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Perspective

Perspective on "Stereochemistry of polypeptide chain conformations"

Ramachandran GN, Ramakrishnan C, Sasisekharan V (1963) J Mol Biol 7: 95–9

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Abstract. Despite its apparent simplicity the "Ramachandran map" has been an enormously successful tool for describing and understanding protein structure. Thirty-five years after its invention, it is still used daily for checking the quality of experimental and modeled protein structures. It is, moreover, founded on a rational, reduced-coordinate model of the polypeptide chain which continues to be useful in computational attempts at predicting protein folding.

Key words: Ramachandran map – Protein structure – Molecular modeling – Conformational analysis

Living in the midst of an explosion in structural molecular biology, it is difficult to remember that at the beginning of the 1960s only a handful of protein structures had been solved by X-ray crystallography and little was known of the range of the folding patterns that the polypeptide chain could adopt. The only simplifying feature of these patterns was the existence of regular secondary structures, the α-helix and the β-sheet, which were the result of stereochemical insight on the part of Pauling [1, 2], rapidly confirmed by the fiber diffraction work carried out by Perutz [3]. The first protein structures solved, hemoglobin [4] and myoglobin [5], although integrating these fundamental building blocks exhibited considerably more complex forms, whose analysis clearly required new mathematical and graphical tools. However, in the early 1960s, computers were only just beginning to enter the lives of chemists and biologists. Force fields as we know them today were already evolving from their spectroscopic roots [6], but computations on biopolymers were still in the future (this did not exclude some courageous attempts at fold prediction [7]). Similarly, only the most rudimentary graphic systems were available, although the importance of visualization in structural biology would soon become clear [8].

It was in this setting that G.N. Ramachandran (more commonly addressed, with the southern Indian penchant for shortening names, as "GNR") and his colleagues proposed to represent peptide chain conformations on a two-dimensional map. The map was defined by the dihedrals ϕ and ψ, which describe the bonds on either side of an amino acid α-carbon (ϕ: C′-N-Cα-C′, ψ: N-Cα-C′-N). This was an inspired use of reduced coordinates. By choosing to ignore side-chain conformations, rotations around the partially conjugated peptide linkage and deformations in bonded geometry, protein conformations were reduced to a problem of $2N$ variables for N amino acids (gaining roughly a factor of 50 over Cartesian coordinates and even a factor of 3 over a complete dihedral angle description).

Simple steric calculations (using minimum contact distances between classed atom pairs) enabled the "Ramachandran map" to be divided up into allowed and forbidden regions (the latter representing roughly 75% of the map!). Although obtained for a dipeptide, this result was equally applicable to polypeptides with either regular or complex folded conformations. Indeed, the original paper already showed that helical parameters could be mapped onto ϕ/ψ space (see also Ref. [9]), helping to rationalize the nature and the relationships of not only the α-helix and the β-sheet, but also the other helical forms which had recently been identified (2.2,-ribbon, π- and γ-helices, and Ramachandran's own, triple helical collagen structure [10]). The map also played an important role in understanding the structural role of specific amino acids such as proline or glycine, which could either constrain or expand the normally allowed domains.

Thirty-five years on, the Ramachandran map has been calculated and recalculated with increasingly sophisticated treatments of both molecular [11] and quantum mechanics [12], but its basic content remains unchanged. It has become an indispensable tool for all those dealing with protein structures as the touchstone for judging the quality of both experimental and simulated protein conformations [13], and it is also present in

most of the latest models of protein folding as a means of correctly biasing peptide conformational sampling (see, for example, Ref. [14]).

I arrived at the Indian Institute of Science in Bangalore (founded by J.N. Tata, at a site chosen by Sir William Ramsay) in 1976 to begin my theoretical studies of biopolymers. During my postdoctoral research with GNR, I did not expect that the famous map would have such a profound influence, but, looking back, I see two factors which have influenced my work and that of many others in our domain – the power of simple models and the importance of appropriate analytical tools. Reduced-coordinate models, on which the Ramachandran map is based, continue to play a major role in describing the static and dynamic conformations of both proteins [15] and nucleic acids [16]. With their help, considerable progress has been made in understanding the governing principles behind protein folding, even if reliable predictions on all but the smallest proteins are still out of reach. A new challenge faces us today in the case of the RNAs, where the passage from two-dimensional base pairing schemes to three-dimensional conformations is far from trivial [17].

Without replacing the Ramachandran map, protein conformational analysis tools have progressed, notably by extending a simple description of the polypeptide chain into fold classifications which help to reveal the principles and the evolution of protein architecture [18]. With the appearance of molecular dynamics simulations it has also become necessary to develop tools for analyzing protein conformational fluctuations [19, 20]. Similar analysis problems are posed by nucleic acids. While it is now possible to describe the subtle variations in the geometry of the double helix [21], the number of significant variables per nucleotide step makes it difficult to achieve the simplicity of the Ramachandran maps, although attempts continue to be made in this direction [22]. DNAs have recently been seen to adopt a surprising range of conformations [23, 24], but it is once again RNAs and their protein complexes which represent the hardest challenge for future theoretical studies.

In all these areas, I think we would do well to remember that simple techniques, handled intelligently, can be as powerful, and sometimes have a further-reaching impact, than those relying on the latest feats of technical prowess.

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