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# HERA—A Program to Draw Schematic Diagrams of Protein Secondary Structures

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***ABSTRACT*** **A program is described which generates hydrogen bonding diagrams of protein structures and optionally helical wheels and helical nets. The program can also be used simply to calculate the connectivities of β-strands and to automatically extract simple structural motifs such as hairpins or Greek keys. The program greatly reduces the effort required to produce these diagrams and offers considerable flexibility in the information which can be represented. The usefulness of the program is illustrated by several examples including comparing homologous families, correlating protein structure with attributes of individual residues, and extracting all examples of the ψ-loop motif from the Brookhaven Data Bank.**

**Key words: hydrogen bonding diagram, motifs, helical wheel, helical net, protein structure**

## INTRODUCTION

An important tool in the understanding and analysis of protein structures is the ability to represent these structures graphically. There are now several packages available for displaying and interacting with the detailed three-dimensional structures on a computer graphics terminal, and these are widely used in protein crystallography. However, for many applications, such as studying the overall folding pattern, or comparison of a large number of protein structures, simpler diagrams, such as those drawn by Richardson,[1] hydrogen bonding diagrams, or the schematic diagrams drawn by Levitt and Chothia[2] or Sternberg and Thornton,[3] are more appropriate.

With the exception of the Richardson diagrams, which can now be generated automatically,[4] these representations have had to be drawn by hand. This is particularly tedious and time-consuming in the case of hydrogen bonding diagrams, and this has limited the application of this otherwise very useful representation in the analysis of protein structures.

We describe here a program, HERA, which will generate such diagrams automatically, based on secondary structure assignments calculated using the algorithm of Kabsch and Sander.[5] The diagrams allow clear visualization of the overall topology of a given protein, and structural motifs such as Greek keys and Rossman folds can be readily identified by visual inspection. In addition, the hydrogen bonding diagrams provide a useful framework on which to display various attributes of the individual residues, such as solvent accessibility, hydrophobicity, conservation index, etc.

Information about helical residues can be effectively represented in the form of helical wheels and helical nets, and an option within HERA also allows these to be drawn for one or more helices. Again the possibility of adding extra information about individual residues to a basic helical wheel proves very useful, and we show one example in which amino acid hydrophobicity and solvent accessibility can be conveniently correlated by displaying both on the same helical wheel.

The possibility of generating these schematic diagrams automatically reduces considerably the time required to compare different proteins, or to locate structural features of interest. However, where large numbers of proteins are to be analyzed, even the process of visual inspection of hydrogen bonding diagrams can become laborious, and an automated means of extracting structural motifs would further reduce the effort involved. A final option is to produce a file containing the connectivities of sequentially adjacent β-strands, and to automatically search for simple β-sheet motifs such as Greek keys or β-hairpins. As an example of this we have used HERA to search the Brookhaven Data Bank for all examples of ψ-loops (defined by a +2 connection between two adjacent strands) and we present an initial analysis and classification of the examples found.

## MATERIALS AND METHODS

The program is written in Fortran 77 and is currently running on a MicroVAX II. Input secondary structure assignments are taken from the output file of Kabsch and Sander's DSSP program. Alterna-

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tively, output from a modified version of the algorithm, in which helices and sheets are extended one residue at each end if possible (D. K. Smith, personal communication), can be used. The original atomic coordinates from which the secondary structure is calculated are taken from the Brookhaven Data Bank.[6] Additional information to be plotted on the diagram can be read either from the secondary structure file, e.g., whole residue accessibilities, or from a second file whose format can be specified. Output is in the form of a postscript file, which can be printed on a laserwriter or other suitable device. We also plan to modify HERA for use on a Silicon Graphics Iris workstation to allow more interactive use.

The logical steps involved in the running of HERA are illustrated in the flowchart in Figure 1. After recording the options the program reads in the secondary structure assignment file and, if necessary, data from a second file. The program can then either calculate a hydrogen bonding diagram and/or helical nets and helical wheels for a single protein, or search a list of proteins for a given β-sheet topology.

## Hydrogen Bonding Diagram

HERA generates hydrogen bonding diagrams which illustrate the main chain–main chain hydrogen bonding patterns within the sheets and helices. The hydrogen bonding partners are those defined in the output of the DSSP program. A typical hydrogen bonding diagram of a 150 residue protein takes around 1.5 CPU minutes to calculate.

