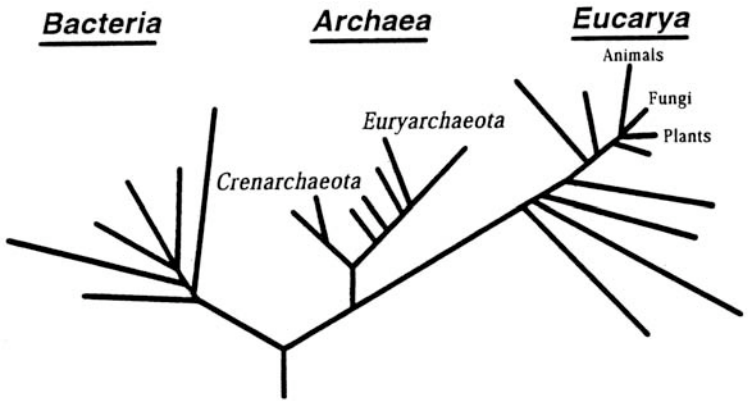
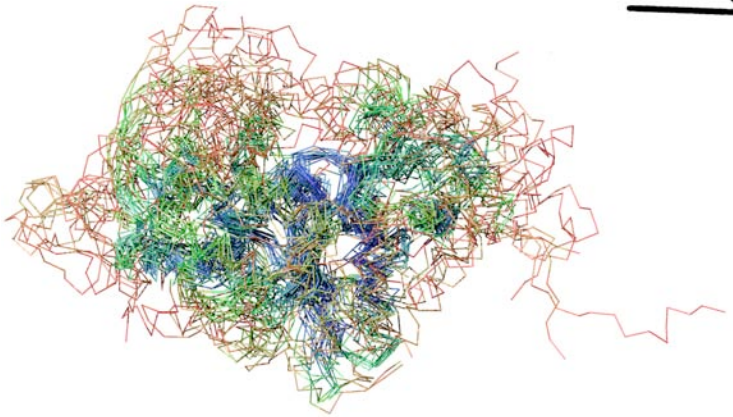
Perth Computational Biology Workshop June 2004

Bioinformatics II - Evolution of Protein Structure

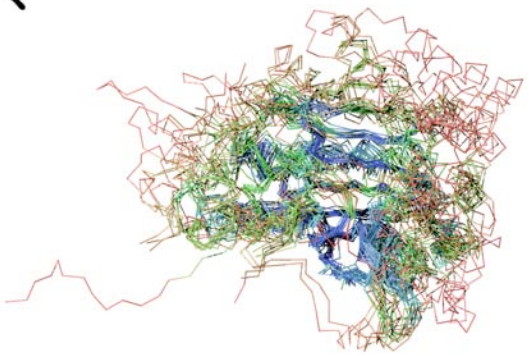
Evolution of Protein Structure

in the Aminoacyl-tRNA Synthetases





class I

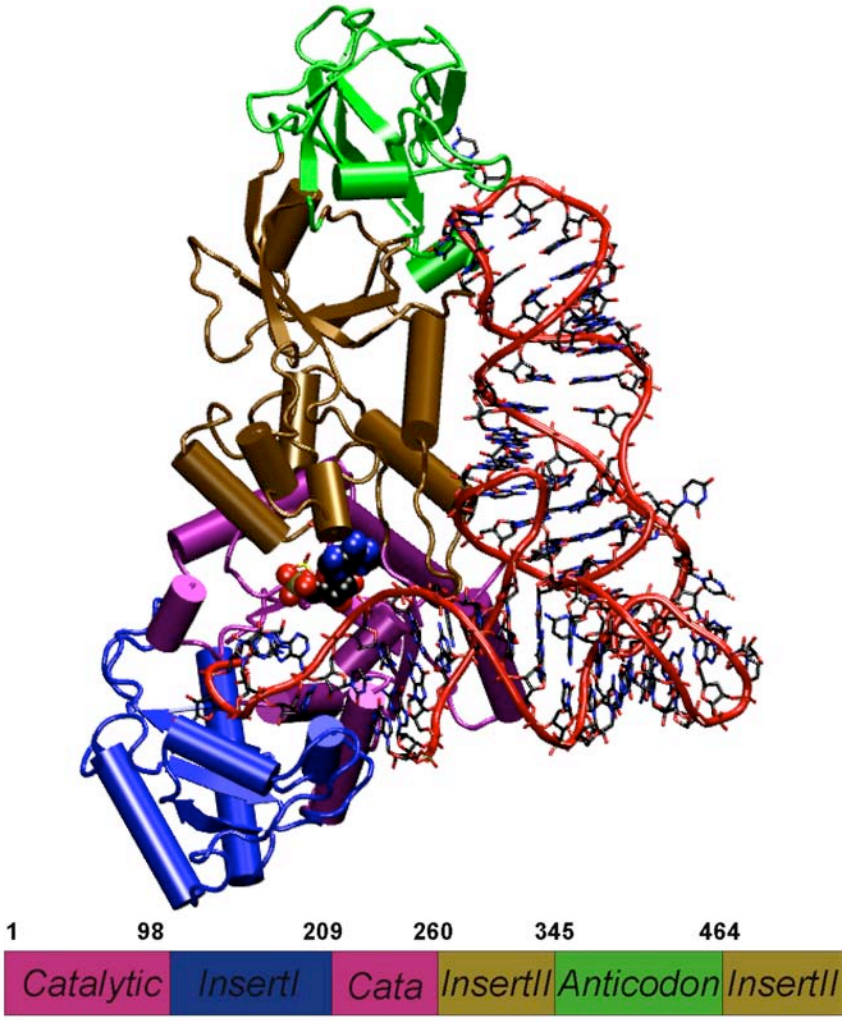


class II

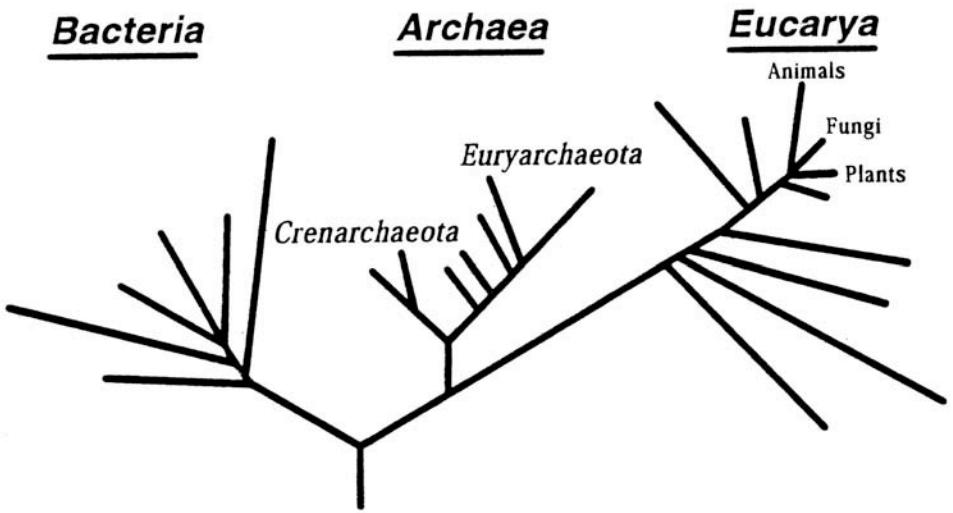
Zan Luthey-Schulten

Department of Chemistry, Beckman Institute,
Center for Biophysics and Computational Biology
University of Illinois at Urbana-Champaign

