Applications of HMMs in Computational Biology

BMI/CS 576
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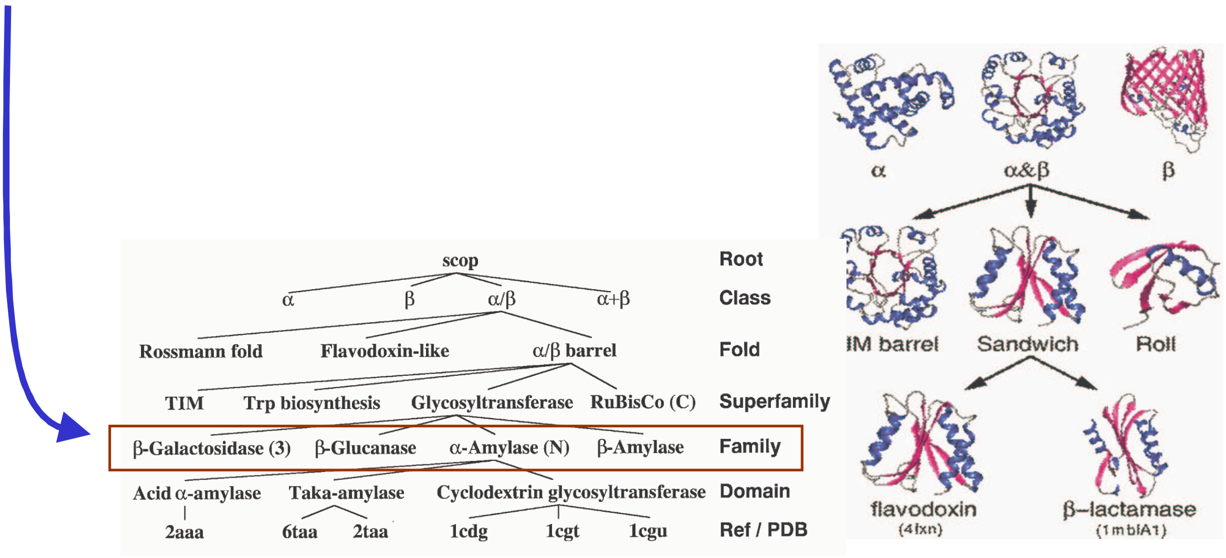
The protein classification task

