Inferring the Past: Phylogenetic Trees (chapter 12)

- The biological problem
- Parsimony and distance methods
- *Models for mutations and estimation of distances*
- Maximum likelihood methods

Estimation of distances

- Many alternative ways to derive the distances d_{ij} exist
- We can construct a simple stochastic model for the evolution of a DNA sequence…
- …and then obtain the distances from the model
- Key points:
  - mutations at sites are rare events in the course of time => poisson process
  - sites evolve individually and by an identical mechanism
  - number of mismatched bases is a sum of mutations at individual sites => binomial variable

A stochastic model for base substitutions

- Consider a single homologous site in two sequences
- Assume the sites diverged for time length t: the sites are separated by time 2t
- Suppose that the number of substitutions in any branch of length t has a Poisson distribution with mean λt
- Probability that k substitutions occur is given by the Poisson probability $e^{-\lambda t}(\lambda t)^k/(k!)$, k = 0, 1, 2, …

Substitutions at one site

- General model: P(substitution results in base j | site was base i) = m_{ij}
- Felsenstein model: $m_{ij} = \pi_j$, with $\pi_j \geq 0$ and $\pi_1 + \pi_2 + \pi_3 + \pi_4 = 1$
- Assume that the set of probabilities π_j is same at every position in the sequence

Substitutions at one site (2)

- Probability $q_{ij}(t)$ that a base i at time 0 is substituted by a base j a time t later
- $q_{ij}(t) = e^{-\lambda t} + (1 - e^{-\lambda t})\ \pi_j$, if i = j
- $q_{ij}(t) = (1 - e^{-\lambda t})\ \pi_j$, otherwise

Substitutions at one site (3)

- We assume stationarity: distribution of base frequencies is the same for every time t
- In other words, we want that

P(base a time t later = j) π_j^0

- For our simple model, this can be shown to hold

Estimating distances

- Distances should take into account the mutation mechanism
- Average of λt substitutions occur at a particular site on a branch of length t
- However, some of the substitutions do not change the base (A -> A or A -> G -> A, for example)

Mean number of substitutions in time t

- What is the chance H that a substitution actually changes a base?
- $H = \sum \pi_i(1 - \pi_i) = 1 - \sum\pi_i^2$
- Average number of real substitutions is then λtH
- Distance K between two sequences is

$K = 2\lambda tH$

Estimating distances from sequence data

- We want to estimate $K = 2\lambda tH$ from sequence data
- The chance $F_{ij}(t)$ that we observe a base i in one sequence and a base j in another is

$F_{ij}(t) = \sum_l \pi_l q_{li}(t) q_{lj}(t)$

by averaging over the possible ancestral nucleotides

Estimating distances from sequence data

- Expression $F_{ij}(t) = \sum_l \pi_l q_{li}(t) q_{lj}(t)$ can be simplified by assuming that the mutation process is reversible:

$\pi_i m_{ij} = \pi_j m_{ji}$ for all $i \neq j$

- From this it can be shown that

$\pi_i q_{ij}(t) = \pi_j q_{ji}(t)$ for all i, j and $t > 0$

- Now the model simplifies into $F_{ij}(t) = \pi_i q_{ij}(2t)$

Estimating distances from sequence data

- What is the probabilitity $F = F(t)$ that the letters at a particular position in two immediate descendants from the same node are identical?

$F = \sum_i \pi_i q_{ii}(2t) = e^{-2\lambda t} + (1 - e^{-2\lambda t})(1 – H)$

Putting the sites together

- Assume that
  - sites evolve independently of one other and
  - mutation process is identical at each site
  - The two sequences have been aligned against each other and gaps have been removed
- Do the bases at site i in the sequences differ?

$X_i = 1$ if the ith pair of sites differ

$X_i = 0$ otherwise

Putting the sites together (2)

- $P(X_i = 1) = 1 – F = (1 - e^{-2\lambda t})H$
- Now $D = X_1 + … + X_s$ is the number of mismatched pairs of bases
- D is a binomial random variable with parameters s and 1 – F
- Notice that D is the Hamming distance for the sequences

Putting the sites together (3)

- F is unknown and has to be estimated from the sequence data
- Recall that the observed proportion of successes is a good estimator of the binomial success probability: estimate 1 – F with D/s
- $D/s = (1 - e^{-2\lambda t})H$
- $2\lambda t = -\log(1 – D/(sH))$
- Finally, we obtain $K = 2\lambda tH = -H \log(1 – D/(sH))$

Jukes-Cantor formula

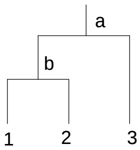
- Estimate $2\lambda tH = -H \log(1 – D/(sH))$ of the distance K is known as the Jukes-Cantor formula
- When H (chance that a substitution actually occurs) approaches 1, the estimate decreases and approaches the Poisson mean $2\lambda t$
- H is usually not known and has to be estimated from the data as well

