CLOSED CODON MODELS: JUST A HOPELESS DREAM?

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ABSTRACT. The “Lie closure” of a set of matrices is the smallest matrix Lie algebra (a linear space of matrices closed under the operation \([A, B] = AB - BA\)) which contains the set. In the context of Markov chain theory, if a set of rate matrices form a Lie algebra, their corresponding Markov matrices are closed under matrix multiplication, which has been found to be a useful property in phylogenetics. Inspired by previous research involving Lie closures of DNA models, it was hypothesised that finding the Lie closure of a codon model could help to solve the problem of mis-estimation of the synonymous/non-synonymous rate ratio, \(\omega\). There is a second method of finding a Lie algebra associated to a model: instead of beginning the Lie closure process with the smallest linear space that contains the model (the linear closure), we change any non-linear constraints of the model to additive ones, which results in an alternative linear space for which the Lie closure is found. Under both processes, it was found that closed codon models would require thousands of parameters and any partial solution to this problem that was of a reasonable size violated stochasticity. Investigation of toy models indicated that finding the Lie closure of matrix linear spaces which deviated only slightly from a simple model resulted in a Lie closure that was close to having the maximum number of parameters possible. Given that Lie closures are not practical, we propose further consideration of the variants of linearly closed models.

1. Introduction

It is of interest to evolutionary biologists to determine what biological and chemical mechanics contribute to the evolution of genomes. By making comparisons between rates of substitutions in amino acids, the changes in the functionality of a genome can be inferred. Alternatively, a comparison of rates of substitutions of DNA nucleotides allows observation of the underlying random processes of genome evolution. Both the studies of functionality and underlying processes are of interest to biologists as their simultaneous consideration allows for more accurate modeling of evolutionary data. The analysis of codons (triplets of DNA, each of which codes for an amino acid) allows one to analyse factors of both DNA rates of change and amino acid rates of change at once.

A typical characteristic of codon models is inclusion of the synonymous/non-synonymous relative rate, \(\omega\), as a model parameter. A synonymous mutation is one between two codons that code for the same amino acid and hence the functionality of the gene does not change under such a mutation. For example codons AAA and AAG both code for the amino acid lysine so a mutation from AAA to AAG is synonymous. A non-synonymous mutation is one where the amino acid does change. For example AAA and AAC code for amino acids lysine and asparagine respectively, so a mutation between these codons would change the functionality of the gene. \(\omega\) is the relative rate of synonymous to non-synonymous mutations.

As there are four DNA nucleotides, there are 64 \((= 4 \times 4 \times 4)\) codons which may lead one to think that such a model would be computationally expensive to use when it is considered that the maximum number of free parameters for a codon model would be 4032 \((= 64 \times 64 - 64)\). Despite this, codon models currently in use can simultaneously model aspects of both functionality of a gene and underlying DNA process with as few as two free parameters. The branch-site codon models described in [16], for example, take into account proportion/s of codon sites conforming to value

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ranges of ω meaning that the proportion value/s are the parameters; there can be as few as one of these. The Muse-Gaut codon model [9] (from now referred to as MG) takes into account ω and the frequency of DNA nucleotides; a total of four free parameters.

A common way to represent models of evolution is with matrices where an off diagonal \((i,j)^{th}\) entry of rate matrix \(Q\) represents the rate in which state \(j\) changes to state \(i\) and diagonal entries are chosen to give \(Q\) zero column sum. Note here that this differs to the usual convention of an off-diagonal \((i,j)^{th}\) entry of such a matrix to represent the rate of state \(i\) changing to state \(j\) and hence off-diagonal entries of the matrix are chosen to give zero row sum. Mathematically, a model which contains free parameters can be represented by a set of matrices, \(Q\). For any given set of rate matrices, there can be generated a corresponding set of transition matrices \(M\) where an off-diagonal \((i,j)^{th}\) entry of transition matrix \(M\) represents the probability of state \(j\) changing to state \(i\) in a given time period and the diagonal entries are chosen to give a unit column sum.

In the case of DNA models, research by [11] found practical merit in having a set of Markov matrices which are closed under matrix multiplication. If there are two Markov matrices, \(M_1\) and \(M_2\), acting on different segments on the same branch of a phylogenetic tree, in order to find the overall process, \(\hat{M}\), for that branch it is required to multiply \(M_1\) and \(M_2\) together. Therefore, if a set of Markov matrices, \(\mathcal{M}\), are closed under matrix multiplication and \(M_1, M_2 \in \mathcal{M}\), then \(\hat{M}\) in this scenario would also belong to \(\mathcal{M}\). For a set of rate matrices \(\mathcal{Q}\) and its corresponding set of transition matrices \(\mathcal{M}\), it has been shown that \(\mathcal{M}\) is closed under matrix multiplication iff \(\mathcal{Q}\) forms a Lie algebra [11, 10]. Therefore, demanding that \(\mathcal{Q}\) forms a Lie algebra will ensure \(\hat{M} \in \mathcal{M}\).

Further studies by [11] found that the general time reversible model [14] (from now referred to as GTR) does not have this property, i.e. if \(M_1\) and \(M_2\) are of GTR form then it is not always the case that \(\hat{M}\) is of GTR form as well.

[15] have conducted similar research on codon models. They have demonstrated that if two phylogenetic processes on the two branches of a two taxa phylogenetic tree have the same underlying value of \(ω\) then the average process over the tree is estimated, the resulting process does not necessarily have the same value of \(ω\). It seems sensible given previous research on the mis-estimation of substitution probabilities in DNA models to assume that a codon model which forms a Lie algebra would be less prone to mis-estimation of \(ω\), however it is an open problem to construct such a model. In this paper, we explore two methods of finding a Lie algebra to represent a codon model: one is finding the smallest Lie algebra which contains a model and the other changes the operations in a codon model’s formulation in such a way that the resulting space forms a Lie algebra. Both methods present inherit difficulties concerning the large size of a such a codon model. The method of finding the smallest Lie algebra which contains the model has the additional difficulty of there not being an unambiguous definition of the \(ω\) parameter.

