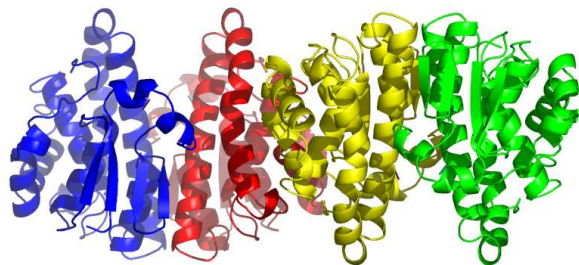


1aqw

Evolutionary trace report by **report_maker**

March 26, 2010



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1 INTRODUCTION

From the original Protein Data Bank entry (PDB id 1aqw):

Title: Glutathione s-transferase in complex with glutathione

Compound: Mol id: 1; molecule: glutathione s-transferase; chain: a, b, c, d; synonym: gst; ec: 2.5.1.18; engineered: yes; mol id: 2; molecule: glutathione; chain: e, f, g, h; engineered: yes

Organism, scientific name: Homo Sapiens;

1aqw contains a single unique chain 1aqwA (209 residues long) and its homologues 1aqwB, 1aqwC, and 1aqwD. Chains 1aqwE, 1aqwF, 1aqwG, and 1aqwH are too short to permit statistically significant analysis, and were treated as a peptide ligands.

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2 CHAIN 1AQWA

2.1 Q5TZY3 overview

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2.2 Multiple sequence alignment for 1aqwA

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For the chain 1aqwA, the alignment 1aqwA.msf (attached) with 180 sequences was used. The alignment was downloaded from the HSSP database, and fragments shorter than 75% of the query as well as duplicate sequences were removed. It can be found in the attachment to this report, under the name of 1aqwA.msf. Its statistics, from the *alistat* program are the following:

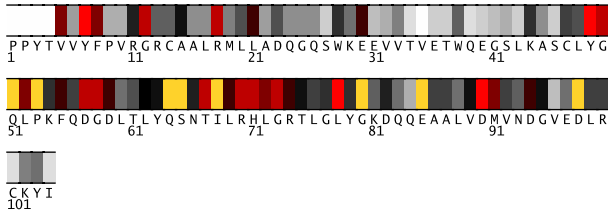


Fig. 1. Residues 1-104 in IaqwA colored by their relative importance. (See Appendix, Fig.10, for the coloring scheme.)

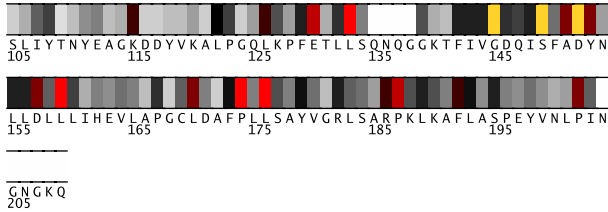


Fig. 2. Residues 105-209 in IaqwA colored by their relative importance. (See Appendix, Fig.10, for the coloring scheme.)

```

Format:                MSF
Number of sequences:   180
Total number of residues: 35500
Smallest:              162
Largest:               209
Average length:        197.2
Alignment length:      209
Average identity:       34%
Most related pair:     99%
Most unrelated pair:   12%
Most distant seq:      31%

```

Furthermore, <1% of residues show as conserved in this alignment.

The alignment consists of 55% eukaryotic (40% vertebrata, 2% arthropoda, <1% plantae), and <1% prokaryotic sequences. (Descriptions of some sequences were not readily available.) The file containing the sequence descriptions can be found in the attachment, under the name IaqwA.descr.

2.3 Residue ranking in IaqwA

The IaqwA sequence is shown in Figs. 1–2, with each residue colored according to its estimated importance. The full listing of residues in IaqwA can be found in the file called IaqwA.ranks.sorted in the attachment.

2.4 Top ranking residues in IaqwA and their position on the structure

In the following we consider residues ranking among top 25% of residues in the protein. Figure 3 shows residues in IaqwA colored by their importance: bright red and yellow indicate more conserved/important residues (see Appendix for the coloring scheme). A Pymol script for producing this figure can be found in the attachment.

