Structural Alignment of Proteins

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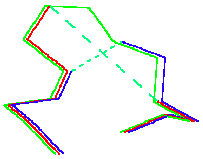
Princeton University
CS597A, Fall 2007

Goal

Align protein structures

```
1  2  3  4  5  6  7  8  9  10 11 12 13 14
PHE ASP ILE CYS ARG LEU PRO GLY SER ALA GLU ALA VAL CYS
PHE ASN VAL CYS ARG THR PRO --- --- --- GLU ALA ILE CYS
PHE ASN VAL CYS ARG --- --- --- THR PRO GLU ALA ILE CYS
```



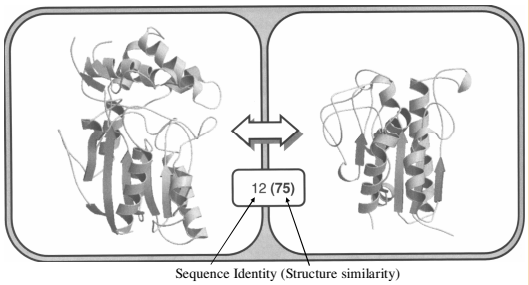
[Marian Novotny]

Terminology

Superposition
- Given correspondences, compute optimal alignment transformation, and compute alignment score

Alignment
- Find correspondences, and then superpose structures

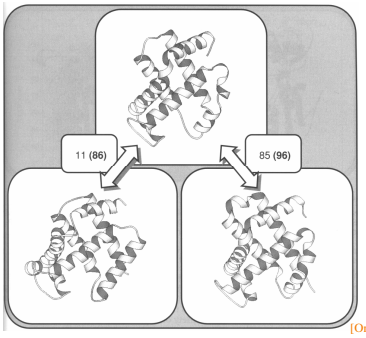
Structure vs. Sequence



Sequence Identity (Structure similarity)

[Orengo04, Fig 6.2]

Structure vs. Sequence

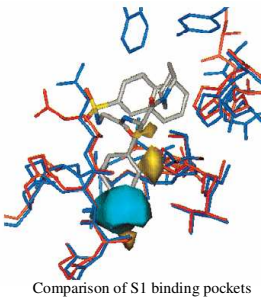


[Orengo04, Fig 6.1]

Applications

Fundamental step in:
- Analysis
- Visualization
- Comparison
- Design

Useful for:
- Structure classification
- Structure prediction
- Function prediction
- Drug discovery



Comparison of S1 binding pockets of thrombin (blue) and trypsin (red).

[Katzenholtz00]

Goals

Desirable properties:

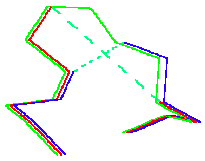
- Automatic
- Discriminating
- Fast

Theoretical Issues

NP-complete problem

- Arbitrary gap lengths
- Global scoring function

```
1  2   3   4   5   6   7   8   9   10  11  12  13  14
PHE ASP ILE CYS ARG LEU PRO GLY SER ALA GLU ALA VAL CYS
PHE ASN VAL CYS ARG THR PRO --- --- --- GLU ALA ILE CYS
PHE ASN VAL CYS ARG --- --- --- THR PRO GLU ALA ILE CYS
```



Methodological Issues

Choices:

- Representation
- Scoring function
- Search algorithm

Methodological Issues

Factors governing choices:

?

Methodological Issues

Factors governing choices:

- Application: homology detection, drug design, etc.
- Granularity: atom, residue, fragment, SSE
- Representation: inter-molecular, intra-molecular
- Scoring: geometric, gaps, chemical, structural, etc.
- Correspondences: sequential, non-sequential
- Gap penalty: expect gaps near loops, etc.
- Flexibility: rigid, flexible
- Target: single protein, representative proteins, PDB

Methodological Issues

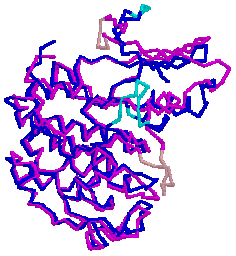
Representations:

- Residue positions
- Local geometry
- Side chain contacts
- Distance matrices (DALI)
- Properties (COMPARER)
- SSEs (SSM, VAST)
- Geometric invariants

Methodological Issues

Scoring functions:

- Distances (RMSD)
- Substitutions
- Gaps



Methodological Issues

Search algorithms:

- Heuristics (CE)
- Monte Carlo (DALI, VAST)
- Dynamic programming (STRUCTAL, SSAP)
- Graph matching (SSM)

Outline

Alignment issues

Example alignment methods ←

Fold prediction experiment

Function prediction experiment

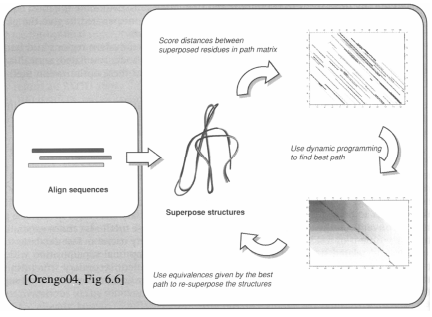
Example Methods

SSAP	Taylor & Orengo, 1989
STRUCTAL	Subbiah, Laurents & Levitt, 1993 Gerstein & Levitt 1998
DALI	Holm & Sander, 1993 Holm & Park, 2000
DEJAVU /LSQMAN	Kleywegt, 1996
CE	Shindyalov & Bourne, 1998
SSM	Krissinel & Henrick, 2003

+ 30 others!

