

Industry

- 1) Polovodiče a.s., Prague.
- 2) Reflex s.r.o., Prague.
- 3) Vakuum Praha, Prague.
- 4) Delong Instruments, Prague.
- 5) Crytur s.r.o., Turnov.

Slovakia, Hungary and Poland (selected as an example)

1) Crystal optics group at the Electrotechnical institute at the SAS in Pieš any.

- 2) Multilayers for SR at the Institute of Physics of the SAS in Bratislava.
- 3) X-ray holography at the Institute for Solid State Physics in Budapest.
- 4) X-ray waveguides at the Institute of Physics at the PAS in Warsava.

During and after the realization of the synchrotron source, formation of many new groups is expected.

OPPORTUNITIES FOR PROTEIN CRYSTALLOGRAPHY AT THE CENTRAL EUROPEAN SYNCHROTRON LABORATORY

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We were witnesses of a huge increase of knowledge about life sciences in the last three decades. We already understand many processes taking place in organisms on a molecular level. We understand many intermolecular interactions governing the immune reactions of organism against diseases or parasites and are beginning to understand differences between proteins from different organisms and therefore we have tools to design new generation drugs highly efficient against bacteria and viruses, without causing any harm to human or animal health. We understand better the processes of aging, the deceases causations and new positive habits are gradually introduced into the daily life of people. The life expectancy increased by 10–15 years during this period of understanding the principles of life on the molecular level.

Diffraction analysis of the structure of biological macromolecules utilizing synchrotron radiation is behind these changes positively influencing the quality and length of our lives. The structure and function of most of biological molecular systems known today was elucidated using this particular method. Structures determined by protein crystallography comprise more than 90 % of all structures deposited in the Protein Structure Database and almost 6 000 new records accumulates each year, most of them originating from synchrotron radiation sources.

Structure biology and diffraction methods

The necessity of synchrotron radiation for the development of our knowledge on the life nature (from biology, agriculture up to medicine and health care) follows namely from the fact that there is no other method allowing an efficient direct observation of such a large molecular complexes with sufficient accuracy. Thanks to synchrotron radiation we can observe the spatial structure of molecular systems composed of millions of atoms and observe the interplay and cooperation of many tenths of macromolecules. This knowledge is principal for understanding a function of living organisms (e.g. elucidation of structure and function of ribosomes). Moreover, using the synchrotron radiation one can achieve such high accuracy of measurement that a

transfer of a single electron can be detected even in large proteins explaining thus an immense increase of catalytic efficiency seen in enzymes, etc.

Special experiments also allow an imaging of the structure changes taking place during the biochemical reaction with a speed higher than it is necessary for direct observation of most of the biochemical reactions (~ 100 ps). In addition to quick, reliable and accurate imaging of the structure, a special configuration of beamline allows observation of the dynamics of the molecular systems.

The scientific use of synchrotron radiation and applications resulting from protein structure analysis in industry, medicine and health care were the reasons why 17 sources of synchrotron radiation have been build in the western region of the European Union, thus providing more than 40 diffraction beamlines for advanced measurements in this part of Europe.

Contrary to the rapidly growing number of synchrotrons in the western part of EU, the eastern region of Europe (Czech Republic, Poland, Slovakia, Slovenia, Hungary, Austria, Bulgaria, Romania, Latvia, Estonia, Lithuania) have no experimental arrangement of this type to date.

Diffraction beamlines at the synchrotron sources around the world

There are more than 70 sources of synchrotron radiation build in 23 countries all over the world, most of them in Japan, EU and USA (see Table 1).

Synchrotrons have usually several beamlines dedicated to the macromolecular crystallography (Table 2). A priority has the Advanced Photon Source (APS) in Chicago with 18 beamlines specialized on protein crystallography. The number of dedicated beamlines is roughly proportional to the number of newly produced structures of macromolecular complexes per year. For example, 45 beamlines in the EU correspond to 1700 solved structures and 75 macromolecular beamllines in United States correspond roughly to 2800 protein structures solved in the USA in 2007.



