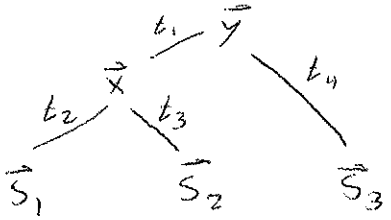
## Review from previous lecture

Given some sequences $\vec{s}_1, \vec{s}_2, \vec{s}_3$ and a tree $T$, we can compute the likelihood of the sequences given the tree provided that we have some model of the probability that the sequences change from one to another.




$$Pr(\vec{s}_1, \vec{s}_2, \vec{s}_3 \mid T) = \sum_{\vec{y}} \sum_{\vec{x}} Pr(\vec{y}) \cdot Pr(\vec{x} \mid \vec{y}, t_1) \cdot Pr(\vec{s}_1 \mid \vec{x}, t_2) \cdot Pr(\vec{s}_2 \mid \vec{x}, t_3) \cdot Pr(\vec{s}_3 \mid y, t_4)$$

### Transition Probabilities

So how do we get these transition probabilities?

Most phylogenetic methods do not try to model indels, so we assume sequences can be aligned:

ATG GGA ...
ATG GGC ...
ATG AGT ...

We now define characters in our sequences:

* nucleotides
* amino acids
* codons

We then write:

$$Pr(\vec{s}_1 \mid \vec{s}_2, t) = \prod_{i=1}^{L} Pr(\vec{s}_{1,i} \mid s_{2,i}, i, t)$$

This formulation assumes that sites evolve independently.

This is usually simplified to:

$$Pr(\vec{s}_1, \vec{s}_2 \mid t) = Pr(s_{1,i} \mid s_{2,i}, t)$$

This formulation assumes sites evolve identically as well.

# Jukes-Cantor model

Simplest case: characters are nucleotides, each nucleotide is equally likely to mutate to any other.

Let's say our initial probability distribution over nucleotides at a site is:

$$\vec{p}_0 = \begin{pmatrix} p_A \\ p_C \\ p_G \\ p_T \end{pmatrix}$$

Let $w_{ij}$ be the probability that a single substitution changes nucleotide from $i$ to $j$:

$$w_{ij} = \begin{cases} 1/3 & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases}$$

we can write a matrix $\underline{W} = [w_{ij}] = \begin{pmatrix} 0 & 1/3 & 1/3 & 1/3 \\ 1/3 & 0 & 1/3 & 1/3 \\ 1/3 & 1/3 & 0 & 1/3 \\ 1/3 & 1/3 & 1/3 & 0 \end{pmatrix}$

After exactly one substitution, the new probability distribution over nucleotides is

$$\underline{W}\,\vec{p}_0$$

So what about after some amount of time? We don't know exactly how many substitutions have occurred, but assuming a molecular clock, the average will be $\mu t$ where $\mu$ is substitution rate and $t$ is time.

If substitutions are independent, then $\Pr(m|\mu t) = e^{-\mu t}\frac{(\mu t)^m}{m!}$

So:

$$\begin{aligned}
\vec{p}(t) &= \Pr(m=0|\mu t)\cdot\vec{p}_0 + \Pr(m=1|\mu t)\,\underline{W}\,\vec{p}_0 + \Pr(m=2|\mu t)\cdot\underline{W}^2\vec{p}_0 + \dots \\
&= \sum_{m=0}^{\infty} \Pr(m|\mu t)\,\underline{W}^m\,\vec{p}_0 \\
&= \sum_{m=0}^{\infty} e^{-\mu t}\frac{(\mu t)^m}{m!}\underline{W}^m\,\vec{p}_0 \\
&= e^{-\mu t}\left(\sum_{m=0}^{\infty}\frac{(\mu t\underline{W})^m}{m!}\right)\vec{p}_0 \\
&= e^{-\mu t}\,e^{\mu t\underline{W}}\,\vec{p}_0 \\
&= e^{\mu t(\underline{W}-\underline{I})}\,\vec{p}_0 = e^{-t\underline{P}}\,\vec{p}_0
\end{aligned}$$

where $\underline{P} = \underline{W} - \underline{I}$ is transition matrix or substitution matrix.

