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Soldiers of Science: A Profile

THE INDIAN WIZARD OF BIOPHYSICS : REMEMBERING G. N. RAMACHANDRAN IN THE INTERNATIONAL YEAR OF CRYSTALLOGRAPHY

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Abstract: An Indian soldier of science who had implanted deep foot prints in the biophysical world of peptides, proteins and imaging is none other than G.N. Ramachandran. Hardly has another Indian biophysicist received such world wide acclaim. The year 2013 marked the 50th year of his much lauded and used Ramachandran map and has been celebrated in India with gusto, worthy of his remarkable contribution. As the year passed by, it is imperative that we salute the great soul yet again. It is no mere coincidence with respect to G.N. Ramachandran that after the year long celebrations of 2013, the year 2014 will be celebrated world-wide as the International Year of Crystallography. It is essential to emphasize that any celebration with respect to crystallography is incomplete without remembering Ramachandran. His life and contributions are now widely known, but a recount of the tales will always remain relevant, and the budding generation of young scientists must realize his value over and over again.

Keywords: G.N. Ramachandran; International year of crystallography 2014; Ramachandran map; Collagen helix; Convolution technique

Introduction

For a biologist, especially biochemist / biophysicist / structural biologist, the "Ramachandran map" needs no introduction. In a way, this map (also called phi(ϕ)-psi(ψ) map), which accounts for the "torsional angles" in peptides and proteins, is the holy grail of structural biology and X-ray crystallography is no exception (Nelson and Cox, 2004; Ramachandran *et al.*, 1963). It is over 50 years that this map has been the guiding light for structural biologists - validating three-dimensional structures (Laskowski *et al.*, 2013). It has survived for 50 years and will surely do so for many more years to come. As we embark upon the celebration of International year of crystallography in 2014 commemorating 100 years of Laue diffraction, it must be emphasized that the contributions of the creator of the Ramachandran map to X-ray crystallography is monumental (Rose, 2013). It is surprising thus to note that the family tree of macromolecular crystallographers recently chartered by Jaskolski *et al.* failed to make a mention or even a footnote about G.N. Ramachandran, who gave the world the map (Jaskolski *et al.*, 2014). In addition to the map, G.N. Ramachandran had immense contribution to protein X-ray crystallography in its formative years and the sapling of macromolecular crystallography that he implanted in India is now a deeply rooted, sub-rooted "banyan tree" (Vijayan, 2013a). He could have either been included in the "treeless" section along with four others or in the branch of family tree that includes

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luminaries from Cambridge (Jaskolski *et al.*, 2014). In light of this omission, it is imperative that we recount the life and achievements of G.N. Ramachandran yet again for a broader realization.

Gopalasamudram Narayana Iyer Ramachandran (or simply GNR or G. N. Ramachandran) was one of the maverick Indian scientists of 20th century, for whom the initial of his name "G" was synonymous to "Genius". He achieved immortality in the field of protein sciences and imaging through his contribution of "biophysical triad" - the "Madras Helix" (collagen triple helix), the "Ramachandran plot" and the "convolution technique for image reconstruction" providing a fundamental backbone to understand protein and peptide structures. Such diverse multiple contributions to science are phenomenal. That he and his colleagues had ***manually calculated*** all the dihedral angles and inter-atomic distances in proteins and peptides due to absence of any sort of computers during 1950s-1970s in India, helps fathom his excellence, especially in respect of the present age of lightening speed super computing system (Mohanti, 2012)! The full proof thoroughness of his discoveries and their diverse implications has assured that all biochemistry or biophysics text book mentions his discoveries without failure. It must be appreciated that in addition to being a great scientist, Ramachandran was a teacher par excellence who could explain even a highly complicated concept in a very lucid language to be understood by high school students indicating his outstanding oration ability as well. Moreover, the multi-faceted and talented Ramachandran had written poems on science, religion, philosophy and the Upanishads (Sarma, 1998). We assume thus the relevance of his contributions and life sketch being re-told gains epic proportions and would inspire generations of blooming scientists.

