

Effective sizes and time to migration–drift equilibrium in geographically subdivided populations



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HIGHLIGHTS

- A class of diploid populations is studied, structured into subpopulations or demes.
- We derive new expression for the variance effective size.
- The variance and inbreeding effective sizes are compared.
- A novel additive genetic variance effective size is introduced.
- Migration–drift equilibrium is characterized, and the time to reach it is quantified.

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ABSTRACT

Many versions of the effective population size (N_e) exist, and they are important in population genetics in order to quantify rates of change of various characteristics, such as inbreeding, heterozygosity, or allele frequencies. Traditionally, N_e was defined for single, isolated populations, but we have recently presented a mathematical framework for subdivided populations. In this paper we focus on diploid populations with geographic subdivision, and present new theoretical results. We compare the haploid and diploid versions of the inbreeding effective size (N_{ei}) with novel expression for the variance effective size (N_{eV}), and conclude that for local populations N_{eV} is often much smaller than both versions of N_{ei} , whenever they exist. Global N_{eV} of the metapopulation, on the other hand, is close to the haploid N_{ei} and much larger than the diploid N_{ei} . We introduce a new effective size, the additive genetic variance effective size N_{eAV} , which is of particular interest for long term protection of species. It quantifies the rate at which additive genetic variance is lost and we show that this effective size is closely related to the haploid version of N_{ei} . Finally, we introduce a new measure of a population's deviation from migration–drift equilibrium, and apply it to quantify the time it takes to reach this equilibrium. Our findings are of importance for understanding the concept of effective population size in substructured populations and many of the results have applications in conservation biology.

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1. Introduction

There are various concepts of the effective population size (N_e), which are often quite different from the census size N , and important for many areas of population and quantitative genetics. The first version of N_e was introduced by Wright (1931, 1938) in order to quantify the rate at which the degree of inbreeding increases over time in a single isolated population due to random

sampling of alleles from one generation to the next, so called genetic drift. Caballero (1994), Wang and Caballero (1999), Waples (2002, 2010) and Charlesworth (2009) provide overviews of the different types of effective size, and Wang (2005), Palstra and Ruzzante (2008) and Luikart et al. (2010) present estimators (\hat{N}_e) of N_e from molecular genetic data.

The definition of any notion of effective size requires that genetic drift is quantified in some way, and for this purpose one uses the Wright–Fisher (WF) population (Wright, 1931; Fisher, 1958) as a yardstick or reference. The WF population is homogeneous and haploid, with non-overlapping generations and of constant size. A general diploid, age-structured and geographically subdivided non

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WF population is said to have effective size N_e , if some characteristic that quantifies how the genetic composition changes over time, is the same as for a WF population of size N_e . Two of the most commonly used notions of N_e , the inbreeding effective size (N_{ei}) and the variance effective size (N_{eV}), use the rate of increased inbreeding, and the variance of allele frequency change, respectively, as quantifiers of genetic drift. The eigenvalue effective size (N_{eE}) focuses on long term rates at which genetic variants are lost, as quantified by the largest non-unit eigenvalue of the Markov chain that describes how allele frequencies change over time.

We have recently developed a general mathematical framework for several types of effective size of structured populations (Hössjer et al., 2014, 2015), applied it with respect to diploid N_{ei} to genetic conservation of the Fennoscandian wolf population (Laikre et al., in press) and implemented parts of the framework into a publicly available software (Olsson et al., under revision). In this paper we provide further theoretical results for a diploid, selection and mutation free metapopulation with sexual reproduction including random selfing. The metapopulation is geographically subdivided into a number of subpopulations. We focus on N_{ei} , N_{eV} and N_{eE} , and introduce a novel additive genetic variance effective size (N_{eAV}) that quantifies how fast the additive genetic variance of a quantitative trait is lost. We compare the diploid with the haploid version of N_{ei} , reflecting whether inbreeding is defined for pairs of genes within individuals or not. Whereas these effective sizes are very close for a homogeneous population of constant size, for structured populations they sometimes differ a lot. The purpose of this paper is to investigate in more detail how different N_e relate to each other and vary over time for subdivided populations, with three major novelties.

First, we derive novel and general formulas for the variance effective size N_{eV} , and compare N_{eV} in detail with N_{ei} . In Hössjer et al. (2014) we only considered some simplified scenarios under which N_{eV} is essentially equivalent to the haploid N_{ei} . The expressions for N_{eV} in this paper are more realistic and closer to the quantity estimated by the temporal method (Jorde and Ryman, 2007). The comparison between this novel N_{eV} and N_{ei} is complicated by (a) the fact that N_{ei} does not always exist when immigration into a subpopulation from genetically distinct neighbors causes the amount of inbreeding to decrease, and (b) that separate treatment is needed for local effective sizes of subpopulations and the global effective size of the metapopulation. We conclude that, whenever they exist, the diploid and haploid N_{ei} are essentially equivalent for local populations, whereas globally the diploid N_{ei} is smaller than the haploid N_{ei} . On the other hand, local N_{eV} is often much smaller than the diploid and haploid local N_{ei} . We also show that globally, N_{eV} is essentially equivalent to the haploid version of N_{ei} when subpopulations are weighted proportionally to how many offspring they produce.

Second, the haploid and diploid N_{ei} , and certain versions of N_{eV} , will approach N_{eE} when the metapopulation converges to migration–drift equilibrium. The relation between the inbreeding and variance effective sizes therefore depends crucially on how far away from this equilibrium the population is. We derive new mathematical results in order to quantify a population's distance to migration–drift equilibrium, and the time it takes to reach it within a given tolerance level. Since this time is inversely proportional to the rate of migration between subpopulations, the equilibrium limit is of practical interest only for populations that are either close to it or have an appreciable amount of gene flow between their subpopulations.

Third, the time to migration–drift equilibrium depends on the current amount of inbreeding within individuals and coancestry between them. These are quantified by inbreeding and coancestry coefficients (Wright, 1922; Cotterman, 1940; Malécot, 1948), and we derive new improved upper bounds for the coancestry coefficients between individuals, given a certain amount of inbreeding.

One of the most important applications of N_e is conservation biology (Traill et al., 2010; Allendorf et al., 2013). Our systemization of effective sizes sheds further light on the 50/500 rule, according to which an effective size of 50 (500) is required for short (long) term protection of species (Franklin, 1980). The first part of this rule is based on the assumption that rate of inbreeding is the most important concept for short periods because of its relevance for predicting the future impact of accumulated deleterious mutations and inbreeding depression (Lynch et al., 1995; Frankham, 2005). This is quantified by the diploid version of N_{ei} when inbreeding increases over time. This diploid inbreeding effective size has been used as a yardstick to compare other notions of effective size with (Harris and Allendorf, 1989).

The second part of the 50/500 rule is based on the assumption that the rate at which additive genetic variance of a quantitative trait is lost is the quantity of primary importance for conservation over longer periods of time (Franklin, 1980; Lande and Barrowclough, 1987; Allendorf and Ryman, 2002; Jamieson and Allendorf, 2012). The figure 500 relies on some assumptions on how genetic drift is balanced by new mutations, and although these assumptions have been discussed (Lynch and Lande, 1998), it is in any case important to assess how genetic drift impacts additive genetic variance. It has been largely unclear which N_e the 500 rule applies to, and e.g. Harmon and Braude (2010) have suggested that the variance effective size N_{eV} is the quantity of interest. Our results, however, imply that the haploid version of N_{ei} is more relevant since it is essentially equivalent to the quantity N_{eAV} introduced here that measures the rate at which additive genetic variation is lost.

The paper is organized as follows: We start by defining the Wright–Fisher model in Section 2, and a geographically structured population in Section 3. Then we introduce various measures of inbreeding and subpopulation differentiation in Section 4. These are used in Sections 5 and 6 in order to define and compare a number of different notions of effective size. Section 7 treats migration–drift equilibrium, and in Section 8 we discuss extensions and consequences of our work. Longer mathematical derivations are gathered in Appendices A–E. A list of the most commonly used notation can be found in Table 1.

2. Wright–Fisher model

A detailed description of the Wright–Fisher model is helpful in order to define subdivided populations in Section 3 and the various notions of effective size in Section 5. The WF population consists of $2N$ gene copies, is homogeneous, haploid, of constant size, and with non-overlapping generations. Although the WF model is haploid, it may be conceptualized as a diploid population with N individuals in each generation, which we refer to as the census size. We will display a number of formulas for the WF model below that can be deduced, for instance, from results in Crow and Kimura (1970) or Ewens (2004), and throughout the paper it is assumed that generations $t = \dots, -1, 0, 1, \dots$ are non-overlapping, with $t < 0$ representing the past, $t = 0$ the present and $t > 0$ the future.

For the simplest version of the WF model it is assumed that the gene exists in two versions (alleles), a and A , none of which mutates or has a selective advantage. Let p_t be the frequency of allele A in generation t , i.e. the fraction of gene copies that have this allele. Reproduction from a parental generation t to an offspring generation $t + 1$ is defined by randomly drawing the offspring's gene copies from the parental generation, with replacement. Since there are no mutations and no selection, this implies that the conditional distribution of the frequency of A in the offspring

Table 1
Notation for selected quantities.

Symbol	Definition
t	Generation number for a population with non-overlapping generations, where $t = 0$ is the present generation.
T	Number of generations back to founder generation.
N	Total census size.
N_e	Effective population size.
s	Number of subpopulations.
i, j, k, l	Subpopulation number.
N_i	Local census size of subpopulation i .
N_{ei}	Local effective size of subpopulation i in isolation.
M_{ki}	Observed forward migration rate from subpopulation k to subpopulation i between generations t and $t + 1$.
M_{ki}	Forward migration rate from subpopulation k to subpopulation i in one generation.
M	Overall forward migration rate.
B_{ik}	Backward migration rate from subpopulation i to subpopulation k in one generation.
w_i	Weight assigned to subpopulation i .
γ_i	Reproductive weight of subpopulation i .
τ	Length of time interval of genetic drift.
N_{eV}	Variance effective size.
$N_{eI, \text{dipl}}$	Diploid version of inbreeding effective size.
$N_{eI, \text{hapl}}$	Haploid version of inbreeding effective size.
N_{eAV}	Additive genetic variance effective size.
N_{eE}	Eigenvalue effective size.
N_{eXi}	Local effective size of type X ($= I, V$) for subpopulation i in generation t .
N_{eXT}	Global (total) effective size of type X ($= I, V$) in generation t .
p_{ti}	Frequency of allele A in subpopulation i and generation t .
p_t	Subpopulation weighted frequency of allele A in generation t .
p	Frequency of allele A in all subpopulations of the founder generation.
\mathbf{P}	Transition matrix for the Markov chain of allele frequencies.
f_t^{inbr}	Inbreeding coefficient of individuals of subpopulation i in generation t .
f_t^{inbr}	Subpopulation weighted inbreeding coefficient in generation t .
f_{ij}^{co}	Coancestry coefficient of individuals of subpopulations i and j in generation t .
f_{ij}^{hinbr}	Haploid inbreeding coefficient of a gene pair from subpopulations i and j in generation t .
f_t^{hinbr}	Subpopulation weighted haploid inbreeding coefficient in generation t .
f_{ij}^{cov}	Standardized covariance of allele frequency change in subpopulations i and j from founder generation up to generation t .
f_t^{var}	Standardized variance of subpopulation weighted allele frequency change up to generation t .
$A_{ij,kl}$	Matrix entry of linear recursion of standardized covariances of allele frequency change.
$G_{ST,t}$	Coefficient of gene differentiation in generation t .
$g_{ST,t}$	Predicted coefficient of gene differentiation in generation t .
V_t	Variance of quantitative phenotype in generation t .
V_{At}	Additive genetic variance of quantitative phenotype in generation t .
v_{At}	Expected additive genetic variance of quantitative phenotype in generation t .

generation, given the frequency of A in the parental generation, is a standardized binomial;

$$p_{t+1}|p_t \sim \frac{\text{Bin}(2N, p_t)}{2N}. \tag{1}$$

Eq. (1) has several consequences. It is first of all easy to see that allele frequencies have no systematic drift, so that $E(p_{t+\tau}|p_t) = p_t$ for any positive integer τ . It can also be shown that the variance of allele frequency change over τ generations satisfies

$$\frac{\text{Var}(p_{t+\tau} - p_t|p_t)}{p_t(1-p_t)} = \frac{E[(p_{t+\tau} - p_t)^2|p_t]}{p_t(1-p_t)} = 1 - \left(1 - \frac{1}{2N}\right)^\tau. \tag{2}$$

We will use a version of (2) that is easier to generalize to subdivided populations. To this end, we assume that the population starts from a founder population T generations before the present ($t = -T$). Since the right hand side of (2) is independent of p_t , it follows that

$$\frac{\text{Var}(p_{t+\tau} - p_t)}{E[p_t(1-p_t)]} = 1 - \left(1 - \frac{1}{2N}\right)^\tau, \tag{3}$$

where variance and expectation in (3) are taken with respect to allele frequency variation from the founder population up to generation $t > -T$.

Next we introduce the inbreeding coefficient f_t^{hinbr} of generation t . This is the probability that two randomly chosen distinct gene copies of generation t are identical by descent (ibd), i.e. originate from the same gene copy of the founder generation. The

subscript *hinbr* refers to the fact that this a *haploid inbreeding* coefficient, since the two gene copies are drawn without taking individual origin into account. These haploid inbreeding coefficients satisfy a recursion

$$f_{t+\tau}^{\text{hinbr}} = \left[1 - \left(1 - \frac{1}{2N}\right)^\tau\right] \cdot 1 + \left(1 - \frac{1}{2N}\right)^\tau \cdot f_t^{\text{hinbr}}, \tag{4}$$

over τ generations. This follows from the fact that $1 - [1 - 1/(2N)]^\tau$ is the probability that a gene copy pair from generation $t + \tau$ has the same ancestral gene copy of generation t . If so, they are ibd with certainty, and if not, their ibd probability is f_t^{hinbr} .

In order to model the long term rate at which genetic variants are lost, we notice that (1) describes a Markov chain with state space

$$\mathcal{X} = \left\{0, \frac{1}{2N}, \dots, \frac{2N-1}{2N}, 1\right\}$$

and transition matrix $\mathbf{P} = (P_{xy}; x, y \in \mathcal{X})$, whose elements have the form

$$P_{xy} = P(p_{t+1} = y|p_t = x) = \binom{2N}{2Ny} x^{2Ny} (1-x)^{2N(1-y)}.$$

A genetic variant is lost when one allele (A or a) takes over the whole population. This corresponds to the two absorbing states $x = 0$ and $x = 1$. From this it follows that \mathbf{P} has two of its

eigenvalues equal to 1. The multiplicative rate at which genetic variants are lost is determined by the third largest eigenvalue

$$\lambda_3(\mathbf{P}) = 1 - \frac{1}{2N} \tag{5}$$

of \mathbf{P} , so that the larger the population is the closer to 1 is this rate, and the longer time it takes for one allele to become fixed.

3. A geographically subdivided population

In this section we specify the demographics and reproduction model of a monoecious and diploid population with $s \geq 2$ homogeneous subpopulations that represent geographic substructure. The local census sizes N_i and the number of breeding individuals N_{ei} of all subpopulations $i = 1, \dots, s$ are the same for all generations, so that $N = \sum_i N_i$ is the time invariant census size. We interpret N_{ei} as a local effective size of i if this subpopulation would be isolated from all other subpopulations. Therefore the two indices of N_{ei} refer to effective e and subpopulation number i (note that the latter is not the same as inbreeding I).

It is assumed that there is some exchange of migrants between subpopulations from each generation t and the next generation $t + 1$. The migration pattern varies randomly over time, as specified by a square forward migration matrix $\mathcal{M}_t = (\mathcal{M}_{tki})$ of order s . For each pair k, i of subpopulations, \mathcal{M}_{tki} refers to the average number of offspring of all individuals in k of generation t that migrate to i , whereas $N_k \mathcal{M}_{tki}$ is the total number of migrants from k to i between generations t and $t + 1$. In order for subpopulation sizes to remain constant, the relation

$$N_i = \sum_{k=1}^s N_k \mathcal{M}_{tki} \tag{6}$$

must hold for all i and t . The stochasticity of \mathcal{M}_t reflects the randomness of the migration process, but it is assumed that the expected forward migration matrix $\mathbf{M} = E(\mathcal{M}_t) = (M_{ki})$ is constant over time. For each pair k, i of subpopulations, M_{ki} equals the expected number of offspring of an individual in k that migrate to i , whereas $N_k M_{ki}$ is the expected total number of migrants from k to i . By taking the expected value of both sides of (6), it follows that

$$N_i = \sum_{k=1}^s N_k M_{ki} \tag{7}$$

must hold for all subpopulations i , in order to keep their local census sizes constant. The overall forward migration rate $M = 1 - \sum_i (N_i/N) M_{ii}$ is the expected fraction of offspring that live in another subpopulation than their parents.