If the sheet residues are to be included in the diagram these are positioned first. The sheets, as defined by DSSP, are treated one at a time as follows: The residues in the sheet and their bridge partners are read into an array. Sheets defined by DSSP which contain just two residues connected by a bridge are not included. The residues are assigned strand numbers within the sheet and the connectivity of the strands is calculated. If the sheet forms a continuously hydrogen-bonded barrel, the barrel is "opened" at a position which minimizes the number of hydrogen bonds to be broken. The residues are inserted one strand at a time into a buffer array according to the strand connectivity, using the hydrogen bonding to the previous strand to establish the orientation and position of the strand. When the entire sheet has been entered into the buffer array, an "optimal" orientation for the sheet relative to all previously calculated sheets is determined, and the sheet inserted into a final 60 × 60 array in the appropriate orientation. This is repeated until all the sheets have been inserted.

The next stage is to plot helices. The initial and final residues of each helix are recorded. The best position and orientation for each helix are calculated by searching the top and bottom residues already placed in the final array for the residues closest to one of the helix terminii. If two helices are assigned to the same column, the helix closest in sequence is inserted first. If there is no room for the helix in the selected column the helix is inserted into an empty column of the array. For all helical proteins the program inserts each new helix into a separate column.

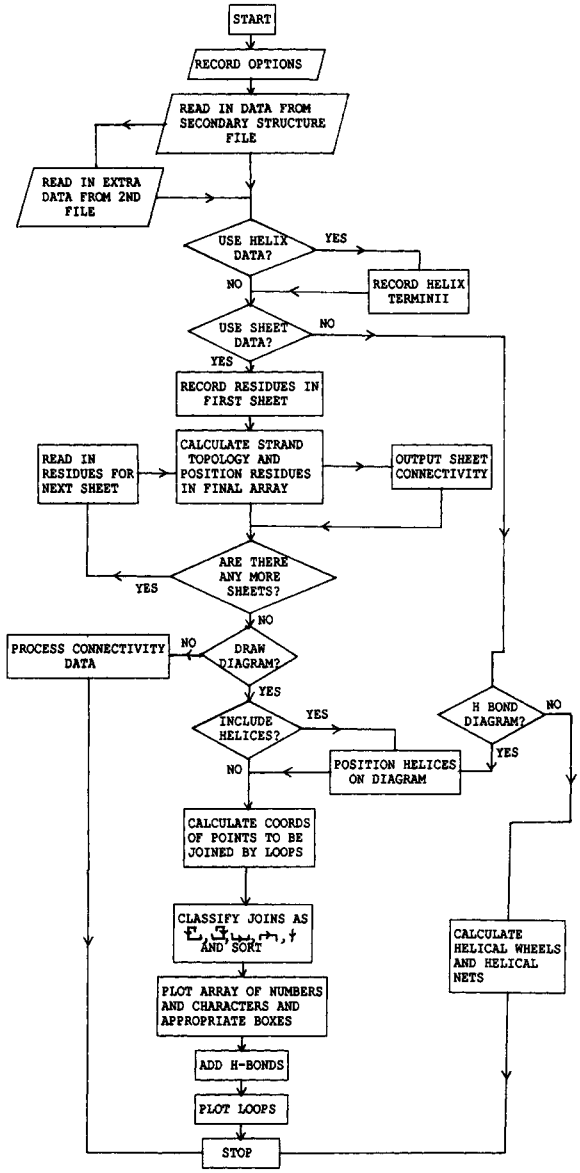



Fig. 1. Flow diagram representing the logical steps involved in the calculation of the hydrogen bonding diagram.

The loops between the secondary structural elements are represented on the diagram by lines connecting the appropriate residues. This is computationally more straightforward than trying to fit all the loop residues into the space defined by the ends of the strands or helices. A list of coordinates of points on the diagram to be joined is compiled by

searching the sequence for the beginnings and ends of loops. To reduce confusion due to overlapping or unnecessary crossing of lines, the list of loop coordinates is divided into five classes depending on the type of loop to be drawn (Fig. 1). These classes are each sorted independently according to the horizontal distance between the end points, and then drawn so that loops with a larger end-point distance are drawn further away from the center of the diagram.

### Options

A certain amount of flexibility is possible within the scope of the current program to allow users to tailor the diagram to their specifications. Clearly the range of possible ways in which such a diagram can be drawn and the variety of information which could be displayed on it are very large indeed, and no automated procedure could hope to satisfy individual needs perfectly. The options which are available in the current version are shown in Table I. There are options which allow just part of the protein to be drawn, specified either by a particular residue range, or one or more sheets. A simpler view of the topology of the molecule can be obtained by plotting just the sheets and including the helices in the loop regions. The order in which the sheets appear from left to right on the diagram can also be changed and each sheet can be independently flipped from left to right or from top to bottom to highlight particular features. It is also possible to specify ones own strand beginnings and ends, i.e., to supercede the Kabsch and Sander definitions. However, since the program will always use the bridge partners specified by DSSP, this is really only useful for making minor changes such as extending or shortening strands by one or more residues.

