

## Effects of dominance on the probability of fixation of a mutant allele

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**Abstract** We consider whether the fixation probability of an allele in a two-allele diploid system is always a monotonic function of the selective advantage of the allele. We show that while this conjecture is correct for intermediate dominance, it is not correct in general for either overdominant or underdominant alleles, and that for some parameter ranges the fixation probability can initially decrease and then increase as a function of the amount of selection. We have partial results that characterize the ranges of parameters for which this happens.

**Keywords** Fixation probability · Monotonicity · Dominance

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### 1 Introduction

Mutations occurring in the genome provide opportunities for species to adapt to the ever changing environment. Studying the fate of newly risen mutations in the population thus enables understanding of how species evolve in response to environmental

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stimuli. Many mutations have little or no effect on the fitness of an individual. These mutations enter and exit the population randomly. Other mutations increase fitness and have a higher probability of spreading across the population. Deleterious mutations are selected against and have a lower probability of being retained in the population. Fisher was the first to examine the fixation probability of a favorable new mutation in a finite population of size  $N$  [5–7]. Malécot generalized the probability of fixation to an arbitrary initial frequency  $p$  of the favorable allele in 1952 [11]. In 1957, Kimura deduced the general formula for the fixation probability by means of a diffusion approximation based on the Kolmogorov backward equation [2,9]. This formula relates the probability of fixation of a new allele with the strength of selection  $s$ , the initial frequency  $p$ , the effective population size  $N_e$ , and the dominance parameter  $h$ . The dominance parameter  $h$  determines how fit the heterozygotes are in relation with the homozygotes. In a two-allele diploid system where  $A$  refers to the new allele and  $a$  is the wild-type allele,  $A$  is said to be dominant if  $Aa$  and  $AA$  individuals have the same fitness.  $A$  is recessive if  $Aa$  and  $aa$  individuals have the same fitness. If the fitness of  $Aa$  individuals falls between the fitnesses of  $AA$  and  $aa$  individuals,  $A$  is said to be of intermediate dominance. If  $Aa$  individuals are the most fit in the population,  $A$  is called an overdominant allele. When the fitness of  $Aa$  individuals is the lowest of the three genotypes,  $A$  is an underdominant allele.

The fixation probability for a new allele with dominant, recessive, or intermediate dominance is a monotonic function over  $s$  [1]. This means that the probability of fixation of a favorable allele increases as  $s$  increases. The effect of  $h$  on the fixation probability depends on  $p$ . For any given positive  $s$ , the fixation probability increases as  $h$  increases when  $p$  is lower than a certain threshold. When  $p$  is higher than the threshold, the fixation probability decreases as  $h$  increases. The threshold increases as  $s$  increases [1]. Therefore when experimenting with a new mutant allele that has intermediate dominance, we can alter the strength of selection on the allele directly to either eliminate it from the population or propagate it across the population.

On the other hand, the relationship between the fixation probability of an overdominant or underdominant allele and the other factors is more complex [2,4,12]. In the case of overdominance, when the initial allele frequency is above a threshold, applying positive selection on a favorable allele results in a fixation probability that is lower than neutral. This threshold frequency is positively correlated with  $s$  and negatively correlated with  $h$ . It was also noted that the favorable allele in the population must be at high frequency in order for positive selection to decrease the fixation probability relative to neutral [1]. Attempts have been made to study the behavior of overdominant alleles in more detail. Ewens and Thomson [4] showed that the average time an overdominant allele takes to fix in or disappear from a finite population is dependent on  $p$ ,  $s$ , and the deterministic equilibrium gene frequency,  $m$ . When  $m$  is between 0.2 and 0.8, the mean fixation time increases with increasing overdominance regardless the value of  $p$ . When  $m$  is outside the range, the relationship between the mean fixation time and the magnitude of overdominance is dependent on  $p$ . The fixation probability of an overdominant allele has also been studied by Nei et al. [12]. They fixed the initial allele frequency and studied the impact of changing  $s$  and  $h$  on fixation probability and noted that when the equilibrium allele frequency is greater than 0.5, the probability is determined by fitness of heterozygotes rather than mutant homozygotes. Thus they

concluded that overdominance enhances the probability of fixation of advantageous mutations. However, the precise roles that  $h$ ,  $s$ , and  $p$  play in determining when the fixation probability for selected alleles is lower than neutral alleles have not been analyzed quantitatively. Without knowing how these variables interact, we are unable to alter the behavior of new mutant alleles precisely in the population.

The purpose of this study is to re-examine the monotonic properties of the fixation probability of an allele with initial frequency  $p$  as a function of  $s$ . While the fixation probability is always monotonic over selection  $s$  for intermediate dominance ( $0 \leq h \leq 1$ ), we show that, for some parameter ranges with both overdominant and underdominant selection, the fixation probability can initially increase as a function of  $s$  for small  $s$  and then eventually decrease, or conversely can initially decrease and then eventually increase. In the underdominant and overdominant cases, this can happen whether or not the initial frequency of the favored allele is less than or greater than the infinite-population-size equilibrium frequency, which is stable with overdominance and unstable with underdominance. We will also identify the precise combinations of  $p$  and  $h$  that result in a lower probability of fixation under positive selection than neutral or result in a higher probability of fixation under negative selection than neutral. These findings will enable us to better understand the behavior of alleles in the population.

In Sect. 2, we will review the fixation probability function that Kimura described and set up the framework in which all later proofs are based on. Mathematical analyses for different combinations of variables are presented in Sects. 3–8. The biological implications and relevance will be discussed in Sect. 9.

### 2 Preliminaries

Let  $p$  be the population frequency of a new allele  $A$  in a two-allele system with diploid fitnesses per generation

$$(AA) \ 1 + \sigma \quad (aA) \ 1 + h\sigma \quad (aa) \ 1$$

Here  $a$  is the background or wild-type allele. If  $N_e$  is the diploid effective population size, the scaled relative selection coefficients are

$$(AA) \ s \quad (aA) \ hs \quad (aa) \ 0 \tag{1}$$

where  $s = 2N_e\sigma$ . The probability of eventual fixation at the new allele  $A$ , as formulated by Kimura, is

$$\Pi(s, p, h) = \frac{\int_0^p e^{s[(2h-1)x^2 - 2hx]} dx}{\int_0^1 e^{s[(2h-1)x^2 - 2hx]} dx} \tag{2}$$

for  $-\infty < s < \infty$  [2, 8, 9]. Except in the case of genic selection ( $h = 1/2$ ), we can complete the squares in the exponent in (2) and obtain the equivalent form

$$\pi(s, p, \alpha) = \Pi(s, p, h) = \frac{\int_0^p e^{\beta s(u-\alpha)^2} du}{\int_0^1 e^{\beta s(u-\alpha)^2} du} = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta s u^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta s u^2} du} \tag{3}$$

In equation (3),  $0 < p < 1$  and

$$\alpha = \frac{h}{2h - 1} \text{ and } \beta = 2h - 1$$

[3]. The range  $0 < \alpha < 1$  corresponds to over and underdominant selection, in which case  $p = \alpha$  is the infinite-population-size equilibrium frequency [3]. In these cases,  $\beta s > 0$  corresponds to overdominant selection and  $\beta s < 0$  to underdominant selection.

