Final Report

Cross Cut Review of Research in Structural Biology
Advanced Photon Source
January 24, 2007

Review Committee:

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Howard Einspahr, Research Fellow, Bristol Myers Squibb (Retired), APS SAC
Sine Larsen, European Synchrotron Radiation Facility, External Reviewer
Douglas Ohlendorf, University of Minnesota, External Reviewer
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Introduction:

The reviewers met at the Advanced Photon Source (APS) on January 24, 2007, together with the APS Scientific Advisory Committee (SAC), which has a cross-disciplinary membership, to review structural biology science at the APS. The primary emphasis of the review was macromolecular crystallography (also known as protein crystallography or PX). Appendixes A and B contain the review objectives and the agenda for the day. Included on the agenda were public presentations, an open poster session, and a closed session with the APS SAC members, invited reviewers, and the Directors (or their designees) of all APS Collaborative Access Teams (CATs) that focus on structural biological research. This report provides comments and summarizes the final recommendations to the APS. *(Note: This report is not intended to replace the individual detailed CAT sector review reports. It is intended rather as an overview of an entire field of research at the APS with specific recommendations directed toward improving opportunities and usage for the field, not individual beamlines.). Appendix C contains the summary News item report published in APS News in March 2007 of the APS PX Cross-cut Review.*

Comments and Recommendations (recommendations in bold italics):

1. The committee was impressed by the outstanding quality of science being done at the variety of APS protein crystallography (PX) beamlines. By two key measures, (i) publications in the top-tier journals (*Science*, *Nature* and the top 20 ISI rated Journals) and (ii) Protein Data Bank (PDB) deposited structures, APS is the most-productive and highest-impact facility in the world. We suggest, however, that there are currently unrealized opportunities to extract further important comparative detail. For example, what is the breakdown of publications and top-tier publications per beamline? This information would enable comparisons within APS and more specific comparisons with the output of other facilities? What fractions of a beamline's publications are from general users (GUs), from CAT members, and from staff? It was also noted that, for publications in the top three Journals (*Science*, *Nature*, and *Cell*), APS performed no better than, for example, ALS or NSLS. ***We recommend that these more detailed data be collected and made available for use by the APS and the public.***

2. According to the statistics provided by the APS Users Office during the meeting, in the past few years, the fraction of PX rapid-access beam time requests has increased steadily. This trend reflects a fundamental change in practice as samples become smaller and beam time must be expended simply to identify useful samples for PX experiments. Beam time allocation on a

"when-needed," as well as on an "as-needed" basis, will become an increasingly more popular way for users to efficiently manage their experiments. It is also a more efficient way to distribute beam time to users. ***We recommend that all PX proposals be rapid access and that PX beamlines structure their scheduling to accommodate this mode of access. This change might help to counteract the perception in the community that it is difficult to obtain useful beam time at the APS since one needs to apply too far in advance of when the time is needed (i.e., when crystals are ready).***

3. APS SAC members from the physical sciences have the perception that there is more PX capacity than is being utilized because the great majority of all PX proposals get beam time (the average actual ratio is 93% of PX GU proposals receive beam time). They believe that to preserve standards of excellence, it is more healthy to have oversubscription (i.e., where some fraction of proposals–perhaps 25%, do not get beam time). This perception is incorrect; PX projects, and most of those in the physical sciences for that matter, are peer reviewed under highly stringent conditions just to obtain funding in the first place–most likely much more stringent conditions than those imposed by synchrotron proposal review committees. This process serves as a filter for bad proposals before they even get to the APS. Conversely, failure of vetted proposals to get their needed beam time does not signal a healthy situation at all: rather it means that research approved and funded by scientific agencies is delayed or does not get done and suggests that policies governing the conduct of research could seriously be at cross purposes. ***We recommend that APS management not use rule-of-thumb oversubscription as a sole metric of quality of research done on its beam lines.***

4. ***We recommend that APS enhance the ease of access to details of PX activities at the APS, by creating a prominent direct link to them from the APS homepage***. *[Post Meeting Note: This issue was already being studied by the APS.]*

5. Many of the beamlines do "production" structural analysis, meaning routine data collection to support, for example, the structural genomics efforts. These studies take advantage of the tunability of synchrotron radiation for MAD phasing or of the high intensity for high-throughput applications. This work may sometimes not be rated as exciting, i.e., achieving the *Science*, *Nature*, and *Cell* publication category, but it generates nevertheless many papers and PDB structure depositions. It is agency-approved, important work that needs to be done, and it is usually endorsed as a research program, for example by the NIH PSI (Protein Structure Initiative). ***We recommend that such 'bread-and-butter' work be sustained but, of course, not be allowed to reduce the ability at APS to do the cutting-edge difficult projects.***

6. BioCARS is arguably the best example at APS of a facility with beamlines that have an important unique niche. Their beamlines are the only ones in the United States where Biological Safety Level 'BSL' 3 studies can be conducted. In addition, they have the only beamline in the U.S. capable of Laue sub-nanosecond time-resolved studies. In the past, these time-resolved studies could only be done when APS was in single-bunch mode. The nearly completed BioCARS ID line refurbishment will allow Laue data collection in the normal 24-bunch mode. This should result in many more cases of this interesting frontier science of biological structure, function, and dynamics.

7. We suggest that lack of standardization in some areas may become a problem. Since beamlines have grown up independently, due to their independent funding, with a variety of different hardware, software control cannot be identical from beamline to beamline. However, beamlines can be made more similar and they are to a large extent moving in that direction. Since

automation is being added, a potential additional problem is use of non-standard pucks. ***We recommend that the APS encourage the beamlines to make every effort to use standard pucks to allow crystals shipped to the APS to be easily movable between any suitable beamline.***

8. ***The current APS beamtime application form should make consideration by other suitable beamlines the default so as to get more proposals into the available pool.*** *[Post Meeting Note: this recommendation has been implemented by the APS.]*

9. The movement towards handling small (<10 um) crystals with micro-diffractometers is a timely development that has the potential to allow data collection from previously unusable samples. However, in parallel to this is the need for users to screen significant numbers of crystals for those that diffract. Currently such proposals receive low scores in the GU review process. ***We recommend that these proposals should be supported if the science is strong, such as for categories like membrane proteins or large complexes, and the GU scoring system should make provisions for this type of proposal. Such screening for useful samples could take advantage of available time on BM lines, as perhaps the best location for it.***

10. Mail-in data collection is being offered to CAT members on several beamlines. Only one beamline offers the service to General Users (SGX-CAT, 31-ID, although usage of this capability at present is poor–see point 11***). We recommend that the APS encourage the CATs to make this mode of data collection available to the GU community. APS management should also make it a policy to encourage general users to take better advantage of this service on beamlines that offer it.***

11. The very low usage of the GU time at the SGX CAT, which is entirely mail-in, is troubling. ***We recommend that the APS facilitate interactions with SGX-CAT and others CATs (e.g., IMCA-CAT and SER-CAT) that provide this service to members to get this important category of use up and running.***

12. ***User solicitation should also be increased. Some beamlines post notices on crystallographic bulletin boards (BBs) like the CCP4bb, concerning beamtime availability and application procedures. This should be routinely done for undersubscribed beamlines, e.g., SBC-CAT's 19-BM and SGX mail-in.***

13. Special mention needs to be given to the large quantity of proprietary research done at the APS by the pharmaceutical companies, namely by the IMCA and SGX CATs. The sector reviews for each of these in 2006, for example, took note of a wide variety of excellent science for drug lead compound discovery. IMCA CAT also recently showed a 'top ten' in the world performance of publications output from synchrotron beamlines (Oct 2006), even though 75% of their beam time supports proprietary research, much of which will never be published. These activities are a big asset to the APS in, for example, being able to champion examples of such research that is important and relevant to society's needs.

14. Given that a majority of CATs at the APS, 45% of its users, and 45% of its publications are from the structural biology community, ideally, the APS should have as part of its organizational structure, a Structural Biology Group led by a respected structural biologist. ***However, we recognize the realities of APS operational funding by DOE/BES, and so we recommend that APS add to its organizational structure a senior life scientist to assist the APS management in developing new and nurturing existing users in the life sciences. This individual could potentially have a joint appointment with a research division at Argonne or***

with a neighboring university i.e., with their research group locally placed and ideally with an emphasis on SR PX methods.

15. ***We also recommend that, at least every two years, a SAC cross cut review of structural biology take place; the attendance of all the CAT Directors somehow needs to be guaranteed, perhaps by pre-agreement on the event date, to optimally capture the science emphasis requirement.***

16. ***For the PX CATs we recommend that the PX CAT directors regularly meet to discuss common accomplishments and problems. These directors could, for example, appoint a rotating Chair to represent PX to the APS administration and thus (i) provide a contact for consultation with management when issues arise that are of potential concern to structural biology sectors and, as needed, (ii) provide coordinated representation of the structural biology interests at committee meetings in which APS facility management and planning are discussed.***

Key Facts End Notes:-

A. Summary of APS PX hardware

Denny Mills: "As of the end of FY06 (October 2006) we had 49 independently operating beamlines (that really means beamlines that can operate more or less independently, for as is well known if there are two beamlines on one ID, one of the beamlines does not have full control of the ID energy and may not be able to run truly independently 100% of the time. This is the way DOE asks APS to count beamlines, so that there are no fractional beamlines, but APS does have beamlines that are not scheduled 100% of the time for the above reason.)

The current list of APS PX beamlines is:

14-BM-C BioCARS
14-BM-D BioCARS (due to be mothballed due to lack of funds, but it did operate in FY06)
14-ID BioCARS
17-BM IMCA
17-ID IMCA
19-BM SBC
19-ID SBC
22-BM SER
22-ID-D SER
23-ID GMCA (first of several lines on the canted IDs)
24-ID NE
31-ID SGX

The remaining 37 beamlines are not PX, the exception being 5-ID DND, which does some PX but is not dedicated to PX, so excluding DND, 12/49 or ~25% of the beamlines are fully PX. If all the branch lines are built out on all the planned canted ID lines for PX, APS will have 11 new PX beamlines by FY2010 (note that some existing PX beamlines may be turned off (i.e., recognizing the obvious risk that the funding effort fails.). A good, realistic, estimate might then be 20 PX lines by 2010, i.e., approximately a doubling of current APS capacity.

This can be looked at from a sector point of view as well. Again, as of the end of FY06 APS had 6 sectors dedicated to PX (14, 17, 19, 22, 23, 31) and 20 sectors not so dedicated (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 20, 32, 33, and 34). That percentage is about 6/26 = 23%. (Note also: APS has 2 PX sectors, 21, and 24, and 2 non-PX sectors, 26, and 30, under construction/commissioning. Furthermore four APS sectors remain unassigned out of a total of 34.)"

B. APS PX beam time request data

Susan Strasser: "The number of regular BTRs (beam time requests) and rapid-access BTRs per cycle, the total for the four-year period, as well as the number and percentage of regular and rapid-access BTRs that didn't receive time, provide data which show clearly that for the most part, all BTRs that are received by the proposal deadline (regular BTRs) receive time. There is a small oversubscription, 10% overall for the three-year period, but the range per cycle is 0-28%. For rapid-access BTRs, the story is a little different (see detailed figures 1-3 below).

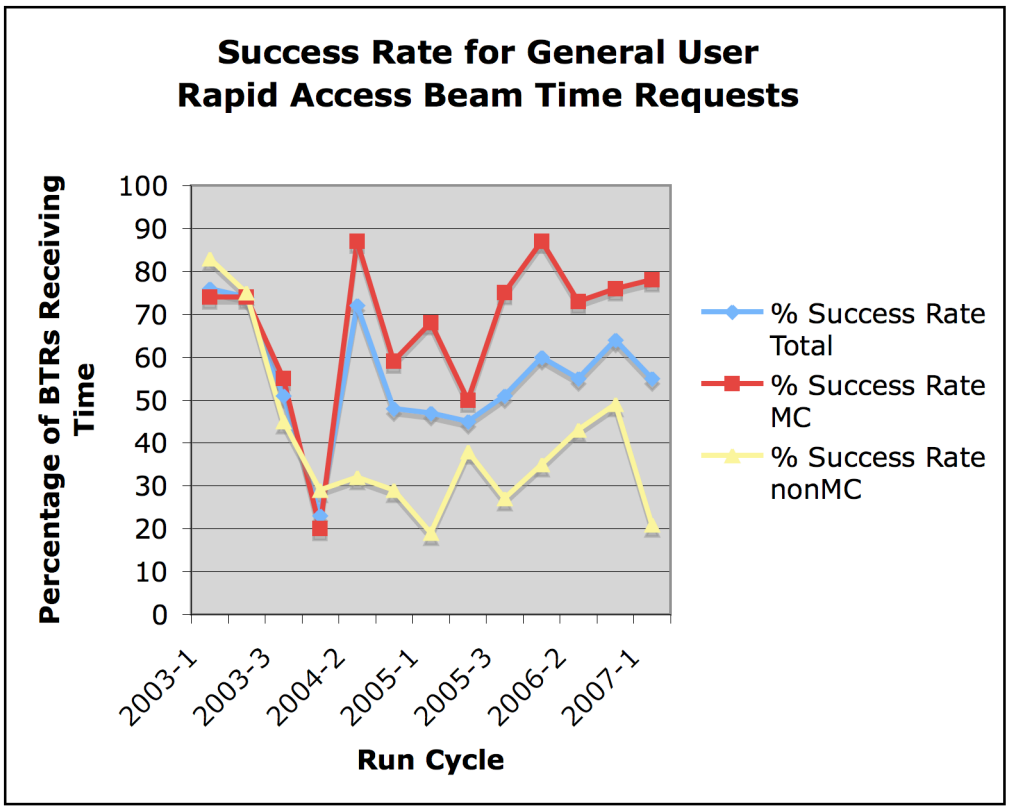

Figure 1. Success rate (% of submitted beam time requests receiving time) for all rapid-access beam time requests (total, macromolecular crystallography, and non-macromolecular crystallography) since Run 2003-1.

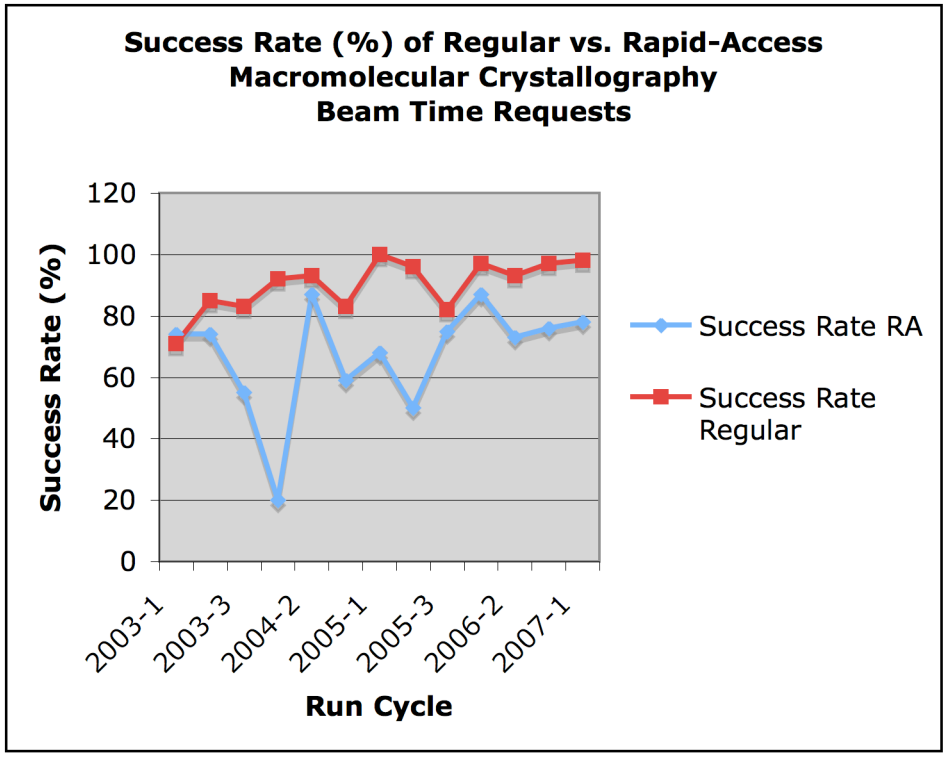

Figure 2. Success rate (% of submitted beam time requests receiving time) for macromolecular crystallography beam time requests (regular vs. rapid-access) since Run 2003-1.

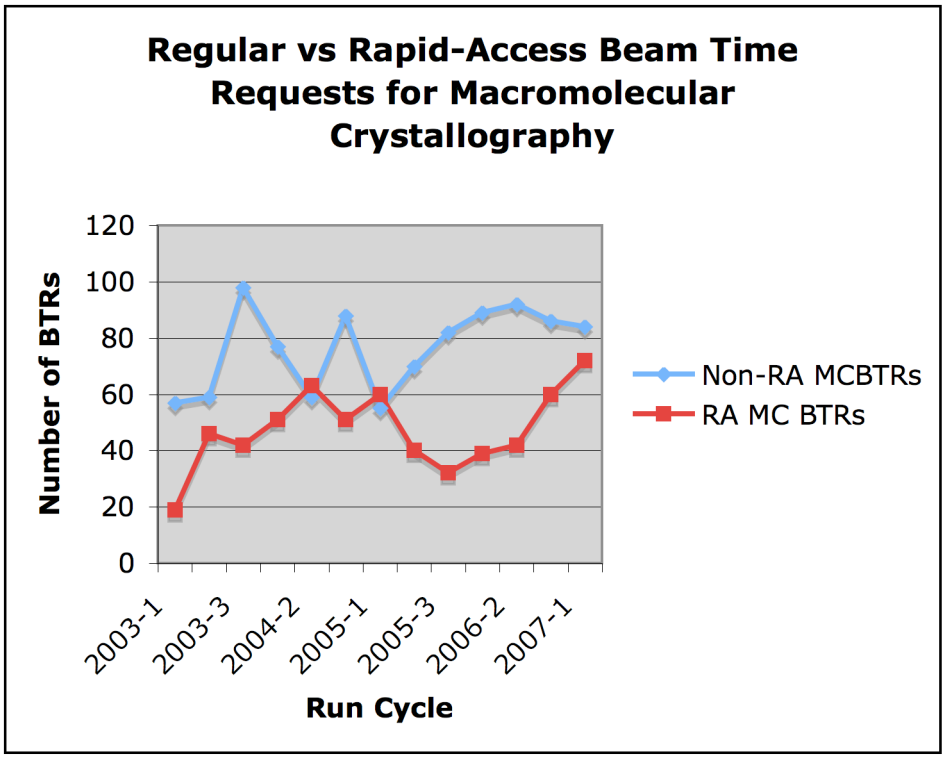

Figure 3. Number of submitted beam time macromolecular crystallography requests (regular vs. rapid-access) since Run 2003-1.

APPENDIX A: Cross cut Review Objectives

Purpose: To review the structural biology science program at the Advanced Photon Source concentrating on macromolecular (i.e., known as protein) crystallography ('PX') considering specifically aspects such as:-

1. What is the level of productivity of the APS protein crystallography beamlines, as measured by the papers published and PDB database entries?

2. What is the impact and importance of the APS work to the protein crystallography community nationally and globally?

3. Projecting into the future, what will be required to maintain APS competitiveness in protein crystallography on the national and international scene?

Context
APS PX beamlines do not fall under the responsibility of the Department of Energy, Office of Basic Energy Sciences (DOE-BES). Nevertheless BES is responsible for the effective operation of facilities such as APS on behalf of all users in all science research disciplines, i.e., BES is the steward.

APPENDIX B
Detailed Agenda
The talks are available at:-
http://www.aps.anl.gov/News/Meetings/APS_Cross_Cut_Reviews/2007/

Chair: Howard Einspahr

8:00 a.m. **Welcome, Introduction of Invited Reviewers, and Charge to the Review Committee**
J. Murray Gibson, Advanced Photon Source

8:05 **Overview: Structural Biology on the World Scene–What it Means to the APS**
John Helliwell, Cross-cut Review Chair

8:30 **Sector 14**
Vukica Srajer, Associate Project Manager, BioCARS

8:55 **Sector 17**
Lisa Keefe, IMCA-CAT Director

9:20 **Sector 19**
Andrzej Joachimiak, SBC-CAT Director

9:45 **Sector 22**
John Chrzas, SER-CAT Sector Manager

10:10 **Break**

Chair: John Helliwell

10:30 **Sector 23**
Robert Fischetti, GM/CA-CAT Associate Director

10:55 **Sector 24**
Malcolm Capel, NE-CAT Deputy Director

11:20 **Sector 31**
Kevin D'Amico, SGX-CAT Director

11:45 **Sectors 5 and 21**
Denis Keane/Wayne Anderson, DND-CAT and LS-CAT Directors

12:10 **Panel Discussion – Review Chair and Invited Reviewers**

12:45 **Concluding Remarks**
Murray Gibson

Bldg. 402 Lower-level Gallery; 1:00 – 2:00 p.m

1:00 **Poster Session and No-host Buffet Luncheon**

Bldg. 401. Room A5000 Lower-level Gallery; 2:00 – 4:30 p.m.

2:00 **Executive Closed Session – CAT Directors, Invited Reviewers, SAC members**
Sine Larsen, Discussion Leader
4:30 **Adjourn**

Appendix C; Extract from APS News March 2007:-

SCIENCE NEWS

1. Cross-cut Review of Protein Crystallography

The fourth in the APS series of cross-cut reviews sponsored by the APS Scientific Advisory Committee (SAC), this year's review of protein crystallography pioneered a new review structure. John Helliwell, APS SAC member and Chair of the review, began the public morning session with an excellent overview presentation entitled S□ tructural Biology: The World Scene--What it Means to the APS.□ This comprehensive talk-- spanning global facilities and user perspectives, with a summary of published long-term strategies--set the stage for the eight presentations that followed, one from each sector hosting research in structural biology. Presenters were asked to focus their presentations on vision, describing how the particular sector fits into the current scientific structure of the APS, as well as how it fits into the future of the APS and the world scene. In addition, each speaker presented examples of current research.

Following the presentations, John Helliwell and invited reviewers Sine Larsen (ESRF) and Douglas Ohlendorf (University of Minnesota) held a panel discussion, noting specific strengths identified in the presentations and responding to questions from the audience. Of particular interest were topics such as screening for good-quality crystals in membrane protein research and paths to higher-brilliance x-ray sources. A poster session held during lunch enabled SAC members, funding agency representatives, audience participants, and speakers to discuss research conducted at each of the beamlines at a more detailed level and meet many of the other beamline staff members.

The afternoon session was closed, with only SAC members, invited reviewers, and one management representative from each structural biology sector in attendance. Topics ranged from demand for beam time, funding issues, competition worldwide, ease of access for crystallographers, statistics, and most important at present for the APS, the major expansion in available beam time for protein crystallography, with new sectors coming on line complete with canted undulators. Beamline representatives, SAC members, and reviewers discussed possible solutions to the most pressing issues. A comprehensive report with recommendations to the APS is being prepared by the Cross-cut Review Committee. Highlights of this report will be made available shortly.