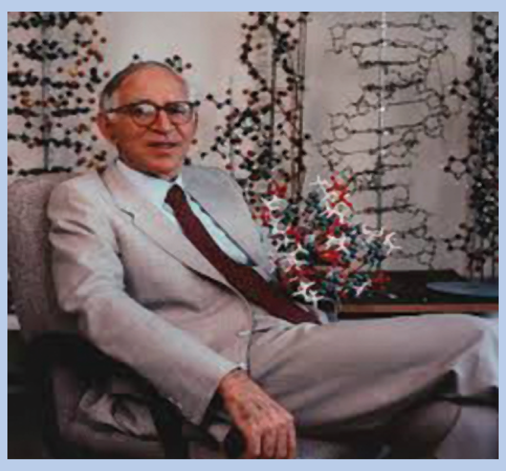
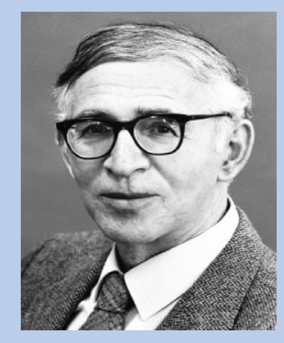


Aaron Klug

1926 - 2018



Biography

Aaron Klug was born in Želva, Lithuania but moved to Durban, South Africa (at the age of two), where he grew up. He earned his MA at the University of Cape Town, where he started with X-ray crystallography under R. James, who had worked with Bragg. Klug moved to Cambridge in 1948, where he earned his PhD under D. Hartree in 1952. Denied a US visa, he went to Birkbeck College, London in 1953 where he met Rosalind Franklin, who sparked his interest in virology. In 1962, he moved to MRC in Cambridge and became Director of the LMB at MRC from 1985 to 1996. He was President of the Royal Society from 1995 to 2000. He received the 1982 Nobel Prize in Chemistry "for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes". He was knighted by Queen Elizabeth II in 1988.

TMV structure

Inspired by the technical virtuosity of Rosalind Franklin, Klug was inspired to start his career in structural biology, starting with TMV, taking over from Franklin after her untimely death in 1958. The first structure of TMV was obtained in 1965.

THE ROYAL SOCIETY

Phil. Trans. R. Soc. Lond. B (1999) **354**, 531–535

The tobacco mosaic virus particle: structure and assembly

A. Klug

MRC Laboratory of Molecular Biology, Cambridge CB2 2QH, UK

A short account is given of the physical and chemical studies that have led to an understanding of the structure of the tobacco mosaic virus particle and how it is assembled from its constituent coat protein and RNA. The assembly is a much more complex process than might have been expected from the simplicity of the helical design of the particle. The protein forms an obligatory intermediate (a cylindrical disk composed of two layers of protein units), which recognizes a specific RNA hairpin sequence. This extraordinary mechanism simultaneously fulfils the physical requirement for nucleating the growth of the helical particle and the biological requirement for specific recognition of the viral DNA.

Keywords: helix; protein disk; RNA; nucleation; X-ray analysis

Table 1. *Tobacco mosaic virus (TMV) structure and assembly*[a]*—a selected chronology 1936–1977*

1936–1939	Isolation, characterization, and first X-ray studies (Stanley, Bawden, Pirie, Bernal and Fankuchen)
1947–1955	Isolation of protein subunits and reaggregation into helical rods (Schramm)
1952–1955	Resumption of X-ray work—TMV shown to be a helix (Watson and Franklin)
1955	Self-assembly of infectious particles from separate components (Fraenkel-Conrat and Williams)
1956–1958	First one-dimensional Fourier maps, helical geometry and general description of structure (Franklin, Caspar, Klug and Holmes)

