Mutation and Recombination with Tight Linkage

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Abstract. An exact solution of the mutation-recombination equation in continuous time is presented, with linear ordering of the sites and at most one mutation or crossover event taking place at every instant of time. The differential equation may be obtained from a mutation-recombination model with discrete generations, in the limit of short generations, or weak mutation and recombination. The solution relies on the multilinear structure of the dynamical system, and on the commuting properties of the mutation and recombination operators. It is obtained through diagonalization of the mutation term, followed by a transformation to certain measures of linkage disequilibrium that simultaneously linearize and diagonalize the recombination dynamics. The collection of linkage disequilibria, as well as their decay rates, are given in closed form.

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1 Introduction

It is well known that the treatment of population genetic models with recombination is haunted by the nonlinearity that recombination introduces into the dynamical equations. However, the nonlinear dynamical system may be transformed to a linear one, as was noted in the early work of Geiringer [16] and Bennett [4], as well as the more recent approaches via genetic algebras (e.g., Lyubich [28], McHale and Ringwood [29], and Ringwood [36]; see also the review by Holgate [22]). All these approaches work through suitable transformations of variables (from gamete frequencies to linkage disequilibria, i.e., measures of the deviation from statistical independence of sites), which render the recombination dynamics linear. The procedure, known as *Haldane linearization* [29, 36], is fairly general in that it works for arbitrary numbers of loci and alleles and arbitrary recombination distributions (i.e. arbitrary patterns of recombination events). It relies on a multilinear transformation that yields a hierarchical system of equations, which may then be solved in a recursive manner. Also, mutation (but not selection) may be included [29, 36]. Unfortunately, however, explicit calculations, as well as results, are unwieldy, so that there is little hope of including other evolutionary forces.

In order to analyze the interplay of recombination with other processes, one therefore tends to resort to approximations. Much work has been done on the interaction between selection, mutation, and recombination in the multilocus context (see, e.g., [15]). Here, the recombination rate is usually large compared with both the mutation rate and the selection intensity, so that a separation of time scales is appropriate. After an initial phase, the population reaches the state of quasi-linkage equilibrium (QLE), and the dynamics may be approximated, to first order in the selection intensity, by the much simpler dynamics on the so-called QLE manifold; this approach was introduced by Nagylaki [30, 31] for two loci, and further developed for multiple loci by Turelli and Barton [39], Barton and Turelli [3], Nagylaki [33], and Nagylaki, Hofbauer and Brunovský [34]. Such analyses are most valuable in situations where the loci in question are only loosely linked (e.g. in quantitative genetics, where the relevant loci are assumed to be widely scattered over the genome): Then, only a short initial phase is required to approach the QLE manifold. If, however, time scales fail to separate, the dynamics can become more complicated, and limit cycles may occur [1, 19].

With sequencing techniques becoming powerful enough to yield population sequence data, one is also interested in smaller regions of the genome with resolution at sequence level. These regions are sometimes carefully chosen to be devoid of, or low in, selection or recombination (as with large parts of the mitochondrial DNA). But with nuclear genes, which are now moving into focus, recombination can no longer be ignored; after all, intragenic recombination rates seem to be of the order of mutation rates (i.e., about 10^{-9} per nucleotide site per generation) or even ten times higher in some genes recently analyzed [10, 18, 37]. In contrast to the multilocus context, however, linkage is not loose but very tight here. If recombination is still the dominant evolutionary force (e.g., if selection is absent and mutation rates are small with respect to recombination rates), QLE will eventually be established, but the time required will be governed by the slow time scale of recombination. In line with this, significant linkage disequilibria are frequently observed [10, 27, 37], although they often fall off quickly with distance, e.g. [27, 37].

With *both* recombination and mutation events being rare, a continuous-time description is appropriate, with mutation and crossover events occurring independently of each other (i.e., without interference), and at most one such event possible at any instant of time; after all, double crossovers are extremely rare even in a stretch of a million basepairs. (Note that the absence of double events is a natural consequence of events happening independently in continuous time, and does not require interference.) Also, in analogy with continuous-time *selection* models [32, Chap. 8.4], Hardy-Weinberg proportions may be expected to provide a good approximation.

The aim of this article is to solve the resulting differential equation exactly, for an arbitrary number of sites, under the joint action of mutation and recombination, but without selection and genetic drift. To be more precise, we will elaborate on the situation with N linearly ordered sites, a finite alphabet at every site, and an infinite population. The benefit of this special model is that, unlike the more general approaches, it leads to explicit and simple results. Linkage disequilibria that at the same time linearize and diagonalize the dynamics can be defined right away. They are different from all previously established measures of linkage disequilibrium known to the author, e.g., [4, 8, 28, 33, 38, 39]. The simplifications involved give rise to the hope that the model will also lend itself to the introduction of other evolutionary forces, such as selection, migration, or drift, in situations where the single-crossover assumption provides a valid description.

In Section 2, we shall set out by formulating the mutation-recombination equation in continuous time, with special emphasis on its tensor-product structure. The latter will serve to define mutation and recombination operators. Further, a connection with a discrete-generation model will be established. Section 3 is devoted to the diagonalization of the mutation term, which corresponds to a transformation from relative frequencies to (generalized) multivariate moments. In Section 4, the procedure is illustrated by means of an example. In Section 5, the commuting properties of the mutation and recombination operators will be established, and exploited to define suitable linkage disequilibria, which decouple and converge to zero exponentially. The collection of linkage disequilibria, as well as their rates of decay, will be given in simple closed form. The results will be summarized and discussed in Section 6.

2 The mutation-recombination equation

Consider a linear arrangement of N autosomal sites labelled by the elements of an ordered index set $L := \{1, 2, \ldots, N\}$. Each site i is equipped with a variable σ_i, which may take values from a finite set (the 'alphabet') $\mathcal{A}$. This way, a type may be denoted by $\boldsymbol{\sigma} := (\sigma_1, \sigma_2, \ldots, \sigma_N) \in \mathcal{A}^N$. We are primarily interested in the molecular context, where variables may be interpreted as nucleotides (or purines and pyrimidines if particularly simple examples are sought), and types may be identified with sequences. We may, however, think in terms of a multilocus context as well, where 'variables' correspond to 'alleles', and 'sites' and 'types' must be read as 'loci' and 'gametes', respectively.

We posit a population of infinite size in Hardy-Weinberg equilibrium, the composition of which is given by the relative frequencies $p^{\boldsymbol{\sigma}}$ of types $\boldsymbol{\sigma}$ ($p^{\boldsymbol{\sigma}} \geq 0$, $\sum_{\boldsymbol{\sigma}} p^{\boldsymbol{\sigma}} = 1$). We shall use superscripts throughout for letters, types, or coordinates of vectors, and reserve subscripts for sites, as will become clear in a moment. The linear arrangement of sites, and the corresponding sitewise action of the recombination and mutation operators, is appropriately captured through some vector space structure, which has been used to advantage previously, e.g. [23, 24, 25, 36, 20, 26], and will be heavily drawn on in the solution of our problem.

Let $e^1, \ldots, e^m$ be the canonical unit vectors of $V := \mathbb{R}^m$, where $m := |\mathcal{A}|$, and a one-to-one correspondence between unit vectors and letters in $\mathcal{A}$ is implied. Then, the set

$$\{e^{\sigma_1} \otimes e^{\sigma_2} \otimes \cdots \otimes e^{\sigma_N} | \sigma_i \in \mathcal{A}\} \tag{2.1}$$

is the canonical basis of $W := \bigotimes^N V$, where every copy of V corresponds to one site of the sequence. Here, $\otimes$ denotes the tensor (or Kronecker) product, and $\bigotimes^N$ the N-fold tensor product. The relative frequencies may then be collected into a vector in $W = \mathbb{R}^{(m^N)}$ (more precisely, a vector in the unit simplex embedded in W):

$$p = \sum_{\boldsymbol{\sigma}} p^{\boldsymbol{\sigma}} e^{\boldsymbol{\sigma}}, \quad \text{where} \quad e^{\boldsymbol{\sigma}} := e^{\sigma_1} \otimes e^{\sigma_2} \otimes \cdots \otimes e^{\sigma_N}. \tag{2.2}$$

Let us now consider the dynamics of the population in continuous time, under the assumption that mutation and recombination proceed independently of each other and at most one mutation or crossover event takes place at any instant of time. At site i, mutation from letter α to letter β is assumed to happen at rate $\mu_i m^{\beta\alpha}$, where μ_i is a site-dependent rate factor, and the $m^{\beta\alpha}$ are the elements of a stochastic matrix (i.e., $m^{\beta\alpha} \geq 0$, and $\sum_\beta m^{\beta\alpha} = 1$), which is the same for every site. This formulation will simplify matters in what follows; in order not to restrict the model class, we must allow $m^{\alpha\alpha} \neq 0$, i.e., we allow the possibility that letter α mutates to itself. Put differently, letters at site i mutate at rate μ_i, independently of all other sites, and

$m^{\beta\alpha}$ is the conditional probability that letter β results upon mutation of letter α. Note that, if $m^{\alpha\alpha} \neq 0$, μ_i differs from the mutation rate in the usual sense, since it also accounts for 'fictitious' events. Note also that interactions between sites (as inherent in codon-based mutation models, for example) are not included in the framework. However, site-dependent mutation matrices are easily accomodated as long as the sites remain independent. In order to keep the notation as simple as possible, we do not develop this in the main text, but summarize the corner stones required for the generalization in the Appendix.

Crossovers occur at rate ρ_i between sites i and $i+1$. This partitions L into $[1, i]$ and $[i+1, N]$, where we define $[a, b]$ as the ordered set $\{a, a+1, \dots b\}$ for $b \geq a$. The newly formed type will agree with the maternal one at sites in $[1, i]$, and with the paternal one at sites in $[i+1, N]$, or vice versa. That is, the crossover process for types $\boldsymbol{\sigma}$ and $\boldsymbol{\sigma'}$ may be summarized as

$$\begin{array}{ccc} (\sigma_1, \sigma_2, \dots, \sigma_N) & & (\sigma_1, \sigma_2, \dots, \sigma_i, \sigma'_{i+1}, \dots, \sigma'_N) \\ + & \xrightarrow{\rho_i} & + \\ (\sigma'_1, \sigma'_2, \dots, \sigma'_N) & & (\sigma'_1, \sigma'_2, \dots, \sigma'_i, \sigma_{i+1}, \dots, \sigma_N). \end{array} \tag{2.3}$$

Likewise, the mutation process reads

$$(\sigma_1, \dots, \sigma_{i-1}, \sigma_i, \sigma_{i+1}, \dots, \sigma_N) \xrightarrow{\mu_i m^{\sigma'_i \sigma_i}} (\sigma_1, \dots, \sigma_{i-1}, \sigma'_i, \sigma_{i+1}, \dots, \sigma_N). \tag{2.4}$$

The differential equations describing the dynamics of the frequencies $p^{\boldsymbol{\sigma}}$ read

$$\begin{aligned} \dot{p}^{\boldsymbol{\sigma}} := \frac{d}{dt} p^{\boldsymbol{\sigma}} \quad &= \quad \sum_{i=1}^{N} \mu_i \sum_{\sigma'_i} \big(m^{\sigma_i \sigma'_i} p^{(\sigma_1, \dots, \sigma_{i-1}, \sigma'_i, \sigma_{i+1}, \dots, \sigma_N)} - p^{\boldsymbol{\sigma}} \big) \\ &\quad + \sum_{i=1}^{N-1} \rho_i \big(p^{(\sigma_1, \dots, \sigma_i, *, *, \dots, *)} \cdot p^{(*, *, \dots, *, \sigma_{i+1}, \dots, \sigma_N)} - p^{\boldsymbol{\sigma}} \big) , \end{aligned} \tag{2.5}$$

where '$*$' means 'wildcard', i.e., $p^{(*, \dots, *, \sigma_a, \dots, \sigma_b, *, \dots, *)}$ denotes the marginal frequency of types that read $\sigma_a, \dots, \sigma_b$ at sites $a, \dots, b$. Of course, $p^{\boldsymbol{\sigma}} = p^{\boldsymbol{\sigma}}(t)$, but we will usually suppress the time dependence. Clearly, (2.5) defines a unique flow, which leaves the unit simplex invariant, that is, $p^{\boldsymbol{\sigma}}(t) \geq 0$ for all $\boldsymbol{\sigma}$, and $p^{(*, *, \dots, *)}(t) \equiv 1$.

There is a straightforward connection of the continuous-time model with a discrete-generation model, which will be established in Subsection 2.2. Since this connection is best described with reference to the natural tensor product formulation of mutation and recombination, we are going to work this out first. We assume the reader to be familiar with elementary facts of multilinear algebra, e.g. [17, Chap. 1] or [35, Chap. V]. For a mapping $A : V \to V$, we define $A_i : W \to W$ by

$$A_i(\xi_1 \otimes \cdots \otimes \xi_N) = \xi_1 \otimes \cdots \otimes \xi_{i-1} \otimes (A\xi_i) \otimes \xi_{i+1} \otimes \cdots \otimes \xi_N \, ; \tag{2.6}$$

i.e. A_i maps ξ_i to $A\xi_i$ and leaves all other sites unchanged (note that it is sufficient to define mappings for vectors with tensor product structure if linear extension to all vectors in W is implied). A_i may be written as

$$A_i = (\bigotimes{}^{i-1} \mathbf{1}) \otimes A \otimes (\bigotimes{}^{N-i} \mathbf{1}) = \underbrace{\mathbf{1} \otimes \cdots \otimes \mathbf{1}}_{i-1 \text{ sites}} \otimes A \otimes \underbrace{\mathbf{1} \otimes \cdots \otimes \mathbf{1}}_{N-i \text{ sites}}, \tag{2.7}$$

where $\mathbf{1}$ denotes the identity. Likewise, for any set $G \subseteq L = \{1, 2, \ldots, N\}$,

$$A_G := \prod_{g \in G} A_g \, ; \tag{2.8}$$

here and in what follows, multiplication of mappings is understood as composition. We shall use (2.7) and (2.8) as a general agreement for linear mappings, with subscripts indicating sites or sets of sites, respectively.

