Macromolecular Modeling System: The Insulin Dimer

Garland R. Marshall, Ph.D., Janis Beitch, Robert A. Ellis, M.S., and John M. Fritsch, Ph.D., St. Louis

A macromolecular modeling system has been developed which allows a display of a protein as determined by crystallography. This system consists of a micro-LINC-300 computer which is interfaced to a special purpose computer constructed from macromodules[1] and an Evans and Sutherland matrix multiplier and line drawing scope as shown in figure 1.

Macromodules are restructurable digital computer elements which allow one to design and construct quickly a special purpose machine. In this case, the macromodules store the coordinates and connectivity supplied them through the LINC. Upon a single command from the LINC, the macromodular components supply the coordinates and the command words to the matrix multiplier and scope for display of the molecule. The system requires approximately 10-20 microseconds per bond for the display with scaling, position and rotation under control of parameter knobs. This means that molecules of the size of carboxypeptidase (MW 34,600) can easily be displayed and viewed under dynamic control.

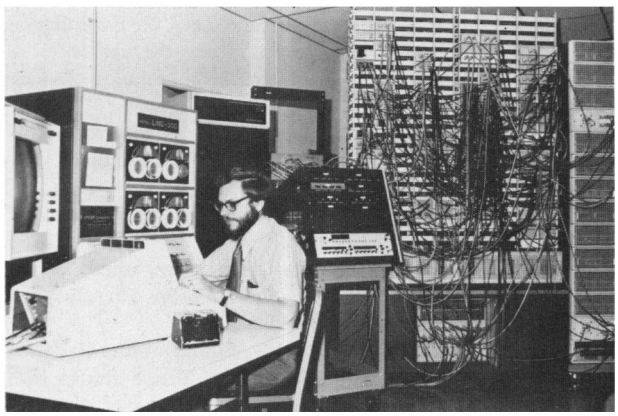

FIG. 1. Macromolecular modeling system from left to right: Evans and Sutherland LDS-1 vector display; micro-LINC-300 computer; (foreground) LINC display and keyboard with operator (R.A.E.); Evans and Sutherland vector generator and matrix multiplier; macromodule console; macromodular computer and LINC interface (below); and macromodular memory.

The algorithms necessary for such a display system have already been described for a small computer system.[2,3] The macromolecular modeling system is only a logical outgrowth of the previous system in that it requires more extensive hardware capability.

An additional feature is the computer-controlled Arriflex 16 mm. movie camera[4] which allows us to animate movies extremely conveniently. Simply filming the CRT display is not acceptable due to the beat frequency between the frame rate of the camera and the rate of display of the picture. For this reason, the computer controls the film advance and shutter of the movie camera in order to synchronize the display and framing.

A movie of insulin illustrating this display system was made with coordinates furnished by Prof. D. C. Hodgkin and co-workers at Oxford.[5] The three-dimensional nature of the model of insulin was illustrated with the kinetic depth effect. Continuous rotation of the displayed structure gives a good three-dimensional effect. The following structural features of the insulin dimer were emphasized in the film:

1. *Dimer peptide chains.* This was first demonstrated by growing the peptide chain of molecule one by the addition of one residue at a time with only the alpha carbons shown and connected (carbon alpha display) and with the cystine disulfide bridges shown. Then the second molecule was similarly generated while the first was displayed. The resulting picture is shown in figure 2. A similar display was generated showing the full backbone

From the Department of Physiology and Biophysics and Computer Systems Laboratory, Washington University, St. Louis, Missouri 63110.

Dr. Marshall is Established Investigator, American Heart Association.

Paper presented at the Fiftieth Anniversary Insulin Symposium, Indianapolis, Indiana, October 18-20, 1971.

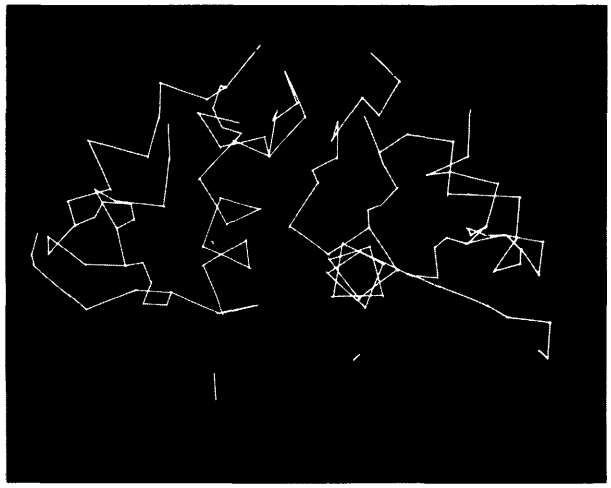

FIG. 2. Insulin dimer viewed directly down B chain helix of molecule one. Carbon alpha display with disulfide bridges and histidine-zinc coordination bonds shown.

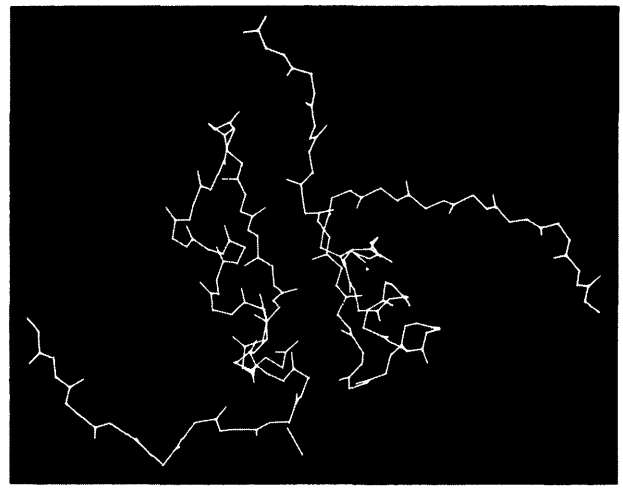

FIG. 4. Backbone display of the two B chains in the insulin dimer. The antiparallel β-pleated sheet formed between the two chains is evident in the center.

display (all atoms except side chains). Other variations included the backbone plus histidine residues and their zinc coordination bonds as well as the full display of the entire structure of both molecules as shown in figure 3.

