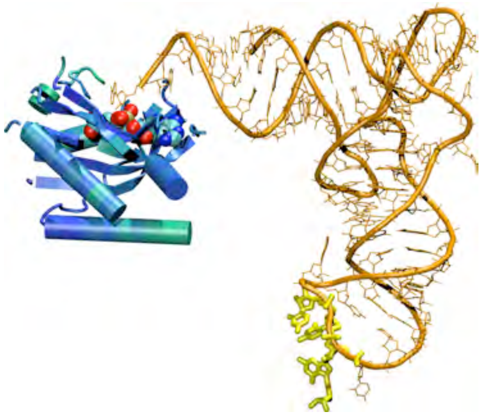
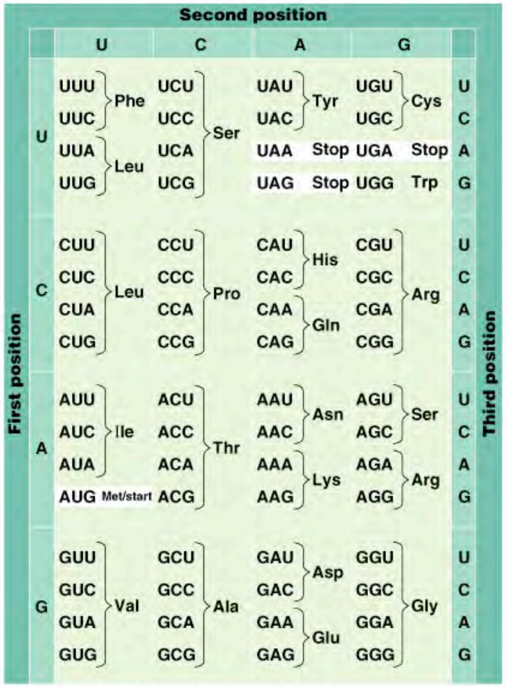
Evolution of Protein Structure





	Second position								
First position	U		C		A		G		Third position
U	UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys	U
	UUC		UCC		UAC		UGC		C
	UUA	Leu	UCA		UAA	Stop	UGA	Stop	A
	UUG		UCG		UAG	Stop	UGG	Trp	G
C	CUU	Leu	CCU	Pro	CAU	His	CGU	Arg	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	Gln	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	Lys	AGA	Arg	A
	AUG	Met/start	ACG		AAG		AGG		G
G	GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	Glu	GGA		A
	GUG		GCG		GAG		GGG		G

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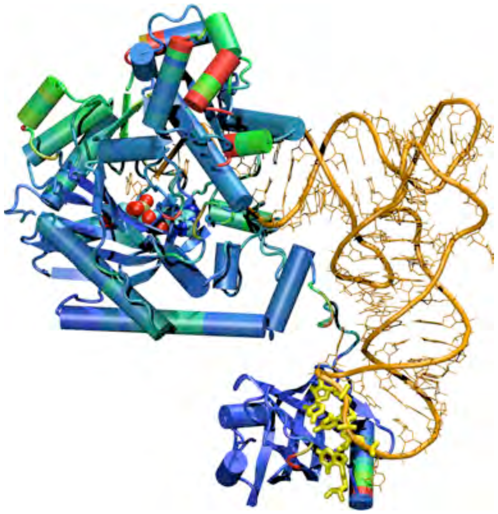
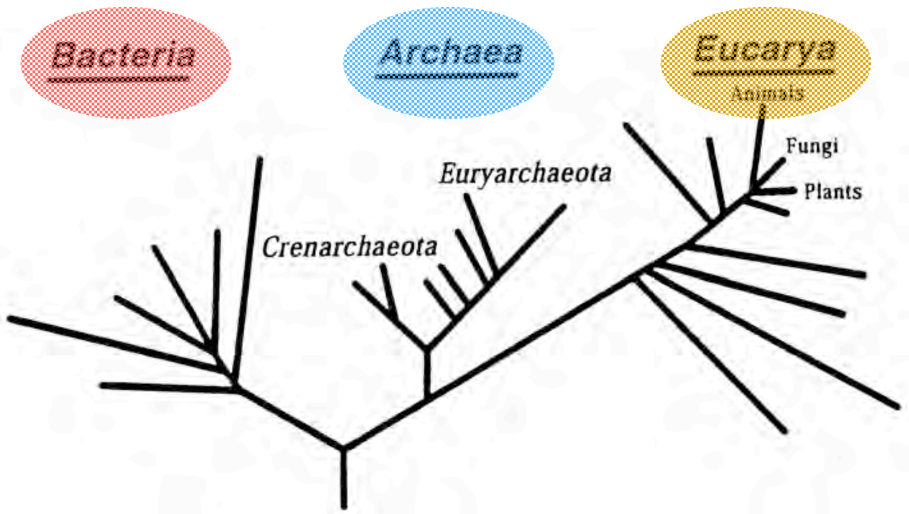


Luthey-Schulten Group

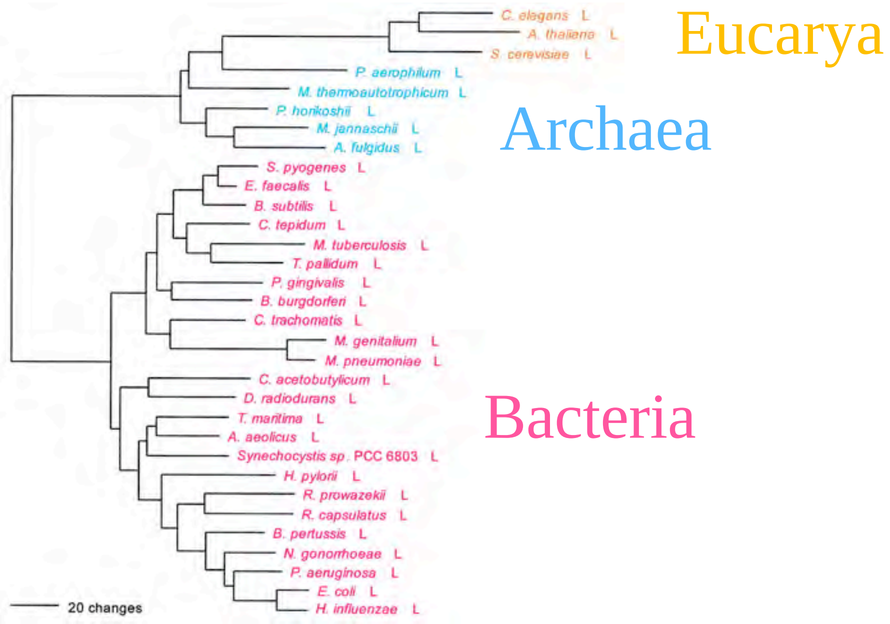
Department of Chemistry, Biophysics, and Beckman Institute
University of Illinois at Urbana-Champaign

Universal Phylogenetic Tree

three domains of life



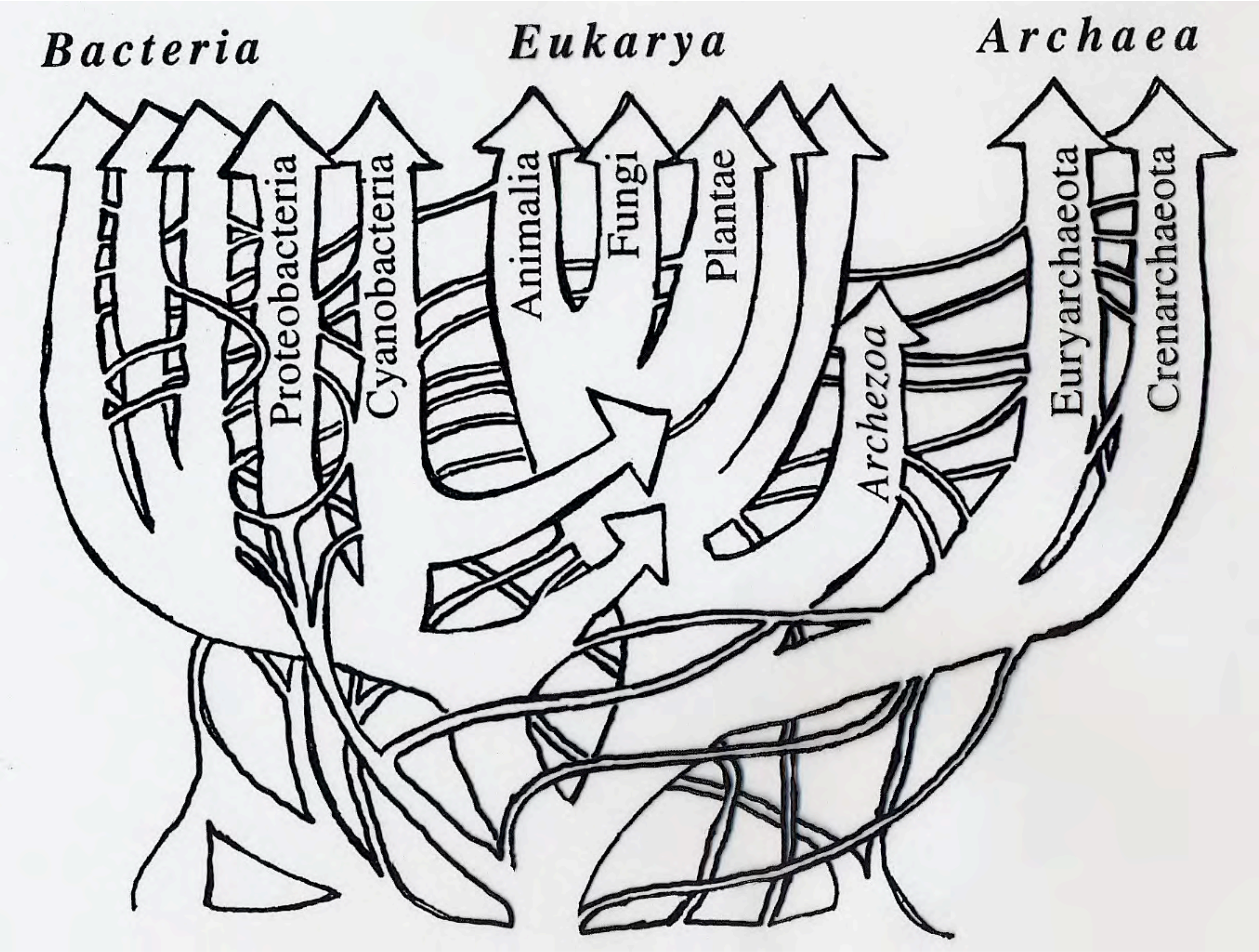
Based on 16S rRNA



Leucyl-tRNA synthetase displays the full canonical phylogenetic distribution.

for review see Woese *PNAS* 2000

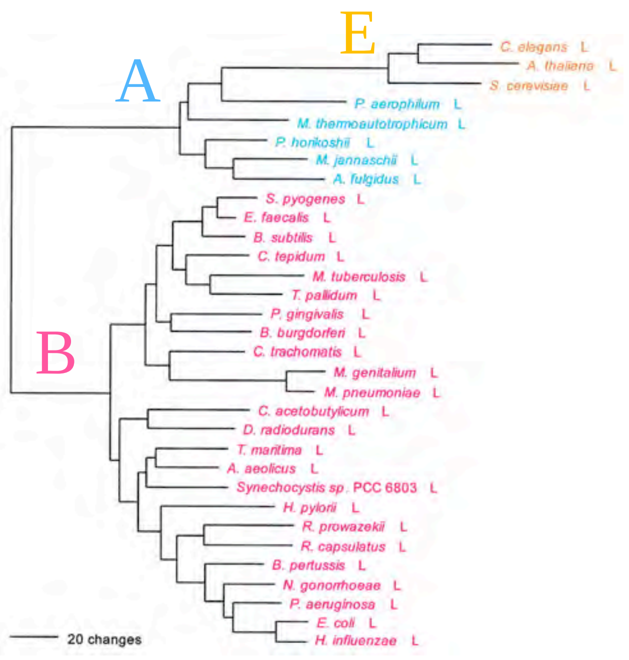
Woese, Olsen, Ibba, Soll *MMBR* 2000



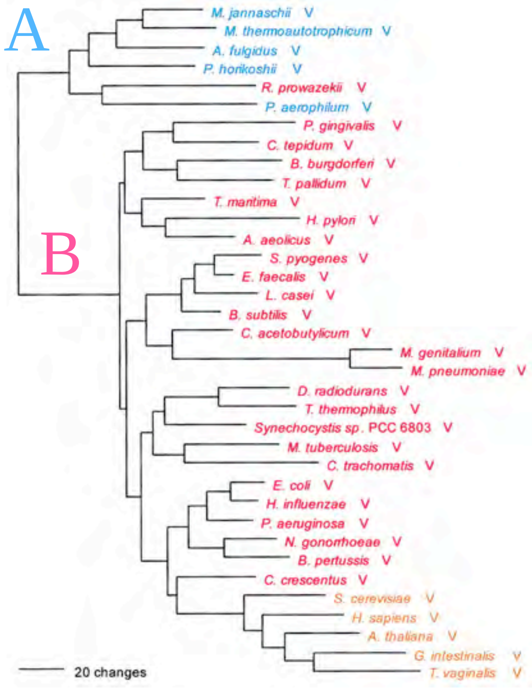
After W. Doolittle, modified by G. Olsen

Phylogenetic Distributions

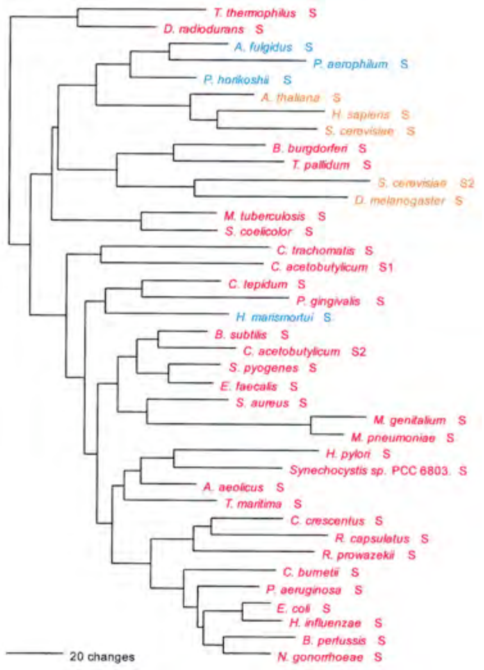
Full Canonical



Basal Canonical



Non-canonical



increasing inter-domain of life Horizontal Gene Transfer

"HGT erodes the historical trace, but does not completely erase it…." G. Olsen

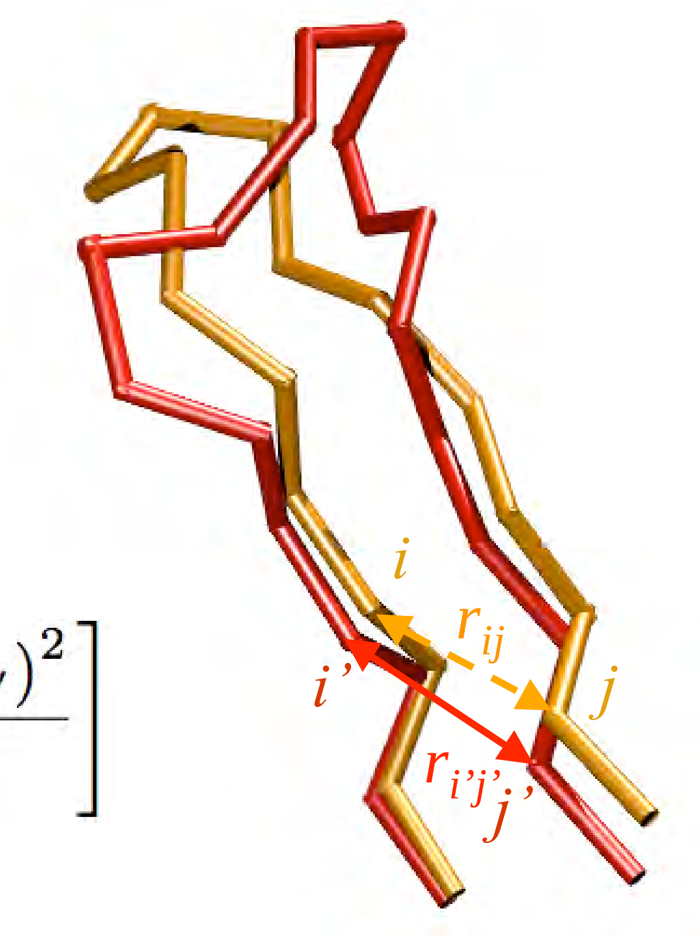
Protein Structure Similarity Measure

Q_H Structural Homology

fraction of native contacts for aligned residues + presence and perturbation of gaps

