Interpolated Markov Models for Gene Finding

BMI/CS 776

www.biostat.wisc.edu/bmi776/

Spring 2015

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Goals for Lecture

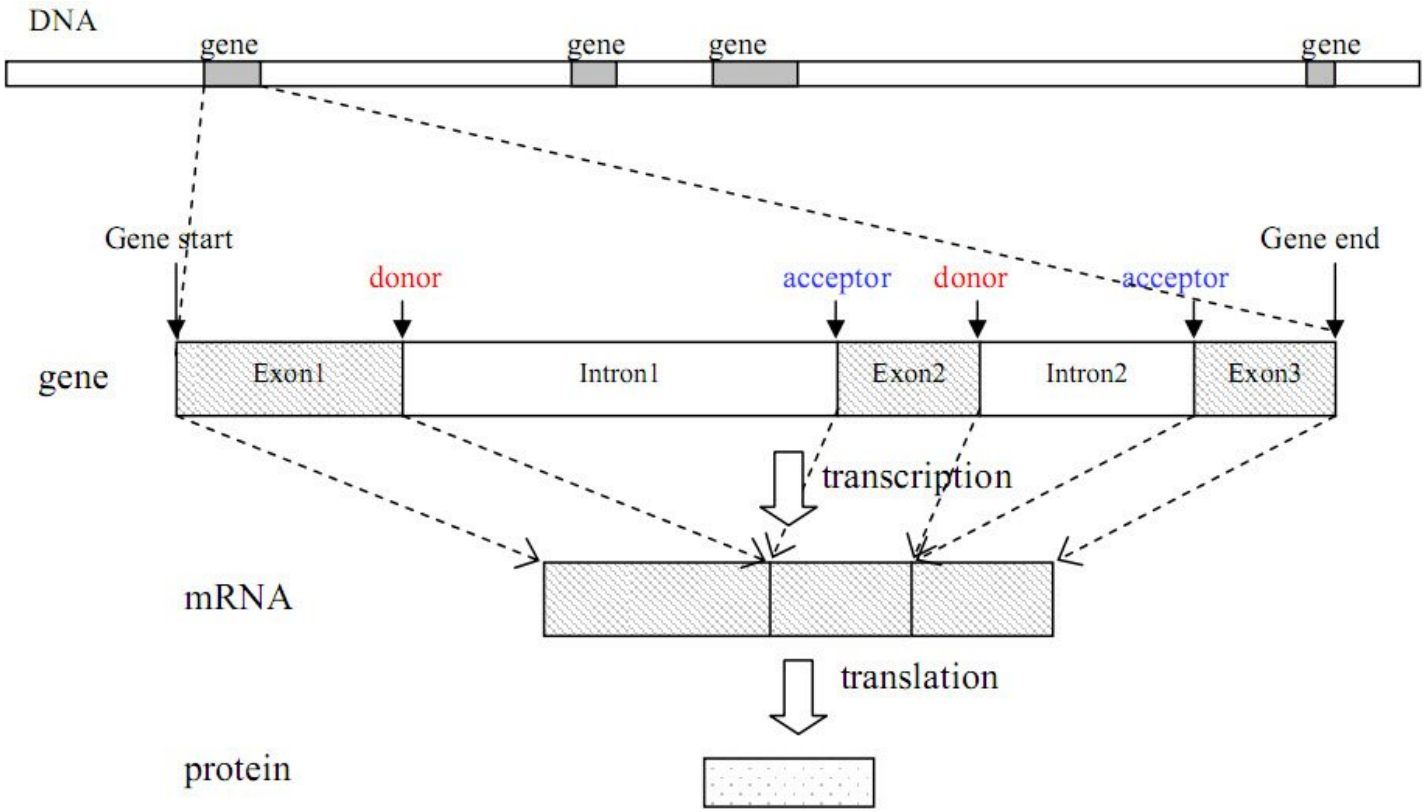
the key concepts to understand are the following

- the gene-finding task
- the trade-off between potential predictive value and parameter uncertainty in choosing the order of a Markov model
- interpolated Markov models
- back-off models