2. *Dimer interactions.* This was examined by growing one chain of molecule two while continuously displaying one chain of molecule one. It was clearly shown that of the possible interaction between A_1-B_2, A_1-A_2, B_1-A_2, or B_1-B_2, the ones between B_1 and B_2 were apparent and most probably of a β-pleated sheet nature, as shown in figure 4.

3. *Invariant residues.* The possible importance of residues which have remained invariant over the known insulin sequences to the structure and possible biological activity was shown for two cases. Invariant residues whose role is critical in the dimer interface (B_{12}, B_{16}, B_{24}) were shown in both molecules with the alpha carbon backbone display as shown in figure 5. The invariant residues (A_1, A_5, A_{19}, A_{21}) were similarly shown. These may be important for biological activity, as they are on the surface of the crystal structure and do not appear important in dimer or hexamer interactions.

In conclusion, it is hoped that the motion picture film on the insulin dimer illustrated both the capability

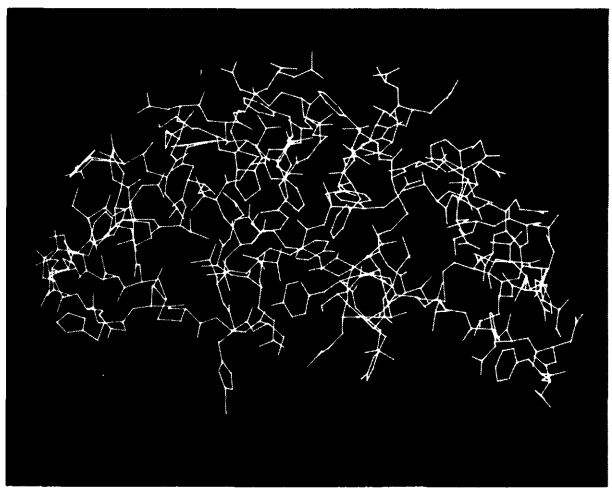

FIG. 3. Insulin dimer complete with side chains.

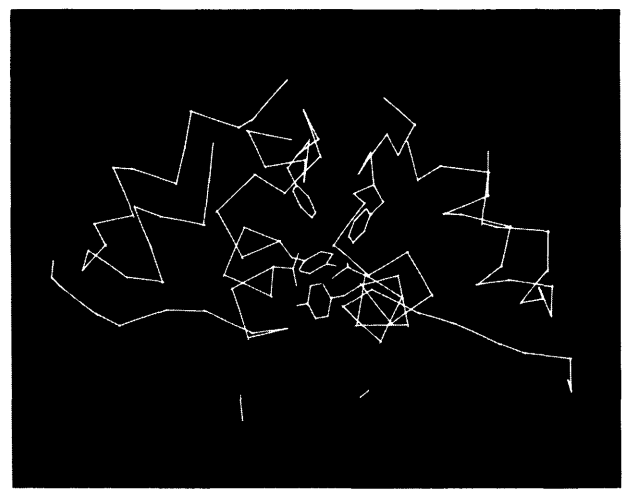

FIG. 5. Insulin dimer showing species in variant residues (B_{12}, B_{16}, B_{24}) which are probably involved in dimer interaction.

and flexibility of display which one can obtain with the molecular modeling system described as well as the beauty and significance of the crystal structure as determined by Prof. D. C. Hodgkin and her co-workers at Oxford.

Further development of the molecular modeling system should allow its direct use in crystallography to fit an electron density map with a molecular model.

ACKNOWLEDGMENTS

The following must be singled out of the many who have contributed either directly or indirectly to the production of this film: Guy Dodson, Tom Blundell and David Barry of Oxford for their stimulation; Charles Molnar and Gerald Johns of C.S.L. for encouragement and technical support; and Gary Parker and David Shupe of C.S.L. for film editing and other contributions.

REFERENCES

[1] Ornstein, S. M., Stucki, M. J., and Clark, W. A.: A functional description of macromodules. Proceedings, A.F.I.P.S., 1967 Spring Joint Computer Conference, Vol. 30. Washington, D.C., Thompson Book Co., 1967, p. 337-355.

[2] Barry, C. D., Ellis, R. A., Graesser, S. M., and Marshall, G. R.: CHEMAST: A computer program for modelling molecular structures, Proceedings, Int. Fed. Information Processing Societies, Ljublana, Yugoslavia. North-Holland Publishing Co., 1971. In press.

[3] Barry, C. D., Ellis, R. A., Graesser, S. M., and Marshall, G. R.: Organic Molecular Models by Computer. Symposium on Computer Applications in Organic Chemistry. Abstracts, 162nd National American Chemical Society Meeting, Washington, D.C., 1971.

[4] Johns, G. C.: In preparation.

[5] Blundell, T. L., Cutfield, J. F., Cutfield, S. M., Dodson, E. J., Dodson, G. G., Hodgkin, D. C., Mercola, D. A., and Vijayon, M.: Atomic positions in rhombohedral 2-zinc insulin crystals. Nature (London) 231:506-11, 1971.