

**International Workshop on
Science with and Instrumentation for
Ultrafast Coherent Diffraction Imaging of
Single Particles, Clusters, and Biomolecules (SPB)
at the European XFEL**

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Uppsala, Sweden

A.P. Mancuso
European XFEL GmbH
Albert-Einstein-Ring 19
Hamburg
22761 Germany

H.N. Chapman
Center for Free Electron Laser Science
DESY & University of Hamburg
Notkestraße 85
Hamburg
22607 Germany



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1 Preamble

This document describes the findings and recommendations of the inaugural SPB workshop held in Uppsala, Sweden, in November 2008, which was hosted by David van der Spoel and Janos Hajdu of Uppsala University. This summary addresses three key areas: the scope of the SPB instrument required to perform single particle imaging science, elements of the design of this instrument, and the ramifications for the beamline and facility posed by the scope (particularly the proposed photon energy range) of the instrument.

Due to the relatively long delay between the workshop date and the publication of this report, recent developments, advances, and observations obtained from experiments at FLASH and LCLS, and from the analysis of their data, have been considered in this report. In particular, since the time of the workshop, it has become apparent that nanocrystals are an attractive and complementary sample to single particles, and present an alternative route to successful analysis [3]. The instrument also aims to accommodate this imaging modality, as the requirements are not substantially different from that for single particle imaging, and as the potential benefit is high.

The workshop addressed three main areas: the defining science, the instrument required to perform experiments related to this science, and, importantly, the required data analysis tools to interpret the unique, voluminous data sets that are expected to be produced.

Three working groups met during the workshop:

- WG 1: Instrumentation (Convener: Henry Chapman)
- WG 2: Simulation of signal formation and radiation damage (Convener: Guyla Faigel)
- WG 3: Data analysis and its needs (Convener: David van der Spoel)

The results of these working groups are presented below without making reference to the specific group. New results are added where considered useful.

2 Scope of the instrument

The SPB instrument will be designed to image single particles, which explicitly includes:

- 1) Isolated, non-crystalline biomolecules
- 2) Nano-crystals of biomolecules
- 3) Atomic clusters
- 4) Other single particles, in particular, those of a “reproducible” nature

This scope defines important parameters, such as:

- 1) Maximum sample size
- 2) Beam size at focus/foci
- 3) Wavelength range of incident beam
- 4) Detector parameters, such as pixel number and size
- 5) “Smart” beamstop parameters

- 6) Sample delivery mechanisms
- 7) Required sample to detector(s) propagation distance
- 8) Volume and length of the X-ray hutch required for the instrument

