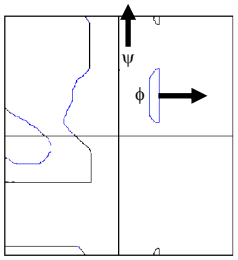
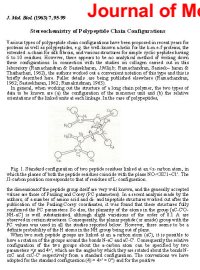
## G.N. Ramachandran and His Plot

**The Story of the "Stereochemistry of Polypeptide Chain Configurations"**

**Journal of Molecular Biology**

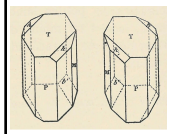


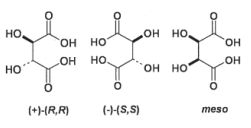



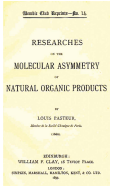
*"This would be a general lecture not related to photochemistry & photophysics"*
V. Ramamurthy

**Configuration** and **Conformation** (polymers and organic stereochemistry)

**April 24, 2021**

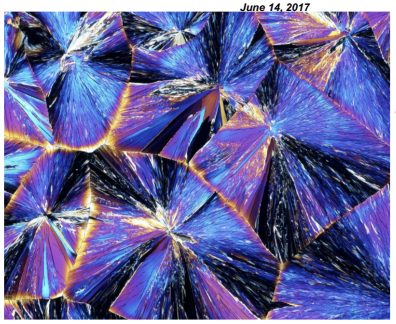





**1860**

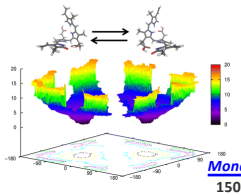
*How Pasteur's Artistic Insight Changed Chemistry* The New York Times
*June 14, 2017*



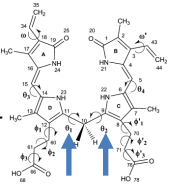
*"… are the atoms arranged at the corners of an irregular tetrahedron or on the spirals of a dextrogyrate helix."*

**Chirality in Nature**

Pasteur and the art of chirality J.Gal
***Nature Chemistry*** **9**, 604–605(2017)



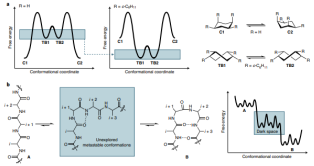
**Bilirubin, the metabolic degradation product of heme undergoes a clinically important photochemical E/Z isomerisation ( phototherapy for neonatal jaundice)**

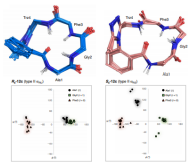


*Monatshefte für Chemie – ChemicalMonthly*
**150**, 801–812(2019)

**Torsion angles**

**Illuminating the dark conformational space of macrocycles using dominant rotors**
D.B.Diaz ..... A.K.Yudin ***Nature Chemistry*** 13, 218-225 (2021)





***"The observation of unusual conformations of 16- to 22-membered rings has been made possible by controlling their interconversion using dominant rotors, which represent tunable atropisomeric constituents with relatively high rotational barriers."***

*J. Mol. Biol.* **(1963) 7, 95-99**

**Stereochemistry of Polypeptide Chain Configurations**

Various types of polypeptide chain configurations have been proposed in recent years for proteins as well as polypeptides, e.g. the well-known α-helix for the L-α c-f proteins, the extended α-chain for silk fibroin, and various structures for simple cyclic peptides having 6 to 10 residues. However, there appears to be no analytical method of writing down these configurations. In connection with the studies on collagen carried out in this laboratory (Ramachandran & Sasisekharan, *1961a,b*; Ramachandran, Sasisek- haran & Thathachari, 1962), the authors worked out a convenient notation of this type and this is briefly described here. Fuller details are being published elsewhere (Ramachandran, 1962; Sasisekharan, 1962; Ramakrishnan, 1963).

In general, when working out the structure of a long chain polymer, the two types of data to be known are (a) the configuration of the monomer unit and (b) the relative orientations of the linked units at each linkage. In the case of polypeptides,

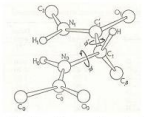


Fig. 1. Standard configuration of two peptide residues linked at an <x-carbon atom, in which the planes of both the peptide residues coincide with the plane NC-<XC1~C1'. The N-carbon position corresponds to that of residues of L- configuration.

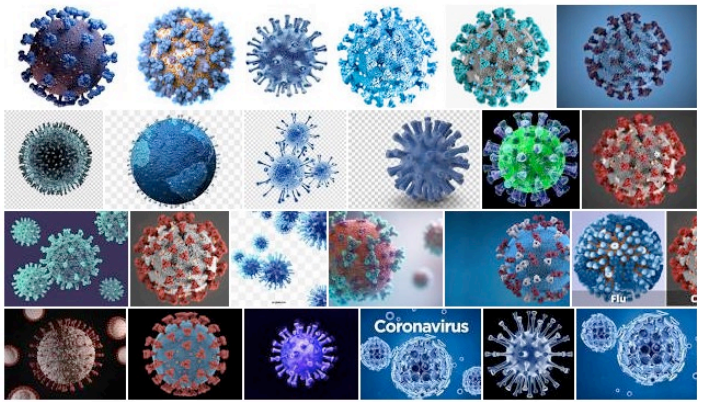
the dimensions of the peptide group itself are very well known, and the generally accepted values are those of Pauling and Corey (PC parameters). In a recent analysis made by the authors, of a number of amino acid and di- and tripeptide structures worked out after the publication of the Pauling-Corey coordinates, it was found that these structures fully confirmed the PC parameters. So also, the planarity of the atoms in the group [αC-CO-NH-αC'] is well substantiated, although slight variations of the order of 0.1 A are observed in certain structures. Consequently, the planar peptide (or amide) group with the PC values was used in all the studies reported below. However, there seems to be a definite probability of the H atoms in the NH group being out of plane.

When two such peptide groups are linked at an α-carbon atom (αC), it is possible to have a rotation of the groups around the bonds N-αC and αC-C'. Consequently the relative configuration of the two groups about the α-carbon atom can be specified by two parameters <p and <p', which are the angles by which they are rotated about the bonds N-αC and αC-C' respectively from a standard configuration. The conventions we have adopted for the standard configuration (<p = <p' = 0°) and for the positive

95

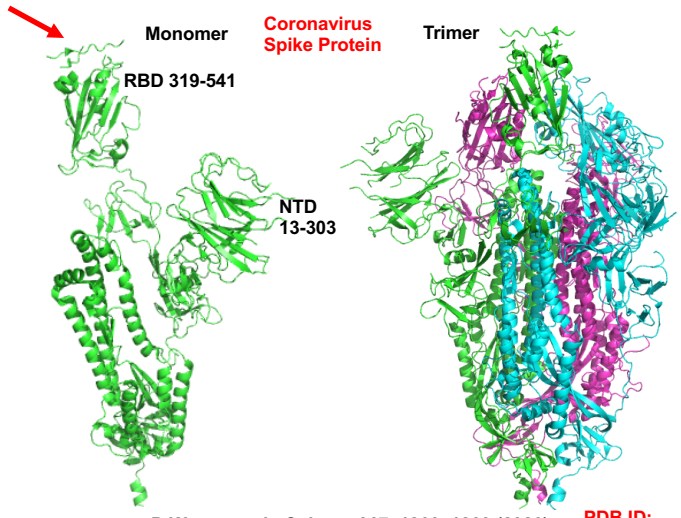
**J.Mol.Biol. (1963) 7, 95-99**

## Coronavirus: A Public Health Nightmare and an Artists Delight



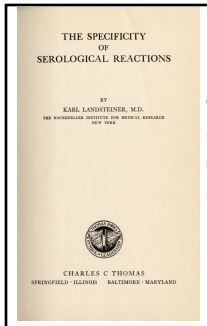

"a piece of bad news wrapped up in protein."

