

# Models of strong selection in large samples

Ivan Krukov, Simon Gravel

---

## Abstract

Neutral models of genetic diversity tend to be easier to analyze than models including selection. Under the neutral Wright-Fisher model, the number of lineages that contribute to ancestry of a sample decreases back in time due to coalescent events. As a consequence, useful recursion equations can be derived for patterns of polymorphism. By contrast, under negative selection, the number of relevant lineages can increase as we go back in time, due to selective deaths. As a result, the equivalent recursion equations do not close. However, given a sufficiently large sample size, the expected reduction in the number of contributing lineages due to coalescence is larger than the increase due to selection, so the net number is unlikely to increase. We use this observation to derive asymptotically closed recursion equations for the distribution of allele frequencies in finite samples. We show that this approach is accurate under strong drift and strong natural selection. We derive several asymptotic results to determine when the sample size is sufficiently large for drift to overcome the effect of selection.

---

## 1. Introduction

The allele frequency spectrum ( $AFS$ ) is an important summary of genetic diversity that is commonly used to infer demographic history and natural selection (). Given a demographic scenario of population size histories and migrations, the diffusion approximation or coalescent simulations can be used to obtain a predicted  $AFS$  (). By comparing predictions to the observed  $AFS$ , one can compute likelihoods for different demographic scenarios. Unfortunately, the  $AFS$  calculations can be time consuming with complex demographic models, for example with multiple populations, or with large sample sizes ().

In the absence of selection, efficient computational shortcuts can be used. In particular, recursion equations have been derived for moments of the allele frequency distribution (Kimura and Crow,

1964; Ewens, 1972; Jouganous et al., 2017). Recently, these recursions have been useful in fitting complex demographic models to genetic data (Jouganous et al., 2017; Kamm et al., 2017).

In the presence of natural selection, the corresponding recursion equations do not close (Jouganous et al., 2017) – they form an infinite set of coupled ordinary differential equations. Moment-based closure approximation have been developed (Jouganous et al., 2017), but these are not robust to strong selection and their convergence properties are not well understood.

Closure of the moment equations under the neutral Wright-Fisher model occurs because the number of parental lineages that contribute to the present day sample is equal to or smaller than the sample size, due to coalescent events back in time (Kingman, 1982). To describe a sample of size  $n$ , we need to recursively consider samples of size  $n' \leq n$ . This does not hold under negative selection – due to selective deaths, the number of parental lineages  $n'$  can be larger than  $n$ . As we demonstrate later, this leads to a potentially infinite number of terms in the equations. This is similar to the ancestral selection graphs (ASG), (Krone and Neuhauser, 1997), where the number of relevant lineages can increase back in time.

The interplay of drift and selection is important to consider. In large sample sizes, there are many more common ancestry events than selective deaths, so the number of contributing lineages is unlikely to increase back in time. This suggests that large sample sizes can lead to almost-closed recursion equations, as we will demonstrate here.

An additional complication is multiple and/or simultaneous coalescent events – which emerge with large sample sizes (Bhaskar et al., 2014). The standard coalescent model only allows one event per generation, but we also need to consider higher-order events, *e.g.* multiple two-lineage or three-lineage mergers. These multiple-lineage coalescent events oppose the effect of selection by rapidly decreasing the number of contributing lineages (Nelson et al., 2019).

In this article we derive these asymptotically-closed recursions in the Wright-Fisher model, and study their behavior and applications for modeling the distribution of allele frequencies under strong selection.

## 2. Background

We consider a haploid Wright-Fisher model of size  $N$ , focusing on a single biallelic locus. For a present sample with  $n_o$  (offspring) lineages at time  $t$ , we want to know how many parental lineages ( $n_p$ ) have been sampled from time  $t - 1$  (Fig. 1). Under a neutral coalescent model (Fig. 1A), the

number of contributing parental lineages at  $t - 1$  is  $n_p \leq n_o$ , as the number of lineages decreases due to coalescent events.

To model the interplay of selection and drift, we consider a two-stage selection scheme (Fig. 1B). First, in a neutral process,  $n_p$  parents at  $t - 1$  produce a (potentially infinite) number  $n_g$  gametes for an intermediate  $t - \frac{1}{2}$  generation,  $n_p \leq n_g$ . Second, the  $n_g$  gametes are sampled (with rejection) into  $n_o$  offspring at time  $t$ . The number of rejected samples depends on the strength of negative selection,  $s$ . With stronger negative selection, more gametes will be rejected, so that  $n_o \leq n_g$ . We want to show that as  $n_o$  increases, asymptotically  $n_o \leq n_p$ .

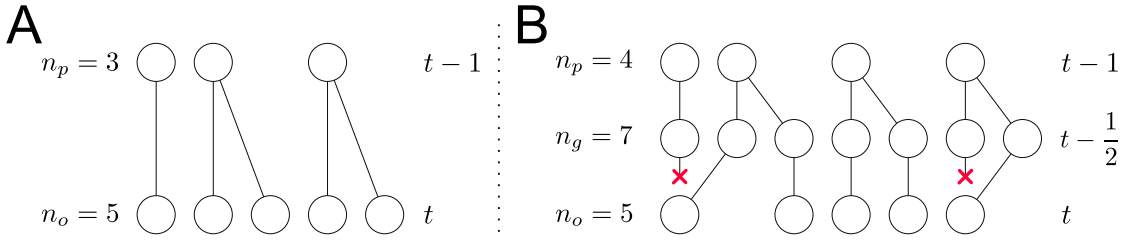


Figure 1: Realizations of sampling parental lineages under neutrality (A) and selection (B). **A** Under neutrality, possible coalescent events imply that number of parental lineages  $n_p$  at  $t - 1$  is less than or equal to  $n_o$  offspring lineages at  $t$ . **B** With selection, we add an intermediate gamete  $n_g$  generation at  $t - \frac{1}{2}$ . Production of gametes is neutral, so  $n_p \leq n_g$ . Gametes are sampled with rejection into offspring, so  $n_o \leq n_g$ . Rejected samples shown with red crosses.  $n_p$  - parental sample size (at  $t - 1$ ),  $n_g$  - number of gametes (at  $t - \frac{1}{2}$ ),  $n_o$  - offspring (current) sample size (at  $t$ ).

In the Kingman coalescent, only a single coalescent event is allowed per generation, in approximation that sample size is much smaller than the population size:  $n_o \ll N$ . This implies that under neutrality  $n_p \in [n_o - 1, n]$ . However, Bhaskar et al. (2014) show that with increasing sample size, higher order coalescent terms contribute more substantially. This means that to describe the sample of size  $n_o$ , we need to consider  $n_p$  potentially in the range  $n_p \in [1, n]$ .

The number of gametes,  $n_g$  is equal to the number of parents plus the number of coalescent events,  $n_g = n_p + n_c$ . At the selection stage, the number of gametes is the number of offspring plus the number of rejected samplings ( $n_r$ ) due to selective deaths:  $n_g = n_o + n_r$ . Thus, the number of contributing parental lineages is  $n_p = n_o + n_r - n_c$ . Thus we can see that the coalescent events and selective deaths are affecting the number of parents in opposite directions.

