



Axel Brunger

Professor of Molecular and Cellular Physiology, of Neurology, of Photon Science and, by courtesy, of Structural Biology
Molecular & Cellular Physiology

Bio

BIO

Axel Brunger received his Physics Diploma at the University of Hamburg in 1980, and his Ph.D. degree from the Technical University of Munich in 1982 working with Klaus Schulten. He held a NATO postdoctoral fellowship and subsequently became a research associate with Martin Karplus at the Department of Chemistry, Harvard University. In 1987 he joined the faculty in the Department of Molecular Biophysics and Biochemistry at Yale University. In 2000, he moved to Stanford University where he is Professor and Chair of the Department of Molecular and Cellular Physiology. He also holds an appointment as Investigator in the Howard Hughes Medical Institute. In 1995 he was awarded the Röntgen Prize for Biosciences from the University of Würzburg. In 2003, he received the Gregori Aminoff Award of the Royal Swedish Academy. In 2005 he was elected member of the National Academy of Sciences. In 2011 he received the DeLano Award of the American Society for Biochemistry and Molecular Biology, in 2014 he received the Bernard Katz Award of the Biophysical Society, and the Carl Hermann Medal of the German Crystallographic Society, and in 2016 he received the Trueblood Award of the American Crystallographic Association. In 2021 he was elected member of the American Academy of Arts & Sciences.

Early in his career, Brunger began developing tools for interpreting x-ray crystallography diffraction data. Scientists use x-ray crystallography to determine molecular structures by crystallizing the molecules and then bombarding them with x-rays. From the data produced by the diffracted x-rays, scientists can calculate a three-dimensional model of the molecule. Brunger's powerful computational methodology revolutionized structural calculation, accelerating its automation and making protein crystallography accessible to non-experts.

Brunger also developed a major computational tool called the "free R value," to rate a molecular model's quality and how likely it is to be correct. The free R value has since become a standard criterion for judging agreement between a crystallographic model and its experimental x-ray diffraction data.

Since the mid-1990s, Brunger has applied his expertise in structural biology to study the molecular mechanisms of synaptic proteins that enable nerve cell communication.

In 1998, Brunger and his team showed that the corkscrew-shaped SNARE proteins assemble into quartets of one syntaxin-1, one synaptobrevin, and two SNAP-25 helices. The proteins all lie in parallel, with their heads pointing in the same direction, to promote membrane fusion.

Since moving to Stanford University in 2000, Brunger and his collaborators have developed a reconstituted system that enables them to study synaptic fusion at greater level of detail than possible in neurons. The team studied the molecular mechanism of neuronal SNAREs, complexin, and synaptotagmin, as well as other factors involved in priming and pre-synaptic plasticity.

In 2015, Brunger's team used electron cryo-microscopy to determine the structure of the supercomplex of SNAREs, the ATPase NSF, and the adapter protein #SNAP. This subnanometer-resolution structure, along with functional studies, revealed first glimpses of the molecular mechanism of NSF-mediated SNARE complex disassembly, which allows SNARE to be recycled for the next round of synaptic vesicle fusion.

In 2017, the team determined atomic-resolution structures of the complex of the calcium sensor synaptotagmin-1, the regulator complexin, and the SNARE complex, revealing two essential interfaces that are essential for fast synchronous release of neurotransmitters. . These structures suggest an unlocking mechanism that is triggered by Ca²⁺ binding to the synaptotagmin molecules, leading to SNARE complex zippering, and membrane fusion.

ACADEMIC APPOINTMENTS

- Professor, Molecular & Cellular Physiology
- Professor, Photon Science Directorate
- Professor, Neurology & Neurological Sciences
- Professor (By courtesy), Structural Biology
- Member, Bio-X
- Member, Wu Tsai Neurosciences Institute

ADMINISTRATIVE APPOINTMENTS

- Chair, Department of Molecular and Cellular Physiology, (2013-2017)

HONORS AND AWARDS

- Elected Member, American Academy of Arts & Sciences (2021)
- Trueblood Award, American Crystallographic Association (2016)
- Carl Hermann Medal, German Crystallographic Society (DGK) (2014)
- Katz Award, Exocytosis & Endocytosis Group, Biophysical Society (2014)
- DeLano Award, American Society for Biochemistry and Molecular Biology (2011)
- Elected Member, National Academy of Sciences (2005)
- Gregori Aminoff Prize, The Royal Swedish Academy of Sciences (2003)
- Röntgen Prize in Biosciences, University of Würzburg, Germany (1995)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Investigator, Howard Hughes Medical Institute (1987 - present)