$$Q_H = \aleph\left[q_{aln} + q_{gap}\right]$$

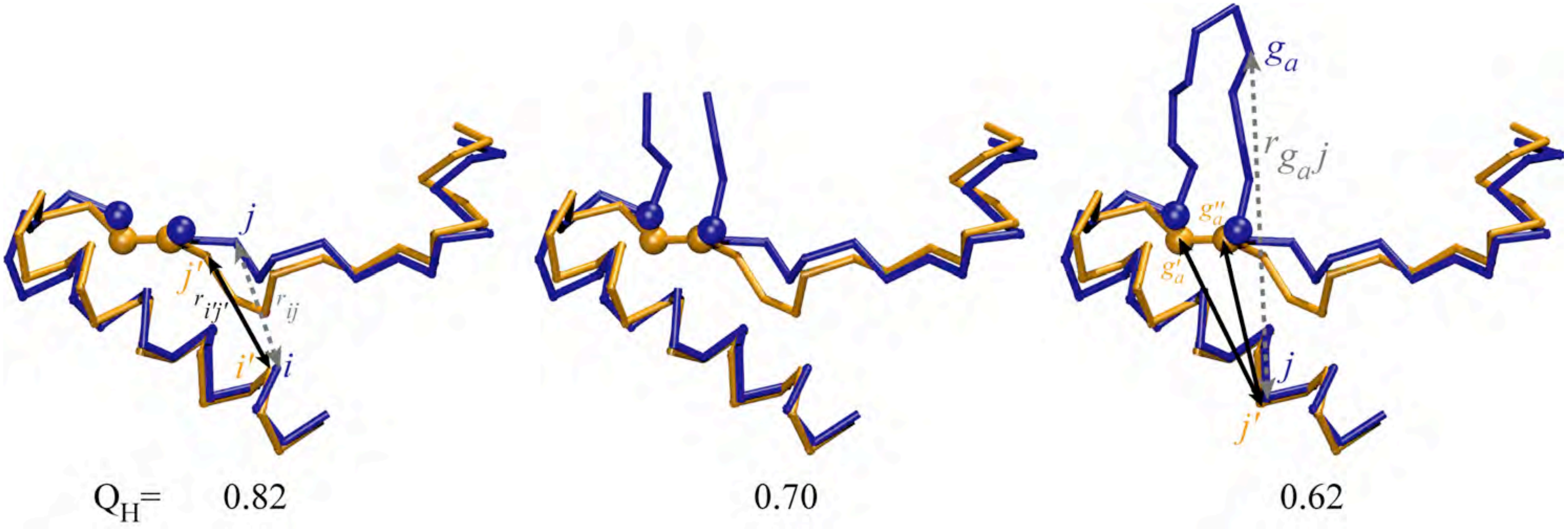
$$q_{aln} = \sum_{i<j-2} \exp\left[-\frac{(r_{ij} - r_{i'j'})^2}{2\sigma_{ij}^2}\right]$$

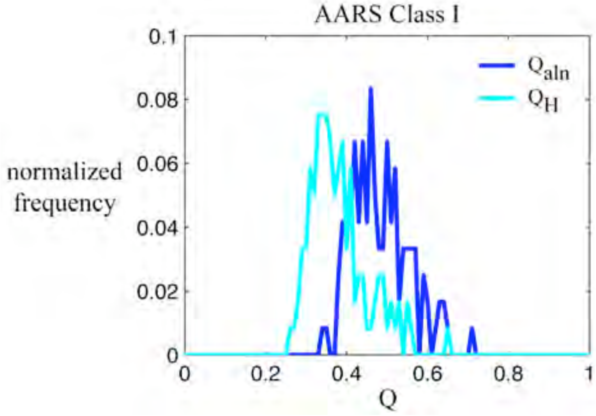


O'Donoghue & Luthey-Schulten *MMBR* 2003.

Structural Similarity Measure the effect of insertions

“Gaps should count as a character but not dominate” C. Woese

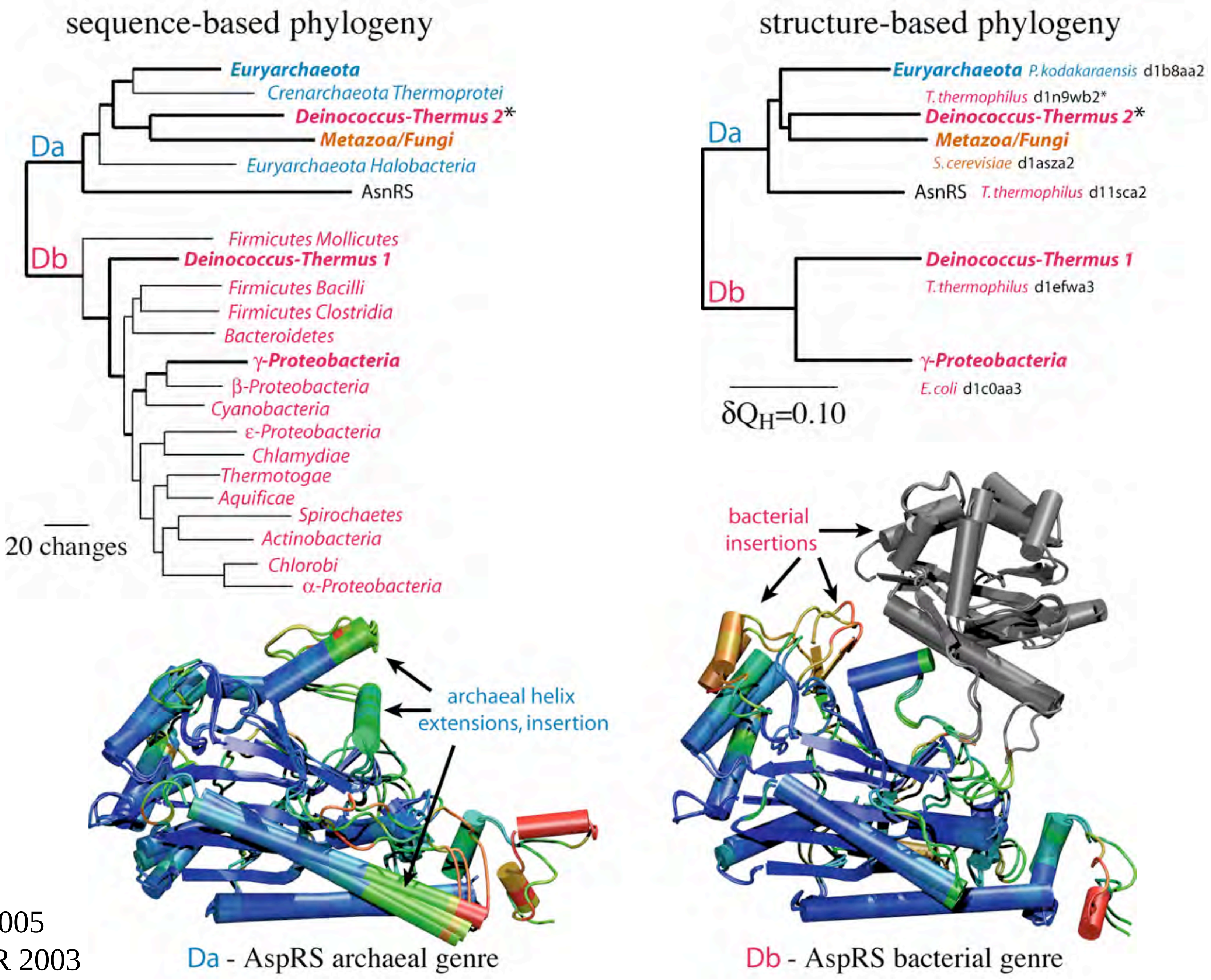




$$q_{gap} = \sum_{g_a} \sum_{j}^{N_{aln}} \max \left\{ \exp\left[-\frac{\left(r_{g_a j} - r_{g'_a j'}\right)^2}{2\sigma^2_{g_a j}} \right], \exp\left[-\frac{\left(r_{g_a j} - r_{g''_a j'}\right)^2}{2\sigma^2_{g_a j}} \right] \right\}$$

$$+ \sum_{g_b} \sum_{j}^{N_{aln}} \max \left\{ \exp\left[-\frac{\left(r_{g_b j} - r_{g'_b j'}\right)^2}{2\sigma^2_{g_b j}} \right], \exp\left[-\frac{\left(r_{g_b j} - r_{g''_b j'}\right)^2}{2\sigma^2_{g_b j}} \right] \right\}$$

