Project no.: **LSHG-CT-2003-503420**

Project acronym: **BIOXHIT**

Project full name: **Biocrystallography (X) on a Highly Integrated Technology Platform for European Structural Genomics**

Instrument type: **IP**

Priority name: **Life Sciences, Genomics and Biotechnology for Health**

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Project coordinator organisation name: **EMBL Hamburg**

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0. Executive Summary

The European Commission has given Europe a huge boost in the field of structural biology and in particular structural genomics and proteomics, awarding the European leaders in the field 10 Million Euro for the integrated project BIOXHIT. The project aimed to create a common platform throughout Europe for researchers working in the field of biological crystallography. BIOXHIT stands for "Biocrystallography on a Highly Integrated Technology Platform" for European Structural Genomics. The goal has been to take the best of current technologies at major European centres for research in structural biology, develop them further and weave them into a single platform that integrates and standardises the best of current technology, and spread it throughout Europe with the aim of providing new effective tools for understanding complex biological processes at the molecular level.

The BIOXHIT project was launched on January 1st, 2004. Within its lifetime of 4.5 years, the BIOXHIT Partners set out to develop, assemble and deliver an integrated platform for high-throughput structure determination using X-ray crystallography with synchrotron radiation. BIOXHIT has brought together scientists from all European synchrotrons and leading software developers in both academic and industrial groups in a timely and unprecedented joint effort. The ambitions of the project's objectives, the inter-dependence of its research tasks and a combination of a strongly focused research programme with networking, training and mobility of staff have been addressed under an efficient management structure.

The BIOXHIT developments spanned the whole range of components required for an efficient high-throughput "pipeline" linking the crystallisation of a protein to the delivery of its 3D-structure, and requiring minimal user intervention due to its integrated logistics. Although the developments keep being deployed and tested, the main project results have become fully accessible to the wider life sciences research community. Remote access facilities and an extensive program of training and dissemination at both synchrotron facilities and at satellite centres formed an essential part of the project's activities.

In this short executive summary we are not attempting to distil all the scientific achievements and breakthroughs that occurred during the last year and a half of the project. For details, the reader may advance to page **12**, the Annexes to this final activity report as well as to the four periodic activity reports where detailed progress has been reported in all 141 scientific tasks and 37 training, dissemination and management tasks that were active throughout the project. It is important to note that all the 178 project tasks were continuously reviewed and modified to make them reflect the development of the state-of-the-art, both within the project as well as elsewhere.

One immediate effect of BIOXHIT, which benefits the community already now, is a significant reduction in the time involved in obtaining each structure. Robots, for example, can perform tasks automatically, quickly, and at a consistent and high precision, replacing time-consuming manual steps. The project specifically calls for improvements in the process by which samples are handled, the equipment needed to detect X-ray patterns, and the computers and software needed to model structures. A result of this more researchers will be attracted to work on 3D protein structures.

BIOXHIT has definitely contributed to make Europe a substantial player in this area. As well as uniting technologies, BIOXHIT has also led to the integration of other relevant European and national activities, giving us the strength to be a major competitor in structural proteomics on a global scale.

Training activities are a cornerstone of the project. Four advanced Training, Implementation and Dissemination centres have been created outside the participating laboratories to disseminate the BIOXHIT know-how. A proactive training effort has first taken place at synchrotron facilities, and then was spread to satellite centres to disseminate technologies in biological crystallography to local European communities.

1. Project execution

1.1. General project objectives

The recently acquired knowledge of a large number of genome sequences provides a unique opportunity to decipher quantitatively the roles of biological molecules in complex processes within cells, organs and organisms. An essential step in accomplishing this is the determination of their atomic structures allowing a more complete description of the roles of molecules in living systems, both in health and disease. Acquiring structural information on biological macromolecules on a genomic scale constitutes the heart of structural proteomics. The only techniques for determining 3D structures of biological macromolecules at atomic detail and at an appropriate rate are biological X-ray crystallography (biocrystallography) and NMR-spectroscopy. Biocrystallography has been responsible for about 85% of all biomolecular structures (and for 95% of all but the smallest proteins) deposited in the Protein Data Bank (http://www.rcsb.org/pdb) and the Molecular Structural Database (http://www.ebi.ac.uk/msd/). Biocrystallography has undergone a tremendous transition in the last decades: whereas determining a macromolecular crystal structure used to require years, it now typically may take only a few weeks, if not days; and the potential for further acceleration is far from exhausted. Furthermore, recent technological advances have made a wide range of new biological problems amenable to crystallographic study. Although obtaining large amounts of a protein in soluble form is still in many cases an important issue, biocrystallography is in principle applicable to the complete spectrum of biological macromolecules, from all organisms (eubacteria and archeae to human) and of all sizes (from small domains to gigantic ribosome or virus particles).

The cornerstone of any HTP structural initiative is synchrotron radiation. While about 10 to 15 years ago most 3D-structures of biological macromolecules were still solved using X-ray laboratory sources, the use of synchrotron radiation is now paramount. Synchrotron radiation is indispensable because of its intensity, which is many orders of magnitude higher than that of laboratory sources, its low divergence, which is required to resolve in detail the observed diffraction data and of its tuneability, which gives access to a versatile experimental method for solving the so-called “phase problem” by exploiting anomalous dispersion.

Funding bodies in the United States and Japan have years ago recognised the importance of synchrotron-based HTP technologies in structural biology and their vital strategic importance for functional genomics/proteomics projects *[Structural Biology and Synchrotron Radiation: Evaluation of Resources and Needs*, **BIOSYNC**, 1997; http://www.ornl.gov/hgmis/biosync/*]*. This has led them to fund a large-scale development effort at central research facilities, particularly at synchrotron sites, together with a number of major SG initiatives in North America and in Japan, most of them with guaranteed and dedicated synchrotron beamline access. The most recent **BIOSYNC** report (before the start of BIOXHIT) from October 2002 *[Biological Applications of Synchrotron Radiation: An Evaluation of the State of the Field*, **BIOSYNC**, 2002; http://biosync.sdsc.edu/*]* strongly recommended that the funding for synchrotron facilities in the USA be increased even further. Although this was recognised in Europe *[Review of the needs for European synchrotron and related beam-lines for biological and biomedical research*, **ESF**, 1999; http://www.esf.org/*]*, no large-scale concerted funding scheme has yet been implemented. The Sixth Framework Programme of the European Commission, with its vision of integrating and strengthening the *European Research Area*, provided a timely opportunity for a major effort in support of European structural biology, in the form of an integrated project with a thematic emphasis on the development of HTP technologies. BIOXHIT is precisely such a project.

The central objective of the BIOXHIT project was to face the challenge posed by the structural genomics initiatives already underway in the USA and in Japan, and to develop, assemble, standardise and provide a highly integrated technology platform for HTP structural biology. This could only be achieved through a coordinated project’s effort in bringing together 28 research groups and a few subcontracted SMEs in Europe, with all of them being at the forefront of technical methodologies and scientific insight in 3D macromolecular structure determination. Biocrystallography is the method of choice, and synchrotron radiation is the principal source of X-rays for data acquisition. The project Partners comprise all European synchrotron radiation facilities (including those which have been under design or construction) and

internationally recognised European leaders in hardware and software development directly related to high-throughput methodologies.

The user-base for biocrystallography is becoming ever larger as more and more laboratories undertake such studies. However, the actual work is increasingly carried out by researchers who are not specialist-crystallographers. This puts a heavy onus on the Partners to develop more robust and automated procedures, allowing HTP with the minimum intervention from the user, whilst maintaining clear laboratory records of the procedures employed and retaining high quality of the measured data and consequently the models derived. This needs the mobilisation of the Partners' expertise and resources through efficient collaboration.

The approach proposed within BIOXHIT for Europe may be contrasted with that adopted in the USA for pilot structural genomics programs. In the USA, a number of independent pilot projects were set up to develop and apply technology for HTP protein structure determination. No attempt was made to coordinate the work among the various projects. This coordinated approach for structural biology hardware and software gives the following advantages:

(i) sufficient experience exists to select one, or a small number, of developments for each area to be addressed
(ii) the sharing of the resultant developments, within a standard framework, will mean that resultant procedures can be quickly implemented at many facilities
(iii) the cost of such an integrated approach will be considerably less than individual uncoordinated actions
(iv) there will be a significant benefit for the users of the facilities as they will have a common standard for both sample transportation and for carrying out the data collection.

European synchrotron facilities are eager to adopt this approach. The developers themselves are aware of the fact that the user-base for biocrystallography is becoming ever larger as more and more laboratories undertake such studies, and that the actual work is increasingly carried out by researchers, who have little or no crystallographic expertise. Having had, separately, to address the challenge of developing more robust and automated procedures, they are now ready to face it collectively by designing and producing, in a stepwise manner, increasingly integrated software, endowed with extensive capabilities for communication with synchrotron hardware. This fully integrated combination of instrumentation and software is the ultimate aim of BIOXHIT. Through the establishment of this state-of-the art capability, BIOXHIT will be instrumental in increasing European competitiveness in Structural Biology and will provide an essential resource to all future structural proteomics and related projects in Europe.

Within its life time of four years the BIOXHIT project set out to deliver:
(i) an extension of the limits of current crystallisation technologies towards the use of smaller crystallisation drops, less protein consumption, higher quality crystals for X-ray diffraction, enhanced stability of crystals in the X-ray beam
(ii) advanced synchrotron beamline technologies developed towards standard, automated and easy-to-operate beamlines providing high quality stable X-rays automatically delivered to the sample
(iii) improved means of automated and reliable handling and characterisation of crystals in order to optimally plan the actual diffraction experiment
(iv) a structure determination pipeline consolidated from the bottom-up to ensure the success of the experiment at the earliest possible stage and to allow direct feedback to data collection and crystallisation
(v) a logistics architecture geared towards maximum automation, efficient data management and full project tracking including the possibility of remote control
(vi) efficient bioinformatics software developed to link the above steps together
(vii) high level training in new hardware and software technologies provided to researchers both within and outside the BIOXHIT consortium.

The developments in BIOXHIT were aimed to create the capability not only of solving macromolecular structures at a higher rate, but also of producing better data and hence higher-quality structural results than what was possible before. This technology encompasses the components necessary to produce an efficient

pipeline linking crystallisation to 3D-structure determination. It operates with minimal user intervention and is fully accessible to the wider life sciences research community. The outcome of BIOXHIT is targeted towards an increase in European competitiveness in structural biology, and hence in all the biomedical, biotechnological and pharmaceutical commercial sectors.

An important objective is the appropriate training of the rapidly growing user community. For this purpose, BIOXHIT's programme has included an establishment of a number of Training, Implementation and Dissemination (TID) centres outside the participating laboratories to disseminate the know-how, according to the directives set out in the Framework 6 guidelines. The software integration effort has already culminated in the creation of remote access facilities, which will enable users to operate the HTP facilities from their home laboratories through secure Internet connections. The BIOXHIT training model with the establishment of the TIDs has already now proven very successful and has received praise from both the project SAB and external reviewers.