Slide by Rachel Kolodny

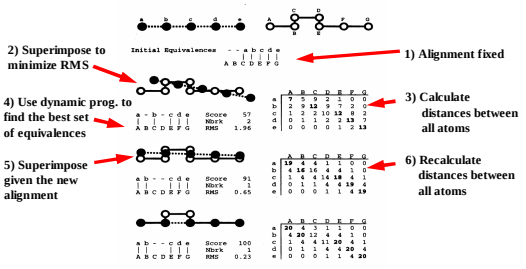
STRUCTAL



[Orengo04, Fig 6.6]

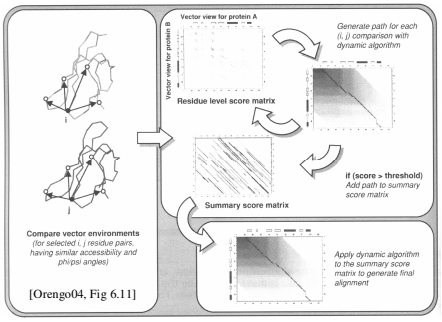
[Subbiah93, Gerstein98]

STRUCTAL



[Subbiah93, Gerstein98]

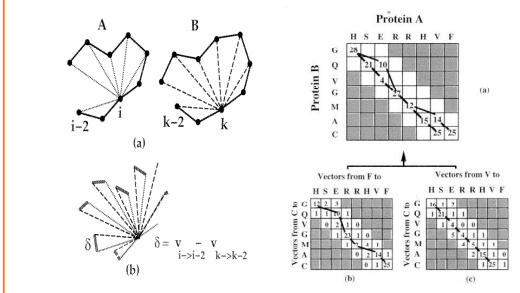
SSAP



[Orengo04, Fig 6.11]

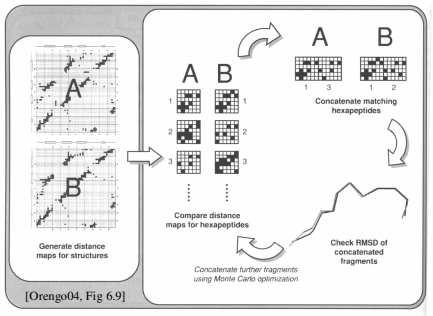
[Orengo96]

SSAP



[Orengo96]

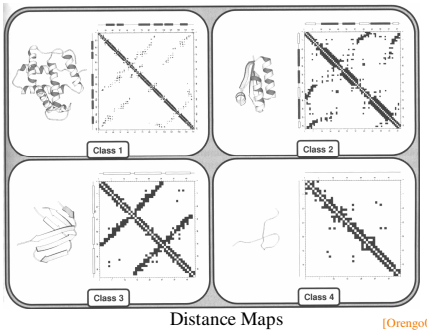
DALI



[Orengo04, Fig 6.9]

[Holm93]

DALI



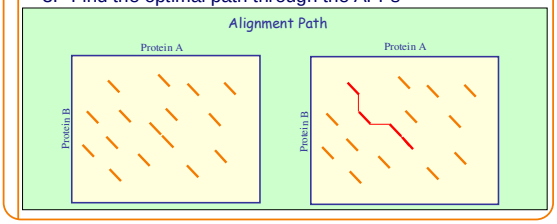
Distance Maps

[Orengo04, Fig 6.7]

CE

Basic steps:

1. Compare octameric fragments to create candidate aligned fragment pairs (AFP)
2. Stitch together AFPs according to heuristics
3. Find the optimal path through the AFPs



SSM

Two-step solution:

1. **Graph representation of structures**
2. **Graph matching**

SSM

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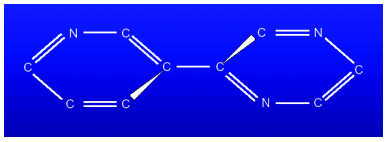
Graph representation of molecular structures



- **Simple and intuitive, however results in intractably large graphs for proteins**
- **Solution: build graphs over stable substructures, such as secondary structure elements (SSEs). Having a correspondence between SSEs, one may use that for the 3D alignment of all core atoms.**

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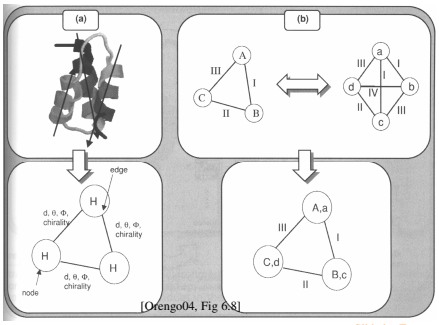
SSM



[Orengo04, Fig 6.8]