3 Outline of the instrument

3.1 Schematic of the apparatus

The diffraction imaging interaction chamber and detector arrangement

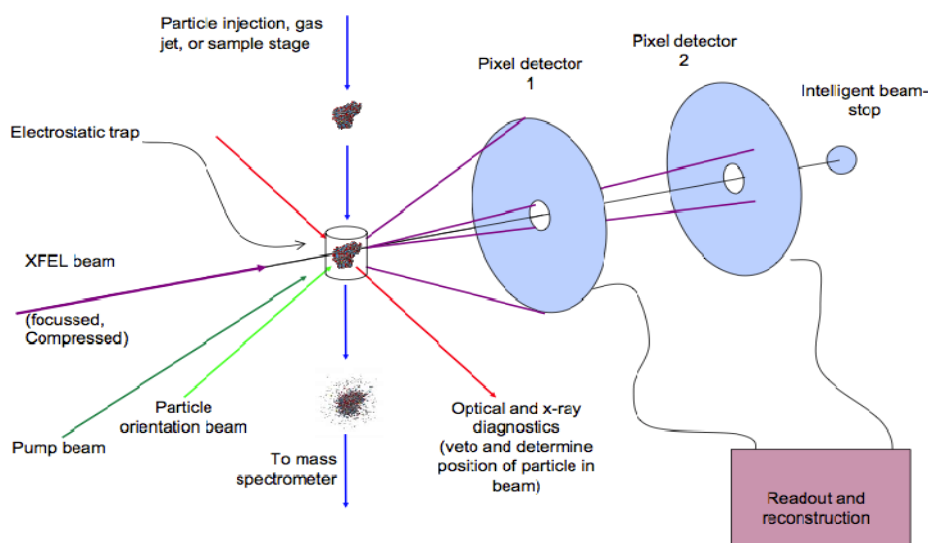


Figure 1. Schematic of the proposed SPB instrumentation

3.2 Desired focusing

The desired (and in some sense required) focusing depends chiefly on the spatial size of the samples to be imaged. At SPB, the imaging of very large specimens (i.e. tens of microns), such as whole eukaryotic cells, is not envisaged. This essentially leaves two spatial scales to be investigated. The first addresses proteins and clusters, which have a size of typically less than 100 nm in diameter, and the other is on the less than 1 μm scale (including large complexes, such as the Nuclear Pore Complex, etc. [1]). The discussions at the workshop considered that the focal size should be larger than the sample itself (to minimise the intensity variation in the sample illumination) and recommended a 5 μm , a 2 μm , and a 100 nm focus. It is difficult to envisage a reproducible sample that is as large as 5 μm , so an approximately 1 μm focus and a 100 nm focus are considered herein.

3.3 Sample delivery method(s)

A variety of sample delivery (injection) technologies was presented at the workshop. These technologies included droplet sources, scanned fixed samples, ions, and aerodynamic sources. Scanned samples may include objects arranged on a substrate in a regular grid (or located in pre-

measured positions). Each position in the array can be hit once by an FEL pulse in the fashion of “diffraction before destruction”. Samples may include 2D crystals [2] embedded in a thin layer of ice. This implies that a cryogenic sample stage is required. Given that the damage width from a single shot is about 50 microns, and that one may require 10^6 patterns, the stage must access at least $50 \times 50 \text{ mm}^2$.

Recent demonstrations have shown that liquid jet technology and aerodynamic injection technology are viable methods of delivering single particles to an FEL beam. In particular, water jets have been used to deliver nanocrystals to FEL beams [3], and aerodynamic injection systems have been demonstrated in single-particle diffraction experiments at FLASH [4] and LCLS [5]. Aerosols are generated by various means, including electrospray ionization, nebulization, or spark generation. These aerosols are delivered to the FEL beam by entraining charge-neutral particles into a narrow beam using an aerodynamic lens stack. The lens stack consists of a series of orifices and differentially pumped skimmers that bring particles into an axial flow while reducing the pressure of the gas medium. Aerosols of charged particles can additionally be trapped or focused using electrostatic or RF fields. Aerodynamic delivery systems are considered perhaps more useful for single molecule systems, as they eliminate the large amount of water surrounding the sample, which would likely obfuscate the scattering signal of a single molecule inside. The injection system should include a trap or efficient pump to remove the spent sample from the chamber environment.

A further option is the use of an ion injector to deliver and trap ionized samples in the interaction region. This method was recently demonstrated for biological macromolecules [6] and may represent another path to injecting samples into the interaction region.

Time-resolved structural studies often require an optical pump pulse, which may either need to be integrated with the beamline (e.g. co-linear with the X-ray beam) or integrated with the injector. These types of experiments also require diagnostics to measure the relative timing of the pump and probe pulses, such as photodiodes or pulse-arrival monitors (such as currently under development at LCLS). If the pixel detector is sensitive to visible light, it will require a filter to prevent contamination of the diffraction data by the pump pulse. Optical pulses may be used not only to photoexcite samples but to prepare them in other ways, such as aligning molecules.

3.4 Required detector parameters

The detector parameters include pixel size, total number of pixels, frame rate, buffer size, dynamic range, noise level, and others. An important experimental parameter for coherent imaging is the sampling of the diffraction pattern, which is accounted for by the pixel size and the available propagation distance.