By the start of BIOXHIT in January 2004 there were seven European synchrotrons (DESY, SRS, ESRF, ELETTRA, MAXLAB, SLS, BESSY) with a total of approximately 30 beamlines for biological crystallography. The definition and implementation of standards for those beamlines were major deliverables of BIOXHIT. Common beamline control and data collection software should require less training for users visiting different synchrotron sites and make X-ray diffraction experiments more efficient. Standardised equipment such as crystal mounts and containers should allow the transport of prepared samples to any synchrotron. The combination of state-of-the-art instrumentation and software was the ultimate aim of BIOXHIT.

Standards for Data Management and Data Exchange are vital if the results of the technological developments within BIOXHIT were to be exploited to their full potential. The HTP platforms result in a large volume of data that must be tracked, stored and made available to others both during and after the structure determination process. The need for robust and reliable data storage, annotation and transfer is addressed and here BIOXHIT closely follows the standardisation developments in other projects (including SPINE and e-HTPX, PIMS and others through regular coordination meetings.

The BIOXHIT project was designed and, as we witness by now, has become instrumental in increasing European competitiveness in Structural Biology and already provides an essential resource to all future structural genomics/proteomics as well as other types of HTP projects in Europe. In the long term, BIOXHIT will also have the lasting effect of spawning extensive collaboration between the Partners, which will encourage them to mobilise new resources to pursue this collaboration further.

1.2. Contractors involved

The scale of BIOXHIT requires a concerted effort of European centres that lead the field in the development of technology and the provision of automated and integrated facilities in the field of biocrystallography. In order to meet the proposed objectives of BIOXHIT the Partners have been carefully selected according to their expertise and their potential contributions to the overall project. BIOXHIT has mobilised on the one hand all European synchrotron facilities with beamlines equipped for macromolecular crystallography, either already in existence at the start of the project (DESY, ESRF, SRS, SLS, ELETTRA, MAXLAB) or planned or under construction during the course of the project (SOLEIL, DIAMOND, LLS, PETRA); and on the other hand most of the software developers active in fields relevant to HTP structure determination. This represents the greatest possible mobilisation of resources at the European level, both in terms of infrastructure and of scientific talents. The 21 Partners (comprising 23 research groups from 10 European member states), Table 1, fall into five categories:

(i) Core development and implementation sites (Partners 1A, 2, 3 and 4). By the beginning of 2004 these were the major European synchrotron sites EMBL/DESY Hamburg, ESRF Grenoble, SRS Daresbury and SLS Villigen. Based on their history and their experience in constructing, maintaining and operating synchrotron beamlines for a large user community, they fully contributed to many workpackages and constituted the sites for early implementation of the BIOXHIT pipeline.

(ii) Central contributors to software and hardware developments (Partners 1B, 1C, 5, 7, 9, 10, 11 and 13). These partners are identified based on their core expertise, which is absolutely essential to the overall goals of the project.

(iii) Leading research groups in the field (Partners 6, 8, 12, 14, 15, 16 and 21). This group of Partners provided a special expertise relevant to a given area of the project; therefore, their contributions are limited to a few workpackages. Nevertheless, the contributions from these Partners are essential to reach the overall goals of BIOXHIT.

(iv) New and future synchrotron sites (Partners 17, 18 and 19). This group of Partners contributed much less compared to other Partners to the science and technology developments of BIOXHIT. The three future synchrotron sources were observing the developments, were able to steer them by discussions with other Partners, and had full access to them once it became important with respect to implementing BIOXHIT developments at the their sites.

(v) Exploitation and intellectual property expert (Partner 20) The SME EMBL-EM has been chosen to work out possible exploitation of knowledge-mechanisms together with the Management Team of BIOXHIT.

In addition, there are 6 more research groups involved in BIOXHIT as third parties, Table 1. They do provide a contribution to the project, which however is rather narrow and intricately linked to the contributions of other Partners, see the table below. Involvement of these third parties proved essential to enable BIOXHIT to make use of their specific expertise.

The BIOXHIT Partners comprised the authors of programs and packages in worldwide use in macromolecular crystallography, such as the CCP4 suite, MOSFLM for data integration, SHELXD for substructure solution, SHARP for experimental phasing, ARP/wARP for automated map interpretation and model building, REFMAC for structure refinement (Partner 8). These packages constituted the 2004's state of the art in their respective domains of application. They have already been used as basic building blocks in the ongoing efforts to assemble HTP structure determination capabilities in the US.

Table 1. BIOXHIT Partners and their institutions.

Partner Role[1)]	Partner No in Annex 1	Partner No in CPFs	Partner name	Partner short name	Country	Date enter project	Date exit project
CO	1A	1	EMBL Hamburg	EMBL-HH	DE	1	54
CR	1B	4	EMBL Grenoble	EMBL-GR	FR	1	54
CR	1C	7	EBI Hinxton	EMBL-EBI	UK	1	54
CR	2	2	ESRF Grenoble	ESRF	FR	1	54
CR[5)]	3	3	SRS/STFC Daresbury	CCLRC(SRS)	UK	1	54
CR	4	5	SLS Villigen	PSI	CH	1	54
CR	5	6	Global Phasing Ltd. Cambridge	GPHL	UK	1	54
CR	6	8	NKI Amsterdam	NKI	NL	1	54
CR	7	9	ELETTRA Trieste	ELETTRA	IT	1	54
CR	8	10	University of York	UOY	UK	1	54
CR	9	11	PSF Berlin	FUB	DE	1	54
CR[5)]	10	12	CCP4/STFC Daresbury	CCLRC-CCP4	UK	1	54
CR[2)]	11	13	AFMB Université Aix-Marseilles	UNIV-MRS	FR	1	54
CR	12	15	University of Göttingen	UNIGOE	DE	1	54
CR	13	17	SOLEIL Saclay	SOLEIL	FR	1	54
CR[2)]	14	18	IFOM Milano	FIRC-IFOM	IT	1	54
CR	15	20	MAXLAB-Lund University	MAXLAB	SE	1	54
CR	16	21	University of Copenhagen	UKBH	DK	1	54
CR	17	24	DIAMOND Chilton	DIAMOND	UK	1	54
CR	18	25	LLS Barcelona	LLS	ES	1	54
CR	19	26	HASYLAB/DESY Hamburg	DESY	DE	1	54
CR	20	27	EMBLEM	EMBLEM	DE	1	54
TP	1A	16	Max-Planck Group Hamburg	MPG-ASMB	DE	1	54
TP	2	14	IBS Grenoble	IBS	FR	1	54
TP	2	19	MRC-LMB Cambridge	MRC-LMB	UK	1	54
TP[2)]	11	22	LEBS-CNRS Gif-sur-Yvette	LEBS-CNRS	FR	1	54
TP	12	23	IBM Barcelona CSIC	IBM	ES	1	54
CR[3)]	21	28	University of Vienna	UNIVIE	AUT	13	54
TP[4)]	22	29	University of Oxford	UOX	UK	37	54

[1)] CO = Coordinator, CR = Contractor, TP = third party.

1.3. Work performed and end results

For full details on the worked performed and the end results achieved within BIOXHIT the reader is referred to the four year annual periodic activity reports and their annexes. Below only a brief summary is presented.

After some delay in hiring during the first year, the number of the EC-funded appointments within BIOXHIT has reached the expected level during Years 2-4 of the project, Figure 1. Overall, more than 200 researchers, with 70 funded by the project, have been working on BIOXHIT goals at the various Partners' institutions. Averaged over the 4.5 years about 30 researchers have been fully employed and in total the project has supported 127 EC-funded person-years. The full list of the BIOXHIT EC-funded personnel is given in Annex 4.1 to this report.

Overall, BIOXHIT was generally well on schedule, despite the initial delay in hiring. However, some activities suffered from the fact that the funding came to an end after month 54 and that during Year 4 a number of BIOXHIT-employed people moved on to take up other appointments before projects are finished. As a result, some of the planned deliverables were defined as '*delayed beyond BIOXHIT*', in the sense that although for most of them their development is continuing, the results were not achieved by the time the project came to an end.

In total 299 deliverables had been planned throughout the project, Table 2. The majority of them, 240, have been successfully achieved during the project. 37 deliverables are denoted as '*delayed beyond BIOXHIT*' since some activities are indeed continuing after the end of the project and will produce a few more of the anticipated results. Some of the initially foreseen developments became obsolete or turned out to be intractable within a reasonable amount of time and with reasonable effort. Consequently, such tasks were considered abandoned within the timeframe of BIOXHIT and the respective 22 deliverables cancelled. Similar situation is with the project's milestones, Table 2. Out of 94 planned milestones 82 have been reached, 11 are delayed to beyond BIOXHIT and 1 was cancelled. Thus the overall success of the project is evident and it is a consequence of the efficient monitoring of Partners' activities. However it also reflects the fact that many Partners mobilised significant resources, which were not funded from BIOXHIT.

Table 2. Overview of the status of the BIOXHIT milestones and deliverables throughout the whole duration of the project. Their availability for general public (e.g. a web link) is described in annual period reports and their annexes.

Milestones				**Deliverable**			
total	**achieved**	**delayed to beyond BIOXHIT**	**abandoned**	**total**	**achieved**	**delayed to beyond BIOXHIT**	**abandoned**
94	82	11	1	299	240	37	22

The launch of the project followed the BIOXHIT kick-off meeting in Hamburg in April 2004. The 1st Annual Project Meeting was held in Barcelona on December 1-4, 2004 as part of an EU Joint Meeting for projects in Structural Genomics and Proteomics. The 2nd Annual Meeting was at the ESRF premises in Grenoble, France, on January 18-19, 2006 and the 3rd at the DIAMOND site in Didcot, UK, on February 20-21, 2007. The final project meeting took place in Hamburg from April 17-18, 2008. Particularly the third and the forth year projects are described in more detail below. Prior to the 3rd BIOXHIT Annual Meeting a one-day conference on "*The Role of Structures in Biology – Past, Present and Future*" was held at he premises of Project Partner 17, Diamond on 19th February 2007. International experts in the field of the use of synchrotron radiation in biological research presented their point of view as well as representatives from major funding agencies and the industrial sector. The conference was followed by the 3rd BIOXHIT Annual Meeting, 20th – 21st February 2007. BIOXHIT highlights from each scientific Section including lectures from two of the BIOXHIT TID centres were presented. This was accompanied by poster presentations from the BIOXHIT community as well as some external guests. The topics covered crystallisation technology,

synchrotron beamlines, beamline end-stations and data collection, data processing and structure determination, databases and networking, training, implementation and dissemination. Out of the anticipated 140 participants more than 40 were interested scientists from outside the BIOXHIT project and company representatives. In addition, a British company, Molecular Dimensions Ltd., Suffolk, UK, requested and was granted to organise an exhibition stand at the conference. Prior to the 4th BIOXHIT Annual Meeting a one-day conference on "*Synchrotrons and Lasers for Structural Systems Biology*" was held at the premises of Partners 1A and 19 on 16th April 2008. In six keynote lectures international experts in the field of the use of synchrotron radiation in biological research have presented their point of view of what the future of Structural Biology may look like once the new X-ray sources become available. The conference was followed by the 4th BIOXHIT Annual Meeting, 17th-18th April 2008. 22 BIOXHIT highlights from each scientific Section including those from the four BIOXHIT TID centres and representatives of the user community were presented. The meeting was accompanied by 27 poster presentations from the BIOXHIT project as well as some external attendees. The topics covered crystallisation technology, synchrotron beamlines, beamline end-stations and data collection, data processing and structure determination, databases and networking, training, implementation and dissemination. Out of the 150 participants more than one third were interested scientists from outside the BIOXHIT project and company representatives. The large number of participants demonstrates the advancement of many BIOXHIT tasks that have become ready for a wider dissemination to the scientific community. It also portrays the close cooperation of BIOXHIT with related EU-projects. Finally, it shows that BIOXHIT is a project with high visibility and a strong impact in the scientific community.

