BIOGRAPHICAL SKETCH

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NAME: Robert M. Glaeser

eRA COMMONS USER NAME (credential, e.g., agency login): rmglaeser

POSITION TITLE: Biophysicist Staff Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin, Madison	B.S.	1959	Physics & Mathematics
University of California, Berkeley	Ph.D.	1964	Biophysics
Oxford University	Postdoc	1963-64	Quantum Chemistry
University of Chicago	Postdoc	1964-65	Quantum Chemistry

A. Personal Statement

My research career has involved a mixture of development of methodology for structural biology, with a major emphasis on electron microscopy, and applications of this methodology to specific, biological projects. My current research activity focuses on two topics: (1) why specimen preparation is currently so unreliable, and what might be a better way to prepare specimens; and (2) ways to achieve the full amount of phase contrast with cryo-EM specimens.

My interest in specimen preparation, which initially was focused on maintaining the native, hydrated structure of specimens in the vacuum of the EM, was renewed when Taylor and I were invited to write a retrospective on preparing grids for cryo-EM. We drew attention to the fact that the standard picture of what such specimens looked like did not include the potentially harmful consequences of interacting with the air-water interface. My own response, in collaboration with Dr. Bong-Gyoon Han, was to develop affinity grids, in order to immobilize particles and thus prevent their interaction with the air-water interface. In addition, I have begun to address the issue of ensuring that the remaining sample is thin, but not so thin that the air-water interface still touches the protein particles, even though they have been immobilized on the structure-friendly support film.

My active involvement in the development of phase plates for electron microscopes, first proposed by Boersch in 1947, began when the work of Nagayama and Danev revitalized that long-dormant concept. I soon established, however, that radiation-induced changes in the surface potential of phase-plate materials made such devices extremely difficult to work with, even after Nagayama had overcome many other limitations that had stymied previous developments. This work, in turn, led me to an ongoing collaboration with the lab of Holger Mueller, aimed at use of the ponderomotive potential as the basis of phase plates for electron microscopy.

In addition, I have authored/edited two books that improve access to the theory and methods of high-resolution structure determination by electron microscopy:

Glaeser RM, Downing K, DeRosier D, Chiu W, Frank J. 2007. *Electron crystallography of biological macromolecules*: Oxford University Press

Glaeser RM, Nogales E, Chiu W (Editors). 2021. *Single-particle Cryo-EM of Biological Macromolecules*. IOP Publishing

Ongoing Research Support consists of:

- R21 GM135666 (PI: Bong-Gyoon Han) 01/01/20-12/31/21 (no-cost extension to 12/31/22)

Technology to Prepare Thin, Large-area Samples for Cryo-EM
Methods to remove excess sample from the perimeter of EM grids will be investigated, as alternatives to blotting the face of the grid with filter paper.

- R01 GM<award number> (PI: Holger Mueller) <dates for the current, 4-year renewal>

<Title in italics, for this grant>
Development of technology to produce in-focus phase-contrast images in electron cryo-microscopy (cryo-EM). This phase plate uses a resonant, high-finesse Fabry-Perot cavity (both to focus and also to build up the recirculating power of a laser beam to the level required) to produce a 90-degree phase shift for the unscattered beam in an electron diffraction pattern.

B. Positions and Honors

Positions and Employment

2006-present	Biophysicist Staff Scientist, Lawrence Berkeley National Laboratory
2006-present	Emeritus Professor, University of California, Berkeley
1978-1983	Divisional Dean, Biological Sciences, University of California, Berkeley
1976-2006	Professor, University of California, Berkeley
1971-1976	Associate Professor, Biophysics, University of California, Berkeley
1966-1971	Assistant Professor, Biophysics, University of California, Berkeley
1965-2006	Faculty Scientist, Life Sciences Division, Lawrence Berkeley National Laboratory
1965-1966	Lecturer, Division of Medical Physics, University of California, Berkeley