2. Defining the codon model

The MG model [9] defines the rate of change from codon \(J = (j_1, j_2, j_3)\) to codon \(I = (i_1, i_2, i_3)\) as follows:

\[
Q_{IJ} = \begin{cases} 
\pi_{i_k} & \text{synonymous} \\
\omega \pi_{i_k} & \text{non-synonymous} \\
0 & \text{multiple nucleotide substitutions needed}
\end{cases}
\]

where \(I \neq J\) and \(k\) is the codon position that is undergoing a mutation \(\pi_{jk}\) is the frequency of nucleotide \(j_k\). The diagonal entries of \(Q_{IJ}\) are chosen to give zero column sum.
We will be looking at MG “style” codon models which are based on the original MG model. In defining this set of models, we use $\otimes$ to signify the Kronecker product of matrices. As an example of this operation, consider the two matrices:

$$A = \begin{pmatrix} 3 & 1 \\ 0 & -2 \end{pmatrix}, \quad B = \begin{pmatrix} 4 & 2 \\ -1 & 1 \end{pmatrix}.$$  

The Kronecker product of $A$ and $B$ is as follows:

$$A \otimes B = \begin{pmatrix} 3B & 1B \\ 0B & -2B \end{pmatrix} = \begin{pmatrix} 12 & 6 & 4 & 2 \\ -3 & 3 & -1 & 1 \\ 0 & 0 & -8 & -4 \\ 0 & 0 & 2 & -2 \end{pmatrix}.$$  

Following the derivation given in [15], for a DNA rate matrix $Q$, we first express the rates of change of codons with consideration only to the underlying DNA rate substitution process as follows:

$$Q_{\text{triplet}} = Q \otimes I \otimes I + I \otimes Q \otimes I + I \otimes I \otimes Q,$$

where $I$ is the $4 \times 4$ identity matrix. Note that the assumption of equal rates of change across codon sites is made. This assumption can be relaxed but in our case it will remain for simplicity. Another assumption made in all codon models is that the rate of multiple substitutions is zero, e.g. the rate of $\text{AAA} \rightarrow \text{AGG} = 0$ as two DNA mutations are required. This property is automatically present in the $Q_{\text{triplet}}$ matrix as given.

We define a $64 \times 64$ matrix $G$ to contain information about the rates of change of codons with respect to their amino acid counterparts. It contains $\omega$ for non-synonymous substitutions, 1 for synonymous substitutions and 0 for prohibited substitutions (to and from stop codons). Note that it is not necessary for $G$ to have zero entries for matrix entries that represent multiple substitution mutations. We then define the MG style codon model as

$$Q_{\text{codon}} = Q_{\text{triplet}} \circ G,$$

where the $\circ$ operation first finds the element-wise product of the two matrices and then resets the diagonal entries to ensure zero column sum.

In the original MG paper, the Felsenstien 81 model [2] was assumed for the underlying DNA rate substitution process. However, any DNA rate process can be used to produce a codon model in the above formulation. In this analysis, we illustrate our discussion with the Kimura 2 parameter model (from now referred to as K2ST) [8] and the Jukes Cantor model (from now referred to as JC) [6] as our underlying DNA rate processes. An MG process with an underlying model of JC is denoted as JC-MG, and similarly, an MG process with K2ST as the underlying model is denoted as K2ST-MG.

### 3. Finding the Lie closure of a model

In this section, both the general process for finding the Lie closure of an arbitrary set of matrices and the specific results of finding the Lie closures for models JC-MG and K2ST-MG are discussed.

For a given codon model, we consider two methods for finding a linear space associated to it. Firstly, we look at the smallest linear space that contains the model. This is a fairly straightforward process as we presently illustrate. We define $\text{Mat}_{n \times m}(\mathbb{R})$ to be the set of all $n \times m$ matrices with real entries. Note that $\text{Mat}_{n \times m}(\mathbb{R})$ forms a linear space under matrix addition.

**Definition 3.1.** The **linear closure** of a set of $n \times m$ matrices, $A$, is the intersection of all linear sub-spaces of $\text{Mat}_{n \times m}(\mathbb{R})$ which contain $A$. More simply, this can be described as the smallest linear space which contains $A$. 

For the examples we consider in this paper, to obtain the linear closure of \( A \subseteq \text{Mat}_n(\mathbb{R}) \) it is sufficient to take the set, \( \mathcal{X} \), of polynomial constraints on the matrix entries of members of \( A \), and remove the non-linear polynomials in \( \mathcal{X} \). Caution is required however, since in general there exists case where this process gives the incorrect answer for the linear closure.

As an example of the process of finding the linear closure of a matrix set, we find the linear closure for the following set of matrices defined using two parameters

\[
A = \left\{ \begin{pmatrix} x & xy \\ y & y \end{pmatrix} : x, y \in \mathbb{R} \right\}. \tag{1}
\]

Equivalently we may define this set in terms of constraints on the matrix entries: \( \mathcal{X} = \{ A_{11}A_{22} = A_{12}, A_{21} = A_{22} \} \). The first constraint is non-linear, this is discarded. The second constraint is linear so this remains as a constraint on the linear closure. The linear closure of \( A \) is then

\[
\{ A \in \text{Mat}_{2 \times 2} : A_{21} = A_{22} \} = \left\{ \begin{pmatrix} x & z \\ y & y \end{pmatrix} : x, y, z \in \mathbb{R} \right\} = \text{span} \left\{ \begin{pmatrix} 1 & 0 \\ 0 & 0 \end{pmatrix}, \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}, \begin{pmatrix} 0 & 0 \\ 1 & 1 \end{pmatrix} \right\},
\]

which is a matrix linear space with three free parameters, i.e. it is three dimensional linear space.

An alternative process to this is that instead of considering the linear closure of a space, we define the “linear version.”

