Early ribbon drawings of proteins

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The ubiquitous ribbon drawings of protein structures that are commonly made these days using programs such as Molscript or Ribbons had their origin ~20 years ago in drawings made by hand. Some earlier schematic drawings had been made of individual proteins: Dick Dickerson was the first to make a protein schematic[1] and Irving Geis the first to show successive peptide planes with ribbons[2]; ribbon drawings, using various conventions, were made by a few others[3], most notably Bo Furugren[4]. My husband David and I had made 'worm drawings' for our own staphylococcal nuclease and superoxide dismutase structures, and for other proteins[5] (Fig. 1*a*). However, the first attempt to illustrate the full range of known protein structures (only 75 different ones, then!) with a consistent system of representation was the 1981 article "The anatomy and taxonomy of protein structure"[6] (Fig. 1*b*–*d*).

During the 1970s we had compared protein structures and studied β-sheets in particular, mainly using two-dimensional topology diagrams, which helped identify the right-handedness of β-sheet crossover connections and define Greek key β-barrels. The early structural analyses of Janet Thornton and Cyrus Chothia also used two-dimensional topology diagrams. In 1979, Chris Anfinsen asked me to do a systematic survey for *Advances in Protein Chemistry*, and for that I needed a better way of illustrating the three-dimensional structures in order to show the comparisons and classifications directly. Before writing the article, I spent an entire year working out the visualization system, learning the techniques, and making nearly 100 drawings: mostly the basic line drawings of each domain with standard scale and viewpoint (Fig. 1*b*), plus some in different orientations, of multiple subunits (Fig. 1*c*), with shading (Fig. 1*d*), or with side chains or other details added. (Fortunately, study sections were in those days less insistent on evaluating one's 'productivity' solely by the number of papers published per year.) I traveled to the NIH, using Richard Feldmann's black-and-white molecular display to choose viewpoint and print out Cα traces at a consistent scale. The drawings were made in pencil on tracing paper over the printout, while also looking at a smaller version of the structure in stereo view, and finally traced in India ink. Shaded black-and-white (Fig. 1*d*) or color versions were made by sticking on pieces of overlay film and cutting to fit the ribbon edges. Dave monitored the blackness of my ink, touched up line quality under a microscope, and photographed high-contrast negatives for printing.

Making these drawings was a fascinating process. First, the structures are very aesthetically pleasing — especially, for me, the varied and elegant curves of β-sheets. Second, making a drawing can change one's scientific understanding of a protein, sometimes revealing a preferable structural classification and once even correcting a chain tracing[7]. Third, defining the conventions of representation was surprisingly complex and interesting (for more on this aspect, see ref. 8). Not only were those conventions modified from various precursors and elaborated in new ways, but there is an inherent logical conflict that dictates a certain level of inconsistency.

Specifically, the definition for how to connect the peptide plane orientation from one residue to the next, which is the fundamental basis of 'ribbons', is context dependent. In a helix, the direction of consecutive CO vectors is nearly parallel, in a β-strand it is nearly antiparallel, and in loops it is often near 90° but has no sensible structural or visual meaning. Several later computer-based systems tried using a consistent definition for all parts, but they were soon abandoned because the results looked confusing (for example, β-strands flipping over every residue).

I finally chose smoothed arrows for β-strands with thickness to make their orientation clearer, smoothed spiral ribbons without thickness for helices, and rounded 'ropes' for loops. Surprisingly, these disparate parts look visually unified and intelligible. Local orientation of arrows was also smoothed in the direction between strands, to strengthen the

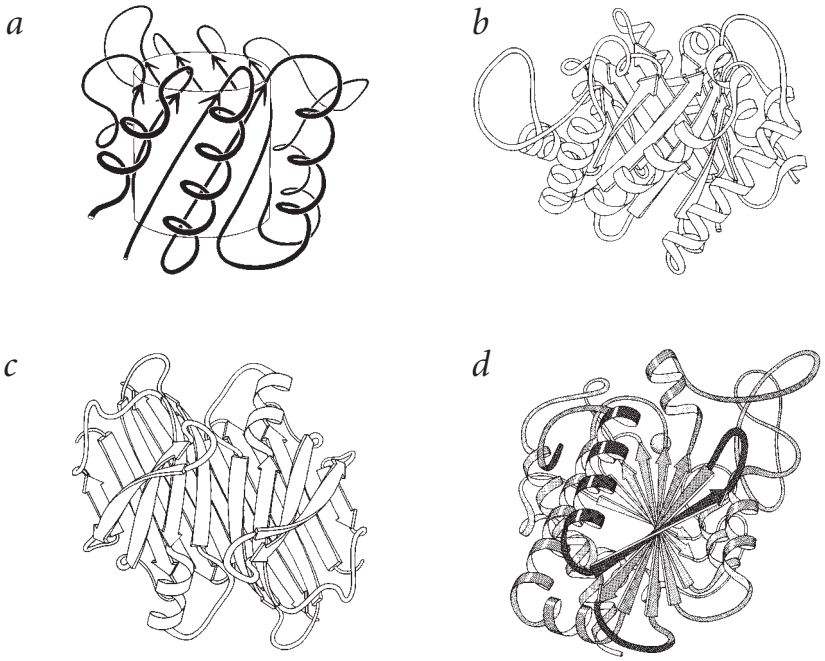

Fig. 1 Some early schematic drawings of protein structures. ***a***, Triose phosphate isomerase 'worm' drawing[5]. ***b***, Triose phosphate isomerase ribbon drawing[6]. ***c***, Prealbumin dimer[6]. ***d***, Carboxypeptidase A[6].

impression of a continuous β-sheet. To ensure an unambiguous path for the chain, slight shifts were occasionally needed where three segments cross (Fig. 1*d*). Where a β-strand turns over, it was drawn to show both sides of the ribbon (Fig. 1*b*,*c*), which mimics what you see with two eyes for a real object. When two strands cross obliquely an optical illusion occurs (usually illustrated in textbooks by a pair of vertical lines with a single oblique line hidden behind them; this line appears crooked), so I offset the outlines of the rear arrow slightly to make it appear straight (Fig. 1*c*). Without formal training in art (or, for that matter, in biochemistry or crystallography), I had to learn these tricks by trial and error.

Ribbon drawings are an excellent tool for first comprehending the overall organization of a protein structure, on which one can later hang the important details. Decisions about representation, secondary structure, and viewpoint, whether done by hand or by a computer algorithm, are inherently arbitrary and subjective but also serve to communicate ideas about which structural aspects are important.

As computer graphics became more powerful, effective programs were gradually developed to produce ribbon drawings quite similar to my hand-drawn ones. The programs are perhaps not quite as good with β-sheets, since they do not use the tricks described above, but they are actually better at representing helices, since they can show irregularities and can indicate chain direction by outward flaring of the peptide plane. Most crucially, they are enormously easier, and many allow interactive rotation of the molecules. I have not made any hand-drawn schematics in many years — these days, I do ribbons in Mage[9].

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