

SUPPLEMENTARY MATERIAL

Influence of selection on the probability of fixation at a locus with multiple alleles

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The Supplementary Material is divided into two main sections. In Section 1 we give descriptive material and relatively non-technical explanations of the results presented in the main text. In Section 2 we give the detailed calculations that lead to the results given in the main text.

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1 Descriptive material

1.1 Description of the model

In Section 1.1 of the Supplementary Material, we give details underlying the *stochastic differential equation* for the allele frequencies, as given in Eq. (1) of the main text.

We consider a finite population of diploid sexual organisms that reproduce by random mating. We assume an equal sex ratio and no sexual dimorphism.

Selection is taken to act at a single unlinked locus where there are n alleles, that we label $1, 2, \dots, n$.

All indices that we use, such as i and j , run from 1 to n (the number of alleles).

We work under a diffusion approximation, where frequencies and time have continuous values, and we take the time, t to start at zero (i.e., $t \geq 0$).

Much of what follows uses vectors and matrices. We adopt the convention that all vectors are *column* vectors with n elements, while all matrices are *square* matrices of size $n \times n$. Furthermore, a T superscript is used to denote the transpose of a vector.

A special matrix that we shall use is denoted by $\mathcal{D}(\mathbf{z})$. This represents a square matrix where the elements of the vector $\mathbf{z}$ lie on the diagonal, and all other elements of the matrix are zero.

Dynamics

The basic dynamics of the model is expressed in terms of $\mathbf{X}(t)$, which is a *column vector* with n components

$$\mathbf{X}(t) = (X_1(t), X_2(t), \dots, X_n(t))^T \quad (\text{S1.1})$$

where $X_i(t)$ is the random frequency of allele i at time t . The frequency vector, $\mathbf{X}(t)$, has non-negative elements ($X_i(t) \geq 0$) and is normalised to unity ($\sum_{i=1}^n X_i(t) = 1$). A realisation (or particular value) of $\mathbf{X}(t)$ is denoted by a lower case symbol, such as $\mathbf{x}$.

An $n \times n$ matrix which appears in the analysis is written as $\mathbf{V}(\mathbf{x})$. Its elements are given by

$$V_{i,j}(\mathbf{x}) = x_i \delta_{i,j} - x_i x_j \quad (\text{S1.2})$$

where $\delta_{i,j}$ denotes a Kronecker delta ($\delta_{i,j}$ equals 1 if $i = j$ and is 0 otherwise).

Under the diffusion approximation, the set of allele frequencies, $\mathbf{X}(t)$, obeys an equation which determines how this quantity changes from time t to time $t + dt$ due to selection and drift. The equation is

$$d\mathbf{X}(t) = \mathbf{F}(\mathbf{X}(t))dt + \mathbf{M}(\mathbf{X}(t))d\mathbf{W}(t) \quad (\text{S1.3})$$

and is subject to the initial frequencies being given by

$$\mathbf{X}(0) = (y_1, y_2, \dots, y_n)^T \equiv \mathbf{y}. \quad (\text{S1.4})$$

The two terms on the right hand side of Eq. (S1.3) involve the following.

1. The quantity $\mathbf{F}(\mathbf{x})$, which is a vector with n components, written $F_i(\mathbf{x})$, that is associated with selection. In the present work we take selection to be either *multiplicative* or *additive* in character, which means the genotype composed of the i and j alleles has a fitness proportional to $(1+s_i)(1+s_j)$ or $(1+s_i+s_j)$, respectively, and we refer to the s_i as *selection coefficients*. We assume $|s_i| \ll 1$ so genic selection and additive selection are very similar, and to leading order in the s_i both schemes of selection yield

$$F_i(\mathbf{x}) = x_i \left(s_i - \sum_{j=1}^n s_j x_j \right). \quad (\text{S1.5})$$

With $\mathbf{s}$ the n component column vector of selection coefficients,

$$\mathbf{s} = (s_1, s_2, \dots, s_n)^T \quad (\text{S1.6})$$

we can compactly write

$$\mathbf{F}(\mathbf{x}) = \mathbf{V}(\mathbf{x})\mathbf{s}. \quad (\text{S1.7})$$

It is useful to define

$$\mathbf{R} = 2N_e \mathbf{s} \quad (\text{S1.8})$$

which is a scaled version of the vector of selection coefficients. We write the scaled differences of selection coefficients as

$$R_{i,j} = R_i - R_j. \quad (\text{S1.9})$$

2. The quantity $\mathbf{W}(t)$ is a vector containing n independent normal random functions of time (Wiener processes [1]) that capture the randomness of genetic drift, while $\mathbf{M}(\mathbf{x})$ is an $n \times n$ matrix that is given in terms of the square root of the matrix $\mathbf{V}(\mathbf{x})$ as¹

$$\mathbf{M}(\mathbf{x}) = \sqrt{\frac{\mathbf{V}(\mathbf{x})}{2N_e}} \quad (\text{S1.10})$$

where N_e is the effective population size.

We use an *overbar* to denote an *expected value*, with expected values subject to the initial frequencies given by $\mathbf{y}$ (Eq. (S1.4)). Thus the mean allele frequencies at time t are written as $\bar{\mathbf{X}}(t)$ and these obey $\bar{\mathbf{X}}(0) \equiv \mathbf{X}(0) = \mathbf{y}$.

