Embeddability of Kimura 3ST Markov matrices

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Abstract

In this note, we characterize the embeddability of general Kimura 3ST Markov matrices in terms of their eigenvalues. As a consequence, we are able to compute the volume of such matrices and compare it to the volume of all Markov matrices within the model. Moreover, we provide an example showing that, in general, mutation rates are not identifiable from substitution probabilities under the Kimura 3ST model. This example also illustrates that symmetries between mutation probabilities do not necessarily translate into symmetries between the corresponding mutation rates.

1 Introduction

Genomic data expressed by means of sequence alignments is widely used to infer phylogenetic relationships between species. Substitution models are used to describe the evolutionary process that leads from one DNA sequence to another. These models are usually given in terms of a family of Markov matrices with a prescribed structure. The entries of these matrices represent the conditional probabilities of nucleotide substitution between one sequence and the other. Usually, the structure imposed by the model is explained by some biological / biochemical properties observed (e.g. the Kimura 3ST model [Kim81]) or some computational /mathematical convenient assumption to deal with the model (e.g the General Time-Reversible model [Tav86]). Markov chains are useful to model evolution and presume that all sites in the sequences evolve independently and according to the same probabilities. A general assumption in modelling evolution corresponds to regarding time as a continuous variable where substitution events always happen at the same rate, which remains constant throughout the whole evolutionary process. This leads to the homogenous continuous-time substitution models, where only Markov matrices that are the exponential of a rate matrix are considered. Clearly this is used as an approximation to biological reality where it is well known that transition rates vary over time [HPCD05, HSP10] and also among the different branches of the phylogenetic tree [LSB98]. However, given the bias / variance compensation of the statistical analysis [BA02], modelling phylogenetic evolution as a non-homogeneous process is not statistically feasible in practice (cf. [SFSJ12]).

A different approach appears when one regards the evolutionary process as a whole and only takes into account the conditional probabilities between the original and the final sequences, without caring about local rates or intermediate probabilities. Counting relative frequencies of substitution leads to a Markov matrix, which in general, will not be of exponential form. This approach leads to the so-called algebraic models, where “algebraic” refers to the fact that the probabilities of pattern observation at the leaves of a phylogenetic tree evolving under these models are given by algebraic expressions in terms of the parameters of the model, that is, the substitution probabilities rather than the rates.

A natural question is then to decide whether the obtained Markov matrix is the exponential of some rate matrix, whose entries would be some kind of average of the rates involved throughout the evolutionary process. This question is known in the literature as the embedding problem for Markov matrices. The reader is referred to [Dav10] for a nice overview of the problem from a mathematical point of view, and what is known in general for $n$-dimensional matrices. In a more biological and applied setting, the paper by Verbyla et al. [VYP13] deals with this problem and the possible consequences for phylogenetic inference.

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In this note, we deal with the embedding problem from a more theoretical perspective. The goal is to obtain a characterization for the embeddability for the matrices of the Kimura 3ST model \[Kim81\]. From our results, we will be able to compute the whole volume of embeddable Kimura 3ST matrices and compare it with the volume of the whole space of Markov Kimura 3ST matrices.

The organization of this note is as follows. In section 2, we recall some definitions and basic facts concerning the embedding problem and the Kimura 3 parameter model. In section 3, we prove the main theorem which characterizes those Markov Kimura 3ST matrices being embeddable in terms of inequalities to be satisfied by the eigenvalues. As a consequence of this result, in section 4, we are able to compute the volume of embeddable matrices and compare it to the volume of all Markov Kimura 3ST matrices. Finally, we conclude in Section 5 discusses implications and possibilities for future work with some easy implications for submodels and possibilities of future work.

