PconsC4: fast, free, easy, and accurate contact predictions.

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Abstract

Motivation: Residue contact prediction was revolutionized recently by the introduction of direct coupling analysis (DCA). Further improvements, in particular for small families, have been obtained by the combination of DCA and deep learning methods. However, existing deep learning contact prediction methods often rely on a number of external programs and are therefore computationally expensive.

Results: Here, we introduce a novel contact predictor, PconsC4, which performs on par with state of the art methods. PconsC4 is heavily optimized, does not use any external programs and therefore is significantly faster and easier to use than other methods.

Availability: PconsC4 is freely available under the GPL license from <https://github.com/ElofssonLab/PconsC4>. Installation is easy using the pip command and works on any system with Python 3.5 or later and a modern GCC compiler.

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Introduction

To predict the structure of a protein from no other information than its sequence has been a major challenge in bioinformatics for decades. With the introduction of direct coupling analysis (DCA) to improve contact predictions (Weigt *et al.*, 2009) significant progress in protein structure prediction was reported in 2011 (Morcos *et al.*, 2011; Marks *et al.*, 2011). These methods have then been used to predict the structure of hundreds of protein families with high accuracy to an unprecedented accuracy (Ovchinnikov *et al.*, 2017). One disadvantage of DCA methods is that they require very large multiple sequence alignments to provide accurate contact predictions. This problem has been overcome by refining the initial DCA prediction with deep learning methods (Skwark *et al.*, 2014; Wang *et al.*, 2017).

Although the structure can accurately be predicted for many protein families, there still exist many families where the predictions are not sufficiently accurate. Although predictions are better for larger families, many other factors also seem to be important (Michel *et al.*, 2017a). The exact reason for what is needed to improve the predictions is not well understood. But it is not unlikely that the underlying multiple sequence alignments are not optimal. It might therefore be possible to improve the predictions if alternative multiple sequence alignments are examined or metagenomics data is included. Given the computational costs of earlier deep learning contact predictions methods it has been difficult to exhaustively examine alternative alignments for each protein family.

Here, we present a novel deep learning approach, PconsC4, that performs as well, or even better, than earlier methods. More importantly it is freely available, significantly faster and easier to install than alternative methods. This provides all users with an easy way to explore alternative multiple sequence alignments or other parameters for contact predictions.

Implementation

Below follows a short description of PconsC4, for details see the supporting information. PconsC4 is trained on a set of 2791 proteins culled from PDB and benchmarked on two datasets without any

homology to the training set. One validation set is identical to the benchmark set in PconsC3 (Michel *et al.*, 2017b). Additionally, we benchmarked PconsC4 on 44 proteins from CASP12, see Tables S2-S5. Multiple sequence alignments are created using three iterations of HHblits (Remmert *et al.*, 2011) and an e-value threshold of 1.0. Other alignment methods and cut-offs as well as combinations of different alignments were tested but did not provide significant improvements.

From each position in the multiple sequence alignments 72 features are calculated and fed into the PconsC4 network. These include: 68 one-dimensional sequential features and four pairwise features; the GaussDCA score (Baldassi *et al.*, 2014), APC-corrected mutual information, normalized APC-corrected mutual information, and cross-entropy.

At the core of PconsC4 is the U-net architecture (Ronneberger *et al.*, 2015), designed for image segmentation. It is composed of a series of convolutional layers, down- and up-sampling, with shortcut connections to help convergence.

To include secondary structure information but remain independent of external predictors, we took the pre-trained network from ProQ4 (Menéndez Hurtado *et al.*, 2018), that takes all the one-dimensional inputs and predicts secondary structure, dihedral angles, and surface accessibility for each residue. PconsC4 takes the output of the second to last layer, transforms them into two-dimensional features via an outer product, and concatenates them to the rest of the inputs.

Finally, the network produces four outputs: the probability of a contact for the thresholds of 6, 8, or 10 Å, and the distance measured as S-score.

To reduce the number of dependencies and overall run time, we re-implemented GaussDCA as a Python package using Pythran (Guelton *et al.*, 2015) resulting in a speedup of a factor of three. Optimization details are in section 2 of the supplementary information.