Protein structure encodes evolutionary information



sequence-based phylogeny

structure-based phylogeny

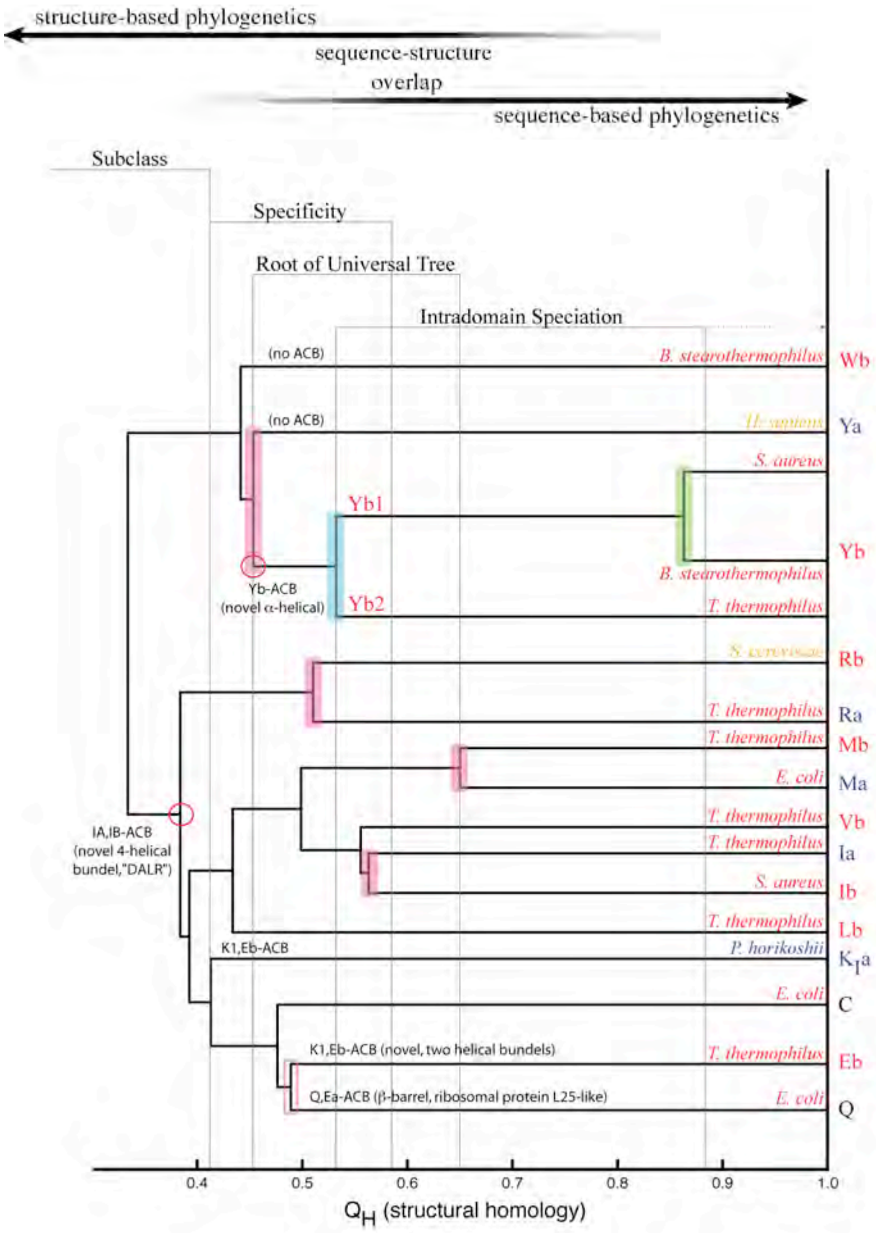
Da - AspRS archaeal genre

Db - AspRS bacterial genre

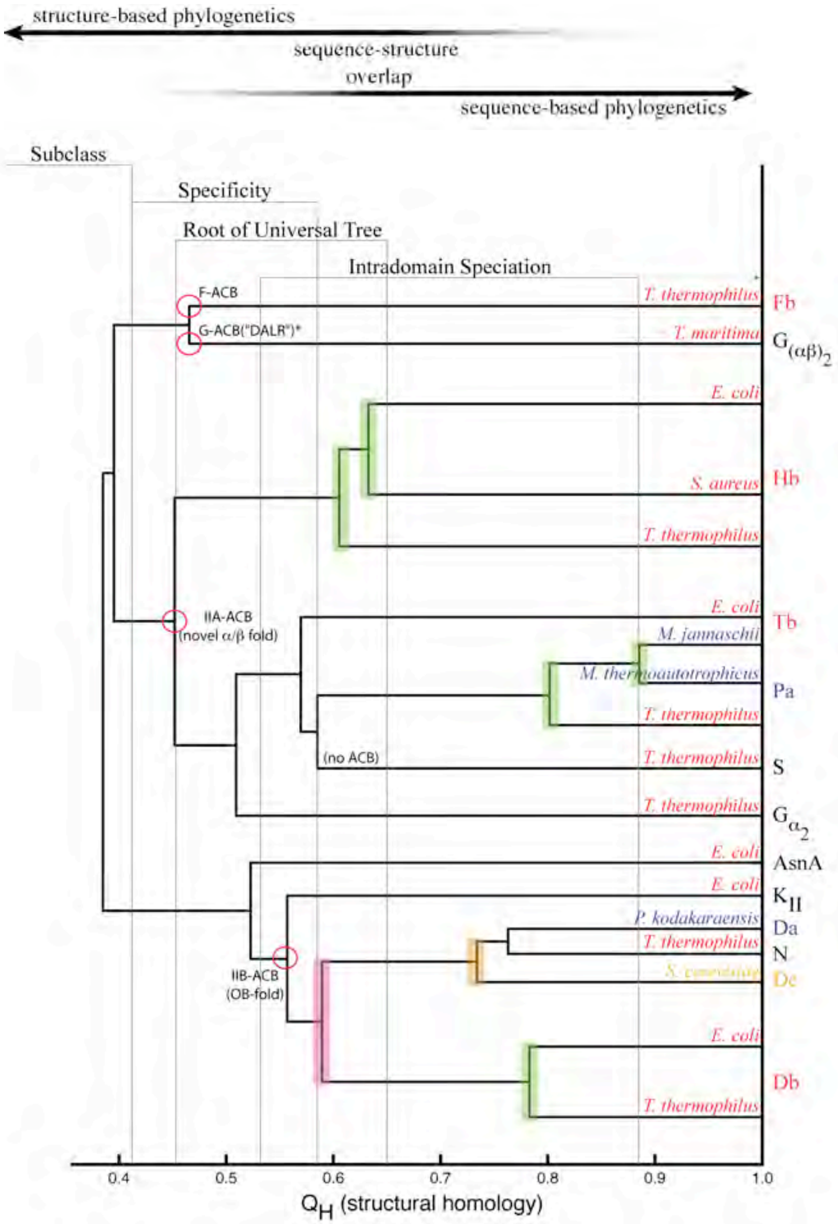
JMB 2005
MMBR 2003

Protein structure reveals distant evolutionary events

Class I AARSs



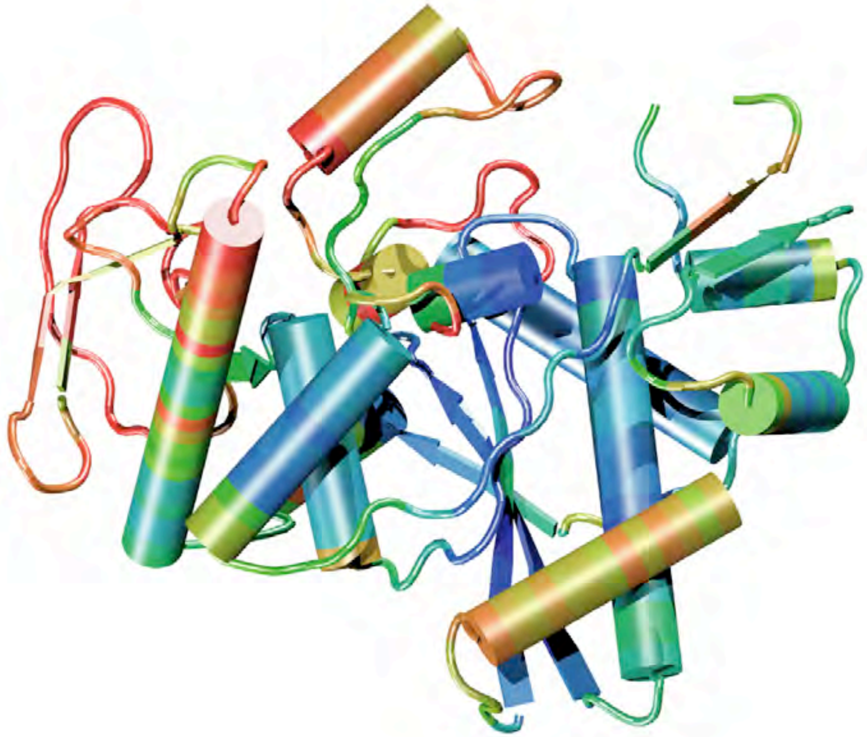
Class II AARSs



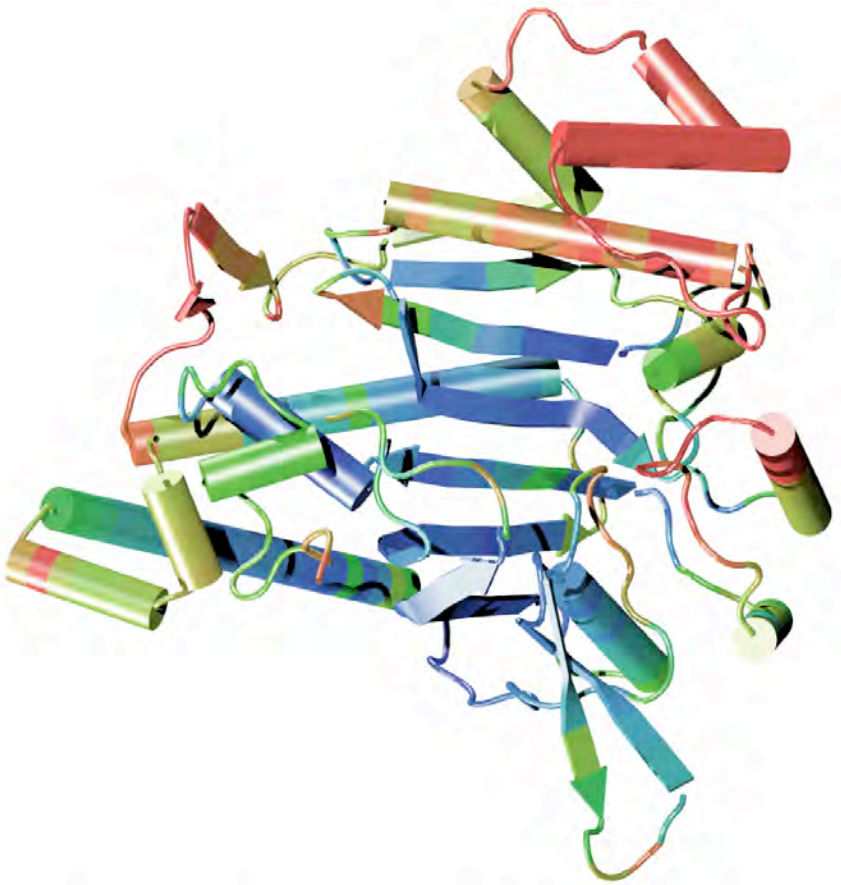
Protein structure reveals distant evolutionary events

Class I AARSs

Class II AARSs

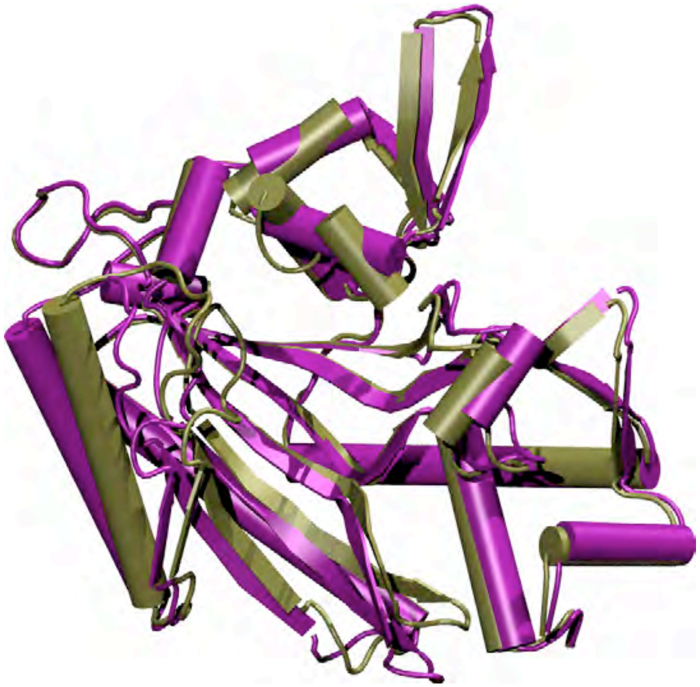


Class I Lysyl-tRNA Synthetase

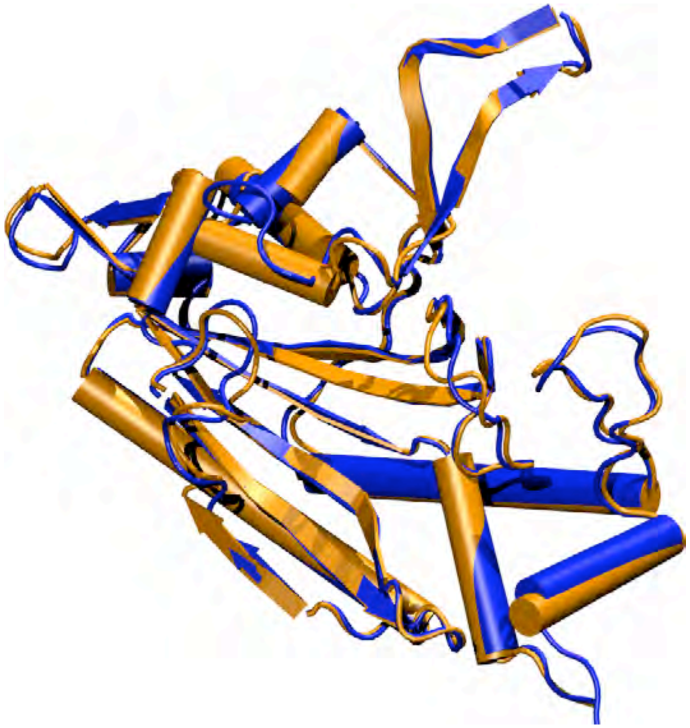


Class II Lysyl-tRNA Synthetase

Sequences define more recent evolutionary events



Conformational changes in the same protein.



Structures for two different species.

ThrRS
T-AMP analog, 1.55 A.
T, 2.00 A.

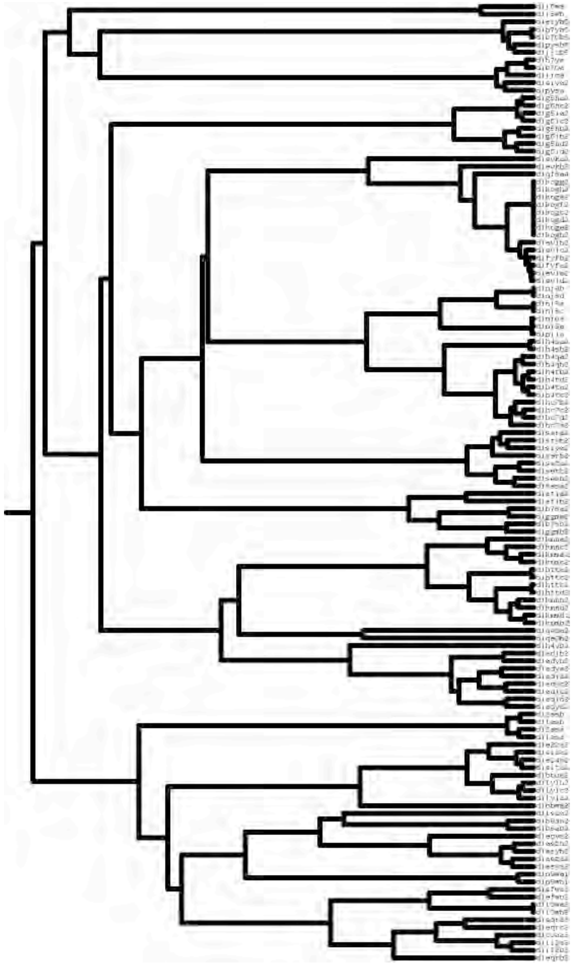
Q_H = 0.80
Sequence identity = 1.00

ProRS
M. jannaschii, 2.55 A.
M. thermoautotrophicus, 3.20 A.

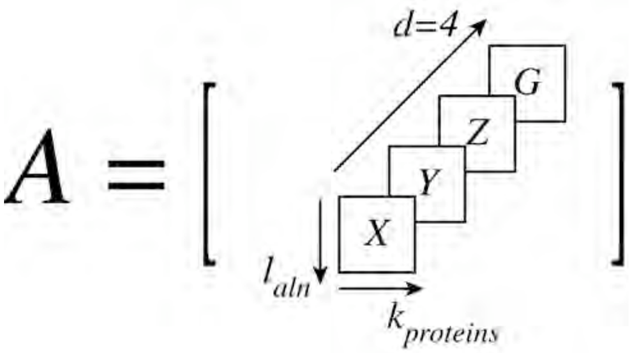
Q_H = 0.89
Sequence identity = 0.69

Non-redundant Representative Sets

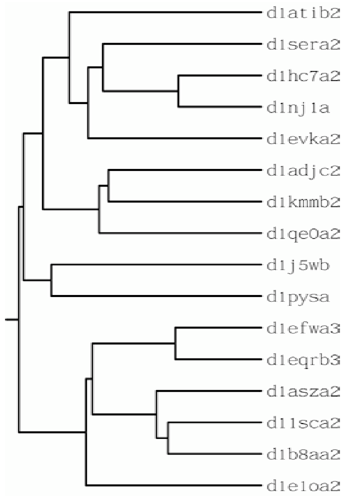
Too much information
129 Structures

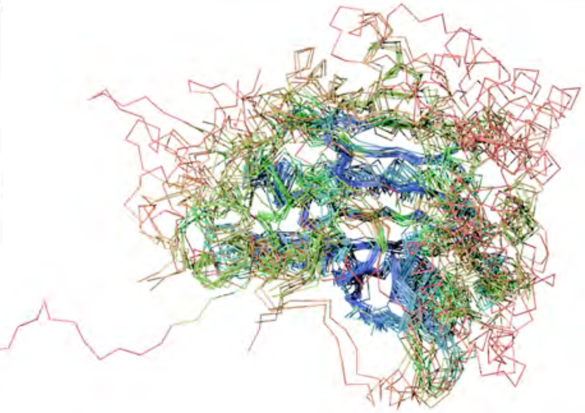


Multidimensional QR factorization of alignment matrix, *A*.



Economy of information
16 representatives





QR computes a set of maximal linearly independent structures.

P. O’Donoghue and Z. Luthey-Schulten (2003) *MMBR* **67**:550-571.

P. O’Donoghue and Z. Luthey-Schulten (2005) *J. Mol. Biol.*, **346**, 875-894.

Numerical Encoding of Proteins in a Multiple Alignment

Encoding Structure

Rotated Cartesian + Gap = 4-space

Aligned position $(x_{C_\alpha}, y_{C_\alpha}, z_{C_\alpha}, 0)$

Gapped position $(0, 0, 0, g)$

Gap Scaling $$g = \gamma \frac{\|X\|_{F_4} + \|Y\|_{F_4} + \|Z\|_{F_4}}{\|G\|_{F_4}}$$

adjustable parameter

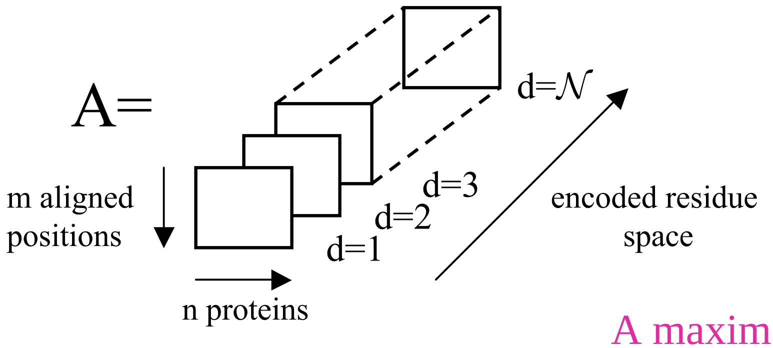
Sequence Space

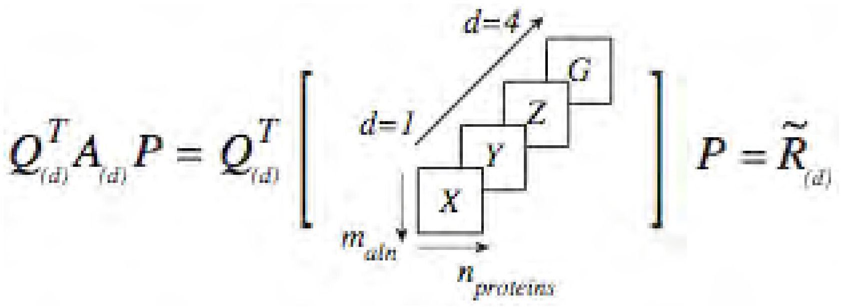
Orthogonal Encoding = 24-space

23 amino acids (20 + B, X, Z) + gap

A = (1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0)
B = (0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0)
C = (0,0,1,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0)
…
GAP = (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,1)

Alignment is a Matrix with Linearly Dependent Columns





A maximal linearly independent subset can be determined with respect to a threshold, e.g., similarity measure threshold.

