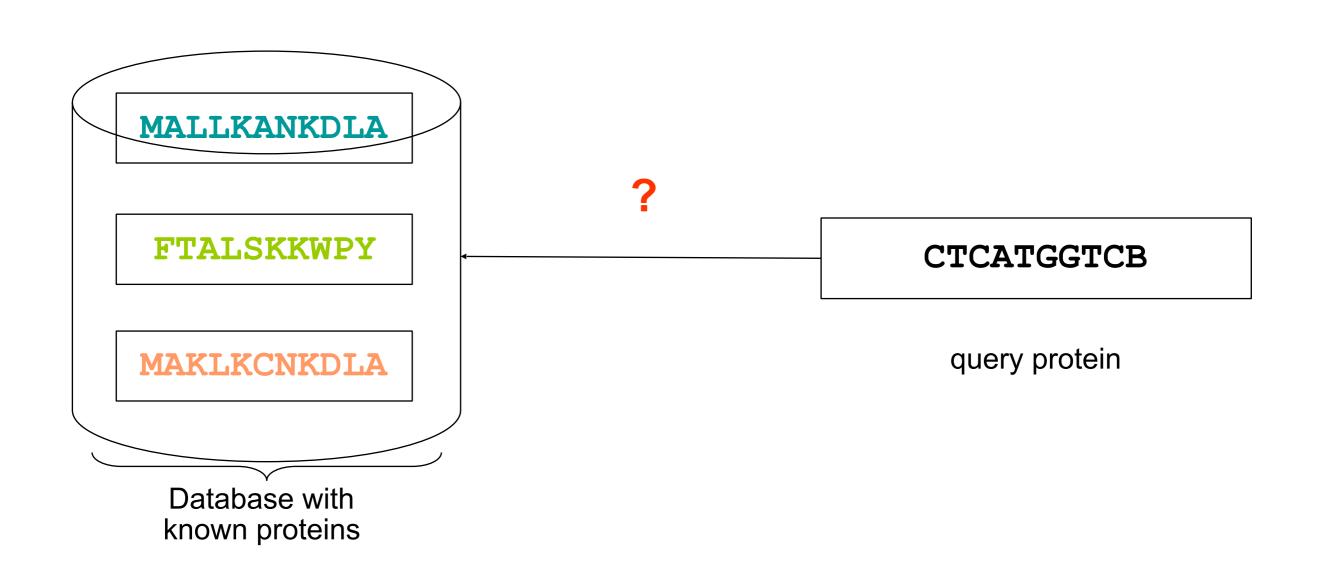
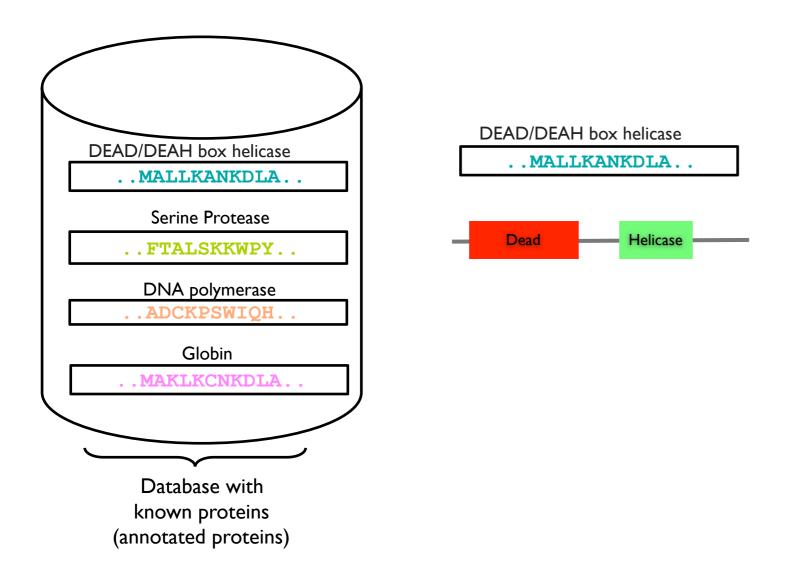
# Profile Hidden Markov Models HMMer

