Simulation and display of macromolecular complexes*

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An interactive program for building, manipulating and displaying molecules has been written. The program provides perspective, planar, and stereoscopic views on a computer terminal display. The views are given both for standard observer locations relative to the object and for locations determined and varied by the user. The user can rotate the whole molecule or parts of it relative to any axis in space, which can also be one of the bonds. The whole molecule or parts of it can be translated in a given direction and bond connections can be added or eliminated by the user. One of the subroutines enables juxtaposition of two molecular fragments in such a fashion that two given bonds are aligned and two planes and two corresponding points coincide. Hence the user can join two molecular fragments at a sought relative orientation and location. Another option includes a duplication of a given unit, e.g. an amino-acid or a DNA base. The program is running on the Roswell Park Univac 70 Computer which employs a time sharing system, but it has been written with an emphasis on flexibility and an easy adaptability to any computer. The display at the Roswell Park computer is supported by a hard copy unit, but plotter drawings can also be generated. The program is written in FORTRAN. In our laboratory the program is employed as one of the tools in the study of template properties of polynucleotides and their specific interactions with polypeptides. Few examples are illustrated.

INTRODUCTION

The program described below was developed in our laboratory in connection with a study of the interaction of proteins with DNA and RNA. The feasibility of such a study has significantly increased with the recent progress in the general theoretical and experimental study of conformations of molecules in solution on one hand[1–11] and with the progress in the study of the interaction of polypeptides with polynucleotides on the other hand[12–18].

The theoretical approach to the question of steric complementarity and energetics of polynucleotide–polypeptide complexes may be based on the known stereochemistry of nucleic acids and proteins and on interaction energy calculations. Physical model building is a very valuable tool but this technique suffers from the excessive amount of time required for construction of the models. The most versatile approach is through computational methods which allow rapid construction and transformation of molecules, as well as visual display of the model. A polynucleotide of a selected base sequence and a peptide with selected amino-acid residues can be manipulated under visual observation into positions which would allow them to interact optimally, avoiding at the same time steric conflict between the two structures. The combined man-machine capability can eliminate an enormous amount of unnecessary calculations. Once the computer model building and visualization has established the stereochemically compatible configurations, the strength of the interactions can be calculated and energy minimization procedures may be applied.

Widely used computational and graphic programs include: OR TEP[19], CHEMGRAF[20,21], CRYSNET[22]. The CHEMGRAF and CRYSNET have the graphics and displaying features as well as a model building feature and are particularly powerful in crystallography.

Recently an 'evolving macromodular molecular modelling system' has been developed by Barry *et al.*[23]. The program described below resembles that of Barry *et al.*[23] in its interactive displaying features. The convenience of our program is in its flexibility and adaptability to any system, including systems lacking sophisticated graphics hardware. We have laid emphasis on manipulating molecular structures, with options of building or decomposing any molecule. The way the program is written will enable users to introduce into it any additional features according to their need.

DESCRIPTION OF THE PROGRAM

The *input* to the program is a *file* which contains Cartesian coordinates of atoms and their connections. The specification of a connection will show up graphically in the form of a segment of line between two given atoms. The input may optionally include additional information such as atom and residue names. The program includes the option of *duplicating* any unit and *building* a combined structure out of the given unit according to given bond lengths, bond angles and dihedral angles. Bonds and atoms can be inserted and deleted.

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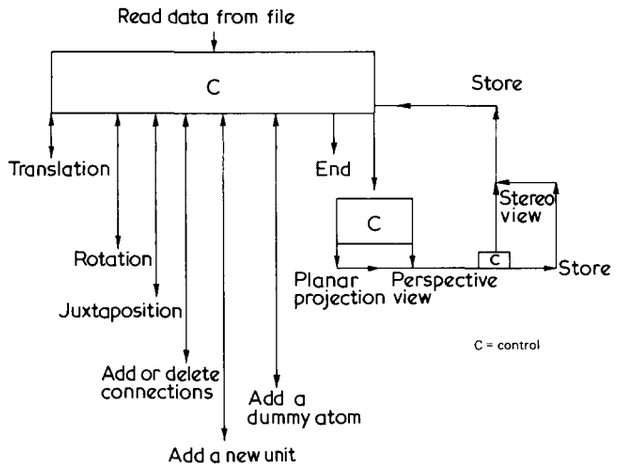