- 1) Noise level. The detector must be single photon sensitive to 5σ (at least at low intensities), or data from weakly scattering single particles will not be able to be interpreted. The presence of false signals in the diffraction data has the potential to limit the assembly of many very weak 2D diffraction patterns into a single 3D pattern. Even at higher intensities, the noise must be lower than the Poisson noise due to the photon counting statistics.

- 2) Dynamic range. The bigger the better. The range of relevant spatial length scales in a sample often spans two orders of magnitude,

$$\frac{S_{object}}{d_{res}}, \text{ where } S_{object} \text{ is the size of the sample and } d_{res} \text{ the resolution}$$

and the measured intensity drops off with spatial frequency as [7]

$$I(f) \propto f^{-m}, \text{ where } f \text{ is spatial frequency and } m = 3-4.$$

At high resolution, the molecular and atomic structure of proteins becomes apparent, giving a fall-off of $m \leq 2$, as observed in SAXS or crystallography measurements. Nevertheless, spanning the full diffraction intensity range implies that an ideal dynamic range of five to six orders of magnitude would be required. As such, a dynamic range represents a formidable technical challenge in detector manufacture, as high as practically possible is desired. An upstream and downstream detector (which measure high and low spatial frequencies, respectively) ameliorates the need for a single detector to span the entire dynamic range.

- 3) Pixel size. The required pixel size is governed by the size of the sample, the propagation distance between sample and detector, and the desired sampling rate of the diffraction data. For realistic values of sample size (1 μm), propagation distance (4 m), wavelength (1 \AA), and sampling ($\sigma \geq 4$), we find that the pixel size of the proposed AGIPD detector of 200 μm is not intrinsically a limiting factor, assuming enough pixels are available. For samples larger than 1 μm , smaller pixels or longer propagation lengths than envisaged would be necessary to satisfy the sampling condition. Relaxing the sampling condition to the theoretically possible $\sigma \geq 2$ brings a commensurate increase in the size of sample we can investigate; however, $\sigma \geq 4$ is a conservative and viable sampling ratio to invert experimental data.
- 4) Number of pixels. For single objects, the number of (useful) pixels is limited by the bandwidth of the incident radiation. Assuming 0.5% natural bandwidth and a safe sampling ($\sigma \geq 4$), very few pixels can be exploited (however, see recent work by Abbey et al. [8], which indicates it may be possible to lift this restriction if the spectrum was measured on each pulse), but, using a monochromator of 1×10^{-4} bandwidth with the same sampling, we find that detector widths of more than 2 000 pixels can be usefully exploited. The pixel requirement is similarly increased when the sample exists in the form of a crystal or nanocrystal, as the often narrow peaks produced from these specimens must be located and their centroids found. For imaging the fringes around these narrow peaks must also be resolved. In these cases, it is conceivable that even higher pixel counts are required.

For imaging single particles, with a detector of limited pixel number, the number of resolution elements in a reconstructed image is limited to

$$N_{res} = \frac{N_{det}}{2\sigma},$$

where σ is the linear sampling ratio. An experimentally conservative sampling ratio is four (4), while the theoretical minimum is close to two (2) [9].

- 5) Frame rate. Ideally, the detector should work at a frame rate commensurate with the rate that pulses are delivered.
- 6) Buffer size. As large as can practically be built.
- 7) Linearity. Linear or well-calibrated, in particular distinguishing single photon counts at low intensity and linear to within Poissonian statistics for higher intensities.
- 8) Geometry. Two (or more) part detector with upstream and downstream components for high and low resolution information respectively. An aperture of adjustable size in the centre of the detector to allow the direct beam (and low resolution information) to pass through the detector is required.