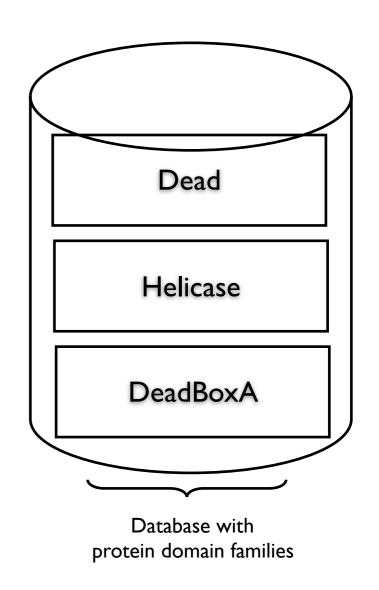
## Homology Detection



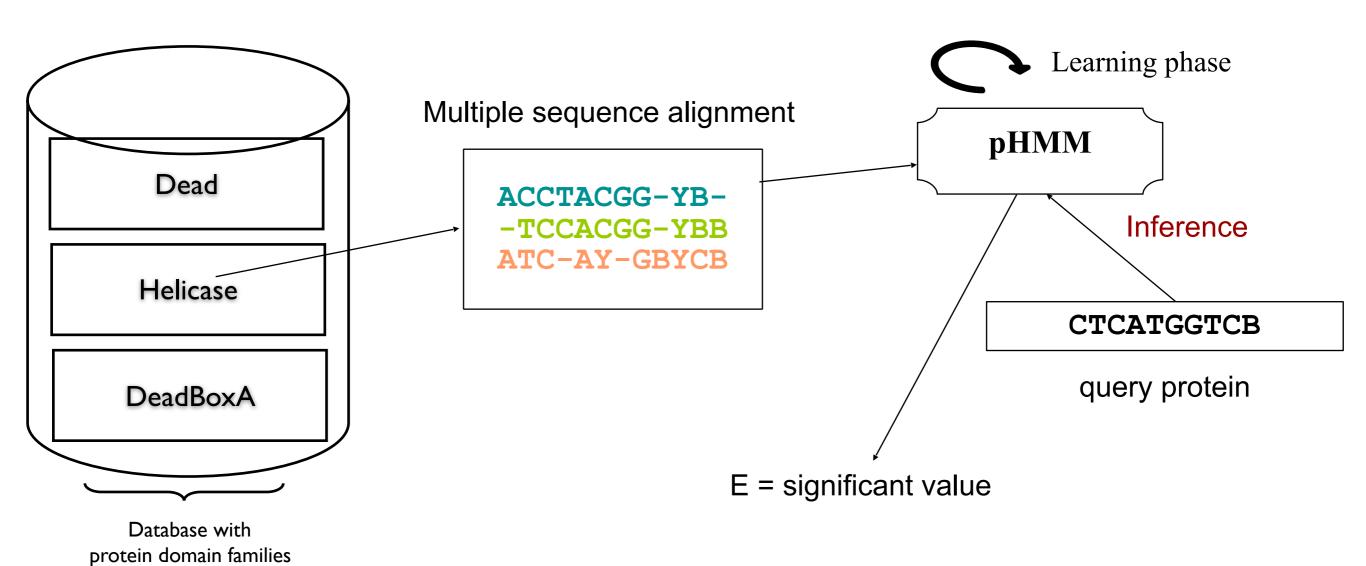
## Homology Detection

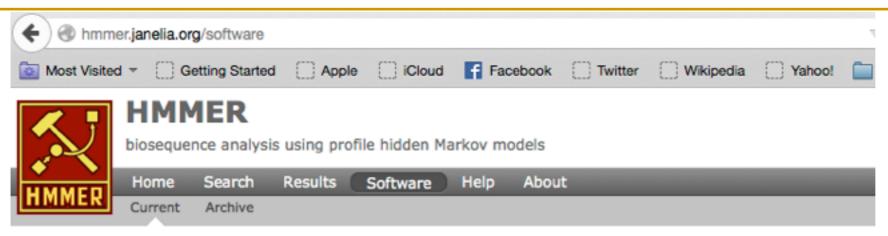
- → To improve homology detection, we can classify known protein sequences according to their functional regions (domains).
  - Proteins are generally comprised of one or more domains.





## profile HMMs





#### The current version of HMMER

#### **Download**

The current version is HMMER 3.1b2 (05 March 2015).

```
[HTTP]
Source:
                                                          [FTP]
                                                                                   5.8 MB
with Linux/Intel ia32 binaries:
                                                          [FTP]
                                                                     [HTTP]
                                                                                   18.1 MB
with Linux/Intel x86_64 binaries:
                                                          [FTP]
                                                                     [HTTP]
                                                                                   20.2 MB
with MacOSX/Intel binaries:
                                                          [FTP]
                                                                      [HTTP]
                                                                                   13.5 MB
```

If you are looking for older versions of the software, try the archive link at the top of the page.

#### **Documentation**

Release notes and User's Guide: [PDF, 116 pages].

#### Briefly, to compile from source:

```
% tar zxf hmmer-3.1b2.tar.gz
% cd hmmer-3.1b2
% ./configure
% make
% make check
```

## Building HMMER models

#### hmmbuild [-options] <hmmfile output> <alignment file input>

```
Options for selecting alphabet rather than guessing it:
  --amino : input alignment is protein sequence data
   --dna : input alignment is DNA sequence data
   --rna : input alignment is RNA sequence data
Alternative model construction strategies:
                    : assign cols w/ >= symfrac residues as consensus [default]
  --fast
  --hand : manual construction (requires reference annotation)
  --symfrac <x> : sets sym fraction controlling --fast construction [0.5]
  --fragthresh \langle x \rangle: if L \langle x \langle L \rangle, tag sequence as a fragment [0.5]
Alternative relative sequence weighting strategies:
  --wpb : Henikoff position-based weights [default]
            : Gerstein/Sonnhammer/Chothia tree weights
  --wasc
  --wblosum : Henikoff simple filter weights
  --wnone : don't do any relative weighting; set all to 1
  --wgiven : use weights as given in MSA file
  --wid \langle x \rangle: for --wblosum: set identity cutoff [0.62] (0<=x<=1)
```

## Searching with HMMER

#### hmmsearch [options] <hmmfile> <target seqfile>

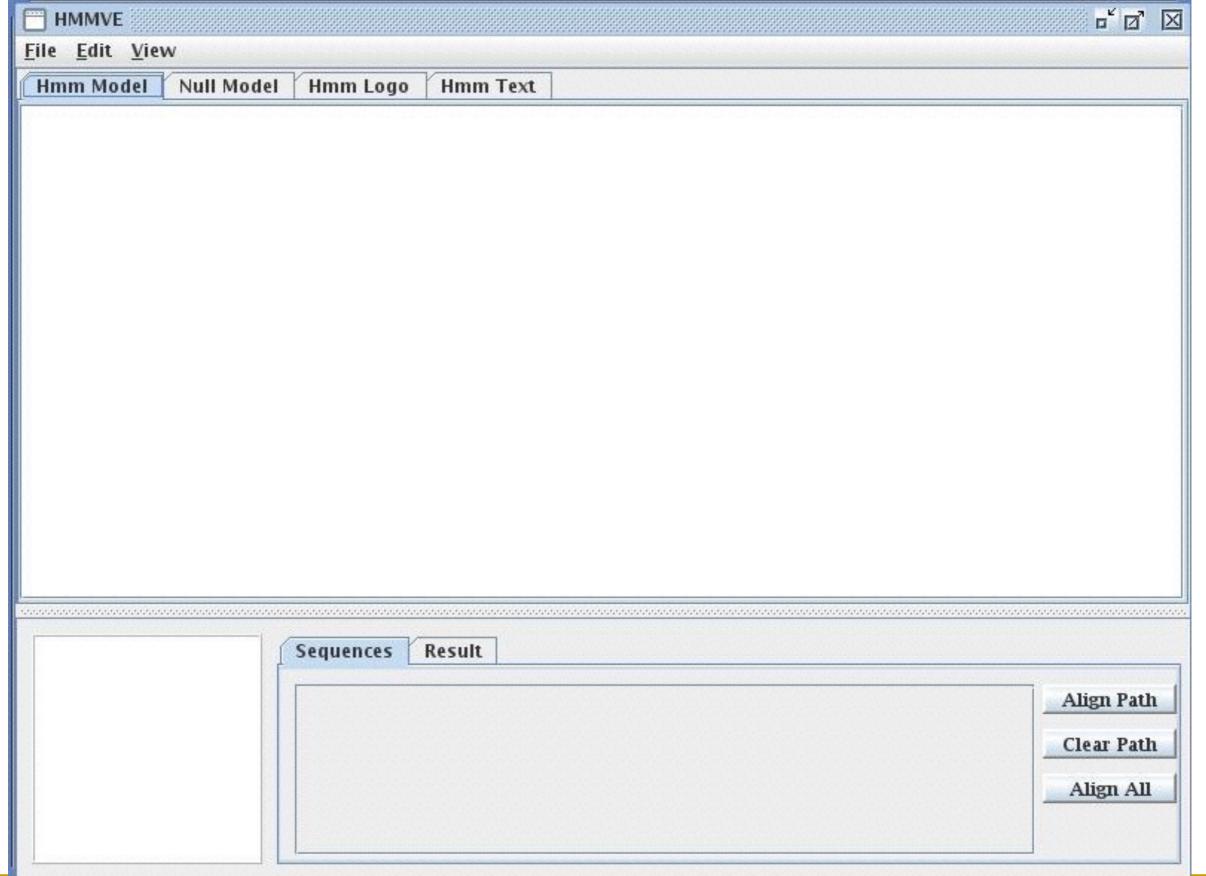
```
options directing output:
  -o <f>
                  : direct output to file <f>, not stdout
  -A < f >
                  : save multiple alignment of all hits to file <s>
                 : save parseable table of per-sequence hits to file <s>
  --tblout <f>
  --domtblout <f>: save parseable table of per-domain hits to file <s>
                  : prefer accessions over names in output
  --acc
                  : don't output alignments, so output is smaller
  --noali
                 : unlimit ASCII text output line width
  --notextw
  --textw <n>
                 : set max width of ASCII text output lines [120] (n>=120)
options controlling reporting thresholds:
             : report sequences \leq this E-value threshold in output [10.0] (x>0)
  -E <x>
            : report sequences >= this score threshold in output
  --domE <x>: report domains <= this E-value threshold in output [10.0]
                                                                          (x>0)
  --domT < x>: report domains >= this score cutoff in output
```