Table 1: Performance in PPV for the L top-ranked contact with a sequence separation of > 5 residues. Results for all, small families with Meff (Baldassi *et al.*, 2014) $<$ and for short-, (5, 12), medium- (12, 23) and long: (23, ∞) ranges. Average runtime and external dependencies.

	All	Small	Short	Med	Long	Time [s]	Deps.
PlmDCA	0.36	0.12	0.14	0.15	0.26	84	-
GaussDCA	0.34	0.12	0.14	0.15	0.25	27	-
PSICOV	0.34	0.11	0.13	0.14	0.22	114	-
PhyCMAP	0.32	0.29	0.24	0.19	0.18	718	1,3
PconsC3	0.57	0.36	0.25	0.25	0.37	2931	1,2,3,4,5,6
Metapsicov	0.59	0.39	0.27	0.26	0.36	1158	1,3,7,8,9
PconsC4	0.65	0.42	0.29	0.28	0.45	12 (56*)	-

1: PSIPRED, 2: NetSurfP, 3: PSI-BLAST, 4: PhyCMAP, 5: PlmDCA, 6: GaussDCA, 7: PSICOV, 8: Freecontact, 9: CCMpred.

* Timing without pre-loading the network.

Results and Discussion

Table 1 shows a performance comparison of different methods running on the same alignments. PconsC4 performs 14% better than PconsC3 on the benchmark dataset and 10% better than Metapsicov. These improvements are consistent across short, medium, and long range contacts and for all thresholds (Figures S1-2). Additional evaluations are also presented in the supplementary information. As shown in Figures S3-4, the predicted scores are well calibrated, i.e. the reported scores reflect the real probability for a contact to exist. This enables easy comparison of alternative alignments.

All machine learning methods perform significantly better than the DCA methods for smaller families. PconsC4 approaches maximum performance at around 10^2 effective sequences compared with 10^5 for the DCA methods (Figure S5).

The overall performance is comparable to meta-meta predictors such as DNCON2 (Adhikari *et al.*, 2018) or other deep learning methods (Wang *et al.*, 2017). However, a direct comparison is difficult as these programs are either not available for download, too slow to run for large scale experiments, or cannot be used with a specific multiple sequence alignment.

The main advantage of PconsC4 is that it is fast and easy to use. Starting from a single input alignment PconsC4 predicts the contacts in less than one minute (or 12 s if the network is preloaded).

This is more than 25 times faster than PconsC3 or Metapsicov, while still consistently outperforming them. Since PconsC4 is not tied to any specific alignment method, it can directly take advantage of any improvement on this front, such as the use of alternative alignment strategies (Buchan and Jones, 2017) or metagenomics data (Ovchinnikov *et al.*, 2017), and thus be easily integrated into pipelines.

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Supplementary materials to "PconsC4: fast, free, easy, and accurate contact predictions."

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Contents

1	Results	1
1.1	ROC and calibration curves	3
1.2	Precision as a function of the alignment depth	6
2	GaussDCA optimization	6
2.1	GaussDCA and compressed alignments	6
2.2	Fast estimation of the expected similarity threshold, θ , in Gauss-DCA	7
3	Training	7
3.1	Description of inputs	7
3.1.1	One-dimensional inputs	7
3.1.2	Two-dimensional inputs	8
3.2	Training and testing sets	8
4	Pipeline	8
5	Instructions	11
5.1	Installation	11
5.2	Example usage	11
5.3	Supported formats	11
6	Training and test sets	12

1 Results

Here we report more detailed comparisons on the test sets. First, in Table S1 we compare short, medium, and long range contacts, showing that PconsC4 is better than previous methods at all ranges. Figures S1 and S2 show the receiver operating characteristic curves.

We also include an expanded version of the Table 1, Table S1 including CASP12 and other methods. For benchmarking GaussDCA we used the Julia implementation and CCMpred for PlmDCA. The times were measured on a machine with an Intel i7-4770 CPU and a NVIDIA 1070Ti GPU for CCMpred.

PconsC4 seems to be better calibrated than earlier methods, as shown in Figures S3 and S4. This means that a predicted score of 0.2 indicates that there is a 20% chance for a contact to exist. A perfectly calibrated predictor would lie on the diagonal (dotted line).