Given: amino-acid sequence of a protein

Do: predict the *family* to which it belongs

GDLSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGNVCVLAHHFGKEFTPPVQAAYAKVVAGVANALAHKYH

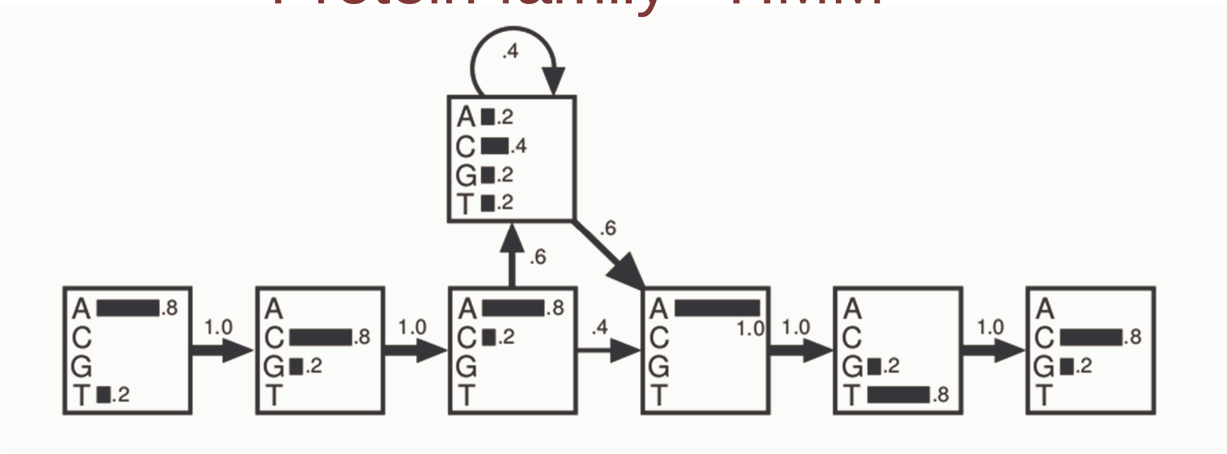


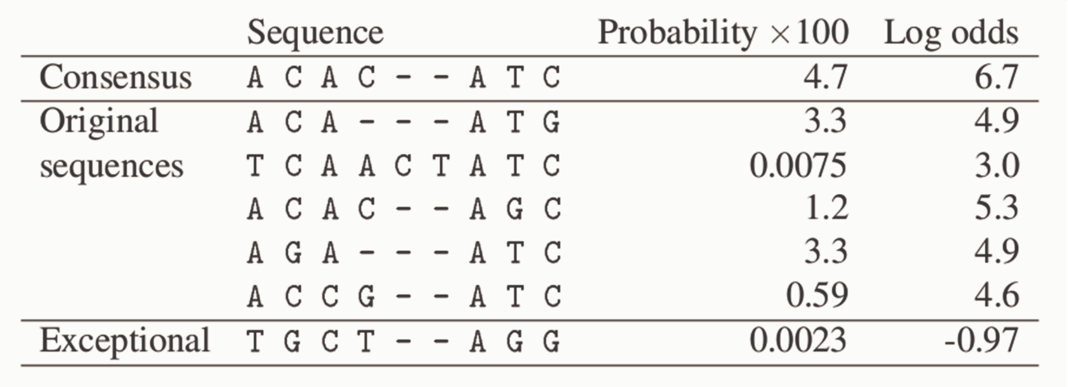
Protein family - a simplified view

```
A C A - - - A T G  ⎫
T C A A C T A T C  ⎪
A C A C - - A G C  ⎬  family
A G A - - - A T C  ⎪
A C C G - - A T C  ⎭
-----------------------------
A C A C - - A T C     query 1
A A A C - - A T C     query 2
T G C T - - A T C     query 3
```

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

Protein family - HMM





	Sequence	Probability × 100	Log odds
Consensus	A C A C - - A T C	4.7	6.7
Original sequences	A C A - - - A T G	3.3	4.9
	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

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

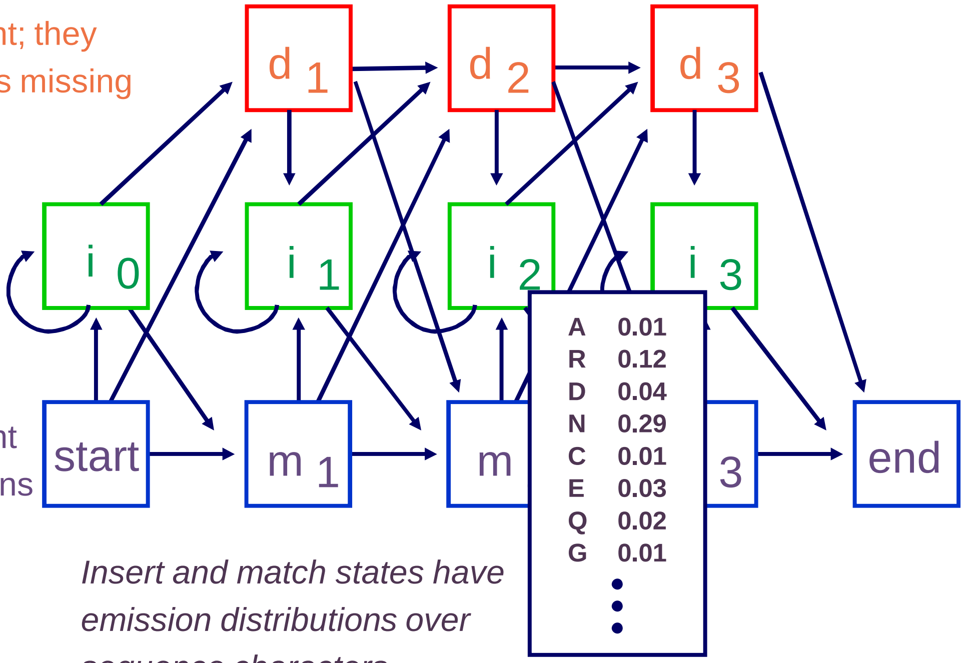
Profile HMMs

- profile HMMs are used to model families of sequences

Delete states are silent; they Account for characters missing in some sequences

Insert states account for extra characters in some sequences

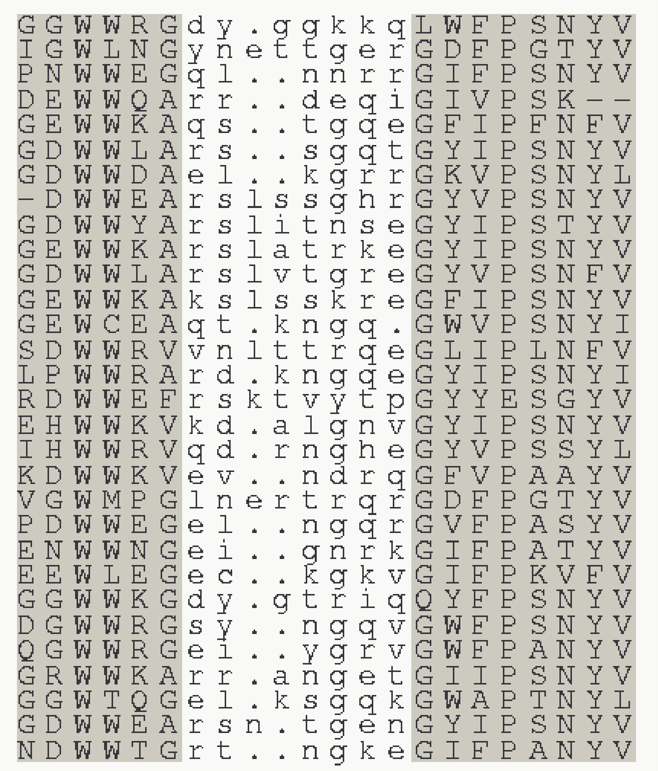
Match states represent key conserved positions