The simplest and best known example is the island model of Wright (1951). It has equally large subpopulations or islands ($N_i = N_{ei} = N/s$), and the same amount of migration between all pairs of them ($M_{ki} = M/(s - 1)$ for $i \neq k$). The one- and two-dimensional stepping stone models of Kimura (1953) and Weiss and Kimura (1965) position subpopulations over a grid, with local migration from each subpopulation to one of its two or four neighbors. A more general class of subdivided populations is treated in Hössjer et al. (2014, 2015) and references therein, with subpopulation sizes and migration patterns of any form. Fig. 1 illustrates four different types of geographic subdivision.

There is also a square backward migration matrix $\mathbf{B} = (B_{ik})_{i,k=1}^s$ of order s whose elements $B_{ik} = N_k M_{ki}/N_i$ specify the expected fraction of genes in subpopulation i of generation $t + 1$ whose parents in generation t live in subpopulation k . Unless all subpopulations have the same size, the forward and backward migration matrices \mathbf{M} and \mathbf{B} will differ. Since the row sums of \mathbf{B}

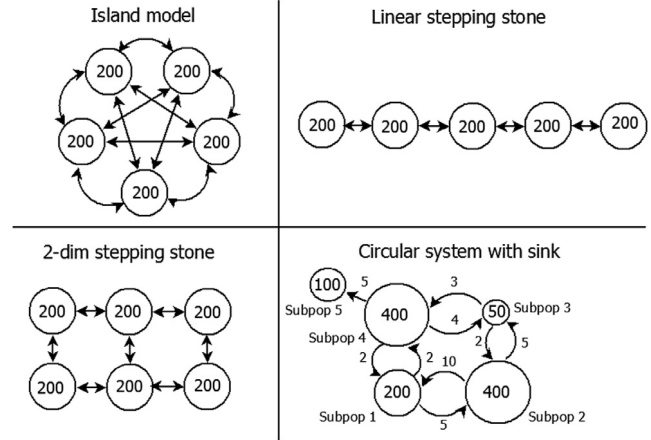


Fig. 1. Four different metapopulations with their subpopulations depicted as circles, and their local census and effective sizes shown as numbers within circles. Directed arrows are drawn between all pairs k, i of subpopulations for which the forward migration rate between two consecutive generations is positive ($M_{ki} > 0$). The island model and the two stepping stones models have the same value of M_{ki} for all such pairs of subpopulations. These are related to the overall forward migration rate M as $M_{ki} = M/4$ for the island model, $M_{ki} = 5M/8$ for the linear stepping stone model and $M_{ki} = 3M/10$ for the two-dimensional stepping stone model. For the lower right population, the expected number $N_k M_{ki}$ of migrants from k to i is shown, corresponding to a forward migration rate of $M = 0.033$. This system has subpopulations 1–4 located along a circle, with migration back and forth possible between neighbors, and the fifth subpopulation is a sink that only receives migrants. This metapopulation has previously been studied in Hössjer et al. (2014), and higher values of M are obtained by modifying the expected number of migrants proportionally between all pairs of subpopulations. Fig. 4 plots the required time to migration–drift equilibrium as a function of M , for all four metapopulations.

are one (cf. (7)), it is the transition matrix of a Markov chain with state space $\{1, \dots, s\}$. We will assume that this Markov chain has a unique stationary distribution $\boldsymbol{\gamma} = (\gamma_1, \dots, \gamma_s)$.

The mathematical theory for diploid populations is much more complicated than for haploid ones. In order to obtain more explicit inbreeding and diversity expressions, we will assume a reproduction model where gametes first migrate randomly between subpopulations, then mating and selfing are random within each subpopulation, as specified in Example 2 of Hössjer et al. (2015). This corresponds to a reproduction cycle between generations t and $t + 1$ that can be decomposed into the following three steps:

1. For each subpopulation $k = 1, \dots, s$ of generation t , a random subset N_{ek} of all its N_k individuals is selected as breeders, and their $2N_{ek}$ genes are put into a pool.
2. For each subpopulation $i = 1, \dots, s$ of generation $t + 1$, its $2N_i$ genes are drawn randomly with replacement in the following manner: At first the parental pool number k is chosen with probability B_{ik} , and then a parental gene is chosen randomly from all the $2N_{ek}$ possible genes of this pool.
3. For each subpopulation $i = 1, \dots, s$, the $2N_i$ drawn genes from Step 2 are randomly paired to form N_i diploid individuals.

It follows from Steps 2 and 3 of this reproduction scheme that the joint distribution of the number of migrating genes from all subpopulations $k = 1, \dots, s$ to i is multinomial

$$(2N_1 \mathcal{M}_{t1i}, \dots, 2N_s \mathcal{M}_{t si}) \sim \text{Mult}(2N_i; B_{i1}, \dots, B_{is}),$$

and in particular that (6) holds, since the row sums of \mathbf{B} are one.

Although Steps 1–3 are an essentially haploid reproduction scheme, it follows from Hössjer et al. (2015) that it provides a good approximation of a diploid and geographically structured population whose genotype frequencies are close to Hardy–Weinberg equilibrium within each subpopulation. This is a reasonable assumption if mating within subpopulations is close to random.

4. Measures of inbreeding and genetic diversity

In this section we introduce measures of inbreeding and diversity that will be used in the next section to define various effective sizes. In Sections 4.1–4.2 we consider variation at one single locus that represents an autosomal segment, such as a genetic marker or a gene. Since each individual carries two copies of this gene, the total number of gene copies in subpopulation i is $2N_i$ at each generation. For simplicity, we will refer to these gene copies as genes. In Sections 4.3–4.4 we will also consider genetic variation at multiple loci.

4.1. Covariances of allele frequency change

Consider one single locus with a gene that exists in two variants (alleles) A and a . We let p_{ti} be the fraction of genes of subpopulation i and generation t that carry allele A , whereas the remaining fraction $1 - p_{ti}$ of genes of subpopulation i in this generation have allele a . It is assumed that the population was founded $T > 0$ generations ago, and we require that the frequency $p_{-T,i} = p$ of A is the same for all subpopulations i of the founder generation $t = -T < 0$. We introduce the standardized covariances

$$f_{tij} = \frac{\text{Cov}(p_{ti} - p, p_{tj} - p)}{p(1 - p)} \quad (8)$$

between allele frequency change in i and j from the founder generation up to generation t , for all pairs i, j of subpopulations. Let \mathbf{f}_t be a column vector of length s^2 that contains all standardized covariances (8) of generation t . Because of the random mating, selfing and migration assumptions of Section 3, this vector will satisfy the same linear time recursion

$$\mathbf{f}_{t+1} = \mathbf{1} - \mathbf{A}(1 - \mathbf{f}_t) \quad (9)$$

as for a haploid population (Hössjer et al., 2014, Example 2 of Hössjer et al., 2015), where $\mathbf{1}$ is a column vector of s^2 ones, and $\mathbf{A} = (A_{ij,kl})$ is a square matrix of order s^2 , with rows and columns indexed by subpopulation pairs i, j and k, l respectively. These elements have the form

$$A_{ij,kl} = \left(1 - \frac{1}{2N_i}\right)^{\delta_{ij}} B_{ik} B_{jl} \left(\frac{1 - \frac{1}{2N_{ek}}}{1 - \frac{1}{2N_k}}\right)^{\delta_{kl}}, \quad (10)$$

where B_{ik} is the backward migration rate from i to k , N_{ek} is the number of breeding individuals of k , and δ_{ij} equals 1 or 0 when $i = j$ or $i \neq j$ respectively.

In order to summarize the allele frequency change by one single number, all subpopulations are assigned non-negative weights w_1, \dots, w_s that sum to one. This includes a number of possible weighting schemes, such as uniform weights ($w_i = 1/s$), weights proportional to local census sizes ($w_i = N_i/N$), weights proportional to number of breeding individuals ($w_i = N_{ei}/\sum_j N_{ej}$), reproductive weights ($w_i = \gamma_i$, see Fisher, 1958; Felsenstein, 1971) and local weights for some subpopulation $j \in \{1, \dots, s\}$ ($w_i = \delta_{ij}$). Let

$$p_t = \sum_i w_i p_{ti} \quad (11)$$

be the weighted frequency of allele A for all subpopulations. The standardized variance

$$f_t^{\text{var}} = \frac{\text{Var}(p_t - p)}{p(1 - p)} = \frac{\text{Var}\left[\sum_i w_i (p_{ti} - p)\right]}{p(1 - p)}$$

$$= \frac{\sum_{i,j} w_i w_j \text{Cov}(p_{ti} - p, p_{tj} - p)}{p(1 - p)} = \sum_{i,j} w_i w_j f_{tij} \quad (12)$$

quantifies the amount of genetic drift from the founder generation up to generation t , according to the prechosen subpopulation weights. In the second step of (12) we invoked (11) and used that all w_i sum to one, and in the last step we inserted the definition of f_{tij} in (8). This reveals that the standardized variance is a weighted average of all standardized covariances.

4.2. Inbreeding and coancestry coefficients

Let f_t^{inbr} be the inbreeding coefficient of subpopulation i at generation t . This is the probability that a pair of distinct genes within the same individual of subpopulation i and generation t is identical by descent, i.e. descends from the same gene of the founder generation $t = -T$. The coancestry coefficient f_{tij}^{co} is similarly defined as the probability that a gene pair from two different individuals of subpopulations i and j of generation t is ibd. In order to average these quantities over subpopulations, we let w_i be the probability of picking an individual from i , so that

$$f_t^{\text{inbr}} = \sum_i w_i f_{ti}^{\text{inbr}} \quad (13)$$

and $f_t^{\text{co}} = \sum_{i,j} w_i w_j f_{tij}^{\text{co}}$ are the inbreeding and coancestry coefficients of generation t , when subpopulations are weighted as w_i . In particular, if subpopulation weights are proportional to local census sizes ($w_i = N_i/\sum_j N_j$), Eq. (13) coincides with the traditional definition of the inbreeding coefficient, the probability that a pair of distinct genes from a randomly chosen individual of the metapopulation is ibd.

If the individual origin of all genes is hidden, it is not possible to distinguish between inbreeding and coancestry coefficients. We may then regard the population as haploid, and let f_{tij}^{hinbr} be the ibd probability of a gene pair drawn from subpopulations i and j of generation t . We refer to this quantity as a haploid inbreeding coefficient (hinbr). Since the probability is $1/(2N_i - 1)$ and $1 - 1/(2N_i - 1)$ that a gene pair from the same subpopulation i is drawn from the same or from different individuals, it follows that

$$f_{tij}^{\text{hinbr}} = \begin{cases} \frac{1}{2N_i - 1} f_{ti}^{\text{inbr}} + \left(1 - \frac{1}{2N_i - 1}\right) f_{tii}^{\text{co}}, & i = j, \\ f_{tij}^{\text{co}}, & i \neq j. \end{cases} \quad (14)$$

The corresponding weighted haploid inbreeding coefficient of generation t is

$$f_t^{\text{hinbr}} = \sum_{i,j} w_i w_j f_{tij}^{\text{hinbr}}. \quad (15)$$

Let f_{tij}^{gid} be the ibd probability of two genes drawn randomly with replacement from subpopulations i and j at time t . We will refer to it as a gene identity (gid), although its original definition (Nei, 1975, Chapter 6) was in terms of identity by state (ibs) rather than ibd sharing. Since the probability is $1/(2N_i)$ of drawing the same gene twice if $i = j$, the gene identity and haploid inbreeding coefficients are related as

$$f_{tij}^{\text{gid}} = \begin{cases} \left(1 - \frac{1}{2N_i}\right) f_{tij}^{\text{hinbr}} + \frac{1}{2N_i}, & i = j, \\ f_{tij}^{\text{hinbr}}, & i \neq j. \end{cases} \quad (16)$$

In Appendix A we prove that gene identities for individuals from different subpopulations $i \neq j$, satisfy

$$0 \leq f_{ij}^{\text{gid}} \leq \begin{cases} \frac{1}{4N_j} + \sqrt{\left(\frac{1}{4N_j}\right)^2 + f_{ii}^{\text{gid}} \left(f_{jj}^{\text{gid}} - \frac{1}{2N_j}\right)}, \\ \text{if } f_{iii}^{\text{gid}} \geq f_{ijj}^{\text{gid}}, \\ \frac{1}{4N_i} + \sqrt{\left(\frac{1}{4N_i}\right)^2 + f_{ijj}^{\text{gid}} \left(f_{iii}^{\text{gid}} - \frac{1}{2N_i}\right)}, \\ \text{if } f_{iii}^{\text{gid}} \leq f_{ijj}^{\text{gid}}. \end{cases} \quad (17)$$

The right hand side of (17) improves (is smaller than) the upper bound $\sqrt{f_{iii}^{\text{gid}} f_{ijj}^{\text{gid}}}$ derived in Hössjer et al. (2014).

There is a close relationship between the standardized covariances (8), inbreeding coefficients, coancestry coefficients, and gene identities (14). First, it is shown in Hössjer et al. (2014) that the column vector of all s^2 gene identities f_{ij}^{gid} of generation t satisfies the same time recursion (9) as the corresponding vector f_t of standardized covariances. The initial condition $f_{-T,ij} = 0$ imposed on the standardized covariances, is approximately valid for all $f_{-T,ij}^{\text{gid}}$ as well, if all genes of the founder generation $-T$ are regarded as different by descent, and no subpopulation is very small. Under these circumstances the approximation

$$f_{ij} \approx f_{ij}^{\text{gid}} \quad (18)$$

is accurate. Second, it can be seen from the definition of the essentially haploid reproduction scheme of Section 3 that

$$f_{ii}^{\text{inbr}} = f_{iii}^{\text{co}} \quad (19)$$

for each subpopulation i , since genes pair up randomly to form individuals in the last Step 3 of this scheme. It follows from (14) and (19) that the diploid inbreeding coefficient f_{ii}^{inbr} of subpopulation i equals the corresponding haploid one f_{iii}^{inbr} , and from (16) and (18) we deduce that both of these inbreeding coefficients are essentially equivalent to the standardized variance f_{iii} . On the other hand, there is sometimes a big difference between the subpopulation weighted diploid and haploid inbreeding coefficients f_t^{inbr} and f_t^{hinbr} in (13) and (15), when subpopulations are close to isolated.

4.3. Subpopulation differentiation

The coefficient of gene differentiation (Wright, 1951; Nei, 1973, 1977) at one single locus is a number

$$G_{ST,t} = \frac{\sum_i w_i (p_{ii} - p_t)^2}{p_t (1 - p_t)} \quad (20)$$

between 0 and 1 that for each generation t quantifies how much allele frequencies differ between subpopulations, when these are assigned non-negative weights w_i that sum to one. The scenario $G_{ST,t} = 0$ corresponds to identical subpopulations ($p_{ii} = p_t$ for all i) and $G_{ST,t} = 1$ to a system in which different alleles are fixed in the various subpopulations ($p_{ii} = 0$ or 1, and not all p_{ii} equal). Given information from the founder generation $t = -T$ only, the allele frequencies p_{ii} of any subsequent generation $t > -T$ are random, and so is $G_{ST,t}$. We may compute a prediction

$$g_{ST,t} = \frac{\sum_i w_i E[(p_{ii} - p_t)^2]}{E[p_t(1 - p_t)]} = \frac{\sum_i w_i f_{iii} - \sum_{i,j} w_i w_j f_{ijj}}{1 - \sum_{i,j} w_i w_j f_{ijj}}$$

of $G_{ST,t}$ based on the assumption of equal allele frequencies $p_{-T,i} = p$ in all subpopulations of the founder generation. It is also a

number between 0 and 1, where 0 corresponds to genetically identical subpopulations (all $f_{ij} = f$ for some $0 \leq f < 1$) and 1 to a system where individuals of different subpopulations are unrelated ($f_{ij} = 0$ for all $i \neq j$) but those from the same subpopulation are fully related (f_{iii} close to 1 for all i).