As far as the information displayed for each residue is concerned, several combinations of residue number, one letter code, and accessibility are possible. In addition it is also possible to specify a second file containing information not normally defined in the secondary structure file which can also be included in the diagram. The format of this file can be specified by the user at the beginning of the program. As indicated in the options table, up to four attributes of each residue can be drawn on one diagram. Up to two values can be written inside the box for each residue, one attribute can be used to specify the shape of the box and one can specify whether the edge of the box is drawn solid or dotted. The shape and edge of the box can each have two states, and each state can be specified by a single value, e.g., secondary structure, or by a range of values.

**TABLE I. Input Options**

| | |
|---|---|
| A | Diagram or calculation required |
| 1 | Hydrogen bonding diagram |
| 2 | Helical wheel(s) |
| | Helical net(s) |
| 3 | Calculate strand connectivities and extract structural features |
| B | General information for hydrogen bonding diagram |
| 1 | Input secondary structure file |
| 2 | Residue range |
| 3 | DRAW helices and sheets |
| | OR sheets only |
| | OR helices only |
| 4 | DRAW all sheets |
| | OR range of sheets |
| 5 | Interchange order of sheets |
| 6 | Flip each sheet independently about vertical axis on page |
| 7 | Flip each sheet independently about horizontal axis on page |
| 8 | Alterations in beginning and end residue of each strand |
| 8 | Threshold energy of hydrogen bonds to be drawn |
| C | Information about individual residues |
| 1 | Numbers/characters to be plotted for each residue: consecutive residue numbers |
| | OR brookhaven sequence numbers |
| | OR DSSP accessibility |
| | OR added integer data from another file |
| | AND one letter code |
| | OR data from another file |
| 2 | Shape of box specified by |
| | OR secondary structure |
| | OR accessibility |
| | OR data from another file |
| 3 | Dotted or solid box perimeter specified by secondary structure |
| | OR accessibility |
| | OR data from another file |

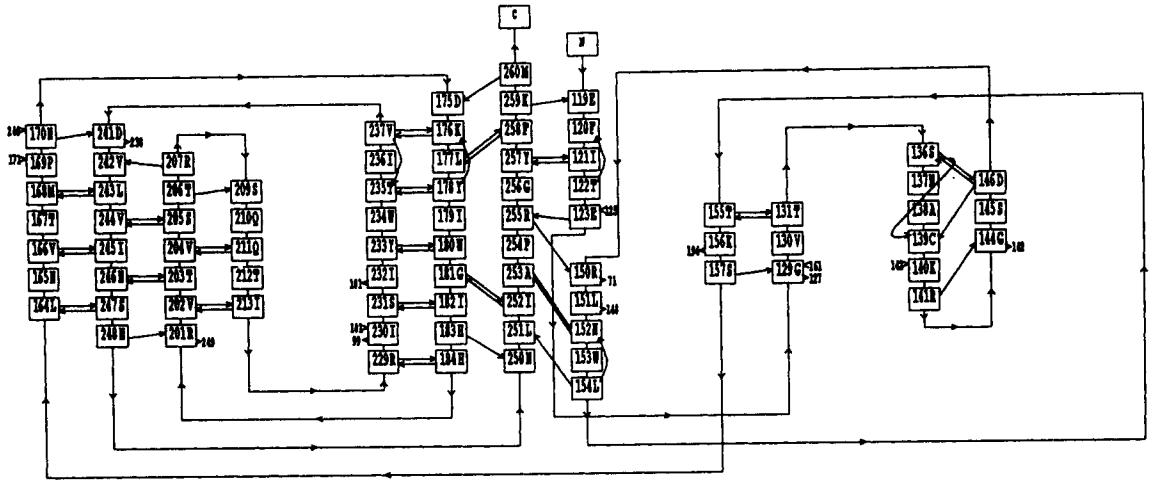
### Helical Wheels and Helical Nets

Helical wheels and helical nets are drawn for the range of helices specified by the user, assuming an α-helical conformation containing 3.6 residues per turn. One helical net is drawn for each helix. For helical wheels, one wheel is drawn for each group of 18 residues, since these constitute a complete helical repeat. Helical wheels display the residue number, one-letter code, and accessibility in concentric rings. In addition the hydrophobicity[7] of the amino acids is represented by arrows with length proportional to the magnitude of the hydrophobicity and dotted or solid to represent positive and negative values.