Aminoacyl-tRNA synthetases

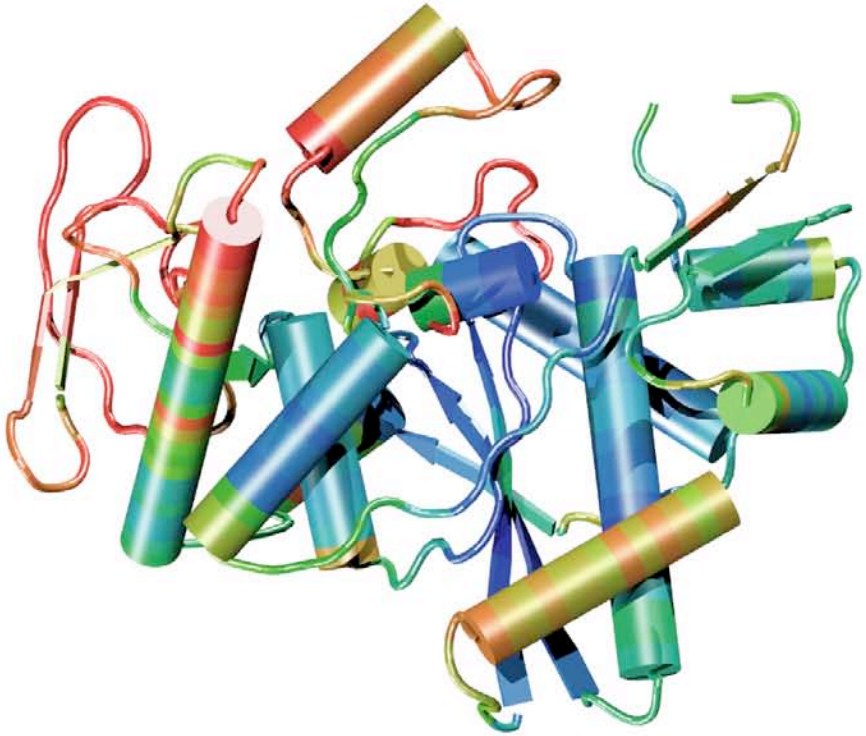


Universal Tree of Life

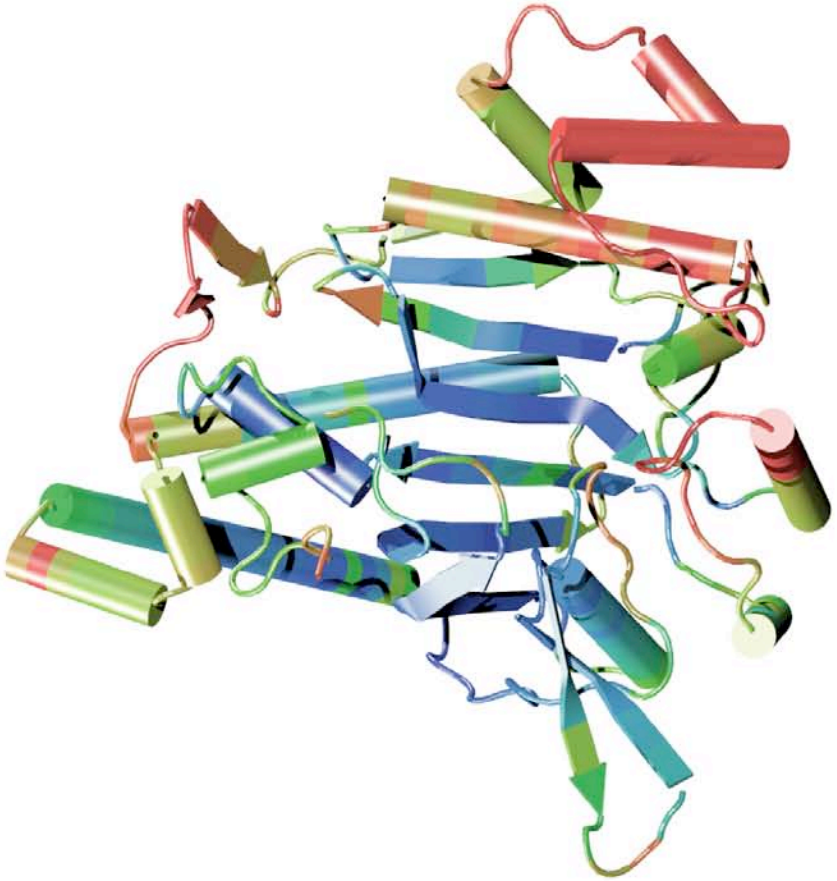


Woese *PNAS* 1990, 2002.

Structural Conservation in the Catalytic Domain of the AARSs



Class I Lysyl-tRNA Synthetase

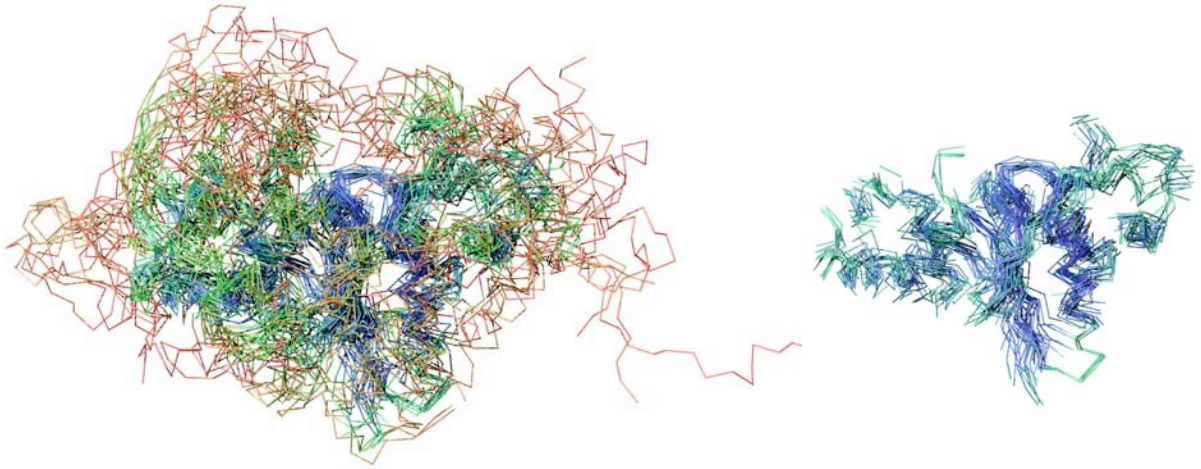


Class II Lysyl-tRNA Synthetase

Why Study the Evolution of Protein Structure?

1. Important for Homology Modeling

Better profiles improve database searches and give better alignments of distant homologs.
Allows mixing of sequence and structure information systematically.



13% sequence id
in the core (blue)

2. Learn how evolutionary dynamics changed protein shape.

Mapping a protein of unknown structure onto a homologous protein of known structure is equivalent to defining the evolutionary pathway connecting the two proteins

3. Impact on protein structure prediction, folding, and function

Evolutionary profiles increase the signal to noise ratio

Outline

1. Summarize evolutionary theory of the universal phylogenetic tree.

Methods

2. Introduce a structure-based metric which accounts for gaps,
   and show that evolutionary information is encoded in protein structure.

3. Introduce multidimensional QR factorization for computing
   non-redundant representative multiple alignments in sequence or structure.

Applications

4. Non-redundant multiple alignments which well represent the evolutionary history
   of a protein group provide better profiles for database searching.

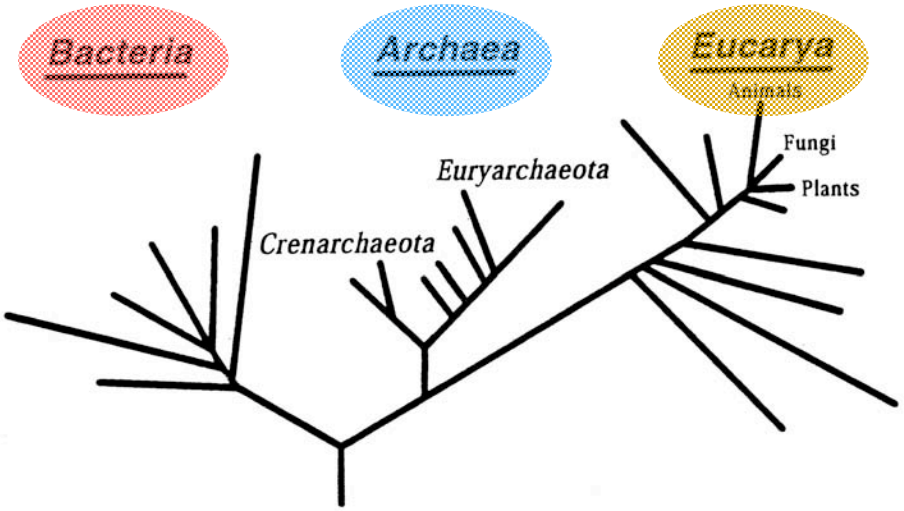
   Eliminate bias inherited from structure or sequence databases.

