

Steven J. Ludtke

Biographical Information

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Current Position

*Assistant Professor & Co-director of the National Center for Macromolecular Imaging
Verna and Marris McLean Department of Biochemistry and Molecular Biology
Baylor College of Medicine*

Educational Background

BS in Physics, Caltech, June 1990

MA in Physics, Rice University, May 1993

Advisor: Dr. H.W. Huang

Thesis: Concentration dependent phase transition of a small protein in synthetic lipid multilayers.

PhD in Physics, Rice University, May 1996

Advisor: Dr. H.W. Huang

Thesis: Membrane interactions of magainin and melittin, a comparison of 2 channel forming peptides.

Postdoctoral Fellow, 1996-2000, Verna & Marris McLean Department of Biochemistry
Baylor College of Medicine, TX

Research

My current work focuses on a technique known as single particle reconstruction. In this technique, electron cryo-microscopy is used to record projection images of individual molecules or macromolecular assemblies embedded in vitreous ice. These randomly oriented particle images are then processed using a complex sequence of algorithms including multidimensional alignment, deconvolution, Fourier and real-space reconstruction techniques, etc. The final result is a 3D structure of the original molecule. For the last 7 years, much of my effort has been focused on developing EMAN, a software suite for performing single particle reconstructions, now in active use by over 300 researchers around the world. In addition to performing reconstructions, this suite of programs serves as a development test-bed for novel algorithms that push the capabilities of this technique towards atomic resolution. It is capable of producing a reconstruction very rapidly and reproducibly with minimal human intervention. Previous programs required a great deal of human effort to use, and relied heavily on human judgment in the actual image processing procedure. I am now actively working on several biologically interesting molecules, including Fatty Acid Synthase, GroEL, Ca⁺⁺ release channel, LDL and IP3 receptor. Typical reconstructions using this technique can now achieve better than 1 nm resolution, and are capable of dealing with specimen motion/heterogeneity. The latest microscopes are capable of recording measurable signal to near-atomic resolution, but achieving this resolution in 3D reconstructions will require considerable research into new reconstruction algorithms. Some of my other interests include: membrane/peptide interactions, scientific database technology, scientific visualization/animation and computational Grid applications.

National & International Scientific Participation

Conference Organization

- Organizer of Workshop on Electron Cryomicroscopy data processing, University of Houston, March 15-19, 2005.
- Organizer of EMAN Workshop, NCMI and University of Houston, April 16-17, 2004
- Organizer of Workshop on Single Particle Reconstructions held at the Univ. of Houston Dec. 11-15, 2002.
- Co-organizer of Workshop on Algorithms for Single Particle Processing at the National Center for Macromolecular Imaging, April 2000.

Grant and Journal Reviews

- NIH review panel BST-D51, June 2004, Oct. 2004, Feb 2005
- NIH review panel BST-A, Nov 2005
- Ad-hoc reviewer DOE Genomes to Life proposal
- Ad-hoc reviewer NSF career development award proposal
- Reviewed dozens of papers on single-particle analysis for a variety of journals

Editorships

- Co-guest editor for a special issue of the Journal of Structural Biology on single particle processing, 2001.

Memberships

- Member Microscopy Society of America, from 1998
- Member Biophysical Society, from 1992
- Member American Physical Society, from 1992
- Member American Crystallographic Association, from 2002

Invited Presentations

- “Visualizing Transmembrane Helices and Beta Strands: New Frontiers in Electron Cryomicroscopy”. Boston University. December, 2005.
- “Strategies for single particle reconstruction at high resolution”. Scripps Institute. November, 2005.
- “EMEN: Electron Microscopy Electronic Notebook”. European Bioinformatics Institute, Cambridge, UK. October, 2005.
- “Visualizing Transmembrane Helices and Beta Strands: New Frontiers in Electron Cryomicroscopy”. UTHSC San Antonio, Sept. 2005.
- “Electron Cryomicroscopy and Single Particle Reconstruction”. Quarterly HIPCAT meeting, BCM, May 2005.
- “EMEN2 – A Distributed Object-oriented Electronic Notebook for Data Archival, Sharing and Mining”. Workshop on Structural and Computational Proteomics of Biological Complexes. Rice Univ. May, 2005.
- “EMAN Workshop”. 12 hours of lectures/demos. Univ. of Houston. March 2005.
- “Single Particle Reconstruction” Rice Chapter of SIAM. Rice University, November, 2004.
- “Resolution, Heterogeneity and Dynamics in Single Particle Reconstruction” Keck Lecture. Rice University, September 2004.