Table S1: Precision for the top L contacts, where L is the sequence length, at different distance thresholds. Short: (5, 12], medium: (12, 23], long: (23, ∞).

Method	Benchmark set		
	Short	Medium	Long
PlmDCA	0.14	0.15	0.26
GaussDCA	0.14	0.15	0.25
PSICOV	0.13	0.14	0.22
PhyCMAP	0.24	0.19	0.18
PconsC3	0.25	0.25	0.37
MetaPSICOV	0.27	0.26	0.36
PconsC4	0.29	0.28	0.45

Table S2: Performance in PPV for the L top-ranked contact with a sequence separation of > 5 residues, average runtime in seconds on the benchmark set, and external dependencies (except for alignment methods).

	Benchmark set	CASP12	Time [s]	Deps.
PlmDCA (CCMpred, GPU)	0.36	0.26	84	-
PlmDCA (CCMpred, CPU)	0.36	0.26	393	-
GaussDCA (Julia)	0.34	0.25	27	-
GaussDCA (Pythran)	0.34	0.25	10	-
PSICOV	0.34	0.20	114	-
PhyCMAP	0.32	0.22	718	1,3
PconsC3	0.57	0.39	2931	1,2,3,4,5,6
Metapsicov	0.59	0.43	1158	1,3,7,8,9
PconsC4	0.65	0.46	56	-
PconsC4 (pre-loaded)	0.65	0.46	12	-

1: PSIPRED, 2: NetSurfP, 3: PSI-BLAST, 4: PhyCMAP, 5: PlmDCA, 6: GaussDCA, 7: PSICOV, 8: Freecontact, 9: CCMpred.

1.1 ROC and calibration curves

Figure S1: ROC curves on the Benchmark set

Figure S2: ROC curves on CASP12

Figure S3: Calibration curves on the Benchmark set

Figure S4: Calibration curves on CASP12

1.2 Precision as a function of the alignment depth

The Figure S5 shows performance vs. number of effective sequences. Here we use the same definition as in (Baldassi *et al.*, 2014a): the number of sequences that are significantly different from each other. While statistical methods, like DCA, benefit from a constant improvement for larger number of effective sequences, PconsC4 starts to plateau at around 10^2 sequences. This suggests that it is capable of learning to ignore the noise in DCA methods, even when the signal is weak.

Figure S5: PPV vs. number of effective sequences on the benchmark set. The top L contacts are considered.

2 GaussDCA optimization

In the reimplementaion of GaussDCA we made two differences with respect to the reference implementation that improve the speed, while keeping the results exactly the same.

2.1 GaussDCA and compressed alignments

Much of the CPU time is spent computing sequence weights, which means we need to compute all pairwise Hamming distances between sequences in the multiple sequence alignment. In a naive implementation, we store the alignment as a 2D array of int8. The compiler can then use SIMD instructions to combine several numbers to fit them in the word size of the CPU.

The Julia implementation of Gaussdca, (Baldassi *et al.*, 2014b), uses a manually compressed alignment: since we have only 21 states, we only need 5 bits

per symbol, so we can manually pack up to 12 amino acids in a single 64 bits int, that fits our CPU optimally. To compute the distance, we need to XOR the sequences, and count the number of 5-bit regions where it differs. This gives us a 50% increase in packing efficiency with respect to the naive 8-bit storage.

In our re-implementation we found that the naive version is actually faster, probably because it is easier for the compiler (GCC 7) to optimize. Further improvements can be obtained activating auto-vectorization (GCC flag `-ftree-vectorize`), suggesting that the code emitted by Pythran is more suitable for vectorization.

2.2 Fast estimation of the expected similarity threshold, θ , in GaussDCA

Two sequences are considered similar if their Hamming distance is below a given threshold. (Baldassi *et al.*, 2014a) introduced an automatic estimation as the average fraction of differences across the alignment, and implemented it by directly counting them, which is $\mathcal{O}(m^2)$ on the number of sequences in the alignment.