A change of variables in (3) leads to

$$\pi(s, p, \alpha) = \Pi(s, p, h) = \frac{\int_{-\alpha L}^{(p-\alpha)L} e^{\pm v^2} dv}{\int_{-\alpha L}^{(1-\alpha)L} e^{\pm v^2} dv} \tag{4}$$

where  $L = \sqrt{|\beta s|}$  and the choice of signs is “+” for overdominant selection ( $\beta s > 0$ ) and “−” for underdominant selection. It follows from (4) that  $\lim_{s \rightarrow \pm\infty} \pi(s, p, \alpha)$  always converges to 0, 1/2, or 1 at an exponential rate in  $s$  for fixed  $\alpha$  or  $h$ .

The goal here is to understand the monotonicity of  $\pi(s, p, \alpha)$  as a function of  $s$  with parameters  $p$  and  $h$ . The following symmetry principle, which essentially describes what happens when we interchange  $A$  and  $a$ , will be helpful in reducing the number of cases.

**Lemma 1** (*The Symmetry Principle*) *If*

$$p^* = 1 - p, \quad h^* = 1 - h, \quad \text{and } s^* = -s \tag{5}$$

*then*  $\Pi(s^*, p^*, h^*) = 1 - \Pi(s, p, h)$ . *In particular*

$$\Pi(s, p, h) = 1 - \Pi(-s, 1 - p, 1 - h) \tag{6}$$

*Proof* We work with  $\pi(s, p, \alpha)$ . The change of parameters above gives

$$\alpha^* = 1 - \alpha \quad \text{and} \quad \beta^* = -\beta$$

The change of variable  $v = -u$  then shows  $\pi(s^*, p^*, \alpha^*) = 1 - \pi(s, p, \alpha)$ . □

### 3 Intermediate dominance

Intermediate dominance is defined by  $0 \leq h \leq 1$ . In this case, the fixation probability is monotonic as a function of  $s$ .

**Theorem 1** *Assume  $0 \leq h \leq 1$  and  $0 < p < 1$  for fixed  $p$ . Then the fixation probability  $\Pi(s, p, h)$  is strictly increasing as a function of  $s$  for  $-\infty < s < \infty$ . Moreover, it converges to 1 as  $s \rightarrow \infty$  and converges to zero as  $s \rightarrow -\infty$ .*

*Proof* Although intuitively obvious, the proof is not immediate even for genic selection ( $h = 1/2$ ). The formulation in equations (3) and (4) holds only if  $h \neq 1/2$ . If  $h = 1/2$ , then  $\Pi(s, p, 1/2) = (1 - e^{-sp})/(1 - e^{-s})$  [3] and

$$\frac{\partial \Pi}{\partial s}(s, p, 1/2) = \frac{e^{-sp}}{(1 - e^{-s})^2} \left( p + (1 - p)e^{-s} - e^{-s(1-p)} \right)$$

This is positive for all  $s$  by the convexity of the function  $h(p) = e^{-sp}$ . (Equivalently,

$$g(p) = p + (1 - p)e^{-s} - e^{-s(1-p)}$$

satisfies  $g(0) = g(1) = 0$  and  $g''(p) = -s^2e^{-s(1-p)} < 0$  for  $0 < p < 1$ , so that  $g(p) > 0$  for  $0 < p < 1$ .)

The proof for  $h \neq 1/2$  is similar in spirit to this argument, but is more complex since we will not be able to use convexity. For  $h \neq 1/2$ , define  $\alpha = h/(2h - 1)$  and  $\beta = 2h - 1$  as before. Then  $2\alpha - 1 = 1/(2h - 1)$ , so that  $\alpha \leq 0$  if  $0 \leq h < 1/2$  and  $\alpha \geq 1$  if  $1/2 < h \leq 1$ .

Differentiating the expression

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta su^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta su^2} du}$$

with respect to  $s$  leads to

$$\frac{\partial \pi}{\partial s}(s, p, \alpha) = \frac{G(s, p)}{\left( \int_{-\alpha}^{1-\alpha} e^{\beta su^2} du \right)^2} \tag{7}$$

for

$$G(s, p) = \int_{-\alpha}^{1-\alpha} e^{\beta su^2} du \int_{-\alpha}^{p-\alpha} \beta u^2 e^{\beta su^2} du - \int_{-\alpha}^{1-\alpha} \beta u^2 e^{\beta su^2} du \int_{-\alpha}^{p-\alpha} e^{\beta su^2} du. \tag{8}$$

In particular  $G(s, 0) = G(s, 1) = 0$ . Also

$$\frac{\partial G}{\partial p}(s, p) = -\beta e^{\beta s(p-\alpha)^2} \left( \int_{-\alpha}^{1-\alpha} u^2 e^{\beta su^2} du - (p - \alpha)^2 \int_{-\alpha}^{1-\alpha} e^{\beta su^2} du \right) \tag{9}$$

Then we have shown

**Lemma 2** For a fixed  $s$ ,  $(\partial/\partial p)G(s, p_0) = 0$  for  $p = p_0$  implies

$$\int_{-\alpha}^{1-\alpha} u^2 e^{\beta su^2} du = (p_0 - \alpha)^2 \int_{-\alpha}^{1-\alpha} e^{\beta su^2} du. \tag{10}$$

It follows by substituting equation (10) into (8) that

$$G(s, p_0) = \beta \left( \int_{-\alpha}^{1-\alpha} e^{\beta su^2} du \right) \int_{-\alpha}^{p_0-\alpha} \left( u^2 - (p_0 - \alpha)^2 \right) e^{\beta su^2} du \tag{11}$$

whenever  $(\partial/\partial p)G(s, p_0) = 0$ ,

In general, we say that a point  $p_0$  is a *singular value* of a function  $F(p)$  if  $F'(p_0) = 0$ . Similarly,  $p_0$  is a *singular value for  $p$*  of  $G(s, p)$  if  $\frac{\partial}{\partial p}G(s, p_0) = 0$ . We have as a general principle

**Lemma 3** Let  $F(p)$  be a smooth function defined for  $0 \leq p \leq 1$  such that  $F(0) = F(1) = 0$ . If  $F(p_0) > 0$  at all singular values  $p_0$  of  $F(p)$  in the interval  $0 < p < 1$ , then  $F(p) > 0$  for all  $p$  with  $0 < p < 1$ .

Similarly, if  $F(p_0) < 0$  at all singular values  $p_0$  of  $F(p)$  in  $0 < p < 1$ , then  $F(p) < 0$  for  $0 < p < 1$ .

In other words, if  $F(0) = F(1) = 0$ , in order to show that  $F(p) > 0$  for  $0 < p < 1$ , it is sufficient to show that  $F(p_0) > 0$  at all singular values  $p$ . The proof follows from the fact that if the minimum value of  $F(p)$  for  $0 \leq p \leq 1$  is negative, then the minimum value must be attained at a singular value  $p_0$  of  $F(p)$  with  $0 < p_0 < 1$ .

Fix a value of  $s$  and consider the function

$$F(p) = G(s, p)$$

Then  $F(0) = F(1) = 0$  since  $G(s, 0) = G(s, 1) = 0$  in equation (8). Then if  $p = p_0$  is a critical point of  $F(p)$ ,  $G(s, p_0)$  must satisfy the relation (11).

