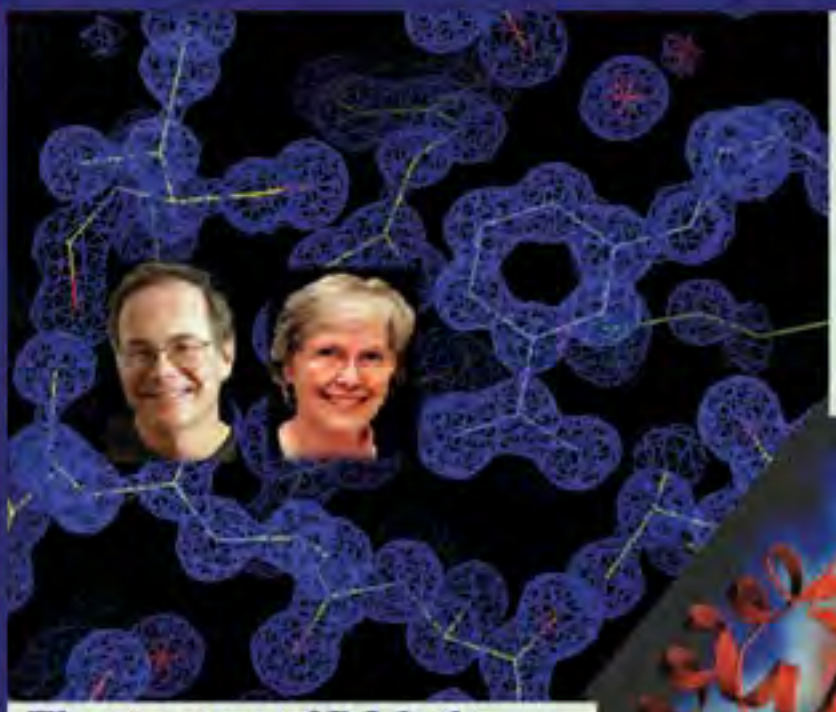
ACA RefleXions

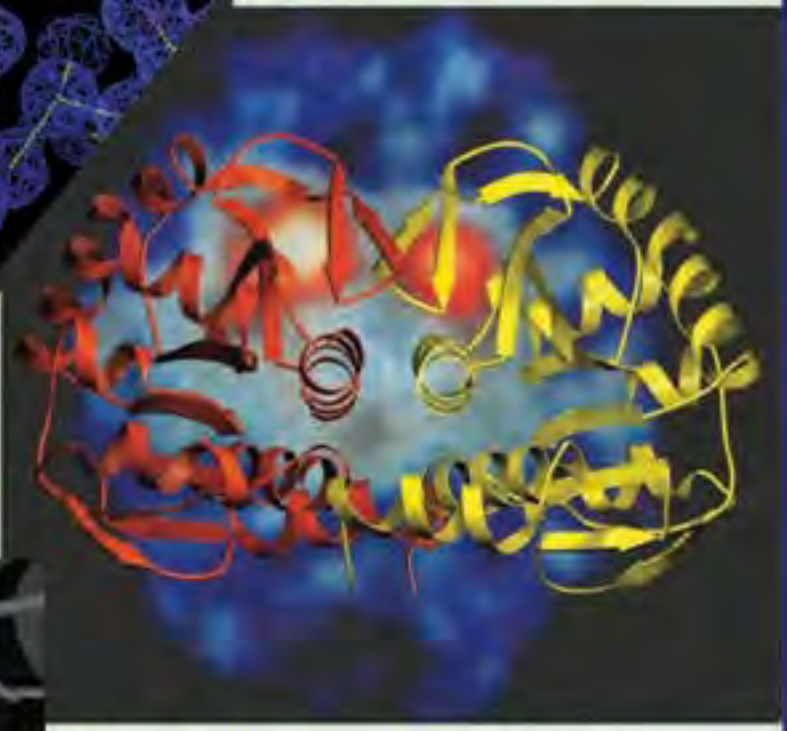
American Crystallographic Association
Structure Matters

Number 1

Spring, 2015



Greg Petsko and his collaborator for the last 35 years, Dagmar Ringe, with the ultrahigh resolution electron density map of amino peptidase A.



The structure of DJ-1, the protein associated with Parkinson's disease, superimposed on a PET scan of the brain of a Parkinson's patient.

At left, the active site of cytochrome P450cam with its substrate camphor colored green. The activated oxygen intermediate of the P450 reaction is depicted in the flame in the center.

Buerger Award at Philadelphia ACA Meeting

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ACA RefleXions

ACA - Structure Matters

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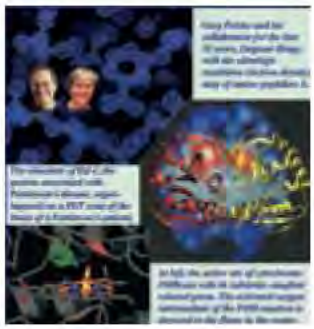
Table of Contents

To Be Honored in Philadelphia

Laurence Marks
Warren Award

Greg Petsko
Buerger Award

Jan Zhang
Etter Early Career Award



What's on the Cover
Page 6

Contributions to ***ACA RefleXions*** may be sent to either of the *Editors*:

Judith L. Flippen-Anderson ..... acareflexions@gmail.com

Thomas F. Koetzle ..... tkoetzle@aol.com

Cover:	Connie Rajnak	Art in Science:	Edgar Meyer
Historian:	Virginia Pett	Book Reviews:	Joe Ferrara
Photographer:	Peter Müller	Net RefleXions:	Amy Sarjeant
Copy Editing:	Jane Griffin	News & Awards:	Chiara Pastore
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Please address matters pertaining to advertisements, membership inquiries, or use of the ACA mailing list to:

Marcia J. Colquhoun, Director of Administrative Services
American Crystallographic Association
P.O. Box 96, Ellicott Station
Buffalo, NY 14205
tel: 716-898-8692; fax: 716-898-8695
marcia@hwi.buffalo.edu

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President's Column

It is indeed an honor to pen my first column as President of the ACA. It is both an exciting and challenging time for ACA, and I am thrilled at the opportunity to help steer the society forward. Of course, none of that would be possible without the tireless efforts of our staff in Buffalo, for which Council and the entire ACA are grateful. Council bids farewell to Cheryl Stevens (Past President), Patrick Loll (Secretary) and Eric Montemayor, who served as our second Young Scientist Scientific Interest Group representative to Council. Eric made invaluable contributions with his perspective on and network of early career crystallographers – the future of our society. Council also welcomes three new members in their place: Tom Terwilliger (Vice President), Diana Tomchick (Secretary) and Yulia Sevryugina (YSSIG Rep).

Among the many exciting events on deck for 2015, we also begin the post-International Year of Crystallography era. I think we can all agree that IYCr was a tremendous success and that we enjoyed a wonderful year of science and education. As such, we need to endeavor to keep the momentum of the IYCr going as we look toward the future. Two resources for this are worth noting – our own ACA website: ***http://www.iycr2014.org/aca/home***, wherein resources have been amassed over the past year and folks are welcome to continue contributions, as well as the International Union of Crystallography's IYCr Legacy site: ***http://iycr2014.org/legacy***. The future of the latter will no doubt be discussed at length at the "Crystallography for the Next Generation: The Legacy of the IYCr" conference in Rabat, Morocco, April 23-24, 2015. The ACA clearly sees the value in maintaining accessible archives of the outstanding resources IYCr has generated. Finally, a third resource that ACA has been operating independently of IYCr activities is of course our own History Portal: ***http://www.amercrystalassn.org/history_home***. If you have not yet explored this resource – drop what you are doing and do so. This is an amazing collection of our history as a society and as a discipline. Virgina Pett deserves a world of thanks for her efforts on this.

July 2015 will of course have our Annual Meeting in Philadelphia. The SIGs have proposed an outstanding program, and Chairs Louise Dawe and Kraig Wheeler have developed a very rich schedule. Past President Martha Teeter has already highlighted a number of interesting sessions and activities that have a particular focus on education (see President's Column, Winter *RefleXions*). I would like to reiterate some thoughts in that regard to encourage making the implicit educational activities at our meetings more explicit, and to do this at the planning stages. Why make this comment? Well, this brings me to one of our first challenges/opportunities. We all need to give some thought as to what we wish to experience at and as a result of our annual meetings. One thing the meetings have always done rather well is to educate our membership across generations and career stages. I think you will agree that doing that even better will be a good thing, and one step in that direction is to increase our awareness of the educational components of our mission. Thus, as SIGs consider topics for future meetings, keep in mind opportunities for proposing purely educational and/or tutorial sessions beyond strictly the workshop format. Moreover, this 'awareness' is by no means at the expense of our scientific content. Quite the opposite, as I see a synergy here that can be made even more effective. And while I have you on meetings, Council would love to get some more feedback from our membership – both in terms of the meetings themselves, and also with regard to ACA services and offerings in general. We have asked for feedback in the past as part of our strategic planning efforts. The next request will come via a survey card in your Philadelphia registration packet – coupled to a raffle to encourage you to respond.

I would like to shift gears a bit (yet not entirely!) and make a few comments on our relationship with the American Institute of Physics. As you know, the ACA is a Member Society of the AIP. This relationship is perhaps transparent to the average member (save for receiving *Physics Today* and vendor services at meetings), yet this brings us to another potential opportunity. The AIP has recently undergone a major overhaul of its bylaws and governance structure, the details of which are beyond the scope of this column, yet in sum, we now have an ACA Director (Charlie Carter) on the newly restructured AIP Board of Directors. In terms of function, this board essentially parallels for AIP what ACA Council does for ACA – finances, auditing, membership, etc. Directors are appointed for three-year terms and may be appointed to two consecutive terms after which they would have to leave the Board for at least one year. Charlie was President of the ACA in 2002. We now also have a "Named Representative" from the ACA who will attend meetings of the AIP Corporation and vote on various issues as required. At present yours truly is this individual, yet Council agreed that going forward this position will be held by an incoming Vice President for the three years he/she is on Council.

What does this mean for the ACA going forward? In some respects this remains to be seen, yet AIP has made it clear that they wish to provide an enhanced value to us as a member society. Discussions are ongoing, yet here is another opportunity to be thinking about what one hopes to 'get' from their society and how the parent can contribute. You will have an opportunity to chime in on your survey card in Philly.

Turning to *Structural Dynamics*, ACA's peer-reviewed, open access journal (see ***http://sd.aip.org***), all I can say is 'Wow.' Things are off to a great start and are moving quickly. I encourage you to check out their ad on pp. 16-18 in this issue of *RefleXions*, where you will find some impressive statistics on downloads and time-to-publish. Moreover, *SD* has some impressive plans coming down the pike for special issues. In addition to reading the exciting articles, let me encourage you to submit as well!

Finally, let me remind everyone that nominations for the 2016 Etter, Trueblood, Bau and Fankuchen awards are due April 1. Please see the awards descriptions on the ACA Awards page (***http://www.amercrystalassn.org/content/pages/main-awards-prizes***) and consider supporting a deserving colleague.

Thanks for reading.

Chris Cahill

RefleXions from Canada

There will be several regional meetings organized at various locations in Canada in 2015. The first one that I would like to mention is the 3rd Annual Meeting of the Protein Structure, Function and Malfunction (PSFaM) two-day symposium that is to be held at the Canadian Light Source (CLS) in Saskatoon, Saskatchewan on May 7-8, 2015. An excellent list of invited speakers should draw a large audience to this meeting. The Keynote Speakers include: So Iwata, Imperial College, London; Hans Vogel, University of Calgary; Marek Michalak, University of Alberta; and Marius Schmidt, University of Wisconsin, Milwaukee. There is a panel of 9 other speakers from the 3 prairie provinces of Canada: Manitoba, Saskatchewan, and Alberta. There will also be oral and poster presentations featuring the work of graduate students and post-doctoral fellows. More information on the PSFaM meeting, along with a complete list of the invited speakers, can be found on the website: ***http://cmcf.lightsource.ca/psfam/***.

Shortly after the PSFaM Meeting there will be a workshop on the diffraction methods of X-ray crystallography associated with the 98th Meeting of the Chemical Society of Canada (CSC) to be held in Ottawa, June 13-17, 2015. This workshop will be the 6th Canadian Chemical Crystallography Workshop (CCCW); it will take place during the week preceding the CSC meeting on June 8-12, 2015. The 2015 version is being organized by Ilia Korobkov at the University of Ottawa; dates and details can be found at the website: ***http://www.canadiancrystallraphy.ca/cccw15/index.html***.

The third meeting that I would like to draw readers' attention to is the 24th Annual Meeting of the Buffalo, Hamilton and Toronto (BHT) crowd. This year the organizing committee consists of Jeff Lee from the University of Toronto and Jean-Philippe Julien from the Sick Children's Hospital, Toronto. Gerald Audette and Vivian Saridakis of York University have developed the Scientific Program. The date for the 2015 BHT Meeting will be Friday November 6, and it will be held in Hamilton, Ontario at McMaster University. The keynote speaker and his/her presentation will be on the following website: ***https://bht.research.sickkids.ca/*** when it has been finalized.

Next, for this issue, I would like to highlight briefly the contributions to structural biology made by two laboratories in Canada, one from central Canada and the other from western Canada.

Alba Guarné

Alba Guarné's lab is in the Department of Biochemistry and Biomedical Sciences at McMaster University, Hamilton, Ontario. Alba studied for her PhD in Barcelona and then did a post-doctoral stint with Wei Yang at the NIH. It was at the NIH that Alba developed her interests in DNA and the proteins that regulate its intricate repair processes after faulty replication and in the processes of regulation of DNA replication in bacteria and in eukaryotes. In addition to the roles that various proteins have in the regulation of DNA replication, the very important function of correcting DNA polymerase errors in newly replicated DNA is one highlight of the research ongoing in her laboratory. Alba and her colleagues have determined the structure of one of the key proteins involved in the DNA mismatch repair pathway, MutL. It is a multidomain, hence a multifunction, protein that mediates several key functions including mismatch recognition, mutated strand recognition and removal. Fig. 1 portrays the

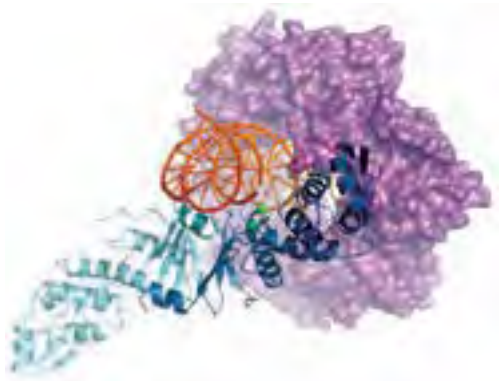


Fig. 1. The sliding β-clamp (PDB ID: 3BEP) bound to DNA activates MutL (PDB ID: 3KDK) by threading the DNA onto the MutL endonuclease active site. This figure represents a model of the complex between MutL (blue ribbon) and the sliding β-clamp (purple surface) in the presence of DNA (orange ribbons). The model was generated from the docking of the crystal structures of the endonuclease domain of MutL to the sliding β-clamp bound to DNA and adjusted with small angle X-ray scattering data of the MutL: clamp complex and biochemical and genetic data that identified the active site residues as well as the divalent metal ion (spheres) requirements of the reaction.

interactions of MutL, DNA, and the sliding β-clamp (structure determined in the lab of John Kuriyan, PDB ID: 3BEP). This model was developed in the Guarné laboratory by the application of protein crystallography and small angle X-ray scattering experiments coupled with biochemical and genetic data that identified the residues defining the MutL endonuclease active site. Future studies of mismatch repair in the Guarné lab are aimed at understanding how MutL coordinates this mismatch repair protein with the DNA replication proteins. One can read more about Alba's research on her informative website: ***http://www.fhs.mcmaster.ca/biochem/guarne_alba.html***.

The second laboratory that I would like to feature in this short article is that of Natalie Strynadka in the Department of Biochemistry and Molecular Biology at the University of British Columbia, Vancouver, BC. Natalie received her PhD at the University of Alberta. She was a post-doctoral fellow in the laboratory of Susan Jensen, also at the University of Alberta, where Natalie developed her passion for the study of antibiotic resistance and the development of novel antibiotics against bacteria. Natalie's research focuses on three distinct areas, each one hopefully leading to a successful combatant against bacterial resistance to

Natalie Strynadka

current antibiotic regimens and/or to the development of new antibiotics. Recent work in the Strynadka laboratory includes the determination of the structure of the plasmid-mediated New Delhi metallo-β-lactamase (NDM-1) bound to several of the β-lactam antibiotic substrates that it rapidly degrades. This research has elucidated the substrate specificity of NDM-1 and is leading the way for the design of new classes of antibiotics. A second accomplishment of the lab is the structure determination of the multifunctional membrane-spanning penicillin-binding protein 2a (PBP2a) from the "superbug" Methicillin-resistant Staphylococcus aureus (MRSA). PBP2a has a low affinity for β-lactam antibiotics so its transpeptidase activity remains high even at the penicillin or cephalosporin concentrations that inhibit other transpeptidases of the bacterial cell wall synthetic enzymes. This structural work is being used to augment the development of new potential antibiotics aimed at PBP2a and therefore in combating MRSA infections.

The Stynadka lab is also leading the way in the structural elucidation of the molecular details comprising the complex type III secretion system (T3SS) present in many pathogenic Gram-negative bacteria. These protein complexes or injectisomes (Fig. 2) consist of approximately 24 unique proteins that combine

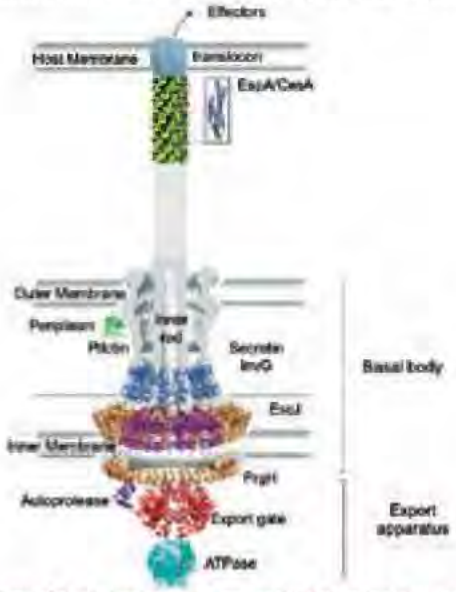


Fig. 2. A view of the injectisome as presently determined by members of the Strynadka lab. Energy for "injecting" toxins through the needle-like syringe is presumably generated by the ATPase in the export apparatus. The effector pathogens pass through the inner membrane and the outer membrane of the pathogenic bacterium and then through the molecular needle where they are secreted through a pore-forming complex (translocon) into the host cell.

their functions to "inject", in a syringe-like manner, virulent toxic proteins into the host cytoplasm. The T3SS apparatus is thus an excellent target for the design of antibacterial drugs. Natalie's lab has combined a variety of physical techniques, X-ray crystallography, NMR spectroscopy, cryo-electron microscopy and mass spectroscopy with Rosetta-based molecular modeling to come up with the current molecular model of the massive multi-membrane-spanning complex, shown in Fig. 2. Further details into the research ongoing in Natalie's lab can be found on her webpage: *www.strynadkalab.biochem.ubc.ca*.

