

GENETICS

Supporting Information

<http://www.genetics.org/content/suppl/2011/04/28/genetics.111.129288.DC1>

A Unified Treatment of the Probability of Fixation when Population Size and the Strength of Selection Change Over Time

D. Waxman

SUPPORTING INFORMATION

The Supporting Information presented here is separated into background material followed by six separate parts. In Part 1 an alternative derivation is given for the probability of fixation when the effective population size and the strength of selection may change up to time T , but do not change beyond time T . In Part 2 a limiting case of the probability of fixation is determined, while in part 3 it is shown how Equation (4) of the main text, for the fixation probability, simplifies when conditions are static. In Part 4 a useful transformation of the diffusion equation is made and a property of the population size in this equation is exposed. In Part 5 details are given of a way to numerically evaluate the quantity $E_p[e^{-S_\infty X(T)}]$ (which appears in Equation (4) of the main text). Lastly, in Part 6, we give details of the generalisation of Equation (4) of the main text to include stochastic fluctuations in population size and the strength of selection.

Background

Consider a single locus that determines fitness in a population of randomly mating diploid individuals of (variance) effective size $N_e(t)$ at time t . The locus has two alleles, denoted A and a , and is subject to semidominant selection where, at time t , the relative fitnesses of AA , Aa and aa genotype individuals are $1 + 2s(t)$, $1 + s(t)$ and 1 , respectively. Until Part 6 of the Supporting Information, we will assume that $N_e(t)$ and $s(t)$ change deterministically.

We write the relative frequency (henceforth referred to as the *frequency*) of allele A at time t as $X(t)$. Given an initial A allele frequency of y at time u , the probability density of the A allele frequency at later time t , at frequency x , is written as $K(x, t|y, u)$. Under a diffusion approximation $K(x, t|y, u)$ obeys the forward diffusion equation

$$-\frac{\partial}{\partial t}K(x, t|y, u) = -\frac{1}{4N_e(t)}\frac{\partial^2}{\partial x^2}[x(1-x)K(x, t|y, u)] + s(t)\frac{\partial}{\partial x}[x(1-x)K(x, t|y, u)] \quad (\text{S1})$$

(Kimura 1955) and is subject to the initial condition $K(x, u|y, u) = \delta(x - y)$ where $\delta(x)$ denotes a Dirac delta function of argument x .

The result of the main text for the fixation probability, Equation (4), is given here for completeness:

$$P_{\text{fix}}(p) = \frac{1 - E_p[e^{-S_\infty X(T)}]}{1 - e^{-S_\infty}} \quad (\text{S2})$$

where p is the frequency at time $t = 0$, S_∞ is the value of $4N_e(t)s(t)$ when $t \geq T$ and $E_p[\dots]$ denotes the conditional expectation $E[\dots|X(0) = p]$.

In what follows, we shall repeatedly make use of the relation

$$E_p[e^{-S_\infty X(T)}] \equiv E[e^{-S_\infty X(T)}|X(0) = p] = \int_0^1 e^{-S_\infty x} K(x, T|p, 0) dx \quad (\text{S3})$$

where the last equality follows since $K(x, T|p, 0)$ is the probability density, at frequency x , of $X(T)$, conditional on $X(0) = p$.

PART 1

To give more insight into Equation (4) of the main text (reproduced in Equation (S2) above), and for use in Part 6 of the Supporting Information, we give another derivation of Equation (S2).

We use a property of $K(x, t|y, u)$ that follows from Equation (S1) being first order in time derivatives and linear, namely

$$K(x, t|y, u) = \int_0^1 K(x, t|z, r)K(z, r|y, u) dz \quad (\text{S4})$$

where $u \leq r \leq t$. Equation (S4) is often known as the Chapman-Kolmogorov equation.

