

*Images from  
San Antonio ACA Meeting*

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Contributions to the *ACA Newsletter* may be sent to either of the Co-Editors:

*Connie Chidester* .....*Judith L. Flippen-Anderson*  
 2115 Glenwood Dr. ....Code 6030  
 Kalamazoo, MI 49008.....*Naval Research Laboratory*  
 .....*Washington, DC 20375*  
 tel. 616-342-1600 .....tel. 202-767-3463  
 fax 716-852-4846 .....fax 202-767-6874  
 conniechidester@earthlink.net .....flippen@nrl.navy.mil

Articles by e-mail or on diskettes are especially welcome. Deadlines for newsletter contributions are: February 1 (Spring), May 1 (Summer), August 1 (Fall) and November 1 (Winter). Matters pertaining to advertisements, membership inquiries, or use of the ACA mailing list should be addressed to:

Marcia J. Evans, Administrative Manager  
 American Crystallographic Association  
 c/o Hauptman-Woodward Medical Research Institute  
 73 High Street, Buffalo, NY 14203-0906  
 phone: 716-856-9600, ext. 321; FAX: 716-852-4846  
 email: marcia@hwi.buffalo.edu

**ACA HOME PAGE** <http://www.hwi.buffalo.edu/ACA/>

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**President's Column**



In the face of unsettling developments in the Israeli-Palestinian conflict, the IUCr Congress and General Assembly was necessarily moved from Jerusalem to Geneva. This was a disappointment, but we all should be grateful to the organizers, who effected this transfer without a hitch.

We celebrate the election of Bill Duax to the Presidency of the IUCr. Congratulations, Bill; matters are in good hands! And congratulations too, to Japan for their winning proposal for the 2008 meeting.

The ACA serves as the regional representative of all crystallographers in the western hemisphere, and the IUCr, through the USNCCr took the initiative to explore ways to better serve this population. Substantive discussions took place in Geneva with around twenty representatives from Latin and South America. I was unable to attend, as I had left the day before. The following was synthesized from reports from Past President Bill Stallings and USNCCr Chair Marvin Hackert, who did attend, and to whom I am grateful.

Graciella Diaz De Delgado presented a draft of a set of bylaws prepared in order to establish a SIG of the ACA. Discussions revealed divergent opinions on the possible benefits of setting up such a SIG, and the bottom line was a need for better communication. Several of the representatives felt that a SIG was not the appropriate vehicle to build stronger relations between the ACA and other crystallographers in the western hemisphere. It was pointed out that prior efforts on the part of the ACA Council to implement representation on the Council from Mexico had foundered, and that formation of a SIG could provide more effective two-way communication on which to build a stronger basis for such representation on Council. There were different opinions, too, on the wisdom of accepting assistance from the United States community. Nonetheless, it would be worthwhile to build a fund that can be used to extend financial support for Pan-American participation, and I hope that ACA members will consider contributing to a special fund established for this purpose. This will appear among the list of special funds on the (sigh) second page of the new dues form.

On another note, those of us fortunate enough to participate in the first half of the meeting were treated to an evening of Israeli dancing on Saturday night, which created the environment for an all too brief celebration of their joyous heritage. The instructor had all participants moving nearly in unison through a cycle of at least 25 different dances, none of which lasted for longer than a few repeated motifs. It was, in a word, splendid!

*Charlie Carter*



*Newsletter Editors and native at the San Antonio meeting banquet*

### *Corrections*

*The editors regret that in the Summer Newsletter the identities of the Martin J. Buerger Award and the Bertram E. Warren Award recipients were interchanged. Please note that Professor James Ibers will receive the Buerger Award and Professor Takeshi Egami will receive the Warren Award. (See page 4.)*

### **Editor's note:**

In the past the ACA Newsletter has not had an editorial column. However, a happy thought occurred to us recently: -that editorials need not necessarily be written by the editors. *Other* journals often publish "guest" editorials; perhaps we should try that too. As it happened, we had just received an article from Cele Abad-Zapetero which seemed ideal for this purpose. The following is reprinted from *Crystallography and Crystallographers: Personal reflections on the past, the present and the future of crystallography on the occasion of the 125-year anniversary of Zeitschrift für Kristallographie. Z. Kristallogr.* **217**, 2002, 26.

We hereby invite others to submit appropriately philosophical thoughts when the mood strikes.

**NOTE: The contact information listed in the 2002 Exhibit Show Guide for Emerald Biostructures was incorrect. Please contact Emerald at: 7869 NE Day Rd. W., Bainbridge Island, WA 98110, Phone (206) 780-8535; Fax (206) 780-8549; info@emeraldbiostructures.com**

## *Protein Crystallography is Dead: Long Live Protein Crystallography!*

I ventured into the field of protein crystallography in the early seventies, a few years after my undergraduate degree in physics from the Spanish educational system. This was a system where trespassing the boundaries of traditional disciplines was not encouraged. I was interested in biophysics as a general area of scientific enquiry and I needed to find a venue for my scientific interest and curiosity. Three years of independent work at the University of Salamanca, Spain, reading textbooks, papers and attending lectures in biochemistry, microbiology and genetics gave me enough background to move on. However, I needed to have more formal training in the field. Complementing my scientific studies with studying English allowed me to come to the U.S. with a Fulbright Scholarship in 1972 to pursue graduate studies in biophysics at the University of Texas at Austin.

There, I encountered protein crystallography as a worthwhile field of endeavor for PhD work, mentored by Profs. Marvin L. Hackert, Hugo Steinfink and Larry Fox. Six extraordinary years at Purdue University with Prof. Michael G. Rossmann completed my training, and I ended up using protein crystallography as a tool to design drugs in the pharmaceutical industry. A practical use for protein crystallography was an amazing, and certainly unforeseen, professional and technical development.

In those years, the annual meetings of the ACA were vibrant with methodology sessions related to protein crystallography. All the different facets of protein crystallography were presented and discussed: the chemical trickery of growing crystals and preparing multiple isomorphous derivatives; methods and strategies of data collection and pro-

cessing; the difficulties of extracting anomalous signals; the subtlety of using molecular replacement techniques to solve structurally related proteins; and discussions on the best pathway to a successful refinement. Of course, there were also sessions on novel structures, but these were relatively few.

Protein Crystallography has become the unexpected victim of the ingenuity, inspiration and hard work of protein crystallographers themselves. Years of crystallographic and mathematical expertise are now canned in effective, rapid and user-friendly software packages, covering all aspects of the process: from Patterson function solution and heavy atom location to phase calculation and model refinement. Rapid computers with practically unlimited disk space and memory drive all this crystallographic wizardry. Protein crystallography, as a discipline of further technological development appears to be dead, or is it?

The icons of the structural revolution in the biological sciences propelled by the success of protein crystallography can be seen in those myriads of molecular images in textbooks and scientific journals in areas far removed from crystallography. Novel protein structures are unveiled all over the world at the rate of two-to-three per day and the number of homologous protein structures and protein:inhibitor complexes analyzed daily

runs probably in the hundreds. The Protein Data Bank now holds over sixteen thousand protein (or protein-nucleic) acid entries, just prior to the structural genomics revolution.

Thus, is it worth teaching crystallography? Is it a legitimate field of study? Yes, but in a different context. Protein crystallography shares concepts and mathematical tools with other methods of structural study (i.e. electron microscopy, image reconstruction, fiber diffraction, NMR, etc.). In view of the power and effectiveness of crystallographic software, the teaching of macromolecular crystallography should be included within the framework of other diffraction and image reconstruction methods as hands-on classes. Courses emphasizing not the grinding details of all the structural methods, but their strengths, limitations and future extensions to other experimental set-ups should be planned. The amazing possibilities of routine access to synchrotron sources of tunable, intense X-rays for all kinds of structural analysis should be emphasized to inspire new generations to devise novel experimental designs.

Indeed, there is much that remains to be done, both in quantity and quality. The number of protein and macromolecular structures that remain to be uncovered by crystallographic or diffraction methods is staggering. It is worth mentioning that the first draft of the human genome is estimated to contain a minimum of approximately 40,000 proteins, with several thousands or several tens of thousands having been sequenced in organisms ranging from bacteria to fruit fly. The numbers *per se* should keep protein crystallographers busy for a few decades, even after developing high throughput methods, so popular now in the first years of the twenty first century.

It should not be forgotten, that in spite of how streamlined the process of protein structure determination is, 'direct methods', analogous to the ones used in the small molecule crystallography domain, are not yet routine in protein crystallography. Mathematical and computational crystallographers are still trying to cut open a clear path in this realm of protein crystallography. This goal appears closer and even reachable; much more so than only a few years ago. Achieving this goal would certainly be a precious feather in the cap of methods development and mathematical crystallography.

A well-known fact should also be mentioned. The refinement R-factors in most of the refined proteins (~20%) do not reach the level achieved by small molecule crystallography (<10%). Possibly, our refined protein structures do not fully account for all the atomic intricacies (i.e. motions, conformational variations, solvent structure among others). Whether this is an inherent limitation of protein crystallography or just restricted by our current tools is an open question.

It is the novel results and future experimental developments that intrigue me the most, and where I would suggest the most spectacular and amazing functional discoveries will be made. The physico-chemical dissipative processes that are responsible for life are dynamic and far from thermodynamic equilibrium. Currently, protein crystallography is unveiling the structures of pieces in a detached, context-free environment. Processes such as the functioning of biological clocks, signal transduction and

organismic development are dynamic processes. The complexity and subtlety of these processes demand that macromolecular crystallographers fine-tune their tools and experimental methods to get closer to the dynamic reality where macromolecules 'play their act.' In spite of known successes, time-resolved diffraction studies of macromolecules are still in their infancy. In addition, would it ever be possible to examine the spatial and temporal order of dissipative structures using scattering or diffraction methods combined with synchrotron radiation sources?

After learning its methods and seeing the amazing development that has followed, I can say that protein crystallography is not dead and will never be. On the contrary, It will live forever ingrained within the fabric and texture of biochemistry, structural and molecular biology, cell biology and so many other fields. Its practitioners are now disguised as prominent molecular and cell biologists, biochemists, protein and materials engineers, drug designers, and many other biophysical and biomedical researchers. It is subjacent in all the branches of scientific enquiry that attempt to understand life processes at the molecular and structural level.

*Cele Abad-Zapatero*

### 2003 Martin J. Buerger Award

The M. J. Buerger Award recognizes mature scientists who have made contributions of exceptional distinction in areas of interest to the ACA. The award committee (J. A. Kaduk, R. H. Blessing, G. Bricogne, and S. Doublié) is pleased to announce that the winner of the 2003 Buerger Award is **James A. Ibers** of Northwestern University.

No other chemist/crystallographer active today has played a more prominent role in the development of crystallography as the most important structural method of the chemical sciences. His voluminous (more than 821 publications) and excellent research record has had enormous impact on the progress of modern structural inorganic chemistry. He is among the 150 most-cited chemists, and his influence is magnified by his mentorship of the many students and postdocs who have gone on to prominence. It is no accident that all crystallographers trained in his lab run well-aligned diffractometers, scrutinize the output of computer codes, express themselves carefully, and think that science should be fun.

Today Jim is known as a chemist who uses structural data, but an important part of his early work was the calculation of scattering factors. His concern for fundamental crystallographic parameters led

to his Co-Editorship of *Volume 4* of the *International Tables for X-ray Crystallography*. He is recognized for having compiled and integrated a simple-to-use and reliable software system which forms the basis of at least two of the program packages marketed today.

The central importance of structural data to the field of inorganic chemistry can be traced to Jim's long service on the editorial board of *Inorganic Chemistry*, which led to service on several other editorial boards. His insistence on careful data collection, thoughtful refinement, and interpretation of the structures in light of bonding theory raised the standard of structural chemistry.

Hydrogen bonding was an early theme of Jim's scientific work; the book *Hydrogen Bonding in Solids*, (written with Walter Hamilton in 1968), is still a classic. He later moved into transition metal chemistry; an enduring interest was the bonding of small molecules (CO, NO, N<sub>2</sub>, CO<sub>2</sub>, CS<sub>2</sub>, etc.) to transition metals. Studies of synthetic oxygen carriers led him into bioinorganic chemistry (Fe-S clusters and models for Cu-containing proteins). Experience with porphyrin complexes developed into studies of low-dimensional conductors. An interest in the activation of C-H bonds also grew out of the work with small ligands. Solid state chemistry is Jim's most recent interest. He was attracted in part by the crystallographic problems, which are both exacting and central.

Jim has served the crystallographic community as a member and Secretary/Treasurer of the USNCCr and on several IUCr committees and Commissions. Jim's contributions to crystallography mirror those of Martin Buerger himself, and make this award especially appropriate.

*James A. Kaduk*



**James A. Ibers to receive  
Martin J. Buerger Award**



**Takeshi Egami to receive  
Warren Award**

### 2003 Bertram E. Warren Diffraction Physics Award

The Warren Award Selection Committee, (Paul Butler, Chair; Jacqueline Johnson; Ian Robinson; and Boguslaw Stec) is pleased to announce that the recipient of the 2003 Warren Prize of the ACA is Professor Takeshi Egami of the University of Pennsylvania. Prof Egami is cited for his pioneering use of pair distribution functions from diffraction data to study disorder and defects in imperfect crystals leading to new understanding of the physics of complex materials.

Professor Egami earned his Bachelors's degree in Applied Physics in 1968 from the University of Tokyo and his Ph.D. in Materials Science and Engineering from the U.Pennsylvania in 1971. He did his postdoctoral research at the University of Sussex in the UK and was a visiting scientist in Germany for a year before returning to the U. Pennsylvania in 1973 as Assistant Professor in the Department of Materials Science and Engineering. He became full professor in 1980 and is currently Department Chairman and Director of the Materials Characterization Facility. Despite these administrative duties Egami remains a pioneering and active researcher.

Professor Egami's research using x-ray and neutron diffraction methods to study structures in disordered materials on multiple length scales is of fundamental importance to materials science. His recognition of the importance of local correlations in the real-space structure of disordered crystalline materials, and the way in which these can reveal physically important effects that are masked in the average structures obtained by conventional crystallography has led to a new way of viewing chemical and

structural disorder. His research covers a broad range of materials and his work has led to new insights into colossal magnetoresistant (CMR) manganites, ferroelectric and piezoelectric oxides, nano-crystalline powders of ceria used in automotive catalytic converters, quasicrystals, and high T<sub>c</sub>-cuprates. He has succeeded in establishing quantitative connections between structure and properties by careful attention to the details of the experimental approach and interpretation. He has pioneered the application of atomic pair distribution function (PDF) methods to defective crystals and his insights from these studies have substantially influenced both the theory and the modeling of complex materials. He possesses a rare balance of ability in both theory and experiment which allows him to leverage his advances in both areas. For example, he followed up his theoretical predictions about electron lattice coupling and superconductivity in high-T<sub>c</sub> materials with insightful single-crystal phonon measurements revealing a previously unnoticed anomalous break in the phonon dispersion due to the electron-lattice interaction.

The same questions of intrinsic and extrinsic local structure in complex materials are fundamental to many technologically important substances such as polymers, shape-memory alloys and elastic interfaces. As such, his work lays an invaluable foundation for future efforts at unraveling structure in many classes of materials. The advent of new high-intensity sources like the APS and SNS opens up a plethora of new opportunities for this area of research which, in turn, will be invaluable in fully exploiting these new major facilities as tools for the understanding of materials.

Professor Egami's key role in the development of the PDF methodology, his many significant contributions that used PDF to shed new light on the physics of disordered crystals, and the impact of his efforts on the future of materials science in general make this award a particularly fitting recognition of his contributions. It is also particularly fitting that the earliest application of PDF methods to study amorphous carbon were made by Bertram E. Warren for whom the prize is named.

Paul Butler

*Frank Allen with David Bardwell at the CCDC Exhibitor's booth at the San Antonio ACA Meeting*



### *Frank Allen to Receive Herman Skolnik Award*

The Herman Skolnik Award of the ACS Division of Chemical Information, recognizing outstanding contributions to and achievements in the theory and practice of chemical information science, will be presented at the Fall 2003 ACS meeting in New York to Dr. Frank Allen. Dr. Allen has driven the development of much of the software for data acquisition and validation, and for the retrieval and analysis of information in the Cambridge Structural Database (CSD), and has also pioneered many of its research applications. His success during his career at the Cambridge Crystallographic Data Centre (CCDC) is attested to by the widespread and increasing use that is now being made of the CSD, which is distributed to over 50 countries world-wide and to more than 100 commercial organizations, principally pharmaceutical and fine chemicals companies in the USA, Western Europe and Japan. Dr. Allen has worked at CCDC since 1970, following undergraduate and graduate studies (BSc, ARCS, DIC, PhD) at Imperial College, London and postdoctoral work at the University of British Columbia. He moved to the embryo CCDC in 1970, first as a Research Associate and then as Senior Research Associate. He was promoted to Principal Scientist in 1989, and Scientific Director in 1997, where he has had overall responsibility for the scientific development of the CCDC. **He becomes Executive Director of the CCDC in October 2002**, following the retirement of Dr. David Hartley. Allen's scientific contributions are detailed in over 200 publications that cover three major research categories: chemical crystallography, chemical information science, and data compilations and handbooks. Also worthy of particular note is his close involvement with the CIF format, which has become the *lingua franca* for the exchange of crystallographic information, his continuing work on the electronic submission and validation of experimental data, so as to ensure the integrity of the structural information in crystallographic databases, and the formal links he has helped to establish between the CCDC and many of the world's primary scientific journals. Allen's achievements have been widely recognized. Much of his work is concerned directly with crystallography, and he has been the Editor of *Acta Crystallographica B* from 1993-2002, and held a range of senior positions in the BCA, the European Crystallographic Association and the IUCr. He has helped to organize many microsymbiosia, meetings and conferences on behalf of these organizations, and was Co-Director of an Erice Crystallography School in 1998. He became a Fellow of the Royal Society of Chemistry in 1992, was awarded the RSC Silver Medal and Prize for Structural Chemistry in 1994, and was appointed to the Editorial Board of *Chemical Communications* in 1999, and to a Visiting Professorship at the University of Bristol, UK in 2002. He is a member of the International Advisory Board of the Protein Data Bank (RCSB) and has done much to promote the scientific value of all of the crystallographic databases in the international arena.

Bill Town CINF Awards Committee, Ass't Chair

### Michael M. Woolfson Awarded 6th Ewald Prize

Professor Michael M. Woolfson was awarded the sixth Ewald Prize for his exceptional contributions in developing the conceptual and theoretical framework of direct methods along with the algorithm design and computer programs for automatic solutions that changed the face of structural science and for his contributions to crystallographic education and international collaboration, which have strengthened the intellectual development of crystallographers worldwide. The award was presented as part of the Opening Ceremony of the Geneva IUCr Congress on August 6 2002, and Professor Woolfson gave a gracious and interesting lecture. The Prize consists of a medal, a certificate and an award of US\$ 30,000. It is presented once every three years during the triennial International Congress of Crystallography. Previous recipients have been: G.N. Ramachandran (1999); M.G. Rossmann (1996); N. Kato (1993); B.D. Vainshtein (1990); and J.M. Cowley and A.F. Moodie (1987).

### Clifford G. Shull Prize Announced

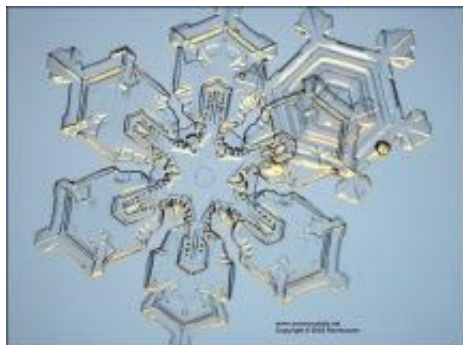
At the inaugural meeting of the American Conference on Neutron Scattering (ACNS) on June 23-27, 2002, NSSA President James Rhyne announced the establishment of the Clifford G. Shull Prize in Neutron Science of \$5,000 to be awarded every two years. Shull shared the 1994 Nobel Prize for Neutron Scattering with Canadian researcher Bertram Brockhouse. Dr. Robert Shull, son of the Nobel prize winner and the leader of the Magnetic Materials Group at NIST presented a review of Cliff Shull's life and accomplishments to the ACNS attendees. Nominations will be solicited by the prize committee starting next year with the winner of the first Shull Prize to be announced at the 2004 ACNS.

Julie Borchers, NSSA Secretary,  
julie.borchers@nist.gov

### Call for applications for ICDD Scholarships

To encourage promising graduate students to pursue crystallography oriented research, the International Centre for Diffraction Data (ICDD) has established the Ludo Frevel Crystallography Scholarship Fund. Recipients will receive a \$2,250 award. Applications must be received by the ICDD by 31 October 2002.

Snowcrystals.  
..see page 15



### Neutron Protein Crystallography Capability at the Spallation Neutron Source at ORNL

On May 28, 2002 at the ACA meeting in San Antonio, a Steering Committee including scientific personnel with expertise in protein crystallography, enzymology, and neutron instrumentation was formed to look into the requirement of a dedicated neutron protein crystallography instrument at the Spallation Neutron Source (SNS). The SNS will be the world's most intense source of neutrons when it becomes operational in 2006 at Oak Ridge, Tennessee. The protein crystallography Steering Committee members are Gerry Bunick (ORNL), Chris Dealwis (University of Tennessee), Leif Hanson (University of Tennessee), Thomas Koetzle (BNL), Andrew Mesecar (University of Illinois, Chicago), Arthur Schultz (ANL), P. Thiagarajan (ANL), and Jinkui Zhao (SNS).

Although protein crystallography at the third generation x-ray synchrotrons can identify protons for problems where highly ordered crystals are available, these x-ray structures measured at cryo-temperatures are usually insufficient to understand the solvation shells and protonation states. Enzymologists and protein crystallographers are seeking complementary techniques to identify the protons and water molecules at active sites of enzymes, in order to elucidate the mechanistic details of their function. Based on its recently demonstrated success in identifying protons and bound water molecules, even at a relatively modest resolution of 2.0 Å, neutron proton crystallography carried out at room temperature has great potential to play a major role in the understanding of the mechanisms of enzymes (I. Tsyba & R. Bau, "Neutron Diffraction Studies on Proteins", *Chemtracts-Inorganic Chemistry* **15**, 233-257, 2002). Some of the unique features of neutron diffraction are its ability to "see" hydrogen atoms; to distinguish between hydrogen and deuterium in order to characterize H/D distributions; and to obtain data with the sample maintained at room temperature (because there is no radiation damage). The major reasons for the limited impact of neutron protein crystallography to date are the lack of suitable instruments and the limited flux at the presently available neutron sources, which means that very large crystals generally are required. This situation will change with the advent of the SNS, which will allow for unprecedented higher data rates. The Steering Committee plans to work towards building support among the scientific community and the funding agencies for the neutron protein crystallography instrument at the SNS.

The Steering Committee feels strongly that neutron protein crystallography is extremely important for solving a number of important problems in enzymology and structural biology, and that the SNS offers a unique opportunity to increase the productivity of this technique. The Committee has adopted action items for the coming year including: (1) To hold focused workshops bringing the scientific community together, to discuss the scientific problems that require neutron protein crystallography and the forming of an SNS Instrument Development Team (IDT), and (2) To showcase the science using neutron protein crystallography at the *Transactions Symposium* at the 2003 ACA annual meeting in Cincinnati.

P. Thiagarajan



### Pauling Prize Committee Report

Established in honor of the late Linus Pauling, no more than five prizes are awarded annually to posters presented by graduate or undergraduate students. The Pauling Prize consists of \$200 and a copy of Pauling's *General Chemistry*. The committee had to make difficult choices this year because there were so many excellent posters that could easily have won a prize in past years. After careful considerations of each poster for scientific merit, layout, and orally presentation, we selected five winners. Brief

### Oxford Prize Winners

The Oxford Cryosystems Poster Prize is awarded to the best poster presentations at the annual ACA meeting dealing with low temperature analysis. Above left: **Xiangyun Qui** with PPX143: *Unusual Charge Transfers between Inplane Orbitals in Layered  $\text{La}_{0.92}\text{Sr}_{2.08}\text{Mn}_2\text{O}_7$* . At right: **David Cooper** with PPX089: *The Crystal Structure of the PDZ Domains of Syntenin*.

summaries of their posters are provided below:

**Brian Helfrich** of Kansas State University presented the poster titled *Design of Ternary Crystals*. By carefully placing hydrogen bond donors and acceptors on molecules, Brian was able to assemble coordination complexes with open-frameworks. He has demonstrated that, despite the competing intermolecular forces that exist in solutions of coordination complexes, hydrogen-bonding substituents on ligands may be used to engineer crystals. His mentor is Alicia Beatty. **Editor's Note: Brian also won the Crystal Engineering Prize for this poster; see his picture, page 27**

**Francisco Hernandez-Guzman** of Hauptman Woodward Institute presented the poster titled *Crystal Structure of Human Placental Estrone Sulfatase, A Membrane-bound Enzyme in Estrogen Biosynthesis*. Francisco described how estrone sulfatase catalyzes the hydrolysis of estrone releasing unconjugated steroids. The enzyme is implicated in intracrine



biosynthesis of estradiol that is responsible for proliferation of hormone dependent breast tumors. Francisco also proposed how the membrane is anchored to the membrane of the endoplasmic reticulum. His mentor is Debashis Ghosh,

**Andrey Kovalevsky** of SUNY-Buffalo presented the poster titled *Photocrystallography, IR and DFT Calculations of Solid-State Photo Induced Linkage Isomers of RuSO<sub>2</sub> Complexes*. Andrey combined spectroscopy and diffraction in the study of excited states of Ru-complexes in crystals. He used light excitation of diffractometer-mounted Ru-crystals, kept at low temperatures, to study the nature of short-lived species. He further analyzed the side-on coordinated SO<sub>2</sub> species by IR and DSC. Relative stabilities of the intermediates were estimated by DFT methods. His mentor is Philip Coppens.

**Sonia I. Patenaude** of University of Ottawa presented the poster titled *Structure- Function Relationship of the ABO Blood Group Glycosyltransferases*. Sonia examined the basis of substrate specificity using glycosyltransferase A which converts the O-antigen to the A-antigen and glycosyltransferase B that converts the O-antigen to B-antigen. The two enzymes differ only in 4 amino acid residues. Sonia also described their enzyme mechanism based on enzyme-substrate interactions. Her mentor is Stephen V. Evans.

**Samantha Perez-Miller** of Indiana University Medical School presented the poster titled *A 1.4 Å Structure of Mitochondrial Aldehyde Dehydrogenase: Understanding Nicotinamide Isomerization*.