Table 3 Keynote lectures and BIOXHIT highlight presentation as well as the poster presentations given at the project's kick-off and annual meetings and adjacent conferences.

	Keynote lectures	**BIOXHIT highlight lectures**	**Poster presentations**
First annual meeting	n/a	12	11
Second annual meeting	4	10	25
Third annual meeting	11	19	28
Forth annual meeting	6	22	27
Total	**21**	**63**	**91**

In addition to the annual meetings and the conferences, many BIOXHIT workshops or ad-hoc meetings on specific scientific topics were organised. There were 5 of those in 2004, 14 in 2005, 15 in 2006, 12 in 2007 and 9 in 2008 thius totalling to 55 workshops. The workshops covered not only activities from the scientific sections as well as the training activities organised by the BIOXHIT TID centres, but also collaborations with other projects, such as SPINE2, PIMS or DNA. All of the workshops were well attended and provided a forum for fruitful interactions. A notable feature of the overall pattern of activities is the unprecedented degree of collaboration between groups of scientists associated with various European synchrotrons. The establishment of a close and productive cooperation between the staff at synchrotron beamlines, and of a spirit of collaboration in the pursuit of common solutions to common challenges has been installed and is fundamental to the success of the project.

Overall, the members of the BIOXHIT consortium have been very active in presenting the project and its achievements to the scientific community, journalists and the lay public. 481 lectures were given throughout the project year and 52 tutorials along with 49 workshops. 158 posters were presented at several meetings and conferences. The number of articles published amount to 68. In addition, interviews have been given and websites, slideshows and brochures produced to disseminate the project's results. The full list is given in the Final Plan for Using and Disseminating the Knowledge.

1.4. Methodologies and approaches employed

BIOXHIT objectives involved activities in the following areas:

(i) hardware developments in HTP crystallisation, beamline components and end-station equipment
(ii) software developments in automatic evaluation of crystallisation experiments; beamline automation; automated data collection, data processing and structure determination; data storage, and project information management
(iii) sample preparation, storage, manipulation and handling
(iv) design of innovative protocols for the diffraction experiment itself
(v) aspects of logistics, remote access, remote control and integration
(vi) establishment of European standards in a number of key areas to facilitate the developments in instrumentation and software.

1.5. Impact of the project on its industry and research sector

BIOXHIT was reviewed after two years of its duration (mid-term review) by international experts in the field. The review took place at the occasion of the 2nd Annual Project Meeting in Grenoble, France, January 18-19, 2006. The project Scientific Advisory Board (SAB) also met at the same occasion. The overall evaluation of the project's performance in the first two years by both the reviewers and the SAB was very positive. In general, the SAB stated that "*after two years, BIOXHIT is close to fruition; much of the preliminary work has produced results, which will enter soon the HT structure solution pipeline, with evident benefits for the whole EU structural biology community*". The SAB members met for the next time in February 2007 (month 38 of the project) at the occasion of the BIOXHIT third Annual Meeting. The overall evaluation of the SAB could be exemplified by the statement *"the integration of hundreds of researchers within the same cultural and technological context is an achievement that cannot be underestimated, and is one of the most important results of the Project; a result that cannot be adequately described by any deliverable or milestone"*.

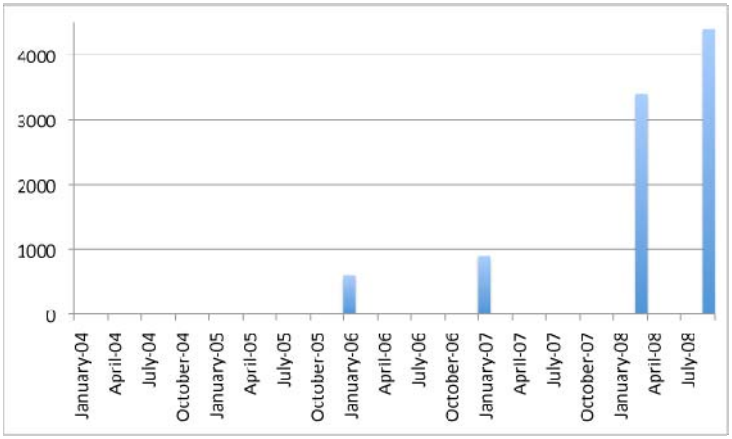
BIOXHIT was again reviewed (consolidated review) shortly after its annual meeting in April 2008 by international experts in the field. The project Scientific Advisory Board (SAB) also met at the same occasion. The overall evaluation of the project's performance by both the reviewers and the SAB was very positive. The overall evaluation of the SAB could be exemplified by the following statements '*BIOXHIT has shown that there is still a major need for further development, in order to exploit the potentials offered by synchrotron radiation in the study of biological matter. There is a growing number of genomes being sequenced in which wide biological variability is evident, but which has been barely explored. There is potential for tackling complex molecular assemblies that regulate much of the cell activity. Macromolecular crystallography, thus, will not simply fill slots in the landscape of individual protein structures, but will provide the framework and stimulating ideas through which biological processes can be interpreted, from the components and their assembly, down to the detailed atomic and mechanistic level. It is quite possible that, in this context, new ways of seeing and interpreting macromolecular 3D structures will emerge.'* and *'BIOXHIT has achieved a unique task in linking together, extremely effectively, the European synchrotron sources, together with some ongoing EC Integrated Projects. It can be firmly stated that investment in the development of SR-based structural biology methods is still an urgent and high level priority, whose outcomes will be critical to the development of advanced biological research on high-complexity systems.'*. The minutes of the SAB are included in the Annexes to the forth annual report.

The conclusions from the consolidated review report (see **Annex 4.2** for details) may be illustrated by the following: *"BIOXHIT is a European effort with the unprecedented task of uniting and significantly improving the efficiency of the European synchrotron sources in the area of structural biology. The accomplishments of BIOXHIT surpass by a large degree any other similar attempts in the US and Asia where such coordination efforts have been rather difficult and largely unsuccessful. In comparison with other similar projects elsewhere in the world, BIOXHIT has managed the tremendous amount of workpackages within the budget and the management team should be commended for their excellent guidance and achievements*.' and '*The BIOXHIT results have already made significant impacts both within and outside Europe and are expected to become even far reaching with a proper continuation or by integrating them into a new integrated project. There is no question that continued research in this fundamental area will continue to be needed and have impact for future basic and applied life science research. If the EU is to continue to be a leader or at a minimum keep up with the worldwide efforts, it is*

critical that a program like BIOXHIT continue over the next several years."

2. Dissemination and use

Dissemination of the results of BIOXHIT has been an important activity of the project. As was mentioned above, almost 500 lectures have been presented by BIOXHIT Partners on various occasions. It can therefore be anticipated that BIOXHIT related developments will the subject of lectures way beyond the lifetime of the project. Further dissemination activities include the regular updates of the official project web site www.bioxhit.org, and a BIOXHIT slide show, which is also published on the project web site. The information on the project is widely disseminated via the Internet and the number of web links mentioning the project (as judged from the number of web pages that mention 'BIOXHIT' as found by Google search engine, Figure to the right) has increased from 600 at the beginning of 2006 to 900 at the beginning of 2007, to 3,400 in March 2008 and finally to 4,400 at the time of this reporting. This demonstrates that BIOXHIT is widely recognised and is making a strong impact in the field of X-ray crystallography for biological macromolecules.



BIOXHIT Google hits

During the course of the project 65 articles have been published in scientific journals on achievements and results obtained throughout the project. It can be anticipated that the publication of further project results will continue beyond the lifetime of the project. In addition to the refereed articles in scientific journal about 500 scientific presentations were held a conferences and meetings and about 160 posters presented. These are listed in the following. Again, it must be anticipated that BIOXHIT related developments will be continued to be presented at scientific conferences for years to come. During the lifetime of the project, a number of articles were published which were targeted at the general public. In addition, a project brochure was created and the project web site designed and built.

The four BIOXHIT Training, Implementation and Dissemination (TID) centres in Oulu, Finland, (http://www.biochem.oulu.fi/BIOXHITWEB/index.html), in Poznan, Poland (http://tid.ibch.poznan.pl/), in Heraklion, Greece (http://www.imbb.forth.gr/people/petratos/index.html) and in Oeiras, Portugal (http://tid.itqb.unl.pt/) have fully matured and towards the end of the project not only carried the main load of the BIOXHIT training activities but they were also actively engaged in dissemination of the project's achievements through their training activities.

The benefits that BIOXHIT is providing for the Structural Biology community are hard to approximate. However, from January 2005 (one year after the start of BIOXHIT) until now about 20,000 three-dimensional structures of biological macromolecules determined by X-ray crystallography using synchrotron radiation have been deposited in the PDB (http://www.rcsb.org/pdb). Our conservative estimate is that BIOXHIT developments have contributed in one way or another to the determination of a considerable fraction of these structures. This demonstrates convincingly that the developments, which BIOXHIT has made to happen, do not only affect the synchrotron and methods development community, but that BIOXHIT is beginning to make a real impact in biological and medicinal research.

3. Project Highlights

In the following a few of the project's achievements are described in more detail.

3.1 Highlights on coupling crystallisation with X-ray data collection

Protein crystallisation is still, after the expression of soluble proteins, the major bottleneck in protein structure determination. Considerable efforts are underway worldwide to enhance the basic understanding of protein crystallisation and to target it towards growing crystalline samples that are sufficiently good to produce diffraction patterns suitable for subsequent X-ray structure determination. One approach is to set up crystallisation experiments in a massively parallel way automatically by robotics, while at the same time minimising protein consumption and enhancing reproducibility. The sheer number of experiments requires that the results and their time dependence are collected automatically and stored in a database. With this enormous amount of data at hand, the outcome of the crystallisation experiments can be linked to the physicochemical properties of the protein and more can be learned about why and when and under what conditions it crystallises. The role of the BIOXHIT project in this was to link the existing and future facilities together and to coordinate them with the needs at the synchrotron beamlines. This should provide the possibility of crystallisation at the synchrotron site, thus allowing direct feedback from the diffraction experiment to the crystallisation. This should also allow crystal improvement studies to be carried out at the synchrotron site in challenging projects, where it has proved difficult to obtain good quality crystals of sufficient size for testing in the home laboratory.