### Searching for Simple Protein Motifs

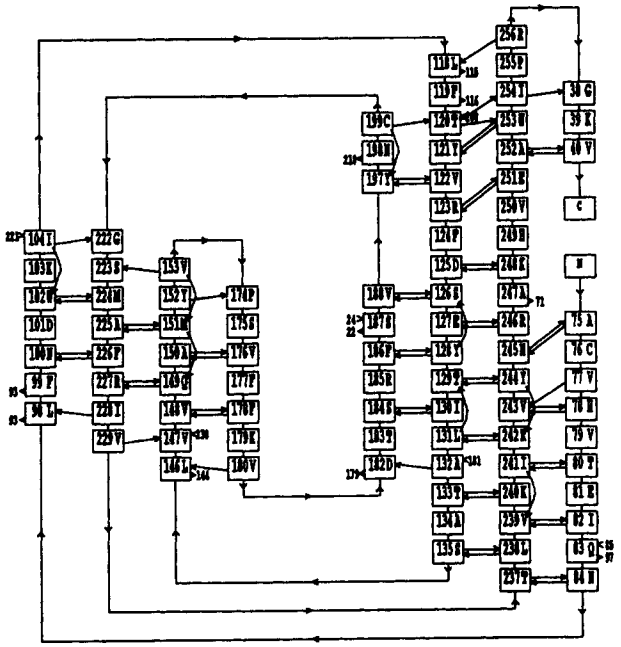
The final option within HERA calculates the connectivities of sequentially adjacent β-strands within each sheet. The connectivities are defined according to the notation of Richardson.[8,9] Each connection is defined by a number which represents the number of strands it crosses over in the sheet and in which direction, with an "x" added for crossover connections.

a



HAEMAGGLUTININ

b



RHINOVIRUS COAT PROTEIN

Fig. 2. Hydrogen bonding diagrams illustrating the jelly roll domains of **(a)** influenza virus haemagglutinin (1HMG) (residues 119–260 of chain A) and **(b)** human rhinovirus coat protein (4RHV) (residues 75–end of chain 1 and residues 38–40 of chain 3). The Brookhaven sequence number and one-letter codes are shown for each residue.

