.12}$$

where ε_1 is the probability measure concentrated at 1, and we have proved that p_n converges weakly to p.

Thus, if

$$\int \frac{q(dx)}{1-x}$$

converges, then although q necessarily has no atom there, an atom of probability will grow up at the upper limit of fitness, sufficient to maintain the viability at $1-\beta$. More precisely, for almost all $\xi<1$

$$\lim_{n\to\infty} p_n(\xi,1] = 1-\beta\int_{(0,\xi]} \frac{q(dx)}{1-x} \tag{4.13}$$

will exist, and will not become small as $\xi\to 1$. It is this growth of an apparently new class of highly fit indviduals which suggests the name for this case.

It may seem paradoxical that it is the convergence of the integral in (4.1) which results in the appearance of the atom in (4.12), so that a rapidly decaying mutant fitness distribution produces 'meritocracy'. The point is that a slowly decaying tail, making the integral diverge, can carry enough fitness to keep the mean above $1-\beta$, without sacrificing absolute continuity.

The assignment of the critical situation in which there is equality in (4.1) to the meritocratic rather than the democratic case is somewhat arbitrary, but is justified by the different method of analysis and the failure (in general) of the exponentially fast convergence.

5. Aristocracy

The only situation excluded from the two preceding arguments is that in which (4.6) fails, so that

$$u_n/u_{n-1} \to \sigma < 1 \qquad (n \to \infty). \tag{5.1}$$

When this occurs, $f_n \leqq u_n \leqq \sigma^n$, and this implies that q is concentrated on $[0,\sigma]$. Since only fitness ratios are relevant, the scale of fitness may be changed by a factor so that 1 becomes again the upper limit of the support of q (thus returning either to the democratic or to the meritocratic case), unless the upper limit of the support of p_0 exceeds that of q.

Thus the only new possibility is that in which the mutant fitness distribution is concentrated on an interval $[0,\sigma]$, where σ is strictly less than the upper limit of fitness of the original population (taken without loss of generality to be 1). This is described as *aristocracy*; some of the non-mutant descendants of the original generation are inherently fitter than all possible mutants.

In this case the argument of the last section goes through unchanged, except that the argument after (4.10) now ends with

$$\frac{v_n}{v_{n-1}} \geqq \alpha - \frac{n\alpha^n}{v_{n-1}} \geqq \alpha - \frac{n\alpha^n}{m_{n-1}} \to \alpha,$$

since

$$m_n \geqq \xi^n p_0[\xi, 1]$$

for $\alpha < \xi < 1$. Hence (4.11) is still true (the limiting viability is $1-\beta$), and p_n converges weakly to the measure p defined in (4.12). Notice however that p does now depend on p_0, but only through the upper limit of its support.

Combining the three cases, we have the following table, of which one point worth noting is that the limiting viability is always at least $1-\beta$.

	Democracy	Meritocracy	Aristocracy
Limiting viability	s	$1-\beta$	$1-\beta$
Limiting fitness distribution	absolutely continuous with respect to q	has atom at greatest mutant fitness	has atom at greatest non-mutant fitness
Limit independent of p_0	yes	yes	no

6. Unbounded fitness

It will be clear that the analysis so far depends heavily on the assumption that all fitnesses are bounded; the typical behaviour is that of partial accumulation at or near the upper limit of fitness. It may however be asked what happens to (1.2) if q and p_0 are not restricted to a finite interval. In order that (1.2) should be determinate, it is clearly necessary to suppose that all the moments μ_n and m_n are finite.

In this situation the argument through (2.1) and (2.3) to (4.5) is still valid, except that the positive numbers f_n will not satisfy (4.3). Indeed, if q has unbounded support, $\Sigma f_n z^n$ will converge for no $z > 0$, and in the terminology of [4] (u_n) is a generalised renewal sequence of the wild variety. It is still true (see Section 7) that u_n/u_{n-1} increases with n, but now

(6.1) $$u_n/u_{n-1} \to \infty \qquad (n \to \infty).$$

The argument of Section 4 can be extended to show that

$$v_n/v_{n-1} \to \infty,$$

so that

(6.2) $$w_n \to \infty \qquad (n \to \infty);$$

the viability increases without limit.

This seems to be all that can be said in general, but it is illuminating to consider an example. Suppose for instance that p_0 and q are both the negative exponential distribution with unit mean, so that

(6.3) $$\mu_n = m_n = n!, \quad f_n = \alpha n!$$

with $\alpha = \beta(1-\beta)^{-1}$. It is then easy to show from (4.4) and (4.5) that

(6.4) $$u_n = \alpha n!\{1 + O(n^{-1})\}, \quad W_n = (1-\beta)^{n-1} n!\{1 + O(n^{-1})\},$$

so that

(6.5) $$w_n \sim (1-\beta)n,$$

and from (2.7) the variance of p_n is

$$\int x^2 p_n(dx) - w_n^2 \sim \beta n^2 . \tag{6.6}$$

The linear growth of w_n derives from the exponential tail of the fitness distribution. A tail decaying like $\exp(-x^\gamma)$ would typically make w_n increase as $n^{1/\gamma}$.

7. Completely monotone renewal sequences

In Section 4 the fact was used that a renewal sequence (u_n), for which the corresponding sequence (f_n) is completely monotone, is itself completely monotone. This is the discrete version of a result of Reuter [11], and the proof of Reuter's theorem given in [2] adapts easily to the discrete setting.

