A Markovian genomic concatenation model guided by persymmetric matrices

Andrew G. Hart†
Marcelo Sobottka‡∗

† Departamento de Ingeniería Matemática and Centro de Modelamiento Matemático, Universidad de Chile, Chile.
‡ Departamento de Matemática, Universidade Federal de Santa Catarina, Brazil

Abstract

The aim of this work is to provide a rigorous mathematical analysis of a stochastic concatenation model presented by Sobottka and Hart (2011) which allows approximation of the first-order stochastic structure in bacterial DNA by means of a stationary Markov chain. Two probabilistic constructions that rigorously formalize the model are presented. Necessary and sufficient conditions for a Markov chain to be generated by the model are given, as well as the theoretical background needed for designing new algorithms for statistical analyses of real bacterial genomes. It is shown that the model encompasses the Markov chains satisfying intra-strand parity, a property observed in most DNA sequences.

Keywords: stochastic matrix, Markov chain, DNA sequence.

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1 Introduction

One of the fundamental issues in the study of genomes is their primary structure, that is, the distribution of nucleotides along DNA sequences. The identification of statistical patterns in the primary structure of DNA sequences has revealed several underlying patterns in genomes [2, 10, 11, 18] and has enabled scientists to propose models for evolutive pressures and mutational mechanisms that might act on organisms [1, 6, 18] as well as to construct bioinformatics tools. For example, in [3], a maximum likelihood approach was used to perform analyses of DNA sequences in order to estimate evolutionary trees, while in [20], a measure of the long-range correlation between the nucleotide bases of DNA sequences was used to classify bacteria. In addition, strand compositional asymmetry (SCA) was used to detect replication origins in bacteria [4], while [17] used interpolated Markov models to identify genes in bacteria. [8] proposed a maximization model to describe the organization and distribution of genes in bacterial DNA and [12] presented a stationary stochastic process for modeling the placement of coding and non-coding regions within a genome that incorporates the phenomenon of start codons appearing within coding regions.

The aim of this work is to provide a rigorous formalization of a stochastic concatenation model for capturing the primary structure of bacterial DNA sequences which was presented in [18]. The model, henceforth referred to as the S-H model, allowed novel statistical symmetries in the mononucleotide and dinucleotide distributions of a collection of bacterial chromosomes to be observed. A key feature of the model is a persymmetric matrix of probabilities which plays a role in determining the nucleic acids seen along a DNA sequence. The persymmetric matrices constitute a special class of matrices which has been employed in models from various fields (see for example [13, 14, 15]) and which has been widely studied (see for example [5, 6, 16, 19]).

∗Corresponding author.
E-mail addresses: ahart@dim.uchile.cl (A. Hart), marcelo.sobottka@ufsc.br (M. Sobottka).
A genome is a duplex of DNA strands, each strand consisting of a sequence of nucleotides. The nucleotides are of four types: adenine (A), cytosine (C), guanine (G) and thymine (T). Of these types, adenine is complementary to thymine while cytosine is complementary to guanine. Each nucleotide on one DNA strand pairs with its complement on the opposite strand. This chemically induced pairing between the two strands causes the strands to assume a ladder-like arrangement which is then twisted to attain the famous helix. The chemical composition of DNA molecules endows a strand with an intrinsic reading direction: each strand can only be read in one direction by the genetic machinery of the cell. Furthermore, the way strands combine to form a duplex means that the two strands are read in opposite directions: they are said to be antiparallel.

We shall identify each nucleotide type with a number in \( N := \{1, 2, 3, 4\} \) (\( A \equiv 1, C \equiv 2, G \equiv 3 \) and \( T \equiv 4\)). Let \( \alpha : N \to N \) be the involution which maps each nucleotide to its complement, that is, \( \alpha(i) = 5 - i \).

The S-H model is a concatenation model which has at its core a first-order Markov chain whose one-step transition matrix \( P = (P_{ij})_{i,j \in N} \) is derived from a positive parameter \( m \) and a positive persymmetric matrix \( \mathcal{L} = (L_{ij})_{i,j \in N} \):

\[
P_{ij} = \frac{L_{ij}M_j}{\sum_{k \in N} L_{ik}M_k},
\]

where \( M_1 = M_4 := m/(2m + 2) \) and \( M_2 = M_3 := 1/(2m + 2) \). The Markov chain governs how the DNA sequence grows in both directions from an initial nucleotide called the origin by appending nucleotides in three steps. Step 1. a nucleotide of type \( j \) is randomly selected with probability \( M_j \). Step 2. with probability \( 1/2 \), the nucleotide tries to join the end (consonant with the DNA reading direction ) or beginning (contrary to the reading direction) of the sequence. Step 3. In the first case, the nucleotide is appended to the sequence with probability \( L_{ij} \), where \( i \) is the type of the last nucleotide in the sequence; in the latter, the nucleotide is prepended to the sequence with probability \( L_{\alpha(k)\alpha(j)} \), where \( k \) is the type of the initial nucleotide. This scheme is illustrated in Figure 1.

Provided nucleotides accumulate evenly at the ends of the DNA strand, after a long time one would obtain (with probability 1) a sequence with the initial nucleotide at its midpoint. One half would be generated by the stationary Markov chain \( \bar{P}, \bar{\pi} \), where the transition matrix \( \bar{P} \) is given by (1) and the chain’s stationary distribution \( \bar{\pi} = \pi_\alpha(i) \) and \( \bar{P}_{ij} = \frac{\pi_\alpha(i) L_{\alpha(j)\alpha(i)}}{\pi_\alpha(i)} \), for \( i, j \in N \). The model is consistent with the observation reported by geneticists that bacterial DNA sequences are usually composed of two distinct segments called chirochores (see [4]). Furthermore, if one estimates the transition matrices \( \bar{P} \) and \( P \) for the segments prior to and following the origin nucleotide respectively, one usually finds that \( \bar{P}_{ij} = \frac{\pi_\alpha(i) L_{\alpha(j)\alpha(i)}}{\pi_\alpha(i)} \) (see [8]).

Figure 1: A schematic presentation of the S-H model for constructing bacterial DNA sequences. Assuming the reading sense of the sequence is from left to right, a new nucleotide of type \( C \) is selected with probability \( 1/(2m + 2) \) and is appended to the end of the sequence with probability \( L_{32} \), while a nucleotide of type \( T \) is selected with probability \( m/(2m + 2) \) and will be attached to the beginning of the sequence with probability \( L_{\alpha(3)\alpha(4)} \). The final DNA sequence obtained is the concatenation of two Markovian processes: one starting at position zero and extending to the right, whose estimated transition matrix is \( P \); and the other terminating at zero, whose estimated transition matrix is \( \bar{P} \).

