Michael G. Rossmann (1930–2019)

Michael George Rossmann passed away peacefully in the early morning of 14 May 2019, 2 months before his 89th birthday. Only a few weeks earlier, he had been excited about returning to work after treatment for an illness. Michael was the Hanley Distinguished Professor of Biological Sciences and was a member of the Purdue University faculty for 55 years (1964–2019). During his long and productive career, Michael helped to establish and define the very basis of structural biology as it is known today. He was a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the Royal Society of London. Michael's contributions were recognized by numerous awards, including the Canada Gairdner Foundation International Award, the Louisa Gross Horwitz Prize, the Gregori Aminoff Prize, the Paul Ehrlich and Ludwig Darmstaedter Prize, and the Ewald Prize. With his departure, science has lost a giant in structural biology, and the scientific community at large has lost a mentor and a friend.

Michael was born on 30 July 1930 in Frankfurt, Germany. In 1939, as World War II ignited, he immigrated to England with his mother. He obtained BS and MS degrees from the University of London in mathematics and physics, and he completed his PhD studies in chemical crystallography at the University of Glasgow with J. Monteath Robertson. Michael attributed his interest in crystallography to a pioneer in X-ray diffraction, Kathleen Lonsdale, from whom he first heard about crystallography as a schoolboy. After obtaining his PhD degree, Michael worked with William Lipscomb at the University of Minnesota, where for 2 years he determined structures of terpenoids and wrote computer programs for solving and analyzing structures. After hearing about the exciting project on the structure determination of hemoglobin by Max Perutz from a lecture by Dorothy Hodgkin at the Fourth Congress and General Assembly of the International Union of Crystallography in Montreal in 1957, Michael wrote to and joined Perutz in 1958 at the then Medical Research Council Unit for Molecular Biology, Cavendish Laboratory, University of Cambridge. There, Michael led the computational effort for the structure determination of hemoglobin[1], a result that, together with the structure of myoglobin,

Credit: Roger Castells Graells

was recognized with the Nobel Prize in chemistry to Perutz and to John Kendrew, respectively, in 1962.

The time that Michael spent at the Medical Research Council in Cambridge was a seminal period in shaping his scientific vision and career. While working on hemoglobin, Michael noticed the structural similarity between myoglobin and the α- and β-chains of hemoglobin, and he was fascinated by the evolutionary and methodological implications of this observation. He asked himself whether the discovery of a common fold could have been made by a direct comparison of the diffraction patterns of their crystals. In a landmark paper in 1962 with David Blow, Michael demonstrated that the relationship between identical or similar subunits within a crystallographic asymmetric unit can be identified by rotating the Patterson function until it attains a maximal coincidence with the original Patterson, an algorithm called the 'rotation function'[2]. Michael and colleagues further established a translation function, also based on the Patterson synthesis, to determine the relative position between the subunits once the rotation is known. The same idea is applicable to finding relationships between identical or similar subunits in different crystals; this molecular replacement method that uses a known structure to solve similar but unknown structures in new crystals later became the most frequently used tool for solving macromolecular crystal structures and currently accounts for about 85% of all new structures deposited in the Protein Data Bank.

The discovery of protein-fold conservation and the development of methods for detecting non-crystallographic symmetry (NCS) among identical or similar subunits within the crystallographic asymmetric unit guided Michael's choice of research for most subsequent investigations and was a major reason for his desire to study viral structures. Viruses, he learned from Francis Crick and James Watson's hypothesis during afternoon tea, would contain many identical protein subunits based on considerations of their limited genomic capacity. Michael reasoned that *n*-fold NCS effectively reduces the size of the structure to be solved by a factor of *n*, while the number of observable intensities remains the same. This redundancy could then be used to facilitate phase determination by averaging among NCS-related subunits. When Michael moved to Purdue University in 1964 to establish his own laboratory, his first grant application was already entitled "X-ray Determinations of Proteins and Viruses." However, it would take tremendous innovation in the following decades for Michael — and the field — to conquer the daunting task of viral structure determination, which in turn contributed greatly to the methodological foundation for modern structural biology.

One of Michael's fundamental innovations relates to diffraction-data collection and processing. When Michael started working on the icosahedral southern bean mosaic virus[3], his first viral target, he realized that the oscillation technique that Uli Arndt and Alan Wonacott had re-introduced at the time could reduce exposure times relative to the times required for the prevailing precession method. Furthermore, during the structure determination of the human rhinovirus HRV14[4], when the much more intense synchrotron radiation was just coming into being, Michael thought about skipping the crystal alignment procedure that would cause unnecessary radiation damage to the crystals. He introduced the 'American Method' for data collection, in which experimenters 'shoot first and ask questions later', a reference to the American Wild West cowboy tradition. Michael developed new theories and software for auto-indexing reflections from randomly oriented oscillation data, refining crystal setting parameters, integrating intensities, and scaling individual diffraction images onto a common relative scale. Now, oscillation

Credit: Hao Wu

data are measured almost always from randomly oriented crystals without crystal alignment, and the data-processing methods that Michael pioneered formed the basis of the popular Denzo and Scalepack programs (later embedded in HKL-2000 software) for diffraction-data processing.

