



APS Upgrade: Optimal Beam Properties for Macromolecular Crystallography and Other Biological Applications

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APS Workshop

Argonne, August 10/11, 2006

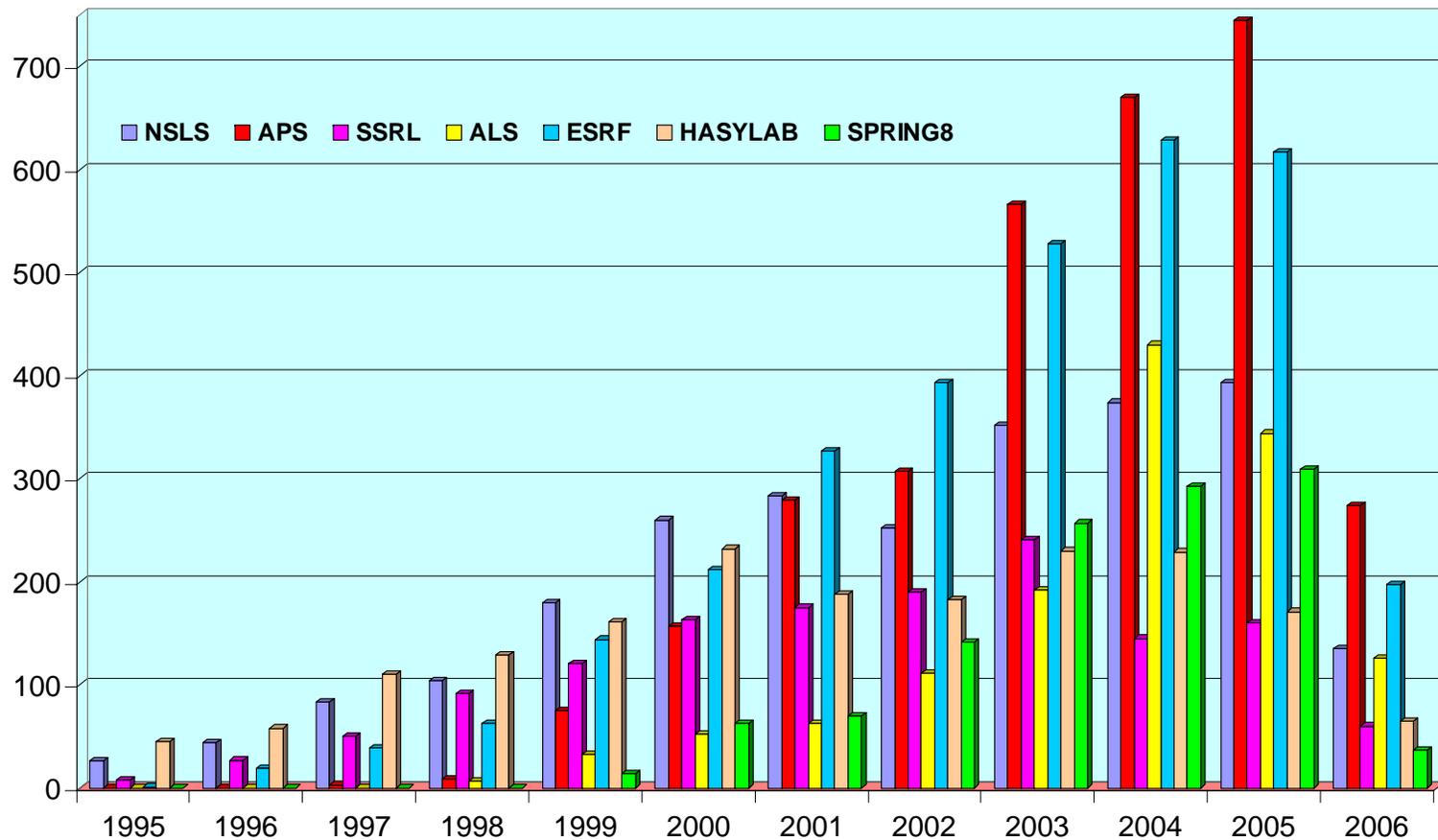


Currently APS PX Beamlines Provide an Outstanding Facilities for Synchrotron Data Collection