The paper is organized as follows. Section 2 discusses the probabilistic interpretation of the form (1) of the matrix \( P \) in greater depth than [8]. Two different probabilistic constructions are presented, the first of which provides the justification for the description of DNA sequence growth given above. Section 3 introduces the set
of \( \mathcal{R} \)-generated matrices as matrices of the form (1), where \( \mathcal{R} \) is the set of positive persymmetric matrices, and establishes several algebraic characterizations of such matrices. The non-uniqueness of the persymmetric matrix \( \mathcal{L} \) and positive parameter \( m \) that define an \( \mathcal{R} \)-generated matrix is then considered in Section 4 where a couple of equivalence relations on \( \mathcal{R} \) are considered. This leads to an examination of various properties of \( \mathcal{R} \)-generated matrices as used in the S-H model in Section 5. Finally, we discuss some measures for determining how closely a DNA sequence conforms to the S-H model and make concluding remarks in Section 6.

\section{Probabilistic interpretation of \( P \)}

In \cite{LS}, a formal description of the way nucleotides are appended to a DNA sequence using the persymmetric matrix \( \mathcal{L} \) and the parameter \( m \) was presented, but the explicit connection with stochastic matrices of the form (1) was left for the reader to deduce. Here, we more rigorously discuss how the form (1) of the stochastic matrix \( P \) arises from the DNA-sequence growth mechanism described above. In addition, we shall present an alternative probabilistic interpretation of the growth mechanism.

\subsection{Interpretation}

To begin, consider the growth of a DNA sequence whose initial nucleotide is taken to be of type \( i \). Let \( (\beta_t, ~ t \geq 0) \) be a Bernoulli scheme on \( N \) with common distribution \( M = (M_1, M_2, M_3, M_4) = (m, 1, 1, m)/(2m+2) \), that is, an independent and identically distributed sequence of random variables on \( N \) with \( \beta_s \sim M \). Consider two coupled stochastic processes \( (V_t, ~ t \geq 0) \), which evolves on the state space \( N \), and \( (W_t, ~ t \geq 0) \), which is a Bernoulli \( \{0, 1\}\)-process where \( W_t \) is 1 with probability \( L_{V_t, \beta_t} \) (that is, \( W_t \sim B(L_{V_t, \beta_t}) \)). By setting \( V_0 := i \) as the type of the initial nucleotide from which the DNA sequence grows, the process \( (V_t, ~ t \geq 0) \) evolves as a deterministic function of \( (\beta_t, ~ t \geq 0) \) and \( (W_t, ~ t \geq 0) \) as follows:

\[
V_{t+1} := \beta_tW_t + V_t(1 - W_t) = \begin{cases} 
\beta_t, & \text{if } W_t = 1 \\
V_t, & \text{if } W_t = 0 
\end{cases}, \quad \forall t \geq 0.
\]

Note that, while \( V_t \) denotes the type of the last nucleotide appended to the sequence, \( \beta_t \) corresponds to the mechanism responsible for proposing the type, say \( j \), of the next nucleotide to concatenate to the sequence, and \( W_t \) corresponds to the mechanism responsible for accepting or rejecting the new nucleotide in the sequence. If \( \beta_t = j \), then \( j \) is accepted as the type of the next nucleotide provided that \( W_t = 1 \), in which case \( V_{t+1} \) is set to \( j \). Otherwise, the nucleotide of type \( j \) is discarded and no nucleotide is appended. In that case, \( V_{t+1} \) takes the value of \( V_t \). In this way, \( t \) counts the number of nucleotides proposed rather than the length of the DNA sequence while the number of acceptances, given by \( \sum_{u=1}^{t} W_u \), is one less than the length of the DNA sequence, since it doesn’t count the initial nucleotide. For all \( i \in N \) and \( t \geq 0 \), we define

\[
\gamma_i := \Pr(W_t = 1 \mid V_t = i) = \sum_{j \in N} \Pr(W_t = 1, \beta_t = j \mid V_t = i)
\]

\[
= \sum_{j \in N} \Pr(W_t = 1 \mid \beta_t = j, V_t = i) \Pr(\beta_t = j \mid V_t = i)
\]

\[
= \sum_{j \in N} \Pr(W_t = 1 \mid \beta_t = j, V_t = i) \Pr(\beta_t = j) = \sum_{j \in N} L_{ij}M_j.
\]

Next, define a sequence \( (\tau_s, ~ s \geq 0) \) of stopping times by \( \tau_0 := 0 \) and

\[
\tau_{s+1} := \min \{ t > \tau_s : W_{t-1} = 1 \}.
\]

The \( \tau_s \)’s mark the nucleotide type proposals that were accepted. By construction, they constitute a series of renewal times. Note that \( (V_t, ~ t \geq 0) \) is a discrete step function which transitions to a new nucleotide whenever \( t \in \{\tau_s, ~ s \geq 0\} \). More precisely, for all \( s \geq 0 \), \( V_t = V_{\tau_s} \) for \( t = \tau_s, \tau_s + 1, \ldots, \tau_{s+1} - 1 \). Let \( i \in N \) and \( w \in \{0, 1\} \). The random variable \( \beta_t \) is independent of \( W_u \) for \( u < t \) and the distribution of \( W_t \) is completely determined by the
value of $\beta_t$ and $V_t$. Consequently, the event $\{W_t = w\}$ is conditionally independent of $\{W_u = 0\}$ for all $u < t$ given $V_t = i$. For $i \in N$ and $t > u \geq 0$, we have

$$
\Pr(W_t = 1, W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i) = \Pr(W_t = 1 \mid W_{t-1} = 0, \ldots, W_u = 0, V_u = i) \cdot \\
\Pr(W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i) \\
= \Pr(W_t = 1 \mid V_t = i, W_{t-1} = 0, \ldots, W_u = 0, V_u = 0) \cdot \\
\Pr(W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i) \\
= \Pr(W_t = w \mid V_t = i) \Pr(W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i) \\
= \gamma_i \Pr(W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i)
$$

and

$$
\Pr(W_t = 0, \ldots, W_u = 0 \mid V_u = i) = (1 - \gamma_i) \Pr(W_{t-1} = 0, \ldots, W_u = 0 \mid V_u = i).
$$

Hence, for $s \geq 0$, $t \geq 1$ and $i \in N$, we obtain

$$
\Pr(\tau_{s+1} - \tau_s = t \mid V_{\tau_s} = i) = \Pr(W_{\tau_{s+t-1}} = 1, w_{\tau_{s+t-2}} = 0, \ldots, W_{\tau_s} = 0 \mid V_{\tau_s} = i) \\
= \Pr(W_{\tau_{s+t-2}} = 0, \ldots, W_{\tau_s} = 0 \mid V_{\tau_s} = i) \gamma_i \\
= \Pr(W_{\tau_{s+t-3}} = 0, \ldots, W_{\tau_s} = 0 \mid V_{\tau_s} = i)(1 - \gamma_i)\gamma_i \\
= \ldots \\
= (1 - \gamma_i)^{t-1}\gamma_i.
$$

Conditional on $V_{\tau_s} = i$, $\tau_{s+1} - \tau_s$ is thus a geometric random variable taking values on the positive integers:

$$
\tau_{s+1} - \tau_s \mid V_{\tau_s} = i \sim \text{geom}(\gamma_i), \quad s \geq 0, \ i \in N.
$$

Observe that the distribution of $\tau_{s+1} - \tau_s$ is completely determined by the value of $V_{\tau_s}$ and is independent of any events prior to $\tau_s$ if $V_{\tau_s}$ is given. Furthermore, $\tau_{s+1} - \tau_s \mid V_{\tau_s} = i$ is identically distributed as $\tau_1 \mid V_0 = i$, for all $s > 0$.