As part of the development of xtalPIMS, Figure 3.1 a, a certain configuration of computing resources to allow access to images has been suggested. This entails one computer to serve images, another to serve the database and a third computer to serve the web site. For smaller labs, it is likely that the database and the imager service functionality will be co-located on the same machine, although this is likely to be dependent on other factors, e.g. the use of PIMS within the lab. Progress has also been made on the optimisation of queries to the PIMS database for accessing image and crystallisation-related data.

Partner 1A (EMBL-HH) has developed and successfully tested a system for the setup of free-interface diffusion experiments. In order to investigate the possibilities for commercialisation, Partner 1A has initiated contacts with relevant SMEs. In the system, crystals can be grown from volumes of less than 5 nL in a multitude of reaction chambers, Figure 3.1 b. The system allows the controlled and automatic addition of sample and the controlled delivery of both sample and crystallisation solution on a CD-like crystallisation chip, Figure 3.1 c. The system was successful in 4 test cases with proteins. In contrast to the commercial system from Fluidigm (Topaz chip system), the BIOXHIT system works without the need of pumps or pressure driven valves. The production costs of the chips are also expected to be a fraction of the typical costs of a Topaz chip. The ability to investigate the intrinsic diffraction quality of crystals in-situ was also demonstrated successfully.

Figure 3.1 a. The Protein Information management System

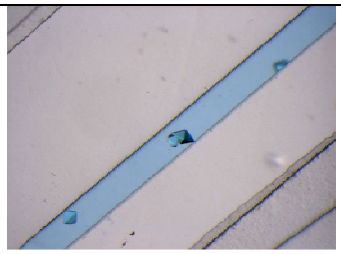


Figure 3.1 b. Crystals grown in a microfluidics

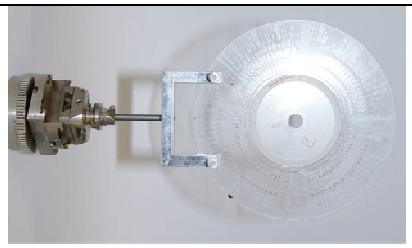


Figure 3.1 c. Microfluidics crystalliser

3.2. Highlights on synchrotron technologies

The highlights on the beam position monitors that made it to the stage of the commercialisation are described in *The Final Plan for Using and Disseminating the Knowledge*.

3.3. Highlights on beamline end-stations and data collection

Beamline end-stations are highly congested arrangements of various apparatuses and equipment with very little space affordable for sample handling throughout the experiment. The end-station components have to be carefully aligned and their operation synchronised. Therefore, it is absolutely crucial for the success of the experiment that the end-station can be completely automated and operated without the user being physically present. This involves improved means of automated and reliable handling and characterisation of the crystal in order to optimally plan the actual diffraction experiment.

The highlights on the new X-ray fluorescent detectors and the standard test crystals that made it to the stage of the commercialisation are described in *The Final Plan for Using and Disseminating the Knowledge*. Other highlights are described below.

3.4. High precision kappa-goniometer with fully motorised goniometer head

The International Kappa Workgroup was established withtin BIOXHIT in 2004 to bring all those scientists together who were aiming to use multi-axis goniometers for smart reorientation of the crystalline samples during data collection. The aims cover all aspects from instrument design, and control software development as well as data collection strategy calculations with on-the-fly data processing feedbacks. Although the Kappa Workgroup was initially started by BIOXHIT members, its size has increased very fast and now contains collaborators from the US and Australia.

MK2 mini-Kappa models have been used at ESRF/MRC-BM14 and on the ESRF MX MAD beamlines (Partners 1B and 2). The Kappa head has been extensively tested in terms of collision prevention. Complete calibration to increase precision has been carried out successfully. The STAC software has been installed and is fully available within the DNA interface. The wizard to ease the configuration of the Mini-Kappa's collision parameters in the MD2 has been developed.

The experience with MK2 mini-Kappa has been used to define the modifications for the MK3 version, Figure 3.4.a. Several points were improved including the stiffness of the anti-collision detection system, the stability of the friction breaks, the resistance of the clutch systems to users manipulations (ruby balls/hard tempered steel discs), and finally the stiffness of the Kappa and Phi axis (ceramic ball bearings). Control procedures have been established to fully characterise the devices, and to track their precision over time. Typical SOC (sphere of confusion) of 5 micrometer is now achieved at any kappa angles. The collision map, Figure 3.4.b, is advantageous to the one from currently available devices. The mini-Kappa MK3 version is becoming commercially available from the company ACCEL GmbH, where Partner 1B would be providing training to help the use of mini-Kappa together with the reorientation software STAC.

The Kappa goniometer was assembled, commissioned and tested at several BIOXHIT Partner sites, including ESRF, SLS and DIAMOND. New, high precision bearings were developed in collaboration with and manufactured by the company ADR. They provide an eccentricity below 1 µm for Kappa and phi and have the opening which is sufficiently wide to insert a slip ring.

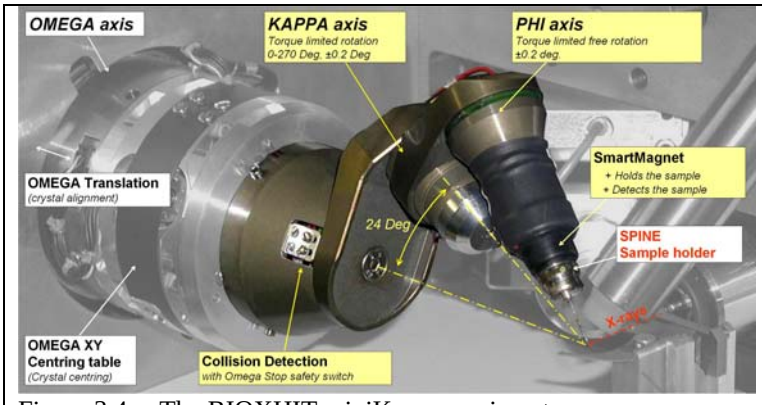


Figure 3.4.a. The BIOXHIT miniKappa goniometer

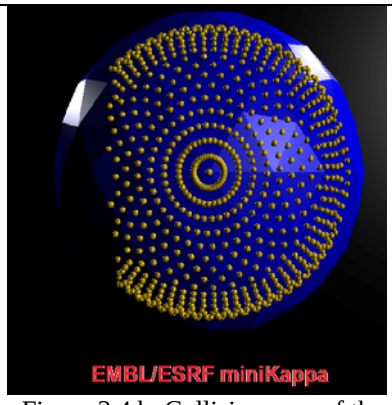


Figure 3.4.b. Collision map of the miniKappa goniometer

3.5. Automated centring and tomography of crystalline samples

Crystal centring algorithms developed within BIOXHIT, XREC and C3D, are now implemented at many Partner sites. In addition to work on the individual optical centring algorithms the developers have been collaborating on testing joint procedures. Further advancements occurred on the hardware side, including better optical illumination in the visible range and crystal detection via UV illumination and fluorescence.

One example is a joint combination of XREC and C3D employed by Partner 3 (SRS) which was successfully transferred to beamlines at Partner 17 (Diamond). The implementation is shown in Figure 3.5.a. Background image is stored within the GUI at the start of the experiment and is subsequently subtracted form the crystal image. The automatic crystal centring and the movement of x, y and z is carried out based on weighted average of C3D and XREC output.

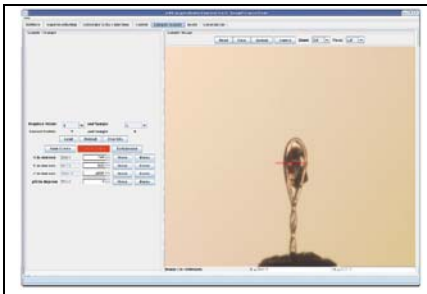


Figure 3.5.a. Implementation of crystal centring in Generic Data Acquisition

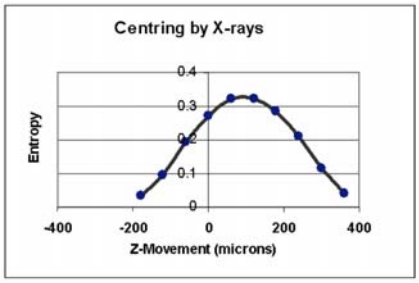


Figure 3.5.b. Crystal centring by X-rays using entropy

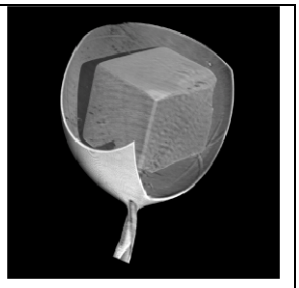


Figure 3.5.c. Crystal shape reconstruction by X-ray tomography

In some cases where optical crystal centring fails (particularly for small crystals) it may be advantageous to use X-rays for centring using entropy values. A direct approach was used from ADSC detectors directly with modified C programs from ADSC. In this case total number of spots were used to plot against movement of x, y and z of the goniometer, Figure 3.5.b.

We have also developed a proof-of-principle of crystal shape determination by both via optical and X-ray tomography, Figure 3.5.c. A detailed study on performing tomographic experiments on traditional MX station and the feasibility is assessed of the 3D reconstruction of the separated objects of the crystalline sample, the solvent around and the sample holder has been submitted for publication. The data gathered on this way allows optimisation during centring to avoid cracks and other crystal defects, as well as optimising the orientation of the absorbing volume using multi axis goniometers. Further possibilities for more sophisticated processing of diffraction data with accurate absorption correction is also highlighted.

3.6. Sophisticated and robust algorithms for modelling statistical results of data collection

A particularly unique part of the work done on this topic has been the extensive use of the ground-breaking advances that took place towards the design of strategies on the basis of a statistical model of radiation damage in proteins (Partner 1A). The software BEST, developed by Partner 1A (EMBL-HH), now takes into account anisotropy in diffraction, mosaicity, disorder and, perhaps most importantly, radiation damage, for optimising instrumental parameters. This task succeeded well beyond expectation in establishing a solid statistical basis for planning experiments, which can deliver a constant $I/\sigma(I)$ ratio throughout the resulting dataset. This advance was implemented in the version 3.2 of BEST. The correctness and robustness of these new developments towards the quantitative prediction of radiation damage has been extensively tested and validated by collection of real data on the ESRF ID14-4 beamlines ID14-2,4, ID23-1, ID29 and BM14 during 2007, followed by comparison of the predicted statistics with the observed ones. For a broad variety of samples, including e.g. 30S ribosomal crystals, good agreement between predicted and observed data statistics is achieved, provided the condition of sample bathing in the beam is satisfied, Figure 3.6.a. Another new option of optimising the crystal orientation for a single omega sweep has been introduced in BEST. The tests demonstrated strong dependency of the results of initial crystal characterisation on the crystal orientation, therefore the strategy procedure requires sample re-assessment in a chosen orientation. Overall,

BEST implements the estimation of the attainable resolution limit for a given sample under optimal data collection parameters. The limit is given by the either the total exposure time allowed by the user or objectively by the radiation damage model, Figure 3.6.b. This measure provides a generalised estimate of the sample quality (combining the diffraction strength, mosaicity, background scattering etc.) and makes it independent on the experimental conditions selected for characterising the crystal.