- Physically small, stable, high brilliance and high flux X-ray beam
- Access to X-rays with broad energy range
- Fast and large CCD detectors
 - Large number of diffraction orders measured in very short time
- Fast and accurate crystal and detector positioning
- Rapid crystal mounting, alignment, change and high-resolution crystal visualization
- Crystal preservation using cryocooling
- Robust and efficient data reduction software in multi-cpu computing environment
- Design, control and evaluation of crystallographic experiments in near real time
- Acquisition and processing of data measured to the limit of crystal diffraction takes less than an hour
- Optimize signal to noise, radiation dose, redundancy etc.
- All components optimized for speed and efficiency
- Fast network with TB data storage system
- Robotics and automation beamline operations, data collection and structure determination

APS is the Most Important Resource for Macromolecular Crystallography in US

- Overall PX sectors and users are very happy with APS performance and reliability
- In 2005 43% of US PDB deposits originated from data obtained at APS (34% total)



Bioscience Experiments Conducted at the APS

- Macromolecular crystallography
 - MAD/SAD phasing
 - Very large macromolecular assemblies – nano-machines
 - Ultra high resolution data collection
 - Membrane proteins
 - Time-resolved crystallography – structures of intermediates and the reaction mechanism
 - Kinetic crystallography – trapping kinetic intermediates by cryofreezing
- Fiber diffraction from biological systems
- Powder diffraction from proteins
- Small and wide angle x-ray solution scattering (SAXS, WAXS)
- X-ray absorption fine structure (XAFS)
- Time-resolved x-ray scattering
- X-ray microscopy (incl. fluorescence): imaging living biological systems
- Biomolecules under high pressure



Quote from APS Users's Meeting (JMG), May 2006

- We have unique opportunity to bring APS to world-leading level in the next decade (proposal has been solicited by DOE-BES, due late 2006)
 - Reduce lattice emittance to ~ 1 nm with ID beamports unchanged
 - Most straight sections longer (8 m), special undulators, utilizing unique properties of APS to tailor x-ray beams
 - “Crab” cavities for ps pulses and controlled coherence
 - Optimized and upgraded beamlines



What X-ray Crystallography Capabilities are Missing at the APS?

- PX beamline optimized for very small (micrometer-size) crystals
- PX beamline optimized for low energy
 - These beamlines should be included in the APS upgrade plans
- Large-scale x-ray area detector development
 - Detector development is critical to many areas of biological science and should be included in the APS upgrade plans



Need for Microbeam

- Very small crystals: reduce scatter from non-crystalline material
- Selective exposure of small crystal volumes:
 - very asymmetric shape of crystal (e.g. needle): reduce scatter from non-crystalline material
 - very small, well ordered domains
- Reducing radiation damage in exposed volume:
 - photo-electrons travel several μm ($\sim 6\mu\text{m}$ for 18 keV initial energy)
 - large fraction of damaging energy is not deposited in the illuminated volume for micrometer size beams
 - energy deposit per distance traveled is not uniform, very high at end of travel
- Photo-electrons ejected predominantly in direction of electric field vector



Need for Microbeam

- Need beam of 1 - 2 μm horizontal width at 18 keV photon energy
- Vertical beam size can be larger:
 - is not the predominant direction of photo-electrons
 - due to rotation around horizontal axis, vertical dimension of exposed volume will be larger than crystal thickness
- Source horizontal size is large (650 μm FWHM) in direction of polarization (only 20 μm FWHM in vertical direction)
- Large horizontal demagnification required for current lattice:
 - two step demagnification:
 - (1) normal demagnifying beamline optics
 - (2) focusing on horizontal defining slits = virtual source
 - (3) re-imaging virtual source on sample
- Proposed upgrade, if one of the 82 μm FWHM ($\sigma_x=35 \mu\text{m}$) ports is granted:
 - one step horizontal demagnification possible

Size and Flux Estimates of Microbeam (current lattice)

- Imaging horizontal source on slits
 - source to 2nd crystal at 18 keV (Si-220) 53.30 m
 - 2nd crystal to slits 6.38 m
 - demagnification 8.35:1
 - width of horizontal focus 78 μm FWHM
- Imaging virtual source (slits) on sample
 - slits to focusing mirror 12.04 m
 - focusing mirror to sample 1.46 m
 - demagnification 8.25:1
- Size of image of slits at sample
 - aberration free image of 20 μm wide slits 2.4 μm
 - bimorph allows to shape mirror to required elliptical figure
 - aberrations determined by residual surface figure error
 - Gaussian figure error of 0.3 μrad rms creates beam size of 2.1 μm FWHM
 - convoluted size of image of 20 μm slits 3.2 μm FWHM
 - of 10 μm slits 2.4 μm FWHM

