Isolation-By-Distance-and-Time in a Stepping-Stone model

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Abstract

With the great advances in ancient DNA extraction, population genetics data are now made of geographically separated individuals from both present and ancient times. However, population genetics theory about the joint effect of space and time has not been thoroughly studied. Based on the classical stepping-stone model, we develop the theory of Isolation by Distance and Time. We derive the correlation of allele frequencies between demes in the case where ancient samples are present in the data, and investigate the impact of edge effects with forward-in-time simulations. We also derive results about coalescent times in circular/toroidal models. As one of the most common way to investigate population structure is to apply principal component analysis, we evaluate the impact of this theory on plots of principal components. Our results demonstrate that time between samples is a non-negligible factor that requires new attention in population genetics.

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1 Introduction

Geography plays a central role in the pattern of genetic differentiation within a species. Seminal work on describing the evolution of continuous populations was done by Wright and Malécot. They studied genetic differentiation and inbreeding in continuously distributed population (Wright, 1943; Malécot, 1948). The resulting idea is that, under the assumption of local dispersion, genetic differentiation accumulates with distance. This pattern of genetic structure is called Isolation–By–Distance (IBD), which is detected by computing measures of differentiation such as F_{ST} (Wright, 1943; Nei, 1973; Weir and Cockerham, 1984), or correlation coefficients (Malécot, 1955; Kimura and Weiss, 1964). Understanding the effect of geographic distance on population structure is an important task for population geneticist, as it is a source of neutral genetic variation (Slatkin, 1985; Rousset, 1997). Furthermore, IBD has been observed in humans and many other species (Sharbel et al., 2000; Castric and Bernatchez, 2003; Ramachandran et al., 2005; Hellberg, 2009; Karakachoff et al., 2015).

The role of geography in neutral genetic variation has been widely studied partly because of the existence of many population genetic studies of individuals living at the present time and sampled in different locations. Because of the development of methods for sequencing DNA from fossils, genomes of individuals alive at previous times are now available to bring new information about the evolutionary processes that affected a species in the past. Since the first studies of ancient DNA (aDNA) three decades ago (Higuchi et al., 1984; Pääbo, 1985), techniques to retrieve DNA molecules from ancient bones have tremendously developed (Pääbo et al., 2004).

In modern evolutionary biology, the similarity of differentiation in space and time is acknowledged (Depaulis et al., 2009; Andreello et al., 2011; Teacher et al., 2011). Theoretical developments predict the effect of time on F_{ST} and related quantities (Skoglund et al., 2014). Epperson (2000) studied patterns of isolation by distance and time in ecology by using stochastic spatial time series and Identity by descent probabilities. However such theoretical studies remain scarce.

The effect of separation in time can be studied using classical statistical methods in population genetics, such as principal component analysis (PCA) (Patterson et al., 2006). PCA is widely used to determine relatedness between individuals, and is a convenient way to represent geographic patterns (Novembre et al., 2008). But PCA can also capture the differentiation between ancient and modern samples: the percentage of variance explained by time can be expressed on the same scale as the percentage of variance

57 explained by geography (Skoglund et al., 2014). Unfortunately, PCA does
 58 not give a complete picture of how differentiation quantities such as F_{st} and
 59 correlations of allele frequencies evolve in time and space.

60 In this article we generalize the theory of IBD to allow for difference
 61 in the times at which different individuals are sampled. We call this the
 62 theory of isolation by distance and time (IBDT). We base our work on the
 63 stepping-stone model of Kimura (1953) and add to the theoretical results
 64 known for this model (Kimura and Weiss, 1964; Weiss and Kimura, 1965;
 65 Maruyama, 1971a; Nagylaki, 1983; Cox et al., 2002; De and Durrett, 2007).
 66 We start by briefly reviewing the original results for the infinite stepping-
 67 stone model at equilibrium and the decay of correlation of allele frequencies
 68 with distance. Then, we extend the original work to derive the correlation
 69 between individuals separated by distance and time. We perform simulations
 70 that show the validity of the analytic results, even in the case of a finite
 71 number of populations where some demes are subject to edge effect. We also
 72 derive the expected coalescence times between samples separated by time
 73 and space in circular and toroidal models (Slatkin, 1991, 1993). Finally we
 74 consider the consequences of IBDT on PCA in the common case of a dataset
 75 made of a large proportion genomes from present-day individuals and few
 76 ancient genomes.

77 2 The stepping-stone model

78 The stepping-stone model describes the distribution of allele frequencies in
 79 an infinite set of demes in different locations of the space represented by
 80 Cartesian coordinates. We start by describing the 1-Dimensional case. Let
 81 $p(k)$ be the frequency of one allele at a bi-allelic locus in population k and
 82 $\bar{p}$ be the overall allele frequency. In each generation, $p(k)$ is updated with
 83 the following three steps (Crow et al., 1970):

- 84 • Exchange a proportion m_i of migrants with demes at a distance i .
- 85 • Exchange a proportion m_∞ of migrants with a deme that has fixed
 86 allele frequency $\bar{p}$. The meaning of this step is discussed later.
- 87 • Sample gametes of the next generation in the population.

88 In the case considered by Kimura and Weiss (1964), migrants are ex-
 89 changed only between neighboring locations in the first step, so that $m_i =$
 90 $0, i > 1$. The second step consists of exchanges of migrants with an external
 91 population at rate m_∞ . This event is equivalent to reversible mutations

occurring. The formulation of the model states that every locus is bi-allelic, and the number of loci is fixed. As a consequence, the mutation model is a reversible mutation model with probability m_∞ , and $m_i \gg m_\infty$. Random sampling of step 3 is represented by a random change in the allele frequency $\epsilon(k)$, with $E[\epsilon(k)] = 0$, and $E[\epsilon(k)^2] = p(k)(1 - p(k))/2N_e$, where N_e is the effective population size of a deme (Wright, 1940; Kimura and Crow, 1963).

