BIOGRAPHICAL SKETCH

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NAME: Leighton Coates

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

POSITION TITLE: STS Instrument Systems Science and Technology Manager

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 Sheffield, U.K.	BSc Class 2-1	05/99	Biochemistry
University of Southampton, U.K.	Ph. D.	09/03	Protein Crystallography
University of Southampton, U.K.	Post doc	06/05	Protein Crystallography
Los Alamos National Laboratory	Post doc	04/07	Neutron Beamline Scientist

A. Personal Statement

After my work at the University of Southampton, which involved using neutron protein crystallography to study the catalytic mechanism of aspartic proteases, I relocated to Los Alamos National Laboratory to work as a neutron beamline scientist at the Protein Crystallography Station (PCS). During my time at the PCS, a proof of principle neutron time of flight (TOF) beamline, I was involved in developing and supporting the neutron user community by providing expertise and support in neutron data collection, processing, and refinement. In 2007 I relocated to the Spallation Neutron Source (SNS) at Oak Ridge National Laboratory to design, construct, commission, and operate the Macromolecular Neutron Diffractometer (MaNDi). The MaNDi instrument entered the general user program at the SNS in 2014, allowing data collection from crystals an order of magnitude smaller in volume than the PCS. Due to the high time resolution of the decoupled neutron moderator that MaNDi views, it has the unique capability to collect neutron diffraction data from crystals of large proteins and multi-subunit protein complexes up to 300 Å on edge, which has expanded the number of systems that can be studied with neutrons. Since MaNDi entered the user program, I have driven innovation in instrument hardware, sample environment, and data acquisition systems to expand the scientific possibilities of the MaNDi instrument. Recently, I have been involved in the development, testing, and application of three-dimensional profile fitting techniques to TOF neutron protein crystallography data. This has enabled MaNDi to collect complete and accurate datasets from smaller crystals and more challenging systems. These advancements recently allowed the MaNDi instrument to collect high-quality neutron crystallography data from a small crystal of the SARS-CoV-2 Main Protease, enabling the protonation states of the catalytic dyad and substrate binding cleft to be experimentally determined. This enzyme is essential for viral replication and is a primary drug target, so the determination of protonation states can help in the design of more potent inhibitors. My research interests include the relationship between structure and function in biological systems and applying new computational techniques in neutron and X-ray crystallography. I have published over 118 peer-reviewed articles in the fields of structural biology, neutron instrumentation, and software development; see ORCID (0000-0003-2342-049X) for a full and up to date list. Four key publications that highlight my experience and qualifications for this project are

1) Sullivan, B., Archibald, R., Vandavasi, V.G., Langan, P.S., Coates, L., Lynch, V., Volumetric Segmentation via Neural Networks Improves Neutron Crystallography Data Analysis. 2019 19th IEEE/ACM International Symposium on Cluster, Cloud, and Grid Computing (CCGRID) DOI: 10.1109/ccgrid.2019.00070 (2019)

2) Sullivan, B., Archibald, R., Langan, P.S., Dobbek, H., Bommer, M., McFeeters, M.L, Coates, L., Wang, X.P., Gallmeier, F., Carpenter, J.M., Lynch V., Langan, P. Improving the Accuracy and Resolution of Neutron Crystallographic Data by 3D profile Fitting of Bragg Peaks in Reciprocal Space. (2018) Acta Cryst Section D: Structural Biology 74, 11, 1085-1095

3) Sullivan, B., Archibald, R., Azadmenesh, J., Vandavasi, V.G., Langan, P.S., Coates, L., Langan, P., BraggNet: integrating Bragg peaks using neural networks. (2019) Journal of Applied Crystallography, 52, 854-863

4) Coates, L., Cuneo, M.J., Frost, M.J., He, J., Weiss, K.L., Tomanicek, S.J., McFeeters, H., Vandavasi, V.G., Langan, P., Iverson, E.B. The Macromolecular Neutron Diffractometer MaNDi at the Spallation Neutron Source (2015) Journal of Applied Crystallography, 48, 1302-1306.