- “Extending the Limits of Single Particle Reconstruction” Gordon Conference on Diffraction Methods in Structural Biology, Bates College, Maine, July 2004.
- “Improving Resolution and Veracity of Single Particle Reconstructions” McGovern Lecture, Texas Medical Center, May 2004.
- “Seeing GroEL at 6 Å by Single Particle CryoEM” Agouron Institute, April 2004
- “EMAN Workshop” NCMI and University of Houston, April 2004
- “Resolution, Heterogeneity and Dynamics in Single Particle Reconstruction”. Structure group seminar. UT SW Med. Ctr. January 2004.
- “Single Particle Reconstruction” Scripps Institute, November, 2003
- “Design of SPARX, Adding Cryo-EM Support to Phenix”. Annual PHENIX workshop. Texas A&M, September, 2003.
- “Automatic Particle Selection Methodologies in EMAN”. Scripps workshop on Automatic Particle Selection, April 2003.
- "EMAN: Software for single particle analysis". Univ. of Texas, Austin. March 2003.
- NCMI Single Particle Reconstruction Workshop. University of Houston, December 2002.
- “Object oriented Database and Electronic Notebook for Electron Cryomicroscopy”. European Bioinformatics Institute symposium on databases in single particle analysis. Cambridge, England. November 2002.
- “Merging Focal Paris for Contrast Enhancement”. MSA Ann. Meeting, Aug 2002.
- “Image Restoration in Sets of Noisy Electron Micrographs”. IEEE International Symposium on Biomedical Imaging, July 2002.
- “Fast and Accurate 3D Structures from Individual Molecules with EMAN”. ACA Annual Meeting, May 2002.
- “Single Particle Software Development at the NCMI”. Agouron Institute Workshop, March 2002.
- "Semiautomated Single-Particle Analysis for Fast, Accurate Structures". Gordon Conference on 3D Electron Microscopy, June 2001.
- "Fast and accurate single particle reconstructions using EMAN". NIH, Bethesda, MD, May 2001.
- "Single Particle Processing: Fast and Accurate Macromolecular Structures". symposium on High Resolution Electron Cryo-Microscopy of Macromolecular Machines. Houston, TX, March 2001.
- "Single particle analysis of macromolecules and complexes: how to get started". Microscopy Society of America annual meeting, Philadelphia, PA, August 2000.

- “Direct Fourier Inversion and Resolution Criteria”. NCMI Workshop on Algorithms for Single Particle Processing, April 2000.
- "Introduction to single particle processing". Lawrence Berkeley Labs, September 1999.
- A series of tutorial lectures on single particle processing at a week-long single particle processing tutorial at the Pittsburgh Supercomputing Center, July 1999.
- "Single particle reconstruction of biological macromolecules". Biomedical Image Analysis & Visualization, a workshop at the Pittsburgh Supercomputing Center, July 1998.
- "Interactions of Amphipathic Helical Peptides with Bilayers". HAMBP Seminar, Rice University, Mar. 1995.

Teaching:

- Scripps Workshop on Single Particle Analysis, Nov 2005. 16 hours of lab/lecture on single particle reconstruction.
- Computational Mathematics (4 lectures), BCM, 2005-6.
- Structure of Macromolecules (2 lectures), BCM, 2004-5.
- Guest lecture Rice Univ. BIOS589, “Computational Molecular Biophysics”
- EMAN Workshop, April 2004. 12 hours of lectures and tutorial.
- Scripps Workshop on Single Particle Analysis, Nov. 2003. 17 hours of lectures and tutorial over a 6 day workshop.
- NCMI Single Particle Reconstruction Workshop, Dec. 2002. 16 hours of lectures and tutorials over a 5 day workshop.
- Pittsburgh Supercomputing Center workshop on single particle processing, July 1998. 8 hours of lectures and tutorials during a week-long workshop.
- Freshman & sophomore physics lab section at Rice University, 7 semesters.

Publications

- Jiang W, Ludtke S.J. (2005) Electron cryomicroscopy of single particles at subnanometer resolution. *Curr Opin Struct Biol.*15(5):571-7.
- Ludtke, S.J., Serysheva, I.I., Hamilton, S.L. and Chiu, W. (2005) The pore structure of the closed RyR1 channel. *Structure.* 8:1203-11.
- Sitharaman, B., Kissell, K.R., Hartman, K.B., Tran, L.A., Baikalov, A., Rusakova, I., Sun, Y., Khant, H.A., Ludtke, S.J., Chiu, W., Laus, S., Toth, E., Helm, L., Merbach, A.E. and Wilson, L.J.. (2005) Superparamagnetic gadonanotubes are

high-performance MRI contrast agents. *Chem. Commun.* 31:3915-7.