## Visualising profile HMM

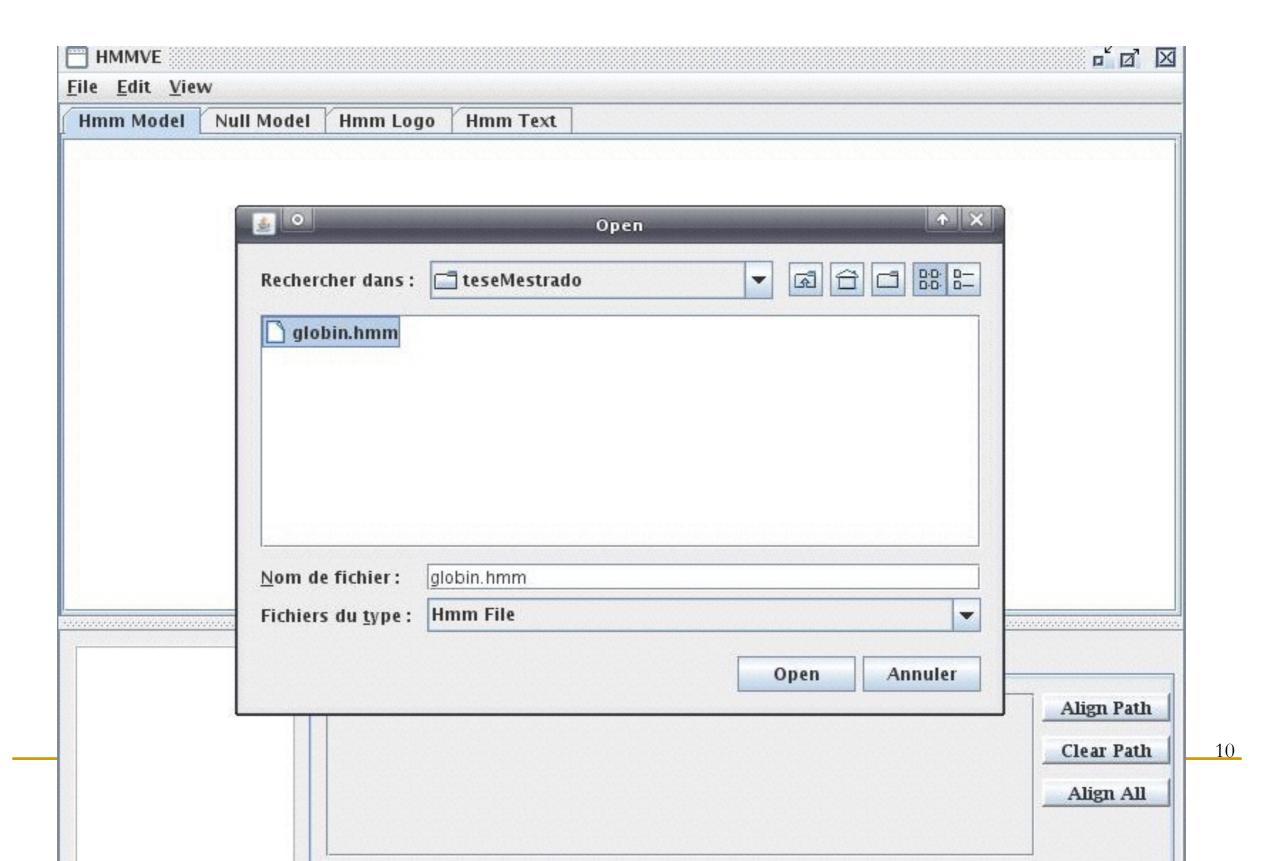
```
jsilva@pretinha:~$ cd HMMEditor/
jsilva@pretinha:~/HMMEditor$ ls

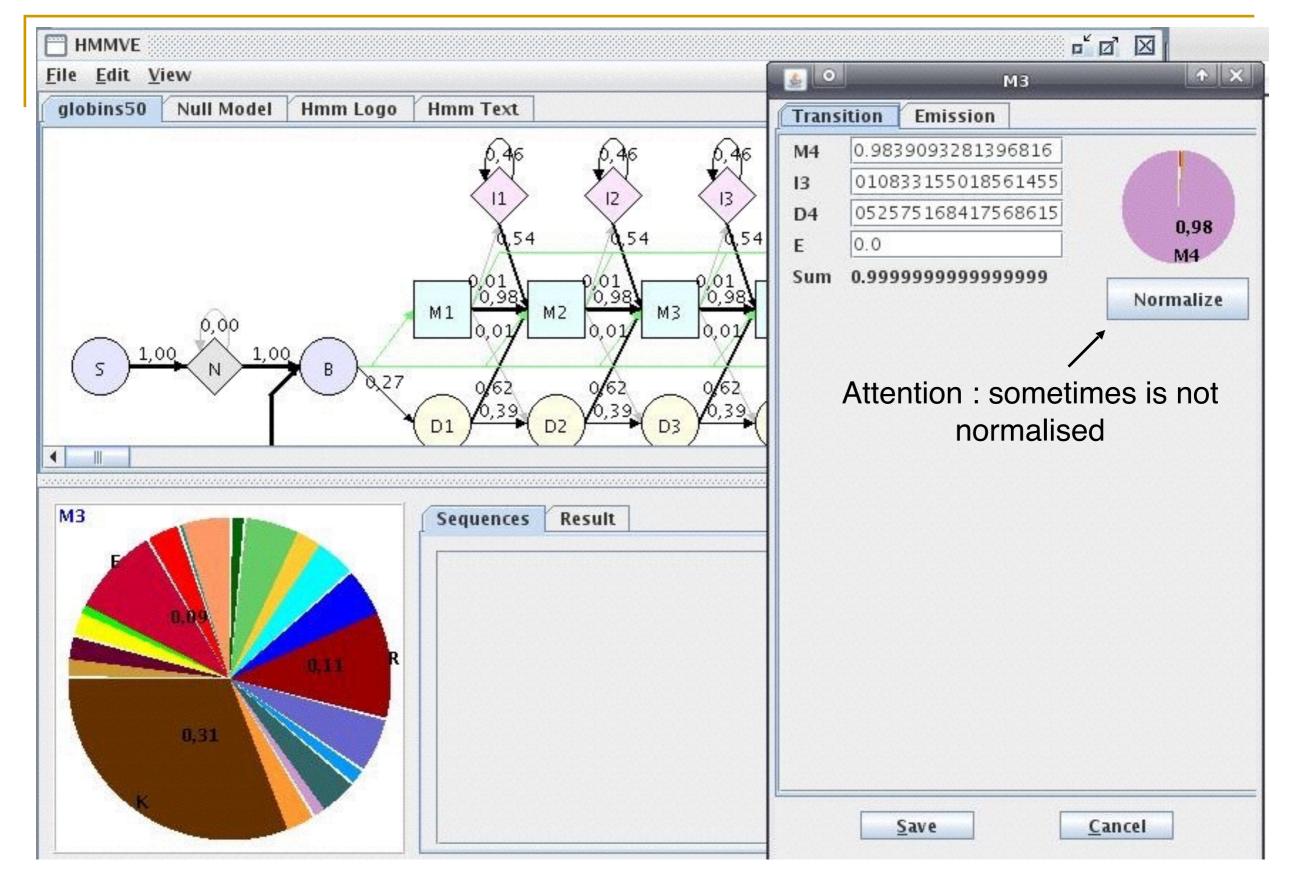
HMMVE_1.1.jar
jsilva@pretinha:~/HMMEditor$ pwd
/home/jsilva/HMMEditor
jsilva@pretinha:~/HMMEditor$ ls

HMMVE_1.1.jar
jsilva@pretinha:~/HMMEditor$ java -jar HMMVE_1.1.jar
```