**Back row: Francisco Hernandez-Guzman, Joshua Sakon, Kimberly Terry, Jeff Wilson. In front: Sonia Patenaude, Christina DeWitt and Samantha Perez-Miller**

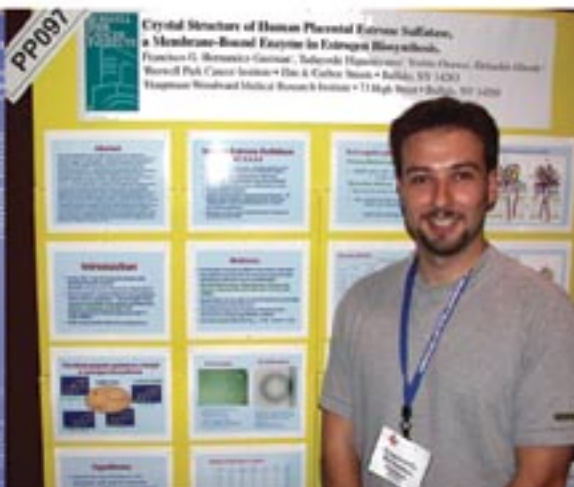
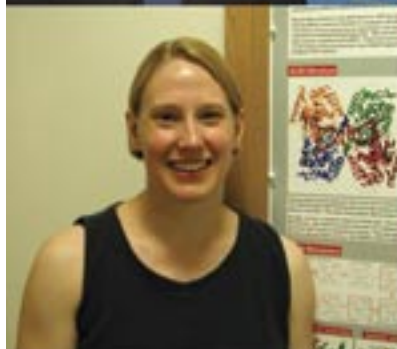
The catalytic mechanism of aldehyde dehydrogenases has remained somewhat controversial because nicotinamide mononucleotide, the business end of the NADH is conformationally disordered in known structures, or has been found in different positions in the different structures. Samantha was able to stabilize the nicotinamide in position by mutation of the conserved active site Cys to Ser. Based on the high-resolution structures of the mutant in the presence of oxidized and reduced NADH, she proposed a most plausible enzyme mechanism for the hydride transfer and activation of a water molecule. Her mentor is Thomas D. Hurley.

Honorable Mentions were awarded to **Jeff Wilson, Kimberly Terry, Nicklaus Steussy, Christina DeWitt,** and **Leanne Wybenga-Groot.**

These young scientists made outstanding original contributions that advanced the science of chemistry or biology. We encourage them to take an active leadership role in the crystallographic community. If they remain active in our society, our future will be in great hands.

*Joshua Sakon, Pauling Prize Committee Chair*

**With posters: Andrey Kovalevsky at left; Samantha Perez-Miller below; Sonia Patenaude, center; Francisco Hernandez-Guzman at right**





**Ron Jenkins (1932-2002)**

Dr. Jenkins held many prestigious honors including Licentiate of the Royal Institute of Chemistry, Fellow and Chartered Physicist of the Institute of Physics, Distinguished Fellow of the International Centre for Diffraction Data, and Honorary member of the BCA. Ron's technical achievements were applauded by the technical community; he was the recipient of numerous awards including the 1982 Gold Medallist of the New York Chapter of the Society for Applied Spectrometry, the 1986 Birks Award in X-ray Spectrometry, the 1993 Barrett Award in X-ray Diffraction, and the 2001 Jenkins Award for lifetime achievement in the advancement of the use of X-rays in materials analysis. The Jenkins Award was established in his honor for his career of dedication to the advancement of analytical X-rays, characterized by his diverse roles as practical analyst, applications specialist, author of landmark texts, educator, Executive Director of the ICDD, and member of the Denver X-ray Conference Organizing Committee. Ron authored a number of textbooks on X-ray analytical methods, 11 book chapters, and approximately 230 papers dealing with X-ray applications and instrumentation. He also served as a reviewer for several publications. Ron had a passion and enthusiasm for teaching which he applied to workshops, lectures, and clinics given around the world.

In his years at the ICDD, Ron served as a member of the Board of Directors, as Principal Scientist, and as Executive Director and Corporate Secretary. He directed the efforts to convert the Powder Diffraction File® to CD-ROM technology, helped to create the journal, *Powder Diffraction*, expanded the ICDD Grant-in-Aid Program, worked to internationalize the ICDD by increasing its membership, and directed the Denver X-ray Conference.

Ron's affirmation and dedication to the Christian faith was exemplified as his research interests expanded beyond X-ray analysis to studies of scientific artifacts, including the Shroud of Turin. Lecturing on this topic to more than 6000 people, Ron also served as an expert X-ray diffractionist on the Shroud of Turin Research Project.

Aside from his role as a world-renowned scientist, Ron was a humanitarian in the truest sense of the word. His compassion for life, coupled with his charismatic sense of humor, was evident in all aspects of his life, always bringing leadership and enthusiasm to the tasks at hand. Ron's passion for teaching became a life-long goal. He is remembered for his gift of mentoring, his story-telling abilities, his love of music, and his Christian and family values.

Following is Ron's obituary. The family has mentioned that they can be contacted at Ron's e-mail address, [Jenkins@icdd.com](mailto:Jenkins@icdd.com), for those that would like to send a personal message.

The X-ray community has lost one of its leaders. All those who benefited from Ron's unselfish sharing of his many talents have lost a caring, compassionate friend.

*Tim Fawcett, Executive Director,  
ICDD*

Dr. Jenkins, born in 1932 in Oxford, England, died peacefully on June 19, 2002 of prostate cancer at his home in Downingtown, PA. A Celebration of Life Service was held at the West Chester Church of the Nazarene, West Chester, PA. 19382.

Dr. Jenkins studied Chemical Physics at Oxford Polytechnic Institute in England and obtained his Ph.D. from the Polytechnic Institute of New York. He was a Licentiate of the Royal Institute of Chemistry, a Fellow and Chartered Physicist of the Institute of Physics, a Distinguished Fellow of the International Centre for Diffraction Data and an Honorary Member of the BCA.

Dr. Jenkins worked as an analytical chemist at Esso Research in Abingdon, England, and later as head of the X-ray Applications Lab for Philips Electronics in the Netherlands. He was transferred to the US in 1971 and became the Principal Scientist for Philips Electronics Instruments. In 1985 he accepted the position of Principal Scientist with the ICDD and in 1996 was appointed its Executive Director.

...In addition to his technical achievements, Dr. Jenkins was a member of STURP (Shroud of Turin Research Project) and lectured over 50 times to about 6000 people regarding the artifact. His book *Closing the Gap between Science and Religion* outlines his dedication to the Christian faith. He was most recently a member of the Church of the Nazarene, where he served as Council member and Choir Director. He was also a trustee of the Eastern Nazarene College in Quincy, Massachusetts for many years.

Dr. Jenkins is survived by his wife of 47 years, Phyllis, his five children and five grandchildren. The family requests that donations be given to American Cancer Society.



*Snowcrystals . . . see page 15*



**John White 1922-2001**

John Greville White, who played a role in the determination of the crystal structure of vitamin B12, died 22 August 2001 in Missoula, Montana, age 79. He was born in Saltcoats, Ayrshire, Scotland on 27 March 1922 and studied chemistry at the University of Glasgow, where he obtained Bachelor of Science and Doctoral degrees in 1944 and 1947 respectively. He then moved to Princeton University where he taught physical chemistry for eight years. The following ten years were spent at the RCA laboratories in Princeton, NJ. He was then appointed Professor of Physical Chemistry at Fordham University in

New York City where he remained until his retirement in 1986. He went to Missoula in 1992. John leaves a wife, Julie, a daughter Susan who is an Associate Professor and Chair of the Chemistry Department at Bryn Mawr College, and a son, Ian, who lives with his family in Clinton, Montana.

While he was at Glasgow University John determined the crystal structures of several polycyclic aromatic hydrocarbons in the laboratory of J. M. Robertson. Some of these studies were done in collaboration with Sidney Abrahams. These structures included naphthalene, anthracene, coronene, pyrene, dibenz[a]anthracene, and benzoperylene. These determinations have formed the basis of our understanding of the packing forces in such aromatic structures.

At Princeton, John decided to tackle a more difficult problem and opted for one of the most difficult of the time, vitamin B12. This material had been isolated at Merck Laboratories in New Jersey and John started work on it in 1949. When he found that Dorothy Hodgkin was working on the same problem, they both decided, he wrote, that “the problem was certainly large enough for two

groups, but that we should keep in touch on progress, and this was done.” In those days electron density maps were tedious to calculate but John derived electron density maps of the vitamin and compared his with those derived in Hodgkin’s lab in Oxford, England. Their combined work led to a report of the structure of the vitamin in 1954. John is a coauthor of at least five articles on vitamin B12 and his data were used in many of the structure refinements by Ken Trueblood at UCLA. John wrote “The Royal Society actually published the final papers with which I was involved on my fortieth birthday, which was rather ironical in view of the elapsed time since the first photographs were taken.”

John continued to be active in crystallography and wrote a chapter on the subject for Glasstone’s “Treatise on Physical Chemistry.” He also published over 75 scientific research articles. On a personal note, he and his wife Julie welcomed me to the U.S. when I first arrived at which time we were able to compare electron-density maps.

*Jenny P. Glusker*

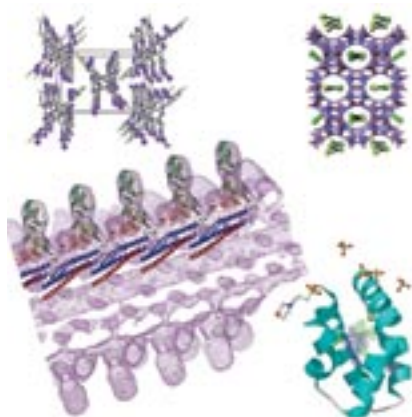
**Contributors to this issue**

Charlie Carter, Cele Abad-Zapatero, Jim Kaduk, Paul Butler, Bill Town, P. Thiyagarajan, Julie Borchers, Joshua Sakon, David Cooper, Tim Fawcett, Jenny Glusker, Dan Anderson, William Pennington, Keiichi Namba, Valeri Petkov, Frank Rotella, Jane Richardson, Bill Duax, Bob Sweet, Jim Fait, Claude LeComte, Tom Terwilliger, Carol Brock, Jesus Valdes-Martinez, Christer Aakeröy, Lee Brammer, Alicia Beatty, Dario Braga, Brian Helfrich, Hugo Steinfink, Jeffrey Deschamps, Ed Meyer, Gloria Borgstahl, Ardeschir Vahedi-Faridi, Marilyn Olmstead, Sergey Lindeman, Sue Byram, Tom Mason, Simon Billinge, Chris Bystroff, Yancho Devedjiev, Zygmunt Derewenda, Bernhard Rupp, Larry DeLucas, Howard Einspahr, Allan D'Arcy, Bob Cudney, Maryjane Tremayne, Abraham Clearfield, Clint Potter, Bridget Carragher, Bob Glaeser, John Spence, Larry Falvello, Fred Hollander, Ward Smith, Bill Stallings, Zhong Ren, Andrew Mesezar, Patrick Carroll, Richard Staples, Nicholas Silvaggi, Michiyoshi Nukaga, Ethan Merritt, John Bollinger, John Hart, Marilyn Yoder, Roman Hillig, Art Olson, Alexander McPherson, David Sayre, John Miao, Bernie Santarsiero, Karl Volz, Jeanette Krause Bauer, Bobby Barnett

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*Images from San Antonio*



**Upper left:** from *Crystal Engineering-1 Session: Polymorphic Interconversions of Tetrapyrrolylpyrazine Through Decomposition of Halogen-Bonded Complexes*. William T. Pennington<sup>1</sup>, Rosa D.B. Walsh<sup>1</sup>, Clifford W. Padgett<sup>1</sup>, Timothy W. Hanks<sup>2</sup>. <sup>1</sup>Dept. of Chemistry, Clemson University, <sup>2</sup>Dept. of Chem., Furman University. **Crystal packing of tpp-6I2 chains.**

**Upper Right:** *Impact of Scattering on Nanoscience and Nanotechnology-1 Session: Structure of Nanocrystalline Materials by the Atomic Pair Distribution Function Technique*, Valeri Petkov, and Simon J.L. Billinge, Dept. of Physics and Astronomy, Michigan State University. **Cs intercalated into the pores of zeolite. The framework is zeolite-ITQ4 with long 7Å wide channels that are filled with Cs<sup>+</sup> ions.**

**Lower right:** from the *Poster Session on New Macromolecular Structures: Granulysin Crystal Structure and a Structure-Derived Lytic Mechanism*, Daniel H. Anderson<sup>1,2</sup>, Michael Sawaya<sup>1,2</sup>, Duilio Cascio<sup>2</sup>, William A. Ernst<sup>2</sup>, Robert Modlin<sup>2,3</sup>, Alan Krensky<sup>4</sup>, David Eisenberg<sup>1,2</sup>. <sup>1</sup>Howard Hughes Medical Institute, <sup>2</sup>UCLA DOE, Molecular Biology Institute, <sup>3</sup>UCLA School of Medicine, <sup>4</sup>Dept. of Pediatrics, Stanford University. **Many aspects of granulysin's function may be read from its crystal structure. In the granulysin crystal, the negative solvent ions bind in a sheet. The crystalline granulysin is oriented relative to the ion sheet as a very similar protein has been predicted to initially bind a bacterial membrane prior to lysis. The wire grid in the figure represents a hollow core that we think facilitates the left and right parts sliding past each other during lysis. These molecules have been suspected of conformation change as they dig into membranes.**

**Lower left:** from the *Electron Microscopy of Biological Macromolecules Session: Structural Mechanisms of Self-assembly and Polymorphic SuperCoiling of the Bacterial Flagellum*, Keiichi Namba, Protonic NanoMachine Project, ERATO, JST & Advanced Technology Research Laboratories, Matsushita Electric Industrial Co., Ltd. **Docking of the atomic model of the flagellar protofilament into a cryoEM density map of the filament. The atomic model of the straight protofilament obtained by X-ray crystallographic analysis of a core fragment of flagellin was slightly twisted for docking.** [Samatey, F.A. et al, (2001) *Nature* 410, 331-337]. A similar figure was published in a *Science* news article by Dennis Normilein (March 15, 2001) about the *Nature* paper .

## Crystallography Web Watch

The ACA Communications Committee continues its “Web Watch” in an attempt to keep members informed of useful (and fun) web sites, primarily of the crystallographic persuasion. While some of these sites may be well known to you, other readers might not know about them...

**MAD Phasing** — You have certainly heard the term “MAD phasing”, and you may have even solved a structure using the MAD phasing method, but do you understand the theory behind it? A nice presentation of the theory of MAD phasing can be found at Ethan Merritt’s University of Washington web site on anomalous x-ray scattering: <http://www.bmsc.washington.edu:80/scatter/>

**Maximum Likelihood** — Another technique you’ve probably come across but may not fully understand is structure refinement using the method of maximum likelihood. Randy Read’s maximum likelihood section of the Protein Crystallography Course at the Cambridge Institute for Medical Research (UK) web site provides a good starting point: <http://www-structmed.cimr.cam.ac.uk/Course/Likelihood/likelihood.html>

**Protein Structure Validation** — The Richardsons’ 3D Protein Structure Laboratory and Kinemage Home Page features, among other services, *MolProbity*, a web service for protein structure validation using all-atom contacts and geometrical criteria provided by the Richardson laboratory at Duke University. <http://kinemage.biochem.duke.edu/> (see article, page 17)

**Software/Documentation Links** — The Structural Chemistry Section of the University of Manchester (UK) web site provides access to many web links of interest to the crystallographer. Among them are links to documentation on UNIX, scripting languages and a number of popular software packages, as well as many crystallographic web sites: <http://spec.ch.man.ac.uk/Prog.html>

**Snowflakes** — With the winter season “around the corner”, can thoughts of snow be far away for most of us? Information about the physics of snow crystals and snowflakes can be found at [Snowcrystals.net](http://www.snowcrystals.net) of the California Institute of Technology (Caltech) web site. The figures at right are from the *Patricia Rasmussen Collection 2002* (© Rasmussen 2002). [Snowcrystals.net](http://www.snowcrystals.net) also details the history of early scientific observations and photographs of snow crystals, how to take photos of snowflakes, preserving snow crystals, and unusual snowflakes: <http://www.its.caltech.edu/~atomic/snowcrystals/>

**Molecular Graphics Movies** — Eric Francoeur of the Max-Planck Institute for the History of Science maintains a web site devoted to the history of visualization of biological macromolecules. The site is a gallery of early molecular graphics movies (two at present), including the crystal structure of the insulin dimer: <http://www.umass.edu/molvis/francoeur/movgallery/moviegallery.html#sequence1>

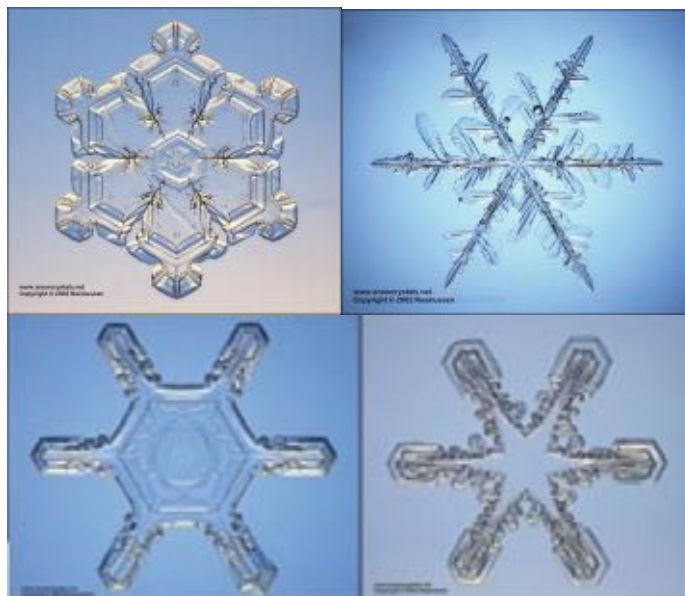
**For the Macintosh user** — CrystalMaker Software (UK) sells two programs for use on a Macintosh platform. The first, *CrystalMaker*, allows users to build, display and manipulate crystal and molecular structures, and the second, *CrystalDiffract*, to simulate, display and manipulate x-ray and neutron powder diffraction patterns from any crystal structure displayed in *CrystalMaker*: <http://www.crystallmaker.co.uk/>

Another program for building, studying and visualizing crystal structures on a Macintosh computer *CrystalDesigner* can be purchased from Crystal Structure Design AS, a software vendor in Norway: <http://www.crystaldesigner.no/>

**Hard-to-find Books** — Looking for a hard-to-find or an out-of-print book? Look no further than Alibris. Alibris offers millions of new, used and hard-to-find books from a worldwide network of booksellers and from their own shelves. A search by subject for “crystallography” turned up some 500 titles by authors such as Bragg, Buerger, Bijvoet, Guinier, Lipson, Lonsdale, Pauling, Wilson and Wyckoff, and the prices seemed fairly reasonable, too: <http://www.alibris.com>

**Reciprocal Net** — Indiana University, in collaboration with a number of other universities and Los Alamos National Laboratory, maintains a distributed database of molecular structure information. The Reciprocal Net project is funded by the National Science Foundation and is expected to become part of the National Science Digital Library in 2003. The structural information can be accessed graphically (stick models with which users may interact) as well as digitally: <http://www.recipnet.indiana.edu>

Have a favorite web site that you’d like to see in a future **Crystallography Web Watch** and possibly linked on the ACA web site? If so, send the web address and a short (1 or 2 sentence) description to **Frank Rotella** ([fjrotella@anl.gov](mailto:fjrotella@anl.gov)).



Patricia Rasmussen Collection 2002 (© Rasmussen 2002)

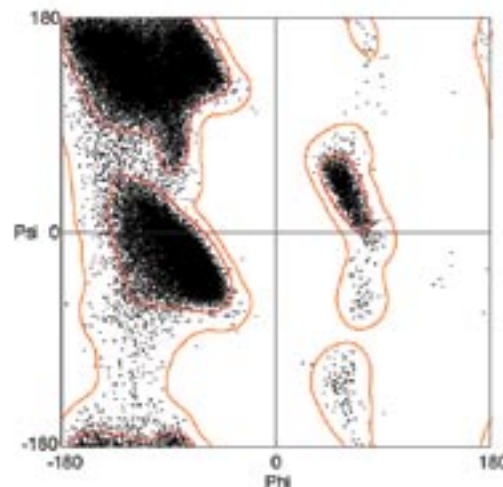
## Macromolecular Structure Validation and Improvement Program

Jane Richardson spoke in the Protein Folding and Design session of the San Antonio ACA meeting about the *MolProbity* web service for protein structure validation that is available on Jane and David Richardson's web site at <http://kinemage.biochem.duke.edu> (along with the free open-source software, data, examples, and literature references).

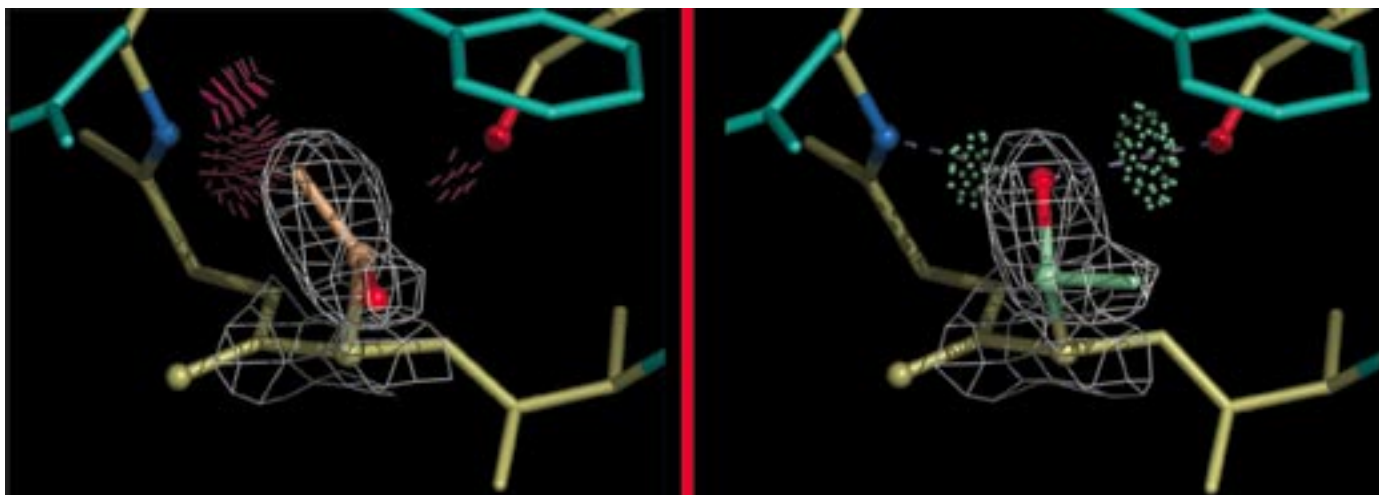
*MolProbity* (by Ian W. Davis) is an interactive macromolecular structure validation tool which uses the all-atom contact analysis and geometrical criteria developed by the Richardson lab at Duke University. The geometrical aspects include new Ramachandran criteria (see plot) that differentiate strained but plausible conformations from truly worrisome outliers, C $\beta$  deviation as a measure of bond angle distortions, and a new sidechain rotamer library in which each entry represents both a peak in the high-quality data and a reasonable energy minimum. Much more accurate structures were used than available for ProCheck, plus filtering by B-factor. The all-atom contacts not only provide an independent and sensitive indicator of fitting problems, but can often show how to correct the model. A current focus of the Richardsons' research is the use of all-atom contacts to analyze and improve macromolecular structures, including application to structural genomics as part of the SouthEast Collaboratory for Structural Genomics.

You can use *MolProbity* interactively on the web by uploading your own protein or nucleic acid coordinates in PDB format, or by specifying a file from the PDB site ([www.rcsb.org](http://www.rcsb.org)) by its four-character code. The program *Reduce* (by J. Michael Word) adds missing hydrogens and optimizes local H-bond networks, including automatic flips of Asn, Gln, and His where needed. There is online help in the form of a *MolProbity User Manual*. An online tutorial is also available, which guides the new user through the process of analyzing a typical structure.

In her talk, Jane showed an example from the PDB: the sulfate-binding protein 1SBP in which there was a "backwards threonine" (see figure at left below). *MolProbity* clearly highlighted the all-atom clashes and distorted C $\beta$  geometry, displayed in 3D online in the Java version of *Mage* (by David C. Richardson). She then demonstrated how the model can be corrected in the interactive *Mage/Probe* system, which provides an idealized sidechain with choosable rotamers, rotatable angles, and real-time update of the all-atom contacts; the result is shown at bottom right. A simpler version of the contact display can be used while rebuilding in O or XtalView.



*Favored and allowed regions of the general case Ramachandran plot (Gly, Pro, and pre-Pro are treated separately) for 81,234 high-resolution, low-B residues. The "outlier" region covers 58% of the plot but only 0.05% of the data.*



*A "before" picture of 1SBP Thr32 as deposited in the PDB (with 2FoFc electron density). Red spikes are the "clash" portion of the all-atom contacts, with atomic overlaps >0.4Å.*

*An "after" image of the sidechain: idealized, rebuilt, and positionally refined. The clashes are replaced with H-bonds (green dots), and Rcryst lowers about 0.07% with each such fix-up (Rfree, when available, decreases more)*



*Awards Banquet. Top left: Ira Flatow receiving Wood Award from Charlie Carter; Dan Anderson and Katherine Kantardjieff with mementos from Charlie of their 2001 service as Local Chairs; Next row: Marcia Evans and her daughter Vanessa Vair and Patti Coley; Narasinga Rao receiving Service Award from Charlie; Jeff Deschamps and Jeff Bell. Third row: Judith Flippen-Anderson testing light for camera; Doug Dorset; Kay Onan; Carroll Johnson. Last row: Ann Wolff (2003 food & entertainment coordinator), Bobby Barnett, and Dave Rognlie; Graciela Diaz de Delgado with Iris Torriani.*

**2002 ACA Meeting - San Antonio**

The **2002 ACA Annual Meeting**, in conjunction with the **American Association for Crystal Growth** was held in the Henry B. Gonzales Convention Center in San Antonio May 25-30, 2002. A highlight of the meeting was the presentation of the **2002 Patterson Award** to **Doug Dorset**. His fine lecture will be published in the Winter issue of the *ACA Newsletter*. Reports on the *Transactions Symposium on Crystal Structure Determinations from Powder Diffraction Data*, the *Crystal Engineering* symposium, and the Patterson Award Symposia on *Electron Crystallography* and *Electron Microscopy of Biological Macromolecules* are on following pages, along with reports on most of the scientific sessions.

The ACA Service Award was presented to **Narasinga Rao** "in appreciation for many years of wise financial counsel" (see photo center of facing page). The **Elizabeth A. Wood Award** "for excellence in bringing science to the attention of a wider audience" was presented to **Ira Flatow** (facing page at top left). See page 8-9 for **Pauling and Oxford Awards**.