Awards and Major Professional Activities

2021-2022	CZI Visual Proteomics Steering Council
2021	The Berkeley Lab Prize – Lifetime Achievement Award
2019-2020	Edward A Dickson Emeriti Professor, UC Berkeley
2018	Glenn T. Seaborg Award and Metal, UCLA Department of Chemistry & Biochemistry
2016-2020	Member, International Academic Advisory Board, Beijing Advanced Innovation Center for Structural Biology
2016	Member, National Academy of Sciences
2016	Member, American Academy of Arts and Sciences
2004	Distinguished Scientist Award for the Biological Sciences, Microscopy Society of America
2001	Chair, Gordon Conference on 3-D Electron Microscopy
1999-2001	US National Committee, International Union Crystallography
1998-2003	US National Committee, International Union Pure and Applied Biophysics
1994-1997	Council Member, Biophysical Society
1992	Elizabeth R. Cole Award, Biophysical Society
1988-1989	Alexander von Humboldt Award (at Max-Planck-Institute for Biochemistry, Martinsried)
01/86-12/86	President, Electron Microscopy Society of America
1983-1986	Member, National Advisory Committee on Electron Microscopy, NIH Division of Research Resources
1983-1984	Guggenheim Foundation Fellow (at MRC Lab Molec. Biol., Cambridge)

C. Contributions to Science

Areas of work for which my lab is internationally well recognized include:

I. establishing the extent to which radiation damage limits imaging at high resolution, the need to use averaging of noisy images to overcome those limitations, and the extent to which biological samples tolerate increased amounts of radiation exposure at liquid nitrogen temperature
   1. Glaeser, R.M., 1971. Limitations to Significant Information in Biological Electron Microscopy as a Result of Radiation Damage. Journal of Ultrastructure Research 36, 466-482
   2. Glaeser, R.M., K.A. Taylor, 1978. Radiation-Damage Relative to Transmission Electron-Microscopy of Biological Specimens at Low-Temperature - Review. Journal of Microscopy-Oxford

112, 127-138.

II. the use of frozen-hydrated specimens to preserve native, hydrated structure
    1. Taylor KA, Glaeser RM. 1974. Electron-Diffraction of Frozen, Hydrated Protein Crystals. *Science* 186: 1036-37
    2. Taylor, K.A., R.M. Glaeser, 2008. Retrospective on the early development of cryoelectron microscopy of macromolecules and a prospective on opportunities for the future. Journal of Structural Biology 163, 214-223

III. addressing the hazards associated with the air-water interface
    1. Han, B.-G., Z. Watson, H. Kang, A. Pulk, K.H. Downing, J. Cate, R.M. Glaeser, 2016. Long shelf-life streptavidin support-films suitable for electron microscopy of biological macromolecules. Journal of Structural Biology 195, 238-244
    2. Armstrong M, Han B.-G, Gomez S, Turner J, Fletcher DA, Glaeser RM. 2020. Microscale Fluid Behavior during Cryo-EM Sample Blotting. *Biophysical Journal* 118: 708-1
    3. Glaeser RM. 2021. Preparing Better Samples for Cryo–Electron Microscopy: Biochemical Challenges Do Not End with Isolation and Purification. *Annual Review of Biochemistry* 90:451-474
    4. Han, B.-G., R. M. Glaeser, 2021 Simple assay for adsorption of proteins to the air–water interface. *Journal of Structural Biology* **213**, 107798,

IV. analysis of the theoretical limitations of performance in biological EM
    1. Henderson, R., R.M. Glaeser, 1985. Quantitative analysis of image contrast in electron micrographs of beam-sensitive crystals. Ultramicroscopy 16, 139-150
    2. Glaeser RM. 1999. Review: Electron crystallography: Present excitement, a nod to the past, anticipating the future. *Journal of Structural Biology* 128: 3-14
    3. Glaeser RM, Hall RJ. 2011. Reaching the Information Limit in Cryo-EM of Biological Macromolecules: Experimental Aspects. *Biophysical Journal* 100: 2331-37
    4. Glaeser RM. 2019. How Good Can Single-Particle Cryo-EM Become? What Remains Before It Approaches Its Physical Limits? *Annual Review of Biophysics* 48: 45-61

V. development of devices for in-focus phase contrast in transmission electron microscopy
    1. Danev R, Glaeser RM, Nagayama K. 2009. Practical factors affecting the performance of a thin-film phase plate for transmission electron microscopy. *Ultramicroscopy* 109: 312-25
    2. Glaeser, R.M., 2013. Invited Review Article: Methods for imaging weak-phase objects in electron microscopy. Review of Scientific Instruments 84, 111101
    3. Schwartz O, Axelrod JJ, Campbell SL, Turnbaugh C, Glaeser RM, Muller H. 2019. Laser phase plate for transmission electron microscopy. *Nature Methods* 16: 1016-2020
    4. Turnbaugh C, Axelrod JJ, Campbell SL, Dioquino JY, Petrov PN, et al. 2021. High-power near-concentric Fabry–Perot cavity for phase contrast electron microscopy. *Review of Scientific Instruments* 92: 053005