First, assume  $0 \leq h < 1/2$ . Then  $\alpha = h/(2h - 1) \leq 0$  and  $\beta = 2h - 1 < 0$ . Since  $0 \leq -\alpha < u < p_0 - \alpha$  inside the integral in (11), the integrand  $u^2 - (p - \alpha)^2 < 0$ . Since  $\beta < 0$ , it follows that  $G(s, p_0) > 0$  whenever  $(\partial/\partial p)G(s, p_0) = 0$ . This implies that  $G(s, p) > 0$  for all  $0 < p < 1$  by Lemma 3. Hence  $(\partial/\partial s)\pi(s, p, \alpha) > 0$  for all  $p$  and  $s$  by equation (7). Thus  $\pi(s, p, \alpha)$  is an increasing function of  $s$ . The case  $1/2 < h < 1$  follows by symmetry (Lemma 1).

We next identify the limits as  $s \rightarrow \pm\infty$ . First, assume  $s > 0$ . Assuming  $\alpha \leq 0$  and  $\beta = 2h - 1 < 0$ , we can write

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta su^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta su^2} du} = \frac{\int_{-\alpha L}^{(p-\alpha)L} e^{-v^2} dv}{\int_{-\alpha L}^{(1-\alpha)L} e^{-v^2} dv}$$

where  $L = \sqrt{-\beta s} = \sqrt{|\beta|s}$ . In particular  $0 \leq -\alpha L < (p - \alpha)L < (1 - \alpha)L$ . It follows from the identity

$$\int_A^B e^{-v^2} dv = \int_A^\infty e^{-v^2} dv - \int_B^\infty e^{-v^2} dv$$

for  $0 < A < B$  and the relation  $\int_A^\infty e^{-v^2} dv \sim (1/2A)e^{-A^2}$  as  $A \rightarrow \infty$  that

$$\lim_{s \rightarrow \infty} \pi(s, p, \alpha) = 1.$$

Now assume  $s < 0$ . It follows from a similar argument based on the relation  $\int_0^A e^{v^2} dv \sim (1/2A)e^{A^2}$  as  $A \rightarrow \infty$  that

$$\lim_{s \rightarrow -\infty} \pi(s, p, \alpha) = 0$$

□

#### 4 Underdominance with $s > 0$ and $0 < p < \alpha$

Assume  $h < 0$  and  $s > 0$ . Then  $\alpha = h/(2h - 1)$  satisfies  $0 < \alpha < 1/2$  with  $\beta = 2h - 1 < 0$ . Since  $0 < p < \alpha$ , this corresponds to the initial frequency of the favored allele  $A$  being less than the infinite-population unstable equilibrium frequency  $p_0 = \alpha$ . Our results in this case are

**Theorem 2** Assume  $h < 0$ ,  $s > 0$ , and  $0 < p < \alpha$ . Then

- (i)  $\pi(s, p, \alpha)$  is decreasing as  $s$  increases for  $s \geq \tau_1$ , where  $\tau_1$  is given by

$$\tau_1 = \frac{\ln(\frac{\alpha}{\alpha-p})}{p(2\alpha - p)(1 - 2h)} \tag{12}$$

- (ii) If  $3\alpha - 1 < p < \alpha$ , which is automatically satisfied if  $p < \alpha$  and  $h \geq -1$ , then  $\pi(s, p, \alpha)$  is increasing in  $s$  near  $s = 0$ . This means that  $\pi(s, p, \alpha)$  increases near  $s = 0$  but decreases for  $s \geq \tau_1$ .
- (iii) If  $0 < p \leq 3\alpha - 1 < \alpha$ , which can only happen if  $h < -1$ , then  $\pi(s, p, \alpha)$  is decreasing for all  $s \geq 0$ .

*Proof* We begin with part (i). For simplicity set

$$a = \alpha \quad \text{and} \quad b = 1 - \alpha$$

Since  $0 < \alpha < 1/2$ ,  $0 < a < b$  with  $a + b = 1$ . We write the fixation probability (3) as in equation (4):

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta su^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta su^2} du} = \frac{f(L)}{g(L)} \tag{13}$$

where  $L = \sqrt{-\beta s} = \sqrt{|\beta|s}$  and

$$f(L) = \int_{-aL}^{-(a-p)L} e^{-v^2} dv, \quad g(L) = \int_{-aL}^{bL} e^{-v^2} dv. \tag{14}$$

Then

$$\frac{\partial \pi}{\partial L}(s, p, \alpha) = \left( \frac{f'(L)}{g'(L)} - \frac{f(L)}{g(L)} \right) \frac{g'(L)}{g(L)}. \tag{15}$$

By equation (14),  $g(L) > 0$  and

$$g'(L) = be^{-(bL)^2} + ae^{-(aL)^2} > 0.$$

Hence

$$\frac{\partial \pi}{\partial s}(s, p, \alpha) = \frac{|\beta|}{2L} \frac{\partial \pi}{\partial L}(s, p, \alpha) > 0 \tag{16}$$

if and only if

$$\frac{f'(L)}{g'(L)} > \frac{f(L)}{g(L)}. \tag{17}$$

Again by (14)

$$\frac{f'(L)}{g'(L)} = \frac{1 - \left(\frac{a-p}{a}\right)e^{p(2a-p)L^2}}{1 + \frac{b}{a}e^{-(b-a)L^2}} \leq 0 \tag{18}$$

whenever

$$L^2 \geq \frac{\ln\left(\frac{a}{a-p}\right)}{p(2a-p)} \tag{19}$$

where  $L^2 = |\beta|s$ . Since  $f(L)$  and  $g(L)$  are both positive, it follows from equations (15) and (16) that  $f'(L)/g'(L) \leq 0$  is sufficient for  $(\partial/\partial s)\pi(s, p, \alpha) < 0$ . It follows that  $\pi(s, p, \alpha)$  is a decreasing function of  $s$  as long as equation (19) is satisfied. This completes the proof of part (i).



For part (ii), we consider  $(\partial/\partial s)\pi(0, p, \alpha)$ . By equations (7) and (8)

$$\frac{\partial \pi}{\partial s}(0, p, \alpha) = G(0, p) = -\beta \frac{p(1-p)(p-(3\alpha-1))}{3} > 0 \tag{20}$$

since  $\beta = 2h - 1 < 0$  and  $3\alpha - 1 < p < \alpha$ . Since  $\alpha = h/(2h - 1)$ ,  $3\alpha - 1 = (h + 1)/(2h - 1)$ . Thus  $3\alpha - 1 \leq 0$  if  $h \geq -1$ , so that  $3\alpha - 1 < p$  is automatic if  $h \geq -1$ . This completes the proof of part (ii) of Theorem 2.

Finally, assume  $h < -1$  and  $p \leq 3\alpha - 1$ . Then we can write equation (18) in the form

$$\frac{f'(L)}{g'(L)} = H(t) = \frac{1 - Ce^{At}}{1 + De^{-Bt}}, \quad t = L^2 \tag{21}$$

where

$$\begin{aligned} A &= p(2a - p) > 0, & B &= b - a = 1 - 2\alpha > 0, \\ C &= (a - p)/a > 0, & D &= b/a > 1 \end{aligned} \tag{22}$$

Let  $\Delta(t) = 1 + De^{-Bt}$  be the denominator in (21). Then

$$\begin{aligned} \Delta(t)^2 H'(t) &= -ACe^{At} - ACDe^{(A-B)t} + BDe^{-Bt} - BCDe^{(A-B)t} \\ &< (-AC(1 + D) + BD(1 - C))e^{(A-B)t} \\ &= \frac{-p(1-p)}{a^2} (3\alpha - 1 - p)e^{(A-B)t} \end{aligned} \tag{23}$$

In particular, if  $0 < p \leq 3\alpha - 1$ , then  $H'(t) < 0$  for all  $t > 0$ .