Applications of Evolutionary Profiles

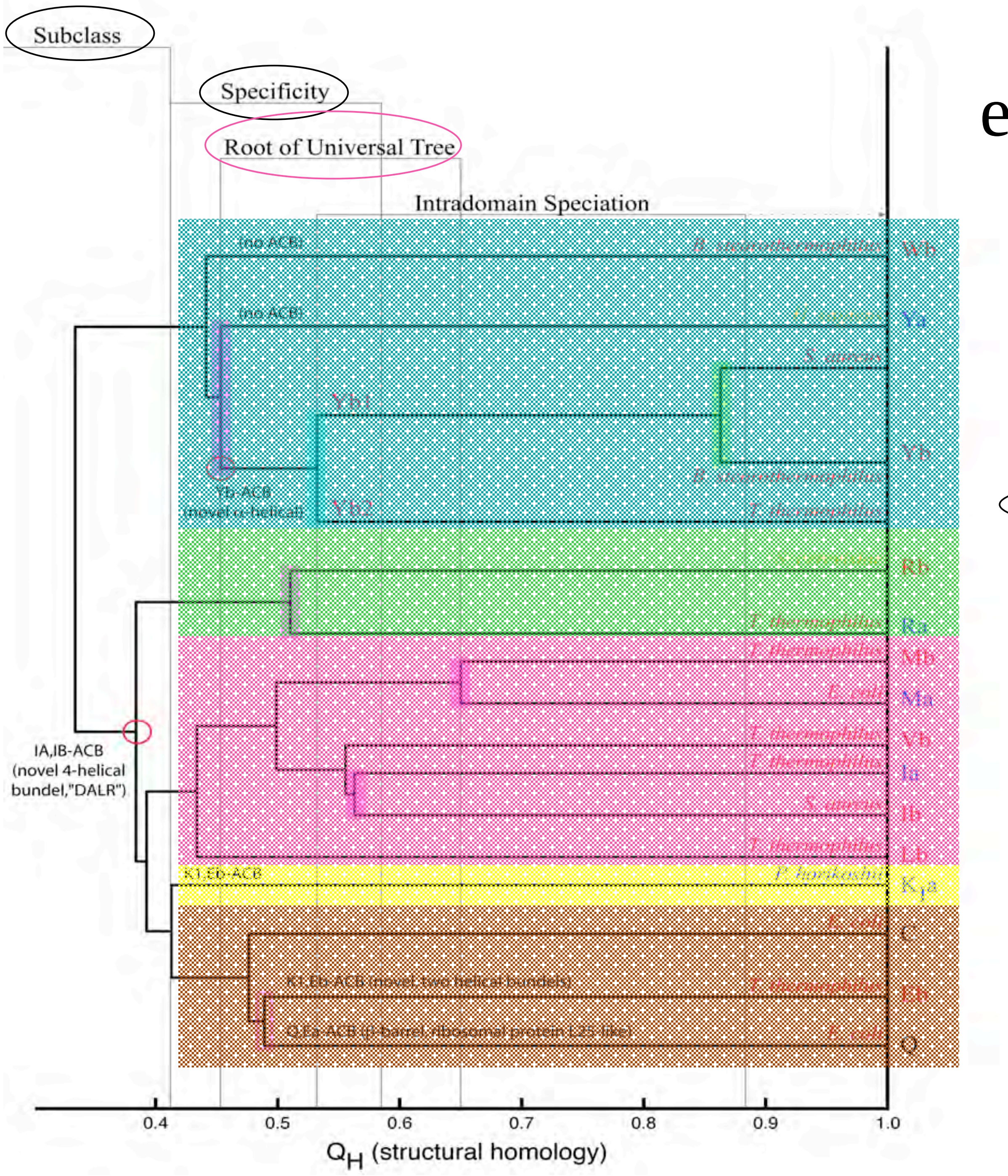
I. **Genome Annotation** AARS - MJ1660

II. **Conserved Core -- Folding Nuclei? HD Exchange?**

III. **Functional Ancestor ?**

IV. **Classification of Protein Structures -** Superfamilies

Class I AARSs evolutionary events

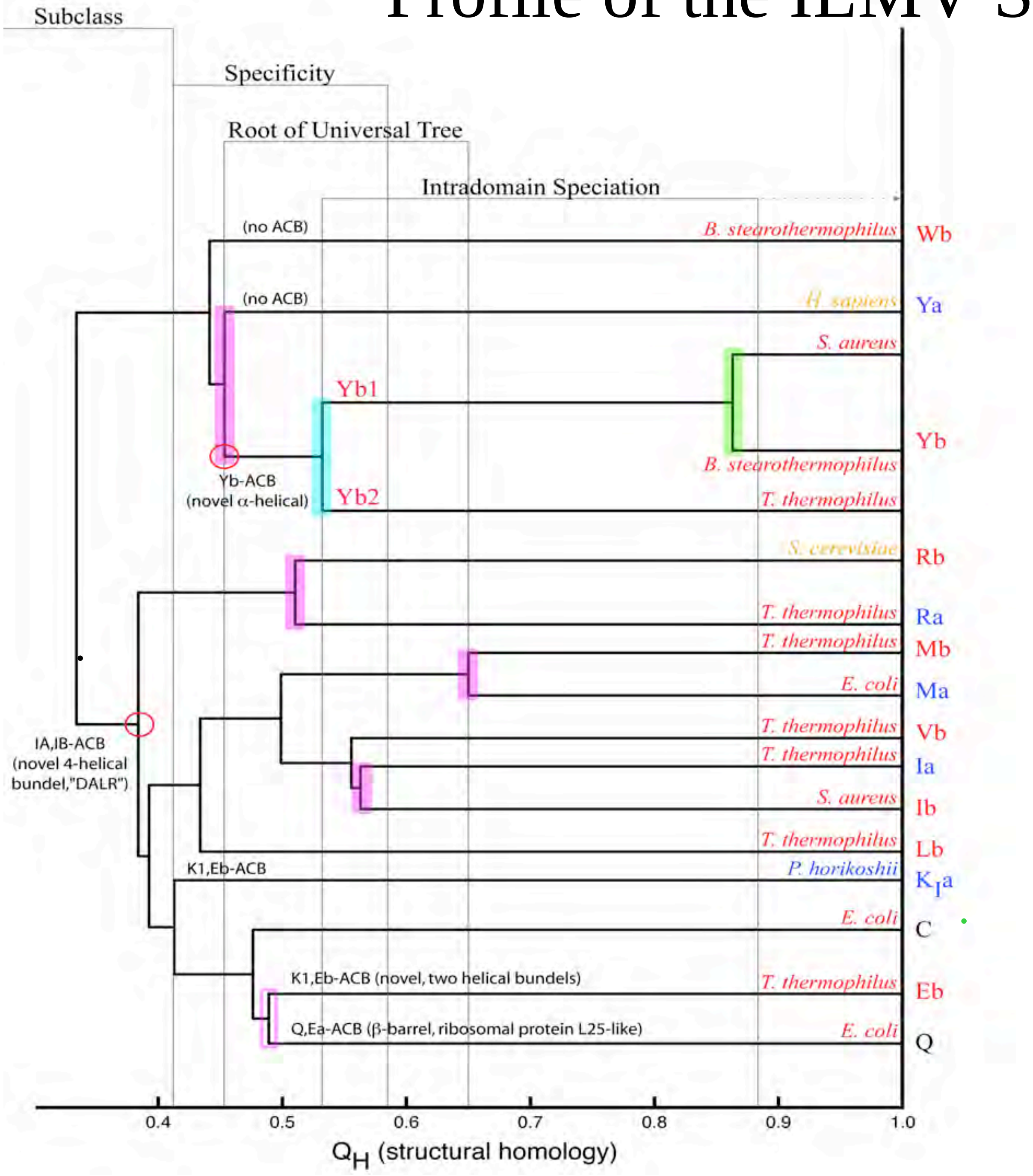


5 Subclasses

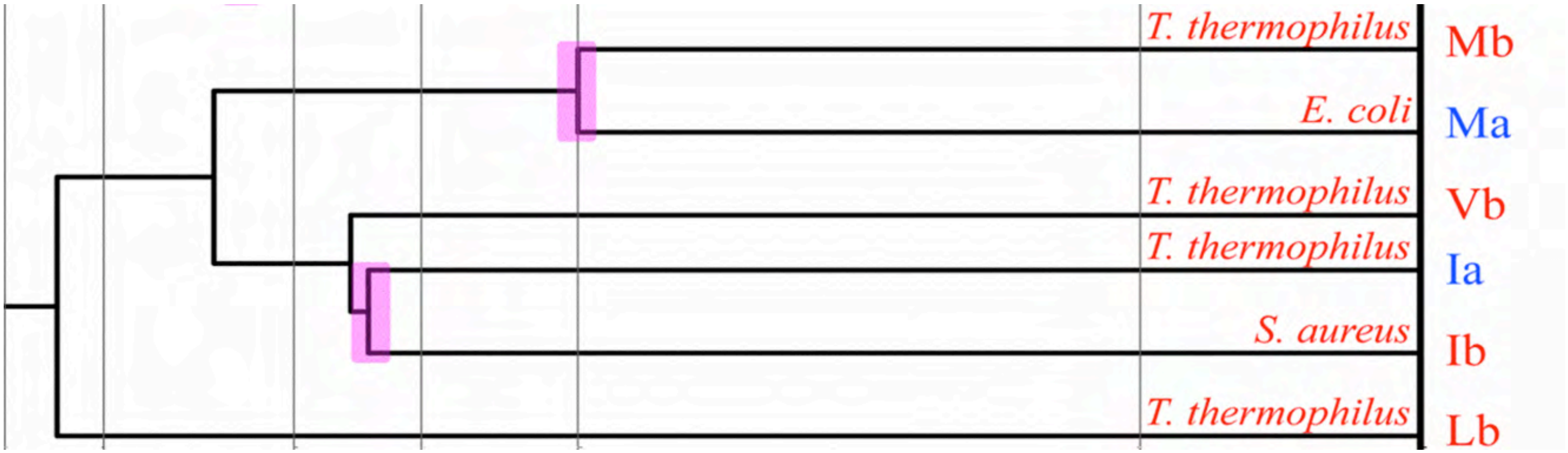
Specificity – 11 Amino acids

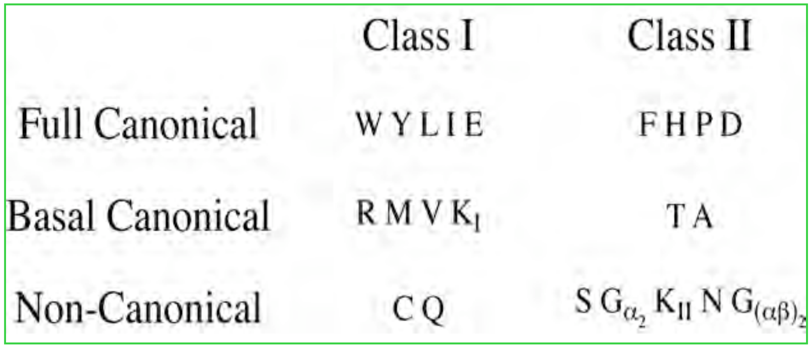
Domain of life A,B,E

Profile of the ILMV Subclass?



Profile of the ILMV Subclass





	Class I	Class II
Full Canonical	W Y L I E	F H P D
Basal Canonical	R M V K_I	T A
Non-Canonical	C Q	S G_{α_2} K_{II} N $G_{(\alpha\beta)_2}$

How many sequences are needed to represent the Subclass ILMV?

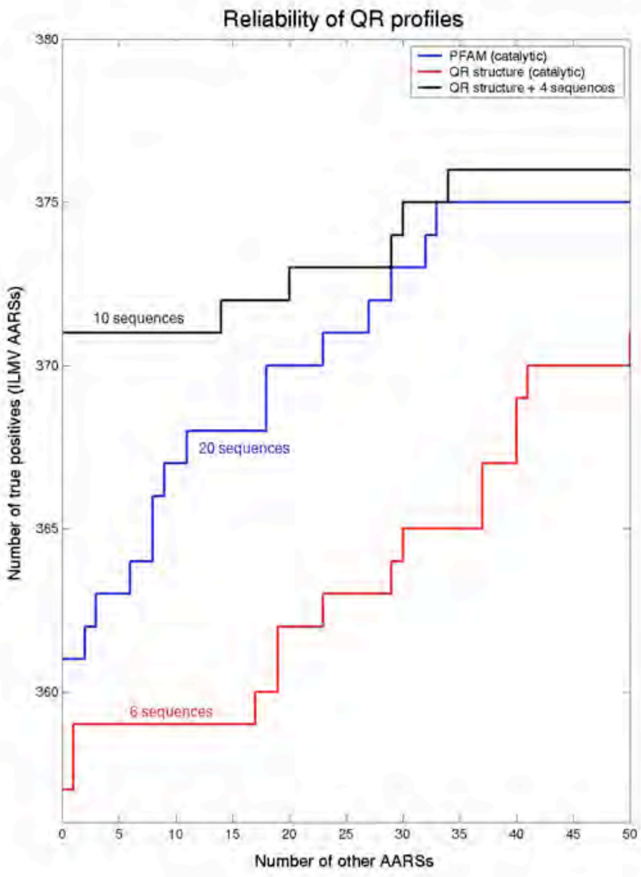
If each of ILMV was full canonical, then we would need 4x3=12 sequences.

Since M and V are basal, we need **at least** 2x3 + 2x2 = 10 sequences.

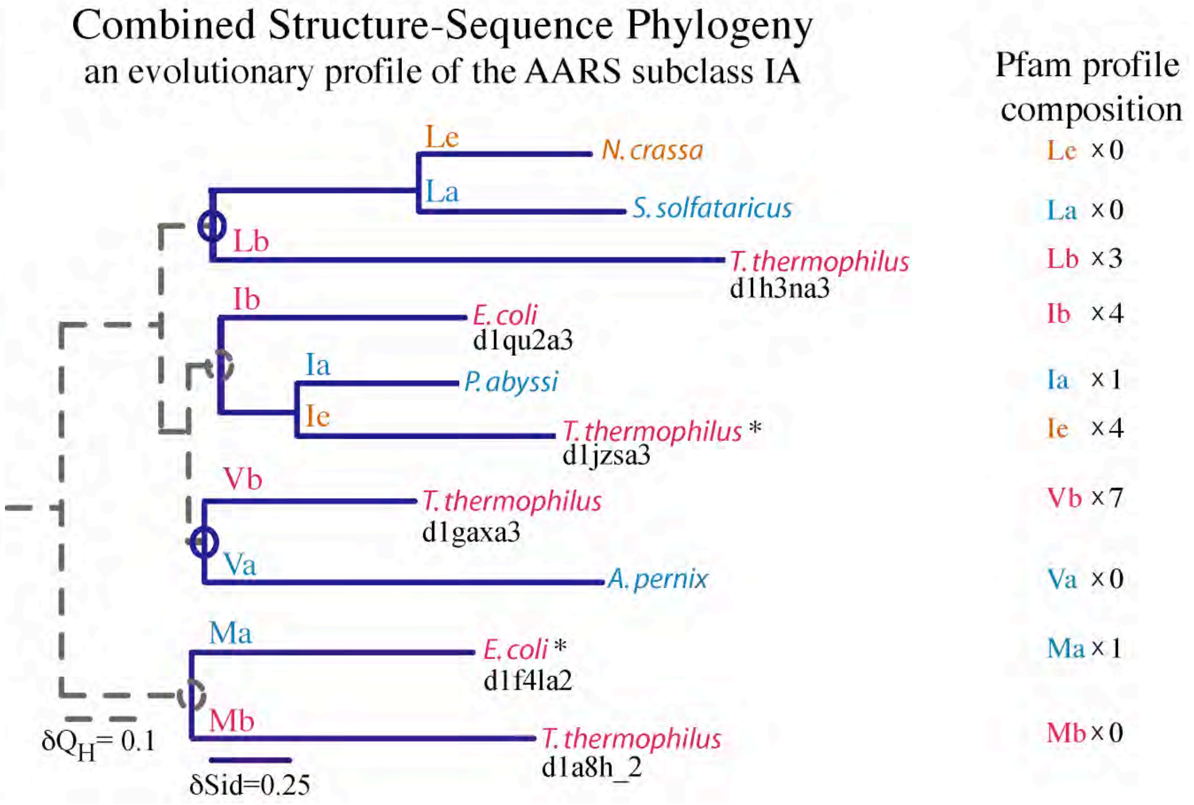
We have 6 structures.

Evolutionary Profiles for Homology Recognition

AARS Subclass ILMV



false positives



The composition of the profile matters.
Choosing the right 10 sequence makes all the difference.

A. Sethi, P. O'Donoghue, Z. Luthey-Schulten (2005) *JMB, PNAS*

Genome Annotation

M.jannaschii genome was completely sequenced in 1996.
Genome had four missing AARSs:

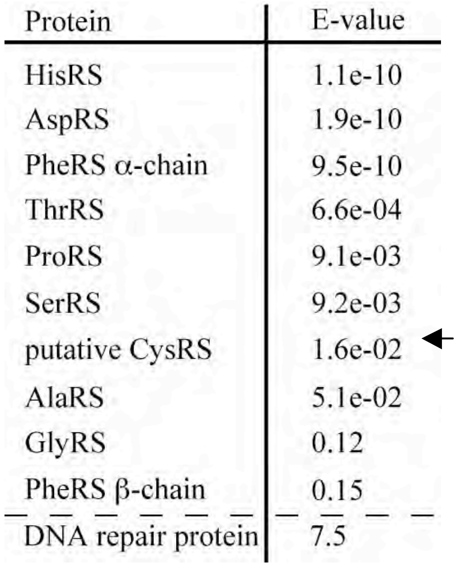
AsnRS } Indirect Mechanism
GlnRS

LysRS Class I AARS

CysRS ?