B. Positions and Honors

Positions and Employment

2007-2020	Neutron Instrument Scientist, Oak Ridge National Laboratory
2008-2010	Adjunct Assistant Professor, The University of Alabama in Huntsville
2019-2021	President of the Pittsburgh Diffraction Society
2020-Present	STS Instrument Systems Science and Technology Manager, Oak Ridge National Laboratory

Other Experience and Professional Memberships

Reviewer for: Acta Crystallographica Sections D and F, Biochemistry, IUCrJ, Journal of Medicinal Chemistry, J. Mol. Biol., Journal of Applied Crystallography, JACS, PNAS, ACS Catalysis, Nature Communications, Nature Chemical Biology

2005-Present	American Crystallographic Association
2006-Present	Neutron Scattering Society of America
2008-Present	Pittsburgh Diffraction Society
2019-2020	Executive Committee International Symposium on Diffraction Structural Biology
2020-Present	International Society of Neutron Instrument Engineers

Honors

2003	Outstanding Postgraduate Presentation, University of Southampton
2009	ORNL Significant Event Award
2012	ORNL Supplemental Performance Award
2013	ORNL Significant Event Award
2018	ORNL Supplemental Performance Award
2020	UT-Battelle 2020 Awards Night Research Accomplishment Award
2021	Elected Fellow of the American Crystallographic Association

C. Contributions to Science

1) My main contribution to science has been made in the field of macromolecular crystallography, where I have constructed new instrumentation and developed computational techniques for the application of neutron protein crystallography to biomedical research. Revealing the fine atomic details in a macromolecular structure is only made possible by the unique scattering properties of the neutron. An exquisitely sensitive probe for locating hydrogen positions and experimentally determining protonation states at near-physiological temperatures free from radiation damage induced artifacts that are commonly encountered with ionizing probes such as X-rays or electrons. During my career, I have utilized neutrons in combination with other

probes and experimental techniques to investigate a range of biological systems using novel approaches in protein and inhibitor labeling.

Since I became a staff member at Oak Ridge National Laboratory (ORNL) in 2007, I have been responsible for the design, construction, and operation of a macromolecular neutron beamline (MaNDi) at the Spallation Neutron Source (SNS) that was specifically designed to collect protein diffraction using neutrons. The MaNDi instrument has advanced neutron techniques allowing data to be collected on smaller crystals, larger unit cell sizes, and more rapidly than other neutron beamlines. Neutrons are a non-ionizing probe, and thus samples are not damaged by interaction with the probe. However, neutron data collection typically occurs over several days, and short-lived reaction intermediates would decay during data collection. Therefore, I pioneered cryo crystallography in neutron protein crystallography enabling the study of transient intermediates.

Currently, a second target station (STS) is being designed and constructed at the SNS. The STS delivers a high brightness of the cold neutrons that are ideally suited for studying biology and soft matter. This enables the use of even smaller samples and enables new sorts of experiments to become feasible, such as pump-probe and kinetic measurements. I have recently designed a neutron protein crystallography instrument called EWALD for the STS that utilizes a small, high-brightness coupled moderator, that when combined with advances in neutron optics, will deliver 59 times the performance of the MaNDi instrument at SNS. In 2020 I transitioned to a new position at the STS as the Instrument Systems Science and Technology Manager. In my current position, I manage a group of scientists that will design and construct the next generation of neutron instruments at the STS.

a) Coates, L., Sullivan, B. The macromolecular neutron diffractometer at the Spallation Neutron Source. Methods in Enzymology (Book Chapter) DOI: 10.1016/bs.mie.2019.11.020 ISSN: 0076-6879 (2020)

b) Coates, L., Robertson, L. Ewald: An extended wide-angle Laue diffractometer for the second target station of the Spallation Neutron Source (2017) Journal of Applied Crystallography, 50, pp. 1174-1178.

c) Coates, L., Cuneo, M.J., Frost, M.J., He, J., Weiss, K.L., Tomanicek, S.J., McFeeters, H., Vandavasi, V.G., Langan, P., Iverson, E.B. The Macromolecular Neutron Diffractometer MaNDi at the Spallation Neutron Source (2015) Journal of Applied Crystallography, 48, pp. 1302-1306.

d) Coates, L., Tomanicek, S., Schrader, T.E., Weiss, K.L., Ng, J.D., Jüttner, P., Ostermann, A. Cryogenic neutron protein crystallography: Routine methods and potential benefits (2014) Journal of Applied Crystallography, 47 (4), pp. 1431-1434.

