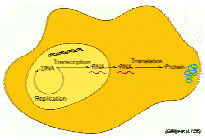
Machine Learning

10-701/15-781, Spring 2008

Machine Learning in Computational Biology

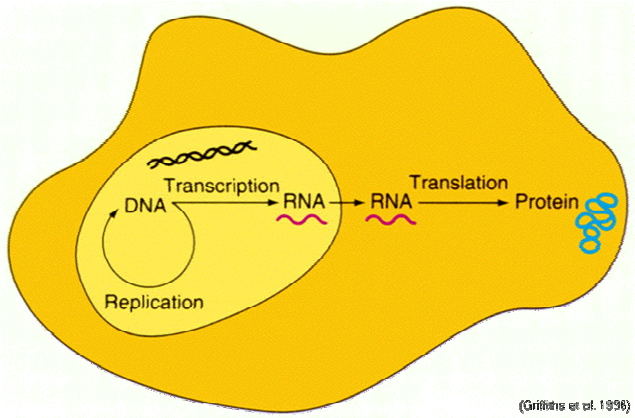
Eric Xing



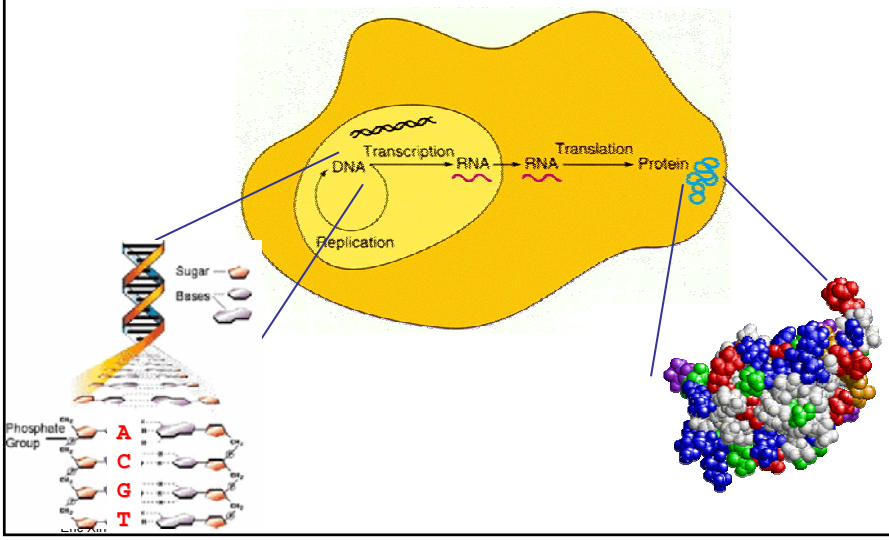
Lecture 20, April 7, 2008

Reading:

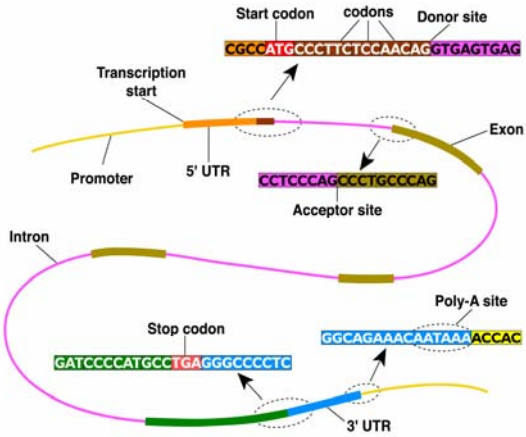
The Central Dogma



Genome and Proteome



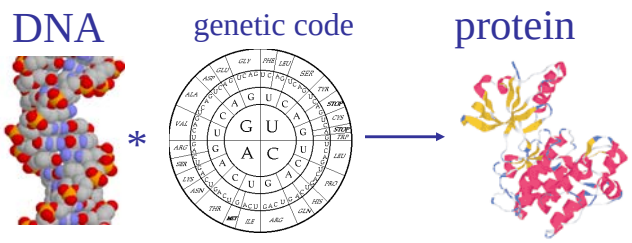
Gene Structure in DNA



- The inference problem: predicting locations of the genes on DNA

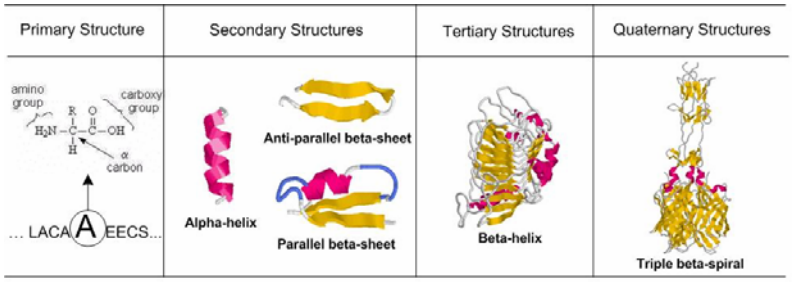
Proteins are coded by DNA

- There are between 30,000 to 40,000 genes in the human genome



- The human gene inventory corresponds to ~1.5% of the genome (coding regions)