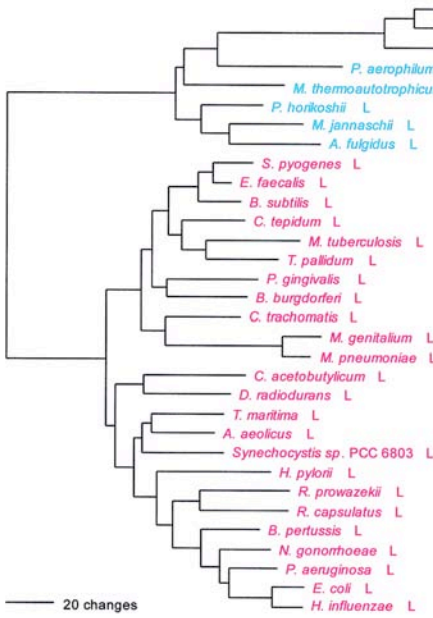
   Important for bioinformatic analysis (substitution matrices, knowledge based potentials structure pred., genome annotation) and evolutionary analysis.

5. Depict the evolution of structure and function in Aspartyl-tRNA synthetase.

Universal Phylogenetic Tree

three domains of life





Eucarya

Archaea

Bacteria

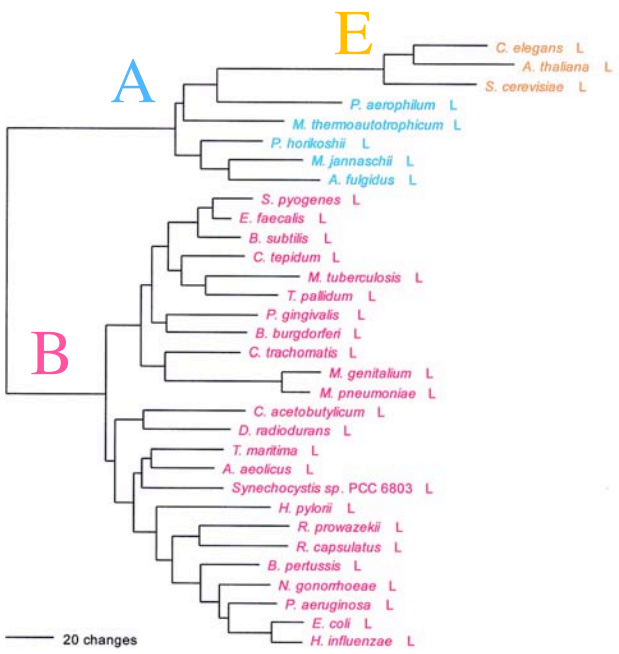
Leucyl-tRNA synthetase displays the full canonical phylogenetic distribution.

