G. N. Ramachandran: A brief profile

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The structure of our genetic material was decoded and published in 1953 by Francis Crick and James Watson, revealing the double-helical shape of DNA- the building block of life made of protein, which is one of the most crucial and abundant biomolecules. Biomolecules play an indispensable role in all life processes, including medication development for various diseases, also used to study the structure of a virus. Biomolecules range from small molecules to large molecules. Proteins are made of long-chain polymers called polypeptides. There can be one or multiple polypeptides chains that come together to form a protein. Like strings of pearl, proteins are made of repeating units or monomers of amino acids that are linked by the peptide bonds. This chain folds into intricate shapes or motifs such as helices and sheets. The molecule structure is important because it will determine what function will protein performs in the body. Incorrect folding of peptide chains causes proteins to function incorrectly, and folding errors manifest as diseases. But the structure of this complex molecule had remained puzzling till the 1950s.

Did you know an Indian scientist discovered the structure of the human body's most abundant protein? It wasn't Linus Pauling or Francis Crack but an Indian scientist from Madras who first discovered the triple helix structure of collagen - it is the most abundant protein in the human body found in the bone, skin, muscles, and tendons. It is the substance that holds the body together. This discovery was made by **Gomalasamudran Narayana Ramachandran**, in India in 1955. The understanding of proteins in the human body started in the early 1950s when scientists were researching the structure of various bio-molecules. G. N. Ramachandran was born on 8 October 1922 in the town of Ernakulum, Kingdom of Cochin, British India to a Tamil Brahmin family. Ramachandran was the eldest son of G. R. Narayana Iyer and Lakshmi Ammal. Since childhood, Ramachandran had a deep absorption in mathematics, and his father Narayana Iyer had considerable influence in shaping Ramachandran's interest in mathematics. He completed his B.Sc. honors in Physics from the University of Madras. Ramachandran's father wanted his son to take up the Indian Civil Service Examination. However, he failed to persuade his son in doing so. He then sent Ramachandran to Delhi to take the Indian Railway Engineering Service Examination. But even this was not liked by Ramachandran. It was presumed that he deliberately performed poorly in the entrance examination to ensure that he was not selected.

After this, he began his academic career as a student of electrical engineering at the Indian Institute of Science (IISc), Bangalore in 1942. Quickly realising his interest in physics, he switched to the Department of Physics to complete his master's and doctoral thesis under the supervision of Nobel laureate Sir C. V. Raman. Under the able guidance of Raman, Ramachandran did his post-graduate research in the areas of optics and X-ray topography of diamonds. He mostly studied crystal physics and crystal optics, created an X-ray focusing mirror for the X-ray microscope. The resulting field of crystal topography is used extensively in studies involving crystal growth and solid-state reactivity. In 1947 Ramachandran obtained a DSc degree that is equivalent to a doctoral degree. In 1947, Ramachandran went to the Cavendish Laboratory in Cambridge, England, headed by Sir Lawrence Bragg. At Cambridge, he worked with W. A. Wooster and A. Lang on a crystallographic project and from it emerged a mathematical theory for determining the elastic constants of crystals from measurements of diffuse X-ray reflections, a technique used to decipher the structures of bio-molecules such as DNA and proteins. He received a Ph.D. degree in 1949 from Cambridge University. While at Cambridge, Ramachandran met Linus Pauling and was greatly influenced by his lectures on modelling studies of polypeptide chains.

In the same year, Ramachandran returned to Bangalore and worked as an Assistant Professor in Physics till 1952, when he began his journey in the field of biochemical research. At 29, he became a Professor of Physics at the University of Madras, with Raman's recommendation. In 1952, he got a laboratory of his own; studying biomolecules would be the lab's theme, the crystal physicist had decided, but he had trouble deciding which projects were worthy of attention. Right around then, a former colleague from England, the renowned crystallographer J. D. Bernal, who was on a visit to Madras, informed Ramachandran that many research groups were stumbling with the structure of collagen. Knowing that leather is largely made up of collagen, Ramachandran decided to use it as a source to study because good-quality pictures of collagen were important in his research but the shark fin-collagen that was available in the Biochemistry Department did not give the desired results. Ramachandran paid a visit to the Central Leather Research Institute (CLRI), which was close to Madras University, for this. While beef Achilles tendon was effortlessly available in India, the Kangaroo tail tendon would get the best diffraction images, in theory. Thus, a helpful deputy director of CLRI got the kangaroo collagen from Australia, especially for Ramachandran.

During those days, the only available information on the fibrous protein was that one-third of its total amino acid content was glycine. Using this fact, and the pictures of the collagen which Ramachandran took, together with his postdoctoral fellow, Gopinath Kartha, he proposed a triple helix structure for collagen – also called the Madras helix. Ramachandran and his research group's findings were published in the renowned journal *Nature* on August 7, 1954. The triple helical structure of collagen paved the way for the famous Ramachandran plot. Further Ramachandran and his colleague set on the path to understand and describe the structure of polypeptide chains. They surveyed the crystal structures available to determine how close two atoms could approach, and thus deduce the permissible interatomic distances within a polypeptide chain. Ramachandran decided to use this information to examine the various polypeptide confirmation then known and also to develop a good 'yardstick' that could be used for examining and assessing any structure in general, but peptides in particular. The result which emerged from these calculations in 1962, – now commonly known as the Ramachandran Plot – was published in the *Journal of Molecular Biology* in 1963 and has become an essential tool in the field of protein conformation.