Anon. Quoted by Peter Medawar in *From Aristotle to Zoos*

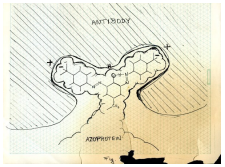


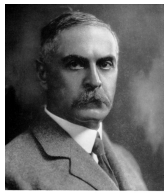

D.Wrapp et al., *Science* 367, 1260–1263 (2020)

PDB ID: 6VSB

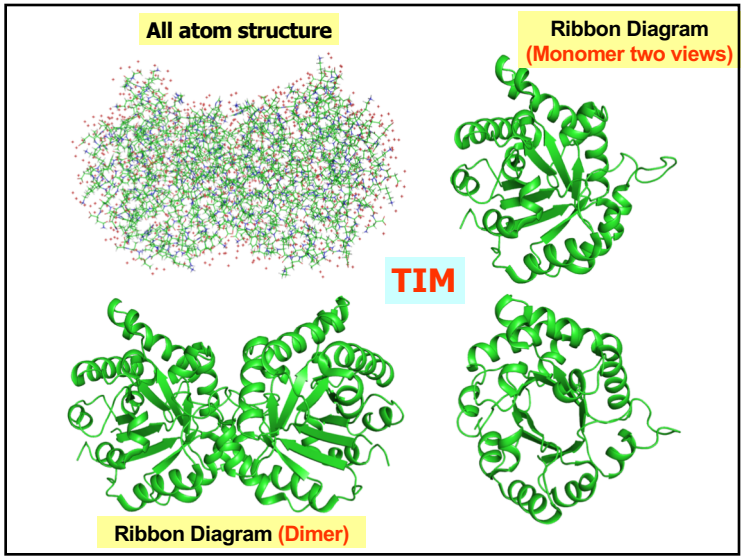



"I think the protein must contain sidechains with active groups" (*ca* 1936)

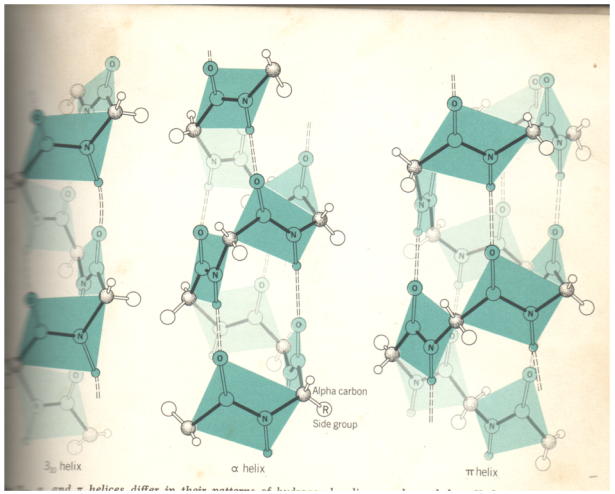


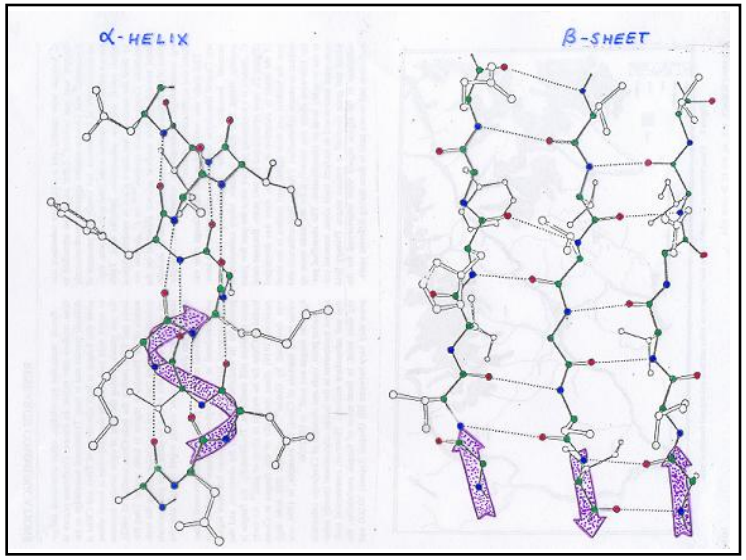


THE PAULING BLOG

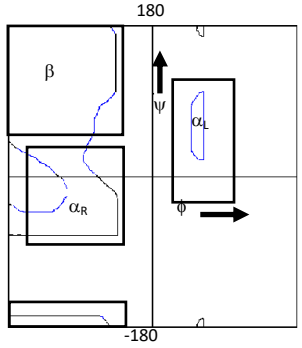


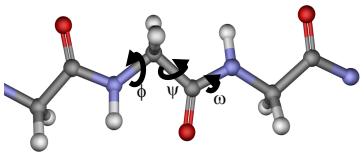
**Illustrations of the Polypeptide Helices by Irving Geis (1969)**

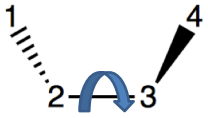



## Polypeptide Stereochemistry

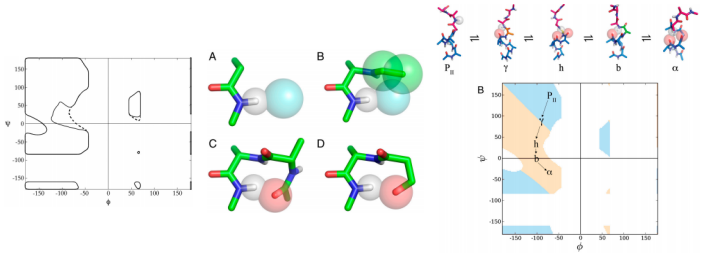



**Ramachandran Map**
**Islands of allowed structures**
**Transformation of a three dimensional problem into two dimensions.**

**Redrawing the Ramachandran plot after inclusion of hydrogen-bonding constraints**
**L. L. Porter and G. D. Rose PNAS (2011) *108*, 109–113**