The Gene Finding Task

Given: an uncharacterized DNA sequence

Do: locate the genes in the sequence, including the coordinates of individual *exons* and *introns*



Sources of Evidence for Gene Finding

- **signals**: the sequence *signals* (e.g. splice junctions) involved in gene expression
- **content**: statistical properties that distinguish protein-coding DNA from non-coding DNA
- **conservation**: signal and content properties that are conserved across related sequences (e.g. orthologous regions of the mouse and human genome)

Gene Finding: Search by Content

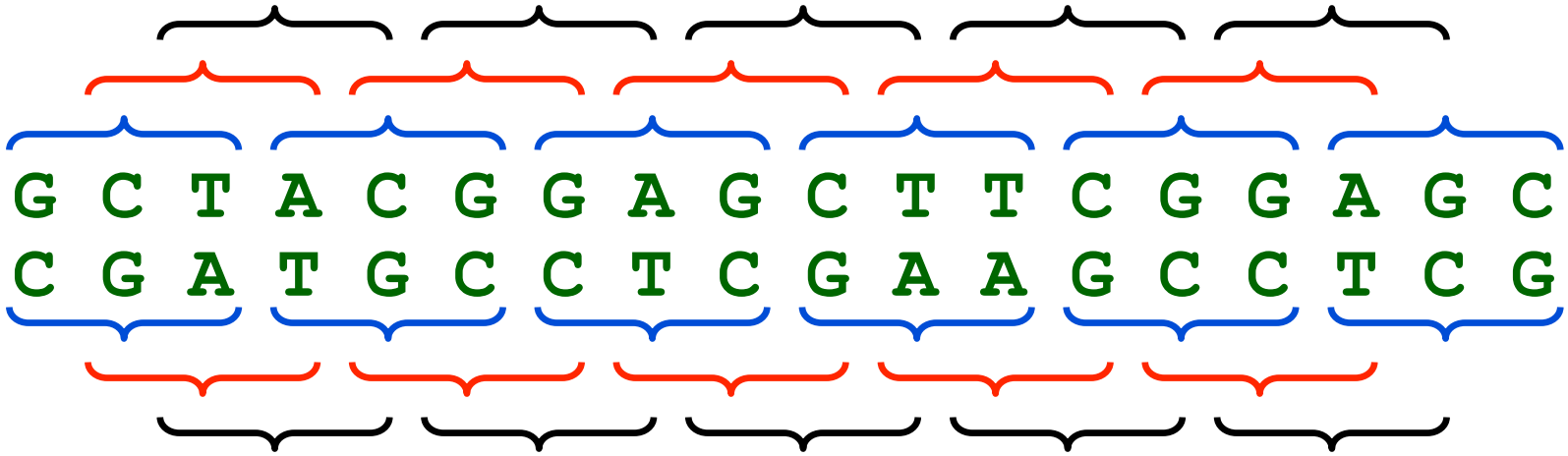
- encoding a protein affects the statistical properties of a DNA sequence
  - some amino acids are used more frequently than others (Leu more popular than Trp)
  - different numbers of codons for different amino acids (Leu has 6, Trp has 1)
  - for a given amino acid, usually one codon is used more frequently than others
    - this is termed *codon preference*
    - these preferences vary by species

Codon Preference in E. Coli

AA	codon	/1000
Gly	GGG	1.89
Gly	GGA	0.44
Gly	GGU	52.99
Gly	GGC	34.55
Glu	GAG	15.68
Glu	GAA	57.20
Asp	GAU	21.63
Asp	GAC	43.26

