Identifiability of Phylogenetic Mixture Models

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The Main Results: Two-tree Mixtures

Theorem

The tree parameters of the phylogenetic mixture model $\mathcal{M}_{T_1} * \mathcal{M}_{T_2}$ are generically identifiable under the Jukes-Cantor and Kimura 2-parameter models if T_1, T_2 are trivalent with $n \geq 4$ leaves.

Theorem*

The continuous parameters of the phylogenetic mixture model $\mathcal{M}_{T_1} * \mathcal{M}_{T_2}$ are generically identifiable under the Jukes-Cantor and Kimura 2-parameter models if T_1, T_2 are trivalent with $n \geq 5$ leaves.

Outline

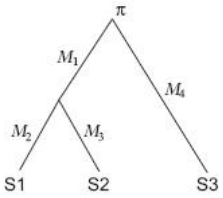
1. Phylogenetic Mixture Models
2. Group-based Phylogenetic Models
3. The Identifiability Problem
4. Proof of Tree Identifiability
    1. Quartets
    2. Sextets
5. Proof* of Parameter Identifiability
6. Some Mathematical Surprises

Phylogenetic Models

Let T be a trivalent tree with n leaves. Leaves are labeled by $[n] := \{1, 2, 3, \ldots, n\}$.

Associated to each edge of tree e is a Markov (structured) transition matrix M_e.

Once we specify T, and the M_e, get a probability distribution of characters at the leaves of the tree.



$$Prob(i, j, k) = \sum_{l=1}^{4} \sum_{m=1}^{4} r_l M_1(l, m) M_2(m, i) M_3(m, j) M_4(l, k)$$

Think of phylogenetic model as a map

$$\phi_T : \Theta \subseteq \mathbb{R}^k \to \Delta_{4^n}$$

Given by polynomials:
$\mathcal{M}_T := \mathrm{im}\phi_T = \phi_T(\Theta)$, is the phylogenetic model.

Phylogenetic Mixture Models

Suppose there are k classes of sites in the genome.
Each class $j \in [k]$ evolved according to tree T_j on n leaves.
Assuming that the classes are hidden, we observe a probability distribution of the form:

$$\phi_{T_1,\dots,T_k}(\pi, \{M_e\}) = \pi_1 \cdot \phi_{T_1}(\{M_e^1\}) + \pi_2 \cdot \phi_{T_2}(\{M_e^2\}) + \cdots + \pi_k \cdot \phi_{T_k}(\{M_e^k\})$$

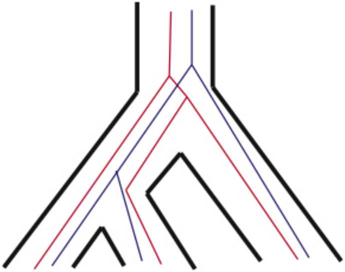
where π_j is the relative proportion of sites of class j.

Definition

Let $T_1, \dots, T_k$ be trees with n leaves. The phylogenetic mixture model

$$\mathcal{M}_{T_1} * \mathcal{M}_{T_2} * \cdots * \mathcal{M}_{T_k} = \left\{ \sum_{j=1}^{k} \pi_j p^j : \pi_j \geq 0, \sum \pi_j = 1, p^j \in \mathcal{M}_{T_j} \right\}.$$

Why Mixture Models?



- Differing gene tree topologies
- Could explain evolution with recombination

Group-based Models

For remainder we focus on group-based models. Phylogenetic models with structured transition matrices.

$$\begin{pmatrix} \alpha & \beta \\ \beta & \alpha \end{pmatrix} \quad \begin{pmatrix} \alpha & \beta & \beta & \beta \\ \beta & \alpha & \beta & \beta \\ \beta & \beta & \alpha & \beta \\ \beta & \beta & \beta & \alpha \end{pmatrix} \quad \begin{pmatrix} \alpha & \beta & \gamma & \gamma \\ \beta & \alpha & \gamma & \gamma \\ \gamma & \gamma & \alpha & \beta \\ \gamma & \gamma & \beta & \alpha \end{pmatrix} \quad \begin{pmatrix} \alpha & \beta & \gamma & \delta \\ \beta & \alpha & \delta & \gamma \\ \gamma & \delta & \alpha & \beta \\ \delta & \gamma & \beta & \alpha \end{pmatrix}$$

Cavender-Farris-Neyman (CFN), Jukes-Cantor (JC), Kimura 2-Parameter (K2P), Kimura 3-Parameter (K3P)

Transition structure is governed by a finite Abelian group G, such that

$$M_e(g,h) = f_e(g-h).$$

Theorem (Evans-Speed 1993, Hendy-Penny 1993)

Group-based models can be diagonalized by means of the discrete Fourier transform over G (Hadamard conjugation). In the Fourier coordinates, group-based models are toric varieties.