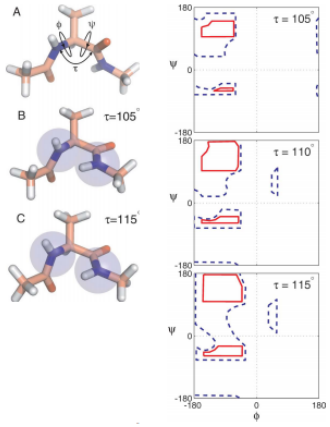



**No general biochemistry textbook is complete without a ϕ, ψ-map of the alanine dipeptide . This iconic plot is a compact representation of a profound organizing idea, one that ranks among the fundamentals of structural biochemistry**

## Revisiting the Ramachandran plot from a new angle

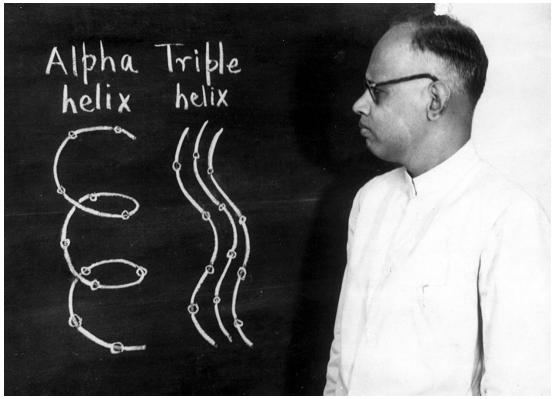
A.Q. Zhou, C.S. O'Hern, and L. Regan  Protein Science (2011) *20*,1166—1171

**The "Ramachandran plot" is an iconic image of modern biochemistry.**

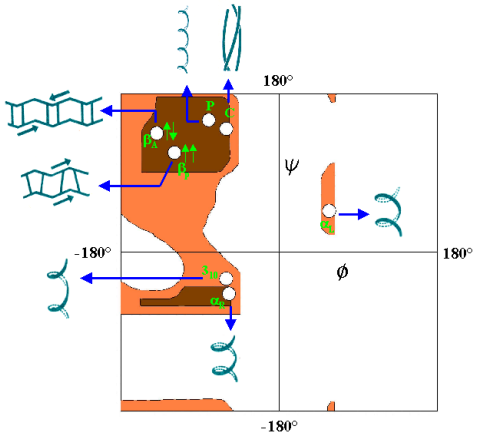



In summary, we have shown that the distribution of backbone dihedral angles observed in proteins of known structure is well explained by Ramachandran and coworker's original analysis of an alanyl dipeptide, where only repulsive hard-sphere interactions together with bond length and angle constraints determine the allowed phi/psi angles

**We find no need to invoke additional interactions to explain the backbone conformations of proteins.**




## Ramachandran Map

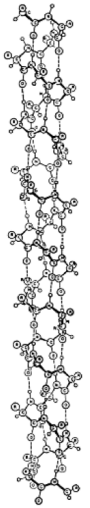



G. N. Ramachandran

(1922-2001)

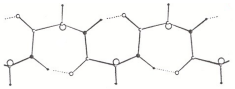
$\alpha_R$: Right-handed α-helix; $\alpha_L$: Left-handed α-helix; $3_{10}$: $3_{10}$-helix
$\beta_A$: Antiparallel β-sheet; $\beta_P$: Parallel β-sheet; P: Polyproline helix; C: collagen

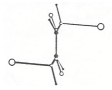
**Today the Ramachandran diagram is taught in all classes on protein structure and is featured in every textbook to give insight into the forces that determine the structures of proteins. But there is nothing in this diagram beyond what Pauling and Corey knew well: they built models of their proposed structures that embodied all features of the Ramachandran diagram. Apparently they understood the principle so well that they felt no need to explain them by a diagram of this sort.**



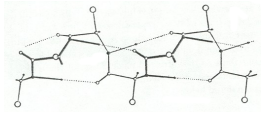
The discovery of the α-helix and β-sheet, the principal structural features of proteins
David Eisenberg, Proc. Natl. Acad. Sci USA., 100, 11207, 2003

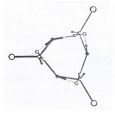
A LITTLE HISTORY





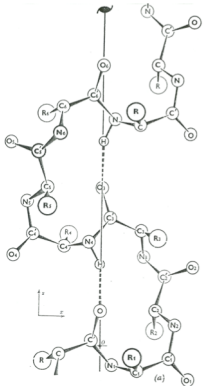
Projection of $2_7$ chain



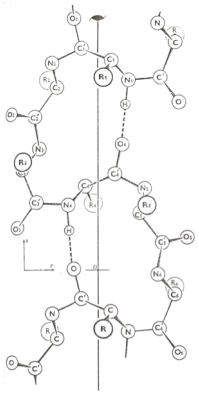


Projection of $3_{10}$ chain

M. L. Huggins, 1943, Chem. Rev., 32, 195



Projection of $2_{13}$ chain



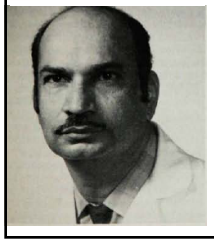
Projection of $2_{14}$ chain

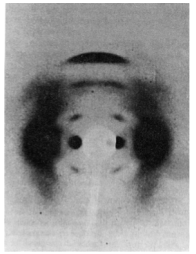
L. Bragg, J. C. Kendrew and M. F. Perutz, 1950, Proc. Roy.Soc. A 203, 321.

Madras 1967

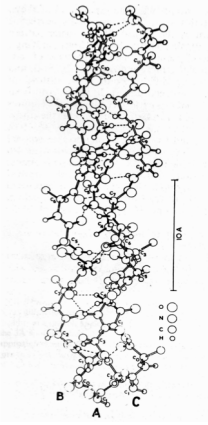
Continued…

G. N. Ramachandran
1922 - 2001





Collagen
Triple helix

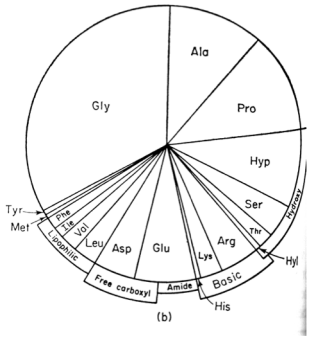


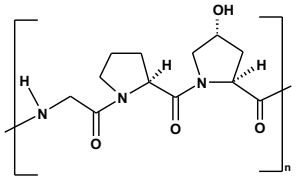

Early 1950s (Madras)

Gopinath Kartha
1927-1984

# Collagen

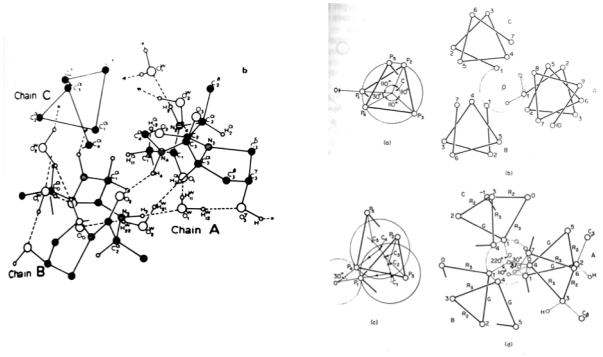
- Large fibrous protein
- Major component of bone, tendon, cartilage and teeth
- The most abundant mammalian protein
- Unusual amino acid composition
- Proteins are polymers formed by linking monomeric amino acids together



