Biallelic Mutation-Drift Diffusion in the Limit of Small Scaled Mutation Rates

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Abstract

The evolution of the allelic proportion $x$ of a biallelic locus subject to the forces of mutation and drift is investigated in a diffusion model, assuming small scaled mutation rates. The overall scaled mutation rate is parametrized with $\theta = (\mu_1 + \mu_0)N$ and the ratio of mutation rates with $\alpha = \mu_1/(\mu_1 + \mu_0) = 1 - \beta$. The equilibrium density of this process is beta with parameters $\alpha \theta$ and $\beta \theta$. Away from equilibrium, the transition density can be expanded into a series of modified Jacobi polynomials. If the parameters $\alpha$ or $\theta$ change, this eigenexpansion also has to change, such that modeling, e.g., growing or shrinking populations is cumbersome.—If the scaled mutation rates are small, i.e., $\theta \ll 1$, it may be assumed that polymorphism derives from mutations at the boundaries. A model, where the interior dynamics conform to the pure drift diffusion model and the mutations are entering from the boundaries is derived. In equilibrium, the density of the proportion of polymorphic alleles, i.e., $x$ within the polymorphic region $[1/N, 1 - 1/N]$, is inversely related to the distance from the origin at the boundaries and symmetric $\alpha \beta \theta (\frac{x}{1-x} + \frac{1}{1-x}) = \alpha \beta \theta x(1-x)$, while the mutation bias $\alpha$ influences the proportion of monomorphic alleles at 0 and 1. Analogous to the expansion with modified Jacobi polynomials, a series expansion of the transition density is derived, which is connected to Kimura’s well known solution of the pure drift model using Gegenbauer polynomials. Two temporal and two spatial regions are separated. The eigenvectors representing the spatial component within the polymorphic region depend neither on the on the scaled mutation rate $\theta$ nor on the mutation bias $\alpha$. Therefore parameter changes, e.g., growing or shrinking populations or changes in the mutation bias, can be modeled relatively easily, without the change of the eigenfunctions necessary for the series expansion with Jacobi polynomials. With time,
the series converges to the equilibrium solution.

**Keywords:** biallelic mutation-drift model, small scaled mutation rate, orthogonal polynomials, equilibrium density, transition density.

### 1. Introduction

In this manuscript, it is assumed that the proportion \( x \) in the population of the first allelic type of a biallelic locus is evolving independently according to a biallelic mutation drift model (e.g., Wright, 1931; Ewens, 2004; Griffiths and Spanò, 2010; Song and Steinrücken, 2012). In the diffusion limit, the biallelic mutation drift model is usually parametrized with the two parameters \( \theta_1 = \mu_1 N \) and \( \theta_0 = \mu_0 N \), where \( \mu_1 \) and \( \mu_0 \) are the mutation rates towards alleles one and zero, respectively, and \( N \) is the haploid effective population number or size. For small scaled mutation rates, polymorphism probably derives from a mutation at the boundaries and the analysis simplifies. The following reparametrization is then convenient: \( \alpha = \mu_1 / (\mu_1 + \mu_0) = 1 - \beta \) and \( \theta = \theta_1 + \theta_0 \). According to simulations partially published in Vogl and Clemente (2012) (see their Fig. 1, for a polymorphic sample), this simplification holds for \( 2 \theta_0 \theta_1 / (\theta_0 + \theta_0) < 0.02 \) or \( \alpha \beta \theta < 0.01 \). Note that this assumption of small scaled mutation rates was already discussed by Wright (1931) and underlies much of population genetic theory, e.g., the derivation of the Ewens-Watterson estimator of \( \theta \) (Ewens, 2004; Watterson, 1975) or Poisson Random Field approaches (e.g., Sawyer and Hartl, 1992; RoyChoudhury and Wakeley, 2010).

Assuming a single segregating mutation and thus, implicitly, small scaled mutation rates, alleles can be polarized into ancestral and derived with information from related species or populations (outgroup information). In the absence of selection and for constant \( N \), the density of the proportion of mutant polymorphic alleles \( x \) converges to be inversely related to the distance from the ancestral state, *i.e.*, proportional to \( 1/x \) or \( 1/(1-x) \), depending on the ancestral state (Wright, 1931). In equilibrium, equal amounts of mutant alleles originate from the two boundaries (Wright, 1931), such that the density of the proportion of polymorphic alleles becomes proportional to \( 1/x + 1/(1-x) = 1/(x(1-x)) \).
While the small scaled mutation rate assumption has been very important in population genetic theory, particularly with data analysis, only few attempts have been made to link the model with general mutation rates to one with small scaled mutation rates. Gutenkunst et al. (2009) present a model for the analysis of site frequency spectra that considers two parameter regions. Within the polymorphic region, i.e., between $1/N$ and $1 - 1/N$ allelic proportions evolve according to a selection, migration, and drift model. Mutations are considered as follows (Gutenkunst et al., 2009): “Because the diffusion equation [incorporating selection, migration, and drift] is linear, we can solve simultaneously for the evolution of all polymorphism by continually injecting $\phi$ density at low frequency in each population (at a rate proportional to the total mutation flux $\theta$), corresponding to novel mutations.” Mutations are assumed to only arise at the boundaries, presumably in equal proportions. The authors do not justify this assumption any further.—This model of mutations from only the boundaries is essentially the one considered in this article. In contrast to Gutenkunst et al. (2009), who use a grid based numerical approach for solving the diffusion equation, herein, changes in the mutation bias are allowed and orthogonal polynomials are used. The latter are exact, if assumptions are met, and offer a connection to other theoretical work.

Independently from Gutenkunst et al. (2009), Vogl and Clemente (2012) analyzed a Moran model of mutation, selection, and drift and motivated a simpler model with mutations only entering from the boundaries. This assumption was justified by the observation that in equilibrium each particle spends only a proportion of time in the polymorphic region of approximately $2\alpha\beta\theta \log(N)$, which is small unless $N$ is very large. With the diffusion model, however, the limit of the population size to infinity $N \to \infty$ is considered. This makes the above argument obsolete and necessitates a new justification, which will be provided herein.

**Outlook.** First, the general biallelic mutation and drift Moran model and the corresponding forward diffusion model will be reviewed, which can be solved using a series expansion of (modified) Jacobi polynomials (Griffiths and Spanò, 2010; Song and Steinrücken, 2012; Vogl, 2014). Then the assumption of small scaled mutation rates will be introduced, the modified Moran model with mutations only from the boundaries will be reviewed, and
the corresponding diffusion model will be derived. A dynamical system using orthogonal Gegenbauer polynomials will be motivated. This system converges to an equilibrium solution with time. This equilibrium density will be compared to the general equilibrium solution. Finally, an example involving a change in the mutation bias will be shown.

2. The General Mutation-Drift Model

2.1. Moran and Diffusion Models

Assume a population of $N$ haploid individuals; each may assume the state of zero or one, corresponding to the two arbitraritly labeled alleles. With the decoupled Moran model (Baake and Bialowons, 2008; Etheridge and Griffiths, 2009; Vogl and Clemente, 2012), either i) (mutation) at a rate of $\mu = \mu_0 + \mu_1$, a random individual $i$ is picked to mutate to type one with probability $\mu_1/\mu$ or to type zero with probability $\mu_0/\mu$; or ii) (genetic drift) at a rate of one, a random individual $i$ is replaced by another random individual $j$. Thus, the rate of change of the allelic proportion $x$ per unit time of the mean is caused by mutation

$$M_\delta x = \frac{1}{N^2} \theta(\alpha - x)N,$$

and that of the variance by genetic drift

$$V_\delta x = \frac{2}{N^2} x(1 - x)N^2.$$

Scaling space with $1/N$ and time with $1/N^2$ and taking the appropriate limits, the Kolmogorov forward (or Fokker-Planck) generator of the process becomes

$$L_f = \left( \frac{\partial^2}{\partial x^2} x(1 - x) \right) - \left( \frac{\partial}{\partial x} \theta(\alpha - x) \right).$$

The forward diffusion equation

$$\frac{\partial}{\partial t} \phi(x, t) = L_f \phi(x, t)$$

then describes the evolution of the probability of the allelic proportion $x$ forward in time $t$. This is the same temporal direction as the transitions in the Wright-Fisher and Moran models.
2.2. Modified Jacobi Polynomials

For the following, we will briefly recapitulate the theory of orthogonal polynomials; a more detailed review can be found in Vogl (2014).