Let $P_i(\mathbf{y})$ denote the fixation probability of allele i , when the initial frequencies are given by $\mathbf{y}$. Fixation of one allele excludes fixation of all other alleles, whose frequencies are driven to zero. Thus fixation events are mutually exclusive, and are the only possible outcomes at large t . This leads to the fixation probabilities coinciding with the long time limit of mean allele frequencies (see e.g., [3]):

$$\lim_{t \rightarrow \infty} \bar{\mathbf{X}}(t) = \mathbf{P}(\mathbf{y}) \equiv (P_1(\mathbf{y}), P_2(\mathbf{y}), \dots, P_n(\mathbf{y}))^T. \quad (\text{S1.11})$$

Furthermore, the elements of $\mathbf{P}(\mathbf{y})$ represent a probability distribution and are normalised:

$$\sum_{i=1}^n P_i(\mathbf{y}) = 1. \quad (\text{S1.12})$$

¹The square root in Eq. (S1.10) denotes the *principal square root* of the matrix. Since $\mathbf{V}(\mathbf{x})$ is symmetric and non negative definite, the matrix $\mathbf{M}(\mathbf{x})$ also has these properties (see e.g., [2]).

1.2 Expansion of the fixation probability

In Section 1.2 of the Supplementary Material, we give a brief *sketch* of a way to expand the set of fixation probabilities, $\mathbf{P}(\mathbf{y})$, up to second order in the scaled selection coefficients, $\mathbf{R}$. Full details of the calculations are given in Section 2 of the Supplementary Material.

In the results that follow, $\mathbf{s}$ is replaced everywhere by $\mathbf{R}/(2N_e)$ and hence all expressions are given in terms of $\mathbf{R}$. As in the main text, we use a T superscript to denote the transpose of a vector, an *overbar* to denote an *expected value*, with all expected values subject to the initial frequencies given by $\mathbf{y}$ (Eq. (S1.4)). We also make use of $\mathcal{D}(\mathbf{z})$, the square matrix with elements of the vector $\mathbf{z}$ on the diagonal, and all other elements zero.

Expression for $\mathbf{P}(\mathbf{y})$ in terms of statistics of $\mathbf{X}(t)$

As noted in Section 1.1 of the Supplementary Material, the long time limit of the mean allele frequencies are the fixation probabilities: $\lim_{t \rightarrow \infty} \bar{\mathbf{X}}(t) = \mathbf{P}(\mathbf{y})$. We use this to determine an expression for $\mathbf{P}(\mathbf{y})$ in terms of statistics of $\mathbf{X}(t)$.

Beginning with Eq. (S1.3), and using Eq. (S1.7), we obtain

$$d\mathbf{X}(t) = \frac{\mathbf{V}(\mathbf{X}(t))\mathbf{R}}{2N_e}dt + \mathbf{M}(\mathbf{X}(t))d\mathbf{W}(t). \quad (\text{S1.13})$$

On averaging Eq. (S1.13), the $d\mathbf{W}$ term vanishes (it has a mean of zero). This leads to

$$\frac{d\bar{\mathbf{X}}(t)}{dt} = \frac{\overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}}{2N_e}. \quad (\text{S1.14})$$

Integrating Eq. (S1.14) from $t = 0$ to $t = \infty$ and using $\bar{\mathbf{X}}(0) = \mathbf{y}$ and $\lim_{t \rightarrow \infty} \bar{\mathbf{X}}(t) = \mathbf{P}(\mathbf{y})$ we obtain

$$\mathbf{P}(\mathbf{y}) = \mathbf{y} + \frac{1}{2N_e} \int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}dt. \quad (\text{S1.15})$$

Equation (S1.15) represents $\mathbf{P}(\mathbf{y})$ in terms of statistics of $\mathbf{X}(t)$, but with some work we can develop this expression further to

$$\begin{aligned} \mathbf{P}(\mathbf{y}) = & \mathbf{y} + \mathbf{V}(\mathbf{y})\mathbf{R} + \frac{1}{2N_e} \int_0^\infty \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R} \right. \\ & \left. - \overline{\mathbf{V}(\mathbf{X}(t))\mathbf{R}\mathbf{X}^T(t)\mathbf{R}} - \overline{\mathbf{X}(t)\mathbf{R}^T\mathbf{V}(\mathbf{X}(t))\mathbf{R}} \right] dt \end{aligned} \quad (\text{S1.16})$$

which is exact within the framework of the diffusion approximation (see Part 2 of the Supplementary Material for detailed calculation of this).

The expression in Eq. (S1.16) is amenable to expansion in $\mathbf{R}$ to second order for the following reasons.

- (i) All $\mathbf{R}$ dependence of the first two terms of the right hand side is explicit (recall that $\mathbf{y}$ represents the initial frequencies and hence is independent of $\mathbf{R}$). Thus no work needs to be done on these terms.

- (ii) The contribution of the remaining terms on the right hand side to $P_i(\mathbf{y})$ can all be written as $\sum_{j,k=1}^n R_j R_k A_{i,j,k}$ where $A_{i,j,k}$ involves an integral of statistics of $\mathbf{X}(t)$ (such as $\delta_{i,j} \int_0^\infty \overline{V_{j,k}(\mathbf{X}(t))} dt$). Then, since $R_j R_k$ is second order in $\mathbf{R}$, calculation of $\sum_{j,k=1}^n R_j R_k A_{i,j,k}$ to second order in $\mathbf{R}$ only requires that $A_{i,j,k}$ be calculated to *zeroth* order in $\mathbf{R}$, i.e., calculated under neutrality, and this can be done.

Expansion

Proceeding in this way, we find that the approximate form of $\mathbf{P}(\mathbf{y})$ that contains all terms up to second order in $\mathbf{R}$ is

$$\mathbf{P}(\mathbf{y}) \simeq \mathbf{y} + \mathbf{V}(\mathbf{y})\mathbf{R} + \frac{1}{3} \left(\mathcal{D}(\mathbf{R}) - \mathbf{y}^T \mathbf{R} - \mathbf{y} \mathbf{R}^T \right) \mathbf{V}(\mathbf{y})\mathbf{R}. \quad (\text{S1.17})$$

For full details of the calculation, see Section 2 of the Supplementary Material.