2) Recently, we have started to research the Main Protease enzyme from SARS-CoV-2 using a combination of room temperature Neutron and X-ray diffraction, enzyme kinetics, and Molecular dynamics, revealing its structural plasticity and unusual active site protonation states. The main protease from SARS- CoV-2, the etiological agent of COVID-19, is an essential enzyme for viral replication, possessing an unusual catalytic dyad composed of Cys145 and His41 residues. We used neutrons to reveal the fine atomic details present the structure of this cysteine protease as they are an ideal probe for locating hydrogen positions and experimentally determining protonation states at near-physiological temperature. Our observations have provided critical information for structure-assisted and computational drug design, allowing precise tailoring of inhibitors to the enzyme's electrostatic environment.

a) Pavlova, A., Lynch, D.L, Daidone, I., Zanetti-Polzi, L., Smith, M.D., Chipot, C., Kneller, D.W., Kovalevsky, A., Coates, L., Golosov, A.A., Dickson, C.J., Velez-Vega, C., Duca, J.S., Vermaas, J.V., Pang, Y,T., Acharya, A., Parks, J.M., Smith, J.C., Gumbart, G.C., Inhibitor binding influences the protonation states of histidines in SARS-CoV-2 main protease. (2021) Chemical Science DOI: 10.1039/D0SC04942E

b) Kneller, D. W., Phillips, G., Weiss, K.L., Zhang, Q., Coates, L., Kovalevsky, A. Direct Observation of Protonation State Modulation in SARS-CoV-2 Main Protease upon Inhibitor Binding with Neutron Crystallography. (2021) Journal of Medicinal Chemistry **2021** *64* (8), 4991-5000

c) Kneller, D. W., Phillips, G., Kovalevsky, A. & Coates, L. Room-temperature neutron and X-ray data collection of 3CL Mpro from SARS-CoV-2. (2020) Acta Cryst. F76, 483-487.

d) Kneller, D.W., Phillips, G., O'Neill, H.M., Jedrzejczak, R., Stols, L., Langan, P., Joachimiak, A., Coates, L., Kovalevsky. A. Structural plasticity of SARS-CoV-2 3CL Mpro active site cavity revealed by room temperature X-ray crystallography (2020) Nature Communications 11, Article number: 3202

e) Kneller, D.W., Phillips, G., Weiss, K.L., O'Neill, H.M., Pant, S., Zhang, Q., Coates, L., Kovalevsky. A. The unusual zwitterionic catalytic site of SARS-CoV-2 main protease revealed by neutron crystallography. (2020) J. Biol. Chem. 295(50) 17365–17373

3) Ion channels are integral membrane proteins that facilitate the passive diffusion of ions across cellular membranes. Despite initial appearances, ion channels are highly sophisticated systems responsible for controlling heart pace, regulating hormone secretion, and generating the electrical impulses that underly the nervous system. Ion channels are often gated, opening or closing in response to a specific stimulus, such as the binding of a ligand or the sensing of a change in voltage across the membrane. Ion transport is often highly selective and facilitated by a pore within the protein that contains the selectivity filter (SF), which is regulated by a series of hydrophobic gates that alter their conformation to open and close the ion channel. I have used neutrons, hard and soft X-rays to investigate the contents of the selectivity filter in Potassium selective ion channels. While also developing new computational techniques to generate composite omit maps that were crucial in identifying a disordered hydrophobic gate at the bottom of the SF in a potassium selective ion channel.

a) Langan, P. S., Vandavasi, V. G., Kopec, W., Sullivan, B., Afonne, P. V., Weiss, K. L., de Groot, B. L. & Coates, L. The structure of a potassium-selective ion channel reveals a hydrophobic gate regulating ion permeation (2020). IUCrJ 7, 835-843.

b) Coates, L., Ion permeation in potassium ion channels Acta Cryst D 76 Acta Crystallographica Section D: Biological Crystallography (2020) D76, 118-123

c) Langan, P.S., Vandavasi, Sullivan, B., Harp, J., Weiss, K.L., Coates, L., Crystallization of a potassium ion channel and X-ray and neutron data collection. Acta Crystallographica Section:F Structural Biology Communications F75, 435-438 (2019)

d) Langan, P.S., Vandavasi, V.G., Weiss, K.L., Afonine, P.V., Omari, K.E., Duman, R., Wagner, A., Coates, L. Anomalous X-ray Diffraction Studies of Ion Transport in K+ channels. Nature Communications (2018) 9:4540 | DOI: 10.1038/s41467-018-06957-w