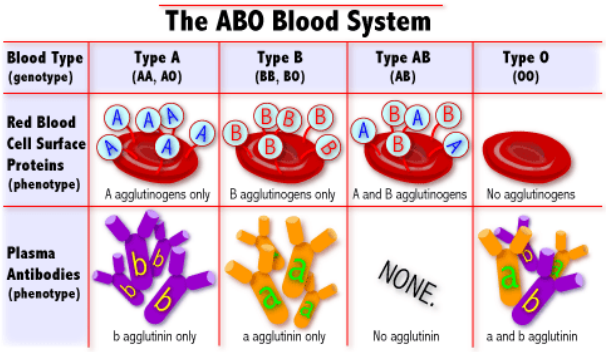
Protein Structure Hierarchy



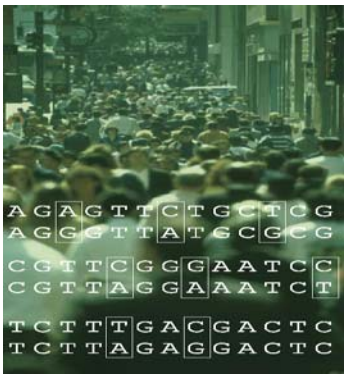
- The inference problem: predicting the structures from sequences

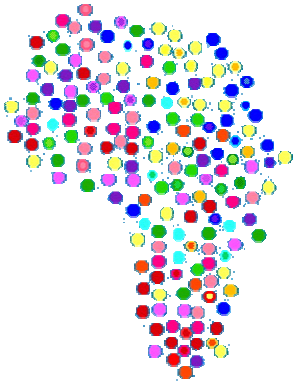
APAFSVSPASGACGPECA

Genetic Polymorphisms



Genetic Demography

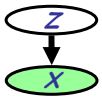




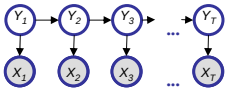
- Are there genetic prototypes among them ?
- What are they ?
- How many ? (how many ancestors do we have ?)

Computation Biology and ML

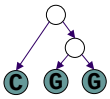
- Mixture and infinite mixture
  - clustering of genetic polymorphisms



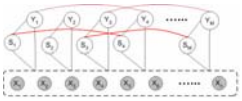
- Hidden Markov Models
  - gene finding



- Trees
  - sequence evolution



- Conditional Random Fields
  - protein structure prediction



Computation Biology and ML

- Mixture and infinite mixture
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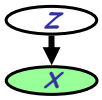


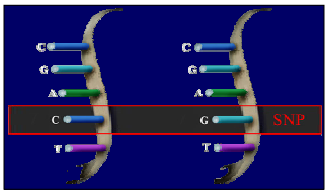
- HMMs
  - gene finding
- Trees
  - sequence evolution
- CRMs
  - protein structure prediction

Biological Terms

- Genetic polymorphism a difference in DNA sequence among individuals, groups, or populations

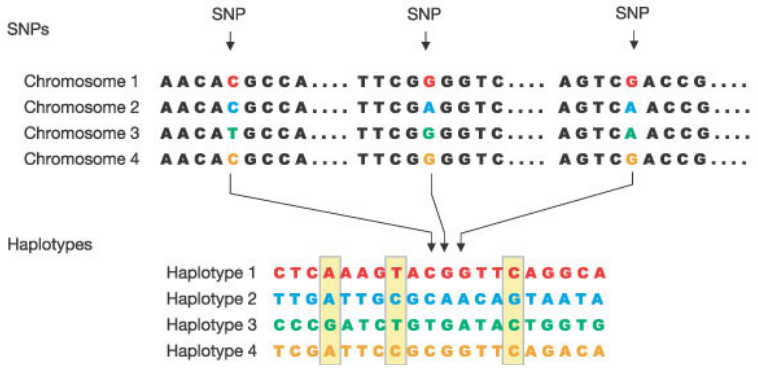
- **Single Nucleotide Polymorphism (SNP):** DNA sequence variation occurring when a single nucleotide - A, T, C, or G - differs between members of the species

  – Each variant is called an "allele"
  – Almost always bi-allelic
  – Account for most of the genetic diversity among different (normal) individuals, e.g. drug response, disease susceptibility



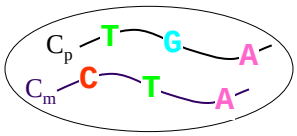
From SNPs to Haplotypes

- Alleles of adjacent SNPs on a chromosome form **haplotypes**

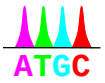


- Useful in the study of disease association or genetic evolution

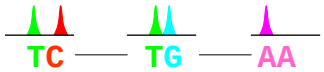
Phase ambiguity of SNPs "haplotypes"



