Statistical Machine Learning Methods for Bioinformatics

IV. Neural Network & Deep Learning Applications in Bioinformatics

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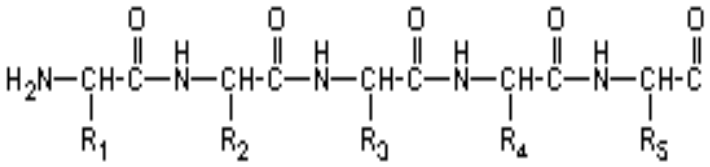
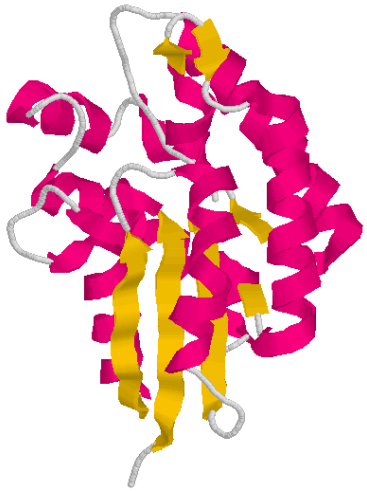
Neural Network & Deep Learning Application in Bioinformatics

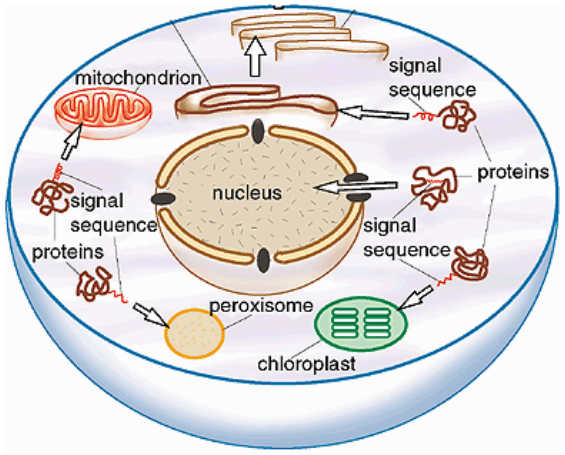
- Neural network is one of the most widely used methods in bioinformatics.
- Deep learning is the most popular method in bioinformatics
- It is used in gene structure prediction, protein structure prediction, gene expression data analysis, … Almost anywhere when you need to do classification.
- Here we specifically focus on applying neural networks to protein structure prediction (**secondary structure**, solvent accessibility, disorder region, **contact map, fold classification**).

Sequence, Structure and Function

AGCWY……



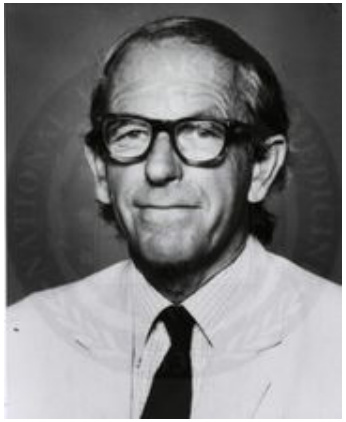


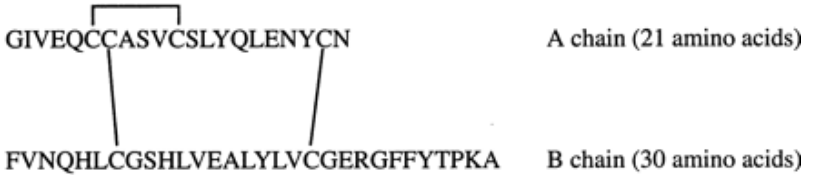


Cell

Protein Sequence – Primary Structure

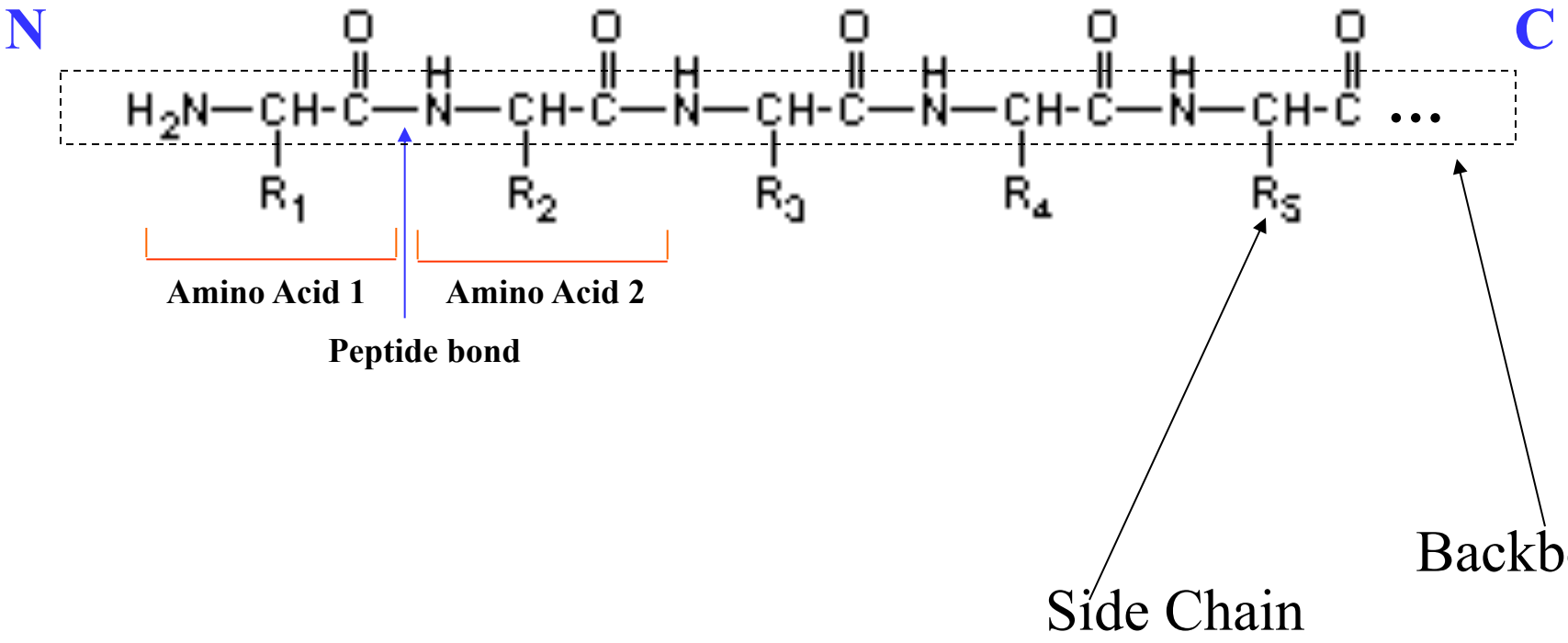
- The first protein was sequenced by Frederick Sanger in 1953.
- Twice Nobel Laureate (1958, 1980) (other: Curie, Pauling, Bardeen).
- Determined the amino acid sequence of insulin and proved proteins have specific primary structure.



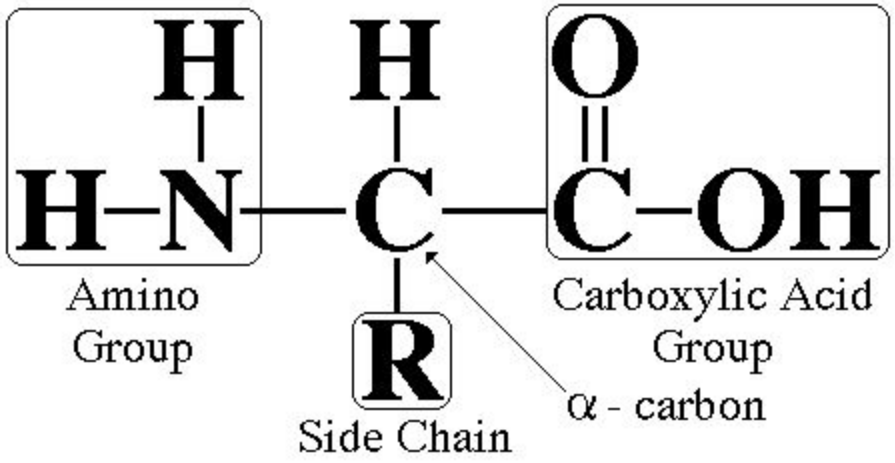


Protein Sequence

A directional sequence of amino acids/residues



Amino Acid Structure



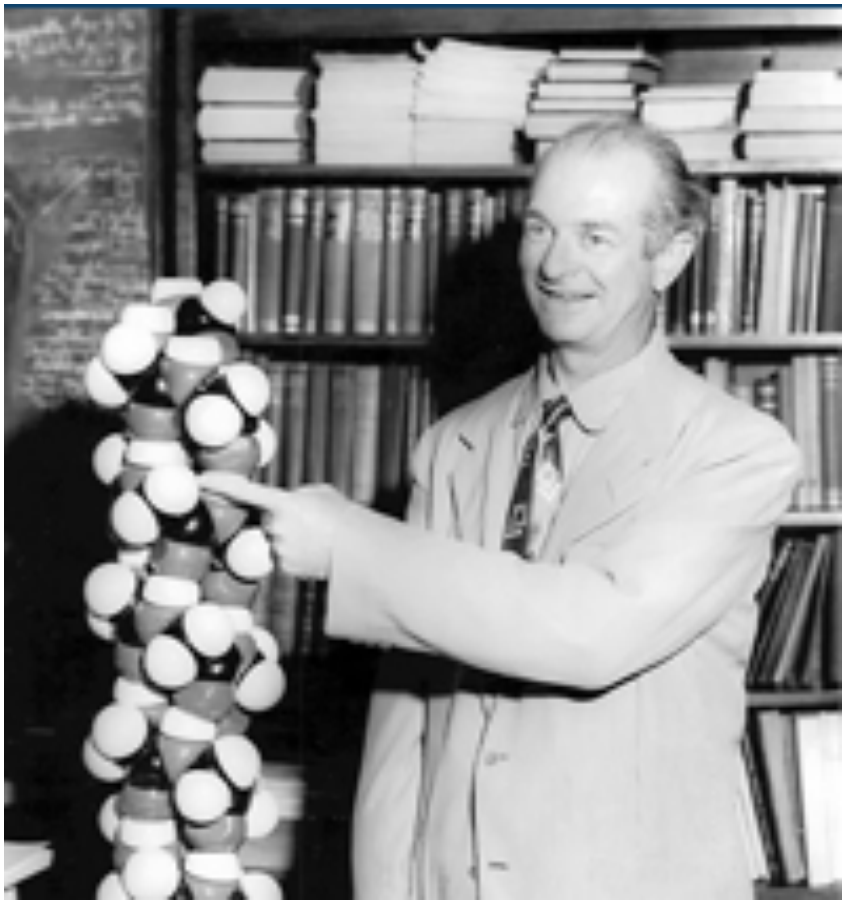
Amino Acids

Amino acid	Abbrev.	Side chain	Hydro-phobic	Polar	Charged	Small	Tiny	Aromatic or Aliphatic	van der Waals volume	Codon	Occurrence in proteins (%)
Alanine	Ala, A	$-CH_3$	X	-	-	X	X	-	67	GCU, GCC, GCA, GCG	7.8
Cysteine	Cys, C	$-CH_2SH$	X	-	-	X	-	-	86	UGU, UGC	1.9
Aspartate	Asp, D	$-CH_2COOH$	-	X	negative	X	-	-	91	GAU, GAC	5.3
Glutamate	Glu, E	$-CH_2CH_2COOH$	-	X	negative	-	-	-	109	GAA, GAG	6.3
Phenylalanine	Phe, F	$-CH_2C_6H_5$	X	-	-	-	-	Aromatic	135	UUU, UUC	3.9
Glycine	Gly, G	-H	X	-	-	X	X	-	48	GGU, GGC, GGA, GGG	7.2
Histidine	His, H	$-CH_2-C_3H_3N_2$	-	X	positive	-	-	Aromatic	118	CAU, CAC	2.3
Isoleucine	Ile, I	$-CH(CH_3)CH_2CH_3$	X	-	-	-	-	Aliphatic	124	AUU, AUC, AUA	5.3
Lysine	Lys, K	$-(CH_2)_4NH_2$	-	X	positive	-	-	-	135	AAA, AAG	5.9
Leucine	Leu, L	$-CH_2CH(CH_3)_2$	X	-	-	-	-	Aliphatic	124	UUA, UUG, CUU, CUC, CUA, CUG	9.1
Methionine	Met, M	$-CH_2CH_2SCH_3$	X	-	-	-	-	-	124	AUG	2.3
Asparagine	Asn, N	$-CH_2CONH_2$	-	X	-	X	-	-	96	AAU, AAC	4.3
Proline	Pro, P	$-CH_2CH_2CH_2-$	X	-	-	X	-	-	90	CCU, CCC, CCA, CCG	5.2
Glutamine	Gln, Q	$-CH_2CH_2CONH_2$	-	X	-	-	-	-	114	CAA, CAG	4.2
Arginine	Arg, R	$-(CH_2)_3NH-C(NH)NH_2$	-	X	positive	-	-	-	148	CGU, CGC, CGA, CGG, AGA, AGG	5.1
Serine	Ser, S	$-CH_2OH$	-	X	-	X	X	-	73	UCU, UCC, UCA, UCG, AGU,AGC	6.8
Threonine	Thr, T	$-CH(OH)CH_3$	X	X	-	X	-	-	93	ACU, ACC, ACA, ACG	5.9
Valine	Val, V	$-CH(CH_3)_2$	X	-	-	X	-	Aliphatic	105	GUU, GUC, GUA, GUG	6.6
Tryptophan	Trp, W	$-CH_2C_8H_6N$	X	-	-	-	-	Aromatic	163	UGG	1.4
Tyrosine	Tyr, Y	$-CH_2-C_6H_4OH$	X	X	-	-	-	Aromatic	141	UAU, UAC	3.2

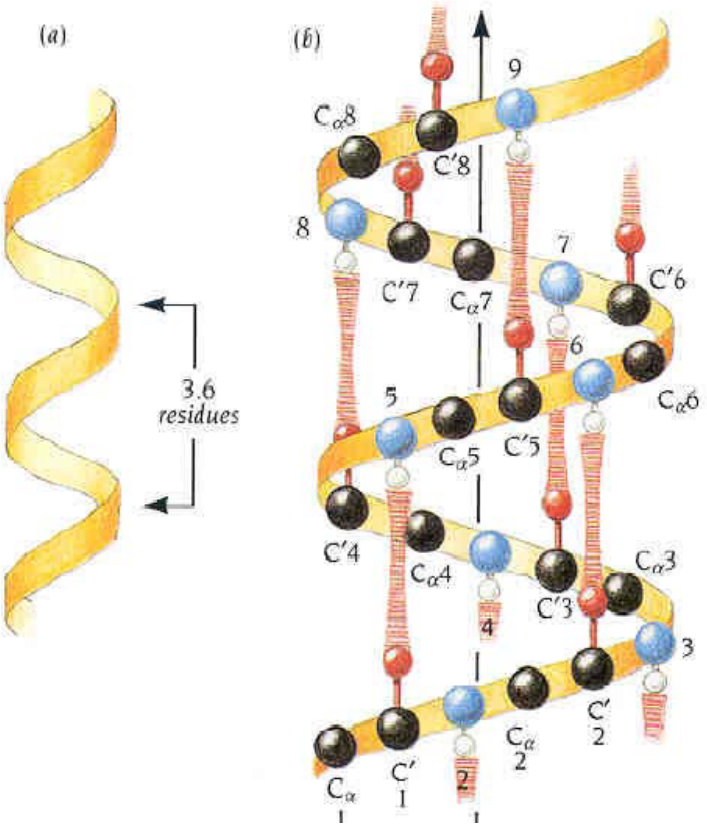
Hydrophilic

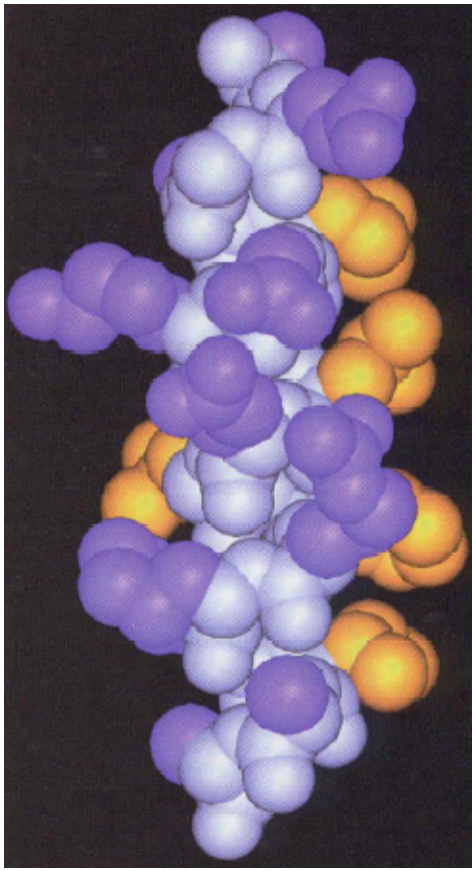
Protein Secondary Structure

- Determined by hydrogen bond patterns
- 3-Class categories: alpha-helix, beta-sheet, loop (or coil)
- First deduced by Linus Pauling et al.