**Definition 3.2.** Given a set, \( A \), of \( n \times m \) matrices with polynomial constraints on the matrix entries and fixed \( n \times m \) matrix, \( B \), the **linear version** of \( A \) at \( B \) is the tangent space of \( A \) taken at \( B \).

**Lemma 3.1.** To find a linear version of a set of matrices with polynomial constraints where \( B \) has unit entries everywhere, any polynomial constraints of degree \( \geq 2 \) on the original matrix set are replaced by changing each multiplication operation to an addition operation.

**Proof.** For a matrix set \( A \) with polynomial constraints \( \mathcal{X} \) on the matrix entries, consider arbitrary \( C \in A \) and \( f \in \mathcal{X} \):

\[
f(C) = a_1c_{11}^{k_{11;1}}c_{12}^{k_{12;1}}...c_{nm}^{k_{nm;1}} + ... + a_p c_{11}^{k_{11;p}}c_{12}^{k_{12;p}}...c_{nm}^{k_{nm;p}} = 0.
\]

where \( a_i \in \mathbb{R}, c_{ij} \) are the matrix entries of \( C \) and \( k_{ij;l} \in \mathbb{N} \cup \{0\} \). To find the tangent space of \( A \) at \( B \), we first consider paths in \( C(t) \in A \) with matrix entries \( c_{ij}(t) \) where \( c_{ij}(0) = 1 \) (i.e. \( C(0) = B \)). Therefore \( f \in \mathcal{X} \) becomes

\[
f(C(t)) = a_1c_{11}(t)^{k_{11;1}}c_{12}(t)^{k_{12;1}}...c_{nm}(t)^{k_{nm;1}} + ... + a_p c_{11}(t)^{k_{11;p}}c_{12}(t)^{k_{12;p}}...c_{nm}(t)^{k_{nm;p}} = 0.
\]

To find the tangent space, we differentiate the constraints on \( A \) with respect to \( t \) and set \( t = 0 \) (as \( C'(0) \) is tangent space at \( B \)):

\[
\frac{d}{dt} \bigg|_{t=0} (a_1c_{11}(t)^{k_{11;1}}c_{12}(t)^{k_{12;1}}...c_{nm}(t)^{k_{nm;1}} + ... + a_p c_{11}(t)^{k_{11;p}}c_{12}(t)^{k_{12;p}}...c_{nm}(t)^{k_{nm;p}}) = \frac{d}{dt} \bigg|_{t=0} 0,
\]

then using the chain rule and product rule, we differentiate the first term only:
\[ \frac{d}{dt} \bigg|_{t=0} a_1c_{11}(t)^{k_{11;1}}c_{12}(t)^{k_{12;1}}...c_{nm}(t)^{k_{nm;1}} = a_1(k_{11;1}c'_{11}(0)c_{11}(0)^{k_{11;1}}c_{12}(0)^{k_{12;1}}...c_{nm}(0)^{k_{nm;1}} \]
\[ + k_{12;1}c'_{12}(0)c_{11}(0)^{k_{11;1}}c_{12}(0)^{k_{12;1}}...c_{nm}(0)^{k_{nm;1}} \]
\[ + k_{nm;1}c'_{nm}(0)c_{11}(0)^{k_{11;1}}c_{12}(0)^{k_{12;1}}...c_{nm}(0)^{k_{nm;1}} \]
\[ = a_1(k_{11;1}c'_{11}(0) + k_{12;1}c'_{12}(0) + ... + k_{nm;1}c'_{nm}(0)) \]

as \( c_{ij}(0) = 1 \forall i, j \). A similar procedure can be used for the other terms of \( f \) so that the tangent of the constraint at \( B \) is

\[ a_1(k_{11;1}c'_{11}(0) + k_{12;1}c'_{12}(0) + ... + k_{nm;1}c'_{nm}(0)) + ... + a_p(k_{11;p}c'_{11}(0) + k_{12;p}c'_{12}(0) + ... + k_{nm;p}c'_{nm}(0)) = 0 \]

which is equivalent to changing every multiplication operation between \( c_{ij} \) entries with addition. As \( f \) was an arbitrary element of \( X \), we can say that this applies to all \( f \in X \).

In the case of sets of rate matrices whose constraints on matrix entries are polynomial, \( Q \), we set \( B \) (the point at which we take the tangents) to be the matrix which has unit value off-diagonal entries and whose diagonal entries ensure zero column sum. To find the linear version of \( Q \), we treat constraints on off diagonal entries the same way as they are treated in Lemma 3.1 \((c_{ij}(0) = 1)\) and treat diagonal entries to be the entry required to ensure zero column sum.

For our example, we take the linear version at \( B \) being the \( 2 \times 2 \) matrix with unit entries. The constraint of \( A_{11}A_{22} = A_{12} \) is changed to \( A_{11} + A_{22} = A_{12} \) so that our linear version of the set would be

\[ \left\{ \begin{pmatrix} x & xy \\ y & y \end{pmatrix} : x, y \in \mathbb{R} \right\} \to \left\{ \begin{pmatrix} x & x + y \\ y & y \end{pmatrix} : x, y \in \mathbb{R} \right\} = \text{span} \left\{ \begin{pmatrix} 1 & 1 \\ 0 & 0 \end{pmatrix}, \begin{pmatrix} 0 & 1 \\ 1 & 1 \end{pmatrix} \right\} \mathbb{R} \]

which has two free parameters, hence is a two dimensional matrix linear space. Note that the number of free parameters in the linear version is the same as the original.

As a more practical example of these processes we examine a variation of the HKY model [5] by adding the constraints of \( \pi_A = \pi_G \) and \( \pi_C = \pi_T \). The matrix representation of this model has three free parameters:

\[ Q_{HKY} = \left\{ \begin{pmatrix} * & \pi_A \kappa & \pi_A & \pi_A \\ \pi_A \kappa & \pi_A & \pi_A & \pi_A \\ \pi_C & \pi_C & \pi_C & \kappa \\ \pi_C & \pi_C & \pi_C & \kappa \end{pmatrix} : \pi_A, \pi_C, \kappa \in \mathbb{R} \right\} \]

where * denotes that the entry is chosen to give zero column sum.

