Lethal mutations with fluctuating heterozygous effect: The lethal force of effective dominance

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ABSTRACT

The theory of population genetics leads to the expectation that in very large populations the frequencies of recessive lethal mutations are close to the square root of the mutation rate, corresponding to mutation-selection balance. There are numerous examples where the frequencies of such alleles are orders of magnitude larger than this result. In this work we theoretically investigate the role of temporal fluctuations in the heterozygous effect (h) for lethal mutations in very large populations. For fluctuations of h, around a mean value of $\bar{h}$, we find a biased outcome that is described by an *effective dominance coefficient*, h_{eff}, that is generally less than the mean dominance coefficient, i.e., $h_{\text{eff}} < \bar{h}$. In the case where the mean dominance coefficient is zero, the effective dominance coefficient is *negative*: $h_{\text{eff}} < 0$, corresponding to the lethal allele behaving as though overdominant and having an elevated mean frequency. This case plausibly explains mean allele frequencies that are an order of magnitude larger than the equilibrium frequency of a recessive allele with a constant dominance coefficient. Our analysis may be relevant to explaining lethal disorders with anomalously high frequencies, such as cystic fibrosis and Tay-Sachs, and may open the door to further investigations into the statistics of fluctuations of the heterozygous effect.

1 Introduction

Lethal, recessive alleles can result from a variety of mutational processes, including insertions, deletions, inversions, duplications and substitutions [1]. The rate at which each of these mutations arise is not known with much accuracy, but is believed to be rare. For example, lethal recessive alleles occur at a per base pair mutation rate of the order of 10^{-8} [2]. Natural selection is expected to

take action once homozygotes of the recessive alleles appear, and eventually a balance between mutation and selection becomes established, where the loss of lethal mutations, via homozygotes, is balanced by the arrival of new mutations. This scenario is expected to play out in large, effectively infinite, populations, where theory predicts that a mutation rate $\sim 10^{-8}$ leads to an equilibrium mutation frequency in the vicinity of 0.0001 (see e.g., [3]). It has been a cause of much interest, then, that a number of lethal recessive disorders have reached frequencies that are orders of magnitude greater. For example, Tay-Sachs has a frequency of the lethal mutation (*mutation frequency* for short) of 0.0133 among Ashkenazic Jews and 0.0015 in non-Jewish populations [4]. The cystic fibrosis ΔF508 mutation has a mean frequency of 0.022 in the European Union [5] and sickle-cell anaemia, in some parts of sub-Saharan Africa, has a mutation frequency that can be as high as 0.15 [6] (although it should be noted that lethality amongst homozygotes is not universal, even in sub-Saharan Africa; the best example of lethality is the mutation in the SLC4A1 gene in Papua New Guinea and Malaysia [7]).

When the population size is sufficiently large that it excludes genetic drift as the cause of any departure from mutation-selection equilibrium, heterozygote advantage, or overdominance, remains as the most likely underlying genetic mechanism for producing such high mutation frequencies, probably due to the action of pleiotropic effects [8]. For some disorders, such as sickle-cell anaemia, overdominance is well established [9]. More generally, however, evidence is much more speculative. For example, a selective advantage of Tay-Sachs heterozygotes against tuberculosis has been suggested [4] (but see [10]), and cystic fibrosis carriers have been implicated with resistance to cholera [11] as well as tuberculosis [12]. With lethality, the usual one gene-two allele-three genotype model simplifies to a two-genotype model, that applies in the stage of the life

cycle where the lethal genotype is absent. In this model the fitness of the heterozygote can be taken to be relative to that of the wild-type homozygote. As such, the mutant frequency is directly influenced by the fitness of the carrier of the lethal allele (namely the heterozygote), and this fitness can fluctuate due to a variety of biotic and physical (environmental) changes. Such changes can proceed over all time scales [13]. Relevant examples include periodic bouts of tuberculosis epidemics, which are thought to have influenced the prevalence of cystic fibrosis, which we know to have been quite common on occasion since the seventeenth century, but relatively absent during more recent history [12]. In the UK, annual deaths attributed to tuberculosis were greater than 35 000 (approx 0.1% of population) at the beginning of the twentieth century and did not drop below 5 000 (approx 0.01%) until the mid 1950s [14], where the mortality rate has remained ever since.

