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M. Sundaralingam (1931–2004): distinguished nucleic acid researcher

Sunda being felicitated by H. Hauptman on the occasion of his retirement party.

The nucleic acid crystallographic community lost one of its prolific contributors on 26 December 2004 when Muttaiya Sundaralingam, along with his wife Indrani, succumbed to the tsunami in his native country Sri Lanka. Although the duplex structure of DNA was worked out in 1953, stereochemical principles underlying the chemical etiology of nucleic acid structure and conformations began to emerge only later on and Sundaralingam (affectionately called Sunda) made major contributions in this area in a career spanning nearly four decades.

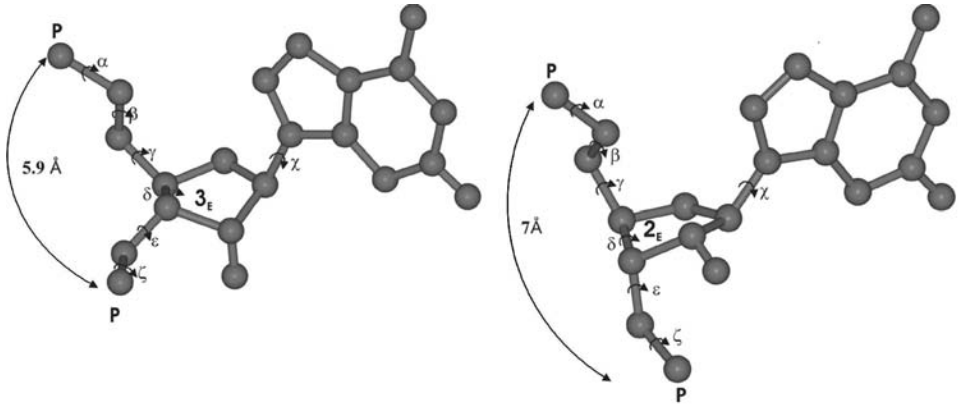
Sunda, coming from a large family, where education was given high priority, was forced by his father to become a Tamil language teacher in an elementary school, so that he, being a physically challenged child due to polio in early childhood, could be looked after by his parents. But he rebelled and challenged this, as he had marked his plans to realise his passionate dreams: to make a mark in science and to avoid the condemned life of drudgery. He went on to pursue higher studies to earn an Honours degree in chemistry and became a teacher not in languages but in chemistry at his *alma mater* the University of Ceylon (Sri Lanka), Colombo. A turning point was when he succeeded in gaining admission in the renowned school of crystallography headed by G. A. Jeffrey at the University of Pittsburgh, USA. Sunda quickly adapted himself to the academic and social verve in America. Being a chemist, he swiftly found some organic molecules and determined their three dimensional structures through single-crystal X-ray crystallographic techniques to earn a PhD in 1961. Sunda treasured the friendship and advice of his mentor at all times, more so, when he had to make critical decisions in his scientific career. Sunda, along with Jeffrey, regularly contributed articles on crystal structures of sugar derivatives to *Carbohydrate Research* for a number of years based on the database he had created in his own laboratory. It was incredible that he had, at his finger tips, conformational details on every one of these structures.

Sunda's initiation to nucleic acids research began with the crystal structure of 3′CMP with Lyle Jensen, at the University of Washington, Seattle. His penchant for conformational analysis was revealed by the influential article he published in the *Journal of the American Chemical Society* in 1965 on the possible conformations of five-member furanose rings in nucleic acids, and this was to be the forerunner to many significant contributions that followed. This classic, I suspect, fuelled a number of modelling investigations leading to early understanding of the sugar-pucker-dependence of nucleic acids and their constituents. An improved and finer description of the furanose ring conformation based on the concept of pseudorotation, initially with Cornelius Altona, and later with Eric Westhof and Thiagaraja Rao, delineated several sugar-pucker-dependent correlations with the internal parameters. These paradigms were invaluable in understanding the dynamics of furanose rings in nucleic acids systems studied by X-ray, NMR and computational techniques and continue to be cited extensively.

Sunda with R. Langridge, R. Dickerson, H. Sobel and T. Steitz at an international symposium organized by the Department of Crystallography and Biophysics, University of Madras, during January 1978.

After a short stint at Children's Cancer Research Foundation and Harvard Medical School in Boston, where he interacted with R. Langridge and C. Cohen, Sunda moved to become an Associate Professor at the Case Western Reserve University, Cleveland, in 1966. It is here that he vigorously set in motion extensive investigations of the nucleic acid constituents and determined crystal structures of a large number of nucleosides, nucleotides, nucleoside antibiotics and a number of minor nucleosides occurring in transfer RNAs. His discerning ability to envision beyond the apparent in these structures culminated in yet another influential article in *Biopolymers* in 1969 which turned out to be a citation classic. Here, he proposed a comprehensive picture of the restricted nature of the conformation of the nucleotide repeat and internucleotide phosphodiester linkages employing conformational wheels. These wheels of Sundaralingam guided stereochemical generalizations and, most importantly, clarity for their preferred conformations. These studies facilitated the interpretation in structural terms of physicochemical properties, such as the unper-

