Applications of HMMs in computational biology

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Lecture based on Mark Craven's class at University of Wisconsin

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http://cw.felk.cvut.cz/wiki/courses/b4m36bin/start

Overview

- Hidden Markov models
  - the relationship between states and symbols remains hidden,
  - three important general tasks to be solved,
- two biological tasks solved with HMMs
  - characterization/classification of protein families,
  - gene finding.

Hidden Markov models (HMMs)

- in the Markov models it is clear which state accounts for each symbol of the observed sequence,
- HMMs distinguish between the observed and hidden part of a problem
  - multiple states could account for each observed sequence symbol,
  - the link between states and symbols makes the hidden part of the problem,
- the parameters of an HMM
  - as in Markov chain models, we have transition probabilities

$$a_{kl} = P(\pi_i = l | \pi_{i-1} = k)$$

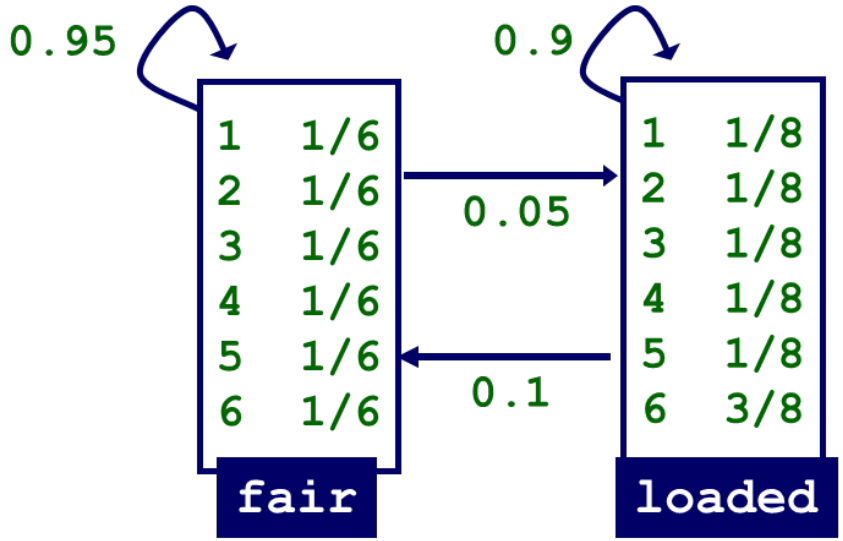
    where π represents a path (sequence of states) through the model
  - in addition, emission probabilities decouple states and symbols

$$e_k(b) = P(x_i = b | \pi_i = k)$$

    where $e_k(b)$ is the probability of emitting character b in state k.

Example HMM – dishonest casino

- Consider a dishonest casino
  - they use a fair die most of the time,
  - but occasionally they switch to a loaded die,
- HMM model
  - observable symbols = the outcomes of rolls = $\{1,2,3,4,5,6\}$,
  - hidden states = the two dice = $\{$fair, loaded$\}$,



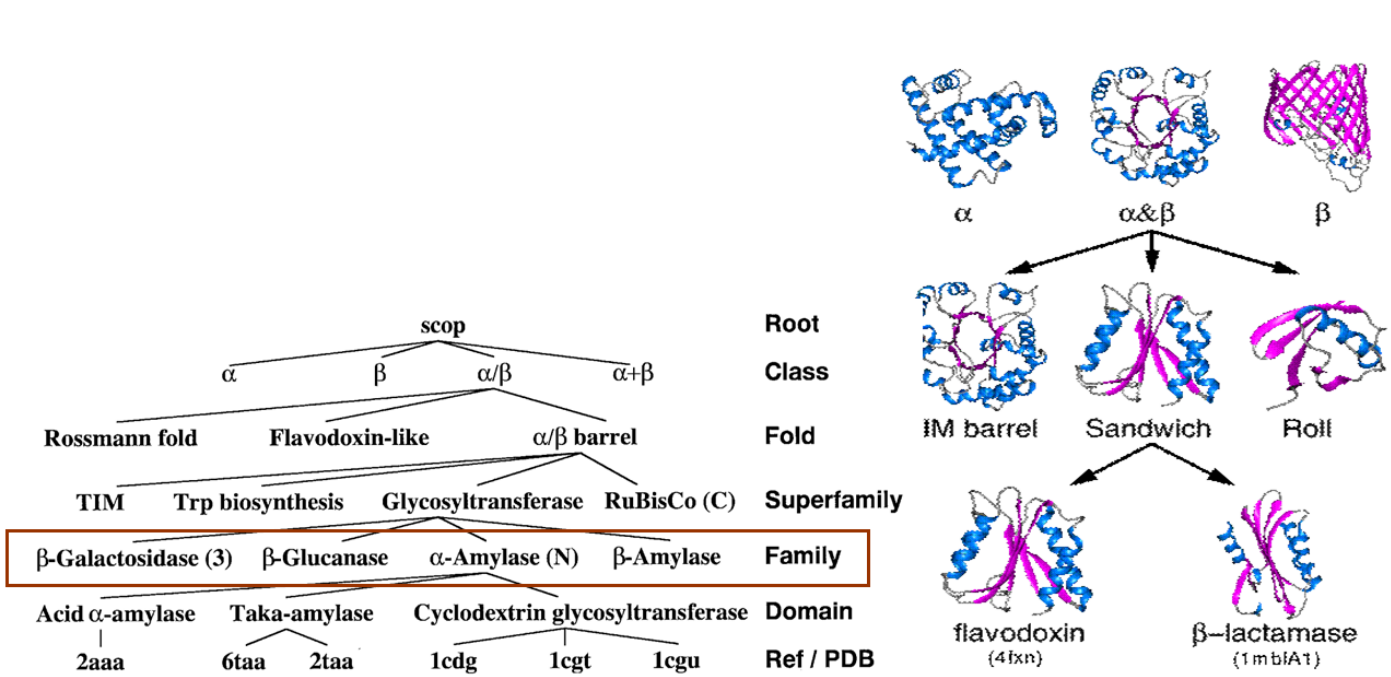
Three important HMM questions

- How likely is a given sequence X given the model M?
  - $P(X|M) = \sum_\pi P(X, \pi|M)$, Forward algorithm,
  - assume a particular model of casino, calculate the probability of a certain sequence of rolls,
  - classification = when having more models, find the best match,
- What is the most probable "path" for generating a given sequence?
  - $\pi^* = \text{argmax}_\pi P(X, \pi|M)$, Viterbi algorithm,
  - having a sequence of rolls, decide which part is fair and which is not,
  - segmentation = "split" the sequence among states,
- How can we learn the HMM parameters given a set of sequences?
  - $\theta^* = \text{argmax}_\theta P(X|\theta, M)$, Forward-Backward (Baum-Welch) algorithm,
  - having a long sequence of rolls and a rough casino model, learn its probs,
  - learning = find a model that generalizes well to unseen sequences.