Our interest is in the changes in allele frequency in one generation. We consider $\tilde{p}(k) = \bar{p} - p(k)$, the deviation from the average frequency. Given these three steps,

$$\tilde{p}'(k) = (1 - \sum_{i=1}^{\infty} m_i - m_\infty) \tilde{p}(k) + \frac{m_1}{2} (\tilde{p}(k-1) + \tilde{p}(k+1)) + \frac{m_2}{2} (\tilde{p}(k-2) + \tilde{p}(k+2)) + \dots + \epsilon(k). \quad (1)$$

To simplify the notation, we define the operators S and L ,

$$S\tilde{p}(k) = \tilde{p}(k+1), S^{-1}\tilde{p}(k) = \tilde{p}(k-1), \quad (2)$$

$$L = (1 - \sum_{i=1}^{\infty} m_i - m_\infty) S^0 + \sum_{i=1}^{\infty} \frac{m_i}{2} (S^i + S^{-i}), \quad (3)$$

so that,

$$\tilde{p}'(k) = L\tilde{p}(k) + \epsilon(k). \quad (4)$$

The quantity of interest in this model is the correlation of allele frequencies between two demes at locations k_1 and k_2 . Let $r(k)$ be the correlation coefficient of allele frequencies between populations that are k steps apart. Assuming equilibrium, we have

$$r(k) = \frac{\rho(k)}{\rho(0)} = \frac{E[\tilde{p}(k_1)\tilde{p}(k_2)]}{\rho(0)} = \frac{E[L\tilde{p}(k_1)L\tilde{p}(k_2)]}{\rho(0)}, \quad (5)$$

where $\rho(k)$ is the covariance in frequencies in demes k steps apart. The mathematical treatment of equation (5) by Weiss and Kimura (1965) using the spectral representation of a correlation (Doob, 1953) gives the general formula

$$r(k) = \frac{C}{2\pi} \int_0^{2\pi} \frac{\cos(k\theta)d\theta}{1 - [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^2}, \quad (6)$$

where C is the normalizing constant.

Equation (6) can be approximated by an exponential function of k :

$$r(k) = e^{-\sqrt{\frac{2m_\infty}{m_1}}k}. \quad (7)$$

114 This simple formula conveys the important idea that in one dimension, the
 115 correlation of allele frequencies between populations decays exponentially
 116 with distance. In the 2-Dimensional and 3-Dimensional cases, the cor-
 117 relation function is more difficult to approximate. Using modified Bessel
 118 function, it is shown that correlation at a given distance is lower in these
 119 cases than in the 1-Dimensional case (Weiss and Kimura, 1965).

120 3 Isolation-by-Distance-and-Time

121 3.1 1-Dimensional case

122 We are here interested in the case where genetic samples are collected from
 123 demes that are in different locations and at different times (measured in
 124 generations). Let $\rho(k, t)$ be the covariance between allele frequencies of two
 125 demes separated by k steps and t generations. We denote the coordinates of
 126 these demes by (k_1, t_1) and (k_2, t_2) , and the deviations in allele frequencies
 127 $\tilde{p}(k_1)^{(t_1)}$ and $\tilde{p}(k_2)^{(t_2)}$. Since we assume the distribution of allele frequencies
 128 is stationary in both time (equilibrium distribution) and space (all migration
 129 rates are equal), we can consider these coordinates to be $(0, 0)$ and (k, t) with
 130 no loss of generality. Following previous notation

$$\rho(k, t) = E[\tilde{p}(k_1)^{(t_1)} \tilde{p}(k_2)^{(t_2)}] = E[\tilde{p}(k)^{(t)} \tilde{p}(0)^{(0)}]. \quad (8)$$

131 To characterize the evolution of the covariance between allele frequencies
 132 with respect to time t , we iteratively apply the operator L defined in equation
 133 (3). This operation describes the potential trajectories of an allele, and
 134 results in a quantity similar to a propagator. This process leads to

$$\rho(k, t) = L^t \rho(k) \quad (9)$$

135 with $\rho(k) = \rho(k, 0)$ (see Appendix A).

136 Let $r(k, t)$ be the correlation between allele frequencies of two demes
 137 separated by k steps and t generations, equations (5) and (9), combined
 138 with the general formula of equation (6) gives

$$r(k, t) = \frac{C}{2\pi} \int_0^{2\pi} \frac{[\sum_{i=0}^{\infty} m_i \cos(i\theta)]^t \cos(k\theta) d\theta}{1 - [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^2}. \quad (10)$$

139 and the constant C is set such that $r(0, 0) = 1$ (Appendix B).

140 This equation reduces to

$$r(k, t) = \frac{C}{2\pi} \int_0^{2\pi} \frac{[1 - m_1 - m_{\infty} + m_1 \cos(\theta)]^t \cos(k\theta) d\theta}{1 - (1 - m_1 - m_{\infty} + m_1 \cos(\theta))^2} \quad (11)$$

141 in the standard stepping-stone model, where demes only exchange migrants
142 with their closest neighbors at rate $m_1/2$. An exact formula for this integral
143 can be calculated and is notable for its size and lack of utility (Appendix
144 C).

145 One noteworthy feature of equation (10) is that the decay of the cor-
146 relation with time is not affected by the effective population size N_e . This
147 result is different from what is expected for an isolated population: the level
148 of differentiation as a function of the number of generations separating two
149 samples is larger when the effective population size is small, reflecting the
150 increased magnitude of genetic drift. However, in the particular case of an
151 equilibrium stepping-stone model, the covariance of allele frequencies be-
152 tween the demes is not a function of the effective population size, a result
153 already known in the spatial context (see equation (7)) (Kimura and Weiss,
154 1964). This result becomes clear when considered in terms of coalescence
155 times. Between the time the first and second samples are taken, the trajec-
156 tory of the first sample depends only on the migration process. There is no
157 possibility of coalescence.

158 3.2 Two dimensions and more.

