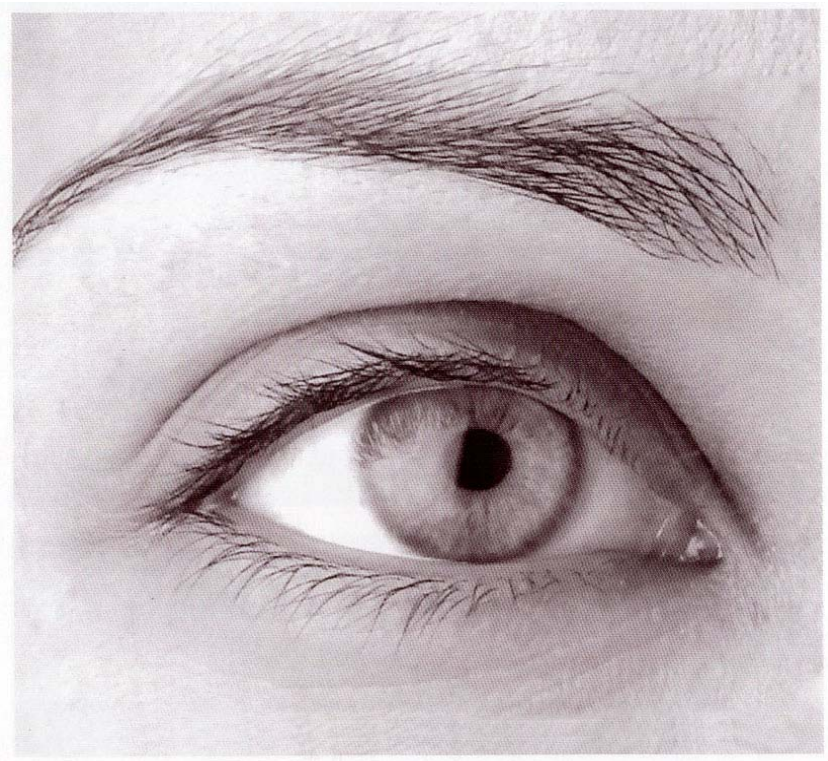
ALBA BIOMEDICAL BEAMLINE (ABME)



A Proposal for the ALBA S.A.C.

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1. Justification and Overview

1.1 Summary

A general purpose imaging and therapy beamline is proposed through the Spanish Synchrotron Users' Association (AUSE): the ALBA Biomedical (ABME) beamline.

The ABME is conceived as a dual experimental hutch beamline, one for the radiation therapy program and a second one for the imaging program; only one hutch will be active at a time. The purpose is to source the primary beamline with a single superconducting wiggler device to enhance the characteristics of the primary beam to the appropriated range of energies needed for medical applications.

This conceptual design has been prepared by ABME members of AUSE in coordination with ESRF scientists based on potential user needs, the currently available source specifications, and impact on ALBA as a facility.

The ABME beamline will be a national facility at the Spanish Synchrotron Facility. It is designed for the purpose of imaging biological tissue and conducting radiation therapy research using brilliant, monochromatic x-ray light. The proposed ABME research facility aims to be in the first phase of beamlines to be constructed at the Spanish Synchrotron.

The ABME facility is intended to improve upon existing dedicated biomedical synchrotron facilities by having the capacity to conduct imaging and radiation therapy on live humans, animals and plants.

The ABME facility will be designed to accommodate human patients from the moment when the necessary scientific evidence and experience is available and recommendations for medical use are clearly exposed. This will position the ABME facility as a world leader in medical applications with Synchrotron Radiation (SR).

The two major research tools provided by the proposed beamline are x-ray imaging and x-ray therapy. The ABME facility will address the interests of scientist and clinicians in the diagnosis and treatment of cancer (breast tumours and paediatric oncology), circulatory and respiratory disease (coronary heart disease, asthma), neurological (brain and spinal cord injuries), and musculo-skeletal disease and kinesiology (arthritis and injuries related with sport medicine), as well as conducting research which may increase the range of potential medical applications of SR.

The facility will offer the opportunity to use different techniques for research; Projection and computed tomography Imaging using K-edge Subtraction (KES), Diffraction Enhanced Imaging (DEI), Phase Contrast Imaging (PhC) and Fluorescence imaging, will be available for biomedical imaging research. The beamline will also be capable of Photon Activation Therapy (PAT) and Microbeam Radiation Therapy (MRT) for cancer radiation research. Continued monitoring of new and developing techniques and technologies will be maintained during the construction phase to ensure that the ABME facility remains at the cutting edge of medical SR uses.

1.2. Medical applications of Synchrotron radiation

The proposal suggests setting up a beamline whose main purpose is medical and which functions as a radiodiagnostic and therapy for human patients: However, it is fully intended that this station also acts as a space for research and development in these disciplines and related technologies.

Synchrotron light combines extremely high intensity, small apparent source size, high collimation, tunability, and a continuous energy spectrum (from the far infrared region up to hard X-rays), making this a uniquely useful tool for biomedical imaging and therapy. These characteristics of synchrotron radiation enable entirely new X-ray imaging techniques that can take advantage of unusual sources of image contrast. Conventional radiography produces images through the differential absorption of X-rays, but synchrotron-based imaging techniques can also produce high-resolution images using differences in the refraction and scatter of X-rays as they pass through tissue. Furthermore, synchrotron monochromators allow tuning to narrow energy bands that correspond to radiation absorption by individual elements. This adds another dimension to X-ray imaging: specific chemical elements can be mapped with high sensitivity and unprecedented resolution.

The extremely high intensity and collimation of synchrotron X-rays will also enable novel methods of radiation therapy that cannot be achieved with any other type of X-ray source. Some of these methods show great promise for the treatment of cancer.

1.2.1. IMAGING

1.2.1.1. Mammography

Breast imaging is a subject of intense inquiry within a number of research groups involved with synchrotron work. Diffraction Enhanced Imaging (DEI) is a technique particularly sensitive to subtle differences in the imaging of soft tissue, and has the potential to dramatically reduce the radiation dose to breast tissue during mammography. DEI provides images of the X-ray refraction and apparent absorption of an object using three sources of X-ray contrast: refraction, scatter, and absorption. The first two are properties not previously accessible by conventional radiography, and result in images with exquisite contrast. Using a mammography phantom, contrast enhancements in excess of 25 times that of conventional mammography have been observed by DEI.

1.2.1.2. Vascular imaging

Imaging of the cardiovascular system, particularly by K-edge subtraction (KES), was one of the first applications of synchrotron-based medical imaging. This resulted in the development of angiography with low doses of contrast agent introduced intravenously, rather than with intra-arterial injection of larger doses. If translated to a clinical setting, the new technique may obviate the need for hospitalization and lead to a much safer outpatient procedure for evaluating heart disease. These pioneering studies of coronary angiography could lead to critical research on the pathogenesis of tissue damage and on the dynamics of tissue repair resulting from micromyocardial infarcts.

It is expected that these fundamental vascular studies in heart muscle will be extended to examinations of the angiogenic response to disease- or treatment-induced damage (e.g., cancer and cancer treatment) in many other tissues and organs. In vivo micro-CT of the

vasculature of larger biological specimens (i.e., full transverse or sagittal sections of organs up to the size of lungs) could be studied using the full width of the ABME X-ray beam fan.

1.2.1.3. Bronchography

Groundbreaking experiments in synchrotron bronchography were conducted at Brookhaven National Laboratory in 1998 using xenon inhalation contrast (Chapman and Thomlinson). Recent studies (Renier, Bayat, Thomlinson) at the European Synchrotron Research Facility have shown that the spatial resolution provided by phase contrast and K-edge imaging is at the level of the respiratory lobule (terminal bronchiole and alveoli). Regional abnormalities in lung ventilation due to alterations in small airway function (such as those observed in asthma and chronic obstructive pulmonary disease) are particularly difficult to evaluate using traditional lung function tests. However, air–tissue interfaces appear with startling clarity using phase contrast and a respiration-gated synchrotron radiation computed tomography (SRCT) technique. These techniques allow direct quantification of xenon (Xe) as an inhaled contrast agent based on K-edge subtraction imaging (Bayat). The dynamics of Xe wash-in can be used to calculate regionally specific quantitative maps of lung ventilation. More recently, the development of spiral CT has allowed the acquisition of 3D images of the pulmonary bronchial tree and airspaces. This exciting technique gives access to quantitative measurements of regional lung volume, ventilation, and mechanical properties before, during and after experimentally induced bronchoconstriction. In vivo and ex vivo animal models for the study of acute and chronic pulmonary disease are expected to form a core part of the ABME research program. We anticipate that this unique approach will be used for testing the efficacy of pharmaceuticals on respiratory dysfunction.

1.2.1.4. Musculoskeletal imaging

Conventional X-ray sources are effective for imaging bony tissue, but are not sufficiently bright to image cartilage, ligaments and tendons. Diffraction-enhanced and phase contrast imaging, however, provide remarkable detail of such tissues. Diagnosis and outcome of injuries to joint ligaments, tendons and cartilage have tremendous impact on long-term productivity, quality of life, and health care costs in animals and humans. Biomechanical and biological parameters of normal and injured knee ligaments have been defined in rabbit and sheep models as well as in human subjects. Visualizing and quantifying the structural differences in the collagen organization between normal and healing ligaments is key to understanding joint injury, degenerative joint disease and osteoarthritis. Such images are expected to provide quantitative data that may lead to early diagnosis and accurate prognosis of degenerative changes.

