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Revisiting the time until fixation of a neutral mutant in a finite population – A coalescent theory approach

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HIGHLIGHTS

- Fixation times of neutral mutations usually estimated by diffusion approximations.
- Here a coalescent theory approach is used to estimate these fixation times.
- The two approaches converge for large populations but differ for small populations.
- Coalescent approximations are more accurate for small population sizes.

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ABSTRACT

Evaluation of the time scale of the fixation of neutral mutations is crucial to the theoretical understanding of the role of neutral mutations in evolution. Diffusion approximations of the Wright–Fisher model are most often used to derive analytic formulations of genetic drift, as well as for the time scales of the fixation of neutral mutations. These approximations require a set of assumptions, most notably that genetic drift is a stochastic process in a continuous allele-frequency space, an assumption appropriate for large populations. Here equivalent approximations are derived using a coalescent theory approach which relies on a different set of assumptions than the diffusion approach, and adopts a discrete allele-frequency space. Solutions for the mean and variance of the time to fixation of a neutral mutation derived from the two approaches converge for large populations but slightly differ for small populations. A Markov chain analysis of the Wright–Fisher model for small populations is used to evaluate the solutions obtained, showing that both the mean and the variance are better approximated by the coalescent approach. The coalescence approximation represents a tighter upper-bound for the mean time to fixation than the diffusion approximation, while the diffusion approximation and coalescence approximation form an upper and lower bound, respectively, for the variance. The converging solutions and the small deviations of the two approaches strongly validate the use of diffusion approximations, but suggest that coalescent theory can provide more accurate approximations for small populations.

1. Introduction

The study of the fixation process of neutral mutations in the last decades has been instrumental to the advancement of theoretical population genetics, as well as to the understanding of the evolutionary process. The stochastic process that accompanies the genetic process, known as genetic drift, is responsible to drive newly arisen neutral mutations to one of two eventual outcomes, assuming the absence of other forces – fixation as the sole allele in the population or loss from the population. Both the probability with which these events occur (Kimura, 1962; McKane and Waxman, 2007; Otto and Whitlock, 1997; Whitlock, 2003) and the time scale of the fixation and loss processes (Burrows and Cockerham, 1974; Kimura and Ohta, 1969a, 1969b; Kimura, 1980; Waxman, 2012; Whitlock, 2003) has been extensively studied.

The most widely used model for description of the genetic process is the Wright–Fisher model (Fisher 1922; Wright 1931). In this model discrete generations and a discrete gene pool are assumed. The gene pool in each generation is generated by sampling with replacement using the allele frequency of the

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previous generation's gene pool, thus inducing a binomial distribution on the allele frequencies in the following generation. One of the main mathematical approaches to deal with genetic drift is the diffusion approximation of the Wright–Fisher model, first introduced by Fisher (1922) and Wright (1931), and later developed and extended by Kimura (1964). The diffusion approach is a *prospective* approach that approximates the process by a diffusion of the probability density along the frequency space, assumed to be continuous, over time. This approach has had a significant influence on the development of the theory of neutral genetic variation and modern evolutionary theory, as it enables the description of quantities for many phenomena, such as the time to fixation and loss of alleles (Kimura and Ohta, 1969a, 1969b). An important special case of these results describes the time of fixation of a neutral mutation conditioned on the occurrence of such a fixation, a process known as the 'conditional fixation process' (Kimura and Ohta, 1969a).

Another approach that was developed to study genetic drift and genetic processes is coalescent theory (Kingman, 1982a). This approach adopts a *retrospective* backwards-looking viewpoint on the genetic process. Instead of asking how a certain generation's allele frequency affects the allele frequencies in the following generation, the coalescent approach is to ask how long ago lineages of copies of a certain allele separated from their most recent common ancestor (MRCA). Put in other words, the coalescence time of copies of an allele is the time it would take for them to coalesce if the process was to be run backwards. This approach has considerable computational and practical advantages when addressing questions regarding processes that occurred in the past, since only surviving lineages need be taken into account (Rosenberg and Nordborg, 2002). The first papers of coalescent theory dealt with simple ideal populations, but like the diffusion approach, they were later supplemented with many studies extending the approach's principles to various violations of the ideal population (Hein et al., 2005; Nordborg, 2008).