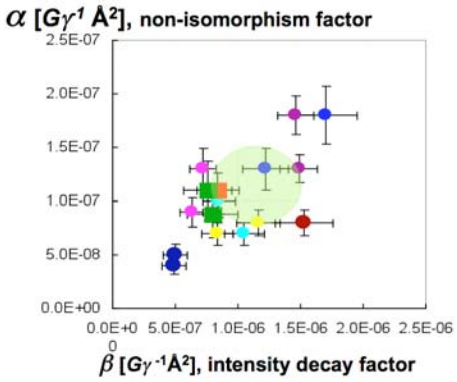


Figure 3.6.a. Relationship between the radiation damage parameters (non-isomorphism and the intensity decay) forming the ground for the BEST data collection strategy prediction

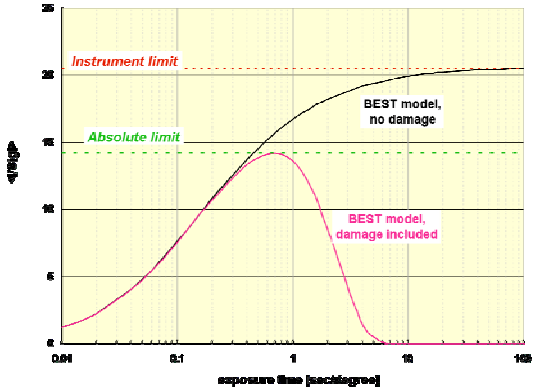


Figure 3.6.b. Estimation of the optimum exposure time with no account for crystal radiation damage (black) and with proper statistically-based account (red). The latter indicates that there is the single optimum setup that will provide the best quality of the diffraction data.

3.7. Remote data collection

The software integration effort in BIOXHIT culminated in the creation of remote access facilities, which enable users to operate the HTP facilities from their home laboratories through Internet connections. Remote access to facilities means that researchers no longer need to be physically present at the synchrotron site in order to participate in an experiment. Remote access to compute power, software and databases will play even more important role in the future by enabling the efficient sharing of resources and data, as researchers will be able to make use of these resources regardless of their physical location. It will make it possible for different parts of a structure determination to be performed seamlessly at different physical locations whilst still preserving the integrity of the process and the results.

The remote access to the ESRF MX beamlines, meaning allowing users to collect data from their home institutes has been established during BIOXHIT Years 3 and 4 (this was following one of the urgent recommendations of the SAB and the reviewers of the project after year 2), Figure 3.7.a. The ESRF data collection applications (mxCuBE, a desktop/fat-client application) have been successfully adapted. The first decision was on the network access to the ESRF computing infrastructure from the outside, through the Internet. VNC and similar products were discarded due to their poor performance (namely the crystal camera video); instead the NoMachine/NX was selected, allowing a user to open an X-Windows KDE session running in the beamline computer, but being displayed in their local PC. While the server has to be bought by the ESRF, the client ran by the users is free of charge. The beamline scientist is responsible for the working status of the beamline, for loading the users' crystals inside the sample changer robot, and finally for allowing the remote users to remotely conduct their experiments. The users, Figure 3.7.b, really liked the remote data collection: '*The connection speed is fine, there is little difference with being on the beamline. It was a very good day with amazing experience!*'.

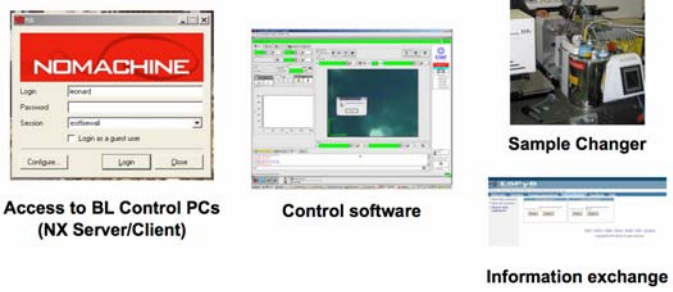


Figure 3.7.a. The main components of the remote data collection setup at the Partner 2 (ESRF) beamlines

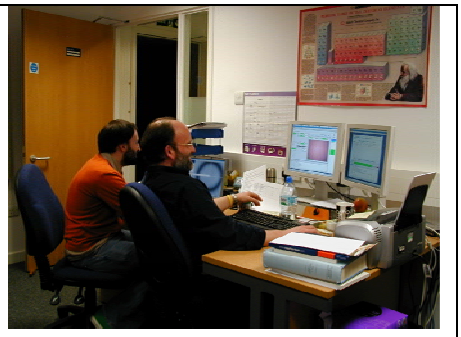


Figure 3.7.b. Happy users carrying out data collection at the ESRF while being at a workshop in Oulu (Finland).

3.8. Highlights on data processing and structure determination

Traditionally crystallographic structure determination has been viewed as a linear process with little to no feedback to the preceding steps. Furthermore, it did not develop with high-throughput operation in mind, so that, in most respects, it still presents a challenge for complete automation. This section in BIOXHIT aimed to assess the potential of feedback in consolidating the whole process, and to design and implement a structure determination pipeline whose use ensures the success of the diffraction experiment at the earliest possible stage, and which allows direct feedback to data collection and even decisions in choices of strategy. Robust steps have been taken in this direction, with an unprecedented degree of synergy and coordination between different Partners, both in terms of hardware and of software. The paradigm of "Smart Data Collection" has actually started to become a reality, and the practical impact of the new capabilities put in place has been strikingly demonstrated by successful experiments, which would have been beyond reach a short time ago. The central part of these activities, devoted to structure determination, has seen very significant advances in both the individual techniques and their degree of integration.

3.9. Comprehensive multi-option structure determination pipeline

All existing programs and procedures are being gradually assembled into an integrated system where multiple choices are available along the structure determination path. Partner 1A has extended the development of its Auto-Rickshaw software pipeline for automated structure solution by incorporating into it a combination of molecular replacement and single anomalous diffraction (MRSAD) to complement the pre-existing model refinement, experimental phasing, phase enhancements and automated model building methods. MRSAD phasing requires a search model and/or sequence as well as X-ray data from derivatised protein crystals or X-ray data collected at longer wavelengths. The procedure is initiated by a Web-based graphical user interface for data and parameter input and for monitoring progress in structure determination. A large number of possible structure solution and phase enhancement paths are possible, and the optimal path is selected by the decision-makers as the structure solution evolves. This MRSAD option can be used for reducing the bias from a MR solution, building a complete structure from a partial and/or fragmented model, or when SAD phasing alone is not enough to solve the structure. AutoRickshaw has been successfully running on a large and fast cluster and at the time of the 4th Annual BIOXHIT meeting in April 2008 has been made available to the crystallographic community worldwide.

3.10. Low resolution refinement and automated model building

Automated model building and refinement methods with ARP/wARP have progressed at many levels (Partners 1A and 6), from some basic recognition algorithms to the improved communication between all the programs involved, including those dealing with molecular replacement.

The effectiveness of model refinement at low resolution in the context of the ARP/wARP suite, has been enhanced Partner 6 with an introduction of a novel use of restraints. The approach taken makes use of the implementation of flexible, user-specified restraints in the REFMAC refinement program. From within

ARP/wARP, restraints are automatically formulated for its hybrid model, consisting of part protein model, part free atom model. The restraints for the free atoms promote "general" protein geometry amongst the free atoms, as well as extend the geometric features of the protein model into the free atom model. A prototype of a program to generate these restraints and its interfacing with REFMAC has been developed.

To complement this work, Partner 8 has added pseudo-restraints into the refinement program REFMAC to enable refinement of yet chemically unidentified structures. It now can handle many types of chemical information including bonds, angles, torsions and planarities. These restraints allow a smooth transition from electron density to full atomic model, and thus enhance the chance of success of automatic model building and refinement, Figure 3.10.a.

3.11. Molecular Replacement as a Structural Genomics tool, to automate structure solution at the synchrotron

A notable new development in Molecular Replacement (MR) has been the BALBES package from the York group (Partner 8), Figure 3.11.a. This development has had an aim to marry the increasing wealth of information in the PDB with MR techniques, and to develop better combinations of MR with experimental phase information and density modification. The BALBES system is updated every half-month by taking all newly released entries from the PDB website and analysing them against the "older" database. New entries for which experimental data are available are tried against the old database. The current version of the system is able to solve 75-80% of structures from PDB automatically. This is already higher than what is reported in PDB, according to which around 67% of all structures are solved by MR. A web server for automatic MR has already been designed by Partner 8 and opened up to the user community.

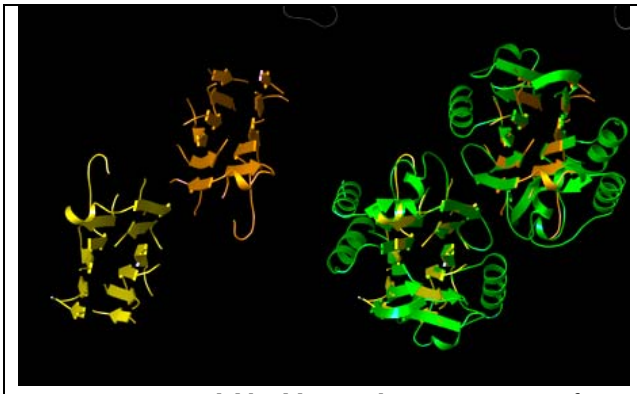


Figure 3.10.a. Model building with ARP/wARP. Left – the current release, version 7.0. Right – the version with implementation of the conditional restraints.

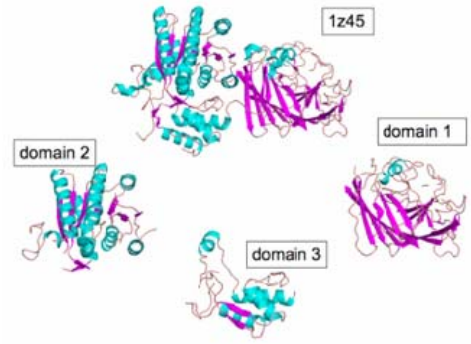


Figure 3.11.a. Structure solution of an isomerase 1z45 with BALBES. Three different domains from other isomerases were automatically identified in the PDB and successfully used for the structure determination of 1z45.

3.12. Highlights on training, implementation and dissemination

Most of the BIOXHIT objectives require active dissemination of knowledge and communication between Partners and the community outside the consortium, including SMEs. This implies a significant amount of training of staff involved in the project and well as of the users of the hard- and software technology platform created. Training, implementation and dissemination (TID) formed a cornerstone of the BIOXHIT activities.

3.13. Implementation of TID centre local infrastructures for training, implementation and dissemination of the BIOXHIT-developed technologies.