Childhood and early education

GNR was born on 8th October, 1922 in Ernakulam district of Kerala in pre-independence era when every citizen was struggling for a free, strong and resurgent India (Sarma, 1998). The turmoil notwithstanding, GNR was provided a chance for decent education owing to his parents, father G.R. Narayana Iyer (who was a professor of Mathematics) and mother Lakshmi Ammal, who believed strongly that education is the path to glory and strong India. As such Ramachandran was exposed to challenging theories in mathematics, thus building a strong foundation, even before he went to college and developed a deep interest in mathematics since his childhood. His life thus reiterates the importance of mathematics being the backbone of science education, a factor largely ignored in today's system of education. He stood first in the entire Madras State in his Intermediate Examination in 1939 and joined St. Joseph's College in Trichy pursuing a Bachelor's degree (B.Sc.-Honours degree as was called) in physics (Sarma, 1998). Yet again he stood first class first among all physics students of Madras Presidency (Mohanti, 2012). He seems to have earned a habit of ranking amongst the best and so did he for the rest of his life as well.

Higher education

Following an existing societal trend, Ramachandran's father wished to send his son for either of Indian Civil Service or Indian Railway Engineering Service instead of any Master of Science (M.Sc.) degree! Interestingly, GNR failed in both the entrance examinations, surely by design, and joined Indian Institute of Sciences (I.I.Sc), Bangalore for his M.Sc. degree in Electrical Engineering in 1942 (Sarma, 1998). At that time, the legendary Nobel laureate Prof. C.V. Raman (recipient of 1930 Nobel prize in Physics for Raman effect) was the director of I.I.Sc. and head of the department of physics. One brilliant mind ignited the other, highlighting the importance of exposing students to inspiring greats. C.V. Raman's achievements inspired GNR and thus very soon he decided to switch over to physics as his subject of study. In fact, Prof. Raman himself requested the head of the electrical engineering department to allow Ramachandran to join the physics department. However, when the request was deliberately refused for a number of times, Raman admonished the head of electrical engineering department and was quoted as saying: "I am admitting Ramachandran into my department as he is a bit too bright to be in yours..........." (Sarma, 1998). How far-sighted Raman was! GNR solved an equation related to principles of optics within the first week of his joining in Raman's department and eventually he became the most distinguished student of Raman's tutelage. Raman's satisfaction and pleasure was evident in one of the quotes from Ramachandran: "Raman recommended me for a scholarship of 60 rupees a month. But the administrators of the institute said that I had to have a master's degree. Raman said, 'Don't worry about it, I will give you a fellowship of 130 rupees a month, you get an associateship degree from the institute" (Mohanti, 2012). GNR was thus relieved of any courses to be taken and engaged only in research. The degree that was awarded to him was called A.I.I.Sc (the Associateship of the Indian Institute of Science) (Sarma, 1998).

In addition to research, Ramachandran delivered lectures on crystallography, starting with symmetry. He studied a book on group theory by Herman Weyl, on which he commented: "... it became very useful throughout, particularly in my work on logic.... That changed my whole attitude to science" (Mohanti, 2012). Indian Institute of Science was, however, not a degree granting institution in those days and GNR obtained his M.Sc. degree in 1944 from the Madras University. His M.Sc. dissertation contained the result of the theoretical and experimental investigation that he carried out on the propagation of light through optically heterogeneous media (Sarma, 1998).

Subsequently, he continued his research work with Prof. Raman for a doctoral degree. His doctoral research involved photo-elasticity and thermo-optic behavior of different solids like, diamond, fused quartz, fluorspar, zinc blend etc. He also coined the term 'topograph' during X-ray diffraction study of crystals (Sarma, 2001). Such was his brilliance and independence that the research paper emanating from his work was published with Ramachandran as the single author and without Raman's name (Ramachandran, 1948)! While the mentee indeed needs to be lauded, what is equally awe-inspiring is the dimension that the mentor (C.V Raman) possessed – the freedom he provided, the integrity and sacrifice for science and the altruism he demonstrated! Such student-teacher relationships are a rare commodity now!

A D.Sc. degree was thus awarded to GNR in 1947 (it is interesting to note that this year coincided with India's ascendance as a free country). He then decided to go to Cambridge to work in the Cavendish laboratory for a second doctoral degree, probably for a more career oriented concern. Ramachandran obtained the prestigious scholarship for higher studies in England provided by the Royal Commissioners of the 1851 Exhibition. Ramachandran explained his judgment: "...I decided to work for a doctoral degree because then there would be something to show for my work; simply getting a few publications does not impress authorities in India. My decision may have definitely helped me in getting my first job in Madras..." (Sarma, 1998). Probably his logic was justified. In Cambridge, Ramachandran worked in three projects - instrumentation, electronics and the development of a mathematical theory to study diffuse X-ray diffraction (Sarma, 1998). In Cambridge he also met another genius, Linus Pauling, for the first time at an age of just 25, which might have restructured Ramachandran's research orientation yet again. For Ramachandran, Pauling was a great hero, who had just discovered the alpha helical structure of polypetides and emotionally he wrote a poem on Pauling, which is oft quoted and a part of it is reproduced here (Mohanti, 2012):

"Linus Pauling
Is a name to conjure with,
In chemical bonding
And whatever forthwith
Follows for all matter,
Both inanimate and alive
Their nature and character
And how they will behave.
His great alpha helix,
That opened the path
For the solution of structures
Of all biopolymers,
Is a star that will adorn
The firmament of Science,
For it has revealed to biologists
Completely new ways."