To determine the fixation probability, given an A allele frequency of p at time $t = 0$, we determine the behaviour of $K(x, t|p, 0)$ at large values of t . We work under the assumption that $s(t)$ and $N_e(t)$ do not change when the time is larger than a specific time, T , hence

$$4N_e(t)s(t) = S_\infty \text{ (a constant)} \quad \text{for } t \geq T. \quad (\text{S5})$$

We take Equation (S5) into account when making specific choices of r , y and u in Equation (S4):

$$K(x, t|p, 0) = \int_0^1 K(x, t|z, T)K(z, T|p, 0)dz. \quad (\text{S6})$$

The factor $K(z, T|p, 0)$ in Equation (S6) is potentially complicated since it is determined by the time-dependent changes of $N_e(t)$ and $s(t)$ that occur from time 0 to time T . By contrast, $K(x, t|z, T)$ applies for the range of times where the strength of selection and the population size have achieved constant values.

In the work of McKane and Waxman (2007) and Waxman (2011), ‘zero current’ boundary conditions were imposed on the solution of the forward diffusion equation¹. Zero current boundary conditions, in contrast to the approach adopted by Kimura (1955), ensure that probability is conserved and lead to an interpretation of Equation (S1) that is consistent with underlying the Wright-Fisher model for all x including $x = 0$ and $x = 1$, *i.e.*, including fixation and loss (see Waxman 2011). We apply these boundary conditions in the present context.

For times $t > T$, where the strength of selection and the population size have achieved the constant values s_∞ and N_∞ , we can write

$$K(x, t|z, T) = \sum_{n=0}^{\infty} \Phi_n(x)\Psi_n(z)e^{-\lambda_n(t-T)} \quad (\text{S7})$$

where $\Phi_n(x)$ ($\Psi_n(z)$) is an eigenfunction of the forward (backward) diffusion operator associated with eigenvalue λ_n :

$$-\frac{1}{4N_\infty} \frac{d^2}{dx^2} [x(1-x)\Phi_n(x)] + s_\infty \frac{d}{dx} [x(1-x)\Phi_n(x)] = \lambda_n \Phi_n(x) \quad (\text{S8})$$

$$-\frac{y(1-y)}{4N_\infty} \frac{d^2}{dy^2} \Psi_n(y) - s_\infty y(1-y) \frac{d}{dy} \Psi_n(y) = \lambda_n \Psi_n(y). \quad (\text{S9})$$

For $K(x, t|z, T)$ to be a solution of the appropriate diffusion equation, the eigenfunctions appearing in Eqs. (S7), (S8) and (S9) are orthogonal and normalised (Waxman 2011) in the sense

$$\int_0^1 \Phi_n(x)\Psi_m(x)dx = \delta_{m,n} \quad (\text{S10})$$

where $\delta_{m,n}$ is a Kronecker delta, which equals 1 when $m = n$ and vanishes otherwise.

A key feature of the analysis of McKane and Waxman (2007) and Waxman (2011) is that under ‘zero current’ boundary conditions, there are two eigenfunctions of the forward and backward eigenvalue equations

¹Zero current boundary conditions correspond to the probability current density $-\frac{1}{4N_e(t)} \frac{\partial}{\partial x} [x(1-x)K(x, t|y, u)] + s(t)x(1-x)K(x, t|y, u)$ vanishing at $x = 0$ and $x = 1$. Since $K(x, t|y, u)$ is a probability density, it is an integrable function of x with the consequence that $x(1-x)K(x, t|y, u)$ vanishes at $x = 0$ and $x = 1$. Accordingly, zero current boundary conditions can be taken as requiring that $\frac{\partial}{\partial x} [x(1-x)K(x, t|y, u)]$ vanishes at $x = 0$ and $x = 1$. See McKane and Waxman (2007) and Waxman (2011) for further details.

with zero eigenvalue. These are given the labels $n = 0$ and $n = 1$ and as $t \rightarrow \infty$ only terms with these labels persist in Equation (S7):

$$\lim_{t \rightarrow \infty} K(x, t|z, T) = \Phi_0(x)\Psi_0(z) + \Phi_1(x)\Psi_1(z). \quad (\text{S11})$$