We want to describe the time-evolution of the allele-frequency spectrum (*AFS*) in a sample size  $n_o$  at time  $t$ , which we denote as  $\Phi_{n_o}^{(t)}$ . We construct this recursively in terms of smaller sample sizes,  $n'$ . In this section, we follow the exposition in Jouganous et al. (2017), using drift ( $\mathcal{D}_{n' \rightarrow n}$ ) and selection ( $\mathcal{S}_{n' \rightarrow n}$ ) operators. These operators are sparse matrices that describe changes in allele frequencies in going from sample size  $n'$  to sample size  $n$  due to coalescent and selection events, respectively (Jouganous et al., 2017).

Under neutrality (Fig. 1A), we have  $n_p \in [1, n_o]$ , therefore:

$$\Phi_{n_o}^{(t)} = \sum_{n_p=1}^{n_o} \mathcal{D}_{n_p \rightarrow n_o} \Phi_{n_p}^{(t-1)} \quad (1)$$

This equation is closed with respect to the sample size  $n_o$ .

To include the effect of selection, we consider first the production of gametes from the parental generation as a neutral process. Changing the subscripts in (1) to refer to Fig. 1B, we have:

$$\Phi_{n_g}^{(t-\frac{1}{2})} = \sum_{n_p=1}^{n_g} \mathcal{D}_{n_p \rightarrow n_g} \Phi_{n_p}^{(t-1)}$$

Then, the produced gametes are sampled with rejection into  $n_o$  offspring:

$$\Phi_{n_o}^{(t)} = \sum_{n_g=n_o}^{\infty} \mathcal{S}_{n_g \rightarrow n_o} \Phi_{n_g}^{(t-\frac{1}{2})}$$

Combining the two expressions above, we get:

$$\Phi_{n_o}^{(t)} = \sum_{n_g=n_o}^{\infty} \sum_{n_p=1}^{n_g} \mathcal{S}_{n_g \rightarrow n_o} \mathcal{D}_{n_p \rightarrow n_g} \Phi_{n_p}^{(t-1)} \quad (2)$$

Since we need to consider a potentially infinite number of gametes produced ( $n_g$ ), the equation (3) is no longer closed with respect to sample size.

Using  $n_g = n_o + n_r = n_p + n_c$ , we can re-write the above as:

$$\Phi_{n_o}^{(t)} = \sum_{n_r=0}^{\infty} \sum_{n_c=0}^{n_o+n_r-1} \mathcal{S}_{(n_o+n_r) \rightarrow n_o} \mathcal{D}_{(n_o+n_r-n_c) \rightarrow (n_o+n_r)} \Phi_{n_o+n_r-n_c}^{(t-1)} \quad (3)$$

This shows that the allele frequency spectrum in a sample size  $n_o$  at present is a function of the AFS in the previous generation, with the sample size  $n_o + n_r - n_c$ .

IK: I don't like this explanation, since I feel that the equation doesn't add much to the figure.

The opposing effects of drift and selection on the number of lineages can be clearly seen in the context of the size of the ancestral selection graph (*ASG*): in which the number of lineages is described by continuous-time a birth-death process (Krone and Neuhauser, 1997; Wakeley, 2009).

$$n \rightarrow \begin{cases} n + 1 & \text{at rate } \frac{2Nsn}{2N} \text{ (selection)} \\ n - 1 & \text{at rate } \frac{n(n-1)}{2N} \text{ (coalescence)} \end{cases} \quad (4)$$

The coalescence term is quadratic with respect to the sample size  $n$ , while the selection term is linear. The rate of coalescence is higher than the rate of selective events if the number of lineages  $n > 2Ns + 1$ .

Our goal is to further investigate the interplay of selection and drift, and their effect on the *AFS*. First, we propose a construction that allows us to calculate the *AFS* under strong selection and large sample size, accounting for high-order coalescent terms. Second, we show that with increasing sample size, the system becomes asymptotically closed. We construct exact and approximate probability distributions that describe the number of contributing lineages. Additionally, we derive a normal approximation that allows us to calculate the quantile function of the sample size for a desired degree of closure.

### 3. Results

#### 3.1. Markov process construction

An alternative way to describe the time-evolution of the *AFS* (3), is to consider a single transition-probability matrix,  $\mathbf{P}$ , that describes the change due to drift and selection as a single term, and explicitly models derived and ancestral states:

$$\Phi_{n_o}^{(t)} = \mathbf{P} \Phi_{n_o}^{(t-1)} \quad (5)$$

IK:  $n_o$  and  $n$  (without subscript) are the same thing. I use  $n_o$  explicitly everywhere, but I can probably drop the subscript when it's clear from context.

$\mathbf{P}$  is a square  $n_o \times n_o$  matrix, and it enumerates the number of derived alleles ( $i$ ) at a biallelic locus in a sample of size  $n_o$ .  $\mathbf{P}$  includes contributions from all possible configurations of parents  $n_p$ , weighted by the probability of the relevant coalescent/selective event. We will need to keep track of sample size and number of derived alleles in the offspring ( $o$ ) and parents ( $p$ ) lineages for a given generation. For example, we use  $\frac{i_p}{n_p}$  (read as “ $i_p$  out of  $n_p$ ”) to denote a sample of size  $n$  with  $i$  derived in the parental generation (at  $t - 1$ ).

Instead of using the summation formulation presented in (3), we use recursive conditional probabilities, where transitions are defined in terms of transitions in smaller sample sizes. Each entry of the matrix,  $\mathbf{P}_{(i_o, i_p)}$  is a transition probability from  $i_p$  to  $i_o$  derived alleles with sample sizes  $n_p$  and  $n_o$ , respectively. The key observation is that to construct such probabilities, we can condition on a set of coalescent events  $\{\Lambda\}$  in a smaller sample size:

$$\begin{aligned} \mathbf{P}_{(i_o, i_p)} &= P \left[ \frac{i_o}{n_o} \middle| \frac{i_p}{n_p} \right] \\ &= \sum_{\lambda \in \{\Lambda\}} P(\lambda) P \left[ \frac{i_o}{n_o} \middle| \frac{i_p}{n_p}, \lambda \right] \\ &= \sum_{\lambda \in \{\Lambda\}} P(\lambda) P \left[ \frac{i_o - |\lambda|_{i_o}}{n_o - |\lambda|_{n_o}} \middle| \frac{i_p - |\lambda|_{i_p}}{n_p - |\lambda|_{n_p}} \right] \end{aligned}$$

Above,  $|\lambda|$  denotes the size of the coalescent event. The third equality ascertains that conditioning on a coalescent event is equivalent to subtracting relevant lineages from the sample. This yields a recurrence where transition probabilities in a sample of size  $n$  can be described recursively in terms of transition probabilities in smaller sample sizes,  $n' \in [1, n - 1]$ .

The full derivation of  $\mathbf{P}$  for neutral and  $\mathbf{P}_s$  for selective cases can be found in the appendix. This involves enumerating all the coalescent and selective events between samples of different sizes. We avoid it here for brevity.

