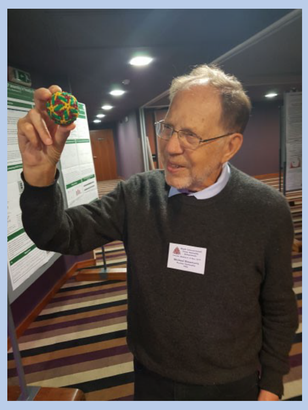
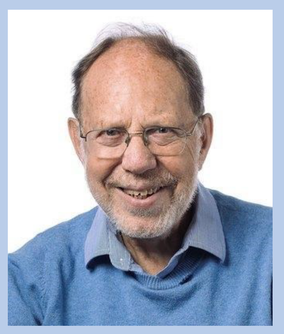


Michael Rossmann
1930 - 2019



Biography

Michael Rossmann was born on 30 July, 1930 in Frankfurt, Germany and died on 14th May 2019, at the age of 88.

He attended schools in Holland and Germany, where he joined a radio club and built a receiver to listen to news from the UK. He moved to England in 1939, where he joined the Friends' School in Saffron, Walden of which Kathleen Lonsdale was one of the school's governors. There, he had his first contact with crystallography.

Lonsdale had worked with W. H. Bragg, and had her own crystallography group at University College, London. He obtained BS and MS degrees from the University of London in mathematics and physics.

In 1953 he moved to Glasgow, and completed his PhD studies in chemical crystallography at the University of Glasgow with J. Monteath Robertson and received a Ph.D. from that University in 1956 in Chemical Crystallography. The title of his thesis was "A Study of Some Organic Crystal Structures".

Michael Rossmann, back row, 4th from the left, with Max Perutz and other staff outside the hut, 1958.

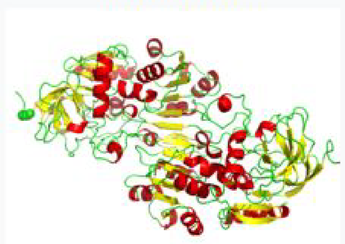
In 1956 he moved to the University of Minnesota, where he worked for two years with William Lipscomb, publishing several papers on the structure of terpenoids (plant products with about 30 non-hydrogen atoms), and writing computer programs for analyzing structures.

In 1958, he joined Max Perutz in the then "Medical Research Council Unit for Molecular Biology", Cavendish Laboratory, University of Cambridge. There, he led the computational effort for the structure determination of hemoglobin (1960), a result that, together with the structure of myoglobin, was recognized with the Nobel Prize in chemistry to Max Perutz and to John Kendrew, respectively, in 1962. In 1964, he joined the Purdue University faculty, where he remained for more than 50 years, becoming the Hanley Distinguished Professor of Biological Sciences.

Crystallography

Michael discovered the "Rossmann Fold" protein motif, first in the enzyme lactate dehydrogenase, while on sabbatical in the lab of Bror Strandberg in Sweden, in the late 1960s.
Subsequently, he found it in hundreds of other proteins. He realized that different isozymes might have similar structures,

Rossmann-like alpha/beta/alpha sandwich fold



NAD/NADP binding rossmann fold domains. The picture depicts the beta-alpha folding in alcohol dehydrogenase.

Rossmann realized that many of the larger protein molecules are made up of identical or closely similar subunits, based on predictions of the protein part of virus structures by Crick and Watson (1956). In 1960, He realized that one should be able to recognize the relationship between two similar chains in hemoglobin without any heavy atoms. The first paper on molecular replacement was in 1962, with David Blow. This calculation is known as a rotation function today. For the case of hemoglobin, he realized that one should be able to work out a complete structure (without heavy atoms) based on the symmetry between the alpha and beta chains. He called this non-crystallographic symmetry (NCS) and he did the rotation-function calculation by Christmas ,1960. He wrote the code, worked out the many consequences, and showed feasibility.

Acta Cryst. (1962). **15**, 24

The Detection of Sub-Units Within the Crystallographic Asymmetric Unit

BY MICHAEL G. ROSSMANN AND D. M. BLOW

M. R. C. Unit for Molecular Biology, Cavendish Laboratory, Cambridge, England

(*Received* 27 *February* 1961)

The number of structurally identical units within one unit cell often exceeds the number of general positions. The angular relationships between any two units, not related by space-group symmetry, can be found by rotating the Patterson function until the rotated and original Patterson functions are brought into maximum coincidence. For such a rotation, the rotation function

$$R = \sum_{\mathbf{h}} [|F_{\mathbf{h}}|^2 \{ \sum_{\mathbf{p}} |F_{\mathbf{p}}|^2 G\}]$$

has a maximum value. G is an interference function which has large values only when the point $\mathbf{p}$ in reciprocal space is brought close to $\mathbf{h}$ by the rotation.