for review see Woese *PNAS* 2000

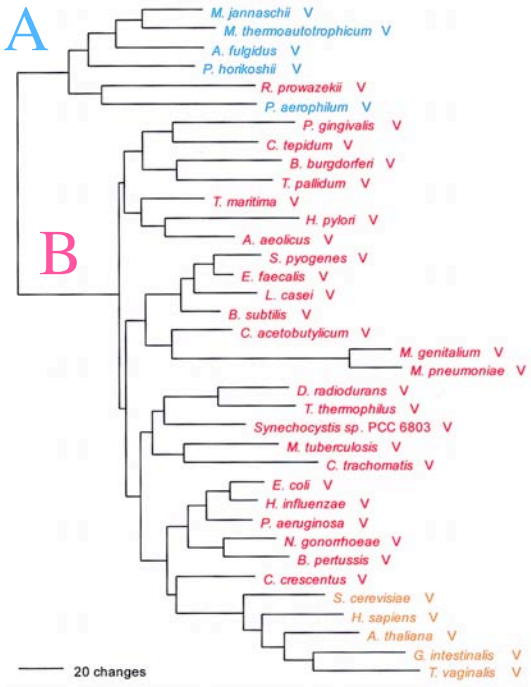
Woese, Olsen, Ibba, Soll *MMBR* 2000

Phylogenetic Distributions

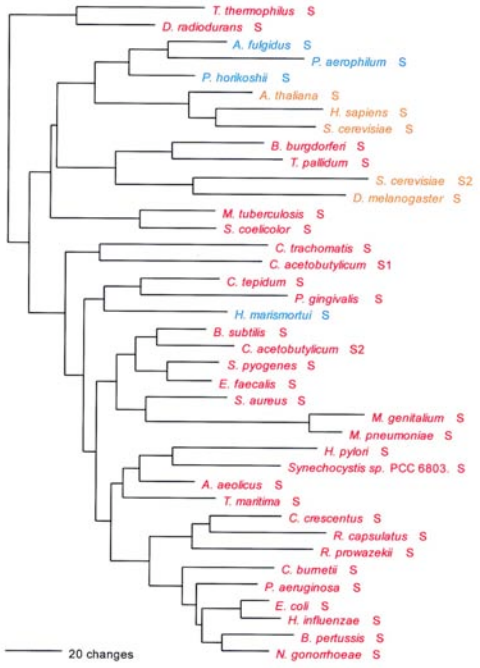
Full Canonical



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

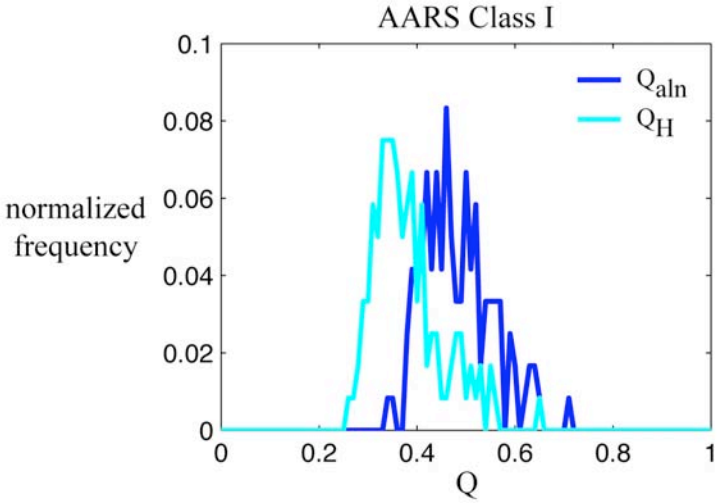
Protein Structure Similarity Measure

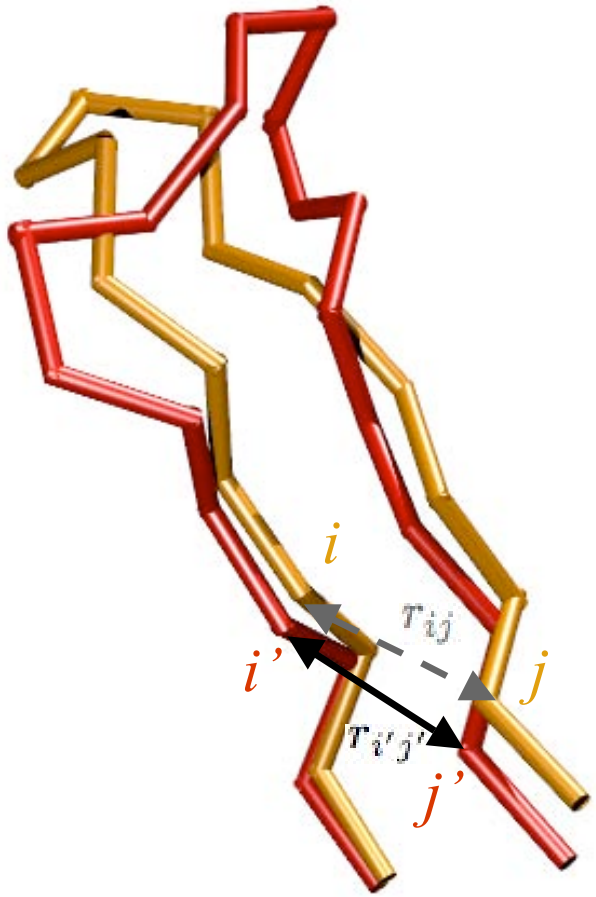
Q_H Structural Homology

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

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

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





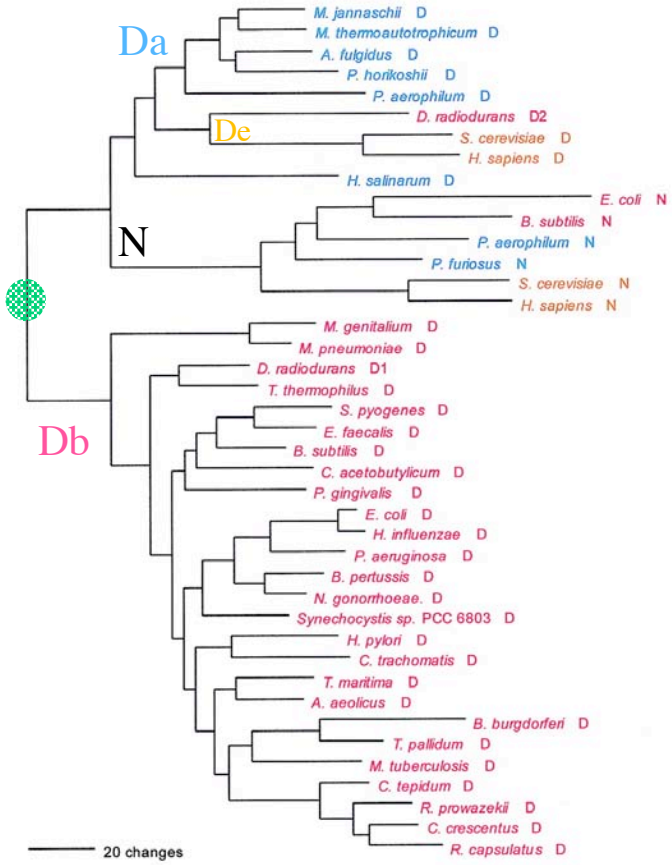
"Gaps should count as a character but not dominate" C. Woese