It then follows from equation (21) that  $f'(L)/g'(L)$  is strictly decreasing for  $L > 0$ . We claim that this implies

$$\frac{f'(L)}{g'(L)} < \frac{f(L)}{g(L)} \tag{24}$$

for all  $0 < L < \infty$ .

To prove this, set

$$Q(x) = g(L)f(x) - f(L)g(x)$$

Then  $Q(0) = Q(L) = 0$  since  $g(0) = f(0) = 0$  by (14). It follows that  $Q'(x_0) = 0$  for some  $x_0$  with  $0 < x_0 < L$ . Then

$$\begin{aligned} Q'(x_0) = 0 &= \left( \frac{f'(x_0)}{g'(x_0)} - \frac{f(L)}{g(L)} \right) g'(x_0)g(L) \\ &> \left( \frac{f'(L)}{g'(L)} - \frac{f(L)}{g(L)} \right) g'(x_0)g(L) \end{aligned} \tag{25}$$

since  $f'(x)/g'(x)$  is decreasing,  $g'(x_0) > 0$ , and  $g(L) > 0$ . This implies the relation (24) for all  $L > 0$ . Then, by arguing as in equations (15) and (16),  $\pi(s, p, \alpha)$  is strictly decreasing in  $s$  for  $0 < s < \infty$ . This completes the proof of Theorem 2.  $\square$

If  $h > 1$ , then  $1/2 < \alpha < 1$  and  $\alpha < 3\alpha - 1$ , where  $3\alpha - 1 = (h + 1)/(2h - 1) < 1$  only if  $h > 2$ . The symmetry lemma now implies

**Corollary 1** Assume  $h > 1$  and  $\alpha < p < 1$ . Then

- (i)  $\pi(s, h, \alpha)$  has a local maximum for  $s < 0$  (and hence fails to be monotonic for  $s < 0$ ) if  $\alpha < p < 3\alpha - 1$ . The condition  $p > \alpha$  is sufficient if  $h \leq 2$ .
- (ii)  $\pi(s, h, \alpha)$  is an increasing function of  $s$  for  $s < 0$  if  $h > 2$  and  $3\alpha - 1 < p$ .

Again by the symmetry lemma, the underdominant case with  $h < 0$ ,  $s > 0$ , and  $p > \alpha$  is essentially equivalent to the underdominant case with  $h > 1$ ,  $s < 0$ , and  $p < \alpha$ , which we will consider later. We next consider an overdominant case that is mathematically similar to the preceding section.

**5 Overdominance with  $s < 0$  and  $0 < p < \alpha$**

Assume  $h < 0$  and  $s < 0$ , so that the heterozyge  $Aa$  is most fit. As in the previous section,  $\alpha = h/(2h - 1)$  satisfies  $0 < \alpha < 1/2$  and  $\beta = 2h - 1 < 0$ . We also assume  $0 < p < \alpha$ , so that the initial frequency of the disfavored allele  $A$  is less than the infinite-population stable equilibrium frequency. Then

**Theorem 3** Assume  $h < 0$ ,  $s < 0$ , and  $0 < p < \alpha$  for  $\alpha = h/(2h - 1)$ . Then

- (i) If  $3\alpha - 1 \leq p < \alpha$ , which is automatically satisfied if  $h \geq -1$ , the fixation probability  $\pi(s, p, \alpha)$  is strictly increasing as  $s$  increases in the range  $-\infty < s \leq 0$ .
- (ii) If  $0 < p < 3\alpha - 1 < \alpha$ , which can only happen if  $h < -1$ ,  $\pi(s, p, \alpha)$  has a local maximum strictly between  $s = -\tau_2$  and  $s = 0$ , where  $\tau_2$  is a positive constant independent of  $p$  that is defined below. The fixation probability is strictly decreasing as  $s$  increases for  $s < 0$  near zero and for  $0 \leq s < \infty$ . It is strictly increasing as  $s$  increases for  $s \leq -\tau_2$ . (Here  $s > 0$  is the underdominant case discussed in the previous section.)
- (iii) If  $p = 3\alpha - 1$ , which can only happen if  $h < -1$ , the fixation probability  $\pi(s, p, \alpha)$  is strictly increasing as  $s$  increases for  $s < 0$  and strictly decreases as  $s$  increases for  $s > 0$ . In particular,  $s = 0$  is the unique maximum point of  $\pi(s, p, \alpha)$ .

*Proof* The proof of part (i) is similar to the previous section. Since  $s < 0$  and  $\beta = 2h - 1 < 0$ , the fixation probability  $\pi(s, p, \alpha)$  in (3) satisfies

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta su^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta su^2} du} = \frac{f(L)}{g(L)} \tag{26}$$

where  $L = \sqrt{|\beta s|}$ ,  $a = \alpha$ ,  $b = 1 - \alpha$ , and

$$f(L) = \int_{-aL}^{-(a-p)L} e^{v^2} dv, \quad g(L) = \int_{-aL}^{bL} e^{v^2} dv. \tag{27}$$

Moreover

$$\frac{f'(L)}{g'(L)} = H(t) = \frac{1 - Ce^{-At}}{1 + De^{Bt}}, \quad t = L^2 \tag{28}$$

where  $A, B, C, D$  are the same positive constants as in (22). If  $\Delta(t) = 1 + De^{Bt}$  is the denominator in (28), then

$$\begin{aligned} \Delta(t)^2 H'(t) &= (1 + De^{Bt})(ACe^{-At}) - (1 - Ce^{-At})(BDe^{Bt}) \\ &< (AC(1 + D) - BD(1 - C))e^{(B-A)t} \\ &= \frac{p(1-p)}{a^2}(3\alpha - 1 - p)e^{(B-A)t}. \end{aligned} \tag{29}$$

Since  $3\alpha - 1 \leq p < \alpha$  by assumption,  $H'(t) < 0$  for all  $t > 0$ , and  $f'(L)/g'(L)$  is decreasing for  $L > 0$ . As before, this implies (24) and hence  $\frac{\partial \pi}{\partial L}(s, p, \alpha) < 0$ . Since  $L = \sqrt{|\beta s|} = \sqrt{(-\beta)(-s)}$  for  $s < 0$ , this implies that  $\pi(s, p, \alpha)$  is a decreasing function of  $|s|$  in the range  $-\infty < s < 0$  and hence an increasing function of  $s$  in the same range. This completes the proof of part (i).

For part (iii), assuming  $p = 3\alpha - 1$ , the argument in (29) implies that  $\pi(s, p, \alpha)$  is strictly increasing in  $s$  for  $s < 0$ , and the argument in (23) implies that  $\pi(s, p, \alpha)$  is strictly decreasing in  $s$  for  $s > 0$ . This completes the proof of part (iii).

The situation for part (ii) is more complicated. First, as in equation (20) above, since  $p < 3\alpha - 1$  and  $\beta < 0$ ,

$$\frac{\partial \pi}{\partial s}(0, p, \alpha) = G(0, p) = -\beta \frac{p(1-p)(p - (3\alpha - 1))}{3} < 0.$$

Therefore,  $\pi(s, p, \alpha)$  is strictly decreasing around  $s = 0$ , and hence is strictly increasing as a function of  $|s|$  for small  $s < 0$ .