Michael James

Highlights from 2014 Fall ACA Council Meeting

The 2014 Fall Council Meeting was held at Hauptmann-Woodward Institute in Buffalo, NY on October 15. Much discussion revolved around the role that ACA should play in the future of science and how it should serve crystallographers in North America and internationally.

Earlier in the year the membership was contacted electronically about the subject of strategic planning for ACA. Responses to this survey were discussed, and suggestions to obtain additional input from members included meetings between the Strategic Planning Committee and ACA members at the 65th Annual Meeting in Philadelphia, July 25-29, 2015. Many of the responses obtained both electronically and by personal contact emphasized that ACA should begin to shift focus to educational and career opportunities for young crystallographers. In fact, this shift may be occurring naturally, as evidenced by the number of workshops (four) and sessions (five) to be devoted to these topics at the Philadelphia meeting. Potential future ACA annual meeting locations discussed included the Canadian locations of Banff and Toronto.

Outreach to the scientific community and to the general public is also an important function of ACA. President Martha Teeter noted that the *Crystallography and Sustainability* Transactions Symposium at this year's ACA meeting, organized by Cora Lind-Kovacs and Robin Rogers, may provide material for crystallographers to talk about the impact of crystallography today. Council agreed that this information should be disseminated widely. IUCr representative Hanna Dabkowska noted that a summary could be posted on the IUCr website.

Speaking of the 2015 ACA meeting, the Young Scientists Special Interest Group (YSSIG) Council Representative Eric Montemayor reported that YSSIG would have 16 sponsored and co-sponsored sessions in Philadelphia, including new topics on Diversity and Career Development. They are looking forward to a well-funded and well-attended YSSIG mixer, a central part of the young scientist experience at the meeting. YSSIG has looked into the idea of having a non-traditional (i.e., less expensive for attendees) meeting in years that IUCr meets.

Amadeo Biter and Kimberly Stanek, with assistance from Eric Montemayor, have volunteered to provide regular contributions to a YSSIG Page in the *RefleXions*, which should also include updates on projects such as high-school outreach activities, many of which were tied to the International Year of Crystallography 2014 (IYCr2014). Martha Teeter submitted a detailed report from the *Ad Hoc* Task Force on the IYCr of activities held in the US and Canada in 2014, including workshops, exhibitions, symposia and web events. Many events were supported in part by ACA. The task force recommended continuing several of these events, including the US Crystal Growing Contest and interactions of ACA members with schools using models developed during IYCr. The task force also hopes to make available outreach materials highlighting the importance of crystallography, tailored for community and political leaders, and to support synchrotron outreach events in the International Year of Light 2015.

Vice President Chris Cahill reported on discussions with the Leadership Team of the American Institute of Physics (AIP), the federation of physical science societies, including ACA. Many points were made about how could ACA best exploit the resources available through AIP, including media services at annual meetings, assistance with logistics, and archiving of historical materials. Chris stressed that the potential exists for a new and different relationship between ACA and its parent organization. During the Executive Officer/Headquarters' report, Bill Duax provided additional historical context on the relationship between AIP and ACA. He noted that if AIP approves their new governance structure, it will involve the appointment of an ACA Representative who will cast the ACA's vote at all meetings of the AIP Corporation. ACA will also have a seat on the AIP Board of Directors (currently held by Charlie Carter). Bill also outlined the accounting being performed at the headquarters relating tasks performed to specific revenue streams; an updated report will be provided at the Spring 2015 Council meeting.

Michael James, the Canadian Representative, participated in the meeting via videoconference. The biggest thing to happen in Canada in 2014 was the 23rd Congress and General Assembly of the International Union of Crystallography (Montréal, Quebec, August 5-12, 2014). There were about 2,100 attendees (including 205 registrants from Canada), and the co-chairs for the Congress were Mirek Cygler (University of Saskatchewan) and Albert Berghuis (McGill University). The highlights of the Congress were two microsymposia, *Enzymes* and *Macromolecular Machines*, dedicated to the memory of Louis Delbaere, which included many excellent talks and were well attended. Michael reported that the National Research Council of Canada is relinquishing responsibility for the Canadian National Committee for Crystallography (CNCCr) and the transfer to the Canadian Light Source is in progress. He participated in a teleconference of Canadian crystallographers concerning the future roles of the CNCCr; possibilities suggested included the organization of workshops and regional meetings. There was much discussion concerning retaining the affiliation with ACA, versus forming a Canadian organization that would interact with ACA as a North American Association similar to those found in Europe and Asia. To foster a sense of heightened inclusion with ACA, some participants voiced the desire to have one annual meeting in five held in Canada and to have more educational topics presented at the annual meeting.

Last, but not least, considerable thanks are due to the services of the outgoing ACA officers: Martha Teeter as President and Patrick Loll, who served as Secretary for three years.

Diana Tomchick

Contributors to this Issue

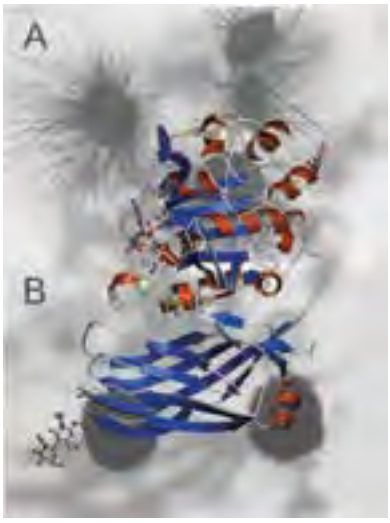
Cele Abad-Zapatero, Jason Benedict, Amadeo Biter, Charlie Bugg, Chris Cahill, Majed Chergui, Grace Chik, Bridget D'Amelio, Joe Ferrara, Ana Ferreras, Frank Fronczek, Allyson Fry, Ilia Guzei, Michael James, Matthew McGrath, Jason Mercer, Caitlin Murphy, Peter Müller, Joe Ng, Chiara Pastore, Greg Petsko, Virginia Pett, Connie Rajnak, Amy Sarjeant, Yulia Sevryugina, Cherie Shleifer, Paul Swepston, Brian Toby, Diana Tomchick

Gregory Petsko, Gyula and Katica Tauber Professor of Biochemistry and Chemistry Emeritus at Brandeis University, and Adjunct Professor in the Department of Neurology and Center for Neurologic Diseases at Harvard Medical School and Brigham & Women's Hospital is to be presented with the **Buerger Award** at the ACA Annual Meeting in Philadelphia in July.

Greg supplied the three images shown on the cover as well as the image at below right.

Top: Greg Petsko and his collaborator for the last 35 years, Dagmar Ringe, with the ultrahigh resolution electron density map of amino peptidase A. – Petsko has spent virtually his entire scientific career in partnership with Ringe, and states that nearly everything for which he is best known has been done in collaboration with her, and that their 35 year professional association has been the high point of his scientific life.

Middle: The structure of the Parkinson's disease-associated protein DJ-1, superimposed on a PET scan of the brain of a Parkinson's patient. – Mutations in this protein cause autosomal recessive disease, and the structure, determined by postdoc Mark Wilson[1], has proven of great value in understanding the function of the protein and how the mutations affect its function. This was the first structure of any protein directly connected with either Parkinson's or Alzheimer's disease.



Bottom: The active site of cytochrome P450cam with its substrate camphor colored green. The activated oxygen intermediate of the P450 reaction is depicted in the flame in the center. – This enzyme is, in the words of the noted mechanistic enzymologist George Kenyon, the biological equivalent of a blowtorch. The structure was determined by postdoc Ilme Schlichting[2] as part of a project that led to structures for every kinetically-significant intermediate in the reaction pathway of this enzyme, what Petsko and Ringe call the culmination of decades of their work on structural enzymology.

At Right: The structure of the pro hormone processing enzyme Kex2[3]. **–** The structure was solved by Dagmar Ringe and her postdoc Todd Holyoak in collaboration with Robert Fuller of the University of Michigan. The enzyme, discovered by Jeremy Thorner of the University of California, Berkeley, is the archetypal member of the mammalian burin family that is responsible for maturation of many critical hormones. The structure revealed the basis for its dibasic residue specificity and calcium ion dependence. The structure is shown superimposed on an image of the filamentous growth state of the pathogenic fungus *Candida albicans*, for which Kex2 is a virulence factor (A), and the non-filamentous state produced by deletion of the gene (B).

References:

[1] The 1.1-Å resolution crystal structure of DJ-1, the protein mutated in autosomal recessive early onset Parkinson's disease, by Mark A. Wilson, Jennifer L. Collins, Yaacov Hod, Dagmar Ringe, and Gregory A. Petsko. *Proc Natl Acad Sci USA*, **2003**, *100*, 9256-61.

[2] The catalytic pathway of cytochrome p450cam at atomic resolution, by Ilme Schlichting, Joel Berendzen, Kelvin Chu, Ann M. Stock, Shelley A. Maves, David E. Benson, Robert M. Sweet, Dagmar Ringe, Gregory A. Petsko, and Stephen G. Sligar. *Science*, **2000**, *287*, 1615-22.

[3] 2.4 Å resolution crystal structure of the prototypical hormone-processing protease Kex2 in complex with an Ala-Lys-Arg boronic acid inhibitor by Todd Holyoak, Mark A. Wilson, Timothy D. Fenn, Charles A. Kettner, Gregory A. Petsko, Robert S. Fuller, and Dagmar Ringe. *Biochemistry*, **2003**, *42*, 6709-18.

PANalytical Award Supports Young Scientists

PANalytical is one of the world's leading suppliers of analytical X-ray instrumentation and software. The company seeks to reward early-career scientists who have demonstrated innovative thought to their research when using an X-ray analytical technique with a $5,000 prize. The Award in 2012 went to Thomas Bennett (UK). Ana Cuesta (Spain) received the 2013 Award for her investigation of yeelimite, the most important phase in calcium sulfoaluminate cements.

The winner of the 2014 Award will be decided in early 2015 by a selection committee that includes established research scientists unaffiliated to PANalytical. Submissions for the 2015 Award will be possible from June 1, 2015 with a deadline of **December 1, 2015** (see: ***www.panalytical.com/award***). Applicants must publish a paper during the period January 1, 2014 – December 1, 2015 that demonstrates ground-breaking thinking in a topical field. There are no restrictions on the manufacturer of the X-ray equipment used. Questions can be addressed to ***award@panalytical.com***.

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PRESIDENT

Christopher Cahill

Dept of Chemistry
George Washington Univ
725 21st St, NW
Washington, DC20052
cahill@gwu.edu

VICE PRESIDENT

Tom Terwilliger

Los Alamos National Lab
MS M888
Los Alamos, NM 87545
terwilliger@lanl.gov

PAST PRESIDENT

Martha Teeter

2540 Bombadil Lane
Davis, CA 95616
teeter@ucdavis.edu

SECRETARY

Diana Tomchick

Dept of Biophysics
Univ of Texas
SW Medical Center
500 Kingston Dr
Irving, TX 70561
diana.tomchick@utsouthwestern.edu

TREASURER

James Kaduk

Biological & Chemical Sciences
Illinois Inst of Technology
Naperville, IL 60540
kaduk@polycrystallography.com

CANADIAN REPRESENTATIVE

Michael James

Dept of Biochemistry
Univ of Alberta
Edmonton, AB T6G 2H7
Canada
michael.james@ualberta.ca

CHIEF FINANCIAL OFFICER

S.N. Rao

4507 E Chuckwalla Cyn
Phoenix, AZ 85044
azrao4507@gmail.com

IUCr REPRESENTATIVE

Hanna Dabkowska

McMaster Univ
Hamilton, ON L8S 4M1
Canada
dabkoh@mcmaster.ca

YSSIG REPRESENTATIVE

Yulia Sevryugina

Dept of Chemistry
Texan Christian Univ
TCU Box 298860
Fort Worth, TX 76129
y.sevryugina@tcu.edu

CHIEF EXECUTIVE OFFICER

William Duax

H. A. Hauptman Distinguished Scientist, Hauptman-Woodward Medical Research Institute
Buffalo, NY 14203
duax@hwi.buffalo.edu

DIRECTOR OF ADMINISTRATIVE SERVICES

Marcia Colquhoun

ACA, P. O. Box 96, Ellicott Station
Buffalo, NY 14205
716 898-8692
Fax: 716 898-8695
marcia@hwi.buffalo.edu

BOOKKEEPER

Jessica Addiss

ACA, Buffalo, NY 14205
716 898-8693
jaddiss@hwi.buffalo.edu

MEMBERSHIP SECRETARY

Kristina Vitale

ACA, Buffalo, NY 14205
716 898-8600
kvitale@hwi.buffalo.edu

CANADIAN DIVISION OFFICERS

Louise Dawe, Chair, 2014-2015

Chemistry Science Bldg
Wilfred Laurier Univ
75 University Ave W
Waterloo, ON N2L 3C5
ldawe@wlu.ca

Brian Patrick, Secretary, 2013-2014

Dept of Chemistry
Univ of British Columbia
2036 Main Mall
Vancouver, BC V6T 1Z1
bpatrick@chem.ubc.ca

CO-EDITORS

Judith Flippen-Anderson
acareflexions@gmail.com

Thomas Koetzle
tkoetzle@aol.com

STAFF

Photographer
Peter Müller
Dept of Chemistry
MIT
Cambridge, MA 02139
pmueller@mit.edu

Book Reviews
Joe Ferrara
Rigaku Americas Corp
9909 New Trails Dr
The Woodlands, TX
77381
joseph.ferrara@rigaku.com

Cover
Connie Rajnak
conniechidester@earth-link.net

Historian
Virginia Pett
Emerita,
College of Wooster
Wooster, OH 44691
pett@wooster.edu

Art in Science
Edgar Meyer
Emeritus,
Texas A&M Univ
Taos, NM 87571
model_em@yahoo.com
http://molecular-sculpture.com

Puzzle Corner
Frank Fronczek
Chemistry Dept
Lousiana State Univ
Baton Rouge, LA 70803
ffroncz@lsu.edu

Net RefleXions
Amy Sarjeant
Dept of Chemistry
Northwestern Univ
Evanston, IL 60208
asarjeant@northwestern.edu

News & Awards
Chiara Pastore
Imperial College
London, UK
chiara.pastore@
googlemail.com

Copy Editing
Jane Griffin
Dept of Structural Biology
H-W MRI
Buffalo, NY 14203
griffin@hwi.buffalo.edu

Nominations for 2015

ACA Awards: Nominations for the **Bau, Fankuchen,Trueblood, and Etter Early Career** awards are due by April 1, 2015.

ACA Offices and Committees: In fall 2015 we will elect a new ACA Vice President and Treasurer, and one person to each of the ACA Standing Committees (Continuing Education, Communications, and Data, Standards & Computing). To suggest a candidate for one of the above positions, please contact a member of the Nominating Committee: **Louise Dawe: ldawe@wlu.ca**, **Ward Smith: smithwar@nigms.nih.gov** and **Martha Teeter: teeter@ucdavis.edu**. Full details describing the criteria for all ACA awards and offices can be found on the website.

2015 Dues are Due: Please renew promptly and remember to support your favorite ACA Award Funds.

NOTE: It is now possible to renew online.

ACA website: www.AmerCrystalAssn.org

Send all nominations to: marcia@hwi.buffalo.edu

Communications

Edward Snell (12-15)
Structural Biology
Hauptman-Woodward MRI
Buffalo, NY 14203
esnell@hwi.buffalo.edu

Graciela Diaz de Delgado (13-16)
Departamento de Química
Facultad de Ciencias
Universidad de Los Andes
Mérida, Venezuela
gdiazdedelgado@gmail.com

Ilya Guzei (14-17)
Dept of Chemistry
Univ of Wisconsin - Madison
Madison, WI 53558
iguzei@chem.wisc.edu

Katrina Forest (15-18)
Dept of Bacteriology
Univ of Wisconsin - Madison
Madison, WI 53706
forest@bact.wisc.edu

Continuing Education

Amy Sarjeant, (12-15)
Dept of Chemistry
Northwestern Univ
Evanston, IL 60208
asarjeant@northwestern.edu

Kraig Wheeler, (13-16)
Dept of Chemistry
Eastern Illinois Univ
Charleston, IL 61920
kawheeler@eiu.edu

Edward Collins (14-17)
Microbiology & Immunology
Univ of North Carolina
Chapel Hill, NC 27599
edward_collins@med.unc.edu

Andy Howard (15-18)
Biological & Chemical Sciences
Illinois Inst of Technology
Chicago, IL 60616
howard@iit.edu

Data, Standards & Computing

John Westbrook (12-15)
Dept of Chemistry
Rutgers Univ
Piscataway, NJ 08854
jwest@rcsb.rutgers.edu

Peter Müller (14-17)
Dept of Chemistry
MIT
Cambridge, MA 02139
pmueller@mit.edu

Tom Terwilliger (13-16)
Los Alamos National Lab
MS M888
Los Alamos, NM 87545
terwilliger@lanl.gov

Stephen Burley (15-18)
Center for Integrative Proteomics Research
Rutgers State Univ of New Jersey
Piscataway, NJ 08854
sburley@proteomics.rutgers.edu

SCIENTIFIC INTEREST GROUP OFFICERS - 2015

Biological Macromolecules

Susan Buchanan, Chair
Lab of Molecular Biology
NIDDK/NIH
Bethesda, MD 20892
skbuchan@helix.nih.gov

Barry Finzel, Chair-elect
Medicinal Chemistry
Univ of Minnesota
Minneapolis, MN 55455
barry_finzel@yahoo.com

Blaine Mooers, Secretary
Biochemistry & Molecular Biology
Univ of Oklahoma
Oklahoma City, OK 73104
blaine-mooers@ouhsc.edu

General Interest

Stacey Smith, Chair
Dept of Chemistry & Biochemistry
Brigham Young Univ
Provo, UT 84602
ssmith@chem.byu.edu

Graciela Diaz de Delgado, Chair-elect
Quimica - Fac de Ciencias
Univ de Los Andes-Venezuela
Edif A La Hechicera
Merida 5101 Venezuela
ssmith@chem.byu.edu

