Muttaiya Sundaralingam (1931-2004):
A Pioneering Stereochemist and Crystallographer of Nucleic Acids

On the morning of December 26, 2004, Muttaiya Sundaralingam and his wife Indrani did not survive the major tsunami as it hit the coast of Sri Lanka in Trincomalee following the submarine earthquake which had occurred a couple of hours earlier off the coast of Sumatra. Dr. Sundaralingam left us with central contributions in the field of the stereochemistry of nucleic acids. He was also a major player in the development of the crystallography of nucleic acids from single bases to large macromolecules.

Sunda, as he was known in the nucleic acid community, was born in Taiping, Malaysia, on September 21, 1931 into a family of eight brothers and four sisters. His father was a hospital attendant. At a young age, he was struck by polio and overcame it, but was left with a weak leg. He was educated both in Malaysia and Sri Lanka and attended King Edward VII School in Taiping (1939-1948), Kokuvil Hindu College (1949-1951), and the University of Ceylon-Colombo (1952-1956). After two years as an assistant lecturer in the Department of Chemistry in the University of Ceylon-Colombo, at the age of 26 with his Bachelor of Sciences degree in his luggage, he ventured to the United States by steamship to pursue his education. In those days, the trip took one month and must have been a rather overwhelming personal experience. Within just three years, he obtained a PhD in Chemistry in the field of Crystallography at the University of Pittsburgh under the supervision of Professor G.A. Jeffrey (1915-2000), a renowned crystallographer of carbohydrates.

Five years earlier, G.A. Jeffrey had moved to the University of Pittsburgh from Leeds, UK, to start a Chemical Crystallography laboratory with a strong emphasis on accurate structure analyses. This meant laborious visual intensity measurements coupled with new techniques of refinement and accuracy assessment that could be applied, thanks to the introduction of digital computing to crystallography. Although they published little together, the impact of Jeffrey on young Sunda was strong and long lasting (see Figure 1). After obtaining his PhD, Sunda moved in 1962 to Lyle H. Jensen’s group in Seattle, first as a postdoctoral fellow and later as a research instructor. There, he carried out a high precision X-ray analysis of the nucleotide cytidine-3’-phosphate that was published in 1965 in the Journal of Molecular Biology. That structure was among those previously determined by the Norwegian crystallographer Sven Furberg that were so critical to Watson and Crick when they developed the model of B-DNA. Sunda’s 3’-CMP publication was the first in a series of landmark papers on accurately determined molecular structures and the stereochemistry of nucleic acid constituents, culminating in a highly cited 1969 paper in Biopolymers.

Through the introduction of a comprehensive conformational nomenclature based on a series of crystal structures, this seminal paper laid the foundation for conformational analysis of nucleotides and polynucleotides and gave the first stereochemical rules on the preferences in the complex series of single bonds of the sugar-phosphate backbone. The organization of data into conformational wheels and pairwise conformational correlation maps conclusively showed (1) that rotations about single bonds were restricted and (2) that correlations between them existed. Through his numerous crystal structure determinations and analyses that followed, Sunda built a coherent picture for nucleotides in which the preferred conformations about single bonds reinforce one another through a variety of conformational properties and weak interactions (see Figure 2). He recognized stereochemical properties by combining chemical insight with crystallographic precision and analysis. He introduced the concept of a conformationally “rigid” nucleotide in a famous 1973 paper presented at the Jerusalem Symposium on Quantam Chemistry and Biochemistry, organized by E.D. Bergmann and B. Pullman. The rigid nucleotide concept was much disputed and attracted a series of experimental and theoretical objections. The choice of the word “rigid” may have been unfortunate; exceptions and oddities are common throughout biology. Today the conformational preferences Sunda determined in the late sixties are appreciated and are still valid within the vastly extended data set of crystal structures of nucleic acids.

Having soon realized the crucial role of the sugar ring in the determination of the conformation of the nucleotide unit and, ultimately, the polynucleotide architecture, he studied the sugar conformations in detail. He formalized the nomenclature of sugar puckers following the early NMR work of Christine Jardetzky, and in the early seventies, together with Cornelis Altona, introduced the famous pseudorotational representation of the five-membered ring sugar puckers, still widely used today in NMR as well as X-ray crystallography to describe the various puckering modes in nucleic acid sugars.