Application of the R function to horse haemoglobin gives a dominant peak that corresponds accurately to the relative orientation of the α and β chains.

One of Rossmannn'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. By using many cycles of 20-fold NCS averaging, with gradual phase extension, the resolution of a map can be dramatically improved. 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.
Since his early days, Rossmann was keen to apply the latest capabilities of computing to crystallography. In the early 1980s he pushed for acquisition of a supercomputer. After vectorizing the computer programs, calculations that had taken six weeks with the southern bean mosaic virus (1980) took only a fraction of a day for the HRV14 work (1985). This work laid the foundation for a molecular understanding of cell entry of enteroviruses (2002) and for the development of capsid-binding inhibitors against a broad range of enteroviruses (2010).
Another of Rossmann's fundamental innovations relates to diffraction-data collection and computational processing. He invented the "American method" (shoot first and answer questions later), skipping the crystal-alignment procedure that would cause unnecessary radiation damage to the crystals. This was done during the structure determination of the human rhinovirus HRV14 (1985), when much more intense synchrotron radiation was coming into being. Rosmann 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 data are almost always measured 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. Rossmann's development of computational methods for crystallography, which started early with first-generation mainframe computers, was a major contribution to the field.
In today's crystallography, there are only a few well-known methods for calculating structures: Isomorphous replacement (Max Perutz's idea); Molecular replacement (MR); and multiple-wavelength anomalous dispersion (MAD) by Hendrickson and Smith (1985, 1998). Molecular replacement is particularly useful if one already has a similar structure. It is also useful if one has many identical units.

Virology

At Purdue, Michael's central focus was the determination of the three-dimensional, atomic-resolution structure of viruses, and studying how viruses interact with their environment. Starting out with x-ray crystallography, he immediately recognized the value of the concept of molecular replacement to viruses.

Evolutionary structural conservation was a common thread that kept coming back to Rossmann, 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) Rossmann recognized a common nicotinamide adenine dinucleotide-binding domain, and he proposed that it constituted an ancient nucleotide-binding domain required for reactions dating back to the first primitive cells (1974). 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.

Together with contributions from Stephen Harrison, Rossmann demonstrated that, in contrast to expectations, crystal-structure determination of icosahedral viruses could proceed once the necessary tools and technologies had been developed. 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 a ccomplishments on important biological assemblies.

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Chemical and biological evolution of a nucleotide-binding protein

Michael G. Rossmann, Dino Moras & Kenneth W. Olsen
Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907

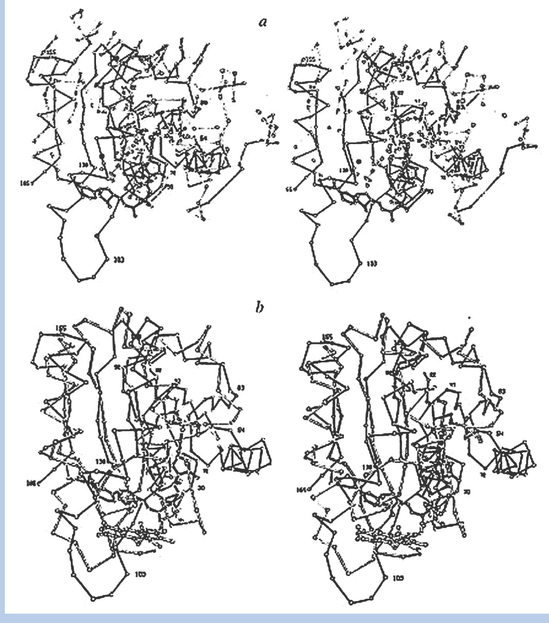


Fig. 4 Comparison of (*a*) phosphoglycerate kinase (PGK) and (*b*) flavodoxin with LDH. Conventions used are described in Fig. 3. The black ball is the Mg^{2+} site in PGK.

In renewing his grant in about 1980, NIH was encouraging him toward animal viruses. He collaborated with Roland Rükert on polio virus, which turned out to be very similar to rhinovirus. However, when Jack Johnson joined the lab, work on southern bean mosaic virus started, Rossmann's first viral target (1980). When the structure was first revealed, its basic 'jelly-roll' fold and the subunit organization were remarkably similar to those of tomato-bushy-stunt virus, whose structure was solved earlier by Harrison (1978).