However, the most recent and comprehensive analysis of recessive lethal disorders claimed that no evidence of a heterozygote effect could be found [15]. On this basis, it was concluded in [15] that *ascertainment bias* was the most probable cause of the reported departure of lethal mutation frequencies from what would be expected from mutation-selection balance.

A recent theoretical treatment of the lethal recessive model followed on from [15] and highlighted the disproportionate influence of transitory weak overdominance on equilibrium mutation frequencies [16]. Thus where [15] identified a greater discrepancy with diseases with lower mutation rates, [16] explicitly established that as the mutation rate decreases, the influence of overdominance on the equilibrium mutation frequency increases. Specifically, where heterozygotes have a selective advantage, the equilibrium mutation frequency becomes essentially independent of the mutation rate. Here, we build upon this observation by considering the situation that, although the heterozygous effect (also

referred to as the dominance coefficient of the lethal allele) may, on average, be zero, fluctuations around this mean value over time may be disproportionately influenced by episodes of overdominance relative to those of partial recessivity. By doing so we propose a mechanistic explanation, in addition to the presence of an ascertainment bias, underpinning the observation of disease mutations being out of mutation-selection balance. Thus we present an analysis for fluctuating heterozygous effect in the strong selection context of lethal mutations, which appears to be lacking in the literature.

We can incorporate a non-zero mean value of the heterozygous effect into the model. However, taking the mean heterozygous effect to be zero constitutes a useful null model which may provide an explanation in its own right, or point to the need of a non-zero mean heterozygous effect, which may be hard to detect in the presence of temporal fluctuations of the heterozygous effect.

2 Model

We base our analysis on the extension of an explicit model of a diploid dioecious population with equal sex ratio [16]. In this model, generations are discrete, census is made in adults, and the life cycle is as follows.

Life cycle	
Adults (start of generation)	
↓	gamete production and mutation; random mating
Zygotes	
↓	death of all adults; viability selection
Juveniles	
↓	number regulation
Adults (start of next generation)	

At the start of a generation, we assume each diploid adult produces haploid gametes that randomly fertilize one another to form zygotes. Viability selection then acts at a single biallelic locus, and determines the probability a zygote will survive to reproduce. We write the two alleles at the locus as a and A, and generally the aa, aA and AA genotypes have different viabilities. A common way of parameterising relative fitnesses (equivalent here to relative viabilities) is in terms of a selection coefficient, s, which determines the difference in relative fitness of the two homozygotes, and a dominance coefficient, h, which determines the relative fitness of the heterozygote. In terms of s and h, the relative fitnesses of the three genotypes are $w_{aa} = 1-s$, $w_{aA} = 1-hs$, and $w_{AA} = 1$, respectively. In the present work we take the a allele to be the cause of a genetic disease, to the extent this allele is lethal in homozygous form. This entails $s = 1$ and leads to the relative fitnesses

$$w_{aa} = 0, \qquad w_{aA} = 1 - h, \qquad w_{AA} = 1. \tag{1}$$

Relative fitnesses, like absolute fitnesses, are non-negative, and this puts restrictions on the possible values of the dominance coefficient, h. For the relative fitness of the heterozygote to be non-negative, i.e., for $w_{aA} = 1-h \geq 0$, requires h to be restricted to the range

$$-\infty < h \leq 1. \tag{2}$$

In terms of the dominance coefficient, h, the disease-causing allele (the a allele) is overdominant if $h < 0$, completely recessive if $h = 0$, partially recessive if $0 < h < 1$ (which includes having additive effects on fitness, when $h = \frac{1}{2}$), and completely dominant if $h = 1$. There is no possibility of underdominance ($h > 1$) since this would violate Eq. (**??**), and lead to negative relative fitnesses.

We incorporate one-way mutation into the model, from the wild-type allele to the disease-causing allele, such that in any generation, each A allele in the population has probability u of undergoing mutation to the a allele:

$$A \underset{u}{\to} a \tag{3}$$

and remains unchanged with probability $1 - u$.

Generally, there is the non-selective process of number regulation in the life cycle. The individuals that remain in the population after this process become the adults of the next generation. Number regulation is a source of randomness in the dynamics of the frequency of the lethal allele (random genetic drift), but this plays little or no role in the case of a very large population, and is neglected in the present work. However, such randomness will be relevant to extensions of this work to finite populations.