After a brief period with Robert Langridge in Boston and three years as associate professor at the Case
Western Reserve University, in 1969 Sunda moved to the University of Wisconsin in Madison where he remained for 21 years. In Madison, he set up a dynamic biological crystallography group, that soon was heavily involved in attempting to crystallize tRNA and solve its structure. The pursuit of a three-dimensional structure of tRNA had started soon after R.W. Holley established its cloverleaf structure. In 1968, five groups reported crystallizations of tRNAs, but it was another three years before high resolution X-ray diffraction was obtained. Soon, two crystal forms emerged: an orthorhombic form in Alex Rich's laboratory and a monoclinic form in Sunda's laboratory and soon after in Aaron Klug's laboratory. The monoclinic form was important because the crystal lattice dimensions limited the overall size of the tRNA molecule and indicated that it could not be cigar-shaped, as had been widely anticipated.

In June of 1974, Sunda, with his long time collaborator S.T. Rao, organized the Fourth Annual Harry Steenbock Symposium on “Structure and Conformations of Nucleic Acids and Protein-Nucleic Acid Interactions” in Madison, Wisconsin. At the symposium, the groups led by Alex Rich at MIT and by Aaron Klug at the MRC Cambridge reported the first folds at 3 Å resolution of yeast tRNA^Phe^.

Sunda continued to produce important crystal structures and insightful reviews on nucleic acids in Madison and, from 1990, at the Ohio State University in Columbus where he was the Ohio Regent’s Eminent Scholar and Professor of Chemistry and Biochemistry. His contributions are diverse and include the unexpected side-by-side complex of distamycin molecules in the minor groove of nucleic acid helices, the role of C-H...O hydrogen bonding in structural biology, and X-ray structures at very high resolution. His drive and motivation kept him going even after his official retirement in December of 2002, so much so, that in 2003 he published three papers in Structure.

Sunda was an intense, sometimes passionate lecturer (see Figure 3). His lectures were full of vitality, surprising comparisons, and unexpected jokes. He was moved by a deep conviction of the fantastic power of X-ray structures for unraveling biological phenomena. He had an incredible knack for animating the beauty of crystal structures and for targeting their key points and biological impact. Not surprisingly, such charismatic talks attracted students to biological crystallography. As a teacher, he was demanding, sometimes eager or even quick-tempered, but never unconcerned or indifferent. Several of the students he trained became eminent in various areas of structural biology. I did not meet all of them but I would like to mention those that overlapped the time I spent as a postdoctoral fellow in Sunda’s laboratory. James Hogle solved the structure of the polio virus as well as several other viral proteins; Stephen Sprang solved several structures of G proteins and their complexes involved in signal transduction; Janet Smith solved many structures of biosynthetic enzymes; John McAlister developed some of the early
molecular modeling programs. Many other students, including John Rubin, Ethan Merritt, Dave Stout, Gale Strasburg, Bob Bergstrom, and Richard Brennan, are successfully involved in biological crystallography throughout the United States.

Postdoctoral fellows from all over the world came to work in Sunda's laboratory and several later established distinguished laboratories in their own countries, including Narayanarao Yathindra (India) in theoretical studies and Hiroshi Mizuno (Japan) in protein crystallography. My encounter with Sunda, first with his writings and later with the man himself, led to a major turn in my professional life; since then, his teachings in nucleic acid stereochemistry and crystallography form the core of my scientific interests. I have an immense admiration for Muttaiya Sundaralingam, both as a man and as a scientist, for his generosity in sharing his formidable intellect and his daring insights into chemical biology and the amazing beauty of the molecules of life.

In his last years, Sunda was often in a wheelchair suffering from physical pain in his legs. On the last day, he battled together with his loving and beloved wife against the biggest wave in centuries; fortunately, his contributions are here to stay. Muttaiya Sundaralingam and his wife Indrani are survived by their three children Sharmini, Rohan, and Mohan, as well as their three grandchildren Nirvan, Kiran, and Sahanna.

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