

DeepSF: Deep CNN for mapping protein sequences to folds

Zhiyang's presentation about [1]

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Context of the Problem

Background Information

Context of the problem.

- ① The structures of most ($> 99\%$) proteins are unknown
- ② Protein fold recognition enables us to associate a protein sequence to a protein fold
 - Identifying protein homologs that share the same protein fold
 - With this protein fold, determine its protein structure [Tramontano2003]
 - With this protein structure, determine its protein function
 - [Osadchy2011,OConnor2010,Tramontano2003,Hegyi1999]
 - [OConnor2014a, *From Contents: Unit 2, How Do Cells Decode Genetic Information into Functional Proteins?: §2.4 The Functions of Proteins Are Determined by Their Three-Dimensional Structures*]
 - [OConnor2014, *From Contents: Unit 2, How Do Cells Decode Genetic Information into Functional Proteins?: §2.4 The Functions of Proteins Are Determined by Their Three-Dimensional Structures*]

Problem Definition - 1

What is the problem that [1] is solving?

Problem description...

- ① Problems with sequence-based methods, especially sequence alignment methods (including profile-sequence and profile-profile alignment methods)
 - Methods for mapping protein sequences to protein folds are indirect
 - Can't explain relationship between protein sequences & protein folds, even machine learning (ML) methods
 - traditional ML methods also can't work for classifying data into large number of categories (> 1000)
 - multi-layer perceptron
 - support-vector machines
 - ensemble classifiers
 - kernel-based learning
- ② Other methods have methodological limitations

Problem Definition - 2

What is the problem that [1] is solving?

Problem description... Continued.

- ① Protein fold recognition enables us to associate a protein sequence to a protein fold
 - With this protein fold, we can determine its protein structure
 - With this protein structure, we can determine its protein function

Specifically... Solve the protein fold recognition problem.

- ① Given a protein sequence, map it to a protein fold **directly**
- ② Explain relationship between protein sequences & protein folds

Problem Importance

Why is it important?

Why is this problem important?

- This facilitates protein structure prediction
- Knowing about protein folds help us in protein structure prediction
- Protein structure prediction enables protein function prediction
- Knowing about protein structure and function facilitates:
 - drug/medication design [Nogrady2005, §1.6.4, pp. 54] [Golan2008, Chapter 1, pp. 4]
 - biotechnology [Walsh2014, Chapter 2]
 - synthetic biology [Zhao2013d, Chapter 2]
 - personalized [Cullis2015, Chapter 2, pp. 26] or precision medicine [Mousa2020, §24.3.2, pp. 778]
 - gene therapy [Wecker2010, Chapter 5, pp. 51]

What are the Knowledge Gaps in [1]?

How would [1] address these knowledge gaps?

List of knowledge gaps:

- Lack of direct methods for mapping protein sequences to protein folds
- Methods can't explain relationship between protein sequences & protein folds

Proposed Solution(s) - 1

What do they proposed to address the knowledge gap?

Proposed Solution(s).

- Use 1-D deep convolutional neural network (deep CNN)
- Use 3-level homology reduction strategy for dataset to avoid using same data in training, validation, and testing

Proposed Solution(s) - 2

What do they proposed to address the knowledge gap?

Proposed Solution(s).

- Use input feature generation and label assignment from PSI-BLAST.
- Specifically, use position-specific scoring matrix
- Train all mini-batches for 100 epochs

Proposed Solution(s) - 3

What do they proposed to address the knowledge gap?

Proposed Solution(s).

- Distance metrics

① Euclid-D, Euclidean distance, $(Q, T) \mapsto \sqrt{\sum_{i=1}^N (Q_i - T_i)^2}$

② Manh-D, Manhattan distance, $(Q, T) \mapsto \sum_{i=1}^N |Q_i - T_i|$

③ Corr-D, Pearson's Correlation score,
 $(Q, T) \mapsto \log(1 - \text{Corr}(Q, T))$