The same result can be obtained in linear time by counting the number of occurrences of each symbol in each column (called the bincount function), and computing the 2-combination $\binom{n}{2}$. For an alignment of C columns and an alphabet of size Q :

$$n_{matches} = \sum_c^C \sum_q^Q \binom{\#alignment_c = q}{2} \quad (1)$$

3 Training

3.1 Description of inputs

3.1.1 One-dimensional inputs

From the columns of the multiple sequence alignment we can compute the probability of finding each amino acid or gap, p_i . For amino acids, we compute the average frequency $\langle p_i \rangle$ as the observed frequency of the amino acid on the Uniref50 dataset. The expected probability of gap $\langle p_- \rangle$ is estimated from each alignment. We consider a total of 23 amino acid states, the usual 20, plus the gap state, plus B (asparagine or aspartic acid) and X (unknown).

For each column we can compute self-information as the vector of entries:

$$I_i = \log_2(p_i / \langle p_i \rangle), \quad (2)$$

and the partial entropies are defined as:

$$S_i = p_i \log_2(p_i / \langle p_i \rangle) \quad (3)$$

The sequence is given as one hot encoding.

3.1.2 Two-dimensional inputs

The two-dimensional inputs are mutual information (MI), normalized mutual information (NMI), cross entropy (H), and GaussDCA.

Mutual information is defined as:

$$MI(x, y) = \sum_{x, y} p(x, y) \log \left(\frac{p(x, y)}{p(x)p(y)} \right) \quad (4)$$

We also include two more inputs that are adjusted versions of MI. The first is normalized mutual information, where we think of MI as an analogue of a covariance, and NMI is the Pearson correlation coefficient. The entropies of the columns play the role of the variances:

$$NMI(x, y) = \frac{MI(x, y)}{\sqrt{S(x)S(y)}} \quad (5)$$

And lastly, cross entropy is calculated as an additive normalization of mutual information:

$$H(x, y) = S(x) + S(y) - MI(x, y) \quad (6)$$

The Average Product Correction (APC) (Dunn *et al.*, 2008) is applied to all two-dimensional inputs except for cross entropy.

3.2 Training and testing sets

PconsC4 is trained on a set of 2891 proteins culled from PDB using PISCES (Wang and Dunbrack, Jr., 2003) with a maximum sequence identity 20%, minimum resolution 2.0 Å, maximum R-factor 0.3. Furthermore, chains from the same ECOD (Cheng *et al.*, 2014) H-group as any protein in the benchmark dataset or dating from after 2016-05-01 was removed to avoid potential overlap with the test datasets. Out of these 2891 proteins, 100 randomly selected proteins were used as a validation set for optimization, see Table S3 and S4. For benchmarking, two datasets are used, the same 180 proteins, Table S5 as in (Michel *et al.*, 2017) and the 44 proteins from CASP12 with available structures, Table S6

4 Pipeline

We include a schematic of the complete pipeline, see Figure S6.

In the upper left corner are the 1D inputs being fed to the pre-trained model taken from ProQ4 (Menéndez Hurtado *et al.*, 2018). It is pre-trained to predict secondary structure and surface accessibility for each residue (golden outputs in the middle left).

The 128 output channels of the second to last layer are used to extract relevant 1D features. These are then transformed into 2D features by the outer product and combined with the remaining 2D features (GaussDCA, Mutual Information, Normalized Mutual Information, and Cross Entropy). The concatenation is then passed on to the U-net block (lower rectangle).

U-net was developed for image segmentation and combines convolutional layers, max pooling (downwards arrows) to increase the effective receptive field,

upsampling (upwards arrows) to recover the original size, and skip connections (horizontal arrows) to help convergence.

The final predictions are shown on the upper right: contact maps at the three distance thresholds and distance as S-score. The branch predicting S-score is solving a regression problem with a Mean Squared Error loss, whereas the other three output branches are classifying the probability of a contact for the thresholds of 6, 8, or 10 Å, and use a cross entropy loss.

All intermediate convolutional layers are followed by a ELU (Clevert *et al.*, 2015) non linearity, Batch Normalization (Ioffe and Szegedy, 2015), and a Dropout layer (Srivastava *et al.*, 2014) with a probability of 0.1. Weights are initialized using the He distribution as described in the ResNet paper (He *et al.*, 2016). A weight decay of 10^{-12} on the L^2 -norm is applied for regularization. All output layers have an appropriate function to ensure the output is in the valid range, sigmoid in our case.

