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What history tells us XXV. Construction of the ribbon model of proteins (1981) The contribution of Jane Richardson

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1. Introduction

In 1991, Carl-Ivar Branden and John Tooze published *Introduction to protein structure* (Branden and Tooze 1991): 'with its superb pictures and accessible text, the book quickly acquired a strong following among graduate students and newcomers to the field' (Ernberg and Holmes 2004). Publication of this book was a testimony to the rapid increase of knowledge on the structure of proteins that had occurred in the 1970s. The description of protein structure had lagged behind that of DNA, and the first 'sausage' model of myoglobin in 1957 was a deep disappointment even for John Kendrew, revealing no obvious rules of protein folding. These rules progressively emerged in the 1970s and the beginning of the 1980s.

But Branden and Tooze's book was also the popularization of a new way of representing proteins with coloured ribbons, and a particular emphasis on secondary structures, β-strands and α-helices. Jane Richardson, working at Duke University, played a major role in the development and rapid acceptance of these new diagrams (Bahar 2004). I will successively present the context in which this new representation emerged, and the decisive role of Jane Richardson. What is most noticeable is that, 30 years later, the way of representing proteins remains identical despite the huge progress made in understanding how proteins fulfil their functions. This representation was shown to be perfectly adapted to two new research objectives that emerged in the following years: the design of artificial proteins and the description of the internal movements of proteins involved in their function as nanomachines. In the conclusion, I will argue that the importance of representations in scientific work is often underestimated.

2. The rise of a new representation

For protein crystallographers working at the end of the 1960s, two problems had to be addressed simultaneously. The first was to compare the different structures that were progressively revealed by X-ray crystallography, to search for resemblances between them and to classify them: to do taxonomy of proteins. The second was to find a solution to the folding problem. Following the work of Chris Anfinsen, it was widely admitted that the native state of proteins corresponded to an energy minimum. However, Cyrus Levinthal had demonstrated that this minimum could not be reached by a random search process in the range of times required for protein folding. Some rules had to guide the folding process.

Both issues were solved by considering that the association of secondary structures into super-secondary ones was the basis of protein structures, and a major step in the protein folding pathway. The first example of a super-secondary structure emerged from the work of S Rao and Michael Rossmann in 1973 on a comparison between different dehydrogenases (Rao and Rossmann 1973): a

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precisely organized association of β-strands and α-helices was responsible for the binding of the nucleotide moiety. The order in which the different secondary structures were organized into a super-secondary one, what was called the topology, was simultaneously explored by Michael Levitt and Cyrus Chothia (Levitt and Chothia 1976) and Jane Richardson (Richardson 1977). Some topologies seemed to be preferred (Richardson 1976), such as the Greek key (Richardson 1977), simplifying the folding problem. Drawing the topologies allowed a classification of proteins: different classifications were rapidly proposed at the beginning of the 1980s (Richardson 1981; Rossmann and Argos 1981).

But the problem of protein representation remained unsolved, despite the early efforts of Richard Dickerson (Dickerson and Geis 1969). What was looked for was a form of representation permitting an immediate and simple comparison of protein structures. After some early attempts by Jane Richardson (Richardson *et al.* 1975; Low *et al.* 1976), the present ribbon representation was first proposed by Michael Levitt and Cyrus Chothia in an article published in 1976 (Levitt and Chothia 1976). But the drawing remained poor, and they did not insist on the novelty of this representation. They abandoned it in favour of more abstract models in further publications (Chothia *et al.* 1977). It was Jane Richardson who immediately grasped its interest. She adopted it, introduced colours, presented this new representation in a poster in 1979 (Richardson *et al.* 1980) and devoted to it a large place in the long review that she published in *Advances in Protein Chemistry* in 1981 (Richardson 1981). These representations were rapidly reproduced up to the point that, twenty years later, she still expressed amazement that 'a whole generation of scientists see protein structures through my eyes' (Bahar 2004).

3. The contribution of Jane Richardson

The impact of this new representation was immediate. A survey of the diagrams of protein structures produced between 1980 and 1985 in different journals (*Proceedings of the National Academy of Sciences, Journal of Molecular Biology*) shows the rapid adoption of the new representation.

The beauty and quality of the diagrams proposed by Jane Richardson – with a smart use of colours to distinguish the different motifs – contributed to their acceptance. It is interesting to compare the review written by Jane Richardson in 1981 (Richardson 1981) with that written by Michael Rossmann and Patrick Argos the same year (Rossmann and Argos 1981). Both present the same recently acquired results on protein structure, but the rare 'beautiful' diagrams in Rossmann and Argos's review are borrowed from Jane Richardson!

Jane Richardson spent 2 years improving these representations. Her investment in this task has three roots. The first is her interest, not only in the taxonomy of proteins and their classification, but also in the use of this taxonomy to establish the evolutionary relations between these proteins (Bahar 2004). This is why a representation immediately revealing the resemblances, as well as the differences, between proteins was crucial to her. The second reason for doing such an unusual job was the personal importance she gave to representations. For her, representing was not a task consisting simply in producing an image of a well-described reality. Representation is not the simple illustration of data; it is a way to organize and to select these data (Richardson *et al.* 1992). Representing is as important as accumulating data. It orients future research work. The third was her sense of aesthetics, and her interest in the similarities of form in highly different objects. The name she gave to a motif formed of four β-strands, the Greek key, in reference to its presence on Greek pottery (but also in American Indian weavings) helped to give these motifs high visibility (figure 1).

