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Assessment of Other Categories of Predictions

Evaluation of residue–residue contact predictions in CASP9

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ABSTRACT

This work presents the results of the assessment of the intramolecular residue–residue contact predictions submitted to CASP9. The methodology for the assessment does not differ from that used in previous CASPs, with two basic evaluation measures being the precision in recognizing contacts and the difference between the distribution of distances in the subset of predicted contact pairs versus all pairs of residues in the structure. The emphasis is placed on the prediction of long-range contacts (i.e., contacts between residues separated by at least 24 residues along sequence) in target proteins that cannot be easily modeled by homology. Although there is considerable activity in the field, the current analysis reports no discernable progress since CASP8.

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Key words: CASP; intramolecular contacts; residue–residue contact prediction; protein structure modeling.

INTRODUCTION

Interactions among protein residues are crucial in stabilizing the tertiary structure[1,2] and knowing them can be of invaluable help in modeling of protein structure. Prediction of contact maps of proteins—even in the simplified form of a binary matrix—can help both free modeling (FM) and hard template-based modeling (TBM) methods. Several algorithms for deriving an approximate structure of a protein from its contact map have been developed,[3–7] reaching different levels of accuracy. Clearly, the application of contact maps to structure prediction requires that at least a fraction of contacts is identified with high accuracy; the exact number depends on the difficulty of the problem (FM/TBM), protein length, and distribution of contacts along the sequence, among others. Skolnick and coworkers, for example, state that their algorithm is able to successfully fold a small protein using on average one contact for every seven residues.[7] Other authors report that the tertiary structure of a protein can be modeled with an average RMSD lower than 5.0 Å provided that at least 25% of contacts are correct.[6] Even if the correctly predicted contacts are too few or too inaccurate for generating a structure, they may still be used for selecting a better template or a model from among alternative ones or to narrow the search space of possible conformations.[8–11]

Several rather successful three-dimensional structure prediction methods and model quality assessment methods are already taking advantage of contact prediction tools in their pipelines.[12,13] For example, I-TASSER, one of the most successful structure prediction servers in recent CASPs,[14,15] has been recently upgraded by adding an *ab initio* contact prediction module, which significantly improved its performance and increased the quality of the resulting models on hard targets by 4.6% on the average.[16] In some cases, quality of I-TASSER models improved by as much as 30%, resulting in *de facto* conversion of essentially "non-foldable" targets into "foldable ones."

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Additional Supporting Information may be found in the online version of this article.
Abbreviations: 3D, three-dimensional; RR, residue–residue contact; RMSD, root mean square deviation.

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Various approaches have been developed to predict contacts, and they can be roughly subdivided into three broad categories:

1. Methods using homologous proteins with known structures.[17–20] These are clearly very reliable, but their usefulness is limited to cases where templates can be identified. They are especially helpful for effective combining of information derived from several templates, when these are available.
2. Methods relying on machine learning and mathematical modeling algorithms—such as hidden Markov models,[21,22] neural networks,[22–26] support vector machines,[27–29] genetic algorithms,[30] graph theory,[31] and other techniques[32]—to recognize contacts from features identified in protein structures. These methods can obviously be applied to virtually any target.
3. Methods exploiting evolutionary information. These are based on the concept of correlated mutations,[33–36] stating that similar patterns of mutations correspond to similar contacts. Some methods[37,38] combine this approach with machine learning techniques.

Ever since the contact prediction category was introduced in CASP in 1996,[39] the number of methods has been steadily increasing. Discussions within the community in the first few years of the experiment led to the development of a standard procedure for the assessment of predictions, which has remained stable in the last three CASPs.[40–42] This enabled us to carry out the evaluation in an automatic fashion. We use this occasion to remind interested readers of the existence of a discussion forum (http://www.forcasp.org/) where alternative evaluation methods can be proposed and discussed.

MATERIALS AND METHODS

Contact definition and targets

We use the intramolecular contact definition as accepted in previous CASPs.[40–42] A pair of residues is considered in contact if the distance between their C_β atoms (C_α in case of Gly) is lower than 8.0 Å. We distinguish three types of contacts, depending on the number of amino acids separating the residues along the sequence: (i) long range contacts (separation $\geq$ 24); (ii) medium range contacts ($12 \leq$ separation ≤ 23), and (iii) short range contacts ($6 \leq$ separation ≤ 11). Contacts between residues separated by less than six residues are usually associated with the protein secondary structure and are not considered here. The most valuable in structure prediction are the long range contacts, and here we concentrate on this.

