in real devices (practical or otherwise). But although quantum mechanics has been one of the most successful theories of the past century, nobody can confidently claim to understand why it works so well; for instance, how two entangled particles seem to communicate with each other at a distance, without any interaction, is beyond anybody’s comprehension. There is a nagging feeling that we are missing something. A quantum-information industry may indeed be just around the corner, but its underlying principles remain largely mysterious.

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COMPUTATIONAL BIOLOGY

Protein predictions

Eleanor J. Dodson

Predicting the three-dimensional structure of a protein from its amino-acid sequence is a dauntingly complex task. But with colossal computer power and knowledge of other structures, it can be done.

Fifty years have passed since the Nobel-prizewinning discovery that the amino-acid sequence of a protein determines its three-dimensional structure — yet computational biologists are still unable to predict the shape of a protein from its sequence. Given that there are many more protein sequences available than structures, and that protein shape is crucial for understanding cellular and physiological processes, a method for predicting such structures is vital. The paper by Qian et al.1 (page 239 of this issue), in which the structure of a protein containing 112 amino acids is accurately predicted, thus represents a real breakthrough. The authors’ model was sufficiently accurate to act as the starting point in the X-ray structure determination of the protein.

Most structural information on proteins is derived from X-ray and nuclear magnetic resonance (NMR) experiments. These have revealed the general characteristics of proteins — for example, sequence motifs that form secondary structural elements such as helices and sheets. Such elements are organized to generate the overall protein architecture, mainly as a result of internal interactions between hydrophobic amino-acid side chains buried within the structure.

The shape of a protein corresponds to the lowest-energy conformation of that molecule and reflects the combined properties of the constituent amino acids. Low-energy conformations are often found in certain structural elements of proteins, but in general there is no simple correlation between amino-acid sequence and protein structure; quite different sequences can adopt very similar folds.

Once a protein structure is known, it is fairly easy to see the atomic interactions that underpin it. But it is much harder to take an amino-acid sequence and work out the optimal interactions that determine how it will fold. First, it is necessary to quantify the energy contributions from various types of interaction. The effects of molecular conformations on these contributions must then be assessed. But even a relatively small protein can have a bewilderingly large number of possible conformations. Although some progress has been made towards devising a structural prediction method, crystallographers have so far had no reason to worry about their job security.

The field was greatly stimulated by a network set up in 1994 to provide a critical assessment of structure prediction (CASP)2. The main goal of the CASP network is “to obtain an in-depth and objective assessment of our current abilities and inabilities in the area of protein structure prediction”. Every two years the organizers provide the amino-acid sequences of a set of proteins for which undisclosed crystal structures exist. Modellers are challenged to predict structures for the proteins, and these are then assessed against the crystallographic results. The assessors use various scoring systems, but the most rigorous test is the one used by Qian et al.2 to test their own models — can the prediction be used in ‘molecular replacement’ searches that allow the raw data from X-ray diffraction studies to be related to the structure of the compound being investigated? Normally, a previously determined structure of a protein with a similar amino-acid sequence is used for this purpose.

Qian and colleagues’ models2 passed the molecular-replacement test with flying colours (Fig. 1): one of the authors’ ab initio predictions was used successfully as a molecular-replacement model. Furthermore, the authors used their method to refine ten NMR models of protein structures, yielding results that were in better agreement with X-ray data than the original models. And finally, they were able to improve the molecular-replacement scores of several models that started from protein structures distantly related to that of the target protein. This gives the lie to the old crystallographers’ adage that computational modelling is a time-consuming way to make a poor model worse.

The authors used a program called Rosetta to make their structural predictions. The program begins by mapping fragments of the sequence under review against existing information from previously determined structures, to identify likely structural motifs. It then constructs many rough, low-resolution models from these fragments and tests them against energy criteria (which are dominated by hydrophobic interactions). In this way, a large set of possible low-energy conformations is identified, one of which is likely to be that adopted by the protein.

At the next stage, the energy profile of every atom in the protein is incorporated into the low-energy models. Rosetta explores a huge range of randomly generated side-chain and backbone conformations, again calculating their effects on molecular energy. The resulting energy ‘landscape’ can vary dramatically — for example, small shifts of a single atom can make or break a hydrogen bond.

Figure 1 | Model test. Qian et al.2 have developed a computational method for predicting the three-dimensional structure of a protein from its amino-acid sequence. Here, their predicted structure (grey) of a protein is overlaid with the experimentally determined crystal structure (shown in colour) of that protein. The agreement between the two is excellent, with the amino-acid side chains overlapping particularly well.

*This article and the paper concerned were published online on 14 October 2007.
The whole procedure is iterative — solutions are repeatedly assessed, the lowest-energy models are clustered to identify common features and then further effort is concentrated on more variable regions. Rosetta also analyses peptide sequences found in analogous proteins from species of organisms other than that of the target sequence, as such proteins are expected to have similar three-dimensional structures to the target molecule. The whole process is terminated when conformations are identified that have significantly lower energies than the average energy of the protein.