We take² $\Phi_0(x) = \delta(x)$ and $\Phi_1(x) = \delta(1-x)$: these are probability densities associated with the A allele frequency having the precise values 0 and 1, respectively, and correspond to loss and fixation of the A allele. Using Equation (S11) in Equation (S6), we arrive at $\lim_{t \rightarrow \infty} K(x, t|p, 0) = \Phi_0(x) \int_0^1 \Psi_0(z)K(z, T|p, 0)dz + \Phi_1(x) \int_0^1 \Psi_1(z)K(z, T|p, 0)dz$ and the coefficient of $\Phi_1(x)$ in this expression is the probability of fixation. We thus find

$$P_{\text{fix}}(p) = \int_0^1 \Psi_1(z)K(z, T|p, 0)dz = E_p [\Psi_1(X(T))]. \quad (\text{S12})$$

The eigenfunction $\Psi_1(y)$ of the backward eigenvalue equation has zero eigenvalue; it obeys Equation (S9) with $n = 1$ and $\lambda_1 = 0$. The eigenfunction is subject to $\Psi_1(0) = 0$ and $\Psi_1(1) = 1$ which result from Equation (S10) with $m = 1$ and $n = 0$ or $n = 1$. It follows that $\Psi_1(y) = \frac{1 - e^{-S_\infty y}}{1 - e^{-S_\infty}}$. We can thus write Equation (S12)

$$\text{as } P_{\text{fix}}(p) = E_p \left[\frac{1 - e^{-S_\infty X(T)}}{1 - e^{-S_\infty}} \right] = \frac{1 - E_p [e^{-S_\infty X(T)}]}{1 - e^{-S_\infty}}.$$

PART 2

In this part of the Supporting Information we obtain the limiting case of Equation (S2) when $T \rightarrow 0$.

Given that $K(x, t|p, 0)$ obeys the forward diffusion equation, Equation (S1), a direct calculation, assuming $[N_e(t)]^{-1}$ and $|s(t)|$ remain bounded for $0 \leq t \leq T$, yields $\left| E_p [e^{-S_\infty X(T)}] - e^{-S_\infty p} \right| = O(T)$ and hence as $T \rightarrow 0$, Equation (S2) collapses to $P_{\text{fix}}(p) = \frac{1 - e^{-S_\infty p}}{1 - e^{-S_\infty}}$ which is Equation (2) of the main text.

PART 3

When population size and the strength of selection are independent of time ($N_e(t) = N_e$ and $s(t) = s$) the expectation $E_p [e^{-S_\infty X(T)}]$ appearing in Equation (S2) takes a simple form which allows Equation (S2) to be significantly simplified.

To establish the form of $E_p [e^{-S_\infty X(T)}]$ we use Equation (S3) and obtain an equation for the quantity $\int_0^1 e^{-S_\infty x} K(x, T|p, 0)dx$ by multiplying Equation (S1) (with t replaced by T), by $e^{-S_\infty x}$ and integrating over all x . When N_e and s are independent of time we obtain

$$\begin{aligned} -\frac{\partial}{\partial T} \int_0^1 e^{-S_\infty x} K(x, T|p, 0)dx &= -\frac{1}{4N_e} \int_0^1 e^{-S_\infty x} \frac{\partial^2}{\partial x^2} [x(1-x)K(x, T|p, 0)] dx \\ &+ s \int_0^1 e^{-S_\infty x} \frac{\partial}{\partial x} [x(1-x)K(x, T|p, 0)] dx. \end{aligned} \quad (\text{S13})$$

Integrating the first term on the right hand side by parts twice, the second term once by parts, and using $4N_e s = S_\infty$, leads to

$$-\frac{\partial}{\partial T} \int_0^1 e^{-S_\infty x} K(x, T|p, 0)dx = -\left[\frac{e^{-S_\infty x}}{4N_e} \frac{\partial}{\partial x} [x(1-x)K(x, T|p, 0)] \right]_{x=0}^{x=1}. \quad (\text{S14})$$

²There are two eigenfunctions associated with zero eigenvalue. Different linear combinations of these eigenfunctions also have zero eigenvalue. In the present work we have made the particular choice of these eigenfunctions made by Waxman (2011); an alternative, but equivalent choice of these eigenfunctions has been made by McKane and Waxman (2007).