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

Protein structure encodes evolutionary information

Sequence Phylogeny

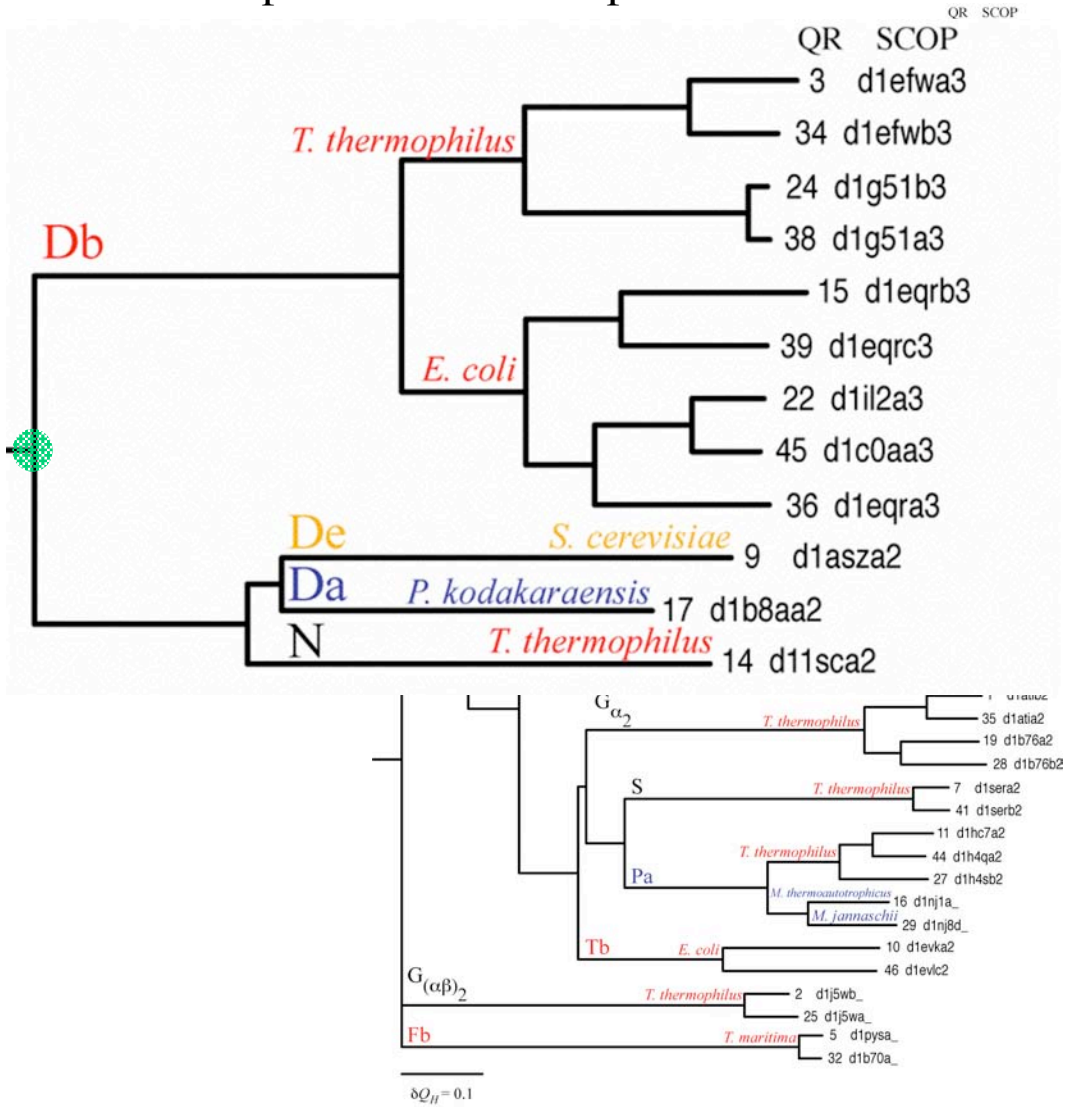
AspRS-AsnRS Group



Woese, Olsen, Ibba, Soll *MMBR* 2000

Structure Phylogeny

AspRS-AsnRS Group Class II AARSs

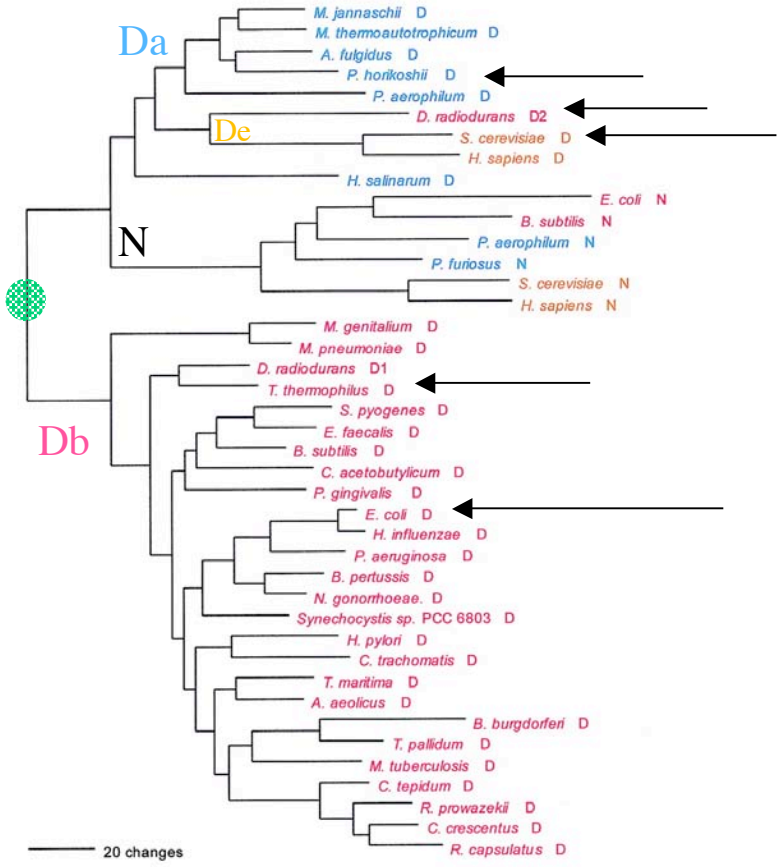


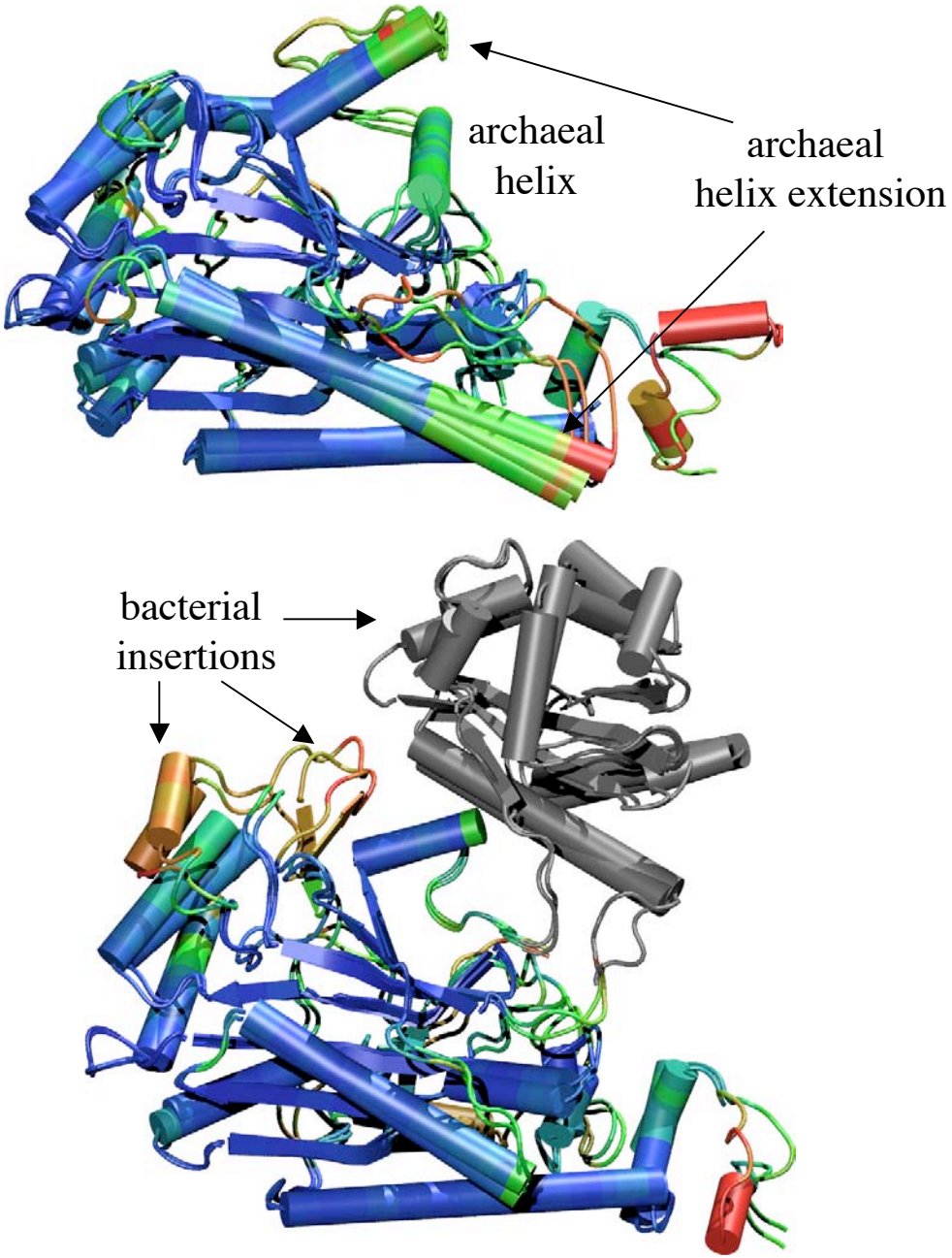
O'Donoghue & Luthey-Schulten *MMBR*.2003.