Deriving analytic equations to describe the timescale of the conditional fixation process is crucial to the understanding of the polymorphism observed in many loci and in many organisms, since neutral mutations on their way to fixation induce polymorphism in a monomorphic locus, or enhance the polymorphism of an already polymorphic locus for the time scale of the fixation process (Kimura, 1984). Thus equations describing the time scale of the conditional fixation process, accompanied by the mutation rate and the probability of fixation of neutral mutations, can be applied to the analysis of the observed genetic variation in nature, and to explain the observed polymorphism in many organisms and loci. Deriving approximations to the Wright–fisher model in order to generate predictions for the timescales of the conditional fixation process of mutations is also instrumental in the study of the role of neutral mutations in evolution, as a source of genetic variation (Kimura, 1984; Ohta, 1992), and has been shown to effect population's evolvability (Draghi and Wagner, 2008; Wagner, 2008).

While the importance of Kimura's and Ohta's original result regarding the time to fixation of a neutral mutant has been acknowledged (Watterson, 1996), an analytic confirmation of this result using an alternative approach is of importance. This is so since the diffusion approach forces continuity on the frequency space, an assumption that is violated especially in small populations, which are of particular interest in population genetics and conservation genetics. In this study the standard coalescent (n-coalescent) model (Kingman, 1982b) of the Wright–Fisher model is used, a model that does not assume a continuous frequency space, to derive the mean time of the conditional fixation process of a mutation, as well as its variance. It is shown that the conditional fixation and the coalescence of the entire population are processes with identical time scales (although they do not occur simultaneously and only partially overlap; Campbell, 1999), but result in a different approximation of the conditional fixation process. The diffusion approximation and the coalescence approximation converge for large populations, but differ for finite populations. Explicit Markov chain analysis of the Wright–Fisher model focusing on small populations ($N \leq 100$) are used to compare the diffusion approximations with the coalescence approximations.

2. The diffusion and coalescence approximations

2.1. The diffusion approximation of the conditional fixation process

The diffusion approach is based on formulating the Wright–Fisher model using the Fokker-Plank diffusion equation (known also as the Kolmogorov forward equation), and approximates the probability density of the allele frequency over time. In order to describe a diffusion process, the frequency space is formulated as a continuous random variable rather than a discrete random variable, although in a finite population an allele can attain only a finite number of different allele frequencies (Waxman, 2011). Under this formulation, the mean and variance of $T(p,N)$, the time to fixation of a neutral allele with initial frequency p in a population of size N (the full formulation takes into account the variance effective population size N_e, but here the population is considered to be ideal, thus $N=N_e$), is given by (Kimura and Ohta, 1969a; Narain, 1970)

$$E[T(p,N)] = \frac{-4N(1-p)ln(1-p)}{p} \tag{1}$$

$$Var[T(p,N)] = 32N^2\left[\frac{(1-p)ln(1-p)}{p} + \sum_{k=1}^{\infty}\frac{1-p^k}{k^2}\right] - (E[T(p,N)])^2 \tag{2}$$

For a neutral mutation, which initially appears in the population at only one copy, the diffusion approximation for the mean time to (conditional) fixation is therefore

$$E\left[T_{fix}(N)\right] = -8N^2\left(1-\frac{1}{2N}\right)\ln\left(1-\frac{1}{2N}\right) \approx 4N-1 \tag{3}$$

Note that the second order approximation of $\ln\left(1-\frac{1}{2N}\right)$ is needed here, as the second order term is significant and cannot be neglected. The diffusion approximation for the variance is given by

$$\begin{aligned}\mathrm{Var}\left[T_{fix}(n)\right] &= 32N^2\left[(2N-1)\ln\left(1-\frac{1}{2N}\right) + \sum_{k=1}^{\infty}\frac{1-\left(\frac{1}{2N}\right)^k}{k^2}\right] \\ &\quad -(E\left[T\left(\frac{1}{2N},N\right)\right])^2 \approx \left(\frac{16}{3}\pi^2-48\right)N^2-\frac{1}{3}\end{aligned} \tag{4}$$

The two convergences in Eqs. (3) and (4) are rapid and can be applied to small population sizes as well. Note that when taking $p\to 0$ instead of $p=\frac{1}{2N}$ to demonstrate the conditional fixation time of a neutral mutation, the result is Eqs. (3) and (4) without the constant terms, and these are the results that most often appear in the literature (and are more convenient when dealing with large populations and continuous frequency spaces).

The diffusion approximation of the Wright–Fisher model is extensively used in population genetics to obtain approximations of biologically significant phenomena, such as the time to fixation of a neutral mutation. The diffusion approximation of a neutral allele converges to the Wright–Fisher model for large populations (Guess, 1973). The error of the diffusion approximation has been studied both numerically and analytically (Ethier and Norman, 1977; Ewens, 1963; Kimura, 1980; Zhao et al., 2013), and have mostly been found to be quite accurate. However, it has been pointed out that the diffusion theory may be vulnerable near the

boundaries of fixation and loss, as well as for small population sizes (Tyvand and Thorvaldsen, 2010), due to the assumptions of the diffusion formulation.