A	0.01
R	0.12
D	0.04
N	0.29
C	0.01
E	0.03
Q	0.02
G	0.01
•	
•	
•	

Insert and match states have emission distributions over sequence characters

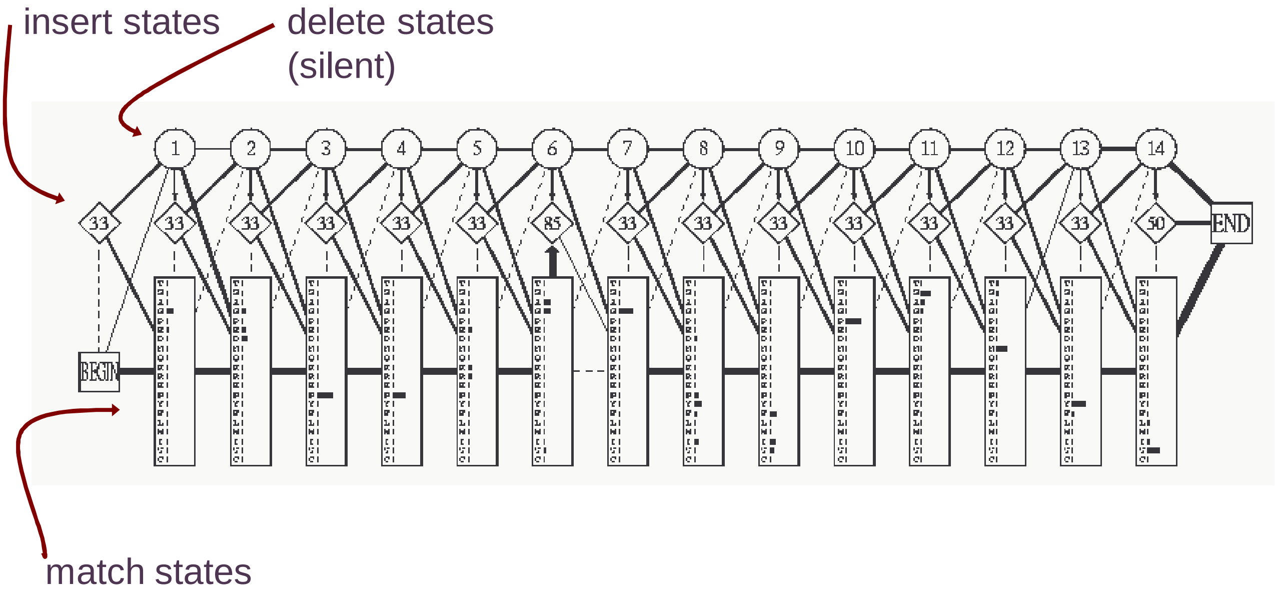
Multiple alignment of SH3 domain



```
GGWWRGdy.ggkkqLWFPSNYV
IGWLNGynettgerGDFPGTYV
PNWWEGql..nnrrGIFPSNYV
DEWWQArr..deqiGIVPSK--
GEWWKAqs..tgqeGFIPFNFV
GDWWLArs..sgqtGYIPSNYV
GDWWDAel..kgrrGKVPSNYL
-DWWEArslssghrGYVPSNYV
GDWWYArslitnseGYIPSTYV
GEWWKArslatrkeGYIPSNYV
GDWWLArslvtgreGYVPSNFV
GEWWKAkslsskreGFIPSNYV
GEWCEAqt.kngq.GWVPSNYI
SDWWRVvnlttrqeGLIPLNFV
LPWWRArd.kngqeGYIPSNYI
RDWWEFrsktvytpGYYESGYV
EHWWKVkd.algnvGYIPSNYV
IHWWRVqd.rngheGYVPSSYL
KDWWKVev..ndrqGFVPAAYV
VGWMPGlnertrqrGDFPGTYV
PDWWEGel..ngqrGVFPASYV
ENWWNGei..gnrkGIFPATYV
EEWLEGec..kgkvGIFPKVFV
GGWWKGdy.gtriqQYFPSNYV
DGWWRGsy..ngqvGWFPSNYV
QGWWRGei..ygrvGWFPANYV
GRWWKArr.angetGIIPSNYV
GGWTQGel.ksgqkGWAPTNYL
GDWWEArsn.tgenGYIPSNYV
NDWWTGrt..ngkeGIFPANYV
```

Figure from A. Krogh, An Introduction to Hidden Markov Models for Biological Sequences