PROFESSIONAL EDUCATION

- Diplom, University of Hamburg , Physics (1980)
- Ph.D., Technical Univ. of Munich , Biophysics (1982)

LINKS

- My Lab Site: <http://atbweb.stanford.edu>

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

Nerve cells communicate by releasing the contents of neurotransmitter-bearing synaptic vesicles into the space between adjoining cells. This process depends on a handful of proteins that promote vesicle and nerve cell membrane fusion. The Brunger lab team uses structural and biophysical tools to capture this machinery at different stages of vesicle fusion. These structures (Figure 1) then provide the framework for further investigations, using microscopy and live neurons, into the functional and dynamic aspects of the system.

SNARE proteins, found in both nerve cell and vesicle membranes, set the stage for fusion by zipping together into a parallel, four-helix bundle that juxtaposes the two membranes. Brunger and his collaborators determined the first x-ray crystal structure of the neuronal SNARE complex, as well as the structures of other key components of the synaptic release machinery. Recently, the Brunger's team visualized the SNARE complex bound to the Ca²⁺-sensor synaptotagmin-1 and to the regulator complexin, revealing two interfaces that are essential for fast synchronous release of neurotransmitters. The structure of this three-part complex suggests that it is in a primed and locked state. Action-potential-driven Ca²⁺ ions bind to the synaptotagmin proteins, unlock the complex, and trigger membrane fusion on a sub-millisecond timescale.

After fusion has occurred, SNARE complexes are recycled by the ATPase NSF, which breaks down the SNARE complex into its individual components. The Brunger team visualized this molecular machine at near-atomic level and obtained the first glimpses of how this SNARE-recycling machine works. The SNARE complex resembles a rope with a left-handed twist, and NSF uses adapter proteins called SNAPs to grasp the "rope" in multiple places. The SNAPs wrap around the SNARE complex with a right-handed twist, suggesting that the disassembly occurs via a simple unwinding motion that frees the zipped SNARE proteins.

The Brunger team is also using structural and functional studies to explore other machinery relevant to neurotransmitter release, such as factors involved in priming and pre-synaptic plasticity. Their research may one day provide new possibilities for targeting therapeutics to control neurotransmitter release.

Teaching

STANFORD ADVISEES

Doctoral Dissertation Reader (AC)

Lynnette Jackson

Doctoral Dissertation Advisor (AC)

Nisha Gopal, Yousuf Khan, Jiahao Liang

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biophysics (Phd Program)
- Molecular and Cellular Physiology (Phd Program)
- Neurosciences (Phd Program)
- Structural Biology (Phd Program)

Publications

PUBLICATIONS

- **Analysis of tripartite Synaptotagmin-1-SNARE-complexin-1 complexes in solution.** *FEBS open bio*
Jaczynska, K., Esquivies, L., Pfuetzner, R. A., Alten, B., Brewer, K. D., Zhou, Q., Kavalali, E. T., Brunger, A. T., Rizo, J.