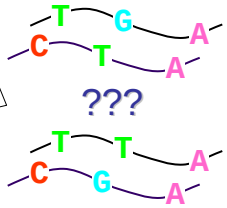
A heterozygous diploid individual



sequencing



The **Genotype:** pairs of alleles with association of alleles to chromosomes unknown



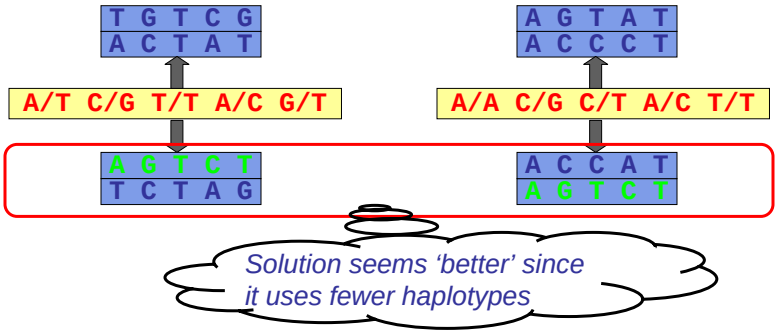
Haplotype $h \equiv (h_1, h_2)$ possible associations of alleles to chromosome

- This is a mixture modeling problem!

Haplotype Inference

Why is it approachable?

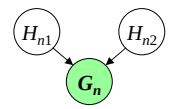
- Many of the haplotypes appear many times
- Data for many individuals allows inference



Finite mixture model

- The probability of a genotype *g*:

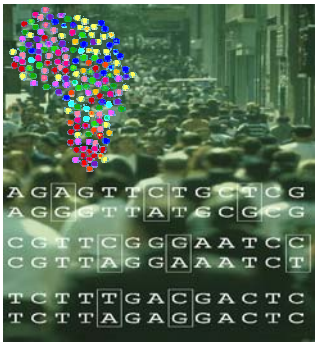
$$p(g) = \sum_{h_1, h_2 \in \mathcal{H}} p(h_1, h_2)\, p(g \mid h_1, h_2)$$

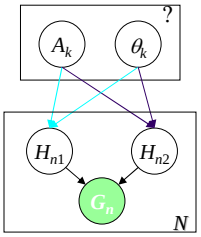


Population haplotype pool — **Haplotype model** — **Genotyping model**

- Standard settings:
  - *p(h1,h2)= p(h1)p(h2)* Hardy-Weinberg equilibrium
  - |H| = K fixed-sized population haplotype pool
- Problem: *K* ? H ?

Ancestral Inference





Essentially a clustering problem but...

(A)(C)(C)(T)(T)(G T)
(C)(C)(A)(T)(C T)
1 ACCTTGT
M ACCATCT
ACCTTGT
ACCATTGT

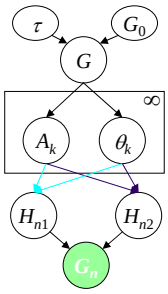
- Better recovery of the ancestors leads to better haplotyping results (because of more accurate grouping of common haplotypes)
- True haplotypes are obtainable with high cost, but they can validate model more subjectively (as opposed to examining saliency of clustering)
- Many other biological/scientific utilities

Being Bayesian about ...

- Population haplotype identities
- Population haplotype frequencies
- Number of population haplotypes
- Associations between population haplotype and individual haplotype/genotype

A Hierarchical Bayesian Infinite Allele model

Bayesian Haplotype Inference via the Dirichlet Process (Xing et al. ICML2004)



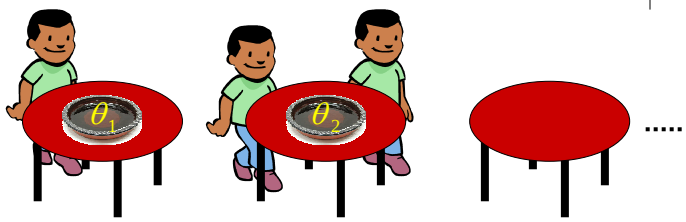
- Assume an individual haplotype h is stochastically derived from a population haplotype a_k with nucleotide-substitution frequency θ_k:

$$h \sim p(h \mid \{a, \theta\}_k).$$

- Not knowing the correspondences between individual and population haplotypes, each individual haplotype is a mixture of population haplotypes.

