# Modeling structural RNA families with Infernal

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Janelia Farm Research Campus

GTAACCGTAAATAATAAACTTTTGAAGTCTAAGCTCATCATATCTATTCA
TCCTTTGGATTCAAGACATTTTTTAAAAAATGCGCAATCACTATAAACCA
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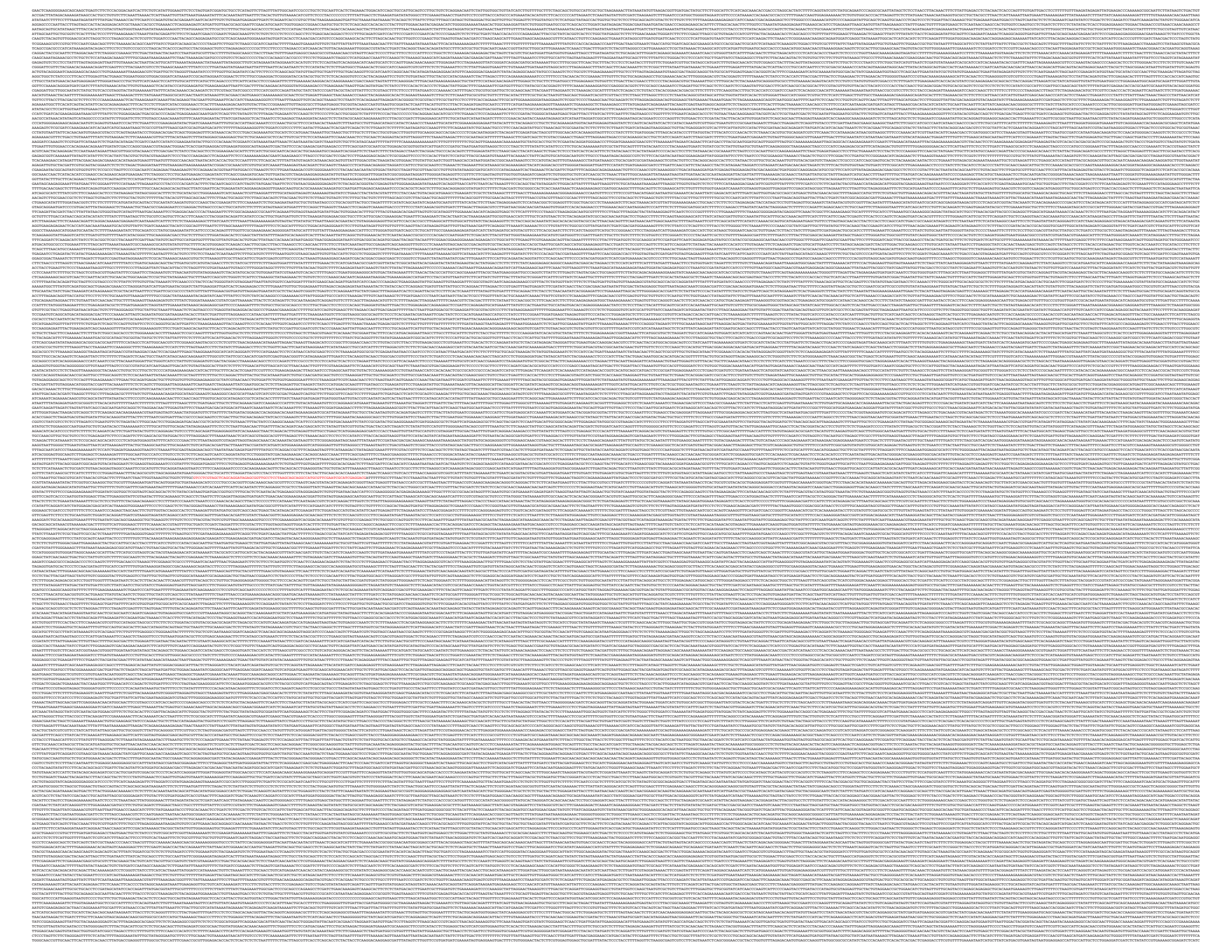


## What are we looking for?

Protein-coding genes: DNA → mRNA → protein

Functional RNA genes: DNA → RNA

## How can we find genes?

**By searching for similarity with known genes indicative of shared evolutionary history**

Gene family: group of evolutionarily related (*homologous*) genes in different genomes

Homology search: given one or more homologs of a family, find more

**Homologous genes often share similar functions, structures and sequences**

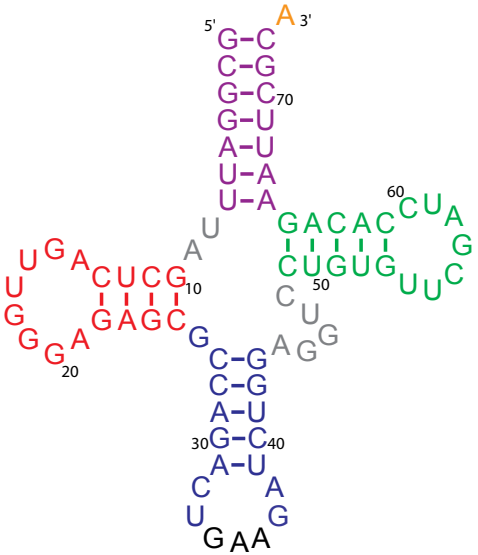
# Most proteins and RNAs adopt a conserved 3-dimensional structure that is responsible for their function in the cell

Three representations of a transfer RNA:

## Primary sequence

GCGGAUUUAGCUCAGUUGGG
AGAGCGCCAGACUGAAGAUC
UGGAGGUCCUGUGUUCGAUC
CACAGAAUUCGCA

## Secondary structure




## 3-dimensional structure

**Most proteins and RNAs adopt a conserved 3-dimensional structure that is responsible for their function in the cell**

Three representations of a transfer RNA:

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GCGGAUUUAGCUCAGUUGGG
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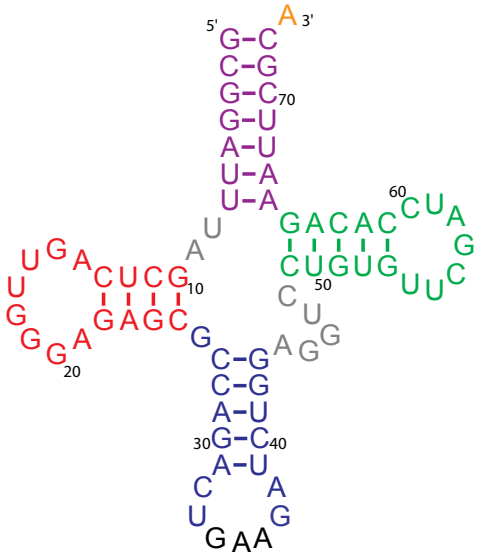


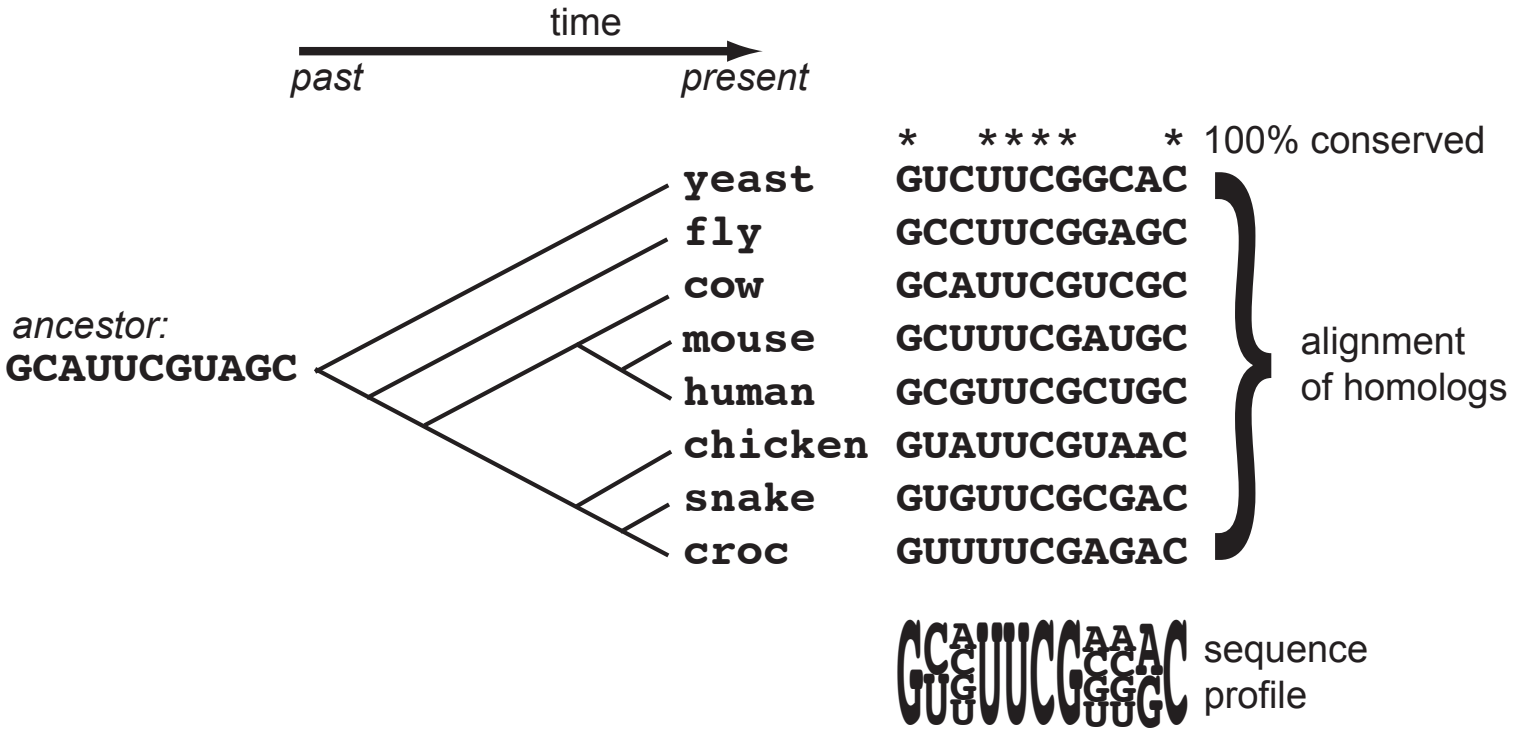
3-dimensional structure

**BLAST:** given a single sequence, search genomes for similar sequences.

**Homologous proteins and RNAs conserve different sequence and structural features to different degrees.**

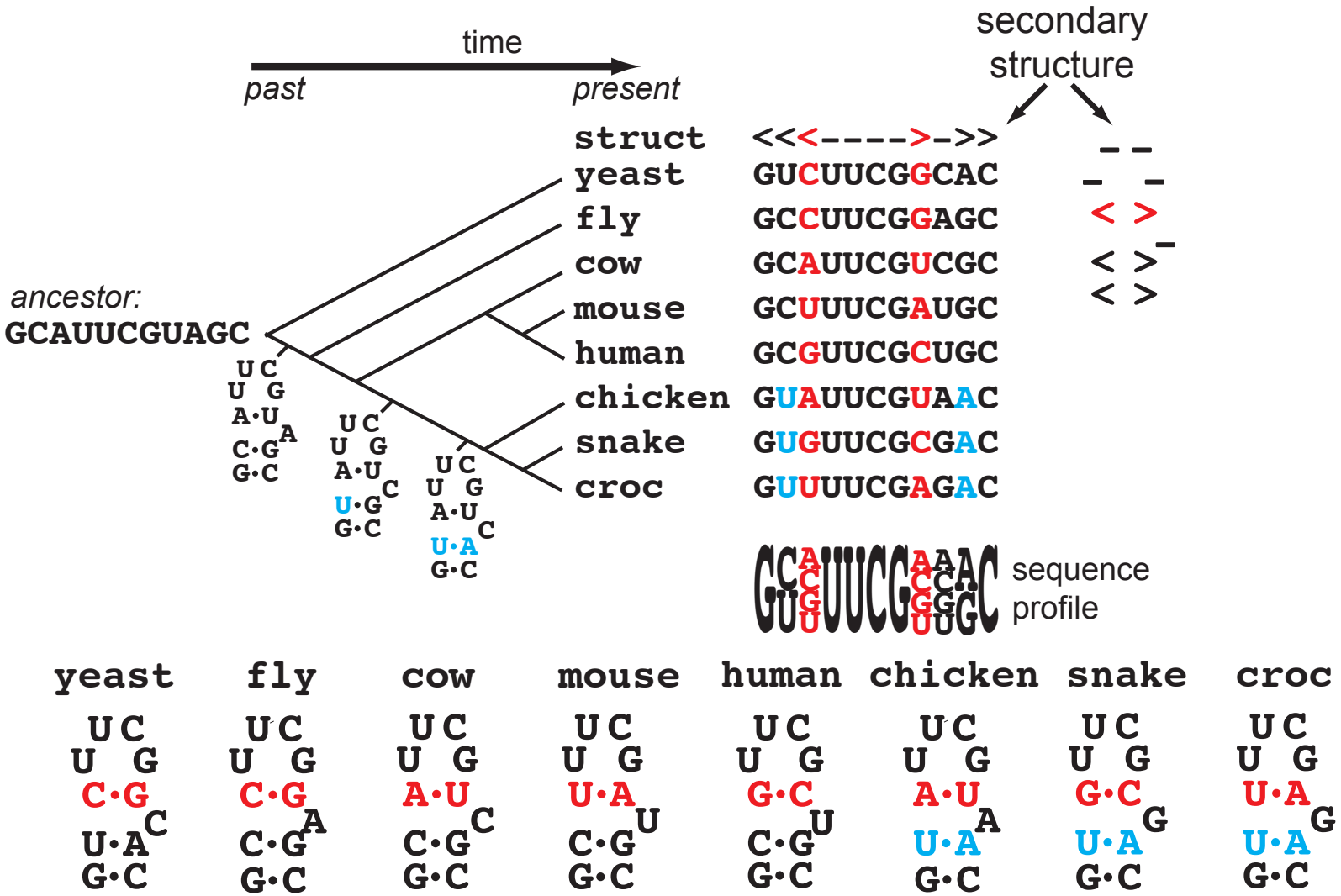
# Sequence conservation provides information for homology searches

Conservation levels vary across alignment columns.

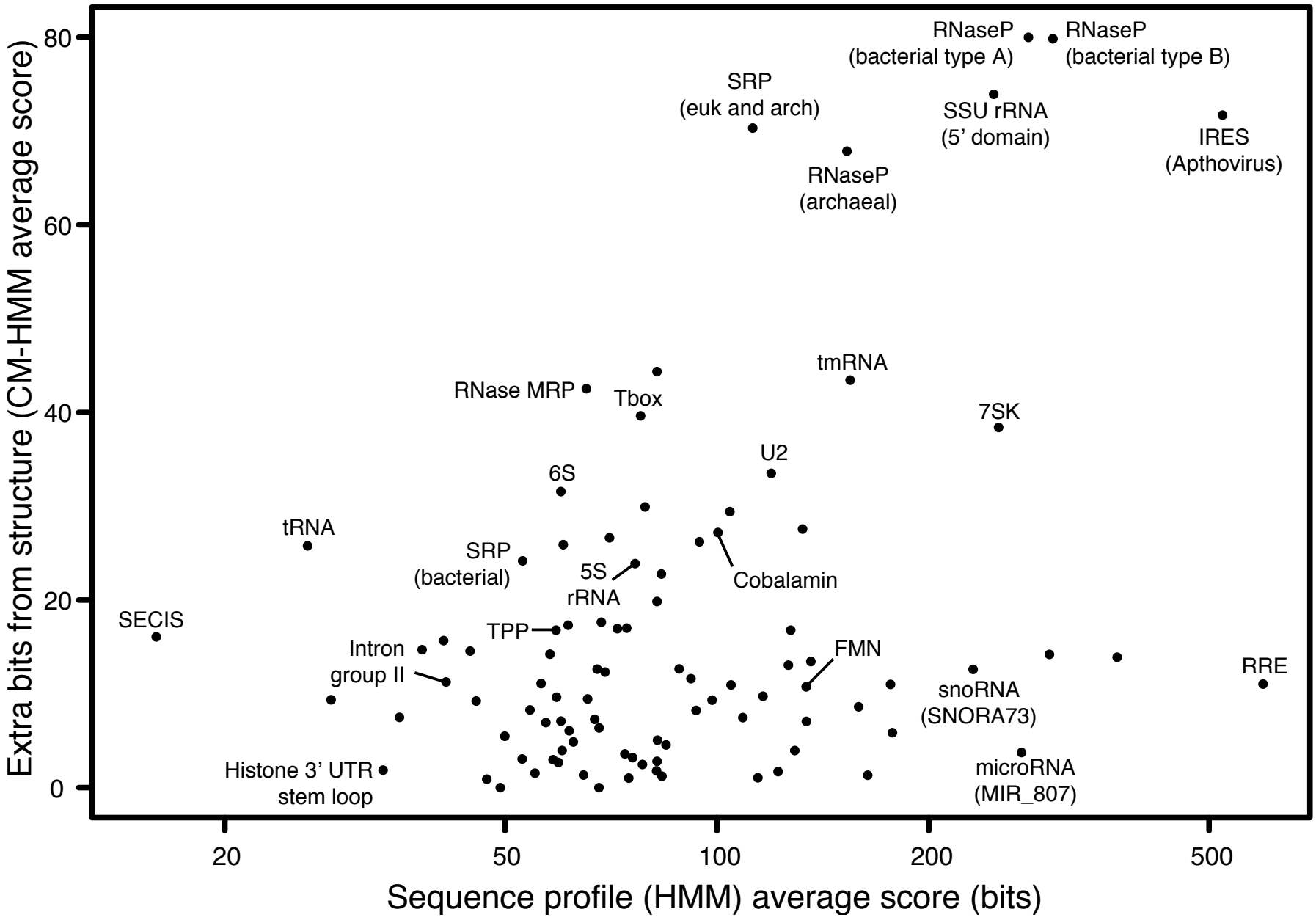


# Structure conservation provides additional information

Base-paired positions covary
to maintain Watson-Crick complementarity.



# Levels of sequence and structure conservation in RNA families



# Eddy lab software for profile probabilistic models (since 1994)

| | sequence profiles | sequence and structure profiles |
|---|---|---|
| models | profile HMMs | covariance models (CMs) |
| software | HMMER | Infernal |
| main use | proteins | RNAs |
| database | Pfam (14831 families) | Rfam (2208 families) |
| performance for RNAs | faster but less accurate | slower but more accurate |


http://hmmer.janelia.org

Eddy, SR. PLoS Comp. Biol., 7:e1002195, 2011.

Eddy, SR. PLoS Comp. Biol., 4:e1000069, 2008.

Eddy. SR. Bioinformatics, 14:755-763, 1998.


http://infernal.janelia.org

Nawrocki EP, Kolbe DL, Eddy SR Bioinformatics, 25 (10):1335-1337, 2009.

Eddy SR, Durbin R. Nucleic Acids Research, 22:2079-2088, 1994.

# Profile HMMs: sequence family models built from alignments

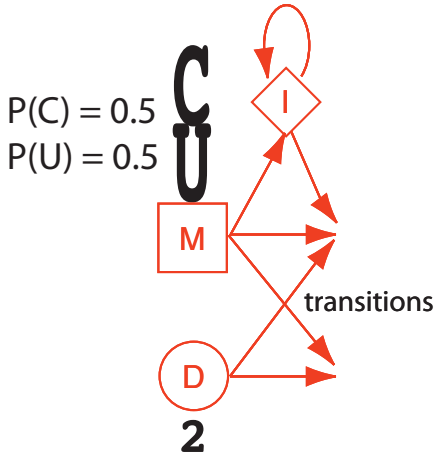

| | |
|---|---|
| yeast | GUCUUCGGCAC |
| fly | GCCUUCGGAGC |
| cow | GCAUUCGUCGC |
| mouse | GCUUUCGAUGC |
| human | GCGUUCGCUGC |
| chicken | GUAUUCGUAAC |
| snake | GUGUUCGCGAC |
| croc | GUUUUCGAGAC |

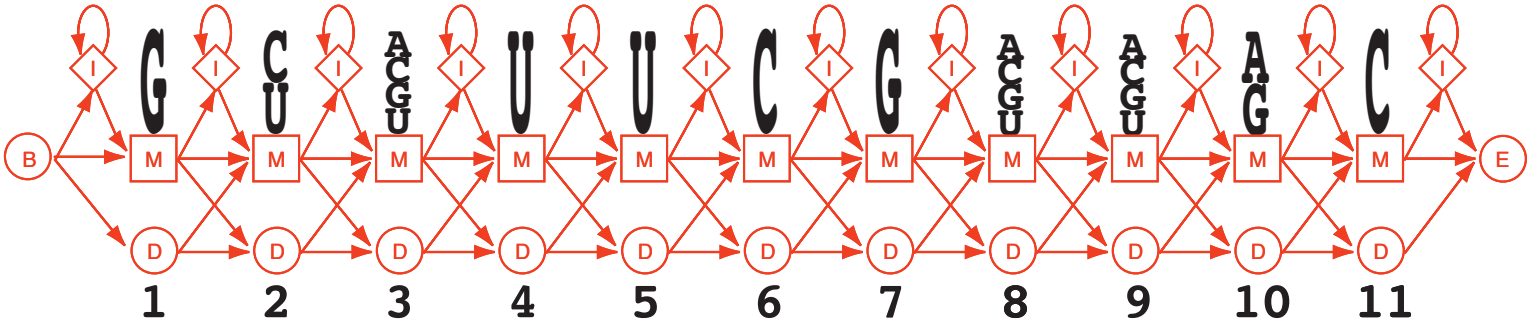
One HMM node per alignment column

3 states per node:
(M) Match: emits residues
(I) Insert: inserts extra residues
(D) Delete: deletes residues

HMMs generate homologous sequences.

Node for column 2:



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**Given a sequence, the most likely path that could have generated that sequence can be computed.**

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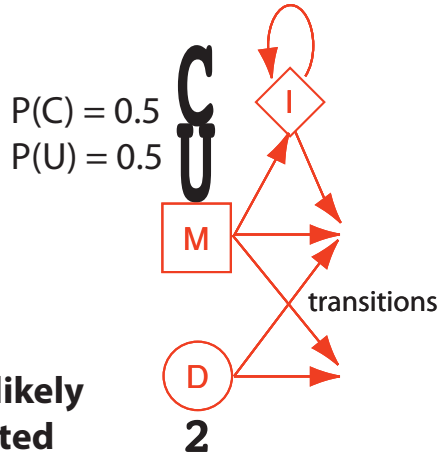


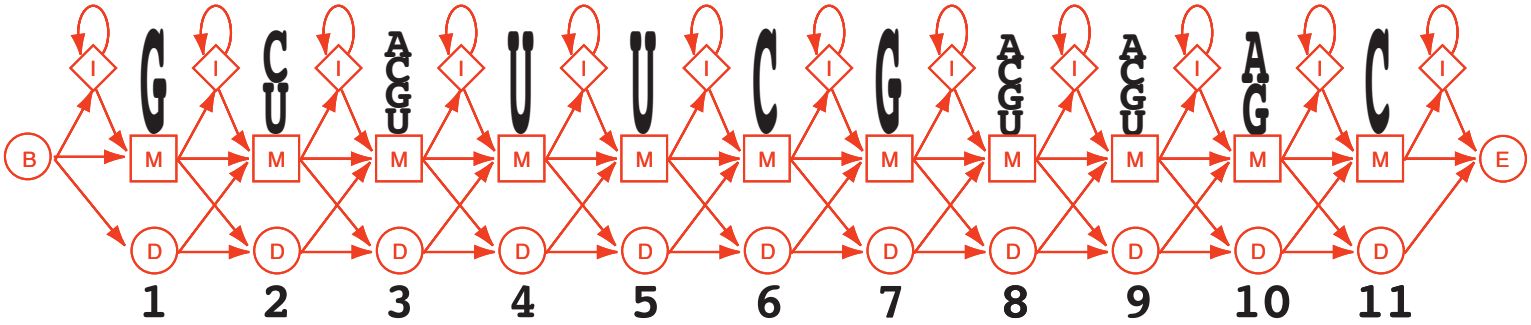

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| chicken | GUAUUCGUAAC |
| snake | GUGUUCGCGAC |
| croc | GUUUUCGAGAC |
| worm | GCGUUCGCGGC |

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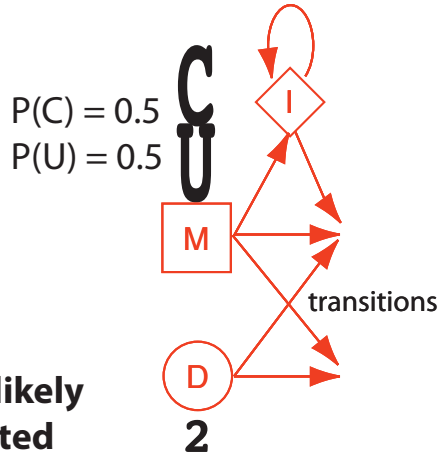


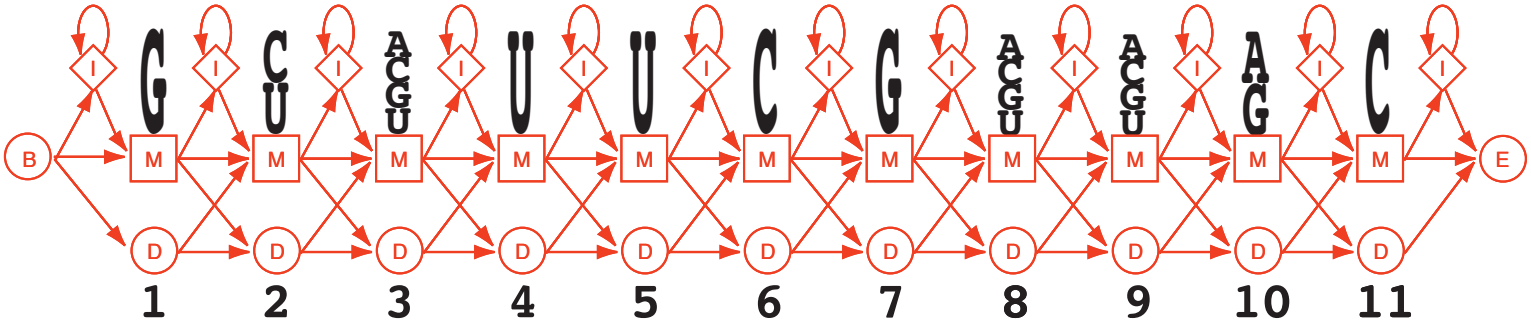


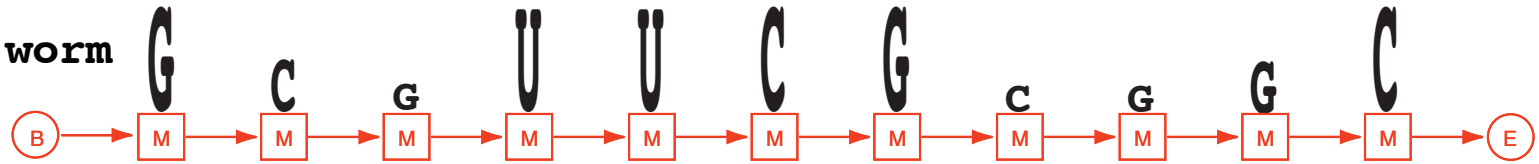

# Profile HMMs: sequence family models built from alignments


```
yeast    GU.CUUCGGCAC
fly      GC.CUUCGGAGC
cow      GC.AUUCGUCGC
mouse    GC.UUUCGAUGC
human    GC.GUUCGCUGC
chicken  GU.AUUCGUAAC
snake    GU.GUUCGCGAC
croc     GU.UUUCGAGAC
worm     GC.GUUCGCGGC
corn     GUGAUUCGU.GC
```