Cysteinyl-tRNA(Cys) formation in *Methanocaldococcus jannaschii*: the mechanism is still unknown. *J. Bacteriology*, Jan. 2004, **186:**8-14.
Ruan B, Nakano H, Tanaka M, Mills JA, DeVito JA, Min B, Low KB, Battista JR, and Söll D.

M. jannaschii genome database search using EP of class II AARS with HMMER

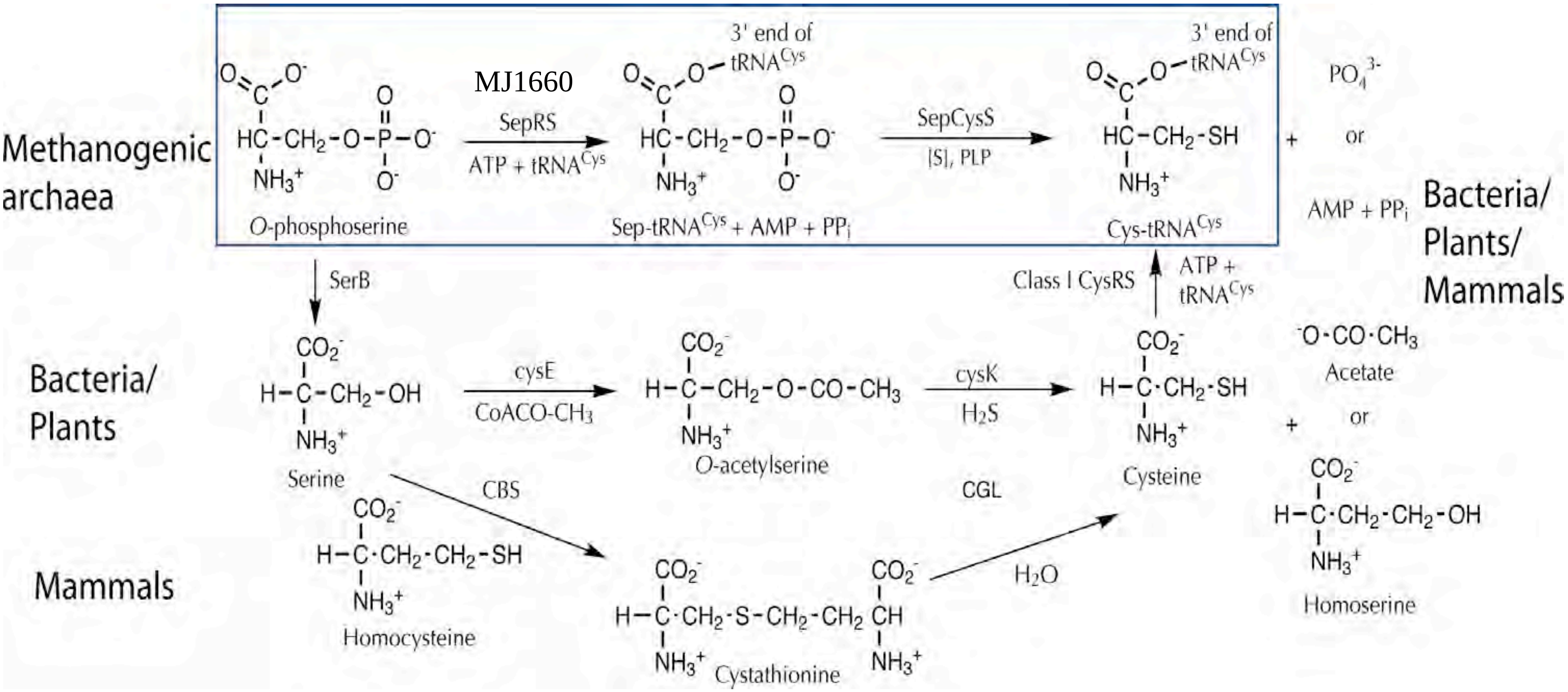


Protein	E-value
HisRS	1.1e-10
AspRS	1.9e-10
PheRS α-chain	9.5e-10
ThrRS	6.6e-04
ProRS	9.1e-03
SerRS	9.2e-03
putative CysRS	1.6e-02
AlaRS	5.1e-02
GlyRS	0.12
PheRS β-chain	0.15
DNA repair protein	7.5

← MJ1660

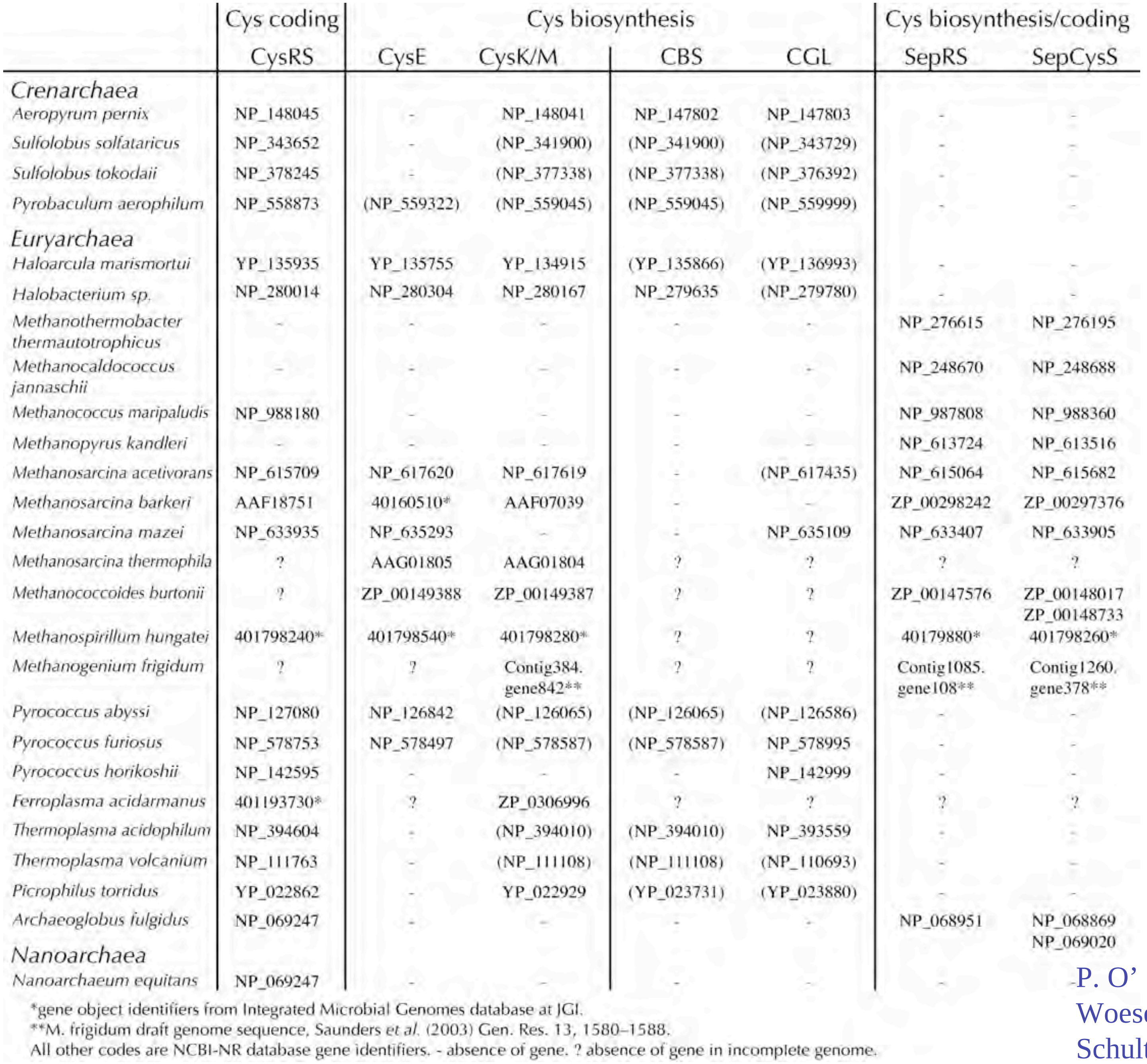
Sethi, et. al., PNAS, **102** ,2005

Connections of Direct and Indirect Pathways for Cysteinyl-tRNA formation to Cysteine Biosynthesis



Sauerwald et al., Science, 307, 2005, 1969-1972.

Genes for Cysteine Biosynthesis and Aminoacylation

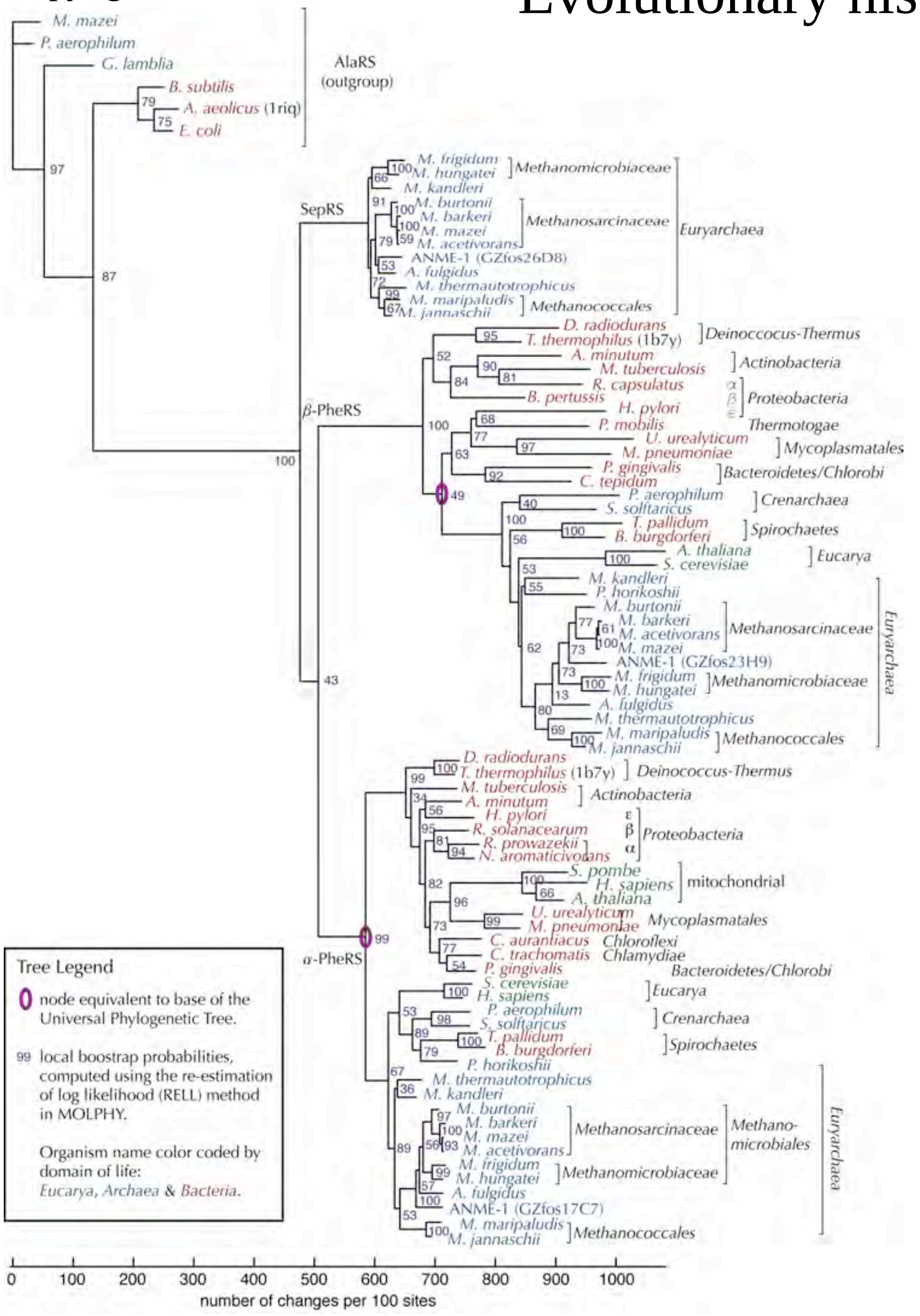


	Cys coding	Cys biosynthesis				Cys biosynthesis/coding	
	CysRS	CysE	CysK/M	CBS	CGL	SepRS	SepCysS
Crenarchaea							
Aeropyrum pernix	NP_148045	-	NP_148041	NP_147802	NP_147803	-	-
Sulfolobus solfataricus	NP_343652	-	(NP_341900)	(NP_341900)	(NP_343729)	-	-
Sulfolobus tokodaii	NP_378245	-	(NP_377338)	(NP_377338)	(NP_376392)	-	-
Pyrobaculum aerophilum	NP_558873	(NP_559322)	(NP_559045)	(NP_559045)	(NP_559999)	-	-
Euryarchaea							
Haloarcula marismortui	YP_135935	YP_135755	YP_134915	(YP_135866)	(YP_136993)	-	-
Halobacterium sp.	NP_280014	NP_280304	NP_280167	NP_279635	(NP_279780)	-	-
Methanothermobacter thermautotrophicus	-	-	-	-	-	NP_276615	NP_276195
Methanocaldococcus jannaschii	-	-	-	-	-	NP_248670	NP_248688
Methanococcus maripaludis	NP_988180	-	-	-	-	NP_987808	NP_988360
Methanopyrus kandleri	-	-	-	-	-	NP_613724	NP_613516
Methanosarcina acetivorans	NP_615709	NP_617620	NP_617619	-	(NP_617435)	NP_615064	NP_615682
Methanosarcina barkeri	AAF18751	40160510*	AAF07039	-	-	ZP_00298242	ZP_00297376
Methanosarcina mazei	NP_633935	NP_635293	-	-	NP_635109	NP_633407	NP_633905
Methanosarcina thermophila	?	AAG01805	AAG01804	?	?	?	?
Methanococcoides burtonii	?	ZP_00149388	ZP_00149387	?	?	ZP_00147576	ZP_00148017 ZP_00148733
Methanospirillum hungatei	401798240*	401798540*	401798280*	?	?	40179880*	401798260*
Methanogenium frigidum	?	?	Contig384. gene842**	?	?	Contig1085. gene108**	Contig1260. gene378**
Pyrococcus abyssi	NP_127080	NP_126842	(NP_126065)	(NP_126065)	(NP_126586)	-	-
Pyrococcus furiosus	NP_578753	NP_578497	(NP_578587)	(NP_578587)	NP_578995	-	-
Pyrococcus horikoshii	NP_142595	-	-	-	NP_142999	-	-
Ferroplasma acidarmanus	401193730*	?	ZP_0306996	?	?	?	?
Thermoplasma acidophilum	NP_394604	-	(NP_394010)	(NP_394010)	NP_393559	-	-
Thermoplasma volcanium	NP_111763	-	(NP_111108)	(NP_111108)	(NP_110693)	-	-
Picrophilus torridus	YP_022862	-	YP_022929	(YP_023731)	(YP_023880)	-	-
Archaeoglobus fulgidus	NP_069247	-	-	-	-	NP_068951	NP_068869 NP_069020
Nanoarchaea							
Nanoarchaeum equitans	NP_069247	-	-	-	-	-	-

*gene object identifiers from Integrated Microbial Genomes database at JGI.
**M. frigidum draft genome sequence, Saunders *et al.* (2003) Gen. Res. 13, 1580–1588.
All other codes are NCBI-NR database gene identifiers. - absence of gene. ? absence of gene in incomplete genome.