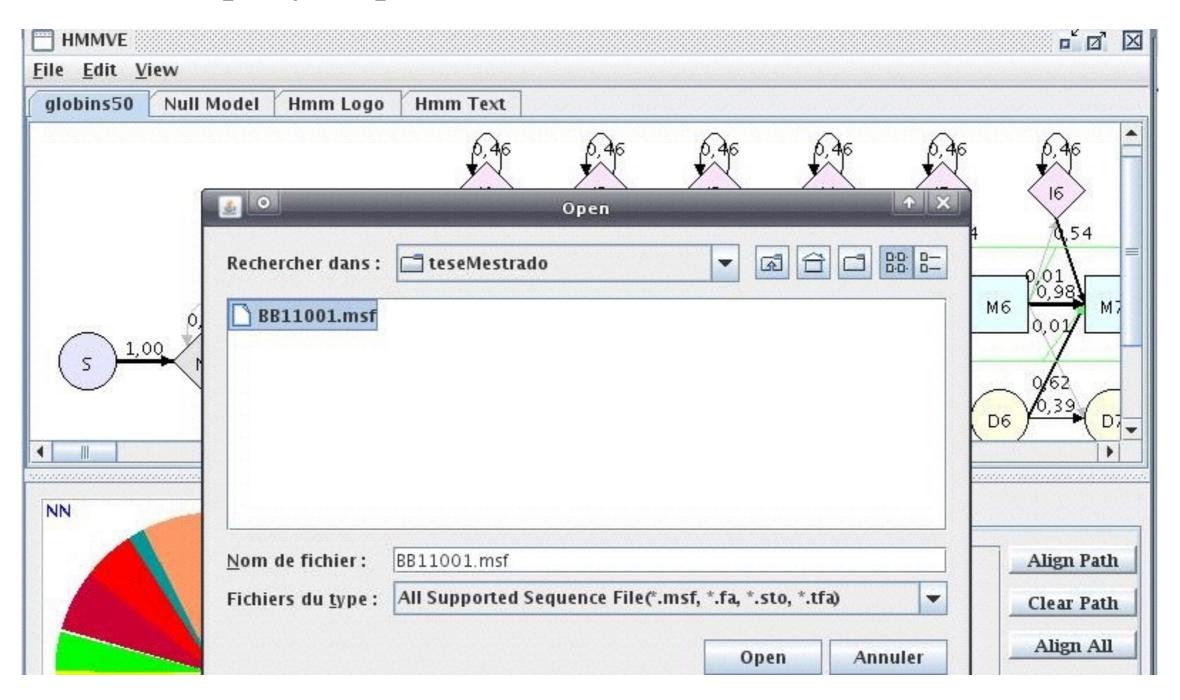


- File  $\rightarrow$  open HMM...
- Select a pHMM model.