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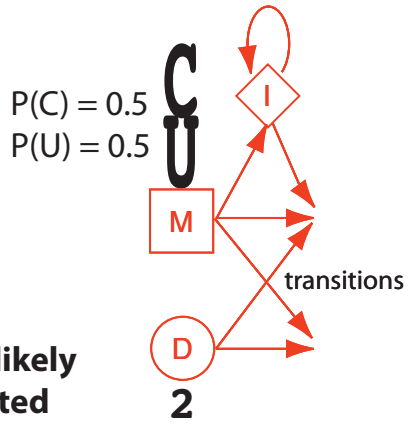
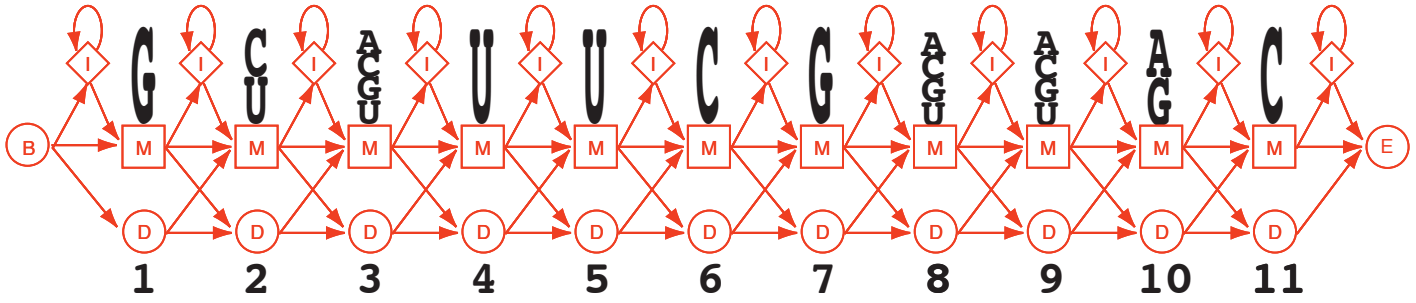
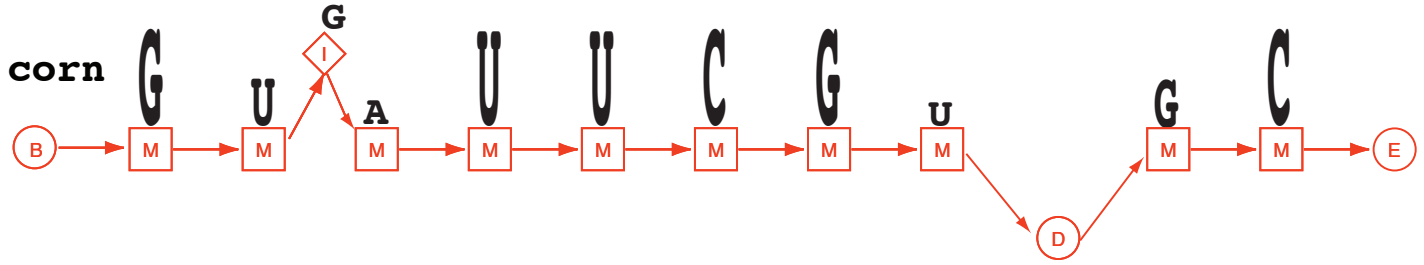
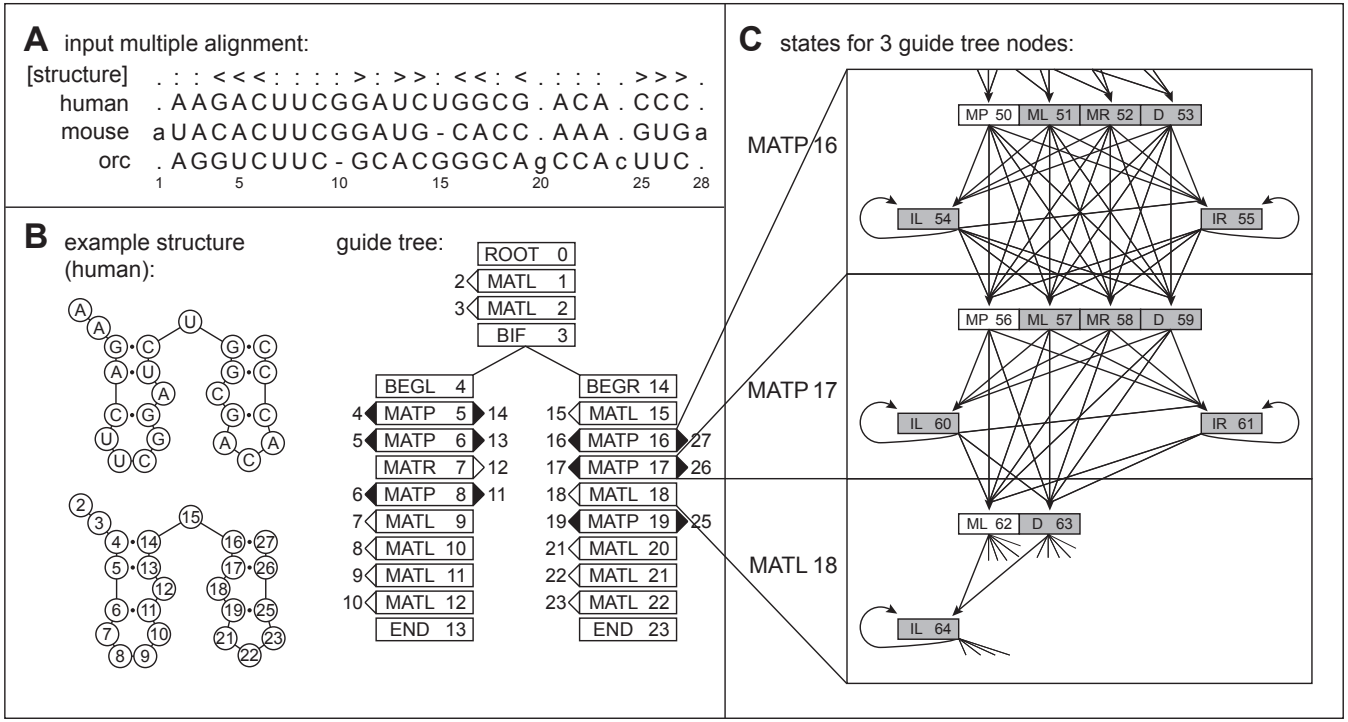
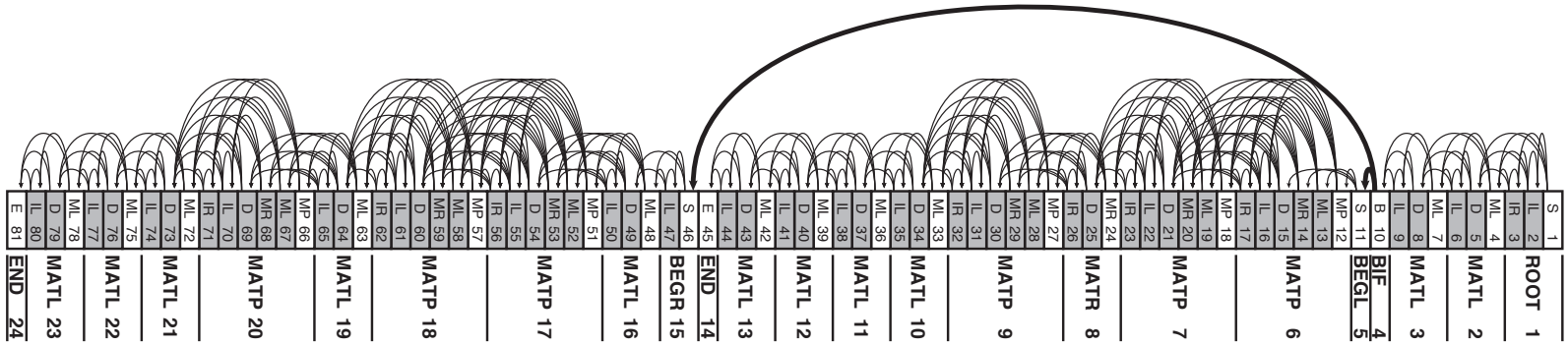


# Covariance models (CMs) are built from structure-annotated alignments

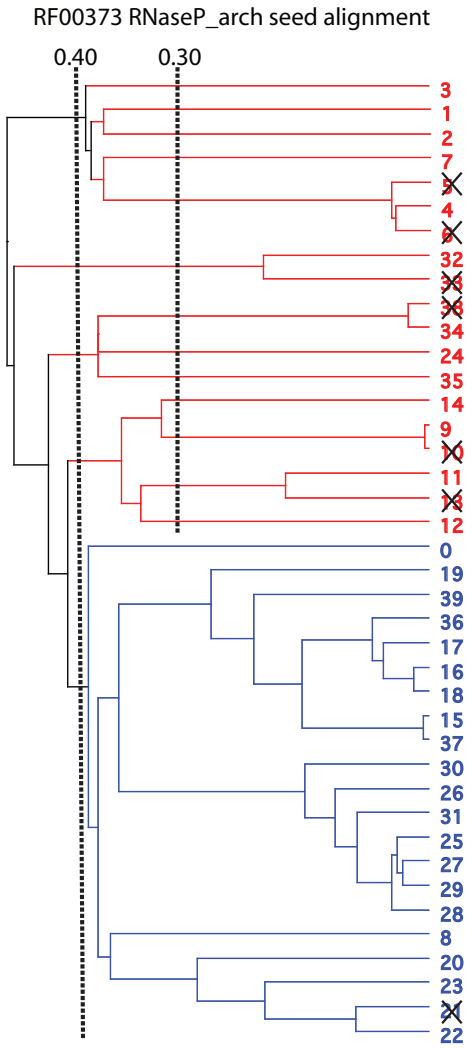


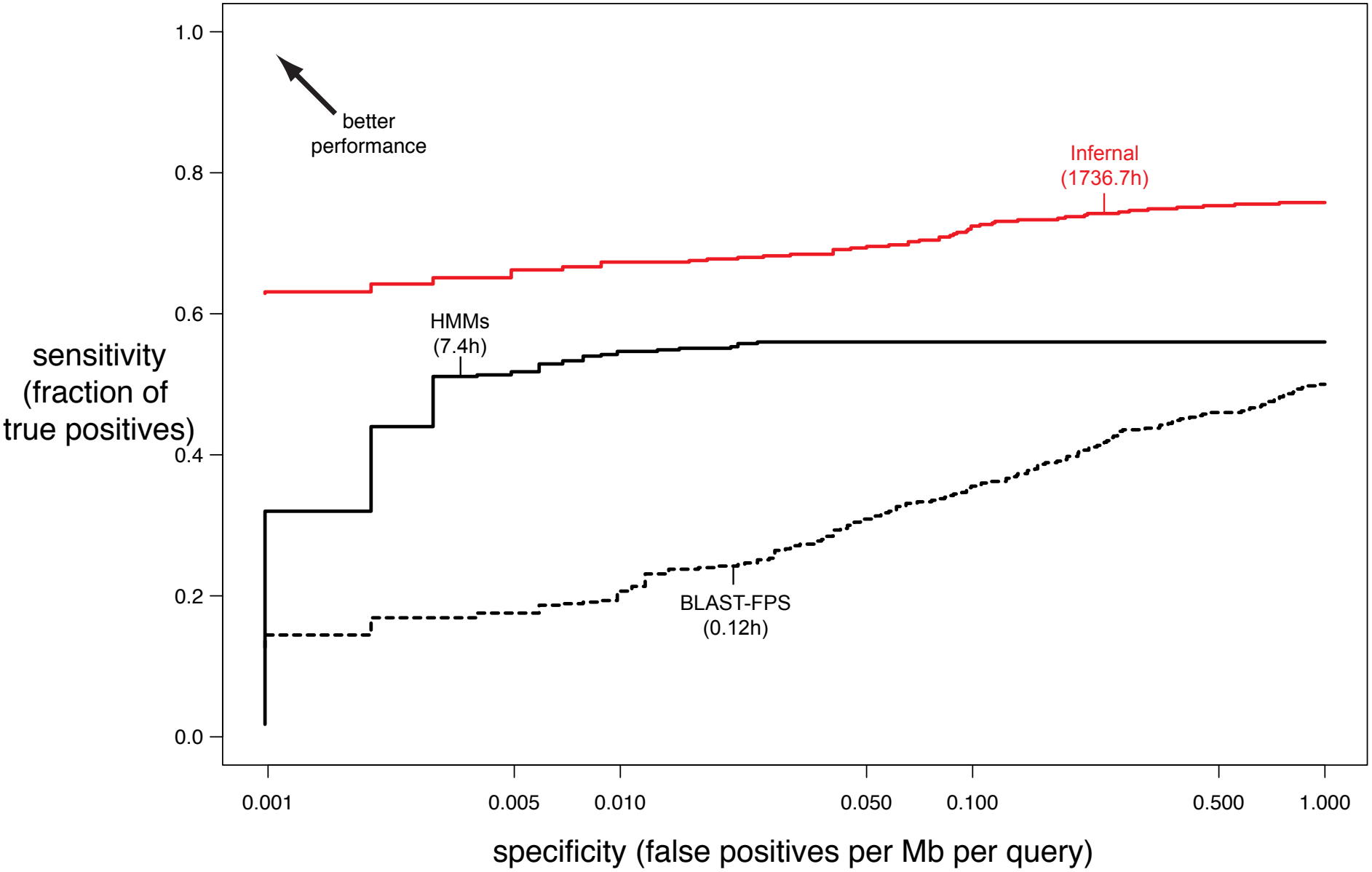
# Is the added complexity worth it?
# RMARK: a challenging internal RNA homology search benchmark for use during Infernal development

- RMARK construction - for each of the 1446 Rfam 10 seed alignments:
  - cluster sequences by sequence identity given the alignment
  - look for a training cluster and testing cluster such that:
    - no training/test sequence pair is $> 60\%$ identical
    - at least five sequences are in the training set
  - filter test set so no two test seqs $> 70\%$ identical
  - 106 families qualify, with 780 test sequences
  - test seqs are embedded in a 10 Mb pseudo-genome of "realistic" base composition

Example:



# Infernal outperforms primary-sequence based methods on our benchmark (and others*, not shown)




*Freyhult EK, Bollback JP, Gardner PP. Genome Res. 2007 17: 117-125.

# CM searches are especially slow for large RNAs

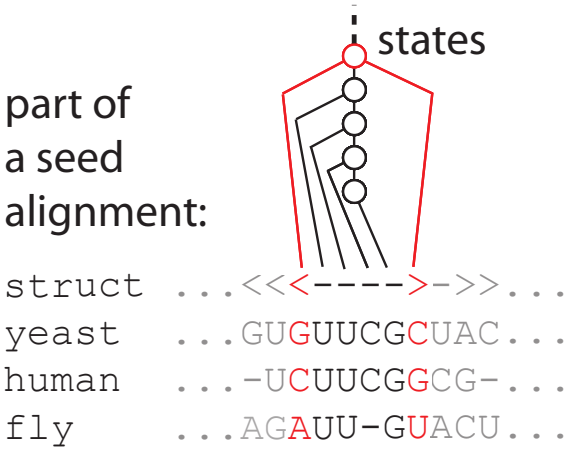
| | | search (min/Mb) | | |
|---|---|---|---|---|
| family | length | HMM | CM | CM/HMM |
| tRNA | 71 | 0.34 | 27.0 | 79.4 |
| Lysine riboswitch | 183 | 0.80 | 133.2 | 166.7 |
| SRP RNA | 304 | 1.32 | 276.4 | 214.4 |
| RNaseP RNA | 365 | 1.56 | 733.4 | 470.3 |

# Why CM homology search is so slow

- CM homology search algorithms align/score all subsequences of length $1..W$ as they scan along the target sequence looking for high scoring hits

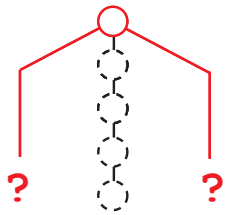
Example: Finding a hairpin loop

part of a seed alignment:





where's the loop?




NNN...NNNNNN...NNN
1 W

W*(W-1)/2 possibilities

if W=100 ~ 5000 possibilities
if W=200 ~ 20000 possibilities

We could save time by restricting the possible loop lengths considered.

**One idea: take advantage of the generative capacity of CMs to generate sequences and examine loop length distribution.**

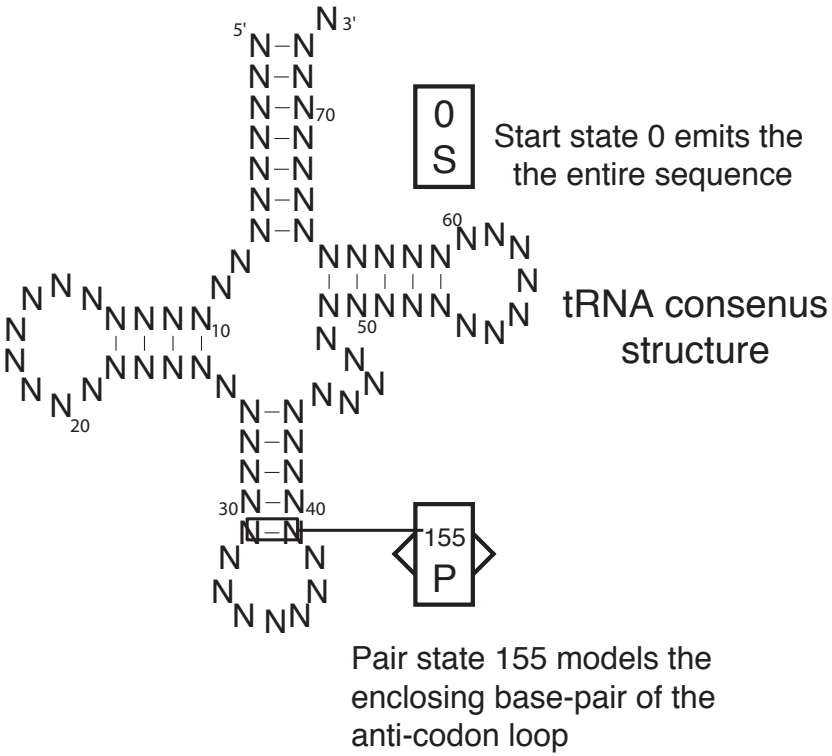
# Query-dependent banding (QDB) strategy

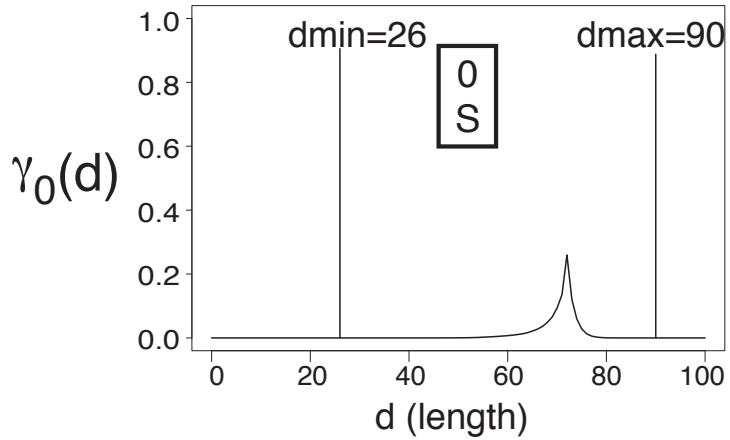
- Calculate $\gamma_v(d)$ probability each state $v$ will emit/align to subsequences of length $d$, for $d = 0..Z$

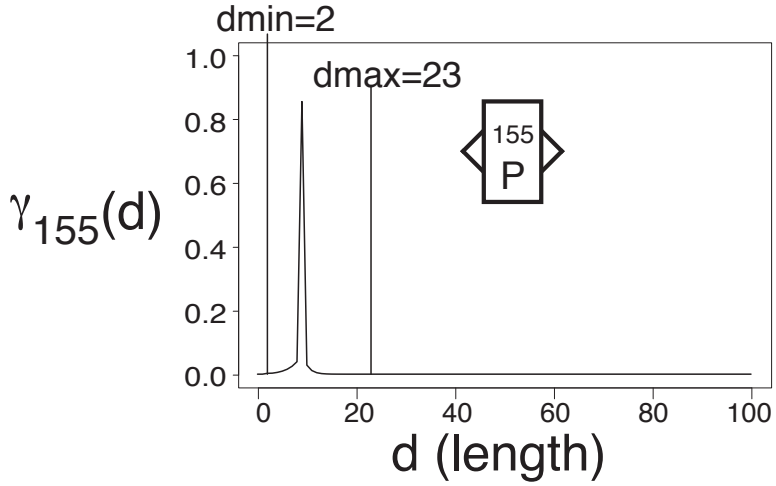
for states $v = M-1$ down to 0:

| | | |
|---|---|---|
| $v$ = end state ($E$): | $\gamma_v(0) = 1$<br>$\gamma_v(d) = 0$ | for $d = 1$ to $Z$ |
| $v$ = bifurcation ($B$): | $\gamma_v(d) = \sum_{n=0}^{d} \gamma_y(n) * \gamma_z(d-n)$ | for $d = 0$ to $Z$ |
| else ($v = S, P, L, R$): | $\gamma_v(d) = 0$<br>$\gamma_v(d) = \sum_{y \in C_v} \gamma_y(d - (\Delta_v^L + \Delta_v^R)) * t_v(y)$ | for $d = 0$ to $(\Delta_v^L + \Delta_v^R - 1)$<br>for $d = (\Delta_v^L + \Delta_v^R)$ to $Z$ |

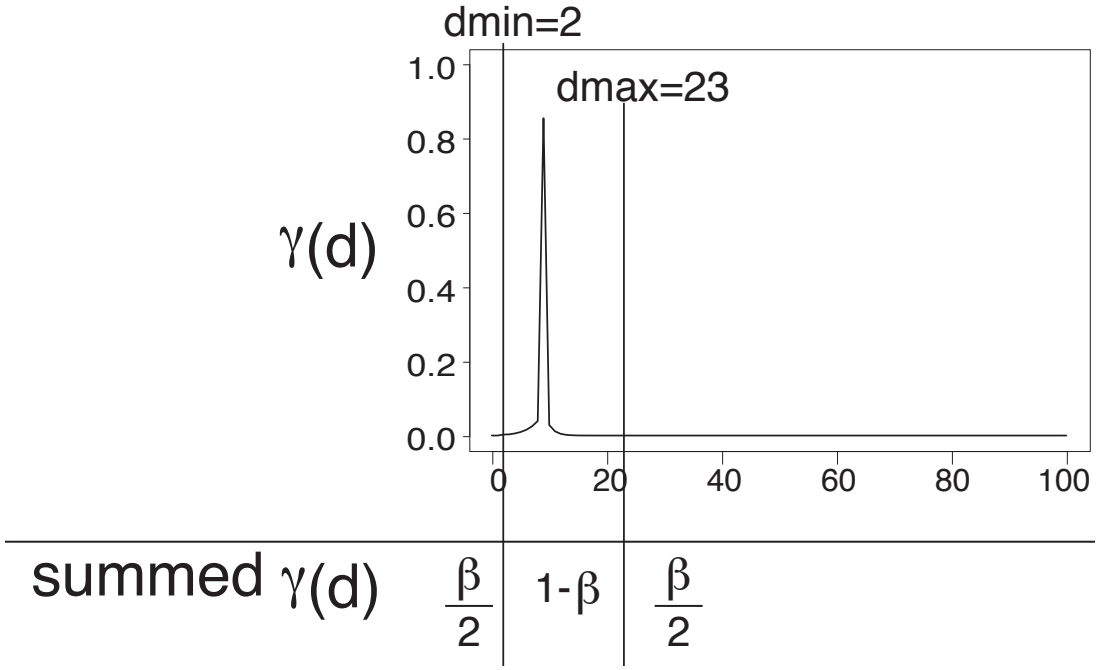
## QDBs for a tRNA CM:



# The $\beta$ parameter controls amount of probability loss



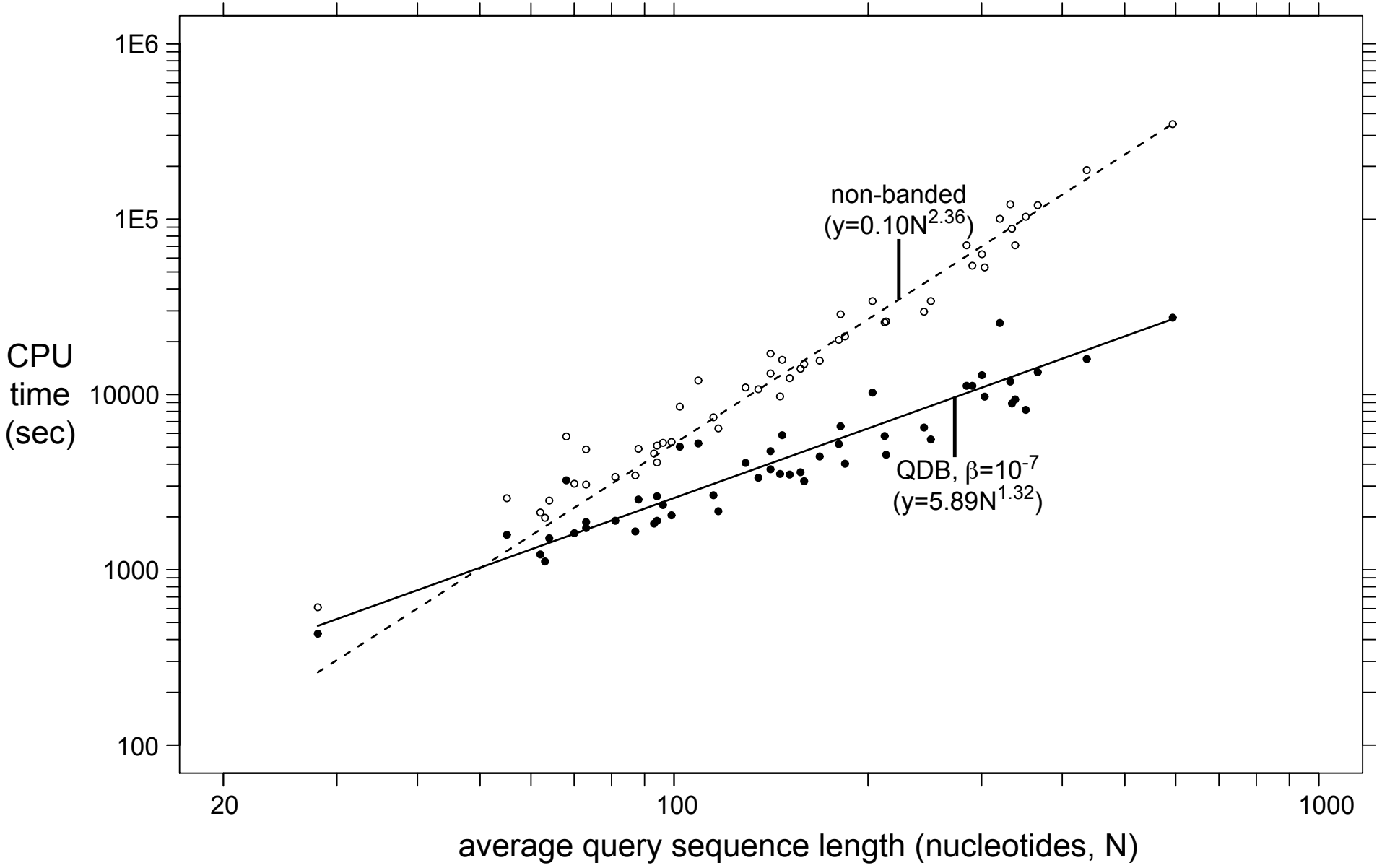

$$\sum_{d=0}^{\text{dmin}-1} \gamma(d) < \frac{\beta}{2}$$

$$\sum_{d=\text{dmin}}^{\text{dmax}} \gamma(d) = 1 - \beta$$

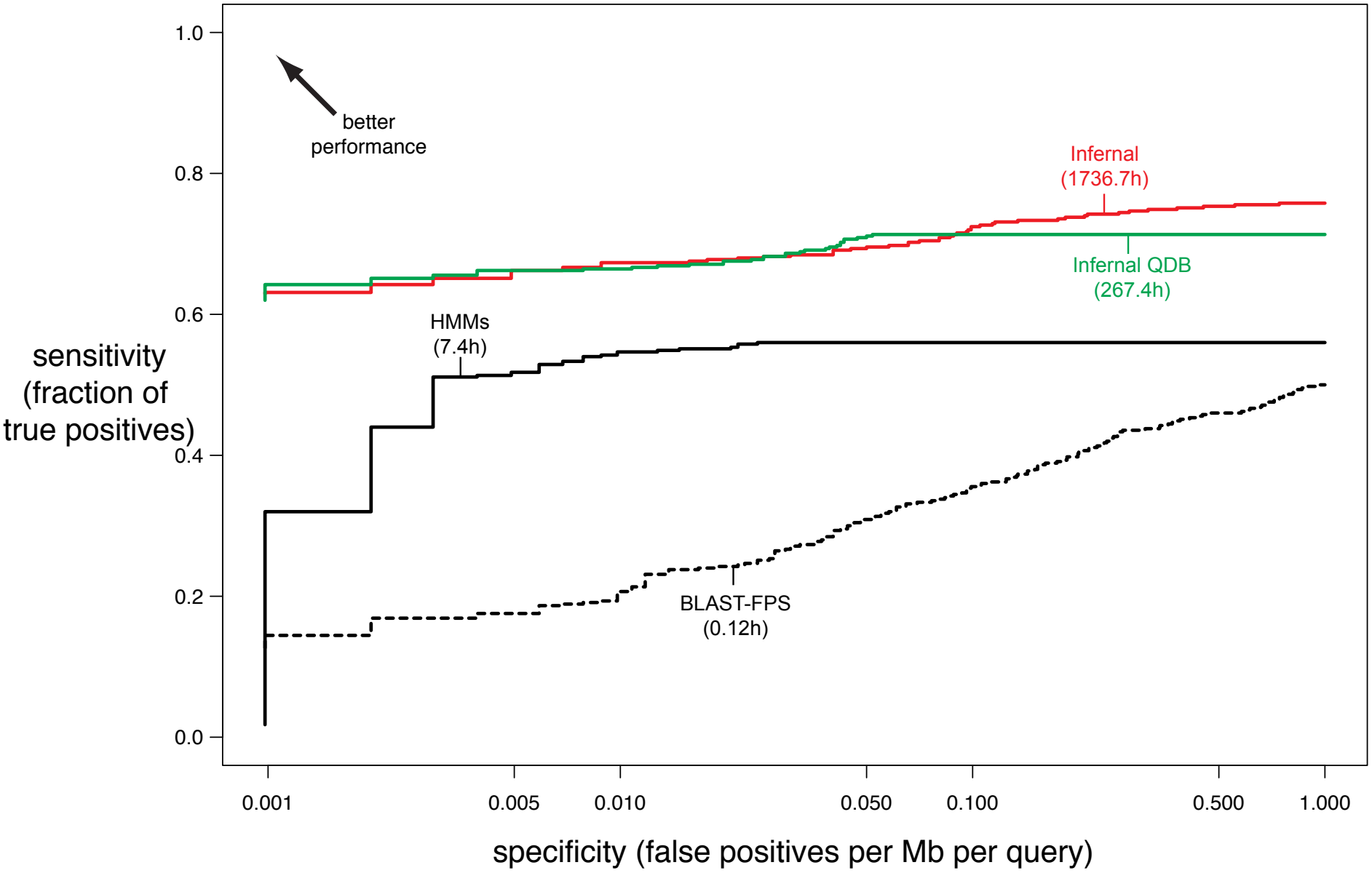
$$\sum_{d=\text{dmax}+1}^{Z} \gamma(d) < \frac{\beta}{2}$$

- $\beta$ is typically very small
  for example: $0.0000001(10^{-7})$
- Higher $\beta$ gives more acceleration
  but at larger cost to accuracy

# Empirical time complexity of CM homology search



# QDB sacrifices very little sensitivity and gives 6-fold speedup

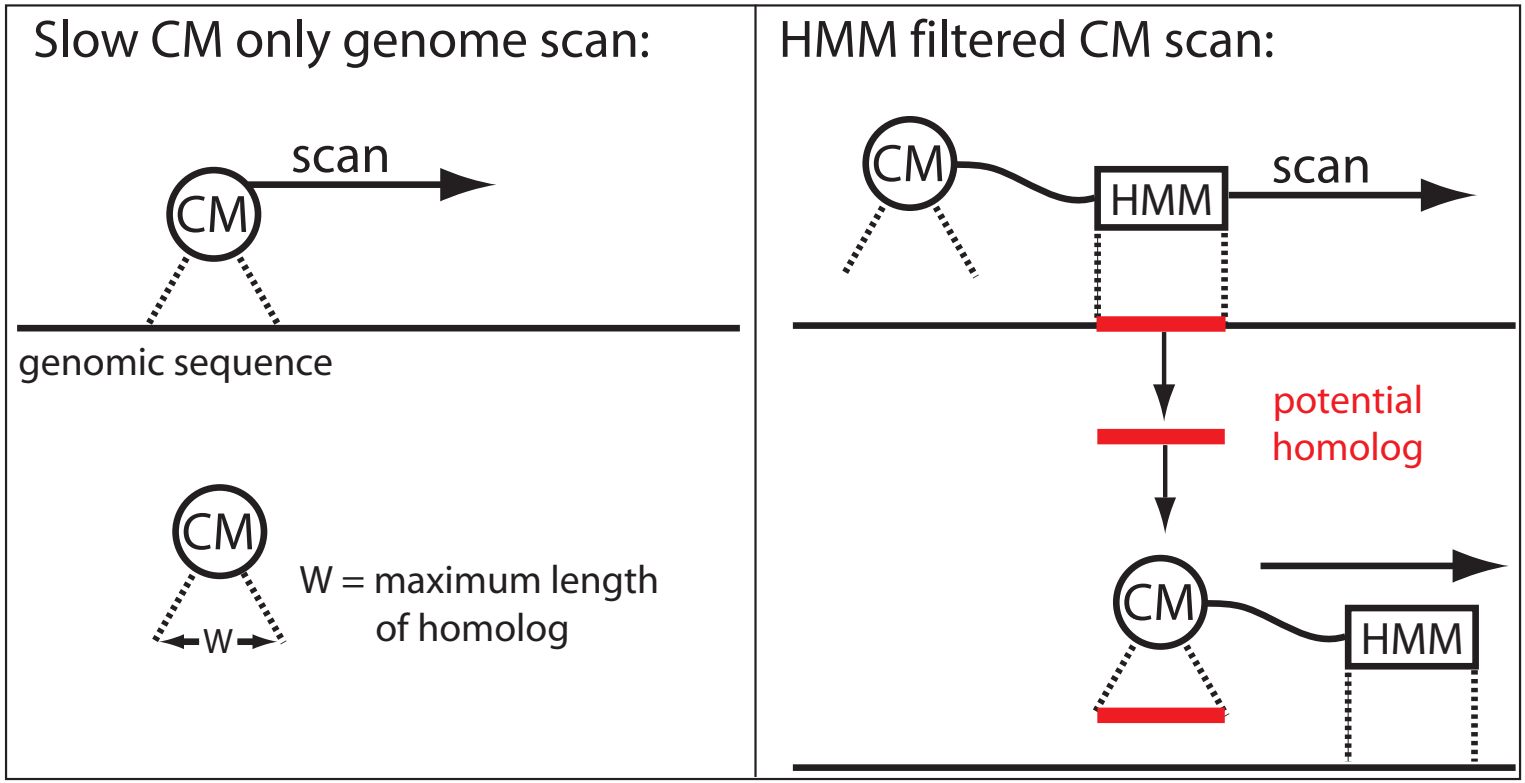


# CM homology searches are still slow

| | | search (min/Mb) | | | |
|---|---|---|---|---|---|
| family | length | HMM | QDB CM | QDB CM/HMM | non-banded CM/HMM |
| tRNA | 71 | 0.34 | 9.6 | 28.2 | 79.4 |
| Lysine riboswitch | 183 | 0.80 | 33.8 | 42.3 | 166.7 |
| SRP RNA | 304 | 1.32 | 50.5 | 38.3 | 214.4 |
| RNaseP RNA | 365 | 1.56 | 81.6 | 52.3 | 470.3 |

