EUREKA PROJECT E!2261 - EUROCARE X-RAY

1. General description

Project	E! 2261 - EUROCARE X-RAY	**Status**	Announced - 23-JUN-2000
Title	**Single Crystal X-Ray Diffraction Of Weakly Diffracting Materials**		
Class	Sub-Umbrella	**Technological area**	Medical and Biotechnology
Start date	15-OCT-1999	**End date**	15-AUG-2003
Duration	46 months	**Total cost**	1.8 Meuro
Partner sought	No		

Summary Research And Development Of Single Crystal X-Ray Diffraction Technology Which Can Be Used To Study Weakly Diffracting Materials. The New Technology Will Have To Incorporate Several Dominant Aspects Which Have Not Been Combined Before

Budget and duration

Phase	Budget(Meuro)	Duration (Months)
Definition phase	1.19	24
Implementation phase	0.61	12
Total	**1.8**	**46**

Member contribution

Member	Contribution	Position	Since
The Netherlands	**58.00%**	**Contact Member**	**14-SEP-1999**
United Kingdom	42.00%	Participating Member	23-JUN-2000

Participants

Company	Country	Type	Role
Bruker Nonius B.V.	**The Netherlands**	**Large company**	**Main**
Bede Scientific Instruments Ltd.	United Kingdom	SME	Partner

2. Project outline

Project description

Single crystal X-ray diffraction is a technology used to study the atomic structure of materials. A small and intense X-ray beam is used to illuminate a sample. The X-rays give a characteristic diffraction pattern. By recording X-ray patterns under several angles, an atomic structure can be derived using strong algorithms.
Customers for diffraction equipment are universities, science institutes and laboratories of major companies. The technology is rapidly evolving. In order to study weakly diffracting materials (often proteins for drug research), strong X-ray sources are needed, with very narrow beams.
In contrast to visible light, it is very difficult to focus an X-ray beam. By nature, X-ray lenses do not exist, while regular spherical mirrors will not work (the X-rays are just absorbed). In order to produce a bright but narrow beam, an extremely strong source is used, with a diaphragm at some distance in front of it. Often a graphite crystal is used to make the X-rays monochromatic, by selecting one reflection of the monochromator crystal.
It is obvious that generating a lot of X-rays and subsequently selecting a small part of them is not an efficient method, which also has practical limits in brightness. Moreover, the high power rotating anode generators needed for these X-rays are larger and require a lot of maintenance, because of the co-existence in a small area of cooling water, high voltage and lubricating liquids to allow the anode to rotate.
Over the last few years, the situation has changed. Several universities and university spin-offs have managed to make flat and toroidal, total reflection mirrors on which the X-rays are reflected under a very small angle and focused. These mirrors can focus the X-ray beam, generating a brighter X-ray beam, albeit with a small loss in spectral purity of the emitted X-ray beam, compared to monochromator crystals. More recently, complicated curved multilayers, in which the condition for diffraction is met over a wider range of angles, have been designed. This has resulted in a spectrally very pure X-ray beam. Both approaches have the effect that an X-ray bundle, diverging from a spot source, can be 'reflected' into a converging beam. This principle opens the way to the development of X-ray optics.
On another path, new, so-called Microfocus sources have been developed in which the electron beam, which hits the target to generate X-rays, is much smaller than in the traditional rotating anode sources. With these sources, a very small, but intense X-ray beam can be generated. Future sources using this technology will be much smaller, have lower running costs and use much less power.
Several academic and commercial groups worldwide have manufactured prototype source/option configurations which could be feasible for X-ray diffraction. NONIUS has purchased and evaluated several of those configurations, and selected some of them to continue research. NONIUS has concluded a partnership with BEDE SCIENTIFIC LTD., located in Durham (UK). BEDE is a well established player in the field of X-ray diffraction for process control, with the

emphasis on quality control of semiconductor wafers. BEDE has extensive experience in the development of X-ray sources and related optics. The X-ray configuration established by BEDE shows promising performance and is a logical candidate to be incorporated in the proposed R & D programme with NONIUS. BEDE has no experience in single crystal X-ray diffraction, and as such is complementary to NONIUS.

The partners will strive to develop and X-ray chain for single crystal crystallography. The requirements for such an X-ray chain are very critical. The immense amount of variation in designing sources, optics and detectors with the new technologies described above, require a large investment in R & D to be able to judge the feasibility of a combination and match the requirements with possibilities.

Three dominant aspects play a role in the feasibility of the new optics technology for the said diffraction purposes:

1. The divergence and dimension of the beam
2. The monochromaticity of the beam
3. The brightness of the beam.

All three aspects will have to be studied from the point of view of diffraction (the end-user) as well as from the point of view of optics technology. The partners therefore plan to cooperate on all three aspects.

Keywords: X-ray, diffraction.

Technological development envisaged

Introduction:

The requirements of an X-ray beam for single crystal crystallography on weakly diffracting, large molecule crystals are very critical. The immense amount of variation in designing sources and optics with the new technologies described above, require a large investment in R & D to be able to judge the feasibility of a combination, and match requirements with possibilities.

