Markov Chain Models (Part 2)

BMI/CS 576

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Higher order Markov chains

- the Markov property specifies that the probability of a state depends only on the probability of the previous state
- but we can build more "memory" into our states by using a higher order Markov model
- in an *n*th order Markov model

$$P(x_i \mid x_{i-1}, x_{i-2}, \ldots, x_1) = P(x_i \mid x_{i-1}, \ldots, x_{i-n})$$

Selecting the order of a Markov chain model

- higher order models remember more “history”
- additional history can have predictive value
- example:
  - predict the next word in this sentence fragment
    “… the__” (duck, end, grain, tide, wall, …?)
  - now predict it given more history
    “… against the __” (duck, end, grain, tide, wall, …?)

    “swim against the __” (duck, end, grain, tide, wall, …?)

Selecting the order of a Markov chain model

- but the number of parameters we need to estimate grows exponentially with the order
  - for modeling DNA we need $O(4^{n+1})$ parameters for an *n*th order model
- the higher the order, the less reliable we can expect our parameter estimates to be
  - estimating the parameters of a 2nd order Markov chain from the complete genome of *E. Coli*, we’d see each word > 72,000 times on average
  - estimating the parameters of an 8th order chain, we’d see each word ~ 5 times on average

Higher order Markov chains

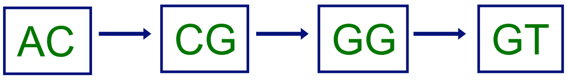
- an nth order Markov chain over some alphabet A is equivalent to a first order Markov chain over the alphabet A^n of n-tuples

- example: a 2nd order Markov model for DNA can be treated as a 1st order Markov model over alphabet

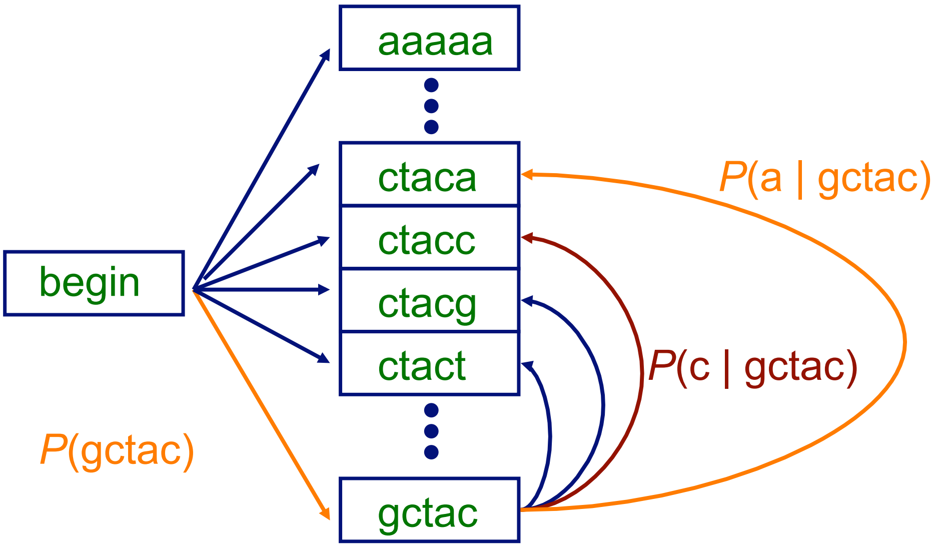
  AA, AC, AG, AT, CA, CC, CG, CT, GA, GC, GG, GT, TA, TC, TG, TT

- caveat: we process a sequence one character at a time

  A C G G T



A fifth-order Markov chain

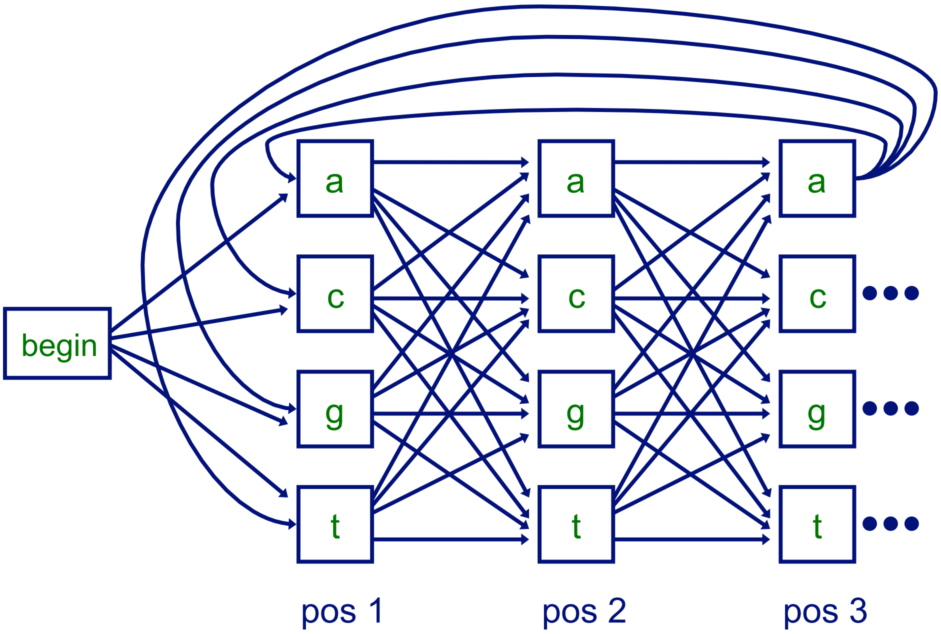


$$P(gctaca) = P(gctac)P(a \mid gctac)$$

Inhomogenous Markov chains

- in the Markov chain models we have considered so far, the probabilities do not depend on our position in a given sequence
- in an *inhomogeneous* Markov model, we can have different distributions at different positions in the sequence
- consider modeling codons in protein coding regions

