Using Sequence Motifs for Enhanced Neural Network Prediction of Protein Distance Constraints

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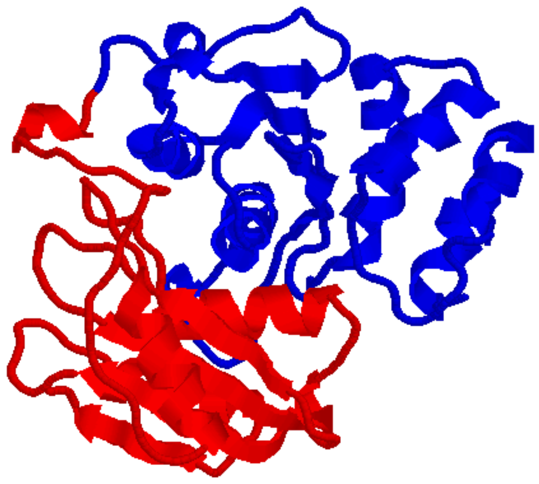
Outline:

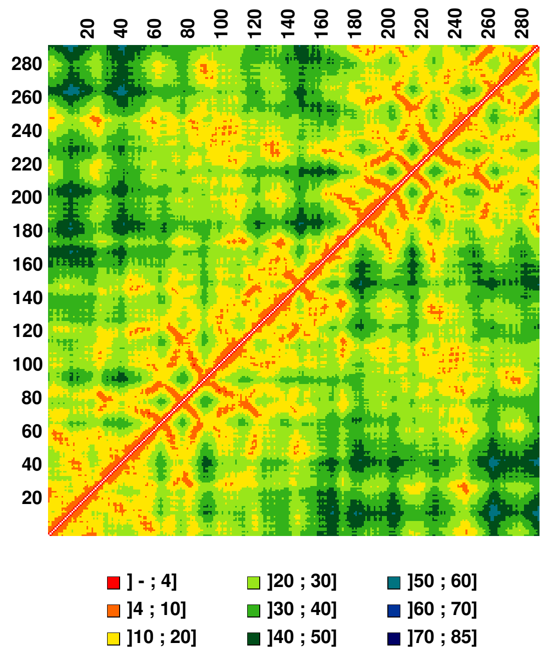
- Introduction
- Statistical analysis: distributions and motifs
- Neural networks: prediction and behavior
- Conclusion

Introduction

- Prediction of 3D distances from sequence.
- 3D structure and distance map:

  PDB entry 1ctt





- Predicting distance constraints between C^{α}