Next, by a change of variables

$$\frac{\int_{-a}^b u^2 e^{\beta su^2} du}{\int_{-a}^b e^{\beta su^2} du} = \frac{\int_{-aL}^{bL} v^2 e^{v^2} dv}{L^2 \int_{-aL}^{bL} e^{v^2} dv}.$$

for  $L = \sqrt{\beta s}$ . Then

**Lemma 4** For arbitrary  $a > 0, b > 0$ , and  $L > 0$ ,

$$\lim_{L \rightarrow \infty} \frac{\int_{-aL}^{bL} v^2 e^{v^2} dv}{L^2 \int_{-aL}^{bL} e^{v^2} dv} = (\max(a, b))^2 \tag{30}$$

*Proof* This follows from the relations

$$\int_0^A e^{v^2} dv \sim \frac{1}{2A} e^{A^2} \quad \text{and} \quad \int_0^A v^2 e^{v^2} dv \sim \frac{A}{2} e^{A^2}$$

for large positive  $A$ , where we assume for simplicity that  $0 < a \leq b$ . □

If  $0 < a < b$  with  $a + b = 1$ , Lemma 4 says that the limit of the ratio in the expression (30) is  $b^2$ . The next lemma gives some explicit constants.

**Lemma 5** *Suppose that  $0 < a < d < c < b$  satisfy*

$$b^2 > (1 + 2(b - c))d^2$$

*Then*

$$\frac{\int_{-aL}^{bL} e^{v^2} dv}{L^2 \int_{-aL}^{bL} e^{v^2} dv} > a^2$$

*whenever*

$$L^2 > \frac{d^2}{d^2 - a^2} L_0^2 \quad \text{for} \quad L_0^2 = \frac{\frac{d^2 - a^2}{b^2 - a^2} + \frac{2d^2(c+a)}{b^2 - c^2}}{b^2 - d^2(1 + 2(b - c))}$$

*Proof* Define

$$f(L) = \int_{-aL}^{bL} v^2 e^{v^2} dv \quad \text{and} \quad g(L) = L^2 \int_{-aL}^{bL} e^{v^2} dv.$$

Then

$$\begin{aligned} \frac{f'(L)}{g'(L)} &= \frac{b^2 + a^2 e^{(a^2 - b^2)L^2}}{\frac{2}{L} e^{-b^2 L^2} \int_{-aL}^{bL} e^{v^2} dv + 1 + e^{(a^2 - b^2)L^2}} \\ &\geq \frac{b^2 + a^2 e^{(a^2 - b^2)L^2}}{\frac{2}{L} e^{-b^2 L^2} \int_{-aL}^{bL} e^{v^2} dv + 1 + \frac{1}{(b^2 - a^2)L^2}}, \end{aligned} \tag{31}$$

where we use the identity  $e^{-x} \leq 2/x$  for  $x > 0$  for the last inequality.

Now, pick some  $c$  and  $d$ ,  $a < d < c < b$ , satisfying

$$b^2 > (1 + 2(b - c))d^2,$$

which is possible since  $b > a$ , as long as  $c$  is close to  $b$  and  $d$  is close to  $a$ . Then

$$\begin{aligned} \frac{2}{L} e^{-b^2 L^2} \int_{-aL}^{bL} e^{v^2} dv &= \frac{2}{L} e^{-b^2 L^2} \left( \int_{-aL}^{cL} e^{v^2} dv + \int_{cL}^{bL} e^{v^2} dv \right) \\ &\leq \frac{2}{L} e^{-b^2 L^2} \left( e^{c^2 L^2} (c+a)L + e^{b^2 L^2} (b-c)L \right) \\ &= 2(c+a)e^{-(b^2-c^2)L^2} + 2(b-c) \\ &\leq \frac{2(c+a)}{(b^2-c^2)L^2} + 2(b-c). \end{aligned} \tag{32}$$

Substituting equation (32) into equation (31) we derive

$$\begin{aligned} \frac{f'(L)}{g'(L)} &\geq \frac{b^2 + a^2 e^{(a^2-b^2)L^2}}{\frac{2(c+a)}{(b^2-c^2)L^2} + 2(b-c) + 1 + \frac{1}{(b^2-a^2)L^2}} \\ &\geq \frac{b^2 + \frac{a^2}{(b^2-a^2)L^2}}{\frac{2(c+a)}{(b^2-c^2)L^2} + 2(b-c) + 1 + \frac{1}{(b^2-a^2)L^2}} \geq d^2 \end{aligned} \tag{33}$$

providing that

$$L^2 \geq L_0^2 = \frac{\frac{d^2-a^2}{b^2-a^2} + \frac{2d^2(c+a)}{b^2-c^2}}{b^2 - d^2(1 + 2(b-c))}. \tag{34}$$

Then for any  $L > L_0$ , we have, by the mean value theorem [or by arguing as in (25)], that there is an  $M, L_0 < M < L$ , such that

$$\frac{f(L) - f(L_0)}{g(L) - g(L_0)} = \frac{f'(M)}{g'(M)} \geq d^2 \tag{35}$$

where the last inequality follows from equation (33). On the other hand, we can rewrite equation (35) as

$$\frac{f(L)}{g(L)} \frac{1 - \frac{f(L_0)}{f(L)}}{1 - \frac{g(L_0)}{g(L)}} \geq d^2.$$

Now,

$$g(L_0) = L_0^2 \int_{-aL_0}^{bL_0} e^{v^2} dv \leq L_0^2 \int_{-aL}^{bL} e^{v^2} dv = \frac{L_0^2}{L^2} g(L);$$

thus,

$$\frac{g(L_0)}{g(L)} \leq \frac{L_0^2}{L^2} < 1.$$

It follows that

$$\frac{f(L)}{g(L)} \frac{1}{1 - \frac{g(L_0)}{g(L)}} \geq \frac{f(L)}{g(L)} \frac{1 - \frac{f(L_0)}{f(L)}}{1 - \frac{g(L_0)}{g(L)}} \geq d^2,$$

or

$$\frac{f(L)}{g(L)} \geq \left(1 - \frac{g(L_0)}{g(L)}\right) d^2.$$

Hence,

$$\frac{f(L)}{g(L)} \geq \left(1 - \frac{g(L_0)}{g(L)}\right) d^2 \geq \left(1 - \frac{L_0^2}{L^2}\right) d^2 > a^2$$

as long as

$$L^2 > \frac{d^2}{d^2 - a^2} L_0^2. \tag{36}$$

In conclusion, in light of equation (34) and equation (36), as long as equation (36) holds, we can ensure that

$$\frac{f(L)}{g(L)} > a^2.$$

□

For  $a = \alpha$  and  $b = 1 - \alpha$ , it follows from the preceding lemma that we have

$$\frac{\int_{-\alpha}^{1-\alpha} u^2 e^{\beta su^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta su^2} du} > \alpha^2$$

whenever

$$|s| > \tau_2 > \frac{\frac{d^2}{d^2 - a^2} L_0^2}{|\beta|} \tag{37}$$

with  $L_0$  given in equation (34). (Recall  $L^2 = |\beta s|$ .) This implies that for  $s < -\tau_2$ , the right hand side of  $\partial G/\partial p$  in (9) is positive for  $s < -\tau_2$ . Therefore,  $G(s, p)$  is an increasing function of  $p$  for  $s < -\tau_2$ . As  $G(s, 0) = 0$ , we conclude that  $G(s, p) > 0$  for  $s < -\tau_2$  and  $0 < p \leq p_0$ , and so the function  $\pi(s, p, \alpha)$  is a strictly increasing function as long as  $s < -\tau_2$ .