P. O’ Donoghue, A. Sethi, C. Woese, and Z. Luthey-Schulten, PNAS, 2005.

Evolutionary history of SepRS

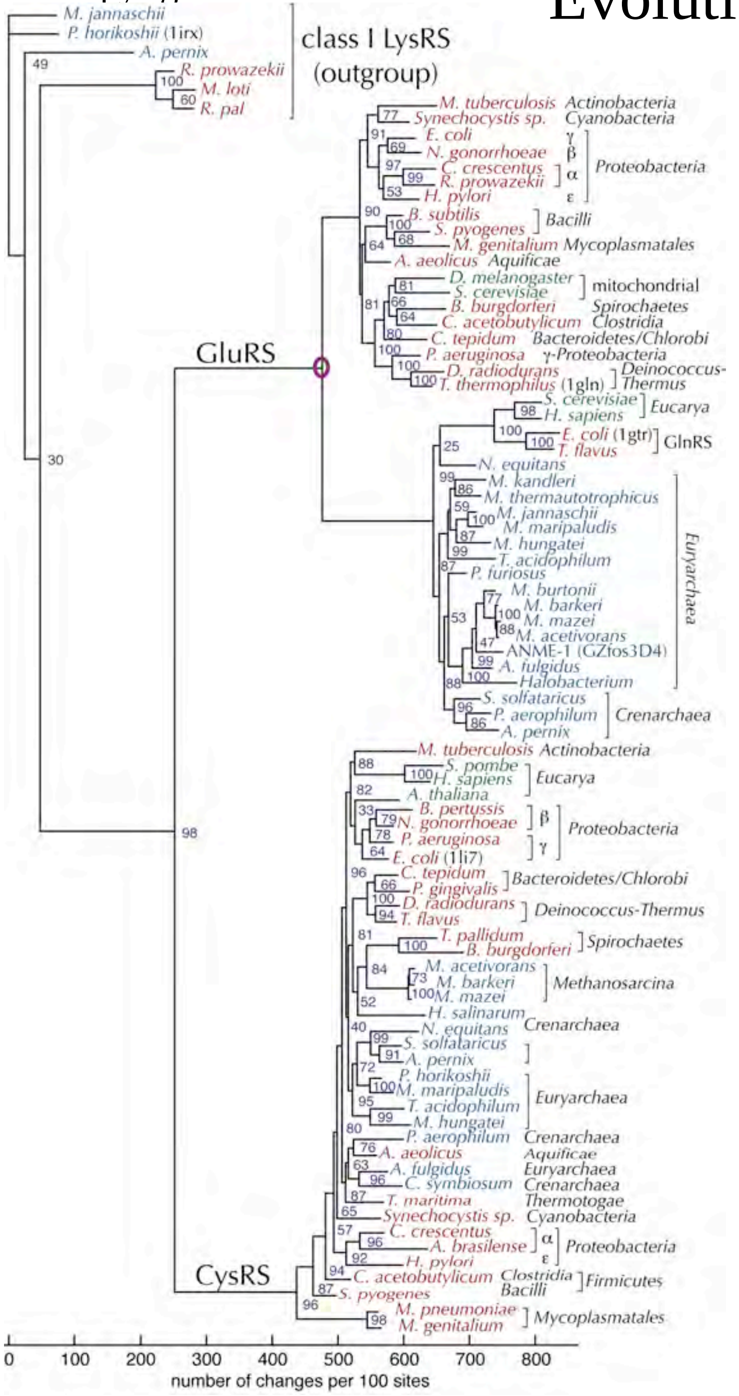


Same pattern as euryarchaeal portion of rRNA tree.

Was present in LUCAS.

P. O' Donoghue, A. Sethi, C. Woese, and Z. Luthey-Schulten, PNAS, 2005.

Evolutionary history of class I CysRS



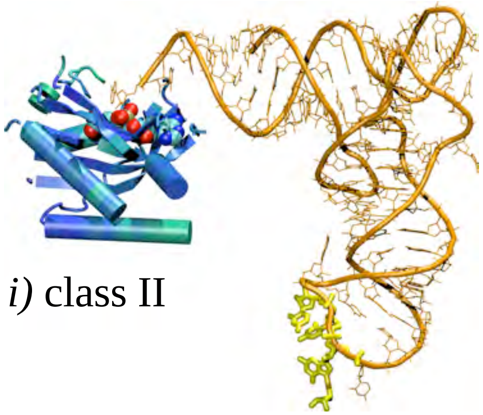
Bacterial groupings from UPT tree also seen in CysRS phylogeny.

Multiple HGT events of the direct route to archaeal organisms.

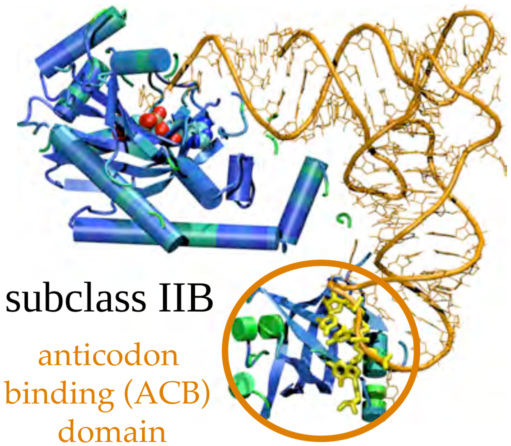
The direct route to cysteine aminoacylation was also present in the LUCAS.

P. O’ Donoghue, A. Sethi, C. Woese, and Z. Luthey-Schulten, PNAS, 2005.

Evolution of Structure and Function in AspRS

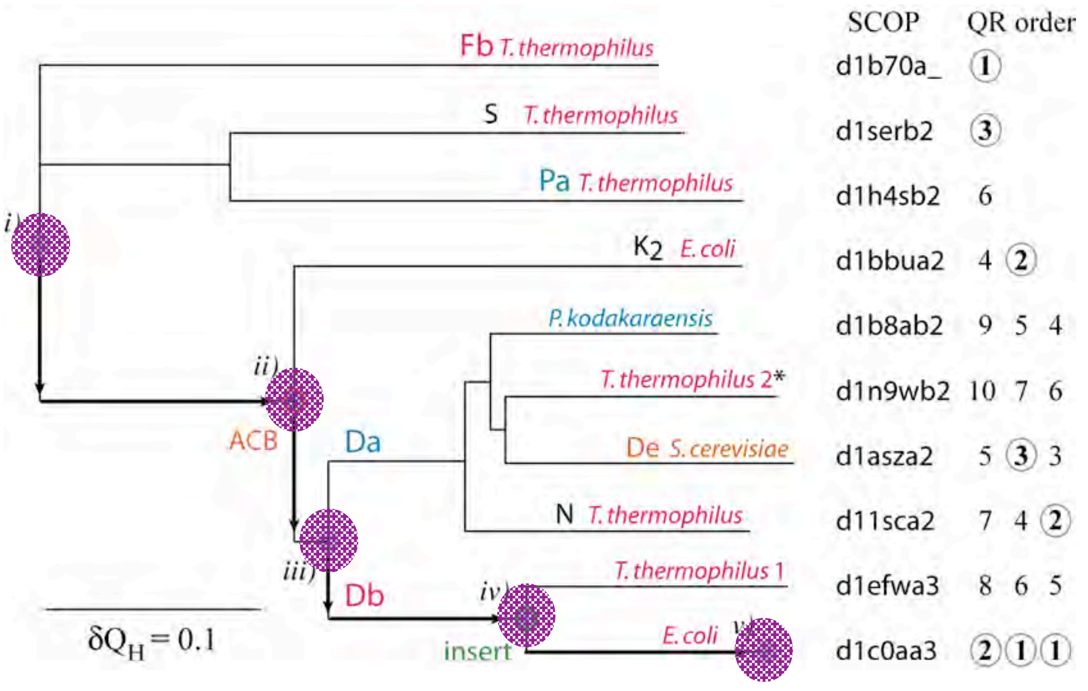


i) class II

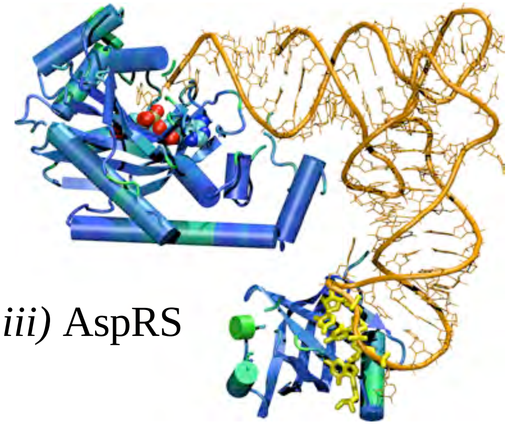


ii) subclass IIB

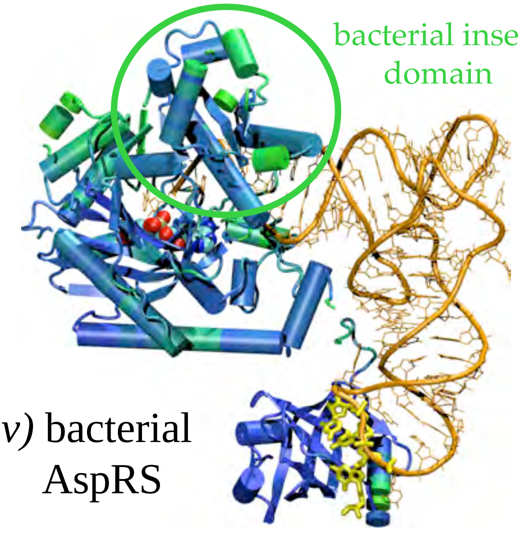
anticodon binding (ACB) domain



SCOP	QR order		
d1b70a_	①		
d1serb2	③		
d1h4sb2	6		
d1bbua2	4	②	
d1b8ab2	9	5	4
d1n9wb2	10	7	6
d1asza2	5	③	3
d11sca2	7	4	②
d1efwa3	8	6	5
d1c0aa3	②	①	①