The maximum sample size is  $n = N$ , the size of the entire population. We expect that in the regime where  $n \ll N$ , the calculations with the present model do not differ substantially from the prediction under the standard coalescent, or (Jouganous et al., 2017). In the limit where  $n \rightarrow N$ , we expect the transition probabilities in  $\mathbf{P}_s$  to approach those in the full Wright-Fisher model (*i.e.* (Ewens, 2004, eq. 1.58)).

Similar to (3), the transition probability matrix with selection ( $\mathbf{P}_s$ ), involves considering a large

number of intermediate lineages. In practice, we limit the number of selective events to at most one per lineage – which means that the maximum number of contributing lineages is  $2n_o$  – one selective death for each offspring. This allows us to model strong selection, while limiting the number of coalescent configurations we need to consider when building  $\mathbf{P}_s$ . While it should in principle be possible to include additional selective events, we do not pursue this here.

The above restriction implies that under strong selection with large number of derived lineages  $i$ , there is a possibility that some probability is *missing* from  $\mathbf{P}_s$ . However, since this model forms a proper Markov chain, we can calculate the total missing probability, by subtracting the total probability for a given derived allele count  $i$  from 1. This gives a rather natural proxy to checking how many extra lineages are required by selection. As we show further, this missing probability tends to 0 with increasing sample size.

The recursive nature of these calculations makes them relatively inefficient. Using a dynamic programming algorithm, we implement the construction of the neutral matrix  $\mathbf{P}$  in the order of  $O(n^3)$  operations. The selection transition probability matrix  $\mathbf{P}_s$  needs  $O(n^4)$  operations, due to the need to consider intermediate lineages. The increase in complexity makes this approach unsuitable for large sample sizes, but we derive several approximations in the following sections.

### 3.2. Calculation of allele frequency spectra

Once truncated matrix  $\mathbf{P}_s$  is constructed, it can be used to calculate the allele frequency spectrum. For the infinite sites model at equilibrium, we can approximate the equilibrium *AFS*  $\Phi$  as a solution to a linear system:

$$\Phi = \Phi Q + n\mu e_1 \quad (6)$$

where  $\mu$  is the per-site mutation rate, and  $e_1$  is the first column of the identity matrix of size  $n$ . Figure 2 shows the comparison of the *AFS* calculated from Equation (??), the diffusion approximation (Ewens, 2004, eq. 9.23), and the calculation performed in **Moments** (Jouanous et al., 2017). Panels A and B show the *AFS* under neutrality, C and D under strong negative selection. Under neutrality, all the models agree, yielding similar *AFS*. When the sample size is equal to the population size (Fig. 2B), we also include the *AFS* from the full Wright-Fisher model, which the other three calculations agree with.

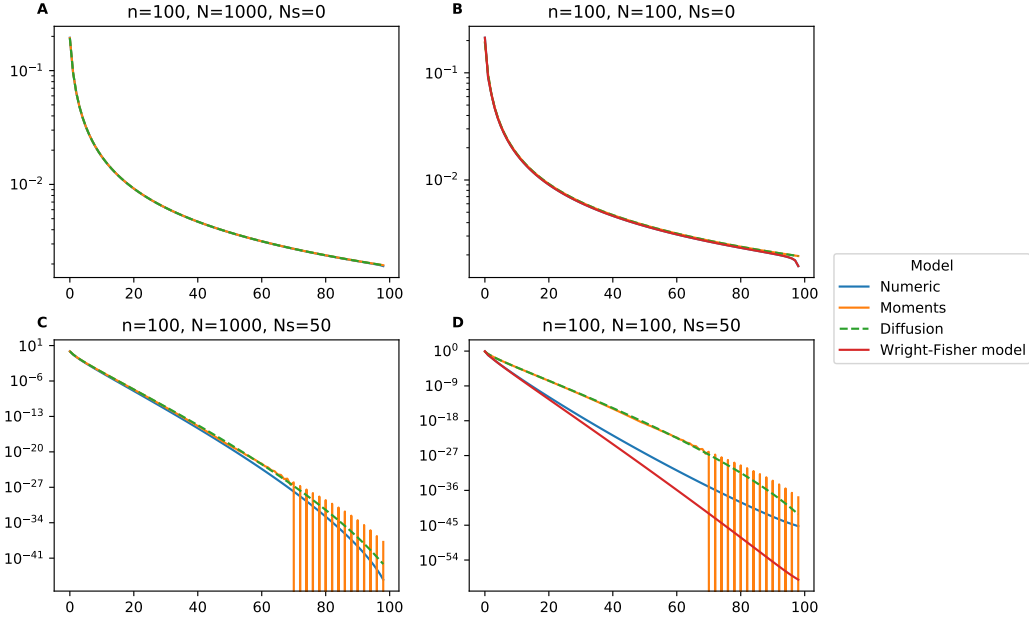


Figure 2: Normalized allele frequency spectra in a sample of size  $n = 100$ , for highly deleterious alleles ( $Ns = 50$ ). (A) shows the frequency spectrum in a sample from a large population ( $N = 1000$ ), (B) in a small population ( $N = 100$ ).

Figure ??C shows a comparison at strong negative  $Ns = 50$ , with the population size ( $N = 1000$ ), which is substantially larger than the sample size ( $n = 100$ ). There is a small deviation between the approaches at large allele frequencies. At stronger selection coefficients, **Moments** suffers from numerical instability, while the diffusion approximation performs well.

If the sample size is the same as the population size ( $n = N = 100$ ) (Fig. 2D), the diffusion approximation and **Moments** perform detract from the Wright-Fisher prediction. The approach presented here (??) shows a better match to the Wright-Fisher model at small allele frequencies, but deviates later. We believe that the disagreement is due to the fact that we only allow at most one selective event per lineage, while there is no such limitation in the Wright-Fisher model.

### 3.3. Closure properties

To investigate the closure properties of  $\mathbf{P}_s$ , we can calculate the total probability that more than  $n$  parental lineages contribute to the sample of a given size. By construction, the sum of rows of  $\mathbf{P}_s$  should correspond to the total probability mass that included configurations contribute (Fig.