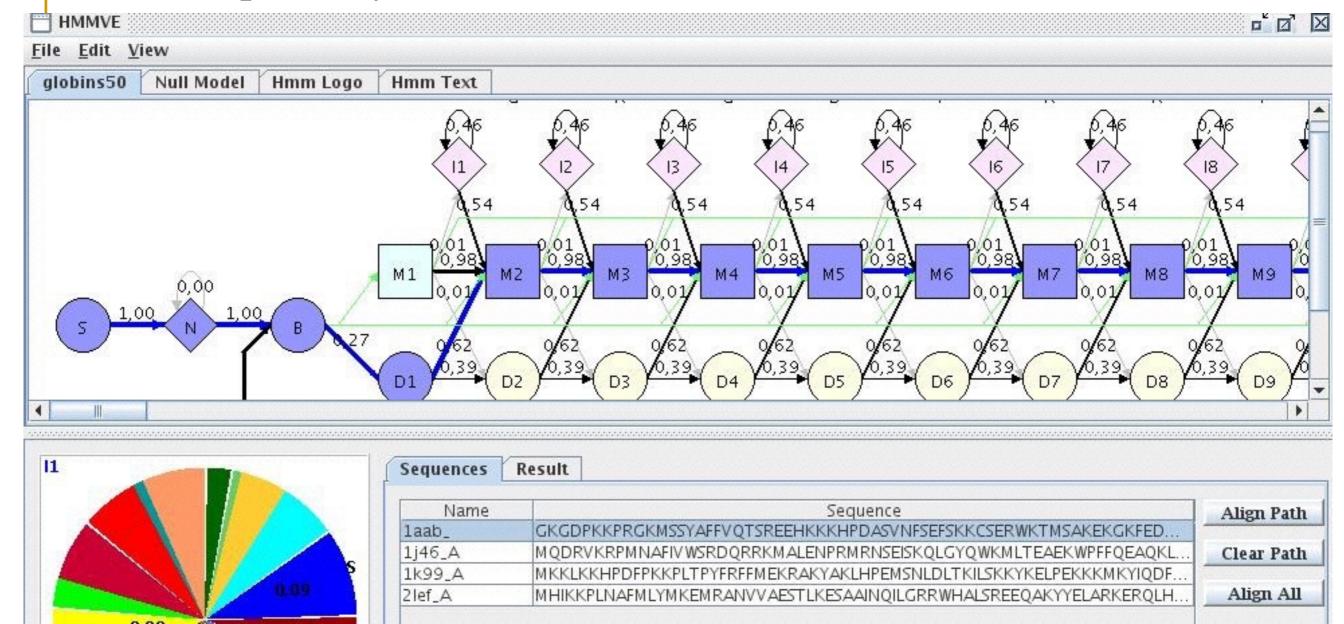




- File → open Sequence...
- Select the query sequence in fasta format.



## Viterbi pathway

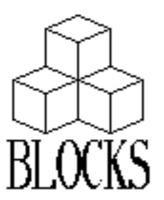


## pHMMs packages

- Softwares
  - □ HMMER → <a href="http://hmmer.janelia.org/">http://hmmer.janelia.org/</a>
  - □ SAM → <a href="http://compbio.soe.ucsc.edu/sam.html">http://compbio.soe.ucsc.edu/sam.html</a>
- Databases of pHMMs





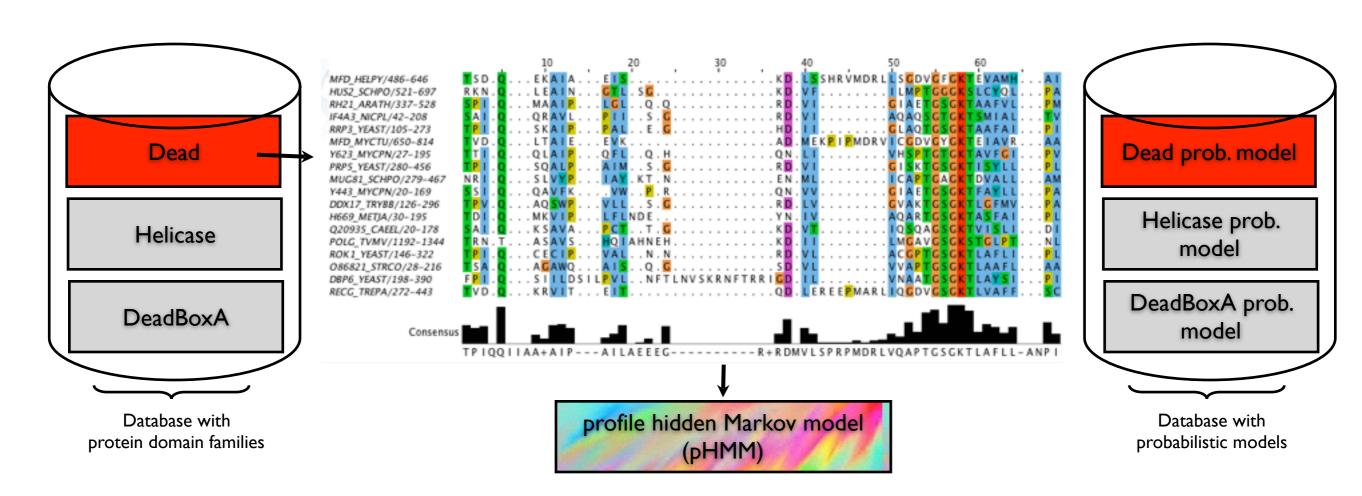






## Pfam 31.0 (March 2017, 16712 entries)

→ Known domains are described with probabilistic models representing the consensus among domain sequences



## **Species**



HOME | SEARCH | BROWSE | FTP | HELP | ABOUT

1271 architectures

81109 sequences



#### Family: *DEAD* (PF00270) Summary Domain organisation Clan Alignments **HMM logo** Trees

Curation & model

Species

Interactions

Structures





Pfam includes annotations and additional family information from a range of different sources. These sources can be accessed via the tabs below.

Wikipedia: DEAD/DEAH box helicase Pfam InterPro

This is the Wikipedia entry entitled "DEAD/DEAH box helicases". More...

#### DEAD/DEAH box helicase Edit Wikipedia article

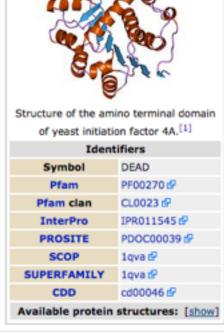
The DEAD/DEAH box helicases are a family of proteins whose purpose is to unwind nucleic acids. The DEAD box helicases are involved in various aspects of RNA metabolism, including nuclear transcription, pre mRNA splicing, ribosome biogenesis, nucleocytoplasmic transport, translation, RNA decay and organellar gene expression. [2]

#### References

- 1. ^ Johnson ER, McKay DB (December 1999). "Crystallographic structure of the amino terminal domain of yeast initiation factor 4A, a representative DEAD-box RNA helicase" @. RNA. 5 (12): 1526-34. doi:10.1017/S1355838299991410 @. PMC 1369875 @. PMID 10606264 @.
- 2. ^ de la Cruz J, Kressler D, Linder P (May 1999). "Unwinding RNA in Saccharomyces cerevisiae: DEAD-box proteins and related families" @. Trends Biochem. Sci. 24 (5): 192-8. doi:10.1016/S0968-0004(99)01376-6 @. PMID 10322435 @.
- Aubourg S, Kreis M, Lecharny A (January 1999). "The DEAD box RNA helicase family in Arabidopsis thaliana" . Nucleic Acids Res. 27 (2): 628–36. doi:10.1093/nar/27.2.628 @. PMC 148225 @ . PMID 9862990 @.