On the interval \([0, 1]\) we are looking for solutions of the Kolmogorov forward equation

Substituting the function \(\phi(x, t) = \sum_{i=0}^{\infty} e^{-\lambda_i t} w(x) f_i(x)\) into the Kolmogorov forward equation, results in

\[
-\lambda_i w(x) f_i(x) = \left( \frac{d^2}{dx^2} x(1-x) w(x) f_i(x) \right) + \left( \frac{d}{dx} \theta(\alpha - x) w(x) f_i(x) \right),
\]

(5)

where \(i\) indexes the eigenvectors and \(w(x)\) is the weight function

\[
w^{(\alpha, \theta)}(x) = x^{\alpha-1}(1-x)^{\beta-1}.
\]

(6)

It can be shown that all eigenvectors are real and can be ordered such that \(\lambda_0 < \lambda_1 < \lambda_2 < \cdots < \lambda_i < \cdots \to \infty\). Corresponding to each eigenvalue \(\lambda_i\) is a unique (up to a normalization constant) eigenfunction \(f_i(x)\), which has exactly \(i\) zeros in the interval.

This solution of the Kolmogorov forward equation (5) can be algebraically transformed to a solution of the corresponding Kolmogorov backward equation

\[
-\lambda_i f_i(x) = \left( x(1-x) \frac{d^2}{dx^2} f_i(x) \right) + \left( \theta(\alpha - x) \frac{d}{dx} f_i(x) \right).
\]

(7)

This backward equation (7) is closely related to the differential function fulfilled by the classical Jacobi polynomials (Abramowitz and Stegun, 1970). Define the modified Jacobi polynomials (Song and Steinrücken, 2012)

\[
R_i^{(\theta, \alpha)}(x) = P_i^{(\beta \theta - 1, \alpha \theta - 1)}(2x-1),
\]

(8)

where \(P_i^{(\alpha, \beta)}(z)\) are the classical Jacobi polynomials (Abramowitz and Stegun, 1970). It can be shown that these modified Jacobi polynomials fulfil the backward equation (7) with the corresponding eigenvalues

\[
\lambda_i = i(i + \theta - 1).
\]

(9)

With the weight function \(w^{(\theta, \alpha)}(x)\), the modified Jacobi polynomials are orthogonal:

\[
\int_0^1 R_i^{(\theta, \alpha)}(x) R_j^{(\theta, \alpha)}(x) w^{(\theta, \alpha)}(x) dx = \delta_{i,j},
\]

(10)
where \( \delta_{i,j} \) denotes the Kronecker delta, i.e., \( \delta_{i,j} \) is zero for \( i \neq j \) and one for \( i = j \). The proportionality constant \( \Delta^{(\alpha, \theta)} \) is finite

\[
\Delta^{(\alpha, \theta)} = \frac{\Gamma(i + \alpha \theta) \Gamma(i + \beta \theta)}{(2i + \theta - 1) \Gamma(i + \theta - 1) \Gamma(i + 1)}.
\]

The set of \( R^{(\theta, \alpha)}_i(x) \) forms a basis of the Hilbert space \( L^2([0, 1]) \) with the weight function \( w^{(\theta, \alpha)}(x) \) (Song and Steinr"ucken, 2012).

For \( i \geq 1 \), the \( R^{(\theta, \alpha)}_i(x) \) satisfy the recurrence relation

\[
R^{(\theta, \alpha)}_{i+1}(x) = \frac{(i + 1)(i - 1 + \theta)}{(2i + \theta)(2i - 1 + \theta)} R^{(\theta, \alpha)}_i(x) \\
- \frac{\theta^2(\beta^2 - \alpha^2) - 2\theta(\beta - \alpha)}{2(2i + \theta)(2i - 2 + \theta)} R^{(\theta, \alpha)}_{i-1}(x),
\]

while \( R^{(\theta, \alpha)}_0(x) = 1 \) and \( R^{(\theta, \alpha)}_1(x) = \theta(x - \alpha) \) (Song and Steinr"ucken, 2012).

If \( \theta > 0 \), the forward equation has a stationary beta density proportional to the weight function:

\[
f(x \mid \theta, \alpha, \beta, t \to \infty) = \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(\beta \theta)} w^{(\theta, \alpha)}(x) R^{(\theta, \alpha)}_0(x) = \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(\beta \theta)} x^{\alpha \theta - 1}(1 - x)^{\beta \theta - 1} = \text{beta}(x \mid \alpha \theta, \beta \theta).
\]

The evolution of \( x \) forward in time is given by the expansion:

\[
f(x \mid \theta, \alpha, \beta, t) = w^{(\theta, \alpha)}(x) \left( c_0 + \sum_{i=1}^{\infty} e^{-i(i+\theta-1) t} c_i R^{(\theta, \alpha)}_i(x) \right).
\]

In practice, the expansion needs to be terminated at a finite \( n \). The constants \( c_i \) are determined such that the initial conditions are met, i.e., an initial probability density \( f(x) \), defined within the interval, is represented by the series expansion

\[
f(x) = w^{(\theta, \alpha)}(x) \left( c_0 + \sum_{i=1}^{n} c_i R^{(\theta, \alpha)}_i(x) \right).
\]

By minimizing the weighted least squares error function

\[
E(c_0, \ldots, c_n) = \int_0^1 w(x)^{-1} \left( f(x) - \sum_{i=0}^{n} c_i w(x)^{(\theta, \alpha)} R^{(\theta, \alpha)}_i(x) \right)^2 dx.
\]
the coefficients are determined to be

\[ c_i = \frac{1}{\Delta_i} \int_0^1 R_i^{(\theta, \alpha)}(x) f(x) \, dx. \]  

(17)

Often an initial density corresponding to a Dirac delta function at a point \( p \) in \([1/N, 1-1/N]\), \( f(x) = \delta(x - p) \), is considered (e.g., Kimura, 1955). Then the expansion becomes

\[ f(x | \theta, \alpha, p, t) = w^{(\theta, \alpha)}(x) \left( c_0 + \sum_{i=1}^{n} e^{-i(\theta-1)t} R_i^{(\theta, \alpha)}(x) \frac{R_i^{(\theta, \alpha)}(p)}{\Delta^{(\theta, \alpha)}_i} \right). \]  

(18)

This corresponds to formula (4.68) in Ewens (2004), where \( n \to \infty \) and the eigenfunctions are assumed to be normed, such that division by the proportionality constant \( \Delta^{(\theta, \alpha)}_i \) is unnecessary.

From the orthogonality relation (10) and \( R^{(\theta, \alpha)}_0(x) = 1 \), it can be deduced for all \( i \geq 1 \) and thus also for all times

\[ 0 = \int_0^1 R_i^{(\theta, \alpha)}(x) R_0^{(\theta, \alpha)}(x) w(x) \, dx = \int_0^1 R_i^{(\theta, \alpha)}(x) w^{(\theta, \alpha)}(x) \, dx. \]  

(19)

Therefore the probability mass over the whole interval \([0, 1]\) comes only from the equilibrium term, i.e., the beta density (13); all other terms \( R_i^{(\theta, \alpha)}(x) w^{(\theta, \alpha)}(x) \) with \( i \geq 1 \) shift this mass within the interval.

**Expression of the modified Jacobi polynomials as linear combinations of Beta densities.**

Note that a polynomial times a beta results in a weighted sum of beta densities. This can be made even more explicit by using the following representation of the modified Jacobi polynomials (compare Abramowitz and Stegun, 1970, 22.3.1)

\[ R_i^{(\theta, \alpha)}(x) = \sum_{m=0}^{i} \frac{(-1)^{i-m} \Gamma(i + \alpha \theta) \Gamma(i + \beta \theta)}{\Gamma(i - m + 1) \Gamma(m + \alpha \theta) \Gamma(m + 1) \Gamma(i - m + \beta \theta)} x^m (1-x)^{i-m} \]  

(20)

to obtain

\[ w_i^{(\theta, \alpha)}(x) R_i^{(\theta, \alpha)}(x) = \sum_{m=0}^{i} \frac{(-1)^{i-m} \Gamma(i + \alpha \theta) \Gamma(i + \beta \theta)}{\Gamma(i - m + 1) \Gamma(m + \alpha \theta) \Gamma(m + 1) \Gamma(i - m + \beta \theta)} x^m (1-x)^{i-m+\alpha \theta-1} \]  

\[ = \sum_{m=0}^{i} \frac{(-1)^{i-m} \Gamma(i + \alpha \theta) \Gamma(i + \beta \theta)}{\Gamma(i - m + 1) \Gamma(m + 1) \Gamma(i + \theta)} \text{beta}(x \mid m + \alpha \theta, i - m + \beta \theta). \]

(21)
2.2.1. Data: Likelihood, Joint and Posterior Densities, and the Marginal Distribution with Modified Jacobi Polynomials

While often a Dirac delta starting density was considered (e.g., Kimura, 1955; Ewens, 2004), we will usually have a sample of size \( M \) with \( y \) alleles of type one. Given the allelic proportion \( x \) the distribution of alleles is naturally modeled as a binomial

\[
Pr(y \mid x, M) = \binom{M}{y} x^y (1 - x)^{M-y}.
\]  