Jason Mercer, Secretary
48 Nichole Cres
Kitchener, ON N2E 2Z3 Canada
jason.mercer@gmail.com

Fiber Diffraction

Joseph Orgel, Chair
Pritzker Institute
Illinois Inst. of Technology
Chicago, IL 60616
orgel@iit.edu

Paul Langan, Chair-elect
Oak Ridge National Lab
P O Box 2008 MS6475
Oak Ridge, TN 37831
langanpa@ornl.gov

Rama Madurapantula, Secretary
Dept of Biology
Illinois Inst of Technology
Chicago, IL 60616
rmadhura@hawk.itt.edu

Industrial

Peter Wood, Chair
CCDC
12 Union Rd
Cambridge CB2 1EZ UK
secretary@ccdc.cam.ac.uk

Eugene Cheung, Chair-elect
Amgen Inc.
360 Binney St
Cambridge, MA 02142
eugene.cheung@amgen.com

Mark Oliveira, Secretary
Alkermes, Inc
852 Winter St
Waltham, MA 02451
mark.oliveira@alkermes.com

Light Source

Marian Szebenyi, Chair
MacCHESS
Cornell Univ
Ithaca, NY 14853
dms35@cornell.edu

Allen Orville, Chair-elect
Photon Sciences, Bldg 475
Brookhaven National Laboratory
Upton, NY 11973
amorv@bnl.gov

Corie Ralston, Past-chair
Lawrence Berkeley National Lab
Berkeley Center for Structural Biology
Berkeley, CA 94720
cyralston@lbl.gov

Neutron Scattering

Anna Llobet, Chair
Lujan Neutron Scattering Center
Los Alamos National Lab
Los Alamos, NM 87501
allobet@lanl.gov

William Ratcliff, Chair-elect
NCNR NIST
100 Bureau Dr MS 6102
Gaithersburg, MD 20899
william.ratcliff@nist.gov

Huibo Cao, Past-chair
Quantum Condensed Matter Division
Oak Ridge National Lab
Oak Ridge, TN 37831
caoh@ornl.gov

Materials Science

Simon Billinge, Chair
Applied Physics & Applied Math
Columbia Univ
New York, NY 10027
sb2896@columbia.edu

James Nielsen, Chair-elect
Dept of Chemistry
Colorado State Univ
Fort Collins, CO 80523
james.neilson@colostate.edu

Tyrel McQueen, Past-chair
Chemistry, Physics & Astronomy
The Johns Hopkins Univ
Baltimore, MD 21218
mcqueen@jhu.edu

Powder Diffraction

Craig Brown, Chair
NIST
MS 6102
Gaithersburg, MD 20899
craig.brown@nist.gov

Tiffany Kinnibrugh, Chair-elect
Willowbrook, IL 60527
kinnibrught@gmail.com

Michael Lufaso, Past-chair
Dept of Chemistry
Univ of North Florida
Jacksonville, FL 32224
michael.lufaso@unf.edu

Service Crystallography

Bruce Noll, Chair
Bruker AXS
5465 East Cheryl Parkway
Madison, WI 53711
bruce.noll@gmail.com

Victor Young, Chair-elect
Dept. of Chemistry
Univ of Minnesota
Minneapolis MN 55455
vyoung@umn.edu

Stacey Smith, Secretary
Dept of Chemistry & Biochemistry
Brigham Young Univ
Provo, UT 84602
ssmith@chem.byu.edu

Small Molecules

Christine Beavers, Chair
Advanced Light Source
Lawrence Berkeley National Lab
Berkeley, CA 94720
cmbeavers@lbl.gov

Yulia Sevryugina, Chair-elect
Advanced Light Source
Lawrence Berkeley National Lab
Berkeley, CA 94720
cmbeavers@lbl.gov

Louise Dawe, Secretary
Chemistry Science Building
Wilfred Laurier Univ
Waterloo, ON N2L 3C5 Canada
ldawe@wlu.edu

Small Angle Scattering

Shuo Qian, Chair
Biology & Soft Matter Division
Oak Ridge National Lab
Oak Ridge, TN 37831
qians@ornl.gov

Alex Hexemer, Chair-elect
ALA LBL
One Cyclotron Rd
Berkeley CA 94720
ahexemer@lbl.gov

Angela Criswell, Secretary
Rigaku Americas Corp
9009 New Trails Dr
The Woodlands, TX 77381
angela.criswell@rigaku.com

Young Scientists

George Lountos, Chair
Basic Science Program
SAIC, PO Box B
Frederick, MD 21702
lountosg@mail.nih.gov

Martin Donakowski, Chair-elect
Dept of Chemistry
Naval Research Lab
Washington DC 2003
martindonakowski@gmail.com

Kimberley Stanek, Secretary
Dept of Chemistry
Univ of Virginia
Charlottesville VA 22903
kas4wk@virginia.edu

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Dept Biological Science
Univ Alabama-Huntsville
Huntsville, AL 35899
256 824-3715
ngj@email.uah.edu

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Dept of Chemistry
Univ of Toledo
Toledo, OH 43606
cora.lind@utoledo.edu

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Dept of Materials Sci & Eng
Univ of Tennessee
Knoxville, TN 37996
crawn@utk.edu

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Dept Physics & Astronomy
Brigham Young Univ
Provo, UT 84602
branton@byu.edu

MARILYN OLMSTEAD (15)
Dept of Chemistry
UC - Davis
Davis, CA 95616
olmstead@chem.ucdavis.edu

JOSEPH REIBENSPIES (15)
Dept of Chemistry
Texas A&M Univ
College Station, TX 77842
j-reibenspies@tamu.edu

KRAIG WHEELER (15)
Dept Chem & Phys Sci
Eastern Illinois Univ
Charleston, IL 61920
kawheeler@eiu.edu

STEPHEN BURLEY (16)
Center for Integrated
Proteomic Research
Rutgers Univ
Piscataway, NJ 08854
sburley@proteomics.rutgers.edu

MAGALY HICKEY (16)
Alkermes, Inc
440 Pond St
Westwood, MA 02090
mbhickey@gmail.com

AMY SARJEANT (16)
Dept of Chemistry
Northwestern Univ
Evanston, IL 60208
asarjeant@northwestern.edu

PETER STEPHENS (16)
Dept Physics & Astronomy
Stony Brook Univ
Stony Brook, NY 11794
peter.stephens@stonybrook.edu

JENNIFER AITKEN (17)
Bayer School of Natural
& Environmental Scis
Chemistry & Biochemistry
Duquesne Univ
Pittsburgh, PA 15282
aitkenj@duq.edu

OLUWATOYIN ASOJO (17)
Dept of Pediatrics
Baylor Coll of Medicine
Houston, TX 77030
cyj2102@columbia.edu

ANA GONZALEZ (17)
SLAC
Stanford SRL
Menlo Park, CA 94025
ana@slac.stanford.edu

BRIAN MATTHEWS (17)
Inst of Molecular Biology
Univ of Oregon
Eugene, OR 97403
brian@uoregon.edu

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CCDC, Cambridge, UK
groom@ccdc.cam.ac.uk

SCOTT MISTURE (15) (ICDD Rep)
Alfred Univ, Alfred, NY
misture@alfred.edu

PETER MOECK (15) (MSA Rep)
Portland State Univ, Portland, OR
pmoeck@pdx.edu

BCST Co-Chairs:

DAVID WALT (NAE) (16)
Tufts Univ, Medford, MA
david.walt@tufts.edu

TIMOTHY SWAGER (15)
MIT, Cambridge, MA
tswager@mit.edu

NRC STAFF

Ana Ferreras
Senior Program Officer
aferreras@nas.edu

Pam Gamble
Administrative Assistant
pgamble@nas.edu

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Net RefleXions, Spring 2015

Did you know you're currently sitting on a gold mine of crystallographic and chemical data? At least, if you keep your smartphone in your back pocket you are. Obviously anyone with a smartphone and an Internet connection can find answers to the most arcane questions. But what if you want to be a little more systematic about your searching? What tools are available to you to get the information you need with as little typing as possible? As usual, *Net RefleXions* has you covered!

This column has devoted space in the past to quite a few apps that help with structure visualization, though these often require having files already in your possession. But what if you don't have the files on-hand and want to get them straight from the source? The folks at the Cambridge Crystallographic Data Centre (CCDC) recently released a new version of their structure retrieval app for the web (***www.ccdc.cam.ac.uk/getstructures***).

A view of the CCDC's Get Structures web app.

The new form requires a CCDC number, CSD refcode, or a DOI to access structural and publication information for any of the 750,000+ structures in their database. Once a record is retrieved, a list of all refcodes associated with it will appear and the visitor can scroll through these. The selected structure is then displayed as a freely rotatable 3D image and as a 2D diagram. Users have access to all JMol functionalities to modify the 3D image, display a packing diagram, and calculate metric data. Measurements are displayed on the image, which can then be saved as a png file. In addition to the excellent graphics and structure manipulation, the site also provides CCDC and publication information, with DOI links to the journal. Whether you're searching for a specific structure or just want to read the publications that spawned such refcodes as BIKINI or BADBOY, the CCDC has what you need.

One of the best parts about this new web app is that the 3D graphics are rendered using JSMol, which is compatible with iOS devices. This makes the website perfectly suitable for use on your mobile devices, with all the same functionality still available. For you protein types, the PDB web search app works equally well on a smart phone, and it has advanced searching capabilities, too (***http://www.rcsb.org/pdb/home/home.do***).

You might be wondering why a person would want to access structural data straight from their smartphone. If you have one of a number of mobile apps from some of your favorite publishers, you might want to do just that. The ACS mobile app, available from the App Store or from Google Play, gives you instant access to all the most recent articles published by ACS. Users can set up filters to focus on articles from their most favorite journals. Likewise, the RSC has also developed a mobile app (available from the App Store or Google Play). Users can select from a list of journals to follow. Wiley publications are available through the Wiley Online Library (***http://onlinelibrary.wiley.com/***). Users with an institutional license to view journal content can register an account on the website. Once registered, journal content is available through the website or users can subscribe to various Wiley journals through the App Store to view all content, from recently accepted articles to back issues, on mobile devices. Journals such as *Angewandte Chemie, Int. Ed.* and *Advanced Materials* are two that crystallographers may find interesting.

A few back issues of *Angewandte Chemie*, available on your smart phone.

If a particular manuscript catches your eye from any of these apps, you can access the document via PDF or HTML, or e-mail yourself a link. And if you can't wait until you get to your computer, simply copy the article DOI and paste it into the CCDC's *Get Structures* app for the full 3D structure.

Finally, if you're just interested in keeping up with the headlines, check out the *Science News* app available from Newsfusion, Ltd. on the App Store or Google Play. This handy news aggregator collects stories from science magazines such as *Scientific American* and sorts them by topic. Users can browse the most recent headlines in Chemistry, Physics, Biology, and Nanotechnology just to name a few. The app provides a brief summary of the news and a link to the article website.

In this age of smartphones and constantly accessible data, it's nice to know you're never far away from that all-important article or a fascinating crystal structure. And you thought you had nothing but lint hanging out in your back pocket!

Amy Sarjeant

Structural Dynamics

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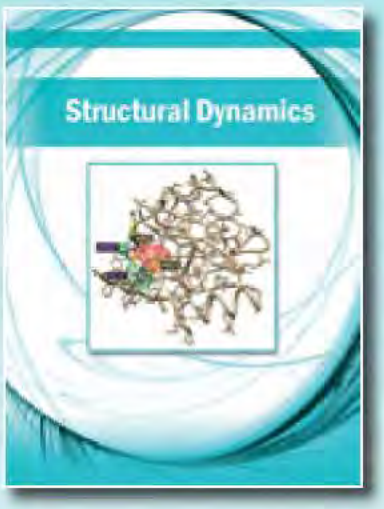

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The electronic structure of matter probed with a single femtosecond hard x-ray pulse
J. Szlachetko, C. J. Milne, J. Hoszowska, J.-Cl. Dousse, W. Błachucki, J. Sà, Y. Kayser, M. Messerschmidt, R. Abela, S. Boutet, C. David, G. Williams, M. Pajek, B. D. Patterson, G. Smolentsev, J. A. van Bokhoven and M. Nachtegaal
Struct. Dyn. **1**, 021101 (2014) *> 3300 Downloads in 2014*

Ultrafast structural and electronic dynamics of the metallic phase in a layered manganite
L. Piazza, C. Ma, H. X. Yang, A. Mann, Y. Zhu, J. Q. Li and F. Carbone
Struct. Dyn. **1**, 014501 (2014) *> 950 Download in 2014*

Femtosecond single-electron diffraction
S. Lahme, C. Kealhofer, F. Krausz and P. Baum
Struct. Dyn. **1**, 034303 (2014) *> 900 Downloads in 2014*

Ultrafast electron diffraction using an ultracold source
M. van Mourik, W. Engelen, E.J.D. Vredenbregt and O.J. Luiten
Struct. Dyn. **1**, 034302 (2014) *> 900 Downloads in 2014*

UPCOMING SPECIAL TOPIC ISSUES:

- ***Biology with X-ray Lasers 2***
  Guest Editor: Abbas Ourmazd
  University of Wisconsin-Milwaukee, United States
  Publication: July - August 2015
- ***Protein Dynamics***
  Guest Editors: George N. Phillips, Jr. and José Onuchic
  Rice University, United States
  Publication: September - October 2015

Structural Dynamics is a high impact, open access, and online-only journal that highlights research articles on structural determination and dynamics of chemical and biological systems and solid materials, enabled by the emerging new instruments (e.g. XFELs, high harmonic generation, electron sources, etc.) and new experimental and theoretical methodologies. The Journal publishes Short Communications, Topical Reviews, Research Articles and Special Topic issues.

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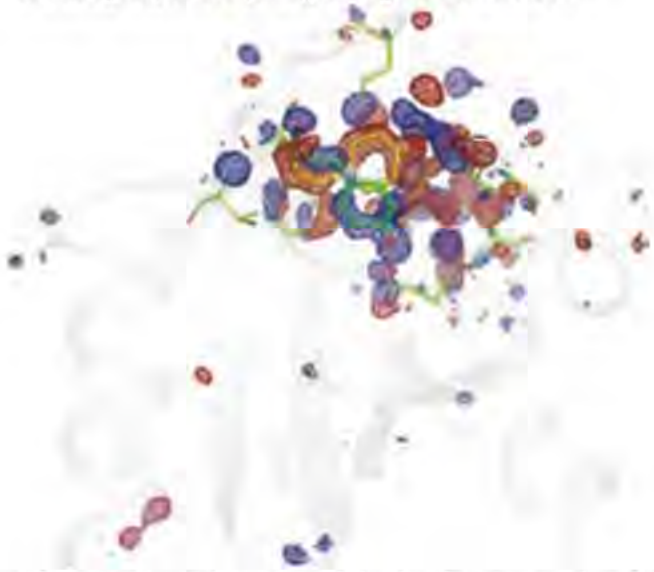
Recently Published - Theory and Modeling

A split-beam probe-pump-probe scheme for femtosecond time-resolved protein x-ray crystallography

Jasper J. van Thor and Anders Madsen

Struct. Dyn. 2, 014102 (2015); doi.org/10.1063/1.406354



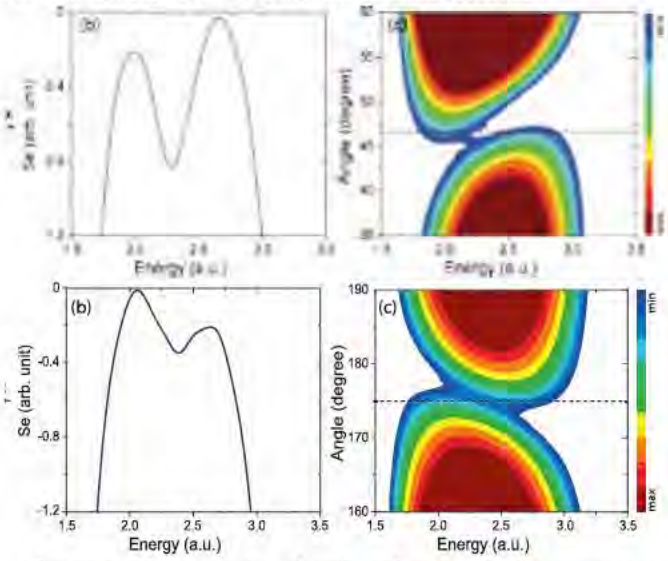
Abstract: In order to exploit the femtosecond pulse duration of X-ray Free-Electron Lasers (XFEL) operating in the hard X-ray regime for ultrafast time-resolved protein crystallography experiments, critical parameters that determine the crystallographic signal-to-noise (I/σI) must be addressed. For single-crystal studies under low absorbed dose conditions, it has been shown that the intrinsic pulse intensity stability as well as mode structure and jitter of this structure, significantly affect the crystallographic signal-to-noise. Here, geometrical parameters are theoretically explored for a three-beam scheme: X-ray probe, optical pump, X-ray probe (or "probe-pump-probe") which will allow experimental determination of the photo-induced structure factor amplitude differences, ΔF, in a ratiometric manner, thereby internally referencing the intensity noise of the XFEL source. In addition to a non-collinear split-beam geometry which separates un-pumped and pumped diffraction patterns on an area detector, applying an additional convergence angle to both beams by focusing leads to integration over mosaic blocks in the case of well-ordered stationary protein crystals. Ray-tracing X-ray diffraction simulations are performed for an example using photoactive yellow protein crystals in order to explore the geometrical design parameters which would be needed. The specifications for an X-ray split and delay instrument that implements both an offset angle and focused beams are discussed, for implementation of a probe-pump-probe scheme at the European XFEL. We discuss possible extension of single- crystal studies to serial femtosecond crystallography, particularly in view of the expected X-ray damage and ablation due to the first probe pulse.

Articles coming soon:

Molecular alignment dependent electron interface in attosecond ultraviolet photoionization

Kai-Jun Yan & Andre D. Bandrauk

Struct. Dyn. 2, 014101 (2015); doi:10.1063/1.4906126



Abstract: We present molecular photoionization processes by intense attosecond ultraviolet laser pulses from numerical solutions of time-dependent Schrödinger equations. Simulations performed on a single electron diatomic show minima in molecular photoelectron energy spectra resulting from two center interference effects which depend strongly on molecular alignment. We attribute such sensitivity to the spatial orientation asymmetry of the photoionization process from the two nuclei. A similar influence on photoelectron kinetic energies is also presented.

