Statiscal Properties of Phylogenetic Tree Construction Methods

Consistency, Long Branch Attraction; Robustness to Model Violations, ...

Of the 3 methods of tree construction we have learned about --

MP, distance methods ML - which is best?

...

For sure, one wants a statistical estimator to be CONSISTENT

(informally. if your data is perfectly in accord with the model [or method], the method X reconstructs the true tree.)

For the formal definition, suppose you have chosen a specific model with parameters $M_0 = (T, N)$ N = numerical parameters and your data consists of site pattern frequencies computed from n independent trials of the experiment. i.e. n sites were generated under M_0 independently.

Focusing only on the tree for notational ease (easy extension to (T, N)), then let $\hat{T}_n$ denote the estimator from your method based on a sample of size n. Suppose $\varepsilon > 0$ is arbitrary. Then if

$$\lim_{n \to \infty} \text{Prob}\left(\underbrace{\|\hat{T}_n - T\| < \varepsilon}\right) = \underline{\qquad\qquad}$$

measurement of how close $\hat{T}_n$ is to the true value T

probabilistic quantification of when $\hat{T}_n$ will be with ε of T

let the sample size go to ∞

then $\hat{T}_n$ is a CONSISTENT ESTIMATOR of T $= (T,N)$

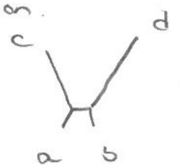
Formalization of a very basic requirement for inference.

If $\hat{T}_{method}$ is not consistent, in practice no amount of data collection will help you to estimate T with "method."

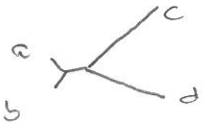
Which methods are consistent?

⋮

Parsimony and Long Branch Attraction.

We know that a metric tree 

can be hard to infer since a,b are the closest, i.e. their DNA sequences should look the most similar, but a,c are sister. Indeed, NJ was introduced to address this issue. We might expect parsimony to struggle for such trees. For such a tree, a "method" might infer



a tree in which the long branches are attracted.

≡ Long Branch Attraction

This phenomenon (LBA) extends to larger trees $n > 4$ and can throw off inference if too remote an outgroup is contained in data. Another way to view this is taxa c,d are essentially independent if those terminal branch lengths are long enough.

We will show that parsimony (MP) can be inconsistent under a "2-state JC" model called the Cavendar-Ferris-Neyman CFN model. "Felsenstein Zone"

Method:

Details: Parsimony on a 4-taxon tree

Model: Explained below CFN 2-state model

Data: Pattern frequencies	xxyy	xyxy	xyyx
	↑	↑	↑
Counts from data	n_1	n_2	n_3

(order reversed in book.)

3-trees to choose from

T_1: ab|cd $\quad ps(T_1) = n_1 + 2n_2 + 2n_3 = 2n - n_i$

T_2: ac|bd $\quad ps(T_2) = 2n_1 + n_2 + 2n_3 = 2n - n_2$

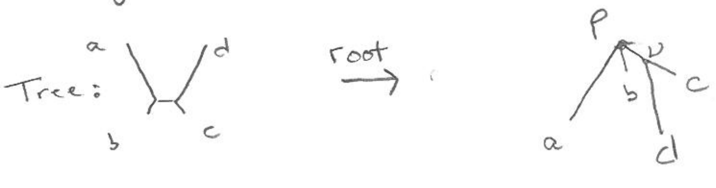
T_3: ad|bc $\quad ps(T_3) = 2n_1 + 2n_2 + n_3 = 2n - n_3$

where n = # of informative sites

Parsimony Criterion: Choose T_i with n_i largest (so $2n - n_i$ smallest)

= End data analysis.

Begin: Generate sequences assuming the CFN model



Book: Here root at a

2-states.

Root Distribution is $P_\rho = (.5\ .5)$

2 Markov matrices one for short edges, one for long edges

$$M_{long} = \begin{pmatrix} 1-q, & q \\ q & 1-q \end{pmatrix} \qquad M_{short} = \begin{pmatrix} 1-p & p \\ p & 1-p \end{pmatrix} \qquad p, q \in (0, .5)$$

With this model

$$\text{xxyy} \qquad p_1 = (1-q)^2 p(1-p)^2 + 2q(1-q)p(1-p)^2 + q^2p^3$$

$$\text{xyxy} \qquad p_2 = (1-q)^2p^2(1-p) + 2q(1-q)p^2(1-p) + q^2(1-p)^3$$

p. 168 book

$$\text{xyyx} \qquad p_3 = (1-q)^2p^3 + 2q(1-q)p(1-p)^2 + q^2p(1-p)^2$$

↑

Work (including HW)

If MP were to choose the true tree T_1, then since

$$\lim_{n\to\infty} \frac{n_i}{n} = p_i$$ it must be that $p_1 > p_2, p_3$

To test this, we compute

Assuming $p, q \in (0, 1/2)$ Why?