Now

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{|\beta s|u^2} du}{\int_{-\alpha}^{1-\alpha} e^{|\beta s|u^2} du}.$$

Since the integrand in the numerator integral is strictly decreasing over the two (negative) limits of integration, we see

$$\int_{-\alpha}^{p-\alpha} e^{|\beta s|u^2} du \leq pe^{|\beta s|\alpha^2}. \tag{38}$$

Dividing the fractional expression of  $\pi(s, p, \alpha)$  by  $e^{|\beta s|\alpha^2}$  and applying (38), we arrive at

$$\begin{aligned} \pi(s, p, \alpha) &\leq \frac{p}{\int_{-\alpha}^{1-\alpha} e^{|\beta s|(u^2-\alpha^2)} du} \leq \frac{p}{\int_{\alpha}^{1-\alpha} e^{|\beta s|(u^2-\alpha^2)} du} \\ &\leq \frac{p}{\int_{1/2}^{1-\alpha} e^{|\beta s|(u^2-\alpha^2)} du} \leq \frac{p}{\int_{1/2}^{1-\alpha} e^{|\beta s|((1/2)^2-\alpha^2)} du} \\ &= \frac{p}{0.5 - \alpha} e^{-|\beta s|((1/2)^2-\alpha^2)}. \end{aligned}$$

□

As in Corollary 1, the symmetry lemma implies

**Corollary 2** Assume  $h > 1$  and  $\alpha < p < 1$ . Then

- (i)  $\pi(s, h, \alpha)$  is a decreasing function of  $s$  for  $s > 0$  if  $\alpha < p < 3\alpha - 1$ . The condition  $p > \alpha$  is sufficient if  $h \leq 2$ .
- (ii)  $\pi(s, h, \alpha)$  has a local maximum for  $s > 0$  (and hence fails to be monotonic for  $s > 0$ ) if  $h > 2$  and  $3\alpha - 1 < p$ .

**6 The borderline case  $p = \alpha = h/(2h - 1)$**

We can have  $0 < \alpha < 1$  only if  $h < 0$  or  $h > 1$ . Then  $\beta = 2h - 1$  has the same sign as  $h$ , and the alleles are overdominant if  $\beta s > 0$  and underdominant if  $\beta s < 0$ . If  $\beta s > 0$ ,  $0 < \alpha < 1/2$  if and only if  $s < 0$ , or equivalently if and only if the wild-type homozygote  $aa$  is more fit.

**Theorem 4** Assume  $p = \alpha$  where  $0 < \alpha < 1$ . Then in the overdominant case ( $\beta s > 0$ )

$$\begin{aligned} \lim_{s \rightarrow \infty} \pi(s, p, \alpha) &= 0 \quad \text{if } 0 < \alpha < 1/2 \\ &= 1 \quad \text{if } 1/2 < \alpha < 1 \end{aligned} \tag{39}$$

while in the underdominant case ( $\beta s < 0$ )

$$\lim_{s \rightarrow \infty} \pi(s, p, \alpha) = 1/2 \text{ for all } \alpha \tag{40}$$

*Proof* By the Symmetry Lemma 1, we can assume  $h < 0$ . Then  $\beta = 2h - 1 < 0$  and  $0 < \alpha < 1/2$ . As in equation (3)

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^0 e^{\beta s u^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta s u^2} du} = \frac{\int_{-\alpha L}^0 e^{\pm v^2} du}{\int_{-\alpha L}^{(1-\alpha)L} e^{\pm v^2} du} = \frac{f(L)}{g(L)} \tag{41}$$

where  $f(L)$  and  $g(L)$  are the numerator and denominator of the immediately preceding ratio,  $\pm$  has the same sign as  $\beta s$ , and  $L = \sqrt{|\beta s|}$ .

First, assume  $s > 0$ , which is the underdominant case  $\beta s < 0$ . As in equations (18) and (21),

$$\frac{f'(L)}{g'(L)} = H(t) = \frac{1}{1 + D e^{-Bt}}, \quad t = L^2 = |\beta s|$$

where  $B = b - a = 1 - 2\alpha > 0$  and  $D = b/a > 1$ . In particular,  $H(t)$  is a strictly increasing function of  $t$  for  $t \geq 0$ . The argument in equation (25) then implies  $f'(L)/g'(L) > f(L)/g(L)$  for all  $L > 0$ . Hence  $\pi(s, p, \alpha)$  is increasing for  $s > 0$  by equations (15) and (16).

A parallel analysis for  $s < 0$  beginning with equations (26) and (27) shows that  $\pi(s, p, \alpha)$  is also strictly increasing in  $s$  for  $-\infty < s < 0$ .

Finally, the relations in (39) and (40) follow from (41) and the asymptotic relations

$$\int_A^\infty e^{-v^2} dv \sim \frac{1}{2A} e^{-A^2} \quad \text{and} \quad \int_0^A e^{v^2} dv \sim \frac{1}{2A} e^{A^2}$$

for large positive  $A$ . □

### 7 The cases with $0 < \alpha < p < 1$

These cases correspond to overdominance and underdominance with the initial allele frequency of  $A$  greater than the equilibrium frequency. The overdominant case  $s > 0$ ,  $h > 1$ , and  $p > \alpha$  is essentially equivalent to the overdominant case  $s < 0$ ,  $h < 0$ , and  $p < \alpha$  by Lemma 1. The underdominant case  $s > 0$ ,  $h > 1$ , and  $p > \alpha$  is equivalent to the underdominant case  $s > 0$ ,  $h < 0$ , and  $p < \alpha$ . These two cases were handled in the preceding two sections.

Similarly, the overdominant case  $s < 0$ ,  $h < 0$ , and  $\alpha < p < 1$  is equivalent to the overdominant case  $s > 0$ ,  $h > 1$  and  $0 < p < \alpha$ , and the underdominant case  $s > 0$ ,  $h < 0$ , and  $\alpha < p < 1$  is equivalent to the underdominant case  $s < 0$ ,  $h > 1$ , and  $0 < p < \alpha$ . Both of these cases are considered in the next section.



### 8 The cases $h > 1$ and $0 < p < \alpha$

Here  $\alpha = h/(2h - 1)$  satisfies  $1/2 < \alpha < 1$  and  $\beta = 2h - 1 > 0$ . The case  $s < 0$  with  $0 < p < \alpha$  corresponds to underdominance with the initial frequency of the unfavored allele less than the unstable equilibrium frequency  $p_0 = \alpha$ . Similarly,  $s > 0$  with  $h > 1$  corresponds to overdominance with initial frequency of the favored allele  $A$  less than the infinite-population unstable equilibrium frequency.

This case is similar to the earlier cases with  $h < 0$  and  $0 < p < \alpha$  except that now  $s < 0$  is underdominant for  $h > 1$  and  $s > 0$  is the overdominant case, which is the reverse of the situation before.