159 So far, we have focused on the 1-Dimensional case for the sake of simplicity.
160 However, it is important to investigate the decay in higher dimensions as it
161 is common in practice to have samples taken from a 2-Dimensional or even
162 3-Dimensional habitat. The general formula for the correlation in higher
163 dimensions can be obtained with no more theoretical development. In their
164 work on the stepping-stone model, Kimura and Weiss derived a general for-
165 mula for the correlation that can be extended to any number of dimensions.
166 In their work they only gave approximations for 1, 2 or 3 dimensions as these
167 are the practical cases. Using general formula (3.11) of Weiss and Kimura
168 (1965), we can write the correlation 10 in 2 dimensions

$$r(k_1, k_2, t) = \frac{C_2}{(2\pi)^2} \int_0^{2\pi} \int_0^{2\pi} \frac{[\sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} m_{i_1 i_2} \cos(i_1 \theta_1) \cos(i_2 \theta_2)]^t \cos(k_1 \theta_1) \cos(k_2 \theta_2) d\theta_1 d\theta_2}{1 - (\sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} m_{i_1 i_2} \cos(i_1 \theta_1) \cos(i_2 \theta_2))^2}. \quad (12)$$

169 The generalization to obtain the correlation in n dimensions is straight-
170 forward (Appendix D).

171 We perform a numerical integration of equation (12) to investigate the
172 decay of correlation with distance and time in one dimension and higher.
173 Correlation decreases as a function of distance and time in 1, 2 and 3 di-
174 mensional models (Figure 1). In addition, for equal values of the migration

175 and mutation rates the correlation decrease is much larger with respect to
176 time and geography in higher dimension models, consistently with previous
177 results (Maruyama, 1970a, 1971a). Numerical integration is done using the
178 *R* package *cubature*.

179 3.3 Simulations in one dimension and two dimensions.

180 When considering realistic examples, a finite number of demes is present in
181 the data. As a consequence, correlation patterns are affected by the prox-
182 imity of the edge of the sampling scheme (Maruyama, 1970b). Another
183 effect of the finite number of demes is that the overall allele frequency can
184 drift away from the theoretical allele frequency. An alternative is to con-
185 sider a finite, non-circular model, and to deal with edge issues independently
186 (Felsenstein, 2015). To investigate to which extent the analytic theory de-
187 veloped in the previous section is valid in a finite stepping-stone model with
188 temporal sampling, we perform simulations.

189 Backward in time simulation software such as *ms* (Hudson, 2002), or
190 *fastsimcoal* (Excoffier and Foll, 2011), are usually used to investigate IBD in
191 a stepping-stone models (Novembre et al., 2008). Temporal sampling can
192 be investigated in such model by simulating gene trees where lineages from
193 isolated demes are joined to the stepping-stone demes at a chosen time in
194 the past (Skoglund et al., 2014). Mutations are then randomly placed on the
195 gene tree. Such a simulation is needed to understand the influence of time
196 and distance on genetic differentiation, but does not precisely reproduce
197 the process of the above model which assumes reversible mutation rather
198 than the infinite site model. The infinite site model does not have a true
199 equilibrium for any one site, only a pseudo-equilibrium.

200 We wrote a C program that performs forward in time simulations. The
201 simulation program precisely follows the model presented in the previous
202 section. At the initial time, the allele frequencies in all the demes are equal
203 to the allele frequencies in the outside infinite-sized population. Then the
204 program runs for a large number of generations until the stationary distri-
205 bution of the allele frequencies is reached.

206 In the 1-Dimensional case, we simulate 100 demes. For the 2-Dimensional
207 case, we simulate a total of 2500 demes on a 50×50 grid. We assume all
208 the demes have the same effective population size. We sample the allele
209 frequencies at several times in the past. Correlation between demes fit very
210 closely the theory of equations (11) and (12) provided that demes are taken
211 sufficiently far away from the edge of the grid (Figure 2). The edge effect
212 directly increases the correlation between demes, and is present when com-

paring present and ancient samples. In both 1 and 2 dimensions, the edge effect disappears in the simulations (Figure 3). As predicted by Maruyama, the edge effect is less strong with lower migration rates.

4 Coalescence times

4.1 Coalescence times in one dimension

Coalescence times in a stepping-stone model can be derived under some assumptions. In particular, we consider a case with migration only between neighboring demes and low mutation rate. Expected coalescence times between genes that are in different demes is a function of the locations of these demes. These coalescence times are of interest because they closely related to F_{ST} and coefficients of identity-by-descent (Slatkin, 1991). Under the assumption of a circular 1-Dimensional stepping-stone model with n_d demes, two genes A_1 and A_2 have an expected coalescence time

$$E[T_{A_1 A_2}] = 2N_e n_d + (n_d - k) \frac{k}{2m}, \quad (13)$$

where N_e is the effective population size per deme, m the migration rate between neighboring demes (previously m_1), and k is the distance between the two demes (Slatkin, 1991). Considering a circular arrangement of the demes makes the analysis simpler, as only the distance between the demes matters, and there are no edge effects. In addition it has been shown that linear/planar and circular/toroidal stepping stone models are very similar when considering population away from the edges (Maruyama, 1971a,b). To study a case similar to the infinite stepping-stone model, we assume n_d is large.

We extend the previous theoretical result in the case where two genes are sampled at different times. Let us assume that the sampled genes are in population k_1 and k_2 . The number of generations between the two sampling times is $t = t_1 - t_2$, and we assume, with no loss of generality, that $t_1 = 0$ and $t_2 = t$ generations in the past. The coalescence process between these two genes can be divided in three phases. The first phase corresponds to the genealogy that traces back to the ancestor of the present gene, called $A_1^{(t)}$, at generation t . This ancestor is in population $k_1^{(t)}$. The two other parts correspond to the time until the coalescence event between $A_1^{(t)}$ and A_2 . They are respectively the time until the gene $A_1^{(t)}$ and A_2 are in the same deme, then the time to the common ancestor of these two genes. This

part has already been described, and the expectation is given in equation (13) (Slatkin, 1991). The expected coalescence time between A_1 and A_2 is then written

$$E[T_{A_1 A_2}] = t + E[T_{A_1^{(t)} A_2}]. \quad (14)$$

The variable $T_{A_1^{(t)} A_2}$ is the coalescence time between a random gene in the unknown population $k_1^{(t)}$ and a random gene in population k_2 . To represent the uncertainty about the population $k_1^{(t)}$, we derive the probability distribution of the position $k_1^{(t)}$ at time t , given position k_1 at time 0. Using this probability distribution we rewrite the expectation (14) as

$$E[T_{A_1 A_2}] = t + \sum_{x=0}^{n_d-1} E[T_{A_1^{(t)} A_2} | k_1^{(t)} = x] p(k_1^{(t)} = x). \quad (15)$$