The protein classification task

- Given: amino-acid sequence of a protein,
- Do: predict the family to which it belongs.

GDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVCVLAHHFGKEFTPPVQAAYAKVVAGVANALAHKYH



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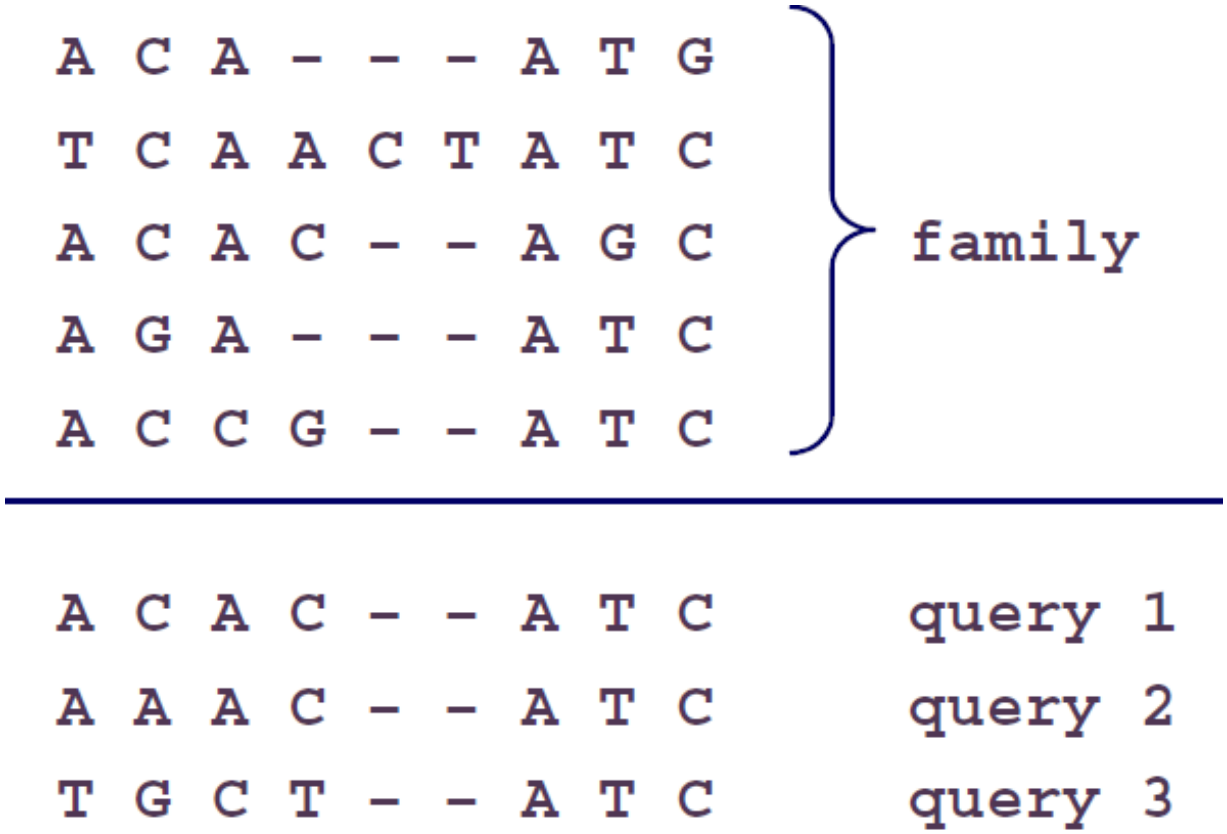
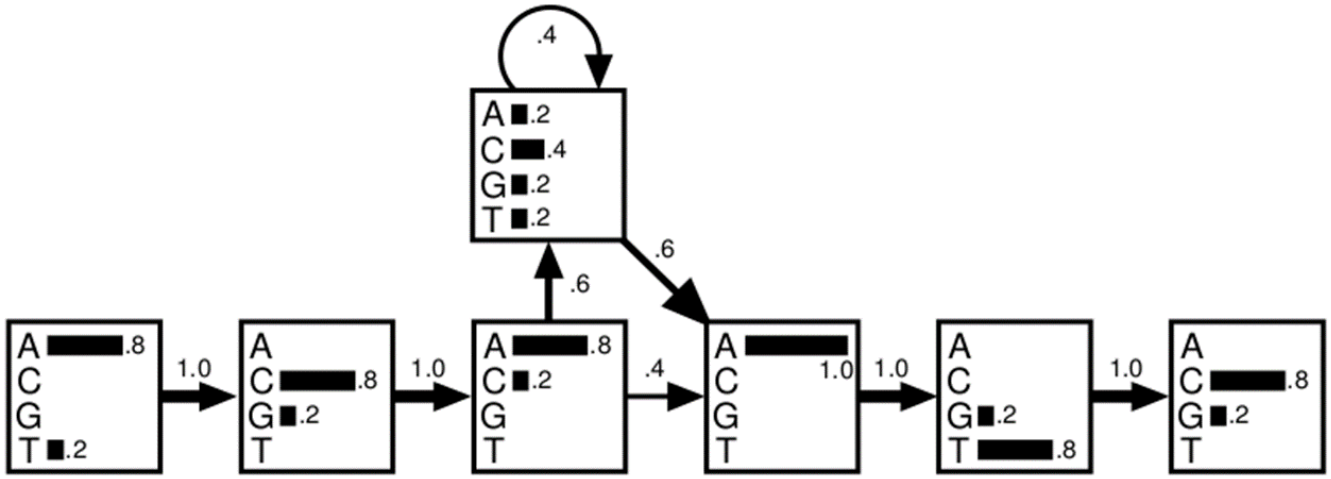
Protein family – a simplified view

- Let us have a multiple sequence alignment for a protein family
  - how could we model the family?
  - do the aligned query sequences belong to the family?