**Theorem 5** Assume  $h > 1$  and  $0 < p < \alpha = h/(2h - 1)$ . Then

- (i) For  $s < 0$ , the fixation probability  $\pi(s, p, \alpha)$  is strictly decreasing as a function of  $|s|$  for  $-\infty < s < -\tau_3 < 0$ , where

$$\tau_3 = \frac{\ln(\frac{\alpha}{\alpha-p})}{p(2\alpha - p)(2h - 1)} \tag{42}$$

- (ii) For  $s < 0$  and  $2\alpha - 1 \leq p < \alpha$ , then  $\pi(s, p, \alpha)$  is strictly decreasing as a function of  $|s|$  for all  $s < 0$ .
- (iii) For  $s > 0$ ,  $\pi(s, p, \alpha)$  is a strictly increasing function of  $s$  in all cases. In all cases with  $0 < p < \alpha$ ,

$$\lim_{s \rightarrow \infty} \pi(s, p, \alpha) = 1$$

*Proof* For part (i), assume  $s < 0$ , which is the underdominant case. Since  $\beta = 2h - 1 > 0$ ,  $\beta s < 0$  and we can write the fixation probability

$$\pi(s, p, \alpha) = \frac{\int_{-\alpha}^{p-\alpha} e^{\beta s u^2} du}{\int_{-\alpha}^{1-\alpha} e^{\beta s u^2} du} = \frac{f(L)}{g(L)} \tag{43}$$

for  $L = \sqrt{|\beta s|}$  and

$$f(L) = \int_{-aL}^{-(a-p)L} e^{-v^2} dv, \quad g(L) = \int_{-aL}^{bL} e^{-v^2} dv. \tag{44}$$

Here  $a = \alpha$  and  $b = 1 - \alpha$  as before, except that now  $b < a$ . The argument from equations (15) to (19) implies  $\frac{\partial \pi}{\partial L}(s, p, \alpha) < 0$  for  $L = \sqrt{\beta(-s)}$  provided that

$$s \leq -\tau_3 = -\frac{\ln(\frac{\alpha}{\alpha-p})}{p(2\alpha - p)(2h - 1)} \tag{45}$$

Since  $\partial L/\partial s < 0$ , it follows that  $\pi(s, p, \alpha)$  is strictly increasing as  $s$  increases for  $s < -\tau_3$ . This completes the proof of part (i).

For part (ii), assume  $2\alpha - 1 \leq p < \alpha$ . As in (18), we can write

$$\frac{f'(L)}{g'(L)} = H(t) = \frac{1 - Ce^{At}}{1 + De^{Bt}}, \quad t = L^2 \tag{46}$$

where now

$$\begin{aligned} A &= p(2\alpha - p) > 0, & B &= a - b = 2\alpha - 1 > 0, \\ C &= (a - p)/a > 0, & D &= b/a > 0 \end{aligned} \tag{47}$$

If  $\Delta(t) = 1 + De^{Bt}$  is the denominator in (46),

$$\Delta(t)^2 H'(t) = -ACe^{At} - (A - B)CDe^{(A+B)t} - BDe^{Bt} < 0 \tag{48}$$

for all  $t \geq 0$  since

$$A - B = p(2\alpha - p) - (2\alpha - 1) = (1 - p)(p - (2\alpha - 1)) \geq 0$$

Thus  $\pi(s, p, \alpha)$  is a strictly decreasing function of  $|s|$  for all  $s < 0$ .

For part (iii), assume  $s > 0$ . As before,  $\pi(s, p, \alpha)$  is given by equation (43) with  $L = \sqrt{\beta s}$  and

$$f(L) = \int_{-aL}^{-(a-p)L} e^{v^2} dv, \quad g(L) = \int_{-aL}^{bL} e^{v^2} dv. \tag{49}$$

As in (28),

$$\frac{f'(L)}{g'(L)} = H(t) = \frac{1 - Ce^{-At}}{1 + De^{-Bt}}, \quad t = L^2 \tag{50}$$

for the positive constants  $A, B, C, D$  in (47).

If  $\Delta(t) = 1 + De^{-Bt}$  is the denominator in (50), then

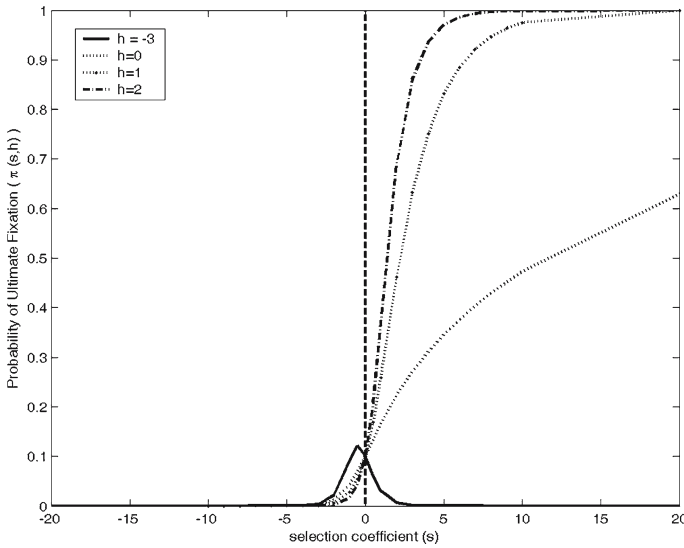
$$\Delta(t)^2 H'(t) = ACe^{-At}(1 + De^{-Bt}) + BDe^{-Bt}(1 - Ce^{-At}) > 0$$

for all  $t \geq 0$  since  $C = (\alpha - p)/\alpha < 1$ . It follows as before that  $f'(L)/g'(L)$  is increasing in  $L$  and hence that  $\pi(s, p, \alpha)$  is strictly increasing in  $s$ .

Finally,  $\lim_{s \rightarrow \infty} \pi(s, p, \alpha) = 1$  follows from the representation

$$\pi(s, p, \alpha) = \frac{\int_{-aL}^{-(a-p)L} e^{v^2} dv}{\int_{-aL}^{bL} e^{v^2} dv} \tag{51}$$

together with the asymptotic relation  $\int_0^A e^{v^2} dv \sim (1/2A)e^{A^2}$  for large positive  $A$ . The convergence is uniform in  $p$  for  $0 < \epsilon \leq p \leq \alpha$  for any  $\epsilon > 0$ . □