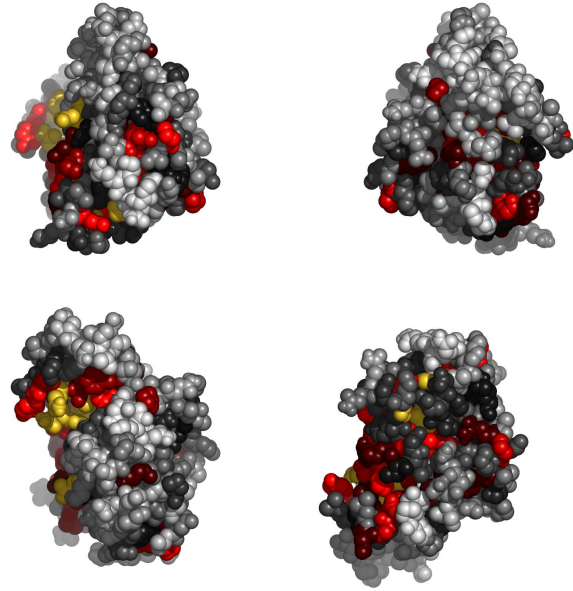


Fig. 3. Residues in IaqwA, colored by their relative importance. Clockwise: front, back, top and bottom views.

2.4.1 Clustering of residues at 25% coverage. Fig. 4 shows the top 25% of all residues, this time colored according to clusters they belong to. The clusters in Fig.4 are composed of the residues listed

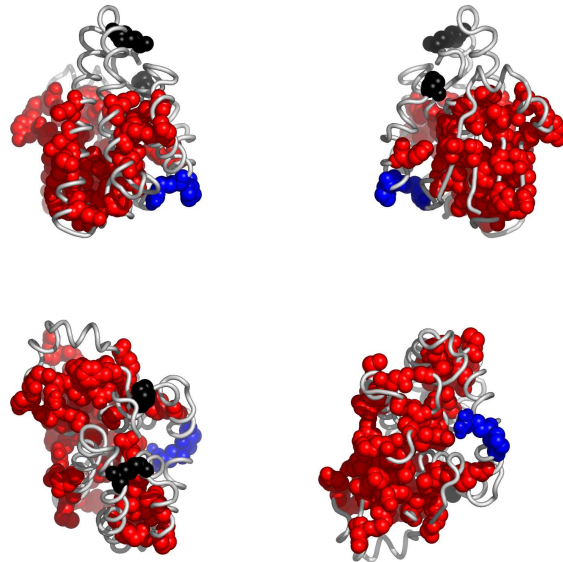


Fig. 4. Residues in IaqwA, colored according to the cluster they belong to: red, followed by blue and yellow are the largest clusters (see Appendix for the coloring scheme). Clockwise: front, back, top and bottom views. The corresponding Pymol script is attached.

in Table 1.

Table 1.		
cluster color	size	member residues
red	48	5, 7, 8, 12, 18, 21, 30, 49, 50, 51 52, 53, 55, 57, 58, 59, 62, 64, 65 67, 68, 69, 70, 71, 72, 73, 74, 78 80, 85, 90, 91, 94, 98, 126, 130 133, 145, 149, 151, 152, 153, 157 159, 170, 174, 176, 192
blue	2	186, 187

Table 1. Clusters of top ranking residues in 1aqwA.

2.4.2 *Overlap with known functional surfaces at 25% coverage.*
The name of the ligand is composed of the source PDB identifier and the heteroatom name used in that file.

MES binding site. Table 2 lists the top 25% of residues at the interface with 1aqwMES2500 (mes). The following table (Table 3) suggests possible disruptive replacements for these residues (see Section 3.6).

Table 2.					
res	type	subst's (%)	cvg	noc/ bb	dist (Å)
30	E	E (65) D (27)K F (1)N Y (1)LV . (1)A	0.21	11/3	3.24
192	F	F (32) Y (51) V (2) . (1) R (1) L (3) W (2) H (1)G A (1)T	0.23	8/1	3.69

Table 2. The top 25% of residues in 1aqwA at the interface with MES. (Field names: res: residue number in the PDB entry; type: amino acid type; substs: substitutions seen in the alignment; with the percentage of each type in the bracket; noc/bb: number of contacts with the ligand, with the number of contacts realized through backbone atoms given in the bracket; dist: distance of closest approach to the ligand.)