3 Results

3.1 Basic dynamics of the frequency

We use X_t to denote the frequency of the disease-causing allele (the a allele) in generation t, and shall often refer to this just as the *frequency*. The corresponding frequency of the wild-type allele (the A allele) is $1 - X_t$.

In a very large population, random genetic drift (due to number regulation) plays a negligible role. The frequency (of the disease-causing allele) can then be treated as behaving deterministically and, as far as the behaviour of the frequency is concerned, the number of adults in the population is effectively infinite. We shall use the phrase *infinite population* to describe such a situation.

For an infinite population, the rule that relates the frequency in the next

generations t and $t+1$ has the form

$$X_{t+1} = X_t + F(X_t) \tag{4}$$

where $F(x)$ is the evolutionary *force* which acts on the frequency of the disease-causing allele, when it has the value x. If, in any generation, the force is non-zero, then the frequency will be different in the following generation.

When the force $F(x)$ has a small magnitude ($|F(x)| \ll 1$), as we shall assume, the frequency will only change by a small amount each generation. The behaviour of the frequency can then be accurately analysed under a continuous time approximation of Eq. (**??**). Writing $X(t)$ for the continuous time approximation of X_t, we have

$$\frac{dX(t)}{dt} = F(X(t)). \tag{5}$$

The form of the force $F(x)$ appearing in Eqs. (**??**) and (**??**) is derived in Part A of the Supplementary Material (see also [16, 17]). The exact result for the force $F(x)$ has a complicated form (see Eq. (A9) of Part A of the Supplementary Material) that makes it hard to see its essential features. To circumvent this, we shall use a simple approximation for the force that applies under the conditions that: (i) the mutation rate, u, is extremely small, (ii) the magnitude of the dominance coefficient, $|h|$, is small, and (iii) because the most important behaviour of the force manifests itself at low frequencies, the frequency itself also takes small values. These conditions correspond to

$$u \lll 1, \qquad |h| \ll 1, \qquad x \ll 1 \tag{6}$$

and when applicable we find that the force is well approximated by

$$F(x) \simeq u - hx - x^2 \tag{7}$$

(see Part B of the Supplementary Material for details). An illustration of the different forms that $F(x)$ can take, depending on the value of h, is given in Figure 1.

FIGURE 1 HERE

The force $F(x)$ in Eq. (**??**) has a maximum value, written $F_{\max}$, that is given by

$$F_{\max} \equiv F_{\max}(h) = \begin{cases} u + \dfrac{h^2}{4} & \text{for } h < 0 \\ \\ u & \text{for } h \geq 0 \end{cases} \tag{8}$$

(see Part C of the Supplementary Material for details). A relatively large value of the maximum means the force has the potential to produce relatively large changes in the frequency. It follows form Eq. (**??**) that when h is negative and $|h| \gg 2\sqrt{u}$, the maximum of the force will be much larger than when h is zero or positive.

When h is constant (independent of time) there is an equilibrium corresponding to a stable polymorphism at a frequency we write as $x^* \equiv x^*(h)$. At this frequency the force vanishes:

$$F(x^*) = 0. \tag{9}$$

The frequency of the stable polymorphism is given by

$$x^* \equiv x^*(h) = \begin{cases} \dfrac{|h| + \sqrt{h^2 + 4u}}{2} & \text{for } h < 0 \\ \sqrt{u} & \text{for } h = 0 \\ \dfrac{2u}{h + \sqrt{h^2 + 4u}} & \text{for } h > 0 \end{cases} \tag{10}$$

and simple approximations follow from Eq. (**??**) (see Part C of the Supplementary Material), as follows. When h is negative and obeys $|h| \gg 2\sqrt{u}$, but is still small (consistent with Eq. (**??**)), we have $x^* \simeq |h|$. Thus in this negative range of h we have x^* essentially independent of the mutation rate. By contrast for $h \geq 0$ the result for x^* in Eq. (**??**) has a value that is small because the mutation rate is very small ($u \lll 1$). In particular, if $h \gg 2\sqrt{u}$ (but still small) then $x^* \simeq u/h$.