The model is trained for 100 epochs (full passes over the training data) using the Adam optimizer at an initial learning rate of 0.001. The learning rate is decreased by a factor of 0.5 if the S-score training loss did not decrease over the last five epochs. The training dataset is shuffled after each epoch. The final model was selected by taking the epoch with minimum S-score loss on the validation dataset (epoch 29).

Figure S6: The example is the protein 2AV5 chain D from the benchmark set.

5 Instructions

5.1 Installation

On a machine with Python 3.5 or higher and pip, PconsC3 can be installed using the following commands:

```
pip install numpy Cython pythran
wget https://github.com/ElofssonLab/PconsC4/releases/download/0.2/\
pconsc4-0.2.tar.gz
pip install pconsc4-0.2.tar.gz
```

Once additional space is granted in PyPI (Python Package Index), a simple `pip install pconsc4` will be sufficient.

A deep learning backend compatible with Keras will also be needed. We recommend Tensorflow:

```
pip3 install -U tensorflow
```

5.2 Example usage

```
import pconsc4

# Load the deep learning model
model = pconsc4.get_pconsc4()

# It is possible to re-use on different alignments
pred_1 = pconsc4.predict(model, 'path/to/alignment1')
pred_2 = pconsc4.predict(model, 'path/to/alignment2')

# Show pred_1 on the screen:
import matplotlib.pyplot as plt
plt.imshow(pred_1['contacts']['cmap'])
plt.show()

# Save pred_2 in CASP format:
from pconsc4.utils import format_contacts_casp
print(format_contacts_casp(pred_2['contacts']['cmap'],
                           seq_2, min_sep=5))
```

5.3 Supported formats

The program accepts alignments in `.fasta`, `.a3m`, or `.aln`, without line wrapping.

6 Training and test sets

PconsC4 is trained on a set of 2891 proteins culled from PDB using PISCES (Wang and Dunbrack, Jr., 2003) on 2017-09-14 with the following criteria: maximum sequence identity 20%, minimum resolution 2.0 Å, maximum R-factor 0.3. Furthermore, chains from the same ECOD (Cheng *et al.*, 2014) H-group as any protein in the benchmark dataset or dating from after 2016-05-01 was removed to avoid potential overlap with the test datasets. Out of these 2891 proteins, 100 randomly selected proteins were used as a validation set for optimization.