2022

- **The core complex of the Ca²⁺-triggered presynaptic fusion machinery.** *Journal of molecular biology*
Brunger, A. T., Leitz, J.
2022: 167853
- **Nanomolar inhibition of SARS-CoV-2 infection by an unmodified peptide targeting the prehairpin intermediate of the spike protein.** *Proceedings of the National Academy of Sciences of the United States of America*
Yang, K., Wang, C., Kreutzberger, A. J., Ojha, R., Kuivanen, S., Couoh-Cardel, S., Muratcioglu, S., Eisen, T. J., White, K. I., Held, R. G., Subramanian, S., Marcus, K., Pfuetzner, et al
2022; 119 (40): e2210990119
- **Nanomolar inhibition of SARS-CoV-2 infection by an unmodified peptide targeting the pre-hairpin intermediate of the spike protein.** *bioRxiv : the preprint server for biology*
Yang, K., Wang, C., Kreutzberger, A. J., Ojha, R., Kuivanen, S., Couoh-Cardel, S., Muratcioglu, S., Eisen, T. J., White, K. I., Held, R. G., Subramanian, S., Marcus, K., Pfuetzner, et al
2022
- **Discovery of a drug to treat airway mucus hypersecretion.** *Clinical and translational medicine*
Dickey, B. F., Lai, Y., Frick, M., Brunger, A. T.
2022; 12 (8): e972
- **Structural conservation among variants of the SARS-CoV-2 spike postfusion bundle.** *Proceedings of the National Academy of Sciences of the United States of America*
Yang, K., Wang, C., White, K. I., Pfuetzner, R. A., Esquivies, L., Brunger, A. T.
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- **A feature-guided, focused 3D signal permutation method for subtomogram averaging.** *Journal of structural biology*
Jacob Peters, J., Leitz, J., Guo, Q., Beck, F., Baumeister, W., Brunger, A. T.
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- **Inhibition of calcium-triggered secretion by hydrocarbon-stapled peptides.** *Nature*
Lai, Y., Fois, G., Flores, J. R., Tuvim, M. J., Zhou, Q., Yang, K., Leitz, J., Peters, J., Zhang, Y., Pfuetzner, R. A., Esquivies, L., Jones, P., Frick, et al
2022
- **The protein-folding problem: Not yet solved.** *Science (New York, N.Y.)*
Moore, P. B., Hendrickson, W. A., Henderson, R., Brunger, A. T.
1800; 375 (6580): 507
- **Screening of Hydrocarbon-Stapled Peptides for Inhibition of Calcium-Triggered Exocytosis.** *Frontiers in pharmacology*
Lai, Y., Tuvim, M. J., Leitz, J., Peters, J., Pfuetzner, R. A., Esquivies, L., Zhou, Q., Czako, B., Cross, J. B., Jones, P., Dickey, B. F., Brunger, A. T.
2022; 13: 891041
- **Conformational dynamics of auto-inhibition in the ER calcium sensor STIM1.** *eLife*
van Dorp, S., Qiu, R., Choi, U. B., Wu, M. M., Yen, M., Kirmiz, M., Brunger, A. T., Lewis, R. S.
2021; 10
- **Conformational dynamics of auto-inhibition in the ER calcium sensor STIM1** *ELIFE*
van Dorp, S., Qiu, R., Choi, U. B., Wu, M. M., Yen, M., Kirmiz, M., Brunger, A. T., Lewis, R. S.
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- **Prefused lysosomes cluster on autophagosomes regulated by VAMP8.** *Cell death & disease*
Chen, Q., Hao, M., Wang, L., Li, L., Chen, Y., Shao, X., Tian, Z., Pfuetzner, R. A., Zhong, Q., Brunger, A. T., Guan, J., Diao, J.
2021; 12 (10): 939
- **The AAA+superfamily: a review of the structural and mechanistic principles of these molecular machines.** *Critical reviews in biochemistry and molecular biology*
Khan, Y. A., White, K. I., Brunger, A. T.
2021: 1-32
- **Sec17/Sec18 can support membrane fusion without help from completion of SNARE zippering.** *eLife*

- Song, H., Torng, T. L., Orr, A. S., Brunger, A. T., Wickner, W. T.
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- **Molecular Characterization of AMPA-Receptor-Containing Vesicles.** *Frontiers in molecular neuroscience*
Peters, J. J., Leitz, J., Oses-Prieto, J. A., Burlingame, A. L., Brunger, A. T.
2021; 14: 754631
 - **Deorphanizing FAM19A proteins as pan-neurexin ligands with an unusual biosynthetic binding mechanism.** *The Journal of cell biology*
Khalaj, A. J., Sterky, F. H., Sclip, A., Schwenk, J., Brunger, A. T., Fakler, B., Sudhof, T. C.
2020; 219 (9)
 - **Role of Aberrant Spontaneous Neurotransmission in SNAP25-Associated Encephalopathies.** *Neuron*
Alten, B. n., Zhou, Q. n., Shin, O. H., Esquivies, L. n., Lin, P. Y., White, K. I., Sun, R. n., Chung, W. K., Monteggia, L. M., Brunger, A. T., Kavalali, E. T.
2020
 - **NSF-MEDIATED DISASSEMBLY OF ON- AND OFF PATHWAY SNARE COMPLEXES AND INHIBITION BY COMPLEXIN**
Choi, U., Zhao, M., White, I., Brunger, A.
WILEY.2019: 19–20
 - **Synaptic vesicle fusion: today and beyond.** *Nature structural & molecular biology*
Brose, N., Brunger, A., Cafiso, D., Chapman, E. R., Diao, J., Hughson, F. M., Jackson, M. B., Jahn, R., Lindau, M., Ma, C., Rizo, J., Shin, Y., Sollner, et al
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Brunger, A. T., Choi, U. B., Lai, Y., Leitz, J., White, K. I., Zhou, Q.
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 - **Nsf-Mediated Disassembly of On-and Off Pathway Snare Complexes and Inhibition by Complexin**
Choi, U. B., Zhao, M., White, K., Brunger, A.
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 - **The pre-synaptic fusion machinery CURRENT OPINION IN STRUCTURAL BIOLOGY**
Brunger, A. T., Choi, U. B., Lai, Y., Leitz, J., White, K., Zhou, Q.
2019; 54: 179–88
 - **Resolving indexing ambiguities in X-ray free-electron laser diffraction patterns** *ACTA CRYSTALLOGRAPHICA SECTION D-STRUCTURAL BIOLOGY*
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2019; 75: 234–41
 - **Resolving indexing ambiguities in X-ray free-electron laser diffraction patterns.** *Acta crystallographica. Section D, Structural biology*
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White, K. I., Zhao, M., Choi, U. B., Pfuetzner, R. A., Brunger, A. T.
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 - **NSF-mediated disassembly of on and off-pathway SNARE complexes and inhibition by complexin.** *eLife*
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2018