The jelly-roll fold was subsequently observed in numerous viral capsid proteins, including those of HRV14 (1985) and canine parvovirus (1991), providing additional molecular evidence of divergent molecular evolution from common ancestors. The Rossmann team were the first to map the structure of HRV14, the human common cold virus, to an atomic level (1985). It was seen to be very similar to the southern-bean-mosaic virus (the southern-bean and tomato-bushy-stunt viruses have 3 identical subunits A, B and C. In the picornaviruses, A is VP1, B is VP3 and C is VP2). During a sabbatical in Sweden with Bror Standberg, working with John Erickson in 1971, he used the rotation function to show the orientation of the satellite-tobacco-necrosis virus in the crystal itself. That virus was T=1, for which the structure should have been obvious, but initially it looked to be octahedral, with 24 symmetric units instead of 60, as expected according to Caspar and Klug (1962). As it turned out, the virus was indeed icosahedral but the necrosis virus had crystallized in a very special way, where one of its icosahedral two-fold axes was at 45 degrees with respect to the crystallographic two-fold screw axis. The two were 90 degrees apart, giving rise to octahedral symmetry which created peaks twice as high as the icosahedral peaks. So, there were really two of these viruses and they must have separate peaks. Thus, both Aaron Klug was correct, and Rossmann's rotation function was also correct; only Rossmann's interpretation was wrong. This ended a brief but distasteful "fight" with Klug.

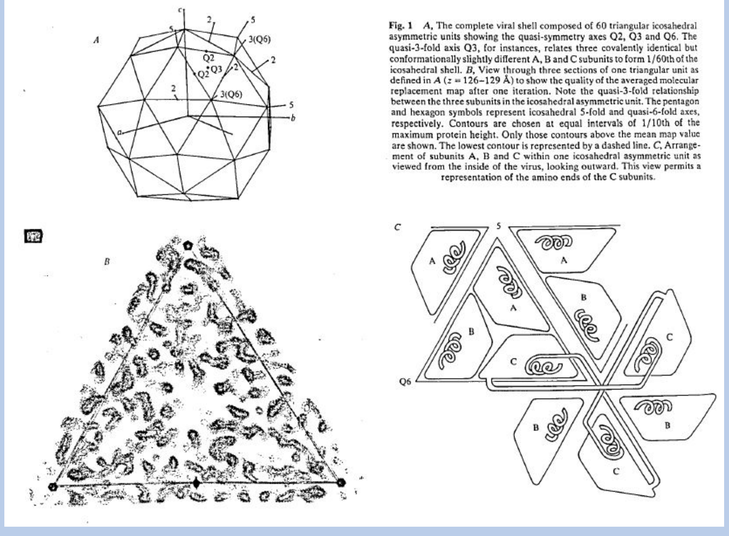
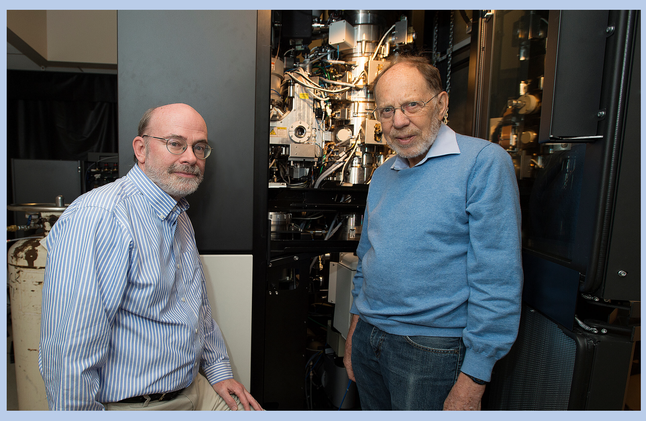


Fig. 1 *A*, The complete viral shell composed of 60 triangular icosahedral asymmetric units showing the quasi-symmetry axes Q2, Q3 and Q6. The quasi-3-fold axis Q3, for instances, relates three covalently identical but conformationally slightly different A, B and C subunits to form 1/60th of the icosahedral shell. *B*, View through three sections of one triangular unit as defined in *A* ($z = 126–129$ Å) to show the quality of the averaged molecular replacement map after one iteration. Note the quasi-3-fold relationship between the three subunits in the icosahedral asymmetric unit. The pentagon and hexagon symbols represent icosahedral 5-fold and quasi-6-fold axes, respectively. Contours are chosen at equal intervals of 1/10th of the maximum protein height. Only those contours above the mean map value are shown. The lowest contour is represented by a dashed line. *C*, Arrangement of subunits A, B and C within one icosahedral asymmetric unit as viewed from the inside of the virus, looking outward. This view permits a representation of the amino ends of the C subunits.