Nei (1973, 1977) has extended the coefficient of gene differentiation to settings where there are L_t biallelic genetic markers $x = 1, \dots, L_t$ of generation t , with $A(x)$ and $a(x)$ the two alleles at locus x . Let $p_{ii}(x)$ be the frequency of allele $A(x)$ in subpopulation i and generation t . The multilocus version of (20) is defined as

$$G_{ST,t} = \frac{\sum_i w_i \sum_x (p_{ii}(x) - p_t(x))^2}{\sum_x p_t(x)(1 - p_t(x))}, \quad (21)$$

where $p_t(x) = \sum_i w_i p_{ii}(x)$ is the subpopulation weighted frequency of $A(x)$. Assuming that the frequency $p_{-T,i}(x) = p(x)$ of $A(x)$ is the same in all subpopulations i of the founder generation, we define the standardized covariances for each locus x as in (8), with $p_{ii}(x)$ and $p(x)$ instead of p_{ii} and p . But since the time recursion (9) of the standardized covariances does not depend on the founder allele frequency, it follows that f_{ij} will be identical at all loci x . The predicted coefficient of gene differentiation

$$g_{ST,t} = \frac{\sum_i w_i \sum_x E[(p_{ii}(x) - p_t(x))^2]}{\sum_x E[p_t(x)(1 - p_t(x))]} = \frac{\sum_i w_i f_{iii} - \sum_{i,j} w_i w_j f_{ijj}}{1 - \sum_{i,j} w_i w_j f_{ijj}} \quad (22)$$

is therefore the same, regardless of number of loci. In the last step of (22) the term $\sum_x p_t(x)(1 - p_t(x))$ is canceled out in the numerator and denominator.

4.4. Additive genetic variance

Consider a quantitative trait (or phenotype) with value Y_{ii}^u for individual $u = 1, \dots, N_i$ of subpopulation i in generation t . We assume that the genetic component of this trait originates from a number of polymorphic loci $x = 1, \dots, L_t$, where each replacement of the $a(x)$ allele by the other allele $A(x)$ at locus x increases the expected value of the phenotype by σ , whereas each replacement of the $A(x)$ allele by $a(x)$ decreases the expected phenotype by the same amount. This is equivalent to saying that if the locus is homozygous for the $A(x)$ allele, its expected phenotype marginally increases by 2σ , compared to if it is homozygous for the $a(x)$ allele. Write

$$Y_{ii}^u = m_{ii} + 2\sigma \sum_{x=1}^{L_t} (p_{ii}^u(x) - p_{ii}(x)) + (\epsilon_{ii}^u - \bar{\epsilon}_i),$$

where ϵ_{ii}^u is an environmental effect and $2p_{ii}^u(x) \in \{0, 1, 2\}$ is the number of copies of $A(x)$ for individual u of subpopulation i , whereas $m_{ii} = \sum_{u=1}^{N_i} Y_{ii}^u / N_i$, $p_{ii}(x) = \sum_{u=1}^{N_i} p_{ii}^u(x) / N_i$ and $\bar{\epsilon}_i = \sum_{u=1}^{N_i} \epsilon_{ii}^u / N_i$ refer to average values of the phenotypes, allele frequencies and environmental effects among all individuals of subpopulation i and generation t . When subpopulations are assigned weights w_i , the phenotype mean and variance of generation t are $m_t = \sum_i w_i m_{ii}$ and

$$V_t = \sum_{i=1}^s \frac{w_i}{N_i} \sum_{u=1}^{N_i} E[(Y_{ii}^u - m_t)^2] = V_{tA} + V_{t\epsilon}, \quad (23)$$

where expectation is taken over all environmental effects and the random allocation of the $2N_i p_{ii}(x)$ copies of the $A(x)$ allele among

all $2N_i$ gene copies, for all subpopulations i and loci x . In the last step of (23) we assumed that environmental and genetic effects are independent, so that V_t splits into an environmental variance component $V_{t\epsilon}$ and an additive genetic variance component

$$\begin{aligned} V_{tA} &= \sigma^2 \sum_i w_i \sum_x E[(2p_{ii}^1(x) - 2p_t(x))^2] \\ &= \sigma^2 \sum_i w_i \left[\sum_x \frac{2N_i - 2}{2N_i - 1} 2p_{ii}(x)(1 - p_{ii}(x)) \right. \\ &\quad \left. + 4(p_{ii}(x) - p_t(x))^2 \right] \\ &\approx \sigma^2 \sum_i w_i \left[\sum_x 2p_{ii}(x)(1 - p_{ii}(x)) + 4(p_{ii}(x) - p_t(x))^2 \right] \\ &= 2\sigma^2 \sum_x \left[p_t(x)(1 - p_t(x)) + \sum_i w_i (p_{ii}(x) - p_t(x))^2 \right] \\ &= 2\sigma^2 \sum_x p_t(x)(1 - p_t(x))(1 + G_{ST,t}). \end{aligned} \tag{24}$$

In the second step of (24) we used that $2p_{ii}^1(x)$ has a hypergeometric distribution with parameters $2N_i$, $p_{ii}(x)$ and 2. This follows from the fact that there are $2N_i$ gene copies at locus x in subpopulation i , a fraction $p_{ii}(x)$ of which have allele $A(x)$. When genotypes are allocated to all individuals of subpopulation i , the $2N_i$ gene copies are paired randomly. Therefore, the number of $A(x)$ alleles assigned to each individual u is obtained by drawing two alleles without replacement from the pool of $2N_i$ gene copies, $2N_i p_{ii}(x)$ of which have allele $A(x)$. In the third approximate step of (24) we assumed that N_i are large for all subpopulations with positive weights, and in the last step we invoked the definition of the multilocus coefficient of gene differentiation (21).

Let $v_{tA} = E(V_{tA})$ be the expected additive genetic component of generation t . It follows from the approximate expression of V_{tA} in (24), the definition of standardized covariances in (8), and the definition of $g_{ST,t}$ in (22), that

$$\begin{aligned} v_{tA} &= 2\sigma^2 \sum_x p(x)[1 - p(x)] \left(1 - 2 \sum_{i,j} w_i w_j f_{ij} + \sum_i w_i f_{ii} \right) \\ &= 2\sigma^2 \sum_x p(x)[1 - p(x)] \left(1 - \sum_{i,j} w_i w_j f_{ij} \right) (1 + g_{ST,t}). \end{aligned} \tag{25}$$

5. Effective sizes

In Sections 5.1–5.4 we consider a number of effective sizes $N_e = N_e([t, t + \tau])$ that quantify the predicted amount by which a given characteristic changes per generation over a time interval $[t, t + \tau]$ of length t that starts at $t \geq 0$, when subpopulations i are assigned non-negative weights w_i that sum to one. In contrast, the effective size in Section 5.5 quantifies the long term rate per generation at which genetic variants are lost, i.e. the limit $\tau \rightarrow \infty$.

5.1. Variance effective size

As in Section 4.1 we consider genetic variation at one single locus with alleles A and a , and let $p_t = \sum_i w_i p_{ii}$ be the subpopulation weighted frequency of A in generation t . Since p_t is scalar, it is possible to compare its rate of change with the allele frequency change of a WF model. The variance effective size N_{eV} (Crow, 1954) is the size of a WF population whose standardized variance of allele frequency change $p_{t+\tau} - p_t$ between generation t

and $t + \tau$ is the same as in the studied population. In order to obtain a tractable expression for N_{eV} , expectation is *not* with respect to allele frequency variation from generation t , but rather from the founder generation $-T$ up to $t + \tau$. In view of (3), this gives

$$\begin{aligned} 1 - \left(1 - \frac{1}{2N_{eV}} \right)^\tau &= \frac{E[(p_{t+\tau} - p_t)^2]}{E[p_t(1 - p_t)]} \\ &= \frac{E[(p_{t+\tau} - p)^2] - E[(p_t - p)^2]}{E[p_t(1 - p_t)]} \\ &\quad + \frac{-2\text{Cov}(p_{t+\tau} - p_t, p_t - p)}{E[p_t(1 - p_t)]} \\ &= I + II. \end{aligned} \tag{26}$$

The first term on the right hand side of (26) can be expressed in terms of the standardized variances (12), as

$$I = \frac{f_{t+\tau}^{\text{var}} - f_t^{\text{var}}}{1 - f_t^{\text{var}}} = \frac{\sum_{i,j} w_i w_j (f_{t+\tau,ij} - f_{ij})}{\sum_{i,j} w_i w_j (1 - f_{ij})}. \tag{27}$$

In previous work (Hössjer et al., 2014) we only considered the case $T = t = 0$, so that $p_t = p$ and hence the second term II of (26) vanished. This is far too simplistic, and in Appendix B we derive the more general expression

$$II = \frac{2\mathbf{w}(\mathbf{I} - \mathbf{B}^\tau)\bar{\mathbf{f}}_t\mathbf{w}'}{\sum_{i,j} w_i w_j (1 - f_{ij})}, \tag{28}$$

where $\mathbf{w} = (w_1, \dots, w_s)$ is a row vector of subpopulation weights, and $\bar{\mathbf{f}}_t = (f_{ij})_{i,j=1}^s$ is a square matrix of order s that contains all standardized covariances (8). It follows from (28) that $II = 0$ for reproductive weights $\mathbf{w} = \boldsymbol{\gamma}$, since $\boldsymbol{\gamma} = \mathbf{B}\boldsymbol{\gamma}$ is a stationary distribution of \mathbf{B} .

5.2. Diploid inbreeding effective size

The diploid version of the inbreeding effective size, $N_{el,dipl}$, is based on the inbreeding coefficients (13). It is defined as the size of a WF population whose inbreeding coefficient increases by the same relative amount between generations t and $t + \tau$ as in the studied population. This gives

$$\begin{aligned} 1 - \left(1 - \frac{1}{2N_{el,dipl}} \right)^\tau &= \frac{f_{t+\tau}^{\text{inbr}} - f_t^{\text{inbr}}}{1 - f_t^{\text{inbr}}} \\ &= \frac{\sum_i w_i (f_{t+\tau,i}^{\text{inbr}} - f_{ti}^{\text{inbr}})}{\sum_i w_i (1 - f_{ti}^{\text{inbr}})}, \end{aligned} \tag{29}$$

since (4) implies that the left hand side of (29) equals $(f_{t+\tau}^{\text{inbr}} - f_t^{\text{inbr}})/(1 - f_t^{\text{inbr}})$ for a WF population of size $N_{el,dipl}$. The original effective size definition of Wright is essentially a special case of (29) with $\tau = 1$ and $f_t^{\text{inbr}} = 0$.

5.3. Haploid inbreeding effective size

The haploid version of the inbreeding effective size, $N_{el,hapl}$, is based on the haploid inbreeding coefficients (15). It is defined as the size of a WF population whose haploid inbreeding coefficient increases by the same relative amount between generations t and $t + \tau$ as in the studied population. Similarly as for the diploid inbreeding effective size, we deduce from (4) that

$$1 - \left(1 - \frac{1}{2N_{el,hapl}} \right)^\tau = \frac{f_{t+\tau}^{\text{hinbr}} - f_t^{\text{hinbr}}}{1 - f_t^{\text{hinbr}}}$$

$$\begin{aligned}
 &= \frac{\sum_{i,j} w_i w_j (f_{t+\tau,ij}^{\text{hinbr}} - f_{ij}^{\text{hinbr}})}{\sum_{i,j} w_i w_j (1 - f_{ij}^{\text{hinbr}})} \\
 &\approx I.
 \end{aligned}
 \tag{30}$$

In the last step of (30) we inserted the definition of I in (27) and used the fact that $f_{ij}^{\text{hinbr}} \approx f_{ij}$, which follows from (14), (16) and (18). Consequently, the haploid inbreeding effective size will differ from the variance effective size, unless $I = 0$.

5.4. Additive genetic variance effective size

For the additive genetic variance effective size, we will look at the rate at which the expected additive genetic variance v_{tA} in (25) decays in absence of mutations, so that the number of polymorphic loci L_t is a non-increasing function of t . We define N_{eAV} as the size of a WF population for which this decay rate is the same between generations t and $t + \tau$ as in the studied population. This gives

$$\begin{aligned}
 1 - \left(1 - \frac{1}{2N_{eAV}}\right)^\tau &= \frac{v_{tA} - v_{t+\tau,A}}{v_{tA}} \\
 &= I + \frac{1 - \sum_{i,j} w_i w_j f_{t+\tau,ij}}{1 - \sum_{i,j} w_i w_j f_{ij}} \frac{g_{ST,t+\tau} - g_{ST,t}}{1 + g_{ST,t}} \\
 &\approx I,
 \end{aligned}
 \tag{31}$$

where in the last step we assumed $g_{ST,t} \approx g_{ST,t+\tau}$, which is increasingly accurate as t increases and $g_{ST,t}$ converges to a nonzero limit.

In order to motivate (31), we will show that its left hand side equals the decay rate of additive genetic variance for a biallelic single locus WF model of size N_{eAV} , with frequency p_t in generation t for allele A . To this end, we use (24) in order to conclude that $V_{tA} \approx 2\sigma^2 p_t(1 - p_t)$ and $v_{tA} \approx 2\sigma^2 E[p_t(1 - p_t)]$. From this it follows that

$$\begin{aligned}
 v_{tA} - v_{t+\tau,A} &\approx 2\sigma^2 \{E[p_t(1 - p_t)] - E[p_{t+\tau}(1 - p_{t+\tau})]\} \\
 &= 2\sigma^2 E(p_{t+\tau} - p_t)^2.
 \end{aligned}$$

Making use of (3) we conclude that the left hand side of (31) equals $(v_{tA} - v_{t+\tau,A})/v_{tA}$ for a WF population of size N_{eAV} , as claimed.

It follows from (30) and (31) that the haploid inbreeding and additive genetic variance effective sizes are essentially equivalent, i.e.

$$N_{eI, \text{hapl}} \approx N_{eAV}.
 \tag{32}$$

5.5. Eigenvalue effective size

The eigenvalue effective size N_{eE} (Crow, 1954; Nagylaki, 1980; Ewens, 1982) characterizes the long term multiplicative rate at which one of the two alleles, A or a , is lost. In order to specify this rate, we introduce the column vector

$$\mathbf{p}_t = (p_{t1}, \dots, p_{ts})'
 \tag{33}$$

of allele frequencies of A in all subpopulations. For the reproduction model of Section 3, this is a Markov chain with a huge state space

$$\mathcal{X} = \left\{0, \frac{1}{2N_1}, \dots, \frac{2N_1 - 1}{2N_1}, 1\right\} \times \dots \times \left\{0, \frac{1}{2N_s}, \dots, \frac{2N_s - 1}{2N_s}, 1\right\},$$

and a transition matrix $\mathbf{P} = (P_{\mathbf{x},\mathbf{y}}; \mathbf{x}, \mathbf{y} \in \mathcal{X})$ with entries

$$P_{\mathbf{x},\mathbf{y}} = P(\mathbf{p}_{t+1} = \mathbf{y} | \mathbf{p}_t = \mathbf{x}).$$

It is the largest non-unit eigenvalue of \mathbf{P} that determines the rate at which one of the two alleles gets fixed. When migration is

possible between all subpopulations, in one or several generations, the backward migration matrix \mathbf{B} is irreducible. Then there are only two absorbing states of the Markov chain (33), either $\mathbf{x} = (0, \dots, 0)$ if A gets fixed in all subpopulations, or $\mathbf{x} = (1, \dots, 1)$ if A takes over all subpopulations. Because of this, 1 is an eigenvalue of \mathbf{P} with multiplicity 2, and it is the third largest eigenvalue $\lambda_3(\mathbf{P})$ of \mathbf{P} that determines the fixation rate. We define N_{eE} as the size of a WF population for which the rate of lost variants $\lambda_3(\mathbf{P})$ is the same as in the studied population. From (5) we deduce that

$$1 - \frac{1}{2N_{eE}} = \lambda_3(\mathbf{P}).
 \tag{34}$$

This eigenvalue effective size is in general substantially larger than N_{ei} , and often at least as large as the sum of the local effective sizes N_{ei} .