  Sequence separation 17

  atoms. Y W Q R N A A L P P K T R E V E D D C F E G Q

- Other methods to complete the construction of 3D coordinates.

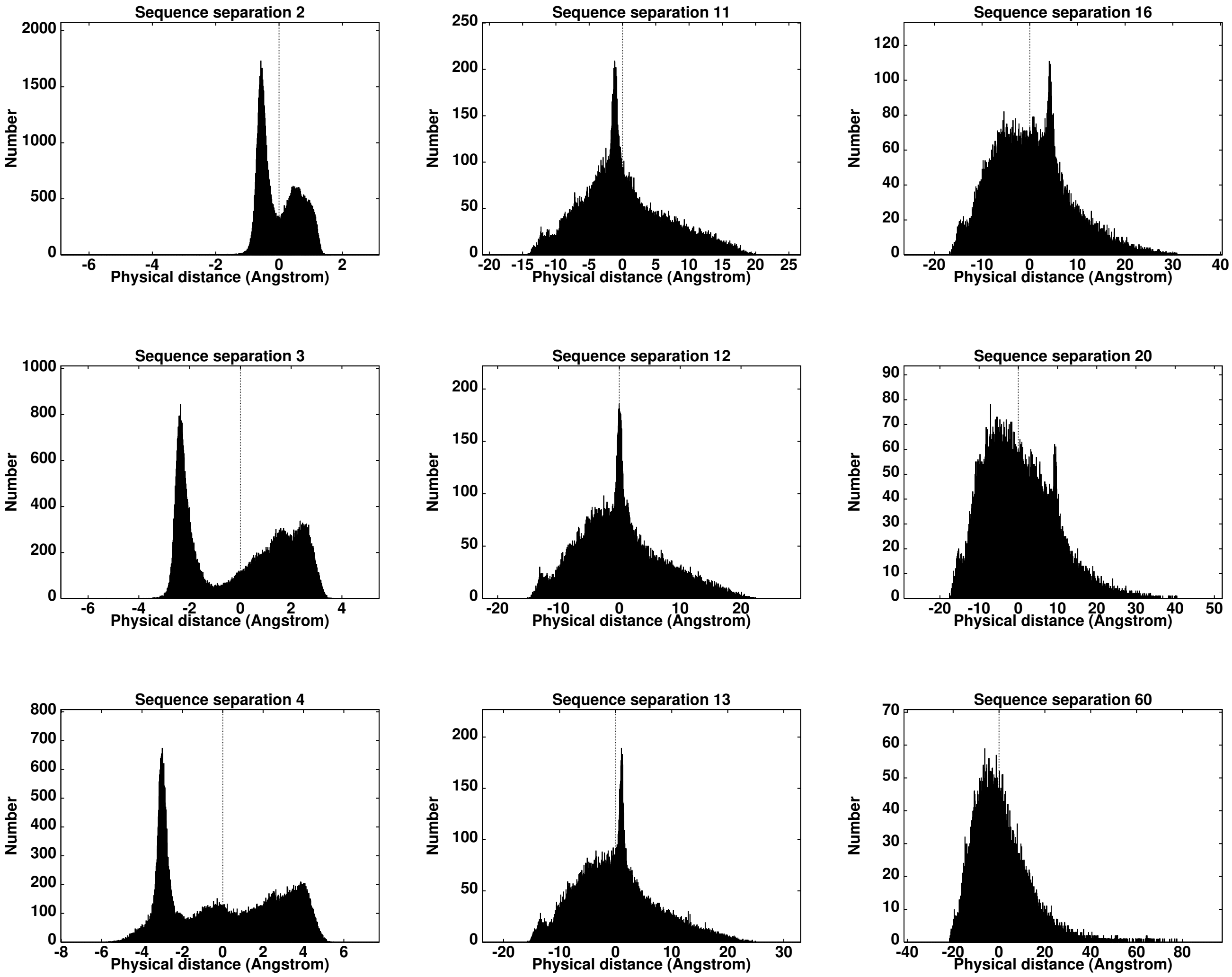
- Previous work: CPHmodels (Lund et al., 1997)
(http://www.cbs.dtu.dk/services/CPHmodels/)
  - NN better than pair probability density functions.
  - Use predictions in homology building (loops).
- Relating NN behavior to statistical features.
- Significant improvement of NN predictions.