Another of Michael's fundamental innovations dealt with phase extension coupled to NCS density averaging, which has become an essential component of molecular replacement averaging in viral structure determination. In the structure determination of HRV14, isomorphous replacement and density averaging enabled reliable phase determination only to a resolution of about 5 Å. By using many cycles of 20-fold NCS averaging with gradual phase extension from a resolution of 5 Å, a high-quality electron density map was obtained at a resolution of 3.5 Å, which permitted complete tracing of the four chains in the asymmetric unit[4]. In the structure determination of canine parvovirus, *ab initio* phasing starting from only an initial spherical shell model was attempted using 60-fold NCS averaging and phase extension in steps of one reciprocal lattice point at a time[5]. Today, crystal structure determinations that begin with experimental phasing (isomorphous replacement or anomalous dispersion) are usually supplemented with some type of phase extension based on density modification (solvent flattening, histogram matching, etc.), even in the absence of NCS.

Michael's seminal work, together with independent groundbreaking contributions from Stephen Harrison, demonstrated that in contrast to expectations, crystal structure determination of icosahedral viruses was possible once the necessary tools and technologies had been developed. These structures have had an enormous impact on the understanding of how viral pathogens assemble, attach and deliver their genomes into host cells and how they interact with the immune system. These techniques, initially conceived and developed for the study of complex enzymes and viruses, have stimulated the field of structural biology in general and have promoted numerous accomplishments on important biological assemblies.

As many viruses cannot be easily crystallized, Michael also recognized, fairly early on, the importance of cryo-electron microscopy (cryo-EM). In those days, cryo-EM was often limited to a resolution of 10–20 Å, and Michael helped to develop a 'hybrid' technology in which cryo-EM investigations were augmented by crystallographic determination of the component proteins to produce structures of whole viruses at 'pseudoatomic resolution'. Together with his colleague, the virologist Richard Kuhn, Michael used the hybrid method to determine structures of the lipid envelope–containing Sindbis virus and the flaviviruses dengue virus and West Nile virus. More recently, and with the 'resolution revolution' in cryo-EM, the Rossmann–Kuhn collaboration led to near-atomic-resolution structures of Zika virus by modern cryo-EM methodology alone[6].

Evolutionary structural conservation was a common thread that kept coming back to surprise Michael throughout his career, starting with his discovery of the similarity between the hemoglobin chains and myoglobin. While studying lactate dehydrogenase and other dehydrogenases, targets that were more attainable than viruses when he first started his independent laboratory, Michael recognized a common nicotinamide adenine dinucleotide–binding domain in those early structures, and he proposed that it constituted an ancient nucleotide-binding domain required for reactions dating back to the first primitive cells[7]. This nucleotide-binding domain fold, composed of alternating β-strands and α-helices, is frequently referred to as the 'Rossmann fold' and represents one of the most common protein folds across evolution. In another example, when the structure of southern bean mosaic virus was first revealed, to the surprise of all concerned, its basic 'jelly-roll' fold and the subunit organization were remarkably similar to those of tomato bushy stunt virus, whose structure was solved 1 year earlier by Harrison. The jelly-roll fold was subsequently observed in numerous viral capsid proteins, including those of HRV14 and canine parvovirus, providing additional molecular evidence of divergent molecular evolution from common ancestors.

Finally, one cannot discuss Michael's myriad contributions without remarking on his unwavering enthusiasm for life and his lovely, almost childlike curiosity about everything around him. He walked or biked to his office as his way of staying fit, and was a competitive sailor, an ardent hiker, and a downhill skier well into his golden years. He loved visiting new places, such as Mila Mountain (Lhasa, Tibet) in 2012, and those of us who were privileged to be his trainees all deeply cherish our memories of these fantastic trips. Despite his scientific accomplishments, Michael was quite humble and was an extraordinary mentor and friend. Michael also enjoyed understanding the diverse cultural backgrounds of his trainees and often spent time with them on activities outside the laboratory. Many of us had the pleasure of knowing Audrey, his wife of many years until her death, and his second wife Karen, as well as his children

and grandchildren. His annual Christmas letters that chronicled the adventures of his family in each passing year were always awaited with great anticipation. For all scientists, young and old, Michael Rossmann was a spectacular role model for living life richly, never taking one's eyes off the goal, and never giving up. He was a towering figure in science and life at large, and he will be greatly missed. ❐

Hao Wu[1,2*] and Eddy Arnold[3]

[1]*Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, USA.* [2]*Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, MA, USA.* [3]*Center for Advanced Biotechnology and Medicine, and Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA.*

**e-mail: wu@crystal.harvard.edu*

Published online: 8 July 2019
https://doi.org/10.1038/s41594-019-0271-5

References

1. Perutz, M. F. et al. *Nature* **185**, 416–422 (1960).
2. Rossmann, M. G. & Blow, D. M. *Acta Crystallogr.* **15**, 24–31 (1962).
3. Abad-Zapatero, C. et al. *Nature* **286**, 33–39 (1980).
4. Rossmann, M. G. et al. *Nature* **317**, 145–153 (1985).
5. Tsao, J. et al. *Science* **251**, 1456–1464 (1991).
6. Sirohi, D. et al. *Science* **352**, 467–470 (2016).
7. Rossmann, M. G., Moras, D. & Olsen, K. W. *Nature* **250**, 194–199 (1974).