Horizontal Gene Transfer in Protein Structure

Sequence Phylogeny

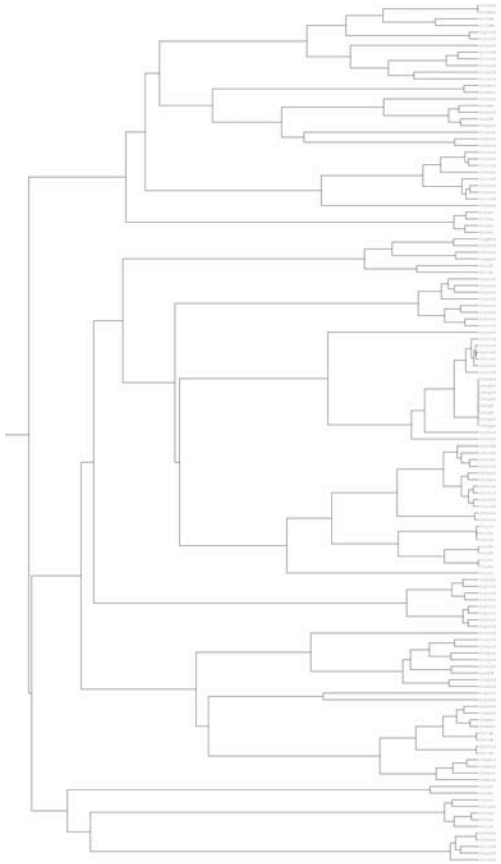
AspRS-AsnRS Group



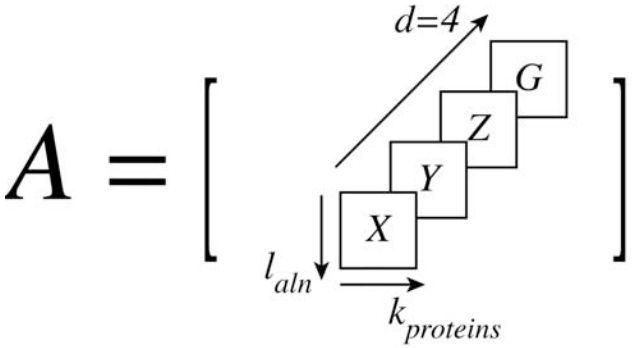


Non-redundant Representative Sets

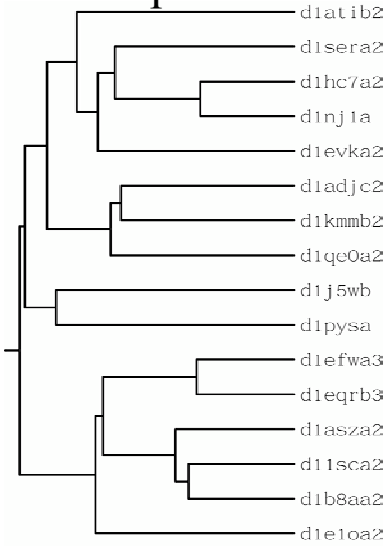
Too much information
129 Structures

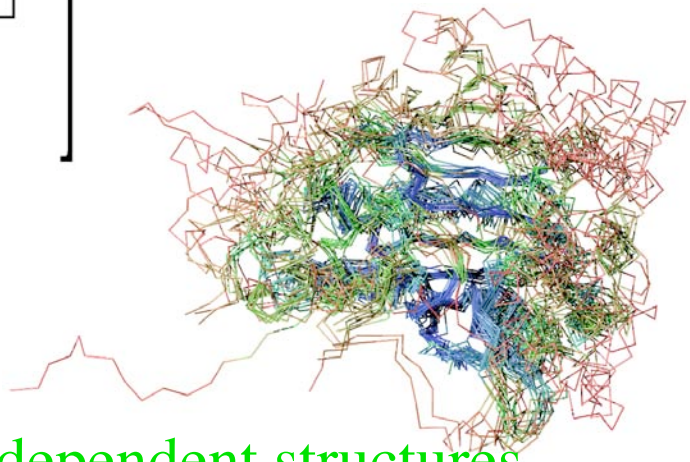


Multidimensional QR
factorization
of alignment matrix, ***A***.



Economy of information
16 representatives





QR computes a set of minimal linearly dependent structures.

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

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 $g = \eta \dfrac{\|X\|_{F_4} + \|Y\|_{F_4} + \|Z\|_{F_4}}{\|G\|_{F_4}}$

adjustable parameter

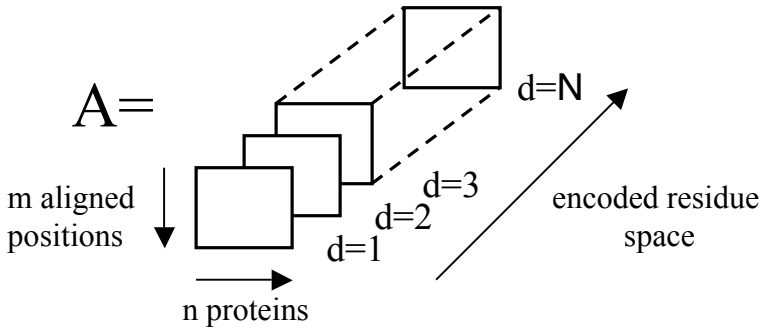
Sequence Space

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 Matrix



A Multiple Alignment is a Matrix with Linearly Dependent Columns

redundancy is equivalent to linear dependence

QR factorization

Re-orders the columns of A, segregating the linearly independent columns from the dependent ones without scrambling the information in A. SVD not an option.

$$Q^T AP = \tilde{R}$$

$$\tilde{A} = AP$$

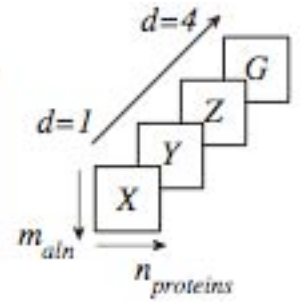
Q^T – orthogonal matrix of product of Householder transformations.

P – permutation matrix encodes column pivoting which exchanges columns of A and puts the redundant or similar proteins to the right hand side.

Multidimensional QR

N **simultaneous** QR factorizations, one for each d-dimension.

$$Q^T_{(d)} A_{(d)} P = Q^T_{(d)} \left[\right] P = \tilde{R}_{(d)}$$



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

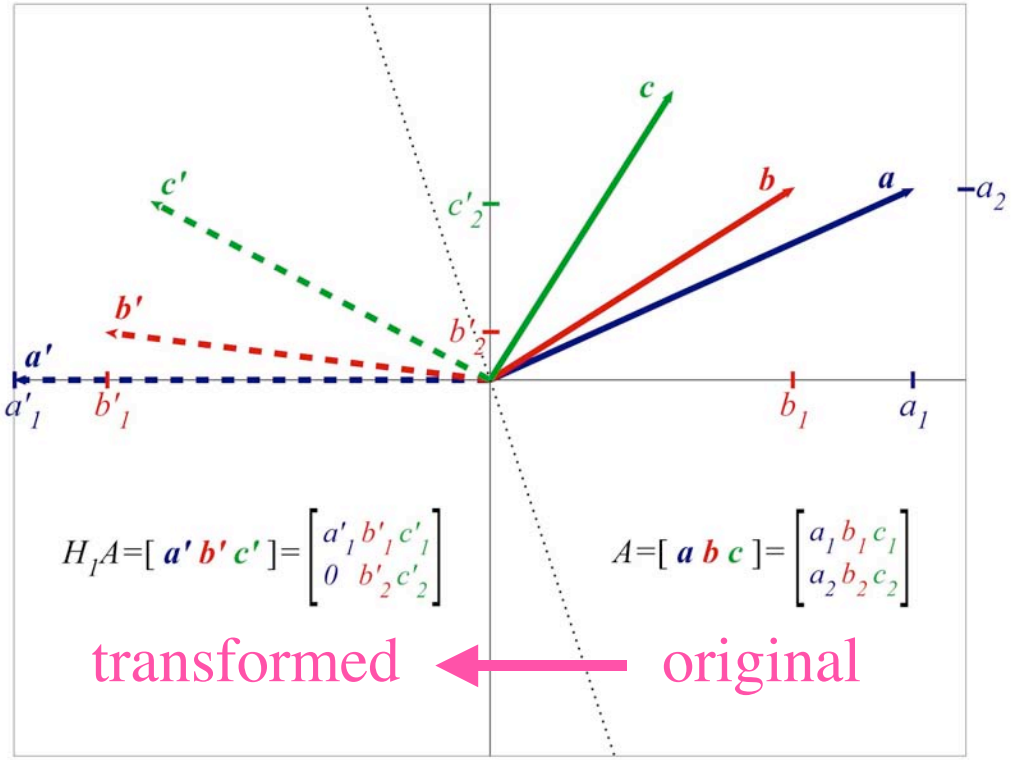
L. Heck, J. Olkin, and K. Nagshineh (1998) *J. Vibration Acoustics* **120**:663.

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

The QR establishes an **order** of linear dependence

by applying Householder transformations and permutations

$$Q^T = H_n \ldots H_1$$



Three 1-D (2 residue) proteins **a** **b** **c.**

a is our measuring stick, reference frame.

The transformation reveals that
b is more linearly dependent on **a**,
so the permutation swaps **b'** with **c'**.

Given **a**, **c** adds more information to the system than **b**.