*ACA President Charles Carter presenting Patterson Award to Doug Dorset*



*At left: the indefatigable Local Chairs Marvin Hackert and Ray Davis.*

*At right and below right: the equally dedicated and conscientious Program Chairs Wally Cordes and Travis Gallagher.*



Crystallographers are usually interested in patterns, and meeting attendees will certainly remember the beautiful and interesting carpeting throughout the meeting rooms of the Convention Center. The carpet borders, which seemed to be characters of some strange alphabet, were especially intriguing. Robert Salluce, PR manager for the Convention & Visitors Bureau, and formerly Project Coordinator of the Convention Center Expansion Project, provided some information for the curious, along with the carpet tile images at left. *"The carpeting . . . tells the story of San Antonio by using iconographic images from the city's history and cultural experience. The patterns were developed by artist Celia Alvarez Munoz, in collaboration with the center's design architects Kell Munoz and their staff, after a process that included public input. Celia is an accomplished world-renowned artist .. who .. coordinated the process and the ideas. The brands, in particular, are cool -- as there are two "cattle brand" patterns, positioned next to each other. One is based upon registered South Texas cattle brands, while the other patterns juxtapose contemporary symbols".* So -- the "strange alphabet" is made up of cattle brands.



*At right: happy crystallographers, returning to the riverwalk hotels after a long day of science, enjoying MARGueritas, good food and good company aboard the MARbarge.*







*Enjoying the opening reception at the Hyatt Regency in San Antonio: (top, from left: Suzanne Fortier, Chris Gilmore, Fusen Han, Bill Watt, Bryan Craven and Robin Shirley; 2nd row: Marcia Evans, Vanessa Vair, Robert Lam, Jeffrey Bell, Charlie Carter and Jane Griffin; 3rd row: Richard Harlow, John Parise, Tom Koetzle, Jeff Deschamps, Bill Stallings, Gary Newton. Lower left: Cele Abad-Zapetaro and Marvin Hackert; Jane Griffin and Bill Duax on near side of table.*



From left: Leif Hanson, Ed Westbrook, Jim Fait, Howard Robinson, Wayne Anderson, Bob Sweet, Paul Phizackerly.

### New Methods in Macromolecular Crystallography

New technology and innovative methods accompany good science. So it is with PX. Synchrotron sources, new detectors, the steady march of increasing computer capacity, and innovative computing algorithms provide the muscle to drive the current trend to greater speed and accuracy in structure solving. This session focused on these innovations. **Ed Westbrook** is one of the pioneers in the development of imaging detectors for diffraction experiments, and he discussed new developments, starting with those outside his group. A number of groups are developing detectors that employ discrete semiconductor devices. Here devices will be made in two layers: a simple top layer of silicon will absorb x-rays and store the resulting charge. This will be “bump-bonded” to a bottom layer that carries the readout electronics. These will not soon be made more than a few cm across, so one will have to arrange some mechanism of “shingling” a surface to get a large detector. A second possibility is the use of thin-film transistor (TFT) technology to produce a single, monolithic detective surface relatively inexpensively. This device will require a photocathode surface; elemental selenium is a possible choice. The idea seems promising, but a chronic difficulty is that the readout is noisy.

Westbrook himself is pursuing three separate lines of development. Firstly his group has devised and are developing a new faster read-out scheme for the charge-coupled device (CCD) detectors that are in general use today. Secondly they are working with the Bruker / Nonius company in development of the detector system wherein the image of a x-ray sensitive phosphor is projected on a large CCD by a huge (f 0.8) compound lens. Finally, they are attempting to develop an innovative detector system wherein thin chips of Si are plasma-drilled; each hole is filled with a p-or n-type semiconductor; and these semiconductor columns become the basis for pixellation of the detector surface. Again, cm-scale devices will need to be shingled to produce a workable area detector.

Mathematical physics and innovative numerical methods have been the core of crystallography since the early days; thus it continues today. They help us to interpret our measurements in terms of structure. An important goal always must be not to over-interpret our data. **Ethan Merritt** described a procedure for comparing the validity of different techniques for modeling anisotropy in protein structure, which he applied to several refinements at resolutions between 1 and 2Å. He compared the results of modeling anisotropy first by assigning the standard six anisotropic displacement parameters (ADPs) to individual atoms, then by treating each peptide chain as a rigid group exhibiting translational, librational, and screw motions (known as the TLS method). A conclusion he drew fairly reliably is that the TLS method works well over this entire resolution range. The ADP method becomes preferable to TLS at

resolutions higher than somewhere around 1.6Å, but the precise resolution at which this happens is dependent on the specific structure. Both the ADP and TLS methods performed better than purely isotropic refinement.

Modern PX depends absolutely on our ability to supercool (freeze) macromolecular crystals to prevent radiation damage in the x-ray beam. Workers have always asked, “If cold is good, is colder better?” Several groups have tried to work at temperatures in the low teens (Kelvin) rather than at the ~100K accessible with liquid nitrogen as a cryogen, but it’s hard work. Finally several have succeeded, and **Leif Hansen** reported on the result of a collaboration among three groups. They adopted a cryostat that directs a fine, high-velocity stream of gaseous helium on the specimen. The advantages of this approach are that it is parsimonious in its use of liquid He, and that cooling is very good. The disadvantage is that the stream itself must be hard to hit when one applies the specimen crystal. In careful measurements performed on multiple crystals of two different proteins, the group found that colder seems to be better. Multiple data sets measured from the same crystal clearly showed less damage at the lower temperature. The one cloud on the horizon (iceberg in the sea) might be that frequently the crystals held at roughly 20K showed cracks. This group’s current hypothesis is that there is an unrecognized phase change that hydrated protein crystals experience at this low temperature, and the strains of this are cracking the crystals.

**“If cold is good, is colder better?”**

In the mechanisms of many biological macromolecules, a single hydrogen atom may govern the course of the reaction being catalyzed. A powerful but perhaps underused tool for determination of structures that involve H atoms is neutron scattering. Neutrons scatter from atomic nuclei, not from electrons like x-rays, so the issue of scattering amplitude is substantially more subtle. For example, simple hydrogen atoms (protons) scatter with negative amplitude. On the other hand deuterons (a neutron and a proton) scatter with a strong positive amplitude similar to that of other atoms like C, N, O, etc. **Benno Schoenborn** pioneered the use of neutrons for macromolecular crystallography and stimulated several triumphs in interpretation of structure because protons could be found accurately. He reported the completion of a new neutron-diffraction station at the Los Alamos spallation neutron source. The station has an arc-like neutron area detector, and will employ pseudo-Laue methods to measure data. The neutrons are created by collisions between high energy protons and a tungsten target. Their momentum determines their

wavelength by the deBroglie equation. Time resolution within the detector reveals the speed, hence momentum, hence wavelength of the neutron. The BioCARS Laue software has been modified to analyze these data, and preliminary results seem to be satisfactory. The station has recently begun operations.

Synchrotron-radiation sources are expensive to operate, and one always looks for ways to make this use efficient. Two groups described their efforts to produce reliable and easy-to-use software to operate their synchrotron beamlines. **Howard Robinson** described how several beamlines at Brookhaven's NSLS are using software that organizes the data-collection and beamline-control functions into a single integrated package, which can be operated either at the beam lines or remotely over the Web. He also demonstrated a prototype information-management system that carries users' personal information, descriptive information about the project, and experimental data throughout an experiment, from the initial application for beam time through the measurements, to the wrap-up and summary of the work. Data can be harvested more-or-less automatically from the experimental data stream for construction of this summary.

**Jim Fait** gave a first report of the software system that is about to be given its first public exposure at the new South-East Regional Collaborative Access Team beamlines at the Advanced Photon Source. The system is a nice mixture of the system Fait helped to develop for IMCA-CAT and new innovations for SER-CAT.

One of the big wastes of time at synchrotron beamlines is the time spent getting in and out of the radiation hutches. Occasionally it's necessary to do this frequently when one is exchanging crystals, trying to find the best one for data measurement. We have long dreamt of having a mechanism to do this work for us. The principal impediment has been the uncertainty of how best to handle crystals that need to be kept exhaustively under cryogenic conditions. Difficulties are both frosting of the apparatus and the problems of getting mechanisms to work when they're cold. Finally someone has done something about it, and there are several mechanisms (robots) available now. A couple of them are produced as commercial products. We heard reports on two "home built" models.

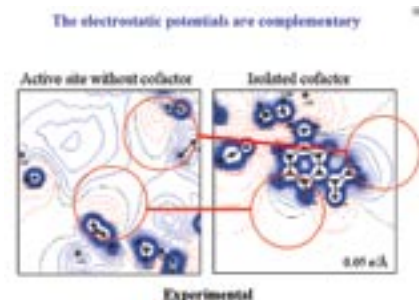
**Paul Phizackerly** reported on a sample-changing mechanism he has produced at the SSRL. He employed a commercial four-motion programmable robot to drive a "cold clamp" and other manipulation tools. The apparatus combats frosting by warming things up at strategic moments. The crystals are meant to be stored and shipped in a cannister that is a cylinder of metal with magnetized holes on its surface, 64 of them on each. The cylinder has sufficient thermal mass to keep crystals cold during transfer from one cryogenic environment to another, and it fits nicely into the standard shipping dewar. The robot goes through an almost balletic motion to extract a crystal from the cannister, apply it to the magnetic goniometer head on the x-ray camera, and replace it after the diffraction measurement.

Finally **Gyorgyi Snell** reported on a device engineered at Lawrence Berkeley Laboratory. Here the concept is quite different in that there is no motor-driven commercial robot. Instead all motions are driven by off-the-shelf pneumatic actuators, and

the motions are a few simple linear motions and a rotation. The crystal on its mounting pin is moved by a collet-like clamp that is kept cold to keep the crystal frozen during manipulation. Again, there are various cooling, heating, and drying cycles that seem to prevent icing effectively. Crystals on their mounting pins are stored in hockey-puck sized aluminum disks carrying 16 crystals that can be stacked seven high for transport in a shipping dewar. This device is used regularly by crystallographers from the Syrrx company when they visit the ALS to collect data.

Bob Sweet

*Image from Claude Lecomte, P027: Electrostatic complementarity of the cofactor NADP<sup>+</sup> in the active site of Aldose reductase; the electrostatic potentials were calculated from ultra high resolution x-ray diffraction collected at APS and modelled using refinement program MOPRO (C.Lecomte, B.Guillot, C.Jelsch, B.Muzet, LCM3B, CNRS, U. Henri Poincarè Nancy, and A. Podjarny, IGBMC, Strasbourg, A.Joachimiak (APS))*



### *New Experimental Methods in Macromolecular Crystallography: Posters*

This session had many good posters, with lots of practical innovations for use at both the synchrotron and the home lab. A variety of methods and innovations were presented, and the poster presentations were very well attended.

One topic that received input from several groups is the extension of phasing methods, both for the home lab and the synchrotron. The SAS method has been extended to home lab phasing using Cr radiation to phase sulfur, and using optimized data collection at the synchrotron, with results being reported on new structures. Also reported were direct measurement of phases, and extension of these phases to structure factors.

As the quality of data improves, refinement model improvements, using calculated hydrogen atoms and valence density modeling, become more viable. Adding hydrogen atoms to the model improves fits even with lower resolution data, as interferences between residue side chains become apparent earlier in the refinement process, and can be fitted better. The valence density modeling, when the quality of data supports it, allows for detailed studies of the electrostatics of the active site, helping understanding of enzyme function.

This session also had a number of posters on hardware development, mostly from commercial vendors. These posters highlighted the advances in CCD technology, new ideas in crystal mounting, and also new methodologies for crystal growth in conditions that mimic microgravity, with promising results. The CrystalKap vial for crystal mounting and recovery is especially interesting for PX work.

Jim Fait

### ***Structural Genomics: Are the Pieces Ready Yet?***

Once again a large and enthusiastic crowd came to see how structural genomics is shaping up. The session included academic and industrial groups and focused on the overall status of structural genomics as well as on methods.

**Sung-Hou Kim** answered the title question for the session right at the beginning with a clear “No, the pieces aren’t quite ready yet.” He described structural genomics as a route to improve the inference of protein function. His objective is to generate a kind of dictionary. This dictionary would associate molecular functions with groups of proteins with common structural features. The Berkeley structural genomics center focuses on *Mycoplasma genitalium*, a minimal organism. He gave some examples of how such a dictionary works: in one case sequence comparisons gave no information but structure matched a methyltransferase; in another, sequence and structure gave no obvious matches but led to a good guess (NTP hydrolase); in others, neither sequence nor structure gave useful clues. Sung-Hou described a distance-geometry method for describing the relationships among folds. A most interesting aspect was that the space of folds is not at all uniformly populated.

**Jim Pflugrath** followed up with some technology for structural genomics: a robot for handling mounted crystals. The ACTOR system developed by Abbott Labs and Rigaku/MSU uses simultaneously up to five 12-crystal magazines that accept standard mounted pins. It is useable by both small-scale and structural genomics-scale projects, and includes automatic centering of the loop in the x-ray beam (which works well if the crystal is about the size of the loop). A nice feature is that a table of instructions for what to do with each crystal can be uploaded to the system.

**Les Tari** gave another view of structural genomics: a commercial view of how high-throughput crystallography can be used for structure-based drug design. He described an impressive set of techniques, from 96-tube high-density fermentation to 96-tube purification and nanoliter crystallization that Syrrx has developed into a structure-determination pipeline. He then went on to talk about the application of this to anti-infectives (over 40 structures solved) and to kinases. He also talked about a pilot project to work very hard on a limited number of targets (6) that were difficult human proteins. In just a few months his group obtained 3 structures using the nanodrop method, one of which was determined at quite high resolution (1.5 Å). The approach of searching very thoroughly in crystallization space as well as in the space of expression/purification systems was very successful.

**Andrzej Joachimiak** answered the title question a little differently: “All the pieces are there, we just have to put them together.” He then went on to describe what he called “low-cost” approaches to a cloning/expression/purification/crystallization/structure determination pipeline. He emphasized the difficulty of optimizing crystallization conditions as a bottleneck in structure determination. Andrzej described a robotic system for crystal mounting, including a prototype UV-light-based method for crystal centering. He described several structures determined in

a semi-automatic fashion, including one done in 21 days from gene to maps.

**Bernhard Rupp** described some additional technology for structural genomics: methods for molecular replacement. The big problem in this area is the presence of model bias. Bernhard described how this could be addressed in a systematic way by using automated and adaptive template generation and iterative model-building, combining techniques developed by others. Bias was reduced by random coordinate shifts and repetitive model-building.

**Chuck Kissinger** talked about a pilot high-throughput crystallography project on a big scale. He described a set of automated systems for all the steps in protein production and structure determination, though significant human interpretation is involved. Quality control is emphasized throughout the system. This system was applied to a set of bacterial targets suitable for antimicrobial design. This yielded 53 new structures 14-50 kDa and 7 new folds. He described some lessons learned. Information management is a major concern; a good LIMS system is essential. Surprisingly, increases in throughput have come from intelligent processes, not automation or technological advances (though automation is necessary). The quality of structures is similar to “hand-crafted” ones. The mean resolution was 2 Å, range 1.3 -2.9Å, and the free-R and percentage of residues in most-favored regions of the Ramachandran plot was similar to the overall PDB. Chuck also mentioned that crystallographers resist automation, and that many different software packages can be assembled into high-efficiency pipelines. He said that the map-fitting step is the biggest hurdle to full automation.

*Tom Terwilliger*

### ***Questions: Processing CCD and Image-Plate Data***

This session was imagined as an opportunity for experienced and newer users of area detectors to listen to and interact with those who develop image-processing software. Integration, especially of weak reflections, was discussed in the first half of the session; scaling of frames was covered in the second. Participants included **Michael Ruf** and **George Sheldrick** (Bruker Nonius; software developed by Bruker), **Klaus Bartels** (Mar), **Rob Hoof** (Bruker Nonius; software developed by Nonius), **Zbyszek Otwinowski** (Denzo), **Thad Niemeyer** (Rigaku) and **Harry Powell** (CCP4). **Andy Howard** began each half of the session with an overview of the important questions.

Speakers seemed to agree that the different approaches are converging and that there is more consensus than in the past about how integration and scaling should be done. There are important differences, however, between programs developed for macromolecular and small-molecule applications. Advanced users asked enough questions to make clear the need for continuing discussion. Many new users, however, were relieved to hear that it is probably safe to use the program packages in default mode when no special precision or accuracy is required.

*Carol Brock*

**(The) objective is to generate a kind of dictionary. This dictionary would associate molecular functions with groups of proteins with common structural features.**

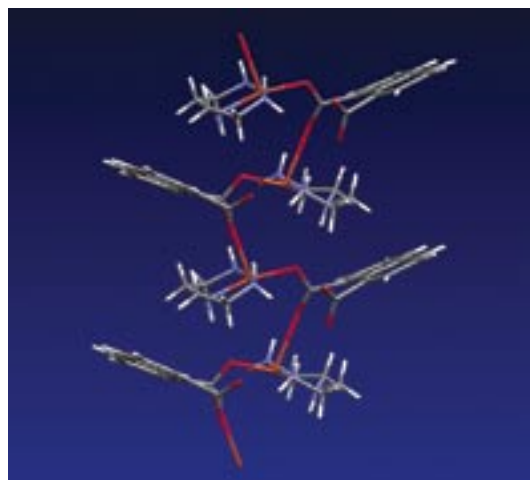
## Symposium on Crystal Engineering

The two-day symposium on Crystal Engineering featured an impressive and particularly international line-up of speakers from nine countries. Despite the substantial lure of the San Antonio Riverwalk, the symposium remained well-attended from early Sunday morning until late Monday afternoon, which again demonstrates that good science can prevail even in the face of icy margaritas, freshly made gorditas (“little fat ones”), and late night salacious Salsa.

The first half-day session, entitled *Crystal Growth, Polymorphism, and Intermolecular Forces*, provided many good examples of the successful (and essential) integration of several different analytical techniques in the study of structure and property. **Gautam R. Desiraju** provided an insightful and (at times) provocative overview of weak hydrogen bonds (or should that be hydrogen bridges?) in the context of crystal engineering. **Dario Braga** gave a topical talk on polymorphism that provided several keywords, notably serendipity and seeding, that were revisited several times during the symposium. The oft-neglected topic of crystal growth was given much needed attention by **Jennifer Swift** who described some elegant AFM studies of cholesterol nucleation and growth. **Ray Davis** subsequently managed to make those normally unassuming (at best) phase-diagrams spring to life using thermomicroscopy and some sensational videos. The session was rounded off by **Susan Reutzler-Edens** who provided a much appreciated industrial (real-life?) perspective on the importance of structural purity in the context of pharmaceutical materials.

Session II followed under the title of *Directed Assembly of Extended Organic Architectures*, though this was interpreted quite liberally to include network structures in which the direction of the organic component was given more than a little help for a variety of (inorganic) metal centers. In inimitable style, **Angelo Gavezzotti** from Milano presented some new ideas for developing forcefields for modelling crystal structures and understanding and predicting the way molecules pack. He further touched upon the intriguing idea of “virtual crystallography”, namely computationally generating many potential crystal structures for particular molecules and then examining why certain potential structures are NOT formed. **Bill Pennington** (Clemson, SC) followed and discussed the polymorphic interconversion of tetra-2-pyridylpyrazine via halogen bonds involving encapsulated I<sub>2</sub> molecules (see On the Cover, p.13). He also introduced us to “Paw”lymorphs of the Clemson University tiger mascot. **Alicia Beatty** (Notre Dame) then described her strategy for designing materials that aimed to mimic the absorbent qualities of clays. Her approach used self-assembly of anionic hydrogen bonded layers that are intercalated by cation head groups of molecules able to serve as pillars between the layers. **Mike Zaworotko** (South Florida) illustrated the use of rigid metal carboxylate building blocks in designing both extended structures and nanometer-sized discrete molecules based upon geometric principles. The session concluded with an example of modular design, using ionic hydrogen bonds to link metal-late ions in which the central metal could be changed while maintaining the same crystal structure. Since such a change also produces a change in crystal color; the possibility of tuning crystal color by forming mixed metal crystals was realized.

The theme of Session III on Monday morning was *Construction of Inorganic-Organic Hybrid Materials*, which was launched with the plenary lecture by **M. Wais Hosseini**, who flew in from Strasbourg to attend the meeting. We were treated to a lecture in which he, in his words, “stuck to the real hard facts” concerning molecular tectons. He convinced us that his combination of ligand synthesis and metal coordination leads to predictable supramolecular assemblies such as inorganic helicates. Following Wais were **Steve Keller** (Columbia, MO), who described polyoxometallate/coordination polymer structures, and **Jesus**



from Jesus Valdes-Martinez: an image of the Cu(II) polymer

**Valdes-Martinez** (Mexico City), who showed us a “beautiful nightmare,” where one crystal structure contained three different copper(II) complexes (a monomer, a dimer, and a 1-D coordination polymer). So much for predictability! **Lee Brammer** (now making his home in Sheffield, U.K.) then proposed the provocative idea that the Ag(I) ion can be considered just “a really big H<sup>+</sup>” in solid-state assemblies of Ag(I)carboxylates; therefore these metal complexes are analogous to carboxylic acid dimers. Rounding out the morning’s session was “local boy” **Eric Bosch**, (Springfield, MO) who has developed a probe for metal coordination by using a ligand that snaps closed, resulting in  $\pi$  stacking, upon complexation.

For the final half-day the focus shifted from crystal design to applications in a session entitled *Function and Reactivity of Engineered Materials*. In the plenary lecture for this session **Omar Yaghi** presented his work on the design of massively porous materials which have metal-organic frameworks using rigid organic di- and polycarboxylate linkers. In his introduction he dispelled the popular beliefs that: (a) highly catenated frameworks have minimum porosity; (b) a catenate framework is less stable than an open framework; (c) the use of long linkers results in highly catenated frameworks. Crystalline materials of high porosity (up to 91%) were shown and their application in the uptake and potential storage of gases such as methane and hydrogen was explored. **Fabrizia Grepioni** discussed an alternative approach to nanoporosity based on reversible solid-gas reactions, particularly in the case of vapours of bases and acids. **Joe Lauher** argued that “engineering” implies the existence of a precise goal to direct the efforts of the investigator. He showed how the principles of crystal engineering could be used to prearrange di- and even triacetylene molecules in the solid state so that

they could undergo a topochemical reaction and polymerize in the desired way. Topochemical polymerisation requires control of distance and symmetry. **Mark Hollingsworth** offered insight into ferroelectric and ferroelastic domain switching in a series of crystalline organic inclusion compounds. These are characterised by the presence of molecules with large dipole moments that can reorientate under the effect of external pressure. Some very interesting videos obtained by videomicroscopy of the domain switching in both urea and calixarene systems were shown. **Robin Rodgers** discussed the importance of ionic liquids in green chemistry applications and their relationship to crystal engineering.

**Christer Aakeröy**, the symposium organizer, took advantage of his *dulcis in fundo* position to wrap up the two days microsposium with some notes on the lectures and speakers. The “scientific part” of his talk was devoted to discussing the results of a study of competition in hydrogen bond formation between functional groups. A particularly noteworthy example was that of three molecules all linked together in hierarchical fashion.

This symposium was clearly atypical for many ACA sessions (a dearth of anomalous scattering, R-factors, and reciprocal space), yet it did provide numerous telling illustrations of the way in which modern crystallography continues to (a) improve our understanding of fundamental science and (b) provide the means for solving real chemical problems.

Finally the importance of the financial contribution from the ACS Petroleum Research Fund and the special contribution from the ACA, which permitted this geographically and scientifically diverse group of speakers to converge at this symposium to present and discuss some of the latest developments and thinking in the field of crystal engineering, is recognized. The ACS journal *Crystal Growth & Design* sponsored a very pleasant dinner by the river for the speakers.

*Christer Aakeröy, Lee Brammer, Alicia Beatty, Dario Braga*

### **CE Poster Session: Crystal Engineers rally in San Antonio**

Did you miss it? The Crystal Engineers staged a dramatic coup in the center of the Henry B. Gonzales Convention Center during the poster session Sunday night, May 26, 2002. The unruly bunch were a bit anxious when a small tape recorder was clicked on – “this isn’t going to end up in court, is it?” asked one nervous demonstrator. He needn’t have feared, as subsequent attempts to decipher the incomprehensibly garbled tape have failed.

The uprising began when the CE crowd realized that they had more single contributors for the Sunday session than any section (well, except for “New Structures”). Realizing that there was strength in numbers, they banded together with the Monday and Tuesday CE sessions, turning up in full force for the poster judging. Luckily, no one was harmed in the incident, and the throng dwindled as the beer concession closed. But not before a judging cabal had gathered to make their final decision on the Crystal Engineering poster prize winners. With so many great entries and enthusiasm among the participants, it was difficult to select a winner, but here are the results:

Special honorable mentions were made for four posters: **Eric Bruton**, graduate student of Lee Brammer, gave a very well-received poster on a systematic supramolecular study of oximes with di- and tri-acids. **Colin Rodger**, from the same research group, also was recognized for a study of silver-pyrimidine coordination polymers, demonstrating the effect of long chain alkynyl groups on 3-D assembly. **Colin Seaton**, a graduate student from Maryjane Tremayne’s group, was given mention for his contribution detailing powder diffraction structure solution. Last but certainly not least, undergraduate student **Alton Lan** (Joe Lauher’s group) impressed the judges

with a well-presented poster on host-guest co-crystals for topochemical polymerization (not to mention the fact that he managed to use the word “excogitating” in his poster abstract).

The Crystal Engineering poster prize, sponsored by the Royal Society of Chemistry journal *Cryst. Eng. Comm.*, was awarded to **Brian Helfrich** of Kansas State University, a graduate student of Christer Aakeröy. Brian, who also won a Pauling award for his poster presentation, detailed a successful strategy for assembling ternary co-crystals by taking advantage of pKa differences of the components. We congratulate him and thank him and the rest of the participants for providing the crystallography crowd with some insights into the latest goings-on in crystal engineering.

*Alicia Beatty*



*Brian Helfrich, winner of both the CE Poster Prize and a Pauling Award*

### **WANTED!**

The Materials Research Lab from DIP Universidad de Guadalajara, Guadalajara, Jal. Mexico is looking for a donation of a vertical X-ray generator in good working condition which would allow us to put in use precession and Weissenberg cameras for teaching and research purposes. We can afford the cost of shipping it to Mexico. Anyone interested in helping us to continue teaching X-ray crystallography in this part of the world please contact me at MRL. DIP, Universidad de Guadalajara. Apdo. Postal 2-638 CP44281 Guadalajara Jal., Mexico. fax: + 52 333 656 36 39; email: [gcastel@ucea.udg.mx](mailto:gcastel@ucea.udg.mx)

*A. Guillermo Castellanos-Guzman*

### General Interest I

The first session of the General Interest Group Sunday morning contained an eclectic mix of papers in keeping with the aim of this group. Maximum attendance was about 35, held down largely by the parallel session paying tribute to Bob Sparks. The session opened with the presentation of the charge density study in the very rare mineral Kovdorskite,  $\text{Mg}_2\text{PO}_4\text{OH}\cdot 3\text{H}_2\text{O}$  by **Charles Lake and Bryan Craven**. The net charges obtained for  $\text{Mg}^{2+}$ ,  $(\text{PO}_4)^{3-}$  and  $\text{OH}^-$  are respectively +1.1, -2.0 and -0.5, while for water molecules they were 0.0, +0.1 and +0.2. Bond critical points were located for all bonds except for the hydroxyl  $\text{H}\cdots\text{O}$  hydrogen bond, showing that the OH group contributes little to hydrogen bonding in this structure.