The right hand side vanishes under the ‘zero current’ boundary conditions imposed by McKane and Waxman (2007) and Waxman (2011). We then have $\frac{\partial}{\partial T} \int_0^1 e^{-S_\infty x} K(x, T|p, 0) dx \equiv \frac{\partial}{\partial T} E_p \left[e^{-S_\infty X(T)} \right] = 0$ corresponding to $E_p \left[e^{-S_\infty X(T)} \right]$ being independent of T . We can take $T = 0$ and arrive at

$$E_p \left[e^{-S_\infty X(T)} \right] = e^{-S_\infty p}. \quad (\text{S15})$$

Using this last result in Equation (S2) shows that when parameters are time-independent, the fixation probability reduces to $P_{\text{fix}}(p) = \frac{1 - e^{-S_\infty p}}{1 - e^{-S_\infty}}$, *i.e.*, Equation (2) of the main text.

The property of Equation (S15), that under static conditions $E_p \left[e^{-S_\infty X(T)} \right]$ is independent of T (and hence equals its value when $T = 0$) is a Martingale property of the diffusion approximation that appears to have been first identified by Ewens (1964). It can also be derived by noting that $e^{-S_\infty y}$ is a linear superposition of $\Psi_0(y)$ and $\Psi_1(y)$, the two eigenfunctions of the backward equation with zero eigenvalue.

PART 4

Transformation of the diffusion equation

In this part of the Supporting Information, we transform the diffusion equation, Equation (S1), by replacing the time t by the ‘drift time’ given in Equation (5) of the main text:

$$\tau = \int_0^t \frac{N_e(0)}{N_e(u)} du \quad (\text{S16})$$

and determine a key property of $N_e(t)$.

We shall compare populations with the same value of $N_e(0)$ and hence consider $N_e(0)$ a fixed parameter.

We can, in principle, solve Equation (S16) for t and obtain it as a function of τ , which we write as $t(\tau)$.

Defining

$$\tilde{K}(x, \tau|y, \sigma) = K(x, t(\tau)|y, t(\sigma)) \quad (\text{S17})$$

we find that Equation (S1) becomes

$$\begin{aligned} -4N_e(0) \frac{\partial}{\partial \tau} \tilde{K}(x, \tau|y, \sigma) &= -\frac{\partial^2}{\partial x^2} \left[x(1-x) \tilde{K}(x, \tau|y, \sigma) \right] \\ &+ R(\tau) \frac{\partial}{\partial x} \left[x(1-x) \tilde{K}(x, \tau|y, \sigma) \right] \end{aligned} \quad (\text{S18})$$

where

$$R(\tau) = 4N_e(t(\tau))s(t(\tau)). \quad (\text{S19})$$

By virtue of its position in Equation (S18) the quantity $R(\tau)$ encapsulates selection and population size in a single term that we call the ‘overall strength of selection’. Note that the time arguments of N_e and s in Equation (S19) are $t(\tau)$ and hence are determined by the relationship between t and τ of Equation (S16), *i.e.*, are determined by the way that N_e varies over time.

Equation (S18) is the diffusion equation that is obtained from the original diffusion equation, Equation (S1), when it is transformed to depend on the drift time, τ .

Property of $N_e(t(\tau))$

Let us now demonstrate a property of the quantity $N_e(t(\tau))$ appearing in Equation (S19). We consider the two cases, where $N_e(t)$ either increases with t or where it decreases with t .

1) Increasing $N_e(t)$ (*i.e.*, $dN_e(t)/dt > 0$). This immediately yields (i) $N_e(t_1) > N_e(t_2)$ for $t_1 > t_2$. From Equation (S16) we obtain (ii) $t(\tau) > \tau$. It follows from (i) and (ii) that $N_e(t(\tau)) > N_e(\tau)$.