The joint density of \( y \) and \( x \) after multiplication with the equilibrium beta density (13) is

\[
Pr(y, x \mid \alpha, \theta, M) = \binom{M}{y} \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(\beta \theta)} x^y + \alpha \theta - 1 (1 - x)^{M+y+\beta \theta - 1}. 
\]  

Integrating out \( x \) results in the beta-binomial compound distribution

\[
Pr(y \mid \alpha, \theta, M) = \binom{M}{y} \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(\beta \theta)} \int_0^1 x^y + \alpha \theta - 1 (1 - x)^{M+y+\beta \theta - 1} dx
\]

\[
= \binom{M}{y} \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(\beta \theta)} \frac{\Gamma(\alpha \theta + M + \theta)}{\Gamma(y + \alpha \theta + M + \beta \theta)}. 
\]  

The posterior of \( x \) (i.e., the conditional probability density of \( x \) after observing the data \( y \) given \( M \)) is a beta density

\[
Pr(x \mid \alpha, \theta, y, M) = \frac{\Gamma(M + \theta)}{\Gamma(y + \alpha \theta) \Gamma(M - y + \beta \theta)} x^{y+\alpha \theta - 1} (1 - x)^{M+y+\beta \theta - 1} 
\]

\[
= \text{beta}(x \mid y + \alpha \theta, M - y + \beta \theta). 
\]  

2.2.2. Example: A Change in the Mutation Bias with Modified Jacobi Polynomials

As an example, assume that the population had been in equilibrium with parameters \( \alpha_a \) and \( \theta \), to switch to a new mutation bias \( \alpha_c \) at time \( t_c \), while \( \theta \) has remained constant throughout. Then the expansion until time \( t_c \) contains only the equilibrium beta density. The change of the mutation bias necessitates a change in the eigenvectors from \( w(\theta, \alpha_a) R_1^{(\theta, \alpha_a)} \) to \( w(\theta, \alpha_c) R_1^{(\theta, \alpha_c)} \). The coefficients for the new eigensystem are (compare formula 17)

\[
c_i = \frac{1}{\Delta t} \int_0^1 R_i^{(\theta, \alpha_c)}(x) w(\theta, \alpha_a) R_0^{(\theta, \alpha_a)} dx.
\]  

The evolution of the proportion \( f(x) \) between \( t_c \) and the present time is given by the series expansion (14) with the \( c_i \) from equation (26).
While one such change may not be too cumbersome to implement in a computer program, approximating, e.g., exponentially growing or shrinking populations by many piecewise linear changes can be if equilibrium has not been reached, since then for each change a sum over all terms in the expansion is needed and equation (20) needs to be modified to
\[ c_i = \frac{1}{\Delta t} \int_0^1 R_i^{(\theta, \alpha)}(x) w^{(\theta, \alpha)} \sum_i R_i^{(\theta, \alpha)} \, dx. \] (27)
A substantial improvement can be the use of the assumption of mutations only from the boundaries, where such a change of the eigensystem is not necessary. This will be investigated in the next section.

3. Mutation-Drift With Small Scaled Mutation Rates

3.1. Pure Drift Diffusion

In this subsection, the pure drift diffusion model is reviewed, as it is the basis for the boundary mutation-drift model. In the interior, i.e., inside the polymorphic region between \([1/N, 1 - 1/N]\), the dynamics of the allelic proportion \(x\) are influenced only by drift, such that the forward generator simplifies to
\[ \mathcal{L}_f = \frac{\partial^2}{\partial x^2} x(1 - x), \] (28)
and the corresponding Kolmogorov forward equation to
\[ \frac{\partial}{\partial t} \phi(x, t) = \mathcal{L}_f \phi(x, t) = \frac{\partial^2}{\partial x^2} x(1 - x) \phi(t, x). \] (29)

Note that with the general mutation drift Kolmogorov forward equation (4) the boundaries are regular, i.e., accessible and non-absorbing, whereas with the pure drift model the boundaries are usually considered exit boundaries, i.e., accessible and absorbing (Ewens, 2004).

The dynamics of the polymorphic region have been analyzed by Kimura (1955) and Song and Steinrücken (2012) using Gegenbauer polynomials (e.g., Kimura, 1955; Ewens, 2004; Song and Steinrücken, 2012). Tran et al. (2013) suggested to augment the eigenvectors by boundary terms, which results in a “global” solution that, in addition to the polymorphic region within \([1/N, (N - 1)/N]\) includes the boundaries zero and one.
We will follow this strategy, while maintaining the connection to the modified Jacobi polynomials Song and Steinrücken (2012) as defined in (8).

For $i \geq 2$, define the following set of orthogonal polynomials with boundary terms:

$$H_i(x) = \frac{(-1)^i}{i} \delta(x) + \delta(x-1) + U_i(x),$$  \hspace{1cm} (30)

with

$$U_{i+2}(x) = x^{-1}(1-x)^{-1}G_i(x) = -\frac{2}{i+2} C^{(3/2)}_i(2x-1) = R^{(\theta=2, \alpha=1/2)},$$  \hspace{1cm} (31)

where the $G_i(x)$ are the modified Gegenbauer polynomials Song and Steinrücken (2012), the $R^{(\theta=2, \alpha=1/2)}$ are defined in (8) Song and Steinrücken (2012), and the $C^{(\alpha)}(z)$ correspond to the classical ultraspherical or Gegenbauer polynomials with $\alpha = 3/2$ Abramowitz and Stegun, 1970, chap.22 used by Kimura (1955).

Note that, for $i \geq 2$, the boundary terms of $H_i(x)$, i.e., the Dirac delta function, at zero and one are

$$\begin{align*}
\int_0^1 xU_i(x) \, dx &= 1/i \\
\int_0^1 (1-x)U_i(x) \, dx &= (-1)^i/i.
\end{align*}$$  \hspace{1cm} (32)

Expression of the modified Gegenbauer polynomials as linear combinations of Beta densities. The modified Gegenbauer polynomials can be represented explicitly as polynomials and also as linear combinations of beta densities, as with the modified Jacobi polynomials (eq. 21):

$$U_{i+2}(x) = \sum_{m=0}^i (-1)^{i-m+1} \frac{(i+1)!}{m!(i-m+1)!} \frac{(i+1)!}{(i-m+1)!} x^m(1-x)^{i-m}$$

$$= \sum_{m=0}^i (-1)^{i-m+1} \frac{(i+1)!}{(m+1)!(i-m+1)!} \text{beta}(x|m+1, i-m+1).$$  \hspace{1cm} (33)

In this case, the beta densities have integer parameters greater than one, i.e., are polynomials.

**Lemma 1.** The set of eigenvectors $H_i(x)$, for $i \geq 2$, can be derived from the modified Jacobi polynomials in equation Song and Steinrücken (2012) multiplied by the weight function, $w^{(\theta, \alpha)}(x)R_i^{(\theta, \alpha)}(x)$, if i) only terms in a Taylor expansion in $\theta$ up to zeroth order are kept in the polymorphic region $[0, 1]$, while ii) terms that, for $\theta \to 0$, vanish in the
interior and converge to point masses at the boundaries are set to those values there; compactly,

\[ w^{(\theta, \alpha)}(x) R_i^{(\theta, \alpha)}(x) = H_i(x) + O(\theta). \]  

**Proof.** For \( i \geq 1 \),

\[
w^{(\theta, \alpha)}(x) R_i^{(\theta, \alpha)}(x) = \sum_{m=0}^{i} \frac{(-1)^{i-m} \Gamma(i+\alpha \theta) \Gamma(i+\beta \theta)}{\Gamma(m+1) \Gamma(i-m+1) \Gamma(m+\alpha \theta) \Gamma(i-m+\beta \theta)} \cdot x^{m+\alpha \theta - 1} (1-x)^{i-m+\beta \theta - 1}
\]

\[
= \sum_{m=1}^{i-1} \frac{(-1)^{i-m} \Gamma(i) \Gamma(i)}{\Gamma(m+1) \Gamma(i-m+1) \Gamma(m)} \cdot x^{m-1} (1-x)^{i-m-1} + (-1)^i \delta(x)/i + O(\theta)
\]

\[
= \sum_{m=0}^{i-2} \frac{(-1)^{i-m-1} \Gamma(i) \Gamma(i)}{\Gamma(m+2) \Gamma(i-m+1) \Gamma(i-m+1)} \cdot x^m (1-x)^{i-m-2} + (-1)^i \delta(x)/i + O(\theta)
\]

\[
= \sum_{m=0}^{j} \frac{(-1)^{j-m+1} \Gamma(j+2) \Gamma(j+2)}{(m+1)! (j-m)! (j-m+1)! m!} x^m (1-x)^{j-m}
\]

\[
= U_i(x) + (-1)^i \delta(x)/i + O(\theta)
\]

\[
= H_i(x) + O(\theta),
\]

where \( j = i - 2 \).

