

# The Handbook of Brain Theory and Neural Networks

EDITED BY  
Michael A. Arbib

EDITORIAL ADVISORY BOARD  
George Adelman • Shun-ichi Amari • James A. Anderson  
John A. Barnden • Andrew G. Barto • Françoise Fogelman-Soulie  
Stephen Grossberg • John Hertz • Marc Jeannerod • B. Keith Jenkins  
Mitsuo Kawato • Christof Koch • Eve Marder • James L. McClelland  
Terrence J. Sejnowski • Harold Szu • Gerard Toulouse  
Christoph von der Malsburg • Bernard Widrow

EDITORIAL ASSISTANT  
Prudence H. Arbib

A Bradford Book  
**THE MIT PRESS**  
Cambridge, Massachusetts  
London, England

- Brindley, G. S., and Lewin, W. S., 1968. The sensations produced by electrical stimulation of the visual cortex. *J. Physiol. (Lond.)*, 196: 479-493.
- Cha, K., Horch, K., and Normann, R. A., 1992. Mobility of performance with a pixelized vision system. *Vis. Res.*, 32:1367-1372.
- Chizeck, H. J., 1992. Adaptive and nonlinear control methods for neuroprostheses, in *Neural Prostheses: Replacing Motor Function After Disease or Disability* (R. B. Stein, H. P. Peckham, and D. Popovic, Eds.), New York: Oxford University Press, pp. 298-328.
- Engel, A., Konig, P., Kreiter, A. K., Schillen, T. B., and Singer, W., 1992. Temporal coding in the visual cortex: New vistas on integration in the nervous system. *Trends Neurosci.*, 15:218-226.
- Girvin, J. P., 1988. Current status of artificial vision by electrocortical stimulation. *Neuroscience*, 15:58-62. ♦
- Leake, P. A., Hrdack, G. T., Rebscher, S. J., and Snyder, R. L., 1991. Chronic intracochlear electrical stimulation induces selective survival of spiral ganglion neurons in neonatally deafened cats. *Hear. Res.*, 54:251-271.
- Loeb, G. E., 1989. Neural prosthetic interfaces with the nervous system. *Trends Neurosci.*, 12:195-201. ♦
- Loeb, G. E., 1990. Cochlear prosthetics. *Annu. Rev. Neurosci.*, 13:357-371.
- Loeb, G. E., Levine, W. S., and He, J., 1990. Understanding sensorimotor feedback through optimal control. *Cold Spring Harbor Symp. Quant. Biol.*, 55:791-803.
- Loeb, G. E., Zamin, C. J., Schulman, J. H., and Troyk, P. R., 1991. Injectable microstimulator for functional electrical stimulation. *Med. Biol. Eng. Comput.*, 29:NS13-NS19.
- Merzenich, M. M., and Grajski, K., 1990. Cortical network changes underlying representational plasticity. *Cold Spring Harbor Symp. Quant. Biol.*, 55:873-887.
- Miyamoto, R. T., Osberger, J. M., Robbins, A. M., Myrea, M. Y., and Kessler, K., 1994. Prelingually deafened children's performance with a nucleus multichannel cochlear implant. *Am. J. Otol.*, 14:437-443.
- Moore, D. R., and Kowachuck, N. E., 1988. Auditory brainstem of the ferret: Effects of unilateral cochlear lesions on cochlear nucleus volume and projections to the inferior colliculus. *J. Comp. Neurol.*, 272:503-515.
- Popovic, D., 1993. Finite state model of locomotion for functional electrical stimulation systems. *Prog. Brain Res.*, 97:397-407.
- Prochazka, A., 1993. Comparison of natural and artificial control of movement. *IEEE Trans. Biomed. Eng.*, 1:7-17. ♦
- Rall, W., 1962. Electrophysiology of a dendritic neuron model. *Bio-phys. J.*, 2:145-167.
- Ranck, J. B., Jr., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: A review. *Brain Res.*, 98:417-440. ♦
- Wilson, B., Finley, C., Lawson, D., Wolford, R., Eddington, D., and Rabinowitz, W., 1991. Better speech recognition with cochlear implants. *Nature*, 352:236-238.
- Wise, K. D., and Najafi, K., 1991. Microfabrication techniques for integrated sensors and microsystems. *Science*, 254:1335-1342. ♦