Fourier Coordinates

For each split $A|B$ in tree introduce a set of Fourier parameters

$$\{a_g^{A|B} : g \in G\}.$$

Theorem (Evans-Speed 1993, Hendy-Penny 1993)

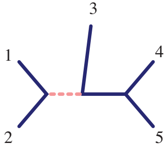
In the Fourier coordinates, a group-based phylogenetic model is given parametrically by:

$$q_{g_1,\ldots,g_n} = \begin{cases} \prod_{A|B \in \Sigma(T)} a^{A|B}_{\sum_{a \in A} g_a} & \text{if } g_1 + \cdots + g_n = 0 \\ 0 & \text{if } g_1 + \cdots + g_n \neq 0 \end{cases}$$

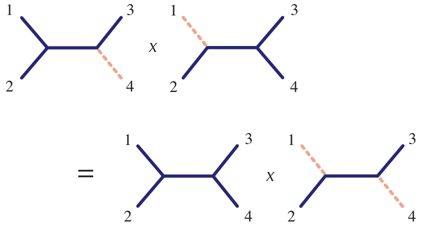
In the JC, K2P, K3P, we take $G = \mathbb{Z}_2 \times \mathbb{Z}_2 = \{A, C, G, T\}$.
In the K2P model, we have $a_G^{A|B} = a_T^{A|B}$ for all $A|B$
In the JC model, we have $a_C^{A|B} = a_G^{A|B} = a_T^{A|B}$ for all $A|B$.

Doodles for Group-Based Models

$$q_{CCTGC} = a^1_C a^2_C a^3_T a^4_G a^5_C a^{12|345}_A a^{123|45}_T$$



$$q_{CGTA} q_{ACTG} = q_{CGCG} q_{ATTA}$$



The Identifiability Problem

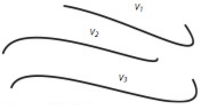
Definition

The tree parameters $T_1, \dots, T_k$ in a k-class phylogenetic mixture model are identifiable if for all

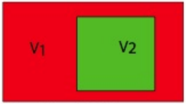
$$p \in \mathcal{M}_{T_1} * \cdots * \mathcal{M}_{T_k}$$

there does not exist another set of k trees $T'_1, \dots, T'_k$ such that

$$p \in \mathcal{M}_{T'_1} * \cdots * \mathcal{M}_{T'_k}.$$



Identifiable



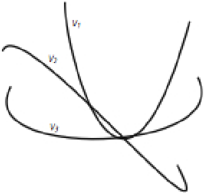
Not Identifiable

Generic Identifiability

Definition

The tree parameters in a k-class phylogenetic mixture model are generically identifiable if for all nonequal multisets $T_1, \ldots, T_k$, and $T'_1, \ldots, T'_k$,

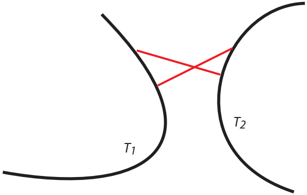
$$\dim(\mathcal{M}_{T_1} * \cdots * \mathcal{M}_{T_k} \cap \mathcal{M}_{T'_1} * \cdots * \mathcal{M}_{T'_k}) < \dim(\mathcal{M}_{T_1} * \cdots * \mathcal{M}_{T_k}).$$



Generic Identifiability of Continuous Parameters

Definition

Fix trees $T_1, \ldots, T_k$ on n leaves. The continuous parameters of phylogenetic mixture model are generically identifiable if $\phi_{T_1,\ldots,T_k}$ is one-to-one (off of a set of measure zero (up to label swapping)).



Past Work on Identifiability of Tree Mixtures

- Identifiability Results:
  - Allman and Rhodes (2006) $T_1 = \ldots = T_k$, $k < n$.
  - Stefankovic and Vigoda (2007) $T_1 = \ldots = T_k$, JC, K2P
  - Matsen, Mossel, and Steel (2008)
- Non-Identifiability Results:
  - Matsen and Steel (2007)
  - Stefankovic and Vigoda (2007)
  - Mossel and Vigoda (2005)

Algebraic Methods for Proving Identifiability

Proposition

Let $\mathcal{M}_0$ and $\mathcal{M}_1$ be two algebraic models. If there exist polynomials f_0 and f_1 such that

$$f_i(p) = 0 \text{ for all } p \in \mathcal{M}_i, \text{ and } f_i(p) \neq 0 \text{ for some } p \in \mathcal{M}_{1-i}, \text{ then}$$

$$\dim(\mathcal{M}_0 \cap \mathcal{M}_1) < \min(\dim \mathcal{M}_0, \dim \mathcal{M}_1).$$

Proposition

Let $\mathcal{M}_0$ and $\mathcal{M}_1$ be two algebraic models. If there is a polynomial f_0 such that

$$f_0(p) = 0 \text{ for all } p \in \mathcal{M}_0, \text{ and } f_0(p) \neq 0 \text{ for some } p \in \mathcal{M}_1, \text{ and}$$

$$\dim \mathcal{M}_1 \leq \dim \mathcal{M}_0 \text{ then}$$

$$\dim(\mathcal{M}_0 \cap \mathcal{M}_1) < \min(\dim \mathcal{M}_0, \dim \mathcal{M}_1).$$

Proof of Tree Parameter Identifiability

Theorem

The tree parameters of the phylogenetic mixture model $\mathcal{M}_{T_1} * \mathcal{M}_{T_2}$ are generically identifiable under the Jukes-Cantor and Kimura 2-parameter models if T_1, T_2 are trivalent with $n \geq 4$ leaves.