Next, define the process $(U_s, s \geq 0)$ by $U_s := V_{\tau_s}$. Suppose that $V_{\tau_s} = i$ for some fixed $s \geq 0$. Then $V_{\tau_{s+1}}$ is determined by $\beta_{\tau_{s+1} - 1}$ and $V_{\tau_s} = \beta_{\tau_{s-1}}$, which are independent of all $\beta_t$, $V_t$ and $W_t$ for all $t$ prior to $\tau_s - 1$. Consequently, $(U_s, s \geq 0)$ has the Markov property:

$$
\Pr(U_{s+1} = j \mid U_s = i, U_{s-1} = i_1, \ldots, U_0 = i_s) = \Pr(U_{s+1} = j \mid U_s = i),
$$

for all $i_1, i_2, \ldots, i_s \in N$ and $s \geq 0$. Finally, since each $\tau_s$ essentially marks a point at which the process $((\beta_t, V_t, W_t), t \geq 0)$ is restarted, we have

$$
\Pr(U_{s+1} = j \mid U_s = i) = \Pr(V_{\tau_{s+1}} = j \mid V_{\tau_s} = i) = \Pr(V_{\tau_1} = j \mid V_{\tau_0} = i) = \Pr(U_1 = j \mid U_0 = i) =: P_{ij},
$$

for all $s \geq 0$. Therefore, $(U_s, s \geq 0)$ is a time-homogeneous Markov chain on the finite state space $N$. The following theorem gives the form of the one-step transition matrix $P = (P_{ij})_{i,j \in N}$ in terms of $\mathcal{L}$ and $M$.

**Theorem 1.** The one-step transition matrix $P = (P_{ij})_{i,j \in N}$ of the Markov chain $(U_s, s \geq 0)$ is given by

$$
P_{ij} := \frac{L_{ij}M_j}{\sum_{k \in N} L_{ik}M_k}.
$$

**Proof.** Let $\tau := \tau_1$. Now,

$$
P_{ij} = \Pr(U_1 = j \mid U_0 = i) \\
= \Pr(V_\tau = j \mid V_0 = i) \\
= \sum_{t=1}^{\infty} \Pr(V_t = j, \tau = t \mid V_0 = i) \\
= \sum_{t=1}^{\infty} \frac{\Pr(V_t = j, \tau = t \mid V_0 = i)}{\Pr(\tau = t \mid V_0 = i)} \Pr(\tau = t \mid V_0 = i) \\
= \sum_{t=1}^{\infty} \frac{\Pr(V_t = j, \tau = t \mid V_0 = i)}{\sum_{k \in N} \Pr(V_t = k, \tau = t \mid V_0 = i)} \Pr(\tau = t \mid V_0 = i).
$$

(2)
There is another way to represent how new nucleotides are added to a DNA sequence which provides an alternative distribution $M$ preserves the persymmetry of one-step transition matrix of $(\beta_{t-1} = j, W_{t-1} = 1, V_0 = 0, u = 1, \ldots, t-2 | V_0 = i)$. However, $\Pr(W_{t-1} = 1) \Pr(\beta_{t-1} = j, V_{t-1} = 1) \Pr(W_u = 0, u = 1, \ldots, t-2 | V_0 = i) = \Pr(W_u = 0, u = 1, \ldots, t-2 | V_0 = i) = L_{ij} M_j \Pr(W_u = 0, u = 1, \ldots, t-2 | V_0 = i)$ and substituting this into (2) yields

$P_{ij} = \sum_{t=1}^{\infty} \frac{\Pr(V_t = j, \tau = t | V_0 = i)}{\sum_{k \in N} \Pr(V_t = k, \tau = t | V_0 = i)} \Pr(\tau = t | V_0 = i) = \sum_{t=1}^{\infty} \frac{L_{ij} M_j \Pr(W_u = 0, u = 1, \ldots, t-2 | V_0 = i)}{\sum_{k \in N} L_{ik} M_k} \Pr(\tau = t | V_0 = i) = \frac{L_{ij} M_j}{\sum_{k \in N} L_{ik} M_k}$.

Clearly, the matrix $P$ is invariant to rescaling $\mathfrak{L}$. The only effect of rescaling $\mathfrak{L}$ by some constant, say $h$, is to multiply the mean $1/\gamma_i$ of the distribution of $\tau_{s+1} - \tau_s | V_t = i$ by a factor of $1/h$. Of course, while such scaling preserves the persymmetry of $\mathfrak{L}$, it only makes sense if $0 < h < \min\{1/\gamma_i : i \in N\}$.

2.2 Alternative interpretation

There is another way to represent how new nucleotides are added to a DNA sequence which provides an alternative derivation of the Markov chain on $N$ with one-step transition matrix $P$ of the form (1). Let $(Y_s, s \geq 0)$ be a Markov chain on the set of nucleotides $N$ with transition matrix $K = (K_{ij})_{i,j \in N}$ given by $K_{ij} = L_{ij} / \sum_{k \in N} L_{ik}$. Thus, the one-step transition matrix of $(Y_s, s \geq 0)$ is obtained by converting the positive persymmetric $\mathfrak{L}$ into a stochastic matrix by normalizing its rows to sum to unity. Next, let $(B_s, s \geq 0)$ be a Bernoulli scheme on $N$ with common distribution $M$. Since $(Y_s, s \geq 0)$ is a positive recurrent Markov chain on the finite state space $N$ and $(B_s, s \geq 0)$ is an i.i.d. sequence also on $N$ that is independent of $(Y_s, s \geq 0)$, the joint process $((Y_s, B_s), s \geq 0)$ is a positive recurrent Markov chain on the state space $N \times N$ with one-step transition matrix $(R_{(i,k),(j,l)})_{(i,k),(j,l) \in N^2}$ given by $R_{(i,k),(j,l)} = K_{ij} M_{jl}$.