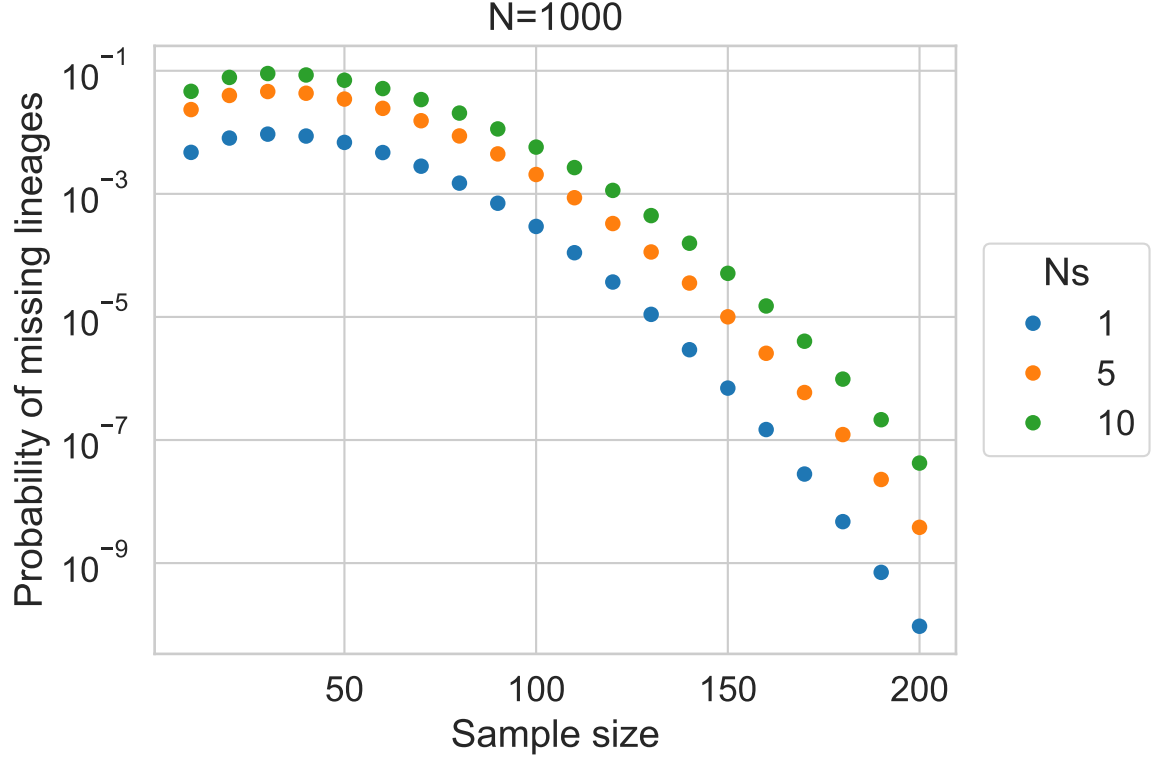


Figure 3: Probability that unaccounted lineages contribute to the transition probabilities. The probabilities are calculated as 1 minus the sum of probabilities for the state where every allele is derived.

8). Thus, the probability that some number of configurations are unaccounted for, with  $j$  derived alleles in the parental sample, is given by  $1 - \sum_{i=0}^n \mathbf{P}_s(i, j)$ . This probability depends on the number of derived alleles carried by the parental sample: the more derived alleles, the higher the likelihood of a selective event. Figure 3 shows the probability of missing configurations in a sample size of  $n = 200$  in the worst-case scenario, with  $j = 200$  derived lineages.

Since the expected number of drift events increases quadratically and the number of selective events increases only linearly, the probability that we need additional lineages decreases rapidly with sample sizes.

#### 4. Asymptotic closure properties

We now want to determine what sample size is sufficient so that the number of coalescent events due to drift is almost always larger than the number of selection events, such that the system remains closed (3). We derive several approximations to the model proposed in the first section, in order to get a better understanding of this behavior.

In the following derivations, we are assuming that the derived allele is present at frequency  $x$ , as opposed to explicitly modeling the count of derived alleles  $??$ , which simplifies the calculations. When looking for the upper bound on the number of rejected lineages, we take  $x = 1$ , since only derived alleles experience selection.

##### 4.1. Mean number of contributing lineages

For a given sample size, the probability that  $n_p$  parents have contributed is:

$$Pr(n_p|n_o) = \sum_{n_g} Pr(n_p|n_g)Pr(n_g|n_o) \quad (7)$$

Where  $n_p$  and  $n_g$  is the number of contributing parents and gametes, respectively (Fig. 1B).

As a first order approximation, we can model the expectation  $E[n_p|n_o]$  as the sum of lineages used under drift  $\tilde{E}[n_p|n_o]$  (Fig. 1A) plus the number of extra lineages required by selection,  $E[n_r|n_o]$ .

$$\begin{aligned} \hat{E}[n_p|n_o] &= \tilde{E}[n_p|n_o] + \hat{E}[n_r|n_o] \\ &= N \left[ 1 - \left( 1 - \frac{1}{N} \right)^n \right] + n \left( \frac{xs}{1 - xs} \right) \\ &\underset{N \gg n}{\approx} \frac{nx s}{1 - xs} - \frac{n^2}{2N} \end{aligned}$$

The expectations can be derived directly or from the corresponding probability distributions

4.2. The second approximation is made under the assumption that the sample size is much smaller than the population size. The increase of the number of lineages due to selection is linear. Drift decreases the number of lineages as a quadratic term with respect to the sample size. This is analogous to the results from the ancestral selection graph (Krone and Neuhauser, 1997), eq. (4). Solving (4.1) for  $n_o^* > \hat{E}[n_p|n_o]$  yields  $n_o^* \geq 2Nxs$ . This represents a critical sample size, above which drift outpaces selection. Note again the similarity to (4).