We take a brief digression into the Ramachandran plot.

Nowadays, biochemists can quickly understand which structures are possible and which aren't, and compare known and unknown structures intuitively. The Ramachandran plot had changed the perspective of how biochemists study molecules of interest and revealed complex biological processes. Researchers use the Ramachandran Plot to visualize energetically allowed regions for backbone dihedral angles ? against ? of amino acid residues in protein structure. Ramachandran plot is a plot with ? on one axis and ? on the other. Since two successive peptide units are hinged at the C? atom, a pair of peptide units have only two degrees of freedom (rotations ? and ?) around the bonds linking each C? atom to the neighbouring peptide units. It was a brilliant flash of insight for Ramachandran to treat this as a mathematical problem of rotation of two rigid planes containing interacting hard spheres that must avoid bumping against each other. Using the contact limits, if the rotations result in sterically unacceptable contacts, such confirmations are considered disallowed. This reasoning was the genesis of the Ramachandran plot.

The dihedral, ?, of the protein backbone is restricted due to the planarity of the amide bond (C and N) and the hybridization of the involved atomic orbitals. This results in a resonance structure with partial double binding and a permanent dipole moment (with negatively charged oxygen). Therefore, rotation around ? requires a large amount of energy (80 kJ/mol). The values of the dihedral angles ? and ? are restricted by the steric hindrance between the atoms of neighbouring peptide bonds and side-chain atoms. The Ramachandran plot shows the statistical distribution of the combinations of the backbone dihedral angles ? and ?. In theory, the allowed regions of the Ramachandran plot show which values of the ?/? angles are possible for an amino acid, X, in an ala-X-ala tripeptide. In practice, the distribution of the ?/? values observed in a protein structure can be used for structure validation.

In today’s world when researchers or scientist need to check the structure of an unknown protein, researchers compare data obtained from crystallographic studies and from theoretical calculations. The more the plots match, the more confident scientists can be that their structure is the right one.

Fourier transforms also fascinated Ramachandran. He applied Fourier transforms for developing the theory of Image Reconstruction from shadowgraphs (such as X-Radiographs) using the Convolution Technique. In 1971 Ramachandran along with A. V. Lakshminarayana published a seminal research paper on three-dimensional image reconstruction. This marked the beginning of studies on tomographic methods. This idea was adopted for the development of Catscan equipment which has played an important role in the development of medical diagnosis and surgery. In 1976 Ramachandran turned his attention to Fundamental theory and Mathematical philosophy which led to the development of a new Boolean Algebra Vector Matrix Formulation.

Ramachandran was awarded the prestigious Jawaharlal Nehru Fellowship in 1968 for research on protein and polypeptide conformation, he was one of its first recipients. Notable awards that Ramachandran received include the Shanti Swarup Bhatnagar Award for Physics in India (1961) and the Fellowship of the Royal Society of London. In 1999, the International Union of Crystallography honoured him with the Ewald Prize for his outstanding contributions to crystallography. He was nominated for the 1964 Nobel Prize in Chemistry by Sir C. V. Raman for his fundamental contributions to protein structure and function, but didn't win the prize. During his lifetime, Ramachandran also penned several books and held scientific conferences in Madras inviting top-notch international scientists. In the 1980s, Ramachandran’s extraordinary mind started showing symptoms of Parkinson’s disease, and his health started deteriorating. An ailing GNR retired in 1989 and died due to a cardiac arrest in April 2001 at the age of 78 and left behind him a legacy of scientific discoveries.

> “...Ramachandran, a remarkable creative individual with an active mind that never relaxed, constantly striving to shed light on one problem or another. His life has been one of varied experience punctuated by ups and downs, success and failure, as is the case with many other famous scientists of our times. Ramachandran suffered serious psychiatric problems during most of his adult life. Fortunately, they did not impact on his scientific creativity or productivity; it simply added a new dimension to his life. In spite of all that he put India on the map of molecular biophysics. Clearly Ramachandran belongs in the same league as some of the most famous Indian scientists of this century, for example Sir C. V. Raman, M. N. Saha or S. N. Bose (of Bose-Einstein Statistics fame). Clearly his contributions in the field of biophysics are of the Nobel Prize calibre.”
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> Raghupathy Sarma in Ramachandran: A Biography of the Famous Indian Biophysicist (1998)

Today the world is suffering from the COVID -19 pandemic. Following this circumstance, each and every scientist is remembering the work of G. N. Ramachandran. Because of his detailed discovery about the structure of protein, researchers and scientist can use protein for vaccine and drug development by knowing its structure.
