Nobel Laureate Lectures

NO.BL.01 THE SAS MAXIMAL PRINCIPLE. Herbert Hauptman, Hauptman-Woodward Medical Research Institute, Inc., 73 High Street, Buffalo, New York 14203-1196 USA

When SAS diffraction data are available, the phase problem may be formulated as one of global optimization. Although the objective function has a myriad of local maxima, its global maxima, no more than two, are readily found by means of the newly derived SAS tangent formula. The initial applications show that the method is capable of producing, ab initio, the values of thousands of phases with acceptable average errors (< 50°) and interpretable maps, even with experimental data at a resolution of about 2.5Å.

The method described here also solves the associated redundant system of linear congruences, an alternative formulation of the phase problem when SAS data are available.

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NO.BL.02 LIGHT, CHARGE, AND PROTEIN STRUCTURES. Johann Deisenhofer, HHMI / UT Southwestern Medical Center, 5323 Harry Hines Blvd. Dallas, Texas 75235-9050

Some of the most fundamental processes in the biosphere, such as photosynthesis and cell respiration, involve the interaction of light with, and the movement of charges through proteins and bound pigments. Light driven electron transfer reactions have also been found in DNA repair enzymes. The 3-D structures of the photosynthetic reaction center, the cytochrome b/c1 complex, and DNA photolyase are suitable examples for the discussion of such processes. Personal bias in their selection cannot be denied.

NO.BL.03 DIRECT METHODS. Jerome Karle, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D. C. 20375-5341, U.S.A.

A central feature of various approaches to structure determination that fall under the general terminology, "direct methods," will be discussed, starting with the Patterson function and bringing the subject up to the present. This includes, of course, various methods for phase determination. It appears that the central feature, which is very useful, also is the source of a limitation on the applicability of various direct methods. Comparisons among the various methods will be made, including their origins in theory and practice. The question arises concerning whether there may be another approach that avoids the problem. This matter will also be discussed.

NO.BL.04 THE DEVELOPMENT OF SLOW NEUTRON SPECTROSCOPY: 1950-1965. Bertram N. Brockhouse, Dept. Of Physics, McMaster University Hamilton, Ontario L8S 4M1 Canada

A discourse on the development of experimental methods for study of the inelastically-scattered neutrons by a crystal and the interpretation of the results in terms of the molecular and magnetic dynamics of the specimen crystal on an atomic scale.

NO.BL.05 PROTEIN CRYSTALLOGRAPHY AND COMPUTING: RECOLLECTIONS OF THE 50s. John Kendrew, The Old Guild Hall, 4 Church Lane, Linton Cambridge, CB1 6JX UK

The 50s were the golden age of basic science, and especially of biology; crystallography, which advanced rapidly during those years, played a major role in this. Our work in Cambridge on the structures of proteins and DNA owed a great deal to good luck and indeed to accidents. With the exception of Jim Watson none of the members of our early group were trained as biologists - or indeed as crystallographers: Max Perutz and I began as chemists and Francis Crick as a physicist. On the protein side Max and I thought that to solve the structure of proteins was the most important problem in biology (this was before the importance of DNA was realised), and that crystallography was the most hopeful method. Until I began the work in 1946 I had never done a course in X-ray crystallography and had to learn at least a little about the subject as I went along. Another piece of good luck was that the Medical Research Council supported us generously for more than ten years during which there were no results and only a few incorrect papers: could it happen today?

Several technical advances were very important; the first rotating anode x-ray tubes (ours was home-made in the Cavendish workshop); and the first densitometer suitable for measuring intensities. Finally there was the electronic computer. The first Cambridge computer was EDSAC I, using thermionic valves and with a store of only 512 words; it began to operate in the early 50s. I was the first member of the group to use it seriously, stimulated by my student Hugh Huxley, so I had to learn programming as well as crystallography; and programming had to be done in machine language because Fortran had not yet been invented. And of course had the computer arrived ten years later the structures would have only come out ten years later - computing by hand methods would have been quite impracticable. So the timely arrival of EDSAC was also a piece of luck for us. Or was it luck?

When my 6 Angstrom model of myoglobin came out one of the first people to see it was Desmond Bernal, one of the gurus of molecular biology and a man so wise that everyone called him Sage; when he saw it he said "I always knew proteins would look like that". What did he mean and how did he know?

And when we got the 2 Angstrom structure we had to build the models with steel rods; we had no computer graphics. Looking back on those times from today makes one feel nostalgic and the methods we used seem now very primitive; but it was great fun.

NO.BL.06 Clifford G. Shull

NO.BL.07 THE IDEAL ALLOSTERIC ENZYME. William N. Lipscomb, Harvard University, Cambridge, MA

Structures for the T and R forms of dimeric chorismate mutase indicate a very simple allosteric mechanism for activation by tryptophan and inhibition by tyrosine. These allosteric effectors bind at the same allosteric sites some 20 Å and 30 Å away from the active sites of the dimer.

Activation by tryptophan is caused by its second ring which pushes apart the allosteric domain of one monomer, A, from the long helix of the other monomer, B. This helix connects to the active site of the other monomer, thus loosening the structure allowing binding residues to converge onto the substrate.

Inhibition by tyrosine, which tightens the enzyme, is promoted by its smaller aromatic ring, and especially by hydrogen bonds between its OH group and ThrB145 (of helix H8, chain B) and Arg A76 (of helix H5, chain A). Phenylalaninedoes not form these two hydrogen bonds and is not an effector.

Catalysis involves a hydrogen bond, or proton donation, to the oxygen of the enolpyruvate part of the substrate, a new mechanism unlike that in other chorismate mutases.

Reference:
N. Sträter, K. Håkansson, G. Schnappauf, G. Braus and W. N.Lipscomb, *Proc. Natl. Acad. Sci. USA* **93**, 3330 (1996).

NO.BL.08 Hartmut Michel