We shall assume without loss of generality that $Y_0 = B_0$. Define a sequence of stopping times $(T_s, s \geq 0)$ by $T_0 := 0$ and

$T_{s+1} := \min\{t > T_s + 1 : Y_{t-1} = B_{t-1} = Y_{T_s} \text{ and } Y_t = B_t\}$,

for $s \geq 0$. By definition, $Y_{T_s} = B_{T_s}$ for all $s \geq 0$ and $Y_{T_s-1} = B_{T_s-1}$ for all $s \geq 1$. Observe that if $Y_{T_s}$ and $B_{T_s}$ are given, for example, $Y_{T_s} = B_{T_s} = i$, then

$T_{s+1} - T_s = \min\{t > T_s + 1 : Y_{t-1} = B_{t-1} = Y_{T_s} \text{ and } Y_t = B_t\} - T_s = \min\{t > 1 : Y_{t-1} = B_{t-1} = i \text{ and } Y_t = B_t\}$.

Thus, $T_{s+1} - T_s$ is independent of $T_s$ if $Y_{T_s}$ is given. Furthermore, $T_{s+1} - T_s | Y_{T_s} = i$ has the same distribution as $T_1 | Y_0 = i$. Thus, each $T_s$ is a renewal time at which the Markov chain $((Y_s, B_s), s \geq 0)$ is restarted.

Next, define the stochastic process $(X_s, s \geq 0)$ by $X_s := Y_{T_s}$. Since $((Y_s, B_s), s \geq 0)$ is a Markov chain and $(T_s, s \geq 0)$ is a sequence of stopping times at which it renews, one may employ the strong Markov property to deduce that $(X_s, s \geq 0)$ is also a Markov chain. It only remains to compute its one-step transition matrix.
Theorem 2. The Markov chain \((X_s, s \geq 0)\) has one-step transition matrix \(P = (P_{ij})_{i,j \in N}\), where

\[ P_{ij} := \frac{L_{ij}M_j}{\sum_{k \in N} L_{ik}M_k}. \]

Proof. Fix \(X_0 = B_0 = i\) and let \(T := T_1\). Then,

\[
P_{ij} = \Pr(X_1 = j \mid X_0 = i)
= \sum_{t=2}^{\infty} \Pr(Y_T = j, T = t \mid X_0 = i)
= \sum_{t=2}^{\infty} \Pr(Y_t = j \mid T = t, X_0 = i) \Pr(T = t \mid X_0 = i)
= \sum_{t=2}^{\infty} \Pr(Y_t = j, B_t = j \mid Y_t = B_t, Y_{t-1} = i) \Pr(T = t \mid X_0 = i)
= \sum_{t=2}^{\infty} \Pr(Y_t = j, B_t = j \mid Y_{t-1} = i) \Pr(T = t \mid X_0 = i)
= \sum_{t=2}^{\infty} \sum_{k \in N} \Pr(Y_t = k, B_t = k \mid Y_{t-1} = i) \Pr(T = t \mid X_0 = i)
= \sum_{k \in N} \frac{K_{ij}M_j}{\sum_{k \in N} K_{ik}M_k} \sum_{t=2}^{\infty} \Pr(T = t \mid X_0 = i)
= \frac{L_{ij}M_j}{\sum_{k \in N} L_{ik}M_k} \sum_{t=2}^{\infty} \Pr(T = t \mid X_0 = i),
\]

since

\[
\sum_{t=2}^{\infty} \Pr(T = t \mid X_0 = i) = 1
\]

and

\[
\Pr\{Y_t = j, B_t = j \mid Y_{t-1} = i\} = \Pr\{Y_t = j \mid Y_{t-1} = i\} \Pr(B_t = j) = K_{ij}M_j.
\]

Thus, the mechanism by which nucleotides are appended to a DNA sequence according to a Markov chain with transition matrix \(P\) may also be described as follows. Suppose that the last nucleotide in the sequence is of type \(i\). Then, one simply waits until both the Markov chain \((Y_s)\) and the i.i.d. sequence \((B_s)\) simultaneously return to state \(i\) and both immediately jump to the same state, say \(j\). When such a consecutive pair of concordant events occurs, a nucleotide of type \(j\) is appended to the sequence. At this point, this scheme is repeated, but using \(j\) as the initial state, so that one waits for \(A\) coincident return of the two processes to state \(j\) followed by simultaneous transitions to a new state, say \(k\), and so on. The Markov chain \(Y_s\) transitions from \(i\) to \(j\) with probability \(K_{ij}\) while \(B_s\) selects \(j\) with probability \(M_j\). In contrast to the original description given in [18] and in Section [1], two nucleotides of types \(j\) and \(k\) are selected with probabilities \(M_j\) and \(K_{ij}\) respectively and a nucleotide of type \(j\) is then appended to the end of the sequence if and only if they are of the same type. In essence, the mechanism by which nucleotides are appended to the DNA sequence can be thought of as carrying out acceptance rejection sampling, by repeatedly drawing independent sample nucleotides from the distributions \((K_{ij}, j \in N)\) and \(M\) until they agree (assuming \(i\) is the type of the nucleotide at the end of the sequence). In this case, the number of draws needed in order to obtain a suitable nucleotide is a geometric random variable with mean \(1/\sum_{j \in N} K_{ij}M_j\). The first interpretation also amounts to performing acceptance-rejection sampling, but with a two-step procedure in
which a nucleotide type \( j \) is first proposed by sampling it from the distribution \( M \) and then is added to the DNA sequence according to an unfair coin toss with probability \( L_{ij} \).

Finally, we note that if the matrix \( \mathcal{L} \) is rescaled so that \( \sum_{i,j \in \mathbb{N}} L_{ij} = 1 \), it admits the natural interpretation as the stationary dinucleotide probability distribution, that is,

\[
L_{ij} = \Pr(Y_t = i, Y_{t+1} = j), \quad i, j \in \mathbb{N}, \ t \geq 0.
\]

As noted above, \( \mathcal{L} \) remains persymmetric under this kind of rescaling.

### 3 \( \mathcal{L} \)-generated matrices

Let \( \mathcal{S}_4 \) be the set of all \( 4 \times 4 \) stochastic matrices, and let \( \mathcal{L} \) be the cone of positive persymmetric matrices (matrices \( \mathcal{L} = (L_{ij})_{i,j \in \mathbb{N}} \) with positive entries such that \( L_{ij} = L_{\alpha(i)\alpha(j)} \) for all \( i, j \in \mathbb{N} \)). Given \( P \in \mathcal{S}_4 \) we will say that \((P, \pi)\) is a stationary Markov chain if the vector \( \pi = (\pi_i)_{i \in \mathbb{N}} \) is such that \( \pi P = \pi \).