- Menetret, J.F., Hegde, R.S., Heinrich, S.U., Chandramouli, P., Ludtke, S.J., Rapoport, T.A., and Akey, C.W. (2005). Architecture of the ribosome-channel complex derived from native membranes. *J. Mol. Biol.* 348,445-57.
- Serysheva, I.I., Hamilton, S.L., Chiu, W., Ludtke, S.J. (2005). Structure of Ca²⁺ Release Channel at 14 Å Resolution. *J. Mol. Biol.*, 345, 427-431.
- Zhu, Y., Carragher, B., Glaeser, R.M., Fellmann, D., Bajaj, C., Bern, M., Mouche, F., de Haas, F., Hall, R.J., Kriegman, D.J., Ludtke, S.J., Mallick, S.P., Penczek, P.A., Roseman, A.M., Sigworth, F.J., Volkman, N., and Potter, C.S. (2004). Automatic particle selection: results of a comparative study. *J Struct Biol* 145, 3-14.
- Mao, Y., Vyas, N.K., Vyas, M.N., Chen, D.H., Ludtke, S.J., Chiu, W., and Quiocho, F.A. (2004). Structure of the bifunctional and Golgi-associated formimino-transferase cyclodeaminase octamer. *Embo J* 23, 2963-2971.
- Ludtke, S.J., Chen, D.H., Song, J.L., Chuang, D.T., and Chiu, W. (2004). Seeing GroEL at 6 Å resolution by single particle electron cryomicroscopy. *Structure (Camb)* 12, 1129-1136.
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- Brink, J., Ludtke, S.J., Kong, Y., Wakil, S.J., Ma, J., and Chiu, W. (2004). Experimental verification of conformational variation of human fatty acid synthase as predicted by normal mode analysis. *Structure (Camb)* 12, 185-191.
- Booth, C.R., Jiang, W., Baker, M.L., Zhou, Z.H., Ludtke, S.J., and Chiu, W. (2004). A 9 angstroms single particle reconstruction from CCD captured images on a 200 kV electron cryomicroscope. *J Struct Biol* 147, 116-127.
- Serysheva, I.I., Bare, D.J., Ludtke, S.J., Kettlun, C.S., Chiu, W., and Mignery, G.A. (2003). Structure of the type 1 inositol 1,4,5-trisphosphate receptor revealed by electron cryomicroscopy. *J Biol Chem* 278, 21319-21322.
- Ludtke, S.J., and Chiu, W. (2003). Focal pair merging for contrast enhancement of single particles. *J Struct Biol* 144, 73-78.
- Ludtke, S.J., Nason, L., Tu, H., Peng, L., and Chiu, W. (2003). Object oriented database and electronic notebook for transmission electron microscopy. *Microsc Microanal* 9, 556-565.

- Serysheva, I., Ludtke, S.J., Baker, M.R., Chiu, W., and Hamilton, S.L. (2002). Structure of the voltage-gated L-type Ca²⁺ channel by electron cryomicroscopy. *Proc Natl Acad Sci U S A* 99, 10370-10375.
- Ludtke, S.J., and Chiu, W. (2002). Image restoration in sets of noisy electron micrographs. In *IEEE International Symposium on Biomedical Imaging*. pp. WA-SS-2.2, IEEE: Washington, D.C.
- Brink, J., Ludtke, S.J., Yang, C.Y., Gu, Z.W., Wakil, S.J., and Chiu, W. (2002). Quaternary structure of human fatty acid synthase by electron cryomicroscopy. *Proc Natl Acad Sci U S A* 99, 138-143.
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- Saad, A., Ludtke, S.J., Jakana, J., Rixon, F.J., Tsuruta, H., and Chiu, W. (2001). Fourier amplitude decay of electron cryomicroscopic images of single particles and effects on structure determination. *J Struct Biol* 133, 32-42.
- Ludtke, S.J., and Chiu, W. (2001). Electron micrographs: computer enhancement and use for molecular 3-dimensional reconstruction. In *Encyclopedia of Life Sciences, Volume 6*. (London: Nature Publishing Group), pp. 212-217.
- Ludtke, S.J., and Chiu, W. (2001). Editorial: Special Issue on Single Particle Processing. *J Struct Biol* 133, 89.
- Ludtke, S.J., Jakana, J., Song, J.L., Chuang, D.T., and Chiu, W. (2001). A 11.5 Å single particle reconstruction of GroEL using EMAN. *J Mol Biol* 314, 253-262.
- Jiang, W., Baker, M.L., Ludtke, S.J., and Chiu, W. (2001). Bridging the information gap: computational tools for intermediate resolution structure interpretation. *J Mol Biol* 308, 1033-1044.
- Ludtke, S.J., Baldwin, P.R., and Chiu, W. (1999). EMAN: semiautomated software for high-resolution single-particle reconstructions. *J Struct Biol* 128, 82-97.
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- Ludtke, S.J., He, K., Heller, W.T., Harroun, T.A., Yang, L., and Huang, H.W. (1996). Membrane pores induced by magainin. *Biochemistry* 35, 13723-13728.
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- Wu, Y., He, K., Ludtke, S.J., and Huang, H.W. (1995). X-ray diffraction study of lipid bilayer membranes interacting with amphiphilic helical peptides: diphytanoyl phosphatidylcholine with alamethicin at low concentrations. *Biophys J* 68, 2361-2369.
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