Because of its size, \mathbf{P} is less tractable than \mathbf{A} , the matrix that appears in the linear recursion (9) of standardized covariances. Denote its largest eigenvalue by $\lambda = \lambda_1(\mathbf{A})$. It follows from (10) that if the backward migration matrix \mathbf{B} is irreducible and aperiodic, so is \mathbf{A} . The Perron–Frobenius Theorem (Cox and Miller, 1965) then implies that $0 < \lambda < 1$ is unique and real valued. Hössjer (2015) considers a large class of reproduction schemes that includes the one in Section 3, and proves that

$$\lambda = \lambda_3(\mathbf{P}).
 \tag{35}$$

Combining (34) and (35) we find that

$$1 - \frac{1}{2N_{eE}} = \lambda.
 \tag{36}$$

Compared to (34), this equation is often preferable to use when computing the eigenvalue effective size.

6. Comparison between effective sizes

In this section we will analyze the effective sizes of Section 5. We recall from (32) that N_{eAV} is very close to $N_{el, \text{hapl}}$, and therefore we only compare $N_{el, \text{dipl}}, N_{el, \text{hapl}}, N_{eV}$ and N_{eE} . Since this comparison is very different for local and global populations, we treat them separately in Sections 6.1–6.2. The corresponding theoretical results can be found for general populations in Appendix D, and for the island model in Appendix E. For simplicity, we will assume that the inbreeding and variance effective sizes are instantaneous ($\tau = 1$).

6.1. Local effective size

For a diploid subdivided population, the instantaneous local haploid and diploid inbreeding effective sizes of subpopulation i are essentially the same,

$$N_{eli, \text{dipl}} = N_{eli, \text{hapl}} = N_{eli}.
 \tag{37}$$

They quantify how much the inbreeding coefficient or gene diversity of i changes from one generation to the next, whereas the local variance effective size N_{eVi} tells how much allele frequencies of i change. They are all defined by assigning subpopulation i full weight ($w_i = 1$), and they differ from N_{ei} in that they account for migration between i and the other subpopulations. Local effective sizes are commonly compared using N_{ei} as gold standard (Waples and England, 2011; Ryman et al., 2014). But since N_{eli} includes the effect of migration, it is a more relevant quantity than N_{ei} for predicting how inbreeding changes. Both N_{eli} and N_{eVi} are very close to N_{ei} when i is almost isolated from the other subpopulations, or when there is little differentiation between them. But

$$N_{eVi} < N_{ei} < N_{eli}
 \tag{38}$$

when the migration rate between i and the rest of the metapopulation is large and the subpopulations are differentiated, with a substantial downward bias of N_{eVi} . This phenomenon has been described for the island model by Ryman et al. (2014), and in Appendices D.1 and E we show more generally that it is caused by the extra term II of (26). Intuitively, immigration into i from the other subpopulations will magnify allele frequency shift in i between generations t and $t + 1$, and thereby cause N_{eVi} to decrease. The impact of immigration into i on N_{eli} is just the opposite. Since immigrants are more distantly related to individuals in i , in the diploid case they will typically cause the inbreeding coefficient within i to either increase at a slower rate, so that N_{eli} becomes larger, or even cause the inbreeding coefficient to decrease, so that N_{eli} is undefined. This difference between N_{eli} and N_{eVi} persists and gets more extreme when the system approaches a migration–drift equilibrium (see Figs. 2 and 3). Whereas N_{eVi} remains below N_{ei} , the local inbreeding effective size

$$N_{eli} \rightarrow N_{eE} \tag{39}$$

converges to the eigenvalue effective size.

6.2. Global effective size

The instantaneous global (total) inbreeding and variance effective sizes $N_{eIT,dipl}$, $N_{eIT,hapl}$ and N_{eVT} quantify how inbreeding coefficients, gene diversities and allele frequencies of the whole population change from one generation to the next. This corresponds to using a scheme where all or most of the subpopulations have positive weights ($w_i > 0$). It is shown in Appendix D that $N_{eIT,dipl}$ is a harmonic average of all local N_{eli} , provided that these exist. If the subpopulations are almost isolated with little differentiation at start, $N_{eIT,dipl}$ will initially be close to a harmonic average of the local effective sizes N_{ei} , and then gradually increases towards N_{eE} when the migration–drift equilibrium of (39) is approached. The global haploid inbreeding and variance effective sizes $N_{eIT,hapl}$ and N_{eVT} , on the other hand, are initially much larger than $N_{eIT,dipl}$, before migration–drift equilibrium is attained. In particular, for reproductive subpopulations weights we have

$$N_{eIT,dipl} < N_{eIT,hapl} \approx N_{eVT}, \tag{40}$$

since the II term of (28) vanishes. Then $N_{eIT,hapl}$ and N_{eVT} will start at a level that equals the sum of all local effective sizes, or larger, and after that gradually converge to the N_{eE} limit (see Appendices D.2 and E for details). This is illustrated in Fig. 2 for a metapopulation with two subpopulations. It is not until the system has reached equilibrium that N_{eVT} and $N_{eIT,dipl}$ get close to one another, and

$$N_{eIT,dipl}, N_{eIT,hapl}, N_{eVT} \rightarrow N_{eE} \tag{41}$$

as $t \rightarrow \infty$.

There are at least two reasons for the very different behavior of N_{eVT} and $N_{eIT,hapl}$ on one hand, and $N_{eIT,dipl}$ on the other. First, in contrast to the local variance effective size, for reproductive subpopulation weights there is no downward bias of N_{eVT} due to immigration, since $II = 0$ in (28). Even though the allele frequency shift in each subpopulation is magnified by immigration from the other parts of the metapopulation, these shifts will not have the same direction in all subpopulations and therefore more or less cancel out. Second, it follows from (14)–(15) and (29)–(30) that $N_{eIT,dipl}$ quantifies rate of changes within individuals, whereas $N_{eIT,hapl}$ essentially quantifies temporal changes of coancestry coefficients. If the subpopulations are almost isolated and genetically distinct from start, the coancestry coefficients between subpopulations will differ a lot from the inbreeding coefficients within individuals. If distinct alleles are close to fixation in different subpopulations for a long time, the rate of

change of the coancestry coefficients between subpopulations is small (a large $N_{eIT,hapl}$), whereas the inbreeding coefficients continue to increase at a much faster rate within all subpopulations (a small $N_{eIT,dipl}$).

7. Migration–drift equilibrium

It is evident from Figs. 2 and 3 that the relationship between the local or global variance and inbreeding effective sizes depends crucially on how far away from migration–drift equilibrium the system starts in generation 0, and how long time it takes to attain this equilibrium. In this section we will develop tools to quantify this. Recall that the population in generation t is characterized by the vector \mathbf{f}_t of standardized covariances f_{ij} in (8). It is shown in Hössjer et al. (2014) that $0 \leq f_{ii} \leq 1$, $f_{ij} = f_{ji}$, and from the Cauchy–Schwarz inequality we deduce

$$0 \leq f_{ij} \leq \sqrt{f_{ii}f_{jj}}. \tag{42}$$

Due to symmetry, it suffices to consider the set \mathcal{F} of admissible values of all f_{ij} with $1 \leq i \leq j \leq s$, which is a subset of the $s(s + 1)/2$ -dimensional unit cube. By studying the long term behavior (9) of the standardized covariances, it can be seen that migration–drift equilibrium corresponds to a one-dimensional subset

$$\mathcal{F}^{eq} = \{f_{ij}, 1 \leq i \leq j \leq s; f_{ij} = 1 - cr_{ij}, 0 < c \leq c_{max}\} \tag{43}$$

of \mathcal{F} , with $\mathbf{r} = (r_{ij}; 1 \leq i, j \leq s)'$ the right eigenvector of \mathbf{A} with eigenvalue λ . Without loss of generality we assume that the elements of \mathbf{r} and the corresponding left eigenvector $\mathbf{l} = (l_{ij}; 1 \leq i, j \leq s)$ are normalized so that

$$\sum_{i,j} l_{ij} = \sum_{i,j} l_{ij}r_{ij} = 1. \tag{44}$$

The upper bound c_{max} of c in (43) is imposed to ensure that $\mathcal{F}^{eq} \subset \mathcal{F}$. We notice that \mathcal{F}^{eq} is a line segment between the two end points $\mathbf{1} - c_{max}\mathbf{r}$ and $\mathbf{1}$. These end points correspond to the minimal and maximal amount of inbreeding that is possible under equilibrium. In order to quantify how far away from equilibrium a population system is, we define for any $\mathbf{f} = (f_{ij}) \in \mathcal{F}$ a projection

$$\mathbf{f}^{eq} = (f_{ij}^{eq}) = \pi(\mathbf{f}) \tag{45}$$

down to \mathcal{F}^{eq} as $f_{ij}^{eq} = 1 - \min((1 - f^{var}), c_{max})r_{ij}$, where $f^{var} = \sum_{i,j} l_{ij}f_{ij}$. The distance of \mathbf{f} to migration–drift equilibrium is a number

$$d(\mathbf{f}, \mathcal{F}^{eq}) = \max_{i,j} \frac{|f_{ij} - f_{ij}^{eq}|}{1 - f_{ij}^{eq}} \tag{46}$$

between 0 and 1 that is well defined if $f_{ij} < 1$ for at least one subpopulation pair i, j . Indeed, since \mathbf{A} is a non-negative and irreducible matrix if there are no isolated components of the metapopulation, all l_{ij} and r_{ij} are strictly positive by the Perron–Frobenius Theorem, and therefore $f_{ij}^{eq} < 1$ holds for all pairs i, j of subpopulations.

The distance measure (46) has two important properties. It is first of all invariant

$$d((1 - c)\mathbf{f} + c\mathbf{1}, \mathcal{F}^{eq}) = d(\mathbf{f}, \mathcal{F}^{eq})$$

with respect to all convex linear combinations $0 \leq c < 1$ of the standardized covariance vector \mathbf{f} and a totally inbred population $\mathbf{1}$, at least if all the standardized covariances are sufficiently large. Second, the convergence rate

$$d(\mathbf{f}_t, \mathcal{F}^{eq}) \rightarrow 0 \text{ as } t \rightarrow \infty \tag{47}$$

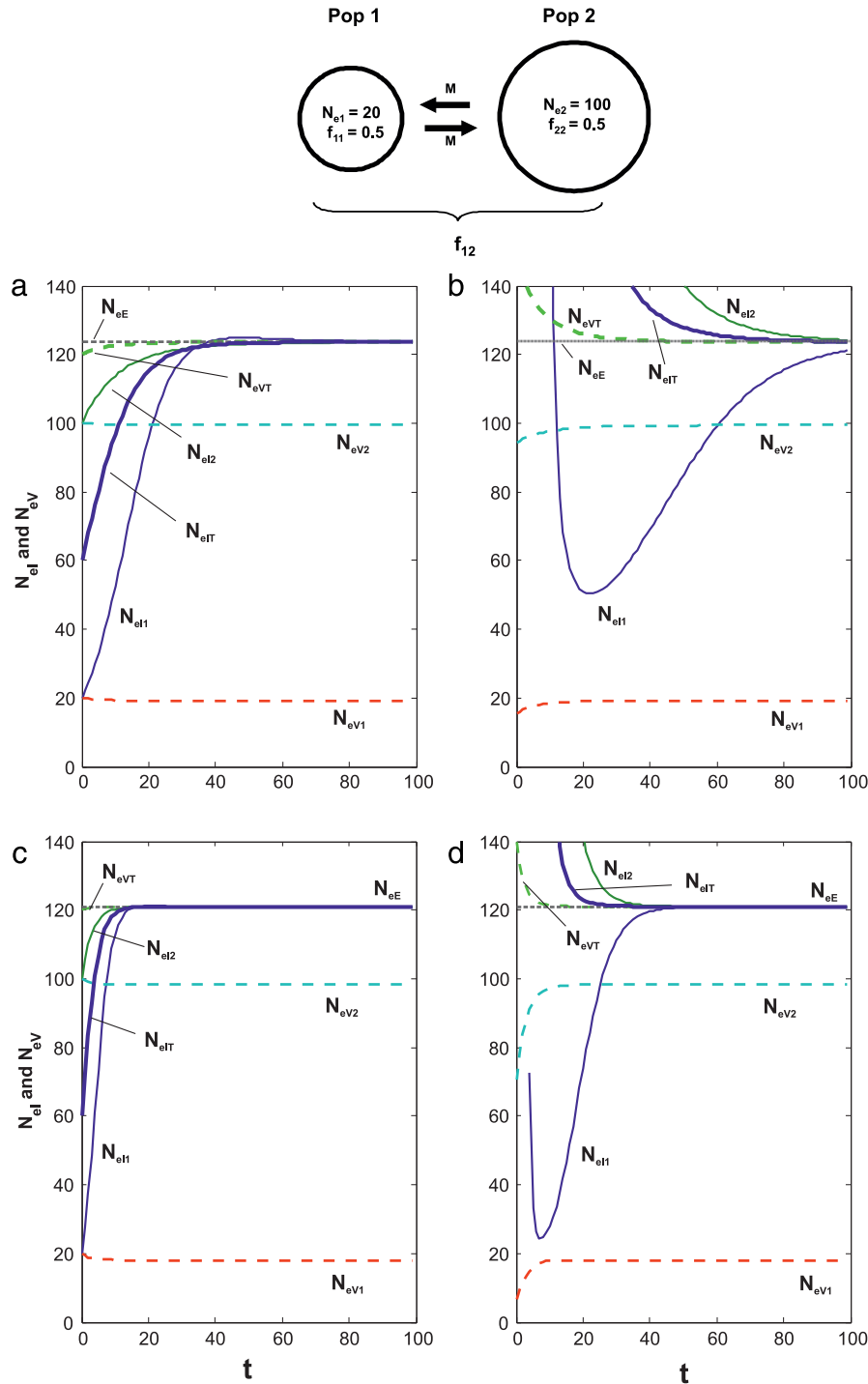


Fig. 2. Plots of N_{eE} (dotted) and local and global diploid $N_{el} = N_{el, dipl}$ (solid) and N_{ev} (dashed) for two populations of size $N_1 = N_{e1} = 20$ and $N_2 = N_{e2} = 100$ between generations t and $t + 1$ for $t = 0, \dots, 99$ when the expected exchange is M migrants per generation. Initially ($t = 0$) $f_{11} = f_{22} = 0.5$ in all plots, whereas $f_{12} = 0.5$ ((a) and (c); left) or $f_{12} = 0$ ((b) and (d); right), and the migration rate is $M = 1$ ((a) and (b); upper) or $M = 3$ ((c) and (d); lower). Note that subplot a describes the behavior of the N_e curves for all scenarios of the present population model where $M = 1$ and $f_{11} = f_{12} = f_{22}$ and that the same holds true for subplot (c) when $M = 3$.

towards migration–drift equilibrium determines the speed at which the local or global inbreeding effective sizes approach N_{eE} . In more detail, it is shown at the end of [Appendices D.1](#) and [D.2](#) that the instantaneous local or global diploid and haploid inbreeding effective sizes between generations t and $t + 1$ satisfy

$$\begin{aligned} &|N_{el, dipl}^{-1} - N_{eE}^{-1}| \\ &|N_{el, hapl}^{-1} - N_{eE}^{-1}| \leq 2 [d(\mathbf{f}_t, \mathcal{F}^{eq}) + d(\mathbf{f}_{t+1}, \mathcal{F}^{eq})], \end{aligned} \quad (48)$$

whenever these effective sizes exist. The same relation holds for the variance effective size when reproductive subpopulation weights are used.