This article incorporates text from the public domain Pfam and InterPro IPR011545 €

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DEAD/DEAH box helicase

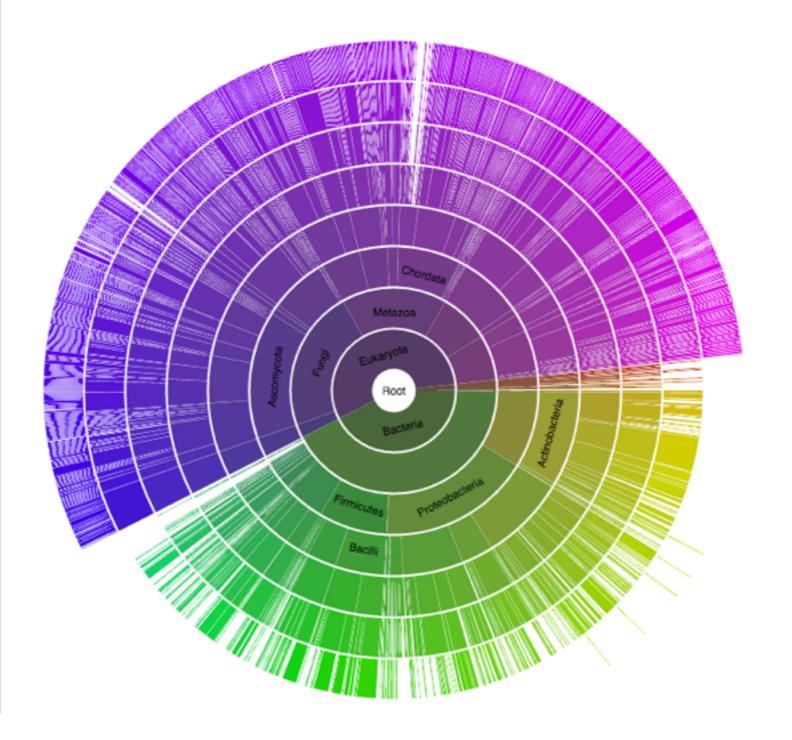
5319 species

Comments or questions on the site? Send a mail to pfam-help@ebi.ac.uk. European Molecular Biology Laboratory

#### Species distribution

Sunburst Tree

This visualisation provides a simple graphical representation of the distribution of this family across species. You can find the original interactive tree in the adjacent tab.



#### Family: *DEAD* (PF00270)





Summary

**Domain organisation** 

Clan

**Alignments** 

**HMM logo** 

**Trees** 

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Jump to... 🌵





#### Alignments

We store a range of different sequence alignments for families. As well as the seed alignment from which the family is built, we provide the full align proteomes ☐ (RP) sets, the UniProtKB sequence database. More...

#### View options

We make a range of alignments for each Pfam-A family. You can see a description of each <u>above</u>. You can view these alignments in various ways others may not be available for all families, most commonly because the alignments are too large to handle.

	Seed	Full	R	epresentati	ve proteom	UniProt	NCBI	Meta	
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)	(180618)	(362201)	(12814)
Jalview	~	~	~	~	~	~	~	~	~
HTML	~	-	×	×	×	×	×	×	×
PP/heatmap	$\times_1$	-	×	×	×	×	×	×	×

Cannot generate PP/Heatmap alignments for seeds; no PP data available

Key: ✓ available, X not generated, - not available.

#### Format an alignment

	Sood	Seed Full		epresentati	ve proteom	es	UniProt	NCBI	Meta
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)	(180618)	(362201)	(12814)
Alignment:	0	0	0	0	0	0	0	0	0
Format:	Stockholm	٥							
Order:	<ul><li>Tree</li></ul>		O Alphat	petical					
Sequence:	<ul><li>Inserts I</li></ul>	ower case	O All upp	oer case					
Gaps:	Gaps as "."	or "-" (mixed)							
Download/view:	<ul><li>Downloa</li></ul>	nd	O View						
Generate									

#### Download options

We make all of our alignments available in Stockholm format. You can download them here as raw, plain text files or as gzip d-compressed files.

	Seed	Full	R	Representative proteomes				NCBI	Meta
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)	UniProt (180618)	(362201)	(12814)
Raw Stockholm	~	~	~	~	~	~	-	-	~
Gzipped	~	~	~	~	~	~	-	-	~

You can also download a FASTA format file containing the full-length sequences for all sequences in the full alignment.

#### Family: *DEAD* (PF00270)

1271 architectures



2

#### Summary

**Domain organisation** 

Clan

#### **Alignments**

**HMM logo** 

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#### Jump to... 🌵





#### **Alignments**

We store a range of different sequence alignments for families. As well as the seed alignment from which the family is built, we provide the full alignments proteomes (P) using the family HMM. We also generate alignments using four representative proteomes (RP) sets, the UniProtKB sequence database, database. More...

#### View options

We make a range of alignments for each Pfam-A family. You can see a description of each <u>above</u>. You can view these alignments in various ways but pothers may not be available for all families, most commonly because the alignments are too large to handle.

	Seed	Full	R	epresentativ	e proteomo	es	UniProt	NCBI	Meta
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)	(180618)	(362201)	(12814)
Jalview	~	~	~	~	~	~	~	~	~
HTML	~	-	×	×	×	×	×	×	×
PP/heatmap	$\times_1$	-	×	×	×	×	×	×	×

Cannot generate PP/Heatmap alignments for seeds; no PP data available

**Key:** ✓ available, X not generated, — not available.

#### Format an alignment

	Seed	Seed Full		epresentati	ve proteom	UniProt	NCBI	Meta	
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)	(180618)	(362201)	(12814)
Alignment:	0	0	0	0	0	0	0	0	0
Format:	FASTA	0							
Order:	<ul><li>Tree</li></ul>		Alphab	etical					
Sequence:	<ul><li>Inserts I</li></ul>	lower case	All upp	er case					
Gaps:	No gaps (un	aligned)							
Download/view:	Downloa	ad	O View						
Generate									

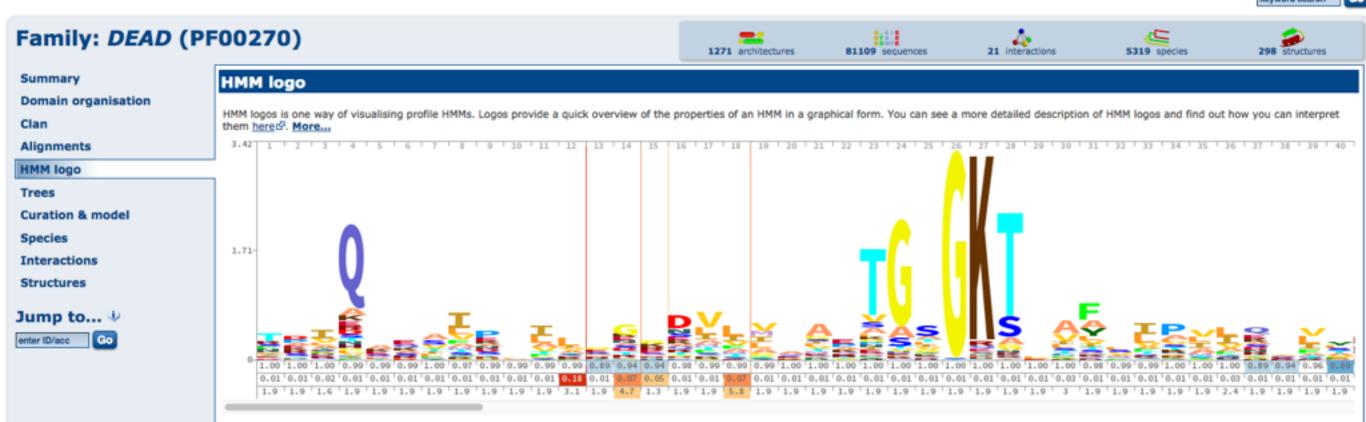
#### **Download options**

We make all of our alignments available in Stockholm format. You can download them here as raw, plain text files or as gzip decompressed files.