Let \( F : \mathbb{R} \times (0, +\infty) \to \mathcal{S}_4 \) be the map which takes \((\mathcal{L}, m)\) to the matrix \( F(\mathcal{L}, m) \), which is given for all \( i, j \in \mathbb{N} \) by

\[
(f(\mathcal{L}, m))_{ij} := \frac{L_{ij}M_j}{\sum_{k=1}^L L_{ik}M_k}, \quad \text{where} \quad M_{\ell} = \begin{cases} m/(2m+2) & \text{if } \ell = 1, 4, \\ 1/(2m+2) & \text{if } \ell = 2, 3. \end{cases}
\]

Since \( \mathcal{L} \) is a positive matrix and \( m > 0 \), the matrix \( F(\mathcal{L}, m) \) is primitive, that is, irreducible and aperiodic.

**Definition 3.** We say that \( P \in \mathcal{S}_4 \) is \( \mathcal{L} \)-generated if there exist \((\mathcal{L}, m) \in \mathcal{L} \times (0, +\infty)\) such that \( P = F(\mathcal{L}, m) \).

Let \( \Phi : \mathcal{S}_4 \times (0, +\infty) \to \mathcal{L} \) be the map defined for all stochastic matrices \( P, \tilde{m} > 0 \) and \( \tilde{s} > 0 \) by

\[
\Phi(P, \tilde{m}, \tilde{s}) := \tilde{s} \begin{pmatrix}
a_{p, p, 1}^{11} \kappa_p / \tilde{m} & a_{p, p, 1}^{12} / \tilde{m} & 1 & \kappa_p / \tilde{m} \\
a_{p, p, 1}^{21} a_p^m & a_{p, p, 1}^{22} a_p^m & \epsilon_p & \tilde{m} \\
a_{p, p, 1}^{21} a_p^m & a_{p, p, 1}^{22} a_p^m & a_{p, p, 1}^{22} a_p^m & \kappa_p / \tilde{m} \\
a_{p, p, 1}^{11} a_p^m & a_{p, p, 1}^{21} a_p^m & a_{p, p, 1}^{22} a_p^m & 1
\end{pmatrix}, \quad \text{where} \quad \kappa_p := \frac{P_{14} P_{13}}{P_{23} P_{24}}; \quad \epsilon_p := \frac{P_{14} P_{13}}{P_{23} P_{24}}.
\]

From (3) it follows that if \( P \) is an \( \mathcal{L} \)-generated matrix for some \( \mathcal{L} = (L_{ij})_{i,j \in \mathbb{N}} \in \mathcal{L} \) and \( m \in (0, +\infty) \), then the nine ratios that appear in (4) become:

\[
a_{p, p, 1}^{ij} = L_{ij} / L_{\alpha(i)\alpha(j)}; \quad \kappa_p = L_{14} m / L_{13} \quad \text{and} \quad \epsilon_p = L_{23} / L_{24} m.
\]

**Theorem 4.** For any \( \mathcal{L} \)-generated matrix \( P \),

\[
F^{-1}(P) = \left\{ (\Phi(P, \tilde{m}, \tilde{s}), \tilde{m}) : \tilde{m} > 0, \tilde{s} > 0 \right\}.
\]

**Proof.** Let \( P = F(\mathcal{L}, m) \) for some fixed \( \mathcal{L} \in \mathcal{L} \) and \( m > 0 \).

Given \( \tilde{\mathcal{L}} := \Phi(P, \tilde{m}, \tilde{s}) \) for any choice of \( \tilde{m}, \tilde{s} > 0 \), it is straightforward to check that \( F(\tilde{\mathcal{L}}, \tilde{m}) = F(\mathcal{L}, m) = P \). Therefore, \( \{ (\Phi(P, \tilde{m}, \tilde{s}), \tilde{m}) : \tilde{m} > 0, \tilde{s} > 0 \} \subseteq F^{-1}(P) \).

On the other hand, suppose \( \mathcal{L}' = (L'_{ij})_{i,j \in \mathbb{N}} \in \mathcal{L} \) and \( m' > 0 \) are such that \( \mathcal{L}' \in F^{-1}(P) \). Note that, since \( P = F(\mathcal{L}, m) \), it follows from (3) that

\[
a_{p, p, 1}^{ij} = L_{ij} / L_{\alpha(i)\alpha(j)}; \quad \kappa_p = L_{14} m / L_{13} = L_{14} m' / L_{13}'; \quad \epsilon_p = L_{23} / L_{24} m = L_{23} / L_{24} m'.
\]

Hence, \( \mathcal{L}' = \Phi(P, m', L_{13}') \) and so \( F^{-1}(P) \subseteq \{ (\Phi(P, \tilde{m}, \tilde{s}), \tilde{m}) : \tilde{m} > 0, \tilde{s} > 0 \} \), which completes the proof. \( \square \)

Since \( \Phi \) is linear in \( \tilde{s} \), instead of working with \( \Phi \) we can work with the map \( \varphi : \mathcal{S}_4 \times (0, +\infty) \to \mathcal{L} \) defined by

\[
\varphi(P, \tilde{m}) := \Phi(P, \tilde{m}, 1).
\]

Then, \( F^{-1}(P) = \{ (\varphi(P, \tilde{m}), \tilde{m}) : \tilde{m} > 0, \tilde{s} > 0 \} \). The next corollary is a simple consequence of (3) and Theorem 4.
Corollary 5. A stochastic matrix $P$ is $\aleph$-generated if and only if $P$ is obtained by probability-normalizing the rows of the matrix $\mathcal{L} := \varphi(P, 1)$. \hfill \qed

Given a vector $a = (a_1, a_2, a_3, a_4) \in \mathbb{R}^4$, let $D(a)$ be the $4 \times 4$ diagonal matrix with $a$ on its diagonal.

Corollary 6. A stochastic matrix $P$ is $\aleph$-generated if and only if there exists a strictly positive vector $x = (x_i)_{i \in N} \in \mathbb{R}^4$ such that $D(x)P \in \aleph$.

Proof. Suppose that $P$ is $\aleph$-generated and define $x$ to be the vector with elements given by $x_i := \sum_{k=1}^{4} (\varphi(P, 1))_{ik}$. Then, from Corollary 5 we have that $D(x)P = \varphi(P, 1) \in \aleph$.