The algorithms used in Rosetta are sophisticated, and the computing resources required to carry out the calculations, to keep track of results and to plan future strategies, are awesome. The authors therefore used a procedure called Rosetta@home, which distributes the calculations across a network of home computers — more than 70,000 in June 2006 — whose owners allow the program access to their idle machines.

There is still much to be done. Cynics might mutter that one success doesn’t prove that Qian and colleagues’ method is truly general, and that it should be assessed further using known structures. Nevertheless, this approach demonstrates real progress in several respects: the use of enormous computational power; the exploitation of known three-dimensional structures; the development of powerful search algorithms that relate those structures to new sequences; and the steadily improving tactics used to determine low-energy conformations of molecules. The benefits will be seen in structure-based drug design and in improved models for crystallographic calculations. And in the future, this method might provide structural information about intractable molecules that are difficult to study experimentally.

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Figure 1 | Structure of metal phthalocyanines. Metal phthalocyanines are a class of molecule that comprises an organic, four-leaf-clover structure with a metal at the centre. Heutz et al.1 show that the magnetic state of films of these molecules can be switched by controlling their crystalline structure.

MATERIALS SCIENCE

Magnetic blue

Jeroen van den Brink and Alberto F. Morpurgo

A commonly used blue dye is more than just a pretty colour. This material and its relatives are semiconductors, and their magnetic properties can be controlled by engineering their crystal structure.

Organic compounds are rarely magnetic, but metal phthalocyanine (MPC) materials are notable exceptions to this rule. Reporting in Advanced Materials, Heutz et al.1 now show that the magnetism of MPCs can be controlled. By changing the crystal structure of an MPC film, the authors switched the material from being in a magnetically ordered state to a non-magnetic one. This approach might provide a method for customizing the magnetism of molecular materials.

MPCs are flat molecules that take the shape of a four-leaf clover. They consist of an outer ring, formed from nitrogen, carbon and hydrogen atoms, with a metal atom bound at the centre (Fig. 1). The first molecule of this class was discovered at the beginning of the twentieth century, and had a copper atom in the middle. Because of its brilliant blue colour, the compound was immediately seized upon for use in paints and dyes. The hue also inspired the name ‘phthalocyanine’, which was taken from the Greek-derived words for rock oil (naphtha) and blue (cyan).

Since then, more than 70 MPCs have been synthesized, each with a different central atom or group of atoms. The properties of these compounds vary widely. For example, simply attaching chlorine atoms to the aromatic rings in copper phthalocyanine (CuPc) modifies the electronic absorption spectrum of the molecules. This process is used to add subtle green tones to blue paint. No great conceptual leap is required to see that similar structural modifications to MPCs could result in compounds with other interesting properties.

In fact, chemists have long known how versatile MPCs can be. Apart from their common use as dyes in the textile and paper industry, they can also act as catalysts, and they have even been investigated as anticancer agents. But perhaps their most interesting characteristics are their magnetic and electronic properties. If a transition-metal atom is placed in the centre of the ring, MPCs carry a magnetic moment because of the particle spin of the transition-metal atom. The spin value varies depending on the metal used, so that MPCs can be thought of as nanomagnets, the magnetic strength of which can be controlled at a molecular level.

Physicists are only just starting to explore systematically the full potential of MPC-based compounds. The leitmotif of this work is the addition of electrons to the materials to probe changes in their electrical and magnetic properties. Of particular interest is the unexpectedly large number of electrons that can be hosted by MPCs — up to four or five on a single molecule. The resulting charge density can be tuned by adding electron-donating atoms (such as lithium, potassium or rubidium) to the materials. This ‘electron-doping’ technique has also been used on buckminsterfullerene (C₆₀), the famous football-shaped carbon molecule that has been a fertile playground for condensed-matter physicists for almost two decades.

The latest experiments on MPCs have produced some surprises. These compounds are usually semiconductors, but several MPC films turn into metallic conductors when electron-doped with potassium atoms2. The variation of conductance with the amount of potassium incorporated into the films provides information about which molecular orbitals the donated electrons occupy in each MPC (ref. 3). Other experiments reveal that the magnetic properties of manganese-containing MPCs can be tuned by varying the concentration of lithium dopants4.

The big idea behind all this work is that it should be possible to engineer the electronic properties of solids by chemical actions at a molecular level. This proposal is certainly not new. But researchers who have attempted this in the past have almost invariably been confronted with a harsh reality: small molecular modifications made to tune the bulk electronic properties of a solid often cause drastic changes to the packing of the molecules in that solid. Such changes to the crystal packing cannot usually

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