Size and Flux Estimates of Microbeam (current lattice)

- Imaging vertical source on sample
 - source to focusing mirror 72.68 m
 - focusing mirror to sample 0.50 m
 - demagnification 145:1
- Size of image of vertical source at sample
 - aberration free image 0.14 μm FWHM
 - bimorph allows to shape mirror to required elliptical figure
 - aberrations determined by residual surface figure error
 - Gaussian figure error of 0.3 μrad rms creates beam size of 0.7 μm FWHM
 - convoluted size of image 0.7 μm FWHM



Size and Flux Estimates of Microbeam (Before & After Upgrade)

	Before	After
• Flux from undulator	2.37×10^{13} ph/s/0.1% BW	8.1×10^{13} ph/s/0.1% BW
• 3.1 cm magnetic period	1 m long, 100 mA	2.1 m long, 200 mA
• at $E_{\text{phot}} = 18\text{keV}$		
• into horizontal x vertical angle	$15.9 \times 11.0 \mu\text{rad}^2$	$11.0 \times 16.6 \mu\text{rad}^2$
• Passing through 20 μm slits	0.238	no slits
• Si-220 double crystal bandwidth	$\sim 4.6 \times 10^{-5}$	$\sim 4.6 \times 10^{-5}$
• Losses in windows, other	0.8	0.8
• Estimate of flux on sample	2.1×10^{11} ph/s	3.0×10^{12} ph/s
• Estimate of flux density at sample	9×10^{16} ph/s/ mm^2	3×10^{18} ph/s/ mm^2
• Convergence angles of flux on sample		
• horizontal	1.1 mrad	1.6 mrad
• vertical	1.6 mrad	0.9 mrad
• Exposure time to reach dose limit $D_{1/2} = 4.3 \times 10^7$ Gy	2 seconds	0.06 seconds



X-ray Source Requirements for Time-resolved Macromolecular Crystallography



- Pulse duration: structural changes to be probed span sub-ps to sec and min
 - 100 ps available presently at synchrotron sources
 - Longer pulse trains quite suitable for slow reactions
 - Sub-100 ps desirable to probe very fast structural changes:
 - Short-lived intermediates
 - Fast protein relaxation
 - Rapid ligand migration
- Caution: same as in ps time-resolved spectroscopy, effects of laser induced heating need to be taken into account
- Advantage of spontaneous emission (storage ring, ERL) over SASE (FEL):
 - Predictable timing of pulse
 - Better synchronization of laser excitation

Example: it takes 1-2 ps for vibrationally excited heme in myoglobin to cool,
based on ps TR Resonance Raman studies

Kitagawa et al., Biopolymers 76, 207, 2002



X-ray Source Requirements for Time-resolved Macromolecular Crystallography

- X-ray energy: few % bandwidth at 12-15 keV
 - Harder X-rays diffract less strongly and are detected less efficiently
 - Undulators better sources than wigglers:
 - high peak intensity
 - low polychromatic background
 - reduced spatial and harmonic overlap
 - data processing software can handle wavelength normalization in the presence of sharp spectral features
(Srajer et al., J. Sync. Rad 7: 236, 2000)
 - better data as judged by R_{merge} , completeness, map quality
(Bourgeois et al., Acta Cryst. D 56: 973, 2000)
- X-ray flux: $> 10^{10}$ photons/pulse needed for single pulse image acquisition
 - At present, at TR PX beamlines (APS 14-ID, ESRF ID09, PF-AR NW-14) >10 -100 single X-ray pulses needed
 - The aim of the 14-ID upgrade: single pulse acquisition in hybrid and 24-bunch mode (dual, inline undulators; KB mirror pair – focused beam size 80 (h) X 50 (v) μm^2)
 - Single-pulse acquisition will allow study of fast, irreversible processes
 - Higher pump laser pulse energies can be used (crystal motion not a problem)