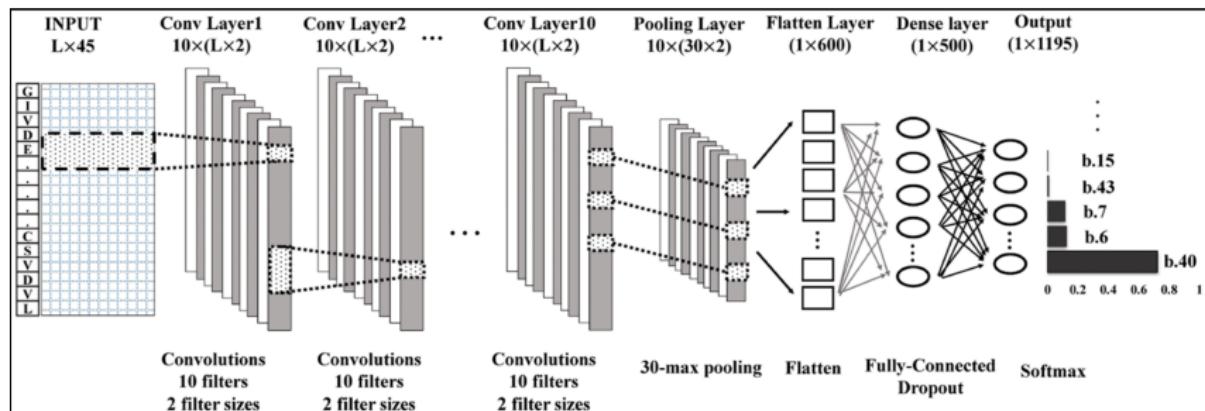
④ KL-D, KL-Divergence, $(Q, T) \mapsto \sum_{i=1}^N (Q_i \log \frac{Q_i}{T_i} + T_i \log \frac{T_i}{Q_i})$

- Group of folds:

- ① large: > 50
- ② medium: $6-50$
- ③ small: < 5

Proposed Solution(s) - 3

Architecture for a 1-D deep CNN



Dataset and Methods

Which datasets were used?

- SCOP 1.75 was used for training and validation (§3.1)
- SCOP 2.06 (§3.2) and CASP (§3.3) was used for test

Experimental Results - 1

Evaluation of distance metrics based on clustering accuracy

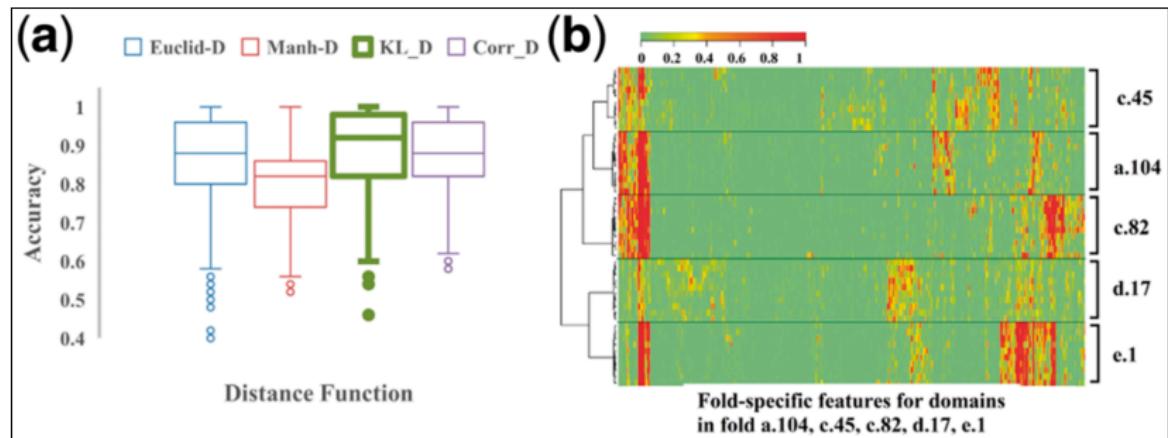


Figure: The prediction accuracy at family/superfamily/fold levels for top 1, top 5 and top 10 predictions of DeepSF and PSI-BLAST, on SCOP 1.75 test dataset

Experimental Results - 1

How do their proposed solutions compare with existing solutions?

Table 1.

The prediction accuracy at family/superfamily/fold levels for top 1, top 5 and top 10 predictions of DeepSF and PSI-BLAST, on SCOP 1.75 test dataset

| Level | Methods | Top1 | Top5 | Top10 |
|-----------------------------|-----------|--------|--------|--------|
| Family (1272 proteins) | DeepSF | 76.18% | 94.50% | 97.56% |
| | PSI-BLAST | 96.80% | 97.40% | 97.60% |
| Superfamily (1254 proteins) | DeepSF | 50.71% | 77.67% | 77.67% |
| | PSI-BLAST | 42.20% | 51.40% | 54.60% |
| Fold (718 proteins) | DeepSF | 40.95% | 70.47% | 82.45% |
| | PSI-BLAST | 5.60% | 11.60% | 16.20% |

Experimental Results - 2

How do their proposed solutions compare with existing solutions?

Table 2.

The accuracy of DeepSF on SCOP 2.06 dataset and its subsets

| DeepSF | Top1 | Top5 | Top10 |
|------------------|--------|--------|--------|
| SCOP2.06 dataset | 73.00% | 90.25% | 94.51% |
| 'Large' folds | 79.64% | 94.87% | 97.81% |
| 'Medium' folds | 74.16% | 75.61% | 76.06% |
| 'Small' folds | 67.93% | 86.86% | 94.74% |

Experimental Results - 3

How do their proposed solutions compare with existing solutions?

Table 3.