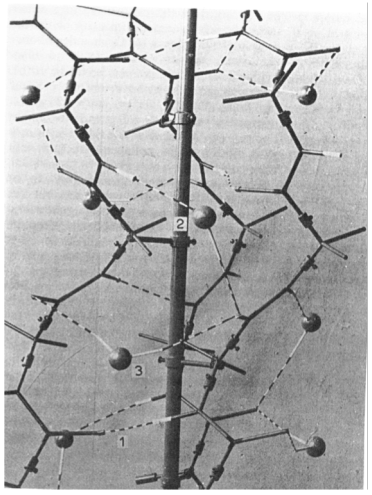




Gly - Pro - Hyp

Triple helix viewed down the helix axis




**Wire model of Collagen**



**•Structure of collagen.**

Ramachandran GN. *Nature.* 1956 ,177(4511):710-1.

**•Structure of collagen.**

Ramachandran GN and Kartha G. *Nature.* 1955 ,176(4482):593-5.

**•Structure of collagen.**

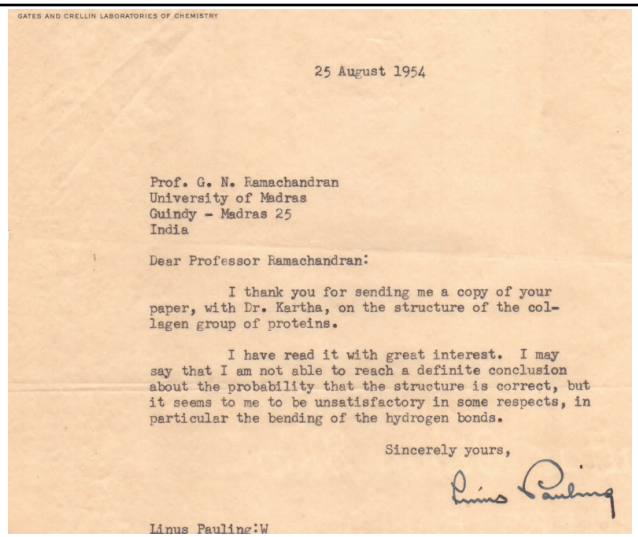
Ramachandran GN and Kartha G. *Nature*. 1954 ,174(4423):269-70.

**•Structure of polyglycine II.**

Crick FH and Rich A. *Nature.* 1955,176(4486):780-1.

**•The structure of collagen.**

Rich A and Crick FH. *Nature.* 1955 ,176(4489):915-6.



GATES AND CRELLIN LABORATORIES OF CHEMISTRY

25 August 1954

Prof. G. N. Ramachandran
University of Madras
Guindy - Madras 25
India

Dear Professor Ramachandran:

I thank you for sending me a copy of your paper, with Dr. Kartha, on the structure of the collagen group of proteins.

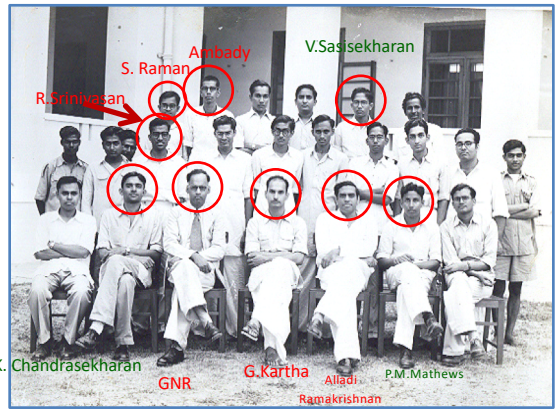
I have read it with great interest. I may say that I am not able to reach a definite conclusion about the probability that the structure is correct, but it seems to me to be unsatisfactory in some respects, in particular the bending of the hydrogen bonds.

Sincerely yours,

Linus Pauling

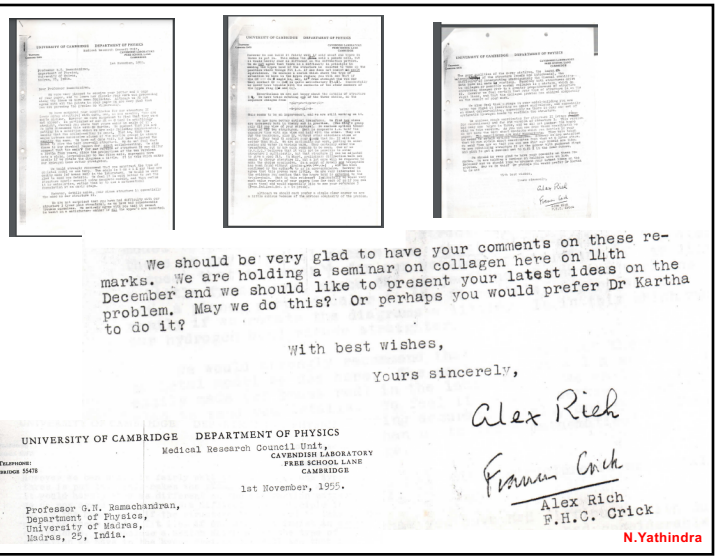
Linus Pauling:W

**Physics in Madras**




1955

Photo Courtesy: N Yathindra



We should be very glad to have your comments on these remarks. We are holding a seminar on collagen here on 14th December and we should like to present your latest ideas on the problem. May we do this? Or perhaps you would prefer Dr Kartha to do it?

With best wishes,

Yours sincerely,

Alex Rich

Francis Crick

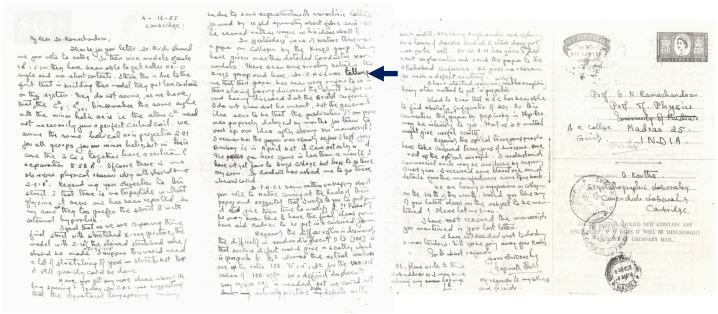
Alex Rich
F.H.C. Crick

UNIVERSITY OF CAMBRIDGE DEPARTMENT OF PHYSICS
Medical Research Council Unit,
CAVENDISH LABORATORY
FREE SCHOOL LANE
CAMBRIDGE
1st November, 1955.

Professor G.N. Ramachandran,
Department of Physics,
University of Madras,
Madras, 25, India.