We now define operators such that the recombination-mutation equation (2.5) can be generalized to elements x of W^+, the positive cone of W, and written in the form

$$\dot{x} = f_{\widehat{\mathcal{M}}}(x) + f_{\widehat{\mathcal{R}}}(x), \tag{2.9}$$

where $f_{\widehat{\mathcal{M}}}$ and $f_{\widehat{\mathcal{R}}}$ both map W^+ into W and correspond to the action of mutation and recombination, respectively (we shall get rid of the hats in the next section, after transformation to our favourite coordinate system). The vector x may be understood as the vector of *absolute* frequencies, as opposed to the *relative* frequencies p.

Let $\widehat{M} := (m^{\beta\alpha})_{\beta,\alpha \in \mathcal{A}}$ be the matrix of mutation probabilities. To avoid nongeneric cases, we shall assume $\widehat{M}$ as diagonalizable (further assumptions, like symmetry, irreducibility, or aperiodicity, are not required). Then, with $\widehat{M}_i$ according to definition (2.6), $\widehat{M}_i$ is the mutation operator which acts on site i while leaving all other sites unchanged, and

$$f_{\widehat{\mathcal{M}}}(x) = \widehat{\mathcal{M}} x \, , \quad \text{where} \quad \widehat{\mathcal{M}} := \sum_{i=1}^{N} \mu_i (\widehat{M}_i - \mathbf{1}) \tag{2.10}$$

is the overall mutation operator. (We use $\mathbf{1}$ to denote the identity on V or W alike, since there will be no danger of confusion.)

Whereas mutation is a simple linear operation on W, recombination is a nonlinear operation on (the positive cone of) W, but a linear one on $W \otimes W$. To see this, consider first the linear form $\hat{\ell} : \; V \to \mathbb{R}$ defined by

$$\hat{\ell}(\xi) = \xi^1 + \cdots + \xi^m, \tag{2.11}$$

where ξ is represented as $\xi = \xi^1 e^1 + \cdots + \xi^m e^m$. Equivalently, $\hat{\ell}(\xi) = \hat{u} \cdot \xi$ with $\hat{u} := (1, 1, \ldots, 1)^T$. Now, consider the mapping $\hat{h}_G : \bigotimes^N V \to \bigotimes^{|G|} V$ defined by

$$\hat{h}_G(\xi_1 \otimes \cdots \otimes \xi_N) = \Big(\prod_{i \in (L \setminus G)} \hat{\ell}(\xi_i) \Big) \Big(\bigotimes_{j \in G} \xi_j \Big). \tag{2.12}$$

The mapping $\hat{h}_G$ may be written as

$$\hat{h}_G = \mathbf{1} \otimes \cdots \otimes \mathbf{1} \otimes \hat{\ell} \otimes \mathbf{1} \otimes \cdots \otimes \mathbf{1} \otimes \hat{\ell} \otimes \mathbf{1} \otimes \cdots \otimes \mathbf{1} \tag{2.13}$$

with $\hat{\ell}$ at every site in $L \setminus G$, and $\mathbf{1}$ at every site in G. Here, $V \otimes \mathbb{R}$ and $\mathbb{R} \otimes V$ are identified with V, according to the usual convention [17].

Loosely speaking, $\hat{h}_G$ 'picks' sites in G and sums over all others; in particular, $\hat{h}_L(x) = x$. For a probability distribution p, $\hat{h}_G(p)$ may be understood as the marginalization mapping which averages over the sites in $L \setminus G$ (denoted by a $*$ as in (2.5)), and yields the vector of marginal probabilities with respect to the sites in G. In particular, one has $\hat{h}_\emptyset(p) = p^{(*,*,\ldots,*)} = 1$.

We now have two possibilities for defining recombination operators. They differ by a normalizing factor and both coincide for elements p of the unit simplex. We define $\widehat{R}_{i|L} : W^+ \to W$ by

$$\widehat{R}_{i|L}(x) = \frac{1}{\hat{h}_\emptyset(x)} \big(\hat{h}_{[1,i]}(x) \otimes \hat{h}_{[i+1,N]}(x)\big) \tag{2.14}$$

along with $\widehat{R}_{i|L}(0) := 0$ as our recombination operator which describes the action of a crossover event between sites i and $i+1$. More precisely, it gives the frequencies of the types produced by such an event. We use the subscript $i|L$ here to hint at the partitioning of sites in L, and also to avoid confusion with the notation for linear mappings acting at site i according to (2.7) and (2.8). The normalization factor $\frac{1}{\hat{h}_\emptyset(x)}$ is included to make $\widehat{R}_{i|L}$ positive homogeneous of degree one. It turns out that, this way, recombination conserves normalization on the entire positive cone, not just on the unit simplex. (The inclusion of the normalization factor in the definition of $\widehat{R}_{i|L}$ is the only aspect where the restriction to W^+ instead of W is actually required. The alternative definition, omitting the normalization factor, is valid on all of W, but homogeneous of degree two; it will be required later.)

The action of $\widehat{R}_{i|L}$ on x results in a product state, that is, linkage equilibrium, of the interval $[1, i]$ with the interval $[i + 1, N]$, whether or not x itself is a product state. The recombination operator may also be written as $\hat{R}_{i|L}(x) = \frac{1}{\hat{h}_\emptyset(x)} \hat{r}_{i|L}(x \otimes x)$, where $\hat{r}_{i|L} : W \otimes W \to W$ is given by

$$\hat{r}_{i|L}(x_1 \otimes x_2) = \big(\hat{h}_{[1,i]}(x_1)\big) \otimes \big(\hat{h}_{[i+1,N]}(x_2)\big) \, ; \tag{2.15}$$

note that $\widehat{R}_{i|L}$ is not linear, whereas $\hat{r}_{i|L}$ is.

We may thus finally write the recombination part of our dynamics as

$$f_{\widehat{\mathcal{R}}}(x) = \sum_{i=1}^{N-1} \rho_i \big(\widehat{R}_{i|L}(x) - x\big) = \sum_{i=1}^{N-1} \rho_i (\widehat{R}_{i|L} - \mathbf{1})(x) \, , \tag{2.16}$$

which reduces to the recombination part of Eq. (2.5) for elements p of the unit simplex.

The ingredients of the mutation-recombination equation (2.9) have thus been specified through (2.10) and (2.16). Note that $\widehat{M}_i$ and $\widehat{R}_{i|L}$ conserve normalization:

$$\hat{h}_\emptyset(\widehat{M}_i x) = \hat{h}_\emptyset\big(\widehat{R}_{i|L}(x)\big) = \hat{h}_\emptyset(x). \tag{2.17}$$

For mutation, this is simply due to the unit column sums of $\widehat{M}$; for recombination, one relies on

$$\hat{h}_\emptyset\big(\widehat{R}_{i|L}(x)\big) = \frac{1}{\hat{h}_\emptyset(x)} \hat{h}_\emptyset\big(\hat{h}_{[1,i]}(x) \otimes \hat{h}_{[i+1,N]}(x)\big) = \frac{1}{\hat{h}_\emptyset(x)} \big(\hat{h}_\emptyset(x) \otimes \hat{h}_\emptyset(x)\big) = \hat{h}_\emptyset(x). \tag{2.18}$$

Note that, on W^+, $\hat{h}_\emptyset(x) = \|x\|_1$.

The following two Subsections contain some supplementary material, the first concerning an alternative view on the recombination operator, the second establishing the relationship between discrete and continuous time. They are not required for the derivation of the main results, which will commence in Section 3.

2.1 *An explicit picture of the recombination process*

We have, so far, defined $\widehat{R}_{i|L}$ through the marginalization operation acting on single copies of W^+. However, a more explicit picture of the recombination process may also be employed. To this end, consider the *syngamy operator* $\varphi:\ W^+ \to W \otimes W$ defined by

$$\varphi(x) = \frac{1}{\hat{h}_\emptyset(x)}(x \otimes x) = \frac{1}{\hat{h}_\emptyset(x)} \sum_{\boldsymbol{\sigma},\boldsymbol{\sigma}'} x^{\boldsymbol{\sigma}} x^{\boldsymbol{\sigma}'} e^{\boldsymbol{\sigma}} \otimes e^{\boldsymbol{\sigma}'} , \tag{2.19}$$

which describes how zygotic frequencies are obtained from gametic ones. Note that $\varphi(x)$ is symmetric in the sense that $e^{\boldsymbol{\sigma}} \otimes e^{\boldsymbol{\sigma}'}$ and $e^{\boldsymbol{\sigma}'} \otimes e^{\boldsymbol{\sigma}}$ have the same coefficient $x^{\boldsymbol{\sigma}} x^{\boldsymbol{\sigma}'}$; this reflects the fact that only autosomal sites are considered.

Let us now write $W \otimes W$ as $V_1 \otimes \cdots \otimes V_N \otimes V_1' \otimes \cdots \otimes V_N'$ where it is understood that $V_i = V_i' \equiv V$, and define the twist operator which interchanges V_i and V_i', i.e. a mapping $\tau_i : W \otimes W \to W \otimes W$ with

$$\begin{aligned} &\tau_i(\xi_1 \otimes \cdots \otimes \xi_N \otimes \xi_1' \otimes \cdots \otimes \xi_N') \\ &\quad = \xi_1 \otimes \cdots \otimes \xi_{i-1} \otimes \xi_i' \otimes \xi_{i+1} \otimes \cdots \otimes \xi_N \otimes \\ &\qquad\;\; \xi_1' \otimes \cdots \otimes \xi_{i-1}' \otimes \xi_i \otimes \xi_{i+1}' \otimes \cdots \otimes \xi_N' \end{aligned} \tag{2.20}$$

(obviously, the notation deviates slightly from our general convention here). Clearly, one has $\tau_i^2 = \mathbf{1}$, and $\tau_i \tau_j = \tau_j \tau_i$. Further, let $\tau_{[a,b]} := \tau_a \tau_{a+1} \dots \tau_b$ (and, more generally, $\tau_G := \prod_{g \in G} \tau_g$). Then, $\tau_{[1,i]}$ interchanges sites before and including i, whereas $\tau_{[i+1,N]}$ interchanges those after site i. Since both events involve a crossover after site i and occur with equal probability, a crossover after site i is adequately described by the mapping $\frac{1}{2}(\tau_{[1,i]} + \tau_{[i+1,N]})$.

Finally, meiotic segregation into haploid genomes is achieved by the mappings
$g_{\rm m}, g_{\rm p}:\quad W \otimes W \to W$ defined by

$$g_{\rm m}(x_1 \otimes x_2) = \hat{h}_\emptyset(x_2)\, x_1, \tag{2.21}$$

$$g_{\rm p}(x_1 \otimes x_2) = \hat{h}_\emptyset(x_1)\, x_2. \tag{2.22}$$

If the first copy of W is identified with the maternal and the second copy with the paternal gamete, then $g_{\rm m}$ and $g_{\rm p}$ 'pick' the sites which are now (possibly after crossover) in the maternal and paternal positions, respectively, and the overall meiotic operator reads $(1/2)(g_{\rm m} + g_{\rm p})$.

Thus, $\widehat{R}_{i|L}$ may be written as the sequence of syngamy, crossover, and meiosis events, i.e.

$$\widehat{R}_{i|L}(x) = \frac{1}{4}\big((g_{\rm m} + g_{\rm p}) \circ (\tau_{[1,i]} + \tau_{[i+1,N]}) \circ \varphi\big)(x). \tag{2.23}$$

Clearly, $g_{\rm p} = g_{\rm m}\tau_L$ and $g_{\rm m} = g_{\rm p}\tau_L$. Hence,

$$g_{\rm m}\tau_G = g_{\rm p}\tau_L\tau_G = g_{\rm p}\tau_{L\setminus G}. \tag{2.24}$$

In particular, $g_{\rm m}\tau_{[1,i]} = g_{\rm p}\tau_{[i+1,N]}$, and $g_{\rm m}\tau_{[i+1,N]} = g_{\rm p}\tau_{[1,i]}$. Further, one has $(g_{\rm p}\tau_G)(x_1 \otimes x_2) = (g_{\rm p}\tau_{L\setminus G})(x_2 \otimes x_1)$, and hence,

$$(g_{\rm p}\tau_{[i+1,N]})(x \otimes x) = (g_{\rm p}\tau_{[1,i]})(x \otimes x). \tag{2.25}$$

Thus, Eq. (2.23) simplifies to

$$\begin{aligned} \widehat{R}_{i|L}(x) &= (g_{\rm p}\tau_{[1,i]})\big(\varphi(x)\big) = \frac{1}{\hat{h}_\emptyset(x)}\,(\hat{h}_{[1,i]} \otimes \hat{h}_{[i+1,N]})(x \otimes x) \\ &= \frac{1}{\hat{h}_\emptyset(x)}\,\hat{r}_{i|L}(x \otimes x) \end{aligned} \tag{2.26}$$

in agreement with Eq. (2.14).