3.5 “Smart” beam stop

1) Single shot intensity monitor

The total intensity of each pulse needs to be monitored on a shot-to-shot basis. This could be done with a Gas Monitor Detector (GMD), for example.

a) Wavefront monitor and intensity profile monitor

It is beneficial to know the intensity and wavefront profile of the incident FEL pulses at the sample position, in the case that these pulses are structured on the same scale as the samples under investigation. One way in which this could be monitored is through the use of a profile monitor to observe the undiffracted beam at the most downstream position of the hutch. Such a monitor would compose of a 2D detector to measure the intensity profile, which could then be used to retrieve the wavefront properties through computational methods.

b) Other monitors (e.g. pulse duration)

A host of other diagnostics will be required for the efficient and convenient operation of the SPB instrument. Here we highlight the potential usefulness of a pulse duration monitor, which would be of value in the imaging problem (knowing the pulses are “short” allows one to make assumptions about the dynamics of a sample’s structure during the pulse) as well as for pump-probe measurements (to help determine accurate time resolutions). At present, the technology to make this measurement shot-to-shot does not yet exist in a form that is compatible with simultaneous diffraction measurements, though developments in this direction should be noted and incorporated in the SPB instrument, if possible. Some ideas for pulse duration determination rely on measurement of the pulse spectrum, which, as noted above, may also be necessary to improve the extraction of sample structure data from diffraction patterns.

3.6 Required sample to detector distance

The required propagation distance is a function of the detector pixel size, wavelength λ of the radiation and the size w of the sample under investigation. Essentially, the angle subtended by a pixel must be less than half the period of the finest fringe pattern generated by the sample, or $\alpha_{\text{pixel}} < \lambda / (2w)$. This requirement also depends on the detector modulation transfer function, which describes the detected contrast of a 100%-contrast fringe pattern incident on the detector and is related to the point spread function or degree of crosstalk between pixels.

4 Desired energy range for the beamline

The instrument should operate at the longest wavelength that supports the desired resolution. As not all applications require atomic resolution, this means exploring softer photon energies than initially envisaged. At the time of the workshop, SPB (at the SASE 1 beamline) was proposed to operate at a fixed energy of 12.4 keV. To accommodate longer wavelengths, this specification has since been revised. The minimum energy now possible is 3 keV; however, the minimum energy where 4σ of the beam is transmitted is conservatively estimated to be 5 keV, due to limitations in the length of the beam delivery mirrors [10]. Additionally, the desire to span a greater range of wavelengths (including extending the short wavelength limit) is motivated by methods of phasing single-particle and nanocrystal data using anomalous dispersion at elemental absorption edges.

4.1 Ramifications for beamline optics

The key ramifications of catering to lower energies for the beamline optics, is the need for longer mirrors to be used as the wavelength of the incident radiation increases. The finite length of state-of-the-art mirrors gives rise to the limitations described in the preceding paragraph.

5 Signal formation and radiation damage

The signal formation and radiation damage working group (WG) found that further modeling of damage and signal formation processes, preferably using the method of Molecular Dynamics (MD), is necessary. The WG identified the need to remain aware of progress at FLASH regarding experimental insights into photon-matter interactions, but was confident the key interactions have been identified, however the cross-sections for some processes need to be refined. More detailed information can be found in Appendix C, "Working Group II Report: Signal formation and radiation damage".

6 Data analysis tools and computational requirements

The workshop acknowledged that novel data analysis methods need to be, and are presently being, developed to interpret the type of data collected and to handle the large amounts of data expected to be collected. These include (but are not limited to) the Bayesian method of Ourmazd et al. [11] and the method due to Elser et al. [12]. Both of these methods are designed to work with the very low diffraction signals expected from hard X-ray, single molecule coherent imaging work.

Parallelized software for nanocrystallography has been developed and has demonstrated processing over 10^7 diffraction patterns, which needs to be scaled up for XFEL data rates.

7 Geometrical considerations

7.1 Required propagation distance

The instrument should accommodate a sample to detector distance that is commensurate with sampling the diffraction signal from an object of at least 1 μm in extent, and preferably more.