Although Figure 1 is schematic, it correctly illustrates that the maximum force is larger, for $h < 0$, than the value it has for $h \geq 0$. Figure 1 also correctly illustrates the ordering of the sizes of the stable polymorphism frequency, for different values of h. In particular, the following features (indicated in Figure 1) hold: (i) the maximum value of the force satisfies $F_{\max}(h < 0) > F_{\max}(h \geq 0)$ with $F_{\max}(h \geq 0) = u$; (ii) the frequency of the stable polymorphism (the frequency where the force vanishes) obeys $x^*(h < 0) > x^*(0) > x^*(h > 0)$. In Table 1 we give an illustration of the different numerical values that $F_{\max}$ and x^* can take for three different values of h, for a given mutation rate.

TABLE 1 HERE

The results in Table 1 complement Figure 1, by giving plausibly realistic

examples of the considerable differences that can arise in the maximum force, $F_{\max}$, and the frequency of the stable polymorphism, x^*, from relatively small differences in h. In particular, the value of $F_{\max}$ that arises for the negative value of h in Table 1 is four orders of magnitude larger than the corresponding value of $F_{\max}$ for non-negative h. Also in Table 1, the frequency of the stable polymorphism, for the negative value of h, is two orders of magnitude larger than the corresponding value for h equal to zero.

3.2 Behaviour of $X(t)$ for fluctuating h

When h has a *constant value* (i.e., is independent of time), we can solve Eq. (**??**) and obtain a form for the frequency, $X(t)$, that approaches the stable polymorphism frequency, x^*, at large times. Some results for this case are given in [17].

For time-dependent h the situation is more complex. If h has a *known* time dependence, then we can solve Eq. (**??**) with a known time-dependent force (time dependent because h depends on time) and determine $X(t)$ (numerical methods may be needed to obtain the solution).

The assumed more common situation, that we shall focus upon in this work, is where h *randomly fluctuates* (equivalently, that h is a *stochastic process*, or that the selection contains *noise* [18, 19]), and we only have knowledge of some statistical properties of h. We shall work under the assumption that no systematic changes occur in the environment over time. Thus as far as h is concerned, all times are statistically equivalent, with no single time distinguished in any way. This means the stochastic process $h(t)$ is *temporally homogeneous*[1] [20]. With $E[...]$ denoting the mean (or expected) value, which is obtained from an average over many realisations of $h(t)$, the following are then the most basic

[1] Temporal homogeneity means the correlation of $h(t_1)$ and $h(t_2)$ only depends on t_1 and t_2 in the combination $t_1 - t_2$.

statistical properties of $h(t)$.

1. The mean value of $h(t)$.

   We write this as $\bar{h}$ thus

$$E[h(t)] = \bar{h}. \tag{11}$$

2. The strength of the autocorrelations of $h(t)$ over time.

   We write this as σ^2 and define it by

$$\int_{-\infty}^{\infty} E[\big(h(t+r) - \bar{h}\big)\,\big(h(t) - \bar{h}\big)]dr = \sigma^2. \tag{12}$$

We shall make some additional assumptions about the statistics of $h(t)$, in order to specify details underlying Eq. (**??**). First, we take $h(t)$ to have Gaussian statistics [20, 21], which are determined by the mean value of $h(t)$ and pairwise correlations between $h(t)$ at different times. The mean value of $h(t)$ and the strength of correlations of $h(t)$ ($\bar{h}$ and σ^2, respectively), take constant values, given our assumption of temporal homogeneity of $h(t)$. Next, we assume the following. (1) Correlations between $h(t_1)$ and $h(t_2)$ are appreciable over a *non-zero* range of $t_1 - t_2$, a range we term the *correlation time* and denote by t_c. (2) The correlation time, t_c, is significantly smaller than the time it takes the frequency ($X(t)$) to change appreciably[2]. To obtain the behaviour of the frequency over times that are large compared with t_c, we approximate t_c as being negligibly small[3], which corresponds to treating the fluctuations of $h(t)$ in the 'white noise' limit [20]. The form of $h(t)$ is then given by $h(t) = \bar{h} + \sigma dW(t)/dt$ where $W(t)$ is a standard Wiener process (or Brownian motion), and represents

[2] If $h(t)$ is correlated over relatively long times, then it ceases to behave like random fluctuations and is more plausibly represented as a known time-dependent function of time.