Inferring the Past: Phylogenetic Trees (chapter 12)

- The biological problem
- Parsimony and distance methods
- Models for mutations and estimation of distances
- *Maximum likelihood methods*

Maximum likelihood methods

- Consider the tree on the right with three sequences
- Probability $p(i_1, i_2, i_3)$ of observing bases i_1, i_2 and i_3 can be computed by summing over all possible ancestral bases,

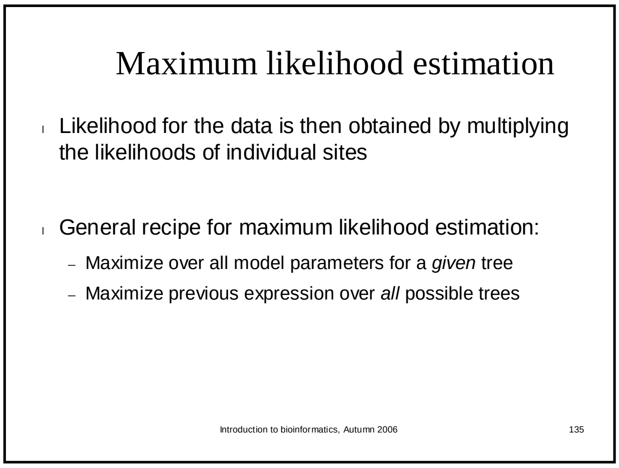


$$p(i1, i2, i3) = \sum_a\sum_b \pi_a q_{ai3}(t_2)q_{ab}(t_2-t_1)q_{bi2}(t_1)q_{bi1}(t_1)$$

- Hard to compute for complex trees

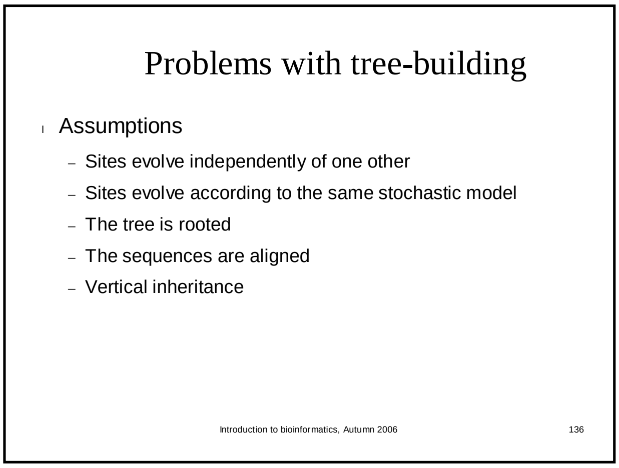
Maximum likelihood estimation

- We would like to calculate likelihood $p(i_1, i_2, …, i_n)$ in the general case
- Calculations can be arranged using the peeling algorithm
- Basic idea is to move all summation signs as far to the right as possible



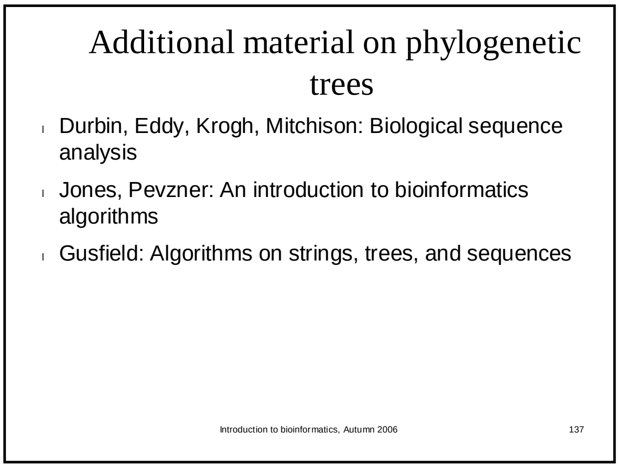
Maximum likelihood estimation

- Likelihood for the data is then obtained by multiplying the likelihoods of individual sites
- General recipe for maximum likelihood estimation:
  - Maximize over all model parameters for a *given* tree
  - Maximize previous expression over *all* possible trees



Problems with tree-building

- Assumptions
  - Sites evolve independently of one other
  - Sites evolve according to the same stochastic model
  - The tree is rooted
  - The sequences are aligned
  - Vertical inheritance



Additional material on phylogenetic trees

- Durbin, Eddy, Krogh, Mitchison: Biological sequence analysis
- Jones, Pevzner: An introduction to bioinformatics algorithms
- Gusfield: Algorithms on strings, trees, and sequences