To calculate the linear closure of this model, linear constraints such as \( A_{14} = A_{24} \) are kept but non-linear constraints such as \( A_{12}A_{41} = A_{13}A_{43} \) are discarded. Thus the linear closure of this model is

\[ \left\{ \begin{pmatrix} * & \gamma & \alpha & \alpha \\ \gamma & * & \alpha & \alpha \\ \beta & \beta & * & \delta \\ \beta & \beta & \delta & * \end{pmatrix} : \alpha, \beta, \gamma, \delta \in \mathbb{R} \right\} \]

which is Model 4.4b (a four dimensional matrix linear space) in the Lie-Markov model (LMM) hierarchy described in [4]. This is different to the linear version, with respect to \( B \) as defined above,
which would change the non-linear constraints such as $A_{12}A_{41} = A_{13}A_{43}$ to linear constraints such as $A_{12} + A_{41} = A_{13} + A_{43}$ so that the linear version of the model is

$$
\left\{ \begin{pmatrix}
\ast & \alpha + \kappa & \alpha & \alpha \\
\alpha + \kappa & \ast & \alpha & \alpha \\
\beta & \beta & \ast & \beta + \kappa \\
\beta & \beta & \beta + \kappa & \ast
\end{pmatrix} : \alpha, \beta, \kappa \in \mathbb{R} \right\}.
$$

This is Model 3.4 (a three dimensional matrix linear space) in the LMM hierarchy [4].

In our analysis, we will be using both Lie closures of codon models and Lie closures of linear versions of codon models.

**Definition 3.3.** A **Lie algebra**, $\mathcal{L}$, is a vector space over a field, $\mathbb{F}$, with an additional operation of the Lie bracket $[.,.] : \mathcal{L} \times \mathcal{L} \rightarrow \mathcal{L}$, which, for $x, y, z \in \mathcal{L}$ and $\lambda \in \mathbb{F}$ satisfies:

(i) $[x, y] = -[y, x],$
(ii) $[\lambda x, y] = \lambda [x, y],$
(iii) $[x, [y, z]] + [y, [z, x]] + [z, [x, y]] = 0.$

Note here that in matrices where $[A, B] = AB - BA$, the third condition of a Lie algebra is automatically satisfied by the first two conditions and hence plays no role in finding the Lie closure.

**Definition 3.4.** The **Lie closure** of a set of matrices, $\mathcal{A}$, is the intersection of all matrix Lie algebras which contain $\mathcal{A}$. More simply, this can be described as the smallest matrix Lie algebra which contains $\mathcal{A}$.

Once the linear closure of a set of matrices is found, Lie brackets of the linear space’s basis elements are calculated: it is sufficient to only work with the basis elements of the linear closure due to the space being linear and the Lie bracket operation being bi-linear. In matrices, we define the Lie bracket operation as $[A, B] = AB - BA$. A matrix vector space that is closed under the Lie bracket operation is a Lie algebra. If a Lie bracket is found to be in the existing linear space, the Lie bracket is ignored and another is tried. If a Lie bracket is not in the existing linear space, it is added to the basis. The stop condition is when all Lie brackets of the basis elements are in the linear space. At this point, we have found the Lie closure of the linear space.

To find the Lie closure of our previous example described in equation [1] we take Lie brackets of the basis elements in the linear closure. We see that

$$
\begin{pmatrix}
1 & 0 \\
0 & 0
\end{pmatrix}
\begin{pmatrix}
0 & 1 \\
0 & 0
\end{pmatrix}
-\begin{pmatrix}
0 & 1 \\
0 & 0
\end{pmatrix}
\begin{pmatrix}
1 & 0 \\
0 & 0
\end{pmatrix}
= \begin{pmatrix}
0 & 1 \\
0 & 0
\end{pmatrix}
$$

which is in the linear closure so there is no further action to be taken. On the other hand

$$
\begin{pmatrix}
0 & 0 \\
1 & 1
\end{pmatrix}
\begin{pmatrix}
1 & 0 \\
0 & 0
\end{pmatrix}
-\begin{pmatrix}
1 & 0 \\
0 & 0
\end{pmatrix}
\begin{pmatrix}
0 & 0 \\
1 & 1
\end{pmatrix}
= \begin{pmatrix}
0 & 0 \\
1 & 1
\end{pmatrix}
$$

which is not in the linear closure so it is added to the basis. Therefore our new space is

$$
\text{span}\left\{ \begin{pmatrix}
1 & 0 \\
0 & 0
\end{pmatrix}, \begin{pmatrix}
0 & 1 \\
0 & 0
\end{pmatrix}, \begin{pmatrix}
0 & 0 \\
1 & 1
\end{pmatrix}, \begin{pmatrix}
0 & 0 \\
1 & 0
\end{pmatrix} \right\}_\mathbb{R}
$$

which is a four dimensional matrix linear space. As this space now spans all $(2 \times 2)$ matrices, we know that any Lie bracket in this space will be contained in the space so we now have the Lie closure of the matrix set.

In the $Q_{HKY^*}$ example, the linear closure is in the LMM hierarchy [11] and hence is a Lie algebra so no further computation is necessary to find the Lie closure of that matrix set (so the Lie closure
of $Q_{HKY^*}$ is a four dimensional matrix linear space). The linear version of $Q_{HKY^*}$ also forms a Lie algebra so the Lie closure of the linear version of $Q_{HKY^*}$ is equal to the linear version (a four dimensional matrix linear space).

![Diagram](image)

**Figure 1.** If we begin with a model, the other matrix sets generated by the model will be nested as shown. For example, linear closures being inside Lie closures represents that when the Lie closure and linear closure are not equal then the Lie closure is the larger space of which the linear closure is a linear subspace of. The Lie closure of the linear version does not fit into this diagram easily as it can be both inside or outside of the linear closure, however it will be inside the Lie closure.

