Biomedical Imaging at PETRA III and PETRA IV - new opportunities for research and industry

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Book of Abstracts

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PETRA IV - The Ultimative 3D X-ray Microscope

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The PETRA IV project is DESY's plan to upgrade PETRA III to an ultra-low emittance source for hard X-rays. The new source will enable groundbreaking studies in many fields of science and industry, in fields as energy, life and health, transport and technology, earth and environment and information technology.
Being diffraction limited up to X-rays of about 10 keV, PETRA IV will be the ultimate three-dimensional X-ray microscope for biological, chemical and physical processes under realistic conditions with highest resolution and sensitivity.
In 2019, the conceptual design of the new facility was completed. In the next phase, the technical design and the science driven new beamline portfolio will be developed.

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Bio-imaging experiments using Scanning X-ray microscopy at the Hard X-ray Micro/Nano-Probe beamline P06 (DESY)

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The scanning X-ray microscopy beamline P06 is used frequently for microscopic X-ray imaging of the distribution of metals in biological material like cells, cell clusters and tissues. The experiment is optimized for fast mapping of trace elements from phosphorus to uranium by X-ray fluorescence spectrometry with sub-micrometer resolution. Two-dimensional projections, but also X-ray fluorescence tomography is measured within scan ranges from micrometer to millimeter. Cryogenic sample environments are available. X-ray fluorescence can be complemented by speciation analysis (XAS), and - in case of bones - by XRD. A new development for imaging at highest resolution is the addition of scanning coherent diffraction imaging (ptychography) for imaging of the light element matrix which is invisible for XRF at enhanced resolution. The capability of the instrument is illustrated by various user experiments.

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HZG imaging activities at beamlines P05, P07 (and P03)

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Helmholtz-Zentrum Geesthacht operates multiple imaging setups at beamlines P05, P07 and P03 of PETRA III and offers to its users full-field (micro- and nanotomography, radiography) and scanning techniques (scanning X-ray nanodiffraction).

While the focus of our activities is set around materials science related research, these instruments are actively used and appreciated by a wide range of users from life-science due to the ability of our instruments to provide multiple contrast modes (absorption contrast, phase contrast, diffraction contrast) and thereby to resolve fine structures from samples with very little density contrast.

All our techniques, whether used by us or provided to our users, are part of the GEMS-Platform, a worldwide unique infrastructure of large-scale research facilities and a suite of techniques tailored precisely to the demands of materials research.

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Nanoscopic X-ray Fluorescence Imaging of Cells with a High Energy X-ray Cryo Nano-probe

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Several essential metal ions participate in the control of numerous metabolic and signaling pathways, but their rich coordination chemistry and redox properties confer them a propensity to randomly coordinate and catalytically react inside the cell with protein sites other than those tailored for that purpose. Investigating metal homeostasis and its dysfunctions is crucial to better understand the cell functions and the influence on cellular pathology [1]. The associated challenge to analytical chemistry techniques, consists in locating and quantifying these elements, mostly present at trace level, within the highly complex intracellular landscape. As such, cutting-edge technique providing quantitative imaging for detailed study of elemental homeostasis or the intracellular distribution of metal-based drugs at biologically relevant concentration in a label-free fashion is highly desirable. The synchrotron X-ray fluorescence (XRF) nanoprobe as developed today provide the required sensitivity and spatial resolution to elucidating the 2D and 3D distribution, concentration of elements particularly metals inside entire cells at the organelle level. The new state-of-the-art Nano-Imaging

beamline ID16A-NI at ESRF offers unique capabilities for X-ray imaging at nanometer scale delivering an extremely bright, nanofocused beam (> 5×1011ph/s at Δλ/λ~10 2) at high energies (~30nm at 17kev [2]. X-ray tomography techniques offer the potential to image and quantify 'thick' cells and tissues in 3D without excessive sample preparation [3,4]. Recently, we reported the use of correlative synchrotron X-ray holographic and X-ray fluorescence nanotomography to quantify elemental 3D distribution within fixed or freeze-dried single cells [5] but also on frozen-hydrated cells. We will illustrate the capabilities of this techniques to provide quantitative nanoscopic cryo-XRF of cell as diverse as cancer cells exposed to organometallic drugs, neurons or cancer cells exposed to metal-based nanowires.