## Protein Structure Prediction

Burkhard Rost and Chris Sander

### Introduction

**What is a protein?** The information for life is stored by a four-letter alphabet in the genes. Proteins perform most important tasks in organisms, such as catalysis of biochemical reactions, transport of nutrients, recognition and transmission of signals. Proteins are formed by joining amino acids into a long, stretched chain, the protein sequence. Proteins differ in the number (from 30 to 30,000) and in the arrangement of the amino acids (called *residues*, when joined in proteins). In water, the chain folds up to a unique three-dimensional (3D) structure. The main driving force is the need to pack residues for which a contact with water is energetically unfavorable into the interior of the molecule. This is only possible if the protein forms regular patterns of a macroscopic substructure called *secondary structure* (Figure 1; see Brändén and Tooze, 1991).

**What determines protein function and structure?** The 3D structure of a protein determines its function. The 3D structure is uniquely determined by the sequence. Can the code be deciphered—i.e., can 3D structure be predicted from sequence? In principle, yes; but the computer time required to predict 3D structure from first principles is many orders of magnitude beyond today's possibilities. However, one reason to want to know the structure is rational drug design.

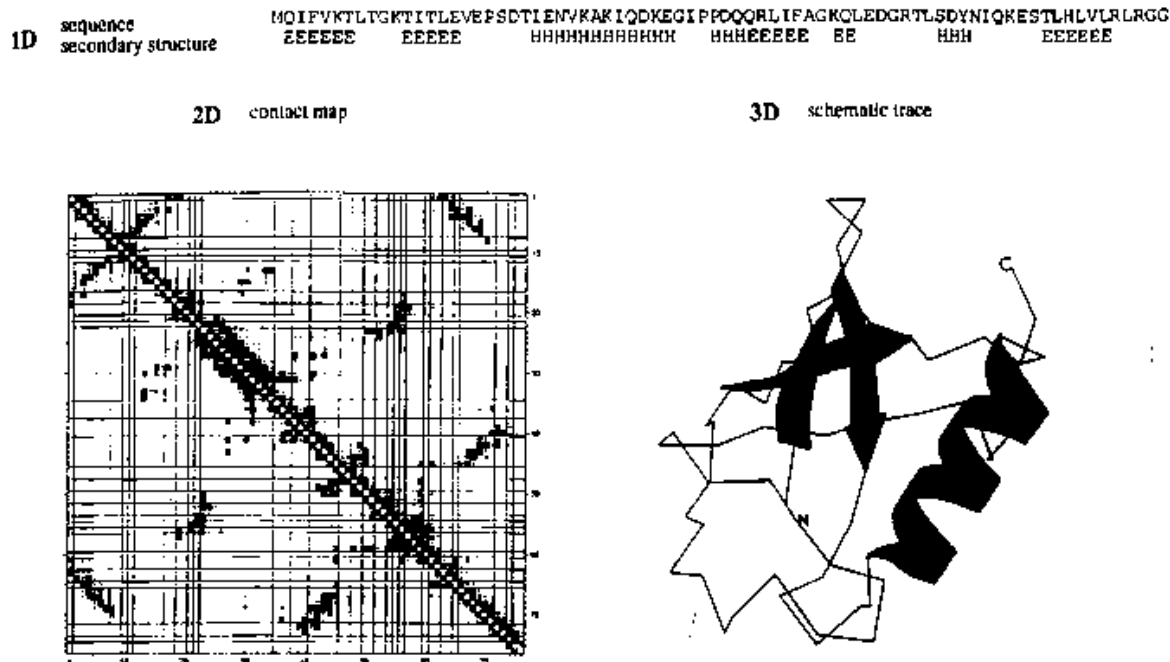
**Why not simply look by microscope at the 3D structure?** The techniques to experimentally determine 3D structure of a protein are rather complicated. Today, the sequence is known for some 36,000 proteins, but only for 2000 has the 3D structure been determined by experiment. Large gene sequencing projects increase the sequence-structure gap further. The most accurate way to predict 3D structure from sequence is by

homology modeling—i.e., search for a protein with similar sequence that has a known 3D structure and then model the 3D structure of the unknown protein in analogy to the known one. Such techniques lead to a reduction of the sequence-structure gap by some 9000 proteins.