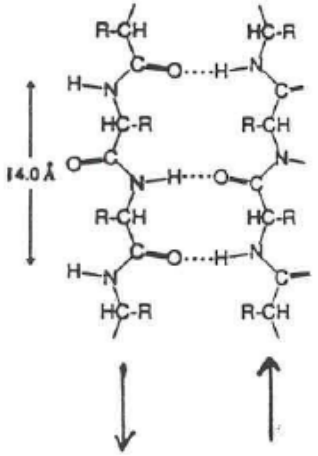
Alpha-Helix

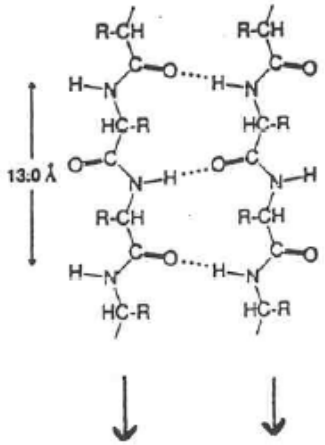


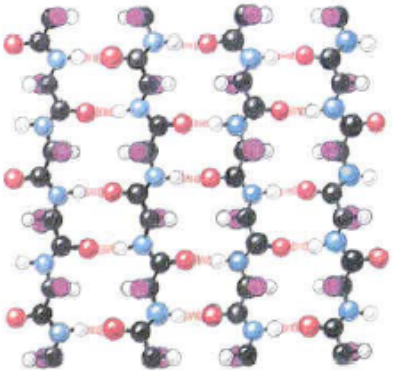


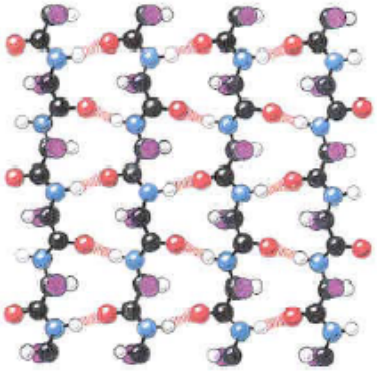
Jurnak, 2003

Beta-Sheet







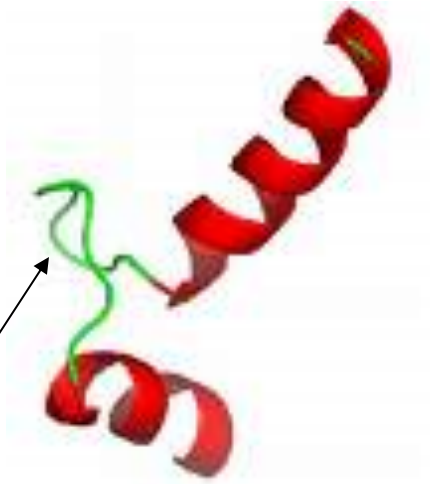


Anti-Parallel

Parallel

Non-Repetitive Secondary Structure

Beta-Turn



Loop

Tertiary Structure

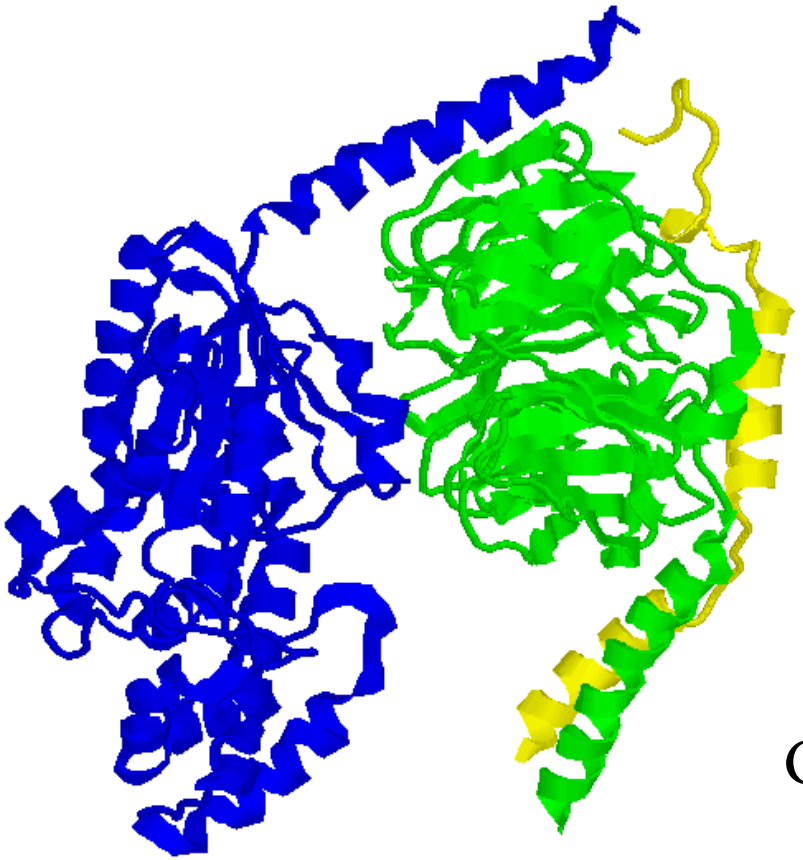
- John Kendrew et al., Myoglobin
- Max Perutz et al., Haemoglobin
- 1962 Nobel Prize in Chemistry

Perutz Kendrew

myoglobin

haemoglobin

Quaternary Structure: Complex



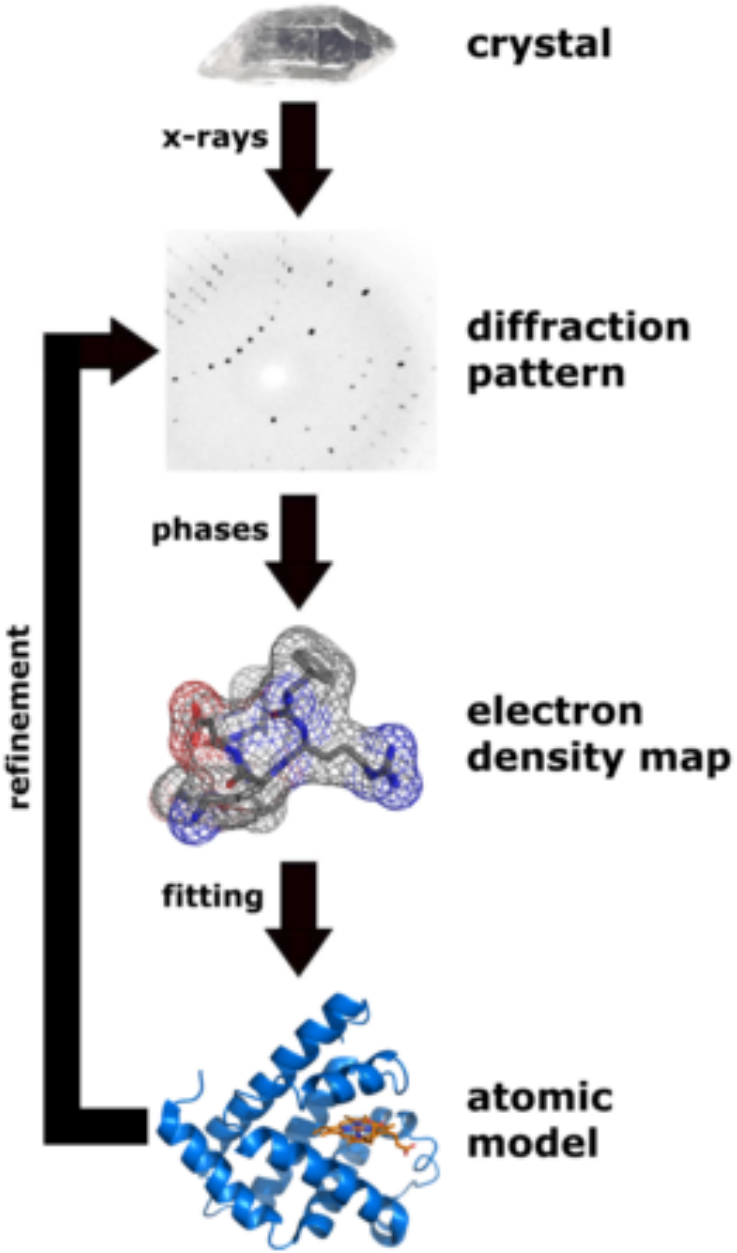
G-Protein Complex

Anfinsen's Folding Experiment

- Structure is uniquely determined by protein sequence
- Protein function is determined by protein structure

Protein Structure Determination

- X-ray crystallography
- Nuclear Magnetic Resonance (NMR) Spectroscopy
- X-ray: any size, accurate (1-3 Angstrom (10^{-10} m)), sometime hard to grow crystal
- NMR: small to medium size, moderate accuracy, structure in solution

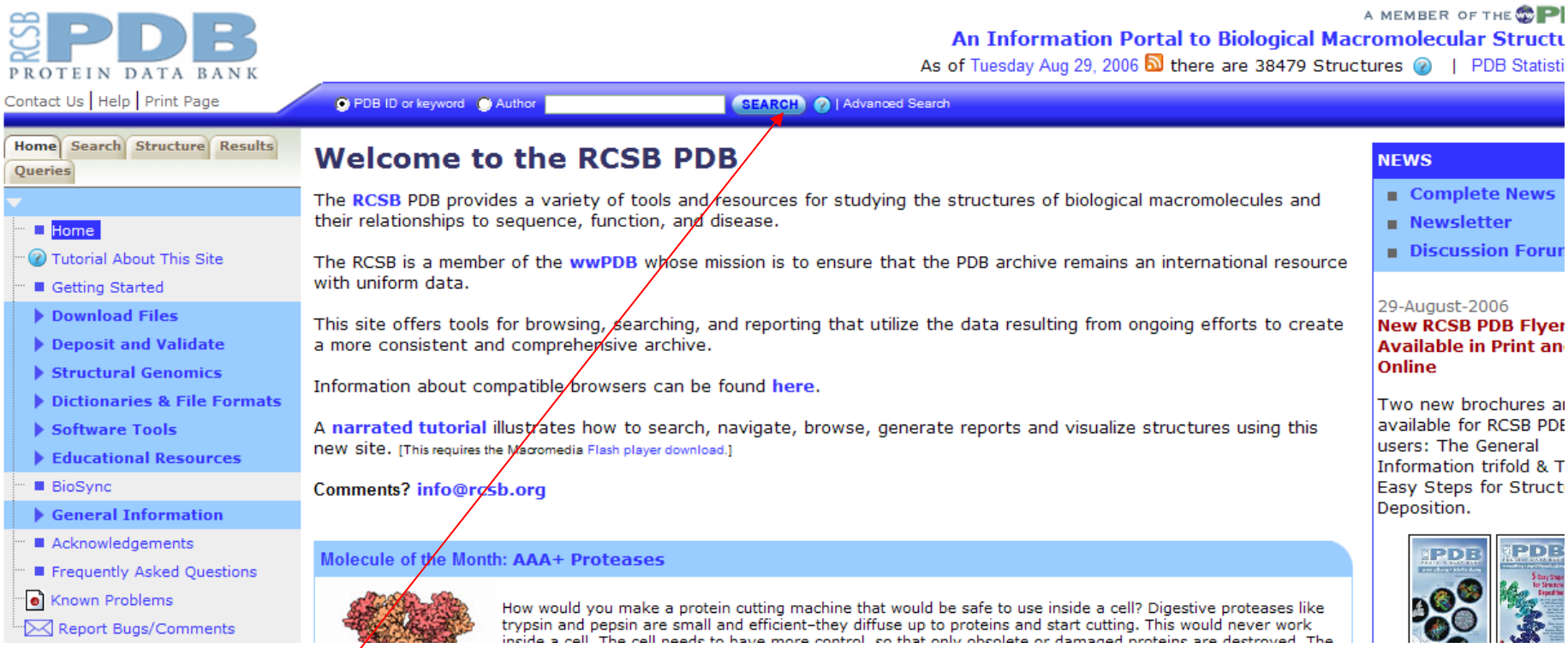


Wikipedia, the free encyclopedia

Pacific Northwest National Laboratory's high magnetic field (800 MHz, 18.8 T) NMR spectrometer being loaded with a sample.