Cryo-EM



Quoting Rossmann: "Since the 1950s X-ray crystallography had been the standard method for determining the structure of viruses, but it requires a relatively large amount of virus, which isn't always available; it can be very difficult to do, especially for viruses like Zika that have a lipid membrane and don't organize accurately into a crystal; and it takes a long time. In early days, cryo-EM was often limited to a resolution of 10–20 Å, and Rossmann 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 (2002), the dengue flavivirus (2002), and West Nile virus (2003).

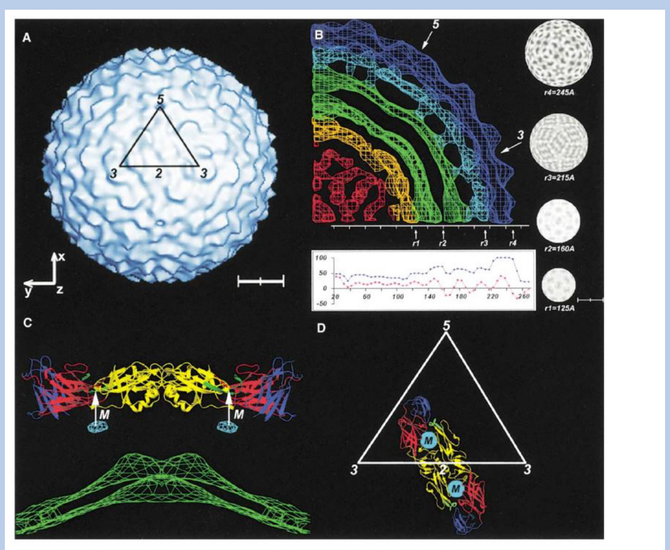


Figure 1. The CryoEM Density
(A) Surface-shaded representation of dengue-2 cryoEM reconstruction at 24 Å resolution, showing the outline of one icosahedral asymmetric unit and the definition of the coordinate system. Scale bar represents 100 Å.
(B) Central crosssection showing the cryo-EM density with a plot of the maximum (blue) and averaged (purple) density. Arrows indicate the position of the 5-fold and 3-fold axes. Shown also are radial density sections at the defined radii, r1, r2, r3, and r4. Higher density representing protein is shown in dark shading. Scale bar represents 175 Å.
(C) Ribbon drawing of the E dimer situated on an icosahedral 2-fold axis, showing the largest uninterpreted electron density peak outside the lipid bilayer, probably representing the M protein (light blue), located close to the hole between the E dimers. The white arrow indicates the position of the dimer holes. The outer leaflet of the lipid bilayer is shown in green. The domains I, II, and III of an E monomer are shown in red, yellow, and blue, respectively. The fusion peptides are in green.
(D) Ribbon drawing showing the position and orientation of the E dimer associated with an icosahedral 2-fold axis. Shown in white is the outline of one icosahedral asymmetric unit. The domains of E are colored as in (C). The portion of the membrane protein M below the dimer is indicated.

In 1980, Rosssmann took a sabbatical with Richard Henderson at Cambridge to learn EM. There, he met Alwyn Jones, "the King of Crystallographic Computer Graphics" and, in the tradition of Rossmann's innovative computational methods, invited Jones to Purdue to install his early Frodo program, the first useful graphics program, on a "homemade" computer.

Rossmann and Kuhn have since long worked with cryo-electron microscopy, focusing on determining how viruses enter and infect their hosts. More recently, and with the 'resolution revolution' in cryo-EM, they obtained near-atomic-resolution structures of Zika virus by modern cryo-EM methodology alone (2016). Now, a structure can be solved through electron microscopy, and the virus is viewed in a more native state.