Protein family – a reasonable HMM

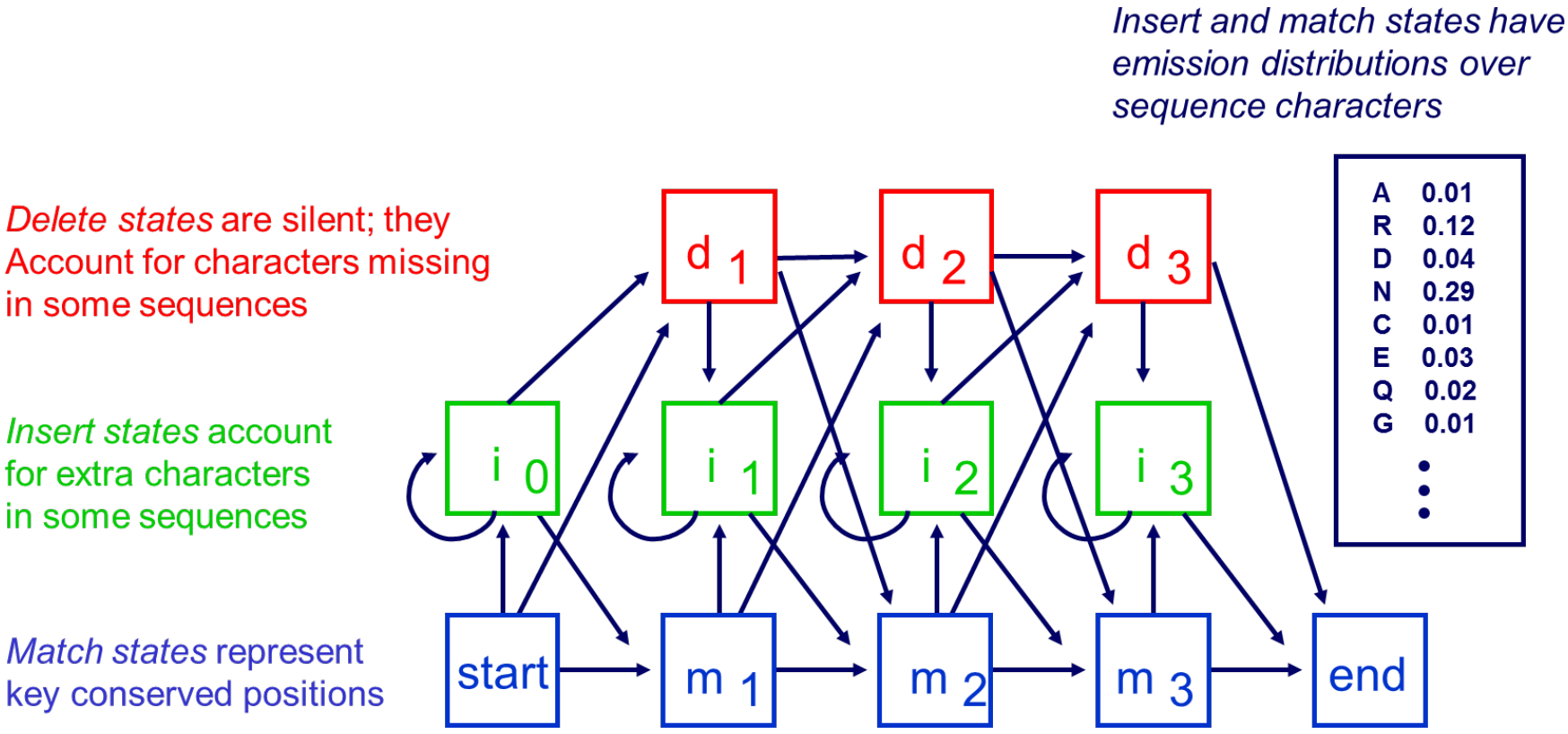


	Sequence	Probability $\times 100$	Log odds
Consensus	A C A C - - A T C	4.7	6.7
Original	A C A - - - A T G	3.3	4.9
sequences	T C A A C T A T C	0.0075	3.0
	A C A C - - A G C	1.2	5.3
	A G A - - - A T C	3.3	4.9
	A C C G - - A T C	0.59	4.6
Exceptional	T G C T - - A G G	0.0023	-0.97

Krogh: An Introduction to HMMs for Biological Sequences, CMMB 1998.

Profile HMMs

- profile HMMs are used to model families of sequences.



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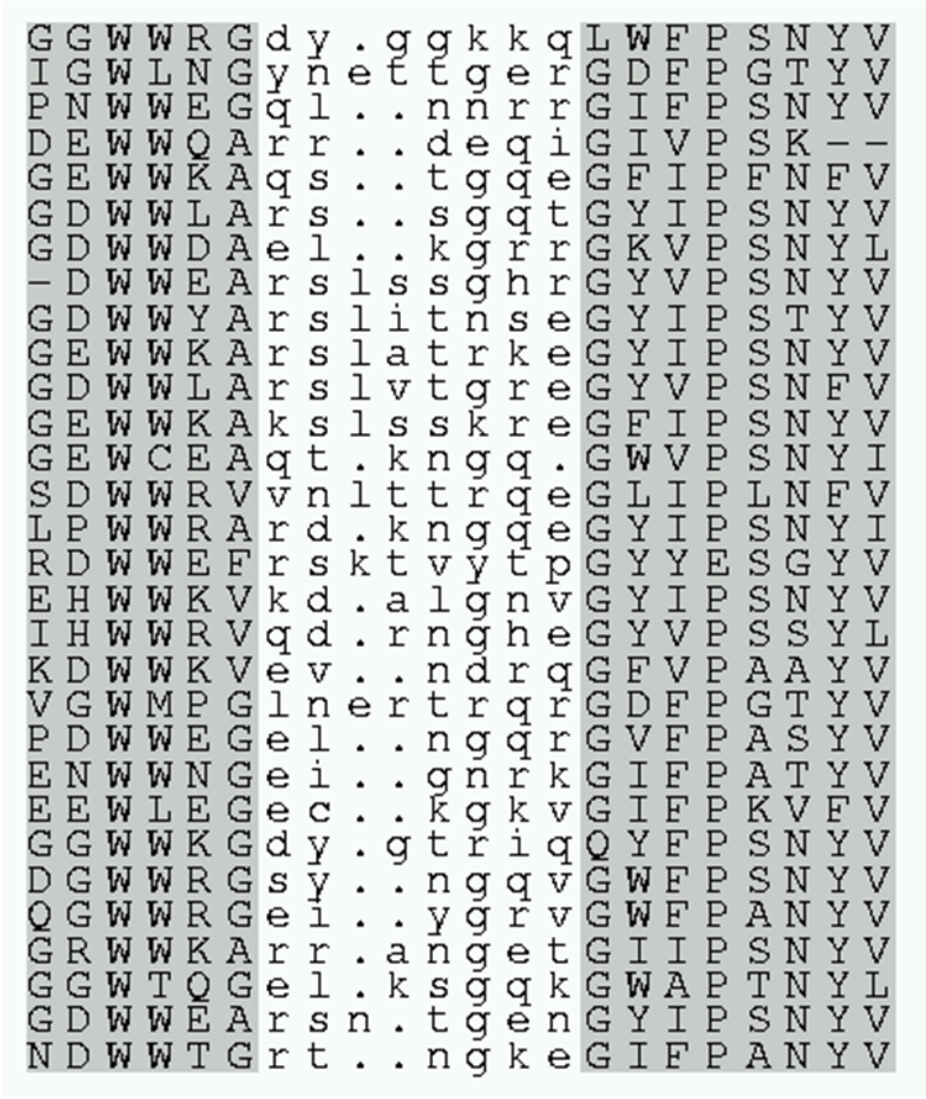
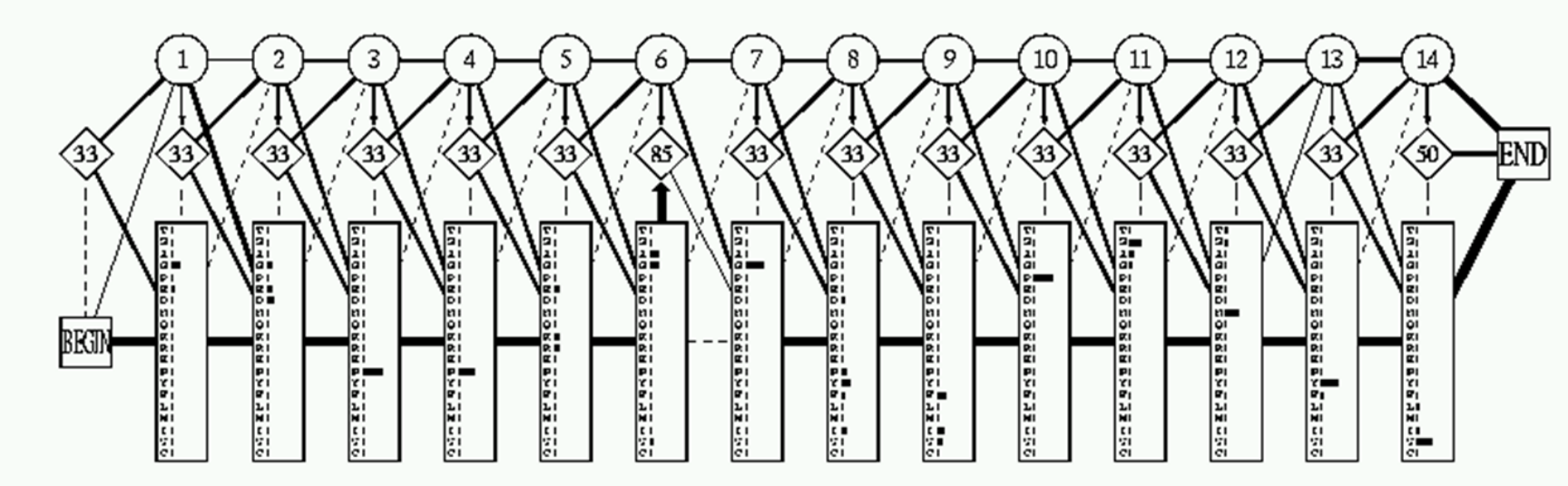
Multiple alignment of SH3 domain