	virus		protein disk		assembly
1965	(Holmes, Klug; Cambridge) first 3D map; 12 Å resolution		(Leberman, Finch, Klug; Cambridge)	1958	physicochemical studies of the protein (Lauffer, Caspar)
		1966	first X-ray studies, 17-fold symmetry	1963	Caspar: review on assembly
		1971	EM image reconstruction; 20 Å resolution	1970	(Klug, Butler; Cambridge) 'phase diagram' of protein aggregates (Durham)
1968	(Holmes, Stubbs; Heidelberg)	1972	first X-ray 3D map; 15 Å resolution (with Gilbert)	1971	20S disk shown to nucleate assembly (Butler)
1975	7 Å resolution	1975	5 Å resolution; chain traced (with Champness)	1976	nucleation region of RNA sequenced (Butler, Zimmern)
1977	4 Å resolution; RNA: protein contacts	1977	2.8 Å resolution; atomic model (with Bloomer)	1977	mechanisms of initiation and elongation shown
1978	(Stubbs, Namba, Caspar; Brandeis)				
1978→	higher resolution (Stubbs)				

[a] This deals mainly with the chronology of structural determinations and experiments on assembly. It omits the more biochemical and biological parts of the history, e.g. the discovery of the infectivity of the RNA by Gierer & Schramm and by Fraenkel-Conrat; the use of mutants in Melchers's laboratory to study the effects of changes in the protein subunit, and by Wittmann to test the genetic code; the sequencing of the protein in Tübingen and Berkeley.

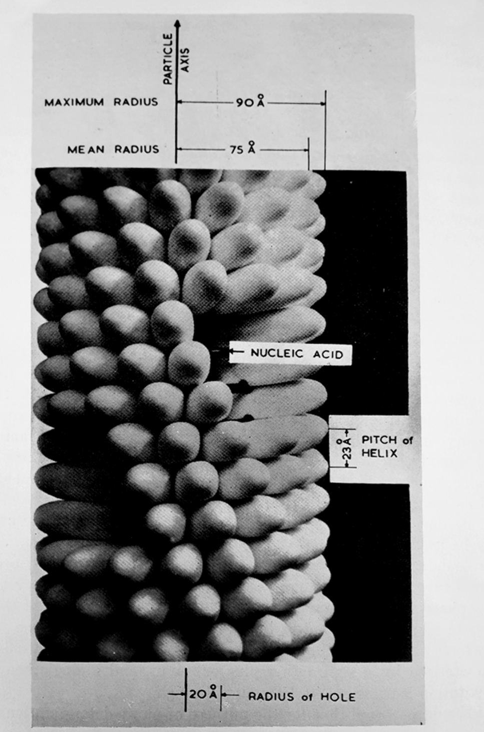


FIG. 1. A model of tobacco mosaic virus, based mainly on the X-ray diffraction studies of Rosalind Franklin (Franklin *et al.*, 1959). About one-tenth of the total length of the virus particle is shown.

The virus protein is in the form of a large number of small equivalent subunits set in helical array about the particle axis. The structure repeats after 69 Å in the axial direction, and the repeat contains 49 subunits distributed over 3 turns of the flat, major helix of pitch 23 Å. The shape of the subunits as represented is rather schematic, but is such that the helical array has a hollow core of diameter 35–40 Å

General virus structure

Advances in Virus Research 1960. 7:225-325

THE STRUCTURE OF SMALL VIRUSES

Dedicated to the memory of the late Rosalind E. Franklin (July 25, 1920–April 16, 1958)

A. Klug and D. L. D. Caspar

Crystallography Laboratory, Birkbeck College (University of London), London and Children's Cancer Research Foundation, Boston, Massachusetts

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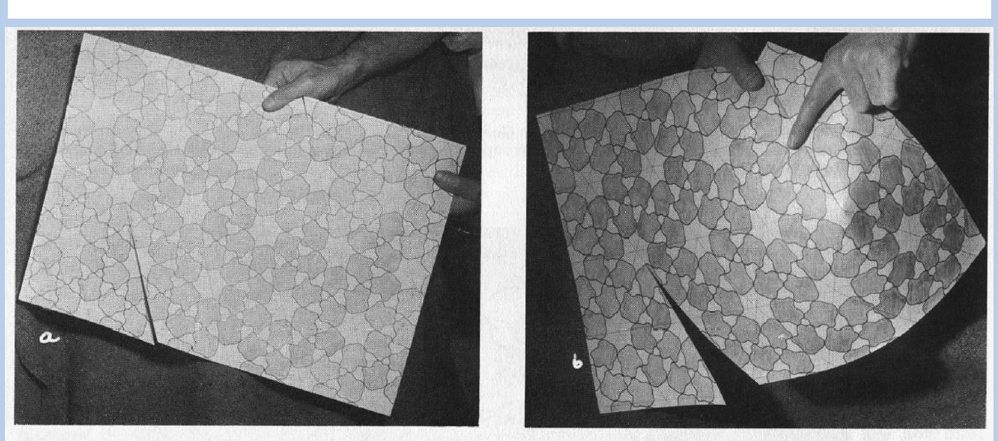
Physical Principles in the Construction of Regular Viruses