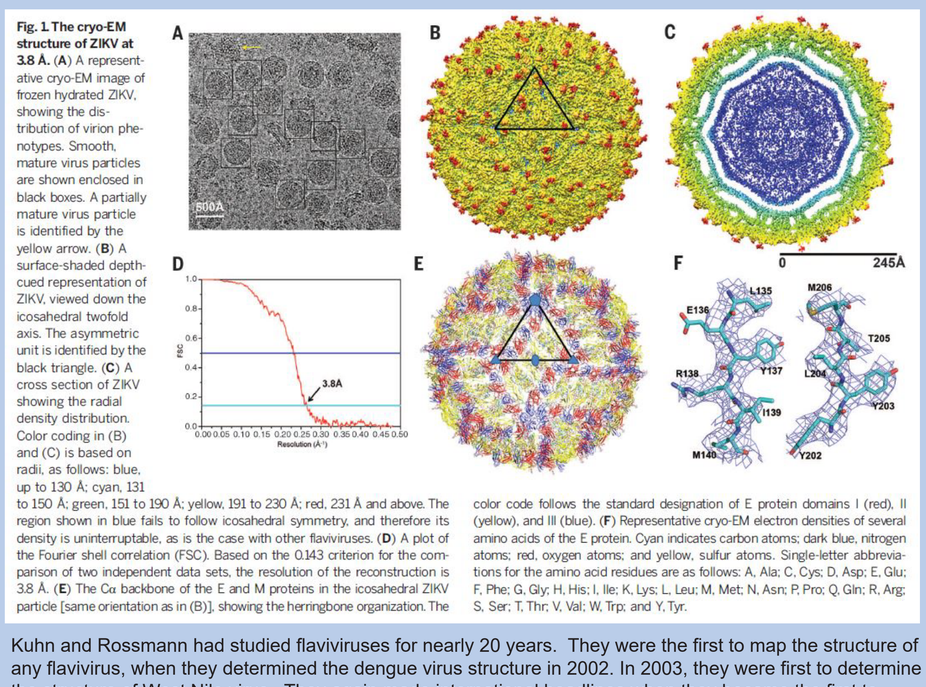


Fig. 1. The cryo-EM structure of ZIKV at 3.8 Å. (**A**) A representative cryo-EM image of frozen hydrated ZIKV, showing the distribution of virion phenotypes. Smooth, mature virus particles are shown enclosed in black boxes. A partially mature virus particle is identified by the yellow arrow. (**B**) A surface-shaded depth-cued representation of ZIKV, viewed down the icosahedral twofold axis. The asymmetric unit is identified by the black triangle. (**C**) A cross section of ZIKV showing the radial density distribution. Color coding in (B) and (C) is based on radii, as follows: blue, up to 130 Å; cyan, 131 to 150 Å; green, 151 to 190 Å; yellow, 191 to 230 Å; red, 231 Å and above. The region shown in blue fails to follow icosahedral symmetry, and therefore its density is uninterruptable, as is the case with other flaviviruses. (**D**) A plot of the Fourier shell correlation (FSC). Based on the 0.143 criterion for the comparison of two independent data sets, the resolution of the reconstruction is 3.8 Å. (**E**) The Cα backbone of the E and M proteins in the icosahedral ZIKV particle [same orientation as in (B)], showing the herringbone organization. The color code follows the standard designation of E protein domains I (red), II (yellow), and III (blue). (**F**) Representative cryo-EM electron densities of several amino acids of the E protein. Cyan indicates carbon atoms; dark blue, nitrogen atoms; red, oxygen atoms; and yellow, sulfur atoms. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

Kuhn and Rossmann had studied flaviviruses for nearly 20 years. They were the first to map the structure of any flavivirus, when they determined the dengue virus structure in 2002. In 2003, they were first to determine the structure of West Nile virus. They again made international headlines when they became the first to determine the structure of the Zika virus (2016). At the time, the mosquito-borne virus had been declared an epidemic and scientists were frantically trying to stop its spread. Two years later, they created the most accurate picture of Zika to date, and with it, the potential for antiviral compounds and vaccines. They identified regions within the Zika virus structure where it differs from other flaviviruses, such as dengue, West Nile, yellow fever, Japanese encephalitis and tick-borne encephalitic viruses. Most recently, the team determined the way some antibodies neutralize infections caused by Zika virus.

Honors

- 1978 Fellow of the American Academy of Arts and Sciences
- 1984 Member of the American Academy of Arts and Sciences
- 1984 Member of the National Academy of Sciences
- 1996 Member of the Royal Society of London
- 1999 Fellow of the American Association for the Advancement of Science
- 2001 Paul Ehrlich Prize
- 2001 Ludwig Darmstädter Prize
- 1996 Ewald Prize
- 1987 Canada Gairdner Foundation International Award
- 1990 Louisa Gross Horwitz Prize from Columbia U
- 1994 Gregori Aminoff Prize, awarded by the Royal Swedish Acad. Sci.
- 1995 Purdue Medal of Honor
- 2000-06 presidential appointee to the National Science Board
- 2016 Raymond and Beverly Sackler International Prize in Biophysics

Acknowledgements

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