Krogh: An Introduction to HMMs for Biological Sequences, CMMB 1998.

A profile HMM trained for the SH3 domain

- delete states (silent) = upper line,
- insert states = middle line,
- match states = bottom line,
- line strength $\approx$ transition probability.



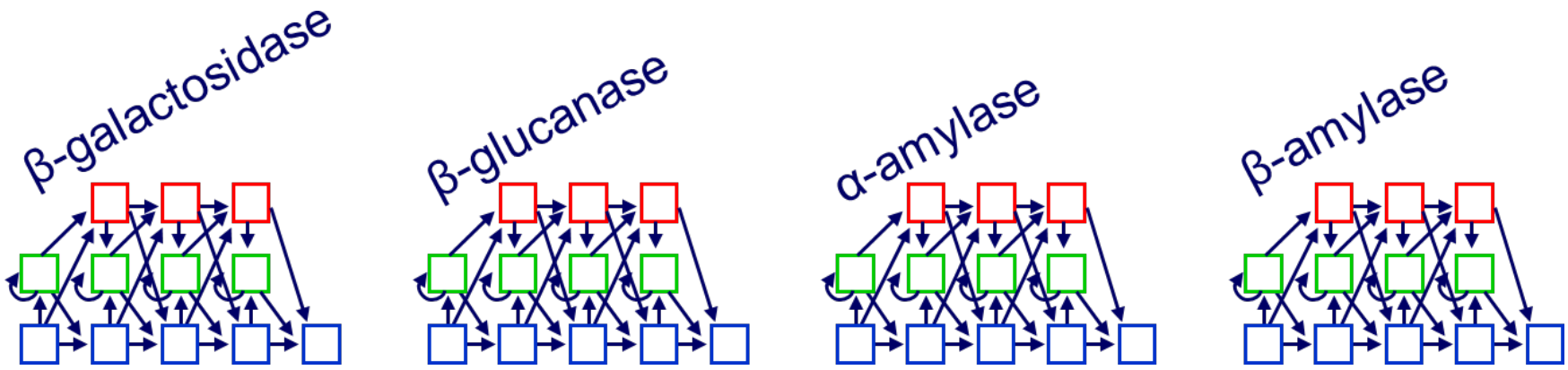
Krogh: An Introduction to HMMs for Biological Sequences, CMMB 1998.

Profile HMMs

- to classify sequences according to family, we can train a profile HMM to model the proteins of each family of interest,
- given a sequence x, use Bayes' rule to make classification

$$P(c_i|x) = \frac{P(x|c_i)P(c_i)}{\sum_j P(x|c_i)P(c_i)}$$

- use Forward algorithm to compute $P(x|c_i)$ for each family c_i.