4XPXA 4XT6A 4XTBA 4XU4A 4XUOA 4XUWA 4XVVA 4XXXA 4XY5A 4XZFA 4Y2FA 4Y6WA 4Y7SA 4Y88A
4Y91A 4Y9WA 4YAAA 4YBGA 4YE7A 4YG0A 4YI8A 4YMYA 4YNHA 4YNXA 4YQDA 4YSIA 4YTKA 4YTLA
4YTV A 4YU8A 4YUCA 4YWZA 4YX1A 4YZ6A 4Z2NA 4Z3HA 4Z47A 4Z4AA 4Z85A 4Z8WA 4ZAVA 4ZBHA
4ZC3A 4ZCEA 4ZDSA 4ZF7A 4ZGFA 4ZGMA 4ZHW A 4ZJ9A 4ZJHA 4ZJUA 4ZLDA 4ZMKA 4ZMKA 4ZOTA
4ZQXA 4ZSIA 4ZV5A 4ZVAA 4ZVCA 4ZVFA 4ZX2A 4ZY7A 4ZY9A 4ZYAA 4ZZ1A 5A0NA 5A1QA 5A3AA 5A3DA
5A4AA 5A67A 5A6WA 5A8CA 5A99A 5A9AA 5A9TA 5AE0A 5AG8A 5AGIA 5AGRA 5AIGA 5AIMA 5AIZA
5AJGA 5AJJA 5AMHA 5AMTA 5AOTA 5AOYA 5AOZA 5AQ0A 5AZBA 5AZWA 5AZYA 5B1NA 5B1RA 5B3KA
5B3PA 5B42A 5B4ZA 5BOIA 5BOWA 5BP9A 5BPXA 5BTYA 5BVL A 5BX1A 5BXGA 5BY4A 5BY5A 5BY8A
5BYKA 5C12A 5C17A 5C1EA 5C2MA 5C30A 5C5GA 5C5ZA 5C6SA 5CDKA 5CE7A 5CHPA 5CKLA 5CL8A
5CNWA 5COFA 5COTA 5COWA 5CR9A 5CTVA 5CUMA 5CVWA 5CWGA 5CXUA 5CYVA 5D22A 5D2FA 5D3KA
5D3XA 5D7UA 5D8MA 5D8VA 5DAWA 5DBLA 5DFS A 5DGJA 5DHD A 5DJEA 5DJOA 5DLBA 5DLOA 5DM2A
5DMAA 5DMAA 5DMAA 5DOMA 5DP2A 5DPGA 5DPOA 5DRFA 5DTCA 5DTXA 5DXLA 5DZ9A 5DZEA 5E0LA
5E10A 5E1WA 5E2CA 5E3QA 5E50A 5E5YA 5E6XA 5E9PA 5EC6A 5ECD A 5EDFA 5EDLA 5EH1A 5EIPA 5E1UA
5EJUA 5EKYA 5EMIA 5EOHA 5EP2A 5EPEA 5EQ0A 5EQVA 5EQZA 5EUBA 5EV5A 5EVFA 5EWOA 5EYNA
5EYRA 5EYSA 5EZQA 5EZUA 5F18A 5F47A 5F4CA 5F5LA 5F6RA 5F7GA 5F8ZA 5FA8A 5FAFA 5FAZA 5FB2A
5FBFA 5FCEA 5FD9A 5FDBA 5FENA 5FF3A 5FFHA 5FFSA 5FHVA 5FIDA 5FMTA 5FOTA 5FPZA 5FQIA
5FS4A 5FSVA 5FU5A 5FUBA 5FZSA 5G2HA 5G38A 5G3QA 5HB7A 5HBDA 5HBPA 5HBQA 5HD9A 5HDWA
5HE9A 5HGZA 5HI8A 5HJ1A 5HJ9A 5HKQA 5HQHA 5HQT A 5HRPA 5HRR A 5HRSA 5HTLA 5HUSA 5HWAA
5HWIA 5HWVA 5HXFA 5HYAA 5HZ6A 5HZ8A 5I0YA 5I1SA 5I45A 5I5CA 5I5NA 5I77A 5I8JA 5I9PA 5IA7A
5IBWA 5ICUA 5IDBA 5IDVA 5IEOA 5IG0A 5IGCA 5IGEA 5IGFA 5IHFA 5IHW A 5I16A 5I18A 5I1FA 5IMAA
5IMUA 5IO9A 5IOCA 5IODA 5IQNA 5IT3A 5ITMA 5IUCA 5IWBA 5IWH A 5IXBA 5IXHA 5J1ZA 5J2OA 5J3QA
5J4FA 5J4LA 5J4RA 5J5LA 5J8EA 5JA5A 5JBR A 5JDKA 5JE5A 5JEDA 5JEEA 5JELA 5JGJA 5JH8A 5JICA
5JIGA 5JJ2A 5JJOA 5JJXA 5JLBA 5NULA 7A3HA

Table S4: PDB code and chain identification for proteins in the validation set

1H97A 1J5XA 1N12A 1NFPA 1ODMA 1OZ9A 1QJPA 1SENA 1TQGA 1U6TA 1WLJA 1XYIA 1ZI8A 2CAYA
2HE7A 2HNGA 2HQQA 2I1HA 2NQ3A 2OA2A 2OO3A 2OSOA 2P58A 2P5DA 2PSPA 2RH2A 2RIQA 2W3GA
2WY4A 2YGOA 2Z8PA 2ZHJA 3A4CA 3D06A 3D1PA 3DT5A 3EJVA 3FILA 3FMYA 3G5TA 3GPJA 3H5JA 3H7IA
3HRGA 3INO A 3JU3A 3LO8A 3LZWA 3MC3A 3MMHA 3N6YA 3QPAA 3U4VA 3U8VA 3VGPA 3ZRXA 3ZZLA
4A02A 4A4JA 4BOQA 4CCVA 4ETXA 4EUNA 4F2EA 4HDDA 4I71A 4I95A 4JG2A 4K0NA 4KEXA 4L3UA 4N7CA
4NDSA 4ONRA 4Q2SA 4Q7OA 4RO3A 4TKBA 4V17A 4V3IA 4WHIA 4WJQA 4WNBA 4XKZA 4XVVA 4XXXA
4YBGA 4YE7A 4YTLA 4ZX2A 5A9AA 5A9TA 5AE0A 5C17A 5E0LA 5E50A 5FENA 5HGZA 5IOCA 5J2OA