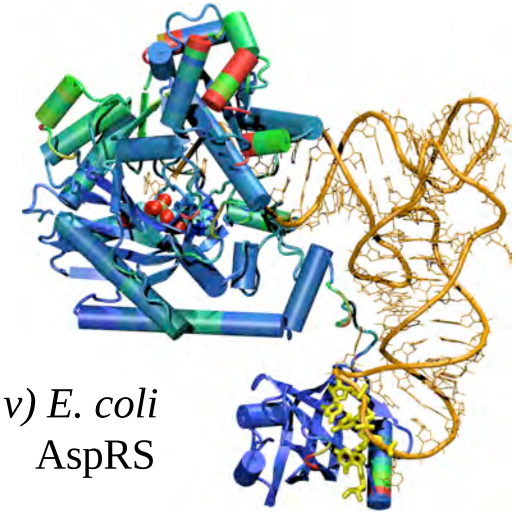


iii) AspRS



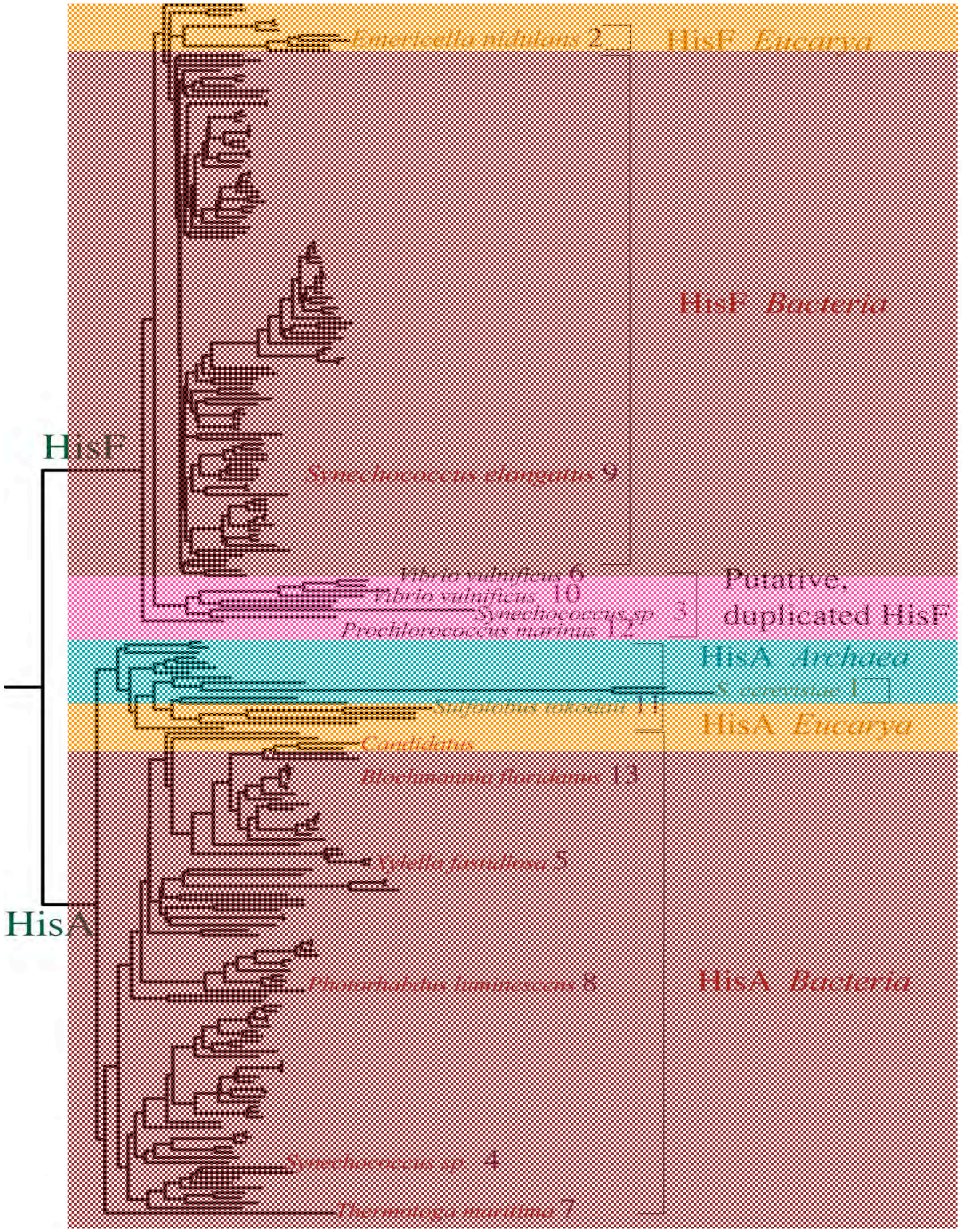
bacterial insert domain

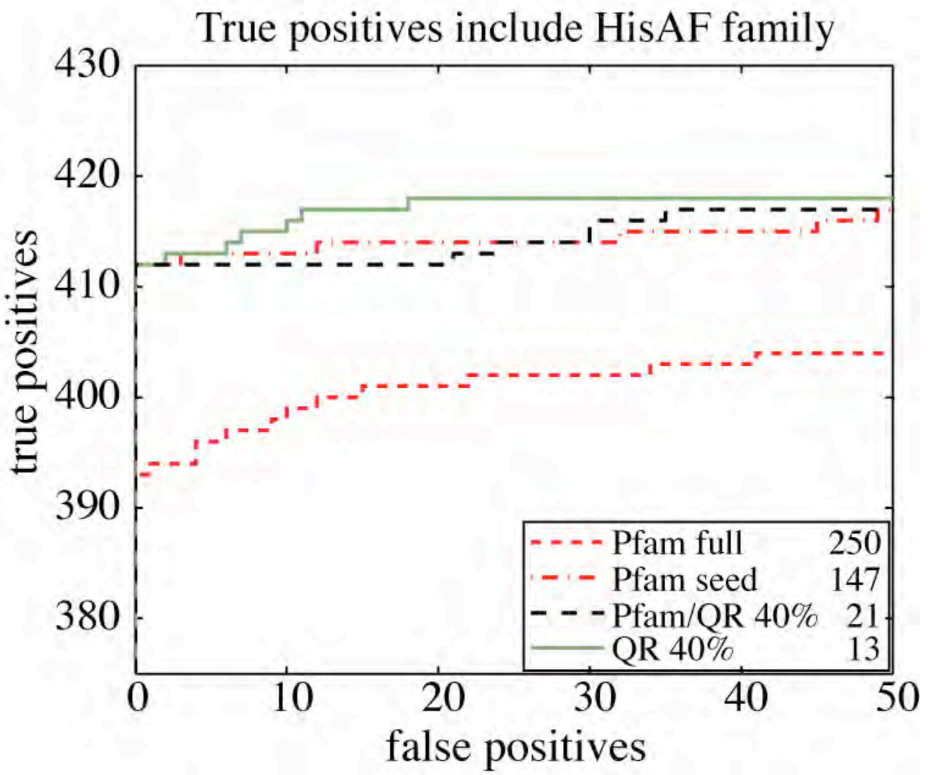
iv) bacterial AspRS



v) E. coli AspRS

Evolutionary profile for HisA-HisF family



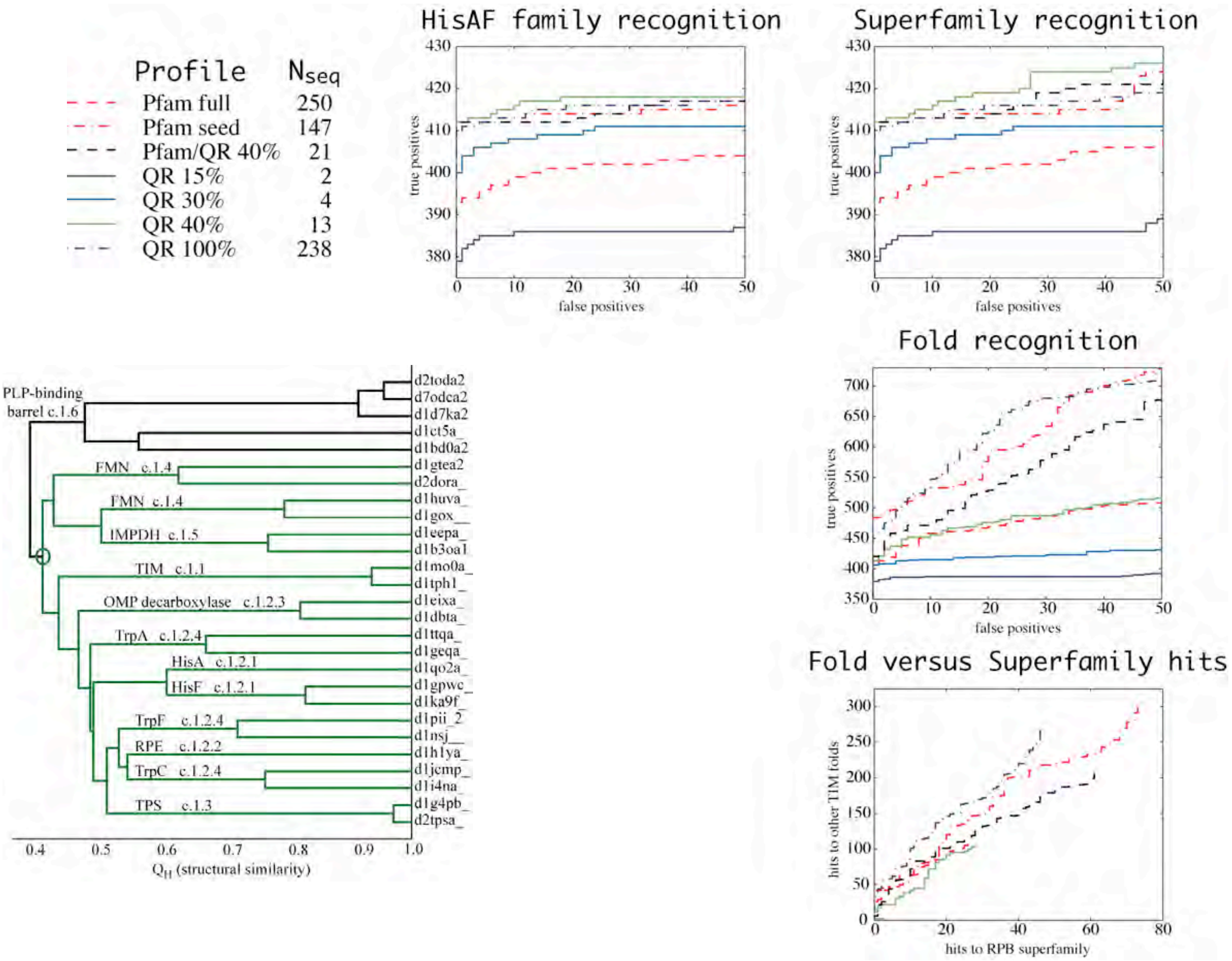


EP outperforms popular profile methods with an economy of information.

Sethi, et. al., PNAS, 2005.

Economy of Information

How many sequences are needed for profiles?



	Profile	N_{seq}
- - -	Pfam full	250
-·-·	Pfam seed	147
- - -	Pfam/QR 40%	21
—	QR 15%	2
—	QR 30%	4
—	QR 40%	13
-·-·	QR 100%	238

HisAF family recognition

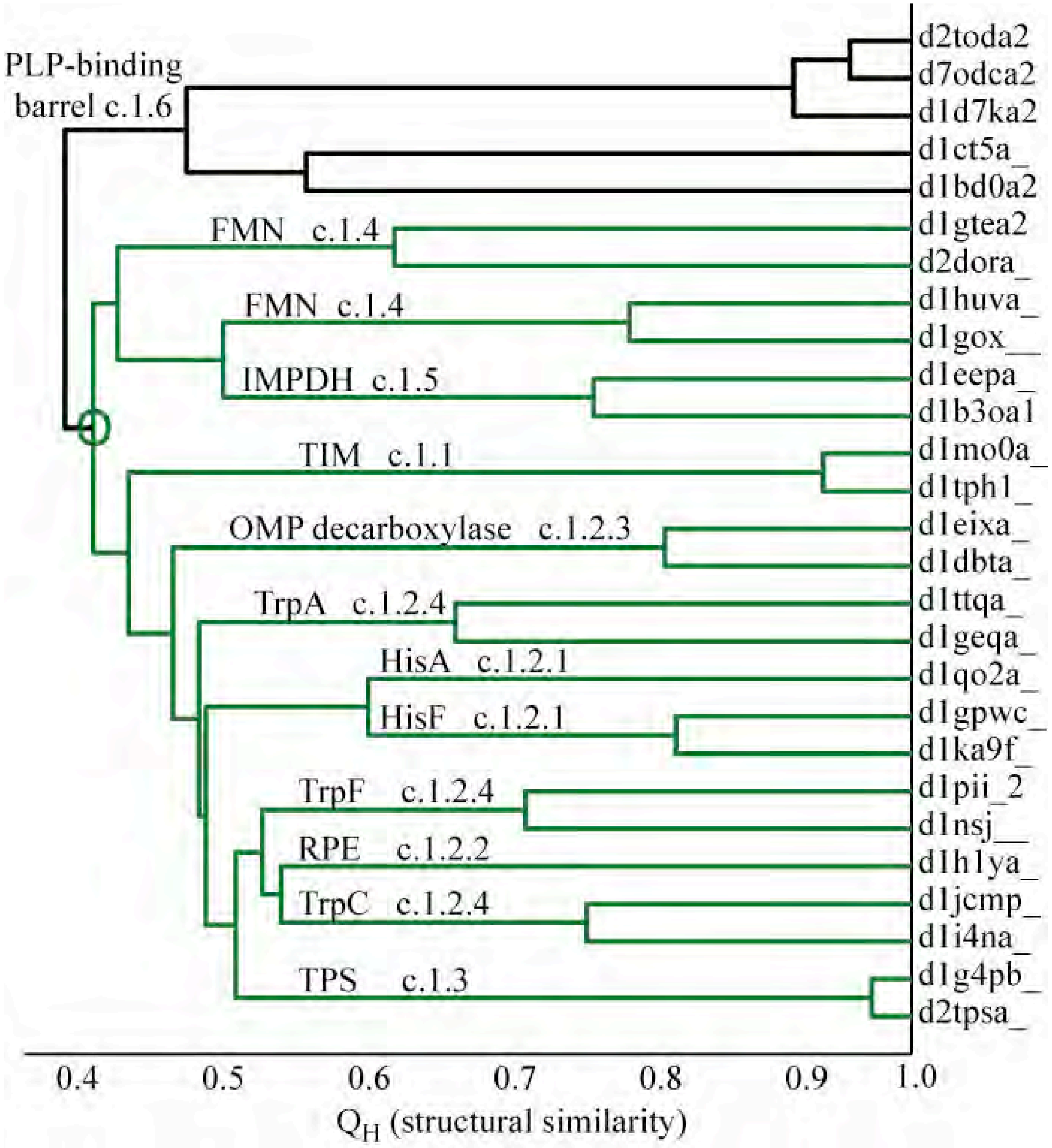
Superfamily recognition

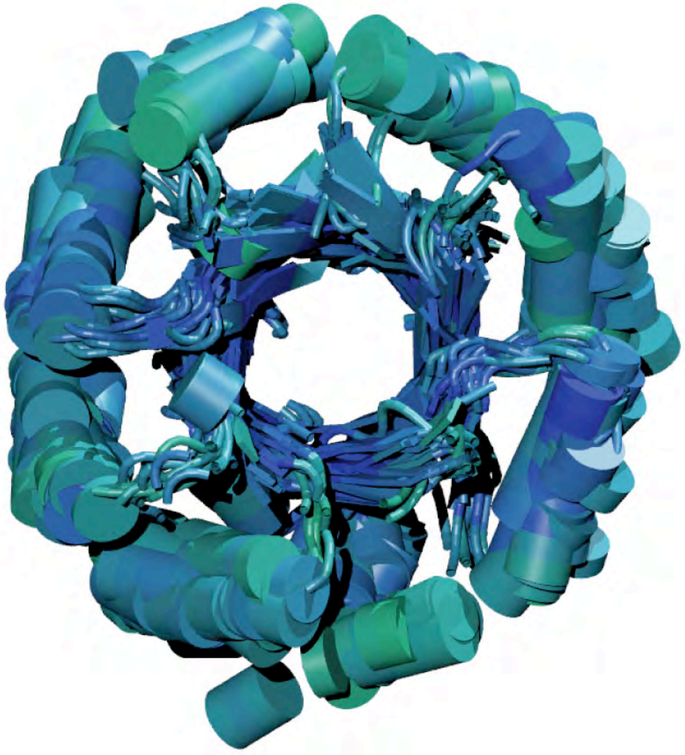
Fold recognition

Fold versus Superfamily hits

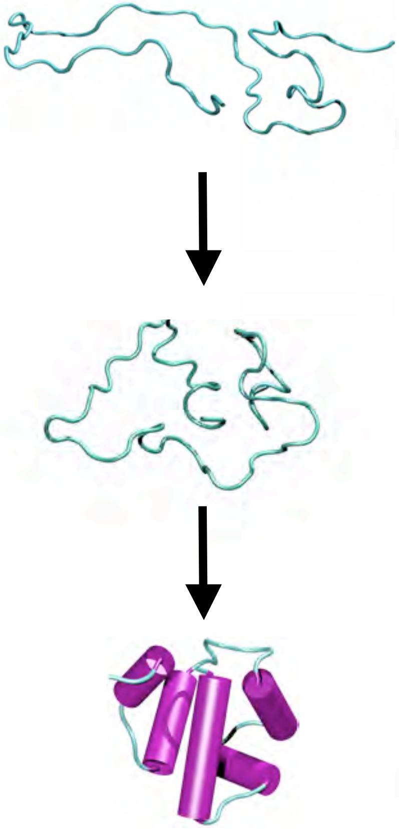
A. Sethi, P. O'Donoghue, ZLS, PNAS **102**, 2005

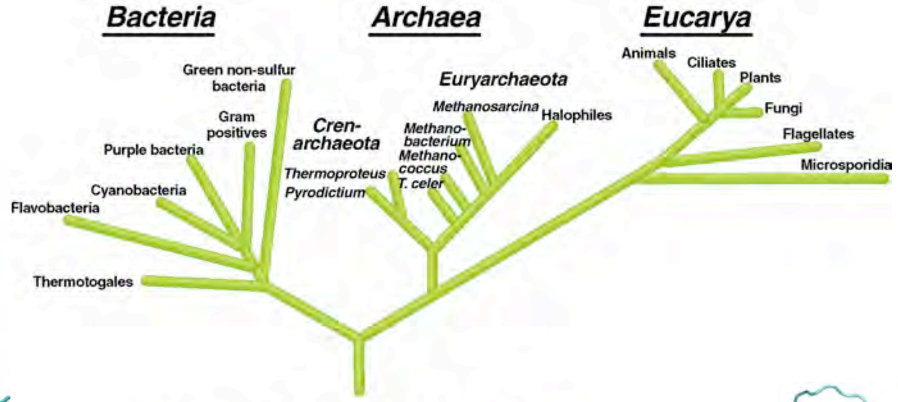
Reclassification of TIM barrel Superfamilies ?