Strategy: Prove theorem for quartets $n = 4$ (using linear invariants), then lift to arbitrary sized trees:

Proposition

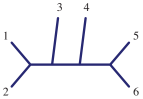
Let T_1, T_2, T_3, T_4 be n leaf trivalent trees. Suppose that there is a four element set $Q \subseteq [n]$ such that $\{T_1|_Q, T_2|_Q\} \neq \{T_3|_Q, T_4|_Q\}$. Then

$$\dim(\mathcal{M}_{T_1} * \mathcal{M}_{T_2} \cap \mathcal{M}_{T_3} * \mathcal{M}_{T_4}) < \dim(\mathcal{M}_{T_1} * \mathcal{M}_{T_2}).$$

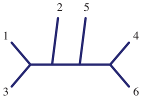
From Six to Infinity

Proposition

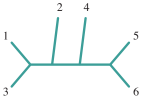
There are no quartet-matched pairs of trees with 5 leaves. The only pair of quartet-matched pairs of trees on 6 leaves are:



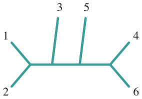
T_1



T_2



T_3



T_4

Proposition

There are linear invariants that distinguish T_1, T_2 from T_3, T_4.

Theorem (Matsen, Mossel, Steel 2007)

If two-tree mixtures are identifiable for trivalent trees with $n = 6$ trees, they are identifiable for all trees with $n \geq 6$ leaves.

Identifiability of Continuous Parameters

Theorem*

The continuous parameters of the phylogenetic mixture model $\mathcal{M}_{T_1} * \mathcal{M}_{T_2}$ are generically identifiable under the Jukes-Cantor and Kimura 2-parameter models if T_1, T_2 are trivalent with $n \geq 5$ leaves.

$$\begin{pmatrix} \alpha & \beta & \beta & \beta \\ \beta & \alpha & \beta & \beta \\ \beta & \beta & \alpha & \beta \\ \beta & \beta & \beta & \alpha \end{pmatrix} \qquad \begin{pmatrix} \alpha & \beta & \gamma & \gamma \\ \beta & \alpha & \gamma & \gamma \\ \gamma & \gamma & \alpha & \beta \\ \gamma & \gamma & \beta & \alpha \end{pmatrix}$$

Definition

Theorem* means that the result holds with high probability.

Proposition

Let $\phi : \mathbb{C}^d \to \mathbb{C}^m$ be a rational map. Then there is a Zariski open set $\Theta \subseteq \mathbb{C}^d$, such that $\#\phi^{-1}(\phi(\theta))$ is constant over Θ.

1. So to prove* the Theorem* for a particular size tree, generate random rational parameter choices θ and then symbolically solve the simultaneous polynomial system

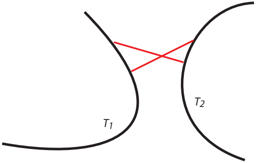
$$\phi(t) = \phi(\theta)$$

   and hope for one solution.
2. We check this using software SINGULAR, for JC and K2P on 4 and 5 leaf trees.
3. Recovering parameters uniquely on quartets $\implies$ recover edge lengths $\implies$ recover parameters on arbitrary sized trees.

Why $n = 5$ in Theorem*?

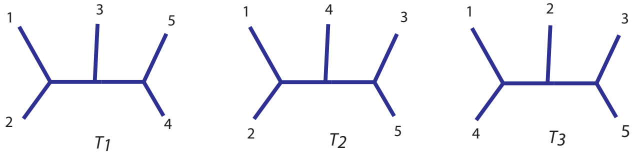
Proposition*

For T a four leaf tree under the Jukes-Cantor model, the continuous parameters in $\mathcal{M}_T * \mathcal{M}_T$ are not generically identifiable. The map $\phi_{T,T}$ is generically 6-to-1 (up to label swapping).



For biologically relevant parameters, we observed between 1 and 4 biologically relevant preimages.

Another Mathematical Surprise



Theorem

For the Jukes-Cantor model

$$\overline{\mathcal{M}_{T_2}} \subseteq \overline{\mathcal{M}_{T_1} * \mathcal{M}_{T_3}}.$$

Can the closure be dropped; i.e. does it happen for biologically meaningful parameter values?

Future Directions

- Develop methods to remove the * from a Theorem*
- Deal with the other group-based models (CFN, K3P)

  (K3P: current joint work with M. Casanellas - computational)
- Beyond group-based models, GTR, GMM
- Beyond 2-tree mixtures to *k*-tree mixtures

  (Recent work: M. Casanellas, J. Fernández-Sánchez, A. Kedzierska: some non-identifiability results)