- The number and identity of the population haplotypes are unknown
  - use a Dirichlet Process to construct a prior distribution G on $\mathcal{H} \times \mathcal{R}^J$.
- Inference: Markov Chain Monte Carlo

Chinese Restaurant Process



$$P(c_i = k \mid \mathbf{c}_{-i}) = \begin{array}{ccc} 1 & 0 & 0 \\ \frac{1}{1+\alpha} & \frac{\alpha}{1+\alpha} & 0 \\ \frac{1}{2+\alpha} & \frac{1}{2+\alpha} & \frac{\alpha}{2+\alpha} \\ \frac{1}{3+\alpha} & \frac{2}{3+\alpha} & \frac{\alpha}{3+\alpha} \\ \frac{m_1}{i+\alpha-1} & \frac{m_2}{i+\alpha-1} \quad \cdots & \frac{\alpha}{i+\alpha-1} \end{array}$$

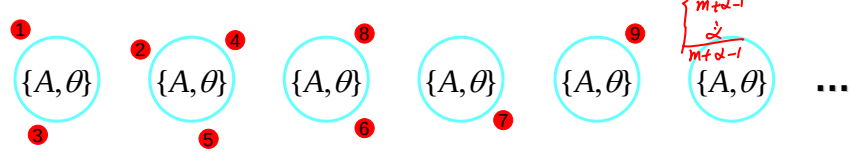
CRP defines an exchangeable distribution on partitions over an (infinite) sequence of integers

The DP Mixture of Ancestral Haplotypes

- The customers around a table form a cluster
  - associate a mixture component (*i.e.*, a population haplotype) with a table
  - sample $\{a, \theta\}$ at each table from a base measure G_0 to obtain the population haplotype and nucleotide substitution frequency for that component

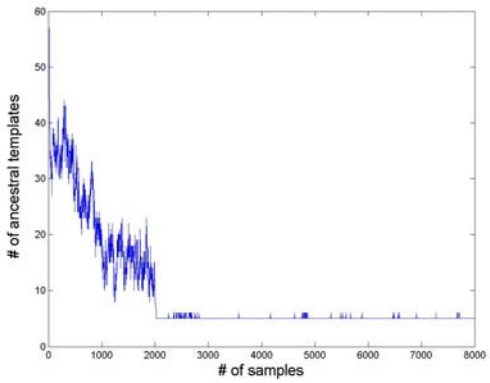
$P(c_i \mid c_{-i}, h_i, (A)) = P(c_i \mid c_{-i}) P(h_i \mid A)$

$\begin{cases} \frac{m_i}{m+\alpha-1} \\ \frac{\alpha}{m+\alpha-1} \end{cases}$



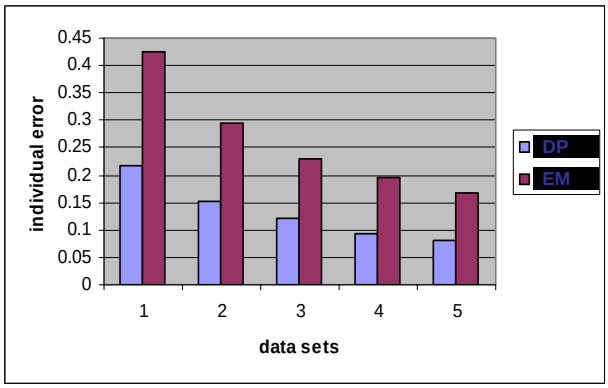
  - With $p(h \mid \{A, \theta\})$ and $p(g \mid h_1, h_2)$, the CRP yields a posterior distribution on the number of population haplotypes (and on the haplotype configurations and the nucleotide substitution frequencies)