1.3. Future Trends

In meetings held over the last few months with technical and scientific managers involved in different biomedical beamlines, as well as from specialist papers and meetings with other experts in medical imaging and radiotherapy, it is clear to us that the good results achieved with medical uses of synchrotron light will soon lead to the re-design and reform of existing and new hutches to make them fit for human patients.

Indeed, work is already ongoing on cross-evaluation of high-resolution mammograms with the analysis of mammary-tissue pathologies using X-ray diffraction with SACS. This work should lead

to a single test that allows both imaging and determining the pathological anatomy of the tissue being explored. In the area of therapy, efforts are being focused on developing techniques for the treatment of tumours in central nervous system tissue, as well as peripheral metastases.

We also expect to see an increase in collaborative work with the pharmaceutical industry, aimed at in-vivo monitoring and imaging of the therapeutic effects of specific drugs in animal and human patients. Likewise, in molecular biology we will soon see studies on the combined effects of certain pharmaceutical compounds and the irradiation of the target tissue.

The need for this installation may indeed clash with the consolidation or growth of already-established areas of research that are users of synchrotron light. Indeed, more 'classical' applications are supported by a solid background of many years, as well as a large community of researchers. The need for biomedical beamlines, however, is based more on future projections and a constant social demand for solutions to hitherto intractable problems. The promise implicit in these approaches, and the need to ensure their development, makes us think that new installations dedicated to biomedicine are necessary if we are to meet growing social needs and expectations in this area.

1.4. Strategic and Institutional Context

Because of its geographical location, at the core of a cluster of biomedical and clinical research facilities that is unparalleled in Southern Europe, ALBA is a perfect candidate for a medical beam station, taking to fruition and clinical practice the promise of high-definition X-Ray medical imaging and high-accuracy radio-therapy. Indeed, biomedical research using synchrotron light is at the forefront of research in this area, and a very significant impact on technological innovation can be foreseen.

Biomedical research in Spain has undergone a period of spectacular growth in the last few years, as demonstrated by the growth in the number of articles published in leading journals and the activity of large hospital clusters in cities such as Madrid, Barcelona, Seville, Valencia, etc.

As has been amply shown in a number of studies carried out in the ESRF's ID-17 station, synchrotron light presents a number of characteristics that make it highly interesting and relevant for diagnostic and therapeutic applications.

Furthermore, a biomedical beamline at ALBA will also benefit from its location near a university campus that houses a medical and veterinary faculties, a veterinary hospital of national reference, a high-performance sport research centre (the CAR St Cugat) and some of the best biological and biomedical research institutes and centres in Spain. This outstanding set of circumstances, coupled with the ability to perform *in vivo* studies on subjects and thus support important linear studies aimed at real medical problems, is expected to attract an impressive amount of interest and support from the health discipline. This case is only strengthened when taking into account the other key biomedical resources – both material and human – that are available in the greater Barcelona area.

A recent study[1] (CAMI *et al., 2002*) shows that Catalonia produces the majority of publications in the areas of radiotherapy and nuclear medicine (32% of the total), and is second in biophysics,

[1] Camí J, Suñen E, Carbó JM y Coma L. *Producción Científica Española en Biomedicina y Ciencias de la Salud (1994-2000).* Informe del Instituto de Salud Carlos III-Fondo de Investigación Sanitaria. http://www.isciii.es/paginas/fis/mapa

after Madrid (24% of total). Indeed, within a radius of 15 Km (10 miles) around the proposed site for ALBA, there are 6 large general hospitals with access to high-technology medical equipment, and a further 10 smaller hospitals with very good radiodiagnostic, radiotherapy and nuclear medicine services.

Crucially, the presence of a large number of general hospitals with experience in high-technology imaging and radiotherapy technologies would not only assist in the design of new experiments and techniques, but would also facilitate the transfer of knowledge and technologies from the research element of the proposed biomedical station from the R&D laboratories to wider clinical use.

Furthermore, these hospitals are also part of the network of hospitals training medical specialists in Spain (the MIR programme), and every year they take on nine (9) new trainee doctors in specialisms related to radiodiagnosis and radiotherapy. Thus, and given the fact that specialist-training in Spain lasts four years, there is at any one time over 30 trainees with an interest in this installation.

The reasoning behind this proposal for a medical beamline is not only scientific – although the technologies involved would in themselves justify such a proposal – but also reflects a number of key strategic and socio-economic factors which may be taken into consideration.

The strategic case also impinges on this concentration of biomedical expertise, as Catalunya and more specifically the area around Barcelona, have explicitly stated the aim of becoming one of the key 'bioregions' in Europe. This development ensures the continued support of policy-makers and other key stakeholders in research-policy for a biomedical line, as well as guaranteeing a high public profile for the infrastructure as a whole – no longer an abstruse piece of equipment for scientists only, but a useful tool of benefit to the whole community.

Of key importance, in terms of the comparative advantages of Spanish research in this subject area, this infrastructure would be one of only 4 similar facilities worldwide. Having such a facility available in Spain would ensure access to Spanish researchers needing this infrastructure, since beam time on the other international installations is not easily obtained. Potentially, this also offers the possibility of addressing the tendency for synchrotron technology to appear inaccessible to less obvious user communities. Both of these advantages can be critical when it comes to sustaining the hard-won excellence in biomedical sciences that has developed in Spain over the last few years. Although the research programs supported by this facility will seek to address primarily clinical issues, a parallel focus on new research and development in synchrotron imaging and radiation therapy will keep Spanish science in this area to the vanguard of international science.

Furthermore, the proposed structure of this laboratory, at the centre of a network of trained scientists, technicians and medical practitioners, and embedded from birth in a network involving some of the top biomedical synchrotron beamlines in the world, will allow the development of training-through-research activities and highly-qualified personnel in an area of crucial importance for human knowledge in Spain.

It can be argued that building a synchrotron solely for medical purposes would not be justified in view of the current state of the art. However, it can equally be argued that when a new synchrotron is being built in a region that has declared its intention of becoming a bioregion, and

which presents a very significant biomedical potential, it would be difficult to justify not having a beamline for biomedical purposes.

2. Scientific Case

2.1. Techniques

Experiments that use SL in medicine in the existing laboratories can use different techniques to obtain either images or a therapeutic effect.

Summary of Imaging and therapy methods

Technique	Energy Range (KeV)	Applications
KES	20- 60	Lung imaging, angiography.
DEI	20- 90	Breast, lung and cartilage imaging
PhC	20- 90	Soft tissue (Breast)
CT	20- 90	Bronchography, bone, brain
MRT	80- 120	Nervous system tumours
PAT	80- 120	Nervous system tumours

Phase- Sensitive X- Ray Imaging

The conventional approach of x-ray image formation relies on absorption as the sole source of contrast and draws exclusively on ray or geometrical optics to describe and interpret image formation. This approach ignores another, potentially more useful source of contrast-phase information. Phase-sensitive techniques, which can be understood using wave optics rather than ray optics, offer ways to augment or complement standard absorption contrast by incorporating phase information.

Clinical and biological studies stand particularly well poised to benefit from the development of phase-sensitive techniques. Absorption contrast works well in distinguishing between hard and soft tissue: Heavier elements, like calcium in bones and teeth, have a much higher absorption cross section than the lighter elements that constitute soft tissues. However, in many clinical situations, such as mammography, there is a need to distinguish between different kinds of soft tissue - for instance between tumours and normal tissue. Because the absorption is small to begin with, and differences in density and composition are slight, standard x-ray imaging is not as successful at this task.

The behaviour of x rays as they travel through a sample (such as a patient) can be described using a complex index of refraction, just as in conventional optics. In the x-ray region, the index of refraction, n, deviates only slightly from unity; it can be written as $n = 1- \delta - i\beta$, where β describes

the absorption of x rays and the phase-shift term δ incorporates refractive effects. At typical mammography x-ray energies of 15-25 keV, the phase-shift term can be up to 1000 times greater than the absorption term, on the order of 10-7, compared to 10-10. Thus it may be possible to observe phase contrast when absorption contrast is undetectable. X rays passing through regions of differing δ pick up different relative phases, which corresponds to being refracted and produces a distorted wave front. These phase differences are detected by the various phase-contrast techniques.

Phase contrast may also prove useful in biological and medical studies because it falls off less quickly at higher energies than absorption contrast: $\delta \alpha E^{-2}$, whereas $\beta \alpha E^{-4}$. Phase contrast relies only on refraction of x rays, not on absorption, and so imaging can be done at higher energies where the absorbed radiation dose can be less, thereby reducing potential damage to tissues.

Several research groups are exploring ways of exploiting phase information as a source of image contrast. These approaches fall into three broad categories: interferometry, diffractometry, and in-line holography (or free propagation contrast).

Diffraction Enhanced Imaging

Diffraction enhanced x-ray imaging (DEI) is a new technology that makes use of x-ray refraction and scattering as well as absorption in developing image contrast. The new sources of contrast are particularly well suited for soft tissue imaging, which is one of the present difficulties with conventional x-ray sources (breast, lung and cartilage imaging).