**Dave Duchamp** extended the potentials used in the program CrystMol 2.0 so that calculations can be done on organo-silicon molecules. He uses the Cambridge Crystallographic Database to test the applicability of his software.

**Carol Brock** discussed reasons for the occurrence of large numbers of crystallographically independent molecules and fragments in structures. This is usually due to conflicts in packing that cause frustrations and complicate the resultant structure. She illustrated her talks with examples in which the numbers varied from 9 to 5 to 4.

*From Ed Meyer: the core of a gold Metallo-organic complex; a sculpture used to illustrate Supramolecular Chain Assemblies Formed by Interaction of a p Molecular Acid Complex of Mercury with p-Base Trinuclear Gold Complexes, A. Burini, J.P. Fackler, Jr., R. Galassi, T.A. Grant, M.A. Omry, M.A. Rawashdeh-Omry, B.R. Pietroni & R.J. Staples, J.A.C.S. (2000) 122,11264-11265. The central Au-C-N core of the complex was modelled in Wenge wood from West Africa as part of Ed's Trinitatis series of sculptures*



**Ed Meyer** has been working for some time on making wooden models of complex molecules by programming a computer controlled milling machine. He showed some of these models that are objects of beauty aside from their utility in teaching and research. He concluded his presentation with computer-generated motion pictures of molecules.

Compounds containing transition metals and halogens can form supramolecular hydrogen bonded arrays. **John Swearingen**, Lee Brammer and Gordon Anderson devised a synthetic strategy using perhalometallate anions and N – H containing cations and showed how this method can be used to construct crystalline compounds in 1-, 2- and 3-dimensions.

The great need for ceramics to meet various requirements in wireless technologies motivated the solid state chemistry group at NIST and collaborators at other institutions to study the very complicated phase diagrams in the alkaline-earth – niobates and tantalates. This is indeed a Herculean effort and easily explains why nine authors are shown on this paper. In this last paper of the morning session **Winnie Wong-Ng** did a masterful job presenting the crystal chemistry and structures of some of the phases obtained in these systems. As she pointed out, this is a multi-billion dollar industry and the discovery of materials with better dielectric constants, low dielectric losses, and etc. can have an enormous influence on this technology as well as prove profitable to the discoverers.

Hugo Steinfink

### General Interest II

Sessions sponsored by the General Interest Group (GIG) usually consist of presentations on cutting edge techniques and advances in crystallography. The GIG session II at this year's meeting was no exception. **Kristin Kirschbaum** began the session with a presentation on 'single' crystal studies on cracked crystals. Their solution to this problem was to treat the cracked crystal as a non-merohedral twin. This technique could prove quite useful the next time the only crystal you have either cracks on cooling or was already cracked before the diffraction experiment. **Michael Ruf** discussed remotely controlled diffraction experiments. The procedures developed by their research group may allow synchrotron 'users' to conduct their experiments from the comfort of their office. **Bernard Santarsiero** gave a presentation on the x-ray diffraction of very small crystals using synchrotron radiation. A similar talk in a GIG session 1998, which focused on small inorganic crystals, inspired our group to take some small crystals to a synchrotron.

The final three talks in this session were all related to computational techniques in crystallography: **Jeffrey Roach** discussed the use of the local squaring function in phase refinement, **Malgorzata Rowicka**



*In front: Malgorzata Rowicka, Carroll Johnson, Kristin Kirschbaum; behind: Michael Ruf, Jeff Deschamps, Bernie Santarsiero*

### General Interest II, continued

talked about an 'Ultimate Fast Fourier Transform' that could take advantage of crystallographic symmetry to reduce the computation time. During her presentation she showed that for a few very limited cases some software already supports this. Their group has worked out the parameters for 130 of the 230 space groups and plans to complete the remaining 100 space groups. The final presentation was by **Carroll Johnson** who was looking ahead at emerging mathematic concepts that may be of use to crystallographers.

*Jeffrey Deschamps*



*From left: William Watson, Peter Müller, Joao Barbosa, Gloria Borgstahl, William Montfort, Martha Teeter, Tsu-yi Teng, Amy K. Katz, James Knapp*

### General Interest III

One of the best sessions of the meeting was held on the last day. This GIGIII session included two half day sessions of talks on protein crystallography. The morning session was started by a provocative talk by **Martha Teeter** concerning protein/solvent dynamics. Eight 0.9 Å crambin structures were refined against data collected over a range of temperatures passing through the glass transition temperature. Great sympathy was felt by the audience for her 0.54 Å diffraction data. This crystal diffracted off the edge of the detector and the high resolution limit for crambin has still not been reached! Where will it end? Then **Peter Müller** gave a very helpful discussion on the use of SHELXPRO and the bond-valence method to identify metal atom types in protein structure. **Tsu-yi Teng's** talk showed that helium data (40 K) did not protect protein crystals from radiation damage any more than nitrogen temperatures (150 K) did. After the coffee break, **Gloria Borgstahl** spoke on a fine phi slicing study of the effects of crystal perfection and cryocooling on mosaicity and crystal quality. The bottom line: perfect microgravity-grown insulin crystals with single mosaic domains when cryocooled retained their long range mosaic domain structure which resulted in a higher signal to noise ratio in the 0.9 Å diffraction data. **Joao Barbosa** joined the session from Brazil and described their synchrotron facility in Sao Paulo and their collaborative structural biology group. The morning session was concluded by **William Montfort's** talk on NO transport from the saliva of blood-sucking insects to the tissue of potential victims. This fascinating research included dynamic, spectroscopic and ultra-high resolution crystal studies of nitrophorin in complex with NO and CO. Every once in a while, just to ensure our state of awareness, Bill had one of the blood suckers with and without the blood meal, crawl across the screen.

The afternoon GIGIII session started with a presentation by **Ardi Vahedi** demonstrating that one can soak manganese superoxide dismutase crystals in a 0.7% peroxide solution and still collect a 1.55 Å data set at room tempera-

ture. The presented electron density maps showed evidence for partial peroxide binding to the active site manganese. **Jeff Habel** demonstrated that the anomalous scattering signal from a limited number of sulfur atoms in the asymmetric unit can successfully be used to obtain interpretable electron density maps. This research clearly has great ramifications for the future significance of sulfur SAS-phasing. The detailed work on mutations of mitochondrial aldehyde dehydrogenase presented by **Heather Larson** showed an interesting relationship between disorder in the active site and the inability to restore native-like activity. It was of general interest to see in one of Heather's statistics that there is no correlation between the number of alcoholics in a given population and the number of people having a mutation of the aldehyde dehydrogenase gene. In other words the adverse effects in response to alcohol consumption seems not to be a deterrent. It was in this context that a person in the audience revealed himself as a mushroom expert, explaining that he personally knew about a specific mushroom found in Germany, the consumption of which releases an inhibitor for aldehyde dehydrogenase. He explained (accompanied by much laughter) that he would not recommend eating the mushroom while having a 2 or 3 glasses of wine.

**Amy Katz** who presented right after the coffee break had the simple but ingenious idea of utilizing the PDB and CSD Data Banks to examine the optimum coordinate numbers in iron complexes. Her talk clearly made the point that there is massive amount of information present in Data Banks waiting to be processed. **James Knapp** demonstrated the feasibility of time-resolved-study to show that photolysis triggered movement of the heme iron in Hemoglobin. It strongly proved that time-resolved-crystallography is at the cutting edge in helping us to better understand enzyme mechanisms. The session concluded with an excellent presentation by **William Watson** who proved that only the best of scientists can get thrown out of a bar (referring to an event that happened to Bill at the YSSIG mixer at the Howl at the Moon bar). His inspirational talk presented their novel use of rhenate to obtain MAD phases and revealed the first ever crystal structure of acylhomoserine lactone (AHL) synthase showing a phosphopantetheine-binding fold.

The session and the conference ended with a bang when Bill Duax treated us all to his rendition of the "Mother Teresa" song followed by three sequential summersaults. The organizers wished they had a camcorder along. He's still got it!

*Gloria Borgstahl  
and Ardeschir Vahedi-Faridi*



### Small Molecule Structures and Techniques: P150

Revisiting a classic technique by Hassel and Strømme, **Sergey Lindeman** and **Jay Kochi** presented the results of *in-situ* crystallization of benzene/Br<sub>2</sub>, toluene/Br<sub>2</sub> and hexamethylbenzene/Br<sub>2</sub>. The experimental procedure yielded previously unknown phases that are in agreement with theoretical models. While benzene and toluene form end-on, non-centered  $\pi$ - $\sigma^*$  complexes with Br<sub>2</sub>, crystallization of hexamethylbenzene with bromine yielded Br<sub>2</sub>-solvated C<sub>6</sub>Me<sub>6</sub>Br<sup>+</sup>Br<sub>3</sub><sup>-</sup>.

These well-formed crystals and beautiful structures should serve as a reminder that the old masters had techniques that are still applicable today.

Marilyn Olmstead



From Sergey Lindeman: benzene...dibromine donor-acceptor stacks partially interpenetrating each other in triplexes along three-fold axis.

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### Computational Crystallography: A Tribute to Robert A. Sparks

At the ACA-Los Angeles 2001 meeting, ACA Council approved a session on Computational Crystallography, proposed by Joseph A. Reibenspies of Texas A&M U. as a tribute to Robert A. Sparks. It was intended to honor and interact with Bob while he remained active in many areas of crystallography. Unfortunately, Bob's death while returning home from the ACA-Los Angeles meeting turned this into a memorial. But what a legacy he left, as the full audience found in the talks ranging from basics of four-circle diffractometers to autoindexing to CCD detector diffractometers to twinning to detection of missed symmetry to high throughput structures to absolute structure determination to single-wavelength anomalous scattering to time-resolved crystallography. Bob was interested in all of these and instrumental in the development of some. As **Larry Falvello** of Zaragoza U. pointed out in his presentation on the four-circle diffractometer and its algorithms, Bob wrote software actively on many of the session topics from 1956 to 2001, 'two lifetimes of work'.

**Joe Reibenspies** chaired the daylong session, and we had the pleasure of sharing it with Bob's family members, including Barbara Selfridge, Peter Sparks, and Irina Danilova. **Sue Byram** of Bruker AXS reviewed Bob's personal and professional history, including companies he founded, patents he produced, his love of teaching crystallography, and the products he produced – from the minicomputer controlled PI bar four-circle diffractometer to the SMART CCD series. His software included the seminal autoindexing of reflections to determine the unit cell automatically, the XTL first minicomputer structure solution and refinement, later profile fitting and search-match for powders, and current GEMINI twinned crystal indexing, XSHLL molecular display, and FINDSYM for detecting correct symmetry.

**Bill Clegg** of Newcastle U. declared that 'autoindexing and its derivatives transformed diffractometer-based unit cell determination 30 years ago', and detailed its principles and practice. **Charles Campana** of Bruker AXS reviewed the changes in



*In front: Barbara Selfridge, Irina Danilova, Peter Sparks, and Regine Herbst-Irmer; middle: Simon Parsons, Sue Byram, Ton Spek, Larry Falvello, Bill Clegg; back: Joe Reibenspies, George Sheldrick, Charles Campana, and Victor Young.*

crystallography and computing over Bob's 50-year professional lifetime, highlighting his vision for new equipment and new software, and pointed out that Bob chose a commercial instrument company as the best place for his scientific contributions. **George Sheldrick** of Goettingen U. opened his remarks about structure determination from weak anomalous signals, by saying that he and Bob had disagreed about the viability of measuring such small anomalous differences on a laboratory source – but that now he feels Bob was right in his optimistic belief in these methods. **B. C. Wang** followed with a detailed discussion on computational methods to extract phase information from single wavelength data. He said that he and Bob shared a vision that small molecule and biological macromolecule crystallography would one day merge back into one field, as methods develop.

**Edgar Meyer** of Texas A&M U. remarked on Bob's development in 1970 of a 3D color display customized for Meyer's laboratory – predating Evans and Sutherland and other early display manufacturers. **David Watkin** of Oxford U. presented state-of-the-art structure analysis with the latest CCD diffractometers for chemistry, declaring that these have revolutionized crystallography and could have a big impact on analytical chemistry. **Ton Spek** of Utrecht U. reviewed the validation of correct space group assignments by avoiding missed symmetry, including the fundamental contributions of Richard Marsh of Caltech (who was present at the session), and the software created by Yvon LePage (MISSYM), Bob Sparks (FINDSYM), and Ton Spek (ADDSYM), the latter two based on LePage's algorithm.

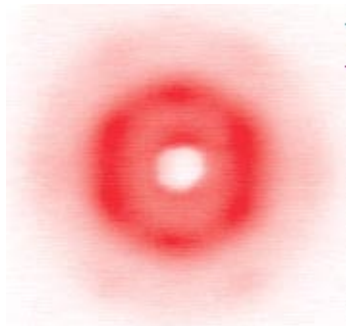
**Philip Coppens** of SUNY-Buffalo reported on new time-resolved methods to repeatedly excite a molecule and probe for structural change for a period of microseconds. **Regine Herbst-Irmer** of Goettingen U. and **Victor Young Jr.** of the U. of Minnesota presented the latest methods for handling non-merohedral twinned crystals, relating these to the algorithms developed since 1994 by Sparks for indexing such twins. The session concluded with **Simon Parsons** of the U. of Edinburgh presenting challenging cases of precise structure determination of light atom structures. A number of participants commented on the breadth of Bob's interests, as evidenced by the day's discussions.

*Susan K. Byram*



*see  
page  
19*

## Impact of Scattering on Nanoscience and Nanotechnology



*From Tom Mason: the light scattering pattern from a shear-ordered emulsion.*

This interdisciplinary aspect of the field was underscored and highlighted in the plenary talk by **Doug Lowndes** (ORNL) and is the guiding principle behind a new interdisciplinary nanosciences center at Oak Ridge. In this field, progress tends to be fastest at the boundaries between traditional disciplines and this theme was clearly reiterated throughout the symposium. As an example of the diversity of problems under study, we heard about subjects ranging from research to understand the novel electronic properties of complex transition metal oxides (**Ray Osborn**, Argonne), through studies of nanoporous glassy materials used in the encapsulation of radioactive waste (**Pappannan Thiyagarajan**, Argonne), the characterization of the perfection of photolithographically created nanostructures (**Ron Jones**, NIST), to videos of scattering from dancing nano-scale oil drops under shear (**Thomas Mason**, ExxonMobil). **Millie Firestone** (Argonne) described how biomimetic lipid based complex fluids can be used as scaffolds for inorganic nanoparticles, and even functional proteins, and **Paul Sokol** (Penn State) what inelastic neutron scattering can tell us about what happens in a buckytube full of hydrogen.

The range of scattering techniques used was also varied, and the problem of scattering off nanostructured materials is leading to novel applications of scattering and ingenious extensions of scattering techniques. Wide angle scattering can be analyzed to include both Bragg and diffuse, and elastic and inelastic components to reveal structures as a function of nanometer lengthscale, and this is being applied to materials whose crystallinity extends only over these lengthscales (**Valeri Petkov**, Michigan State U.). Small angle scattering (SAS) is applied in an enormous range of systems and is particularly suited to characterizing nanophase materials. **George Wignall** (ORNL) studied micelle formation in suspensions of diblock copolymers and **Ricardo Aparicio** (Campinas, Brazil) combined low resolution diffraction with SAXS to understand the shape of biological enzymes. **Charlie Glinka** (NIST) emphasized

the importance of careful data analysis, especially from dense systems such as mesoporous materials. Reflectography is also widely used, from studying the magnetization in the interfaces of metallic multilayers (**Dan Haskel**) to giving us a physicist's view of diarrhea as **Jaroslav Majewski** (LANL) described the study of the binding of cholera toxin to synthetic lipid membranes. The Haskel study also used x-ray circular dichroism and the Majewski study used grazing incidence diffraction, highlighting another important feature of scattering studies in the nanosciences: often more than one technique is required to solve a problem. An elegant use of electron diffraction using nanometer sized beam-spots allowed a detailed study of stripe ordered phases in manganite materials (**Jian-min Zuo**, U. Illinois, Urbana). The ability to apply scattering to the complex problems in the nanosciences is in large-part made possible by improvements in facilities and instrumentation such as the Spallation Neutron Source being built at Oak Ridge. **Ian Anderson** gave an upbeat progress report as the project moves through its main construction and instrument design phase. **Doug Tobias** gave an overview of the status of computer modeling to understand nanophase materials by describing simulations of lipid dynamics. Another aspect of the symposium was to bring in young scientists who gave some of the best talks of the symposium, including **Emil Bozin** (Michigan State U.), **Shiv Halasyamani** (U. Houston) and **Xiaoping Wang** (Argonne) who gave an impressive account of how, using a low-tech home-made diffractometer at the Intense Pulsed Neutron Source, a great deal of information can be gained about the

formation kinetics of gas clathrate hydrates and how this is going to help us avoid a catastrophic natural disaster in case the clathrate hydrates under the oceans suddenly were to release the massive quantities of methane they contain.

*Simon J. L. Billinge, Paul Butler*

*Picture on opposite page: The Howl at the Moon Party (YSSIG mixer).*

*Above, from left: Douglas Ho and Judith Gallucci; Johanna Mazlo, Huiying Li, Jennifer Stine Elam, (part of) Dan Anderson; Francisco Hernandez-Guzman with Howl at the Moon Cooks; below: Matt Vetting, Teresa Clarke, and Jeff Habel*

**The ability to apply scattering to the complex problems in the nanosciences is in large-part made possible by improvements in facilities and instrumentation such as the Spallation Neutron Source being built at Oak Ridge.**

**Protein Folding & Design**

The short-lived journal of the same name as this session was eventually merged with the journal “*Structure*”, proving, as if it weren’t obvious, that the fields are inseparable. The speakers in this session talked about what we can learn about folding from crystal structures, and how our knowledge of folding is being tested by redesigning protein sequences and designing new proteins.

**Vivian Yee** from the Cleveland Clinic Foundation started the session with a description of the dramatic structural (and functional!) effect of a conservative point mutation (Val->Leu) in factor VIII. **J. Martin (Marty) Scholtz** of Texas A&M described the experiments of his graduate student, which indicated that designed mutations altered the solubility of the protein HPr and (hence?) its tendency to form amyloid fibers. **John Desjarlais** of Xencor discussed the progress in automating and constraining the search for new sequences that fold to a target structure, as well as the high throughput screening technologies, that have led to dramatic changes in enzyme activity and specificity. **Lynne Regan** of Yale designed and characterized new proteins built from motifs using an All-the-Best (ATB) sequence selection strategy.

**Jane Richardson** of Duke University taught us a lesson in the importance of hydrogens in sidechain packing and introduced her new, interactive MAGE tools for evaluating and correcting mistakes in crystal structures (<http://kinemage.biochem.duke.edu/molprobity/>). Try it! It’s like an automatic guided tour of your crystal structure. (See article on page 17)

**Steve Mayo** from CalTech demonstrated the design of template-based *de novo* sequences that were specific enough to stabilize subtle changes in the protein conformational state. In the last talk of the session, **Andrew Doig** of UMIST (Manchester, UK) shocked us with proof that N-methylated peptides, with sequences extracted from amyloid forming proteins, dissolve amyloid fibers! Is this the cure for Alzheimer’s disease? Stay tuned.

*Chris Bystroff*



top, from left: *Martin Scholtz, Chris Bystroff, Lynne Regan, Vivian Yee, Andrew Doig. John Desjarlais, Stephen Mayo and Jane Richardson in photo beneath.*



## Difficult Structures

The session on difficult structures, on Monday afternoon, was chaired by **Zbigniew Dauter** (NCI) and **Zygmunt Derewenda** (Univ. of Virginia). The aim was to present representative cases of genuinely difficult crystallographic problems.

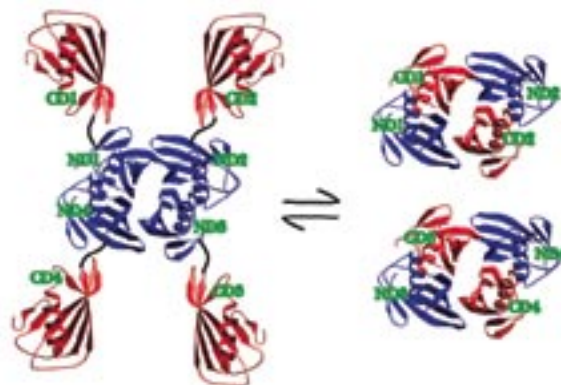
The first speaker, **Kanagalaghatta Rajashankar (Raj)**, described a study of uracil-DNA glycosylase from *T. maritima*. The crystals of this 21 kDa protein were unstable and standard techniques of MIR and MR, as well as attempts to produce SeMet derivative had failed. However, the native dataset contained an anomalous signal, which opened the only avenue of structure determination. After solving the structure on the 'anonymous' anomalous scatterer, an Fe<sub>4</sub>S<sub>4</sub> cluster was identified when the structure was finally solved, and the presence of iron was *a posteriori* confirmed by the fluorescence scan.

**Patrick Loll** talked about his experiences with vancomycin, a 1.5 kDa antibiotic which falls into the class of the most difficult crystallographic projects, outside the power of direct methods but not large enough to be probed by techniques developed for macromolecular applications. The most challenging of the structures was that of the aglycon, in spite of good diffraction to 1.0 Å resolution. The breakthrough in this case was provided by two chlorines, which eventually yielded sufficient anomalous signal to allow the SnB algorithm to break the impasse.

The third speaker, **Alexander Urzhumtsev**, described heroic efforts to directly phase crystals of the Low Density Lipoprotein (bad cholesterol) particles, diffracting to barely 27 Å. Several ingenious low-resolution phasing algorithms were applied and the resulting model provided useful cross validation for ongoing electron microscopy studies.

After the coffee break, two speakers from CARB talked about difficulties that the 'high-throughput' approach may often face. **Chris Lehmann** described the study of the autoinducer-2 production protein, where a Hg derivative provided sufficient phasing but the resulting model failed during refinement, eventually revealing twinning. Finally, **Alexei Teplyakov** presented a difficult case of one of the *H. influenzae* proteins, HI0065, solved using relatively poor phasing provided by SeMet crystals diffracting to 3.2 Å. The key difficulty was the identification of a correct number of molecules in the asymmetric unit. Eventually a pseudo three-fold axis was discovered which finally led to structure solution and refinement.

The session did not attract many posters. Perhaps this is indicative of the increasing power of crystallographic software, and low incidence of problem structures. The only poster shown was by **Yancho Devedjiev**, from the Derewenda group, who presented a study of the yeast peroxisomal thioesterase II. A homologous protein from *E. coli* was solved a couple of years ago by the same group and was shown to be a dimer of monomers, each with an internal repeat. The yeast enzyme proved difficult because the SeMet derivative would not crystallize, and Br soaking was not productive due to the acetate found in the crystallization medium. The structure was solved by SIRAS using anomalous scattering from iodide ions, but surprisingly consisted of a tetramer of only the first repeat, indicating proteolysis of the sample. This illustrates a unique domain swapping in the protein, explaining the ambiguity in the literature regarding the oligomeric state of these proteins.



*From Yancho Devedjiev: Unique domain swapping in the thioesterase family that includes E. coli TEII and mammalian peroxisomal enzymes: left, the structure of the tetramer of the yeast enzyme as inferred from the crystal structure of the N-terminal domain (ND); right, dimeric arrangement, as observed earlier in the E. coli enzyme (Li et al, Nat Str Biol (2001), 7,555)*

While it is becoming clear that fewer protein structures present technical difficulties than in the recent past, discussion of such cases is necessary and the session on difficult structures was very useful.

*Zygmunt Derewenda*

## Biological Macromolecule Structures and Techniques Posters

Biological and Macromolecule Structures and Techniques contained quite a diverse collection of science. One group of posters demonstrated impressive methodological advances (P001, P003, P005, P016, P017A) while others focused on insights into biology gained from crystal structure studies (P009, P011, P013, P014 and P017).

Poster 001 by **Bobby Barnett** and co-workers at Proctor & Gamble described a remarkably robust structure of a thermophile protease, Aqualysin, from *T. aquaticus*. The extreme stability of the enzyme may be the clue to the fact that despite 1.95 Å the structure could be refined to a R/Rfree of 17.5/14.3 using SHELXL, which places it as an outlier in terms of better than expected quality in the resolution vs. Rfree as recently published by Kleywegt and Jones (*Structure* 10(4):465-72).

True atomic resolution (0.92 Å) and an exceptionally well-refined water structure of a *Serratia* endonuclease were the highlights of P017A by **Kurt Krause**, M.D. Miller and P. LeMagueres, U. Houston. Equally as interesting as the atomic resolution is the fact that this protein crystallizes in nearly 50% of the conditions in the Hampton Screen I, opening the possibility of systematically varying crystallization agents and correlating resulting changes in the local water structure and the crystal contacts.

Rational engineering of crystal contacts to improve diffraction quality and resolution was demonstrated in P003 (**Jan Czepas, Derewenda group**). By point mutation of Glu and Lys surface residues with high conformational entropy to Ala, drastic resolution improvements could be achieved. In some cases where the elimination of the charged residue by Ala substitution destabilized the interactions, mutation to Arg allowed creation of a favorable epitope for crystal contacts.

P005 **Yuegang Zhang** and co-workers at Argonne National Laboratory Bioscience Divisions showed that, given quality data, it is now routinely possible to determine *ab initio* structures within a few hours. Their 1.4Å MAD structure of EC1535 was (semi) automatically solved and refined in 8 hrs including data collection, in line with reports from many other groups.

**Ansgar Phillipsen** from Biozentrum, U. Basel presented in P016 his Windows-based visualization program DINO, which can import a wide variety of data created by commonly used programs. DINO then allows unlimited combination of the data objects (e.g. atoms, maps, surfaces) and properties (B-factors, charge, rmsd, etc) to create quite elegant visual presentations of complex material (freely available from [www.dino3d.org](http://www.dino3d.org)).

Iron sequestration in micro-organisms has attracted attention as it plays a major role in the virulence of human pathogens, and in P009, **Andrew Ferguson** (Deisenhofer group) provided a beautiful structural explanation of siderophore receptor gating by analyzing conformational changes in the iron binding outer membrane transporter FecA of *E. coli*. Binding of Fe-citrate leads to a cascade of conformational loop changes that close the outer pocket of the receptor, forming the first step of a four-stage transport mechanism.

An antibody F<sub>ab</sub> structure from the Wilson lab at Scripps was presented by **Robyn Stanfield** (P011), this time obtained from mice with a systemic lupus-like syndrome. Work on the complex bound to the DNA target is in progress.