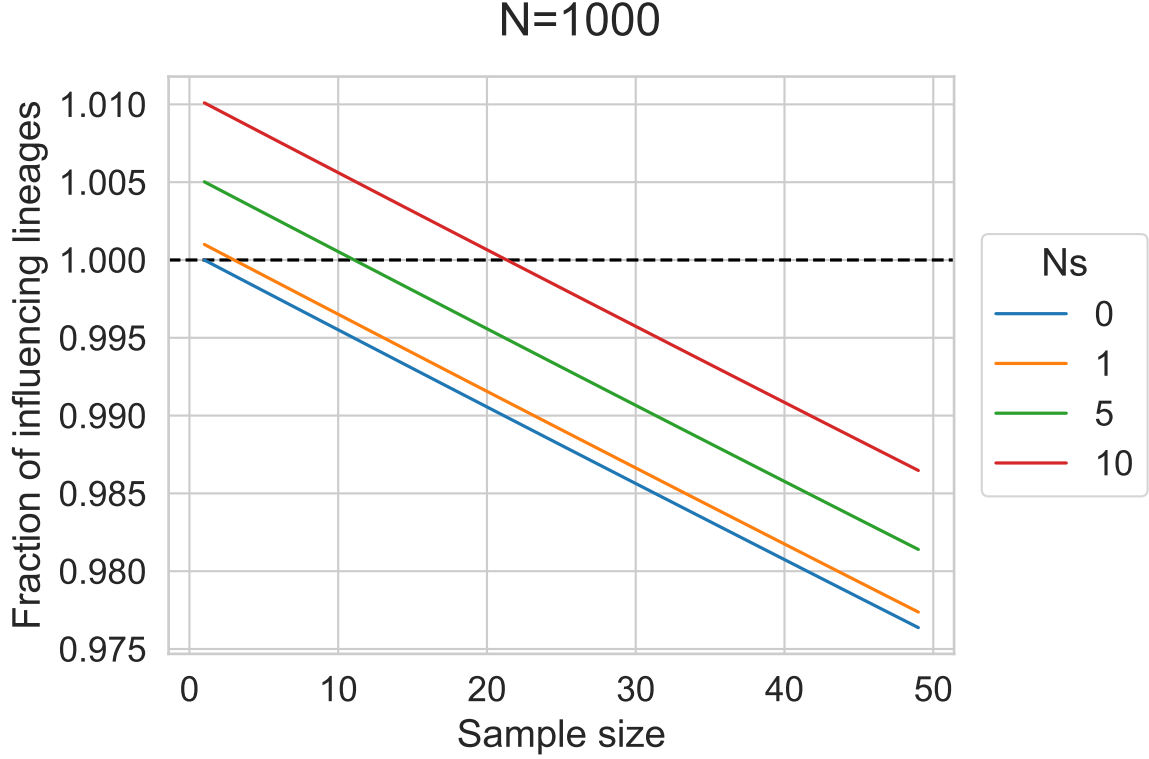


Figure 4: Critical sample size for different selection coefficients. The Y axis shows the fraction of parental lineages over the sample size,  $\frac{x}{n}$ , each line corresponds to a different selection coefficient. Above  $\frac{x}{n} \geq 1$ , selection dominates, below – drift. The critical sample size, where the expected number of parental contributing lineages is smaller than the sample size is well-approximated by  $2Ns$ .

Figure 4 shows the critical sample size for several selection coefficients, assuming the entirety of the sample is derived ( $x = 1$ ) in a population of  $N = 1,000$ . The Y axis shows the fraction of contributing parental lineages to the sample size,  $\frac{x}{n}$ . Above the horizontal line  $\frac{x}{n} > 1$ , selection dominates. Below, drift reduces the number of used lineages. The intercept of the line with  $\frac{x}{n} = 1$  is the critical sample size, which is well-approximated by  $2Nsx$ .

#### 4.2. Distribution of number of contributing lineages

We now construct a probability distribution of the number of contributing lineages one generation into the past 1C, (7).

The number of parental lineages used by drift can be modelled by the modified occupancy

(Arfwedson) distribution (Wakeley, 2009; O'Neill, 2019; Johnson et al., 2005). This is given by:

$$P(\mathcal{R} = r | \mathcal{G} = g) = \frac{S_2(g, r)N!}{(N - r)!N^g} \quad (8)$$

where  $S_2(g, r)$  is a Stirling number of the second kind, which is the number of ways to partition  $g$  gametes into  $r$  parents (see Johnson et al. (2005) section 10.4 for a thorough treatment). Note that the under drift, the number of parents will be smaller or equal to the number of gametes  $r \leq g$ .

The distribution of the number of gametes,  $n_g$  is given by the negative binomial, parameterized by the total number of trials before  $n$  successes:

$$P(\mathcal{G} = g | n) = \binom{g-1}{n-1} (1 - xs)^n (xs)^{g-n} \quad (9)$$

Here, the number of gametes can be larger than the sample size  $n \leq g$ , if selection is present ( $s < 0$ ) **SG: Are you not using  $s > 0$ ?**.

Combining the two distributions together through 7, we get:

$$Pr(\mathcal{R} = r | n) = \sum_{g=1}^{\infty} \frac{S_2(g, r)N!}{(N - r)!N^g} \binom{g-1}{n-1} (1 - xs)^n (xs)^{g-n} \quad (10)$$

This distribution does not appear to have a simple analytical form. However, it can be computed efficiently using methods presented in (O'Neill, 2019). Figure 5 shows the distribution of the number of contributing parental lineages for several selection coefficients for a sample  $n = 20$ . In the absence of selection, the distribution has zero probability above  $n = 20$ , as no extra lineages can be sampled. As the strength of selection is increased, we begin requiring larger number of lineages.

We defined the critical sample size as  $E[n_p | n] = n$ . However, the distributions in ?? show that there is a large probability that  $n_p > n$  at  $n_{crit} = 2n = 20$ . In order to guarantee that drift will out-pace selection, we can calculate the cumulative distribution - Figure ?. This shows that a sample size in which the majority of lineages are accounted for can be substantially larger than the critical sample size of equation (?). To derive a convenient analytical approximation, we turn to the normal approximation in the next section.