To describe the probability distribution of position $k_1^{(t)}$ at time t given that a gene is in population k_1 at time 0, we consider a random walk with transition matrix

$$M = \begin{pmatrix} 1-m & \frac{m}{2} & 0 & \dots & 0 & \frac{m}{2} \\ \frac{m}{2} & 1-m & \frac{m}{2} & \dots & 0 & 0 \\ 0 & \frac{m}{2} & 1-m & \dots & 0 & 0 \\ \dots & \frac{m}{2} & 0 & 0 & \dots & \frac{m}{2} \\ \frac{m}{2} & 0 & 0 & \dots & \frac{m}{2} & 1-m \end{pmatrix}. \quad (16)$$

Using standard results about Markov chains (Ross et al., 1996), we know that the vector of probabilities for the position at time t , $P_{k_1^{(t)}}$ is expressed such as

$$P_{k_1^{(t)}} = M^t P_{k_1} \quad (17)$$

with P_{k_1} is the initial probability distribution of gene A_1 's position. The initial probability distribution is trivial and P_{k_1} is a vector of 0 with a 1 in the k_1^{th} entry. Exact formula for this matrix power can be obtained using tridiagonal matrix properties (Al-Hassan, 2012). However we can also express an approximation for the probability distribution of this process at time t . This random process is symmetrical, centered in k_1 , and using classical results about Brownian motion, has a variance proportional to t . We can approximate the probability distribution by a Normal distribution, and

$$P(k_1^{(t)} = x | k_1) = \mathcal{N}(x; k_1, mt). \quad (18)$$

269 The accuracy of this approximation can be verified with simulations using
 270 equation (17). The approximation is relevant for sufficiently large values
 271 of t , depending on the migration rate. The expected coalescence time in a
 272 1-Dimensional circle can then be written

$$E[T_{A_1 A_2}] = 2N_e n_d + t + \frac{1}{\sqrt{2\pi m t}} \int_0^{n_d-1} (n_d - |x - k_2|) \frac{|x - k_2|}{2m} e^{-\frac{(x-k_1)^2}{2mt}} dx. \quad (19)$$

273 Coalescence time between genes is an increasing function of distance
 274 and time between demes (Figure 4). Asymptotically, when t is large, the
 275 expected time for two genes to be in the same population can be approx-
 276 imated by a linear function of time between the samples (Figure 4). The
 277 right part of equation (19) is the integral of a product of a positive function
 278 that depends only on the distance between demes and a Gaussian kernel
 279 with variance mt . As the time gets large, relatively to m , the Gaussian ker-
 280 nel becomes flat, and the integral is almost constant (Figure 4). In practice,
 281 this implies that in a population at equilibrium, the geography does not
 282 matter when the sample is very old.

283 4.2 Coalescence times in two dimensions

284 In the case of a 2-Dimensional habitat with $n_{d1} \times n_{d2}$ demes, the expected
 285 coalescence time between two genes A_1 and A_2 is

$$E[T_{A_1 A_2}] = N_e n_{d1} n_{d2} + \frac{S(i, j)}{2N_e m}, \quad (20)$$

286 where $S(i, j)$ is a function of i and j , the number of demes between the two
 287 genes. We assume in this case that the migration in each direction is the
 288 same.

289 Using the same conditioning as in equation (14), we can derive the ex-
 290 pectation for the coalescence time of genes A_1 in population $\mathbf{k}_1$ and A_2 in
 291 population $\mathbf{k}_2$, t generations in the past. We have

$$E[T_{A_1 A_2}] = t + \sum_{x_1=0}^{n_{d1}-1} \sum_{x_2=0}^{n_{d2}-1} E[T_{A_1^{(t)} A_2} | \mathbf{k}_1^{(t)} = (x_1, x_2)] p(\mathbf{k}_1^{(t)} = (x_1, x_2)). \quad (21)$$

292 The probability distribution of the position of gene A_1 at time t , $\mathbf{k}_1^{(t)}$
 293 is known using the same random walk as in the 1-Dimensional case. The
 294 distribution can be approximated by a bivariate Normal distribution with

mean $\mathbf{k}_1$, and covariance matrix Σ , where Σ is diagonal with terms $mt/2$ in the diagonal. In the anisotropic case where migration rate would be different in the two dimensions, m_1 and m_2 , Σ would have m_1t and m_2t as diagonal terms. The evaluation of this function for samples separated in distance and time shows a similar pattern to the 1-Dimensional case (Figure 4). However for a same migration rate, the expected times for two genes to be in the same deme in the 2-Dimensional toroidal model are smaller than in the 1-Dimensional circular model. Then, if there is the same number of demes, with same effective population sizes, e.g. $n_d N_e = n_{d1} n_{d2} N_e$, the expected coalescence times are smaller in the 2-Dimensional case. This result is already known when comparing samples taken at the same generation and remains true when t is positive (Slatkin, 1993).

5 Connection with PCA

Because there is a close connection between PCA and coalescence times (McVean, 2009), our results are relevant to using PCA to compare ancient and modern samples. PCA is a useful way to represent the main axes of variation in the data and has proven to be a powerful tool to infer genetic relationships when applied to ancient DNA data (Skoglund et al., 2012; Haak et al., 2015).

5.1 Ancient samples are shrunk towards 0.

In population genetics, PCA is usually performed by computing the eigenvectors, and eigenvalues of the matrix of covariances in the genotypes of different individuals. Although there are other ways to compute principal components, this one is convenient in population genetics because the number of variables is usually larger by several orders of magnitude than the number of samples. The effect of differences in the sampling times can be evaluated using the dependence of the covariance matrix described by equation (10). To illustrate, consider a 2-Dimensional even repartition of 10×10 demes, and ancient samples taken in several randomly chosen demes at $t = 1000$ generations in the past (Figure 5A). By calculating the theoretical covariance matrix and its first two eigenvectors, we obtain the first two principal components that reproduce geography of the demes (Novembre et al., 2008; Engelhardt and Stephens, 2010). Figure (5B) shows that principal components mimic the geography of the present demes, but ancient demes are not superposed on the corresponding present-day sample

330 from the same deme. Instead, ancient samples move towards the center of
331 the first and second principal components.