GDP-D-mannose 4,6-Dehydratase (winner in the complex name category) plays an important role in plant cell wall synthesis. P013 by **Anne Mulichak** and co-workers at Michigan State U. showed the corresponding MUR1 gene product from *A. thaliana* in complex with its cofactor NADPH, which forms a tetramer in contrast to its *E. coli* ortholog, probably related to the location of the cofactor at the tetramer interface. The substrate complex reveals clear conformational changes suggestive of a negative allosteric mechanism.

P014 by **J. Myers** and Y. Shamoo (Rice U.) showed a variety of complexes of UP1 and modified human telomeric repeat DNA single strands to probe specific RNA-protein interactions (ssDNA can be used as UP1 does not distinguish it from RNA). It appears in fact that a number of postulates regarding specifics of nucleotide/UP1 binding need to be refined.

Finally, **Sue Roberts** and coworkers at U. Arizona (P017) showed the most beautiful crystal pictures of this session, from the *E. coli* multi-copper oxidase CueO. Can you guess the crystal color? Cu-MAD data and a 1.4Å resolution allowed nearly complete auto-building of the structure using warpNtrace ([www.embl-hamburg.de/ARP](http://www.embl-hamburg.de/ARP)) and revealed a novel conformation of the trinuclear Cu cluster, with the role of additional Cu(II) sites in a Met-rich helix still under investigation.

Bernhard Rupp

The American Association of Crystal Growth (AACG) co-sponsored a four-session series on crystallization of biological macromolecules, which was supported in part by NASA funds. All of these sessions proved to be popular and were especially well attended.

### High Throughput Biocrystallization

This session was organized and chaired by **Howard Einspahr** (Bristol-Myers Squibb). It was evident that several of the speakers were exploring the use of ever smaller drop sizes, but the suppressive effects of an aggressive defense of nanodrop patent claims by Syrrx, a structural genomics company, became very evident as the session unfolded. Also noteworthy from several of the presentations was the increasing use of batch methods under oil for microliter and submicroliter screening for crystallization conditions.

**George DeTitta** (Hauptmann-Woodward Inst.) provided an overview of the screening system in Buffalo, which has been in operation for two years now and has been applied to over 600 protein samples. The system uses a microbatch-under-oil method to produce 1536 experiments from 600 µl of protein. The 1536 conditions were chosen by use of an incomplete factorial procedure and represent something less than 10% of a much larger space of conditions. George said they most commonly use droplets composed of 200 nl protein and 200 nl precipitant.

**Larry DeLucas** (University of Alabama at Birmingham), whose abstract described a fascinating array of new tools for rapid identification and optimization of crystallization conditions at minimal cost in terms of protein, was advised by counsel not to show any slides related to use of droplets less than one microliter in size. When he came to that section in his prepared remarks, he substituted pictures of his dogs, a multi-talented collection of show animals. He also described adaptation of incomplete factorial methods for rapid identification of crystallization conditions and automation for precise control of vapor equilibration rates pre- and post-nucleation in crystal growth experiments.



Larry DeLucas' dogs

**Heike Krupka** (LLNL) outlined her work with the Crystallization Center of the *M. tuberculosis* Structural Genomics Consortium in adapting the automated design of crystallization screens by CRYSTOOL for use in automated setup, tracking, and analysis of crystallization experiments. In their experience, testing roughly 300 CRYSTOOL-generated conditions is usually sufficient for success. In practice, they use 288 conditions in three 96-well Greiner plates. Custom conditions are designed based on a selection of 27 precipitants, 12 buffers with 5 pHs, 25 additives, and 7 detergents.

**Naomi Chayen** (Imperial College) produced the most memorable quote of the session: "High throughput is not enough, what we need is *high output*." She made the point that while getting initial crystallization conditions may be adapted to automated methods, optimization of initial conditions may not be. She also provided some alarming statistics: success rates of pilot structural genomics projects going from clone to structure are a humbling 5-10%. She typically works with drop sizes between 0.3 and 0.7  $\mu\text{l}$  and has been doing so for years. While she is a strong advocate of microbatch methods under oil, she still uses hanging drop methods a great deal and uses oil layering on top of reservoirs to slow down kinetics of equilibration.

**John Adams** (RoboDesign) described a fully-automated room-sized system for storage, retrieval, microscope image acquisition, and scoring and analysis of crystallization experiments. While this system was designed to service the needs of a prominent structural genomics company, John said that RoboDesign will now be working to produce a scaled down version that would serve the needs of the typical protein crystallography laboratory. There was immediate interest in this new product.

**Duncan McRee** (Syrrx) announced that during the time between when he submitted his abstract and when he left for San Antonio, the number of crystallization drops that had been set up at Syrrx grew from 2 million to 3 million. Syrrx uses a highly automated system to set up crystals and screen images for crystal growth. Using this system they process about 450 protein constructs per month for Syrrx, Scripps, and the JCSG. Based on a database of results from these trials, Duncan provided some analyses of crystal hits with various reagents including those from commercial screens, pointing to the Hampton PEG ION screen, among others, as very productive.

*Howard Einspahr*

## ***New Macromolecular Crystals, Techniques and Hardware***

This year's ACA meeting in San Antonio was a bumper crop for crystals and this session was big contributor to the harvest. The session attendees were awakened from their taco and margarita doldrums by a truly exceptional presentation by **Jarmila Jancarik** of the University of California Berkeley. Jarmila, the author of disputably the most referenced crystallization paper in

protein crystallography on sparse matrix crystallization screens opened her bag of crystallization tips and tricks for those in attendance. Following an overview on their lab's approaches to cloning, expression and purification in a structural genomics setting, Jarmila presented numerous crystallization case studies, each with a moral from the lesson. Samples are prepped with centrifugal filter devices for concentration and checked for monodispersity by dynamic light scattering (DLS). Appropriate buffers and additives are also evaluated and selected by DLS; those providing a monodisperse sample are appropriate for inclusion in crystallization experiments. A handy tip: use the reagents which produce clear drops as potential crystallization additives. A pre-crystallization test was presented which is a procedure for determining the appropriate protein concentration for crystallization screening. Jarmila mentioned the importance of setting crystallization experiments within 1 hour of purification, a point which was brought to attention in more than one presentation at this year's ACA meeting. Fresh is best.

**A handy tip: use the reagents which produce clear drops as potential crystallization additives. . . the importance of setting crystallization experiments within 1 hour of purification - Fresh is best.**

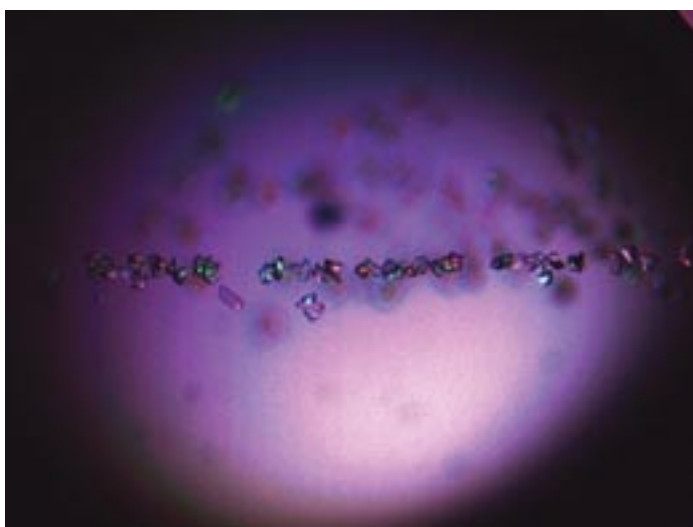
Like many industrial crystallographers, with the choice of only one travel meeting to attend per year, **Annie Hassell** of GlaxoSmithKline made this her meeting of choice and gave a great presentation to boot. Annie is a crystallization Jedi master for kinases, as if ordinary protein crystallization was not enough of a challenge. Annie's use of *The Force* includes designing constructs using homologous models as well as limited proteolysis. A

typical proteolysis might utilize 0.5-1 microgram of target protein with 8 different proteases, with overnight incubation and with subsequent analysis of major gel bands using mass spec and analytical centrifugation. Typically Annie's group clones and expresses out the fragments rather than setting the actual proteolyzed pieces. Repeated ion exchange is a frequently utilized purification tool, although one case was reported where crystals grew from a sample with 4 different phosphorylation states. Once again DLS was plugged as a powerful tool for buffer selection as well as additives (ATP analogs). Size exclusion columns are sometimes run to rid excess ligands from the kinase samples. Annie uses one of the most powerful yet underutilized techniques in crystallization, the crystallographer's Voldemort, "seeding" with good results, especially cross seeding with apo forms to grow kinase-ligand complex crystals. Microseeding is utilized more than macroseeding. Annie's additive elixirs include DTT, BME, detergents, glycerol, propanediol, polyethylene glycols (lower molecular weight), magnesium sulfate, magnesium chloride, and even dilute concentrations of screen reagents (1-5% v/v).

**Allan D'Arcy** of Morphochem, traveling across the globe from Switzerland immersed the attendees in a superb deluge of microbatch and practical approaches that are a definition of crystallization simplicity and efficiency. Allan's last step before crystallization is typically an SEC column, although Allan showed us pictures of crystals from the purest and

## *New Macromolecular Crystals, Techniques and Hardware, continued*

dirtiest of samples. Once again the pitch for fresh samples and immediate screening was made as well as the effectiveness of DLS to identify unimodal samples which crystallize 70 to 80% of the time. Allan primarily utilizes microbatch for screening using a mixture of silicon and paraffin oils as well as pure silicon oil. When using microbatch, once crystals appear Allan likes to add reservoir around the microbatch experiment to stabilize the crystal and prevent dry drops. Allan demonstrated and reminded us that microbatch minimizes sample oxidation, makes temperature variation easier and allows increased reagent and sample concentrations by incorporating silicon oil in the experiment. In the 20-30% of the unimodal DLS cases with no crystals, Allan modifies the protein by making complexes (adding an inhibitor), proteolysis, deglycosylation, and site directed mutagenesis. Allan also is a prolific seeder, seeding from crystals as well as oils into fresh drops, or even moving a crystal to a fresh solution each day. Nucleation sites might be added to screens as it was noted lots of crystals appear on fibers in drops.



*From Allan D'Arcy: streak seeding crystals.*

In closing crystal dehydration to improve diffraction was touched upon as well as putting crystals in high concentrations of PEG and even gentle cross linking. Taking the final edge off the morning before the coffee, **Jay Spurlino** from 3D Pharmaceuticals unveiled a number of effective, up until now closely held crystallization secrets demonstrating their groups ability to come up with truly great ideas. After discussing the need for fast, compact, flexible and protein conserving crystallization techniques, Jay presented the 3DP-1000 Solution Screen, a sparse matrix screen with 54 salts, polymers and organics, 26 additives, 11 buffers, 8 detergents, and a broad pH range. Using a customized 1536 well plate for sitting drop vapor diffusion, rapid crystallization setup and equilibration is achieved. Also described was a unique ThermoFluor® methodology which combined with screen conditions helped to eliminate reagents which do not stabilize the sample.

After coffee, **Tom Tisone**, founder and President of Cartesian Technologies, described the very impressive use of non contact microfluidics and automation for protein crystallization. The technology addresses issues such a sample size, accuracy, precision, reproducibility and evaporation through the use of a positive displacement solenoid ink jet technology, synQUAD™. The technology has been applied to hanging and sitting drop vapor diffusion applications as well as microbatch, even eliminating the need for subsequent sample mixing for microbatch. The hardware has been selected and successfully utilized by companies needing automation for high throughput crystallization and structural genomics for both hanging and sitting drop vapor diffusion.

Moving along a tangent of microfluidics, **Mark van der Woerd** from Universities Space Research Association presented their efforts to date on a novel technique with which they have grown diffraction quality protein crystals in very small volumes, utilizing chip-based, microfluidic LabChip™ technology in cooperation with Caliper Technologies. Mark described, with well done and quite impressive movies depicting how microfluidics can be utilized to generate customized networks, active fluid control, and a sealed environment, as well as accurate, reproducible and controlled fluid movement. The technology also affords little waste and small dead volumes. Based on the chip format described in the presentation, macromolecular crystallization using microfluidic technology is envisioned as a fully automated system, which will use the tele-science concept of remote operation towards development into a research facility aboard the International Space Station.

Wrapping up a most excellent crystallization session was materials scientist turned entrepreneur, **Bob Haushalter** of Parallel Synthesis Technologies. Bob's unique background, combining small molecule crystallography, chemistry and materials science, has led him into exploring nanoengineered surfaces for the epitaxial nucleation of protein crystals. Bob presented exceptional evidence that surfaces do exist that can reduce the activation energy for crystallization. Creating combinatorial libraries of heterogeneous and epitaxial nucleants, manufactured by deposition techniques, crystals of various proteins were grown on these surfaces using standard vapor diffusion methodologies and hardware. The preparation of these surfaces was presented as well as images that suggest the effects are based on new type of epitaxy whereby the nanoengineered surface modulations, which encompass the range of likely protein unit cells, induce an ordered layer of protein molecules which form the nucleus of the protein crystal. At the conclusion of the session it was crystal clear that crystal growers must continue the pursuit of classic and novel approaches as well as scour the horizon and perhaps fields outside our own for new ways to nucleate, grow and produce crystals of biological macromolecules.

*Bob Cudney*



*Transactions Symposium on Crystal Structure Determination from Powder Diffraction Data*

*In front: Abe Clearfield, Maryjane Tremayne, Lachlan Cranswick, Hideo Toraya. Back: Carmelo Giacovazzo, Jim Kaduk, Peter Stephens, John Parise, Cam Hubbard, Chris Gilmore, Bill David*

The transactions symposium at the San Antonio Annual Meeting dealt with the subject of Crystal Structure Determinations from Powder Diffraction. **Abraham Clearfield**, the symposium organizer and chairman, in his opening remarks pointed out that powder patterns contain an enormous amount of information about the system, giving rise to the pattern. However, the initial stumbling block to obtaining structural data was the lack of mathematical methods of peak shape duplication. It was not until the early 1980s that software began to appear that would allow for decomposition of the powder pattern to obtain accurate intensities. Since then, there has been great progress in both hardware and software for all aspects of structure determination and refinement. This symposium was convened to highlight just how far we have progressed.

The formal papers were initiated by **Lachlan Cranswick** and **Robin Shirley** from Birkbeck College, who dealt with methods of indexing the powder pattern. This is the first step in structure solution and is decidedly non-trivial. The use of a variety of different algorithms and approaches is recommended. The program Crysfire 2001 supports nine indexing programs. Crysfire's list of potential solutions can be analyzed with the Checkcell graphical helper tool. Since indexing programs often favor low-volume, low-symmetry settings and may not reliably report the reduced cell, Crysfire and Checkcell form a powerful combination for locating the correct solution.

EXPO, developed by **Carmelo Giacovazzo** and his colleagues at Bari University, has been a much used and successful program for *ab initio* structure solutions from powder data. EXPO 2001 is a new improved version of this popular program. New features include an improved method of assigning integrated intensities to overlapped peaks in the Le Bail procedure of pattern decomposition, an improved refinement scheme, a new algorithm for automatic labeling of electron density peaks and a Monte Carlo technique for completing the structure after the heavy atoms have been located. The program uses chemical information such as bond distances and angles with suspected coordination numbers for the heavy elements in a special way termed the POLPO method. The program searches the atoms bonded to these atoms within the constraints given. The solution of several difficult structures was detailed in an impressive demonstration.

**The solution of several difficult structures was detailed in an impressive demonstration.**

**Hideo Toraya** from the Ceramics Research Laboratory of the Nagoya Institute of Technology addressed the problem of powder patterns with low angular resolution, i.e. when the majority of the peaks cannot be resolved. He recommends the use of rigid body approximations in direct space methods, which he states is effective with inorganic as well as molecular type crystals. As an example, he described a new hydrothermally synthesized calcium silicate. 94% of the reflections could not be resolved. By applying simulated annealing methods to a model consisting of four free  $\text{Ca}^{2+}$  and two rigid  $\text{SiO}_4$  groups, a solution was found. A technique of re-annealing was also recommended to avoid being trapped into local minima. The technique was also effective with zeolites.

In house powder data of organic crystals affected by preferred orientation are often difficult to solve by direct-space methods. **Maryjane Tremayne** at the University of Birmingham used two global optimization techniques, a heuristic one based on Monte Carlo sampling and a new evolutionary algorithm based on differential evolution (DE). It was determined that the DE method is fast and reliable and all calculations can be done on a desktop PC. The DE calculation can be fully controlled with only four parameters where these parameters were either defined according to the complexity of the structure or a number of calculations

performed over a range of parameter values. The method was demonstrated for a number of solutions of organic compounds. (See figure, opposite page.)

Since I rarely think of terephthalates, it was a shock to find out from **Jim Kaduk** of BP Chemicals how terribly complicated the metal terephthalates are. Solving their structures required creative application of Monte Carlo simulated annealing techniques to both in-house and synchrotron powder data. Model building and real space optimization was necessary to reveal the cation positions.

According to **John Parise**, SUNY Stony Brook, the introduction of new types of high pressure cells that can maintain static pressures from 0.01-100 GPa and temperatures from 10 to 300K and 300 to 2000K has greatly aided the discovery of new phases and other phenomena at high pressures. Use of high brightness synchrotron x-ray and high flux neutron sources has greatly improved the quality of the data. High-pressure data normally suffers from poor peak to background discrimination and peak resolution. Minimization of parasitic scattering from the cell and the effects of lattice strain further improves the data. Parise illustrated with a treatment of the high pressure FeS phases. Complete characterization of the atomic and magnetic structures

of these phases required a combination of X-ray and neutron-scattering from samples held *in situ* under the conditions that they are stable.

**Cam Hubbard** discussed the use of the Powder Diffraction File (PDF) published by the International Center for Diffraction Data (ICDD) to help establish phase identification, corrosion and decomposition products in the varied fields of mineralogy, materials science, manufacturing and pharmaceuticals. In powder structure solutions, it may often happen that the pattern does not index due to the presence of a minor phase. Identification of this phase through the PDF allows the crystallographer to properly proceed with the structure solution. The evolving needs for structure solutions, along with the needs of combinatorial chemistry, computational materials science and pharmaceutical laboratories will require ever more accurate data and data base expansion. Furthermore, there is a need for greater cross-linking of characterization with property databases. Intelligent planning for the future is an ICDD priority.

Solution of organic structures from powder data becomes very difficult when more than fifteen fully flexible torsion angles are involved or three or more molecules are present in the asymmetric portion of the unit cell. **Bill David** from ISIS has considerable experience with such problems and recommended using maximum likelihood, rather than least-squares analysis for structure solution and to make use of prior chemical information as much as possible. In this connection, knowledge of torsion angles in related structures would prove helpful. Finally, developing new algorithms for global optimization beyond simulated annealing and genetic algorithms is in order.

For large complex structures powder data may be of poor resolution and **Chris Gilmore**, of the University of Glasgow, ponders the question -can much information be gleaned from such data. Sometimes, all you get are envelopes of the peaks. These could be used to place molecules in the unit cell and then use model-building algorithms to obtain more molecular detail. Heavy atoms may be located even from proteins using powder data at about 4Å resolution.

**Peter Stephens** of SUNY Stony Brook discussed his work with PSSP (Powder Structure Solution Program) that has been put in the public domain. This program has incorporated many of the latest techniques of structure solution, including recent algorithmic improvements, incorporating a hybrid of Monte Carlo and microcanonical techniques. Peter's experience in the use of PSSP for the solution of several structures of drugs highlighted some of the difficulties encountered and how they were overcome.

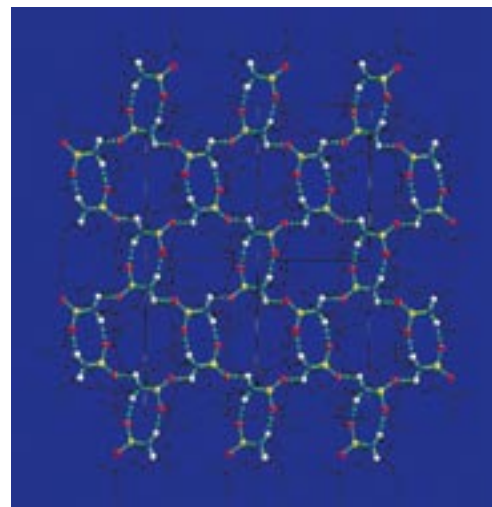
At one time, it was thought that zeolite structures could not be solved by direct methods and therefore distance least-squares modeling was used. **Michael Deem**

at UCLA (now moved to Rice University) described a Monte Carlo scheme with parallel tempering to determine the crystal structure of all publicly known zeolites. This display was quite impressive as there were no failures. It would be interesting to see the method applied to new structures. I can't restrain myself from interjecting that my group solved the first zeolite structure in 1986 utilizing direct methods. The trick was to use contours of  $0.1e/\text{Å}^3$  in the E-maps, and to assign minimum intensities to absent but not systematically absent reflections.

**Rob Grothe** and associates, at the Howard Hughes Medical Institute and UCLA-DOE Molecular Biology Institute, are developing a program for structure determination from anisotropic powder diffraction data collected on an area detector. Each reflection produces a ring with a unique pattern of angular variation. Because each ring depends upon the way in which that set of planes is distributed in space the distribution of intensity around each ring is different. This difference allows overlapping reflections to be partially resolved. An orientation function can be mapped to a unit sphere and parameterized by texture coefficients in a hyperspherical harmonic series. A model including unit cell parameters, atomic coordinates and the texture coefficients is refined to bring the calculated diffraction image into agreement with the observed image. The technique is being used in connection with protein structure analysis but is still in the formative stage.

A most important speaker, **Robert Von Dreel**, could not attend due to family illness. However, portions of Bob's contribution were presented by Peter Stephens to whom we extend our thanks for doing double service. By combining high-resolution synchrotron X-ray powder diffraction data and stereochemical restraints, it has been demonstrated that the Rietveld refinement of protein crystal structures is feasible. Molecular replacement was used to solve a previously unknown protein crystal structure. Powder data analysis has been able to clearly identify the position and orientation of the ligand in a protein/ligand complex by the difference induced in the electron density maps. Bob, we sorely missed you and hope all goes well with Veronica.

*Abraham Clearfield*



*from Maryjane Tremayne: one of several arenesulfonamides solved from laboratory X-ray powder diffraction data using the direct-space based differential evolution technique*

*Note: for other images from the Transactions Symposium, see cover of Spring ACA Newsletter.*

**Symposium on Electron Microscopy of Biological Macromolecules**

In addition to the day-long Symposium on Electron Crystallography that was organized in conjunction with this year's Patterson Award to Doug Dorset, the Spring 2002 Meeting featured three half-day sessions on Electron Microscopy of Biological Macromolecules. Electron microscopy of samples embedded in vitreous ice ("cryo-EM") has recently developed as a powerful way to visualize the three-dimensional assembly of macromolecules into various complexes and machines, and thus it is regarded as providing an important bridge between structural genomics and cell biology (Nature (2002) 417, 894-896).

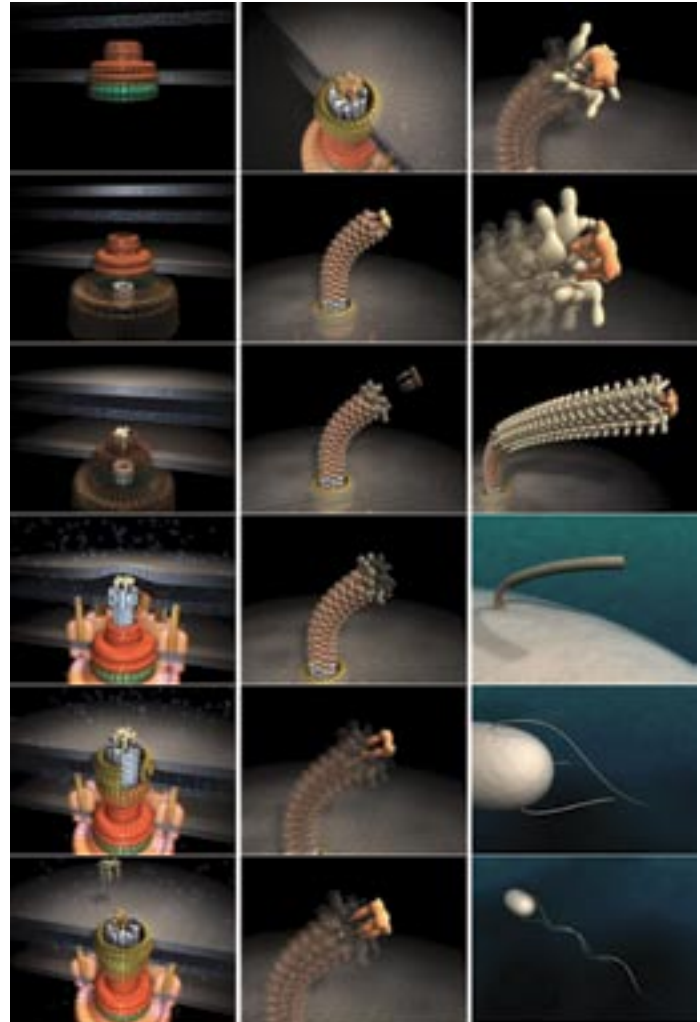
The first of these three sessions focused on the quantitative interpretation of cryo-EM density maps. **Wah Chiu** opened this session by demonstrating how computational tools for fold recognition can aid the interpretation of EM density maps at ~8 Å resolution, leading (by structural homology) to candidate-functions of specific domains within a large structure. This was followed by two talks that described computational tools that are being developed for fitting already-known atomic models (of component macromolecules) into cryo-EM density maps of larger complexes, even when the latter are not themselves determined at atomic resolution. **Niels Volkmann** introduced new tools for estimating the error of fitting structures into density maps, and for scoring the confidence that can be associated with a candidate fitting. **Willy Wriggers**, in turn, introduced a fast rotational search algorithm that extends Crowther's 2-D FFT to include the third rotational angle. The session then concluded with two dramatic examples in which large assemblies were characterized by docking known atomic structures of subunits into medium-resolution cryo-EM maps. In the first of these, **Keiichi Namba** presented a comprehensive



*Rapid Automated cryo-electron microscopic structure determination illustrated using tobacco mosaic virus. (Clint Potter and Bridget Carragher, The Scripps Research Institute.)*

and stunning survey of the bacterial flagellar apparatus, (see also *On the Cover*, page 13), after which **Huilin Li** described the atomic contacts by which protofilaments of tubulin assemble themselves into the eukaryotic microtubule.