The three dominant aspects (mentioned in the description) play a role in the feasibility of the new optics technology for the said diffraction purposes.

1. Beam divergence and dimension:

For X-ray diffraction on a generally very small sample (50-100 micron), the X-ray beam should be either focused, quite parallel or have a minimal divergence. The proposed microfocus source and optics technology requires the optics to catch an as large as possible portion of X-ray light coming from the source. Therefore, the optics have to be as close as possible to the point source. The curvature and roughness of the optics are critical parameters for the resulting divergence of the beam.

It is unknown whether high divergence is limited in the sort of analyses of the proposed technology and what the effect is on the resulting data quality. Therefore some research of the limitations is needed, and some research within the source and optics set-up to reduce divergence or to what extent reduction of the divergence is needed.

In more detail, NONIUS and BEDE plan to collaborate in this research and do some development of test set-ups as follows:

NONIUS will study in detail the effect of the spot profile on the accuracy of diffraction data. In more detail, larger divergence will lead to overlapping spots. Overlap will lead to difficulties in determination of positions,

and thus to inaccuracy in the diffraction data. Although probably some software routines for separation or deconvolution can be developed, the better approach is to minimize overlap.
BEDE will study the variables that determine the final beam divergence. The curvature of the mirror is playing an important role of course, but also the precise positioning (and adjustments) relative to the source. It should be taken into account that the real shape of the source is small, but not the ideal point source.
2. Beam monochromaticity:
In the study of a sample, the X-ray wavelength plays an important role. Diffraction of the X-ray beam occurs at certain angles between lattice planes in the crystal, depending on the wavelength of the X-ray light (Bragg's Law). Different X-ray wavelengths will lead to diffraction spots at different locations. Therefore, preferably monochromatic light (containing one wavelength) is needed.
An X-ray optic is a complicated device. In the total reflection mirrors reflection only occurs at the 'critical angle'. In the ideal situation only one wavelength fulfils the the 'critical angle' condition on the mirror and is hence reflected. In practice, however, a 'band' of wavelengths is transmitted. If, for example, a Copper X-ray tube is used, two characteristic wavelengths called Cu K-alpha and Cu K-beta are present as well as some 'white' radiation, which normally has higher energy (lower wavelength). The white and the K-beta radiation is to be suppressed avoid X-ray the diffraction patterns on the detector from in fact consisting of two (or more) patterns, which are often overlapping. Filters, collimators and software may correct or take into account some of the effects, but the better approach seems to start at the source/optics combination. NONIUS and BEDE will collaborate in order to explore limitations and possibilities in more detail.
NONIUS will study the effect of smearing of diffraction spots due to a bad monochromaticity (especially K-beta suppression) on data quality and types of research that can be done. NONIUS does not have to start at zero, as many of the related problems play a role in the existing technology as well. Combined source/optics with thin metal filters and collimators will be made and evaluated.
BEDE will study the effect of the materials used and the curvatures of the total reflection mirror on resulting X-ray spectra. A few prototypes will be developed and evaluated. At the same time BEDE will study the possibilities and effects of using curved, multilayer mirrors, which have a spectrally purer X-ray output. A few prototypes will be developed and evaluated.
In their research the companies will seek feedback from knowledge centres to act as sparring partners. More specifically it is envisaged that some specialist professors from DURHAM UNIVERSITY (UK) and UTRECHT UNIVERSITY (NL) will act as scientific advisors. These people have broad experience in this field and have already indicated their great interest in the technology as described. A workshop will be organised regularly to evaluate data and discuss future steps.
3. Brightness:
The brightness of a diffraction spot at the level of the pattern detector is the result of a convolution within a long chain. Source power, light efficiency, collection

efficiency, mirror reflectivity, collimator characteristics, usable spot size and distances all play a role. Furthermore, the generator power setting influences the spot size because of space charge effects in the X-ray tube. For protein research especially, the brightness should be as high as possible, to make the weakest reflections (diffraction spots) just visible. NONIUS and BEDE will again collaborate in R & D to optimize brightness (and spot size) in more detail.
NONIUS will study the effect of brightness on the visibility of the weakest diffraction spots, taking into account reasonable measuring time and dynamic range limitations of the detectors. Furthermore, the continuous illumination of samples with a very bright and localized spot may damage the sample structure thus leading to inaccurate data. The latter study will be done on proteins especially.
BEDE will study the effect of source power, source spot size and optics geometry on final spot power, using the limitations defined by NONIUS' research. A feasible figure will be defined and used as a starting point for further chain development.

Markets application and exploitation

* Universities
* Laboratories of large (pharmaceutical) companies

The end products developed in this project will be exploited by the respective companies.