Figure 1 Flow diagram

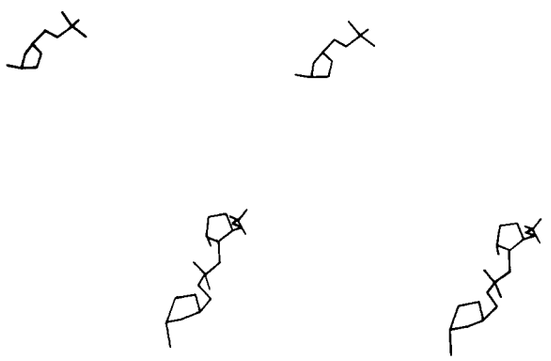

Figure 2 A stereoscopic view of two joint units of phosphoribose and a third unit to be added

Figure 3 A stereoscopic view of three phosphoribose units. The third unit has been juxtaposed at a dummy atom. In this stage which is following that of *Figure 2*, the planes spanned by atoms 1, 2, 3 and 2, 3, 4 are coincident

The program provides *perspective*, planar, and *stereoscopic* views on a computer terminal display. The views are given both for standard observer locations relative to the object and for locations determined and varied by the user. Hence the user can determine the angle of observation, and the distance of the observer from the object by providing the desired eye position. The *size* of the picture can be either standard or variable.

Rotations

A general rotation requires specification of atom numbers, angle of rotation and the axis of rotation. A rotation can involve the whole molecule or a part of it, including a single atom. Whenever atom numbers are not provided a rotation of the whole molecule will result. The axis of rotation can be any line in space and can be specified by providing the coordinates of two points on the axis or by the numbers of two atoms which define it. The latter case amounts to a rotation around a given bond.

Translations

The direction of a translation and the magnitude of the displacement may be determined by a translation vector. A translation can also imply a displacement to a given point.

Juxtaposition

The juxtaposition operation displaces and rotates one molecular fragment relative to another which remains fixed. The user has to specify three points defining planes in each of the structures. The result of the operation is a coincidence of two points, colinearity of two bonds and coplanarity of two planes in the two structures. The juxtaposition operation is the initial step in joining a molecular fragment at a given location and a given orientation and may be followed by required translations and rotations.

Dummy atoms

The subroutine Dumat allows the creation of a dummy atom at any place in the polymer. Once this atom has been created its coordinates are stored at the end of the designated residue in the molecule. This procedure is useful in simulation of hydrogen bonds and attachment of new ligands at sought bond lengths and bond and dihedral angles.

The present version of the program is running on the Roswell Park Univac 70 computer, which employs a time sharing system, but it has been written with an emphasis on flexibility and an easy adaptability to any computer. The language is FORTRAN. The display at the Roswell Park computer is supported by a hard copy unit, but plotter drawings can also be generated. An adaptation to other computers would require a modification of the plotting subroutine and a different enumeration of tape or disk units. The *output* consists of pictures generated at the display and a new file of coordinates and connections. In our computer this file is stored on disk but tape storage or punched cards are easy to generate. The hard copy unit enables the user to trace all the steps performed. Except for a general idea of the structure of the program and input format the user is relieved from memorizing the procedure, since the various steps become self explanatory by messages on the screen. A flow diagram (*Figure 1*) and a few illustrations are provided below.

Each stage shown in the flow diagram may represent seve several steps, in each of which the user makes a decision about the parameters.

The illustrations in *Figures 2–6* represent the building

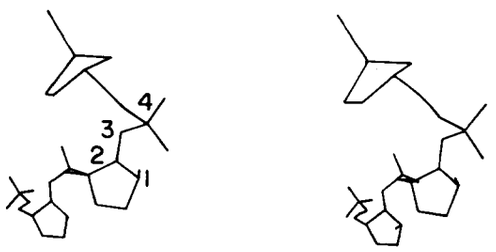

Figure 4 Same as *Figure 3*. The bond connecting atoms 2 and 3 has been drawn

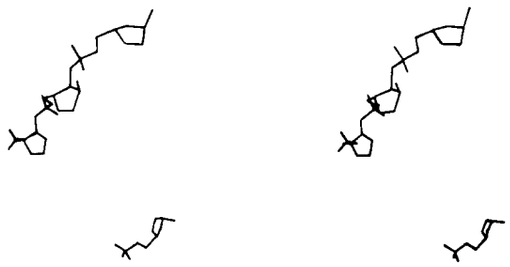

Figure 5 A stereoscopic view of three phosphoribose units as in *Figure 4,* but with an adjustment at dihedral angles to conform with a helical structure. A fourth unit to be added in the next stage is shown

