ResQ: An approach to unified estimation of B-factor and residue-specific error in protein structure prediction

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SUPPLEMENTARY MATERIALS

Supplementary Methods

Text S1. I-TASSER pipeline

The iterative threading assembly refinement (I-TASSER) is a hierarchical template-based approach to protein structure prediction that consists of four steps of template recognition, structure assembly, consensus-based model selection, and structure refinement [1, 2].

Starting from the query sequence, I-TASSER first identifies multiple template structures from the PDB by LOMETS, which consists of multiple threading programs [3]. The target sequence is then split into threading-aligned and threading-unaligned regions. Continuous fragments on the aligned regions are excised from the template structures which are used to reassemble the full-length models by iterative replica-exchange Monte Carlo simulations, where the threading unaligned regions are built by a lattice-based *ab initio* folding procedure [4]. The models of the lowest free energy are identified by clustering structure decoys from the Monte Carlo assembly simulations using SPICKER [5].

Following SPICKER, a second round simulation is conducted from the cluster centroid models with restraints containing analogous templates from TM-align search [6]. Finally, the coarse-grained models are subject to the fragment-guided molecular dynamic simulations (FG-MD) for atomic-level structure refinement [7].

Text S2. Feature design for local structure quality prediction

In order to estimate the residue specific quality (RSQ) of predicted models, five sources of information were collected, including structural variations of model assembly simulations, variation on the threading and structural alignment templates, threading alignment coverage, and the consistency between the model and the sequence-based predictions of structural features, which are detailed below.

(I) Structural variation of assembly simulations. It is well known that the residues at different locations have different degrees of variation in the structural assembly simulations. In general, the regions with a higher uncertainty (e.g. the disorder regions or those with less spatial restraints) tend to have a higher variation during the simulations and therefore with a lower modeling accuracy. The lower panel of Figure 1 presents an example of the I-TASSER structural assembly simulations on the PhoQ histidine kinase catalytic domain (PDB ID: 1id0A). The superposition of the decoy structures in the I-TASSER simulations shows higher variations on the middle loop region (D96-L111) that connects two alpha helices (Figure 1C), where the final model has a bigger deviation from the native structure (Figure 1B).

Here, we quantify the degree of variation of the *j*th residue in the structural assembly simulations

by the average and standard deviation, i.e.,

$$\begin{cases} \mu_j = \frac{1}{N}\sum_{i=1}^{N} d_{ij}, \\ \nu_j = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(d_{ij}-\mu_j\right)^2} \end{cases} \qquad j = 1, \cdots, L \tag{S1}$$

where L is the length of the query sequence; N is the number of decoys in the SPICKER cluster; d_{ij} is the distance for the jth residue between the ith decoy and the centroid structure model after the TM-score superposition [8]. In SPICKER, a centroid model is calculated by averaging the coordinates of all decoy structures for each specific residue after the RMSD superposition [5].

In addition, the relative cluster size, which is defined as the number of decoys in a SPICKER cluster divided by the total number of decoys submitted for clustering, is also used as one of the features. Though this feature is the same for all residues in a model, it does help in predicting the magnitude of the distances.

(II) Structural variation of templates from LOMETS threading. If the jth residue on the query sequence is aligned to N_j templates by LOMETS [3], the corresponding structural variation of the LOMETS threading templates is defined as:

$$\lambda_j = \frac{1}{N_j}\sum_{n=1}^{N_j} d_n(j) \tag{S2}$$

where $d_n(j)$ is the distance between the jth residue on the model and the residue on the nth template that is aligned to this residue. The distance is calculated after superposing the template structures on the query model by the TM-score rotation matrix [8], with alignments generated by threading. Only the top 10 templates are considered, where the N_j can be different for different residues. In case that N_j is zero, the value of λ_j is set to a high value (10 Å).

(III) Structural variation of templates from TM-align structure alignment. To count for the similarity of the query structure model with analogous proteins in the PDB, we scan the model against a representative set of the PDB structures using TM-align [6]. The structural variation of the top 10 structural templates with the highest TM-scores, in comparison to the query model, is calculated using the same equation (Eq. S2), but with N_j and $d_n(j)$ defined by the TM-align structural templates.