Wikipedia, the free encyclopedia

Storage in Protein Data Bank



Search database

Search protein 1VJG

```
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SEQRES   2 A   21  TYR GLN LEU GLU ASN TYR CYS ASN
SEQRES   1 B   29  PHE VAL ASN GLN HIS LEU CYS GLY SER HIS LEU VAL GLU
SEQRES   2 B   29  ALA LEU TYR LEU VAL CYS GLY GLU ARG GLY PHE PHE TYR
SEQRES   3 B   29  THR PRO LYS
FORMUL   3  HOH   *31(H2 O1)
HELIX    1   1 GLY A    1  CYS A    7  1                                   7
HELIX    2   2 SER A   12  ASN A   18  1                                   7
HELIX    3   3 GLY B    8  GLY B   20  1                                  13
HELIX    4   4 GLU B   21  GLY B   23  5                                   3
SSBOND   1 CYS A    6    CYS A   11                          1555   1555
SSBOND   2 CYS A    7    CYS B    7                          1555   1555
SSBOND   3 CYS A   20    CYS B   19                          1555   1555
CRYST1   78.608   78.608   78.608  90.00  90.00  90.00 I 21 3        24
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.012721  0.000000  0.000000        0.00000
SCALE2      0.000000  0.012721  0.000000        0.00000
SCALE3      0.000000  0.000000  0.012721        0.00000
ATOM      1  N   GLY A   1      45.324  26.807  11.863  1.00 24.82           N
ATOM      2  CA  GLY A   1      45.123  27.787  12.967  1.00 24.93           C
ATOM      3  C   GLY A   1      43.756  27.627  13.605  1.00 25.16           C
ATOM      4  O   GLY A   1      43.107  26.591  13.438  1.00 25.00           O
ATOM      5  N   ILE A   2      43.313  28.661  14.323  1.00 25.21           N
ATOM      6  CA  ILE A   2      42.050  28.622  15.065  1.00 25.39           C
ATOM      7  C   ILE A   2      40.818  28.303  14.200  1.00 25.69           C
ATOM      8  O   ILE A   2      39.935  27.565  14.635  1.00 25.56           O
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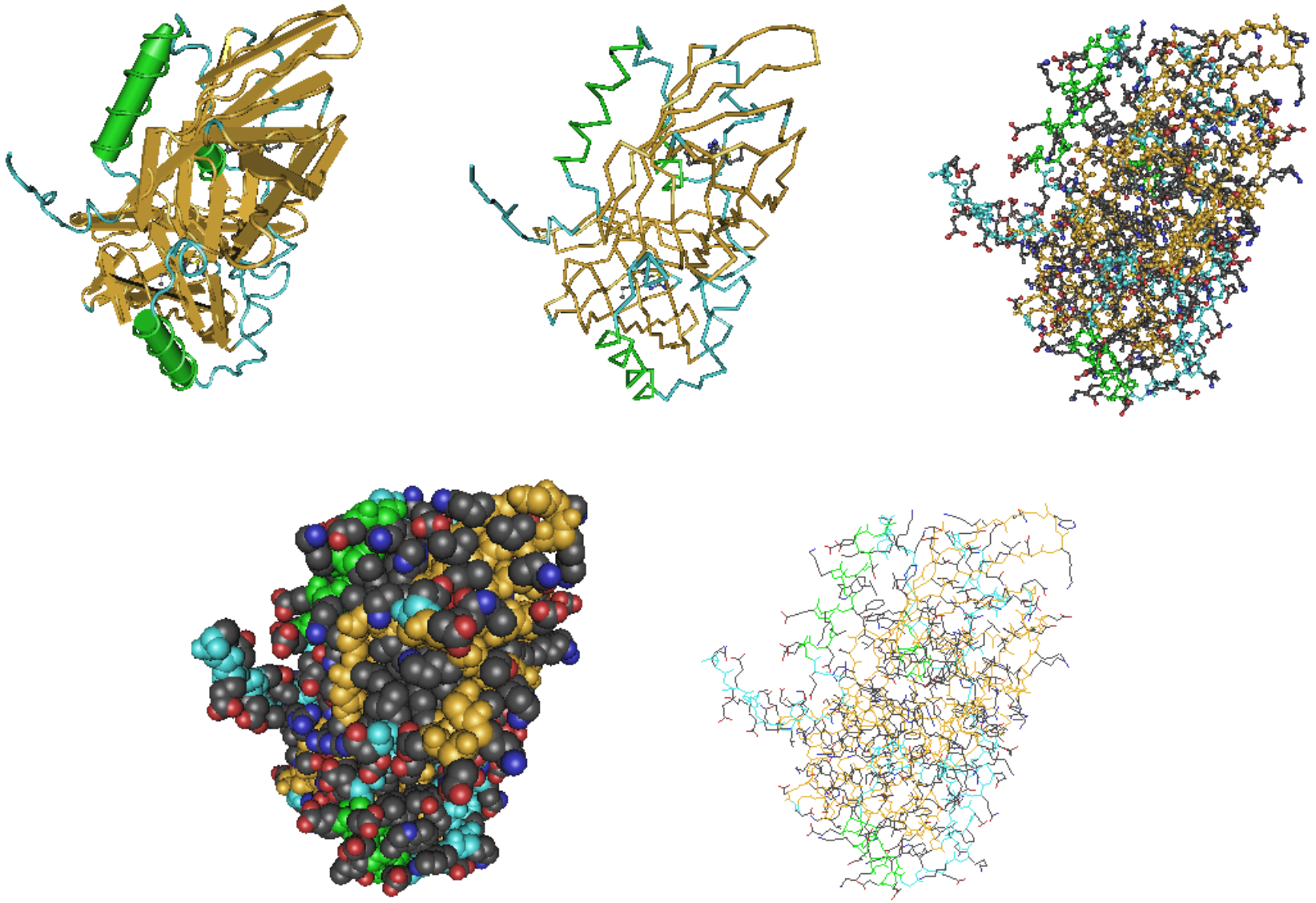
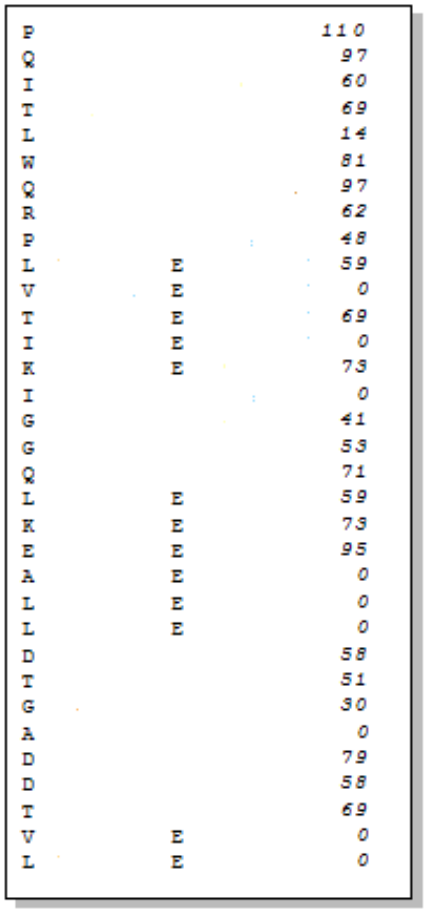
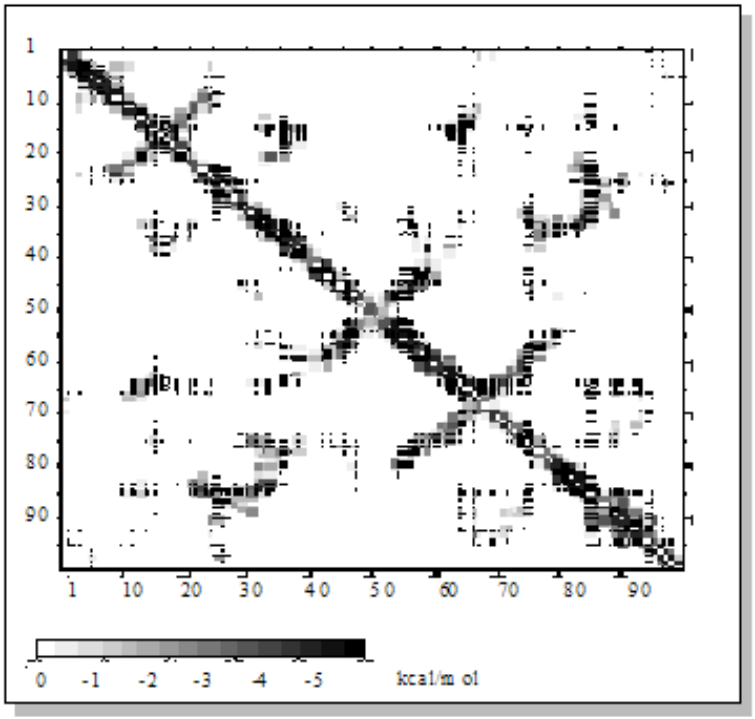


J. Pevsner, 2005

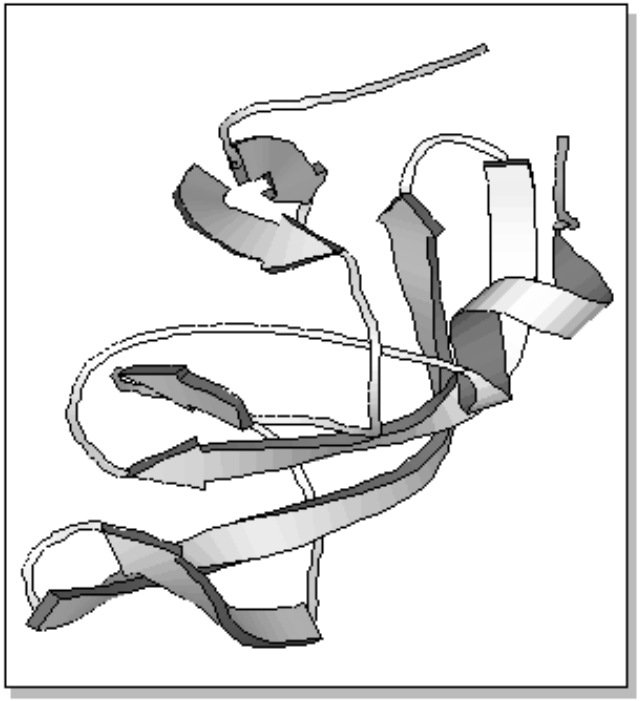
1D, 2D, 3D Structure Prediction



1D



2D



3D

B. Rost, 2005

Importance of Computational Modeling

The Nobel Prize in Chemistry 2013

Photo: A. Mahmoud
Martin Karplus
Prize share: 1/3

Photo: A. Mahmoud
Michael Levitt
Prize share: 1/3

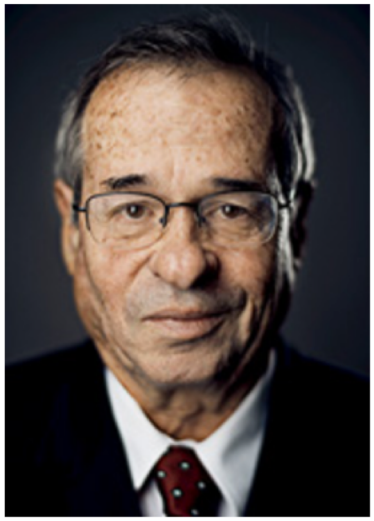
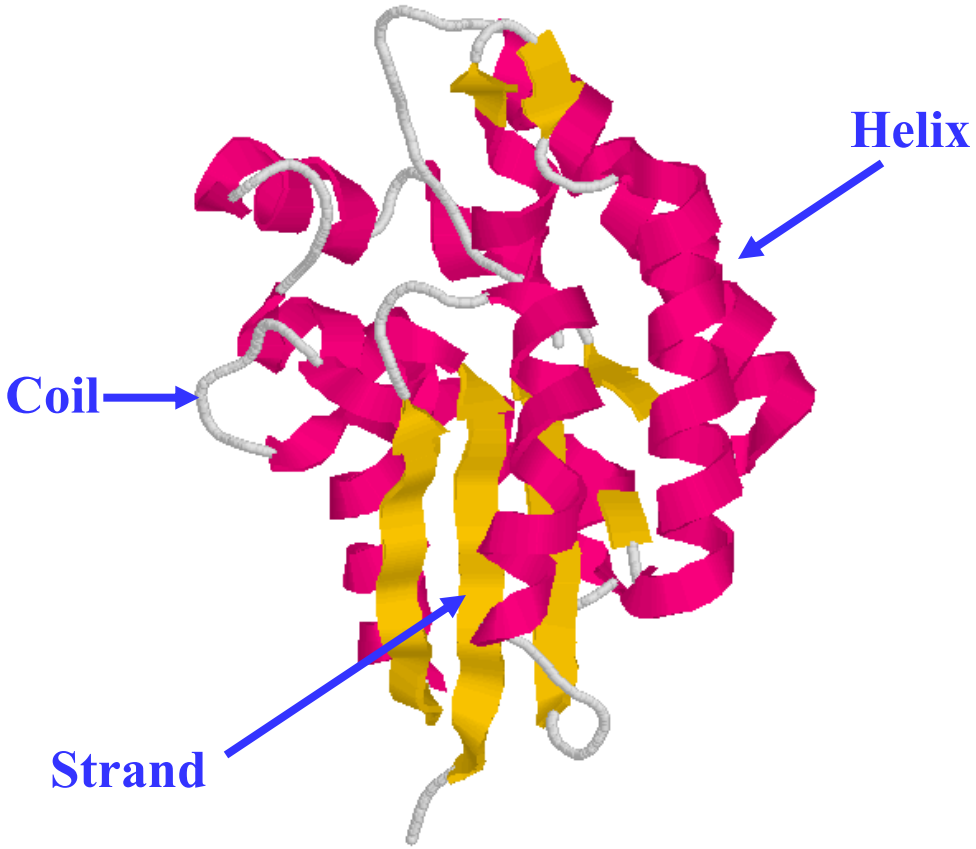


Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

1D: Secondary Structure Prediction



MWLKKFGINLLIGQSV…

Neural Networks + Alignments

CCCCHHHHHCCCSSSSS…

Accuracy: 78%

Pollastri et al. *Proteins*, 2002. **Cheng et al.. *NAR*, 2005**

How to Use Neural Network to Predict Secondary Structure

- Create a data set with input sequences (x) and output labels (secondary structures)
- Encode the input and output to neural network
- Train neural network on the dataset (training dataset)
- Test on the unseen data (test dataset) to estimate the generalization performance.

Create a Data Set