Coming Soon:

A perspective: On the relevance of slower-than-femtosecond time scales in chemical structural-dynamics studies by Philip Coppens

More Upcoming Special Topic Issues:

Invited Articles of the 3rd International Conference on Ultrafast Structural Dynamics – A collection of papers discussing the latest developments aimed at understanding real-time structural changes in materials science, chemistry, and biology using a variety of techniques including: Ultrafast electron diffraction, scattering and microscopy; Ultrafast x-ray diffraction, scattering and spectroscopy; and Ultrafast multidimensional vibrational and electronic spectroscopies. ***cusd2015.ethz.ch/***

Guest Editor: Steve Johnson.

Publication Issue: November - December 2015

Soft X-ray in Energy and Time (SXET) – This issue will have reports on the current status and new developments in soft x-ray absorption and emission spectroscopy as well as its resonant processes towards the Heisenberg limit (time versus energy limit). It will feature technical and methodological developments for high energy resolution or ultrafast time-resolved approaches addressing new scientific questions for solid, liquids, gases and interfaces.

Publication Issue: January - February 2016

Referee Acknowledgment

The Editor-in-Chief, the Associate Editors, and the Editorial Board Members would like to extend our sincere appreciation to the efforts of the peer-review community whose reviews keep the standards of the journal at a high level. A complete listing is available at ***Struct. Dyn. 2, 010201 (2015); dx.doi.org/10.1063/1.4907748.***

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Structural Dynamics is a high impact, gold open access publication - all published articles will be freely available to all readers giving authors the broadest possible distribution of their research and statisying all open access mandates being handed down by various governmental funding agencies.

Publication Charges & Open Access Fees: Open access is also an "author pays" model. The submission charge was waived for the first 50 papers published in *Structural Dynamics*. Starting in 2015 authors will be assessed an Article Processing Charge of ***USD2200,*** which covers the cost of publication and allows the author to retain copyright through a Creative Commons Attribution 3.0 Unported License.

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ABSTRACT DEADLINE: MARCH 31, 2015

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Louise Dawe
ldawe@wlu.ca

Kraig Wheeler
kawheeler@eiu.edu

Program Co-Chairs

Poster Chair
Ilia Guzei
iguzei@chem.wisc.edu

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pmueller@mit.edu

Workshops

Intro to Modeling High-Pressure Single-Crystal Diffraction Data
Organizers: Elinor Spencer, Nancy Ross, Carla Slebodnick

Serial Crystallographic Data Analysis with Cheetah & CrystFEL
Organizers: Nadia Zatsepin, Tom Grant, Eddie Snell, Cornelius Gati

Rietveld Refinement Analysis
Organizers: Clarina Dela Cruz, Oliver Gourdon

SAS: Structural Biology & Soft Matter
Organizer: Richard Gillian

Transactions Symposium

Crystallography for Sustainability
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US Crystal Growing Contest

Contest participants Alexis and Heather (11th grade) from South Lewis Central School located in Turin, NY. Photo: Anne Huntress.

"We are all winners as [the United States Crystal Growing Contest] provoked interest, discussion, and learning." – Excerpt from thank you note from teacher Angela Marshall and her 5th grade students at Blessed Sacrament School in Washington, DC.

International Year of Crystallography (IYCr) activities concluded with the announcement of the winners of the first annual United States Crystal Growing Competition (USCGC, *http://www.uscrystalgrowingcompetition.org/*), organized by Jason Benedict of the University at Buffalo (UB). The nationwide competition, based upon a similar contest developed in Canada, challenged America's youth in grades K-12 to grow the largest, highest quality crystal of potassium aluminum sulfate possible over a five-week period. USCGC was designed to be an important scientific outreach activity to provide students and teachers with a fun, hands-on STEM activity as well as an exciting competition. Sponsored in part by ACA, the USCGC brings the science of crystals into America's classrooms.

Participants sent in almost 70 crystals from eight different states around the US. Winners in the "Best Overall Crystal" category, both from New York, each took home $200 and included Renee Aga of Amherst Middle School for the K-8 division and Torrey Black's students from Buffalo's Charter School for Applied Technologies in the 9-12 division.

Winners of Best Overall Crystal for grades 9-12: (left to right) Kianne Fernandez, Zahra Ahmed, and Kathyryn Hartzell from Torrey Black's 11th grade class at the Charter School for Applied Technology in Buffalo, NY. Photo: Torrey Black.

Winners of the "Best Quality Crystal" (a category that only ranks the quality and not the size of crystal) also received a $200 prize and included the 8th grade students of Valerie Rickert from Saint Gilbert School in Grayslake, IL for the K-8 division and the team of Caleb Deckert and Hugo Andre from Timbercreek High School in Orlando, FL for grades 9-12.

A check for $100 for the "Best Teacher Crystal" was awarded to John Thurmond of the Illinois Mathematics and Science Academy in Aurora, IL.

The contest used social media to advertise and provide contest updates, including a live image of the contest judging! The winners were announced via the contest Twitter account: *@USCrystalComp*. Many participants sent in pictures of their progress, which were also shared with the world via social media.

The contest, which began during National Chemistry Week in mid-October and concluded in early December, was judged by a number of UB Professors from Chemistry and Physics: Timothy Cook, Philip Coppens, Ekin Atilla-Gokcumen and Luis Velarde (Chemistry), and Andrea Markelz (Physics).

For many participants, teachers and students alike, this was their first opportunity to perform experiments in crystal growth. Many remarked that they found the instructional "How to grow a single crystal" video series posted on the Benedict Research Lab's YouTube channel to be instrumental in their success!

IYCr was an exciting year for outreach in the science of crystals. In addition to USCGC, other successful events included the Video Contest for School Children (*https://www.facebook.com/IYCr2014VideoContest*) and the Wisconsin Crystal Growing Contest (*http://xray.chem.wisc.edu/WICGC.html*, see p. 24). As we move past IYCr and begin the International Year of Light, it is critical that we expand our efforts to directly involve students and educators in fun and exciting crystal-based activities. We need to encourage students (and parents) to become informed and excited about crystallography!

The USCGC gratefully acknowledges the contributions of Martha Teeter, Jessica Addiss, Ilia Guzei, and the Benedict Research Group graduate students (notably Jordan Cox and Ian Walton), and the support of our sponsors: ACA, Ward's Scientific, and the UB Department of Chemistry. Please consider helping with the 2015 contest. For more information, please visit the USCGC website or e-mail Jason Benedict at *jbb6@buffalo.edu*.

Jason Benedict

Jason Benedict, National Coordinator of USCGC, holding a crystal of potassium aluminum sulfate. Photo: Douglas Levere.

Henry Chapman

2015 Leibniz Prize Awarded to Henry Chapman for Pioneering Work in Femtosecond Crystallography

Henry Chapman, who directs the Coherent Imaging Team at the Center for Free-Electron Laser Science at the DESY light source in Hamburg and is a member of the Advisory Board for *Structural Dynamics*, is one of the recipients of the 2015 Gottfried Wilhelm Leibniz Prize, funded by the German research foundation Deutsche Forschungsgemeinschaft (DFG). The Leibniz Prize is the highest German research prize and is awarded every year to ten distinguished researchers and academics working in Germany in recognition of their outstanding research.

Chapman received the award for his "pioneering work in the development of femtosecond crystallography." In serial femtosecond crystallography, scientists collect single-shot diffraction patterns from a liquid stream of nanocrystals using extremely short and bright pulses produced by X-ray free electron lasers (XFELs). A series of detectors capture the diffraction patterns produced by thousands of nanocrystals, randomly oriented in the sample stream, and the data derived are merged and processed using specialized software. The advantages over classical crystallography are important. With high-intensity pulses it is possible to record diffraction of microcrystalline material, unchaining protein crystallography from its major bottleneck requirement for large and well-ordered crystals. At the same time the short duration of the pulses limits the effects of radiation damage: the irradiated sample produces diffraction before any atomic rearrangement could occur, and then disintegrates due to the power of the radiation. Moreover, since radiation damage does not represent an obstacle, cryo-cooling of the sample is not necessary and the diffraction data are collected at room temperature, the physiological temperature for most proteins.

In recent years, Chapman and his collaborators from universities in the USA and Europe have used serial femtosecond XFEL to determine the structure of many different proteins. For example, in a seminal work that appeared in the journal *Science* in January 2013, researchers solved the XFEL structure of the protease cathepsin B from *T. brucei*, the single-celled parasite that causes African sleeping sickness, in complex with an inhibitor. Using an unconventional procedure, they crystallized the protein inside living insect cells, obtaining microcrystals, and they derived a structure that displayed unexpected features. Their work provided important clues for designing novel therapeutic strategies that could help in fighting the disease (Redecke *et al*., *Science*, **339**, 227-30, 2013). In a second example, researchers managed to solve the first XFEL structure of a serotonin receptor, a membrane protein belonging to the GPCR protein family; this is a beacon of hope for many crystallographers who routinely struggle with capricious membrane proteins that just don't want to form well-ordered macrocrystals (Liu *et al*., *Science*, **342**, 1521-4, 2013). And finally, just as the International Year of Crystallography was giving way to the International Year of Light, another ground-breaking experiment led to the characterization of short-lived conformations that the photoactive yellow protein (a bacterial blue light receptor) displays when it is activated by light. The research demonstrates that XFEL can access and capture important reaction intermediates that only exist for the duration of one millionth of one billionth of a second and opens the field of photoinduced protein dynamics, and, in general, of femtosecond dynamics, to crystallography (Tenboer *et al*., *Science*, **346**, 1242-6, 2014).

Most of the research mentioned here was carried out at the Linac Coherent Light Source, the world's first hard X-ray laser, located at the Stanford Linear Accelerator Center (SLAC) and functional since 2009. In 2011 a second XFEL was inaugurated in Riken, Japan (the SPring-8 Ångstrom Compact Free Electron Laser, or SACLA), and a third one will open in Europe in 2016. This, the first European XFEL, will be located at the DESY light source in Hamburg, Germany, and will exhibit unprecedented performance. It will be able to deliver the highest number of light flashes per second (a mind-blowing 27,000), generating a maximum energy of 17.3 GeV and an average brilliance of 1.6×10^{25} [photons/s/mm^2/mrad^2/0.1% bandwidth], seven orders of magnitude higher than the average brilliance of 3rd generation synchrotron light (data taken from: ***http://www.xfel.eu/overview/in_comparison/***). The new crystallographic century is surely off to a very bright start!

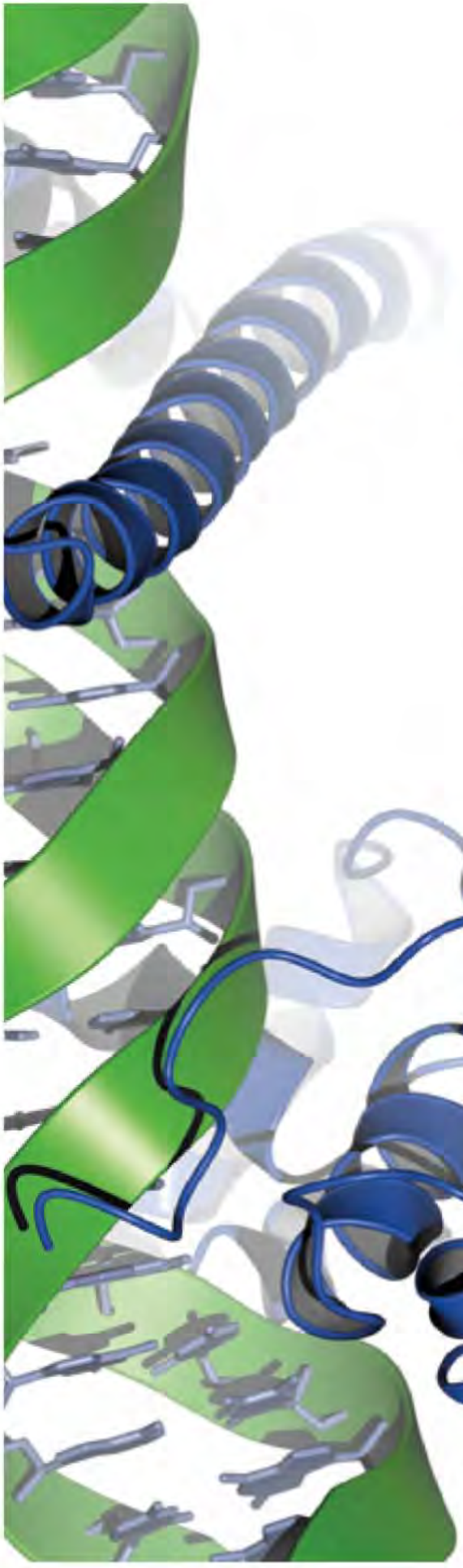
Chiara Pastore

USNCCr Funding Available for Crystallographic Education

The US National Committee for Crystallography (USNCCr) has reserved some funds to support crystallographic educational activities in the US, including the participation of attendees from Latin America. In particular, the USNCCr has provided support for the ACA Small Molecule Summer School for many years and supported a number of activities promoting the 2014 International Year of Crystallography. The committee is now welcoming other requests for activities that benefit the US and/or Latin American crystallographic communities in the range of a few hundred, or, in exceptional cases, up to a few thousand dollars.

To apply for funds, please request the application form from the USNCCr Chair, Joseph Ng (***ngj@uah.edu***) or the National Academy of Sciences' Staff Officer, Ana Ferreras (***aferreras@nas.edu***), and send the completed request to both of them. The committee meets twice a year, so funding requests should be made at least 6 to 12 months in advance of the event.

Brian Toby, USNCCr Past-Chair, and Joe Ng, USNCCr Chair



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First Wisconsin Crystal Growing Contest

As part of the International Year of Crystallography 2014 celebration, the UW-Madison Molecular Structure Laboratory organized the first statewide Wisconsin Crystal Growing Competition and a "History and Significance of X-rays" lecture tour.

High-school students from 26 schools across the state competed for prizes by growing large blue crystals of $CuSO_4 \cdot 5(H_2O)$; see figure below. Awards for top student and teachers' crystals in the "best quality" and "best overall" categories included cash prizes and certificates. One of the submitted crystals met no judging criteria at all, yet it was so beautiful that a new category "organizers' favorite crystal" was created (see the middle photo in the figure). The award ceremony took place at the UW-Madison

Award winning crystals of $CuSO_4 \cdot 5(H_2O)$ from the Wisconsin Crystal Growing Contest.

Chemistry Department. The ceremony included an introduction by the department chair, a talk about the significance of crystallography by Paula Piccoli, the award presentation, an exhibit of all the submitted crystals, tours of the departmental X-ray facility, and a reception. Students, teachers, parents, and winners as well as non-winners attended. There was great interest in looking at the submitted crystals, and all the crystals are currently on prominent display in a glass cabinet at the Chemistry Department.

The teachers provided valuable feedback about the contest and inspired us to hold the contest in 2015:

Jamie Lauer (Chemistry Teacher, Hartford Union High School, Hartford, WI):

"It was a great cross-curriculum assignment, as we investigated the types of crystals produced using the earth science teacher as our resource. Before the start of class each day, students would attend to their crystals and would even help others with the growing process. They learned quickly what worked well and also learned how to fail. This activity brought out 'true learning' in the classroom. Many students chose to name their crystals: Jessie White, Dusty, Adidas, DuWayne the Rock Crystal, DuWayne II, and Lapis Lazuli (blue block from Minecraft game). Next year I am going to incorporate this contest again in my own classroom."

Lynn Dehnel (Ashwaubenon High School, Ashwaubenon, WI):

"It is so fun to see [my students] excited about chemistry! In fact, I have had kids coming in after school and in between classes to check on their crystals. I'm pretty sure I have not had this many kids in my room on a Friday after school in a long time."

Ron Cerveny (Flambeau High School, Tony, WI):

"We had a unique group of kids this year who really enjoyed the project. They, too, arrived early or checked in between classes to monitor the process. Some also named their crystals. A young lady wanted to make a necklace out of her crystal – it looked so attractive to her. … Their engagement levels … far exceeded my expectations. Because of their interest, we were able to examine X-ray crystallography (I had some slides for projection demos from Madison several years ago), the Bragg equation, colligative properties and other topics that we would not do at such depth in other years."

Lynn Ponto (Science Teacher, Weyauwega-Fremont High School, Weyauwega, WI):

"It was a great opportunity for both of my girls that worked on the crystals. They learned how to work together and share the responsibility of lab work because they worked on the same crystals consecutive hours of the day. They had to leave detailed instructions for each other and understood the importance of meticulous records. They also had to discuss variations in procedures to improve the crystals, making this realistic research work. They enjoyed this experience very much."

Holding the award ceremony on campus achieved other vital goals of the contest: it provided the students with an opportunity to tour a flagship university, to sense what science looks like at a chemistry department, and to visit an X-ray laboratory where expert crystallographers demonstrated instruments and tools used by researchers to explore molecular structure in depth. A full account of the contest was published in *J. Chem. Ed.* **2014**, *91*, 2013-2017.

The lecture tour served to inform the audiences about the significance of crystallography in life and science, the discovery of X-rays, and the discovery of X-ray diffraction by crystals. A total of 11 lectures in several states at graduate and undergraduate institutions were delivered.

This exciting scientific project required a lot of effort, but fortunately it was possible due to volunteer help from over 30 of my colleagues and with the support of the numerous sponsors: ACA, Bruker AXS, The Evjue Foundation, IUCr, Rigaku, and Sigma-Aldrich, to whom I am indebted for their generous assistance. Organizing the 2015 Crystal Growing Contest will certainly be a smoother and less time-consuming process. The details of the 2015 Contest can be found at ***http://xray.chem.wisc.edu/WICGC_2015.html***.

Ilia Guzei

YSSIG Looks Forward to the 2015 Annual Meeting in Philadelphia!

YSSIG will host an **SPS Undergraduate and Graduate Student Reception** at the Philadelphia meeting, sponsored jointly with the Society of Physics Students. We invite all undergraduates, graduate students and their mentors, as well as others who might be interested, to join us on Sunday, July 26, for a reception highlighting undergraduate research. Research posters by undergraduates will be highlighted and presented in this special session dedicated to undergraduates; refreshments will be provided. In addition, a speaker to be announced will give a short talk. Pre-registration is required through the meeting website: ***http://www.amercrystalassn.org/2015-mtg-homepage***. Krystle J. McLaughlin of Lehigh University will lead the session.

We will also host the traditional **Career Odyssey Panel**, where panelists from the crystallographic community will share their own experiences, take questions and give advice on career opportunities and possibilities. The panel will reflect the breadth and diversity of career trajectories in the crystallographic community, and will include, among others, Cora Lind-Kovacs. Join us for a wide-ranging, possibly life-changing, discussion on Sunday, July 26; come one, come all! Smita Kakar of the National Cancer Institute will chair.