Even though contact predictions were submitted for whole targets, we performed the assessment on a domain level, according to the definitions agreed on by the assessors.[43] Similarly to previous CASPs, targets for residue contact prediction were limited to the FM and TBM/FM domains, because in the case of closer homology, contacts can easily be derived from templates. One domain in the FM category (T0537-D2) was excluded from assessment because of its very short length (31 residues). In the end, evaluation was performed on the 28 "difficult" target domains (25 FM and 3 TBM/FM). A more unbiased view of the success of *de novo* contact prediction methods would require to limit the analysis only to nontemplate based "new fold" targets; however, the paucity of the latter (just four in the current edition of the experiment[43]) does not allow to draw any statistically sound conclusion from their analysis.

Table I
A Short Description of Best 10 Publicly Available Servers Participating in CASP9

Server name and URL address (*standalone software free to download)	Description
MULTICOM-CLUSTER[28] http://casp.rnet.missouri.edu/download/svmcon1.0.tar.gz (*)	Method is based on the support vector machine approach. The input data include secondary structure, solvent accessibility, and sequence profile for 9-residue windows.
PROC_S3; PROC_S1 http://www.abl.ku.edu/Pred_CMAP/	*Ab-initio* prediction methods are based on Random Forest models—a machine-learning technique using over 1000 sequence-related features.
DISTILL[24] http://dbstill.ucd.ie/distill/	The method is based on 2D-recursive neural networks.
SAM-T08[45] http://compbio.soe.ucsc.edu/SAM_T08/ SAM-T06 http://compbio.soe.ucsc.edu/SAM_T06/	*Ab initio* contact prediction servers using neural networks and information about correlated mutations in the multiple sequence alignments, which are built using hidden Markov models.
MULTICOM-CONSTRUCT[26]; MULTICOM-REFINE[26] http://casp.rnet.missouri.edu/download/nncon1.0.tar.gz (*)	Both methods are based on recursive neural networks. MULTICOM-REFINE also incorporates a module to predict contacts in beta-sheets.
SVMSEQ[27] http://zhanglab.ccmb.med.umich.edu/SVMSEQ_CASP9	Machine-learning-based method for *ab initio* contact prediction trained on a variety of sequence-derived features, which include both local features and in-between segment features. The vector of features has over 700 components for short, medium, and long range contacts.
FRAGHMMENT[21] http://bioinfo8.limbo.ifm.liu.se/FragHMMent/	The method is based on hidden Markov models trained on alignments of local descriptors of protein structure.

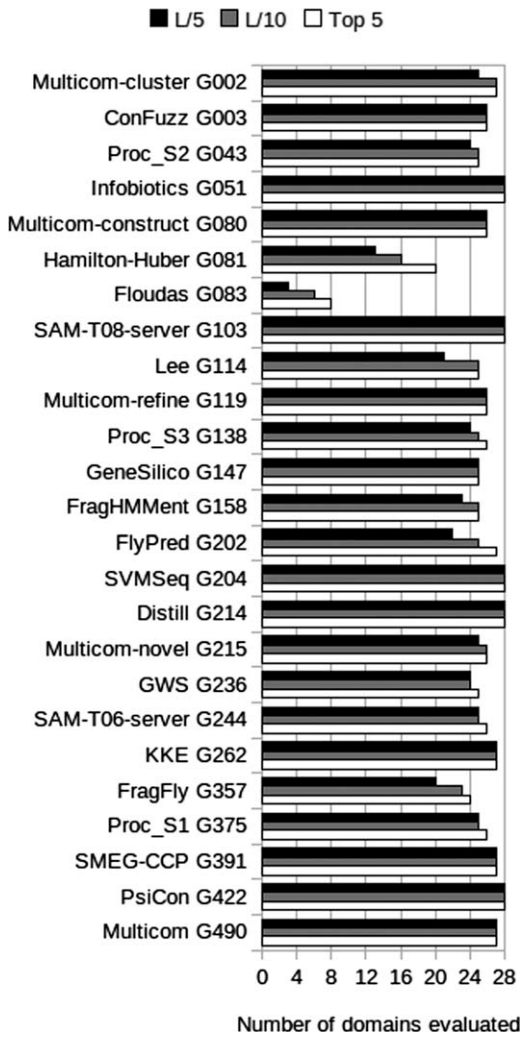

Figure 1

Number of targets evaluated for each group using the *L*/10, *L*/5, and Top-5 lists of contacts.