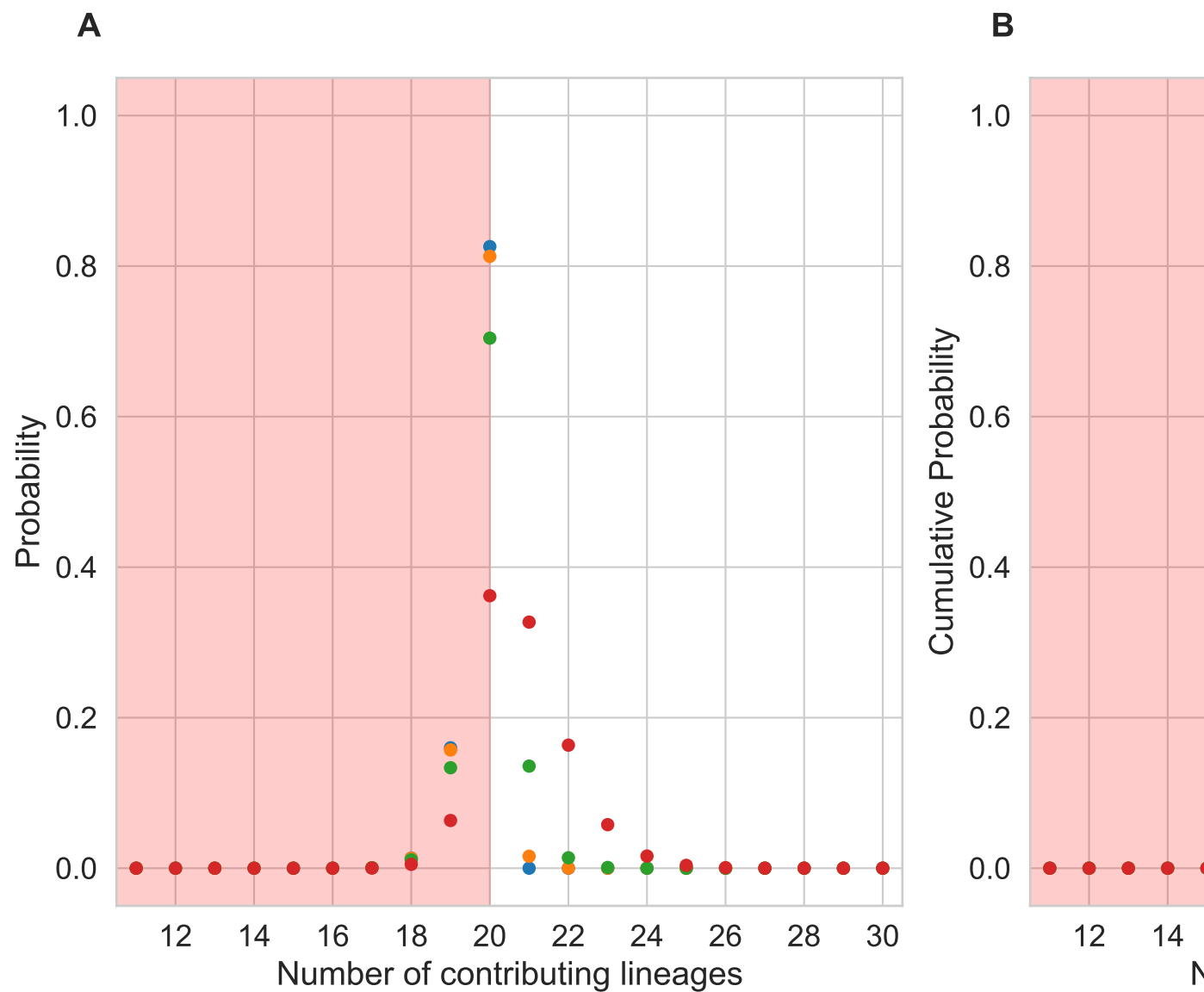


Figure 5: **A** The distribution and **B**, cumulative distribution of the number of parental contributing lineages one generation into the past ( $n = 20$ ,  $N = 1000$ ). Shaded red area shows the drift-dominated regime, where the number of lineages is smaller than the sample size.

### 4.3. Normal approximation

Finally, we can construct a normal approximation to the distribution of the number of contributing lineages. The occupancy distribution is approximated by the normal (O'Neill, 2019) when  $n \ll N$ . Likewise, the number of failures (eq. (??)) before a given number of successes, can be approximated by the normal distribution. In the case of large population size, as required by the approximation of the occupancy by the normal, we can approximate the total number of contributing lineages as the sum of lineages contributed by the two distributions **SG: What does that mean? Why do you need an approximation? Were you not computing a bound?**. The random variable which is a sum of two normally-distributed random variables is also normal, with  $\mu = \mu_1 + \mu_2$  and  $\sigma^2 = \sigma_1^2 + \sigma_2^2$ . By combining the required expectations and variance, we find that the normal approximation then has the form:

$$Pr(\mathcal{R} = r|n) \approx \mathcal{N}(\mu = [(sn)/(1-s) + N(1 - (1 - 1/N)^n)], \quad (11)$$

$$\sigma = \sqrt{N \left( (N-1) \left(1 - \frac{2}{N}\right)^n + \left(1 - \frac{1}{N}\right)^n - N \left(1 - \frac{1}{N}\right)^{2n} \right) + \frac{ns}{(1-s)^2}} \quad (12)$$

**SG: Tell people N to make self contained** Figure 6 shows the quantiles of the normal approximation. We see that up to 99% of the lineages will be contained within the sample of 200 with  $Ns = 20$ . Larger percentiles will require larger sample sizes.

## 5. Conclusion

Classically, the coalescent considers models in the absence of natural selection. Since selection can increase the number of contributing lineages back in time, the coalescent can no longer be represented by trees, but instead acquires a graph structure. The ancestral selection graphs (Krone and Neuhauser, 1997) deal with this in the limit of large population size ( $N$ ).

The large population size approximation implies that the sample size  $n$  is much smaller than the whole population ( $n \ll N$ ), so it is unlikely that more than one coalescent event will happen per generation. However, recent work (Bhaskar et al., 2014; Nelson et al., 2019) pointed out that this assumption is unreasonable with sample sizes pertinent to modern experiments. As a results,

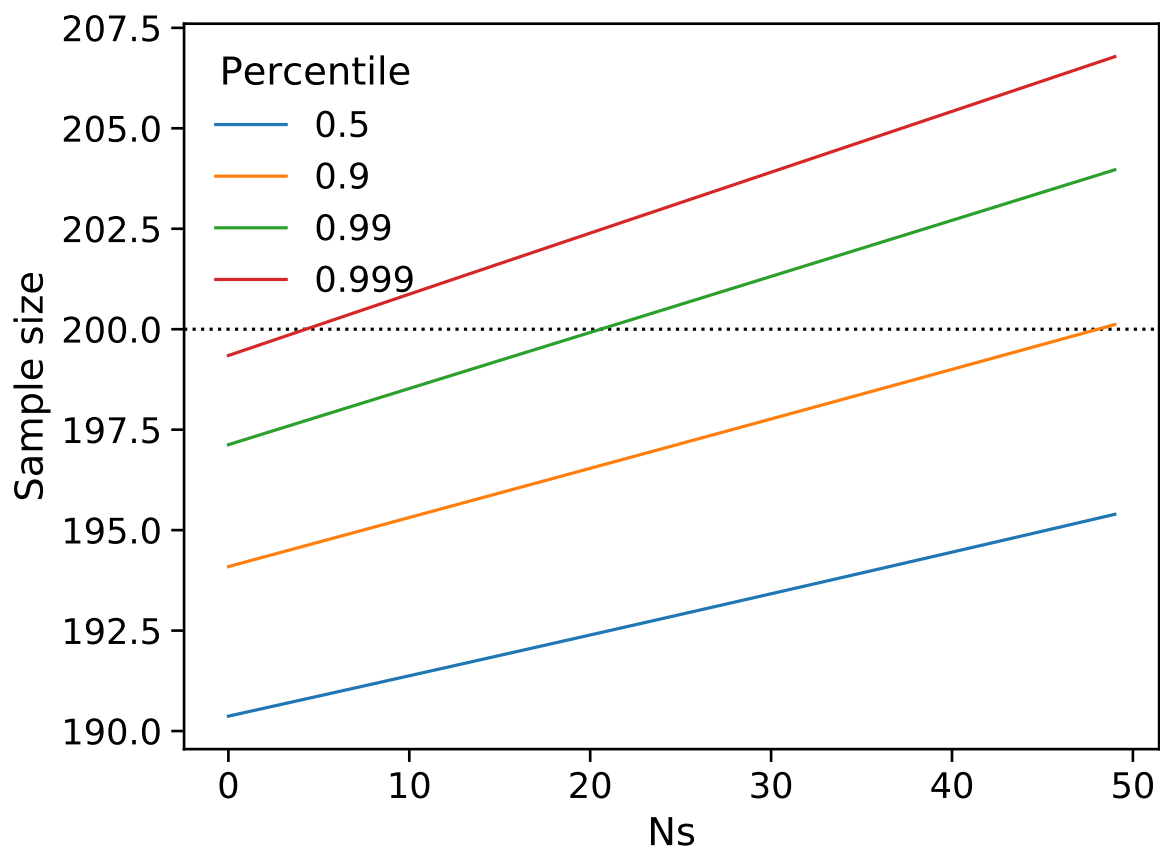


Figure 6: The quantile function of the closure of the sample **SG: What is that?**. Each line corresponds to different percentile of the normal approximation. Black dashed line shows the reference sample size  $n = 200$  **SG: does it play a special role? If not why mention it (or have this line, really)?**. **SG: It also seems like showing the cumulative distributions themselves would be more intuitive. E.g  $\log(\text{missingp})$ . Also would be nice to have the numerical calculation. Could you get the cumulative distribution for the occupancy distribution from the Oneil algo?**

models that consider multiple coalescent events per generation are gaining increased relevance in the field (?).