N.Yathindra

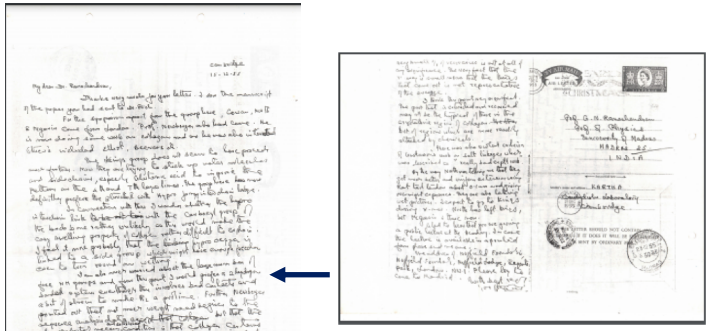
**Kartha to Ramachandran December 4, 1955**



**"Dr. FHCC (Francis Crick, Cambridge) was telling me……I do not know what he meant but the general idea seems to be that the publication of our paper was purposely delayed by months for them (Randall, Kings College, London) to work up our idea of seeing the manuscript !**

N.Yathindra

Kartha to Ramachandran 15 December 1955



***"I am also worried about the large number of free NH groups and from that point I would prefer a 2 hydrogen bonded system even though that involves bad contacts and a bit of strain to make $R_2$ a proline."***

N. Yathindra

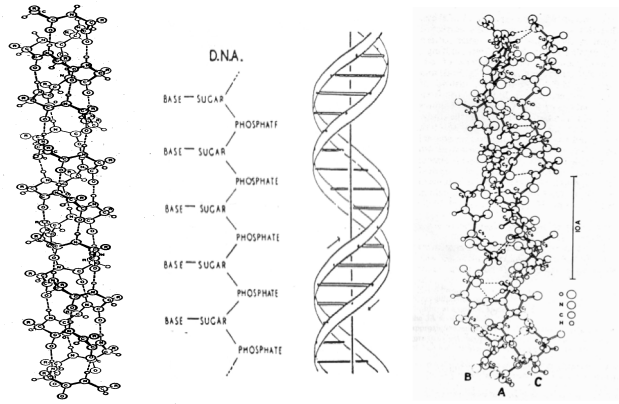
## Ramachandran on Collagen

**The importance of hydrogen-bonds for helix formation became established with the theoretical elucidation of the now well-known alpha-helix by Pauling in 1951.** Once the parameters of the helix were found from stereochemistry, it took no time at all to prove the correctness of these by X-ray diffraction, as was done by Perutz. **Within a year or two** of the demonstration of the alpha-helix in the KMEF group of fibrous proteins, **came the even more exciting double helix for DNA as proposed by Watson and Crick in 1953. The helix era had begun.**

Continued…

I mention all these because I was encouraged to enter this field by reading the beautiful series of papers published by Pauling and coworkers in 1951, and, when I was appointed Professor and Head at the newly started Physics Department in Madras in 1952, I chose X-ray diffraction, and X-ray crystallography in particular, as the main theme of our laboratory, and their application to biomolecules as the main aspect of this field that is to be pursued vigorously. **However, I did not know where to begin, and which molecules, or biopolymers, were the most profitable ones to study. This problem was resolved by the happy coincidence of a visit by Prof. J. D. Bernal to Madras in the early 50s. When I put this question to him, he told me that he was not very happy with the various structures of collagen** that had been proposed in the literature at that time, and that the problem was wide open. Even more than that, he indicated that there were some specimens of shark fin ray collagen (elastoidin) in the Department of Biochemistry of Madras itself.

**From: G. N. Ramachandran "Stereochemistry of Collagen", *International Journal of Peptide and Protein Research*, 1988,31,1-16.**




α-helix
**Pauling (1951)**

DNA double helix
**Watson & Crick (1953)**

Collagen triple-helix
**Ramachandran (1954)**

## Linus Pauling on Collagen

**In 1951 Professor Corey and I proposed a structure for collagen, involving three polypeptide chains twisted about one another…. It is well known that our structure turned out not to be right.** In a lecture on the stochastic method and the structure of proteins that I gave in Stockholm in 1953, at the Thirteenth International Congress of Pure and Applied Chemistry, I pointed out that in applying the stochastic method the first step is to make a hypothesis, a guess…. In order for the stochastic method to be significant, the principles used in formulating the hypothesis must be restrictive enough to make the hypothesis itself essentially unique; in other words, an investigator who makes use of this method should, I contended, be allowed only one guess…. **At that time (1953), however, I contended that Professor Corey and I together should be allowed two guesses on collagen, and I stated that we were determined that our second one would be right**

Continued…

As you all know, it turned out that Professor Corey and I did not get to make our second guess. **In 1955 Professor Ramachandran and his coworker G. Kartha described the striking triple-helical structure of collagen that is now generally accepted as being essentially correct. Although I may have some feeling of regret that Professor Corey and I did not succeed in making our second guess (which I trust would have turned out to be the right one), I may point out that the problem was a very difficult one**, and that Professor Ramachandran and his coworkers deserve great credit for their successful attack on it, and for their continuing vigorous effort in the solution of the many difficult problems in the field of protein structure and other aspects of structural chemistry to which they have devoted themselves for many years.

**From Pauling's presidential address at the International Symposium held at the University of Madras, 18-21 January 1967. Conformation of Biopolymers, (ed. Ramachandran, G. N.) Academic Press, New York and London, 1967, pp. 4-5.**

## Francis Crick on DNA and Collagen

**I think what needs to be emphasized about the discovery of the double helix is that the path to it was, scientifically speaking, fairly commonplace. What was important was not the way it was discovered but the object discovered - the structure of DNA itself.** You can see this by comparing it with almost any other scientific discovery. Misleading data, false ideas, problems of personal interrelationships occur in much if not all scientific work. Consider, for example, the discovery of the basic structure of collagen, the major protein of tendons, cartilage, and other tissues. **The 'basic fiber of collagen is made of three long chains wound around one another. Its discovery had all the elements that surrounded the discovery of the double helix. The characters were just as colourful and diverse. The facts were just as confused and the false solutions just as misleading. Competition and friendliness also played a part in the story. Yet nobody has written even one book about the race for the triple helix. This is surely because, in a very real sense, collagen is not as important a molecule as DNA.**

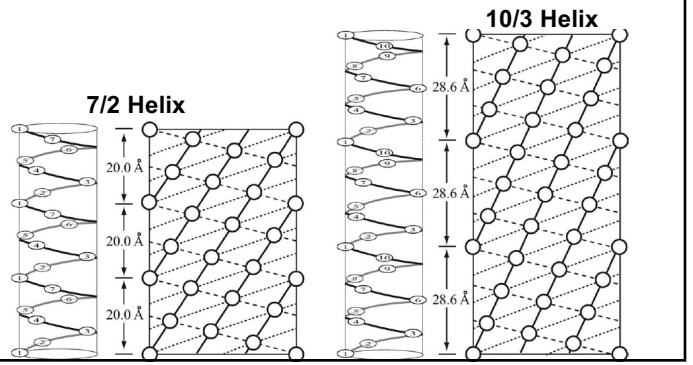
Continued…

Of course this depends to some extent on what you consider important. Before Alex Rich and I worked (quite by accident, incidentally) on collagen, we tended to be rather patronizing about it. "After all," we said, "there's no collagen in plants." In 1955, after we got interested in the molecule, we found ourselves saying, "Do you realize that one-third of all the protein in your body is collagen?" But however you look at it, DNA is more important than collagen, more central to biology, and more significant for further research. So, as I have said before: it is the molecule that has the glamour, not the scientists.