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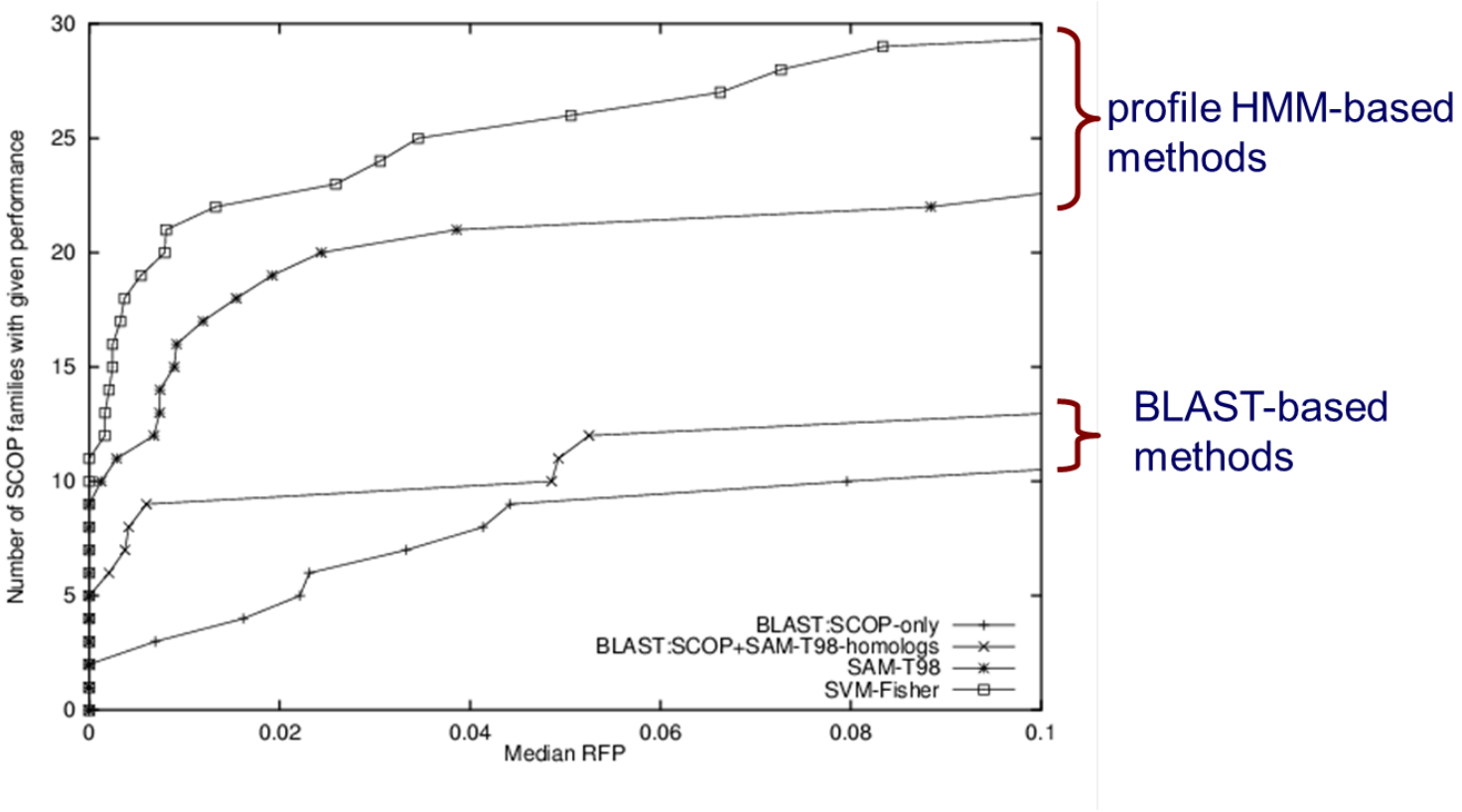
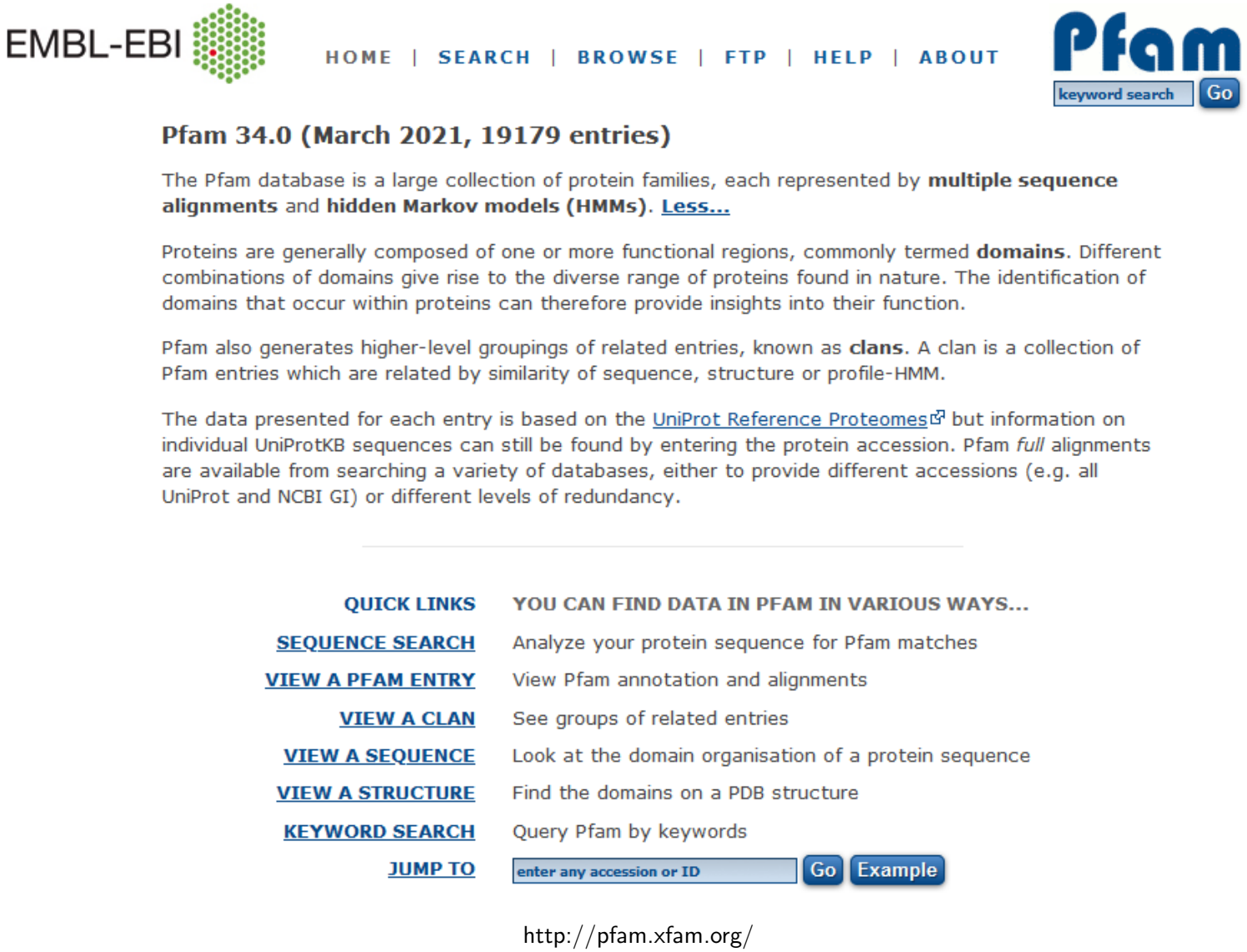
Profile HMM accuracy



Jaakola et al., ISMB 1999.

- classifying 2447 proteins into 33 families,
- x-axis represents the median # of negative sequences that score as high as a positive sequence for a given family's model.