Table S5: PDB code and chain identification for proteins in the benchmark set

1AHSC 1C2YD 1C9YA 1CCTA 1COZA 1DBRA 1DCHF 1EDIA 1EFDN 1F46B 1F68A 1FHIA 1FJRB 1FSOG 1G61A
1GJJA 1GLGA 1GPSA 1H68A 1I95E 1I97T 1IMBB 1IMXA 1IR1S 1IS9A 1JGPR 1JH0L 1K6LH 1KNVB 1KNYB
1KQPA 1LDIA 1LQKB 1M12A 1MB6A 1MFRP 1MR7A 1N2ZB 1N5BA 1N60C 1NQLB 1OAGA 1OTFF 1P3HE
1PCFA 1PDFE 1PS1A 1RD9D 1RH7C 1RL9A 1S3FB 1S68A 1SUDA 1SWXA 1SYHA 1TD4A 1TFKB 1TJLD
1UWZB 1VCRA 1VJNA 1VQZA 1W8AA 1W9GB 1WD5A 1WIGA 1WPVB 1X0PJ 1X48A 1X8HA 1X91A 1XBAA
1XQFA 1XS6A 1Y4HD 1Y60C 1YG6F 1YHQO 1YQFF 1YWSA 1Z7ME 1ZD7B 1ZJ0A 1ZWYC 2A84A 2A9KB
2AMCA 2AV5D 2B9NX 2BWEL 2C2OA 2CB6A 2CCCA 2CDMC 2CJRB 2CSMA 2D0PB 2D2CN 2DI0C 2E2AB
2EJNA 2FORA 2FEEB 2FJCO 2GVIA 2H44A 2HGHA 2HI7B 2HJJA 2HL0A 2I9LI 2IA9E 2I19B 2J1KQ 2J3WA
2J8WB 2JOVA 2JYNA 2KYSA 2KZSA 2M0MB 2NQ2A 2NR9A 2OF5H 2OGFD 2OHCA 2OJ5C 2ONKC 2OPIA
2PAVP 2PLSF 2Q7RA 2QQDE 2QYFD 2RDOL 2RMRA 2RTBB 2VGRA 2VT8A 2WNKA 2WNYA 2XVTF 2Y9PB
2YADB 2YZOA 2ZITD 3A1JB 3ANZW 3AXGI 3B2UB 3B71B 3B7AA 3BLAB 3BP9B 3CPWT 3CVZC 3CXJC
3D2QD 3DBYF 3DKXB 3EB6B 3EW1A 3G74B 3GUVA 3GYVA 3GZFC 3H8DB 3H90A 3HPGL 3HTYJ 3I9OB
3IQZF 3K43B 3K8RB 3KZLA 3LW5L 3M71A 3MEZA 3N1GA 3NJSA 3O7JA 3OFEB 3OQIA 3P45J 3PC7B 3PJZA
3QE7A 3QNQA 3RBYB 3T3TB 3UD2B 3UWSA 3UYUB 3V3LB 3VHHB 3VX6A 3ZNUG 3ZUXA 4A5ZB 4AI3A
4ARB 4AU0B 4DLHB 4E1YB 4E6FA 4F0DA 4HBRC 4I0SH 4IZJC 4J32B

Table S6: PDB code and chain identification for CASP12 targets

T0859 T0860 T0861 T0862 T0863 T0864 T0865 T0866 T0868 T0869 T0870 T0872 T0877 T0878 T0879 T0880
T0882 T0883 T0884 T0885 T0886 T0889 T0891 T0892 T0893 T0894 T0895 T0900 T0902 T0903 T0904 T0907
T0909 T0912 T0917 T0918 T0920 T0921 T0922 T0928 T0929 T0930 T0932 T0933 T0942 T0943 T0944 T0945
T0948

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