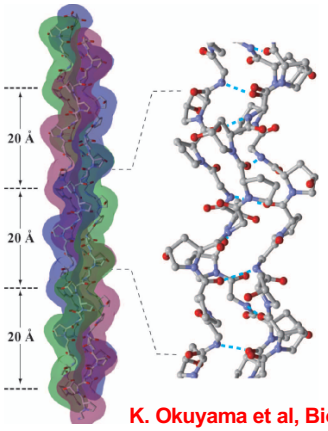
From Francis Crick, What Mad Pursuit: A Personal View of Scientific Discovery, Basic Books, New York, 1989, p. 67.

In the paper by Ramachandran and Ambady (Current Science, 23,349,1954) the existence of extra spots that conflict with the existence of a 20A$^0$ repeat, which is solely based on a schematic illustration, is a matter of controversy. Furthermore, even Ramachandran himself neglected these extra spots when he proposed his last triple helix model

K. Okuyama et al, Bioploymers, 97, 607, 2012

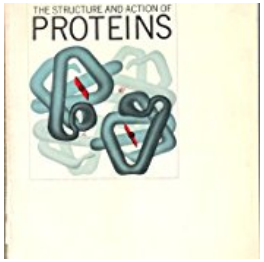



"The average molecular structure of collagen does not correspond to the prevailing Rich and Crick model, but corresponds instead to a triple stranded 7/2 helical model"

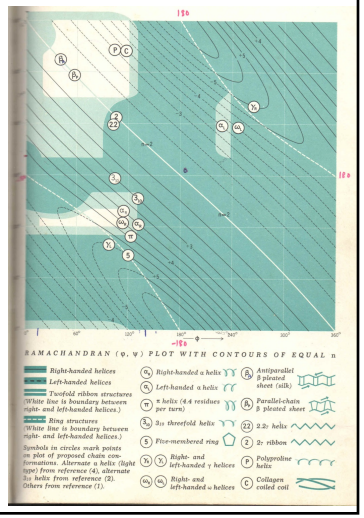



K. Okuyama et al, Bioploymers, 97, 607, 2012

## Naming the Map or Plot




R.E.Dickerson and I. Geis
1969




"Apparently yet another shift is being considered by the IUPAC-IUB Commission on Biochemical Nomenclature. This will achieve consistency with the usage of organic chemists, but will make the literature virtually unreadable. ..... According to traditional sources, there are two types of sin; Sins of omission and sins of commission. This is most definitely a sin of Commission."

G. N. Ramachandran

Collagen: Proceedings of a Symposium at CLRI, Madras, November 29-30, 1960
(Collagen, Ed. Ramanathan N, Interscience, John Wiley, 1962

Page 25

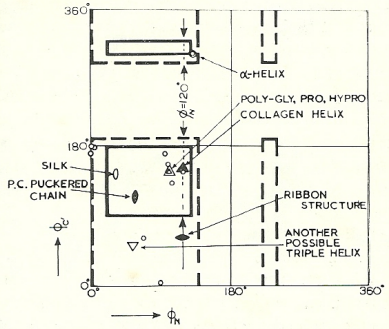



Fig. 7. Possible stereochemical configurations for the residues joined at an α-carbon atom (see text for the definition of $\phi_N$ and $\phi_{C'}$). Only the regions enclosed by the continuous lines are fully allowed; those enclosed by the dashed lines are allowed only if some short contacts are permitted. The open circles represent the configurations found in di- and tri-peptides and the other symbols represent those found in polypeptide and protein structures.

V Sasisekharan in Collagen (1960/62)

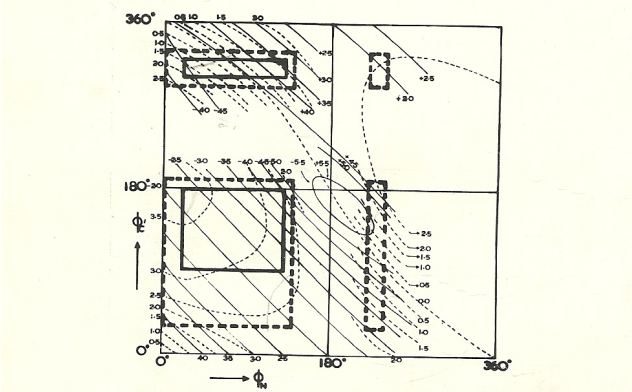



Fig. 4. Allowed ranges of $\phi_N$ and $\phi_{C'}$ (——) Normally allowed range. (- -) —Outer limit. (——) Number of residues per turn. (- -) Resolved height $h$.

Stereochemistry of Polypeptide Chain Configurations
GN Ramachandran, C Ramakrishnan, V Sasisekharan
Journal of Molecular Biology, 7, 95-99, 1963

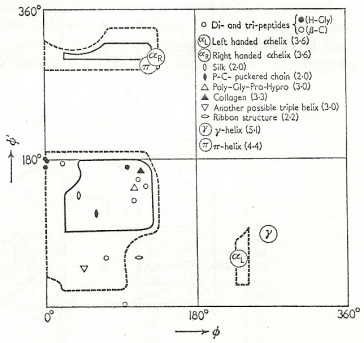



Fig. 3. Contours of constant $n$ (——) and constant $h$ (- - - - -) corresponding to the angle N—αC—C′ = 110°. The boundaries of the fully allowed and outer limit regions are also shown.

Stereochemistry of Polypeptide Chain Configurations
GN Ramachandran, C Ramakrishnan, V Sasisekharan
Journal of Molecular Biology, 7, 95-99, 1963

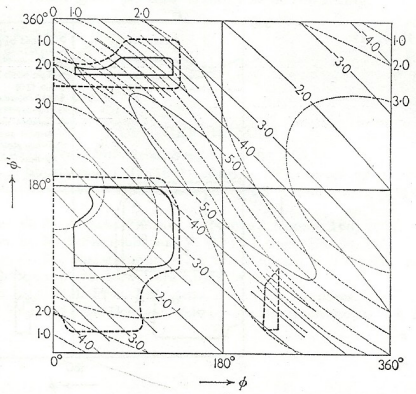
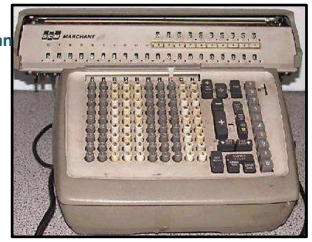


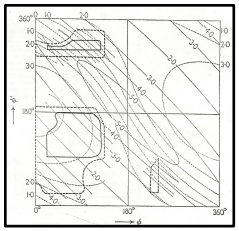

Fig. 2. The fully allowed (——) and outer limit (— — —) regions of ($\phi$, $\phi'$) for angle N—αC—C′ = 110° along with the configurations of various known di-, tri- and polypeptide and protein structures.