For the general case, to find the Lie closure of a model, first the linear closure is found and then Algorithm 1 (see below) is used. An alternative method for finding a Lie algebra associated with a model is to find the Lie closure of its linear version. The nesting of the spaces that can be generated from a model is depicted in Figure 1.

### 3.1. Examples of closures and versions in DNA models.

The symmetric DNA model (GTR [14] with uniform base distribution) has matrix form

$$Q_{SYM} = \begin{pmatrix}
* & a & b & c \\
 a & * & d & e \\
 b & d & * & f \\
 c & e & f & *
\end{pmatrix} : a, b, c, d, e, f \in \mathbb{R}.$$

**Lemma 3.2.** The Lie closure of $Q_{SYM}$ is the set of $4 \times 4$ matrices whose row and column sums are zero which is known as the doubly stochastic model.

**Proof.** Clearly, $Q_{SYM}$ is a linear space as all constraints on it are linear, e.g. $Q_{12} = Q_{21} \forall Q \in Q_{SYM}$.

We define the symmetric matrix $S_{ij}$ as the $(4 \times 4)$ matrix with unit entries in positions $(i, j)$ and $(j, i)$, zero entries in all other off-diagonal entries and diagonal entries are set to ensure zero column sum. We also define an anti-symmetric matrix $T_{ij}$ as the $(4 \times 4)$ matrix with unit entry in position $(i, j)$, $-1$ in position $(j, i)$, zeros in all other off-diagonal entries and whose diagonal entries are set to give zero column sum. Clearly the set $\{S_{12}, S_{13}, S_{14}, S_{23}, S_{24}, S_{34}\}$ is a basis for $Q_{SYM}$.

Each time a Lie bracket is taken of two symmetric matrices, an anti-symmetric matrix is produced. For example consider the Lie bracket $[S_{12}, S_{13}]$:
Our input is the basis for the linear space $L$: $\{A_1, A_2, \ldots, A_n\}$;

$V = [1, n]$, $\#V$ tracks the dimension of $L$ at certain stages of the algorithm #;

$k = 1$;

\begin{verbatim}
while $V[k] \neq V[k + 1]$ do
  $i = 1$;
  while $i \leq V[k]$ do
    $j = V[k]$;
    while $j \leq V[k + 1]$ do
      if $i < j$ then
        Attempt to solve $\text{Lie}(A_i, A_j) = a_1A_1 + a_2A_2 + \ldots + a_mA_m$ where $m$ is the current
dimension of $L$ and $a_l \in \mathbb{R}$;
        if Solution can be found then
          $\text{None}$
        else
          $\text{Lie}(A_i, A_j)$ is appended to $L$
        end
      else
        $\text{None}$
      end
    end
    $j = j + 1$
  end
  $i = i + 1$
end

Append $V$ with current dimension of $L$;

$k = k + 1$;
\end{verbatim}

\textbf{Algorithm 1}: For a given matrix linear space, this algorithm will give the Lie closure.

\[
\begin{pmatrix}
-1 & 1 & 0 & 0 \\
1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
-1 & 0 & 1 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
- \begin{pmatrix}
-1 & 0 & 1 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\begin{pmatrix}
-1 & 1 & 0 & 0 \\
1 & -1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
= \begin{pmatrix}
0 & 1 & -1 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
= T_{12} - T_{13} + T_{23}.
\]

For distinct $a, b, c, d$ in $\{1, 2, 3, 4\}$, the Lie brackets of the basis elements of $\mathcal{Q}_{SYM}$ can be summarised as follows:

\[
[S_{ab}, S_{cd}] = 0,
[S_{ab}, S_{ac}] = T_{ab} - T_{ac} + T_{bc}.
\]

Hence we have
where each $U_i$ is a $4 \times 4$ matrix which is both anti-symmetric and doubly stochastic and has zero entries in all of its $i^{th}$ row and column. We see that $U_4 = U_1 - U_2 + U_3$ and hence the $\{U_1, U_2, U_3\}$ is a linearly independent set which spans the space of doubly stochastic anti-symmetric matrices. The set spanned by denoting $L$ 

\[
\begin{align*}
[S_{23}, S_{24}] &= T_{23} - T_{24} + T_{34} = U_1 \\
[S_{32}, S_{34}] &= T_{41} - T_{43} + T_{13} = U_2 \\
[S_{12}, S_{14}] &= T_{12} - T_{14} + T_{24} = U_3 \\
[S_{12}, S_{13}] &= T_{12} - T_{13} + T_{23} = U_4,
\end{align*}
\]

is a linearly independent set which spans the space of doubly stochastic anti-symmetric matrices. It forms a Lie algebra and hence is the Lie closure of SYM.

Consider the GTR model \[14\] which has matrix form

\[
Q_{GTR} = \left\{ \begin{pmatrix}
* & \alpha \pi_A & \beta \pi_A & \gamma \pi_A \\
\alpha \pi_C & * & \delta \pi_A & \varepsilon \pi_C \\
\beta \pi_C & \delta \pi_C & * & \eta \pi_C \\
\gamma \pi_T & \varepsilon \pi_T & \eta \pi_T & *
\end{pmatrix} : \alpha, \beta, \gamma, \delta, \varepsilon, \eta, \pi_A, \pi_G, \pi_C, \pi_T \in \mathbb{R} \right\}.
\]