- Download proteins from Protein Data Bank
- Select high-resolution protein structures (<2.5 Angstrom, determined by X-ray crystallography)
- Remove proteins with chain-break (Ca-Ca distance > 4 angstrom)
- Remove redundancy (filter out very similar sequences using BLAST)
- Use DSSP program (Kabsch and Sander, 1983) to assign secondary structure to each residue.

Train and Test

- Use one data set as training dataset to build neural network model
- Use another data set as test dataset to evaluate the generalization performance of the model
- Sequence similarity any two sequences in test and training dataset is less than 25%.

Create Inputs and Outputs for Feed-Forward NN for a Single Sequence

Protein Sequence:

MWLKKFGINLLIGQSVQTRSWYYCKRA

How to encode the input for each position?

How to encode the output for each position?

SS Sequence:

CCCCHHHHHHEEEEEHHHHEEEEEECC

Create Inputs and Outputs for Feed-Forward NN for a Single Sequence

Protein Sequence:

MWLKKFGINLLIGQSVQTRSWYYCKRA

Use 20 inputs of 0s and 1s for each amino acid
Use 3 inputs to encode the SS alphabet

SS Sequence:

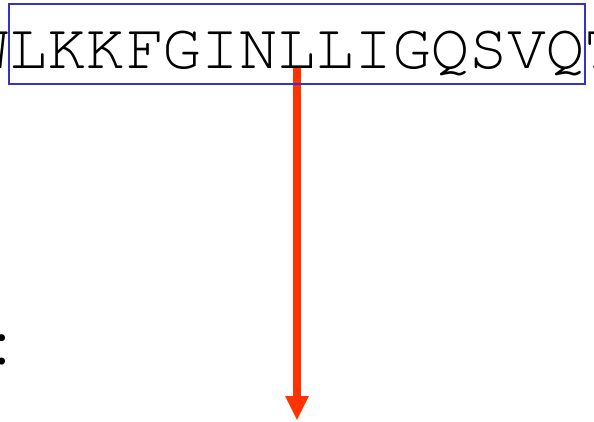
CCCCHHHHHHEEEEEHHHHEEEEEECC

100: Helix, 010: Extended strand, 001: Coil
Similarly for 20 different amino acids

Use a Window to Account for Context

Protein Sequence:

MWLKKFGINLLIGQSVQTRSWYYCKRA



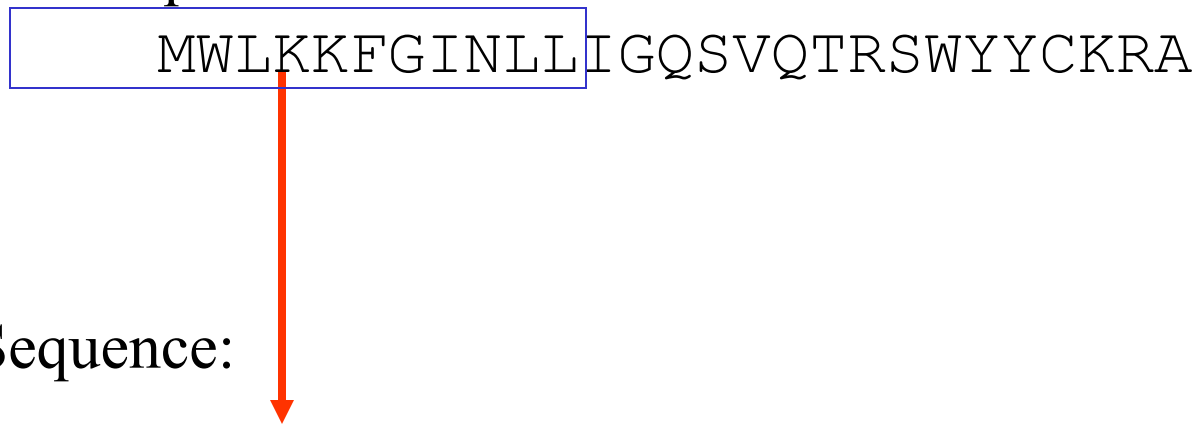
SS Sequence:

CCCCHHHHHHEEEEEHHHHEEEEEECC

Total number of inputs is window size (*l*) * 20. *l* is a parameter to tune.

Use an Extra Input to Account for N- and C- Terminal Boundary

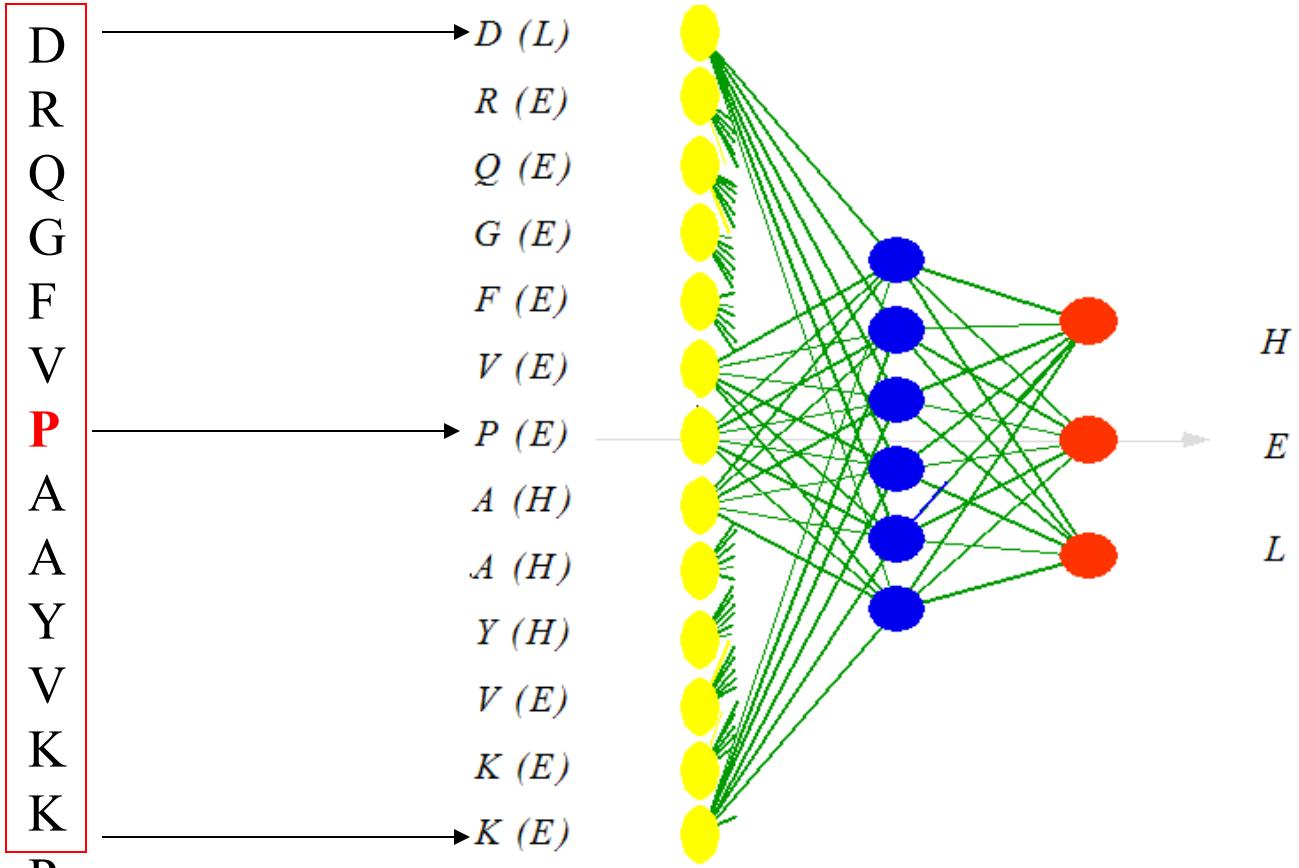
Protein Sequence:



Add an extra input for each position to indicate if it is out of the boundary of the sequence.

Total number of inputs is window size (l) * 21. l is a parameter to tune.

Secondary Structure Prediction (Generation III – Neural Network)



Output:
Prob (H)
Prob (E)
Prob (L or C)

B. Rost, 2005

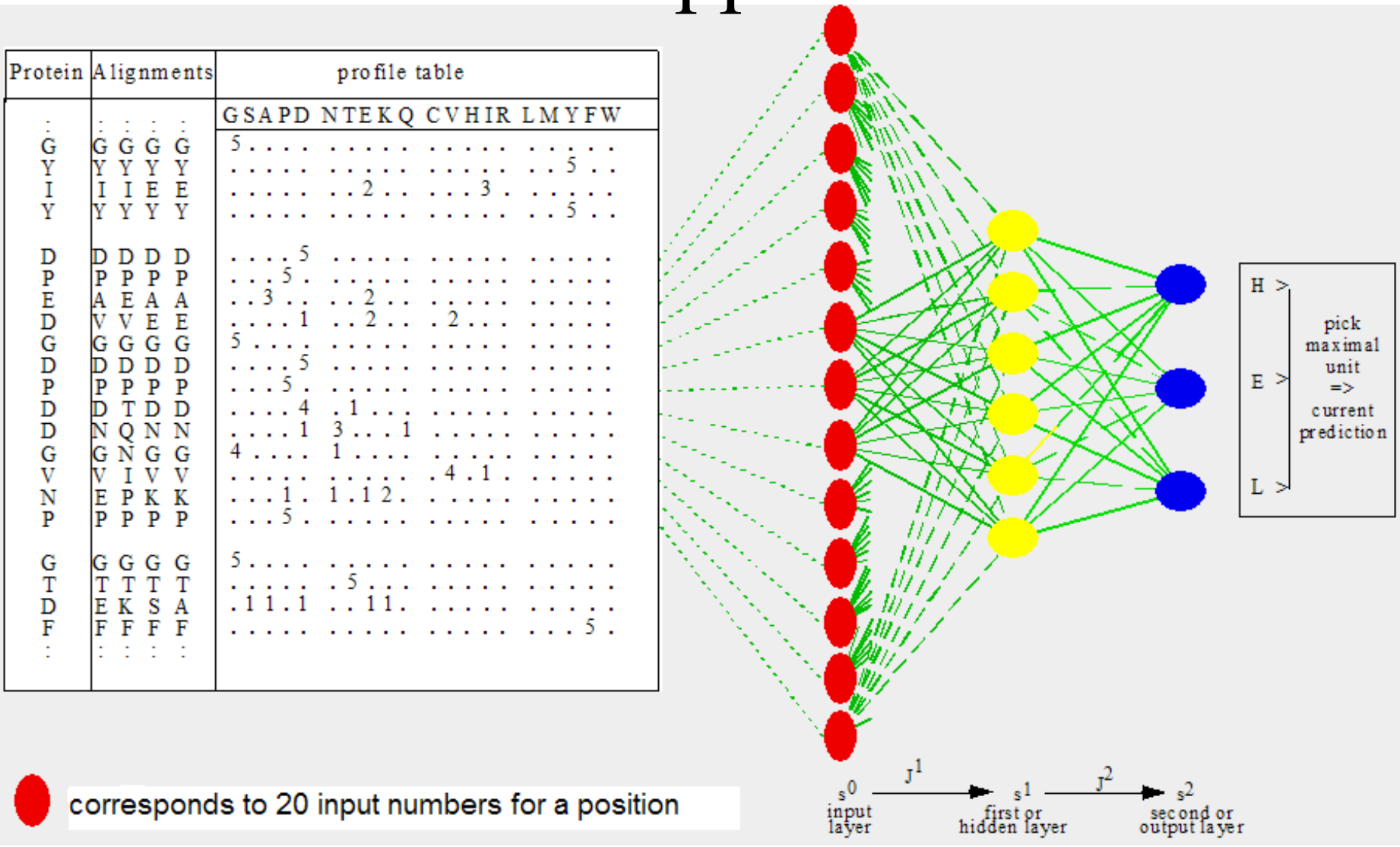
Evolutionary Information is Important

- Single sequence yields accuracy below 70%.
- Use all the sequences in the family of a query sequence can improve accuracy to 78%.
- Structure is more conserved than sequence during evolution. The conservation and variation provides key information for secondary structure prediction.

How to Find Homologous Sequences and Generate Alignments

- Use PSI-BLAST to search a query sequence against the very large non-redundant protein sequence database (NR database, compiled at NCBI)
- Combine the pairwise alignment between the query sequence and other sequences into a multiple sequence alignment using the query sequence as the center.
-

PhD Approach



Comments: frequency is normalized into probability and sequence needs to be weighted.

Reference: Rost and Sander. Proteins, 1994.

B. Rost, 2005

PSI-PRED Approach

- PSI-PRED does not use probability matrix instead it uses the another kind of profile: Position Specific Scoring Matrix generated by PSI-BLAST during sequence search.
- The weighting of the sequences is done implicitly by PSI-BLAST.