**Why can homology modeling be successful?** The exchange of few residues can already destabilize a protein. This implies that the majority of the  $20^N$  possible sequences of length  $N$  form different structures. But has evolution created such an immense variety? The evolutionary pressure to conserve function and the discontinuity of the universe of structures have the result that structure is more conserved than sequence. Evolution has produced pairs of proteins which have the same 3D structure with only 25% identical residues. For such pairs, 3D structure can be predicted rather accurately by homology.

**Can the egg be unboiled?** When an egg is boiled, the proteins it contains unfold. Can this procedure be reversed in theory? Or, can the encrypted code of protein folding be deciphered from sequence? Current tools to predict 3D structure from sequence are rather limited (Rost and Sander, 1994b). The problem has to be simplified. One extreme simplification is to predict one-dimensional (1D) strings of secondary structure assignment (Figure 1).

**How can neural networks predict protein structure?** In practice, the most successful predictions are based on an analysis of common features in the data bank of known 3D structures. Artificial neural networks are well suited for pattern classification. Here, we shall attempt to show how neural networks can be used to predict protein structure. First, we give examples of



**Figure 1.** Hierarchy of protein structure. *1D.* The amino acid sequence determines the formation of 3D structure. Here, the chain of ubiquitin (1ubq) is shown. The 3D structure can be projected onto a 1D string of repetitive patterns: the secondary structure (*H*,  $\alpha$ -helix; *E* [extended],  $\beta$ -strand; and *blank*, loop). *2D.* The 3D structure can be projected onto a 2D matrix: the entry at position *ij* of the matrix gives the contact between residue *i* and residue *j* (plot by *Conax*: M. Scharf, 1989,

*Analyse von Paarwechselwirkungen in Proteinen*, University of Heidelberg, Department of Physics). *3D.* The trace of the protein chain in 3D is plotted schematically. *C* gives the end and *N* the beginning of the protein. The longer helix is on the right-hand side, while three of the strands are indicated by arrows (plot by *Molscript*: P. Kraulis, 1991, *MOLSCRIPT: A program to produce both detailed and schematic plots of protein structures*, *J. Appl. Crystallogr.*, 24:946-950).

how the data bank of known 3D structures can be used to predict secondary structure and, following that, other structural features. Finally, we briefly review attempts to predict entire 3D structures.

### Prediction of Secondary Structure

#### Presenting the Protein to the Network

The usual goal of secondary structure prediction methods is to classify a pattern of adjacent residues as either H ( $\alpha$ -helix), E (for extended  $\beta$ -strand), or L (for loop = all others). Sequences are translated into patterns by shifting a window of adjacent residues through the protein and looking up the secondary structure for the central residue (Figure 2).

Networks used for secondary structure prediction are multi-layer feedforward networks (Figure 2). The network error is given by the difference between actual network output (uniquely determined by the choice of connections) and desired output (looked up from data bank). *Training or learning* means changing the connections such that the error decreases for the given examples (gradient descent; see, e.g., *BACKPROPAGATION: BASICS AND NEW DEVELOPMENTS AND LEARNING AS HILL-CLIMBING IN WEIGHT SPACE*). If training is successful, the patterns are correctly classified. But how can new patterns be classified correctly? The hope is that the network extracts general rules by the classification of the training patterns. The generalization ability is checked by another set of test samples for

which the mapping of sequence window to secondary structure is known as well. Sufficient testing is crucial (Rost and Sander, 1994a).

