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Mini-Review

Unraveling the Triple Helix: The Legacy of G.N. Ramachandran in Biophysics

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ABSTRACT

Gopalasamudram Narayana Ramachandran or simply G.N. Ramachandran is a distinguished Scientist in the field of Biophysics, who made significant contributions in understanding the structures of peptide proteins that make up the building blocks of life. His work on discovering the structure of collagen and devising "The Ramachandran phipsi plot" was vital to understanding how the structures of proteins were made up and has left an indelible mark in medical science. This historical vignette explores his groundbreaking discoveries on the triple Helix structure of collagen and applications of X-ray crystallography. It also delves into his relentless pursuit of knowledge and the hardships that he had to overcome in the said pursuit. Through this exploration, we aim to celebrate the life and achievements of a true pioneer whose work continues to inspire and drive advancements in medical science today.

Keywords: Peptide proteins; X-ray crystallography; Helix structure; Phipsi plot

Introduction

Born on October 8, 1922, in Ernakulam, Kerala, Ramachandran is widely regarded for his groundbreaking contributions to science, particularly for discovering the triple helix structure of collagen[1,2]. He was instrumental in establishing two renowned molecular biophysics centers: one at the University of Madras, Chennai and another at the Indian Institute of Science, Bangalore. These centers gained international acclaim for their biophysics research. Beyond his scientific achievements, Ramachandran was a mentor to numerous young minds, inspiring them to make significant strides in their respective fields. He was also an accomplished poet and an exceptional educator, known for his ability to simplify complex concepts. This article explores his extraordinary career, examining his key discoveries and his enduring legacy as a mentor and pioneer in the scientific community.

Early life

Ramachandran was born into a family steeped in academic excellence, with his father, G.R. Narayana Iyer, being a prominent mathematics professor and the principal of Maharajah's College **(Figure 1)**. This environment fostered Ramachandran's early interest in mathematics and science. He excelled in his studies, topping the state of Madras in physics during his Intermediate examinations. In 1939, he enrolled in a B.Sc. (Honours) in physics at St. Joseph's College, Trichy, where he graduated with distinction in 1942[3]. His father initially encouraged him to pursue the Indian Civil Service Examination and Indian Railway Engineering Service Examination, but Ramachandran, uninterested in these paths, intentionally underperformed to avoid selection.

Ramachandran then joined the Indian Institute of Science, Bangalore, to pursue a Master's degree in Electrical Engineering, graduating in 1944. During this time, he had the privilege of

meeting Sir C.V. Raman, the 1930 Nobel Laureate in Physics, who mentored him and encouraged him to switch to the Physics department. Under Raman's guidance, Ramachandran focused on optics and X-ray crystallography, earning a D.Sc. (equivalent to a PhD) from Madras University in 1947.

Figure 1: GN Ramachandran.

Eager to expand his research, Ramachandran moved to Cambridge, England, to work at the Cavendish Laboratory, led by Sir William Lawrence Bragg. There, he collaborated with W.A. Wooster and A. Lang on crystallography projects and developed a mathematical theory for determining the elastic constants of crystals. His work earned him a PhD from Cambridge in 1949. Ramachandran also met Linus Pauling, whose discovery of the alpha helix structure of proteins greatly influenced his later work on collagen.

After returning to the Indian Institute of Science in 1949, Ramachandran worked as an assistant professor in physics until 1952. He then became the Head of the Physics Department at Madras University at just 29, where he founded the Department of Molecular Biophysics and a state-of-the-art X-ray crystallography laboratory with the help of Sir A.L. Mudaliar, the Vice Chancellor. He left Madras University in 1970 following a change in leadership, which led him back to the Indian Institute of Science, where he continued his pioneering research.

Contributions

Collagen structure discovery: Ramachandran's interest in biophysics was sparked after attending Linus Pauling's lectures and he was especially drawn to Pauling's research on protein structures. In 1952, Professor J.D. Bernal's suggestion that Ramachandran investigate the collagen structure led him to focus on this problem. At that time, existing models for collagen were unsatisfactory and Ramachandran, alongside his first post-doctoral student Gopinath Kartha, began working on X-ray diffraction patterns from kangaroo tail tendons[4]. They developed a model for the collagen structure consisting of three parallel left-handed helical polypeptide chains in a hexagonal arrangement, with glycine residues at every third position.

Their initial model evolved further with more studies and they refined it to depict a coiled coil structure, which they first published in 1955. This triple helix model was a significant step forward in understanding protein structure, though it initially faced skepticism and criticism. Notably, Francis Crick and James Watson, who had unraveled the DNA double helix, disputed the hydrogen bonding details in Ramachandran's model. Later studies revealed that collagen's structure indeed features an average of 1.5 hydrogen bonds per chain, confirming Ramachandran's initial model.

The Ramachandran Plot

The controversies surrounding collagen's structure led Ramachandran to develop a mathematical model to understand polypeptide structures more broadly. Along with colleagues V. Sasi Sekharan and C. Ramakrishnan, Ramachandran conducted a comprehensive survey of protein crystal structures, leading to the development of the "Ramachandran Plot." This plot has since become a fundamental tool in structural biology and stereo-chemistry for evaluating the conformations of polypeptides and proteins.

Other notable contributions

Ramachandran's work spanned various areas of crystallography, including phase determination, X-ray intensity statistics and crystallographic formulas. In 1971, he coauthored a pioneering paper on three-dimensional image reconstruction, laying the groundwork for modern techniques like Computerized Axial Tomography (CAT), a crucial tool in medicine today.

Throughout his career, Ramachandran received numerous prestigious awards, including his election as a Fellow of the Royal Society in 1977 and the Ewald Prize from the International Union of Crystallography in 1999. He was also nominated for the Nobel Prize for his contributions to protein structure research.

Later Life

In the 1980s, Ramachandran began showing signs of Parkinsonism and was cared for by his wife, Rajam. After her sudden death in 1998, his health deteriorated rapidly and he passed away on April 7, 2001. He is survived by his two sons-Ramesh, a professor of astrophysics at Harvard and Hari, a researcher at the Institute of Plasma Physics in Ahmedabad-as well as his daughter, Vijaya, a professor of computer science at the University of Texas at Austin.

Conclusion

Ramachandran's legacy extends far beyond his remarkable scientific achievements. His contributions to molecular biophysics, particularly in the study of collagen, have left an indelible mark on the field. He is rightly regarded as one of India's most brilliant scientists, deserving of recognition alongside figures like Srinivasa Ramanujan in mathematics and Subramanya Chandrasekhar in astrophysics. His work continues to inspire future generations of researchers and his intellectual legacy remains a beacon for scientific progress worldwide.

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