

# Identifying evolutionary trees and substitution parameters for the general Markov model with invariable sites

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## Abstract

The general Markov plus invariable sites (GM+I) model of biological sequence evolution is a two-class model in which an unknown proportion of sites are not allowed to change, while the remainder undergo substitutions according to a Markov process on a tree. For statistical use it is important to know if the model is identifiable; can both the tree topology and the numerical parameters be determined from a joint distribution describing sequences only at the leaves of the tree? We establish that for generic parameters both the tree and all numerical parameter values can be recovered, up to clearly understood issues of ‘label swapping.’ The method of analysis is algebraic, using phylogenetic invariants to study the variety defined by the model. Simple rational formulas, expressed in terms of determinantal ratios, are found for recovering numerical parameters describing the invariable sites.

*Key words:* Phylogenetics, invariable site model, identifiability, phylogenetic invariants

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## 1 Introduction

If a model of biological sequence evolution is to be used for phylogenetic inference, it is essential that the model parameters of interest — certainly the tree parameter and usually the numerical parameters — be identifiable from the joint distribution of states at the leaves of the tree. Though often unstated, the assumption that model parameters are identifiable underlies the use of both Maximum Likelihood and Bayesian inference methods. As increasingly complicated models, incorporating across-site rate variation, covarion structure, or other types of mixtures, are implemented in software packages, there is a real possibility that non-identifiability could confound data analysis. Unfortunately, our theoretical understanding of this issue lags well behind current phylogenetic practice.

One natural approach to proving the identifiability of the tree topology relies on the definition of a phylogenetic distance for the model, and the 4-point condition of Buneman [1]. For instance, Steel [2] used the log-det distance to establish the identifiability of the tree topology under the general Markov model and its submodels. Such a distance-based argument shows additionally that 2-marginalizations of the full joint distribution suffice to recover the tree parameter, since distances require only two-sequence comparisons. Once the tree has been identified, the numerical parameters giving rise to a joint distribution for the general Markov model can be determined by an argument of Chang [3].

However, for more general mixture models and rates-across-sites models no appropriate definition of a distance is known, so proving the identifiability of the tree parameter requires a different approach. (Though distance measures have been developed for GTR models with rate-substitution [4,5], these require that one know the rate distribution completely, and identifiability of the rate distribution has yet to be addressed. Although identifiability of the popular GTR+I+ $\Gamma$  model of sequence evolution was considered in [6], there are gaps in the argument, as was pointed out to us by Ané [7].)

In [8], the viewpoint of algebraic geometry is used to show the generic identifiability of the tree parameter for the covarion model of [9] and for certain mixture models with a small number of classes. Though this result is far more general than previous identifiability results, it still fails to cover the type of rate-variation models currently in common use for data analysis, and does not address identifiability of numerical parameters at all. Much more study of the identifiability question is needed.

In this paper, we focus on the *general Markov plus invariable sites*, GM+I, model of sequence evolution, a model that encompasses the GTR+I model

that is of more immediate interest to practitioners. Note that previous work on GM+I by Baake [10] focused on *non*-identifiability. In that paper parameter choices for the 2-state GM+I model on two distinct 4-taxon trees are constructed that give rise to the same pairwise joint distributions (2-marginals). As both sets of parameters have 50% invariable sites, this shows that the identifiability of the tree parameter cannot generally hold on the basis of 2-sequence comparisons, even if the distribution of rate factors is known. Furthermore, it shows a well-behaved phylogenetic distance cannot be defined for this model, as existence of such a distance would imply tree identifiability.

Here we prove that all parameters for the GM+I model are indeed identifiable, through 4-sequence comparisons. By identifiable, we mean *generically identifiable* in a geometric sense: For a fixed tree, the set of numerical parameters for which the joint distribution could have arisen from either a) a different tree, or b) a ‘significantly different’ (in a sense to be made clear later) choice of numerical parameters on the same tree, is of strictly lower dimension than that of the full numerical parameter space. (For a concrete example of generic identifiability, recall the results of Steel and Chang on the general Markov model: assumptions that the Markov edge matrices  $M_e$  have determinant  $\neq 0, 1$  and that the distribution of states at the root has strictly positive entries ensure identifiability of all parameters. These are generic conditions.) Thus for natural probability distributions on the parameter space, with probability one a choice of parameters is generic.

Although identifiability of the tree parameter for GM+I follows from more general results in [8], that paper did not consider identifiability of numerical parameters. Our arguments here are tailored to GM+I and yield stronger results addressing numerical parameters as well as the tree. Our approach is again based on the determination of *phylogenetic invariants* for the model. While the invariants described in [8] are invariants for more general models than GM+I, the ones given in this paper apply only to GM+I and its submodels, and are of much lower degree. As a byproduct of the development of these GM+I invariants, we are led to rational formulas for recovering all the parameters related to the invariable sites from a joint distribution. Indeed, these formulas are crucial to our identification of numerical parameters.

These formulas can be viewed as GM+I analogs of the formulas for the proportion of invariable sites in group-based+I models that were found by the capture-recapture argument of [11]. In the group-based setting, those formulas were developed into a heuristic means of estimating the proportion of invariable sites from data without performing a full tree inference. This has been implemented in `SplitsTree4` [12]. However, it remains unclear whether a similar useful heuristic can be found for the formulas presented in this paper.

Since our algebraic methods at times employ computational commutative algebra software packages, and these tool are not commonly used in the phylogenetics literature, we have included some examples of code in Appendix A.

## 2 The GM+I Model

Let  $T$  denote an  $n$ -taxon tree, by which we mean a tree with  $n$  leaves labeled by the taxa  $a_1, a_2, \dots, a_n$  and all internal vertices of valence at least 3. We say  $T$  is *binary* if all internal nodes have valence exactly 3.

We begin by describing the parameterization of the  $\kappa$ -state GM+I model of sequence evolution along  $T$ , where  $\kappa = 4$  corresponds to usual models of DNA evolution. The *class size parameter*  $\delta$  denotes the probability that any particular site in a sequence is invariable: conceptually, the flip of a biased coin weighted by  $\delta$  determines if a site is allowed to undergo state transitions. If a site is invariable, it is assigned state  $i \in [\kappa] = \{1, 2, \dots, \kappa\}$  with probability  $\pi_I(i)$ . Here  $\boldsymbol{\pi}_I = (\pi_I(1), \dots, \pi_I(\kappa))$  is a vector of non-negative numbers summing to 1 giving the state distribution for invariable sites.