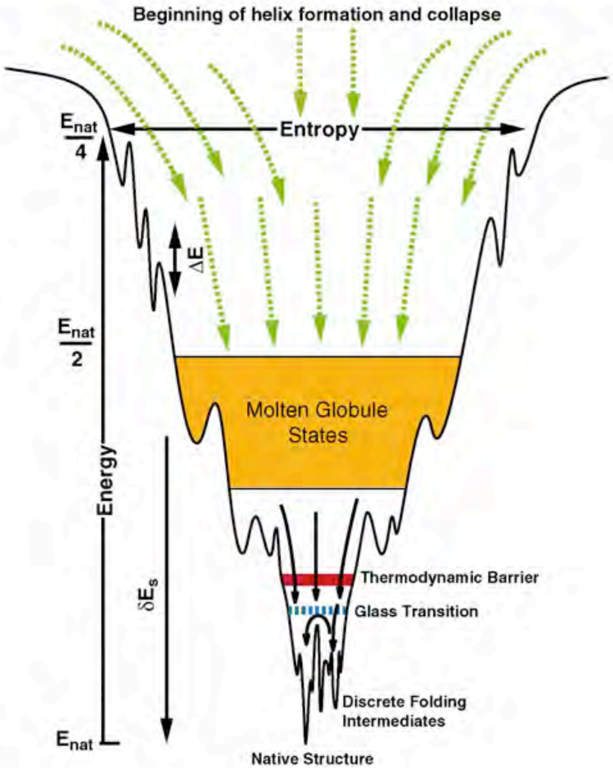


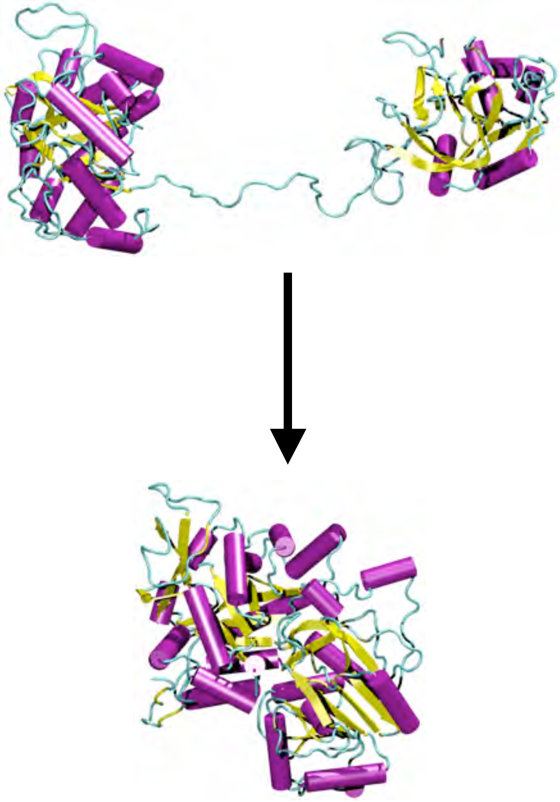


Unifying the Worlds of Sequence and Structure

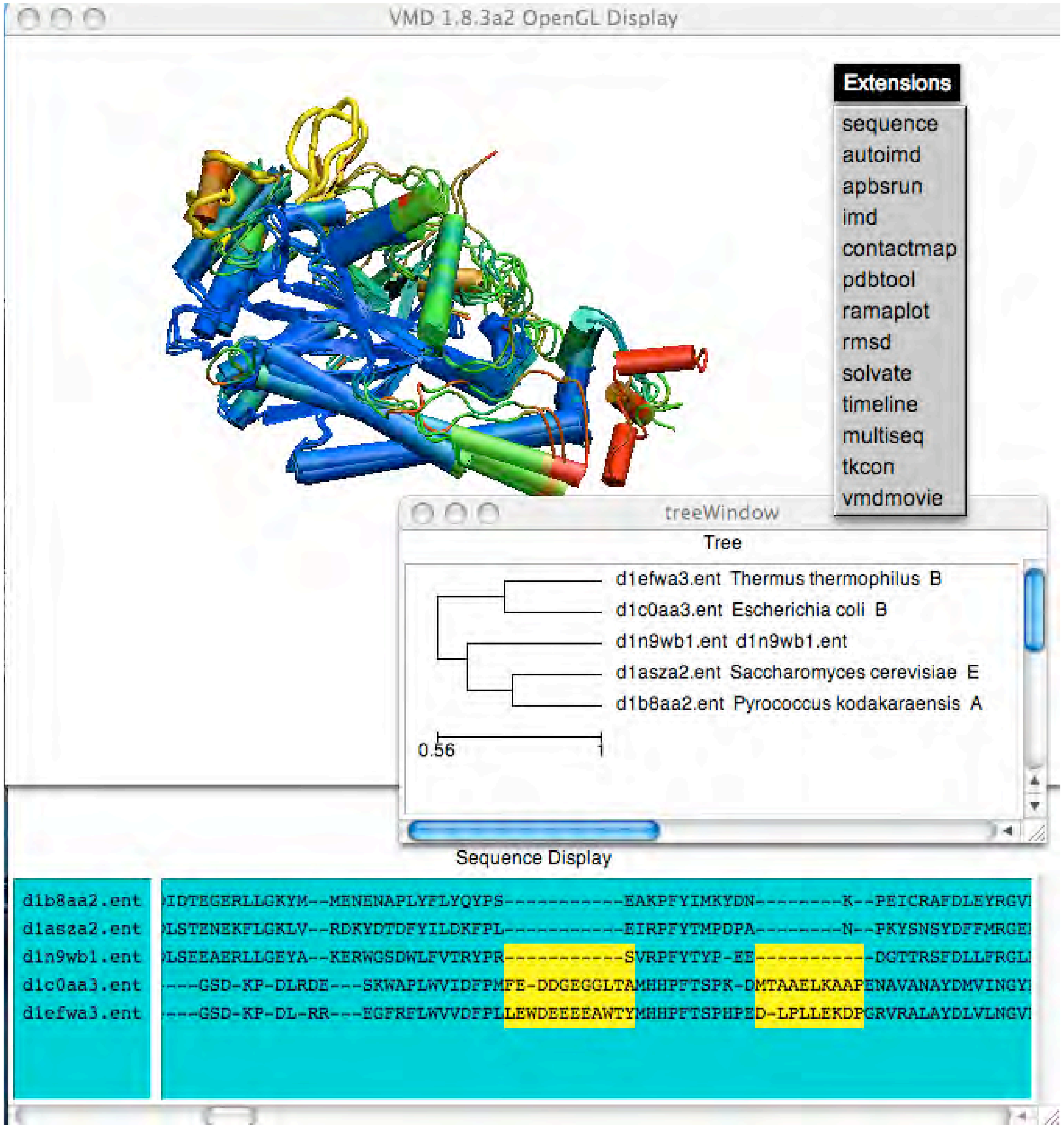








Multiseq in VMD : Merging the sequence and structure worlds

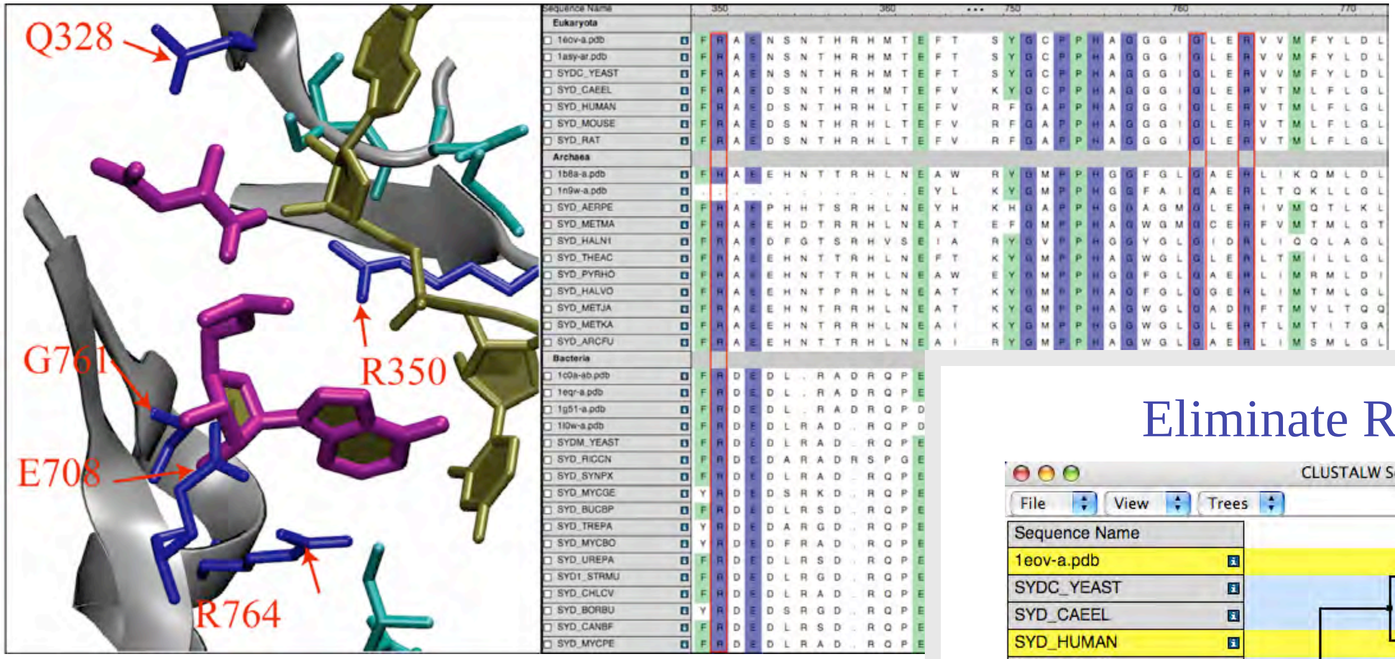

VMD 1.8.3a2 OpenGL Display
Extensions
sequence
autoimd
apbsrun
imd
contactmap
pdbtool
ramaplot
rmsd
solvate
timeline
multiseq
tkcon
vmdmovie
treeWindow
Tree
d1efwa3.ent Thermus thermophilus B
d1c0aa3.ent Escherichia coli B
d1n9wb1.ent d1n9wb1.ent
d1asza2.ent Saccharomyces cerevisiae E
d1b8aa2.ent Pyrococcus kodakaraensis A
0.56
1
Sequence Display

```
d1b8aa2.ent  IDTEGERLLGKYM--MENENAPLYFLYQYPS-----------EAKPFYIMKYDN--------K--PEICRAFDLEYRGV
d1asza2.ent  LSTENEKFLGKLV--RDKYDTDFYILDKFPL-----------EIRPFYTMPDPA--------N--PKYSNSYDFFMRGE
d1n9wb1.ent  LSEEAERLLGEYA--KERWGSDWLFVTRYPR-----------SVRPFYTYP-EE-----------DGTTRSFDLLFRGL
d1c0aa3.ent  ---GSD-KP-DLRDE---SKWAPLWVIDFPMFE-DDGEGGLTAMHHPFTSPK-DMTAAELKAAPENAVANAYDMVINGY
d1efwa3.ent  ---GSD-KP-DL-RR---EGFRFLWVVDFPLLEWDEEEEAWTYMHHPFTSPHPED-LPLLEKDPGRVRALAYDLVLNGV
```

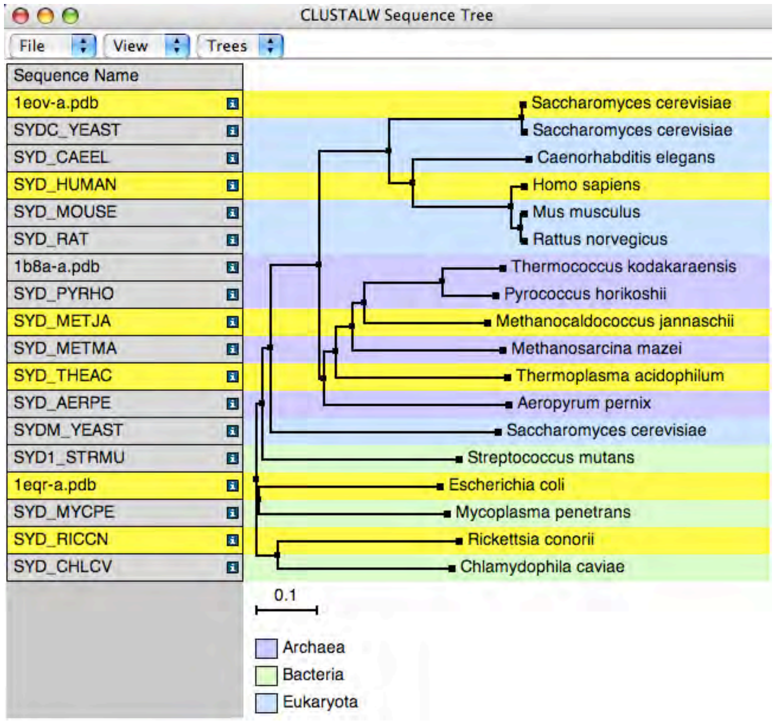
Version 1.83

2006 MultiSeq: New Features

Analyze the Evolution of Sequence and Structure



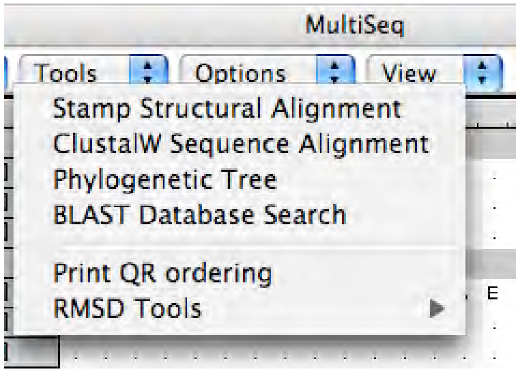
Eliminate Redundancy



Sequence Name	
1eov-a.pdb	Saccharomyces cerevisiae
SYDC_YEAST	Saccharomyces cerevisiae
SYD_CAEEL	Caenorhabditis elegans
SYD_HUMAN	Homo sapiens
SYD_MOUSE	Mus musculus
SYD_RAT	Rattus norvegicus
1b8a-a.pdb	Thermococcus kodakaraensis
SYD_PYRHO	Pyrococcus horikoshii
SYD_METJA	Methanocaldococcus jannaschii
SYD_METMA	Methanosarcina mazei
SYD_THEAC	Thermoplasma acidophilum
SYD_AERPE	Aeropyrum pernix
SYDM_YEAST	Saccharomyces cerevisiae
SYD1_STRMU	Streptococcus mutans
1eqr-a.pdb	Escherichia coli
SYD_MYCPE	Mycoplasma penetrans
SYD_RICCN	Rickettsia conorii
SYD_CHLCV	Chlamydophila caviae

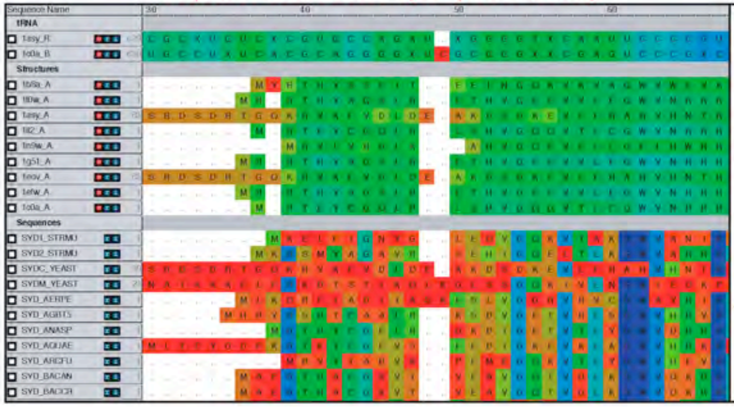
□ Archaea
□ Bacteria
□ Eukaryota

Plus More Functions

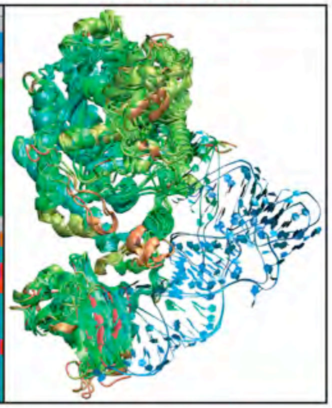


Copyright 200

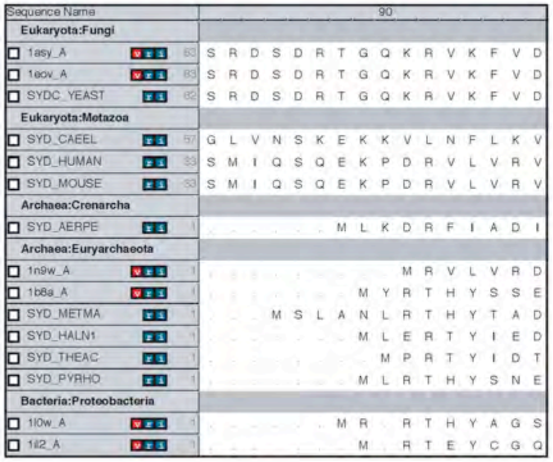
View structural data colored by structural conservation and sequence data colored by sequence identity



Synchronization between 1D and 3D views

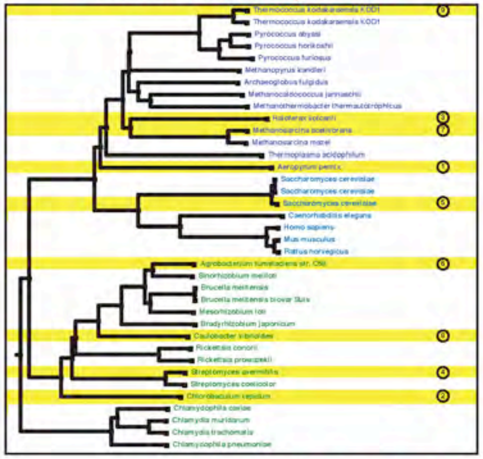


Group data by taxonomic classification

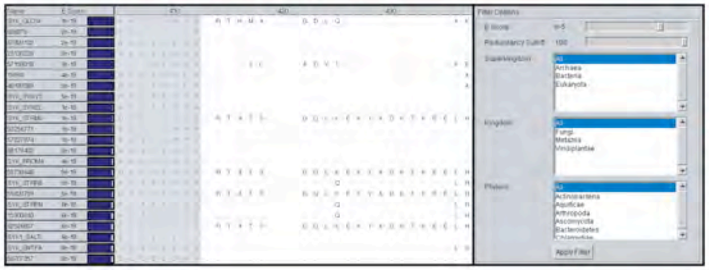


```
Sequence Name                          90
Eukaryota:Fungi
□ 1asy_A        83  S R D S D R T G Q K R V K F V D
□ 1eov_A        83  S R D S D R T G Q K R V K F V D
□ SYDC_YEAST    82  S R D S D R T G Q K R V K F V D
Eukaryota:Metazoa
□ SYD_CAEEL     57  G L V N S K E K K V L N F L K V
□ SYD_HUMAN     33  S M I Q S Q E K P D R V L V R V
□ SYD_MOUSE     33  S M I Q S Q E K P D R V L V R V
Archaea:Crenarcha
□ SYD_AERPE      1              M L K D R F I A D I
Archaea:Euryarchaeota
□ 1n9w_A         1                    M R V L V R D
□ 1b8a_A         1                M Y R T H Y S S E
□ SYD_METMA      1        M S L A N L R T H Y T A D
□ SYD_HALN1      1              M L E R T Y I E D
□ SYD_THEAC      1                  M P R T Y I D T
□ SYD_PYRHO      1              M L R T H Y S N E
Bacteria:Proteobacteria
□ 1l0w_A         1              M R   R T H Y A G S
□ 1il2_A         1                M   R T E Y C G Q
```

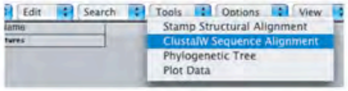
View sequence or structure phylogenies and eliminate redundancy with QR



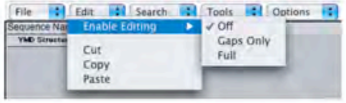
Import data directly from BLAST databases



Align sequences with Clustal



Sequence Editor: Manually adjust alignments or sequences



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QR Algorithms

Mike Heath (UIUC)

Protein Structure Prediction

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Ken Suslick (UIUC)