Table 1. Sources of synchrotron radiation have already been built in more than 20 countries. The table summarizes the sources with energy of electrons from 0.3 to 6 GeV. The number in the third column shows the total number of synchrotrons build in the country. All information used in table is based of actual information on WEB servers of different quality and are a subject of changes in the course of time.

Country	Installation site	No.	Country	Installation site	No.
Germany	BESSY, ELSA Bonn, DELTA Dortmund, DORIS, PETRA, ANKA Karlsruhe	6	USA	APS Argone IL, CAMD LA, Duke NC, ALS Berkeley CA, SURF-3 NIST MD, CHESS Ithaca NY, Stanford CA, Aladdin WI, NSLS I and II Upton	13
France	ESRF Grenoble, SOLEIL St. Aubin, LURE Orsayv (closed)	3	Japan	Hiroshima, Nano-Hana, Kashiwa (Tokio), SPring-8 (Nishi-Harima), Kusatsu, Okasa- ki, Tsukuba (Teras, NIJI II,IV, Photon Fac- tory, Accum.Ring KEK), Sendai, Tosu, Rokkasho	17
Sweden	Lund, MAX I, II, III, IV	4	Russia	DELSY Dubna, Siberia I,II –Moscow, VEPP 2M, 3, 4M, Siberia SM (Novosibirsk)	7
Denmark	Aarhus	2	China	Beijing, Hefei NSRL (Univ. Sci & Tech. od China), Shanghai SSRF }Inst. Nucl. Res.	4
Italy	ELETTRA Trieste, Frascati	2	Ukraine	Charkov Pulse Stretcher, Kiev ISI-800	2
GB	Diamond, SRS	2	Jordan	Sesame	1
Switzerland	SLS Villigen (Paul Scherrer Institute)	1	India	Indore	1
Spain	ALBA Barcelona (in construction)	(1)	Brazil	Campinas LNLS	1
Czech Republic	Central European Synchrotron Laboratory, Brno (project only)	0	South Korea	Pohang	1
Singapore	Nakhon Ratchasima SSLS (Nat. Univ. of Singapore)	1	Canada	Saskatoon	1
Taiwan	Hsinchu, SRRC (Synch. Rad. Res. Ctr.)	1	Australia	Melbourne	1
Thailand	NSRC (Siam Photon)	1	Armenia	CANDLE Yerevan (project only)	0

Diffraction beamlines at the Central European Synchrotron Laboratory

Because of necessity of a close cooperation between the two beamlines and also similar equipment required in the adjacent laboratories, the group for molecular structure determination is divided into three parts:

Macromolecular Structure Beamline-1 (MSB-1)

Laboratory of the complex molecular systems maintaining the operation of beamline MSB-1 supports a quick, reliable and accurate structure determination of large molecular complexes.

Experimental technique: Source of radiation for MSB-1 is an undulator optimized for the use at the fixed wavelength $\sim 1\,$ Å. The X-ray optics offers a diameter of the primary beam from 10 to 200 $\,$ m with optimum for $\sim 50\,$ m. The precise micro-diffractometer with more circles will allow for 100% completeness of the collected experimental data. Automated changer of the liquid nitrogen cooled samples pre-prepared in the standardized Dewar vessels assures quick and safe mounting and dismounting of measured

crystals. Cryocooling and the in-line microscope for sample centering are required. High speed CCD detector (read-out time in parts of second) with large detection area optionally allows a continuous data collection without use of the shutter providing thus new challenges in accuracy of structure determination.

Because of rapid development in the synchrotron instrumentation, the final detailed choice of suppliers and the equipment parameters should be done later.

