BIOGRAPHICAL
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M. Vijayan and L. N. Johnson

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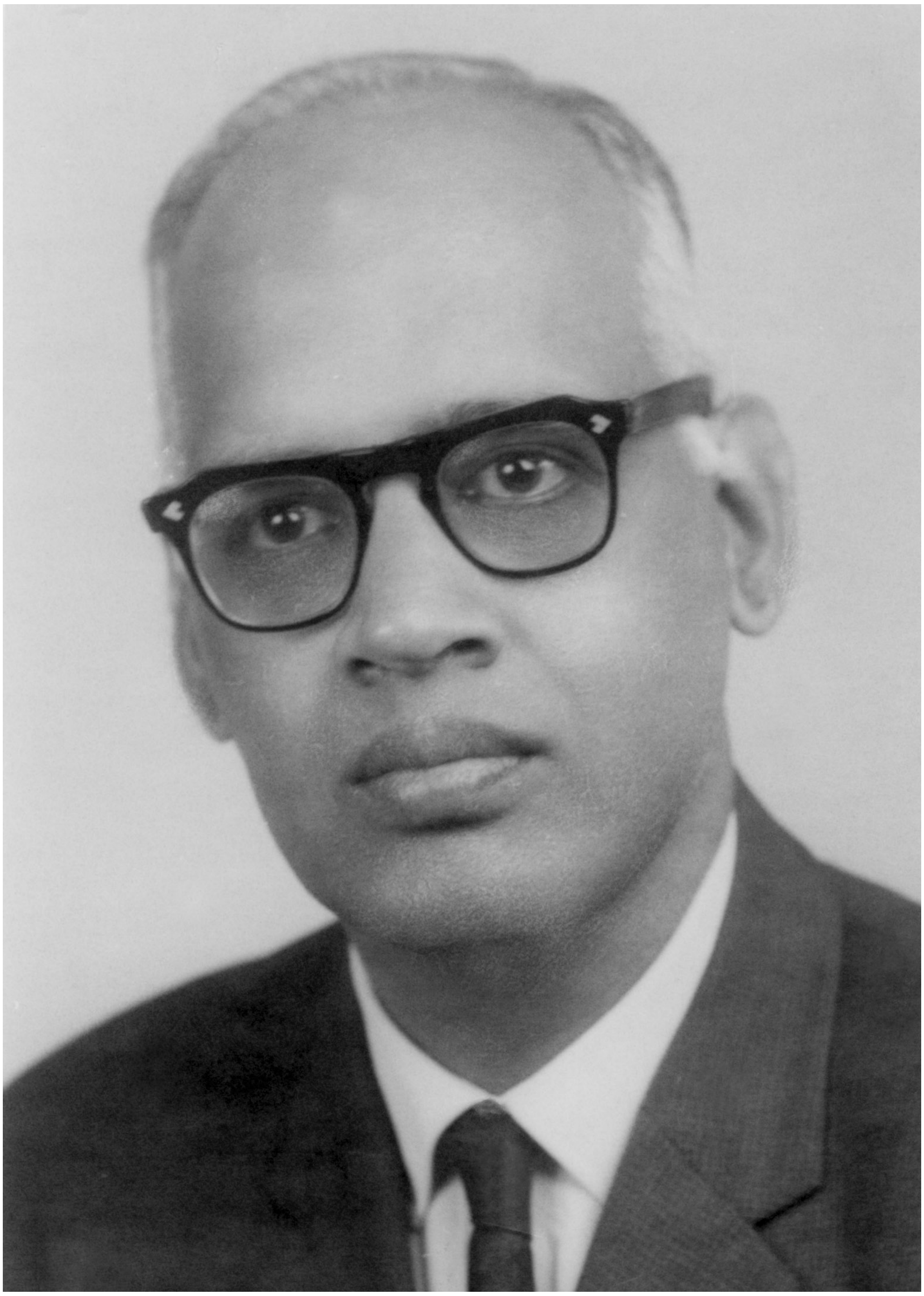

G. N. Ramachandran

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BY M. VIJAYAN[1] AND L. N. JOHNSON[2] FRS

