On a Multilocus Wright-Fisher Model with Mutation and a Svirezhev-Shahshahani Gradient-like Selection Dynamics

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In this paper we introduce a multilocus diffusion model of a population of $N$ haploid, asexually reproducing individuals. The model includes parent-dependent mutation and interlocus selection, the latter limited to pairwise relationships but among a large number of simultaneous loci. The diffusion is expressed as a system of stochastic differential equations (SDEs) that are coupled in the drift functions through a Shahshahani gradient-like structure for interlocus selection. The system of SDEs is derived from a sequence of Markov chains by weak convergence. We find the explicit stationary (invariant) density by solving the corresponding stationary Fokker-Planck equation under parent-independent mutation, i.e., Kingman’s house-of-cards mutation. The density formula enables us to readily construct families of Wright-Fisher models corresponding to networks of loci.

Keywords: Stationary Fokker-Planck equation; probability flow; Girsanov’s theorem; bivariate Beta distribution; diffusion approximation; interaction in pairwise links.

1 Introduction

Recent and future advances of biotechnology will produce time series data of allele frequencies, see [42], [45]. The coupled Wright-Fisher model below is a step towards developing tools for analysis of such data.

The Wright-Fisher model for a single locus has been extensively studied in population genetics c.f. [13], [22] or [17] pp. 92–99. An alternative equivalent formulation
of the Wright-Fisher model is given in [31]. The overview in [6] presents applications to ecology and linguistics, too.

One of the present authors and his co-workers used recently a Potts model [11] in structural learning and analysis of coupled loci for the *Pneumococcus* derived from a whole genome alignment [41]. We introduce here a Potts-like structure of interactions consisting of first and second order interactions as in the Potts model which will produce an explicit selective fitness term, which is in fact a Shahshahani gradient-like structure, as is shown below.

This is related to the work on Quasi-Linkage Equilibrium in which the dynamics of the full genotype distribution, including correlations between alleles at different loci, is given a parametric form by the allele frequencies. In [33, eqns (41)-(43)] Neher and Shraiman find in the Quasi-Linkage Equilibrium approximation a probability density with a broadly similar structure as the one expressed in this paper. The technical details are, however, completely different from this work.

Here we prove the weak convergence of a sequence of Markov chains with the allele frequencies of all loci as the state space via conditionally independent locuswise multinomial sampling to the limiting diffusion by basically applying the direct techniques of [40] and [38]. Those techniques were tailored especially for Wright-Fisher models. The general methods are by semigroups of operators [16] or Stein’s method [3]. Diffusion approximation via duality with a coalescent, see [32], is involved are we are relying on some results due to [39] obtained by moment duality.

The uniqueness of the probability measure induced by the limiting diffusion (uniqueness of the martingale problem) is established by a change of drift technique and Girsanov’s theorem. The possibility of this change of the drift depends on the additive appearance of Shahshahani gradient-like structure derived from a fitness potential in the drift function.

The paper is organized as follows.

## 2 An Outline: The Wright-Fisher SDEs coupled by a Svirezhev-Shahshahani gradient form

### 2.1 The Multiallele Wright-Fisher Process

We start with the (single locus) M-allele Wright-Fisher diffusion process by means of a system of stochastic differential equations.

Denote by $x = (x_1, \ldots, x_{M-1})$ the generic element $\in \mathbf{K}$, the probability simplex

$$\mathbf{K} := \{x \in \mathbb{R}^{M-1} | x_l \geq 0, \sum_{l=1}^{M-1} x_l \leq 1\}. \quad (2.1)$$

In this $x_M$ serves as a shorthand notation for $1 - \sum_{k=1}^{M-1} x_k$. Let $\mu(x)$ be a real vector valued function of $x \in \mathbf{K} \mapsto \mathbb{R}^{M-1}$ satisfying suitable assumptions (specific forms will be encountered later) and let for $x \in \mathbf{K}$

$$d_{kl}(x) = \begin{cases} x_k(1 - x_k), & k = l \\ -x_kx_l, & k \neq l \end{cases}. \quad (2.2)$$
For ease of writing, \( d_{kl}(x) \) is sometimes denoted by \( d_{kl} \). \( D(x) \) is the \((M-1) \times (M-1)\) covariance matrix with arrays given in (2.2). Let \( X(t) \) be a random variable

\[ X(t) \in K, \quad t > 0, \]

such that the process \( X = \{ X(t) | t > 0 \} \) satisfies (e.g., in the strong sense) the multivariate stochastic differential equation (SDE)

\[ dX(t) = \mu(X(t))dt + \sigma(t) \, dW(t), \tag{2.3} \]

where \( W = \{ W(t) = (W_1(t), \ldots, W_{M-1}(t)) | t > 0 \} \) is an \( M-1 \) dimensional Wiener process. The multivariate diffusion process corresponding to this SDE is called the \( M \)-\textit{allele Wright-Fisher diffusion}. \( \mu(x) \) is the drift function and \( D(x) \) is the diffusion (also known as genetic drift) matrix of the \( M \)-allele Wright-Fisher diffusion. The presence of (2.2) is the hallmark of the Wright-Fisher diffusions.

The weak convergence of a sequence of Markov chains to the \( M \)-allele Wright-Fisher diffusion on \( K \) is proved in \[9, \text{p. 62}], \[37], \[38], \[39], \text{and} \[40]. \] K. Sato proved also in \[37] that under some weak conditions on \( \mu(x) \)'s (satisfied in this paper) that the limiting process stays in \( K \).

The general methods for weak convergence of a sequence of Markov chains to a multivariate diffusion as given in \[43, \text{Chapter 11.2-11.3}\] are not directly applicable in the cited work. The reasons for this are as follows. First, the diffusion function \( d_{kl}(x) \) yields a degenerate elliptic operator, see Appendix 10. This leads to the question of conditions on the functions \( \mu(x) \) for the martingale problem associated to the generator of (2.2) to have a unique solution. These conditions are treated in \[14], see also \[39]. \] The degenerate elliptic operators corresponding to Wright-Fisher diffusion are studied in \[12]. \] Second, the probability simplex \( K \) has intricate geometric properties, c.f., \[23]. \] Third, the results on the existence of an invariant measure for a multidimensional diffusion, see \[5], are for these reasons not applicable to Wright-Fisher diffusions.

### 2.2 The Multilocus and Multiallele Wright-Fisher SDE

Let \( x_i^{(i)} \) for \( i = 1, \ldots, L \) be the frequency of allele type \( k \) at locus \( i \) in a finite population, and

\[ K_i = \{ x \in R^{M_i-1} | x_1^{(i)} \geq 0, \sum_{i=1}^{M_i-1} x_i^{(i)} \leq 1 \}, \tag{2.4} \]

and \( x_i^{(i)} \) equals \( 1 - \sum_{k=1}^{M_i-1} x_k^{(i)} \). We stack these into a single column vector,

\[ x = (x^{(1)}, x^{(2)}, \ldots, x^{(L)}), \tag{2.5} \]

\[ = (x_1^{(1)}, \ldots, x_{M_1-1}^{(1)}, x_1^{(2)}, \ldots, x_{M_2-1}^{(2)}, \ldots, x_1^{(L)}, \ldots, x_{M_L-1}^{(L)}). \]

Hereafter we have \( K := \times_{i=1}^{L} K_i \) instead of (2.1), so that \( x \in K \). We define with (2.2) for for all \( i, l \) and \( k \) \( d_{kl}^{(i)}(x) \) by

\[ d_{kl}^{(i)}(x) \text{ def } \begin{cases} x_k^{(i)} (1 - x_k^{(i)}), k = l \\ -x_k^{(i)} x_l^{(i)}, k \neq l \end{cases} \tag{2.6} \]
$D^{(i)}(x)$ is the $(M_i - 1) \times (M_i - 1)$ covariance matrix with arrays given in (2.6), which means that $D^{(i)}(x)$ depends only on the allele frequencies $x_{k}^{(i)}$ at locus $i$. Next, $O_{ij}$ is a $(M_i - 1) \times (M_j - 1)$ matrix of zeroes. We introduce now the quadratic $\sum_{i=1}^{L}(M_i - 1) \times \sum_{j=1}^{L}(M_j - 1)$ block diagonal diffusion matrix

$$D(x) \defeq \begin{pmatrix} D^{(1)}(x) & O_{12} & \ldots & \ldots & O_{1L} \\ O_{21} & D^{(2)}(x) & \ldots & \ldots & O_{2L} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ O_{L1} & \ldots & \ldots & \ldots & D^{(L)}(x) \end{pmatrix}.$$ \hspace{1cm} (2.7)

Next we consider for $t > 0$

$$X(t) = \left( X^{(1)}(t) \ldots X^{(L)}(t) \right),$$

where each random variable $X^{(i)}(t)$ assumes values in $K_i$, respectively.

In this paper we determine a sequence of Markov chains that after a scaling and interpolation of discrete time will converge weakly to a $K$-valued stochastic process $\{X(t) \mid t \geq 0\}$ that satisfies an SDE of the form

$$dX(t) = \mu(X(t))dt + G(X(t)) dt + D^{1/2}(X(t))dW(t),$$ \hspace{1cm} (2.8)

where $)^T$ is the vector transpose

$$W(t)^T = \left( W^{(1)}(t), \ldots, W^{(L)}(t) \right),$$

and $W^{(i)}$ are independent Wiener processes, each with $M_i - 1$ independent component Wiener processes. The drift function is thus of the form $\mu(x) + G(x)$, where

$$\mu(x) = \left( \mu^{(1)}(x), \ldots, \mu^{(L)}(x) \right),$$

here each $\mu^{(i)}(x)$ depends only on $x^{(i)}$, and

$$G^T(x) = \left( G^{(1)}(x), \ldots, G^{(L)}(x) \right),$$

where

$$G^{(i)}(x) = D^{(i)}(x) \nabla_{x^{(i)}} V(x),$$ \hspace{1cm} (2.9)

with the gradients

$$\nabla_{x^{(i)}} V(x)^T = \left( V_{x^{(i)}}^{'}, V_{x^{(i)}_{x^{(i)}}}^{'}, \ldots, V_{x^{(i)}_{x^{(i)}_{i-1}}}^{'} \right).$$

for a function $V(x) (=fitness potential)$ explicitly constructed below of at most pairwise interaction between the $L$ loci. In view of the definition of $D(x)$ in (2.7) it holds that

$$G(x) = D(x) \nabla_x V(x),$$ \hspace{1cm} (2.10)

where

$$\nabla_x V(x)^T = (\nabla_{x^{(1)}} V(x), \nabla_{x^{(2)}} V(x), \ldots, \nabla_{x^{(L)}} V(x)).$$
appropriate dimensions, then

\[ \mu \text{ allele Wright-Fisher diffusion processes as given in (2.8).} \]

If loc.cit given as the pair of coupled SDEs

\[ \text{Example 2.1. Wright-Fisher model with selection but without mutation, [27, ch. 15, section F, example (b)].} \]

decomposition to act on respective locus without interaction. Hence, were \( D(x) \) to be removed (\( \approx \) weak selection), \( \{X(t) \mid t \geq 0\} \) will consist of an \( L \) independent \( M \)-allele Wright-Fisher diffusion processes as given in (2.8). If \( \mu(x) \) is the zero vector of appropriate dimensions, then

\[ dX(t) = D(X(t))\nabla_x V(X(t)) \, dt + D^{1/2}(X(t)) \, dW(t). \tag{2.11} \]

is a Svirezhev-Shahshahani gradient SDE for the allelic frequency dynamics. The Svirezhev-Shahshahani gradient is discussed in [7, pp.42-43] and [44, p. 222-223, p. 303], the paper [24] introduces a Wright-Fisher model, where a Svirezhev-Shahshahani gradient lies in the diffusion matrix.

In order to make these statements a bit more transparent at this stage, we look at a two-locus two alleles (\( L = 2, M_i = 2, i = 1, 2 \)) Wright-Fisher model with selection but no mutation, [27] ch. 15, section F, example (b)].

**Example 2.1.** The Wright-Fisher model with selection but without mutation is in loc.cit. given as the pair of coupled SDEs

\[
\begin{align*}
\frac{dX_i^{(1)}}{dt} &= hX_i^{(1)}(1 - X_i^{(1)})X_i^{(2)} \, dt + \sqrt{X_i^{(1)}(1 - X_i^{(1)})}dW_i^{(1)}, \\
\frac{dX_i^{(2)}}{dt} &= hX_i^{(2)}(1 - X_i^{(2)})X_i^{(1)} \, dt + \sqrt{X_i^{(2)}(1 - X_i^{(2)})}dW_i^{(2)}. 
\end{align*}
\tag{2.13}
\]

We find now \( V(x) \) so that the drift in (2.13) is of the form (2.12). Here \( x = (x^{(1)}, x^{(2)}) \), since \( M_i = 2 \), and \( 0 \leq x^{(i)} \leq 1, i = 1, 2 \). We have here a special case of the construction in section 4.3, the exact details for this special case are found in Example 6.3. Let \( V(x) \) be a function of \( \sum_{i=1}^{2} K_i \) to \( \mathbb{R} \) given by

\[ V(x) = hx^{(1)}x^{(2)}. \]

Then the gradient is

\[ \nabla_x V(x) = \begin{pmatrix} V_{x^{(1)}}' \\ V_{x^{(2)}}' \end{pmatrix} = \begin{pmatrix} hx^{(2)} \\ hx^{(1)} \end{pmatrix}. \]

By (2.7)

\[ D(x) = \begin{pmatrix} D^{(1)}(x) & O_{12} \\ O_{21} & D^{(2)}(x) \end{pmatrix}, \tag{2.14} \]

where

\[ D^{(i)}(x) = x^{(i)}(1 - x^{(i)}), i = 1, 2, O_{12} = O_{21} = 0. \]
Then
\[ D(x) \nabla_x V(x) = \begin{pmatrix} hx^{(1)}(1 - x^{(1)}x^{(2)}) \\ hx^{(2)}(1 - x^{(2)}x^{(1)}) \end{pmatrix}. \] (2.15)

Hence (2.13) is an instance of (2.12). We rewrite (2.15) as
\[ D(x) \nabla_x V(x) = \begin{pmatrix} x^{(1)}(hx^{(2)} - hx^{(1)x^{(2)}}) \\ x^{(2)}(hx^{(1)} - hx^{(1)x^{(2)}}) \end{pmatrix} = \begin{pmatrix} x^{(1)}(V'_{x^{(1)}(x)} - V(x)) \\ x^{(2)}(V'_{x^{(2)}(x)} - V(x)) \end{pmatrix}. \] (2.16)

At this point the expressions can be related to (an underlying) deterministic dynamics for \( x(t) = (x^{(1)}(t), x^{(2)}(t)) \), when (2.13) is written as
\[ \begin{align*}
\frac{dx^{(1)}}{dt}(t) &= x^{(1)}(V'_{x^{(1)}(x)}(x(t)) - V(x(t))) \\
\frac{dx^{(2)}}{dt}(t) &= x^{(2)}(V'_{x^{(2)}(x)}(x(t)) - V(x(t))),
\end{align*} \] (2.17)
which is a so-called replicator equation, and in general mathematical terms, this is a gradient system, the Svirezhev-Shahshahani gradient system, see, e.g., [7, p. 103, pp. 349–351]

3 A Markov Chain of Allele Frequencies: Assumptions and the Transition Probability

We consider a very large population of \( N \) haploid, asexually reproducing individuals. A new generation is brought to life as follows: first we sample, independently and with replacement, \( N \) new individuals from the previous generation, with the probability of choosing an individual of haplotype \( \sigma \) scaled by a selection coefficient \( v_\sigma \), c.f., the next section. Subsequently, we let a mutation event occur at each locus (independently).

There are \( L \geq 1 \) loci. The symbol \( \sigma \) specifies the allele types at these \( L \) loci, \( \sigma = (\sigma_1, \ldots, \sigma_L) \), where \( \sigma_j \in S_j = [1, \ldots, M_j] \), i.e., we accept different numbers of possible allele types at different loci. We write \( \sigma \in \times_{i=1}^L S_i \). An individual \( r \) is represented by its allelic vector \( \sigma(r) \in \times_{i=1}^L S_i, r = 1, \ldots, N \).

Let \( x^{(i)}_k \) be the frequency of individuals carrying allele type \( k \) at locus \( i \). Thus
\[ x^{(i)}_k = \frac{1}{N} \sum_{r=1}^N \delta_{\sigma_i(r),k}, \quad k \in [1, \ldots, M_i], \] (3.1)
where \( \delta_{i,k} \) is the Kronecker delta (or the Iverson bracket). Let us set
\[ x^{(i)} = \left(x^{(i)}_1, \ldots, x^{(i)}_{M_{t-1}}\right). \] (3.2)

In sections 6 and 7 \( x^{(i)} \) will be treated as an \( M_i - 1 \times 1 \) vector, but at this stage this interpretation is not operationally necessary. Thus \( x^{(i)} \) lies in the simplex \( K_i \) in (2.4).