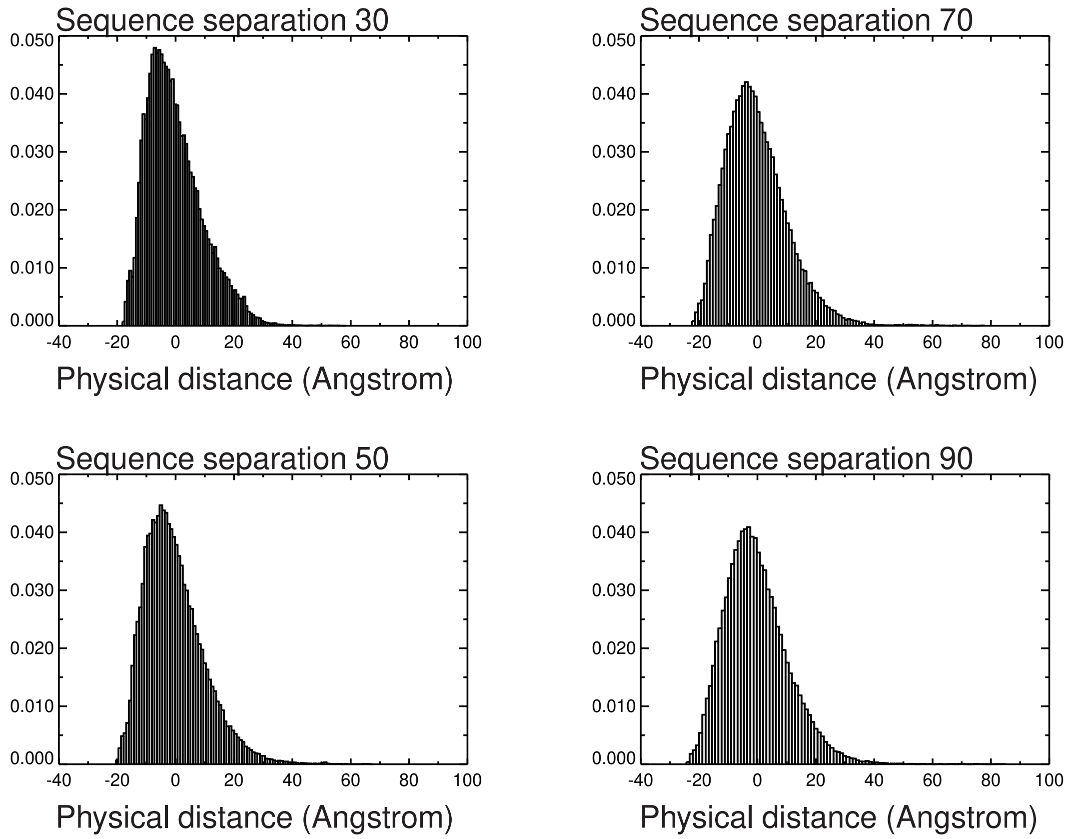
Data set

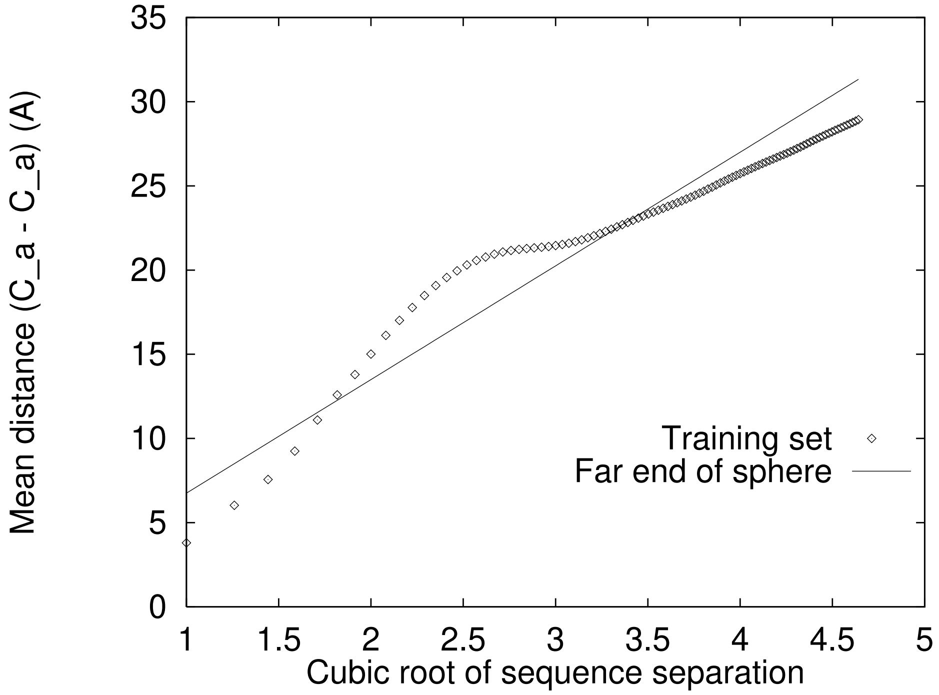
- Construction of non-redundant data set.
- Using entries from PDB, rel. 82; (Bernstein et al., 1977).
- X-ray resolution better than 2.5 Å.
- Threshold curve: $T = 290/\sqrt{L}$.
  (Sander & Schneider, 1991; Lund et al., 1997).
  (http://www.cbs.dtu.dk/services/RedHom/)
- Resulting set of 650 sequences.
- Use 10 cross validation sets.

Statistical analysis
Distance distributions

- Sequence separation and 3D distances
  (Reese et al., 1996).
- Distributions translated by their means.
- Bimodal for small sequence separations.
  Universal for large sequence separations.