[1] *Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India*
[2] *Laboratory of Molecular Biophysics, University of Oxford, Rex Richards Building, South Parks Road, Oxford OX1 3QU, UK*

FAMILY BACKGROUND AND EDUCATION

Gopalasamudram Narayana Ramachandran, the eldest son of G. R. Narayana Iyer and Lakshmi Ammal, was born on 8 October 1922. G. R. Narayana Iyer, who had previously taught at Tirunelveli in Tamilnadu, had joined the Mathematics Department of the Maharaja's College at Ernakulam in the erstwhile Cochin state, which is now part of Kerala. He rose to become the principal of the college. Ramachandran had his schooling at Ernakulam. He also completed the intermediate course at the same city. He was a brilliant student who was particularly good in mathematics. He stood first in the intermediate examination in the entire Madras University, to which most of the colleges in south India were then affiliated. He then joined, in 1938, the BSc (Hons) course in physics in St Joseph's College, Trichy. Ramachandran completed the course, again standing first in the Madras University.

EARLY RESEARCH CAREER

Ramachandran joined the Electrical Engineering Department of the Indian Institute of Science, Bangalore, in 1942. At that time, physics graduates could also join the electrical engineering course. He soon came under the spell of C. V. Raman FRS, who was then the Head of the Physics Department, and eventually moved to that department. Ramachandran obtained his MSc degree by research from the Madras University (the Institute then did not award

degrees) for his thesis entitled 'Optics of heterogeneous media' (2)*. He continued under the supervision of Raman for his doctoral work in the general area of optics (3). His work also involved X-ray topography and diffraction. He submitted his DSc thesis in 1947.

Ramachandran then secured a coveted 1851 Exhibition Scholarship and went to England to work at the Cavendish Laboratory at Cambridge. The laboratory was then headed by Sir Lawrence Bragg FRS, the founding father of X-ray crystallography (Phillips 1979). Ramachandran did not work directly under Bragg because he was assigned to W. A. Wooster. That was the time when Max Perutz (FRS 1954), J. C. (later Sir John) Kendrew (FRS 1960) and others were making, under the inspiration of Bragg, seminal contributions to what we now call structural biology. It is ironic that Ramachandran, who himself later turned out to be a pioneer in the field, did not have any significant interaction with that group in the same laboratory. Instead he was primarily involved in the study of diffuse X-ray scattering and its use in the determination of elastic constants (4). This led to the award of his PhD by Cambridge University in 1949.

The tale of two cities

Ramachandran returned to the Physics Department of the Indian Institute of Science in 1949 as an Assistant Professor. Along with Gopinath Kartha and others, he established an X-ray crystallography laboratory in the department, a laboratory that was subsequently led by S. Ramaseshan and then by M. A. Viswamitra, and served as the cradle of much of Indian crystallography.

In the meantime, Dr A. Lakshmanaswamy Mudaliar, the Vice-Chancellor of the Madras University, decided to establish a department of physics at Madras. He invited C. V. Raman to found and head the department. By that time, Raman had retired from the Indian Institute of Science and had started his own research institution at Bangalore, the Raman Research Institute. He declined the invitation, but recommended young Ramachandran, whom he reckoned to be as good as himself, to the post. Thus, in 1952 Ramachandran became the founder head and full Professor of the Department of Physics at the Madras University at the comparatively young age of 29 years. That marked the beginning of an extraordinarily productive period in his career that lasted for almost 20 years. The period was also marked by a unique relationship between the veteran Vice-Chancellor and the young scientist. Mudaliar treated Ramachandran almost as a son and provided him with all administrative and financial support. Ramachandran's mandate was to develop a world-class research centre at Madras, which indeed he did. Most of the major contributions of Ramachandran to biophysics and crystallography emanated from the period when he was at Madras.