Furthermore, we have a set of non-negative integers or the occupancy distribution of the \( M_i \) alleles,
\[ J^{(i)} = \left\{ j^{(i)} = (j^{(i)}_1, \ldots, j^{(i)}_{M_i}) \in \mathbb{Z}_{+}^{M_i} \mid \sum_{k=1}^{M_i} j^{(i)}_k = N \right\}. \] (3.3)
For example, $j_k^{(i)} = N \cdot x_k^{(i)}$. Thus $J^{(i)}$ can be regarded as subset of $K_i$ consisting of all the lattice points with mesh $1/N$. The number of distinguishable occupancy distributions in $J^{(i)}$ is equal to $\binom{M_i - 1 + N}{N}$. Corresponding to (2.5) we have

$$j = (j^{(1)}, j^{(2)}, \cdots, j^{(L)})$$

and

$$j \in \times_{i=1}^{L} J^{(i)}.$$  

Let now $n = 0, 1, 2, \ldots$ represent discrete time and $N > 0$. We consider a Markov chain, homogeneous in discrete (scaled) time, $Y^{(N)} = \{Y^{(N)}(\frac{n}{N})\}_{n \in \mathbb{Z}}$, with the state space $\times_{i=1}^{L} J^{(i)}$. The transition probability is for any $j \in \times_{i=1}^{L} J^{(i)}$ and $k \in \times_{i=1}^{L} J^{(i)}$ denoted by

$$P_{j,k} = P\left(Y^{(N)}\left(\frac{n+1}{N}\right) = k \mid Y^{(N)}\left(\frac{n}{N}\right) = j\right).$$

For each locus $i$ there is the random process of occupation numbers $Y_i^{(N)} = \{Y_i^{(N)}(\frac{n}{N})\}_{n \in \mathbb{Z}}$, with the state space $J^{(i)}$ so that $Y^{(N)}(\frac{n}{N}) = \left(\begin{array}{c} Y_i^{(N)}(\frac{n}{N}) \\ \vdots \\ Y_L^{(N)}(\frac{n}{N}) \end{array}\right)_{1 \leq i \leq L}$.

**Assumption 3.1.** The locus-wise component processes $Y_i^{(N)}$ at any time $n + 1$ are conditionally independent of each other given the process $Y^{(N)}$ at time $n$: For any $j \in \times_{i=1}^{L} J^{(i)}$ and $k \in \times_{i=1}^{L} J^{(i)}$ and any $n \geq 0$ it holds that

$$P_{j,k} = \prod_{i=1}^{L} P\left(Y_i^{(N)}\left(\frac{n+1}{N}\right) = k^{(i)} \mid Y^{(N)}\left(\frac{n}{N}\right) = j\right).$$

There is clearly for any locus $i$ a vector process of random occupation numbers, i.e.,

$$Y_i^{(N)}(n) = \left(Y_i^{(N)}\left(\frac{n}{N}\right), Y_i^{(N)}\left(\frac{n}{N}\right), \cdots, Y_i^{(N)}\left(\frac{n}{N}\right)\right),$$

where, if we sum over the allele types at any locus $i$, $\sum_{r=1}^{M_i} Y_i^{(N)}\left(\frac{n}{N}\right) = N$.

The transition probability $P_{j,k}$ is given by specification of the conditional probabilities $P\left(Y_i^{(N)}\left(\frac{n+1}{N}\right) = k^{(i)} \mid Y^{(N)}\left(\frac{n}{N}\right) = j\right)$. If $j \in \times_{i=1}^{L} J^{(i)}$ and $k \in J^{(i)}$, we take

$$P\left(Y_i^{(N)}\left(\frac{n+1}{N}\right) = k^{(i)} \mid Y^{(N)}\left(\frac{n}{N}\right) = j\right) = \frac{N!}{k_1^{(i)}! \cdots k_{M_i}^{(i)}!} p_1^{(i)}(j) k_1^{(i)} \cdots p_{M_i}^{(i)}(j) k_{M_i}^{(i)}.$$

which is a multinomial distribution, where $p_k^{(i)}(j)$ is the probability of the allele type $k$ at locus $i$. Our goal is to express the dependence of

$$[p_1^{(i)}(j), \cdots, p_{M_i-1}^{(i)}(j)] \in K_i$$
on $j$. For any $j$ we may compute the corresponding relative frequency vector $x \in K$, of the form (2.5) for the current population. We drop, for simplicity of expression, the
dependence on the $L$ occupancy distributions in $j$ in the formulas that in the rest of this section.

We start by the fraction of individuals with haplotype $\sigma = (\sigma_j, \cdots, \sigma_{j_L})$ denoted by $f(\sigma)$. This is simply the product of the (relative) population frequencies for an allele $\sigma_j \in S = [1, \cdots, M]$, for each locus,

$$f(\sigma) = \prod_{i=1}^{L} x_{\sigma_j}^{(i)},$$

(3.9)

i.e. this is the product of fractions picked from $[M]$ according to $(\sigma_j, \cdots, \sigma_{j_L})$ and $(3.10)$.

Let us next define $f_k^{(i)}(\sigma)$ as the conditional frequency of the haplotype $\sigma$ given $\sigma_i = k \in S_i$, which is simply the same expression as above but with Kronecker delta $\delta_{\sigma_i,k}$ substituted for $x_{\sigma_i}^{(i)}$,

$$f_k^{(i)}(\sigma) = \delta_{\sigma_i,k} \prod_{j \neq i}^{L} x_{\sigma_j}^{(j)} = \frac{\delta_{\sigma_i,k}}{x_k^{(i)}} f(\sigma).$$

(3.10)

If $x_k^{(i)} = 0$ for the population at a time, then $f(\sigma) = 0$ by (3.9), we can take by convention $f_k^{(i)}(\sigma) = 0$. The function $v_\sigma$ gives the viability of an individual with the allelic vector $\sigma$. We set

$$\bar{v} = \sum_{\sigma \in L_i \times S_i} f(\sigma) v_\sigma, \quad \bar{v}_k^{(i)} = \sum_{\sigma \in L_i \times S_i} f_k^{(i)}(\sigma) v_\sigma.$$  

(3.11)

$\bar{v}$ can be interpreted as the average selection strength for the population as a whole (in the current state $x \in \times_{i=1}^{L} K_i$, and $\bar{v}_k^{(i)}$ is the average selection strength for allele type $k$ at locus $i$.

Without mutation, the probability of drawing an individual with allele type $k$ at locus $i$ is

$$q_k^{(i)} = \frac{\sum_{\sigma \in L_i \times S_i} \delta_{\sigma_i,k} f(\sigma) v_\sigma}{\sum_{\sigma \in L_i \times S_i} f(\sigma) v_\sigma},$$

(3.12)

which can be in view of (3.11) written as

$$q_k^{(i)} = x_k^{(i)} \frac{\bar{v}_k^{(i)}}{\bar{v}}.$$  

(3.13)

Let next $v_k^{(i)}$ be the probability that an $l$-allele at locus $i$ mutates to an $k$-allele at locus $i$ after the selection event. In this $v_k^{(i)}$ does not depend on $j$. Any other allele type can mutate into a $k$-allele, as governed by the probabilities $v_l^{(i)}$, so the final probability of ending up with a $k$-allele at locus $i$ is $p_k^{(i)} = \sum_{l=1}^{M_i} v_l^{(i)} q_l^{(i)}$. As the probability of no mutation can be written as $v_{kk}^{(i)} = 1 - \sum_{l \neq k} v_l^{(i)}$, we get

$$p_k^{(i)} = \sum_{l=1}^{M_i} v_l^{(i)} q_l^{(i)} = \sum_{l \neq k} v_l^{(i)} q_l^{(i)} + v_{kk}^{(i)}$$

(3.14)

$$= \sum_{l=1}^{M_i} v_l^{(i)} q_l^{(i)} + \left( 1 - \sum_{l=1}^{M_i} v_l^{(i)} \right) q_k^{(i)} = \sum_{l \neq k} v_l^{(i)} q_l^{(i)} - v_{kk}^{(i)} q_k^{(i)} + q_k.$$
By inserting (3.13) we obtain

\[ p_k(i) = \sum_{l=1}^{M_i} \left[ v_{lk}^i x_l^i \left( \frac{v_l}{\bar{v}} \right) - v_{kl}^i x_k^i \left( \frac{v_k}{\bar{v}} \right) \right] + x_k^i \left( \frac{v_k}{\bar{v}} \right). \] (3.15)

This completes the description of the transition probability in (3.8). We proceed by re-scalings and translations of the quantities in \( p_k(i) \) to get over to a continuous time SDE.

4 The Drift Function

4.1 Scaling of the Transition Probability; The limiting Drift function

With \( L \) loci, and \( M_i \) alleles at locus \( i \), let us consider for all \( l, k \) and all \( i \) the parameters \( u_{lk}^i, \bar{m} \) and \( \bar{m}_k^i \) obtained by scaling and shifting with the inverse population size the parameters of (3.15) as follows:

\[ u_{lk}^i = \frac{v_{lk}^i}{\bar{v}}, \quad \bar{m} = \bar{v} - \frac{1}{N}, \quad \bar{m}_k^i = \frac{v_k}{\bar{v}} - \frac{1}{N}. \] (4.1)

Then it follows by straightforward substitutions in (3.15), lemma 10.3 gives the detailed limiting argument, that as \( N \to +\infty \)

\[ \frac{p_k(i) - x_k^i}{1} \to p_k^i(x), \]

where

\[ p_k^i(x) = \sum_{l=1}^{M_i} \left[ u_{lk}^i x_l^i - u_{kl}^i x_k^i \right] + x_k^i \left( \bar{m}_k^i - \bar{m} \right). \] (4.2)

For things to make the desired sense, \( p_k^i(x) \) in (4.2) should be the \( k \)th component of the vector for locus \( i \) in \( \mu(x) + D(x) \nabla x V(x) \) for some suitable \( V(x) \). In order to establish this we start by making an extra assumption, the parent-independent mutation. This assumption is also known as Kingman’s house of cards assumption, see [25] and [31].

Assumption 4.1.

\[ u_{lk}^i = u_k^i \] (4.3)

for all \( l, k \) and \( i \). In addition we assume that

\[ u_k^i > 0 \] (4.4)

for all \( k \) and \( i \). \( \square \)
Lemma 4.1. Assume that (4.3) holds. Let
\[ g_k^{(i)} = \sum_{l=1, l \neq k}^{M_i} \left[ u_{lk}^{(i)} x_l^{(i)} - u_{kl}^{(i)} x_k^{(i)} \right] \]  
(4.5)

Then
\[ g_k^{(i)} = u_k^{(i)} - \bar{u} x_k^{(i)} , \]  
where
\[ \bar{u}^{(i)} = \sum_{l=1}^{M_i} u_l^{(i)} \]  
(4.7)

and in (4.2)
\[ p_k^{(i)}(x) = g_k^{(i)} + x_k^{(i)} \left( \bar{m}_k^{(i)} - \bar{m} \right) . \]  
(4.8)

Proof: By (4.5) and (4.3) we get
\[ g_k^{(i)} = \sum_{l=1, l \neq k}^{M_i} \left[ u_{lk}^{(i)} x_l^{(i)} - u_{kl}^{(i)} x_k^{(i)} \right] = u_k^{(i)} (1 - x_k^{(i)}) - x_k^{(i)} \sum_{l=1, l \neq k}^{M_i} u_l^{(i)} . \]

Now we evoke \( \bar{u}^{(i)} = \sum_{l=1}^{M_i} u_l^{(i)} \) and get
\[ = u_k^{(i)} (1 - x_k^{(i)}) - \left( \bar{u}^{(i)} - u_k^{(i)} \right) x_k^{(i)} = u_k^{(i)} - \bar{u}^{(i)} x_k^{(i)} . \]

Hereewith we set
\[ \mu^{(i)}(x) \overset{\text{def}}{=} \begin{pmatrix} u_1^{(i)} - \bar{u}^{(i)} x_1^{(i)} \\ \vdots \\ u_{M_i-1}^{(i)} - \bar{u}^{(i)} x_{M_i-1}^{(i)} \end{pmatrix} . \]  
(4.9)

4.2 Population fitnesses

Next we study the second term in the right hand side of \( p_k^{(i)}(x) \) in (4.2), i.e., \( x_k^{(i)} \left( \bar{m}_k^{(i)} - \bar{m} \right) \).

Here \( \bar{m}_k^{(i)} \) and \( \bar{m} \) are expressing a population fitness, which is a quantitative trait of a population, thought of as mapping the genotype to the expected reproductive success of an organism. Here we have
\[ \bar{m} = \sum_{\sigma} f(\sigma) m_{\sigma}, \quad \bar{m}_k^{(i)} = \sum_{\sigma} f_k^{(i)}(\sigma) m_{\sigma}, \]  
(4.10)

where \( m_{\sigma} \) is the Potts-type interaction map
\[ m_{\sigma} \overset{\text{def}}{=} 1 + \sum_{r=1}^{L} h_r(\sigma_r) + \sum_{1 \leq r < s \leq L} J_{rs}(\sigma_r, \sigma_s), \]  
(4.11)

i.e. selective interaction between loci is limited to pairwise links. We assume a double symmetry in the sense that
Assumption 4.2.
\[ J_{rs}(k,l) = J_{sr}(l,k). \] (4.12)

Then we get (see Appendix A)
\[ \bar{m} = \sum_{\sigma \in \times_{i=1}^{L} S_i} f(\sigma)m_\sigma = 1 + \sum_{r=1}^{L} \sum_{t=1}^{M_r} h_r(t)x_t^{(r)} + \sum_{1 \leq r < s \leq L} \sum_{t=1}^{M_r} \sum_{n=1}^{M_s} J_{rs}(t,n)x_t^{(r)}x_n^{(s)}, \] (4.13)
and (see Appendix A),
\[ \bar{m}_k^{(i)} = 1 + h_i(k) + \sum_{r \neq i}^{L} \sum_{t=1}^{M_r} h_r(t)x_t^{(r)} + \sum_{r \neq i}^{L} \sum_{t=1}^{M_r} \sum_{m=1}^{M_s} J_{ir}(k,m)x_t^{(r)}x_m^{(s)}, \] (4.14)
which yields
\[ x_k^{(i)} \left( \bar{m}_k^{(i)} - \bar{m} \right) = \]
\[ x_k^{(i)} \left( h_i(k) - \sum_{k' = 1}^{M_i} h_i(k')x_k^{(i)} + \sum_{r \neq i}^{L} \sum_{t=1}^{M_r} \left[ J_{ir}(k,t) - \sum_{k' = 1}^{M_i} J_{ir}(k',t)x_k^{(i)} \right] x_t^{(r)} \right). \] (4.15)

Let us set for simplicity of writing
\[ \bar{h}_i(k) \overset{\text{def}}{=} \left( h_i(k) + \sum_{r \neq i}^{L} \sum_{m=1}^{M_r} J_{ir}(k,m)x_m^{(r)} \right). \] (4.16)

Then we have the following lemma.

**Lemma 4.2.** For \( k = 1, \ldots, M_i - 1, \)
\[ x_k^{(i)} \left( \bar{m}_k^{(i)} - \bar{m} \right) = \sum_{l=1}^{M_i} d_{kl}^{(i)} \bar{h}_i(l) \] (4.17)

The proof is a lengthier technical exercise recapitulated in Appendix E.

**Lemma 4.3.**
\[ \sum_{l=1}^{M_i} d_{kl}^{(i)} \bar{h}_i(l) = \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \bar{h}_i(l) - x_k^{(i)} x_{kl}^{(i)} \bar{h}_i(M_i). \] (4.18)
Proof:
\[
\sum_{l=1}^{M_i} d^{(i)}_{kl} \bar{h}_i(l) = \sum_{l=1}^{M_i-1} d^{(i)}_{kl} \bar{h}_i(l) + d^{(i)}_{kM_i} \bar{h}_i(M_i) \\
= \sum_{l=1}^{M_i-1} d^{(i)}_{kl} \bar{h}_i(l) - x^{(i)}_k x^{(i)}_{M_i} \bar{h}_i(M_i).
\]
\[(4.19)\]

The following identity holds for any function \(V(x)\) that has the required partial derivatives.

**Lemma 4.4.**
\[
\sum_{l=1}^{M_i-1} d^{(i)}_{kl} (x) V'_{x_i^{(i)}}(x) = x^{(i)}_k \left[ V'_{x_k^{(i)}}(x) - \sum_{l=1}^{M_i-1} x^{(i)}_l V'_{x_l^{(i)}}(x) \right].
\]
\[(4.20)\]

Proof:
\[
\sum_{l=1}^{M_i-1} d^{(i)}_{kl} (x) V'_{x_i^{(i)}}(x) = -x^{(i)}_k \sum_{l=1, l \neq k}^{M_i-1} x^{(i)}_l V'_{x_l^{(i)}}(x) + (1 - x^{(i)}_k) x^{(i)}_k V'_{x_k^{(i)}}(x) \\
= -x^{(i)}_k \sum_{l=1, l \neq k}^{M_i-1} x^{(i)}_l V'_{x_l^{(i)}}(x) + x^{(i)}_k V'_{x_k^{(i)}}(x).
\]
\[\square\]

We construct explicitly the potential \(V(x)\) in Svirezhev-Shahshahani gradient form \(D(x) \nabla_x V(x)\).