In order to quantify the convergence rate in (47), we define the time

$$\tau_\varepsilon = \min\{t \geq 0; d(\mathbf{f}_t, \mathcal{F}^{eq}) \leq \varepsilon\} \quad (49)$$

it takes for the system to get within distance ε from migration–drift equilibrium, where $0 \leq \varepsilon \leq 1$ is a given tolerance level. For any

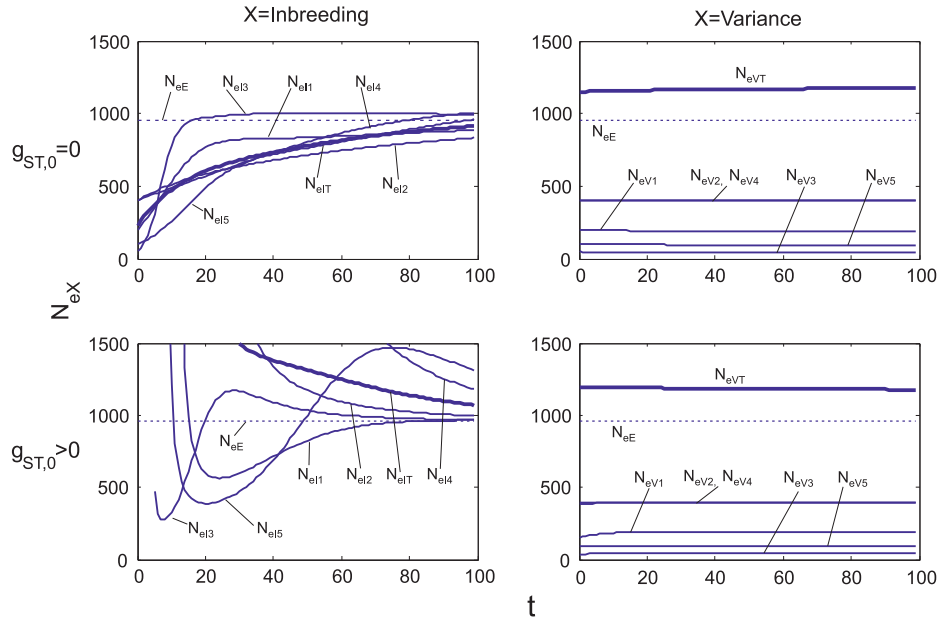


Fig. 3. Plots of various effective sizes for the circular population system with a sink (Fig. 1) between generations t and $t + 1$ for $t = 1, \dots, 99$. The plots to the left show the global diploid inbreeding effective size $N_{eIT} = N_{eIT,dipl}$ with size proportional weights $w_i = N_i/N$ (thick solid line), local inbreeding (haploid or diploid) effective sizes N_{eli} for all five subpopulations $i = 1, \dots, 5$ (thin solid lines), and eigenvalue effective size N_{eE} (dotted line). The plots to the right show the global variance effective size N_{eVT} with size proportional weights (thick solid line), local variance effective sizes N_{eVi} for all five subpopulations $i = 1, \dots, 5$ (thin solid lines), and eigenvalue effective size N_{eE} (dotted line). In the first $t = 0$ generation there is no subpopulation differentiation in the upper subplots (standardized covariances $f_{0ij} = 0.1$ for all pairs of subpopulations) and some subpopulation differentiation in the lower subplots ($f_{0ii} = 0.1, f_{0ij} = 0$ when $i \neq j$). In the upper left plot, all local curves N_{eli} start at the corresponding census size N_i and then gradually converge to $N_{eE} = 957$. For the two curves with $N_i = 400$ the $i = 2$ curve is slightly below the $i = 4$ curve. In the lower left subplot, it is the $i = 3$ curve that first drops below upper $N_{eli} = 1500$ limit of the graph, followed by the $i = 5, i = 1, i = 2$ and $i = 4$ curves.

population system it can be derived by first finding \mathbf{f}_t recursively for all $t \geq 0$ from (9), and then computing $d(\mathbf{f}_t, \mathcal{F}^{eq})$ from the left and right eigenvectors \mathbf{l} and \mathbf{r} of \mathbf{A} . It turns out that the rate of convergence towards migration–drift equilibrium is determined by how much smaller the modulus $|\lambda_2|$ of the second largest eigenvalue of \mathbf{A} is compared to λ . It is shown in Appendix C that a rough upper bound of the time to equilibrium is

$$\tau_\varepsilon \leq \frac{C_\varepsilon}{\log \frac{\lambda}{|\lambda_2|}} \leq \frac{C_\varepsilon}{1 - \frac{|\lambda_2|}{\lambda}}, \tag{50}$$

where in the last step we assumed that $|\lambda_2|/\lambda$ is close to 1, whereas

$$C_\varepsilon = \max \left[0, \log \left(\frac{d(\mathbf{f}_0, \mathcal{F}^{eq})}{\varepsilon} \right) \right]$$

quantifies how far away from equilibrium the system is from start ($t = 0$). It is also argued that $1 - |\lambda_2|/\lambda$ is of the same order or smaller than the forward migration rate M , depending on how global or local migration is. Therefore, the time it takes to attain equilibrium is at least of the order $1/M$, with a proportionality constant that depends on how far away the system is from equilibrium at $t = 0$.

Since τ_ε depends on ε , it may be wise to report τ_ε for several values of this tuning parameter. Fig. 4 illustrates that $\tau_{0.01}$ and $\tau_{0.1}$ are highly dependent on M and the degree of subpopulation differentiation at start. It is evident that the convergence time for small migration rates is far too large to be of interest in many management applications. For such migration scenarios, N_{eE} is of limited relevance, unless the system starts very close to equilibrium.

Notice that the predicted coefficient of gene differentiation (22) satisfies the same invariance property as the distance measure d , in that its value remains the same if \mathbf{f}_t is replaced by $(1 - c)\mathbf{f}_t + c\mathbf{1}$.

In addition, $g_{ST,t}$ will attain the same value

$$g^{eq} = \frac{\sum_{i,j} w_i w_j r_{ij} - \sum_i w_i r_{ii}}{\sum_{i,j} w_i w_j r_{ij}} \tag{51}$$

for any $\mathbf{f}_t \in \mathcal{F}^{eq}$. The implication of this is that migration–drift equilibrium (43) corresponds to a unique predicted coefficient of gene differentiation (51), regardless of how much inbreeding there is in the population, that is, regardless of where along the line segment \mathcal{F}^{eq} the vector \mathbf{f}_t of standardized covariance is located. Although the exact form of g^{eq} depends on the migration model, it roughly ranges from 0, for a metapopulation whose expected number of immigrants per generation is substantially larger than 1 ($NM \gg 1$), up to 1 for a model with completely isolated subpopulations ($M = 0$). An explicit formula for g^{eq} is derived for the island model in Appendix E. If the weights $w_i w_j$ for subpopulation pairs are replaced by l_{ij} , formula (51) simplifies to

$$g^{eq} = 1 - \sum_i l_i r_{ii},$$

where $l_i = \sum_j l_{ij}$.

8. Discussion

In this paper we compared the inbreeding, variance and eigenvalue effective sizes, with a particular focus on geographically structured populations. We also gave an explicit characterization of migration–drift equilibrium for a subdivided population, and the time it takes to reach this equilibrium. These results are important, since subpopulations behave as more or less isolated units before equilibrium. The time it takes to reach this limit therefore influences, e.g., the extent to which short and long term and conservation genetic goals are reached for separate subpopulations as well

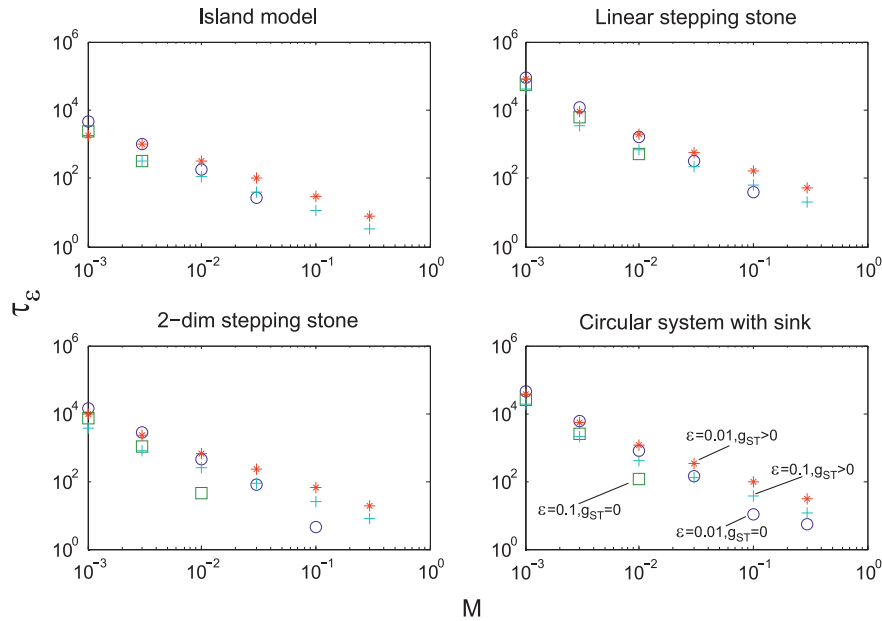


Fig. 4. The required number τ_ϵ of generations to reach migration–drift equilibrium with tolerance level ϵ is shown on a log–log scale as a function of the forward migration rate M , for each of the four metapopulations of Fig. 1. The number of migrants is adjusted between all pairs of subpopulations proportionally, so that the overall migration rate equals M . The symbols represent different combinations of tolerance levels and subpopulation differentiation scenarios for the $t = 0$ generation. τ_ϵ is given for $\epsilon = 0.1$ (squares) or $\epsilon = 0.01$ (circles) when there is initially no subpopulation differentiation, with standardized covariances $f_{ij} = 0.1$ for all pairs i, j of subpopulations. τ_ϵ is also given for $\epsilon = 0.1$ (pluses) or $\epsilon = 0.01$ (stars) when there is initial subpopulation differentiation, with $f_{iii} = 0.5$ and $f_{ij} = 0$ for identical or different ($i \neq j$) subpopulations. Symbols are missing whenever $\tau_\epsilon = 0$. It is seen that τ_ϵ increases dramatically when the migration rate gets low. For small migration rates, it takes a somewhat longer time to reach equilibrium when subpopulations are genetically similar initially, whereas for large migration rates, it takes longer time to reach equilibrium when subpopulations are genetically distinct from start. The convergence time τ_ϵ is smaller for systems with more global migration, in particular for the island model and to some extent for the 2-dimensional stepping stone model.

as for the metapopulation as a whole. An important topic of future research is to describe the migration–drift equilibrium more explicitly in terms of genetic differentiation between subpopulations, for a system with a pre-specified demography. It should be noted, however, that the migration–drift equilibrium concept is restricted to populations whose size is either constant over time (as in this paper), or at least varies cyclically. It is not directly applicable to human and other populations whose size steadily increases, or to small, threatened populations that steadily decrease.

Our starting point was that the rate of changed inbreeding and additive genetic variance of quantitative traits are the most appropriate concepts for short and long term predictions, respectively. We found that the inverse of the variance effective size is sometimes a poor approximation of both of these rates for geographically subdivided systems, for local populations as well as for the metapopulation. When the inbreeding rate of a subpopulation or of the total population is positive, its inverse is equivalent to a diploid version of the local or global inbreeding effective size, respectively. In the same way, the negative rate of change of the additive genetic variance of a local population or of the metapopulation, can be approximated in most cases by the inverse of a haploid version of the local or global inbreeding effective size.

But inbreeding coefficients may decrease locally or globally for some generations in a system with substantial gene flow between genetically distinct subpopulations. Then the diploid local or global inbreeding effective size is not defined (see also Laikre et al., in press). The reason is that the Wright–Fisher model is a too simplistic reference model, which is not able to reproduce decreased inbreeding rates. It can be seen from Figs. 2 and 3 that even when $N_{el,dipl}$ exists, it may still behave quite chaotically in parameter regions where the inbreeding coefficient increases very slowly. The same phenomenon can be observed for the local (but not the global) haploid inbreeding effective size, when additive genetic variance of a local population increases for some generations due to gene flow from neighboring subpopulations.

In view of these limitations of the inbreeding effective size, an alternative would be to use the more general concept

$$\Delta f_{i,dipl} = 1 - \left(1 - \frac{f_{t+\tau}^{inbr} - f_t^{inbr}}{1 - f_t^{inbr}} \right)^{1/\tau}$$

$$\tau=1 \frac{f_{t+1}^{inbr} - f_t^{inbr}}{1 - f_t^{inbr}} \tag{52}$$

for diploid models and short term protection. It is the rate at which inbreeding changes per generation between t and $t + \tau$, with $y^{1/\tau} = \text{sgn}(y)|y|^{1/\tau}$. Notice that

$$\Delta f_{i,dipl} \in \left[1 - \left(\frac{1}{1 - f_t^{inbr}} \right)^{1/\tau}, 1 \right]$$

may be negative or positive, and the diploid inbreeding effective size $N_{el,dipl} = 1/(2\Delta f_{i,dipl})$ is defined when $\Delta f_{i,dipl} > 0$, but undefined when $\Delta f_{i,dipl} < 0$. In particular, when $\tau = 1$ we refer to $\Delta f_{i,dipl}$ as the instantaneous amount of changed inbreeding.

Fig. 5 shows a number of instantaneous $\Delta f_{i,dipl}$ curves for the sink population system of Fig. 1. It illustrates the advantage of using the rate of changed inbreeding as criterion instead of the corresponding $N_{el,dipl}$ curves, shown in the lower left subplot of Fig. 3. Whereas the local and global $N_{el,dipl}$ curves are defined only after a substantial number of generations, the local and global $\Delta f_{i,dipl}$ curves are defined at all time points.

For long term protection, we may similarly use $\Delta f_{i,hapl}$ as the rate at which the gene identity (or haploid inbreeding coefficient) changes between generations t and $t + \tau$. In particular, when $\tau = 1$, $\Delta f_{i,hapl}$ is the instantaneous rate of changed gene identity.

The above considerations suggest that it may sometimes be preferable to focus on inverse effective population sizes. We may then regard the haploid or diploid version of (52) as a yardstick to

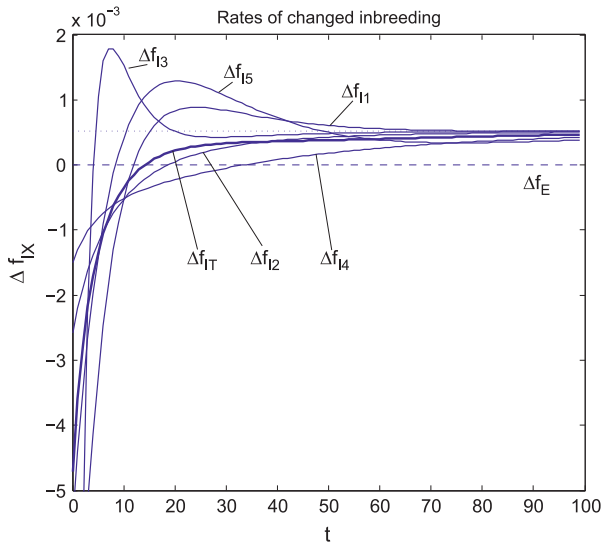


Fig. 5. The diploid rates (52) of changed inbreeding $\Delta f_i = \Delta f_{i, \text{dip}}$ are shown for the circular population with sink in Fig. 1, during $t = 100$ generations. All curves refer to instantaneous rates (length of time interval $\tau = 1$ in (52)), and they are derived from the lower left subplot of Fig. 3, with the same subpopulation differentiation of generation 0 ($f_{0ii} = 0.1, f_{0ij} = 0$ when $i \neq j$). The global Δf_{IT} curve is drawn as a thick solid line, and the local Δf_{it} curves ($i = 1, \dots, 5$) as thin solid lines. The dotted line corresponds to the eigenvalue effective size, with $\Delta f_E = 1/(2N_{eE}) = 5.22 \cdot 10^{-4}$. It can be seen that migration causes inbreeding to decrease in all subpopulations for quite a long time at first, before it starts to increase. The curve that first becomes positive is Δf_{13} , followed by $\Delta f_{15}, \Delta f_{11}, \Delta f_{12}$ and Δf_{14} .

compare the other notions N_{eX} of effective size with. To this end, we translate such an N_{eX} into an “equivalent rate

$$\Delta f_X = \frac{1}{2N_{eX}} \quad (53)$$

of changed inbreeding”. For the variance effective size, it follows from (26) that Δf_V equals a standardized variance of allele frequency change per generation between t and $t + \tau$, whereas for the eigenvalue effective size Δf_E gives the long term rate at which alleles are lost. But on the other hand, the inbreeding rate scale (52)–(53) is sometimes less intuitive than the effective size scale, which is also much more well known and understood among biologists. For instance, it may seem more difficult to distinguish the two inbreeding rates 0.001 and 0.01 than the corresponding effective sizes 500 and 50.

