Reports

The Need for Better Macromolecular Models

Abstract. Atomic models useful for small molecules become clumsy, expensive, and even inaccurate when used to represent the large molecules important in biology. More convenient models, authoritatively designed and semi-mass-produced, would be of the greatest value both for teaching and biological research.

Many of the most important current theories of biological structure and function at the molecular level depend on detailed space relationships between atoms in macromolecules. These include theories of DNA (deoxyribonucleic acid) structure, of protein synthesis and structure, of enzyme action, and of antigen-antibody relationships.

These theories are hard for anyone to understand in quantitative detail unless he has a three-dimensional mechanical model of the molecules to look at and manipulate. Unfortunately, the present commercial models—which are excellent for representing small molecules and have contributed tremendously to organic and inorganic chemical progress at the research level as well as at the teaching level—are unsatisfactory for these large biological molecules. As big-molecule models, they are expensive, clumsy, badly connected, and frequently fail to represent correctly, according to our best current knowledge, some of the essential structures, such as peptide bonds and aromatic rings. As a result, the advanced research laboratories in molecular biology commonly make their own macromolecular models in their own shops, often at a cost of thousands of dollars for so elementary a model as a single turn of a DNA double helix. It follows that many laboratories and many good research minds outside these few centers are essentially excluded from participation in detailed discussion of such biochemical structural problems, and the new developments are more difficult to teach or to explain than they ought to be.

I believe that this lack of widely available macromolecular models is therefore a major bottleneck to our progress in biochemistry and molecular biology. It is the purpose of this note to suggest that it might be profitable if some national agencies or organizations interested in the biological field would set up an expert committee to look into the question of semi-mass-production of cheaper and more accurate macromolecular models, possibly under subsidy if necessary. The function of the committee would be to solicit ideas, to determine objectives and standards for such an operation, and to get it started. It would need to include workers in several fields, in particular, some x-ray or electron-diffraction experts on molecular dimensions; organic and quantum chemists, especially persons interested in steric effects; molecular biologists and biophysicists, who know what kind of accuracy is needed and what compromises could be made for mass production; persons who know the scientific apparatus market; and some who know the economics and technology of various methods of model manufacture, such as plastic molding. But the value to biological teaching and research might be many times greater than the cost of such a survey.

The possibilities that such a group could study may become clearer if I list several desirable features that I think could be incorporated in macromolecular models.

1) Molded plastic construction, possibly hollow, with ball-and-socket joints, like the "poppet bead" necklaces that are often used now for lecture demonstrations of intertwined macromolecular helices, chromosome rearrangements, and so on. Models of this type could be light, well connected, and cheap, with costs measured in pennies per atom instead of dollars per atom as at present. The flexibility of the plastic is not as great a drawback as some might think, because it can mirror the flexibility associated with the variable amplitude of thermal vibrations and with the "softness" of the van der Waals' radii in real molecules. An asymmetrical ball-and-socket joint can be used because biological chains commonly also have a built-in asymmetry or polarity of direction.

2) A small scale, possibly in the range from 2 to 5 mm/A. Present models of large molecules are hard to hold together and to support because of their bulk and weight, which varies with the cube of the scale used and could be reduced by a factor of over 100 by going to a 2 mm/A scale. Two different small scales might be useful, a very small one for examining long-range features such as secondary and tertiary coiling, and a larger one for greater accuracy in details.

3) Molding of rigid groups of atoms as single units, wherever possible. This would include aromatic rings, peptide bonds, cyclic sugars, phosphate groups, and —CH_3, —NH_2, —OH, and —CH_2— groups. This can increase by an order of magnitude the cheapness and accuracy of the models as well as the ease of assembly.

4) More accuracy in atomic shapes, for example in the thickness of aromatic rings (3.4 A), the planarity of conjugated amino groups (as in peptides), and the directional variation of nonbonding orbital radii in O, N, and S atoms.

5) Better methods for representing hydrogen bonds. Insert-magnets, with north pole for the donor, south pole for the acceptor, are said to have been tried and might be workable. A good representation of hydrogen bonds is important for many reasons, but one interesting one is that it would permit fitting water molecules accurately into and around the other molecular structures. This is essentially impossible in present models, although some have conjectured that it may be of the greatest structural importance in biology.

6) Representation of hindered rotation about bonds, for example by puckering the ball-and-socket connectors. A C—C single bond would have three favored angular orientations between the groups on the two ends. The physical barriers amount to 2 or 3 kcal/mole per bond and could add up to considerable energy in a long molecule with incorrect orientations. This means that the possible configurations of such molecules are much more limited than is generally appreciated from the use of present free-rotation models, and the choice of the best configuration might be biologically very important.

In the ideal model, some other lesser features may also deserve considera-

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Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* **125**, 16 (1957)].

tion. One would be the use of model materials of unit density. This would give the models neutral buoyancy in water and they could be suspended unsupported, so that their "spontaneous" three-space configurations would have greater fidelity. This could be of particular value in coiling-uncoiling and replication problems. Other useful inventions for an ideal model would be a way to represent strong ionic and electrostatic attractions, or the weak charge-transfer forces. In fact, it would be desirable, although it is probably not feasible, to represent all the major chemical force-fields with strengths more or less according to scale.