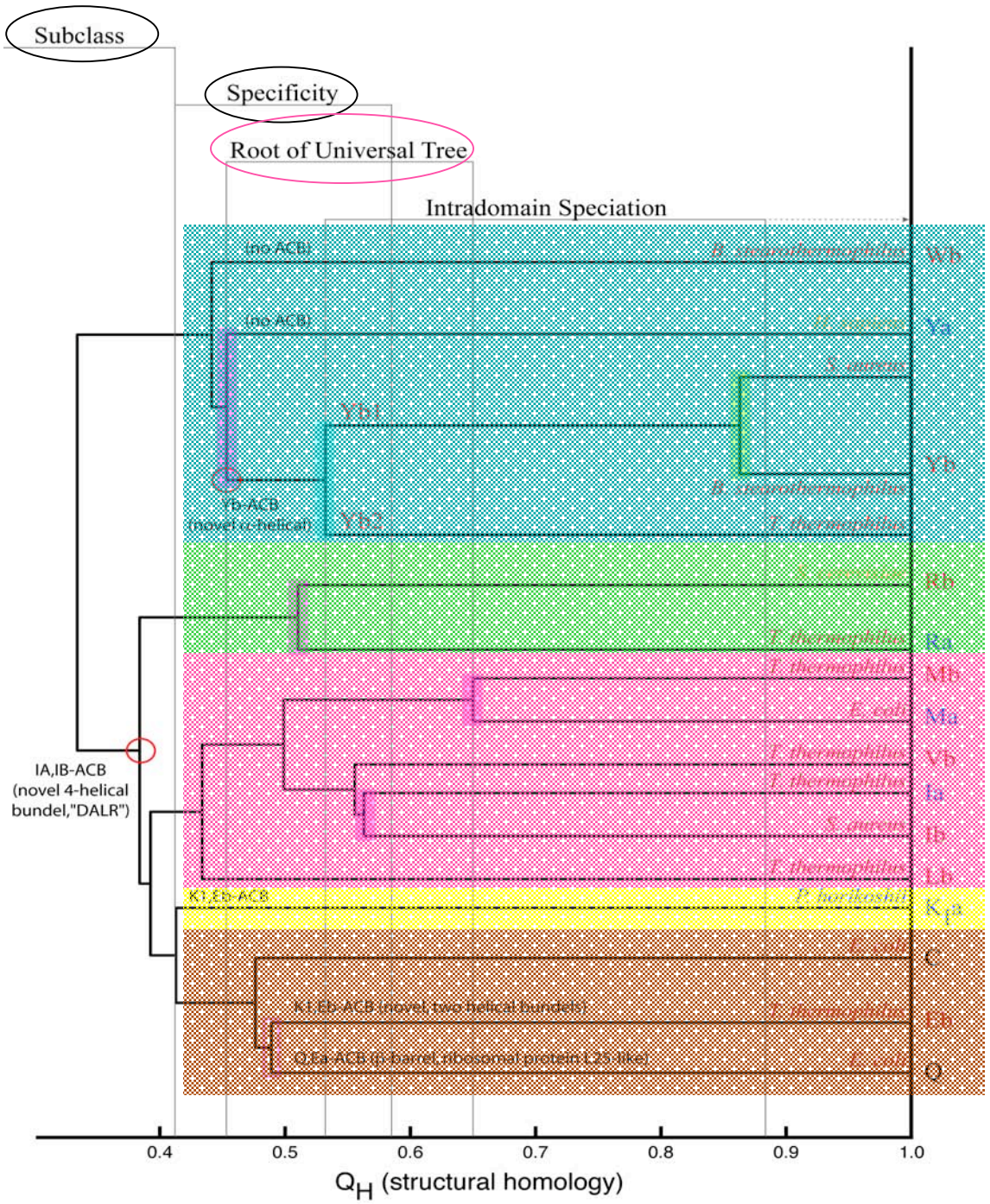
Multiply aligned proteins exist in a higher dimensional space, so this magnitude is computed with a matrix p-norm:

$$\|a_j\|_{F_p} = \left(\sum_{d=1}^{4} \sum_{i=k}^{m_{aln}} |a_{ijd}|^p\right)^{1/p}$$

adjustable parameter

Householder, *J. Assoc. Comput. Mach.*, 1958.

Class I AARSs evolutionary events

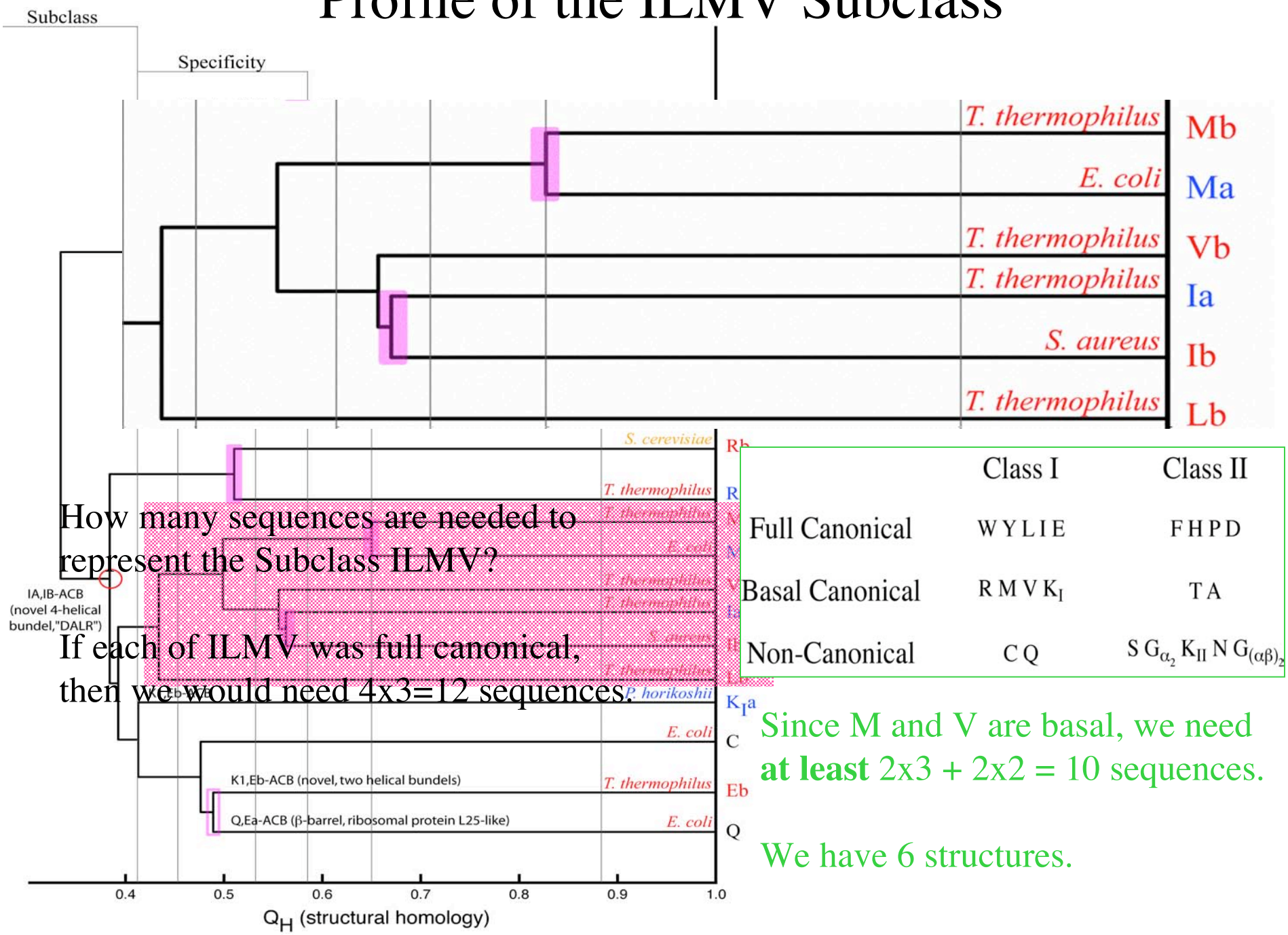


5 Subclasses

Specificity – 11 Amino acids

Domain of life A, B, E

Profile of the ILMV Subclass



How many sequences are needed to represent the Subclass ILMV?