The second session then moved on to report technology-developments that aim to automate many of the steps in cryo-EM that must currently be done "by hand." **Clint Potter** and **Peijun Zhang** pre-



*From Keiichi Namba: Self-assembly process of the bacterial flagellum. The assembly starts from the rotor complex of the flagellar motor in the cytoplasmic membrane, and after the type III protein export apparatus is formed on the cytoplasmic surface of the motor complex, flagellar proteins are selectively exported into the central channel and pushed out to the distal end where they assemble by the help of cap complexes.*

sented their respective development of software that is capable of automated data collection. As Potter demonstrated, automation of data collection can be combined with "real-time" merging of the data, and in the case of Tobacco Mosaic Virus - a helical sample - it has even been possible to obtain a 3-D density map in less than 24 hours. **Steve Ludtke** then described how he is automating the process of merging data for non-helical particles within his EMAN software package, and **Ravi Malladi** described work in progress to automate the identification and "boxing out" of single particles. This second session then concluded with two application papers that exemplify the need for high-throughput technology. The first of these was by **Jacqueline Milne**, who described the marvelously complex and well designed machinery of the pyruvate dehydrogenase complex from *B. stearothermophilus*, an 11 megadalton "catalytic machine." The second was a *tour de force* update on the progress that **Helen Saibil** has made in characterizing the machine-like twisting and stretching changes in structure of

## Symposium on Electron Microscopy of Biological Macromolecules, continued

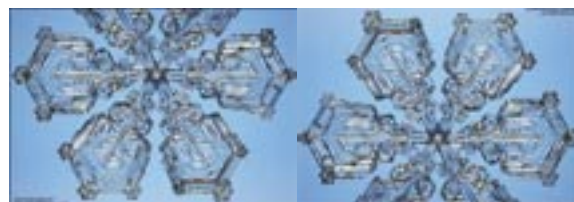
GroEL chaperonin during its biochemical cycle, work that now stands at 9.5 Angstroms resolution.

The third and final session moved on to describe work in which 2-D crystals are used in order to obtain 3-D density maps at high enough resolution to allow *de novo* modeling of the structure at atomic resolution. **Yoshinori Fujiyoshi** described recent work on the membrane protein, bacteriorhodopsin, for which the resolution now stands at 2.5Å in-plane and ~3Å perpendicular to the plane of the membrane. This refined structure shows an rms difference of only 0.78Å relative to the ~1.6Å x-ray structure; provides unique information on the charge-status of ionizable groups; and allows structural studies under extreme conditions such as the investigation of changes in rotamer conformation of a key arginine residue (R82) and associated bound-water molecules at pH 10. This was followed by a report from **Teresa Head-Gordon** of progress that is being made to use electron-scattering factors that accurately reflect the substantial perturbation of atomic coulomb potentials caused by chemical bonding. As may not be widely appreciated, chemical bonding effects are most prominent at resolutions below ~2 Å for electron scattering, whereas the opposite is true for x-ray scattering. This third session then concluded with two additional reports involving 2-D crystals of membrane proteins. **Sriram Subramaniam** described crystals of OxIT, a bacterial oxylate: formate antiporter, which show diffraction to 3Å in high-resolution images. The current 3-D map at 6.5Å resolution reveals a

helix-packing geometry that creates a relatively large chamber half-way through the membrane. **Ansgar Philippsen** then reported on the ongoing work with 2-D crystals of aquaporin, in which the 2.2Å resolution structure of the related glycerol porin was used to improve the 3.8Å EM map. A critical difference in the “filter 1” region of the channel has been identified as likely to account for the difference in solute selectivity of the aquaporins and the glycerol porin.

Considerable enthusiasm was expressed by many of the participants in favor of continued presentation of electron crystallography and electron microscopy talks at future ACA meetings. The time could, indeed, be no more propitious than now, to provide for a greatly increased presence of electron diffraction and electron microscopy within the crystallography community.

*Bob Glaeser*



*Snowcrystals, see page 15*

## Electron Crystallography

Electron diffraction and imaging has a fascinating history in both biology and materials science. A special session on this topic was organized this year to honor **Doug Dorset's** achievements in this field because he was to receive the Patterson Award at the San Antonio ACA Meeting. The morning was devoted to applications in biology, and the afternoon to materials science, with Doug's award lecture after lunch. The recent solution of several membrane proteins, difficult or impossible to crystallize for X-ray work, the solution of the ribosome at 1nm resolution, and the development of cryomicroscopy have been dramatic recent developments in this exciting field. Talks by **Ken Downing** on Tubulin, **Bing Jap** on two-dimensional crystallization techniques, on the phase problem by **Chris Gilmore**, on electron crystallography generally by **John Fryer**, and on new methods by **John Spence** and by **Laurie Marks** (for surfaces) all reflected this excitement. Doug provided a wonderful overview of the field, with emphasis on electron crystallography of organic crystals (rather than biology), as discussed in his valuable recent book. It was interesting to see the large number of X-ray people at the morning session, curious to hear details of the cryomicroscopy method and its successes. In materials science, the ability to obtain images of atoms in crystals at about one Angstrom resolution has now had a huge scientific payoff, while the convergent beam diffraction method has provided us with the first extinction-free structure factor measurements from fine-grained crystals, based on analysis by the perfect-crystal theory. **Osamu Terasaki** discussed his work on mesoporous material, **Yimei Zhu** on charge-density measurements by CBED

imaging, **J.M.Zuo** discussed electron nano-crystallography, **Mike Treacy** discussed electron imaging from glasses, while **Youn Kim** discussed energy-filtered diffraction patterns from diatom frustules.

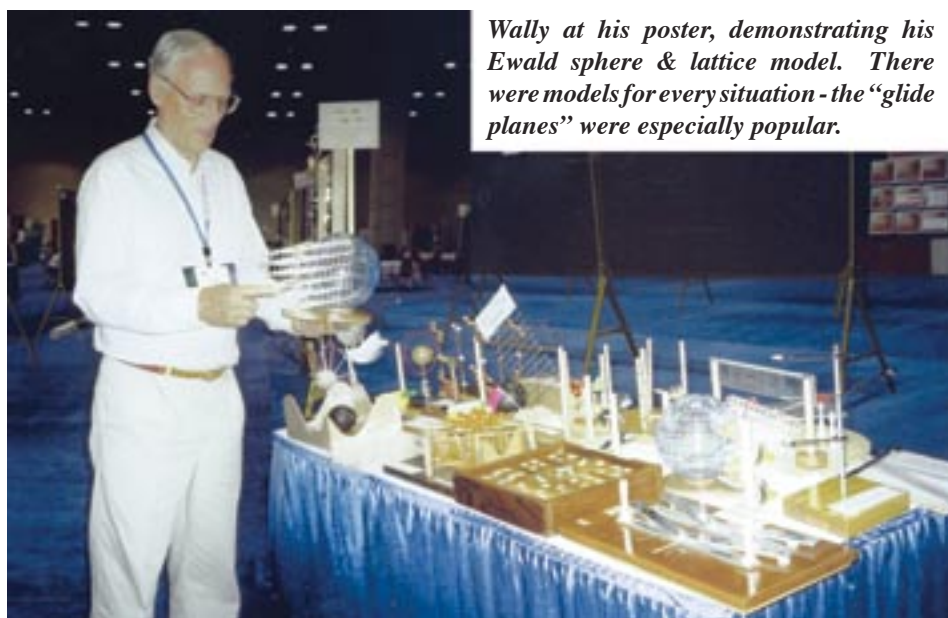
Two things are driving this growth in electron diffraction and imaging methods - in biology, the urgent need to determine the shape of large macromolecules, at sub-nanometer resolution, which cannot be crystallised, and in materials science, the boom in nanoscience, for which the electron microscope provides the ideal probe. In biology, the development of cryomicroscopy has been crucial, and we have the prospect of solving subunits by XRD, while understanding their organization and assembly by tomographic cryo-TEM. (For imaging and diffraction, as against spectroscopy, the amount of useful elastic scattering per unit damage does appear to be less using electron diffraction than XRD, as recently pointed out by Richard Henderson). For inorganic materials, the collection of the X-ray emission, energy-loss spectrum and diffraction patterns from sub-nanometer areas are now routinely combined with atomic-resolution imaging in the same instrument, while tomographic imaging, well developed in biology, is just emerging in materials science. All these new methods, together with the appearance of aberration correctors and monochromators for TEMs, promise an exciting future for electron crystallography.

*John Spence*

## Teaching Techniques

This free-wheeling session, chaired by **Wally Cordes**, had no abstracts or speaker list; it was advertised to be a *sharing of teaching strategies and techniques used to start the classes of a course in crystallography*. The only “aid” was a comprehensive list of topics that Wally usually covers in his introductory crystallography course, which was left up for reference. With any other chairperson, or with an audience less vitally interested in teaching, this plan of action might not have worked; however as it happened, the session was well attended and the audience participation was terrific. Every time there was a lag in participation, Wally had a story ready about some technique he had used over the years, and this always seemed to stimulate more stories from other people.

Wally started the session by relating his “janitor” story, which others in the crystallographic community may have heard before,



*Wally at his poster, demonstrating his Ewald sphere & lattice model. There were models for every situation - the “glide planes” were especially popular.*

but I had not, and so will try to recall it. Wally has the same idea that many teachers would concur with: that success is highly dependent on *getting their attention in the first couple of minutes*. So one year he dressed up as a janitor, complete with overalls, pail and bucket, and when the (very large) class started to filter in they observed him scrubbing the floor up in front (he said it needed it anyway). This went on until a few minutes after the start time, when restlessness was beginning to be apparent, and finally he stood up and said “Dang, that Professor Cordes didn’t show up again! Well, never mind, I’ve heard his lecture enough by now that I can give it just as well.” *Connie Chidester*

## Authorship Issues

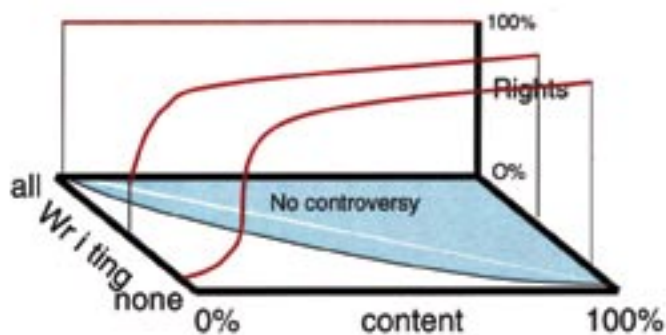
**Carol Brock** chaired the session, which was organized by the Service Crystallography SIG as a special evening program. The evening sessions at ACA meetings traditionally deal with themes of general interest not normally covered in the main scientific program. On this occasion the evening session was intended as a forum for airing opinions and concerns regarding authorship in the rapidly changing world of scientific publishing and with special attention to the continuously evolving role of the service crystallographer.

The eight talks in the program fell into three main categories, although the presentations were largely free-ranging as well as engaging. The first two talks dealt with authorship in general, including crystallographic authorship in chemical journals. The opening speaker was **Steve Ritter**, Senior Editor at *Chemical and Engineering News*, a chemist and journalist by training, who has written extensively on authorship ethics. Steve presented a circumspect view of scientific authorship; he made it clear that the policy at American Chemical Society journals dictates that anyone who is responsible for the scientific veracity of the contents of a paper should be an author. The second speaker in the session, **Larry Falvello**, dealt with the changing nature of crystallographic authorship, from the beginnings of x-ray diffraction to the present, and included some examples of “ethically interesting” practices on the part of both chemists and crystallographers.

The second main category of presentations was that of authorship rights and ethics for crystallographers who provide analytical services. Four practicing crystallographers from three countries gave their analyses of the topic from quite different viewpoints. All emphasized the importance of proper training in crystallographic practices, and the often understated importance of high-quality crystallographic peer review was mentioned several times. **Ton Spek** of Utrecht University described the authorship practices at his institution, where the crystallographer is regarded as a scientific collaborator. He used a recent, highly visible example of misinterpreted diffraction data to emphasize the importance of training for crystallographers and reviewers. **Phil Fanwick** of Purdue University described the different levels of importance of a crystallographic contribution to a scientific publication, and how these confer correspondingly differing degrees of authorship rights and responsibilities to the crystallographer. **Fred Hollander** of the University of California at Berkeley presented an engaging semi-quantitative analysis of the relationship between the crystallographer’s contribution and authorship rights. This was neatly summarized in a three-dimensional graph (see figure, opposite). **Andrew Bond** of the Cambridge University Chemical Laboratory gave a thought-provoking presentation in which the nature of the service crystallographic contribution was tied in with the evolving nature of scientific publication. Andrew specifically proposed that for routine structure analyses with clear-cut results,

"Rights" of Authorship for Service Crystallographers

Dimensional space for authorship rights.



From Fred Hollander: proposed dimensional space for authorship, emphasizing the combined effects of writing and content contributions. Every service crystallographer wants to be in the blue zone.

published in papers in which the structure is not the main scientific objective, the crystallographer could recuse himself from the by-line of the scientific publication and instead receive a concrete attribution in the appropriate crystallographic database. This presentation, just before the coffee break, generated a lively discussion that continued into the recess. On the whole, however, as was stated explicitly by Phil Fanwick, there does not seem to be a necessary or desirable global policy for crystallographic authorship.

The third main category was the journal-database nexus, and was covered in two very well received talks at the close of the program. Rich Eisenberg, Editor-in-Chief of the high-impact ACS journal *Inorganic Chemistry*, which is one of the leading publishers of analytical crystal structure work, described the present and future of publishing at *Inorganic Chemistry*, and reprised the earlier speakers' opinions on the necessity of good training and good peer review for diffraction work. From his talk it was clear that the integration of electronic media into the review and publication process was well underway at ACS Journals, and that the role of crystallographers and structure analyses in the process was being given the necessary consideration. The closing talk in the session was given by Frank Allen, Director of the Cambridge Crystallographic Database, which now has holdings of more than a quarter million single-crystal structure determinations. Frank's lively talk dealt broadly with authorship, and he succinctly stated the policy of the database regarding the authorship attribute – it is recorded exactly as it appears in the scientific journal. Frank did indicate, however, that a separate field for the crystallographer's attribution was technically feasible. He also dealt with direct author-to-database submission of structures that are published in scientific journals, a practice that is being used by a growing number of journals.

The Authorship Issues session provided the large audience with an interesting program that addressed a number of issues – ethics, authorship rights and responsibilities, and the rapidly changing author-journal-database pipeline. The program was organized with a great deal of help from Wally Cordes, to whom all involved in the session owe a great debt of gratitude for his support and assistance throughout the organization of this productive contribution to this year's meeting.

Larry Falvello

Structure-Based Drug Design

The session was well attended, with seven oral presentations and twelve posters. The clear message of the session was that structure-based methods continue to be important tools in drug design in today's environment of automated chemistry, ultra high throughput screening and in silico methods. The caution that an inhibitor does not necessarily a drug make was also a prominent message. Cele Abad-Zapatero from Abbott Laboratories kicked off the session with a cautionary tale of the design of inhibitors of human PTP1B, a phosphatase therapeutic target for the treatment of type II diabetes. Despite elegant design work to occupy 2 adjacent binding pockets on the enzyme and the resulting nanomolar inhibition with enhanced selectivity over other human phosphatases, the compound failed for lack of bioavailability. Scott Rowland from BioCryst Pharmaceuticals emphasized the difference between a drug and an inhibitor, pointing out that ADME-related problems eliminate 40% of good inhibitors from being drug candidates. The use of structural information to design

The caution that an inhibitor does not necessarily a drug make was also a prominent message.

libraries of compounds with favorable ADME characteristics together with in silico screening is a powerful approach to enhance the success rate of the drug design process. Rachel Powers

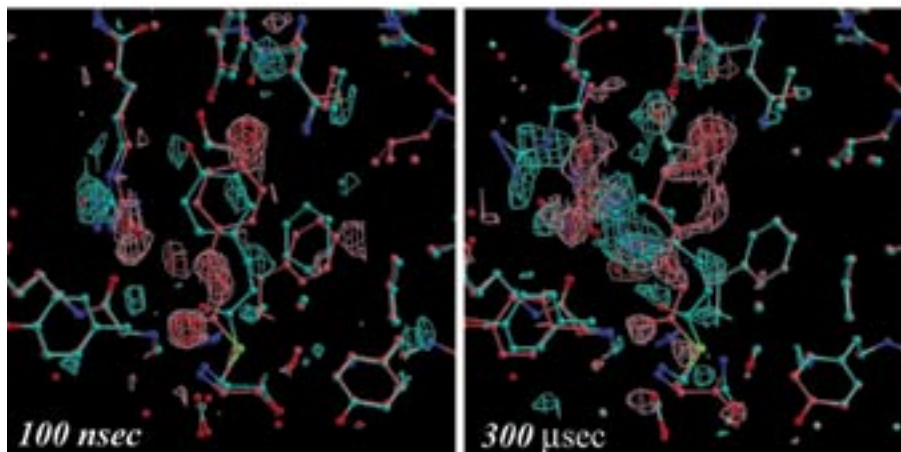
from Northwestern University used the program DOCK together with a database of 200,000 commercially available compounds to screen for novel inhibitors of AmpC Beta-Lactamase. Fifty-three of the most promising hits were purchased and assayed; three of these exhibited IC<sub>50</sub> values of 2 μM or better. The crystal structure of the tightest binding molecule of the 3 showed the predicted binding mode was very close and this co-crystal structure provides a useful starting point for further inhibitor design. Lisa Shewchuk from GlaxoSmithKline described design efforts against the ATP-binding site of CDK2 and the use of CDK2 mutants as a "surrogate" kinase structure for drug design studies of other, related kinases less amenable to crystallization. Ernst Ter Haar of Vertex described the crystal structures of another kinase, GSK3b, and described its potential as a target for Type 2 Diabetes. Corey Strickland from Schering Plough presented work on designing inhibitors of Farnesyl Protein Transferease, with a large active site. The importance of buried hydrophobic surface area in inhibitor binding was stressed, as was the importance of the need to consider other inhibitor properties other than binding affinity in designing drug candidate molecules. Also presented in the poster session were topics including high throughput crystallography methods applied to drug design, steps toward automated ligand fitting into density and a property-based database of ligand interactions with HIV protease.

Ward Smith and Bill Stallings

## Macromolecular Motions and Dynamic Processes

*Lights! Camera! Action!* If you are tired of old-fashioned, static images of your favorite macromolecules, and are searching for methods to add a fourth dimension to your three-dimensional structures, then you may want to seek out presentations that include "Movie" in the title or abstract at the next ACA meeting. You may also want to bring some popcorn, your favorite beverage, your imagination, and paper and pen to take good notes. The session on *Macromolecular Motions and Dynamic Processes* was filled with molecular movies of proteins, enzymes, and RNA in action, folded in with structural, kinetic and thermodynamic studies. The underlying theme is that you need to combine experimental data from a variety of sources to construct a complete description of conformational changes and dynamics in biological function.

The first three speakers, along with one poster, presented time-resolved crystallographic studies on proteins, enzymes, and RNA. The investigators highlighted the use of state-of-the-art, time-resolved polychromatic Laue X-ray diffraction. The opening presentation was given by **Zhong Ren** of Renz Research Inc., who really "shook-up" the audience with his movie of a "Protein Quake" that occurs during the reaction cycle of photoactive yellow protein (PYP). The movie was produced from a time-series of x-ray structures that were determined from polychromatic, Laue x-ray diffraction data acquired at several time-points ranging from nanoseconds to seconds. The Laue data were collected at the European Synchrotron Radiation Facility (ESRF), and most recently at BioCARS at the Advanced Photon Source, Argonne National Lab. The experiment involved excitation of the 4-hydroxycinnamic acid chromophore of PYP using a 10 nanosecond laser pulse at 495nm, followed by an experimentally set time delay, and then rapid Laue x-ray data collection. Ren and colleagues have also developed novel Laue x-ray diffraction data collection strategies and new computational methods that lead to high-quality electron density maps (see **figure**). In the final analysis, they found that the laser light triggers an initial and rapid isomerization event that causes the chromophore to flip at the "epicenter" of



*From Zhong Ren: difference electron density maps for the chromophore region of the E46Q mutant of the photoactive yellow protein for 100ns and 300microsec delays between the laser and the X-ray pulses. Maps are calculated to 1.8Å and contoured at +/- 2.8sigma and +/-3sigma, respectively. Negative electron density and the dark structure are shown in red while positive density and tentative structures of the intermediates are shown in blue. Data was collected at BioCARS beamline ID-B at APS (Spencer Anderson, The University of Chicago).*

the reaction cycle. Within the tens of nanoseconds that follow after the excitation event at the epicenter, structural changes propagate or "quake" throughout PYP via an extensive hydrogen bond network. These structural changes ultimately lead to phototactic responses in *Ectothiorhodospira halophila* from which PYP was isolated.

**Vukica Srajer** from the University of Chicago and BioCARS presented a poster entitled "Time-resolved Macromolecular Crystallography at BioCARS" that not only highlighted her most recent results from time-resolved Laue x-ray studies on the photodissociation of carbon monoxide from myoglobin, but also highlighted progress and new developments at BioCARS. Srajer and colleagues showed that they can detect CO docking sites with only 20% occupancy, and small structural changes (0.2 to 0.4 Å) via Laue x-ray diffraction. BioCARS is one of three branches of the multidisciplinary Consortium for Advanced Radiation Sources (CARS) at the University of Chicago. They have designed, constructed and commissioned an insertion device beamline at the APS, 14-ID, for time-resolved diffraction studies of macromolecules. The beamline is part of a National User Facility for macromolecular crystallography that is funded by the National Institutes of Health. Both Laue and monochromatic experiments can

be conducted at the beamline, and the BioCARS facility also hosts a laser lab that has a variety of lasers and microspectrophotometers that can excite, trigger and monitor reactions within crystals. So grab your crystals because BioCARS facilities are available to the general user community, and Laue time is now available; --it's all about *TIME!*

**Barry Stoddard** from the Fred Hutchinson Cancer Research Center discussed his time-resolved x-ray structural studies on the enzyme isocitrate dehydrogenase (IDH). The Stoddard group, in collaboration with others, has been attempting to identify and determine the x-ray structures of numerous reaction intermediates proposed to exist along the multi-step reaction cycle of IDH. He emphasized that so far, it has been necessary to utilize a combination of physical and chemical trapping, rapid diffraction methods, and kinetic analysis in the crystal to visualize discrete catalytic species during the IDH reaction. Using site-directed mutagenesis, slow-substrates and flash-cooling to chemically and physically trap intermediates, in combination with monochromatic and steady-state or time-resolved polychromatic x-ray data collection, Stoddard and coworkers have been able to demonstrate that the intermediate, oxalosuccinate, predicted 30 years ago, actually forms and is stable during the IDH reaction. He also showed that

small conformational changes and proper orientation of substrates during the course of the IDH reaction are extremely important for efficient catalysis.

**Christine Dunham** from the University of California, Santa Cruz, pinch hit for **Bill Scott** and gave an informative presentation on the structural motions that take place during the hammerhead ribozyme-catalyzed reaction. She demonstrated that crystals of the hammerhead ribozyme cleave 5-times faster in the crystal than in solution, and that, remarkably, divalent cations are not necessary for catalysis, *i.e.* monovalent cations are sufficient. She presented a series of x-ray structures representing four intermediates during the RNA catalytic cycle, that had been “trapped” using combinations of freeze-trapping, chemical modification, and reinforced crystal lattice modification methodologies. She completed her talk with a molecular movie of ribozyme catalysis complete with special effects including the sound of breaking bonds.

**Patrick Loria** of Yale University presented an intriguing talk on the use of solution state NMR spectroscopy to study protein motion. In particular, the time-dependent excursions from the equilibrium structure of RNase A were implicated in the functioning of this enzyme. Modern NMR spectroscopy can now accurately quantitate the kinetics and thermodynamics of protein motion, and these state-of-the-art experiments were applied to RNase-A where it was demonstrated that the rates and thermodynamics of motion measured by NMR were comparable to those values measured for enzyme catalysis. During the question and answer period he noted an interesting observation for Ribonuclease A, in that the  $\mu$ s-to-ms dynamics observed by NMR show some correlation with the RMSD of the numerous x-ray structures of RNase A available. However, he observes no apparent relation between the dynamics of the atoms and their crystallographic B-factors.

**Jill Trehwella** of Los Alamos National Laboratory presented her work on small-angle neutron scattering studies of second-messenger mediated signal transduction proteins including the  $\text{Ca}^{2+}$ -calmodulin dependent kinase myosin light chain kinase (MLCK) and the cAMP-dependent protein kinase. Her presentation highlighted how important it was to combine or hybridize structural data from small-angle solution scattering studies with conventional x-ray diffraction studies to fully characterize the conformational transitions and associations in the activation mechanisms of proteins. She showed how neutron scattering data from the cAMP-dependent protein kinase holoenzyme (catalytic subunits C) reconstituted with deuterated regulatory subunits (R) revealed the shapes and dispositions of the R and C subunits. By fitting the crystal structures of the C-subunit and R-subunit to the neutron data, her group was able to determine the molecular boundaries of the entire protein. The final quaternary structural model shows that the R-subunits dimerize in a dumbbell shape with the cAMP binding domains in the weight position separated by a bar. One catalytic subunit then binds to each of the R-subunits in the bar domains region. The C-domains do not touch. She then went on to show how neutron scattering studies revealed that the catalytic cleft between the large and small domains of the catalytic subunit closes via a hinge motion upon binding of pseudo-substrates.

**Tobin Sosnick** concluded the session with a thorough presentation on the mechanisms for thermodynamic stability of RNA structure. Using a combination of experimental methods including small angle x-ray scattering, hydroxy radical protection, and CD spectroscopy, his lab investigated the equilibrium folding of the catalytic domain of bacterial RNaseP RNAs from a thermophile, *Bacillus stearothermophilus*, and a mesophile, *Bacillus subtilis*. Their results indicate that the intermediate state of a thermotransition for a thermophile is significantly *less* structured than the intermediate state of a mesophile, even though their native structures are very similar. He also showed that the increased cooperativity in folding/unfolding transitions of thermophiles also leads to an increase in thermal stability. He pointed out that such a mechanism is fundamentally different than the strategy used by thermophilic proteins because most proteins fold without intermediates near their melting transition and are largely devoid of structure. Therefore, protein folding and temperature transitions are already maximally cooperative, and attempting to enhance their stability by altering the “reference” state is not a viable option.

*Look out Spielberg!* What was clear from all of these presentations is that imagination, resourcefulness, and a lot of hard work is necessary to create macromolecular movies and to understand how molecular motions and dynamic processes drive biological function. It is too bad that Hollywood doesn't give out Academy Awards for such *tour de force* work, but maybe someday the ACA will come up with some sort of “Best Macromolecular Motion Picture” award.

Andrew Mesecar

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**FYI The American Institute of Physics Bulletin of Science Policy News #75: June 20, 2002**

***Raising the Profile: House Vote on NSF Bill***

It is generally agreed that the National Science Foundation has had a relatively low profile in Congress and among the general electorate. A clear sign of how that is changing is the House of Representatives' overwhelming vote in early June for H.R. 4664, the ***Investing in America's Future Act***. This authorizing bill would begin a doubling of the foundation's budget over five years. Constituents wishing to write to their representative about this vote can do so through a House of Representatives e-mail web site. Go to <http://www.house.gov/writerep/>. There were 397 yes votes in favor of the passage of this bill. Twenty-five Members voted no, and 12 Members did not vote.





