Model-based Distances

Recall that 1 weakness of the Hamming distance = proportion of sites that differ is that it fails to account for back substitutions or multiple substitutions on an edge

and unless sequences are very closely related, the Hamming distance tends to under estimate the amount of evolutionary distance between 2 taxa.

To address this, we use our models JC, K2P, K3ST, GTR, GM to "correct" the Hamming distance and to account for unseen changes.

Example: Jukes - Cantor model and Jukes- Cantor distance

Parameters: single edge thought of as path from taxon a to b in tree

$\vec{p_0} = (.25 \;\; .25 \;\; .25 \;\; .25)$

$$Q = \begin{pmatrix} -\alpha & \alpha/3 & \alpha/3 & \alpha/3 \\ & -\alpha & & \\ & & -\alpha & \\ & & & -\alpha \end{pmatrix},$$ branch length t, and Markov matrix $M(t) =$

$$M = \begin{pmatrix} 1-a & a/3 & a/3 & a/3 \\ & 1-a & & \\ & & 1-a & \\ & & & 1-a \end{pmatrix}$$ with $a(t) = \frac{3}{4}\left(1 - \frac{4}{3}\alpha t\right)$

Assuming the JC model, the expected pattern frequency array is

$$P = \text{diag}([.25 \;\; .25 \;\; .25 \;\; .25])\, M(t) = \begin{pmatrix} \frac{1}{4}(1-a) & a/12 & a/12 & a/12 \\ a/12 & \frac{1}{4}(1-a) & a/12 & a/12 \\ a/12 & & \ddots & \\ a/12 & & & \end{pmatrix}$$ with a as above

[No data here. Yet.]

If we interpret α = rate in units $\dfrac{\#\text{ substitutions}}{\text{time}}$, then

$\swarrow$(model at single site)

$$\alpha t = \left(\frac{\#\text{ substitutions per site}}{\text{time } t}\right)(\text{time } t)$$

$$\boxed{\alpha t = \#\text{ of substitutions over time } t}$$

including those hidden ones

This is (will be) the Jukes Cantor distance once we solve for it.

$$a(t) = a = \frac{3}{4}\left(1 - e^{-\frac{4}{3}\alpha t}\right)$$

$$\Rightarrow \boxed{\alpha t = -\frac{3}{4}\ln\left(1 - \frac{4}{3}a\right)} \quad = \#\text{ of subst. per site over elapsed time } t$$

Since we don't have a in hand, we must estimate it from data,

i.e from the empirical pattern freq. array

In theory, S_0 and S_1 disagree with probability $\underbrace{12(a/12)}_{\text{Sum of off-diagonal entries}} = a$

Thus, we estimate a with $\hat{a} = \dfrac{\#\text{ of sites with non-constant pattern}}{\#\text{ of sites } n}$

= Hamming distance!

Defn: The Jukes-Cantor distance $d_{JC}(S_0, S_1)$ between aligned sequences is

$$d_{JC} = -\frac{3}{4}\ln\left(1 - \frac{4}{3}\hat{a}\right) \qquad \hat{a} = d_{\text{Hamming}}(S_0, S_1)$$

Ex.

$$S_0: \quad A\ A\ A\ \boxed{C}\ G \qquad G\ C\ \boxed{A}\ \boxed{T}\ G$$
$$S_1: \quad A\ A\ A\ \boxed{T}\ G \qquad G\ C\ \boxed{T}\ \boxed{A}\ G$$

$$d_{Hamming}(S_0,S_1) = 3/10 = .3$$

$$d_{JC}(S_0,S_1) = -\frac{3}{4}\ln\left(1-\frac{4}{3}(.3)\right) \approx .38$$

Several Comments:

- $d_{JC} = .38 > .3 = d_{Hamming}$ to account for hidden mutations

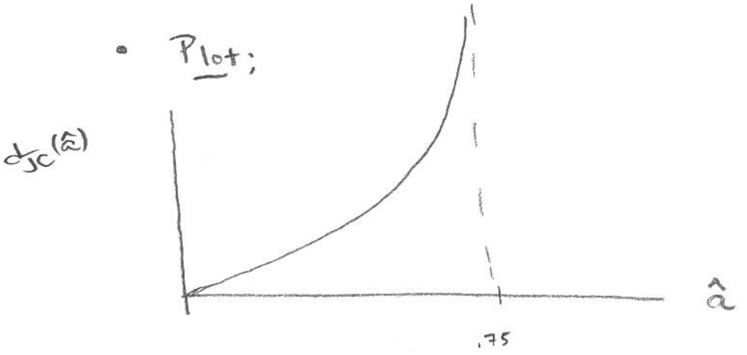
- $d_{JC}(s_0,s_1) = -\frac{3}{4}\ln\left(1-\frac{4}{3}\hat{a}\right) \Rightarrow 0 \leq \hat{a} < \frac{3}{4}$ for the log to make sence

This makes sense: if 2 sequences are generated at random using the root distribution ($\frac{1}{4}$ $\frac{1}{4}$ $\frac{1}{4}$ $\frac{1}{4}$) then S_0 and S_1 will agree roughly $1/4$ of the time and disagree in roughly $\hat{a} = 3/4$ of the sites $d(s_0,s_1) >>> 0$

S_0: _ _ _

S_1: _ _ _

- Plot:

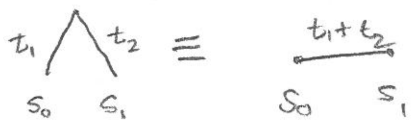


Thus as $\hat{a}$ gets close to .75, $d_{JC}(S_0,S_1) \rightarrow \infty$, huge distances

"Saturated sequences"

informally, you can not differentiate them from 2 randomly selected sequences

- Since JC is time-reversible, on a tree



or more generally we can consider paths in trees.

Similar methods can be used to derive distance formulas for K2P, K3ST, GTR.

$$d_{K2P}(S_1, S_2) = \frac{-1}{2} \ln(1 - 2\hat{b} - \hat{e}) - \frac{1}{4} \ln(1 - 2\hat{e})$$

$\hat{b}$ = proportion of observed transitions

$\hat{e}$ = proportion of observed transv.

$$d_{K3}(S_1, S_2) = \frac{-1}{4} \left(\ln(1 - 2\hat{b} - 2\hat{c}) + \ln(1 - 2\hat{b} - \hat{d}) + \ln(1 - 2\hat{c} - \hat{d}) \right)$$

$\hat{b}$, $\hat{c}$, $\hat{d}$ are best estimates for $M_{K3P} = \begin{pmatrix} * & b & c & d \\ & & & \end{pmatrix}$

$\underline{\underline{\text{OR}}}$ $P = \text{diag}([\,1/4 \;\; 1/4 \;\; 1/4 \;\; 1/4\,])\, M_{K3P}$

If $\hat{c} = \hat{d}$, then this simplifies to K2P.

There is also a more general GTR distance ⇝ see book. Requires

1) normalization 2) Knowledge of Trace of a matrix.

Why normalize?

Eg. JC model

<u>Probability</u>: (<u>Model</u>)

$$d_{JC}(S_1, S_2) = \frac{-3}{4} \ln\left(1 - \frac{4}{3} a\right)$$

<u>Estimate</u> from data.

$$d_{JC}(S_0, S_1) = \frac{-3}{4} \ln\left(1 - \frac{4}{3} \hat{a}\right)$$

$$\underbrace{\alpha t}_{\text{Intertwined}}$$

$$\alpha t = 2\alpha\left(\frac{t}{2}\right) = 4\alpha\left(\frac{t}{4}\right) = c\alpha\left(\frac{t}{c}\right)$$

we can compute the product αt, but neither α or t separately

However, α represents a <u>total</u> mutation rate: in JC

$$\underbrace{\frac{1}{4}\alpha}_{\text{rate leaving State A}} + \underbrace{\frac{1}{4}\alpha}_{G} + \underset{C}{\frac{1}{4}\alpha} + \underset{T}{\frac{1}{4}\alpha} = \alpha$$

rate leaving state

Normalize so that $\alpha = 1$

$$Q = \begin{pmatrix} -1 & 1/3 & 1/3 & 1/3 \end{pmatrix} \text{ etc.}$$

$$\alpha t = 1(t) = \frac{\#\text{ of subst.}}{t} \cdot t$$

$$= t \ \#\text{ of substitutions}$$

i.e. t measures the expected number of substitutions over the elapsed time.

MATLAB eg's