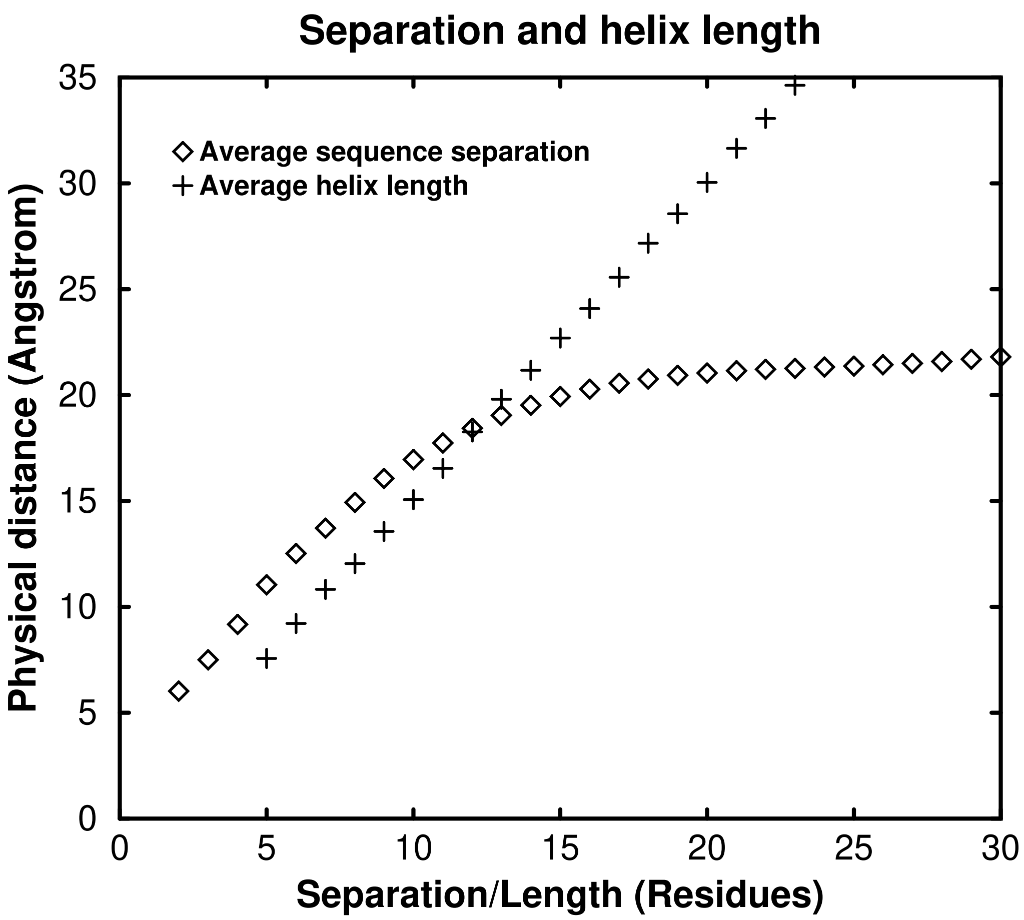




(Lund et al., 1997)

Helix lengths

- Computing the exact physical length in α-helices of increasing lengths.
- Compare to 3D distance at corresponding sequence separations.



Sequence motifs and information content

- Sequence windows corresponding to given separation.

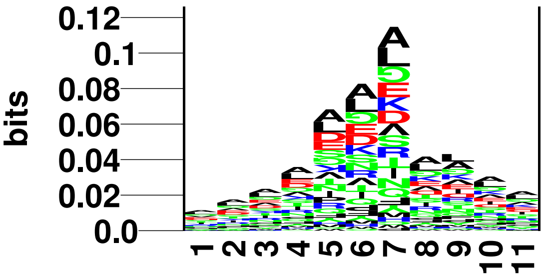
- Compare windows: $dist < t$ to $dist \geq t$.

- Sequence logos using the relative entropy: $I = \sum_k q_k log_2 \frac{q_k}{p_k}$

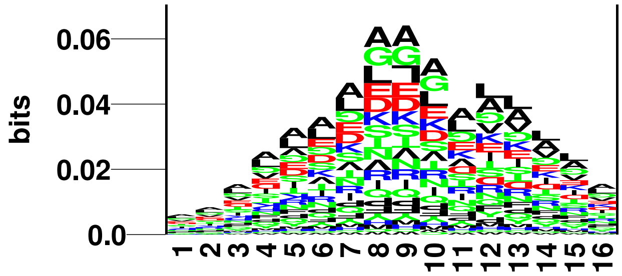
Sequence logos

(Schneider & Stephens, 1990)