turbed chain dimensions of polynucleotides, and paved the way for rational model building of nucleic acids and polynucleotides. An extension of these ideas, following the crystal structure determination of the first dinucleoside monophosphate, UpA, culminated in the proposal of the concept of the 'rigid' nucleotide in 1973 to stress the fact that the 5′ phosphate has a stabilizing influence in conserving the preferred conformation of nucleotides. I firmly believe that the use of the word rigid was meant to convey compellingly that there exists a conspicuously preferred conformation for nucleotides articulated by near-neighbourhood bond correlations dictated by short-range interactions. This would be, despite their expected inclination to be flexible in the absence of constraints such as a partial double bond as in peptides. Thus, Sunda implied that conformational analysis of polynucleotides is not as hopeless as it was thought to be, and as a first approximation, they can be regarded as composed of such preferred units. Although the choice of the word rigid was debated, it is gratifying to see that Sunda's premise is, by and large, relevant even now, more than three decades later, and is vindicated by the rather large database of nucleic acid structures available today, derived from both X-ray and NMR investigations. Moreover, it is flattering that other investigators have found it appropriate to adopt similar usage conveying identical gesticulations. In any case, Sunda's assertion provided a fillip to the field and helped lay a strong foundation towards developing stereochemical principles governing nucleic acid conformations. He elicited more criticisms than accolades, perhaps because of his rather abrasive nature of challenging the unchallenged.



Compact and extended forms of the preferred nucleotide repeat.

It was natural for Sunda to take up the exigent work on macromolecular nucleic acids when he moved to the University of Wisconsin, Madison in 1969 to pursue the crystal structure determination of yeast $tRNA^{Phe}$. It was during this time that some of his former teachers from Pittsburg, T. Sakurai and R. McMullan, worked with him. Although his group promptly heralded success in obtaining for the first time crystals of yeast $tRNA^{Phe}$ in the monoclinic form in 1972, he was unlucky not to be able to determine its structure before the MRC group at Cambridge, UK. The Harry Steenbock Symposium he organized in the summer of 1974 turned out to be a historically important meeting in tRNA research, as several hidden tertiary structural features were unfolded here for the first time, in the presence of all the major players seeking the glory of elucidating the structure of tRNA. I distinctly remember that it was here in this meeting that Paul Sigler dreamed of, and set the target for, the crystal structure of the ribosome that followed in 25 years. Sunda continued his research on yeast $tRNA^{Phe}$

and *E. coli* $tRNA^{Arg}$ and came out with new insights on stereochemical principles that included conformation of messenger RNA bound to tRNAs.

His occasional indulgence in modelling investigations led to a left-handed helix for the Ikehara polycyclonucleosides to account for the observed inverse cotton effect, non-feasibility of the highly folded conformation (found in UpA) as a loop effecting phosphodiester, articulation of near-neighbor bond correlation in nucleic acid duplexes christened subsequently as crank-shaft motion, and several insights concerning nucleic acid conformations.

Sunda always felt that he was missing out on proteins especially when new paradigms about protein architecture were so often forthcoming. His notable contributions were in the crystal structure determination of troponin C and the suggestion that reverse turns might serve as water-mediated structural intermediates in the folding–unfolding process of α-helices. He subsequently determined crystal structures of several other proteins that included calmodulin, phospholipase A_2 and flavodoxin. He also had his other signature contribution in carbohydrates and phospholipids, especially relating to nomenclature and conformation analysis.

Another decisive moment in his career was when he took up the position of Ohio Regents Eminent Scholar at the Ohio State University, Columbus in 1989. His irresistible connection with nucleic acid research gave him a fresh zest there that led him to determine a large number of crystal structures of DNA, RNA and DNA·RNA fragments with a variety of sequence contexts and with drugs. His discerning studies of double drug complexes and RNA tetraplexes that provided clues to possible multistranded nucleic acid complexes were particularly conspicuous.

Sunda attracted a number of bright students and post docs through his charismatic discourse on the unique ability of X-ray diffraction techniques to visualize biological macromolecules. Many of them are placed at leading institutions in US, Europe and Asia and are well known for their contributions. He was particularly ecstatic when one of his former students determined the structure of polio virus which crippled him in his childhood.

He travelled widely despite his physical disability and enjoyed giving lectures. He was known for his lucid and forceful oration. His was a very interactive personality and mixed freely with students and peers. G. N. Ramachandran after listening to Sunda at the Moscow IUCr Congress invited him to visit his center at Chennai in 1966 and thus began the latter's long Indian connection. Several from this center (including Rao and myself) and many others from India had the benefit of working with him. For me, it was a remarkable experience leading to an enduring friendship with him and his family. Our joint paper, which appeared just a couple of months before his demise, concludes a life-long scientific collaboration.

He was the Steenbock Professor of Biomolecular structure and chairman of Biophysics PhD program at the University of Wisconsin, Madison. As a John Guggenheim Foundation Fellow, he spent a year of sabbatical at University of Oxford, UK. He was a recipient of the chemistry alumni award and distinguished achievement award from the University of Pittsburg. He was also an NIH career development awardee and received a grant from the NIH for his research work on nucleic acids for over three decades until his retirement.

With an effervescent and exuberant personality, an infectious smile and a walking stick, Sunda captured the attention wherever he went. He was warm and compassionate. He enjoyed his science and life as well as he could and never allowed himself to be subjugated. He was very active until the end and published

more than half a dozen papers in 2004. It was painful to see him confined to a wheelchair with deteriorating health in his later years. His wife Indrani, endowed with extraordinary patience, supported him throughout his scientific career and accompanied him to the last. Sunda's optimistic approach should serve as an inspiration to those passionate for practicing science.

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