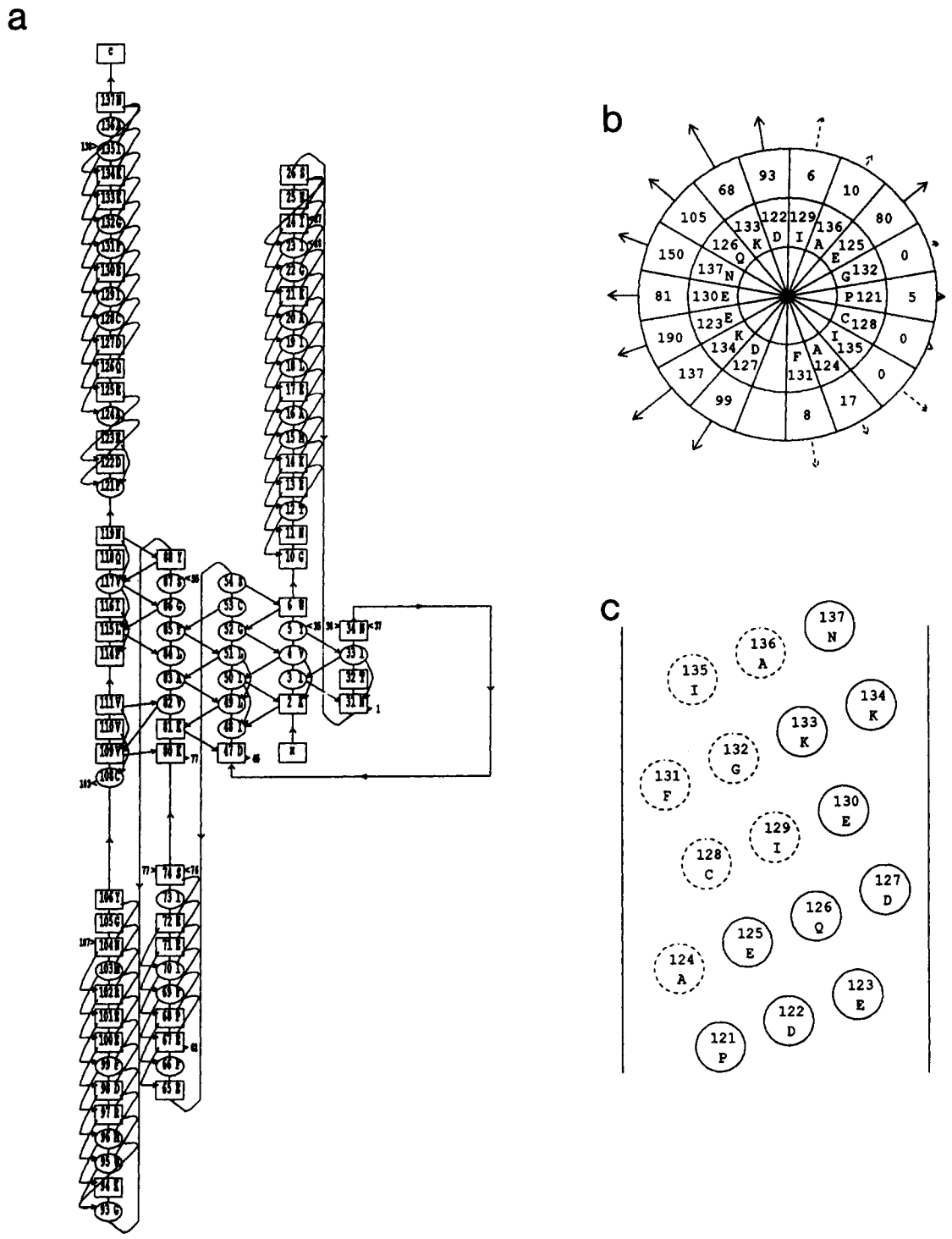



Fig. 3. **(a)** Hydrogen bonding diagram illustrating both sheet and helical regions of flavodoxin (4FXN). The Brookhaven sequence number and one-letter code are shown within the box for each residue. The shape of each box is determined by the absolute solvent accessible area of the residue as calculated using the Kabsch and Sander algorithm. Circular boxes represent residues with a solvent accessible area of up to 20 $Å^2$ and rectangular boxes represent residues with more than 20 $Å^2$ solvent accessible area. **(b)** Helical wheel representing the last helix of flavodoxin (residues 121–137). The one-letter code and Brookhaven residue number are drawn in the innermost ring, and solvent accessible area (calculated as in **a**) in the second ring. The arrows represent the hydrophobicity of the residues. The length of the arrow is proportional to the absolute value of the hydrophobicity; solid arrows represent hydrophilic residues (negative hydrophobicity) and dotted arrows represent hydrophobic residues. **(c)** Helical net representation of the same helix as in **b** showing one-letter code and residue number. Hydrophobic residues are represented by dotted circles and hydrophilic residues by solid circles.

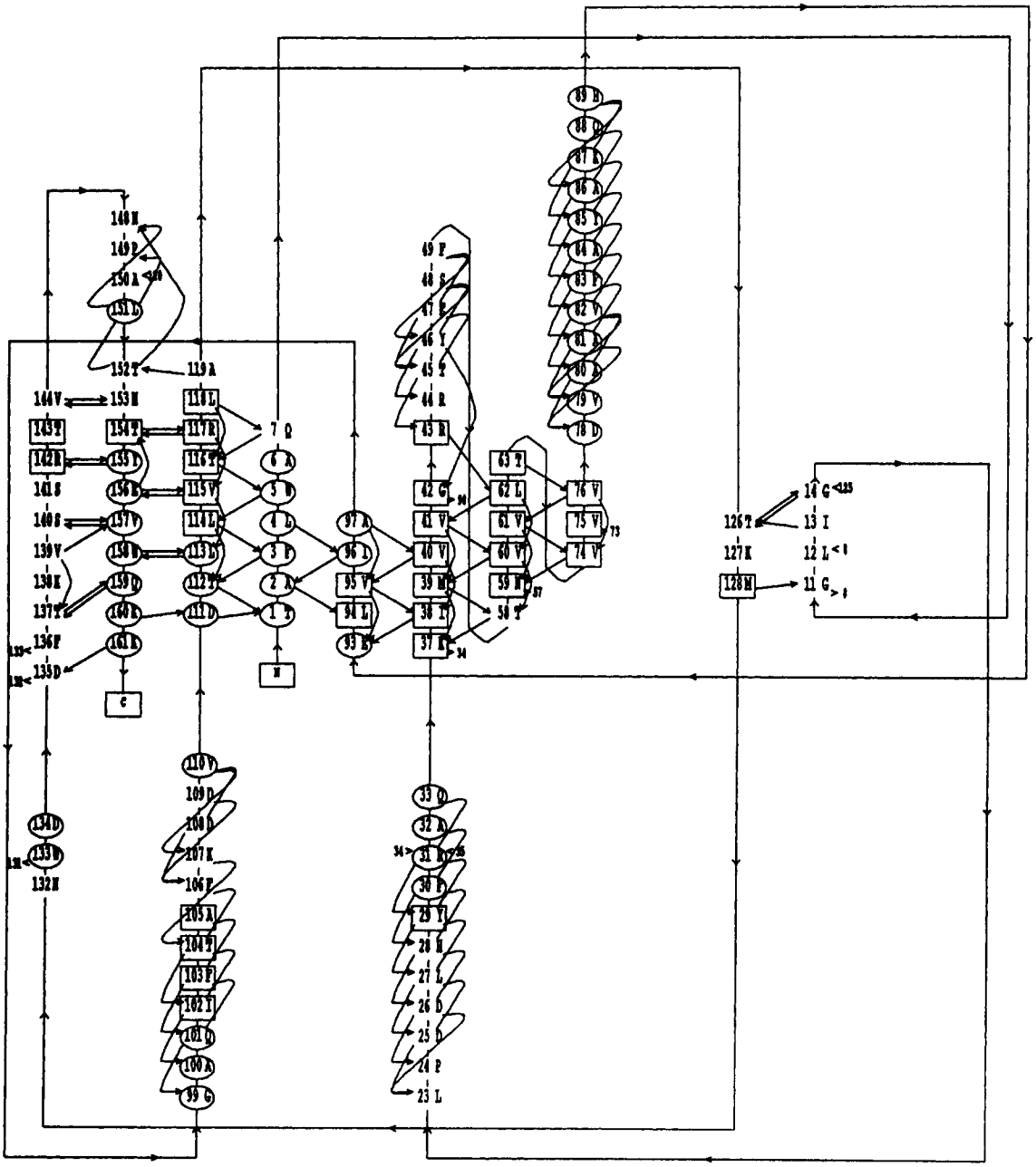
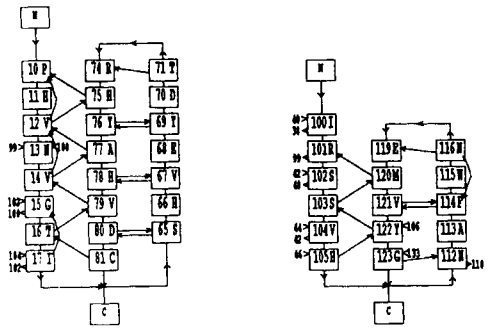