### 4.3 The Potential \(V(x)\)

Let us first expand our basic notation in (3.2) (now a column vector) as follows. We introduce the \(M_i \times 1\) vector
\[
x^{(i)} = \begin{pmatrix}
  x^{(i)}_1 \\
  \vdots \\
  x^{(i)}_{M_i}
\end{pmatrix}.
\]
\[(4.21)\]

We stack these vectors to the \(\sum_{i=1}^{L} M_i \times 1\) vector (written in the transposed \((T)\) form for economy of space)
\[
x^T = (x^{(1)}, x^{(2)}, \ldots, x^{(L)})
\]
\[(4.22)\]
\[
= (x_1^{(1)}, x_{M_1}^{(1)}, x_1^{(2)}, \ldots, x_{M_2}^{(2)}, \ldots, x_1^{(L)}, \ldots, x_{M_L}^{(L)}).
\]
Let \( h \) be the \( \sum_{i=1}^{L} M_i \times 1 \) vector of one locus selection parameters

\[
h^T = (h_1(1), h_1(2), \cdots, h_1(M_1) \cdots h_L(1), h_L(2), \cdots h_L(M_L)).
\]

The next goal is to define a \( \sum_{i=1}^{L} M_i \times \sum_{r=1}^{L} M_r \) matrix \( A \) so that the quadratic form

\[
\mathbf{x}^T A \mathbf{x}
\]

can be used to define the desired potential \( V(\mathbf{x}) \).

Let first \( \mathbf{0}^{(i)} \) denote the \( M_i \times M_i \) matrix of zeroes for \( i = 1, 2, \ldots, L \) (not to be confused with the zero matrices of other dimensions in (2.7)). These matrices \( \mathbf{0}^{(i)} \) are inserted as block matrices in the main diagonal of \( A \), i.e.,

\[
A \overset{\text{def}}{=} \begin{pmatrix}
\mathbf{0}^{(1)} & \mathbf{J}_1(M_2) & \mathbf{J}_1(M_3) & \cdots & \cdots & \cdots & \mathbf{J}_1(M_L) \\
\mathbf{J}_2(M_1) & \mathbf{0}^{(2)} & \mathbf{J}_2(M_3) & \cdots & \cdots & \cdots & \mathbf{J}_2(M_L) \\
\vdots & \vdots & \vdots & \ddots & \cdots & \cdots & \vdots \\
\mathbf{J}_l(M_1) & \cdots & \cdots & \mathbf{J}_l(M_{l-1}) & \mathbf{0}^{(i)} & \mathbf{J}_l(M_{i+1}) & \cdots & \mathbf{J}_l(M_L) \\
\vdots & \vdots & \vdots & \vdots & \ddots & \cdots & \vdots & \vdots \\
\mathbf{J}_L(M_1) & \mathbf{J}_L(M_2) & \mathbf{J}_L(M_3) & \cdots & \cdots & \cdots & \mathbf{0}^{(L)}
\end{pmatrix}
\]

(4.23)

Here \( \mathbf{J}_i(M_l) \) is a block matrix of dimension \( M_i \times M_l \). It is given as

\[
\mathbf{J}_i(M_l) = \begin{pmatrix}
J_{il}(1,1) & J_{il}(1,2) & \cdots & J_{il}(1,M_l) \\
J_{il}(2,1) & J_{il}(2,2) & \cdots & J_{il}(2,M_l) \\
\vdots & \vdots & \ddots & \vdots \\
J_{il}(M_l,1) & J_{il}(M_l,2) & \cdots & J_{il}(M_l,M_l)
\end{pmatrix}
\]

(4.24)

by means of the two locus selection parameters at locus \( i \). By the symmetry assumption \( J_{il}(l,k) = J_{lk}(i,l) \) \( \mathbf{J}_i(M_l) \) is a symmetric matrix. Thus, a generic \( 1 \times \sum_{r=1}^{L} M_r \) row in \( A \) looks like

\[
J_{i1}(k,1), \ldots J_{i1}(k,M_1), J_{i2}(k,1), \ldots J_{i2}(k,M_2), \ldots, \mathbf{0}^{(i)}_k, \ldots, J_{iL}(k,1), \ldots J_{iL}(k,M_L)),
\]

(4.25)

where now \( \mathbf{0}^{(i)}_k \) is the \( k \)th row of in \( \mathbf{0}^{(i)} \) with \( M_i \) zeroes. We note also that \( \mathbf{J}_i(M_l) \) and \( \mathbf{x}^{(i)} \) in (4.21) are compatible for the matrix multiplication \( \mathbf{J}_i(M_l) \mathbf{x}^{(l)} \).

We observe that the elements in the \( \sum_{i=1}^{L} M_i \times 1 \) vector \( A \mathbf{x} \) are by the construction above for all cases of \((i,k)\) nothing but the expressions

\[
\sum_{r=1}^{L} \sum_{m=1}^{M_r} J_{ir}(k,m)x^{(i)}_m.
\]

(4.26)

By the symmetry of \( \mathbf{J}_i(M_l) \)'s the matrix \( A \) is a symmetric matrix. We set

\[
W(\mathbf{x}) \overset{\text{def}}{=} \mathbf{x}^T h + \frac{1}{2} \mathbf{x}^T A \mathbf{x}.
\]

(4.27)

We note that \( W(\mathbf{x}) \) is a function of \( \sum_{i=1}^{L} M_i \) variables, and that a partial derivative like \( \frac{\partial}{\partial x_m} W(\mathbf{x}) \) means differentiation w.r.t. the appropriate position in \( \mathbf{x} \). It turns out that

\[
V(\mathbf{x}) := W(\mathbf{x})
\]

(4.28)

is the function sought for the Svirezhev-Shahshahani gradient form.
4.4 The Svirezhev-Shahshahani gradient

Lemma 4.5.

\[ \sum_{l=1}^{M_i} d_{kl}^{(i)} \tilde{h}_i(l) = \sum_{l=1}^{M_i-1} d_{kl}^{(i)} V'_{x_i^{(i)}}(\mathbf{x}) \]  

(4.29)

Proof: We prove the assertion of the lemma by expanding the right hand side of (4.29). The pertinent partial derivatives are for \( l = 1, \ldots, M_i - 1 \)

\[ V'_{x_i^{(i)}}(\mathbf{x}) = \frac{\partial}{\partial x_{i}^{(i)}} W(\mathbf{x}) - \frac{\partial}{\partial x_{M_i}^{(i)}} W(\mathbf{x}), \]

since the derivative of the inner function is \( \frac{d}{dx} x_i^{(i)} = 1 - \sum_{k=1}^{M_i-1} x_i^{(i)} \) in \( W \) w.r.t \( x_i^{(i)} \) equals \(-1\). We note that

\[ \frac{\partial}{\partial x_{i}^{(i)}} \mathbf{X}^T \mathbf{h} - \frac{\partial}{\partial x_{M_i}^{(i)}} \mathbf{X}^T \mathbf{h} = h_i(l) - h_i(M_i). \]

Next, since \( A \) is a symmetric matrix,

\[ \nabla_{\mathbf{x}} \left[ \frac{1}{2} \mathbf{X}^T A \mathbf{x} \right] = A \mathbf{x}. \]

Hence we obtain by (4.26) that

\[ \frac{\partial}{\partial x_{i}^{(i)}} W(\mathbf{x}) = \sum_{r=1}^{L} \sum_{m=1}^{M_r} J_{ir}(l, m) x_{m}^{(r)} \]

and

\[ \frac{\partial}{\partial x_{M_i}^{(i)}} W(\mathbf{x}) = \sum_{r=1}^{L} \sum_{m=1}^{M_r} J_{ir}(M_i, m) x_{m}^{(r)}. \]

Hence

\[ V'_{x_i^{(i)}}(\mathbf{x}) = \frac{\partial}{\partial x_{i}^{(i)}} W(\mathbf{x}) - \frac{\partial}{\partial x_{M_i}^{(i)}} W(\mathbf{x}) \]

\[ = h_i(l) - h_i(M_i) + \sum_{r=1}^{L} \sum_{m=1}^{M_r} J_{ir}(k, m) x_{m}^{(r)} - \sum_{r=1}^{L} \sum_{m=1}^{M_r} J_{ir}(M_i, m) x_{m}^{(r)}. \]

In view of (4.16) we have thus shown that

\[ V'_{x_i^{(i)}}(\mathbf{x}) = \tilde{h}_i(l) - \tilde{h}_i(M_i). \]

(4.30)

Hence

\[ \sum_{l=1}^{M_i-1} d_{kl}^{(i)} V'_{x_i^{(i)}}(\mathbf{x}) = \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \tilde{h}_i(l) - \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \tilde{h}_i(M_i). \]

(4.31)

The last term is

\[ \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \tilde{h}_i(M_i) = \tilde{h}_i(M_i) \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \]

\[ = \tilde{h}_i(M_i) - \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \tilde{h}_i(l). \]

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\[
\begin{align*}
= \tilde{h}_i(M_i) \left[ \sum_{l=1 \atop l 
eq k}^{M_i-1} \left( -x_k^{(i)} x_l^{(i)} + x_k^{(i)} - (x_k^{(i)})^2 \right) \right] \\
= \tilde{h}_i(M_i) x_k^{(i)} \left[ -1 - \sum_{l=1 \atop l 
eq k}^{M_i-1} x_l^{(i)} + 1 - x_k^{(i)} \right] \\
= \tilde{h}_i(M_i) x_k^{(i)} \left[ (-1)(1 - x_k^{(i)} - x_{M_i}^{(i)}) + 1 - x_k^{(i)} \right] \\
= \tilde{h}_i(M_i) x_k^{(i)} \left[ -1 + x_k^{(i)} + x_{M_i}^{(i)} + 1 - x_k^{(i)} \right] = x_k^{(i)} x_{M_i}^{(i)} \tilde{h}_i(M_i).
\end{align*}
\]

Thus we have in (4.31) that
\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)} V'_{x_l^{(i)}}(x) = \sum_{l=1}^{M_i-1} d_{kl}^{(i)} \tilde{h}_i(l) - x_k^{(i)} x_{M_i}^{(i)} \tilde{h}_i(M_i)
\]

which is the left hand side of (4.29), as claimed. □

In view of the preceding lemma 4.1
\[
p^{(i)}(x) = u_k^{(i)} - \bar{u} + x_k^{(i)} \left( \bar{m}_k^{(i)} - \bar{m} \right)
\]

and by lemma 4.2
\[
p^{(i)}(x) = u_k^{(i)} - \bar{u} + \sum_{l=1}^{M_i} d_{kl}^{(i)} \tilde{h}_i(l)
\]

and by lemma 4.5 for the potential in (4.28)
\[
p^{(i)}(x) = u_k^{(i)} - \bar{u} + \sum_{l=1}^{M_i-1} d_{kl}^{(i)} V'_{x_l^{(i)}}(x).
\]

By rules of matrix calculus we observe that $\sum_{l=1}^{M_i-1} d_{kl}^{(i)} V'_{x_l^{(i)}}(x)$ is the $k$th component in the $(M_i - 1) \times 1$ - vector
\[
D^{(i)}(x) V'_{x_l^{(i)}}(x).
\]

When define an $(M_i - 1) \times 1$ vector
\[
G^{(i)}(x) \equiv \begin{pmatrix}
  x_1^{(i)} \left( \bar{m}_1^{(i)} - \bar{m} \right) \\
  \vdots \\
  x_{M_i-1}^{(i)} \left( \bar{m}_{M_i-1}^{(i)} - \bar{m} \right)
\end{pmatrix},
\]

we have shown that
\[
G^{(i)}(x) = D^{(i)}(x) V'_{x_l^{(i)}}(x).
\]
Thus adding
\[ G(x) = D(x) V'_x (x) = \begin{pmatrix} D^{(1)}(x) \nabla_{x^{(1)}} V(x) \\ \vdots \\ D^{(L)}(x) \nabla_{x^{(L)}} V(x) \end{pmatrix} \]
to \( \mu(x) \) in (4.9), we have an explicit expression for the drift function in (2.11). Next we prove the weak convergence of the sequence of interpolated Markov chains to (2.11).

5 The Diffusion Approximation

The studies summarized in this section prove the weak convergence of a sequence of the Markov chains defined in section 3 to a diffusion process and consist of straightforward verifications the conditions for weak convergence found in [10, Theorem 7.1], [37, Lemma 4.1], see also [16, ch.10 thm 3.5].

These conditions correspond one-to-one to the technical lemmas in Appendix D, and are given as (E.4), (E.8), (E.9) and (E.10). The level of mathematical effort herewith is merely to verify that these conditions are valid in the current situation, not to contribute to a general advancement of diffusion approximation.

We recall variables (4.1) scaled by the inverse population size, or, more conveniently:

**Assumption 5.1.** For all \( l, k \) and all \( i \)

\[ v^{(i)}_{lk} = \frac{u^{(i)}_{lk}}{N}, \]  
\[ \bar{v} = 1 + \frac{\bar{m}}{N}, \]  
\[ \bar{v}^{(i)}_{k} = 1 + \frac{\bar{m}^{(i)}_{k}}{N}, \]

where \( \bar{m} \) is given in (4.11) and \( \bar{m}^{(i)}_{k} \) is in (4.15).

We normalize in (3.7) to get

\[ X^{(N)}_{i,k}(n) = \frac{1}{N} Y^{(N)}_{i,k} \left( \frac{n}{N} \right) \]  
\[ X^{(N)}_{(i)}(n) = \left( X^{(N)}_{i,1}(n), X^{(N)}_{i,2}(n), \ldots, X^{(N)}_{i,M_i-1}(n) \right). \]

We have thus also

\[ X^{(N)}(n) = \left\{ X^{(N)}_{(i)}(n) \right\}_{1 \leq i \leq M}, \]  
\[ X^{(N)} = \left\{ X^{(N)}(n) \right\}_{n \geq 0}, \]  
\[ X^{(N)}_{i,k}(n) = \frac{1}{N} Y^{(N)}_{i,k} \left( \frac{n}{N} \right). \]
and

\[ X^{(N)} = \left\{ X^{(N)}(n) \right\}_{n \geq 0}. \]  

Let us next define the process \( \{X^{(N)}(t) \mid t \geq 0\} \) as the piece-wise constant continuous time interpolation of the process \( X^{(N)} \) in (5.7)

\[ X^{(N)}(t) = X^{(N)} \left( \frac{1}{N} \lfloor tN \rfloor \right), \quad 0 \leq t < +\infty, \]

where \([x]\) is the integer part of a real number \(x\). Let now for every \(i \in \{1, \ldots , L\}\)

\[ D^{(i)} \overset{\text{def}}{=} \left\{ f|_{K_i} \mid f \in C^4(\mathbb{R}^{\sum_{i=1}^{L} M_i}) \quad \text{and} \quad \frac{\partial}{\partial x_i} f|_{K_i} = \left( \frac{\partial}{\partial x_i} f \right)|_{K_i} \right\}. \]  

(5.10)

\(D^{(i)}\) contains the restrictions of four times differentiable real valued functions \(f\) on \(\mathbb{R}^{\sum_{i=1}^{L} M_i}\) to \(K\) such that the restriction of a partial derivative of \(f\) to \(K_i\), \(\left( \frac{\partial}{\partial x_i} f \right)|_{K_i}\), equals the same partial derivative of the restriction \(f|_{K_i}\). The requirement of \(C^4\)-functions in the domain is implicitly needed in the uniqueness part of the proof of the next proposition and is due to \([14]\). The differential generator \(\mathcal{L}\) of the desired limiting process is defined by

\[ \mathcal{L} = \sum_{i=1}^{L} \sum_{k=1}^{M_i-1} p_k^{(i)}(x) \frac{\partial}{\partial x_k^{(i)}} + \frac{1}{2} \sum_{i=1}^{L} \sum_{k=1}^{M_i-1} \sum_{l=1}^{M_i-1} \left[ d_{kl}^{(i)}(x) \right] \frac{\partial^2}{\partial x_k^{(i)} \partial x_l^{(i)}} \]  

with the domain given from (5.10) by

\[ \mathcal{D} = \times_{i=1}^{L} D^{(i)}. \]

**Proposition 5.1.** If the assumptions \(3.1, (4.3)\) and \((4.4)\) hold, and if \(X^{(N)}(0) \to x_0\), as \(N \to +\infty\), then the process \(\{X^{(N)}(t) \mid t \geq 0\}\) converges under the scalings in Assumption \(5.1\) weakly as \(N \to +\infty\) to \(\{X(t) \mid t \geq 0\}\), which is the unique solution of the martingale problem for \(\mathcal{L}\) (5.11).