All sites that are not invariable mutate according to a common set of parameters for the GM model, though independently of one another. For these sites, we associate to each node (including leaves) of  $T$  a random variable with state space  $[\kappa]$ . Choosing any node  $r$  of  $T$  to serve as a root, and directing all edges away from  $r$ , let  $T_r$  denote the resulting directed tree  $T$ . A *root distribution* vector  $\boldsymbol{\pi}_{GM} = (\pi_{GM}(1), \dots, \pi_{GM}(\kappa))$ , with non-negative entries summing to 1, has entries  $\pi_{GM}(j)$  specifying the probability that the root variable is in state  $j$ . For each directed edge  $e = (v \rightarrow w)$  of  $T_r$ , let  $M_e$  be a  $\kappa \times \kappa$  Markov matrix, so that  $M_e(i, j)$  specifies the conditional probability that the variable at  $w$  is in state  $j$  given that the variable at  $v$  is in state  $i$ . Thus entries of all  $M_e$  are non-negative, with rows summing to 1.

For the GM+I model on an  $n$ -taxon tree  $T$  with edge set  $E$ , the stochastic parameter space  $S \subset [0, 1]^N$  is of dimension  $N = 1 + (\kappa - 1) + (\kappa - 1) + |E|\kappa(\kappa - 1) = 2\kappa - 1 + |E|\kappa(\kappa - 1)$ . The parameterization map giving the joint distribution of the variables at the leaves of  $T$  is denoted by

$$\begin{aligned} \phi_T : S &\longrightarrow [0, 1]^{\kappa^n}, \\ \mathbf{s} &\longmapsto P. \end{aligned}$$

We view  $P$  as an  $n$ -dimensional  $\kappa \times \dots \times \kappa$  array, with dimensions corresponding to the ordered taxa  $a_1, a_2, \dots, a_n$ , and with entries indexed by the states at the leaves of  $T$ . The entries of  $P$  are polynomial functions in the parameters

s explicitly given by

$$P(i_1, \dots, i_n) = \delta \epsilon(i_1, i_2, \dots, i_n) \boldsymbol{\pi}_I(i_1) + (1 - \delta) \sum_{(j_v) \in \mathcal{H}} \left( \boldsymbol{\pi}_{GM}(j_r) \prod_e M_e(j_{v_i}, j_{v_f}) \right). \quad (1)$$

Here  $\epsilon(i_1, i_2, \dots, i_n)$  is 1 if all  $i_j$  are equal and 0 otherwise, the product is taken over all edges  $e = (v_i \rightarrow v_f) \in E$ , and the sum is taken over the set of all possible assignments of states to nodes of  $T$  extending the assignment  $(i_1, \dots, i_n)$  to the leaves: If  $V$  is the set of vertices of  $T$  then

$$\mathcal{H} = \left\{ (j_v) \in [\kappa]^{|V|} \mid j_v = i_k \text{ if } v \text{ is a leaf labeled by } a_k \right\}.$$

For notational ease, the entries of  $P$ , the *pattern frequencies*, are also denoted by  $p_{i_1 \dots i_n} = P(i_1, \dots, i_n)$ .

We note that while a root  $r$  was chosen for the tree in order to explicitly describe the GM portion of the parameterization of our model, the particular choice of  $r$  is not important. Under mild additional restrictions on model parameters, changing the root location corresponds to a simple invertible change of variables in the parameterization. (See [13], [14], or [15] for details.) This justifies our slight abuse of language in referring to the GM or GM+I model on  $T$ , rather than on  $T_r$ , and we omit future references to root location.

Note that equation (1) allows us to more succinctly describe any  $P \in \text{Im}(\phi_T)$  as

$$P = (1 - \delta)P_{GM} + \delta P_I \quad (2)$$

where  $P_{GM}$  is an array in the image of the GM parameterization map on  $T$  and  $P_I = \text{diag}(\boldsymbol{\pi}_I)$  is an  $n$ -dimensional array whose off-diagonal entries are zeros and whose diagonal entries are those of  $\boldsymbol{\pi}_I$ .

### 3 Model Identifiability

We now make precise the various concepts of identifiability of a phylogenetic model. To adapt standard statistical language to the phylogenetic setting, for a fixed set  $A$  of  $n$  taxa and  $\kappa \geq 2$ , consider a collection  $\mathcal{M}$  of pairs  $(T, \phi_T)$ , where  $T$  is an  $n$ -taxon tree with leaf labels  $A$ , and  $\phi_T : S_T \rightarrow [0, 1]^{\kappa^n}$  is a parameterization map of the joint distribution of pattern frequencies for the model on  $T$ . We say *the tree parameter is identifiable* for  $\mathcal{M}$  if for every  $P \in \cup_{(T, \phi_T) \in \mathcal{M}} \text{Im}(\phi_T)$ , there is a unique  $T$  such that  $P \in \text{Im}(\phi_T)$ . We say that *numerical parameters are identifiable on a tree  $T$*  if the map  $\phi_T$  is injective, that is if for every  $P \in \text{Im}(\phi_T)$  there is a unique  $\mathbf{s} \in S_T$  with  $\phi_T(\mathbf{s}) = P$ . We

say the *model*  $\mathcal{M}$  is *identifiable* if the tree parameter is identifiable, and for each tree the numerical parameters are identifiable.

It is well-known that such a definition of identifiability is too stringent for phylogenetics. First, unless one restricts parameter spaces, there is little hope that the tree parameter be identifiable: One need only think of any standard model on a binary 4-taxon tree in which the Markov matrix parameter on the internal edge is the identity matrix. Any joint distribution arising from such a parameter choice could have as well arisen from any other 4-taxon tree topology.