# Filtering as a complementary acceleration strategy

- Main idea: search database with faster method first, hits above some threshold survive the filter and are searched with the slow CM.
- Weinberg and Ruzzo* developed HMM filters for faster searches.
- Others have also worked on this (Sun and Buhler †, Zhang and Bafna‡)



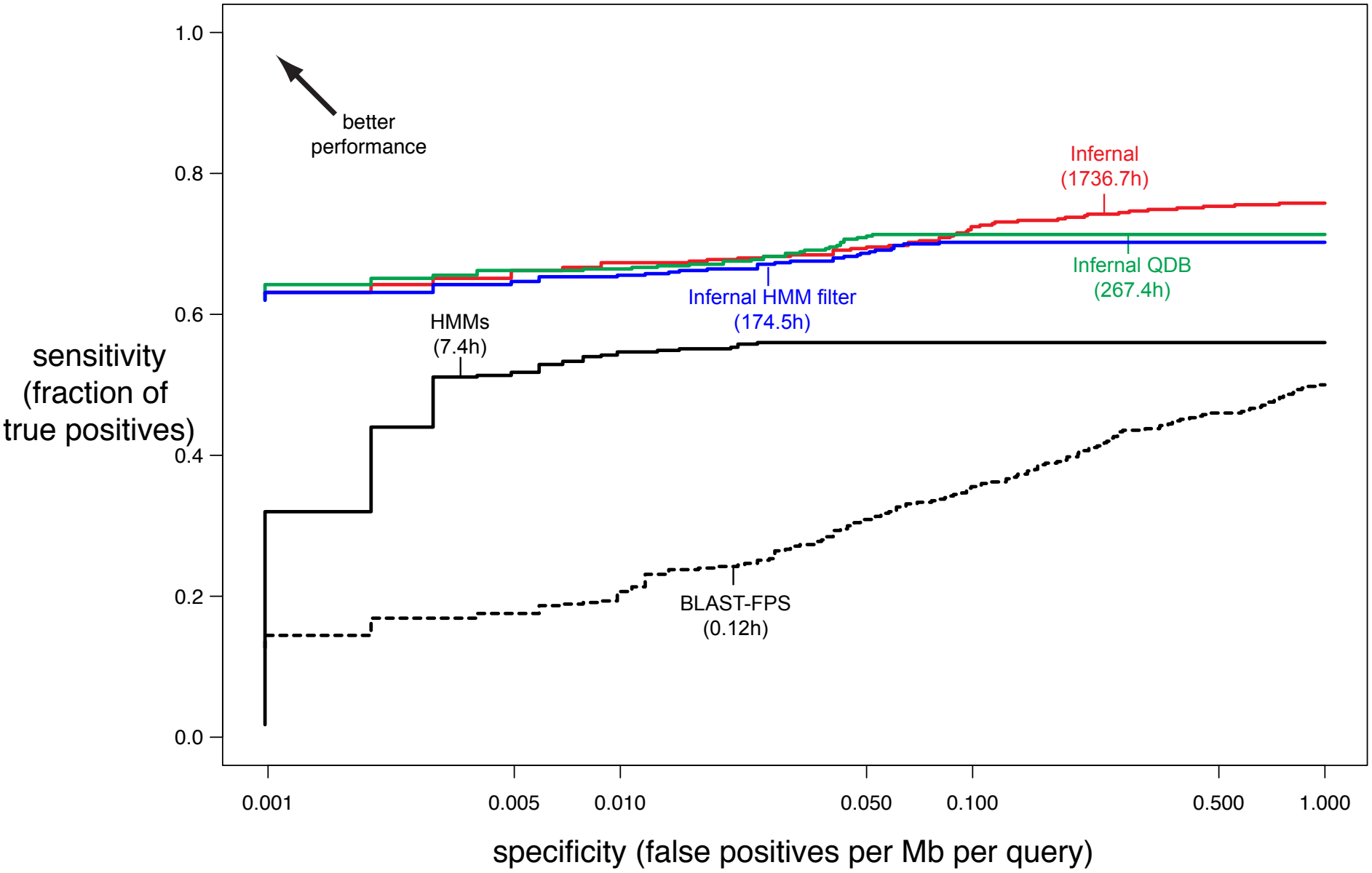


*Weinberg Z, Ruzzo WL. 22(1):3539, 2006.

†Sun Y, Buhler J, Comput. Systems Bioinf., p145-156, 2008.

‡Zhang S et al., Bioinformatics. 22(14):e557-e565, 2006.

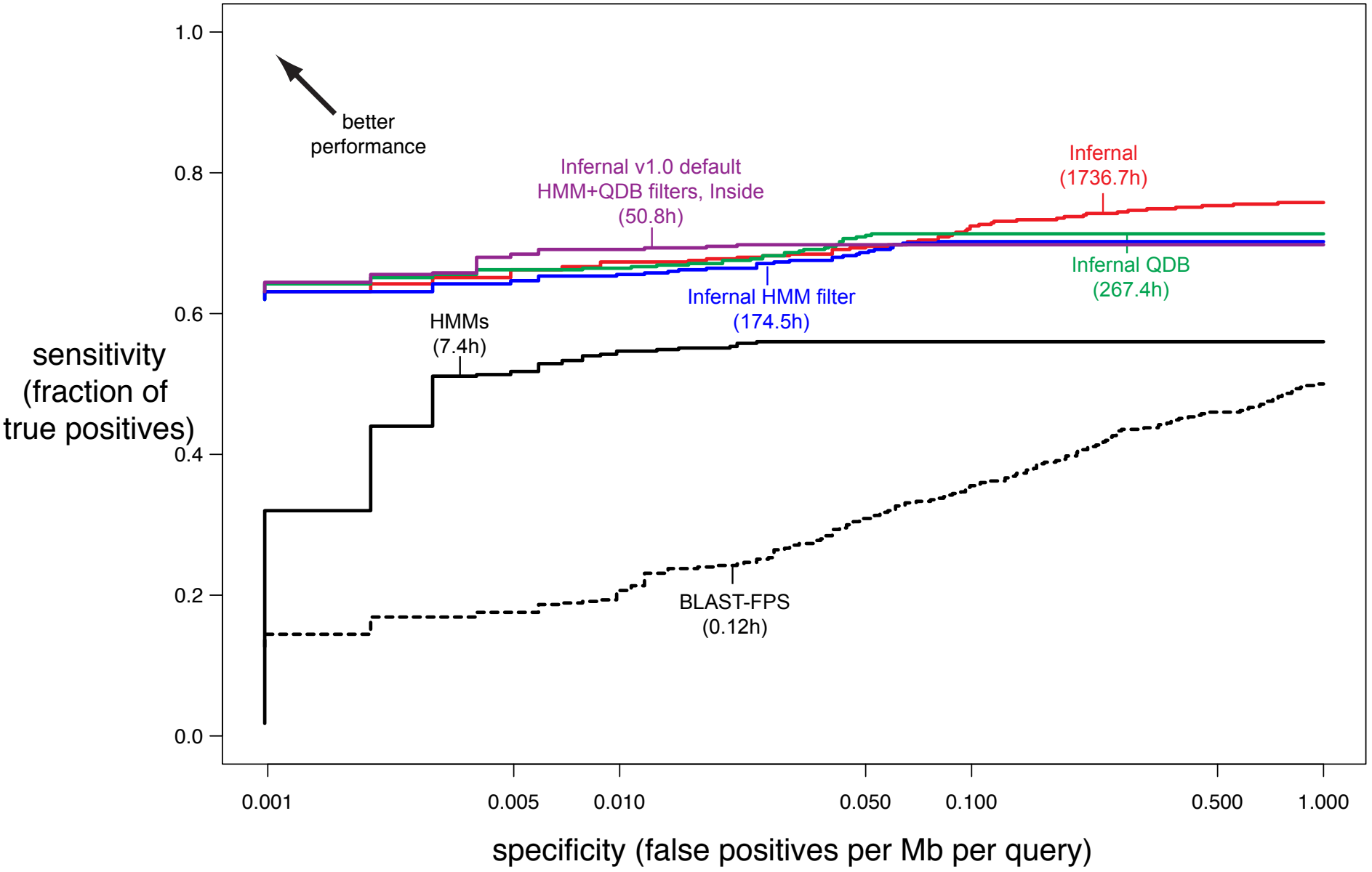
# HMM filters achieve 10-fold speedup at very small cost to accuracy



# Combining QDB and HMM filters yields greater acceleration

The more powerful, slower Inside algorithm is used post-filtering.

Infernal is now 30-fold faster and slightly more sensitive.

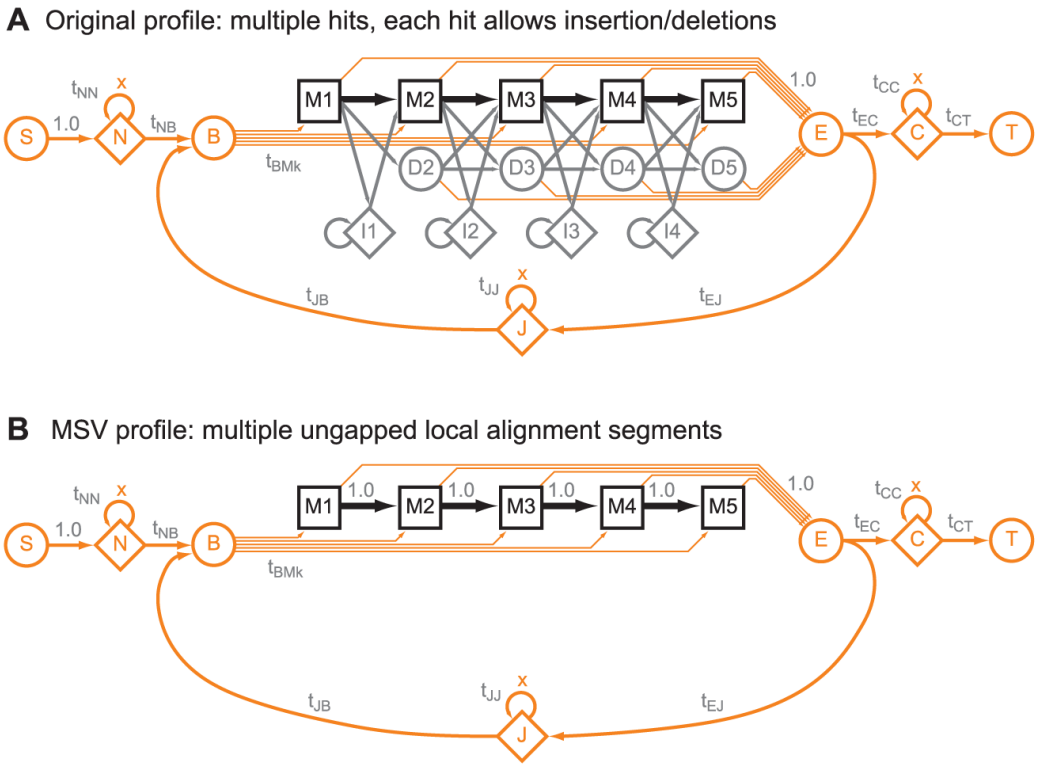


# CMs are nearly as fast as HMMs (usually)

| | | search (min/Mb) | | | |
|---|---|---|---|---|---|
| family | length | HMM | HMM+QDB filtered CM | HMM+QDB filtered CM/HMM | non-banded CM/HMM |
| tRNA | 71 | 0.34 | 8.8 | 25.9 | 79.4 |
| Lysine riboswitch | 183 | 0.80 | 2.2 | 2.8 | 166.7 |
| SRP RNA | 304 | 1.32 | 6.0 | 4.5 | 214.4 |
| RNaseP RNA | 365 | 1.56 | 1.8 | 1.2 | 470.3 |

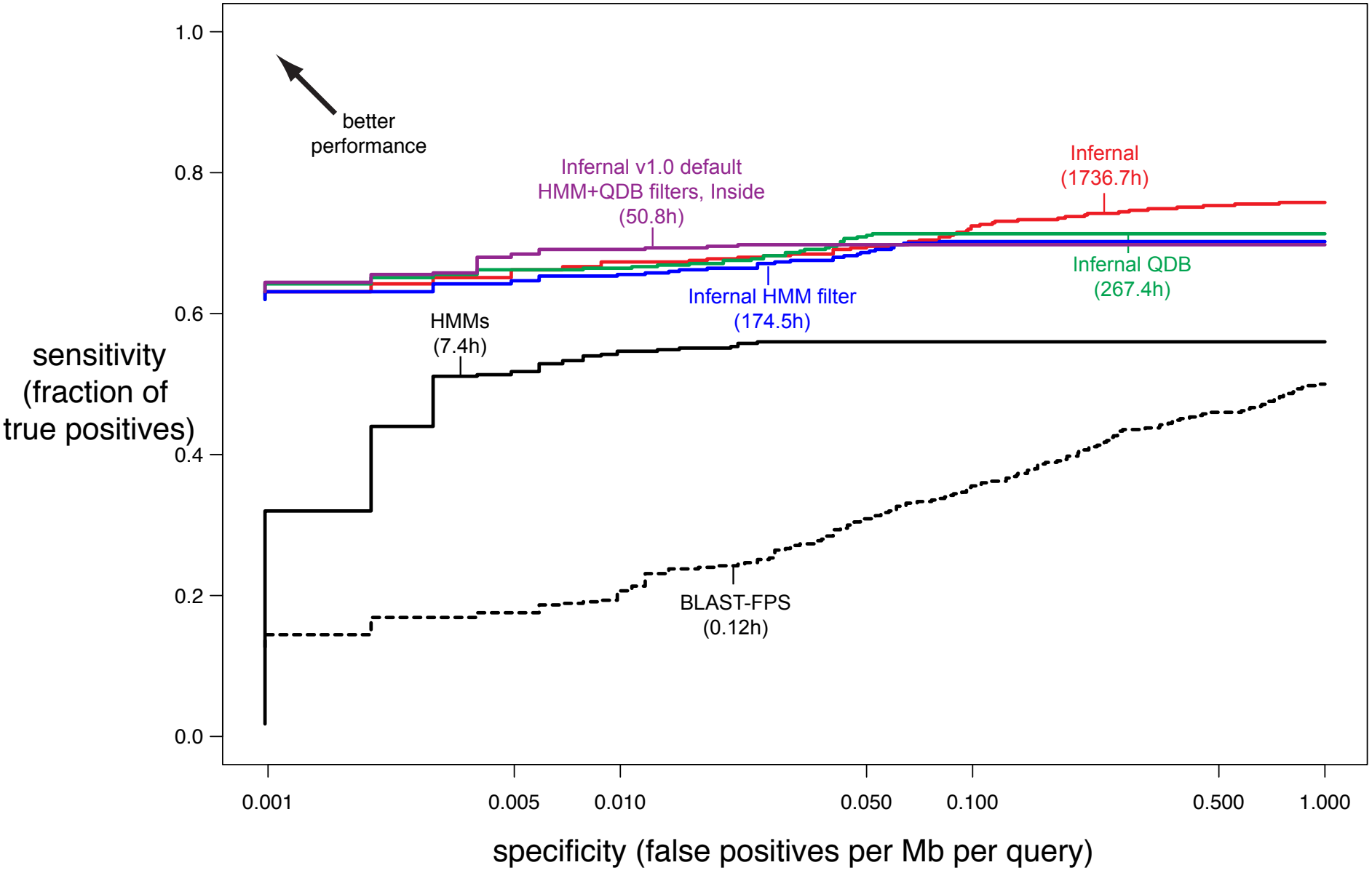
# With HMMER3, HMMs got about 100x faster using an MSV filter

- MSV (Multiple Segment Viterbi) algorithm, which disallows inserts and deletes, can be computed using 16-fold vector parallelism with low-precision (8-bit) scores*.



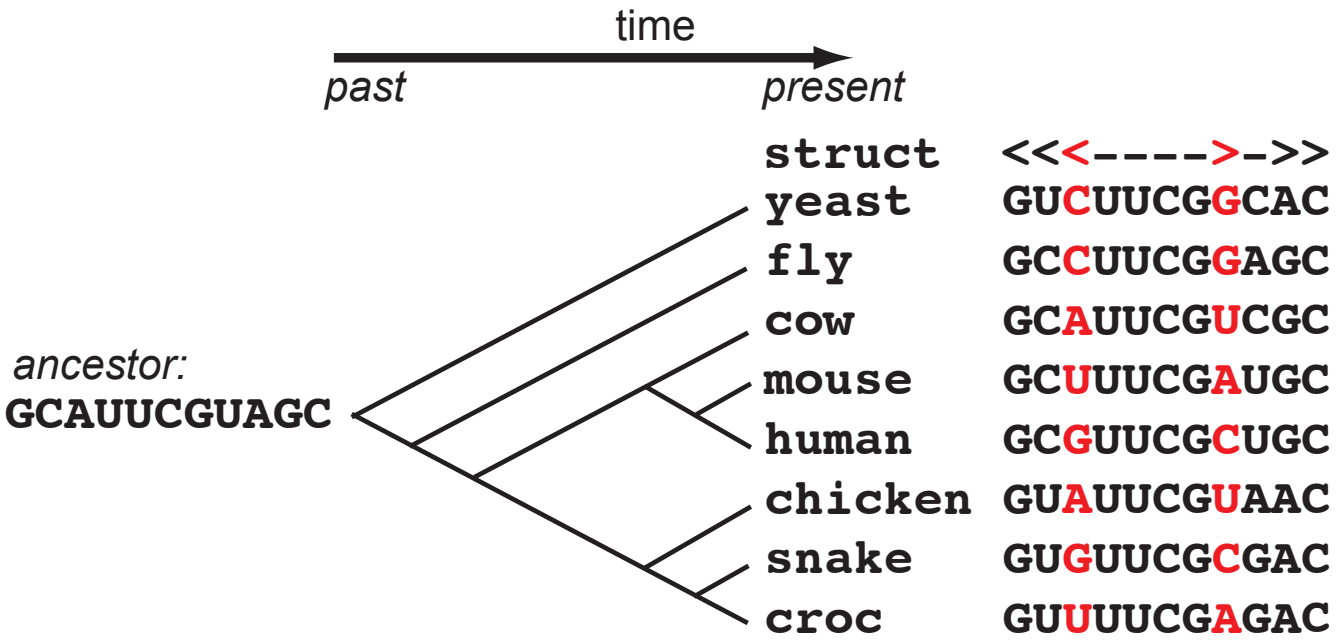

*Eddy SR. PLoS Comp. Biol., 7:e1002195, 2011

# Using faster HMM filters could only accelerate Infernal by about 15% (7.4/50.8)



**CMs can also be used to create structural alignments of homologous RNAs.**

- Given known homologs, place homologous residues in the same columns.

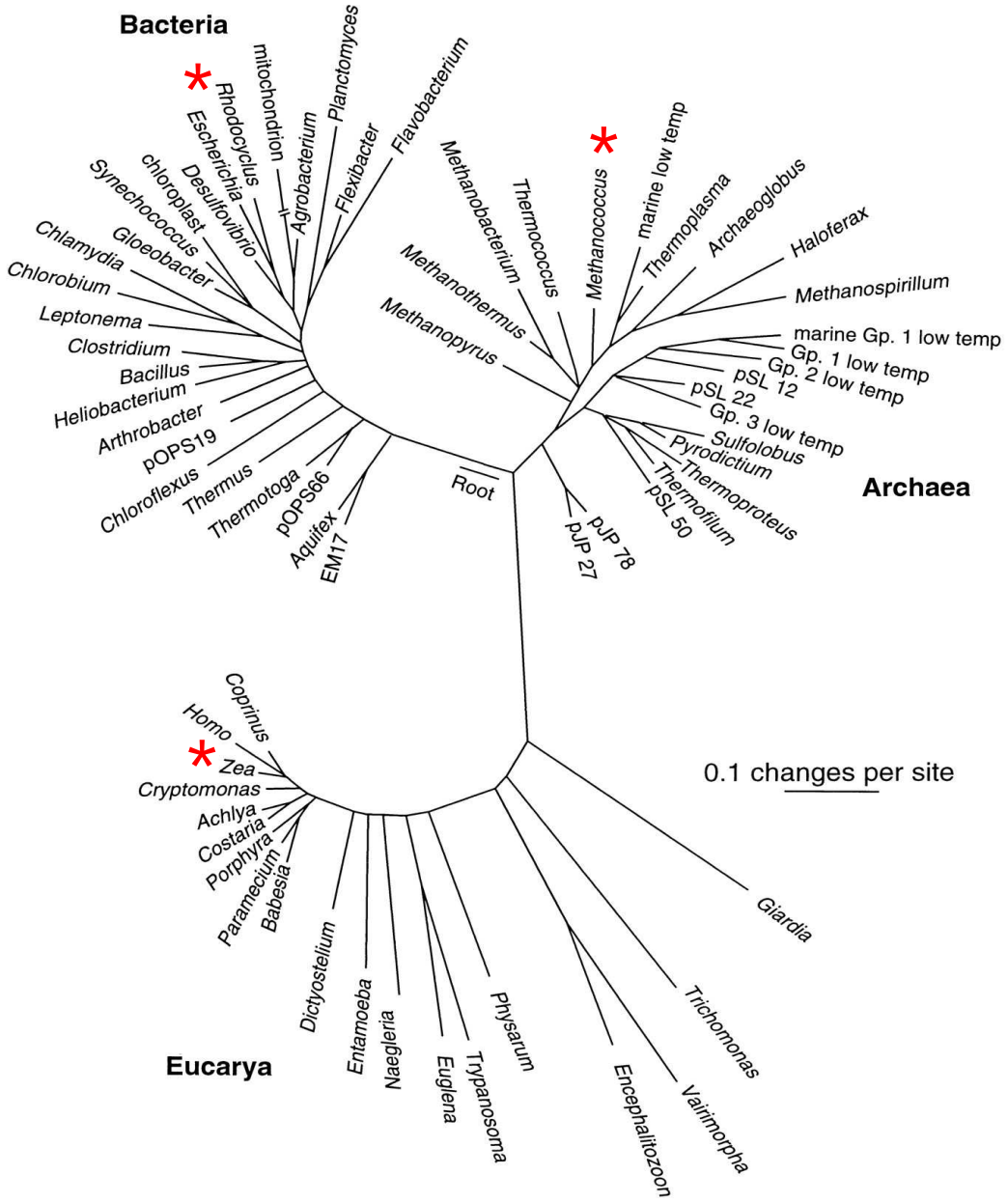



- Alignments of SSU rRNA have commonly been used for phylogenetic inference.

- However, CM alignment is too slow for SSU alignment.
  Aligning a single SSU sequence takes more than 10 minutes.

# Small subunit ribosomal RNA and the tree of life

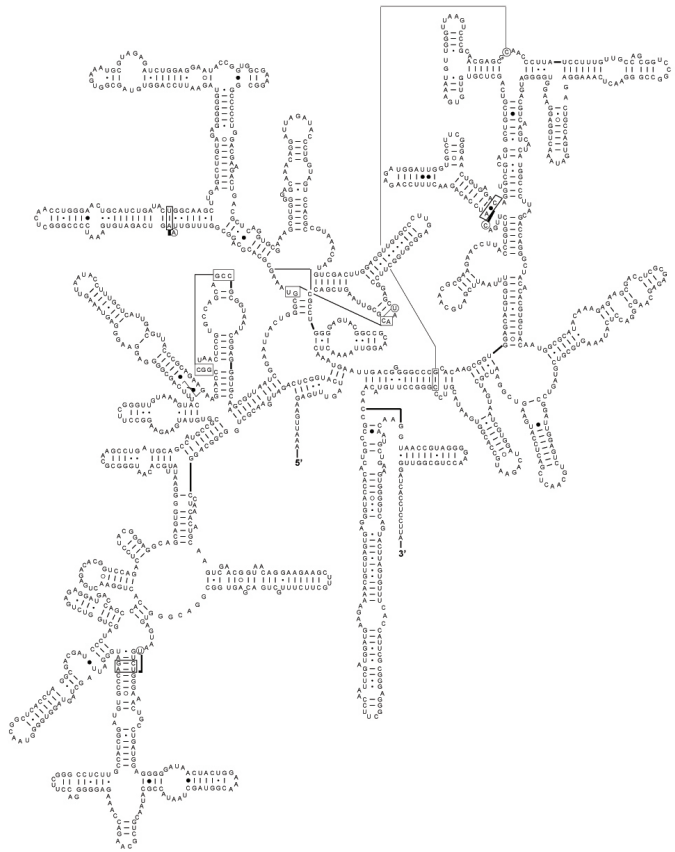
- 1977 - Carl Woese decided to classify all living things phylogenetically
- needed "*a molecule of appropriately broad distribution*" for comparative analysis
- SSU rRNA was chosen
  - universally distributed
  - highly conserved
  - large enough to provide sufficient data (1500-1800 nt)
  - readily isolated



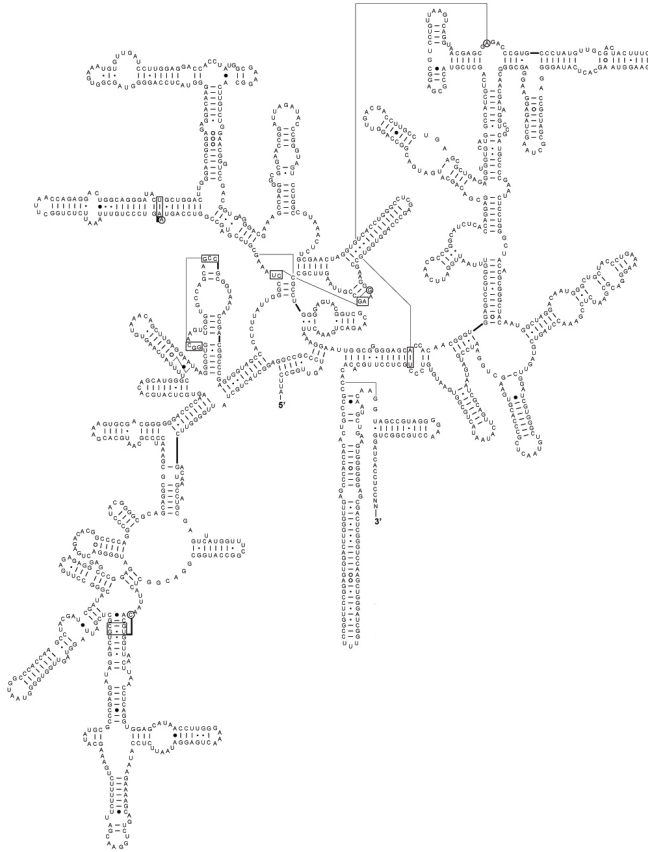

Pace, Science:276; 1997

# Universal conservation of SSU rRNA

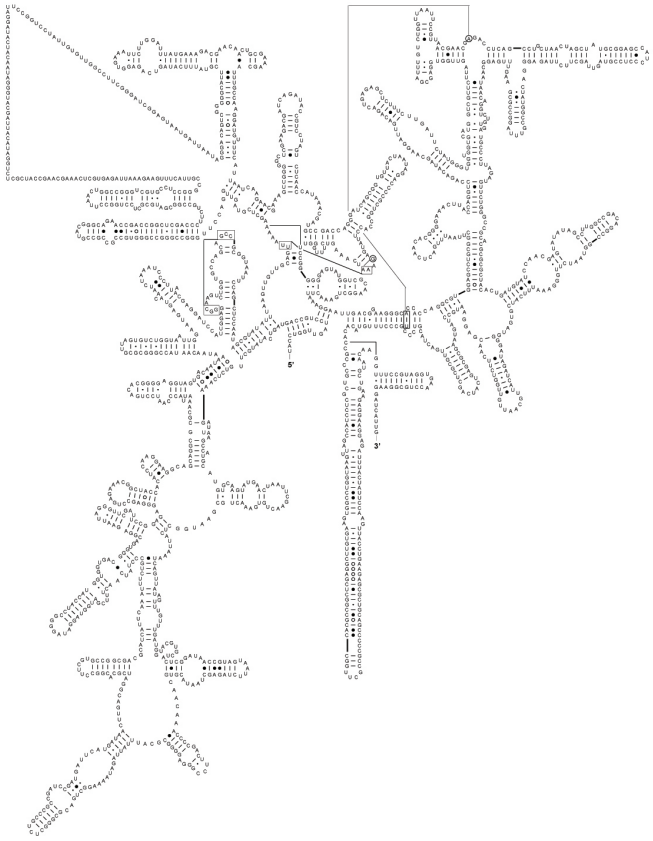
*Escherichia coli*



*Methanococcus vannielii*



*Zea mays*



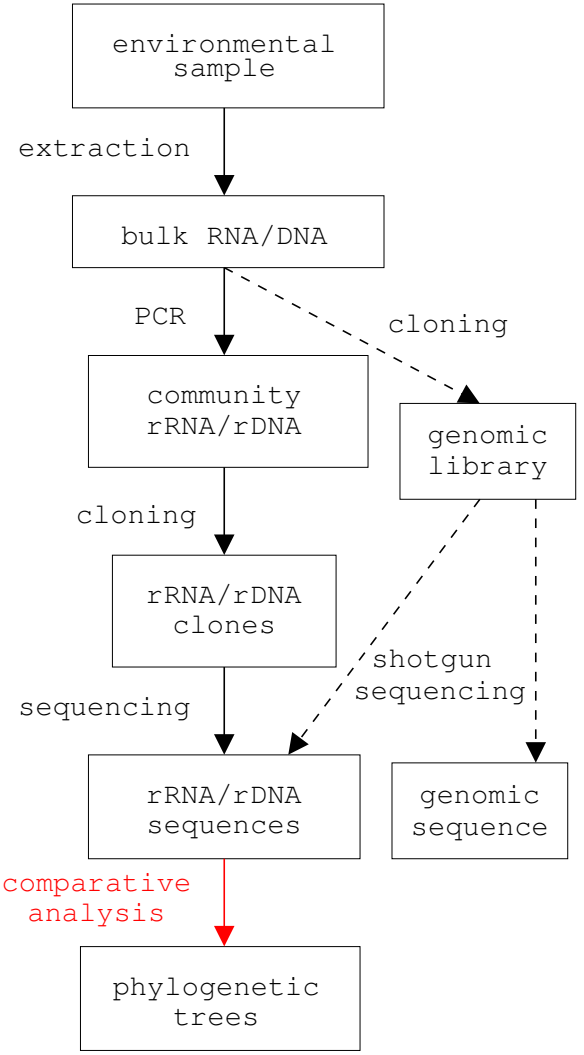
Secondary structure diagrams from:
URL:http://www.rna.ccbb.utexas.edu/