Reading Frames

- a given sequence may encode a protein in any of the six reading frames



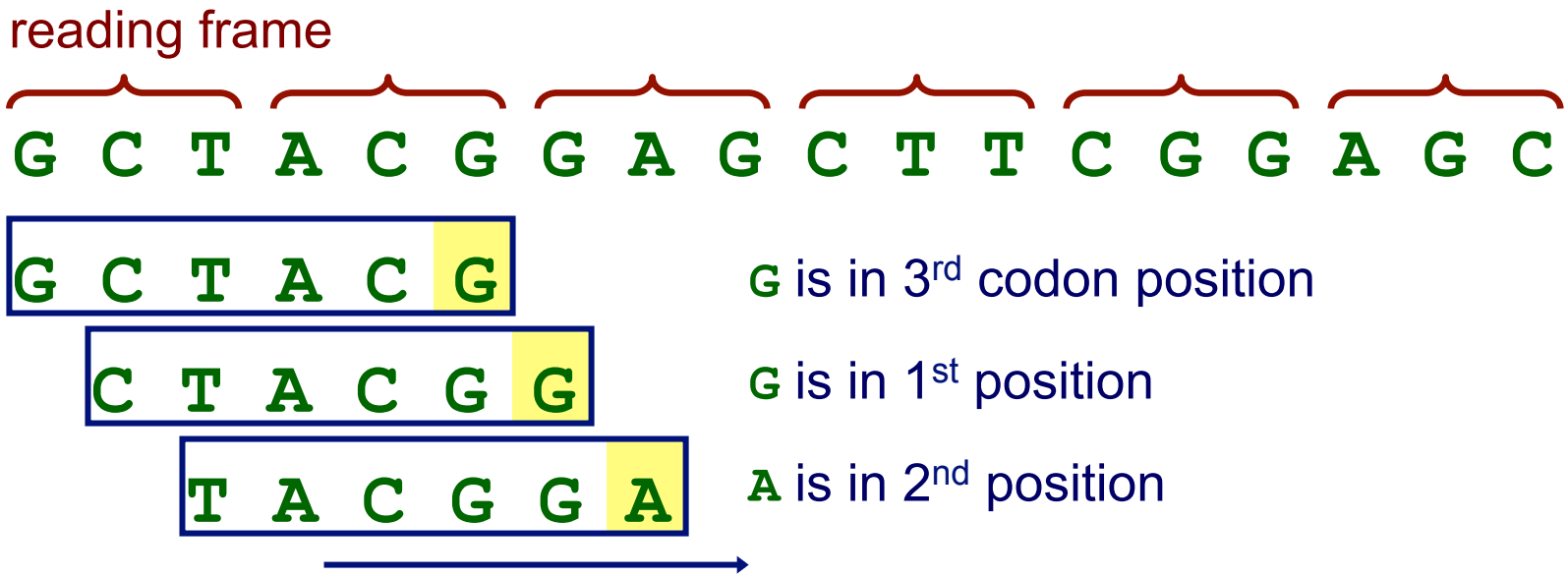
Open Reading Frames (ORFs)

- an ORF is a sequence that
  - starts with a potential start codon
  - ends with a potential stop codon, *in the same reading frame*
  - doesn't contain another stop codon in-frame
  - and is sufficiently long (say > 100 bases)

- an ORF meets the minimal requirements to be a protein-coding gene in an organism without introns