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

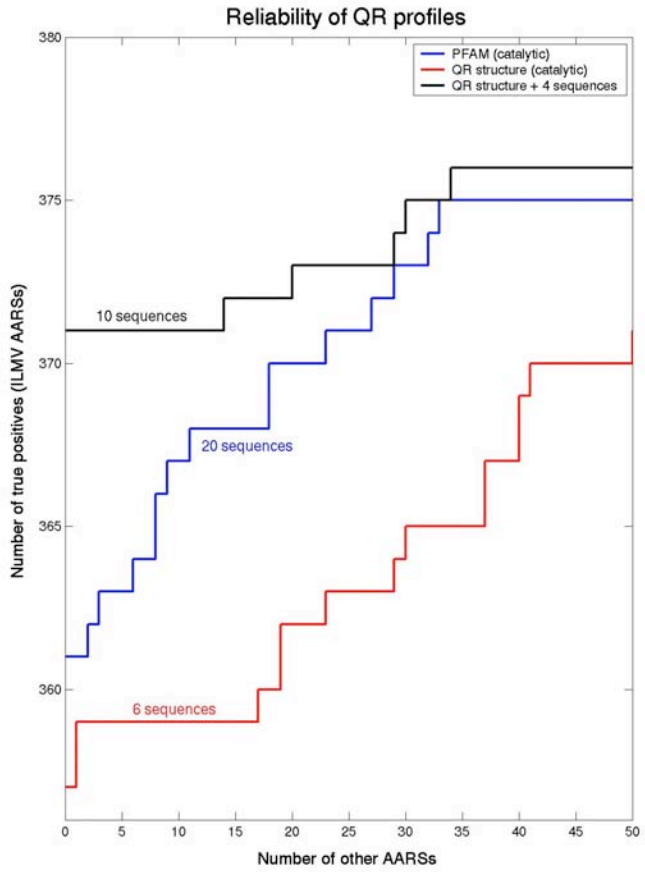
	Class I	Class II
Full Canonical	W Y L I E	F H P D
Basal Canonical	R M V K_I	T A
Non-Canonical	C Q	S G_{α_2} K_{II} N $G_{(\alpha\beta)_2}$

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

We have 6 structures.

Non-Redundant Profiles for Database Searching
AARS Subclass ILMV

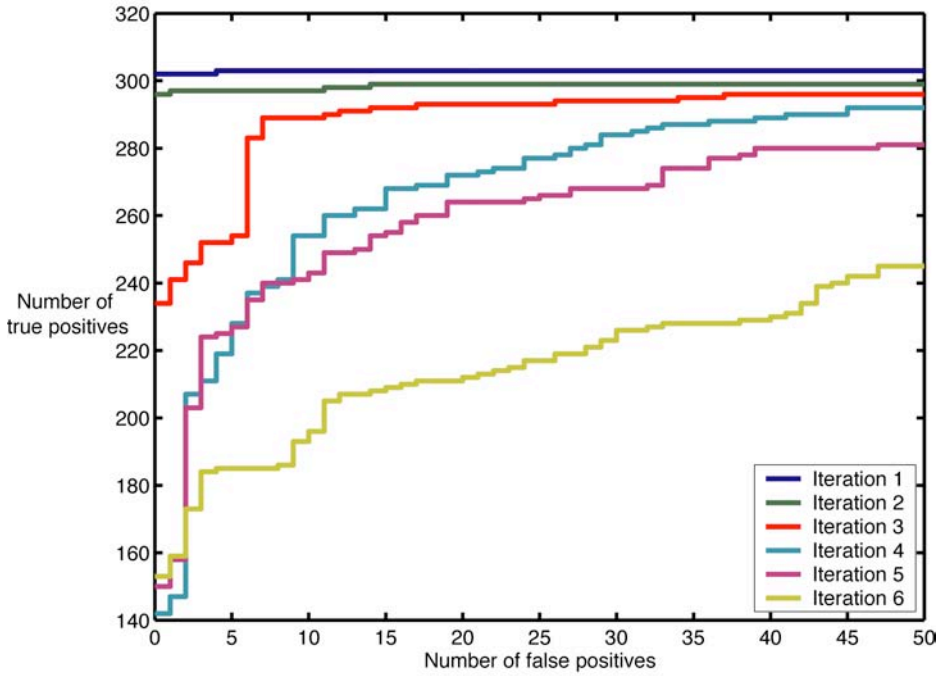
HMMER



false positives

Choosing the right 10 sequence makes all the difference.

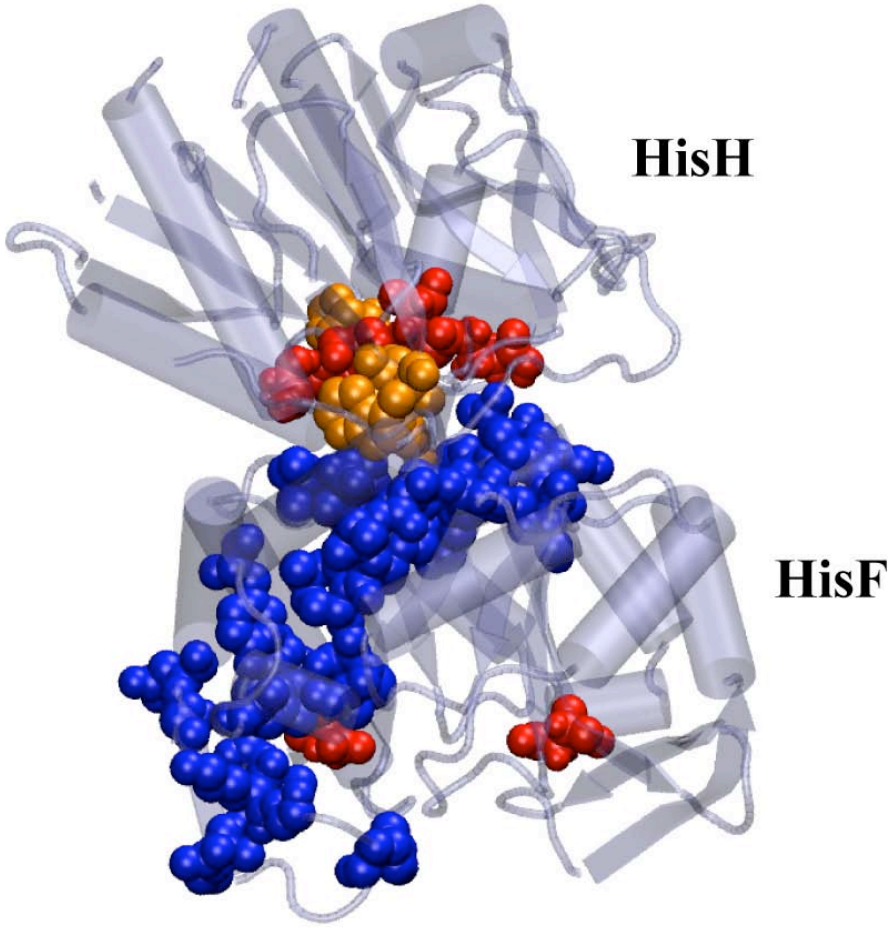
Psi-Blast



Starting with a non-redundant profile, **accuracy diminishes with Psi-blast iterations** which add in bias. **Repair with QR filter.**

A. Sethi, P. O'Donoghue, Z..Luthey-Schulten

Evolutionary Structure/Sequence Profiles Suggest Reaction Pathway



R. Amaro and Z. Schulten, *MD Simulations of Substrate Channeling*, Chemical Physics Special Issue, 2004 (in press). *FE Landscapes of Ammonia Channeling*, PNAS 2003

Summary

Evolutionary information is encoded in protein structure.

- Protein structure can be used to investigate early evolutionary events.
- Accounting for gaps is important for comparing homologous structures.

Multidimensional QR factorization computes non-redundant sets from multiple sequence or structure alignments which well represent the evolutionary history of the group.

Structure databases are limited, but multiple structural alignments provide accurate alignments, especially in the case of distant homologies

Supplement the structures with an appropriate number and type of sequences (in accord with the phylogenetic topology) to produce minimal representative profiles.

Acknowledgements

Patrick O'Donoghue
Rommie Amaro
Anurag Sethi
John Eargle
Corey Hardin
Michael Baym
Michael Janusyzk

Felix Autenrieth
Taras Pogorelov

Graphics Programmers VMD

John Stone, Dan Wright, John Eargle

Collaborators

Evolutionary Studies

Gary Olsen, Carl Woese (UIUC)

Algorithms

Mike Heath (UIUC)
Rob Russell (EMBL) **STAMP**

Protein Structure Prediction

Peter Wolynes, Jose Onuchic,
Ken Suslick

Funding: NSF, NIH, NIH Resource for Macromolecular Modeling and Bioinformatics