**Remark 1.** The \( H_i(x) \) are obviously independent of \( \theta \) and \( \alpha \) for \( i \geq 2 \).

Note that the integral including the boundary terms is

\[
\begin{align*}
-\int_0^1 xH_i(x) \, dx &= 0 \\
-\int_0^1 (1-x)H_i(x) \, dx &= 0
\end{align*}
\]

(36) the boundary terms offset the probability mass in the interior.

The first two polynomials are \( U_2(x) = -1 \) and \( U_3 = (2 - 4x) \); the recurrence relation to calculate all other polynomials is (Song and Steinrücken, 2012)

\[
U_{i+1}(x) \frac{(i+1)(i-1)}{2i(2i-1)} = U_i(x) \left(x - \frac{1}{2}\right) - U_{i-1}(x) \frac{(i-1)}{2(2i-1)}. \]

(37)
The $U_i(x)$ solve the differential equation:

$$-\lambda_i U_i(x) = \frac{\partial^2}{\partial x^2} U_i(x), \quad (38)$$

with

$$\lambda_i = i(i-1). \quad (39)$$

Thus the $\lambda_i$ are also independent of $\theta$ and $\alpha$ for $i \geq 2$. The $U_i(x)$ are orthogonal with the weight function

$$w(x) = x(1-x). \quad (40)$$

and the proportionality constant is

$$\Delta_i = \frac{i-1}{(2i-1)i}. \quad (41)$$

A probability density defined between zero and one can be represented by an expansion of the $H_i(x)$:

$$f(x) = b_1 \delta(x-1) + b_0 \delta(x) + \sum_{i=2}^n (c_i H_i(x)), \quad (42)$$

where

$$\begin{cases} b_0 = \int_0^1 x f(x \mid t = 0) \, dx, \\ b_1 = 1 - b_0 = \int_0^1 (1-x) f(x \mid t = 0) \, dx. \end{cases} \quad (43)$$

Should $f(x)$ have point masses at the boundaries, these are included in this integration. The coefficients $c_i$ can be calculated using

$$c_i = \frac{1}{\Delta_i} \lim_{N \to \infty} \int_{1/N}^{1-1/N} x(1-x)U_i(x) f(x) \, dx, \quad (44)$$

where the limit indicates that the integration includes only the polymorphic region, i.e., no point masses at the boundaries.

### 3.1.1. Pure Drift: Dynamics at the Boundaries

With the pure drift Moran model, the monomorphic boundaries gain from the flow out from the polymorphic region. For the boundary at one, the flow of probability mass out from $(N-1)/N$ to one per unit time, symbolized by $\frac{\partial}{\partial t} F((N-1)/N)$, is given by the strength of drift. This is, after the appropriate scaling and taking the limits,

$$\frac{\partial}{\partial t} F((N-1)/N) = \frac{N-1}{12} \phi((N-1)/N, t), \quad (45)$$
and similarly at the other boundary. Since the boundaries are the only way to lose probability mass from the inside, we also have
\[
\frac{\partial}{\partial t} \left( F\left( \frac{N-1}{N} \right) + F\left( \frac{1}{N} \right) \right) = -\frac{\partial}{\partial t} \int_{1/N}^{1-1/N} \phi(x,t) \, dx ,
\]
where similarly the summation was replaced by the appropriate integral. Together, we have
\[
-\frac{\partial}{\partial t} \int_{1/N}^{1-1/N} \phi(x,t) \, dx = \frac{N-1}{N} \phi(1/N,t) + \frac{N-1}{N} \phi((N-1)/N,t) .
\]
Furthermore, it is more likely that proximity to a boundary translates into preferably exiting through this boundary. A simple set of boundary conditions that accomplish this is
\[
-\frac{\partial}{\partial t} \int_{1/N}^{1-1/N} \phi(x,t)(1-x) \, dx = \frac{N-1}{N} \phi(1/N,t) .
\]

Equations (48) imply that the flow out of the polymorphic region per unit time is equal to the force of drift at \(x = 1/N\) and \(x = (N-1)/N\), respectively, times the amount present there, while the probability to exit through a certain boundary is given by the distance to it.

### 3.1.2. Pure Drift: A Different Route to the Solution

In this subsection, the series expansion used to solve the pure drift Kolmogorov forward equation is reached via a route, where an expansion with a general function of time \(\tau_i(t)\) is considered, rather than the usual \(e^{-\lambda_i t}\), and where the forward diffusion equation is integrated using the eigenvectors \(U_i(x)\); this strategy also provides the behavior at the boundaries. This prepares the way for the solution of the boundary mutation drift model later.

**Lemma 2.** The series expansion
\[
f(x,t) = b_1 \delta(x-1) + b_0 \delta(x) + \sum_{i=2}^{n} (\tau_i(t)H_i(x)) ,
\]
where the \(\tau_i(t)\) fulfill the dynamic system
\[
\frac{d}{dt} \tau_i(t) = -\lambda_i \tau_i(t) .
\]
with the starting conditions in equations (48) provides the global solution (also incorporating boundary terms, Tran et al., 2013), of the pure drift forward diffusion equation (29) in the limit $N \to \infty$.

**Proof.** The strategy of Kimura (1955), Appendix II, is followed.—Integrating the differential equation (38), we get

\[-\lambda_i \int_0^1 U_i(x) \, dx = \int_0^1 \frac{d^2}{dx^2} x(1-x) U_i(x) \, dx \]

\[= \int_0^1 \left( \frac{d}{dx} (x-1-x) \right) U_i(x) + (1-2x) U_i(x) \, dx \]

\[= \left[ x(1-x) \frac{d}{dx} U_i(x) + (1-2x) U_i(x) \right]_0 \]

\[= -U_i(0) - U_i(1). \]

(51)

Conditional on eventual fixation at the boundary one, the forward generator is (Ewens, 2004, section 4.6):

\[L^{(1)}_i = \left( \frac{\partial^2}{\partial x^2} x(1-x) \right) - \left( \frac{\partial}{\partial x} (1-x) \right). \]

(52)

Applying this generator to $U_i(x)$ and integrating, results in

\[\int_0^1 \frac{d^2}{dx^2} x(1-x) - \left( \frac{d}{dx} (1-x) \right) U_i(x) \, dx \]

\[= \int_0^1 \frac{d}{dx} \left( x(1-x) \frac{d}{dx} U_i(x) + (1-2x) U_i(x) - (1-x) U_i(x) \right) \, dx \]

\[= \left[ x(1-x) \frac{d}{dx} U_i(x) - xU_i(x) \right]_0 = -U_i(1). \]

(53)

From equations (51, 53, and 32), we obtain for all $i$

\[-\lambda_i \int_0^1 x U_i(x) \, dx = \int_0^1 \frac{d^2}{dx^2} x(1-x) - \left( \frac{d}{dx} (1-x) \right) - U_i(x) \, dx \]

\[= -U_i(1). \]

(54)

Substituting

\[f(x, t) = \sum_{i=2}^n (\tau_i(t) U_i(x)) \]

into

\[-\frac{\partial}{\partial t} x \phi(x, t) = - \left( \frac{\partial^2}{\partial x^2} x(1-x) - \frac{\partial}{\partial x} (1-x) \right) \phi(t, x), \]

(56)
integrating and taking the limit $N \to \infty$, we obtain

$$-rac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} x \phi(x, t) \, dx = -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} \sum_{i=2}^{\infty} (\tau_i(t) x U_i(x)) \, dx = \sum_{i=2}^{\infty} (\tau_i(t) U_i(1)) = \phi(1, t).$$

This corresponds to the limit $N \to \infty$ of equation (48) for boundary one. Combining this result with equation (54), we obtain

$$-\frac{d}{dt} \sum_{i=2}^{n} \left( \tau_i(t) \frac{1}{\lambda_i} U_i(1) \right) = \sum_{i=2}^{\infty} (\tau_i(t) U_i(1)).$$

The solution of the system of differential equations

$$\frac{d}{dt} \tau_i(t) = -\lambda_i \tau_i(t)$$

fulfils equation (58) for all $i$. An analogous calculation for the boundary at one and summing the results for both boundaries, shows that the series expansion using the Gegenbauer polynomials fulfils both the pure drift diffusion equation as well as the boundary conditions in the limit $N \to \infty$. Noting that, with the $U_i(x)$ augmented by the boundary terms, whatever leaves the polymorphic region for each $H_i(x)$ at $x = 1/N$ and $x = (N - 1)/N$ in the limit $N \to \infty$, is added to the monomorphic boundaries at $x = 0$ and $x = 1$, respectively, completes the proof.

**Remark 2.** With the starting conditions, it follows that $\tau_i(t) = c_i e^{-\lambda_i t}$, which can also be obtained by separation of variables.