2) Decreasing $N_e(t)$ (i.e., $dN_e(t)/dt < 0$). This immediately yields (i) $N_e(t_1) < N_e(t_2)$ for $t_1 > t_2$. From Equation (S16) we obtain (ii) $\tau > t(\tau)$. It follows from (i) and (ii) that $N_e(t(\tau)) > N_e(\tau)$.

Thus in both cases we have $N_e(t(\tau)) > N_e(\tau)$ and this generally holds for an $N_e(t)$ that exhibits only increase or only decrease.

PART 5

The quantity $E_p[e^{-S_\infty X(T)}]$ that appears in Equation (S2) can be determined by numerically solving a diffusion equation. To establish this we first note that $K(x, t|y, u)$ not only obeys Equation (S1) but also the backward equation

$$\frac{\partial}{\partial u} K(x, t|y, u) = -\frac{y(1-y)}{4N_e(u)} \frac{\partial^2}{\partial y^2} K(x, t|y, u) - s(u)y(1-y) \frac{\partial}{\partial y} K(x, t|y, u) \quad (\text{S20})$$

subject to

$$\begin{aligned} K(x, t|y, t) &= \delta(x-y) \\ K(x, t|0, u) &= \delta(x) \\ K(x, t|1, u) &= \delta(1-x) \end{aligned} \quad (\text{S21})$$

The second and third conditions in Equation (S21) follow from the first condition since $K(x, t|0, u)$ and $K(x, t|1, u)$ are independent of u , by virtue of Equation (S20), and hence may be evaluated at $u = t$.

If we multiply $K(x, T|y, u)$ by $e^{-S_\infty x}$ and integrate from $x = 0$ to $x = 1$ we obtain the result $G(y, u) \stackrel{\text{def}}{=} \int_0^1 e^{-S_\infty x} K(x, T|y, u) dx = E[e^{-S_\infty X(T)} | X(u) = y]$. The quantity $G(y, u)$ is often known as the Laplace-Stieltjes transform of $X(t)$, and in the present case it is evaluated at the solution of Equation (S1). The equation for $G(y, u)$ follows from Equation (S20) by multiplying $e^{-S_\infty x}$ and integrating from $x = 0$ to $x = 1$. It reads

$$\frac{\partial}{\partial u} G(y, u) = -\frac{y(1-y)}{4N_e(u)} \frac{\partial^2}{\partial y^2} G(y, u) - s(u)y(1-y) \frac{\partial}{\partial y} G(y, u) \quad (\text{S22})$$

and is subject to (i) $G(y, T) = e^{-S_\infty y}$, (ii) $G(0, u) = 1$ and (iii) $G(1, u) = e^{-S_\infty}$ which follow from Equation (S21).

Equation (S22), subject to the initial condition (i), and the boundary conditions (ii) and (iii) is a well defined mathematical problem for $G(y, u)$ that can be solved by a standard numerical technique such as the Crank Nicholson method (see e.g., Press *et al.* 2007). Thus we 'integrate backwards' from $u = T$ to $u = 0$ and obtain $G(y, 0) = E[e^{-S_\infty X(T)} | X(0) = y] \equiv E_y[e^{-S_\infty X(T)}]$ which, when used in Equation (S2), yields a numerical estimate of the fixation probability.

PART 6

The result in Equation (S2) for the fixation probability has a wider applicability than just for Equation (S1). In a more general case, we assume we assume there are both deterministic changes and stochastic fluctuations in $N_e(t)$ and $s(t)$ for times $t \leq T$, but only stochastic fluctuations for times $t > T$. Then the diffusion operator may be 'time averaged' and results in a time-independent form for $t > T$ that differs from Equation (S1). Time averaging over correlated fluctuations in the strength of selection was first carried out by Takahata *et al.* (1975) and we adopt the same approach here, implicitly assuming that the correlations persist over many generations.