DEI basic principle is base upon the introduction of fine selectivity for the angular deviation of x-rays traversing the subject. It uses collimated x-ray beams produced by a perfect crystal monochromator and an analyser crystal positioned between the subject and the detector.

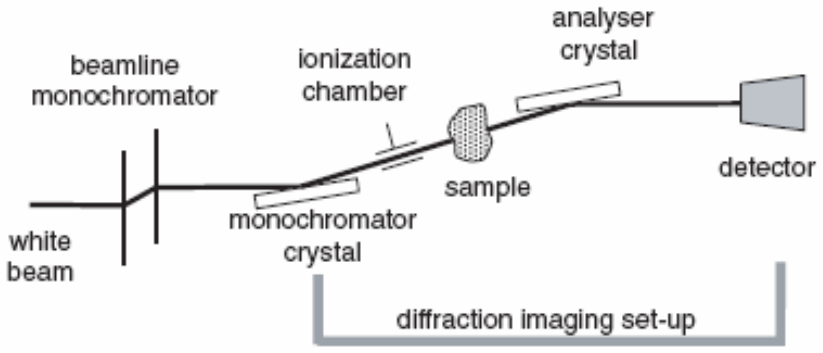


Figure 1. Typical experimental set-up with SR source. The white beam is monochromatized by the beamline monochromator. The DI set-up consists of a monochromator, a linear/rotating stage for the sample, an analyser crystal and a detector.
[Bravin A. Exploiting the x-ray refraction contrast with an analyser: the state of the art J. Phys. D: Appl. Phys. 36 (2003) A24–A29]

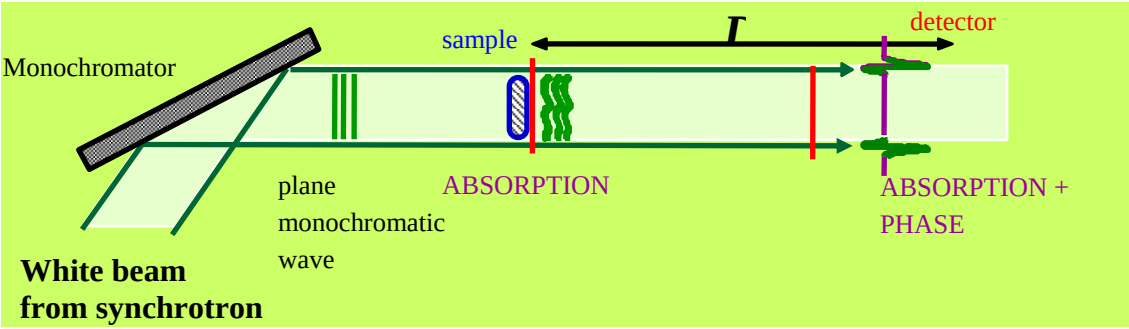
DEI's angular sensitivity allows measuring, besides the x-ray attenuation of the subject, the gradient of x-ray index of refraction, and the yield of "ultra-small-angle scattering". Since DEI's contrast mechanism does not rely on the absorption of the subject, it is ideally suited for soft-tissue imaging.

Propagation Phase- Contrast Imaging

If just a detector, and no analyser crystal, is in the beam path, the x-rays emerging from the sample at their various angles will propagate through free space until they reach the detector. With the detector immediately behind the sample, one will get a conventional absorption image. If the source is very highly coherent and the detector is placed very far behind the sample, one will observe a fringe pattern as different components of the beam, having been diffracted by the sample, interfere with each other on further propagation through space. This regime corresponds to Fraunhofer or farfield diffraction. The interference pattern contains useful phase information, but extracting that information is an ongoing computational and physics challenge.

With the detector placed at an intermediate distance, one gets Fresnel or near-field diffraction. Here, a combination of imaging and diffraction effects is found, typically involving interference fringes at the edges of features. These fringes improve edge visibility. The optimum positioning of the detector for best enhancement effects varies from sample to sample, depending on the x-ray wavelength and the size of the features of interest.

This "in-line" phase-sensitive technique, exploiting Fresnel diffraction and dubbed phase-contrast imaging (although it is distinct from optical phase-contrast imaging), was first explored by Anatoly Snigirev and co-workers at ESRF and by Wilkins and colleagues at CSIRO. It is very similar to the original techniques for holography developed by Dennis Gabor in 1948.



In practice, obtaining a phase-sensitive image just involves setting the detector (film or CCD camera) at a distance D on the order of one tenth of a meter from the sample. An absorption image is obtained if D is small (mm range). This corresponds to the fact that the region in the sample that affects the image at a point of the detector has a size $r = \sqrt{(\lambda D)}$, the radius of the first Fresnel zone. When D is a few mm, the size of this zone is below the resolution of the detector (mm), and no interference will be observed: only absorption contrast will be effective. For larger values of D, but with r remaining small with respect to the size *a* of the object to be imaged, the edges of the object behave independently, and are the only contribution to the image. The best sensitivity to a phase

object of size *a* is obtained for a distance $D \approx a^2/2l$, but then the image is a hologram which does not look much like the object.

The phase variations across the beam at the sample exit lead to variations in intensity, hence to contrast, provided the phase has a non-vanishing two-dimensional Laplacian, $(\partial^2\varphi/\partial x^2) + (\partial^2\varphi/\partial y^2) \neq 0$. They show up, for increasing values of D, through the appearance of a black-white line at the phase jumps, then by a set of Fresnel interference fringes which become more and more obtrusive: the image is then an in-line hologram.

The set-up used essentially consists in a monochromator made up of perfect silicon crystals, located a distance D from the insertion device (a variable gap wiggler or an ondulator) which acts as its photon source. Of course, phase inhomogeneities give an image also if they do not arise from the sample. To avoid these unwanted images, the optical elements in the beamline (beryllium windows, filters and monochromators) are submitted to unusually stringent demands.

K-Edge Subtraction

The K-Edge subtraction (KES) method relies on the abrupt change in photoelectric absorption associated with an element. This absorption is due to the promotion of a K shell electron to the continuum. To be use for medical or biological imaging, this absorption edge needs to be in a photon energy range that will allow the x-rays to traverse the object. Most of the elements that have an interest for medicine have absorption edges in excess of 30 KeV. To obtain sensitivity to the element, a subtraction method is used. Over a narrow energy range, most elements and compounds in the body change very little and thus can be considered nearly constant. Thus if the transmission is measured at two energy incrementally displaced from the absorption edge, a subtraction of the logarithm intensity will result in a image proportional to the projected density of the contrast material. This approach gives sensitivity to the contrast agent in the 1 mg/cm^2 range with modest exposures.

Phase

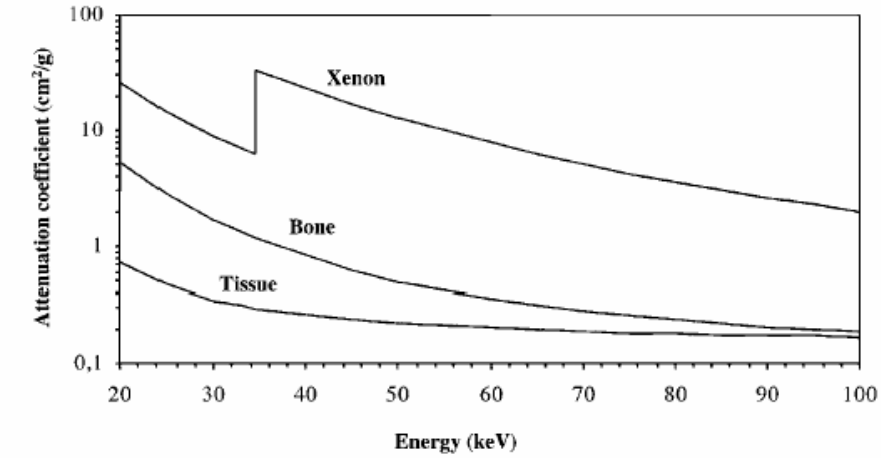


Figure 1. Attenuation coefficients of Xe, bone and lung tissue expressed as a function of photon energy. The attenuation coefficient of Xe increases by a factor of 5.4 when the absorption edge at 34.56 keV is crossed.
[S Bayat. Quantitative functional lung imaging with synchrotron radiation using inhaled xenon as contrast agent. Phys. Med. Biol. 46 (2001) 3287–3299]

The monochromatic beams are focused and crossed at the sample, beyond which they diverge and are recorded by the dual-line Ge detector.

The KES method was originally developed for human coronary angiography. Subsequently the method has been used in many other fields of medical imaging. For KES imaging, a contrast agent is introduced into the organ to be imaged, and two simultaneous images are recorded using two X-ray energies that bracket the K-absorption edge of the contrast agent. The difference image in a logarithmic scale yields the distribution of the contrast agent while the signal from the other parts of the object is eliminated.