Convergence of Ancestral Inference



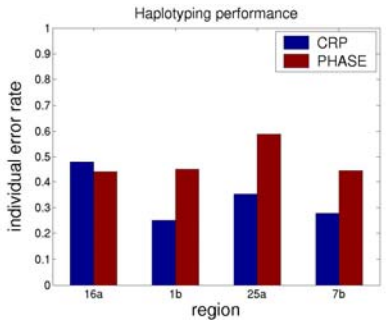
Results on simulated data

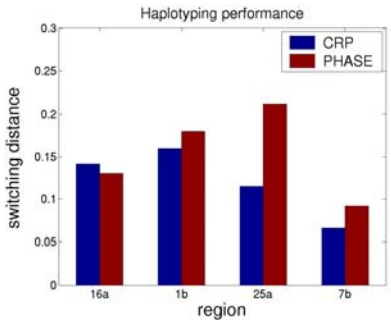
- DP vs. Finite Mixture via EM



Results

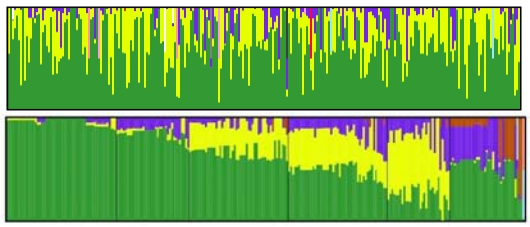
The Gabriel data





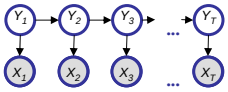
Population structure

- DATA: 256 European individuals with 103 loci



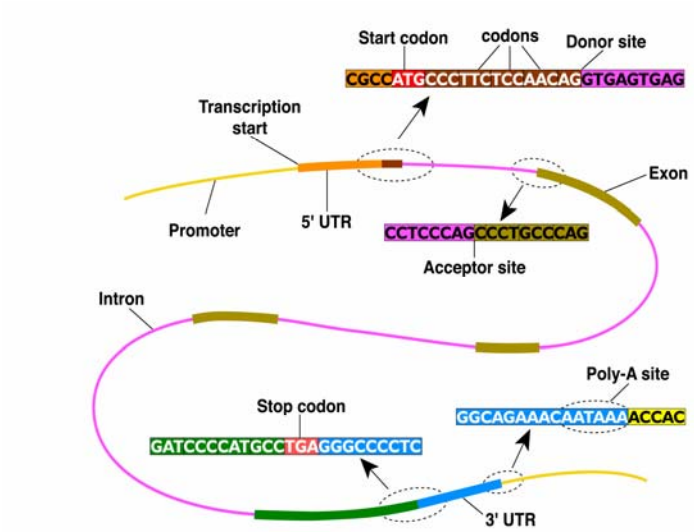
Computation Biology and ML

- Mixture and infinite mixture
  - clustering of genetic polymorphisms
- HMMs
  - gene finding
- Trees
  - sequence evolution
- CRMs
  - protein structure prediction



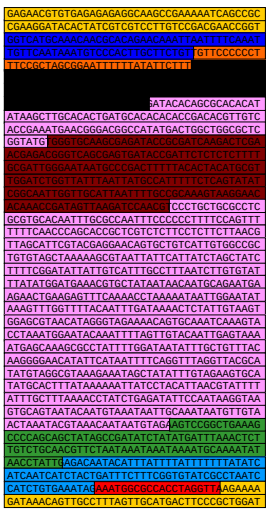
The challenge

Typical structure of a gene



Gene Finding

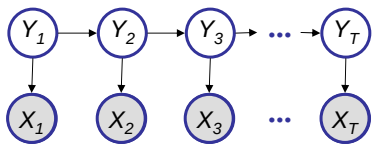
- Given un-annotated sequences,
- delineate:
  - transcription initiation site,
  - exon-intron boundaries,
  - transcription termination site,
  - a variety of other motifs: promoters, polyA sites, branching sites, etc.
- The hidden Markov model (HMM) $P(x|c)$



Hidden Markov Models

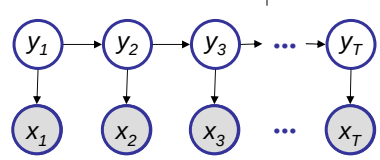
The underlying source:
genomic entities,
dice,

The sequence:
Ploy NT,
sequence of rolls,

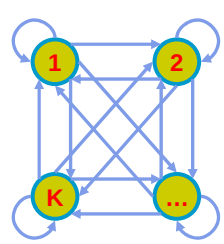


Definition (of HMM)

- Observation space
  - Alphabetic set: $\mathbb{C} = \{c_1, c_2, \cdots, c_K\}$
  - Euclidean space: $\mathbb{R}^d$
- Index set of hidden states
  $\mathbb{I} = \{1, 2, \cdots, M\}$
- Transition probabilities between any two states
  $p(y_t^j = 1 \mid y_{t-1}^i = 1) = a_{i,j}$,
  or $p(y_t \mid y_{t-1}^i = 1) \sim \text{Multinomial}(a_{i,1}, a_{i,2}, \ldots, a_{i,M}), \forall i \in \mathbb{I}$.
- Start probabilities
  $p(y_1) \sim \text{Multinomial}(\pi_1, \pi_2, \ldots, \pi_M)$.
- Emission probabilities associated with each state
  $p(x_t \mid y_t^i = 1) \sim \text{Multinomial}(b_{i,1}, b_{i,2}, \ldots, b_{i,K}), \forall i \in \mathbb{I}$.
  or in general:
  $p(x_t \mid y_t^i = 1) \sim \text{f}(\cdot \mid \theta_i), \forall i \in \mathbb{I}$.

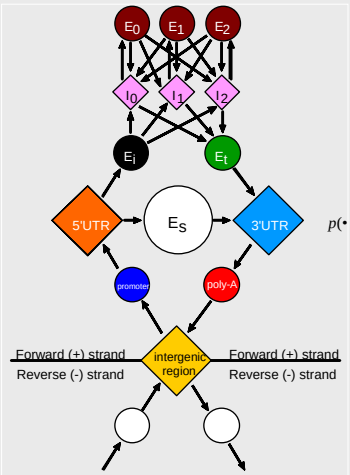


Graphical model

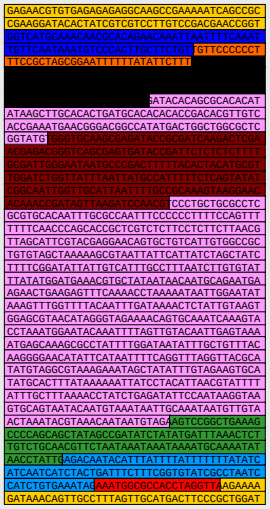


State automata

GENSCAN (Burge & Karlin)

