Generalizing the model

Features of $\left\{\begin{matrix}\text{GTR}\\ \text{GM}\end{matrix}\right.$ model: independence assumption

gains you data, but likely unrealistic

identically distributed

If aligned sequences are long, perhaps unrealistic to use same parameters on each site.

A common way to address this is with a MIXTURE MODEL

Simple Example: Fix T.

Suppose you have 3 classes of sites (slow, medium, fast evolving) and choose GTR parameters for each of them. Compute the expected pattern frequency arrays

$$\begin{tikzcd} P^{slow} & P^{medium} & P^{fast} \\ \vec{p}_1, Q_1, \{t_e^1\} \arrow[u] & \vec{p}_2, Q_2, \{t_e^2\} \arrow[u] & \vec{p}_3, Q_3, \{t_e^3\} \arrow[u] \end{tikzcd}$$

Additionally, choose weighting or mixture parameter α_1, α_2 $(k=2)$

then the joint frequency array is

$$P = \alpha_1 P_1 + \alpha_2 P_2 + (1-\alpha_1-\alpha_2) P_3$$

Each P_i is called a MIXTURE COMPONENT and the number of parameters to infer is

$$\underset{\underset{\#\text{ component}}{\uparrow}}{3}\,(\underset{\underset{\vec{p}}{\uparrow}}{3} + \underset{\underset{Q}{\uparrow}}{5} + \underset{\underset{\text{b.l.}}{\uparrow}}{2n-3}) + \underset{\underset{\#\text{ of components }-1}{\uparrow}}{2}$$

The α_i are called the weights or mixing parameters

Note that for a fixed binary tree on n taxa that if a mixture uses K components, then the number of numerical parameters to be inferred increases roughly by a factor of K. i.e. increases a lot.

For both biological and practical reasons, mixture models with fewer parameters are used in practice. Some examples include:

- GTR+I ≡ GTR + Invariable sites model

  Two classes of sites: those that are free to mutate (GTR)

  those that are variable due to perhaps functional constraints (I)

  Parameters: GTR : $\vec{p}_Q$, Q $3+6=9$

  I : $\vec{p}_I$ $=3$

  weights: s $=1$

  Excluding branch lengths, this is an 13-parameter model. I.e. 4 additional parameters.

  A variation sets $p_I = p_Q$, i.e. assumes the base distribution is the same over all sites, both variable and invariable.

- GTR + rate variation (discrete)   Lots of variation

  Assumes k classes of sites but that the mutation rate is scaled depending which class you are in.

Example: GTR + rate variation k classes # of classes chosen by user.

Numerical parameters (excluding branch lengths on T) are

- GTR parameters $\vec{p}, Q$ used for <u>all</u> sites
- classes weights $s_1, s_2, \dots, s_k$ $\sum s_i = 1$, $s_i > 0$ distribution of sites to classes
- rates $r_1, r_2, \dots, r_k$ $r_i \geq 0$ scaling rate for i-th class

The pattern frequency array is

$$P = s_1 P_1 + s_2 P_2 + \dots + s_k P_k$$

where P_i is the expected pattern freq array for the i-th class

P_i is computed using $\vec{p}, \underbrace{r_i Q}_{\text{scaled version of } Q, \text{ with scaling factor the rate } r_i.}$ and branch lengths $\{t_e\}$

$r_i > 1$, $r_i < 1$, etc.

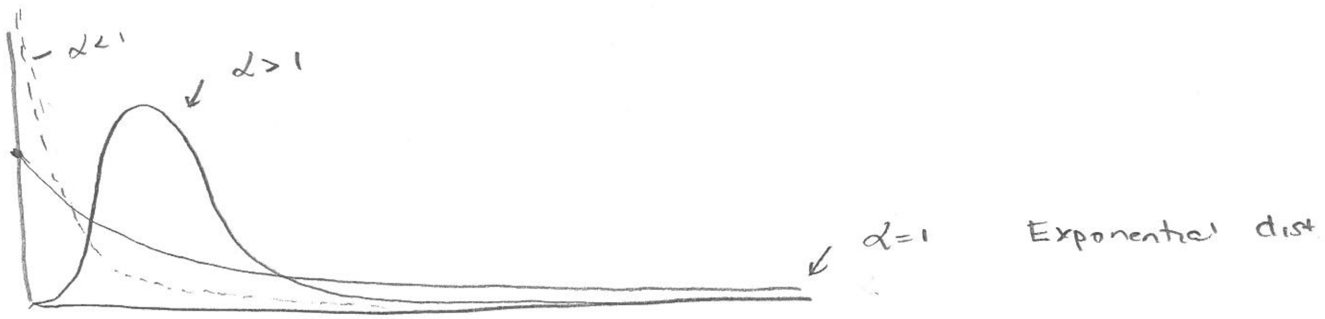
visual effect.