When, after decades as Vice-Chancellor, Lakshmanaswamy Mudaliar eventually retired in 1969, Ramachandran found it difficult to adjust to the new regime. He left Madras in 1970 and returned to Bangalore in 1971, after a year-long sojourn at Chicago, to establish the Molecular Biophysics Unit at the Indian Institute of Science. The unit eventually grew into a major internationally recognized centre for frontline research in structural biology. Although Ramachandran left the field in the late 1970s, he remained at Bangalore for most of his

* Numbers in this form refer to the bibliography at the end of the text.

remaining years. Ramachandran spent most of his adult life in two cities, first at Bangalore, then at Madras (now Chennai) and then again at Bangalore. He established leading research centres of crystallography and structural biology at both places. As Ramachandran himself is reported to have remarked, his story may be called the Tale of Two Cities.

Collagen

When he moved to Madras in 1952, Ramachandran was not entirely certain what major problem he should address. By then, Linus Pauling ForMemRS had already proposed the α-helix and β-sheet models of the polypeptide chain. The momentous discovery of the double-helical structure of DNA was only a year away. Ramachandran was helped to make up his mind by a visit of the legendary J. D. Bernal FRS to Madras during 1952–53. Bernal felt that the structure of collagen was a major unresolved problem at that time and suggested that Ramachandran might examine it. Ramachandran quickly followed up this suggestion and started by taking a fibre diffraction photograph of collagen at the newly established X-ray laboratory at Madras.

Fibre patterns, of course, do not provide detailed information. Using the fibre pattern and the available biochemical and physicochemical information, Ramachandran and Kartha published the first approximation to their model in *Nature* in 1954 (5). It was known at that time that one-third of the residues in collagen are glycine and that collagen also contained a large proportion of proline and hydroxyproline. The first approximate model built by Ramachandran and Kartha essentially consisted of three left-handed three-fold helices arranged at the apices of an equilateral triangle. They assumed every third residue to be glycine. Glycine is the simplest amino acid with no side chain and only this residue can be accommodated at the interface of the three helices. The model contained no intrachain hydrogen bonds. The hydrogen bonds were all between the chains.

A detailed examination showed that the first model was not entirely compatible with the fibre pattern. The fit between the model and the pattern became perfect, when the three helices were made to coil around a common axis. Now each of the three helices had 3.3 residues per turn and they had a right-handed coil around the common axis. This is the well-accepted coiled-coil structure of collagen. The modified structure was published in 1955, again in *Nature* (6).

Ramachandran's coiled-coil structure of collagen contained two interchain hydrogen bonds per tripeptide. Two British groups, particularly Francis Crick (FRS 1959) and Alex Rich, maintained that there could only be one interchain hydrogen bond. The formation of the second hydrogen bond would involve unacceptable steric contacts. The controversy involving the one-hydrogen-bonded structure and the two-hydrogen-bonded structure raged for a time (9). But in retrospect, as it often happens, this controversy seems somewhat meaningless. It turns out that in addition to the one interchain hydrogen bond that everybody agreed on, there could be a water bridge connecting two chains. In a related development, Ramachandran and his student Manju Bansal worked in the 1970s at Bangalore on the role of hydroxyproline in collagen. Its main role seems to be the formation of a water bridge between adjacent chains (18). It was therefore not a straight choice between one or two interchain hydrogen bonds. The real situation seemed to involve a direct interchain hydrogen bond and a water bridge that often involved a hydroxyproline.

Much water has flowed downstream since Ramachandran last worked on collagen. In recent years, many crystal structures of oligopeptides incorporating collagen-like and indeed natural collagen sequences have been solved. These structures confirm the Ramachandran model of collagen, including the water bridges, often involving hydroxyproline.