A profile HMM trained for the SH3 domain



insert states

delete states (silent)

match states

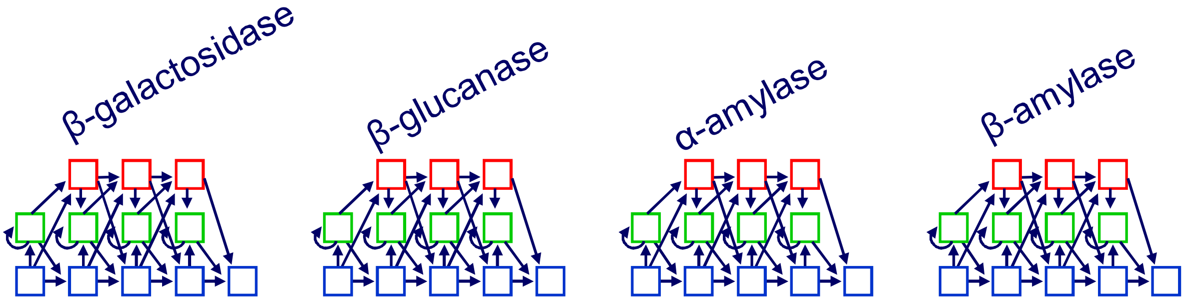
Figure from A. Krogh, An Introduction to Hidden Markov Models for Biological Sequences

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

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

- use Forward algorithm to compute $P(x \mid c_i)$ for each family c_i



β-galactosidase

β-glucanase

α-amylase

β-amylase

Profile HMM accuracy

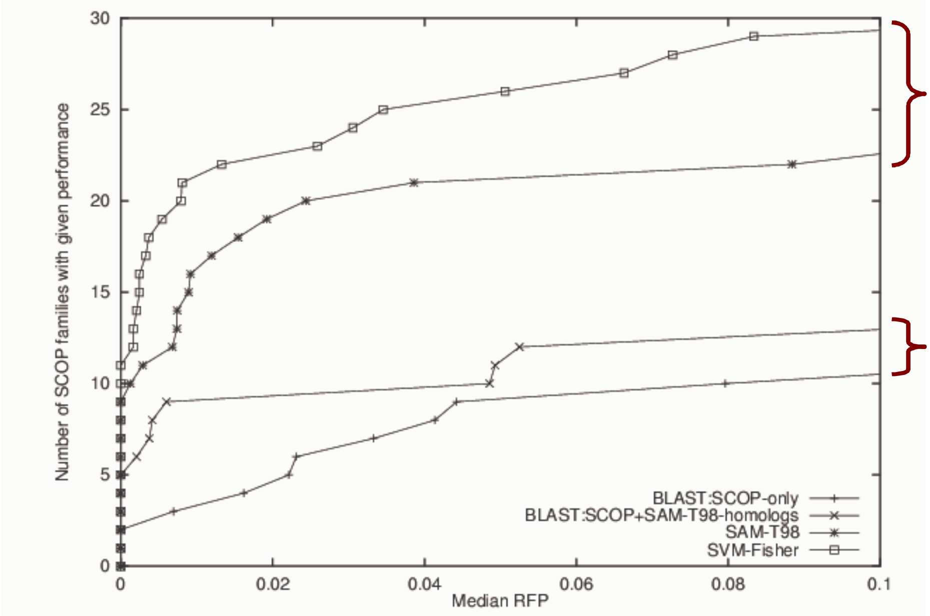


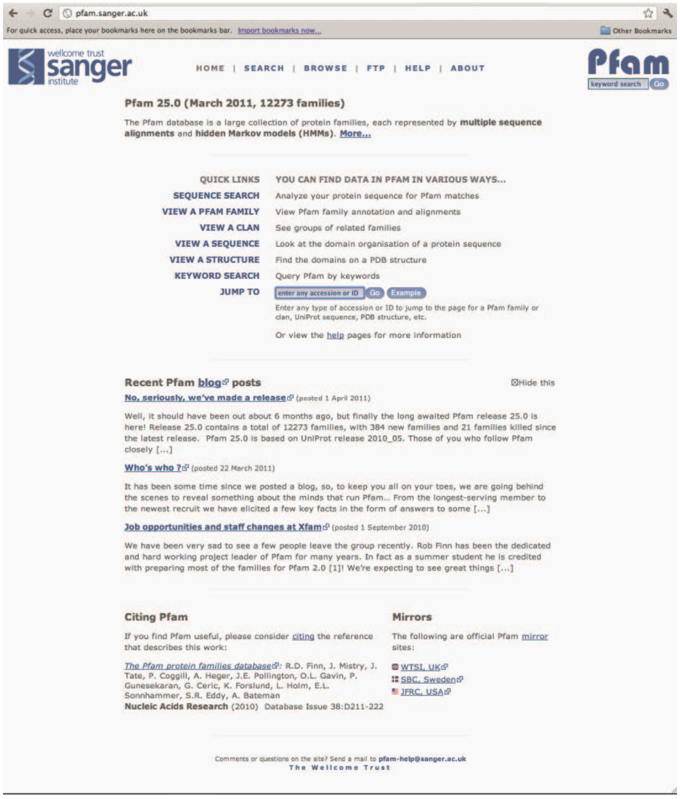
Figure from Jaakola et al., ISMB 1999

profile HMM-based methods

BLAST-based methods

- classifying 2447proteins 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

See Pfam database for a large collection profile HMMs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Other Bookmarks
wellcome trust sanger institute
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Pfam
keyword search
Go

Pfam 25.0 (March 2011, 12273 families)

The Pfam database is a large collection of protein families, each represented by **multiple sequence alignments** and **hidden Markov models (HMMs)**. More...