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Phase Constrast X-Ray tomography of biological tissues: methods and applications

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X-rays imaging can provide information about the functional (interior) architecture of complex biological organisms and tissues down to the sub-cellular level. Until recently, however, this potential of hard x-rays in view of penetration, spatial resolution, contrast, and compatibility with environmental conditions was significantly limited by the lack in suitable in x-ray optics. With the development of lens-less diffractive imaging and coherent focusing, the situation has changed. We now have nanofocused coherent x-ray synchrotron beams at hand to probe nanoscale structures both in scanning and in full field imaging and tomography. We explain how the central challenge of inverting the coherent diffraction pattern can be mastered by different reconstruction algorithms in the optical far and near-field. In particular, we present full field projection imaging at high magnification, recorded by illumination with advanced x-ray waveguide optics [1], and show how imaging and diffraction can be combined to investigate biomolecular structures within biological cells.

In this talk we present examples of biophysical and biomedical applications [2,3], with a focud on 3d virtual histology of human brain tissue [4], and discuss the novel opportunities offered by PETRAIV.

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Multimodal X-ray imaging of biological specimens

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Structural investigations of biological systems often involve the application of several highly sensitive and complementary methods able to provide statistically significant results. X-ray ptychography [1] is a robust and promising scanning coherent-diffraction imaging technique, yielding quantitative optical density contrast at dose-limited spatial resolutions beyond the fabrication limits of X-ray optics. Its scanning nature allows for simultaneous X-ray fluorescence (XRF) mapping, that enables artefact-free correlations of trace elements with highly resolved specimen's morphology [2,3]. Moreover, ptychography can also be combined with computed tomography, yielding quantitative 3D electron-density maps of extended specimens down to sub-100-nm spatial resolutions [4]. Thanks to its sensitivity, ptychography is particularly suitable for imaging biological tissues and cells, whose irradiation sensitivity sets a stringent requirement for highly efficient use of every X-ray photon they interact with. By using high-quality coherent X-ray beams, low-background setups, and optimized scanning routines, multimodal scanning X-ray microscopy aspires to an excellent tool for high-resolution structural investigations of weakly absorbing sub-cellular structures in 3D.

Here, we present the application of ptychography with concurrent XRF mapping at beamline P11 at the low-emittance synchrotron storage ring PETRA III, DESY. We developed a scanning X-ray microscope featuring a Fresnel zone plate as an illumination-forming optic, high-throughput scanning unit, and a high-framerate detector. We used the correlative method to image a population of macrophages treated with iron-oxide nanocontainers for tuberculosis drugs. We further applied the concurrent imaging techniques to study the mineralization of a human bone matrix [5]. Recently, we have upgraded our X-ray microscope with a rotation stage permitting ultrafast tomographic measurements. We will demonstrate its operation with ptychographic tomograms of representative specimens. Finally, further applications, in reference to emerging diffraction-limited synchrotron light sources, will be addressed.

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Imaging biological cells by scanning SAXS

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X-rays provide high resolution due to their small wavelength and high penetration power, allowing for imaging of comparatively large, three-dimensional objects. For these reasons, X-rays have been established as complementary probes for bio-imaging, in addition to well-established methods such as visible light fluorescence microscopy and electron microscopy (EM). Scanning small angle X-ray scattering (SAXS), in particular, is well suited for systems with some degree of order, such as bundles of parallel filaments, or high-density aggregates. The method exploits two unique features of X-ray imaging: not only are highly focused beams used to spatially resolve different constituents of biological cells, but each individual scattering pattern contains a wealth of information about the internal structure on molecular length scales.
I will present scanning SAXS experiments that were performed at dedicated synchrotron beamlines, which provide a small beam between 100 nm and 2 µm in diameter, high flux, high-end pixel detectors and a sample environment suitable for cell samples, e.g. ID13 at the ESRF and P10 PETRA III/DESY. I will summarize the most important results we recently obtained on different biological systems, such as components of the cytoskeleton and the DNA in the nucleus.

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High-energy Full-Field Imaging at EMBL-Hamburg

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Exploiting the high brigthness of PETRA III, we have been successfully using the ‘untouched’ beam from an U32 undulator for the homogeneous illumination of crystal mounts for detecting individual crystals (Polikarpov et al. (2019) Acta Cryst. D75:947).

Recently, we have expanded the imaging experiments to various small organisms, in particular platynereis dumerilii. Using technologies in place for high-throughput crystallography, full 3D tomograms of such samples can be recorded in less than 5 minutes, opening exciting perspectives for large-scale studies.