# Environmental surveys target SSU

- mid 1980s - Norman Pace develops methodology for determination of SSU sequences without cultivation
- many different environments have been surveyed
- known biodiversity has been greatly expanded:
  - recognized bacterial phyla:
    11 in 1987, 36 in 1998, 52 in 2003, 67 in 2006...
- SSU databases contain millions of sequences:

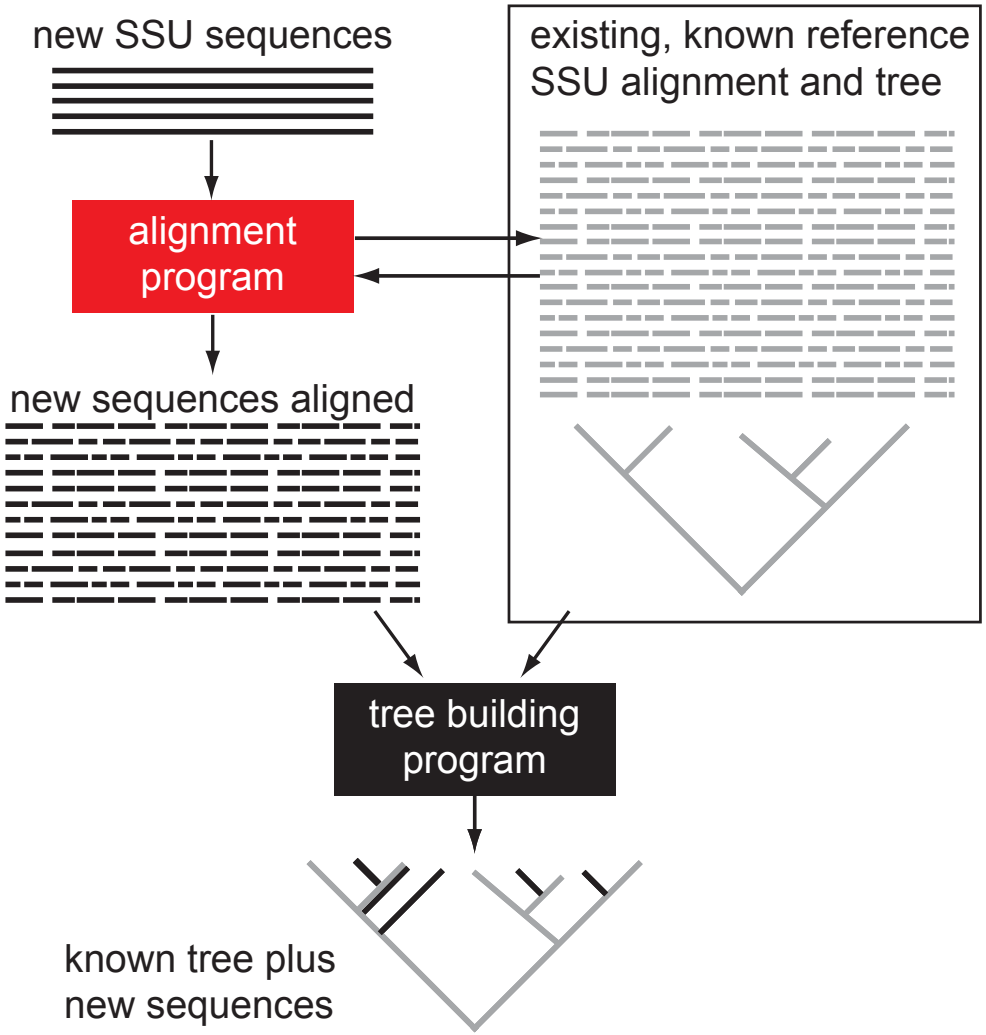
| name | # seqs | # citations |
|---|---|---|
| Silva | 3.2M | 1125 |
| RDP | 2.6M | 1170 |
| Greengenes | 1.0M | 1012 |

Silva: Pruesse et al., 2007 NAR 35.21:7188-96
RDP: Cole et al., 2009 NAR 37:D141-45
Greengenes: DeSantis et al., 2006 AEM 72:5069-72




adapted from: Hugenholtz, Genome Biology:2002 3(2)

# The comparative analysis step:
# Alignment and Phylogenetic Inference




Goals of the alignment program:

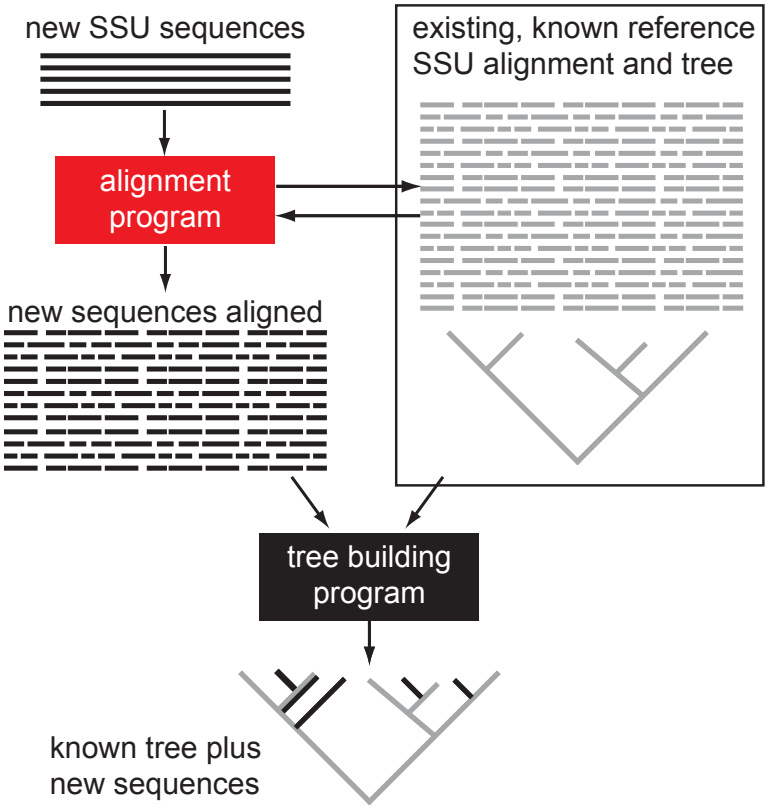
accurate: because alignment errors confound phylogenetic inference

fast: to handle up to millions of seqs

# Environmental surveys target SSU rRNA

Two types of questions:
What organisms (known/unknown) are in my sample?
What is the phylogeny of a set of organisms?

Main assumption:
SSU gene tree approximates organismal tree.




Goals of the alignment program:

accurate: b/c alignment errors confound phylogenetic inference
fast and scalable: to handle up to millions of seqs
flexible: to be useful for all 3 domains

Sampling of recent SSU studies

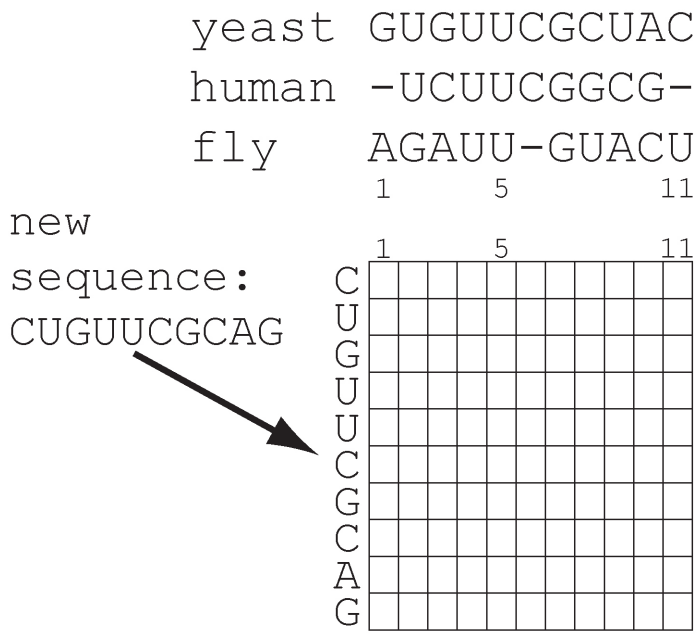
| environment/ phylogeny | domain(s) | #seqs | year |
|---|---|---|---|
| soil, many others | bacteria | 21,752 | 2007 |
| cecal microbiota of mice | bacteria | 5,088<br>4,157 | 2005<br>2006 |
| Sargasso sea | all 3 | 1,164 | 2004 |
| hydrothermal vents | eukarya | 374 | 2002 |
| endolithic environment (pore space of rocks) | archaea, bacteria | 342<br>588 | 2005<br>2007 |
| oxidized iron deposits, marine tidal mat, microbial steamers | bacteria | 308 | 2004 |
| soil & burrow casts of earthworms | archaea, bacteria | 204 | 2002 |
| tidal flat sediment | archaea | 90 | 2005 |
| salt marsh | eukarya | 79 | 2003 |
| dipteran hindgut | bacteria | 59 | 2007 |
| bumble bee phylogeny | eukarya | ~200 | 2007 |
| anaplasma phylogeny | bacteria | 21 | 2003 |
| protostome phylogeny | eukarya | 20 | 2002 |

# Accelerating CM alignment using HMMs

- **main idea:** use fast HMM when it's accurate, appealing to CM when it's not
- need some type of measure of confidence in regions of the HMM alignment

HMM alignment

- each column of the grid corresponds to a column of the seed alignment
- each row of the grid corresponds to a position of the new sequence



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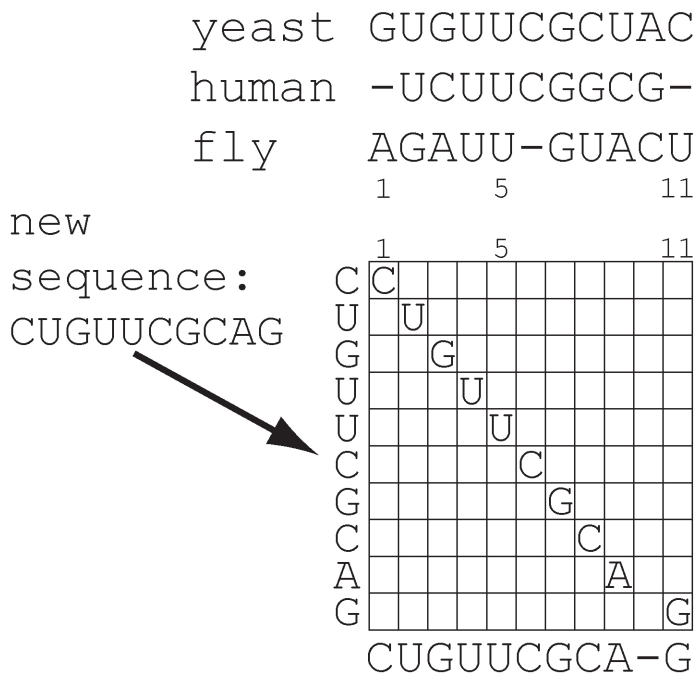

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HMM alignment

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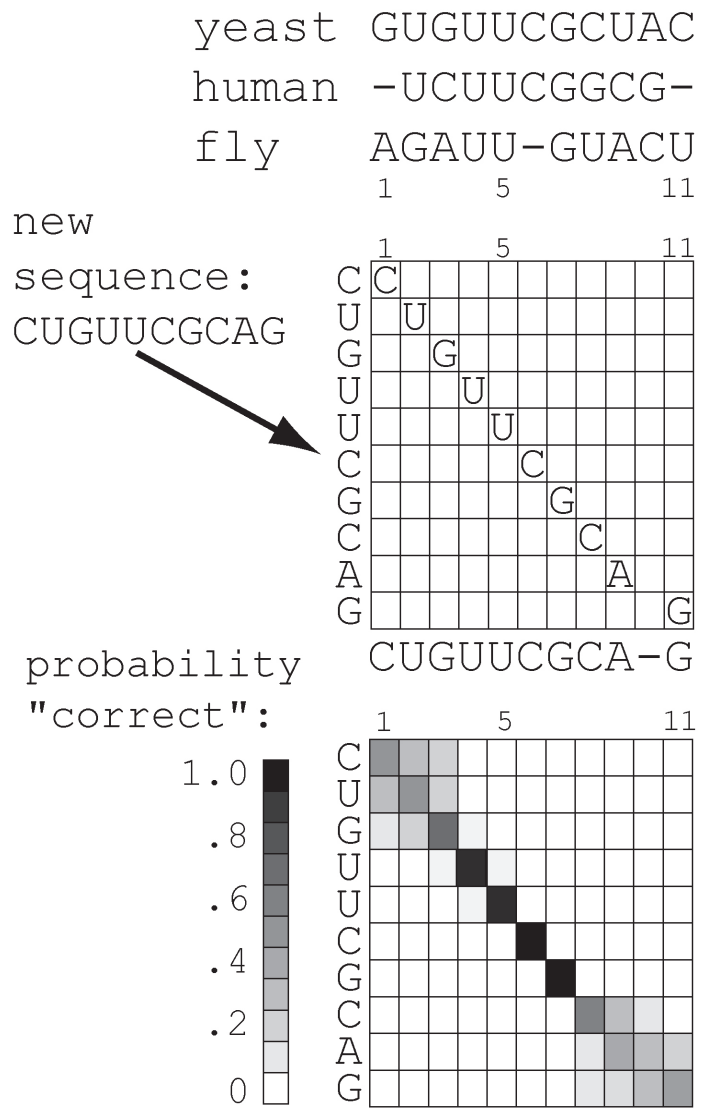
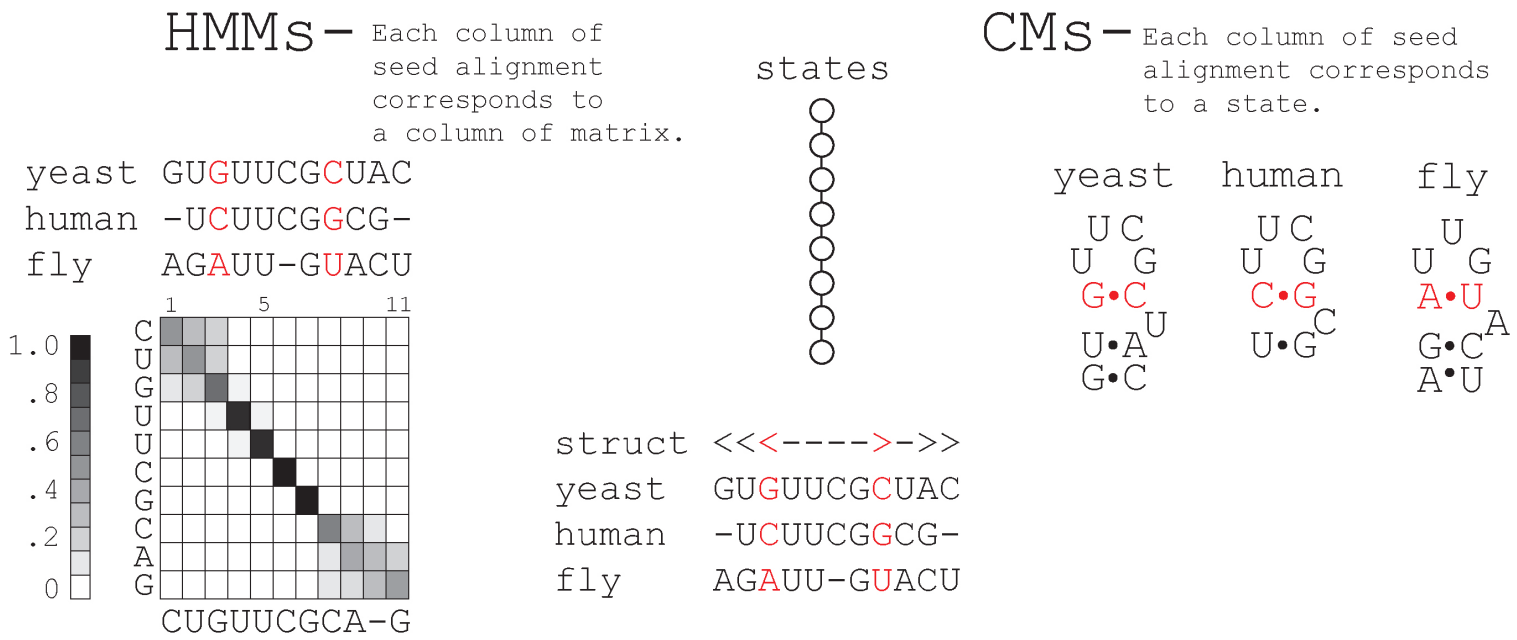
**How can we use this information during CM alignment?**



# HMM bands accelerate CM alignment

- **main idea:** eliminate potential alignments the HMM tells us are very improbable



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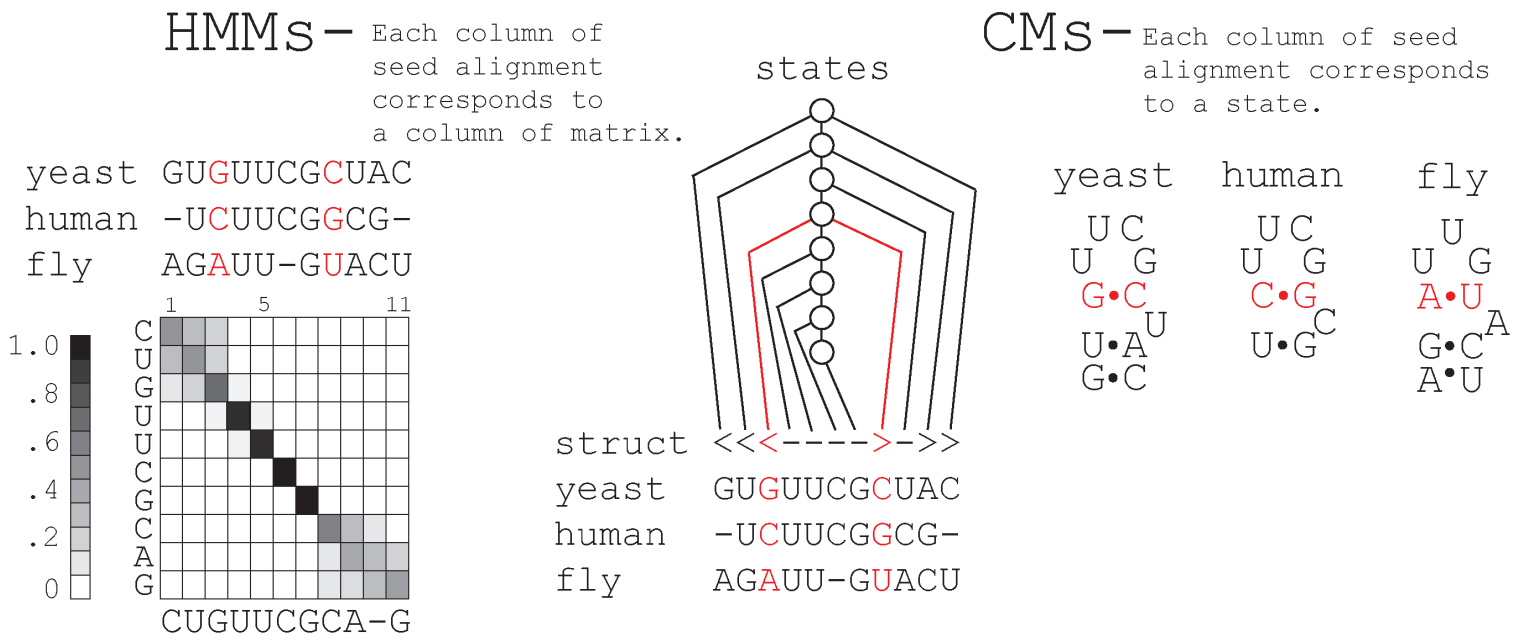

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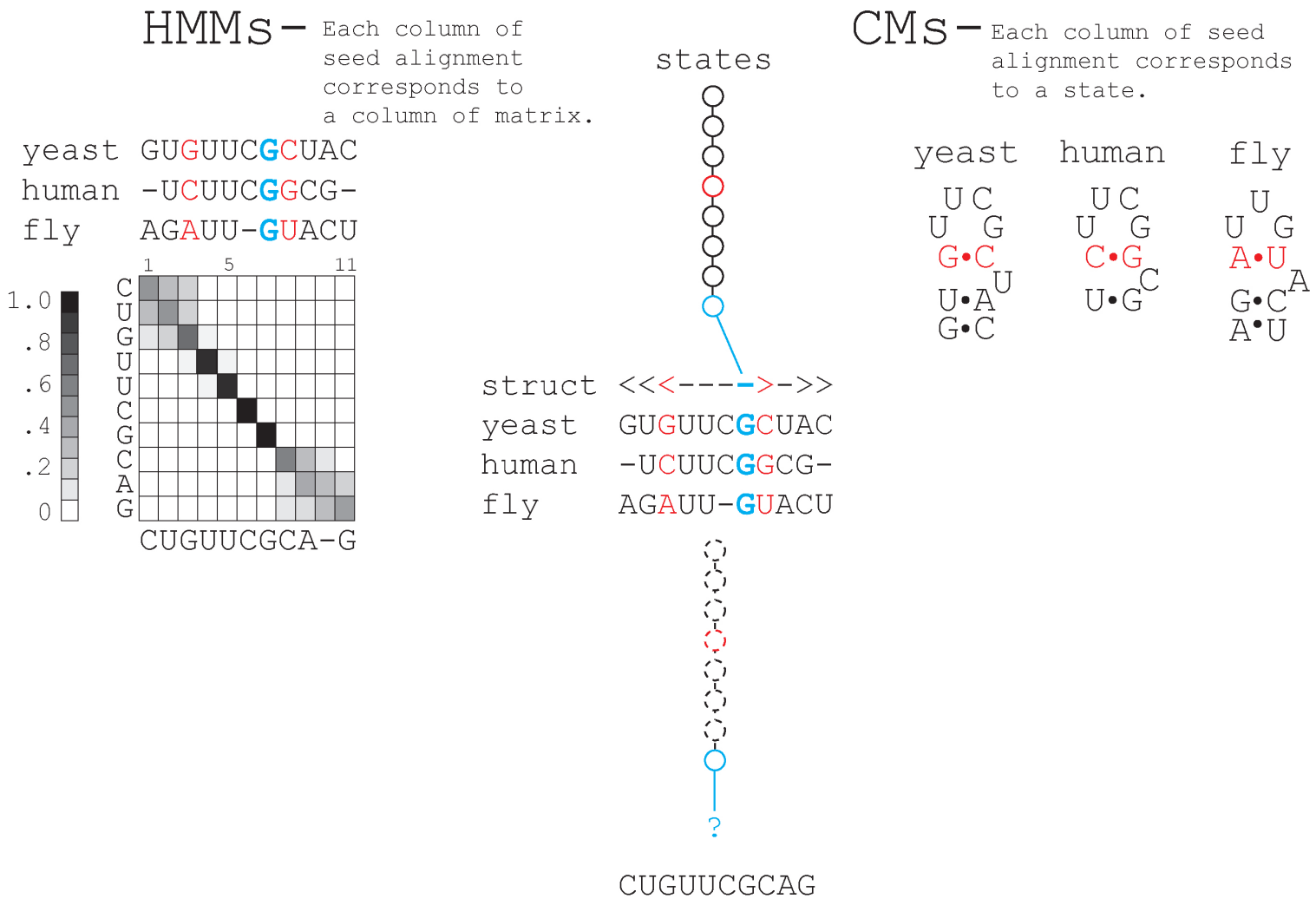

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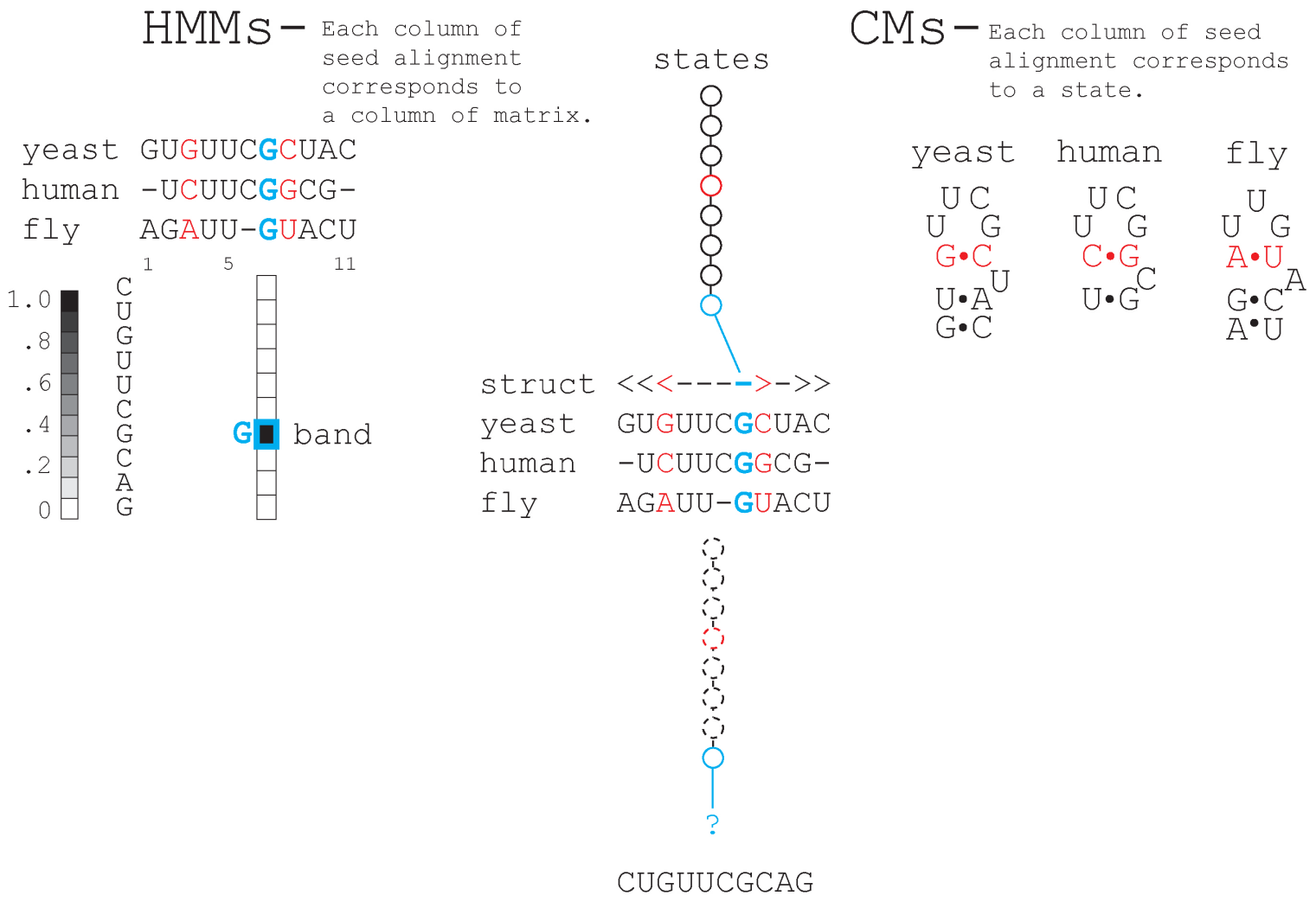

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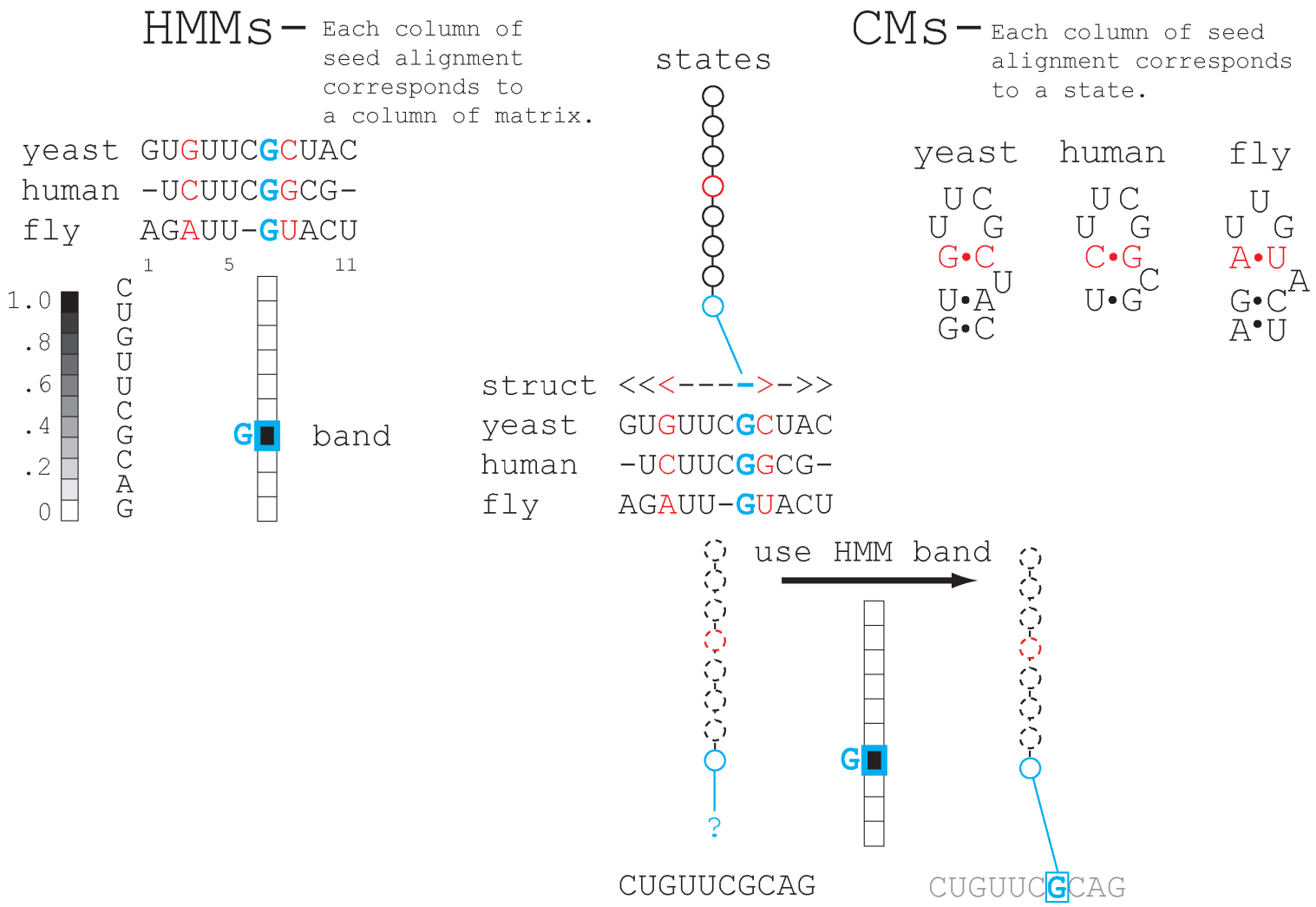