332 Using 100 demes from a 1-Dimensional simulation described above, we
333 apply PCA to the allele frequencies at the 6000 simulated loci. To remove
334 the edge effect, we simulate 200 demes, and consider only the 100 demes in
335 the center. We also include allele frequencies from past generations for sev-
336 eral demes. PC1 shows the 1-Dimensional pattern of isolation-by-distance
337 as expected, and ancient samples are closer to 0 (Figure 6A). The distance
338 between the scores of ancient individuals and the center of the principal com-
339 ponent decreases as the sampling time increases. In practice, the true allele
340 frequencies are not known, and the covariance matrix is estimated on indi-
341 viduals. When working with sampled individuals instead of allele frequency,
342 the same pattern is still visible. A subsampling of 10 diploid individuals
343 for each deme at the present time, and 1 diploid individual for each ancient
344 deme shows the same shrinkage of PC scores for ancient individuals (Figure
345 6B).

346 When applying PCA on allele frequencies from the 2-Dimensional sim-
347 ulations, the time effect is visible on the first two components. We study
348 the case of a 10×10 grid, with no edge effects, and ancient samples taken
349 from 4 demes at different times in the past (Figure 6C). The first and sec-
350 ond principal components reproduce the geography of the samples, and the
351 ancient samples are moved towards the center of the plot (Figure 6D).

352 This shrinkage effect of time can be understood considering the shape of
353 the covariance function. The first and second principal components repre-
354 sent the 2-Dimensional Isolation-By-Distance pattern. This pattern causes
355 the covariance matrix at time $t = 0$ to have a "block Toeplitz with Toeplitz
356 blocks" form (Novembre and Stephens, 2008). However the pairwise co-
357 variance between present-day individuals ($t = 0$) and between ancient and
358 present-day individuals ($t > 0$) does not have the same shape (Figure 1).
359 Equation (10) implies that in a stepping-stone model the covariance as a
360 function of distance flattens when comparing present and ancient individu-
361 als. As a consequence, the scores of ancient samples are moved towards the
362 center of the principal components reproducing the local correlation pattern.
363 Thus ancient samples can cluster with present samples at different locations,
364 even in an equilibrium stepping-stone model.

365 5.2 One component for the time differentiation

366 Links between PCA and population genetics quantities, such as coalescence
367 times and F_{ST} have been studied (McVean, 2009; Duforet-Frebourg et al.,

2015; Baran and Halperin, 2015) and show that these values can be estimated from principal components. In the 2-population case, McVean (2009) showed that the distance between individuals on the appropriate principal component is approximately a linear function of the square root of the time, Δ , until the lineages of the two individuals are in the same deme. If there are ancient and present samples, they can be considered as two groups, and Δ is the time corresponding to the first two parts of the coalescence process between the lineages, described in the previous section. The time separating the individuals is a source of variance important enough to be reflected in the principal components (Skoglund et al., 2014). In this case, one component separates the two groups and the distance between groups is approximately proportional to $\sqrt{\Delta}$. In Appendix E, we compute the expectation of Δ if there are several present-day and one ancient individuals sampled.

We analyze the case with 50 contiguous populations sampled from a circular 1-Dimensional stepping-stone model with $n_d = 1000$. We assume $m_1 = 0.1$, and one deme is sampled in the past. We apply PCA by computing the eigenvectors of the individuals correlation matrix. The first principal component represents the IBD pattern between the present demes (Figure 7A). The second principal component corresponds to the differentiation between the ancient deme, and the present demes. The average distance on PC2 between the two groups (present and ancient) is an increasing function that can be approximated by a linear function of the square root of Δ (Figure 7B).

6 Conclusions and discussion

We have generalized the Kimura-Weiss theory of a stepping-stone model to the case where samples are taken at different times, a theory we call Isolation-by distance-and-time (IBDT). The correlation between individuals decreases as a function of both geographic distance and time. This result is accentuated in higher dimensions. When considering IBDT patterns, the edge effect applies when considering a linear model with a finite number of demes, similarly to the standard stepping-stone model. However simulations shows that in both 1 and 2 dimensions, this effect vanishes at a rate depending of the migration rate. We have also derived the expected coalescence times under the assumption of a circular, or toroidal model and low mutation rate. As the time between samples increases, the coalescence time between samples can be approximated by a linear function of time.

The connection between IBDT theory and PCA is of interest as it gives

insights about what to expect from the PC plots that compare ancient and present-day samples. When considering only principal components reproducing geography, scores of the ancient samples may not cluster with the population at the same location. Such a result can occur even in the case of a population at equilibrium in a stepping-stone model, with no complex demographic history. This behavior of PCA is important to note as it could result in the inference of a non-existent ancient demographic event. The genetic differentiation created by time can be observed on another principal component. An important question that remains is in which conditions the proportion of variance explained by time is larger than the proportion of variance explained by Geography. In this unlikely event, the first principal component would not reproduce geography of the samples but rather the time line of the samples.

The limitations of PCA to investigate population structure in a spatio-temporal context highlights the need for new theoretical developments to analyze population structure when present-day and ancient samples are combined. This is especially apparent when considering the complex demographic scenarios already inferred about the history of modern humans (Pickrell and Reich, 2014). Important theoretical work has already been done to test specific hypothesis (Durand et al., 2011; Loh et al., 2013). Another way to test different past demographic events is with intensive simulation procedures, such as Approximate Bayesian Computations (Beaumont et al., 2002; Csilléry et al., 2010). In this case, theoretical developments on mechanistic models such as the stepping-stone model are important to perform simulations efficiently (Baird and Santos, 2010).

We studied the classical stepping-stone model under the assumptions of a stationary distribution of the allele frequencies in both time and space. These assumptions are not valid in all cases. The time-stationary distribution is not reached when recent events such as range expansions occurred, causing asymmetry in the site frequency spectrum (Hallatschek et al., 2007; Peter and Slatkin, 2013). Spatial non-stationarity and anisotropy can occur when migration pattern is uneven between all populations, or migration is favored in one direction (Jay et al., 2013; Duforet-Frebourg and Blum, 2014; Petkova et al., 2014). The correlation of allele frequencies is then not only a function of space and time, but also of the locations of each deme in the habitat.