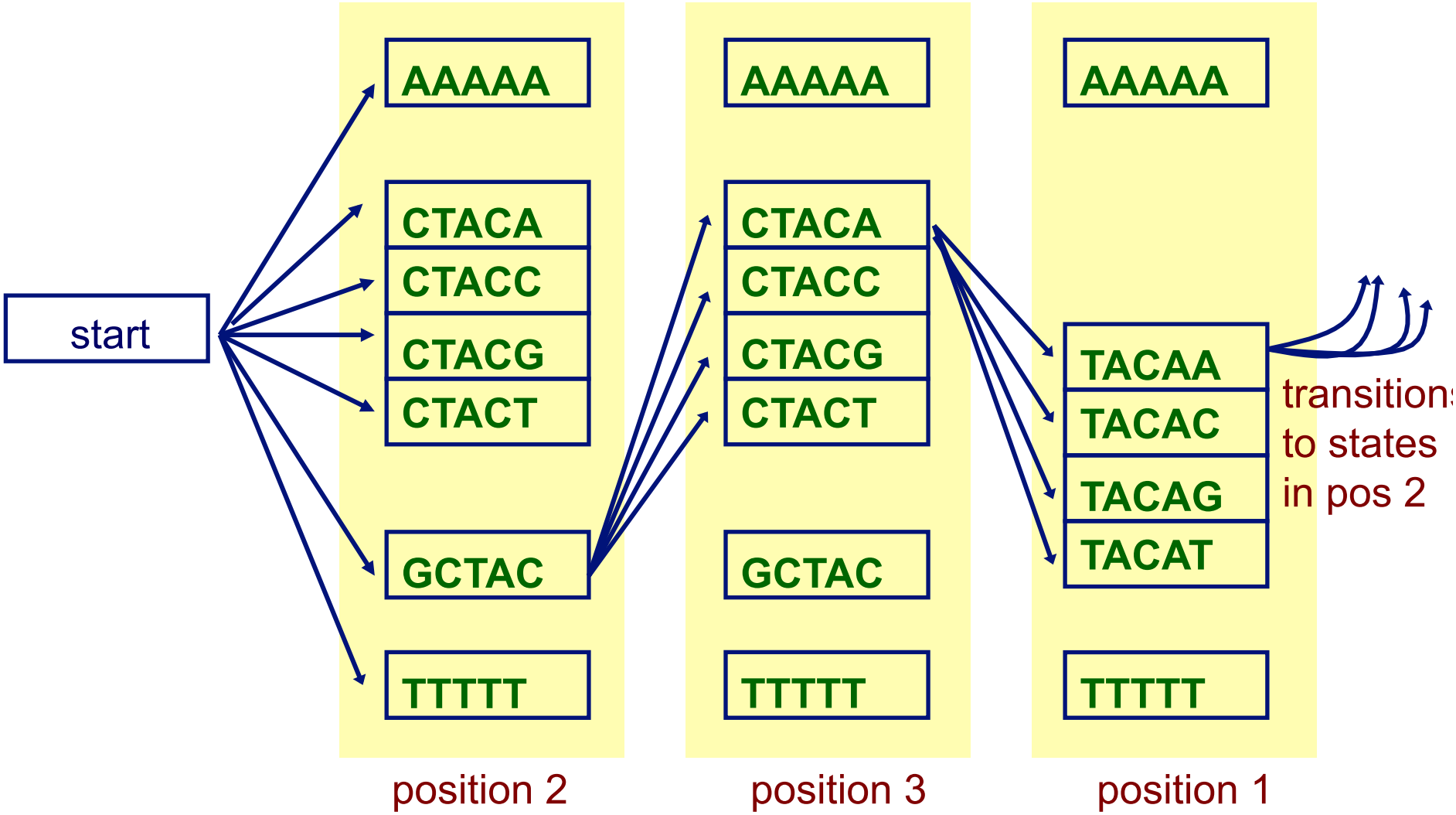
Markov Models & Reading Frames

- consider modeling a given coding sequence
- for each “word” we evaluate, we’ll want to consider its position with respect to the reading frame we’re assuming



- can do this using an inhomogeneous model

A Fifth Order Inhomogeneous Markov Chain



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 “…you__” (are, give, idiot, say, see, too, …?)
  - now predict it given more history

    “…can you___”

    “…say can you___”

    “…oh say can you___”

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
- suppose we have 100k bases of sequence to estimate parameters of a model
  - for a 2nd order homogeneous Markov chain, we'd see each history 6250 times on average
  - for an 8th order chain, we'd see each history ~ 1.5 times on average

Interpolated Markov Models

- the IMM idea: manage this trade-off by interpolating among models of various orders
- *simple* linear interpolation:

$$P_{\text{IMM}}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \lambda_0 P(x_i) + \lambda_1 P(x_i \mid x_{i-1}) + \ldots + \lambda_n P(x_i \mid x_{i-n},\ldots,x_{i-1})$$

- where $\sum_i \lambda_i = 1$

Interpolated Markov Models

- we can make the weights depend on the history
  - for a given order, we may have significantly more data to estimate some words than others
- *general* linear interpolation

$$P_{\text{IMM}}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \lambda_0 P(x_i)$$
$$+ \lambda_1(x_{i-1}) P(x_i \mid x_{i-1})$$
$$\ldots$$
$$+ \lambda_n(x_{i-n},\ldots,x_{i-1}) P(x_i \mid x_{i-n},\ldots,x_{i-1})$$