Macromolecular Structure Beamline-2 (MSB-2)

Laboratory of anomalous diffraction maintaining the operation of beamline MSB-2 is specialized to MAD and SAD structure determination, reliable location of ions in biomacromolecular structures, and other specialized tasks. *Experimental technique*: Source of radiation for MSB-2 is undulator easily and reliably tunable in a range of wavelengths 0.6-2.0 Å. The X-ray optics will have the optimum characteristics for diameter of primary beam $\sim 50~$ m at sample. Fluorescence detectors are necessary for exact set-



Table 2. Beamlines dedicated to protein crystallography at some sources of synchrotron radiation. A priority in a number of beamlines devoted to macromolecular crystallography has APS in Chicago (10 for MAD measurements, 6 monochromatic, 1 for fibre diffraction and 1 for membrane proteins). The BM in the beamline name is for "Bending Magnet" and the ID is for undulator ("Insertion Device").

Synchrotron	Names of macromolecular beamlines		
APS Argonne NL	5ID-B 8-BM 14-BM-C 14-BM-D 14-ID-B 17-BM 17-ID 19-BM 19-ID 21-ID-D 21-ID-F 22-BM 22-ID 23-BM-B 23-ID-B 23-ID-D 24-ID-C 31-ID other: 18-ID		
NSLS Brookhaven	X3A X4A X4C X6A X8C X9A X9B X12B X12C X25 X26C X29A other: X1A X3B		
SSRL Stanford U.	BL1-5 BL7-1 BL9-1 BL9-2 BL11-1 BL11-3 BL12-2 other: BL4-2 BL6-2 BL7-3 BL9-3		
ALS Univ. CA	4.2.2 5.0.1 5.0.2 5.0.3 8.2.1 8.2.2 8.3.1 other: 12.3.1		
CHESS Cornell U.	A1 F1 F2		
CAMD Louisiana	GCPCC		
ESRF Grenoble	BM1A BM14 BM16 BM26 BM30A ID09 ID13 ID14-1 ID14-2 ID14-3 ID14-4 ID23-1 ID23-2 ID29		
DESY Hamburg	BW7A BW7B X11 X12 X13 X31 BW6		
MAXII Lund	I711 I911-1 I911-2 I911-3 I911-4 I911-5		
SRS Daresbury	PX7.2 PX9.5 PX9.6 PX10.1 PX14.1 PX14.2		
DIAMOND UK	I02 I03 I04 I04.1 micro I24 polymers I22 small I19 powder I11		
BESSY Berlin	14.1 14.2 14.3 (7T-WLS-2 superconducting WLS)		
LURE Orsay	DW21B DW32 D41A		
SLS PSI Villigen,	X06SA X10SA		
SOLEIL Saint-Aubin	ID-10C ID-10M		
ELETTRA Trieste	5.2R (another under construction)		
Spring-8 Japan	BL12B2 BL24XU BL26B1 BL26B2 BL32B2 BL38B1 BL40B2 BL41XU BL44B2 BL44XU BL45XU		
Photon Factory Japan	BL-5A BL-6A BL-17A BL-18B AR-NW12A		
LNLS Brazil	D02A-SAXS2 D03B-MX1 W01B-MX2		
NSRRC Taiwan	BL13B1 BL13C1 BL17B2		
PAL PLS Pohang	6B-MX1 6C1-MX2 4A (high flux)		
BSRF Beijing	3W1A 1W2B		
AS Melbourne	3-BM1 3-ID		

tings of the optimum wavelengths for anomalous diffraction measurements. The beamline is equipped by microdiffractometer with the automated sample changer, cryocooling and the in-line microscope. High speed CCD detector (read-out time in parts of second) with a large detection area optionally allows for a continuous data collection without use of shutter.

Because of rapid development in the synchrotron instrumentation, the final choice of suppliers and the equipment parameters should be done later.

Working group for structure analysis

The group maintains the operation of laboratories necessary for fluent operation of both beamlines MSB-1 and MSB-2. It includes the physical and chemical laboratories (microscopes, lasers, consumables), biochemical laboratory (crystallizer, incubators, storage boxes, freezer, microscopes, consumables), cold room (microscope, storage boxes) and computing room (terabyte data storage and optical network for high-speed transmission of data to the users home laboratories).