A stepping-stone model is not the only model to describe spatial population structure. As an alternative to discrete models, continuous models can also be considered to study evolutionary processes (Maruyama, 1972; Barton et al., 2002, 2010). Isolation-by-Distance-and-Time can be studied in a

445 continuous framework. In the same way, results about coalescence times in
446 a stepping-stone model can be connected to previous theory on coalescence
447 in a continuous population (Wilkins and Wakeley, 2002).

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Figure 1: Correlation as a function of distance between demes k steps appart in 1, 2 and 3-Dimensional models. The correlation is evaluated for different number of generations t between the demes. The migration and mutation rates are used for all models, and $m_1 = .01$ and $m_\infty = 4.10^{-4}$.

Figure 2: Comparison between theoretical results and simulations in the 2 dimensional case with $m_1 = .02$ and $m_\infty = 10^{-5}$. The solid lines represent the theory prediction. The dots represent the simulation results evaluated for demes at a distance 4, 10 or 16 from the edges. Since in the simulations several pairwise comparisons between demes have the same distance in space and time, we keep the median of these pairwise correlations.

Figure 3: Mean squared error between simulations and theory in 1 and 2 Dimensions as a function of the distance to the edge. The error is evaluated for $m_{\infty} = 10^{-5}$ and $m_1 = .01, .005, .001, .0005$.

Figure 4: Top row: Expected time for two genes to be in a same deme in a 1-Dimensional circular stepping-stone model with $N_e = 100$, $m = .01$, and $n_d = 51$ demes. Bottom row: Expected time for two genes to be in a same deme in a 2-Dimensional toroidal stepping-stone model with $N_e = 100$, $m = .01$, and $n_d = 51 \times 51$ demes. Left column: Expected times as a function of the time between the samples. Colors indicate the geographic distance between samples. Right column: Expected times as a function of geographic distance between the samples. Colors indicate the time between samples. Sampling consists in 45 time points evenly separated by 50 generations.

Figure 5: Panel A. Sampling scheme of a 10×10 grid of demes. Brown triangles represent demes where ancient individuals are sampled 1000 generations in the past. Panel B. First 2 eigenvectors of the covariance matrix between populations of Panel A. Parameters used are $m_1 = .01$ and $m_\infty = 10^{-5}$. Color code is the same as in Panel A. Brown arrows start from the position of the present deme where an ancient sample is taken, and end where the ancient sample is projected on the principal components.

Figure 6: Panel A. First principal component for the 1-Dimensional simulation described above, with $m_1 = .01$ and $m_\infty = 4.10^{-5}$. PCA is performed on allele frequency data from each of the 100 demes, and ancient allele frequencies are taken in 5 populations at 8 times in the past. Panel B. First principal component for the 1-Dimensional simulation described above. In each deme, 10 diploid individuals are sampled at the present time. One diploid individual is sampled in 5 demes at 8 times in the past. Panel C. Sampling scheme of a 10×10 grid of populations. Demes marked by a triangle are demes where ancient individuals were sampled. Panel D. plot of $PC1$ and $PC2$ for the 2-Dimensional simulation with $m_1 = .001$ and $m_\infty = 10^{-5}$. Ancient samples are taken at different times in the past for 4 demes.

Figure 7: Panel A. Principal components for a 1-Dimensional stepping-stone with 50 present demes, and 1 ancient deme. The PCA is performed several times, with an ancient deme sampled at different times. Panel B. Average distance between present demes and ancient deme on $PC2$ as a function of $\sqrt{\Delta}$

450 Appendix A

451 Using the notations in Weiss and Kimura (1965), we calculate the covariance
452 of the allele frequencies $\rho(k)$ between two populations that are spatially
453 separated by k units of distance. This quantity is defined by

$$\rho(k) = E[\tilde{p}(0)\tilde{p}(k)]. \quad (22)$$

454 In the case where the demes are also separated by t units of time, we define

$$\rho(k, t) = E[\tilde{p}(0)^{(0)}\tilde{p}(k)^{(t)}]. \quad (23)$$

455 and in the particular case of $t = 1$,

456

$$\begin{aligned} \rho(k, 1) &= E[\tilde{p}(k)^{(1)}\tilde{p}(0)^{(0)}] \\ &= E[\tilde{p}(k)'\tilde{p}(0)] \\ &= E[(L\tilde{p}(k) + \epsilon(k))\tilde{p}(0)] \\ 457 &= E[L\tilde{p}(k)\tilde{p}(0)] + E[L\epsilon(k)\tilde{p}(0)] \\ &= LE[\tilde{p}(k)\tilde{p}(0)] \\ &= L\rho(k). \end{aligned}$$

458 By induction, we show that for any value of $t > 0$

$$\rho(k, t) = L^t \rho(k). \quad (24)$$

459 Let's assume that for a time $t > 0$ equation (24) is true,

$$\begin{aligned} \rho(k, t+1) &= E[\tilde{p}(k)^{(t+1)}\tilde{p}(0)^{(0)}] \\ &= E[(L\tilde{p}(k)^{(t)} + \epsilon(k)^{(t)})\tilde{p}(0)] \\ &= E[L\tilde{p}(k)^{(t)}\tilde{p}(0)] + E[L\epsilon(k)^{(t)}\tilde{p}(0)] \\ 460 &= LE[\tilde{p}(k)^{(t)}\tilde{p}(0)] \\ &= L\rho(k, t) \\ &= L^t \rho(k). \end{aligned}$$

461 Then to obtain the correlation of allele frequencies $r(k, t)$ between two
462 demes, we have $\rho(0, 0) = \rho(0)$ and

$$r(k, t) = \frac{\rho(k, t)}{\rho(0, 0)} = \frac{L^t \rho(k)}{\rho(0)} = L^t r(k). \quad (25)$$

Appendix B

We established in equation (11) that $r(k, t) = L^t r(k)$, and using the general expression in equation (6) we have,

$$\begin{aligned} r(k, t) &= L^t \frac{C}{2\pi} \int_0^{2\pi} \frac{\cos(k\theta) d\theta}{1 - [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^2} \\ &= \frac{C}{2\pi} \int_0^{2\pi} \frac{L^t \cos(k\theta) d\theta}{1 - [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^2}. \end{aligned}$$