Scientific career and achievements

Ramachandran returned to India in June of 1949 after getting his PhD degree from Cambridge within two years (!) and joined the department of physics at I.I.Sc., Bangalore as an assistant professor (Ramakrishnan, 2001; Sarma, 2001).

By then biological research had caught the fancy of scientific world. In 1951, Pauling and his associates showed that some of the proteins like keratin, myosin, epidermin and fibrinogen chains were wound up in a screw-like form that they called "alpha helix" (Pauling *et al.*, 1951). This is a single stranded helical structure, which helped explain not only the structure of polypeptide chains but also of several proteins, including some of the keratins thus laying the foundation stone of macromolecular crystallography. Pauling's helix was soon confirmed by studies of X-ray diffraction by natural protein chains in hair and as well as in synthetic protein chains (Pauling *et al.*, 1951). Pauling's structure was noteworthy in two aspects. In the first place, the helix seemed "irrational"; it did not have an integral number of amino acid residues in each turn but 3.6 residues! Secondly, it led crystallographers to study the nature of diffraction by a helical structure in mathematical terms (Pauling *et al.*, 1951). Such an analysis had an everlasting influence on further studies of biological structures. Coincidentally in 1952, the vice chancellor of the University of Madras - Sir A.L. Mudaliar - appointed Ramachandran as a Professor cum head of the department of newly built experimental physics division in his University; this being an outcome of the fact that Sir C.V. Raman himself refused the offer and recommended Ramachandran's name instead (Balaram, 2013; Balasubramanian, 2011; Sarma, 2001). It was under such a backdrop that Ramachandran got interested in the area of macromolecular crystallography like his scientific hero Pauling and set up a fully equipped modern X-ray crystallographic laboratory at Madras with the wholehearted financial as well as administrative support from Sir A.L. Mudaliar (Balasubramanian, 2011). Rest was, of course, history.

The Madras Helix: The excitement in the structural biology field was increased manifold when Watson and Crick unraveled the double helical structure of the DNA in 1953 (Watson and Crick, 1953). At the same time, Ramachandran was attracted to J.D. Bernal's remarks that structural proposals for collagen were unsatisfactory and thus he was trying to determine the 3D structure of animal collagen in association with a group of brilliant and enthusiastic scientists (Ramakrishnan, 2001). It was a challenge Ramachandran happily accepted, collagen being readily available from the neighboring organization of Central Leather Research Institute, and finally, Ramachandran and Kartha could successfully publish the 3D structure of collagen "triple helix" in the journal Nature in 1954 (Ramachandran and Kartha, 1954) and the revised model in 1955 (Ramachandran and Kartha, 1955). If the alpha helix is designated as the California helix (Pauling), if the double helix (DNA) is the British helix (Watson and Crick) then collagen can be appropriately called as the **Madras helix** (Balasubramanian, 2011)! Ramachandran's contribution to macromolecular crystallography is thus irrefutable.

Their proposed collagen model consisted of three parallel left-handed helical polypeptide chains standing side-by-side and packed together in a hexagonal array (Green and Berman, 2013; Ramachandran and Kartha, 1954, 1955). Every third residue in each chain was a glycine facing common central axis, a novel concept. Unfortunately, the model was highly criticized by Rich and Crick (Rich and Crick, 1955) due to the presence of (i) less than allowable non-bonded inter-atomic distances based on the sum of van der Waals radii and (ii) two interchain H-bonds instead of one H-bond as reported earlier by Rich and Crick. The controversies probably left Ramachandran hurt and wounded and created an unfair legacy, that of the acceptance of triple-helical structure of collagen without due credit to Ramachandran. However, the same controversies, combined with the "never-give-up" spirit of stodgy Ramachandran also led him and his students to the marvelous and immortal discovery of the Ramachandran plot.

The Phi-Psi Map: To solve the first controversy stated above, Ramachandran along with his students V. Sashishekharan and C.