Table 3.		
res	type	disruptive mutations
30	E	(H) (FW) (R) (Y)
192	F	(E) (K) (QD) (T)

Table 3. List of disruptive mutations for the top 25% of residues in 1aqwA, that are at the interface with MES.

Figure 5 shows residues in 1aqwA colored by their importance, at the interface with 1aqwMES2500.

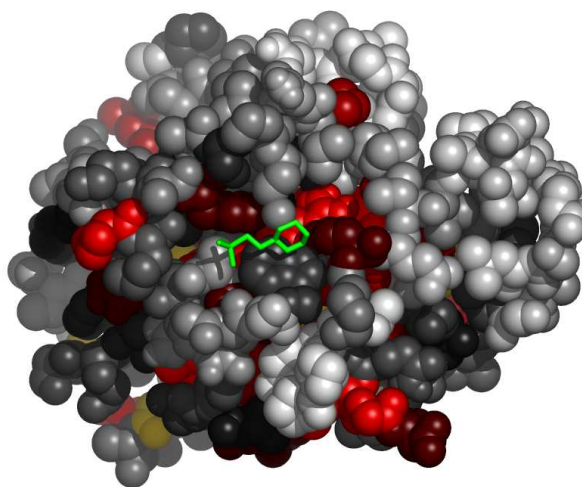


Fig. 5. Residues in 1aqwA, at the interface with MES, colored by their relative importance. The ligand (MES) is colored green. Atoms further than 30Å away from the geometric center of the ligand, as well as on the line of sight to the ligand were removed. (See Appendix for the coloring scheme for the protein chain 1aqwA.)

Interface with the peptide 1aqwF. Table 4 lists the top 25% of residues at the interface with 1aqwF. The following table (Table 5) suggests possible disruptive replacements for these residues (see Section 3.6).

Table 4.					
res	type	subst's (%)	cvg	noc/bb	dist (Å)
53	P	P(98)V. L	0.01	5/1	3.75
64	Q	Q(96) E(3).	0.01	31/10	2.66
51	Q	Q(62) N(33)L K(1) E(1) S(1)	0.03	87/11	2.05
65	S	T(23) S(73)GC .A	0.03	14/8	2.75
7	Y	Y(90) . (7)DPH V	0.08	6/0	3.45
50	G	Q(14)K P(34) G(41) R(2)H	0.13	6/6	3.93

continued in next column

Table 4. continued					
res	type	subst's (%)	cvg	noc/bb	dist (Å)
8	F	E(1)N D(3)FA AF(53) W(33) . (6)YV P(1) L(1)TS	0.16	15/0	3.42
52	L	V(27) L(59) A(1) I(7) M(1) C(2)	0.19	27/25	2.87

Table 4. The top 25% of residues in 1aqwA at the interface with 1aqwF. (Field names: res: residue number in the PDB entry; type: amino acid type; substs: substitutions seen in the alignment; with the percentage of each type in the bracket; noc/bb: number of contacts with the ligand, with the number of contacts realized through backbone atoms given in the bracket; dist: distance of closest approach to the ligand.)

Table 5.		
res	type	disruptive mutations
53	P	(YR)(H)(T)(KE)
64	Q	(Y)(FWH)(T)(VCAG)
51	Q	(Y)(FWH)(T)(CG)
65	S	(KR)(Q)(H)(FMW)
7	Y	(K)(Q)(R)(M)
50	G	(ER)(K)(Y)(FWH)
8	F	(K)(E)(Q)(R)
52	L	(R)(Y)(H)(TKE)

Table 5. List of disruptive mutations for the top 25% of residues in 1aqwA, that are at the interface with 1aqwF.

Figure 6 shows residues in 1aqwA colored by their importance, at the interface with 1aqwF.

Interface with 1aqwC. Table 6 lists the top 25% of residues at the interface with 1aqwC. The following table (Table 7) suggests possible disruptive replacements for these residues (see Section 3.6).