(IV) Threading alignment coverage. In addition to the structural variations, two more features related to residue conservation are extracted from the multiple threading alignments. We first select up to 200 top templates based on the alignment scores, the sequences of which are mapped onto the query sequence according to the threading alignments but ignoring the gaps from query; the sequence alignment mapping forms a multiple sequence alignment (MSA). The first feature extracted from the MSA is the alignment coverage on the query residue, which is defined as the fraction of templates out of all the top 200 templates that have the residue aligned. The second feature is similar to the first one but only consider the good templates (n_{good}), which have the Z-score (Z) above the program-specific cutoff (Z_{cut}) that was defined to distinguish the bad and good templates [3]. If n_{good} is less than 10, the top 10 templates will be used as ranked by the ratios (Z/Z_{cut}).

(V) Consistency between model and sequence-based structural feature predictions. The last feature group that we exploit is the consistence between the final model and the sequence-based predictions of secondary structure (SS) and relative solvent accessibility (RSA). This feature can be helpful since the accuracy of the sequence-based predictors for these local structure features are in general more robust than the tertiary structure modeling. In this study, we used the PSSpred and SOLVE programs [2] to generate the SS and RSA predictions, respectively, for the query sequence. STRIDE [9] was used to assign the SS and RSA from the 3D structural models. Thus, each residue is represented by five consistency features: the PSSpred profile (i.e., three probabilities for being in alpha-helix, beta-strand, or random coil states), the difference between the predicted and the assigned RSA values, and a binary feature indicating whether the predicted SS is identical with that in the model.

To investigate the contributions of the above features to the RSQ predictions, we categorize the 12 features into three groups: Group-A contains 3 features from structural assembly simulations described in (I); Group-B contains 4 features from threading and structural alignment searches described in (II-IV); Group-C contains 5 features of sequence-based local feature predictions described in (V). The importance and contribution of these features to the final ResQ prediction are evaluated based on their performance on the 835 test proteins, which are summarized in Table S1. Generally, the intermediate modeling features from Group-A generated RSQ slightly lower than that by Groups B and C, demonstrating their importance in local quality prediction. However, a combination of all the features achieves the lowest RSQ than all individual feature groups.

Text S3. Feature design for B-factor profile prediction

Two groups of features are used for the B-factor profile prediction.

(I) Template-based BFP assignment. The B-factor of each query residue is assigned on the basis of the experimental B-factor values of the top homologous/analogous templates that are identified by the LOMETS and TM-align searches:

$$b_q(j) = \frac{1}{n_j} \sum_{i=1}^{n_j} b_t(i, j) \tag{S3}$$

where n_j is the number of the templates that have a residue aligned on the query residue j, and $b_t(i, j)$ is the normalized B-factor value of the residue taken from the ith template that is aligned to residue j. Up to 240 templates from LOMETS and 50 from TM-align search are considered in Eq. S3. When there is no alignment on a residue (i.e. n_j=0), $b_q(j)$ is set to 0.

In addition to the B-factor from templates, the threading alignment coverage with all templates, i.e. Feature IV in Text S2, is also exploited as one feature for the BFP prediction here.

(II) Sequence profile. The query sequence is searched by PSI-BLAST [10] (with parameters '*-j 3 -h 0.001*') through the NCBI non-redundant sequence database, with the sequence profile represented in the form of a position-specific scoring matrix (PSSM). For each residue, a sliding window with width =9 residues is used to extract features from the PSSM after converting its elements x to the range of (0, 1) by $1/[1+\exp(-x)]$. The secondary structure and solvent accessibility, which are both derived from the PSI-BLAST sequence profiles by PSSpred, are also used as features for the B-factor prediction. The hypothesis of using the sequence profile for B-factor prediction is that the more conserved residues in sequence families are often structurally more stable and therefore

have a lower B-factor, and vice versa.

Text S4. Test of ResQ on CASP decoys

Results on CASP9 decoys: Table S5 summarizes the results of the local structure quality prediction by ResQ, compared to the top-performing MQAPs in CASP9. The average of Δd by ResQ is 3.073 Å, which is 0.527 Å lower than the second best method (QMEANclust [11]) from other laboratories, which corresponds to a *p*-value in the student *t*-test below 10^{-56}. If considering the distance error after the TM-score normalization, the distance error of ResQ (0.117) is also the lowest among all the predictors. However, the PCC and AUC scores are statistically indistinguishable between ResQ and the top three predictors, although ResQ's value is ranked at the top.