YSSIG will once again host the ever-popular **YSSIG Mixer, sponsored jointly with Bruker**! Come see old friends and make new ones over food and drinks at 8 PM Sunday, July 26 at the City Tap House Logan. We look forward to seeing you there.

Finally, YSSIG's very own Jarrod French and Andrew Torelli will lead the session **Professional Development: Communicating Your Science** on Monday, July 27. The session will provide members of all ages the opportunity to learn how best to communicate science. Planned speakers include a professional science writer and an expert on science policy. We also hope to include talks aimed at how to effectively communicate with funding agencies and their program officers. This is a fantastic opportunity for young scientists, as well as for those who are more established, to learn to distill and disseminate our scientific message to the various communities with whom we must communicate. We hope you can attend, as we're sure this will be an exciting, lively and informative session.

Amadeo Biter

Top:Participants in the undergraduate special session at last year's meeting in Albuquerque. Middle: Last year's YSSIG mixer at Ibiza Bar. Bottom: The venue for this year's mixer, City Tap House Logan. Albuquerque photos by Peter Müller.

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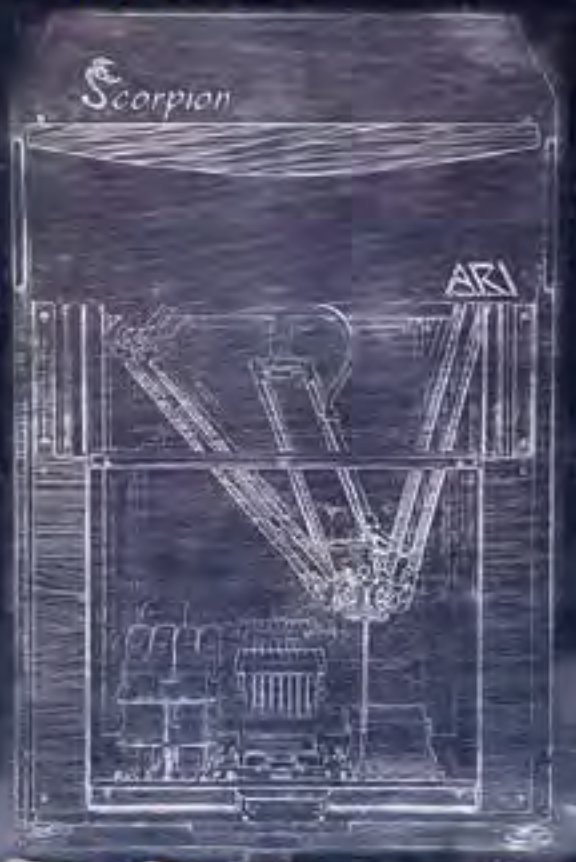

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Notes of a Protein Crystallographer: Reading, Hearing and Touching Our Predecessors

I have always considered books as one of the major achievements and treasures of human culture and, like the Argentinian writer Jorge Luis Borges (1899-1986), I can envision paradise as being some kind of immense library. In my view, libraries are icons of the cultural achievements of human societies and, at the personal level, are a unique transforming element in peoples' lives. Collectively and individually, books have enabled younger generations to expand their knowledge and to broaden their professional horizons beyond the limitations of the 'master-apprentice' cycle. With books and with the knowledge derived from them, younger generations could choose and follow their vocations and contribute to their own happiness and to the enrichment of their societies. With the appearance of electronic media and the new icons of our age, e-books and the online resources, these options and opportunities have developed in ways that were totally unimaginable to the inventors and pioneers of the printing presses. However, I surmise that there are experiences that the new electronic media may never make possible.

Fig. 1. First page of the book *Fifty Years of X-ray Diffraction* published to commemorate the fiftieth anniversary of the discovery of the diffraction of X-rays by crystals in the work of Laue, Friedrich and Knipping published in 1912. This is a copy formerly belonging to the Chemistry Library of the California Institute of Technology. Insert: Detail of the seal of the Caltech Library visible on the first page. The copy was withdrawn from the library and donated to the bookstore for sale.

On the occasion of the International Year of Crystallography (IYCr2014), these thoughts came to me as I was reading a book that was purposely prepared to commemorate fifty years of X-ray diffraction and was published in 1962 to celebrate the experiment of Laue, Friedrich and Knipping and the ensuing revolution in the sciences that cascaded after the insights and results of the Braggs (Ewald, 1962) (Fig.1). The invitation for the 1962 celebration was issued by the Ludwig Maximilian University of Munich, where the original discovery was made; the Bavarian Academy of Sciences where it was first made public; and by the IUCr, in its capacity as the umbrella organization for over 3,500 researchers all over the world that were then involved in X-ray related work.

As acknowledged in the book's introduction, the year 1912 marked the birth of two branches of the physical sciences. The best-known, X-ray crystal structure analysis, related to the Braggs (W.H. and W.L. Bragg, father and son) while the lesser-known X-ray spectroscopy is linked in the main to the names of H.G.J. Moseley and M. de Broglie. The history and new development in these two well-established lines of research in the physical sciences are well reviewed in the first part of the book, with contributions by the pioneers (the Braggs) as well as the second generation of brilliant scientists such as J.D. Bernal, J. Monteath Robertson, Linus Pauling and Kathleen Lonsdale (later Dame Lonsdale) in structural analysis and M. Siegbahn in X-ray spectroscopy. All through the first part there are interesting detours related to the physics of X-rays in the context of what was known at the time. The IUCr has also published two extensive and attractive volumes (Schenk, 1998, 2008) reviewing the status of crystallography across the sciences with modern perspectives.

The perceptions and insights about the history and contemporary status of the field are unique in the 1962 volume and are worth mentioning. I was surprised to read in a quotation from Roentgen's third communication in March 1897 that indeed Roentgen himself had tried several times to diffract the mysterious rays but failed:

"Ever since I began working on X-rays, I have repeatedly sought to obtain diffraction with these rays [...]. But in each case a change of experimental conditions [...] failed to confirm it. [...] I have not succeeded to register a single experiment from which I could gain the conviction of the existence of diffraction of X-rays with a certainty which satisfies me."

These failed attempts highlight the unique intuition of Laue in the milieu of the Department of Physics at the University of Munich (pp. 31-47) and the superb experimental skills of Friedrich and Knipping to plan the initial experiment with the crystal of copper sulfate and obtain the striking and conclusive results with Zincblende. The early days of X-ray diffraction have been masterfully and thoroughly presented in a recent book published by the IUCr (Authier, 2013; reviewed in *ACA RefleXions*, Spring 2014) that I recommend you read if you are interested in the historical themes of our field; in many ways Authier's book complements and extends the 1962 volume reviewed here.

There is also section IV of the 1962 volume on the growing field of crystallography with a review by W.L. Bragg of the expanding power of X-ray analysis. At this time in the history of the field, the structures of cholesteryl iodide, penicillin and Vitamin B_{12} (181 atoms) by Dorothy Hodgkin and coworkers were important milestones in the 1940's and 1950's. One can feel the excitement of W.L. Bragg when he describes the latest achievements of the diffraction methods in unveiling the structures of DNA and the recently obtained structures of myoglobin (2,500 atoms) and the soon forthcoming hemoglobin structure with 5,000 atoms in the asymmetric unit. Bragg emphasizes that these most recent results were obtained without trial-and-error methods and the lack of any assumptions about the structure.

There is also a look by Sir Lawrence into a 'crystal ball' regarding the size and complexity of structural data in the future. As a small tribute to *Acta Crystallographica* and even to the current PDB, I would like to mention a reflection by the younger Bragg regarding the complexity of the forthcoming

structures anticipated by 1965 (Fig. 2).

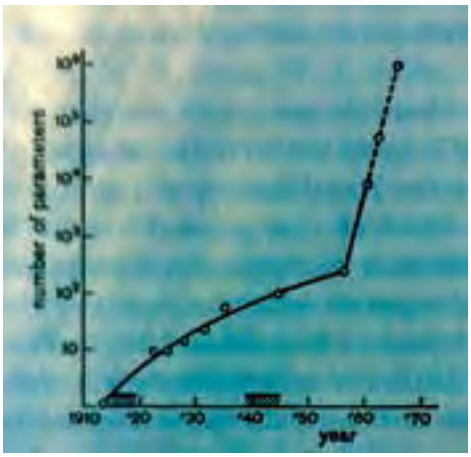

Fig. 2. Photo image, reproduced from the 1962 volume, of the plot presented in the lecture by W.L. Bragg in an attempt to extrapolate the size of the biological structures that might be solved by X-ray in the near future. He suggested that the structures of viruses might appear by 1965 or so. It certainly took longer than that, with the structure of Tomato Bushy Stunt Virus, the first icosahedral virus, solved in 1979 by Steve Harrison and colleagues.

"I end this lecture with a graph, in which the years are plotted horizontally, and the number of parameters in typical structure determinations are plotted vertically on a logarithmic scale (Fig.2). […] If we prolong the graph we conclude that we shall reach the million mark in 1965. […] How the million parameters will be listed in *Acta* is a problem I leave to the editors at the time. I have high hopes that I shall see the great day."

But I did find the second part the most interesting one. It is worth quoting the words of the editor (none other than P.P. Ewald) as to the intentions of the second section of the volume:

"There is nowadays, a general demand for more of the human touch in presenting science to the coming generation, for more detail about the men whose memory is handed down by the laws named after them (a few, like Roentgen, even achieve the status of becoming immortalized in a unit!) but whose personality is effaced as the circle of their students fades out. At which schools did they learn their art when they were young, with whom did they form friendships that lasted throughout their scientific life? What was their own evaluation of their work, what their hopes and their disappointments, their outlook on science and life?"

I cannot do justice to the details about the human content of the 1962 volume in these notes. I would suggest that you find a copy in your nearest library or better still consult the complete electronic version that the IUCr made available on the occasion of the XVIII IUCr congress in Glasgow (1999) (***http://www.iucr.org/publ/50yearsofxraydiffraction***). Because many of the pioneers of the field were no longer alive at the time, there are articles written in memoriam of several of the heroes of the field, among them Laue himself, W.H. Bragg, A. Schoenflies, W.T. Astbury, and P. Knipping (pp. 278-368). There you can read insightful anecdotes and commentaries, sometimes obtained from their autobiographies or personal notes, and others written by their close colleagues or friends.

The section of Personal Reminiscences (Section VII, pp. 508-691) is priceless with contributions by J. D. Bernal, J.M. Bijvoet, W.L. Bragg, M.J. Buerger, G.G. Darwin, A. Guinier, K. Lonsdale, A.L. Patterson, and Linus Pauling among many others.

I was particularly impressed by the personal portrait that emerges from one of my heroes among the pioneers of the crystallography of molecules of biological interest, both small and macromolecules, J.D. Bernal (i.e. 'Sage'). Bernal's four-page account of his time at the Royal Institution (1923-27) is a marvel of sincerity and candor. This was the time when the spectrometer designed by Bragg senior was the key instrument for data collection and tedious structure analysis. A few quotes will illuminate Bernal's style and originality:

"I myself remember being given a few days of instructions on Kathleen Lonsdale's spectrometer and deciding that I was not made for it: to spend a whole day for only two accurate reflections was quite beyond my patience."

Sage was put onto designing a very different apparatus from scratch.

"I was given a few pieces of brass made up by Jenkinson, some miners' lamp glasses, a little aluminium foil for the window, plenty of sealing wax to stick everything together."

Other parts included glass tubing, a bit of mercury to make a diffusion pump, copper and iron wires and other assorted parts. […]. The path was not easy:

"It was after three months when I had not been able to get even the trace of an X-ray out of the apparatus, after endlessly burning myself and breaking things, that I decided that experimental physics was not for me and I went up to Sir William with the plea to be allowed to go back to the theory of crystallography."

Bernal eventually went back to design the first rotation camera to record diffraction data from graphite and solve the structure. How he did do that? In his own words:

"[…] I had to make my own cylindrical camera which I did in the most amateur way out of a piece of brass tubing which I had cut with a hack-saw, bored a hole in it, stuck in with sealing wax a smaller piece of brass tubing with two bits of lead with pin holes through them for the aperture. The film was held together in place with bicycle clips and I used an old alarm-clock and a nail to mount and turn the crystal."

And the most amazing thing of it all is that:

"It worked and remained as a prototype of all existing cylindrical cameras as is shown by the fact that the diameters of the cameras have remained essentially the same ever since."

I do hope that this brief and perhaps superficial review of the content of this remarkable book about the history of crystallography will give you a sense of what the pioneers of the field were doing professionally, and I encourage you to read other sections of the volume for your personal enjoyment. As I have tried to illustrate, the style and conception of the book is such that it conveys not only the pioneers' scientific insights and achievements but also their thoughts, uncensored commentaries, viewpoints and experiences that do indeed enrich and expand our understanding of who they were and how their motivations, passions and experiences prompted their human and professional actions. One has the sense of listening to them as they freely speak about the events of those amazing years.

There is one final note that I would like to add associated to the last part of the title of this essay. I did know about the existence of this book before, but the way in which the copy that I now own ended up in my hands is worth mentioning. I was visiting

the Caltech campus in 2011 to attend the PhD defense of our son Pablo. The day before, I was strolling the campus visiting the lab of Max Delbrück and Linus Pauling in the Chemistry Building, and this was exhilarating in its own way.

In addition, there was an obligatory visit to the campus bookstore. In the section of used books is where I found a thick book with red covers that had been 'withdrawn from the Chemistry Library of the California Institute of Technology' and was on sale for five dollars. Unbelievable! What a treasure!! Being from the Chemistry Library it is quite probable that it had been consulted by Linus Pauling himself or even donated by him, since he had probably received a free copy from the IUCr as a contributor. I can even dream that he might have edited a handwritten pencil correction to one of the errata in the book on p. 8.

In summary, besides the personal recollections and anecdotes of many of our predecessors on the origin and development of crystallography, fifty years after the momentous discovery of the diffraction of X-rays by crystals, which I tried to summarize above, I do treasure this book because it is quite possible that it was touched by the 'master' himself thus making the copy an invaluable treasure. This would not have been possible in our electronic era. I think that in this IYCr2014 it is appropriate to look back to the accomplishments of our predecessors, honor them, and to endeavor to get a better picture of who they were as human beings.

Cele Abad-Zapatero

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Join Us in July in Philadelphia!

Meeting logo designed by Jason Mercer

Commentary – The USNCCr: An Exit Interview

I write this in the beginning of 2015, noting a transition in my life: I am no longer connected with the US National Committee for Crystallography (USNCCr). I spent six years (two terms) as a committee member and was then elected for one term each as vice-chair and chair. Twelve years with the USNCCr has been longer than I have worked in my career with any one employer, so this seems major to me.

One of my goals when I became chair was to increase communication with the overall crystallographic community, to improve the visibility of the USNCCr as well as to open up more of our discussions. I did write a few articles for *ACA RefleXions* (Spring 2012, Winter 2012 and Winter 2014), and I would like to finish up by reviewing some of what the Committee has done in recent years and offer my own opinions on where I would like to see the Committee go in the future (particularly, of course, now that it is no longer my job to see that it actually happens). Before doing so, since the USNCCr is run by the National Academy of Sciences (NAS), an organization that takes creation of consensus documents very seriously, I need to make clear that everything that follows here is my own opinion and that I am not speaking for the USNCCr, the NAS, or anyone else. I also want to make clear that I am not taking credit for our accomplishments. Everything the USNCCr achieves comes from the efforts of our volunteer-members and our NAS staff liaison; very little of that work has come from me.

Background. If you missed my previous *RefleXions* columns and are not familiar with the USNCCr, let me recap a bit here. The ACA and USNCCr both have connections to crystallography and crystallographers in the US, but in fact they are quite different types of organizations. The ACA is an international professional society; I would assume that since you are reading this you have an interest or involvement in crystallography and thus are a member of the ACA. (If not, you should be.) The ACA runs excellent meetings every year, sited in the US or Canada; it has just started a new journal, *Structural Dynamics*, published jointly with AIP; it runs many fine awards for crystallography and is thoroughly worthy of your fairly small dues payment.

In contrast, the USNCCr is an elected panel run by the Board on International Scientific Organizations (BISO) of the NAS. The main role of the USNCCr is to represent US crystallography, and in particular the interests of US-based crystallographers (regardless of citizenship), within the International Union of Crystallography (IUCr). The IUCr runs an international meeting every three years and publishes both the *Acta Crystallographica* journals and the *International Tables for Crystallography* volumes. The IUCr does quite a bit else, including the development of CIF and co-sponsoring some regional meetings. While some other international scientific unions allow individuals to join, only countries can

join the IUCr. (Examples of other US National Committees can be found on the BISO web site, ***http://sites.nationalacademies.org/PGA/biso***). Countries join the IUCr via Adhering Bodies, such as the NAS through the USNCCr. IUCr membership dues for the US, as well as support for five delegates to attend and vote at triennial IUCr General Assemblies, is paid by the NSF, which also provides limited funds to run the Committee. The IUCr recently began recognizing regional affiliates for Europe, Asia, and North and Latin America, and the ACA is one of these, but there is no formal role for them in the IUCr.

The USNCCr consists of 12 elected members; four are elected each year to a three-year term. Bylaws prohibit members from being elected to more than two full terms, unless elected as an officer. Members or past members may be elected to be vice-chair or secretary for an additional three years. The vice-chair then automatically serves another three-year term as chair. In addition, the ACA President, Vice President and Treasurer (if residents of the US) are also automatically voting members of the USNCCr, as are any US residents elected to the IUCr Executive Committee (EC). Finally there are three non-voting members, providing the USNCCr with representation from the International Centre for Diffraction Data, the Microscopy Society of America and the Cambridge Crystallographic Data Centre.

Beyond interactions with the IUCr, the bylaws of the USNCCr require the Committee, "to promote the advancement of the science of crystallography in the United States…" and charge it, "to take any other action directed toward the benefit and advancement of the science of crystallography in the United States and throughout the world." This certainly overlaps with interests of the ACA, but the USNCCr has the charter to focus specifically on US needs.

Back in the good old days, the USNCCr had funds to bring members together twice a year for full-day meetings and we had funding for extensive NAS support. This is no longer the case. Funding constraints have forced the Committee to have web-based "virtual" meetings and caused severe cutbacks in staffing support. One short face-to-face meeting is held at ACA meetings, but travel must be self-funded. Virtual meetings have their advantages, but with 15+ participants they are much less effective. One challenge for the USNCCr will be to find a way to recover some of the effectiveness that has been lost with the decreased funding.

