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EDITORIAL

Remembering Ramachandran: Marking an Anniversary

January is a favoured month for scientific meetings in India. A recent conference in Bangalore was unusual in that it marked the 50th anniversary, a truly golden jubilee, of a scientific paper published from Madras University. The path breaking report introduced the Ramachandran Map into the literature of biochemistry and structural biology. The conference was intended to be a celebration of a past triumph; for some an occasion to discuss progress in the field, for others a time to recall and introspect. It is not often that a paper published from India has had as lasting an impact on a discipline as this contribution, circumspectly titled 'Stereochemistry of Polypeptide Chain Configurations', which first appeared in 1963 (Ramachandran, G. N., Sasisekharan, V. and Ramakrishnan, C., *J. Mol. Biol*., 1963, **7**, 95). This paper provided a remarkably simple and elegant approach to understanding the three-dimensional arrangement of atoms in the backbone of polypeptide chains, which lie at the heart of protein structures. The paper by Ramachandran *et al.* used the readily appreciated idea of atoms as hard spheres, defined by a finite radius, to suggest that non-bonded atoms in spatial configurations of molecules cannot approach closer than the sum of their radii (the van der Waal's radii long discussed in the literature of physics and chemistry). The contortions of a long polymeric, polypeptide chain were readily described using two variable parameters at each discrete monomeric residue. These parameters were the dihedral angles or torsion angles, defined by the positional coordinates of four sequentially linked atoms along the polymer backbone, denoted with the Greek symbols phi and psi. Structure space in three dimensions could then be analysed comfortably on a two-dimensional phi–psi plot. Using a hard sphere model Ramachandran *et al.* were then able to delineate clearly the regions of conformational (phi–psi) space, which were 'allowed' for amino acid residues in proteins. The 'contact criteria' used to demarcate allowed and disallowed regions were strikingly simple, brooking no violations. The phi–psi plot appeared when there were, for all practical purposes, no experimental observations from protein crystal structures. The myoglobin and hemoglobin structures were appearing at moderate resolution in the late 1950s, work for which John Kendrew and Max Perutz received the 1962 Nobel Prize for chemistry. When observations of residue conformations became available in the mid 1960s, it was apparent that amino acid residues did indeed largely obey the dictates of the Ramachandran map. In the decades that have followed, hundreds of thousands of individual amino acid phi–psi values have accumulated. In a striking vindication of the original Ramachandran construction, 'experimental maps' conform almost entirely to that originally outlined in the 1963 paper. Ramachandran died in 2001 at a time when his name had already entered the textbooks of biochemistry. He had effectively stopped working in the field about twenty years earlier. In a development which would undoubtedly have pleased him, the importance of Ramachandran's map remains undiminished with time, continuing to provide new insights as the technologies of structural analysis, primarily X-ray diffraction and NMR spectroscopy, advance to expand the database of protein structures. Molecular dynamics simulations, carried out on increasingly powerful computers, allow molecules to explore torsional angle space, Ramachandran space, in a manner that could scarcely have been anticipated in the 1960s. As members of Ramachandran's department in Bangalore (and I am one) basked in the warm glow of reflected glory at the recent symposium, I could not but help reflect on the man and his times.

G. N. Ramachandran came to the Indian Institute of Science in 1942 to study for a Master's degree in Electrical Engineering. C. V. Raman was the dominant presence at the Institute. When Ramachandran persistently tried to move to the physics department, legend has it that Raman facilitated the transfer by telling the Head of Electrical Engineering: 'I am admitting Ramachandran into my department as he is a bit too bright to be in yours' (Sarma, R., *Ramachandran: A Biography of the Famous Indian Biophysicist*, Adenine Press, New York, 1998). In the 1940s under the influence of Raman, Ramachandran began researches in optics and the emerging technique of X-ray diffraction. The year of India's independence, 1947, saw him submitting a Ph D thesis. Ramachandran was already marked by his contemporaries as a scientist of extraordinary promise. His passion for science is evident in letters written from England in 1947, to a friend from IISc and later a colleague at Madras University, S. Swaminathan who was to become an eminent organic chemist (reproduced in the biography by Raghupathy Sarma). In one, he asks Swaminathan: 'Are you working on

stereochemistry or some other branch? Did you try the cyclohexanone problem? What happened to the paludrine patent?' His early letters reveal a deep and instinctive appreciation of the importance of stereochemistry. Few students of physics in India (and indeed anywhere else) would have worried about stereochemistry and the cyclohexane problem in the mid 1940s, while pursuing research in optics and crystallography. Ramachandran, probably influenced by his mentor Raman, appears uncomfortable in England and less than enthusiastic about his scientific environment in Cambridge. In one of his early letters he says: 'I sometimes wonder whether Professor Raman was not right in advising me not to come here'. He ends a December 1947 letter with the salutation *Jai Hind*, undoubtedly influenced by the times.