Ramakrishnan analyzed all the X-ray diffraction pictures published until then on amino acids, peptides and proteins and tried to find out what sets of bond angles and shapes they have taken most often (Balasubramanian, 2011; Ramachandran *et al.*, 1974; Ramachandran *et al.*, 1963; Ramachandran and Sasisekharan, 1968). The survey revealed that nonbonded atoms, in fact, approached each other much more closely than the sum of their van der Waals radii! Using a hard sphere model Ramachandran and his students could soon enlist the entire conformational space for all the amino acids in a protein or peptide based on their 'normal limits' of contact distances for each pair of atoms. They also found the normal limit to be further reduced by 0.1 Å, to yield the so-called 'extreme limits' to accommodate Pauling's α helix (Mohanti, 2012). Since the peptide chain backbone is essentially made up of planar rigid peptide units, Ramachandran's brilliant mind considered that a pair of successive peptide units has only two degrees of freedom (rotation of φ and ψ) around the bonds linking each Cα atom to the neighboring peptide units. He treated this as a mathematical problem of rotation of two rigid planes containing interacting hard spheres that must avoid bumping against each other (Sarma, 1998). Using the contact limits, if the rotations resulted in sterically unacceptable contacts, such conformations were considered to be disallowed. While, the allowable non-bonded distances were used to determine allowable ranges for the two torsion angles - *phi* and *psi.* These led to the origin of the famous "Phi-Psi Map" or "Ramchandran Map" in protein science (Laskowski *et al.*, 2013; Ramachandran *et al.*, 1963). The experimental proof of the Ramachandran plot came almost immediately, when Sir John Kendrew published the atomic resolution structure of myoglobin (Kendrew *et al.*, 1958). Observed ϕ and ψ values confirmed the correctness of the Ramachandran Plot. Details of the map was published first time in January 1963 in the Journal of Molecular Biology (Laurence, 2013; Ramachandran *et al.*, 1963). With a stroke of genius Ramachandran put to rest the controversies and ensured that such controversies never erupted again providing a referral for "correctness" of three-dimensional structures of proteins and peptides.

Initially, different solved protein or peptide structures were used to validate the map, but from 1970s almost all the solved new protein or peptide structures are being validated through this map (Ramachandran and Sasisekharan, 1968; Richardson *et al.*, 2013; Sarma, 1998)! The constraint on the allowable conformations can be used to guide the generation of 3D structures of polypeptide chains. The glamour and the significance of this discovery is evident from the fact that the minimal allowable contacts and resultant allowable torsion angles for polypeptide chains determined in the early 1960s are still valid even after 50 years! No doubt, the work was highly complemented and appreciated by whole scientific world of which Janet Thornton's comment deserves special mention: '...I think that this major discovery highlights the importance of clear thought and vision that do not always need expensive equipment and huge teams of people' (Mohanti, 2012). This should specially resonate amongst scientists in countries where research is done under great financial constraints. It is worthwhile to mention here that though Ramachandran, along with his last PhD student Manju Bansal, tried to answer the second point of criticism by Rich and Crick, it was resolved when Helen Berman *et al.* proved from a single crystal study that there are on average 1.5 H-bonds in collagen triple-helix and neither 1 nor 2 (Bansal and Ramachandran, 1978; Bansal *et al.*, 1975; Bella *et al.*, 1994).

Another interesting fact about the phi-psi map is that Ramachandran along with his two brilliant students - R. Chandrasekaran and K.S. Chandrasekaran - could also explain the absolute configuration of carbohydrates in 1967 (Ramachandran *et al.*, 1967). The plot was also extended to describe nucleic acid and polynucleotide structures, made possible with the help of his luminous student pair - V. Sasisekharan and A.V. Lakshminarayanan (Sasisekharan *et al.*, 1967).

GNR organized two international symposia in 1963 and 1968 where he could successfully invite and host some of the most famous Molecular Biologists and Biophysicists like Linus Pauling, Severe Ochoa, Maurice Wilkins, Paul Flory and many others in Madras (Sarma, 1998).

Inspite of being instrumental in building the molecular biology department in Madras University, Ramachandran resigned from Madras University after Mudaliar's retirement due to some unavoidable circumstances and came back to Indian Institute of Science, his alma mater, in 1970 to initiate Molecular Biophysics Unit (MBU) (Balasubramanian, 2011), which oversaw consolidation and expansion of macromolecular crystallography in India over the years (Vijayan, 2013b).