Participating groups

Twenty-seven groups, including eighteen servers, submitted residue–residue contact predictions in CASP9. Although these numbers are higher than in the last CASP[42] (22 and 14, respectively), according to the submitted abstracts, only very few prediction groups used new methods.[44] The remaining groups used modified versions of methods already tested in previous CASPs. A detailed list of the best publicly available RR servers participating in CASP is provided in Table I. As it can be appreciated from the short description of the servers given in the table, all of them are based on some machine learning technique.

Prediction format and contact lists

The format for submitting predictions was the same as in previous CASPs[40–42]: predictors were asked to submit a list of pairs of residues, together with the corresponding probabilities of the two residues being in contact.

Different predictors submitted different numbers of contacts per target. To compare them, we first sorted the contacts according to their predicted probabilities and then generated lists of *L*/5 and *L*/10 best predicted contacts,[40–42] where *L* is the length of the domain sequence. We also used a list containing only the five top predictions (Top-5 list) to evaluate cases where predictors submitted only a very small number of contacts. The assessment was performed on all three lists, whenever possible.

The number of contact lists evaluated for each group is summarized in Figure 1. Two groups (G179 and G201) are not included due to insufficient number of submitted contact predictions.

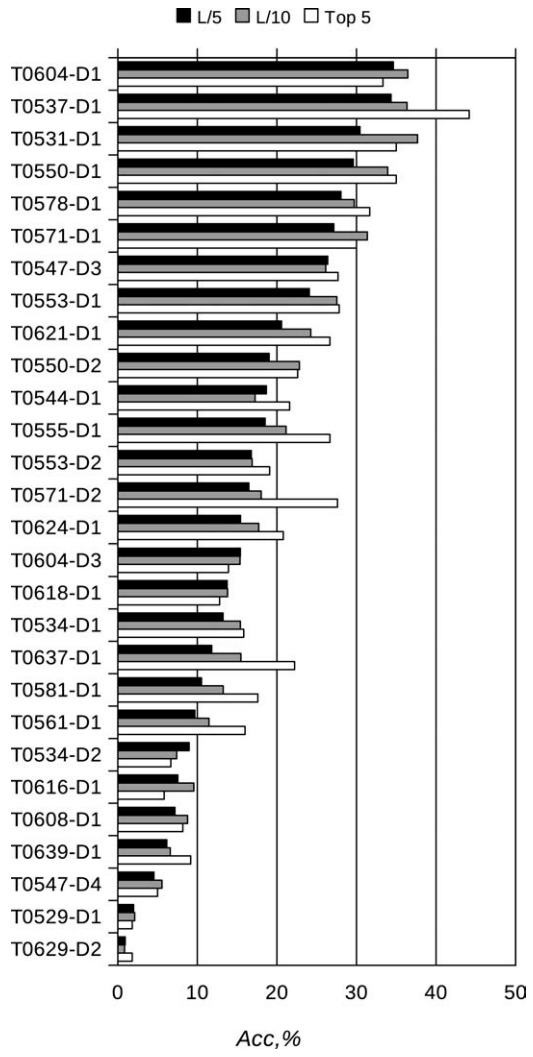

Figure 2

Average value of the accuracy (*Acc*) obtained by the participating groups for each of the targets using the *L*/10, *L*/5, and Top-5 lists of contacts.