It is difficult not to imagine that the importance she gave to representations was linked to the fact that she was an outsider in protein chemistry, first working as a technician with her husband. She started graduate studies in philosophy

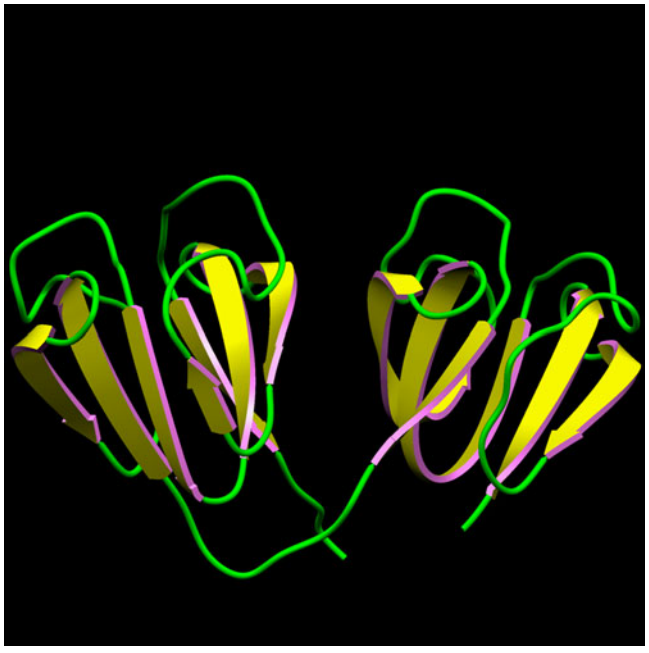

Figure 1. Richardson representation of the structure of γ-D crystallin (Basak *et al.* 2003 *J. Mol. Biol.* **328** 1137–1147) showing the Greek Key motifs. Illustration provided by Garima Agarwal and N Srinivasan of Indian Institute of Science, Bangalore, and made using SETOR software (Evans 1993 *J. Mol. Graph.* **11** 134–138).

before turning to the characterization of protein structures. The distance between reality and its representation by models is a problem which has attracted the attention of philosophers since Plato!

The increasing place occupied in these years by computers in structure solving and model building, and the newly offered possibility to 'manipulate' these models on the screens of graphics terminals (Francoeur and Segal 2004) might wrongly suggest that the new representation was imposed by computer scientists. The reverse was true: in 1986, six years after the first handmade drawings had been published by Jane Richardson, an algorithm to create ribbon models of proteins was elaborated by Mike Carson and Charles Bugg (Carson and Bugg 1986).

4. The resistance of the ribbon model to the passing of time

The rapid adoption of this representation does not explain its survival 30 years later. In evolutionary biology, it is necessary to explain in selective terms not only the adoption of a new trait but also its persistence. In the case of the ribbon model, the explanation is probably that this model was well adapted (preadapted) to two major developments that occurred in the late 1980s and 1990s: the rise of artificial protein design, and the functional parallel made between proteins and nano-machines. In evolutionary terms, using these representations to design new proteins, or to explain the internal movements underpinning protein functions, were two exaptations of a model initially selected for its capacity to make the comparison between protein structures easy.

The design of artificial proteins may follow different ways. The way that appeared the simplest, and which was initially retained, was to design proteins with the most common structural motifs and topologies. This was the road followed by Jane and David Richardson with the four-helix bundle proteins, betabellins and betadoublets (Richardson *et al.* 1992; Quinn et *al.* 1994). They were pioneers in a project that retrospectively appears as a first step towards synthetic biology: to build new proteins was the way to check that the principles of protein folding and stability had been fully understood. Our conviction is that the protein models they produced paved the way to the engineering of new proteins. Nevertheless, the results were disappointing: the proteins that were obtained were not as stable as the native proteins, and the first studies were followed by a long period of tedious work in attempts to increase the stability of the first designed proteins.

More surprising is the fact that the ribbon model of proteins was well adapted to a description of the internal movements of proteins involved in their functioning as nanomachines.

Considering proteins as nanomachines became common after the discovery that one of the most fundamental enzymes of the living world, ATPase, which synthesizes the energy currency used in all organisms, functions as a motor with two parts, a rotor and a stator (Block 1997). It preceded a special issue in 1998 of the journal *Cell* on 'macromolecular machines'. The cell appeared in the words of Bruce Alberts who introduced this special issue as 'a collection of protein machines' (Alberts 1998).

The success of this metaphor had been prepared by the previous work of physicists in molecular dynamics and on isolated macromolecules, and of protein chemists who carefully described the 'structural mechanisms for domain movements in proteins': the shear and hinge motions (Gerstein *et al.* 1994). Every machine is formed of rigid and mobile parts: although the internal movements of a protein are highly complex, involving modifications at different levels of protein structure, super-secondary structures outlined by the ribbon model could be considered in a first approximation as forming the rigid parts of the proteins. The ribbon model of proteins was therefore well adapted to a representation of the behaviour of proteins as machines: it highlighted the relative movements of the rigid parts of the macromolecules.

5. Conclusions

Major discoveries in science are often seen as resulting from the development of new technologies, allowing the description and study of new phenomena, or from the relating of different and hitherto unexplained phenomena in an explanatory model.

To introduce a new representation is an event that is as important in the construction of scientific knowledge as technological developments and the unveiling of new phenomena. It orients observations and research in specific directions. Jane Richardson made such a contribution. Her merit is to have understood better than others the importance of these representations, not only for the popularization of results, but also for the development of research itself.

The elaboration of scientific knowledge is a more complex process than is usually described for science students. The elaboration of new representations and models, in which choices have to be made, shows that science is the result of a human construction of reality, not something imposed by nature. Outsiders, as was Jane Richardson, casting an original and slightly out of phase look at the phenomena under study, can have a preeminent role in this process.

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