### 3.2. No Net-Flow Boundary Condition

Substituting the function $eq(x) = x^{-1}(1 - x)^{-1}$ into the pure drift forward equation (29), shows that $eq(x)$ is a (local) equilibrium solution:

$$\frac{\partial}{\partial t} eq(x) = \frac{\partial^2}{\partial x^2} x(1 - x) eq(x) = 0 = \frac{\partial^2}{\partial x^2} x(1 - x) x^{-1}(1 - x)^{-1} = 0.$$  

In fact, there is no net flow into or out of an arbitrary interval $[a, b]$ within $[1/N, (N-1)/N]$, as can be deduced by integration:

$$\int_a^b \frac{\partial}{\partial t} eq(x) \, dx = \int_a^b \frac{d^2}{dx^2} x(1 - x) eq(x) \, dx = \int_a^b \frac{d^2}{dx^2} x(1 - x)x^{-1}(1 - x)^{-1} \, dx = 0.$$
Obviously, $eq(x)$ does not fulfill the boundary conditions in equation (48), as the probability mass in the vicinity of $x = (N - 1)/N$ and $x = 1/N$ would continually lead to loss by drift.

Only if this loss is balanced exactly by probability mass continually replenished from the boundaries, a function proportional to $eq(x)$ may therefore be the polymorphic part of a global equilibrium solution. Considering the symmetry of $eq(x)$ and the boundaries $[1/N, (N - 1)/N]$, this process would have to be symmetric.

A population genetic force that may accomplish this is mutation. While the assumption that in equilibrium mutations from the boundaries exactly offset the loss through drift at both boundaries may sound improbable, the next subsection makes just that plausible.

3.3. The Boundary Mutation-Drift Diffusion Model

3.3.1. The Boundary Mutation-Drift Diffusion Model: Slow Time Scale; Mutation

For the boundary mutation-drift model, we are searching for solutions for the pure drift Kolmogorov forward equation (29) with boundary conditions that include mutations given some starting density for all times. This model should approximate the general mutation drift Kolmogorov forward equation (3) for small scaled mutation rates. For this, a spectral decomposition is used as before. We make the ansatz

$$\phi(x, t) = H_0^\alpha(x) + \sum_{i=1}^{\infty} \tau_i(t) H_i(x),$$

(62)

with the eigenvectors $H_i(x)$ identical to those in (30) for $i \geq 2$. Continuing with the strategy of expanding the eigenfunction to zeroth order in $\theta$ and including boundary terms, we obtain for $i = 0$

$$H_0^\alpha(x) = w^{\theta, \alpha}(x) R^{\theta, \alpha}(x) = \beta \delta(x) + \alpha \delta(x - 1) + O(\theta).$$

(63)

The eigenfunction for $i = 1$ can be obtained from equation (64), such that

$$
\begin{align*}
H_0^{(\alpha)}(x) &= \beta \delta(x) + \alpha \delta(x - 1), \\
H_1(x) &= -\delta(x) + \delta(x - 1).
\end{align*}
$$

(64)

Obviously, these two eigenfunctions are unaffected by the dynamics in the polymorphic region inside $[1/N, (N - 1)/N]$. 

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Note that the only probability mass of these two eigenfunction is at the boundaries, such that only eigenvectors with $i \geq 2$ have nonzero probability masses in the polymorphic region. Hence, the model separates two spatial regions: the monomorphic boundaries and the polymorphic interior. The corresponding eigenvectors are $\lambda_0 = 0$ and $\lambda_1 = \theta$. As $\theta \ll 1$ and the $\lambda_i > 1$ for all eigenvalues with $i > 2$, two different temporal regions can be separated, in addition to the two different spatial regions. Thus, evolution is modeled as a two-time process, where the slow dynamics of $b_0(t)$ and $b_1(t)$ are evolving independently from the polymorphic region, while the fast dynamics in the polymorphic region are in dynamic equilibrium with the slow dynamics at the boundaries. Generally, we are thus looking at a system of differential equations, which for the slowly evolving part of the system is

\[
\begin{cases}
\tau_0(t) = 1, \\
\frac{d}{dt}\tau_1(t) = -\theta \tau_1(t).
\end{cases}
\]

(65)

Initially, $b_1(t = 0) = \Pr(x = 1 | t \to \infty) = \int_0^1 xf(x | t = 0) \, dx$. The solution over time is $\tau_1(t) = (b_1(t = 0) - \alpha)e^{-\theta t}$, such that the boundary values will slowly, at a rate of $\theta$, approach the equilibrium values

\[
b_1(t) = \alpha + (b_1(t = 0) - \alpha)e^{-\theta t} = 1 - b_0(t)
\]

(66)

Note that $b_0(t)$ and $b_1(t)$ correspond to the probability mass currently at the boundaries plus the probability mass within the polymorphic region expected to be fixed by drift at the respective boundaries. They would only be identical to the probability mass currently at the boundaries, if there were no probability mass in the polymorphic region.

3.3.2. The Boundary Mutation-Drift Diffusion Model: Fast Time Scale; Drift and Mutation

For small scaled mutation rates, i.e., $\theta \ll 1$, Vogl and Clemente (2012) suggested to approximate the Moran model presented above by a model, where the dynamics of polymorphic alleles are only governed by drift, while mutations only occur in the monomorphic states at the boundaries, i.e., at $x = 0$ or $x = 1$. A motivation of this model was that the probability of a mutation hitting a polymorphic allele is approximately $2\alpha \beta \theta \log(N)$, which is small if $N$ is not overly large. Simulations in Vogl and Clemente (2012) show that
for the statistic “frequency of polymorphism in a sample of size two” the approximation holds well for $\alpha\beta\theta < 0.01$ (see their Fig. 1 and note that $2(\theta_0\theta_1)/(\theta_0 + \theta_0) = \alpha\beta\theta < 0.01$).

In the diffusion limit, $N$ is assumed to approach infinity, such that this argument becomes obsolete and other considerations are needed.

With small scaled mutation rates, the influence of mutations relative to the effect of drift is small, if $x$ is away from the immediate vicinity of the boundaries. Mutations affect the mean of $x$ increasing or decreasing it by $1/N$ with probabilities $\alpha\theta(1 - x)$ and $\beta\theta x$, respectively. Compared to the probability of the same increase or decrease by drift $x(1 - x)$, this is appreciable only close to the boundaries, i.e., close to zero, where $x$ is equal to or smaller than $\alpha\theta$, or close to one, where $(1 - x)$ is equal to or smaller than $\beta\theta$. In Fig. 1, the region close to zero is presented for a population in equilibrium with $\alpha\theta = 0.03$ and $\beta\theta = 0.015$ (these parameter values are actually close to the maximum $\alpha\beta\theta$ allowed by the approximation of small scaled mutation rates). In the Figure, the rates of the population genetic forces (i.e., mutation and drift) are multiplied with the equilibrium beta density to show the relative equilibrium contributions of mutation and drift in different regions of $x$. It can be seen, that the relative force of drift is almost constant between zero and one, since the density of $x$ times the probability of drift is not far from constant, except extremely close to the boundaries, where it drops sharply to zero. In the vicinity of zero, the mutational force towards zero has almost no influence (i.e., it is indistinguishable from a horizontal line at zero), while the mutational force towards one is larger than that of drift between zero and about $\alpha\theta = 0.03$ and diminishing from there. For small $\theta$, the force of drift in equilibrium is approaching a horizontal line at the level $\alpha\beta\theta$ between zero and one (excluding the boundaries, where it is zero), while the forces of mutation approach delta functions at zero and one.

These considerations are analogous to those in Stephan (1997) and Tautz (2000): a selective force below that of drift has little or no influence on evolution, analogous to the uncertainty principle in quantum physics. In our case case, this uncertainty principle is applied to the force of mutation instead of selection.

As the probability of mutation per Moran event is $\mu$, the scaled mutation rate per unit of
time in the diffusion model becomes \( N^2 \mu = N\theta \), such that the mutational terms become
\[
\begin{align*}
N\alpha\theta\delta(x) \int_0^1 (1-x)\phi(x,t) \, dx & \quad \text{at 0} \\
N\beta\theta\delta(x-1) \int_0^1 x\phi(x,t) \, dx & \quad \text{at 1}.
\end{align*}
\]

While, with the general model, the effects of mutation are incorporated in the Kolmogorov forward equation \((67)\) by the term \( \theta \frac{\partial}{\partial x} (\alpha - x) \), with the small scaled mutation model, they are incorporated by the delta functions at the boundaries \((67)\):
\[
\frac{\partial}{\partial t} \phi(x,t) = \frac{\partial^2}{\partial x^2} x(1-x)\phi(x,t) + N\alpha\theta\delta(1/N - x)b_0(t) + N\beta\theta\delta(x - (N-1)/N)b_1(t),
\]
with \( b_0(t) = \int_0^1 (1-x)\phi(x,t) \, dx \) and \( b_1(t) = \int_0^1 x\phi(x,t) \, dx \) as above. This equation implies that the allelic proportions \( x \) are subject to drift everywhere in the polymorphic region; additionally, mutants arrive at \( x = 1/N \) and \( x = (N-1)/N \) with rates per generation of \( \alpha\theta b_0(t) \) and \( \beta\theta b_1(t) \), respectively.