- The raw PSSM is transformed into values within [0,1] using sigmoid function.

Reference: Jones, Journal of Molecular Biology, 1999.

PSI-PRED Input

Position-based scoring matrix used

A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
-3	-4	-4	-4	-3	-4	-4	-4	-2	-1	-1	-4	-1	8	-5	-3	-3	0	2	-2
0	-1	-1	3	-4	3	4	1	-1	-4	-4	0	-3	-4	-2	-1	-2	-4	-3	-3
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-2	-3	-1	-5	-3	-3	-4	-5	-4	3	4	0	4	2	-4	-3	-2	-3	-2	0
0	3	0	-2	-3	-1	0	0	-2	0	0	1	0	-1	-3	2	0	-4	-3	0
-1	1	3	-2	-4	0	-2	4	-2	-4	-4	0	-3	0	-3	0	0	-3	0	-4

Window of 15 rows

A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
0.4	0.3	0.3	0.3	0.2	0.9	0.3	0.3	0.4	0.4	0.4	0.3	0.4	0.9	0.1	0.4	0.4	0.5	0.7	0.4
0.3	0.2	0.3	0.8	0.4	0.3	0.7	0.1	0.6	0.2	0.4	0.3	0.5	0.2	0.1	0.4	0.8	0.2	0.3	0.2
0.1	0.1	0.4	0.3	0.5	0.1	0.1	0.3	0.1	0.1	0.4	0.2	0.4	0.9	0.3	0.4	0.4	0.9	0.3	0.6
0.6	0.3	0.3	0.1	0.3	0.5	0.5	0.2	0.1	0.4	0.4	0.3	0.6	0.9	0.1	0.5	0.1	0.5	0.7	0.4

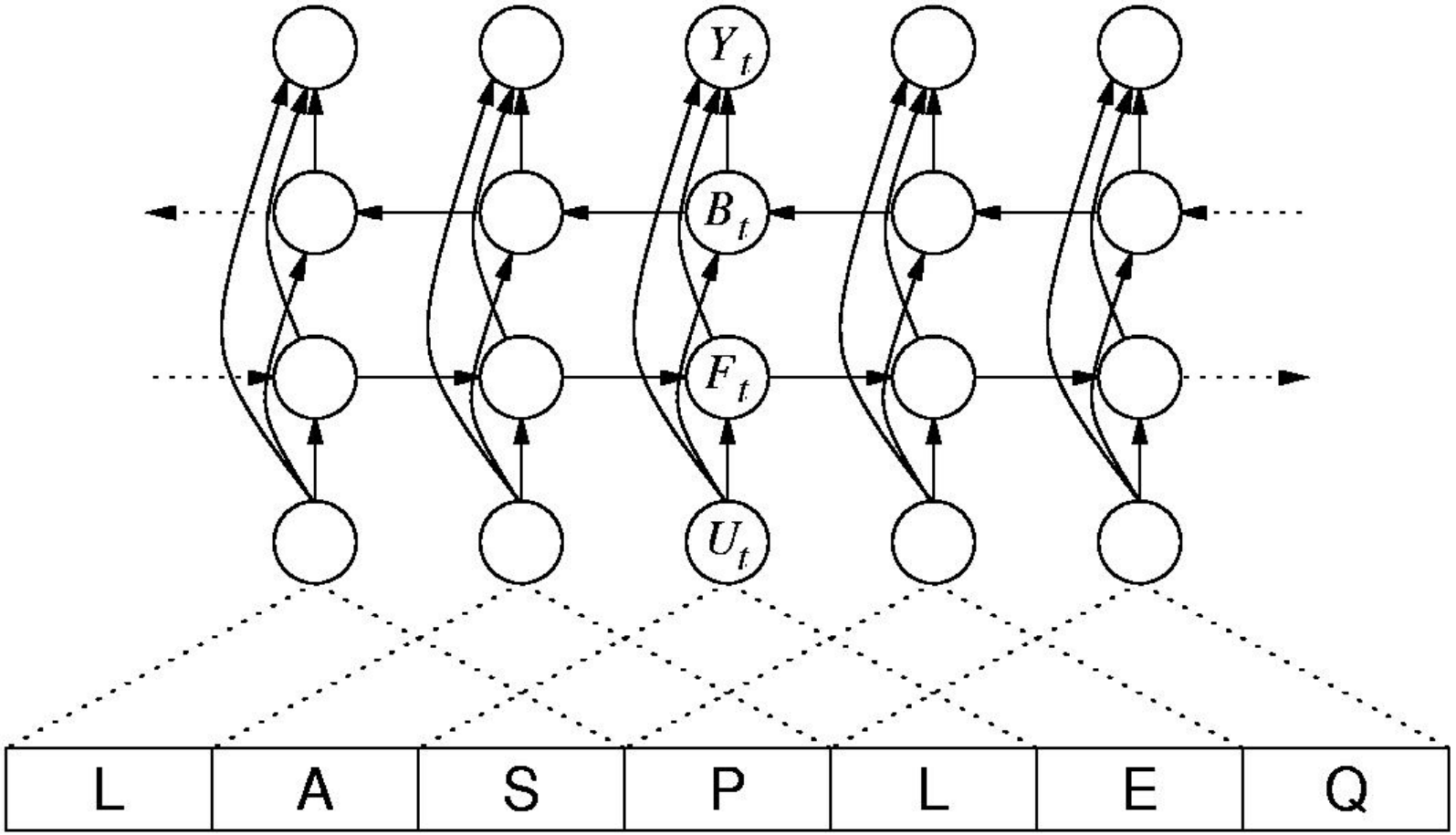
Reference: Jones, Journal of Molecular Biology, 1999.

SSpro Approach

- SSpro uses probability matrix as inputs
- SSpro uses an information theory approach to weight sequences
- The main novelty of SSpro is to use 1-Dimensional Recurrent Neural Network (1D-RNN)

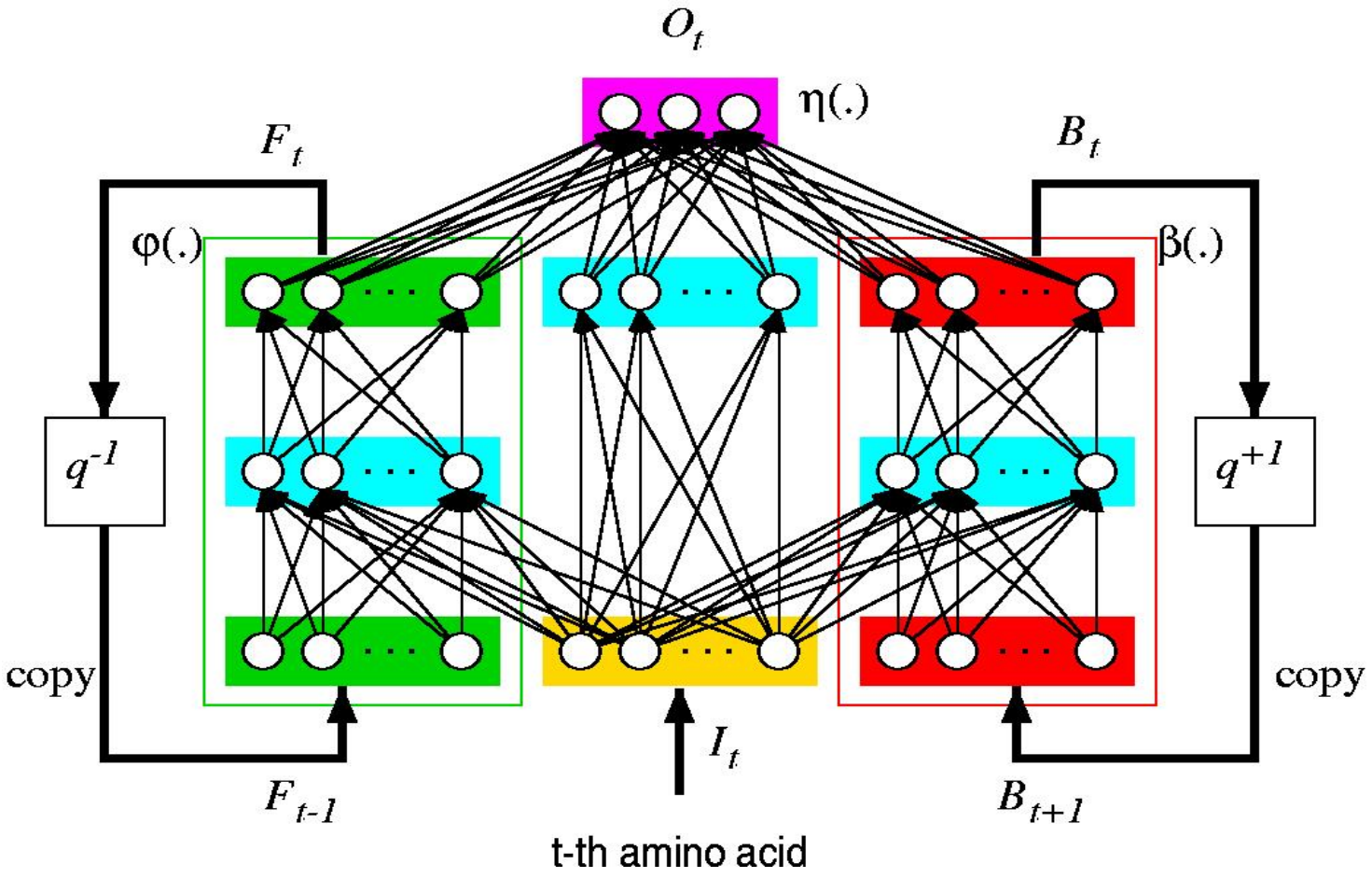
Pollastri et al.. Proteins, 2002.

Bi-directional Input Output Hidden Markov Model for SS Prediction



Baldi, 2004

1D-Recursive Neural Network



Baldi, 2004

Advantage and Disavantages of SSpro

- Directly take a sequence with variable length as inputs.
- Hopefully can utilize more information than a fixed-window approach
- More complex, thus harder to implement than feed-forward neural network.

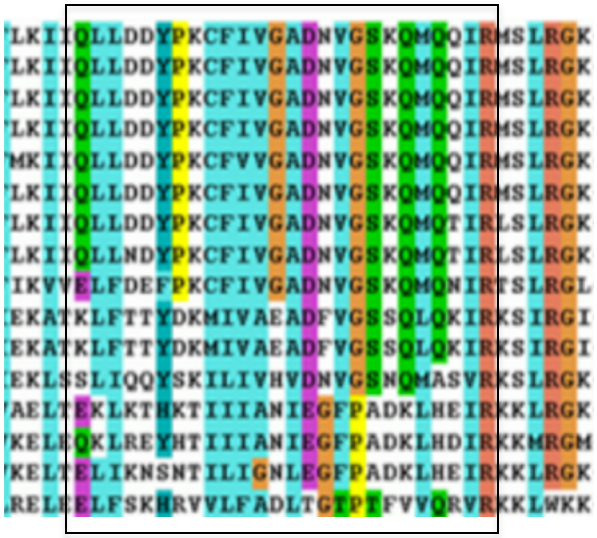
Second Neural Network to Smooth Output Predictions

- Raw output from one neural network may contain weird predictions such as helix of length 1. But minimum length is 2.
- So use another neural network to smooth output. The inputs are a window of predicted secondary structure. The outputs are the true secondary structures.
- The second neural network makes the predictions more protein-like.

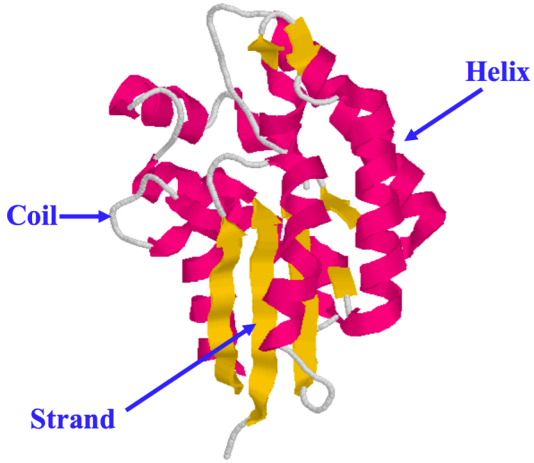
Deep Learning for Secondary Structure Prediction

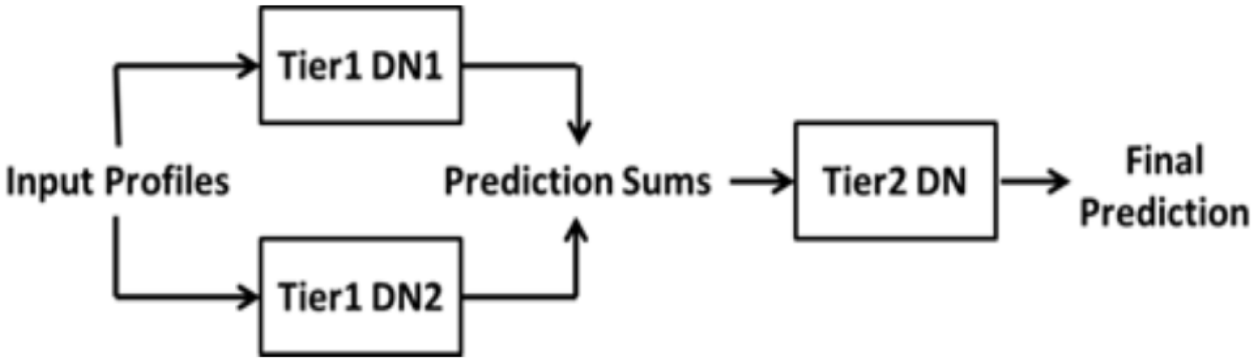
M. Spencer, J. Eickholt, J. Cheng. **A Deep Learning Network Approach to ab initio Protein Secondary Structure Prediction**. *IEEE Transactions on Computational Biology and Bioinformatics, 2015*

Deep Learning for Secondary Structure Prediction



Window Size = 19





Rank	Layers	Nodes[a]	Q_3 (%)	Sov (%)
1	4	600	80.24	73.07
2	5	400	79.96	72.67
3	3	500	80.00	72.37
4	4	300	79.84	72.48
5	6	300	79.82	72.50
6	3	400	79.89	72.20
7	6	400	79.87	72.15
8	6	200	79.70	72.24
9	5	500	79.42	71.03
10	4	400	79.35	70.83
11	4	500	79.39	70.31
12	3	600	79.07	70.06

Spencer et al., *IEEE Transactions on Computational Biology and Bioinformatics*, 2014.

Deep Learning for Secondary Structure Prediction Project (2nd project)