## 2 Preliminaries

We denote by $M_k(K)$ the space of all square $k$-matrices with entries in a field $K$, where $K$ is $\mathbb{R}$ or $\mathbb{C}$. Given a matrix $A \in M_k(K)$, we say that $B \in M_k(K)$ is a logarithm of $A$ if $e^B = A$, where the exponential of a matrix is defined as

$$e^X = \sum_{n \geq 0} \frac{X^n}{n!}.$$  

It is easy to see that $\det(e^X) = e^{\det(X)}$, so the determinant of any matrix of the form $e^X$ is never 0. Given a non-negative complex number $x \in \mathbb{C} \setminus \mathbb{R}_-$, we will denote by $\log(x)$ its principal logarithm, that is, the only logarithm of $x$ that lies in the strip $\{z \mid -\pi < \text{Im}(z) < \pi\}$. Although the exponential map of matrices is far from being injective, it is known that if $A$ is a matrix with no negative eigenvalues, there is a unique logarithm $X$ of $A$ all of whose eigenvalues are given by the principal logarithm of the eigenvalues of $A$ (Theorem 1.31 of \[Hig08\]). We will refer to this as the principal logarithm of $A$ and we will denote it by $\text{Log}(A)$. In the particular case where the matrix $A$ is diagonalizable, $A = SDS^{-1}$ then $\text{Log}(A) = S\text{Log}(D)S^{-1}$, where $\text{Log}(D)$ is the diagonal matrix with diagonal entries equal to the principal logarithm of the eigenvalues of $A$.

**Definition 2.1.** A matrix $M \in M_k(\mathbb{R})$ is said to be a Markov matrix if all the entries are non-negative and the rows sum to one.

A matrix $Q \in M_k(\mathbb{R})$ is said to be a rate matrix if all the non-diagonal entries are non-negative and the rows sum to zero.

If $Q$ is a rate matrix, it is well-known that $e^{tQ} = \sum_{n \geq 0} \frac{t^n Q^n}{n!}$ is a Markov matrix for all $t \geq 0$. That is why rate matrices are also referred as Markov generators \[Dav10\]. However, not every Markov matrix can be obtained in this way. A Markov matrix $M$ is said to be embeddable if $M = e^Q$ for some rate matrix $Q$. The embedding problem tries to decide which (Markov) matrices are embeddable, that is, which matrices can be written as $M = e^Q$, where $Q$ is a rate matrix.

In this work we deal with the substitution model introduced by Kimura in \[Kim81\]. The Kimura 3ST model assigns different parameters to different type of substitutions: one parameter for transitions, i.e. substitutions between purines ($A \leftrightarrow G$) or pyrimidines ($C \leftrightarrow T$), and two parameters for transversions, i.e. substitutions that change the type of nucleotide: from purine to pyrimidine or vice versa. Ordering the set of nucleotides as $A, G, C, T$, the Markov matrices within the model are described by the following structure:

**Definition 2.2.** A matrix $M \in M_4(\mathbb{C})$ is Kimura with 3 parameters (K3 for short) if it has the following structure:

$$M = \begin{pmatrix} a & b & c & d \\ b & a & d & c \\ c & d & a & b \\ d & c & b & a \end{pmatrix}. $$

For ease of reading we will use the notation $M = K(a, b, c, d)$. 

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When $M$ is a Markov matrix, the structure above describes the symmetry between the substitution probabilities of the Kimura 3ST model. Keeping the order of the nucleotides, if $i, j = A, G, C, T$, the $(i, j)$-entry corresponds to the probability of nucleotide $i$ being replaced by nucleotide $j$. The submodels of Kimura 3ST model, namely Kimura 2ST [Kim80] and Jukes-Cantor [JC69], appear when more symmetries are considered: $c = d$ and $b = c = d$, respectively.

The following lemma claims that K3 matrices are strongly connected to the following Hadamard matrix:

$$S := \begin{pmatrix}
1 & 1 & 1 & 1 \\
1 & 1 & -1 & -1 \\
1 & -1 & 1 & -1 \\
1 & -1 & -1 & 1
\end{pmatrix}.$$

Note that $S^2 = 4 \cdot Id$, thus $S^{-1} = \frac{1}{4}S$.

**Lemma 2.3.** A matrix is K3 if and only if it can be diagonalized through $S$. In this case, $K(a, b, c, d) = SDS^{-1}$, where

$$D = \text{diag}(a + b + c + d, a + b - c - d, a - b + c - d, a - b - c + d).$$

In particular, a K3 matrix is real if and only if its eigenvalues are all real numbers.

**Proof.** The proof is straightforward and follows by direct computation.

3 Kimura matrices with no repeated eigenvalues

The first result of this section describes how to compute the principal logarithm of a K3 Markov matrix and characterizes when it is a Markov generator.