IUCr Representation. There are many crystallographers in the US, but the maximum number of votes any one country can have in the General Assembly is five. This means that within the IUCr we can foster change only through persuasion and consensus building. Considering the many different national customs that need to be merged in an international organization, this is as things should be. I think we have been quite pleased with fairly recent changes in the IUCr.

One area that is improved from my perspective is the nominations process for IUCr elected offices. This process has become more open and has resulted in a larger number of highly qualified candidates. Another fairly recent change in the IUCr bylaws requires the EC to have at least one member from each of the three regions (Asia, Europe and the Americas), thus ensuring broader representation.

The USNCCr needs to present (next in 2016) names of crystallographers to run for IUCr offices and, of at least equal importance, to populate the ~20 IUCr Commissions, which do so much of the good things that come from the Union. While looking for US-based scientists to nominate is important, it is also critical to work together with other countries to see that the IUCr leadership is appropriately diverse in geography, age and gender; this requires the USNCCr to look for talent outside our borders.

In recent decades, IUCr meetings have tended to rotate between Europe, Asia and North America. However, there was a fairly long delay to return to the Americas after the very successful 1996 Seattle meeting. For this reason the USNCCr was very supportive of the Canadian bid, originally led by the sadly missed Louis Delbaere, for what became the wonderful 2014 Montréal meeting. Looking forward, after the 2017 IUCr meeting in Asia (Hyderabad) and the 2020 meeting in Europe (Prague), I hope to see the 2023 meeting return to the Americas. Toward this end, member Joe Reibenspies helped the USNCCr sponsor a contest to ask attendees in Montréal what US city they would like to see for a 2023 IUCr meeting. Hawaii won, not surprisingly, but this may not be the best venue to propose. To have a US-based meeting, a bid must be presented in 2017 to the IUCr delegates. I hope for a combined IUCr/ACA meeting, which requires coordination in the bid. One issue that will need to be addressed is a perception that it can be difficult for international scientists to obtain a visa for conferences in the US. In fact, there is a quite successful service run by BISO to help foreign scientists attend US-based conferences (see ***http://sites.nationalacademies.org/PGA/biso/visas/***). The US may in fact offer easier access than many other venues.

Young Scientist Activities. The USNCCr has taken an active role in supporting the ACA Small Molecule Summer School, as well as assisting several macromolecular instructional activities. Many members also teach in these workshops. Further, thanks to hard work by NAS staff in writing NSF proposals, we have also been able to provide travel assistance to help bring younger scientists to IUCr Congresses. Our staff liaison, Ana Ferreras, has guided us in evolving the fellowships into a more expansive program, where each young scientist is assigned a mentor, attends several events and learns about the governance of the IUCr. We now call this our Young Observers' Program, since they are encouraged to attend the IUCr General Assembly sessions. I honestly would have expected that exposure to these sessions would be more likely to cause young people to flee than join, but this has in fact been well received. Conducting this program takes considerable effort to solicit and review applications, and to organize activities and communicate with the awardees. I am in awe of the many members who made this happen, especially Amy Sarjeant and Cora Lind-Kovacs.

Latin America Outreach. The USNCCr wishes to help foster growth in crystallography in countries to our south. For quite a while we have provided some financial assistance to US workshops typically earmarked for bringing young Latin American scientists

here. We have also hosted networking events at IUCr meetings. What is new is that at the 2014 Montréal meeting, the formation of a new regional crystallographic organization, the Latin American Crystallographic Association (LACA), was announced and was then recognized as a regional affiliate by the IUCr. We hope that interactions with LACA can help guide the USNCCr as to how to best use our available resources for this outreach.

There has also been some discussion of a possible South American bid for a 2023 IUCr Congress. I admit to mixed feelings about this because one of my reasons for favoring an IUCr meeting in the US is to increase local crystallographers' access, which may be decreased given the difficulties and costs of international travel particularly for many younger scientists. A meeting in South America could pose similar difficulties. Nonetheless, the presence of a strong crystallographic community in our hemisphere is in everyone's best interests, so I would encourage the USNCCr to coordinate with LACA on a bid and provide any requested assistance.

Crystallographic Education. Probably the most valuable action from the USNCCr in the past decade was the excellent 2006 white paper, *Crystallography Education Policies for the Physical and Life Sciences: Sustaining the Science of Molecular Structure in the 21st Century*, which was coauthored with the ACA. My predecessor as chair, Katherine Kantardjieff, led this. (The report can be downloaded from ***http://sites.nationalacademies.org/PGA/biso/IUCr/PGA_071551***). The report describes the value and importance of including crystallography within US scientific education. If anything, since the time of that report there has been further erosion of our field from the academic curriculum. I find this ironic, considering that if anything it is even more common for scientists to be either consumers of crystallographic results or to directly utilize crystallographic studies in their work. Certainly in my field, powder diffraction crystallography, we have seen tremendous growth for both roles. Further, with the loss of these educational programs, who will perform future crystallographic analyses? Who will educate future generations of crystallography experts? I would like to see the USNCCr lead follow-up actions to create a national-level strategy, which I think is best done in the context of several workshops.

I would like to see crystallographers use these workshops to work out curricula appropriate for different types of students and research professionals, depending on what type of work they will do, and then propose a professional certification program. Since many schools do not have faculty qualified to deliver such courses, the education will need to be delivered by some sort of distance-learning approach. Massive open on-line courses are currently in fashion, but there are certainly other options. The various summer schools and similar courses are wonderful, but these are only a start on a crystallographic education and are also only available to a relatively small number of people each year. We need to think as a community about what else is needed.

The USNCCr has a standing subcommittee on crystallographic education, now chaired by Kraig Wheeler. Kraig has a little bit of work to do in preparation for the 2015 Philadelphia ACA meeting, for which he and Louise Dawe are the program chairs, but he is very interested in seeing his subcommittee take a more active role. While subcommittees have tended to rely on USNCCr members, my personal opinion is that the USNCCr would be more effective by encouraging non-members to be active. This would also help the nominations subcommittee with identifying potential future USNCCr members.

Community Outreach. Another area where crystallographic education can be important is in K-12 education. Our field is one that even young children can immediately relate to. Everyone can understand about crystals and learn what makes them special. Symmetry is also something that people can conceptually access and they often enjoy. For many years the USNCCr has led and sponsored an outreach event for K-12 educators called "Crystallography: World of Wonders," coupled to a number of ACA meetings, and has distributed "Crystal Jars" for younger children to try their hand at growing crystals. Claudia Rawn has done so much of this, but many others have volunteered as well.

We should not overlook the need for outreach to other scientists. They can then better appreciate what can and cannot be done by automated instruments and what knowledge is needed by the next generation of scientists, both non-specialists and those who will work in our field.

For 2013-2014, the predominant focus of the USNCCr was on the International Year of Crystallography (IYCr). Alas, these efforts were badly hurt by the cutback of NSF funding, which resulted in fewer meetings and less staff support from the NAS when it was most needed. We prepared a supplementary NSF proposal for additional outreach activities, but that was not funded. The USNCCr devoted about three years worth of our private income on IYCr projects such as student travel, sponsoring software for 3D printing, and a video contest amongst other outreach activities, but I wish we could have done much more. My favorite among these activities was the 2014 World of Wonders workshop at this year's ACA meeting. This one was run cooperatively with the New Mexico Museum of Natural History and Science and was coupled to a public talk on artist M.C. Escher.

Crystallographic Databases. Another area of focus for the USNCCr has been with crystallographic databases, which also has a standing subcommittee (chair to be determined). The USNCCr has been concerned that results be provided to and be released by databases in a timely manner and has had discussions with database organization representatives on the subject of duration of "data embargoes." We also organized a database forum during an evening at the 2013 ACA meeting.

While we need database organizations to be healthy and vibrant, we are also concerned that costs for inorganic and small-molecule databases may prevent access for many scientists. These two goals may appear to be in conflict, because if database subscription income falls, the database centers' existence becomes threatened. Nonetheless, I think the USNCCr needs to take an advocacy role in seeing that database access is wide and facile and that students become educated in the use of these most valuable tools. It is worthy of note that nearly every major database currently has representation amongst the membership of USNCCr, so the committee is an excellent forum for these discussions.

Research Resources. An additional standing subcommittee of

the USNCCr has the name Research Resources (chair Claudia Rawn). In practice the major focus of this subcommittee is interaction with the scientific user facilities (mostly neutron and synchrotron sources) that are available in the US. Recent years have brought some disruptive changes, and it has become painfully obvious that there is no organization advocating for the interests of the crystallographic uses of these facilities. In 2014 the entire membership of the USNCCr has written to the sponsor of some of these facilities to discuss improving this representation and better engineering future redirections. Recognizing how important crystallography is within the output from our nation's scientific user facilities, I think one of the most valuable tasks for the USNCCr is to continue this dialog and perhaps to widen it if the response is not satisfactory.

The Future. The restrictions we saw in funding will continue to challenge the effectiveness of the USNCCr, and adapting to this will certainly be a challenge. Perhaps more frequent, but shorter virtual meetings would help.

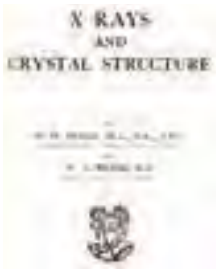
It may seem very early, but 2015 and 2016 will be critical years for planning a bid to host the IUCr for a US meeting in 2023, since the decision will be made in 2017. Likewise the next two years will be important in identifying individuals to recommend for roles in the IUCr. Fortunately, there is some time before travel fellowships and mentoring for 2017 need to be considered, but if there is interest the mentoring program can be launched into a process not tied to IUCr Congress years.

I hope that the USNCCr will continue its activities in community outreach, but I do feel that this is a critical time to begin work on developing educational objectives for undergraduate and post-graduate education. The USNCCr also has an important role to play in database support, and I hope that it will take on an even larger role in advocacy for crystallography at the nation's scientific user facilities. The USNCCr now has a partner and advisor in LACA, so Latin American outreach can become even more successful.

What can be achieved for all of these tasks depends on the time that members can volunteer. If the USNCCr can integrate community members productively, much more can be accomplished. If you are interested in being nominated for election to the USNCCr, contact any one of the members whose term expires in 2016 (Stephen Burley, Magali Hickey, Amy Sarjeant or Peter Stephens) as they will constitute the 2015 Nominations Subcommittee. Likewise the members just elected, with terms ending at the end of 2017, will handle nominations in 2016. I am particularly proud that the USNCCr membership has historically been highly diverse with respect age and gender, as well as the members' professional interests, and I hope that continues. I am very honored that I have had the opportunity to be part of this organization.

Brian Toby

Editor: The 2015 USNCCr roster can be found on p. 13. For information on USNCCr funding for crystallographic education, see p. 22.



X Rays and Crystal Structure: W.H. Bragg and W.L. Bragg, G. Bell and Sons, London, 1915, vii + 228 pp. + index.

This is the 100th anniversary of the publishing of this title, and it thus seems appropriate for a revisit in January 2015. I found an original edition on Amazon for a very reasonable price – about $40 including shipping from the UK. However, you can read the book on line in its entirety by searching for "Bragg 1915" at Google Books.

X Rays and Crystal Structure was published in early 1915, after the start of World War I and only three years after the discovery of X-ray diffraction by Max von Laue. The book appeared about six months before W.L. Bragg (son) was sent to France. It was while he was in France, working out how to locate German artillery positions by "sound-ranging," that W.L. learned he had won the 1915 Nobel Prize with his father (W.H.). W.L. was 25 and is still the youngest Nobel Laureate in the sciences.

W.H. wrote the book's preface in 1914. Here W.H. notes that publication was delayed by "the times" and as a result he wrote the preface himself. It is not clear why, except that maybe because he was the elder scientist. In the last paragraph W.H. states, "I am anxious to make one point clear, viz., that my son is responsible for the 'reflection' idea which has made it possible to advance, as well as much the greater portion of the work of unraveling crystal structure to which the advance has led." This makes it very clear for whom Bragg's law, $n\lambda=2d\sin\theta$, is named – namely, W.L. Bragg.

Chapter 1 is an introduction to the nature of X-rays and provides a glimpse into the problem of the dual particle/wave nature of light (and X-rays) and how the dual nature was unresolved as of 1915, in fact not to be resolved until 1924 by de Broglie. The Braggs also provide an introduction to von Laue's work that showed the wavelength of X-rays is on the same order as the distances between atoms in crystals so that ordered arrays behave like diffraction gratings. This provides the entrée to Chapter 2, "Diffraction of Waves."

In Chapter 2 the Braggs describe the diffraction of X-rays by a lattice of particles using the wave theory of light, deriving Bragg's law. Chapter 3 provides a discussion of the spectrometer W.H. used for measuring diffraction data, a device we would immediately recognize as forerunner of the four-circle diffractometer many of us used earlier in our careers. The authors use the term spectra to describe both the set of wavelengths that are emitted by a source as well as the reflections created when Bragg's law is satisfied.

Chapter 4 delves into the topic of "The Properties of X-rays" and focuses primarily on the work by Barkla on absorption. The concept of the scattering power is touched upon. It is worth noting that the concept of the scattering factor had not yet been applied to diffraction.

Chapter 5 covers the concept of crystal structure in the classic sense of a macroscopic solid with well-defined faces that are unique for each compound. Six crystal systems are given, as the trigonal and hexagonal are merged into one system – hexagonal. A brief description of symmetry is also provided.

Chapter 6 provides a detailed description of the then current state of knowledge regarding X-ray spectra. The relationship between wavelength and atomic number is developed. At the end of the chapter the spectra for a source observed by diffraction from the diamond (111) reflection are shown. We clearly see the alpha1/alpha2 split, but the reason for this was not known at that time.

The next chapters are the most interesting. Here, the Braggs develop crystal structure analysis. Chapters 7, 8 and 10 are "The Analysis of Crystal Structure," Parts 1, 2 and 3 respectively, with the intervening Chapter 9 titled "The Relation between Crystal Symmetry and the Arrangement of Atoms."

Chapter 7 starts off with a comparison of the structures of NaCl and KCl. The authors reach the conclusion they are similar based on the metrics of the diffraction angles. The Braggs do observe the intensities of the 111 reflections for the two materials are related to the atomic weight of the atoms.

In Chapter 8 the structures of the homologous series of carbonates: $MgCO_3$, $CaCO_3$, $MnCO_3$, $FeCO_3$ and $ZnCO_3$ are described, and the Braggs solidify the relationship of scattering power to atomic weight in, "*We conclude that the alternate planes* [of $FeCO_3$] *become equal in scattering power when their masses per unit area are equal*."* Just two pages later the idea of constructive and destructive interference is used to approximate the relationship of the intensities of the 100, 110 and 111 reflections of NaCl. This new information is used to solve the structure of FeS, which is rhombohedral not cubic. Is this the first structure solved by phasing?

Chapter 9 describes the basics of symmetry. This is a necessary prelude to Chapter 10, which attempts to describe the structure of more complicated materials like SiO_2, S_8, Fe_2O_3, Al_2O_3 and some spinels.

The temperature factor is described in Chapter 11, as is absorption as it applies to the diffracted radiation. The Braggs start to see the relationship between scattering angle and intensity stating, "Possibly the scattering by a single atom depends on the angle of scattering, though this does not seem likely to account for an effect [the inverse relationship between intensity and angle] which seems the same for all atoms. It is strange than no explanation is forthcoming of so simple and obvious an effect. *It must certainly be answered if progress is not to be delayed*." Clearly they had grasped the importance of the scattering factor but did not understand it yet.

The final chapter is "The Analysis of Laue Photographs," which applies Bragg's law to the interpretation of Laue diffraction patterns.

In summary what the Braggs knew at the beginning of 1915 was that X-rays were diffracted by the planes in a crystal lattice, the angle of the diffraction followed Bragg's law, the scattering power of a plane was proportional to the atomic weight, the position of the atom in the unit cell affected the intensity of the reflection by changing the phase relationships, and temperature and absorption were effects that needed correction.

Joe Ferrara

* The italics here are theirs, not mine.

Updates from 2014-15 AIP Science & Technology Fellows

Caitlin Murphy:

As a Congressional Energy Fellow, the beginning of the 114th Congress has been quite an exciting experience for me! The top priority of the new majority party was S.1 – a bill to legislatively approve the Keystone XL pipeline – and this dominated the Senate floor for nearly three weeks. The debate surrounding Keystone XL provided a great opportunity to learn about Senate politics and procedure. For example, the two sides of the debate were often portrayed as pro- and anti-pipeline, but the real debate was about whether to circumvent the established permitting process in order to accelerate approval of the proposed pipeline. And while the specific legislation being considered was to approve a single pipeline, the Senators' positions often reflected their more fundamental beliefs, about free trade, fossil fuels and the environment, or the balance of federal power.

My primary responsibility during the Keystone XL debate was to track the amendments, which was a fascinating experience. Each amendment reflected a Senator's effort to add a new layer to the legislation being considered. Some amendments were offered purely for messaging purposes; for example, the Senate took a number of votes on whether climate change was real and caused by human activity. Other amendments were directly related to the proposed pipeline project, such as Senator Franken's S.Amdt.17, which would have required the Keystone XL project to be constructed with iron, steel and manufactured goods produced in the United States.

One of the most rewarding opportunities of my fellowship was helping to draft Senator Franken's floor speech, in which he conveyed the importance of his amendment, both for the state of Minnesota and for manufacturers throughout the United States. Because I helped to prepare the Senator's remarks, I was granted Senate floor privileges to hear Senator Franken deliver his speech, which was incredible. Another benefit of amendment tracking was the opportunity for extensive face-to-face time with the Senator. Before each vote, I would explain what the various amendments did and offer my vote recommendations. Quite often these discussions took place directly adjacent to the Senate floor, which meant I also got to observe many other Senators interacting with their staff members and preparing to debate the various amendments.

The next major focus was on the topic of a recent Energy and Natural Resources (ENR) Committee hearing: liquefied natural gas (LNG) exports. During the hearing, it was fascinating to hear Senators on both sides of the debate defend their states' interests and priorities. I helped to prepare Senator Franken's comments and questions, which centered on his concerns that increased LNG exports will drive up domestic natural gas prices. In addition, I drafted language to highlight the federal government's prominent role in driving the natural gas revolution, by providing research and development funding for many technologies used in hydraulic fracturing.

Following the debate at the ENR hearing, Senator Franken decided that he needed to know more about whether the interests of all Americans were being adequately represented in the review of LNG export applications. So, I helped to draft language for a letter that the Senator – and 15 of his colleagues – recently sent to the Department of Energy (DOE) asking for clarification about whether the projected negative impacts on certain regions and sectors were being considered in their decisions regarding LNG exports. It was very rewarding to help Senator Franken present his arguments, and I look forward to hearing the answers to the questions he posed to DOE.