	Seed	Full	R	epresentati	ve proteom	es	UniProt (180618)	NCBI (362201)	Meta
	(181)	(81109)	RP15 (18454)	RP35 (45242)	RP55 (72823)	RP75 (103504)			(12814)
Raw Stockholm	~	~	~	~	~	~	-	_	~
Gzipped	~	~	~	~	~	~	-	-	~

You can also download a FASTA format file containing the full-length sequences for all sequences in the full alignment.

## Logo



#### Family: *DEAD* (PF00270)

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**Alignments** 

**HMM logo** 

Trees

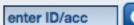
#### **Curation & model**

Species

Interactions

**Structures** 

#### Jump to... 🏵





This section shows the detailed information about the Pfam family. You can see the definitions of section of the help pages.

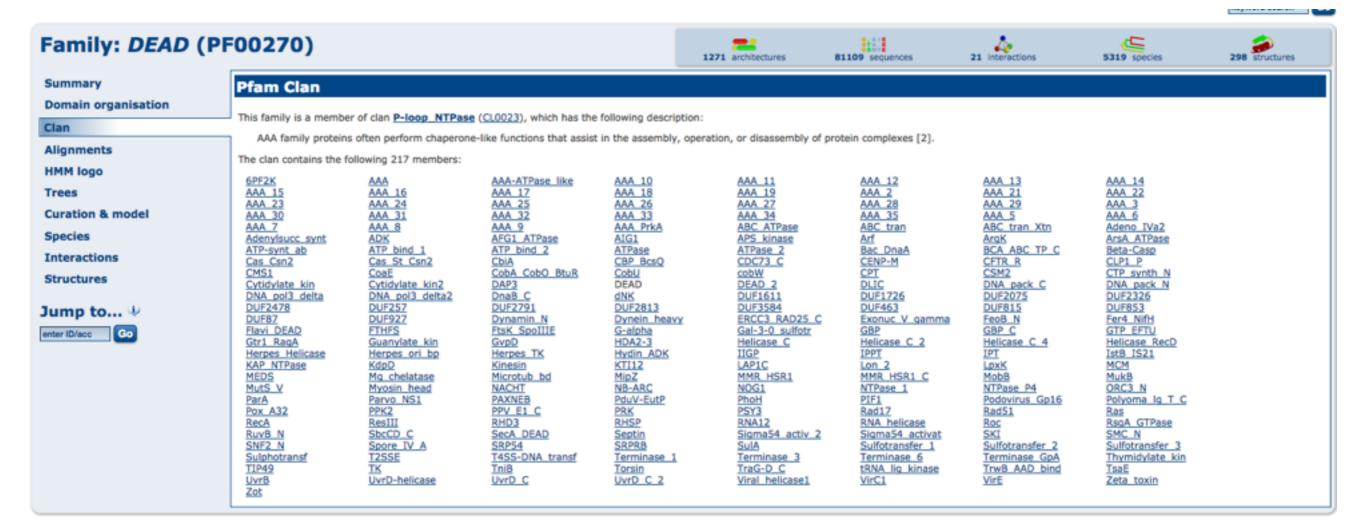
#### **Curation**

١,		
	Seed source:	Published_alignment
	Previous IDs:	none
	Type:	Domain
	Author:	Bateman A, Bruskiewich R, Sonnhammer ELL
	Number in seed:	181
	Number in full:	81109
	Average length of the domain:	
	Average identity of full alignment:	22 %
	Average coverage of the sequence by the domain:	

#### **HMM** information **(**

HMM build commands:	build method: hmmbuild -o /dev/nullhand HMM SEED search method: hmmsearch -Z 26740544 -E 1000cpu 4 HMM pfa									
Model details:	Parameter Sequence Domain									
	Gathering cut-off	26.0	24.1							
	Trusted cut-off	26.0	24.1							
	Noise cut-off	25.9	24.0							
Model length:	176									
Family (HMM) version:	28									
Download:	download the raw HMM for	this family								

## Clans



#### Family: *DEAD* (PF00270)





#### Summary

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enter ID/acc



#### **Domain organisation**

Below is a listing of the unique domain organisations or architectures in which t

There are 33324 sequences with the following architecture: DEI

X7F901 9RHOB [Roseivivax isoporae LMG 25204] DEAD/DEAH box helicase {E DEAD

Show all sequences with this architecture.

There are 4751 sequences with the following architecture: DEAl

W7YL34 9BACL [Paenibacillus pini JCM 16418] ATP-dependent RNA helicase Y2 DEAD

Show all sequences with this architecture.

There are 3666 sequences with the following architecture: CarD

USOIE7 9CYAN [Gloeobacter kilaueensis JS1] Transcription-repair-coupling fac

Show all sequences with this architecture.



DEAD

W9YGA6\_9EURO [Capronia coronata CBS 617.96] Adenosinetriphosphatase {ECO:0000313|EMBL:EXJ88710.1} (980 residues)

Helicase C HA2

Show all sequences with this architecture.

There are 3224 sequences with the following architecture: RecG\_wedge, DEAD, Helicase\_C

W7UXIO\_RUMFL [Ruminococcus flavefaciens 007c] ATP-dependent DNA helicase RecG {ECO:0000256|RuleBase:RU363016} (678 residues)

DEAD RecG\_wedge -

Show all sequences with this architecture.

There are 2988 sequences with the following architecture: DEAD, Helicase\_C, DUF4217

W10JU9 OGAPD [Ogataea parapolymorpha (strain ATCC 26012 / BCRC 20466 / JCM 22074 / NRRL Y-7560 / DL-1) (Yeast) (Hansenula polymorpha {ECO:0000313|EMBL:ESX02922.1} (742 residues)

DEAD

Show all sequences with this architecture.

There are 2919 sequences with the following architecture: DEAD, Helicase\_C, DbpA

A0A140L5S6 9CLOT [Thermotalea metallivorans] DEAD-box ATP-dependent RNA helicase CshA {ECO:0000313|EMBL:KXG75901.1} (528 residues DEAD

Show all sequences with this architecture.