The boundary conditions analogous to those with pure drift \((68)\) are:
\[
\begin{align*}
-\frac{\partial}{\partial t} \int_1^{(N-1)/N} x\phi(x,t) \, dx & = \frac{N-1}{N} \phi((N-1)/N, t) + N\beta\theta b_1(t) \\
-\frac{\partial}{\partial t} \int_0^{(N-1)/N} (1-x)\phi(x,t) \, dx & = \frac{N-1}{N} \phi(1/N, t) + N\alpha\theta b_0(t).
\end{align*}
\]

3.3.3. The Boundary Mutation-Drift Diffusion Model: General Solution

Theorem 3. Starting from a density \( f(x) \) within the unit interval (eq. \(29\)) and with the boundary conditions in (eq. \(69\)) but letting \( N \to \infty \), the following function provides the general solution for all times of the Kolmogorov forward equation of pure drift diffusion
\[
\phi(x,t) = H_0^{(\alpha)}(x) + \sum_{i=1}^{\infty} \tau_i(t) H_i(x),
\]
with the previously defined eigenfunctions (eqs. \(64\) and \(30\)); the \( \tau_i(t) \) are given by a system of linear inhomogenous first order differential equations
\[
\begin{align*}
\frac{d}{dt} \tau_1(t) & = -\theta \tau_1(t) \\
\frac{d}{dt} \tau_i(t) & = -\lambda_i \tau_i(t) - (2i-1)i(-1)^i \alpha \theta b_0(t) + \beta \theta b_1(t), \quad \text{for } i \geq 2.
\end{align*}
\]
The starting values, \( \tau_i(t=0) \) for \( i \geq 1 \), are given by the expansion of the initial density \( f(x) \) into the eigensystem.
Proof. The slowly evolving part of the system is given in (66). For the fast evolving part, note that from equation (44), the coefficients for expanding the delta function are:

\[ c_i = \lim_{N \to \infty} \left( \frac{1}{\Delta_i} \int_0^1 x(1-x)U_i(x)N\delta((N-1)/N - x) \, dx \right) \]

\[ = \lim_{N \to \infty} \left( \frac{(N-1)U_i((N-1)/N)}{N\Delta_i} \right) \]

\[ = \frac{U_i(1)}{\Delta_i}, \tag{72} \]

and analogously for the boundary at zero. Similarly, the incoming probability mass needs to be distributed among the eigenfunctions proportional to their contributions at the boundaries, which are \((-1)^i/i\) at zero and \(1/i\) at one.

Substituting

\[ f(x, t) = \sum_{i=2}^n (\tau_i(t)U_i(x)) \tag{73} \]

into

\[ -\frac{\partial}{\partial t} x\phi(x, t) = -\left( \frac{\partial^2}{\partial x^2} x(1-x) - \frac{\partial}{\partial x} (1-x) \right) \phi(t, x) - N\beta\delta(x-(N-1)/N)b_1(t), \tag{74} \]

integrating and taking the limit \(N \to \infty\), we obtain

\[ -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} \phi(x, t) dx = -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} \sum_{i=2}^\infty (\tau_i(t)xU_i(x)) \, dx \]

\[ = \sum_{i=2}^\infty (\tau_i(t)U_i(1)) + N\beta b_1(t) \frac{U_i(1)}{i\Delta_i} \]

\[ = \phi(1, t) + N\beta b_1(t). \tag{75} \]

This corresponds to the limit \(N \to \infty\) of equation (69) for boundary one. This equation leads to

\[ -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} \sum_{i=2}^\infty \left( \tau_i(t) \frac{1}{\lambda_i} U_i(1) \right) \, dx = \sum_{i=2}^\infty (\tau_i(t)U_i(1)) + N\beta b_1(t) \frac{U_i(1)}{i\Delta_i}. \tag{76} \]

The solution of the system of equations

\[ \frac{d}{dt} \tau_i(t) = -\lambda_i \tau_i(t) - (2i-1)i\beta b_1(t) \tag{77} \]

fulfills equation (76) for all \(i\).

Analogously, we obtain for the boundary at zero

\[ -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} (1-x)\phi(x, t) dx = -\frac{d}{dt} \lim_{N \to \infty} \int_{1/N}^{1-1/N} \sum_{i=2}^\infty (\tau_i(t)(1-x)U_i(x)) \, dx \]

\[ = \sum_{i=2}^\infty (\tau_i(t)U_i(0)) + N\beta b_1(t) \frac{(-1)^iU_i(0)}{i\Delta_i} \]

\[ = \phi(0, t) + N\alpha b_0(t), \tag{78} \]
such that eventually

\[ \frac{d}{dt} \tau_i(t) = -\lambda_i \tau_i(t) - (2i - 1)i(-1)^i \alpha \theta b_0(t), \tag{79} \]

Summing equations (77) and (79), we obtain

\[ \frac{d}{dt} \tau_i(t) = -\lambda_i \tau_i(t) - (2i - 1)i \left((-1)^i \alpha \theta b_0(t) + \beta \theta b_1(t)\right), \tag{80} \]

The same considerations as with lemma (2) complete the proof.

**Remark 3.** Note that the differential equations (71) for \( i \geq 2 \) can be rearranged to

\[ \frac{d}{dt} \frac{\tau_i(t)}{2i - 1}((-1)^i \alpha \theta b_0(t) + \beta \theta b_1(t)) + \tau_i(t) = -\lambda_i. \tag{81} \]

Thus, separation of variables may be used.

3.3.4. The Boundary Mutation-Drift Diffusion Model: Equilibrium Solution

**Corollary 4.** The equilibrium solution of the dynamic system with the slowly evolving part given by equation (66) and the boundary condition (69) is given by

\[ \text{Eq}(x | \theta, \alpha) = \text{Pr}(x | \theta, \alpha) = \left(\frac{\beta}{x(1-x)} + \frac{\alpha \beta \theta}{\log(N - 1)}\right) \delta(x - 1). \tag{82} \]

where the interior region is bounded by \( 1/N \) and \( (N - 1)/N \) in the limit \( N \to \infty \).

**Proof.** For any starting value, \( \tau_i(t \to \infty) = 0 \), such that \( b_0(t \to \infty) = \beta \) and \( b_1(t \to \infty) = \alpha \). Substituting these values into the dynamical system (eq. 71) and setting the derivates to zero results in:

\[ 0 = -(2i - 1)i(\alpha \theta (-1)^i + \alpha \beta \theta) - \lambda_i \tau_i(t). \tag{83} \]

From this, it follows that, for all odd \( i \), \( \tau_i(t \to \infty) = 0 \), and, for all even \( i \),

\[ \tau_i(t \to \infty) = \alpha \beta \theta (4i - 2)/i \lambda_i = -\alpha \beta \theta (4i - 2)/(i - 1). \tag{84} \]

The function

\[ \phi(x, t \to \infty) = H_0(x) + \alpha \beta \theta \sum_{i=1}^{\infty} c_{2i} H_{2i}(x) \tag{85} \]

corresponds to the modified Gegenbauer expansion of the equilibrium solution for \( N \to \infty \) where

\[ c_{2i} = \frac{1}{2^{2i}} \int_0^1 x(1-x)U_{2i}(x)x^{-1}(1-x)^{-1} dx = -\frac{2(2i-1)}{2i-1} = \frac{4(2i) - 2}{2i - 1}. \tag{86} \]

Since the function \( x^{-1}(1-x)^{-1} \) is symmetric, the boundary terms correspond to half the integral over the series expansion, which is \( \lim_{N \to \infty} 2 \alpha \beta \theta \log(N - 1) \).
Remark 4. Eq\(x|\theta, \alpha\) fulfils the boundary conditions in \(69\), also before taking the limit \(N \to \infty\), as can be shown by substitution. As long as \(N\) is not too large, Eq\(x|\theta, \alpha\) is a proper probability density, i.e., everywhere greater than zero and integrating to one over the interval. Eq\(x|\theta, \alpha\) corresponds to the equilibrium solution for the single mutation-drift Moran model [Vogl and Clemente, 2012].

3.3.5. Data: Likelihood, Joint and Posterior Densities, and the Marginal Distribution with Modified Gegenbauer Polynomials

The following theorem motivates the interpretation of the boundary mutation-drift model system using modified Gegenbauer polynomials as a Taylor series expansion to first order in \(\theta\) of the solution of the general mutation drift model with Jacobi polynomials.