2.2. The coalescence approximation of the MRCA of the entire population

The coalescence process of the entire population, whereby all gametes are followed from a given generation backward in time until they coalesce to the MRCA, is similar to the conditional fixation process (suggested by Campbell, 1999; Ewens, 2004; Tajima, 1990) since they both describe the increase in frequency of a single gamete to frequency of 1, conditioned on eventual fixation. Using Coalescent theory, it is possible to approximate the time from a given generation, for example from the fixation generation, to the time of the coalescence of all gametes in the population. For this purpose the basic coalescent model, the Standard coalescent or n-coalescent (Kingman, 1982a, 1982b), is clearly the most appropriate model since it deals with an ideal diploid population of constant size N, and no selection, recombination or other external genetic forces on the system are included in the model. The standard coalescent assumes a sample of n gametes from the population at time $t=0$, traces the genetic process backwards in time, and asks at what time do the lineages of these n samples coalesce, i.e. what is the first generation in which the lineages have a common ancestor. Under these assumptions, the expected time to the MRCA (TMRCA) of n samples is given by (Templeton, 2006)

$$E[TMRCA(n)] = 4N\left(1-\frac{1}{n}\right) \tag{5}$$

and the variance is given by (Appendix A)

$$\mathrm{Var}[\mathrm{TMRCA}(n)] = 16N^2\left(\sum_{i=2}^{n}\frac{1}{i^2(i-1)^2}\right) - 4N\left(1-\frac{1}{n}\right) \tag{6}$$

The linear term in Eq. (6) is often dropped (e.g. Hamilton, 2009; Hein et al., 2005; Templeton, 2006), but for our purposes the precise formulation will be kept (the linear term is dropped when the coalescence process is approximated by a continuous-time coalescence process or when large populations are assumed, see Appendix A). Therefore the mean and variance of the coalescence time of the entire population of N individuals to a single gamete is approximated by

$$E[\mathrm{TMRCA}(2N)] = 4N\left(1-\frac{1}{2N}\right) = 4N-2 \tag{7}$$

$$\begin{aligned}\mathrm{Var}[\mathrm{TMRCA}(2N)] &= 16N^2\left(\sum_{i=2}^{2N}\frac{1}{i^2(i-1)^2}\right) - 4N\left(1-\frac{1}{2N}\right)\\ &\approx \left(\frac{16}{3}\pi^2-48\right)N^2-4N+2\end{aligned} \tag{8}$$

3. The conditional fixation process and the coalescent

The conditional fixation and the coalescence process are similar processes since they follow the increase of a single copy of an allele to a point where the allele is the only allele in the population. However, these process are not identical, as noted by Campbell (1999), and they overlap only for the period of transition from the generation of the MRCA of the fixation generation (the 'MRCA generation') to the generation of fixation. The conditional fixation process includes, in addition, the period from the first occurrence of the mutation to the MRCA generation and the coalescence process includes in addition the period from the fixation generation until the MRCA generation changes (the generations following the fixation generation may have the same MRCA generation as the fixation generation). In order to show that the two process are of similar time lengths, one has to show that the two additional periods, prior to the MRCA generation and after the fixation generation, are of the same length. This was shown by Campbell (1999). His proof consisted of noting the generation of fixation of a certain allele as F_i; C_i as the MRCA generation of F_i; F_{i+1} as the generation in which the population is for the first time after F_i fixed for an allele with a different MRCA than C_i; and C_{i+1} as the MRCA generation of F_{i+1}. The conditional fixation process consists of the interval C_i+1 to C_{i+1} plus the interval C_{i+1} to F_{i+1} and the coalescence process consists of the interval C_i to F_i plus the interval F_i to $F_{i+1}-1$. At the steady state of the process, the non-overlapping intervals of the two processes (F_i to $F_{i+1}-1$ and C_i+1 to C_{i+1}) have to be of the same length, since otherwise at some point either C_i will occur after F_i or before F_{i-1}, which is not possible.

Tajima (1990) also makes an argument that the length of the coalescence process should be the same as the conditional fixation process, but he uses the Moran model (Moran, 1958) instead of the Wright–Fisher model for the theoretical argument. His argument is based on the fact that in the Moran model at the time step before fixation of a neutral mutant (the Moran model is not based on generation time steps) $2N-1$genes have the mutant as the MRCA (which is also the MRCA of the fixation generation) and one gene belongs to a non-mutant lineage. The branch lengths for these lineages are not affected by conditioning the process on eventual fixation, only the branching pattern is affected. Hence, Tajima suggests using the coalescence times as approximation of the conditional fixation process. However, this argument fails to include the time between the appearance of the mutation to the MRCA and the time this MRCA is maintained after fixation, both of which could be substantial, hence the argument needs to be complemented by proving that these two intervals are identical, as shown by Campbell.