2.2 *Discrete and continuous time*

The dynamical systems of population genetics may be formulated in discrete and continuous time, and may be considered as different idealizations of the real world. The behaviour is usually very similar in both cases, although it must be noted that Hardy-Weinberg proportions are only an approximation in continuous time; see [32, Chap. 8, p. 193]. With recombination, most investigations have been in discrete time; cf. all references cited so far. However, corresponding continuous-time models have occasionally been considered, e.g. [1]. Rather than going into a discussion which is the 'correct' or even 'better' description, it seems to be more useful to establish a connection between them (as was done in [21] for mutation-selection models, and in [33] for selection-recombination models). To this end, let us consider a situation with discrete generations of duration Δt where mutation is followed by recombination without interference. In line with our continuous-time notation, let us define $\gamma_i := 1 - e^{-\rho_i \Delta t}$ as the probability of a crossover event between sites i and $i+1$, and $\mathcal{V} := \exp(\widehat{\mathcal{M}} \Delta t)$ as the mutation matrix with elements $v^{\boldsymbol{\sigma}'\boldsymbol{\sigma}}$, which represent the probability of mutation from $\boldsymbol{\sigma}$ to $\boldsymbol{\sigma}'$ within one generation. Since $\widehat{\mathcal{M}}$ is a Markov generator, $\mathcal{V}$ is a stochastic matrix automatically. Further, from the definition of $\widehat{\mathcal{M}}$ in (2.10), and the fact that the $\widehat{M}_i$ commute, one has $\mathcal{V} = \bigotimes_{i=1}^{N} \exp(\mu_i \Delta t (\widehat{M} - \mathbf{1}))$, which implies that $v^{\boldsymbol{\sigma}'\boldsymbol{\sigma}}$ is the product of independent mutation probabilities at individual sites. One has, to first order in Δt,

$$\gamma_i = \rho_i \Delta t + O\big((\Delta t)^2\big), \quad \text{and} \quad \mathcal{V} = \mathbf{1} + \Delta t \big(\sum_i \mu_i \widehat{M}_i - \mathbf{1} \big) + O\big((\Delta t)^2\big). \tag{2.27}$$

The relative frequencies after one generation then read

$$\begin{aligned} p^{\boldsymbol{\sigma}}(t+\Delta t) \;=\; & \prod_{i=1}^{N-1} (1-\gamma_i) \sum_{\boldsymbol{\sigma}'} v^{\boldsymbol{\sigma}\boldsymbol{\sigma}'} p^{\boldsymbol{\sigma}'} \\ & + \sum_{i=1}^{N-1} \gamma_i \prod_{j \neq i} (1-\gamma_j) \sum_{\boldsymbol{\sigma}'} v^{\boldsymbol{\sigma}\boldsymbol{\sigma}'} p^{(\sigma_1', \dots, \sigma_i', *, \dots, *)} \cdot p^{(*, \dots, *, \sigma_{i+1}', \dots, \sigma_N')} \\ & + \sum_{i<j} \gamma_i \gamma_j \prod_{k \neq i,j} (1-\gamma_k) \sum_{\boldsymbol{\sigma}'} v^{\boldsymbol{\sigma}\boldsymbol{\sigma}'} p^{(\sigma_1', \dots, \sigma_i', *, \dots, *, \sigma_{j+1}', \dots, \sigma_N')} \cdot p^{(*, \dots, *, \sigma_{i+1}', \dots, \sigma_j', *, \dots, *)} \\ & + \;\; \text{(terms involving more than two crossovers).} \end{aligned} \tag{2.28}$$

Expanding (2.28) to first order in Δt, one obtains, using (2.27) and rearranging terms:

$$\begin{aligned} p^{\boldsymbol{\sigma}}(t+\Delta t) = p^{\boldsymbol{\sigma}}(t) &+ \Delta t \sum_{i=1}^{N} \mu_i \sum_{\sigma_i'} \big(m^{\sigma_i \sigma_i'} p^{(\sigma_1, \dots, \sigma_{i-1}, \sigma_i', \sigma_{i+1}, \dots, \sigma_N)} - p^{\boldsymbol{\sigma}} \big) \\ &+ \; \Delta t \sum_{i=1}^{N-1} \rho_i \big(p^{(\sigma_1, \dots, \sigma_i, *, *, \dots, *)} \cdot p^{(*, *, \dots, *, \sigma_{i+1}, \dots, \sigma_N)} - p^{\boldsymbol{\sigma}} \big) + O\big((\Delta t)^2\big), \end{aligned} \tag{2.29}$$

which, in the limit $\Delta t \to 0$, yields (2.5). This is the limit of short generations, which is equivalent to the limit of weak mutation and recombination through the rescaling $t \to t/\varepsilon$, $\mu_i \to \mu_i \varepsilon$, and $\rho_i \to \rho_i \varepsilon$ for all μ_i and ρ_i, where ε is a small parameter. We may therefore work with the differential equation as long as mutation and recombination rates per site and generation are small, as is certainly the case in molecular applications. For similar reasons, the mutation model with independent mutation events in continuous time is the standard model used in coalescent theory and analysis of population sequence data [14]. Models describing mutation and selection as going on in parallel in continuous time have also simplified matters quite a bit in the realm of so-called sequence space models [2, 40]. We shall see that, with mutation and recombination as well, the differential equation is somewhat simpler and allows for *exact* solutions. To find them, we shall now proceed in two steps. We first perform a similarity transform which diagonalizes the mutation operator. We then define suitable linkage disequilibria which linearize and diagonalize the equations in one shot. These quantities are based on suitable compositions of the recombination operator. Since the mutation and recombination operators commute, this transformation will not interfere with mutation.

3 Diagonalization of the mutation term

We shall first diagonalize $f_{\widehat{\mathcal{M}}}$, and then transform $f_{\widehat{\mathcal{R}}}$ accordingly. To get prepared, we first establish the behaviour of $\hat{r}_{i|L}$ under certain linear transformations. Let A and B both map V into itself, and let A_j, B_j and A_G, B_G be the corresponding mappings from W into itself. Then the definition of $\hat{r}_{i|L}$, Eq. (2.15), yields

$$\begin{aligned}\hat{r}_{i|L}\big((A_j x_1)\otimes x_2\big) &= \big(\hat{h}_{[1,i]}(A_j x_1)\big)\otimes\big(\hat{h}_{[i+1,N]}(x_2)\big)\\ &= A_j\hat{r}_{i|L}(x_1\otimes x_2)\qquad\text{for}\quad j\in[1,i];\end{aligned}\tag{3.1}$$

the evaluation for $j\in[i+1,N]$ will be postponed until later. Eq. (3.1) reflects the fact that $\hat{r}_{i|L}$ acts as identity on the first i sites of the first argument. Likewise,

$$\hat{r}_{i|L}\big(x_1\otimes(B_j x_2)\big) = B_j\hat{r}_{i|L}(x_1\otimes x_2)\quad\text{for}\quad j\in[i+1,N].\tag{3.2}$$

Thus, more generally,

$$\begin{aligned}&\hat{r}_{i|L}\big((A_G x_1)\otimes(B_H x_2)\big)\\ &\quad=\ \big(A_{G\cap[1,i]}B_{H\cap[i+1,N]}\big)\,\hat{r}_{i|L}\big((A_{G\cap[i+1,N]}x_1)\otimes(B_{H\cap[1,i]}x_2)\big).\end{aligned}\tag{3.3}$$

Let us now write $\widehat{M}$ in diagonalized form (recall this was assumed to be possible) to read $\widehat{M}=BMB^{-1}$, where $M:=\operatorname{diag}(\lambda^0,\dots,\lambda^{m-1})$ holds the eigenvalues, and the columns of B are the corresponding (right) eigenvectors of $\widehat{M}$, namely $b^0,\dots,b^{m-1}$ (the reason for the numbering from 0 to $m-1$ will become clear in a moment). Since $\widehat{M}$ has unit column sums (it is a stochastic matrix), we may choose $\lambda^0=1$ without loss of generality, and assume that b^0 has column sum 1. Then, the corresponding *left* eigenvector (i.e. the first row of B^{-1}) reads $\hat{u}=(1,1,\dots,1)$. It follows from $B^{-1}B=\mathbf{1}$ that $\hat{u}\cdot b^k=\delta_{k,0}$, or

$$\hat{\ell}(b^k)=\delta_{k,0}\,.\tag{3.4}$$

Let us now use the colums of B as the new basis of V, and the columns of $B_L=\bigotimes^N B$ as the new basis of W, and introduce corresponding representations η, y, and q of ξ (vectors in

V), x (vectors in the positive cone of W), and p (probability vectors in W), i.e. $\xi = \sum_k \eta^k b^k$, $x = B_L y$, and

$$p = B_L q, \quad q = B_L^{-1} p. \tag{3.5}$$

The vector q is an alternative representation of the point p in the unit simplex, and will be referred to as the vector of *(generalized) moments*, for reasons to become clear later.

Mutation is absent if either $\mu_i \equiv 0$ (for an arbitrary stochastic matrix $\widehat{M}$), or $\widehat{M} = \mathbf{1}$ (for arbitrary μ_i). The latter shows that *any* change of basis compatible with (3.4) may be used in the case without mutation.

Due to (3.4), the linear form (2.11) transforms according to

$$\hat{\ell}(\xi) = \hat{\ell}(\eta^0 b^0 + \cdots + \eta^{m-1} b^{m-1}) = \eta^0 =: \ell(\eta), \tag{3.6}$$

which may also be written as $\ell(\eta) = u \cdot \eta$ with $u = (1, 0, \ldots, 0)^T$. It follows that y inherits its normalization from x, i.e. $h_\emptyset(y) = y^{(0,0,\ldots,0)} = \hat{h}_\emptyset(x)$, where we have set $h_H := \mathbf{1} \otimes \cdots \otimes \mathbf{1} \otimes \ell \otimes \mathbf{1} \otimes \cdots \otimes \mathbf{1} \otimes \ell \otimes \mathbf{1} \otimes \cdots \otimes \mathbf{1}$ with ℓ at sites in $L \setminus H$, and $\mathbf{1}$ at sites in H, in analogy with (2.13). This mapping selects the components of q that have a 0 at the sites in $L \setminus H$, i.e., it averages over the sites in $L \setminus H$ and yields the (marginal) moments corresponding to sites in H. In particular, $q^{(0,0,\ldots,0)} = p^{(*,*,\ldots,*)} = 1$.

We now find the differential equation for the new variables:

$$\begin{aligned} \dot{y} &= B_L^{-1} \dot{x} \\ &= B_L^{-1} \big(f_{\widehat{\mathcal{M}}}(B_L y) + f_{\widehat{\mathcal{R}}}(B_L y) \big) . \end{aligned} \tag{3.7}$$

By construction, the new mutation term is diagonal:

$$f_{\mathcal{M}}(y) := B_L^{-1} f_{\widehat{\mathcal{M}}}(B_L y) = \sum_i \mu_i B_L^{-1} (\widehat{M}_i - \mathbf{1}) B_L y = \sum_i \mu_i (M_i - \mathbf{1}) y. \tag{3.8}$$

The recombination term transforms according to

$$\begin{aligned} f_{\mathcal{R}}(y) &:= B_L^{-1} f_{\widehat{\mathcal{R}}}(B_L y) \\ &= B_L^{-1} \sum_{i=1}^{N} \rho_i \big(\widehat{R}_{i|L}(B_L y) - B_L y \big) . \end{aligned} \tag{3.9}$$

The new recombination operator for site i thus takes the form

$$\begin{aligned} R_{i|L}(y) &:= B_L^{-1} \widehat{R}_{i|L}(B_L y) \\ &= \frac{1}{h_\emptyset(y)} \, B_L^{-1} \hat{r}_{i|L} \big((B_L y) \otimes (B_L y) \big) \\ &= \frac{1}{h_\emptyset(y)} \, \big(\hat{h}_{[1,i]}(B_{[i+1,N]} y) \otimes \hat{h}_{[i+1,N]}(B_{[1,i]} y) \big), \end{aligned} \tag{3.10}$$

where, in the last step, Eq. (3.3) has been used. But, due to (2.13) and (3.6), $\hat{h}_{L \setminus G}(B_G y) = h_{L \setminus G}(y)$. Thus,

$$R_{i|L}(y) = \frac{1}{h_\emptyset(y)} \, (h_{[1,i]} \otimes h_{[i+1,N]})(y \otimes y) = \frac{1}{h_\emptyset(y)} \, r_{i|L}(y \otimes y) \, , \tag{3.11}$$

where, generally, $r_{i|L}(y_1 \otimes y_2) := h_{[1,i]}(y_1) \otimes h_{[i+1,N]}(y_2)$.

So, after the change of basis, the mutation-recombination equation reads

$$\begin{aligned} \dot{y} &= f_{\mathcal{M}}(y) + f_{\mathcal{R}}(y) \\ &= \sum_{i=1}^{N} \mu_i (M_i y - y) + \sum_{i=1}^{N-1} \rho_i \big(R_{i|L}(y) - y\big) \\ &=: f(y)\,. \end{aligned} \tag{3.12}$$

Eq. (2.17) now takes the form

$$h_\emptyset(M_i y) = h_\emptyset\big(R_{i|L}(y)\big) = h_\emptyset(y), \tag{3.13}$$

i.e. M_i and $R_{i|L}$ again conserve normalization.

Let us pause here to consider the transformed quantities in coordinate representation. The vector y may be written as

$$y = \sum_{\boldsymbol{n}} y^{\boldsymbol{n}} b^{\boldsymbol{n}}, \quad b^{\boldsymbol{n}} := b^{n_1} \otimes b^{n_2} \otimes \cdots \otimes b^{n_N}\,, \tag{3.14}$$

where $\boldsymbol{n} := (n_1, \ldots, n_N) \in \{0, 1, \ldots, m-1\}^N$. Since $\ell(b^k) = \delta_{k,0}$, one has

$$h_{[a,b]}(y) = \sum_{n_a, \ldots, n_b} y^{(0,\ldots,0,n_a,\ldots,n_b,0,\ldots,0)}\, b^{n_a} \otimes \cdots \otimes b^{n_b}, \tag{3.15}$$

which is a vector in $\bigotimes^{b-a} V$. The recombination operator for site i then reads

$$\begin{aligned} R_{i|L}(y) &= \frac{1}{y^{(0,\ldots,0)}}\, r_{i|L}\Big(\sum_{\boldsymbol{n},\boldsymbol{n}'} y^{\boldsymbol{n}} y^{\boldsymbol{n}'}\, (b^{\boldsymbol{n}} \otimes b^{\boldsymbol{n}'})\Big) \\ &= \frac{1}{y^{(0,\ldots,0)}} \sum_{\boldsymbol{n}} y^{(n_1,\ldots,n_i,0,\ldots,0)} \cdot y^{(0,\ldots,0,n_{i+1},\ldots,n_N)}\, b^{\boldsymbol{n}}\,, \end{aligned} \tag{3.16}$$

where $\ell(b^k) = \delta_{k,0}$ has again been used.