The group should conduct its own scientific activities oriented to the development of technologies for the structure determination and especially to the topics dependent on the heavy use of synchrotron radiation. The workers will be evaluated not only for services provided to the guest scientists, but equally for their scientific work.

In spite of the fact that the design of the diffraction beamlines at synchrotron in Brno is economic, it will provide above standard services compared to standing synchrotron facilities at this time [2]. It will also ensure new more advanced technologies for the structure determination and refinement of large molecular complexes.

The group will run its own scientific research oriented on topics extremely demanding for synchrotron measurements. For example systematic analysis of structure variations and movements due to the environment changes (pollutants, pH changes, etc.), analysis of interactions between bio-macromolecules and polymers used in food, cosmetics, drug preparations, etc. These topics are painful for external laboratories just because of problems with frequent transport of many sensitive samples. Having a local laboratory will ensure 100% usage of both beamlines because it can exploit any excessive time in cases where external users are not able to use all their regularly ordered beamtime.

The experimental equipment of the diffraction beamlines is designed to allow also the standard structure determination of organic or inorganic compounds, minerals, polymers, etc. if required.

Challenges of the diffraction beamlines at the CESLAB and benefits for Eastern Region of the European Union

Geographical aspects

Diffraction beamlines in Brno will provide quick and easy access for all interested users from densely populated region containing many university towns comprising more than 40 million inhabitants (Czech Republic, Slovakia, Hungary, Austria, Slovenia, the south Poland). The town Brno lies at a distance of 2–3 hours of travel from the capitals of four countries of the European Union (Praha, Wien, Bratislava, Budapest – an agglomeration of 5 millions of inhabitants). In addition, three of these countries concentrated 90 % of their research into these towns. In spite of the fact that these countries have a large research potential, none of them has any synchrotron equipment.

Other users of diffraction beamlines are expected also from more distant areas (the north Poland, Latvia, Estonia, Lithuania, Bulgaria and Romania). They will be offered the possibility to send flash frozen samples via FEDEX and to perform the experiment with the beamline scientist on line communicating with the guest scientist via camera. The interest from the western European countries already possessing synchrotrons can be expected namely in the case of special services that are not available at their local beamlines.

Short distances are significant for protein crystallography because the sample preparation for measurement is usually very expensive, time consuming and the samples are very sensitive and often loose quality with time. That is

also the reason why the diffraction beamlines for protein crystallography require specialized laboratories with a cold room in very close proximity and specialized personnel providing necessary help to the synchrotron users.

The principal task of the diffraction beamlines at the CESLAB is an encouragement of the structure biology oriented research in the East European region with the aim to increase efficiency of R&D results in practical applications and thus exploit fully a large potential in universities and the applied research in this area.

Protein crystallography in the Czech Republic

Medical and biological sciences in the Czech Republic are on high level and the numbers of scientists and their results correspond to the European level. For example, almost 10 % of all complexes of HIV protease deposited in the PDB [2, 3] were published by Czech groups; the structure of protein with the lowest R factor was refined by Ondráček *et al*, 2007; structure determination of large complexes with molecular weight 640 kDa (Skálová *et al*, 2006) [4], etc. However, because of critical lack of experimental time at synchrotrons the number of scientists really solving the crystal structures is several times lower than it is in the west part of the EU. In spite of this fact, the quality of published papers is high in comparison with the world average. However, the Czech structure biology has problems because of critical absence of the synchrotron time.

A total number of people interested in macromolecular structure determination using synchrotron radiation are estimated more than 200 in the Czech Republic. Some of them took part in the education activities of the Czech and Slovak Crystallographic Association (CSAS) and also published their contributions in our journal Materials Structure (www.xray.cz/ms). The courses of "Protein crystallization" passed more than 100 students, the "practical courses on structure determination" passed more than 40 students, the conference "STRUCTURE-2006" organized by our Association in Grenoble (France) had almost 90 participants from the Czech Republic, etc. The list of laboratories working in the protein crystallography in the Czech and Slovak Republics is attached at the end of this paper.