QUICK LINKS	YOU CAN FIND DATA IN PFAM IN VARIOUS WAYS...
SEQUENCE SEARCH	Analyze your protein sequence for Pfam matches
VIEW A PFAM FAMILY	View Pfam family annotation and alignments
VIEW A CLAN	See groups of related families
VIEW A SEQUENCE	Look at the domain organisation of a protein sequence
VIEW A STRUCTURE	Find the domains on a PDB structure
KEYWORD SEARCH	Query Pfam by keywords
JUMP TO	enter any accession or ID Go Example Enter any type of accession or ID to jump to the page for a Pfam family or clan, UniProt sequence, PDB structure, etc. Or view the help pages for more information

Recent Pfam blog posts ☒Hide this

No, seriously, we've made a release (posted 1 April 2011)

Well, it should have been out about 6 months ago, but finally the long awaited Pfam release 25.0 is here! Release 25.0 contains a total of 12273 families, with 384 new families and 21 families killed since the latest release. Pfam 25.0 is based on UniProt release 2010_05. Those of you who follow Pfam closely [...]

Who's who ? (posted 22 March 2011)

It has been some time since we posted a blog, so, to keep you all on your toes, we are going behind the scenes to reveal something about the minds that run Pfam… From the longest-serving member to the newest recruit we have elicited a few key facts in the form of answers to some [...]

Job opportunities and staff changes at Xfam (posted 1 September 2010)

We have been very sad to see a few people leave the group recently. Rob Finn has been the dedicated and hard working project leader of Pfam for many years. In fact as a summer student he is credited with preparing most of the families for Pfam 2.0 [1]! We're expecting to see great things [...]

Citing Pfam

If you find Pfam useful, please consider citing the reference that describes this work:

The Pfam protein families database: R.D. Finn, J. Mistry, J. Tate, P. Coggill, A. Heger, J.E. Pollington, O.L. Gavin, P. Gunesekaran, G. Ceric, K. Forslund, L. Holm, E.L. Sonnhammer, S.R. Eddy, A. Bateman
Nucleic Acids Research (2010) Database Issue 38:D211-222

Mirrors

The following are official Pfam mirror sites:

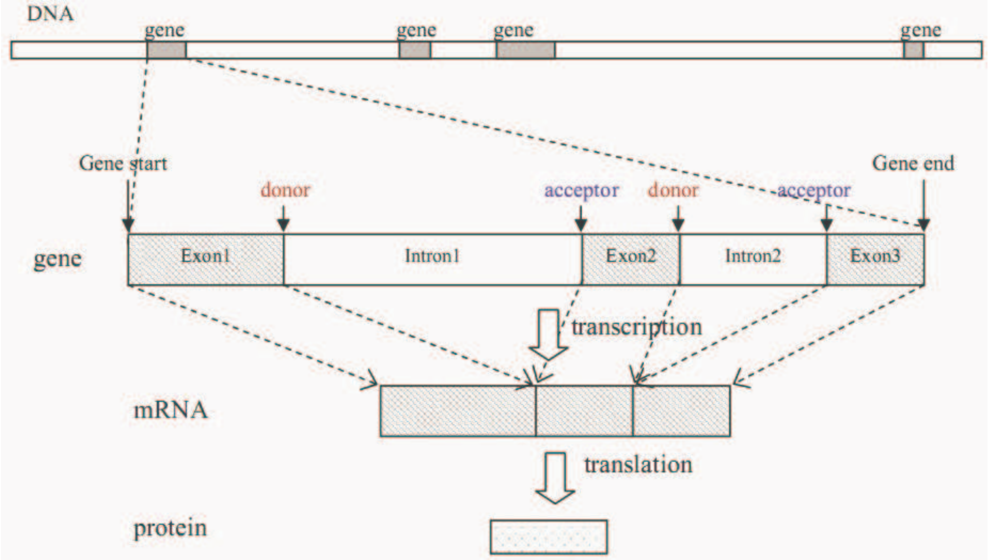
- WTSI, UK
- SBC, Sweden
- JFRC, USA

Comments or questions on the site? Send a mail to **pfam-help@sanger.ac.uk**
The Wellcome Trust