A number of extensions are of interest. First, one of the most frequently used notions of N_e is the linkage disequilibrium effective size N_{eLD} (Hill, 1981; Waples, 2006; Waples and Do, 2010). A general theory of N_{eLD} for subdivided populations is still lacking, but results for the island model (Waples and England, 2011) reveal that N_{eLD} may deviate substantially from the inbreeding and variance effective sizes. Second, in order to obtain estimates of $N_{eI, \text{dip}}$ and $N_{eI, \text{hap}}$ from real data, it is necessary to estimate identity by descent sharing. This is a non-trivial task, but hidden Markov models have recently been applied to estimate inbreeding coefficients (Leutenegger et al., 2003) and coancestry coefficients (Lynch and Ritland, 1999; Browning and Browning, 2011). Third, our new effective size concept, N_{eAV} , focuses on changes of the additive genetic variance of a quantitative trait. An interesting topic of future research is to consider dominance and epistasis effects as well. Such an analysis may reveal that there is no longer a close relationship (32) between the phenotype based effective size on one hand, and the haploid inbreeding effective size on the other.

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Appendix A. Derivation of upper bound (17) for gene identities

In order to prove (17), we assume there are C ibd classes of the founder generation $t = -T$, and let P_{tic} be the frequency of class c in subpopulation i at generation t . For instance, if the first C_1 ibd classes correspond to allele A , and the remaining $C - C_1$ ibd classes to allele a , then $p_{ti} = \sum_{c=1}^{C_1} P_{tic}$. The (expected) gene identity of subpopulations i and j of generation t is an expectation

$$f_{ij}^{\text{gid}} = E(F_{ij})$$

of the corresponding observed gene identity

$$F_{ij} = \sum_c P_{tic} P_{tjc}, \quad (54)$$

with respect to all reproduction cycles from the founder generation up to generation t . We will first prove that

$$0 \leq F_{ij} \leq \begin{cases} \frac{1}{4N_j} + \sqrt{\left(\frac{1}{4N_j}\right)^2 + F_{tii} \left(F_{tjj} - \frac{1}{2N_j}\right)}, & \text{if } F_{tii} \geq F_{tjj}, \\ \frac{1}{4N_i} + \sqrt{\left(\frac{1}{4N_i}\right)^2 + F_{tjj} \left(F_{tii} - \frac{1}{2N_i}\right)}, & \text{if } F_{tii} \leq F_{tjj}, \end{cases} \quad (55)$$

for two different subpopulations i and j . Suppose that F_{tii} and F_{tjj} are fixed. Since (55) is symmetric with respect to F_{tii} and F_{tjj} , we may without loss of generality assume $F_{tii} \geq F_{tjj}$ and $P_{tic} > 0$ for $c = 1, \dots, \tilde{C}$, whereas $P_{tic} = 0$ and $P_{tjc} > 0$ for $c = \tilde{C} + 1, \dots, C$. Then $x = \sum_{c=1}^{\tilde{C}} P_{tjc}$ satisfies $0 \leq x \leq 1$. It follows from (54) and the Cauchy–Schwarz inequality that given x , F_{tjj} is maximized by putting $P_{tjc} = xP_{tic}$ for $c = 1, \dots, \tilde{C}$. We may therefore assume that this relation holds, so that

$$F_{tjj} = F_{tii}x, \quad (56)$$

and

$$\sum_{c=1}^{\tilde{C}} P_{tjc}^2 = F_{tii}x^2. \quad (57)$$

Since $\sum_{c=\tilde{C}+1}^C P_{tjc} = 1 - x$ and $P_{tjc} \geq 1/(2N_j)$ for $c = \tilde{C} + 1, \dots, C$, it follows from (57) that

$$F_{tjj} - F_{tii}x^2 = \sum_{c=\tilde{C}+1}^C P_{tjc}^2 \geq \frac{1-x}{2N_j}, \quad (58)$$

$$\Downarrow$$

$$x \leq \frac{1}{4F_{tii}N_j} + \sqrt{\left(\frac{1}{4F_{tii}N_j}\right)^2 - \frac{1}{2F_{tii}N_j} + \frac{F_{tjj}}{F_{tii}}}.$$

Hence, in order to maximize F_{tjj} we plug the upper bound of x in (58) into (56), and the result is identical to the first part of (55).

In order to prove (17) we notice that (55) can be written as

$$F_{tjj} \leq g(F_{tii}, F_{tjj}) = \min [g_1(F_{tii}, F_{tjj}), g_2(F_{tii}, F_{tjj})],$$

where

$$g_1(x, y) = \frac{1}{4N_j} + \sqrt{\left(\frac{1}{4N_j}\right)^2 + x \left(y - \frac{1}{2N_j}\right)},$$

$$g_2(x, y) = \frac{1}{4N_i} + \sqrt{\left(\frac{1}{4N_i}\right)^2 + y\left(x - \frac{1}{2N_i}\right)}.$$

Since both g_1 and g_2 are concave, so is g , and it follows from Jensen's Inequality that

$$\begin{aligned} f_{ij}^{\text{gid}} &= E(F_{ij}) \\ &\leq E[g(F_{ii}, F_{ij})] \\ &\leq g[E(F_{ii}), E(F_{ij})] \\ &= g(f_{ii}^{\text{gid}}, f_{ij}^{\text{gid}}), \end{aligned}$$

as was to be proved.

Appendix B. Derivation of variance effective size formula (28)

In Hössjer and Ryman (2014), it is shown that the frequency vector (33) of allele A is a vector valued autoregressive process

$$\mathbf{p}_{t+1} = \mathbf{B}\mathbf{p}_t + \boldsymbol{\varepsilon}_{t+1} \tag{59}$$

over generations, with \mathbf{B} the backward migration matrix, and $\boldsymbol{\varepsilon}_t$ a random $s \times 1$ column vector that quantifies genetic drift due to individuals' varying reproductive success. It satisfies

$$E(\boldsymbol{\varepsilon}_{t+1} | \mathbf{p}_t) = \mathbf{0}. \tag{60}$$

Recall that the frequency of allele A is the same ($= p$) in all subpopulations of the founder generation $t = -T$, so that $\mathbf{p}_{-T} = p(1, \dots, 1)'$. We use (59)–(60) and the fact that the backward migration matrix has row sums 1 to deduce

$$E(\mathbf{p}_t) = \mathbf{B}^{t+T} p(1, \dots, 1)' = p\mathbf{B}^{t+T}(1, \dots, 1)' = p(1, \dots, 1)', \tag{61}$$

where expectation is with respect to allele frequency dynamics from the founder population up to generation t . In order to verify (28), we first rewrite (11) in vector notation as $\mathbf{p}_t = \mathbf{w}\mathbf{p}_t$. Then we insert this formula and (61) into (26), and find that

$$\begin{aligned} II &= \frac{2E[\mathbf{w}(\mathbf{p}_t - \mathbf{p}_{t+\tau})(\mathbf{p}_t - p\mathbf{1})' \mathbf{w}']}{p(1-p) - E[(p_t - p)^2]} \\ &= \frac{2\mathbf{w}E[(\mathbf{p}_t - E(\mathbf{p}_{t+\tau} | \mathbf{p}_t))(\mathbf{p}_t - p\mathbf{1})' \mathbf{w}']}{p(1-p) - \sum_{i,j} w_i w_j E[(p_{ti} - p)(p_{tj} - p)]} \\ &= \frac{2\mathbf{w}(\mathbf{I} - \mathbf{B}^\tau)E[(\mathbf{p}_t - p\mathbf{1})(\mathbf{p}_t - p\mathbf{1})' \mathbf{w}']}{p(1-p) - \sum_{i,j} w_i w_j E[(p_{ti} - p)(p_{tj} - p)]}, \end{aligned} \tag{62}$$

where \mathbf{I} is the identity matrix of order s , and in the last step we used $E(\mathbf{p}_{t+\tau} | \mathbf{p}_t) = \mathbf{B}^\tau \mathbf{p}_t$, which is a consequence of (59)–(60). Formula (28) follows by first dividing the numerator and denominator of the right hand side of (62) by $p(1-p)$, and then using the definition of \mathbf{f}_t as a matrix of standardized covariances f_{ij} in (8).

Appendix C. Convergence to migration–drift equilibrium

In order to verify convergence to migration–drift equilibrium, we introduce the eigenvalues $\lambda = \lambda_1, \dots, \lambda_{s^2}$ of \mathbf{A} (including multiplicity), sorted in descending order of their moduli, and let $\mathbf{A} = \mathbf{Q}^{-1}\mathbf{D}\mathbf{Q}$ be the Jordan decomposition of \mathbf{A} , so that \mathbf{D} is an upper triangular matrix with all its eigenvalues along the diagonal ($d_{kk} = \lambda_k$). It follows from this representation of \mathbf{A} and iterated use of (9) that

$$\mathbf{1} - \mathbf{f}_t = \mathbf{Q}^{-1}\mathbf{D}^t\mathbf{Q}(\mathbf{1} - \mathbf{f}_0). \tag{63}$$

Since $\mathbf{r} = (r_{ij})'$ is the right eigenvector of \mathbf{A} with eigenvalue λ , it is the first column of \mathbf{Q}^{-1} , whereas the corresponding left

eigenvector $\mathbf{l} = (l_{ij})$ is the first row of \mathbf{Q} . From this we conclude that

$$\begin{aligned} \frac{1 - f_{ij}}{\lambda^t} &= (1 - f_0^{\text{var}})r_{ij} \left[1 + P_{ij}^2 \left(\frac{|\lambda_2|}{\lambda}\right)^t + \dots + P_{ij}^{s^2} \left(\frac{|\lambda_{s^2}|}{\lambda}\right)^t \right] \\ &\rightarrow (1 - f_0^{\text{var}})r_{ij} \end{aligned} \tag{64}$$

as $t \rightarrow \infty$, where $f_0^{\text{var}} = \sum_{ij} l_{ij}f_{0ij}$ is the amount of genetic drift up to generation 0, averaged over the components l_{ij} of the left eigenvector, P_{ij}^k are polynomial and sinusoidal functions of t for $k = 2, \dots, s^2$ and each pair i, j of subpopulations.

The right hand limit of (64) corresponds to migration–drift equilibrium, and it is attained when $(1 - f_{ij})/(1 - f_{ikl})$ converges to r_{ij}/r_{kl} for all quadruples i, j, k, l of subpopulations. It follows from (44) and (63) that

$$f_t^{\text{var}} = \sum_{ij} l_{ij}f_{tj} = \lambda^t f_0^{\text{var}}.$$

Hence for all sufficiently large time points the projection (45) of \mathbf{f}_t onto the equilibrium set \mathcal{F}^{eq} satisfies

$$\mathbf{f}_t^{\text{eq}} = \pi(\mathbf{f}_t) = \mathbf{1} - \lambda^t(\mathbf{1} - \mathbf{f}_0^{\text{var}})\mathbf{r}.$$

Together with (46) and (64), this implies that approximately

$$\begin{aligned} d(\mathbf{f}_t, \mathcal{F}^{\text{eq}}) &= \max_{i,j} \left| \sum_{k=2}^{s^2} P_{ij}^k \left(\frac{|\lambda_k|}{\lambda}\right)^t \right| \\ &\leq d(\mathbf{f}_0, \mathcal{F}^{\text{eq}}) \left(\frac{|\lambda_2|}{\lambda}\right)^t, \end{aligned} \tag{65}$$

where in the last step we assumed that all P_{ij}^k are constant in t . This is true for instance when all eigenvalues of \mathbf{A} are distinct.

The upper bound (50) of τ_ε follows immediately from the right hand side of (65), and it only depends on the subpopulation differentiation at time 0 and $|\lambda_2|/\lambda$. In order to find a fairly simple approximation of $|\lambda_2|/\lambda$, we first replace \mathbf{A} in (10) by another matrix $\mathbf{A}(\infty)$ with elements $A_{ij,kl}(\infty) = B_{ik}B_{jl}$ that correspond to an infinitely large population ($N_i = N_{ei} = \infty$). This matrix $\mathbf{A}(\infty)$ has a simpler form than \mathbf{A} , and its s^2 eigenvalues (including multiplicity) can be expressed explicitly as $\gamma_i\gamma_j$ for $1 \leq i, j \leq s$, where $\gamma_1 = 1, \gamma_2, \dots, \gamma_s$ are the eigenvalues of \mathbf{B} , listed in descending order of their magnitudes $|\gamma_i|$. If no subpopulation is isolated, \mathbf{B} is an irreducible matrix with $|\gamma_2| < 1$. It follows that the magnitudes of the two leading eigenvalues of $\mathbf{A}(\infty)$ are $\lambda(\infty) = 1 \times 1 = 1$ and $|\lambda_2(\infty)| = 1 \times |\lambda_2| = |\lambda_2|$. Since the elements of \mathbf{A} are obtained by perturbing those of $\mathbf{A}(\infty)$ by an amount at most $O(1/\min(N_{ei}))$, the eigenvalues will be perturbed by the same order (van der AA et al., 2007). Hence we obtain

$$\frac{|\lambda_2|}{\lambda} = \frac{|\gamma_2| + O[1/\min(N_{ei})]}{1 - \frac{1}{2N_{eE}}} \approx |\gamma_2|, \tag{66}$$

where in the last step we assumed $|\gamma_2|$ to be of larger order than $1/N_{ei}$ for all i . For a metapopulation with almost isolated subpopulations, $1 - |\gamma_2|$ is a small number, and (50) implies that τ_ε is roughly inversely proportional to $1 - |\gamma_2|$, at least when the latter quantity is of larger order than the inverse of all N_{ei} .

For the island model, it is easy to see that

$$\gamma_2 = \dots = \gamma_{s^2} = 1 - \frac{s}{s-1}M \implies 1 - |\gamma_2| = \frac{s}{s-1}M.$$

More generally, $1 - |\gamma_2|$ will be of the same order as the migration rate M for population systems with global migration (similar values of M_{ik} for all $i \neq k$), whereas $1 - |\gamma_2|$ will be of smaller order than M for population systems with local migration ($M_{ik} > 0$ only when i and k are neighbors). The conclusion is that for systems with global migration, τ_ε is approximately inversely proportional to M , whereas for systems with local migration it is even larger.

Appendix D. Comparison between variance and inbreeding effective sizes

In this appendix we make a detailed comparison between three effective sizes; the variance effective size (26), the diploid inbreeding effective size (29), and the haploid inbreeding effective size (30). We will confine ourselves to instantaneous effective sizes, so that the length τ of the time interval of genetic change is 1.

Starting with the diploid inbreeding effective size, we can rewrite (29) as

$$\begin{aligned} \frac{1}{2N_{el,dipl}} &= \Delta f_i \\ &= \frac{\sum_i w_i (f_{t+1,i} - f_{ti})}{\sum_i w_i (1 - f_{ti})} \\ &= \sum_i w'_i \Delta f_{fi} \\ &= \sum_i w'_i \frac{1}{2N_{eli}}, \end{aligned} \tag{67}$$

when $\tau = 1$, where we removed superscript inbr for the inbreeding coefficients of all subpopulations (cf. the discussion at the end of Section 4.2), and $\Delta f_{fi} = (f_{t+1,i} - f_{ti}) / (1 - f_{ti})$ quantifies the relative amount by which the inbreeding coefficient of subpopulation i changes between generations t and $t + 1$. In the third step of (67) we introduced weights w'_i that are proportional to $w_i(1 - f_{ti})$ and sum to 1. In the last step of (67) we defined the local diploid inbreeding effective size $N_{eli} = 1 / (2\Delta f_{fi})$ of i between generations t and $t + 1$. It is the value of the inbreeding effective size in (67) when subpopulation i has full weight ($w_i = 1$). Multiplying both sides of (67) by 2, we find that the diploid inbreeding effective size

$$\frac{1}{N_{el,dipl}} = \sum_i w'_i \frac{1}{N_{eli}} \tag{68}$$

is a weighted harmonic average of all N_{eli} .