Micro-planar beam Radiation Therapy (MRT)

Conventional radiation therapy has limited success in treating brain tumours because of its potential damage to the surrounding normal central nervous system (CNS) tissue. This limitation makes treating high-grade gliomas palliative rather than curative. Radiation is thought to damage the normal CNS in part by injuring the microvasculature. Microbeam Radiation Therapy (MRT), an innovative approach to therapy, appears to address this limitation. MRT, initiated at the National Synchrotron Light Source (NSLS), BNL, and currently pursued also at the European Synchrotron Radiation Laboratory (ESRF), Grenoble, France, uses segmented x-ray beams as parallel, thin (<100 μm wide) planes of synchrotron-generated x rays (microplanar beams, or microbeams). Single-exposure unidirectional MRT is tolerated at in-beam doses up to 10-fold larger than that of broad-beam irradiation by the normal brains of adult rats, weanling rats, duck embryos, and piglets. All these studies used beam widths of about 27 μm and beam spacings of 75-200 μm on-centre. Furthermore, unidirectional MRT preferentially kills the intracranial rat 9LGS tumour at doses quite tolerated by the normal brain. MRT demonstratively has a larger therapeutic index for 9LGS (ratio of maximum dose tolerated by normal tissue to minimum dose ablating tumour) than do broad beams.

MRT's 10-fold advantage in the brain's tolerance for in-beam microbeam doses represents about a 3-fold advantage when the average (or "integrated") dose is used instead, indicating that it is not merely due to the "volume factor" (the ratio of total tissue volume to the volume of in-beam tissue, which was about 3 in the studies). Therefore, a biological effect must be involved. We hypothesize that normal-tissue-sparing of MRT is due to the replacement of lethally injured endothelial cells in the direct microbeam paths with their neighbours surviving between the beams. This repair may fail in the tumour because of its lesser-developed microvasculature.

Photon Activation Therapy (PAT)

The objective of patient treatment planning protocols in cancer radiotherapy is to deposit maximum energy per gram of tumour and minimize the dose to surrounding normal tissues. However, within the tumour treatment volume, only the cellular DNA, whose mass is merely 0.25% the mass of the entire cell, has been identified as the critical target for killing the cell with radiation. Therefore, the probability that the quanta of energy emitted by photons will interact and be absorbed at the DNA target site is extremely small. One approach that can be taken to increase the efficacy of the radiation is to introduce high Z atoms into the DNA. These atoms have a higher probability for absorbing radiation than that of the ordinary biological atoms (C, O, H, and N). Furthermore, when

activated by photons whose energies are suitable for inducing a photoelectric effect in the atom, the emission of low energy, short-range Auger electrons, can act like an energy sink directly in the DNA. These electrons increase the effective radiation dose to tumour while sparing surrounding normal tissues. Photon Activation Therapy (PAT) takes this approach in an attempt to improve cancer radiotherapy.

PAT utilizes a drug to transport and attach high Z atoms to tumour cell DNA, and photons whose energies are suitable for inducing a photoelectric effect in the atoms to impart dense, clustered ionisation directly at the critical target and significantly increase the probability of non-repairable, lethal damage to the tumour cell. This binary approach to cancer treatment can avail itself of either synchrotron radiation or implanted brachytherapy seeds as the sources of radiation, depending upon the required energy for activating the high Z atom.

Synchrotron radiation is an ideal source because photon energies can be precisely tuned to the absorption edges of the various atoms to meet the requirements for the induction of a photoelectric effect, provided that the activating energy is capable of penetrating the body to the depth of tumour. In those cases where the activating energy is too low to achieve penetration, the interstitial implantation of radioactive brachytherapy seeds directly into the tumour can be applied. The therapeutic gain from the implanted radiation sources, in combination with the DNA-localized high Z atom, can then be predicted through experimentation with synchrotron radiation. X-ray microtomography techniques using synchrotron radiation can also be used to search for and identify the intracellular localization of the high Z atoms within the cell.

2.2. Training programme

A training programme is being developed with two separate but complementary aspects.

On the one hand, training must be provided for future medical specialists, focused on the provision of training and expertise in the uses and advantages of the different applications of these applications. Early consultations on this programme have already begun and a first draft of this programme, prepared by the Catalan will be available for the SAC interviews.

On the other hand, a research and development programme in this area has been developed, which will be implemented with the collaboration of the ESRF and the Canadian Light Source's biomedical beamlines. We are confident that this research will begin its activities in 2005.

2.3. Research centres and Hospitals

A significant number of the most scientifically active public research centres and Hospitals have expressed an interest in collaborating in the development of the beamline itself and the training programme associated with it.

For a number of reasons, at the time of submission, expressions of interest from these institutions and researchers were not available. They will be presented to the SAC during the evaluation interviews in 2005.

3. Experimental Station Specifications

In order to implement this vision, we propose to build a medical beamline with two hutches – one located closer to the main ring and dedicated to radiotherapy (RST) and a second hutch, at twice the distance from the ring, devoted to medical imaging diagnostics (RSI).

The RST would be located some 30 m away from the storage ring. This station would be the first one that would have to be built and would allow the development, using animals, of the protocols necessary to implement, in as little time as possible, a human radiotherapy service.

Whilst the second station was under construction, this first station would also allow the first trials in radiodiagnosis. The second station (RSI) would be some 70 to 100 m from the storage ring. The final distance would have to be adjusted according to the dimensions of the beam and the energy flux.

Once the building phase was concluded we should be left with two specialised stations – one for diagnosis and the other for radiotherapy. Both should function as a clinical service for human patients, but also as research centres for new biomedical applications of synchrotron light.

3.1 Infrastructure and Laboratories

The following section gives a more detailed overview of the requirements of the infrastructure. Space requirements are modelled on the requirements at the ESRF ID-17 biomedical beamline.

Beamline control room

A control room next to each experimental hutch is required. One can be the principal and one secondary. The size of the principal control room has to be about 40 m2. For the secondary, half that could be sufficient.

Workshop area

An area for a small workshop for small sample preparation, creating and adapting set-ups and sample holders should be available (at least 20 m2). If there are two experimental hutches, a technical area has to foreseen in both cases.

Storage areas

It is necessary to have large storage areas in order to stock set-ups, phantoms, as well as consumables for animal care and cell biology.

Computing rooms

At the beamline. It must host the main computing system for data handling (image reconstruction, data treatment). A 20-30 m2 space should be sufficient.

Sample preparation laboratories

Used for the preparation of contrast agents, filling of plastic phantoms, final preparation of biological samples and tissues, etc. It should be equipped with a sink, a couple of working benches and a chemical hood. A 20-30 m2 area should be sufficient.

Patient room

In view of clinical trials a room for hosting a patient has to be foreseen. Space for a bed and for installation of emergency devices has to be allocated.

Patient preparation room

Next to the irradiation room, a patient preparation room has to be envisaged. This room has to be "hospital standard" from architectural point of view (floor, ceiling) to permit sterilisation if necessary. If a fluoroscopy unit has to be foreseen it should be located in this space (lead shielding doors, etc). It might serve for:

- catheter implantation and permeability tests
- administration of drugs
- small emergency care units

The path to bring the patient to the irradiation room has to be:

- as short as possible
- not through technical areas

The irradiation room has to be flexible to be transformed in a "radiological cabinet like" room. Equipment for covering instruments should be foreseen (tent, etc).

Annexed laboratories

Animal facility

To host animals for short and long term. The facility should be prepared for the following animal models

Rodents (rats, mice, nude mice): for radiotherapy protocols (survival after treatment), brain permeability studies (Cerebral Blood Volume and Flow), effect of drugs combined with radiotherapy (antiangiogenic drugs, chemotherapic).

Rabbits. Lung studies (asthma, pulmonary disease, bronchopathia cronica obstructiva), bone studies (long term follow up of implantations, effect of osteoporosis drugs), angiography studies (spinal circulation, brain angiography).

Large animals: in view of clinical protocols, before to submit proposals to Ethical Committee. Possible interesting models are pigs (for radiotherapy: brain irradiation. For imaging: central circulation (heart, arteries)).

Facility.

An equipped facility for hosting these animals, even for long term (at least rodents) should be in the vicinity of the beamline (max. 1-2 km) and easily accessible, if not available at the beamline itself.

Whatever the case, in the very close vicinity of the beamline (max 100-200 m), a space for final animal preparation has to be foreseen.

A 20-30 m2 space for anaesthesia, small surgery (f.i. introduction of catheters) has to be included.

For comparison, the ESRF has a 145m2 animal house, which can host rodents (up to 500), rabbits (up to 20) and large animals (up to 4 pigs). Annexed there is a surgical-preparation room for animals (20 m2)

Cell laboratory

Living cells are used in various contexts:

- for implantation in animals (tumour cells)
- for direct irradiation (PAT studies),
- metal content-effect studies (micro-fluorescence analysis),
- bystander effect studies (single cell irradiation).

The facility has to allow:

- cell culture (incubators)
- cell treatment (basic instrumentation, laminar flow hood)
- cell analysis (counting, centrifugation etc)

The laboratory might be classified L1, but L2 is more appropriate (for handling human cancer cells). L3 is probably not necessary (transgenic) and must be separated in any case.

For comparison, the ESRF presently has an L1 laboratory at the beamline (15 m2), which will be upgraded to L2.

It is not necessary that this laboratory be in the close vicinity of the beamline. Anyway, it has to be rather close (better next) to the animal facility and the molecular biology laboratory. If this laboratory is not at the beamline, at least a room where last-minute manipulation is possible and equipped with a laminar hood and incubators (~20 m2).