Finally, the next major focus in the energy portfolio will be ENR budget hearings, where representatives from each Department over which ENR has jurisdiction will appear to answer questions about their FY16 budget requests. This promises to be an incredible learning experience, and I look forward to describing it in more detail in the next issue of *RefleXions*!

Matthew McGrath:

Firehose.

That's the best way to describe my first five weeks as an AIP State Department fellow. It's like trying to drink from a firehose.

I've been in new situations before. I've had to learn new jobs before. Why is this so different?

The primary reason is probably the time scale on which events happen. In the academic world, one has time to read, write, run experiments, and analyze data. Deadlines come up, but one generally knows about them well in advance (conferences, thesis defenses, self-imposed deadlines to finish manuscripts). The workload is high, but relatively predictable. Perhaps this is because I've never been a full professor or the director of a research institution.

Here at the State Department, things change. Quickly. My schedule is completely open when I arrive Monday morning, but within a matter of hours Monday and Tuesday become filled up by meetings and phone calls. The list of things I want to accomplish gets thrown out the window so I can focus on "short-fuse" items: requests that come from higher up the hierarchy with a short turn-around time (not yet shorter than a day, although depending on the bureau it's not uncommon to respond to requests in a few hours).

While exciting, this pace has also led to many moments of frustration. I'm used to having more freedom over my schedule. I'm used to being able to plan for things, and to anticipate them. In the State Department, life is more about responding. Depending on the bureau you are in, this can occupy most or all of your life.

Regional bureaus, such as Europe or the Western Hemisphere, are known to be much faster paced than functional bureaus, such as the Bureau of Oceans and International Environmental and Scientific Affairs (OES), where I'm located. Crises happen frequently in countries; they occur more rarely in international environmental affairs.

Part of the firehose I mentioned above is responding to new things. When you don't know what action you're supposed to take, or even who to talk to, things take more time. Not to mention that it can be easy to step on proverbial toes. There is a hierarchy in the department. Sending an email to someone too high in the system about a trivial detail means it will be ignored. At the same time, not including someone in an email who is supposed to be there (because they have equities in the issue you're dealing with) leads to another set of problems. Just knowing whom to include, therefore, is a skill to acquire, and not a trivial one.

The second part of the firehose is just the sheer amount of information at my fingertips. People continuously send me email. I'm on a variety of news feeds highlighting various issues I'm dealing with. I attend lectures and seminars at think tanks. I'm trying to do background research for some projects, which involves sifting through hundreds of pages of reports by the United Nations. And then there are the cables. I love cables. These are reports drafted and sent out by the embassies in all countries. They let you know what is happening on the ground, and give you a feel about what priority items are. Along with the news sources, cables are the best way to figure out what you should be focusing on right now.

Five weeks is not a long time to be at any job. I don't even have the training wheels off yet, so my impressions of how this massive piece of machinery known as the Department of State works will certainly change. The creation of foreign policy is complex, and seems to be at times a bottom-up process, at times top-down, and often influenced by external events. All of this makes for an unpredictable, hectic, and extremely exciting environment to work in.

Editor: AIP Science & Technology Fellowships are available at the Department of State and in Congress. (For details on AIP fellowship programs including application procedures, go to: ***http://www.aip.org/policy/fellowships/overview***).

From the Editor's Desk

Readers have called our attention to two errors in the winter issue of *RefleXions*. On the cover, Paul Swepston pointed out that 'Hot Springs, AK' should be 'Hot Springs, AR' (Arkansas). Joe Ferrara indicated that Laurie Betts authored the review of Svante Pääbo's *Neanderthal Man*, which we mistakenly attributed to Joe himself.

Allyson Fry (***afry3@jhu.edu***) has written commenting on the editors note found on page 41 of the winter *RefleXions* (see Ally's letter on the column opposite). While providing background for some news items related to evolution and climate science taken from the National Center for Science Education (NCSE) website (see: ***www.ncse.com***), our editors note also mentioned the Musuem of the Bible currently under construction by the Green family, the owners of Hobby Lobby, in Washington, DC.

Allyson Fry writes:

Dear *RefleXions* Editors,

I am writing you regarding the "***NCSE - Update on Teaching Evolution***" that appeared in the Winter 2014 issue of *RefleXions*. I personally am a crystallographer who is also a Christian who agrees with evolution and the teaching of it in schools and does not see it in conflict with my religious beliefs (as is documented as a view held by Christians on the NCSE website). While I do not necessarily agree theologically and socially with everything the CEO of Hobby Lobby believes, the glancing statement [in your editors note] about the Bible museum he is building in DC implies that the country could not be moving forward on teaching evolution while people find religious truth in the Bible and personal importance of conveying that truth. While it is possible that the Bible museum that he is building could be analogous to the Creation Museum (see: ***www.creationmuseum.org***), [which] clearly does undermine the tenants of NCSE, that has yet to be seen and does not seem to be the focus of the museum as described by [a] recent *Washington Post* article [dated September 12, 2014] nor does the fact that this privately funded museum is being built have any direct effect on the teaching of evolution in schools. I believe that generalized statements like the one made in this update unnecessarily pit science and religion against each other and further increase the divide between scientists and those who believe science is out to attack their religious beliefs. Statements like this wrongly imply that science and religion can not coexist.

Sincerely,

Ally Fry

Index of Advertisers

ACA Living History – Charles E. Bugg

In his memoir Charlie describes how an academic crystallographer reinvented himself as the CEO of a biotechnology firm. The company he founded, BioCryst Pharmaceuticals, applies structure-based drug design to invent drugs for cancer, gout, Marburg, Ebola, influenza, and hereditary angioedema. During his career he assumed a leadership role in the NASA efforts to grow protein crystals in space. He also was President of the ACA (1987) and Editor-in-Chief of *Acta Crystallographica* (1987-1996).

I was supposed to be an orthopedic surgeon, not a crystallographer. My father was a prominent orthopedic surgeon. He had a private practice and was on the faculty in Orthopedics at Duke in Durham, North Carolina, where I was born and raised. My mother handled the finances for his practice. I was also destined to attend Duke University, where both of my parents, my grandfather and multiple other relatives attended college. My father's number one recreation, which also became mine, was hunting and fishing. These were very productive activities in rural North Carolina back then. It was a wonderful time for me to grow up in the South.

My mother was a strong influence in my life from the earliest times I can remember. I initially attended Calvert School, now renamed Durham Academy, a private school where all of my close friends were enrolled. However, my mother was a strong advocate of public schools, and she served a number of years on the Durham School Board. Although I think my family could have afforded private school at the time, she moved me to Morehead School, a public elementary school, when I was in the fourth grade. This school was in a pretty rough neighborhood. It seemed that I was routinely roughed up every day after school, and I made it clear that I thought I really should return to Calvert. My mom's solution was to hire a retired professional boxer to give me lessons in how to take care of myself. She sent me back into the jungle, where I finished elementary school. I actually ended up making some very good friends there, who had interesting backgrounds that I would have totally missed if I had stayed in private school.

Academic crystallography. I was admitted to Duke as a pre-med student in the summer of 1959. A real stroke of good luck was meeting Bebe Bradshaw on the first day of freshman orientation. She was and is my soul mate and has been a key support and driving force in all aspects of my life and career since those early years at Duke. My goal of becoming an orthopedic surgeon was gradually replaced by my interest in science; I really was turned on by physical chemistry, thanks to a superb professor, Marcus Hobbs. Professor Hobbs arranged for me to be admitted to the Rice graduate program. There I was fortunate to be accepted as a student in the laboratory of Ronald Sass, a young, dynamic faculty member pursuing various research programs in crystallography. I quickly became an expert in Weissenberg photography and manually estimated the intensities of thousands of film spots by comparing each separately with diffraction spots produced on standardized filmstrips. Computing was also a major challenge at the time, but it was fortunate that the Department of Electrical Engineering at Rice had recently constructed a computer that was available at night and on weekends. This computer occupied a complete floor of the engineering school and was constantly breaking down. It probably had a tiny fraction of the power of a modern smartphone, but it beat calculating Fourier maps by hand. When my PhD thesis was completed in 1965 I did not know exactly what I wanted to do with the rest of my life. Philip Handler, the Chairman of Biochemistry at Duke, was charismatic, knowledgeable and persuasive in his view that crystallography was a wonderful opportunity for me in biology. With help from Dr. Sass, a postdoctoral position was arranged at Caltech, in the laboratory of Dick Marsh and Bob Corey, and I joined them in the spring of 1965.

At Caltech my crystallography training moved to an entirely new level under the supervision of Dick Marsh. Dick is a notorious stickler for high precision in all aspects of crystallographic structural studies, beginning with collection of accurate diffraction data and through the final writing of a proper manuscript describing the analysis and results. I like to think that much of his obsession with doing everything as perfectly as possible rubbed off on me during my time with him, and that I, in turn, have had some success in passing those principles on to my students and postdoctoral fellows. Following the Watson-Crick discovery of the double helical structure of DNA, there was broad interest in better understanding the detailed atomic-level structures of nucleic acid components so that more precise models of nucleic acids could be developed. I was fortunate to obtain crystals of cytidylic acid, one of the four components of RNA, and the crystallographic analysis of that nucleotide became my first major project at Caltech. This also began what eventually became a multi-year career in crystallographic studies of nucleic acid components and their analogs.

The 1960's were a great time to be in science, and many career opportunities were available. I interviewed with several chemical companies and was especially excited by the broad research programs at DuPont. I ended up accepting a position with their polymer fiber division, at their research laboratories located in Kinston, North Carolina. Within six months, however, it was clear to me that a large company, even one as outstanding as DuPont, was not where I wanted to spend the rest of my life. I greatly missed the freedom and stimulation of academia. I submitted an application to NIH for a postdoctoral fellowship to continue my studies of nucleic acid components. I was delighted when I was awarded the fellowship and fortunately Dick Marsh was happy to accept me back into his lab.

In 1968 an unusual opportunity fell into my lap. The University of Alabama in Birmingham (UAB) had received a large NIH grant to establish an interdisciplinary Institute of Dental Research in Birmingham, which was home to one of the top dental schools in the country. I accepted positions as Assistant Professor in the Department of Biochemistry, Investigator in the Institute of

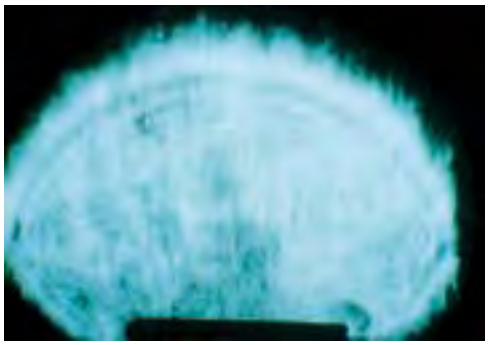
Dental Research, and Investigator in the Laboratory of Molecular Biology. I was extremely fortunate to be joined by my Caltech colleague Ulf Thewalt, who was eager to continue the fruitful crystallographic collaboration we had initiated in Pasadena. Our crystallography group undertook a variety of structural studies of purine and pyrimidine derivatives along with other molecules of biological interest. We also initiated productive studies of calcium and phosphate complexes and compounds, much to the joy of my colleagues in the dental field. I also enjoyed the benefit of collaborating with another of my Caltech colleagues, Mani Subramanian, who joined my group shortly after Ulf departed for a new faculty position in Germany. I think that these structural studies added significantly to the foundation for understanding the base stacking interactions of natural and modified purines and pyrimidines and the interactions that occur in biological systems between calcium and phosphate ions and various biological ligands. Howard Einspahr did a particularly beautiful job bringing together data from all of our calcium structures with other data from the Cambridge Structural Database to lay out a comprehensive picture of how calcium ions interact with various biological ligands.

In 1971, the UAB Cancer Center was designated one of the first Comprehensive Cancer Centers by the National Cancer Institute, and I served as the first Associate Director for Basic Sciences in the Center. We had an especially productive collaboration at that time with John Montgomery, a prominent medicinal chemist at nearby Southern Research Institute (SRI), and he was constantly urging me to focus our crystallographic studies on some of the important protein targets in cancer. It became increasingly clear to me that we needed to expand our Birmingham program into protein crystallography if we were going to take full advantage of opportunities in our new Cancer Center. UAB had a policy of optional faculty sabbaticals every seven years, and I decided to use this opportunity to learn the essentials of protein crystallography.

Sabbatical in Oxford. So, in the spring of 1974, Bebe packed up our three young children, and we took off for Oxford. My lab at Oxford was located next door to Dorothy Hodgkin, who had received the 1964 Nobel Prize in Chemistry for the structures of penicillin and vitamin B_{12}. She had transitioned to proteins and was then working on the structure of insulin. I was immediately at home and comfortable with Dorothy, who was incredibly warm and welcoming, and I felt that we shared a common bond in transitioning from small-molecule crystallography to protein crystallography. I quickly joined Margaret Adams on her studies of the enzyme 6-phosphogluconate dehydrogenase. Margaret was still in the early stages of determining this crystal structure, and she enthusiastically invited me to join her on this project. She proved to be a wonderful teacher who spent countless hours with me on details of protein crystallography. Margaret also provided me with another lifelong benefit when she introduced me to John Helliwell, a bright and enthusiastic graduate student working on this crystallographic project. John was at the early stage of his graduate research, so we were pretty much on the same level in our protein crystallography training and we were able to fully share the learning experience. We became close friends and continued to collaborate over the years after we left Oxford.

The PNP project. Shortly after my return from sabbatical in Oxford, John Montgomery and I undertook a project that would eventually cover many years of our future careers. We selected the human enzyme purine nucleoside phosphorylase (PNP) for pursuing structure-based drug design guided by protein crystallography. PNP had been demonstrated to be essential for normal immune responses since children born with defects in the gene for PNP lacked T-cell immunity. Inhibitors of PNP might prove useful clinically for treating T-cell mediated diseases, including a variety of autoimmune diseases, T-cell leukemias, and T-cell lymphomas. In addition, inhibition of PNP would block the biological synthesis of guanine from guanosine and could thus be used to inhibit the synthesis of uric acid, for treatment of gout. We knew that it would be a long and difficult road through the crystallographic studies, and through the eventual design, synthesis and development of inhibitors. Thus it was encouraging to have a target that might lead to drugs with multiple potential applications.

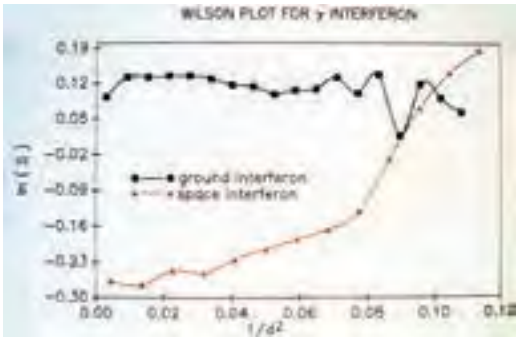
At this stage, John Helliwell had completed his doctoral studies and moved to Daresbury in northern England where one of the newly constructed synchrotron facilities was available. John had developed a beam line for X-ray crystallography, and he was delighted to join us as a collaborator on the structural studies of PNP. Bill Cook crystallized the enzyme and Steve Ealick led all of the crystallographic studies of PNP and of multiple complexes of the enzyme, work which encompassed much of the period between 1981 and 1985. The crystallographic analysis was a fairly difficult undertaking at the time since the crystals had a very high 80% solvent content, and thus diffracted relatively weakly.



A triglycine sulfate crystal growing in space with growing crystal face at the bottom. The disruptive density-driven convective flow seen on Earth is essentially eliminated in microgravity. This results in a more uniform growth process, which is governed by the rate of solute diffusion from the solution to the growing crystal surface. (Courtesy of Marshall Spaceflight Center.)

Crystallization in space. In 1985, our crystallography program at UAB took an unusual turn toward space. NASA was in the midst of designing the Space Station, and much of this work was being coordinated at the Marshall Space Flight Center in Huntsville, Alabama. Larry DeLucas developed into a charismatic leader of our space efforts, in collaboration with multiple NASA colleagues. By 1994 we had performed experiments on sixteen Shuttle flights. A total of 81 different proteins, provided by some 40 collaborators from protein crystallography groups around the

world, were included in crystal growth experiments. The most encouraging results were obtained in the space experiments with proteins that had been studied extensively, with successful crystallization results already obtained on Earth. Among this subset of proteins, there were several striking examples of improved crystal order as evidenced by enhanced diffraction resolutions and reproducible data from relative Wilson plots. At the time of this writing a huge set of double-blinded protein crystal growth experiments has just recently been returned from the Space Station for analysis by Larry and his collaborators, to evaluate the long-range potential of microgravity protein crystal growth.

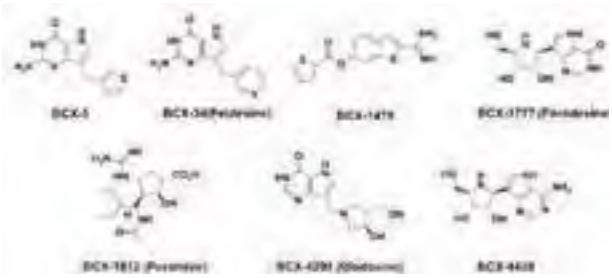


Relative Wilson plots comparing crystals of gamma interferon. Earth-grown crystals (black) are similar; the slope is zero. Space-grown crystals compared with Earth-grown crystals (red) are more highly ordered, giving a sloping line.

Service to ACA and *Acta*. In 1987, I had the pleasure of serving as the President of the American Crystallographic Association, and I decided to focus on the future of protein crystallography for my after-dinner talk the following year at the Philadelphia ACA meeting. I showed plots of the past growth of the Cambridge Structural Database and of the current growth rate of the Brookhaven Protein Data Bank, and I suggested that the plots overlaid pretty nicely when comparing the early stages of small-molecule crystallography with the then current growth rate for new protein crystal structures. If we assumed that the two growth functions were going to be approximately the same, I suggested that we could reasonably expect thousands of new protein crystal structures to be forthcoming during the next few years. This suggestion was met with considerable skepticism from my colleagues, but the Brookhaven Protein Data Bank soon saw a dramatic increase in the number of deposited structures. I later served as Chairman of the Brookhaven Protein Data Bank Advisory Board, which gave me an opportunity to help campaign for the increased funding that would be required for the Data Bank to handle the huge influx of new data. The last time I looked, the Protein Data Bank has data for well over 100,000 protein structures and is still growing rapidly. I also had the pleasure of serving as Editor-in-Chief of *Acta Crystallographica* and chairing the IUCr Commission on Journals during the 1987-1996 period. After much discussion with the protein crystallography community, and with the enthusiastic support of André Authier, President of the IUCr at the time, we initiated *Acta Crystallographica*, Section D, titled "*Biological Crystallography*," which is now one of the most popular journals in the *Acta* family.