**Theorem 5.** Consider again a sample of size \(M\) from a binomial distribution \(22\) conditional on the allelic proportion \(x\), where \(y\) is the number of alleles of the first type. The probability distribution \(\Pr(y|M, \theta, \alpha)\) resulting from a Taylor expansion to first order in \(\theta\) at \(\theta = 0\) of the beta-binomial compound distribution (eq. \(24\)), where the beta distribution \(13\) is taken as a prior, is identical to the marginal distribution of \(y\) resulting from taking the equilibrium density Eq\(x|\theta, \alpha\) (equation \(82\)) as a prior for the allelic proportion \(x\), and then taking the limit \(N \to \infty\) while integrating the resulting joint density over \(x\).

**Proof.** The beta-binomial compound distribution \(24\) is expanded into a power series in \(\theta\) at \(\theta = 0\) up to first order. For a polymorphic sample, \(1 \leq y \leq M - 1\), the Taylor series expansion of the beta-binomial compound distribution at \(\theta = 0\) is:

\[
\Pr(y|\theta, \alpha, M) = \binom{M}{y} \frac{\Gamma(\theta)}{\Gamma(\alpha\theta)\Gamma(\beta\theta)} \frac{\Gamma(y + \alpha\theta)\Gamma(M - y + \beta\theta)}{\Gamma(M + \theta)} + O(\theta^2)
\]

\[
= \alpha\beta\theta \binom{M}{y} \frac{\Gamma(y)\Gamma(M - y)}{\Gamma(M)} + O(\theta^2) \quad (87)
\]

For a monomorphic sample with \(y = 0\), the derivative of \(\Pr(y = 0|\theta, \alpha, M)\) with respect
to $\theta$ is:

$$d\frac{d}{d\theta} \Pr(y = 0 | \theta, \alpha, M) = d\frac{d}{d\theta} \left( \frac{\Gamma(\theta)}{\Gamma(\alpha \theta) \Gamma(M + \beta \theta)} \right)$$

$$= \frac{d}{d\theta} \left( \frac{\beta \theta (1 + \beta \theta)(2 + \beta \theta) \cdots (M - 1 + \beta \theta)}{\theta (1 + \theta)(2 + \theta) \cdots (M - 1 + \theta)} \right)$$

$$= \beta \left( \frac{\beta}{1 + \theta} + \frac{\beta}{2 + \theta} + \cdots + \frac{\beta}{M - 1 + \theta} - \frac{1}{1 + \theta} - \frac{1}{2 + \theta} - \cdots - \frac{1}{M - 1 + \theta} \right) \times$$

$$\times \frac{(1 + \beta \theta)(2 + \beta \theta) \cdots (M - 1 + \beta \theta)}{(1 + \theta)(2 + \theta) \cdots (M - 1 + \theta)}. \tag{88}$$

Thus the Taylor series expansion at $\theta = 0$ is to first order:

$$\Pr(y = 0 | \theta, \alpha, M) = \beta - \alpha \beta \theta \sum_{y=1}^{M-1} \frac{1}{y} + O(\theta^2), \tag{89}$$

and analogously for $\Pr(y = M | \theta, \alpha, M)$.

For polymorphic samples, the joint density of the binomial and the equilibrium density $\Eq(x | \theta, \alpha)$ (equation 82) is

$$\Pr(1 \leq y \leq M - 1, x | \alpha, \theta, M) = \alpha \beta \theta x^{y-1} (1 - x)^{M-y-1}. \tag{90}$$

Integrating over $x$ and taking the limit $N \to \infty$, such that the integration boundaries are 0 and 1, respectively, results in the marginal distribution:

$$\Pr(1 \leq y \leq M - 1 | \alpha, \theta, M) = \int_{0}^{1} \alpha \beta \theta x^{y-1} (1 - x)^{M-y-1} dx$$

$$= \alpha \beta \theta \left( \frac{M}{y} \right) \frac{\Gamma(y) \Gamma(M-y)}{\Gamma(M)} \tag{91}$$

$$= \alpha \beta \theta \frac{M}{y(M-y)}.$$

This is identical to the first order expansion (87).

For a monomorphic sample, e.g., $y = 0$, the joint density is

$$\Pr(y = 0, x | \alpha, \beta) = \beta + \alpha \beta \theta (- \log(N - 1) + (1 - x)^{-1} x^{M-1}). \tag{92}$$
Using the series expansion \((1 - x)^{-1} = \sum_{i=0}^{\infty} x^i\) results in
\[
- \log(N - 1) + \int_{1/N}^{1-1/N} (1 - x)^{-1} x^M \, dx = \int_{1/N}^{1-1/N} -(1 - x)^{-1} + (1 - x)^{-1} x^{M-1} \, dx
\]
\[
= \int_{1/N}^{1-1/N} \sum_{i=0}^{\infty} (-x^i + x^i x^{M-1}) \, dx
\]
\[
= -\int_{1/N}^{1-1/N} \sum_{i=1}^{M-1} x^{i-1} \, dx
\]
\[
= -\sum_{i=1}^{M-1} \frac{1 - 1/N}{i} - (1/N)^i.
\]
(93)

In the limit \(N \to \infty\), this converges to \(-\sum_{i=1}^{M-1} 1/i\). The marginal distribution of the monomorphic sample then is
\[
\Pr(y = 0 \mid \alpha, \beta) = \frac{1}{\beta + \alpha \beta \theta} \sum_{i=1}^{M-1} \frac{1}{i}.
\]
(94)

This is identical to the first order expansion (89). The analogous calculation for \(y = M\) completes the proof.

**Remark 5.** For polymorphic samples, the joint density (91) is a polynomial that can be represented without loss by the modified Gegenbauer polynomials, as long as \(M \leq N\). As long as
\[
\max(\alpha, \beta) \cdot \theta \sum_{y=1}^{M-1} \frac{1}{y} \leq 1,
\]
(95)

the following joint probability for monomorphic samples, for \(y = 0\):
\[
\Pr(y = 0 \mid \alpha, \beta) = \beta + \alpha \beta \theta \left( -\sum_{i=1}^{N} \frac{1}{i} + \sum_{i=M}^{N} x^{i-1} \right)
\]
(96)

and analogously for \(y = M\), results a proper joint density. This is also a polynomial in \(x\) and can therefore be represented without loss using the modified Gegenbauer polynomials. Note that polynomials can generally be represented as a linear combination of beta densities with integer parameters. Furthermore, the order of the expansion \(N\) in effect takes the role of the effective population size, with the series expansion.

### 3.3.6. Numerics

With the statistical language “R” (“www.r-project.org”) and its high-precision algebra package “Rmpfr”, the terms of the modified Gegenbauer polynomials up to the order
50 can be calculated within minutes using this method. With an expansion of order $N$, the beta-binomial posterior distributions (equation 25) of samples of size $N$ can be represented exactly.

With terms up to $i = 50$, the equilibrium expansion is shown in Fig. 2. Note that an expansion using $d_i$ as coefficients results in an approximation proportional to the delta function at zero or one (also shown in Fig. 2). Further approximations to beta densities that arise in the analysis of real data are also shown in Fig. 2.

3.3.7. Example: A Change in the Mutation Bias with Modified Gegenbauer Polynomials

For short introns, Clemente and Vogl (2012) argue that in *Drosophila melanogaster* a change in mutation bias from mildly to strongly biased towards AT over GC can explain the observed pattern of site frequency spectra. The model they used for analyses was based on quasi-equilibrium depending on the frequencies at the boundaries. In this subsection, a more precise model is investigated.

Suppose that the mutation bias changes from $\alpha_a(t = 0) = 1/3$ to $\alpha_c(t > 0) = 2/3$, while $\theta$ remains constant. We want to obtain the prior density analogous to the equilibrium density $(x(1-x))^{-1}$ at an arbitrary time $t$ thereafter. Initially, $b_0(t = 0) = 2/3$, $b_1(t = 0) = 1/3$, while the function in the interior is $2/9 \theta x^{-1}(1-x)^{-1}$. At time $t = 0$, the equilibrium starting condition can be expanded to:

$$H_{\alpha a}^{(0)}(x) + \sum_{i=2}^{\infty} \bar{c}_i H_i(x) \approx \frac{2}{3} \delta(0) + \frac{1}{3} \delta(1) + \frac{2}{9} \theta \sum_{i=2}^{\infty} \frac{((-1)^i + 1)(2i-1)}{i-1} H_i(x).$$

(97)

Set the $\tau_i(0) = \bar{c}_i$. Considering first the slow dynamics, which are independent from the fast dynamics, $b_1(t)$ will eventually increase from $1/3$ to $2/3$:

$$b_1(t) = \frac{2 - e^{-\theta t}}{3}.$$  

(98)