D. L. D. CASPAR AND A. KLUG*

The Children's Cancer Research Foundation, The Children's Hospital Medical Center, and the Department of Biophysics, Harvard Medical School, Boston, Massachusetts;

**Medical Research Council Laboratory of Molecular Biology, University Postgraduate Medical School, Cambridge, England.*



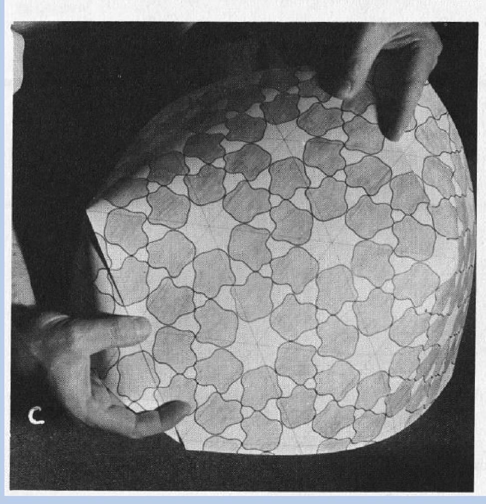


FIGURE 7. The folding of the net of Fig. 6 into a closed surface:

(a) Slitting along a line joining two lattice points.

(b) Forming a cone by transforming a 6-vertex into a 5-vertex. Note that the bonding pattern of Fig. 6 is preserved locally.

(c) Forming another 5-vertex has produced part of a closed surface. In this example, the disposition of 5-vertices has been chosen in such a way that a complete surface with icosahedral symmetry would have triangulation number T = 4.

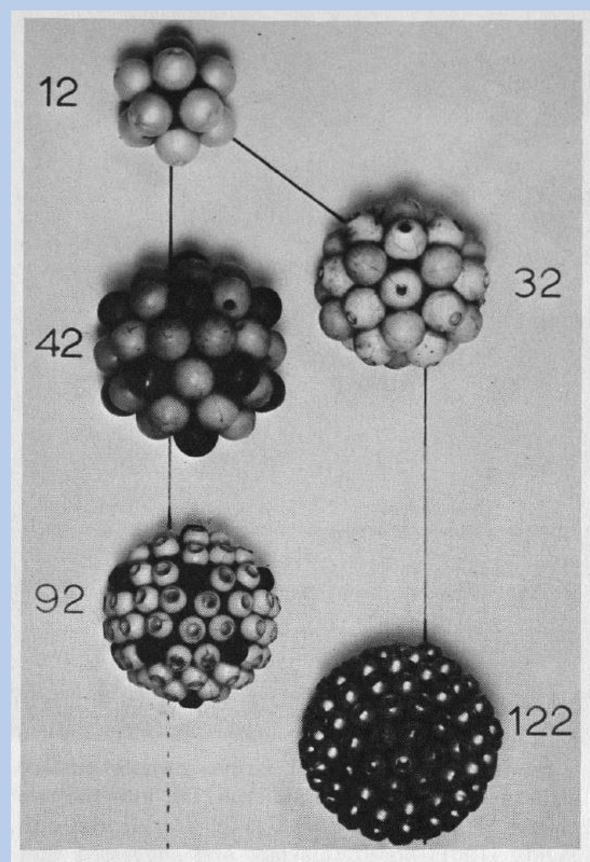


FIGURE 11. The arrangement of hexamer and pentamer morphological units in the lower members of the two icosahedral classes P = 1 (at left) and P = 3 (at right).