4. Explicit Markov chain analysis

The different solutions obtained by the diffusion approach and the coalescent approach, although very similar, predict different mean and variance for the length of the conditional fixation process, especially for small population sizes. In order to evaluate the two solutions, an explicit Markov chain analysis was performed to calculate the mean and variance of the conditional fixation for small populations ($N \le 100$). Assuming that in each generation the mutant allele can be in $2N$ different states, state 1 to 2N, representing the number of copies of the allele in the population, the conditional fixation is a Markovian process with one absorbing state, $2N$. If p_{ij} is the probability transition matrix between states for the regular (unconditioned) fixation and loss process (i.e. $p_{ij} = \binom{2n}{j}\left(\frac{i}{2n}\right)^j\left(1-\frac{i}{2n}\right)^{2n-j}$) then the transition matrix for the conditional process is $p^*_{ij} = p_{ij}\frac{j}{i}$ (Ewens, 2004). If we define the matrix P to be the matrix p^*_{ij} without the absorbing state, that is the matrix p^*_{ij} with the last row and column removed, then the fundamental matrix of the Markov chain is (Kemeny and Snell, 1967)

$$M = (I_{2N-1}-P)^{-1} \tag{9}$$

where I_{2N-1} is the $2N-1$ by $2N-1$ identity matrix. The mean time to reach the absorbing state starting at state k is given by the k_{th} element of the vector $w = M\cdot\mathbf{1}$, where $\mathbf{1}$ is a vector of length $2N-1$ of ones. Thus the mean time of the conditional fixation is the first element of w, as the process is initiated with one copy of the allele.

The variance of the process, starting at k copies of the allele, is the k_{th} element of the vector (Kemeny and Snell, 1967)

$$v = (2M - I_{2N-1}) - w_{had} \tag{10}$$

where w_{had} is the Hadamard product of w with itself (i.e., a vector with the elements of w squared). The variance of the conditional fixation process is the first element of v.

The mean and variance of the conditional fixation process where explicitly calculated for $N \leq 100$ and compared to the analytic solutions of Eqs. (3), (4), (7) and (8). Fig. 1 shows the coalescence approximation for the mean and variance of the conditional fixation process and the results of the Markov chain analysis. The difference between the analytic approximations from both approaches and the explicit results are shown in Fig. 2.

5. Discussion

In this work a simple coalescent model was used to study the time to fixation of a neutral mutation, conditioned on fixation, and the approximation results were compared with the diffusion approximation of these time scales. Both approaches aim to approximate the Wright–Fisher model of the genetic process. A priori, since these two approaches rely on different assumptions, such as continuous frequency space in the diffusion approach and a discrete space in the coalescent approach, the two approaches may have produced approximations that diverge significantly for some parts of the parameter space. The results presented in this work strongly validate Kimura's and Ohta's original result (Kimura and Ohta, 1969a), in the sense that very similar approximations, that do not diverge significantly one from the other, are obtained using a different approach that describes the same process, while using a different set of assumptions. Both approximations overestimate the mean time of fixation, but the coalescence approximation represents a tighter upper-bound than does the diffusion approximation (Fig. 2A). The diffusion approximation also overestimates the variance of the time to fixation, but the coalescence approximation underestimates the variance, although to a lesser degree (Fig. 2B). Thus the diffusion approximation and coalescence approximation define an upper and lower bound for the variance of the process, respectively, with the latter deviating less from the Markov chain analysis results.

Waxman (2011) emphasizes the fact that Kimura's diffusion approximation does not cover the fixation and loss of alleles, only the intermediate frequency range between 0 and 1. He explores an alternative diffusion approximation on a discrete frequency space, showing that problematic behavior of the diffusion approximation near the boundaries is most noticeable when examining phenomena of loss and fixation (McKane and Waxman, 2007), and when the continuity assumption on the frequency space is mostly violated, i.e. in small populations. Since genetic drift in small populations is of special interest in some fields of biology such as conservation genetics (Allendorf et al., 2012) or founder speciation (Templeton, 2008), a solid theory encompassing small population sizes in necessary.