*Discussions at Poster Sessions and other venues. Center: George Sheldrick; top left: Yael Pazy Benhar, Marie Coté, Anne Mulichak, and Michael Becker; Bill Stallings at poster with Bhuvaneshwari Mahalingam; second row: B.C. Wang and colleague; Tom Koetzle and Bryan Craven; 3rd row: Dario Braga and Charlie Carter; Barry Finzel and Gary Bryant; from left in bottom row: Bill Stallings and Richard Schevitz; George DeTitta and Jeff Deschamps; Robert Gould and Bill Duax.*



### Cool Structures

The cool structure talks started out with a presentation about new anti-inflammatory drugs based on dibenzoyl diselenide by **Frederico Martinez-Ramos**. Then we heard about the great structural debate of  $\text{NO}^+$  and  $\text{NO}^0$  forms in nitric oxide iron complexes. **Javier Ellena** explained how additional chemistry

and accurate crystallography are used hand in hand to solve the issue.

**Patrick Carroll** showed us many cool structures which he had solved in the last year. The figure above left is one of the many examples he showed: a zinc porphyrin complex that forms a dimeric pair of “hugging” molecules.

**Marilym Olmstead** displayed the structure of the first endohedral fullerene that violates the isolate pentagon rule. To demonstrate the many different isomers possible, she showed us models built from toy store purchases which even glow in the dark. **William Ojala** described the work of his lab to observe halogens that participate in close, Lewis Acid-Base interactions with the nitrile group similar to the iodine atom. **Evgeny Dikarev** showed some great structures of tetra- and di-metallic complexes coordinated by neutral substrates. This demonstrated the Lewis acidic nature of these metallic clusters and the possible ability to tune this effect. We

thank all presenters for providing stimulating chemistry which resulted in some very good discussions. *Richard Staples*



*Marilym Olmstead with endohedral fullerene models*

### Funding Opportunities and Effective Grant Writing

At the San Antonio meeting the Young Scientists SIG organized a short session to provide a forum for the discussion of funding opportunities and effective grant writing. The session comprised a panel discussion with **Andrew Barron** of Rice U., **Charles Edmonds** of the NIH Nat'l. Inst. of Gen. Med. Sci., **Elizabeth Goldsmith** of the U. Texas Southwestern Medical Center, and **Brian Matthews** of U. Oregon. The session was well attended by a group of young scientists ranging from graduate students to new investigators.

This session brought to the foreground issues and suggestions that were not well known, at least by those in attendance. Much of the discussion focused on issues concerning new investigators. For example, the NIH's R21 grants, small 2 year grants that require little or no preliminary data, are often useful for new investigators who are trying to amass enough data to support an R01 grant. The panel also delivered some sound advice about negotiating for, and managing start-up funds. One of the attendees brought up the fact that some professors advise students and post-docs *not* to immediately worry about writing grants, but instead to use the start-up money to generate data for a competitive grant. The panel pointed out that there are various agencies and foundations that award grants without requiring extensive preliminary data. Also, the panel advised that when negotiating for start-up funds, new investigators should think about asking for the funds to be dispensed over a period of several years, as this may help to increase the amount of money obtained. They also reminded the audience not to overlook indirect costs when negotiating for start-up money, like charges for using specialized equipment and machine shop costs.

**A valuable source of information about grant writing, and one that no one but the panel members seemed to know about, is the . . . (CRISP) database**

Another focus of the discussion was sources of information, and how to use information effectively. A valuable source of information about grant writing, and one that no one but the panel members seemed to know about, is the Computer Retrieval of Information on Scientific Projects (CRISP) database (URL: <http://www.crisp.cit.nih.gov>). Briefly, this database allows one to search by name of primary investigator, topic, date, etc, and will return a digest of all successful grant proposals meeting the search criteria. This information can be enormously helpful, for example, in guiding the focus of a grant to match a particular study section. Panel members also cautioned the young scientists not to overlook their university's office of sponsored programs as a source of information about funding opportunities. In addition, they reminded the audience that there are many more granting institutions than NIH and NSF, and that these other offices (like the Department of Defense, or the Office of Naval

research) should not be neglected.

Finally, several points came out of the discussion that, in retrospect, are purely common sense, but nevertheless would most likely never have occurred to the majority of those in attendance. For instance, the simple revelation that people are responsible for reading and evaluating each grant proposal. Though this is obvious, novice grant writers often fail to grasp the importance of following precisely the prescribed format for the particular grant proposal form. I would finally like to thank all the panel members and those in attendance for making this a very successful session. *Nicholas R. Silvaggi*

## Enzyme Mechanism

Several unifying themes were evident in the work presented in this session on the final day. One theme may be summarized by the rubric "one structure is not enough!", as enzymes are dynamic molecules and it appears to be generally accepted that a single crystal structure cannot present a complete picture of an enzyme's mechanism. Many contributors built their mechanistic story on evidence from an impressive set of relevant structure determinations. A second theme was the dramatic effect of higher resolution structural work on the level of detail that can be extracted to support models for mechanism. Most of the work presented was based on structures refined to better than 2Å resolution, an indication that such high quality data has become commonly achievable. A third theme was the direct relevance of much of the work to drug design.

A particularly impressive example of all these themes was the illumination of the HPPK reaction trajectory as presented by **Jaroslav Blaszczyk** (Michigan State Univ.). This enzyme catalyzes the transfer of pyrophosphate from ATP to 6-hydroxymethyl-7,8-dihydropterin, a necessary step in the microbial folate pathway. Blaszczyk and coworkers were able to capture six of seven proposed states along the reaction trajectory, all at resolutions of 1.6Å or better. Refinement of individual anisotropic displacement parameters proved useful as an indicator of which ligand moieties were most tightly or loosely associated with the active site at a particular intermediate state. The presentation was capped by a movie showing the major conformational changes occurring during the catalytic cycle.

The three unifying themes were also evident in a set of presentations relevant to  $\beta$ -lactam antibiotics such as penicillin. **Nicholas Silvaggi** (Univ. Connecticut) and co-workers were able to capture a transition-state analogue for the action of D-ala-D-ala-transpeptidase in cross-linking peptidoglycans during bacterial cell wall synthesis. This is a structural first for this important class of  $\beta$ -lactam-sensitive enzymes. Comparison of this 1.1Å complex to structures of the apo-protein implicates Tyr 159 as the most likely general base involved in deacylation. DD-peptidase is a target for  $\beta$ -lactam antibiotics, but antibiotic resistance can arise through selection for efficient  $\beta$ -lactamases in the targeted bacteria. So the talk by **Michiyoshi Nukaga** (U. Conn.) on a Class A  $\beta$ -lactamase at 0.9Å resolution may be seen as the flip side of the same story. Nukaga and coworkers used heroic measures to crystallize a cephalosporin-resistant mutant lactamase: determination of Cymal-6 as a critical detergent, micro-seeding with native crystals to nucleate crystallization of the mutant, followed by macro-seeding to yield diffraction quality crystals. The dramatic pay-off was an atomic resolution structure in which the visibility of individual hydrogen atoms allowed the unambiguous assignment of hydrogen-bonding networks at the active site (see figure). As a consequence, Nukaga was able to rule out one of two proposed mechanisms for hydrolysis. **Tao Sun**, from the same U. Conn. group, presented a poster describing work on a different (Class D)  $\beta$ -lactamase. **Matthew Miller** (Northwestern University) contributed yet another aspect of the  $\beta$ -lactam story by presenting a series of structures containing  $\beta$ -lactam synthetase. This series included

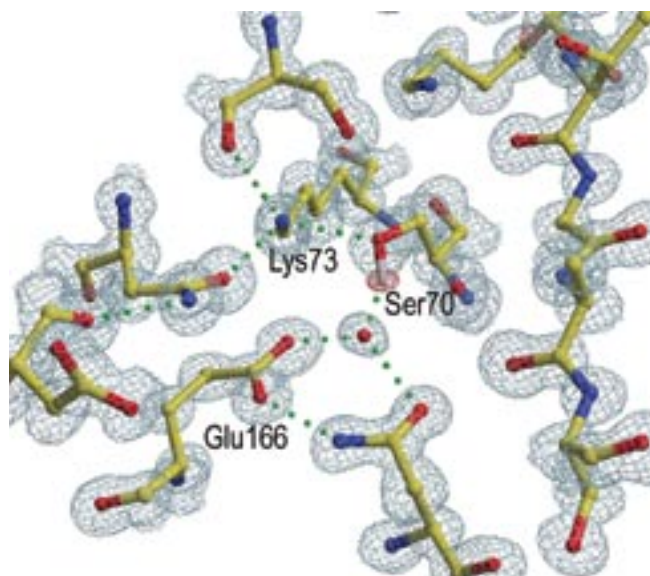
the apo-enzyme and complexes with substrates, inhibitors, and products. Reaction in the crystalline complex between ATP and the dead end inhibitor CMA yielded a structure containing the proposed reaction intermediate and showed the pyrophosphate product to be trapped in the interior of the binding site.

Two talks focused on enzymes central to cellular signalling and regulation pathways. **Jeffrey Taylor** (Duke University) presented structural models for transition state intermediates in the reaction cycle of the mammalian protein geranylgeranyltransferase. GGase performs a necessary post-translational modification (prenylation) of many G proteins. Among the ensemble of structures determined was an unanticipated complex that suggested a step in the catalytic mechanism not previously identified by biochemical means. This finding is a reminder that crystallography can be a tool for elucidating enzymatic mechanisms, not just a method for confirming or disproving mechanisms proposed by biochemists.

**Hao Wu** (Weill Medical College) contributed to our understanding of the structural basis of caspase inhibition. The pan-caspase inhibitor protein p35 is cleaved by caspases; the post-cleavage fragment that forms a stable complex with the caspase, preventing further caspase activity. Wu presented a 130kD complex of caspase-8 with the p35 cleavage product at 3Å resolution. Surprisingly, she finds a covalent linkage between the caspase catalytic Cys and the inhibitory p35 fragment. Covalent linkage was confirmed by MALDI/TOF and SDS-PAGE. Why is this state, normally an intermediate in the caspase reaction, trapped as a stable inhibited form? That is a fascinating question - one that may be answerable if higher resolution structures can be obtained.

The oral session was rounded out by presentations on *myo*-inositol synthesis (**Bog Stec**, Rice University) and a comparison of human carbonic anhydrase II and III (**David Duda**, University of Florida).

A survey of the poster session revealed that the average resolu-



From Michiyoshi Nukaga: 0.9Å 2Fo-Fc map (1.0 $\sigma$ ) of SHV-2  $\beta$ -lactamase active site, showing Fo-Fc peak (3.0 $\sigma$ ) for hydrogen on reactive Ser70.

tion of structures presented in this section was approximately 1.97 Å, and that the majority of posters presented work based on multiple crystal structures. Particularly notable contributions included a poster by **Sonia Patenaude** explicating the substrate specificity and catalytic mechanism of the ABO blood group glycosyltransferases GTA and GTB. (**Editor's note: Sonia was a Pauling winner, see page 9**) **Julio Blanco** presented work on the apoenzyme and inhibitor-bound structures of aspartate-β-semialdehyde dehydrogenase from *E. coli* and three other infectious organisms, a study that promises to provide insights into mechanism and substrate specificity (see also the following report). More and more, the field of structural enzymology is relying on ensembles of high resolution structures to tell complete stories about enzyme mechanism.

*Ethan Merritt*

### **Enzyme Mechanism Posters**

It is my pleasure to report on several posters from this year's annual meeting in San Antonio. I will describe briefly some of the outstanding and interesting posters I looked at.

First, in order of appearance in the abstracts book, is **Julio Blanco's** poster, P065. Being involved in questions of enzyme catalysis myself, I was quite interested in this poster. Briefly, ASADH is part of the pathway responsible for aspartate biosynthesis. Blanco and coworkers have managed to express and crystallize ASADH from three pathogens: *Vibrio cholerae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. The poster described the crystallization and structure determination of the apoenzyme, a NADP/inhibitor complex, and an acyl intermediate. Interestingly, the intermediate was trapped by soaking native crystals with two substrates. The active cysteine residue subsequently reacted with the substrate ASA, leading to a thioester intermediate. By depriving the enzyme of phosphate, the investigators were able to stabilize this intermediate. This work provides structural insight into the catalytic mechanism of ASADH, and has applications in developing novel antibiotics.

Another outstanding poster was P068, presented by **Douglas R. Davies**. This work was interesting because of the unique nature of the enzyme. Tdp-1 catalyzes the hydrolysis of a phosphodiester bond between a tyrosine residue and the 3' phosphate of DNA. The structure presented in this poster highlighted a unique active site cleft, designed to bind a protein substrate on one side and DNA on the other. The enzyme is a monomer having two similar domains. Conserved histidine, lysine, and asparagine residues on each monomer form the single active site. The structural information described in this work has helped to tentatively identify the nucleophilic histidine residue responsible for initiating the reaction.

P070, by **Igor V. Kurinov** described work on dianthin antiviral protein, an N-glycosidase with anti-HIV activity, rDAP in its apo form, and in complexes with two substrate analogs. The authors also modeled a fragment of RNA in the active site of DAP to clarify how the enzyme binds and reacts with RNA. DAP is a ribosome-inactivating protein, which acts by removing an adenine base from the 28S rRNA. DAP has been shown to have broad antiviral activity, including anti-HIV properties.

Finally, **Jie Yang's** poster P081, provided a good example of the way high resolution X-ray studies can be used to probe mechanistic

details of enzyme catalysis. It has been known that the P+1 loop provides most of the substrate binding contacts for cAMP-dependent protein kinase, but kinetic data showing that mutations in the P+1 loop affect not only  $K_m$  but  $K_{cat}$  as well suggest that there is a catalytic role for this structural element. This work is very exciting because it uses crystallography to help explain observations from other lines of investigation. In this case, the structures of cAMP-dependent protein kinase mutant Y204A in complex with MgATP and an inhibitory peptide were undertaken to investigate the structural reasons for the interesting kinetic observations. By comparing the mutant structures with the native, the authors postulated that the P+1 loop may be important for positioning active site residues for catalysis. In the Y204A structure, they saw that mutation of Y204, which is part of a hydrophobic core beneath the catalytic loop, to alanine appears to disrupt the hydrophobic core, and thus affect positioning of the catalytic loop as well as the P+1 loop. This type of work is exemplary because it highlights the advantages gained by cooperation between different fields of investigation.

*Nicholas R. Silvaggi*

**(Editor's Note: by request Nicholas did not review the posters that were candidates for Pauling and Oxford prizes. However, several of these won awards. See pages 8-9)**

## Computer and Network Security

The modern crystallographer is utterly dependent on computing resources for performing his or her day-to-day work. Computers control instruments, store and manipulate data, perform crystallographic calculations, and support the applications used to produce reports of the results. More and more, computers are also a primary means of disseminating information, from laboratory and staff information to instrument schedules to crystallographic data and reports. That being the case, every crystallographer should be concerned with cybersecurity, for computers and computer networks are subject to continual hostile attacks. The *Computer and Network Security* session, chaired by **John Bollinger** (Indiana U.), focused on current computer security threats and solutions, and on how services can still be provided even in a secure context.

Bollinger introduced the topic with a general overview of many of the relevant issues. According to him, "computer security consists of policies, procedures, and active measures that serve to protect computers, computer networks, and data from damage, unauthorized use, and disruption of service." He emphasized that crystallographic laboratories are prime hacking targets. The general themes of the discussion included creating and following an appropriate security policy, reducing exposure (mainly by restricting the services offered by any host to those required for it to fulfill its role), and choosing secure implementations of required services. Some specific suggestions included avoiding use of traditional telnet and ftp services (which transfer unencrypted passwords over the network); using a local service, such as TCP Wrappers or a personal firewall, to perform network access control at the application level; enforcing the use of strong passwords; disabling or removing unnecessary or unused software and system accounts; avoiding software with a history of security problems; making backups; and keeping informed about current vulnerabilities and threats.

**Nigam Rath** (U. of Missouri St. Louis) followed up with an account of how a virus infected his laboratory network and caused serious disruption of his laboratory's activities, and how the network was redesigned to be more resistant to any future incursion. The virus arrived as an e-mail attachment that was not caught by the client computer's antivirus software, and a member of the laboratory staff infected the computer by opening it. It infected the instrument control and offline storage systems via writable, shared directories accessible from the infected client, and the entire lab was soon infected. Some of the computers required a complete rebuild. The most notable measure instituted in the wake of the incident was a partitioning of the lab network into a less secure portion containing user workstations and other systems that communicate with the rest of the university network, and a more secure portion, isolated from the outside, containing the instrument control computer

and other essential laboratory resources. Computers in the less secure part of the network were granted only read access to any resources exported by the computers in the more secure part.

**Jeffrey Deschamps** (Naval Research Laboratory) discussed using a web server to provide unrestricted information freely while at the same time offering restricted information securely to authorized clients. He discussed both software security options including encryption technologies and usage tracking, but one of the most interesting areas he discussed was hardware-based security options. One commercially available device he described works in conjunction with the protected server to change the user's effective password at very frequent intervals, while securely providing the necessary authentication information to the user as needed; use of such a device narrows the window for a hostile snooper to crack an intercepted password to only one or a few minutes. Hardware-based security approaches can be much stronger than software-only approaches, but unfortunately the expense of implementing a hardware-based security infrastructure is relatively high and scales with the number of users.

**The virus arrived as an e-mail attachment that was not caught by the client computer's antivirus software, and a member of the laboratory staff infected the computer by opening it. It infected the instrument control and offline storage systems via writable, shared directories accessible from the infected client, and the entire lab was soon infected.**

**Keith Brister** (Consortium for Advanced Radiation Sources) completed the session's formal program with a description of a web-based interface that provides a secure means for remote users to configure and control their experiments running at BioCARS. A key feature of the CARS approach is that the user interface (a custom web-based application) is

decoupled from the instrument control hardware and software. An intruder cannot, therefore, damage or compromise the beamline's essential equipment via the exposed web server, but a legitimate user can access available CARS resources and experimental results both while conducting experiments and afterward. This is a fine example of how attention to security need not preclude providing valuable services to users.

It was clear from the session proceedings that security concerns are highly relevant to modern crystallographic practice, but that they need not thwart efforts to provide information and services via computer networks. Systems that expose known vulnerabilities or that do not follow good general security practices are likely to be compromised, however. The type and level of security measures employed at any particular point should depend on the potential damage that a system compromise could cause and the cost to recover, and some kinds of security measures (maintaining up-to-date offline backups, for instance) reduce the recovery cost significantly. Perhaps it is trite to say so, but for crystallographers it is particularly true: security is everyone's problem.

*John C. Bollinger*

## New Structures

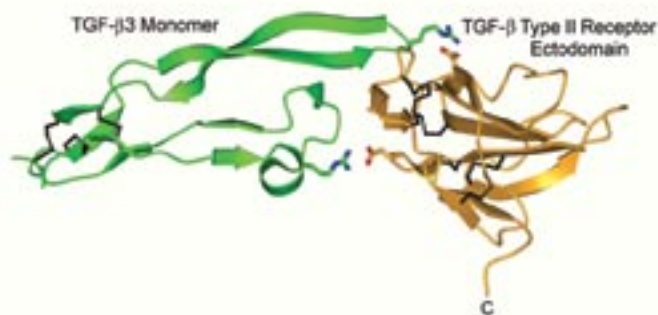
This was the final macromolecular session of the ACA meeting. Six oral presentations were chosen from 34 submitted abstracts. The talks were selected to cover a broad range of biological molecules, including receptor:ligand complexes, DNA bound proteins, RNA-binding proteins, and virus structures.

**M. Sundaramoorthy** presented the N-terminal type IV collagen structure solved by Br-MAD techniques. The enzyme domain is a dimer of trimers. The assembly contains domain swapped regions that are highly conserved structurally and are involved in trimer assembly. Sundaramoorthy also related the problem he had with reviewer's dissatisfaction with sequence determination from structure. The protein was isolated from native bovine lens, the human sequence was used for much of the model building for their structure. The authors were required to sequence the bovine protein from DNA to verify the sequence assignment based on the crystal structure.

**John Walker** reported the structure of Ku heterodimer both in the presence and absence of DNA. The Ku heterodimer contains subunits of Ku70 and Ku80 and is involved in the repair of double-strand DNA breaks in mammalian cells. In the DNA bound form the protein makes a ring around the DNA that is observed in a  $\beta$ -conformation. There are no base specific contacts between Ku and DNA. Walker proposed that the preformed nature of the Ku ring structure, the positively-charged DNA binding surface, and the lack of base specific contacts explains Ku's ability to bind DNA ends without regard to DNA sequence.

**Robert Lucas** presented the crystallization problems and subsequent crystal structure of brome mosaic virus. Lucas presented some nice atomic force microscopy (AFM) figures of crystals documenting the many crystal morphology problems encountered. They observed a strong variance in morphology with different ratios of precipitant and virus. Lucas was able to use AFM imaging to monitor the size and homogeneity of the crystal particles and overcome crystallization problems.

The structure of a receptor:ligand complex of the ectodomain TGF- $\beta$ 3 was described by **John Hart** (see figure below) This cytokine signals through a receptor heterodimer. There is uncertainty whether the assembly is cooperative or allosteric. Although they see conformational changes that are indicative of an allosteric model, they suspect they have trapped an open, conformation that may be a crystal artifact.



Another example of a difficult interpretation of a crystal structure was presented by **Jon Robertus**. The 2.65 Å crystal structure of testis/brain-RNA-binding protein (TB-RBP) was described. The protein mediates expression of certain mRNA and links associated mRNA to microtubule motor proteins that mediate movement of RNA. The protein is predominantly  $\alpha$ -helical, and a Dali search indicates that it is a novel protein fold. The monomer exhibits a flat, six-seven  $\alpha$ -helical arrangement. The oligomeric unit in the crystal is a dimer of tetramers, with a pseudo 4-fold of monomers. The interactions between monomers are very complementary, with many polar interactions. The octamer contains a central cavity that is large enough to pack an H or Y RNA element. The crystal structure supports results from electron microscopy studies, where an 8-ring assembly is observed with RNA in the middle.

**Mirek Cygler** wrapped up the session with a report on rRNA modifying enzymes, pseudouridine synthase RsuA and methyltransferase RlmB. These proteins are involved in ribosome maturation. RsuA was solved in complex with uridine 5'-monophosphate. The structure contains 3 domains. The central domain containing the catalytic site and the uracil binding sites is structurally conserved between rRNA and rRNA pseudouridine synthases. In contrast, the structure of RlmB reveals a novel methyltransferase fold in the C-terminal domain. Interestingly, the domain contains a knotted polypeptide. The N-terminal domain shows similarity to ribosomal proteins L30 and L7.

Marilyn Yoder

## Selected Macromolecular Structure Posters

**Christian Banchs** presented P086, showing the 3.5 Å structure of actin, polylysine, and latrunculin A determined by Christian and co-workers at the University of Florida College of Medicine. It's hard to get high-resolution structural information from many self-assembling proteins because the assembly process runs away and you get lumps, not crystals. The authors induced assembly of actin by addition of polylysine, but terminated filament formation by presence of the assembly inhibitor latrunculin. Their structure confirms the hypothesis that actin forms an intermediate antiparallel dimer on its way to polymerization as a filament. See Bubb, *et al.*, *J. Biol. Chem.* (2002) **277**(23), 20999-1006.

**David Cobessi** (P088, D.Cobessi, Z.Zhang, L.-S. Huang, E.A.Berry, Lawrence Berkeley Nat'l. Lab.) presented a 3.5 Å structure of ubiquinone-succinate dehydrogenase, completing the set of structures of the mitochondrial respiratory chain. This membrane protein was purified from chicken heart mitochondria (wow!). They used the extrinsic part of *E.coli* fumarate reductase as a search fragment for molecular replacement. Fo-Fc and anomalous difference Fouriers brought up peaks for the flavin and the redox centers: Fe<sub>2</sub>S<sub>2</sub>, Fe<sub>4</sub>S<sub>4</sub>, Fe<sub>3</sub>S<sub>4</sub>, and an iron heme. The intrinsic membrane domain was located in a 3Fo-2Fc Fourier. This is one of the first structures of a eukaryotic membrane protein.

**Marie Coté**, (with Dona Ho & M.M.Georgiadis, Waksman Inst. and Rutgers Univ., P090) showed a new method for determining structures of DNA. They co-crystallize the DNA with the N-terminal domain of Maloney murine leukemia virus reverse transcriptase, then solve the structure by molecular replacement starting from the MMLV RT model. The protein holds the

### New Macromolecular Posters, con't

DNA end-wise rather than clamped, so the DNA structure is arguably not too biased by its contacts. In the two examples on the poster, the protein straddled a crystallographic 2-fold, with non-symmetric DNA in-between. They modeled the DNA as overlapped atoms at half-occupancy. Space-group purists, please close your eyes.

**MtaN**, the N-terminal domain of Mta, constitutively Activates its own transcription and causes overexpression of at least three other **Multi-drug Transporter** proteins. **Michael Godsey** *et al.* P094 determined its structure by MAD phasing of a selenomethionyl variant. In comparison to a related protein, the MtaN DNA contacts are similarly arrayed, but the dimer is completely different. The apo-MtaN as in the crystal probably can't bind DNA. The authors have since obtained MtaN/DNA crystals, but that structure didn't make it to the poster, posters frequently being snapshots of projects.

**Andreas Heine**, (and J.D.Toker, P.Wentworth, K.D.Janda, & I.A.Wilson, Scripps Research Inst.,P096,) showed the 1.25 Å structure of a catalytic antibody. Catalysis is thought to work by binding a reaction intermediate of this non-biological cycloaddition. This work is a piece of the catalytic antibody puzzle without a self-contained punchline.

The work shown by **Siyang Sun** (and Yousif Shamoo, Rice University, P098) will become one piece in a larger puzzle. The core domain of bacteriophage RB69 configures single-stranded DNA templates for recognition by the replisome. This system is simpler to study than the entire T4 replisome.

The structure presented by **Sherwin Montañó**, (and co-workers at Waksman Inst. and Rutgers Univ. ,P100) will also become part of a larger picture, The DNA-binding domain of ND80 (NDt80), along with other proteins, activates transcription during sporulation of yeast (the familiar kind). They solved a domain structure in one crystal form (1 ordered Se atom in 272 residues, **wow!**), then by molecular replacement solved the structure of almost the whole protein in a different crystal form. The authors showed a structural mapping of contacts to other proteins, but the order of meiotic events and the connectivity of the transcription complex have not been fully determined yet.