Its linear version is

\[
\begin{pmatrix}
* & \alpha + \pi_A & \beta + \pi_A & \gamma + \pi_A \\
\alpha + \pi_G & * & \delta + \pi_G & \varepsilon + \pi_G \\
\beta + \pi_C & \delta + \pi_C & * & \eta + \pi_C \\
\gamma + \pi_T & \varepsilon + \pi_T & \eta + \pi_T & *
\end{pmatrix} : \alpha, \beta, \gamma, \delta, \varepsilon, \eta, \pi_A, \pi_G, \pi_C, \pi_T \in \mathbb{R}
\]

which, although having ten free parameters, is a nine dimensional vector space. This can be shown by denoting $L_i$ as the matrix generated when each parameter except $i$ is set to zero then we can assert that the set $\{L_\alpha, L_\beta, L_\gamma, L_\delta, L_\varepsilon, L_\eta, L_\pi_A, L_\pi_G, L_\pi_C, L_\pi_T\}$ is not linearly independent as $L_\alpha + L_\beta + L_\gamma + L_\delta + L_\varepsilon + L_\eta = L_\pi_A - L_\pi_G - L_\pi_C = L_\pi_T$. In its own right, this set of matrices does not form a Lie algebra therefore the Lie closure of this space is not trivial. The linear version of $Q_{GTR}$ is not contained in the DS model and hence must be contained in a LMM of a higher dimension than 9. It is not contained in models 10.12 or 10.34 of the LMM hierarchy \[3\] and hence we conclude that the Lie closure of the linear version of $Q_{GTR}$ must contain the set of $4 \times 4$ matrices which have zero column sum, known as the General Markov Model (GMM) \[1\]. As GMM is the largest $4 \times 4$ rate matrix set, we conclude that Lie closure of the linear version of $Q_{GTR}$ cannot be bigger than GMM and is therefore equal to GMM.

Another example is the GTR model \[14\] assuming that $\pi_A = \pi_G$ and $\pi_C = \pi_T$. This model has matrix form

\[
Q_{GTR^*} = \left\{ \begin{pmatrix}
* & \alpha \pi_A & \beta \pi_A & \gamma \pi_A \\
\alpha \pi_A & * & \delta \pi_A & \varepsilon \pi_A \\
\beta \pi_C & \delta \pi_C & * & \eta \pi_C \\
\gamma \pi_C & \varepsilon \pi_C & \eta \pi_C & *
\end{pmatrix} : \alpha, \beta, \gamma, \delta, \varepsilon, \eta, \pi_A, \pi_C \in \mathbb{R} \right\}.
\]

There are only two linear constraints on this matrix set: $A_{21} = A_{12}$ and $A_{43} = A_{34}$. Non-linear constraints of this matrix set such as $A_{31}A_{14} = A_{41}A_{13}$ are discarded to find the linear closure:

\[
\begin{align*}
[S_{23}, S_{24}] &= T_{23} - T_{24} + T_{34} = U_1 \\
[S_{32}, S_{34}] &= T_{41} - T_{43} + T_{13} = U_2 \\
[S_{12}, S_{14}] &= T_{12} - T_{14} + T_{24} = U_3 \\
[S_{12}, S_{13}] &= T_{12} - T_{13} + T_{23} = U_4,
\end{align*}
\]
When finding the Lie closure of this set, Lie brackets of elements of the linear closure are found. We notice in particular that the Lie bracket
\[
\begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
\end{pmatrix}
\begin{pmatrix}
-1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 \\
\end{pmatrix}
\]
\[
= \begin{pmatrix}
0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 \\
-1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
\end{pmatrix}
\]
is not in the linear closure of $Q_{GTR^*}$. Therefore we conclude that the linear closure is not a Lie algebra in its own right and hence the Lie closure will have a higher dimension than the linear closure. In any case: as with the linear version of GTR, this set is not contained in the DS model (and hence will have a dimension greater than 9), neither is it contained in models 10.12 or 10.34 of the LMM hierarchy [3] so therefore the Lie closure of it will be, again, GMM.

The model proposed by [13], often referred to the Tamura Nei model (TN), has the matrix form:

\[
Q_{TN} = \begin{pmatrix}
\pi_A & \pi_A & \pi_A \\
\pi_G & \pi_G & \pi_G \\
\pi_C & \pi_C & \pi_C + \kappa_2 \\
\pi_T & \pi_T & \pi_T + \kappa_2 \\
\end{pmatrix}
\]

\[
: \kappa_1, \kappa_2, \pi_A, \pi_G, \pi_C, \pi_T \in \mathbb{R}
\]

This is an interesting example as both its linear closure and linear version form Lie algebras. Since these models also have purine/pyrimidine symmetries, they are in the LMM hierarchy given in [3]. The linear version has the form

\[
\begin{pmatrix}
\pi_A + \kappa_1 & \pi_A & \pi_A \\
\pi_G + \kappa_1 & \pi_G & \pi_G \\
\pi_C & \pi_C & \pi_C + \kappa_2 \\
\pi_T & \pi_T & \pi_T + \kappa_2 \\
\end{pmatrix}
\]

\[
: \kappa_1, \kappa_2, \pi_A, \pi_G, \pi_C, \pi_T \in \mathbb{R}
\]

which is model 6.8a of the LMMs [3]. The linear closure on the other hand is

\[
\begin{pmatrix}
\alpha & \pi_A & \pi_A \\
\beta & \pi_G & \pi_G \\
\pi_C & \pi_C & \gamma \\
\pi_T & \pi_T & \delta \\
\end{pmatrix}
\]

\[
: \alpha, \beta, \gamma, \delta, \pi_A, \pi_G, \pi_C, \pi_T \in \mathbb{R}
\]

which is model 8.8 of the LMMs [3].

### 3.2. Incorporating the $\omega$ parameter into Lie closures of codon models.

The use of linear versions (which leads to use of Lie closures of linear versions) changes the $\omega$ parameter from a multiplicative operation to an additive one. It is of interest to define a new matrix, $G^*$, to represent the action of $G$ in linear versions. In off-diagonal entries, the matrix $G^*$ is defined to have unit entries for entries representing non-synonymous mutations which require only one nucleotide mutation and are not to or from stop codons; and zero entries everywhere else. Its diagonal entries are chosen to give zero column sum. Additionally, because we are not multiplying $Q_{\text{triplet}}$ by $G$, we are required to add the extra constraint on $Q_{\text{triplet}}$ of zero values for entries that represent mutations to or from stop codons. For any linear version of an MG style codon model, $G^*$ is automatically in the basis for the space so the $\omega$ parameter can be defined as being the coefficient of $G^*$. 