An inhomogeneous Markov chain



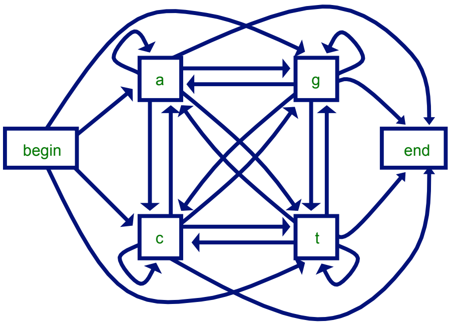
Example application

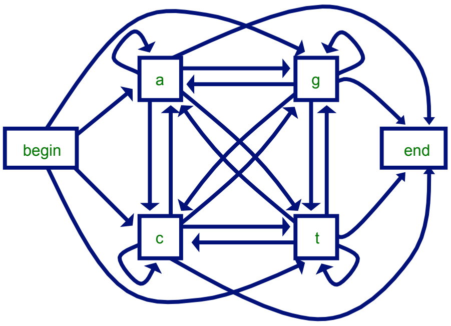
- CpG islands
  - CG dinucleotides are rarer in eukaryotic genomes than expected given the marginal probabilities of C and G
  - but the regions upstream of genes are richer in CG dinucleotides than elsewhere – *CpG islands*
  - useful evidence for finding genes

- could predict CpG islands with Markov chains
  - one to represent CpG islands
  - one to represent the rest of the genome

CpG islands as a classification task

1. train two Markov models: one to represent CpG island sequence regions, another to represent other sequence regions (*null*)





2. given a test sequence, use two models to
   - determine probability that sequence is a CpG island
   - classify the sequence (*CpG* or *null*)

Markov chains for discrimination

- parameters estimated for CpG and null models
  - human sequences containing 48 CpG islands
  - 60,000 nucleotides

$P(c \mid a)$

+	a	c	g	t
a	.18	.27	.43	.12
c	.17	.37	.27	.19
g	.16	.34	.38	.12
t	.08	.36	.38	.18

CpG

-	a	c	g	t
a	.30	.21	.28	.21
c	.32	.30	.08	.30
g	.25	.24	.30	.21
t	.18	.24	.29	.29

null

Markov chains for discrimination

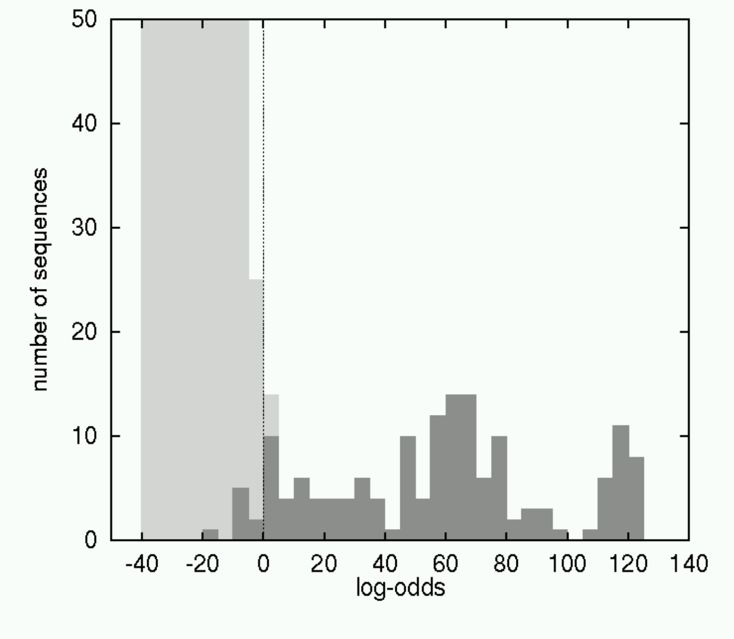
- using Bayes' rule tells us

$$P(CpG \mid x) = \frac{P(x \mid CpG)P(CpG)}{P(x)}$$

$$= \frac{P(x \mid CpG)P(CpG)}{P(x \mid CpG)P(CpG) + P(x \mid null)P(null)}$$

- if we don't take into account prior probabilities of two classes ($P(CpG)$ and $P(null)$) then we just need to compare $P(x \mid CpG)$ and $P(x \mid null)$

Markov chains for discrimination



- light bars represent negative sequences
- dark bars represent positive sequences (i.e. CpG islands)
- the actual figure here is not from a CpG island discrimination task, however

Figure from A. Krogh, “An Introduction to Hidden Markov Models for Biological Sequences” in Computational Methods in Molecular Biology, Salzberg et al. editors, 1998.