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- **Conformational change of syntaxin linker region induced by Munc13s initiates SNARE complex formation in synaptic exocytosis** *EMBO JOURNAL*
Wang, S., Choi, U. B., Gong, J., Yang, X., Li, Y., Wang, A. L., Yang, X., Brunger, A. T., Ma, C.
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- **The primed SNARE-complexin-synaptotagmin complex for neuronal exocytosis.** *Nature*
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- **C-terminal domain of mammalian complexin-1 localizes to highly curved membranes.** *Proceedings of the National Academy of Sciences of the United States of America*
Gong, J., Lai, Y., Li, X., Wang, M., Leitz, J., Hu, Y., Zhang, Y., Choi, U. B., Cipriano, D., Pfuetzner, R. A., Südhof, T. C., Yang, X., Brunger, et al
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- **Advances in X-ray free electron laser (XFEL) diffraction data processing applied to the crystal structure of the synaptotagmin-1 / SNARE complex.** *eLife*
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- **N-terminal domain of complexin independently activates calcium-triggered fusion.** *Proceedings of the National Academy of Sciences of the United States of America*
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- **IOTA: integration optimization, triage and analysis tool for the processing of XFEL diffraction images** *JOURNAL OF APPLIED CRYSTALLOGRAPHY*
Lyubimov, A. Y., Uervirojnangkoorn, M., Zeldin, O. B., Brewster, A. S., Murray, T. D., Sauter, N. K., Berger, J. M., Weis, W. I., Brunger, A. T.
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- **Recent Advances in Deciphering the Structure and Molecular Mechanism of the AAA plus ATPase N-Ethylmaleimide-Sensitive Factor (NSF)** *JOURNAL OF MOLECULAR BIOLOGY*
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- **Simultaneous single-molecule epigenetic imaging of DNA methylation and hydroxymethylation** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*
Song, C., Diao, J., Brunger, A. T., Quake, S. R.
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- **Atomic resolution experimental phase information reveals extensive disorder and bound 2-methyl-2,4-pentanediol in Ca²⁺-calmodulin** *ACTA CRYSTALLOGRAPHICA SECTION D-STRUCTURAL BIOLOGY*
Lin, J., van den Bedem, H., Brunger, A. T., Wilson, M. A.
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- **High-density grids for efficient data collection from multiple crystals.** *Acta crystallographica. Section D, Structural biology*
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- **A high-transparency, micro-patternable chip for X-ray diffraction analysis of microcrystals under native growth conditions** *ACTA CRYSTALLOGRAPHICA SECTION D-BIOLOGICAL CRYSTALLOGRAPHY*
Murray, T. D., Lyubimov, A. Y., Ogata, C. M., Huy Vo, H., Uervirojnangkoorn, M., Brunger, A. T., Berger, J. M.
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- **ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes** *NATURE*
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- **Enabling X-ray Free Electron Laser Crystallography for Challenging Biological Systems from a Limited Number of Crystals** *ELIFE*
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Zhao, M., Wu, S., Zhou, Q., Vivona, S., Cipriano, D. J., Cheng, Y., Brunger, A. T.
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