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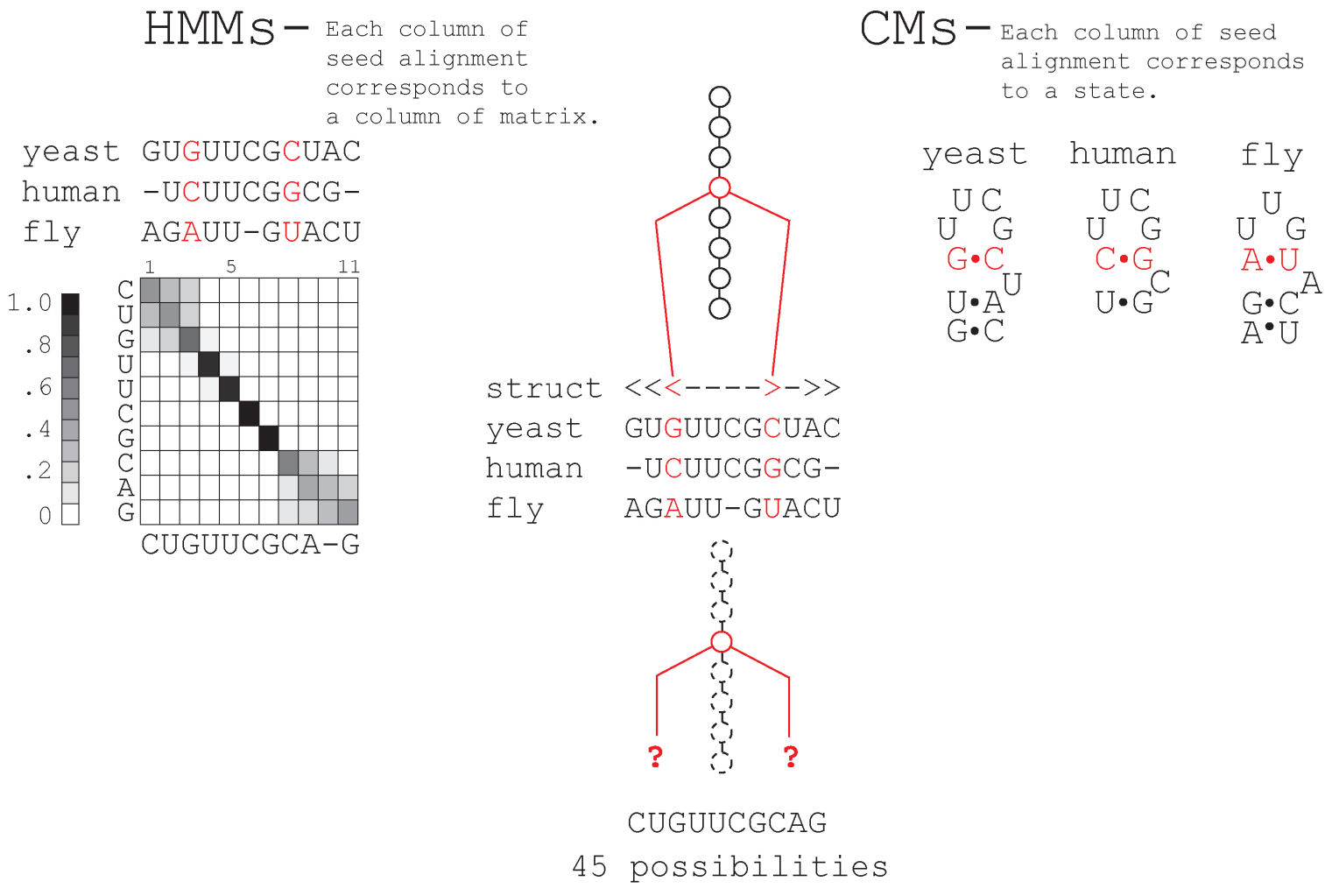

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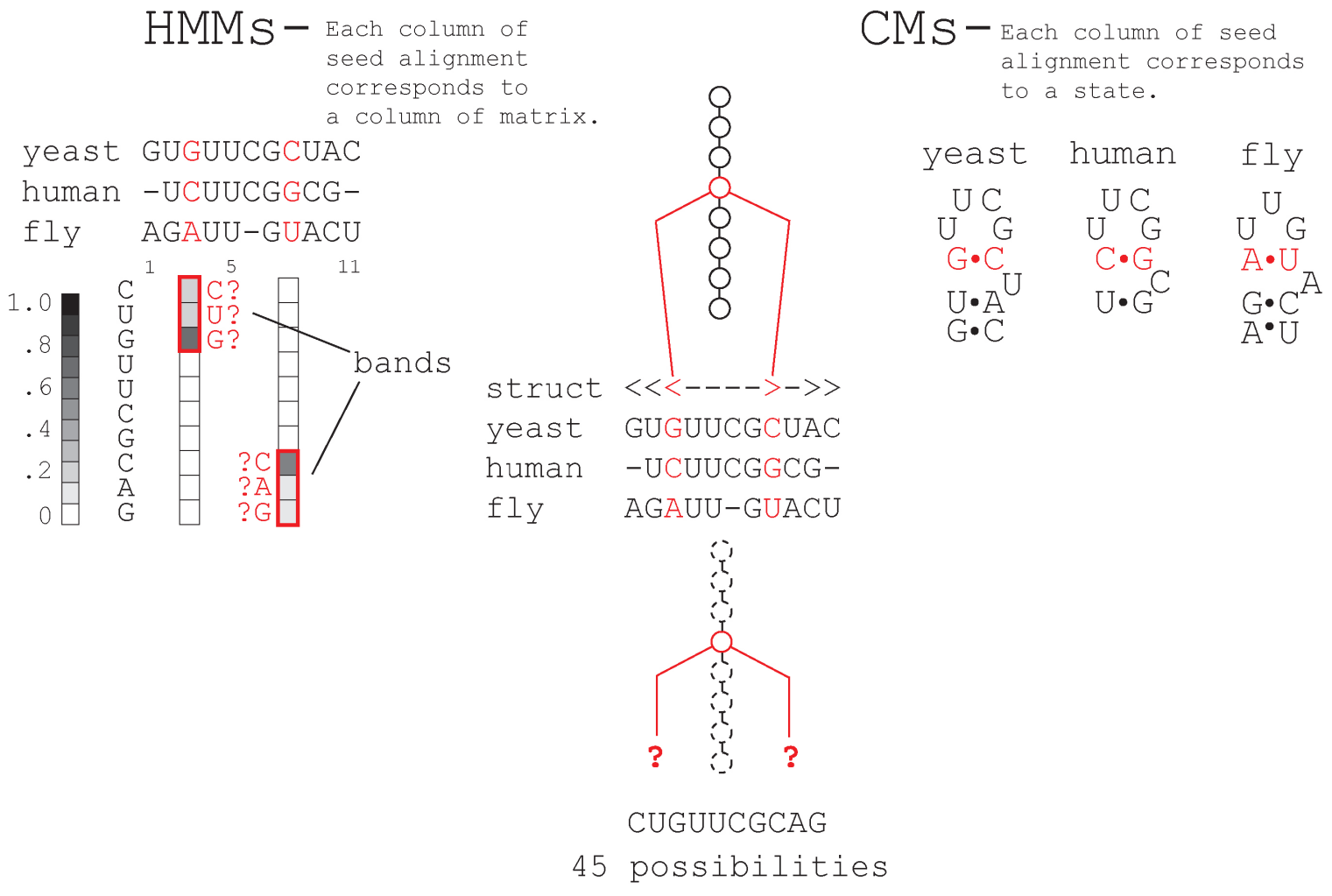

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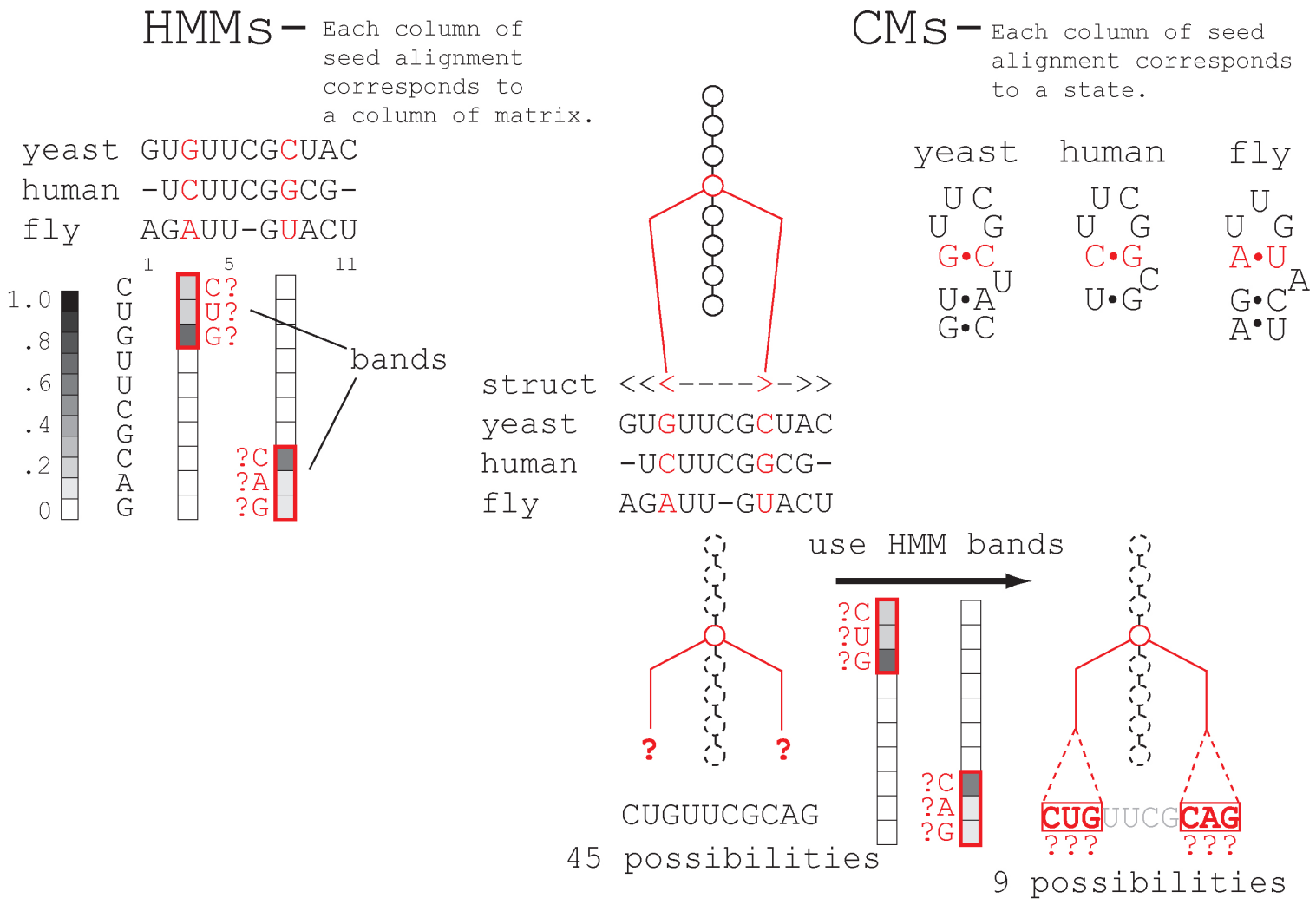
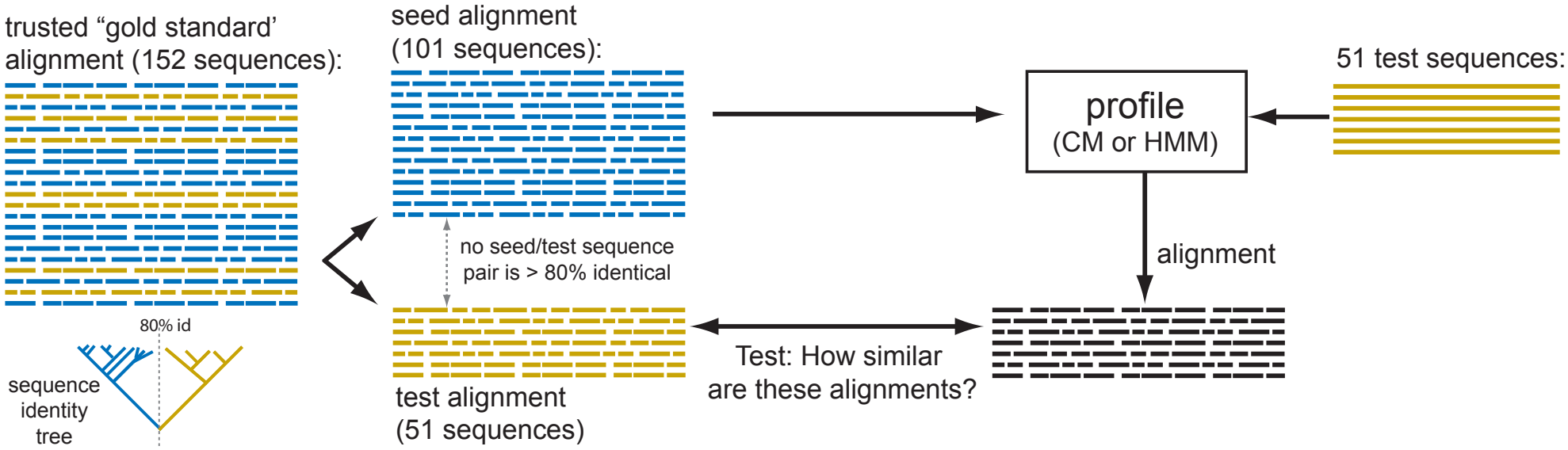


# Determining the impact on speed and accuracy

- Does the banded CM approach sacrifice accuracy relative to non-banded CM alignment?
- 'Gold standard' testing dataset
  - structural alignment of 152 bacterial SSU sequences from Robin Gutell's database
  - this is the CRW bacterial seed alignment filtered to 92% identity
  - determined by 'manual' comparative analysis



## CMs are (slightly) more accurate, but much slower than HMMs

| | alignment accuracy | time (sec/seq) |
|---|---|---|
| Muscle-3.8.31 (*de novo*) | 95.4% | 0.49 |
| HMMER3 (HMMs) | 96.8% | 0.04 |
| non-banded CMs | 98.1% | ? |

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| HMMER3 (HMMs) | 96.8% | 0.04 |
| non-banded CMs | 98.1% | ? |
| HMM banded CMs | 98.1% | 0.50 |

# HMM banding accelerates CM alignment 1000-fold

| | alignment accuracy | time (sec/seq) |
|---|---|---|
| Muscle-3.8.31 (*de novo*) | 95.4% | 0.49 |
| HMMER3 (HMMs) | 96.8% | 0.04 |
| Infernal 1.1 (CMs) | 98.1% | 0.50 |

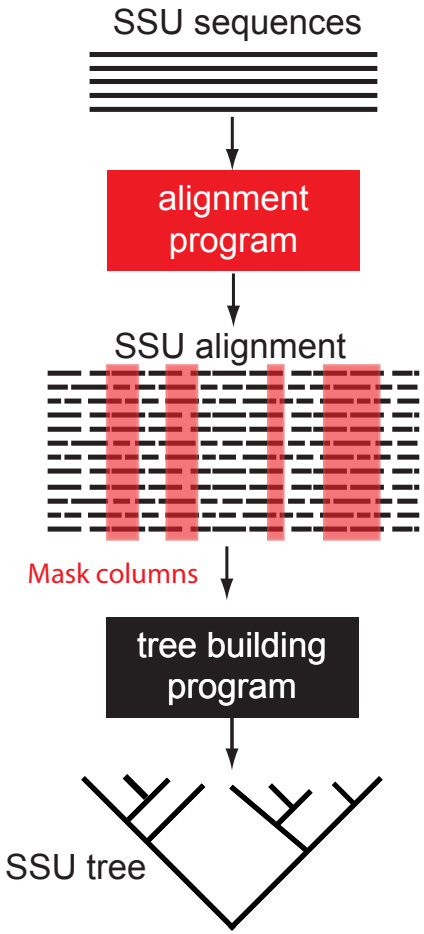
Muscle: Edgar, R.C. Nucleic Acids Res 32(5), 1792-97.

HMMER: hmmer.janelia.org

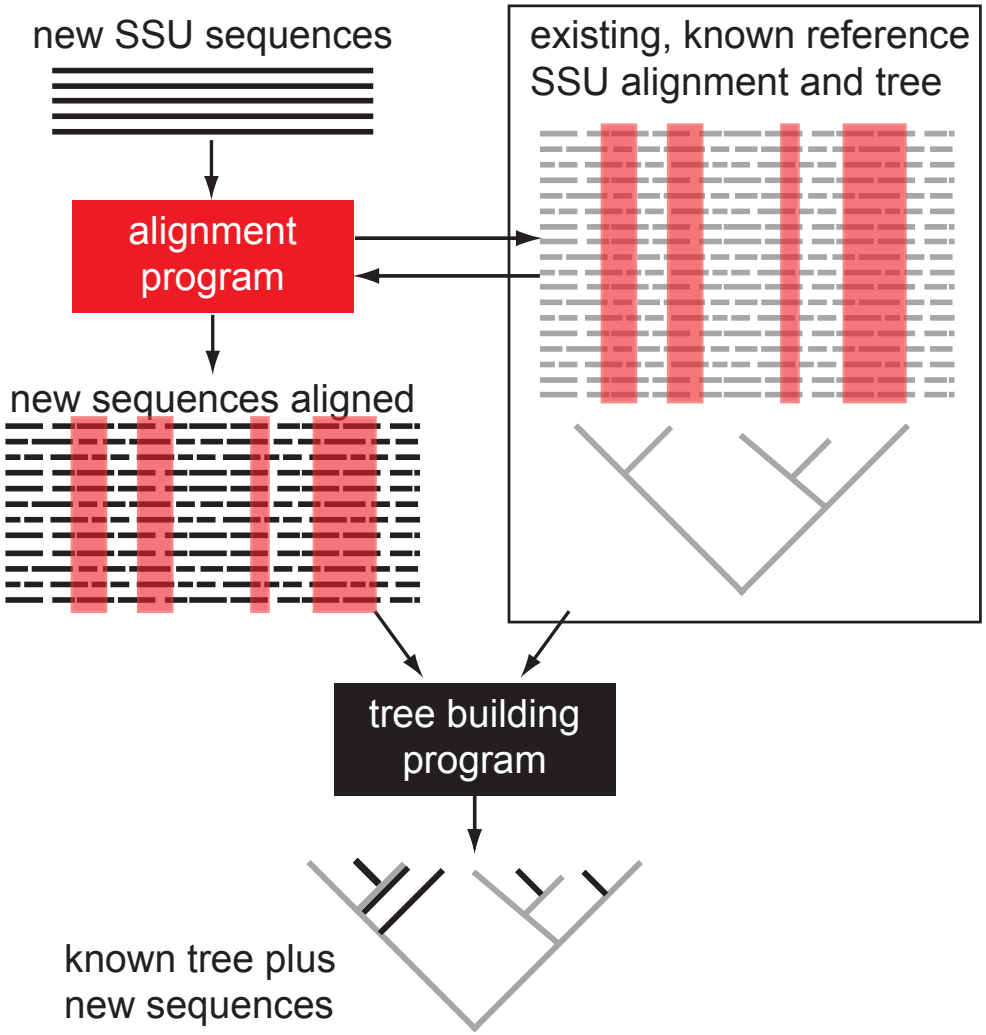
Infernal: infernal.janelia.org

# Probabilistic models allow direction calculation of useful quantities

- Posterior decoding algorithm computes the posterior probability that each nucleotide is correctly aligned given the model
  - allows HMM banding for CM alignment ($O(N^3 log(N))$ reduced to close to $O(N^2)$
  - useful for identifying and removing (masking) columns that are not reliably aligned prior to phylogenetic inference



# The comparative analysis step:
# Alignment and Phylogenetic Inference

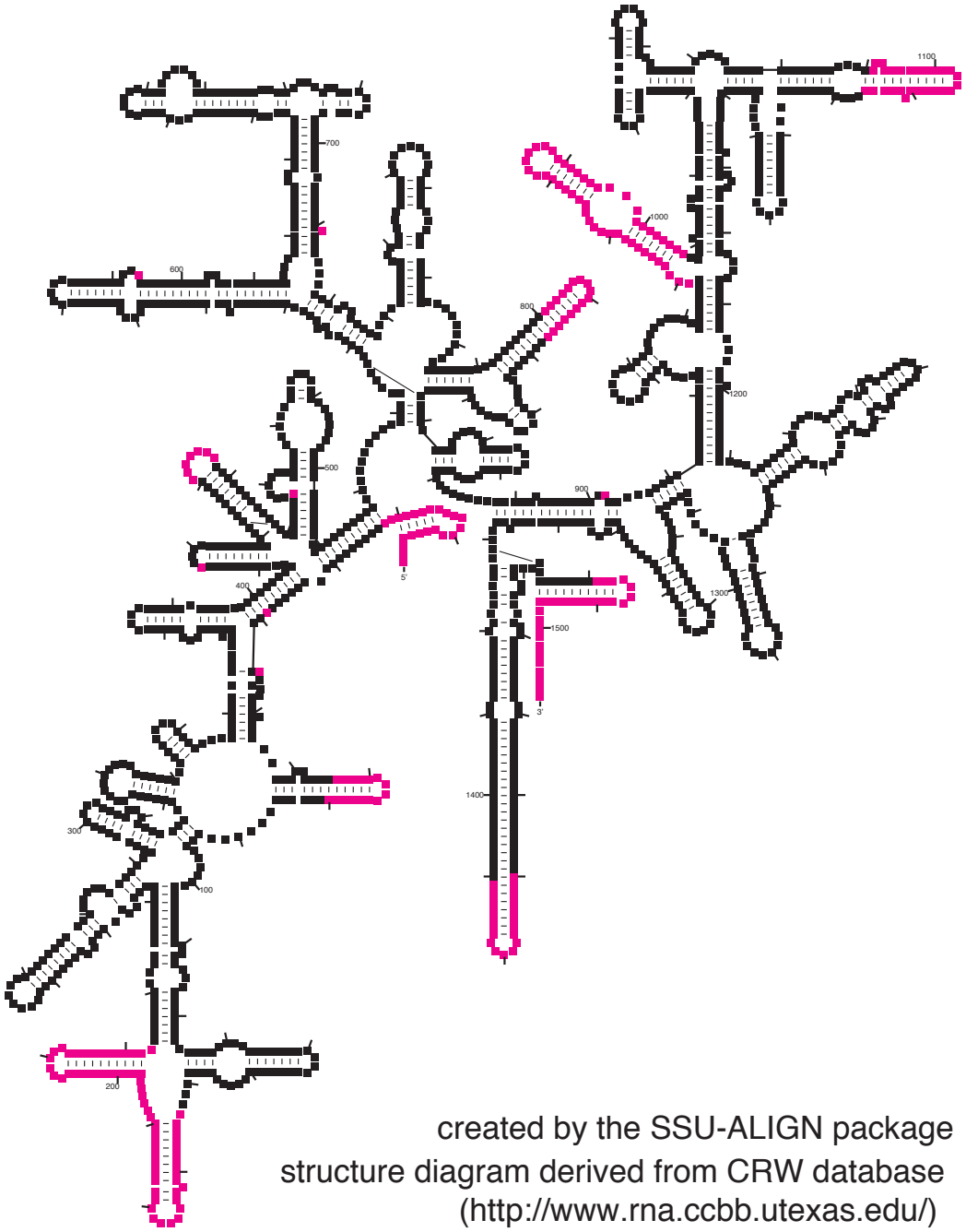



Goals of the alignment program:

accurate: because alignment errors confound phylogenetic inference

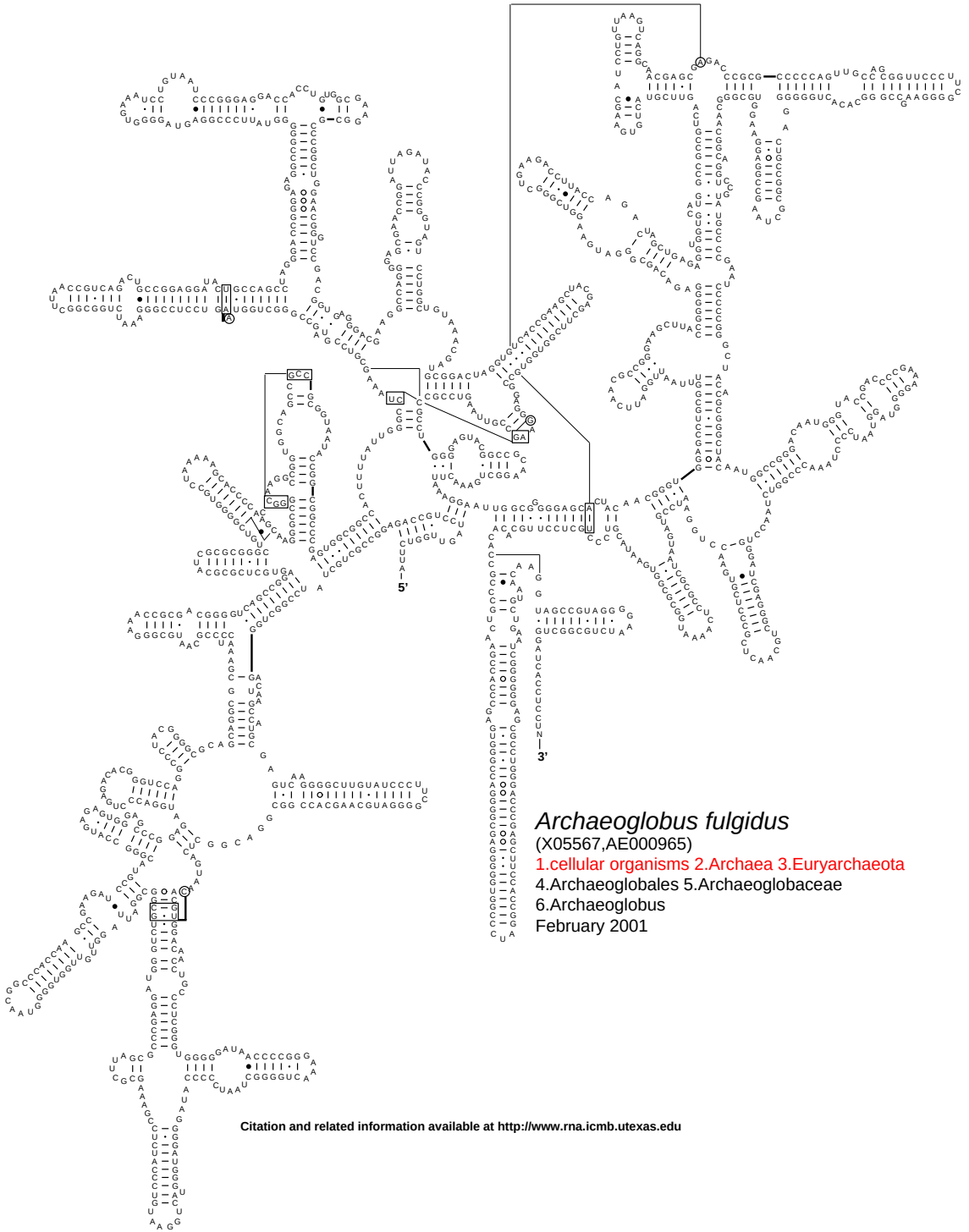
fast: to handle up to millions of seqs

Phil Hugenholtz's manually created mask imposed on archaeal SSU
black: included in alignment (1257)
pink: excluded from alignment (251)



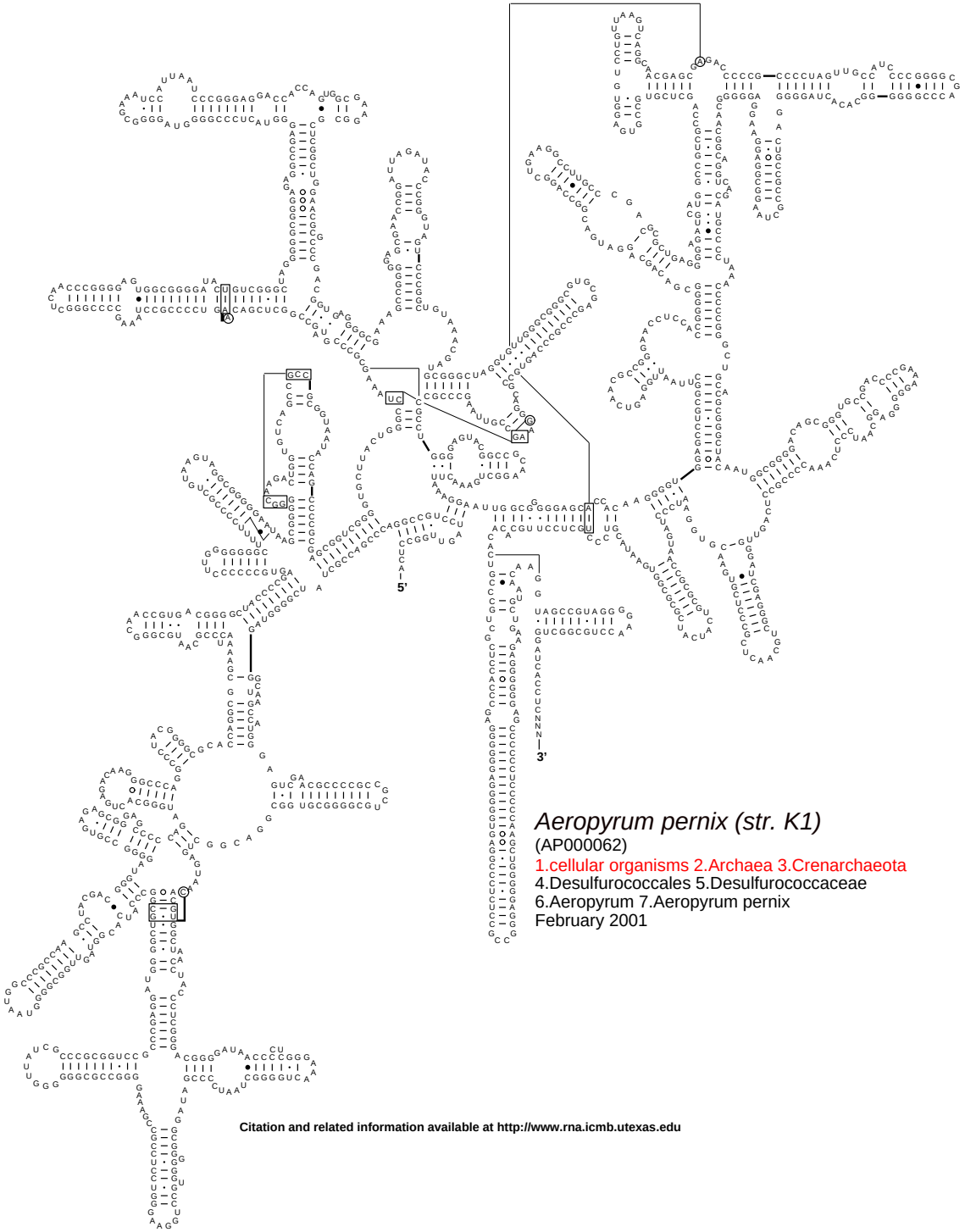

created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

# Secondary Structure: small subunit ribosomal RNA



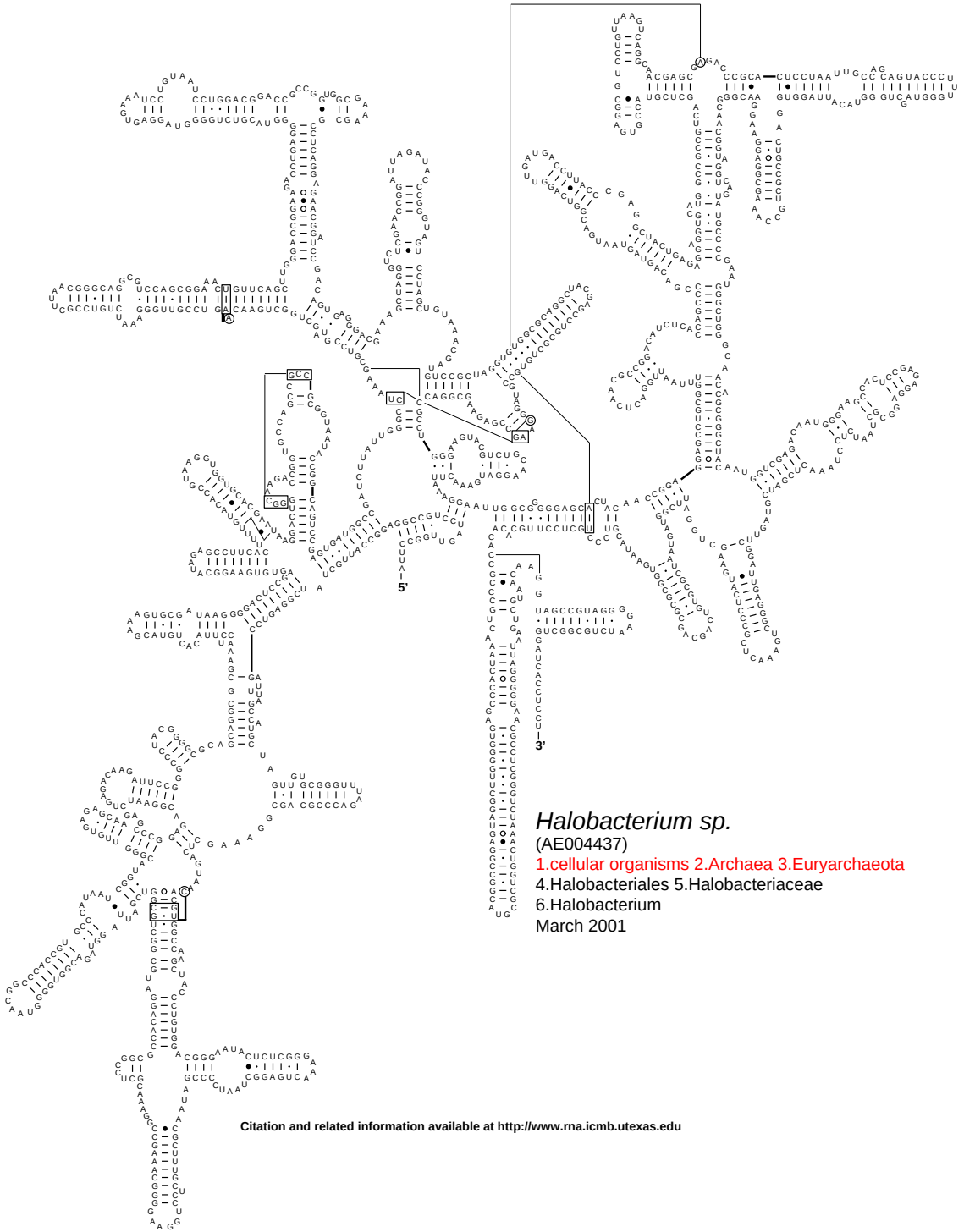

*Archaeoglobus fulgidus*
(X05567,AE000965)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Archaeoglobales 5.Archaeoglobaceae
6.Archaeoglobus
February 2001