[3] The approach we adopt, that the correlation time is non-zero but we treat as being negligible, plays an important role in the way the noise is treated (see Part D of the Supplementary Material).

white noise fluctuations [20, 21] (see Part D of the Supplementary Material for further details).

3.2.1 Averaging over the fluctuations

In the absence of a detailed history of the fluctuations of $h(t)$ over time, a rational procedure is to average over the fluctuations. We thus shall consider the distribution (probability density) of $X(t)$, which arises from an average over all realisations of the fluctuations of $h(t)$, and which determines all statistics of $X(t)$ (such as the mean and variance).

Let $\phi(x,t)$ denote the distribution of $X(t)$ when evaluated at a frequency of x. In Part D of the Supplementary Material we show that this distribution obeys the diffusion equation

$$-\frac{\partial}{\partial t}\phi(x,t) = -\frac{1}{2}\frac{\partial^2}{\partial x^2}\left[\sigma^2 x^2 \phi(x,t)\right] + \frac{\partial}{\partial x}\left[F_{\text{eff}}(x)\phi(x,t)\right] \tag{13}$$

where

$$F_{\text{eff}}(x) = u - h_{\text{eff}}x - x^2 \tag{14}$$

with

$$h_{\text{eff}} = \bar{h} - \tfrac{1}{2}\sigma^2. \tag{15}$$

The quantity $F_{\text{eff}}(x)$ in Eq. (**??**) represents the *effective deterministic force* which acts on the frequency in the presence of fluctuations in h, assuming frequencies are small ($x \ll 1$). The effective force, $F_{\text{eff}}(x)$, which depends on the *effective dominance coefficient*, h_{eff}, now takes over the role of the force $F(x)$ of Eq. (**??**), which applies when h is not random. While Eq. (**??**) applies for $0 \leq x \leq 1$, it is adequate to use $F_{\text{eff}}(x)$ in this equation for results that are largely determined by low frequencies, such as the stationary distribution (see

next section).

We note that despite the fact that fluctuations in h are symmetrically distributed around the mean value, $\bar{h}$, they have a systematic influence on the frequency, and lead to an effective dominance coefficient that lies at the value $h_{\text{eff}} = \bar{h} - \frac{1}{2}\sigma^2$ (cf. Eqs. (**??**) and (**??**)). Since $\sigma^2 \geq 0$ the effective dominance coefficient is generally less than the mean value, $\bar{h}$. Such behaviour[4] plausibly follows from Figure 1, where a negative value of h has a much larger influence on the force than the equal and opposite positive value.

In the case where the mean dominance coefficient is zero ($\bar{h} = 0$) the effective dominance coefficient h_{eff}, appearing in Eqs. (**??**) and (**??**), is negative, and has the value $-\frac{1}{2}\sigma^2$. This corresponds to what could be described as 'fluctuation induced overdominance' of the lethal allele. Another way of saying this is that when h exhibits variation over time around an average value of zero, as described above, the form of the effective force given in Eq. (**??**), makes it explicit that there is an effective dominance coefficient acting that is negative, corresponding to overdominance.

3.2.2 The stationary distribution and its properties

In the absence of any information about the state of the disease allele at any particular time, we shall describe the frequency of the disease allele using the *stationary distribution*. This is the time-independent distribution of the frequency which becomes established at long times, irrespective of the initial state of the frequency. Adopting the stationary distribution is the most parsimonious approach since it contains no information about earlier (unknown) states of the

[4]The form of h_{eff} in Eq. (**??**) has a wider applicability than just fluctuating h. For the alternative selection scheme $w_{aa} = 0$, $w_{aA} = 1 - \zeta$ and $w_{AA} = 1 + \eta$, where $|\zeta|$ and $|\eta|$ are small, an approximation for the force is $F(x) \simeq u - (\eta + \zeta)x - x^2$ (see Eq. (B2) of Part B of the Supplementary Material). When there are fluctuations in the fitnesses of the non-lethal genotypes, i.e., in ζ and η, all results will be equivalent to just h fluctuating providing $\eta(t) + \zeta(t)$ has the same statistical properties as those we have adopted for $h(t)$.

frequency, and is the unique time-independent distribution that embodies all information we have about the frequency.