λ is a function of the given history

The GLIMMER System

[Salzberg et al., Nucleic Acids Research, 1998]

- system for identifying genes in bacterial genomes
- uses 8^{th} order, inhomogeneous, interpolated Markov chain models

IMMs in GLIMMER

- how does GLIMMER determine the λ values?
- first, let's express the IMM probability calculation recursively

$$P_{\text{IMM,n}}(x_i \mid x_{i-n},\ldots,x_{i-1}) =$$
$$\lambda_{\text{n}}(x_{i-n},\ldots,x_{i-1})P(x_i \mid x_{i-n},\ldots,x_{i-1}) \; +$$
$$[1-\lambda_n(x_{i-n},\ldots,x_{i-1})]P_{\text{IMM,n-1}}(x_i \mid x_{i-n+1},\ldots,x_{i-1})$$

- let $c(x_{i-n},\ldots,x_{i-1})$ be the number of times we see the history $x_{i-n},\ldots,x_{i-1}$ in our training set

$$\lambda_n(x_{i-n},\ldots,x_{i-1}) = 1 \quad \text{if} \quad c(x_{i-n},\ldots,x_{i-1}) > 400$$

IMMs in GLIMMER

- if we haven't seen $x_{i-n},\ldots,x_{i-1}$ more than 400 times, then compare the counts for the following:

*n*th order history + base	(*n-1*)th order history + base
$x_{i-n},\ldots,x_{i-1},a$	$x_{i-n+1},\ldots,x_{i-1},a$
$x_{i-n},\ldots,x_{i-1},c$	$x_{i-n+1},\ldots,x_{i-1},c$
$x_{i-n},\ldots,x_{i-1},g$	$x_{i-n+1},\ldots,x_{i-1},g$
$x_{i-n},\ldots,x_{i-1},t$	$x_{i-n+1},\ldots,x_{i-1},t$

- use a statistical test (χ^2) to get a value d indicating our confidence that the distributions represented by the two sets of counts are different

IMMs in GLIMMER

- putting it all together

$$\lambda_n(x_{i-n},\ldots,x_{i-1}) = \begin{cases} 1 & \text{if } c(x_{i-n},\ldots,x_{i-1}) > 400 \\ d \times \dfrac{c(x_{i-n},\ldots,x_{i-1})}{400} & \text{else if } d \geq 0.5 \\ 0 & \text{otherwise} \end{cases}$$

where $d \in (0,1)$

IMM Example

- suppose we have the following counts from our training set

ACGA	25	**CGA**	100	**GA**	175
ACGC	40	**CGC**	90	**GC**	140
ACGG	15	**CGG**	35	**GG**	65
ACGT	20	**CGT**	75	**GT**	120
	$\overline{100}$		$\overline{300}$		$\overline{500}$

χ^2 test: $d = 0.857$ χ^2 test: $d = 0.140$

$\lambda_3(\mathbf{ACG}) = 0.857 \times 100/400 = 0.214$

$\lambda_2(\mathbf{CG}) = 0$ (d < 0.5, $c(\mathbf{CG}) < 400$)

$\lambda_1(\mathbf{G}) = 1$ ($c(\mathbf{G}) > 400$)

IMM Example (Continued)

- now suppose we want to calculate $P_{\text{IMM},3}(T \mid ACG)$

$$P_{\text{IMM},1}(T \mid G) = \lambda_1(G)P(T \mid G) + \left(1 - \lambda_1(G)\right)P_{\text{IMM},0}(T)$$
$$= P(T \mid G)$$

$$P_{\text{IMM},2}(T \mid CG) = \lambda_2(CG)P(T \mid CG) + \left(1 - \lambda_2(CG)\right)P_{\text{IMM},1}(T \mid G)$$
$$= P(T \mid G)$$

$$P_{\text{IMM},3}(T \mid ACG) = \lambda_3(ACG)P(T \mid ACG) + \left(1 - \lambda_3(ACG)\right)P_{\text{IMM},2}(T \mid CG)$$
$$= 0.214 \times P(T \mid ACG) + (1 - 0.214) \times P(T \mid G)$$