Results on CASP10 decoys: Different from CASP9, an adjusted two-stage procedure was proposed to the test registered MQAPs in CASP10. In Stage-1, a small number of selected models (up to 20) covering the whole range of model accuracy was released, which was followed by the release of a larger number of models (up to 150) with model quality distributed uniformly in Stage-2. One purpose of such design was to examine the robustness of single-model based methods without considering the feature of structural consensus in Stage-1.

We tested ResQ on the decoys from both stages of CASP 10 and the results are summarized in Tables S6 and S7, respectively. The Δd of the ResQ for Stage-1 is 4.01 Å, which is 0.15 Å lower than the second best predictor from MQAPfrag2 [12] (4.16 Å) but the difference is not statistically significant (*p*-value is 0.18 in the Student's *t*-test). The TM-score normalized distance error by ResQ is also marginally lower than MQAPfrag2 (0.130 vs. 0.132). The PCC of ResQ also outperforms other predictors; but the AUC score of ResQ is slightly lower than that of ModFOLD4 [13] (0.849 vs. 0.857). The data suggests the possibility to further improve ResQ for single-model based local structure quality prediction by exploring multiple statistical potentials [14].

For decoys in the Stage-2 of CASP10, the Δd data is generally lower than that of Stage-1 for all the methods, including the single-model based methods. This is probably due to the fact that the decoy models have on average a better quality in Stage-2, which makes the local quality prediction relatively easier (see data in Figure 1A). Again, the Δd and PCC by ResQ outperform other methods, which are 0.33 and 7% better (with respective *p*-values 10^{-4} and 10^{-25} in the Student's *t*-test) than the second best predictor from MULTICOM-REFINE [15]. The Δd of ResQ was 0.524 Å lower (with a *p*-value 10^{-8} in the Student's *t*-test) when compared with MQAPfrag2 [12], the second best predictor in Stage-1. These data demonstrate the robustness of the ResQ predictions for both cases with only a few decoys and many decoys, compared to the state-of-the-art MQAP methods.

Results on CASP11 decoys: CASP11 followed a similar two-stage procedure for MQAP decoy release, where the results of ResQ together with the top MQAP predictors are listed in Tables S8 and S9 for decoys in Stage-1 and Stage-2, respectively. In Stage-1, the ResQ Δd prediction is lower than other MQAP predictors based on both actual distance and the TM-score normalized distance.

In Stage-2, however, ResQ is obviously outperformed by DAVIS-QAconsensus that is a method designed by CASP organizers to control other MQAP prediction methods [16]. DAVIS-QAconsensus uses the structural consensus of the target model with all other submitted models as the only feature for RSQ prediction, a feature not used by ResQ. This result highlights the dominant importance and advantage of the structural consensus in RSQ estimations with increasing decoy models, especially at the current stage when an efficient physics-based quality estimation function is not yet available. The distance error of ResQ in the Stage-2 is also outperformed by

ModFOLDclust2 and ModFOLD5 [13], but the difference is not statistically significant. Similarly, the PCC and AUC values by ResQ are among the top but slightly lower than the best MQAP predictors in both Stages.

Supplementary Tables

Table S1. The results RSQ prediction based on different groups of features. Numbers in parentheses are the number of features in each group.

Feature group	d_o (Å)	d_p (Å)	Δd (Å)
A (3)	4.302	3.376	2.48
B (4)	4.302	3.405	2.62
C (5)	4.302	2.278	3.29
A+B (7)	4.302	3.448	2.44
A+C (8)	4.302	3.389	2.47
B+C (9)	4.302	3.414	2.61
A+B+C (12)	4.302	3.461	2.40

Table S2. Summary of RSQ predictions by ResQ on different structure regions for the 506 testing proteins that have a C-score >-1.5.

	Aligned regions			Unaligned regions		
	alpha	beta	coil	alpha	beta	coil
d_o (Å)	2.2	1.7	3.6	10.8	8.7	12.5
d_p (Å)	1.8	1.5	2.6	7.9	6.7	8.4
Δd (Å)	1.1	0.9	1.9	5.1	5.2	6.2

Table S3. Summary of the B-factor predictions by ResQ on all 635 test proteins.

Approach	PCC	AUC
Template-based assignment	0.54	0.768
Profile-based training	0.59	0.785
Combination of both	0.61	0.793

Table S4. Comparison of ResQ with SMOQ [17] and PROFbval [18] on RSQ and BFP predictions for 635 test proteins. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o using Eq. (2).