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3D in vitro cell culture models for the assessment of neurotoxicity

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We talk about neurotoxicity when exposure to natural or manmade toxic substances interferes with normal nervous system activity and function. Neurotoxicity might disrupt or even kill neurons or the surrounding glia cells by interfering with neural function. Special attention must be given to

susceptible subgroups, the very young (developmental neurotoxicity, DNT) and the aging population. So far, neurotoxicity has been evaluated by using animals. Currently, there is an international consensus that new approach methods (NAMs), e.g. based on stem cells, are needed that inform on neurotoxicity in a faster, cheaper and more human-relevant way than current animal experiments. Only the use of such methods allows gain of information on the neurotoxic hazard of the approx. 30,000 chemicals that are currently in use within our every-day life.
In recent years, we have been developing human stem cell-based cell systems that aim at serving as test methods for life stage-specific neurotoxicity. Therefore, we use human primary neural progenitor cells (hNPC) or human induced pluripotent stem cells (hiPSC) as our cellular templates. One focus of this work lies on the study of human relevance of the in vitro models. These are then further used for toxicity studies. Here, some of the models will be presented. For analysing DTN, we apply the test methods NPC1-6 using high content imaging. Here, we recently investigated the toxicity of flame retardants for brain development. In addition, we set up hiPSC-derived neural cultures for analysing neuronal network formation on microelectrode arrays.
In summary, this talk should give an overview over the cellular work we perform to study neurotoxicity. Such data is currently feeding into novel hazard and risk assessment paradigms at a regulatory level. Here we collaborate with the European Food Safety Authority and the US-Environmental Protection Agency on how to implement such NAMs for regulatory decision-making.

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Visions for following the fate of nanoparticles in cells via synchrotron radiation

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In the context of biological environment nanoparticles are hybrid materials, which apart from the "bulk" particle also involve the corresponding surface chemistry and a corona of adsorbed molecules from the environment, such as proteins [1]. Upon cellular internalization the nanoparticles may degrade into their individual parts [2]. This process can be followed by using radiotracers [3], fluorescence [4], and mass spectroscopy [5]. Furthermore adsorption of proteins can be probed by fluorescence correlation spectroscopy [6] or nuclear magnetic resonance [7]. It will be discussed how such experiments could be also investigated using synchrotron radiation.
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Biomedical applications of ultrafast beams: status and plans

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Nowadays, there is a raising interest in ultrafast lasers applications in a broad range of fields, including accelerator technology, medicine and biology. Ultrashort laser pulses can be used in the technology of two photon laser scanning microscopy and generation of ultrashort low energy electron pulses in laser driven radio-frequency gun. It is assumed that accelerators of this type can make a revolution in radiation therapy of tumors by delivering an ultrashort low energy electron pulses.
In our recent studies, using two photon microscopy technique, we demonstrated a novel approach for the investigation of oxidative stress in human living red blood cells (RBCs) that could efficiently be applied in clinical research and testing of antioxidant compounds. We showed that two-photon laser scanning imaging is a valuable tool for studying oxidative stress in living RBCs not only under oxidative stress related different pathological conditions, including aging and radiation exposure on the organism, but also in the studies of the effects of different natural or chemically synthesized compounds.
Regarding the application of ultrashort low energy electron pulses, currently we study their biological effect on the whole body rat irradiation to understand the effect of ultrashort pulsed electron beam on the organism, which will serve as a good basis for future cancer treatment studies. Overall first results indicate that the LD50 for electron beam whole body rat irradiation is 2.5 Gy, and therefore we used 2 Gy and 2 Hz repetition rate radiation for the main experiments to maintain the optimal survival rate. After the whole body rat irradiation by the low energy ultrashort-pulsed electron beam, pathological processes in animals' immune system increase up to the 3rd day, and the processes of recovery start from the 7th day of exposure continuing up to 14th and 28th days, demonstrating partial recovery of immune system in shorter period than in case of irradiation with X-rays or gamma-rays.

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X-ray fluorescence imaging of biological samples at P06 / Petra III under cryogenic conditions

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From Basic Synchrotron Research to First Clinical Applications: X-ray Darkfield Imaging for Lung Diseases

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This contribution will review our efforts, key achievements, and pitfalls during our ten-year journey to translate grating-based X-ray darkfield imaging from the optical bench to clinical bedside.

Early Years of Grating-Based Imaging: Grating-based phase- and darkfield-contrast X-ray imaging has been translated from synchrotron sources to laboratory benches about a decade ago [1-3]. This milestone has increased the interest in grating-based phase- and darkfield-contrast in the medical community, as it provided a perspective to implement phase-contrast and darkfield imaging also with conventional X-ray generators, which are compatible with presently used medical X-ray systems in radiology.