The coefficients of the interior eigenfunctions evolve according to a linear inhomogenous first order differential equation (eq. 71):

$$\frac{d}{dt} \tau_i(t) = -\frac{2}{9} \theta ((\frac{2}{3} - \frac{1}{3} e^{-\theta t})(-1)^i(2i - 1)i - \frac{1}{3} \theta (\frac{2}{3} - \frac{1}{3} e^{-\theta t}) (2i - 1)i - \lambda_i \tau_i(t))$$

$$= -\frac{2}{9} \theta ((-1)^i + 1)(2i - 1)i - \frac{1}{3} \theta (2(-1)^i - 1)(2i - 1)i e^{-\theta t} - \lambda_i \tau_i(t).$$

(99)
With the starting conditions $\tau_i(0) = \bar{c}_i$, the solution to the differential equation (99) is, for odd $i$

$$\tau_i(t) = \frac{3}{2i(2i-1)} \frac{e^{-\theta t} - e^{-\lambda_i t}}{\lambda_i - \theta}.$$  \hspace{1cm} (100)

and for even $i$

$$\tau_i(t) = -\frac{4(2i-1)i}{9\lambda_i} - \frac{5}{2i(2i-1)} \frac{e^{-\theta t} - e^{-\lambda_i t}}{\lambda_i - \theta}.$$

(101)

Note that even though $\theta$ does not increase and the equilibrium density is identical before and after the change in mutation bias, the even eigenfunctions and thus also the probability mass in the interior increase transiently. Since $\theta \ll \lambda_i$, especially for higher $i$, a quasi-equilibrium will result rapidly. A graph of the time course of the modified Gegenbauer expansion of the equilibrium density with $\theta = 0.01$ is presented in Fig. 3.

4. Summary and Conclusion

In this article, the starting point is the general biallelic mutation-drift diffusion equation with two parameters, the scaled mutation rate $\theta = \mu N$, where $\mu$ is the mutation rate per reproduction event and $N$ the haploid effective population size, and the allelic mutation bias $\alpha = \mu_1/\mu = 1 - \beta$. The evolution of the population allelic proportion $x$ over the appropriately scaled time can be found by expanding into a series of modified Jacobi polynomials (e.g., Griffiths and Spano, 2010; Song and Steinrücken, 2012). The equilibrium density corresponds to a beta (Wright, 1931). If the parameters change, e.g., if the mutation bias changes or the population shrinks or grows, the Jacobi expansion needs to be changed. For continually changing parameters, this is cumbersome.

With small scaled mutation rates $\theta \ll 1$, the interior dynamics are governed by drift and are relatively fast, while mutations influence the dynamics mainly at the boundaries at a relatively slow rate. This fact was already used in much of population genetics theory (e.g., for deriving the Ewens-Watterson estimator of $\theta$). Gutenkunst et al. (2009) used the same approximation in their program $\delta a\delta i$. In analogy to the discrete model (Vogl and Clemente, 2012), a model with mutations only from the boundaries is developed. The equilibrium solution of this boundary-mutation drift model has an interior part of $\alpha/\theta x^{-1}(1-x)^{-1}$ (see also RoyChoudhury and Wakeley, 2010), while the allelic proportions at the boundaries are influenced only by the mutation bias. For small $\theta$,
the beta-binomial compound distribution, which results from the general model, can be expanded to first order in $\theta$ to result in a marginal distribution. The same marginal distribution is obtained with the use of the boundary-mutation drift equilibrium density, after taking the limit $N \to \infty$. For the temporal part, a system of linear differential equations is derived that corresponds to the general solution of the boundary-mutation drift model. This solution using the orthogonal Gegenbauer polynomials seems to correspond to the numeric solution using a grid in $\delta a \delta i$ (Gutenkunst et al., 2009), who presumably assumed unbiased mutations. Since in equilibrium the joint density of the allelic proportion $x$ given a sample of moderate size $M$ is proportional to a beta density with integer coefficients, a polynomial of order $M - 1$ for a polymorphic sample, the solution presented here also has the advantage of producing the exact joint and posterior densities. Furthermore, the use of orthogonal polynomials connects to other, earlier theoretical work. In contrast to using Jacobi polynomial expansions, which are applicable also to large scaled mutation rates with $\alpha\beta\theta > 0.01$, the Gegenbauer polynomial expansion does not require a change of the basis if parameters change, e.g., because populations grow or shrink, and is thus more convenient, when the assumption of small scaled mutation rates can be justified.

Additionally considering directional selection, as Gutenkunst et al. (2009) and Vogl and Clemente (2012) have done for their models, is an obvious generalization of the approach in this article. Song and Steinrücken (2012) provide as a starting point their model and analysis with general mutation rates.

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References

Abramowitz, M. and Stegun, I., editors (1970). *Handbook of Mathematical Functions*. Dover, 9th edition.

Baake, E. and Bialowons, R. (2008). Ancestral processes with selection: branching and moran models. Volume 80 of *Banach center publications*, pages 33–52. Warsaw (Poland): Institute of Mathematics, Polish Academy of Sciences.

Clemente, F. and Vogl, C. (2012). Unconstrained evolution in short introns?—An analysis of genome-wide polymorphism and divergence data from *Drosophila*. *J. Evol. Biol.*, 25(10), 1975–90.

Etheridge, A. and Griffiths, R. (2009). A coalescent dual process in a Moran model with genic selectio. *Theor. Pop. Biol.*, 75, 320–330.

Ewens, W. (2004). *Mathematical Population Genetics*. Springer, N.Y., 2nd edition edition.

Griffiths, R. and Spanò, D. (2010). Diffusion processes and coalescent trees. In *Probability and Mathematical Genetics: Papers in Honour of Sir John Kingman*, pages 358–375. Cambridge University Press, Cambridge, UK.

Gutenkunst, R., Hernandez, R., Williamson, S., and Bustamante, C. (2009). Inferring the Joint Demographic History of Multiple Populations from Multidimensional SNP Frequency Data. *PLoS Genetics*, 5, e1000695.

Kimura, M. (1955). Solution of a process of random genetic drift with a continuous model. *Proc. Natl. Acad. Sci. USA*, 41, 144–150.

RoyChoudhury, A. and Wakeley, J. (2010). Sufficiency of the number of segregating sites in the limit under finite-sites mutation. *Theor. Pop. Biol.*, 78, 118–122.

Sawyer, S. and Hartl, D. (1992). Population genetics of polymorphism and divergence. *Genetics*, 132, 1161–1176.

Song, Y. and Steinrücken, M. (2012). A simple method for finding explicit analytic transition densities of diffusion processes with general diploid selection. *Genetics*, 190, 1117–1129.

Stephan, W. (1997). Mathematical model of the hitchhiking effect, and its application to dna polymorphism data. In O. Arino, editor, *Advances in Mathematical Dynamics—Molecules, Cells and Man*, pages 29–45. World Scientific.

Tautz, D. (2000). A genetic uncertainty problem. *Trends Genet.*, 16, 475–477.

Tran, T., Hofrichter, J., and Jost, J. (2013). An introduction to the mathematical structure of the WrightFisher model of population genetics. *Theory in Biosciences*, 132, 73–82.

Vogl, C. (2014). Biallelic Mutation-Drift Diffusion in the Limit of Small Scaled Mutation Rates. *Theoretical Population Biology*.

Vogl, C. and Clemente, F. (2012). The allele-frequency spectrum in a decoupled Moran model with mutation, drift, and directional selection, assuming small mutation rates. *Theoretical Population Genetics*, 81, 197–209.

Watterson, G. (1975). On the number of segregating sites in genetical models without recombination. *Theoretical Population Biology*, 7, 256–276.

Wright, S. (1931). Evolution in Mendelian populations. *Genetics*, 16, 97–159.
Figure 1. Comparison of the influence of drift (thick line) and of a mutation towards allele one (greater than 0) or towards allele 0 (horizontal line at $y = 0$).
Figure 2. Approximate densities using the Gegenbauer polynomial expansion with terms up to $i = 52$. A) Approximation proportional to the sum of the Dirac delta function \( \lim_{N \to \infty} \left( \frac{1}{N} \int_0^1 x (1 - x) U_i(x) N \delta((N - 1)/N - x) \, dx \right) \) at one and that at zero; B) approximation to the equilibrium improper density $x^{-1}(1 - x)^{-1}$ (wiggly line) and the function $x^{-1}(1 - x)^{-1}$ (smooth line); C) approximation to the joint posterior density for a sample with $y = 1$, $M = 1$ (wiggly line) and the joint density $2 x^{1-1}(1 - x)^{1-1}$ (smooth line); D) approximation to the joint posterior density for a sample with $y = 3$, $M = 6$ (wiggly line) and the joint density $\binom{6}{3} x^{3-1}(1 - x)^{3-1}$ (smooth line).
Figure 3. The time course of the polymorphic part of the allele proportions $x$ after a change in the mutation bias. The thin line represents the improper equilibrium distribution $x^{-1}(1-x)^{-1}$. The time is (A) $t = 0$, (B) $t = 0.1$, (C) $t = 1$, and (D) $t = 100$. 