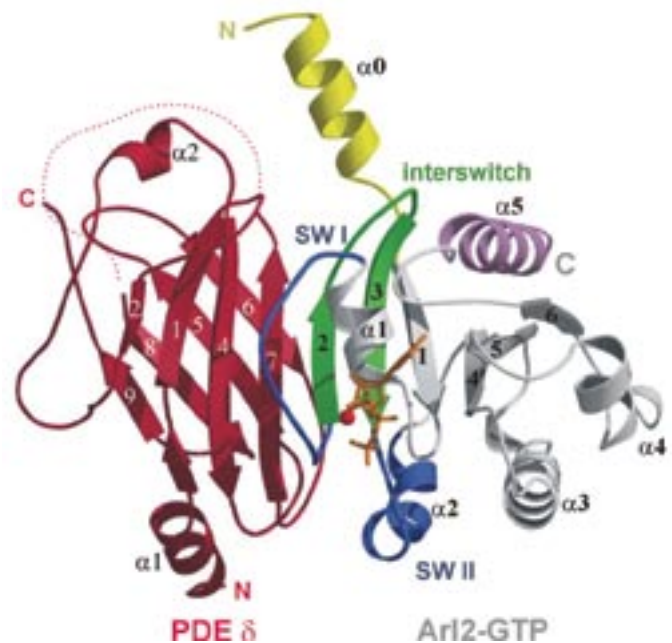
*Herpesvirus saimiri* interferes in host cell regulation to maintain the host in a state favorable to the virus. **Ursula Schultze-Gahmen and Sung-Hou Kim**, Lawrence Berkeley Nat'l Lab, P104, showed the structural changes in host cyclin-dependent kinase 6 induced by viral cyclin. The V-cyclin makes more contacts to CDK6 than the host cyclin, and holds the kinase in an active conformation, without requiring phosphorylation. The host cell can't suppress this activity.

*Pseudomonas aeruginosa* (as in cystic fibrosis) uses sugar binding as part of its infectivity mechanism. **Wolfram Tempel**, (and co-workers at Univ. of Georgia, P107), showed their 1.28 Å crystal structure of the galactophilic lectin-1, with galactose bound (with Ca<sup>2+</sup> mediation). This is a molecular replacement structure, starting from the previous no-galactose structure. Strangely, this lectin seems to work as a fragment vaccine in mice, but hasn't been fingered as a drug target.

**Pappannan Thiagarajan** (and J.Gallas, K. Littrell, G. Zajac, Argonne, P108) explored the size and shape of aggregated synthetic melanin (as in skin color) by small-angle x-ray scattering. The flat melanin molecules stack 3.4 Å apart (same as the typical base stacking in DNA), forming disks about 30-50 Å wide. The absorption spectra (and thus skin color) shift in accordance with the molecule and aggregate dimensions. Wider melanin sheets aggregated into thicker stacks result in better protection from ultraviolet light.

**Patrick van Roey**, (and co-workers at Wadsworth Center, Albany, NY, P110) showed their structure of the catalytic domain of the homing nuclease I-TevI. This enzyme makes a double-stranded break in DNA at intron- or intein-insertion sites, thus promoting mobility of introns and inteins. This 2 Å structure was determined by SIRAS with an ethyl mercuric phosphate derivative (see Van Roey, *et al. EMBO J.* (2001) **20**(14) 3631-7). The poster showed the locations of residues that could be a catalytic site, but the conserved residues are too far apart to be a single site. This one seems to operate by a mechanism different from other homing endonucleases and restriction enzymes.

I hope I correctly deciphered the alphabet soup of poster P113B presented by **Roman Hillig** (see Hanzal-Bayer, *et al. Embo J.* (2002) **21**(9), 2095-2106). The structure on the poster was the complex of GTP-bound Arl2 and its effector PDEδ, forming a continuous β-sheet. It's not completely clear what these proteins are doing, but the authors think that PDEδ transports some prenylated protein, regulated by Arl2. Arl seems to stand for ARF-like regulator of vesicular transport. ARF is not an exclamation of a large canine, but ADP-Ribosylation Factor. PDE means PhosphoDiEsterase. Arl2 is a GTP-ase of the RAS superfamily, and has very different



From Roman Hillig: overall architecture of the complex of Arl2-GTP:PDE delta (crystal-form2, with the N-terminal helix of Arl2 taken from form 1 (yellow))

### *New Macromolecular Posters, con't*

conformations in its GDP and GTP forms. PDE $\delta$  binds Arl2 only in its GTP-bound state. The figure is similar to one published in the *Embo J.* article. The authors co-expressed Arl2 and PDE $\delta$  in *E. coli*. Most of the crystals were non-merohedral twins (bummer!). The search fragment for molecular replacement contained less than half the scattering matter.

The anaerobic parasite *Trichomonas vaginalis* asymptotically hides in the male urethra, but causes all kinds of symptoms (Trichomoniasis) when sexually transmitted to women. The structure of its ferredoxin determined by **Kurt Krause** (and C.R. Crossnoe, P. LeMagueres, Univ. of Houston, P113A.) shows how the antibiotic Metronidazole works to kill this organism. Unlike other ferredoxins, this one has a cavity that allows access of Metronidazole to the Fe<sub>2</sub>S<sub>6</sub> cluster. Reduction to a radical activates the antibiotic, and the radical form in turn damages other *T. vaginalis* cell contents. For details, see Crossnoe, *et al. J. Molecular Biology* (2002), **318**(2), 503-18.

The most familiar poster I looked at was P084, presented by me. We solved the structure of granulysin, a human protein very toxic to tuberculosis, leprosy, and other less fashionable organisms. At the abstract deadline, it was a 1.5 Å structure, but was 0.96 Å by poster time. The methods (MAD phasing, ARP/wARP, SHELXL) seemed miraculous a little while ago, but on my poster were reduced to little more than what you see here, as they have become seemingly routine. Out of the clear blue (density), I fabricated a story about how the structure conferred membrane lysis ability on the granulysin molecule. When I became literate enough to write the paper, I learned that my structure-based story echoed the experimental work. I guess that's why the collaborators got so happy. There's a ton of information in a crystal structure! **(Editor's note: see *On the Cover*, page 13)**

*Daniel Anderson*



*The courtyard familiar to Erice meeting attendees. see opposite page.*



An International School of Crystallography Course entitled “From Genes to Drugs via Crystallography” was held 23 May to 2 June 2002 at the Ettore Majorana Foundation and Centre for Scientific Culture, Erice, Sicily. This was the 33rd course of Crystallography and the fourth on drug design held at Erice by the International School. Others were held in April 1983, June 1989 and May 1996.

The Director of the Course was **Neera Borkakoti** of Medavir UK, Ltd., Cambridge, aided by **Peter Goodford** of Oxford University. **John Irwin** of Northwestern University, Chicago, was there to ensure that all powerpoint presentations and hands-on computer sessions were satisfactory, and his presence was a great relief to many speakers. 33 Nations were represented by the attendees. The overall aim of this meeting was to describe progress in structure-based drug design, and to review the use of this information in the design of new drugs. What was particularly nice about this meeting was that there were no concurrent sessions (except for some workshops), so that we could attend all talks.

The course was intensive and consisted of lectures and workshops. Plenary lectures by invited speakers were interspersed by brief oral presentations by younger scientists. Subjects of the workshops were varied: practical protein crystallizations, using the PDB, using the CSD and Relibase, molecular docking and virtual screening using FlexX, checking results with WHATCHECK, identifying your protein using bioinformatics, and obtaining database information on metal ions. These were very well attended and gave students many chances to ask questions either during the workshops or later during the social events. There were many posters displayed by attendees and the quality of presentations of these posters was very high. There was also a competition for construction of a flow-chart which would illustrate the title of the meeting, *the concept of the pathways from genes to drugs*. Attendees at the meeting were divided into groups and worked hard to present their flow-charts, some on paper, others by acting out their ideas. This competition increased our awareness of many aspects of the steps involved in proceeding from structural genomics to the synthesis of candidate drugs.

The course was introduced by **Herb Hauptman** who gave a fascinating overview of the history of crystallography and the scientific ideas (particularly mathematical) that made it all possible. His talk proceeded from Gauss, Fourier and Galois, via Roentgen and Ewald, to improved therapies for prevention, diagnosis and treatment of disease. **Tom Blundell** introduced studies of genome sequences and “high-throughput crystallography” in drug discovery, stressing achievements in the last 30 years, while **Peter Goodford** described milestones in therapy. He reminded us that inoculation for smallpox was known in Constantinople as early as 1717, and introduced in England by Jenner in 1788, while the usefulness of digitalis was recognized in 1775. Many drugs followed until thalidomide was introduced with sad consequences. This changed the subsequent course of drug design.

The information content of this meeting was outstanding. We were introduced to experimental details of wet methods of preparing pure proteins (including membrane proteins) and getting crystals by making mutant proteins. We were told about high-throughput gene-to-crystal technology, with the robots designed by users, and how to detect or avoid multimer formation during



**Lodovico Riva di Sanseverino**

crystallization trials. We heard about methods for assessing errors in data. We also were introduced to methods of studying protein evolution and conserved residues in proteins. This led to discussions of predictions of protein folding, an acknowledged difficult problem, and the organization of folds and motifs in determined macromolecular structures. Some catalytic motifs were described. An identification of these can often lead to an understanding of the catalytic mechanism. It was noted that in 2000 91% of newly determined structures were similar to a previously determined structure. Several talks were given on drug design with the pharmacophore as a possible model. This entity is defined as the ensemble of steric and electronic features needed to ensure the best possible interactions with a specific biological target system so that an expected biological effect is triggered. Multiple hydrogen bonding and multiple site targeting were described. We were shown how the crystallographer could make some suggestions for drug design from the results of his/her labors. These lectures led to specific systems, such as signal transducing enzymes, that were described. Here we were getting into multienzyme systems. We heard about ribosomes and viruses. Recent technological advances in methods for studying macromolecular structures were described. These included, in addition to X-ray diffraction, electron cryomicroscopy, mass spectrometry, high-throughput screening, and energetics. A special session on ribosome structure and ribosome-antibiotic interactions illustrated the power of the results of such methods.

Erice is an ancient walled Sicilian town on the top of a hill some 2600 ft. above sea level on the far west coast of Sicily near Trapani. The guidebooks note that this town is now a center for scientific conferences and that you are as likely to see scientists with labels on their lapels as you are to see tourists. This meeting location is ideal for encouraging scientific interactions between attendees. Each participant can eat at any of the many restaurants in town and **Lodovico Riva di Sanseverino**, aided by **Paola Spadon**, made sure that we all enjoyed Sicilian hospitality, with parties, folk songs, wonderful cooking (Lodovico’s recipes) and a masked ball in Palermo. Walks through the stone streets are full of interest (in sunshine and in deep fog). The view over the ocean and local countryside from the room used for coffee breaks is fantastic. An expedition to nearby Greek temples completed our introduction to Sicily.

*Jenny Glusker*

**IUCr XIX Congress and General Assembly**

The 19<sup>th</sup> Congress and General Assembly of the IUCr took place in Geneva, Switzerland August 6-15, 2002. Both Joel Bernstein, as Chair of the Organizing Committee, and Menahem Kaftory, who chaired the Program Committee, did exceedingly well with the difficult task of adapting plans from their home soil in Israel to the site in Switzerland. The General Assembly elected W. L. Duax (USA) as the new Executive Committee President, replacing Henk Schenk (The Netherlands), who became the Immediate Past President. E.N. Baker (New Zealand), who formerly held that office, has now left the Committee as has the former Vice President, M. Tanaka (Japan), and Ordinary Members J.C.A. Boeyens (South Africa), and H. Fuess (Germany). L.A. Aslanov (Russia) is the new Vice President; S. L. Larson (Denmark) remains General Secretary and Treasurer; and G.W. Heger (Germany), I. Torriani (Brazil), Y. Ohashi (Japan), and D. Viterbo (Italy) were elected as new Ordinary Members. M.A. Carrondo (Portugal) and Z. Zhang (People's Republic of China) will continue their terms as Ordinary Members.



*Bill Duax, Henk Schenk, and Howard Flack at the reception for delegates.*



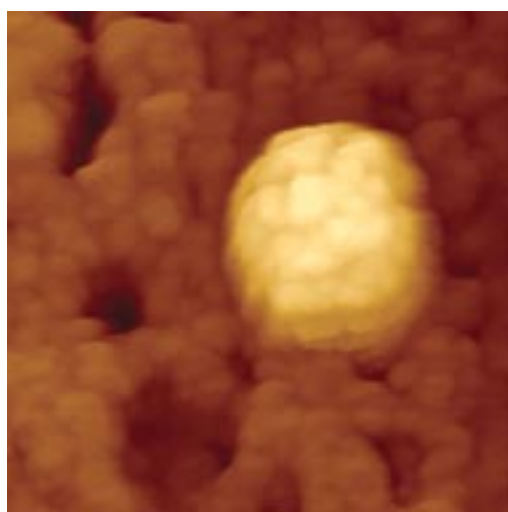
*Art Olson with models*

The Congress was very well attended; 1961 were registered for the scientific sessions, and attendance at microsymbiosia all during the Congress was consistently high as well. This brief report certainly will not do justice to 27 Keynote Lectures, 545 oral presentations and 945 posters; readers can look forward to coming issues of the *IUCr Newsletter* for more extensive reports. In the meantime, though, I cannot resist commenting on a few of the presentations that especially piqued my interest. The presentations I selected have in common imaging methods for biological specimens; both older methods applied to smaller things and new methods.

**Keiichi Namba** gave a Keynote Address on *Structural Mechanisms of Self-Assembly and Polymorphic Supercoiling of the Bacterial Flagellum*. (see *On the Cover, page 13, and the figure in the San Antonio ACA meeting report, page 42*). These remarkable and beautiful images result from combining model-building, x-ray fiber diffraction and cryo-electron microscopy techniques.

In the microsymbiosium on *Advances in Molecular Visualization*, **Art Olson** clearly delighted in showing off molecular models made with a new toy, a color solid printer, (ZCorp 406) which his group at the Scripps Research Institute has been using. These physical models are useful for teaching, and also for research because they can be held and manipulated while using their interactive software to create an *Augmented Reality* environment. They call this the creation of a *Tangible Interface*. Art showed an example in which he manually docked a drug molecule they have designed into a protein receptor site while watching the computer graphics version of the model he was holding. Strange and wonderful.

Atomic Force Microscopy has been gaining respect as techniques improve. **Alexander McPherson** chaired the microsymbiosium on *AFM and Single Molecule Analyses of Macromolecules*. He gave an instructive introduction to AFM and also presented the work of his group at U.C. Irvine on imaging virus particles. They have applied some of the techniques used in electron microscopy, such as immunolabeling with gold particles and histological and chemical treatments, to AFM and have been quite successful in obtaining images of virion surfaces over a wide size range (diameters 17 – 100 nm) with sufficient resolution to see structural features such as capsomeres. This technique is well suited to fill the gap between diffraction methods and light microscopy.

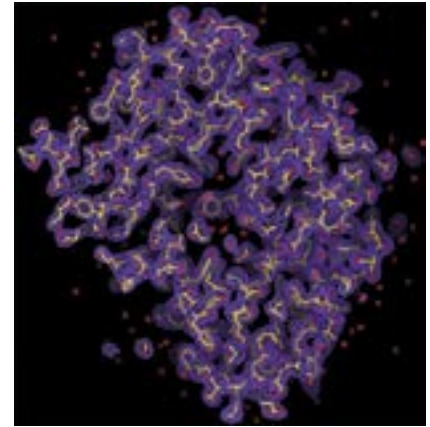


*AFM image of a single virion of mouse leukemia virus (MuLV) emerging from the surface of an infected fibroblast. The scan size is 0.45 μm<sup>2</sup>*

Good progress has been made on an entirely different way of imaging at atomic resolution that allows, in theory, the possibility to obtain images of single molecules by diffraction. In the microsymbiosium on Holography and X-ray Microscopy, **David Sayre** gave a provocative history of this Oversampling method of imaging, and **John Miao** reported more specifically on the

technique that could be used to image single macromolecules. The astonishing figure at right is from *PNAS* (2001) 98, 6641-6645, Jianwei Miao, Keith O. Hodgson, and David Sayre, (©2001 National Academy of Sciences, U.S.A). X-ray free electron lasers (X-FELs) capable of delivering the extremely intense x-ray pulses that would be required for resolution and are also ultra-short (single molecules would not be likely to withstand radiation damage if the pulses were longer) - are not yet available. For that reason, it was necessary to use a computer simulation to demonstrate the validity of the phasing method.

In the simulation, diffraction images were accumulated from multiple copies of a single rubisco molecule irradiated with 10 femtosecond X-FEL pulses. (In the actual case, identical macromolecules could be selected and inserted one at a time in the X-FEL beam by using mass spectrometry spraying techniques. Either the molecules would be oriented before exposure using laser fields, or the otherwise random orientations would be sorted afterward using established cryo-EM methods.) The resulting diffraction images, unlike the usual Bragg peaks observed with crystalline samples, are continuous, and can be sampled at a spacing finer than the Nyquist frequency, which corresponds to surrounding the electron density with a no-density region. This "oversampling" increases the number of independent equations without increasing the number of unknown variables. In the simulation, a 3-D diffraction pattern from  $10^6$  identical rubisco molecules was constructed. Random phases were assigned to start and then the iterative algorithm developed for the purpose was able to achieve the accurate electron density map in the figure in a few hundred iterations. Eventually, a wide range of entities impossible to image by traditional crystallographic techniques such as whole biological cells, amorphous materials, and imperfect or very small crystals may prove to yield images by this method. *Connie Chidester*



*3-D electron density map of the rubisco molecule contoured at  $2\sigma$*



## ACA 2004 July 17-22—Chicago, IL

The annual meeting of the ACA will be held in downtown Chicago at the Hyatt Regency Hotel on Wacker Drive. The hotel is located on the Chicago Riverwalk along the south side bank of the Chicago River adjacent to Michigan Avenue, nicknamed the "Magnificent Mile," and near Lake Michigan, Lake Shore Drive, and Grant Park. The conference and exhibition will be held in the East Tower of the hotel. The banquet will be in the Crystal Ballroom in the West Tower of the hotel, overlooking the Tribune and Wrigley buildings. Navy Pier, the Art Institute, the Field Museum, Shedd Aquarium, Adler Planetarium, and the Museum of Contemporary Art are all located nearby. Grant Park is the site for several summer festivals and concerts. Both airports, O'Hare and Midway, are located within twenty miles of the downtown area.

Chicago is home to several universities, and is a city of great restaurants, jazz and blues venues, museums, theaters, sport's teams, etc. Here are some websites that might be interesting to explore:

- [chicagoreader.com](http://chicagoreader.com) . . . Great for restaurant listings, concert listings, etc.
- [jazzinstituteofchicago.org](http://jazzinstituteofchicago.org) . . . Information on jazz clubs, concerts, etc.
- [chicago.il.org](http://chicago.il.org) . . . Good tourism site, and check out the free trolley system.
- [cityofchicago.org](http://cityofchicago.org) . . . Good tourism site, and help in getting around town.

*Bernie and Karl*



### LOCAL CHAIRS:

**Bernie Santarsiero** (bds@uic.edu)  
and **Karl Volz** (kvolz@uic.edu).

### PROGRAM CHAIRS:

**Christer Aakeröy** aakeroy@ksu.edu  
and **Marilyn D. Yoder** myoder@cctr.umkc.edu



*Photo is courtesy of Terry and Melody Howe, ChicagoPhotography.com.*

## ACA 2003, July 26-31, 2003

### Northern Kentucky Convention Center, Covington, KY

Covington, Kentucky is located across the Ohio River from Cincinnati, Ohio and is minutes from the Cincinnati/Northern Kentucky International Airport. All scientific sessions, posters and the exhibit show will be held in the Northern Kentucky Convention Center (<http://www.nkycc.com/>).

The ACA2003 meeting (<http://www.che.uc.edu/aca/>) will begin with workshops on Saturday, July 26. These workshops will feature topics from the first stages of crystallography, namely crystallization, and continue through data processing and finally structural information deposition.

#### Workshops:

Crystals & Rotax Suite of Programs for Chemical Crystallography  
 CCP4 Suite of Programs for Macromolecular Crystallography  
 Cambridge Structural Database  
 Crystallization Techniques & Secrets

Scientific Symposia and Sessions will commence on Sunday morning, July 27 and conclude on Thursday afternoon, July 31. Consult the *Call for Papers* for detailed information on workshops and sessions.

#### Symposia:

Transactions Symposium: **Neutron Diffraction**  
 (co-organizers: Gerry Bunick & Leif Hanson)

Special Symposium: **Time-Resolved Crystallography**  
 (co-organizers: Phil Coppens & Keith Moffat)

Martin J. Buerger Award Symposium: 2003 Awardee is **Dr. James Ibers**

Bertram Warren Award Symposium: 2003 Awardee is **Takeshi Egami**

#### Tentative Oral Sessions

organized by the ACA-SIGs and the AACG, include:

- Incommensurate Structures
- Membrane Proteins
- Grant Writing & Interviewing Skills
- Genomics
- Crystal Growth Solutions & Techniques
- Nucleation Processes
- Fiber Diffraction
- Dynamics of Macromolecules
- Important Structural Science in Chemical Crystallography and Problem Structures Encountered
- Service Crystallography Laboratory Practices
- New and High Resolution Macromolecular Structures
- High-Energy Materials
- Small Angle Scattering Instrumentation
- Hard & Soft Materials

#### Poster Sessions Sunday, July 27-Tuesday, July 29

#### Vendor Exhibits & Sponsored Activities

will be scheduled throughout the week

#### Social Events:

Saturday, July 26—Opening Reception: Newport Aquarium  
 Sunday, July 27—Mentor/Mentee Dinner: Chez Nora  
 Monday, July 28—Midweek Mixer: Jack Quinn's Irish Pub  
 Wednesday, July 30—Banquet: Embassy Suites Hotel  
 Thursday, July 31—Riverboat Dinner Cruise



#### Important Upcoming Dates:

**Abstract deadline: March 1, 2003**

**Advanced Registration deadline: June 1, 2003**

**Advanced Hotel Registration deadline: June 24, 2003**

On-line abstract submission instructions, on-line registration and further meeting information will be posted to the ACA2003 site at <http://www.che.uc.edu/aca/> or consult the ACA web site.

**Local Chair: Bobby Barnett**, Procter & Gamble,  
 barnett.bl@pg.com

**Program Chair: Jeanette Krause Bauer**, University of  
 Cincinnati, jeanette.krause@uc.edu



**OCTOBER 2002**

- 7-9 **29th Annual Stanford Synchrotron Radiation Laboratory Users' Meeting**, Menlo Park, CA.

**DECEMBER 2002**

- 11-15 **Electron Cryomicroscopy Single Particle Image Processing and Visualization Workshop**, see <http://ncmi.bcm.tmc.edu/workshop2002>. Contact: Steve Ludtke [sludtke@bcm.tmc.edu](mailto:sludtke@bcm.tmc.edu) or Dana Feinberg [feinberg@bcm.tmc.edu](mailto:feinberg@bcm.tmc.edu).

**MARCH 2003**

- 17-21 **ICDD Spring Meeting**, ICDD Headquarters, Newtown Square, PA.

**JUNE 2003**

- 4-15 **High Pressure Crystallography, 34th Crystallographic Course** Erice, Italy. [www.crystalalice.org](http://www.crystalalice.org). Contact Prof. Andrzej Katrusiak: [katran@amu.edu.pl](mailto:katran@amu.edu.pl)

**Meeting Calendar****JULY 2003**

- 14-19 **Gordon Research Conference in Structural Biology**,

- 21-26 **Aperiodic-2003**, Belo Horizonte, Brazil.

- 26-31 **American Crystallographic Association Annual Meeting, ACA 2003**, Covington, KY. (see page 59).

**AUGUST 2003**

- 4-8 **Denver X-ray Conference**, Marriott Tech Center Hotel, Denver, CO.

- 10-13 **AsCA'03/Crystal-23**, Cable Beach Club resort, Broome, Western Australia.

- 14-15 **Workshop on Biological Structure**, Cable Beach Club resort, Broome, Western Australia.

- 14-19 **Sagamore Meeting** run by the IUCr Commission on Charge, Spin and Momentum Densities, Cable Beach Club resort, Broome, Western Australia.

- 24-30 **21st European Crystallographic Meeting**, Durban, South Africa

**SEPTEMBER 2003**

- 2-6 **ECNS 2003 European Conference on Neutron Scattering**, Montpellier, France. Contact: R. Vacher, CNRS-SPM, Montpellier, [rene@ldv.univ-montp2.fr](mailto:rene@ldv.univ-montp2.fr); tel: 33 4 67 14 34 49; fax: 33 4 67 14 34 98.

**JUNE 2004**

- 10-21 **Polymorphism: Solvates and Phase Relationships**. Erice, Italy.

**Coming Attractions**

In the winter issue of the *ACA Newsletter*, look for:

**Doug Dorset's Patterson Address.****Election Results**

Report on the *7th Annual Structural Biology Symposium* at the University of Texas Medical Branch, Galveston, May 17-19, 2002

Report on the **First American Conference on Neutron Scattering (ACNS)**, June 23-27, 2002, Knoxville, TN. organized by the Neutron Scattering Society of America (NSSA)

Report on the *51st Annual Denver X-ray Conference*, July 29 - August 2, 2002.

Review of the **Pittsburg Diffraction Conference**, Oct. 3-5, 2002, Pittsburg, PA.

Reports on *2002 ACA Meeting Workshops*.

Reports from *2002 ACA Meeting Student Travel Awardees*.

Pictures of the **Vendors** at the 2002 ACA Meeting.

An extensive **BOOKS** Section.

**among other things . . .**

**POSITIONS AVAILABLE**

*It is expected that the employers listed in this publication are equal opportunity employers who wish to receive applications from qualified persons regardless of age, national origin, race, religion, sex or physical handicaps. Please inform the Editor when the positions are filled, and of any positions that do not give opportunities to all applicants. Ads will appear in two successive newsletters unless the Editor is notified that the advertisement should be continued longer or discontinued earlier.*

For the most up-to-date listings check the ACA Home Page under the Positions Vacant heading: [www.hwi.buffalo.edu/ACA/](http://www.hwi.buffalo.edu/ACA/)

**Postdoctoral Positions: Structural Biology**

**University of North Carolina at Chapel Hill:** NIH-funded postdoctoral positions are available to examine the structure and action of promiscuous drug receptors (*Science* **292**: 2329), drug-processing enzymes (*Nature Structural Biology* **9**: 337), and protein-DNA complexes (*Science* **279**: 1504). Successful candidates will have experience in protein expression and purification; previous experience in protein crystallography is desired but not required. Send a CV and three letters of reference to: Matthew R. Redinbo, Depts of Chemistry and Biochemistry & Biophysics CB#3290, Chapel Hill, NC 27599-3290, [redinbo@unc.edu](mailto:redinbo@unc.edu)

**POSITIONS PREVIOUSLY LISTED****Protein Crystallographer - Postdoctoral**

There is an opening for a postdoctoral position in protein structure determination and analysis. Applicants with experience in biological X-ray crystallography, protein expression, and purification can send a C.V., and addresses of three references to Dr. Narendra Narayana, Dept. of Biochemistry, Case Western Reserve University., Cleveland, OH 44106, email: [nxn17@po.cwru.edu](mailto:nxn17@po.cwru.edu)