Even if such ‘special’ parameter choices are excluded so the tree parameter becomes identifiable, identifiability of numerical parameters also poses problems, as noted by Chang [3]. For example, consider the 3-taxon tree with the GM model. Then multiple parameter choices give rise to the same joint distribution since the labeling of the states at the internal node can be permuted in  $\kappa!$  ways, as long as the Markov matrix parameters are adjusted accordingly [14]. The occurrence of this sort of ‘label-swapping’ non-identifiability in statistical models with hidden (unobserved) variables is well-known, but is not of great concern. However, even for this model more subtle forms of non-identifiability can occur, in which infinitely many parameter choices lead to the same joint distribution. These arise from singularities in the model, and can be avoided by again restricting parameter space. Such ‘generic’ conditions for the GM model have already been mentioned in the introduction.

We therefore refine our notions of identifiability. Because we are concerned primarily with model where the maps  $\phi_T$  are given by polynomials, we give a formulation appropriate to that setting. Recall that given any collection  $\mathcal{F}$  of polynomials in  $N$  variables, their common zero set,

$$V(\mathcal{F}) = \{z \in \mathbb{C}^N \mid f(z) = 0 \text{ for all } f \in \mathcal{F}\},$$

is the *algebraic variety* defined by  $\mathcal{F}$ . If the algebraic variety is a proper subset of  $\mathbb{C}^N$ , then it is said to be *proper*.

**Definition 1** *Let  $\mathcal{M}$  be a model on a collection of  $n$ -taxon trees, as defined above.*

- (1) *We say the tree parameter is generically identifiable for  $\mathcal{M}$  if for each tree  $T$  there exists a proper algebraic variety  $X_T$  with the property that*

$$P \in \bigcup_{(T, \phi_T) \in \mathcal{M}} \phi_T(S_T \setminus X_T) \text{ implies } P \in \phi_T(S_T \setminus X_T) \text{ for a unique } T.$$

- (2) *We say that numerical parameters are generically locally identifiable on a tree  $T$  if there is a proper algebraic variety  $Y_T$  such that for all  $\mathbf{s} \in S_T \setminus Y_T$ , there is a neighborhood of  $\mathbf{s}$  on which  $\phi_T$  is injective.*

- (3) *We say the model  $\mathcal{M}$  is generically locally identifiable if the tree parameter is generically identifiable, and for each tree the numerical parameters are generically locally identifiable.*

Note that the notion of ‘generic’ here is used to mean ‘for all parameters but those lying on a proper subvariety of the parameter space,’ and such a variety is necessarily of lower dimension than the full parameter space. Using the standard measure on the parameter space, viewed as a subset of  $\mathbb{R}^N$ , this notion thus also implies ‘for all parameters except those in a set of measure 0.’

In the important special case of parameterization maps defined by polynomial formulas, such as that for the GM+I model, generic local identifiability of numerical parameters is equivalent to the notion in algebraic geometry of the map  $\phi_T$  being *generically finite*. In this case, there exists a proper variety  $Y_T$  and an integer  $k$ , the degree of the map  $\phi_T$ , such that restricted to  $S_T \setminus Y_T$  the map  $\phi_T$  is not only locally injective but also  $k$ -to-1: That is, if  $\mathbf{s} \in S_T \setminus Y_T$  and  $P = \phi_T(\mathbf{s})$ , then the fiber  $\phi_T^{-1}(P)$  has cardinality  $k$ .

Because of the label swapping issue at internal nodes, for the GM model and GM+I on an  $n$ -taxon tree  $T$  with vertex set  $V$ , fibers of generic points will always have cardinality at least  $\kappa!(|V| - n)$ . Thus for these models, the best we can hope for is generic local identifiability of the model (both tree and numerical parameters) where the generic fiber has exactly this cardinality. That in fact is what we establish in the next section.

## 4 Generic Identifiability for the GM+I model

We begin our arguments by determining some phylogenetic invariants for the GM+I model. The notion of a phylogenetic invariant was introduced by Cavender and Felsenstein [16] and Lake [17], in the hope that phylogenetic invariants might be useful for practical tree inference. Their role here, in proving identifiability, is more theoretical but illustrates their value in analyzing models.

For a parameterization  $\phi_T$  given by polynomial formulas on domain  $S_T \subseteq \mathbb{R}^N$ , we may uniquely extend to a polynomial map with domain  $\mathbb{C}^N$ , given by the same polynomial formulas, which we again denote by  $\phi_T : \mathbb{C}^N \rightarrow \mathbb{C}^{\kappa^n}$ .

**Remark 2** *Extending parameters to include complex values is solely for mathematical convenience, as algebraic geometry provides the natural setting for our viewpoint. The collection of stochastic joint distributions (arising from the original stochastic parameter space) is a proper subset of  $\text{Im}(\phi_T)$ .*

The *phylogenetic variety*,  $V_T$ , is the the smallest algebraic variety in  $\mathbb{C}^{\kappa^n}$  containing  $\phi_T(\mathbb{C}^N)$ , *i.e.*, the closure of the image of  $\phi_T$  under the Zariski topology,

$$V_T = \overline{\text{Im}(\phi_T)} \subseteq \mathbb{C}^{\kappa^n}.$$

**Remark 3**  $V_T$  coincides with the closure of  $\text{Im}(\phi_T) = \phi_T(\mathbb{C}^N)$  under the usual topology on  $\mathbb{C}^{\kappa^n}$ . However, while  $V_T \cap [0, 1]^{\kappa^n}$  contains the closure of  $\phi_T(S_T)$  under the usual topology, these need not be equal.

Let  $\mathbb{C}[P]$  denote the ring of polynomials in the  $\kappa^n$  indeterminates  $\{p_{i_1 \dots i_n}\}$ . Then the collection of all polynomials in  $\mathbb{C}[P]$  vanishing on  $V_T$  forms a prime ideal  $I_T$ . We refer to  $I_T$  as a *phylogenetic ideal*, and its elements as *phylogenetic invariants*. More explicitly, a polynomial  $f \in \mathbb{C}[P]$  is a phylogenetic invariant if, and only if,  $f(P_0) = 0$  for every  $P_0 \in \phi_T(\mathbb{C}^{\kappa^n})$ , or equivalently, if, and only if,  $f(P_0) = 0$  for every  $P_0 \in \phi_T(S_T)$ .