Ramachandran's stellar career in India began at IISc in 1949 when he established one of the earliest groups in the country in the area of X-ray crystallography. He did not stay long; moving to Madras in the autumn of 1952 to become head of a newly established physics department, at the remarkably young age of thirty. The University had hoped to entice Raman, then in his sixties, who in turn suggested Ramachandran. A benign and supportive Vice Chancellor, A. Lakshmanaswamy Mudaliar backed the young star to the hilt facilitating the flowering of a department in a university, which remains unmatched in its accomplishment even decades later. Together with Gopinath Kartha, Ramachandran produced a model for the structure of the most abundant mammalian protein collagen, based on meagre fiber diffraction data and superb structural intuition. The collagen triple helix which appeared in 1953, and is accepted as essentially correct today, was in some ways an even more difficult structure to deduce at that time than the DNA double helix, which appeared a year earlier. A controversy with an English group led by Francis Crick soon followed which undoubtedly took its toll, but had one silver lining. Crick argued that the Ramachandran structure of collagen had unacceptable steric contacts between non-bonded atoms, setting in motion the work at Madras on optimal steric contact distances, which eventually laid the groundwork for the development of the Ramachandran Map. Looking back decades later, one cannot escape the feeling that in this apparently unequal contest, David does successfully prevail over Goliath.

In the 1950s and 1960s Ramachandran brought the world of science to Madras. His department became the leading centre in India and one of the most productive in the world in the areas of crystallography and biomolecular conformational analysis. Two major international meetings in 1963 and 1967 were attended by virtually most of the major figures in the field. There have rarely been conferences in India which have had such a major impact.

It is hard to create a good department or institution in India; it is however very easy to destroy the best rather quickly. Madras in the late 1960s, in a changing political climate, turned increasingly unfavourable for unfettered scientific research, compelling Ramachandran to return to the place where he had begun, the IISc. He began a new department which he named 'molecular biophysics', presumably to avoid confusion with radiation biophysics which had a strong presence in India at that time. The term 'structural biology' was yet to be invented. The department's subsequent rise to prominence, even after Ramachandran effectively left the field in 1979, was undoubtedly based on the strong focus of research in an area in which he had already established a major school. For the last two decades of his life, until his passing in 2001, Ramachandran was not actively engaged in the area in which he had made so many seminal contributions. He was largely absent from public view. Sadly, modern science often requires a constant reiteration of activity in a field. Isolation may have been primarily responsible for the fact that Ramachandran was not more widely recognised in India and abroad.

Ramachandran was a brilliant man. There were areas where he entered only briefly, but nevertheless produced fundamentally important insights. Three-dimensional image reconstruction, which today lies at the heart of tomography and the ubiquitous CAT scans and magnetic resonance imaging, was a field where his lone paper had a significant impact. He was among the first to recognise the importance of anomalous dispersion in X-ray diffraction, publishing a key paper in this journal in the early 1950s. There were other areas in which his forays were brief but important, but none quite matched the lasting impact of his work on the conformations of biomolecules. Ramachandran was a difficult man, as highly creative individuals often are. Temperamentally unstable, he was childlike and naïve, at times, in his enthusiasm for science; unreasonable, demanding and impatient at others. He brought to his research a clarity of thought which allowed him to see the core of a problem, unobscured by a wealth of irrelevant detail. In India Ramachandran's work, unrecognized by a Nobel prize, has never received the level of public acclaim accorded to many others. He remained a 'scientist's scientist' till the very end. Our Nobel fetish has ensured that Ramachandran's work is not more widely used as an inspirational model for students entering science. Curiously, scrolling down the Nobel foundation's roll call of honour I realised that many pieces of work have not stood the test of time. In retrospect, there is a sense of satisfaction that Ramachandran and his map will remain in the biochemistry textbooks for a long time to come. For those of us, whose paths crossed that of Ramachandran, the golden jubilee of his celebrated paper was an occasion to reflect on the man and his work. It was a rare privilege to have known him.

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