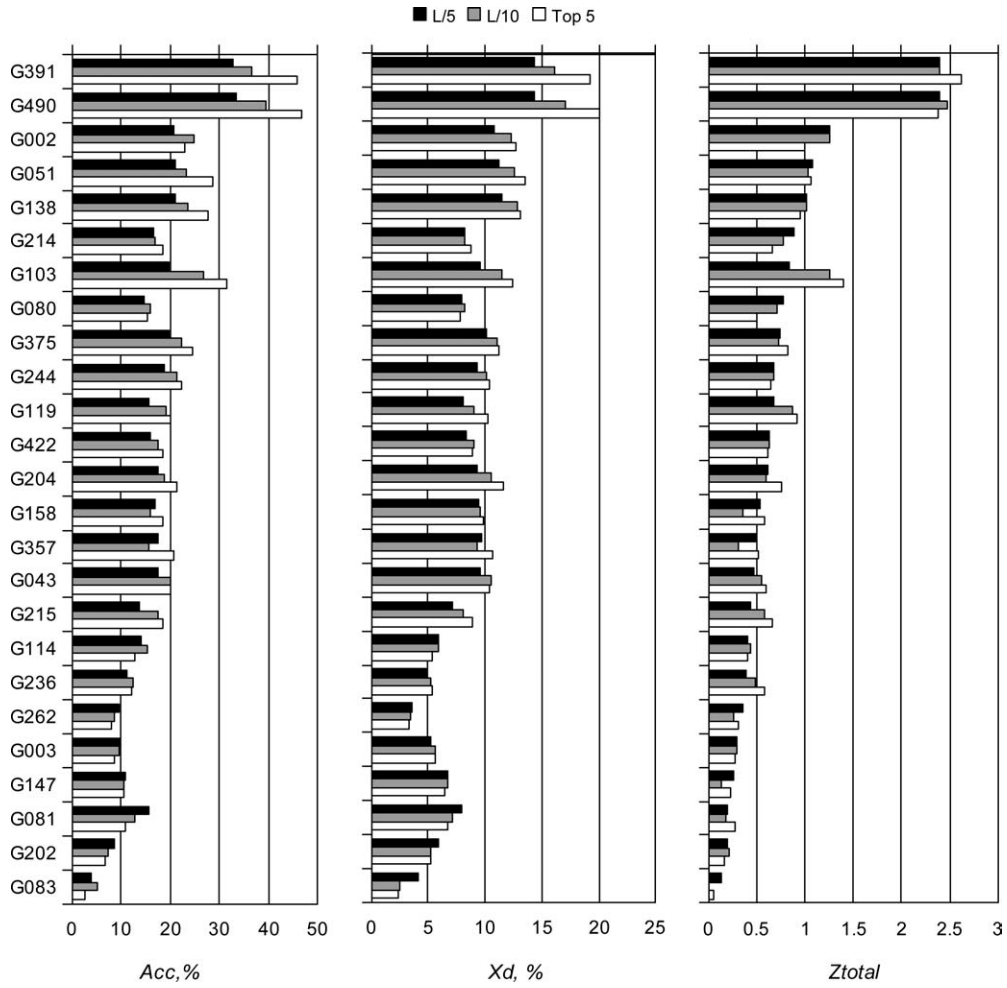

Figure 3

Acc (a), X_d (b), and *Z*-score (c) values for the participating groups.

Evaluation criteria and scores

Since CASP6, predictions in the RR category are evaluated using two measures: *Acc* and X_d.[40–42] Accuracy (*Acc*) is defined as the percentage of correctly predicted contacts with respect to the total number of contacts in the evaluated list:

$$Acc = \mathrm{TP}/(\mathrm{TP} + \mathrm{FP}),$$

where TP and FP are the numbers of correctly and incorrectly predicted contacts, respectively[1].

The X_d score is defined as:

$$X_d = \frac{\sum_{i=1}^{i=15}(P_iP - P_ia)}{15 \times d_i}$$

where P_iP is the fraction of predicted contacts in bin *i*, and P_ia—the fraction of all residue pairs in bin *i*. The 15 bins include ranges of distances from 0 to 4 Å, 4 to 8 Å, 8 to 12 Å, etc. This score estimates the deviation of the distribution of distances in the list of contacts from the distribution of distances in all pairs of residues in the protein.[40,41] The higher the X_d, the higher the precision of the predicted contacts with respect to randomly selected pairs. X_d is close to zero for randomly selected pairs.

Prediction groups are ranked according to the *Z*-scores computed from the distributions of the *Acc* and X_d values for each target domain. The final per-target *Z*-scores are recalculated from the "cleaned" distributions, where only the groups that scored above the level of the mean minus two standard deviations in the original all-group distribution are considered. This elimination of the poorest per-target scores from the final calculations is done to remove possible bias in scores due to trivial errors in the submission/algorithm. The per-domain *Z*-scores for

[1]In descriptive statistics, this definition of *Acc* is usually called positive predictive value (*PPV*) or precision. We retained the name "accuracy" here for consistency with the previous CASP assessments.