#### Prediction Performance of Simple Neural Networks

Networks of the type described reach values for three-state overall prediction accuracy of around 60%. This is comparable to the performance of non-network methods. In the five years following the first application of neural networks to the prediction of secondary structure (Qian and Sejnowski, 1988), more than 20 groups have followed (Hirst and Sternberg, 1992; Rost and Sander, 1994a). Prediction accuracy was not improved significantly without using biological expertise, as we shall see in the next section.

#### Using Evolutionary Information of Multiple Sequences

Some residues can be replaced by others without changing the structure. But not every amino acid can be replaced by any other. On the contrary, the residue substitution patterns are very specific for a certain 3D structure. Can this information be used to improve the prediction accuracy for neural networks? Indeed, using evolutionary information as derived from a database of proteins with homologous 3D structure improves the performance accuracy by about 10 percentage points to > 72% (Rost and Sander, 1994a). The basic procedure is as follows: First, sequences of proteins which are similar enough in se-

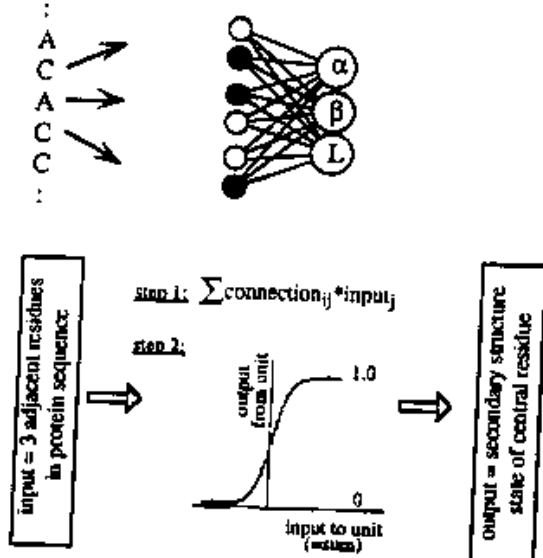


Figure 2. Neural network for secondary structure prediction. Here, for simplicity, a window of three residues is used as input (for actual applications, 10 to 30 residues are used). For each position in the window, two input units (for simplicity, two instead of 20 amino acids) are used: the first is set to one (shaded dark) if the amino acid is an A, the second if it is a C. The signal is transmitted via the connections between input and output layer. At each output unit, two computational steps are performed. First, the input signal is multiplied with the connection, and this product is summed over all input units. Second, from this sum, the output of each output unit is compiled according to the trigger function shown.

quence to know that they are similar as well in 3D structure are aligned (optimal fit). Second, for each residue position, it is counted how often any of the 20 amino acids occur in the alignment at that position. Third, the counts are used as input to a network.

#### Prediction of Structural or Functional Protein Class

According to the relative content in secondary structure, proteins can be classified into *structural classes*. From the predicted secondary structure, the relative content of secondary structure of a protein can be calculated to predict structural class (Rost and Sander, 1994a). An alternative approach is to directly predict the secondary structure content of a protein by a neural network that uses as input a vector of 20 components giving the frequency with which each amino acid occurs in a particular protein (Muskal and Kim, 1992).

A different task is to predict that two proteins are similar in terms of function or 3D structure. Methods have been based (1) on multiple feedforward networks (Frishman and Argos, 1992), using proteins of similar sequences as input; (2) on simple feedforward networks, using different amino acid features as input (Wu et al., 1992); and (3) on Kohonen maps (see SELF-ORGANIZING FEATURE MAPS: KOHONEN MAPS), using residue pair frequencies as input (Ferrari and Ferrara, 1992). Whereas feedforward networks are useful to learn a classification into known features (secondary structure, structural class), the Kohonen maps have been applied to render a general classification scheme (e.g., *A* and *B* are similar, and *A* is more

similar to *C* than *B*). Such a classification is in general a priori not evident (and in itself provides a controversial research area, attempting to answer questions like "Are we more similar to an orangutan than to a pig?").

#### Prediction of Other Structural or Functional Features

Most applications of neural networks use a similar sliding window input as described above. Approaches address the predictions of surface exposure, disulfide bonds, and function-specific sequence motifs.