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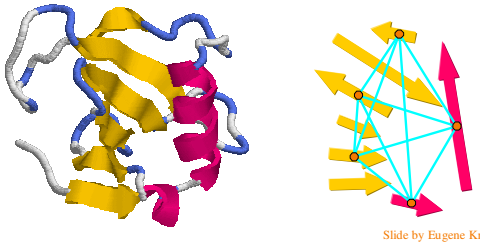
Graph representation of protein SSEs

E. M. Mitchell et al. (1990) J. Mol. Biol. 212:151
A. P. Singh and D. L. Brutlag (1997) ISMB-97 4:284



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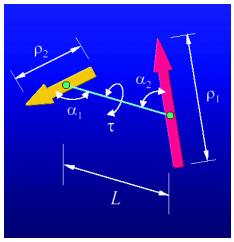
Protein graph labeling



Composite label of a vertex

- **type - helix or strand**
- **length r**

Composite label of an edge

- **length *L* (directed if connects vertices from the same chain)**
- **vertex orientation angles a_1 and a_2**
- **torsion angle t**

Vertex and edge labels are matched with thresholds on particular quantities

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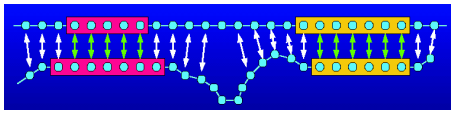
C_α alignment

- **SSE-alignment is used as an initial guess for C_α-alignment**
- **C_α-alignment is an iterative procedure based on the expansion of shortest contacts at best superposition of structures**



- **C_α-alignment is a compromise between the alignment length N_a and *r.m.s.d.* The optimised quantity is**

$$Q = \frac{N_a^2}{\left(1 + (r.m.s.d./R_0)^2\right) N_1 N_2}$$

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Statistical significance of match

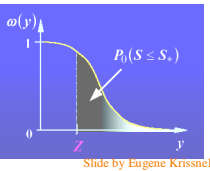
- **The overall probability of getting a particular match score by chance is the measure of the statistical significance of the match**

$$P_{value} = 1 - \left(1 - P(S_{N_a}) P(S_{r.m.s.d.}) \prod_{SSE} P(S_{SSE})\right)^{N_{combinations}}$$

- **P_M is traditionally expressed through so-called *Z*-characteristics**

$$P_0 = P(S_{N_a})\, P(S_{r.m.s.d.}) \prod_{SSE} P(S_{SSE})$$

$$P_0 = \int_Z^\infty \omega(y)dy \qquad \omega(y) = \sqrt{\frac{2}{\pi}} \exp\left(-\frac{1}{2}y^2\right)$$



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SSM output

- **Table of matched Secondary Structure Elements (SSE alignment)**
- **Table of matched core atoms (C_a - alignment) with dists between them**
- **Rotational-translation matrix of best structure superposition**
- ***R.m.s.d.* of C_a - alignment**
- **Length of C_a - alignment N_a**
- **Number of gaps in C_a - alignment N_g**
- **Quality score *Q***
- **Probability estimate for the match P_M**
- ***Z* - characteristics**
- **Sequence identity**

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List of matches

Structure Alignment Results

explanation of output

Query: pdb entry **1ldc**, chain A : 478 residues.
L-LACTATE DEHYDROGENASE: CYTOCHROME C OXIDOREDUCTASE 1 LDC 3 (FLAVOCYTOCHROME B<2>)
(E.C.1.1.2.3) MUTANT WITH TYR 143 1 LDC 4 REPLACED BY PHE (Y143F) COMPLEXED WITH PYRUVATE 1 LDC 5

Examined 19295 entries (39511 chains),
Matches 1–14 of 14.

Back to query

reset results

##	Scoring			Rmsd	N_{algn}	N_g	$\%_{seq}$	Query $\%_{sse}$	Target (PDB entry)			
	Q	P	Z						Match	$\%_{sse}$	N_{res}	Title
1	1.00	82.6	27.4	0.00	478	0	100	100	1ldc:A	100	478	L-LACTATE DEHYDROGENASE: CYTOCHROME C OXIDOREDUCTASE 1 LDC 3 (FLAVOCYTOCHROME B<2>) (E.C.1.1.2.3) MUTANT WITH TYR 143 1 LDC 4 REPLACED BY PHE (Y143F) COMPLEXED WITH PYRUVATE 1 LDC 5
2	0.99	62.7	23.8	0.30	478	1	100	100	1lco:A	91	480	L-LACTATE DEHYDROGENASE; 1 LCO 4
3	0.98	59.5	23.1	0.41	478	1	100	100	1ltd:A	89	481	FLAVOCYTOCHROME B<2> (E.C.1.1.2.3) COMPLEXED WITH SULFITE 1 LTD 3
4	0.94	59.1	23.1	0.56	478	1	100	97	1fcb:A	91	494	FLAVOCYTOCHROME B$B<2> (E.C.1.1.2.3) 1 FCB 3
5	0.91	55.4	22.3	0.51	474	2	98	97	1kbi:A	86	504	CRYSTALLOGRAPHIC STUDY OF THE RECOMBINANT FLAVIN-BINDING DOMAIN OF BAKER'S YEAST FLAVOCYTOCHROME B2: COMPARISON WITH THE INTACT WILD-TYPE ENZYME