Table II
Results of the Student's *t*-Tests on the *Acc* Scores Calculated for the *L*/5 Sets of Contacts

	G391	G490	G002	G051	G138	G214	G103	G080	G375	G244	G119	G422
G391	—	26	25	27	23	27	27	25	24	24	25	27
G490	0.449	—	25	27	24	27	27	26	25	25	26	27
G002	0.006	0.006	—	25	23	25	25	25	24	24	25	25
G051	0.006	0.005	0.468	—	24	28	28	26	25	25	26	28
G138	0.004	0.005	0.443	0.261	—	24	24	24	24	24	24	24
G214	0.002	0.001	0.23	0.072	0.258	—	28	26	25	25	26	28
G103	0.009	0.009	0.478	0.315	0.469	0.171	—	26	25	25	26	28
G080	0.001	0	0.026	0.055	0.112	0.285	0.112	—	25	25	26	26
G375	0.004	0.004	0.438	0.189	0.44	0.282	0.377	0.131	—	25	25	25
G244	0.001	0.001	0.313	0.094	0.299	0.398	0.23	0.223	0.322	—	25	25
G119	0.001	0.001	0.05	0.085	0.161	0.371	0.151	0.161	0.187	0.293	—	26
G422	0.001	0.001	0.16	0.004	0.08	0.415	0.042	0.355	0.055	0.164	0.451	—

For each pair of groups, the numbers under the diagonal show the *P*-values, and those above—the numbers of common domains evaluated. Shaded cells correspond to the statistically indistinguishable groups at the 0.05 significance level.

Acc and X_d are added and then averaged over N domains attempted by a prediction group for the resulting cumulative score expressed as:

$$Z_{\text{total}} = 1/N \sum_{i=1}^{N} (Z_{\text{Acc}_i} + Z_{\text{Xd}_i}).$$

We also compared the results of each pair of prediction groups "head-to-head," by computing the fraction of common targets for which one group outperformed the other according to both the *Acc* and X_d scores. The statistical significance of the differences in performance between any two groups was assessed using a paired Student's *t*-test on both the *Acc* and X_d scores.

RESULTS

Figure 2 shows the average *Acc* score for each of the targets. The accuracy for long range contacts in the *L*/5 lists ranges from 1% to about 35%, indicating that targets presented very different levels of difficulty for RR prediction. In particular, two targets (T0529-D1 and T0629-D2) seem particularly hard, with an average accuracy of 1 and 2%, respectively. A similar analysis using the X_d score (see Fig. S1, Supporting Information) confirms this conclusion. Domain T0629-D2 has very few native long range contacts, while T0529-D1 is a completely novel fold.

The results of the per group assessment are summarized in Figure 3 and Tables II and III. Figure 3 shows the values of *Acc*, X_d, and Z_{total} for all groups averaged over all predictions containing a sufficient number of contacts.

In general, there is a tendency for the accuracy of almost all groups to increase as the number of evaluated contacts decreases (from *L*/5 to *L*/10 to Top 5), demonstrating that methods are reasonably good in correctly ranking their predictions.

The best results, regardless of the considered list of contacts, were obtained by groups "Smeg_CCP" (G391) and "Multicom" (G490). These groups submitted predictions for almost the complete set of targets (27 targets

Table III
Head-To-Head Comparison of Participating Groups

		Group II											
		G391	G490	G002	G051	G138	G214	G103	G080	G375	G244	G119	G422
Group I	G391	—	19.2	68.0	70.4	65.2	74.1	51.9	80.0	66.7	70.8	80.0	74.1
	G490	26.9	—	64.0	63.0	62.5	77.8	63.0	80.8	64.0	68.0	80.8	70.4
	G002	24.0	32.0	—	48.0	47.8	48.0	44.0	72.0	33.3	45.8	64.0	48.0
	G051	22.2	25.9	40.0	—	45.8	57.1	50.0	65.4	52.0	56.0	65.4	60.7
	G138	30.4	29.2	39.1	33.3	—	58.3	58.3	66.7	62.5	45.8	58.3	62.5
	G214	14.8	18.5	48.0	28.6	33.3	—	39.3	57.7	48.0	40.0	57.7	46.4
	G103	33.3	29.6	40.0	35.7	41.7	57.1	—	57.7	40.0	44.0	57.7	50.0
	G080	12.0	11.5	24.0	26.9	29.2	30.8	38.5	—	48.0	28.0	26.9	42.3
	G375	16.7	20.0	54.2	36.0	37.5	52.0	32.0	52.0	—	36.0	52.0	48.0
	G244	16.7	20.0	45.8	36.0	41.7	48.0	36.0	64.0	40.0	—	64.0	60.0
	G119	12.0	15.4	28.0	19.2	33.3	34.6	34.6	46.2	44.0	24.0	—	50.0
	G422	22.2	22.2	28.0	17.9	25.0	46.4	25.0	42.3	32.0	32.0	46.2	—

Cells show the percentages of cases in which the Acc score of the group designated with the row label is higher than that of the group designated with the column label. Cases where the accuracy is the same were not counted, and therefore the percentages at the opposite sides of the diagonal do not necessarily add up to 100%. Computations were performed on the *L*/5 lists of contacts.