Table 6.					
res	type	subst's (%)	cvg	noc/bb	dist (Å)
174	P	P(88)S T(2)G K(2) L(1)E A(1) . (1)D	0.08	39/2	3.14
130	E	E(61)	0.12	31/3	1.99

continued in next column

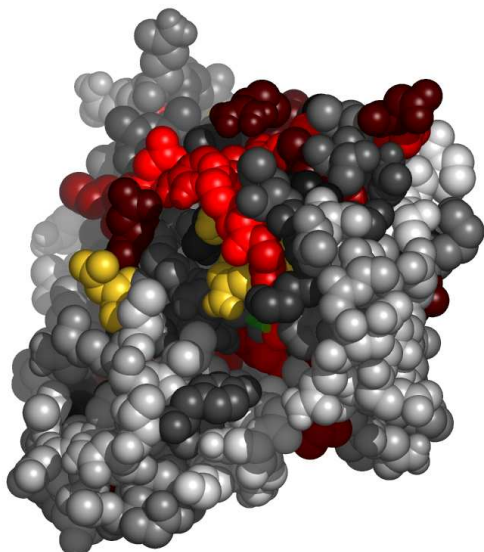


Fig. 6. Residues in 1aqwA, at the interface with 1aqwF, colored by their relative importance. 1aqwF is shown in backbone representation (See Appendix for the coloring scheme for the protein chain 1aqwA.)

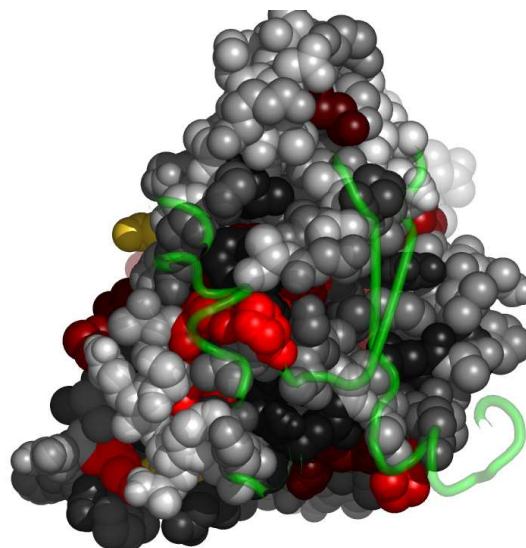


Fig. 7. Residues in 1aqwA, at the interface with 1aqwC, colored by their relative importance. 1aqwC is shown in backbone representation (See Appendix for the coloring scheme for the protein chain 1aqwA.)

res	type	subst's (%)	cvg	noc/ bb	dist (Å)
		S (28) V (1) A (2) D . (1) KR T (1) NFC Q (1)			

Table 6. The top 25% of residues in 1aqwA at the interface with 1aqwC. (Field names: res: residue number in the PDB entry; type: amino acid type; substs: substitutions seen in the alignment; with the percentage of each type in the bracket; noc/bb: number of contacts with the ligand, with the number of contacts realized through backbone atoms given in the bracket; dist: distance of closest approach to the ligand.)

res	type	disruptive mutations
174	P	(R) (Y) (H) (K)
130	E	(H) (FW) (Y) (R)

Table 7. List of disruptive mutations for the top 25% of residues in 1aqwA, that are at the interface with 1aqwC.

Figure 7 shows residues in 1aqwA colored by their importance, at the interface with 1aqwC.

Interface with the peptide 1aqwE. Table 8 lists the top 25% of residues at the interface with 1aqwE. The following table (Table

9) suggests possible disruptive replacements for these residues (see Section 3.6).

res	type	subst's (%)	cvg	noc/ bb	dist (Å)
98	D	D (92) E (1) A H (2) S (1) L . I N	0.02	7/0	2.90

Table 8. The top 25% of residues in 1aqwA at the interface with 1aqwE. (Field names: res: residue number in the PDB entry; type: amino acid type; substs: substitutions seen in the alignment; with the percentage of each type in the bracket; noc/bb: number of contacts with the ligand, with the number of contacts realized through backbone atoms given in the bracket; dist: distance of closest approach to the ligand.)

res	type	disruptive mutations
98	D	(R) (H) (FW) (Y)

Table 9. List of disruptive mutations for the top 25% of residues in 1aqwA, that are at the interface with 1aqwE.

Figure 8 shows residues in 1aqwA colored by their importance, at the interface with 1aqwE.

