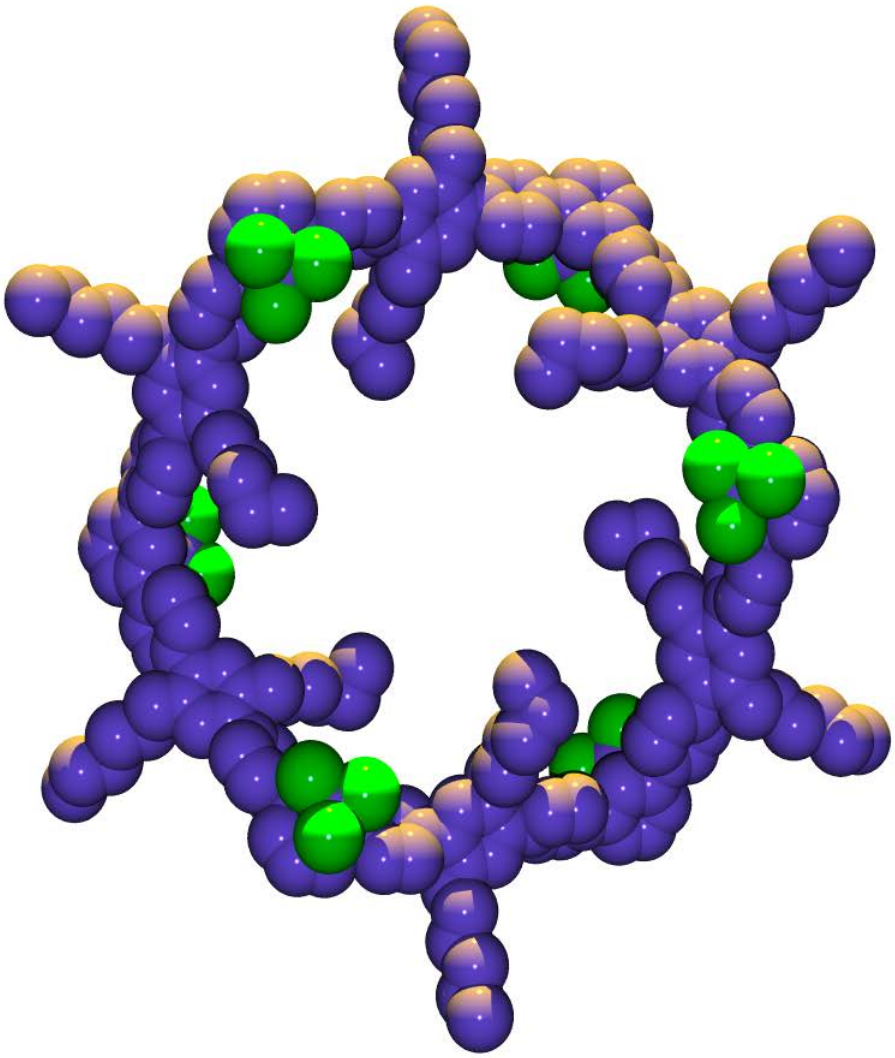
22ND ANNUAL BRUKER/MIT SYMPOSIUM

ON THEIR SHOULDERS

Saturday, February 24th 2018



A Message from the Director of the Diffraction Facility

Dear participants of the Bruker/MIT Symposium,

As the director of the X-Ray Diffraction Facility of the MIT Department of Chemistry, it is my pleasure to welcome you to the 22nd annual Bruker/MIT Symposium.

In the late 17th century, Isaac Newton famously said "If I have seen further it is by standing on the shoulders of Giants." All of us in the scientific community find ourselves metaphorically standing on the shoulders of our teachers and mentors, some of them giants in their own rights, and all of us take for granted methods, truths and facts that were invented, discovered and established decades or even centuries ago. There always are certain members of our community who push the envelope a little further than most everybody else, who dare to think further than the rest of us and who, thus, allow their students and colleagues to reach ever increasing heights.

2017 has been one of significant losses, as several of the leading heads of our small community of chemical crystallographers have passed away. Under the motto **On Their Shoulders** I would like to pay tribute to the groundbreaking contributions of Howard Flack, Dick Marsh, Phillip Coppens, Isabella Karle and others and also to remember them as human beings, as the one is inseparably connected with the other.

In this spirit I wish us all a successful and enjoyable meeting,

Sincerely,

Peter Mueller
Director, X-Ray Diffraction Facility
MIT Department of Chemistry

ABSTRACTS:

HONORING FOUR GREAT CRYSTALLO-GRAPHERS: PHILIP COPPENS, HOWARD FLACK, ISABELLA KARLE AND DICK MARSH

Sue Byram, Bruker AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373;
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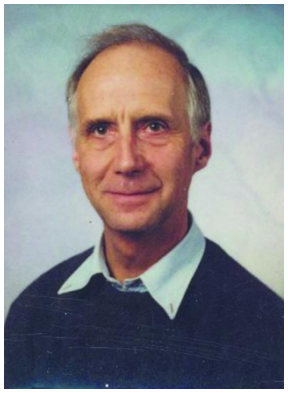
It's been an honor to interact over my career in crystallography with these great colleagues we lost in 2017: Philip Coppens, Howard Flack, Isabella Karle and Dick Marsh. My own mentor, Bob Sparks (fondly referred to by Peter Mueller as the godfather of crystallographic computing) fostered my first contacts in particular with Dick Marsh and Mrs. Karle. We will share some photos and stories by them and about them, and how we knew and will now remember them.

Cary Bauer with Phil Coppens, SUNY Buffalo 2016.



Howard Flack, IUCr Journals site

Jerome and Isabella Karle.

Mike Takase, Dick Marsh and Larry Henling, Cal Tech 2014.

Dick Marsh and Linus Pauling at Cal Tech 1986.

Dick Marsh and Sue Byram, Cal Tech 2014.

MEMORIES OF GIANTS: DICK MARSH, PHILIP COPPENS AND HOWARD FLACK

Bruce Foxman, Brandeis University,
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My short presentation will focus on the achievements and lives of Dick Marsh, Philip Coppens and Howard Flack. I have gathered anecdotes - both scientific and personal - from my own encounters with the Great Ones, but also from a very special Inner Circle of their friends and mine.

FORTY YEARS OF MARSHING: A NAME TURNED INTO A VERB

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The assignment of a proper space group to a crystal structure, *i.e.* the one that uniquely describes its symmetry, is not always trivial. Real world issues such as disorder and pseudo-symmetry may blur the way to a unique assignment. Often one has to settle with the best approximation given the data and the purpose of the study.

For various reasons, structure analysts do not always report their structures with the best symmetry description. That may lead to false claims of supposedly interesting chemistry that in hindsight are purely based on refinement artefacts.

In the late 1970s, Dick Marsh together with Verner Schoemaker started to investigate and report on this type of problems in reported structures in published papers. Early papers had titles such as 'Some Incorrect Space groups in Inorg. Chem., Volume 16'.

Over time, Dick published numerous similar corrections. Others picked up this type of investigations as well. Not everybody was happy when their name featured in papers of 'Marshed' structures. A very relevant issue is that the underlying experimental data (*e.g.* reflection data and images) are not always available. Those primary data are needed for a proper 'verdict'.

Dick did his explorations by flipping through journal issues, looking for suspect ORTEP illustrations. Nowadays, in combination with the archived data in the CSD, easy to use tools are available to spot routinely structures with missed symmetry.

Issues like missed symmetry led eventually to the idea to routinely check structure reports prior to publication. The IUCr introduced the checkCIF facility for that purpose.

One would assume that, given the readily available tools, missed symmetry and Marshed structures are no longer an issue. For that reason, all structures entered in the CSD during the 5 years 2013-2017 were inspected with the ADDSYM tool in PLATON. The result of that analysis will be shown.

TO BE OR NOT TO BE --- MARSHED

Michael Takase, California Institute of Technology,
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Like Shakespeare influenced literature, Dick Marsh influenced many in the field of crystallography. I will discuss my experiences with both the myth and the man as well as some things that made Dick truly unique.

WHY CRITICAL STRUCTURE VALIDATION IS STILL IMPORTANT – A CASE STUDY

Peter Müller, Mass. Institute of Technology,
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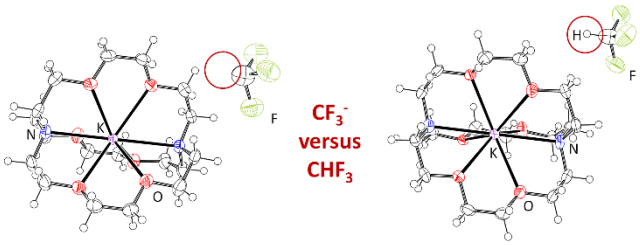
e-mail: pmueller@mit.edu

Powerful as the method may be, crystal structure determination is complex and not usually trivial. In order to learn the most from a given diffraction experiment, one has to thoroughly understand the method and one has to carefully and skillfully perform every step of structure determination. This presentation will introduce an example where a careful redetermination[1] of a crystal structure based on the original data challenges the chemistry behind the originally published work[2].



References

[1] S. Becker & P. Müller, *Chem. Eur. J.* **2017**, *23*, 7081 – 7086.
[2] A. Lishchynskyi, F. M. Miloserdov, E. Martin, J. Benet-Buchholz, E. C. Escudero-Adán, A. I. Konovalov, V. V. Grushin, *Angew. Chem. Int. Ed.* **2015**, *54*, 15289–15293.

IDEAL - INVARIOM DERIVED ELECTRON ANALYSIS

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With the introduction of large shutterless detectors, data quality to high resolution has dramatically improved over the last few years. Data to 0.5 Å and beyond can be collected with only one detector setting, with short exposure times, and short overall experiment times. Traditionally structures are refined using an Independent Atom Model (IAM), although good data beyond the traditional 0.83 Å reveals additional electron density that cannot be modeled appropriately. Often practitioners choose to cut data to preserve a low structure reliability criteria *R*1, sacrificing additional information and overall structure quality.

IDEAL lets you have the cake and eat it too! IDEAL uses a database of bond-oriented deformation density parameters derived from the invariom[1] database of ab initio calculations of model compounds. IDEAL generates BEDE (Bond Electron Density) and LONE (Lone Pair Electron density) for refinement with an extended version of XL. XL uses IAM scattering factors and in addition, models scattering contributions of bonds and lone pairs.

IDEAL delivers structures with increased model accuracy and provides access to more detailed model properties. IDEAL is easy to use and seamlessly integrated with APEX3.

References

[1] The generalized invariom database (GID).
B. Dittrich*, C. B. Hübschle, K. Pröpper, F. Dietrich, T. Stolper, and J. J. Holstein.

ATOMS IN MOTION: CREATING AND CHARACTERIZING DYNAMIC CRYSTALLINE MATERIALS

A lecture in honor of the late Professor Philip Coppens

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In over 430 peer-reviewed publications, the late Professor Philip Coppens (1930-2017) is credited with critically important contributions in charge density and time-resolved X-ray diffraction methods. In both theory and practice, his contributions impacted virtually every aspect of high resolution electron density measurements: helium temperature experiments, data reduction, multipole modelling, combined analysis of charge and spin densities, derived electrostatic properties, multipolar data bases, and applications to chemical bonding and material science.

Much of Philip's later work involved the development and application of time-resolved X-ray diffraction methods to monitor light-induced transformations in small molecule systems. His notable achievements in the area of

photocrystallography include the structural determination of metastable intermediates in sodium nitroprusside, photochemistry in supramolecular systems, the development of software for the analysis and refinement of monochromatic and Laue X-ray diffraction, and the picosecond structural dynamics of organometallic complexes.

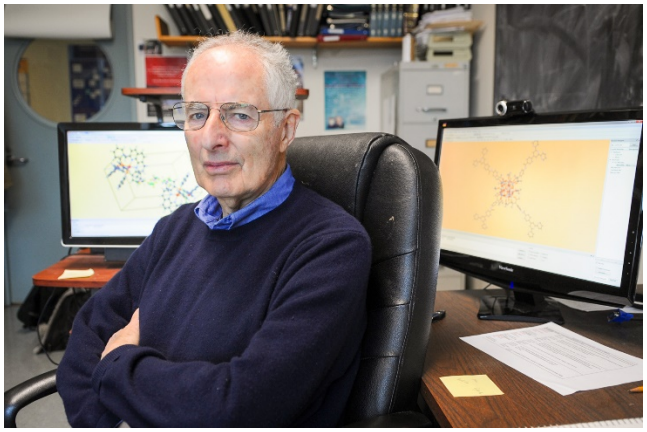


Image of late Professor Philip Coppens in his office.
Photo credit: Nancy J. Parisi.

In addition to a brief remembrance of Philip, the lecture will showcase the exciting science involving the design, synthesis, and characterization of dynamic crystalline materials. Organic luminescent solids are an attractive alternative to current light emitting materials nearly all of which contain Pt, Ir, Re, or rare earth metals. Recently it has been shown that crystals of bromine-containing organic molecules are capable of exhibiting phosphorescence lifetimes of milliseconds and longer. Because of their long lifetimes, the luminescent materials are ideal for study by the pump-probe in-house time-resolved X-ray diffraction developed collaboratively by the Benedict and Coppens groups. Upon photo-excitation, crystals of 1,4-dibromo-2,5-bis(octyloxy)benzene exhibit a decrease in the intermolecular Br···Br contacts in the lattice. Attempts to rationalize these changes using computational modeling will be discussed along with some new results from other compounds in this class of organic light emitting molecules.

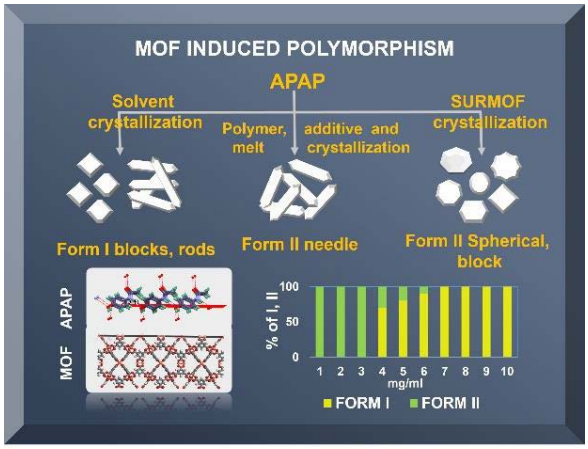
Recent results in which crystalline materials are used to convert light into useful work will also be described. The Benedict group is developing photo-switchable diarylethene-based linkers capable of transforming typically passive materials such as metal-organic frameworks into materials with chemical and physical properties that may be controlled externally with light. Recent successes in the synthesis of photo-responsive materials as well as challenges associated with transferring the solution state photo-reactivity into the solid-state will be presented.

Poster abstracts

SURMOF induced polymorphism and crystal morphological engineering of the acetaminophen polymorphs: Advantage of heterogeneous nucleation

Geetha Bolla & Allan S Myerson* , MIT,
e-mail: bollag@mit.edu

The fundamental understanding and study of the heterogeneous nucleation on molecular surfaces has been challenging and increased interest in pharmaceutical industry as well as in material science due to potential applications.[1-2] Engineering the shape and solid form of crystalline solids (which is called as morphological engineering) is of great importance in the pharmaceutical industry and has led to significant efforts in recent decades to understand the underlying crystal growth mechanisms. Despite the fact that self-assembled monolayers[3] are a well-established method to result in various less stable polymorphs or crystalline shapes (different faces), those results are practical due to the limitation in contribution to the surface. Finding a new prominent method with new design surface is an urgent necessity to result in a single pot experiment. Surface metal organic frame works (SURMOFs)[4] are basically combination of the self-assemble monolayers (SAMs) and followed by metal organic frame works (MOFs) on its surface have been studied recently with different applications different directions. However, it has not yet been explored well in many directions especially in polymorph screening and morphological engineering. MOFs are highly porous crystalline the impact and contribution on the surface as heterogeneous layer would be effective compare to the usual SAM surface.



Scheme 1: SURMOF induced polymorphism in Acetaminophen.

We were successful the dual advantage in the case of Acetaminophen here (APAP) afforded less stable polymorph along with morphology change by developing the recent reported SURMOF thin film methods. Having the advantage in controlled orientation of the MOFs on the basis of the ground SAM functional group and finally it would allow controlled growth of the target functional group of the small organic molecules. Which, prominently leads different nucleation direction than usual crystallization. We were successful to get Form II from solution crystallization with template SURMOF thin film with block morphology. In addition, present study MOF heterogeneous nucleation will allow and open a real challenge for new metastable polymorph search of drug along with morphology change based on complementary interactions at the SURMOF interface with dual advantage. This is the first time study of MOF induced polymorphism. Scheme 1.

References

[1] A. J. Cruz-Cabeza and J. Bernstein, *Chem. Rev.*, **2014**, *114*, 2170–2191.
[2] M. Lahav and L. Leiserowitz, *Phys. Scr.*, **2015**, *90*, 118003.
[3] J. C. Love, L. A. Estroff, J. K. Kriebel, R. G. Nuzzo and G. M. Whitesides, *Chem. Rev.*, **2005**, *105*, 1103−1169.
[4] S. Hermes, F. Schro, R. Chelmowski, C. Wöll and R. A. Fischer, *J. Am. Chem. Soc.*, **2005**, *127*, 13744–13745.

Novel rhenium(I) phosphazane complexes with applications towards CO_2 reduction catalysis

Matthew R. Crawley, University at Buffalo,
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To date, a wide range of rhenium(I)-based CO_2 reduction catalysts have been studied in the literature, however, very few feature phosphorus-donors, and none feature phosphazane ligands. Phosphazane ligands exhibit far greater tunability both in terms of electronic structure as well as steric demand, in comparison to other supporting ligands currently in use. Our work looks to expand the library of ligands currently utilized in CO_2 reduction as well as other forms of small-molecule activation. A series of Re(I) chelating-phosphazane (PNP) complexes supported by polypyridyl and carbonyl ligands have been designed, synthesized, and in addition to routine characterization, their structural and electrochemical properties have been examined via single-crystal X-ray diffraction studies and cyclic voltammetry. Our findings show that the monomeric Re (dppa) (bpy) $(CO)_2$ OTf (dppa = bis(diphenylphosphino) amine, bpy = 2,2'-bipyridine) complex reduces CO_2 to CO and water in the presence of trifluoroethanol (TFE) with excellent catalyst longevity. Additionally, functionalized analogues of dppa have been synthesized and the ramifications of the electronic properties of the phosphazane ligands on electrocatalytic performance were assessed.

Crystal structures of Large-Volume Commercial Pharmaceuticals

James Kaduk*, Illinois Institute of Technology,
e-mail: kaduk@polycrystallography.com

As part of a continuing project, the room-temperature crystal structures of several commercial pharmaceutical APIs have been solved using synchrotron X-ray powder diffraction data (11-BM at APS), and optimized using density functional techniques. The molecules to be discussed include:

1. Terazosin hydrochloride dihydrate (Hytrin), which was originally solved (but only approximately) using data contained in the Powder Diffraction File database.

2. Bretylium tosylate (Bretylol and others), which exhibited significant decomposition in the beam.

3. Oxybutynin hydrochloride hemihydrate (Dytropan and Lyrinel XL), which has not been described as a hemihydrate, and which exhibits X-ray induced photoreduction of a triple bond.

4. Levocetirizine dihydrochloride (Xyzal), which solves and refines better in $P2_1/n$ rather than the true space group $P2_1$.

5. Methylpednisolone acetate (Medrol).

The presentation may also include progress (or lack thereof) on februxostat Form G (Uloric and Adenuric), as well as other new structures as they are solved.

Using Non-conjugated Side Chains to Control Crystal Packing

William Mullin, Tufts University,
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Conjugated systems have been widely used in the design and fabrication of electronic devices. These small molecules are employed in the solid state, typically in thin films and single crystals. Transitioning from a solution state to a solid state can change optoelectronic behaviors of these molecules, creating a need for understanding how solid state packing influences these properties. There has been substantial investigation on the use of non-conjugated side chains to allow for non-covalent bias and tuning of solid-state packing, and in turn, optoelectronic properties. Perfluoroarene-arene stacking yields an interesting variety of intra- and intermolecular stacking patterns, and allows a level of control over solid state packing. Recent developments have explored the usefulness of this synthon in a new molecular model featuring a variety of chromophores in a phenylene-ethynylene inspired system, with noticeable effects on crystal packing patterns and optoelectronic properties. This new information will be useful in the design of small molecules to be employed in electronic devices.

Tuning Stimulus Response and Material Properties in Mechanofluorochromic Phenylene Ethynylene Oligomers

Seth Sharber, Tufts University
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Non-covalent strategies for tuning molecular packing in solids have become increasingly useful for biasing material properties, and are necessary in stimuli-responsive systems to engineer and tune properties on demand. Mechano-fluorochromic (MC) materials, which show switchable fluorescence with mechanical force that is often reversible with heat or solvent vapor, have seen rapid development in recent years, though crystallographic analysis of the mechanisms governing these changes in fluorescence. Our lab has previously studied three-ring phenylene ethynylene oligomers (PEs) bearing perfluorinated benzyl ester pendants on the central terephthalate, a form of side-chain engineering in which the well-studied perfluoroarene-arene (ArF-ArH) supramolecular synthon intramolecularly induces a twist into the conjugated backbone, which significantly affects solid-state optical properties by interrupting conjugation and preventing chromophore aggregation. Coincidentally, many of our PEs show reversible MC behavior, which can be tuned according to two lesser utilized parameters: the length of alkyl chains on terminal substituents, and the regiochemistry of fluorination in the side chains. In a series of N,N-dialkylaniline substituted PEs with thermally reversible MC, we may tune the temperature required to recover the original fluorescence of films after mechanical grinding according to the length of the terminal alkyl chains. In a separate series of compounds that have different fluorination patterns in tetrafluorinated side chains (the ArF ring), four sets each of three regioisomers show regular trends in their solid state optical properties according to the fluorination pattern, as well as the ability to alternate between bathochromic and hypsochromic shifts in the MC transition. Crystallographic analysis in both studies offers significant mechanistic insight into their MC responses and elucidates the utility of side-chain engineering in the stimuli-responsive properties of these PEs.

Using Crystallographic Data to Explore the Origins of Allosteric Regulation

Gemma R. Topaz, Boguslaw Stec, Dumazo Ngesina, and Kimberly Stieglitz, Roxbury Community College,
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Archaeoglobus fulgidus of the prokaryotic domain Archaea, possess an unusual dual-function enzyme, functioning as an inositol monophosphatase (IMPase), and fructose 1,6-bisphosphatase (FBPase) known as AF2372. This enzyme cleaves the phosphate group from inositol 1-phosphate to form di-myo-inositol, an osmolyte unique to hyperthermophilic archaea (Chen, L., and Roberts, M. F. 1998). The enzyme also cleaves a phosphate group from fructose 1,6-bisphosphate at C-1 (Stieglitz, K. *et al.* 2002). Higher eukaryotes (and some bacteria) employ both IMPases and FBPases in their cells as two separate gene products from tandem genes that most likely evolved from a gene duplication. A. fulgidus shows structural similarities to mammalian IMPase and FBPase cooperative enzymes, suggesting a possible evolutionary connection (Stieglitz, K. et al. 2002). However there are key differences as the mammalian FBPases have been found to exhibit allosteric inhibition with adenosine monophosphate (AMP) (Kelley-Loughnane and Kantrowitz 2001). A crucial difference is the presence of a tyrosine in the AMP binding site of mammalian enzymes which is a phenylalanine in AF2372. Therefore a

F113Y AF2372 mutant was proposed to confer AMP sensitivity. Site-directed mutagenesis was performed, and a mutant plasmid was constructed. Mutant FBPase protein was over-expressed, purified and characterized by kinetic studies with natural and synthetic substrates in the presence and absence of AMP within the biotechnology laboratory Research Science course (SCI281) at Roxbury Community College. The crystal structure of the mutant has been determined and compared to the wild-type structure. Changes in the AMP binding and active site architecture and at the dimer interfaces of this mutant among conserved residues within the FBPase superfamily may shed some light on how eukaryotic FBPases are regulated and/or evolved into cooperative enzymes.

Thanks be to:

Charlene Tsay for help with the abstract book, setting up in the morning and many other things,

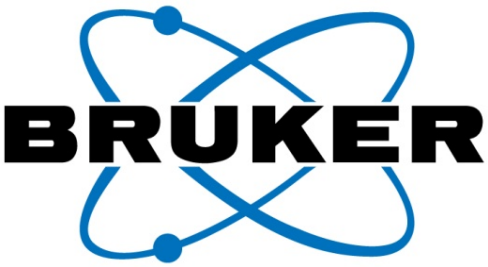
Shao-Liang Zheng who gave me the idea for this year's topic,

Cary Bauer for moral (and other) support and for assuming chauffeur duties,

all speakers and poster-authors

and

BRUKER-AXS for financial support



SCHEDULE

Saturday, January 24th: 8:30 a.m. to 5:00 p.m. in **room 66-110**

08:30 - 09:00 Light Breakfast

09:00 - 09:15 Opening Remarks

09:15 - 10:00 Sue Byram (Bruker AXS)
Honoring Four Great Crystallographers: Philip Coppens, Howard Flack, Isabella Karle and Dick Marsh

10:00 - 10:30 Bruce Foxman (Brandeis University)
Memories of Giants: Dick Marsh, Phillip Coppens and Howard Flack

10:30 - 10:45 Coffee Break

10:45 - 11:45 Ton Spek (Utrecht University)
Forty Years of Marshing: A Name Turned Into a Verb

11:45 - 12:15 Mike Takase (Cal Tech)
To Be or Not To Be --- Marshed

12:15 - 02:30 Lunch with Poster Session in **room 6-321** (Moore room)

02:45 - 03:15 Peter Müller (MIT)
Why Critical Structure Validation is Still Important -- A Case Study

03:15 - 03:45 Michael Ruf (Bruker-AXS)
IDEAL - Invariom Derived Electron AnaLysis

03:45 - 04:00 Coffee Break

04:00 - 05:00 Jason Benedict (University at Buffalo)
Atoms in Motion: Creating and Characterizing Dynamic Crystalline Materials

05:00 - 05:30 Poster Prize and Closing Remarks