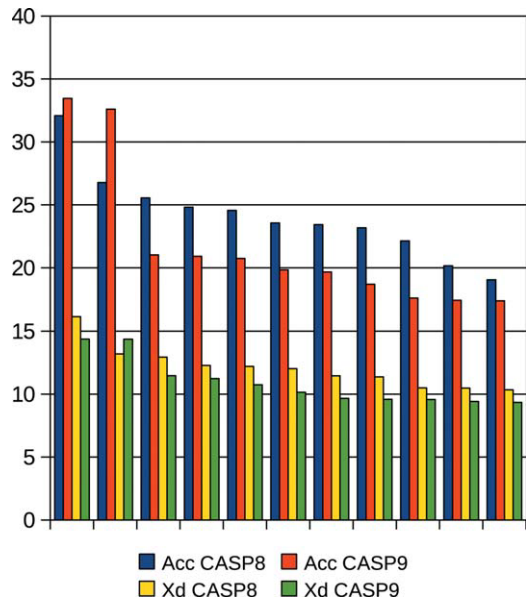

Figure 4

Comparison of the results obtained by the best twelve predictors in CASP8 and CASP9. The 12 groups were selected based on the *Acc* score.

out of 28), and their results are statistically better than those of other groups but indistinguishable between themselves according to the paired *t*-tests (Table II). This conclusion is confirmed by the head-to-head comparison of group scores over commonly predicted targets (Table III). The methods used by groups G391 and G490 are very similar and rely on the 3D structures submitted by CASP9 servers for deriving distance constraints through a consensus strategy. The remaining groups submitted predictions of significantly lower quality (Fig. 3), and the 10 groups ranked below the top two are statistically indistinguishable from each other (Table II). The results based on the X_d scores are very similar and presented in the Supporting Information (Tables S1 and S2).

Comparison with previous CASPs

Only 12 targets were used for the RR assessment in CASP8 compared to the 28 assessed here. The average *Acc* and X_d values obtained by RR groups in this CASP are 16.8% and 8.5%, respectively. When the two very difficult domains T0629-D2 and T0529-D1 are not considered, the corresponding numbers increase to 18.0% and 9.2%. For comparison, in CASP8,[42] the average *Acc* and X_d values were 21.1% and 10.1%, respectively. This would suggest that either the CASP9 methods are slightly worse than those in CASP8 or that the targets for this experiment are more difficult to handle. We believe that the drop in scores is due to a higher difficulty of the CASP9 targets, as discussed in another work in this issue.[46] This reasoning is further corroborated by the fact that many of the same methods were tested both in CASP8 and CASP9, providing a direct means of comparison.

Figure 4 shows the results of comparison of the best twelve groups in CASP9 and CASP8 according to both the *Acc* and X_d scores. Also, in this case, predictions submitted to CASP9 seem to be relatively less accurate than those submitted in the previous experiment.

CONCLUSIONS

The analysis of the RR predictions submitted in CASP9 suggests that improvement in the methods (if any) was more than offset by the increased target difficulty. It is also somewhat disappointing to observe that the best results are obtained by leveraging the ability to predict tertiary structures and to derive contact predictions from them, rather than the opposite. Because the main reason for predicting contacts is to aid in the prediction of structure and not the other way around, the emergence and relative success of techniques relying on the already predicted structures seems to be of limited importance. Perhaps, we should limit assessment to only the targets where model building remains highly unreliable, although few of these are available in any single CASP. Or we should proceed as now, noting the deficiencies in the currently most successful techniques and hoping for the emergence of methods capable of making an independent contribution to structure modeling.

In any case, the CASP RR contact prediction data collected over more than a decade, and the developed standard assessment procedure, provide a useful reference for predictors to evaluate novel ideas and algorithms. We hope that the still growing community in this area will soon make important advancements, significantly influencing *ab initio* structure prediction in general.

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