Gene Recognition in GLIMMER

- essentially ORF classification
- for each ORF
  - calculate the prob of the ORF sequence in each of the 6 possible reading frames
  - if the highest scoring frame corresponds to the reading frame of the ORF, mark the ORF as a gene
- for overlapping ORFs that look like genes
  - score overlapping region separately
  - predict only one of the ORFs as a gene

GLIMMER Experiment

- 8^{th} order IMM vs. 5^{th} order Markov model
- trained on 1168 genes (ORFs really)
- tested on 1717 annotated (more or less known) genes

GLIMMER Results

TP FN FP & TP?

Model	Genes found	Genes missed	Additional genes
GLIMMER IMM	1680 (97.8%	37	209
5th-Order Markov	1574 (91.7%)	143	104

The first column indicates how many of the 1717 annotated genes in *H.influenzae* were found by each algorithm. The 'additional genes' column shows how many extra genes, not included in the 1717 annotated entries, were called genes by each method.

- GLIMMER has greater sensitivity than the baseline
- it's not clear if its precision/specificity is better

An Alternative Approach: Back-off Models

- devised for language modeling
  [Katz, *IEEE Transactions on Acoustics, Speech and Signal Processing*, 1987]

$$P_{BACK}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \begin{cases} (1-\delta)\dfrac{c(x_{i-n},\ldots,x_i)}{c(x_{i-n},\ldots,x_{i-1})}, & \text{if } c(x_{i-n},\ldots,x_i) > k \\ \lambda P_{BACK}(x_i \mid x_{i-n+1},\ldots,x_{i-1}), & \text{otherwise} \end{cases}$$

- use *n*th order probability if we've seen this sequence (*history* + *current character*) k times
- otherwise back off to lower-order

An Alternative Approach: Back-off Models

$$P_{BACK}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \begin{cases} (1-\delta)\dfrac{c(x_{i-n},\ldots,x_i)}{c(x_{i-n},\ldots,x_{i-1})}, & \text{if } c(x_{i-n},\ldots,x_i) > k \\ \lambda P_{BACK}(x_i \mid x_{i-n+1},\ldots,x_{i-1}), & \text{otherwise} \end{cases}$$

- why do we need δ and λ ?
- δ: save some probability mass for sequences we haven't seen
- λ: distribute this saved mass to lower-order sequences (different λ for each history; really $\lambda(x_{i-n+1},\ldots,x_{i-1})$)
- this is important for natural language, where there are many words that could follow a particular history

Simple Back-off Example

$$P_{BACK}(x_i \mid x_{i-n},\ldots,x_{i-1}) = \begin{cases} (1-\delta)\dfrac{c(x_{i-n},\ldots,x_i)}{c(x_{i-n},\ldots,x_{i-1})}, & \text{if } c(x_{i-n},\ldots,x_i) > k \\ \lambda P_{BACK}(x_i \mid x_{i-n+1},\ldots,x_{i-1}), & \text{otherwise} \end{cases}$$

- given training sequence: **TAACGACACG**
- suppose δ = 0.2 and k = 0

$$P_{BACK}(A) = \frac{4}{10} \qquad P_{BACK}(A \mid A) = (1-\delta)\frac{1}{4} = 0.2$$

$$P_{BACK}(C) = \frac{3}{10} \qquad P_{BACK}(C \mid A) = (1-\delta)\frac{3}{4} = 0.6$$

$$P_{BACK}(G) = \frac{2}{10} \qquad P_{BACK}(G \mid A) = \left[\frac{\delta}{P_{BACK}(G)+P_{BACK}(T)}\right] \times P_{BACK}(G) = \frac{0.2}{0.3} \times 0.2$$

$$P_{BACK}(T) = \frac{1}{10} \qquad P_{BACK}(T \mid A) = \left[\frac{\delta}{P_{BACK}(G)+P_{BACK}(T)}\right] \times P_{BACK}(T) = \frac{0.2}{0.3} \times 0.1$$