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3DS3 and 3DS5 3D-SHOTGUN Meta-Predictors in CAFASP3

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ABSTRACT **The performance of the 3DS3 and 3DS5 3D-SHOTGUN meta-predictors in CAFASP3 is reported. The 3D-SHOTGUN meta-predictors are fully automatic fold recognition servers that attempt to incorporate into the prediction process a number of successful strategies that human predictors often apply. Namely, the input to 3D-SHOTGUN are the top five models predicted by a number of independent fold recognition servers and its output are hybrid models, assembled by using the recurrent structural information from the input models. The resulting hybrid models are, on average, more accurate and more complete than the input models. When evaluated on a large set of prediction targets, the 3D-SHOTGUN servers show increased sensitivities and significantly better specificities. For CAFASP3, the 3DS3 and 3DS3 and 3DS5 used a preliminary implementation of the 3D-SHOTGUN method, which lacked a refinement step. Although this did not have a significant effect on the easier targets, for the hardest prediction targets, where the input models had significant structural conflicts, the 3D-SHOTGUN models contained a number of non-native-like features such as fragmentation and overlaps. The CAFASP3 evaluation identified the 3D-SHOTGUN meta-predictors within the top three most sensitive and most specific servers. A fully automated refinement step to the 3D-SHOTGUN method is currently being implemented, and preliminary results indicate that in addition to "cleaning up" such undesirable features, it is able to further increase the accuracy of the resulting models. Proteins 2003;53:517–523.**

Key words: homology modeling; protein fold recognition; protein structure prediction; critical assessment of protein structure prediction; 3D-SHOTGUN meta-predictor

INTRODUCTION

Improving the performance of automatic structure prediction and modeling methods is becoming increasingly important as a result of the various genome-sequencing and structural genomics projects.[1–3] The more experimental structures are determined, the more biologists would like to automatically obtain relatively accurate models for proteins at various homology distances. Despite progress in the automated methods witnessed in the past years,[4–6] the Critical Assessment Structure Prediction (CASP) experiments have shown that the combined use of human expertise and automated methods can often result in more successful predictions.[2]

One particularly successful human strategy has been the application of a number of independent methods to extract a prediction from the top ranking predictions. This has proven useful because for some prediction targets, one method may succeed in producing a correct prediction while others fail, yet for other targets, this same method may fail while the others succeed. Because it is impossible to determine a priori for which targets a given method will succeed, different methods need be considered. In CASP4, we filed consensus predictions using the results of the fully automated servers of CAFASP2 under the group name CAFASP-CONSENSUS.[4] This group performed better than any of the CAFASP2 servers[4] and ranked seventh among all other human predictors of CASP4.[7] This finding showed that a fully automated meta-predictor, using the predictions of a number of independent servers, could be very powerful. Following CAFASP2, a neural network-based method named *pcons* was developed.[8] This method fully automates the procedures used by the CAFASP-CONSENSUS, namely, it selects from the various input models the one that is considered to be more likely to be correct.

3D-SHOTGUN[9] is a novel, fully automatic, highly sensitive and specific fold recognition (FR) meta-predictor method, reminiscent of the so-called cooperative algorithms of Computer Vision, in which local operations appear to cooperate to form global order.[10] 3D-SHOTGUN derives a prediction from information culled from the top predicted models of a number of independent FR methods. 3D-SHOTGUN does not simply select a model from among the individual models but it generates more complete and accurate hybrid models. The 3D-SHOTGUN methods have shown their superior performance in the large-scale LiveBench experiments LiveBench-4[6] and LiveBench-6 (see the report in this issue), where they have been ranked as the very top performers in sensitivity and specificity. Here I summarize 3D-SHOTGUN's performance in the last CAFASP3 experiment.