4 An example

Here, we illustrate by an example what we have done so far, and anticipate how we shall proceed to solve Eq. (3.12). To this end, assume that $\mathcal{A} = \{+1, -1\}$, and mutation is symmetric. Let us choose $e^+ := e^1$, $e^- := e^2$, and

$$\widehat{M} = \begin{pmatrix} 1/2 & 1/2 \\ 1/2 & 1/2 \end{pmatrix}. \tag{4.17}$$

Diagonalization of the mutation part (Section 3) then gives

$$M = \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}, \qquad B = \frac{1}{2}\begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}, \tag{4.18}$$

and $B^{-1} = 2B$. The same B (but not the same M) would be obtained for $\widehat{M} = \begin{pmatrix} 1-a & a \\ a & 1-a \end{pmatrix}$; a very straightforward generalization would occur for (larger) symmetric matrices with all (proper) mutation entries equal to a.

But let us, for definiteness, stick to the simplest case (4.17). The change of basis corresponds to the transformation from probabilities to multivariate moments [8, 38, 39]. This is because $B^{-1}\xi = (\xi^1 + \xi^2, \xi^1 - \xi^2)^T$, and the components of q are given by

$$q^{\boldsymbol{n}} = \langle (\boldsymbol{\sigma})^{\boldsymbol{n}} \rangle \,, \tag{4.19}$$

where $\boldsymbol{n} \in \{0,1\}^N$, $(\boldsymbol{\sigma})^{\boldsymbol{n}} := (\sigma_1)^{n_1} \cdot (\sigma_2)^{n_2} \cdot \cdots \cdot (\sigma_N)^{n_N}$, and $\langle \, . \, \rangle$ denotes expectation. These are just the moments

$$\langle (\boldsymbol{\sigma})^{\boldsymbol{n}} \rangle := \sum_{\boldsymbol{\sigma}} (\boldsymbol{\sigma})^{\boldsymbol{n}} p^{\boldsymbol{\sigma}} \,. \tag{4.20}$$

We have used parentheses to indicate that superscripts mean exponentiation, not upper indices, here. Note also that, by abuse of notation, we do not distinguish between random variables and their values, because the meaning is clear.

For example, for $N = 3$ and lexicographic ordering of components, one has, in coordinate form:

$$\begin{aligned}
p &= (p^{(+,+,+)}, p^{(+,+,-)}, p^{(+,-,+)}, p^{(+,-,-)}, p^{(-,+,+)}, p^{(-,+,-)}, p^{(-,-,+)}, p^{(-,-,-)})^T, \\
q &= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,1)}, q^{(1,0,0)}, q^{(1,0,1)}, q^{(1,1,0)}, q^{(1,1,1)})^T \\
&= (1, \langle\sigma_3\rangle, \langle\sigma_2\rangle, \langle\sigma_2\sigma_3\rangle, \langle\sigma_1\rangle, \langle\sigma_1\sigma_3\rangle, \langle\sigma_1\sigma_2\rangle, \langle\sigma_1\sigma_2\sigma_3\rangle)^T.
\end{aligned} \tag{4.21}$$

According to Eq. (3.15), one obtains, for example,

$$\begin{aligned}
h_1(q) &= (q^{(0,0,0)}, q^{(1,0,0)})^T, \\
h_{[2,3]}(q) &= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,1)})^T,
\end{aligned}$$

and, according to Eq. (3.16), the recombination operator which introduces a partition after the first site reads

$$\begin{aligned}
R_{1|L}(q) &= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,1)}, \\
&\quad\; q^{(1,0,0)}, q^{(1,0,0)} \cdot q^{(0,0,1)}, q^{(1,0,0)} \cdot q^{(0,1,0)}, q^{(1,0,0)} \cdot q^{(0,1,1)})^T \\
&= (1, \langle\sigma_3\rangle, \langle\sigma_2\rangle, \langle\sigma_2\sigma_3\rangle, \langle\sigma_1\rangle, \langle\sigma_1\rangle\langle\sigma_3\rangle, \langle\sigma_1\rangle\langle\sigma_2\rangle, \langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle)^T.
\end{aligned} \tag{4.22}$$

Similarly,

$$\begin{aligned}
R_{2|L}(q) &= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,0)} \cdot q^{(0,0,1)}, \\
&\quad\; q^{(1,0,0)}, q^{(1,0,0)} \cdot q^{(0,0,1)}, q^{(1,1,0)}, q^{(1,1,0)} \cdot q^{(0,0,1)})^T \\
&= (1, \langle\sigma_3\rangle, \langle\sigma_2\rangle, \langle\sigma_2\rangle\langle\sigma_3\rangle, \langle\sigma_1\rangle, \langle\sigma_1\rangle\langle\sigma_3\rangle, \langle\sigma_1\sigma_2\rangle, \langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle)^T.
\end{aligned} \tag{4.23}$$

Application of $R_{1|L}$ to $R_{2|L}(q)$ yields

$$\begin{aligned}
&R_{1|L}(R_{2|L}(q)) \\
&\quad= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,0)} \cdot q^{(0,0,1)}, \\
&\quad\qquad q^{(1,0,0)}, q^{(1,0,0)} \cdot q^{(0,0,1)}, q^{(1,0,0)} \cdot q^{(0,1,0)}, q^{(1,0,0)} \cdot q^{(0,1,0)} \cdot q^{(0,0,1)})^T \\
&\quad= (1, \langle\sigma_3\rangle, \langle\sigma_2\rangle, \langle\sigma_2\rangle\langle\sigma_3\rangle, \langle\sigma_1\rangle, \langle\sigma_1\rangle\langle\sigma_3\rangle, \langle\sigma_1\rangle\langle\sigma_2\rangle, \langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\rangle)^T.
\end{aligned} \tag{4.24}$$

The mutation-recombination equation (3.12) reads

$$\begin{aligned}
\dot{q} &= (0, -\mu_3 q^{(0,0,1)}, -\mu_2 q^{(0,1,0)}, -(\mu_2+\mu_3+\rho_2) q^{(0,1,1)} + \rho_2 q^{(0,1,0)} \cdot q^{(0,0,1)}, \\
&\quad -\mu_1 q^{(1,0,0)}, -(\mu_1+\mu_3+\rho_1+\rho_2) q^{(1,0,1)} + (\rho_1+\rho_2) q^{(1,0,0)} \cdot q^{(0,0,1)}, \\
&\quad -(\mu_1+\mu_2+\rho_1) q^{(1,1,0)} + \rho_1 q^{(1,0,0)} \cdot q^{(0,1,0)}, \\
&\quad -(\mu_1+\mu_2+\mu_3+\rho_1+\rho_2) q^{(1,1,1)} \\
&\quad +\rho_1 q^{(1,0,0)} \cdot q^{(0,1,1)} + \rho_2 q^{(1,1,0)} \cdot q^{(0,0,1)})^T \\
&= (0, -\mu_3 \langle\sigma_3\rangle, -\mu_2 \langle\sigma_2\rangle, -(\mu_2+\mu_3+\rho_2)\langle\sigma_2\sigma_3\rangle + \rho_2 \langle\sigma_2\rangle\langle\sigma_3\rangle, \\
&\quad -\mu_1\langle\sigma_1\rangle, -(\mu_1+\mu_3+\rho_1+\rho_2)\langle\sigma_1\sigma_3\rangle + (\rho_1+\rho_2)\langle\sigma_1\rangle\langle\sigma_3\rangle, \\
&\quad -(\mu_1+\mu_2+\rho_1)\langle\sigma_1\sigma_2\rangle + \rho_1\langle\sigma_1\rangle\langle\sigma_2\rangle, \\
&\quad -(\mu_1+\mu_2+\mu_3+\rho_1+\rho_2)\langle\sigma_1\sigma_2\sigma_3\rangle + \rho_1\langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle + \rho_2\langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle)^T. \qquad (4.25)
\end{aligned}$$

The explicit notation in terms of expectations is suggestive because one virtually 'sees recombination at work': crossovers 'break up' moments into products of lower order moments; $R_{i|L}$ brings about a split after site i.

Note that the simplicity of the recombination process depends crucially on the ordering of the associations being compatible with the linear ordering of sites. This is guaranteed by the single-crossover assumption but would, for example, be violated by a recombination distribution separating site 2 from sites 1 and 3 consistently, so as to produce $\langle\sigma_1\sigma_3\rangle\langle\sigma_2\rangle$. This bracket notation is restricted to the two-letter case, however, wherefore the (generalized) moments q will be required for a larger alphabet.

Eq. (4.25) is how far we got in Section 3. But let us now, for this example, preview how the diagonalization of the recombination term will work out. In Definition 5.6, we shall define a collection of linkage disequilibria. They will be collected into a vector z, which, for this specific example and in coordinate form, reads

$$\begin{aligned}
z &= (q^{(0,0,0)}, q^{(0,0,1)}, q^{(0,1,0)}, q^{(0,1,1)} - q^{(0,1,0)} \cdot q^{(0,0,1)}, \\
&\quad q^{(1,0,0)}, q^{(1,0,1)} - q^{(1,0,0)} \cdot q^{(0,0,1)}, q^{(1,1,0)} - q^{(1,0,0)} \cdot q^{(0,1,0)}, \\
&\quad q^{(1,1,1)} - q^{(1,0,0)} \cdot q^{(0,1,1)} - q^{(1,1,0)} \cdot q^{(0,0,1)} + q^{(1,0,0)} \cdot q^{(0,1,0)} \cdot q^{(0,0,1)})^T \\
&= (1, \langle\sigma_3\rangle, \langle\sigma_2\rangle, \langle\sigma_2\sigma_3\rangle - \langle\sigma_2\rangle\langle\sigma_3\rangle, \\
&\quad \langle\sigma_1\rangle, \langle\sigma_1\sigma_3\rangle - \langle\sigma_1\rangle\langle\sigma_3\rangle, \langle\sigma_1\sigma_2\rangle - \langle\sigma_1\rangle\langle\sigma_2\rangle, \\
&\quad \langle\sigma_1\sigma_2\sigma_3\rangle - \langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle - \langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle + \langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\rangle)^T. \qquad (4.26)
\end{aligned}$$

Obviously, every coordinate of z is a special kind of correlation function, which is derived from one moment along with all products of lower-order moments arising through independent crossovers at single sites, decorated with a minus sign if the number of crossovers is odd. Note that the term $\langle\sigma_1\sigma_3\rangle\langle\sigma_2\rangle$ is absent from $z^{(1,1,1)}$, because crossovers work by only inserting brackets.

Our main result will be Theorem 5.8, which implies that the coordinates of z are decoupled and, with the exception of $z^{(0,0,0)}$, decay exponentially, as implied by the equations

$$
\begin{aligned}
\dot{z}^{(0,0,0)} &= 0 \\
\dot{z}^{(0,0,1)} &= -\mu_3 \, z^{(0,0,1)} \\
\dot{z}^{(0,1,0)} &= -\mu_2 \, z^{(0,1,0)} \\
\dot{z}^{(0,1,1)} &= -(\mu_2 + \mu_3 + \rho_2) \, z^{(0,1,1)} \\
\dot{z}^{(1,0,0)} &= -\mu_1 \, z^{(1,0,0)} \\
\dot{z}^{(1,0,1)} &= -(\mu_1 + \mu_3 + \rho_1 + \rho_2) \, z^{(1,0,1)} \\
\dot{z}^{(1,1,0)} &= -(\mu_1 + \mu_2 + \rho_1) \, z^{(1,1,0)} \\
\dot{z}^{(1,1,1)} &= -(\mu_1 + \mu_2 + \mu_3 + \rho_1 + \rho_2) \, z^{(1,1,1)}.
\end{aligned}
\tag{4.27}
$$

At this stage, this may, of course, be verified with the help of the product rule and explicit evaluation of the dynamical system (4.25), e.g.

$$
\begin{aligned}
\dot{z}^{(1,0,1)} &= \frac{d}{dt}(q^{(1,0,1)} - q^{(1,0,0)} \cdot q^{(0,0,1)}) \\
&= \dot{q}^{(1,0,1)} - \dot{q}^{(1,0,0)} \cdot q^{(0,0,1)} - q^{(1,0,0)} \cdot \dot{q}^{(0,0,1)} \\
&= -(\mu_1 + \mu_3 + \rho_1 + \rho_2) q^{(1,0,1)} + (\rho_1 + \rho_2) q^{(1,0,0)} \cdot q^{(0,0,1)} \\
&\quad + (\mu_1 q^{(1,0,0)}) \, q^{(0,0,1)} + q^{(1,0,0)} \, (\mu_3 q^{(0,0,1)}) \\
&= -(\mu_1 + \mu_3 + \rho_1 + \rho_2) \, (q^{(1,0,1)} - q^{(1,0,0)} \cdot q^{(0,0,1)}) \\
&= -(\mu_1 + \mu_3 + \rho_1 + \rho_2) z^{(1,0,1)}.
\end{aligned}
\tag{4.28}
$$

As a consequence, the linkage disequilibria will decay exponentially, e.g.

$$
z^{(1,0,1)}(t) = \exp\big(- (\mu_1 + \mu_3 + \rho_1 + \rho_2) t \big) z^{(1,0,1)}(0). \tag{4.29}
$$

But let us have a closer look at the system of equations (4.28). The role of the mutation rates should be clear immediately: Since $M = \operatorname{diag}(1,0)$, one has $M - \mathbf{1} = \operatorname{diag}(0,-1)$, and the rate of mutational decay of $z^{(n_1,n_2,n_3)}$ is simply $\sum_i \mu_i n_i$. As to recombination, define n_j (n_k) to be the leftmost (rightmost) index of $z^{(n_1,n_2,n_3)}$ that is non-zero. Note that, in this representation, non-zero indices indicate sites involved in the linkage disequilibrium, whereas a 'zero' index corresponds to a site that is averaged over in the original variables, and is thus irrelevant to the linkage disequilibrium. (We speak of 'non-zero' instead of 'one' since this is what carries over to a larger number of letters). Thus, j and k are the extreme sites relevant to the linkage disequilibrium $z^{(n_1,n_2,n_3)}$. The rate of decay due to recombination is then $\rho_{n_j} + \rho_{n_j+1} + \cdots + \rho_{n_k-1}$ (in our $N = 3$ example, this sum may comprise zero, one, or two terms). This is the rate at which sites j and k are separated (known as their *two-locus recombination rate*), the simple form being due to the single-crossover assumption. Put differently, ρ_i contributes to the decay rate if a crossover after site i separates two non-zero sites. We shall see that this is the case quite generally.