- Training dataset with sequences and secondary structures (1180 sequences) and test dataset (126 sequences). (training data was created by Pollastri et al. and test data was created by Rost and Sander.) (http://calla.rnet.missouri.edu/cheng_courses/mlbioinfo/ss_train.txt(and ss_test.txt)
- Generate multiple alignments using generate_flatblast.sh in Pspro 1.2 package (http://sysbio.rnet.missouri.edu/multicom_toolbox/tools.html)

Secondary Structure Prediction Project (continued)

- Generate inputs and outputs (probability matrix or Position Specific Scoring Matrix)
- Develop a deep learning method (e.g. convolutional/recurrent neural network to predict contacts)
- Test the method on test dataset

References for the Project:

- B. Rost and C. Sander. Combining Evolutionary Information and Neural Networks to Predict Protein Secondary Structure. *Proteins*. 1994.
- D.T. Jones. Protein Secondary Structure Prediction Based on Position-Specific Scoring Matrices. *JMB*. 1999.
- G. Pollastri, D. Przybylski, B. Rost, and P. Baldi. Improving the prediction of protein secondary structure in three and eight classes using recurrent neural networks and profiles. *Proteins*. 2002
- J. Cheng, A. Randall, M. Sweredoski, and P. Baldi. SCRATCH: a protein structure and structural feature prediction server. Nucleic Acids Research. 2005.
- Spencer, Matt, Jesse Eickholt, and Jianlin Cheng. "A deep learning network approach to ab initio protein secondary structure prediction." *IEEE/ACM transactions on computational biology and bioinformatics (TCBB)* 12.1 (2015): 103-112
- Wang, Sheng, et al. "Protein secondary structure prediction using deep convolutional neural fields." *Scientific reports* 6 (2016): 18962

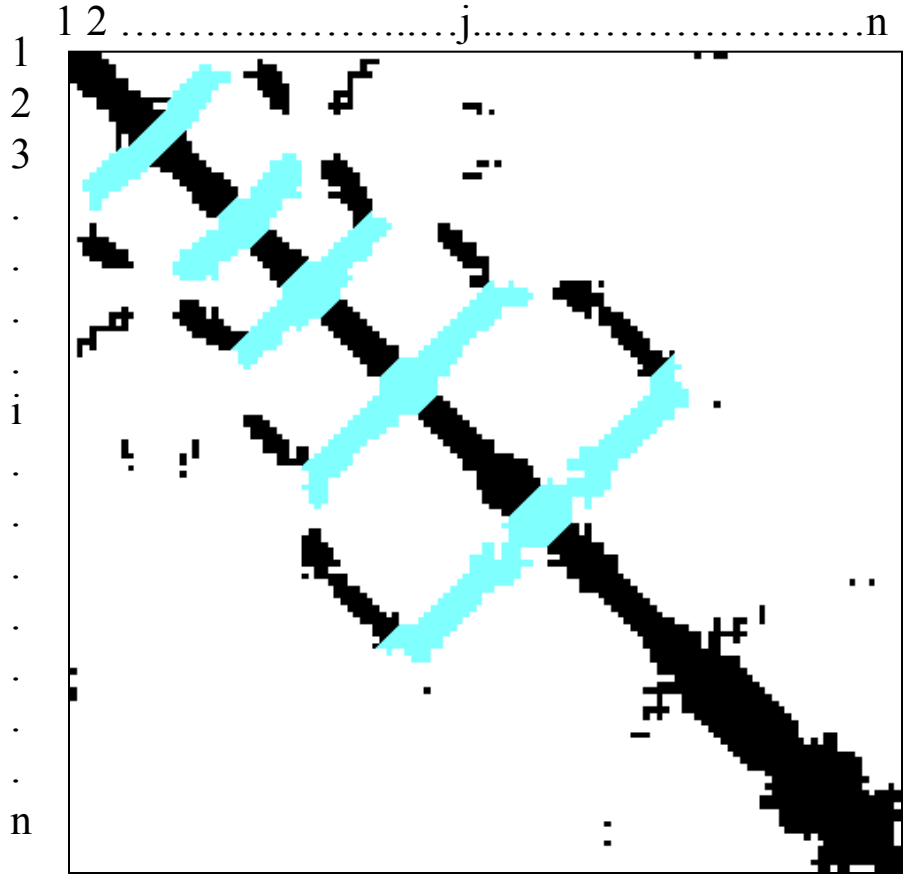
2D: Contact Map Prediction

3D Structure

2D-Recursive Neural Network

Support Vector Machine

2D Contact Map



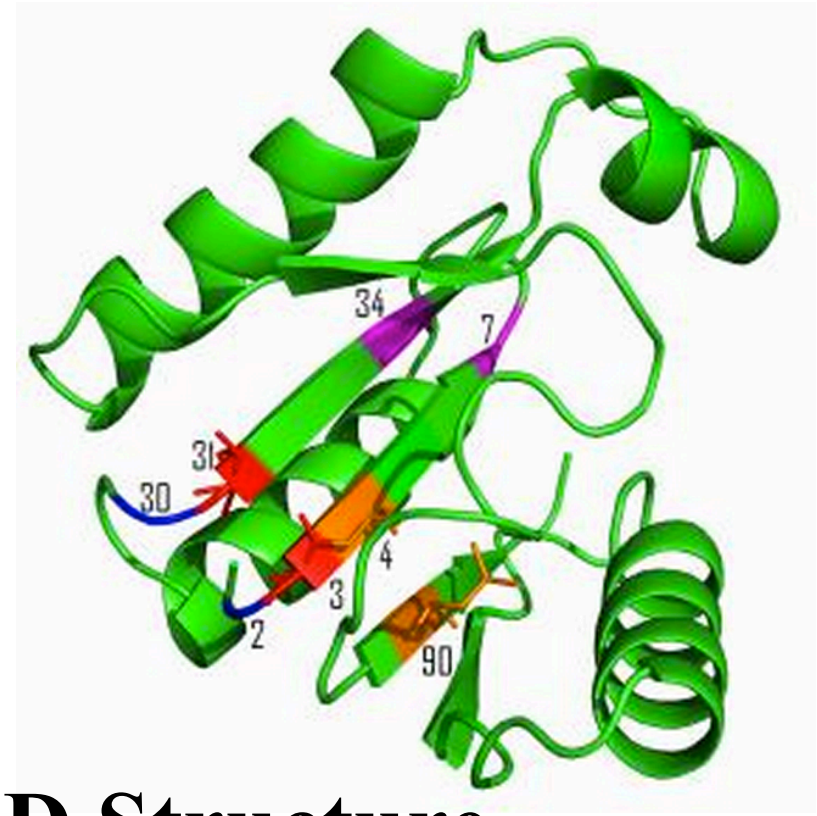
Distance Threshold = 8A°

Cheng, Randall, Sweredoski, Baldi. *Nucleic Acid Research*, 2005
Cheng and Baldi. *BMC Bioinformatics*, 2007.

Residue-Residue Contact Prediction

1D Sequence

SDDEVYQYIVSQVKQYGIEPAELLSRKYGDKAKYHLSQRW



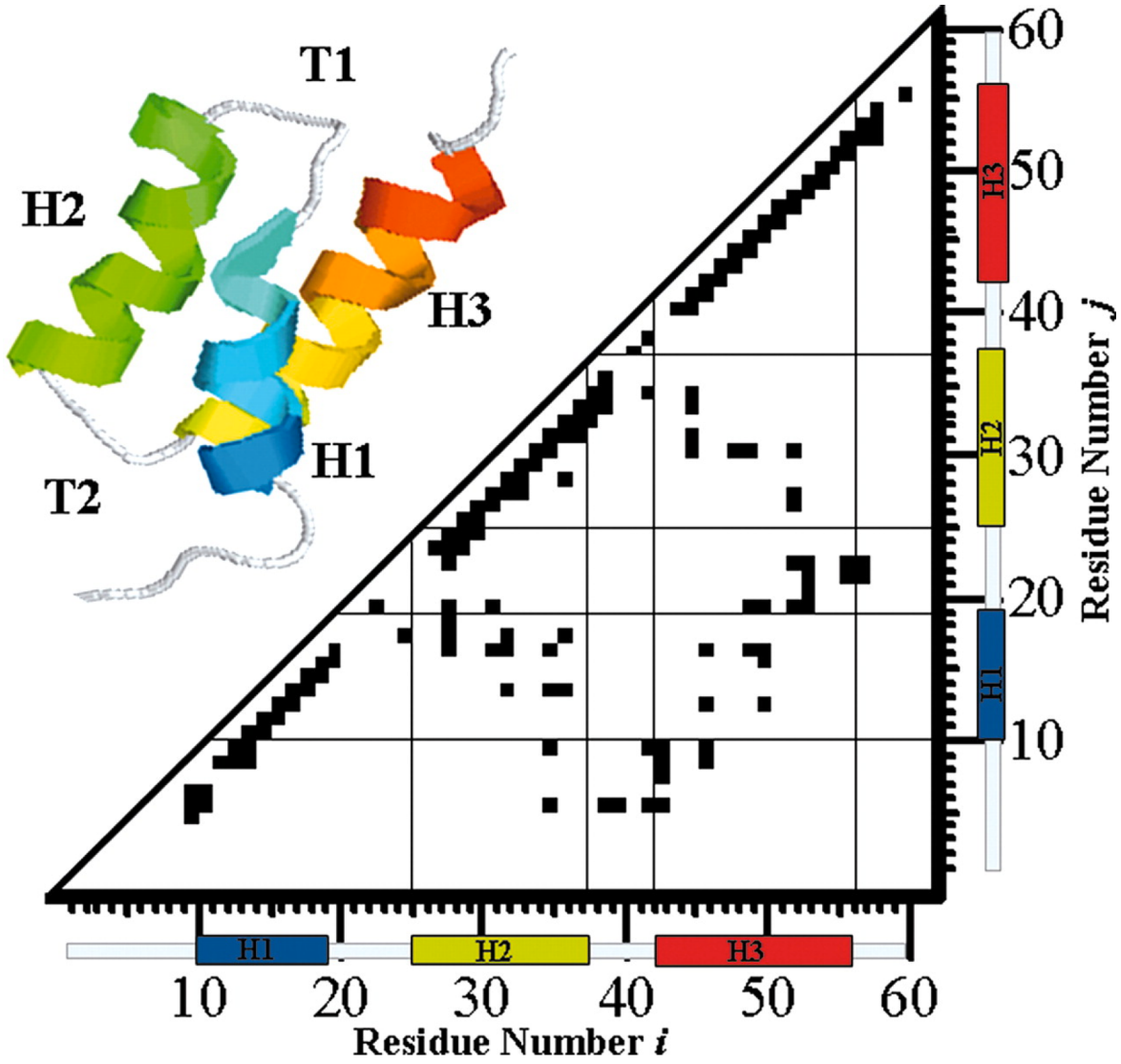
3D Structure

Objective:

Predict if two residues (*i*, *j*) are in contact (spatially close), i.e. distance(i, j) < 8 Angstrom

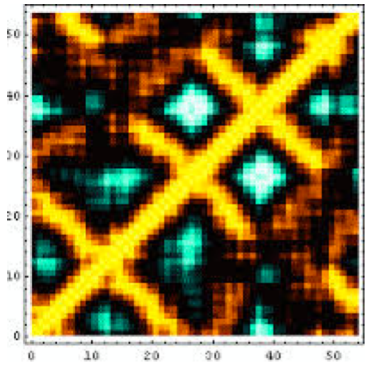
Eickholt & Cheng, 2012

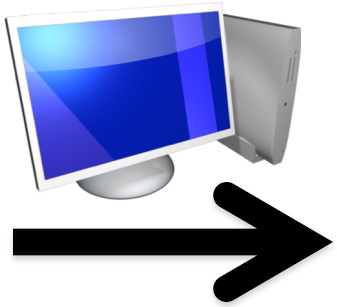
Visualization of Contact Map



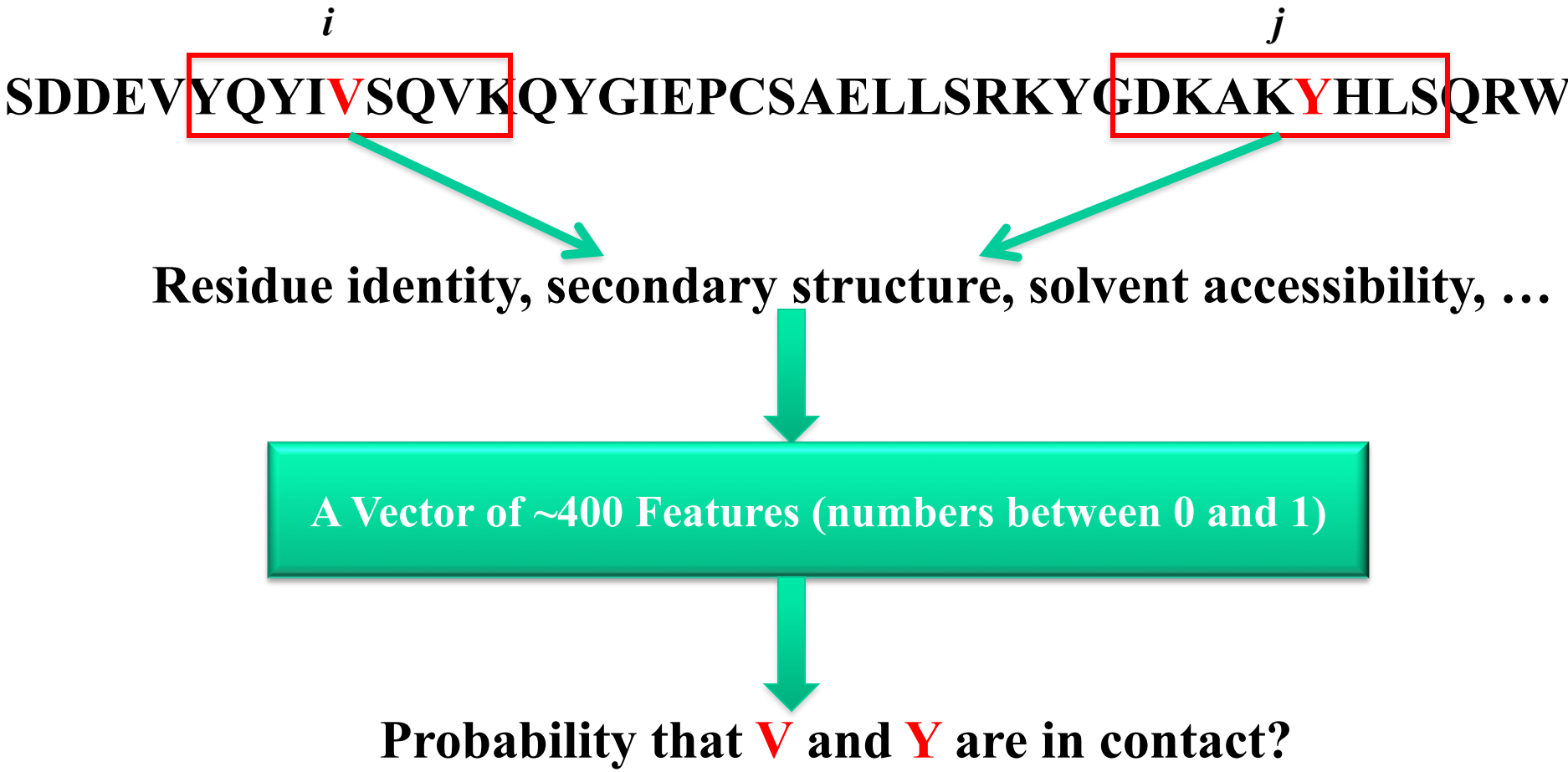
Itoh, Sasao, 2006

Contact-Based Structure Prediction





A Binary Classification Problem



Cheng & Baldi, 2007; Tegge et al., 2009; Eickholt & Cheng, 2012

Input Features

i *j*

SDDEVYQYIVSQVKQYGIEPCSAELLSRKYGDKAKYHLSQRW

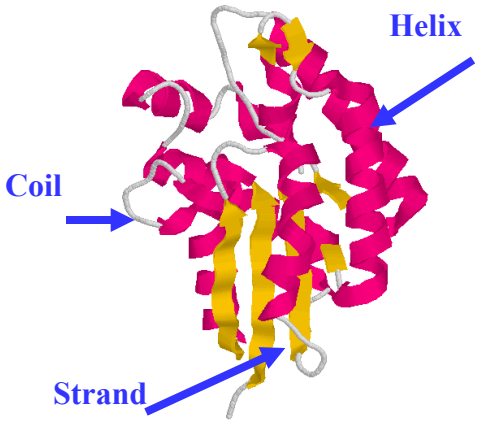
20 binary numbers

A 10000000000000000000
C 01000000000000000000
D 00100000000000000000

.
.
.
.
.
.
.
.

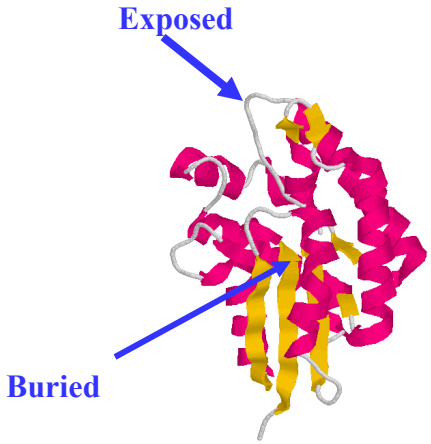
Y 00000000000000000001

3 numbers



Helix 100
Strand 010
Coil 001

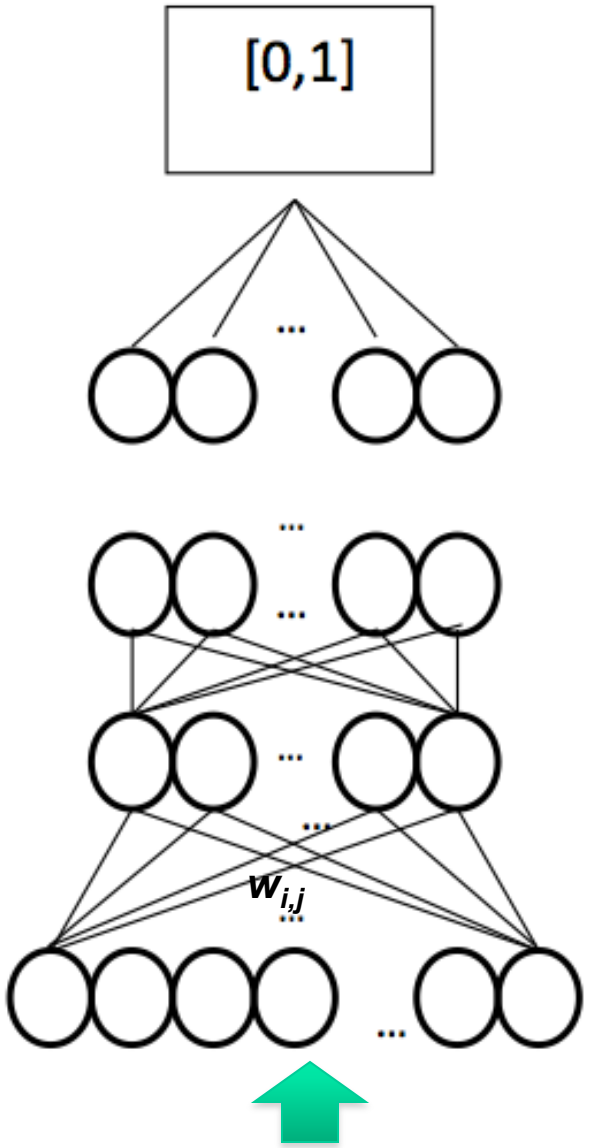
2 numbers