As we proceed, we consider first the special case of 4-taxon trees. We highlight the  $\kappa = 2$  case, in part to illustrate the arguments for general  $\kappa$  more clearly, and in part because we can go further in understanding the 2-state model.

Consider the 4-taxon binary tree  $T_{ab|cd}$ , with taxa  $a, b, c, d$  as shown in Figure 1.

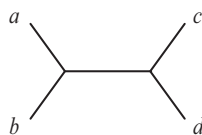


Fig. 1. The 4-taxon tree  $T_{ab|cd}$

Suppose that  $P$  is a  $2 \times 2 \times 2 \times 2$  pattern frequency array, whose indices correspond to states  $[2] = \{1, 2\}$  at the taxa in alphabetical order. Then the internal edge  $e$  of  $T$  defines the split  $ab | cd$  in the tree, and we define the *edge flattening*  $F_e$  of  $P$  at  $e$ , a  $2^2 \times 2^2$  matrix, by

$$F_e = \begin{pmatrix} p_{1111} & p_{1112} & p_{1121} & p_{1122} \\ p_{1211} & p_{1212} & p_{1221} & p_{1222} \\ p_{2111} & p_{2112} & p_{2121} & p_{2122} \\ p_{2211} & p_{2212} & p_{2221} & p_{2222} \end{pmatrix}. \quad (3)$$

Notice that the rows of  $F_e$  are indexed by the states at  $\{ab\}$  and the columns by states at  $\{cd\}$ . The flattening  $F_e$  is intuitively motivated by considering a ‘collapsed’ model induced by  $e$ : taxa  $a$  and  $b$  are grouped together forming a single variable  $\{ab\}$  with 4 states, and the grouping  $\{cd\}$  forms a second variable with 4 states.



This construction can be generalized in a natural way: suppose  $T$  is an  $n$ -taxon tree, and  $P$  a  $\kappa \times \dots \times \kappa$  array with indices corresponding to the taxa labeling the leaves of  $T$ . Then for any edge  $e$  in  $T$ , we can form from  $P$  the matrix  $F_e$  of size  $\kappa^{n_1} \times \kappa^{n_2}$ , where  $n_1$  and  $n_2$  are the cardinalities of the two sets of taxa in the split induced by  $e$ .

From [15] (for a more expository presentation, see also [18]), we have:

**Theorem 4** *For the 2-state GM model on a binary  $n$ -taxon tree  $T$ , the phylogenetic ideal  $I_T$  is generated by all  $3 \times 3$  minors of all edge flattenings  $F_e$  of  $P$ . Moreover, for the  $\kappa$ -state GM model on an  $n$ -taxon tree  $T$ , the phylogenetic ideal  $I_T$  contains all  $(\kappa + 1) \times (\kappa + 1)$  minors of all edge flattenings of  $P$ .*

Using this result, we can deduce some elements of the phylogenetic ideal for the GM+I model for any number of taxa  $n \geq 4$  and any number of states  $\kappa \geq 2$ .

**Proposition 5** *(Phylogenetic Invariants for GM+I)*

- (1) *For the 4-taxon tree  $T_{ab|cd}$  and the 2-state GM+I model, the cubic determinantal polynomials*

$$f_1 = \begin{vmatrix} p_{1112} & p_{1121} & p_{1122} \\ p_{1212} & p_{1221} & p_{1222} \\ p_{2112} & p_{2121} & p_{2122} \end{vmatrix} \quad \text{and} \quad f_2 = \begin{vmatrix} p_{1211} & p_{1212} & p_{1221} \\ p_{2111} & p_{2112} & p_{2121} \\ p_{2211} & p_{2212} & p_{2221} \end{vmatrix}$$

*are phylogenetic invariants. These are the two  $3 \times 3$  minors of the matrix flattening  $F_{ab|cd}$  of equation (3) that do not involve either of the entries  $p_{1111}$  or  $p_{2222}$ .*

- (2) *More generally, for  $n \geq 4$  and  $\kappa \geq 2$ , consider the  $\kappa$ -state GM+I model on an  $n$ -taxon tree  $T$ . Then for each edge  $e$  of  $T$ , all  $(\kappa + 1) \times (\kappa + 1)$  minors of the flattening  $F_e$  of  $P$  that avoid all entries  $p_{i_1 \dots i_\kappa}$ ,  $i \in [\kappa]$  are phylogenetic invariants.*

**PROOF.** We prove the first statement in detail. From equation (2), for any  $P = \phi_T(s)$  we have  $P = (1 - \delta)P_{GM} + \delta P_I$ , where  $P_{GM}$  is a 4-dimensional table arising from the GM model on  $T$  and  $P_I = \text{diag}(\pi_I)$  is a diagonal table with entries giving the distribution of states for the invariable sites. Flattening

these tables with respect to the internal edge of the tree, we obtain

$$\begin{aligned}
F_{ab|cd} &= (1 - \delta)F_{GM} + \delta F_I \\
&= (1 - \delta) \begin{pmatrix} \tilde{p}_{1111} & \tilde{p}_{1112} & \tilde{p}_{1121} & \tilde{p}_{1122} \\ \tilde{p}_{1211} & \tilde{p}_{1212} & \tilde{p}_{1221} & \tilde{p}_{1222} \\ \tilde{p}_{2111} & \tilde{p}_{2112} & \tilde{p}_{2121} & \tilde{p}_{2122} \\ \tilde{p}_{2211} & \tilde{p}_{2212} & \tilde{p}_{2221} & \tilde{p}_{2222} \end{pmatrix} + \delta \begin{pmatrix} \pi_I(1) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \pi_I(2) \end{pmatrix}. \quad (4)
\end{aligned}$$

By Theorem 4, all  $3 \times 3$  minors of  $F_{GM}$  vanish. Since the ‘upper right’ and ‘lower left’ minors of  $F_{ab|cd}$  are the same as those of  $F_{GM}$ , up to a factor of  $(1 - \delta)^3$ , they also vanish.