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MATERIALS AND METHODS

The 3D-SHOTGUN method was recently described.[9] Consequently, here I briefly outline its components. 3D-SHOTGUN first collects the top n (usually $n = 5$) models of m ($m = 3$ or $m = 5$) different, previously developed FR methods, referred to as the "initial models." Because 3D-SHOTGUN is independent of the initial model-generating methods, it can be applied to any set of models. The 3DS3 (3DS5) implementation of 3D-SHOTGUN uses as input $m = 3$ ($m = 5$) independent servers. 3DS3 considers the top models from the following servers: ffas,[11] 3dpsm,[12] and the *inbgu* consensus.[13] 3DS5 considers the top models of the following 1): another version of 3D-SHOTGUN named "SHGU," which itself considers the top five models of each of the five components of the *inbgu* server,[13] (2) ffas, (3) 3dpsm, (4) GenThreader,[14] and (5) Fugue.[15] Occasionally, if the last two servers did not produce results on time, they were replaced by the results of other CAFASP servers. SHGU is available at the bioinbgu Web site at http://www.cs.bgu.ac.il/~bioinbgu, and 3DS3 is available through the *bioinfo* meta-server[16] at http://bioinfo.pl/meta. Because in CASP5/CAFASP3 the performances of the 3DS3 and 3DS5 implementations were slightly higher than that of SHGU and because 3DS5 uses as input the models produced by SHGU, here I focus on the performance of the 3DS3 and 3DS5 versions of 3D-SHOTGUN.

After collecting the $m \times n$ initial models, 3D-SHOTGUN applies the following steps: (1) assembly, (2) confidence assignment, (3) selection, and (4) refinement. In the assembly step, each of the initial models is used as a framework on which to build the new hybrid, assembled model, using a tallying procedure that exploits the recurring structural similarities detected among the initial models. The following is a brief description of the assembly step (for details, see Ref. [9]). Each of the initial models is considered one at a time. For each model *M,* regions of structural similarity to each of the other initial models are first identified. Each initial model that shares some structural similarity with model *M* is superimposed on *M* (using only the shared similarity to compute the transformations), thereby generating a multiple structural alignment. To build the assembled model, coordinates for each residue in the multiple alignment are selected by using a voting scheme. For each residue *i* and each model *N* containing *i,* the number of other models that include *i* in their superposition on *N* are counted. The coordinates of residue *i* in the assembled model are copied from a model having the highest count. In the case in which residue *i* is present in *M* and there is a tie, the coordinates are taken from *M.*

Thus, the resulting hybrid, assembled models contain the most frequent structural features of the models in the multiple alignment and often include coordinates for more residues than any of the initial models. The rationale of this strategy is that recurring structural features obtained by independent agents are more likely to be correct, because there are more ways to be wrong than there are to be right. Thus, a recurring feature is less likely to represent a recurrent error. It should be noted that the multiple structural alignment for each model *M* can contain structurally different models sharing only a few secondary structure elements in common with *M* and that the resulting assembled model is a truly hybrid model, a composite of structural features from the various models in the multiple alignment. However, as will be described below, this assembly can produce regions with collisions and fragmentation for those targets having little structural recurrence among the initial models.

In the confidence assignment step, scores are assigned to each of the assembled models, based on the initial scores and on the structural similarities of the assembled models. The score assigned to the assembled model $M_{i,j}$ is computed as $s'_{i,j} = \sum_{k,l} s_{k,l} \times sim(M_{i,j}, M_{k,l})$, where the indices k and l run over all models and $sim(M_{i,j}, M_{k,l})$ is the MaxSub similarity score[17] between the assembled models $M_{i,j}$ and $M_{k,l}$. MaxSub is a sequence-dependent quality assessment measure that aims at identifying the maximum superimposable subset of C_α atoms of a model and an experimental structure and produces a single normalized score that represents the quality of the model. MaxSub reports scores in the range of 0.0 (for an incorrect model) to 1.0 (for a perfect model). In the 3DS3 implementation $s_{i,j}$ corresponds to the (normalized) original score reported for model j by method i. In the 3DS5 implementation, the actual original score $s_{i,j}$ reported by the servers is ignored; instead, $s'_{i,j} = 1/j$ is used.