7.2 Required hutch volume

The hutch should comfortably house all the required instrumentation described herein. In particular, the hutch should be long enough to accommodate a downstream wavefront sensor. A sample preparation laboratory is also required to be located very near to the hutch, to optimize preparedness of specimens, and hence most effectively use the FEL beam.

8 Conclusions and recommendations

The authors conclude that, to serve the widest interests of the scientific community, the SPB instrument should be developed to include:

- A broad photon energy range that includes Ångström scale resolution as well as softer (down to 3 keV) x-rays.
- Two focal sizes, one of $\sim 1 \mu\text{m}$ and the other 100 nm, as well as access to the unfocused beam
- Two sample injection systems, one aerosol-based and the other liquid-jet-based
- A cryogenic scanning sample stage able to access at least $50 \times 50 \text{ mm}^2$
- Two pixel detectors built to the specifications described within this report
- A “smart” beamstop that includes a single shot flux monitor, a wavefront/beam profile monitor, and as many other diagnostics as practical

Furthermore, the custodian(s) of the SPB instrument should be actively involved in the development of data analysis tools and data handling procedures to most effectively use the unprecedented amount of data that is expected to be created at the instrument.

With these recommendations in mind, it is clear that an instrument with the above capabilities will be a broadly useful, user-accessible instrument for future single particle imaging at the European XFEL.



Figure 2. Participants in the inaugural SPB Workshop in Uppsala, Sweden (November 2008)

9 References

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A Workshop participants

Speakers

Name	Affiliation	Email
Bogan, Michael	SLAC, Stanford, USA	mbogan@SLAC.Stanford.EDU
Bortel, Gábor	Solid State Physics and Optics, Budapest, Hungary	gb@szfki.hu
Boutet, Sebastian	SLAC, Stanford, USA	sboutet@slac.stanford.edu
David, Christian	Paul Scherrer Institut, Switzerland	Christian.david@psi.ch
Elser, Veit	Cornell University, USA	ve10@cornell.edu
Graafsma, Heinz	DESY, Hamburg, Germany	heinz.graafsma@desy.de
Grossmann, Jörg Günther	Liverpool University, UK	j.g.grossmann@dl.ac.uk
Hajdu, Janos	Uppsala University, Sweden	janos@xray.bmc.uu.se
Hau-Riege, Stefan	Lawrence Livermore National Laboratory, USA	hauriege1@llnl.gov
Kewish, Cameron	Paul Scherrer Institut, Switzerland	cameron.kewish@psi.ch
Kuepper, Jochen	Fritz-Haber-Institut der MPG, Berlin, Germany	jochen@fhi-berlin.mpg.de
Maia, Filipe	Uppsala University, Sweden	filipe@xray.bmc.uu.se
Möller, Thomas	Technical University Berlin, Germany	Thomas.moeller@physik.TU-Berlin.de
Nave, Colin	Diamond Light Source, UK	colin.nave@diamond.ac.uk
Ourmazd, Abbas	University of Wisconsin– Milwaukee, USA	Ourmazd@uwm.edu
Thibault, Pierre	Paul Scherrer Institut, Switzerland	pierre.thibault@psi.ch
Tschentscher, Thomas	XFEL Inc. Germany	thomas.tschentscher@desy.de
Weierstall, Uwe	Arizona State University, USA	weier@asu.edu
Ziaja-Motyka, Beata	DESY, Hamburg, Germany	ziaja@mail.desy.de

Organizers

Name	Affiliation	Email
Van der Spoel, David	Uppsala University, Sweden	spoel@xray.bmc.uu.se
Faigel, Gyula	Solid State Physics and Optics, Budapest, Hungary	gf@szfki.hu
Chapman, Henry	DESY, Hamburg, Germany	henry.chapman@desy.de
Pfeiffer, Franz	Paul Scherrer Institut, Switzerland	franz.pfeiffer@psi.ch