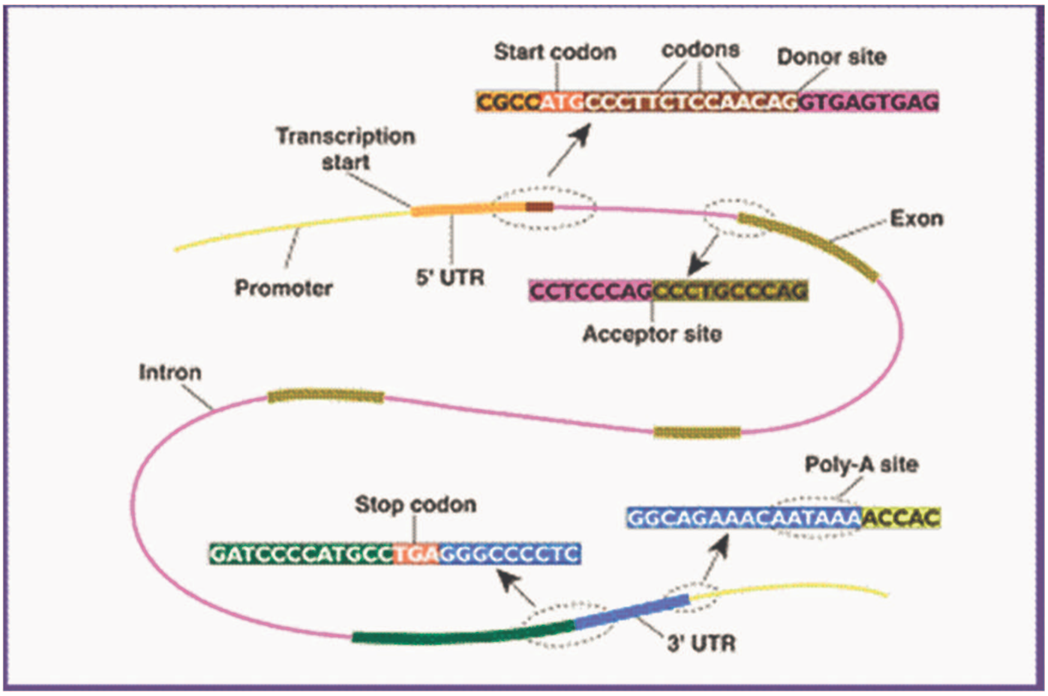
The gene finding task

Given: an uncharacterized DNA sequence

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



Eukaryotic gene structure

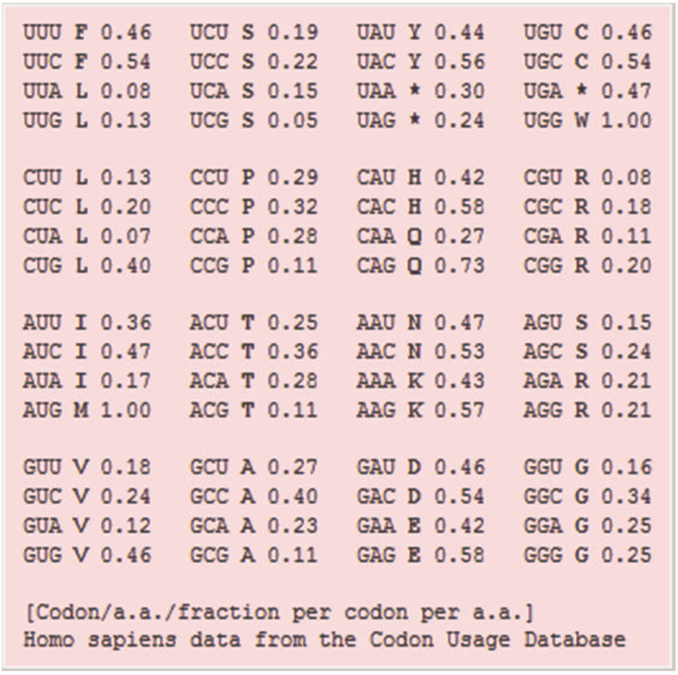


Sources of evidence for gene finding

- **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. syntenic regions of the mouse and human genome)

Gene finding: search by content

- encoding a protein affects the statistical properties of a DNA sequence



```
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
```

The GENSCAN HMM for Eukaryotic Gene Finding [Burge & Karlin ‘97]