In the selection step, the representative assembled model with highest s' score is reported.

Finally, the refinement step is aimed at relieving possible non-protein-like assemblies (e.g., fragmentation and collisions) that can occur when there is little structural recurrence among the initial models. However, at the time CASP5 took place, this step was not yet implemented; thus, the output of the 3DS3 and 3DS5 servers filed to CAFASP were simply the unrefined assembled models.

RESULTS

The 3D-SHOTGUN meta-predictors were ranked within the top performers both in the CAFASP automatic evaluation and in the CASP human assessment. The ranks varied depending on the evaluation, from rank-1 in some of the evaluations to rank-3 in others (see the CAFASP3 automatic evaluation at the CAFASP3 Web site at http://www.cs.bgu.ac.il/≈dfischer/CAFASP3 and the reports of the human assessors in this issue). In general, it would be safe to conclude that the best performers in CAFASP3 were a group of similarly accurate three meta-predictors: 3D-SHOTGUN, robetta, and the pmod variation of pcons (see the reports of the last two servers in this issue). This result is consistent with the large-scale evaluations of LiveBench (see Ref. [6] and see the LiveBench-6 report in this issue).

3D-SHOTGUN's Performance on Selected Targets

To illustrate the performance of 3D-SHOTGUN, I have selected 21 targets in which the CAFASP3 evaluation found the 3DS3 or the 3DS5 models to be among the top best three models for the particular target (Table I). For

TABLE I. Selected 3DS3 and 3DS5 Predictions

		3DS3		3DS5	
Target	Category	MaxSub	Score	MaxSub	Score
T0169	HMH	6.3	100.0	6.5*	10.61
T0165	HMH	5.0*	100.0	5.0	10.46
T0195	HMH	5.6*	100.0	5.5	10.40
T0189	HMH	5.0	100.0	5.0*	10.25
T0150	HM	8.1*	100.0	7.9	9.61
T0185_2	HM	6.6*	100.0	6.6*	9.28
T0185_3	HMH	4.6	100.0	5.3	9.28
T0186_1	HM	8.1	100.0	8.3*	9.16
T0186_2	HMH	3.7*	100.0	2.8	9.16
T0191	HMH	2.7	100.0	2.9*	8.98
T0137	HM	9.4	100.0	9.4*	8.96
T0168	FR	2.5	100.0	2.6	8.28
T0141	HMH	3.3	100.0	3.4	6.67
T0151	HM	7.1	100.0	6.9	5.69
T0138	FR	5.3	92.1	5.6*	9.36
T0157	FR	4.5	63.4	4.7*	6.94
T0159_2	FR	2.5	62.9	2.9*	6.46
T0147	FR	1.6	50.9	2.2	6.20
T0173	FR	0.0	25.9	1.2	4.19
T0148_1	FR	2.4	17.0	3.1	3.02
T0135	FR	2.8	11.0	2.1	3.12

Asterisks indicate predictions with MaxSub scores higher than any other CAFASP server. Category, the target's category as classified in CAFASP3; MaxSub; the MaxSub score of the predicted model; Score, the confidence score attached by the server.

each target and model two numbers are shown. The first is the MaxSub score^{17} (see Materials and Methods) of the model (compared to the native structure) times 10 (for clarity, all MaxSub scores shown here are multiplied by 10). The second number is the confidence score as reported by the server. The table lists the targets in decreasing order of the predicted 3DS3 confidence score. Notice that the confidence scores reflect to a large extent the difficulty of the targets, with the highest scores corresponding to the easiest prediction targets. Asterisks indicate predictions that were ranked as the best server model (among all other CAFASP servers' models) for that particular target. The 3D-SHOTGUN predictions that received zero MaxSub scores (not shown) are considered as incorrect. No good predictions were produced by any other server for most of the targets with incorrect 3D-SHOTGUN predictions (only two targets incorrectly predicted by 3D-SHOTGUN had predictions of other servers with MaxSub scores above 2.0).