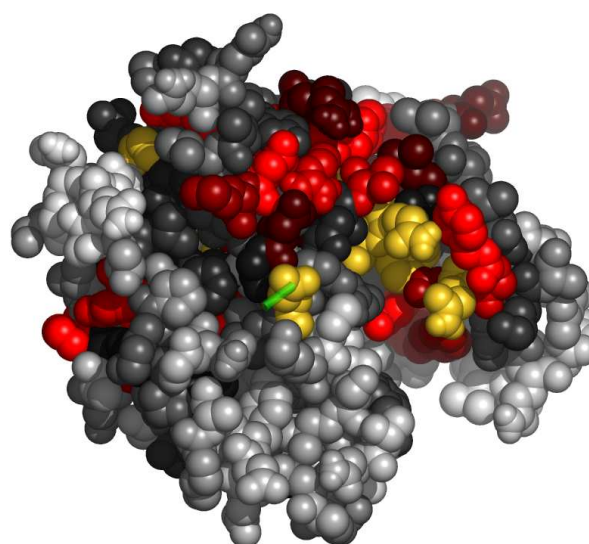


Fig. 8. Residues in 1aqwA, at the interface with 1aqwE, colored by their relative importance. 1aqwE is shown in backbone representation (See Appendix for the coloring scheme for the protein chain 1aqwA.)

Interface with 1aqwB. Table 10 lists the top 25% of residues at the interface with 1aqwB. The following table (Table 11) suggests possible disruptive replacements for these residues (see Section 3.6).

Table 10.					
res	type	subst's (%)	cvg	noc/ bb	dist (Å)
64	Q	Q(96) E(3).	0.01	70/3	2.35
98	D	D(92) E(1)A H(2) S(1)L.I N	0.02	16/0	2.28
51	Q	Q(62) N(33)L K(1) E(1) S(1)	0.03	1/0	4.85
90	D	D(84) E(2) T(1) S(3) H(1) A(1)Y. N(2) I(1)	0.07	45/8	1.82
49	Y	F(83)	0.09	53/3	2.90

continued in next column

Table 10. continued					
res	type	subst's (%)	cvg	noc/ bb	dist (Å)
67	T	Y(8)K L(2)A T(1) I(1) N(1)M	0.10	43/7	2.74
		A(86) T(8) S(5).			
		Y(71) H(26) L(1)FS			
		N(14)Q R(72) E(1) C(1) S(2)M H(2)V K(1)F L(1)A			
		M(58) I(20) V(7) A(3) E(2) L(2) Q(1). T(1) S(1)			
74	R	G(2) A(3) R(63) E(6) D(7) T(8) N(1) K(3) S(2)L	0.20	113/10	1.92
		E(32) N(22) D(29) Q(4) K(1) G(5)C L(1).PA S(1)I			
91	M	M(58) I(20) V(7) A(3) E(2) L(2) Q(1). T(1) S(1)	0.18	59/25	2.89
70	R	N(14)Q R(72) E(1) C(1) S(2)M H(2)V K(1)F L(1)A	0.13	86/1	3.59
94	D	E(32) N(22) D(29) Q(4) K(1) G(5)C L(1).PA S(1)I	0.24	60/16	2.73
62	L	M(4) L(62) I(26) V(3) Y(1).	0.25	13/2	3.93

Table 10. The top 25% of residues in 1aqwA at the interface with 1aqwB. (Field names: res: residue number in the PDB entry; type: amino acid type; substs: substitutions seen in the alignment; with the percentage of each type in the bracket; noc/bb: number of contacts with the ligand, with the number of

contacts realized through backbone atoms given in the bracket; dist: distance of closest approach to the ligand.)

Table 11.		
res	type	disruptive mutations
64	Q	(Y) (FWH) (T) (VCAG)
98	D	(R) (H) (FW) (Y)
51	Q	(Y) (FWH) (T) (CG)
90	D	(R) (H) (FW) (K)
49	Y	(K) (R) (EQ) (M)
67	T	(KR) (QH) (FMW) (NE)
71	H	(E) (Q) (K) (MD)
70	R	(T) (Y) (D) (E)
91	M	(Y) (H) (R) (T)
74	R	(Y) (T) (D) (FW)
94	D	(R) (H) (FW) (Y)
62	L	(R) (Y) (H) (T)

Table 11. List of disruptive mutations for the top 25% of residues in 1aqwA, that are at the interface with 1aqwB.