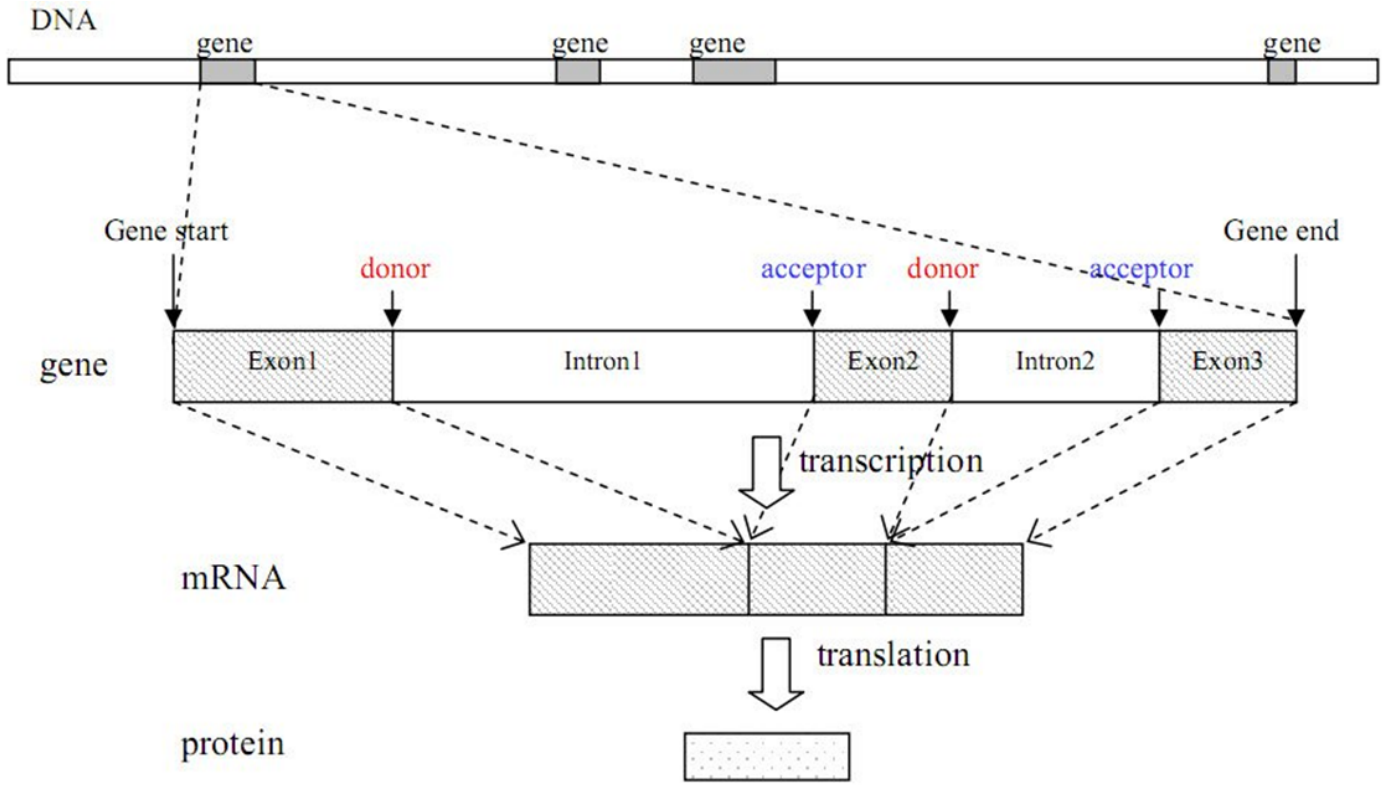
Pfam database – a large collection profile HMMs



http://pfam.xfam.org/

The gene finding task

- Given: an uncharacterized DNA sequence,
- Do: locate the genes in the sequence, including the coordinates of individual exons and introns.



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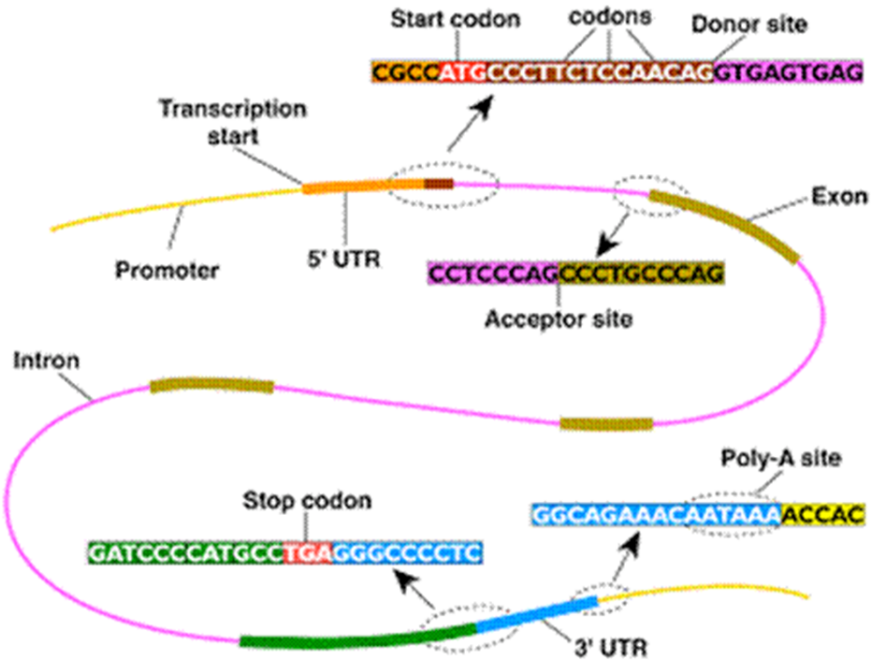
Eukaryotic gene structure and evidence for gene finding

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



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Gene finding: search by content