In this work we show that increasing the sample size has another unexpected consequence. As sample size increases, the larger number of lineages needed due to selection can be masked by coalescent events. In this sense, the large sample size rescues the model from effect of selection. This means that recursion equations needed to calculate sample properties are asymptotically closed with large population size.

At first approximation,  $2Nsx$  is a critical sample size, where the decrease of lineages due to coalescent back in time out-competes the increase due to selection (eq. (??)). Further, we derive the full probability distribution for the number lineages needed with given selection coefficient and sample size (eq. (10)). Unfortunately, the distribution does not have a closed form, so we derive a normal approximation to the number of lineages that contribute to a sample (eq. (11)). The normal approximation then allows us to get a quantile function that we use to find if the model preserves closure with some confidence level.

This work has several implications. First, we can combine the model described here with the jackknife approximation (Jouganous et al., 2017). This will allow us to construct a more robust inference framework that can account for large sample size and strong selection.

Further, the results here suggest that effect of weak selection may be detectable in studies with large sample sizes. This may open up a way for new investigations of natural selection in population genetics.

## References

- Bhaskar, A., Clark, A.G., Song, Y.S., 2014. Distortion of genealogical properties when the sample is very large. *Proceedings of the National Academy of Sciences* 111, 2385–2390. doi:10.1073/pnas.1322709111.
- Ewens, W.J., 1972. The sampling theory of selectively neutral alleles. *Theoretical Population Biology* 3, 87–112. doi:10.1016/0040-5809(72)90035-4.
- Ewens, W.J., 2004. *Mathematical Population Genetics: I. Theoretical Introduction..* volume 27 of *Interdisciplinary Applied Mathematics*. 2 ed., Springer New York, New York. OCLC: 958522782.



- Johnson, N., Kemp, A., Kotz, S., 2005. Occupancy distributions, in: Univariate Discrete Distributions. 3 ed.. John Wiley & Sons, Ltd. Wiley Series in Probability and Statistics.
- Jouganous, J., Long, W., Ragsdale, A.P., Gravel, S., 2017. Inferring the joint demographic history of multiple populations: Beyond the diffusion approximation. *Genetics* 206, 1549–1567. doi:10.1534/genetics.117.200493.
- Kamm, J.A., Terhorst, J., Song, Y.S., 2017. Efficient computation of the joint sample frequency spectra for multiple populations. *Journal of Computational and Graphical Statistics* 26, 182–194. doi:10.1080/10618600.2016.1159212.
- Kimura, M., Crow, J.F., 1964. The number of alleles that can be maintained in a finite population. *Genetics* 49, 725–738.
- Kingman, J.F.C., 1982. The coalescent. *Stochastic Processes and their Applications* 13, 235–248. doi:10.1016/0304-4149(82)90011-4.
- Krone, S.M., Neuhauser, C., 1997. Ancestral processes with selection. *Theoretical Population Biology* 51, 210–237. doi:10.1006/tpbi.1997.1299.
- Nelson, D., Kelleher, J., Ragsdale, A.P., McVean, G., Gravel, S., 2019. Coupling wright-fisher and coalescent dynamics for realistic simulation of population-scale datasets. *bioRxiv* , 674440doi:10.1101/674440.
- O'Neill, B., 2019. The classical occupancy distribution: Computation and approximation. *The American Statistician* , 1–12doi:10.1080/00031305.2019.1699445.
- Wakeley, J., 2009. *Coalescent Theory - an Introduction*. W. H. Freeman, New York.

## 6. Appendix

### 6.1. Table of symbols

Symbol	Generation	Meaning
$p$	$t - 1$	Parental generation
$c$	$t - \frac{1}{2}$	Contributing (intermediate, selection only)
$o$	$t$	Offspring (current) generation

Symbol	Meaning
$n$	Sample size
$i$	Number of derived alleles in sample $n$ .
$\frac{i}{n}$	$i$ derived <i>out of</i> $n$ total alleles

## 6.2. Neutral case

We want to construct the entries in the probability matrix  $P \left[ \frac{\cdot}{n_o} \middle| \frac{\cdot}{n_p} \right]$  in terms transition probabilities in smaller sample sizes. Under neutrality, the number of contributing parental lineages  $n'_p$  (at  $t - 1$ ) can not be larger than the number of offspring lineages  $n_o$ . Since  $\mathbf{P}$  is square,  $\max(n_p) = \max(n_o) = n$ . Thus, our aim is to express every entry of  $\mathbf{P}$ ,  $P \left[ \frac{\cdot}{n} \middle| \frac{\cdot}{n} \right]$ , in terms of  $P \left[ \frac{\cdot}{n-1} \middle| \frac{\cdot}{n-1} \right]$ . Since we never require extra lineages ( $n_p \leq n_o$ ), the recurrence is closed.

To calculate the transition probabilities, we first condition on the state of the last parental allele drawn, and then on the coalescent event that last offspring lineage participates in. The recurrence is shown in figure 7. The panel on the right depicts the coalescent event for each term. Empty circles represent ancestral alleles, filled circles – derived. The square box represents a sample of size  $n - 1$ . The first three terms in the sum correspond to the cases where the last parent that we drew was ancestral, last three – derived.

When calculating a single entry in 7, the variables have the following ranges.


$$\begin{aligned}
 n_p &= n \\
 i_p &\in [0, n] \\
 n_o &= n \\
 i_o &\in [0, n]
 \end{aligned} \tag{13}$$


The recurrence is calculated while  $n > 1$ , with the following base cases:


$$\begin{aligned}
 P \left[ \frac{1}{1} \middle| \frac{1}{1} \right] &= 1 \\
 P \left[ \frac{0}{1} \middle| \frac{0}{1} \right] &= 1 \\
 P \left[ \frac{0}{1} \middle| \frac{1}{1} \right] &= 0 \\
 P \left[ \frac{1}{1} \middle| \frac{0}{1} \right] &= 0
 \end{aligned}$$

$$\begin{aligned}
P \left[ \frac{i_o}{n_o} \middle| \frac{i_p}{n_p} \right] = & \left( \frac{n - i_o}{n} \right) \left\{ \left( 1 - \frac{n-1}{N} \right) P \left[ \frac{i_o}{n_o-1} \middle| \frac{i_p}{n_p-1} \right] \right. \\
& + \left( \frac{i_o}{N} \right) P \left[ \frac{i_o-1}{n_o-1} \middle| \frac{i_p}{n_p-1} \right] \\
& \left. + \left( \frac{n-i_o-1}{N} \right) P \left[ \frac{i_o}{n_o-1} \middle| \frac{i_p}{n_p-1} \right] \right\} \\
& \left( \frac{i_o}{n_o} \right) \left\{ \left( 1 - \frac{n-1}{N} \right) P \left[ \frac{i_o-1}{n_o-1} \middle| \frac{i_p-1}{n_p-1} \right] \right. \\
& + \left( \frac{i_o-1}{N} \right) P \left[ \frac{i_o-1}{n_o-1} \middle| \frac{i_p-1}{n_p-1} \right] \\
& \left. + \left( \frac{n-i_o}{N} \right) P \left[ \frac{i_o}{n_o-1} \middle| \frac{i_p-1}{n_p-1} \right] \right\}
\end{aligned}$$


Coalescent event









Last parent is ancestral







Last parent is derived

Figure 7: Recurrence defining transition probabilities in a model without selection. Right panel shows coalescent events corresponding to each summand. Each transition probability is defined in terms of transition in a smaller sample size. First three terms are conditional on the last parent having an ancestral state, last three – derived. Filled circles – derived alleles; empty circles – ancestral alleles; square brackets – sample of size  $n - 1$ .