Fig. 4. Hydrogen bonding diagram of sheet and helical regions of dihydrofolate reductase (3DFR). Superimposed on the diagram is information about the predicted secondary structure calculated using the algorithm of Robson and Garnier. Circles represent residues which have been predicted as helical and rectangles represent residues predicted as sheet.

In this case the program reads in a list of secondary structure files, which are processed by the β-sheet topology routines used for calculating the hydrogen bonding diagram, thus generating the topology of each sheet. The β-strands, numbered sequentially from the N-terminus, are then taken two at a time and, if they are in the same sheet, their connectivity is calculated. The connectivities can either be output as a list which could be further pro-

Fig. 5. Hydrogen bonding diagrams of all the examples of ψ-loops extracted from the Brookhaven Data Bank. **(a)** Single ψ-loops (i) of "+2,−1" topology: from left to right elongation factor TU (1ETU), thermolysin (7TLN), and pyrophosphatase (1PYP) (ii) of "+2,−1x" topology: carboxypeptidase (5CPA) and $\alpha_1$-antitrypsin. **(b)** Double ψ-loops of glyceraldehyde 3-phosphate dehydrogenase (3GPD), endothiapepsin (4APE), and carboxypeptidase (5CPA). The other aspartic proteinases have a topology similar to endothiapepsin.