Defining an \( \omega \) parameter for the linear closure (and hence Lie closure) of an MG style codon model case is less clear. When the linear closure of the codon model is found, for example, of K2ST-MG we start with parameters \( \{a, b, \omega\} \) (which would result in matrix entries \( \{a, b, a\omega, b\omega\} \)) and the linear closure has parameters \( \{a, b, a\omega, b\omega\} \rightarrow \{c_1, c_2, c_3, c_4\} \) (i.e. there are now 4 independent parameters) which means that there is no longer an \( \omega \) parameter. Like the linear version, it would seem logical for \( \omega \) to be the coefficient of the \( G^* \) matrix. Therefore in practice, the basis for the linear closure should be defined in a way to include \( G^* \) (which would only require a change of basis). This leaves the question of how \( \omega \) itself should be calculated.

One possible way to calculate \( \omega \) is \( \frac{1}{2}(\frac{c_1}{c_1} + \frac{c_4}{c_2}) \); an average of the synonymous/non-synonymous rate ratios. Another method proposes that \( \omega_1 = \frac{c_4}{c_1}, \omega_2 = \frac{c_4}{c_2} \) and hence \( \omega = \omega_1 \frac{c_1}{c_1 + c_2} + \omega_2 \frac{c_2}{c_1 + c_2} \); a weighted average where the weights are the frequencies of the types of substitutions. It is currently an open question to how \( \omega \) is to be calculated; especially as the situation is more complicated in MG-style codon models whose linear closures have more than 4 parameters.

3.3. Lie closures of codon models. In our analysis of codon models, first the codon model was defined in the way we have discussed in Section 2. The linear closure was found of both JC-MG and K2ST-MG, the linear version of K2ST-MG was found, and then the Algorithm 1 was applied to these linear spaces. It should be noted here that the linear closure and linear version of JC-MG are the same linear space only with different bases and hence have the same Lie closure. This is not the case for K2ST-MG, for this codon model the linear closure and linear version are different linear spaces; this is because the model has non-linear constraints.

We found the dimensions of both the Lie closure of K2ST-MG and the Lie closure of the linear version of K2ST-MG are at least 2036. The dimension of the Lie closure of JC-MG was at least 1996. The full Lie closure for both models was not found due to the computational difficulty of the problem; it is estimated that if the Lie closure order is actually 1996 then it would take 2.6 years to confirm this result on a desktop computer running the computation written in its current state and if the Lie closure order is bigger than 1996 then the computation would take even longer. In order to find this result in a quicker time, we would be required to use a faster computer and/or optimize the computer code however there is little practicality in finding the full Lie closure as we can easily tell from these preliminary results that the full Lie closure is far too large to be of use.

We had predicted that the Lie closures of K2ST-MG and JC-MG would not be too large to be of practical use. Had this been the case, we would have begun analysis on how these new models might estimate or mis-estimate \( \omega \). Failing this, we thought that given the Lie closure of a linear version of a model can be a smaller space than the Lie closure of the same model, then finding the Lie closure of the linear version of a model might yield more useful results but this was also too large to be of practical use. In order for the Lie closure (or the Lie closure of the linear version) to be smaller, the starting model would have to be simpler but the only way we can make a codon model that is simpler than JC-MG is to set \( \omega \) to a constant value which would ruin the whole point of the exercise as we are trying to reduce mis-estimation of \( \omega \).

3.4. Further analysis: partial Lie closures. It was thought, given that finding a full Lie closure of a MG style codon model was not practical, that we could instead create a partial Lie closure; that is to begin to close the Lie algebra but not completely do so. We now define more precisely what we mean by a partial Lie closure.

In Algorithm 1 above, we can see that any element added to \( \mathcal{L} \) can be represented as a Lie bracket of the original \( n \) matrices from the linear closure. We define the generation of an element of \( \mathcal{L} \) as the number of Lie brackets necessary to build that element from the elements of the linear closure +1. For example, we would say that \( B = [A_1, [[A_2, A_3], A_1]] \) (where \( A_1, A_2, A_3 \) are in the linear closure of the original matrix set) would belong to generation 4 as there are 3 Lie bracket
operations required to build this element from the elements of the linear closure. When building a partial Lie closure, we will calculate elements up to a fixed generation. For example, if one was interested in a Lie closure up to generation 4 then first generation 1 elements would be calculated followed by generations 2, 3 and 4. This process is really the same as the algorithm for finding the Lie closure (described in algorithm 1) apart from the stop condition and the order in which Lie brackets are calculated (and possibly appended to $L$).

It was hoped that a model that was partially Lie closed would have similar enough properties to Lie algebras that the mis-estimation of $\omega$ could be reduced. We tried to find a partial closure of the JC-MG model. Unfortunately, problems arose regarding “stochasticity.”

A zero column sum matrix must be stochastic in order to be classified as a rate matrix. A matrix is stochastic when its off diagonal entries are non-negative. This is a requirement of rate matrices as it does not make sense to have a negative rate of one state changing to another. Sometimes given a matrix vector space, constraints must be put on the basis coefficients in order to achieve stochasticity. For example, for the set of matrices

$$\mathcal{A} = \text{span} \left\{ A_1 = \begin{pmatrix} -2 & 1 & 1 \\ 1 & -2 & 1 \\ 1 & 1 & -2 \end{pmatrix}, A_2 = \begin{pmatrix} 0 & -1 & -1 \\ -1 & 0 & 1 \\ 1 & 1 & 0 \end{pmatrix} \right\}$$

with a typical element $a_1 A_1 + a_2 A_2 : a_1, a_2 \in \mathbb{R}$, we must place constraints on $a_1$ and $a_2$ in order for matrices in $\mathcal{A}$ to be stochastic. One possible set of constraints is $a_1 \geq 0$ and $a_1 \geq |a_2|$. Sometimes however, there are no constraints that will ensure non-trivial stochasticity, for example consider the set

$$\mathcal{B} = \text{span} \left\{ B_1 = \begin{pmatrix} -2 & 1 & 1 \\ 1 & -2 & -1 \\ 1 & 1 & 0 \end{pmatrix}, B_2 = \begin{pmatrix} -2 & 1 & -2 \\ 1 & -2 & 1 \\ 1 & 1 & 1 \end{pmatrix} \right\}$$

with the typical element $b_1 B_1 + b_2 B_2 : b_1, b_2 \in \mathbb{R}$. We see that the only way an element of $\mathcal{B}$ can be stochastic is if we set $b_1 = b_2 = 0$.