Conversely, if $D(x)P = \mathcal{L} \in \aleph$ for some $x \in \mathbb{R}^4$, then $P = f(\mathcal{L}, 1)$ and $x$ contains the row sums of $\mathcal{L}$. \hfill \qed

Note that given an $\aleph$-generated matrix $P$, there exist infinitely many vectors $x$ that satisfy the stated property, all of which are collinear. Because of this, we can decide whether or not a stochastic matrix is $\aleph$-generated by setting

$$x_P = \left(\frac{P_{j\alpha(i)}}{P_{i\alpha(j)}}\right)_{i \in N} = \frac{1}{\sum_{k=1}^{4} (\varphi(P, 1))_{jk}} \left(\sum_{k=1}^{4} (\varphi(P, 1))_{ik}\right)_{i \in N},$$

for a fixed $j \in \{1, 2, 3, 4\}$, and checking whether or not $D(x_P)P$ belongs to $\aleph$. Observe that $x_P$ is expressed in terms of elements of $P$. In particular, we can choose

$$x_P = \left(\frac{P_{11}}{P_{11}}, \frac{P_{13}}{P_{21}}, \frac{P_{22}}{P_{33}}, 1\right).$$


4 $\aleph$-families and generators

From the preceding discussion, it is evident that a given $\aleph$-generated stochastic matrix can be generated using any one of a multitude of persymmetric matrices. We proceed to examine this non-uniqueness in greater detail.

Definition 7. The $\aleph$-family of an $\aleph$-generated matrix $P$ is the set

$$\aleph(P) := \{\varphi(P, \tilde{m}) : \tilde{m} > 0\}.$$

The family of generators of an $\aleph$-generated matrix $P$ is the set

$$\aleph_G(P) := \{\varphi(P, \tilde{m}) : \tilde{m} > 0\}.$$

The import of the next theorem is that $\aleph$ can be partitioned into equivalence classes. Firstly, any persymmetric matrix can be used to generate a whole host of $\aleph$-generated matrices simply by varying the value of the parameter $m$. Thus, there are families of persymmetric matrices that give rise to disjoint collections of $\aleph$-generated matrices and these families are mutually exclusive, partitioning the space $\aleph$ into equivalence classes. Secondly, for each $\aleph$-generated matrix $P$, there is a set of persymmetric matrices, each of which generates $P$ when combined with the appropriate value of $m$. This leads to an equivalence relation on the set $\aleph \times (0, \infty)$.

Theorem 8. Suppose $P$ and $Q$ are two $\aleph$-generated matrices. Then:

(i) Either $\aleph(P) \cap \aleph(Q) = \emptyset$ or $\aleph(P) = \aleph(Q)$.

(ii) Either

(a) $\aleph_G(P) \cap \aleph_G(Q) = \emptyset$ and $P \neq Q$; or

(b) $\aleph_G(P) = \aleph_G(Q)$ and $P = Q$.

Proof.
(i) Suppose $\mathcal{N}(P) \cap \mathcal{N}(Q) \neq \emptyset$ and choose an $\Sigma = (L_{ij})_{i,j \in N} \in \mathcal{N}(P) \cap \mathcal{N}(Q)$. Let $m^{(1)}, m^{(2)} \in (0, +\infty)$ be such that $P = f(\Sigma, m^{(1)})$ and $Q = f(\Sigma, m^{(2)})$.

We begin by proving that $\mathcal{N}(P) \subseteq \mathcal{N}(Q)$. Let $\mathfrak{B} = (B_{ij})_{i,j \in N} \in \mathcal{N}(P)$ and let $m^{(3)} > 0$ be such that $P = f(\mathfrak{B}, m^{(3)})$. Since $P$ and $Q$ can be generated by the same $\Sigma$, they share the same ratios $a_{ij}^{P}$ listed in $\Sigma$, that is,

$$a_{ij}^{P} = a_{ij}^{Q} \quad (7)$$

The other two ratios for $P$ will satisfy the following equalities:

$$\kappa_{p} := P_{14}/P_{13} = B_{14}m^{(3)}/B_{13} = L_{14}m^{(1)}/L_{13},$$

$$\epsilon_{p} := P_{23}/P_{24} = B_{23}/B_{24}m^{(3)} = L_{23}/L_{24}m^{(1)},$$

which means that

$$B_{14}m^{(3)}/B_{13}m^{(1)} = L_{14}/L_{13}, \quad \text{and} \quad B_{23}m^{(1)}/B_{24}m^{(3)} = L_{23}/L_{24}. \quad (8)$$

On the other hand, the last two ratios for $Q$ are:

$$\kappa_{q} := Q_{14}/Q_{13} = L_{14}m^{(2)}/L_{13} = B_{14}m^{(3)}/B_{13}m^{(1)} = \frac{m^{(2)}}{m^{(1)}}\kappa_{p},$$

$$\epsilon_{q} := Q_{23}/Q_{24} = L_{23}/L_{24}m^{(2)} = B_{23}m^{(1)}/B_{24}m^{(3)}m^{(2)} = \frac{m^{(1)}}{m^{(2)}}\epsilon_{p}, \quad (9)$$

where the last equality in each line follows from (8).

Setting $\tilde{m} := m^{(2)}m^{(3)}/m^{(1)}$, and taking (7) and (9) together with the last line in the proof of Theorem 4 yields $\varphi(Q, \tilde{m}) = \varphi(P, m^{(3)}) = \mathfrak{B}$. Therefore, $\mathfrak{B} \in \mathcal{N}(Q)$ and so $\mathcal{N}(P) \subseteq \mathcal{N}(Q)$.

Next, let $\mathfrak{B} \in \mathcal{N}(Q)$. By symmetry, another application of the above argument allows us to conclude that $B \in \mathcal{N}(P)$ and hence $\mathcal{N}(Q) \subseteq \mathcal{N}(P)$. Therefore, $\mathcal{N}(P) = \mathcal{N}(Q)$.

(ii) By definition, either $f^{-1}(P) = f^{-1}(Q)$, in which case $P = Q$, or $f^{-1}(P) \cap f^{-1}(Q) = \emptyset$ and $P \neq Q$. Now, $\mathcal{N}(P) \subseteq f^{-1}(P)$ since $f^{-1}(P) = \{s \Sigma : s > 0, \Sigma \in \mathcal{N}(P)\}$, and the result follows.

**Definition 9.** Given an $\mathcal{N}$-generated matrix $P$ and $\tilde{m} \in (0, +\infty)$, we define the $\tilde{m}$-canonical representative of $\mathcal{N}(P)$ to be the matrix $\Sigma_{P,\tilde{m}} := \varphi(P, \tilde{m}/\epsilon_{p})$.