Collaboration between Caspar and Klug resulted in establishing the principles of symmetrical patterns in viruses.

TABLE 1. THE CLASSES OF ICOSAHEDRAL DELTAHEDRA (SEE ALSO FIG. 8) Tabulation of the Triangulation Number T

Class										
P = 1	1		4		9		16		25	....
P = 3		3				12			27	....
Skew Classes				7		13		19 21		....

Triangulation No. $T = Pf^2$ where $P = h^2 + hk + k^2$, h and k any pair of integers with no common factor and f = 1, 2, 3, 4, ...

No. of structure units S = 60 T

No. of morphological units M = 10 T + 2 = 10(T − 1) hexamers + 12 pentamers

Some established virus examples (for references, see text)

Phage φX, T = 1; Turnip yellow mosaic virus T = 3; Herpes, Varicella T = 16; Adenovirus, Infectious canine hepatitis T = 25.

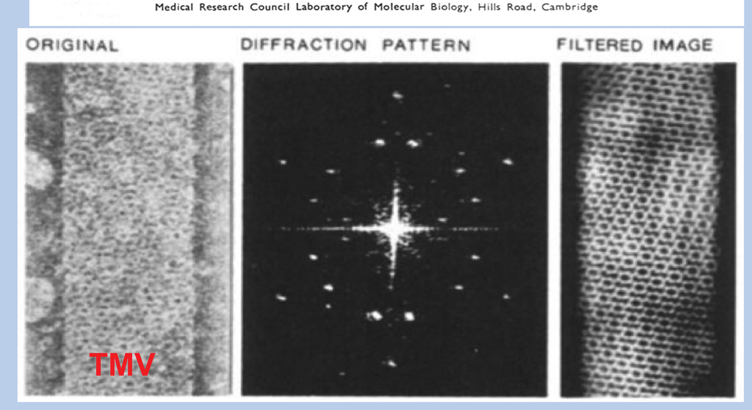
EM image-processing

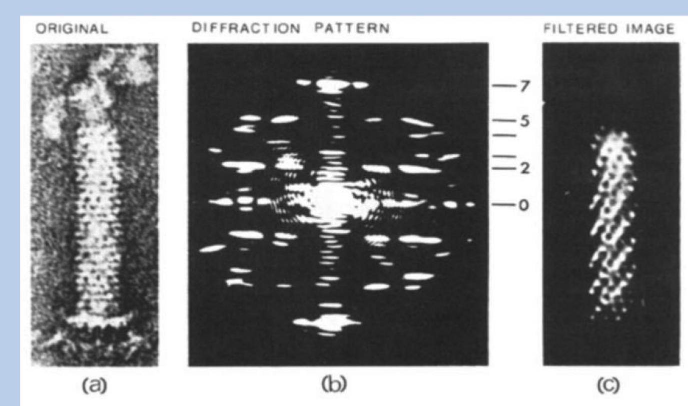
Nature October 1, 1966 VOL. 212

OPTICAL FILTERING OF ELECTRON MICROGRAPHS: RECONSTRUCTION OF ONE-SIDED IMAGES

By DR. A. KLUG and DR. D. J. DE ROSIER

Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge





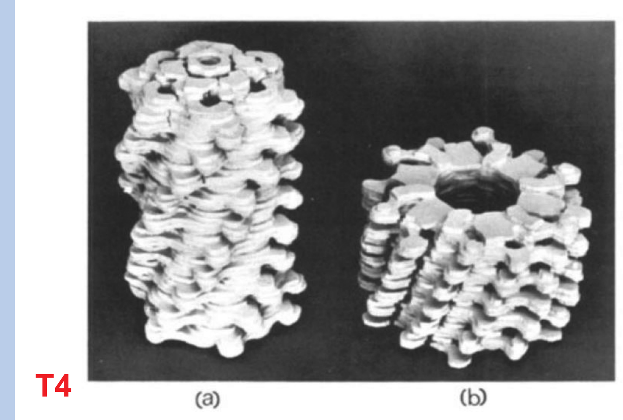


Figure 4 (*Top*) Optical filtering of the tail of bacteriophage T4. The axial spacing of the annuli in the tail (*a*) is approximately 38 Å, corresponding to the layer line marked 7 in (*b*). *Figure 5* (*Bottom*) Models of three-dimensional reconstructions of (*a*) the extended tail of bacteriophage T4, diameter approximately 240 Å. (*b*) Polysheath which closely resembles the contracted sheath, diameter approximately 300 Å.