**Proof:**

The proof is in three steps. The first, **Step a)** identifies the drift \(\mu(x) + D(x)V'_{x}(x)\) and diffusion \(D(x)\) of a limiting process. It remains to prove the uniqueness of the martingale problem defined by this drift and diffusion. If the Siverezhev-Shahshahani gradient form is removed, we are faced with independent and uncoupled multiallelic processes, where the uniqueness result of \([14]\) can be applied, as shown in **Step b)**. In step **Step c)**, we use the finding in **Step b)** by adding the Siverezhev-Shahshahani gradient form. We can then apply the Girsanov theorem on transformation of drift and measure to prove the desired uniqueness.

**Step a)** The convergences, which are uniform in \(x \in \times_{i=1}^{L} K_i\), in \((E.4)\), \((E.8)\), \((E.9)\) and \((E.10)\) with the continuous limiting drift \(\mu(x) + D(x)V'_{x}(x)\) and the diffusion (genetic drift) \((E.10)\) as well as \((E.12)\), for every locus and for every allele type at every locus, have been shown in the Appendix D.
By these facts the assertion in the proposition follows by, see e.g., [10, Theorem 7.1], and [37, Lemma 4.1.], if the martingale problem associated to the differential operator $L$, or $\text{MP}(\mu + \nabla V, D)$ (c.f. (2.11)) is unique. We shall now establish the desired uniqueness by first proving uniqueness for an uncoupled system of SDE’s.

**Step b) No selection** Now we consider at every locus $i$ the multivariate diffusion $Y^i = \{Y^i(t) = (Y^i_1(t), \ldots, Y^i_{M_i-1}(t)) \mid t \geq 0\}$ with values in $K_i$, and with the notation \((4.9)\) satisfying
\[
dY^i(t) = \mu^{(i)}(Y^i(t))dt + D^{(i)}(Y^i(t))^{1/2}dW^i(t). \tag{5.12}
\]

For diffusions with values in $K_i$ and with diffusion matrix $D^{(i)}(x)$, it holds, here we need $C^4$ in the domain $\mathcal{D}$, by [14], or, [8, p.991], [39] p.134 and p. 135 Corollary 2.1, that if for every $y \in K_i$
\[
\sum_{k=1}^{M_i-1} \mu^{(i)}(y) \leq 0, \text{ with } \sum_{k=1}^{M_i-1} y_k = 1 \tag{5.13}
\]
and for every $k$
\[
\mu^{(i)}(y) \geq 0 \text{ if } y_k = 0, \tag{5.14}
\]
then the martingale problem corresponding to $(Y^i, \mu^{(i)}(y), D^i)$ has a unique solution. We check next that these conditions hold. First, if $\sum_{k=1}^{M_i-1} y_k = 1$, then
\[
\sum_{k=1}^{M_i-1} \mu^i_k(y) = \sum_{k=1}^{M_i-1} \left( u_k - \bar{u}^{(i)} y_k \right) = \sum_{k=1}^{M_i-1} u_k - \bar{u}^{(i)} \sum_{k=1}^{M_i-1} y_k = -\bar{u}^{(i)} \sum_{k=1}^{M_i-1} y_k = -u^{(i)} \leq 0,
\]
and (5.13) is checked. For (5.14) we observe that if $y_k = 0$, then
\[
\mu^i_k(y) = u_k - \bar{u}^{(i)} y_k = u_k > 0.
\]
Hence, the martingale problem $\text{MP}(\mu^{(i)}(y), D^i)$ has a unique solution. By (4.9) we have $\mu(y) = (\mu^{(1)}(y), \ldots, \mu^{(L)}(y))$. As the processes $Y^{(i)}$ are independent and uncoupled, it follows that the martingale problem corresponding to the diffusion
\[
\text{MP}(\mu(y), D)
\]
and represented by the system of locus-wise decoupled stochastic differential equations
\[
dY(t) = \mu(Y(t))dt + D^{1/2}(Y(t))dW(t), \tag{5.15}
\]
has a unique solution $P$. 

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Step c) Change of drift and change of measure

The equation (4.36) is clearly obtained from (5.15) by a change of drift. Let now $P$ the unique probability measure such that $X$ satisfies

$$dX(t) = \mu(X(t))dt + D^{1/2}(X(t))dB(t), \quad (5.16)$$

w.r.t. a $P$-Wiener process $B = \{B^{(i)}\}_{i=1}^L$. Then we recall (2.11), or,

$$dX(t) = \mu(X(t))dt + D(X(t))\nabla_x V(X(t))dt + D^{1/2}(X(t))dW(t).$$

We set for any $i$ and $t > 0$

$$H(t) = (-1) \cdot D^{1/2}(X(t))\nabla_x V(X(t)). \quad (5.17)$$

The expression $D^{1/2}(x)\nabla_x V(x)$ is well defined on all of $K$ and its vector norm is uniformly bounded there. Then, by [26, Theorem 6.4.7, p. 153] we can thus define $Q$ by the Radon-Nikodym derivative

$$\frac{dQ}{dP} = e^{\int_0^t H(t)^TdB(t) - \frac{1}{2} \int_0^t H(t)^TH(t)dt}.$$

Then the process $\{W(t)\}$ given by

$$W(t) = B(t) + \int_0^t H(s)ds$$

is, by Girsanov's theorem, Wiener processes w.r.t. the measure $Q$, with the same covariances (quadratic variations) as $B(t)$. Then, by matrix multiplication

$$D^{1/2}(X(t))dW(t) = D^{1/2}(X(t))dB(t) + D^{1/2}(X(t))H(t)dt$$

$$= D^{1/2}(X(t))dB(t) - D^{1/2}(X(t))D^{1/2}(X(t))\nabla_x V(X(t))dt$$

$$= D^{1/2}(X(t))dB(t) - D(X(t))\nabla_x V(X(t))dt.$$

When we rearrange this, we get

$$\mu(X(t))dt + D(X(t))\nabla_x V(X(t))dt + D^{1/2}(X(t))dW(t)$$

$$= \mu(X(t))dt + D^{1/2}(X(t))dB(t).$$

Since $dX(t) = \mu(X(t))dt + D^{1/2}(X(t))dB(t)$ via the canonical path space, we have

$$dX(t) = \mu(X(t))dt + D(X(t))\nabla_x V(X(t))dt + D^{1/2}(X(t))dW(t).$$

Hence, by theorem (5.2) of [10] pp.204–205 there is a 1-1 correspondence between the solution $P$ of the martingale problems $MP(\mu, D)$ and the solution $Q$ of $MP(\mu + D\nabla_x V, D)$. Hence $MP(\mu + D\nabla_x V, D)$ has a unique solution. \qed
6 The Stationary Probability Distribution: The Explicit Solution

6.1 The Fokker-Planck Equation and the Probability Flow

Given pre-specified one- and two-locus selection parameters \( h_i(k) \) and \( J_{ij}(k, l) \) and mutation intensities \( u_{ik}^{(i)} \), the probability density function \( P(x, t) \) of the diffusion \( \{X(t) \mid t \geq 0\} \) in occupying state \( x \) at time \( t \) is governed by the multidimensional Fokker-Planck (or Kolmogorov Forward) equation

\[
\frac{\partial P(x, t)}{\partial t} = -\sum_{i=1}^{L} \sum_{k=1}^{M_i-1} \frac{\partial}{\partial x_k^{(i)}} \left[ p_k^{(i)}(x) P(x, t) \right] + \frac{1}{2} \sum_{i=1}^{L} \sum_{k=1}^{M_i-1} \sum_{l=1}^{M_i-1} \frac{\partial^2}{\partial x_k^{(i)} \partial x_l^{(i)}} \left[ d_{kl}^{(i)}(x) P(x, t) \right].
\]

(6.1)

In order to solve this stationary Fokker-Planck equation we are going to study the probability flow \([36, pp. 133–134]\). The reference cited is, however, not the source of the technical details below.

Let now

\[
\nabla J = \left( \nabla x_1^{(1)} J^{(1)}, \ldots, \nabla x_L^{(L)} J^{(L)} \right),
\]

(6.3)

and

\[
\nabla x_1^{(i)} J^{(i)} = \left( \frac{\partial}{\partial x_1^{(i)}} J^{(i)}, \ldots, \frac{\partial}{\partial x_{M_i-1}^{(i)}} J^{(i)} \right).
\]

(6.4)

Then (6.1) can be written as

\[
\frac{\partial}{\partial t} P = -\nabla \cdot J.
\]

Then the solution to the equation (6.1) that satisfies, when existing,

\[
-\nabla \cdot J = 0
\]

(6.5)

is denoted by \( P(x) \) and is called the stationary or invariant probability density w.r.t. to the measure \( dx \) on \( K \). We shall next solve the stationary Fokker-Planck equation. In fact, we shall find a solution under a stronger condition on the probability flow, namely,

\[
J = 0 \quad \text{on} \quad \times_{i=1}^{L} K_i.
\]

(6.6)

The possibility of explicit solution rests upon the presence of the Svirezhev-Shahshahani gradient form.
6.2 The Explicit Solution

6.2.1 Auxiliaries

We set

\[ \pi_i \left( x^{(i)} \right) = \left( x_{M_i}^{(i)} \right)^{2u_{M_i}^{(i)} - 1} \prod_{l=1}^{M_i - 1} \left( x_{l}^{(i)} \right)^{2u_{l}^{(i)} - 1} \ dx. \tag{6.7} \]

This is the non-normalized density of a Dirichlet distribution on \( K_i \), sometimes denoted as \( D \left( u_1^{(i)}, \ldots, u_{M_i - 1}^{(i)}, u_{M_i}^{(i)} \right) \). Due to the functional relationship between the \( M_i \) variables, their joint probability distribution is degenerate, and the density is only for the \( M_i - 1 \) variables inside \( x^{(i)} \). Of course, the numbering of the \( M_i \) alleles is arbitrary, but so is \( \pi_i \left( x^{(i)} \right) \) invariant w.r.t. permutations.

**Assumption 6.1.** We assume that for all \( i \) and \( l \)

\[ u_l^{(i)} > 0. \tag{6.8} \]

Then we set

\[ \pi(\mathbf{x}) \overset{\text{def}}{=} \prod_{i=1}^{L} \pi_i \left( x^{(i)} \right). \tag{6.9} \]

Let next \( V(\mathbf{x}) \) be any sufficiently differentiable fitness potential. We set

\[ P(\mathbf{x}) \overset{\text{def}}{=} \pi(\mathbf{x}) e^{2V(\mathbf{x})}. \tag{6.10} \]

**Lemma 6.1.** Assume \( \text{[4.3]} \) and \( \text{[6.8]} \). Then, for all \( \mathbf{x} \in \times_{i=1}^{L} K_i, k = 1, \ldots, M_i - 1 \), and \( i = 1, \ldots, L \), we have

\[ \frac{1}{2} \sum_{i=1}^{M_i - 1} \frac{\partial}{\partial x_i^{(i)}} \left[ d_{kl}^{(i)}(\mathbf{x}) P(\mathbf{x}) \right] = P(\mathbf{x}) \left[ u_k^{(i)} - \bar{u} + \sum_{l=1}^{M_i - 1} d_{kl}^{(i)}(\mathbf{x}) V'_{x_i^{(i)}}(\mathbf{x}) \right], \tag{6.11} \]

where \( V'_{x_i^{(i)}}(\mathbf{x}) \) is the partial derivative of \( V(\mathbf{x}) \) w.r.t. to \( x_i^{(i)} \).

The proof is a computational exercise recapitulated in Appendix D.

6.2.2 The potential and the probability flow

**Proposition 6.2.** Assume \( \text{[4.3]} \) and \( \text{[6.8]} \). Let the function \( V(\mathbf{x}) \) be defined by \( \text{[4.27]} \) as

\[ V(\mathbf{x}) \overset{\text{def}}{=} W(\mathbf{x}). \tag{6.12} \]

Then, for all \( \mathbf{x} \in \times_{i=1}^{L} K_i \),

\[ P(\mathbf{x}) = \pi(\mathbf{x}) e^{2V(\mathbf{x})} \tag{6.13} \]

solves the equation of zero probability flow

\[ J_k^{(i)} = p_k^{(i)}(\mathbf{x}) P - \frac{1}{2} \sum_{l=1}^{M_i - 1} \frac{\partial}{\partial x_l^{(i)}} \left[ d_{kl}^{(i)}(\mathbf{x}) P \right] = 0, \tag{6.14} \]

and the stationary Fokker-Planck equation \( \text{[6.9]} \).
Proof: We study \( p_k^{(i)}(x)P \). By virtue of (4.33) - (4.35) it holds under (4.3) that

\[
p_k^{(i)}(x)P = \left( u_k^{(i)} - \bar{u} + \sum_{l=1}^{M-1} d_k^{(i)}(x) V_{x_l^{(i)}}(x) \right) P.
\]

By (6.11) we now see that (6.14) is satisfied, i.e., \( J_k^{(i)} = 0 \) and therefore \(-\nabla \cdot J = 0\). □

The normalized stationary density is again denoted by \( P(x) \), i.e.,

\[
P(x) = \frac{1}{Z} \pi(x)e^{2V(x)}.
\]

(6.15)

Here

\[
Z \overset{\text{def}}{=} \int_{x \in K_i} \pi(x)e^{2V(x)}dx
\]

is required to exist when integrated w.r.t. the Lebesgue measure restricted to \( K \).

For a single locus \( L = 1, x = (x_1, x_2, \ldots, x_M) \) with multiple allele types as well as mutation and selection, Watterson [47] finds (with a sketch of the explicit calculations) the stationary density as

\[
P(x_1, x_2, \ldots, x_{M-1}, x_M) = \frac{1}{Z} x^{2u_1-1} \cdots x^{2u_{M-1}} e^{2U(x)} dx_1 \cdots dx_{M-1},
\]

(6.16)

where \( u_l > 0 \) for every \( l \). Watterson states also a method of computation of the constant \( Z \) in one special case. In spite of the obvious similarity with (6.15), we cannot in any straightforward manner regard this as a special case (6.15), since the matrix \( A \) in (4.23) becomes for \( L = 1 \) the \( M \times M \) matrix of zeroes. In [19] the loci are unlinked.

We present next an example of the computation of a stationary density by the techniques above.

Example 6.3. [Two loci, two alleles with selection and mutation] We have \( L = 2, M_1 = M_2 = 2, x = (x^{(1)}, x^{(2)}) \). Then we identify \( x^{(1)} = x^{(1)}_1 = x^{(2)}_1 \) and have \( x^{(2)}_2 = 1 - x^{(1)}_1 \) and \( x^{(1)}_2 = 1 - x^{(2)}_1 \). The augmented state vector is thus

\[
\mathbf{x}^T = \left( x^{(1)}_1, x^{(1)}_2, x^{(2)}_1, x^{(2)}_2 \right).
\]

and

\[
\mathbf{x}^T A \mathbf{x} = 2h x^{(1)}_1 x^{(2)}_1.
\]

When we return to the variables \( x^{(i)} \), this yields

\[
V(x) = \frac{1}{2} \mathbf{x}^T A \mathbf{x} = h x^{(1)}_1 x^{(2)}_1.
\]

Hereafter we obtain as in Example 2.1 the following system of stochastic differential equations

\[
\begin{align*}
\left\{ \begin{array}{l}
dX^{(1)}_t = u^{(1)}_1 dt - (u^{(1)}_1 + u^{(1)}_2)X^{(1)}_t dt + hX^{(1)}_t(1 - X^{(1)}_t)X^{(2)}_t dt + \sqrt{X^{(1)}_t(1 - X^{(1)}_t)}dW^{(1)}_t \\
dX^{(2)}_t = u^{(2)}_1 dt - (u^{(2)}_1 + u^{(2)}_2)X^{(2)}_t dt + hX^{(2)}_t(1 - X^{(2)}_t)X^{(1)}_t dt + \sqrt{X^{(2)}_t(1 - X^{(2)}_t)}dW^{(2)}_t,
\end{array} \right.
\end{align*}
\]

(6.17)
where \( W^{(1)} \) and \( W^{(2)} \) are independent Wiener processes. This is a system of two coupled Wright-Fisher stochastic differential equations with mutation and selection. If \( h = 0 \), the processes are obviously independent.