Small-Animal Trials: After the initial development years of the basic technology and image processing aspects of grating-based imaging, we have then focused on developing a first small-animal darkfield imaging platform [4]. After the first successful in-vivo images [5], this device has been used to carry out several studies on small-animal lung disease models. The results of these studies have clearly demonstrated that darkfield radiography can improve the detection of chronic obstructive pulmonary disease (COPD) [6,7], lung fibrosis [8], lung cancer, pneumothorax, pneumonia, or damage due to mechanical ventilation.

Translation to clinical requirements: Based in these small-animal results, we then continued to develop the technology further to high energies and large fields-of-view to be compatible with the technical requirements of typical clinical chest X-ray applications. These efforts have led to successful demonstration experiments in in-vivo large-animal models [9] and human cadavers [10], and allowed us to subsequently refine the technology, image processing and dose requirements such that a first clinical prototype was finally in reach. The latter has been constructed during the last three years at the TUM Klinikum rechts der Isar, and finally cleared for patients end of 2019. During this process we have addressed all regulatory issues, i.e. approval according to the German medical device regulations, approval by the national ethics board, and approval by the German radiation safety authorities.

Results from first patient study: Presently we are conducting a first patient study to demonstrate the potential of darkfield chest radiography to improve detection and precise diagnosis of lung diseases, with a particular focus on chronic obstructive pulmonary disease (COPD). In this presentation, we will review the most important findings of approx. hundred patients.

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State-of-the-Art and Challenges of Clinical Cancer Imaging - Potentials of Synchrotron Radiation-Based Imaging in the Preclinical and Translational Setting - a Physicians Perspective

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Heinz-Peter Schlemmer will give a concise summary of cutting-edge clinical cancer imaging including current limitations and challenges, which will be followed by a comprehensive presentation of Willi Wagner presenting preclinical and translational research on high-resolution synchrotron-based imaging of lung cancer.

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Exploiting the complementarity between X-ray Scattering and Absorption techniques to investigate breast cancer metastasis

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Breast cancer is the leading cause of cancer death in women worldwide. Systemic changes in the elemental composition of the microenvironment between the cancer cells and the host stroma play an important role in supporting the growth and progression of the tumor. Excessive accumulation of the trace elements Fe, Zn, and Cu and its relationship with the matrix of the tumor microenvironment remodeling has been reported. Although the knowledge of breast carcinogenesis is being progressively elucidated with 2D cell-culture experiments, they are not able to reproduce the real physiological pattern of the tumor microenvironment where the surroundings cells are equally as important as the tumor cell itself. X-ray fluorescence (XRF) has been successfully exploited to detected trace elements in breast tissues, nevertheless, this technique is not sensitive to light elements such as carbon and oxygen, the major constituents of the breast tissues matrix. This information can be complemented by using the Rayleigh-to-Compton ratio technique (R/C). Likewise, the microenvironment remodeling comprises collagen fibrils rearrangements which can be investigated by Small-angle X-ray scattering (SAXS).
At this presentation, it will be shown the results of a pilot experiment exploiting the complementarity of the X-ray scattering and spectroscopy signals tomographically acquired, to map three-dimensionally the changes due to cancer progression.

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T-REXX: a dedicated endstation for time-resolved serial synchrotron crystallography

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In order to fully understand the mechanisms of biological processes, time-resolved methodologies that allow us to comprehend how function is linked to changes in molecular structure are required. Time-resolved X-ray crystallography provides a means of directly visualising structural rearrangements associated with function. The T-REXX endstation on EMBL beamline P14 at PETRA III is a dedicated endstation for time-resolved serial crystallography and entered user operation in March 2019. I will present the current status and first results from T-REXX.

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Three-dimensional characterization of specific soft-tissue X-ray staining protocols by high-resolution imaging

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Recently, novel X-ray staining protocols have been developed, which are able to specifically enhance the contrast for one special type of cell structure (eosin-based stain for cytoplasm[1]; cell-nuclei specific stain based on modified hematein staining [2]). For better understanding of the staining process, a quantitative characterization of those X-ray staining protocols inside the soft tissue is required at high spatial resolution to determine the exact distribution of the stain within the cell structure. Here spatial resolutions between 0.5-5 µm are required to visualize the major tissue types in the stained human tissue and at the same time to image a representative fraction of the tissue for good statistics.