We write the stationary distribution as $\hat{\phi} \equiv \hat{\phi}(x)$. This is the time independent solution of Eq. (**??**). In terms of the composite parameters

$$\alpha = \frac{2\bar{h}}{\sigma^2} \text{ and } \beta = \frac{4\sqrt{u}}{\sigma^2} \tag{16}$$

and the scaled frequency

$$\hat{x} = \frac{x}{\sqrt{u}} \tag{17}$$

the solution for the stationary distribution is

$$\hat{\phi} = \frac{\hat{x}^{-(1+\alpha)} \exp\left[-\frac{\beta}{2}\left(\hat{x} + \hat{x}^{-1}\right)\right]}{2\sqrt{u}K_\alpha\left(\beta\right)} \tag{18}$$

(see Part E of the Supplementary Material for details) where $K_\alpha(\beta)$ denotes a modified Bessel function of the second kind of order α and argument β [22].

Following from Eq. (**??**), the mean allele frequency in the stationary distribution is

$$E_{\text{stat}}\left[X\right] = \sqrt{u}\frac{K_{1-\alpha}\left(\beta\right)}{K_\alpha\left(\beta\right)}. \tag{19}$$

and the variance is

$$\text{Var}_{\text{stat}}\left(X\right) = u\left[\frac{K_{2-\alpha}\left(\beta\right)}{K_\alpha\left(\beta\right)} - \left(\frac{K_{1-\alpha}\left(\beta\right)}{K_\alpha\left(\beta\right)}\right)^2\right] \tag{20}$$

(see Part E of the Supplementary Material for details).

3.2.3 Results for $\bar{h} = 0$

When $\bar{h} = 0$, the parameter α in Eq. (**??**) vanishes and Eq. (**??**) reduces to $E_{\text{stat}}\left[X(t)\right]_{\bar{h}=0} = \sqrt{u}K_1\left(\beta\right)/K_0\left(\beta\right)$. For comparison, we note that in the situa-

tion where h takes the constant value of 0 (i.e., h does not contain fluctuations), the equilibrium value of the frequency, associated with a stable polymorphism, is $x^*|_{h=0} \equiv x^*(0) = \sqrt{u}$ (see Eq. (**??**)). A measure on the *typical effect* of fluctuations in h on the frequency can be taken as the ratio of the mean frequency of the stationary distribution (which takes into account fluctuations in h), to the equilibrium frequency (which applies in the absence of fluctuations in h). For the case of $\bar{h} = 0$ we thus define

$$R_0 \stackrel{\text{def}}{=} \frac{E_{\text{stat}}\left[X(t)\right]_{\bar{h}=0}}{x^*(0)} = \frac{K_1(\beta)}{K_0(\beta)}. \tag{21}$$

Generally, we have $R_0 \geq 1$, corresponding to an *enhancement* of the mean stationary frequency, in the presence of fluctuations, over the equilibrium value in the absence of fluctuations. In Figure 2 we plot R_0 against $\sigma^2/(4\sqrt{u}) \equiv 1/\beta$, which is a scaled measure of the strength of the fluctuations in h.

FIGURE 2 HERE

It is evident from Figure 2 that at $\sigma = 0$ the ratio R_0 has the value 1. This follows because in the absence of fluctuations in h the expected value of the stationary distribution coincides with the stable polymorphism frequency that applies when h has the constant value of 0.

Assuming a mutation rate of $u = 10^{-8}$, the maximum value of σ used in Figure 2 is $\sigma = 0.2$, which is perhaps slightly large for the approximations adopted.

A small β approximation accurately describes the dependence of R_0 on $1/\beta = \sigma^2/(4\sqrt{u})$. With γ denoting Euler's constant ($\gamma \simeq 0.5772$), the small β

approximation reads

$$R_0 \simeq \frac{\beta^{-1}}{\ln\left(2\beta^{-1}e^{-\gamma}\right)} = \frac{1}{4}\frac{\sigma^2}{\sqrt{u}}\frac{1}{\ln\left(\frac{\sigma^2}{\sqrt{u}}\frac{e^{-\gamma}}{2}\right)}. \tag{22}$$

For $\beta^{-1} > 10$ the error between Eqs. (**??**) and (**??**) is smaller than 2%. Equation (**??**) shows that R_0 grows *substantially* slower than linearly with $\beta^{-1} = \sigma^2/\sqrt{u}$, at large values of this parameter.