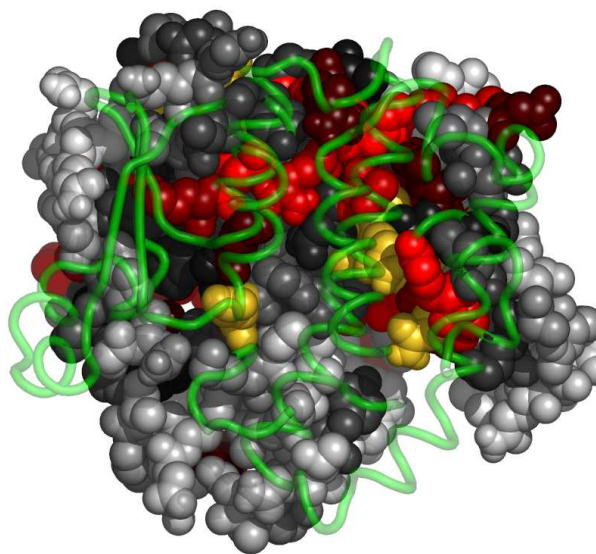


Fig. 9. Residues in 1aqwA, at the interface with 1aqwB, colored by their relative importance. 1aqwB is shown in backbone representation (See Appendix for the coloring scheme for the protein chain 1aqwA.)

Figure 9 shows residues in 1aqwA colored by their importance, at the interface with 1aqwB.

3 NOTES ON USING TRACE RESULTS

3.1 Coverage

Trace results are commonly expressed in terms of coverage: the residue is important if its “coverage” is small - that is if it belongs to

some small top percentage of residues [100% is all of the residues in a chain], according to trace. The ET results are presented in the form of a table, usually limited to top 25% percent of residues (or to some nearby percentage), sorted by the strength of the presumed evolutionary pressure. (I.e., the smaller the coverage, the stronger the pressure on the residue.) Starting from the top of that list, mutating a couple of residues should affect the protein somehow, with the exact effects to be determined experimentally.

3.2 Known substitutions

One of the table columns is “substitutions” - other amino acid types seen at the same position in the alignment. These amino acid types may be interchangeable at that position in the protein, so if one wants to affect the protein by a point mutation, they should be avoided. For example if the substitutions are “RVK” and the original protein has an R at that position, it is advisable to try anything, but RVK. Conversely, when looking for substitutions which will *not* affect the protein, one may try replacing, R with K, or (perhaps more surprisingly), with V. The percentage of times the substitution appears in the alignment is given in the immediately following bracket. No percentage is given in the cases when it is smaller than 1%. This is meant to be a rough guide - due to rounding errors these percentages often do not add up to 100%.

3.3 Surface

To detect candidates for novel functional interfaces, first we look for residues that are solvent accessible (according to DSSP program) by at least 10\AA^2 , which is roughly the area needed for one water molecule to come in the contact with the residue. Furthermore, we require that these residues form a “cluster” of residues which have neighbor within 5\AA from any of their heavy atoms.

Note, however, that, if our picture of protein evolution is correct, the neighboring residues which *are not* surface accessible might be equally important in maintaining the interaction specificity - they should not be automatically dropped from consideration when choosing the set for mutagenesis. (Especially if they form a cluster with the surface residues.)

3.4 Number of contacts

Another column worth noting is denoted “noc/bb”; it tells the number of contacts heavy atoms of the residue in question make across the interface, as well as how many of them are realized through the backbone atoms (if all or most contacts are through the backbone, mutation presumably won’t have strong impact). Two heavy atoms are considered to be “in contact” if their centers are closer than 5\AA .

3.5 Annotation

If the residue annotation is available (either from the pdb file or from other sources), another column, with the header “annotation” appears. Annotations carried over from PDB are the following: site (indicating existence of related site record in PDB), S-S (disulfide bond forming residue), hb (hydrogen bond forming residue), jb (james bond forming residue), and sb (for salt bridge forming residue).