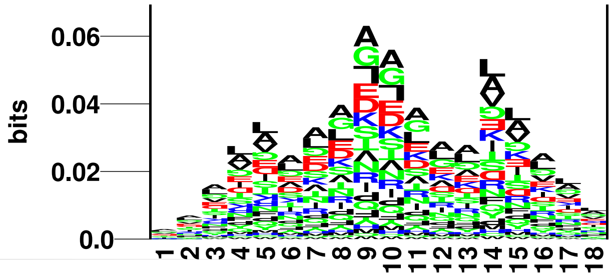
Separation: 2



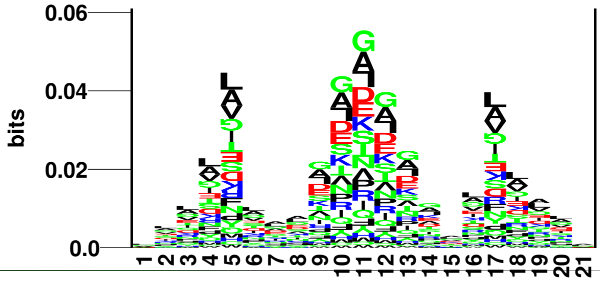
Separation: 7



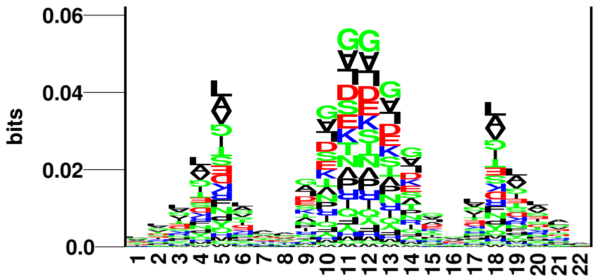
Separation: 9



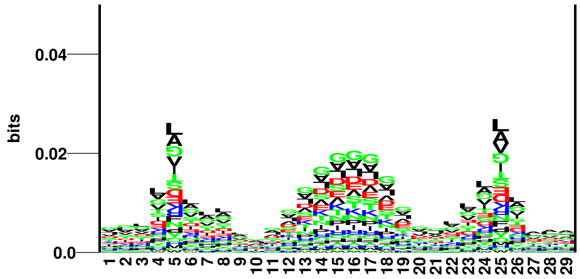
Separation: 12



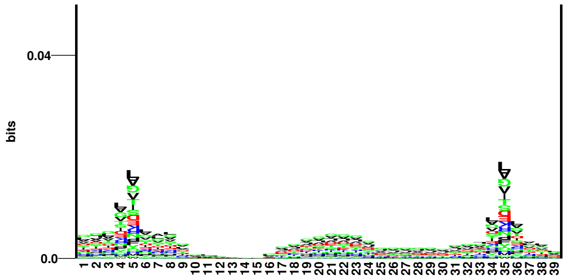
Separation: 13



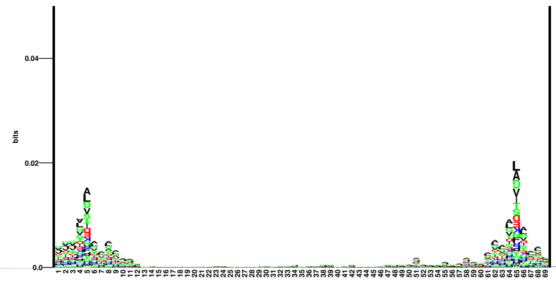
Separation: 20



Separation: 30

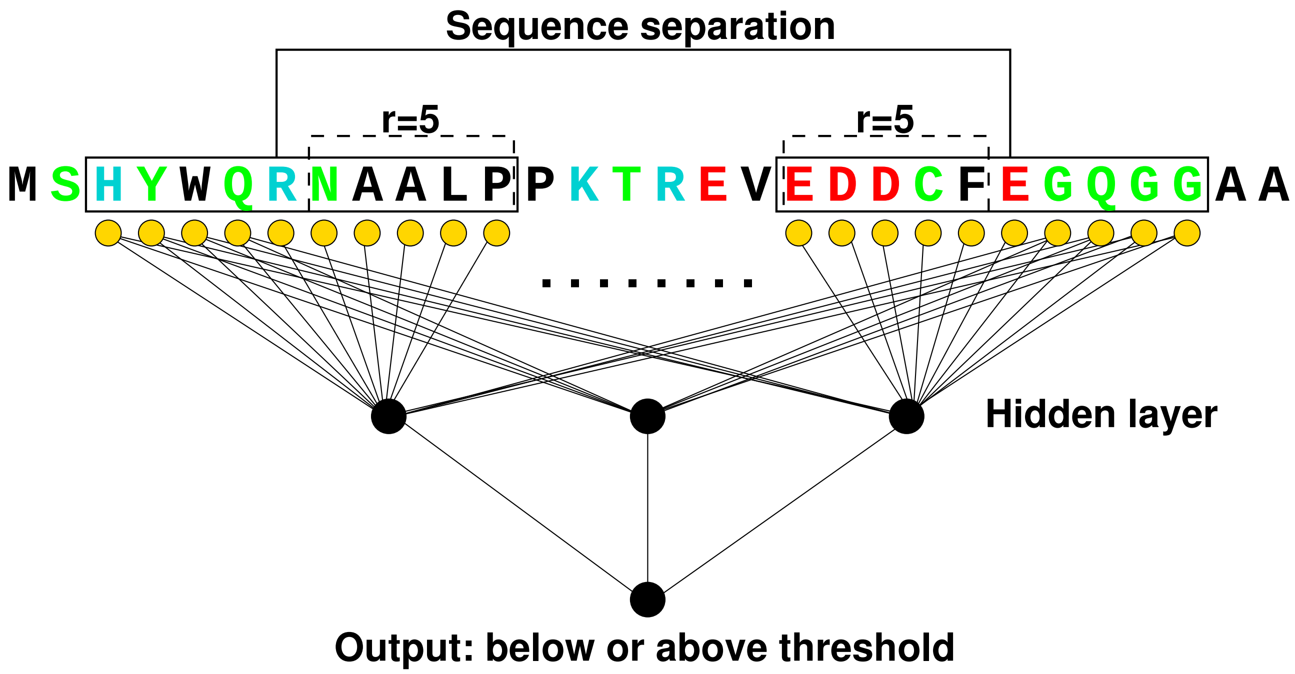


Separation: 60



Neural networks

Architectures:



Evaluation of performance:

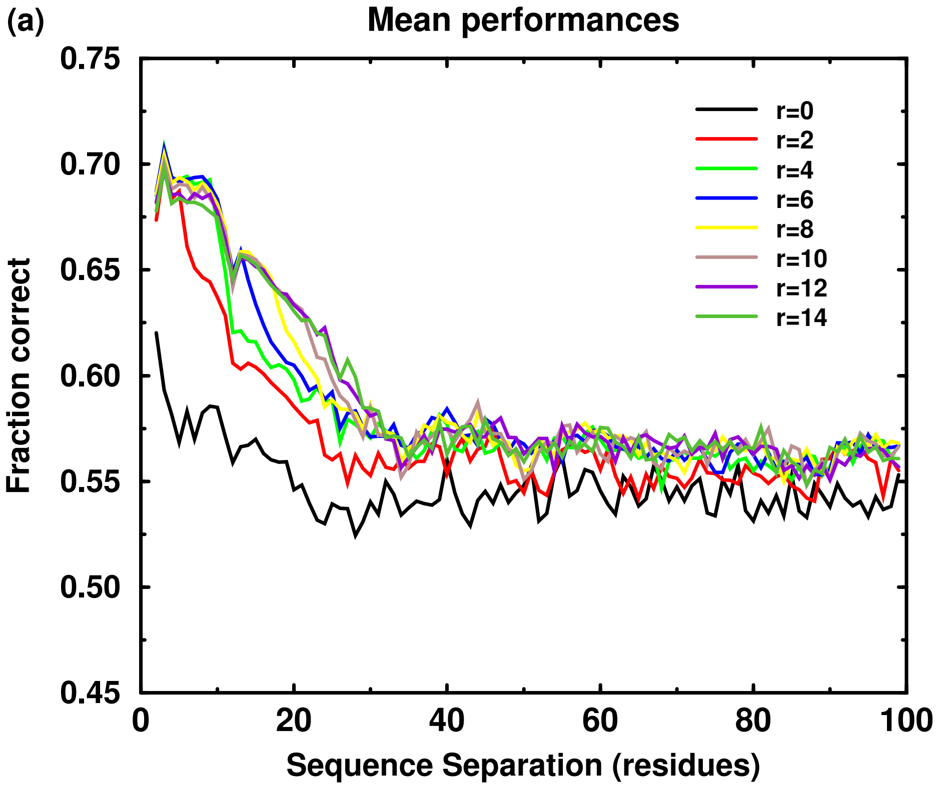
- average over 10 cross-validation sets.
- Correlation coefficient (Mathews, 1975)

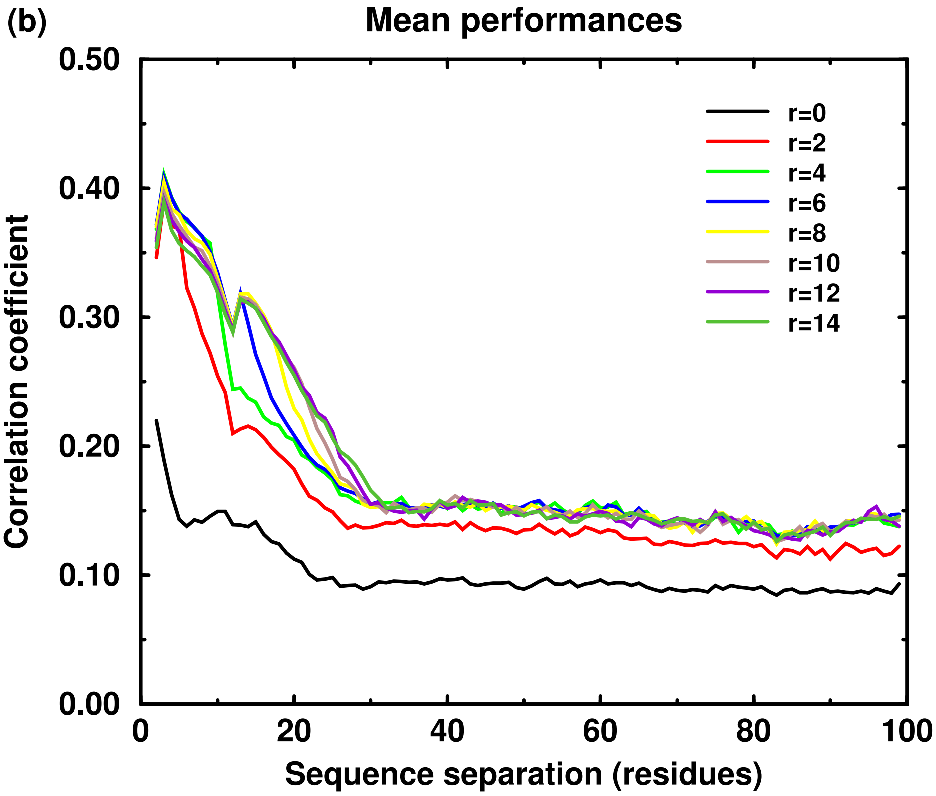
$$C = \frac{P_t N_t - P_f N_f}{\sqrt{(N_t + N_f)(N_t + P_f)(P_t + N_f)(P_t + P_f)}}$$

P_t: true pos.; N_t: true neg.; P_f: false pos.; N_f: false neg.

- 8000 neural networks trained.