Finally, with $R_{i,j} = R_i - R_j$ and defining

$$Q_i \equiv Q_i(\mathbf{y}) = \sum_{j=1}^n R_{i,j} y_j \quad (\text{S1.18})$$

we can rewrite Eq. (S1.17) in the much simpler equivalent form

$$P_i(\mathbf{y}) \simeq y_i \times \left[1 + Q_i + \frac{1}{3} \left(Q_i^2 - \sum_{j=1}^n y_j Q_j^2 \right) \right] \quad (\text{S1.19})$$

which applies for $i = 1, 2, \dots, n$ and is the result presented in the main text.

1.3 Properties of the truncated power series approximation

In Section 1.3 of the Supplementary Material, we expose some limitations of using a truncated power series as an approximation of the ‘exact’ fixation probability (i.e., the fixation probability under the diffusion approximation).

Consider a locus with n alleles. The fixation probability of a particular allele will depend on n initial frequencies (which, however, sum to unity). If the only non-zero initial allele frequencies are that of the particular allele, and one other allele, then the resulting form of the fixation probability is precisely that of an $n = 2$ allele problem. Thus from the $n = 2$ case we can infer some properties about the general n case.

For small selection coefficients, the corresponding fixation probability, under the diffusion approximation, is given by Kimura’s result (Eq. (8) of the main text).

The relevant approximation for the case at hand is a truncated power series in $R_{1,2}$. This reads

$$P_{1,K}(\mathbf{y}) \simeq y_1 \times \left[1 + (1 - y_1) R_{1,2} + \frac{1}{3} (1 - 3y_1 + 2y_1^2) R_{1,2}^2 \right] \quad (\text{S1.20})$$

(it is also given in Eq. (9) of the main text). On intuitive grounds, Kimura’s result, $P_{1,K}(\mathbf{y})$, is an increasing function of the initial frequency, y_1 (as can be

proved). In other words, $\partial P_{1,K}(\mathbf{y})/\partial y_1 > 0$ for $0 \leq y_1 \leq 1$. By contrast, the approximation in Eq. (S1.20) has the property that for sufficiently large $R_{1,2}^2$ the approximation is not an increasing function of y_1 . This signals a breakdown in the approximation. To find the range of $R_{1,2}$ where such a breakdown occurs, we differentiate Eq. (S1.20) with respect to y_1 and look for the values of y_1 where the derivative vanishes. There are two such values, given by

$$y_{\pm} = \frac{1}{R_{1,2}} \left(\frac{1}{2} + \frac{R_{1,2}}{2} \pm \frac{\sqrt{3(R_{1,2}^2 - 3)}}{6} \right). \quad (\text{S1.21})$$

However only for $R_{1,2}^2 - 3 \geq 0$ are the $y_{\pm}$ real. This means the approximation in Eq. (S1.20), will be an increasing function of y_1 when $R_{1,2}^2 < 3$ but it will not be an increasing function of y_1 , for all y_1 , when

$$R_{1,2}^2 \geq 3. \quad (\text{S1.22})$$

This result tells us when, on general grounds, the approximation in Eq. (S1.20) will not have the appropriate behaviour of a fixation probability, namely when $|R_{1,2}| \geq \sqrt{3} \simeq 1.73$.

It follows for general n , that the approximation we have presented in this work will have limitations on the magnitudes of the $R_{i,j}$, and in particular will break down when $|R_{i,j}| \geq \sqrt{3} \simeq 1.73$.

The above motivated us to proceed in this work by conservatively restricting the maximum value of all $|R_{i,j}|$ to unity. From the simulation results given in Table 1 of Section 1.4 of the Supplementary Material, this restriction yields a reliable approximation for $n = 3$ alleles.

1.4 Quality of the approximation

In Section 1.4 of the Supplementary Material, we give an indication of the sort of errors we should expect from the approximations adopted.

In this work we have calculated an approximation of the fixation probability when there are multiple alleles. To obtain the approximation we employed the diffusion approximation of a Wright-Fisher model, which is not exact, along with truncation of a power series.

To give an indication of the sort of errors we should expect, we shall focus on the case of a locus with $n = 3$ alleles, that is subject to additive selection, as considered in Section 4.2 of the main text, with results presented in Figure 3 of the main text. We have used simulations to estimate the errors. The simulations are based on the exact Wright-Fisher model underlying our analysis. In this model, time is discrete, and takes the values $0, 1, 2, \dots$, and the effective population size coincides with the census size, N .

For the simulations, we used the exact form for the evolutionary force, $\mathbf{F}(\mathbf{x})$, of the Wright-Fisher model under additive selection. This has an i 'th element that is given by

$$F_i(\mathbf{x}) = \frac{x_i \left(s_i - \sum_{j=1}^n s_j x_j \right)}{1 + 2 \sum_{j=1}^n s_j x_j} \quad (\text{S1.23})$$

(cf. Eq. (2) of the main text).

The simulations amount to iterating the equation

$$2N\mathbf{X}(t+1) \sim \text{Mult}(2N, \mathbf{X}(t) + \mathbf{F}(\mathbf{X}(t))) \quad (\text{S1.24})$$

where $\mathbf{X}(t)$ is a column vector containing the frequencies of the three alleles in generation t , and $\text{Mult}(n, \mathbf{p})$ denotes a multinomial distribution with parameters n (the number of trials) and $\mathbf{p}$ (a vector containing the probabilities of falling into different categories, on each trial).