An initial problem with 3-D reconstruction from electron micrographs was that structure from both sides was superimposed in the 2-D image. This was overcome by Fourier filtering.

EM image-processing

NATURE VOL. 226 MAY 2 1970 421

Three Dimensional Reconstructions of Spherical Viruses by Fourier Synthesis from Electron Micrographs

by

R. A. CROWTHER
LINDA A. AMOS
J. T. FINCH
D. J. DE ROSIER*
A. KLUG

MRC Laboratory of Molecular Biology, Hills Road, Cambridge

Methods are developed for computing three dimensional density maps from transmission electron micrographs using Fourier transforms. The reconstructions objectively combine data from several different views of one or more particles. When applied to negatively stained spherical viruses, the technique gives clear reconstructions of their surface structures.

The Fourier Transform of an Electron Micrograph: Effects of Defocussing and Aberrations, and Implications for the Use of Underfocus Contrast Enhancement

By Harold P. Erickson and A. Klug

Medical Research Council Laboratory of Molecular Biology, Cambridge, England

The Klug group early realized the importance of considering the effect of the operation conditions (e.g. CTF) of the electron microscope when determining a structure.

3-D reconstruction

130 NATURE, VOL. 217, JANUARY 13, 1968

Reconstruction of Three Dimensional Structures from Electron Micrographs

by

D. J. DE ROSIER
A. KLUG

MRC Laboratory of Molecular Biology, Hills Road, Cambridge

General principles are formulated for the objective reconstruction of a three dimensional object from a set of electron microscope images. These principles are applied to the calculation of a three dimensional density map of the tail of bacteriophage T4.

This is one of the classic papers of EM structural biology, pointing the way to the method of 3D reconstruction that is still basic to the field.

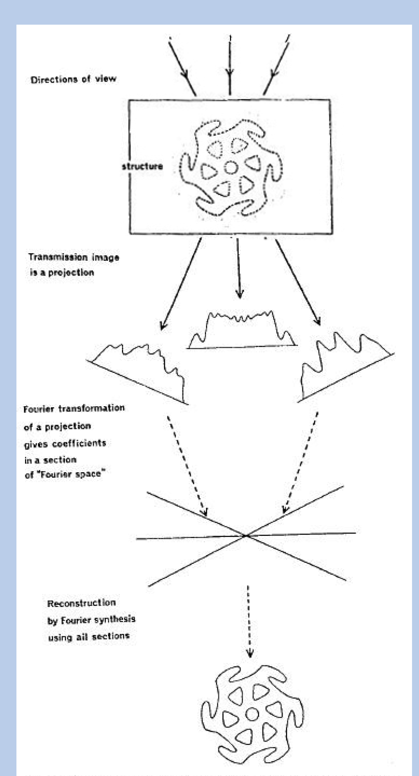


Fig. 6. Schema for the general process of reconstruction of a structure from its transmission images.

Proc. Roy. Soc. Lond. A. **317**, 319–340 (1970)

Printed in Great Britain

The reconstruction of a three-dimensional structure from projections and its application to electron microscopy

BY R. A. CROWTHER, D. J. DEROSIER† AND A. KLUG, F.R.S.

Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge

(*Received* 5 *December* 1969)

In other words, the minimum number of views, m, to reconstruct a particle of diameter D to a resolution of $d(= 1/R_{\max})$ is given by

$$m \simeq \pi D/d.$$

This is the often-cited paper and essential formula used to estimate resolution in 3-D reconstruction, especially relevant to electron tomography.