The prediction accuracy at family/superfamily/fold level for top 1, top 5 and top 10 predictions, on SCOP 2.06 test dataset

| Type | Methods | Top1 | Top5 | Top10 |
|-----------------------------|-----------|--------|--------|--------|
| Family (742 proteins) | DeepSF | 75.87% | 91.77% | 95.14% |
| | PSI-BLAST | 82.20% | 84.50% | 85.30% |
| Superfamily (1754 proteins) | DeepSF | 72.23% | 90.08% | 94.70% |
| | PSI-BLAST | 86.90% | 88.40% | 89.30% |
| Fold (37 proteins) | DeepSF | 51.35% | 67.57% | 72.97% |
| | PSI-BLAST | 18.90% | 35.10% | 35.10% |

Experimental Results - 4

How do their proposed solutions compare with existing solutions?

Table 4.

The performance of the methods on 88 template-based proteins in the CASP dataset

| Method | Top1 | Top5 | Top10 |
|----------------|--------|--------|--------|
| DeepSF | 46.59% | 73.86% | 84.09% |
| HHSearch | 43.20% | 61.40% | 67.00% |
| Cons_HH_DeepSF | 59.10% | 77.30% | 85.20% |
| PSI-BLAST | 15.90% | 31.80% | 47.70% |

Experimental Results - 5

How do their proposed solutions compare with existing solutions?

Table 5.

The performance of the methods on 95 template-free proteins in the CASP dataset

| Method | Top1 | Top5 | Top10 |
|----------------|--------|--------|--------|
| DeepSF | 24.21% | 51.58% | 70.53% |
| HHSearch | 11.58% | 34.74% | 44.21% |
| Cons_HH_DeepSF | 23.16% | 56.84% | 70.53% |
| PSI-BLAST | 8.42% | 15.79% | 32.63% |

Experimental Results - 6

How do their proposed solutions compare with existing solutions?

Table 6.

Accuracy of protein structure predictions on 95 template-free targets

| Methods | TM-score | | | |
|----------|----------|------|------|------|
| | Min | Max | Mean | Std |
| DeepSF | 0.15 | 0.54 | 0.27 | 0.07 |
| HHSearch | 0.11 | 0.52 | 0.25 | 0.08 |

Experimental Results - 2

How do their proposed solutions compare with existing solutions?

Experimental Results - 2.

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Experimental Results - 3

Benchmarking

Benchmarking of results with PSI-BLAST.

- Solution is 12.63-26.32% better than HHSearch on template-free modeling targets.
- Solution is 3.39-17.09% better on hard template-based modeling targets.

Discussion of Experimental Results

What do the experimental results tell us?

Discuss the experimental results.

- Method is robust against:
 - ① sequence mutation
 - ② insertion
 - ③ deletion
 - ④ truncation
- Can solve other protein pattern recognition problems:
 - ① protein clustering
 - ② protein comparison
 - ③ protein ranking

Weaknesses - 1

What are the weaknesses of this paper?

- Poor benchmarking methodology:
 - ① Benchmarked solution (especially in Table 1) against PSI-BLAST (Altschul S.F. et al. , 1997)
 - ② Did not benchmark with other modern solutions for protein fold prediction
 - ① PFPA (2015, IEEE Transactions on NanoBioscience); DOI: 10.1109/TNB.2015.2450233
 - ② random forest (2014, BMC Bioinformatics); DOI:10.1186/1471-2105-15-S11-S14
 - ③ PFP-RFSM (2013, J. Biomedical Science and Engineering); DOI:10.4236/jbise.2013.612145
 - Did not use box plots or bar charts to compare methods for each protein sequence in the datasets:

Weaknesses - 2

What are the weaknesses of this paper?

- Inadequate **cross-referencing of figures and tables** with hyperlinks in the text:
 - ① When figures and tables are not cross referenced with hyperlinks in the text, it takes more work to determine the context for each figure and table that I come across. The location of the figures and tables can be placed
- Did not use the following to compare methods (for each protein sequence, or family of protein folds) in the datasets
 - ① box plots with error bars (or, box-and-whisker plot or box-and-whisker diagram)
 - ② bar charts (normalized to one/unity, using geometric average to avoid bias with respect to the chosen “golden solution”)
 - ③ scatter plots with the 45° degree reference line

Weaknesses - 3

What are the weaknesses of this paper?

- Did not do design space exploration for trade-offs between performance (execution time), accuracy, and memory usage.

Muddy Points

What do I not understand about [1]?

What do I not understand about [1]?

- Why is it bad for top 1 predicted fold, but better for top 5 and top 10 predicted folds?

References

-  Jie Hou, Badri Adhikari, and Jianlin Cheng.
DeepSF: deep convolutional neural network for mapping
protein sequences to folds.
Bioinformatics, 34(8):1295–1303, April 15 2018.