Discuss how to use such a model for simulations ...

Variations: Instead of choosing the rate functions at random, choose them from a distribution. In practice, the Γ-distribution is used or in reality the discrete-Γ.

Gamma distributions in phylogenetics is a 1-parameter family of distributions with the unknown parameter called α = shape parameter.

The densities for various values of α are shown



Notice all $r_i > 0$ are possible rates and the shape of the density says something about the probability of various rates.

See R demo and discuss meaning.

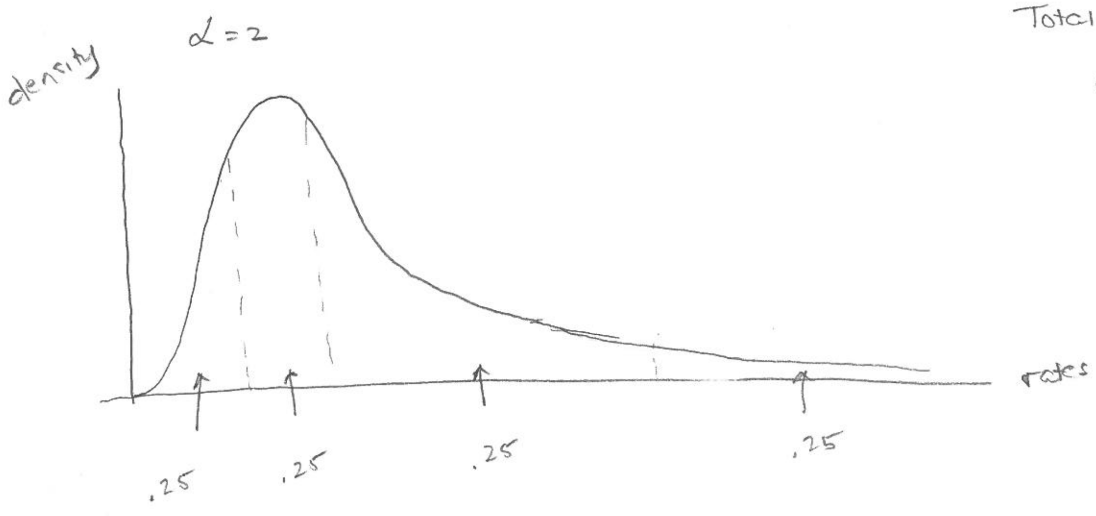
These models are frequently called RATES-ACROSS-SITES models.

In software, an RAS model GTR+Γ is implemented as a GTR+ discrete-Γ. i.e. GTR + dΓ(4) Z. Yang 1994 PAML

↑ # of categories

↑ discrete.

Example: GTR + dΓ(4) Suppose the user choose 4 categories and GTR parameters $\vec{p}, Q$ are known as is the Γ-shape parameter α.



Total are under curve = 1

Areas ⟷ probability

Break the density curve into 4 regions, each of which has area .25

$\Rightarrow$ probability = .25

In each of the four regions, find the mean r_1, r_2, r_3, r_4, then

if a site is chosen to be in class i, $1 \le i \le 4$, the Markov matrix

on a branch of length t is given by

$$M = e^{Q r_i t} \qquad \text{i.e. Scale } Q \text{ by } r_i \text{ and } t.$$

and the expected pattern frequency array is

$$P = \underset{\substack{\uparrow \\ r_1}}{s_1 P_1} + \underset{\substack{\uparrow \\ r_2}}{s_2 P_2} + \underset{\substack{\uparrow \\ r_3}}{s_3 P_3} + \underset{\substack{\uparrow \\ r_4}}{(1-(s_1+s_2+s_3)) P_4}$$

$\vec{p}$, Q for all 4 classes.

Other variants are of course possible.

The most widely used model in practice is

$GTR + I + \Gamma$ secretly $GTR + I + d\Gamma(4)$

Parting comments:

In a $GTR + I + \Gamma$ model, a site belongs to 1 category so that rate applies to that site in <u>all</u> parts of the tree. There are no speed ups or slow downs for that site in different parts of the tree.

Looking at the $K = 4$ categories together, the metric trees they infer are all scalings of 1 tree.