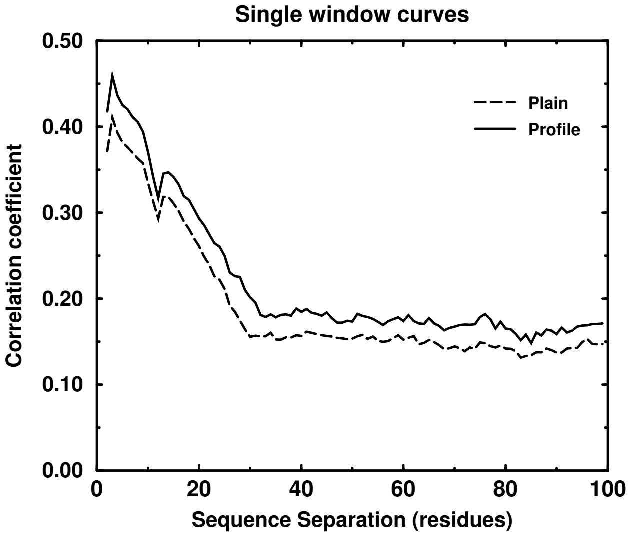
Network performances

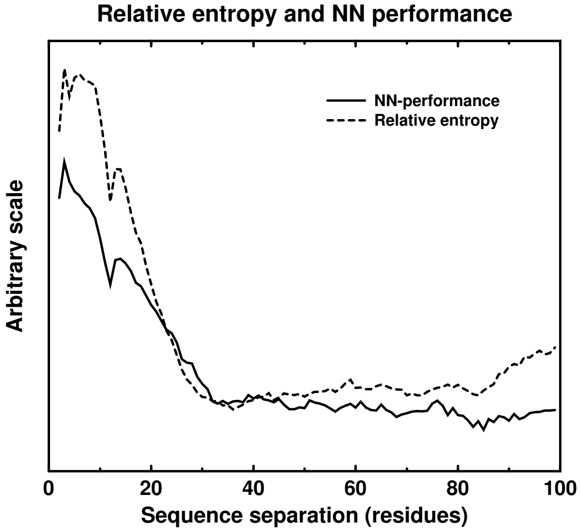




Network analysis

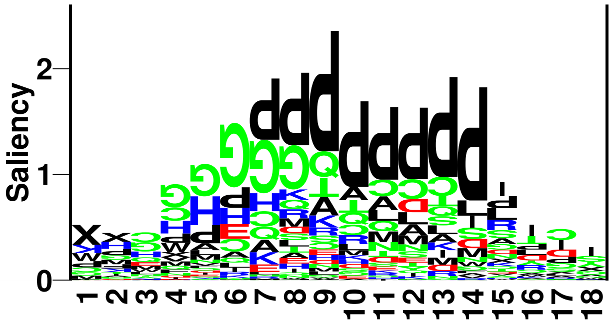
Performance correlated to statistical properties:

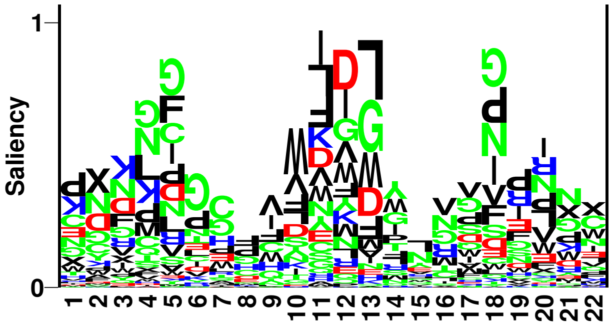




Weight-saliency logos:

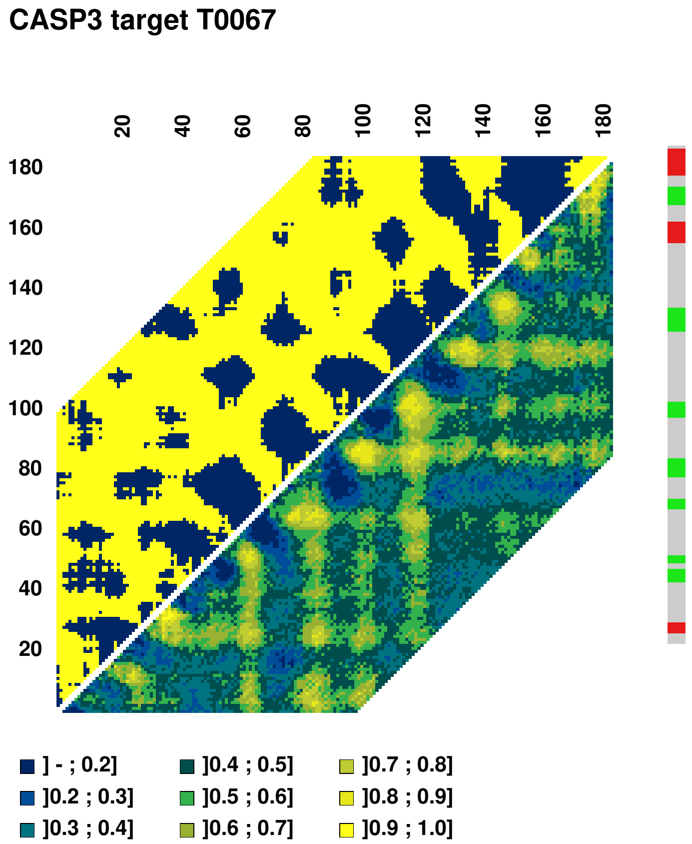
- Main features by the network
- Saliency of weight approx.: $s_{ji} = w_{ji}^2 W_j^2 K$
  (Gorodkin et al., 1997; http://www.wspc.com/journals/ijns/85_6/gorod.pdf)