An estimate of the degree of "hybridness" of the 3D-SHOTGUN models can be obtained by counting the number of initial models used to build the assembled models. The hybrid models shown in Table I that were produced by 3DS3 (3DS5) were assembled by using between 4 and 15, average 11 (for 3DS5: 6–25, average 17) different initial models. Notice that the input for 3DS3 (3DS5) consists of 15 (25) initial models. To estimate how ”mozaic” the hybrids are, we computed the proportion of residues in each model whose coordinates corresponded to those of the initial model used as framework in the assembly (which usually is the model that contributes most to the hybrid; see Materials and Methods). Between 26 and 92%, average 59% (17 and 93%, average 49%), of the coordinates of the 3DS3 (3DS5) models shown in Table I were assembled from the framework model. This shows that the produced models are composed from a number of initial models and that this number varies from target to target. Overall, the 3D-SHOTGUN models are truly hybrid models composed from different parts of the initial models.

Figure 1 shows four examples of 3D-SHOTGUN's predictions. Notice that even though the 3D-SHOTGUN predictions were unrefined models, most confident predictions have little or no fragmentation. However, as the difficulty of the targets increases, so does the structural incompatibility among the initial models. This results in fragmented regions in the 3D-SHOTGUN models for the hardest targets. Thus, the regions of the 3D-SHOTGUN models with non-protein-like features reflect the uncertainty present among the initial models and require subsequent "refinement" (see Materials and Methods).

3D-SHOTGUN's Specificities

The value of any prediction program critically depends on the ability to attach confidence scores to each prediction. Thus, deriving confidence thresholds for prediction programs is essential for their automatic application. Figure 2 shows the number of correct and incorrect predictions as a function of the prediction score for 3DS3 and 3DS5, derived from the same 35 targets considered in the CAFASP3 specificity evaluation (see the CAFASP3 Web site for definitions). The *x* axis is different for each server because the ranges of scores reported by them are different. 3DS3 reports scores between 0 and 100, whereas 3DS5 reports scores between 0 and 11.41. The figure shows that 3DS3 had its first incorrect prediction at a score of 30.3, with 19 correct predictions with higher scores. 3DS5 had 20 correct predictions with scores above 5.0 before its first false positive. If up to three incorrect predictions are considered, then 3DS3 (3DS5) produced 22 (25) correct predictions with scores higher than 26.0 (4.0). Three incorrect predictions account roughly to a 10% error rate in this small test set. The CAFASP3 analysis ranked the 3D-SHOTGUN servers at ranks 1 (3DS5) and 3 (3DS3), with average specificity scores of 22.2 and 24.8 for 3DS3 and 3DS5, respectively. This is consistent with the specificity analysis of LiveBench,^{6} where 3DS5′s specificity was 9.4% higher than that of 3DS3. In addition, the scores corresponding to a 10% error rate in LiveBench-6 were very similar to those found here: 26.4 and 4.6 for 3DS3 and 3DS5, respectively. In summary, 3DS3′s (3DS5′s) predictions with scores higher than 26.4–30.3 (4.6–5.0) can be considered as confident predictions.

All Initial Models Contribute

The 3D-SHOTGUN meta-predictors make use of all input models. However, each of the resulting hybrid models uses one single model as a framework on which the hybrid is assembled. Table II lists the sources of the eight most frequent input models that were used as frameworks for each of the 62 rank-1 models submitted to CAFASP by