Simulated results were obtained by:

1. specifying the value of N along with the values of R_1 , R_2 and R_3 (with the s_i given by $R_i/(2N)$)
2. specifying the initial frequency of allele 2, written y_2 , such that $\mathbf{X}(0) \equiv \mathbf{y}$ has the form

$$\mathbf{y} = \begin{pmatrix} \frac{1}{2N} \\ y_2 \\ 1 - y_2 - \frac{1}{2N} \end{pmatrix}$$

3. iterating Eq. (S1.24) from $\mathbf{X}(0)$ for sufficient generations until fixation of one of the three alleles occurs
4. repeating Step 3 many times, thereby obtaining many trajectories with a common starting set of frequencies, and determining the proportion of these where allele 1 fixes - this is an estimate of $P_1(\mathbf{y})$

In this way we obtain numerical results that can be compared with the approximation given in Eq. (14) of the main text. We have constructed Table 1 for this purpose.

R_1	R_2	R_3	y_2	Approx.	Simulation	Difference
1	$\frac{1}{2}$	0	0.000	2.32	2.33	0%
1	$\frac{1}{2}$	0	0.500	1.91	1.93	-1%
1	$\frac{1}{2}$	0	0.995	1.58	1.63	-3%
$\frac{1}{2}$	1	0	0.000	1.58	1.59	-1%
$\frac{1}{2}$	1	0	0.500	0.91	0.88	4%
$\frac{1}{2}$	1	0	0.995	0.58	0.56	5%
0	1	$\frac{1}{2}$	0.000	0.58	0.61	-5%
0	1	$\frac{1}{2}$	0.500	0.42	0.44	-5%
0	1	$\frac{1}{2}$	0.995	0.33	0.30	13%

Table 1: **Comparing approximate and simulation results of $P_1(\mathbf{y})/y_1$.** For a subset of the parameter-values used in Figure 3 of the main text, we compare approximate results for $P_1(\mathbf{y})/y_1$ (following from Eq. (14) of the main text), with the results of simulations of the exact Wright-Fisher model. Initial frequency values were taken as $(y_1, y_2, y_3) = (\frac{1}{2N}, y_2, 1 - \frac{1}{2N} - y_2)$, and for each value of y_2 , a total of 10^5 frequency trajectories were simulated until one of the alleles achieved fixation. The fixation probability of allele 1 was estimated from the final state of these trajectories. The parameter values used to produce the table are: population size, $N = 100$, scaled selection coefficients, R_i , as given in the table, with values of selection coefficients following from $s_i = R_i/(2N)$. The column ‘Difference’ contains the *percentage difference* of approximate results relative to simulation results.

2 Detailed calculations

In Section 2 of the Supplementary Material, we give full details of the calculations that lead to an expansion of the set of fixation probabilities, $\mathbf{P}(\mathbf{y})$, to second order in the scaled selection coefficients, $\mathbf{R}$.

We use the same notion as that used in Section 1 of the Supplementary Material and the main text. For completeness of Section 2 of the Supplementary Material, we restate the notation adopted.

All vectors are *column* vectors with n elements, while all matrices are *square* matrices of size $n \times n$. Furthermore, a T superscript is used to denote the transpose of a vector, an overbar denotes an expected value, and all expected values are subject to initial frequencies given by $\mathbf{y}$. We also use $\mathcal{D}(\mathbf{z})$ to denote a square matrix, where elements of the vector $\mathbf{z}$ lie on the diagonal, and all other elements are zero. We shall sometimes use $[\mathbf{z}]_i$ to denote the i ’th element of the column vector $\mathbf{z}$.

2.1 Background

We will make use of the following equations, which appear in the main text:

$$V_{i,j}(\mathbf{x}) = x_i \delta_{i,j} - x_i x_j \quad (\text{S2.1})$$

$$d\mathbf{X}(t) = \mathbf{F}(\mathbf{X}(t))dt + \mathbf{M}(\mathbf{X}(t))d\mathbf{W}(t) \quad (\text{S2.2})$$

$$\mathbf{F}(\mathbf{x}) = \mathbf{V}(\mathbf{x})\mathbf{s} \quad (\text{S2.3})$$

$$\mathbf{M}(\mathbf{x}) = \sqrt{\frac{\mathbf{V}(\mathbf{x})}{2N_e}}. \quad (\text{S2.4})$$

In all results that follow, we replace $\mathbf{s}$ by $\mathbf{R}/(2N_e)$. Hence all expressions are given in terms of $\mathbf{R}$.

2.2 Expansion of the fixation probability

In Section 2.2 of the Supplementary Material, we derive the expansion of $\mathbf{P}(\mathbf{y})$ in $\mathbf{R}$. We proceed by:

- (i) expressing $\mathbf{P}(\mathbf{y})$ in terms of $\int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}dt$,
- (ii) deriving an equation for $d\overline{\mathbf{V}(\mathbf{X})}\mathbf{R}/dt$,
- (iii) using the results of steps (i) and (ii) to determine an exact representation of $\mathbf{P}(\mathbf{y})$,
- (iv) calculating $\mathbf{P}(\mathbf{y})$ to second order in $\mathbf{R}$, using the exact representation of step (iii).

(i) Expressing $\mathbf{P}(\mathbf{y})$ in terms of $\int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}dt$

As noted in Section 1.1 of the Supplementary Material, the long time limit of the mean allele frequencies are the fixation probabilities: $\lim_{t \rightarrow \infty} \overline{\mathbf{X}}(t) = \mathbf{P}(\mathbf{y})$ (this follows from a generalisation of arguments given in [3]). Thus we need to determine an expression for $\lim_{t \rightarrow \infty} \overline{\mathbf{X}}(t)$ which, for conciseness we shall write as $\overline{\mathbf{X}}(\infty)$.