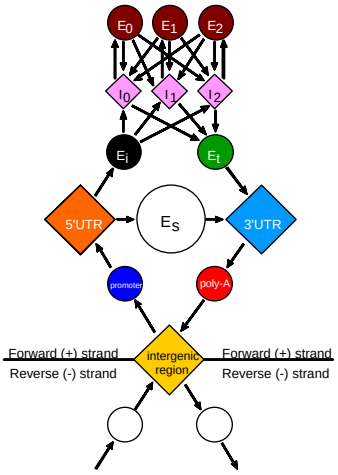


$$p(\bullet \mid y) = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ \theta_4 \end{bmatrix}$$



The Idea Behind a GHMM GeneFinder

- **States** represent standard gene features: intergenic region, exon, intron, perhaps more (promotor, 5'UTR, 3'UTR, Poly-A,..).
- **Observations** embody state-dependent base composition, dependence, and signal features.
- In a GHMM, **duration** must be included as well.
- Finally, **reading frames** and **both strands** must be dealt with.



The HMM Algorithms

Questions:

- **Evaluation**: What is the probability of the observed sequence? Forward
- **Decoding**: What is the probability that the state of the 3rd position is Bk, given the observed sequence? Forward-Backward
- **Decoding**: What is the most likely parsing? Viterbi
- **Learning**: Under what parameterization are the observed sequences most probable? Baum-Welch (EM)

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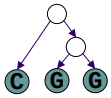
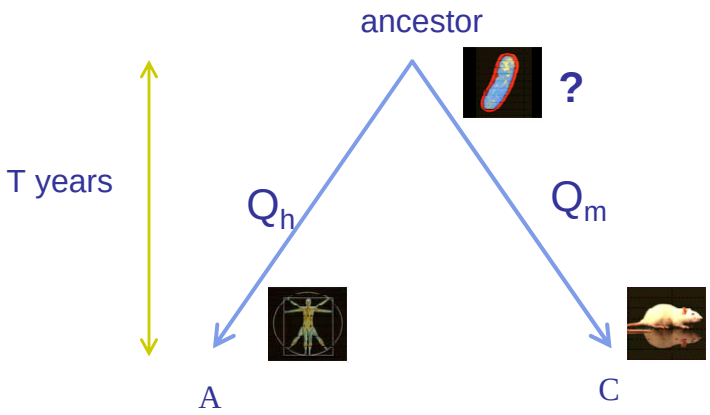
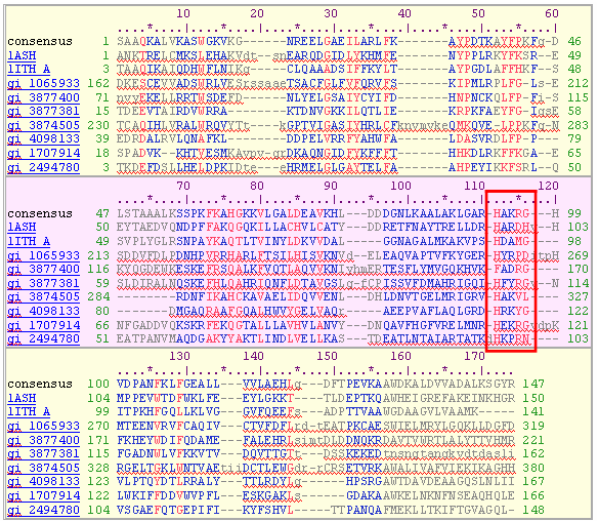


A pair of homologous bases

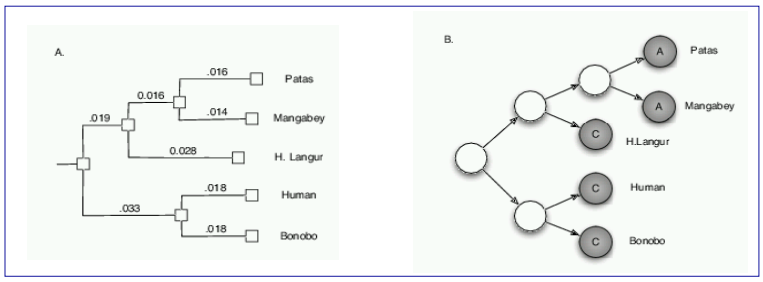


Typically, the ancestor is unknown.