To demonstrate this in the simplest way possible, we transform the diffusion equation using the drift time $\tau = \int_0^t \frac{1}{4N_e(u)} du$ (which differs from the drift time defined in Equation (S16) by an overall constant factor). This drift time eliminates the factor $4N_e(0)$ on the left hand side of Equation (S18) but otherwise leaves it unchanged in form. As already stated, the quantity $R(\tau)$, by virtue of its position in the transformed diffusion

equation plays the role of an effective strength of selection. We can directly follow the approach of Takahata *et al.* (1975), making similar assumptions:

- (i) we assume that $R(\tau)$ has bounded fluctuations around a mean value of \bar{R}
- (ii) with overbars denoting ensemble averages over fluctuations, we assume the correlations of $R(\tau)$ obey $\int_0^\tau (R(\sigma + \sigma_1) - \bar{R})(R(\sigma) - \bar{R})d\sigma = V$ for all σ_1 larger than some small correlation time.

The average of $\bar{K}(x, \tau|y, \sigma)$ over fluctuations is written $\bar{K}(x, \tau|y, \sigma)$ and this obeys (cf. Takahata *et al.* 1975)

$$-\frac{\partial}{\partial \tau} \bar{K}(x, \tau|y, \sigma) = -\frac{\partial^2}{\partial x^2} \{ [x(1-x) + Vx^2(1-x)^2] \bar{K}(x, \tau|y, \sigma) \} + \frac{\partial}{\partial x} \{ [\bar{R}x(1-x) + Vx(1-x)(1-2x)] \bar{K}(x, \tau|y, \sigma) \}. \quad (\text{S23})$$

The eigenvalue equation of the backward diffusion operator associated with Equation (S23) is

$$-y(1-y)[1 + Vy(1-y)] \frac{d^2}{dy^2} \bar{\Psi}(y) - y(1-y)[\bar{R} + V(1-2y)] \frac{d}{dy} \bar{\Psi}(y) = \lambda \bar{\Psi}(y). \quad (\text{S24})$$

To employ the result in Equation (S12) within Part 1 of the Supporting Information, we require the eigenfunction $\bar{\Psi}_1(y)$ with eigenvalue 0 that obeys $\bar{\Psi}_1(0) = 0$ and $\bar{\Psi}_1(1) = 1$. This is $\bar{\Psi}_1(y) = \frac{1 - \left(\frac{1-y/\alpha_+}{1-y/\alpha_-}\right)^\beta}{1 - \left(\frac{1-1/\alpha_+}{1-1/\alpha_-}\right)^\beta}$ where

$\alpha_\pm = \frac{1 \pm \sqrt{1 + 4/V}}{2}$ and $\beta = \frac{\bar{R}}{V\sqrt{1 + 4/V}}$. The form of $\bar{\Psi}_1(y)$ is equivalent to Equation (27) of TAKAHATA *et al.* (1975) under the substitutions $\bar{s} \rightarrow \bar{R}$ and $N \rightarrow 1/4$.

The generalisation of Equation (S2), that includes fluctuations in $N_e(t)$ and $s(t)$ is then given by $P_{\text{fix}}(p) = E_p [\bar{\Psi}_1(X(T))]$.

LITERATURE CITED IN THE SUPPORTING INFORMATION

- Ewens, W. J., 1964 The pseudo-transient distribution and its uses in genetics. *J. Appl. Probab.* 1: 141–156.
- Kimura, M., 1955 Stochastic processes and distribution of gene frequencies under natural selection. *Cold Spring Harbour Symp. Quant. Biol.* 20: 33–53.
- McKane, A. J. and Waxman, D., 2007 Singular solutions of the diffusion equation of population genetics. *J. Theor. Biol.* 247: 849–858.
- Press, W. H., Teukolsky, S. A, and Vetterling, W. T., 2007 *Numerical Recipes 3rd Edition: The Art of Scientific Computing*. Cambridge University Press, Cambridge.
- Takahata, N., Ishii, K. and Matsuda, H., 1975 Effect of temporal fluctuation of selection coefficient on gene frequency in a population. *Proc. Natl. Acad. Sci. USA* 72: 4541–4545.
- Waxman, D., 2011 Comparison and content of the Wright–Fisher model of random genetic drift, the diffusion approximation, and an intermediate model. *J. Theor. Biol.* 269: 79–87.