Note that $(\Sigma_{P,\tilde{m}}, \tilde{m}/\epsilon_{p})$ is a generator of $P$. Furthermore, from (8) if $P$ and $Q$ are two $\mathcal{N}$-generated matrices with $\mathcal{N}(P) = \mathcal{N}(Q)$, then $a_{ij}^{P} = a_{ij}^{Q}$, for all $i, j$ and $\kappa_{p}\epsilon_{p} = \kappa_{q}\epsilon_{q}$. This gives

**Corollary 10.** Two $\mathcal{N}$-generated matrices belong to the same $\mathcal{N}$-family if and only if they have identical canonical representatives, that is, if $P$ and $Q$ are $\mathcal{N}$-generated, then

$$\mathcal{N}(P) = \mathcal{N}(Q) \iff \Sigma_{P,1} = \Sigma_{Q,1} \iff \Sigma_{P,\tilde{m}} = \Sigma_{Q,\tilde{m}}, \text{ for all } \tilde{m} > 0. \quad \square$$

## 5 Properties of $\mathcal{N}$-generated matrices

Given the stationary Markov chain $(P, \pi)$, consider the following related stationary Markov chains: $(P^{\alpha}, \pi^{\alpha})$ is the complement Markov chain of $(P, \pi)$, where $P_{ij}^{\alpha} := P_{\alpha(i)\alpha(j)}$ and $\pi_{i}^{\alpha} := \pi_{\alpha(i)}$; $(P^*, \pi^*)$ denotes the reverse Markov chain of $(P, \pi)$, where $P_{ij}^{*} := \pi_{j}P_{ij}/\pi_{i}$ and $\pi_{i}^{*} := \pi_{i}$; and $(\bar{P}, \bar{\pi})$ is the reverse complement Markov chain of $(P, \pi)$, where $\bar{P}_{ij} = \pi_{\alpha(j)}P_{\alpha(i)\alpha(j)}/\pi_{\alpha(i)}$ and $\bar{\pi}_{i} = \pi_{\alpha(i)}$. Note that $\bar{P} = (P^{\alpha})^{*} = (P^{*})^{\alpha}$ and $\bar{\pi} = (\pi^{\alpha})^{*} = (\pi^{*})^{\alpha}$. The names complement, reverse and reverse complement come from the genetics and Markov chains literature, referring to several kinds of relationship that can exist between nucleotide sequences (genetics), as well as Markov chains.

**Theorem 11.** The matrices $P$, $P^{\alpha}$, $P^{*}$ and $\bar{P}$ are either all $\mathcal{N}$-generated or none of them are.
Proof. Assume $P$ is $\aleph$-generated and take $\Sigma := \varphi(P, 1) = (L_{ij})_{i,j \in \aleph}$.

Define $\Sigma^\alpha = (L^\alpha_{ij})_{i,j \in \aleph} \in \aleph$, where $L^\alpha_{ij} := L_{\alpha(i)\alpha(j)}$. Then,

$$P^\alpha_{ij} = P_{\alpha(i)\alpha(j)} = \frac{L_{\alpha(i)\alpha(j)}}{\sum_{k=1}^{\aleph} L_{\alpha(i)k}} = \frac{L^\alpha_{ij}}{\sum_{k=1}^{\aleph} L^\alpha_{ik}}, \quad i,j \in \aleph$$

and $P^\alpha$ is $\aleph$-generated with $P^\alpha = f(\Sigma^\alpha, 1)$.

To check that $P$ is $\aleph$-generated implies that $P^*$ is also $\aleph$-generated, it suffices by Corollary to set $x_{P^*} = \left(\frac{P^*_{j1}}{P^*_{11}}, \frac{P^*_{j2}}{P^*_{12}}, \frac{P^*_{j3}}{P^*_{13}}, 1\right)$ and prove that $D(x_{P^*})P^* \in \aleph$. In fact, $(D(x_{P^*})P^*)_{ij} = (D(x_{P^*})P^*)_{\alpha(i)\alpha(i)}$ because

$$(D(x_{P^*})P^*)_{ij} = (x_{P^*})_{ij}P^* = \frac{P^*_{\alpha(i)4}}{P^*_{11}} \frac{P^*_{\alpha(i)4} \pi_j}{\pi_i} P^*_{ji} = \frac{\pi_j \pi_{\alpha(i)}}{\pi_1 \pi_4} \frac{P^*_{\alpha(i)4}}{P^*_{11}} P^*_{ji}$$

and similarly

$$(D(x_{P^*})P^*)_{\alpha(i)\alpha(i)} = \frac{\pi_j \pi_{\alpha(i)}}{\pi_1 \pi_4} \frac{P^*_{\alpha(i)4}}{P^*_{11}} P^*_{\alpha(i)\alpha(i)}.$$

while

$$\frac{P^*_{\alpha(i)4}}{P^*_{11}} P^*_{ji} = \frac{L_{\alpha(i)4}}{\sum_{k=1}^{\aleph} L_{\alpha(i)k}} \frac{L_{ji} \sum_{k=1}^{\aleph} L_{ik}}{\sum_{k=1}^{\aleph} L_{ik}} = \frac{L_{\alpha(i)4}}{\sum_{k=1}^{\aleph} L_{\alpha(i)k}} \frac{L_{1j} \sum_{k=1}^{\aleph} L_{1k}}{\sum_{k=1}^{\aleph} L_{1k}} = \frac{L_{\alpha(i)\alpha(j)}}{\sum_{k=1}^{\aleph} L_{\alpha(i)k}} \frac{L_{j1} \sum_{k=1}^{\aleph} L_{jk}}{\sum_{k=1}^{\aleph} L_{jk}} = \frac{P^*_{\alpha(i)4}}{P^*_{11}} P^*_{\alpha(i)\alpha(i)}.$$

Next, to check that $\hat{P}$ is $\aleph$-generated given that $P$ is $\aleph$-generated, we need only note that $\hat{P} = (P^*)^*$ and apply the above two results one after the other.

The proof is completed by realising that $P = (P^\alpha)^* = (P^*)^* = \hat{P}$ and hence being $\aleph$-generated is a solidarity property of the four matrices.$\square$

Most bacterial DNA sequences can be segmented into two halves called chirochore[4] and the two stationary Markov chains that empirically approximate their first-order structure are reverse complements of each other[18]. If the DNA sequence conforms to the S-H model then the dinucleotide distribution in one of the chirochore is approximated by $(P, \pi)$ with $P$ being $\aleph$-generated. However, it was an open question as to whether or not the other chirochore would also be approximated by an $\aleph$-generated Markov chain. Theorem[11] above answers this question in the positive.

Furthermore, it is common to find that the stationary Markov chain $(W, \omega)$ that approximates the first-order structure of an entire DNA sequence satisfies intra-strand parity[1,7], that is, $\omega_iW_{ij} = \omega_{\alpha(i)\alpha(j)}W_{\alpha(i)\alpha(j)} = \tilde{\omega}_iW_{ij}$ for all $i,j \in \aleph$. Intra-strand parity has been observed in the DNA sequences of many organisms such as Bacteria, archaea, plants and animals, but not in other sequences such as those from single-stranded viruses and organelles. The next theorem relates intra-strand parity of dinucleotides to the $\aleph$-generated matrices (cf. the direct characterisation in [7 Proposition 1]) and shows that $\aleph$-generated matrices satisfy a weaker property than intra-strand parity.