Straightforward modifications to this argument give the general case.  $\square$

For arbitrary  $n, \kappa$ , the GM+I model should have many other invariants than those found here. Among these is, of course, the stochastic invariant

$$f_s(P) = 1 - \sum_{\mathbf{i} \in [\kappa]^n} p_{\mathbf{i}}.$$

In the simplest interesting case of the GM+I model, however, we have the following computational result.

**Proposition 6** *The phylogenetic ideal for the 2-state GM+I model on the 4-taxon tree  $T_{ab|cd}$  of Figure 1 is generated by  $f_s$  and the minors  $f_1, f_2$  above;*

$$I_T = \langle f_s, f_1, f_2 \rangle.$$

**PROOF.** A computation of the Jacobian of the parameterization  $\phi_T : S \subset \mathbb{C}^{13} \rightarrow \mathbb{C}^{2^4}$  shows it has full rank at some points, and so  $V_T$  is of dimension 13. If  $I = \langle f_s, f_1, f_2 \rangle$ , then  $I \subseteq I_T$ . Another computation shows that  $I$  is prime and of dimension 13. Thus, necessarily  $I = I_T$ . (The code for these computations is given in Appendix A.)  $\square$

Let  $V_{ab|cd}, V_{ac|bc}, V_{ad|bc}$  be the varieties for the 2-state GM+I models for the three 4-taxon binary tree topologies, with corresponding phylogenetic ideals  $I_{ab|cd}, I_{ac|bc}, I_{ad|bc}$ . Of course Proposition 6 gives generators for each of these ideals — two  $3 \times 3$  minors of the flattenings of  $P$  appropriate to those tree topologies, along with  $f_s$ . A computation (see Appendix A) shows that these three ideals are distinct. Therefore the three varieties are distinct, and their pairwise intersections are proper subvarieties. Thus for any parameters  $\mathbf{s}$  not

lying in the inverse image of these subvarieties,  $T$  is uniquely determined from  $\phi_T(\mathbf{s})$ . Thus we obtain

**Corollary 7** *For the 2-state GM+I model on binary 4-taxon trees, the tree parameter is generically identifiable.*

As  $\dim(V_{ab|cd}) = 13$ , and the parameter space for  $\phi_T$  is 13 dimensional, we also immediately obtain that the map  $\phi_T$  is generically finite. This yields

**Corollary 8** *For the 2-state GM+I model on a binary 4-taxon tree, numerical parameters are generically locally identifiable.*

Note that this does approach does not yield the cardinality of the generic fiber of the parameterization map, which is also of interest. We will return to this issue in Theorem 13.

Further computations show that  $\dim(V_{ab|cd} \cap V_{ac|bd} \cap V_{ad|bc}) = 11$ . As this intersection contains all points arising from the GM+I model on the 4-taxon star tree, which is an 11-parameter model, this is not surprising. In fact, one can verify computationally that the ideal  $I_{ab|cd} + I_{ac|bd} + I_{ad|bc}$  is the defining prime ideal of the star-tree variety. We also note that the ideal  $I_{ab|cd} + I_{ac|bd}$  decomposes into two primes, both of dimension 11. Thus the variety defined by this ideal has two components, one of which is the variety for the star tree.

In principle, the ideal  $I_T$  of all invariants for the GM+I model on an arbitrary tree  $T$  can be computed from the parameterization map  $\phi_T$  via an elimination of variables using Gröbner bases [19]. However, if all invariants for the  $\kappa$ -state GM model on  $T$  are known, they can provide an alternate approach to finding  $I_T$  which, while still proceeding by elimination, should be less computationally demanding.

To present this most simply, we note that because our varieties lie in the hyperplane described by the stochastic invariant, it is natural to consider their projectivizations, lying in  $\mathbb{P}^{\kappa^n-1}$  rather than  $\mathbb{C}^{\kappa^n}$ . The corresponding phylogenetic ideals, which we denote by  $J_T$ , are generated by the homogeneous polynomials in  $I_T$ , and do not contain the stochastic invariant. Conversely,  $I_T$  is generated by the elements of  $J_T$  together with the stochastic invariant.

In addition, we need not restrict ourselves to the GM model, but rather deal with any phylogenetic model parameterized by polynomials.

**Proposition 9** *Suppose  $\tilde{\phi}_T : \mathbb{C}^N \rightarrow \mathbb{C}^{\kappa^n}$  is a parameterization map for some phylogenetic model  $\mathcal{M}$  on  $T$ , with corresponding homogeneous phylogenetic ideal  $\tilde{J}_T$ . Let*

$$\phi_T : \mathbb{C}^N \times \mathbb{C}^\kappa \rightarrow \mathbb{C}^{\kappa^n}$$

be the parametrization map for the  $\mathcal{M}+I$  model given by

$$\phi_T(\mathbf{s}, (\delta, \boldsymbol{\pi}_I)) = (1 - \delta)\tilde{\phi}_T(\mathbf{s}) + \delta \text{diag}(\boldsymbol{\pi}_I).$$

Let  $P'$  denote the collection of all indeterminate entries of  $P$  except those in  $P_{eq} = \{p_{ii\dots i} \mid i \in [\kappa]\}$ . Then the homogeneous phylogenetic ideal  $J_T$  for the  $\mathcal{M}+I$  model on  $T$  is  $J_T = (\tilde{J}_T \cap \mathbb{C}[P']) \mathbb{C}[P]$ . Thus  $J_T$  can be computed from  $\tilde{J}_T$  by elimination of the variables in  $P_{eq}$ .