So for Jukes-Cantor model:

$$P_{ij} = \begin{cases} 1/3 & \text{if } i \neq j \\ -1 & \text{if } i = j \end{cases}$$

and

$$\vec{p}(t) = e^{+\mu t \underline{P}} \vec{p}_0$$

For this very simple $\underline{P}$, it turns out that there is an analytic expression for the matrix exponential:

$$\left[e^{\mu t \underline{P}}\right]_{ij} = \begin{cases} \frac{1}{4} + \frac{3}{4} e^{-\mu t} & \text{if } i = j \\ \frac{1}{4} - \frac{1}{4} e^{-\mu t} & \text{if } i \neq j \end{cases}$$

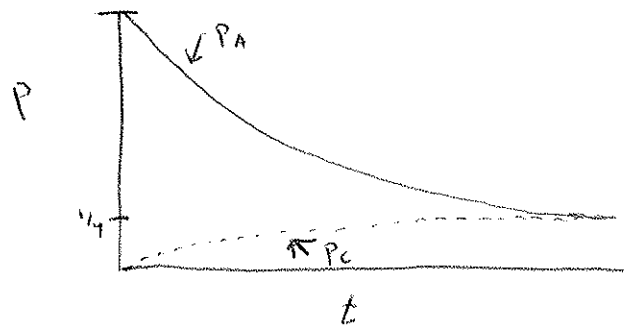
So let's say that

$$\vec{p}_0 = \begin{pmatrix} P_A = 1 \\ P_C = 0 \\ P_G = 0 \\ P_T = 0 \end{pmatrix}$$

Then at time $t$,

$$P_A(t) = \frac{1}{4} + \frac{3}{4} e^{-\mu t}$$

$$P_C(t) = P_G(t) = P_T(t) = \frac{1}{4} - \frac{1}{4} e^{-\mu t}$$




$e^a e^b = e^{a+b}$

Using Jukes-Cantor for maximum likelihood estimate:

AA —— $\mu t$ —— AC

$$\Pr(AA \mid AC, \mu t) = \Pr(A \mid A, \mu t) \cdot \Pr(A \mid C, \mu t)$$

$$= \left(\tfrac{1}{4} + \tfrac{3}{4} e^{-\mu t}\right)\left(\tfrac{1}{4} - \tfrac{1}{4} e^{-\mu t}\right)$$

$$= \tfrac{1}{16}\left(1 + 3e^{-\mu t}\right)\left(1 - e^{-\mu t}\right)$$

$$= \tfrac{1}{16}\left[1 - e^{-\mu t} + 3e^{-\mu t} - 3e^{-2\mu t}\right]$$

$$= \tfrac{1}{16}\left(1 + 2e^{-\mu t} - 3e^{-2\mu t}\right)$$

$$2\Pr(AA \mid \mu t) = 0 = 2\mu t e^{-\mu t} + 6\mu t e^{-2\mu t} = 2\mu t\left(3e^{-2\mu t} + e^{-\mu t}\right)$$

$$e^{\mu t} = 3$$

Not worth the algebra, doesn't clarify the point

| $\mu t$ | $\Pr(AA \mid AC, \mu t)$ |
|---|---|
| 0 | 0 |
| 0.1 | 0.028 |
| 0.5 | 0.077 |
| 0.824 | 0.083 |
| 1.0 | 0.082 |
| 2.0 | 0.07 |
| 4.0 | 0.063 |

For not much data, likelihood is not sharply peaked. Would be more peaked with more data.

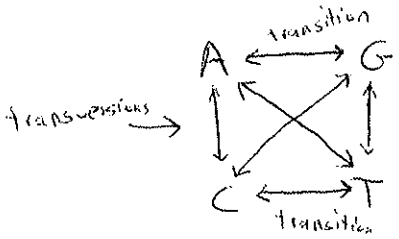
Even for best value of $\mu t$, likelihood $\ll 1$

# More general substitution models

In practice, we typically use models that are more complex than Jukes Cantor and do the calculations using digital computing machines rather than pen and paper.

One example of such a model: HKY85. Captures 2 things not in Jukes-Cantor:

1)




] purines

] pyrimidines

For most polymerases, transitions are more common than transversions. Why?

2) Empirically, most genes have unequal frequencies of the four nucleotides:

$$\phi_A \neq \phi_C \neq \phi_G \neq \phi_T$$

HKY85 substitution matrix

| | A | C | G | T |
|---|---|---|---|---|
| A | * | $\phi_C$ | $\times\phi_G$ | $\phi_T$ |
| C | $\phi_A$ | * | $\phi_G$ | $\times\phi_T$ |
| G | $\times\phi_A$ | $\phi_C$ | * | $\phi_T$ |
| T | $\phi_A$ | $\times\phi_C$ | $\phi_G$ | * |

$\phi_x$ is equilibrium frequency of nucleotide $x$

$\times$ is transition-transversion ratio. Is $\times$ typically $>$ or $<1$?