Figure 2 shows that relatively small fluctuations in h around a mean value of zero, with $\sigma^2 \leq 0.04$, can produce mean allele frequencies that are ~ 20 times larger than the corresponding frequency in the absence of fluctuations.

In addition to the ratio R_0, a statistic of the stationary distribution that quantifies how fluctuations in h cause variability in observed values of the frequency, is the coefficient of variation of the frequency, $\sqrt{\mathrm{Var}_{\mathrm{stat}}\left(X(t)\right)}/E_{\mathrm{stat}}\left[X(t)\right]$. Using Eqs. (**??**) and (**??**) for $\bar{h} = 0$ we find that as $\sigma^2/\left(4\sqrt{u}\right)$ runs from 0 to 100 (the range covered in Figure 2), the coefficient of variation increases from 0 to approximately 2.9.

4 Discussion

In this work we have considered lethal disease-causing mutations in very large populations, where the evolutionary forces acting are primarily selection and mutation.

Our analysis began with considerations of the evolutionary force, $F(x)$, that acts on the frequency of a lethal disease-causing allele. We worked under the assumptions that the mutation rate, from the wild type to the lethal allele, u, was very small, and that the dominance coefficient, associated with the relative fitness of the heterozygote carrier of the lethal allele, h, was also small. Then, when the frequency of the disease-causing allele, x, takes low values we showed

that the force can be well-approximated by the simple function $F(x) \simeq u - hx - x^2$ (Eq. (**??**) and illustrated in Figure 1).

While the focus of this work is on the effects of time-dependent dominance coefficients, it is helpful to first discuss features of the force, $F(x)$, when this coefficient takes a constant value. Figure 1 illustrates how the force changes with x, and shows the feature of the force vanishing at a positive frequency, corresponding to a stable polymorphism with frequency x^*. The form of $F(x)$ is substantially different, for different values of h: when h is negative the force is parabolic, but when h is positive the force is effectively linear in x. One implication of this, for a lethal disease-causing allele with frequency x, is that its evolution is only significantly influenced by the frequency of the lethal genotype, i.e., x^2, when there is overdominance ($h < 0$) and the force is parabolic in shape. In the absence of overdominance (i.e., when $h \geq 0$) the evolution of this allele is primarily influenced by the frequency of the heterozygote carriers, i.e., x, and the force is close to linear in shape. Figure 1 schematically illustrates the differences that small constant values of h can have on the force of evolution, $F(x)$, and on the frequency of the stable polymorphism, x^*, while Table 1 provides some quantitative examples. For the value of u considered in this work, the maximum force of evolution, $F_{\max}$, when $h = -0.025$, is four orders of magnitude greater than when $h \geq 0$. The corresponding stable polymorphism frequency, when $h = -0.025$ is at least two orders of magnitude greater than when $h \geq 0$.

Let us now consider the feature of the lethal allele of interest, namely its frequency. Standard population genetics theory leads to the expectation that in very large populations, the frequencies of recessive, lethal mutations should be close to the square root of the mutation rate, corresponding to an equilibrium between mutation and selection [3]. There are, however, numerous examples of where such alleles have frequencies which are orders of magnitude greater

than this (see the Introduction). This has lead to two main explanations: (i) there is some level of heterozygous advantage experienced by the carriers of the mutation, and (ii) there is a degree of variation around this expectation and we simply fail to observe those in the lower tail of this distribution, i.e., there is an *ascertainment bias* [15]. The origin of this variation is, in [15], not specified, but implicitly assumed to be random and may be due to random genetic drift or some other mechanism. Although there is some theoretical appeal in the hypothesised heterozygous advantage, there has always been a lack of convincing evidence in support of it. We can, however, envisage temporal fluctuations in the dominance coefficient (or heterozygous effect) acting on the population. Such fluctuations could arise from effects that are external to the population, and have a variety of biotic or abiotic origins. When there are fluctuations in the dominance coefficient, a small mean value may not be distinguishable from a mean value of zero in searches that are not highly extensive/sensitive. Beyond this, however, the basic effect of random fluctuations in just the heterozygous effect do not seem to have been previously explored, and the present work constitutes an investigation to see if there is a possible third explanation of the anomalously large frequencies seen of some lethal alleles. We have thus investigated the influence of small transitory fluctuations in the fitness of heterozygotes.