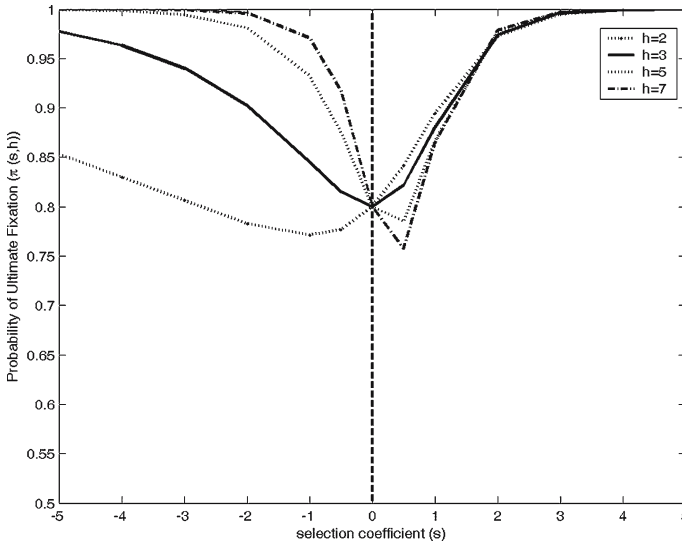


**Fig. 1** Probability of fixation of a new allele when its initial frequency is 0.1 with different dominance factors

### 9 Discussion

The goal of the present work is to show that the fixation probability of new alleles is not monotonic over all real values of  $s$ . At intermediate dominance ( $0 \leq h \leq 1$ ), the probability of eventual fixation of the derived allele  $A$  is a monotonic function of the selection coefficient  $s$  of the homozygote  $AA$  for any fixed initial frequency  $p$  of  $A$ . In contrast, if the new allele  $A$  is overdominant or underdominant, the behavior of the fixation probability curve depends on  $p$ . For instance, for  $p = 0.1$ , the fixation probability is monotonic for  $h \geq 0$  but peaks at a negative value of  $s$  when  $h = -3$  (Fig. 1). We have shown analytically that when  $h < 0$ , the fixation probability fails to be monotonic over all real values of  $s$  if  $0 < p < h/(2h-1) < 0.5$ . The fixation probability also fails to be monotonic over  $s$  when  $h > 1$  and  $0.5 < h/(2h-1) < p < 1$ . More specifically in the overdominance case where  $s < 0$  and  $h < 0$ , if  $0 < p < (1+p)/3 < h/(2h-1) < 0.5$ , then the fixation function is not monotonic. Similarly when  $s > 0$  and  $h > 1$ , the function is not monotonic if  $0.5 < (h/(2h-1)) < (1+p)/3 < p < 1$ . In the underdominance case where  $s < 0$  and  $h > 1$ ,  $0.5 < (1+p)/3 < h/(2h-1) < p < 1$  renders the function not monotonic. When  $s > 0$  and  $h < 0$ , if  $0 < p < h/(2h-1) < (1+p)/3 < 1/2$ , the fixation probability is not monotonic.

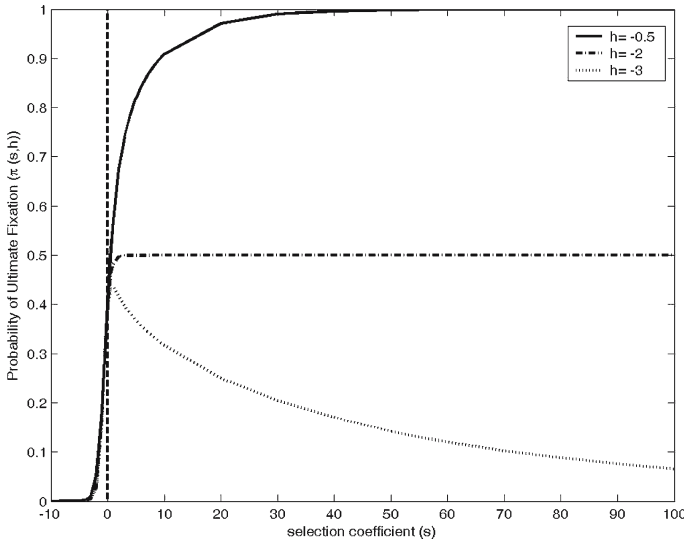
When the derived allele,  $A$ , is overdominant and  $p$  is high, its fixation probability is inversely correlated with  $h$  (Fig. 2,  $s \geq 0$ ). In contrast, the fixation probability increases as  $h$  increases when the derived allele is underdominant (Fig. 2,  $s < 0$ ). This change in relationship between  $h$  and fixation probability can be explained by the impact of heterozygotes have on the frequency of the ancestral allele  $a$ . As the fitness of heterozygotes become higher, they produce more offspring therefore increasing numbers of both alleles in the population. Since  $h$  is positively correlated with frequency of  $a$  and



**Fig. 2** Probability of fixation of a new allele when its initial frequency is 0.8 with different dominance factors

the fixation probability of  $A$  is inversely correlated with frequency of  $a$ , an increase in  $h$  then in turn decreases the fixation probability of  $A$ . In the underdominant case, increase in  $h$  suggests increase in the relative fitness of  $aa$  individuals over the other two genotypes. In order for  $a$  to spread in the population (i.e., fixation of  $A$  goes to 0), the ancestral allele needs to persist in the forms of heterozygotes. Since the heterozygotes are the least fit of the three genotypes, the heterozygous stage creates a barrier for  $a$  to spread. As  $h$  increases, the fitness of heterozygotes decreases and the barrier for  $a$  becomes harder to cross. As fixation probability of  $a$  is inversely correlated with fixation probability of  $A$ ,  $h$  is therefore positively correlated with the fixation probability of  $A$ . These results concur with previous observation that fixation probability is determined by the fitness of heterozygotes rather than mutant homozygotes [12].

We have determined that in the case of overdominance ( $h > 1$  and  $s > 0$ ), when  $0.5 < h/(2h - 1) < (1 + p)/3 < p < 1$ , applying positive selection actually decreases the fixation probability relative to neutral (Fig. 2,  $h=5$  and  $h=7$ ). Our results agree with previous reports that the new allele must be at high frequency to see this effect [1]. At a fixed  $p$  that satisfies the condition, the amount of decrease in fixation probability relative to neutral when applying positive  $s$  is positively correlated with the fitness of the heterozygotes (e.g.,  $h = 5$  and  $h = 7$  in Fig. 2). This decrease in fixation probability can be attributed to the low frequency of  $a$ . As the fitness of heterozygotes increases, number of copies of both alleles increase as well. Since the initial frequency of  $a$  is low, the proportion of increase of  $a$  is much greater than  $A$ . The allele  $a$  then can persist in the population longer thereby decreasing the probability of fixation of  $A$ . Similar findings were reported by Ewens et al. [4] when they studied the average time it takes an allele to fix in the population. They noticed that in the case when  $p$



**Fig. 3** Probability of fixation of a new allele when its initial frequency is 0.4 with different dominance factors

is large and the equilibrium frequency is small [equivalent to  $p > h/(2h - 1)$ ], the average time to fixation increases then subsequently decreases.

When  $0.5 < (1 + p)/3 < h/(2h - 1) < p < 1$ , the fixation probability of an underdominant allele is lower than neutral for some  $s$  (Fig. 2,  $h = 2$  over  $s < 0$ ). Since the heterozygotes are the least fit, it is harder for  $A$  to propagate in the population relative to no selection. As selection on heterozygotes becomes stronger, the fixation probability of  $A$  actually increases. This may seem counter-intuitive, but the low frequency of  $a$  makes it more venerable to the impact of heterozygous disadvantage. Thus  $a$  would disappear from the population faster than  $A$ , leaving  $A$  to have a higher fixation probability at stronger  $s$ . In the case where  $h/(2h - 1) = (1 + p)/3$ , applying either positive selection or negative selection increase fixation probability relative to neutral (Fig. 2,  $h = 3$ ).

We have shown that when  $p = h/(2h - 1)$ , the fixation probability of  $A$  stays at 0.5, regardless of the amount of selection applied (Fig. 3). This phenomenon is seen only when the allele is underdominant. The heterozygotes are selected against, but in a way that neither of the alleles increases or decreases in frequency. This is a case where the fitness of homozygous advantage is balanced with the heterozygous disadvantage.

Knowing how dominance  $h$  and initial allele frequency  $p$  interact in determining the fate of a new allele in the population is important when we are interested in removing an undesired allele from the population. For example, recent studies have investigated the potential for introgressing a desired engineered gene into a pest population to control the pest problem by means of genetically engineered underdominance in the population [10]. It is crucial to know how many mutants to release into the population to achieve the desired outcome in a most cost effective way. This is not a trivial problem. As we have shown in the current study, some combinations of  $h$  and  $p$  can

actually increase the fixation probability of undesired alleles, abolishing the original intent.

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