Structure-based drug design. During the late 1980's, our crystallography group at UAB became increasingly focused on structure-based drug design, and we initiated crystallographic studies of several additional enzymes that we felt would be especially suitable drug design targets, including influenza neuraminidase and complement proteins. Both of these programs were later licensed from UAB to BioCryst. UAB was also focused on new approaches to molecular modeling that might be of broad use in structure-based drug design. Mike Carson led a creative modeling program focused on novel approaches for displaying protein sites by computer graphics in ways that would allow non-crystallographers to see features that would be helpful in drug design. Mike's early work produced the now popular algorithm for ribbon representation of polypeptide chains, and he designed new ways of displaying and interacting with protein sites. Scott Rowland pioneered other creative approaches for predicting interaction patterns that might be applied to drug design through extensive analysis of intermolecular contacts found in small molecule crystal structures from the Cambridge Structural Database.

BioCryst Pharmaceuticals. In 1985 we began to think seriously about seeking funding from private sources. BioCryst Pharmaceuticals, Inc. was incorporated in 1986. Y. S. Babu became our first employee, which turned out to be one of the most productive recruitments I ever made in my career. By 1993, our BioCryst/Ciba Geigy/UAB/SRI collaboration had produced a series of potent inhibitors of human PNP and a lead candidate, BCX-34 (later assigned the generic name peldesine) had been selected for clinical development by BioCryst. A second PNP inhibitor, BCX-5, was partnered with Warner Lambert Pharmaceutical Company for clinical development. When John Montgomery and I originally selected the PNP target for drug design back in the late 1970's, the objective was to end up with drugs for treating patients, so we were finally at an important milestone.



Some of the BioCryst compounds that have reached advanced stages of development.

The challenge we faced at that stage was to come up with the funds necessary to move BCX-34 forward into clinical development. I ended up grossly underestimating how much it would eventually cost to develop a PNP inhibitor, but it was clear that we would need to raise a lot of money to even initiate clinical development properly. Between 1986, when we first incorporated BioCryst, and 1993, we had repeatedly gone back to our original investors to raise additional funds. We had also brought in funding from a couple of prominent venture capitalists from national investment firms. However, these investors were not willing to

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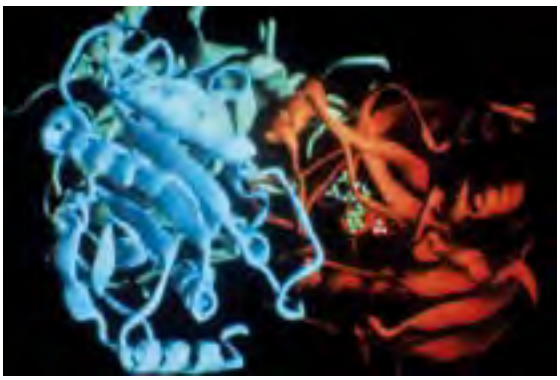
undertake the complete costs that would be required for clinical development of BCX-34, along with our planned expanded program for attacking additional targets. Our investors were painfully aware that drug development is incredibly expensive, very risky with high failure rates, and takes a long time to complete the necessary clinical trials for drug approval by the FDA. It was going to take a lot of capital, available continuously over a number of years, if we were to realize the goal of making our PNP inhibitors and other compounds available for treating patients.

The ideal strategy for us was to take BioCryst public through an initial public offering (IPO) of stock in the company. The bankers, analysts and the major investors involved felt that it would be critical for me to leave UAB and go fulltime with BioCryst. Bebe probably would have vetoed the move if Penny Mann, my wonderfully proficient administrative assistant at UAB, had not agreed to leave the university and come along to keep me organized, but fortunately Penny did. So on January 1, 1994, I jumped from my secure academic nest into the corporate world of biotechnology. It was immediately clear that I had a lot to learn, and I needed to learn it quickly. We successfully completed our IPO on March 7, 1994 and initiated trading on the NASDAQ stock exchange under the stock symbol BCRX.

Drugs for cancer, gout, Marburg, Ebola, influenza, hereditary angioedema. Meanwhile, Vern Schramm and his colleagues at the Albert Einstein College of Medicine (AECOM) had designed more potent PNP inhibitors by retaining the heterocyclic ring system of BCX-34 and BCX-5 and replacing the substituent on the 9-position of the heterocyclic ring with various positively-charged, nitrogen-containing side chains that formed strong contacts in the sugar-binding site of the enzyme. These compounds seemed to have greatly improved pharmacokinetic properties compared to BCX-34 and BCX-5, so BioCryst entered into a license agreement with AECOM for rights to develop these compounds. Two of these compounds entered advanced stages of clinical development. One of these, BCX-1777 (generic name forodesine), was eventually fully licensed to the UK-based pharmaceutical company Mundipharma for development in oncology. A second PNP inhibitor, BCX-4208 (generic name ulodesine), was licensed for a while to Roche for the treatment of psoriasis, but Roche eventually returned the rights to BioCryst where BioCryst continued development through Phase 2 clinical trials for treatment of gout.

An especially frustrating design program was our multi-year effort to develop clinically useful inhibitors of the viral enzyme, RNA polymerase. More recently BioCryst discovered that another compound in the portfolio of molecules licensed from AECOM is a potent inhibitor against hemorrhagic filoviruses, including Marburg and Ebola. The compound (BCX-4430) is currently under active development by BioCryst for treatment of Marburg and Ebola viral infections, with funding from the NIAID division of the National Institutes of Health. NIAID has awarded BioCryst a contract to develop BCX-4430 through Phase 1 for treatment of Ebola virus diseases. A study of BCX-4430 in nonhuman primates infected with Ebola demonstrated an antiviral effect and showed statistically significant survival benefit. BCX4430 is currently in a Phase 1 study.

Under Babu's supervision, the drug design group had impressive success with the development of inhibitors of influenza neuraminidase and serine proteases. The PNP and neuraminidase projects proved to be wonderful learning experiences for guiding future design work, since both enzymes crystallized with packing schemes that permitted ready access to their active sites by diffusion of compounds through the solvent channels in preformed crystals. Consequently, it was possible to perform iterative design of potent inhibitors of these two targets by modeling potential compounds using the native structure, binding the compounds directly to the active site by diffusion into native enzyme crystals, determining the structure of the complex, and seeing directly what additional changes to the inhibitor might be likely to further enhance binding. The PNP project ended up determining the crystal structures of approximately forty complexes that were examined through this iterative process and yielded a wealth of information about factors that would be useful in future design projects. This approach of iterative design also proved to be helpful in making structural changes to improve the clinical potential of potent inhibitors that had undesirable properties, such as toxicity, low solubility, poor bioavailability, poor pharmacokinetics or metabolic instability. By seeing directly what parts of an inhibitor might be modified, without altering the binding interactions, it was often possible to work around problems that prevented a good inhibitor from being a suitable drug candidate.



Ribbon drawing of the PNP trimer, showing BCX-34 bound in the active site.

Following this iterative approach, Babu's team developed peramivir, a potent inhibitor of influenza neuraminidase. Johnson and Johnson (J&J) advanced peramivir up through early Phase 3 US and international clinical trials before deciding that low oral bioavailability of the compound was unsuitable for their commercialization goals. The clinical studies had demonstrated a good safety profile for peramivir, and later in vitro tests against new emerging strains of influenza demonstrated that the compound has activity against multiple strains of influenza, including avian strains that have been of increasing concern as possible pandemic threats. Shionogi successfully completed clinical trials in Japan, which demonstrated that a single intravenous infusion of peramivir is effective for treating seasonal influenza. The intravenous drug is now on the market in Japan, under the trade name of Rapiacta. Peramivir is also approved in South Korea, and licensed to Green Cross Pharmaceuticals, under the trade name

Peramiflu. Meanwhile, BioCryst conducted additional clinical trials with intravenous peramivir (trade name Rapivab) through HHS/BARDA funding. In December 2014 the FDA approved Rapivab (peramivir injection) as a single injection treatment of uncomplicated influenza in adults. This was the first new antiviral treatment for influenza approved by the FDA in 15 years. It was also the first BioCryst designed drug to be approved by the FDA for marketing in the US. In addition, the serine protease inhibitor design program at BioCryst produced a potent inhibitor of the enzyme kallekrein. This orally administered compound (BCX-4161) completed a successful Phase 2 trial for treatment of patients with hereditary angioedema, and is currently in a larger Phase 2 trial treating patients with this devastating disease.

In 2007 I retired as CEO of BioCryst. The company had reached the stage where the focus needed to be on final approval of our drug candidates and commercialization of these drugs. We had established a BioCryst division in 2006 at the Research Triangle in North Carolina to oversee our clinical development and regulatory (i.e., FDA related) activities. The headquarters for BioCryst were moved to North Carolina, after the company recruited Jon Stonehouse to replace me as CEO of BioCryst. All of the research functions have remained in Birmingham under the leadership of Babu who is doing a superb job continuing the structure-based design program.

So what have I learned through these years in the biotechnology industry? First and foremost, it is incredibly difficult and expensive to develop a drug, and the risks involved in moving a compound successfully through the development process are immense. The FDA typically approves 20-30 new drugs each year, although they have done a little better than that recently. A very recent analysis from Tufts University concluded that the average cost of developing a drug currently exceeds $2 billion. What is the chance of a given compound making it successfully through the development process? I have seen figures ranging from 1/500 to 1/10,000. Our experience at BioCryst indicates that those odds are improved by systematic use of structural data during the design and drug optimization process, but a number of initially promising compounds still fail during the clinical stage of development. How long does it take to get a drug from discovery to patients? We started BioCryst in 1986, building initially on several years of research already completed at UAB and SRI, so our experience certainly suggests that it can take many years to get drugs successfully through the development process. The BioCryst drug development programs have required extensive funding over the years, but we have still spent considerably less than the average cost involved in getting drugs to market. Maybe that is attributable to the added efficiency of structure-based design, but we will have to wait and see when the BioCryst compounds now in development reach the market. Above all else, it is clear to me that structure-based design allows a small, focused team to undertake pharmaceutical design and development projects that have generally been the sole purview of large pharmaceutical companies.

The economics of a drug discovery and development company like BioCryst are interesting and somewhat unique. BioCryst has operated in the red, meaning without profits, ever since our founding in 1986. This is not completely surprising considering the long time generally required to move a drug successfully from design, through clinical development and through FDA approval processes. Despite this, BioCryst has remained solvent ever since completing our IPO in 1994. Many of the development costs of the drug candidates have been funded by pharmaceutical partners, and BioCryst has also benefitted from substantial government contracts for developing peramivir and BCX-4430. The deficit between the revenues obtained from these sources and the research and development expenses has been filled over the years by multiple equity offerings. The ability to raise this capital in the equity markets is highly dependent on BioCryst's status as a publicly traded company, which was the original carrot that lured me from academia to pursue the dream of using crystallography to develop important drugs that might eventually make a big difference in the lives of patients.

Before I actually retired as CEO, I was invited to open trading (ring the opening bell) at the NASDAQ stock exchange in recognition of BioCryst's twenty-year anniversary. Bebe and several colleagues from the company, including my long-time Administrative Assistant, Penny Mann, joined me. The main highlight was the picture of Bebe and me together, which was shown off and on during the day on the 100-foot Jumbotron screen at Times Square. I have a blown-up copy of this picture framed in my bathroom at home to remind me each morning of the many exciting, fun and stimulating paths crystallography has allowed me to follow and enjoy during my career.

Charlie Bugg

Bebe and Charlie featured on the NASDAQ Jumbotron in Times Square, in celebration of BioCryst's twentieth anniversary.

Editor: Watch for an extended version of Charlie's memoir that will be available in future on the ACA History Portal. Also take a look at the recent additions to the "ACA Beginnings" section of the website. See: ***www.amercrystalassn.org/history_home.***

Puzzle Corner

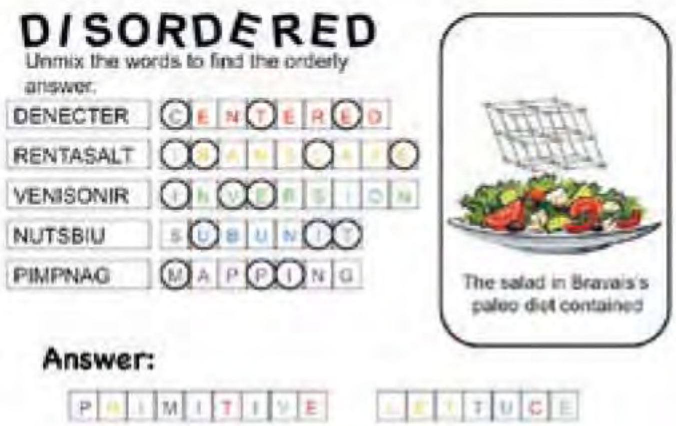
In this issue is the solution to the previous DISORDERED puzzle, a new one, and a new *Crystal Connections* puzzle. Be the first to send me the full solution to the *Connections* puzzle (*ffroncz@lsu.edu*), and your achievement will be mentioned in the next issue of *RefleXions*.

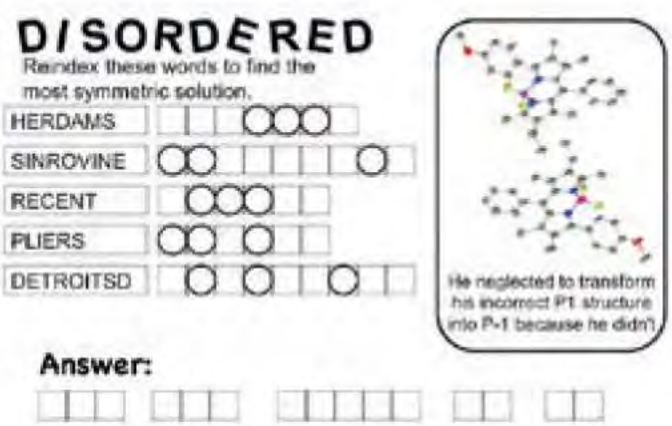
Frank Fronczek

Crystal Connections #2

What do the answers to these clues have in common?

1) Used for scrying by Galadriel
2) The moon's revolution period equals its _____ period
3) Helical inclined plane
4) Tax avoidance by merger with a foreign company
5) Converting words to a different language
6) In phonetics, the semivowel class of approximants.





MARCH - APRIL 2015

30-2 **BCA Spring Meeting.** University of York, UK. *www.crystallography.org.uk*

APRIL 2015

6-10 **MRS Spring Meeting & Exhibit**. San Francisco, CA. *www.mrs.org/spring2015*

7-9 **1st Meeting on Porous Molecular Solids.** Stellenbosch, S. Africa. *http://academic.sun.ac.za/POMOS2015/*

22-24 **Crystallography for the Next Generation: The Legacy of IYCr.** Rabat, Morocco. *www.iycr2014.org/legacy/conference*

MAY 2015

10-13 **Multi-Pole Approach to Structural Science.** Warsaw, Poland. *www.multipole-meetings.org*

19-21 **Modern Methods in Rietveld Refinement for Structure Analysis**. Florida State University, Tallahassee. *www.chem.fsu.edu/nasscc2015/workshop.html*

25-28 **Total Scattering for Nanotechnology on the Como Lake**. Como, Italy. *www.toscalake.com*

JUNE 2015

5-14 **48th Erice Course - Engineering Crystallography: From Molecule to Crystal to Functional Form.** Erice, Italy. *www.crystalerice.org/Erice2015/2015.html*

7-11 **International Conference on Structural Genomics 2015: Deep Sequencing Meets Structural Biology**. Rehovot, Israel. *www.weizmann.ac.il/conferences/ICSG2015*

7-12 **XVIII SAGAMORE Conference on Charge, Spin and Momentum Densities**. Santa Margherita di Pula, Italy. *www.sagamorexviii.org*

JUNE 2015, ctd.

7-20 **Zürich School of Crstallography 2015**. University of Zürich, Switzerland. *www.chem.uzh.ch/linden/zsc/*

JULY 2015

25-29 **ACA 2015 Annual Meeting.** Philadelphia, PA, Sheraton Philadelphia Downtown. ***Program Chairs: Kraig Wheeler & Louise Dawe. www.AmerCrystalAssn.org***

AUGUST 2015

23-28 **ECM 29.** Rovinj, Croatia. *http://ecm29.ecanews.org*

DECEMBER 2015

5-8 **AsCA2015.** Science City, Kolkata, India. *asca.iucr.org/meetings*

JULY 2016

22-26 **ACA 2016 Annual Meeting**. Denver, CO, Sheraton Downtown Denver. ***Program Chairs: Amy Sarjeant & Edward Snell. www.AmerCrystalAssn.org***

MAY 2017

26-30 **ACA 2017 Annual Meeting**. New Orleans, LA. *www.AmerCrystalAssn.org*

AUGUST 2017

21-28 28th Congress and General Assembly of the IUCr. Hyderabad, India. *www.iucr2017.org*

JULY 2018

20-24 **ACA 2018 Annual Meeting**. Toronto, ON, Canada. *www.AmerCrystalAssn.org*

NOTE: New schedule for ACA 2016: The meeting will begin on Friday, July 22. The workshops will be scheduled for all-day on Friday with the opening reception on Friday evening. The exhibit show will open Friday evening and end after the Monday poster session. Poster sessions will run Saturday - Monday, and the microsymposia will run Saturday - Tuesday. The awards banquet will take place Tuesday evening and session planning for 2017 will be on Wednesday morning.

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With the D8 QUEST ECO, making the right choice is easy. Not only is it affordable and economical with minimal maintenance, it is also environmentally friendly offering low power requirements and no external water cooling. Yet, the D8 QUEST ECO still delivers the high performance and quality data you have to come to expect from Bruker.

Contact us for a personal system demonstration **www.bruker.com/d8questeco**

BETTER **MEASUREMENTS.**
BETTER **CONFIDENCE.**
BETTER **WORLD.**

XtaLAB mini

MINI DIMENSIONS

MAJOR IMPACT

Rigaku's XtaLAB mini can make an immediate impact on your research and teaching efforts. Although small in size, the diffractometer has been designed to provide high quality data at an affordable price.

- **PUBLISHABLE STRUCTURES**
- **HANDS ON EXPERIENCE FOR STUDENTS**
- **LOW COST TO BUY, LOW COST TO OWN**
- **UTILIZES STANDARD MOUNTING TECHNIQUES**
- **OPTIONAL LOW TEMPERATURE CAPABILITIES**

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Rigaku Corporation and its Global Subsidiaries
website: www.Rigaku.com | email: info@Rigaku.com