The Identifiability of Covarion Models

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I: Covarion models:

Simple models of sequence evolution (JC, Kimura, HKY, GTR)

assume evolutionary process is

- homogeneous along sequence
- homogeneous through time

Both assumptions are likely violated.

Models with additional realism:

Inhomogeneity along sequence $\rightsquigarrow$ across-site rate-variation models

$\mathcal{M}$+I, $\mathcal{M}$+Γ, $\mathcal{M}$+Γ+I

Inhomogeneity through time $\rightsquigarrow$ Covarion models

Nucleotide example:

2 rate-classes, 'bases' for each class

$$\mathsf{A}^1, \mathsf{C}^1, \mathsf{G}^1, \mathsf{T}^1, \qquad \mathsf{A}^2, \mathsf{C}^2, \mathsf{G}^2, \mathsf{T}^2$$

GTR rate-matrix (4×4): Q

Switching parameters: $s_1, s_2 > 0$

Rate-class scaling factor: $1 > r \geq 0$

Create an 8×8 rate matrix

$$R = \begin{pmatrix} Q - s_1 I & s_1 I \\ s_2 I & rQ - s_2 I \end{pmatrix}$$

$$
\begin{array}{rcc}
 & A^1, C^1, G^1, T^1 & A^2, C^2, G^2, T^2 \\
 & \downarrow & \downarrow \\
A^1, C^1, G^1, T^1 \rightarrow & Q_1 - s_1 I & s_1 I \\
A^2, C^2, G^2, T^2 \rightarrow & s_2 I & Q_2 - s_2 I
\end{array}
$$

Within-class substitution rates: $Q_2 = rQ_1$

Between-class switching rates: s_1, s_2

The combined process is time-reversible, stationary.

Data is *only* A, C, T, G , no superscripts

All rate-class information is hidden.

$$A^1, A^2 \rightsquigarrow A$$

$$C^1, C^2 \rightsquigarrow C$$

$$G^1, G^2 \rightsquigarrow G$$

$$T^1, T^2 \rightsquigarrow T$$

Generalizations:

— κ observable states, c classes, $c\kappa \times c\kappa$ rate matrices

(e.g., protein models $\kappa = 20$, codon models $\kappa = 61$)

— Within-class matrices need *not* be scaled versions of a single Q,

as long as entire process is time-reversible

— Switching only between certain classes

(e.g., incorporate across-site variation)

Tuffley - Steel 1998: mathematical formalization (2 classes, 1 of which invariable)

– only partially captures covarion idea of Fitch - Markowitz (1970)

Galtier 2001: 4-class software implementation

Huelsenbeck 2002: 2-class covarion, but with g rates-across-sites classes $\rightsquigarrow 2g$ classes

Galtier - Jean-Marie 2004: theoretical observations on eigenvectors of scaled covarion models

Guindon - Rodrigo - Dyer - Hulesenbeck 2004: codon model with classes representing selection regimes

Reviews, with further generalization:

- Gascuel - Guindon, 2007 in "Reconstructing Evolution,"
- Wang - Spencer - Susko - Roger, 2007, MBE

Talks Thursday:

- Roger
- Whelan

Other names:

covariotide

covarion-like

site-specific rate variation (SSRV)

Markov-modulated Markov Process (MMM)

II: Identifiability:

A model is **identifiable** if

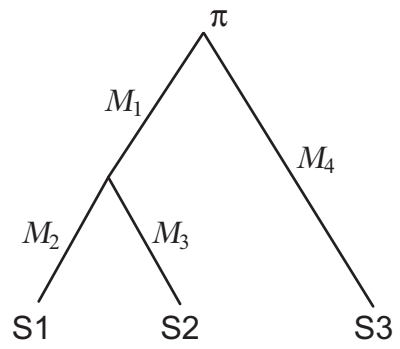
given an exact distribution of site-patterns arising from the model,

"infinite amount of perfect data,"

we can determine all model parameters.

Identifiability is necessary for statistical consistency of inference.

For covarion models,



$$\text{parameters} = \begin{cases} \text{Tree topology } T \\ \text{Substitution rates } Q_i \text{ for class } i = 1, 2, \ldots, c \\ \text{Switching rates } S \text{ between classes} \\ \text{Stationary distribution } \boldsymbol{\mu} \text{ for full process} \\ \text{Edge lengths on tree} \end{cases}$$

It is not simple to see that *any* of these are identifiable.

III: Results:

Theorem: (Allman, R—, 2006)

For generic parameters of the covarion model (and mixture models), the tree topology is identifiable provided $c < \kappa$,

i.e., if fewer classes than observable states.