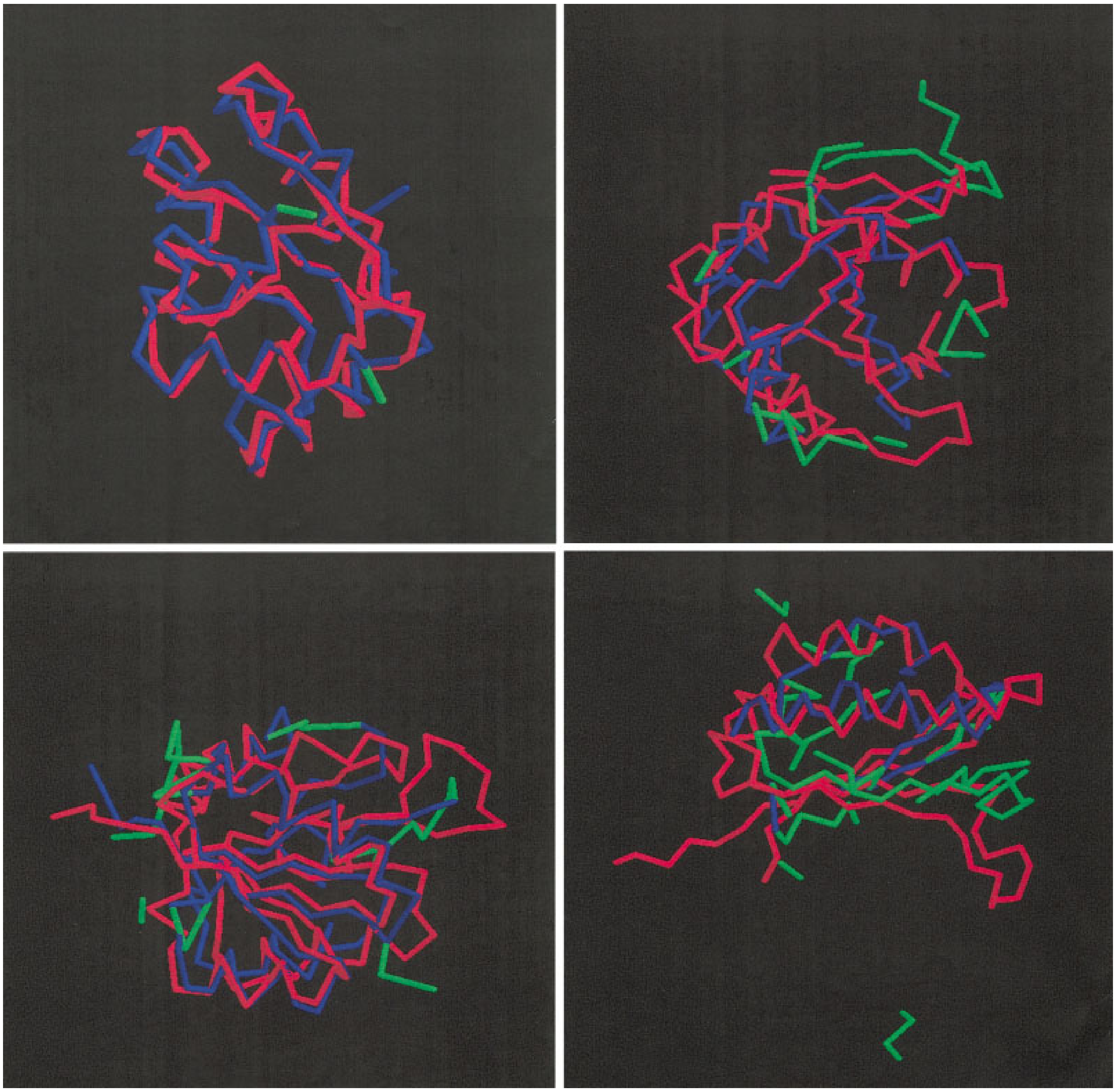

Fig. 1. Selected 3D-SHOTGUN models. MaxSub superposition of the native structures of selected targets (red) with the 3D-SHOTGUN predictions (blue: correctly predicted regions; green: wrongly predicted regions). The 3D-SHOTGUN hybrids are on average more complete and more accurate than the initial models. When enough structural recurrence appears among the initial models, 3D-SHOGTUN's assembly produces largely protein-like hybrids. As the difficulty of the targets increases, so does the structural incompatibility among the initial models and some level of fragmentation can occur in the 3D-SHOTGUN hybrids. Thus, the regions of the 3D-SHOTGUN models that have non-protein-like features reflect the uncertainty present among the initial models. **A:** T0150, 97 residues. 3DS3 model with overall RMSD to native of 2.0 Å. MaxSub score 8.1 with a subset of 94 residues superimposing to native at an RMSD of 1.7 Å. **B:** T0138, 135 residues. 3DS5 model with overall RMSD to native of 4.9 Å. MaxSub score 5.6 with a subset of 106 residues superimposing to native at an RMSD of 2.3 Å. **C:** T0157, 125 residues. 3DS5 model with overall RMSD to native of 6.4 Å. MaxSub score 4.7 with a subset of 84 residues superimposing to native at an RMSD of 2.5 Å. **D:** T0135, 106 residues. 