3.6 Mutation suggestions

Mutation suggestions are completely heuristic and based on complementarity with the substitutions found in the alignment. Note that they are meant to be **disruptive** to the interaction of the protein with its ligand. The attempt is made to complement the following

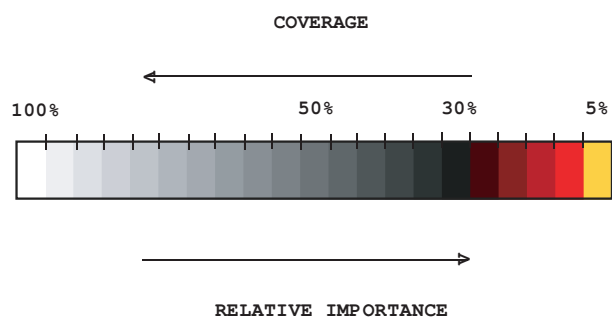


Fig. 10. Coloring scheme used to color residues by their relative importance.

properties: small [*AVGSTC*], medium [*LPNQDEMIK*], large [*WFYHR*], hydrophobic [*LPVAMWFI*], polar [*GTCY*]; positively [*KHR*], or negatively [*DE*] charged, aromatic [*WFYH*], long aliphatic chain [*EKRQM*], OH-group possession [*SDETY*], and NH₂ group possession [*NQRK*]. The suggestions are listed according to how different they appear to be from the original amino acid, and they are grouped in round brackets if they appear equally disruptive. From left to right, each bracketed group of amino acid types resembles more strongly the original (i.e. is, presumably, less disruptive) These suggestions are tentative - they might prove disruptive to the fold rather than to the interaction. Many researcher will choose, however, the straightforward alanine mutations, especially in the beginning stages of their investigation.

4 APPENDIX

4.1 File formats

Files with extension "ranks_sorted" are the actual trace results. The fields in the table in this file:

- `alignment#` number of the position in the alignment
- `residue#` residue number in the PDB file
- `type` amino acid type
- `rank` rank of the position according to older version of ET
- `variability` has two subfields:
 1. number of different amino acids appearing in in this column of the alignment
 2. their type
- `rho` ET score - the smaller this value, the lesser variability of this position across the branches of the tree (and, presumably, the greater the importance for the protein)
- `cvg` coverage - percentage of the residues on the structure which have this rho or smaller
- `gaps` percentage of gaps in this column

4.2 Color schemes used

The following color scheme is used in figures with residues colored by cluster size: black is a single-residue cluster; clusters composed of more than one residue colored according to this hierarchy (ordered by descending size): red, blue, yellow, green, purple, azure, turquoise, brown, coral, magenta, LightSalmon, SkyBlue, violet, gold, bisque, LightSlateBlue, orchid, RosyBrown, MediumAquamarine, DarkOliveGreen, CornflowerBlue, grey55, burlywood, LimeGreen, tan, DarkOrange, DeepPink, maroon, BlanchedAlmond.

The colors used to distinguish the residues by the estimated evolutionary pressure they experience can be seen in Fig. 10.

4.3 Credits

4.3.1 Alistat *alistat* reads a multiple sequence alignment from the file and shows a number of simple statistics about it. These statistics include the format, the number of sequences, the total number of residues, the average and range of the sequence lengths, and the alignment length (e.g. including gap characters). Also shown are some percent identities. A percent pairwise alignment identity is defined as $(\text{idents} / \text{MIN}(\text{len1}, \text{len2}))$ where *idents* is the number of exact identities and *len1*, *len2* are the unaligned lengths of the two sequences. The "average percent identity", "most related pair", and "most unrelated pair" of the alignment are the average, maximum, and minimum of all $(N)(N-1)/2$ pairs, respectively. The "most distant seq" is calculated by finding the maximum pairwise identity (best relative) for all *N* sequences, then finding the minimum of these *N* numbers (hence, the most outlying sequence). *alistat* is copyrighted by HHMI/Washington University School of Medicine, 1992-2001, and freely distributed under the GNU General Public License.

4.3.2 CE To map ligand binding sites from different source structures, *report_maker* uses the CE program: <http://cl.sdsc.edu/>. Shindyalov IN, Bourne PE (1998) "Protein structure alignment by incremental combinatorial extension (CE) of the optimal path". *Protein Engineering* 11(9) 739-747.