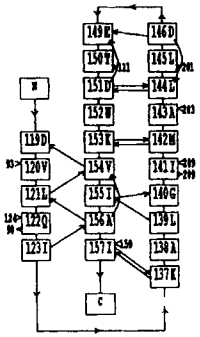
a i



ELONGATION FACTOR TU

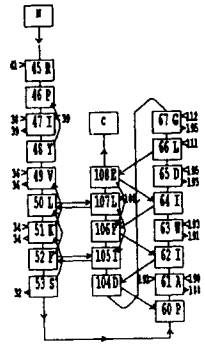


THERMOLYSIN

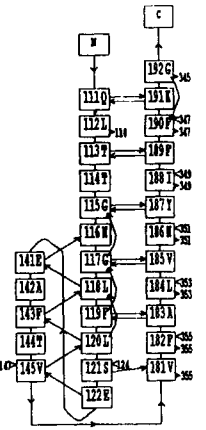


PYROPHOSPHATASE

a ii

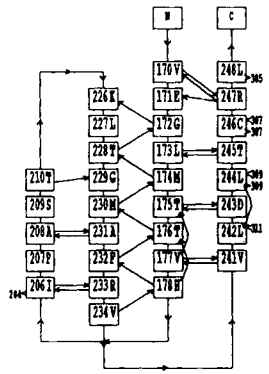


CARBOXYPEPTIDASE A

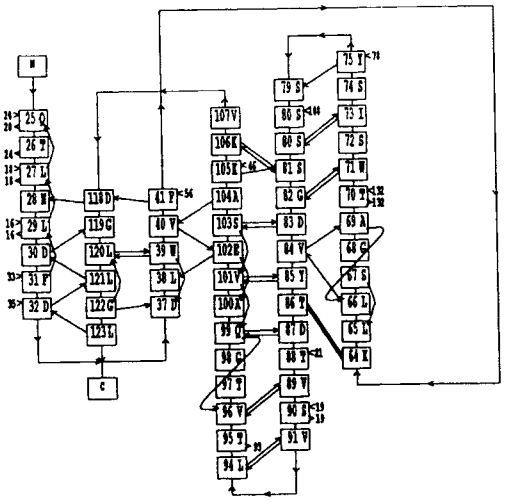


ALPHA-1 ANTITRYPSIN

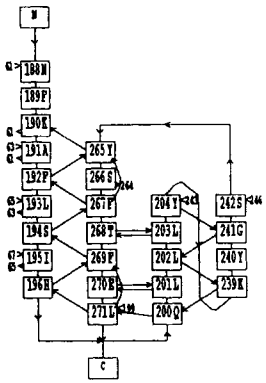
b



GLYCERALDEHYDE 3 PHOSPHATE DEHYDROGENASE



ENDOTHIAPEPSIN



CARBOXYPEPTIDASE A

Fig. 5. Legend appears on page 208.

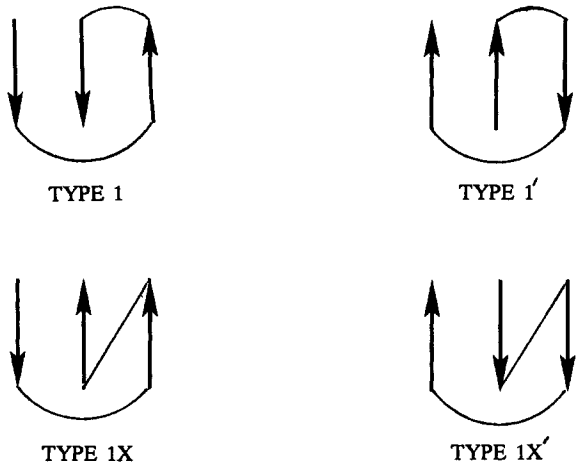



Fig. 6. Schematic diagrams illustrating the strand topologies in the four possible types of single ψ-loop. With the exception of type 1′ these have all been observed in the current data set.

cessed manually, or can be searched to extract simple structural features. In the example illustrated here, the connectivity data are searched for examples of ψ-loops, which are defined by two adjacent strands in the sequence occurring in the same sheet, and having a "+2" connection.

## RESULTS AND DISCUSSION

Since the overall topology of the protein fold is very clearly represented on the hydrogen bonding diagrams, HERA can be used for comparison of structures of proteins belonging to the same homologous family. One such family comprises the viral coat proteins, which have a characteristic "jelly roll" topology. Figure 2 shows hydrogen bonding diagrams of two members of this family; the jelly roll domains of influenza virus haemagglutinin[10] and human rhinovirus coat protein.[11] One can clearly see the common topology involving eight strands in two sheets, as well as the structural variation within the family. Haemagglutinin has two extra small sheets inserted near the N-terminus end of the domain, while the rhinovirus coat protein has two extra short strands inserted into the second sheet of its jelly roll domain. Information such as structurally corresponding strands can easily be extracted from such diagrams.

Residue specific information can also be included. Figure 3a illustrates the addition of accessibility data to a hydrogen-bonding diagram of flavodoxin,[12] including both β-sheet and α-helical regions. Accessibility is indicated by the shape of the box representing each residue, with circular boxes representing buried residues while rectangular boxes represent residues accessible to the solvent. This comparison is qualitative, but HERA can also include the numerical accessibility values within each box if a more quantitative analysis was required.

The figure highlights the predominance of buried residues in the central three strands of the sheet with the ends of the strands and the two edge strands more accessible as expected. Along the helices buried residues occur every three to four residues, corresponding to one face of the helix.

The position of the residues around the helix can be more easily visualized on a helical wheel diagram, and Figure 3b shows a helical wheel representation of the last helix of flavodoxin (residues 121–137). The outer ring of numbers represents the accessibility values, and the buried face of the helix can be easily identified. The helical wheel also provides a means of correlating accessibility with other attributes, such as residue hydrophobicity; the lengths of the arrows around the helical wheel are proportional to the hydrophobicity, with solid and dotted arrows representing hydrophilic and hydrophobic residues, respectively. As expected, the hydrophilic residues in the last helix of flavodoxin tend to be solvent exposed and hydrophobic residues tend to be buried. We plan to use these diagrams to do a more general correlation between residue hydrophobicity and solvent accessibility in α-helices. The helical net in Figure 3c emphasizes the position of the residues along the helix, and the hydrophobic residues are seen to form a buried surface along the helix length.

Figure 4 illustrates how predicted secondary structure data calculated using the algorithm of Robson and Garnier[13] is superimposed on the hydrogen bonding diagram for dihydrofolate reductase.[14] Residues predicted as helix and sheet are denoted by circular and rectangular boxes, respectively, and correctly and incorrectly predicted regions can be easily distinguished. These diagrams are being used in a more general assessment of the correlation between prediction accuracy and tertiary structure.