The Convolution Theory: In his second innings at I.I.Sc., Ramachandran was fascinated in Fourier transforms. He applied the transforms to develop the theory of 3D Image Reconstruction from 2D shadowgraphs using his yet another fascinating discovery – 'the Convolution Technique'. He established this method along with A.V. Lakshminarayanan during his visit to the University of Chicago and published two interesting papers in 1971 (Balasubramanian, 2011). This technique marked the genesis of what today is known as tomography - a method used in diagnosis as CT scan, PET scan, confocal microscopy and many other 2D to 3D image conversion processes including X-ray diffracted crystallographic data processing (Balasubramanian, 2011). It is very unfortunate to learn that GNR actually tried at that time to raise some grant money from agencies to build a tomograph, with no success (Balasubramanian, 2011)! Wish he had C.V Raman yet again to push his case, justifying how visionaries make a difference to the scientific growth of the country.

In 1976, GNR was attracted to Fundamental theory and Mathematical philosophy leading to the development of a new Boolean Algebra Vector Matrix formulation (Sarma, 1998). He retired from MBU in 1978 but continued as a Professor of mathematical philosophy at the institute till 1989 (Mohanti, 2012). During this long journey, Ramachandran had contributed more than 250 outstanding publications with marvelous impact on science and human being (Sarma, 1998). Twenty seven students completed their PhD or M.Sc. degree under his supervision and are continuing to spread significant contribution towards science in the same way as their mentor did.

Extra-scientific activities

Apart from science, multi-talented GNR was the founder member of Indian Academy of Yoga and he translated the Bhagabad Gita into English (Balasubramanian, 2011). He was a connoisseur of Carnatic music and had deep interests in Ragas (Balasubramanian, 2011). He donated most of his prize money to national charities and student scholarships in India (Sarma, 2001).

Honors for the master or not!

The list of National as well as International awards or honors that Ramachandran had received is too long to mention here; amongst which the prestigious Birla Memorial award for Medical Sciences (Sarma, 2001), Shanti Swarup Bhatnagar award (Balasubramanian, 2011), election as a Fellow of the Royal Society, London (FRS) (Mohanti, 2012), Fellow of Royal Society of Arts, London (FRSA) (Mohanti, 2012), founder member of Third World Academy of Sciences (Mohanti, 2012), member of Council of International Union of Pure & Applied Biophysics (IUPAB) (Mohanti, 2012) are prominent. The auditorium at Central Leather Research Institute has been named as 'the Triple Helix Auditorium' as a thoughtful tribute to Ramachandran's discovery (Balasubramanian, 2011). However, the prestigious Nobel Prize was not awarded to the gifted scientist. Surprisingly, no civil awards like Bharat Ratna or Padma Bibhusan were awarded to him either. However, Ramachandran will continue to live in all human minds for a very long time through his remarkable achievements. It could very well be a lesson for all of us – pursue science for the fun of it and to serve the humanity for its betterment; awards are but just a by-product. Ramachandran, anways, has won the biggest prize of them all – immortality!

Personal life

Like a true perfectionist, Ramachandran expected to see his surrounding people to be as intelligent as he was by himself (Mohanti, 2012). Unfortunately everybody was not Ramanchandran and thus GNR sometime failed to maintain his temperament in the laboratory (Mohanti, 2012). In his late sixties, Ramachandran had symptoms of Parkinson's disease and slowly lost control over his physical movements (Sarma, 1998). It did not deter his scientific creativity, though. The ailing Ramachandran was cared for by his wife Rajam whom he married in 1945 (Balasubramanian, 2011). However, in July 1998, Rajam died from a heart attack, and Ramachandran never fully recovered from this blow. Since August 1999, Ramachandran was under nursing care in a hospital in Madras until his death due to cardiac arrest on 7th April, 2001 (Balasubramanian, 2011). He is survived by two sons, Ramesh (Professor of Astrophysics at Harvard University) and Hari (Institute of Plasma Physics, Ahmedabad, India), and a daughter, Vijaya (Professor of Computer Science, University of Texas at Austin) (Mohanti, 2012). Ramachandran touched heights where few can reach and will continue to inspire generation of scientists.

Ramachandran, the Indian

Ramachandran had many lucrative assignments for performing research in the advanced western countries but like his mentor, C.V. Raman, he decided to work in India against all odds. Such great acts will surely inspire patriotism and pride and the zeal to serve the country. His international biographer Raghupathy Sarma has rightly said: "...Ramachandran, a remarkable creative individual with an active mind that never relaxed, constantly striving to shed light on one problem or another." Appropriately, worldwide, when this year is being celebrated as the International year of crystallography, we must remember Ramachandran for his seminal contributions and must include him amongst other luminaries in the 100 years of history of macromolecular crystallography (Jaskolski *et al.*, 2014).

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