For larger N, the whole set of linkage disequilibria is cumbersome to display and manipulate explicitly. For $N = 4$, Figure 1 illustrates the recombination process (without mutation) for just one coordinate, namely of $z^{(1,1,1,1)} = \langle \sigma_1 \sigma_2 \sigma_3 \sigma_4 \rangle$, in our two-letter case.

The task will now be to define such linkage disequilibria in a general and compact form, and investigate their properties. To this end, we shall first note that, since linkage disequilibria are measures of statistical independence of various orders, their definition will involve the inclusion-exclusion principle. Loosely speaking, $z^{(n_1,\dots,n_N)}$ will involve all products of lower-order moments indexed by the ordered partitions of the non-zero n_j's.

We shall proceed as follows. In Subsection 5.1, we shall establish the composition of mutation and recombination operators, and their commuting properties. In Subsection 5.2, the transformation from moments to linkage disequilibria will be performed (Definiton 5.6), along with the back transformation in (5.43). Finally, the independent and exponential decay of our linkage disequilibria will be proved in Theorem 5.8.

5 Diagonalization of the recombination term

We first need some notation for ordered partitions of $L = \{1, 2, \dots, N\}$. For $g \in L \setminus \{N\} = \{1, 2, \dots, N-1\}$, let

$$g|L := \{[1, g], [g+1, N]\} \tag{5.1}$$

be the ordered partition of L into two blocks. Loosely speaking, $g|L$ is the ordered partition which results from a 'split' of L after the element g. For later use, we also define $G|L$ for $G = \{g_1, g_2, \dots, g_{|G|}\} \in \mathcal{P}(L \setminus \{N\})$ (where $\mathcal{P}(H)$ is taken to be the set of all *ordered* subsets of a set H) as

$$G|L \;=\; \{[1, g_1], [g_1+1, g_2], \dots, [g_{|G|}+1, N]\}\,. \tag{5.2}$$

For completeness, $\emptyset|L := L$. Ordered partitions will now be used to investigate the composition of recombination operators.

5.1 *Composition of mutation and recombination operators*

We first establish that recombination operators commute and are idempotent, i.e.

Lemma 5.1. $\quad R_{i|L} R_{j|L} = R_{j|L} R_{i|L}$ *and* $(R_{i|L})^2 = R_{i|L}$.

Proof. Generally, one has

$$h_G r_{\ell|L} = h_G(h_{[1,\ell]} \otimes h_{[\ell+1,N]}) = h_{G\cap[1,\ell]} \otimes h_{G\cap[\ell+1,N]}\,, \tag{5.3}$$

from which it follows that

$$\begin{aligned} h_{[1,k]}\big(R_{\ell|L}(y)\big) \;&=\; \frac{1}{h_\emptyset(y)}\, h_{[1,k]}\big(r_{\ell|L}(y\otimes y)\big) \\ &=\; \begin{cases} \frac{1}{h_\emptyset(y)}\,\big(h_{[1,\ell]}(y)\otimes h_{[\ell+1,k]}(y)\big), & \ell\in[1,k], \\ h_{[1,k]}(y), & \ell\in[k+1,N] \end{cases} \end{aligned} \tag{5.4}$$

and

$$\begin{aligned} h_{[k+1,N]}\big(R_{\ell|L}(y)\big) \;&=\; \frac{1}{h_\emptyset(y)}\, h_{[k+1,N]}\big(r_{\ell|L}(y\otimes y)\big) \\ &=\; \begin{cases} h_{[k+1,N]}(y), & \ell\in[1,k], \\ \frac{1}{h_\emptyset(y)}\,\big(h_{[k+1,\ell]}(y)\otimes h_{[\ell+1,N]}(y)\big), & \ell\in[k+1,N]. \end{cases} \end{aligned} \tag{5.5}$$

It is immediately clear that $R_{i|L}\big(R_{i|L}(y)\big) = \frac{1}{h_\emptyset(y)}\big(h_{[1,i]}(y) \otimes h_{[i+1,N]}(y)\big) = R_{i|L}(y)$. Further, Eqs. (3.11), (5.4), and (5.5) jointly show that, regardless of whether $j \in [1,i]$ or $j \in [i+1,N]$,

$$\begin{aligned} R_{i|L}\big(R_{j|L}(y)\big) &= \frac{1}{h_\emptyset(y)}\Big(h_{[1,i]}\big(R_{j|L}(y)\big) \otimes h_{[i+1,N]}\big(R_{j|L}(y)\big)\Big) \\ &= \frac{1}{h_\emptyset(y)}\Big(h_{[1,j]}\big(R_{i|L}(y)\big) \otimes h_{[j+1,N]}\big(R_{i|L}(y)\big)\Big) \\ &= R_{j|L}\big(R_{i|L}(y)\big), \end{aligned} \tag{5.6}$$

as claimed. □

We shall collect the most important definitions and results of the current Section into a set of graphical rules in Figure 2, starting with Lemma 5.1 and adding others as we go along.

Lemma 5.1 establishes the crucial properties of one-point crossovers, which are the key to the tractability of our model; multiple crossovers (between a given pair $\boldsymbol{\sigma}, \boldsymbol{\sigma'}$) cannot be expressed in terms of $R_{i|L}$'s. Generalizing (3.11), we now introduce the mapping $R_{G|L} : W^+ \to W$ as

$$R_{G|L}(y) = \Big(\prod_{g \in G} R_{g|L}\Big)(y) \tag{5.7}$$

along with $R_{\emptyset|L}(y) := y$. As an immediate consequence, one has

$$R_{i|L} R_{G|L} = R_{(G \cup \{i\})|L}\,. \tag{5.8}$$

It is easily verified along the lines of the proof of Lemma 5.1 that $R_{G|L}$ takes the explicit form

$$R_{G|L}(y) = \frac{1}{\big(h_\emptyset(y)\big)^{|G|+1}}\big(h_{[1,g_1]}(y) \otimes h_{[g_1+1,g_2]}(y) \otimes \cdots \otimes h_{[g_{|G|}+1,N]}(y)\big). \tag{5.9}$$

Let us further note here that Eqs. (5.4) and (5.5) jointly show

$$r_{i|L}\big(R_{j|L}(y_1) \otimes y_2\big) = r_{i|L}(y_1 \otimes y_2) \quad \text{if} \quad j \in [i+1,N] \tag{5.10}$$

and

$$r_{i|L}\big(y_1 \otimes R_{j|L}(y_2)\big) = r_{i|L}(y_1 \otimes y_2) \quad \text{if} \quad j \in [1,i]\,, \tag{5.11}$$

which will be used frequently in what follows. Note that $r_{i|L}(y_1 \otimes y_2)$ reflects the merging of the sites before and including i, of a population defined by y_1, with the sites after i of a population defined by y_2. Relationships (5.10) and (5.11) reflect the plausible fact that this action is unaffected by previous recombination events involving the last sites of the first type, or the first sites of the second type, since these do not enter the recombined type at all.

We have, so far, considered composition of recombination operators; let us now consider mutation. Clearly, $M_i M_j = M_j M_i$. We shall now show that mutation and recombination also commute with each other, i.e.

Lemma 5.2. $\qquad R_{i|L}(M_j y) = M_j R_{i|L}(y)\,.$

Proof. We first recall that $\ell\big(M(\eta)\big) = \ell(\eta)$, and hence

$$h_G(M_j y) = h_G(y) \quad \text{for } j \in L \setminus G\,, \tag{5.12}$$

which reflects the fact that 'picking' sites in G and summing over all others is unaffected by mutations at sites in the complement of G. Together with (3.3), which clearly holds in the same form if $\hat{r}_{i|L}$ is replaced by $r_{i|L}$, this leads to

$$r_{i|L}\big((M_j y_1) \otimes y_2\big) = \begin{cases} M_j r_{i|L}(y_1 \otimes y_2), & j \in [1,i], \\ r_{i|L}(y_1 \otimes y_2), & j \in [i+1, N]; \end{cases} \tag{5.13}$$

$$r_{i|L}\big(y_1 \otimes (M_j y_2)\big) = \begin{cases} r_{i|L}(y_1 \otimes y_2), & j \in [1,i], \\ M_j r_{i|L}(y_1 \otimes y_2), & j \in [i+1, N]\,. \end{cases} \tag{5.14}$$

Since j is either in $[1,i]$ or in $[i+1,N]$, one obtains that mutation and recombination commute:

$$\begin{aligned} R_{i|L}(M_j y) &= \frac{1}{h_\emptyset(M_j y)}\, r_{i|L}\big((M_j y) \otimes (M_j y)\big) \\ &= \frac{1}{h_\emptyset(y)}\, M_j r_{i|L}(y \otimes y) \\ &= M_j R_{i|L}(y)\,. \end{aligned} \tag{5.15}$$

□

Applying Lemma 5.2 repeatedly gives

$$R_{G|L}(M_i y) = M_i R_{G|L}(y). \tag{5.16}$$

This property was noted previously, in a slightly different framework, in [28, p. 269].

With these preparations, we are now ready to determine the time evolution of $R_{G|L}(y)$:

Lemma 5.3. *Along a solution $y = y(t)$ of the mutation-recombination equation (3.12), one has*

$$\frac{d}{dt} R_{i|L}(y) = f\big(R_{i|L}(y)\big)\,.$$

Proof. Differentiating[1] $R_{i|L}(q)$, applying Eq. (3.12), and noting that normalization is unchanged under the flow, one obtains

$$\begin{aligned} \frac{d}{dt} R_{i|L}(y) &= \frac{1}{h_\emptyset(y)}\, r_{i|L}(\dot{y} \otimes y + y \otimes \dot{y}) \\ &= \frac{1}{h_\emptyset(y)}\, r_{i|L}\big((f_{\mathcal{M}} + f_{\mathcal{R}})(y) \otimes y + y \otimes (f_{\mathcal{M}} + f_{\mathcal{R}})(y)\big)\,. \end{aligned} \tag{5.17}$$

[1] The validity of the first step may be checked with the help of a difference quotient and the continuity of the flow.

Clearly, due to the linearity of $r_{i|L}$, one may consider $f_{\mathcal{M}}$ and $f_{\mathcal{R}}$ separately. For the recombination part, one finds

$$\begin{aligned}
&\frac{1}{h_{\emptyset}(y)}\, r_{i|L}\big(f_{\mathcal{R}}(y)\otimes y + y\otimes f_{\mathcal{R}}(y)\big) \\
&\qquad = \frac{1}{h_{\emptyset}(y)} \sum_j \rho_j r_{i|L}\big(R_{j|L}(y)\otimes y + y\otimes R_{j|L}(y) - 2y\otimes y\big) \\
&\qquad = \frac{1}{h_{\emptyset}(y)} \sum_j \rho_j r_{i|L}\big(R_{j|L}(y)\otimes R_{j|L}(y) - y\otimes y\big) \\
&\qquad = \sum_j \rho_j \Big(R_{i|L}\big(R_{j|L}(y)\big) - R_{i|L}(y)\Big) \\
&\qquad = \sum_j \rho_j (R_{j|L} - \mathbf{1})\big(R_{i|L}(y)\big) \\
&\qquad = f_{\mathcal{R}}\big(R_{i|L}(y)\big)\,.
\end{aligned} \tag{5.18}$$

The second step is the decisive one: for $j \in [1, i]$, one reads Eq. (5.11) backwards, and (5.10) forwards; and vice versa for $j \in [i+1, N]$. In the second last step, it has been used that $R_{i|L}$ and $R_{j|L}$ commute.