Molecular biology laboratory

Molecular biology related to SR studies is an emerging subject. Interesting subjects are

- the effect of radiotherapy on cells (production of double strand brakes in various radiotherapy conditions),
- pathway of DNA reparation studies,
- effect of proteins in reparation mechanisms,
- bystander effect.

The laboratory should be close to the cell laboratory, but not necessary next to the beamline (1-2 km far can be sufficient). It should have equipment for electrophoresis, DNA fragment handling, autoclave, and chemical store.

Chemical laboratory

There should be access to chemical laboratory on site, but not at the beamline.

In no case will it be necessary for all the scientific and technical requirements specific to each and all of the experiments to be carried out at the medical beamline to be built on the ALBA site. Although it is already proposed that some will be constructed there, the Universitat Autònoma de Barcelona is located less than 1 Km away, and has available more than 500 laboratories and services which will allow the work needed between experiments.

3.2. Spatial distribution of the Laboratories

The attached schematic of the architecture of the station is a first draft of the possible beam station. It should be said that this was designed purely for purposes of clarity in preparing this proposal, and is not included as a model for the actual building.

From the moment when a decision is made to use the stations for human patients a floor plan must be laid out which minimises the impact that a visually 'aggressive' structure like the synchrotron can have on patients. This impact is increased when the observer is a person who, for whatever circumstance, is already under great stress due to their physical and psychical condition.

To ensure this impact is minimised it would be advisable to build an annexe to the main installation, specially designed to process the admission of patients in the service.

On a lower floor this building should include patient admission, attention and an emergency care service for the patients being treated.

On an upper floor there would be the management and administration of the hutches, as well as the offices of the technicians, scientists and trainees. It would also be useful to have some laboratories for the preparation of samples and final preparation of small animals.The design of

these stations should ensure that human patients and animals never use the same entrances and exits.

The logic behind this design responds to different needs. Patient care installations should be on the ground floor in order to facilitate the logistics of moving patients who may have reduced mobility. At the same time locating patient care on the ground floor would allow the patient building to be built together with the main hutch, with only the upper floor being completed. When human patient protocols were completed, it would only be necessary to finalise the interior partitions. This would be much better for the stability of the beamline.

As has been explained in section 2.1 of this proposal, we are talking of a beamline with two hutches.

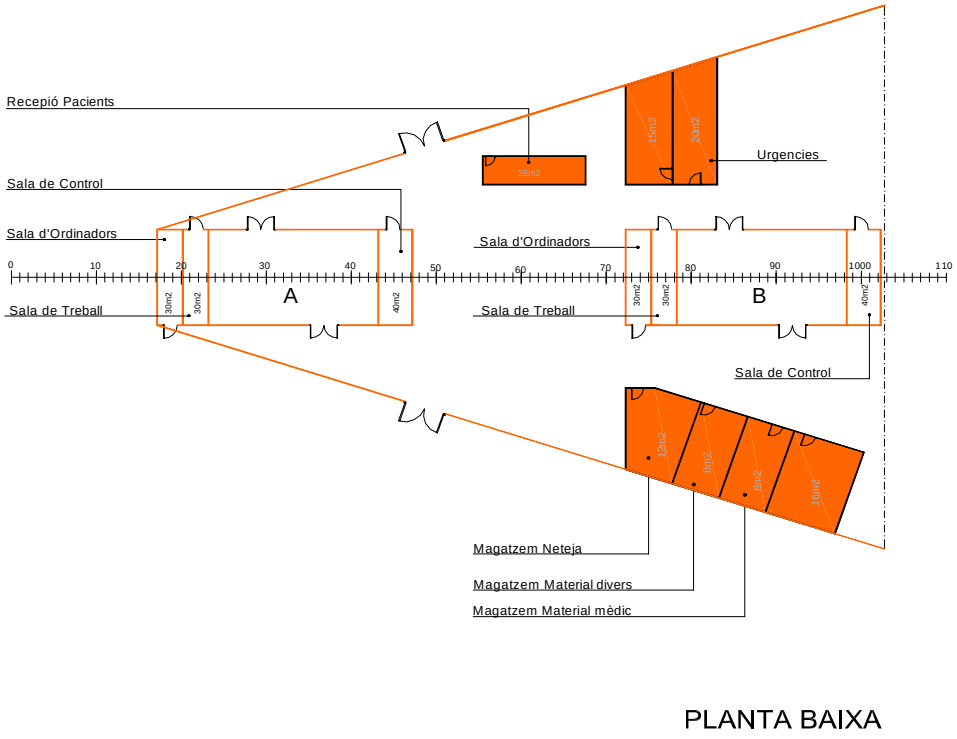


FIGURE 1 *Ground floor of the beamline. The two hutches can be observed together with the annexe building where the facilities for human beings would be located.*

On the ground floor, as can be seen in figure 1, each hutch has a data analysis room, a workroom and a control room. Access to the beamlines for animals and biological samples is always from the opposite side of the patients' entrance, and in the case of small animals is through the upper floor, where the research facilities are located.

Figure 2 shows some of the facilities for researchers, including offices, laboratories and small operating rooms. Neither figure includes any of the facilities that would be required for a public building but space is sufficient to include them. Also, the design provided attempts to minimise the aesthetic clash with other stations.

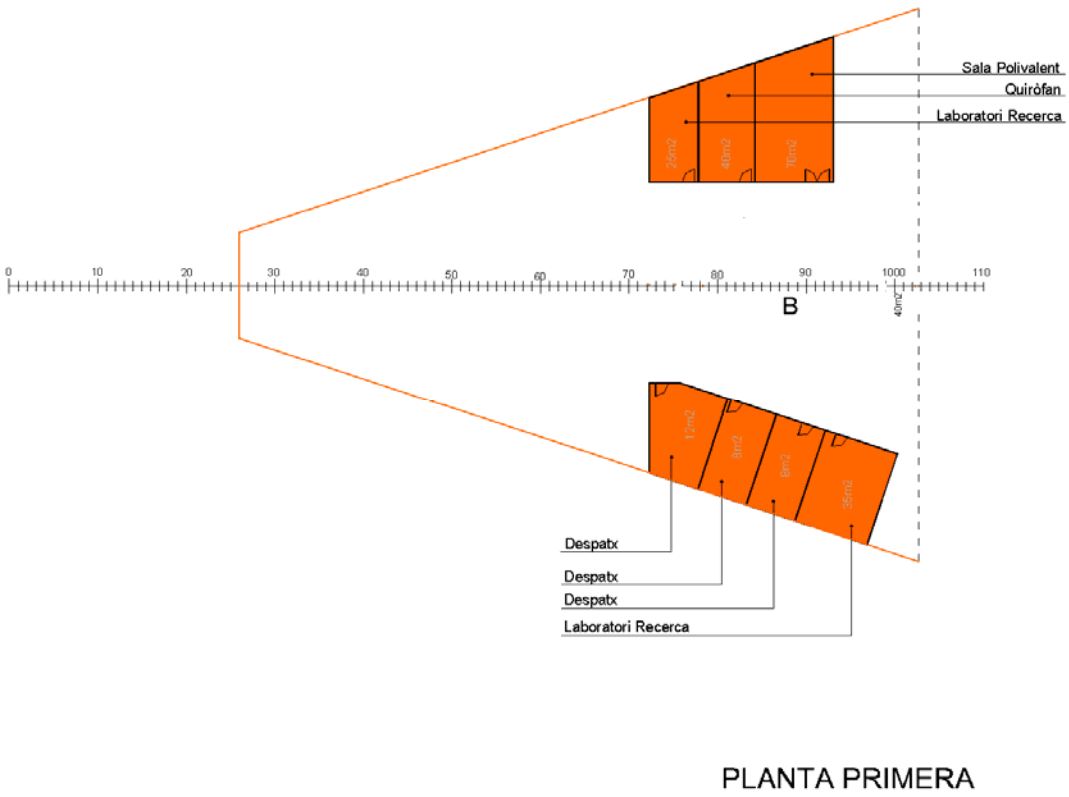


Figure 2 *Upper floor of the annexe building, showing the facilities for researchers.*

We believe that it will be necessary to build both beamline hutches at the same time. After consulting with many experts it has become clear that the option of building both stations separately would only hinder the work, as one complements the other. This view is reinforced by the recommendations made by the Canadian Light Source SAC in the case of the Canadian biomedical beamline.

3.3. Safety Systems

Safety system

ALBA's high intensity, high energy electron beam is a potentially lethal radiation source and hence many redundant measures aimed at preventing accidental exposure of personnel to the beam or exposure to beam-associated radiation sources are in place. ABME beamline will be operated just like a standard ALBA beamline for what concerns the staff safety.

In addition, a fast acting and fast responding Patient Safety System (PSS), linked to the machine RF cavities damping line, must be developed to protect the patients from excessive local or diffused radiation doses.

General safety system

To minimize the biological effects of radiation, special rules and regulations are set forth for individuals occupationally exposed to radiation. The amount of radiation received by persons exposed occupationally should not exceed the dosages specified in the National Radiation Safety Policies and Procedures Manual (Real Decreto 783/2001 del 6 de julio, por el que se aprueba el Reglamento sobre Protección Radiológica contra Radiaciones Ionizantes).