The normalized stationary distribution (density) is by [6.13] equal to
\[
P(x^{(1)}, x^{(2)}) = \frac{1}{Z} \pi_1(x^{(1)}) \pi_2(x^{(2)}) e^{2h x^{(1)} x^{(2)}} dx^{(1)} dx^{(2)}, \tag{6.18}
\]
where
\[
\pi_1(x^{(1)}) = (x^{(1)})^{2u^{(1)} - 1}(1 - x^{(1)})^{2u^{(1)} - 1}
\]
and
\[
\pi_2(x^{(2)}) = (x^{(2)})^{2u^{(2)} - 1}(1 - x^{(2)})^{2u^{(2)} - 1}.
\]

We can in this example determine the normalization constant \( Z \) explicitly. First,
\[
\int_0^1 P(x^{(1)}, x^{(2)}) dx^{(2)} = (x^{(1)})^{2u^{(1)} - 1}(1 - x^{(1)})^{2u^{(1)} - 1} \int_0^1 \pi_2(x^{(2)}) e^{2hx^{(2)} x^{(1)}} dx^{(2)}.
\tag{6.19}
\]
Here
\[
\int_0^1 \pi_2(x^{(2)}) e^{2hx^{(2)} x^{(1)}} dx^{(2)} = \int_0^1 (x^{(2)})^{2u^{(2)} - 1}(1 - x^{(2)})^{2u^{(2)} - 1} e^{2hx^{(1)} x^{(2)}} dx^{(2)},
\tag{6.20}
\]
Here Kummer’s (confluent hypergeometric) function \( M(a, b, z) \) contributes to computing the normalization constant in view of the integral representation [II eqn. 13.2.1]
\[
M(a, b, z) = \frac{\Gamma(b)}{\Gamma(a)\Gamma(b-a)} \int_0^1 e^{zu} u^{a-1} (1 - u)^{b-a-1} du.
\tag{6.21}
\]
Kummer’s function has the expansion [II eqn. 13.1.2]
\[
M(a, b, x) = \sum_{n=0}^{\infty} \frac{a^{(n)} x^n}{b^{(n)} n!}, -\infty < x < \infty,
\tag{6.22}
\]
where \( a^{(0)} = 1, a^{(n)} = a(a+1)(a+2) \cdots (a+n-1) \).

The integral representation of the Kummer function gives by (6.21) in (6.20) with \( a = 2u^{(2)}_1, b - a = 2u^{(2)}_2 \) so that \( b = 2u^{(2)}_2 \)
\[
\int_0^1 (x^{(2)})^{2u^{(2)}_1 - 1}(1 - x^{(2)}) e^{2hx^{(1)} x^{(2)}} dx^{(2)} = \frac{\Gamma(2u^{(2)}_1)\Gamma(2u^{(2)}_2)}{\Gamma(2(u^{(2)}_1 + u^{(2)}_2))} M(2u^{(2)}_1, 2u^{(2)}_2, 2hx^{(1)}).
\]

Then we get in view of (6.19) that
\[
Z = \int_0^1 (x^{(1)})^{2u^{(1)}_1 - 1}(1 - x^{(1)}) e^{2hx^{(1)} x^{(2)}} dx^{(1)}
\]
\[
= \frac{\Gamma(2u^{(2)}_1)\Gamma(2u^{(2)}_2)}{\Gamma(2(u^{(2)}_1 + u^{(2)}_2))} \int_0^1 (x^{(1)})^{2u^{(1)}_1 - 1}(1 - x^{(1)}) e^{2hx^{(1)} x^{(2)}} dx^{(1)}.
\]

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With the expansion in (6.22) we get
\[
\int_0^1 (x^{(1)})^{2u_1^{(1)}-1}(1-x^{(1)})^{2u_2^{(1)}-1} M \left( 2u_1^{(2)}, 2u_2^{(2)}, 2hx^{(1)} \right) dx^{(1)}
= \sum_{n=0}^{\infty} \frac{(2u_1^{(2)})(n)(2h)^n}{(2u_2^{(2)})(n)n!} \int_0^1 (x^{(1)})^{2u_1^{(1)}+n-1}(1-x^{(1)})^{2u_2^{(1)}-1} dx^{(1)}
= \sum_{n=0}^{\infty} \frac{(2u_1^{(2)})(n)(2h)^n}{(2u_2^{(2)})(n)n!} \frac{\Gamma(2u_1^{(1)}+n)}{\Gamma(2(u_1^{(1)}+u_2^{(1)})+n)}.
\]

In summary, we have found
\[
Z = \frac{\Gamma(2u_1^{(2)})\Gamma(2u_2^{(2)})}{\Gamma(2(u_1^{(2)}+u_2^{(2)}))} \sum_{n=0}^{\infty} \frac{(2u_1^{(2)})(n)(2h)^n}{(2u_2^{(2)})(n)n!} \frac{\Gamma(2u_2^{(1)})}{\Gamma(2(u_1^{(1)}+u_2^{(1)})+n)} \Gamma(2u_1^{(1)}+n).
\]

In other words,
\[
P \left( x^{(1)}, x^{(2)} \right) = \frac{(x^{(1)})^{2u_1^{(1)}-1}(1-x^{(1)})^{2u_2^{(1)}-1}(x^{(2)})^{2u_2^{(2)}-1}(1-x^{(2)})^{2u_2^{(2)}-1}e^{2hx^{(1)}x^{(2)}}}{\frac{\Gamma(2u_1^{(2)})\Gamma(2u_2^{(2)})}{\Gamma(2(u_1^{(2)}+u_2^{(2)}))} \sum_{n=0}^{\infty} \frac{(2u_1^{(2)})(n)(2h)^n}{(2u_2^{(2)})(n)n!} \frac{\Gamma(2u_2^{(1)}+n)}{\Gamma(2(u_1^{(1)}+u_2^{(1)})+n)} \Gamma(2u_1^{(1)}+n)}}. \quad (6.23)
\]

If \( h = 0 \), then only the term with \( n = 0 \) (0^0 = 1, 0! = 1) in the summation in the numerator gives a non-zero contribution and the density in (6.23) becomes a product of two Beta densities, or describes two independent loci with two alleles and mutation, as it should. Or, we are for \( h = 0 \) dealing with a pair of independent Wright-Fisher models with mutation.

The probability density function (6.23) might be called a (non-centralized) bivariate Beta density. However, the name bivariate Beta density is already assigned to a different bivariate density, see [21] and its references.

In [15] the two-locus Wright-Fisher model for mutation, selection, and random genetic drift in a panmictic, monocious, diploid population of \( N \) individuals is given a diffusion approximation under various forms of selection. The resulting diffusion processes do not seem to include explicitly the Svirezhev-Shahshahani selection term of (6.17).

\[
7 \quad \text{Svirezhev-Shahshahani gradients and undirected Graphs}
\]

We derive some instances of the multilocus and multiallele model by choices of the structure of \( A \) above. This turns out to be a very flexible and effective way to derive Wright-Fisher diffusions of the form (2.11). These examples are computational desktop constructions and do not necessarily emulate any known real-life biological situations.

In each of these examples the normalization constant is denoted generically as \( Z \), but has to be computed anew in each example. In each of these examples we take also single locus selection parameters as zeroes, i.e.,
\[
h = 0.
\]

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Example 7.1. /Two loci, two alleles with selection and mutation / We have \( L = 2, M_1 = M_2 = 2, \mathbf{x} = (x^{(1)}, x^{(2)}). \) Then we identify \( x^{(1)} = x_1^{(1)}, x^{(2)} = x_1^{(2)} \) and have \( x_2^{(1)} = 1 - x_1^{(1)} \) and \( x_2^{(2)} = 1 - x_1^{(2)} \). The augmented state vector is thus

\[
\mathbf{x}^T = (x_1^{(1)}, x_2^{(1)}, x_1^{(2)}, x_2^{(2)}).
\]

We take

\[
J_2(M_1) = \begin{pmatrix} h_1 & 0 \\ 0 & h_2 \end{pmatrix} = J_1(M_2)
\]

so that in \( \text{(1.24)} \) we obtain the symmetric \( 4 \times 4 \) matrix

\[
A = \begin{pmatrix} 0 & 0 & h_1 & 0 \\ 0 & 0 & 0 & h_2 \\ h_1 & 0 & 0 & 0 \\ 0 & h_2 & 0 & 0 \end{pmatrix}.
\]

Then

\[
\mathbf{x}^T A \mathbf{x} = 2(h_1 + h_2)x_1^{(1)}x_1^{(2)} - 2h_2(x_1^{(1)} + x_1^{(2)}) + 2h_2.
\]

or with the variables \( x^{(i)} \), this yields

\[
V(\mathbf{x}) = (h_1 + h_2)x^{(1)}x^{(2)} - 2h_2 \left( x^{(1)} + x^{(2)} \right) + h_2.
\]

The in the drift functions are then found by lemma \( \text{[1.4]} \) as

\[
df^{(1)}_{11}(\mathbf{x})V_x^{(i)} = x^{(i)} \left( 1 - x^{(i)} \right) \cdot \left[ (h_1 + h_2)x^{(2)} - h_2 \right],
\]

and

\[
df^{(2)}_{11}(\mathbf{x})V_x^{(i)} = x^{(i)} \left( 1 - x^{(i)} \right) \cdot \left[ (h_1 + h_2)x^{(1)} - h_2 \right].
\]

. Hence we obtain the following system of stochastic differential equations

\[
\begin{align*}
\frac{dX_t^{(1)}}{dt} &= \mu^{(1)}(X_t^{(1)})dt + (h_1 + h_2)X_t^{(1)}(1 - X_t^{(1)})X_t^{(2)}dt - h_2X_t^{(1)}(1 - X_t^{(1)})dt + \sqrt{X_t^{(1)}(1 - X_t^{(1)})}dW_t^{(1)} \\
\frac{dX_t^{(2)}}{dt} &= \mu^{(2)}(X_t^{(2)})dt + (h_1 + h_2)X_t^{(2)}(1 - X_t^{(2)})X_t^{(1)}dt - h_2X_t^{(2)}(1 - X_t^{(2)})dt + \sqrt{X_t^{(2)}(1 - X_t^{(2)})}dW_t^{(2)},
\end{align*}
\]

\]

\]

Example 7.2. /Four loci, two alleles with selection and mutation: The General Case / We take \( L = 4, M_i = 2 \) for \( i = 1, 2, 3, 4 \). We set \( \mathbf{x}^T \) is the vector transpose

\[
\mathbf{x}^T = (x^{(1)}, x^{(2)}, x^{(3)}, x^{(4)})
\]

\[
= (x_1^{(1)}, x_2^{(1)}, x_2^{(2)}, x_1^{(3)}, x_1^{(4)}, x_2^{(3)}, x_2^{(4)})
\]

where \( x_2^{(i)} = 1 - x_1^{(i)} \) for \( i = 1, 2, 3, 4 \). Let us furthermore set

\[
\mathbf{0} = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}
\]

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and

\[
\begin{bmatrix}
J_2(M_1) & = & \begin{pmatrix} h_2 & 0 \\ 0 & 0 \end{pmatrix} = J_1(M_2) \\
J_3(M_1) & = & \begin{pmatrix} h_5 & 0 \\ 0 & 0 \end{pmatrix} = J_1(M_3) \\
J_3(M_2) & = & \begin{pmatrix} h_3 & 0 \\ 0 & 0 \end{pmatrix} = J_2(M_3) \\
J_4(M_1) & = & \begin{pmatrix} h_7 & 0 \\ 0 & 0 \end{pmatrix} = J_1(M_4) \\
J_4(M_2) & = & \begin{pmatrix} h_6 & 0 \\ 0 & 0 \end{pmatrix} = J_2(M_4)
\end{bmatrix}
\]

and

\[
\begin{bmatrix}
J_4(M_3) & = & \begin{pmatrix} h_4 & 0 \\ 0 & 0 \end{pmatrix} = J_3(M_4),
\end{bmatrix}
\]

where the right most inequalities are enforced by the symmetry required. These 2 × 2 matrices are symmetric, but in general the matrices \(J_i(M_k)\) cannot always be symmetric, since these matrices are not necessarily square. We are obviously taking here all \(h_i(M_k) = 0\) for ease of work. Then the matrix \(A\) in \(\text{(4.24)}\) boils down to the symmetric 8 × 8 matrix,

\[
A = \begin{pmatrix}
0 & J_2(M_1) & J_3(M_1) & J_4(M_1) \\
J_2(M_1) & 0 & J_3(M_2) & J_4(M_2) \\
J_3(M_1) & J_3(M_2) & 0 & J_4(M_2) \\
J_4(M_1) & J_4(M_2) & J_4(M_3) & 0
\end{pmatrix}.
\]

(7.3)

We get by a simple piece of algebra

\[
A\mathbf{x} = \begin{pmatrix}
h_2x_1^{(2)} + h_5x_1^{(3)} + h_7x_1^{(4)} \\
0 \\
h_2x_1^{(1)} + h_3x_1^{(3)} + h_6x_1^{(4)} \\
0 \\
h_5x_1^{(1)} + h_3x_1^{(2)} + h_4x_1^{(4)} \\
0 \\
h_7x_1^{(1)} + h_6x_1^{(2)} + h_4x_1^{(3)} \\
0
\end{pmatrix}.
\]

(7.4)

When we revert to \(x_1^{(i)} = x^{(i)}\),

\[
\mathbf{x}^T A \mathbf{x} = 2 \left( h_2x^{(1)}x^{(2)} + h_5x^{(1)}x^{(3)} + h_7x^{(1)}x^{(4)} + h_3x^{(2)}x^{(3)} + h_6x^{(2)}x^{(4)} + h_4x^{(3)}x^{(4)} \right).
\]

(7.5)

The Svirezhev-Shahshahani gradient \(\mathbf{D}(\mathbf{x}) \nabla_x V(\mathbf{x})\), a 4×1 vector in this case, comprising the selective interactions between the four loci in the corresponding stochastic differential equation \(\text{(2.8)}\), is

\[
\mathbf{D}(\mathbf{x}) \nabla_x V(\mathbf{x}) = \begin{pmatrix}
x^{(1)}(1 - x^{(1)}) \left( h_2x^{(2)} + h_5x^{(3)} + h_7x^{(4)} \right) \\
x^{(2)}(1 - x^{(2)}) \left( h_2x^{(1)} + h_3x^{(3)} + h_6x^{(4)} \right) \\
x^{(3)}(1 - x^{(3)}) \left( h_5x^{(1)} + h_3x^{(2)} + h_4x^{(4)} \right) \\
x^{(4)}(1 - x^{(4)}) \left( h_7x^{(1)} + h_6x^{(2)} + h_4x^{(3)} \right)
\end{pmatrix}.
\]

(7.6)
Hence we see that every locus interacts with every other in a symmetric manner. Let us agree to regard the four loci as nodes and to draw an undirected edge between two loci, as soon as these appear simultaneously in the same product term in $V(x)$, or are jointly in a component of the vector $G(x)$. Then the current Wright-Fisher model with Svirezhev-Shahshahani selection is represented by the complete graph below.

The normalized stationary distribution (density) is by (6.13) equal to

$$P(x) = \frac{1}{Z} \pi(x) e^{2(h_2x^{(1)}x^{(2)} + h_5x^{(1)}x^{(3)} + h_7x^{(1)}x^{(4)} + h_3x^{(2)}x^{(3)} + h_6x^{(2)}x^{(4)} + h_4x^{(3)}x^{(4)})},$$  \hspace{1cm} (7.7)

where

$$\pi(x) = \prod_{i=1}^{4}(x^{(i)})^{2u_1^{(i)} - 1}(1 - x^{(i)})^{2u_2^{(i)} - 1}$$

is the product of the non-normalized marginal Beta densities. The standardization constant $Z$ can, at least in special cases, again be developed using the Kummer function along the lines of example 7.2 but seems to produce a rather messy final formula.

Example 7.3. \textbf{Four loci, two alleles with selection and mutation Case I} \hspace{1cm} If $h_3 = h_4 = h_6 = 0$ in (7.3) we get the matrix again denoted by $A$,

$$A = \begin{pmatrix} 0 & J_2(M_1) & J_3(M_1) & J_4(M_1) \\ J_2(M_1) & 0 & 0 & 0 \\ J_3(M_1) & 0 & 0 & 0 \\ J_4(M_1) & 0 & 0 & 0 \end{pmatrix}. \hspace{1cm} (7.8)$$

This entails by (7.4), when we revert to $x^{(i)} = x^{(i)}$,

$$Ax = \begin{pmatrix} h_2x_1^{(2)} + h_5x_1^{(3)} + h_7x_1^{(4)} \\ 0 \\ h_2x_1^{(1)} \\ 0 \\ h_5x_1^{(1)} \\ 0 \\ h_7x_1^{(1)} \\ 0 \end{pmatrix}. \hspace{1cm} (7.9)$$

and from (7.5)

$$x^TAx = 2x^{(1)} \left( h_2x^{(2)} + h_5x^{(3)} + h_7x^{(4)} \right)$$
Thus, by (7.6),
\[
\mathbf{D}(X(t))\nabla_x V(x) = \begin{pmatrix}
 x^{(1)}(1 - x^{(1)}) \left( h_2 x^{(2)} + h_5 x^{(3)} + h_7 x^{(4)} \right) \\
 h_2 x^{(2)} (1 - x^{(2)}) x^{(1)} \\
 h_5 x^{(3)} (1 - x^{(3)}) x^{(1)} \\
 h_7 x^{(4)} (1 - x^{(4)}) x^{(1)}
\end{pmatrix}.
\] (7.10)

Hence, in this case the loci 2, 3, 4 do not interact with each other except mediated by the locus 1. This can be representing a possible biologically interesting feature. This is illustrated by graph drawn by the same principle as in the general case, i.e. in the example 6.3.

