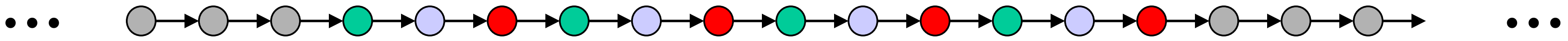
Today’s Lecture

- More HMM examples
- Limitations of HMMs
- PhyloHMMs & PhastCons

HMM Examples (cont'd)

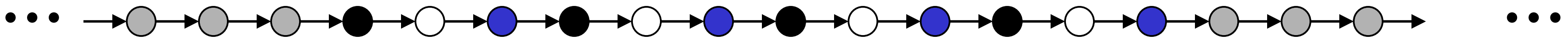
- Simple 7-state prokaryote genome model:
  - 1 state for intergenic regions
  - 3 states for codon positions in top-strand genes
  - 3 for codon positions in bottom-strand genes
- more complex models including sites (with states for each position in site) –
  - promoter elements
  - Shine-Dalgarno (translation start site)
  - (in eukaryotes) splice sites, polyadenylation sites etc.

7-state model for prokaryote genomes



- ⚪ intergenic
- 🟢 first codon position – top strand coding sequence
- 🟣 second codon position – top strand coding sequence
- 🔴 third codon position – top strand coding sequence
- 🔵 first codon position – bottom strand coding sequence
- ○ second codon position – bottom strand coding sequence
- ● third codon position – bottom strand coding sequence

a (very short!) ‘bottom-strand’ gene, in a different region of the genome:



- N.B. the emitted symbols are always ***top strand*** nucleotides!

Other HMM examples (see Durbin *et al.*)

- protein families (like site models – but important to allow insertions & deletions)
- Pair HMMs
- protein structure (symbols emitted are structural elements)

HMM Examples (cont'd)

- Ordinary Markov chain model:
  - states = observed symbols
  - emission probs = 1 or 0
  - transition probs = prob of observing a symbol, given the preceding one.
- Order *k* Markov model
  - states = length *k* words (e.g. $b_1 b_2 \ldots\ b_k$)
  - (unique) symbol emitted by $b_1 b_2 \ldots\ b_k$ is b_k
  - transition prob from $b_1 b_2 \ldots\ b_k$ to $c_1 c_2 \ldots\ c_k$ is non-zero only if
    - $c_1 c_2 \ldots\ c_{k\text{-}1} = b_2 b_3 \ldots\ b_k$, in which case it is

      $\mathrm{P}(b_{k+1} | b_1 b_2 \ldots\ b_k)$ where $b_{k+1} = c_k$

D-segments & 2-state HMMs

- Consider 2-state HMM
  - states 1 & 2, transition probs a_{11}, a_{12}, a_{21}, a_{22}
  - observed symbols $\{r\}$, emission probs $\{e_1(r)\}$, $\{e_2(r)\}$
- Define

  scores $\mathrm{s(r)} = \log(e_2(r)\, a_{22}/(e_1(r)\, a_{11}))$

  $\mathrm{S} = -\mathrm{D} = \log(a_{11}a_{22}/(a_{21}a_{12}))$
- Then if S > 0, the maximal D-segments in a sequence $(r_i)_{i=1,\, n}$ are the state-2 segments in the Viterbi parse.
- So via D-segment algorithm can get Viterbi parse in just one pass through the sequence!
- can allow for non-.5 initiation probs by starting cumul at non-zero value

Limitations of HMMs

- Markov chain cond’n on states is unrealistic
  - biological features have complex dependencies
- In particular, duration modelling frequently unrealistic –
  - can deal with this
    - Increase number of states
    - ‘generalized HMMs’
  - but at cost of speed & elegance
- Other issues (arising with any complex models!)
  - Parameter estimation can be difficult and give suboptimal results
    - many local maxima in complex surface
  - Need to avoid overfitting

Detecting sequence conservation with PhyloHMMs

- PhyloHMMs: Yang 1995; Felsenstein & Churchill 1996
- Siepel A. *et al*. (2005): Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. *Genome Res*. 15:1034-50
  - basis of PhastCons conservation scores (UCSC genome browser)

- Goal: starting from multiple genome sequence alignment, identify
  - conserved regions (regions under purifying selection),

  against background of
  - neutrally evolving regions

PhastCons PhyloHMM

- model:
  - 2-state HMM

    c: conserved state

    n: neutral (or nonconserved) state
  - emitted symbols are *alignment columns*
  - emission probabilities based on *phylogenetic tree* relating sequences
    - discussed in Genome 541, or molecular phylogeny course
  - gaps in alignment treated as *missing data*