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

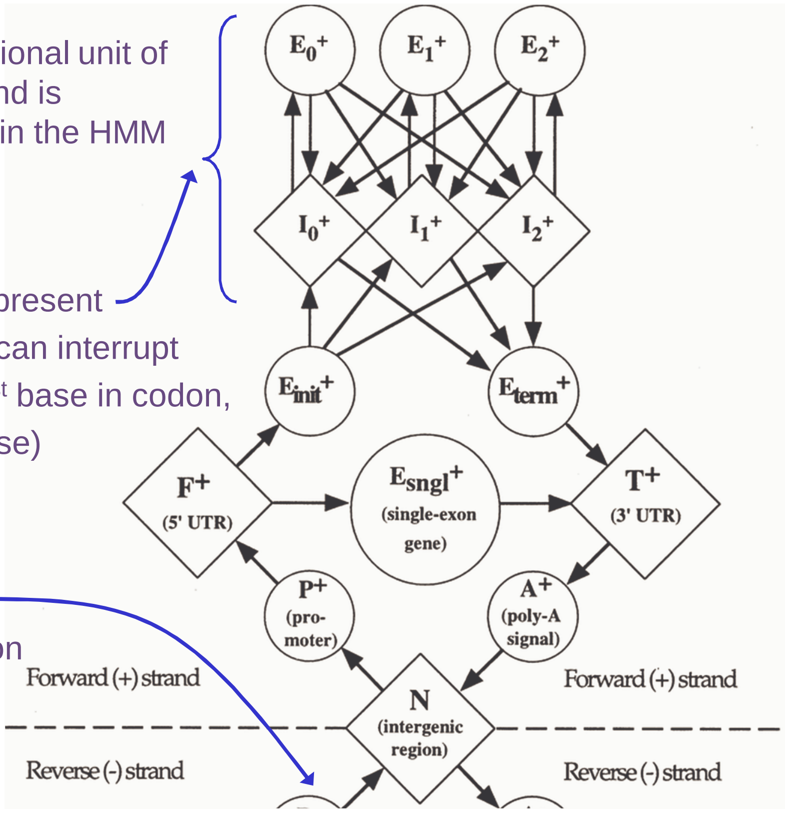


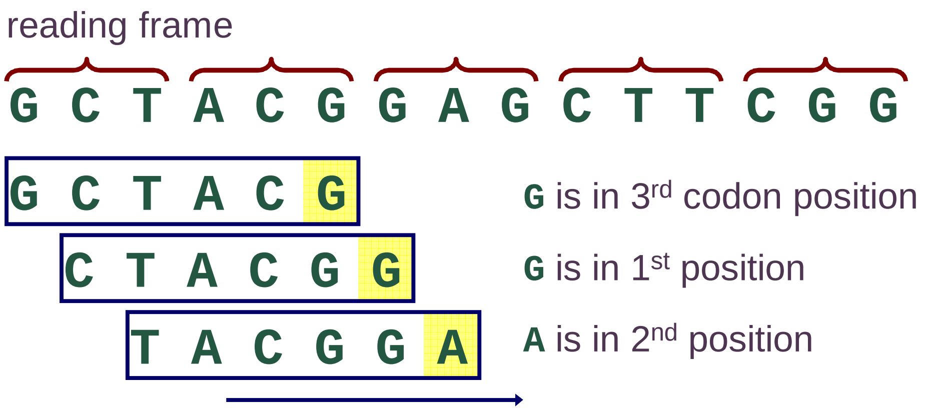
Figure from Burge & Karlin, *Journal of Molecular Biology*, 1997