Dose Limits/Monitoring Requirements. The average annual dose of a radiation worker is about 100 MsV in a period of five consecutive years. There are special regulations for pregnant women and students.

Rooms or areas where radiation- producing equipment is used are posted with this sign.

Patient safety system

Safety system has to be designed to prevent overexposure of the patient. The system used in ESRF consist in an ion chamber that measures the x-ray dose given to the patient, which detects both monochromatic fan-shaped beams at the same time. Two similar dose monitors were installed to provide the redundancy necessary for safety reasons. They are the last beamline components before the patient. Two independent fast-acting shutters are used in case of emergency to stop the beam; each one is capable of stopping the full monochromatic beam. If a problem is detected by the patient safety system, the x-ray beam is shutdown in 10 ms.

4. Beamline specifications

4.1. Source characteristics

Requirements for radiation therapy programs

The applications for Microbeam Radiation Therapy (MRT) and Contrast Enhanced Synchrotron Stereotactic Radiotherapy (CESSR) need a high flux in the hard X-ray range (50-150 keV). MRT, in particular, needs a filtered white beam with a maximum intensity around 100 keV. Dose rate has to reach the range of several hundreds of Gray/s. The horizontal beam size could be limited to 4-5 cm because the target of MRT is a rather small tumour.

CESSR needs an intense monochromatic beam at energies around the platinum K-edge (~78 KeV). Also in this case the horizontal beam size could be limited to 5 cm.

These figures, in terms of dose rate and flux, can be obtained at a 3 GeV machine with a superconducting wiggler source.

Requirements for imaging programs

In vitro and in-vivo imaging programs are foreseen in the two experimental stations. The proposed scientific application requires an intense X-ray flux in the energy range 20 KeV (phase contrast imaging) 100 KeV (imaging of the target before radiotherapy treatment).

In addition, the beam dimensions (horizontal aperture and vertical size) have to match these requirements.

In the first experimental hutch (~ 30 m from the source) in-vivo experiments on small animals are foreseen and require a limited field which can be as low as 5 cm. Imaging before clinical MRT could be also be performed with a limited beam horizontal size even if it would be an advantage to a 15-20 cm wide beam.

In the second experimental hutch (~ 80 m from the source) pre-clinical and clinical imaging programs can profit of the natural divergence of the beam and larger samples can be imaged. A horizontal beam size of about 20 cm should therefore be envisaged for large animal and target recognition in CESSR.

An additional critical point is also the uniformity of the intensity in the horizontal plane.

The source

Two kinds of sources have been preliminary investigated for this proposal. The figures of merit for the specifications of the in terms of flux, dose rate and beam size have been calculated in the following cases considering:

- the parameters of the proposed ALBA wiggler [1]; hereafter called AMBE-W1

- the parameters better tuned for the AMBE beamline project; hereafter called AMBE-W2.

On a first survey both configurations are compatible with the operations of the storage ring, but a more accurate investigation must be made in collaboration with the ALBA storage ring experts. The significant figures have been calculated following the formulas reported in the X-ray Data Booklet [2] and by using the XOP software package [3]. Results are shown in Table1. For sake of comparison, parameters of the ESRF ID17 wiggler are also reported.

Tab.1. Comparison of the parameters for two different superconducting wiggler sources at ALBA with the ESRF ID17 wiggler source.

	AMBE-W1	AMBE-W2	ESRF
electron energy, E (GeV)	3	3	6
$\gamma=E/(mc^2)$	5780	5780	11742
stored current (A)	0,4	0,4	0,2
maximum field on axis (T)	3,5	4,5	1,6
critical energy on the central axis (KeV)	20,94	26,93	33,5
period length (λ_w mm)	60	100	150
number of poles	10	10	11
total radiation power (kW)	8,4	23,1	14,7
K value	19,6	42,03	19,6
max. angular deflection □ (mrad)	3,34	7,1	1,7
length of magnet (m)	0,3	0,5	1,65
central brightness at the critical energy	6,95E+14	6,95E+14	3,06E+15
horizontal aperture at 30 m (2□□) (mm)	200	430	100
vertical beam size at 30 m (20 KeV) (mm)	6,9	7,7	4,2
vertical beam size at 30 m (100 KeV) (mm)	3,5	3,9	2,1
horizontal aperture at 80 m (2□□) (mm)	535	1145	220*
vertical beam size at 80 m (20 KeV) (mm)	18,5	20,5	14,7*
vertical beam size at 80 m (100 KeV) (mm)	9,3	10,4	7,4*

*For the ESRF these values have been calculated at the second experimental station (150 m from the source).

Total power

The total power to be sustained by the front-end and the filters is of 8.4 kW (ABME-W1) and 23.1 kW (ABME-W2) (14.7 kW at the ESRF).

It is not feasible to obtain at a 3 GeV machine a dose rate at the same level of the ESRF without reaching intolerable power and power density values on the optical elements.

Microbeam Radiation Therapy Dose Rate

The radiation produced by the source should be preliminary filtered to remove the useless low energy spectrum and also to reduce the power load to the optical elements.

In these preliminary calculations the beam for MRT applications has filtered by 1 mm carbon, 1 mm aluminium and 1 mm copper (for the ESRF 1.5 mm copper).

Finite element calculation of the optical elements should be performed to calculate whether additional filters should be foreseen.

With these filtering, the proposed superconducting wigglers can deliver up to 2100 Gy/s (ABME-W1) and 4400 Gy/s (ABME-W2) in the 50-150 KeV energy range (15000 Gy/s at the ESRF), after suitable filtration.

On the other hand, the proposed sources (and in particular ABME-W2) will keep the ALBA beamline competitive for MRT patient programs.

In Figure 1, 2, 3 are reported respectively the unfiltered flux spectrum calculated at 30 m from the source on a 30x0.5 mm^2 area (Fig.1), the filtered spectrum for MRT (Fig.2) and the spectral dose rate (Fig.3).

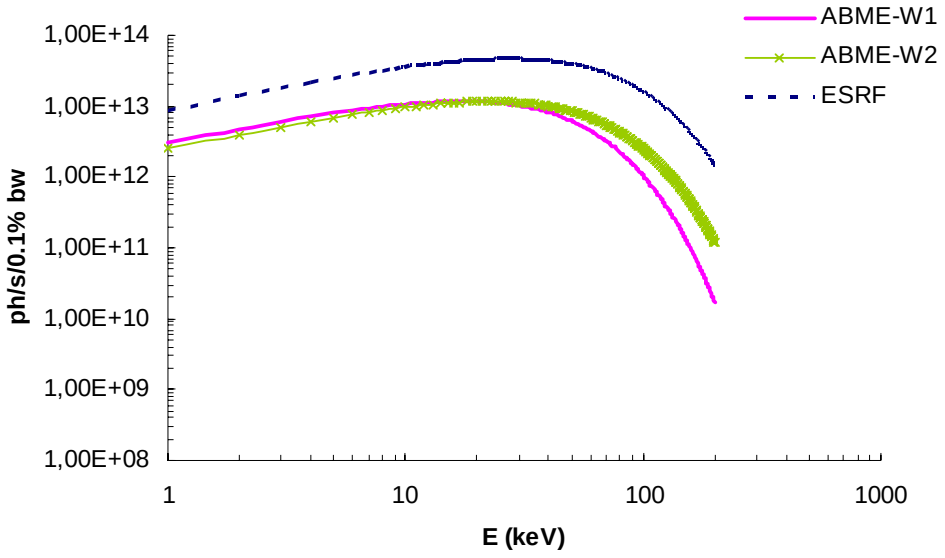


Figure 1. Flux spectrum (not filtered) at 30 m from the source on a 30x0.5 mm^2 area (hor x vert)

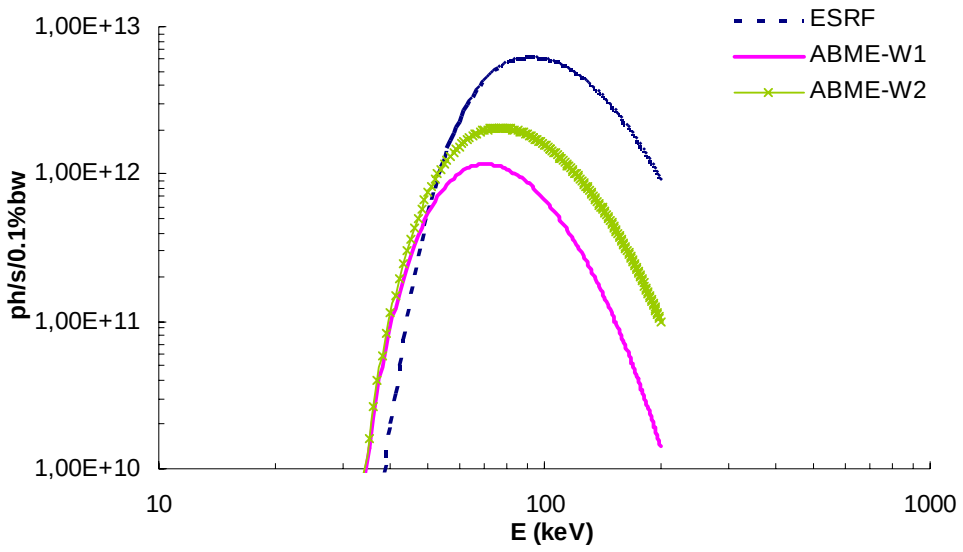


Figure 2. Filtered flux spectrum (ALBA: 1 mm C, 1 mm Al, 1 mm Cu; ESRF 1 mm C, 1.5 mm Cu) at 30 m from the source on a 30x0.5 mm^2 area (hor x vert)