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Match details

1LDC X-RAY DIFFRACTION

File Display Colours Options Settings

Match 17 of 22

Back to match list | first match | << | >> | last match

Query PDB 1ldc:A				Alignment				
N_{res}	$\%_{res}$	N_{SSE}	$\%_{SSE}$	Q	P	RMSD	N_{algn}
478	66	31	65	0.514	30.07	1.191	315
L-LACTATE DEHYDROGENASE: CYTOCHROME C OXIDOREDUCTASE 1 LDC 3 (FLAVOCYTOCHROME B<2>) (E.C.1.1.2.3) MUTANT WITH TYR 143 1 LDC 4 REPLACED BY PHE (Y143F) COMPLEXED WITH PYRUVATE 1 LDC 5				$\%_{seq}$	Z	N_{SSE}	N_{gaps}
				33.3	17.30	20	6

view | download | view superposed | view | download

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SSE alignment

Secondary Structure Alignment

Query PDB 1ldc:A								Target PDB 1huv:A							
10	H1	13	A	ASN	124	LEU	136	<->	1	H1	13	A	ASN	7	LEU	19
11	H1	10	A	THR	137	SER	146	<->	2	H1	10	A	PRO	20	GLY	29
12	H1	10	A	GLU	151	ALA	160	<->	3	H1	10	A	GLU	34	VAL	43
13	SD	3	A	PHE	192	VAL	194	<->	7	SD	3	A	LEU	75	ILE	77
14	H1	10	A	GLY	208	GLY	217	<->	9	H1	14	A	LYS	89	GLY	102
15	SD	4	A	GLN	225	SER	228	<->	10	SD	3	A	PHE	105	LEU	107
16	H1	8	A	SER	234	ALA	241	<->	11	H1	9	A	SER	114	CYS	122
17	SD	5	A	GLN	249	LEU	253	<->	12	SD	5	A	LEU	126	LEU	130
18	H1	15	A	ASP	258	LEU	272	<->	13	H1	15	A	HIS	134	THR	148
19	SD	4	A	LEU	277	THR	280	<->	14	SD	5	A	THR	152	THR	156
20	H1	8	A	ARG	289	LYS	296	<->	15	H1	7	A	ARG	165	ASN	171
21	H1	12	A	THR	331	THR	342	<->	18	H1	12	A	ASN	213	TRP	224
22	SD	6	A	ILE	346	VAL	351	<->	19	SD	7	A	LYS	227	LEU	233
23	H1	11	A	ARG	353	ILE	363	<->	20	H1	11	A	ARG	235	GLU	245
24	SD	4	A	GLY	367	LEU	370	<->	21	SD	4	A	GLY	249	LEU	252
25	H1	16	A	ALA	383	ARG	398	<->	23	H1	10	A	VAL	269	GLY	278
27	SD	5	A	GLU	405	ASP	409	<->	24	SD	3	A	VAL	281	ILE	283
28	H1	11	A	ARG	414	LEU	424	<->	25	H1	11	A	ARG	289	LEU	299
29	SD	4	A	GLY	428	LEU	431	<->	26	SD	4	A	ALA	303	LEU	306
30	H1	35	A	GLY	432	GLY	466	<->	27	H1	35	A	GLY	307	GLY	341

OCA | SCOP domain | SCOP family
GeneCensus | FSSP | 3Dee | CATH | PDBsum

OCA | SCOP domain | SCOP family
GeneCensus | FSSP | 3Dee | CATH | PDBsum
SWISS–PROT: MDLB_PSEPU , GOX_SPIOL
ProtoMap: MDLB_PSEPU , GOX_SPIOL

view | download sequence | view superposed | view | download sequence

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Rotation–translation matrix
(to be applied to the query)

-0.710	0.423	-0.563	X		98.778
-0.471	0.309	0.826	× Y	+	96.485
0.524	0.852	-0.020	Z		-59.445

3D Structural alignment

PDB 1ldc:A	Dist. (Å)	PDB 1huv:A
A: GLY 203	1.42 |||	A: LEU 86
A: ASN 204	0.27 |	A: THR 87
A: FSO 205	2.75 |||||	A: PRO 88
A: LEU 206		
A: GLU 207	1.56 |||	A: LYS 89
A: GLY 208	1.66 |||	A: GLY 90
A: GLU 209	0.77 ||	A: ASP 91
A: LYS 210	0.99 ||	A: LEU 92
A: ASP 211	0.91 ||	A: ALA 93
A: VAL 212	0.95 ||	A: LEU 94
A: ALA 213	1.57 |||	A: ALA 95
A: ARG 214	1.65 |||	A: ARG 96
A: GLY 215	1.55 |||	A: ALA 97
A: CYS 216	1.67 |||	A: ALA 98
A: GLY 217	2.01 ||||	A: THR 99
A: GLN 218	2.99 |||||	A: LYS 100
A: GLY 219		
A: VAL 220		
A: THR 221	2.95 |||||	A: ALA 101
A: LYS 222	1.92 ||||	A: GLY 102