# Secondary Structure: small subunit ribosomal RNA



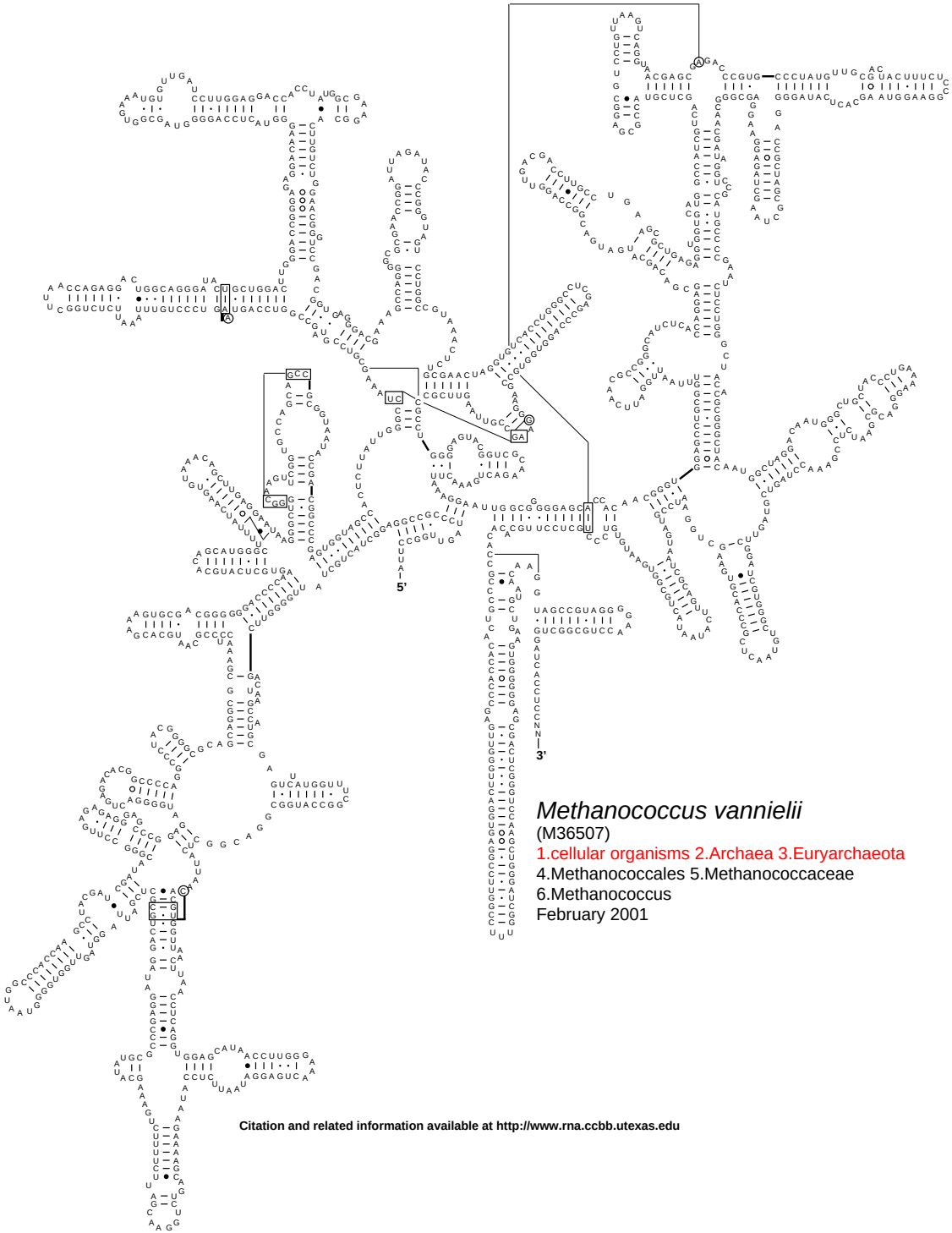

*Aeropyrum pernix (str. K1)*
(AP000062)
1.cellular organisms 2.Archaea 3.Crenarchaeota
4.Desulfurococcales 5.Desulfurococcaceae
6.Aeropyrum 7.Aeropyrum pernix
February 2001

# Secondary Structure: small subunit ribosomal RNA



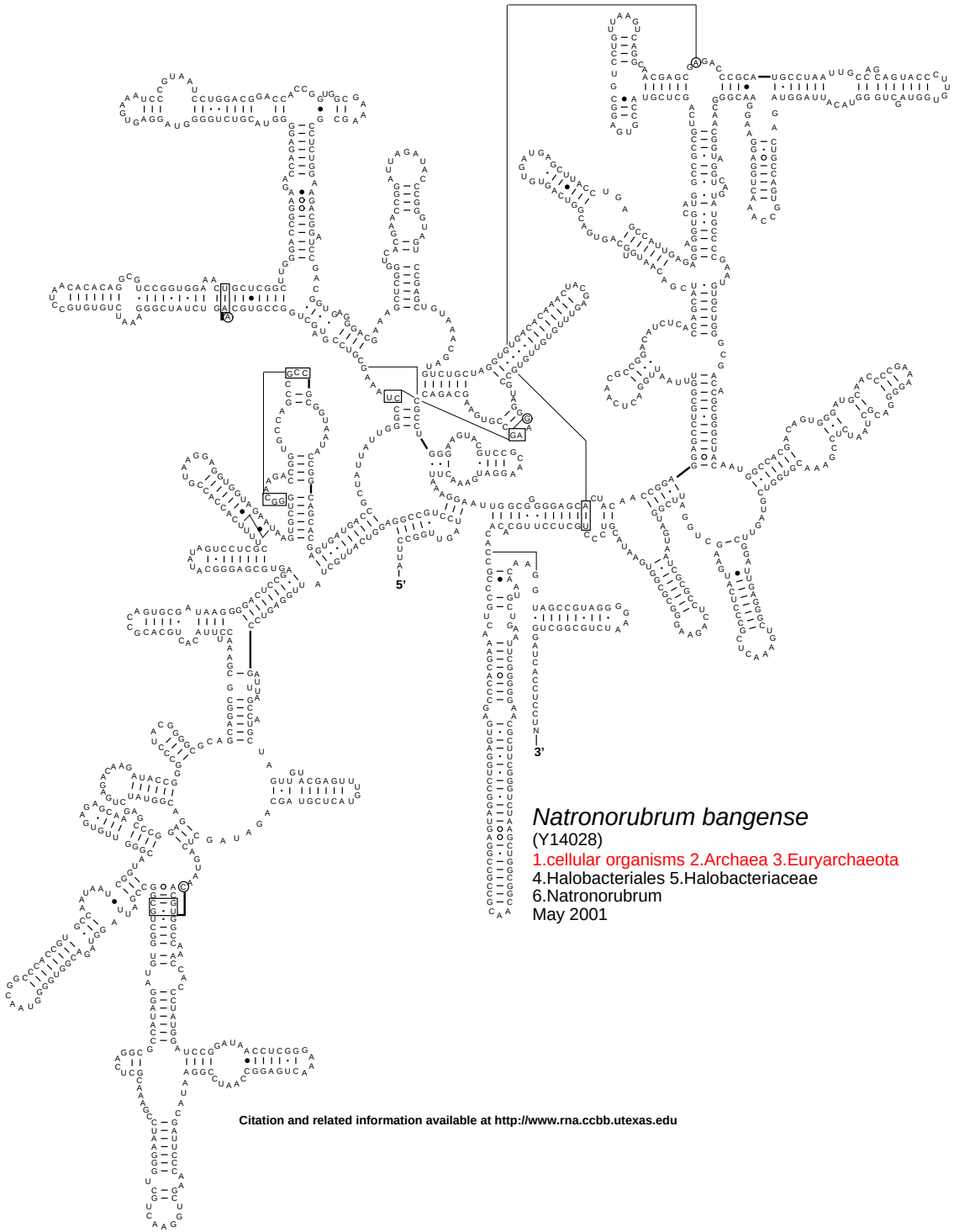

*Halobacterium sp.*
(AE004437)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Halobacteriales 5.Halobacteriaceae
6.Halobacterium
March 2001

# Secondary Structure: small subunit ribosomal RNA



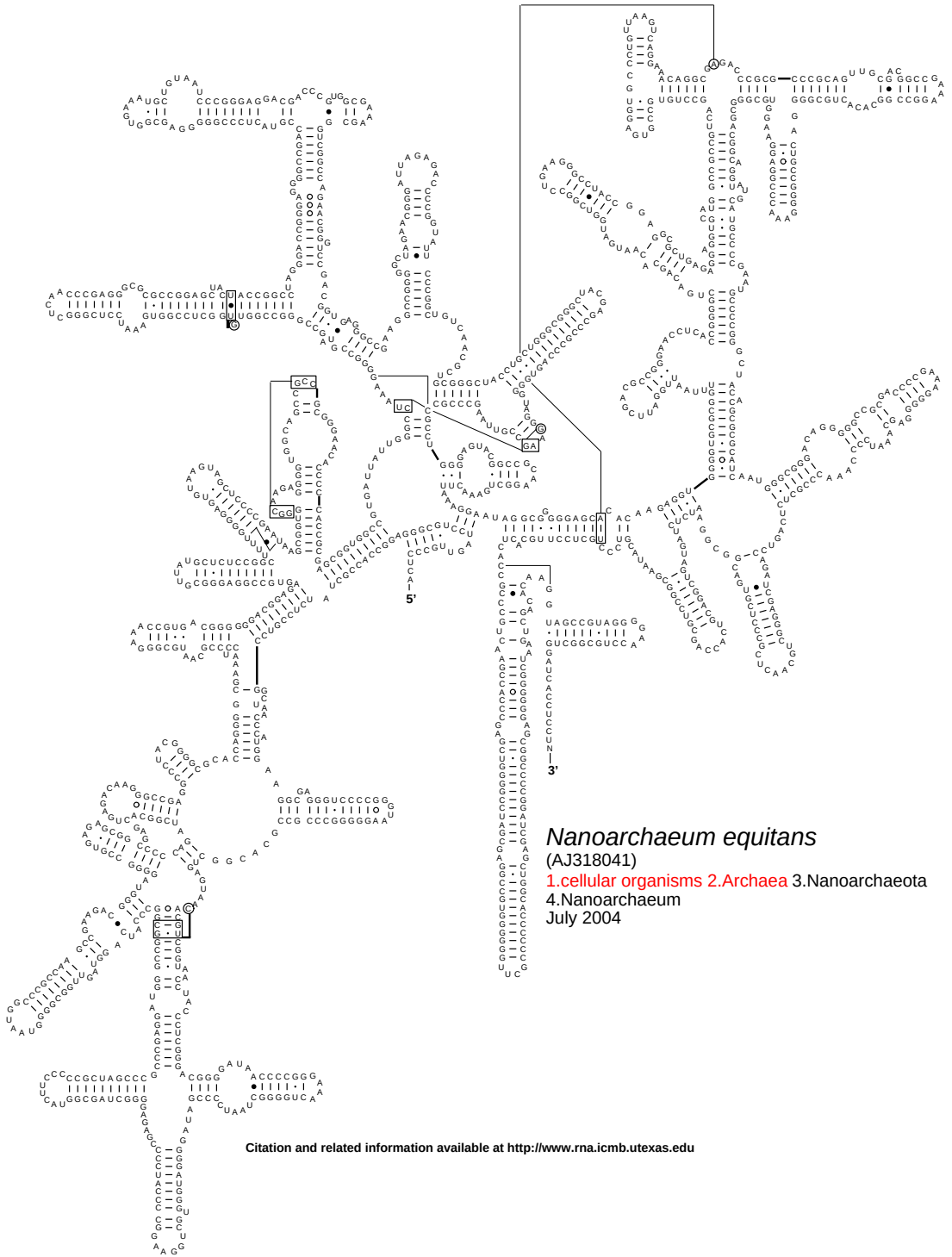

*Methanococcus vannielii*
(M36507)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Methanococcales 5.Methanococcaceae
6.Methanococcus
February 2001

# Secondary Structure: small subunit ribosomal RNA



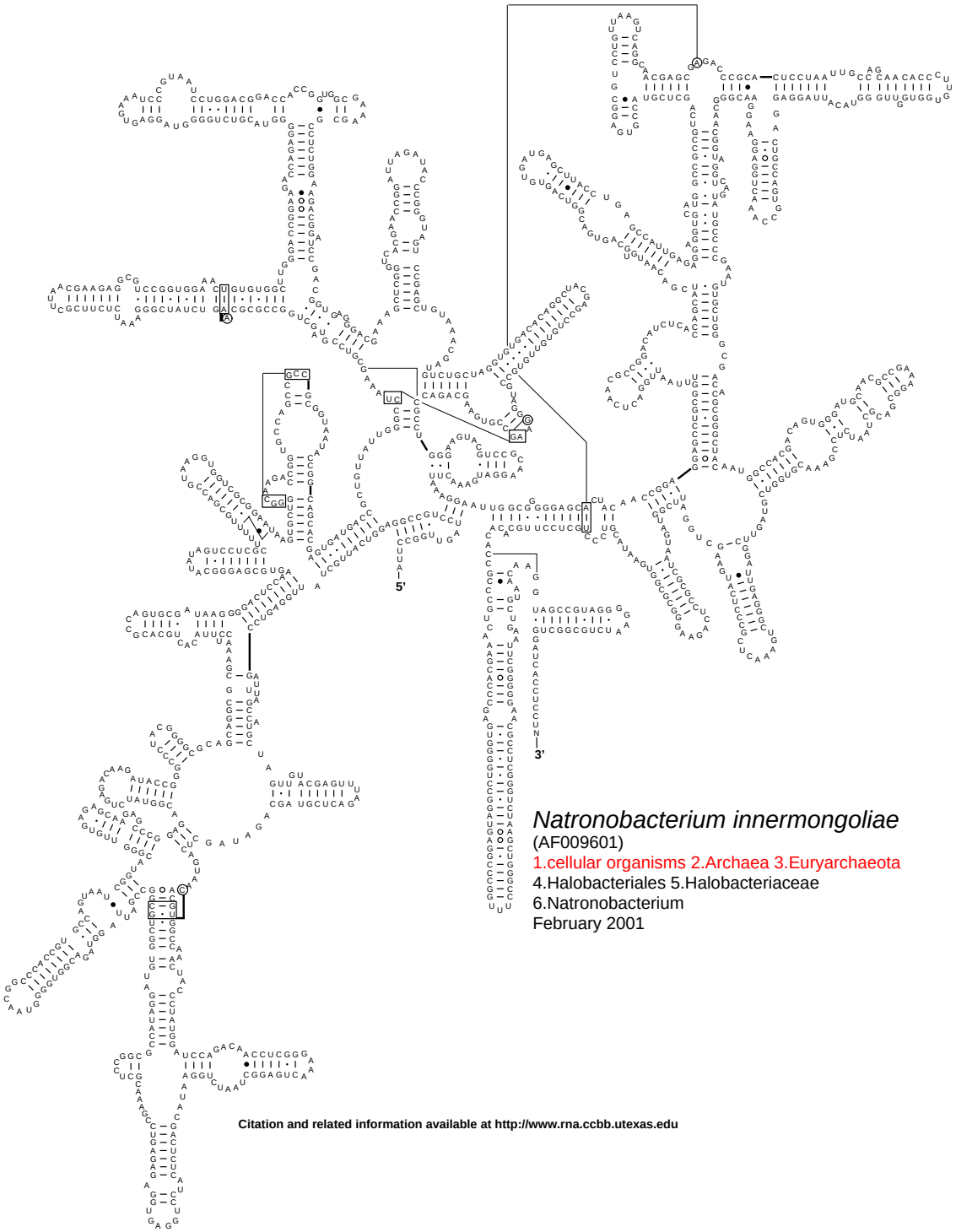

*Natronorubrum bangense*
(Y14028)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Halobacteriales 5.Halobacteriaceae
6.Natronorubrum
May 2001

# Secondary Structure: small subunit ribosomal RNA



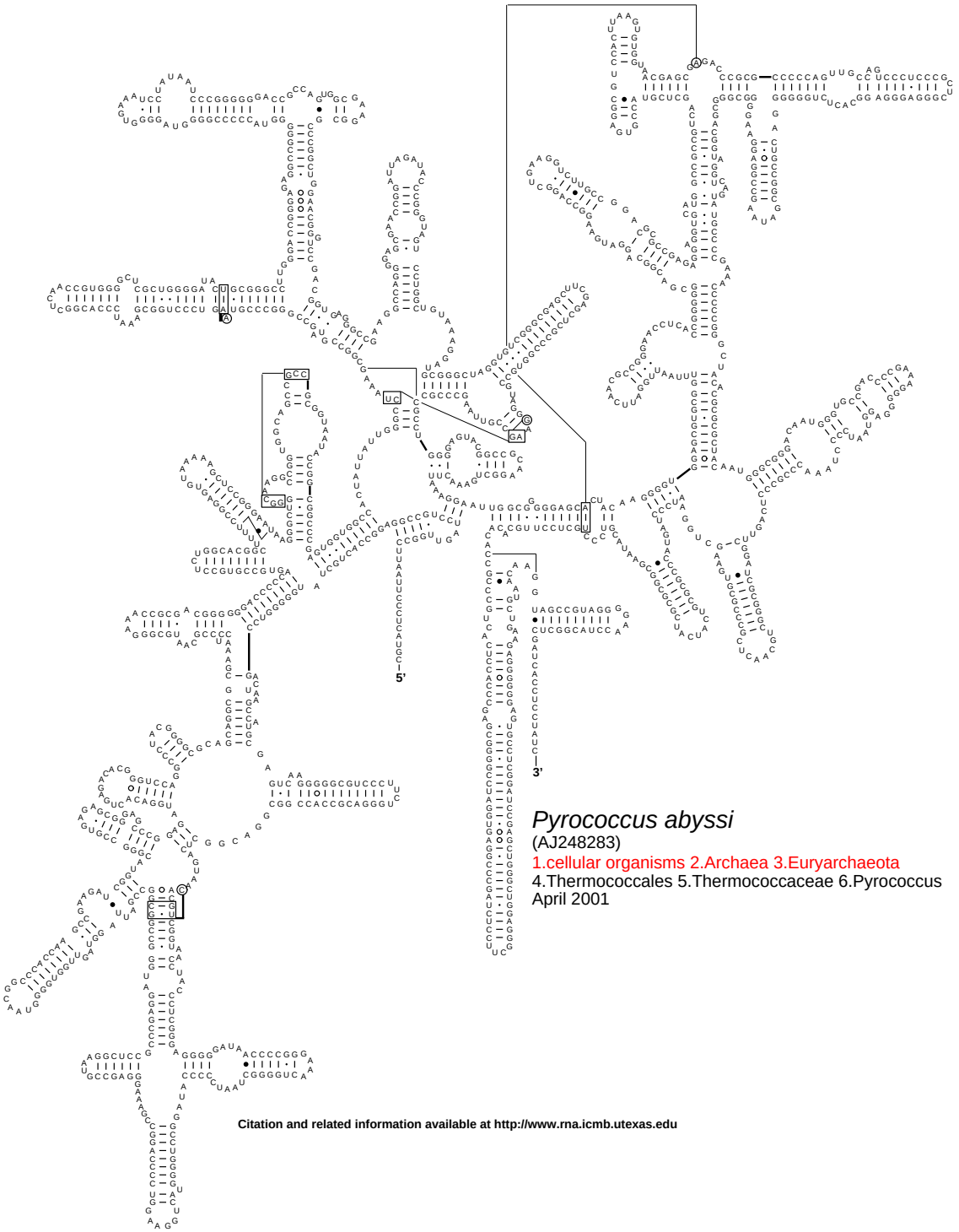

*Nanoarchaeum equitans*
(AJ318041)
1.cellular organisms 2.Archaea 3.Nanoarchaeota
4.Nanoarchaeum
July 2004

# Secondary Structure: small subunit ribosomal RNA



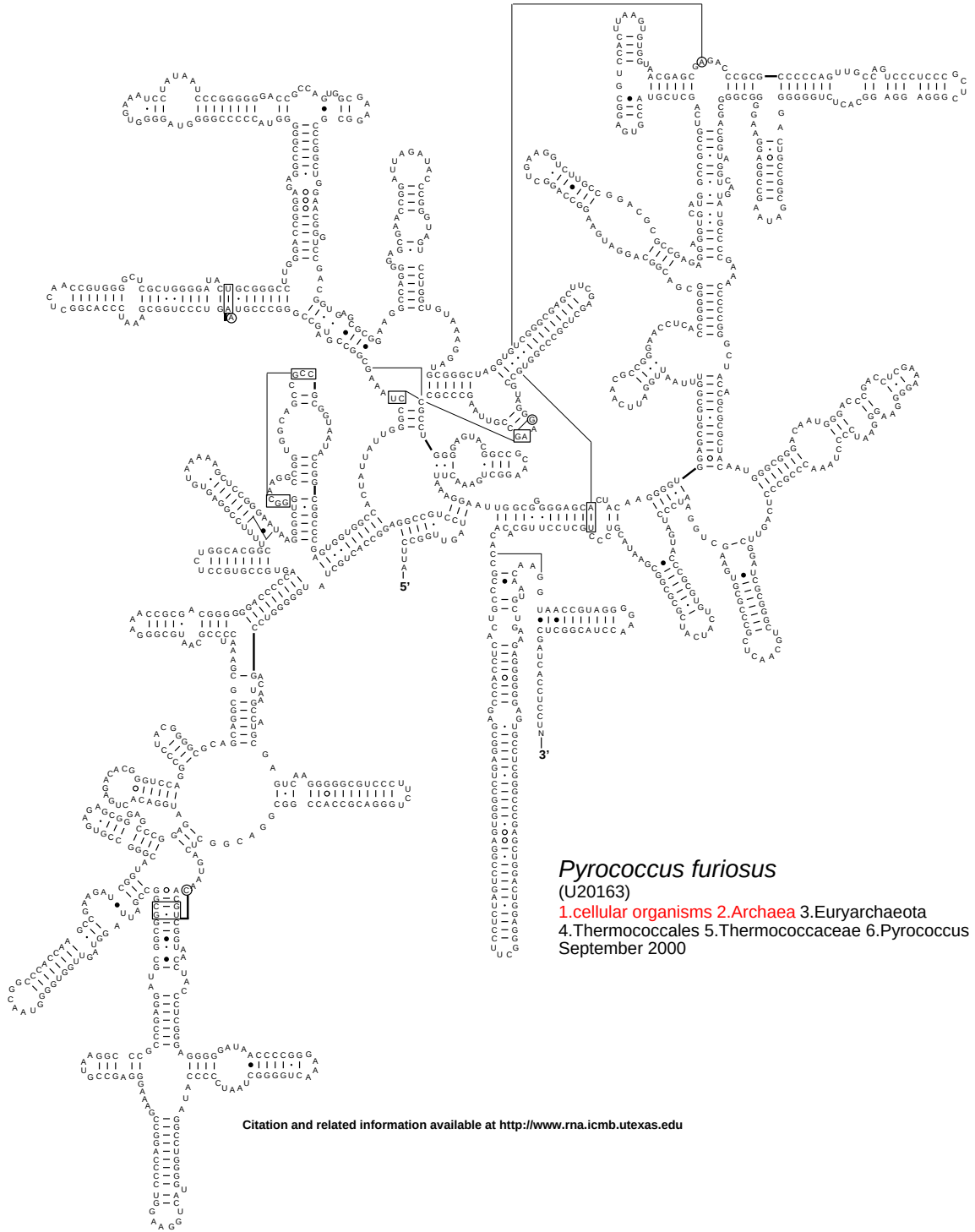

*Natronobacterium innermongoliae*
(AF009601)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Halobacteriales 5.Halobacteriaceae
6.Natronobacterium
February 2001

# Secondary Structure: small subunit ribosomal RNA



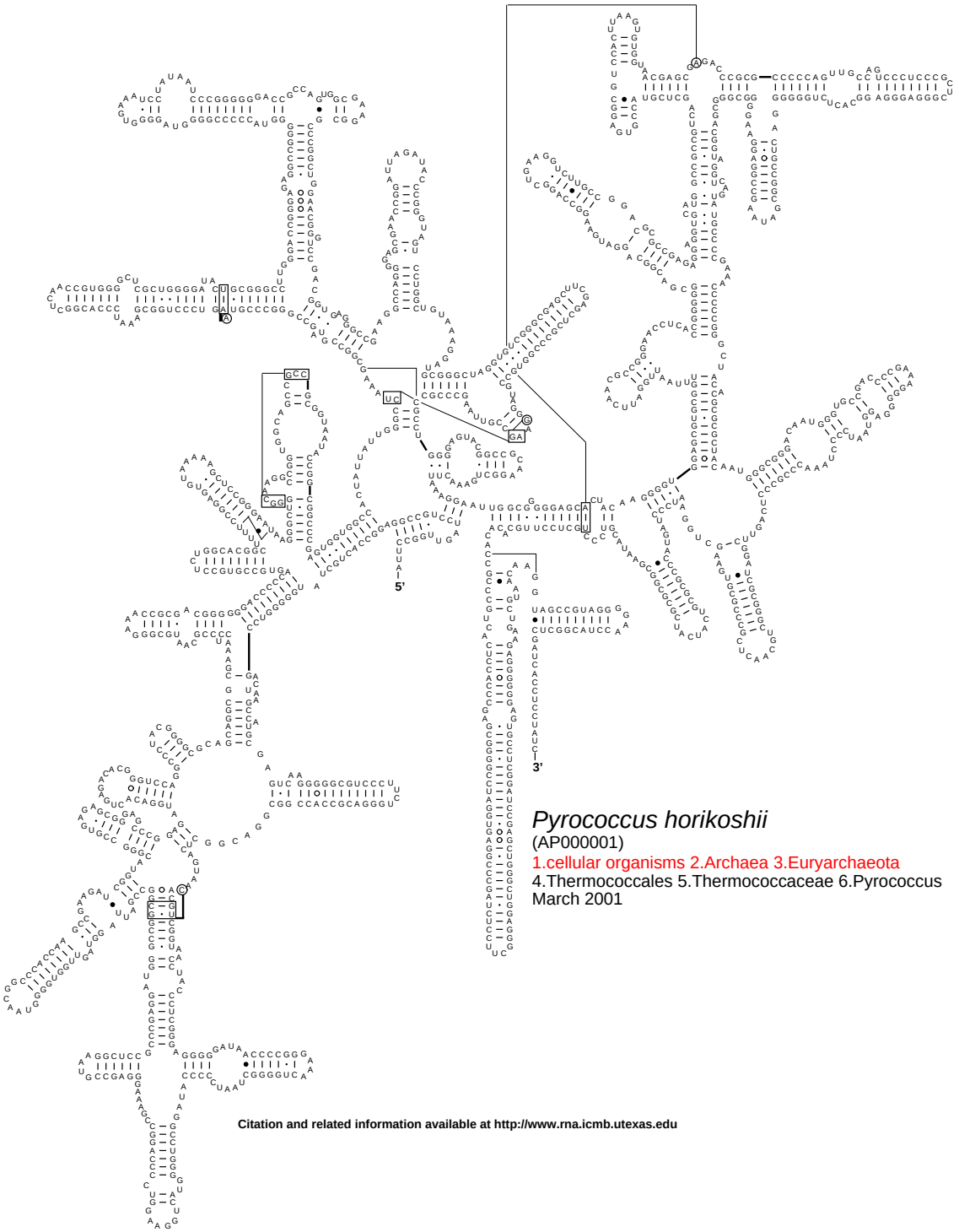

*Pyrococcus abyssi*
(AJ248283)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermococcales 5.Thermococcaceae 6.Pyrococcus
April 2001