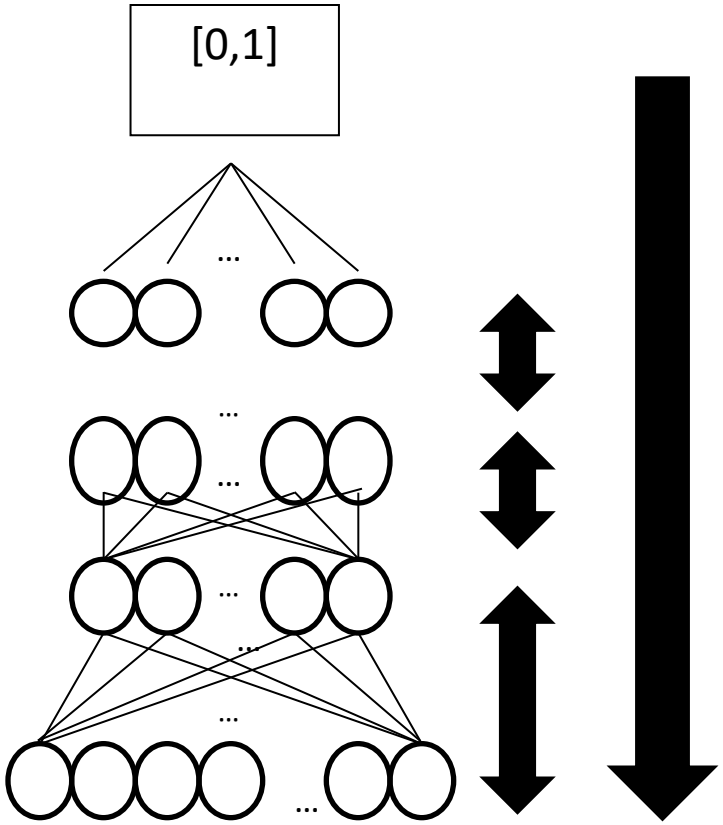
Exposed 10
Buried 01

25 * 18 = 400 features for a pair (*i*, *j*)

Deep Learning Network Architecture

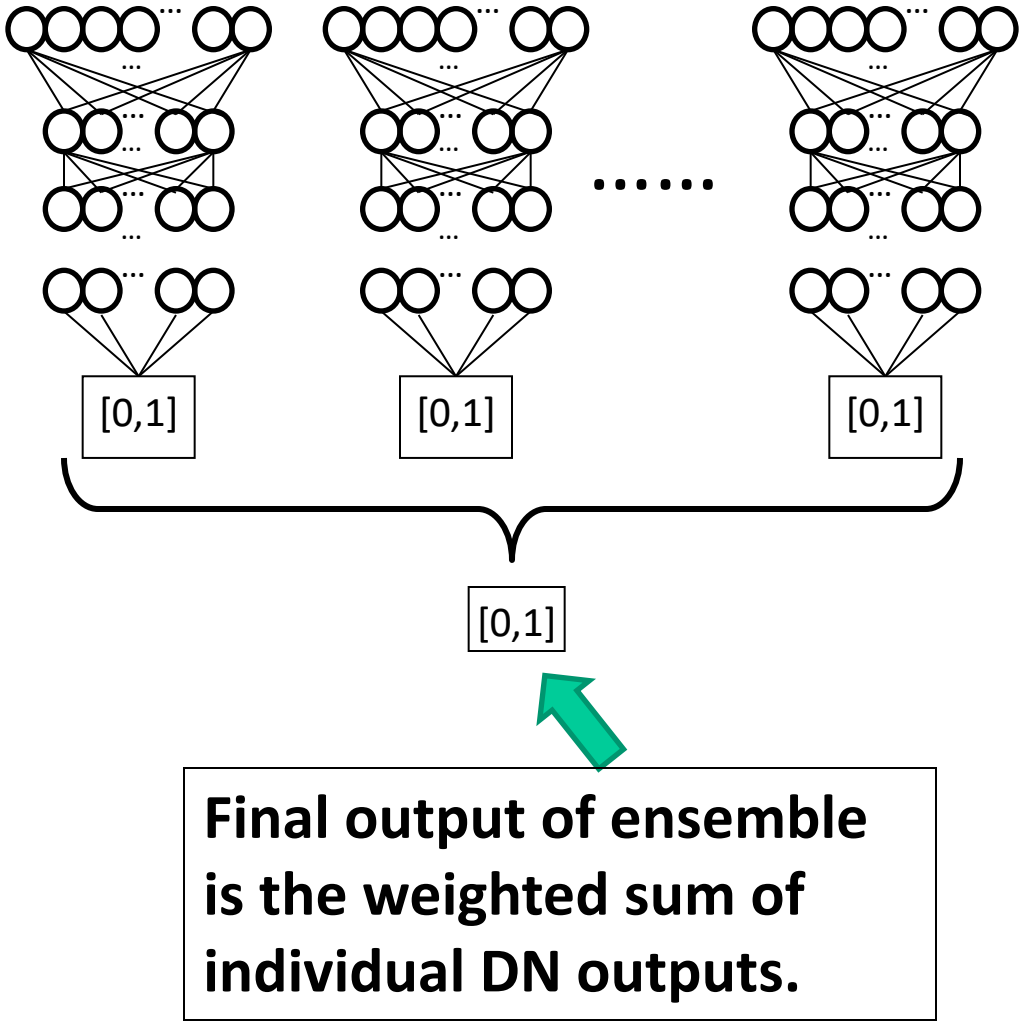


Training a Deep Network



1239 Proteins for Training
Residue Pairs (|i-j| >= 6);
Millions of Residue Pairs

Boosted Ensembles for Contact Prediction



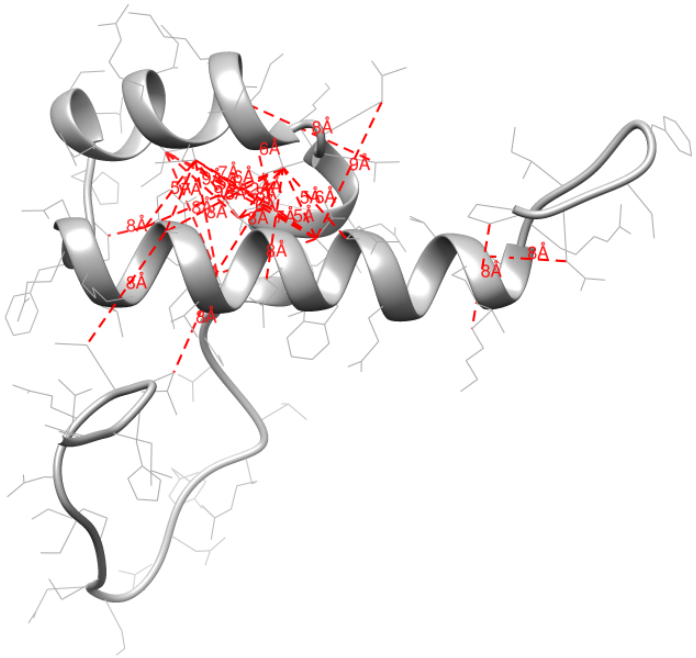
Final output of ensemble is the weighted sum of individual DN outputs.

Eickholt and Cheng, *Bioinformatics* (2012)

Results on Test Data Set (196 Proteins)

Metric	Acc. L/5	Acc. L/5 (one shift)
Short Range (6 <= |i-j| <12)	0.51	0.79
Medium Range (12 <= |i-j| <24)	0.38	0.65
Long Range (|i-j| >= 24)	0.34	0.55

An Example:

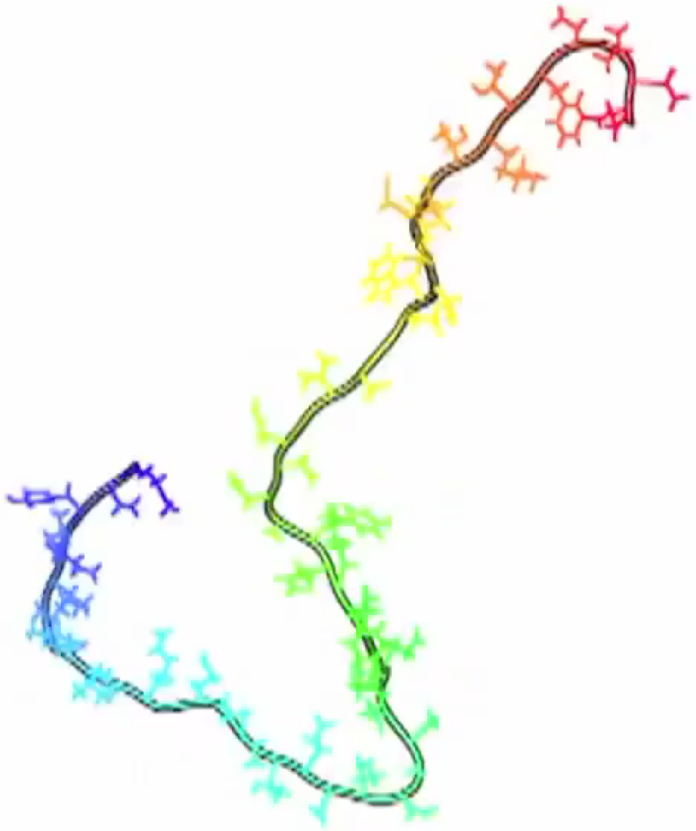


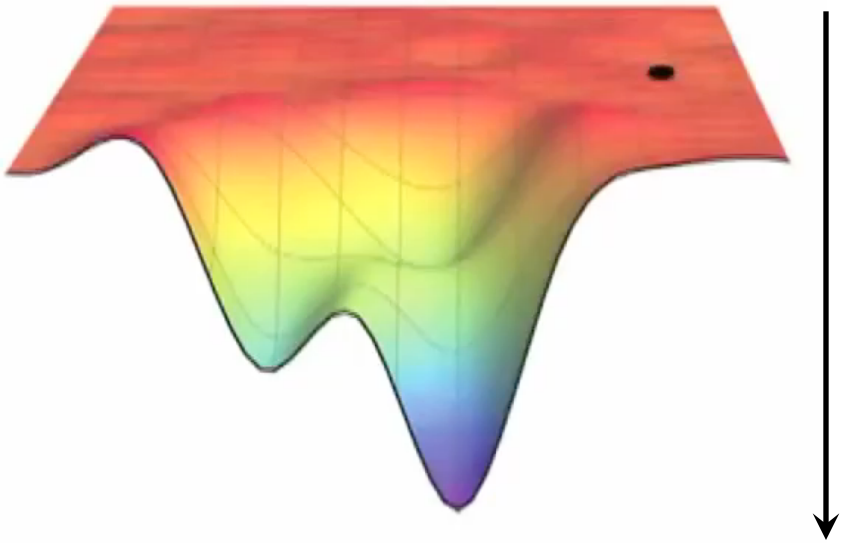
Blind Test on CASP10 Targets

Exact match (96 proteins, long-range contacts)

Method	Acc. L/5
DNcon	**0.30**
SVMcon	0.19

→ 9-fold better than random

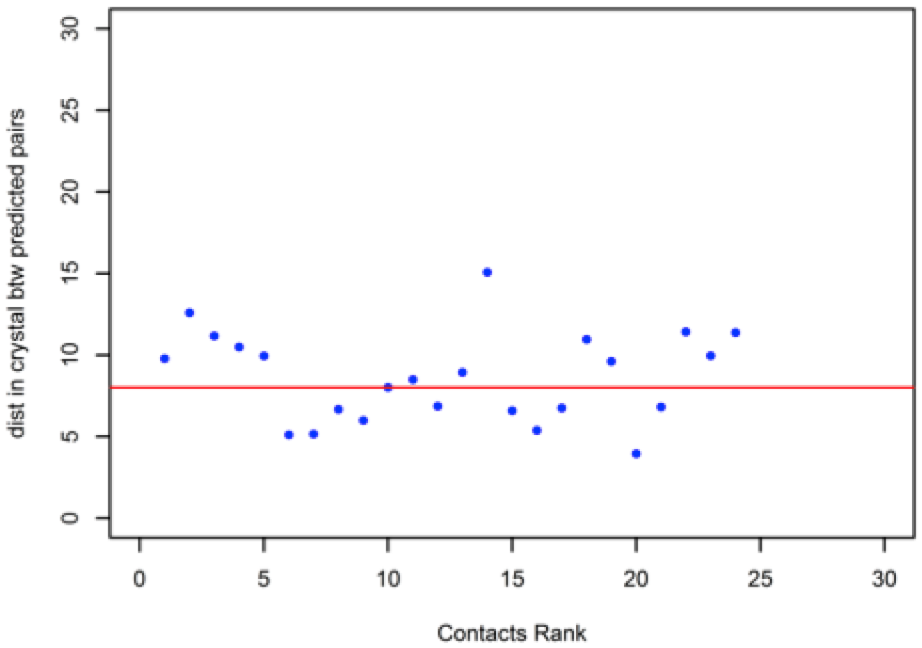


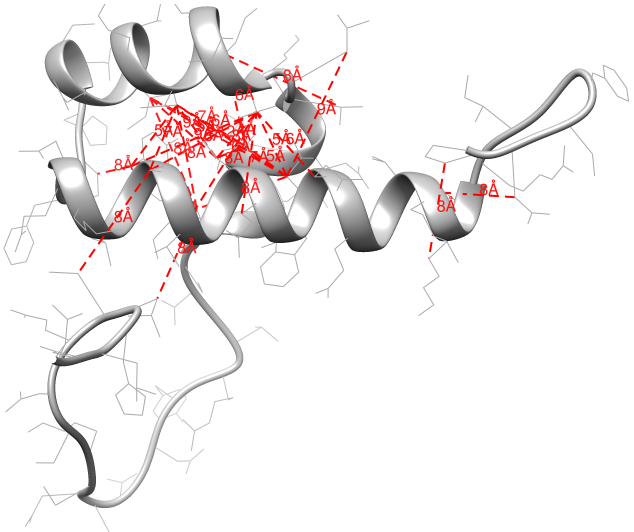


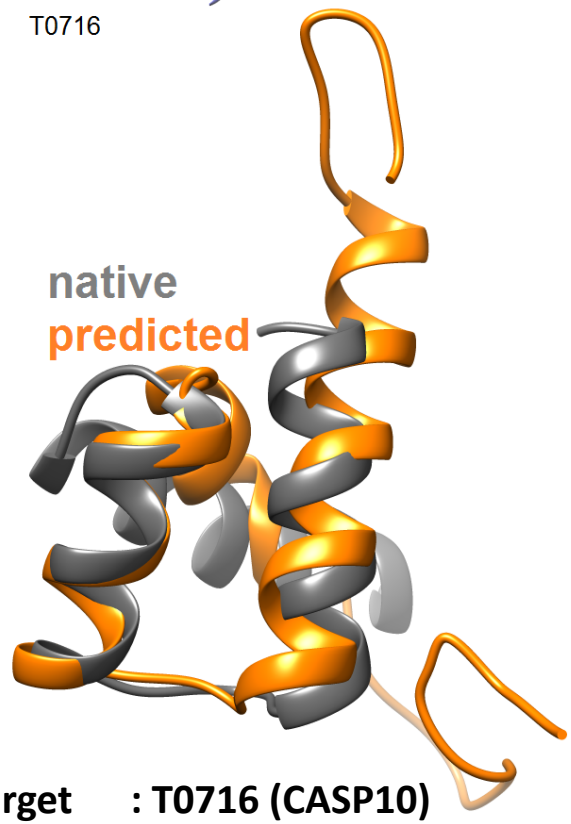
Contact-based energy landscape

Bhattacharya et al., Bioinformatics, 2016.

3D Reconstruction from Predicted Contacts (CASP Target T0716)







Target : T0716 (CASP10)

Length : 71

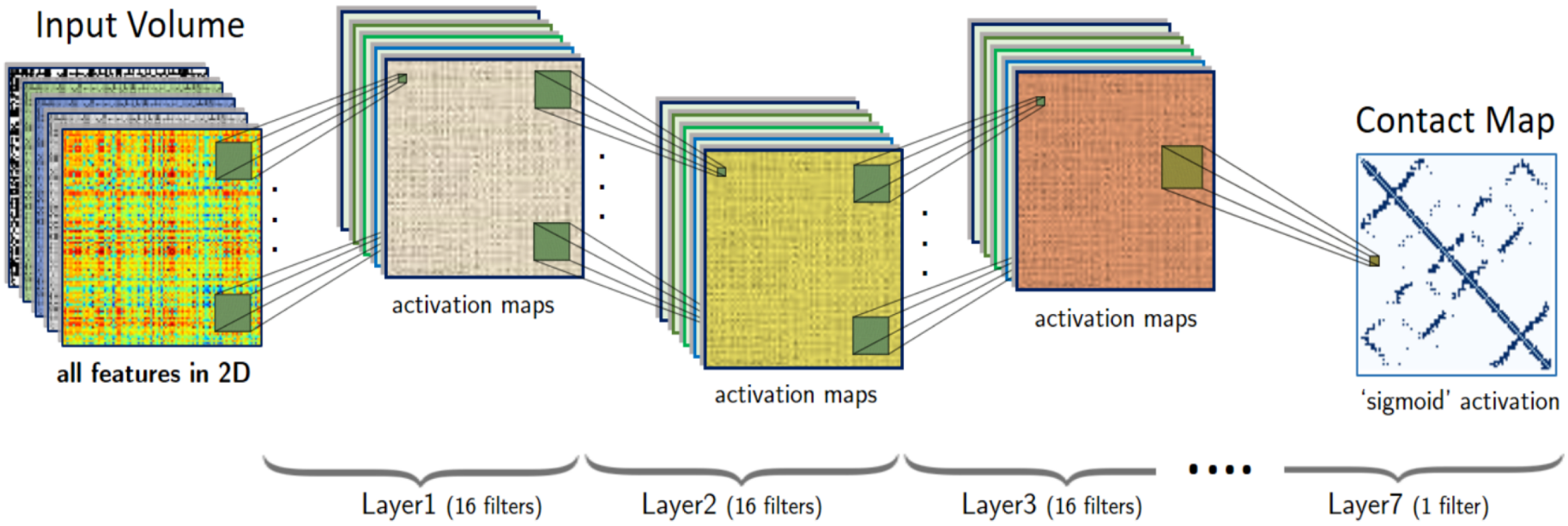
RMSD : 4.3A

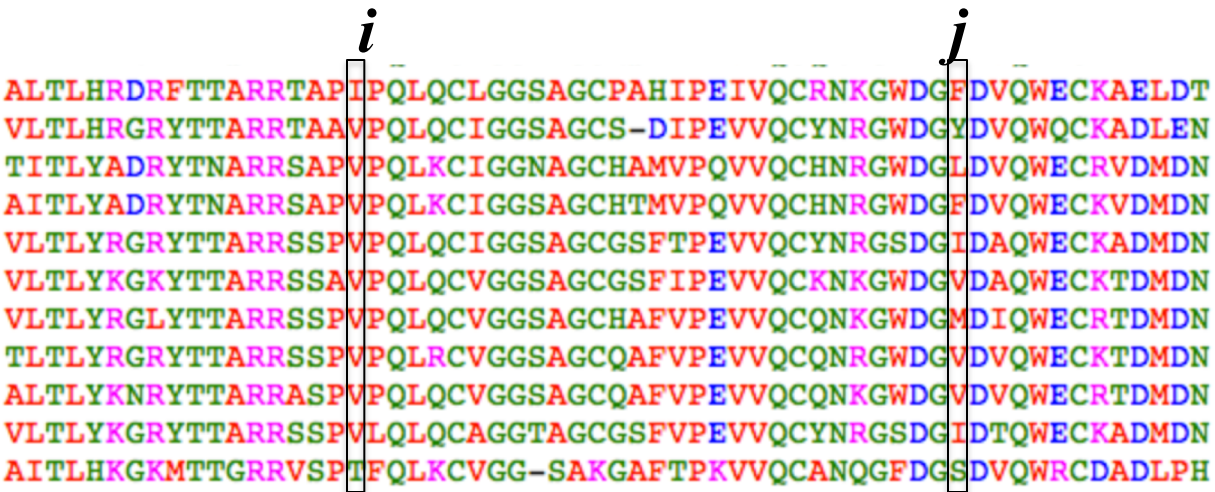
GDT-TS : 0.58

Contacts : DNcon (filtered and selected 0.4L)

Adhikari et al., Proteins, 2015

2D Convolutional Network for Contact Prediction



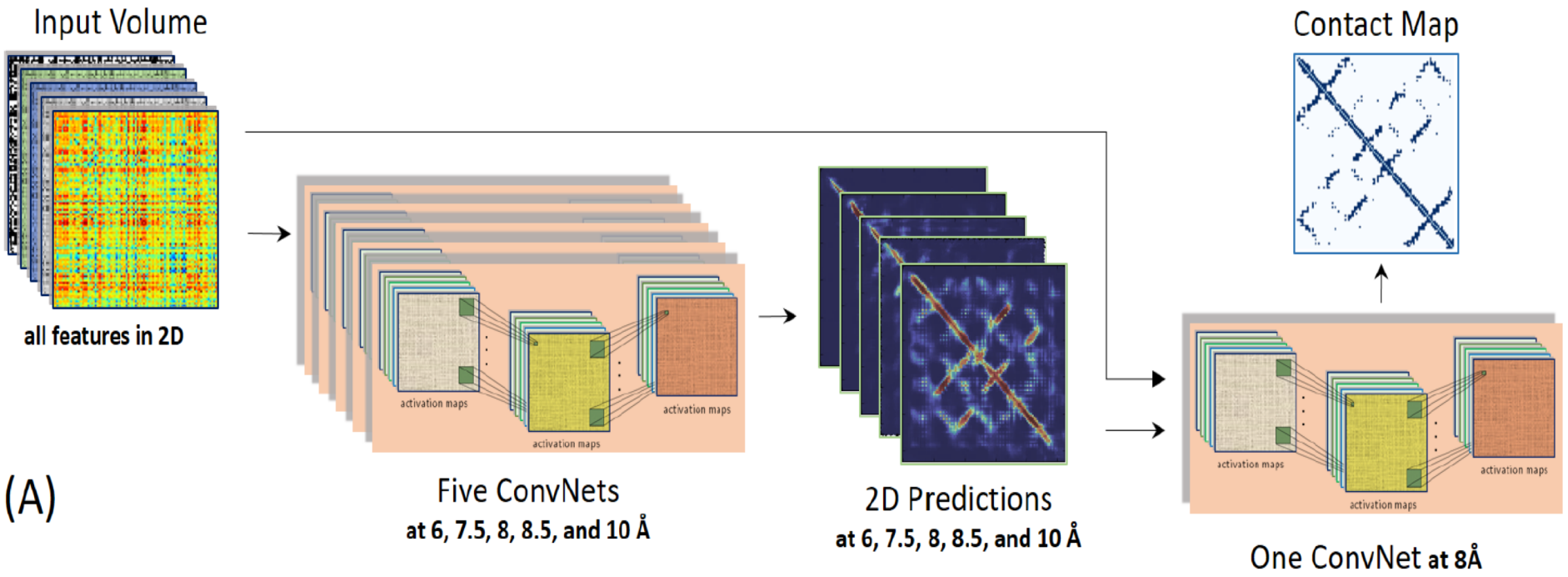


Input Matrix

- **Co-evolution**
- Mutation information
- Secondary structure
- Solvent accessibility
- …

Adhikari et al., 2017

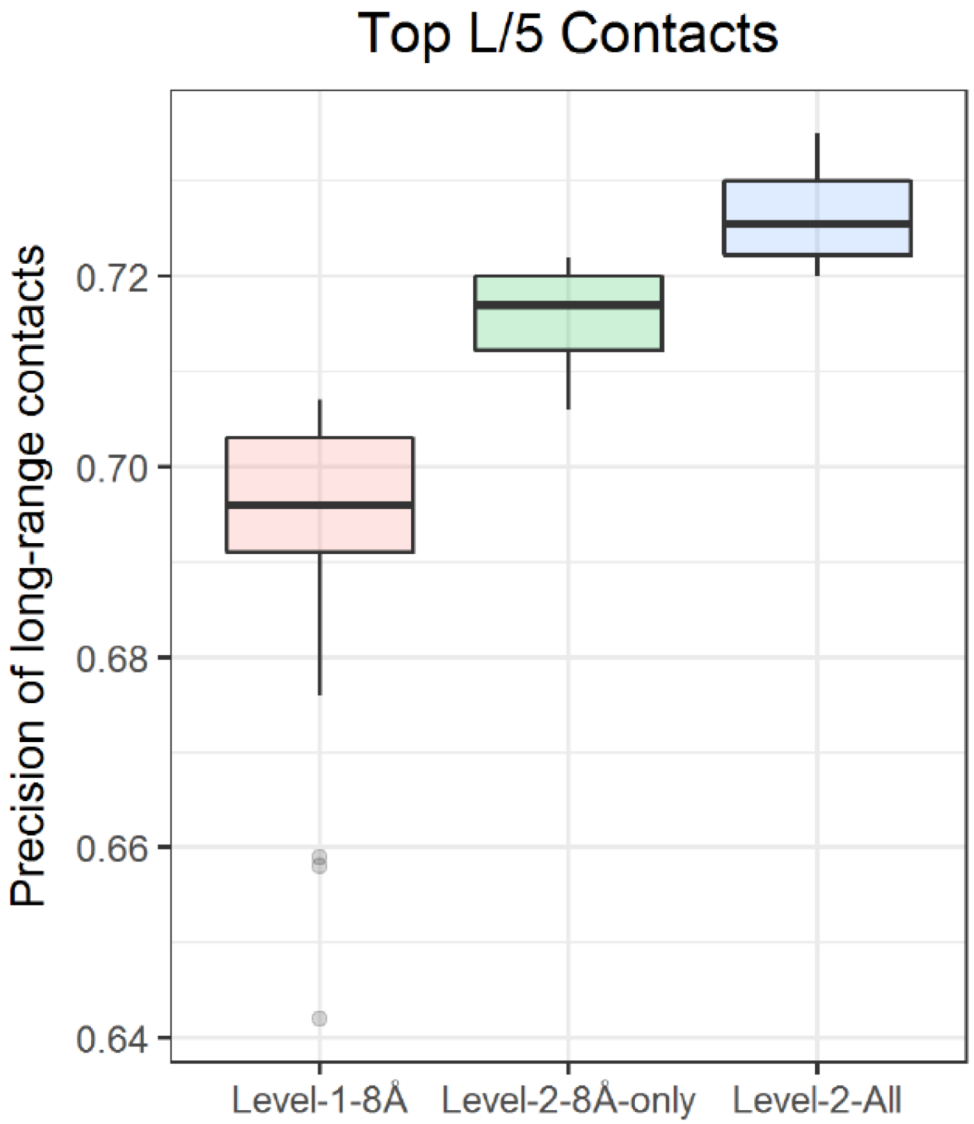
Two-Level Deep Convolutional Neural Networks



- **Training on 1426 proteins**
- **196 proteins validation dataset**
- **CASP10 dataset, CASP11 dataset, and CASP12 dataset**
- **Keras and TensorFlow**
- **Tesla K20 Nvidia GPUs**

Adhikari et al., 20

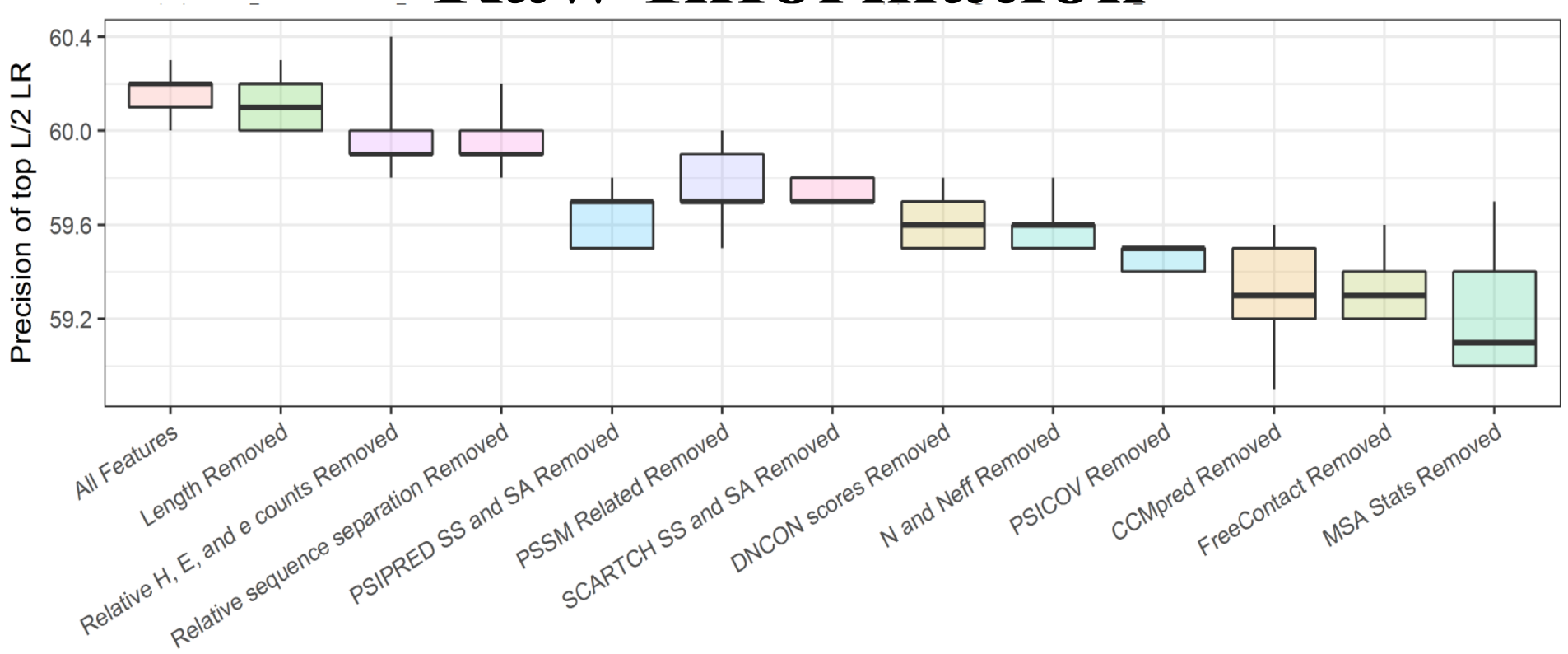
Impact of Two-Level Network



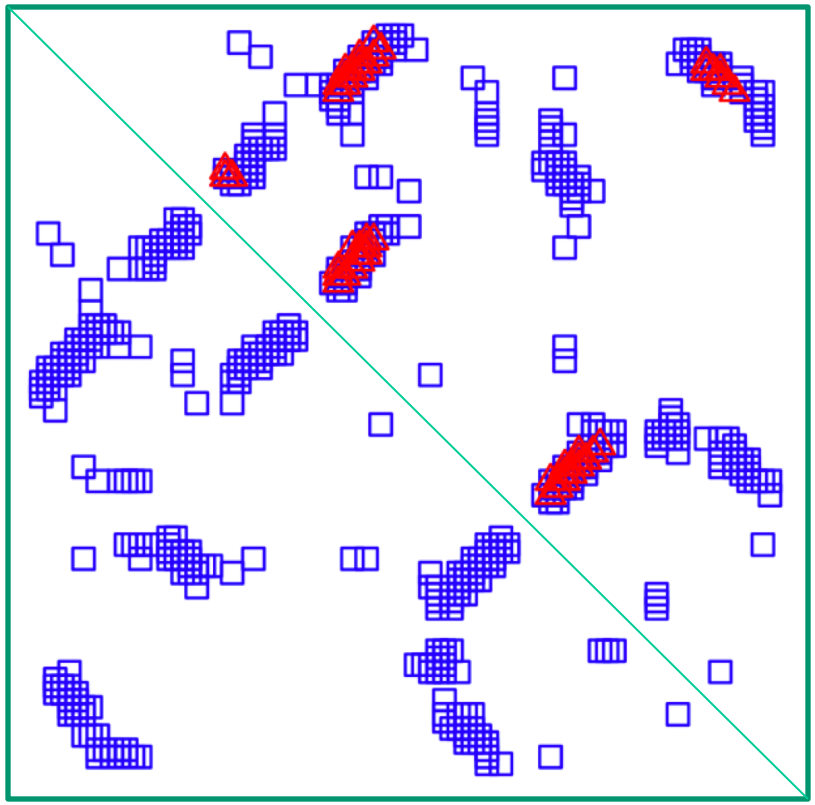
Testing on CASP Datasets

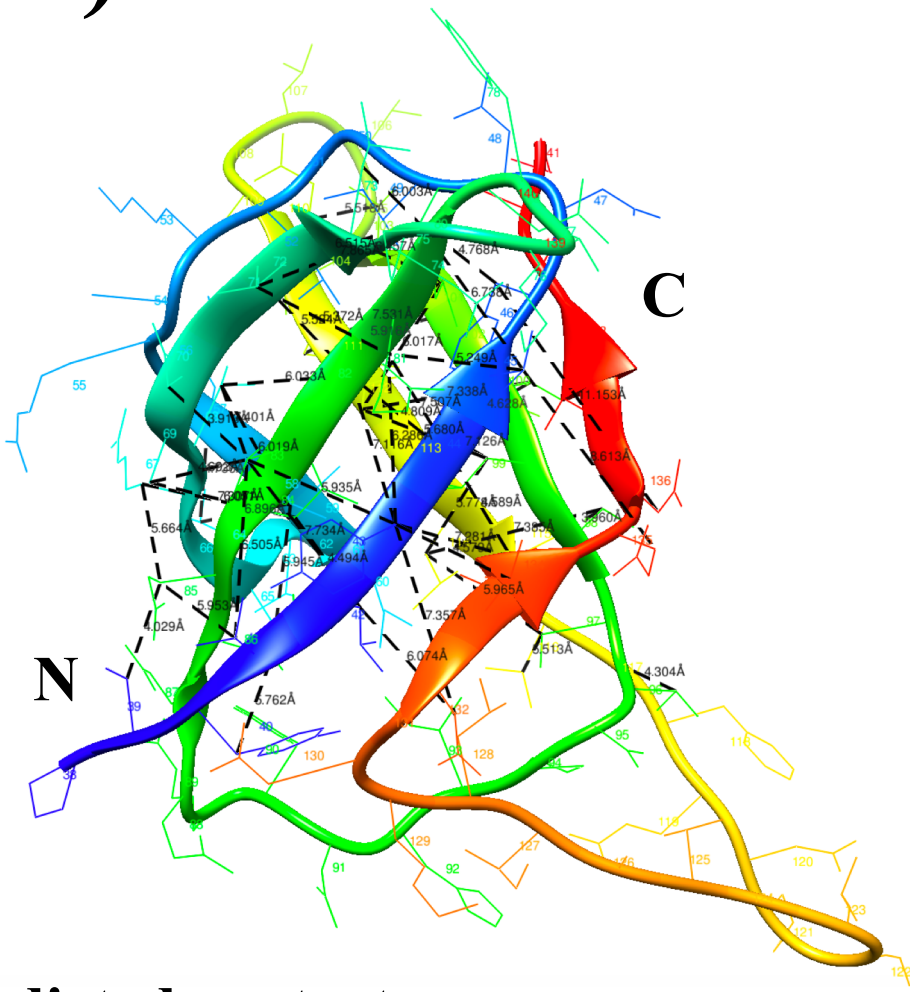
FM Dataset	Domain Count	Precision of top L/5 long-range contacts (%)		
		Top CASP Group	MetaPSICOV	DNCON2
CASP10	15	18.1 (DNCON 1.0)	30.6	35.0
CASP11	30	29.7 (CONSIP2)	34.4	50.0
CASP12	37	46.3 (Raptor-X)	42.9	53.4

Impact of Multiple Sources of Raw Information



CASP12 T0866-D1 (Length = 104)





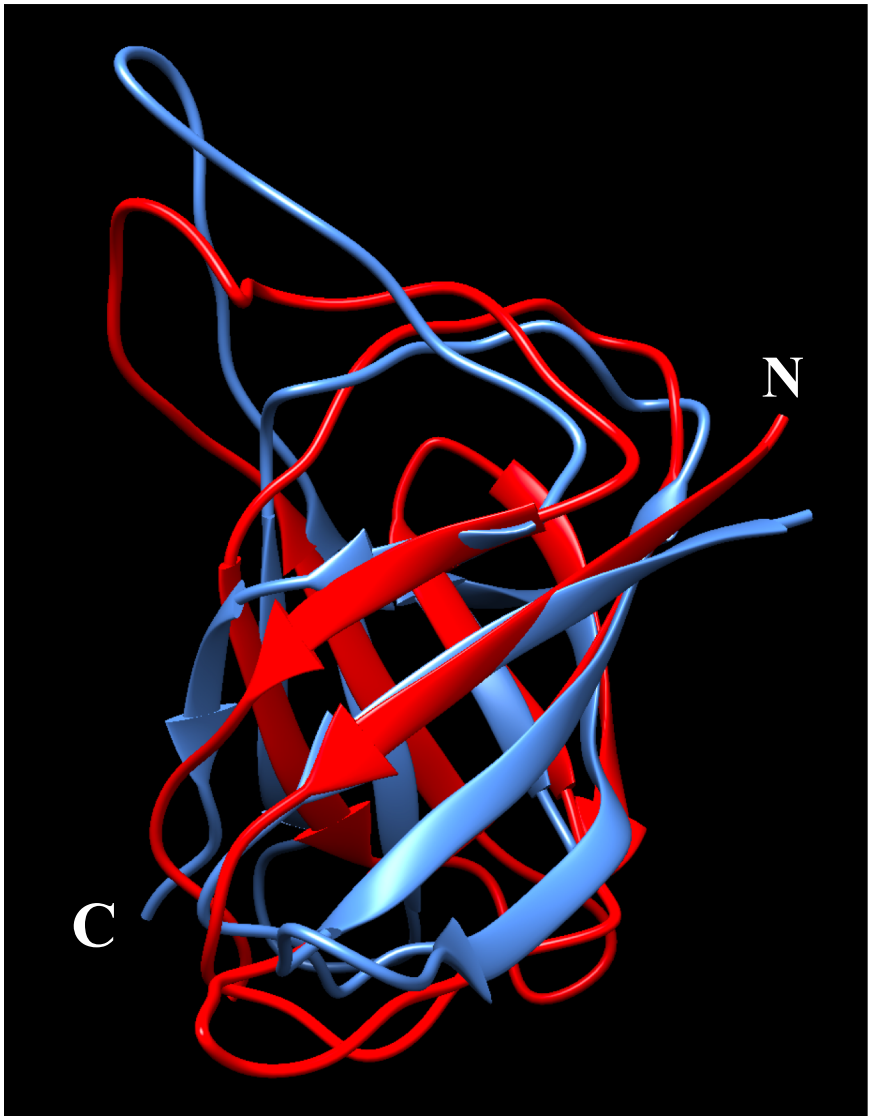
Blue: true contacts

Red: top L/2 = 50 predicted contacts

Precision: 96%

Coverage: 21%

3D Reconstruction from Predicted Contacts



RMSD of Core: 2.3 Å

TM-score: 0.67

Modeling Tool: CONFOLD

Blue: true structure
Red: predicted model

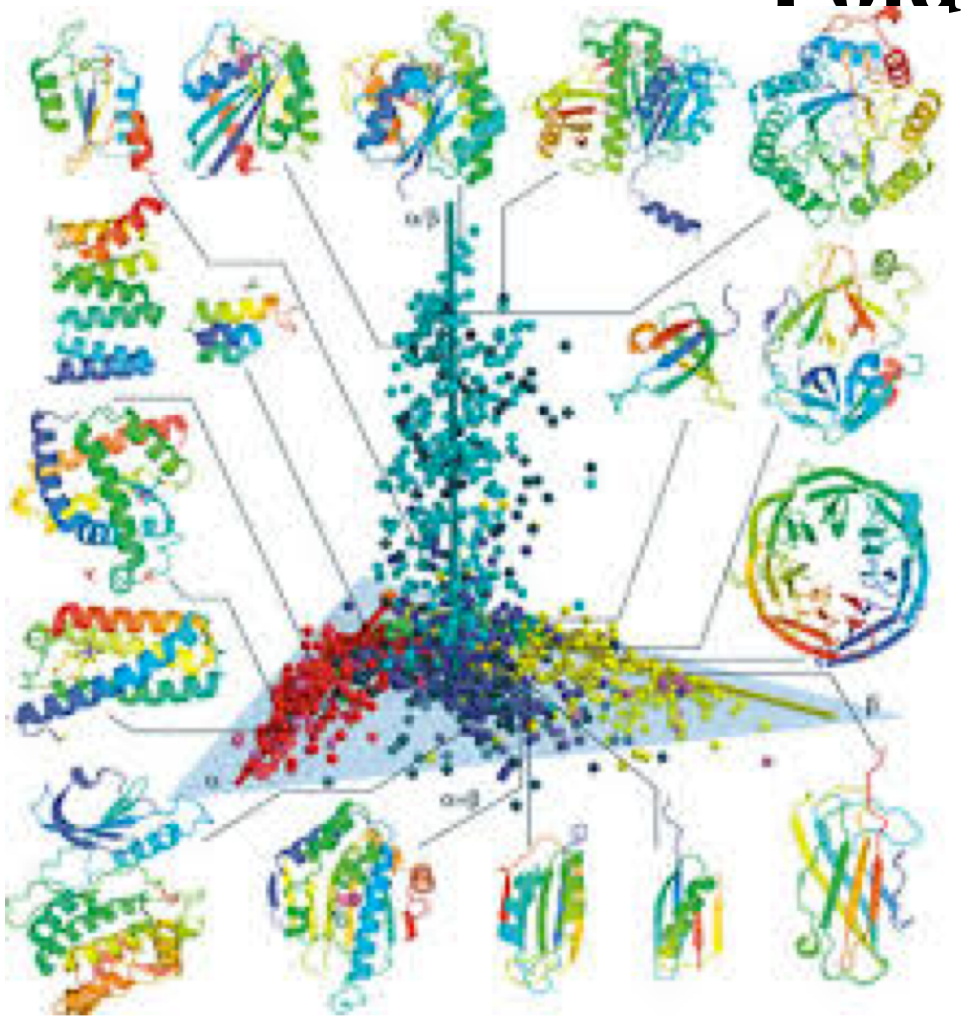
Project 3: Deep Learning for Residue-Residue Contact Prediction

- DNCON2 source code: https://github.com/multicom-toolbox/DNCON2
- Data set: http://sysbio.rnet.missouri.edu/multicom_toolbox/datasets.html
- Develop a simple deep convolutional network to predict protein contacts