Proof: Uses phylogenetic invariants

New:

Theorem: (Allman, R—)

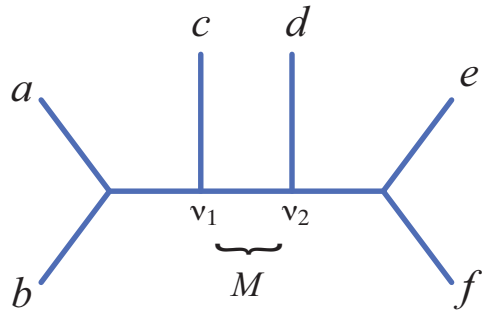
For generic parameters of the covarion model, if the tree topology is known and has at least 7 leaves, then all other parameters are identifiable provided

- $c \leq \kappa$, $\quad$ ($c < \kappa$ for S. Whelan)
- The switching process is irreducible (possible to switch from any class to any other class, through multiple steps)
- the entire process is time-reversible

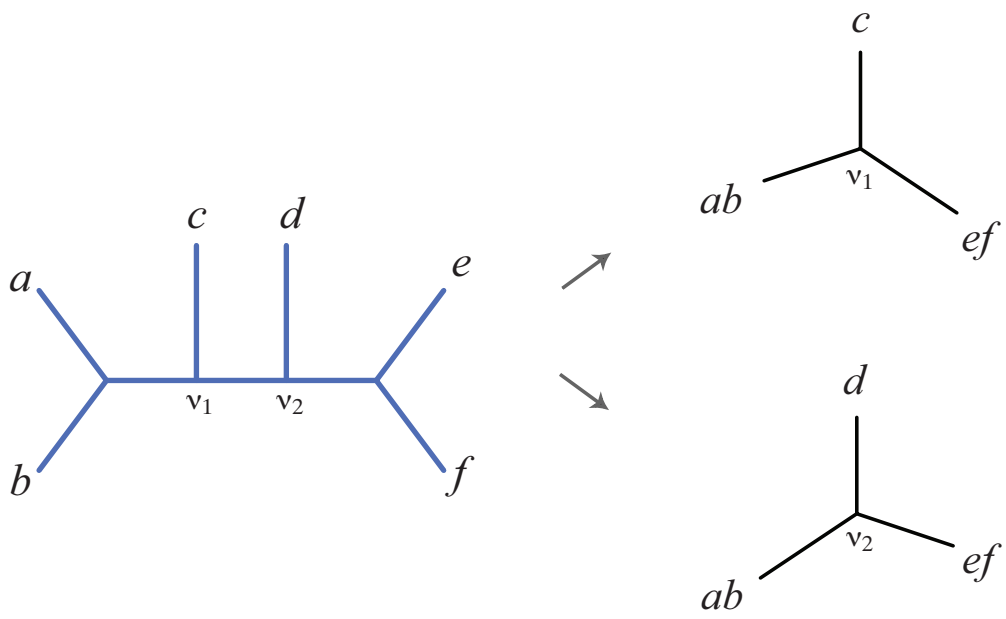
Note: $Q_i = r_i Q$ is *not* necessary.

Sketch of Proof:

With 7 leaves, T has a sub-tree



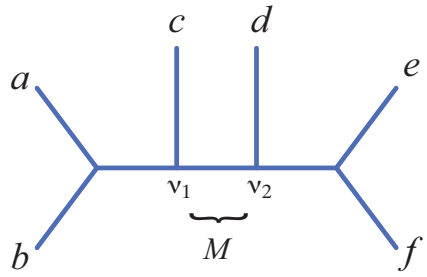
Goal is to identify $M = \exp(Rt)$ deep in tree



A theorem of J. Kruskal (1977) gives algebraic conditions for the identifiability (up to permutations) of general 3-leaf models.

Using Kruskal, we can identify M for the general model

– but must painfully show technical algebraic conditions are met –



$M = \exp(Rt)$ is not an algebraic function of its variables.

But the rows and columns of $M = \exp(Rt)$ are only determined up to permutation, further argument is needed to order correctly

— use special form of R,

pattern of zero/non-zero entries

irreducibility of switching process

time reversibility

Then matrix logarithm recovers R.

Finally, use R and 2-taxa marginalizations to get distances between leaves, which determines edge lengths

Final comments:

Identifiability of covarion model is known only for generic parameters

There may be parameters for which model is *not* identifiable.

but such cases must be 'rare' (of measure zero)

Generic identifiability is common for complex statistical models with hidden variables.

Kruskal's Theorem:

Consider a 3-leaf star model with R hidden states at the central root r and any number of states at the leaves a, b, c.

Let $\boldsymbol{\nu} \in \mathbb{R}^R$ be a root distribution, and $M_{ra},\ M_{rb},\ M_{rc}$ Markov matrices on the edges.

Define $I_a = \max\{k \mid$ *every* set of k rows of M_{ra} is independent$\}$, and I_b, I_c, similarly.

Theorem: If all entries of $\boldsymbol{\nu}$ are non-zero and

$$I_a + I_b + I_c \geq 2R + 2,$$

then the model's probability distribution uniquely determines $\boldsymbol{\nu}$, M_{ra}, M_{rb}, M_{rc}, up to some permutation.

I.e, for some unknown permutation P we may find

$$\boldsymbol{\nu}P^T,\ PM_{ra},\ PM_{rb},\ PM_{rc}.$$