It is now demonstrated that

$$L^t \cos(k\theta) = [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^t \cos(k\theta), \quad (26)$$

where for the convenience of the notation we denote $m_0 = (1 - m_{\infty} - \sum_{i=1}^{\infty} m_i)$. In the particular case of $t = 1$ we have

$$\begin{aligned} L \cos(k\theta) &= \sum_{i=0}^{\infty} \frac{m_i}{2} (S^{+i} \cos(k\theta) + S^{-i} \cos(k\theta)) \\ &= \sum_{i=0}^{\infty} \frac{m_i}{2} (\cos((k+i)\theta) + \cos((k-i)\theta)) \\ &= \sum_{i=0}^{\infty} \frac{m_i}{2} (2 \cos(i\theta) \cos(k\theta)) \\ &= [\sum_{i=0}^{\infty} m_i \cos(i\theta)] \cos(k\theta) \end{aligned}$$

Now assuming that formula (26) holds for any value $t > 0$, we have

$$\begin{aligned} L^{t+1} \cos(k\theta) &= L[L^t \cos(k\theta)] \\ &= L[\sum_{i_1=0}^{\infty} \cdots \sum_{i_t=0}^{\infty} m_{i_1} \cdots m_{i_t} \cos(i_1\theta) \cdots \cos(i_t\theta)] \cos(k\theta) \\ &= \sum_{i_{t+1}=0}^{\infty} [\sum_{i_1=0}^{\infty} \cdots \sum_{i_t=0}^{\infty} m_{i_1} \cdots m_{i_t} \cos(i_1\theta) \cdots \cos(i_t\theta)] \\ &\quad \times \frac{m_{i_{t+1}}}{2} (\cos((k+i_{t+1})\theta) + \cos((k-i_{t+1})\theta)) \\ &= \sum_{i_{t+1}=0}^{\infty} \sum_{i_1=0}^{\infty} \cdots \sum_{i_t=0}^{\infty} m_{i_1} \cdots m_{i_t} m_{i_{t+1}} \cos(i_1\theta) \cdots \cos(i_t\theta) \cos(i_{t+1}\theta) \cos(k\theta) \\ &= [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^{t+1} \cos(k\theta). \end{aligned}$$

We can conclude by induction that formula (26) is true for any positive t .

Then, using equation (26), a general formula for $r(k, t)$ can be expressed

$$r(k, t) = \frac{C}{2\pi} \int_0^{2\pi} \frac{[\sum_{i=0}^{\infty} m_i \cos(i\theta)]^t \cos(k\theta) d\theta}{1 - [\sum_{i=0}^{\infty} m_i \cos(i\theta)]^2}. \quad (27)$$

Constant C is set such that $r(0, 0) = 1$. We do not analytically investigate this constant, however details about the case $t = 0$ can be found in Weiss and Kimura (1965).

480 Appendix C

Let's assume the particular stepping-stone model: $\sum_{i=0}^{\infty} m_i \cos(i\theta) = 1 - m_1 - m_{\infty} + m_1 \cos(\theta)$. Now the correlation between 2 demes k steps apart and t generations is

$$r(k, t) = \frac{C}{2\pi} \int_0^{2\pi} \frac{[1 - m_1 - m_{\infty} + m_1 \cos(\theta)]^t \cos(k\theta) d\theta}{1 - [1 - m_1 - m_{\infty} + m_1 \cos(\theta)]^2}.$$

The fraction can be decomposed in two parts $r(k, t) = C/(2\pi)(A_1(k, t) + A_2(k, t))$ using partial fraction expansion, where

$$A_1(k, t) = \int_0^{2\pi} \frac{[1 - m_1 - m_{\infty} + m_1 \cos(\theta)]^t \cos(k\theta) d\theta}{1 - [1 - m_1 - m_{\infty} + m_1 \cos(\theta)]}$$

$$A_2(k, t) = \int_0^{2\pi} \frac{[1 - m_1 - m_{\infty} + m_1 \cos(\theta)]^t \cos(k\theta) d\theta}{1 + [1 - m_1 - m_{\infty} + m_1 \cos(\theta)]}$$

. Let $\alpha = (1 - m_1 - m_{\infty})/m_1$, we can expand A_1 and A_2 ,

$$A_1(k, t) = -m_1^{t-1} \sum_{i=0}^t \binom{t}{i} \alpha^{t-i} \int_0^{2\pi} \frac{\cos(\theta)^i \cos(k\theta) d\theta}{\alpha - \frac{1}{m_1} + \cos(\theta)},$$

$$A_2(k, t) = m_1^{t-1} \sum_{i=0}^t \binom{t}{i} \alpha^{t-i} \int_0^{2\pi} \frac{\cos(\theta)^i \cos(k\theta) d\theta}{\alpha + \frac{1}{m_1} + \cos(\theta)},$$

To get rid of the integral, we can use the fact that

$$\int_0^{2\pi} \frac{\cos^t(\theta) \cos(k\theta) d\theta}{x + \cos(\theta)} = \frac{1}{2^t} \sum_{i=0}^t a_i^{(t)} \int_0^{2\pi} \frac{\cos((k+i)\theta) + \cos((k-i)\theta) d\theta}{x + \cos(\theta)},$$

481 where

i	0	1	2	3	4	5	Sum
$a_i^{(1)}$	0	1					$2 \times 1 = 2$
$a_i^{(2)}$	2	0	1				$2 \times 1 + 2 = 4$
$a_i^{(3)}$	0	3	0	1			$2 \times (1 + 3) = 8$
$a_i^{(4)}$	6	0	4	0	1		16
$a_i^{(5)}$	0	10	0	5	0	1	32

482 and as given in Weiss and Kimura (1965)

$$\frac{1}{2\pi} \int_0^{2\pi} \frac{\cos(k\theta)d\theta}{x+\cos(\theta)} = \begin{cases} \frac{1}{\sqrt{x^2-1}}(\sqrt{x^2-1}-x)^n, & x > 1, \\ \frac{(-1)^{n+1}}{\sqrt{x^2-1}}(\sqrt{x^2-1}+x)^n, & x < -1. \end{cases}$$