Chromatin -- "zinc fingers"

The Discovery of Zinc Fingers and Their Applications in Gene Regulation and Genome Manipulation

Aaron Klug

MRC Laboratory of Molecular Biology, Cambridge CB2 0QH, United Kingdom; email: akl@mrc-lmb.cam.ac.uk

Annu. Rev. Biochem. 2010. 79:213–31

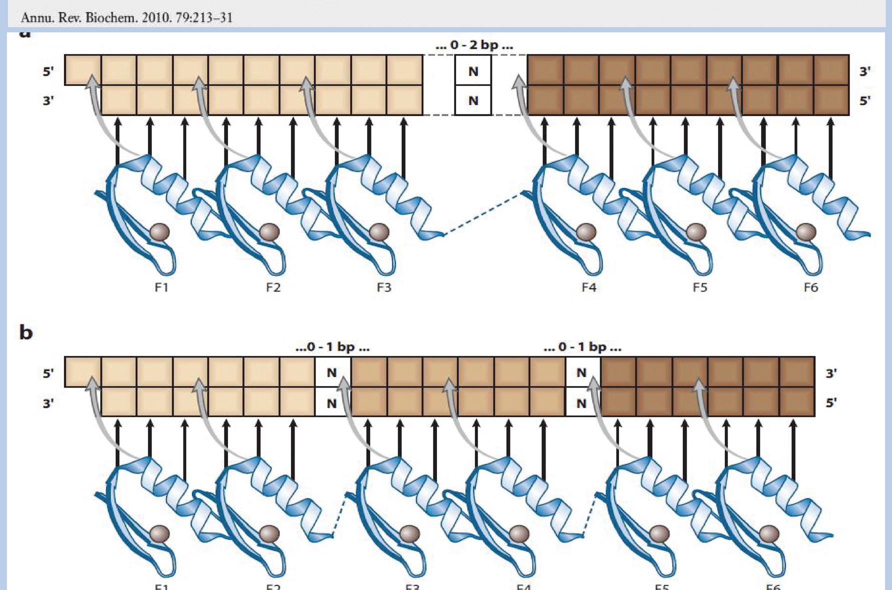


Figure 7

Two modes of generating six-zinc finger proteins for specific recognition of 18-bp sequences (35, 36). (*a*) Two three-finger peptides fused together using an extended canonical linker (2 × 3F scheme). (*b*) These two-finger peptides linked using canonical linkers extended by an insertion of either a glycine residue or a glycine-serine-glycine sequence in the canonical linkers between fingers 2 and 3 and fingers 4 and 5, respectively.

Later in his career, as a result of his studies of chromatin and histones, Klug developed "zinc fingers", which could be engineered to bind to any DNA sequence, thereby finding many potential therapeutic uses.

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Klug A. 1979. Image analysis and reconstruction in the electron microscopy of biological macromolecules. Chem. Scr. 14:245–56,

Klug A 2010. From Virus Structure to Chromatin: X-ray Diffraction to Three-Dimensional Electron Microscopy. Annu. Rev. Biochem. 2010. 79:1–35

Klug A 2010. The discovery of zinc fingers and their applications in gene regulation and genome manipulation. Annu. Rev. Biochem. 2010. 79:213-31.

Nobel Prizes relating to microscopy development and application

I1925 Chemistry: Richard Zsigmondy (ulrtramicroscope)

1953 Physics: Frits Zernike (phase plates)

1971 Physics: Dennis Gabor (holography)

1974 Physiology or Medicine: Albert Claude, Cristian de Duve, George Palade (Cell Biology)

1982 Chemistry: Aaron Klug (3-D reconstruction)

1986 Physics: Ernst Ruska, Gerd Binnig, Heinrich Rohrer (EM and STM)

1999 Chemistry: Ahmed Zewail (DTEM)

2009 Chemistry: Roger Tsien (with Osamu Shimomura and Martin Chalfie (GFP)

2009 Chemistry: Venkatraman Ramakrishnan, Thomas Steitz, Ada Yonath (structural biology)

2014 Chemistry: Eric Betzig, Stefan Hell, William Moerner (super-resolution LM)

2017 Chemistry: Jacques Dubochet, Joachim Frank, Richard Henderson (cryo-EM)

Acknowledgements

The MSA Archivist wishes to credit the information from the MRC/LMB webpages and the obituary in *Nature*.