The major issue with such a quantitative characterization is the fact that no pure attenuation is available at these high spatial resolutions at highly-brilliant synchrotron sources. The high resolution always comes along with propagation-based phase-contrast effects – the so-called edge enhancement - and requires a phase retrieval. The common phase-retrieval methods for single-distances do not provide quantitative values (e.g. Paganin phase retrieval [3]). The grating-based method can clearly and very accurately separate the attenuation and the phase effects. Here, we will elaborate the potential and the remaining challenges of this imaging modality with regard to a quantitative soft-tissue characterization [4], [5].

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Microbeams: Radiotherapy with a vision for the future

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Microbeam radiotherapy (MRT) is a synchrotron-based approach to spatial dose fractionation at the micrometer range. Pre-clinical data suggest that MRT can help to control malignant tumours which are considered radioresistant in clinical radiotherapy.

The international MRT research community expects to see first clinical trials at the European Synchrotron Radiation Facility (ESRF) in France and at the Australian Synchrotron in Melbourne within the next six to ten years.

A brief overview will describe what has been achieved already, followed by a discussion of the potential future development of MRT and how microbeam research could contribute to the biomedical scientific portfolio of the PETRA synchrotron on the DESY campus in Hamburg.

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Materials Development for Biomedical Applicationssupported by Synchrotron Radiation

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The Institute for Medical Technology and Institute for Materials and Joyning Technology of the Otto-von-Guericke University Magdeburg are introducing their vision and research activities which would be suitable for a dedicated biomedical beamline at PETRA III and PETRA IV.
The research plan involves biomaterial alloy design and development based on classical Ti-Al-V and Co-Cr-Mo alloys but also on new biocompatible refractory high-entropy alloys (RHEAs), processing technologies such as drilling, milling and rolling, as well as material-tissue interaction of implants (in vivo / ex vivo) and their damage analysis of explants. Furthermore, new cellular ceramics coated with biocompatible metallic layers should be used for distinct tissue engineering (TE) applications using stem cells. We will cover broad field of biomaterial applications to show the need for a biomedical beamline and in situ synchrotron experiments in our ongoing and future research.

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Towards in vivo imaging of immune cell dynamics using X-ray fluorescence

Authors: Andreas Müller[1]; Christoph Hoeschen[2]; Melanie Fachet[1]

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Despite of ongoing advances in diagnosis and therapy, diseases related to cellular malfunction such as immune system dysregulation and cancer are among the leading causes of death worldwide. Current medical imaging methods based on ionizing radiation are either able to generate morphological information with high spatial resolution (e.g. CT) or functional information with low resolution (e.g. PET) [1]. In contrast, light microscopy-based approaches are limited to preclinical models due to the need for genetically encoded fluorescent labels [2].

X-ray fluorescence imaging of functionalized nanoparticles combines the visualization of biochemical and pathological processes in vivo with a potentially high spatial resolution. However, despite the long measurement times and comparatively high doses, the sensitivities are currently still too low due to the low signal-to-noise ratio due to Compton scattering. The use of gold as a nanoparticle-based contrast agent in X-ray fluorescence imaging has proven to be advantageous both from a technical perspective due to its photoelectric properties and from a molecular point of view through specific functionalization options [3].

The immediate, pre-clinical goal is to improve the X-ray fluorescence imaging with gold nanoparticles in small animals (e.g. mice) with further diagnostic and therapeutic development for humans in the long-term perspective.

This talk highlights various research tasks related to spatial and temporal cell dynamics of the immune systems at the Otto von Guericke University, especially associated with the Health Campus Immunology, Infectiology and Inflammation (GC-I3) and the Research Center Dynamic Systems: Systems Engineering (CDS). In particular, we aim at employing mathematical modelling and correlative intravital imaging approaches in order to establish the use of gold nanoparticles for non-invasive analysis of the dynamics of nanoparticle-loaded immune cells within the living tissue.

This research should critically contribute to the understanding of the dynamics of immune cellular processes during tumour formation, infection or autoimmunity, as well as innovative diagnostic and therapeutic options.