This leads us to the expressions for A_1 and A_2 ,

$$\begin{aligned} A_1(k, t) &= -m_1^{t-1} \sum_{i=0}^t \binom{t}{i} \alpha^{t-i} \frac{1}{2^i} \sum_{j=1}^i \left\{ a_j^{(i)} \frac{(-1)^{k+j}}{\sqrt{(\alpha - \frac{1}{m_1})^2 - 1}} (\alpha - \frac{1}{m_1} + \sqrt{(\alpha - \frac{1}{m_1})^2 - 1})^{k+j} \right. \\ &\quad \left. a_j^{(i)} \frac{(-1)^{k-j}}{\sqrt{(\alpha - \frac{1}{m_1})^2 - 1}} (\alpha - \frac{1}{m_1} + \sqrt{(\alpha - \frac{1}{m_1})^2 - 1})^{k-j} \right\} \\ A_2(k, t) &= m_1^{t-1} \sum_{i=0}^t \binom{t}{i} \alpha^{t-i} \frac{1}{2^i} \sum_{j=1}^i \left\{ a_j^{(i)} \frac{1}{\sqrt{(\alpha + \frac{1}{m_1})^2 - 1}} (\sqrt{(\alpha + \frac{1}{m_1})^2 - 1} - (\alpha + \frac{1}{m_1}))^{k+j} \right. \\ &\quad \left. a_j^{(i)} \frac{1}{\sqrt{(\alpha + \frac{1}{m_1})^2 - 1}} (\sqrt{(\alpha + \frac{1}{m_1})^2 - 1} - (\alpha + \frac{1}{m_1}))^{k-j} \right\} \end{aligned}$$

489 Appendix D

The 2-Dimensional case of the analysis can be detailed by changing the operators L and S . We note the cartesian coordinates of each deme with the couple (i_1, i_2) , and we define the operators S_1 and S_2 such as

$$S_1\tilde{p}(i_1, i_2) = \tilde{p}(i_1 + 1, i_2) \text{ and } S_2\tilde{p}(i_1, i_2) = \tilde{p}(i_1, i_2 + 1).$$

The operator L in two dimensions becomes

$$L = (1 - \sum_{i_1} \sum_{i_2} m_{i_1 i_2} - m_\infty) \frac{(S_1^0 + S_2^0)}{2} + \sum_{i_1} \sum_{i_2} \frac{m_{i_1 i_2}}{4} (S_1^{i_1} + S_1^{-i_1})(S_2^{i_2} + S_2^{-i_2})$$

where $m_{i_1 i_2}$ is the migration rate between demes separated by i_1 and i_2 steps. The correlation in 2 dimensions can be written using the spectral decomposition and for two demes we have

$$r(k_1, k_2, 0) = \frac{C_2}{(2\pi)^2} \int_0^{2\pi} \int_0^{2\pi} \frac{\cos(k_1\theta_1)\cos(k_2\theta_2)d\theta_1d\theta_2}{1 - (\sum_{i_1, i_2=0}^{\infty} m_{i_1 i_2} \cos(i_1\theta_1)\cos(i_2\theta_2))^2}$$

for two populations that are separated by k_1 and k_2 steps at the same generation. Using the same trigonometric properties as in appendix B, we have

$$L^t \cos(k_1\theta_1)\cos(k_2\theta_2) = [\sum_{i_1} \sum_{i_2} (m_{i_1 i_2} \cos(i_1\theta_1)\cos(i_2\theta_2))]^t \cos(k_1\theta_1)\cos(k_2\theta_2)$$

and $m_{00} = (1 - \sum_{i_1} \sum_{i_2} m_{i_1 i_2} - m_\infty)$. As a consequence, the correlation of allele frequencies in 2 dimensions between two populations separated by k_1 and k_2 steps, and t generations is

$$r(k_1, k_2, t) = \frac{C_2}{(2\pi)^2} \int_0^{2\pi} \int_0^{2\pi} \frac{[\sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} m_{i_1 i_2} \cos(i_1\theta_1)\cos(i_2\theta_2)]^t \cos(k_1\theta_1)\cos(k_2\theta_2)d\theta_1d\theta_2}{1 - (\sum_{i_1=0}^{\infty} \sum_{i_2=0}^{\infty} m_{i_1 i_2} \cos(i_1\theta_1)\cos(i_2\theta_2))^2}.$$

To go further, and especially investigate the 3-Dimensional case that can be relevant in practice, it is possible to extend the calculations in n -dimensional models, where two populations are separated by t generations and a vector of steps $(k_1, \dots, k_n)$. Redefining the operators S and L , we can show that the correlation is

$$r(k_1, \dots, k_n, t) = \frac{C_n}{(2\pi)^n} \int_0^{2\pi} \dots \int_0^{2\pi} \frac{[\sum_{i_1, \dots, i_n=0}^{\infty} m_{i_1 \dots i_n} \cos(i_1\theta_1) \dots \cos(i_n\theta_n)]^t \cos(k_1\theta_1) \dots \cos(k_n\theta_n)d\theta_1 \dots d\theta_n}{1 - (\sum_{i_1, \dots, i_n=0}^{\infty} m_{i_1 \dots i_n} \cos(i_1\theta_1) \dots \cos(i_n\theta_n))^2}$$

490 Appendix E

491 We detail the case where two groups are present in the data, the present
492 demes and the ancient deme. The quantity Δ is the time for two genes in
493 different groups to be in the same group. In the case where there is one
494 ancient deme k_2 and one present deme k_1 , using equation (19) we have

$$\begin{aligned} E[\Delta|k_1] &= E[T_{A_1A_2}] - 2N_en_d \\ 495 &= t + \frac{1}{\sqrt{2\pi m_1 t}} \int_0^{n_d} (n_d - |x - k_2|) \frac{|x - k_2|}{2m_1} e^{-\frac{(x - k_1)^2}{2m_1 t}} dx. \end{aligned}$$

496 In the practical case we consider several present time demes $1 \dots n_p$,
497 and one ancient deme. The expectation of Δ has to be conditioned by the
498 probability that A_1 is in a given present population k_1 .

$$E[\Delta] = \sum_{i=1}^{n_p} p(k_1 = j) E[\Delta|k_1 = j]. \quad (28)$$

499 Since we consider a stepping-stone model where all the populations have
500 the same effective population size, we have $p(k_1 = j) = 1/n_p, j = 1 \dots n_p$.

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