- Encoding a protein affects the statistical properties of a DNA sequence
  - some amino acids more frequent (Leu more prevalent than Trp),
  - different numbers of codons for different amino acids (Leu/6, Trp/1),
  - for a given amino acid, one codon often more frequent than others
    - codon preference in E.coli and H. sapiens:

```
UUU F 0.57   UCU S 0.11   UAU Y 0.53   UGU C 0.42
UUC F 0.43   UCC S 0.11   UAC Y 0.47   UGC C 0.58
UUA L 0.15   UCA S 0.15   UAA * 0.64   UGA * 0.36
UUG L 0.12   UCG S 0.16   UAG * 0.00   UGG W 1.00

CUU L 0.12   CCU P 0.17   CAU H 0.55   CGU R 0.36
CUC L 0.10   CCC P 0.13   CAC H 0.45   CGC R 0.44
CUA L 0.05   CCA P 0.14   CAA Q 0.30   CGA R 0.07
CUG L 0.46   CCG P 0.55   CAG Q 0.70   CGG R 0.07

AUU I 0.58   ACU T 0.16   AAU N 0.47   AGU S 0.14
AUC I 0.35   ACC T 0.47   AAC N 0.53   AGC S 0.33
AUA I 0.07   ACA T 0.13   AAA K 0.73   AGA R 0.02
AUG M 1.00   ACG T 0.24   AAG K 0.27   AGG R 0.03

GUU V 0.25   GCU A 0.11   GAU D 0.65   GGU G 0.29
GUC V 0.18   GCC A 0.31   GAC D 0.35   GGC G 0.46
GUA V 0.17   GCA A 0.21   GAA E 0.70   GGA G 0.13
GUG V 0.40   GCG A 0.38   GAG E 0.30   GGG G 0.12

[Codon/a.a./fraction per codon per a.a.]
E. coli K12 data from the Codon Usage Database
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www.geneinfinity.org

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UUU F 0.46   UCU S 0.19   UAU Y 0.44   UGU C 0.46
UUC F 0.54   UCC S 0.22   UAC Y 0.56   UGC C 0.54
UUA L 0.08   UCA S 0.15   UAA * 0.30   UGA * 0.47
UUG L 0.13   UCG S 0.05   UAG * 0.24   UGG W 1.00

CUU L 0.13   CCU P 0.29   CAU H 0.42   CGU R 0.08
CUC L 0.20   CCC P 0.32   CAC H 0.58   CGC R 0.18
CUA L 0.07   CCA P 0.28   CAA Q 0.27   CGA R 0.11
CUG L 0.40   CCG P 0.11   CAG Q 0.73   CGG R 0.20

AUU I 0.36   ACU T 0.25   AAU N 0.47   AGU S 0.15
AUC I 0.47   ACC T 0.36   AAC N 0.53   AGC S 0.24
AUA I 0.17   ACA T 0.28   AAA K 0.43   AGA R 0.21
AUG M 1.00   ACG T 0.11   AAG K 0.57   AGG R 0.21

GUU V 0.18   GCU A 0.27   GAU D 0.46   GGU G 0.16
GUC V 0.24   GCC A 0.40   GAC D 0.54   GGC G 0.34
GUA V 0.12   GCA A 0.23   GAA E 0.42   GGA G 0.25