Homology identification via multiple alignment



Phylogeny



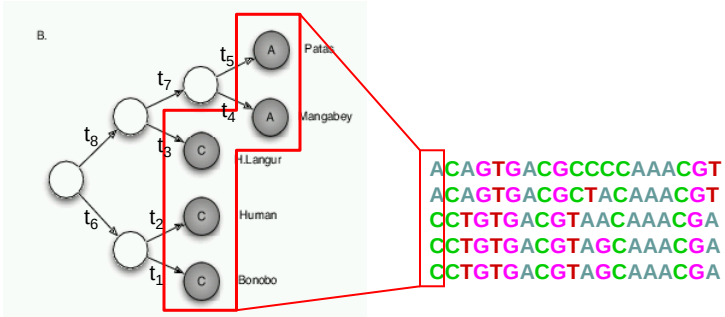
- The shaded nodes represent the observed nucleotides at a given site for a set of organisms
- The unshaded nodes represent putative ancestral nucleotides
- Transitions between nodes capture the dynamic of evolution

Phylogeny methods

- **Basic principles:**
  - Degree of sequence difference is proportional to length of independent sequence evolution
  - Only use positions where alignment is pretty certain – avoid areas with (too many) gaps
- **Major methods:**
  - Parsimony phylogeny methods
  - Likelihood methods

Likelihood methods

- A tree, with branch lengths, and the data at a single site.



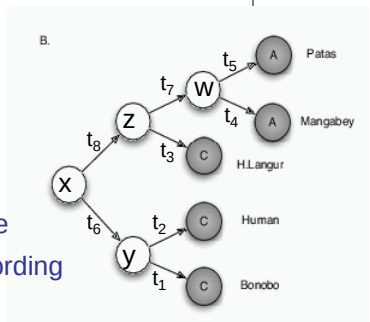
- Since the sites evolve independently on the same tree,

$$L = P(D \mid T) = \prod_{i=1}^{m} P(D^{(i)} \mid T)$$

Likelihood at one site on a tree

- We can compute this by summing over all assignments of states x, y, z and w to the interior nodes:

$$P(D^{(i)} \mid T) = \sum_x \sum_y \sum_z \sum_w P(A, A, C, C, C, x, y, z, w \mid T)$$



- Due to the Markov property of the tree, we can factorize the complete likelihood according to the tree topology:

$$P(A, A, C, C, C, x, y, z, w \mid T) =$$
$$P(x) \quad P(y \mid x, t_6) \quad P(\mathrm{C} \mid y, t_1)\, P(\mathrm{C} \mid y, t_2)$$
$$P(z \mid x, t_8) \quad P(\mathrm{C} \mid y, t_3)$$
$$P(w \mid z, t_7)\, P(\mathrm{A} \mid y, t_4)\, P(\mathrm{A} \mid y, t_5)$$

- Summing this up, there are 256 terms in this case!

Getting a recursive algorithm

- when we move the summation signs as far right as possible:

$$P(D^{(i)} \mid T) = \sum_x \sum_y \sum_z \sum_w P(A, A, C, C, C, x, y, z, w \mid T) =$$

$$\sum_x P(x)$$

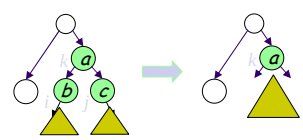
$$\left(\sum_y P(y \mid x, t_6) \quad P(\mathrm{C} \mid y, t_1)\, P(\mathrm{C} \mid y, t_2) \right)$$

$$\left(\sum_z P(z \mid x, t_8) \quad P(\mathrm{C} \mid z, t_3) \right.$$

$$\left. \left(\sum_w P(w \mid z, t_7) P(\mathrm{A} \mid w, t_4) P(\mathrm{A} \mid w, t_5) \right) \right)$$

Felsenstein's Pruning Algorithm

- To calculate $P(x_1, x_2, \ldots, x_N \mid T, t)$



Initialization:

Set $k = 2N - 1$

Recursion: Compute $P(L_k \mid a)$ for all $a \in \Sigma$

If k is a leaf node:

Set $P(L_k \mid a) = 1(a = x_k)$

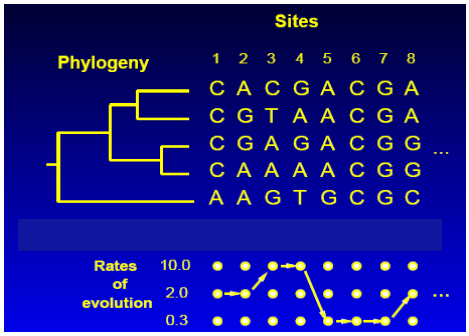
If k is not a leaf node:

1. Compute $P(L_i \mid b)$, $P(L_j \mid b)$ for all b, for daughter nodes i, j
2. Set $P(L_k \mid a) = \sum_{b,\, c} P(b \mid a, t_i) P(L_i \mid b)\, P(c \mid a, t_j)\, P(L_j \mid c)$

Termination:

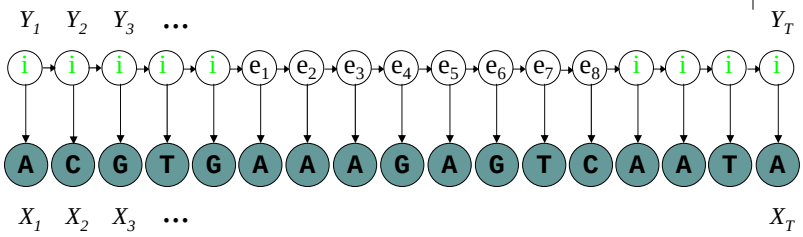
Likelihood at this column = $P(x_1, x_2, \ldots, x_N \mid T, t) = \sum_a P(L_{2N-1} \mid a) P(a)$

Modeling rate variation among sites



- There are a finite number of rates (denote rate i as r_i).
- There are probabilities p_i of a site having rate i.
- A process not visible to us ("hidden") assigns rates to sites.
- The probability of our seeing some data are to be obtained by summing over all possible combinations of rates, weighting appropriately by their probabilities of occurrence.