There are 2443 sequences with the following architecture: DEAD, Helicase\_C, RecQ\_Zn\_bind, RQC, HRDC

G5GBG5 9BACT [Alloprevotella rava F0323] ATP-dependent DNA helicase RecQ {ECO:0000313|EMBL:EHG23164.1} (608 residues)

DEAD RQC

Show all sequences with this architecture.

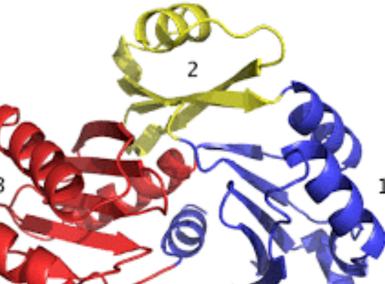
There are 1925 sequences with the following architecture: DEAD, Helicase\_C, RecQ\_Zn\_bind

I3COK8\_9FLAO [Joostella marina DSM 19592] ATP-dependent DNA helicase, RecQ family {ECO:0000313|EMBL:EIJ37151.1} (635 residues)

Show all sequences with this architecture.

DEAD

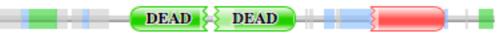




# There are 390 sequences with the following architecture: A0A0B1SH12 OESDE [Oesophagostomum dentatum (Nodular worm)] DEAD | DEAD | Hide all sequences with this architecture. A0A010RA01 9PE | DEAD | A0A016UBZ1 9BILA [Ancylostoma ceylanicum] Uncharacterized prote | DEAD | A0A016UCV1 9BILA [Ancylostoma ceylanicum] Uncharacterized prote | DEAD | A0A016UCV1 9BILA [Ancylostoma ceylanicum] Uncharacterized prote | DEAD | A0A016UCV1 9BILA [Ancylostoma ceylanicum] Uncharacterized prote | DEAD | D

#### Pfam domains

This image shows the arrangement of the Pfam domains that we found on this sequence. Clicking on a domain will the domains. **More...** 

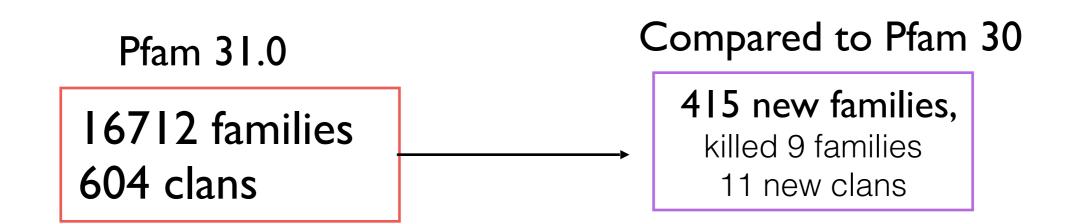


A0A016UBZ1 9BILA [Ancylostoma ceylanicum] Uncharacterized prote Download the data used to generate the domain graphic in JSON format.

e Source	Domain	Ctout	End	Gathering thre	shold (bits)	Score (	bits)	E-va	lue
Source	Domain	Start	EIIG	Sequence	Domain	Sequence	Domain	Sequence	Domain
e disorder	n/a	3	181	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	17	37	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	114	137	n/a	n/a	n/a	n/a	n/a	n/a
e coiled_coil	n/a	125	164	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	142	163	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	190	234	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	205	212	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	238	243	n/a	n/a	n/a	n/a	n/a	n/a
Pfam	DEAD	277	391	26.00	24.10	112.30	61.20	3.1e-29	1.6e-13
disorder	n/a	379	380	n/a	n/a	n/a	n/a	n/a	n/a
Pfam	DEAD	403	523	26.00	24.10	112.30	48.90	3.1e-29	9.4e-10
low_complexity	n/a	404	417	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	405	406	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	411	419	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	539	540	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	546	549	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	567	581	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	585	640	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	591	644	n/a	n/a	n/a	n/a	n/a	n/a
Pfam	Helicase_C	637	747	20.90	20.90	70.60	69.00	1.9e-16	6.2e-16
low_complexity	n/a	659	674	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	681	683	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	688	713	n/a	n/a	n/a	n/a	n/a	n/a
low_complexity	n/a	740	751	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	779	781	n/a	n/a	n/a	n/a	n/a	n/a
coiled_coil	n/a	799	819	n/a	n/a	n/a	n/a	n/a	n/a
disorder	n/a	813	820	n/a	n/a	n/a	n/a	n/a	n/a

## Pfam 31.0

- Based on Uniprot reference proteomes contains 26.7 million sequences,
- 73% of Uniprot reference proteomes have a match to at least one Pfam
- 48% of all residues fall within a Pfam family.



## Manually curated gathering thresholds cut\_ga

- Each Pfam entry has gathering thresholds (GAs)
- All sequence regions that score above the GAs are included in the full alignment for the family.
- GAs, are manually curated, family-specific, bit score thresholds that are chosen by Pfam curators when a family is built.
- Every family has two GAs, a 'sequence' threshold, and a 'domain' threshold.

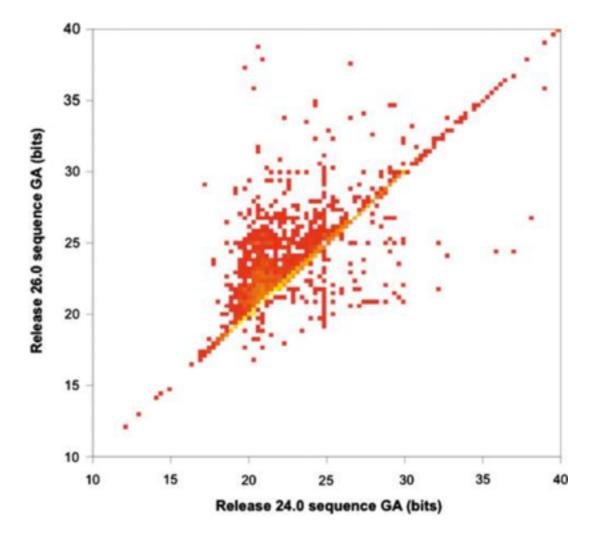
## Criteria for gathering threshold assignment

- GAs are chosen to maximise coverage and exclude any false positive matches.
- The number of false positives is generally unknown, but we can check for overlaps between one Pfam family and another.
- If the same region of a sequence matches two Pfam families, it should be considered a false positive in one of them.
- Another way is to generate artificial false positive sequences.
  - hmmemit and shuffling
  - Domain sequences (same family or not) and shuffling

## Gathering threshold for new families

- When building a new family, the GA choice is often influenced by overlaps with other families.
- Overlap-resolution between old and new families leads to GAs modifications.
- GAs for families in Pfam release 24.0 with GAs of the same families in release

26.0. Overall, 13% of GAs have changed,



## Gathering threshold x E-values