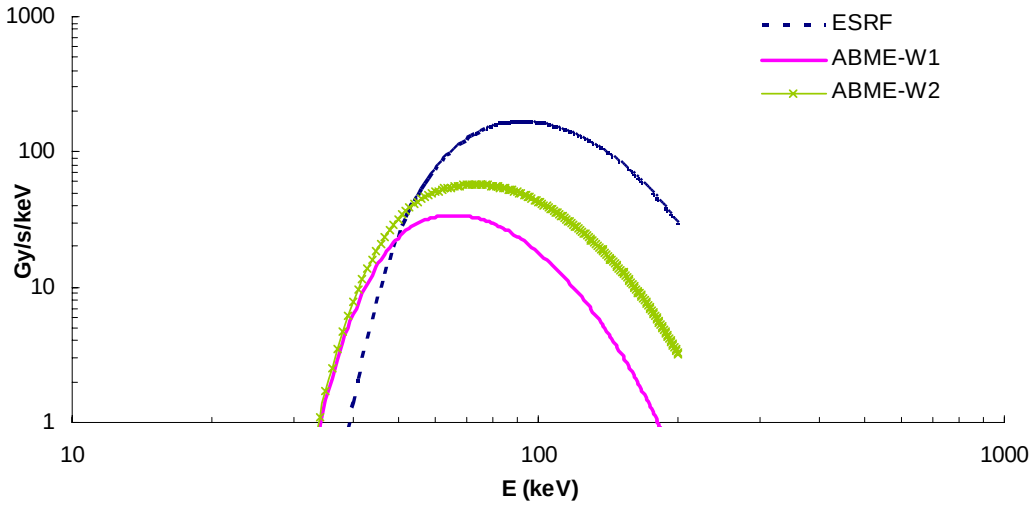


Figure 3 Spectral dose rate at 30 m from the source for the filtered spectrum shown in Fig.2.

The beam for the imaging and CESSR programs

The imaging and CESSR programs require an energy range of 20-100 KeV and dose rates (fluxes) much reduced with respect to the MRT applications. In addition, it has to be considered that for monochromatic applications, the power load produced by a high magnetic field is very difficult to be dissipated. For these reasons, the calculations have been here performed considering a magnetic field of 2T for both the sources. Values of flux are compared with the 0.6T wiggler source at the ESRF (field

used in the same scientific programs). In Tab.3 are reported the expected photon fluence rates (ph/s/mm^2) for a 0.1% monochromator bandpass.

Tab.2. Comparison of the parameters for two different superconducting wiggler sources at ALBA with the ESRF ID17 wiggler source for imaging/CESSR applications

	AMBE-W1	AMBE-W2	ESRF
electron energy, E (GeV)	3	3	6
$\gamma=E/(mc^2)$	5780	5780	11742
stored current (A)	0,4	0,4	0,2
maximum field on axis (T)	2	2	0,6
critical energy on the central axis (KeV)	11,9	11,9	14,4
period length (λ_w mm)	60	100	150
number of poles	10	10	11
total radiation power (kW)	2,7	4,5	2,7
K value	11,2	18,7	8,6
max. angular deflection □ (mrad)	1,9	3,2	0,7
length of magnet (m)	0,3	0,5	1,65
central brightness at the critical energy	6,95E+14	6,95E+14	3,06E+15
horizontal aperture at 30 m (2□□) (mm)	115	191	44
vertical beam size at 30 m (20 KeV) (mm)	5,4	5,4	3,0
vertical beam size at 30 m (100 KeV) (mm)	2,7	2,7	1,5
horizontal aperture at 80 m (2□□) (mm)	305	509	220*
vertical beam size at 80 m (20 KeV) (mm)	14,5	14,5	14,7*
vertical beam size at 80 m (100 KeV) (mm)	7,3	7,3	7,4*

*For the ESRF these values have been calculated at the second experimental station (150 m from the source).

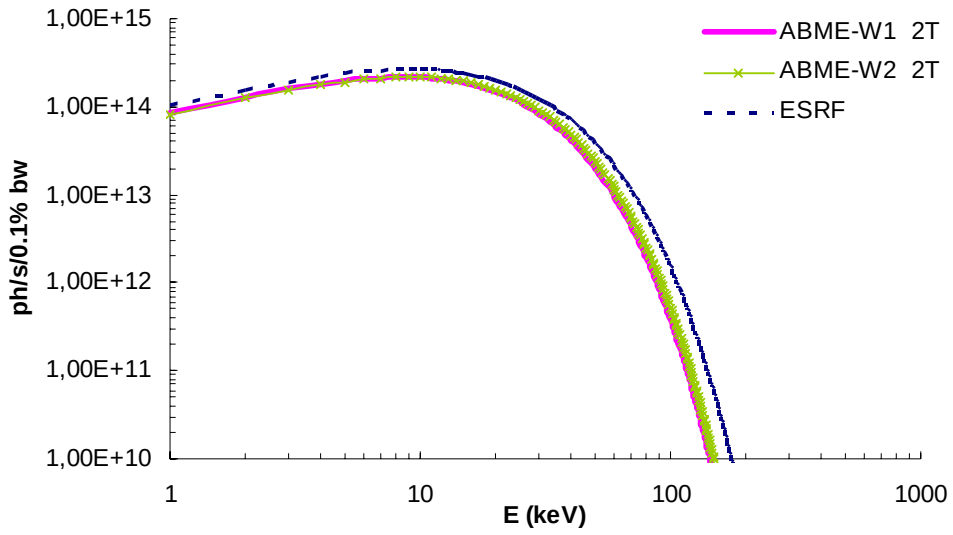


Figure 4. Flux spectrum at 80 m from the source calculated for the ABME wigglers at 2T. The values for the ESRF case correspond to a field of 0.6 T and are calculated at 150 m from the source.

Tab. 3. Expected photon fluence rates (ph/s/mm^2) for a 0.1% bandpass monochromator, calculated at 30 and 80 m from the source, respectively, for the ABME wigglers. For the ESRF source, values are calculated at 30 and 150 m from the source, respectively.

Photon flux (ph/s/mm^2)						
	at 30 m			at 80 m		
Energy (KeV)	*ABME-W1*	*ABME-W2*	*ESRF*	*ABME-W1*	*ABME-W2*	*ESRF**
20	7,75E+11	7,77E+11	3,02E+12	7,44E+10	7,88E+10	9,85E+10
33	6,39E+11	7,33E+11	3,08E+12	3,38E+10	3,79E+10	5,14E+10
80	1,49E+11	2,84E+11	1,60E+12	9,57E+08	1,25E+09	2,8E+09

4.2. Optics and instrumentation

General configuration

The beamline is composed of 2 independent experimental hutches. The beam is delivered in the first hutch at about 30 m from the source and at about 80 m in the second hutch. The first hutch will be dedicated to the MRT program (pre-clinical and clinical) and the second hutch to imaging and CESSR clinical programs. Experiments will run only alternately in the two hutches.

The X-ray beam is transported from the first hutch to the second via an in-vacuum pipe. When the beam is delivered in the second hutch, an additional flying pipe replaces the MRT equipment.

The first part of the beamline

The first part of the beamline begins at the end of the front-end section. This hutch should be composed by two independent parts: the first optical hutch (OH1) and the experimental hutch (EH1). In the EH1 white beam for MRT will be available. In order to permit imaging of the target before irradiation (to access the exact tumour position and size) also monochromatic beam should be available. A fast switch between white and monochromatic beam has to be foreseen (delay of minutes) in order to permit the irradiation without moving the target.

The first optical hutch (OH1)

It will host beamline components for both imaging and radiation therapy programs. It will be about 10 m long. In MRT mode, the beamline components will be in Ultra High Vacuum (UHV) up to the second Beryllium window.

Key instruments

1. Beryllium window to separate the vacuum of the machine/front-end from the beamline vacuum
2. In-vacuum filter system to reduce the power on the other optical elements and to select the beam spectrum for MRT irradiations. A 6-axis system with 3 slots each will allow choosing between a large variety of filtering combinations and thickness. Filters of Carbon, Aluminium, Copper, and Tungsten should be foreseen.
3. X-ray beam position monitor to align the beamline components
4. In-vacuum slit system to preliminary shape the white beam
5. Fast shutter to allow for single exposure of a predetermined time window and for synchronized irradiations with the sample (patient) positioning system. It will also serve for MRT imaging. If the beam is delivered to the OH2 it will be mechanically kept open
6. Monochromator for MRT imaging. Fixed exit, double crystal monochromator allowing a monochromatic beam in the energy range 25-80 KeV is required to use K-edge subtraction techniques using iodine (33.1 KeV), gadolinium (50.5 KeV) or platinum (78 KeV) contrast agents. A double Si(111) bent Laue crystal based monochromator is well adapted to this purpose. An energy spread of few hundreds of eV is more than sufficient for this application. In addition, the Laue geometry allows for a compact system (small crystal size, due to a reduced footprint with respect to the Bragg geometry) and is therefore well adapted to high-energy imaging.
7. Beryllium window to separate the in-vacuum from the in-air part.
8. Multislit collimator to spatially fractionate the beam. It can be installed on an optical table (in air). Only a few prototypes of this instrument exist around the world [4], based on the assembly of alternatively low Z and high Z materials. The layout of this critical element should follow the expertise of the other MRT teams (at the ESRF and at BNL).
9. A secondary slit system (in air) to reshape and clean the beam from scattering after the collimator

Standard beamline components (ion pumps, vacuum gauges, valves to separate different vacuum zones) complete the list of instruments necessary in this hutch.