We begin with Eq. (S2.2), which, using Eq. (S2.3), can be written as

$$d\mathbf{X}(t) = \frac{\mathbf{V}(\mathbf{X}(t))\mathbf{R}}{2N_e}dt + \mathbf{M}(\mathbf{X}(t))d\mathbf{W}(t). \quad (\text{S2.5})$$

Averaging Eq. (S2.5), the $d\mathbf{W}$ term vanishes, and we obtain

$$\frac{d\overline{\mathbf{X}}(t)}{dt} = \frac{\overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}}{2N_e}. \quad (\text{S2.6})$$

Integrating Eq. (S2.6) from $t = 0$ to $t = \infty$, then using $\overline{\mathbf{X}}(0) = \mathbf{y}$ and $\overline{\mathbf{X}}(\infty) = \mathbf{P}(\mathbf{y})$ yields

$$\mathbf{P}(\mathbf{y}) = \mathbf{y} + \frac{1}{2N_e} \int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}dt. \quad (\text{S2.7})$$

It follows that knowledge of $\overline{\mathbf{V}(\mathbf{X}(t))}\mathbf{R}$ is required to find $\mathbf{P}(\mathbf{y})$, and to achieve this we shall next find the equation that $d\overline{\mathbf{V}(\mathbf{X})}\mathbf{R}/dt$ obeys.

(ii) **Deriving an equation for $d\overline{\mathbf{V}(\mathbf{X})}\mathbf{R}/dt$**

We begin by applying the rules of *Ito calculus* (see e.g. [1]) to $V_{i,j}(\mathbf{X})$ and, to lighten the notation, we shall often omit t arguments of $\mathbf{X}(t)$. We obtain

$$dV_{i,j}(\mathbf{X}) = dX_i\delta_{i,j} - dX_iX_j - X_idX_j - dX_idX_j. \quad (\text{S2.8})$$

Then

$$\begin{aligned} dX_idX_j &= [\mathbf{M}(\mathbf{X})d\mathbf{W}]_i [\mathbf{M}(\mathbf{x})d\mathbf{W}]_j \\ &= \left(\sum_{a=1}^n M_{i,a}(\mathbf{X})dW_a \right) \left(\sum_{b=1}^n M_{j,b}(\mathbf{X})dW_b \right) \\ &= \sum_{a,b=1}^n M_{i,a}(\mathbf{X})M_{j,b}(\mathbf{X})\delta_{a,b}dt \\ &= \sum_{a=1}^n M_{i,a}(\mathbf{X})M_{a,j}(\mathbf{X})dt \\ &= \frac{V_{i,j}(\mathbf{X})}{2N_e}dt. \end{aligned} \quad (\text{S2.9})$$

Thus

$$\begin{aligned} dV_{i,j}(\mathbf{X}) &= [\mathbf{F}(\mathbf{X})dt + \mathbf{M}(\mathbf{X})d\mathbf{W}]_i \delta_{i,j} \\ &\quad - [\mathbf{F}(\mathbf{X})dt + \mathbf{M}(\mathbf{X})d\mathbf{W}]_i X_j \\ &\quad - X_i [\mathbf{F}(\mathbf{X})dt + \mathbf{M}(\mathbf{X})d\mathbf{W}]_j - \frac{V_{i,j}(\mathbf{X})}{2N_e}dt. \end{aligned} \quad (\text{S2.10})$$

On averaging this equation all $d\mathbf{W}$ terms vanish and we obtain

$$\begin{aligned} d\overline{V_{i,j}(\mathbf{X})} &= \frac{1}{2N_e} \left(\overline{[\mathbf{V}(\mathbf{X})\mathbf{R}]_i} dt \delta_{i,j} - \overline{[\mathbf{V}(\mathbf{X})\mathbf{R}]_i} X_j dt \right. \\ &\quad \left. - \overline{X_i [\mathbf{V}(\mathbf{X})\mathbf{R}]_j} dt - \overline{V_{i,j}(\mathbf{X})} \right) dt. \end{aligned} \quad (\text{S2.11})$$

The corresponding set of equations, for all i and j , can be collectively written as

$$\frac{d}{dt} \overline{\mathbf{V}(\mathbf{X})} = \frac{1}{2N_e} \left[\mathcal{D} \left(\overline{\mathbf{V}(\mathbf{X})\mathbf{R}} \right) - \overline{\mathbf{V}(\mathbf{X})\mathbf{R}\mathbf{X}^T} - \overline{\mathbf{X}\mathbf{R}^T\mathbf{V}(\mathbf{X})} - \overline{\mathbf{V}(\mathbf{X})} \right]. \quad (\text{S2.12})$$

Multiplying Eq. (S2.12) from the right by $\mathbf{R}$, and using $\mathcal{D} \left(\overline{\mathbf{V}(\mathbf{X})\mathbf{R}} \right) \mathbf{R} = \mathcal{D}(\mathbf{R})\overline{\mathbf{V}(\mathbf{X})}\mathbf{R}$, yields the following form of the equation for $d\overline{\mathbf{V}(\mathbf{X})}\mathbf{R}/dt$ that we shall use

$$\frac{d}{dt} \overline{\mathbf{V}(\mathbf{X})}\mathbf{R} = \frac{1}{2N_e} \left[\mathcal{D}(\mathbf{R})\overline{\mathbf{V}(\mathbf{X})}\mathbf{R} - \overline{\mathbf{V}(\mathbf{X})\mathbf{R}\mathbf{X}^T}\mathbf{R} - \overline{\mathbf{X}\mathbf{R}^T\mathbf{V}(\mathbf{X})}\mathbf{R} - \overline{\mathbf{V}(\mathbf{X})}\mathbf{R} \right]. \quad (\text{S2.13})$$

(iii) **Exact representation of $\mathbf{P}(\mathbf{y})$.**

To obtain a useful representation of the set of fixation probabilities, $\mathbf{P}(\mathbf{y})$, we write Eq. (S2.13) as

$$\begin{aligned} \frac{d}{dt} e^{t/(2N_e)} \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} &= e^{t/(2N_e)} \frac{1}{2N_e} \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{V}(\mathbf{X}(t)) \mathbf{R} \mathbf{X}^T(t)} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{X}(t) \mathbf{R}^T \mathbf{V}(\mathbf{X}(t))} \mathbf{R} \right]. \end{aligned} \quad (\text{S2.14})$$