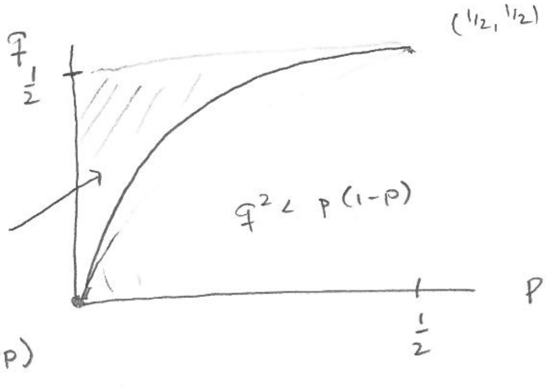
$$p_1 - p_2 = (1-2p)(p(1-p) - q^2)$$

$$p_1 - p_3 = p(1-2p)(1-2q)$$

$p_1 - p_3 > 0$ always, but

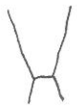
$p_1 - p_2 > 0$ iff $p(1-p) - q^2 > 0$ i.e $p(1-p) > q^2$

i.e. $q^2 < -p^2 + p$



$q^2 > p(1-p)$

Felsenstein Zone

$T =$ 

Theorem: If sequences evolve under the CFN model on T with parameters given as above, then for parameters chosen with $q^2 > p(1-p)$ Maximum Parsimony gives an "inconsistent" estimator of T.

Summary:

Parsimony, a non-model-based method yields inconsistent estimators for sequence data perfectly in accord with a CFN model in some parts of parameter space

ML yields a consistent estimator $\hat{T}_{MLE}$ under many models. (list in text.)

NJ yield a consistent estimator provided the distance used is the appropriate one for the model chosen (GTR $\leftrightarrow$ d_{GTR}, etc.)

Math Students: Identifiability of parameters key to consistency proofs.

Though consistency of $\hat{T}_n$ is essential for sound inference of T, there are other practical considerations

1) Since consistency is concerned with $\lim_{n\to\infty}$, for empirical datasets, how big should n be so that $\hat{T}_n$ is a "good" estimate?

2) Phylogenetic models are of corse a poor description of the true evolutionary process of DNA so how robust our methods to violations of model assumptions? ROBUSTNESS of MLE?

Bootstrapping:

Way to assess support for branches in $\hat{T}$

"The bootstrap"

Suppose $\hat{T}$ is estimated from an alignment of length n

$$\begin{array}{lll} & & n \\ s_1: & A & T \\ \vdots & & T \\ & & C \\ & & T \\ & & \vdots \\ s_\ell: & A & T \\ & & \uparrow \\ & & n\text{-th site} \end{array}$$

and that ML (or any other method) was used to construct $\hat{T} = \hat{T}_n$.

Then

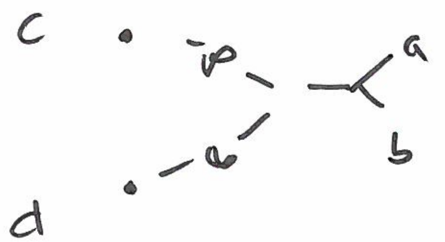
1) Sample with replacement from the columns in the alignment to create a new dataset of length n, say R_1 (= replicate 1)

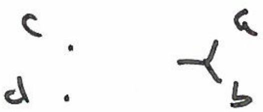
2) Construct a bootstrap tree $\hat{T}_{n,1}$ from alignment R_1 and keep track of the number of edges it has that are on $\hat{T}$

3) Repeat as many times as desired, typically $K = 1000$ times (k=100)

4) Embellish $\hat{T}$ by adding bootstrap support numbers to its branches

The bootstrap support number is proportion of bootstrap trees with that edge





Next: MP can be inconsistent under a "2-state JC" model in some parameter space.

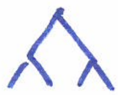
The correct name is the Cavendar-Ferris-Neyman model (CFN) and the "bad" area of parameter space is known as the "Felsenstein model"

DETAILS:

Method: Parsimony

Model: CFN model to generate pattern freq. array

$\vec{p} = (.5, .5)$ uniform

T: 

$$M = \begin{pmatrix} 1-a & a \\ a & 1-a \end{pmatrix}$$

$a = P(X_1 = i \mid X_0 = j)$

i, j diff.

Data:	xxyy	xyxy	xyyx
	↑	↑	↑
Counts	n_1	n_2	n_3

$n_1 + n_2 + n_3 =$ # of pars. informative sites