4.3.3 DSSP In this work a residue is considered solvent accessible if the DSSP program finds it exposed to water by at least 10\AA^2 , which is roughly the area needed for one water molecule to come in the contact with the residue. DSSP is copyrighted by W. Kabsch, C. Sander and MPI-MF, 1983, 1985, 1988, 1994 1995, CMBI version by Elmar.Krieger@cmbi.kun.nl November 18,2002,

<http://www.cmbi.kun.nl/gv/dssp/descrip.html>.

4.3.4 HSSP Whenever available, *report_maker* uses HSSP alignment as a starting point for the analysis (sequences shorter than 75% of the query are taken out, however); R. Schneider, A. de Daruvar, and C. Sander. "The HSSP database of protein structure-sequence alignments." *Nucleic Acids Res.*, 25:226-230, 1997.

<http://swift.cmbi.kun.nl/swift/hssp/>

4.3.5 LaTeX The text for this report was processed using L^AT_EX; Leslie Lamport, "LaTeX: A Document Preparation System Addison-Wesley," Reading, Mass. (1986).

4.3.6 Muscle When making alignments "from scratch", *report_maker* uses Muscle alignment program: Edgar, Robert C. (2004), "MUSCLE: multiple sequence alignment with high accuracy and high throughput." *Nucleic Acids Research* 32(5), 1792-97.

<http://www.drive5.com/muscle/>

4.3.7 Pymol The figures in this report were produced using Pymol. The scripts can be found in the attachment. Pymol is an open-source application copyrighted by DeLano Scientific LLC (2005). For more information about Pymol see <http://pymol.sourceforge.net/>. (Note for Windows users: the attached package needs to be unzipped for Pymol to read the scripts and launch the viewer.)

4.4 Note about ET Viewer

Dan Morgan from the Lichtarge lab has developed a visualization tool specifically for viewing trace results. If you are interested, please visit:

<http://mammoth.bcm.tmc.edu/traceview/>

The viewer is self-unpacking and self-installing. Input files to be used with ETV (extension .etvx) can be found in the attachment to the main report.

4.5 Citing this work

The method used to rank residues and make predictions in this report can be found in Mihalek, I., I. Reš, O. Lichtarge. (2004). "A Family of Evolution-Entropy Hybrid Methods for Ranking of Protein Residues by Importance" J. Mol. Bio. **336**: 1265-82. For the original version of ET see O. Lichtarge, H. Bourne and F. Cohen (1996). "An Evolutionary Trace Method Defines Binding Surfaces Common to Protein Families" J. Mol. Bio. **257**: 342-358.

report_maker itself is described in Mihalek I., I. Res and O. Lichtarge (2006). "Evolutionary Trace Report Maker: a new type of service for comparative analysis of proteins." Bioinformatics **22**:1656-7.

4.6 About report_maker

report_maker was written in 2006 by Ivana Mihalek. The 1D ranking visualization program was written by Ivica Reš. **report_maker** is copyrighted by Lichtarge Lab, Baylor College of Medicine, Houston.

4.7 Attachments

The following files should accompany this report:

- `1aqwA.complex.pdb` - coordinates of 1aqwA with all of its interacting partners
- `1aqwA.etvx` - ET viewer input file for 1aqwA
- `1aqwA.cluster_report.summary` - Cluster report summary for 1aqwA
- `1aqwA.ranks` - Ranks file in sequence order for 1aqwA
- `1aqwA.clusters` - Cluster descriptions for 1aqwA
- `1aqwA.msf` - the multiple sequence alignment used for the chain 1aqwA
- `1aqwA.descr` - description of sequences used in 1aqwA msf
- `1aqwA.ranks_sorted` - full listing of residues and their ranking for 1aqwA
- `1aqwA.1aqwMES2500.if.pml` - Pymol script for Figure 5
- `1aqwA.cbcvg` - used by other 1aqwA – related pymol scripts
- `1aqwA.1aqwF.if.pml` - Pymol script for Figure 6
- `1aqwA.1aqwC.if.pml` - Pymol script for Figure 7
- `1aqwA.1aqwE.if.pml` - Pymol script for Figure 8
- `1aqwA.1aqwB.if.pml` - Pymol script for Figure 9