3DS5 model with overall RMSD to native of 11.9 Å. MaxSub score 2.1 with a subset of 44 residues superimposing to native at an RMSD of 3.1 Å. The low MaxSub score (2.1) of this model reflects that this prediction was relatively poor, with only a few superimposable secondary structure elements. The low prediction score it received (11.0) reflects the little structural recurrence found among the initial models. This is also reflected in the fragmentation of the model.

3DS3 and 3DS5. The table shows that all of the servers contributed to 3D-SHOTGUN's performance. 3DS3 selected as framework the first model from the inbgu server in 33 targets. 3D-PSSM's model number 2 was selected in six targets, and the first model from FFAS in another six targets. In contrast, 3DS5 selected as framework the first models of 3D-PSSM in 15 targets, those of SHGU in 14 targets, and those of FFAS in 9 targets. The other two

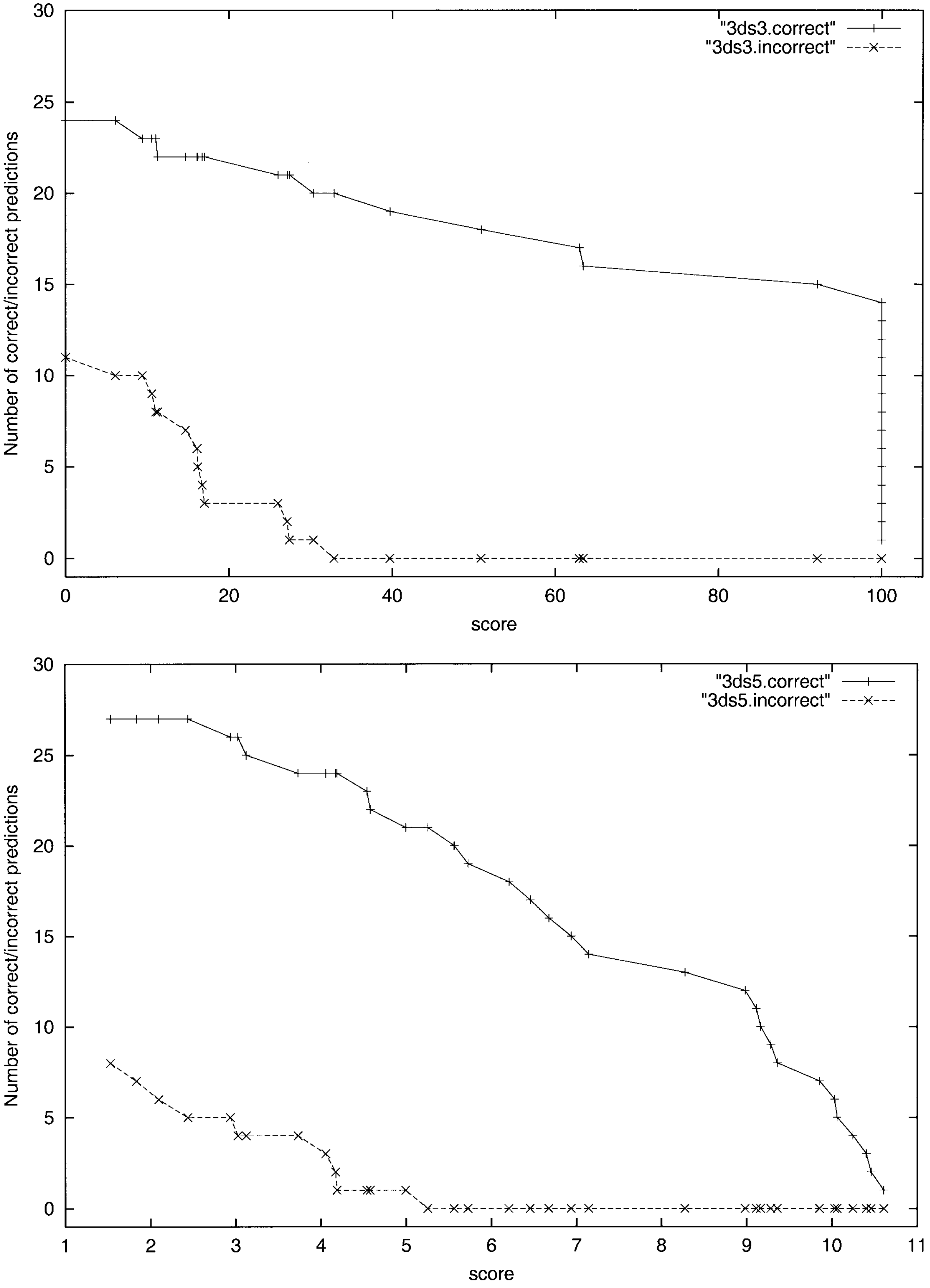
"3ds3.correct"
"3ds3.incorrect"
Number of correct/incorrect predictions
0
5
10
15
20
25
30
score
0
20
40
60
80
100
"3ds5.correct"
"3ds5.incorrect"
Number of correct/incorrect predictions
0
5
10
15
20
25
30
score
1
2
3
4
5
6
7
8
9
10
11