The growth of the structural biology community continues to necessitate training of users of the synchrotron facilities in the new technologies. Already at the start of the BIOXHIT project it was realised that this would

constitute a formidable task if it were to be handled exclusively by the synchrotron core-facilities. In this context it should not be forgotten that many BIOXHIT Partners are already performing immense work in training the user community. The four Training-Implementation-Dissemination (TID) Centres established in during the first part of the project (first in Oulu, Finland and Poznan, Poland and then in Lisbon, Portugal and Heraklion, Greece), have now reached a stage where they are fully operational and can provide a very efficient and important dissemination of BIOXHIT results, Figures 3.13.a,b. During Year 4 the TID centres played a pivotal role in the dissemination of and training in BIOXHIT hardware and software technologies because they possess the background of structural biologists that are competent users of the macromolecular crystallography beamlines at different synchrotron facilities. The virtual data collection platform created by the BIOXHIT core Partners at the TID centres has been used to train users from the region geographically close to the location of the centres. This was further supported by real time remote access data collection sessions at the ESRF. The TID centres have been actively engaged in the development and testing of the BIOXHIT platform and provided a constructive and critical analysis of the associated demonstration material.

Parallel to these activities the TID centres play an important role in dissemination of BIOXHIT results in their local communities. All four TID centres have created websites that serve as good information points. The BIOXHIT TID-committee was in continuous contact with and ensured an optimal operation of the TID centres. Each TID centre had in return a contact person from the TID committee.

Figure 3.13.a. The first joint TID meeting in 2006 at the ESRF, Grenoble, France.

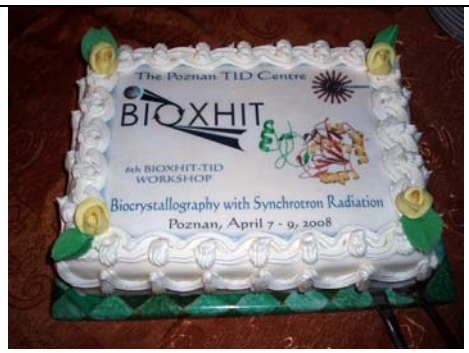


Figure 3.13.b. The cake that was made by the attendees of the 6th BIOXHIT TID workshop in Poznan, Poland.

4. Annex 4.1.

Recruitment and training of staff

The following EC-funded persons have been employed since the beginning of the project:

No.	Partner	First Name	Last Name	Gen	Nation.	Position	Start date	End date
1A	EMBL-HH	Andrea	Cristofori	m	Italian	Programmer	01/11/05	30/06/07
1A	EMBL-HH	Andrey	Bogomolov	m	Russia	Postdoc	23/05/05	15/07/07
1A	EMBL-HH	Annette	Faust	f	Germany	Postdoc	01/03/06	30/06/08
1A	EMBL-HH	Babu	Pothineni	m	India	Technical Officer	01/01/04	31/12/06
1A	EMBL-HH	Binoy	Mathew	m	India	Programmer	01/05/04	30/04/06
1A	EMBL-HH	Brice	Kauffmann	m	France	Postdoc	01/03/04	31/12/05
1A	EMBL-HH	Chris	Steinert	m	Germany	Postdoc	01/07/05	30/06/06
1A	EMBL-HH	Daniela	Janicke	f	Germany	Admin Officer	29/01/04	31/05/07
1A	EMBL-HH	David	Watts	m	UK	Post Doctoral Fellow	01/09/07	30/06/08
1A	EMBL-HH	Gerd	Wellenreuther	m	Germany	Postdoc	01/07/06	30/06/08
1A	EMBL-HH	Gundolf	Schenk	m	German	Intern	01/11/05	30/04/05
1A	EMBL-HH	Helene	Doerksen	f	German	Programmer	01/11/05	30/06/08
1A	EMBL-HH	Jan	Geldof	m	Dutch	Database manager	01/08/05	01/12/05
1A	EMBL-HH	Johan	Unge	m	Swedish	Postdoc	01/07/07	30/04/08
1A	EMBL-HH	Jenny	Magnusson	f	German	Admin. Officer	01/05/07	25/06/07
1A	EMBL-HH	Natalie	Sebastian	f	German	Admin Officer	26/06/07	30/06/08
1A	EMBL-HH	Parthasarathy	Venkataraman	m	India	Programmer	01/10/05	30/06/08
1A	EMBL-HH	Tilo	Strutz	m	Germany	Postdoctoral Fellow (50%)	01/10/04	31/10/06
1A	EMBL-HH	Tilo	Strutz	m	Germany	Postdoctoral Fellow	01/11/06	31/08/07
1A	EMBL-HH	Lifu	Gao	m	China	Programmer	01/01/08	30/06/08
1A	EMBL-HH	Jochen	Mueller-Dieckmann	m	Germany	Scientist (50%)	01/01/08	30/06/08
1A	EMBL-HH	Andrea	Schmidt	f	Austria	Scientist (50%)	01/01/08	30/06/08
1A	EMBL-HH	Philipp	Heuser	m	Germany	Postdoctoral Fellow	01/05/08	30/06/08
1B	EMBL-GR	Claude	Tadonki	m	Cameroon	Post Doctoral Fellow	01/03/06	30/06/08
1B	EMBL-GR	Gael	Seroul	m	France	Software developer (50%)	01/09/05	31/06/08
1B	EMBL-GR	Gudrun	Stranzl	f	Austria	Postdoctoral Fellow	15/01/06	14/06/06
1B	EMBL-GR	John	McGeehan	m	Scotland	Postdoc	15/09/05	31/12/07
1B	EMBL-GR	Max	Nanao	m	USA	Post Doctoral Fellow,	01/01/05	15/05/05
1B	EMBL-GR	Sandor	Brockhauser	m	Hungary	Software Engineer	01/06/04	31/06/08
1C	EMBL-EBI	Abraham	Naim	m	French/ Israeli	Scientist	02/01/04	31/12/06
2	ESRF	Eric	Mathieu	m	France	Technical officer	19/07/04	31/12/07
2	ESRF	Jose	Gabadinho	m	Portugal	Software Engineer	01/08/04	31/12/07
2	ESRF	Michal	Hrouzek	m	Czech	Thesis student	01/11/05	31/10/06

						(50%)		
2	ESRF	Romeu-Andre	Pieritz	m	Brasilian	Software engineer	10/03/05	31/12/07
2	ESRF	Stephanie	Veyrier	f	France	Engineer	11/09/06	21/12/07
3	CCLRC/ SRS	John	Cowan	m	UK	Postdoc	01/10/04	30/06/07
3	CCLRC/ SRS	Mylrajan	Muthusamy	m	India	Presentation	01/01/05	30/06/07
5	GPHL	Lorenzo	Milazzo	m	Italy	Scientist	01/06/04	20/08/06
5	GPHL	Peter	Keller	m	UK	Research sci/, software developer	16/01/06	30/04/08
5	GPHL	Thorstein	Thorsteinsson	m	Iceland	Software engineer	01/01/04	30/09/04
5	GPHL	Thomas	Womack	m	UK	Research sci/, software developer	01/03/2006	30/06/08
6	NKI	Diederick-de	Vries	m	Netherlands	Database expert	01/05/04	29/02/08
6	NKI	Krista	Joosten	f	Netherlands	Postdoc (50%)	01/06/06	30/06/08
6	NKI	Patrick	Celie	m	Dutch	Postdoc	19/09/05	19/06/08
6	NKI	Eirini	Mitsiki	f	Greek	Postdoc	15/03/08	30/06/08
7	ELETTRA	Alessio	Curri	m	Italy	Software Engineer	01/05/04	30/06/08
7	ELETTRA	Enrico	Mariotti	m	Italy	Software engineer	01/10/04	30/11/06
7	ELETTRA	Imre	Toro	m	Hungary	Postdoc	12/06/04	11/12/04
7	ELETTRA	Maurizio	Polentarutti	m	Italy	Postdoc	01/03/04	28/02/05
7	ELETTRA	Stefano	Maraspin	m	Italy	Software Engineer	01/05/04	30/04/06
8	UOY	Christopher	Walker	m	UK	Research Fellow	01/09/04	31/08/06
8	UOY	David	Anderson	m	UK	Postdoc	01/01/04	30/09/04
8	UOY	Fei	Long	m	China	Research Fellow	20/05/04	19/05/08
8	UOY	Samarsena	Buchala	m	India	Research Fellow	06/12/06	31/12/07
9	FUB	Martin	Fuchs	m	Germany	Postdoc	01/07/04	30/06/07
9	FUB	Rainer	Rudert	m	Germany	Postdoc	01/10/07	30/06/08
10	CCLRC/ CCP4	Peter	Briggs	m	UK	Scientist	04/04/04	31/12/07
10	CCLRC/ CCP4	Wanjuan	Yang	f	China	Scientist	06/12/04	05/06/08
11	UNIV-MRS	Patrick	Legaigneur	m	France	Engineer	01/01/04	31/12/05
12	UNIGOE	Gabor	Bunkoczi	m	Hungary	Postdoc	01/07/04	30/09/04
12	UNIGOE	Ina	Dix	f	Germany	Postdoc	17/01/05	31/07/07
12	UNIGOE	Tim	Grüne	m	Germany	Postdoc	01/01/06	31/01/07
12	UNIGOE	Tim	Grüne	m	Germany	Postdoc	01/10/07	31/03/08
13	SOLEIL	Olga	Roudenko	f	Russia	Postdoc	15/11/04	31/10/06
14	FIRC-IFOM	Fabio	Dall'Antonia	m	German-Italian	PostDoc	01/04/04	30/05/06
15	MAXLAB	Krister	Larsson	m	Sweden	Postdoc	14/06/04	15/06/07
16	UKBH	Anette	Jensen	f	Denmark	Ph.D. student	01/09/04	30/06/05
16	UKBH	Heidi	Ernst	f	Denmark	Ph.D. student	01/07/05	31/12/05
16	UKBH	Jens-Christian	Navarro Poulsen	m	Denmark	Research assistant	01/01/05	31/03/05
16	UKBH	Annette	Langkilde	f	Denmark	Scientific Assistant	10/11/07	30/06/08
17	DIAMOND	Josephine	Chan	f	UK	Programmer	01/10/07	30/06/08
21	UNIVIE	Sofia	Macedo	f	Portugal	Postdoc	02/05/06	15/04/08

4. Annex 4.2

Consolidated BIOXHIT review report.

Questions to be answered by the reviewer(s)

1. OVERALL ASSESSMENT

a. Executive summary
Please follow the order of the individual sections of this report

Comments:

BIOXHIT is a European effort with the unprecedented task of uniting and significantly improving the efficiency of the European synchrotron sources in the area of structural biology. The accomplishments of BIOXHIT surpass by a large degree any other similar attempts in the US and Asia where such coordination efforts have been rather difficult and largely unsuccessful. The technology developments of the BIOXHIT project cover a very wide range of synchrotron based structural biology including data management, crystallization, handling samples, data acquisition, structure determination, efficient dissemination schemes. The results have already made significant impacts both within and outside Europe and are expected to become even far reaching with a proper continuation or by integrating them into a new integrated project (see below).