C_a - alignment

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SSM Results

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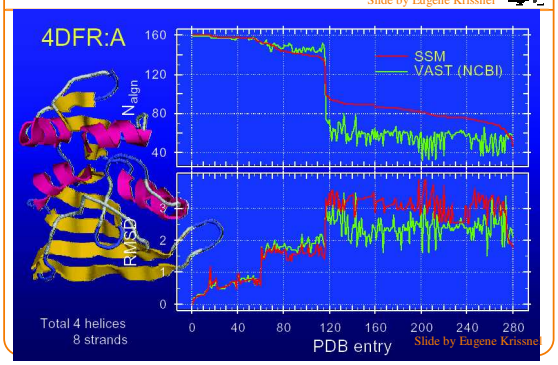

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SSM Results

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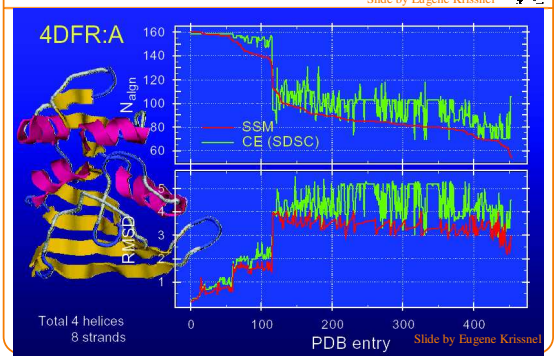

SSM Results

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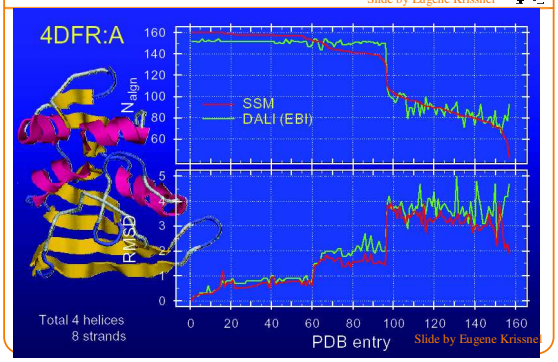

Outline

Alignment issues

Example alignment methods

Fold prediction experiment ←

Function prediction experiment

Fold Prediction Experiments

Evaluate how useful alignment algorithms are for predicting a protein's fold

How?

Fold Prediction Experiments

Kolodny, Koehl, & Levitt [2005]
- ROC curves and geometric measures using CATH

Sierk & Pearson [2004]
- ROC curves using CATH

Novotny et al. [2004]
- Checked a few dozen cases using CATH

Leplae & Hubbard [2002]
- ROC curves using SCOP

Fold Prediction Experiments

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Kolodny, Koehl, & Levitt [2005]

Large scale alignment study

- 2,930 structures (all pairs)
- 6 structural alignment algorithms
- 4 geometric scoring functions
- Evaluation with respect to CATH topology level
- 20,000 hours of compute time

Tested Methods

SSAP	Taylor & Orengo, 1989
STRUCTAL	Subbiah, Laurents & Levitt, 1993 Gerstein & Levitt 1998
DALI	Holm & Sander, 1993 Holm & Park, 2000
DEJAVU /LSQMAN	Kleywegt, 1996
CE	Shindyalov & Bourne, 1998
SSM	Krissinel & Henrick, 2003
Best-of-All	Best of above methods

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Scoring Functions

Consider # aligned residues & geometric similarity:

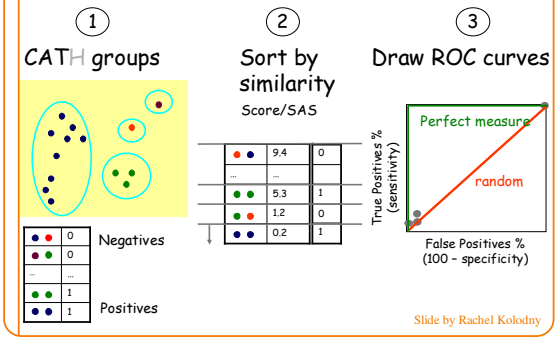
$$SAS = \frac{RMSD \times 100}{N_{mat}}$$

Also penalize gaps:

$$GSAS = \begin{cases} if\,(N_{mat} > N_{gap}) & \frac{RMSD \times 100}{N_{mat} - N_{gap}} \\ else & 99.9 \end{cases}$$

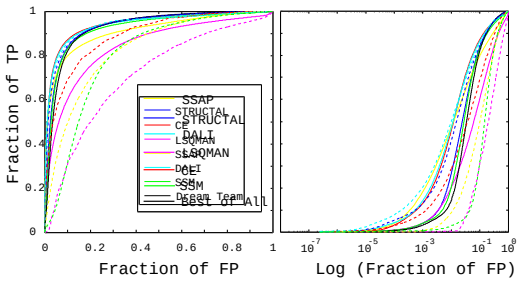
[Kolodny05]

Evaluation Using ROC Curves



Slide by Rachel Kolodny

SAS & Native ROC Curves



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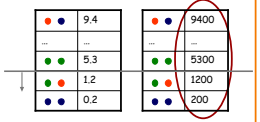
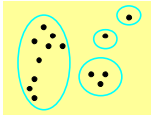
ROC Curve Issues

