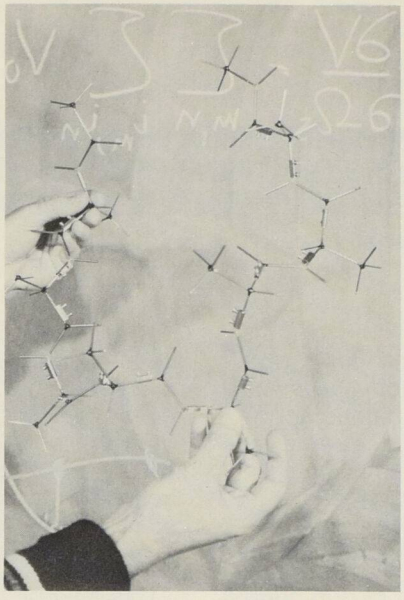
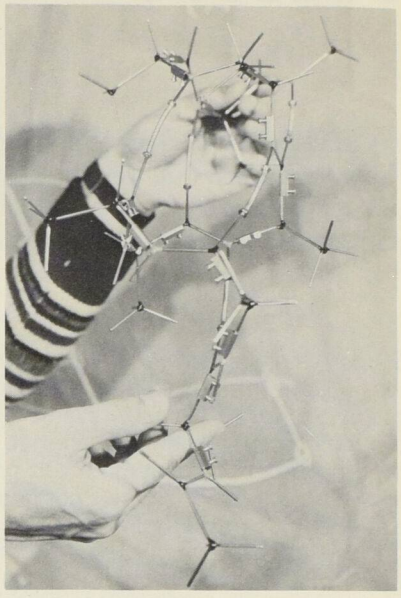
protein folding





The unfolded or denatured form of a peptide (octa-alanine) held by Dr. R. Somorjai. Its two folded forms, one of which is an ∝ -helix, are shown on the right.

Le Dr R. Somorjai tient un modèle de la forme non reployée, ou dénaturée, d'un peptide (octa-alanine). Ses deux formes reployées, dont une hélice ∝, sont visibles à droite.

to be solved in any reasonable length of time, even with the fastest computers. (The road meanders to such an extent that following it accurately would be too time consuming.) Faced with a problem of considerable computational difficulty, Dr. Somorjai decided to take the hierarchical approach: in mathematical terms, he partitions the variables that govern protein folding into "essential" and "none-essential" sets and performs his calculations with respect to only the essential variables. Returning to our illustration, the partitioning corresponds to discovering a ravine which slowly winds down toward the valley and contains the road meandering along its floor. By determining the (essential) direction of the ravine, one also finds the general direction of the road without the necessity of following each (nonessential) meander. Dr. Somorjai has succeeded in translating these qualitative concepts into feasible quantitative mathematical procedures.

In the course of his investigations, Dr. Somorjai carefully follows relevant experimental developments and keeps in close contact with experimentalists. For example, Nuclear Magnetic Resonance measurements on small peptides and hormones in solution, carried out by Dr. R. Deslauriers at NRC's Division of Biological Sciences provide Dr. Somorjai with data which aid in the verification and improvement of his theory. In turn, Dr. Somorjai's calculations will help in interpreting these experimental results in terms of the actual structure and detailed molecular motion of these peptides.

Dr. Somorjai and his collaborators, Research Associate Dr. H. Katz, an applied mathematician, and Dr. E. Ralston, a biochemist and Visiting Scientist from the Free University of Brussels, are also developing and implementing ideas which are natural complements and generalizations of the protein folding problem. In order to realize some of these ideas, the group is exploring the usefulness of mathematical concepts from control theory such as "sensitivity analysis". Sensitivity analysis enables one to compute the influence of external disturbances on a given physical process. For example, the effect of solvent perturbations on the stability of a given folding path can be determined. Another likely application is for the quantitative study of structure-function-activity relationships in general and enzyme-substrate or hormone-receptor interactions in particular. To return to our metaphor: the external influence could be portrayed as the shifting of the whole terrain, mountain and valley, as would happen during an earthquake. This shifting could have several effects: only some sections of the road would change; the road would be completely destroyed but the direction of the ravine containing it would remain the same; or the whole terrain could undergo complete upheaval. Dr. Somorjai feels that protein folding occurs in several stages. The early stage corresponds to seeking out the general direction of the ravine containing the road; this direction should be stable to small external disturbances, otherwise a denatured protein would never renature. In the vicinity of the valley bottom another stage sets in in which accurate tracing of each meander in the road may be essential; on the other hand, the enzyme-substrate or hormone-receptor interaction may correspond more closely to the upheaval of the whole terrain.

Answers to questions of this nature have far-reaching practical implications since they aid in the design of new substances (drugs, hormones, enzymes) of enhanced biological activity. Thus problems which were selected for their intrinsic scientific interest and intellectual challenge can lead to solutions having immediate and real rewards. In fact, Dr. Somorjai, who also holds a position as Adjunct Professor at the University of Illinois Medical Center, is collaborating with Professor Roderich Walter, Head of the Biophysics and Physiology Department at the Center, to design new hormones on the basis of the theoretical considerations sketched above.

"Problems of this complexity demand a collaborative approach; it is also essential that traditional boundaries between individual scientific disciplines disappear. Only a multidisciplinary approach that integrates the concepts and methods of many fields has a legitimate hope of success in finding meaningful solutions to the intricate problems of biology," says Dr. Somorjai. Theoretical biology is, or should be, such an approach and it seems to offer the intellectual excitement and stimulation that attracted the young Bronowski to atomic physics in the twenties. □

David Peat