It is supposed that protein crystallographers will form more than of the synchrotron users. To the date, there are more than 20 laboratories in the Czech Republic that depend on the use of protein crystallography (the list is in the Appendix). In the whole region, there are to this date about 50 laboratories interested in this type of research. The number of users of synchrotron radiation will increase several times soon after the access will be made easier and the waiting periods for access to measurement is shorter.

In spite of the fact that the Czech Republic is a partial member of ESRF, the long-term average of the awarded macromolecular beamline time was one day per year for the whole country and that is a critical situation. The percentage of the used time awarded to the member state is realized mostly at non-diffraction beamlines with low competition of users. The situation in the Czech Republic is provisionally solved by most of laboratories via cooperation with some laboratory in another country, where the synchrotron radiation is easily available. However, the necessity of these measures critically restrains the develop-



Table 3. Some references to the synchrotron radiation on WEB

Sources of radiation for crystallography Synchrotron sources of the world

Synchrotrons in the USA
ALBA, Spain
ESRF Grenoble, France
Anomalous scattering, ID29 at ESRF
ELETTRA, Trieste, Italy
MAX-LAB, Lund
LURE laboratory, Kr a Xe prot.crystallography
synchrotron radiation source
NSLS Brookhaven (www.nsls.bnl.gov)
SSRL Berkeley (Advanced Light Source)
Advanced Photon Source at Ar.Nat.Lab
South Korea
BESSY, Berlin
HASYLAB, Hamburg

ment of the structure biological sciences in the Czech Republic including the numerous applications and inventions resulting from this research. We cannot judge the situation in the nearest countries (Slovakia, Hungary and Poland), but for the external observer the situation appears similar to here.

Conclusions

Enormous revenues of pharmaceutical companies rank them in between the most profitable branches of the world economy. Their incomes are greatly influenced by the latest results of molecular biology. The strong competition for patent priority (the winner takes all) helped in building of large synchrotron facilities with many diffraction beamlines in all advanced countries.

The community of structure biologists in the Czech Republic has restricted access to these facilities and is strongly handicapped by a critical lack of measuring possibilities. The same situation is in all new countries of the EU.

It is evident, that the project of Central European Synchrotron Laboratory (CESLAB) and construction of the diffraction beamlines in the Brno region will bring a remarkable contribution to the advancement of the European science. It will bring many advantages for better cooperation between universities, academic research and industrial companies and thus it is promising for the future economy in this developing part of the European region.

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Appendix

List of some laboratories active in the macromolecular structure determination by synchrotron radiation in the Czech and Slovak Republics

Institute of Macromolecular Chemistry, Academy of Sciences, Laboratory for structure analysis of molecules

Contact: RNDr. Jindřich Hašek, DrSc tel. 267 809 390, hasek@imc.cas.cz, http://www.imc.cas.cz or http://www.xray.cz

Institute of Molecular Genetics, Academy of Sciences Laboratory of Structure Biology

Contact: Ing. Pavlína Řezáčová, PhD tel: 220 183 212, rezacova@img.cas.cz, http://www.img.cas.cz

Institute of Microbiology, Academy of Sciences, Praha Laboratory of Molecular Genetics of Bacteria

Contact: RNDr. Marie Weiserová, PhD tel. 241 062 386, weisero@biomed.cas.cz



Institute of Organic Chemistry and Biochemistry, Academy of Sciences, Department of Biochemistry and Molecular Biology, Proteases of Human Pathogens

Contact: Ing. Jan Konvalinka, PhD tel: 220 183 218, www.uochb.cz,

http://www.uochb.cz/web/structure/232.html?lang=cz

Institute of Microbiology, Academy of Sciences, Praha Laboratory of molecular biology of Bacterial Patogens

Contact: Ing. Petr Šebo, PhD

tel. 241 062 762, sebo@biomed.cas.cz,

http://www.img.cas.cz/public/skupiny/Sebo.html

Institute of Macromolecular Chemistry, Academy of Sciences, Laboratory of X-ray and neutron scattering