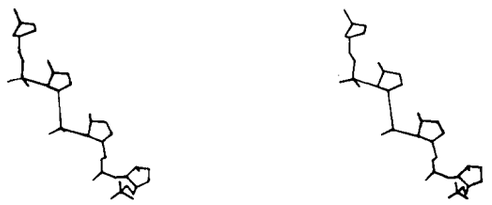

Figure 6 Four phosphoribose units in a helical structure

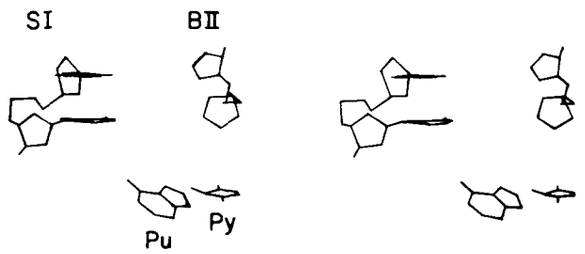

Figure 7 Strand I (SI) includes two phosphonucleotide units. BII, which includes two phosphoribose units is the backbone of strand II. Pu and Py are complementary bases to those in strand I. Strand II is not yet in the helical conformation.

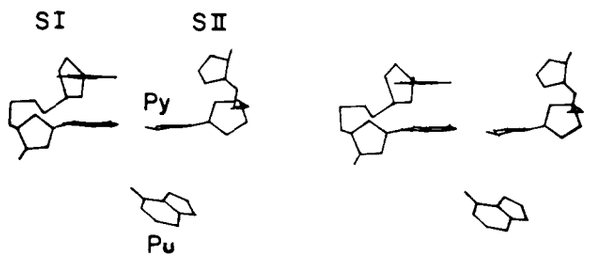

Figure 8 Continuation of the process in *Figure 7,* Py has been attached to the backbone of strand II (SII)

and manipulative capacity of the program. In *Figure 2* we start with two joint units of phosphoribose and a third unit is shown separately. Then a dummy atom is created and positioned (not shown) at the end point of unit No. 2 according to the following specifications: bond length = 1.46 Å, bond angle = 120.0°, and dihedral angle = 110.0°. A similar dummy atom is created at the end of unit 3. In *Figure 3,* we see the outcome of a juxtaposition operation which brings unit No. 3 to the existing chain of two units. In this stage the planes spanned by the three atoms 1, 2, 3, and 2, 3, 4 are coincident. In *Figure 4* unit No. 3 is shown to be attached to the chain by the addition of a connection or bond between atoms 2 and 3. In *Figure 5* the phosphoribose chain, which consists of three units, is transformed to a helical conformation. This is carried out by performing rotations which adjust the dihedral angles, i.e. by adjusting the backbone torsional angle ϕ_1'. In the next stage a fourth unit is generated and in *Figure 6* it is shown to be attached, thus forming four phosphoribose units in a helical structure.

In *Figures 7–11,* we show stages in the building of a double helix of DNA. In *Figure 6,* we see four separate structures which include one strand with two phosphonucleotide units (SI); another strand with the phosphoribose backbone only, and two bases Pu (purine) and Py (pyrimidine), which are complementary to those in strand I. In *Figure 9,* we see the two bases attached to strand II (SII), which is not yet in a helical structure. In *Figures 10* and *11,* we show respectively, side and top views of a double stranded fragment of B-DNA, thus illustrating different conceptual perceptions of the same object.

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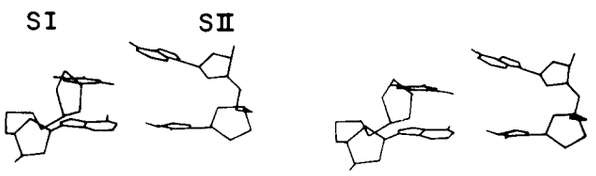

Figure 9 Continuation of process in *Figure 8,* Pu has been attached to strand II (SII)

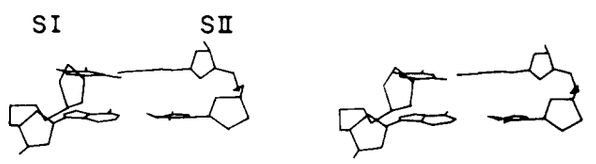

Figure 10 Continuation of the process in *Figure 9.* Adjustment of rotational angles in strand II (SII) has produced a helical structure. This is a side view

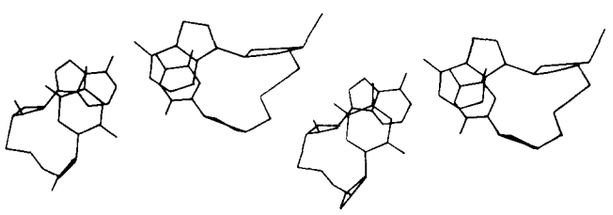

Figure 11 A top view of the same fragment of B-DNA which is shown in *Figure 10,* from a side view

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