Participants

Name	Affiliation	Email
Abela, Rafael	Paul Scherrer Institut, Switzerland	rafael.abela@psi.ch
Altarelli, Massimo	XFEL Inc. Germany	massimo.altarelli@xfel.eu
Andreasson, Jakob	Uppsala University, Sweden	jakoba@xray.bmc.uu.se
Beitra, Loren J.	London Centre for Nanotechnology, UK	l.beitra@ucl.ac.uk
Caleman, Carl	Technical University Munich, Germany	carl.caleman@tum.de
Ekeberg, Tomas	Uppsala University, Sweden	ekeberg@xray.bmc.uu.se
Epp, Sascha	Center for Free Electron Laser Science, Hamburg, Germany	sascha.epp@mpi-hd.mpg.de
Fersini, Francesco	EMBL Hamburg, Germany	f.fersini@embl-hamburg.de
Friemann, Rosmarie	Uppsala University, Sweden	rosie@xray.bmc.uu.se
David, Gauthier	CEA Saclay, France	david.gauthier@cea.fr
Gabrysch, Markus	Uppsala University, Sweden	markus.gabrysch@angstrom.uu.se
Gorelick, Sergey	Paul Scherrer Institut, Switzerland	sergey.gorelick@psi.ch
Groves, Matthew	EMBL Hamburg, Germany	Matthew.Groves@embl-hamburg.de
Gruebel, Gerhard	DESY, Hamburg, Germany	gerhard.gruebel@desy.de
Isberg, Jan	Uppsala University, Sweden	jan.isberg@angstrom.uu.se
Jurek, Zoltan	Solid State Physics and Optics, Budapest, Hungary	jurek@szfki.hu
Kolesar, Vladimir	P. J. Safarik University, Slovakia	vladimir.kolesar@upjs.sk
Kono, Hidetoshi	Japan Atomic Energy Agency, Kyoto, Japan	kono.hidetoshi@jaea.go.jp
Mancuso, Adrian	DESY, Hamburg, Germany	adrian.mancuso@desy.de
Merdji, Hamed	CEA Saclay, France	merdji@drecam.cea.fr
Meulen, Peter van der	Stockholm University, Sweden	meulen@physto.se
Serguei Molodtsov	XFEL Inc. Germany	serguei.molodtsov@desy.de
Moribayashi, Kengo	Japan Atomic Energy Agency, Kyoto, Japan	moribayashi.kengo@jaea.go.jp
Möller, Thomas	Technical University Berlin, Germany	thomas.moeller@physik.tu-berlin.de
Ortiz, Carlos	Uppsala University, Sweden	carlos.ortiz@fysik.uu.se
Papiz, Miroslav	University of Liverpool, UK	miroslav.papiz@stfc.ac.uk

Name	Affiliation	Email
Petri, Marcel	Max Planck Institute for Biophysical Chemistry, Göttingen, Germany	Marcel.Petri@mpibpc.mpg.de
Potdevin, Guillaume	DESY, Hamburg, Germany	guillaume.potdevin@desy.de
Rolles, Daniel	Center for Free Electron Laser Science, Hamburg, Germany	daniel.rolles@asg.mpg.de
Salén, Peter	Stockholm University, Sweden	peter.salen@physto.se
Schropp, Andreas	Technical University Dresden, Germany	andreas.schropp@physik.tu-dresden.de
Schulze-Briese, Clemens	Paul Scherrer Institut, Switzerland	clemens.schulze@psi.ch
Schwenke, Jörg	MAXLAB, Lund, Sweden	jorg.schwenke@maxlab.lu.se
Seibert, Marvin	Uppsala University, Sweden	marvin@xray.bmc.uu.se
Stellato, Francesco	Università di Roma Tor Vergata, Italy	stellato@roma2.infn.it
Stevens, Gregory	University of Zurich, Switzerland	gregory.stevens@bioc.uzh.ch
Svenda, Martin	Uppsala University, Sweden	martin-s@xray.bmc.uu.se
Tegze, Miklos	Solid State Physics and Optics, Budapest, Hungary	mt@szfki.hu
Thomas, Rich	Stockholm University, Sweden	rdt@physto.se
Timneanu, Nicusor	Uppsala University, Sweden	nicusor@xray.bmc.uu.se
Ulfat, Intikhab	Chalmers University, Sweden	intikhab@chalmers.se
Ullrich, Joachim	Max-Planck-Institut fuer Kernphysik, Heidelberg, Germany	c.ries@mpi-hd.mpg.de
Uppsten, Malin	Uppsala University, Sweden	malin-u@xray.bmc.uu.se
Vartaniants, Ivan	DESY, Hamburg, Germany	ivan.vartaniants@desy.de
Wang, Fenglin	DESY, Hamburg, Germany	fenglin.wang@desy.de
Wrona, Krzysztof	DESY, Hamburg, Germany	wrona@mail.desy.de