GENSCAN uses a variety of submodel types

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

Markov models & exons

- 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



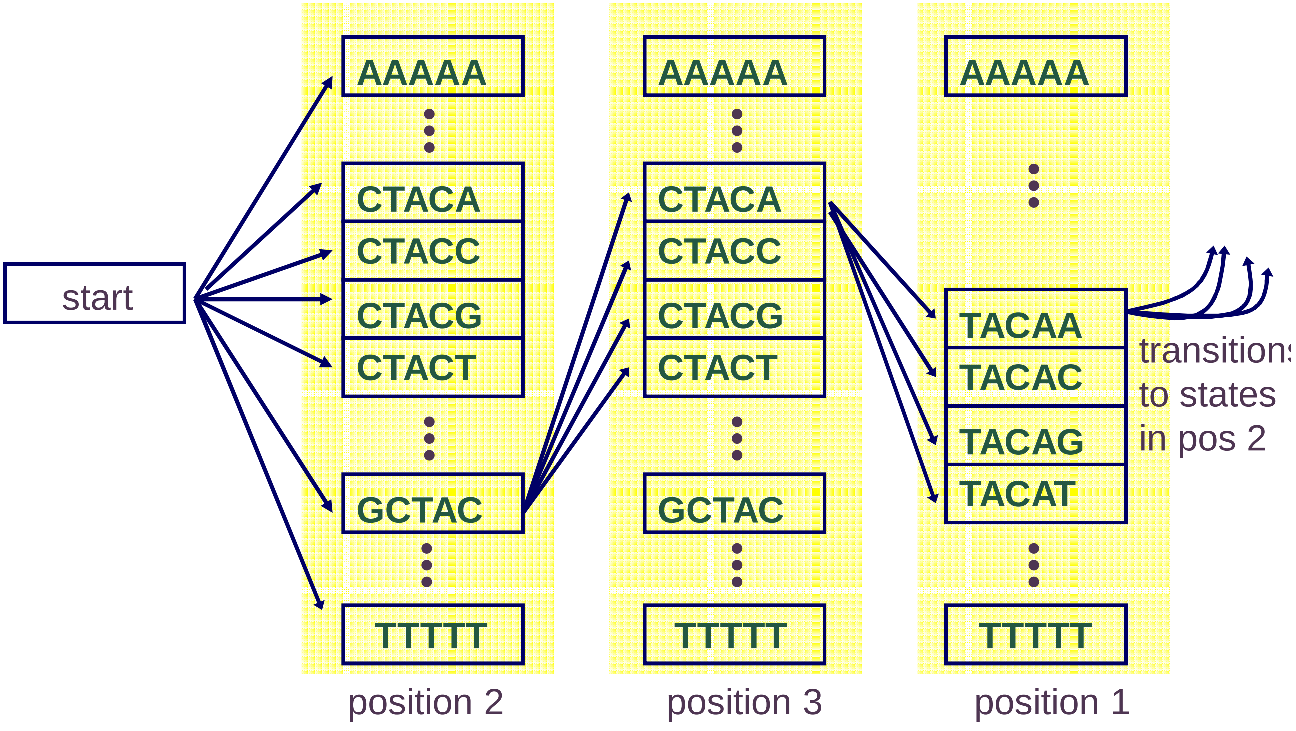
G is in 3rd codon position

G is in 1st position

A is in 2nd position

- can do this using an inhomogeneous model

A fifth-order inhomogenous Markov chain



transitions to states in pos 2

Inference with the gene-finding HMM

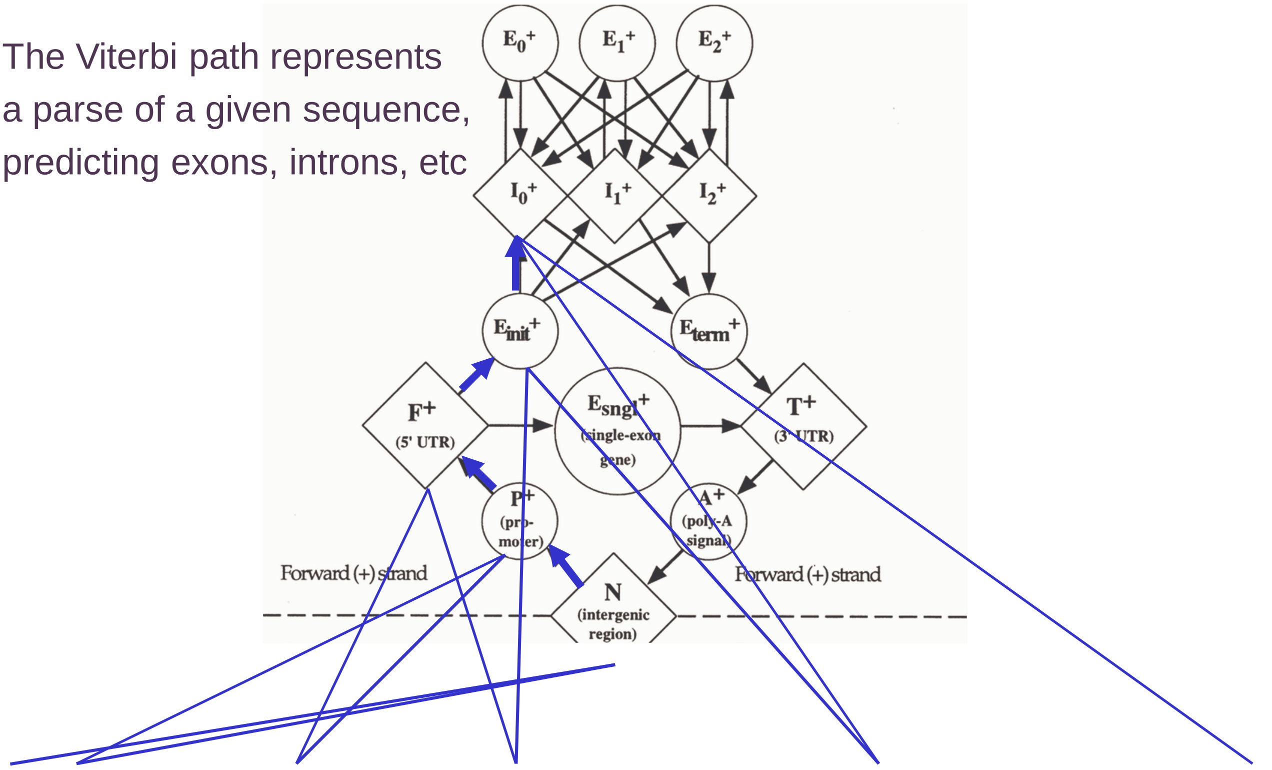
given: an uncharacterized DNA sequence

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

Parsing a DNA sequence

The Viterbi path represents a parse of a given sequence, predicting exons, introns, etc



ACCGTTACGTGTCATTCTACGTGATCATCGGATCCTAGAATCATCGATCCGTGCGATCGATCGGATTAGCTAGCTTAGCTAGGAGAGCATCGATCGGATCGAGGAGGAGCCTATATAAATCAA

Other issues in Markov models

- there are many interesting variants and extensions of the models/algorithms we considered here (some of these are covered in BMI/CS 776)
  - 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*)
  - etc.