**Theorem 12.** Let $(W, \omega)$ be a stationary Markov chain. Then $(W, \omega)$ satisfies $\omega_iW_{ij} = \omega_{\alpha(i)\alpha(j)}W_{\alpha(i)\alpha(j)}$ for all $i,j \in \aleph$ if and only if it is $\aleph$-generated and the matrix $\Sigma := \varphi(W, 1) = (L_{ij})_{i,j \in \aleph}$ that generates it satisfies $S_i = S_{\alpha(i)}$ for $i \in \aleph$, where $S_i := \sum_{k=1}^{\aleph} L_{ik}$. Furthermore, if $W$ complies with intra-strand parity, then its stationary distribution $\omega$ can be explicitly expressed as $\omega = \frac{1}{2(S_1+\sum_{j=1}^{\aleph}) (S_1, S_2, S_2, S_1)}$.

**Proof.**

$[(\rightarrow)]$ It can be seen that $W$ is $\aleph$-generated by observing that $(D(\omega)W)_{ij} = \omega_iW_{ij} = \omega_{\alpha(i)\alpha(j)}W_{\alpha(i)\alpha(j)} = (D(\omega)W)_{\alpha(i)\alpha(j)}$. Next, let $\Sigma = \varphi(W, 1)$. One can easily check that $\omega_iW_{ij} = \omega_{\alpha(j)}W_{\alpha(j)\alpha(i)}$, for $i,j \in \aleph$, implies $\omega_i = \omega_{\alpha(i)}$ for all $i \in \aleph$. Therefore, $\omega_iL_{ik} = \omega_{\alpha(i)}L_{\alpha(i)k} = \omega_iL_{ik} = \sum_{k=1}^{\aleph} L_{\alpha(i)k}$, for all $i \in \aleph$, and hence $\sum_{k=1}^{\aleph} L_{ik} = \sum_{k=1}^{\aleph} L_{\alpha(i)k}$.
Suppose $W$ is obtained by normalizing the rows of a matrix $\mathcal{L} = (L_{ij})_{i,j \in N} \in \mathbb{R}$, that is, $W = \left(\frac{L_{ij}}{S_i}\right)_{i,j \in N}$, where $S_i := \sum_{k=1}^4 L_{ik}$. Suppose that $\mathcal{L}$ satisfies $S_i = S_{\alpha(i)}$ for $i = 1, 2$. It is easy to check that $\omega := \frac{1}{2(S_1 + S_2)}(S_1, S_2, S_2, S_1)$ is the stationary distribution of $W$. Hence, it follows that for all $i, j \in N$,

$$\omega_i W_{ij} = \frac{S_i}{2(S_1 + S_2)} \frac{L_{ij}}{S_i} = \frac{L_{ij}}{2(S_1 + S_2)} = \frac{S_{\alpha(j)}}{2(S_1 + S_2)} \frac{L_{\alpha(j)\alpha(i)}}{S_{\alpha(j)}} = \omega_{\alpha(j)} W_{\alpha(j)\alpha(i)}.$$

\[\square\]

6 Applications and final remarks

This article has given a mathematical analysis of the S-H model and elucidated its properties. We conclude with some remarks about the application of the results that have been presented here. Corollary \(\text{[12]}\) provides a way of deciding whether or not two or more $\mathcal{N}$-generated matrices can be generated from a single persymmetric matrix $\mathcal{L}$ in conjunction with different values of the parameter $m$. Meanwhile, Theorem \(\text{[12]}\) shows that intra-strand parity in dinucleotides is a special case of $\mathcal{N}$-generated matrices. Possessing a weaker structure than that encapsulated by $\mathcal{N}$-generated matrices, it is possible that $\mathcal{N}$-generated matrices may be useful for capturing the dinucleotide structure in genomic sequences that do not exhibit intra-strand parity.

For the purposes of applications, corollaries \([5]\) and \([3]\) are useful for constructing measures of how close the estimated stationary Markov chain of a bacterial DNA sequence is to being $\mathcal{N}$-generated. Given $P \in \mathcal{S}_4$, we can define the following two examples of such measures:

\textbf{Measure 1:} Let $\text{proj}(Q)$ be the orthogonal projection of a $4 \times 4$ positive matrix $Q$ onto $\mathcal{N}$, and define

$$\delta_1(P) := \min_{x = (x_1, x_2, x_3, 1)} \left\| D(x)P - \text{proj}(D(x)P) \right\|.$$

The quantity $\delta_1(P) = 0$ if and only if $P$ is $\mathcal{N}$-generated. Otherwise, $\delta_1(P)$ gives the minimal distance between some matrix $D(x)P$ which generates $P$ according to the model (but which does not belong to $\mathcal{N}$) and the space $\mathcal{N}$. Note that $\delta_1(P)$ can be analytically computed. The minimum in the expression for $\delta_1(P)$ is attained at the point $x = (x_1, x_2, x_3, 1)$, where

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} = \begin{pmatrix} p_{11}^2 + p_{12}^2 + p_{13}^2 \\ -p_{13}p_{24} \\ -p_{12}p_{34} \end{pmatrix} \begin{pmatrix} -p_{24}p_{13} \\ p_{21}^2 + p_{22}^2 + p_{24}^2 \\ -p_{23}p_{22} \end{pmatrix}^{-1} \begin{pmatrix} p_{34}p_{12} \\ -p_{31}^2 + p_{32}^2 + p_{34}^2 \\ p_{32}p_{31} \end{pmatrix}.$$

\textbf{Measure 2:} Let $\epsilon$ be a $4 \times 4$ matrix, $P(\epsilon) := P + \epsilon$, and $x = (x_1, x_2, x_3, 1)$ be a positive vector. Define $\delta_2(P)$ as the solution of the following optimization problem:

$$\min \sum_{i,j \in N} \epsilon_{i,j}^2 \quad \text{subject to} \quad \begin{cases} P(\epsilon) \in \mathcal{S}_4; \\ D(x)P(\epsilon) - \text{proj}(D(x)P(\epsilon)) = 0. \end{cases}$$

As was the case with $\delta_1(P)$, we have $\delta_2(P) = 0$ if and only if $P$ is $\mathcal{N}$-generated, otherwise, $\delta_2(P)$ gives the shortest squared Frobenius distance between $P$ and some $\mathcal{N}$-generated stochastic matrix. There being no closed-form solution to the optimization problem, the computation of $\delta_2(P)$ would need to be implemented using numerical methods.

Finally, the development of statistical hypothesis tests based on these measures together with further statistical analyses and their application to real bacterial genomes are planned for future publication.

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