Novel Procedure for Modeling Ligand/Receptor Induced Fit Effects

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SUPPORTING INFORMATION

The following protein RMSD values provide an estimation of the amount of conformational change associated with the induced fit docking calculations. They also provide some measure of the differences between the pairs of crystal structures. However, it's important to note that these numbers could be misleading. For example, when comparing the induced fit docking structure to R_A (the protein that was crystallized with the ligand used in the induced fit calculation), it is possible to obtain an artificially low RMSD value as well as one that is artificially high. For example, if a large number of residues in the active site of the crystal structure are superimposable with the corresponding residues in the induced fit structure, but a single key residue has a different conformation that actually precludes binding of the ligand in the correct pose, then the RMSD will be low despite the fact that the induced fit structure and potentially the ligand pose are incorrect. To demonstrate this point, the RMSD of two hypothetical proteins in which 5 residues (47 atoms) match perfectly, but in which the χ_1 angle of a single Tyr residues differs by only 40°, would be 0.88 Å. Conversely, it is possible to obtain a high RMSD value in cases where the induced fit structure is accurately predicted. This can happen when a single residue that is flexible and not critical for binding in the induced fit structure is predicted to exist in a conformation that differs substantially from the crystal structure. In this case, the RMSD would be high despite the fact that all key residues necessary to define the interactions between the protein and ligand are perfectly predicted.

Table S1. Receptor RMSDs (excluding hydrogens).

Target	Receptor (R_B)	Ligand (L_A) From:	RMSD (Å)		
			R_B/R_A	R_B/IFD	R_A/IFD
Aldose Reductase	2acr:_	1ah3	1.29	1.03	0.73
Antibody DB3	1dba:H	1dbb	1.59	1.49	0.52
CDK2	1buh:A	1dm2	1.41	0.84	1.13
CDK2	1dm2:A	1aq1	1.11	1.24	1.00
COX-2	3pgh:A	1cx2	1.15	0.63	1.01
COX-2	1cx2:A	3pgh	1.01	0.56	0.91
Estrogen Receptor	1err:A	3ert	1.16	1.24	1.65
Estrogen Receptor (excluding H524)	1err:A	3ert	0.97	0.79	1.10
Estrogen Receptor	3ert:A	1err	1.44	1.41	1.64
Factor Xa (excluding Q192 side chain)	1ksn:A	1xka	0.79	0.67	0.52
Factor Xa	1xka:C	1ksn	1.02	1.33	1.06
Factor Xa (excluding Q192 side chain)	1xka:C	1ksn	0.87	0.48	0.72
HIV-RT	1rth:A	1c1c	1.61	0.89	1.68
HIV-RT	1c1c:A	1rth	1.14	2.29	2.07
HIV-RT (excluding Y181 side chain)	1c1c:A	1rth	1.16	1.26	1.14
Neuraminidase	1nsc:A	1a4q	0.61	0.41	0.51
PPARγ	1fm9:D	2prg	1.62	1.09	1.16
PPARγ	2prg:A	1fm9	1.57	1.48	0.85
Thermolysin (excluding frozen metal ligands)	1kr6:A	1kjo	0.95	0.41	0.81
Thermolysin (excluding frozen metal ligands)	1kjo:A	1kr6	0.96	0.25	1.05
Thymidine Kinase	1kim:A	1ki4	0.63	0.77	0.39

The RMSD values for CDK2 (receptor=1aq1), neuraminidase (receptor=1a4q), and thymidine kinase (receptor=1ki4) are not reported because these are the pairs in which rigid receptor docking worked and therefore induced fit docking was not required.