X-ray Source Requirements for Time-resolved Macromolecular Crystallography

- X-ray focal spot:
 - In principle should be able to match the sample size
 - Investigating small crystals requires small beam but at full flux (short exposures)
 - Small vertical beam size needed for isolating single X-ray pulses by a chopper
 - Low energy fs-ps laser pulses require illumination of smaller crystal volume for efficient photo-initiation – need a small probe X-ray beam
< 50-100 μm focal spot
- Storage ring mode and beamtime availability:
 - Need to isolate a single X-ray pulse in pink mode:
 - Current BioCARS fast chopper can isolate single pulse only in the APS hybrid mode
 - Upgraded chopper will be isolating single pulses in the 24 bunch mode
 - Technically challenging experiments – unlike standard PX data collection require significant beamtime: preferably standard rather than special operating mode

Time-resolved Crystallography: Conclusion and Future Outlook

- Mature phase of the technique: demonstrated ability to detect small structural changes even at relatively low levels of reaction initiation (15-40%)
- Development of essential methods for global time-resolved data analysis is well under way
- Challenges:
 - Application of the technique to other systems of biological interest, photosensitive and beyond
 - Reaction initiation: system-specific efforts to determine suitable reaction initiation method
 - Irreversible processes and smaller crystals: need **more intense X-ray sources** and **faster read-out detectors**
 - **Further improvements in time resolution: sub-100ps X-ray sources?**
 - Combining experimental results from time-resolved crystallography with computational and theoretical approaches to describe reaction pathways completely, including the transition states





Proposed Lattice

- Smaller lattice emittance, much smaller horizontal beam size option, longer straight sections, double beam current will improve microfocus and quality of microbeams
 - Easier beamline optical design with less components for same 1 - 2 μm horizontal focal size
 - 14-times higher flux ($3 \cdot 10^{12}$ ph/s)
 - 30-times higher flux density ($3 \cdot 10^{18}$ ph/s/mm²)
 - Allows to better optimize beam, e.g. less convergence angles, by reducing acceptance angles, shorter focusing elements
 - Some gain in microcrystal macromolecular crystallography



Longer Straight Sections and Special Undulators: Optimizing Magnetic Period of Undulator for Biological Experiments

- Multiple independent indulator beamlines possible per sector
 - Independent wavelength change
 - Independent access to endstation
 - Significant increase in productivity per sector (2-3 times)
- Optimized undulator source
 - Undulator A with 3.3 cm magnetic period is perfect for Se MAD phasing
 - First harmonic provided sufficient flux at Se edge and low heat load on monochromator
 - However, at Br edge flux is too low
 - Shorter magnetic period extends to higher energy in 1st harmonic
 - Higher heat load at low energies, e.g. 7 keV
 - Less overlap between 1st and 3rd harmonics
 - 3.1 cm magnetic period is a good balance



Three Undulators in Straight Section (Current Design and Upgrade Option)