## An Electrically Driven Marchant Calculator From the 1960s

Prof. C. Ramakrishnan

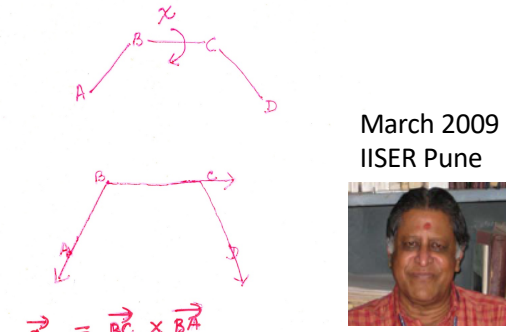
In 1967





**4 Basic Arithmetic Operations**
**No Memory Location**

**N Srinivasan**




March 2009
IISER Pune



**C Ramakrishnan**

**Stereochemistry of Polypeptide Chain Configurations**
**GN Ramachandran, C Ramakrishnan, V Sasisekharan**
***Journal of Molecular Biology*, 7, 95-99, 1963**

***Look Carefully: Legends to Figures 2 and 3 are interchanged***

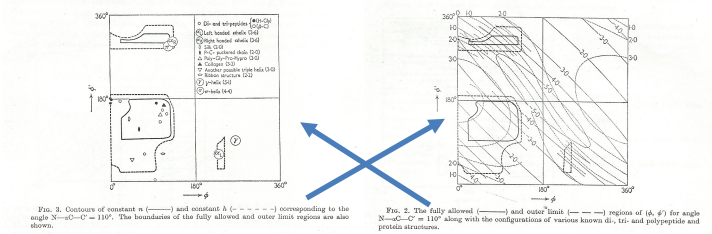


FIG. 3. Contours of constant $\eta$ (——) and constant $h$ (– – – –) corresponding to the angle N—αC—C′ = 110°. The boundaries of the fully allowed and outer limit regions are also shown.

FIG. 2. The fully allowed (——) and outer limit (— — —) regions of ($\phi$, $\phi'$) for angle N—αC—C′ = 110° along with the configurations of various known di-, tri- and polypeptide and protein structures.

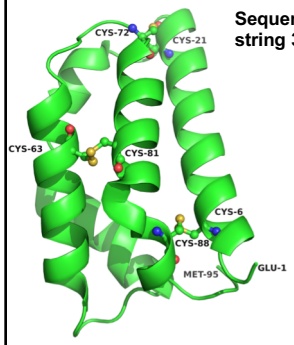
**" Contours of constant n( —— ) and constant h (- - - -)....."**

**"The fully allowed ( —— ) and outer limit (- - - )"**

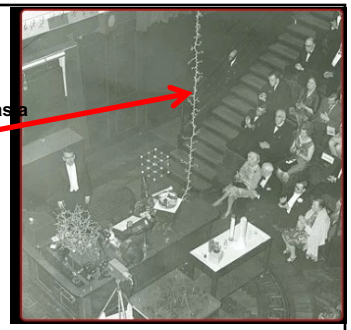
**C. Ramakrishnan**
**1939-2019**


**25 September 1990**

## Hen Egg White Lysozyme
***First Enzyme Structure***



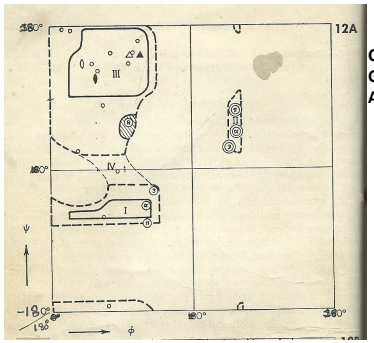

**Sequence model as a string 32 feet long**



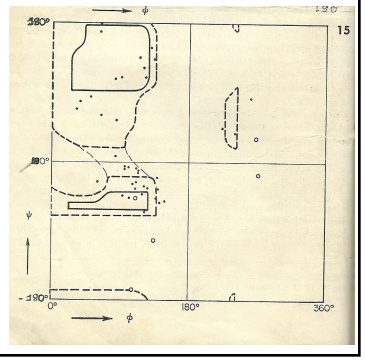
**1965 lecture by D.C.Phillips at the Royal Institution**

***Nature*** ( 1965) **206**, 757–761

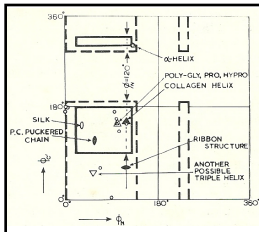
**4 Disulfide bridges**
**105 possible disulfide isomers**



Conformations of Polypeptides and Proteins
GN Ramachandran and V Sasisekharan
Advances in Protein Chemistry, 23, 283, 1968

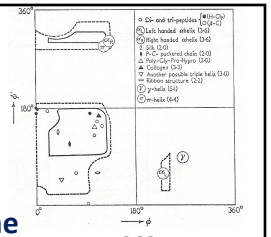


"By the authors request, the publishers have left certain matter of usage and spelling in the form in which they wrote them"

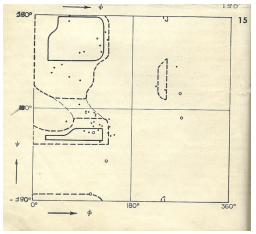



1960/62

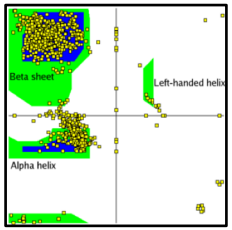
## Evolution of the Ramachandran Map



1963



1968




Today (Google Image)

## Pauling's Left-Handed α-Helix

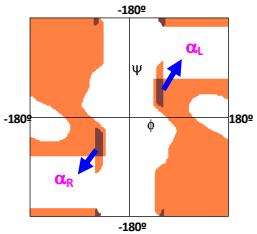
Jack D. Dunitz

Angew. Chem., Int. Ed., 40, 4167, 2001.

A few months after publication of the Pauling structures, Maurice L. Huggins noted that for amino acids with the correct absolute configuration– he was already aware of the Bijvoet result – a left-handed helix would lead to a C(β) ··· O distance of only 2.64Å{ref}. He concluded that "*levo* polypeptide form right-handed spirals and *dextro* polypeptides left-handed spirals, whichever of these two types of structure is correct". The protein chain is, of course, a "*levo* polypeptide".