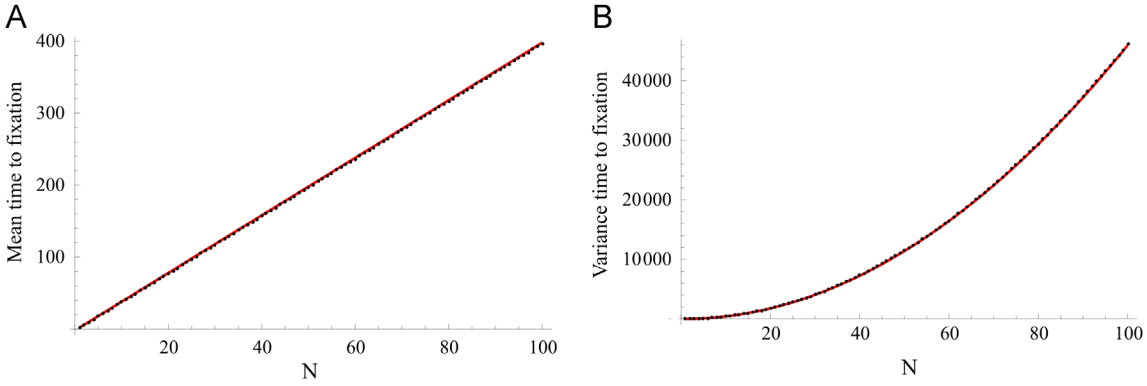

Fig. 1. Mean (A) and variance (B) of the conditional fixation of a neutral mutation. Coalescence approximation in red line, Markov chain analysis results in black dots. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

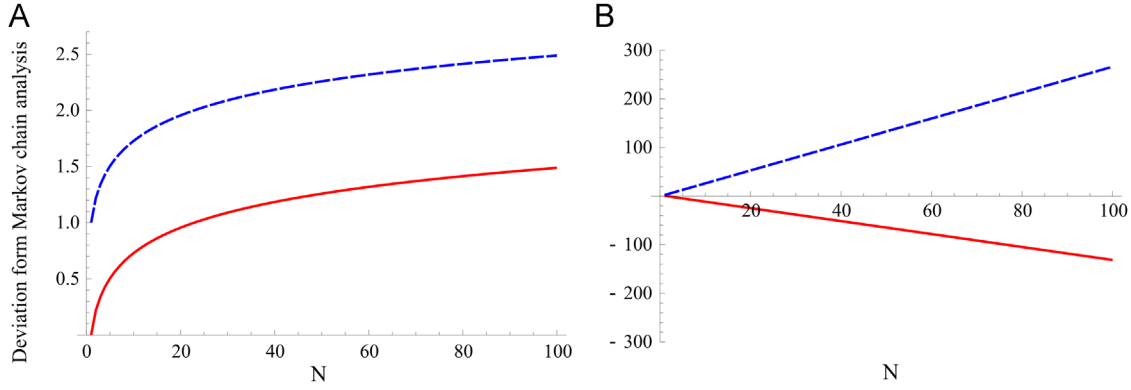

Fig. 2. Deviation of analytic approximations for the mean (A) and variance (B) from the Markov chain analysis results. Deviation of the coalescence approximation in red continuous line; deviation of the diffusion approximation in dashed blue line. Both approximations overestimate the mean, the diffusion approximation overestimates the variance, while the coalescence approximation underestimates the variance. In all cases the deviation of the coalescence approximation is smaller than the deviation of the diffusion approximation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The coalescent approach assumes a discrete frequency space, and therefore should not be biased towards accurate approximation of large populations, like the diffusion approach. However, one of the major assumptions of the coalescent approach is that the coalescence events are consecutive (i.e. at most one coalescence event per generation). This assumption is valid when the expected time between coalescence events is large enough and is more valid for small populations than for large ones, as, for example, the expected time for the first coalescence is $\frac{1}{2N-1}$ (Templeton, 2006), which is longer for small populations. This consecutiveness assumption is expected to cause an overestimation of the mean time to fixation, as seen in Fig. 2A, since multiple coalescence events are allowed in the Wright–Fisher model and not in the coalescent model, and assuming that they occur one after the other stretches the time to fixation (although this overestimation is still smaller than the overestimation of the diffusion approximation).

Evolution depends of the genetic variation in a population, and is influenced also by the neutral variation, for example in its relation to heterozygosity (Waxman, 2012), and its effect on the evolvability of the population (Wagner, 2008). Neutrality may also be only a transient property of an allele, subject to changes in the environment, hence a sufficient level of neutral variation is vital for long-term persistence of populations. The fact that neutral mutations take, on average, longer to fix than beneficial or deleterious alleles under selection (Maruyama, 1977) marks neutral mutations as an especially important source of genetic variation, since it persists for longer periods. Thus a sound theoretical understanding of this process is essential in order to accurately assess the role of neutral mutations in the evolutionary process.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2015.05.019.

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