If the EU is to continue to be a leader or at a minimum keep up with the worldwide efforts, it is critical that a program like BIOXHIT continue over the next several years. BIOXHIT management needs to put together a plan that explains the future challenges clearly and how they propose to overcome such developments. At the moment, the future plans are currently not available to the reviewers.

The technical sections include:

Sect 1. - Development and Implementation of Improved, Low Cost, HTP Crystallization Technologies Common to Laboratories and Synchrotrons (Section Leader: A. Perrakis)

Sect 2. - Synchrotron Technologies (Section Leader: S. McSweeney)

Sect 3. - Beamline End-Stations and Data Collection (Section Leader: C. Nave)

Sect 4. - Data Processing and Structure Determination (Section Leader: G. Bricogne)

The BIOXHIT Working Groups
(formerly Sect 5. - Data Bases and Networking (K. Henrick, section leader))

Sect 6. - Training, Implementation and Dissemination (Section Leader: S. Larsen)

Management team headed by Dr. Victor Lamzin with assistance from Dr. Manfred Weiss

[X] Good to excellent project (The project has fully achieved its objectives and technical goals for the period and has even exceeded expectations)

[ ] Acceptable project (The project has achieved most of its objectives and technical goals for the period with relatively minor deviations)

[ ] Unsatisfactory project (The project has failed to achieve critical objectives and/or is not at all on schedule)

b. Recommendations

Now that the BIOXHIT project is approaching its end, it is highly recommended that they identify tasks which are most important to develop further for the benefit of the community in preparation for a new phase of structural biology in the next 5 to 10 years to come. There is no question that continued research in this fundamental area will continue to be needed and have impact for future basic and applied life science research. With the advent of the most advanced third generation synchrotron light sources such as PETRA-III in Hamburg, upgraded ESRF, and Diamond, protein crystallography will make a quantum leap in capability and impact with super low emittance (extremely parallel and nano beams), pixel array detectors with associated data acquisition systems, and massively parallel computers for real time data processing and structure analysis. To cope with these upcoming developments in the synchrotron hardware, whose impacts have only recently been realized, the technologies developed in the BIOXHIT projects need to go beyond current limits. Here, crystallography will remain central in the future of chemistry and biology, hence needs for further innovation towards extremely small size crystals (perhaps sub-microns), or optimal phasing methods for complex crystal data with several hundred nanometre unit cell dimensions. It might be also crucial for the BIOXHIT technologies to be expanded to non crystalline biological molecules, i.e. small angle X-ray scattering or even coherent diffraction imaging. Data management is equally if not the biggest challenging area and to date, there are no strong solutions to how one manages data from gene to structure at a high rate and for even more complex systems.

Another possibility for the BIOXHIT project to move forward will be bridging the high-throughput structure determination tools and pipelines with most demanding biological studies and systems biology. Within Europe, there are a very large number of biologists who work on competitive biological or medical research topics but are not experiencing the power of structural biology at the atomic resolution yet. Often their targets are membrane protein complexes, protein-protein, protein-lipid or protein-nucleic acids complexes which are not amenable to 3D crystallization. The BIOXHIT could play a pivotal role by proactively engaging these biologists into target-oriented structural and functional studies.

2. OBJECTIVES

a. Have the objectives for the period been achieved?

[X] Yes	[ ] Partially	[ ] No

Comments:

As beautifully demonstrated in the final report and demonstrated during the 4th annual meeting, BIOXHIT management has achieved most of the objectives for the period. The remaining few will be achieved in the remaining period or continued by each party wherever necessary.

b. Are the overall objectives (i) still relevant and (ii) still achievable within the time and resources available to the project?

(i)

[X] Yes	[ ] Partially	[ ] No

(ii)

[X] Yes	[ ] Partially	[ ] No

Comments:

The overall objectives of the BIOXHIT project are indeed still relevant in relation to the advances made elsewhere in the world. Their grand mission is to promote European life science research based on synchrotron X-ray crystallography beyond the current scope by bridging structural biology to much wider communities in biology, biotechnology and medicine. While all the essential parts of the objectives are expected to be achieved within the period of the project, their progress is paving the way forward to the future developments in keeping up with the very recent remarkable developments in the third and next generation synchrotron radiation facilities including the pixel array detector developments at Paul Scherrer Institut/Swiss Light Source, as well as, world wide efforts in developing critical technologies in protein production, crystallization, data collection and analysis for far more difficult targets such as membrane complexes.

c. Do you recommend changes in objectives in order to keep up with the current state-of-the-art?

[ ] Yes	[ ] Partially	[X] No

Comments:

There is no need to change the objectives at the final stage of the project, but it is critical that the BIOXHIT partners will focus their efforts on formulating the next phase project which will bring what they have developed to the next level, either by going further with the high-throughput technologies for the upcoming most advanced synchrotron light sources, or by building up an integrated project on far more complex and demanding biological problems such as structural systems biology.

3. WORKPLAN AND RESOURCES

a. Has the project as a whole been making satisfactory progress in relation to the Description of Work (Annex I to the contract)?

[X] Yes	[ ] Partially	[ ] No

Comments:

The BIOXHIT project team as a whole has made an outstanding progress towards the goals of workpackages.

b. Has each work package (WP) been making satisfactory progress in relation to the Description of Work (Annex I to the contract)?

[X] Yes	[ ] Partially	[ ] No

Comments:

The great majority of the work packages of the BIOXHIT have made impressive progresses. Just to list a few, Section 1 has provided one of the best imaging schemes for crystallization trials. Section 2, Task 2.6.6 led by Prof. G. Sheldrick, developed a piece of software and protocols to survey diffraction intensities measured on CCD detectors early in the BIOXHIT project, which revealed that there are problems with diffraction spots near the corners of tiled CCDs. Prompted by this finding, several CCD detector manufactures have now modified their correction procedures to take into account the lower efficiency of the tiled fibre optics.

In some cases, parallel developments within a section are pursued but they appear necessary to fulfil different requirements of synchrotron light sources. The X-ray beam position monitors (XBPM) in Section 2 is a good example where several difference schemes are exploited in parallel so that the monitors fit characteristics of each synchrotron parameters and optics design. In fact, the developments of various XBPMs have progressed extremely well and some of them are already commercialized or will be soon.

c. Have planned milestones and deliverables been achieved for the reporting period?

[ ] Yes	[X] Partially	[ ] No

Comments:

While most of the major milestones have been achieved, there are some deliverables which have been delayed but are expected to be followed up in due course. The project management has paid attention to these and have made every attempt to catch up. For example, in Section 4, the progress of the DNA project within BIOXHIT was not at the anticipated speed and they decided to reformulate it and started a new project eDNA by Partner 2. Although, it is still an early stage, the eDNA project has already demonstrated a promising start in enhancing the data collection schemes including real time monitoring of radiation damage. However, data management is likely to be the weakest aspect of BIOXHIT, but this is also one of the most challenging.

d. Have resources been deployed as foreseen in Annex I, overall and for each participant?

[X] Yes	[ ] Partially	[ ] No

Comments:

Almost all the partners deployed the resources reasonably.

e. Have costs incurred, i.e., personnel costs and other major cost items, been 1) necessary for the implementation of the project and 2) economic. Note that both aspects 1) and 2) have to be covered in the answer.

[X] Yes	[ ] Partially	[ ] No

Comments:

The people hired for this project, over 200, were all engaged in the necessary tasks to achieve the goals of technology developments, implementation either at the synchrotron facilities or as software packages for much wider audience, and dissemination to outside of the project. In comparison with other similar projects elsewhere in the world, BIOXHIT has managed the tremendous amount of work packages within the budget and the management team should be commended for their excellent guidance and achievements. This efficiency is largely owing to the willingness of all the European synchrotron based structural biologists and other protein crystallographers to cooperate in the BIOXHIT project.

f. For Networks of Excellence (NoEs) only:

f1. Is there evidence of real integration and restructuring of activities between partners (to be evaluated against Indicators of Integration, e.g., exchanges of personnel, shared infrastructures, joint research and training activities, changes of research orientation of individual partners to better integrate into the NoE, etc).

[ ] Yes	[ ] Partially	[ ] No

Comments:

4. WORK PLANNED FOR THE NEXT 18-MONTH PERIOD (NoEs and IPs only)

Is the proposed update to the *Implementation Plan* (IPs) or *Joint Programme of Activity* (NoEs) for the next 18-month period satisfactory

a. from a scientific/technical point of view?

Yes	Partially	No
☐	☐	☐

Comments:

This is the final report of the project, hence no comment.

b. from a management point of view including use of resources?

Yes	Partially	No
☒	☐	☐

Comments:

Although the BIOXHIT is approaching its end of funding, all the partners are keen to sustain and further develop what they have achieved during the last 4 and half years. Indeed, they are planning to continue discussions in the form of the PSC to prepare a new application for FP7, which should be encouraged.

c. concerning non-scientific activities (dissemination, exploitation, training, science-society issues, further integration etc)?

Yes	Partially	No
☒	☐	☐

Comments:

BIOXHIT management should continue activities in further integration of the key technologies/methodologies developed in the Work Packages. In particular, the TID centres are planning additional training workshops even after the end of the contract. Furthermore, new devices, for example, the mini-kappa goniometer, and software packages developed in Sections 1-4 will be implemented in several new synchrotron facilities. There is no doubt that the new methodologies and software tools developed by the BIOXHIT project will benefit individual laboratories throughout the world for their structural studies. Therefore it would be imperative that these activities find steady EU funding and/or sustained support from their own institutions.

5. CONSORTIUM PARTNERSHIP

a. Has the collaboration between the participants been effective?

[X] Yes	[ ] Partially	[ ] No

Comments:

Almost all the participants collaborated in one way or another to achieve the goals of the BIOXHIT project. In particular, the very fruitful collaboration between Sections 3 and 4 on the mini-kappa project, both on hardware development and software implementation, has provided, for the first time, the possibilities in the maximum use of nonisomorphous anomalous scattering for phasing.

b. Have the partners contributed as planned to the project and tasks assigned to them?

[X] Yes	[ ] Partially	[ ] No

Comments:

All the partners including the new third party, Oxford University, have made substantial contributions to the project. In many cases the contributions were beyond initial expectation as exemplified by the positive feedbacks made by the TID centres on remote access to the ESRF beam lines.

c. Do you identify any conflicts or evidence of underperforming partners, lack of commitment or change of interest of any partners? Do you recommend any changes in responsibilities?

[ ] Yes	[ ] Partially	[X] No

Comments:

All the partners, except those who have withdrawn for various reasons, remain very active and commit themselves to the BIOXHIT project. There are no conflicts among the partners that the reviewers are aware of.

6. MANAGEMENT

a. Has the scientific/technical management been performed as required?