Figure 2.

TABLE II. The Eight Most Frequent Sources of Initial Models Used as Frameworks for the Assembly of 3D-SHOTGUN Hybrid Model

3DS3	3DS5
33 inbgu.1	15 foldfit.1
6 foldfit.2	14 shgu.1
6 ffas.1	9 ffas.1
5 foldfit.1	6 genthreader.1
4 foldfit.3	5 fugue.1
3 ffas.2	2 shgu.3
2 ffas.4	2 shgu.2
1 inbgu.3	2 genthreader.2

servers used by 3DS5, genthreader and fugue, were selected in six and five targets, respectively. However, it is important to emphasize that 3D-SHOTGUN builds the hybrid models by considering all models, and all models contributed to the completeness and accuracy of the resulting hybrid models. Thus, it is clear that all five models from all the (three or five) servers contribute to 3D-SHOTGUN's performance.

3D-SHOTGUN Hybrid Models Improve Over the Initial Models

Table III lists six of the targets for which the accuracies of the 3DS3 or 3DS5 hybrid models (as measured by MaxSub) were higher than those of the initial models used as frameworks for the assembly (four of which are illustrated in Fig. 1). For comparison purposes, both the all-C_α root-mean-square deviations (RMSDs) and the MaxSub scores of the models are shown. All six models had higher MaxSub scores than the framework templates, and all except T0135 and T0157 had better RMSDs. T0135 corresponds to the hardest target listed in Table I (lowest confidence score attached by the servers). This means that there was little structural recurrence among the initial models, which, in this case, resulted in a hybrid model with an RMSD higher than the framework template, probably because of the inclusion of unconnected fragments in the hybrid [see Fig. 1(d)]. However, in general, if enough structural similarity exists among the initial models, the hybrid assembly of 3D-SHOTGUN results in higher quality models as measured by both MaxSub and RMSD.