It is plausible, just from the form of the evolutionary force, $F(x)$, given in Figure 1, that even for fluctuations in the heterozygous effect, h, that are symmetrically distributed around a mean value of zero, and hence completely unbiased in value, that a systematic effect on the frequency might be produced, since a negative value of h has a disproportionately greater effect on the force than an equal and opposite positive value. The analysis carried out, where the averaged effect of small, random fluctuations in $h(t)$ around a mean value

of $\bar{h}$ were taken into account, has demonstrated such a systematic effect. In particular, the *effective evolutionary force* acting can be written as $F_{\text{eff}}(x) \simeq u - h_{\text{eff}}x - x^2$, where $h_{\text{eff}} = \bar{h} - \sigma^2/2$ is the *effective dominance coefficient*. Since $\sigma^2 \geq 0$, this form of h_{eff} is generally smaller than $\bar{h}$. That is, the dominance coefficient has an effective value that has been pushed down by the fluctuations, in the direction of overdominance. Indeed, when the mean dominance coefficient is zero ($\bar{h} = 0$), the effective dominance coefficient is $-\sigma^2/2$, corresponding to overdominance of the lethal allele, with the fitness of the heterozygote a factor $1+\sigma^2/2$ larger than that of the wild type homozygote. This could be described as *fluctuation induced overdominance* of the lethal allele. A measure of the effects of this induced overdominance is given by the quantity R_0 (Eq. (**??**)), which is the ratio of the mean stationary frequency, in the presence of fluctuations in h around a mean value of zero, to the equilibrium frequency when h has the constant value of zero. Figure 2 plots the ratio R_0 as a function of a measure of the strength of fluctuations. With no fluctuations we have $R_0 = 1$, but as the magnitude of the fluctuations is increased, the ratio R_0 increases.

What we have presented in this work is thus a mechanism that provides an additional explanation for why some lethal recessive mutations are at inflated frequencies. It is consistent with the observation that, on average, heterozygous effects do not appear to be in operation [15]. With a mean value of the heterozygous effect of zero ($\bar{h} = 0$) and moderate fluctuations ($\sigma^2 \leq 0.04$), our calculations plausibly explain something like a factor of 10 or 20 increase in the allele frequency over the result $\sqrt{u}$, of mutation selection balance of a lethal allele with a constant dominance coefficient of zero (i.e., recessive). The nature of these moderate fluctuations could be periodic episodes of infectious disease, such as tuberculosis, that can span generations as epidemics and which have been implicated in lethal disorders such as Tay-Sachs and cystic fibrosis. However,

some recessive lethal diseases, such as cystic fibrosis, have current frequencies that are significantly in excess of $20 \times \sqrt{u}$. As figure 2 makes clear, R_0 will increase with declining u, but if anything, our working hypothesis of $u = 10^{-8}$ is rather conservative compared with some estimates (e.g., 3.3×10^{-4} [23]. As such, there may be other factors to consider. For example, there may be very small, non-zero mean values of h, that may be obscured by fluctuations, and hence are difficult to detect; such non-zero mean values may have an appreciable effect on the frequencies observed. Future investigations into the properties of fluctuations of h would offer valuable insights into the observed features of lethal and near-lethal alleles.

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TITLES AND LEGENDS TO FIGURES

FIGURE 1: This figure *schematically* illustrates the shape of the force $F(x)$ of Eq. (**??**), as a function of x, for three different values of the dominance coefficient, h. The case $h < 0$, that is illustrated in the figure, applies when $|h| \gg 2u$, which for u small is a very modest restriction on h, while the case $h > 0$ applies for $h \gg 2u$. The figure is schematic in the sense that parameter values have been adopted for the purposes of visualisation rather than realism. Thus numerical relations between features of the three curves are, realistically, much more extreme than those illustrated in the figure, as shown in Table 1.

FIGURE 2: A plot of the ratio R_0 of Eq. (**??**), against $\sigma^2/(4\sqrt{u})$. The ratio R_0 gives the enhancement of the mean frequency in the stationary distribution, over that of the stable polymorphism, due to fluctuations in h. The parameter σ^2 is a measure of the strength of the fluctuations of h.

TABLE 1: Values of the maximum value of the force, $F_{\max}$, and the frequency of the stable polymorphism, x^*, for three different values of h, when the mutation rate is $u = 10^{-8}$.