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Tissue characterization in vivo before, during and after ablation procedures with synchrotron radiation

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In modern medical treatment especially of tumor diseases, the interventional ablation using localized application of energy like e.g. microwave based or radiofrequency based ablation is becoming more and more important in curing of small tumor lesions (typically below 3 cm diameter). The curing rates are very good. However, in some cases, recurrence of the cancer is documented. The problem is actually, that in CT imaging neither the correct boundaries of the tumor can be detected with 100% accuracy, nor e.g. the temperature distribution during a microwave ablation nor the boundaries of the destroyed tissue during the ablation can really be seen. Thus, in some cases, the procedure is not destroying the whole tumor. Then the tumor can start growing again. Or the region that is destroyed is too large and there is healthy tissue destroyed which could effect the health status of the patients as well. In the worst case destroyed healthy tissue might result in secondary tumors. Since the ablation cannot be monitore in MRI or US, an x-ray based method is needed. Due to scatter of the large CT beam as well as the broad energy spectrum the contrast in CT is not sufficient for detecting the subtle differences. Using monoenergetic pencil beams, one could do scatter imaging and or speckle imaging to characterize the tissue differences and the changes during the procedure. The information from both imaging methods can be evaluated using AI based methodology. If that imaging and evaluation is successful, that would really benefit the patients because it would allow the optimal destruction of tumors for example in the liver or the lung or maybe even the pancreas while reducing the chance for recurrence and sparing healthy tissue. Certainly there would also be other applications of such imaging approaches even for tissue characterization in diagnostics.

This will obviously need to be proven on in vivo imaging procedures. Thus, we plan, first to develop the procedures, then measure biopsies, afterwards check with tissue that is going to be engineered and then perform in vivo animal studies, with the ablation being performed in-between two imaging sessions.

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The Promise of FLASH-RT: Ultra-high Dose Rate Radiation Therapy for Cancer

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Radiation therapy is a very common, effective and cost-efficient method for cancer treatment. In many applications, however, clinicians could still benefit from a greater therapeutic ratio – maintaining or improving tumor control while reducing toxicity to nearby healthy tissues. Recent publications have shown that FLASH-RT, or ultrahigh dose rate radiation therapy, has shown promise in doing just this. In pre-clinical studies, researchers have shown that FLASH-RT is at least as effective as conventional radiation therapy in killing tumor cells while exhibiting improved sparing of healthy tissues in a variety of animal models including mice, cats, and mini-pigs. Unfortunately, the mechanism of action for the improved normal tissue sparing is not yet well-understood. In this talk I will summarize the recent pre-clinical research in FLASH-RT, summarize some of the hypothesized mechanisms of action for the FLASH effect and motivate the need for more research in this field.

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Why Biomedical X-Ray Fluorescence Imaging needs a Synchrotron

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In biology and medicine, optical fluorescence is a well-established research tool, but can only provide a severely limited imaging depth. To overcome this depth limitation, X-ray Fluorescence Imaging (XFI) is based on the excitation of fluorescence in the X-ray photon energy range, where the attenuation in tissue is less strong. A typical envisaged application of XFI is early tumor-diagnostics, where gold-nanoparticles functionalized with antibodies are tracked. However, until recently XFI was regarded as unsuited for large objects such as humans due to the intrinsic large background from Compton-scattering, which also affects pre-clinical studies. This problem has been solved, which opens up the path towards future applications of XFI. In this talk I will focus on the question why biomedical XFI requires a synchrotron beamline.

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X-ray microscopy with 1 nm resolution

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The short wavelengths of X-rays allow imaging at high resolution, which is usually only fully exploited in coherent diffractive imaging techniques such as X-ray crystallography. Ptychography provides a robust method to phase coherent diffraction by adding diversity to the measurement with a structured beam, and perhaps the highest diversity is achieved when that beam is the smallest possible probe, created by a lens of high numerical aperture (NA). A high-NA lens is indeed a handy optical element for imaging. A probe focused to a 1 nm spot can not only be used for coherent imaging but can also be used for imaging fluorescence and inelastic scattering. Creating such a lens

appears to be feasible, but challenging. Coupled with a source of sufficient brightness, it could be used for rapid tomographic imaging of complex objects over extended fields of view.

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Helmholtz Imaging Platform - Connecting Imaging Science across the Helmholtz Association and beyond

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Together with Max-Dellbrück-Centre and Deutsches Krebsforschungszentrum, DESY is operating the Helmholtz Imaging Platform (HIP) that brings scientists and engineers together to promote imaging science and foster synergies across imaging modalities and applications within the Helmholtz Association and beyond. This talk introduces the platform and describes the various cross-domain networking tools it offers.