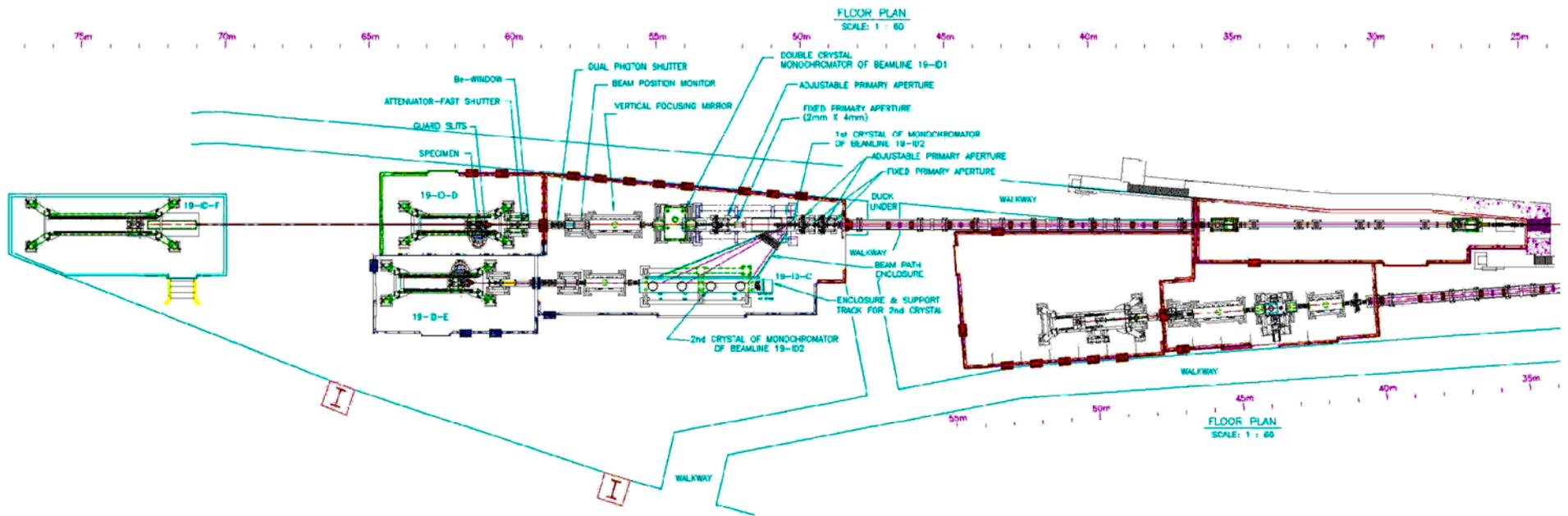


- One beam pipe for all three undulators, 4.8 m long, new design (with integral particle BPMs before, between, and after undulators)
- Between undulators:
Deflector magnets (+ corrector magnet?): each set about 0.35 m long
- Length budget: $1.0 \text{ m} + 0.35 \text{ m} + 2.1 \text{ m} + 0.35 \text{ m} + 1.0 \text{ m} = 4.8 \text{ m}$
APS Upgrade:
8 m straight section would allow for three 2.1 or 2.4 m long undulators
- Need new front end with triple beam mask (design, manufacture by APS)
- Need to adapt new hard X-ray BPMs for triple beam (R&D by GR & APS)