**PROOF.** Extend the parameterization maps  $\tilde{\phi}_T, \phi_T$  to parameterizations of cones by introducing an additional parameter,

$$\tilde{\Phi}_T(\mathbf{s}, t) = t \tilde{\phi}_T(\mathbf{s})$$

$$\Phi_T(\mathbf{s}, (\delta, \boldsymbol{\pi}_I), t) = t \phi_T(\mathbf{s}, (\delta, \boldsymbol{\pi}_I))$$

Then  $\text{Im}(\Phi_T) = \mathbb{C}^\kappa \times \text{proj}(\text{Im}(\tilde{\Phi}_T))$ , where  $\mathbb{C}^\kappa$  corresponds to coordinates in  $P_{eq}$  and ‘proj’ denotes the projection map from  $P$ -coordinates to  $P'$ -coordinates. As  $J_T$  is the ideal of polynomials vanishing on  $\text{Im}(\Phi_T)$ , and  $\tilde{J}_T \cap \mathbb{C}[P']$  the ideal vanishing on  $\text{proj}(\text{Im}(\tilde{\Phi}_T))$ , the result follows.  $\square$

Using this, in the appendix we give an alternate computation to show both part (1) of Proposition 5, and Proposition 6. While this computation is quite fast, a more naive attempt to find GM+I invariants directly from the full parameterization map using elimination was unsuccessful, demonstrating the utility of the proposition. Moreover, we can use this proposition to compute all 2-state GM+I invariants on the 5-taxon binary tree as well. This leads us to

**Conjecture 10** *On an  $n$ -taxon binary tree, the ideal of homogeneous invariants for the 2-state GM+I model is generated by those  $3 \times 3$  minors of edge flattenings that do not involve the variables  $p_{11\dots 1}$  and  $p_{22\dots 2}$ , together with the stochastic invariant.*

Although we are unable to determine all GM+I invariants for the 4-taxon tree for general  $\kappa$ , using only those described in Proposition 5 we can still obtain identifiability results through a modified argument.

**Proposition 11** *For the  $\kappa$ -state GM+I model on binary 4-taxon trees,  $\kappa \geq 2$ , the tree parameter is generically identifiable.*

**PROOF.** By the argument leading to Corollary 7, it is enough to show the varieties  $V_{ab|cd}$ ,  $V_{ac|bd}$ , and  $V_{ad|bc}$  are distinct. Considering, for example, the first

two, we can show that the varieties  $V_{ab|cd}$  and  $V_{ac|bd}$  are distinct, by giving an invariant  $f \in I_{ac|bd}$  and a point  $P_0 \in V_{ab|cd}$  such that  $f(P_0) \neq 0$ .

Using Proposition 5, we pick an invariant  $f \in I_{ac|bd}$  as follows: In the flattening  $F_{ac|bd}$  according to the split  $ac|bd$ , choose any collection of  $\kappa + 1$   $ac$ -indices with distinct  $a$  and  $c$  states, *e.g.*,  $\{12, 13, \dots, 1\kappa, 21, 23\}$ . Using the same set as  $bd$ -indices, this determines a  $(\kappa + 1) \times (\kappa + 1)$ -minor  $f$ .

We pick  $P_0 = \phi_{T_{ab|cd}}(\mathbf{s})$  using the parameterization of equation (1) by making a specific choice of parameters  $\mathbf{s}$ . On  $T_{ab|cd}$ , with the root  $r$  located at one of the internal nodes, choose parameters  $\mathbf{s}$  as follows: Let  $\boldsymbol{\pi}_{GM}, \boldsymbol{\pi}_I$  be arbitrary but with all entries of  $\boldsymbol{\pi}_{GM}$  positive. Pick any  $\delta \in [0, 1)$ . For the four terminal edges choose  $M_e$  to be the  $\kappa \times \kappa$  identity matrix  $I_\kappa$ . For the single internal edge  $e$  of  $T$ , choose any Markov matrix  $M_e$  with all positive entries. For such parameters, the entries of the joint distribution  $P_0 = \phi_{T_{ab|cd}}(\mathbf{s})$  are zero except for the pattern frequencies  $p_{iijj}$ , where the states at the leaves  $a$  and  $b$  agree and the states at the leaves  $c$  and  $d$  agree. Since the entries of  $M_e$  and the root distributions are positive, each of the  $p_{iijj} > 0$ .

But considering the flattening  $F_{ac|bd}$  of  $P_0 = \phi_{T_{ab|cd}}(\mathbf{s})$  with respect to the ‘wrong’ topology  $T_{ac|bd}$ , we observe that the  $\kappa^2$  non-zero entries  $p_{iijj}$  of  $F_{ac|bd}$  all lie on the diagonal of  $F_{ac|bd}$ , in the positions with  $ij$  as both  $ac$ -index and  $bd$ -index. Furthermore, by our choice of  $f$ , a subset of them forms the diagonal of the submatrix whose determinant is  $f$ . Therefore  $f(P_0) \neq 0$ .  $\square$

**Proposition 12** (*Recovery of invariable site parameters*)

- (1) *For the 4-taxon tree  $T_{ab|cd}$  and the 2-state GM+I model, suppose  $P = \phi_T(\mathbf{s})$ . Then generically the parameters in  $\mathbf{s}$  related to invariable sites can be recovered from  $P$  by the following formulas:*

$$\delta = \frac{|A_1| + |A_2|}{|B|}, \quad \boldsymbol{\pi}_I = \frac{1}{|A_1| + |A_2|} (|A_1|, |A_2|),$$

$$\text{where } B = \begin{pmatrix} p_{1212} & p_{1221} \\ p_{2112} & p_{2121} \end{pmatrix},$$

$$A_1 = \begin{pmatrix} p_{1111} & p_{1112} & p_{1121} \\ p_{1211} & p_{1212} & p_{1221} \\ p_{2111} & p_{2112} & p_{2121} \end{pmatrix}, \quad A_2 = \begin{pmatrix} p_{1212} & p_{1221} & p_{1222} \\ p_{2112} & p_{2121} & p_{2122} \\ p_{2212} & p_{2221} & p_{2222} \end{pmatrix}.$$

- (2) *More generally, for the  $\kappa$ -state GM+I model on  $T_{ab|cd}$ , the invariable site parameters can be recovered from a generic point in the image of the*

parameterization map by rational formulas of the form

$$\delta = \frac{\sum_{i \in [\kappa]} |A_i|}{|B|}, \quad \boldsymbol{\pi}_I = \frac{1}{\sum_{i \in [\kappa]} |A_i|} (|A_1|, |A_2|, \dots, |A_n|).$$

Here  $|B|$  is any  $\kappa \times \kappa$  minor of  $F_{ab|cd}$  that omits the all rows and columns indexed by  $ii$ , and  $|A_i|$  is the  $(\kappa + 1) \times (\kappa + 1)$  minor obtained by including all rows and columns chosen for  $B$  and in addition the  $ii$  row and  $ii$  column.