1D Deep Convolutional Neural Network for Protein Fold Classification

Hou et al., Bioinformatics, 2

Sequence-Structure Relationship (Millions of Sequences, but Only Thousands of Folds)



SCOP database: ~1,200 folds

A central problem:

- **Can we directly map protein sequence (language) into folds (semantics)?**

Similar problems:

- **Image Recognition**
- **Natural Language Processing**

Limitation of Existing Methods

- **Sequence alignment (PSI-BLAST, HHSearch): nearest neighbor, indirect**
- **Ab initio folding: computationally intensive, inaccurate, hard to interpret**
- **Machine learning classification (*f*: sequence → fold): only dozens of classes, fixed window, hand crafted features**

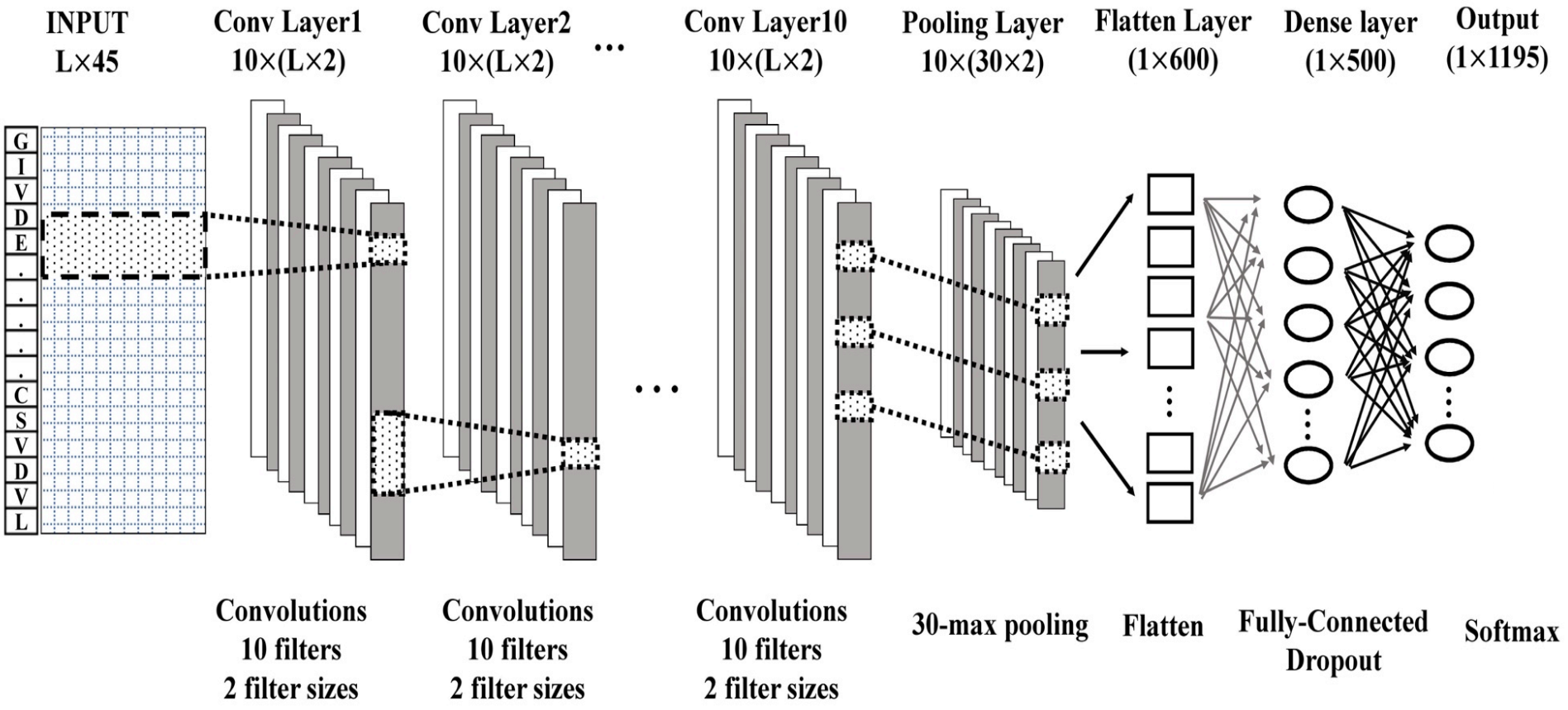
Challenges

- **A very large number of classes (~1,200 folds)**
- **Natural sequence data without informative features**
- **Varied sequence lengths (from dozens to thousands)**

1D Deep Convolutional Neural Network for Fold Classification

- **Classify any protein sequence into thousands of protein folds directly (alignment-free, structure-free)**
- **Automatically extract useful features from sequences of any length**
- **Convert any sequence into hidden semantic features useful for protein comparison, clustering, and structure prediction**

Deep 1D-Convoluational Neural Network



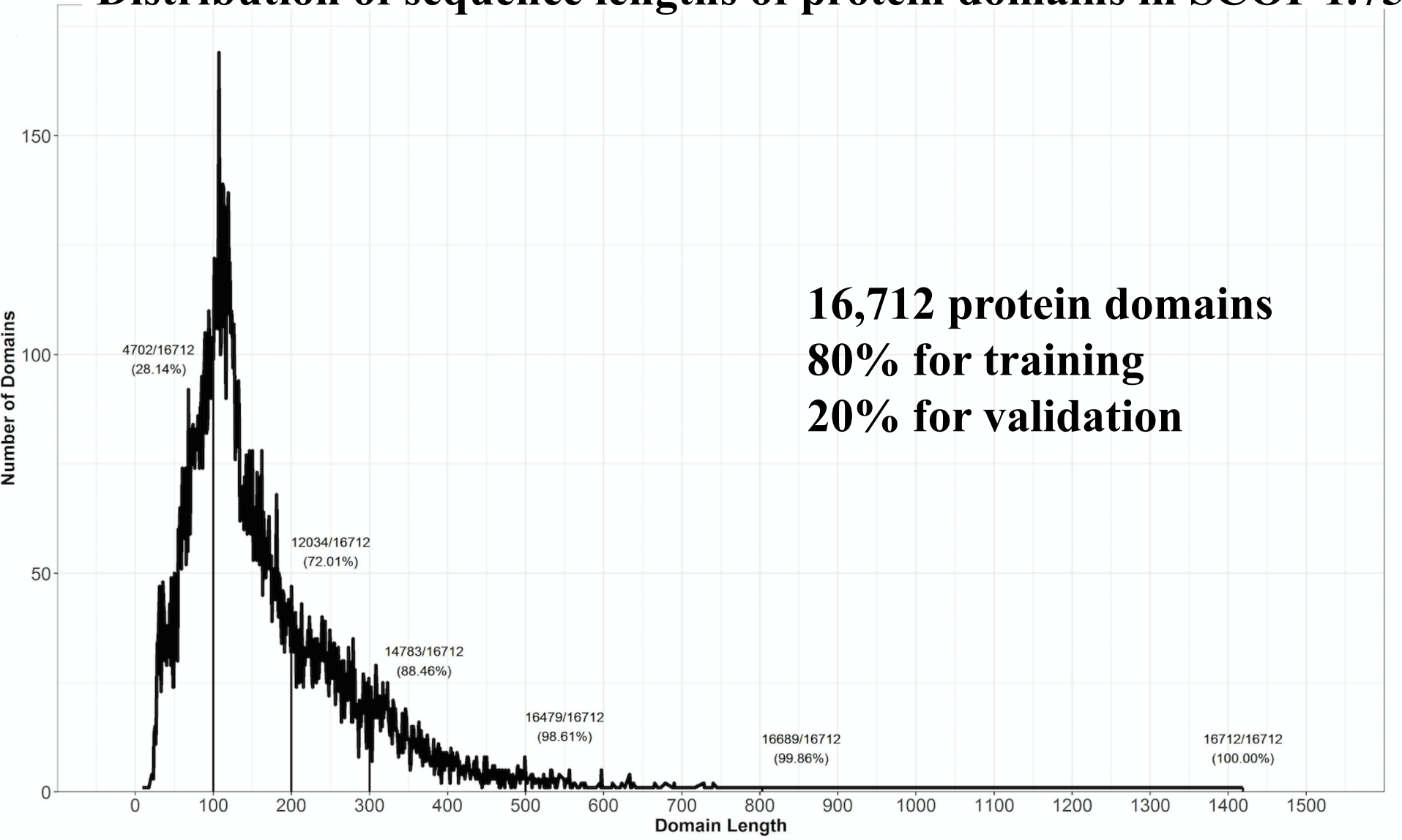
Rectified Linear Unit (ReLU): $f(x) = \max(0, x)$

Output layer: 1,195 nodes with sigmoid function

Hou et al., 20

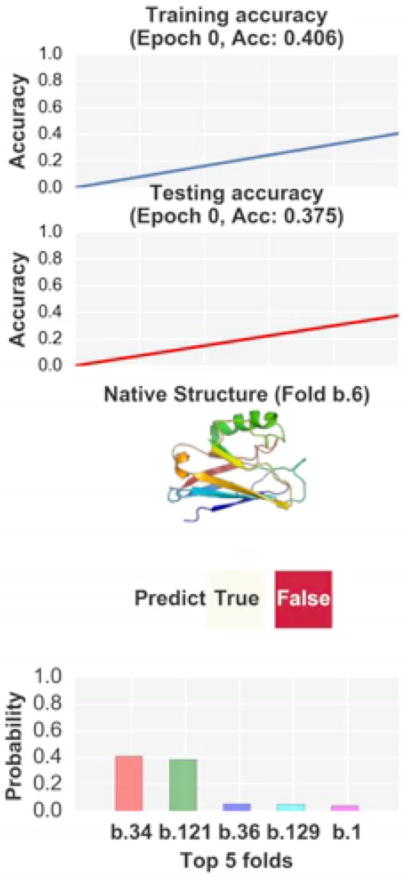
Training and Validation Data

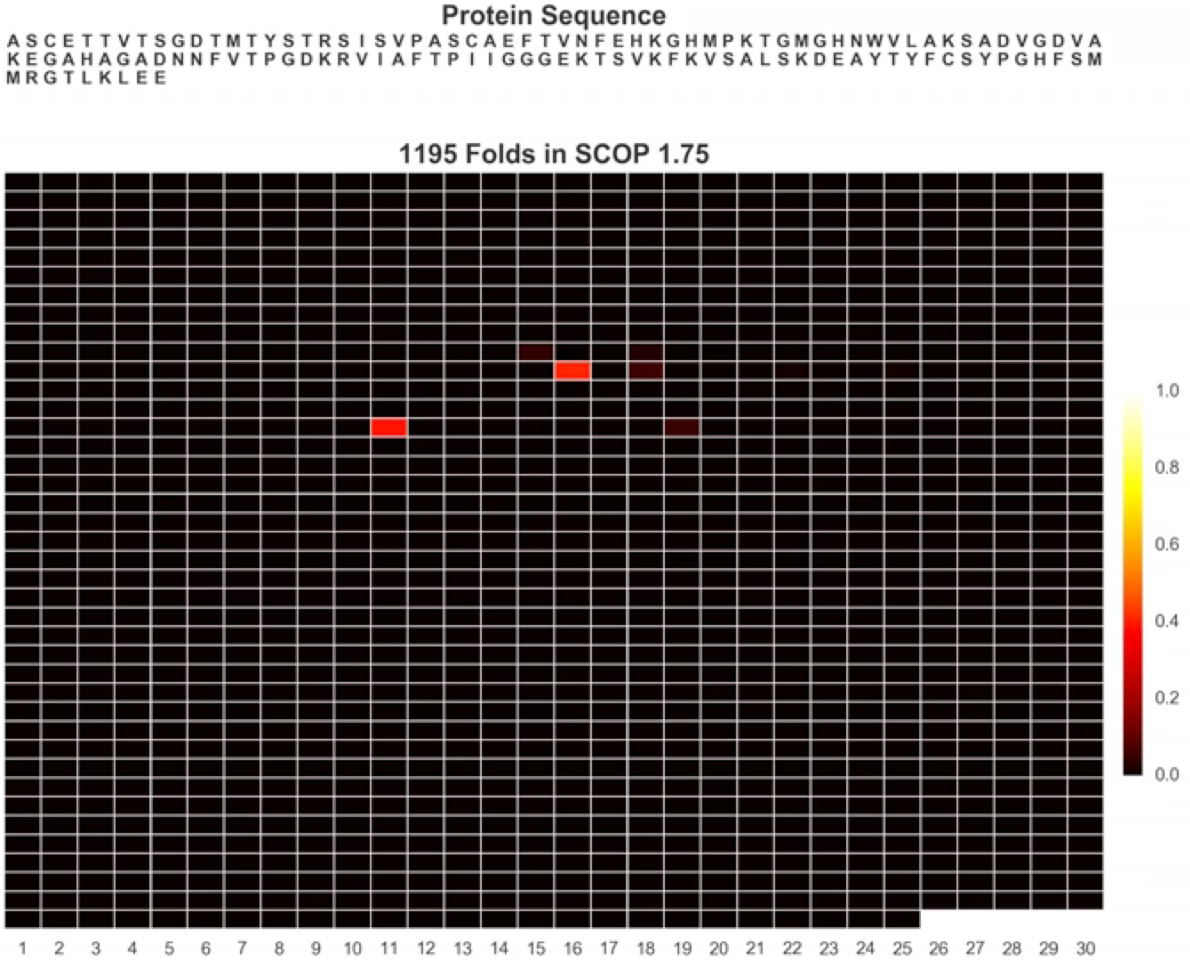
Distribution of sequence lengths of protein domains in SCOP 1.75



16,712 protein domains
80% for training
20% for validation

Demo of Training DCNN





Classification Accuracy on Validation Data

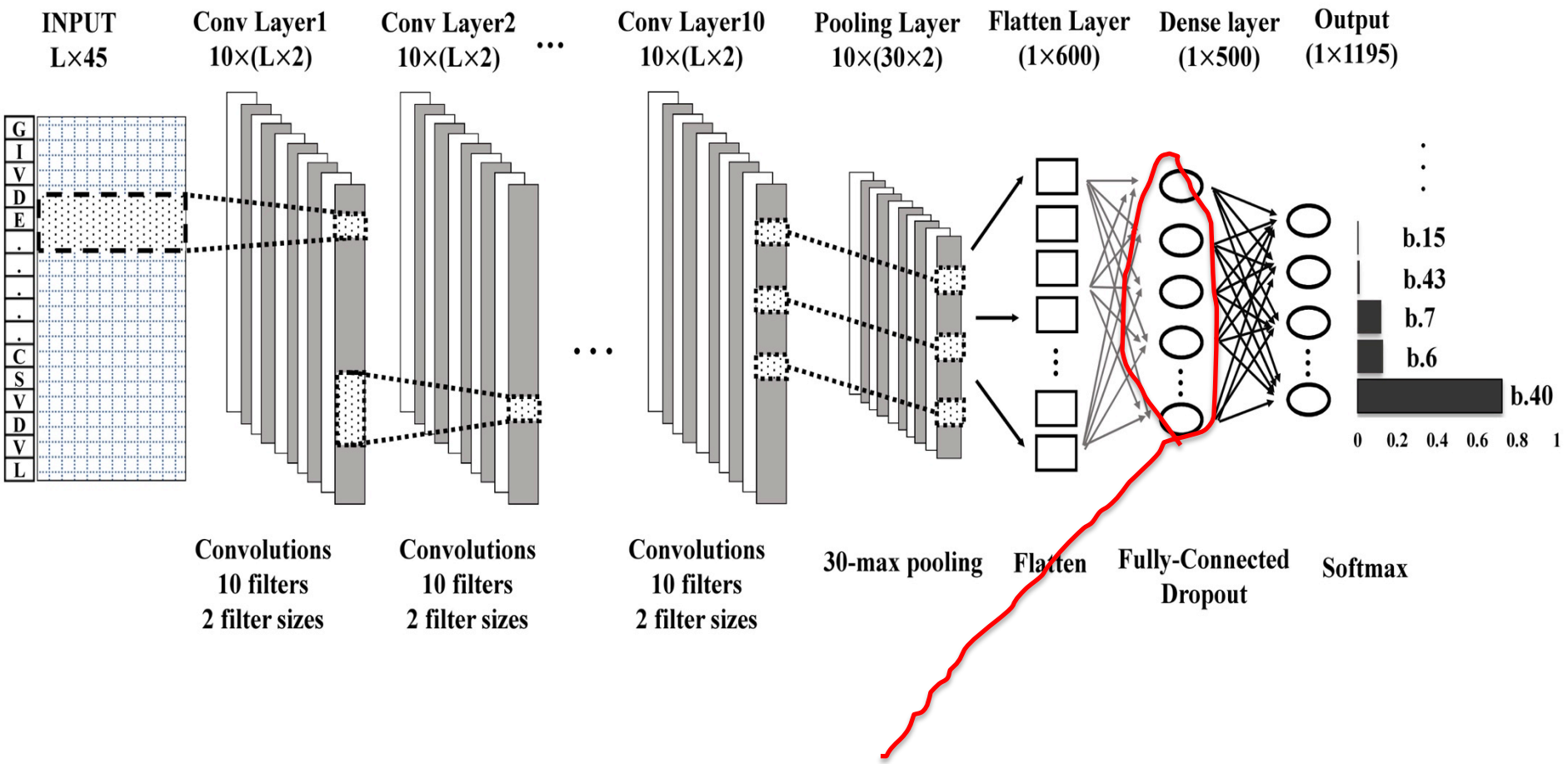
- Average accuracy of **top 1 prediction** on four validation datasets having <95%, 70%, 40%, and 25% identity with the training dataset is **75%**.
- Average accuracy of **top 5 prediction** is **91%**.

Accuracy on Hard Template-based Targets of CASP9-12

88 targets, <10% similarity with SCOP 1.75

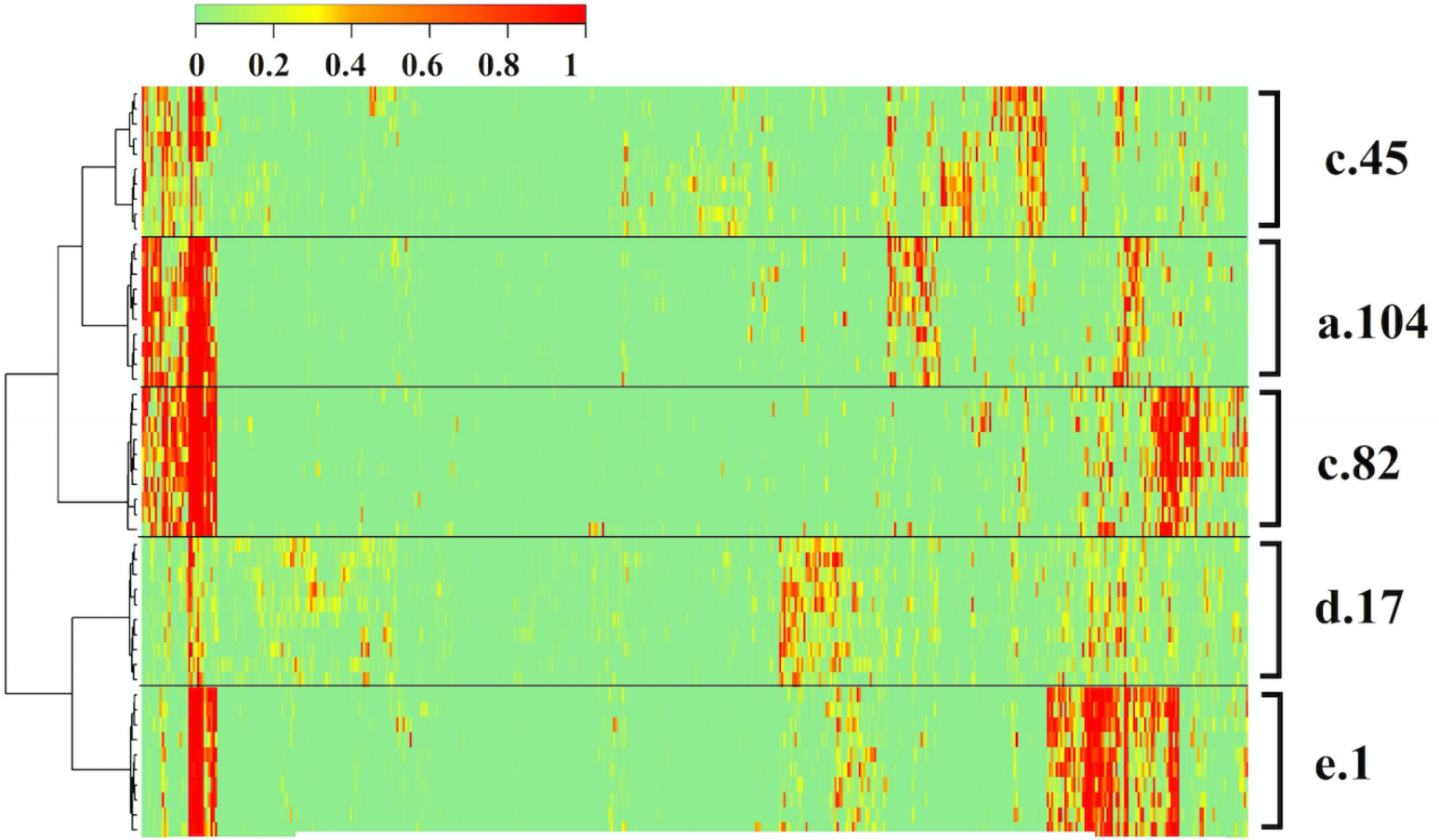
Method	Top1	Top5	Top10
DeepSF	**46.59%**	**73.86%**	**84.09%**
HHSearch	43.20%	61.40%	67.00%
DeepSF + HH	**59.10%**	**77.30%**	**85.20%**
PSI-BLAST	15.90%	31.80%	47.70%

Can the Hidden Features Represent Proteins?



Hidden (Semantic) Features

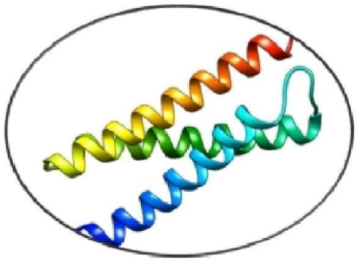
Hidden Features Used for Protein Clustering

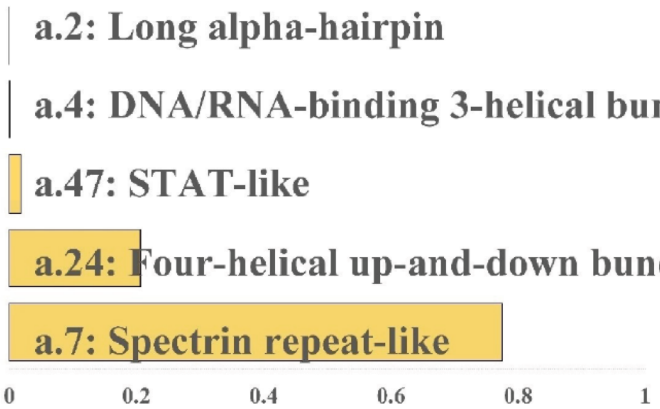


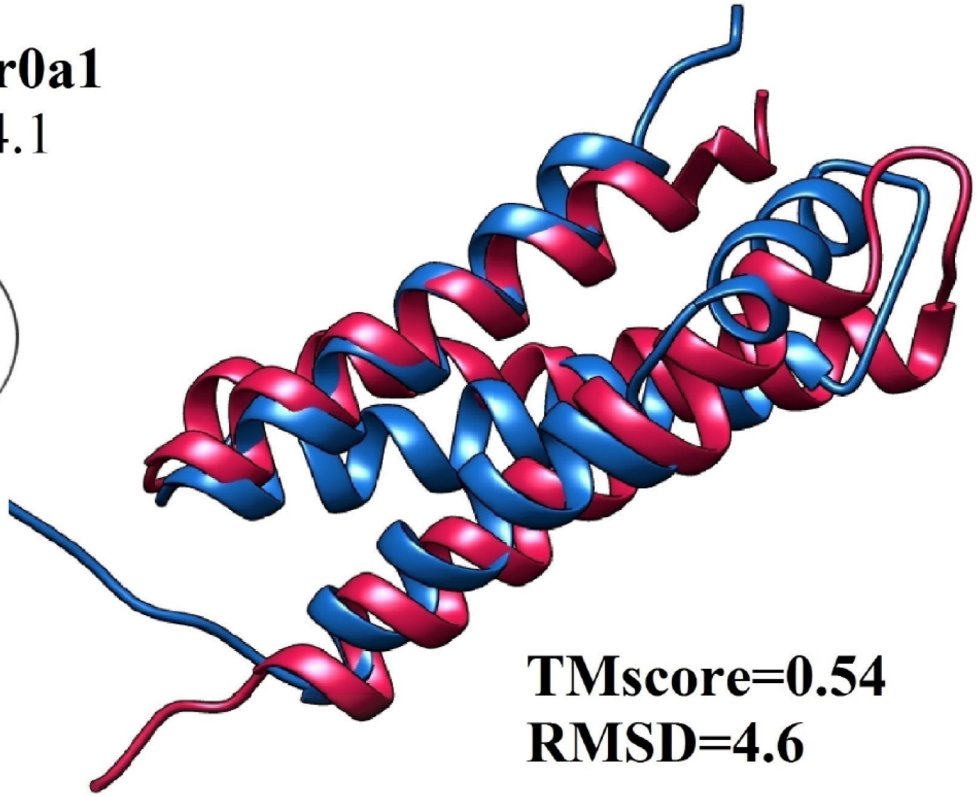
Fold-specific features for domains in fold a.104, c.45, c.82, d.17, e.1

Fold Classification-Assisted Structure Prediction

Template: d1wr0a1
SCOP_id: a.7.14.1







TMscore=0.54
RMSD=4.6

T0862-D1 (DeepSF)

Better than HHSearch model (TMscore = 0.3, RMSD = 8.22)

Project 4

- Develop a deep learning method to classify protein sequences into folds
- DeepSF source code and dataset: https://github.com/multicom-toolbox/DeepSF