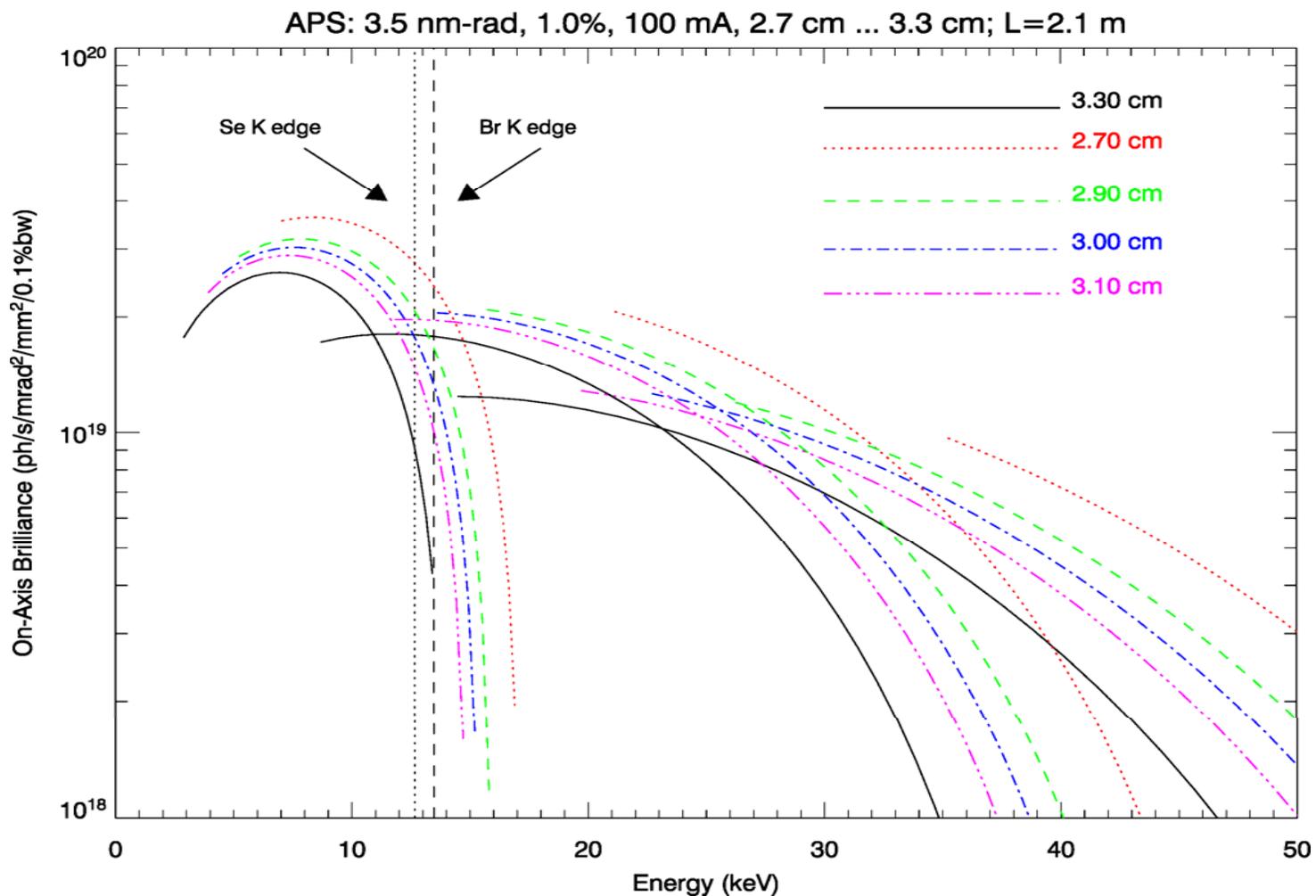


Three Undulator Beamlines

Center and Horizontally Offset Beamline Optics and Endstations



On-Axis Brilliance vs. Undulator Magnetic Period





“Crab” Cavities for ps Pulses and Large Area Coherent Imaging

- "Crab" cavities would provide pulse durations of a few to tens of ps, and potentially large area coherent imaging
- However, only a small fraction of beamtime at such sectors would go towards biological crystallography
- The picosecond pulses would be of great use to the currently small number of biological crystallographers who are doing time-resolved crystallography
- It is not clear if coherence and speckle experiments will be of value for crystallography with three-dimensional crystals, but this should be investigated.



Optimized and Upgraded Beamlines

- Area detectors
 - Current CCD detectors do not take advantage of full potential of the APS x-ray sources (too slow, inadequate dynamic range, insufficient spatial resolution for microbeams, need for higher efficiency, low sensitivity at high energies)
 - New technology is slow coming (Pixel Array Detectors) and is expensive
 - Need for detectors better tailored for specific needs of experiments (faster read out time very low dead time (continuous data collection), spherical detectors, optimized for high-energy, very large surface detectors)
- Improved x-ray beam stability at the sample



APS Upgrade can Create new Capabilities for Biological Beamlines

- Improved microfocus beamlines
- High photon energies
- Time-resolved biological experiments (psec studies, ultra-fastSAX)
- Detection sub-zeptogram quantities of metals in cells and other biologically relevant samples
- Imaging living organisms
- Improved beam stability
- Better detectors



Biology Community at the APS is Supportive of APS Upgrade

- APS upgrade will help to continue operate facility at high performance and reliability and with improved characteristics of the source
- Smaller horizontal source size would be major improvement
 - 2.4 times standard
 - 8 times for 4 sectors possible (with 2 times increase in horizontal divergence)
- Reduced horizontal beam divergence would improve energy dispersion from horizontal-bounce monochromator crystals
 - 1.2 times standard
 - 2.3 times for some sectors (with only 1.1 times reduction in horiz. source size)
- Canted undulators (dual and 2 m long triple) can increase sector productivity but it is important to know how planned upgrade will impact current and future designs



Some Detrimental Effects

- Timing of the upgrade and potential long-term user program suspension
 - Long shut down will seriously undercut - if not terminate - APS' leading role in macromolecular crystallography for structural biology in general and the Protein Structure Initiative in particular
 - Long shutdown would place some sectors in real jeopardy of losing their funding (especially industrial partners)
 - Cost of maintaining staff and facilities during shutdown - if the decision is to proceed with the proposed upgrade funding mechanisms should be provided via the APS to help sectors financially survive the downtime
 - It is critical that the impact on the user program be minimized
 - User program will be affected - users move to other synchrotron facilities
 - Sector upgrades should be coordinated with APS shut down



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