Along the same lines, and with the help of Eqs. (5.13), (5.14), and Lemma 5.2, one obtains for the mutation part

$$\begin{aligned}
&\frac{1}{h_{\emptyset}(y)}\, r_{i|L}\big(f_{\mathcal{M}}(y)\otimes y + y\otimes f_{\mathcal{M}}(y)\big) \\
&\qquad = \frac{1}{h_{\emptyset}(y)} \sum_j \mu_j r_{i|L}\big((M_j y)\otimes y + y\otimes (M_j y) - 2y\otimes y\big) \\
&\qquad = \frac{1}{h_{\emptyset}(y)} \sum_j \mu_j r_{i|L}\big((M_j y)\otimes (M_j y) - y\otimes y\big) \\
&\qquad = \sum_j \mu_j \big(R_{i|L}(M_j y) - R_{i|L}(y)\big) \\
&\qquad = \sum_j \mu_j (M_j - \mathbf{1}) R_{i|L}(y) \\
&\qquad = f_{\mathcal{M}}\big(R_{i|L}(y)\big).
\end{aligned} \tag{5.19}$$

Eqs. (5.17)–(5.19) jointly show that

$$\frac{d}{dt} R_{i|L}(y) = f\big(R_{i|L}(y)\big)\,, \tag{5.20}$$

as claimed. □

Lemma 5.3 shows the plausible fact that, for every solution $y(t)$ of the mutation-recombination equation, $R_{i|L}\big(y(t)\big)$ is a solution as well. Using Lemma 5.3 inductively results in

Corollary 5.4.

$$\frac{d}{dt} R_{G|L}(y) = f\big(R_{G|L}(y)\big) \quad \textit{for} \quad G \in \mathcal{P}(L).$$

5.2 *Decoupling via linkage disequilibria*

In order to define suitable linkage disequilibria, we need a few projectors. As mentioned in the example in Section 4, the basic distinction is between zero sites and non-zero sites. This is taken care of by $U : V \to V$ as defined by its action on the basis vectors of V:

$$b^k \mapsto Ub^k := \begin{cases} b^0, & k = 0, \\ 0, & \text{otherwise.} \end{cases} \tag{5.21}$$

Of course, U is the canonical projection onto the first coordinate of any vector in V, and has matrix representation $U = \operatorname{diag}\{1, 0, \dots, 0\}$. Also observe that, for any $\eta \in V$,

$$\ell(U\eta) = \ell(\eta)\,. \tag{5.22}$$

With our standard agreement (2.8), U_G then projects onto those configurations which only have components in the direction of b^0 at all sites $i \in G$; cf. Fig. 2. Of course, $U^2 = U$, and hence

$$U_G U_H = U_{G \cup H}, \tag{5.23}$$

as well as $U(1 - U) = 0$. Further, we shall need the fact that

$$\mathbf{1} - U_{[1,i]} = \sum_{j=1}^{i} (\mathbf{1} - U_j) U_{[j+1,i]}, \tag{5.24}$$

where we use the convention $U_{[a,b]} = \mathbf{1}$ if $b < a$. To see that (5.24) holds, just note that the right-hand side of (5.24) becomes a telescope sum after employing (5.23).

To abbreviate further notation, we shall now introduce

$$P_{i|L} := (\mathbf{1} - U_{[1,i]})(\mathbf{1} - U_{[i+1,N]}) \tag{5.25}$$

and

$$Q_{i|L} := (\mathbf{1} - U_i)(\mathbf{1} - U_{[i+1,N]}). \tag{5.26}$$

The meaning of these projectors is best understood by considering their action on the basis vectors ('configurations'), as illustrated in Fig. 2. $P_{i|L}$ projects onto those configurations which have at least one b^0 in both $[1, i]$, *and* $[i + 1, N]$. Since a configuration with b^0 at site i is indexed by a string which reads zero at site i, we shall loosely say that $P_{i|L}$ projects onto those configurations which have at least one zero in both $[1, i]$, *and* $[i + 1, N]$. Likewise, $Q_{i|L}$ projects onto those configurations which are non-zero at site i, and have at least one non-zero site after i. From (5.23), it is clear that

$$Q_{i|L} = (\mathbf{1} - U_i) P_{i|L}; \tag{5.27}$$

in particular, $Q_{1|L} = P_{1|L}$, but $Q_{i|L} \neq P_{i|L}$ for $i \geq 2$. We finally need

$$Q_{G|L} := \prod_{g \in G} Q_{g|L}, \quad \text{along with} \quad Q_{\emptyset|L} := \mathbf{1}\,. \tag{5.28}$$

$Q_{G|L}$ projects onto those configurations which are non-zero at all sites in G, and have at least one non-zero site after $g_{|G|}$.

Let us now examine how U_i and $P_{i|L}$ are related to the action of recombination. We first note that

$$\begin{aligned} U_i R_{i|L}(y) &= \frac{1}{y^{(0,\dots,0)}} \sum_{\substack{\boldsymbol{n} \\ n_i=0}} y^{(n_1,\dots,n_{i-1},0,\dots,0)} \cdot y^{(0,\dots,0,n_{i+1},\dots,n_N)}\, b_{\boldsymbol{n}} \\ &= U_i R_{(i-1)|L}(y), \end{aligned} \tag{5.29}$$

see also Fig. 2. Consider further

$$R_{i|L}(y) - y = \frac{1}{y^{(0,\dots,0)}} \sum_{\boldsymbol{n}} \left(y^{(n_1,\dots,n_i,0,\dots,0)} \cdot y^{(0,\dots,0,n_{i+1},\dots,n_N)} - y^{(n_1,\dots,n_N)} \right) b^{\boldsymbol{n}} \,. \tag{5.30}$$

This expression vanishes if either $n_1, \dots, n_i$ are all zero, or $n_{i+1}, \dots, n_N$ are all zero. Hence,

$$R_{i|L}(y) - y = P_{i|L}\big(R_{i|L}(y) - y\big)\,, \tag{5.31}$$

which implies that recombination only changes y if there is at least one non-zero site in $[1, i]$, as well as one in $[i+1, N]$, i.e. if a crossover after site i separates two non-zero sites (recall that 'zero' corresponds to summation in the original representation.) In our two-letter example, this is easily verified by comparing Eqs. (4.22) and (4.24) with Eq. (4.21).

After these preparations, we now proceed to *splitting operators*

$$S_{i|L}(y) := Q_{i|L} \tilde{R}_{i|L}(y), \tag{5.32}$$

where $\tilde{R}_{i|L}(y) := r_{i|L}(y \otimes y)$ is defined on all of W, agrees with $R_{i|L}(y)$ if y represents an element of the unit simplex (with respect to the original variables), and differs from $R_{i|L}(y)$ by normalization otherwise. More generally, $\tilde{R}_{G|L} := \prod_{g \in G} \tilde{R}_{g|L}$, and

$$S_{G|L}(y) := Q_{G|L} \tilde{R}_{G|L}(y), \tag{5.33}$$

along with $S_{\emptyset|L}(y) := y$. Note that, in contrast to $\tilde{R}_{G|L}$, $S_{G|L}$ is not to be understood as composition of single splitting operators. $S_{i|L}$ is identical to $\tilde{R}_{i|L}$ for all components having a nonzero site i, and at least one non-zero site after i; all other components are annihilated, see Fig. 2. The linear equivalent of $S_{i|L}$ is $s_{i|L}(y_1 \otimes y_2) := Q_{i|L} r_{i|L}(y_1 \otimes y_2)$.

We now investigate the composition of splitting operators with each other. To this end, we first use Eqs. (3.3) and (5.22) to see that

$$r_{i|L}\big((U_G y_1) \otimes (U_H y_2)\big) = U_{G \cap [1,i]} U_{H \cap [i+1,N]} r_{i|L}(y_1 \otimes y_2)\,, \tag{5.34}$$

and thus

$$r_{i|L}\Big(\big((\mathbf{1} - U_G) y_1\big) \otimes y_2\Big) \;=\; (\mathbf{1} - U_{G \cap [1,i]}) r_{i|L}(y_1 \otimes y_2), \tag{5.35}$$

$$r_{i|L}\Big(y_1 \otimes \big((\mathbf{1} - U_H) y_2\big)\Big) \;=\; (\mathbf{1} - U_{H \cap [i+1,N]}) r_{i|L}(y_1 \otimes y_2)\,. \tag{5.36}$$

Using Eq. (5.23) and $\mathbf{1} - U_\emptyset = 0$, one therefore obtains

$$s_{i|L}\big((Q_{j|L} y_1) \otimes y_2\big) \;=\; \begin{cases} Q_{j|L} s_{i|L}(y_1 \otimes y_2), & j \in [1, i-1], \\ 0, & j \in [i, N]; \end{cases} \tag{5.37}$$

$$s_{i|L}\big(y_1 \otimes (Q_{j|L} y_2)\big) \;=\; \begin{cases} 0, & j \in [1, i], \\ Q_{j|L} s_{i|L}(y_1 \otimes y_2), & j \in [i+1, N]. \end{cases} \tag{5.38}$$

Using the definition of splitting operators and Eq. (5.28), applying Eq. (5.37) and (5.38) repeatedly with y_1 replaced by $\tilde{R}_{G|L}(y)$ and y_2 with $\tilde{R}_{H|L}(y)$, and reading Eq. (5.10) in the backward direction, one finds

$$s_{i|L}\big(S_{G|L}(y) \otimes S_{H|L}(y)\big) = \begin{cases} S_{(G\cup H\cup\{i\})|L}(y), & \text{if } G \subset [1,i] \text{ and } H \subset [i+1,N], \\ 0, & \text{otherwise.} \end{cases} \tag{5.39}$$

As a special case of Eq. (5.39), one has $S_{i|L}\big(S_{j|L}(y)\big) = s_{i|L}\big(S_{j|L}(y) \otimes S_{j|L}(y)\big) = 0$ for all i and j. On the other hand, it follows from (5.39) and linearity of $s_{i|L}$ that

$$s_{i|L}\big(S_{j|L}(y) \otimes y + y \otimes S_{j|L}(y)\big) = \begin{cases} 0, & i = j, \\ S_{\{i,j\}|L}(y), & i \neq j, \end{cases} \tag{5.40}$$

since j is either in $[1,i]$, or in $[i+1,N]$.

We now consider the composition of operators of the form $\mathbf{1} - S_{i|L}$ and $\mathbf{1} + S_{i|L}$ and claim

Lemma 5.5. $\big(\mathbf{1} - S_{i|L}\big)\big((\mathbf{1} + S_{i|L})(y)\big) = y,$

and, for $i \neq j$ and $\varepsilon, \delta = \pm 1$,

$$(\mathbf{1} + \delta S_{i|L})\big((\mathbf{1} + \varepsilon S_{j|L})(y)\big) = (\mathbf{1} + \varepsilon S_{j|L}))\big((\mathbf{1} + \delta S_{i|L})(y)\big).$$

Proof. From (5.39) and (5.40), it is clear that

$$\begin{aligned} & S_{i|L}\big(y - S_{j|L}(y)\big) \\ & \quad = s_{i|L}\big(y \otimes y - y \otimes S_{j|L}(y) - S_{j|L}(y) \otimes y + S_{j|L}(y) \otimes S_{j|L}(y)\big) \\ & \quad = \begin{cases} S_{i|L}(y), & i = j, \\ S_{i|L}(y) - S_{\{i,j\}|L}(y), & i \neq j, \end{cases} \end{aligned} \tag{5.41}$$

from which the first assertion follows immediately. Further, it follows for $i \neq j$ and $\varepsilon, \delta = \pm 1$ that

$$\begin{aligned} (\mathbf{1} + \delta S_{i|L})\big((\mathbf{1} + \varepsilon S_{j|L})(y)\big) &= (\mathbf{1} + \delta S_{i|L} + \varepsilon S_{j|L} + \varepsilon\delta S_{\{ij\}|L})(y) \\ &= (\mathbf{1} + \varepsilon S_{j|L})\big((\mathbf{1} + \delta S_{i|L})(y)\big) \end{aligned} \tag{5.42}$$

which is the second assertion. □

Hence, all operators of the form $(\mathbf{1} - S_{i|L})$ and $(\mathbf{1} + S_{j|L})$ commute, and $(\mathbf{1} - S_{i|L})$ and $(\mathbf{1} + S_{i|L})$ are inverses of each other. As a consequence, $\Big(\prod_{g\in G}(\mathbf{1} + S_{g|L})\Big)$ and $\Big(\prod_{g\in G}(\mathbf{1} - S_{g|L})\Big)$ are inverses of each other.

These structures will now serve to define the transformation from moments into linkage disequilibria, along with the back transformation. For this purpose, we restrict ourselves to moment vectors q, i.e. to elements of the unit simplex with respect to the original variables.

Definition 5.6. *Let*

$$z := \Big(\prod_{\ell \in L\setminus\{N\}} (\mathbf{1} - S_{\ell|L})\Big)(q)\,.$$

The coordinates of z will be referred to as linkage disequilibria.

The vector z provides a complete set of variables describing the dynamical system (the transformation defining them is invertible, as we shall see in a moment). Coordinates with at most one nonzero index are, of course, not linkage disequilibria in the true sense: They represent the letter frequencies ($z^{(0,\dots,0,n_i,0,\dots,0)} = q^{(0,\dots,0,n_i,0,\dots,0)}$) in terms of the eigenbasis of the mutation operator, and $z^{(0,0,\dots,0)} = q^{(0,0,\dots,0)} = 1$ is the overall normalization. We shall refer to them as *improper* linkage disequilibria.