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Biological Imaging Opportunities at PETRA IV

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Biomedical imaging using synchrotron radiation: ground truth for imaging in vivo

Author: Claus-Christian Glüer[1]

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In the past decade we have seen a rapid expansion of imaging approaches for preclinical imaging in vivo, including computed tomography (CT), magnetic resonance, fluorescence and bioluminescence, ultrasound and photoacoustic and nuclear medicine approaches. Each of these techniques has strengths and limitations but multimodal assessment permits combined application for morphological, functional, and molecular imaging. However, in general, radiation dose limitation, (movement) artifacts and limited penetration depth limit the image quality and the accuracy of element- or tissue-specific analyses of these in vivo measurements. A powerful strategy thus builds on a combination of longitudinal multimodal imaging in vivo and ex vivo assessment of tissue at the final measurement time point. For the latter, synchrotron radiation (SR) approaches offer intriguing perspectives for a number of applications. I will select a few exemplary fields of study to document this potential. In orthopedic research bone augmentation techniques are undergoing continuous refinements. For example degradable bone cements with osteoinductive potential permit improved fracture healing and fracture prevention. To document the replacement of bone cement by bone ingrowth is extremently challenging since the injected material is very similar to hydroxyapatite. Monochromatic SR techniques may permit differentiation and along with nano- or micro-tomographic morphological imaging this would permit a more objective assessment of the strength of bone tissue ingrowth, replacing the degrading injected material. Similarly, difference in mineralization status e.g. in osteogenesis imperfecta, renal disorders or due to osteoporosis medications may be differentiated using

these approaches. Experience at SR facilities then may guide further development of photon counting spectral CT scanners soon to be introduced into clinical routine.
Element specific imaging can be extremely powerful if turned into truly 3D representations of tissue. SR based x-ray fluorescence imaging or energy-dispersive x-ray spectroscopy are just two options to be pursued. Multimodal imaging in vivo increasingly builds on markers that are visible on several of these modalities. Gold (nano) particles are prime candidates since they can be imaged e.g. by fluorescence, photoacoustics, optical coherence tomography, and computed tomography. As an important area of application theranostic approaches can be named. Here drug delivery nanocarriers (e.g. liposomes) loaded with drugs, markers, and activation agents safely transport drugs to the target location where the drugs are released. Element specific analysis can prove what fraction of the drug actually reaches the target tissue (usually only a few percent of the injected dose, leading to undesirable side effects of the 95+% of the drug at locations of healthy tissue elsewhere in the body) and thus can provide guidance for drug development.
Whatever the specific application there will be a need for automated 3D registration of images generate with different modalities (image fusion) or the same modality with different spatial resolution. Artificial intelligence (AI) methods have recently led to substantial progress in the field of automated image segmentation and registration and thus these techniques should be adapted to the special requirement in the setting of SR based technique. Reduction of imaging artifacts is another related area with promising AI developments.
In summary, linking SR ex vivo techniques to corresponding multimodal in vivo imaging approaches generates unique opportunities not only for experimental studies but also for refinement of clinical imaging approaches.

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Morphological imaging: high-throughput, hierarchical & in-vivo imaging on the levels of full organism, organs, tissues down to cells

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8 micron pixel pitch direct conversion X-ray detector for phase contrast X-ray imaging in biomedical applications

Author: Chris Scott[1]

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When conventional x-ray radiography presents inadequate absorption-contrast, higher sensitivity can be achieved using phase-contrast methods. The implementation of phase-contrast x-ray imaging using propagation-based techniques requires stringent spatial resolution requirements that necessitate lengthy propagation distances and inefficient scintillator-based detectors. Thus, imaging throughput is limited, and the absorbed dose by the sample can be unacceptable for radiation sensitive life science and biomedical applications.

This work develops a hybrid direct X-ray conversion amorphous selenium and complementary metal-oxide-semiconductor detector technology that offers a unique combination of high spatial resolution and quantum efficiency for hard x-rays. A semiconductor fabrication process was developed

for large area compatible vertical detector integration by back-end processing. Characterization of signal and noise performance using Fourier-based methods was performed by modulation transfer function, noise power spectrum, and detective quantum efficiency experiments using radiography and microfocus x-ray sources.

The measured spatial resolution at each stage of detector development was one of the highest, if not the highest reported for hard x-rays. In fact, charge carrier spreading from x-ray interactions with amorphous selenium was shown physically larger than the pixel pitch for the first time. A simultaneous factor of three improvement in quantum efficiency was achieved compared to scintillator-based detectors, despite the detector being a relatively unoptimized prototype.