For the haploid inbreeding effective size, we use the approximation in the last step of (30) with $\tau = 1$ and write

$$\begin{aligned} \frac{1}{2N_{el,hapl}} &\approx \frac{\sum_{i,j} w_i w_j (f_{t+1,ij} - f_{tij})}{\sum_{i,j} w_i w_j (1 - f_{tij})} \\ &= \sum_{i,j} \Delta f_{vij} \\ &= \sum_{i,j} w'_{ij} \frac{1}{2N'_{evij}}, \end{aligned} \tag{69}$$

where w'_{ij} are weights proportional to $w_{ij}(1 - f_{tij})$ that sum to one. In the last two steps of (69) we introduced $\Delta f_{vij} = (f_{t+1,ij} - f_{tij}) / (1 - f_{tij})$ and $N'_{evij} = 1 / (2\Delta f_{vij})$, which can be thought of as a local variance effective size of i when $i = j$, and a local covariance effective size of pair i, j when $i \neq j$, when only the first term I of N_{ev} is taken into account. Multiplying both sides of (69) by 2, we find that the haploid inbreeding effective size

$$\frac{1}{N_{el,hapl}} \approx \sum_{i,j} w'_{ij} \frac{1}{N'_{evij}} \tag{70}$$

is essentially a weighted harmonic average of all N'_{evij} .

For the variance effective size we add the second term (28) of (26) to (69) with $\tau = 1$, multiply by 2, and find that

$$\frac{1}{N_{ev}} = \sum_{i,j} w'_{ij} \frac{1}{N'_{evij}} + \frac{4\mathbf{w}(\mathbf{I} - \mathbf{B})\bar{\mathbf{f}}\mathbf{w}'}{\sum_{i,j} w_i w_j (1 - f_{tij})}. \tag{71}$$

Comparing the expressions for the diploid inbreeding, haploid inbreeding and variance effective sizes in (68), (70) and (71), we notice two major differences:

1. The right hand side of (68) is a weighted average of inverse local inbreeding effective sizes N_{eli} , with weights w'_i for all subpopulations, whereas the right hand sides of (70) and (71) contain weighted averages of inverse local variance and covariance effective sizes N'_{evij} , with weights w'_{ij} for all pairs of subpopulations.
2. The right hand side of (71) contains an extra term due to migration between subpopulations, not present in (68) and (70).

We will comment on the influence that items 1 and 2 have on the difference between the inbreeding and variance effective sizes, locally for one subpopulation and globally for the metapopulation.

D.1. Local effective sizes

For a local weighting scheme $w_i = 1$, the diploid and haploid inbreeding effective sizes in (68) and (70) reduce to N_{eli} and N'_{evii} respectively. For any subpopulation $i = 1, \dots, s$ we have that

$$\begin{aligned} N_{eli} &\approx N'_{evii} = N_{ei}, && \text{if } i \text{ is either isolated or genetically} \\ &&& \text{identical to all other } k \neq i, \\ N_{eli} &\approx N'_{evii} \geq N_{ei}, && \text{if } i \text{ is neither isolated nor genetically} \\ &&& \text{identical to all other } k \neq i. \end{aligned} \tag{72}$$

The left part of (72) follows from (14)–(16), (18)–(19) and the definitions of N'_{evii} and N_{eli} . For the upper right part, we notice that $B_{ii} = 1$ and $B_{ik} = 0$ for $i \neq k$ when i is isolated, so that $A_{ii,ii} = 1 - 1 / (2N_{ei})$ and $A_{ij,kl} = 0$ for all $kl \neq ii$ in (10). It therefore follows from (9) that $N'_{evii} = N_{ei}$. In order to motivate the lower right part of (72) we assume for simplicity $N_i = N_{ei}$, so that the formula for $A_{ij,kl}$ in (10) simplifies, with its last term in brackets equal to 1. From the definition of N'_{evii} and (9) we find that

$$\frac{1}{N'_{evii}} - \frac{1}{N_{ei}} = - \frac{2 \left(1 - \frac{1}{2N_{ei}}\right) \sum_{k,l} B_{ik} B_{il} (f_{tii} - f_{tkl})}{1 - f_{tii}} \tag{73}$$

whenever N'_{evii} is well defined, i.e. when immigration does not cause the standardized variance f_{tii} of i to decrease. Thus $N'_{evii} = N_{ei}$ holds when all subpopulations are genetically identical in generation t ($f_{tkl} = f$ for all k, l). The notation $N'_{evii} \geq N_{ei}$ in (72) symbolizes that this inequality holds in most cases, for instance when all subpopulations have the same amount of genetic drift up to time t ($f_{t,11} = \dots = f_{t,ss} = f$ and hence $f_{tkl} \leq f$ for all k, l). A necessary condition for $N'_{evii} < N_{ei}$ to hold is that $f_{tkk} > f_{tii}$ for at least one subpopulation $k \neq i$ from which i receives immigrants. But this is not a sufficient condition, since in many cases $f_{tki} < f_{tii}$ will hold in spite of this. Unless the migration rates (off-diagonal elements of \mathbf{B}) are large, the $2B_{ik}B_{il}$ weight of the $f_{tii} - f_{tkl}$ term will be much higher than the $B_{ik}B_{il}$ weight of any term $f_{tii} - f_{tkl}$ with $k, l \neq i$.

The local variance effective size N_{evi} is obtained by putting $w_i = 1$ in (71), so that

$$\frac{1}{N_{evi}} = \frac{1}{N'_{evii}} + \frac{4 \sum_k B_{ik} (f_{tii} - f_{tik})}{1 - f_{tii}}. \tag{74}$$

From (72) we conclude that the only difference between N_{eli} and N_{evi} is the second migration term on the right hand side of (74). But this term is typically positive when the other subpopulations $k \neq i$ are not too much related to i , for instance when $f_{tik} \leq f_{tii}$ holds for all $k \neq i$, with strict inequality for at least one subpopulation k that has offspring in i ($B_{ik} > 0$). Therefore, the second term of (74) causes N_{evi} to be increasingly smaller than N'_{evii} , the more migration

there is into i from the other subpopulations (large B_{ik}), and the less genetically related the other subpopulations are to i (smaller f_{tik}).

A more detailed analysis reveals that N_{eVi} is also, in most cases, smaller than N_{ei} . Indeed, combining the formula for N'_{eVi} in (73) with (74), we find that

$$\frac{1}{N_{eVi}} - \frac{1}{N_{ei}} = \frac{4 \left[1 - \left(1 - \frac{1}{2N_{ei}} \right) B_{ii} \right] \sum_k B_{ik} (f_{tii} - f_{tik})}{1 - f_{tii}} - \frac{2 \left(1 - \frac{1}{2N_{ei}} \right) \sum_{k,l \neq i} B_{ik} B_{il} (f_{tkl} - f_{tik})}{1 - f_{tii}}. \tag{75}$$

Repeating the argument below (73) we find that for most population systems, the two numerators of (75) are both positive, and the first is larger unless the migration rates are high. This implies that $N_{eVi} \leq N_{ei}$ will hold for most systems, even under migration–drift equilibrium.

In order to analyze the inbreeding and variance effective sizes when the system approaches migration–drift equilibrium we will use the definitions of N_{eE} and N'_{eVi} in (36) and below (70), the closeness of N_{eVi} and N'_{eVi} derived in (72), and (64), to motivate that

$$\begin{aligned} \left| \frac{N_{eVi}^{-1} - N_{eE}^{-1}}{N'_{eVi} - N_{eE}^{-1}} \right| &\leq 2\lambda [d(\mathbf{f}_t, \mathcal{F}^{eq}) + d(\mathbf{f}_{t+1}, \mathcal{F}^{eq})] \\ &\leq 2 [d(\mathbf{f}_t, \mathcal{F}^{eq}) + d(\mathbf{f}_{t+1}, \mathcal{F}^{eq})] \end{aligned} \tag{76}$$

for all pairs i, j of subpopulations, where in the last step we used $\lambda \leq 1$. In order to verify the first step of (76) we put

$$d_{tij} = \sum_{k=2}^s P_{tij}^k \left(\frac{|\lambda_k|}{\lambda} \right)^t$$

and notice, after some computations, that

$$\begin{aligned} N'_{eVi}^{-1} &= \frac{2(f_{t+1,ij} - f_{tij})}{1 - f_{tij}} = 2 \frac{1 - \lambda + d_{tij} - \lambda d_{t+1,ij}}{1 + d_{tij}} \\ &\approx N_{eE}^{-1} + 2\lambda(d_{tij} - d_{t+1,ij}). \end{aligned}$$

Then we subtract by N_{eE}^{-1} on both sides of the last displayed equation, take absolute values, employ the triangle inequality and finally use $|d_{tij}| \leq d(\mathbf{f}_t, \mathcal{F}^{eq})$. Combining (65) and (76), we find that

$$N_{eVi}, N'_{eVi} \rightarrow N_{eE} \tag{77}$$

as $t \rightarrow \infty$, with a speed of convergence determined by how fast the population system approaches migration–drift equilibrium.

To conclude, we have motivated (37)–(39): The local diploid and haploid inbreeding effective sizes are approximately equal ($= N_{eVi}$), and they also equal the effective number of breeders N_{ei} for an isolated population i , whereas in general they are larger than N_{ei} when i receives immigrants from other subpopulations, and eventually converges to N_{eE} . The local variance effective size also equals N_{ei} when i is isolated, but it is typically smaller than N_{ei} when there is migration into i .

D.2. Global effective sizes

For a global weighting scheme, it follows from item 1 that the global variance and haploid inbreeding effective sizes are typically much larger than the global diploid inbreeding effective size, before migration–drift equilibrium is attained. In order to see this, we notice from (70) that $N_{eIT,dipl}$ is a weighted harmonic average of all N_{eVi} when the local inbreeding effective sizes are all well defined. If the subpopulations are genetically very similar initially in generation 0, we deduce from (72) that $N_{eIT,dipl}$ will start at a value close to a harmonic average of all N_{ei} , and then, due to (77), it

will increase towards N_{eE} as the migration–drift equilibrium limit is approached, in accordance with (41).

In order to compare $N_{eIT,dipl}$ with $N_{eIT,hapl}$ and N_{eVT} , we assume that the subpopulation weights are reproductive, so that $\mathbf{wB} = \mathbf{w}$ and the second term of (26) vanishes. In view of (30) and (40), this implies $N_{eV} \approx N_{eI,hapl}$, and therefore it suffices to consider the haploid inbreeding effective size. We will rewrite the right hand side of (70) in a way that gives more insight, and in particular reveals that $N_{eIT,hapl}$ is at least of the same order as the sum of the local effective sizes N_{ei} . We divide the generation cycle from t to $t + 1$ into one migration phase and one reproduction phase, and split the time recursion (9) for standardized covariances accordingly into two steps

$$f_{tij} \rightarrow f_{t+1,ij}^{hinbr} \rightarrow f_{t+1,ij}. \tag{78}$$

In the first migration step the haploid inbreeding coefficients of the offspring generation $t + 1$ are computed as

$$f_{t+1,ij}^{hinbr} = 1 - \sum_{k,l} B_{ik} B_{jl} (1 - f_{tkl}) \tag{79}$$

when $N_i = N_{ei}$ is assumed, so that the last term of (10) in brackets equals 1. In the second step the standardized covariances

$$1 - f_{t+1,ij} = \begin{cases} \left(1 - \frac{1}{2N_{ei}} \right) (1 - f_{t+1,ii}^{hinbr}), & i = j, \\ 1 - f_{t+1,ij}^{hinbr}, & i \neq j, \end{cases} \tag{80}$$

are calculated from the haploid inbreeding coefficients (cf. (16) and (18)). We use (78)–(79) in order to split (70) into two terms,

$$\begin{aligned} \frac{1}{2N_{eIT,hapl}} &= \frac{\sum_{ij} w_i w_j \left(\sum_{k,l} B_{ik} B_{jl} f_{tkl} - f_{tij} \right)}{\sum_{ij} w_i w_j (1 - f_{tij})} + \sum_{ij} w'_{ij} \frac{f_{t+1,ij} - f_{t+1,ij}^{hinbr}}{1 - f_{tij}} \\ &= \sum_{ij} w'_{ij} \frac{f_{t+1,ij} - f_{t+1,ij}^{hinbr}}{1 - f_{tij}} \\ &= \sum_i \frac{w'_{ii}}{2N_{ei} - 1} \frac{1 - f_{t+1,ii}}{1 - f_{tii}} \\ &= \sum_i \frac{w'_{ii}}{2N_{ei} - 1} \left(1 - \frac{1}{2N'_{eVi}} \right), \end{aligned} \tag{81}$$

and then, in the second step, we invoke the assumption of reproductive weights, in the third step we insert (80), and in the last step we employ the definition of N'_{eVi} below (69). Since the first migration phase of (79) can be viewed as a time recursion for standardized covariances of an infinitely large population, this step will not change the average amount of genetic drift, as the second step above reveals.

It is clear from (81) that $N_{eIT,hapl}$ is at least as large as a weighted harmonic average of all $N_{ei} - 1/2$, multiplied a number ($= 1 / \sum_i w'_{ii}$) of order s . The global haploid inbreeding effective size is therefore always at least of the same order as the sum of all local effective sizes.

Under migration–drift equilibrium, it is easier to insert (77) directly into (70) to deduce that $N_{eIT,hapl}$ has the same asymptotic limit N_{eE} as $N_{eIT,dipl}$, in accordance with (41). It is also possible to deduce the speed at which both of these inbreeding effective sizes converge to N_{eE} . In order to see this, we recall from (68) and (70) that the (total) haploid and diploid inbreeding effective sizes are weighted harmonic averages of N_{eVi} and N'_{eVi} . In conjunction with (76) this proves (48), and in particular, that the (total) haploid and diploid inbreeding effective sizes both converge to the eigenvalue effective size, at the same speed at which the population system converges to migration–drift equilibrium.

Appendix E. Island model

In this appendix we will consider the island model in order to exemplify the theory of Sections 5, 6 and Appendix D. This model has the same forward and backward migration matrix $\mathbf{M} = \mathbf{B} = (B_{ik})_{i,k=1}^s$ with diagonal elements $B_{ii} = 1 - m(s - 1)/s$, and off-diagonal entries $B_{ik} = m/s$, where $m = Ms/(s - 1)$. For simplicity, we assume that the local effective and census sizes are the same ($N_{ei} = N_i = N/s$).

Due to the symmetry of the island model, there are only two possible values $f_{t,\text{same}}$ and $f_{t,\text{diff}}$ of the standardized covariances f_{ij} in (8), depending on whether i equals j or not. For uniform weights $w_i = 1/s$, the predicted coefficient of gene differentiation (22) takes the form

$$g_{ST,t} = \left(1 - \frac{1}{s}\right) \frac{f_{t,\text{same}} - f_{t,\text{diff}}}{1 - \frac{1}{s}f_{t,\text{same}} - \frac{s-1}{s}f_{t,\text{diff}}}, \tag{82}$$

and since $N_i = N_{ei}$, the time recursion in (9)–(10) simplifies to

$$\begin{pmatrix} 1 - f_{t+1,\text{same}} \\ 1 - f_{t+1,\text{diff}} \end{pmatrix} = \begin{pmatrix} \left(1 - \frac{1}{2N_{ei}}\right) (1 - \alpha) & \left(1 - \frac{1}{2N_{ei}}\right) \alpha \\ \beta & 1 - \beta \end{pmatrix} \times \begin{pmatrix} 1 - f_{t,\text{same}} \\ 1 - f_{t,\text{diff}} \end{pmatrix}, \tag{83}$$

where $\beta = m(2 - m)/s$ is the probability that two genes from different islands originate from the same island in the previous generation, and $\alpha = (s - 1)\beta$ is the probability that two genes from the same island descend from different islands. The closely related recursions for haploid ibd probabilities of gene pairs drawn without replacement, appear in Nei (1975), Li (1976) and Ryman and Leimar (2008).

