PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Introduction

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Introduction

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Our understanding of the function of protein molecules was revolutionized in the 1960s by the use of X-ray crystallography to give a three-dimensional picture of their structures at atomic resolution. The structure of myoglobin was rapidly followed by the structure of several hydrolytic enzymes such as lysozyme, carboxypeptidase, ribonuclease, chymotrypsin, and subtilisin; and, not long after, by the much more complicated structure of haemoglobin, composed of four myoglobin-like molecules interacting with each other.

The first hydrolytic enzyme structures showed us how enzymes perform biological catalysis by immobilizing their substrates at the enzyme active site, and gave us definite ideas about the specific functions of different parts of the protein molecules. These ideas had to be treated as hypotheses, because there was no direct method to check them. A few particular points could be proved by cunning but tedious experiments.

In the 1970s Max Perutz pursued his pioneering studies on haemoglobin by exploring the wealth of human haemoglobin mutants which exist in the world's population. Some of these mutants cause important diseases in the third world (sickle-cell anaemia and β-thalassaemia), while others account for specific instances of anaemia and other blood disorders in individual families. Perutz found that many of these mutants allowed him to pinpoint the functions of specific amino acids in the haemoglobin molecule, and to correlate their altered properties with the structural changes they cause. These experiments were possible because of the relative ease of detecting the presence of an unusual haemoglobin molecule, by techniques available in hospital haematology departments all over the world.

In the 1970s new methods of reading the chemical sequence of genes were being developed, and these led to techniques which allowed genes to be transferred from one organism to another, and for the level of their expression to be controlled. These techniques provide a basic technology for protein engineering in the 1980s but further developments were needed in important directions.

First, methods of introducing specific mutations into a gene had to be found. These would allow genetic changes to be made at will and in a totally controlled fashion, instead of waiting for a chance mutational event which would need to be identified and exploited.

Second, our much deeper knowledge of protein function (especially enzyme function) had to be used to design accurate and sensitive methods to measure and to compare the functional properties of different mutants. Such changes can be expressed directly in terms of the energetics of the enzyme's interaction with its substrate.

Because of the complication of protein structures, computers have become essential aids in understanding them. Graphical displays which provide an accurate three-dimensional perception of the structure are invaluable. The third development in hand is to find how to

use the amazing computing power now accessible to us, to guide us in protein design by providing accurate predictions about a structure which has not yet been made.

In this Meeting the latest advances in all these techniques will be presented. A number of specific applications will be discussed, in which the interplay of these three strands of technical advance is exploited to achieve particular ends.

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