Project codes

BSI

AK	research
AKO.KO	experimentation
B	measurement, testing and instruments
BH	physical property measurement
BJN	x-ray analysis
COO.F	x-rays
MVS.TB	algorithms

NACE

33	Manufacture of medical, precision and optical instruments, watches and clocks
73	Research and development

3. Main participant

Company

Bruker Nonius B.V.
Oostsingel 209 Postbus 811, 2600 Av Delft
2612 Hl Delft
The Netherlands

Tel +31 15 215 2400
Fax +31 15 215 3500

www.nonius.nl

Contact

Dr. Lieuwe Boskma
Managing Director

Tel +31 15 269 8748
Fax +31 15 262 7401

boskma@nonius.nl

Organisation type Large company
Participant role Main

Contribution to project

Project leader. 1. Beam divergence and dimension 2. Beam monochromaticity 3. Brightness

---

Expertise

Expertise: expert in the field of X-ray diffraction. The company develops, produces and sells equipment and related products for X-ray diffraction. Four components in their area can be distinguished: 1. X-ray generation 2. Positioning of the crystal 3. Detection/scanning 4. Computers. Furthermore, NONIUS has developed conditioning equipment. These appliances are used to analyse the effects of temperature and pressure on the materials, or preseve the original shape of the crystals. NONIUS has obtained and developed extensive knowledge in the field of X-ray diffraction. All the company's products and related appliances are based on this principle. X-ray diffraction techniques are used to analyse the atomic structure of solid materials, particularly crystals, X-ray techniques are usually utilised for medical purposes. The rays consist of a form of radiation which is comparable to visible Light. The main difference lies in the fact that X-rays are able to penetrate certain opaque materials while illuminating others. These X-ray techniques are mainly used for medical purposes, quality control and safety services. Diffraction can be described as an interaction between X-rays and crystals. Under certain conditions, this interaction manifests itself as a reflection. Crystals as small as those present in table salt can be diffracted. Because the X-rays are able to penetrate the crystal, the mirror-effect (diffraction) will take place in the inner layers of the crystal, the so-called grids. A crystal has many grid surfaces. Because of this, many reflections can be obtained when a crystal is placed in an X-ray beam. By inference, a diffraction pattern is formed. This is the way a diffraction pattern is formed. The X-ray diffraction pattern can be recorded with an X-ray camera. This wall procedure can be repeated under different angles to build up a complete picture. The information provided by this scan, consisting of thousands of digits, is processed by a complicated computer program, resulting in a physical-chemical description of the analysed material. This description offers an extensive insight into the molecular structure. The technique can be used to analyse causes of disease (cancer, AIDS) and cures (new medicines). In the chemical industry, it can be used to develop flavours and dyes. It can also be used during judicial investigations. Universities, Science Institutes and Laboratories of major companies are customers for diffraction equipment. Contribution: 1. Beam divergence and dimension: NONIUS will study in detail the effect of the spot profile on the accuracy of diffraction data. In more detail, larger divergence will lead to overlapping spots. Overlap will lead to inaccuracy in the diffraction data. Although probably some software routines for separation or deconvolution can be developed, the better approach is to minimize overlap. 2. Beam monochromaticity: NONIUS will study the effect of smearing of diffraction spots due to bad monochromaticity (especially K-beta suppression) on data quality and types of research that can be done. NONIUS does not have to start on zero, as many of the related problems play a role in the existing technology as well. Combinations of source/optics with thin metal filters and collimators will be made and evaluated. 3. Brightness: NONIUS will study the effect of brightness on the visibility of the weakest diffraction spots, taking into account reasonable measuirng time and dynamic range limitations of the detectors. Furthermore, the continuous illumination of samples with a very bright and localised spot may damage the sample structure, thus leading to inaccurate data. The latter study will be done on proteins specifically.

4. Partner

Company	**Bede Scientific Instruments Ltd.** Unit 13d, Dh6 5ad Bowburn United Kingdom Tel +44 191 377 2476 Fax +44 191 377 9952 www.bede.com
Contact	**Dr. Graham Fraser** Tel Fax +44 191 377 9954 graham@bede.co.uk
Organisation type	SME
Participant role	Partner

Contribution to project

1. Beam divergence and dimension: 2. Beam monochromaticity 3. Brightness

Expertise

Expertise: well-established player in the field of X-ray diffraction for process control, with emphasis on quality control of semiconductor wafers. BEDE has extensive experience in the development of X-ray sources and related optics. The X-ray configuration established by BEDE shows promising performance and is thus a logical candidate to be incorporated in the proposed R & D programme with NONIUS. Contribution: 1. Beam divergence and dimension: BEDE will study the variables that determine the final beam divergence. The curavature of the mirror plays an important role of course, but so does the precise positioning (and adjustments) relative to the source. It should be taken into account that the real shape of the source is small, but not the ideal point source. 2. Beam monochromaticity: BEDE will study the effect of the materials used and the curvatures of the total relfection mirror on resulting X-ray spectra. A few prototypes will be developed and evaluated. At the same time, BEDE will study the possibilities and effects of using curved, multilayer mirrors, which have a spectrally purer X-ray output. A few prototypes will be developed and evaluated. 3. Brightness: BEDE will study the effect of source power, source spot size and optics geometry on final spot power, using the limitations defined by NONIUS' research. A feasible figure will be defined and used as a starting point for further chain development.