# Secondary Structure: small subunit ribosomal RNA



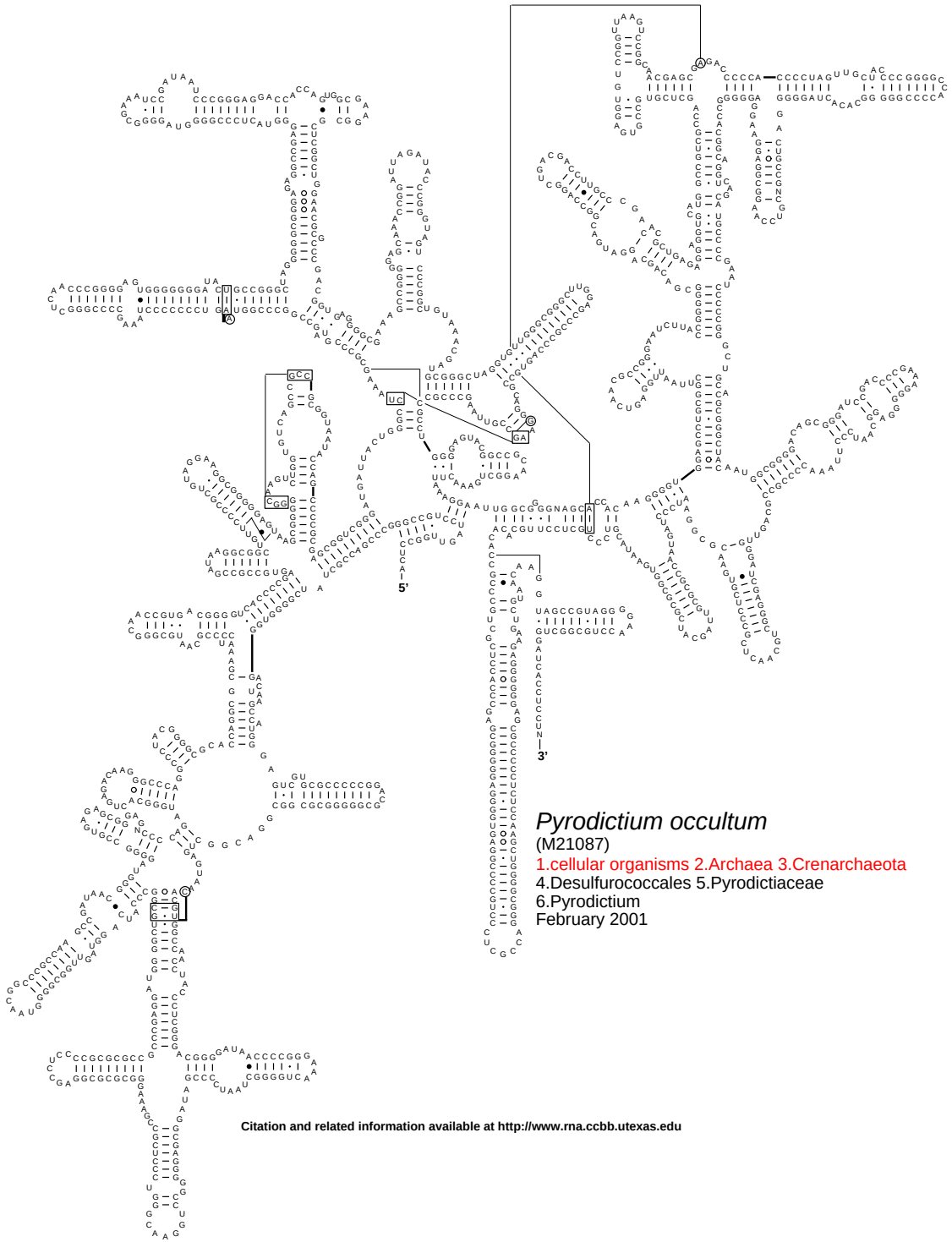

*Pyrococcus furiosus*
(U20163)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermococcales 5.Thermococcaceae 6.Pyrococcus
September 2000

# Secondary Structure: small subunit ribosomal RNA



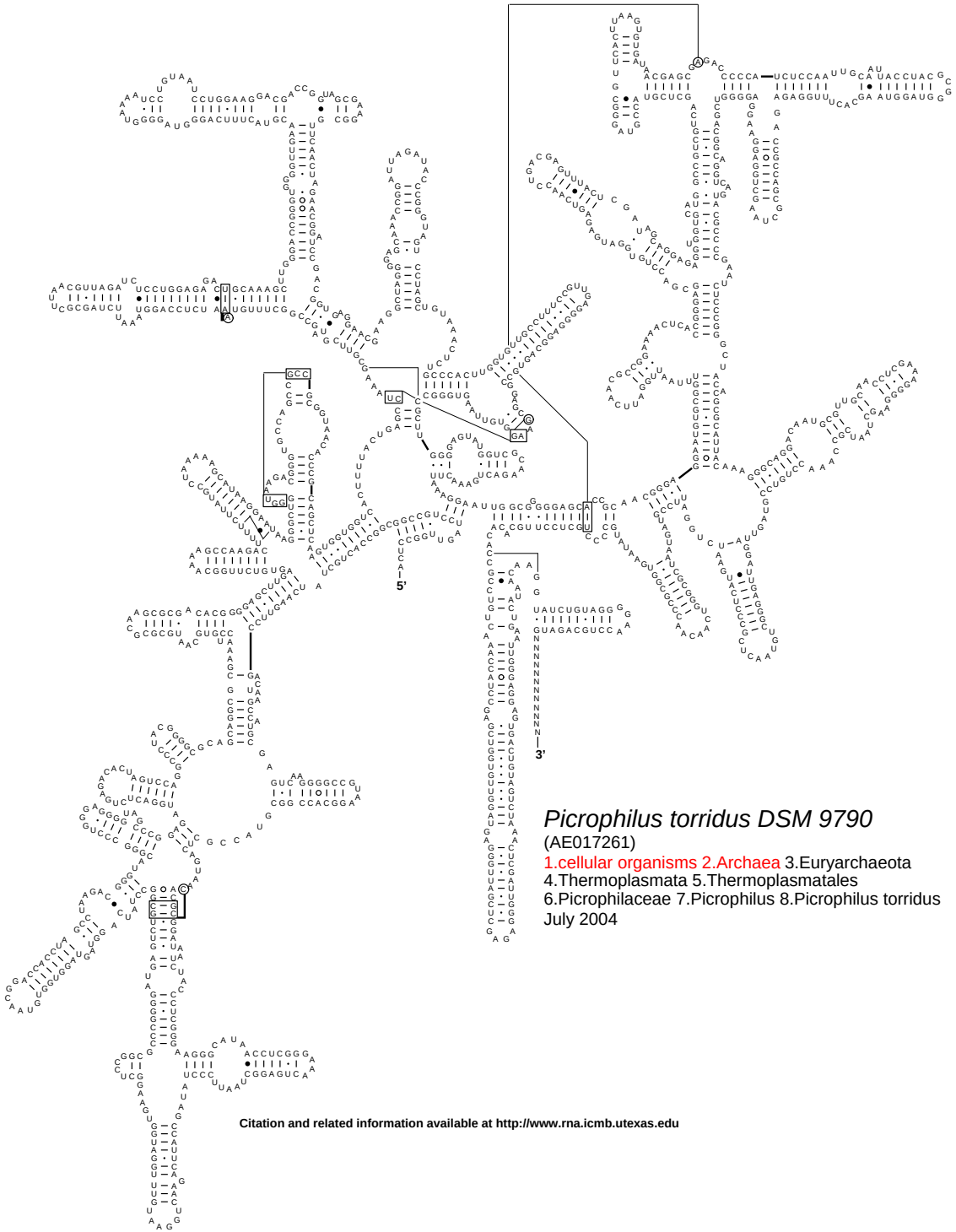

*Pyrococcus horikoshii*
(AP000001)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermococcales 5.Thermococcaceae 6.Pyrococcus
March 2001

# Secondary Structure: small subunit ribosomal RNA




*Pyrodictium occultum*
(M21087)
1.cellular organisms 2.Archaea 3.Crenarchaeota
4.Desulfurococcales 5.Pyrodictiaceae
6.Pyrodictium
February 2001

# Secondary Structure: small subunit ribosomal RNA

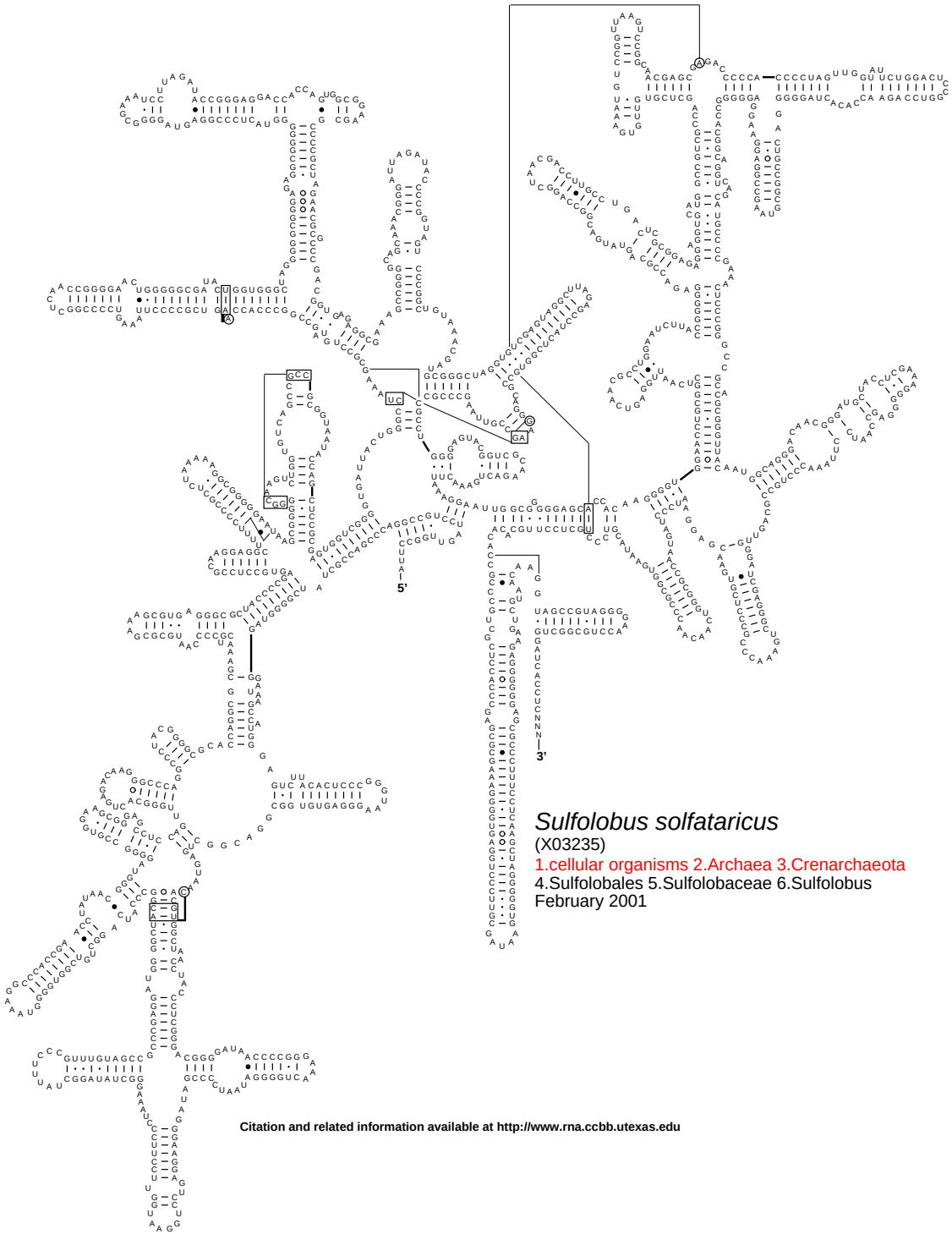



*Picrophilus torridus DSM 9790*

(AE017261)

1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermoplasmata 5.Thermoplasmatales
6.Picrophilaceae 7.Picrophilus 8.Picrophilus torridus
July 2004

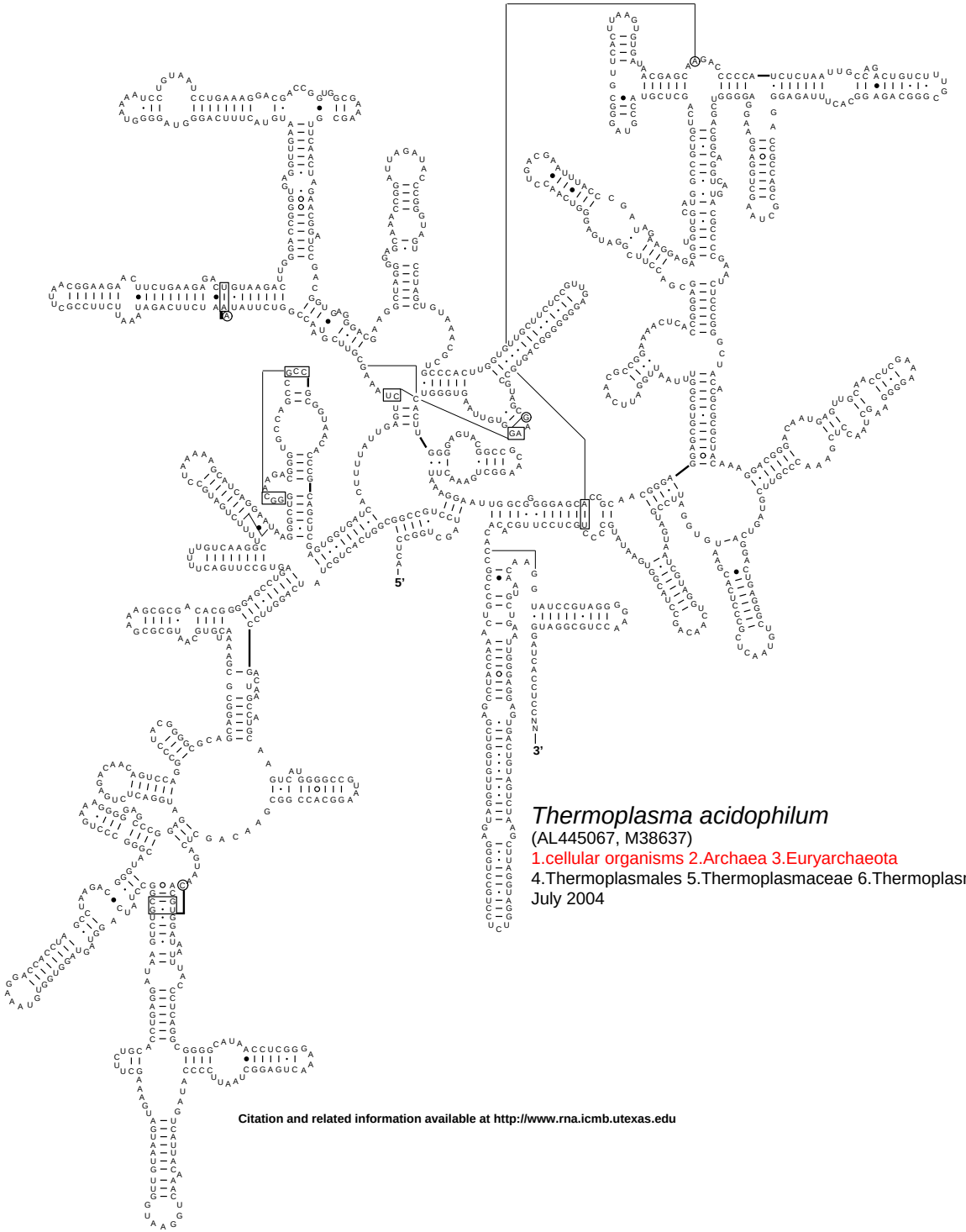
# Secondary Structure: small subunit ribosomal RNA




*Sulfolobus solfataricus*
(X03235)
1.cellular organisms 2.Archaea 3.Crenarchaeota
4.Sulfolobales 5.Sulfolobaceae 6.Sulfolobus
February 2001

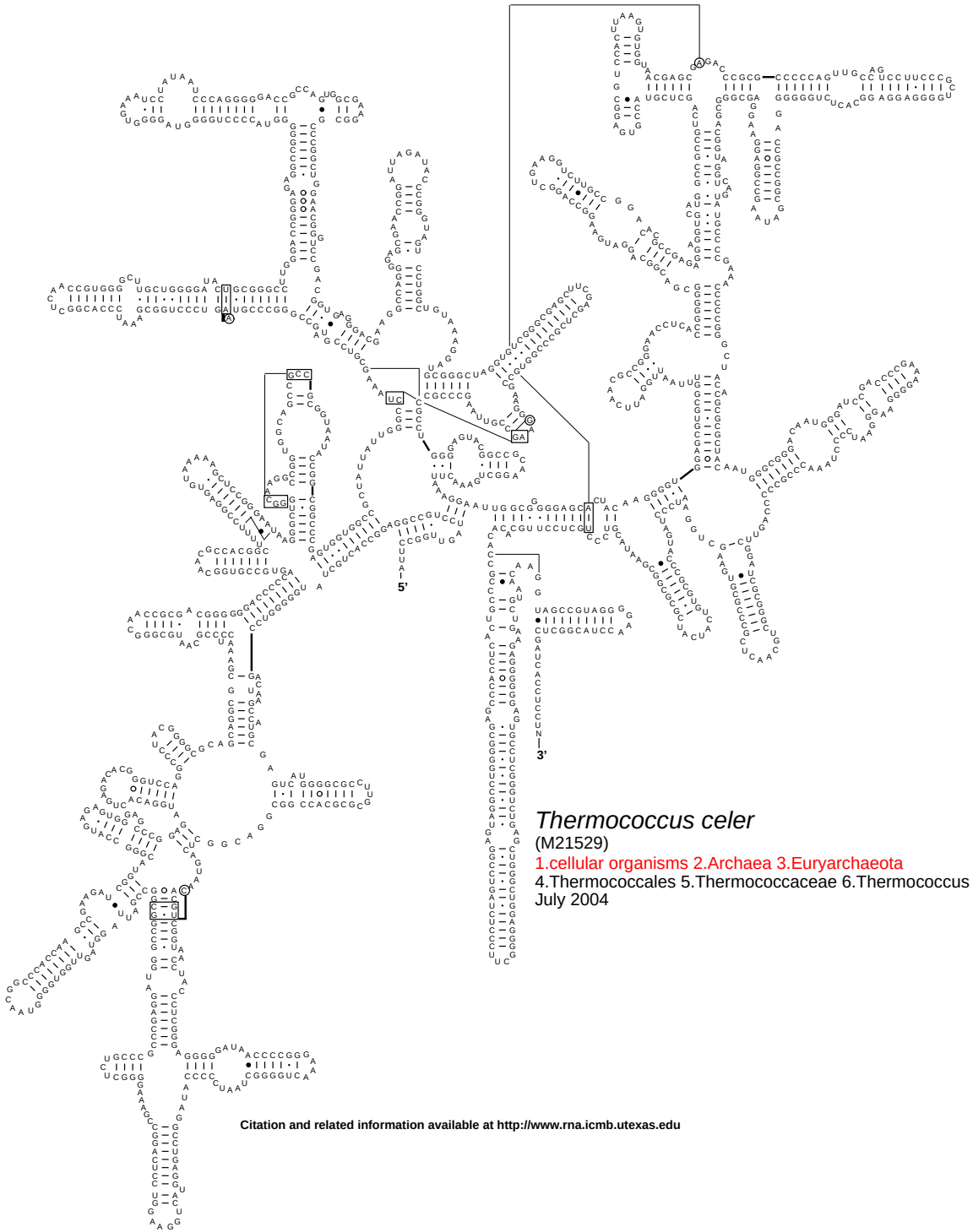
**Citation and related information available at http://www.rna.ccbb.utexas.edu**

# Secondary Structure: small subunit ribosomal RNA




*Thermoplasma acidophilum*
(AL445067, M38637)
1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermoplasmales 5.Thermoplasmaceae 6.Thermoplasm
July 2004

# Secondary Structure: small subunit ribosomal RNA



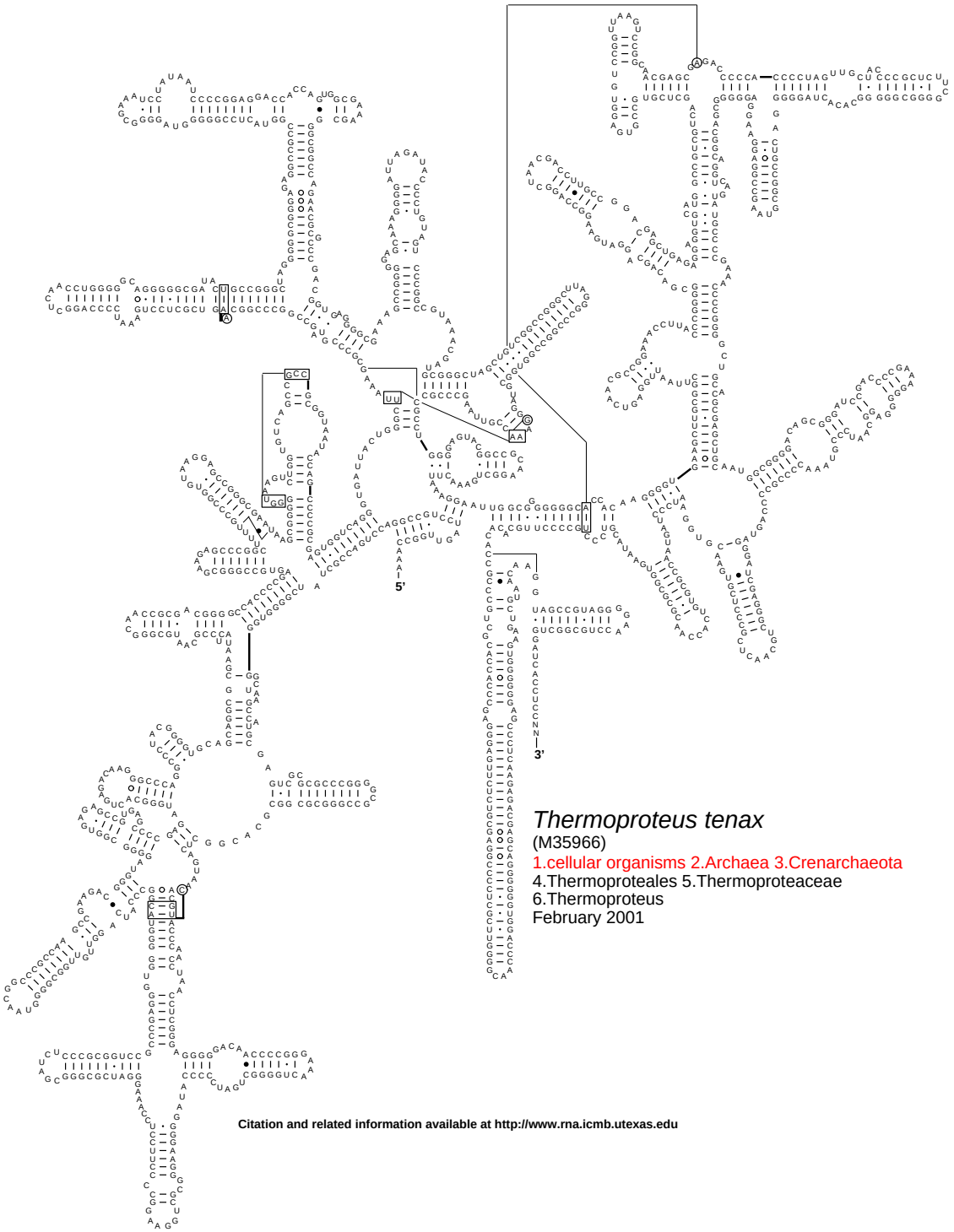

*Thermococcus celer*

(M21529)

1.cellular organisms 2.Archaea 3.Euryarchaeota
4.Thermococcales 5.Thermococcaceae 6.Thermococcus

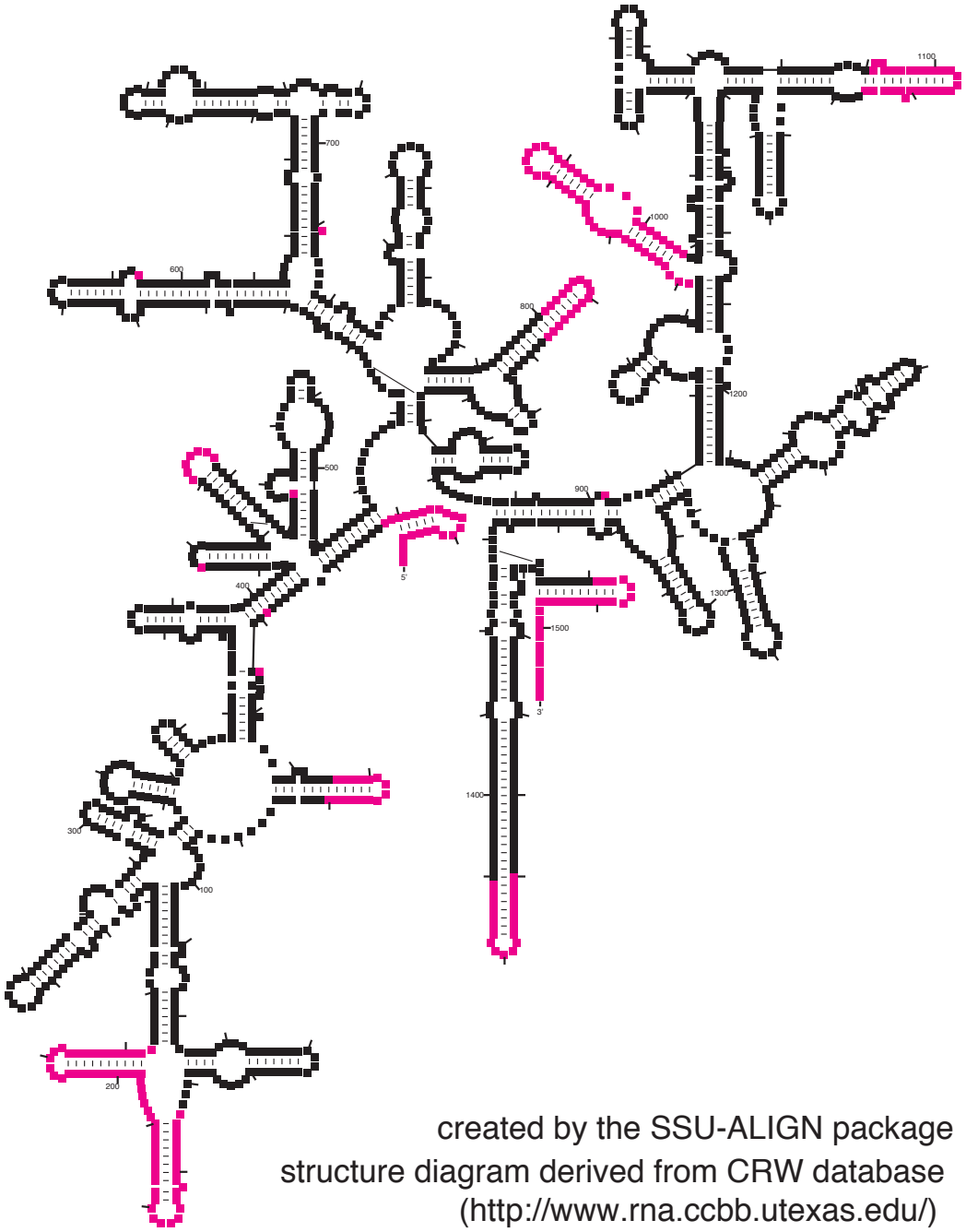
July 2004

# Secondary Structure: small subunit ribosomal RNA



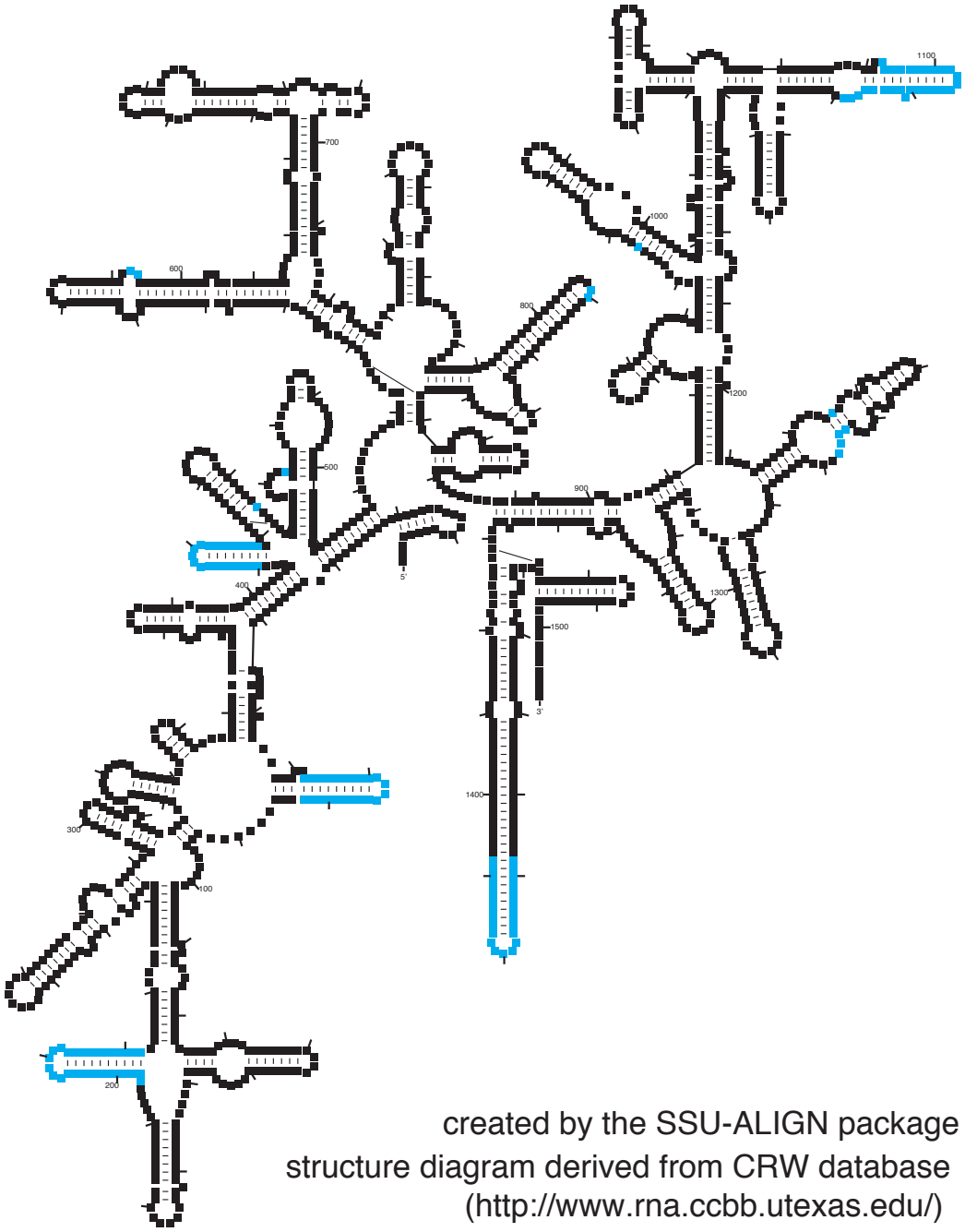

*Thermoproteus tenax*
(M35966)
1.cellular organisms 2.Archaea 3.Crenarchaeota
4.Thermoproteales 5.Thermoproteaceae
6.Thermoproteus
February 2001

Phil Hugenholtz's manually created mask imposed on archaeal SSU
black: included in alignment (1257)
pink: excluded from alignment (251)