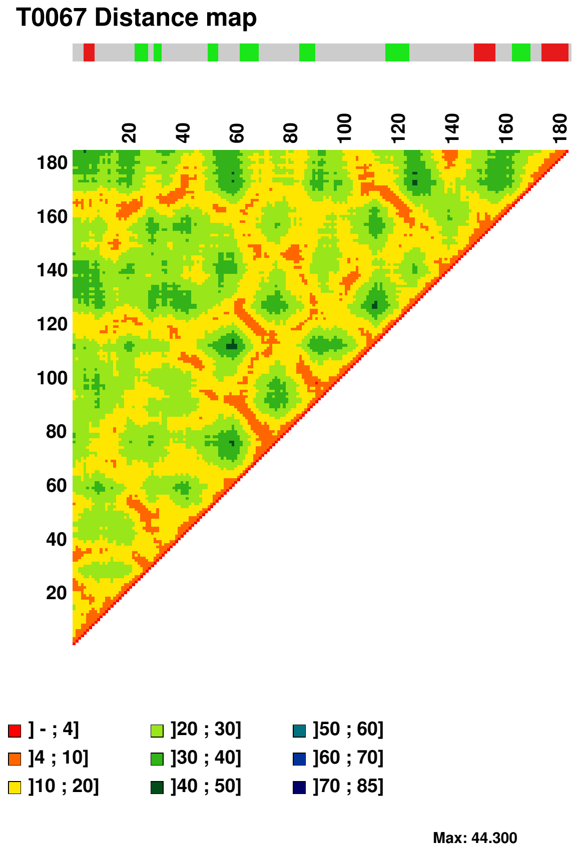




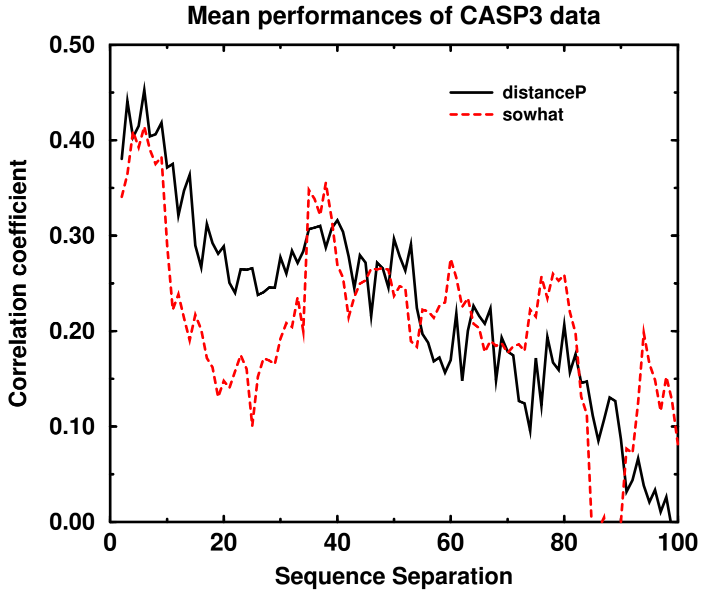
Evaluating on CASP3

Distance constraint prediction vs. true distance map





Performance for increasing sequence separation



Conclusion

- Statistical analysis of distance constraints:
  - Distance distributions and their universality.
  - Sequence motifs and information content.
- Explaining the prediction performance.
- Improved neural network performance.
- Future directions:
  - Include correlations between different sequence separations.
  - Automate the process of 3D determination.

Announcements

New servers

- Prediction of distance constraints:
  http://www.cbs.dtu.dk/services/distanceP/
- Server for graphical interface of matrix plots:
  http://www.cbs.dtu.dk/services/MatrixPlot/

Poster 53 today:

- Organization and Prediction of Structural Domains in Multidomain Proteins.

WWW demo tomorrow 17.30 (mail room):

- The distanceP server:
  predicting protein distance constraints.
- MatrixPlot: visualizing sequence constraints.