The first experimental hutch (EH1)

This hutch is dedicated to the pre-clinical and clinical MRT program. Its length can be estimated in 10 m. Various instruments are common to both programs.

Pre-clinical MRT program

1. Sample positioning system. A goniometer to allow for highly precise unidirectional and crossfired irradiation of the target that should be positioned on the rotation centre. The sphere of confusion should be kept as small as possible (ideally 0.1x0.1x01 mm^3). Irradiations of large areas are performed by vertically scanning the sample through laminar beam at a constant speed. The uniformity of the movement, in particular in speed, is a critical issue. The operation speed range should be 10-200 mm/s to allow a wide range of delivered doses at a fixed gap (and photon spectrum). The layout should be adapted to small (rats) and large (pigs, max 30-50 kg) animals.

2. Dose monitors. In line, calibrated dose monitors (ionisation chambers) are required for the dose control.

3. Detector for imaging. The detector should be a digital system allowing spatial resolution of 50-100 microns. It should be placed on a remote controlled system to be move in and out of the beam switching from imaging to radiation therapy.

4. A shutter to stop the beam in this hutch or to allow it in the second experimental station.

Clinical MRT program

There are two critical elements related to the patient program: the positioning system and safety system (both passive and active). The final target of the MRT treatment has still to be identified: brain tumours in infants or in adults. It is evident that the engineering is completely different in the two cases (weight of the patient, size of the goniometer etc) both conditioning the layout due to the strict requirements in terms of precise positioning and uniformity of the scan.

With regard to the safety system, only general considerations can be made at this stage of the proposal. It should be envisaged to shield not irradiated tissues from scattered radiation (passive safety) and to foresee an automatic fast reaction chain (including local ultra-fast shutters, and wire connection with the machine RF cavities to dump the electron beam) to avoid unwanted overexposures.

The connecting part

The beam is transported from the OH1 to the second experimental hutch via an in-vacuum pipe. The instrumentation of this section consists in ion pumps and vacuum gauges. The pipe must be shielded for radiation until it enters in the second optical hutch.

The second part of the beamline

The second part of the imaging facility will consist of the second optical hutch (OH2), of the second experimental hutch (EH2) and of the beamline control room. Ancillary spaces to host an ambulatory patient care unit, patient reception, fluoroscopy, and sample preparation rooms are in its vicinities.

The second optical hutch (OH2)

This hutch will host the optical elements for the scientific programs foreseen in the second experimental hutch. It should be about 10 m long. In CT imaging, rather wide energy bands are adequate, e.g. from

0.1% to 1%. A so fine energy resolution is not needed in all applications. For instance in radiotherapy/CESSR a bandpass of 5-10 % can be even an optimal solution, which permit to deliver higher fluxes on the target. In addition, other in-vitro and in-vivo pre-clinical imaging applications (non quantitative CT imaging, Phase contrast propagation techniques) can be performed with rather large bandpass.

With regard to the K-edge imaging programs, two beams with energies across the K-edge of the element to be investigated must be delivered.

In order to satisfy both needs, two kinds of monochromators have to be installed and used alternatively.

K-edge imaging monochromator

This monochromator can be based on a single Si(111) bent Laue crystal. By using a beam splitter after the monochromator, two beams of energies distant 500-800 KeV can be produced. These beams are focussed on the sample and recorded simultaneously by two independent line detectors.

CT imaging/CESSR radiotherapy monochromator

- This monochromator should allow a fixed exit beam on a wide energy range (20-100 KeV). Two solutions can be envisaged:
- A double crystal Si(111) bent Laue system which permit an energy bandpass of 0.2-1 % depending on the crystal bending. This solution has been adopted at the ESRF
- A multilayer mirror monochromator. An accurate choice of the mirrors (probably two independent set should be foreseen to cover the full energy range) can permit to have very large energy bandpass (5-7 %) with a consequent increment of the flux on the sample.

Additional instruments

- An in-vacuum slit system to shape the beam before the monochromator.
- A beryllium window to separate the vacuum of the beamline from air
- A set of plastic filters to attenuate the monochromatic X-ray beam
- A slit-system in air to reduce the background scattering from the upstream optical elements
- A fast shutter system to be synchronized with the imaging acquisition
- A shutter to permit the beam to enter in the experimental hutch
- A fast shutter system to be triggered by the patient safety system as first reaction element to avoid over expositions

The second experimental hutch (EH2)

In this hutch pre-clinical imaging programs and CESSR-radiotherapy clinical trials will be performed. It should be about 15 m long. A long hutch is needed for at least three reasons:

- The large variety of applications (in-vitro and in-vivo imaging at different resolutions, cell and animal irradiations etc) necessitates of dedicated set-ups. The different set-ups should be moved in the beam according with the scheduled experiment to reduce time for swapping between experiments

- Phase contrast propagation-based imaging needs long propagation space (even 5-7 m) between the sample and the detector in order to register weak signal.

- The clinical program requires a large space to install the patient positioning system.

In the imaging mode, the sample is scanned vertically through the beams, and in CT a rotation scan is performed to acquire the projections at all angles. A two-dimensional map of the attenuation coefficient is then reconstructed as in a classical medical X-ray scanner. The data acquisition system is based on a digital detector followed by read-out electronics of a large dynamic range. In-vivo pre-clinical imaging scans should be performed within a couple of seconds, while for high resolution in vitro studies, tens of seconds can be foreseen.

For radiotherapy, a patient positioning system has to be foreseen. It should be able to move the patient in the beam, allow projection and CT imaging to precisely identify the target and scan the patient through the beam to deliver the dose following the treatment planning.

Pre-clinical applications

Key instruments

- Dose monitor. A single wide ion chamber, which detects the monochromatic fan beam(s) and is used to measure the X-ray dose imparted to the sample.

- Sample positioning and holder. The large variety of applications necessitates of dedicated set-ups, placed on optical tables in case of small samples or on strong rotating supports for in-vivo imaging.

- Detector. Phase contrast, K-edge, CT imaging requires detectors with very different characteristics in terms of spatial resolution (1-10 microns for microangiography, 50-100 microns for in-vivo K-edge imaging), field of view, and of efficiency in a broad energy range (20-100 KeV). All these requirements cannot be matched by a single commercial detector. The Frelon camera system developed at the ESRF, offers a suitable compromise [5]. To a common electronic/readout system can be coupled a variety of optics, which are easy exchangeable and which can cover the full requirements.

Clinical applications

Apart from safety and software issues, the patient positioning system is the key additional element for moving to pre-clinical to clinical applications. Since the X-ray beam is a fan beam, it is necessary to move the patient through the beam in order to obtain two-dimensional image of the target. For CT scans, attenuation profiles are acquired over a complete rotation of the patient. The patient positioning system, which allows both for positioning of the patient and the scan motions during the data acquisition, is a high precision stage. A very high rigidity of the structure during rotation or translation is especially important for tomography, since any eccentricity of the axis of rotation during the data acquisition will result in artefacts in the reconstructed image. 3D computed tomography is made possible by acquisition of a large number of images during helical motion of the patient.

The same system can be used to irradiate patient in radiotherapy.

It should allow precise adjustment of the vertical axis (Z). The maximum vertical translation speed should be in the order of 500 mm/s with a precision of 1%. The circle of confusion of the rotation axis, which is also related to the rigidity of the structure, should be less than 0.500 mm in the CT mode. The maximum rotation speed should be of 180 deg/s with a precision of a few %.

Construction phase

The goal of the beamline is to host pre-clinical experiments and clinical trials. It is clear that the clinical trials cannot start before a full commissioning of the beamline and the completion of advanced pre-clinical research protocols. Nevertheless, the engineering of both programs should be foreseen from the beginning, in particular to solve problems related to the patient safety system and to foresee all elements compatible with human studies (engineering of the hutches, radioprotection, suitable spaces to allow new instruments etc). The priority in the construction and commissioning should be given to the pre-clinical studies, carried out both in the MRT and in the second experimental hutch, to allow the scientific team to profit of the facility and to get practice with the techniques. The construction and commissioning logic could therefore follow the logical sequence:

- furnishing of the MRT hutch for pre-clinical studies
- beam delivered to the first hutch; commissioning of the instrumentation; first experiments
- furnishing of the second hutch for pre-clinical experiments (this phase can start during the commissioning of the first hutch); commissioning of the instrumentation; first experiment
- completion of the patient system for MRT and its commissioning
- completion of the patient system in the second hutch and its commissioning

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