Contact: Ing. Josef Pleštil, CSc, tel. 267 809 388, plestil@imc.cas.cz, http://www.imc.cas.cz

Charles University, Faculty of Mathematics and Physics, Department of Biomolecular Physics, Physical Institute of the Charles University

Contact: RNDr. Ivan BARVÍK Jr., PhD, tel. 221 911 450, ibarvik@karlov.mff.cuni.cz, http://biomolecules.mff.cuni.cz

Charles University, Faculty of Science and Institute of Microbiology Academy of Sciences, Department of Biochemistry

Contact: Prof. RNDr. Karel Bezouška, CSc, tel. 221 951 272, bezouska@natur.cuni.cz, http://www.natur.cuni.cz

Charles University, Faculty of Science, Praha, Biophysical chemistry of protein complexes

Contact: RNDr. Tomáš Obšil, PhD tel. 221 951 303, http://www.natur.cuni.cz/~obsil, http://www.natur.cuni.cz/~pmc

Biotechnological Institute, Academy of Sciences, Praha, Laboratory of Engineering of Binding Proteins

Contact: Ing. Petr Šebo, PhD tel. 241 062 762, sebo@biomed.cas.cz

Institute of System Biology and Ecology, Academy of Sciences, Nové Hrady,

Laboratory of advanced computation techniques

Contact: Doc. RNDr. Rudiger Ettrich, PhD tel. 386 361 297, ettrich@greentech.cz, http://www.usbe.cas.cz

South Bohemia University České Budějovice, Institute of Physical Biology, Nové Hrady

Contact: Mgr. Ivana Kutá Smatanová, PhD tel. 608 106 109, ivas@greentech.cz, http://www.usbe.cas.cz/index.php?node=365

Pharmaceutical Faculty of Veterinal and Pharmaceutical University in Brno

Contact: Doc. Ing. František Pavelčík, DrSc tel. 541 562 843, pavelcikf@vfu.cz

Masaryk University, Brno, Institute of Experimental Biology

Contact: Doc. RNDr. Jaromír Marek, PhD tel. 549 49 5740, marek@chemi.muni.cz http://www.sci.muni.cz/main.php?stranka=31U4010&po dtext=20

Masaryk University, Brno,

National Center for Research of Biomolecules

Contact: Doc. RNDr. Michaela Wimmerová, Ph.D., http://www.muni.cz/people/854 tel. 549 49 3805, michaw@chemi.muni.cz, http://www.chemi.muni.cz/ncbr/ncbr.html

Mendel University of Agriculture and Forestry Institute of Molecular Biology and Radiobiology, Molecular Biology Group

Contact: Doc. RNDr. Břetislav Brzobohatý, CSc http://www.ibp.cz

Technical University of Ostrava (VŠB) Nanotechnology Centre

Contact: Prof. RNDr. Pavla Čapková, DrSc http://www.cnt.vsb.cz/oblasti/o-centru

Palacký University, Olomouc, Faculty of Natural Sciences, Department of biochemistry

Contact: Prof. Mgr. Marek Šebela, PhD tel. 585 634 927, marek.sebela@upol.cz, http://www.biochemie.upol.cz

Institute of Molecular Biology, Slovak Academy of Sciences, Laboratory of Protein Crystallography

Contact: Ing. Jozef Ševčík, DrSc tel. 02 5930 7435, http://imb.savba.sk

Institute of Molecular Biology, Slovak Academy of Sciences, Department of Microbial Genetics

Contact: RNDr. Imrich Barák, DrSc tel. 02 5930 7418, http://imb.savba.sk

Institute of Molecular Biology, Slovak Academy of Sciences, Department of Biochemistry

Contact: Ing. Eva Kutejová, CSc tel. 02 5930 7442, http://imb.savba.sk

Institute of Neuroimmunology of SAS, ratislava, Structural Protein Neurochemistry, Biotechnology center

Contact: RNDr. Rostislav Škrabana, PhD tel. 02/60296 594, Rostislav.Skrabana@savba.sk, http://www.niu.sav.sk

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