When compared to the complete graph in the preceding example, we see clearly the correspondence between the deleted edges and the zero matrices \( \mathbf{J}_i(M_k) \) of interaction imposed.

\[ \square \]

**Example 7.4.** Four loci, two alleles with selection and mutation Case II / We consider in (7.3) the following special case, i.e., \( h_5 = h_6 = h_7 = 0 \), so that
\[
\mathbf{A} = \begin{pmatrix}
 0 & \mathbf{J}_2(M_1) & 0 & 0 \\
 \mathbf{J}_2(M_1) & 0 & \mathbf{J}_3(M_2) & 0 \\
 0 & \mathbf{J}_3(M_2) & 0 & \mathbf{J}_4(M_3) \\
 0 & 0 & \mathbf{J}_4(M_3) & 0
\end{pmatrix}.
\] (7.11)

This gives, by specialization of the general case,
\[
\mathbf{A}\mathbf{x} = \begin{pmatrix}
 h_2 x_1^{(2)} \\
 h_2 x_1^{(1)} + h_3 x_1^{(3)} \\
 h_3 x_1^{(2)} + h_4 x_1^{(4)} \\
 h_4 x_1^{(3)}
\end{pmatrix}.
\] (7.12)

The return to \( x_1^{(i)} = x^{(i)} \) yields by (7.6)
\[
\mathbf{x}^T \mathbf{A}\mathbf{x} = 2h_2 x^{(1)} x^{(2)} + 2h_3 x^{(2)} x^{(3)} + 2h_4 x^{(3)} x^{(4)}.
\]
We get by (7.6)

\[
\mathbf{D}(\mathbf{x}) \nabla_x V(\mathbf{x}) = \begin{pmatrix}
x^{(1)}(1 - x^{(1)})h_2 x^{(2)} \\
x^{(2)}(1 - x^{(2)}) \left( h_2 x^{(1)} + \frac{h_3 x^{(3)}}{h_4 x^{(4)}} \right) \\
x^{(3)}(1 - x^{(3)}) \left( h_3 x^{(2)} + \frac{h_4 x^{(4)}}{h_4 x^{(3)}} \right) \\
x^{(4)}(1 - x^{(4)})h_4 x^{(3)}
\end{pmatrix}.
\tag{7.13}
\]

In this case the loci 1 and 4 have no direct interaction with each other, but interact through the loci 2 and 3.

The normalized stationary distribution (density) is equal to

\[
P(\mathbf{x}) = \frac{1}{Z} \pi(\mathbf{x}) e^{2 \left( h_2 x^{(1)} + h_3 x^{(2)} + h_4 x^{(3)} \right)},
\tag{7.14}
\]

where

\[
\pi(\mathbf{x}) = \prod_{i=1}^{4} (x^{(i)})^{2u^{(i)} - 1} (1 - x^{(i)})^{2u^{(i)} - 1}
\]

is as in the preceding example. The standardization constant \( Z \) can perhaps be developed using the Kummer function along the lines of example 7.2.

The graph above is drawn by the same principle as in the preceding examples.

\[\square\]

**Example 7.5.** [Four loci, two alleles with selection and mutation Case III] We take in (7.3) \( h_2 = h_3 = h_4 = 0 \) to get the symmetric 8 \( \times \) 8 matrix

\[
A = \begin{pmatrix}
0 & 0 & \mathbf{J}_4(M_1) & \mathbf{J}_4(M_1) \\
0 & 0 & 0 & \mathbf{J}_4(M_1) \\
\mathbf{J}_3(M_1) & 0 & 0 & 0 \\
\mathbf{J}_4(M_1) & \mathbf{J}_4(M_2) & 0 & 0
\end{pmatrix}.
\tag{7.15}
\]

This gives with \( x_1^{(i)} = x^{(i)} \) and by (7.4)

\[
A\mathbf{x} = \begin{pmatrix}
h_5 x^{(3)} + h_7 x^{(4)} \\
h_6 x^{(4)} \\
h_5 x^{(1)} \\
h_7 x^{(1)} + h_6 x^{(2)}
\end{pmatrix}.
\tag{7.16}
\]
Thus
\[ X^TAX = 2 \left( h_5x^{(1)}x^{(3)} + h_6x^{(2)}x^{(4)} + h_7x^{(1)}x^{(4)} \right). \]

Hence we get
\[
D(x) \nabla_x V(x) = \begin{pmatrix}
  x^{(1)}(1 - x^{(1)})(h_5x^{(3)} + h_7x^{(4)}) \\
  x^{(2)}(1 - x^{(2)})(h_6x^{(4)}) \\
  x^{(3)}(1 - x^{(3)})(h_5x^{(1)}) \\
  x^{(4)}(1 - x^{(4)})(h_7x^{(1)} + h_6x^{(2)})
\end{pmatrix}. \tag{7.17}
\]

In this case the locus 1 interacts with the locus 2 only through the locus 4, and the locus 4 interacts with the locus 3 only through the locus 1. The graph is obvious.

Example 7.6. /Three loci, two alleles with selection and mutation. The General Case / If we take \( h_4 = h_5 = h_7 = 0 \) in (7.3), we eliminate \( x^{(4)} \) and what remains or appears in a Wright-Fisher model with \( L = 2 \) and \( M_i = 2 \), for \( i = 1, 2, 3 \) and the \( 6 \times 6 \) matrix, again denoted by \( A \),
\[
A = \begin{pmatrix}
  0 & J_2(M_1) & J_3(M_1) \\
  J_2(M_1) & 0 & J_3(M_2) \\
  J_3(M_1) & J_3(M_2) & 0
\end{pmatrix}. \tag{7.18}
\]

Here we see clearly that the model with three loci and two nodes is nested inside the model with four loci and two nodes. To write down the invariant density here and to inspect various special cases, one only needs to invoke the formulas (7.5) and/or (7.6) with \( h_4 = h_5 = h_7 = 0 \) and other specifications of zeroes.

Example 7.7. /Six loci, two alleles with selection and mutation. The General Case / But \( L = 5 \) and and \( M_i = 2 \), for \( i = 1, 2, 3, 4 \) is, of course nested inside any model with a higher number of loci and two alleles. The for \( L = 6 \) we have the \( 12 \times 12 \) matrix
\[
A = \begin{pmatrix}
  0 & J_2(M_1) & J_3(M_1) & J_4(M_1) & J_5(M_1) & J_6(M_1) \\
  J_2(M_1) & 0 & J_3(M_2) & J_4(M_2) & J_5(M_2) & J_6(M_2) \\
  J_3(M_1) & J_3(M_2) & 0 & J_4(M_3) & J_5(M_3) & J_6(M_3) \\
  J_4(M_1) & J_4(M_2) & J_4(M_3) & 0 & J_5(M_4) & J_6(M_4) \\
  J_5(M_1) & J_5(M_2) & J_5(M_3) & J_5(M_4) & 0 & J_6(M_5) \\
  J_6(M_1) & J_6(M_2) & J_6(M_3) & J_6(M_4) & J_6(M_5) & 0
\end{pmatrix}. \tag{7.19}
\]

If we want to write down the formulas like in the above examples here, we need to amend the matrix (7.6) with the nine additional matrices
\[
J_i(M_k) = \begin{pmatrix}
  h_{ik} \\
  0
\end{pmatrix} (= J_k(M_i))
\]
for $k = 1, 2, 3, 4$ if $i = 5$ and $k = 1, 2, 3, 4, 5$ if $i = 6$ and to perform the necessary matrix multiplications. But even without any numbers we can state something. Suppose we have in (7.19)

$$A = \begin{pmatrix}
0 & J_2(M_1) & J_3(M_1) & J_4(M_1) & 0 & 0 \\
J_2(M_1) & 0 & J_3(M_2) & J_4(M_2) & 0 & 0 \\
J_3(M_1) & J_3(M_2) & 0 & J_4(M_3) & 0 & 0 \\
J_4(M_1) & J_4(M_2) & J_4(M_3) & 0 & J_5(M_4) & J_6(M_4) \\
0 & 0 & 0 & J_5(M_4) & 0 & J_6(M_5) \\
0 & 0 & 0 & J_6(M_4) & J_6(M_5) & 0
\end{pmatrix}.$$ \hspace{1cm} (7.20)

But then it clearly holds, assuming that there are no further zero matrices in (7.20), that the loci 1 to 3 interact with 5 and 6 only through the locus 4, and vice versa by the symmetries assumed. The interaction graph is below.

Example 7.8. \textit{Eight loci, two alleles with selection and mutation. The converse} \hspace{0.5cm} Continuing with Example 7.7 in this manner it is easy to find, by extension of the matrix $A$ in (7.20), and hence $G(x)$ and $V(x)$ and then draw the interaction graph. However, even the converse is true. If we are given the graph in the next figure and are told that there are two alleles at every locus, we can find the corresponding $A$.

Example 7.9. \textit{Two loci, one with three alleles and the other locus with two alleles at two loci} \hspace{0.5cm} If there are, e.g. three alleles at locus 2, $M_1 = 2$, $M_2 = 3$ the corresponding two locus interaction matrices are taken as

$$J_1(M_2) = \begin{pmatrix}
h_1 & h_2 & 0 \\
0 & 0 & 0
\end{pmatrix}$$

and

$$J_2(M_1) = \begin{pmatrix}
h_1 & 0 \\
h_2 & 0
\end{pmatrix}.$$
and matrix $A$ is

$$A = \begin{pmatrix}
0 & 0 & h_1 & h_2 & 0 \\
0 & 0 & 0 & 0 & 0 \\
h_1 & 0 & 0 & 0 & 0 \\
h_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}.$$  

With

$$\mathbf{x}^T = (x_1^{(1)}, x_2^{(1)}, x_1^{(2)}, x_2^{(2)}, x_3^{(2)})$$

we get

$$Ax = \begin{pmatrix}
h_1 x_1^{(2)} + h_2 x_2^{(2)} \\
0 \\
h_1 x_1^{(1)} \\
h_2 x_1^{(1)} \\
0
\end{pmatrix}.$$  

This entails

$$V(x) = V (x_1^{(1)}, x_1^{(2)}, x_2^{(2)}) = x_1^{(1)} (h_1 x_1^{(2)} + h_2 x_2^{(2)}).$$  

From (2.11) we get here

$$D(x) \nabla_x V(x) =$$

$$= \begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix} \begin{pmatrix}
h_1 x_1^{(2)} + h_2 x_2^{(2)} \\
h_1 x_1^{(1)} \\
h_2 x_1^{(1)} \\
0
\end{pmatrix}$$

$$= \begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix} \begin{pmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}$$

$$= \begin{pmatrix}
(x^{(1)} (1 - x^{(1)})) (h_1 x_1^{(2)} + h_2 x_2^{(2)}) \\
h_1 x_1^{(1)} x_1^{(2)} (1 - x_1^{(2)}) + h_2 x_1^{(1)} x_2^{(2)} (1 - x_2^{(2)})
\end{pmatrix}.$$  

We cannot give the corresponding SDE in fully explicit form without treating $D(x)^{1/2}$, which is not meaningful for the current purpose.

8 Final Comments

An ultimate goal to learn the structure of the matrix $A$ from data, which will be done elsewhere, once successful learning algorithms have been established. Here the structure of the SDE

$$dX(t) = \mu(X(t)) dt + D(X(t)) \nabla_x V(X(t)) dt + D^{1/2}(X(t)) dW(t),$$

will be crucial, as $V(X(t))$ is easily determined by the structures to be learned. The studies in [18] and [20] are exploring some of the steps required for statistical inference with (8.23).

There is a certain degree of skepticism on diffusion approximations in population genetics voiced by John F. Kingman in [31, p.39]. Amongst other things, the question
of justifying the stationary density by a diffusion approximation is not simple. Techniques for this are given in [34] for one dimensional Wright-Fisher models.

The problem of ergodicity and existence of an invariant measure is studied in [28] for a class of degenerate multidimensional diffusions, but does not discuss explicitly the Wright-Fisher models. This analysis deals with the properties of transition probability function of the Wright-Fisher diffusion, see, e.g., [4].

In [46] the Fokker-Planck equation associated with Wright-Fisher model with two alleles at a diploid locus under random genetic drift in a population of fixed size without mutation or selection is shown to possess a unique (global) solution. The expression for the invariant density is, roughly stated, a series expansion in terms of Gegenbauer polynomials and eigenvectors of the Wright-Fisher generator. By aid of this density formula these authors can find, e.g., the expectation and the second moment of the absorption time, fixation probabilities, the probability of coexistence, or the probability of heterogeneity. Similar applications using our formula have not been attempted.

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Appendix A: Fitness

For \( \bar{m} \), we have

\[
\bar{m} = \sum_{\sigma} f(\sigma) m_\sigma = \sum_{\sigma} f(\sigma) \left( 1 + \sum_{r=1}^{L} h_r(\sigma_r) + \sum_{1 \leq r < s \leq L} J_{rs}(\sigma_r, \sigma_s) \right)
\]

\[
= 1 + \sum_{r=1}^{L} \sum_{\sigma} f(\sigma) h_r(\sigma_r) + \sum_{1 \leq r < s \leq L} \sum_{\sigma} f(\sigma) J_{rs}(\sigma_r, \sigma_s) \tag{A.1}
\]

\[
= 1 + \sum_{r=1}^{L} \sum_{t=1}^{M_r} h_r(t)x_{r}^{(t)} + \sum_{1 \leq r < s \leq L} \sum_{t=1}^{M_r} \sum_{n=1}^{M_s} J_{rs}(t, n)x_{r}^{(n)} x_{s}^{(n)}. \tag{A.2}
\]

The underbraces are due to the calculations

\[
\sum_{\sigma} f(\sigma) h_r(\sigma_r) = \sum_{m=1}^{M_r} \sum_{\sigma_r=1}^{\sigma_r=t} f(\sigma) h_r(\sigma_r) = \sum_{t=1}^{M_r} h_r(m) \sum_{\sigma} f(\sigma) = \sum_{t=1}^{M_r} h_r(t)x_{t}^{(r)}, \tag{A.2}
\]

and

\[
\sum_{\sigma} f(\sigma) J_{rs}(\sigma_r, \sigma_s) = \sum_{t=1}^{M_r} \sum_{n=1}^{M_s} J_{rs}(t, n) \sum_{\sigma} f(\sigma) = \sum_{t=1}^{M_r} \sum_{n=1}^{M_s} J_{rs}(t, n)x_{r}^{(r)} x_{s}^{(n)}. \tag{A.3}
\]

For \( \bar{m}_{k}^{(i)} \), we have

\[
\bar{m}_{k}^{(i)} = \sum_{\sigma} f_{k}^{(i)}(\sigma) m_\sigma = \sum_{\sigma} f_{k}^{(i)}(\sigma) \left( 1 + \sum_{r=1}^{L} h_r(\sigma_r) + \sum_{1 \leq r < s \leq L} J_{rs}(\sigma_r, \sigma_s) \right)
\]

\[
= 1 + \sum_{r=1}^{L} \sum_{\sigma} f_{k}^{(i)}(\sigma) h_r(\sigma_r) + \sum_{1 \leq r < s \leq L} \sum_{\sigma} f_{k}^{(i)}(\sigma) J_{rs}(\sigma_r, \sigma_s). \tag{A.4}
\]
Per definition it holds that \( f_k^{(i)}(\sigma) = \frac{\delta_{r=k}}{x_k} f(\sigma) \), which gives for the second term

\[
\sum_{r=1}^{L} \sum_{\sigma} f_k^{(i)}(\sigma) h_r(\sigma_r) = \sum_{\sigma} f_k^{(i)}(\sigma) h_i(\sigma_i) + \sum_{r \neq i} f_k^{(i)}(\sigma) h_r(\sigma_r)
\]

\[
= \frac{1}{x_k^{(i)}} \sum_{\sigma; \sigma_i=k} f(\sigma) h_i(\sigma_i) + \frac{1}{x_k^{(i)}} \sum_{r \neq i; \sigma; \sigma_r=k} f(\sigma) h_r(\sigma_r)
\]

\[
= \frac{1}{x_k^{(i)}} h_i(k) \sum_{\sigma; \sigma_i=k} f(\sigma) + \frac{1}{x_k^{(i)}} \sum_{r \neq i; \sigma; \sigma_r=k} \sum_{t=1}^{M_r} h_r(t) \sum_{\sigma; \sigma_t=k} f(\sigma)
\]

\[
= h_i(k) + \sum_{r \neq i} \sum_{t=1}^{M_r} h_r(t) x_i^{(r)}.
\]