DISCUSSION

Although the 3D-SHOTGUN meta-predictors are only preliminary prototypes, they have already shown their superiority in the CAFASP3 and LiveBench experiments. The exploitation of the information from a number of independent sources results in three main improvements. The first is an increased overall sensitivity, because "glitches" (wrong predictions) that servers occasionally produce are averaged out by the other servers. Second, because models are assembled from a number of initial models, the resulting hybrid models are usually more accurate and more complete. Third, and most importantly, the metapredictors have significantly higher specificities, because the confidence score attached to the meta-prediction is more reliable than those of the individual servers. Increased specificity is a critical feature for any prediction method.

The 3D-SHOTGUN meta-predictors prototypes require improvements in a number of aspects. First, a per-residue confidence score needs to be attached to each predicted C_α coordinate, which in a way may represent a "prediction B-factor." This per-residue confidence score can be obtained directly from the structural recurrence information used in the 3D-SHOTGUN assembly process. Second, a refinement step is required to relieve the fragmentation and collisions present in the hardest prediction targets. Several approaches are being investigated. One fully automated approach named SHGUM is being tested at the ongoing LiveBench-7 experiment and was successfully applied to file predictions to CASP (see the Fischer report in this issue). Third, efforts need be invested in the automated servers to better handle multidomain prediction targets. Fourth, analysis of the successful human CASP predictors should hint to further improvements that may be incorporated into the automated methods. Finally, although relatively good predictions are obtained for all "homology-modeling," and all "easy fold recognition" targets, the servers' performance on the harder targets leaves much room for improvement. A correct fold recognition is obtained for roughly half of the targets having no significant sequence similarity to proteins of known structure. A small percentage of such targets corresponds to "new folds," which by definition, cannot be identified with fold recognition techniques. Thus, it is clear that significant improvements are required before the servers are able to produce relatively accurate models for the remaining "identifiable" targets.

ACKNOWLEDGMENTS

The 3DS3 and 3DS5 meta-predictors could not exist without the availability of initial model-generating servers, such as ffas,[11] 3dpsm,[12] GenThreader,[14] and Fugue,[15] and without their easy access throughout Leszek Rychlewski's meta-server at http://bioinfo.pl/meta.

Fig. 2. (overleaf) Specificities of the 3DS3 and 3DS5 meta-predictors. The confidence score of the predictions as reported by the servers is shown in the *x* axis. The *y* axis corresponds to the cumulative number of correct and incorrect predictions with scores higher than a given score. **A:** 3DS3′s specificity. Nineteen correct predictions were obtained with scores >30.3, at which score the first incorrect prediction was found. Twenty-two correct predictions were obtained with scores above a confidence threshold that corresponds to a 10% error rate (in this case, 26.0 with three incorrect predictions). **B:** 3DS5′s specificity. Twenty correct predictions were obtained with scores >5.0, at which score the first incorrect prediction was found. Twenty-five correct predictions were obtained with scores above a confidence threshold that corresponds to a 10% error rate (in this case, 4.0 with three incorrect predictions). Notice that 3DS3 and 3DS5 report confidence scores in different scales. 3DS5 has a slightly higher (about 10%) specificity than 3DS3.

TABLE III. The Accuracy of Some of the 3D-SHOTGUN Hybrids Is Higher Than That of the Framework Templates

	3D-SHOTGUN		Framework template		
Target	RMSD	MaxSub	Model	RMSD	MaxSub
T0169 (3DS5)*	4.9	6.5	genthreader.1	7.1	4.9
T0150 (3DS3)	2.0	8.1	inbgu.1	2.2	7.7
T0185_2(3DS3)	4.0	6.6	inbgu.1	4.1	6.1
T0138 (3DS5)	4.9	5.6	genthreader.2	8.0	4.6
T0157 (3DS5)	6.4	4.7	ffas.1	5.4	3.8
T0135 (3DS5)	11.9	2.1	shgu.2	7.8	1.9

*The parentheses indicate whether the model corresponds to 3DS3 or 3DS5 (see also Table I).

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