This leads to

$$\begin{aligned} \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} &= e^{-t/(2N_e)} \mathbf{V}(\mathbf{y}) \mathbf{R} \\ &\quad + e^{-t/(2N_e)} \frac{1}{2N_e} \int_0^t e^{r/(2N_e)} \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(r))} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{V}(\mathbf{X}(r)) \mathbf{R} \mathbf{X}^T(r)} \mathbf{R} - \overline{\mathbf{X}(r) \mathbf{R}^T \mathbf{V}(\mathbf{X}(r))} \mathbf{R} \right] dr. \end{aligned} \quad (\text{S2.15})$$

Integrating this equation from $t = 0$ to $t = \infty$ yields

$$\begin{aligned} \int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} dt &= 2N_e \mathbf{V}(\mathbf{y}) \mathbf{R} \\ &\quad + \frac{1}{2N_e} \int_0^\infty dt \int_0^t dr e^{-t/(2N_e)} e^{r/(2N_e)} \\ &\quad \times \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(r))} \mathbf{R} - \overline{\mathbf{V}(\mathbf{X}(r)) \mathbf{R} \mathbf{X}^T(r)} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{X}(r) \mathbf{R}^T \mathbf{V}(\mathbf{X}(r))} \mathbf{R} \right]. \end{aligned} \quad (\text{S2.16})$$

On interchanging the order of integration, and evaluating the t integral, we obtain

$$\begin{aligned} \int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} dt &= 2N_e \mathbf{V}(\mathbf{y}) \mathbf{R} + \int_0^\infty \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(r))} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{V}(\mathbf{X}(r)) \mathbf{R} \mathbf{X}^T(r)} \mathbf{R} - \overline{\mathbf{X}(r) \mathbf{R}^T \mathbf{V}(\mathbf{X}(r))} \mathbf{R} \right] dr. \end{aligned} \quad (\text{S2.17})$$

Using this result in Eq. (S2.7) yields the following representation of $\mathbf{P}(\mathbf{y})$ that is exact under the diffusion approximation:

$$\begin{aligned} \mathbf{P}(\mathbf{y}) &= \mathbf{y} + \mathbf{V}(\mathbf{y}) \mathbf{R} + \frac{1}{2N_e} \int_0^\infty \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} \right. \\ &\quad \left. - \overline{\mathbf{V}(\mathbf{X}(t)) \mathbf{R} \mathbf{X}^T(t)} \mathbf{R} - \overline{\mathbf{X}(t) \mathbf{R}^T \mathbf{V}(\mathbf{X}(t))} \mathbf{R} \right] dt. \end{aligned} \quad (\text{S2.18})$$

(iv) Determining $\mathbf{P}(\mathbf{y})$ to second order

We write Eq. (S2.18) as

$$\mathbf{P}(\mathbf{y}) = \mathbf{y} + \mathbf{V}(\mathbf{y})\mathbf{R} + \mathbf{J} \quad (\text{S2.19})$$

where

$$\begin{aligned} \mathbf{J} = & \frac{1}{2N_e} \int_0^\infty \left[\mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} - \overline{\mathbf{V}(\mathbf{X}(t)) \mathbf{R} \mathbf{X}^T(t)} \mathbf{R} \right. \\ & \left. - \overline{\mathbf{X}(t) \mathbf{R}^T \mathbf{V}(\mathbf{X}(t))} \mathbf{R} \right] dt \end{aligned} \quad (\text{S2.20})$$

Since $\mathbf{y}$ and $\mathbf{V}(\mathbf{y})$ are independent of $\mathbf{R}$, the first two terms on the right hand side of Eq. (S2.19) already display their full $\mathbf{R}$ dependence and we need do nothing further with these.

We now focus on Eq. (S2.20) which we write as

$$\mathbf{J} = \mathbf{A} + \mathbf{B} + \mathbf{C} \quad (\text{S2.21})$$

where $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$ are the column vectors

$$\mathbf{A} = \frac{1}{2N_e} \int_0^\infty \mathcal{D}(\mathbf{R}) \overline{\mathbf{V}(\mathbf{X}(t))} \mathbf{R} dt \quad (\text{S2.22})$$

$$\mathbf{B} = -\frac{1}{2N_e} \int_0^\infty \overline{\mathbf{V}(\mathbf{X}(t)) \mathbf{R} \mathbf{X}^T(t)} \mathbf{R} dt \quad (\text{S2.23})$$

$$\mathbf{C} = -\frac{1}{2N_e} \int_0^\infty \overline{\mathbf{X}(t) \mathbf{R}^T \mathbf{V}(\mathbf{X}(t))} \mathbf{R} dt. \quad (\text{S2.24})$$

We shall determine $\mathbf{P}(\mathbf{y})$ to *second order* in $\mathbf{R}$. Since all three terms in $\mathbf{J}$ contain explicit factors of the form $R_i R_j$, we need only determine the coefficients of these factors to *zeroth order* in $\mathbf{R}$. This involves evaluating $\overline{\mathbf{V}(\mathbf{X}(t))}$ and terms of the form $\overline{V_{i,j}(\mathbf{X}(t)) X_k(t)}$ to zeroth order in $\mathbf{R}$, as we shall now do.