Now we assume (A.12), \( J_{rs}(k, l) = J_{sr}(l, k) \). This yields

\[
\sum_{1 \leq r < s \leq L} \sum_{\sigma} f_k^{(i)}(\sigma) J_{rs}(\sigma_r, \sigma_s) = \sum_{r \neq i} \sum_{\sigma; \sigma_i=k} f_k^{(i)}(\sigma) J_{ir}(\sigma_i, \sigma_r) + \sum_{1 \leq r < s \leq L} \sum_{\sigma; \sigma_t=k} f_k^{(i)}(\sigma) J_{rs}(\sigma_r, \sigma_s)
\]

\[
= \frac{1}{x_k^{(i)}} \sum_{r \neq i; \sigma; \sigma_i=k} f(\sigma) J_{ir}(\sigma_i, \sigma_r) + \frac{1}{x_k^{(i)}} \sum_{1 \leq r < s \leq L; \sigma; \sigma_t=k} \sum_{t=1}^{M_r} J_{rs}(t, n) \sum_{\sigma; \sigma_n=k} f(\sigma)
\]

\[
= \sum_{r \neq i} \sum_{t=1}^{M_r} J_{ir}(k, t) x_i^{(r)} + \sum_{1 \leq r < s \leq L} \sum_{t=1}^{M_r} J_{rs}(t, n) x_i^{(r)} x_n^{(s)}.
\]

thus completing the expression for \( \tilde{m}_k^{(i)} \) as

\[
\tilde{m}_k^{(i)} = 1 + h_i(k) + \sum_{r \neq i} \sum_{t=1}^{M_r} h_r(\sigma_r) x_i^{(r)}
\]

\[
+ \sum_{r \neq i} \sum_{t=1}^{M_r} J_{ir}(k, t) x_i^{(r)} + \sum_{1 \leq r < s \leq L} \sum_{t=1}^{M_r} J_{rs}(t, n) x_i^{(r)} x_n^{(s)}.
\]
Appendix B: Proof of Lemma 4.2

Proof: We evaluate \( \sum_{l=1}^{M_l} d_{kl}^{(i)} h_i(l) \). We have from (4.16) that

\[
\sum_{l=1}^{M_l} d_{kl}^{(i)} h_i(l) = \sum_{l=1}^{M_l} d_{kl}^{(i)} h_i(l) + \sum_{l=1}^{M_l} d_{kl}^{(i)} \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(l, m)x_m^{(r)}.
\]

By definition of \( d_{kl}^{(i)} \)

\[
\sum_{l=1}^{M_l} d_{kl}^{(i)} h_i(l) = -\sum_{l \neq k} x_k^{(i)} h_i(l) + x_k^{(i)} (1 - x_k^{(i)}) h_i(k) = -\sum_{r=1}^{M_r} x_k^{(i)} x_r^{(i)} h_i(r) + x_k^{(i)} h_i(k)
\]

\[
= x_k^{(i)} \left( h_i(k) - \sum_{l=1}^{M_l} x_l^{(i)} h_i(l) \right), \tag{B.1}
\]

which identifies the two first terms in the right hand side (4.15). Secondly, we have

\[
\sum_{l=1}^{M_l} d_{kl}^{(i)} \sum_{r \neq k} \sum_{m=1}^{M_r} J_{ir}(l, m)x_m^{(r)}
\]

\[
= -\sum_{l \neq k} x_l^{(i)} \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(l, m)x_m^{(r)} + x_k^{(i)} (1 - x_k^{(i)}) \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)}
\]

\[
= x_k^{(i)} \left( -\sum_{l \neq k} x_l^{(i)} \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(l, m)x_m^{(r)} + (1 - x_k^{(i)}) \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)} \right)
\]

\[
= x_k^{(i)} \left( -\sum_{l \neq k} \sum_{m=1}^{M_r} x_m^{(r)} x_l^{(i)} J_{lr}(l, m) + \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)} - \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} x_m^{(r)} x_k^{(i)} J_{ir}(k, m) \right)
\]

\[
= x_k^{(i)} \left( -\sum_{r=1}^{L_r} \sum_{m=1}^{M_r} x_m^{(r)} x_l^{(i)} J_{lr}(l, m) + \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)} \right)
\]

\[
= x_k^{(i)} \left( \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)} - \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} x_m^{(r)} x_l^{(i)} J_{lr}(l, m) \right)
\]

\[
= x_k^{(i)} \left( \sum_{r=1}^{L_r} \sum_{m=1}^{M_r} J_{ir}(k, m)x_m^{(r)} - \sum_{l=1}^{M_l} x_l^{(i)} J_{ir}(l, m) \right) \tag{B.2}
\]

By adding (B.1) and (B.2) give the expression in (4.15) as desired. \( \blacksquare \)
10 Appendix C: Inverse of $D^{(i)}(x)$

We establish next the inverse of the matrix $D^{(i)}(x)$ explicitly. It holds by (2.9) that $D^{(i)}(x)$ depends only on $x^{(i)}$. The result is as such known, see, e.g., [33, p.1262], but not widely publicized, so we prove it for the sakes of completeness and easy reference. The simple important fact that emerges is that the inverse of $D^{(i)}(x)$ does not exist at the facets of any $K_i$.

**Lemma 10.1.** Assume that $x_k^{(i)} > 0$ for every $k \in \{1, \ldots, M_i\}$. Then the inverse matrix $D_i^{-1}(x^{(i)})$ is given by

$$D_i^{-1}(x^{(i)}) = \left\{ \frac{1}{x_i^{(i)}} \delta_{i,k} + \frac{1}{x_{M_i}^{(i)}} \right\}_{l=1}^{M_i-1}_{k=1}^{M_i-1}.$$  (C.1)

**Proof:** We check that $D_1^{-1}(x^{(i)})D_1(x^{(i)}) = D_1(x^{(i)})D_1^{-1}(x^{(i)}) = I$, where $I$ is the $M_i - 1 \times M_i - 1$ unit matrix. By (2.9) we have

$$\sum_{k=1}^{M_i-1} \left( \frac{1}{x_i^{(i)}} \delta_{k,l} + \frac{1}{x_{M_i}^{(i)}} \right) d_{km} = \sum_{k=1}^{M_i-1} \left( \frac{1}{x_i^{(i)}} \delta_{k,l} + \frac{1}{x_{M_i}^{(i)}} \right) \left( x_k^{(i)} \delta_{k,m} - x_k^{(i)} x_m^{(i)} \right)$$

$$= \sum_{k=1}^{M_i-1} \frac{1}{x_i^{(i)}} \delta_{k,l} x_k^{(i)} \delta_{k,m} - \sum_{k=1}^{M_i-1} \frac{1}{x_i^{(i)}} \delta_{k,l} x_k^{(i)} x_m^{(i)} + \sum_{k=1}^{M_i-1} \frac{1}{x_{M_i}^{(i)}} \delta_{k,l} x_k^{(i)} - \sum_{k=1}^{M_i-1} \frac{1}{x_{M_i}^{(i)}} x_k^{(i)} x_m^{(i)}$$

$$= \delta_{l,m} - x_m^{(i)} + \frac{1}{x_{M_i}^{(i)}} x_m^{(i)} - \frac{1}{x_{M_i}^{(i)}} x_m^{(i)} \sum_{k=1}^{M_i-1} x_k$$

$$= \delta_{l,m} - x_m^{(i)} + \frac{1}{x_{M_i}^{(i)}} x_m^{(i)} - \frac{1}{x_{M_i}^{(i)}} x_m^{(i)} \left( 1 - x_m^{(i)} \right)$$

$$= \delta_{l,m} - x_m^{(i)} + \frac{1}{x_{M_i}^{(i)}} x_m^{(i)} = \delta_{l,m},$$

and the assertion in (C.1) holds, as claimed. \qed

**Appendix D: Proof of lemma 6.1**

We start with a result needed in the proof of the lemma 6.1 but which also shows that $\pi(x)$ is the non-normalized invariant density for

$$dX(t) = \mu(X(t))dt + D^{1/2}(X(t))dW(t),$$  (D.1)

which is (2.8) with the Svirezhev-Shahshahani gradient form removed.

**Lemma 10.2.** Assume (4.3) and (6.8). Then, for all $x \in \times_{i=1}^{L} K_i$, $k = 1, \ldots, M_i - 1$, and $i = 1, \ldots, L$, we have with $g_k^{(i)} = \bar{u}_k^{(i)} - \bar{u}_k^{(i)} x_k^{(i)}$ that

$$\frac{1}{2} \sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} \left[ d_k^{(i)}(x) \pi(x) \right] = g_k^{(i)} \pi(x).$$  (D.2)
Proof: The proof is a straightforward but lengthy computation, but is recapitulated here for the sake of completeness. For any \( k = 1, \ldots, M_i - 1 \) we have

\[
\frac{\partial}{\partial x_i^{(i)}} \left[ \sum_{l=1}^{M_i} d_{kl}^{(i)}(x) \pi(x) \right] =
\]

\[
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_i^{(i)}} \left[ d_{kl}^{(i)}(x) \right] \pi(x) + \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_i^{(i)}} \pi(x). \tag{D.3}
\]

We evaluate first the second term in the right hand side of (D.3). For any \( x_i^{(i)} \) we get by straightforward differentiation and rearrangement that

\[
\frac{\partial}{\partial x_i^{(i)}} \pi(x) = \left[ \frac{1}{x_i^{(i)}} \left( 2u_{i}^{(i)} - 1 \right) - \frac{1}{1 - \sum_{k=1}^{M_i-1} x_k^{(i)}} \left( 2u_{k}^{(i)} - 1 \right) \right] \pi(x). \tag{D.4}
\]

For this we note that \( x_i^{(i)} \) is a variable in one and only one of the factors in \( \pi(x) \). Thus we get by (2.6) that

\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{1}{x_i^{(i)}} \left( 2u_{k}^{(i)} - 1 \right) =
\]

\[
-x_k^{(i)} \sum_{l=1, l \neq k}^{M_i-1} \left( 2u_{k}^{(i)} - 1 \right) + \left( 1 - x_k^{(i)} \right) \left( 2u_{k}^{(i)} - 1 \right)
\]

\[
= -x_k^{(i)} \sum_{l=1}^{M_i-1} \left( 2u_{l}^{(i)} - 1 \right) + \left( 2u_{k}^{(i)} - 1 \right). \tag{D.5}
\]

Next (2.6) gives

\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{1}{1 - \sum_{k=1}^{M_i-1} x_k^{(i)}} \left( 2u_{k}^{(i)} - 1 \right) = \left( 2u_{M_i}^{(i)} - 1 \right) \frac{1}{1 - \sum_{k=1}^{M_i-1} x_k^{(i)}} \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \sum_{k=1}^{M_i-1} x_k^{(i)} x_k^{(i)} \tag{D.6}
\]

Here

\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) = -x_k^{(i)} \sum_{l=1, l \neq k}^{M_i-1} x_l^{(i)} + \left( 1 - x_k^{(i)} \right) x_k^{(i)}
\]

\[
= -x_k^{(i)} \sum_{l=1}^{M_i-1} x_l^{(i)} + x_k^{(i)}
\]

\[
= x_k^{(i)} \left( 1 - \sum_{l=1}^{M_i-1} x_l^{(i)} \right).
\]

This means that in the right hand side of (D.6) we get

\[
\left( 2u_{M_i}^{(i)} - 1 \right) \frac{1}{1 - \sum_{k=1}^{M_i-1} x_k^{(i)}} \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) = x_k^{(i)} \left( 2u_{k}^{(i)} - 1 \right). \tag{D.7}
\]
Hence we have in the right hand side of (D.4) in view of (D.5) and (D.7)

\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} \pi(x) =
-x_k^{(i)} \sum_{l=1}^{M_i-1} (2u_k^{(i)} - 1) + (2u_k^{(i)} - 1) - x_k^{(i)} \left(2u_{M_i}^{(i)} - 1\right) \tag{D.8}
\]

or,

\[
-x_k^{(i)} \sum_{l=1}^{M_i-1} (2u_k^{(i)} - 1) + (2u_k^{(i)} - 1). \tag{D.9}
\]

But we now observe that

\[
-x_k^{(i)} \sum_{l=1}^{M_i} (2u_k^{(i)} - 1) + (2u_k^{(i)} - 1)
= 2(u_k^{(i)} - \bar{u}^{(i)} x_k^{(i)}) + M_i x_k^{(i)} - 1,
\]

where we used the notation in (4.7). When we substitute this in the right hand side of (D.8) we obtain

\[
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} \pi(x) = \left[2(u_k^{(i)} - \bar{u}^{(i)} x_k^{(i)}) + M_i x_k^{(i)} - 1\right] \pi(x). \tag{D.10}
\]

Next we compute the first term in the right hand side of (D.3). By (2.6)

\[
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} d_{kl}^{(i)}(x) = - \sum_{l=1, l \neq k}^{M_i-1} x_k^{(i)} + (1 - 2x_k^{(i)})
= -x_k^{(i)} (M_i - 2) + 1 - 2x_k^{(i)} = -x_k^{(i)} M_i + 1
\]

or,

\[
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} d_{kl}^{(i)}(x) = -x_k^{(i)} M_i + 1. \tag{D.10}
\]

By (D.9) and (D.10) we obtain in (D.3) that

\[
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} d_{kl}^{(i)}(x) \pi(x) = \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} \pi(x)
= \left[2(u_k^{(i)} - \bar{u}^{(i)} x_k^{(i)}) + M_i x_k^{(i)} - 1 - x_k^{(i)} M_i + 1\right] \pi(x)
= \left[2(u_k^{(i)} - \bar{u}^{(i)} x_k^{(i)})\right] \pi(x).
\]

In view of lemma 4.1 we get the result as claimed in the lemma. □

An inspection of the proof above shows that it is strictly valid only in the interior of $K_i$. 42
However, the final result can obviously be extended to the boundary by continuity. Next we prove lemma 6.1.

\textit{Proof of lemma 6.1} For any $k = 1, \ldots, M_i - 1$ we have

$$
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} \left[ d_{kl}^{(i)}(x) P(x) \right] =
$$

\hspace{1cm} (D.11)

$$
= \sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} \left[ d_{kl}^{(i)}(x) \right] P(x) + \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} P(x).
$$

Here

$$
\sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} P(x) = e^{2V(x)} \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} \pi(x) + P(x) \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \left( 2V'_x(x) \right).
$$

Thus we have

$$
\sum_{l=1}^{M_i-1} \frac{\partial}{\partial x_l^{(i)}} \left[ d_{kl}^{(i)}(x) \right] \pi(x) + \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) \frac{\partial}{\partial x_l^{(i)}} \pi(x)
$$

$$
+ P(x) \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) 2V'_x(x).
$$

But by lemma 10.2 or (D.2) in the preceding, we get above

$$
= 2e^{2V(x)} g_k^{(i)} \pi(x) + P(x) \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) 2V'_x(x).
$$

$$
= 2P(x) \left( g_k^{(i)} + \sum_{l=1}^{M_i-1} d_{kl}^{(i)}(x) V'_x(x) \right).
$$

\square

Appendix E: Diffusion approximation: technical steps

This Appendix contains the proofs of the technical conditions on limits of the sequences of conditional incremental moments for the sequence of Markov chains $X^{(N)}$ required in the weak convergence statement of proposition 5.1.
10.1 Conditional Expectation of the Increments

Let us set for $k = 1, \ldots, M$

$$\mu^{(N)}_{i,k} \left( \frac{j}{N} \right) \overset{\text{def}}{=} N \sum_{r \in J_{(i)}(N)} \left( \frac{T_k^{(i)}}{N} - \frac{j_k^{(i)}}{N} \right) P_r \tag{E.1}$$

which is

$$\mu^{(N)}_{i,k} \left( \frac{j}{N} \right) = NE \left[ \left( X_{i,k}^{(N)} (n + 1) - X_{i,k}^{(N)} (n) \right) \mid X^{(N)} (n) = \frac{j}{N} \right].$$

This is, of course, the conditional expectation of the difference ratio

$$\frac{X_{i,k}^{(N)} (n + 1) - X_{i,k}^{(N)} (n)}{\frac{1}{N}}.$$

An analogous interpretation holds for the expressions studied in the other subsections of this Appendix E. We shall next evaluate (E.1) and then expand it as a function of $1/N$ evoking the rescalings in the assumption 5.1. For ease of writing we drop for the moment the subscript for locus in the computations that follow in this section. Hence the analysis holds for any $X_{k}^{(N)} (n + 1) = X_{i,k}^{(N)} (n)$ in (5.5).