Let $N'_{eV,\text{same}} = N'_{eV_{ii}}$ and $N'_{eV,\text{diff}} = N'_{eV_{ij}}$ be the local variance and covariance effective sizes defined below (69). After some calculations it follows from (82) and (83) that

$$\frac{1}{2N'_{eV,\text{same}}} = \frac{f_{t+1,\text{same}} - f_{t,\text{same}}}{1 - f_{t,\text{same}}} = \frac{1}{2N_{ei}} - \left(1 - \frac{1}{2N_{ei}}\right) (2m - m^2) \frac{g_{ST,t}}{1 - g_{ST,t}} \tag{84}$$

and

$$\frac{1}{2N'_{eV,\text{diff}}} = \frac{f_{t+1,\text{diff}} - f_{t,\text{diff}}}{1 - f_{t,\text{diff}}} = (2m - m^2) \frac{g_{ST,t}}{s - 1 + g_{ST,t}}. \tag{85}$$

The bias term due to migration in (71) simplifies to

$$\begin{aligned} 2 \times II &= 4m \frac{\mathbf{w}(\mathbf{I} - \mathbf{1}\mathbf{1}'/s)\bar{\mathbf{f}}_t \mathbf{w}'}{\sum_{i,j} w_i w_j (1 - f_{ij})} \\ &= 4m \frac{g_{ST,t}}{1 - g_{ST,t}}, \end{aligned} \tag{86}$$

for a local weighting scheme, where in the last step we used (82) and the formula for $\bar{\mathbf{f}}_t$ below (28). Insertion of (84) and (86) into (71) gives a local variance effective size

$$N_{eVi} = \frac{N_{ei}}{1 + (2m - m^2) \frac{g_{ST,t}}{1 - g_{ST,t}} + 2N_{ei}m^2 \frac{g_{ST,t}}{1 - g_{ST,t}}}. \tag{87}$$

This expression is very similar to formula (7) of Ryman et al. (2014), with $k = l = 1$. Eq. (87) is obtained by conditioning on allele frequencies of a founder generation, whereas the formula in Ryman

et al. (2014) was derived in a slightly different context; to find the expected value of the variance effective size estimator of Jorde and Ryman (2007).

For the inbreeding effective size we use the definition of N_{ei} below (67), in conjunction with (72) and (84) to deduce that the diploid total and (haploid or diploid) local inbreeding effective sizes equal

$$N_{eIT,\text{dip}} = N_{eIi} = \frac{N_{ei}}{1 - (2m - m^2)(2N_{ei} - 1) \frac{g_{ST,t}}{1 - g_{ST,t}}}. \tag{88}$$

It is the symmetry of the island model that makes the local and global inbreeding effective sizes the same, cf. (68). Comparing (87) and (88), we notice that (38) holds, and the difference between N_{eVi} and N_{eIi} increases with m and $g_{ST,t}$.

For the global variance effective size with uniform weights $w_i = 1/s$, we have $II = 0$. Plugging (84)–(85) into (71), we get a global variance effective and haploid inbreeding effective size

$$\begin{aligned} N_{eVT} = N_{eIT,\text{hap}} &= \frac{1}{w'_{\text{same}} N'_{eV,\text{same}} + w'_{\text{diff}} N'_{eV,\text{diff}}} \\ &= \frac{N_{ei}s}{1 - (1 - m)^2 g_{ST,t}}, \end{aligned} \tag{89}$$

with $w'_{\text{same}} = s(1 - f_{t,\text{same}})/[s(1 - f_{t,\text{same}}) + s(s - 1)(1 - f_{t,\text{diff}})]$ and $w'_{\text{diff}} = 1 - w'_{\text{same}}$ the weights assigned to the two terms in (84) and (85). We notice from (89) that $N_{eVT} = N_{eIT,\text{hap}}$ is at least as large as the total census size $N = N_{ei}s$, and apart from the term $(1 - m)^2$ of the denominator, (89) is identical to a well known expression of Wright (1943). Wright's formula has been generalized in different directions by Whitlock and Barton (1997) and Nunney (1999). Eq. (89) is also a special case of formula (69) in Hössjer and Ryman (2014) that was derived by other methods.

The largest eigenvalue λ of the matrix in (83) is a root of a quadratic characteristic equation. Plugging the solution of this equation into (36), we find that

$$\begin{aligned} N_{eE} &= \frac{1}{\left[\alpha + \beta + \frac{1}{2N_{ei}}(1 - \alpha)\right] \left\{1 - \sqrt{1 - \frac{2\beta}{N_{ei}[\alpha + \beta + \frac{1}{2N_{ei}}(1 - \alpha)]^2}}\right\}} \\ &\approx N_{ei}s \left(1 + \frac{s - 1}{s} \frac{1}{4N_{ei}m}\right), \end{aligned} \tag{90}$$

where in the last step we assumed that m is small and $N_{ei}m$ large, and obtained the same expression as for the nucleotide diversity effective size $N_{e\pi}$ of an island model (Nei and Takahata, 1993). We notice from (90) that N_{eE} is always larger than the total census size $N_{ei}s$. In order to find the value (51) of the predicted coefficient of gene differentiation at equilibrium g^{eq} , we need the right eigenvector $\mathbf{r} = (r_{\text{same}}, r_{\text{diff}})'$ of the matrix in (83) with eigenvalue λ . Using (51) and (90), it follows that

$$\begin{aligned} g^{\text{eq}} &= \frac{s - 1}{s} \cdot \frac{r_{\text{diff}} - r_{\text{same}}}{\frac{1}{s}r_{\text{same}} + \frac{s-1}{s}r_{\text{diff}}} \\ &= \frac{s - 1}{s} \cdot \frac{1}{\frac{\beta}{1 - \gamma} - \frac{1}{s}} \\ &\approx \frac{1}{\frac{s}{s-1} 4N_{ei}m + \frac{s-2}{s-1}}. \end{aligned} \tag{91}$$

This confirms the well known fact that the level of subpopulation differentiation at equilibrium decreases with the migration rate. The right hand side of (91) differs from a formula of Crow and Aoki

(1984) in that the denominator has $(s - 2)/(s - 1)$ rather than 1. The right hand side of (91) is even closer to several $g_{ST,t}$ formulas in Table 2 of Hössjer et al. (2013), for the reproduction scenarios of the island model considered in that paper.

In order to check the consistency of our formulas, we inserted the exact expression for g^{eq} in (91) into (88) and (89), and obtained an equilibrium value of $N_{eIT,dipl}$, N_{eli} and N_{eVT} that is identical to the exact formulas for N_{eE} in (36) and (90).

References

- Allendorf, F.W., Luikart, G., Aitken, S.N., 2013. *Conservation and the Genetics of Populations*, second ed. Wiley-Blackwell, Chichester, UK.
- Allendorf, F.W., Ryman, N., 2002. The role of genetics in population viability analysis. In: Bessinger, S.R., McCulloch, D.R. (Eds.), *Population Viability Analysis*. The University of Chicago Press, Chicago.
- Browning, B.L., Browning, S.R., 2011. A fast powerful method for detecting identity by descent. *Am. J. Hum. Genet.* 88, 173–182.
- Caballero, A., 1994. Developments in the prediction of effective population size. *Heredity* 73, 657–679.
- Charlesworth, B., 2009. Effective population size and patterns of molecular evolution and variation. *Nature Rev. Genet.* 10, 195–205.
- Cotterman, C.W., 1940. A calculus for statistic-genetics (Ph.D. thesis), Ohio State University.
- Cox, D.R., Miller, H.D., 1965. *The Theory of Stochastic Processes*. Chapman and Hall, London.
- Crow, J.F., 1954. Breeding structure of populations. II. Effective population number. In: *Statistics and Mathematics in Biology*. Iowas State Coll. Press, Ames, Iowa, pp. 543–556.
- Crow, J.F., Aoki, K., 1984. Group selection for a polygenic behavioral trait: estimating the degree of population subdivision. *Proc. Natl. Acad. Sci. USA* 81, 6073–6077.
- Crow, J.F., Kimura, M., 1970. *An Introduction to Population Genetics Theory*. The Blackburn Press, New Jersey, USA.
- Ewens, W.J., 1982. On the concept of effective population size. *Theor. Popul. Biol.* 21, 373–378.
- Ewens, W.J., 2004. *Mathematical Population Genetics I. Theoretical Introduction*, second ed. Springer, New York.
- Felsenstein, J., 1971. Inbreeding and variance effective numbers in populations with overlapping generations. *Genetics* 68, 581–597.
- Fisher, R.A., 1958. *The Genetical Theory of Natural Selection*, second ed. Dover, New York.
- Frankham, R., 2005. Genetics and extinction. *Biol. Cons.* 126, 131–140.
- Franklin, I.R., 1980. Evolutionary change in small populations. In: Soulé, M., Wilcox, B. (Eds.), *Conservation Biology: An Evolutionary-Ecological Perspective*. Sinauer Associates, Sunderland, Massachusetts, pp. 135–149.
- Harmon, L.J., Braude, S., 2010. Conservation of small populations: Effective population sizes, inbreeding and the 50/500 rule. In: Braude, S., Low, S.D. (Eds.), *An Introduction to Methods and Models in Ecology and Conservation Biology*. Princeton University Press, Princeton, New Jersey, USA, pp. 125–138. (chapter 12).
- Harris, R.B., Allendorf, F.W., 1989. Genetically effective population size of large mammals: an assessment of estimators. *Conserv. Biol.* 3, 181–191.
- Hill, W.G., 1981. Estimation of effective population size from data on linkage disequilibrium. *Genet. Res.* 38, 209–216.
- Hössjer, O., 2015. On the eigenvalue effective size in structured populations. *J. Math. Biol.* 73 (3), 595–646.
- Hössjer, O., Jorde, P.E., Ryman, N., 2013. Quasi equilibrium approximations of the fixation index under neutrality: The finite and infinite island models. *Theor. Popul. Biol.* 84, 9–24.
- Hössjer, O., Olsson, F., Laikre, L., Ryman, N., 2014. A new general analytical approach for modeling patterns of genetic differentiation and effective size of subdivided populations over time. *Math. Biosci.* 258, 113–133.
- Hössjer, O., Olsson, F., Laikre, L., Ryman, N., 2015. Metapopulation inbreeding dynamics, effective size and subpopulation differentiation - a general analytical approach for diploid organisms. *Theor. Popul. Biol.* 102, 40–59.
- Hössjer, O., Ryman, N., 2014. Quasi equilibrium, variance effective population size and fixation index for models with spatial structure. *J. Math. Biol.* 69 (5), 1057–1128.
- Jamieson, I.G., Allendorf, F.W., 2012. How does the 50/500 rule apply to MVPs? *Trends Ecol. Evol.* 27, 578–584.
- Jorde, P., Ryman, N., 2007. Unbiased estimator for genetic drift and effective population size. *Genetics* 177, 927–935.
- Kimura, M., 1953. 'Stepping stone' model of population. *Ann. Rep. Nat. Inst. Genet. Japan* 3, 62–63.
- Laikre, L., Olsson, F., Jansson, E., Hössjer, O., Ryman, N., 2016. Metapopulation effective size and conservation genetic goals for the Fennoscandic wolf population. In: *Heredity*. <http://dx.doi.org/10.1038/hdy.2016.44>, (in press).
- Lande, R., Barrowclough, G.F., 1987. Effective population size, genetic variation, and their use in population management. In: Soulé, M.E. (Ed.), *Viable Populations for Conservation*. Cambridge University Press, Cambridge, United Kingdom, pp. 87–124.
- Leutenegger, A., Prum, B., Genin, E., et al., 2003. Estimation of the inbreeding coefficient through use of genomic data. *Am. J. Hum. Genet.* 73, 516–523.
- Li, W.-H., 1976. Effect of migration on genetic distance. *Am. Nat.* 110, 841–847.
- Luikart, G., Ryman, N., Tallmon, D.A., Schwartz, M.K., Allendorf, F., 2010. Estimation of census and effective population sizes: The increasing usefulness of DNA-based approaches. *Conserv. Genet.* 11, 355–373.
- Lynch, M., Conery, J., Burger, R., 1995. Mutation accumulation and extinction of natural populations. *Am. Nat.* 146, 489–518.
- Lynch, M., Lande, R., 1998. The critically effective size for a genetically secure population. *Animal Conserv.* 1, 70–72.
- Lynch, M., Ritland, K., 1999. Estimation of pairwise relatedness with molecular markers. *Genetics* 152, 1753–1766.
- Malécot, G., 1948. *Les mathématiques de l'hérédité*. Masson et Cie, Paris.
- Nagylaki, T., 1980. The strong migration limit in geographically structured populations. *J. Math. Biol.* 9, 101–114.
- Nei, M., 1973. Analysis of gene diversity in subdivided populations. *Proc. Nat. Acad. Sci. U.S.A.* 70, 3321–3323.
- Nei, M., 1975. *Molecular Population Genetics and Evolution*. North-Holland, New York.
- Nei, M., 1977. F-statistics and analysis of gene diversity in subdivided populations. *Ann. Hum. Genet.* 41, 225–233.
- Nei, M., Takahata, N., 1993. Effective population size, genetic diversity, and coalescence time in subdivided populations. *J. Mol. Evol.* 37, 240–244.
- Nunney, L., 1999. The effective size of a hierarchically structured population. *Evolution* 53, 1–10.
- Olsson, F., Laikre, L., Hössjer, O., Ryman, N., 2016. GESP: A computer program for modeling genetic effective population size, inbreeding, and divergence in substructured populations (under revision for Molecular Ecology Resource).
- Palstra, F.P., Ruzzante, D.E., 2008. Genetic estimates of contemporary effective population size: What can they tell us about the importance of genetic stochasticity for wild population performance? *Mol. Ecol.* 17, 3428–3447.
- Ryman, N., Allendorf, F.W., Jorde, P.E., Laikre, L., Hössjer, O., 2014. Samples from subdivided populations yield biased estimates of effective size that overestimate the rate of loss of genetic variation. *Mol. Ecol. Resour.* 14, 87–99.
- Ryman, N., Leimar, O., 2008. Effect of mutation on genetic differentiation among nonequilibrium populations. *Evolution* 62 (9), 2250–2259.
- Traill, L.W., Brook, B.W., Frankham, R.R., Bradshaw, C.J.A., 2010. Pragmatic population viability targets in a rapidly changing world. *Biol. Cons.* 143, 28–34.
- van der AA, N.P., ter Morsche, H.G., Mattheij, R.R.M., 2007. Computation of eigenvalue and eigenvector derivatives for a general complex-valued eigensystem. *Electron. J. Linear Algebra* 16, 300–314.
- Wang, J.L., 2005. Estimation of effective population sizes from data on genetic markers. *Phil. Trans. R. Soc. B* 360, 1395–1409.
- Wang, J.L., Caballero, A., 1999. Developments in predicting the effective size of subdivided populations. *Heredity* 82, 212–226.
- Waples, R.S., 2002. Definition and estimation of effective population size in the conservation of endangered species. In: Bessinger, S.R., McCulloch, D.R. (Eds.), *Populations Viability Analysis*. The University of Chicago Press, Chicago.
- Waples, R.S., 2006. A bias correction for estimate of effective population size based on linkage disequilibrium at unlinked gene loci. *Conserv. Genet.* 7, 167–184.
- Waples, R.S., 2010. Spatial-temporal stratifications in natural populations and how they affect understanding and estimation of effective population size. *Mol. Ecol. Resour.* 10, 785–796.
- Waples, R.S., Do, C., 2010. Linkage disequilibrium estimates of contemporary N_e using highly variable genetic markers: a largely untapped resource for applied conservation and evolution. *Evol. Appl.* 3, 244–262.
- Waples, R.S., England, P.R., 2011. Estimating contemporary effective population size on the basis of linkage disequilibrium in the face of migration. *Genetics* 189, 633–644.
- Weiss, G.H., Kimura, M., 1965. A mathematical analysis of the stepping stone model of genetic correlation. *J. Appl. Probab.* 2, 129–149.
- Whitlock, M.C., Barton, N.H., 1997. The effective size of a subdivided population. *Genetics* 146, 427–441.
- Wright, S., 1922. Coefficients of inbreeding and relationship. *Am. Nat.* 56, 330–338.
- Wright, S., 1931. Evolution in Mendelian populations. *Genetics* 16, 97–159.
- Wright, S., 1938. Size of population and breeding structure in relation to evolution. *Science* 87, 430–431.
- Wright, S., 1943. Isolation by distance. *Genetics* 28 (2), 114–138.
- Wright, S., 1951. The general structure of populations. *Ann. Eugenics* 15, 323–354.