First, we need a lemma which follows easily from the definition of the exponential matrix.

**Lemma 3.1.** Let $Q$ be a logarithm of $M$. If $v$ is an eigenvector of $Q$ with eigenvalue $\mu$, then $v$ is an eigenvector of $M$ with eigenvalue $e^\mu$.

**Theorem 3.2.** Let $M$ be a K3 Markov matrix with non-negative eigenvalues $1, x, y, z$. Then,

i) the principal logarithm is equal to $\log(M) = S \text{diag}(0, \log(x), \log(y), \log(z)) S^{-1}$.

ii) $\log(M)$ is a Markov generator if and only if

$$x \geq yz, \quad y \geq zx, \quad z \geq xy. \quad (1)$$

**Proof.** (i) First of all, note that since $M$ is a K3 Markov matrix, all the eigenvalues are necessarily real (Lemma 2.3), and positive by assumption. If $Q = S \text{diag}(0, \log(x), \log(y), \log(z)) S^{-1}$, it is straightforward to check that $e^Q = M$. The first claim follows by the uniqueness of the principal logarithm.

(ii) $\Rightarrow$ Using Lemma 2.3 we have $\log(M) = K(\alpha, \beta, \gamma, \delta)$, where $\alpha = \frac{1}{4}(\log(x) + \log(y) + \log(z))$, $\beta = \frac{1}{4}(\log(x) - \log(y) - \log(z))$, $\gamma = \frac{1}{4}(\log(y) - \log(x) - \log(z))$ and $\delta = \frac{1}{4}(\log(z) - \log(x) - \log(y))$. We only need to check that the non-diagonal entries $\beta$, $\gamma$ and $\delta$ of $\log(M)$ are non-negative if and only if the inequalities (1) are satisfied. This is straightforward: for instance,

$$\beta \geq 0 \iff \frac{\log(x) - \log(y) - \log(z)}{4} \geq 0 \iff \log\left(\frac{x}{yz}\right) \geq 0 \iff x \geq yz.$$

The other inequalities are proved similarly.

**Theorem 3.3.** If a K3 matrix $M \in M_4(\mathbb{R})$ with no repeated eigenvalues has a real logarithm, say $Q$, then all the eigenvalues of $M$ are positive. Moreover, in this case the matrix $Q$ is K3 and unique.
Proof. Because of Lemma 3.1, if the matrix $M$ has no repeated eigenvalues, then $M$ and $Q$ have the same eigenvectors. In particular, they both diagonalize through the matrix $S$ and hence $Q$ must be K3 (Lemma 3.3). Now, let $\mu_2, \mu_3, \mu_4$ be the eigenvalues of $Q$, which are real because so is $Q$. Then the eigenvalues $e^{\mu_2}, e^{\mu_3}, e^{\mu_4}$ of $M$ are necessarily positive. Since $Q$ is K3, it is completely determined by its eigenvalues. □

Corollary 3.4. Let $M$ be a K3 Markov matrix with no repeated eigenvalues. Then $M$ is embeddable if and only if the eigenvalues $x, y, z$ of $M$ are strictly positive, and satisfy

$$x \geq y, y \geq x, z \geq xy.$$  

Proof. It follows directly from theorems 3.2 and 3.3. □

Example 3.5. Although the previous results avoid the case of matrices with repeated eigenvalues, there are some theoretically interesting examples arising from these matrices showing that there are embeddable K81 matrices with negative eigenvalues. Namely, the Markov matrix

$$M = \frac{1}{4} \begin{pmatrix} 1 + e^{-3\pi} - 2e^{-4\pi} & 1 + e^{-6\pi} + 2e^{-4\pi} & 1 - e^{-3\pi} & 1 - e^{-3\pi} \\ 1 + e^{-3\pi} + 2e^{-4\pi} & 1 + e^{-6\pi} - 2e^{-4\pi} & 1 - e^{-3\pi} & 1 - e^{-3\pi} \\ 1 - e^{-3\pi} & 1 - e^{-3\pi} & 1 + e^{-3\pi} - 2e^{-4\pi} & 1 + e^{-6\pi} + 2e^{-4\pi} \\ 1 - e^{-3\pi} & 1 - e^{-3\pi} & 1 + e^{-3\pi} + 2e^{-4\pi} & 1 + e^{-6\pi} - 2e^{-4\pi} \end{pmatrix}$$