Ref: M. L. Huggins, J. Am. Chem. Soc., 74, 3963, 1952

Ramachandran map

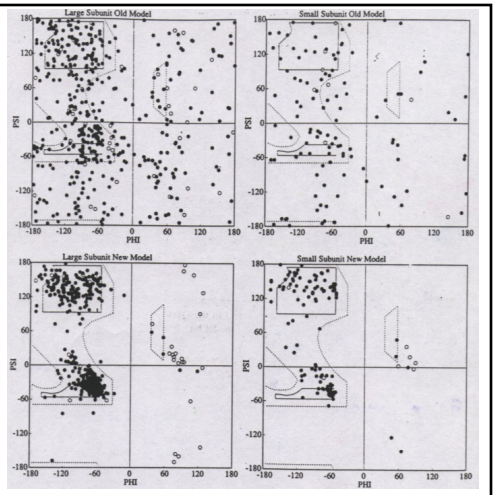



Overlap for L-Ala and D-Ala maps

## RUBISCO

Incorrect Model
1988

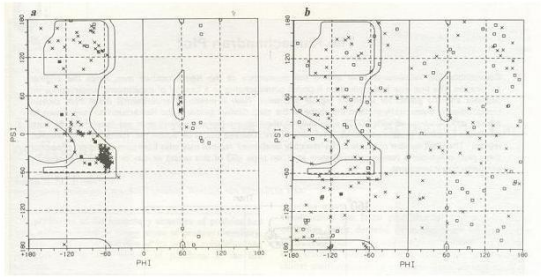
Correct Model
1986/89




"Errors in three dimensions" J. Janin, *Biochimie*, 1990, 72, 705-709

N Srinivasan

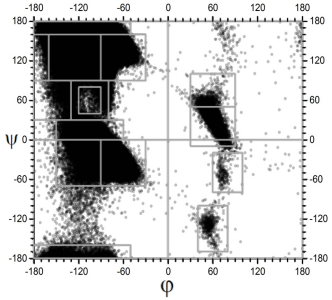
RAMACHANDRAN MAPS FOR TWO STRUCTURAL MODELS FOR LYSOZYME (Goose egg white) DERIVED FROM X-RAY CRYSTALLOGRAPHY

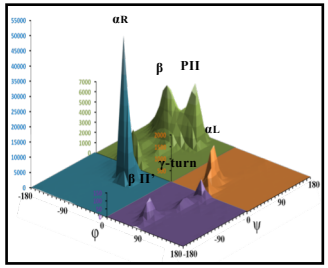


| | CORRECT MODEL | INCORRECT MODEL |
|---|---|---|
| RESOLUTION | 1.6 Å | 2.8 Å |
| R-factor | 15 % | 28 % |

**LH Weaver, DE Tround, BW Mathews, Current Science, 59, 833, 1990**

## The Ramachandran Map after 50 years



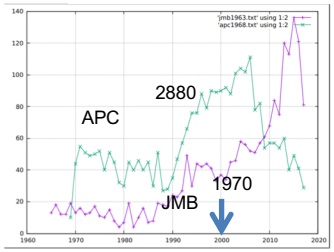



**427766 points**
**< 1.5A**

**Different vertical scales for the four quadrants**

Neha Kalmankar

## Ramachandran in the Age of Scientometrics

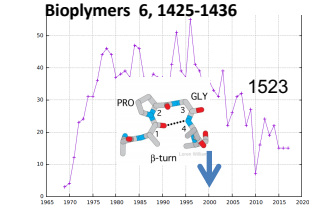


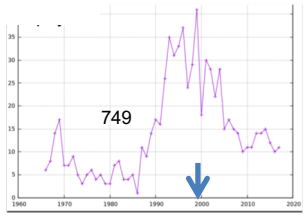

G.N.Ramachandran and V.Sasisekharan (1968) Adv. Protein Chem. 23, 283-437

G.N.Ramachandran, C.Ramakrishnan and V.Sasisekharan (1963) J.Mol. Biol. 7,95-99

C.Ramakrishnan and G.N.Ramachandran (1965) Biophys. J. 5, 909-932

C.M.Venkatachalam (1968) Bioplymers 6, 1425-1436




N. V. Joshi

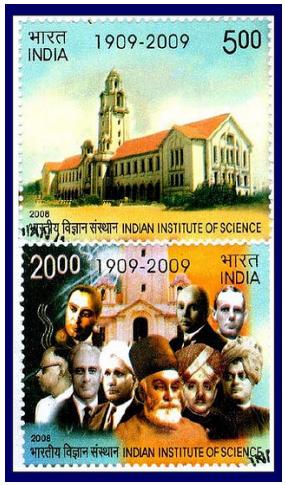
Income Tax Appellate Tribunal - Bangalore

**Income-Tax Officer vs Dr. G.N. Ramachandran on 29 April, 1982**

Equivalent citations: 1982 1 ITD 902 Bang

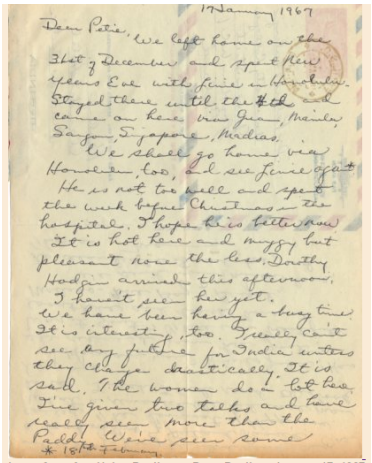
Bench: T Venkatappa, O Subramanian

1. The assessee went to USA. He received stipend of $10,833.33 and $24,111.08 in the calendar years 1977 and 1978, relevant to the assessment years 1978-79 and 1979-80, respectively, from the National Institute of Health (NIH), Bethesda, Maryland, USA. He also received $1,025 and $600 in the said two years, respectively, for giving lectures and also received royalty of $505 in the calendar year 1978. The foreign income was shown in the returns for these two years. No claim for exemption under Section 10(16) was made before the ITO. In appeals, it was held that the amount received by the assessee was not in the nature of salary but in the nature of scholarship



G.N. Ramachandran, F.R.S. with Dorothy Hodgkin N.L., Linus Pauling N.L. and Sir A.L. Mudaliar ( Vice-Chancellor )

## Pauling in Madras - 1967

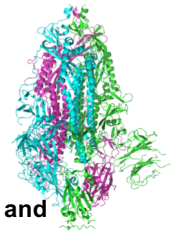


Letter from Ava Helen Pauling to Peter Pauling. January 17, 1967.

We have been having a busy time. It is interesting, too. I really can't see any future for India unless they change drastically. It is sad. The women do a lot here.

## Docking Trimeric Spike on Dimeric ACE2

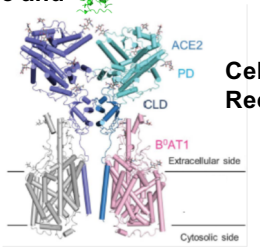
**The SARS CoV-2 Problem**



??

**Spike Protein**

**Target for Therapeutic and Vaccine Design**



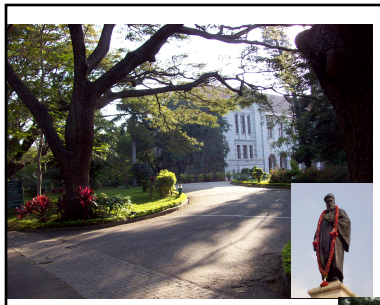

**Cellular ACE Receptor**

G. N. Ramachandran
1922 - 2001

**The Trials and Triumphs of G N Ramachandran**

**A documentary produced by IISER, Pune**

**https://www.youtube.com/watch?v=wC6V_C5hYiE**





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