Rocall the HMM



- The shaded nodes represent the observed nucleotides at particular sites of an organism's genome
- For discrete Y_i, widely used in computational biology to represent segments of sequences
  - gene finders and motif finders
  - profile models of protein domains
  - models of secondary structure

Definition (of HMM)

- Observation space
  - **Alphabetic set:** $\mathbb{C} = \{c_1, c_2, \cdots, c_K\}$
  - **Euclidean space:** $\mathbb{R}^d$
- Index set of hidden states

  $\mathbb{I} = \{1, 2, \cdots, M\}$
- Transition probabilities between any two states

  $p(y_t^j = 1 \mid y_{t-1}^i = 1) = a_{i,j}$,

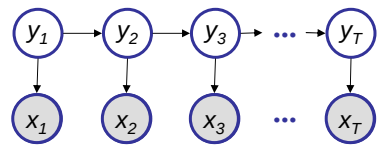
  or $p(y_t \mid y_{t-1}^i = 1) \sim \text{Multinomial}(a_{i,1}, a_{i,2}, \ldots, a_{i,M}), \forall i \in \mathbb{I}$.
- Start probabilities

  $p(y_1) \sim \text{Multinomial}(\pi_1, \pi_2, \ldots, \pi_M)$.
- Emission probabilities associated with each state

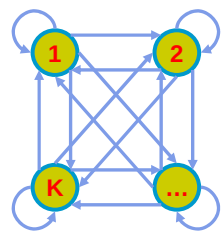
  $p(x_t \mid y_t^i = 1) \sim \text{Multinomial}(b_{i,1}, b_{i,2}, \ldots, b_{i,K}), \forall i \in \mathbb{I}$.

  or in general:

  $p(x_t \mid y_t^i = 1) \sim \text{f}(\cdot \mid \theta_i), \forall i \in \mathbb{I}$.

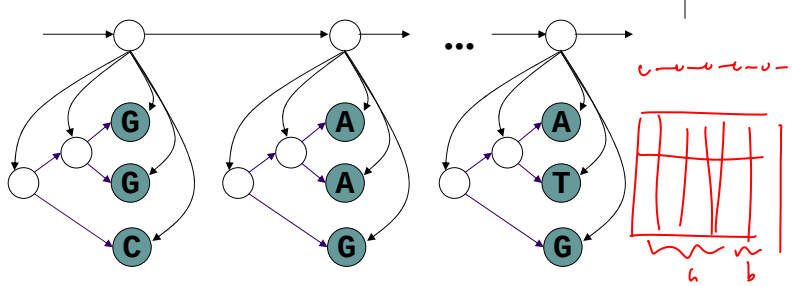


Graphical model



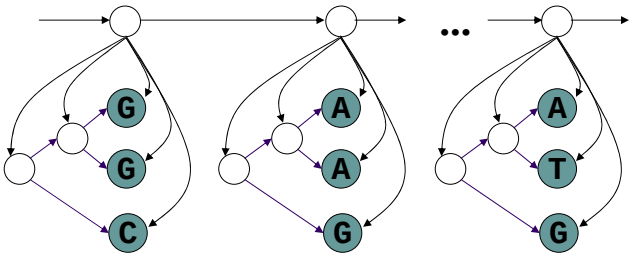
State automata

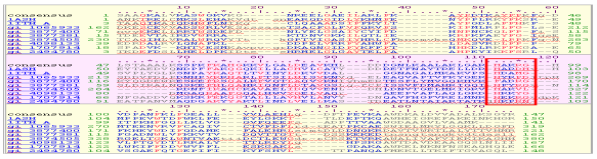
Hidden Markov Phylogeny



- Replacing the standard emission model with a tree
  - A process not visible to us (.hidden") assigns rates to sites. It is a Markov process working along the sequence.
  - For example it might have transition probability Prob ($j|i$) of changing to rate j in the next site, given that it is at rate i in this site.
- These are the most widely used models allowing rate variation to be correlated along the sequence.

Hidden Markov Phylogeny





- this yields a gene finder that exploits evolutionary constraints

A Comparison of comparative genomic gene-finding and isolated gene-finding

- Based on sequence data from 12-15 primate species, McAuliffe et al (2003) obtained sensitivity of 100%, with a specificity of 89%.
  - Genscan (state-of-the-art gene finder) yield a sensitivity of 45%, with a specificity of 34%.