Uses only internal ordering

- Estimation of similarity can be very wrong



Converts a classification gold standard into binary truth



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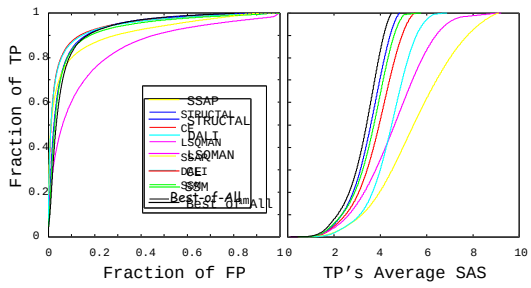
Comparing SAS Values Directly



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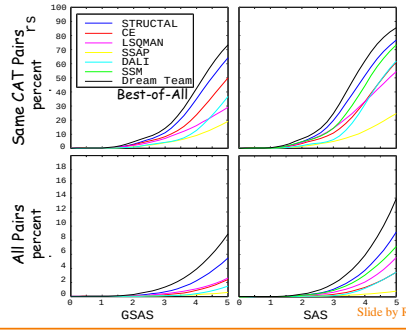
GSAS & SAS Distributions



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Contributions to "Best-of-All"

	Total	SSAP	STRUCTAL	DALI	LSQMAN	CE	SSM
GSAS≤5 Å	275,547 (100%)	832 (0.3%)	**189,871** (69%)	5868 (2.1%)	54,606 (20%)	24,370 (8.8%)	–
SAS≤5 Å	539,755 (100%)	498 (0.09%)	**286,972** (53%)	15,648 (2.9%)	103,408 (19.2%)	15,844 (2.9%)	117,385 (21.8%)
SI≤5 Å	978,531 (100%)	3745 (0.4%)	**497,330** (51%)	24,767 (2.5%)	201,202 (21%)	17,142 (1.8%)	234,345 (24%)
MI≤0.8	880,503 (100%)	4579 (0.5%)	**573,542** (65%)	31,402 (3.6%)	63,088 (7.2%)	72,974 (8.3%)	134,918 (15.3%)

The absolute number of alignments contributed by each method is listed and the percentage of alignments is given in parentheses. The largest contributor is shown in bold.

[Kolodny05]

Outline

Alignment issues

Example alignment methods

Fold prediction experiment

Function prediction experiment ←

Function Prediction Experiment

Evaluate how useful alignment methods are for predicting a protein's molecular function

How?

Data Set

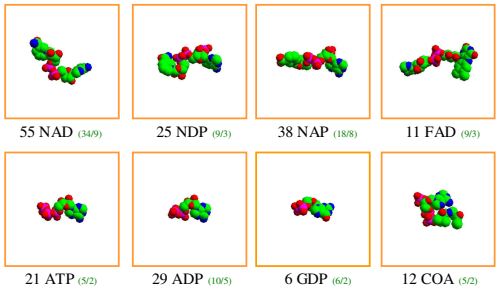
Proteins crystallized with bound ligands
- PDB file must have resolution ≤3 Angstroms
- Ligands must have ≥20 HETATOMS

Classified by reaction/reactant
- PDB file must have an EC number (enzymes only)
- EC number must have a KEGG reaction with a reactant whose graph closely matches ligand in PDB file

Non-redundant
- No two ligands contacting domains with same CATH S95
- No two ligands contacting domains with same SCOP SP
- No two ligands from same PDB file

Data Set

351 proteins / 58 Reactions (189 outliers)



55 NAD (34/9) 25 NDP (9/3) 38 NAP (18/8) 11 FAD (9/3)

21 ATP (5/2) 29 ADP (10/5) 6 GDP (6/2) 12 COA (5/2)

Data Set

REACTION	NAME	#
R00145	NAD	2
R00214	NAD	2
R00342	NAD	7
R00538	NAD	3
R00623	NAD	5
R00703	NAD	5
R01061	NAD	5
R01403	NAD	2
R01778	NAD	3
R00112	NAP	2
R00343	NAP	2
R00625	NAP	2
R00939	NAP	2
R01041	NAP	4
R01058	NAP	2
R01195	NAP	2
R02477	NAP	2
R00703	NAI	2
R00939	NDP	5
R01063	NDP	2
R01195	NDP	2
MISC	NAD	21
MISC	NAP	20
MISC	NAH	2
MISC	NAI	2
MISC	NDP	16

REACTION	NAME	#
R00162	ATP	3
R03647	ATP	2
R00124	ADP	2
R00497	ADP	2
R00756	ADP	2
R01512	ADP	2
R02412	ADP	2
R03647	AMP	2
R00330	GDP	2
R01135	GDP	4
R01130	IMP	3
R02094	TMP	2
R02101	UMP	6
R00965	U5P	2
R00966	U5P	2
R01229	5GP	2
MISC	ATP	16
MISC	ADP	19
MISC	AMP	10
MISC	A3P	5
MISC	GTP	2
MISC	UDP	4
MISC	UMP	1
MISC	5GP	1