$$NE \left[ \left( X_k^{(N)} (n + 1) - X_k^{(N)} (n) \right) \mid X^{(N)} (n) = \frac{j}{N} \right] = E \left[ \left( \frac{Y_k^{(N)}}{N} \right) \mid X^{(N)} (n) = \frac{j}{N} \right] - E \left[ \frac{Y_k^{(N)}}{N} \mid X^{(N)} (n) = \frac{j}{N} \right]$$

and by a property of the multinomial distribution (3.8)

$$= N p_k (j) - j_k.$$

Thus when we return to the full notations

$$\mu^{(N)}_{i,k} \left( \frac{j}{N} \right) = N p_k (j) - j_k = N (p_k (j) - x_k) = N (p^{(i)}_k (j) - x^{(i)}_k). \tag{E.2}$$

By (3.13) we obtain

$$N (p^{(i)}_k (j) - x^{(i)}_k) = N \left\{ \sum_{l=1}^{M} v^{(i)}_{kl} x^{(i)}_l \left( \frac{v^{(i)}_l}{v} \right) - v^{(i)}_{kl} x^{(i)}_k \left( \frac{v^{(i)}_k}{v} \right) \right\} + x^{(i)}_k \left( \frac{1}{v} \right) \left[ \frac{v^{(i)}_k}{v} - \frac{\bar{v}^{(i)}_k}{\bar{v}} \right]. \tag{E.3}$$
When (5.1), (5.2) and (5.3) are inserted in (E.3) we obtain

\[ \mu_{i,k}^{(N)} \left( \frac{j}{N} \right) = N \cdot \left\{ p_k^{(i)}(j) - x_k^{(i)} \right\} = \]

\[
N \left\{ \sum_{l \neq k}^{M} \frac{u_{lk}}{N} x_l^{(i)} \left( 1 + \frac{\bar{m}_k^{(i)}}{N} \right) - \frac{u_{kl}}{N} x_k^{(i)} \left( 1 + \frac{\bar{m}_k^{(i)}}{N} \right) \right\} \\
+ x_k^{(i)} \left( \frac{1}{1 + \frac{N}{m}} \right) (\bar{m}_k^{(i)} - \bar{m}) \right\}.
\]

If \( N \to +\infty \), this expression clearly converges to

\[ p_k^{(i)}(x) = \sum_{l=1}^{M} \left[ u_{lk} x_l^{(i)} - u_{kl} x_k^{(i)} \right] + x_k^{(i)} (\bar{m}_k^{(i)} - \bar{m}) \]  

Lemma 10.3.

\[ \mu_{i,k}^{(N)} \left( \frac{j}{N} \right) \to p_k^{(i)}(x), \]  

(E.4)

as \( N \to +\infty \), uniformly in \( x \in \times_{i=1}^{L} K_i \), where for \( x \in \times_{i=1}^{L} K_i \)

\[ p_k^{(i)}(x) = \sum_{l \neq k}^{M} \left[ u_{lk} x_l^{(i)} - u_{kl} x_k^{(i)} \right] + x_k^{(i)} (\bar{m}_k^{(i)} - \bar{m}) \]  

(E.5)

Proof: It remains to prove that the convergence in (E.4) is in fact uniform in \( x^{(i)} \). To see this, let us check

\[
|\mu_{i,k}^{(N)}(x) - p_k^{(i)}(x)| = \left| \sum_{l \neq k}^{M} \left[ \frac{u_{lk} x_l^{(i)}}{1 + \frac{N}{m}} - 1 \right] - \frac{u_{kl}}{1 + \frac{N}{m}} - 1 \right|
\]

\[
+ x_k^{(i)} \left( \frac{1}{1 + \frac{N}{m}} - 1 \right) (\bar{m}_k^{(i)} - \bar{m}) \right|
\]

\[
\leq \sum_{l \neq k}^{M} \left| \frac{u_{lk} x_l^{(i)}}{1 + \frac{N}{m}} \right| + \left| \frac{u_{kl} x_k^{(i)}}{1 + \frac{N}{m}} \right| \right|
\]

\[
+ x_k^{(i)} \left( \frac{1}{1 + \frac{N}{m}} - 1 \right) (\bar{m}_k^{(i)} - \bar{m}) \right|
\]

\[
\leq \frac{1}{N} \sup_{x^{(i)} \in K_i} \left\{ \sum_{l \neq k}^{M} \left| \frac{u_{lk} x_l^{(i)}}{1 + \frac{N}{m}} \right| + \left| \frac{u_{kl} x_k^{(i)}}{1 + \frac{N}{m}} \right| \right\}
\]

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Then as we invoked the appropriate moments of the multinomial distribution in (3.8). By
\[ \left| \mu_{i,k}^{(N)}(x) - \mu_{i,k}^{(N)}(x) \right| \leq \frac{A}{N}. \]
I.e.,
\[ |\mu_{i,k}^{(N)}(x) - p_k^{(i)}(x)| \leq \frac{A}{N}. \] (E.6)

The result in (E.6) agrees with the notion of uniform convergence of the incremental
conditional moment characteristics of a sequence of Markov chains in both [10] Theorem
7.1, and [37, p. 642].

10.2 Conditional Covariances of the Increments

Again we take for any \( X_k^{(N)}(n+1) \equiv X_i^{(N)}(n) \) in (5.5). Next we set
\[ d_k(N) \left( \frac{1}{N} \right) \overset{\text{def}}{=} N \epsilon \sum_{r \in J_{(i)}} \left( \frac{r_k}{N} - \frac{j_k}{N} \right) \left( \frac{r_l}{N} - \frac{j_l}{N} \right) x_{i,k}. \] (E.7)

which is
\[ d_k(N) \left( \frac{1}{N} \right) = NE \left[ \left( X_k^{(N)}(n+1) - X_k^{(N)}(n) \right) \left( X_l^{(N)}(n+1) - X_l^{(N)}(n) \right) \right] | X^{(N)}(n) = \frac{j}{N} \]

Then
\[ d_k(N) \left( \frac{1}{N} \right) = \frac{1}{N} E \left[ \left( \frac{n+1}{N} \right) - \frac{n}{N} \right] \cdot \left( \frac{n+1}{N} \right) - \frac{n}{N} \right] \right] | X^{(N)}(n) = \frac{j}{N} \]

Take first \( k \neq l \). Then
\[ E \left[ \left( \frac{n+1}{N} \right) - \frac{n}{N} \right] \cdot \left( \frac{n+1}{N} \right) - \frac{n}{N} \right] \right] | X^{(N)}(n) = \frac{j}{N} \]
\[ = E \left[ \left( \frac{n+1}{N} \right) \cdot \left( \frac{n+1}{N} \right) \right] \right] | X^{(N)}(n) = \frac{j}{N} \]
\[ - E \left[ \left( \frac{n+1}{N} \right) \cdot \left( \frac{n}{N} \right) \right] \right] | X^{(N)}(n) = \frac{j}{N} \]
\[ - E \left[ \left( \frac{n}{N} \right) \cdot \left( \frac{n}{N} \right) \right] \right] | X^{(N)}(n) = \frac{j}{N} \]
\[ = E \left[ \left( \frac{n}{N} \right) \cdot \left( \frac{n}{N} \right) \right] | X^{(N)}(n) = \frac{j}{N} \]
\[ - Np_k(j) \cdot j_l - Ns_l(j) \cdot j_k + j_l \]

where we invoked the appropriate moments of the multinomial distribution in (E.8). By
the same token the first term in the right hand side of the inequality above is evaluated
as
\[ E \left[ \left( \frac{n}{N} \right) \cdot \left( \frac{n}{N} \right) \right] | X^{(N)}(n) = \frac{j}{N} \]

\[ \text{Cov} \left( \frac{n+1}{N} \right), \frac{n+1}{N} \right) \right] \]

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Hence we have obtained

\[ d_{kl}^{(N)} \left( \frac{j}{N} \right) = \frac{1}{N} \sum_{j} \left[ -Np_k(j)p_l(j) + N^2 p_k(j)p_l(j) - Np_k(j) \cdot j_l - Np_l(j) \cdot j_k + j_l j_k \right] \]

\[ = \frac{1}{N} \left[ -Np_k(j)p_l(j) + \left( p_k(j) - x_k \right) \cdot N(p_l(j) - x_l) \right] \]

In view of (E.2), (E.4) and (E.6) we have \( p_l(j) = x_l + O \left( \frac{1}{N} \right) \) and \( p_k(j) = x_k + O \left( \frac{1}{N} \right) \) and we proved the following lemma.

**Lemma 10.4.**

\[ d_{kl}^{(N)} \left( \frac{j}{N} \right) \rightarrow -x_k x_l, \quad k \neq l, \quad (E.8) \]

as \( N \rightarrow +\infty \), the convergence is uniform in \( x \).

The limiting genetic drift for \( k = l \) is obtained readily, too. We have

\[ d_{kk}^{(N)} \left( \frac{j}{N} \right) = N E \left[ (X_k^{(N)}(n + 1) - X_k^{(N)}(n))^2 \mid X^{(N)}(n) = \frac{j}{N} \right] \]

\[ = \frac{1}{N} \left\{ E \left[ Y_k^{(N)} \left( \frac{n+1}{N} \right)^2 \mid X^{(N)}(n) = \frac{j}{N} \right] - 2 E \left[ Y_k^{(N)} \left( \frac{n+1}{N} \right) Y_k^{(N)} \left( \frac{n}{N} \right) \mid X^{(N)}(n) = \frac{j}{N} \right] \right\} \]

\[ + E \left[ Y_k^{(N)} \left( \frac{n+1}{N} \right)^2 \mid X^{(N)}(n) = \frac{j}{N} \right] \]

\[ = \frac{1}{N} \left\{ \text{Var} \left[ Y_k^{(N)} \left( \frac{n+1}{N} \right) \mid X^{(N)}(n) = \frac{j}{N} \right] + \left( E \left[ Y_k^{(N)} \left( \frac{n+1}{N} \right) \mid X^{(N)}(n) = \frac{j}{N} \right] \right)^2 \right\} \]

\[-2Np_k(j) j_k + j_k^2 \}

and due to (E.8) it follows that

\[ = \frac{1}{N} \left\{ Np_k(j)(1 - p_k(j)) + N^2 p_k(j)^2 - 2Np_k(j) j_k + j_k^2 \right\} \]

\[ = \frac{1}{N} \left\{ Np_k(j)(1 - p_k(j)) + (Np_k(j) - j_k)^2 \right\} \]

\[ = p_k(j)(1 - p_k(j)) + \frac{1}{N} (N(p_k(j) - x_k))^2. \]

By (E.2), (E.4) and (E.6) we have \( p_l(j) = x_l + O \left( \frac{1}{N} \right) \) and \( p_k(j) = x_k + O \left( \frac{1}{N} \right) \).
Lemma 10.5.

\[ d_{kk}^{(N)} \left( \frac{j}{N} \right) \to x_k(1 - x_k). \]  

(E.9)

uniformly, as \( N \to +\infty. \)

When the findings in the two lemmas above are collected to one statement we have for \( k = 1, \ldots M \) and \( l = 1, \ldots M \) and for every locus \( i \) the expression for \( d_{kl}^{(i)}(x) \).

Now we take \( X_{i,k}^{(N)}(n) \) and \( X_{i,k}^{(N)}(n) \) in (5.5) with two different loci. Let us set

\[ d_{kl}^{(N)} \left( \frac{j}{N} \right) = NE \left[ (X_{i,k}^{(N)}(n + 1) - X_{i,k}^{(N)}(n))(X_{j,l}^{(N)}(n + 1) - X_{j,l}^{(N)}(n)) \mid X^{(N)}(n) = \frac{j}{N} \right]. \]

Lemma 10.6.

\[ NE \left[ (X_{i,k}^{(N)}(n + 1) - X_{i,k}^{(N)}(n))(X_{j,l}^{(N)}(n + 1) - X_{j,l}^{(N)}(n)) \mid X^{(N)}(n) = \frac{j}{N} \right] \to 0. \]  

(E.10)

as \( N \to +\infty, \) uniformly.

Proof: Due to the assumption of conditional independence (3.6) over loci we get

\[ = \frac{1}{N} \left\{ NE \left[ (X_{i,k}^{(N)}(n + 1) - X_{i,k}^{(N)}(n)) \mid X^{(N)}(n) = \frac{j}{N} \right] \right. \]

\[ \frac{1}{N} \left\{ NE \left[ (X_{j,l}^{(N)}(n + 1) - X_{j,l}^{(N)}(n)) \mid X^{(N)}(n) = \frac{j}{N} \right] \right\} \]

The computation in section 10.1 above yields here

\[ = \frac{1}{N} \mu_{i,k}^{(N)} \left( \frac{j}{N} \right) \mu_{j,l}^{(N)} \left( \frac{j}{N} \right). \]

Since \( \mu_{i,k}^{(N)} \left( \frac{j}{N} \right) \) and \( \mu_{j,l}^{(N)} \left( \frac{j}{N} \right) \) converge, as shown in section 10.1 uniformly to finite limits as \( N \to +\infty \), we get the lemma as asserted.

10.3 No Jumps in the Limit

For the diffusion approximation desired we need to check the behaviour of (e.g.,) the fourth moment of the increments defined as

\[ e_{jr,k}^{(N)} \left( \frac{j}{N} \right) \text{ def } = N \sum_{r \in J^{(i)}(N)} \left( \frac{r}{N} - \frac{j}{N} \right)^4 P_{jr}. \]  

(E.11)

This is dependent on the locus \( i \), i.e., \( j_k = j_k^{(i)} \) and \( r_k = r_k^{(i)} \), but we omit once more this for reasons of simplicity of notation in the calculations of this subsection.
Lemma 10.7.

\[ e^{(N)}_{jr,k} \left( \frac{j}{N} \right) \to 0 \quad (E.12) \]

uniformly, as \( N \to +\infty \).

**Proof:** We have

\[ e^{(N)}_{jr,k} \left( \frac{j}{N} \right) = NE \left[ \left( X_k^{(N)}(n + 1) - X_k^{(N)}(n) \right)^4 \mid X(n) = \frac{j}{N} \right] \quad (E.13) \]

First we insert \( Np_k(j) \), invoke the inequality \((a+b)^4 \leq 2^4 a^4 + 2^4 b^4\) and obtain the bound

\[
\leq 2^4 E \left[ \left( Y_k^{(N)} \left( \frac{n+1}{N} \right) - Np_k(j) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] \\
+ 2^4 E \left[ \left( Np_k(j) - Y_k^{(N)} \left( \frac{n}{N} \right) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right].
\]

Here

\[
E \left[ \left( Y_k^{(N)} \left( \frac{n}{N} \right) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] = E \left[ \left( Np_k(j) - j_k \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] \\
= (Np_k(j) - j_k)^4 = (p_k(j) - x_k)^4.
\]

Hence, by (E.4) and (E.2) as above

\[
\frac{1}{N^3} (Np_k(j) - x_k)^4 \to 0,
\]

uniformly in \( x \), as \( N \to \infty \). Next, we bound

\[
E \left[ \left( Y_k^{(N)} \left( \frac{n+1}{N} \right) - Np_k(j) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right].
\]

We know that \( Y_k^{(N)} \left( \frac{n+1}{N} \right) \) conditioned on \( Y^{(N)}(\frac{n}{N}) = j \) has the multinomial distribution (3.8). This means that \( Y_k^{(N)} \left( \frac{n+1}{N} \right) \) is in distribution equal

\[
Y_k^{(N)} \left( \frac{n+1}{N} \right) \overset{d}{=} \sum_{l=1}^{N} \xi_l,
\]

where \( \xi_k = I(Z_l = k) \) is the indicator function of the event, \( Z_l, l = 1, 2, \ldots, N \), are conditionally independent and identically distributed random variables such that \( p_k(j) = P(Z_l = k), k = 1, \ldots, M_i \). Here we apply a technique from [10] p. 308,

\[
E \left[ \left( Y_k^{(N)} \left( \frac{n+1}{N} \right) - Np_k(j) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] = E \left[ \left( \sum_{l=1}^{N} \xi_k - Np_k(j) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right]
\]

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\[ E \left[ \left( \sum_{l=1}^{N} (\xi_k - p_k(j)) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] \]
\[ \leq NE \left[ (\xi_k - p_k(j))^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] + 6 \left( \frac{N}{2} \right) E \left[ (\xi_k - p_k(j))^2 \mid Y^{(N)}(\frac{n}{N}) = j \right] \]
\[ \leq CN^2. \]

Above we evoked the inequality \( E \left[ (\xi_k - p_k(j))^m \mid Y_k(\frac{n}{N}) = j \right] \leq 1 \) for all \( m \geq 1 \). Hence we have that
\[ \frac{1}{N^3} E \left[ \left( Y^{(N)}_k\left(\frac{n+1}{N}\right) - Np_k(j) \right)^4 \mid Y^{(N)}(\frac{n}{N}) = j \right] \leq CN^{-1}. \]

By the preceding we have shown the asserted lemma. \( \square \)