The Ramachandran plot

Probably the most widely cited contribution of Ramachandran is the Ramachandran plot (figure 1) (12). The work leading to the plot had its origin in his work on collagen. The controversy involving the one-hydrogen-bonded and the two-hydrogen-bonded models of collagen hinged on the minimum non-bonded distance between atoms. Ramachandran and his then student V. Sasisekharan undertook in the late 1950s a thorough survey of the non-bonded contacts in the crystal structures of amino acids and related compounds. They found that non-bonded atoms sometimes came much closer than the sum of their respective van der Waals radii. From the data, they prescribed two limiting distances for each type of non-bonded distance, the normal limit within which the distances usually fell and the extreme limit that is sometimes possible. In 1960, C. Ramakrishnan joined Ramachandran as a graduate student and from then on Ramachandran, Sasisekharan and Ramakrishnan together worked on the problem. They realized that, with planar peptide units, the flexibility of the polypeptide chain involved only rotations about the two single bonds hinged at C^{α}, which they then called ϕ and ϕ'; we now call them ϕ and ψ. They then delineated the sterically possible values of ϕ and ψ for an alanyl dipeptide, using the table of normal and extreme limits of non-bonded distances derived from crystal structure data. That of course led to the Ramachandran plot (12). The work involved tremendous calculations. These were essentially pre-computer days, at least in India. All these calculations, spanning several months, were performed by Ramakrishnan on an electric desktop calculator. These calculations formed part of his PhD thesis. By the time the work was published in 1963, there was still only one high-resolution protein structure available, that of myoglobin published in 1959.

Soon after the Ramachandran map was devised, the late Herman Watson plotted all the ϕ, ψ values of myoglobin on the map. Most of them fell in the allowed regions but a substantial number did not. Almost all of these corresponded to glycine residues. As is well known, glycine does not have a side chain and is able to adopt a much wider range of torsion angles than the other amino acids.

Carbohydrates and nucleic acids

Although Ramachandran's major effort in conformational analysis was concerned with proteins and peptides, he initiated work on carbohydrates and nucleic acids. He published a paper on chitin in 1962, along with Ramakrishnan (10), and another in 1963 setting out the rules that govern the conformation of polysaccharides. For example, they were able to show that the structures of cellulose and chitin, composed of β(1→4)-linked glucose and *N*-acetylglucosamine units respectively, had a constrained conformation stabilized by an intrachain hydrogen bond. This analysis on β-linked sugars was important for the contemporary work on lysozyme at the Royal Institution, which Ramachandran visited at about this time and insti-

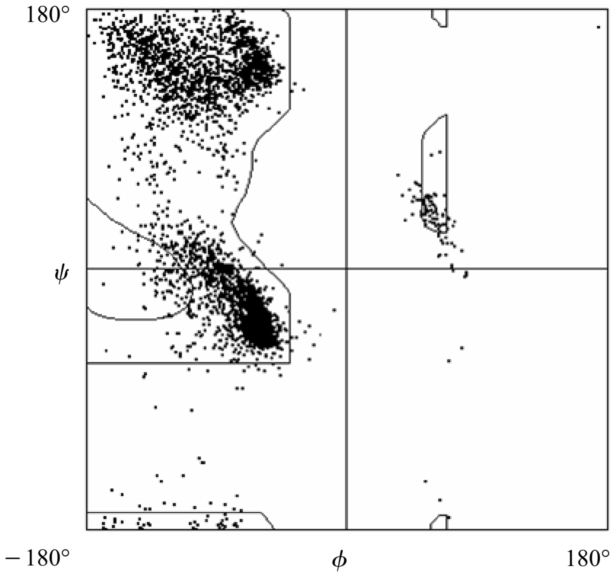

Figure 1. The ϕ and ψ angles in 21 non-redundant protein structures that have been solved to a resolution of 1 Å or better and refined to a crystallographic *R* factor of 10% or better. Open circles correspond to glycine residues. The total number of residues plotted is 4135 omitting glycine residues. In the original Ramachandran plot, the regions in the second and the third quadrants were not connected. The bridge region connecting the two appears when possible departures from the planarity of the peptide group and variations in the bond angle at the α-carbon are taken into account. In some circumstances where there are strong compensating interactions, deviations from the Ramachandran plot may be observed.

gated insightful discussions. Subsequently, the work on polysaccharides was taken over and continued by V. S. R. Rao. Ramachandran also initiated work on nucleic acid conformation, which was later carried forward by Sasisekharan and still later by Manju Bansal at Bangalore.