Determination of $\mathbf{A}$

To determine in $\mathbf{A}$ to second order in $\mathbf{R}$ we first write Eq. (S2.12) as $d\overline{\mathbf{V}(\mathbf{X})}/dt = -\overline{\mathbf{V}(\mathbf{X})}/(2N_e) + O(\mathbf{R})$, and hence

$$\overline{\mathbf{V}(\mathbf{X}(t))} = e^{-t/(2N_e)} \mathbf{V}(\mathbf{y}) + O(\mathbf{R}). \quad (\text{S2.25})$$

This result, used in Eq. (S2.23), leads to the second order approximation $\mathbf{A} \simeq \frac{1}{2N_e} \int_0^\infty \mathcal{D}(\mathbf{R}) e^{-t/(2N_e)} \mathbf{V}(\mathbf{y}) \mathbf{R} dt$ and evaluating the integral yields the explicit result:

$$\mathbf{A} \simeq \mathcal{D}(\mathbf{R}) \mathbf{V}(\mathbf{y}) \mathbf{R}. \quad (\text{S2.26})$$

Determination of **B** and **C**

To determine **B** and **C** to second order in **R** requires the evaluation, to zeroth order in **R**, of terms of the form $\overline{V_{i,j}((\mathbf{X}(t)))X_k(t)}$. Since $V_{i,j}(\mathbf{x}) = x_i\delta_{i,j} - x_ix_j$ it follows that

$$\overline{V_{i,j}((\mathbf{X}(t)))X_k(t)} = \overline{X_i(t)X_k(t)\delta_{i,j}} - \overline{X_i(t)X_j(t)X_k(t)}. \quad (\text{S2.27})$$

We first apply Ito's lemma to $\overline{X_i(t)X_k(t)}$. Omitting t arguments, we obtain $d\overline{X_iX_k}/dt = \overline{V_{i,k}(\mathbf{X})}/(2N_e) + O(\mathbf{R})$. Furthermore, Eq. (S2.25) gives $\overline{\mathbf{V}(\mathbf{X})}$ to zeroth order in **R**. We thus have $d\overline{X_iX_k}/dt = e^{-t/(2N_e)}V_{i,k}(\mathbf{y})/(2N_e) + O(\mathbf{R})$. It follows that

$$\overline{X_i(t)X_k(t)} \simeq y_i\delta_{i,k} - e^{-t/(2N_e)}V_{i,k}(\mathbf{y}) + O(\mathbf{R}). \quad (\text{S2.28})$$

Applying Ito's lemma again, now to $\overline{X_i(t)X_j(t)X_k(t)}$, yields

$$\begin{aligned} \frac{d\overline{X_iX_jX_k}}{dt} &= \frac{\overline{V_{i,j}(\mathbf{X})X_k} + \overline{V_{i,k}(\mathbf{X})X_j} + \overline{V_{j,k}(\mathbf{X})X_i}}{2N_e} + O(\mathbf{R}) \\ &= \frac{\overline{(X_i\delta_{i,j} - X_iX_j)X_k}}{2N_e} + \frac{\overline{(X_i\delta_{i,k} - X_iX_k)X_j}}{2N_e} \\ &\quad + \frac{\overline{(X_j\delta_{j,k} - X_jX_k)X_i}}{2N_e} + O(\mathbf{R}) \\ &= \frac{\overline{X_iX_k}}{2N_e}\delta_{i,j} + \frac{\overline{X_iX_j}}{2N_e}\delta_{i,k} + \frac{\overline{X_iX_j}}{2N_e}\delta_{j,k} \\ &\quad - 3\frac{\overline{X_iX_jX_k}}{2N_e} + O(\mathbf{R}). \end{aligned} \quad (\text{S2.29})$$

Using Eq. (S2.28) yields

$$\begin{aligned} \frac{d}{dt}\overline{X_iX_jX_k} &= \frac{[y_i\delta_{i,k} - e^{-t/(2N_e)}V_{i,k}(\mathbf{y})]}{2N_e}\delta_{i,j} + \frac{[y_i\delta_{i,j} - e^{-t/(2N_e)}V_{i,j}(\mathbf{y})]}{2N_e}\delta_{i,k} \\ &\quad + \frac{[y_i\delta_{i,j} - e^{-t/(2N_e)}V_{i,j}(\mathbf{y})]}{2N_e}\delta_{j,k} - 3\frac{\overline{X_i(t)X_j(t)X_k(t)}}{2N_e} + O(\mathbf{R}) \\ &= \frac{3}{2N_e}y_k\delta_{i,j}\delta_{j,k} - e^{-t/(2N_e)}\left(\frac{V_{i,k}(\mathbf{y})}{2N_e}\delta_{i,j} + \frac{V_{i,j}(\mathbf{y})}{2N_e}\delta_{i,k} + \frac{V_{i,j}(\mathbf{y})}{2N_e}\delta_{j,k}\right) \\ &\quad - \frac{3}{2N_e}\overline{X_iX_jX_k} + O(\mathbf{R}) \end{aligned} \quad (\text{S2.30})$$

with solution

$$\begin{aligned}
\overline{X_i(t)X_j(t)X_k(t)} &\simeq e^{-3t/(2N_e)} y_i y_j y_k + \left(1 - e^{-3t/(2N_e)}\right) y_k \delta_{i,j} \delta_{j,k} \\
&\quad - \left(e^{-t/(2N_e)} - e^{-3t/(2N_e)}\right) \\
&\quad \times \frac{1}{2} \left(V_{i,k}(\mathbf{y}) \delta_{i,j} + V_{i,j}(\mathbf{y}) \delta_{i,k} + V_{i,j}(\mathbf{y}) \delta_{j,k} \right) \\
&\quad + O(\mathbf{R}). \tag{S2.31}
\end{aligned}$$