B Workshop program

Thursday, 20 November 2008

13:00 Welcome

Session I: Plans for X-ray FELs

13:15–14:15 Th. Tschentscher – Status of the European XFEL and plans for a SPB instrument

S. Boutet – Status of the CXI instrument at LCLS

Session II: Scientific cases and samples for particle CDI experiments

14:15–15:15 2 talks, 25+5 min:

- U. Weierstall – Serial crystallography
- J. Hajdu – Cell and bio-particle experiments

15:15–15:45 Coffee break

15:45 – 18:15 5 talks, 25+5 min:

- C. Kewish – Potential of coherent diffractive imaging for protein-nano-crystallography at future XFEL sources
- C. Nave – A comparison of synchrotrons and free electron lasers for X-ray diffraction from sub-micron-sized samples
- Th. Möller – Structure determination of atomic clusters
- J. Küpper – Coherent diffractive imaging of conformer selected and oriented (bio-)molecules
- S. Hau-Riege – Influence of radiation damage

ca. 19:30 Dinner (Uppsala restaurants; suggestions will be provided)

Friday, 21 November 2008

Session III: X-ray delivery and instrumentation (cont'd)

- 8:30–11:00 5 talks, 25+5 min:
- C. David – Nano-focusing x-ray FEL beams
 - P. Thiebault – Ptychography at XFEL sources: wavefront and focal spot characterization
 - M. Bogan – Targeting the XFEL Bulls-eye: Substrate-Free Sample Delivery
 - G. Grossmann – Trapping particles for CDI experiments
 - H. Graafsma – Area detectors for CDI experiments

11:00–11:30 Coffee break

Session IV: Data analysis

- 11:30 – 13:30 4 talks, 25+5 min:
- G. Bortel – Classification of one million noisy, random orientation single molecule diffraction patterns
 - A. Ourmazd – Single step orientation
 - V. Elser – Reconstructing objects from noisy and randomly oriented diffraction patterns
 - F. Maia – Image reconstruction from dynamical objects

13:30–14:30 Lunch

Session V: Instrumentation working groups

- 14:30–18:00 I. Instrumentation (e.g. injectors, x-ray delivery)
Convener: H. Chapman
- II. Simulation of signal formation and radiation damage
Convener: G. Faigel
- III. Data analysis and its needs
Convener: D. van der Spoel
- 19:00 Workshop dinner

Saturday, 22 November 2008

Session VI: Instrumentation working groups

9:00–10:30 Continue working groups and drafting initial working group reports

10:30–11:00 Coffee break

Session VII: The scientific goal

11:00–11:45 WG chairs – Presentation of working group findings

11:45–12:45 Final discussion:

- Identification of most promising science cases
- Distribution of tasks for preparation of workshop report

12:45–13:00 NN – Summary and closure of the workshop

13:00 Lunch

End of workshop

C Working Group II Report: Single formation and radiation damage

G. Faigel, Solid State Physics and Optics, Budapest, Hungary

The working group based the discussion on the general talks in the main part and on six topical talks.