Fast propagation-based phase-contrast x-ray imaging in compact geometries is demonstrated using a conventional low power microfocus source and the phase-contrast technique was applied to imaging mice. The results from this research suggest that hybrid semiconductor technology offers the potential to fill the large performance deficit in high spatial resolution scintillator-based detectors for phase-contrast X-ray imaging and to even enable high speed dynamic phase contrast X-ray imaging when used with more powerful sources of X-rays.

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Orientation Map of Nerve Fibres in Thin Brain Sections by Small Angle X-ray Scattering

Author: Martin Dulle[1]

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The brain is the most complex organ in the body that serves as the center of the nervous system and consists of billions of neurons [1]. The structure and function of the brain is intricately linked to the structural connectome i.e the neurons and neural connections. To better understand function, dysfunction and neurodegenerative disease of the brain, it is essential to have a map of the connectome. The standard method for connectome mapping is Diffusion Magnetic Resonance Imaging (dMRI), which is limited to a spatial resolution of ~500 μm (post mortem) or 2 mm (in vivo), respectively. More recently, 3D polarized light imaging (3D-PLI) has been developed into a powerful tool to determine the nerve fiber (i.e., myelinated axon) orientations and their distribution (FOD) across a thin (60μm), unstained histological brain sections by transmitting polarized light through them and quantifying the resultant birefringence [2].
However, the addressable voxel size is largely anisotropic, which often leads to partial volume effects in voxels comprising fibers running in multiple directions. This means that the average birefringence signal is close zero and FOD cannot be determined reliably. To overcome this, we have started using small angle x-ray scattering (SAXS) to determine the FOD and the structural details of the myelin sheath around the axon [3].
Here, we will demonstrate our recent SAXS results from the thin, unstained histological brain sections. We have carried out 2D scans of several full brain sections of mouse (sectioned along sagittal-cut and coronal-cut direction) and human (few complex ROI) using transmission SAXS at a synchrotron as well as a laboratory x-ray source. We were able to prepare a complete 2D orientational map of nerve fibers from the azimuthal distribution of the scattering peak/arc/rings out of thousands SAXS patterns, collected at a spatial resolution of 100-200μm. We will also present the 3D-PLI results of the corresponding brain sections to obtain a complete picture of the connectome map [4]. Recently Giorgidias et. al. have shown that by measuring a brain slice at different tilt angles the FOD in 3D can be obtained. The underlying principle of their work and our plans in terms of experiments and more detailed analysis of the scattering from nerve fibers are outlined.

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Wrap-Up, Questions, Final discussion

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Tissue characterization in vivo before, during and after ablation procedures with synchrotron radiation

Author: Christoph Hoeschen[1]

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C. Hoeschen, F. Grüner, N. Mahmoodian, S. Weimann, M. Pech

In modern medical treatment especially of tumor diseases, the interventional ablation using localized application of energy like e.g. microwave based or radiofrequency based ablation is becoming more and more important in curing of small tumor lesions (typically below 3 cm diameter). The curing rates are very good. However, in some cases, recurrence of the cancer is documented. The problem is actually, that in CT imaging neither the correct boundaries of the tumor can be detected with 100% accuracy, nor e.g. the temperature distribution during a microwave ablation nor the boundaries of the destroyed tissue during the ablation can really be seen. Thus, in some cases, the procedure is not destroying the whole tumor. Then the tumor can start growing again. Or the region that is destroyed is too large and there is healthy tissue destroyed which could effect the health status of the patients as well. In the worst case destroyed healthy tissue might result in secondary tumors. Since the ablation cannot be monitore in MRI or US, an x-ray based method is needed. Due to scatter of the large CT beam as well as the broad energy spectrum the contrast in CT is not sufficient for detecting the subtle differences. Using monoenergetic pencil beams, one could do scatter imaging and or speckle imaging to characterize the tissue differences and the changes during the procedure. The information from both imaging methods can be evaluated using AI based methodology. If that imaging and evaluation is successful, that would really benefit the patients because it would allow the optimal destruction of tumors for example in the liver or the lung or maybe even the pancreas while reducing the chance for recurrence and sparing healthy tissue. Certainly there would also be other applications of such imaging approaches even for tissue characterization in diagnostics.

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PETRA IV - The Ultimate 3D X-ray Microscope

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Biological Imaging Opportunities at PETRA IV

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Abstract not available.

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Three-dimensional characterization of specific soft-tissue X-ray staining protocols by high-resolution imaging

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