From Lemma 5.5, it is obvious that the back transformation reads

$$q = \Big(\prod_{\ell \in L \setminus \{N\}} (\mathbf{1} + S_{\ell|L}) \Big)(z) \,. \tag{5.43}$$

For practical purposes, the recursive definition of the linkage disequilibria, as well as the back transformation, is cumbersome if N is large. Then, the following explicit version is used more readily (recall that $\mathcal{P}(G)$ is the set of ordered subsets of G):

Lemma 5.7. *For $G \in \mathcal{P}(L \setminus \{N\})$, one has* $\Big(\prod_{g \in G} (\mathbf{1} - S_{g|L}) \Big)(q) = \sum_{H \in \mathcal{P}(G)} (-1)^{|H|} S_{H|L}(q)\,.$

Proof. The proof is by induction over $m = |G|$. From (5.42), the matter is clear for $m = 1$ and for $m = 2$. Now, assume the claim has been established for all G with $|G| = m$. Then, using first the induction hypothesis, then linearity of $s_{i|L}$, and finally (5.39), one finds

$$\begin{aligned}
& S_{i|L} \Big(\prod_{g \in G} (\mathbf{1} - S_{g|L}) \Big)(q) \\
& \quad = \; S_{i|L} \Big(\sum_{H \in \mathcal{P}(G)} (-1)^{|H|} S_{H|L}(q) \Big) \\
& \quad = \; \sum_{H \in \mathcal{P}(G)} \sum_{I \in \mathcal{P}(G)} s_{i|L} \Big(\big((-1)^{|H|} S_{H|L}(q)\big) \otimes \big((-1)^{|I|} S_{I|L}(q)\big) \Big) \\
& \quad = \; \sum_{I \in \mathcal{P}(G)} (-1)^{|I|} S_{(I \cup \{i\})|L}(q).
\end{aligned} \tag{5.44}$$

As a consequence,

$$\begin{aligned}
& (\mathbf{1} - S_{i|L}) \bigg(\Big(\prod_{g \in G} (\mathbf{1} - S_{g|L}) \Big)(q) \bigg) \\
& \qquad = \; \sum_{H \in \mathcal{P}(G)} (-1)^{|H|} S_{H|L}(q) - (-1)^{|H|} S_{(H \cup \{i\})|L}(q) \\
& \qquad = \; \sum_{I \in \mathcal{P}(G \cup \{i\})} (-1)^{|I|} S_{I|L}(q),
\end{aligned} \tag{5.45}$$

which completes the induction step. □

In the same way, one shows:

$$\Big(\prod_{g \in G} (\mathbf{1} + S_{g|L}) \Big)(z) = \sum_{H \in \mathcal{P}(G)} S_{H|L}(z)\,. \tag{5.46}$$

From Lemma 5.7 and (5.46), it is now clear that the transformations from moments to linkage disequilibria, and back again, may be rewritten as

$$z = \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} S_{G|L}(q) \tag{5.47}$$

$$q = \sum_{G\in\mathcal{P}(L\setminus\{N\})} S_{G|L}(z). \tag{5.48}$$

Let us, at this point, return to our two-letter example in Section 4. Here,

$$\begin{aligned} S_{1|L}(q) &= (0,0,0,0,0,\langle\sigma_1\rangle\langle\sigma_3\rangle,\langle\sigma_1\rangle\langle\sigma_2\rangle,\langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle)^T, \\ S_{2|L}(q) &= (0,0,0,\langle\sigma_2\rangle\langle\sigma_3\rangle,0,0,0,\langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle)^T, \\ S_{\{1,2\}|L}(q) &= (0,0,0,0,0,0,0,\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\rangle)^T, \end{aligned} \tag{5.49}$$

along with $S_{\emptyset|L}(q) = q$. It is obvious from comparison with Eqs. (4.21) and (4.26) that $z = q - S_{1|L}(q) - S_{2|L}(q) + S_{\{1,2\}|L}(q)$. Let us take the opportunity to briefly comment on the projectors $Q_{G|L}$ involved in the definition of the splitting operators. From the definition (5.26), and the properties (5.27) and (5.31), it is clear that only splits with an effect on the moments enter the corresponding linkage disequilibrium (for example, $z^{(0,1,1)}$ contains a contribution from $R_{2|L}(q)$, but not from $R_{1|L}(q)$). Furthermore, duplicate terms are excluded (note that $\langle\sigma_1\rangle\langle\sigma_3\rangle$ shows up in both $R_{1|L}(q)$ and $R_{2|L}(q)$, but only once in $z^{(1,0,1)}$, because it is present in $S_{1|L}(q)$, but absent from $S_{2|L}(q)$). There is some arbitrariness involved here: One might as well include splits *before*, instead of *after*, non-zero sites.

The collection of linkage disequilibria now leads to the final result:

Theorem 5.8. *Under the dynamical system (3.12), the linkage disequilibria of Definition 5.6 decay according to*

$$\frac{d}{dt} z = \sum_i \big(\mu_i(M_i - \mathbf{1}) - \rho_i P_{i|L}\big) z\,.$$

Proof. We use z in the form (5.47) and recall that $\tilde{R}_{G|L}(q) = R_{G|L}(q)$. Differentiating, using $h_\emptyset(q) = 1$, and applying (5.33) and Corollary 5.4, one finds

$$\begin{aligned} \frac{d}{dt} z &= \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} \frac{d}{dt} R_{G|L}(q) \\ &= \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} (f_{\mathcal{M}} + f_{\mathcal{R}})\big(R_{G|L}(q)\big). \end{aligned} \tag{5.50}$$

Since both $f_{\mathcal{M}}$ and $Q_{G|L}$ are diagonal, they commute, and the mutation part is settled easily (just with the help of (5.47)):

$$\sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} f_{\mathcal{M}}\big(R_{G|L}(q)\big) = f_{\mathcal{M}}(z) = \sum_i \mu_i (M_i - \mathbf{1}) z. \tag{5.51}$$

The recombination part may be rewritten as

$$
\begin{aligned}
&\sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} f_{\mathcal{R}}(R_G(q)) \\
&\qquad = \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} \sum_i \rho_i P_{i|L} (R_{i|L} - \mathbf{1})\big(R_{G|L}(q)\big) \\
&\qquad = -\sum_i \rho_i P_{i|L} z + \sum_i \rho_i P_{i|L} \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} R_{i|L}\big(R_{G|L}(q)\big). \qquad (5.52)
\end{aligned}
$$

where (3.12) and (5.31) have been used in the first step, and (5.33) and (5.47) in the second.

It remains to be shown that the second sum vanishes. Actually, we shall see that every summand of the second sum vanishes separately. To this end, we first note that, for $j < i$, repeated application of (5.29) leads to

$$
U_{[j+1,i]} R_{i|L} = U_{[j+1,i]} R_{j|L}\,, \qquad (5.53)
$$

which also holds trivially for $j = i$. We then use (5.24), (5.23), and (5.26) to rewrite $P_{i|L}$ as

$$
\begin{aligned}
P_{i|L} &= \sum_{j=1}^{i} (\mathbf{1} - U_j) U_{[j+1,i]} (\mathbf{1} - U_{[i+1,N]}) \\
&= \sum_{j=1}^{i} (\mathbf{1} - U_j) U_{[j+1,i]} (\mathbf{1} - U_{[j+1,N]}) \\
&= \sum_{j=1}^{i} U_{[j+1,i]} Q_{j|L}. \qquad (5.54)
\end{aligned}
$$

As illustrated in the lower panel of Fig. 2, the i-th summand of the second sum in (5.52) then becomes

$$
\begin{aligned}
&\rho_i P_{i|L} \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} R_{i|L}\big(R_{G|L}(q)\big) \qquad (5.55) \\
&\quad = \rho_i \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} Q_{G|L} \sum_{j=1}^{i} U_{[j+1,i]} Q_{j|L} R_{j|L}\big(R_{G|L}(q)\big) \\
&\quad = \rho_i \sum_{j=1}^{i} U_{[j+1,i]} \sum_{G\in\mathcal{P}(L\setminus\{N\})} (-1)^{|G|} S_{(G\cup\{j\})|L}(q) \\
&\quad = \rho_i \sum_{j=1}^{i} U_{[j+1,i]} \sum_{G\in\mathcal{P}(L\setminus\{j,N\})} (-1)^{|G|} \big(S_{(G\cup\{j\})|L}(q) - S_{(G\cup\{j\}\cup\{j\})|L}(q)\big) \\
&\quad = 0. \qquad (5.56)
\end{aligned}
$$

Here, we have used (5.54) and (5.53) in the first step, and (5.28), (5.8), and (5.33) in the second. This proves the claim. $\square$

Let us interpret the result (the reader might like to refer back to the example in Section 4). Linkage disequilibria decay exponentially, with contributions from both mutation and recombination to the decay rates. The contribution from mutation are the eigenvalues (minus one) of the mutation matrix. The decay rates due to recombination are determined by the operator $\sum_i \rho_i P_{i|L}$, in analogy with Lyubich's discrete-time result [28, pp. 252–255] for more general recombination distributions. Recall that $P_{i|L}$ leeaves those components unchanged for which a crossover after site i separates at least two non-zero sites; it annihilates all others. Let n_j (n_k) be the leftmost (rightmost) index of $z^{(n_1,\dots,n_N)}$ that is non-zero, i.e., j and k are the extreme sites involved in the linkage disequilibrium considered. Then, $\sum_i \rho_i P_{i|L}$, by summing up those ρ_i that belong to crossovers separating two non-zero sites, associates with $z^{(n_1,\dots,n_N)}$ the rate at which sites j and k are separated, i.e., $\rho_{n_j} + \rho_{n_j+1} + \dots + \rho_{n_k-1}$. Clearly, the slowest decay rate in the system is given by the smallest of these two-locus recombination rates, namely $\min_i \rho_i$. Therefore, if all ρ_i are positive, all linkage disequilibria (except, of course, the improper ones) converge to zero. Note, however, that the decay rates belonging to the linkage disequilibria are not the only exponential rates that may occur in the original dynamical system. Due to the nonlinear back transformation (5.43), other combinations of the ρ_i will show up as well.

We have thus seen that the coordinates of z are decoupled, and each decays exponentially. An explicit solution to the dynamical system is therefore available, for initial values in the unit simplex, by performing first the linear transformation from frequencies to moments (3.5), then the multilinear one from moments to linkage disequilibria (Definition 5.6), applying Theorem 5.8, and finally retracing the transformation steps via (5.43) and (3.5). This solution may be extended to the entire positive cone via homogeneity (if p is a solution of $\dot{p} = f(p)$, then $x = \hat{h}_\emptyset(x)p$ is a solution of $\dot{x} = \hat{h}_\emptyset(x)\dot{p} = f(\hat{h}_\emptyset(x)p) = f(x)$).

Let us now consider the asymptotic behaviour of the solution in the generic case where none of the μ_i and ρ_i vanishes, and $\lambda^0 = 1$ is the only unit eigenvalue of the mutation matrix. The latter entails that one is the first and stricty largest entry of the diagonal matrix M, and b^0 represents the Perron-Frobenius eigenvector of the mutation matrix. Then one has $\lim_{t\to\infty} \exp\big(-\mu_i t(M - \mathbf{1})\big) = U$, and $\lim_{t\to\infty} \exp\big(-\sum_i \mu_i t(M_i - \mathbf{1})\big) = U_L$ (recall that M acts on V, whereas the M_i act on W). As to recombination, evaluation of the exponential series (with $(P_{i|L})^2 = P_{i|L}$) yields

$$\exp\big(-\sum_i \rho_i t P_{i|L}\big) = \prod_i \big(\mathbf{1} - (1 - e^{-\rho_i t})P_{i|L}\big) \xrightarrow{t\to\infty} \prod_i (\mathbf{1} - P_{i|L}). \tag{5.57}$$

With the help of $U^2 = U$, one obtains $(\mathbf{1} - P_{i|L})U_L = \mathbf{1} - (\mathbf{1} - U_{[1,i]})(\mathbf{1} - U_{[i+1,N]})U_L = U_L$, from which it follows that $\lim_{t\to\infty} z(t) = U_L z(0) = z^{(0,\dots,0)} \cdot \big(\bigotimes^N (1,0,\dots,0)^T\big)$. Recalling that $S_i\big(\bigotimes^N (1,0,\dots,0)^T\big) = 0$, and $z^{(0,\dots,0)} = q^{(0,\dots,0)} = 1$ (normalization), one finds through the back transformation that $\lim_{t\to\infty} q(t) = \lim_{t\to\infty} z(t) = \bigotimes^N (1,0,\dots,0)^T$, and, in the original variables, $\lim_{t\to\infty} p(t) = \bigotimes^N b^0$. As was to be expected, we therefore have global convergence to the mutation equilibrium with independent sites, i.e. overall linkage equilibrium.

Finally, a few remarks are in order concerning more general mutation models. As detailed in the Appendix, the whole solution procedure still goes through if the mutation pattern (not just an overall rate μ_i) is site-dependent, and even if the alphabet varies from site to site. Then, $\widehat{M}_i$ may be chosen to be any matrix that describes mutation at site i while leaving all others unchanged, and M_i is the diagonal matrix which holds its eigenvalues. With this reinterpretation, the main result (Theorem (5.8)) remains valid. For details, see the Appendix.

6 Discussion

We have examined the continuous-time mutation-recombination equation (2.5) with linear arrangement of sites and at most one mutation or crossover event at a time. It relies on the assumptions of an infinite population, neutral evolution, and rare mutation and recombination events. The model can be solved exactly for arbitrary mutation and recombination rates. Although the intermediate calculations are a bit technical in places, the transformations involved (Eq. (3.5) and Definition 5.6) and the final result (Theorem 5.8) are astonishingly simple. Many different measures of linkage disequilibrium are available in the literature, e.g. [4, 28, 33, 38, 39]; see also the review in [6]. Some of them have been used to solve the recombination dynamics through linearization and diagonalization [4, 28]; hence the name of 'principal components' for Bennett's measures. There is no closed formula available for this transformation, however; the coefficients involved depend on the recombination distribution, and recursions are required to determine them. For a thorough review of these and related recursive systems, see [11, 12].

Tensor products have been used previously to investigate the equilibrium structure in models of selection and recombination (e.g. [24, 25]), and to prove Haldane linearizability in models of mutation and recombination [29, 36]. Here, they are employed to find an explicit solution to the mutation-recombination equation. The approach is, of course, equivalent to a description with multi-indices as, for example, employed in [5], but brings out the multilinear structure more clearly. Most importantly, the single-crossover operators $R_{i|L}$ (Eq. (3.11)) form a commutative algebra, cf. Lemma 5.1.