Yes	Partially	No
X		

Comments:

The BIOXHIT management and the PSC have managed both scientific and technical aspects of the project exceedingly well. This project is indeed unique and unprecedented in that all the European synchrotron radiation facilities have collaborated, rather than competed, on a wide range of developments for the maximum benefit of European structural biologists. The management led by Dr. Victor Lamzin of EMBL-Hamburg has really served the entire BIOXHIT in such a way that each partner could play a significant role and he should be commended at the highest level for excellent management.

b. Has the administrative and financial management been performed as required ((including proper handling of contractual matters, maintenance of the consortium agreement, intellectual property rights, technical collective responsibility, sub-contracting, competitive calls)?

Yes	Partially	No
X		

Comments:

This in one of the most efficient management teams among the recent EU FP6 projects as far as the reviewers are aware of. It is inevitable for this size of EU project to have small deviations and issues on financial resources such as short delays in executing purchases and recruitments, but they have been carefully dealt with by the management and the PSC.

c. Have (electronic) information and communication networks been established as required to support interactive working between the teams involved (if relevant)?

Yes	Partially	No
X		

Comments:

The electronic form of the BIOXHIT, both their website and internal bulletin board, serves well the partners for information exchange. Each partner has also used their own websites and the CCP4 bulletin board extensively for spreading the BIOXHIT-derived knowledge as software packages and for announcing workshops, job advertisements etc.

d. Is the consortium interacting in a satisfactory manner with other related 5th and 6th Framework projects or other R&D national/international programmes (if relevant)?

Yes	Partially	No
X		

Comments:

One of the best examples of the involvement of potential users outside the BIOXHIT is the close collaboration with the SPINE and SPINE-II projects, culminating in the implementation of the SPINE standard samples pins by the member synchrotron sites. User-friendly beam line sample environments have been developed by Sections 2, 3, and 4 to fully utilize the potential of this European standard established by these two EU FP-6 projects. Already, talks between the BIOXHIT and non European synchrotron facilities in the USA and Japan have been initiated for compatibility issues in the area of sample pins and storage media.

7. USE AND DISSEMINATION OF KNOWLEDGE

a. Does the project have significant use potential (if applicable)?

Yes	Partially	No
X		

Comments:

The BIOXHIT has produced an impressive array of new technologies and methodologies for macromolecular protein crystallography which have enormous potential for use by the European structural biology community and even worldwide. In particular, software suites for structure determination and refinement, SHELXC/D/E, Arp/Warp, AutoSHARP, Auto-Rickshaw, Raddose to name but a few, have become essential tools in structure determination. Partner 10 STSF-CCP4 has been the world leader in providing a platform for program packages developed by protein crystallographers and they have been instrumental in promoting the use of the programs developed in the BIOXHIT project.

b. Is the Plan for the Use and Dissemination of Knowledge developing in a satisfactory manner?

Yes	Partially	No
X		

Comments:

The BIOXHIT has three direct routes to promote the use and dissemination of the project results. The results of Sections 2 and 3 are almost immediately put in practice in the participating synchrotron facilities for the benefit of general users. Many of the software packages developed in Section 4 are also made available through internet not only to the BIOXHIT members but also to any structural biologists outside of Europe. Numerous workshops/meeting organized by the BIOXHIT project, in particular those by the TID centres, serve as a platform for wider dissemination of the knowledge acquired in the BIOXHIT project.

c. Have the contractors disseminated project results and information as foreseen by the contract and the plan for dissemination and use of knowledge (publications, conferences...)?

Yes	Partially	No
X		

Comments:

Dissemination of the outcome of the BIOXHIT project is already very visible as TID centres in Oulu, Poznan, Oeiras and Heraklion, of which two remarkable examples of Oulu and Oeiras were heard during the Hamburg meeting. These TID centers have been made possible only by the enthusiastic participation of the experts from the Partners. The reviewers are of the opinion that some measures must be urgently found to continue these centers or even expand for dissemination of the outstanding results of the BIOXHIT project in a wider context.

d. Are potential users and other stakeholders (outside the consortium) suitably involved (if applicable)?

Yes	Partially	No
X		

Comments:

As stated above the BIOXHIT has collaborated closely with SPINE (1 & 2) on crystal pins and has an MOU with 3D Repertoire. The collaborations are highly successful. They are also communicating with structural biology groups in other synchrotron facilities in the USA, Asia and Oceania on possible standardization of sample environment and radiation damage issues.

8. OTHER ISSUES

a. Have policy-related and/or regulatory issues been properly handled (if applicable)?

[X] Yes	[ ] Partially	[ ] No

Comments:

Concerning Section 5 which was originally called "Databases and Networking" needed a policy change during the period due to personal circumstances that the Section Leader Kim Henrick, Partner 1C, became unable to be further involved in the project. This problem was handled properly by the BIOXHIT management and the PSC as a policy change and the section was transformed into a set of Working Groups.
Also, following the SAB's remark on the lack of FTEs in Section 1 for information management of crystallization experiments, the Management has decided to invite Oxford University to join as a third party of Partner 6 in Month 37. This has brought XtalPIMS as a new resource to the BIOXHIT which has already proven successful and should be further developed for use by a much wider European community.

b. Have ethical issues been appropriately handled (if applicable)?

[ ] Yes	[ ] Partially	[ ] No

Comments:

There were no ethical issues raised by the BIOXHIT management nor the partners during the meeting in Hamburg.

c. Have safety issues been properly handled (if applicable)?

[X] Yes	[ ] Partially	[ ] No

Comments:

Safety issues such as personnel protection against X-radiation at the synchrotron facilities for the activities associated with the BIOXHIT project have been handled properly.

d. Has progress on the Gender Action Plan been satisfactory (if applicable for this reporting period)?

[X] Yes	[ ] Partially	[ ] No

Comments:

The female employment percentile has increased from the initial 11% to 19% in 2006, and then to 28% in 2008. Two female scientists are involved in the project management. Overall, the gender action plan as explained by Dr. Kristina Djinovic Carugo has worked well during the period.

4. Annex 4.3.
Public availability of the BIOXHIT deliverables and milestones

Deliverable no.	Reference
D 1.1.11	http://icarus.embl-hamburg.de/bioxhit/bioXHITSection1.jsp
D 1.1.14	http://icarus.embl-hamburg.de/bioxhit/pdf/Dispensetest_BIOXHIT_web.pdf
D 1.1.16	https://xtal.nki.nl:4000/svn/LIMS/XtalImageServer/trunk/
D 1.3.3	http://xtal.nki.nl/BIOXHIT
D 1.2.3	http://www.oppf.ox.ac.uk/xtalpims
D 1.3.5	http://xtal.nki.nl/Protocoles/Tecan/DeepWell96Protocol.html
D 3.1.3	http://x06sa.web.psi.ch/science/blresearch.html
D 3.1.5	http://ispyb.esrf.fr
D 3.2.12	J. Appl. Cryst. (submitted for publication)
D 3.2.13	http://www.diamond.ac.uk/Beamlines/Beamlineplan/MX/bioxhit.htm
D 3.4.12	http://www.esrf.fr/UsersAndScience/Experiments/MX/How_to_use_our_beamlines/Run_Your_Experiment/Microspectrophotometer_User_Guide/
D 3.4.14	http://www.srs.ac.uk/px/Bioxhit/
D 3.4.20	http://www.diamond.ac.uk/CMSWeb/Downloads/diamond/Beamlines/MX/bioxhit3.pdf
D 3.4.22	http://www.embl.fr/groups/instr/MS1-R07.pdf
D 3.5.1	http://www.embl-grenoble.fr/groups/instr/MK2.pdf
D 3.5.2	http://www.srs.ac.uk/meetings/bioxhit3/presentations/Bioxhit3_SB.pdf
D 3.5.10	http://www.diamond.ac.uk/CMSWeb/Downloads/diamond/Beamlines/MX/bioxhit3.pdf
D 4.3.1	http://www.globalphasing.com/sharp/
D 4.3.2	http://shelx.uni-ac.gwdg.de/SHELX/
D 4.3.2.B	http://www.embl-hamburg.de/Auto-Rickshaw
D 4.4.4	http://www.arp-warp.org
D 4.4.5	https://xtal.nki.nl:4000/svn/pyWARP/
D 4.4.6	https://xtal.nki.nl:4000/svn/pyWARP/
D 4.5.4	http://www.bioxdm.org/ and http://www.edna-site.org/wiki/index.php/EDNA_Documents#The_spike_and_the_project_agreement_meeting
D 4.5.8	http://www.esrf.fr/UsersAndScience/Experiments/MX
D 5.2.8	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.2.10	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.2.11	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.2.12	http://www.ccp4.ac.uk/MrBUMP/
D 5.2.14	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.2.15	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.2.18	http://www.ccp4.ac.uk/projects/bioxhit_public/
D 5.3.2	http://evc.elettra.trieste.it/vcs/home.do
D 5.3.3	http://evc.elettra.trieste.it/vcs/home.do
D 5.3.4	see report here and from ELETRRA
D 6.2.4	http://ftp.esrf.fr/pub/scisoft/BioXHIT/TID/DNA_manual/DNAmanual_230507.pdf and
D 7.1.12	http://icarus.embl-hamburg.de/bioxhit/bioXHITReports.jsp
D 7.1.13	www.bioxhit.org --> management of the project
D 7.1.14	www.bioxhit.org
D WG1.1.2	https://www.pims-lims.org/svn/pims/crystallization/current/XtalPiMS_BusinessAPI/
D WG1.1.3	https://www.pims-lims.org/svn/pims/crystallization/current/XtalPiMS_BusinessAPI_PlateDBImpl/
D WG1.1.4	https://www.pims-lims.org/svn/pims/crystallization/current/XtalPiMS_BusinessAPI_PIMSDBImpl/
D WG1.2.1	http://www.oppf.ox.ac.uk/xtalpims
D WG1.3.1	https://www.pims-lims.org/svn/pims/crystallization/Annotator
D WG1.5.1	http://www.xtalpims.org
D WG1.5.2	http://www.xtalpims.org
Ms 1.2.2	http://www.oppf.ox.ac.uk/xtalpims
Ms 2.3.3	Reported in D 2.3.3

Ms 2.6.2	http://icarus.embl-hamburg.de/bioxhit/localArea/doc/Interim_Thompson.doc
Ms 4.5.4	http://www.bioxdm.org/ and http://www.edna-site.org/wiki/index.php/EDNA_Documents
Ms 5.2.4	http://www.ccp4.ac.uk/projects/bioxhit_public/
Ms 5.2.5	http://www.ccp4.ac.uk/projects/bioxhit_public/
Ms 5.2.6	http://www.ccp4.ac.uk/projects/bioxhit_public/
Ms 7.1.3	http://icarus.embl-hamburg.de/bioxhit/bioXHITPastWorkshops.jsp
Ms 7.1.4	http://icarus.embl-hamburg.de/bioxhit/bioXHITLocalArea.jsp
Ms 7.1.5	http://icarus.embl-hamburg.de/bioxhit/bioXHIT3rdAnnualMeeting.jsp

4. Annex 4.4
The front page of the BIOXHIT Reporting Database