Writing $\overline{X_i(t)X_k(t)}$ in the form

$$\begin{aligned}
\overline{X_i(t)X_k(t)} &\simeq e^{-3t/(2N_e)} y_i y_k + \left(1 - e^{-3t/(2N_e)}\right) y_k \delta_{i,k} \\
&\quad - \left(e^{-t/(2N_e)} - e^{-3t/(2N_e)}\right) \frac{1}{2} 2V_{i,k}(\mathbf{y}) + O(\mathbf{R}) \tag{S2.32}
\end{aligned}$$

leads, to

$$\begin{aligned}
\overline{V_{i,j}(\mathbf{X}(t))X_k(t)} &\simeq e^{-3t/(2N_e)} V_{i,j}(\mathbf{y}) y_k + \left(e^{-t/(2N_e)} - e^{-3t/(2N_e)}\right) \\
&\quad \times \frac{1}{2} \left(V_{i,j}(\mathbf{y}) \delta_{i,k} + V_{i,j}(\mathbf{y}) \delta_{j,k} - V_{i,k}(\mathbf{y}) \delta_{i,j} \right) \\
&\quad + O(\mathbf{R}) \tag{S2.33}
\end{aligned}$$

and hence

$$\begin{aligned}
\int_0^\infty \overline{V_{i,j}(\mathbf{X}(t))X_k(t)} dt &\simeq \frac{2N_e}{3} \left[V_{i,j}(\mathbf{y}) y_k + V_{i,j}(\mathbf{y}) \delta_{i,k} \right. \\
&\quad \left. + V_{i,j}(\mathbf{y}) \delta_{j,k} - V_{i,k}(\mathbf{y}) \delta_{i,j} \right] \\
&\quad + O(\mathbf{R}). \tag{S2.34}
\end{aligned}$$

We can then write $B_i = -\frac{1}{2N_e} \sum_{j,k=1}^n R_j R_k \int_0^\infty \overline{V_{i,j}(\mathbf{X}(t))X_k(t)} dt$ and $C_k = -\frac{1}{2N_e} \sum_{i,j=1}^n R_i R_j \int_0^\infty \overline{V_{i,j}(\mathbf{X}(t))X_k(t)} dt$ and from these we obtain the second order approximations

$$\mathbf{B} \simeq -\frac{1}{3} \mathbf{V}(\mathbf{y}) \mathbf{R} \mathbf{y}^T \mathbf{R} - \frac{1}{3} \mathbf{V}(\mathbf{y}) \mathcal{D}(\mathbf{R}) \mathbf{R} \tag{S2.35}$$

and

$$\mathbf{C} \simeq -\frac{1}{3} \mathbf{y} \mathbf{R}^T \mathbf{V}(\mathbf{y}) \mathbf{R} - \frac{2}{3} \mathcal{D}(\mathbf{R}) \mathbf{V}(\mathbf{y}) \mathbf{R} + \frac{1}{3} \mathbf{V}(\mathbf{y}) \mathcal{D}(\mathbf{R}) \mathbf{R}. \tag{S2.36}$$

Final form of $\mathbf{P}(\mathbf{y})$

Combining the results for $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$, we obtain

$$\mathbf{J} = \mathbf{A} + \mathbf{B} + \mathbf{C} \simeq \frac{1}{3} \left(\mathcal{D}(\mathbf{R}) - \mathbf{y}^T \mathbf{R} - \mathbf{y} \mathbf{R}^T \right) \mathbf{V}(\mathbf{y}) \mathbf{R}. \quad (\text{S2.37})$$

Using this form of $\mathbf{J}$ in Eq. (S2.19) yields the second order approximation to $\mathbf{P}(\mathbf{y})$:

$$\mathbf{P}(\mathbf{y}) \simeq \mathbf{y} + \mathbf{V}(\mathbf{y}) \mathbf{R} + \frac{1}{3} \left(\mathcal{D}(\mathbf{R}) - \mathbf{y}^T \mathbf{R} - \mathbf{y} \mathbf{R}^T \right) \mathbf{V}(\mathbf{y}) \mathbf{R}. \quad (\text{S2.38})$$

We can write this last result in an alternative way. With $R_{i,j} = R_i - R_j$ and defining

$$Q_i \equiv Q_i(\mathbf{y}) = \sum_{j=1}^n R_{i,j} y_j \quad (\text{S2.39})$$

we find we can write Eq. (S2.38) in the simpler form

$$P_i(\mathbf{y}) \simeq y_i \times \left[1 + Q_i + \frac{1}{3} \left(Q_i^2 - \sum_{j=1}^n y_j Q_j^2 \right) \right] \quad \text{for } i = 1, 2, \dots, n \quad (\text{S2.40})$$

and this is the result presented in the main text.

2.3 Consistency

In Section 2.3 of the Supplementary Material, we make a comment on the *consistency* of the approximation of the fixation probabilities in Eq. (S2.40).

We begin by noting that the set of fixation probabilities (the $P_i(\mathbf{y})$ for $i = 1, 2, \dots, n$) constitute a probability distribution. As such they have the property

$$\sum_{i=1}^n P_i(\mathbf{y}) = 1. \quad (\text{S2.41})$$

Since the right hand side Eq. (S2.41) is independent of the $R_{j,k}$, a consistent expansion of the $P_i(\mathbf{y})$ will have Eq. (S2.41) satisfied at every order of approximation in the $R_{j,k}$. Let us demonstrate how the approximation in Eq. (S2.40) has this property.

At zeroth order in the $R_{j,k}$, we have $P_i(\mathbf{y}) \simeq y_i$ and because $\sum_{i=1}^n y_i = 1$, the zeroth order approximation satisfies Eq. (S2.41). A first order approximation of the $P_i(\mathbf{y})$ is $P_i(\mathbf{y}) \simeq y_i \times (1 + Q_i)$ and because $\sum_{j=1}^n y_j Q_j = 0$, the first order approximation also satisfies Eq. (S2.41). Lastly, we see that the second order approximation in Eq. (S2.40) also satisfies Eq. (S2.41) (using $\sum_{i=1}^n y_i = 1$ twice). Thus, to the order calculated, the $P_i(\mathbf{y})$ in Eq. (S2.40) are consistent with Eq. (S2.41).

References used in the Supplementary Material

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