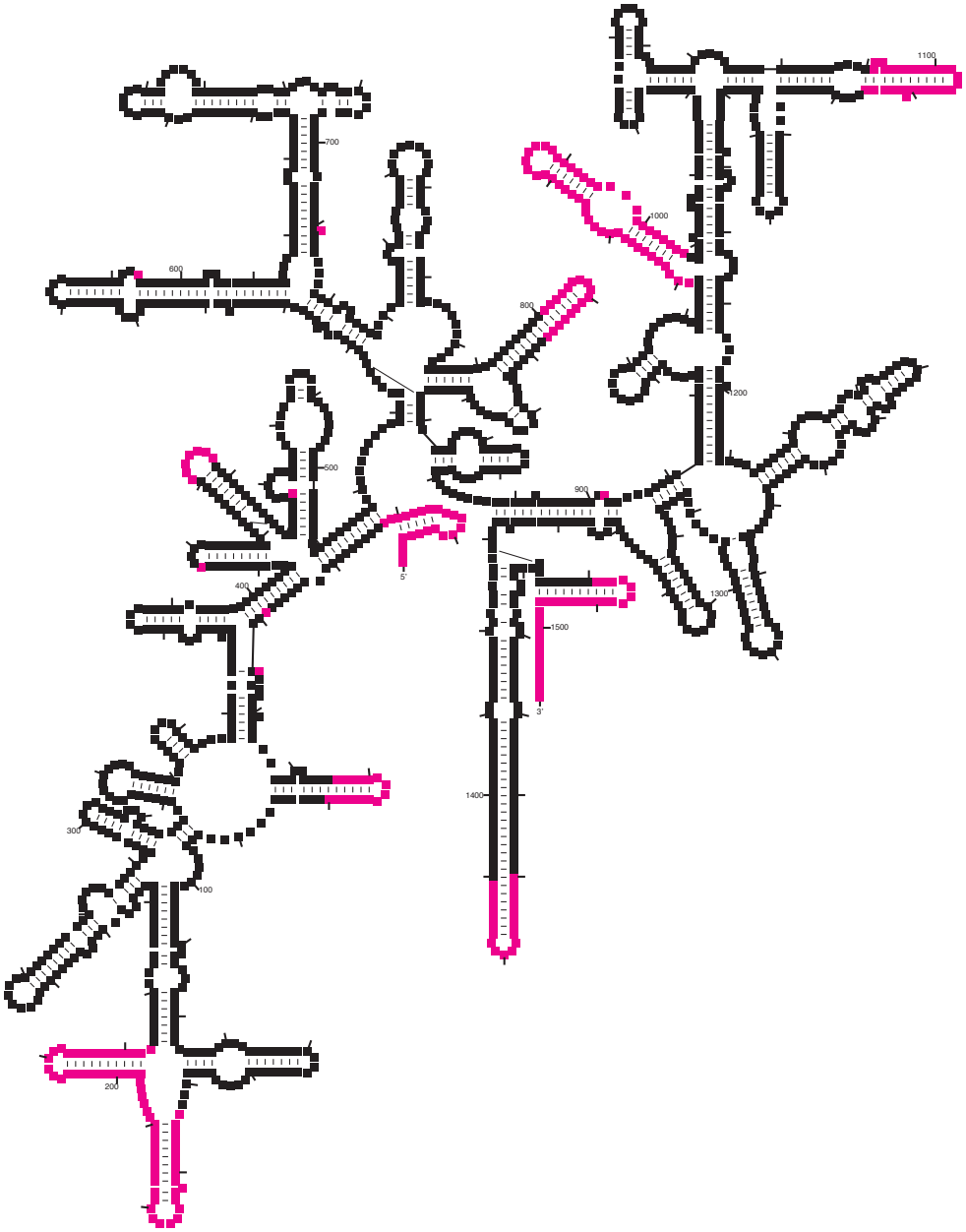

created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

Posterior probability based archaeal SSU mask
black: included in alignment (1376)
blue: excluded from alignment (132)

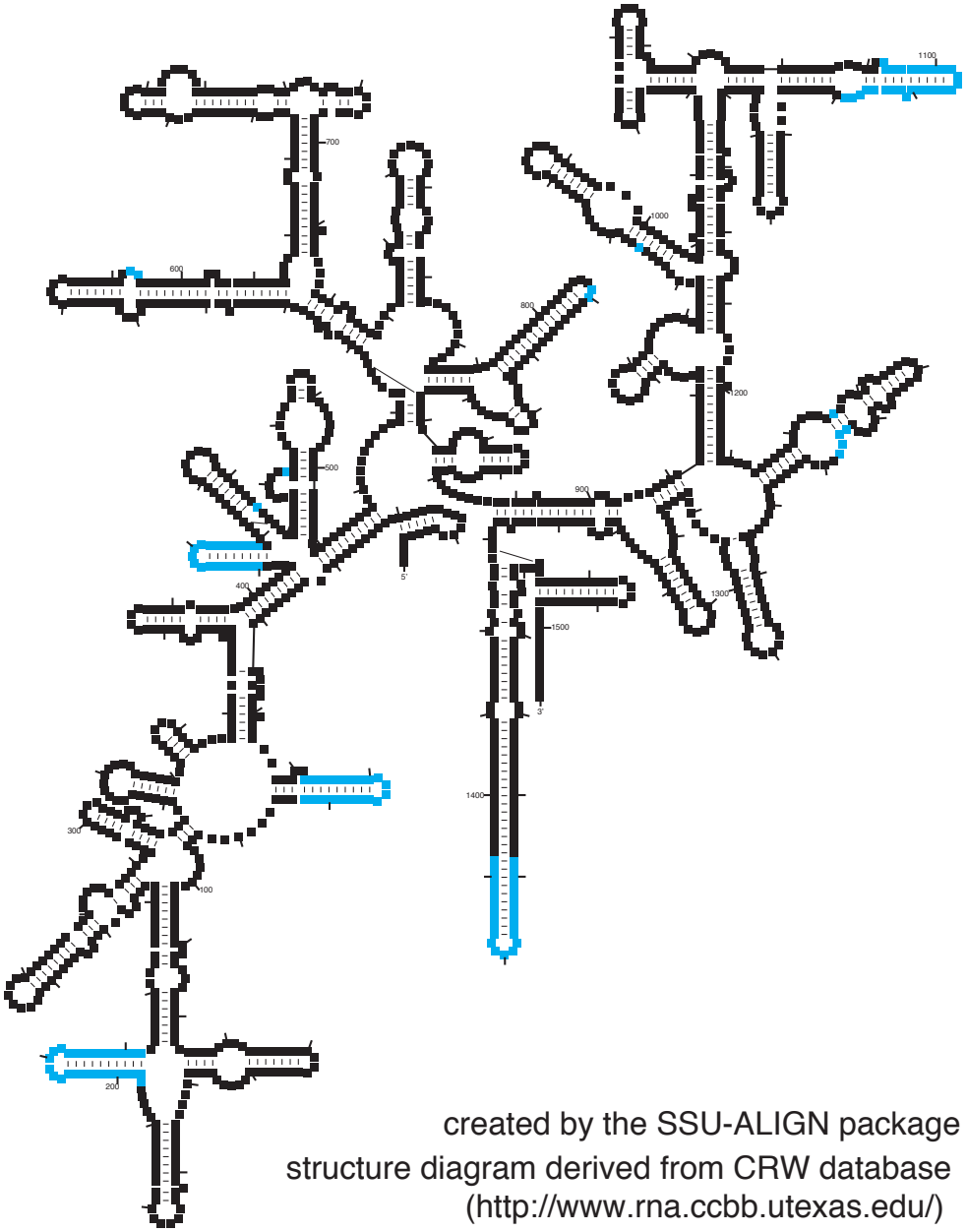



created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

Phil Hugenholtz's manually created mask imposed on archaeal SSU
black: included in alignment (1257)
pink: excluded from alignment (251)

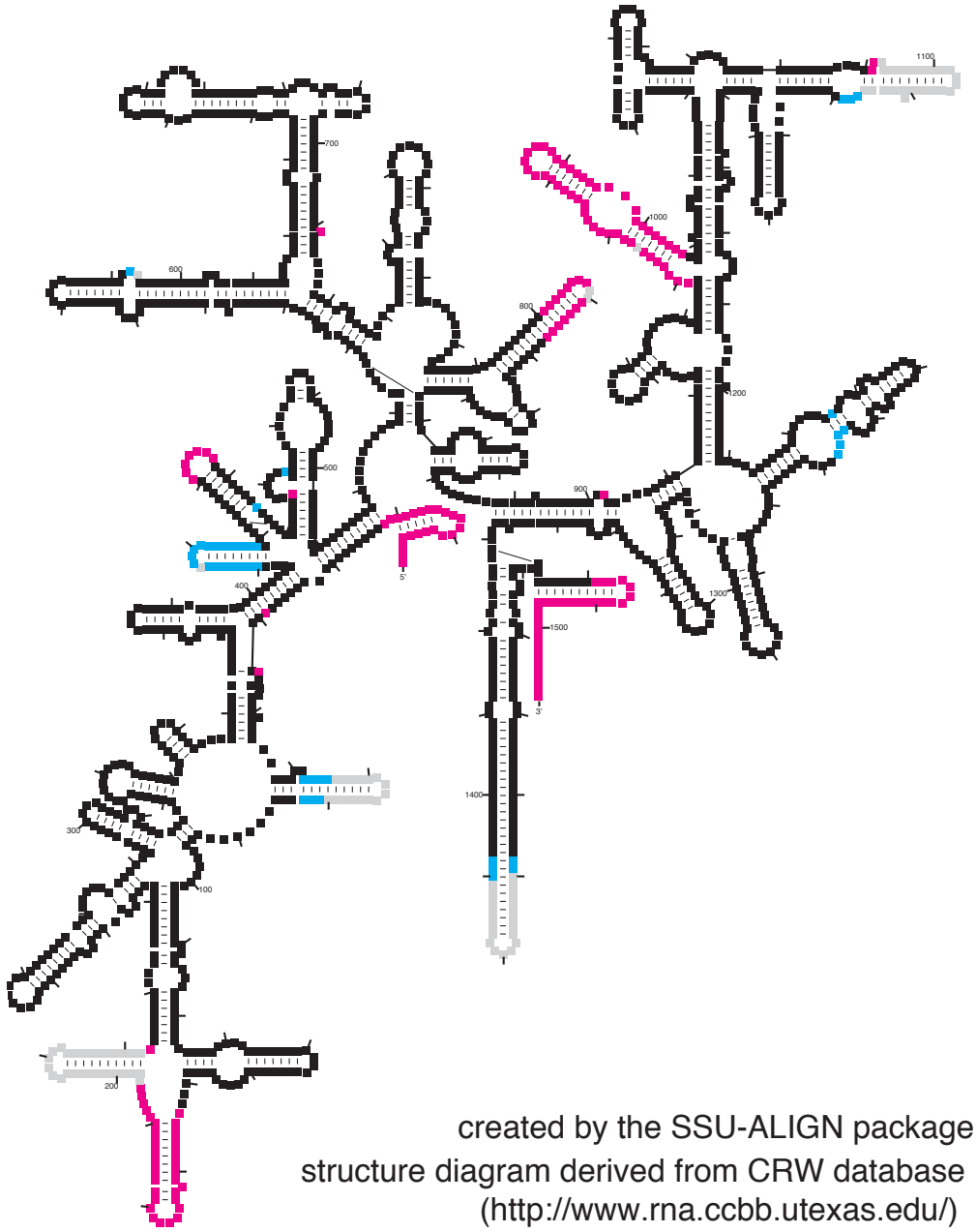


Posterior probability based archaeal SSU mask
black: included in alignment (1376)
blue: excluded from alignment (132)



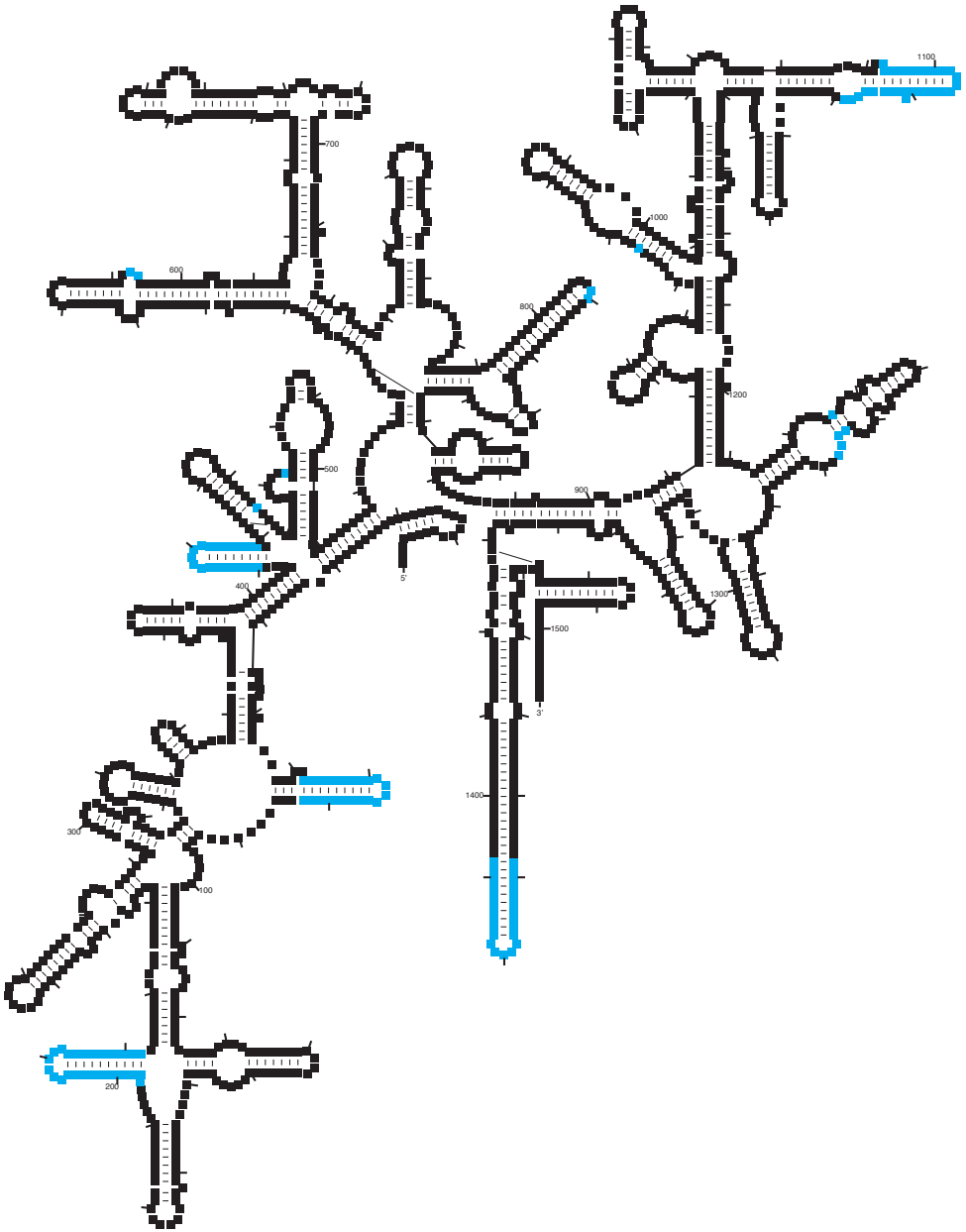
created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

Comparison of manual and posterior-probability-based masks
black: included in both alignment (1216)
pink: excluded only from manual mask (160)
blue: excluded only from PP mask (41)
grey: excluded from both masks (91)

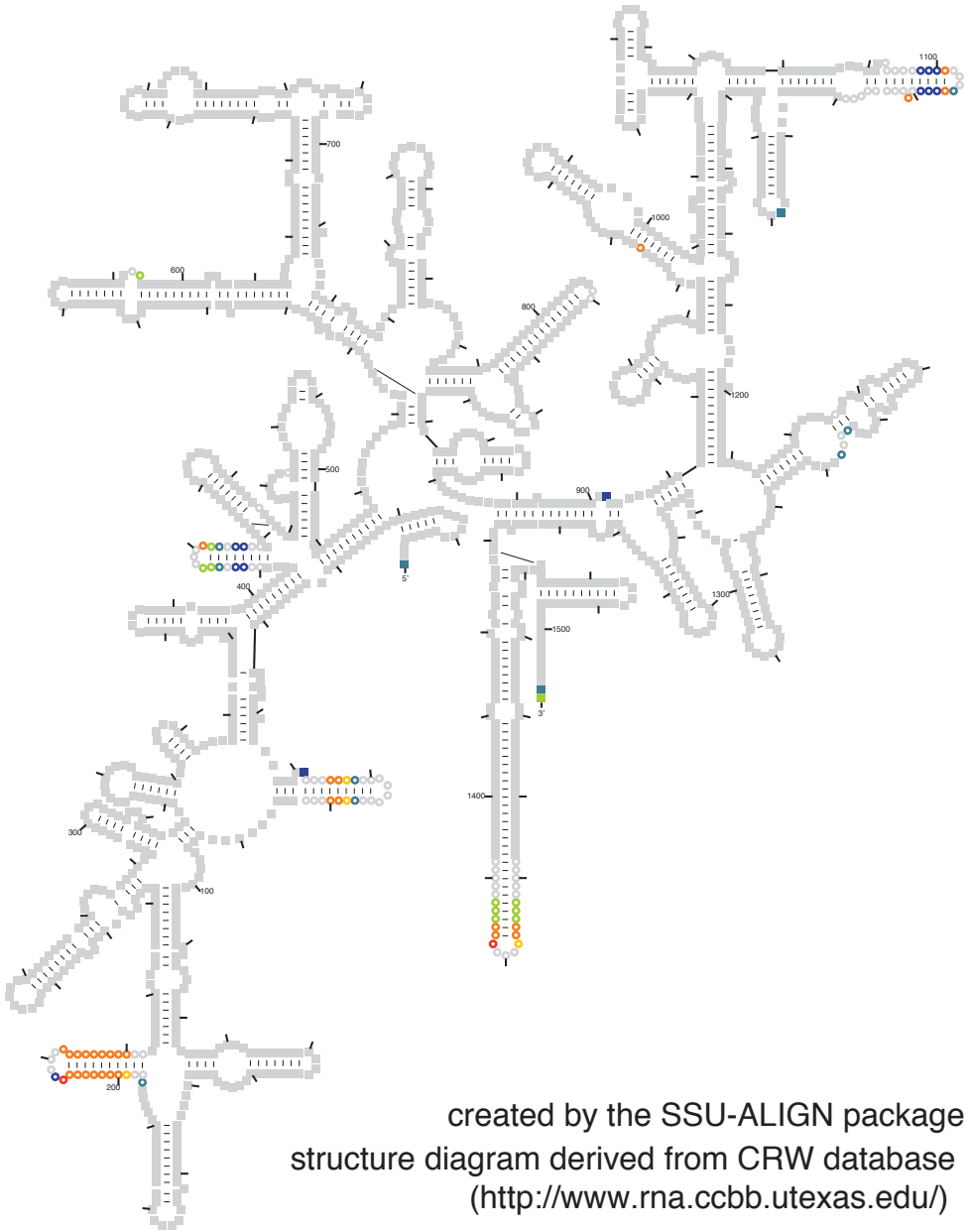



created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

Posterior probability based archaeal SSU mask
black: included in alignment (1376)
blue: excluded from alignment (132)




Probability-based mask colored by deletion frequency
grey: zero to very few deletions (1370/1376)
blue: few deletions ..... red: many deletions
circles indicate excluded positions



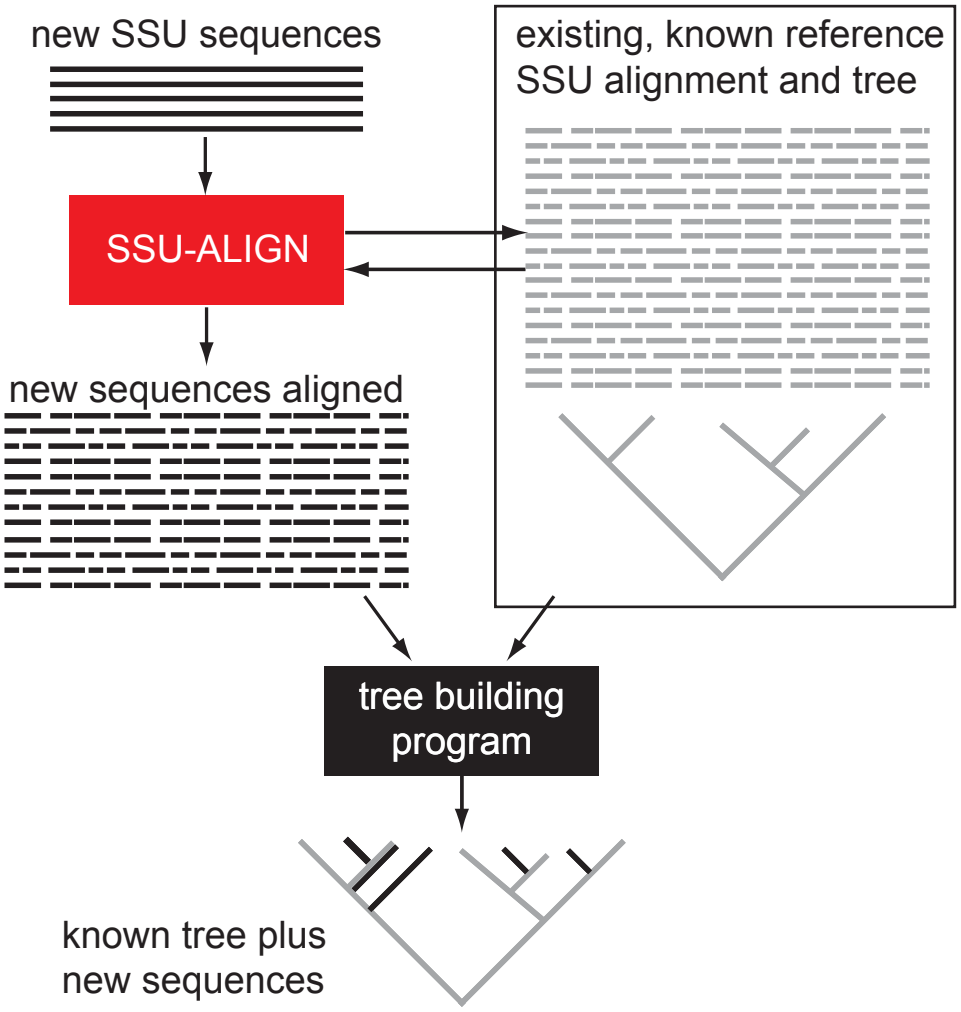

created by the SSU-ALIGN package
structure diagram derived from CRW database
(http://www.rna.ccbb.utexas.edu/)

## HMM banding accelerates CM alignment 1000-fold

| | alignment accuracy | time (sec/seq) |
|---|---|---|
| Muscle-3.8.31 (*de novo*) | 95.4% | 0.49 |
| HMMER3 (HMMs) | 96.8% | 0.04 |
| Infernal 1.1 (CMs) | 98.1% | 0.50 |
| Infernal 1.1 (CMs) posterior probability masked (1302/1530 columns) | 99.5% | 0.50 |

**Infernal produces alignment that are very similar to manually refined alignments.**

# SSU-ALIGN: structural alignment of SSU rRNAs using CMs




**Goals of the alignment program:**

- accurate: because alignment errors confound phylogenetic inference
- scalable to handle up to millions of seqs and fast:

**SSU-ALIGN**

Includes Infernal CMs for archaeal, bacterial and eukaryotic SSU rRNA

accurate:

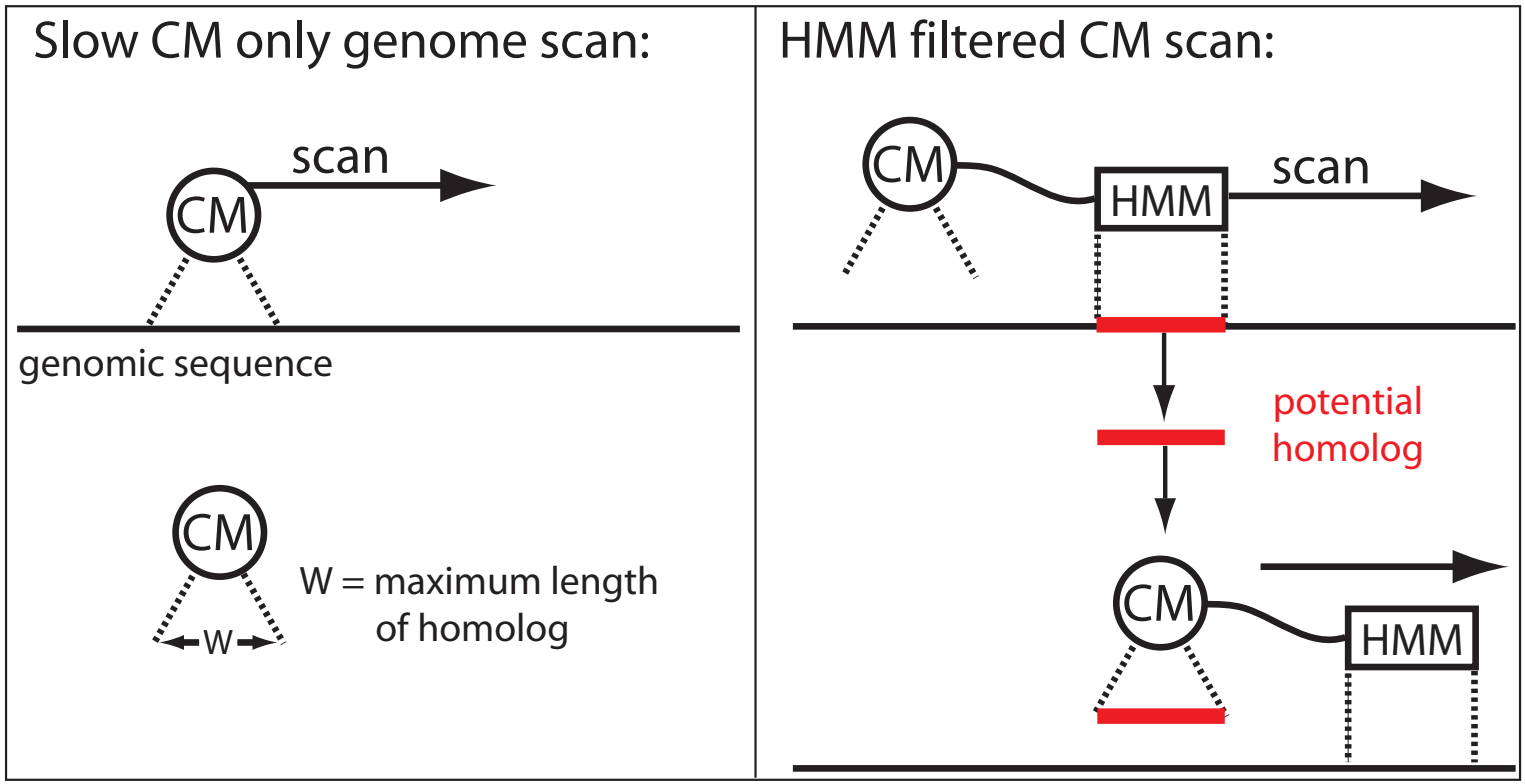
- structural alignment of sequences
- probabilistic masking of ambiguous columns

scalable and fast:

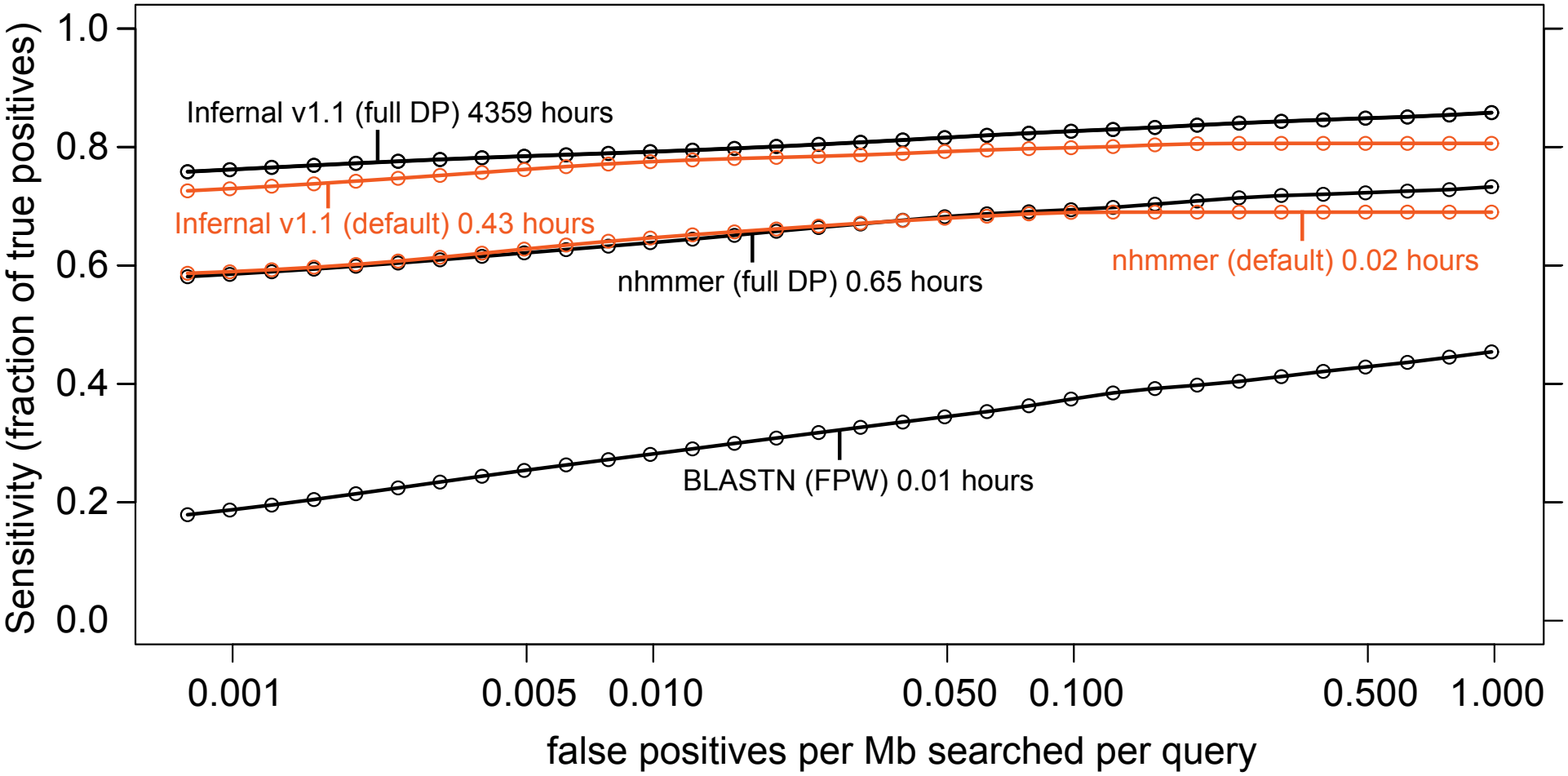
- can generate alignment of millions of seqs
- speed is about 1 second/full length sequence
- easily parallelized on clusters

SSU-ALIGN tutorial tomorrow at 10:30

# HMM banding can be used for homology search too



# Infernal 1.1: RNA homology searches 10,000 times faster



# Acknowledgements

Sean Eddy
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Seolkyoung Jung
Rob Finn
Jody Clements
Fred Davis
Lee Henry
Michael Farrar