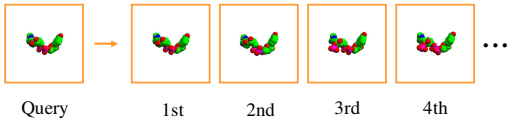
REACTION	NAME	#
R00408	FAD	5
R00924	FAD	2
R01175	FAD	2
MISC	FAD	2
R00351	COA	3
R03552	COA	2
MISC	COA	7
R02961	SAM	3
MISC	SAM	3
R03552	ACO	2
R00291	GDU	2
R03522	GTT	12
R01146	PQQ	3
R00190	PRP	2
R01402	MTA	2
R03435	GP	2
R02986	CBI	4
R01590	ACD	2
R00529	ADX	2
R03491	SIA	2
R00137	NMN	3
R03992	MYA	2
R03509	137	2
MISC	etc	etc

Evaluation Method

"Leave-one-out" classification experiment

ØMatch every ligand against all the others in data set

- Log a "hit" when best match performs same reaction
- Report percentage of hits (correctly classified ligands)



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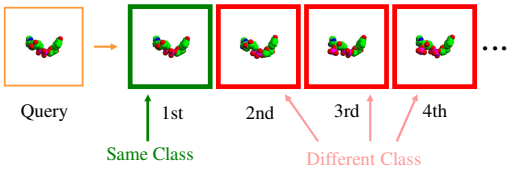

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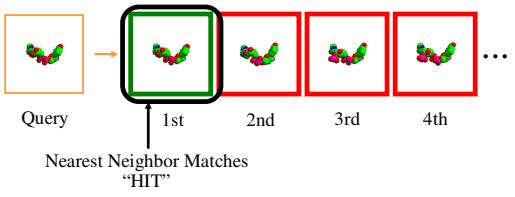
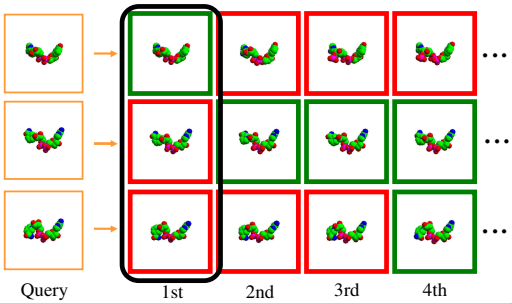


Evaluation Method

Classification rate is 33% is this example



Sequence Alignment Method

Use FASTA to compute Smith-Waterman score for every pair of SCOP domains contacting ligand

```
> fasta34 d1gv0a d1guya

               10        20        30        40        50        60
d1gv0a AGVLDSARFRSFIAMELGVSMQDVTACVLGGHGDAMVPVVKYTTVAGIPVADLISAERIA
       ::::::::::::::::: ::::::: :  ::::::: :::  ::::::::::::::::: .::.
d1guya AGVLDAARYRTFIAMEAGVSVEDVQAMLMGGHGDEMVPLPRFSTISGIPVSEFIAPDRLA
               10        20        30        40        50        60

               70        80        90       100       110       120
d1gv0a ELVERTRTGGAEIVNHLKQGSAFYSPATSVVEMVESIVLDRKRVLTCAVSLDGQYGIDGT
       ..:::::: ::.:::: :: :::.:.::.....:::.... :.::::.  :. : ::::...
d1guya QIVERTRKGGGEIVNLLKTGSAYYAPAAATAQMVEAVLKDKKRVMPVAAYLTGQYGLNDI
               70        80        90       100       110       120

              130       140       150       160
d1gv0a FVGVPVKLGKNGVEHIYEIKLDQSDLDLLQKSAKIVDENCKML
       . :::: :: .:::.: :. :.. .. ::. ::: :
d1guya YFGVPVILGAGGVEKILELPLNEEEMALLNASAKAVRATLDTL
              130       140       150       160

54.487% identity
156 out of 163 amino acids overlap
Smith-Waterman score: 588
```