		SMOQ (B)	SMOQ (B+P)	SMOQ (B+P+S)	PROFbval	ResQ
RSQ	Δd (Å)	3.63 (0.26)	4.30 (0.35)	4.29 (0.32)		2.40 (0.14)
	PCC	0.43	0.45	0.45		0.66
	AUC	0.74	0.75	0.75		0.87
BFP	PCC				0.52	0.61
	AUC				0.75	0.79

Table S5. Comparison between ResQ and other MQAPs for RSQ prediction on the CASP9 decoys. N_m is the total number of models that a predictor submitted. Best scores are highlighted in bold in each category. The decoys were downloaded from http://www.predictioncenter.org/download_area/CASP9/server_predictions/. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o based on Eq. (2).

Methods	Δd	PCC	AUC	N_m	Reference
ResQ	**3.073 (0.117)**	**0.727**	0.883	25694	This paper
QMEANclust	3.600 (0.160)	0.718	0.877	25611	[11]
MULTICOM	3.670 (0.122)	0.720	0.872	24799	[15]
MULTICOM-REFINE	4.121 (0.135)	0.693	0.859	25694	[15]
MULTICOM-CONSTRUCT	4.166 (0.134)	0.655	0.851	24691	[15]
MQAPmulti	4.331 (0.122)	0.679	0.870	24587	[12]
MetaMQAPclust	4.335 (0.123)	0.695	0.876	25057	[12]
MQAPsingle	4.765 (0.138)	0.629	0.843	25057	[12]
PconsM	5.145 (0.140)	0.656	0.878	25572	[19]
ModFOLDclust2	5.163 (0.146)	0.700	**0.898**	25626	[13]
IntFOLD-QA	5.173 (0.150)	0.698	**0.898**	25425	[13]

Table S6. Comparison between ResQ and other MQAPs (identical predictors are discarded) for the local structure quality prediction on the CASP10 decoys of Stage-1. N_m is the total number of models that a predictor submitted. Best scores are highlighted in bold in each category. The decoys were downloaded from http://www.predictioncenter.org/download_area/CASP10/server_predictions/. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o using Eq. (2).

Methods	Δd	PCC	AUC	N_m	Reference
ResQ	**4.010 (0.130)**	**0.666**	0.849	1438	This paper
MQAPfrag2	4.156 (0.132)	0.633	0.828	1438	[12]
MQAPsingle	4.194 (0.132)	0.631	0.826	1438	[12]
ProQ2clust2	4.424 (0.157)	0.594	0.841	1258	[12]
MQAPmulti2	4.634 (0.138)	0.637	0.831	1437	[12]
ModFOLD4_single	4.710 (0.139)	0.620	0.848	1437	[13]
ModFOLD4	4.714 (0.139)	0.637	**0.857**	1437	[13]
Pcons-net	4.856 (0.164)	0.615	0.852	1398	[19]
ModFOLDclust2	4.986 (0.158)	0.628	0.852	1437	[13]
ProQ2clust	5.001 (0.158)	0.596	0.843	1435	[20]
MULTICOM-REFINE	5.119 (0.190)	0.611	0.816	1438	[15]

Table S7. Comparison between ResQ and other MQAP methods for the local structure quality prediction on the CASP10 decoys of Stage-2. N_m is the total number of models that a predictor submitted. Best scores are highlighted in bold in each category. The decoys were downloaded from http://www.predictioncenter.org/download_area/CASP10/server_predictions/. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o using Eq. (2).

Method	Δd	PCC	AUC	N_m	Reference
ResQ	**3.433** (**0.121**)	**0.677**	0.865	10800	This paper
MULTICOM-REFINE	3.773 (0.133)	0.630	0.839	10800	[15]
ModFOLDclust2	3.859 (0.128)	0.668	0.876	10788	[13]
ModFOLD4	3.872 (0.130)	0.658	0.871	10788	[13]
MQAPmulti	3.911 (0.134)	0.632	0.840	9900	[12]
MQAPmulti2	3.928 (0.134)	0.631	0.843	9900	[12]
ProQ2clust	3.938 (0.137)	0.643	0.869	10786	[20]
MQAPfrag2	3.957 (0.134)	0.638	0.847	9900	
MQAPsingle2	3.957 (0.134)	0.638	0.847	9900	[12]
ModFOLD4_single	3.998 (0.141)	0.600	0.844	10788	[13]
Pcomb	4.010 (0.140)	0.655	**0.877**	10788	[19]

Table S8. Comparison between ResQ and other MQAPs (identical predictors are discarded) for the local structure quality prediction on the CASP11 decoys of Stage-1. N_m is the total number of models that a predictor submitted. Best scores are highlighted in bold in each category. The decoys were downloaded from http://www.predictioncenter.org/download_area/CASP11/server_predictions/. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o using Eq. (2).