has eigenvalues $1, e^{-3\pi}$ and $-e^{-4\pi}$ with multiplicity 2. We could extend the principal logarithm to $M$ by allowing matrices with eigenvalues in the strip $\{z \mid -\pi < \text{Im}(z) \leq \pi\}$. In this case, the matrix $Q = S \text{diag}(\log(x), \log(y), \log(z)) S^{-1}$ has still K3 form but it is not real as it has non-real eigenvalues:

$$Q = \frac{1}{4} \begin{pmatrix} -11\pi + 2\pi i & 5\pi - 2\pi i & 3\pi & 3\pi \\ 5\pi - 2\pi i & -11\pi + 2\pi i & 3\pi & 3\pi \\ 3\pi & 3\pi & -11\pi + 2\pi i & 5\pi - 2\pi i \\ 3\pi & 3\pi & 5\pi - 2\pi i & -11\pi + 2\pi i \end{pmatrix}.$$

Nonetheless, $M$ is embeddable, and here we show a couple of Markov generators for it:

$$Q_1 = \frac{1}{4} \begin{pmatrix} -11\pi & 5\pi & 5\pi & \pi \\ 5\pi & -11\pi & \pi & 5\pi \\ \pi & 5\pi & -11\pi & 5\pi \\ 5\pi & \pi & 5\pi & 11\pi \end{pmatrix} \quad Q_2 = \frac{1}{4} \begin{pmatrix} -11\pi & 5\pi & \pi & 5\pi \\ 5\pi & -11\pi & 5\pi & \pi \\ 5\pi & \pi & -11\pi & 5\pi \\ \pi & 5\pi & 5\pi & 11\pi \end{pmatrix}.$$

Remark 3.6. Note that the eigenvalues of the example above do not satisfy the inequalities of Corollary 3.4. In particular, the assumptions of different and non-negative eigenvalues are necessary for these inequalities to characterize the embeddability of K3 Markov matrices. The example above also shows that a K3 Markov matrix $M$ with repeated negative eigenvalues can be embeddable, even if the extended principal logarithm, which has K3 form, is not real. Actually, such a matrix does not have any Markov generator $Q$ with K3 form as this would mean that $Q$ has real eigenvalues (Lemma 3.1) in contradiction with Lemma 3.1. Note that this fact seems to be inconsistent with the original approach of Kimura models via mutation rates, where the symmetries between transition and transversion probabilities tries to be captured not only by the Markov matrices but also by the rate matrices [Kim80, Kim81].

Finally, the existence of two or more Markov generators for the same Markov matrix demonstrates that in general, mutation rates are not identifiable from the mutation probabilities.

4 The volume of embeddable K3 matrices

Roughly speaking, the goal of this section is to measure how many K3 Markov matrices we are rejecting when the continuous-time approach is considered. To this aim, we proceed to represent K3 Markov matrices in a geometrical way as follows (cf. [CFS08]).

Since the rows of K3 matrices sum $a + b + c + d$, the first eigenvalue of K3 Markov matrices must be equal to one. From Lemma 3.3 it is clear that every K3 Markov matrix is determined by the set of the
other eigenvalues $x := a + b - c - d$, $y := a - b + c - d$, $z := a - b - c + d$. This allows us to identify these matrices with coordinates in a 3-dimensional space, so that the space of all K3 Markov matrices describe a 3-dimensional simplex (a regular tetrahedron) with vertices $p_1 = (1, 1, 1), p_2 = (1, -1, -1), p_3 = (-1, 1, -1)$ and $p_4 = (-1, -1, 1)$, corresponding to the identity matrix, and the permutation matrices $P_{(AC)(GT)}, P_{(AC)(CT)}$ and $P_{(AT)(CG)}$, respectively. The centroid of this simplex has coordinates (eigenvalues) $O = (0, 0, 0)$ and corresponds to the matrix

$$M = \frac{1}{4} \begin{pmatrix} 1 & 1 & 1 \ 1 & 1 & 1 \ 1 & 1 & 1 \ 1 & 1 & 1 \end{pmatrix}.$$  

According to this representation, the Jukes-Cantor matrices [JC69] \((b = c = d)\) correspond to the line between the identity vertex and the centroid of the simplex \((x = y = z)\), while Kimura 2ST matrices [Kim80] \((c = d)\) correspond to a plane section of the simplex \((y = z)\).