The solution relies on a collection of linkage disequilibria (Definition 5.6) that both linearize and diagonalize the dynamics automatically, without the need for further calculations. They are different from all other measures of linkage disequilibrium known to the author, and, at the same time, are adapted to the single-crossover assumption in a natural way. Loosely speaking, they involve, for every moment, all products of lower-order moments which result from this moment through (any number of) splitting events, decorated with a sign that counts the number of splits involved. Duplicates are excluded through the action of the projectors $Q_{i|L}$ (defined in Eq. (5.26)), which annihilate crossovers after zero sites. The simplicity of the single-crossover model lies in the fact that certain associations are never produced through independent crossovers. For $N = 3$ biallelic sites, for example, the standard measure of three-way linkage disequilibrium reads

$$\begin{aligned} D \;=\;& p^{(+,+,+)} - p^{(+,*,*)}p^{(*,+,+)} - p^{(+,+,*)}p^{(*,*,+)} - p^{(+,*,+)}p^{(*,+,*)} \\ &+2p^{(+,*,*)}p^{(*,+,*)}p^{(*,*,+)} \end{aligned} \tag{6.1}$$

in terms of relative frequencies, and in terms of our correlation functions (cf., the example in Section 4)

$$\begin{aligned} D \;&=\; \frac{1}{8}\big(\langle\sigma_1\sigma_2\sigma_3\rangle - \langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle - \langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle - \langle\sigma_1\sigma_3\rangle\langle\sigma_2\rangle + 2\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\rangle\big) \\ &=\; \frac{1}{8}\big(z^{(1,1,1)} - z^{(0,1,0)} \cdot z^{(1,0,1)}\big). \end{aligned} \tag{6.2}$$

D agrees with Bennett's measure (his principal components are independent of the recombination distribution for $N = 2, 3$). Note that the $\langle\sigma_1\sigma_3\rangle\langle\sigma_2\rangle$ term does not occur in our $z^{(1,1,1)}$, since it cannot be produced by inserting brackets into $\langle\sigma_1\sigma_2\sigma_3\rangle$; cf. Eq. (4.28). The key simplification of the single-crossover assumption lies in the fact that the quantities that diagonalize the dynamics (i.e., our linkage disequilibria) are independent of the recombination rates. In contrast, in the more general situation, they must be determined via recursions involving the recombination distribution, which do not possess a simple closed solution.

The continuous-time description via single crossover and mutation events is very natural in molecular applications, where mutation and recombination rates per site are small. Our neutral model is met most closely by a gene relieved from selective constraints and evolving towards a pseudogene; Eq. (3.12) then describes the decay of the existing correlations that had been built up by the previous action of selection. For applications to molecular data, however, effects due to finite population size must be considered. We hope that our simple model will lend itself to combination with other evolutionary forces, i.e., selection, migration, or drift. The incorporation of drift is required to predict the pattern of variability that is produced by mutation and intragenic recombination in finite populations at the molecular level. It should be mentioned that mutational and recombinational hot spots do not pose any problem, since the model allows for site-dependent mutation and recombination rates. It should also be remarked that the related problem of recombination and coalescence has already been approached through approximations of the correlation functions [13].

In the realm of deterministic models, the description of evolutionary dynamics of multilocus systems under the joint influence of mutation, selection and recombination is at the heart of numerous theoretical investigations concerning the evolution of sexual reproduction; for a review, see Feldman et al. [15]. Maybe in this context a 'tight-linkage approximation' will be as fruitful when it comes to molecular applications as is the QLE approximation for multilocus systems with loose linkage. A hint in this direction is the observation that the recombination-migration dynamics simplifies significantly in a discrete-time model with single crossover events only [9]. However, it has been noted previously [29] that Haldane linearization of recombination and mutation relies on the fact that both processes conserve normalization [cf. (3.13)], and this is no longer true when selective differences are included; it is therefore expected that this will be a hard problem.

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7 Appendix

Let us briefly outline the generalization of our results for arbitrary alphabets $\mathcal{A}_i$ at site i, with $|\mathcal{A}_i| =: m_i$. To this end, we detach ourselves from the general understanding (2.6) in order to allow for more general mappings which act on a single site while leaving all others unchanged. The local spaces now are $V_i := \mathbb{R}^{m_i}$ with basis vectors $e_1, e_2, \dots, e_{m_i}$, and $W := V_1 \otimes \dots \otimes V_N$. We write the mutation rate from α to β at site i as $\mu_i m_i^{\beta\alpha}$, with the normalization $\sum_\beta m_i^{\beta\alpha} = 1$, and define the matrix $\widehat{\mathfrak{m}}_i := (m_i^{\beta\alpha})_{\beta,\alpha\in\mathcal{A}_i}$, which represents a linear mapping from V_i into itself. The mutation matrix $\widehat{M}_i$ which mutates site i and leaves all others unchanged then reads

$$\widehat{M}_i := \underbrace{\mathbf{1}\otimes\dots\otimes\mathbf{1}}_{i-1\text{ sites}} \otimes A \otimes \underbrace{\mathbf{1}\otimes\dots\otimes\mathbf{1}}_{N-i\text{ sites}}\,. \tag{7.3}$$

With vectors ξ_i in V_i represented as $\xi_i = \xi_i^1 e_1 + \dots + \xi_i^{m_i} e_{m_i}$, the linear form (2.11) becomes $\hat{\ell}_i(\xi_i) = \xi_i^1 + \ldots + \xi_i^{m_i}$, and (2.12) is generalized to

$$\hat{h}_G(\xi_1 \otimes \dots \otimes \xi_N) = \Big(\prod_{i\in(L\setminus G)} \hat{\ell}_i(\xi_i)\Big)\Big(\bigotimes_{j\in G}\xi_j\Big). \tag{7.4}$$

The definition of the recombination operators $\widehat{R}_i$ and $\widehat{R}_G$ then remains the same as in (2.14). The diagonalization of the mutation term (after (3.3)) is now performed separately on every local space, to read $\mathfrak{m}_i = \mathfrak{b}_i \widehat{\mathfrak{m}}_i \mathfrak{b}_i^{-1}$, where $\mathfrak{m}_i := \operatorname{diag}(\lambda_i^0, \dots, \lambda_i^{m_i-1})$ holds the eigenvalues of $\widehat{\mathfrak{m}}_i$ (with $\lambda_i^0 = 1$), and $\mathfrak{b}_i$ holds the basis vectors, namely $b_i^0, \dots, b_i^{m_i-1}$ (where b_i^0 has column sum 1). We then redefine B_i as $B_i := \mathbf{1}\otimes\dots\otimes\mathbf{1}\otimes\mathfrak{b}_i\otimes\mathbf{1}\otimes\dots\otimes\mathbf{1}$ with $\mathfrak{b}_i$ in the ith position. With this reinterpretation, the new representation of vectors ξ_i in V_i reads $\xi_i = \sum_k \eta_i^k b_i^k$, the similarity transform (3.5) remains unaltered, and the linear form (3.6) becomes

$$\hat{\ell}_i(\xi_i) = \hat{\ell}_i(\eta_i^0 b_i^0 + \dots + \eta_i^{m-1} b_i^{m_i-1}) = \eta_i^0 =: \ell_i(\eta_i) \tag{7.5}$$

instead of (3.6), and may be rewritten as $\ell_i(\eta_i) = u_i \cdot \eta_i$ with $u_i = (1, 0, \dots, 0)^T$ a vector with m_i entries. With these ingredients, all quantities after the change of basis formally remain unchanged, in particular h_H (before (3.7), the recombination operators $R_{i|L}$ in (3.11), and the mutation-recombination equation (3.12).

The diagonalization of the recombination term again relies on the projectors $P_{i|L}$ and $Q_{i|L}$, and splitting operators $S_{i|L}$, which remain as in (5.25), (5.26), and (5.32), with U_i generalized to $U_i := \mathbf{1}\otimes\dots\otimes\mathbf{1}\otimes\mathfrak{u}_i\otimes\mathbf{1}\otimes\dots\otimes\mathbf{1}$, and the definition of (5.21) changed into

$$b_i^k \mapsto \mathfrak{u}_i b_i^k := \begin{cases} b_i^0, & k = 0, \\ 0, & \text{otherwise.} \end{cases} \tag{7.6}$$

With these reinterpretations, the remainder of Section 5 reads as before, and, in particular, the main result (Theorem 5.8) remains valid.

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Figure Captions

Figure 1:
Action of recombination on the terms entering $z^{(1,1,1,1)}$ in the two-letter example of Section 4, but for $N = 4$ and without mutation ($\mu_i \equiv 0$). 'Splitting' and 'joining' events occur at the rates indicated, in both directions between the expressions that are joined by straight lines; cf. Eq. (5.4). For example, $\frac{d}{dt}\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\sigma_4\rangle = -\rho_3\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\sigma_4\rangle + \rho_1\langle\sigma_1\sigma_2\rangle\langle\sigma_3\sigma_4\rangle + \rho_2\langle\sigma_1\rangle\langle\sigma_2\sigma_3\sigma_4\rangle$.

Figure 2:
Graphical illustration of action of projectors, recombination and splitting operators, on moments and linkage disequilibria for two letters (as in Section 4) and $N = 7$. The 0010011 coordinate is chosen as example. A vertical bar symbolizes a recombination event at the respective position, that is, 0010011 represents $y^{(0,0,1,0,0,1,1)}$, and 001 | 0011 represents $y^{(0,0,1,0,0,0,0)} \cdot y^{(0,0,0,0,0,1,1)}$. A '$\times$' means that the configuration is annihilated. The upper panel illustrates the equations given at the right. If two operators appear on the same arrow, they both give the same result. The lower panel shows the essential idea in the proof of the main result (Theorem 5.8). The first step alludes to the transformation from moments into linkage disequilibria according to (5.47). The remaining steps illustrate the series of equations leading to (5.56), for $i = 4$. More specifically, in the second step, $R_{4|L}$ is applied separately to every term above, cf. (5.55). The third step uses (5.29), and the last one relies on Lemma 5.1, as illustrated in the upper panel.

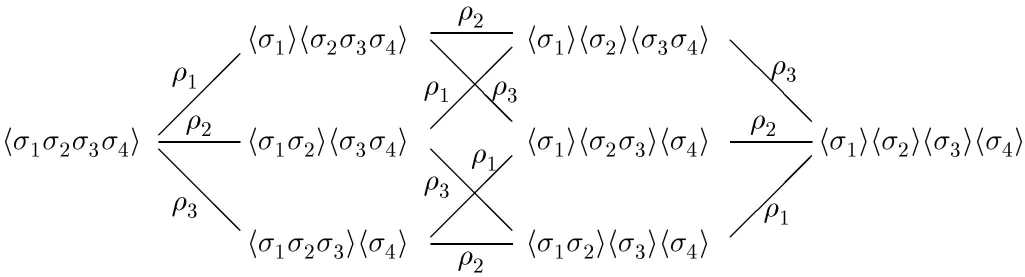
$\langle\sigma_1\sigma_2\sigma_3\sigma_4\rangle$
ρ_1
ρ_2
ρ_3
$\langle\sigma_1\rangle\langle\sigma_2\sigma_3\sigma_4\rangle$
$\langle\sigma_1\sigma_2\rangle\langle\sigma_3\sigma_4\rangle$
$\langle\sigma_1\sigma_2\sigma_3\rangle\langle\sigma_4\rangle$
ρ_2
ρ_1
ρ_3
ρ_1
ρ_3
ρ_2
$\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\sigma_4\rangle$
$\langle\sigma_1\rangle\langle\sigma_2\sigma_3\rangle\langle\sigma_4\rangle$
$\langle\sigma_1\sigma_2\rangle\langle\sigma_3\rangle\langle\sigma_4\rangle$
ρ_3
ρ_2
ρ_1
$\langle\sigma_1\rangle\langle\sigma_2\rangle\langle\sigma_3\rangle\langle\sigma_4\rangle$

Figure 1:

$$
\begin{array}{ccccccccc}
0010011 & \xrightarrow{R_{3|L}} & 001 \mid 0011 & \xrightarrow{R_{3|L}} & 001 \mid\mid 0011 & = & 001 \mid 0011 & \text{(Lemma 5.1)} \\
 & & \times & \xleftarrow{U_3} & 0010011 & \xrightarrow{U_4} & 0010011 & (5.21) \\
 & & \times & \xleftarrow{P_{2|L}} & 0010011 & \xrightarrow{P_{3|L},P_{4|L}} & 0010011 & (5.25) \\
 & & 010011 & \xleftarrow{Q_{2|L},Q_{3|L}} & 0010011 & \xrightarrow{Q_{4|L}} & \times & (5.26) \\
 & & 0010011 & \xrightarrow{R_{4|L}} & 0010 \mid 011 & = & 001 \mid 0011 & (5.29) \\
 & & 001 \mid 0011 & \xleftarrow{S_{3|L}} & 0010011 & \xrightarrow{S_{4|L}} & \times & (5.32)
\end{array}
$$

$$
\begin{array}{cclclclcl}
0010011 & \xrightarrow{\sum_G (-1)^{|G|} S_{G|L}} & 0010011 & - & 001 \mid 0011 & - & 001001 \mid 1 & + & 001 \mid 001 \mid 1 \\
 & \xrightarrow{P_{4|L} R_{4|L}} & 0010 \mid 011 & - & 001 \mid 0 \mid 011 & - & 0010 \mid 01 \mid 1 & + & 0010 \mid 01 \mid 1 \\
 & = & 001 \mid 0011 & - & 001 \mid\mid 0011 & - & 001 \mid 001 \mid 1 & + & 001 \mid 001 \mid 1 \\
 & = & 0 & & & & & &
\end{array}
$$

Figure 2: