

Final Report

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

Review Committee:

J. R. Helliwell, University of Manchester, UK, APS SAC; Chair
Howard Einspahr, Research Fellow, Bristol Myers Squibb (Retired), APS SAC
Sine Larsen, European Synchrotron Radiation Facilities, External Reviewer
Douglas Ohlendorf, University of Minnesota, External Reviewer
Wei Yang, NIH, Bethesda, APS SAC

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 biology 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.)

Comments and Recommendations:

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) and 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.**

APS agrees that more detailed data should be assembled and periodically reviewed (it is already being collected in the APS publications data base). We do not fully agree with the comment that APS performed no better than ALS or NSLS when looking at high-impact publications. Below are several tables showing publications from the three journals mentioned above plus PNAS. Notice that the publication numbers from both ALS and NSLS has been relatively constant over the three-year period but that APS output has continued to grow. In CY06, the APS clearly outperformed the other two facilities. (SSRL does not have a searchable database for easy comparison.)

| | CY04 | | | CY05 | | | CY06 | | |
|--------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| | APS | ALS | NSLS | APS | ALS | NSLS | APS | ALS | NSLS |
| Cell | 7 | 5 | 5 | 6 | 4 | 6 | 14 | 11 | 13 |
| Nature | 15 | 12 | 11 | 14 | 9 | 16 | 11 | 9 | 9 |
| PNAS | 33 | 26 | 23 | 44 | 27 | 20 | 43 | 21 | 23 |
| Science | 11 | 15 | 6 | 9 | 18 | 8 | 20 | 15 | 11 |
| TOTAL | 66 | 58 | 45 | 73 | 58 | 50 | 88 | 56 | 56 |

Representatives of the PX beamlines have suggested that we track the PDB statistics, and we agree with their suggestions. Below are the results from the PDB for CY04, CY05, CY06, and CY07 to date.

| | CY04 | CY05 | CY06 | CY07 (to date) |
|------------|------------|------------|-------------|----------------|
| ALS | 444 | 379 | 468 | 289 |
| APS | 684 | 820 | 1061 | 880 |
| CHESS | 87 | 99 | 84 | 53 |
| NSLS | 394 | 420 | 505 | 393 |
| SSRL | 156 | 184 | 216 | 23 |

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).**

APS will present this proposal to the APSUO and PUC at their January 17 and 18, 2008, meetings for feedback. However, the December 2007 written response from the PX community indicates that they prefer to have both modes of access available on the condition that APS continues to provide expedient reviews of

proposals with rapid-access beam time requests. They also advocated that the APS provide productivity statistics to reviewers. We will look into this carefully, develop a plan, and discuss the process with the PX community. APS agrees the PX community that we should more aggressively promote the availability of rapid-access beam time. We will work with the PX community to develop and execute a promotion plan.

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 healthier 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.**

APS agrees that oversubscription should not be the sole metric for the quality of a beamline. However it must be one of several metrics (including quality and quantity of publications, number of patents, etc.) that allows the APS management to judge or evaluate the productivity of a beamline at the facility.

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.]

APS agrees with this recommendation and proposes a prototype page be developed by 1/21/08. We have begun to develop a draft web page (to be presented to the PX members of the PUC on January 17) that will include ability to use filters to help a user select beamlines. These filters will be technique (Large unit cell crystallography, macromolecular crystallography, Laue, MAD, SAD, and status (Commissioning, Operational, Accepting General Users). Clicking on a beamline number on this Web page will take the user to that beamline's page in the Beamline Directory. In addition, the page will have links to useful APS sites such as User Registration, the General User Program (Proposal System Log-in and General User Program Calendar), APS Publications Database (with individual links to publications for each PX beamline) and reports and presentations (from reviews and workshops geared toward PX users).

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.**

At this point, the APS agrees with the committee's recommendation as the demand for beamtime seems to be in equilibrium with supply. However, we will keep our eyes on this should the situation change.

6. 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 beamline to make every effort to use standard pucks to allow crystals shipped to the APS to be easily movable between any suitable beamline.**

We are in agreement with the Committee that standardization should be encouraged by the APS. The PX community response was that they are "...working to accommodate users who bring different styles of pucks and different styles of pins." APS will discuss this point with the PX community to see if there are things APS can do to drive the standardization process.

7. The current APS beam time application form should make consideration by other suitable beamlines the default so as to get more proposals into the available pool.

This recommendation has been implemented by the APS.

8. 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.**

APS agrees that selective screening can be an important component to structural studies, particularly with large complexes or with samples that are difficult to

crystallize. One possibility to accommodate screening is to set aside some GU time just for screening (in a similar way that some beamlines set aside time for rapid access). If the set-aside for screening is not filled, it could revert to rapid access GU time. This approach would allow the each beamline the flexibility to determine the maximum time that should be allocated to screening. APS will discuss this proposal with the PX community.

9. 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.**

APS supports a balanced portfolio of access modes for users. We also agree that there is a need to encourage general users to take better advantage of the existing services (see the following recommendation) and to that end, as part of our improved website for PX users, will prominently advertise the existing capabilities at the APS. In addition, IMCA-CAT (17-BM and 17-ID) is planning to offer mail-in services to General Users on a limited basis in 2008. The APS will monitor the use of this capability through the General User route on IMCA-CAT and SGX-CAT beamlines. If demand grows larger than capacity, we will work with the PX community to expand the mail-in capabilities for the facility.

10. 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.**

See response to recommendation above.

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

APS will more actively pursue user solicitation through bulletin board postings, advertisements/booths at PX meetings, etc. Below are (funding-dependent) tentative plans for FY08.

- Attend and advertise at the Knoxville ACA meeting*
- Attend and advertise at the IUCr meeting*
- Advertise on the CCP4 bulletin board (and other bbs) using newly developed link for PX*
- Advertise in the Journal of Synchrotron Radiation*

12. 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.**

We agree that having a well-established and respected structural biologist to provide the APS management with advice and guidance regarding the life sciences activities at the APS would be very beneficial. We are continuing to pursue various ways to accomplish this objective including joint appointments, consultants, etc. To date, we have a draft position description (PD) that outlines the expected responsibilities associated with such a position. The APS has also gotten the buy-in of the ANL Director on the importance of such a position and the Director supports its establishment.

13. 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.

We agree with the recommendation that there should be regularly scheduled cross cut review to evaluate the structural biology program at the APS. We would propose a three-year cycle rather than a two-year, and schedule the next cross cut review for 2010. The PX community agrees with our proposal on having the reviews spaced on a wider grid, i.e. every three to five years.

14. 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.

To get user input into operational issues and to make the APS decision-making process more open, the APS management has invited representatives from the APS User Organization (APSUO) Steering Committee and the Partner User Council (PUC) to attend the weekly Operations Meetings. We agree that a unified voice from the PX community would be useful input to APS management and would be willing to work with an elected representative from the PX community. PX CAT Directors currently attend the APS PUC Executive Committee meetings that take place four times a year. This might be a convenient venue for the PX CAT Directors to discuss issues relevant to structural biology with not only the APS, but also with the broader APS user community. Representatives from the PX

community have agreed to meet one day prior to the PUC meetings and have begun the initial phase of providing coordinated input to the APS.