Where large numbers of proteins are to be analyzed, an automated procedure for generating hydrogen bonding diagrams greatly speeds up the process of extracting particular structural motifs of interest. One such motif, which can be easily identified from diagrams illustrating the hydrogen bonding pattern within β-sheets is the so-called ψ-loop which was first identified in the aspartic proteinase family.[15] These are characterised by a "+2" hairpin connection between two sequentially adjacent strands, according to the notation of Jane Richardson.[8,9] We initially identified these motifs by visual inspection, and later modified the program to allow ψ-loops to be identified automatically. A list of the proteins in the Brookhaven Data Bank found to contain ψ-loops, and the associated strand connectivities are shown in Table II.

The most obvious feature of the ψ-loops is their comparative rarity; the motifs are found in only seven unrelated proteins from a database of over 100 nonhomologous structures. This is not particularly

**TABLE II. List of ψ-Loops Found in the Brookhaven Data Bank**

| Protein | Brookhaven Code* | Number of ψ-loops | Strand connectivity |
|---|---|---|---|
| Endothiapepsin | 4APE[16] | 4 | +2,+3x,−1,−1,−2 |
| Penicillopepsin | 2APP[17] | 4 | +2,+3x,−1,−1,−2 |
| Rhizopuspepsin | 3APR[18] | 4 | +2,+3x,−1,−1,−2 |
| Pepsinogen | 1PSG[19] | 2 | +2,+3x,−1,−1,−2 |
| Elongation factor TU | 1ETU[20] | 1 | +2,−1 |
| Thermolysin | 7TLN[21] | 1 | +2,−1 |
| Pyrophosphatase | 1PYP[22] | 1 | +2,−1 |
| Carboxypeptidase A | 5CPA[23] | 3 | +2,−1x; +2,+1x,−2 |
| $\alpha_1$-Antitrypsin | 6API[24] | 1 | −1x,+2 |
| Glyceraldehyde 3-phosphate dehydrogenase | 1GD1,[25]3GPD[26] | 1 | −2,−1,+2 |

*The superscripted numbers in this column correspond to the papers referenced at the end of the text.

surprising, since they require two strands which are capable of hydrogen bonding to each other to allow a third strand in between, a process which seems rather unlikely to occur during protein folding. Even within this rather select group, however, the ψ-loops are not all identical. The simplest ψ-loop (type 1) is composed of three consecutive strands in a +2, −1 topology (Fig. 5ai). There are just three examples of this in the data bank—elongation factor TU,[20] thermolysin,[21] and pyrophosphatase.[22]

A second type of single ψ-loop (type 1X) containing a crossover connection instead of the −1 hairpin is found in the N-terminal region of carboxypeptidase A[23] and in $\alpha_1$-antitrypsin[24] (Fig. 5aii). In carboxypeptidase A the topology is +2, −1x (type 1X); $\alpha_1$-antitrypsin is related to this by a chain reversal and has the topology −1x, +2 (type 1X′). Schematic diagrams illustrating the four possible single ψ-loops and their nomenclature are shown in Figure 6.

The remainder of the ψ-loops occur in pairs (Fig. 5b). Glyceraldehyde 3-phosphate dehydrogenase[25,26] has the topology −2, +1, +2 and consists of a type 1 single ψ-loop with a fourth strand added to the C-terminal end, forming an additional type 1X′ ψ-loop at the same end of the sheet. The C-terminal region of carboxypeptidase A also has one type 1 and one type 1X′ ψ-loop, but these occur at opposite ends of the sheet, giving a different overall topology (+2, +1x, −2). In the aspartic proteinases a double type 1-type 1X′ ψ-loop is created by the insertion of three strands between the second and third strands of a single type 1 ψ-loop. This is illustrated by the N-terminal domain of endothiapepsin[16]; the C terminal domain and the corresponding domains in penicillopepsin[17] and rhizopuspepsin[18] have similar topologies. Pepsinogen[19] has just one domain containing a double ψ-loop similar to endothiapepsin.

We have also used HERA to extract β-hairpins and Greek keys from the Brookhaven Data Bank, and the program could be used to extract any structural feature within one sheet which can be specified by the user in terms of strand connectivities.

## CONCLUSIONS

The examples provided illustrate some of the possible applications of HERA to protein structure analysis. The program reduces considerably the effort required in drawing schematic diagrams, in particular hydrogen bonding diagrams, and offers considerable flexibility both in the organization of the diagram on the page and in the information which can be displayed. The possibility of automatically searching for simple structural motifs greatly aids the task of extracting and analyzing these motifs in order to understand the principles which govern their formation. Our future plans include adapting HERA for interactive use on a graphics workstation, which should further increase the flexibility of its use.

## ACKNOWLEDGMENTS

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