Sequence Alignment Method

Use FASTA to compute Smith-Waterman score for every pair of SCOP domains contacting ligand

```
> fasta34 d1gv0a d1guya

               10        20        30        40        50        60
d1gv0a AGVLDSARFRSFIAMELGVSMQDVTACVLGGHGDAMVPVVKYTTVAGIPVADLISAERIA
       ::::::::::::::::: ::::::: :  ::::::: :::  ::::::::::::::::: .::.
d1guya AGVLDAARYRTFIAMEAGVSVEDVQAMLMGGHGDEMVPLPRFSTISGIPVSEFIAPDRLA
               10        20        30        40        50        60

               70        80        90       100       110       120
d1gv0a ELVERTRTGGAEIVNHLKQGSAFYSPATSVVEMVESIVLDRKRVLTCAVSLDGQYGIDGT
       ..:::::: ::.:::: :: :::.:.::.....:::.... :.::::.  :. : ::::...
d1guya QIVERTRKGGGEIVNLLKTGSAYYAPAAATAQMVEAVLKDKKRVMPVAAYLTGQYGLNDI
               70        80        90       100       110       120

              130       140       150       160
d1gv0a FVGVPVKLGKNGVEHIYEIKLDQSDLDLLQKSAKIVDENCKML
       . :::: :: .:::.: :. :.. .. ::. ::: :
d1guya YFGVPVILGAGGVEKILELPLNEEEMALLNASAKAVRATLDTL
              130       140       150       160

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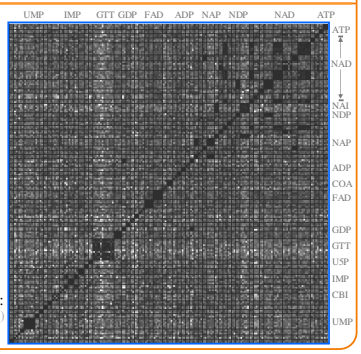
Sequence Alignment Method

Use FASTA to compute Smith-Waterman score for every pair of SCOP domains contacting ligand

$$D(A,B) = 1/\max SmithWaterman(A_i, B_j)_{A_i \in A, B_j \in B}$$

Sequence Alignment Results

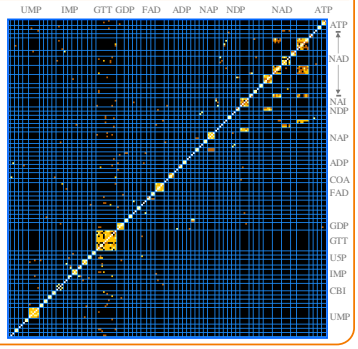
Similarity matrix:



1/SmithWaterman Score:
(Darker means better match)

Sequence Alignment Results

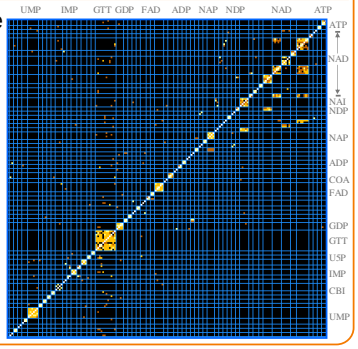
Tier matrix:



Best Matches:
(Beige = Best match)
(Yellow = 1st tier match)
(Orange = 2nd tier match)

Sequence Alignment Results

Classification rate
FASTA = 68%
Random = <1%



Best Matches:
(Beige = Best match)
(Yellow = 1st tier match)
(Orange = 2nd tier match)

Structure Alignment Method

Use CE to compute similarity of protein structures

```
CE - ~/ebi/data/pdbs/1jsu.pdb A ~/ebi/data/pdbs/1hcl.pdb _ scratch
Structure Alignment Calculator, version 1.02, last modified: Jun 15, 2001.
CE Algorithm, version 1.00, 1998
Aligne
Rmsd =
Z-Scor
Gaps =
CPU =
Sequen
```

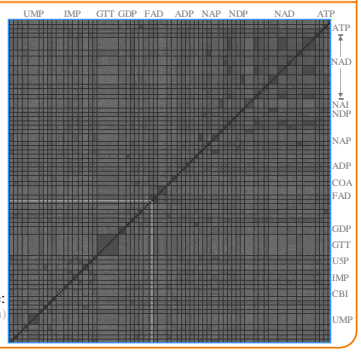
Rmsd = 2.28A
Z-Score = 6.8
Gaps = 30(11.5%)

```
X2 = ( 0.997420)*X1 + ( 0.071548)*Y1 +
     ( 0.005923)*Z1 + (  -93.687386)
Y2 = ( 0.059473)*X1 + (-0.777232)*Y1 +
     (-0.626397)*Z1 + (  119.695427)
Z2 = (-0.040214)*X1 + ( 0.625133)*Y1 +
     (-0.779482)*Z1 + (   84.334198)
```

Image from Shindyalov and Bourne (1998)

Structure Alignment Results

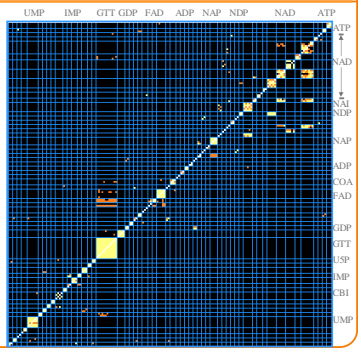
Similarity matrix:



1/CE -Z-Score:
(Darker means better match)

Structure Alignment Results

Tier matrix:



Best Matches:
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Structure Alignment Results

Classification rate:

FASTA	= 68%
CE	= 65%
Random	= <1%

Structure Alignment Results

Classification rate:

FASTA	= 68%
CE	= 65%
Random	= <1%

When Smith-Waterman ≥ 500:

Sequence	= 80%
CE	= 72%
Random	= <1%

When Smith-Waterman < 500:

CE	= 53%
FASTA	= 44%
Random	= <1%

Conclusion

Many algorithms for structural alignment, differing according to

- Application: homology detection, drug design, etc.
- Granularity: atom, residue, fragment, SSE
- Representation: inter-molecular, intra-molecular
- Scoring: geometric, gaps, chemical, structural, etc.
- Correspondences: sequential, non-sequential
- Gap penalty: expect gaps near loops, etc.
- Flexibility: rigid, flexible
- Target: single protein, representative proteins, PDB

None seems best for all situations
All probably provide some benefit over sequence