Some day it would also be most valuable to have molecular models that can represent a chemical reaction, by snapping from some ground-state configuration into some transition-state configuration and on over into the new configuration after the reaction. I tend to believe that certain DNA, enzyme, and other configuration problems may not be solvable by considering merely the static configurations in the dry state, and that we will have to think in terms of the dynamic transition-state configurations of the whole coiled system at the moment of attachment or reaction and in the presence of water.

However this may be, it would appear that it should be feasible to incorporate in molecular models at least some of the features I have mentioned. But I have listed them mainly to exemplify my main point, which is that molecular models could be made which would be cheaper, more widely available, more convenient, and yet more accurate in representing the essential features of macromolecular structures than any models we now have. The production of such models would be of the greatest importance to both research and teaching in the biophysical and biochemical sciences.

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Blood Types in Fur Seals

Abstract. Individual variations exist in the erythrocyte antigens of fur seals (*Callorbinus ursinus*).

Studies of blood type are being conducted on several species of whales and fishes (*1*). They have the common aim of obtaining information useful in the characterization of intraspecific interbreeding populations similar to those that have been demonstrated in human beings and cattle (*2*). Our research shows that such studies have a potential for similar usefulness in the fur seal species (*Callorbinus ursinus*).

Table 1. Summary of fur seal blood types so far differentiated by the absorption of rabbit anti-fur seal serum.

Type	Distinguishing antigens	Individuals collected and date (1958)
1	I, II, III	No. 636, 23 Mar.
2	I, III	No. 132, 24 Mar.; No. 637 and 639, 23 Mar.
3	III	All except those noted here
4	Negative	No. 329, 27 May

Table 2. Reactions of the serums of winter (1959) fur seals with fur seal erythrocytes.

Reaction	Asiatic coast	American coast
A. Number of cell samples reacting positively with serum No. 408 (American coast)		
Positive	2	0
Negative	142	27
Total	144	27
B. Number of serum samples reacting positively with cells of individual No. 113 (Asiatic coast)		
Positive	5	12
Negative	5	8
Total	10	20

The fur seals of the North Pacific Ocean are noted for their interesting migratory and breeding habits. These seals winter in two separate groups off the northern coast of Asia and North America, respectively. These groups move north in the spring to reproduce on the Robben, Komandorski, and Pribilof islands. An international commission representing Canada, Japan, the United States, and the U.S.S.R. was established in 1957 to coordinate the management of this species (*3*). Present biological studies under this commission include efforts to determine the degree to which the total species population may be subdivided into separate breeding stocks, and the extent to which these stocks intermingle in winter. Starting in 1958 these efforts have included some exploratory work in blood typing and serology, carried on independently by Fujino in Japan (*4*) and by Ridgway in the United States (*5*). This paper reports on blood type variations discovered for the first time in this species by Fujino. These variations occurred among seals wintering off northern Honshu, Japan.

Table 1 summarizes the results of observations that demonstrated the individuality of these variations. At least four different blood types occur that distinguish certain individuals from the majority of seals sampled. While these individuals occur in low frequency, additional antigenic variations exist that have not yet been sufficiently characterized. These include one within an antigen that resembles the species-specific human B-like antigen recently described in fin whales (*6*). Isoimmunization, although not yet attempted, would seem to offer a practical possibility for revealing further blood types in this species.

No natural antibodies have yet been found in serums of the horse, cow, pig, goat, and sheep that distinguish individual blood types. However, the normal serums of four rabbits all agglutinated type 1 cells (No. 636), and three of these also agglutinated type 2 cells (No. 639). Titers averaged one in eight.

Isoagglutinins also occur at high frequency. A series of 12 serums contained seven that agglutinated type 1 cells (No. 636), plus one that agglutinated both type 1 cells (No. 636) and type 2 cells (No. 639). Titers averaged one in two. Table 2 outlines a simple method of obtaining data on the frequency of isoagglutinin positive types. (In developing this method recognition must be given to the fact that the isoantibodies in some serums are lost after several freezings and thawings, and that therefore isoserums should be divided into aliquots while they are still fresh.)

While the 234 samples studied in 1958 were collected rather evenly over a range of 4 months (March through June), all individuals of types 1 and 2 were taken on 23 and 24 March. Similarly, out of 144 samples tested in 1959, both isoagglutinin positive individuals were collected on 2 April. These samples were collected during March, April, and May. This nonrandom distribution of types in the early part of the season is suggestive that some localization of breeding stocks is maintained within the winter population from year to year.

The glycerol-freezing technique, as applied in the blood typing of whales (*7*), has been successfully used to preserve intact erythrocytes of fur seals for several months. This observation, together with those on antigenic variations summarized above, leads to the conclusion that there is a good probability that blood type antigens could be used to advantage in research on fur seal populations (*8*).

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References and Notes

1. K. Fujino, *Sci. Repts. Whales Research Inst. Tokyo No. 11* (1956), p. 85; G. J. Ridgway, J. E. Cushing, G. L. Durall, *U.S. Fish Wildlife Serv. Spec. Sci. Rept., Fisheries Ser. No. 257* (1958); A. Suzuki, Y. Shimizu, T. Morio, *Repts. Nankai Regional Fisheries Research Lab., Kochi, No. 8* (1958), p. 104; L. Sprague,