**PROOF.** We give the complete argument in the case  $\kappa = 2$  first. For a joint distribution  $P \in \text{Im}(\phi_T)$ , write  $F_{ab|cd} = (1 - \delta)F_{GM} + \delta F_I$  as in equation (4). Since  $A_1$  is the ‘upper left’  $3 \times 3$  submatrix of  $F_{ab|cd}$ , using linearity properties of the determinant, and that all  $3 \times 3$  minors of  $F_{GM}$  evaluate to zero, we observe that

$$\begin{aligned} |A_1| &= (1 - \delta)^3 \begin{vmatrix} \tilde{p}_{1111} & \tilde{p}_{1112} & \tilde{p}_{1121} \\ \tilde{p}_{1211} & \tilde{p}_{1212} & \tilde{p}_{1221} \\ \tilde{p}_{2111} & \tilde{p}_{2112} & \tilde{p}_{2121} \end{vmatrix} + \begin{vmatrix} \delta\pi_I(1) & 0 & 0 \\ 0 & (1 - \delta)\tilde{p}_{1212} & (1 - \delta)\tilde{p}_{1221} \\ 0 & (1 - \delta)\tilde{p}_{2112} & (1 - \delta)\tilde{p}_{2121} \end{vmatrix} \\ &= \delta\pi_I(1) \begin{vmatrix} (1 - \delta)\tilde{p}_{1212} & (1 - \delta)\tilde{p}_{1221} \\ (1 - \delta)\tilde{p}_{2112} & (1 - \delta)\tilde{p}_{2121} \end{vmatrix}. \end{aligned}$$

Thus we have  $|A_1| = \delta\pi_I(1)|B|$ . Now, if  $|B| \neq 0$ , then

$$\delta\pi_I(1) = \frac{|A_1|}{|B|}.$$

As  $|B|$  does not vanish on all of  $V_T$ , we have a rational formula to compute  $\delta\pi_I(1)$  for generic points on  $V_T$ .

Similarly, since  $A_2$  is the ‘lower right’ submatrix of  $F_{ab|cd}$ , then

$$\delta\pi_I(2) = \frac{|A_2|}{|B|}.$$

Adding these together, we obtain the stated rational expression for  $\delta$ .

Assuming additionally the generic condition that  $\delta \neq 0$ , then we find

$$\boldsymbol{\pi}_I = \left( \frac{|A_1|}{|A_1| + |A_2|}, \frac{|A_2|}{|A_1| + |A_2|} \right).$$

Thus the parameters  $\delta, \boldsymbol{\pi}_I$  are generically identifiable for GM+I on  $T$ .

One readily sees the argument above can be modified for arbitrary  $\kappa$ .  $\square$

Note that when  $\kappa > 2$  the above proposition gives many alternative rational formulas for the invariable site parameters, as there are many options for choosing the matrix  $B$ .

We now obtain our main result.

**Theorem 13** *The  $\kappa$ -state GM+I model on  $n$ -taxon binary trees, with  $n \geq 4$ ,  $\kappa \geq 2$ , is generically locally identifiable. Furthermore, for an  $n$ -taxon tree with  $V$  vertices, the fibers of generic points of  $V_T$  under the parametrization map have cardinality  $\kappa!(|V| - n)$ . Thus for generic points, label swapping at internal nodes is the only source of non-identifiability.*

**PROOF.** Suppose  $T$  is an  $n$ -taxon tree with  $P = \phi_T(\mathbf{s})$ . Choose some subset of 4 taxa, say  $\{a, b, c, d\}$ , and suppose the induced quartet tree is  $T_{ab|cd}$ . Then  $P_{abcd}$ , the 4-marginalization of  $P$ , is easily seen to be of the form  $P_{abcd} = \phi_{T_{ab|cd}}(\mathbf{s}_{abcd})$  where  $\mathbf{s}_{abcd} = g(\mathbf{s})$  and  $g$  is a surjective polynomial function. But the tree  $T_{ab|cd}$  is generically identifiable by Proposition 11, and thus invariable site parameters in  $\mathbf{s}_{abcd}$  are generically identifiable by Proposition 12. As these coincide with the invariable site parameters in  $\mathbf{s}$ , and generic conditions on  $\mathbf{s}_{abcd}$  imply generic conditions on  $\mathbf{s}$ , the invariable site parameters are generically identifiable for the full  $n$ -taxon model.

As an  $n$ -taxon binary tree topology is determined by the collection of all induced quartet tree topologies, one can now see that  $T$  is generically identifiable. Alternately, using the identified invariable site parameters, and assuming the additional generic condition that  $\delta \neq 1$ , note that

$$P_{GM} = \frac{1}{(1 - \delta)} (P - \delta P_I)$$

is a joint distribution arising from general Markov parameters. Thus generic identifiability of the tree can also be obtained from Steel's result for the GM model [2] applied to  $P_{GM}$ .

The generic identifiability of the remaining numerical parameters follows from Chang's argument [3] applied to  $P_{GM}$ . Chang's approach also indicates the cardinality of the generic fiber is  $\kappa!(|V| - n)$  due to the label swapping phenomenon.  $\square$

## 5 Estimating Invariable Sites Parameters

The concrete result in Proposition 12 gives explicit rational formulas for recovering parameters relating to invariable sites from the joint distribution. These can be viewed as generalizations of the formulas found in [11] for group-based models. As [11] develops the group-based model formulas into a heuristic means of estimating the invariable site parameters from data without performing a full Maximum Likelihood fit of data to a tree under a  $\mathcal{M}$ +I model, one might suspect the formulas of Proposition 12 could be used similarly without the need to assume  $\mathcal{M}$  was group-based, or approximately group-based. We emphasize that however useful such an estimate might be, it would not be intended to replace a more statistical but time-consuming computation, such as obtaining the Maximum Likelihood estimates for these parameters.