Methods	Δd	PCC	AUC	N_m	Reference
ResQ	**6.832 (0.137)**	0.611	0.801	1080	This paper
DAVIS-QAconsensus	7.107 (0.170)	0.621	0.836	1080	[16]
ModFOLD5	7.928 (0.139)	**0.634**	**0.852**	1080	[13]
ModFOLD5_single	7.929 (0.139)	0.622	0.845	1080	[13]
ModFOLDclust2	8.312 (0.166)	0.608	0.844	1080	[13]
Pcons-net	8.773 (0.202)	0.548	0.816	1055	[19]
Wallner	9.118 (0.196)	0.543	0.817	1076	[19]
Wang_deep_2	9.345 (0.236)	0.304	0.690	1060	NA
Wang_deep_3	9.632 (0.237)	0.311	0.698	1060	NA
Wang_deep_1	9.694 (0.240)	0.218	0.633	1060	NA

Table S9. Comparison between ResQ and other MQAPs (identical predictors are discarded) for the local structure quality prediction on the CASP11 decoys of Stage-2. N_m is the total number of models that a predictor submitted. Best scores are highlighted in bold in each category. The decoys were downloaded from http://www.predictioncenter.org/download_area/CASP11/server_predictions/. Numbers in parentheses are the values computed after normalization of the distance d_p and d_o using Eq. (2).

Methods	Δd	PCC	AUC	N_m	Reference
DAVIS-QAconsensus	**3.567** (**0.132**)	**0.700**	0.878	8100	[16]
ModFOLDclust2	3.907 (0.135)	0.694	**0.881**	8100	[13]
ModFOLD5	3.955 (0.141)	0.678	0.874	8100	[13]
ResQ	4.006 (0.154)	0.611	0.835	8100	This paper
ModFOLD5_single	4.121 (0.156)	0.612	0.842	8100	[13]
Pcons-net	4.411 (0.165)	0.655	0.867	8031	[19]
Wallner	4.412 (0.160)	0.662	0.870	8076	[19]
ProQ2	5.101 (0.223)	0.485	0.791	8076	[19]
ProQ2-refine	5.116 (0.224)	0.485	0.791	8080	[19]
PconsD	5.130 (0.229)	0.668	0.863	7831	[19]

Table S10. The RSQ results by ResQ for the first QUARK models of 50 protein targets.

Target	TM-score	Δd (Å)
1i3cA	0.69	1.61
1c1lA	0.42	3.68
1czpA	0.61	1.71
1e29A	0.55	2.76
1f86A	0.69	1.6
1gmxA	0.65	1.28
1h4xA	0.74	0.68
1h97A	0.74	1.17
1ithA	0.69	1.42
1jbeA	0.79	0.79
1khyA	0.79	0.99
1nwwA	0.62	4.06
1pbjA	0.56	1.71
1q77A	0.54	2.58
1q9uA	0.5	3.91
1r4vA	0.34	6.96
1rl2A	0.3	6.71
1rxdA	0.58	2.47
1s5uA	0.51	2.52
1sbxA	0.33	6.85
1seiA	0.55	3.28
1ss4B	0.41	6.9
1v05A	0.48	3.72
1v30A	0.45	2.87
1w0nA	0.34	7.18
1yqhA	0.57	4.77
1yrkA	0.3	5.93
1zceA	0.32	6.68
1zd0A	0.34	8.17
1zmaA	0.53	2.29
2b0vA	0.38	4.28
2bwqA	0.58	2.14
2c6uA	0.35	5.36
2cc3A	0.34	7.93
2d9rA	0.54	1.58
2e56A	0.25	8.72
2g2cA	0.58	1.73
2gj3B	0.64	1.75
2gu3A	0.51	2.67
2gu9A	0.49	3.66
2h1cA	0.5	4.5

2hkvA	0.64	1.95
2ib0A	0.72	1.9
2im8A	0.44	5.76
2jdcA	0.67	1.73
2o7aA	0.6	2.89
2o90A	0.5	2.74
2oggA	0.58	2.33
2otmA	0.54	4.1
4nklA	0.62	1.81
Mean	0.53	3.54

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