**Surface exposure.** A simple feature of 3D structure that is also of interest for molecular biology is the extent to which a residue is exposed to the solvent. Holbrook, Muskal, and Kim (1990) used a network to classify amino acid residues as either buried or exposed. The result was evaluated on too small a data set, yielding some 70% accuracy in two states (buried/exposed).

**Disulfide bonds.** Disulfide bonds between cysteine residues (one of the 20 amino acids is cysteine) are often of functional and structural importance. Muskal, Holbrook, and Kim (1990) used a single-layer feedforward network to predict the existence or absence of disulfide bonds.

**Function-specific sequence motifs.** Often, function depends on a rather short (5 to 10 residues) sequence motif (unique pattern of adjacent amino acids). Residues that are associated with particular functions were also subject to neural network predictions. Examples are: (1) sequence motifs that reveal binding of energy storage molecules (Hirst and Sternberg, 1992); (2) sequence motifs specific for particular proteins—e.g., the immunoglobulins (Bengio and Pouliot, in Hirst and Sternberg, 1992); and (3) signal peptide motifs in sequences (Ladunga et al., 1991).

#### Aiming at Prediction in 3D

##### Distance Constraints

The projection of the 3D structure onto a two-dimensional distance matrix (Figure 1) could be an important step on the way to predicting 3D structure. This enterprise was undertaken by Bohr et al. (1990), who used a neural network to predict residues which are closer than 8 angstroms ( $= 8 \cdot 10^{-10}$  m) to any of the 30 residues adjacent in sequence. The predicted fragments of the distance matrix were used for a simple steepest descent energy minimization procedure. The training set comprised 13 proteins. The method was tested on only one protein that has sufficient sequence identity to proteins used for training. (The prediction was worse than the one that could have been obtained by homology modeling.)

##### Spin-Glass Models for Proteins

The putative analogies of the energy landscapes of spin glasses and proteins led to a multitude of models attempting to describe protein folding with the formalism known from spin-glass theory (Elber, 1993). Such models have been used for attempts to predict 3D structure (Goldstein, Luthey-Schulten, and Wolynes, 1992). The principal idea is to define an effective energy function from a database of known 3D structures that is flexible enough to enable description of a large class of structures and simple enough to surpass the multiple minima problem of conventional energy minimization calculations for proteins. The analogy to spin-glass theory consists in constructing an energy function based on pairwise interactions (between

residues). For some cases, such methods are comparable to non-network methods which use statistically derived energy functions (Rost and Sander, 1994b).

### Discussion

*Neural networks can be used for predicting structural features of proteins.* There were at least 50 articles on the application of neural networks for protein structure prediction until 1993. One message of the literature is convincing: neural networks can be used to predict secondary structure, structural class, family relations, surface exposure, functional motifs, distance matrices, and even the 3D structure of proteins.

*Neural network methods are seldom superior to non-network approaches.* The second message of the literature is that networks are superior to alternative techniques, but this answer is not convincing! The general problem is a lack of rigor in evaluating results. A common example is the allowance of significant sequence identity between test and training set. Any evaluation that allows for sequence identity has to be compared to homology modeling. And in this comparison, all prediction methods are clearly inferior. The conclusion is that neural network applications have almost never yielded significant improvements over current techniques (Hirst and Sternberg, 1992). An exception is a network that uses evolutionary information to predict secondary structure (Rost and Sander, 1994a). So far, this is the only example for a neural network prediction of protein structure being clearly superior to alternative techniques.

*Neural network predictions have not been made sufficiently available to biochemists.* Unfortunately, the tendency to overestimate the performance accuracy of network prediction has not contributed much to their acceptance by biochemists. Another problem is that almost none of the network methods is publicly available to those researchers who need predictions.