### 6.3. Selection case

Due to selective deaths, the number of lineages ( $n_c$ ) that contribute to the current generation can be significantly larger than the number of offspring ( $n_o$ ), and especially so with strong selection. We use  $n_c$ , the intermediate number of lineages at time  $t - \frac{1}{2}$ , which can potentially be much larger than the number of parents,  $n_p$ . This is analogous to the gamete intermediates, as presented in the main text. However, the two are not equivalent, since in this formulation we apply selection *and* drift on the intermediate lineages. We model the intermediate contributing alleles as a random sample from  $n_p$  alleles, without replacement.

$$P_s \left[ \frac{i_o}{n} \middle| \frac{i_p}{n} \right] = \sum_{i_c, n_c} P_s \left[ \frac{i_o}{n} \middle| \frac{i_c}{n_c} \right] P_s \left[ \frac{i_c}{n_c} \middle| \frac{i_p}{n} \right] \quad (14)$$

The probability conditional on the contributing lineages ( $P_s \left[ \frac{i_o}{n} \middle| \frac{i_c}{n_c} \right]$ ) is given by equation 8, while  $P_s \left[ \frac{i_c}{n_c} \middle| \frac{i_p}{n} \right]$  is given by the hypergeometric distribution. The support of the hypergeometric distribution means that we can not have  $n_c > n$ . Note that while  $i_c \leq n_c \leq n$ , we can still have  $i_c > i_p$  if  $i_p$  is small. A formulation where a  $n_c$  is potentially infinitely large will be desirable.

Under the current definition,  $P_s$  is not closed, since the cases where  $n_c > n$  are not accounted for. However, as we show in the main text, the formulation is asymptotically closed, as  $n$  increases.

The recursive definition in 8 is analogous to the neutral case, and gives  $P_s \left[ \frac{i_o}{n} \middle| \frac{i_c}{n_c} \right]$ , the probability that  $i_o$  out of  $n$  lineages are derived, given that  $i_c$  out of  $n_c$  contributed to it. To construct this probability, we condition on the coalescent events involving the last offspring allele. We limit the model to at most 1 selective death per lineage. However, in the entire sample, there still can be a large number of selective deaths. There are 6 distinct coalescent events with 0 or 1 selective deaths, with distinct probabilities based on whether the last offspring allele is ancestral or derived. This gives 12 different cases:

For each calculation, the ranges of the variables are:

$$\begin{aligned} n_p &= n \\ i_p &\in [0, n] \\ n_c &\in [1, n] \\ i_c &\in [0, n_c] \end{aligned} \quad (15)$$

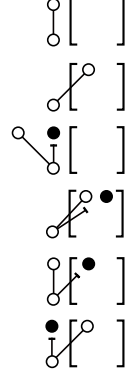
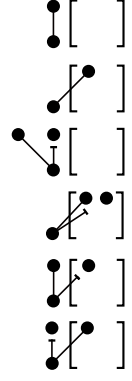
$ \begin{aligned} P_s \left[ \frac{i_o}{n_o} \middle  \frac{i_c}{n_c} \right] = & \left( \frac{1 - (n_c - 1)}{N} \right) \frac{n_c - i_c}{n_c} P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c}{n_c - 1} \right] \\ & + \frac{n_c - i_c}{N} P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c}{n_c} \right] \\ & + \left( 1 - \frac{n_c - 2}{N} \right) \frac{i_c}{n_c} s \left( 1 - \frac{n_c - 1}{N} \right) \frac{n_c - i_c}{n_c - 1} P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c - 1}{n_c - 2} \right] \\ & + \frac{i_c}{N} s \frac{n_c - i_c}{N} P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c}{n_c} \right] \\ & + \frac{i_c}{N} s \left( 1 - \frac{n_c - 1}{N} \right) \frac{n_c - i_c}{n_c} P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c}{n_c - 1} \right] \\ & + \left( 1 - \frac{n_c - 1}{N} \right) \frac{i_c}{n_c} s \left( \frac{n_c - i_c}{N} \right) P_s \left[ \frac{i_o}{n_o - 1} \middle  \frac{i_c - 1}{n_c - 1} \right] \\ \\ & + \left( \frac{1 - (n_c - 1)}{N} \right) \frac{i_c}{n_c} (1 - s) P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c - 1}{n_c - 1} \right] \\ & + \frac{i_c}{N} (1 - s) P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c}{n_c} \right] \\ & + \left( 1 - \frac{n_c - 2}{N} \right) \frac{i_c}{n_c} s \left( 1 - \frac{n_c - 1}{N} \right) \frac{i_c - 1}{n_c - 1} P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c - 2}{n_c - 2} \right] \\ & + \frac{i_c}{N} s \frac{i_c - 1}{N} P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c}{n_c} \right] \\ & + \frac{i_c}{N} s \left( 1 - \frac{n_c - 1}{N} \right) \frac{i_c}{N} P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c - 1}{n_c - 1} \right] \\ & + \left( 1 - \frac{n_c - 1}{N} \right) \frac{i_c}{n_c} s \frac{i_c - 1}{N} P_s \left[ \frac{i_o - 1}{n_o - 1} \middle  \frac{i_c - 1}{n_c - 1} \right] \end{aligned} $	<div style="margin-bottom: 10px;"> <p>Coalescent event</p>  <p>Last offspring is ancestral</p> </div> <div>  <p>Last offspring is derived</p> </div>
--	---

Figure 8: Recurrence defining transition probabilities in a model with selection. Right panel shows coalescent events corresponding to each summand. Each transition probability is defined in terms of transition in a smaller sample size. First six terms are conditional on the last offspring having an ancestral state, last six – derived. Filled circles – derived alleles; empty circles – ancestral alleles; square brackets – smaller sample.

Note that unlike in the neutral case  $n_c$  is now variable. The base cases of the recurrence are:

$$P \left[ \begin{array}{c|c} 1 & 1 \\ \hline 1 & 1 \end{array} \right] = 1 - s$$

$$P \left[ \begin{array}{c|c} 0 & 0 \\ \hline 1 & 1 \end{array} \right] = 1$$

$$P \left[ \begin{array}{c|c} 1 & 2 \\ \hline 1 & 2 \end{array} \right] = s$$

$$P \left[ \begin{array}{c|c} 0 & 1 \\ \hline 1 & 2 \end{array} \right] = \frac{1}{s}$$

$$\text{otherwise} \quad 0$$