GUG V 0.46   GCG A 0.11   GAG E 0.58   GGG G 0.25

[Codon/a.a./fraction per codon per a.a.]
Homo sapiens data from the Codon Usage Database
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www.geneinfinity.org

The GENSCAN HMM for eukaryotic gene finding

Each shape denotes a functional unit of a gene or genomic region and is represented by a submodel in the HMM

Pairs of intron/exon units represent the different ways an intron can interrupt a coding sequence (after 1st base in codon, after 2nd base or after 3rd base)

Complementary submodel (not shown) detects genes on opposite DNA strand

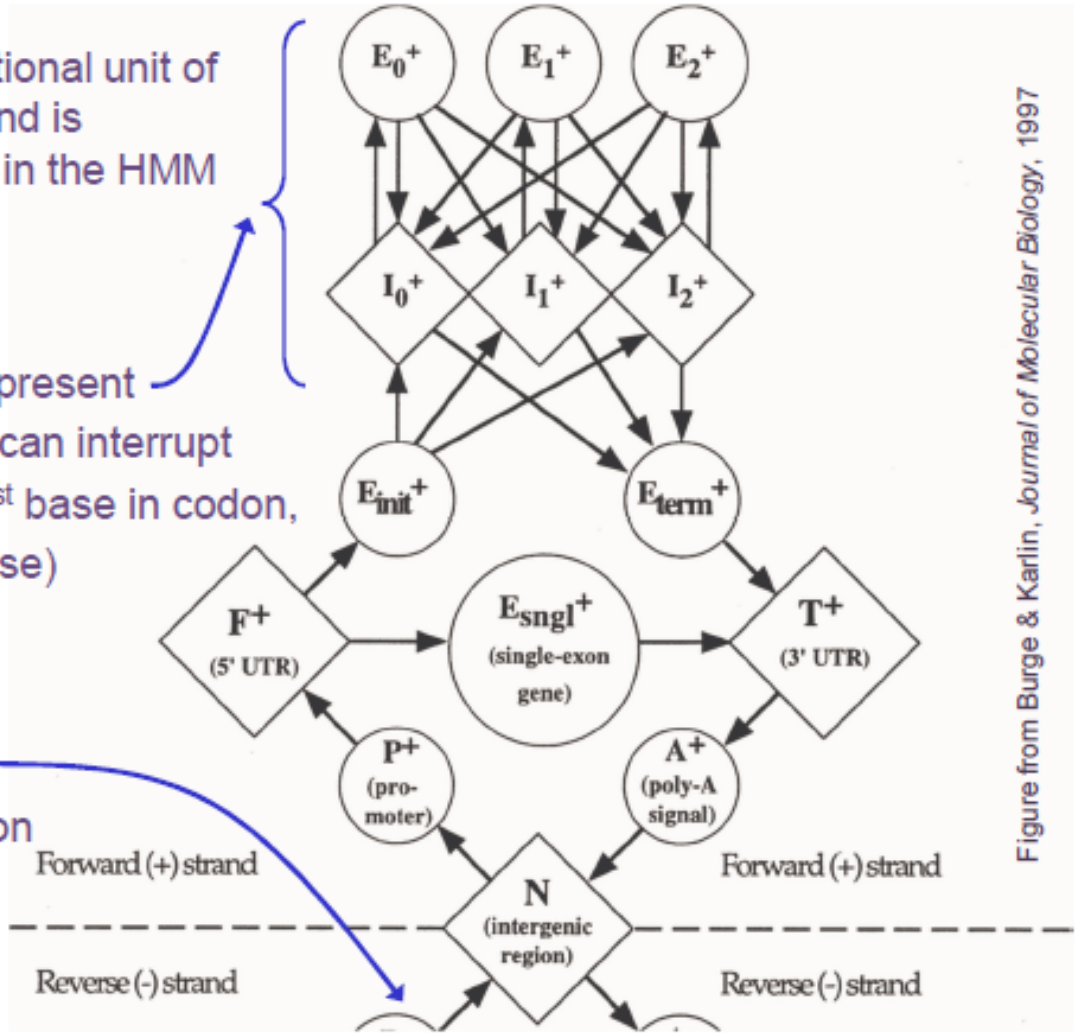
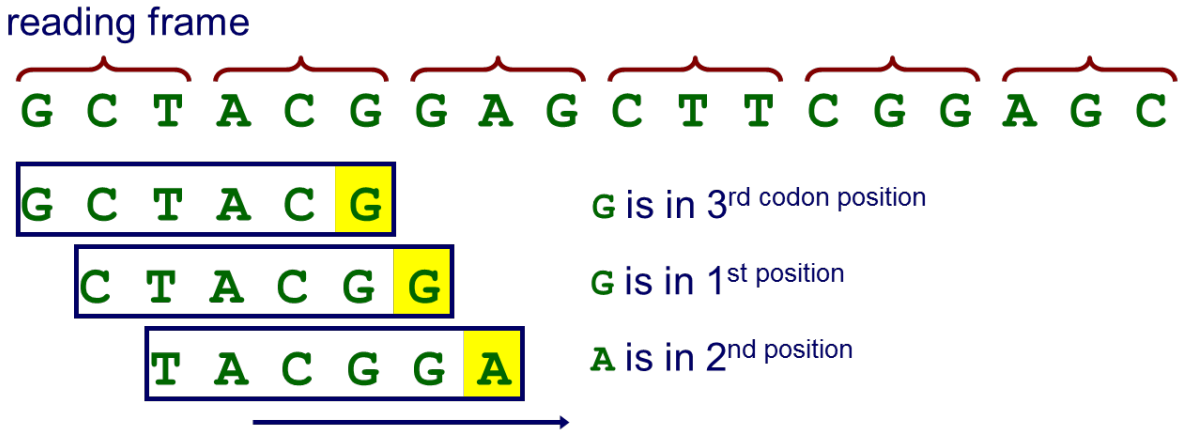


Figure from Burge & Karlin, *Journal of Molecular Biology*, 1997

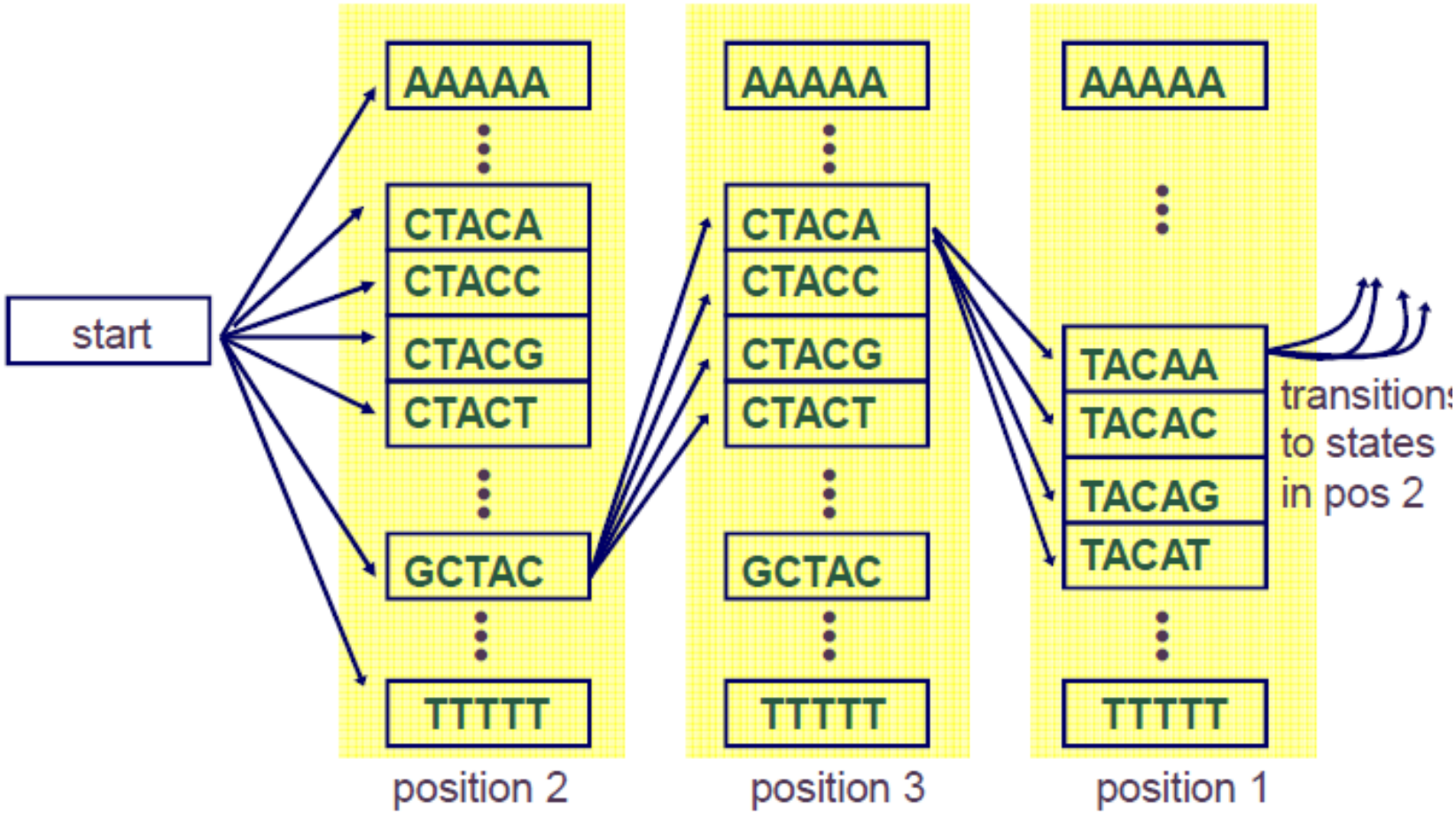
GENSCAN HMM and its submodels

sequence	feature model
exons	5th order inhomogenous
introns, intergenic regions	5th order homogenous
poly-A, translation initiation, promoter	0th order, fixed-length
splice junctions	tree-structured variable memory

- Exon submodel
  - for each "word", consider its position with respect to the reading frame,
  - use an inhomogeneous Markov chain.



A fifth-order inhomogenous Markov chain



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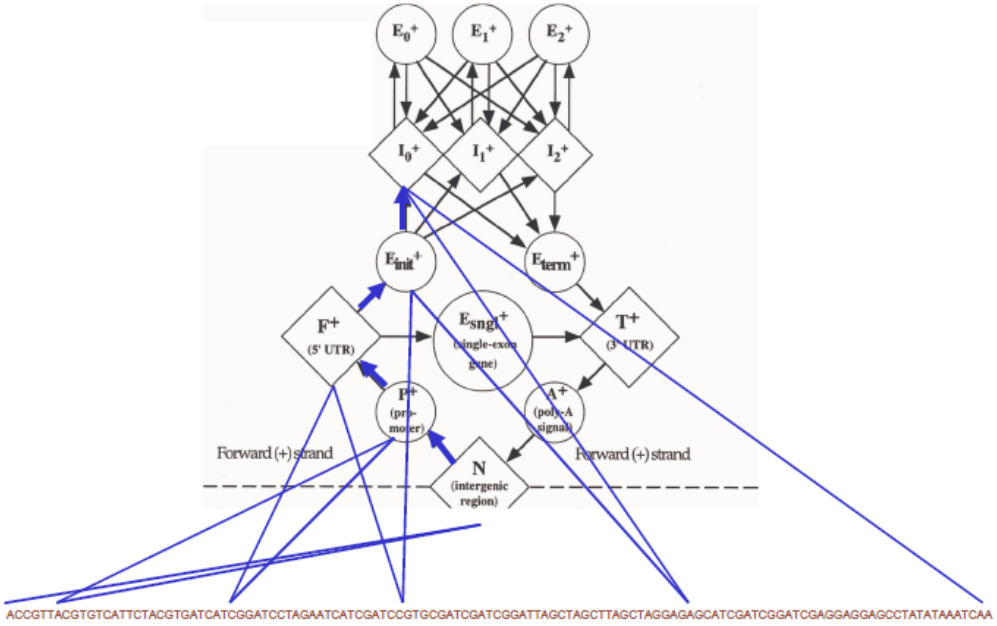
Inference with the gene-finding HMM

- Given: an uncharacterized DNA sequence,
- find: the most probable path through the model for the sequence
  - this path will specify the coordinates of the predicted genes (including intron and exon boundaries),
  - the Viterbi algorithm is used to compute this path.



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Other issues in Markov models

- There are many interesting variants and extensions of the models/algorithms we considered here
  - separating length/composition distributions with semi-Markov models,
  - modeling multiple sequences with pair HMMs,
  - learning the structure of HMMs,
  - going up the Chomsky hierarchy: stochastic context free grammars,
  - discriminative learning algorithms (e.g. as in conditional random fields).