Topical talks:

- Alternative damage models:
 1. Molecular Dynamics model, Zoltán Jurek
 2. Hybrid model, Nicusor Timneanu
 3. Boltzmann transport model, Beata Ziaja
 4. Hydrodynamic model, Gyula Faigel
- Signal formation:
 5. Signal formation in single-particle XFEL imaging, Stefan Hau Riege
 6. Effect of signal degradation and noise on classification, Miklós Tegze

In these talks, the basics and also the latest developments in the field were introduced.

The talks were interactive in the sense that questions were raised during these and the unclear points were clarified immediately. This allowed a much closer interaction between participants. After the talks, the group formulated a common view on some basic questions introduced by the coordinator, and added new questions, as necessary.

These form the basis of the recommendations of the working group.

Sample dynamics

Q1. In which direction (on which damage model) should we put more emphasis?

A1. There is a general agreement between the results of all models. We have to use all models, but we should put the most emphasis on the MD calculations, because we need more and more details to plan experiments and to develop the evaluation procedure. This type of modeling is the most relevant from the point of view of signal formation, since it gives the changing coordinates of all particle (including electrons) and also the ionization states of atoms. This allows the precise calculation of diffraction patterns.

Q2. Are all the basic interactions and processes taken into account well enough, or is there a need for basic research in some area?

A2. Interactions and processes are well identified, but cross sections for highly charged states are uncertain. More work is needed both theoretically and experimentally to obtain reliable cross sections and ionization potentials. Interactions at soft X-ray energies seems to be more complicated (inverse Bremsstrahlung and the effect of classical field should be revisited).

Q3. Is the effect of tamper layer (thickness, composition) well understood?

A3. Basically, yes; however it needs tailoring to every sample. To optimize the effect of tamper, it is recommended to do detailed model calculations before every experiment.

Q4. How does the shape of the molecule effect the shielding (spatial distribution of electrons)?

A4. It has not been investigated. Needs MD modeling.

Q5. What is the effect of sample composition (local inhomogeneities, heavy atoms)?

A5. Average composition is not enough to describe local distortions in inhomogeneous samples. It seems that, for every sample, we need a model calculation to optimize the experimental conditions and facilitate the evaluation process. Needs more study by MD.

Q6. How good is the classical approach?

A6. At high electron energies, it seems to be OK (at the beginning of the pulse), but at longer time scales, there might be significant deviations. More work is needed on this. First of all, we have to explore the literature (on plasma); there are relevant works to be understood.

Signal formation

Q1. Do we understand signal formation (background, time integration, other)?

A1. The basics are understood (elastic scattering from the sample, time integration), but details are not worked out. Needs much more modeling based on MD results. Better estimation of background contributions is needed, and the effect of coherence and wave front distortion should also be studied.

General remarks

The WG has to keep a close connection, first of all with the data analysis WG, but also with the instrumentation WG. The results of radiation damage and signal formation modeling is crucial to successful and correct data evaluation and also for planning the experimental setup.

Validation of modeling by experiments should be done as soon as possible (electron energy, ion energy, and spatial distributions, etc.). One should use data taken at FLASH, but the extension of the analysis to higher energies is not straightforward. Therefore, early experiments at LCLS are essential.

Non-scientific questions

Q1. Do we need a central facility supplied by XFEL, which can calculate the behaviour of the sample? Or should everybody do this for themselves?

A1. Yes, this type of facility would be very advantageous. It would facilitate planning experiments and crosstalk between different areas. Having this facility would increase the success rate of experiments.

Q2. Can we form an interest group (or working group), which work together and update XFEL staff on the most important advances, needs in this area?

A2. Yes

Q2a. How should it operate?

A2a. We should establish common benchmarks, literature database, experimental data bank (sharing), etc.

Q2b. Who will coordinate it?

A2b. It should work under the XFEL umbrella. The coordinator could be the leading beamline scientist. We envisage two levels: the first level for SPB and the second level for the three subgroups.

Q2c. Who will take part in it?

A2c. There should be a sign in form on the homepage. A reminder should be sent out to the workshop participants and other potential experts.