4) I have used neutrons, X-rays, NMR, and molecular dynamics to investigate bacterial antibiotic resistance, particularly relating to the breakdown of β-lactam antibiotics by class A β-lactamases. The catalytic mechanism of class A β-lactamases is often debated due in part to the large number of amino acids that interact with bound β-lactam substrates. Neutron protein crystallography provided experimentally determined protonation states of catalytic residues in key reaction intermediates during antibiotic breakdown. At the same time, molecular dynamics allowed us to determine the proton transfer events between static crystallographic structures. This work revealed the structural changes that the catalytic residues undergo upon the binding of a drug molecule into the active site to prime it for enzymatic breakdown of the bound antibiotic.

a) Langan, P.S., Vandavasi, V.G., Cooper, S.J., Weiss, K.L., Ginell, S.L., Parks, J.M., Coates, L. Substrate Binding Induces Conformational Changes in a Class A β-lactamase That Prime It for Catalysis (2018) ACS Catalysis, 8 (3), pp. 2428-2437.

b) Vandavasi, V.G., Langan, P.S., Weiss, K.L., Parks, J.M., Cooper, J.B., Ginell, S.L., Coates, L. Active-site protonation states in an acyl-enzyme intermediate of a class A β-lactamase with a monobactam substrate (2017) Antimicrobial Agents and Chemotherapy, 61 (1), art. no. e01636-16,

c) Vandavasi, V.G., Weiss, K.L., Cooper, J.B., Erskine, P.T., Tomanicek, S.J., Ostermann, A., Schrader, T.E., Ginell, S.L., Coates, L. Exploring the Mechanism of β-Lactam Ring Protonation in the Class A β-lactamase Acylation Mechanism Using Neutron and X-ray Crystallography (2016) Journal of Medicinal Chemistry, 59 (1), pp. 474-479.

d) Tomanicek, S.J., Standaert, R.F., Weiss, K.L., Ostermann, A., Schrader, T.E., Ng, J.D., Coates, L. Neutron and X-ray crystal structures of a perdeuterated enzyme inhibitor complex reveal the catalytic proton network of the Toho-1 β-lactamase for the acylation reaction (2013) Journal of Biological Chemistry, 288 (7), pp. 4715-4722.

5. Finally, I have also used neutron and X-ray crystallography and NMR to investigate the atomic structure and catalytic mechanism of aspartic proteases. A class of enzymes that are involved in numerous disease conditions, including hypertension, amyloid disease, malaria, and AIDS. In HIV, the proteinase is essential for the maturation of the virus particle, and inhibitors have a proven therapeutic effect in treating AIDS. Thus, inhibitors to this class of enzyme with improved characteristics are therefore much sought after as potential therapeutic agents. This work elucidated the protonation of the two catalytic aspartate residues in the active site and revealed the presence of a low barrier hydrogen bond within the active site of the enzyme that was confirmed by NMR and high-resolution X-ray crystallography.

a) Coates, L., Tuan, H.-F., Tomanicek, S., Kovalevsky, A., Mustyakimov, M., Erskine, P., Cooper, J. The catalytic mechanism of an aspartic proteinase explored with neutron and X-ray diffraction (2008) Journal of the American Chemical Society, 130 (23), pp. 7235-7237.

b) Tuan, H.-F., Erskine, P., Langan, P., Cooper, J., Coates, L. Preliminary neutron and ultrahigh-resolution X-ray diffraction studies of the aspartic proteinase endothiapepsin cocrystallized with a gem-diol inhibitor (2007) Acta Crystallographica Section F: Structural Biology and Crystallization Communications, 63 (12), pp. 1080-1083.

c) Coates, L., Erskine, P.T., Crump, M.P., Wood, S.P., Cooper, J.B. Five atomic resolution structures of endothiapepsin inhibitor complexes: Implications for the aspartic proteinase mechanism (2002) Journal of Molecular Biology, 318 (5), pp. 1405-1415.

d) Coates, L., Erskine, P.T., Wood, S.P., Myles, D.A.A., Cooper, J.B. A neutron laue diffraction study of endothiapepsin: Implications for the aspartic proteinase mechanism (2001) Biochemistry, 40 (44), pp. 13149-13157.

D. Additional Information: Research Support

Current Research Support:

National Institute of General Medical Sciences R01 5R01GM071939, Coates (PI) 4/1/2020 to present
Computational Tools for Neutron Protein Crystallography

Completed Research Support:

Seed Money, Fund Oak Ridge National Lab, Coates (PI) 6/1/2015 to 10/1/2017
Overcoming Antibiotic Resistance: Neutron crystallographic and quantum chemical studies of a beta lactamase enzyme. This project combined Quantum mechanical simulations and neutron crystallography to study antibiotic breakdown.
Role: PI