It was found that any non-trivial partial Lie closure (i.e. a partial Lie closure which is bigger than the linear closure where there can be non-zero coefficients for the basis elements that are not in the linear closure) of the JC-MG codon model with dimension of less than 227 (this was finding the partial Lie closure up to generation 10) violated stochasticity. This means that for a non-trivial partial Lie closure to be stochastic, we would need a dimension $\geq 227$ but such a space would still be too big to be practical.

4. Toy model: an interesting case of symmetries

It is interesting that the Lie closure of a codon model which began with a linear space with a dimension of 2 could have a Lie closure whose dimension is so large. Studying this further has proven to be difficult given the computational difficulty of the problem. A toy model was created in an attempt to better understand the features that could lead to the Lie closure of a vector space being so large.

4.1. The setup. We assumed that the codon length was 3. We then assumed that the number of states is 2 (R and Y) instead of 4 (A, G, C and T). The resulting codon model is $(8 \times 8)$. Like in the MG style codon models, it is assumed that there cannot be two changes happening on the same codon at once so, for example, the rate of $RRR \rightarrow RYY = 0$. We defined our basis model as

$$Q_{\text{triplet}} = Q_2 \otimes I \otimes I + I \otimes Q_2 \otimes I + I \otimes I \otimes Q_1$$
where

\[ Q_1 = \begin{pmatrix} -a & a \\ a & -a \end{pmatrix} \quad \text{and} \quad Q_2 = \begin{pmatrix} -b & b \\ b & -b \end{pmatrix}. \]

This results in

\[ Q_{\text{triplet}} = \begin{pmatrix} * & a & b & 0 & 0 & 0 & 0 & 0 \\ a & * & 0 & b & 0 & 0 & 0 & 0 \\ b & 0 & a & * & 0 & 0 & b & 0 \\ 0 & b & a & * & 0 & 0 & 0 & b \\ b & 0 & 0 & 0 & * & a & b & 0 \\ 0 & 0 & b & 0 & 0 & a & * & b \\ 0 & 0 & b & 0 & 0 & b & 0 & * \\ 0 & 0 & b & 0 & 0 & b & a & * \end{pmatrix}. \]

This matrix is equivalent to a full codon model where a synonymous change is when the third codon position mutates to another nucleotide and a non-synonymous change is when the first or second codon position mutates to another nucleotide. As it currently stands, \( Q_{\text{triplet}} \) forms an abelian Lie algebra so its Lie closure would have dimension 2. What we want to test now is if we make minor adjustments to \( Q_{\text{triplet}} \), what will happen to the size of the Lie closure?

4.2. The results. If matrix entry (7, 5) of \( Q_{\text{triplet}} \) is changed from \( b \) to \( a \), then the dimension for the Lie closure is 25. When similar changes were made to \( Q_{\text{triplet}} \) (swapping \( b \) values to \( a \) values and vice versa), the dimensions of the Lie closures ranged from 13 to 56. (Note that the maximum possible size for a Lie closure of a model of this form is \( 8 \times 8 - 8 = 56 \).) There was a trend that was apparent when the adjusted \( Q_{\text{triplet}} \) was still symmetrical after being altered: the Lie closure tended to be smaller but symmetries were not sufficient to obtain a Lie closure of less than 13.

This is interesting as it shows that as soon as the model deviates from being \( Q_{\text{triplet}} \) the Lie closure is no longer a simple answer. The linear closures of JC-MG and K2ST-MG are far from being as simple as the \((64 \times 64)\) \( Q_{\text{triplet}} \) matrix so it is not surprising that the Lie closures are so large.

5. Further research

So far we have shown that finding the Lie closure or partial Lie closure of codon models is not a viable method of potentially fixing the problems with current codon models. One other avenue yet to be explored is further analysis of linear closures and linear versions.

Both the linear closures and linear versions of codon models are not ridiculously big nor do they violate stochasticity. In our case of analysing the JC-MG model, the linear closure (which is the same as the linear version, only a different basis) is trivial due to JC-MG only having two parameters to begin with. But when the underlying DNA rate substitution process has more parameters, for example HKY, then the linear closure is not trivial and the setup of the linear version is quite different to the original. It has not yet been tested to see if linear closures of codon models mis-estimate \( \omega \) as much as the models themselves but it is possible that this could help as previous exploration \([7, 12]\) found that in DNA models, parameters have been mis-estimated less in DNA models which form linear spaces.

6. Conclusion

Closed codon models seemed like a good idea given previous research on DNA models but they are not a practical solution to the problem of \( \omega \) mis-estimation when finding the average process.
over two branches of the same tree due to how large such models would have to be. A partial solution to a Lie closure of any kind is not feasible as stochasticity, a Markov assumption, is not met for any partial Lie closure of a reasonable size. Given the behaviour of toy models, it would appear that any set of matrices which deviate only slightly from being symmetrical will have a Lie closure as large as possible which confirms that finding the Lie closures of codon models is indeed a pointless endeavour. Linear codon models (linear closures and linear versions of codon models) are of a more practical size and do not violate stochasticity so the next steps are to test mis-estimation of $\omega$ in such models. There also remains the question on how $\omega$ is to be defined in linear closures.

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