One first proves the result when (f_n) is of the special form

$$f_n = \sum_{j=1}^{k} a_j x_j^n , \tag{7.1}$$

where

$$k \geqq 1, \quad a_j > 0, \quad 0 < x_j < 1, \quad \sum_{j=1}^{k} a_j x_j (1 - x_j)^{-1} \leqq 1 . \tag{7.2}$$

In this case

$$U(z) = \sum_{n=0}^{\infty} u_n z^n = \left\{1 - \sum_{n=1}^{\infty} f_n z^n\right\}^{-1}$$
$$= \left\{1 - \sum_{j=1}^{k} a_j x_j z (1 - x_j z)^{-1}\right\}^{-1}$$

is a rational function of degree k with poles at the points z satisfying

$$\sum_{j=1}^{k} a_j x_j z (1 - x_j z)^{-1} = 1 . \tag{7.3}$$

Taking imaginary parts of (7.3),

$$\operatorname{Im}(z) \sum_{j=1}^{k} a_j x_j \,|1 - x_j z|^{-2} = 0 ,$$

so that all roots of (7.3) are real. They clearly cannot lie in $(-\infty, 0]$, and since $u_n \leqq 1$ this means they all lie in $[1, \infty)$. If ζ is one such root, then

$$\lim_{z \to \zeta} (z - \zeta) U(z) = \left\{- \sum_{j=1}^{k} a_j x_j (1 - x_j \zeta)^{-2}\right\} < 0 . \tag{7.4}$$

Hence the roots of (7.3) are simple poles of the rational function $U(z)$, they are

k points $\zeta_1, \zeta_2, \cdots, \zeta_k$ in $[1, \infty)$. The partial fraction expansion of U is therefore of the form

$$U(z) = \sum_{j=1}^{k} \frac{b_j}{\zeta_j - z} \quad (b_j > 0, \zeta_j > 1),$$

whence

$$u_n = \sum_{j=1}^{k} b_j \zeta_j^{-n-1},$$

which is a completely monotone sequence.

To complete the argument, one observes that any completely monotone sequence satisfying (4.3) can be expressed as a limit

$$f_n = \lim_{l \to \infty} f_n(l), \tag{7.5}$$

where $f_n(l)$ is of the form (7.1). The renewal sequence $(u_n(l))$ corresponding to $(f_n(l))$ is completely monotone, and so therefore is the limit

$$u_n = \lim_{l \to \infty} u_n(l). \tag{7.6}$$

Although this is not needed for the present paper, the reverse argument also works as in [2]: the sequence (f_n) corresponding to a completely monotone renewal sequence is itself completely monotone.

There are extensions of these results to the more general setting of [4]. If

$$f_n = \int x^n a(dx), \tag{7.7}$$

for any measure a on an interval $[0, A]$, then

$$\sum_{n=1}^{\infty} f_n \alpha^n \leqq 1 \tag{7.8}$$

for sufficiently small α (for instance for $\alpha = (f_1 + A)^{-1}$). If (u_n) is the generalised renewal sequence corresponding to (f_n), then $(u_n \alpha^n)$ is the renewal sequence corresponding to $(f_n \alpha^n)$, and is therefore completely monotone. Hence u_n is the nth moment of a probability measure on $(0, \alpha^{-1}]$.

More generally, if f_n is of the form (7.7) where the measure a has unbounded support, then (7.5) and (7.6) hold with

$$f_n(l) = \int_{[0,l]} x^n a(dx).$$

It follows that u_n is the nth moment of a probability measure on $(0, \infty)$. In particular u_{n+1}/u_n increases with n, as required in Section 6.

References

[1] Ewens, W. J. (1972) The sampling theory of selectively neutral alleles. *Theoret. Pop. Biol.* **3,** 87–112.

[2] Kingman, J. F. C. (1976) Markov transition probabilities II: completely monotonic functions. *Z. Wahrscheinlichkeitsth.* **9,** 1–9.

[3] Kingman, J. F. C. (1972) *Regenerative Phenomena.* Wiley, London.

[4] Kingman, J. F. C. (1972) Semi-p-functions. *Trans. Amer. Math. Soc.* **174,** 257–273.

[5] Kingman, J. F. C. (1977) The population structure associated with the Ewens sampling formula. *Theoret. Pop. Biol.* **11,** 274–283.

[6] Kingman, J. F. C. (1977) On the properties of bilinear models for the balance between genetic mutation and selection. *Proc. Camb. Phil. Soc.* **81,** 443–453.

[7] Moran, P. A. P. (1976) Global stability of genetic systems governed by mutation and selection. *Proc. Camb. Phil. Soc.* **80,** 331–336.

[8] Moran, P. A. P. (1976) A selective model for electrophoretic profiles in protein polymorphisms. *Genet. Res.* **28,** 47–54.

[9] Moran, P. A. P. (1977) Global stability of genetic systems governed by mutation and selection II. *Proc. Camb. Phil. Soc.* **81,** 435–441.

[10] Ohta, T. and Kimura, M. (1973) A model of mutation appropriate to estimate the number of electrophoretically detectable alleles in a finite population. *Genet. Res.* **22,** 201–204.

[11] Reuter, G. E. H. (1956) Über eine Volterrasche Integralgleichung mit totalmonotonem Kern. *Arch. Math.* **7,** 59–66.

[12] Watterson, G. A. (1976) The stationary distribution of the infinitely-many neutral alleles diffusion model. *J. Appl. Prob.* **13,** 639–651.