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?

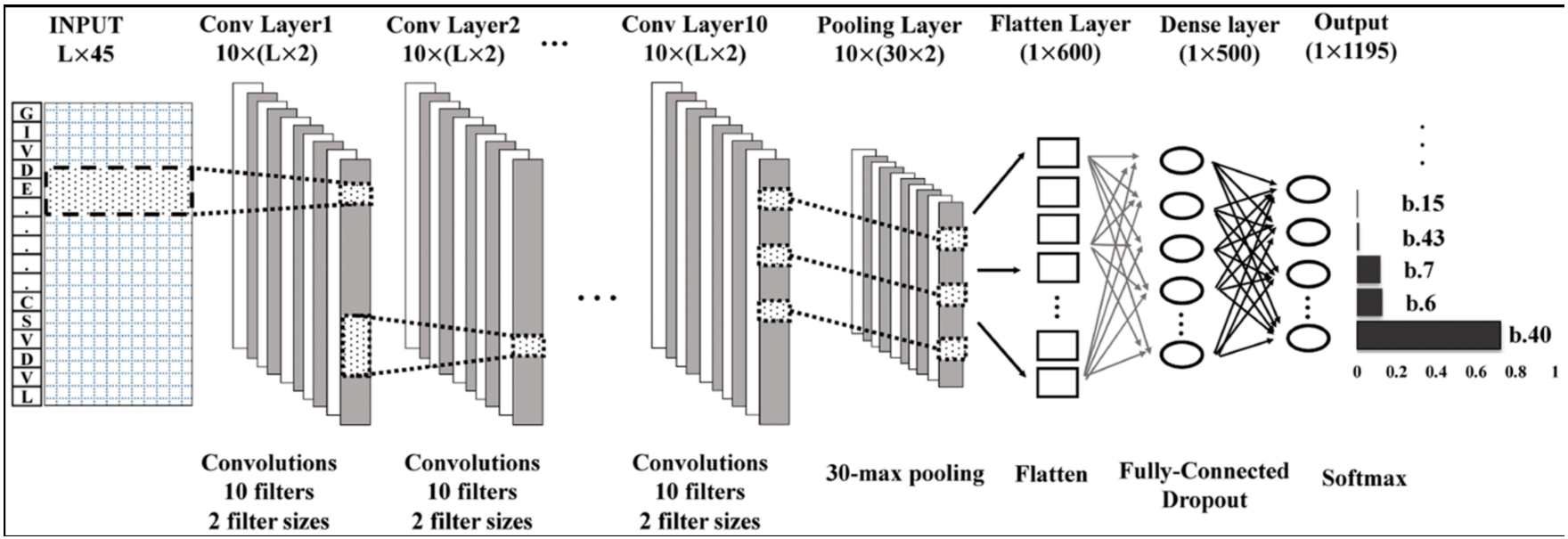
Proposed Solution(s).

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

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

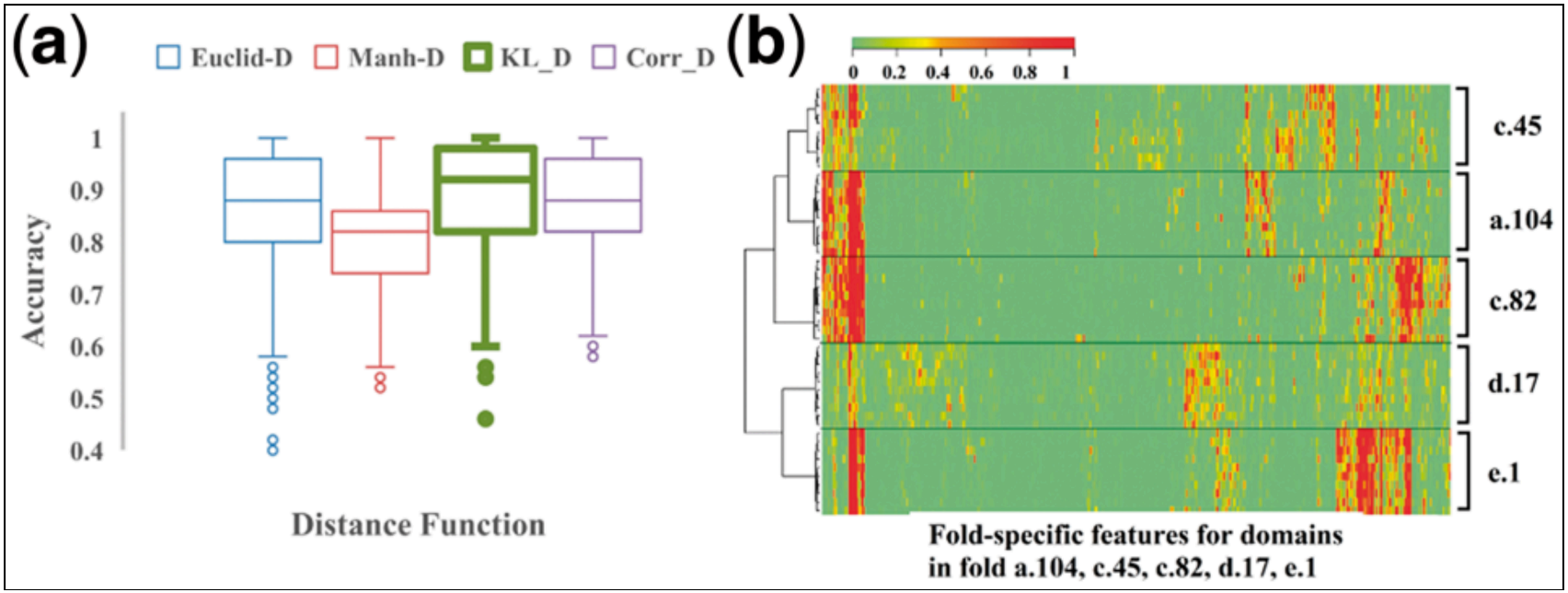


Figure: The prediction accuracy at family/superfamily/fold levels for top 1, top 5 and top 10 predictions of DeepSF and PSI-BLAST, on SCOP 1.75 test dataset

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.