However, it is by no means obvious how to use these formulas well even for a heuristic estimate. First, for a 4-taxon tree we have many choices for the matrix  $B$ , in fact

$$\begin{pmatrix} \kappa^2 - \kappa \\ \kappa \end{pmatrix}^2$$

of them, so even for  $\kappa = 4$ , there are 245,025 basic sets of the formulae. Moreover, while these simple formulae emerged from our method of proof, one could in fact modify them by adding to any of them a rational function whose numerator is a phylogenetic invariant for the GM+I model, and whose denominator is not. Since the invariant vanishes on any joint distribution arising from the model, the resulting formulae will still recover invariable site information for generic parameters. Thus there are actually infinitely many formulas for recovering invariable site parameters.

One can nonetheless consider simple averaging schemes using only the basic formulas of Proposition 12 and find that on simulated data they perform quite well at approximately recovering invariable site parameters from empirical distributions. However, averaging the large number of formulas give here, and then also averaging over a large sample of quartets, as is proposed in [11], is more time consuming than one might wish for a fast heuristic. Moreover, one must be aware that the denominator in these formulas may vanish on an empirical distribution — it is certain to be non-zero only for true distributions for GM+I arising from generic parameters.

Nonetheless, it would be of interest to develop versions of these formulas with good statistical estimation properties, as the GM+I model encompasses models such as the GTR+I model which is often preferred in biological data analysis to group-based+I models. Of course addressing more general rate-variation models would be even more desirable, though our results here are not sufficient for that.



## A Code for Computational Algebra Software

The following code is also available on the authors' websites.

### A.1 Computation for Proposition 6

To show the variety has dimension 13, we execute the following Maple code:

```

pa := Matrix([[p,1-p]]); Mae := Matrix([[1-a,a],[x,1-r]]);
Meb := Matrix([[1-b,b],[s,1-s]]); Mef := Matrix([[1-e,e],[t,1-t]]);
Mfc := Matrix([[1-c,c],[u,1-u]]); Mfd := Matrix([[1-d,d],[v,1-v]]);
P := Array(1..2,1..2,1..2,1..2);
for i from 1 to 2 do for j from 1 to 2 do for l from 1 to 2 do
  P[i,j,k,l]:=0;
  for m from 1 to 2 do for n from 1 to 2 do
    P[i,j,k,l]:=P[i,j,k,l]+pa[1,i]*Mae[i,m]*Meb[m,j]*Mef[m,n]*Mfc[n,k]*Mfd[n,l];
  od;od;
  P[i,j,k,l]:=(1-w)*P[i,j,k,l];
od;od;od;od;
P[1,1,1,1]:=P[1,1,1,1]+w*q: P[2,2,2,2]:=P[2,2,2,2]+w*(1-q):
Q:=ListTools[Flatten](convert(P,listlist)):
J:=VectorCalculus[Jacobian](Q,[a,b,c,d,e,r,s,t,u,v,p,q,w]):
K:=subs({a=1/3,b=1/5,c=1/7,d=1/11,e=1/13,r=1/17,s=1/19,t=1/23,u=1/29,v=1/31,
p=1/3,q=1/5,w=1/7},J):
LinearAlgebra[Rank](K);

```

Using Singular [20], we complete the proof:

```

LIB "matrix.lib"; LIB "primdec.lib";
ring r = 0, (p0,p1,p2,p3,p4,p5,p6,p7,p8,p9,p10,p11,p12,p13,p14,p15),dp;
// Define matrix flattening F_{fab | cd} and polys fs, f1, f2
matrix Fab[4][4]=p0,p1,p2,p3,p4,p5,p6,p7,p8,p9,p10,p11,p12,p13,p14,p15;
matrix UR[3][3]=submat(Fab,1..3,2..4); matrix LL[3][3]=submat(Fab,2..4,1..3);
poly f1=det(UR); poly f2=det(LL);
poly fs = p0+p1+p2+p3+p4+p5+p6+p7+p8+p9+p10+p11+p12+p13+p14+p15-1;
ideal I = fs,f1,f2; // define ideal I
dim(std(I)); // compute dimension of r/I
primdecGTZ(I); // compute primary decomposition of I to show prime

```

### A.2 Computation for intersections of $V_{ab|cd}$ , $V_{ac|bd}$ , $V_{ad|bc}$

Continuing the Singular session above, we execute the following:

```

/* Define ideals Iac, Iad corresponding to two alternative tree
topologies for 4-taxon trees. (So, I = Iab in this notation.) */
// Flattening for ac | bd split
matrix Fac[4][4]=p0,p1,p4,p5,p2,p3,p6,p7,p8,p9,p12,p13,p10,p11,p14,p15;
poly f3=det(submat(Fac,1..3,2..4)); poly f4=det(submat(Fac,2..4,1..3));
ideal Iac = fs,f3,f4;
// Flattening for ad | bc split
matrix Fad[4][4]=p0,p2,p4,p6,p1,p3,p5,p7,p8,p10,p12,p14,p9,p11,p13,p15;
poly f5=det(submat(Fad,1..3,2..4)); poly f6=det(submat(Fad,2..4,1..3));
ideal Iad = fs,f5,f6;
reduce(f1,std(Iac)); // non-zero answer shows f1 not in Iac
reduce(Iac,std(I)); // non-zero shows f3,f4 not in I

```

```

ideal J = I,Iac; dim(std(J)); // show dim is 11
ideal K = J,Iad; dim(std(K)); // show dim is 11
primdecGTZ(K); // show K prime, and thus ideal for star tree

```

### A.3 Computation of 2-state GM+I ideal, 4-taxon trees, using Proposition 9

The following Singular code performs the needed elimination for a binary tree:

```

ideal Igm = minor(Fab,3);
// Eliminate the 'diagonal' variables
ideal Igmi = elim1(Igm,p0*p15);

```

For the star tree, the 2-state GM ideal is known from [15]. Thus elimination can be used to find GM+I invariants. We also show this result agrees with K above.

```

ideal Igm = minor(Fab,3),minor(Fac,3),minor(Fad,3);
// Eliminate the 'diagonal' variables
ideal Igmi = elim1(Igm,p0*p15),fs;
reduce(K,std(Igmi)); // all 0's indicates ideal containment
reduce(Igmi,std(K)); // all 0's indicates ideal containment

```

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