Crystallography

During the 1950s and the 1960s, only part of his work was concerned with conformational analysis. The other part dealt with crystallography. He worked on several aspects of crystallography in collaboration with R. Srinivasan, who was to succeed him as Professor of Physics at Madras, with Parthasarathy and with many others. The first major contribution, in 1956, was concerned with anomalous dispersion. As J. M. Bijvoet ForMemRS had earlier shown, in the presence of anomalous dispersion the Friedel equivalents have unequal intensities. Ramachandran, along with S. Raman, derived the correct formula for calculating phase angles from Bijvoet differences (7). This formula has been used for solving several structures; notable among them in the early years was that of a vitamin B_{12} derivative called Factor V1A by Venkatesan and Dale in Dorothy Hodgkin's laboratory (Dale et al. 1963). The method, which was further elaborated by Ramachandran and Parthasarathy (13), was also used in a probabilistic fashion by Hendrickson & Teeter (1981) in the structure solution of a small protein.

Another area in which Ramachandran's contributions have been outstanding is concerned with Fourier transforms in crystallography. He published several papers in the area and also wrote a book, *Fourier methods in crystallography*, with Srinivasan (1). His ideas were essentially simple. He took different quantities in the reciprocal space, such as F^2, structure factor amplitude and phase angle, and calculated their Fourier transforms in real space. He then used different types of combinations of these quantities to derive additional information. Specifically, the situation frequemtly encountered is one in which part of the structure is known and we need to determine the unknown part of the structure. He devised several syntheses for doing so. In addition to its practical utility, Ramachandran's work illuminates the mind and takes us to the very foundations of crystallography.

Ramachandran worked in many other areas of crystallography, including crystallographic statistics (8, 11), but the work on anomalous dispersion and Fourier transforms stands out among them.

Other contributions

In the foregoing account, three major areas of Ramachandran's contributions have been touched on. He was a many-splendoured scientist and worked in many more areas. For example, in the early 1970s he, along with Lakshminarayanan, devised a new method involving convolutions for image reconstruction (15). This method has since been used extensively, particularly in the computed tomography (CT) scan. He and Chandrasekharan worked out the conformational features of peptides containing L- and D- residues (16). This work turned out to be of considerable significance in relation to peptide antibiotics. During the early 1970s he was concerned about the non-planarity of the peptide group and worked on this problem, among others, with A. S. Kolaskar (17). The non-planarity results not just from rotation about the peptide bond but also from the slight pyramidal nature of the amide nitrogen. C–H···O hydrogen bonds are extensively discussed today. Ramachandran invoked them as early as 1966 in his model of polyglycine (14).

In the late 1970s his work in structural biology and crystallography decreased. He turned his attention to mathematical philosophy and logic. But in 1990 he returned to crystallography with a publication in *Acta Crystallographica* in which he proposed a new method of structure analysis (19). The method, called Real-Atom Grid Approximation (RAGA), involves crystal structure analysis using only amplitudes without the explicit calculation of phase angles.

Ramachandran was very keen on initiating experimental macromolecular crystallography in India. For a variety of reasons, mainly to do with inadequate financial resources, regular macromolecular crystallography in India started to develop only after Ramachandran's active days in structural biology were over. However, the Molecular Biophysics Unit at the Indian Institute of Science, Bangalore, one of the two schools established by him, had a major role in nucleating and leading the macromolecular crystallography efforts. To those of us who have been involved in this effort, Ramachandran has been a great source of inspiration. As Ramachandran wished, we now have a reasonable level of macromolecular crystallographic activity in India, distributed over several centres, although we are yet to scale the heights similar to those that Ramachandran conquered in his chosen areas of endeavour a generation ago.

Personal life

Ramachandran married Rajalakshmi, generally know as Rajam, in 1945. Mrs Ramachandran was a remarkable lady, full of life, grit and determination. She looked after Ramachandran with extraordinary care and devotion. She was his constant companion and a steadying influence on his somewhat turbulent disposition. Their three children, Ramesh Narayan, Vijaya Ramachandran and Harishankar Ramachandran, have had illustrous academic careers. Ramesh Narayan is now a professor at Harvard University, and Harishankar Ramachandran is a faculty member at IIT, Chennai. The daughter, Vijaya, is a professor of computer science at the University of Texas.