*Neural network techniques will continue to be useful for the prediction of protein structure.* First, the problem of predicting protein structure is far from solved. For a sequence of unknown 3D structure for which no homology to a known fold can be detected, the best one can achieve today is a more or less reliable prediction of secondary structure, surface exposure, or functional class. Second, the constantly growing data banks provide an increasing body of information about protein structure. Chances are that methods based on data bank analysis will be the first to practically solve the prediction of protein 3D structure. Third, neural networks might be well suited for appropriately incorporating the increased information. Using

evolutionary information will be one way to improve predictions by networks. Neural network applications can become increasingly important for the research of tomorrow's molecular biology, provided that testing is done with care and that methods become available to potential users.

**Read Map:** Applications of Neural Networks

**Background:** 1.3. Dynamics and Adaptation in Neural Networks

### References

- Bohr, H., Bohr, J., Brunak, S., Fredholm, H., Laurrup, B., and Petersen, S. B., 1990, A novel approach to prediction of the 3-dimensional structures of protein backbones by neural networks. *FEBS Lett.*, 261:43-46.
- Brändén, C., and Tooze, J., 1991, *Introduction to Protein Structure*. New York, London: Garland. ♦
- Elber, R., 1993, New simulation methods for proteins and DNA. *Curr. Opin. Struct. Biol.*, 3:260-264.
- Ferrán, E., and Ferrara, P., 1992, Clustering proteins into families using artificial neural networks. *Comput. Appl. Biosci.*, 8:39-44.
- Frishtman, D., and Argos, P., 1992, Recognition of distantly related protein sequences using conserved motifs and neural networks. *J. Mol. Biol.* 228:951-962.
- Goldstein, R. A., Luthy-Schulten, Z. A., and Wolynes, P. G., 1992, Protein tertiary structure recognition using optimized Hamiltonians with local interactions. *Proc. Natl. Acad. Sci. USA*, 89:9029-9033.
- Hirst, J. D., and Sternberg, M. J. E., 1992, Prediction of structural and functional features of protein and nucleic acid sequences by artificial neural networks. *Biochemistry*, 31:615-623.
- Holbrook, S. R., Muskal, S. M., and Kim, S.-H., 1990, Predicting surface exposure of amino acids from protein sequence. *Protein Eng.*, 3:659-665.
- Ladunga, I., Czáró, F., Csabai, J., and Gezsi, T., 1991, Improving signal peptide prediction accuracy by simulated neural network. *Comput. Appl. Biosci.*, 7:483-487.
- Muskal, S. M., Holbrook, S. R., and Kim, S.-H., 1990, Prediction of the disulfide-bonding state of cysteines in proteins. *Protein Eng.*, 3:667-672.
- Muskal, S. M., and Kim, S.-H., 1992, Predicting protein secondary structure content: A tandem neural network approach. *J. Mol. Biol.*, 225:713-727.
- Qian, N., and Sejnowski, T. J., 1988, Predicting the secondary structure of globular proteins using neural network models. *J. Mol. Biol.*, 202:865-884.
- Rost, B., and Sander, C., 1994a, Combining evolutionary information and neural networks to predict protein secondary structure. *Proteins*, 19:55-72.
- Rost, B., and Sander, C., 1994b, Structure prediction of proteins—Where are we now? *Curr. Opin. Biotechnol.*, 5:372-380. ♦
- Wu, C., Watson, G., McLarty, J., Ermoykonchak, A., and Chang, T.-C., 1992, Protein classification artificial neural system. *Protein Sci.*, 1:667-677.

## Pursuit Eye Movements

Richard J. Krauzlis

### Introduction

When viewing objects, monkeys and humans use a combination of saccadic and pursuit eye movements to keep the retinal image of the object of regard within the high-acuity region near the fovea. While these movements mix seamlessly in normal behavior, their properties and origins are quite distinct. Saccades are ballistic movements that quickly direct the eyes to-

ward a visual target, thereby translating the image of the target from an eccentric retinal location to the fovea. In contrast, pursuit is a continuous movement that slowly rotates the eyes to compensate for any motion of the visual target, minimizing the drift of the target's image across the retina that might otherwise compromise visual acuity. While other mammalian species can generate smooth optokinetic eye movements—which track the motion of the entire visual surround—only primates