Denote by $\varepsilon$ the space of embeddable K3 matrices. Then,

**Proposition 4.1.** $V(\mathcal{E}) = 1/4$.

**Proof.** We can restrict the computation to Markov matrices with no repeated eigenvalues since within the space of all K3 Markov matrices, the subspace of matrices with two or more repeated eigenvalues has measure (i.e. volume) 0. This is because these matrices are constrained by nontrivial algebraic constraints, which make the dimension of the corresponding subspace necessarily smaller.

Therefore, we can take the space $\mathcal{E}$ as the space defined by the inequalities \([1]\). The computation follows easily by cutting the space $\mathcal{E}$ with planes of the form $z = a$ for $a \in [0, 1]$. Then, we obtain a shape like Figure 2. We are led to compute the following integral

$$V(\mathcal{E}) = \int_0^1 \left( \int_0^z \int_{z/x}^{x/z} dy \, dx + \int_0^1 \int_{z/x}^{x/z} dy \, dx \right) \, dz$$

which can be easily shown to be equal to 1/4.

It is straightforward to compute the volume of the space of all K3 Markov matrices from the geometric description above. By applying the well-known formula for the volume of a tetrahedron, we obtained

$$V(K3) = \frac{1}{6} |\det(p_1p_2^2, p_1p_3^3, p_1p_4^4)| = 8/3.$$  

These values illustrate the relative size between the spaces of Markov matrices considered by the original continuous-time approach and the algebraic approach. We note there is a big difference as $V(K3)/V(\varepsilon) \sim 10.67$. 

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**Figure 1:** Simplex representing all Markov K3 matrices. Each matrix is represented by its eigenvalues.
As a compromise solution, we could consider those K3 Markov matrices with positive eigenvalues. It seems clear that any K3 Markov matrix with a negative eigenvalue is too far away from the identity matrix to be considered as biologically realistic (for the expected number of substitutions for such matrices would be infinite). We proceed to compute the volume of these matrices. Write $K_3^+$ for this space, and write $q_2$, $q_3$ and $q_4$ for the midpoints of the edges concurrent at $p_1$ in the K3ST simplex. Then $K_3^+$ is easily decomposed into two tetrahedra: one with vertices $p_1$, $q_2$, $q_3$ and $q_4$, and the other with vertices $q_2$, $q_3$ and $q_4$ and the centroid $O$. Using the same formula as above, we obtain

$$V(K_3^+) = \frac{1}{6} + \frac{1}{3} = \frac{1}{2}.$$  

5 Discussion

In this paper, we have discussed the embedding problem for Markov matrices within the Kimura 3-parameter model. We have obtained a characterization of embeddability for this model under the restriction that there are not repeated eigenvalues. As a byproduct, we have been able to compute and compare the volume of embeddable K3 Markov matrices within the whole space of K3 Markov matrices.

The results obtained here also give information about the evolutionary submodels of Kimura 3ST: Kimura 2ST [Kim80] and Juke-Cantor [JC69].

Jukes-Cantor model is the model obtained when $b = c = d$. It is well-known that all such Markov matrices have eigenvalues 1 and some $\lambda \in \mathbb{R}$ with multiplicity 3. It holds that a necessary condition for a Markov Jukes-Cantor matrix to be embeddable is that $\lambda$ is positive: otherwise, the determinant of $M$ would be negative against the formula $\det(e^Q) = e^{\text{tr}(Q)}$. It follows from Theorem 3.2 that a Markov Jukes-Cantor matrix is embeddable if and only if its eigenvalue $\lambda$ is strictly positive. An easy computation shows that the space the embeddable Jukes-Cantor matrices has volume $\sqrt{3}$ while the space of all Markov Jukes-Cantor matrices has volume $\frac{4}{3}\sqrt{3}$.

Kimura 2ST arises when we impose $b = d$ in the Markov matrix. This is equivalent to require the
second and fourth eigenvalues of Markov matrices in Lemma 2.3 to be equal. The characterization of embeddable K2 matrices is much more technical and we defer it to a forthcoming publication.

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