Ramachandran was a man of many parts and many moods. His temperamental nature is well known to those who dealt closely with him. He worried a great deal and was extremely impatient. Fortunately, these problems did not affect his creativity; perhaps the two went hand in hand. He was brilliant and towered over everyone around him. He knew that. The thought that he did not receive the recognition and support that he deserved seemed to trouble him.

There was another side to his personality. Ramachandran and Mrs Ramachandran were often extraordinarily kind and considerate. He was a connoisseur of music. He was a philanthropist and gave away much of the money he received from awards. He could be extremely charming. He was a brilliant speaker. He was always open to new scientific ideas, and new information excited him.

From the late 1970s there was a considerable reduction in the pace and range of his activities. Over the course of time, Parkinson's disease also began to take a heavy toll. Ramachandran's health deteriorated progressively and in 1997 the couple moved to Gandhinagar, Gujarat, to be near their youngest son, Hari, who was then employed at the Institute of Plasma Research. Then a terrible tragedy struck. Mrs Ramachandran died of a massive heart attack in 1998. That was a time of dilemma for the family. Except for Hari and his family, Ramachandran knew no one intimately in Gujarat. All his friends and relatives were at Chennai or Bangalore. Eventually he was moved to a cottage in the VHS hospital at Chennai, where he remained under the constant care of trained nurses until his death on 7 April 2001. His children visited him frequently. He was surrounded by relatives, friends and old colleagues and students. It was during the last couple of years he spent at Chennai that he received his last major award, the Ewald Prize of the International Union of Crystallography (1999).

The legacy of G. N. Ramachandran

G. N. Ramachandran has been among the most outstanding crystallographers and structural biologists of our times. He is considered by many to be the best scientist to have worked in independent India. The model of collagen developed by him has stood the test of time and has contributed greatly to understanding the role of this important fibrous protein. His pioneering contributions in crystallography, particularly in relation to methods of structure analysis using Fourier techniques and anomalous dispersion, are well recognized. A somewhat less widely recognized contribution of his is concerned with three-dimensional image reconstruction. Much of the foundation of the currently thriving field of molecular modelling was laid by him. The Ramachandran plot remains the simplest and the most commonly used descriptor and tool for the validation of protein structures.

To more than a generation of scientists in India, and some abroad, Ramachandran was a source of scientific and personal inspiration. Many of his contributions were based on simple but striking ideas. He demonstrated how international science could be influenced, even from less well-endowed neighbourhoods, through ingenuity and imagination. It is remarkable that although Ramachandran left structural biology and mainstream research about a quarter of century ago, his presence in the field remains as vibrant as ever. Indeed, Ramachandran established a great scientific tradition. That tradition lives on and thrives in the world, in India, and in the two research schools he founded.

Fellowships

Fellow of the Indian Academy of Sciences
Fellow of the Indian National Science Academy
Hon. Fellow of the National Academy of Sciences, India
Fellow of the Royal Society of Arts
Fellow of the Royal Society
Founder Member of the Third World Academy of Sciences
Hon. Member, American Society of Biological Chemists
Hon. Foreign Member, American Academy of Arts and Sciences, Boston
Hon. Fellow of the Indian Institute of Science, Bangalore

Awards and distinctions

1961 Shanti Swarup Bhatnagar Prize for Physical Sciences
1964 Watumull Memorial Prize for Biophysics
1967 John Arthur Wilson Award by the American Leather Chemists Association
1971 Meghnand Saha Medal of the Asiatic Society
1972 Srinivasa Ramanujam Medal of the Indian National Science Academy
1976 Jagadish Chandra Bose Award of the University Grants Commission
1977 J. C. Bose Medal of the Bose Institute
1978 Fogarty International Medal of the National Institutes of Health
1979 Distinguished Alumni Award of the Indian Institute of Science
1982 Sir C. V. Raman Medal of the Indian National Science Academy
1984 Rameshwardasji Birla Award for Medical Sciences
1999 Ewald Prize of the International Union of Crystallography

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The frontispiece photograph is reproduced by courtesy of the Department of Crystallography and Biophysics, University of Madras.

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